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**Department of Vermont Health Access**

***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 thrombocytopenia. The platelet inhibitors are also indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery.<sup>1-6</sup> The use of these agents as both monotherapy or combination therapy by national and international treatment guidelines is based on the specific clinical indication and the patient's risk for thromboembolic events.<sup>7-17</sup>

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<sub>2</sub>, a platelet aggregant and potent vasoconstrictor. Its use has been the cornerstone of acute treatment for over 15 years; however, evidence from clinical trials demonstrates that aspirin reduces adverse clinical events among a broad group of patients treated for both acute and chronic vascular disease.<sup>18</sup> 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.<sup>19</sup>

Clopidogrel (Plavix<sup>®</sup>) and ticlopidine are both thienopyridines, which work by blocking the adenosine diphosphate receptors found on platelets, leading to a subsequent inhibition of both platelet aggregation and activation.<sup>2,5</sup> 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 the thienopyridines are delayed; therefore, a loading dose is typically required with these agents.<sup>19</sup> 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.<sup>18</sup> In addition, the benefit of thienopyridines as monotherapy or in combination with aspirin in the treatment of coronary artery disease is well established.<sup>19</sup>

The mechanism of action of dipyridamole (Persantine<sup>®</sup>) 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.<sup>3,20</sup> Dipyridamole, particularly when combined with aspirin, is effective for the prevention of stroke.<sup>19</sup> Currently, there is no evidence to support the use of dipyridamole either instead of, or in addition to, aspirin and the thienopyridines in the acute treatment of patients presenting with a non-ST-segment elevation acute coronary syndrome.<sup>18</sup>

The mechanism of action of anagrelide (Agylin<sup>®</sup>) 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.<sup>1,20</sup> Anagrelide is the only platelet inhibitor FDA approved for the treatment of thrombocytopenia 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.<sup>1</sup>

The newest platelet inhibitor to be approved by the FDA is prasugrel (Effient®). Prasugrel is a 3<sup>rd</sup> 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 prasugrel dose being approximately 2.5 to 2.7 times more potent than a 75 mg clopidogrel dose in inhibiting platelet aggregation and thrombus formation.<sup>21</sup> 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, where as prasugrel requires only a single step.<sup>22</sup> 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 effect 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.<sup>23</sup>

Currently, anagrelide, 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.

### **Medications**

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

<b>Generic Name (Trade name)</b>	<b>Medication Class</b>	<b>Generic Availability</b>
<b>Single Entity Agents</b>		
Anagrelide (Agrylin®)	Platelet inhibitors	✓
Clopidogrel (Plavix®)	Platelet inhibitors	-
Dipyridamole (Persantine®)	Platelet inhibitors	✓
Prasugrel (Effient®)	Platelet inhibitors	-
Ticlopidine*	Platelet inhibitors	✓
<b>Combination Products</b>		
Aspirin/dipyridamole (Aggrenox®)	Platelet inhibitors	-

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

**Indications**

**Table 2. Food and Drug Administration Approved Indications<sup>1-6</sup>**

Indication	Single Entity Agents					Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine	Aspirin/Dipyridamole
Acute coronary syndrome		✓ *				
Prevention of postoperative thromboembolic complications of cardiac valve replacement			✓ †			
Recent myocardial infarction, recent stroke or established peripheral arterial disease		✓				
Reduce the incidence of subcutaneous stent thrombosis in patients undergoing successful coronary stent implantation					✓ ‡	
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 thrombocythemia associated with myeloproliferative disorders	✓					

\*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 (STEMI).

†As adjunct to coumarin anticoagulants.

‡As adjunct to aspirin.

§For patients with unstable angina or non-ST-elevation myocardial infarction, and for patients with STEMI when managed with primary or delayed percutaneous coronary 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 function, 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 MIs or transient ischemic attacks, to maintain saphenous vein graft patency after aortocoronary bypass, to manage angina or to reduce post surgical deep vein thrombosis. Aspirin/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.<sup>20</sup>

### **Pharmacokinetics**

**Table 3. Pharmacokinetics**<sup>20</sup>

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
<b>Single Entity Agents</b>				
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*
Ticlopidine	80 to 90	60	None	12.6
<b>Combination Products</b>				
Aspirin/dipyridamole	50 to 75/37	1/not reported	Not reported/none	0.3/14.0

\*Metabolite.

### **Clinical Trials**

The clinical trials supporting the Food and Drug Administration (FDA) approved indications of the platelet inhibitors are outlined in table 4.<sup>22,24-71</sup>

As mentioned previously, aspirin is the only platelet inhibitor that has been evaluated for the treatment of an acute ischemic attack; however, antiplatelet therapy plays an important role in the long term prevention of stroke or transient ischemic attacks (TIAs).<sup>19</sup> 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%.<sup>38</sup> 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.<sup>33,34</sup> 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;  $P=0.043$ ).<sup>39</sup> 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.<sup>30</sup> 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 of 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, 0.80; 95% CI, 0.66 to 0.98, absolute risk reduction, 1.0% per year; 95% CI, 0.1 to 1.8).<sup>24</sup>

With regards to the treatment of acute coronary syndromes, the CLARITY-TIMI 28 trial randomized patients who presented within 12 hours of a ST-segment elevation MI (STEMI) 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).<sup>42</sup> 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, reinfarction or stroke (*P*=0.002); and in death from any cause (*P*=0.03) in patients receiving combination therapy after 15 days.<sup>43</sup> The CURE trial compared long term administration (three to 12 months) of 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 study, the associated reduction was not statistically significant. There was also a weak trend suggesting the possibility of small reductions in death associated with combination therapy that was not statistically significant.<sup>18,19,47</sup> 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 significantly different between the two groups (6.8 vs 7.3%; relative risk, 0.93; 95% CI, 0.83 to 1.05; *P*=0.22).<sup>44</sup> 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 acute coronary syndrome.<sup>18</sup> 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 statistically significant in patients presenting with cerebral ischemia.<sup>40</sup>

The major clinical trial demonstrating the safety and efficacy of prasugrel for its FDA approved indication is the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction). Results demonstrated that prasugrel was significantly more effective than clopidogrel in reducing ischemic events in patients with acute coronary syndrome 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 greater amount 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.<sup>58</sup> 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 with clopidogrel.<sup>59-65</sup>

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Cerebrovascular Conditions (Ischemic Stroke, Transient Ischemic Attack)</b>				
ESPRIT Study Group <sup>24</sup> ESPRIT  Dipyridamole 200 mg BID plus aspirin 30 to 325 mg/day  vs  aspirin 30 to 325 mg/day  Dipyridamole plus aspirin was administered either as a fixed-dose combination or as the two agents administered separately.	MC, OL, RCT  Patients who were referred to one of the participating hospitals within 6 months of a TIA or minor ischemic stroke of presumed arterial origin	N=2,739  Mean follow-up 3.5 years	Primary: Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleeding complication (which ever happened first)  Secondary: Death from all causes, death from all vascular causes, death from all vascular causes and nonfatal stroke, all major ischemic events, all vascular events, major bleeding complications	Primary: Primary outcome events occurred in 173 (13%) patients receiving combination therapy compared to 216 (16%) patients receiving aspirin therapy (HR, 0.80; 95% CI, 0.66 to 0.98; absolute risk reduction 1.0% per year; 95% CI, 0.1 to 1.8).  Patients receiving combination therapy discontinued trial medication more often than those receiving aspirin therapy (470 vs 184 patients), mainly because of headache.  Secondary: The HR for death from all causes and all vascular causes were 0.88 (93 vs 107 patients; 95% CI, 0.67 to 1.17) and 0.75 (44 vs 60 patients; 95% CI, 0.51 to 1.10).  Ischemic events were less frequent with combination therapy (HR, 0.81; 95% CI, 0.65 to 1.01).  Major bleeding complications arose in 35 patients receiving combination therapy compared to 53 patients receiving aspirin therapy, whereas minor bleeding was reported in 171 patients receiving combination therapy compared to 168 patients receiving aspirin therapy (RR, 1.03; 95% CI, 0.84 to 1.25).
Verro et al <sup>25</sup>  Dipyridamole (IR and ER) plus aspirin  vs  aspirin	MA of 6 RCT (4 were DB)  Patients with a history of non-cardioembolic stroke or TIA	N=7,648  Duration varied	Primary: Incidence of nonfatal stroke  Secondary: Composite of stroke, MI or vascular death; subset analysis comparing outcomes with IR and ER	Primary: Combination therapy significantly reduced the risk of nonfatal ischemic and hemorrhagic stroke compared to aspirin therapy (RR, 0.77; 95% CI, 0.67 to 0.89).  Secondary: Combination therapy significantly reduced the risk of the composite of stroke, MI or vascular death (RR, 0.85; 95% CI, 0.76 to 0.94).  Based on four trials, IR dipyridamole plus aspirin did not show a statistically significant reduction in the risk of stroke (RR, 0.83; 95% CI, 0.59 to 1.15) or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			dipyridamole	<p>the composite outcome (RR, 0.95; 95% CI, 0.75 to 1.19) compared to aspirin.</p> <p>Based on two trials, ER dipyridamole plus aspirin 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.</p>
<p>Diener et al<sup>26</sup> ESPS 2</p> <p>Aspirin 25 mg BID</p> <p>vs</p> <p>aspirin/dipyridamole 25/200 mg BID</p> <p>vs</p> <p>dipyridamole ER 200 mg* BID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients who had an ischemic stroke or TIA within 3 months prior to study entry</p>	<p>N=6,602</p> <p>24 months</p>	<p>Primary: Stroke (fatal or nonfatal), death (all cause mortality), combined stroke or death</p> <p>Secondary: TIA and adverse events</p>	<p>Primary: In comparison to placebo, stroke risk was reduced by 18% with aspirin (<math>P=0.013</math>), 37% with aspirin/dipyridamole (<math>P&lt;0.001</math>) and 16% with dipyridamole ER (<math>P=0.039</math>).</p> <p>There was no significant difference in all cause mortality among the active treatment groups (<math>P</math> values not reported).</p> <p>In comparison to placebo, the risk of stroke or death was reduced by 13% with aspirin (<math>P=0.016</math>), 24% with aspirin/dipyridamole (<math>P&lt;0.001</math>) and 15% with dipyridamole ER (<math>P=0.015</math>).</p> <p>Secondary: Aspirin (<math>P&lt;0.001</math>), aspirin/dipyridamole (<math>P&lt;0.001</math>) and dipyridamole ER (<math>P&lt;0.01</math>) were significantly effective in preventing TIA compared to placebo.</p> <p>Headache was the most common adverse event, occurring more frequently in the dipyridamole-treated patients (<math>P</math> values not reported). All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received aspirin in comparison to placebo or dipyridamole (<math>P</math> values not reported).</p>
<p>Sacco et al<sup>27</sup></p> <p>Aspirin/dipyridamole 25/200 mg BID</p> <p>vs</p> <p>aspirin 25 mg BID</p>	<p>Post hoc analysis using data from the ESPS 2</p>	<p>N=3,299</p> <p>Not reported</p>	<p>Primary: Rates of annual strokes, combined stroke or vascular events</p> <p>Secondary: Not reported</p>	<p>Primary: Compared to aspirin therapy, combination therapy was more effective in reducing the risk of stroke (RRR, 23%; <math>P=0.006</math>) and combined stroke or vascular events (RRR, 22%; <math>P=0.003</math>).</p> <p>A more pronounced efficacy was observed for patients &lt;70 years; those with hypertension or prior MI, stroke, TIA or prior cardiovascular disease and smokers (all <math>P&lt;0.01</math>). The greatest relative hazard reduction (44.6%) was noted for patients with a stroke or TIA before the qualifying event.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>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.</p> <p>The difference in efficacy increased in high risk patients.</p> <p>Secondary: Not reported</p>
<p>Leonardi-Bee et al<sup>28</sup></p> <p>Dipyridamole</p> <p>vs</p> <p>dipyridamole plus aspirin</p> <p>vs</p> <p>aspirin</p> <p>vs</p> <p>control (not specified)/placebo</p> <p>Two formulations of dipyridamole were assessed: conventional (150 to 300 mg/day) and modified-release (400 mg/day).</p> <p>The daily dose of aspirin was 50 to 1,300 mg.</p>	<p>MA of 5 RCT (including the ESPS 1 and 2)</p> <p>Patients with previous ischemic stroke and/or TIA</p>	<p>N=11,492</p> <p>Follow-up at 15 to 72 months</p>	<p>Primary: Incidence of stroke (combined fatal and nonfatal)</p> <p>Secondary: Nonfatal stroke; MI (combined fatal and nonfatal); vascular death; composite of nonfatal stroke, nonfatal MI and vascular death</p>	<p>Primary: The incidence of recurrent stroke was reduced by dipyridamole therapy compared to control (OR, 0.82; 95% CI, 0.68 to 1.00; <i>P</i>&lt;0.05), and by combination therapy compared to aspirin therapy (OR, 0.78; 95% CI, 0.65 to 0.93; <i>P</i>&lt;0.05), dipyridamole therapy (OR, 0.74; 95% CI, 0.60 to 0.90; <i>P</i>&lt;0.05) or control (OR, 0.61; 95% CI, 0.51 to 0.71; <i>P</i>&lt;0.05).</p> <p>Secondary: Dipyridamole therapy reduced nonfatal stroke as compared to control, and combination therapy reduced nonfatal stroke as compared to aspirin therapy.</p> <p>Combination therapy significantly reduced the incidence of fatal and nonfatal MI compared to control (<i>P</i>&lt;0.05), but not compared to aspirin or dipyridamole therapies (<i>P</i>&gt;0.05).</p> <p>Vascular death was not altered in any group.</p> <p>Combination therapy also significantly reduced the composite outcome of nonfatal stroke, nonfatal MI and vascular death as compared to aspirin therapy (OR, 0.84; 95% CI, 0.72 to 0.97; <i>P</i>&lt;0.05), dipyridamole therapy (OR, 0.76; 95% CI, 0.64 to 0.90; <i>P</i>&lt;0.05) or control (OR, 0.66; 95% CI, 0.57 to 0.75; <i>P</i>&lt;0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Sacco et al<sup>29</sup></p> <p>Aspirin 25 mg plus dipyridamole ER 200 mg BID</p> <p>vs</p> <p>clopidogrel 75 mg/day plus placebo OR telmisartan 80 mg/day</p>	<p>AC, DB, PC, RCT</p> <p>Patients ≥50 years of age with a recent ischemic stroke (within &lt;90 days before randomization, or 90 to 120 days before randomization if they had ≥2 additional vascular risk factors)</p>	<p>N=20,332</p> <p>2.5 years (mean)</p>	<p>Primary: Recurrent stroke of any type</p> <p>Secondary: Composite of stroke, MI or death from vascular causes</p>	<p>Primary: Confirmed first recurrence of stroke occurred in 1,814 patients. There was no interaction between the treatment benefit of the antiplatelet plus telmisartan (<math>P=0.35</math>). 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.</p> <p>Secondary: The numbers of patients with the secondary endpoint were identical between the two groups (1,333 [13.1%]; HR for aspirin plus dipyridamole ER vs clopidogrel, 0.99; 95% CI, 0.92 to 1.07).</p>
<p>Diener et al<sup>30</sup></p> <p>MATCH</p> <p>Clopidogrel 75 mg/day</p> <p>vs</p> <p>clopidogrel 75 mg/day plus aspirin 75 mg/day</p>	<p>DB, PC, RCT</p> <p>High risk patients with a recent ischemic stroke or TIA, with ≥1 additional vascular risk factor who were already receiving clopidogrel</p>	<p>N=7,599</p> <p>18 months</p>	<p>Primary: Composite of ischemic stroke, MI, vascular death or rehospitalization for an acute ischemic event</p> <p>Secondary: Death, stroke, individual components and various combinations of the primary end points</p>	<p>Primary: There was no significant benefit of combination therapy compared to clopidogrel therapy in reducing the primary outcome (15.7 vs 16.7%, respectively; <math>P=0.244</math>).</p> <p>Secondary: There was no significant benefit of combination therapy compared to clopidogrel therapy in reducing the secondary outcomes.</p> <p>Life-threatening bleeds were higher in the group receiving combination therapy (2.6 vs 1.3%; <math>P&lt;0.0001</math>). Major and minor bleeds were also significantly higher with combination therapy (<math>P&lt;0.0001</math>).</p> <p>[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.]</p>
<p>Markus et al<sup>31</sup></p> <p>CARESS</p>	<p>DB, PC, RCT</p> <p>Patients &gt;18</p>	<p>N=107</p> <p>7 days</p>	<p>Primary: Proportion of patients who were</p>	<p>Primary: ITT analysis revealed a significant reduction in the primary end point: 43.8% of patients receiving combination therapy were MES positive on day seven,</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Clopidogrel 300 mg on day 1, followed by clopidogrel 75 mg/day plus aspirin 75 mg/day on days 2 to 7</p> <p>vs</p> <p>aspirin 75 mg QD</p>	<p>years of age with ≥50% carotid stenosis who experienced ipsilateral carotid territory TIA or stroke within the past 3 months</p>		<p>MES positive on day seven</p> <p>Secondary: Proportion of patients who were MES positive on day two, the rate of embolization on both days two and seven and their percent change from baseline, safety</p>	<p>as compared to 72.7% of patients receiving aspirin therapy (RRR, 39.8%; 95% CI, 13.8 to 58.0; <math>P=0.0046</math>).</p> <p>Secondary: MES frequency/hour was reduced compared to baseline by 61.4% (95% CI, 31.6 to 78.2; <math>P=0.0013</math>) in the combination therapy group at day seven, and by 61.6% (95% CI, 34.9 to 77.4; <math>P=0.0005</math>) on day two.</p> <p>There were four recurrent strokes and seven TIAs in the aspirin therapy 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.</p> <p>MES frequency was greater in the 17 patients with recurrent ipsilateral events compared to the 90 without (<math>P=0.0003</math>).</p>
<p>Kennedy et al<sup>32</sup> FASTER</p> <p>Clopidogrel 300 mg once, followed by 75 mg/day</p> <p>or</p> <p>placebo</p> <p>and</p> <p>simvastatin 40 mg once, followed by 40 mg/day</p> <p>or</p> <p>placebo</p> <p>All patients were also given aspirin 81 mg/day, with a</p>	<p>Factorial design 2 x 2, DB, PC, RCT</p> <p>Patients ≥40 years of age with a TIA or minor stroke, randomized within 24 hours of symptom onset</p>	<p>N=392</p> <p>90 days</p>	<p>Primary: Incidence of stroke (ischemic and hemorrhagic), safety (hemorrhage, myositis)</p> <p>Secondary: Composite of stroke, MI and vascular death</p>	<p>Primary: The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrollment rate because of increased use of statins.</p> <p>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; <math>P=0.19</math>). In the simvastatin group (with or without clopidogrel), 10.6% of patients had a stroke within 90 days compared to 7.3% of patients not taking simvastatin (RR, 1.3; 95% CI, 0.7 to 2.4) for an absolute risk increase of 3.3% compared to placebo (95% CI, -2.3 to 8.9; <math>P=0.25</math>).</p> <p>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; <math>P=0.5</math>). There was no difference between groups for the simvastatin safety outcomes.</p> <p>Secondary: Clopidogrel was associated with a -3.3% risk difference in the secondary end point compared to placebo (95% CI, -9.3 to 2.7; <math>P=0.28</math>). Simvastatin was</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
162 mg loading dose if naïve to aspirin.				associated with a 2.7% risk difference compared to placebo (95% CI, -3.2 to 8.7; $P=0.37$ ).
Gent et al <sup>33</sup> CATS  Ticlopidine 250 mg BID  vs  placebo	DB, MC, PC, RCT  Patients with ischemic strokes occurring from 1 week to 4 months	N=1,072  Up to 3 years (mean 24 months)	Primary: Event rate/year for stroke, MI or vascular death  Secondary: Adverse events	Primary: The event rate/year for stroke, MI or vascular death was 10.8% in the ticlopidine group and 15.3% in the placebo group. Compared to placebo, ticlopidine reduced the RR of stroke, MI or vascular death by 30% ( $P=0.006$ ) in the on-treatment analysis and by 23% ( $P=0.020$ ) using the ITT approach.  Ticlopidine reduced the RR of ischemic stroke by 33% ( $P=0.008$ ) in the on-treatment analysis.  Ticlopidine was beneficial for both men and women (RR, 28.1%; $P=0.037$ and RR, 34.2%; $P=0.045$ , respectively).  Secondary: Adverse events associated with ticlopidine included neutropenia (severe in about 1% of cases), skin rash (severe in about 2% of cases) and diarrhea (severe in about 2% of cases).
Hass et al <sup>34</sup> TASS  Ticlopidine 250 mg BID  vs  aspirin 650 mg BID	Blinded, MC, RCT  Patients with recent a minor stroke or TIA within the past 3 months	N=3,069  2 to 6 years	Primary: Nonfatal stroke or death  Secondary: Adverse events	Primary: Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate, 17 vs 19%; $P=0.048$ ).  Ticlopidine reduced the risk of stroke after three years by 21% (10 vs 13%; $P=0.024$ ).  Secondary: Ticlopidine significantly increased total cholesterol compared to aspirin (9 vs 2%; $P<0.01$ ). Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group, but bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. Severe neutropenia occurred in 0.9% of patients.
Gorelick et al <sup>35</sup> AAASPS  Ticlopidine 250 mg BID	DB, MC, RCT  African American patients who recently had a	N=1,809  Up to 2 years	Primary: Composite of recurrent stroke, MI or vascular death	Primary: There was no significant difference in the percent of patients reaching the primary outcome between ticlopidine and aspirin (14.7 vs 12.3%, respectively; $P=0.12$ ).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs aspirin 325 mg BID	non-cardioembolic ischemic stroke		Secondary: Stroke (fatal and nonfatal)	Secondary: There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group ( $P=0.08$ ).
Fukuuchi et al <sup>36</sup>  Ticlopidine 200 mg QD  vs  clopidogrel 75 mg QD	DB, DD, MC, RCT  Japanese patients 20 to 80 years of age who experienced a non-cardioembolic cerebral infarction $\geq 8$ days prior to enrollment	N=1,151  52 weeks	Primary: Safety (emphasis on hematologic changes, hepatic dysfunction, nontraumatic hemorrhage and other serious adverse reactions)  Secondary: Combined incidence of nonfatal or fatal cerebral infarction, MI or death due to other vascular causes	Primary: During the study period, 15.1 and 7.0 % of ticlopidine- and clopidogrel-treated patients had at least one primary safety end point ( $P<0.001$ ). Significant differences were primarily noted between ticlopidine and clopidogrel for hematologic disorders (2.4 vs 1.0%; $P=0.043$ ) and hepatic dysfunction (11.9 vs 4.2%; $P<0.001$ ).  Study medication was discontinued prematurely due to safety end points in 27 and 17% of patients receiving ticlopidine and clopidogrel, respectively ( $P<0.001$ ). The HR for the risk of discontinuing study medication due to a primary safety end point was 0.559 (95% CI, 0.434 to 0.721) in favor of clopidogrel.  Secondary: The incidence of vascular events did not differ significantly between ticlopidine and clopidogrel (2.6 vs 3.0%, respectively; $P=0.948$ ; HR, 0.977; 95% CI, 0.448 to 1.957).
Uchiyama et al <sup>37</sup>  Ticlopidine 200 mg QD  vs  clopidogrel 75 mg QD	2 DB, DD, Phase II, RCT  Japanese patients 20 to 80 years of age, with a history of cerebral infarctions; the most recent stroke being $>8$ days prior to enrollment	N=1,921  26 to 52 weeks	Primary: Combined endpoint of accessory symptoms and abnormal laboratory changes  Secondary: Combined incidence of vascular events (cerebral infarction, MI, vascular death, TIA, amaurosis fugax, angina pectoris, peripheral artery occlusion,	Primary: Fewer patients in the clopidogrel group (35.0%) experienced the combined safety endpoint compared to those in the ticlopidine group (48.7%). At one month, it was estimated that 83.4 and 69.9% of patients in the clopidogrel and ticlopidine groups were safety event free. At both two and 12 months, the estimated incidence of the safety events was significantly lower with clopidogrel compared to ticlopidine ( $P$ value not reported).  It was estimated that almost twice as many patients (25.6%) in the ticlopidine group experienced symptoms and/or abnormal laboratory findings of hepatic dysfunction compared to the clopidogrel group (13.4%; HR, 0.455; 95% CI, 0.367 to 0.565; $P<0.001$ ).  Secondary: There was no difference in the incidence of the combined efficacy endpoint of cerebral infarction, MI or vascular death with clopidogrel compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			retinal artery occlusion or other vascular event)	ticlopidine (2.6 vs 2.5%; HR, 0.918; 95% CI, 0.518 to 1.626). There were no MIs or vascular deaths; only recurrence of cerebral infarctions.  There was no difference in the total number of vascular events between the clopidogrel (3.6%) and ticlopidine (3.7%) groups (HR, 0.878; 95% CI, 0.545 to 1.412). The incidences of TIA, angina pectoris, PAD or other events were 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%; <i>P</i> value not reported).
<b>Cerebrovascular and Cardiovascular Conditions</b>				
Antithrombotic Trialists' Collaboration <sup>38</sup>  Antiplatelet agents  vs  control  vs  one antiplatelet regimen vs another	MA (197 RCTs compared antiplatelet therapy vs control and 90 trials compared different antiplatelet regimens)  Patients at high risk of occlusive vascular events	N=135,640  Duration varied	Primary: Serious vascular event (nonfatal MI, nonfatal stroke or vascular death)  Secondary: Not reported	Primary: Overall, antiplatelet therapy reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25% and vascular mortality by 15%, with no apparent adverse effect on other deaths.  Aspirin was the most widely studied antiplatelet drug and low dose (75 to 150 mg/day) was at least as effective as higher daily doses for long-term use. In acute settings an initial loading dose of ≥150 mg aspirin may be required.  Clopidogrel reduced serious vascular events by 10% compared to aspirin, which was similar to the 12% reduction observed with ticlopidine.  The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared to aspirin alone.  Secondary: Not reported
CAPRIE Steering Committee <sup>39</sup> CAPRIE  Clopidogrel 75 mg QD  vs	DB, MC, PG, RCT  Patients with recent ischemic stroke (within 6 months with ≥1 week of residual	N=19,185  1 to 3 years (mean 1.91 years)	Primary: Composite of ischemic stroke, MI or vascular death  Secondary: Composite of ischemic stroke, MI,	Primary: The ITT analysis showed that patients treated with 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; <i>P</i> =0.043) in favor of clopidogrel. Corresponding on-treatment analysis yielded a RRR of 9.4% in favor of clopidogrel ( <i>P</i> value not reported).  For the 6,431 patients enrolled in the trial with prior stroke, the RRR for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspirin 325 QD	neurological signs), recent MI (within 35 days) or symptomatic peripheral arterial disease		vascular death and amputation; vascular death; all cause mortality; safety	<p>ischemic stroke, MI or vascular death was 7.3% in favor of clopidogrel (<math>P=0.26</math>), and the RRR for the end point of stroke was 8.0% (<math>P=0.28</math>).</p> <p>For the 6,302 patients enrolled in the trial with MI, a RR increase of 3.7% was associated with clopidogrel (<math>P=0.66</math>).</p> <p>For the 6,452 patients enrolled in the trial with PAD, a RRR of 23.8% was noted in favor of clopidogrel (<math>P=0.0028</math>).</p> <p>Secondary: Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (<math>P=0.076</math>).</p> <p>There was no significant difference between clopidogrel and aspirin with regards to vascular death (1.90 vs 2.06%; <math>P=0.29</math>) and all cause mortality (3.05 vs 3.11%; <math>P=0.71</math>).</p> <p>There were no major differences in terms of safety. Severe rash (<math>P=0.017</math>) and severe diarrhea (<math>P=0.080</math>) were reported more frequently with clopidogrel. Severe upper gastrointestinal discomfort (<math>P=0.096</math>), intracranial hemorrhage (<math>P=0.23</math>) and gastrointestinal hemorrhage (<math>P=0.05</math>) were reported more frequently with aspirin.</p>
<p>De Schryver et al<sup>40</sup></p> <p>Dipyridamole with or without other antiplatelet drugs</p> <p>vs</p> <p>control (no drug or another antiplatelet drug)</p>	<p>MA of 29 RCTs</p> <p>Patients with arterial vascular disease (angina, CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA)</p>	<p>N=23,019</p> <p>Duration varied (<math>\geq 1</math> month in duration)</p>	<p>Primary: Secondary prevention of vascular death and vascular events (vascular death, any death from an unknown cause, nonfatal stroke or nonfatal MI)</p> <p>Secondary: Not reported</p>	<p>Primary: Compared to control, dipyridamole had no clear effect on vascular death (RR, 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole or type of presenting vascular disease did not influence this result.</p> <p>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 statistically significant in patients presenting with cerebral ischemia.</p> <p>There was no evidence that dipyridamole alone was more efficacious than aspirin.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Cardiovascular Indications (Acute Coronary Syndrome, Myocardial Infarction, Angina Pectoris)</b>				
<p>Ho et al<sup>41</sup></p> <p>Clopidogrel, dose not specified</p>	<p>RETRO cohort</p> <p>Patients with ACS discharged on clopidogrel from 127 Veterans Affairs hospitals between October 2003 and March 2005</p>	<p>N=3,137</p> <p>Duration varied (mean follow-up after stopping clopidogrel was 196 days for patients medically treated and 203 days for patients receiving PCI)</p>	<p>Primary: Rate of all cause mortality or acute MI after stopping clopidogrel</p> <p>Secondary: Not reported</p>	<p>Primary: Among medically treated patients the mean duration of clopidogrel treatment was 302 days. Death or acute MI occurred in 17.1% of these patients, with 60.8% of the events occurring during 0 to 90 days, 21.3% during 91 to 180 days and 9.7% during 181 to 270 days after stopping treatment with clopidogrel.</p> <p>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).</p> <p>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.</p> <p>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).</p> <p>Secondary: Not reported</p>
<p>Sabatine et al<sup>42</sup></p> <p>CLARITY-TIMI 28</p> <p>Clopidogrel 300 mg once, followed by 75 mg/day</p> <p>vs</p> <p>placebo</p> <p>Patients received a</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI</p>	<p>N=3,491</p> <p>30 days (study medication given up to, and including, the day of angiography, or up to day</p>	<p>Primary: Composite of an occluded infarct-related artery on angiography, death or recurrent MI before angiography (death or recurrent MI by day eight or hospital discharge in patients who did not</p>	<p>Primary: The primary end point was reached in 15.0% of patients receiving clopidogrel compared to 21.7% for 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%; <i>P</i>&lt;0.001).</p> <p>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%; <i>P</i>=0.03).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>fibrinolytic agent, aspirin, and when appropriate, heparin.</p> <p>Patients were also scheduled to undergo angiography 48 to 192 hours after the start of the study medication.</p>		<p>8 or hospital discharge if no angiography)</p>	<p>undergo angiography)</p> <p>Secondary: Safety</p>	<p>Secondary: The rates of major bleeding and intracranial hemorrhage were similar in the two groups.</p>
<p>COMMIT Collaborative Group<sup>43</sup> COMMIT</p> <p>Clopidogrel 75 mg/day plus aspirin 162 mg/day</p> <p>vs</p> <p>aspirin 162 mg/day</p>	<p>MC, PC, RCT</p> <p>Patients admitted to the hospital within 24 hours of suspected acute MI</p>	<p>N=45,852</p> <p>15 days (mean)</p>	<p>Primary: Composite of death, re-infarction or stroke; death from any cause</p> <p>Secondary: Safety</p>	<p>Primary: Combination therapy produced a highly significant nine percent proportional reduction in death, reinfarction or stroke compared to aspirin therapy (actual reductions 9.2 vs 10.1%, respectively; <math>P=0.002</math>), corresponding to nine fewer events/1,000 patients treated for about two weeks.</p> <p>There was also a significant seven percent proportional reduction in any death in the combination therapy group compared to the aspirin therapy group (7.5 vs 8.1%; <math>P=0.03</math>).</p> <p>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; <math>P=0.59</math>), in patients &gt;70 years of age (<math>P</math> value not reported) or in those given fibrinolytic therapy (<math>P</math> value not reported).</p>
<p>Bhatt et al<sup>44</sup> CHARISMA</p> <p>Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day</p> <p>vs</p> <p>aspirin 75 to 162 mg/day</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥45 years of age with clinically evident cardiovascular disease</p>	<p>N=15,603</p> <p>Median 28 months</p>	<p>Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes</p> <p>Secondary: First occurrence of MI, stroke, death from cardiovascular</p>	<p>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 therapy (RR, 0.93; 95% CI, 0.83 to 1.05; <math>P=0.22</math>).</p> <p>The rate of the primary end point among patients with multiple risk factors was 6.6% with combination therapy and 5.5% with aspirin therapy (RR, 1.2; 95% CI, 0.91 to 1.59; <math>P=0.20</math>), and the rate of death from cardiovascular causes also was higher with combination therapy (3.9 vs 2.2%; <math>P=0.01</math>). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with combination therapy and 7.9% with aspirin therapy (RR, 0.88; 95% CI, 0.77</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			causes or hospitalization for unstable angina, TIA or revascularization procedure; safety	to 1.00; $P=0.046$ ).  Secondary: The secondary end point was reached in 16.7 and 17.9% (RR, 0.92; 95% CI, 0.86 to 1.00; $P=0.04$ ) of patients receiving combination therapy and aspirin therapy, respectively.  The rate of severe bleeding was 1.7 and 1.3% (RR, 1.25; 95% CI, 0.97 to 1.61; $P=0.09$ ) for patients receiving combination therapy and aspirin therapy.
<p>Dasgupta et al<sup>45</sup> Post hoc analysis of CHARISMA</p> <p>Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day</p> <p>vs</p> <p>aspirin 75 to 162 mg/day</p>	<p>DB, MC, PC, RCT</p> <p>Post hoc analysis of patients with diabetic neuropathy in the CHARISMA trial, who were <math>\geq 45</math> years of age with clinically evident cardiovascular disease or multiple atherothrombotic risk factors</p>	<p>N=2,009</p> <p>Median 28 months</p>	<p>Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes</p> <p>Secondary: First occurrence of MI, stroke, death from cardiovascular causes or hospitalization for unstable angina, TIA or revascularization procedure; safety</p>	<p>Primary: Almost all cardiovascular events occurred significantly more frequently in diabetic patients with neuropathy. Patients with diabetic neuropathy had a higher case fatality rate of MI compared to diabetic patients without nephropathy and nondiabetic patients (20 vs 14 vs 11%, respectively), but this higher rate was not statistically significant (<math>P=0.240</math>).</p> <p>Secondary: Patients with nephropathy who were assigned clopidogrel experienced a significant increase in overall mortality (HR, 1.8; 95% CI, 1.2 to 2.7; <math>P=0.006</math>) compared to placebo, as well as significantly increased cardiovascular mortality (HR, 1.7; 95% CI, 1.1 to 2.9; <math>P=0.028</math>).</p> <p>The frequency of bleeding in patients with diabetic nephropathy who received clopidogrel tended to be higher compared to placebo, but this increase was not statistically significant (2.6 vs 1.5%; HR, 1.8; <math>P=0.075</math>).</p>
<p>Hart et al<sup>46</sup> Post hoc analysis of CHARISMA</p> <p>Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day</p> <p>vs</p> <p>aspirin 75 to 162 mg/day</p>	<p>DB, MC, PC, RCT</p> <p>Post hoc analysis of participants with a history of AF in the CHARISMA trial, who were <math>\geq 45</math> years of age with clinically evident</p>	<p>N=593</p> <p>Median 28 months</p>	<p>Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes</p> <p>Secondary: First occurrence of MI, stroke, death from cardiovascular</p>	<p>Primary: There was no difference in the composite of stroke, MI or vascular death between patients receiving combination therapy (35 of 298 patients) and aspirin therapy (27 of 285 patients; <math>P=0.40</math>).</p> <p>Secondary: There was no difference in the composite of stroke, MI, vascular death or rehospitalization (70 vs 66 patients; <math>P=0.93</math>) or all cause mortality (29 vs 25 patients; <math>P=0.69</math>) between the two groups.</p> <p>Stroke (ischemic and hemorrhagic) occurred in 15 patients receiving</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	cardiovascular disease or multiple atherothrombotic risk factors		causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	combination therapy (2.2% per year) and in 14 patients receiving aspirin therapy (2.1% per year; HR, 1.03; 95% CI, 0.49 to 2.13; <i>P</i> =0.94).  Severe or fatal extracranial hemorrhage occurred in six patients given combination therapy compared to three patients given aspirin therapy alone ( <i>P</i> =0.51), while intracranial bleeding occurred in three and one patients ( <i>P</i> =0.62), respectively.
<p>CURE Trial Investigators<sup>47</sup> CURE</p> <p>Clopidogrel (300 mg once, followed by 75 mg/day) plus aspirin</p> <p>vs</p> <p>aspirin</p>	<p>DB, PC, RCT</p> <p>Patients with NSTEMI, presenting within 24 hours of symptom onset</p>	<p>N=12,562</p> <p>3 to 12 months</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal MI or stroke (first primary outcome); composite of the first primary outcome or refractory ischemia (second primary outcome)</p> <p>Secondary: Severe ischemia, heart failure, need for revascularization, safety</p>	<p>Primary: A composite of death from cardiovascular causes, nonfatal MI or stroke occurred in 9.3% of patients in the combination therapy group compared to 11.4% of patients in the aspirin therapy group (RR, 0.80; 95% CI, 0.72 to 0.90; <i>P</i>&lt;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; <i>P</i>&lt;0.001).</p> <p>Secondary: Significant reductions in nonfatal MI (5.2 vs 6.7%), and trends toward reduction in death (5.1 vs 5.5%) and stroke (1.2 vs 1.4%) with combination therapy compared to aspirin therapy were noted (<i>P</i> values not reported).</p> <p>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 <i>P</i>&lt;0.05 vs aspirin therapy).</p> <p>There were significantly more patients with major bleeds in the combination therapy group than in the aspirin therapy group (3.7 vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; <i>P</i>=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; <i>P</i>=0.13).</p>
<b>Procedures and/or Surgery</b>				
<p>Banerjee et al<sup>48</sup></p> <p>Clopidogrel for ≥1 year following PCI</p> <p>vs</p>	<p>RETRO</p> <p>Patients who underwent PCI</p>	<p>N=530</p> <p>2.4±0.8 years (mean follow-up)</p>	<p>Primary: All cause mortality</p> <p>Secondary: Incidence of major adverse</p>	<p>Primary: Twelve (3.5%) patients who received clopidogrel for ≥1 year died compared to 28 (15%) patients who received clopidogrel for &lt;1 year (<i>P</i>&lt;0.001).</p> <p>On a multivariate analysis, the use of clopidogrel for ≥1 year was associated with lower mortality (HR, 0.28; 95% CI, 0.14 to 0.59; <i>P</i>&lt;0.001), independent</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>clopidogrel for &lt;1 year following PCI</p> <p>Patients were free of cardiovascular events for 6 months after PCI, and had follow-up available for &gt;12 months.</p>			<p>cardiovascular events (composite of all cause death, nonfatal MI and repeat coronary revascularization by PCI or CABG)</p>	<p>of traditional cardiovascular risk factors, clinical presentation and DES use.</p> <p>Survival in the &lt;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.</p> <p>Secondary: There were no significant differences in the incidence of nonfatal MI (<math>P=0.50</math>), repeat coronary revascularization (<math>P=0.16</math>) or major adverse cardiovascular events between the two groups (<math>P=0.10</math>). 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.</p>
<p>CURRENT-OASIS 7<sup>49</sup></p> <p>Clopidogrel 600 mg once, followed by 150 mg/day for 6 days, followed by clopidogrel 75 mg/day through day 30 (double dose)</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day for 6 days, followed by 75 mg/day through day 30 (standard dose)</p> <p>and</p> <p>aspirin ≥300 mg/day once, followed by 75 to 100 mg/day through day 30 (low dose)</p>	<p>2x2 factorial design, RCT</p> <p>Patients ≥18 years of age who presented with a NSTEMI or a STEMI</p>	<p>N=25,086 (n=17,263 underwent PCI)</p> <p>30 days</p>	<p>Primary: Composite of cardiovascular death, MI or stroke</p> <p>Secondary: Composite of death from cardiovascular causes, MI, stroke or recurrent ischemia; the individual components of the primary endpoint; death from any cause; bleeding</p>	<p>Primary: The primary outcome occurred in 4.2% of patients in the double-dose group compared to 4.4% with the standard dose group (HR, 0.94; 95% CI, 0.83 to 1.06; <math>P=0.30</math>). 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; <math>P=0.61</math>). A nominally significant interaction between the clopidogrel dose comparison and the aspirin dose comparison for the primary outcome was noted (<math>P=0.04</math>).</p> <p>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; <math>P=0.03</math>). 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; <math>P=0.46</math>).</p> <p>Secondary: Consistent results were observed for each component of the primary outcome, as well as for the expanded composite endpoint for the clopidogrel and aspirin dose comparison. A nominally significant reduction in recurrent ischemia alone was associated with high dose aspirin as compared to low dose aspirin (0.3 vs 0.5%; HR, 0.63; 95% CI, 0.43 to 0.94; <math>P=0.02</math>).</p> <p>The rate of death from any cause did not differ significantly between the</p>

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<p>vs</p> <p>aspirin <math>\geq</math>300 mg/day once, followed by 300 to 325 mg/day through day 30 (high dose)</p> <p>All patients were to undergo early angiography and PCI, if appropriate, no later than 72 hours after randomization.</p>				<p>double and standard dose groups (2.3 vs 2.4%; HR with the double dose, 0.96; 95% CI, 0.82 to 1.13; <math>P=0.61</math>). 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; <math>P=0.10</math>).</p> <p>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; <math>P=0.01</math>). The aspirin groups did not differ significantly with respect to major bleeding (<math>P</math> 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; <math>P=0.04</math>). 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%; <math>P=0.04</math>).</p>
<p>Sabatine et al<sup>50</sup> PCI-CLARITY</p> <p>Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 150 to 325 mg once, followed by 75 to 162 mg/day</p> <p>vs</p> <p>aspirin 150 to 325 mg once, followed by 75 to 162 mg/day</p>	<p>DB, MC, PC, RCT</p> <p>Patients with STEMI who received fibrinolytics and underwent PCI (after mandated angiography in CLARITY-TIMI 28)</p>	<p>N=1,863</p> <p>30 days</p>	<p>Primary: Composite of cardiovascular death, recurrent MI or stroke from PCI to 30 days after randomization</p> <p>Secondary: MI or stroke before PCI, the primary end point from randomization to 30 days</p>	<p>Primary: Pretreatment with clopidogrel significantly reduced the primary end point following PCI compared to pretreatment without clopidogrel (3.6 vs 6.2%; adjusted OR, 0.54; 95% CI, 0.35 to 0.85; <math>P=0.008</math>). 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; <math>P=0.03</math>).</p> <p>Secondary: Overall, pretreatment with clopidogrel significantly reduced the secondary outcome (7.5 vs 12.0%; adjusted OR, 0.59; 95% CI, 0.43 to 0.81; <math>P=0.001</math>).</p> <p>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; <math>P&gt;0.99</math>).</p>
<p>Mehta et al<sup>51</sup> PCI-CURE</p> <p>Prior to PCI, patients received aspirin plus clopidogrel or placebo.</p> <p>After PCI, stented patients received OL aspirin plus a</p>	<p>DB, RCT</p> <p>Patients with NSTEMI ACS from the CURE study undergoing PCI</p>	<p>N=2,658</p> <p>8 months (average duration of follow-up after PCI)</p>	<p>Primary: Composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of PCI; cardiovascular death or MI from</p>	<p>Primary: Four and a half percent of patients in the clopidogrel plus aspirin group had the main primary end point compared to 6.4% in the aspirin group (<math>P=0.03</math>).</p> <p>Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI or any revascularization (<math>P=0.03</math>), and of cardiovascular death or MI (<math>P=0.047</math>).</p> <p>Overall, clopidogrel was associated with a 31% reduction in cardiovascular</p>

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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)			time of PCI to scheduled end of trial  Secondary: Not reported	death or MI, including events before and after PCI ( $P=0.002$ ).  At follow-up, there was no significant difference in major bleeding between the groups ( $P=0.64$ ).  Secondary: Not reported
Steinhubl et al <sup>52</sup> CREDO  Clopidogrel 300 mg once (3 to 24 hours before PCI), followed by clopidogrel 75/day  vs  placebo (3 to 24 hours before PCI), followed by clopidogrel 75 mg/day through day 28, followed by placebo  All patients received aspirin 325 mg prior to PCI, followed by 325 mg/day through day 28, followed by 81 to 325 mg/day.	DB, MC, PC, RCT  Patients undergoing PCI	N=2,116  12 months	Primary: One year incidence of the composite of death, MI or stroke; 28 day incidence of the composite of death, MI or urgent target vessel revascularization  Secondary: Components of the composite end points, administration of clopidogrel <6 hours or ≥6 hours before PCI, need for target vessel revascularization or any revascularization at one year	Primary: Long-term (one year) clopidogrel plus aspirin was associated with a 26.9% RR in the combined risk of death, MI or stroke compared to aspirin therapy (95% CI, 3.9 to 44.4; $P=0.02$ ; absolute reduction, 3%).  Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI or urgent revascularization at 28 days (-18.5%; 95% CI, -14.2 to 41.8; $P=0.23$ ).  Secondary: A similar level of benefit was found in the individual components of the primary end point at one year, although individual outcomes were not significant ( $P$ values not reported). Treatment randomization did not appear to influence the rate of target vessel revascularization or any other revascularization during the follow-up period.  Patients who had received clopidogrel at least six hours before PCI experienced a reduction in the relative combined risk of death, MI or stroke by 38.6% (95% CI, -1.6 to 62.9; $P=0.051$ ) compared to no reduction when treatment was given less than six hours before PCI ( $P=0.051$ ).  Risk of major bleeding at one year increased, but not significantly (8.8 vs 6.7%; $P=0.07$ ).
Lev et al <sup>53</sup>  Clopidogrel 300 to 600 mg	PRO  Patients with	N=292  6 months	Primary: Occurrence of TIMI myocardial	Primary: TIMI myocardial perfusion grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group (85 vs 71%; $P=0.01$ ).

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<p>before PCI, followed by 75 mg/day for 3 to 12 months</p> <p>vs</p> <p>clopidogrel 300 to 600 mg immediately after PCI, followed by 75 mg/day for 3 to 12 months</p> <p>All patients were treated with aspirin 325 mg before PCI, followed by aspirin (dose not specified) for 3 to 12 months.</p>	<p>chest pain and STEMI undergoing emergency PCI</p>		<p>perfusion grade 3 after PCI</p> <p>Secondary: Incidence of re-infarction, stent thrombosis, target vessel revascularization, death</p>	<p>Secondary: The incidence of re-infarction at 30 days (0 vs 3.2%, respectively; <math>P=0.04</math>) and six months (0.6 and 3.9%, respectively; <math>P=0.09</math>) was lower in the pretreatment group.</p> <p>The incidence of stent thrombosis at 30 days (0 vs 2.4%, respectively; <math>P=0.08</math>) and six months (0 and 3.9%, respectively; <math>P=0.02</math>) was lower in the pretreatment group than in the no pretreatment group.</p> <p>The incidence of death and target vessel revascularization were not significantly different between the two groups at 30 days (<math>P=0.6</math> and <math>P=1.0</math>) or six months (<math>P=0.7</math> and <math>P=0.9</math>).</p>
<p>Han et al<sup>54</sup></p> <p>Clopidogrel 600 mg once, followed by 75 mg/day</p> <p>vs</p> <p>clopidogrel 600 mg once, followed by 150 mg/day</p> <p>All patients received aspirin 300 mg/day.</p> <p>All patients received dual antiplatelet therapy on admission followed by maintenance dose administration according to study protocol and PCI was performed within 48 hours of admission.</p>	<p>RCT</p> <p>Patients <math>\geq 18</math> years of age, diagnosed with ACS, planned pretreatment with 600 mg clopidogrel loading dose, presence of <math>\geq 1</math> severe coronary stenosis requiring PCI located in native arteries and suitable for DES implantation</p>	<p>N=813</p> <p>30 days</p>	<p>Primary: Major adverse cardiac event (composite of cardiac death, nonfatal MI and urgent target vessel revascularization)</p> <p>Secondary: Stent thrombosis, major and minor bleeding events</p>	<p>Primary: A total of 13 patients reached the primary end points, including four (1.0%) patients in the 150 mg group and nine (2.2%) in the 75 mg group (<math>P&gt;0.05</math>). There was no significant difference in cumulative major adverse cardiac event-free survival between the two groups. The incidences of MI (two vs five; <math>P&gt;0.05</math>), urgent target vessel revascularization (three vs eight; <math>P&gt;0.05</math>) and cardiac death (one vs one; <math>P&gt;0.05</math>) were similar between the two groups.</p> <p>Secondary: The incidence of stent thrombosis (zero vs six; <math>P&lt;0.05</math>) was significantly lower in the 150 mg group compared to the 75 mg group.</p> <p>There was no significant differences between both groups regarding the risk of major (one vs zero; <math>P&gt;0.05</math>) or minor (two vs one; <math>P&gt;0.05</math>) bleedings.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Bertrand et al<sup>55</sup> CLASSICS</p> <p>Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 325 mg/day</p> <p>vs</p> <p>clopidogrel 75 mg/day plus aspirin 325 mg/day</p> <p>vs</p> <p>ticlopidine 250 mg BID plus aspirin 325 mg/day</p>	<p>RCT</p> <p>Patients receiving a stent placement</p>	<p>N=1,020</p> <p>28 days</p>	<p>Primary: Major peripheral or bleeding complications, neutropenia, thrombocytopenia, early discontinuation due to noncardiac adverse event</p> <p>Secondary: Incidence of cardiac events</p>	<p>Primary: Primary end point occurred in 4.6% of patients in the combined clopidogrel groups and in 9.1% of patients in the ticlopidine group (RR, 0.50; 95% CI, 0.31 to 0.81; <i>P</i>=0.005).</p> <p>Secondary: Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (1.2% with clopidogrel loading dose, 1.5% with clopidogrel without the loading dose and 0.9% with ticlopidine; <i>P</i> values are nonsignificant for all comparisons).</p>
<p>Leon et al<sup>56</sup></p> <p>Aspirin 325 mg/day</p> <p>vs</p> <p>aspirin 325 mg/day plus warfarin</p> <p>vs</p> <p>aspirin 325 mg/day plus ticlopidine 250 mg BID</p>	<p>MC, RCT</p> <p>Patients receiving a stent</p>	<p>N=1,653</p> <p>30 days</p>	<p>Primary: Composite of death, revascularization of target lesion, angiographically evident thrombosis or MI within 30 days</p> <p>Secondary: Achievement of &lt;50% residual stenosis without death or emergency bypass surgery, procedure-related MI, hematologic dyscrasias, hemorrhagic and vascular surgical complications</p>	<p>Primary: The primary end point was observed in 38 patients; 3.6% assigned to aspirin, 2.7% assigned to aspirin plus warfarin and 0.5% assigned to aspirin plus ticlopidine (<i>P</i>=0.001 for the comparison of all three groups).</p> <p>Secondary: Compared to aspirin and aspirin plus warfarin, treatment with aspirin plus ticlopidine resulted in a lower rate of stent thrombosis (<i>P</i>=0.001) following coronary stenting.</p> <p>Hemorrhagic complications occurred in 10 patients; 1.8% with aspirin, 6.2% with aspirin plus warfarin and 5.5% with aspirin plus ticlopidine (<i>P</i>&lt;0.001 for the comparison of all three groups); the incidence of vascular surgical complications was 0.4, 2.0 and 2.0%, respectively (<i>P</i>=0.02).</p> <p>There were no significant differences in the incidence of neutropenia or thrombocytopenia among the three treatment groups and the overall incidence was 0.3% (<i>P</i> values not reported).</p>

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<p>Lee et al<sup>57</sup> DECLARE-DIABETES</p> <p>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</p> <p>vs</p> <p>aspirin plus clopidogrel (as above) plus cilostazol 200 mg immediately after stent placement and continued for 6 months at 100 mg BID</p>	<p>MC, PRO, RCT</p> <p>Diabetic patients ≥18 years of age undergoing DES implantation</p>	<p>N=400</p> <p>9 months</p>	<p>Primary: In-stent late loss at six months</p> <p>Secondary: 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</p>	<p>Primary: At six months, the in-stent late loss was significantly lower in the triple therapy vs dual therapy group (0.25±0.53 vs 0.38±0.54 mm; <i>P</i>=0.025).</p> <p>Secondary: At six months, the in-segment late loss (0.42±0.50 vs 0.53±0.49 mm; <i>P</i>=0.031) and restenosis (8.0 vs 15.6%; <i>P</i>=0.033) were significantly lower in the triple therapy vs dual therapy group.</p> <p>At nine months, there was no difference in the rate of stent thrombosis (0 vs 0.5%; <i>P</i>=0.999). Target vessel revascularization was lower in the triple therapy vs dual therapy group (3.5 vs 8.0%; <i>P</i>=0.053).</p> <p>At nine months, major adverse cardiac events tended to be lower in the triple therapy than in the dual therapy group (3.0 vs 7.0%; <i>P</i>=0.066).</p> <p>Drug discontinuation was more common in the triple therapy vs dual therapy group (14.5 vs 2.5%; <i>P</i>&lt;0.001) with skin rash and gastrointestinal disturbance the most common reasons for termination of cilostazol.</p>
<p>Wiviott et al<sup>58</sup> TRITON-TIMI 38</p> <p>Prasugrel 60 mg once, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>DB, MC, PG, RCT</p> <p>Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; for patients with unstable angina or NSTEMI ischemic symptoms lasting ≥10 minutes and occurring within 72 hours of randomization, a</p>	<p>N=13,608</p> <p>6 to 15 months (median 14.5 months)</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke</p> <p>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</p>	<p>Primary: The composite rate of death 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; <i>P</i>&lt;0.001).</p> <p>Each individual endpoint was analyzed separately and of the three, only nonfatal MI was reduced significantly greater in the prasugrel group (7.4%) than in the clopidogrel group (9.7%; HR, 0.76; 95% CI, 0.67 to 0.85; <i>P</i>&lt;0.001). There were no significant differences reported in the rate of death from cardiovascular causes or in nonfatal stroke.</p> <p>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; <i>P</i>=0.01).</p> <p>Secondary: The composite endpoint of the rate of death from cardiovascular causes,</p>

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	<p>TIMI score <math>\geq 3</math> and either ST-segment deviation <math>\geq 1</math> 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</p>		<p>rehospitalization due to a cardiac ischemic event; urgent target vessel revascularization; stent thrombosis; safety</p>	<p>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; <math>P &lt; 0.001</math>).</p> <p>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 statistically less in the prasugrel group (12.3%) than in the clopidogrel group (14.6%; HR, 0.84; 95% CI, 0.76 to 0.92; <math>P &lt; 0.001</math>).</p> <p>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; <math>P &lt; 0.001</math>).</p> <p>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; <math>P &lt; 0.001</math>).</p> <p>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; <math>P = 0.03</math>).</p> <p>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; <math>P &lt; 0.01</math>).</p> <p>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; <math>P = 0.002</math>).</p> <p>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; <math>P &lt; 0.001</math>).</p> <p>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; <math>P = 0.31</math>).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Wiviott et al<sup>59</sup> Subanalysis of TRITON-TIMI 38</p> <p>Prasugrel 60 mg once, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>DB, MC, PG, RCT</p> <p>TRITON-TIMI 38 patients with a median age of 63 stratified by diabetes</p>	<p>N=13,608 (n=3,146 diabetes population)</p> <p>6 to 15 months (median 14.5 months)</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke</p> <p>Secondary: Rate of cardiovascular death, MI (fatal or nonfatal) or stent thrombosis; safety; net clinical benefit</p>	<p>Overall mortality was not significantly different between the two treatment groups (HR, 0.95; 95% CI, 0.78 to 1.16; <i>P</i>=0.64).</p> <p>Primary: The composite endpoint in patients with diabetes was significantly lower in the prasugrel group (12.2%) than in the clopidogrel group (17.0%; HR, 0.70; 95% CI, 0.58 to 0.85; <i>P</i>&lt;0.001).</p> <p>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; <i>P</i>=0.02).</p> <p>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; <i>P</i>&lt;0.001).</p> <p>Secondary: The rate of cardiovascular death in patients with diabetes was not significantly lower in the prasugrel group (3.4%) than in the clopidogrel group (4.2%; HR, 0.85; 95% CI, 0.58 to 1.24; <i>P</i>=0.40).</p> <p>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; <i>P</i>&lt;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; <i>P</i>=0.006). There was an 18.0% reduction in MI among nondiabetic prasugrel patients compared to a 40.0% reduction in MI among diabetic prasugrel patients.</p> <p>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; <i>P</i>=0.007).</p> <p>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; <i>P</i>=0.81).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>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; <i>P</i>=0.13).</p> <p>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; <i>P</i>=0.001).</p>
<p>Montalescot et al<sup>60</sup> Subanalysis of TRITON-TIMI 38</p> <p>Prasugrel 60 mg once, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>DB, MC, PG, RCT</p> <p>TRITON-TIMI 38 patients with a median age of 58 and 59 in the prasugrel and clopidogrel groups respectively, with STEMI status stratified into either primary PCI (those enrolled within 12 hours of symptom onset) or secondary PCI (those enrolled between 12 hours and 14 days after symptom onset)</p>	<p>N=3,534</p> <p>6 to 15 months (median 14.5 months)</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke at 15 months</p> <p>Secondary: Composite of death from cardiovascular causes, nonfatal MI or urgent target vessel revascularization at 30 days; stent thrombosis; composite of cardiovascular death or nonfatal MI; all individual components of composite endpoints; all cause death rate; safety</p>	<p>Primary</p> <p>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; <i>P</i>=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; <i>P</i>=0.015).</p> <p>Secondary:</p> <p>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; <i>P</i>=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; <i>P</i>=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; <i>P</i>=0.009).</p> <p>Stent thrombosis was significantly lower in the prasugrel group (1.6%) than in the clopidogrel group (2.8%; HR, 0.58; 95% CI, 0.36 to 0.93; <i>P</i>=0.0232).</p> <p>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; <i>P</i>=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; <i>P</i>=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; <i>P</i>=0.113).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>TIMI major bleeding events unrelated to CABG surgery (<math>P=0.645</math>), and TIMI life-threatening bleeding events (<math>P=0.750</math>) were both not significantly different between the two treatment groups.</p> <p>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; <math>P=0.003</math>).</p>
<p>Wiviott et al<sup>61</sup> Subanalysis of TRITON-TIMI 38</p> <p>Prasugrel 60 mg once, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>DB, MC, PG, RCT</p> <p>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 BMS group and 60 for both groups in the DES cohort who received <math>\geq 1</math> coronary stent</p>	<p>N=12,844</p> <p>6 to 15 months (median 14.5 months)</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke</p> <p>Secondary: Composite endpoint of death from cardiovascular causes, nonfatal MI or urgent target vessel revascularization; cardiovascular death; MI; urgent target vessel revascularization; stent thrombosis</p>	<p>Primary: The primary endpoint was reduced significantly greater in stent patients in the prasugrel group (9.7%) compared to the clopidogrel group (11.9%; HR, 0.81; 95% CI, 0.72 to 0.90; <math>P=0.0001</math>).</p> <p>DES 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; <math>P=0.019</math>). This was also seen in BMS patients (10.0 vs 12.0%; HR, 0.80; 95% CI, 0.69 to 0.93; <math>P=0.003</math>).</p> <p>Secondary: The secondary endpoint was reduced significantly greater in stent patients in the prasugrel group (9.7%) compared to the clopidogrel group (11.9%; HR, 0.80; 95% CI, 0.72 to 0.89; <math>P=0.0001</math>).</p> <p>DES 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; <math>P=0.004</math>). This was also seen in BMS patients in the prasugrel group (10.0%) compared to the clopidogrel group (12.0%; HR, 0.82; 95% CI, 0.71 to 0.95; <math>P=0.009</math>).</p> <p>Cardiovascular death was not significantly different in the entire stent cohort (<math>P=0.17</math>), nor was it significant in the DES subgroup (<math>P=0.25</math>), or the BMS subgroup (<math>P=0.16</math>).</p> <p>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; <math>P&lt;0.0001</math>). Rates were also</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>significantly better in the individual prasugrel DES (<math>P=0.003</math>) and BMS (<math>P=0.006</math>) groups.</p> <p>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; <math>P&lt;0.0003</math>). Rates were only significantly better in the prasugrel DES group (2.0%) compared to the clopidogrel group (4.0%; HR, 0.54; 95% CI, 0.38 to 0.76; <math>P&lt;0.0003</math>).</p> <p>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; <math>P&lt;0.0001</math>). Rates were significantly better in the prasugrel DES group (0.70%) compared to the clopidogrel group (1.92%; HR, 0.35; 95% CI, 0.21 to 0.61; <math>P&lt;0.0001</math>). Rates were significantly better in the prasugrel BMS group (0.96%) compared to the clopidogrel group (1.92%; HR, 0.42; 95% CI, 0.31 to 0.59; <math>P&lt;0.0001</math>).</p> <p>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 (<math>P=0.06</math>).</p>
<p>Pride et al<sup>62</sup> Subanalysis of TRITON-TIMI 38</p> <p>Prasugrel 60 mg once, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>DB, MC, PG, RCT</p> <p>TRITON-TIMI 38 patients who underwent PCI without stent implantation</p>	<p>N=569</p> <p>6 to 15 months (median 14.5 months)</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke</p> <p>Secondary: Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or urgent target vessel revascularization; safety</p>	<p>Primary: The primary endpoint occurred in 14.2% of patients randomized to prasugrel and 17.1% of patients randomized to clopidogrel, a nonsignificant 18.0% RRR (HR, 0.82; 95% CI, 0.53 to 1.25; <math>P=0.27</math>).</p> <p>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%; <math>P=0.001</math>).</p> <p>Secondary: There were significant reductions in the incidence of urgent target vessel revascularization (3.6 vs 8.2%; HR, 0.46; 95% CI, 0.22 to 0.98; <math>P=0.040</math>), any target vessel revascularization (4.0 vs 10.1%; HR, 0.40; 95% CI, 0.20 to 0.82; <math>P=0.009</math>), the composite of any revascularization procedure (6.3 vs 12.9%; HR, 0.48; 95% CI, 0.27 to 0.87; <math>P=0.014</math>), and CABG surgery (12.5 vs</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>19.4%; HR, 0.62; 95% CI, 0.40 to 0.98; <math>P=0.041</math>) 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; <math>P=0.11</math>) and all MI (9.8 vs 13.9%; HR, 0.69; 95% CI, 0.41 to 1.14; <math>P=0.14</math>) favoring prasugrel.</p> <p>The incidence of all cause mortality, cardiovascular death and nonfatal and all stroke did not differ significantly between the groups.</p> <p>Non-CABG-related major bleeding was more frequent among patients randomized to prasugrel (2.1 vs 0.0%; <math>P=0.033</math>), and there was a trend toward an increased incidence of non-CABG-related life-threatening bleeding (1.7 vs 0.0%; <math>P=0.057</math>). 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).</p>
<p>Antman et al<sup>63</sup> Subanalysis of TRITON-TIMI 38</p> <p>Prasugrel 60 mg once, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>DB, MC, PG, RCT</p> <p>TRITON-TIMI 38 patients<sup>58</sup></p>	<p>N=13,608</p> <p>6 to 15 months (median 14.5 months)</p>	<p>Primary: Rate of MI, stent thrombosis and urgent target vessel revascularization from randomization to day three and from day three to the end of the trial</p> <p>Secondary: Safety, percent net clinical benefit</p>	<p>Primary: The rate of MI was significantly lower in the prasugrel group (4.27%) than in the clopidogrel group by day three (5.24%; HR, 0.81; 95% CI, 0.70 to 0.95; <math>P=0.008</math>) 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; <math>P&lt;0.0001</math>).</p> <p>The rate of stent thrombosis was significantly lower in the prasugrel group than in the clopidogrel group by day three (0.33 vs 0.67%; HR, 0.49; 95% CI, 0.29 to 0.82; <math>P=0.006</math>) 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; <math>P&lt;0.0001</math>).</p> <p>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; <math>P=0.047</math>) 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; <math>P=0.0003</math>).</p> <p>Secondary: Through the first three days the rate of TIMI major non-CABG bleeding was numerically greater in the prasugrel group (0.74%) compared to the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>clopidogrel group (0.61%), however the difference between the two groups was not statistically significant, (<math>P=0.35</math>).</p> <p>From day three to the end of the trial prasugrel was associated with a statistically 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; <math>P=0.036</math>).</p> <p>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; <math>P=0.025</math>) 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; <math>P=0.028</math>).</p>
<p>Murphy et al<sup>64</sup> Subanalysis of TRITON-TIMI 38</p> <p>Prasugrel 60 mg once, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>DB, MC, PG, RCT</p> <p>TRITON-TIMI 38 patients<sup>58</sup></p>	<p>N=13,608</p> <p>6 to 15 months (median 14.5 months)</p>	<p>Primary: Total number of reoccurrences of the composite endpoint (rate of death from cardiovascular causes, nonfatal MI or nonfatal stroke), risk of second event following initial event, cardiovascular deaths following nonfatal event</p> <p>Secondary: Safety</p>	<p>Primary: Prasugrel demonstrated a significant overall reduction in subsequent events with 195 fewer total primary events compared to clopidogrel (HR, 0.79; 95% CI, 0.71 to 0.87; <math>P&lt;0.001</math>).</p> <p>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; <math>P=0.016</math>).</p> <p>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; <math>P=0.008</math>).</p> <p>Secondary: Recurrent bleeding events occurred infrequently, with TIMI major non-CABG bleeds in four patients treated with prasugrel and two with clopidogrel. There were also five repeat TIMI minor non-CABG bleeds in each treatment group. Among patients with at least one TIMI non-CABG major or minor bleeding event, 17 were reported in the prasugrel group and 13 were reported in the clopidogrel group.</p>
<p>O'Donoghue et al<sup>65</sup> Subanalysis of TRITON-TIMI 38</p> <p>Prasugrel 60 mg once,</p>	<p>DB, MC, PG, RCT</p> <p>TRITON-TIMI 38 patients stratified</p>	<p>N=13,608 (n=7,414 GP IIb/IIIa inhibitor population)</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke</p>	<p>Primary: There was a consistent benefit of prasugrel over clopidogrel in reducing cardiovascular death, MI or stroke at 30 days in patients who did (HR, 0.76; 95% CI, 0.64 to 0.90) and did not (HR, 0.78; 95% CI, 0.63 to 0.97; <math>P=0.83</math>) receive a GP IIb/IIIa inhibitor.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 300 mg once, followed by 75 mg/day</p> <p>Patients were also on concurrent aspirin therapy (75 to 162 mg/day).</p>	<p>by GP IIb/IIIa inhibitor use</p>	<p>30 days</p>	<p>Secondary: Periprocedural MI, urgent target vessel revascularization, stent thrombosis, safety</p>	<p>Secondary: Prasugrel significantly reduced the risk of recurrent MI in subjects by approximately 25% regardless of the use of a GP IIb/IIIa inhibitor, including a comparable benefit toward a reduction in periprocedural MI across both subgroups.</p> <p>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 (<math>P=0.63</math>).</p> <p>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; <math>P=0.46</math>).</p> <p>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; <math>P=0.04</math>). 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; <math>P=0.19</math>). 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 statistically different between subgroups (<math>P=0.39</math>). 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 (<math>P=0.19</math>). 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 (<math>P</math> 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 (<math>P</math> value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Wiviott et al<sup>22</sup></p> <p>Prasugrel 60 mg loading dose, followed by 10 mg/day</p> <p>vs</p> <p>clopidogrel 600 mg loading dose, followed by 150 mg/day</p> <p>Maintenance dose administered upon PCI completion.</p>	<p>AC, DB, DD, RCT, XO</p> <p>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 amenable lesion, objective findings of ischemia within 8 weeks of study, or prior PCI or CABG</p>	<p>N=201</p> <p>28 days (treatment periods were 14 days each)</p>	<p>Primary: Inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at six hours during the loading dose phase and at 14±2 days of the maintenance dose</p> <p>Secondary: Mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate, mean P2Y<sub>12</sub> assay percent inhibition, safety</p>	<p>Primary: For the loading dose phase, mean inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at six hours was significantly greater (higher inhibition of platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (74.8%) compared to the clopidogrel group (31.8%). The mean difference between the two groups was 43.2% (<i>P</i>&lt;0.0001).</p> <p>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% (<i>P</i>&lt;0.0001).</p> <p>Secondary: For the loading dose phase mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate was significantly lower (lower maximal platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (18.9%) compared to the clopidogrel group (52.1%). The mean difference between the two groups was 33.1% (<i>P</i>&lt;0.0001).</p> <p>For the maintenance dose phase mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate at 14±2 days was significantly lower in the prasugrel group (29.2%) compared to the clopidogrel group (40.9%). The mean difference between the two groups was 11.3% (<i>P</i>&lt;0.0001).</p> <p>For the loading dose phase prasugrel also showed significantly greater platelet inhibition with the P2Y<sub>12</sub> assay (89.5%) compared to clopidogrel (38.4%). The mean difference between the two groups was 51.4% (<i>P</i>&lt;0.0001).</p> <p>For the maintenance dose phase prasugrel also showed significantly greater platelet inhibition with the P2Y<sub>12</sub> assay (83.3%) compared to clopidogrel (65.1%). The mean difference between the two groups was 18.9% (<i>P</i>&lt;0.0001).</p> <p>There were no TIMI major bleeding episodes in either treatment group. For TIMI minor bleeding episodes 2% of patients in the prasugrel group</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>experienced a minor bleed compared to 0% in the clopidogrel group.</p> <p>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 statistically significant (<i>P</i> value not reported).</p>
<b>Treatment of Thrombocytopenia</b>				
<p>Anagrelide Study Group<sup>66</sup></p> <p>Anagrelide 0.5 to 1.0 mg QID</p> <p>To be eligible, patients had to have responded to or have been treated for ≥4 weeks at 4 mg/day.</p>	<p>MC, Phase II</p> <p>Patients ≥18 years of age with a diagnosis of PV, CGL, ET or another myeloproliferative process; with a history of thrombocytosis (&gt;900,000/mm<sup>3</sup>) on 2 occasions secondary to a myeloproliferative process</p>	<p>N=577</p> <p>Not reported</p>	<p>Primary: Response to therapy (a reduction of platelet count from pretreatment levels by 50% or to &lt;600,000 mm<sup>3</sup> 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</p> <p>Secondary: Not reported</p>	<p>Primary: Of the 577 patients, 424 were treated for at least four weeks. Of which, 396 (93%) met the criteria for response. Equivalent response rates were seen regardless of diagnosis (<i>P</i>=0.123).</p> <p>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<sup>3</sup>) was reduced to &lt;500,000/mm<sup>3</sup> 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 (<i>P</i>&lt;0.001) as well as for diagnostic subgroups (<i>P</i>&lt;0.05).</p> <p>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.</p> <p>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 (<i>P</i>=0.447).</p> <p>The median duration of first response ranged from 7.7 months for PV patients to &gt;28.6 months for ET patients, with an overall median of 16.7 months.</p> <p>The median duration of therapy was 5.6 months, with a range of 0.03 to 61.00 months.</p> <p>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.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Eighty nine of the 114 patients with CGL also received hydroxurea, 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.</p> <p>Of the 577 patients, 424 were considered evaluable for response, and 396 had an initial response and maintained that response for at least four weeks at a constant dose of anagrelide. Of these, 16 (four percent) needed to have their dose increased by <math>\geq 0.5</math> mg/day on a long-term basis to maintain the same degree of control over platelet counts.</p> <p>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.</p> <p>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%).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Silver et al<sup>67</sup> Subanalysis of Anagrelide Study Group</p> <p>Anagrelide 0.5 to 1.0 mg QID</p> <p>Weekly adjustments to the dose were made to achieve and maintain a platelet count <math>\leq 600,000/\mu\text{L}</math>.</p> <p>These patients previously received hydroxyurea therapy (hydroxyurea-resistant) before being treated with anagrelide.</p> <p>Patients fell into two groups: hydroxyurea-refractory patients and probably, but not definitely, hydroxyurea-refractory patients.</p>	<p>MC, Phase II</p> <p>Patients with CML</p>	<p>N=38</p> <p>Not reported</p>	<p>Primary: Efficacy, safety</p> <p>Secondary: Not reported</p>	<p>Primary: Of the 38 patients who previously received hydroxyurea, 27 (71%) 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 <math>250,000 \pm 360,400/\mu\text{L}</math>. 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 <math>&lt;600,000/\mu\text{L}</math>.</p> <p>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.</p> <p>The symptoms of the group of patients with thrombosis included TIAs, MI, erythromelalgia, DVT and ischemia with or without cutaneous ulceration of the extremities.</p> <p>Secondary: Not reported</p>
<p>Penninga et al<sup>68</sup></p> <p>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</p>	<p>MC, RETRO</p> <p>Patients with chronic myelo-proliferative disease</p>	<p>N=52</p> <p>Not reported</p>	<p>Primary: Complete response (reduction in platelet counts to <math>&lt;600 \times 10^9/\text{L}</math> or to a minimum 50% of pre-treatment level for <math>\geq 4</math> weeks), partial response (20 to 50% reduction of pretreatment level for <math>\geq 4</math> weeks), no</p>	<p>Primary: Forty one (79%) patients responded to treatment, with 39 (75%) being complete responders. All achieved a platelet count <math>&lt;600 \times 10^9/\text{L}</math>, and 34 (65%) achieved a platelet count <math>&lt;400 \times 10^9/\text{L}</math>.</p> <p>Eleven (21%) patients were nonresponders.</p> <p>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 nonresponder 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</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			response (<20% reduction in pretreatment platelet counts)  Secondary: Adverse events	response was 7.9 weeks.  Secondary: Forty two (81%) patients developed adverse effects and 28 (54%) patients reported more than one adverse effect. The most common adverse effect was anemia. Headache and palpitations were the second most common adverse events. Most of the adverse events were seen within a month from initiation of treatment, with patients reporting them as generally mild and transient.
Birgegard et al <sup>69</sup>  Anagrelide 1 to 8 mg/day  Doses were evaluated until the lowest effective dose required to reduce and maintain platelet count <400 x10 <sup>9</sup> /L in symptomatic patients or <600 x10 <sup>9</sup> /L in asymptomatic patients was established.  Patients who were receiving treatment with another agent to control platelets were switched over to anagrelide.	Noncomparative, OL, Phase II, PRO  Patients with a diagnosis of myelo-proliferative disease and a platelet count >600 x10 <sup>9</sup> /L in symptomatic patients or >1,000 x10 <sup>9</sup> /L in all other patients	N=60  2 years	Primary: Clinical effects, short and long term tolerability, patient's management  Secondary: Not reported	Primary: The overall response rate was 73% (67% complete responses [platelet count <400 x10 <sup>9</sup> /L or <600 x10 <sup>9</sup> /L in symptomatic and asymptomatic patients for ≥4 weeks], 6% partial response [reduction of the platelet count to ≥50% of the baseline value]) and the failure rate (platelet count that did not fall below <50% of the baseline value) was 27%. Primary treatment failure (n=16) was usually due to a lack of efficacy at a tolerable dose. In addition, another 14 patients withdrew from treatment before the end of the two year period. The most common reasons for discontinuing treatment were lack of efficacy at a tolerable dose and side effects while in complete response.  Side effects included palpitations (70%), headache (52%), nausea (35%), diarrhea or flatulence (33%), edema (22%) and fatigue (23%). The frequency and severity of side effects was dose dependent.  Patients and doctors rated the feasibility of anagrelide treatment on the 10-grade scale from 7.6 at three months to >9.0 at 24 months. The patients who continued treatment for the full two years (n=30) showed a high degree of satisfaction, as did their doctors.  The hemoglobin level dropped significantly during treatment, this effect first occurring within one week after initiation of treatment (P=0.002). Two patients had a thromboembolic event occur during the study period.  Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Steurer et al<sup>70</sup></p> <p>Anagrelide 0.5 mg BID for 14 days, followed by 1 mg BID and then the dosage was adjusted for each patient</p> <p>In patients pretreated with hydroxyurea or IFN-<math>\alpha</math>, it was allowed to combine anagrelide with one of those compounds.</p>	<p>MC, Phase II</p> <p>Newly diagnosed or pretreated patients with ET, PV or CIMF</p>	<p>N=97</p> <p>6 months</p>	<p>Primary: Platelet counts</p> <p>Secondary: Rate of clinical complications before and during anagrelide therapy, number of patients achieving response (complete, partial or failure to respond)</p>	<p>Primary: Platelet counts decreased significantly during the six month study period from a median baseline count of <math>743 \times 10^9/L</math> (range, 335 to <math>1.912 \times 10^9/L</math>) to <math>441 \times 10^9/L</math> (range, 153 to <math>1.141 \times 10^9/L</math>; <math>P &lt; 0.001</math>).</p> <p>Secondary: During the six months before the study, the rate of major thromboembolic complications was 5%. At the end of the study, the rate decreased to 2%. Seven patients had minor thromboembolic symptoms despite initiation of anagrelide treatment. At the start of the study, the rate of minor thromboembolic complications was 25%. After the study period, the rate decreased to 14%.</p> <p>Fifty patients qualified as complete responders and 25 patients had a very good partial response. The overall (complete, very good partial and partial; <math>n=77</math>) 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.</p>
<p>Harrison et al<sup>71</sup></p> <p>Hydroxyurea 0.5 to 1 mg/day</p> <p>vs</p> <p>anagrelide 0.5 mg BID</p> <p>Doses of hydroxyurea and anagrelide were adjusted to maintain the platelet count <math>&lt; 400,000/mm^3</math>.</p> <p>All patients received aspirin 75 mg/day.</p>	<p>OL, RCT</p> <p>Patients <math>\geq 18</math> years of age with ET who were at high risk for thrombotic or hemorrhagic events</p>	<p>N=809</p> <p>39 months (median follow-up)</p>	<p>Primary: Composite of time from randomization until death from thrombosis, hemorrhage, arterial or venous thrombotic event or serious hemorrhage</p> <p>Secondary: Time to first arterial or venous thrombotic event or to the first serious hemorrhage; time to death; incidence of</p>	<p>Primary: As compared to the hydroxyurea group, the anagrelide group had a significantly higher rate of the composite primary end point (OR, 1.57; 95% CI, 1.04 to 2.37; <math>P=0.03</math>). 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.</p> <p>Secondary: Analyses of the secondary endpoints revealed statistically 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; <math>P=0.004</math>). There were significantly more TIAs in the anagrelide group as well (14 vs 1; OR, 5.72; 95% CI, 2.08 to 15.73; <math>P &lt; 0.001</math>). 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>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>If aspirin was contraindicated, alternative agents were used (e.g., clopidogrel, dipyridamole).</p>			<p>transformation to myelofibrosis, AML, myelodysplasia or PV; control of platelet count</p>	<p><math>P=0.008</math>), with gastrointestinal hemorrhage being most common (OR, 3.54; 95% CI, 1.33 to 9.44; <math>P=0.01</math>). The rate of venous thromboembolism with anagrelide was approximately one fourth that with hydroxyurea (OR, 0.27; 95% CI, 0.11 to 0.71; <math>P=0.006</math>), and there was a significantly lower rate of DVT with anagrelide (OR, 0.20; 95% CI, 0.06 to 0.71; <math>P=0.009</math>). Pulmonary emboli developed in seven patients, five of which were in the hydroxyurea group.</p> <p>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.</p> <p>Anagrelide-treated patients had a significantly increased rate of transformation to myelofibrosis (OR, 2.92; 95% CI, 1.24 to 6.86; <math>P=0.01</math>). The estimated actuarial risk of myelofibrosis five years after trial entry was 2% (95% CI, 0 to 5) and 7% (95% CI, 3 to 10). Myelodysplasia or AML developed in 10 patients, four in the anagrelide group.</p> <p>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 (<math>P&lt;0.001</math> for both time points). PV developed in two patients, one in each treatment group.</p>

\*Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, 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, 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, BMS=bare metal stent, CABG=coronary artery bypass graft, CAD=coronary artery disease, CGL=chronic granulocytic leukemia, CIMF=chronic idiopathic myelofibrosis, CML=chronic myeloid leukemia, DES=drug eluting stent, DVT=deep vein thrombosis, ET=essential thrombocythemia, GP IIb/IIIa inhibitor=glycoprotein IIb/IIIa inhibitor, IFN- $\alpha$ =interferon alpha, MES=microembolic signals, MI=myocardial infarction, NSTEMI=non-ST-segment elevation acute coronary syndromes, NSTEMI=non-ST-segment elevation myocardial infarction, PAD=peripheral arterial disease, PCI=percutaneous coronary intervention, PV=polycythemia rubra vera, STEMI=ST-segment elevation myocardial infarction, TIA=transient ischemic attack, TIMI=thrombolysis in myocardial infarction

**Special Populations****Table 5. Special Populations**<sup>1-6</sup>

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
<b>Single Entity Agents</b>					
Anagrelide	No dosage adjustment required in the elderly.	Not reported	Hepatic dose adjustment is required; initiate therapy with 0.5 mg/day for $\geq 1$ week with careful monitoring of cardiovascular effects.  Contraindicated in severe hepatic impairment.	C	Unknown; use with caution.
Clopidogrel	No dosage adjustment required in the elderly.  Safety and efficacy in children have not been established.	Not reported	No dosage adjustment required.	B	Unknown; use with caution.
Dipyridamole	No dosage adjustment required in the elderly.  Safety and efficacy in children <12 years of age have not been established.	Not reported	Not reported	B	Yes (% not reported); use with caution.
Prasugrel	Use in patients $\geq 75$ years of age is generally not recommended.  Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild to moderate hepatic dysfunction.  Not studied in severe hepatic dysfunction.	B	Unknown; use with caution.
Ticlopidine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Dosage adjustment may be required; a dosage reduction or the dis-	Use is not recommended.	B	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.	continuation of therapy may be required.			
<b>Combination Products</b>					
Aspirin/ dipyridamole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.  Safety and efficacy in children have not been established.*	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	D	Yes/Yes (% not reported for either component).

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

**Adverse Drug Events****Table 6. Adverse Drug Events**

Adverse Event	Single Entity Agents					Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine	Aspirin/Dipyridamole
<b>Cardiovascular</b>						
Angina pectoris	1 to <5	-	✓	-	-	<1
Arrhythmia	1 to <5	-	-	-	-	<1
Atrial fibrillation/flutter	-	1 to 3	-	-	-	-
Cardiac failure	-	1 to 3	-	-	-	2
Cardiovascular disease	1 to <5	-	-	-	-	-
Chest pain	7.8	8	-	-	-	-
Edema	20.6	4	-	-	-	-
Heart failure	1 to <5	-	-	-	-	-
Hypertension	-	4	-	7.5	-	-
Hypotension	-	-	✓	-	-	-
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	-	-	-	-	-
<b>Central Nervous System</b>						
Amnesia	1 to <5	-	-	-	-	2
Anxiety	-	1 to 3	-	-	-	-
Cerebral edema	-	-	-	-	-	<1
Cerebral hemorrhage (includes intracranial and subarachnoid hemorrhage)	-	<1	-	-	<1	<1
Coma	-	-	-	-	-	<1
Confusion	1 to <5	<1	-	-	-	1
Depression	1 to <5	4	-	-	-	-
Dizziness	15.4	2 to 6	14	-	-	-
Fatigue	-	3	-	-	-	6
Fever	-	1 to 3	-	-	-	-
Flushing	-	-	✓	-	-	-
Headache	43.5	3 to 8	2	5.5	-	38 (tolerance usually develops)

Adverse Event	Single Entity Agents					Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine	Aspirin/Dipyridamole
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	-	-	-	-
<b>Dermatologic</b>						
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	-
Purpura	-	-	-	-	2	1
Pruritus	5.5	3	✓	-	1	<1
Rash	8.3	4	2	-	5	<1
Skin disease	1 to <5	-	-	-	-	-
Stevens-Johnson syndrome	-	-	-	-	<1	-
Toxic epidermal necrolysis	-	<1	-	-	-	-
Ulceration	-	-	-	-	-	<1
Urticaria	-	<1	-	-	<1	<1
<b>Endocrine/Metabolic</b>						
Dehydration	1 to <5	-	-	-	-	-
Gout/hyperuricemia	-	1 to 3	-	-	-	-
Hypercholesterolemia/increased cholesterol	-	-	-	7	>10*	-
Hyponatremia	-	-	-	-	<1	-
Pancreatitis	-	<1	-	-	-	<1
<b>Gastrointestinal</b>						
Abdominal distress	-	-	6	-	-	-
Abdominal pain	16.4	2 to 6	-	-	4	18

Adverse Event	Single Entity Agents					Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine	Aspirin/Dipyridamole
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	✓	-	13	13
Dyspepsia	5.2	2 to 5	✓	-	7	>10
Dysuria	1 to <5	-	-	-	-	-
Eructation	1 to <5	-	-	-	-	-
Flatulence	10.2	-	-	-	2	-
Gastritis	1 to <5	-	-	-	-	-
Gastrointestinal distress	1 to <5	-	-	-	-	-
Gastrointestinal hemorrhage	-	1 to 3	-	-	<1	1
Hematemesis	-	-	-	-	-	<1
Hematuria	1 to <5	-	-	-	-	-
Hemorrhoids	-	-	-	-	-	1
Melena	1 to <5	-	-	-	-	-
Nausea	17.1	3	✓	-	7	16
Peptic ulcer	-	-	-	-	<1	-
Rectal bleeding	-	-	-	-	-	2
Retroperitoneal hemorrhage	-	<1	-	-	-	-
Vomiting	9.7	1 to 3	✓	-	2	8
<b>Genitourinary</b>						
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
<b>Hematologic</b>						
Agranulocytosis	-	<1	-	-	<1	-

Adverse Event	Single Entity Agents					Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine	Aspirin/Dipyridamole
Anemia	1 to <5	1 to 3	-	-	-	2
Aplastic anemia	-	<1	-	-	<1	<1
Bleeding	-	Major, 4; minor, 5	-	Major, 2.2; minor, 2.4	-	-
Disseminated intravascular coagulation	-	-	-	-	-	<1
Ecchymosis	1 to <5	-	-	-	-	-
Eosinophilia	-	-	-	-	<1	-
Epistaxis	1 to <5	3	-	-	-	-
Granulocytopenia	-	<1	-	-	-	-
Hematoma	-	1 to 3	-	-	-	-
Hemolytic anemia	-	-	-	-	<1	-
Hemorrhage	1 to <5	-	-	-	-	-
Hypochromic anemia	-	<1	-	-	-	-
Leukopenia	-	<1	-	-	-	-
Lymphadenopathy	1 to <5	-	-	-	-	-
Neutropenia	-	<1	-	-	2	-
Pancytopenia	-	<1	-	-	<1	<1
Prothrombin time prolonged	-	-	-	-	-	<1
Purpura	-	5	-	-	-	-
Thrombocytopenia	1 to <5	<1	✓	-	<1	<1
Thrombocytosis	-	-	-	-	<1	-
Thrombosis	1 to <5	-	-	-	-	-
Thrombotic thrombocytopenic purpura	-	-	-	-	<1	-
<b>Hepatic</b>						
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	-

Adverse Event	Single Entity Agents					Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine	Aspirin/Dipyridamole
<b>Neuromuscular/Musculoskeletal</b>						
Arthralgia	1 to <5	6	-	-	-	6
Arthritis	-	1 to 3	✓	-	-	2
Arthropathy	-	-	-	-	<1	-
Arthrosis	-	-	-	-	-	1
Back pain	5.9	6	-	5	-	5
Fatigue	-	-	✓	-	-	-
Leg cramps	1 to <5	1 to 3	-	-	-	-
Myalgia	1 to <5	-	✓	-	-	1
Myositis	-	-	-	-	<1	-
Neuralgia	-	1 to 3	-	-	-	-
Paresthesia	5.9	1 to 3	✓	-	-	<1
Peripheral neuropathy	-	-	-	-	<1	-
Rhabdomyolysis	-	-	-	-	-	<1
Weakness	-	1 to 3	-	-	-	2
<b>Respiratory</b>						
Asthma	1 to <5	-	-	-	-	-
Bronchiolitis obliterans-organized pneumonia	-	-	-	-	<1	-
Bronchitis	1 to <5	4	-	-	-	-
Bronchospasm	-	-	-	-	-	<1
Cough	6.3	3	-	-	-	2
Dyspnea	11.9	5	-	-	-	<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	-	-	-	-	-

Adverse Event	Single Entity Agents					Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine	Aspirin/Dipyridamole
Tachypnea	-	-	-	-	-	<1
Upper respiratory infection	-	-	-	-	-	1
<b>Other</b>						
Abnormal vision	1 to <5	-	-	-	-	-
Allergic reaction	-	<1	-	-	-	<1
Allergic vasculitis	-	-	-	-	-	<1
Amblyopia	1 to <5	-	-	-	-	-
Anaphylactoid reaction/anaphylaxis	-	<1	-	-	<1	<1
Angioedema	-	<1	-	-	<1	<1
Ante-/peri-/postpartum bleeding	-	-	-	-	-	<1
Asthenia	23.1	-	-	-	-	-
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
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	-	-	-	-	-

\*Increases of 8 to 10% within one month of therapy.

-Event not reported or incidence <1%.

✓ Percent not specified.

### **Contraindications/Precautions**

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

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

In general, thienopyridines increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, treatment with a thienopyridine should be discontinued five days prior to surgery.<sup>2</sup> Specific to treatment with prasugrel, the agent should be used with caution in patients with increased risk factors for bleeding. Risk factors include those patients who are  $\geq 75$  years of age. In this patient population prasugrel should be avoided except in high risk situations such as diabetes or a history of myocardial infarction, where the agent's effect appears to be greater and its use may be considered. Additional bleeding risk factors include patients planning on undergoing a coronary artery bypass graft surgery or other surgical procedures. Patients who are planning on undergoing a coronary artery bypass graft should not be started on prasugrel and those currently being treated with the medication should have it discontinued at least seven days prior to surgery.<sup>4</sup> Thienopyridines also inhibit platelet aggregation for the lifetime of the platelet (seven to 10 days), therefore withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. In addition, thrombocytopenic purpura, sometimes fatal, has been reported following the use of clopidogrel, sometimes after a short exposure (less than two weeks).<sup>2</sup> This warning is applied to all theinopyridines<sup>2,4,5</sup>

The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in cytochrome P450 (CYP) 2C19, and by concomitant medications that interfere with CYP2C19. Because of this, concomitant use of clopidogrel and strong or moderate CYP2C19 inhibitors should be avoided. Omeprazole, a moderate inhibitor, has been shown to reduce the pharmacological activity of clopidogrel if given concomitantly or if given 12 hours apart. Consideration to using another acid reducing agent with less CYP2C19 inhibitory activity should be made. Pantoprazole, a weak CYP2C19 inhibitor, had less effect on the pharmacological activity of clopidogrel than omeprazole. Lapses in clopidogrel therapy should be avoided, and if clopidogrel must be temporarily discontinued, the medication should be restarted as soon as possible. Premature discontinuation of clopidogrel may increase the risk of cardiovascular events.<sup>2</sup>

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

In patients who are being managed with percutaneous coronary intervention or stent placement, premature prasugrel discontinuation can potentially lead to an increased risk of stent thrombosis, myocardial infarction or death; therefore, lapse in therapy should be avoided. If the agent is discontinued due to an adverse event it should be restarted as soon as possible. The medication should also be used with caution in patients with conditions that have the propensity to bleed such as recent surgery or trauma, or severe hepatic impairment.<sup>4</sup>

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

Intracranial hemorrhage was observed in patients receiving aspirin/dipyridamole during clinical trials. Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. Use of aspirin/dipyridamole in patients with a history of active peptic ulcer disease should be avoided. In addition, because of the aspirin component, patients receiving aspirin/dipyridamole should be counseled about the bleeding risks involved with chronic and heavy alcohol intake. As mentioned previously, dipyridamole has a vasodilatory effect; therefore, patients with underlying coronary artery disease who are receiving aspirin/dipyridamole may experience chest pain. In addition, for stroke and transient ischemic attack patients for whom aspirin is indicated to prevent recurrent myocardial infarction or angina pectoris, the aspirin component in the aspirin/dipyridamole combination product may not provide adequate treatment for the cardiac indications. Finally, aspirin/dipyridamole capsules are not interchangeable with the individual components of aspirin and dipyridamole tablets.<sup>6</sup>

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

**Black Box Warning for Plavix<sup>®</sup> (clopidogrel)<sup>72</sup>**

**WARNING**

Diminished effectiveness in poor metabolizers: The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP-450) system, principally CYP2C19. Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome or percutaneous coronary intervention than patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype and can be used 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)<sup>72</sup>**

**WARNING**

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

**Black Box Warning for ticlopidine<sup>72</sup>**

**WARNING**

Ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura and aplastic anemia. Neutropenia/agranulocytosis: Among 2,048 patients in clinical trials, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm<sup>3</sup>), and the neutrophil count was below 450/mm<sup>3</sup> in 17 of these patients (0.8% of the total population).

Thrombotic Thrombocytopenic Purpura: One case of thrombocytopenic purpura was reported during clinical trials. Based on postmarketing data, United States physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of two to four million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated thrombocytopenic purpura may be as high as one case in every 2000 to 4000 patients exposed.

Aplastic anemia: Aplastic anemia was not seen during clinical trials in stroke patients, but United States physicians reported about 50 cases between 1992 and 1998. Based on an estimated patient exposure of two to four million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated aplastic anemia may be as high as one case in every 4,000 to 8,000 patients exposed.

Monitoring of clinical and hematologic status: Severe hematologic adverse reactions may occur within a few days of the start of therapy. The incidence of thrombocytopenic purpura peaks after about three to four weeks of therapy and neutropenia peaks at approximately four to six weeks. The incidence of aplastic anemia peaks after about four to eight weeks of therapy. The incidence of the hematologic adverse reactions declines thereafter. Only a few cases of neutropenia, thrombocytopenic purpura, or aplastic anemia have arisen after more than three months of treatment. Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first three months of treatment, patients receiving ticlopidine must, therefore, be hematologically and clinically monitored for evidence of neutropenia or thrombocytopenic purpura. If any such evidence is seen, ticlopidine should be immediately discontinued.

**Drug Interactions****Table 7. Drug Interactions<sup>20,72</sup>**

<b>Generic Name</b>	<b>Interacting Medication or Disease</b>	<b>Potential Result</b>
Aspirin	Angiotensin converting enzyme Inhibitors	Aspirin may reduce the hypotensive and vasodilator effects of angiotensin converting enzyme Inhibitors.
Aspirin	$\beta$ -blockers	Salicylates (aspirin) may attenuate the blood pressure lowering effects of $\beta$ blockers. In addition, the beneficial effects of $\beta$ -blockers on left ventricular ejection fraction in patients with chronic heart failure may be attenuated.
Aspirin	Carbonic anhydrase inhibitors	Concomitant use may result in carbonic anhydrase inhibitor accumulation and toxicity.
Aspirin	Clopidogrel	The risk of life-threatening bleeding may be increased in high-risk patients with transient ischemic attack or ischemic stroke.
Aspirin	Heparin	Concomitant use may increase the risk of bleeding.
Aspirin	Influenza virus vaccine, intranasal	The risk of Reye syndrome may be increased.
Aspirin	Insulin	The serum glucose lowering action of insulin may be potentiated.
Aspirin	Methotrexate	Increased toxic effects of methotrexate may occur.
Aspirin	Nonsteroidal anti-inflammatory drugs	Nonsteroidal anti-inflammatory drugs may reduce the cardioprotective effect of low-dose, uncoated aspirin. These agents are also gastric irritants.
Aspirin	Sulfipyrazone	Concomitant use may suppress the uricosuria produced by sulfipyrazone.
Aspirin	Sulfonylureas	Increased hypoglycemic effect of sulfonylureas.
Aspirin	Valproic acid	Increased free fraction of valproic acid, possibly leading to toxic effects of valproic acid.
Aspirin	Warfarin	Anticoagulant activity may be enhanced.
Clopidogrel	Azole antifungals (ketoconazole)	Ketoconazole may inhibit the antiplatelet effect of clopidogrel.
Clopidogrel	Proton pump inhibitors	Proton pump inhibitors may decrease the antiplatelet activity of clopidogrel.
Clopidogrel	Salicylates (aspirin)	The risk of life-threatening bleeding may be increased in high-risk patients with transient ischemic attack or ischemic stroke.
Dipyridamole	Adenosine	Dipyridamole may potentiate the pharmacologic effects of adenosine, resulting in profound bradycardia after rapid bolus adenosine administration.
Prasugrel	Nonsteroidal anti-inflammatory drugs	The risk of bleeding may be increased.
Prasugrel	Warfarin	The risk of bleeding is increased.
Ticlopidine	Cyclosporine	Cyclosporine whole blood concentrations may decrease, producing a decrease in pharmacologic effects.
Ticlopidine	Hydantoin	Plasma hydantoin concentrations may be increased, resulting in an increase in adverse effects.
Ticlopidine	Theophyllines	Increased theophylline levels have been noted when administered concomitantly with ticlopidine.

**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.

**Table 8. Dosing and Administration**<sup>1-6</sup>

Generic Name	Adult Dose	Pediatric Dose	Availability
<b>Single Entity Agents</b>			
Anagrelide	<u>Treatment of thrombocytopenia associated with myeloproliferative disorders:</u> Capsule: initial, 0.5 mg QID OR 1 mg BID for $\geq 1$ week; maintenance, adjust to the lowest effective dosage required to reduce and maintain platelet count $< 600,000/\mu\text{L}$ ; maximum, 10 mg/day OR 2.5 mg in a single dose*	<u>Treatment of thrombocytopenia associated with myeloproliferative disorders</u> <sup>†</sup> : Capsule: initial, 0.5 mg/day; maintenance, adjust to the lowest effective dosage required to reduce and maintain platelet count $< 600,000/\mu\text{L}$ ; maximum, 10 mg/day OR 2.5 mg in a single dose*	Capsule: 0.5 mg 1 mg
Clopidogrel	<u>Acute coronary syndrome for patients with non ST-elevation acute coronary syndrome:</u> Tablet: initial, 300 mg one time; maintenance, 75 mg QD <sup>‡</sup>  <u>Acute coronary syndrome for patients with ST-elevation myocardial infarction:</u> Tablet: 75 mg QD <sup>‡§</sup>  <u>Recent myocardial infarction, recent stroke or established peripheral arterial disease:</u> Tablet: 75 mg QD	Safety and efficacy in children have not been established.	Tablet: 75 mg 300 mg
Dipyridamole	<u>Prevention of postoperative thromboembolic complications of cardiac valve replacement:</u> Tablet: 75 to 100 mg QID <sup>  </sup>	Safety and efficacy in children $< 12$ years of age have not been established.	Tablet: 25 mg 50 mg 75 mg
Prasugrel	<u>Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are being managed with percutaneous coronary intervention in patients <math>\geq 60</math> kg:</u> Tablet: initial, 60 mg one time; maintenance, 10 mg QD <sup>‡</sup>  <u>Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are</u>	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	<u>being managed with percutaneous coronary intervention in patients &lt;60 kg:</u> Tablet: initial, 60 mg one time; maintenance, 5 mg QD <sup>†</sup>		
Ticlopidine	<u>Reduce the incidence of subcutaneous stent thrombosis in patients undergoing successful coronary stent implantation:</u> Tablet: 250 mg BID for up to 30 days <sup>#</sup>  <u>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:</u> Tablet: 250 mg BID <sup>**</sup>	Safety and efficacy in children have not been established.	Tablet: 250 mg
<b>Combination Products</b>			
Aspirin/dipyridamole <sup>††</sup>	<u>Reduce the risk of stroke in patients who have had transient ischemia or the brain or completed ischemic stroke due to thrombosis:</u> Capsule: 25/200 mg BID	Safety and efficacy in children have not been established.	Capsule: 25/200 mg

BID=twice daily, QID=four times daily

\*The dosage should be increased by not more than 0.5 mg/day in any one week.

†An open-label safety and pharmacokinetic and pharmacodynamics 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.

¶The safety and efficacy of the 5 mg dose have not been prospectively studied.

#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 tablets.

### **Clinical Guidelines**

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

National and international clinical guidelines regarding the use of platelet inhibitors are outlined below. As mentioned previously, use of these agents as either monotherapy or combination therapy is based on the specific clinical indication and the patient's risk for thromboembolic events.<sup>7-17</sup>

Early aspirin therapy is recommended for patients with an acute ischemic stroke who are not receiving thrombolysis. Antiplatelet therapy is also recommended for long-term secondary prevention in these patients. Recommended therapies include aspirin, aspirin plus dipyridamole extended-release (ER) and clopidogrel.<sup>7,8</sup> According to the American College of Chest Physician treatment guidelines, combination aspirin plus dipyridamole ER is recommended over aspirin, and clopidogrel is suggested over aspirin. In addition, the use of long term aspirin and clopidogrel together in these patients should be avoided due to an increased risk in bleeding. Dual antiplatelet therapy is more favored in these patients who have had a recent acute myocardial infarction, other acute coronary syndrome or a recently placed coronary stent. Duration of dual antiplatelet therapy would then depend on the specific cardiac indication.<sup>8</sup>

Immediate and maintenance treatment with aspirin is recommended for all patients presenting with non-ST-segment elevation acute coronary syndromes (NSTEMI/ACS) who have no clear allergy to aspirin. For patients who have an allergy to aspirin; treatment with clopidogrel is recommended. In addition, clopidogrel is recommended for the treatment in NSTEMI/ACS patients who are at least of moderate risk for an ischemic event. Aspirin and clopidogrel are recommended for the management of patients presenting with a ST-segment elevation myocardial infarction.<sup>8</sup>

In addition, while not Food and Drug Administration approved, the use of clopidogrel in combination with aspirin to reduce the risk of major vascular events, including stroke, can be considered in patients with atrial fibrillation in whom oral anticoagulation with warfarin is considered unsuitable. Patients with atrial fibrillation, who have undergone percutaneous coronary intervention or revascularization surgery, may also be considered for low dose aspirin and/or clopidogrel in combination with anticoagulation therapy to prevent myocardial ischemic events. Of note, this treatment strategy has not been thoroughly evaluated and puts a patient at an increased risk of bleeding.<sup>73,75</sup>

**Table 9. Clinical Guidelines**

Clinical Guideline	Recommendations
American Heart Association/American Stroke Association: <b>Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2011)</b> <sup>7</sup>	<u>Antithrombotic therapy for noncardioembolic stroke or transient ischemic attack (TIA) (specifically, atherosclerotic, lacunar or cryptogenic infarcts)</u> <ul style="list-style-type: none"> <li>• The use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.</li> <li>• Aspirin (50 to 325 mg/day) monotherapy, the combination of aspirin 25 mg and dipyridamole extended-release (ER) 200 mg twice daily and clopidogrel (75 mg/day) monotherapy are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance and other clinical characteristics.</li> <li>• The risk of hemorrhage is increased when aspirin is added to clopidogrel; therefore, the combination is not recommended for routine secondary prevention after ischemic stroke or TIA.</li> <li>• For patients allergic to aspirin, clopidogrel is reasonable.</li> <li>• For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin.</li> </ul>
American College of Chest Physicians: <b>Antithrombotic and Thrombolytic Therapy 8<sup>th</sup> Edition (2008)</b> <sup>8</sup>	<u>Antithrombotic therapy and thrombolytic therapy for ischemic stroke</u> <ul style="list-style-type: none"> <li>• Antiplatelet agents for altering outcomes in acute stroke patients not eligible for thrombolysis:               <ul style="list-style-type: none"> <li>○ Early aspirin therapy is recommended (initial dose, 150 to 325 mg).</li> </ul> </li> <li>• Prevention of cerebral ischemic events in patients with noncardioembolic TIA or stroke: antiplatelet drugs vs placebo or vs an alternative antiplatelet drug:               <ul style="list-style-type: none"> <li>○ Treatment with an antiplatelet drug is recommended. Aspirin monotherapy, the combination of aspirin (25 mg) plus dipyridamole ER (200 mg twice daily) and clopidogrel (75 mg/day) monotherapy are all acceptable options for initial therapy. Aspirin, at a dose of 50 to 100 mg/day, is recommended over high dose aspirin.</li> <li>○ The combination of aspirin and dipyridamole ER (25/200 mg twice daily) is recommended over aspirin, and clopidogrel is suggested over aspirin. However, the use of combination therapy</li> </ul> </li> </ul>

Clinical Guideline	Recommendations
	<p>over aspirin may vary based on cost, tolerability, availability, ease of use and absolute risk.</p> <ul style="list-style-type: none"> <li>○ In most patients, avoiding long term use of the combination of aspirin and clopidogrel is recommended. In those with a recent acute myocardial infarction (MI), other acute coronary syndrome (ACS) or a recently placed coronary stent, clopidogrel plus aspirin (75 to 100 mg) is recommended. The optimal duration of dual therapy depends on the specific cardiac indication.</li> <li>○ For patients who are allergic to aspirin, clopidogrel is recommended.</li> </ul> <ul style="list-style-type: none"> <li>● Prevention of noncardioembolic cerebral ischemic events: oral anticoagulants:             <ul style="list-style-type: none"> <li>○ Antiplatelet agents are recommended over anticoagulation.</li> </ul> </li> <li>● Prevention of cardioembolic cerebral ischemic events:             <ul style="list-style-type: none"> <li>○ In patients with atrial fibrillation (AF) who have suffered a recent stroke or TIA, long term oral anticoagulation is recommended.</li> <li>○ For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, aspirin (75 to 325 mg/day) is recommended.</li> <li>○ In patients with stroke associated with aortic atherosclerotic lesions, antiplatelet therapy is recommended over no therapy. For patients with cryptogenic stroke associated with mobile aortic arch thrombi, oral anticoagulation or antiplatelet agents are suggested.</li> <li>○ In patients with cryptogenic ischemic stroke and a patent foramen ovale, antiplatelet therapy is recommended over no therapy.</li> <li>○ In patients with mitral valve strands or prolapse, who have a history of TIA or stroke, antiplatelet therapy is recommended.</li> </ul> </li> </ul> <p><u>Antithrombotic therapy for non-ST-segment elevation ACS (NSTEMI/ACS)</u></p> <ul style="list-style-type: none"> <li>● Antiplatelet therapies:             <ul style="list-style-type: none"> <li>○ For all patients, without a clear allergy to aspirin, immediate aspirin (162 to 325 mg) administration, followed by daily aspirin (75 to 100 mg/day) is recommended.</li> <li>○ For all patients with an aspirin allergy, immediate treatment with clopidogrel (300 mg), followed by 75 mg/day indefinitely is recommended.</li> <li>○ For patients at moderate or greater risk (e.g., ongoing chest pain, hemodynamic instability, positive troponin or dynamic electrocardiogram changes) for an ischemic event and who will undergo an early invasive management strategy (i.e., diagnostic catheterization followed by anatomy-driven revascularization), the following is recommended:                 <ul style="list-style-type: none"> <li>▪ “Upstream” treatment either with clopidogrel (300 mg bolus, followed by 75 mg/day) or a small-molecule intravenous (IV) glycoprotein (GP) IIb/IIIa inhibitor.</li> <li>▪ Upstream use of clopidogrel and a GP IIb/IIIa inhibitor is suggested; however, scrupulous attention to weight- and renal-based dosing algorithms must be exercised.</li> </ul> </li> <li>○ For patients at moderate or greater risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used, the following is recommended:                 <ul style="list-style-type: none"> <li>▪ Upstream treatment with clopidogrel (300 mg bolus,</li> </ul> </li> </ul> </li> </ul>

Clinical Guideline	Recommendations
	<p>followed by 75 mg/day).</p> <ul style="list-style-type: none"> <li>▪ Upstream use of clopidogrel and a GP IIb/IIIa inhibitor is suggested.</li> </ul> <ul style="list-style-type: none"> <li>○ For patients who undergo percutaneous coronary intervention (PCI), treatment with both clopidogrel and an IV GP IIb/IIIa inhibitor is recommended.           <ul style="list-style-type: none"> <li>▪ A clopidogrel loading dose of 600 mg given at least two hours prior to planned PCI, followed by 75 mg/day is recommended.</li> <li>▪ If ticlopidine is given, a loading dose of 500 mg given at least six hours before planned PCI is suggested.</li> <li>▪ For PCI patients who cannot tolerate aspirin, a clopidogrel (600 mg) or ticlopidine (500 mg) loading dose given at least 24 hours prior to planned PCI is suggested.</li> <li>▪ In patients who have received clopidogrel and who are scheduled for coronary artery bypass graft (CABG) surgery, it is suggested that clopidogrel be discontinued for at least five days prior to the scheduled surgery.</li> </ul> </li> </ul> <p><u>Acute ST-segment elevation MI (STEMI)</u></p> <ul style="list-style-type: none"> <li>• Aspirin:           <ul style="list-style-type: none"> <li>○ Whether or not the patient receives fibrinolytic therapy, aspirin (160 to 325 mg) is recommended over no aspirin therapy at initial evaluation by health-care personnel, followed by indefinite therapy (75 to 162 mg/day).</li> </ul> </li> <li>• Clopidogrel:           <ul style="list-style-type: none"> <li>○ Clopidogrel in addition to aspirin is recommended. The recommended dosing for clopidogrel is 300 mg for patients ≤75 years and 75 mg for patients &gt;75 years if they receive fibrinolytic agents or no reperfusion therapy, followed by 75 mg/day for up to 28 days.</li> <li>○ For patients who have not received a coronary stent, clopidogrel 75 mg/day is suggested to be continued beyond 28 days and up to one year.</li> <li>○ For patients undergoing primary PCI, clopidogrel in addition to aspirin with a recommended initial dosing of ≥300 mg, followed by 75 mg/day is suggested.</li> </ul> </li> </ul> <p><u>The primary and secondary prevention of chronic coronary artery disease (CAD)</u></p> <ul style="list-style-type: none"> <li>• For patients with ACS with and without ST-segment elevation, aspirin, given initially at a dose of 75 to 162 mg and then indefinitely at a dose of 75 to 100 mg/day, is recommended.</li> <li>• For patients with ST-segment elevation ACS, with or without fibrinolytic therapy, clopidogrel administered as a 300 mg loading dose for patients ≤75 years of age and 75 mg starting dose for those &gt;75 years of age and continued daily (75 mg/day) for two to four weeks is recommended.</li> <li>• For patients with NSTEMI ACS, combination therapy with aspirin (75 to 100 mg/day) and clopidogrel (75 mg/day) is recommended for 12 months.</li> <li>• For patients in whom aspirin is contraindicated or not tolerated, clopidogrel monotherapy is recommended.</li> <li>• For patients with symptomatic CAD, aspirin (75 to 100 mg/day) in combination with clopidogrel (75 mg/day) is suggested. This suggestion</li> </ul>

Clinical Guideline	Recommendations
	<p>places a high value on the probable small reduction in arterial vascular risk consequent on adding clopidogrel to aspirin and a low value on avoiding the additional bleeding and high cost associated with clopidogrel.</p> <ul style="list-style-type: none"> <li>• For most patients (except high risk patients) following ACS, aspirin alone (75 to 100 mg/day) is recommended over vitamin K antagonist (VKA) monotherapy or in combination with aspirin.</li> <li>• For high risk MI patients, combined use of moderate intensity VKA plus low dose aspirin (<math>\leq 100</math> mg/day) is suggested for at least three months after the MI.</li> <li>• For long term treatment of patients after PCI, aspirin (75 to 100 mg/day) is recommended.</li> <li>• For patients undergoing PCI with bare metal stent (BMS) placement, aspirin (75 to 100 mg/day) plus clopidogrel is recommended over aspirin monotherapy.</li> <li>• For patients undergoing PCI with BMS placement following ACS, 12 months of aspirin (75 to 100 mg/day) plus clopidogrel (75 mg/day) is recommended over aspirin monotherapy.</li> <li>• For patients undergoing PCI with drug eluting stents (DES), aspirin (75 to 100 mg/day) plus clopidogrel (75 mg/day for at least 12 months) is recommended.</li> <li>• For patients undergoing stent replacement with a strong concomitant indication for VKA, triple antithrombotic therapy is suggested. Four weeks of clopidogrel therapy following BMS and one year of clopidogrel therapy following DES is suggested.</li> <li>• Clopidogrel or ticlopidine are suggested over cilostazol for patients after stent placement. Clopidogrel is recommended over ticlopidine.</li> <li>• In patients with congestive heart failure due to a nonischemic etiology, the routine use of aspirin or VKA is not recommended.</li> <li>• For all patients with CAD undergoing CABG, indefinite aspirin (75 to 100 mg/day) is recommended. It is suggested that aspirin be started postoperatively.</li> <li>• In patients who undergo CABG following NSTEMI ACS, clopidogrel (75 mg/day) for up to nine to 12 months following the procedure in addition to treatment with aspirin is suggested.</li> <li>• For patients who have received clopidogrel for ACS and are scheduled for CABG, it is suggested that clopidogrel be discontinued for five days prior to the scheduled surgery.</li> <li>• For all patients with CAD who undergo internal mammary artery bypass grafting, aspirin 75 to 162 mg/day indefinitely is recommended.</li> <li>• For patients with at least moderate risk for a coronary event, aspirin (75 to 100 mg/day) is recommended over either no antithrombotic therapy or VKA.</li> <li>• For all patients, the routine addition of clopidogrel to aspirin therapy in primary prevention is not recommended. For patients with an aspirin allergy who are at moderate to high risk for a cardiovascular event, monotherapy with clopidogrel is recommended.</li> <li>• For women &lt;65 years of age who are at risk for an ischemic stroke, and in whom the concomitant risk of major bleeding is low, aspirin (75 to 100 mg/day) is suggested over no aspirin therapy.</li> <li>• For women &gt;65 years of age at risk for ischemic stroke or MI, and in whom the concomitant risk of major bleeding is low, aspirin (75 to 100 mg/day) is suggested over no aspirin therapy.</li> </ul>

Clinical Guideline	Recommendations
	<p><u>Antithrombotic therapy in peripheral artery occlusive disease</u></p> <ul style="list-style-type: none"> <li>• Chronic limb ischemia and intermittent claudication:               <ul style="list-style-type: none"> <li>○ Patients with clinically manifest coronary or cerebrovascular disease, life-long antiplatelet therapy in comparison to no antiplatelet therapy is recommended.</li> <li>○ In those without clinically manifest coronary or cerebrovascular disease, aspirin (75 to 100 mg/day) over clopidogrel is suggested. In patients who are aspirin intolerant, clopidogrel over ticlopidine is recommended.</li> <li>○ For all patients undergoing infrainguinal arterial reconstruction, aspirin is recommended (75 to 100 mg, begun preoperatively).</li> <li>○ For patients receiving routine autogenous vein infrainguinal bypass, aspirin is recommended (75 to 100 mg, begun preoperatively).</li> <li>○ For patients receiving routine prosthetic infrainguinal bypass, aspirin is recommended (75 to 100 mg, begun preoperatively).</li> <li>○ In patients undergoing carotid endarterectomy, aspirin (75 to 100 mg) preoperatively to prevent perioperative ischemic neurologic events is recommended. Lifelong postoperative aspirin therapy is recommended (75 to 100 mg/day).</li> <li>○ In nonoperative patients with asymptomatic carotid stenosis (primary or recurrent), lifelong aspirin (75 to 100 mg/day) is recommended. In this patient group, dual antiplatelet therapy with aspirin and clopidogrel is not recommended.</li> <li>○ For patients undergoing lower-extremity balloon angioplasty (with or without stenting), long term aspirin (75 to 100 mg/day) is recommended.</li> </ul> </li> </ul> <p><u>Valvular and structural heart disease</u></p> <ul style="list-style-type: none"> <li>• For patients with rheumatic mitral valve disease with AF who suffer systemic embolism or have left atrial thrombus while receiving VKAs at a therapeutic International Normalized Ratio (INR), the addition of low dose aspirin (50 to 100 mg/day) after consideration of the additional hemorrhagic risks is suggested. An alternative strategy might be the adjustment of VKA dosing to achieve a higher target INR.</li> <li>• In patients with mitral valve prolapse who have documented but unexplained TIA or ischemic stroke, long term aspirin therapy (50 to 100 mg/day) is recommended.</li> <li>• In patients with mitral valve prolapse who have AF, documented systemic embolism or recurrent TIAs despite aspirin therapy, long term VKA therapy is suggested.</li> <li>• In patients with mitral annular calcification complicated by systemic embolism, ischemic stroke or TIA, who do not have AF, aspirin (50 to 100 mg/day) is recommended. For recurrent events despite aspirin therapy, treatment with VKA therapy is suggested to be considered. In patients with mitral annular calcification who have a single embolus documented to be calcific, the data is not sufficient to allow recommendation for or against antithrombotic therapy.</li> <li>• In patients with isolated calcific aortic valve disease who have experienced ischemic stroke or TIA not attributable to another source, aspirin (50 to 100 mg/day) is suggested.</li> <li>• In patients with ischemic stroke associated with aortic atherosclerotic</li> </ul>

Clinical Guideline	Recommendations
	<p>lesions, low dose aspirin (50 to 100 mg/day) over no therapy is recommended. For patients with ischemic stroke associated with mobile aortic arch thrombi, therapy with either VKAs or low dose aspirin (50 to 100 mg/day) is suggested.</p> <ul style="list-style-type: none"> <li>• In patients with ischemic stroke and a patent foramen ovale, antiplatelet agent therapy is recommended. Antiplatelet agent therapy is suggested over VKA therapy.</li> <li>• In patients with mechanical heart valves who have additional risk factors for thromboembolism, such as AF, hypercoagulable state, or low ejection fraction, or who have a history of atherosclerotic vascular disease, the addition of low dose aspirin (50 to 100 mg/day) to long term VKA therapy is recommended. It is suggested that aspirin not be added to VKA therapy in patients with mechanical heart valves who are at particularly high risk bleeding; such as in patients with a history of gastrointestinal bleed or in patients &gt;80 years of age.</li> <li>• In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, aspirin (50 to 100 mg/day) is recommended.</li> <li>• In patients with bioprosthetic valves who have additional risk factors for thromboembolism, including AF, hypercoagulable state, or low ejection fraction, VKA therapy is recommended. The addition of low dose aspirin (50 to 100 mg/day) is suggested to be considered, particularly in patients with history of atherosclerotic vascular disease. It is suggested that aspirin not be added to long term VKA therapy patients with bioprosthetic heart valves who are at particularly high risk of bleeding, such as patients with history of gastrointestinal bleed or in patients &gt;80 years of age.</li> <li>• For patients who have had successful resolution of PVT, the initiation of IV unfractionated heparin (UFH) and VKA therapy is suggested. IV UFH is suggested to be continued until a therapeutic INR is achieved. For a mechanical valve in the aortic position, it is suggested that a higher INR be maintained plus aspirin (50 to 100 mg/day). For a mechanical valve in the mitral position, it is suggested that a higher INR be maintained plus aspirin (50 to 100 mg/day).</li> </ul>
<p>American College of Cardiology/American Heart Association:  <b>American College of Cardiology/American Heart Association 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (2007)</b><sup>9</sup></p>	<p><u>Early hospital care</u></p> <ul style="list-style-type: none"> <li>• Aspirin should be administered as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication.</li> <li>• Clopidogrel should be administered to unstable angina/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.</li> <li>• In patients with a history of gastrointestinal bleeding, when aspirin and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors [PPIs]) should be prescribed concomitantly.</li> <li>• In patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel or an IV GP IIb/IIIa inhibitor.</li> <li>• In patients in whom an early initial conservative (i.e., noninvasive) strategy is selected, clopidogrel should be added to aspirin and anticoagulant therapy as soon as possible after admission, and administered for at least one month and ideally up to one year.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>• In patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, heart failure or serious arrhythmias subsequently appear, then diagnostic angiography should be performed. Either an IV GP IIb/IIIa inhibitor or clopidogrel should be added to aspirin and anticoagulant therapy before diagnostic angiography (upstream).</li> <li>• For patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, or who undergo stress testing and are determined to be “low risk”, continue aspirin indefinitely. Continue clopidogrel for at least one month and ideally up to one year.</li> <li>• For patients in whom CABG surgery is selected, continue aspirin. Discontinue clopidogrel five to seven days before elective CABG.</li> <li>• For patients in whom PCI is selected, continue aspirin. Administer a loading dose of clopidogrel if not started before diagnostic angiography.</li> <li>• For patients in whom medical therapy is selected after angiography and in whom no significant obstructive CAD was found, 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 stenoses), long-term treatment with aspirin and other secondary prevention measures should be prescribed.</li> <li>• For patients in whom medical therapy is selected after angiography and in whom CAD was found on angiography, continue aspirin. Administer a loading dose of clopidogrel if not given before diagnostic angiography.</li> <li>• For patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, continue aspirin indefinitely. Continue clopidogrel for at least one month and ideally up to one year.</li> </ul> <p><u>Long-term medical therapy and secondary prevention</u></p> <ul style="list-style-type: none"> <li>• For patients treated medically without stenting, aspirin (75 to 162 mg/day) should be prescribed indefinitely. Clopidogrel (75 mg/day) should be prescribed for at least one month and ideally for up to one year. For aspirin-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization. For clopidogrel-allergic patients, use ticlopidine (250 mg twice daily).</li> <li>• For unstable angina/NSTEMI patients treated with BMS, aspirin (162 to 325 mg/day) should be prescribed for at least one month, and then continued indefinitely (75 to 162 mg/day). Clopidogrel (75 mg/day) should be prescribed for a minimum of one month and ideally for up to one year (unless the patient is at increased risk of bleeding, then it should be given for a minimum of two weeks).</li> <li>• For unstable angina/NSTEMI patients treated with DES, aspirin 162 to 325 mg/day should be prescribed for at least three months after sirolimus-eluting stent implantation, and six months after paclitaxel-eluting stent implantation then continued indefinitely at a dose of 75 to 162 mg/day. Clopidogrel 75 mg/day should be given for at least 12 months to all post-PCI patients receiving DES.</li> <li>• Clopidogrel 75 mg/day (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as PPIs).</li> </ul>

Clinical Guideline	Recommendations
<p>European Society of Cardiology: <b>Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes (2007)</b><sup>10</sup></p>	<ul style="list-style-type: none"> <li>• Aspirin is recommended for all patients presenting with NSTEMI ACS without contraindication at an initial loading dose of 160 to 325 mg (nonenteric), and at a maintenance dose of 75 to 100 mg long term.</li> <li>• For all patients, an immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily. Clopidogrel should be maintained for 12 months, unless there is an excessive risk of bleeding.</li> <li>• For all patients with contraindication to aspirin, clopidogrel should be given instead.</li> <li>• In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function.</li> <li>• In patients pretreated with clopidogrel who need to undergo CABG, surgery should be postponed for five days for clopidogrel withdrawal if clinically feasible.</li> <li>• Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered with aspirin or clopidogrel.</li> <li>• Interruption of dual antiplatelet therapy with aspirin and clopidogrel during the first 12 months after the initial event is not recommended unless severe, life-threatening bleeding occurs, or surgery is to be performed during which minor bleeding may result in serious consequences.</li> </ul>
<p>American College of Cardiology/American Heart Association: <b>2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)</b><sup>11</sup></p>	<ul style="list-style-type: none"> <li>• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients unless contraindicated.</li> <li>• The use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.</li> </ul>
<p>European Society of Cardiology: <b>Management of Stable Angina Pectoris (2006)</b><sup>12</sup></p>	<p><u>Therapy to improve prognosis</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• The use of unopposed cyclooxygenase (COX)-2 inhibition is not recommended in patients with stable angina pectoris.</li> <li>• 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.</li> <li>• Dipyridamole is not recommended for antithrombotic treatment of stable angina.</li> </ul>
<p>American College of Cardiology/American Heart Association and American College of Cardiology/American Heart Association/ Society for Cardiovascular Angiography and Interventions:</p>	<p><u>STEMI and PCI focused update section</u></p> <ul style="list-style-type: none"> <li>• Recommendations for the use of thienopyridines: <ul style="list-style-type: none"> <li>○ A loading dose of thienopyridines is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following: <ul style="list-style-type: none"> <li>▪ At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI.</li> <li>▪ Prasugrel 60 mg should be given as soon as possible for primary PCI.</li> </ul> </li> </ul> </li> </ul>

Clinical Guideline	Recommendations
<p><b>2009 Focused Update of the 2007 Focused Update and the 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction AND Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update) (2009)<sup>13</sup></b></p>	<ul style="list-style-type: none"> <li>▪ For STEMI patients undergoing nonprimary PCI, the following regimens are recommended:                             <ul style="list-style-type: none"> <li>• If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice.</li> <li>• If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice.</li> <li>• If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than one hour after the PCI.</li> </ul> </li> <li>○ The duration of thienopyridine therapy should be as follows:                             <ul style="list-style-type: none"> <li>▪ In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg/day or prasugrel 10 mg/day should be given for at least 12 months.</li> <li>▪ If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered.</li> </ul> </li> <li>○ In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least five days in patients receiving clopidogrel and at least seven days in patients receiving prasugrel, unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding.</li> <li>○ Continuation of clopidogrel and prasugrel beyond 15 months may be considered in patients undergoing DES placement.</li> <li>○ In STEMI patients with a prior history of stroke and TIA for whom primary PCI is planned, prasugrel is not recommended as part of a dual antiplatelet therapy regimen.</li> </ul> <p><u>Recommendations for the timing of angiography and antiplatelet therapy in unstable angina/NSTEMI</u></p> <ul style="list-style-type: none"> <li>• Patients with definite or likely unstable angina/NSTEMI selected for an invasive approach should receive dual-antiplatelet therapy. Aspirin should be initiated on presentation. Clopidogrel (before or at the time of PCI) or prasugrel (at the time of PCI) is recommended as a second antiplatelet agent.</li> <li>• It is reasonable for initially stabilized high risk patients with unstable angina/NSTEMI to undergo an early invasive strategy within 12 to 24 hours of admission. For patients not at high risk, an early invasive approach is also reasonable.</li> </ul>
<p>National Institute for Health and Clinical Excellence: <b>Myocardial Infarction: Secondary Prevention</b></p>	<ul style="list-style-type: none"> <li>• Aspirin is recommended in all patients after a MI and should be continued indefinitely. Clopidogrel should not be offered as first-line monotherapy after a MI.</li> <li>• Clopidogrel combined with low dose aspirin for 12 months is recommended in patients who have had a NSTEMI ACS who are at</li> </ul>

Clinical Guideline	Recommendations
<p><b>in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)</b><sup>14</sup></p>	<p>moderate to high risk of MI or death. Thereafter, patients may be treated with low-dose aspirin without clopidogrel in the absence of indication for dual antiplatelet therapy.</p> <ul style="list-style-type: none"> <li>• Patients who have been treated with aspirin and clopidogrel within the first 24 hours of an STEMI should continue on dual antiplatelet therapy for at least four weeks. Thereafter, low-dose aspirin should be continued, and clopidogrel discontinued in the absence of indication for dual antiplatelet therapy.</li> <li>• If both clopidogrel and aspirin were not given during the acute phase of a MI, this combination should not routinely be initiated.</li> <li>• Dual antiplatelet therapy with aspirin and clopidogrel should not be used for longer than 12 months after an acute MI unless another indication for dual antiplatelet therapy exists. After a STEMI, the combination of aspirin and clopidogrel is usually recommended for a shorter duration than 12 months.</li> <li>• Clopidogrel monotherapy is an alternative treatment in patients with aspirin hypersensitivity.</li> <li>• Low dose aspirin and a PPI are recommended in patients with comorbid dyspepsia. A full dose PPI and low dose aspirin should be considered in patients with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for <i>Helicobacter pylori</i>.</li> <li>• Patients being treated with warfarin for another indication should continue on warfarin. Those being treated with moderate-intensity warfarin (international normalized ratio 2.0 to 3.0) and are at low risk of bleeding, may be treated with aspirin. The combination of warfarin and clopidogrel is not routinely recommended.</li> </ul>
<p>National Institute for Health and Clinical Excellence: <b>Clopidogrel and Modified-Release Dipyridamole for the Prevention of Occlusive Vascular Events (2010)</b><sup>15</sup></p>	<ul style="list-style-type: none"> <li>• This guidance applies to people who have had an occlusive vascular event, or who have established peripheral arterial disease (PAD). This guidance does not apply to people who have had, or are at risk of, a stroke associated with AF, or who need treatment to prevent occlusive events after coronary revascularization or carotid artery procedures.</li> <li>• For people who have had an ischemic stroke, clopidogrel is recommended as a treatment option. For people who have a contraindication or intolerance to clopidogrel, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to both clopidogrel and aspirin, modified-release dipyridamole alone is recommended as a treatment option.</li> <li>• For people who have had a TIA, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to aspirin, modified-release dipyridamole alone is recommended as a treatment option.</li> <li>• For people who have had a MI, clopidogrel is recommended only when treatment with aspirin is contraindicated or not tolerated.</li> <li>• For people with PAD, clopidogrel is recommended as a treatment option.</li> <li>• For people with multivascular disease, clopidogrel is recommended as a treatment option.</li> <li>• Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.</li> </ul>
<p>American College of Cardiology/American Heart Association:</p>	<p><u>Antiplatelet and antithrombotic drugs</u></p> <ul style="list-style-type: none"> <li>• Antiplatelet therapy is indicated to reduce the risk of MI, stroke or vascular death in individuals with atherosclerotic lower extremity PAD.</li> </ul>

Clinical Guideline	Recommendations
<p><b>American College of Cardiology/American Heart Association 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (2005)</b><sup>16</sup></p>	<ul style="list-style-type: none"> <li>Aspirin (75 to 325 mg/day) is recommended as safe and effective antiplatelet therapy.</li> <li>Clopidogrel (75 mg/day) is recommended as an effective alternative antiplatelet therapy.</li> <li>Warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD.</li> </ul>
<p>European Society of Cardiology, Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease: <b>Expert Consensus Document on the Use of Antiplatelet Agents (2004)</b><sup>17</sup></p>	<p><u>Major recommendations for individual antiplatelet agents</u></p> <p>Aspirin:</p> <ul style="list-style-type: none"> <li>Aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile.</li> <li>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.</li> <li>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., <math>\geq 3\%</math> per annum).</li> <li>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 A<sub>2</sub>-dependent platelet aggregation.</li> <li>No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.</li> <li>The routine use of PPIs 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.</li> <li>NSAIDs 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.</li> <li>Because of potential pharmacodynamic interactions between traditional NSAIDs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring NSAID therapy may benefit from the use of selective COX-2 inhibitors.</li> </ul> <p>Ticlopidine:</p> <ul style="list-style-type: none"> <li>The role of ticlopidine in the present therapeutic armamentarium is uncertain.</li> <li>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.</li> <li>In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent MI.</li> </ul> <p>Clopidogrel:</p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>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 NSTEMI/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.</li> </ul> <p>Dipyridamole:</p> <ul style="list-style-type: none"> <li>Although the combination of low-dose aspirin and extended-release dipyridamole (200 mg twice a day) is considered an acceptable option for initial therapy of patients with noncardioembolic cerebral ischemic events, there is no basis to recommend this combination in patients with ischemic heart disease.</li> </ul>

### Conclusions

The platelet inhibitors play an important role in the treatment and prevention of cerebrovascular and cardiovascular diseases. Anagrelide (Agrylin<sup>®</sup>), dipyridamole (Persantine<sup>®</sup>) and ticlopidine are available generically, and single-entity aspirin is available in several over-the-counter formulations. Clopidogrel (Plavix<sup>®</sup>) and the fixed-dose combination product of aspirin and dipyridamole extended-release (ER) (Aggrenox<sup>®</sup>) are not available generically. Aggrenox<sup>®</sup> is not interchangeable with the commercially available generic formulations of aspirin and dipyridamole since the strengths and delivery mechanisms are different among these products.<sup>1-6</sup>

Aspirin has been the most frequently studied platelet inhibitor and is usually the reference drug to which other treatments are compared.<sup>38</sup> Aspirin is the platelet inhibitor recommended as first line in most treatment guidelines for general use. Aspirin is recommended as a first line option for the initial management of noncardioembolic stroke or transient ischemic attack (TIA), acute coronary syndrome (ACS), and myocardial infarction (MI), and for primary and secondary prevention in patients with cerebrovascular, cardiovascular and peripheral vascular diseases. Low dose aspirin (75 to 150 mg/day) is an effective platelet inhibitor regimen for long term use, but in acute settings an initial loading dose of  $\geq 150$  mg aspirin 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 and clopidogrel is recommended for patients with ACS (non ST-elevation MI and unstable angina) or ST-elevation MI (STEMI), or who undergo percutaneous coronary intervention (PCI) with stenting. 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.<sup>7-17</sup> 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.<sup>29</sup> 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.<sup>7</sup>

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.<sup>39</sup> On the basis of the CURE, COMMIT and CLARITY trials, clopidogrel received a Food and Drug Administration (FDA) indication for the reduction of atherothrombotic events in patients with ACS and MI, and clopidogrel has been incorporated

into the current treatment guidelines for the management of these conditions.<sup>8,24,43,47</sup> Effient<sup>®</sup> (prasugrel) is the newest adenosine diphosphate receptor antagonist to be FDA approved. It 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.<sup>21-23</sup> 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 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.<sup>58</sup> A focused update from 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 planned, is not recommended.<sup>13</sup>

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.<sup>34,35</sup> 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.<sup>56</sup> 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.<sup>5</sup>

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.<sup>26,28</sup> Dipyridamole plus aspirin 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.<sup>26</sup> Dipyridamole plus aspirin 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.<sup>24</sup>

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.<sup>1,66-71</sup>

#### Appendix I: Utilization Within This Drug Class for DVHA: October 1, 2010 to March 31, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Plavix	539	1,037	89.63%	\$421,463.49	\$406.43
Cilostazol	32	55	4.75%	\$2,755.68	\$50.10
Aggrenox	14	30	2.59%	\$9,874.04	\$329.13
Effient	13	22	1.90%	\$8,993.07	\$408.78
Ticlopidine	2	5	0.43%	\$194.07	\$38.81
Dipyridamole	2	4	0.35%	\$407.69	\$101.92
Anagrelide	2	4	0.35%	\$1,032.40	\$258.10
<b>Class Total:</b>	<b>604</b>	<b>1,157</b>	<b>100%</b>	<b>\$444,720.44</b>	<b>\$384.37</b>

#### Recommendations

In recognition of the following factors:

- The well established role of the platelet inhibitors in the management of cardiovascular, cerebrovascular and peripheral vascular diseases.
- The evidence demonstrating a clinical benefit of Plavix<sup>®</sup> (clopidogrel), the recommendations from guidelines and the more favorable safety profile associated with clopidogrel compared to ticlopidine.

- The evidence demonstrating a clinical benefit of Aggrenox<sup>®</sup> (aspirin/dipyridamole extended-release [ER]), the recommendations from guidelines and the recognition that the combination product cannot be interchanged with the individual drug components.
- The availability of generic anagrelide, dipyridamole and ticlopidine.

...it is recommended that the generic for Agrylin<sup>®</sup> (anagrelide) be added to the Department of Vermont Health Access (DVHA) preferred drug list (PDL) as preferred and the brand be added as PA required (see criteria below). No other changes to the platelet aggregation inhibitors managed category are recommended.

Agrylin:

- The patient has had a documented intolerance to the generic formulation of the medication.

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