Platelets play a central role in both the short- and long-term manifestations of atherothrombosis. In acute coronary syndrome (ACS), there is a steep rise in cardiovascular events early, followed by an incremental rise in cardiovascular events over the long term. This long-term event rate is related to persistent platelet activation and thrombin generation. There is therefore a need to optimize both short- and long-term oral antiplatelet and antithrombotic strategies. The benefits of aspirin therapy, when administered early and continued over the long term, were demonstrated in several early randomized trials. The Antithrombotic Trialists’ Collaboration found a 46% reduction in vascular events with antiplatelet therapy (mostly aspirin). However, despite treatment with aspirin and proven therapies, recurrent events remain high. The adenosine diphosphate receptor antagonists, ticlopidine and clopidogrel, inhibit the early steps of platelet activation, degranulation, and release of prothrombotic and inflammatory mediators, while also preventing activation of the glycoprotein IIb/IIIa receptor. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial demonstrated the benefits of aspirin plus clopidogrel in reducing major cardiovascular events (cardiovascular death, myocardial infarction [MI], and stroke reduced by 20%, p = 0.00009) in a broad range of patients with ACS when administered early and continued over the long term. The benefits emerge very rapidly after a 300 mg loading dose. For the large number of patients undergoing percutaneous coronary intervention in the CURE trial, there was a substantial risk reduction with clopidogrel pretreatment followed by long-term therapy (p < 0.002). This benefit was present, regardless of whether intervention was performed early or late. The significant benefits of aspirin and clopidogrel persist for the combined efficacy-safety end point of cardiovascular death, MI, stroke, or life-threatening bleeding when clopidogrel is started early, combined with aspirin and other standard therapies, and continued for up to one year. (J Am Coll Cardiol 2003;41:79S–88S) © 2003 by the American College of Cardiology Foundation

The role of platelets in atherothrombosis. Platelets play a central role in the pathophysiology of atherothrombosis. There are three essential steps involved in the formation of a platelet-rich thrombus after plaque disruption: platelet adhesion, platelet activation, and platelet aggregation. Platelet adhesion occurs shortly after an atherosclerotic plaque has ruptured, eroded, or become disrupted, and it is mediated mainly via the platelet glycoprotein (GP) IIb receptor through its interaction with von Willebrand factor. Platelet activation involves several interrelated processes (Fig. 1). First, the three-dimensional shape of the platelet changes from a smooth discoid appearance into a spinculated form, greatly increasing the surface area of the platelet membrane where thrombin is generated. Next, degranulation or secretion of alpha and dense granules takes place within the platelet. This releases the prothrombotic, inflammatory, and chemo-attractant mediators that propagate, amplify, and sustain the atherothrombotic process. Finally, platelet activation leads to a conformational change in the GP IIb/IIIa receptor, converting the receptor into a form that can bind fibrinogen and link with other platelets (platelet aggregation). This final step occurs relatively late, after atherothrombosis is already far advanced.

Rationale for long-term therapy. In patients with acute coronary syndrome (ACS), there is an ongoing thrombotic stimulus, characterized by persistent platelet activation and thrombin generation. Over months or years, this process plays an important role in the genesis of recurrent ischemic events. Clinically, the results are seen during long-term follow-up of patients with unstable angina or non–ST-segment elevation myocardial infarction (NSTEMI), in whom there is a high rate of recurrent major ischemic events. For example, in a six-month follow-up after hospital discharge of over 8,000 patients with unstable angina or NSTEMI, about 6% of patients developed cardiovascular death, myocardial infarction (MI), or stroke (1). A two-year follow-up found an event rate of approximately 6% to 8% per year (2). Such results have focused attention on the need to optimize long-term oral antiplatelet and antithrombotic strategies in patients with ACS, to accompany standard approaches such as statin therapy, angiotensin-converting enzyme (ACE) inhibition, and smoking cessation.

The clinical observations have been supported by an
increasing accumulation of angioscopic, angiographic, and biochemical data. First, angioscopic studies have shown that, despite the use of short-term antithrombotic therapies, coronary thrombi are still present for up to 30 days after an acute ischemic event. Therefore, a longer duration of antithrombotic therapy may be required to reduce events, perhaps allowing passivation of the culprit lesion (3). Second, there is now good evidence to suggest that patients with ACS have, in addition to the culprit lesion, multiple complex coronary plaques that are associated with adverse clinical outcomes. For example, in a careful angiographic study, patients who were found to have multiple complex coronary plaques had an 11-fold increase in recurrent ACS and a six- to seven-fold increase in multiple adverse cardiac events (4). This suggests that plaque instability may be caused by a widespread process affecting the entire coronary tree (e.g., an inflammatory process) rather than by a single culprit lesion. Third, angioscopic studies have indicated a high rate of coronary thrombi in the coronary artery not supplying the culprit vessel (5). Fourth, biochemical studies have indicated persistent platelet hyperactivity and elevation of markers of the coagulation system, suggesting that the environment for re-thrombosis is still present many months after the initial event (6–8). Fifth, as indicated earlier, long-term studies have demonstrated a significant increase in major cardiovascular events, despite modern day treatments (1,9). In addition, once most short-term antithrombotic therapies are terminated, no added benefit is demonstrated, and clinical events accumulate in both treatment and control groups. This suggests that longer-term antithrombotic therapy is needed (10,11). Such intriguing observations, when coupled with emerging data on the importance of inflammation and coagulation in atherothrombosis, support the concept that a generalized, persis-

**Figure 1.** Platelet activation is an important early step in the pathophysiology of atherothrombosis. Platelet activation involves: 1) a shape change in which the platelet membrane surface area is greatly increased; 2) the secretion of pro-inflammatory, prothrombotic, adhesive, and chemotactic mediators (release reaction), that propagate, amplify, and sustain the atherothrombotic process; and 3) the activation of the glycoprotein (GP) IIb/IIIa receptor from its inactive form. Multiple agonists including thromboxane A2 (TXA2), adenosine diphosphate (ADP), thrombin, serotonin, epinephrine, and collagen, can activate the platelet and thus contribute toward establishing the environmental conditions necessary for atherothrombosis to occur. Aspirin inhibits the production of thromboxane A2 by its effect on the enzyme cyclooxygenase (COX) 1. The ADP receptor antagonists clopidogrel and ticlopidine prevent the binding of ADP to its receptor. The effect of combining aspirin and clopidogrel is synergistic in preventing platelet aggregation. Antithrombins such as unfractionated or low-molecular-weight heparin, hirudin, or bivalirudin are important in interfering with both thrombin-induced platelet activation and coagulation. The GP IIb/IIIa receptor antagonists act at a later step in the process by preventing fibrinogen mediated cross-linking of platelets, which have already become activated. ATP = adenosine triphosphate; PAI = plasminogen activator inhibitor; PDGF = platelet-derived growth factor; vWF = von Willebrand factor.
tent process is an important feature of future plaque disruptions and ischemic events. Acute coronary events commonly result from thrombosis triggered by plaque disruption. Therefore, functional attributes of the plaque, rather than the degree of stenosis alone, may determine the propensity of plaques to rupture, to produce a superimposed thrombus, and ultimately to provoke ischemic events (12). Thus, long-term antithrombotic therapy with additional risk-factor modification has the potential to make a major impact in the prevention of recurrent events. This article focuses primarily on the role of oral antithrombotic therapies in ACS and percutaneous coronary intervention (PCI), including aspirin, and the adenosine diphosphate (ADP) receptor antagonists, clopidogrel and ticlopidine, alone and in combination.

**Aspirin.** Aspirin inhibits platelet cyclooxygenase by irreversible acetylation, thereby preventing the formation of thromboxane A$_2$. In addition to the anti-platelet effects, aspirin also has anti-inflammatory activity, which may contribute to its clinical effectiveness in ACS (Fig. 1). There have been four key randomized trials testing the use of aspirin in unstable angina (Table 1) (13–16). These early studies were performed in the 1970s and 1980s, before the routine use of currently used therapies including heparin, clopidogrel and glycoprotein IIb/IIIa antagonists. They were also performed before the widespread use of invasive procedures such as PCI and coronary artery bypass graft (CABG) surgery, which are now commonly performed in patients with unstable angina and NSTEMI. Nevertheless, these trials individually demonstrated benefits of aspirin over both placebo and untreated control in reducing ischemic events, and they have led to the universal recommendation of aspirin as standard therapy in ACS.

The first large study was the Veterans Affairs (VA) trial, performed between 1974 and 1981, involving 1,338 patients with unstable angina who were treated with 12 weeks of aspirin versus control (13). This study demonstrated a 41% reduction in death or MI (10.1% in the placebo group vs. 5.0% with acetylsalicylic acid, $p = 0.004$) with 12 weeks of treatment with aspirin at a dose of 325 mg daily (13). Mortality was reduced in this trial from 3.3% to 1.6% ($p = 0.054$) with aspirin. In the Canadian Multicenter Trial aspirin therapy was given much longer than in the VA trial, for an average of 18 months after an episode of unstable angina. This study of 555 patients was performed between 1979 and 1984 and demonstrated that aspirin (325 mg four times daily) was superior to control, with a 30% reduction in death or MI at two years ($p = 0.072$ in the intention-to-treat analysis) and a 43% reduction in death alone ($p = 0.035$) (14). In the Montreal Heart study (n = 479), aspirin (325 mg twice daily) given for a very short period (only 6 days) reduced death or MI by 63% (6.3% vs. 2.6%, $p = 0.04$) (15). In the Research on InStability Coronary artery disease (RISC) study, aspirin in a lower dose of 80 mg daily given for one year reduced death or MI by 49% in the 796 patients meeting the inclusion criteria (total of 945 patients randomized) (21.4% vs. 11%, $p = 0.0001$) (16).

In the Antithrombotic Trialists' Collaboration overview (17), among all patients who were at high risk for vascular events, there was a 22% reduction in the composite of vascular death, MI, or stroke (13.2% vs. 10.7%, $p < 0.0001$). Vascular death alone was reduced by 15% ($p < 0.0001$). Among the subset of patients with unstable angina, there was a 46% reduction in vascular events (13.3% vs. 8.0%, $p < 0.0001$) (Table 1).

Aspirin also reduces the frequency of ischemic complications when started before, and continued after, PCI. In an early study of 376 patients undergoing (mostly elective) angioplasty, patients were randomized to receive either aspirin (990 mg) and dipyridamole (225 mg daily) or placebo starting 24 h before angioplasty and continuing for four to seven months after surgery (18). Although the antiplatelet therapy had no effect on reducing the frequency of restenosis, there was a large reduction in periprocedural Q-wave MI when antiplatelet therapy was started before the procedure (6.9% vs. 1.6%; $p = 0.011$). In the only randomized trial of long-term aspirin therapy following angioplasty, aspirin (325 mg daily) given for six months was associated with a significant reduction in MI compared with placebo (1.2% vs. 5.7%; $p = 0.03$) (19).

### Table 1. Randomized Trials of Acetylsalicylic Acid in Unstable Angina

<table>
<thead>
<tr>
<th>Trial (Ref)</th>
<th>Treatment</th>
<th>Follow-Up</th>
<th>Aspirin</th>
<th>Control</th>
<th>Relative Risk Reduction</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterans Affairs Study, 1983 (13)</td>
<td>ASA 325 mg daily vs. placebo</td>
<td>3 months</td>
<td>31/625 (5.0%)</td>
<td>65/641 (10.1%)</td>
<td>41%</td>
<td>0.004</td>
</tr>
<tr>
<td>Canadian Study, 1985 (14)*</td>
<td>ASA 325 mg 4 times daily or control</td>
<td>18 months (mean)</td>
<td>29/276 (10.5%)</td>
<td>41/279 (14.6%)</td>
<td>30%*</td>
<td>0.072</td>
</tr>
<tr>
<td>Montreal Heart Study, 1988 (15)</td>
<td>ASA 650 mg first dose then 325 mg twice daily for 6 days or placebo</td>
<td>6 days</td>
<td>6/243 (2.5%)</td>
<td>15/236 (6.4%)</td>
<td>63%</td>
<td>0.04</td>
</tr>
<tr>
<td>RISC, 1990 (16)</td>
<td>ASA 75 mg for 3 months or placebo</td>
<td>13 months</td>
<td>26/399 (6.5%)</td>
<td>68/397 (17%)</td>
<td>64%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Antithrombotic Trialists' Collaboration Meta-analysis (17)*</td>
<td>Various regimens vs. placebo/ untreated control</td>
<td>various</td>
<td>8.0%</td>
<td>13.3%</td>
<td>46%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Intention to treat analysis is presented. Mortality alone was reduced by 43%, $p = 0.035$. †End point reported is vascular death, MI, or stroke.

ASA = acetylsalicylic acid; RISC = Research on InStability in Coronary artery disease.
The consistent benefit of aspirin in these early studies provides clear proof that effective long-term antiplatelet therapy can improve the prognosis in ACS and PCI. Despite the proven benefits of aspirin, however, recurrent events remain high (8). This underscores the need to continue the search for new agents that can either replace or be used in addition to aspirin for short- and long-term management.

**ADP receptor antagonists in atherothrombosis.** The ADP receptor antagonists, ticlopidine and clopidogrel, are antiplatelet agents that inhibit the early step of platelet activation (Fig. 1). They prevent platelet degranulation and the release reaction, which elaborates prothrombotic and inflammatory mediators from the platelet and also inhibits the transformation of the GP IIb/IIIa receptor to the form that binds fibrinogen and links platelets. These agents act early in the sequence of events leading to the formation of the platelet thrombus, effectively inhibiting platelet aggregation. Ticlopidine and clopidogrel selectively and irreversibly prevent ADP from binding to the platelet ADP receptor P2Y_{12} (20,21). (The active metabolite of clopidogrel is a short-lived thiol derivative of the parent molecule.)

Although both clopidogrel and ticlopidine have been found to be useful clinically for patients with atherosclerosis, ticlopidine is limited by its potential to cause severe neutropenia in about 1% of patients, necessitating close monitoring of blood counts during the first few weeks or months of treatment (22). Also, the full antiplatelet action of ticlopidine is delayed for several days after therapy is initiated, limiting its usefulness in acute situations. By contrast, the full antiplatelet action of clopidogrel takes effect rapidly after a 300 mg bolus, with almost maximal antiplatelet effect observed after only 2 h (23).

In a randomized trial conducted 10 years ago that compared ticlopidine with placebo in 662 patients with unstable angina, there was a 46% reduction in the primary end point of cardiovascular death or MI with ticlopidine (p = 0.009) (24). In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, clopidogrel was directly compared with aspirin in a broad range of patients with atherosclerotic disease for the secondary prevention of ischemic events (25). Patients in the clopidogrel arm of the trial did not receive aspirin. Compared to aspirin, and at a mean of 1.9 years follow-up, clopidogrel was found to significantly reduce the primary outcome of vascular death, MI, or ischemic stroke by 8.7% (95% confidence interval [CI], 0.3% to 16.5%).

**Combination therapy: aspirin and an ADP receptor antagonist in patients after stenting.** The ADP receptor antagonists and aspirin act through complementary and independent mechanisms, and their combination can inhibit both ADP-induced platelet aggregation and thromboxane A2 production (26–28). The superiority of this combination compared with aspirin alone has been demonstrated convincingly in several randomized trials in patients after coronary artery stenting (29–34). A meta-analysis of these trials found a clear benefit from aspirin plus ticlopidine in reducing death and non-fatal MI compared with aspirin alone (odds ratio [OR], 0.23; 95% CI, 0.11 to 0.49; p = 0.0001) or aspirin plus warfarin (OR, 0.51; 95% CI, 0.33 to

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**Table 2. Main Results From the CURE Trial**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo + Aspirin*</th>
<th>Clopidogrel + Aspirin*</th>
<th>Relative Risk Reduction</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>9.3% N = 6303</td>
<td>11.4% N = 6259</td>
<td>0.80</td>
<td>0.00009</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>5.1%</td>
<td>5.5%</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2%</td>
<td>1.4%</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6.7%</td>
<td>5.2%</td>
<td>23%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ST elevation myocardial infarction (Q-wave MI)</td>
<td>3.1%</td>
<td>1.9%</td>
<td>40%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>2.0%</td>
<td>1.1%</td>
<td>43%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4.4%</td>
<td>3.7%</td>
<td>18%</td>
<td>0.03</td>
</tr>
</tbody>
</table>


*In addition to other standard therapies.

CURE = Clopidogrel in Unstable angina Recurrent Events; MI = myocardial infarction.
There have been several observational studies and clinical trials comparing the effects of ticlopidine with the effects of clopidogrel. A meta-analysis of the studies (registries and clinical trials) suggests that the aspirin–plus–ticlopidine combination is at least as efficacious as the aspirin–plus–ticlopidine combination in patients receiving an intracoronary stent (36).

**Aspirin and clopidogrel in ACS: the CURE trial.** The Clopidogrel in Unstable angina Recurrent Events (CURE) trial was designed to test the hypothesis that the clopidogrel–plus–aspirin combination is superior to aspirin alone when initiated early and continued for the long term in the prevention of cardiovascular death, MI, or stroke in patients with NSTE ACS (unstable angina/NSTEMI) (35). The CURE trial was a double-blind, placebo-controlled, international, randomized trial of short- and long-term therapy with clopidogrel versus placebo, in addition to aspirin and other contemporary therapies (including low-molecular-weight and unfractionated heparin, beta-blockers, ACE inhibitors, and lipid-lowering therapies) in patients with NSTE ACS. Patients were eligible if they presented within 24 h of chest pain onset and had objective evidence of ischemia in the form of either elevated cardiac enzymes (or troponin) or electrocardiogram changes compatible with myocardial ischemia (such as ST depression, T-wave inversion, or transient ST elevation). Aspirin was administered to all patients in doses of 75 to 325 mg (median dose, 160 mg). After randomization, no restrictions were placed on the use of other procedures (such as percutaneous transluminal coronary angioplasty [PTCA] or CABG surgery) or medications (including the GP IIb/IIIa antagonists). Overall, 12,652 patients were recruited at 482 hospitals in 28 countries. Of these, 5,491 patients (44%) underwent angiography, 2,072 (16.5%) had CABG surgery, and 2,658 (21.2%) underwent PCI.

A highly significant 20% relative risk reduction (RR) was found with clopidogrel versus placebo in the first co-primary outcome of MI, stroke, or cardiovascular death (9.3% vs. 11.4%; relative RR, 0.80; 95% CI, 0.72 to 0.90; \( p = 0.00009 \)) (Table 2, Fig. 2) (37). Consistent reductions were observed in all components of the primary composite end point, with a 7% reduction in cardiovascular death (5.1% vs. 5.5%; relative RR, 0.93) and a 14% reduction in stroke (1.2% vs. 1.4%; RR, 0.86), but the clearest effect was a 23% reduction in MI (5.2% vs. 6.7%; RR, 0.77). Of these, the most pronounced reduction was in large MIs (with ST elevation or Q-waves), which were reduced by a remarkable 40% (3.1% vs. 1.9%; RR, 0.60; 95% CI, 0.48 to 0.76).

Consistent with this decrease in large MIs was a reduction in the use of thrombolytic therapy (2.0% vs. 1.1%; %RR, 0.57; \( p < 0.001 \)) and in new-onset congestive heart failure with clopidogrel treatment (radiologically confirmed) (4.4% vs. 3.7%; RR, 0.82; \( p = 0.026 \)). These data indicate that the prevention of large MIs with clopidogrel therapy was associated with improved ventricular function, emphasizing the clinical importance of a reduction in these events (Table 2).

**Early benefit of clopidogrel.** The effects of clopidogrel became apparent very early after administration of the 300-mg loading dose, with divergence in the Kaplan–Meier event curves occurring as early as 2 h after randomization. Within 24 h of randomization, a highly significant 34% reduction in cardiovascular death, MI, stroke, or severe ischemia was evident (RR, 0.66; \( p = 0.003 \)). At 30 days, clopidogrel reduced the first primary end point by 21% (\( p < 0.001 \)) (37). During the initial hospitalization, there were reductions in a wide range of other ischemic events, including refractory ischemia, which was defined as: 1) the presence of recurrent chest pain while on maximal medical therapy; 2) the presence of new electrocardiogram changes; and 3) the performance of an intervention by midnight of the next day (2.0% vs. 1.4%; RR, 0.68; \( p = 0.007 \)). “Additional severe ischemia,” defined as recurrent chest pain and new electrocardiogram changes (3.8% vs. 2.8%; RR, 0.74; \( p = 0.003 \)), and “recurrent angina,” which was any other chest pain in hospital (22.9% vs. 20.9%; RR, 0.91; \( p = 0.01 \)), were also reduced. The very rapid emergence of benefits with clopidogrel emphasizes the importance of giving the loading dose immediately after the diagnosis is made (preferably in the emergency room) to obtain the greatest benefits in the largest number of patients.

**Late benefit of clopidogrel.** In the CURE trial, patients were treated with study medication for a maximum of one year after randomization (mean follow-up, nine months). From day 31 up to one year, there was a highly significant incremental reduction of 18% in the primary outcome with clopidogrel (RR, 0.82; \( p < 0.001 \)) (37). This long-term benefit was in addition to the rapid early benefit observed within the first 30 days. Thus, therapy with clopidogrel should continue for the long term—for at least nine months, up to one year. Similar to aspirin, treatment with clopidogrel longer than this period is reasonable, particularly in those patients at increased risk of future events. Safety data with clopidogrel is available for up to three years of treatment in the CAPRIE study, where clopidogrel was generally better tolerated than treatment with aspirin.

**Benefit in addition to proven therapies.** The benefit of clopidogrel was observed in addition to standard therapies already used in unstable angina or NSTEMI, such as aspirin (99.1%), beta-blockers (77.5%), ACE inhibitors (48.9%), lipid-lowering therapy (45.6%), and revascularization with either CABG or PTCA (performed in 38%).

**Benefit in all risk groups.** When the CURE results were stratified according to the TIMI risk score, significant benefits were demonstrated across all levels of risk. Low-risk (4.1% vs. 5.7%; RR, 0.71; RR, 1.6%; \( p < 0.03 \)), intermediate-risk (9.8% vs. 11.4%; RR, 0.71; adjusted RR, 1.6%; \( p < 0.02 \), and high-risk patients (15.9% vs. 20.7%; RR, 0.73; adjusted RR, 4.8%; \( p < 0.003 \)) all benefited, but the greatest absolute benefit was observed in the high-risk patients (38).
Patients with a history of CABG gained additional highly significant advantage from clopidogrel treatment (RR, 0.55; 95% CI, 0.43 to 0.72). Patients undergoing CABG surgery during the initial hospitalization in CURE had a consistent 19% reduction in the primary end point (95% CI, 0.59 to 1.12). Thus, clopidogrel is effective over and above current therapies and across all risk levels, including those patients undergoing CABG surgery after randomization. This emphasizes its value in a very wide spectrum of patients with ACS, irrespective of other medical therapies or interventions used.

**PCI CURE.** The PCI CURE study was a prospectively planned substudy of CURE. Its goals were to investigate: 1) whether patients randomized to clopidogrel derived benefit from pretreatment with clopidogrel and aspirin therapy before angioplasty compared with placebo and aspirin prior to PCI; and 2) whether long-term therapy after PCI is superior to placebo (35,39). Overall, 2,658 patients were included, making PCI CURE one of the largest investigations of contemporary PCI in ACS. Percutaneous coronary intervention was performed at the discretion of the site investigator. After PCI, the vast majority of patients in both treatment arms (>80%) received open-label thienopyridine for a median of 30 days, mainly because of stent placement. Thus, the 30-day results reflect mainly the effects of pretreatment with clopidogrel. The overall results of the PCI CURE substudy from the time of randomization to the end of follow-up (up to one year) revealed a highly significant 31% reduction in cardiovascular death or MI with clopidogrel pretreatment plus long-term therapy after PCI (12.6% vs. 8.8%; RR, 0.69; 95% CI, 0.54 to 0.87; p = 0.002) (Fig. 3). There was a 30% reduction in the primary end point of cardiovascular death, MI, or urgent revascularization from the time of PCI to 30 days (6.4% vs. 4.5%; RR, 0.70; p = 0.03), indicating that pretreatment with clopidogrel was beneficial in preventing major events after PCI. In the per-protocol analysis, when only patients receiving an intracoronary stent were examined, there was a 44% relative RR in cardiovascular death, MI, or urgent target revascularization with clopidogrel pretreatment, compared with placebo (p = 0.017) (40) (Fig. 4).

In the long term, there was a consistent benefit of clopidogrel over placebo from >30 days after PCI to the end of follow-up, during which there was a significant reduction in the combined outcome of cardiovascular death, MI, or rehospitalization (RR, 0.86; p < 0.05). There was also a concurrent reduction in the outcome of cardiovascular death or MI (RR, 0.79; 95% CI, 0.53 to 1.20), consistent with the highly significant overall RR in PCI CURE (Fig. 5) and the late (>30 days) overall benefit in the CURE trial. Furthermore, in patients who had PCI within 72 h of CABG surgery during the initial hospitalization in CURE had a consistent 19% reduction in the primary end point (95% CI, 0.59 to 1.12). Thus, clopidogrel is effective over and above current therapies and across all risk levels, including those patients undergoing CABG surgery after randomization. This emphasizes its value in a very wide spectrum of patients with ACS, irrespective of other medical therapies or interventions used.

**Figure 3.** Percutaneous Coronary Intervention–Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (PCI CURE) trial: overall long-term results from randomization up to one year: cardiovascular death or myocardial infarction. A = median time to PCI; B = 30 days after PCI. ASA = acetylsalicylic acid; PCI = percutaneous coronary intervention. Reprinted with permission from Elsevier Science (The Lancet 2001;358: 527–33).

**Figure 4.** Effects of pretreatment with clopidogrel compared with placebo in stented patients (excludes those receiving open-label thienopyridine before percutaneous coronary intervention [PCI]). All patients received open-label clopidogrel or ticlopidine for a median of 30 days after PCI. Day 0 is the day of PCI. Reprinted with permission from Elsevier Science (The Lancet 2002;359:169).

**Figure 5.** Cardiovascular (CV) death or MI in Percutaneous Coronary Intervention–Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (PCI CURE): consistent benefits of clopidogrel at all non-overlapping time points. MI = myocardial infarction; RRR = relative risk ratio.
admission (n = 544), there was a consistent 38% RR in cardiovascular death or MI (95% CI, 0.37 to 1.05; p = 0.076), compared with patients who delayed intervention (RR, 29%; 95% CI, 0.54 to 0.92; p = 0.01). The benefit of clopidogrel was identical regardless of whether patients underwent PCI during their initial hospitalization (12.0% vs. 8.3%; RR, 0.68; 95% CI, 0.50 to 0.92; p = 0.01) or after discharge (13.8% vs. 9.8%; RR, 0.70; 95% CI, 0.48 to 1.02; p = 0.06). Thus, with both urgent and delayed intervention, consistent benefits were associated with clopidogrel treatment. Taken together, the data from CURE and PCI CURE suggest that in patients with ACS, clopidogrel is beneficial with long-term use, both in patients undergoing PCI and in those treated medically.

**Oral GP IIb/IIIa antagonists.** There have been five large randomized trials of oral GP IIb/IIIa antagonists in patients with a wide range of atherosclerotic disease (41–45). Although these agents once held great promise, there was consistency among all of the randomized trials toward increased mortality with a GP IIb/IIIa agent compared with placebo. A meta-analysis of four large trials in patients with ACS demonstrated a highly significant 37% increase in mortality with the use of a GP IIb/IIIa antagonist (p = 0.001) (46) (Fig. 6). Thirty days after randomization, there was a 40% higher incidence of MI associated with these agents (p = 0.002). Consistent with these results, the large Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO) IV trial of abciximab in ACS demonstrated no benefit and perhaps a trend toward increased mortality at 48 h, compared with 24-h treatment with abciximab (RR, 2.3; p = 0.048 after 24-h abciximab treatment vs. placebo; RR, 2.9; p = 0.007 after 48-h abciximab treatment vs. placebo) (47). In this trial, there was no benefit associated with abciximab in higher-risk patients (e.g., with elevated troponin I or T or those with ST depression at baseline). These results contrast with the proven benefits of short durations of treatment with abciximab and other IV GP IIb/IIIa agents in the setting of PCI (whether or not patients were diagnosed with ACS) (48,49).

The reasons for the increase in mortality with the prolonged use of certain GP IIb/IIIa antagonists in ACS remain speculative. The basic pharmacology and pharmacodynamics of these compounds may be at the root of the problem. However, given the similarities across a wide range of compounds within this class and the heterogeneous clinical conditions in which they have been tested, such considerations are probably of minor relevance. Another factor may be their basic mechanism of action, which occurs at a relatively late step in the formation of a platelet-rich thrombus. For example, GP IIb/IIIa inhibitors do not affect platelet activation and degranulation, unlike ADP receptor antagonists, which are active at these much earlier stages of the atherothrombotic process, where the environmental milieu required for the initiation and propagation of thrombosis is created. This becomes particularly important with long-term therapies. Interestingly, the oral GP IIb/IIIa inhibitor trials also demonstrated a highly significant 78% excess in the incidence of major bleeding. Some have argued, therefore, that they did exert a clinically apparent antplatelet effect, raising the possibility that the reported increase in mortality may be due to a direct toxic effect of these agents (46).

**Bleeding in trials of antithrombotic therapies in ACS.** There is some variability in the definitions of major bleeding used in the various studies of antplatelet therapy in unstable angina/NSTEMI. For example, TIMI “major bleeding” (from the Thrombolysis In Myocardial Infarction trial), GUSTO “severe or life-threatening bleeding,” and CURE “major or life-threatening bleeding” are three commonly used terms for major bleeding. The original criteria for a TIMI “major bleed” are bleeding leading to a hemoglobin drop of 5 g/dl or an intracranial hemorrhage (50). This definition was reported in several large trials of antithrombotic therapy in unstable angina or NSTEMI (51,52). In some trials, a modified TIMI definition has been used, in which each unit of blood transfused is counted as a 1 g/dl drop in hemoglobin. The CURE definition of “life-threatening bleeding” includes not only the two criteria used in the TIMI “major bleeding” definition but also, expanding on this definition, the following criteria: >4 U of red blood-cell transfusion, surgery required to stop bleeding, or any fatal bleed. This CURE “life-threatening bleeding” definition is only a subset of “major bleeding” in CURE and also encompasses “non-life-threatening bleeding,” defined as a blood transfusion of at least 2 U or bleeding leading to significant disability. The CURE “major bleeding” definition is therefore considerably broader than that used in other large randomized trials of ACS, an important consid-
eration when comparing its results with those of various other trials.

Table 3 shows the data for bleeding incidence in CURE using the CURE life-threatening definition as well as the TIMI and GUSTO definitions, demonstrating how, depending on the definition used, the relative risk of bleeding can vary. Because of its large sample size, CURE had more power to assess bleeding incidence than the other ACS trials. Also in this trial, it is important to note that with clopidogrel there was no increase in fatal bleeding, bleeding that required surgical intervention (including post-CABG re-intervention), or intracranial hemorrhage.

Table 4 summarizes the efficacy and bleeding data for contemporary antithrombotic therapies, with distinctions between comparisons of short-term treatments with both short- and long-term therapies (53–55). In the intravenous GP IIb/IIIa antagonist trials, an increase of 62% in major bleeding at 30 days is shown (2.4% vs. 1.4%; RR, 1.62; 95% CI, 1.36 to 1.94; p < 0.0001) (53). For the trials of oral GP IIb/IIIa inhibitors, there is a relative 74% increase in major bleeding compared with placebo (2.4% vs. 4.1%; OR, 1.74; p < 0.001) (46). The aspirin trials revealed an increase in major bleeding of about 60% (1.13 vs. 0.71; RR, 1.6) (17). In the CURE trial, there was a 38% increase in major bleeding (combined non-life-threatening plus life-threatening bleeding) in the clopidogrel group compared with the placebo group (3.7% vs. 2.7%; p = 0.001), with no significant increase in life-threatening bleeding alone (p = 0.13) (37).

In PCI CURE, no significant increase was found in major or life-threatening bleeding with clopidogrel treatment (38). There was also no increase in bleeding with concurrent use of GP IIb/IIIa inhibitors and clopidogrel compared with placebo.

Overall, there was no significant increase in bleeding in the patients (numbering more than 2,000) who underwent CABG surgery after randomization in the CURE trial. The CURE trial is one of the largest randomized investigations of antiplatelet therapy in ACS patients undergoing CABG surgery. In this trial, patients requiring CABG surgery were given clopidogrel in the same manner as aspirin. For example, if aspirin was discontinued for several days before CABG, then it was also recommended that the study drug be discontinued for this period. Most patients undergoing CABG in CURE had the study drug stopped for a short period of time before surgery. If surgery was urgent,
however, CABG proceeded while the patient was still receiving the study drug, as would be the case with aspirin. In those patients in whom the study drug was withheld for five or more days prior to CABG, no increase in bleeding was noted (37). When the study drug was administered within five days prior to CABG (including up to the time of surgery), there was a trend toward an increase in major bleeding (RR, 1.56; p = 0.06), suggesting that it may be better to withhold clopidogrel for a few days prior to CABG, if possible (37). Patients undergoing CABG surgery after randomization had consistent benefits from clopidogrel, and those patients at highest risk (in terms of TIMI risk score) had the greatest absolute benefit. This suggests that all patients who receive clopidogrel early will benefit irrespective of whether their medical management involves PCI or CABG surgery.

**Overall risk-benefit ratio.** The relative benefits of various antiplatelet therapies versus placebo are shown in Table 4. Apart from aspirin, clopidogrel is associated with the largest reduction in relative risk for death or MI in the setting of ACS, compared with other therapies. In CURE, when the primary composite of cardiovascular death, MI, or strokes (all irreversible events) and life-threatening bleeds (mostly reversible) are combined into an efficacy-safety end point, there remains a highly significant benefit of clopidogrel over placebo (RR 0.84; 95% CI, 0.76 to 0.93; p = 0.001). If one expands this outcome to include refractory ischemia requiring intervention or major bleeding, the RR is 0.87 (95% CI, 0.79 to 0.96; p = 0.005). Similar risk-benefit values for other antithrombotic agents in ACS have not been reported.

**Conclusion.** Oral anti-platelet therapies have had a significant impact in preventing major cardiovascular events in patients with NSTE ACS. Aspirin, when administered early and continued for the long term, reduced major ischemic events, including death, MI, and stroke. Development of the oral GP IIb/IIIa antagonists has been disappointing, with either no benefit or a trend toward increased mortality observed in the large, randomized trials testing these agents. By contrast, when the ADP receptor antagonist clopidogrel is added to aspirin, there are incremental reductions in major events, compared with aspirin treatment alone. These benefits emerge very rapidly (as early as 2 h) after administration of a 300-mg loading dose, indicating the importance of starting clopidogrel as early as possible. When aspirin and clopidogrel are continued over the long term (i.e., beyond 30 days) there is a highly significant, incremental 20% reduction in major events with treatment up to one year. These benefits are observed in patients undergoing PCI and CABG surgery after presentation. For patients undergoing PCI who are pretreated with clopidogrel and aspirin and who receive long-term therapy (up to one year) after intervention, a 31% risk reduction in cardiovascular death or MI has been found. This benefit is independent of the timing of PCI, with consistent reductions observed among patients undergoing very early PCI (within 72 h) as well as among those undergoing PCI at a later date.

**References**

10. PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with epti...


