Aspirin and Clopidogrel in Acute Coronary Syndromes

Therapeutic Insights From the CURE Study

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Platelet adhesion, activation, and aggregation are central to thrombus formation, which follows atherosclerotic plaque disruption and causes acute coronary syndromes. Aspirin and clopidogrel exert their antiplatelet effects by inhibiting thromboxane A2 production and adenosine diphosphate–induced platelet aggregation pathways, respectively. Aspirin has proven benefits in primary and secondary prevention of coronary artery disease. Clopidogrel, an alternative antiplatelet agent used in patients with aspirin intolerance, is especially useful in combination with aspirin after coronary stent procedures. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study demonstrates for the first time the benefit of adding clopidogrel to aspirin rather than using aspirin alone in patients having acute coronary syndromes without ST-segment elevation myocardial infarction. Patients who are resistant to aspirin (up to 10%) have higher rates of cardiovascular events and may derive special benefit from the combination therapy. Aspirin resistance can be assessed through platelet aggregometry testing, measurement of urinary thromboxane metabolites, and, possibly, genomic testing in the future.

The CURE1 (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study provides evidence for the usefulness of clopidogrel in patients having acute coronary syndrome (ACS) without ST-segment elevation. The major finding of the study is that clopidogrel given in conjunction with aspirin improves the outcome of patients with ACS compared with aspirin treatment alone. Clopidogrel appears to add incremental value to conventional therapy. The purpose of this review is to critically analyze the findings of several antiplatelet trials with a focus on the CURE study, and to provide guidance in the use of aspirin and clopidogrel for patients with ACS.

PATHOPHYSIOLOGY OF ACS

Acute coronary syndrome is a spectrum of ischemic coronary events that share the same pathophysiology and includes unstable angina, non–ST-segment elevation myocardial infarction (MI), ST-segment elevation MI, and sudden death. Acute thrombus formation on a disrupted atherosclerotic plaque seems to be the major mechanism responsible for the onset of ACS. The magnitude and stability of the thrombus formed is regulated by the nature of the exposed substrate (ie, the biochemical composition of the lesion and the degree of injury); the local rheological conditions; and the presence of certain systemic factors affecting blood thrombogenicity (eg, hyperlipidemia and diabetes).2,3 Conventional antiplatelet therapy with aspirin is designed to diminish platelet aggregation, but aspirin is a relatively weak antiplatelet drug. Moreover, up to 10% of patients do not respond to the antiplatelet effects of aspirin.4 Thus, aspirin effects, though important, are limited.

Plaque disruption depends on both passive and active phenomena.3 Among the different vascular lesions, those characterized by a thin fibrous cap, a large atheromatous core, macrophage infiltration, and a scarcity of smooth muscle cells are gen-

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Platelet aggregation leads to the formation of a red thrombus (secondary hemostasis) that can lead to ACS if the thrombus is not lysed by endogenous tissue plasminogen activator.

The key role of platelet activation and thrombosis in ACS is emphasized by the significant clinical benefits associated with the use of antiplatelet agents, such as aspirin (which blocks thromboxane A2 formation) and clopidogrel (which inhibits ADP-induced platelet aggregation) (Figure 1). However, platelet aggregation is a complex pathophysiologic process; multiple therapeutic agents may be required simultaneously to block its redundant pathways.

ASPIRIN

Historic Antecedents

Aspirin is known today to be an inexpensive, safe, and effective antiplatelet drug but its beginnings were less than easy. Piria isolated salicylic acid from the willow bark in 1838, but it was not until 1893 that Hoffman, a chemist at Bayer’s laboratories, became interested in salicylic acid. At that time, Hoffman’s rheumatic father had grown intolerant to the sodium salicylate available. He developed and purified acetylsalicylic acid, which was marketed in 1899 by the Bayer Company under the name of Aspirin (A for acetylated, and Spir for spiric acid, as salicylic acid was then known). It is ironic that the Bayer Company, which promoted the drug for its efficacy in relieving rheumatological conditions, issued a reassurance for the public that it did not have harmful effects on the heart. Though aspirin was first recognized in the 1950s to reduce the incidence of MI, mechanisms of its action remained unclear until 1967 when Weiss and Aledort published the first article to acknowledge the inhibitory effects of aspirin on platelets. Sir John R. Vane, who received the Nobel Prize for his work, found a dose-dependent inhibition of prostaglandin formation with aspirin, salicylate, and indomethacin, and provided further support for the therapeutic benefits of aspirin. His work and the work of others led also to the discovery of thromboxane A2 and prostacyclin (PGI2) in 1975 and 1976, respectively. Now, more than 100 years after its initial use, as-

Thrombin then converts fibrinogen to fibrin and stabilizes the final clot or red thrombus (secondary hemostasis) that leads in some cases to ACS.

A meta-analysis of several postmortem studies involving patients who had died from cardiovascular causes showed the presence of thrombus on disrupted lesions in approximately two thirds of cases. These “culprit” lesions causing acute coronary events are usually eccentric and moderately stenosed (<50% of the artery’s diameter). The remaining third of acute coronary events are secondary to eroded endothelium, which, in a highly thrombogenic blood milieu, leads to clot formation. Eroded lesions usually induce more severe stenosis and occur more commonly at a younger age, in women, and in diabetic and hyperlipidemic patients. Acute myocardial ischemia, caused by regional alteration in blood flow secondary to acute thrombus formation, can lead to ACS if the thrombus is not lysed by endogenous tissue plasminogen activator.

Figure 1. Platelet activation follows atherosclerotic plaque disruption and consists of conformational changes, increased expression of glycoprotein (GP) Ib/IIa receptors, and degranulation with release of prothrombotic substances such as thromboxane A2 (TXA2) and adenosine diphosphate (ADP). Aspirin, thienopyridines, and GP Ib/IIa receptor inhibitors block various pathways of thrombus formation. AA indicates acetylsalicylic acid; Cox, cyclooxygenase.
pirin is still the most widely used drug in the world.19

How Does Aspirin Work?
Aspirin irreversibly inhibits cyclooxygenase, an enzyme responsible for the formation of eicosanoids, which include PGI2 and thromboxane A2,15,20,21 (Figure 2). Because thromboxane A2 promotes platelet aggregation, the acetylation of cyclooxygenase by aspirin decreases thromboxane generation in platelets, and therefore platelet aggregability, throughout the platelet’s lifetime, which averages 7 to 10 days. Because only 10% of platelets are replaced daily, a single dose of aspirin inhibits aggregation in 50% of the platelets as late as 3 days after administration; however, only 20% of platelets, when not acetylated by aspirin, are enough to promote thrombus formation.22 Aspirin also inhibits PGI2 formation in endothelial cells. PGI2 is an eicosanoid that inhibits platelet aggregation and antagonizes the “blood-thinning” effects of aspirin; but endothelial cells, unlike the platelets, recover their cyclooxygenase function quickly, and this effect of aspirin appears to be short-lived and marginal compared with its antiplatelet effects.22 Aspirin reaches appreciable plasma levels by 20 minutes and exerts its platelet-inhibitory effect within 60 minutes.23 It is recommended that aspirin-naïve patients having ACS chew a loading dose of at least 160 mg of aspirin to receive prompt antiplatelet effect.24,25

The benefits of aspirin emanate not only from its antiplatelet effects, but potentially also from its anti-inflammatory properties. Atherosclerosis is known to be a chronic inflammatory disease of the vessel wall,26 and it is not surprising that in a prospective study involving 543 apparently healthy men participating in the Physicians’ Health Study, baseline C-reactive protein levels predicted future MI and stroke events.27 Incidentally, the benefits of aspirin in this prospective analysis are seen mainly among men whose C-reactive protein levels are in the highest quartile, with a small, nonsignificant reduction among those whose C-reactive protein levels are in the lowest quartile.27 This suggests that a major mechanism of action of aspirin occurs through its anti-inflammatory effects (Figure 3). The relative quantitative antiplatelet and anti-inflammatory benefits of aspirin in the treatment of coronary disease are not entirely clear. Recent evidence also points to potential antioxidative properties of aspirin. In one study,28 long-term administration of aspirin to both normotensive and hypertensive rats resulted in a decrease in nicotinamide adenine dinucleotide phosphate oxidase activity and, therefore, its generation of superoxide anion. However, the antioxidative properties of aspirin still need to be demonstrated in humans.

Antiplatelet Therapy Prevents Cardiovascular Events
The earliest comprehensive evidence for the efficacy of antiplatelet therapy in preventing cardiovascular events comes from the Antiplatelet Trialists’ Collaboration study.29 This study, published in 1994, is a meta-analysis encompassing 145 randomized trials and including approximately 100000 patients, of whom 70000 were considered in the high-risk category because they had, or were at risk for, vascular disease. The meta-analysis found a 25% reduction in the combined end point of MI, stroke, and vascular death in users of antiplatelet therapy (P<.001). There was also a reduction of 34% in nonfatal MI rates, of 25% in nonfatal stroke rates, of 17% in vascular death rates, and of 16% in mortality rates from any cause. No evidence of increase in nonvascular death rates was noted with antiplatelet therapy. Direct comparisons of the different antiplatelet regimens were conducted in 10000 patients, and no advantage of high-dose aspirin or any other antiplatelet drug over the medium dose of aspirin (75-325 mg) was found. Not unexpectedly, the beneficial effect of antiplatelet therapy was demonstrated across all patient subsets of the study, but the benefits were greater in the high-risk group.

The Antithrombotic Trialists’ Collaboration group recently published an updated meta-analysis of all randomized antiplatelet trials in high-risk patients.30 Their systematic review included 287 studies (up to 1997) and involved patients with acute MI; acute ischemic stroke; previous MI; previous stroke or transient ischemic attack; coronary artery disease (CAD) from other categories; and peripheral arterial disease. It also included patients at risk of embolism and other conditions that placed them at high risk (diabetes, hemodialysis, carotid disease). The main outcome measured was serious vascular event defined as nonfatal MI, nonfatal stroke, or vascular death. The Antithrombotic Trialists’ Collaboration group demonstrated a 22% overall odds reduction of serious vascular events in patients taking antiplatelet therapy compared with controls (10.7% vs 13.2%; P<.001) and approximately a one-sixth reduction in all-cause mortality (P<.001). The benefit was highest in patients with acute MI (30% odds reduction) and lowest in patients with acute stroke (11% odds reduction).
reduction). The main outcome was mostly driven by a 34\% reduction in nonfatal MI and a 25\% reduction in nonfatal stroke, as vascular death was reduced by only 15\% (P<.001). Most importantly, indirect comparisons of various aspirin regimens in the meta-analysis showed that a daily dose of aspirin in the range of 75 to 150 mg appears adequate. However, in clinical situations demanding immediate antithrombotic effect, such as ACS, a loading dose of 150 to 325 mg of aspirin is still considered the standard choice. While there was no benefit from adding dipyridamole to aspirin, addition of intravenous glycoprotein (GP) IIb/IIIa inhibitors to aspirin resulted in a 19\% increase in the reduction of serious vascular events.

Several landmark trials established the efficacy of aspirin, particularly in primary and secondary prevention of CAD (Table 1).

Lewis and colleagues\(^1\) conducted one of the earliest placebo-controlled randomized trials of aspirin in patients with ACS. In a multicenter double-blind trial enrolling 1266 men with unstable angina, the combined primary end point of death and nonfatal MI at 12 weeks was reduced by 50\% in patients receiving aspirin rather than placebo. Death and nonfatal MIs were also each reduced by 50\% in the aspirin group. The Second International Study of Infarct Survival (ISIS-2)\(^2\) was a similar landmark trial of acute MI. The study showed that a daily 160-mg aspirin tablet, started within the first day of MI and continued for 5 weeks, conferred a significant 23\% risk reduction in total vascular mortality, as well as a similar magnitude of risk reduction from all-cause mortality. Although the survival curves converged slightly over time, a significant survival benefit was still maintained after 15 months of median follow-up. There was an accompanying small absolute excess in minor bleeding events (0.6\% vs 0.2\%), but no significant increase in hemorrhagic strokes or bleeding events requiring transfusions. Aspirin therapy has now become conventional for all patients suspected of having an ACS.\(^3\)

Aspirin’s benefits in primary prevention of CAD are supported by many trials as well. The US Physicians’ Health Study\(^4\) was the first and largest primary prevention study of aspirin in cardiovascular disease. A total of 22,701 healthy physicians received 325 mg of aspirin on alternating days. The aspirin arm of the study was terminated early (after an average follow-up of 60 months) when a 44\% reduction in the risk of first MI was observed. This beneficial effect was seen primarily in patients older than 50 years. However, there was no beneficial effect of aspirin on cardiovascular mortality (the primary end point). Treated patients also showed a nonsignificant trend toward higher rates of strokes, mostly hemorrhagic, compared with patients taking placebo. The benefits of aspirin in primary prevention of cardiovascular disease in high-risk patients were later corroborated by other primary prevention studies. The Thrombosis Prevention Trial (TPT)\(^5\) demonstrated a 20\% relative reduction in the combined end point of coronary death and nonfatal MI in 5085 high-risk male patients in the United Kingdom. The beneficial effect of the daily 75-mg dose of aspirin used in this study consisted almost entirely in the incidence reduction of nonfatal events. The Hypertension Optimal Treatment (HOT)\(^6\) trial randomized 18,790 hypertensive female and male patients, most of whom with no known CAD, to receive 75 mg of aspirin daily or placebo. A 15\% reduction in vascular events and 36\% reduction in MI were observed, but no significant impact on cardiovascular mortality. A meta-analysis in primary prevention conducted by Sanmuganathan et al\(^7\) included the 3 above trials, along with a study on British male physicians,\(^8\) and found

Table 1. Aspirin Landmark Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Antiplatelet Regimen</th>
<th>Major Findings</th>
<th>Remarks</th>
</tr>
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<tbody>
<tr>
<td>Lewis et al(^9) 1983</td>
<td>1266 Men with unstable angina</td>
<td>324 mg of buffered aspirin solution daily vs placebo for 12 wk</td>
<td>A 50% reduction in the combined primary end point of death/nonfatal MI after 12 wk of follow-up</td>
<td>A significant 51% reduction was observed in each of the individual outcomes of death and nonfatal MI</td>
</tr>
<tr>
<td>ISIS-2 (Second International Study of Infarct Survival)(^2) 1988</td>
<td>17,187 Patients with suspected MI</td>
<td>160 mg of aspirin daily vs placebo for 5 wk</td>
<td>A 23% reduction in total vascular mortality</td>
<td>The significant benefit was persistent at 15 mo of median follow-up</td>
</tr>
<tr>
<td>US Physician’s Health Study(^4) 1989</td>
<td>22,701 Healthy physicians</td>
<td>325 mg of aspirin on alternating days vs placebo</td>
<td>A 44% decrease in first MI; benefits mostly those older than 50 y</td>
<td>Nonsignificant trend toward higher stroke rates; mostly hemorrhagic</td>
</tr>
<tr>
<td>Thrombosis Prevention Trial (TPT)(^5) 1998</td>
<td>5085 High-risk male patients from the United Kingdom</td>
<td>75 mg of aspirin daily vs placebo</td>
<td>A 20% relative reduction in composite of coronary death and nonfatal MI</td>
<td>Benefits mostly derived from reduction in nonfatal MI events</td>
</tr>
<tr>
<td>Hypertension Optimal Treatment (HOT) trial(^6) 1998</td>
<td>18,790 Female and male hypertensive patients (\textasciitilde 92% of patients have no known CAD)</td>
<td>75 mg of aspirin daily vs placebo</td>
<td>A 15% relative reduction in vascular events; 36% reduction in MI</td>
<td>No significant impact on CV mortality</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction.
significant 15% and 30% reductions in cardiovascular events and MI, respectively. They concluded that aspirin in primary prevention is safe and useful in patients with a 1-year coronary event risk greater than or equal to 1.5%. The benefits of aspirin in primary prevention of CAD apply to women as well.39 In an analysis from the Nurses’ Health Study,40 women taking 1 to 6 tablets of aspirin weekly had a 25% (P = .04) relative risk reduction of first myocardial infarction in multivariate analysis. The relative risk reduction of first MI was even higher, reaching 32% (P = .02) in women older than 50 years.

A recent observational study showed a 33% survival benefit from aspirin in a multivariate analysis in stable patients with known or suspected CAD undergoing stress echocardiography.51 The greatest benefit from aspirin was observed in older patients, patients with known CAD, and patients with impaired exercise capacity.

CLOPIDOGREL

An Inhibitor of ADP-Induced Platelet Aggregation

Adenosine diphosphate is a substance released by activated platelets that amplifies platelet aggregation.42 The platelet ADP receptor is coupled to a G protein and subserves calcium release from intracellular stores upon activation. This leads to conformational changes in and activation of the GP IIb/IIIa receptor, and to fibrinogen binding and platelet aggregation.52 Thienopyridine analogues (ticlopidine and clopidogrel) irreversibly inhibit the binding of ADP to its receptor. Clopidogrel has a quicker onset of action, and appears to be safer than ticlopidine, an earlier thienopyridine. Inhibition of ADP-induced platelet aggregation occurs 2 hours after a 300-mg loading dose of clopidogrel.43,44

Clopidogrel was approved in 1997 for use in secondary prevention of cardiovascular disease, and has been in widespread use since then (Table 2). It is most commonly used for the unlabeled indication of antiplatelet activity following percutaneous coronary intervention, where its efficacy is proven.

Thienopyridines Are Superior to Placebo in Preventing Vascular Events

Clopidogrel, the newer thienopyridine, has not been compared with placebo. Older trials, however, compared the therapeutic effects of ticlopidine and placebo and found a statistically significant superiority of ticlopidine. Men and women presenting with thromboembolic stroke and randomly assigned to ticlopidine had a 23% reduction in the combined end point of stroke, MI, and vascular death after a mean follow-up of 2 years.45 Another randomized controlled trial of ticlopidine in patients with unstable angina showed a 46% reduction in the primary combined end point of vascular death and MI compared with placebo.46

CAPRIE: The Rise of a Star

Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE)57 was a randomized head-to-head trial comparing the efficacy and safety of a daily 75-mg dose of clopidogrel with a daily 325-mg dose of aspirin in patients with cardiovascular disease. It included a total of 19185 patients, distributed among 3 separately enrolled groups of patients with recent MI, stroke, or symptoms secondary to peripheral arterial disease. After an average of 1.9 years of follow-up, the data demonstrated a statistically significant 8.7% relative risk reduction in the combined end point of MI, ischemic stroke, and vascular death. Severe intracranial hemorrhage and gastrointestinal bleeding events occurred in 0.33% and 0.52% of patients, respectively, with clopidogrel. The rate of ever-reported gastrointestinal bleeding complication was significantly lower in the clopidogrel group than in the aspirin group (1.99% vs 2.66%; P < .002), and no difference in intracranial hemorrhage, hemorrhagic death, thrombocytopenia, or neutropenia was noted between the 2 groups.48

Despite clopidogrel’s apparent success, the difference between the 2 antiplatelet therapies was modest (equivalent to 5 events per 1000 patients). The cost to save 1 life in the CAPRIE study was $8181 for aspirin and $49367 for clopidogrel, conferring a 7-fold cost advantage to aspirin.52 On the other hand, the

### Table 2. Clopidogrel Landmark Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Antiplatelet Regimen</th>
<th>Major Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel in Unstable angina to prevent Recurrent Events (CURE)41</td>
<td>12,562 Patients with acute non–ST-segment elevation</td>
<td>Aspirin, 325 mg + clopidogrel, 75 mg vs aspirin, 325 mg + placebo</td>
<td>A 20% reduction in composite of nonfatal MI, stroke, and CV death after a mean follow-up of 9 mo</td>
</tr>
<tr>
<td>Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)41</td>
<td>19,185 Patients with recent MI, stroke, or PAD symptoms</td>
<td>Clopidogrel, 75 mg/d vs aspirin, 325 mg/d</td>
<td>An 8.7% relative reduction in the composite of MI, ischemic stroke, and vascular death after an average follow-up of 1.9 y</td>
</tr>
<tr>
<td>Clopidogrel for the Reduction of Events during Observation (CREDO)56</td>
<td>1,216 Patients undergoing elective PCI or at high likelihood to undergo PCI</td>
<td>Aspirin, 325 mg + clopidogrel, 75 mg vs aspirin, 325 mg + placebo (both arms received combination therapy in the first 30 d)</td>
<td>A 26.9% reduction in the composite of death, MI, or stroke after 1 y of follow-up</td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.
Thienopyridine Use After Percutaneous Coronary Intervention

Clopidogrel has an efficacy similar to that of ticlopidine in preventing stent thrombosis. Because of its better safety profile, however, clopidogrel has replaced ticlopidine as the favored thienopyridine following stent implantation. Neutropenia is associated with ticlopidine but not with clopidogrel; and although rare cases of thrombotic thrombocytopenic purpura have been described with clopidogrel (3-4 cases per million), causality has not been established.

Clopidogrel is usually given for 1 month after stent implantation, but many physicians argue for a longer duration of therapy. How long one should use clopidogrel after percutaneous coronary intervention has recently been the subject of a clinical trial. Clopidogrel for the Reduction of Events During Observation (CREDO) was a multicenter, double-blind study of patients with stable and unstable angina who were undergoing percutaneous coronary intervention. The trial demonstrated the safety and efficacy of clopidogrel treatment before the procedure, and the beneficial effects of prolonged (1-year) vs short-term (1-month) dual antiplatelet therapy. Recently, Bhatt and colleagues performed a meta-analysis of the major randomized trials and registries comparing clopidogrel and ticlopidine use after coronary stent deployment. They demonstrated lower rates of major adverse cardiac events and in addition to the known adverse effects with clopidogrel and concluded that clopidogrel plus aspirin should be the standard antiplatelet regimen after stent deployment.

COMBINING CLOPIDOGREL AND ASPIRIN: DOES IT WORK?

Experimental studies have shown synergy between the thienopyridines and aspirin. This is biologically plausible because they act through independent mechanisms. Their combination inhibits ADP-induced platelet activation and thromboxane A2 production, 2 different pathways that affect platelet aggregability. Clopidogrel in Unstable angina to prevent Recurrent Events (CURE), the largest randomized ACS trial to date, tested the efficacy of the combination of aspirin and clopidogrel compared with aspirin alone.

The CURE Trial

Study Design. The CURE study was a randomized, double-blind trial involving 482 centers from 28 countries (mostly European and South American, plus Canada and the United States). It investigated whether prolonged combined treatment with aspirin and clopidogrel would have incremental benefit over aspirin alone in vascular outcomes in patients having ACS without ST-segment elevation MI.

A total of 12,562 patients diagnosed as having ACS without ST-segment elevation were randomized within 24 hours of symptom onset to receive either a combination of aspirin and clopidogrel (6259 patients) or aspirin and placebo (6303 patients).

The clopidogrel group received an immediate loading dose of 300 mg of clopidogrel followed by 75 mg of clopidogrel daily, while aspirin was given to both groups at doses ranging from 75 mg to 325 mg daily at the treating physician’s discretion. Treatment continued from 3 to 12 months (mean, 9 months), during which the patients had serial follow-up evaluations.

The mean age of patients was 64 years. Of this population of 12,562, 39% were women, 23% had diabetes, 59% had hypertension, and 59% were current or former smokers; only 13 were lost to follow-up.

Main Results. Using clopidogrel plus aspirin significantly reduced the risk of the first primary composite end point of nonfatal MI, stroke, and cardiovascular death (9.3% vs 11.4%, for a reduction of 20%) compared with aspirin alone. There was also a significant risk reduction rate of 14% in the second primary composite of cardiovascular death, stroke, nonfatal MI, and refractory ischemia (16.5% vs 18.8%). The superiority of the combined antiplatelet regimen was also observed across a number of important secondary end points: incidence rates were lowered by 26% for severe ischemia, by 9% for recurrent angina, by 8% for revascularization procedures, and by 18% for evidence of heart failure. It must be stressed, however, that the composite end points were driven mainly by the statistically significant decrease in the MI risk reduction rate (5.2% vs 6.7%, for a reduction of 23%), while other individual outcomes showed nonsignificant trends toward lower event rates: a 14% RR for stroke, a 7% RR for cardiovascular death, and a 7% RR for refractory ischemia.

Observations and Subgroup Analyses From CURE. The superiority of the combination of aspirin and clopidogrel appeared early in the course of treatment, with significant benefit occurring during the first 24 hours. This superiority was maintained through the 12-month study. At randomization, 25% of patients were taking lipid-lowering agents, 58% β-blockers, 36% angiotensin-converting enzyme inhibitors, and 72% were receiving unfractionated or low-molecular-weight heparin anticoagulant therapy. Nevertheless, subgroup analyses showed that the benefit of the combined regimen was maintained irrespective of the medications the patients were taking. There was also consistent benefit across different doses of aspirin and various risk groups, though the largest benefit (44% risk reduction) was observed in patients with prior revascularization. Dual antiplatelet therapy was superior whether or not
patients were taking medications of proven survival benefit, such as β-blockers or statins, at randomization. Thus, the incremental benefit of clopidogrel could not be attributed to a higher risk profile of suboptimally treated patients.

**Higher Bleeding Rates With Dual Antiplatelet Therapy.** Patients assigned to the dual antiplatelet regimen had higher rates of major and minor bleeding, but no increase in life-threatening bleeding or intracranial hemorrhage.

Compared with aspirin use alone, a significant 1.38 relative risk of major bleeding episodes (P = .001)—mostly bleeding caused by PGI2 and bleeding at the puncture site—and a significant 2.12 relative risk of minor bleeding episodes (P < .001) were observed in the dual antiplatelet therapy group.

Although 6 of every 1000 patients required blood transfusions, the excess bleeding risk in the combined treatment was no higher than that seen in trials comparing the effects of aspirin and placebo, and lower than that seen in intravenous GP IIb/IIIa inhibitor trials, both of which being accepted treatments.

There was no significant difference in the rates of life-threatening bleeding events (nonsignificant 21% higher rates), hemorrhagic strokes, thrombocytopenia, and neutropenia between the 2 groups of the study. No cases of thrombotic thrombocytopenic purpura occurred in the CURE study.

**Use of Dual Antiplatelet Therapy in Patients Awaiting Percutaneous Transluminal Coronary Artery Angioplasty and Coronary Artery**

No significant excess in bleeding was seen when clopidogrel was stopped a median of at least 5 days before coronary artery bypass graft surgery; however, a 53% higher rate of major bleeding events was observed in the intervention group, and the events were stopped less than 5 days before the procedure.

It is important to note that most patients were recruited from centers where early invasive procedures were not routinely performed (only 462 patients from the United States compared with 2050 patients from Poland, for example). The Therapy with an Invasive or Conservative Strategy (TACTICS)—Thrombolysis in Myocardial Infarction (TIMI) 18 trial showed clear benefit of the early invasive strategy in ACS without ST-segment elevation, and many centers in the United States have adopted a similar aggressive strategy. Tirofiban was used upstream (ie, prior to coronary angiography) in TACTICS to passivate the coronary arteries before cardiac catheterization and potential percutaneous coronary intervention (PCI), which were performed within 4 to 48 hours of randomization. Adding clopidogrel in these circumstances may lead to excessive anticoagulating effects when one considers that aspirin, heparin, and GP IIb/IIIa inhibitors are also all being used. Data from 823 patients who received GP IIb/IIIa inhibitors in the CURE study (5.9% of the combination group and 7.2% of the aspirin alone group) were promising, with a significant 18% reduction in the use of GP IIb/IIIa inhibitors in those assigned to dual antiplatelet therapy rather than aspirin alone. However, bleeding rates in these subgroups of patients were not disclosed. Further studies are needed to define the respective roles and safety of clopidogrel and GP IIb/IIIa inhibitors in upstream therapy (ie, prior to undergoing coronary angiography and intervention). Moreover, the addition of clopidogrel to aspirin resulted in a significant 43% reduction in the use of thrombolytic agents compared with aspirin (1.1% in the combination group and 2% in aspirin alone group), but no data on bleeding rates were provided.

**The PCI-CURE Study**

PCI-CURE, a prospective, randomized, double-blind, placebo-controlled study including 2658 patients from the CURE population who underwent PCI, tested the hypothesis that pretreatment with clopidogrel followed by long-term treatment (mean, 8 months) was superior to no pretreatment and short-term treatment (4 weeks) after PCI. All patients were receiving aspirin, and the randomization was between clopidogrel and placebo. Patients received the study drug for a median of 10 days prior to procedure and had a significant risk reduction of 30% in the primary combined end point of cardiovascular death, MI, and urgent revascularization within 30 days of PCI (4.5% vs 6.4%; P = .03). When events from PCI to end of follow-up were accounted for, long-term therapy with clopidogrel and aspirin (mean, 8 months) showed a significant 17% risk reduction in the combined triple end point compared with the 1-month-only, open-label thienopyridine treatment (18.3% vs 21.7%; P = .03). The benefit conferred by pretreatment and long-term treatment with clopidogrel was seen across all subgroups and as early as 2 days after PCI. This benefit was secondary to lower rates of MI, mostly non-Q-wave MI, while no statistically significant impact on survival was observed. Of interest, benefit from dual antiplatelet therapy was evident prior to the PCI procedure, compared with the effects of aspirin alone. No data regarding the number of patients receiving GP IIb/IIIa inhibitors or the incremental value of clopidogrel in these patients were provided. The authors also mentioned that there were no higher rates of excess bleeding in patients receiving dual antiplatelet treatment along with GP IIb/IIIa inhibitors. Whether these observations from PCI-CURE apply to the highly aggressive therapeutic approach of the United States is not clear, but other studies have found an incremental benefit to pretreatment with clopidogrel, in addition to GP IIb/IIIa inhibitor use, with PCI.  

**Aspirin Resistance: A Potential Target for Combination Therapy With Clopidogrel?**

By using 1 of 2 methods of platelet aggregometry, Gum et al demonstrated that rates of aspirin resistance reached 5% to 10% in a prospective study involving 325 patients with stable cardiac disease who received 325 mg of aspirin daily (as the sole antiplatelet drug) for at least 7 days. The rate of aspirin semiresponders exceeded 20% in that study as well. Moreover, PI2 polymorphism, attributed to a single nucleotide polymorphism in the gene encoding the GP IIIa portion of the
GPⅡb/Ⅲa receptor, was associated with increased risk in patients with ACS; with in-stent thrombosis; and with restenosis associated with coronary stenting.66-69 This is believed to be secondary to decreased platelet inhibition by aspirin, and patients with this sort of aspirin resistance may derive the greatest benefit from dual antiplatelet therapy. It would be interesting to study the pattern of aspirin resistance in a population like that of CURE to test this hypothesis, in view of the potential emergence of genomic testing and platelet aggregometry testing as means to identify aspirin-resistant patients. Recently, Eikelboom et al70 used urinary levels of 11-dehydrothromboxane B2 as a surrogate for aspirin resistance in a case-controlled study from the HOPE trial. They showed that urinary levels of 11-dehydrothromboxane B2 predict future cardiovascular outcomes, with a risk of cardiovascular death 3.5 times higher in patients having urinary levels of 11-dehydrothromboxane B2 in the upper quartile than in those whose levels are in the lower quartile (P<.001).

CONCLUSIONS

The CURE trial showed a significant improvement in the combined outcome of cardiovascular death, nonfatal MI, and stroke with the use of dual oral antiplatelet therapy (aspirin and clopidogrel). This benefit was seen as early as 24 hours after randomization and through to 12 months of follow-up. The combined aspirin and clopidogrel regimen in ACS was also associated with a lower incidence of heart failure, recurrent angina, revascularization, and ischemia. However, these benefits occurred at the expense of increased major and minor bleeding complications. Of note, the perioperative bleeding rate in patients who had received clopidogrel and aspirin in the 5 previous days was increased, and this may complicate use of this combination in patients where early coronary artery bypass graft surgery is anticipated. Pretreatment with clopidogrel a few days before PCI and its prolonged use afterwards for several months (beyond the 1-month routine use of thienopyridines) have shown increased benefit in patients with ACS undergoing PCI. In the future, genomic and platelet aggregometry testing in clinical practice may help identify the aspirin-resistant patient, who will potentially benefit the most from addition of clopidogrel therapy.

The current evidence strongly supports the use of dual antiplatelet therapy (aspirin and clopidogrel) in the long-term treatment (for at least 12 months) of patients with ACS after PCI, after which aspirin should be continued indefinitely. Longer-term clopidogrel use should then be considered based on patient risk. Low-dose aspirin (81 mg) is adequate in secondary prevention because it has similar antiplatelet efficacy and fewer side effects (gastrointestinal hemorrhage, hemorrhagic stroke) than the 325-mg dose. However, a patient presenting in the acute phase of an unstable coronary syndrome should be treated with at least 162 mg of aspirin (corresponding to 2 “baby” tablets) and preferably a full 323-mg aspirin tablet. The most recent data support the use of low-dose aspirin (81-mg daily dose), for primary prevention of CAD in men older than 50 years who are at high and intermediate risk for CAD. The risk estimates for future CAD events can be calculated using validated scores such as the Framingham risk score61 and should be weighed against aspirin side effects. Clopidogrel should substitute aspirin in primary prevention of CAD only in patients who are intolerant or resistant to aspirin. The combination of aspirin plus clopidogrel vs aspirin alone is being studied in both secondary prevention and high-risk primary prevention in the ongoing CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance) trial.

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REFERENCES

22. Fuster V, Dyken ML, Vokonas PS, Hennekens C, for the Special Writing Group. Aspirin as a thera-

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Downloaded From: by a Non-Human Traffic (NHT) User on 11/14/2018
peutic agent in cardiovascular disease. Circula-
1993;87:659-675.

35. Hennekens CH, Dyken ML, Fuster V, Harker LB, Salzman
EW. Aspirin and other platelet-active drugs: the relationship between dose, effectiveness, and side

spective study of aspirin use and primary preven-
tion of cardiovascular disease in women. JAMA.
1991;266:521-527.

43. Savicic M, Hauert J, Bachmann F, Wyld PJ, Gued-
elin B, Cariou R. Clopidogrel loading dose regi-
mens: kinetic profile of pharmacodynamic re-

46. Oween JI, Wofford G, et al. Acute antithrom-
botic effect of a front-loaded regimen of clopidogrel
in patients with atherosclerosis on aspirin. Arterio-

50. Bhatt DL, Bertrand ME, Berger PB, et al. Meta-
analysis of randomized and registry compari-
sions of ticlopidine with clopidogrel after stent-

54. Herbert JM, Dol F, Bernat A, Falotico R, Lale A, Savi
P. The antaggregating and anti thrombotic ac-
tivity of clopidogrel is potentiated by aspirin in sev-
eral experimental models of the rabbit. Thromb.

blind randomized comparison of combined aspi-
rin and ticlopidine therapy versus aspirin or ticlo-
pidine alone on experimental arterial thrombogenesis

60. Moshtagh K, Redondo M, Jamal F, et al. Anti-
platelet effects of clopidogrel compared with aspi-
rin after myocardial infarction: enhanced inhibi-
tory effects of combination therapy. J Am Coll

63. Mehta SR, Yusuf S. The Clopidogrel in Unstable
angina to prevent Recurrent Events (CURE) trial
programme: rationale, design and baseline char-
teristics including a meta-analysis of the ef-
fects of thienopyridines in vascular disease. Eur

67. Topol EJ. The future of antiplatelet therapy: opti-
mizing management in patients with acute coro-
nary syndrome. Clin Cardiol. 2000;23(suppl 6):
VI-23–VI-28.

70. Kastrati A, Schomig A, Seyfarth M, et al. PIA poly-
morphism of platelet glycoprotein IIa and IIIa of re-
esthension after coronary stent placement. Cir-
culation. 1999;100:1050-1051.

74. Norden AT. Platelet glycoprotein IIa polymor-
phism and coronary thrombosis. Lancet. 1997;
350:1189-1191.

75. Walter DH, Schachinger V, Esmer M, Dimmel-
er S, Zeiher AM. Platelet glycoprotein IIb/IIIa pol-
ymorphisms and risk of coronary stent thrombosis. Lan-

78. Eikelboom JW, Hirsch J, Weitz JL, Johnston M, Yi Q,
Yusuf S. Aspirin-resistant thromboxane bio-
synthesis and the risk of myocardial infarction,
stroke, or cardiovascular death in patients at high

81. Executive Summary of the Third Report of the Na-
tional Cholesterol Education Program (NCEP) Ex-
pert Panel on Detection, Evaluation, and Treat-
ment of High Blood Cholesterol in Adults (Adult

84. Bhatt D, Marsao S, Hirsch A, Ringleb, P, Topol E.
Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am J Cardiol.
2002;90:625-628.