Use of Antiplatelet Agents and Anticoagulants for Cardiovascular Disease: Current Standards and Best Practices

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Thrombosis superimposed on arteriosclerosis is the principal cause of mortality and morbidity in patients with arteriosclerosis. The use of antiplatelet agents and anticoagulants in the treatment of arteriosclerosis is well established, based on many large randomized trials. Aspirin is indicated for primary prevention in patients at increased risk of developing symptomatic atherosclerotic vascular disease. For patients with known vascular disease, antiplatelet therapy with aspirin is a well-established treatment. For high-risk patients such as those with acute coronary syndromes (ACS; unstable angina, myocardial infarction), dual antiplatelet therapy with aspirin and clopidogrel is indicated, based on results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial. Platelet glycoprotein IIb/IIIa agents are powerful inhibitors of platelet function and are also effective in ACS, but the benefit is confined to high-risk patients. Anticoagulation with heparin or low-molecular-weight heparin (eg, enoxaparin) is also effective, with an approximately 50% reduction in cardiovascular events. These agents are also indicated for patients undergoing percutaneous coronary intervention. Prolonged dual antiplatelet therapy (at least 6 months) is recommended for patients receiving drug-eluting stents. The efficacy of antiplatelet therapy is thus well established in treating atherothrombosis, but aggressive therapy is associated with an increased bleeding risk. Newer agents may provide improved efficacy with a lower risk of bleeding.

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Key words: Antiplatelet agents • Anticoagulants • Atherothrombosis

Arteriosclerosis is the most common disease in the Western world and will likely become the most common disease worldwide by 2020.[1] It manifests most commonly as stable coronary artery disease and acute coronary syndromes (ACS), including myocardial infarction (MI) and unstable angina. It can also involve other vascular circulations leading to stroke, renal vascular disease, and peripheral vascular disease. The primary process that

produces the clinical manifestations of the disease is atherothrombosis, or the formation of a thrombus superimposed on preexisting arteriosclerosis.[2] Because the disease often does not result in a hemodynamically significant stenosis before development of the thrombus, the acute event is often the first manifestation of the disease. The use of antiplatelet agents and anticoagulants is central to the prevention of progression of disease and development of major adverse clinical events.

Thrombus occurs most commonly at the site of a vulnerable plaque. Pathologically, vulnerable plaques occur in 3 forms: the inflamed, thin-capped fibroatheroma, the plaque prone to erosion, and the plaque with a calcified nodule protruding into the lumen.[3] Of the 3, the thin-capped fibroatheroma is thought to be the most common cause of the thrombosed-ruptured plaque that leads to ACS and sudden cardiac death. There is also mounting evidence that ruptured plaques can lead to progression of stenosis, resulting in stable angina or asymptomatic progression of stenosis. These pathophysiologic processes are likely to occur in other vascular circulations as well, although less is known about these.[4]

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In addition to the presence of a vulnerable plaque, other patient-specific factors are also important in determining the likelihood of a clinical event. Some have termed this "vulnerable blood," referring to an increased propensity for thrombosis.[2] Certain individuals may have an increased likelihood of thrombosis as a result of one of the known causes of a hypercoagulable state, but for most patients it is likely that systemic inflammation, the presence of elevated low-density lipoprotein cholesterol, cigarette smoking, diabetes, or other factors lead to increased thrombogenicity. These various risk factors have been shown to activate leukocyte-platelet interactions, with release of tissue factor and thrombin activation. Increased tissue factor may be an important common pathway for thrombus formation in ACS. In addition, platelets are critical to the interplay between inflammation and coagulation. Following deendothelialization, platelets adhere to the exposed subendothelial collagen and/or von Willebrand factor. Platelets then aggregate primarily through the platelet glycoprotein (GP) IIb/IIIa receptor (or the fibrinogen receptor), leading to a platelet-rich thrombus. Activation of the coagulation cascade leads to the formation of fibrin and an occluding or partially occlusive thrombus. Proinflammatory cytokines such as CD40 ligand and interleukin-1 (IL-1), as well as chemokines, promote thrombosis. Fibrinolysis can modulate the degree of thrombus formation in any individual patient.

This review of antiplatelet agents and anticoagulants in atherothrombosis focuses primarily on their use in coronary artery disease. There is, however, considerable evidence of their value in the prevention of stroke and clinical events in other circulations.

Pharmacology of Antiplatelet Agents and Anticoagulants

Three classes of antiplatelet agents are currently used for the prevention and treatment of atherothrombosis: aspirin, thienopyridines, and platelet GP IIb/IIIa receptor inhibitors.[5] The mechanism of action of each is shown in Figure 1.

Aspirin inhibits platelet activity by irreversibly acetylating cyclooxygenase (COX)-1, thereby blocking the formation of thromboxane A_2, prostacyclin, and other prostaglandins.[5] In addition, aspirin has other anti-inflammatory properties that may also be beneficial, particularly in patients with ACS. The therapeutic benefit of aspirin has been shown for all doses, but higher-dose regimens have not been shown to increase efficacy, and these higher doses are associated with increased risk of gastrointestinal (GI) bleeding.

The thienopyridines, clopidogrel and ticlopidine, are inhibitors of 1 of the 3 adenosine diphosphate (ADP) receptors on the platelet, the P2Y12 receptor.[5] The result is inhibition of ADP-induced platelet activation, platelet aggregation, thromboxane A_2 generation, and GP IIb/IIIa receptor activation. Clopidogrel has largely replaced ticlopidine, due to its improved safety profile, but clopidogrel is a less potent inhibitor of the P2Y12 receptor. Both drugs are rapidly absorbed and have a dose-response relationship with inhibition of platelet aggregation of 30% to 60% after a loading dose. Higher loading doses result in greater inhibition and a lower incidence of resistance. The newest drug in this class, prasugrel, is currently undergoing clinical trials; it seems to have a more rapid onset of action and greater potency.

The platelet GP IIb/IIIa receptor inhibitors prevent the binding of fibrinogen and von Willebrand factor to the GP IIb/IIIa receptor on the

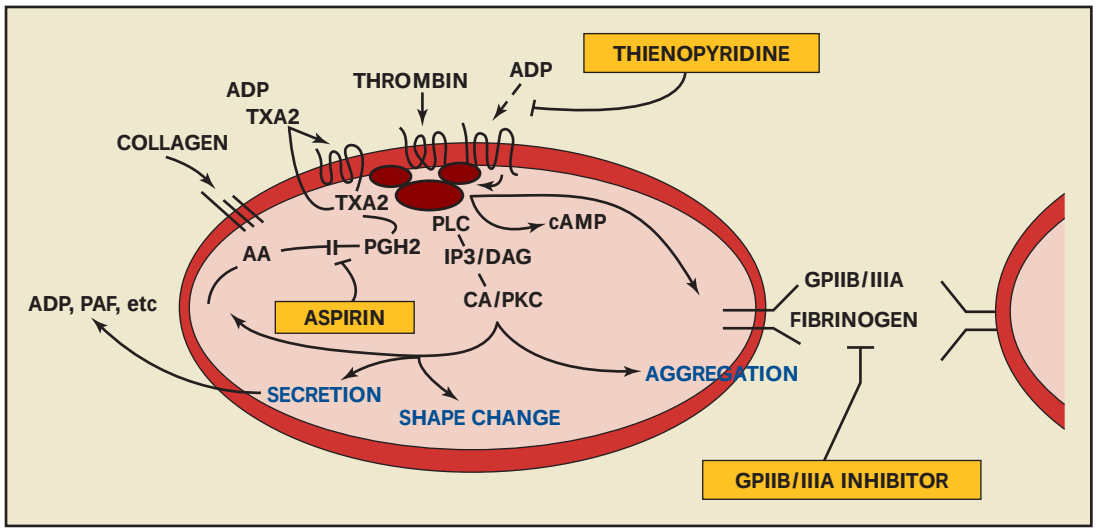


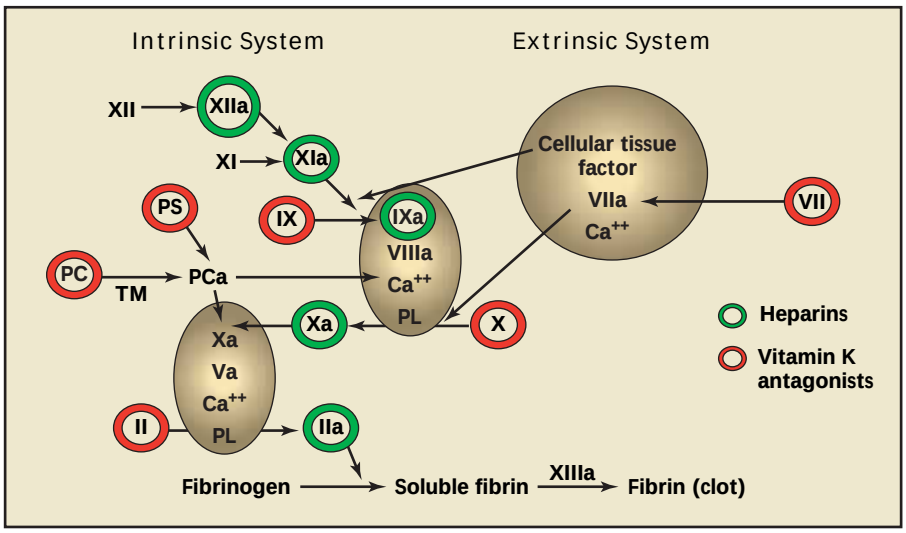
Figure 1. *The mechanism of action of antiplatelet agents. AA, arachidonic acid; ADP, adenosine diphosphate; CA, calcium; cAMP, cyclic-adenosine monophosphate; GP, glycoprotein; IP3/DAG, inositol–1,4,5–triphosphate/diacylglycerol; PAF, platelet-activating factor; PG, prostaglandin; PKC, protein kinase C; PLC, phospholipase C; TXA2, thromboxane A_2. Reproduced from Mason PJ, et al.* Rev Cardiovasc Med. *2004;5:156-163.*

activated platelets, thus inhibiting aggregation.[5] Three GP IIb/IIIa inhibitors are currently approved for use: abciximab, a monoclonal antibody; eptifibatide, a hexapeptide; and tirofiban, a tyrosine derivative. Abciximab and eptifibatide have been approved for use in percutaneous coronary intervention (PCI), eptifibatide and tirofiban for use in ACS. Abciximab forms an irreversible bond with the receptor and thus has a more prolonged antiplatelet activity than eptifibatide and tirofiban, which reversibly bind the receptor and have a much shorter half-life.

Anticoagulants have also been used effectively for patients with atherothrombosis. The mechanism of action of commonly used agents is shown in Figure 2. Heparin is a heterogeneous mixture of varying chain lengths of uronic acid and glycosamine polysaccharides, with molecular weights varying from 5 to 15,000 daltons.[6] Heparin binds with antithrombin 3, which in turn reversibly binds factor IIa and Xa; its anti-Xa and anti-IIa activities are equal. Two low-molecular-weight (LMW) heparins are currently available, dalteparin and enoxaparin. Enoxaparin has been more extensively studied, but both are approved for use in ACS. Enoxaparin has a molecular weight of 5,000 daltons and an anti-Xa/anti-II ratio of 3.3, which may account for its lower bleeding risk when compared with heparin. Fondaparinux is a factor Xa inhibitor, with no inhibition of factor IIa; it has a prolonged half-life of 15 to 18 hours. It is currently being investigated for use in ACS.[7]

Warfarin is the most commonly used anticoagulant. It exerts its anticoagulant actions by inhibiting vitamin K, which is necessary for activation of coagulation factors II, VII, IX, and X. Warfarin is rapidly absorbed and has a prolonged half-life. Because it is metabolized by cytochrome P450, many drugs affect its half-life.

Figure 2. *The mechanism of anticoagulant (antithrombotic) agents: multiple actions on coagulation cascade. The coagulation factors are II, VII, IX, and X, and the coagulation inhibitors are proteins C and S. PS, protein S; PC, protein C; TM, thrombomodulin; PCa, activated protein C; PL, phospholipids. Based on Boneu B, et al.* Sang Thrombose Vaisseaux. *1999;10:291-312.*



Direct thrombin inhibitors bind to 1 of the 3 active binding sites on thrombin and, unlike heparins, are not dependent on binding with antithrombin III.[8] The most commonly used intravenous agents include bivalirudin and argatroban. The oral agent ximelagatran has recently been studied but is not approved for use in the United States.

Current Indications

Primary Prevention

The use of antiplatelet agents and anticoagulants in the prevention of coronary events has been extensively studied for more than 40 years. Whereas most of the available data come from secondary prevention studies, it is well accepted that aspirin should be used for patients with an increased risk of developing symptomatic coronary disease, stroke, or vascular disease. The meta-analysis by the first Antiplatelet Trialists' Collaboration[9] in 1994 demonstrated a 12% reduction in the combined end point of stroke, MI, or vascular death in 27,210 patients receiving aspirin for primary prevention. A more recent meta-analysis of 5 randomized trials of more than 50,000 patients shows that for patients with at least a 5% risk for coronary artery disease within 5 years, aspirin would prevent 6 to 20 MIs but would cause 0 to 2 hemorrhagic strokes and 2 to 4 major GI bleeding events.[10]

The American Heart Association (AHA) guidelines for primary prevention recommend the use of aspirin for patients with a 10-year risk of coronary disease of greater than 10%.[11] Given the lower bleeding risk at lower aspirin doses, 75 to 160 mg of aspirin is recommended as the preventive dose. The primary reason for not recommending aspirin for all patients is the lower benefit, preventing 1 to 4 MIs per year, but equal or greater risk of central nervous system and GI bleeding. There is insufficient information on the use of clopidogrel in this setting, but it is generally thought to be an acceptable alternative for patients intolerant of aspirin. Cost is a consideration, however, and the overall risk of developing symptomatic disease needs to be considered. The combination of aspirin and clopidogrel has not been studied, but given the known increased risk of bleeding when these agents are combined, it would be reasonable to reserve the combined use for those at the highest risk. A large multinational study, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, will address the use of dual antiplatelet therapy for high-risk patients, as well as for those with known vascular disease.[12]

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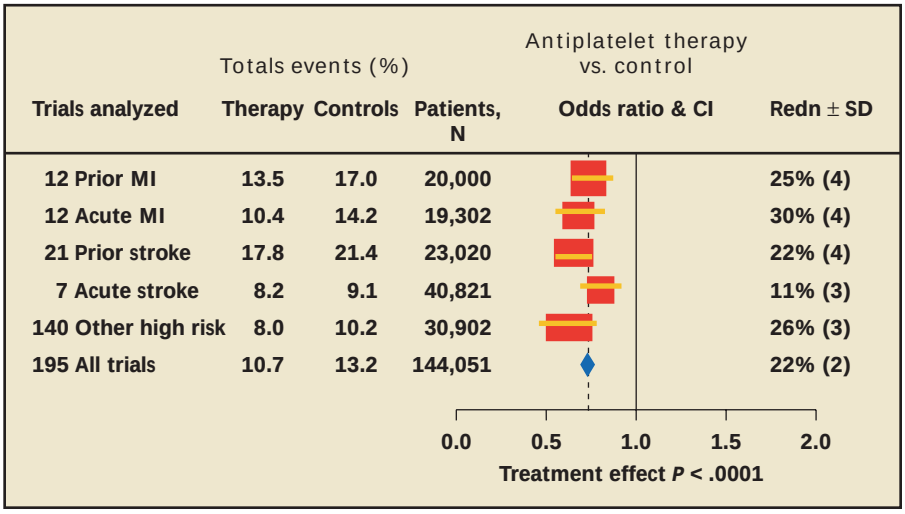
Secondary Prevention

The use of antiplatelet agents for patients with known atherothrombosis has been one of the most extensively studied areas in cardiology. The recent Antithrombotic Trialists' Collaboration meta-analysis, published in 2002, reviewed 287 randomized trials of 135,000 patients that compared an antiplatelet agent and placebo and 77,000 that compared different agents.[13] The study showed, overall, a 22% reduction in cardiovascular events, with benefit seen in patients with prior MI, acute MI, prior stroke, acute stroke, and other high-risk categories such as peripheral vascular disease (Figure 3). Overall, this translated into an absolute reduction in risk of a serious

Figure 3. *A meta-analysis of randomized trials of antiplatelet therapy in high-risk patients. Stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials (red square) along with its 99% confidence interval (CI; horizontal line). Metaanalysis of results for all trials (and 95% CI) is represented by a blue diamond. Redn, reduction; SD, standard deviation. Adapted from Antithrombotic Trialists' Collaboration.*[13]



adverse event of 36 per 1000 with a prior MI, treated for 2 years; 38 per 1000 with acute MI, treated for 1 month; 36 per 1000 with a prior stroke, treated for 2 years; 9 per 1000 treated for an acute stroke; and 22 per 1000 other high-risk patients, including those with peripheral vascular disease, treated for 2 years. The benefit was seen for all doses of aspirin. However, a subsequent analysis of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated that all doses above 75 mg were beneficial but bleeding increased with increasing doses of aspirin; this led to the current recommendation of a 75 to 160 mg dose for secondary prevention.[14]

The use of clopidogrel as an alternative to aspirin was studied in the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, which enrolled 19,185 patients with prior MI, ischemic stroke, or peripheral artery disease.[15] Overall, there was an 8.7% reduction in cardiovascular events in the clopidogrel group compared with the aspirin group. In the prior MI group, no benefit was seen. There was a 7.3% benefit in the ischemic stroke group and a 23.8% reduction in events in the peripheral artery disease group. Currently, the CHARISMA study is evaluating whether dual antiplatelet therapy in similar high-risk patients is superior to aspirin alone.[12]

The use of warfarin for secondary prevention of vascular disease has been studied for more than 40 years. A meta-analysis of 13 trials and 4038 patients showed an odds ratio (OR) of 0.58 in favor of oral anticoagulation.[16] The 6 trials comparing oral anticoagulation versus aspirin showed an OR of 0.79 in favor of oral anticoagulation. The combination of aspirin and moderate- to high-intensity oral anticoagulation further improved outcomes, with an OR of 0.88. The major reason that oral anticoagulation or the combination of aspirin and oral anticoagulation is not routinely recommended is a 2-fold increase in the risk of bleeding (5.5% vs 2.6%).[17] Most of these trials enrolled patients with ACS and/or acute MI, and were conducted before the availability of clopidogrel; a meta-analysis has shown the superiority of aspirin plus ticlopidine over aspirin plus warfarin (OR 0.51; $P = .002$).[18] Little is known about oral anticoagulation for patients with stable coronary disease. In 1 trial of more than 5000 patients at high risk for ischemic events, warfarin, aspirin, and a combination did not differ in outcomes.[19]

Acute Coronary Syndromes

The role of platelets in ACS is central to the pathophysiology of the condition, and therefore antiplatelet and anticoagulant therapies are highly effective in decreasing both short- and long-term complications. Although the 3 clinical presentations of ACS—unstable angina, non-ST elevation MI (NSTEMI), and ST elevation MI (STEMI)—share a common pathophysiology, platelet thrombi play a more important role in the first 2 conditions than in the last.

In the first Antiplatelet Trialists' Collaboration study in 1994, antiplatelet therapy was associated with a 46% reduction in vascular events in patients with unstable angina (13.3% vs 8.0%).[9] In the more recent collaborative study, the 5 trials evaluating patients with ACS (unstable angina and NSTEMI) reported a reduction in events ranging from 30% to as high as 64%.[13] A reduction was also seen in acute MI, with a 30% reduction in cardiovascular events.

The thienopyridine (ADP receptor antagonist) clopidogrel has also been shown to be highly effective in treating ACS.[17] In the CURE trial, 12,562 patients were randomized to receive either a combination of clopidogrel plus aspirin or aspirin alone. The study demonstrated a 20% relative risk reduction (RRR) of cardiovascular events over a 12-month period (Figure 4).[20] The benefit was seen in all risk groups and began after 24 hours. In the subgroup of 2658 patients who underwent PCI, there was an even greater RRR, 31%.[21] As all patients received clopidogrel for 1 month after PCI, the differences in outcome were largely due to early administration before PCI, although the long-term benefit supports therapy for up to 1 year in all patients with ACS. With the widespread use

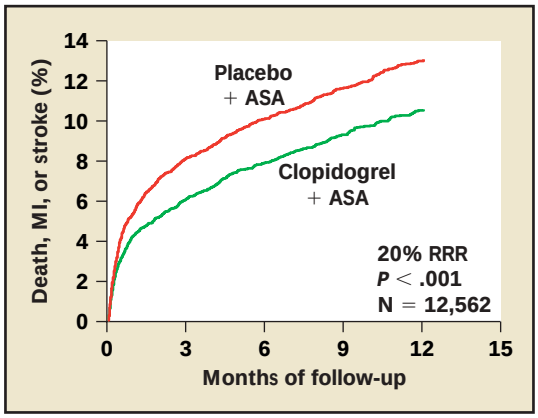


Figure 4. *The 1-year outcome of patients randomized in the CURE trial comparing aspirin with aspirin plus clopidogrel for patients with unstable angina or non-ST elevation myocardial infarction (MI). ASA, aspirin; RRR, relative risk reduction. Reprinted with permission from Yusuf et al.*[20]

of drug-eluting stents today, dual therapy is required for 6 months, and most physicians continue it for at least 1 year for all patients.

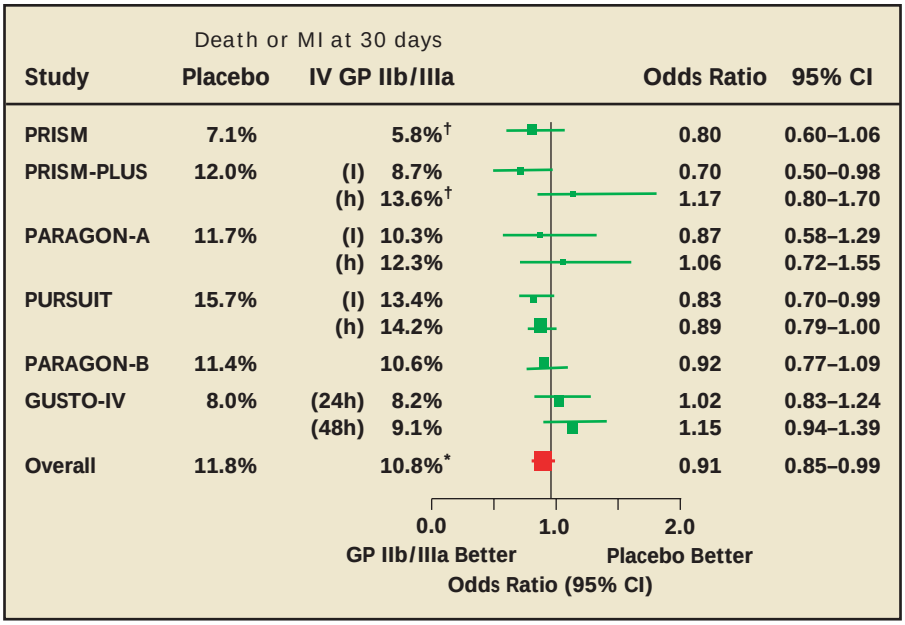
The platelet GP IIb/IIIa antagonists have also been extensively studied in ACS. In a meta-analysis of the 6 major randomized trials of these agents in 31,402 patients with ACS, Boersma and colleagues[22] demonstrated a significant reduction in death and MI at 30 days (11.8% vs 10.8%, OR 0.91) (Figure 5). The benefit was largely a reduction in MI. In another analysis of these trials, a mortality benefit was seen only in patients with diabetes.[23] Early administration was more effective than delayed use, and benefit was confined to those at high risk and those undergoing PCI. The Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-React) trial evaluated the use of GP IIb/IIIa agents for low-risk ACS patients who were receiving aspirin, clopidogrel, and heparin.[24] The study showed no long-term benefit with addition of the GP IIb/IIIa agents. Of the 3 approved drugs, tirofiban and eptifibatide but not abciximab have been approved for use in patients with ACS, based on the results of the randomized trials. However, abciximab is approved for use in patients undergoing PCI.

As a result of these studies, the American College of Cardiology (ACC)/AHA guidelines recommend that any GP IIb/IIIa agent be used in addition to aspirin and heparin for patients with ACS who are undergoing PCI, and that tirofiban and eptifibatide be used for high-risk ACS patients when urgent catheterization is not planned.[25] Combined use with clopidogrel is less clearly defined for those receiving a GP IIb/IIIa agent. In the Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET), a significant benefit was realized for those who were treated with aspirin, a GP IIb/IIIa agent, and clopidogrel, in comparison with those taking aspirin and GP IIb/IIIa agent alone.[26] However, the need for early administration of all 3 agents is unclear, and the current recommendation is for clopidogrel to be given either before or at the time of PCI.[25]

The role of anticoagulants in treating unstable angina/NSTEMI has also been well studied. In 12 trials totaling 17,157 patients, death or MI in the short term was reduced 47% by either unfractionated heparin or LMW heparin (Figure 6).[27] In the 6 studies comparing aspirin with aspirin plus unfractionated heparin, there was a reduction in cardiovascular events from 7.6% to 4.6% with combination therapy. Whereas the uses of both aspirin and heparin are well accepted in clinical practice, the role of LMW heparin is more controversial. In the 6 randomized trials comparing LMW heparin and unfractionated heparin in 21,946 patients, there was a small but significant reduction in death or MI at 30 days (10.1% vs 11.0%; OR 0.91).[27]

Two different LMW heparins have been studied. Enoxaparin was used in 2 trials, the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) and Thrombolysis in Myocardial Infarction 11B (TIMI 11B) trials, both showing a significant advantage over unfractionated heparin. These results led to the recommendation in the ACC/AHA guidelines that either type of heparin is acceptable, but enoxaparin is preferred unless coronary artery bypass is anticipated, because a higher bleeding rate was seen in those who underwent surgery.[25] However, the use of LMW heparin

Figure 5. *A meta-analysis of 6 randomized trials of glycoprotein (GP) IIb/IIIa agents in acute cardiac syndromes: death or myocardial infarction (MI) at 30 days. PRISM, Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PARAGON-A/-B, Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; PURSUIT, Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; GUSTO-IV, Global Utilization of Steptokinase and TPA for Occluded Coronary Arteries; IV, intravenous; GP, glycoprotein; CI, confidence interval; l, low dose; h, high dose. *Without heparin; †with/without heparin. Data from Boersma et al.[22]*



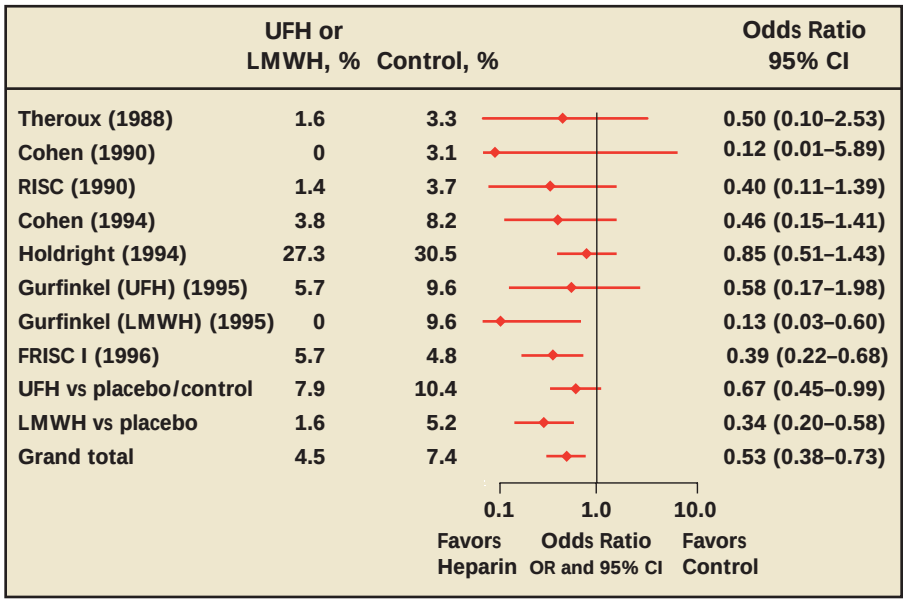


Figure 6. *A meta-analysis of 10 randomized trials of heparin in acute cardiac syndromes—non-ST elevation myocardial infarction. RISC, Research Group on Instability in Coronary Artery Disease; FRISC-I, Fragmin During Instability in Coronary Artery Disease; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; OR, odds ratio; CI, confidence interval. Reproduced with permission from Eikelboom et al.*[27]

for patients with ACS who are to undergo PCI is complicated by the long half-life and the inability to easily measure the drug effect. In the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, the largest trial comparing the LMW heparin enoxaparin with unfractionated heparin in patients with ACS who were undergoing PCI, no differences in death or MI were seen at 30 days.[28] However, when combined in a meta-analysis of all trials totaling 21,946 patients, a small benefit was seen at 30 days (death or MI, 10.1% vs 11%), but there was an increase in major bleeding (4.8% vs 4.1%).[29]

The specific factor Xa inhibitor, fondaparinux, was recently studied in the large, multicenter Organization to Assess Strategies for Ischemic Syndromes 5 (OASIS 5) trial.[30] The study compared fondaparinux with enoxaparin in patients with ACS. In 20,078 patients, fondaparinux resulted in a similar rate of death or MI at 9 days, but less than half the bleeding rate (3.2% vs 7%; $P = .00001$). Surprisingly, at 30 days mortality was lower by 17% and bleeding by 37%, both highly significantly. The decrease in mortality at 30 days was largely explained by the reduction in major bleeding events. This was a new and important observation, stressing the importance of using drugs and dosages that preserve efficacy but minimize bleeding.

Although still unresolved, the findings of these trials support the use of unfractionated heparin, enoxaparin, or fondaparinux in ACS. There may be an advantage of fondaparinux over both enoxaparin and unfractionated heparin based on the most recent OASIS 5 trial.

The management of antiplatelet and anticoagulant therapy in patients with STEMI has also undergone intensive investigation. As in unstable angina/NSTEMI, aspirin is recommended for all patients with STEMI. The ACC/AHA guidelines recommend the use of heparin as a class IIa recommendation when streptokinase is used, but as a class Ia when a fibrin-specific lytic agent such as reteplase, alteplase, or tenecteplase is used.[31] The role of LMW heparin and/or GP IIb/IIIa agents is more controversial. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 (ASSENT-3) trial compared heparin, LMW heparin, and a GP IIb/IIIa agent in patients receiving reteplase for treatment of STEMI.[32] The study showed a benefit of both LMW heparin and GP IIb/IIIa agent over heparin, but no difference between the 2. There was, however, a higher rate of CNS bleeding in those older than 75 years who received LMW heparin. As a result, the guidelines recommend the use of LMW heparin as a class IIb indication, stating that it can be used as an alternative heparin for patients under the age of 75 and for those with normal renal function.[31] Glycoprotein IIb/IIIa agents and clopidogrel are recommended only for those undergoing primary angioplasty. However, these recommendations were made before the recent Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial, conducted largely in Asia, in which the addition of clopidogrel to heparin or streptokinase and aspirin resulted in a 42% reduction in adverse events at 30 days.[33]

The ACC/AHA guideline recommendations for the use of antiplatelet and anticoagulant drugs for patients with ACS are summarized in Figures 7 through 10.

Percutaneous Coronary Intervention

The use of antiplatelet agents and anticoagulants is also essential in PCI. In current practice, 90% of patients receive stents, and the majority receive drug-eluting stents. Whereas aspirin and heparin have been considered

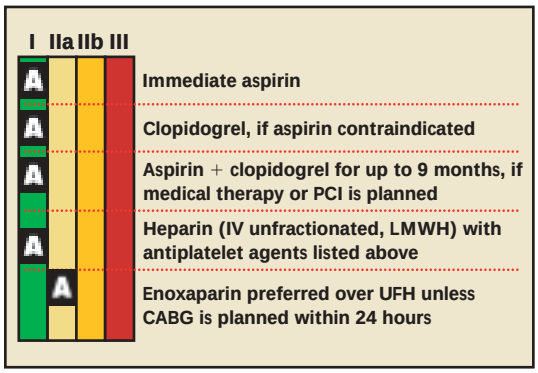


Figure 7. *American College of Cardiology/American Heart Association (ACC/AHA) guideline recommendations for the use of antiplatelet agents and anticoagulants in unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) acute cardiac syndromes. PCI, percutaneous coronary intervention; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; CABG, coronary artery bypass grafting. Levels of evidence: A, multiple randomized trials; B, small randomized trials or registries; C, expert opinion. Classifications: I, should be done; IIa, reasonable to do; IIb, not unreasonable to do; III, should not be done. Adapted from Braunwald et al.*[25]

mandatory during the procedure, to reduce the incidence of abrupt vessel closure following balloon angioplasty, more intensive and prolonged antiplatelet therapy has proven essential to reduce the problem of subacute vessel closure.[34] The mechanism responsible for both the acute and subacute closure is the development of a platelet thrombus, which frequently leads to occlusion of the artery and MI. With bare metal stents, a number of studies have shown the value of the combination of aspirin and a thienopyridine. Although the initial studies demonstrated the effectiveness of ticlopidine, clopidogrel has largely replaced it due to its improved side effect profile and the low incidence of neutropenia. The incidence of subacute thrombosis within 1 month has been reduced to less than 1.5%.[35] When it does occur, however, it is associated with a significant increase in mortality and MI. When drug-eluting stents are used, the risk of subacute thrombosis is increased and prolonged. However, the use of clopidogrel and aspirin for 3 to 6 months has been effective in reducing this risk to the same level as with bare metal stents.[35] The Percutaneous Coronary Intervention in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) study results demonstrated an advantage of aspirin and clopidogrel for 1 year after PCI in patients with ACS; as a result, most interventionists are recommending dual antiplatelet therapy for 1 year for most patients.[21]

Whereas heparin is also standard therapy during PCI, as mentioned above, the LMW heparin enoxaparin is an acceptable alternative to unfractionated heparin.[34] It has become less favored primarily due to the lack of significant benefit over unfractionated heparin and the inability to easily assess the degree of anticoagulation, as can be done with heparin by measuring activated clotting time. Another alternative to heparin is the direct thrombin inhibitors. A meta-analysis of the 9 major trials of thrombin inhibitors for patients with ACS showed a small but significant reduction in mortality and a lower incidence of bleeding.[8] Bivalirudin has been most extensively studied in PCI. In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial, heparin and GP IIb/IIIa agents were compared with bivalirudin in patients undergoing PCI.[36] There was no difference in the primary end points of death, MI, urgent revascularization, or major bleeding. When the components were individually analyzed, however,

Figure 8. *American College of Cardiology/American Heart Association (ACC/AHA) guideline recommendations for the use of platelet glycoprotein (GP) IIb/IIIa agents in unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) acute cardiac syndromes. ASA, aspirin; PCI, percutaneous coronary intervention. *High-risk: age > 75; prolonged ongoing CP; hemodynamic instability; rest CP with ST change; ventricular tachycardia; positive cardiac markers. (See legend for Figure 7 for explanations of levels of evidence and classifications.) Adapted from Braunwald et al.*[25]

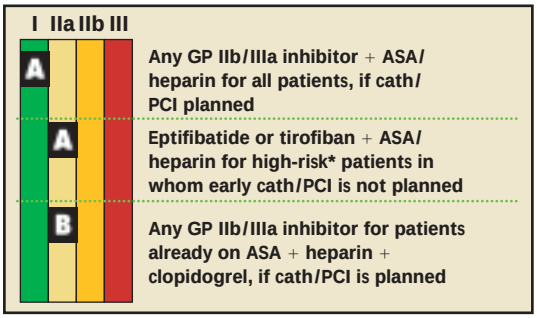
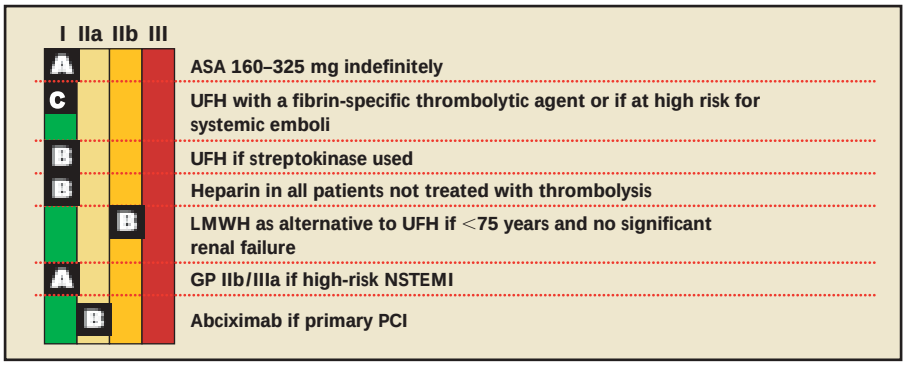


Figure 9. *American College of Cardiology/American Heart Association (ACC/AHA) guideline recommendations for the use of antiplatelet agents and anticoagulants in ST elevation myocardial infarction (STEMI) acute cardiac syndrome. ASA, aspirin; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention. (See legend for Figure 7 for explanations of levels of evidence and classifications.) Adapted from Antman et al.*[31]



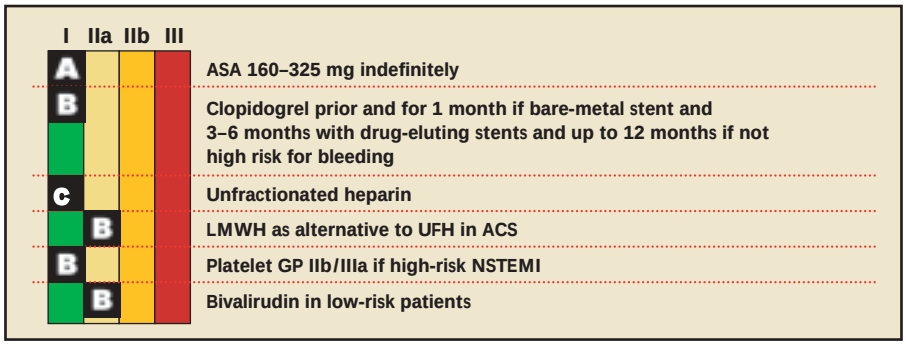


Figure 10. *American College of Cardiology/American Heart Association (ACC/AHA) guideline recommendations for the use of antiplatelet agents and anticoagulants in percutaneous coronary intervention (PCI). ASA, aspirin; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; GP, glycoprotein; NSTEMI, non-ST elevation myocardial infarction. (See legend for Figure 7 for explanations of levels of evidence and classifications.) Adapted from ACC/AHA/SCAI Update.*[34]

a significant reduction in major bleeding was found with bivalirudin, but no difference in other end points. There have been a number of criticisms of this study, including its use of high-dose heparin that may have led to a higher than expected bleeding rate in the heparin group. Nevertheless, bivalirudin is an effective alternative to heparin and is favored over heparin by many. The ongoing Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial will help further define the role of bivalirudin in ACS and PCI.[37]

The combination of coronary artery disease and other conditions that require anticoagulation poses significant management issues.

Special Issues

Concomitant Disease

The combination of coronary artery disease and other conditions that require anticoagulation poses significant management issues. For instance, the patient who has atrial fibrillation or a mechanical valve replacement and who undergoes PCI will require aspirin and clopidogrel in addition to warfarin. The risk of bleeding is clearly increased in this setting, but although there is little information on the need for all 3 agents over the long term, most physicians will continue all 3 if possible.

Drug Resistance

Recently it has been recognized that a substantial number of patients do not obtain an adequate antiplatelet effect from aspirin or clopidogrel. In the Heart Outcomes Prevention Evaluation (HOPE) trial, Eikelboom and colleagues[38] demonstrated that those with the highest level of urinary 11-dehyrothromboxane B_2, a measure of aspirin resistance, had a 1.7-fold greater incidence of death, MI, or stroke. Gum and colleagues,[39] using a platelet function assay, demonstrated resistance to aspirin in 5% of patients, and these patients had an incidence of cardiovascular events of 24% at 2 years, compared with 10% in nonresistant patients. The mechanism of aspirin resistance is probably multifactorial, including poor absorption of the drug, rapid metabolism, increased oxidant stress, and increase in COX-2 expression.

It has also been shown that clopidogrel is associated with an inadequate antiplatelet effect in 4% to 25% of patients. In 1 study, those in the lowest quartile of antiplatelet inhibition had a 40% incidence of cardiovascular events, although those in the top quartile had none.[40] There is some evidence that increasing the dose of clopidogrel can reduce the incidence of clopidogrel resistance.[41] Newer thienopyridines such as prasugrel may have a lower incidence of resistance, and clinical trials are underway to evaluate this agent in comparison to clopidogrel.[42]

Future Directions

Many new, potentially more potent and effective, antiplatelet agents are under development, including new thienopyridines. Direct thrombin inhibitors, as mentioned above, are also under active investigation. The development of direct oral thrombin inhibitors is also an exciting prospect. The oral agent ximelagatran has been investigated in the Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients After Acute Myocardial Infarction (ESTEEM) study in ACS patients and in the Stroke Prevention by Oral Thrombin Inhibition (SPORTIF) II and III trials in patients with atrial fibrillation.[8] Although these studies demonstrated superior outcomes compared with placebo in patients with ACS, or compared with warfarin in patients with atrial fibrillation, the drug did not receive Food and Drug Administration approval, due to a small but concerning incidence of liver function abnormalities. Other agents, including tissue factor inhibitors (TFPI and NAPc2), direct factor Xa inhibitors, and newer direct thrombin inhibitors, are all undergoing study.[7]

Conclusions

The treatment of patients with atherothrombosis with antiplatelet and anticoagulant drugs has produced a very significant reduction in the mortality and morbidity of this condition. In high-risk settings such as in ACS, the use of these drugs has been estimated to reduce adverse events by 70% to 80%. Nevertheless, the benefit of these agents must be weighed against the bleeding risk, which is estimated to range from 1% to 4%.[17] For patients already at risk for bleeding, this risk is obviously much higher, and the decision to use 1 or more of these agents has to take into account the known benefit balanced against the estimated risk of bleeding. The negative impact of bleeding on long-term outcome in ACS patients in the OASIS 5 trial is sobering, and further prediction and prevention of bleeding are clearly necessary. Newer, more effective, but safer agents are needed, and it is likely that many new agents will be available in the near future. Other articles in this supplement address the risks of GI bleeding and the means to minimize them. ■

Main Points

- Three classes of antiplatelet agents are currently used for the prevention and treatment of atherothrombosis: aspirin, thienopyridines, and platelet glycoprotein (GP) IIb/IIIa inhibitors.
- The therapeutic benefit of aspirin has been shown for all doses. Of the thienopyridines, clopidogrel has largely replaced ticlopidine, due to its improved safety profile; the newest drug in this class is prasugrel, currently undergoing clinical trials. Three GP IIb/IIIa inhibitors are currently approved for use: abciximab, eptifibatide, and tirofiban.
- Anticoagulants have also been used effectively for patients with atherothrombosis. These include 2 low-molecular-weight (LMW) heparins, dalteparin and enoxaparin, both approved for use in acute cardiac syndromes (ACS); warfarin, the most commonly used anticoagulant; and intravenous direct thrombin inhibitors, including bivalirudin and argatroban.
- The American Heart Association (AHA) guidelines for primary prevention recommend the use of aspirin 75 to 160 mg for patients with a 10-year risk of coronary disease of greater than 10%. Clopidogrel is generally thought to be an acceptable alternative for patients intolerant of aspirin.
- In the recent Antithrombotic Trialists' Collaboration meta-analysis, patients with known atherothrombosis who were treated with antiplatelet agents showed a 22% reduction in cardiovascular events; this included patients with prior myocardial infarction (MI), acute MI, prior stroke, acute stroke, and peripheral vascular disease.
- In the CAPRIE trial, including patients with prior MI, ischemic stroke, or peripheral artery disease, there was, overall, an 8.7% reduction in cardiovascular events in the clopidogrel group compared with the aspirin group.
- In a recent collaborative study, 5 trials evaluating patients with ACS (unstable angina and non-ST elevation MI) undergoing antiplatelet and anticoagulant therapies reported a reduction in cardiovascular events ranging from 30% to 64%.
- The American College of Cardiology (ACC)/AHA guidelines recommend that any GP IIb/IIIa agent be used in addition to aspirin and heparin for patients with ACS who are undergoing percutaneous coronary intervention (PCI), and that tirofiban and eptifibatide be used for high-risk ACS patients when urgent catheterization is not planned.
- The ACC/AHA guidelines recommend the use of heparin as a class IIa when streptokinase is used, but a class Ia when a fibrin-specific lytic agent such as reteplase, alteplase, or tenecteplase is used.
- The ACC/AHA guidelines recommend the use of LMW heparin as a class IIb indication; it can be used as an alternative heparin for patients under the age of 75 and for those with normal renal function. Glycoprotein IIb/IIIa agents and clopidogrel are recommended only for those undergoing primary angioplasty.
- In PCI with bare metal stents, studies have shown the value of the combination of aspirin and clopidogrel. When drug-eluting stents are used, an aspirin and clopidogrel combination for 3 to 6 months has been effective in reducing risk to the same level as with bare metal stents.
- Heparin is also standard therapy during PCI, but the LMW heparin enoxaparin is an acceptable alternative to unfractionated heparin. Another alternative to heparin is a direct thrombin inhibitor such as bivalirudin.

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