Conundrums in the Combined Use of Anticoagulants and Antiplatelet Drugs

David J. Schneider, MD; Burton E. Sobel, MD

Medical pharmacological therapy typically targets a single process or agent. Examples include the selection of a specific antibiotic to suppress growth or viability of a specific bacterium, administration of a specific hormone to obviate a specific endocrinologic deficiency, and utilization of a specific chemotherapeutic agent selected to annihilate neoplastic cells of a specific type. By contrast, the use of anticoagulants and antiplatelet drugs deviates from this general principle because of several considerations: (1) inevitable interactions that link activation of platelets and activation of the coagulation cascade; (2) the effect of commonly used antithrombotics (eg, heparin and warfarin) on multiple factors in the coagulation cascade; and (3) profound amplification of antithrombotics (eg, heparin and warfarin) on multiple factors in the coagulation cascade; and (3) profound amplification of antithrombotics.

Numerous positive and negative feedback loops in the prothrombotic process confer additional complexity. Important examples of positive loops include activation of coagulation factor (F) V and FVIII by thrombin with consequent augmentation of activation of generation of FXa through what has been called the intrinsic pathway, activation of FIX by the tissue factor/VIIa complex, and activation of FXI and consequently FIX by thrombin. Examples of negative feedback loops include inactivation of FVa and FVIIIa by activated protein C formed by the thrombin/thrombomodulin complex, inhibition of the tissue factor FVIIa complex by tissue factor pathway inhibitor, and inhibition of thrombin by the heparin/antithrombin III complex.

In very general terms, prophylaxis and treatment of prothrombotic states in the venous circulation and atria are best treated with anticoagulation, whereas antiplatelet regimens are generally used to limit thrombosis in the arterial circulation. The combination of anticoagulants and antiplatelet agents is indicated in the treatment of acute arterial thrombosis and the prevention of thrombosis of prosthetic valves. Clinical dilemmas are encountered when a patient has multiple disorders, each of which may require implementation of antithrombotic measures. Examples abound and include the coexistence of atrial fibrillation and an intracoronary stent; concomitant prothrombotic venous and arterial disease; combinations of peripheral, coronary, and cerebrovascular disease; valvular heart disease coupled with coronary artery disease or atrial fibrillation; heart failure and a coincident acute coronary syndrome (ACS); and deep vein thrombosis with or without pulmonary embolism with coexistent myocardial infarction (MI). When such combined conditions are present, the use of both anticoagulant and antiplatelet therapy may, of course, be justified or required. However, as discussed in the present review, because of the profoundly adverse effects of bleeding that may be induced, determination of the intensity and duration of each requires careful assessment of risk for the specific patient who manifests the combined disorders.

Thrombosis, Hemostasis, and Antithrombotic Therapy

Mechanisms of Thrombosis and Hemostasis

The coagulation cascade has often been described to comprise 2 somewhat independent pathways that converge on a common pathway with thrombin generation as the end point of the reactions (Figure 1). This depiction reflects processes recognized, assayed, and reflected by clinical laboratory testing (the prothrombin time measures activity of the “extrinsic pathway” and the activated partial thromboplastin time measures activity of the “intrinsic pathway”). However, it does not accurately reflect hemostasis and thrombosis in vivo. Physiologically, activation of the coagulation cascade and thrombin generation do not occur in solution but are localized to a phospholipid surface. In part, this localization confines the reaction to the specific site of injury. Not all phospholipid surfaces are the same. Platelets support thrombin generation in a manner that is not completely mimicked by other phospholipid surfaces.

The diagram shown in Figure 2 reflects our current understanding of thrombin generation in vivo. It indicates that coagulation occurs in 3 overlapping phases: initiation,
priming, and propagation. Injury to the vessel wall exposes blood to cells with tissue factor on their surfaces. Tissue factor is derived from extravascular sources such as fibroblasts or from sources in blood (so-called protected sources), which include one that results from the interaction between platelets and leukocytes mediated by CD62 (P-selectin) and CD15 (P-selectin glycoprotein (GP) ligand 1).7 FVII binds to tissue factor and is rapidly activated. The FVIIa/tissue factor complex activates FX and FIX. FXa and other proteases can activate FV. The combination of Fxa/FVa on the phospholipid surface cleaves prothrombin to produce small amounts of thrombin.8 Minute amounts of thrombin produced initially then lead to an explosive increase in activation of FXI and FIX and marked generation of thrombin.9

Injury to the vessel wall leads to adherence of platelets mediated by collagen and von Willebrand factor.10 Adherence leads to activation of platelets that increases during priming when the small amount of thrombin generated initially then binds to platelets and activates them through protease-activated receptors. Platelets appear to be pivotal in the initial generation of thrombin. Their activation results in degranulation that releases partially active FV from α granules.11 Collagen and thrombin act synergistically in activation of platelets.12 Thrombin cleaves partially activated FV to a fully active form and activates FXI bound to the platelet surface, which results in primed and activated platelets that rapidly bind cofactors Va and VIIIa as well as FXi.13

During the propagation phase, the initially formed thrombin activates FIX and XI, which thereby accelerates thrombin generation. FX is activated by the FIIa/VIIIa complex that is assembled on the activated platelet surface. Subsequent formation on the platelet surface of FXa/Va complexes leads to a burst of thrombin and fibrin formation.

Thrombin initiates a negative feedback loop when it associates with thrombomodulin and consequently activates protein C, which, in combination with protein S, constitutes an endogenous anticoagulant system by inactivation of FVa and FVIIa. In addition to FVIII activation, thrombin releases FVIII from circulating von Willebrand’s factor, after which its intrinsic instability leads to inactivation.

Platelets contribute to thrombosis in multiple ways (Table 1). Adherence after vascular injury contributes to formation of hemostatic plugs and initiates activation of platelets14 that contribute to thrombosis through (1) the formation of platelet–platelet aggregates mediated by GP IIb-IIIa15 and platelet-leukocyte aggregates mediated by P-selectin16; (2) the release of products from platelet granules17 that support generation of thrombin (such as calcium, FV, and fibrinogen), recruitment of additional activated platelets (through release

Figure 1. The traditional depiction of coagulation in which 2 overlapping cascades of activation of coagulation factors leads to the generation of thrombin and fibrin. The intrinsic and extrinsic cascade are thought to intersect at the activation of Factor X. This diagram facilitates understanding of conventional tests of coagulation such as the prothrombin time (PT, which measures the activity of the extrinsic pathway) and the activated partial thromboplastin time (aPTT, which measures the activity of the intrinsic pathway). In vivo, Factor XII is not activated in the absence of inflammation. Accordingly, this diagram does not describe the current understanding of thrombosis and hemostasis.

Figure 2. An updated framework of coagulation that emphasizes interaction between the classic intrinsic and extrinsic pathways as well as the interaction between the coagulation cascade and the membrane surface of platelets. In this conceptualization, thrombosis and hemostasis entail several stages: initiation, priming, and propagation. During initiation, vessel injury leads to adherence of platelets and exposure of blood to tissue factor. Small amounts of thrombin generated through the classic extrinsic pathway during initiation lead to priming by activating Factors VIII and IX and platelets. Propagation reflects an explosive increase in thrombin generation mediated by the classic intrinsic pathway.
of thromboxane and ADP, and stimulation of vasoconstriction (through release of serotonin and other vasoactive peptides); (3) the formation of thrombin promoted by the phospholipid surface on which coagulation factor complexes form; and (4) a change in the shape of the platelet with pseudopod extension. Thus, activation of platelets and generation of thrombin are intimately entwined.

Antithrombotic Therapy

Antithrombotic therapy falls into 2 categories despite overlapping properties of each: antiplatelet agents with primary effects that limit activation or activity of platelets, and anticoagulants with primary effects that limit activity of the coagulation cascade and thereby generation of thrombin and fibrin. In the context of vessel injury, antiplatelet agents limit generation of thrombin and fibrin, and anticoagulants limit generation or activity of thrombin, which thereby manifests antplatelet effects. When added in vitro to blood, GP IIb-IIIa inhibitors decrease generation of thrombin after clotting has been initiated with tissue factor. Because thrombin is a key platelet agonist, any agent that inhibits its generation or activity will decrease platelet activation after vessel injury. Accordingly, both antiplatelet agents and anticoagulants are antithrombotic agents. Nevertheless, some conditions are managed predominantly with anticoagulants, antiplatelet agents, or both.

**Conditions Generally Treated With Anticoagulants**

In several conditions, such as venous thromboembolic disease, atrial fibrillation, left ventricular dysfunction, and valvular heart disease, the focus of antithrombotic therapy is on anticoagulation. Thrombosis in the venous circulation has been recognized as a pivotal pathophysiological derangement for >100 years. In contrast to the arterial circulation, direct or indirect inhibitors of thrombin are the mainstay of prophylaxis and therapy. Indirect anticoagulants that require endogenous cofactors include unfractionated heparin, low molecular weight heparins, and fondaparinux, a pentasaccharide. These anticoagulants inhibit FXa and FIIa through interaction with antithrombin. Those anticoagulants with shorter chain length, particularly fondaparinux, exhibit greater propensity to inhibit FXa. Anticoagulants that inhibit thrombin directly (with no need for endogenous cofactors) include hirudin, argatroban, and bivalirudin. Differences between the responsivity of venous thrombosis and arterial thrombosis to inhibition of the coagulation cascade per se reflect differences in shear rate in the 2 circulations, differences in endothelial cell function and distensibility of vessels, and differences in the physical nature of the luminal surface among other factors.

**Venous Thromboembolism**

Results of numerous randomized clinical trials and cohort studies have demonstrated the effectiveness of and underlie consensus recommendations for treatment of deep vein thrombosis with directly or indirectly acting antithrombins followed by orally active vitamin K antagonists such as warfarin for 3 to 6 months (see consensus recommendations in Buller et al). Prophylaxis with anticoagulants prevents venous thromboembolic disease and pulmonary embolism associated with immobility and after lower extremity orthopedic surgery (see consensus recommendations in Geerts et al).

**Atrial Fibrillation**

Prophylactic anticoagulation to prevent stroke in patients with persistent or paroxysmal atrial fibrillation (in the latter, particularly if other risk factors are present) constitutes a standard of care (Table 2). An oral vitamin K antagonist at a dosage sufficient to produce a targeted International Normalized Ratio (INR) in the range of 2 to 3 is appropriate and consistent with consensus recommendations.

In aggregate, data from randomized clinical trials are consistent with the view that advanced age, mitral stenosis (particularly rheumatic), and decreased left ventricular function are major determinants of an increased risk of stroke in patients with atrial fibrillation. Vitamin K antagonists reduce the risk of stroke somewhat more effectively than does aspirin, although the overall absolute risk reduction is modest with either. Similar conclusions have been drawn from results of clinical trials in which placebo was compared with either aspirin or a vitamin K antagonist. Although some benefit was noted when antiplatelet drugs were combined with anticoagulation in patients in whom INR values were not elevated to the putative optimal range, benefit conferred by

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### TABLE 1. The Role of Platelets in Thrombosis

<table>
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<th>Action</th>
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<tr>
<td>Adherence (non-activation–dependent)</td>
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<tr>
<td>Shape change</td>
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<tr>
<td>Aggregation (cross-linking, binding of fibrinogen, binding of von Willebrand factor, activation of glycoprotein IIb-IIIa)</td>
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<tr>
<td>Attachment (to cells, von Willebrand factor)</td>
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<tr>
<td>Release of granular products</td>
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<tr>
<td>Growth factors (α-granules)</td>
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<tr>
<td>Support thrombin generation (Ca²⁺, fibrinogen, factor V/Va)</td>
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<tr>
<td>Stimulate vasoconstriction (serotonin, thromboxane A2)</td>
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<tr>
<td>Recruitment of additional activated platelets (thromboxane A2, ADP)</td>
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<tr>
<td>Provide surface for binding of coagulation factors</td>
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### TABLE 2. Indications for Treatment With Anticoagulants

<table>
<thead>
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<th>Condition</th>
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<tr>
<td>Venous thromboembolic disease</td>
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<tr>
<td>Prevention in patients with increased risk (eg, after orthopedic procedures and with prolonged immobility)</td>
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<tr>
<td>Deep venous thrombosis and pulmonary embolism</td>
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<td>Atrial fibrillation (particularly with the following risk factors: age &gt;=75 y; arterial hypertension; previous stroke, transient ischemic attack, or non-CNS systemic embolus; mitral stenosis; left ventricular dysfunction with left ventricular ejection fraction &lt;45%; peripheral arterial disease)</td>
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<tr>
<td>Left ventricular dysfunction</td>
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<tr>
<td>After large (particularly anterior) myocardial infarction</td>
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<tr>
<td>Left ventricular ejection fraction &lt;35%</td>
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<tr>
<td>Prosthetic valves (in combination with low doses [75 to 100 mg] of aspirin)</td>
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<tr>
<td>Acute arterial thrombosis (in combination with long-term antiplatelet therapy)</td>
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CNS indicates central nervous system.
combination of such agents, such as aspirin with oral anticoagulants, is not convincing in the absence of another indication for the use of antiplatelet drugs, such as coronary artery disease. Combined aspirin and clopidogrel did not inhibit thrombin generation in a single-center study in patients with atrial fibrillation. This observation presaged results in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W) study, a large multicenter trial that compared aspirin plus clopidogrel with a vitamin K antagonist. The ACTIVE-W study was stopped early because treatment of patients with atrial fibrillation plus 1 or more risk factors for stroke had a lower incidence of stroke when treated with a vitamin K antagonist compared with aspirin plus clopidogrel.

Left Ventricular Dysfunction

Left ventricular dysfunction predisposes to formation of ventricular mural thrombi that may fragment and embolize, which causes stroke and other sequelae. More than 20 million people in the United States probably have asymptomatic left ventricular dysfunction. The risk of stroke in such patients is as high as 2% annually. Prevention is particularly important in those with a previous embolic event because of the high rate of recurrence in patients who have already suffered a stroke, which reaches 45% after 5 years. Heart failure after acute anterior MI is particularly prone to give rise to stroke attributable to emboli liberated from left ventricular thrombi, and implementation of anticoagulation with a vitamin K antagonist significantly reduces the incidence of stroke. The incidence of stroke associated with heart failure is inversely related to ejection fraction. Accordingly, anticoagulation with oral vitamin K antagonists should be considered for patients with reduced ejection fraction particularly if the reduction is <35% or left ventricular thrombus is identified. As is the case for prophylaxis of stroke associated with atrial fibrillation, the absence of valvular heart disease, the addition of antiplatelet drugs to a regimen of anticoagulation in patients with heart failure should be predicated on anticoagulation because it entails a lower incidence of bleeding complications.

Treatment with clopidogrel, a thienopyridine that inhibits the P2Y12 receptor, reduces the incidence of adverse vascular events in patients with atherosclerotic vascular disease and is an alternative to aspirin in patients who do not tolerate aspirin. The combination of aspirin plus clopidogrel did not reduce the incidence of adverse vascular events in patients with stable vascular disease or in those who were at high risk for vascular disease. By contrast, the combination of aspirin plus clopidogrel reduced the subsequent incidence of cardiac events from 11.4% to 9.3% versus aspirin alone when continued for an average of 9 months after an ACS. The combination of aspirin plus clopidogrel is recommended after coronary stenting and for up to 9 months after an ACS. Premature discontinuation of clopidogrel increases the risk of stent thrombosis and late thrombosis (>6 months after placement) appears to be a risk with drug-eluting stents. Recent consensus recommendations are for combined treatment with aspirin plus clopidogrel for 1 year after placement of a drug-eluting coronary stent.

Anticoagulation with a vitamin K antagonist has been evaluated for many decades in patients with coronary artery disease. Relatively recently, however, low-intensity therapy (INR<2) failed to reduce the incidence of ischemic events. By contrast, higher-intensity therapy (INR>2) reduced the incidence of ischemic events; however, the reduction was accompanied by a 3- to 4-fold increased incidence of major nonfatal bleeding events. The greater incidence of bleeding

<table>
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<tr>
<th>TABLE 3. Indications for Treatment With Antiplatelet Agents</th>
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<tr>
<td>Atherosclerotic vascular disease</td>
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<tr>
<td>Aspirin (75 to 325 mg/d) <strong>long term</strong></td>
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<td>Coronary stents</td>
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<tr>
<td>Aspirin + clopidogrel (clopidogrel is indicated for ≥1 mo for bare metal stents and for 3 to 6 mo for drug-eluting stents, with a consideration of ≥12 mo to prevent late stent thrombosis)</td>
</tr>
<tr>
<td>Acute arterial thrombosis that complicates atherosclerosis in combination with short-term anticoagulants</td>
</tr>
<tr>
<td>Aspirin + clopidogrel for 9 to 12 mo (followed by long-term treatment with aspirin)</td>
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Conditions Generally Treated With Antiplatelet Drugs

Use of antiplatelet agents is the primary antithrombotic therapy for patients with atherosclerotic vascular disease and, in particular, coronary artery disease (Table 3) consistent with the role of platelets in atherosclerosis. Platelets are a key component of microthrombi associated with atherogenesis. A reciprocal interaction exists between atherosclerosis and platelets. Patients with particularly extensive atherosclerosis have particularly high platelet reactivity and platelets appear to contribute to the progression of atherosclerosis. In addition, antiplatelet therapy is preferred compared with

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events has led to consensus recommendations for long-term treatment with aspirin rather than vitamin K antagonists for most patients with coronary artery disease.\textsuperscript{49} Treatment with a vitamin K antagonist compared with the combination of aspirin plus a thienopyridine does not reduce the incidence of cardiac events after coronary intervention.\textsuperscript{50}

**Conditions That Require Antithrombotic Regimens in Which Combined Use of Antiplatelet and Anticoagulant Drugs Is Necessary**

**Management of Patients With Prosthetic Heart Valves**

Although prosthetic valve thrombosis is relatively rare, it can be catastrophic and therefore requires prophylaxis. In a review of 11 randomized clinical trials that involved 2428 patients, Little and Massel\textsuperscript{51} considered studies conducted throughout the world in which oral anticoagulation was compared with oral anticoagulation combined with administration of an antiplatelet agent, either aspirin or dipyridamole, and they reached the following conclusions: (1) the combination regimen resulted in a statistically significant and biologically important diminution in thromboembolic events with a treatment effect of relative risk reduction of 42%; (2) the corresponding relative risk reduction for mortality was 58% and did not differ whether aspirin or dipyridamole was the antiplatelet agent; and (3) major bleeding events increased significantly with combination therapy with an odds ratio of 1.66 and an apparent dose-dependent effect seen with aspirin. Direct comparisons of dipyridamole with aspirin, each in combination with warfarin showed no significant difference in the incidence of thromboembolic events.\textsuperscript{52}

Recommendations in the American College of Cardiology/American Heart Association (ACC/AHA) 2006 Guidelines\textsuperscript{53} for the Management of Patients with Valvular Heart Disease are concordant with these conclusions. Although it is well recognized that the risk of thrombosis on prosthetic valves is greater with valves in the mitral compared with the aortic position and with mechanical compared with bioprosthetic valve replacements, continuous therapeutic anticoagulation with oral agents and frequent monitoring for all patients with mechanical valves are justified. Targeted INR and duration of anticoagulation should be tailored to estimation of risk attributable to the valvular position of the prosthesis, the presence or absence of atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and a hypercoagulable state. Patients at low risk can be managed with a targeted INR value of 2.0 to 3.0, whereas patients at high risk require anticoagulation with a targeted INR of 2.5 to 3.5. Bioprosthetic valves are less prone to be compromised by thrombosis compared with mechanical valves. Accordingly, recommended targeted INR values are in the lower range, and recommended duration of therapy is ≤3 months for patients at low risk with bioprosthetic valves. The recommendations in the ACC/AHA Guidelines are that aspirin (75 to 100 mg/d) should be given to all patients with prosthetic valves regardless of risk stratification and the type and locus of the prosthetic valve.

If an antithrombotic regimen must be interrupted for a surgical procedure that entails a high risk of major bleeding, the use of unfractionated heparin or low molecular weight heparin is justified in patients at high risk. Interruptions of oral anticoagulation for ≤3 days should be the goal. Perioperative bridging therapy with unfractionated and low molecular weight heparin regimens has led to good clinical outcomes.\textsuperscript{54} This strategy has been effective also in patients treated with warfarin for venous thromboembolic disease and arterial thromboembolism as well as those with mechanical heart valves.\textsuperscript{55}

**Acute Arterial Thrombosis**

Acute arterial thrombosis, the proximate cause of MI in the majority of patients, is optimally treated with a combination of antiplatelet and anticoagulant therapy. Even though platelets are pivotal in arterial thrombosis,\textsuperscript{56,57} antiplatelet therapy alone is not sufficient. Heparin was found to be superior to aspirin in patients with unstable angina,\textsuperscript{58} but the combination of aspirin plus heparin followed by aspirin alone more effectively prevented recurrent ischemic events when treatment with heparin had been discontinued.\textsuperscript{59}

The addition of more powerful antiplatelet agents to treatment with aspirin plus the parenteral anticoagulants heparin or enoxaparin leads to an increased reduction in the incidence of ischemic events. Thus, clopidogrel improved short-term outcomes in patients with both non-ST elevation MI\textsuperscript{44} and ST elevation MI.\textsuperscript{60} Similarly, the addition of a GP IIb-IIIa antagonist to treatment with aspirin plus heparin improved outcomes.\textsuperscript{61} Patients treated with aspirin plus tirofiban in the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study exhibited greater mortality compared with that seen with aspirin plus heparin or aspirin plus heparin plus tirofiban.\textsuperscript{62} These results underscore the essential role of anticoagulants in addition to the pivotal role for antiplatelet agents in the treatment of patients with acute thrombotic arterial occlusion, particularly when the anticoagulant is heparin or enoxaparin. Recent results demonstrate that when the anticoagulant is bivalirudin (a direct thrombin inhibitor), the addition of a GP IIb-IIIa inhibitor to an antiplatelet regimen of aspirin does not further reduce the incidence of ischemic events.\textsuperscript{62}

The addition of clopidogrel to treatment with aspirin plus an anticoagulant plus a fibrinolytic agent reduced the incidence of subsequent ischemic events that complicate ST elevation MI.\textsuperscript{60} The reduction was not accompanied by a significant increase in the incidence of bleeding complications. By contrast, the addition of the GP IIb-IIIa antagonist abciximab to the combination of aspirin plus heparin plus a fibrinolytic agent reduced the incidence of ischemic events but at the expense of an increased incidence of bleeding complications.\textsuperscript{63} Similarly, the addition of a GP IIb-IIIa antagonist to treatment with aspirin plus bivalirudin increased the risk of bleeding in patients with ACS.\textsuperscript{62}

Recognition of the profound and negative implications of bleeding complications, as discussed below, has altered the framework for selection of therapy for patients with acute arterial thrombosis. Rather than an exclusive focus on strat-
egies designed to reduce the incidence of recurrent ischemic events, treatment is designed to minimize their incidence without a marked increase in the risk of bleeding. Optimal treatment of patients with acute arterial thrombosis requires a combination of anticoagulants and antiplatelet agents. Brief intense therapy with anticoagulants plus antiplatelet agents is used to stabilize coronary thrombi and prepare the patient for coronary intervention. After coronary intervention, longer-term treatment is implemented with aspirin plus a thienopyridine. A not infrequent challenge to the clinician is when this treatment strategy conflicts with the implications of concomitant conditions that mandate treatment with anticoagulants. A comparison of the risk of bleeding after coronary stenting in patients treated with aspirin plus a thienopyridine compared with aspirin, a thienopyridine, and warfarin demonstrated a substantial (7%) increase in the risk of major bleeding. A larger analysis did not identify an excess of death after 6 months in patients treated with aspirin, a thienopyridine, and warfarin compared with aspirin and a thienopyridine. However, this analysis was retrospective. In general, available information is consistent with the view that a combination of an anticoagulant and antiplatelet therapy that entails the use of aspirin plus a thienopyridine increases the risk of bleeding.

**Risks of Antithrombotic Therapy**

**Bleeding**
The primary objective of antithrombotic therapy is to prevent thrombosis that results in the pathological occlusion of a blood vessel. The challenge is to prevent thrombosis yet maintain hemostasis, namely the capacity to preclude hemorrhage. The most serious adverse effect of antithrombotic therapy is bleeding. The association between bleeding and other consequent deleterious phenomena in patients with an ACS underscores the importance of prevention of bleeding.

Eikelboom and colleagues found that patients with an ACS who experienced major bleeding were 5 times more likely to die in the next month and 1.5 times more likely to die between 1 and 6 months later. The strong association between bleeding and mortality does not by itself establish causality. However, bleeding and transfusion of blood products are associated with other factors that may contribute to an increased risk of death. Bleeding may lead to interruption of antithrombotic therapy, the transfusion of blood products, or both. Antithrombotic therapy is regularly discontinued, at least temporarily, after an episode of major bleeding. Premature discontinuation of antithrombotic therapy after placement of coronary stents is associated with a substantially increased risk of thrombotic occlusion. Transfusion of blood products initiated after an episode of major bleeding is associated with increased mortality. Thus, bleeding must be considered more than simply a minor complication that should be avoided. Bleeding is clearly associated with and may contribute to an increased risk of death. The relative risks ascribable to recurrent ischemia compared with those ascribable to major bleeding and its consequences remain to be determined. Nevertheless, agents that reduce bleeding without a concomitant increase in ischemic complications are likely to lead to improve overall outcomes.

**Thrombosis**
Antithrombotic therapy is, of course, a double-edged sword. As discussed above, its propensity to predispose to bleeding can have profoundly deleterious consequences. Conversely, antithrombotic therapy of insufficient intensity can predispose to recurrent thrombosis with catastrophic complications. The failure to prevent recurrent thrombosis has been described by some as “resistance” to therapy. Defined in this manner, “resistance” reflects multiple genetic and environmental factors. Thus, in many instances “resistance” to antithrombotic agents reflects a predisposition to thrombosis rather than biochemically determined resistance to the agent itself. Because of the multiple causes of “resistance,” some patients who are hyporesponsive to 1 agent may be hyporesponsive to an alternative agent for the same reason or because of altered expression of a gene that drives synthesis of a protein instrumental in pathways affected by both agents.

Premature discontinuation of anticoagulants or antiplatelet drugs with consequent thrombosis must be avoided. Unfortunately, specific antidotes that neutralize effects of all antithrombotic agents or regimens are not routinely available. Protamine can be used to reverse effects of unfractionated and, to a lesser extent, low molecular weight heparin, but this agent entails a risk of recurrent thrombosis. Similarly, administration of vitamin K or replenishment of coagulation factors with fresh frozen plasma can be used to reverse effects of vitamin K antagonists, but such treatments also entail a risk of recurrent thrombosis. Administration of agents that promote thrombosis such as tissue factor or activated FVIIa should be reserved for life-threatening bleeding because of the great risk of recurrent thrombosis.

**Adverse Drug Reactions**
Several specific drug-dependent adverse reactions may require cessation of administration of a particular antithrombotic agent. Perhaps most notable is heparin-induced thrombocytopenia, an unfortunately common phenomenon related to interaction of antibodies against platelet factor IV–heparin complexes. Even in the absence of heparin-induced thrombocytopenia, heparin paradoxically activates platelets despite being an anticoagulant. Treatment of heparin-induced thrombocytopenia that complicates thrombosis requires short-term therapy with a direct thrombin inhibitor followed by administration of orally active vitamin K antagonists. When vitamin K antagonists are used in this setting, loading doses should be avoided and low doses should be used to minimize the risk of gangrene and skin necrosis in patients that have been compromised by heparin-induced thrombocytopenia.

Warfarin-induced skin necrosis is another complication that requires cessation of antithrombotic therapy. This condition occurs in between 0.01% and 1% of patients treated with the drug. The most common underlying predisposing factor is protein C deficiency, but the condition has been seen in rare cases in association with congenital protein S defi-
ciency as well. Reduction of concentrations of the naturally occurring anticoagulant proteins that participate in the protein C system appears to account for increased risk.76

Other drug-class–specific adverse effects that may be encountered include induction of thrombotic thrombocytopenic purpura that may be encountered with thienopyridine derivatives such as clopidogrel and ticlopidine.77,78 Because of its more rapid onset of action and predilection to induce thrombotic thrombocytopenic purpura at a lower incidence, clopidogrel has become the primary member of the class used clinically.

In addition to obvious potentially adverse reactions induced by antithrombotic agents, potentiation of effects of such agents by other classes of drugs developed to target entirely different systems can occur. A cogent example is the anticoagulant effect of statins, which appears to depend primarily on diminished expression of tissue factor and increased expression of thrombomodulin on endothelial cells that can enhance the activity of the naturally occurring endogenous anticoagulant system, in which activation of protein C leads to neutralization and degradation of FVa and FVIIIa. The anticoagulant effects of statins may account for some of their clinical benefit—a so-called beneficial pleiotropic effect. However, unrecognized potentiation of anticoagulant effects may occur, which can lead to adverse effects in patients treated with antithrombotic drugs. Such phenomena may reflect also the profibrinolytic and antiplatelet effects that have been attributed to statins.80

Monitoring of Antithrombotic Therapy

Although thrombosis and hemostasis are dependent on coordinated interactions between platelets and the coagulation cascade, the effects of antithrombotic therapy are monitored most commonly with tests that separately assess the coagulation cascade and platelet function. The most commonly used tests to assess the status of the coagulation cascade are the prothrombin time and the activated partial thromboplastin time. The prothrombin time identifies the interval required for clot formation in response to a physiological stimulus (exposure of recalcified plasma to lipidated tissue factor); however, the relatively short time to clot (10 to 12 seconds) may preclude in vitro detection of effects of diverse agents on clot formation. The activated partial thromboplastin time identifies the interval required for clot formation in response to a nonphysiological stimulus such as kaolin, which leads to primary activation of the intrinsic or contact pathway. Both procedures have utility in monitoring of effects of specific anticoagulants (for vitamin K antagonists, prothrombin time is used; for unfractionated heparin, activated partial thromboplastin time is used) but have limited utility with respect to assessment of effects of newer anticoagulants, particularly those that inhibit predominantly FXa. Because both tests are performed with plasma rather than whole blood, the contributions of platelets to clot formation are not discernible. The presence of undefined concentrations of proteins that bind anticoagulants such as heparin in the test tube can lead to results that are not indicative of the status of the coagulation system in vivo. “Therapeutic” values applicable to anticoagulation with any 1 agent are not necessarily applicable to results with another agent used to treat a patient.

The most commonly used test of platelet function is turbidometric assessment of the aggregation of platelets. This procedure assesses 1 component of activation, the aggregation of platelets. It does not elucidate interactions between platelets and the coagulation system. Several procedures are performed with whole blood to assess clot formation. These include the platelet function analyzer 100 procedure and thromboelastography. The VerifyNow point-of-care system (previously called the rapid platelet function analyzer; AccuMetrics, San Diego, Calif) has been refined to evaluate effects of specific agents such as aspirin, GP IIb-IIIa antagonists, and P2Y12 antagonists. Recent studies have shown that patients in whom inhibition of platelet function is inadequate experience recurrent MI81 and that bleeding occurs in patients given excessive doses.82 These observations underscore the potential value of individualization of dosage. Because activation of platelets may contribute not only to periprocedural complications but also to subsequent cardiovascular events,83 the availability of standardized procedures that accurately and precisely define platelet function may ultimately improve outcomes.

When tests of the coagulation system are performed with whole blood, the influence of antiplatelet therapy on the time to clot formation is evident. The activated clotting time is a common catheterization laboratory test in which coagulation is initiated through activation of the intrinsic or contact pathway. Prolongation of the activated clotting time is seen when patients are treated with GP IIb-IIIa antagonists.84 An adaptation of the activated clotting time in which clotting is initiated with lipidated tissue factor facilitates detection of antithrombotic effects of diverse anticoagulants and antiplatelet agents.85 End point assays that are sensitive to the combined effects of anticoagulants and antiplatelet agents may enhance identification of patients at increased risk of either bleeding or complications attributable to thrombosis.

Antithrombotic Agents in Development

Numerous anticoagulant and antiplatelet agents are in clinical development. Oral and parenteral agents that are direct inhibitors of activated coagulation factors such as FXa, the tissue factor/FVIIa complex, FIIa (thrombin), and FIXa are in clinical trials. Direct anticoagulants offer the promise of induction of a more consistent antithrombotic effect. A new technology that employs aptamers, which is a single strand of nucleic acids that bind to the protein of interest, may offer the promise of rapid neutralization of the effect when the complementary strand is administered. Oral and parenteral antiplatelet agents in development include more powerful inhibitors of the P2Y12 (ADP) receptor as well as inhibitors of the thrombin (protease-activated receptor-1) receptor. Although such agents are promising, when developed they are likely to pose challenges for the clinician if only because the expanding armamentarium will suggest the value of combinations of antithrombotic agents that will not yet have been tested in randomized clinical trials.
Principles Applicable to Management of the Complex Patient

The juridical doctrine of *Lex specialis* (the prevalence of a more specific law over a more general one when 2 laws contradict each other) addresses a paradox worthy of consideration. A law that is highly specific leads to unambiguous application in a very small number of cases but has little general applicability. Conversely, a law that paints with a broad brush may be generally applicable yet irrelevant in highly specific circumstances. The clinician who manages complex patients with antithrombotic treatment regimens encounters analogous conflicts that require resolution. As implied by analogy with *Lex specialis*, clinical trials cannot provide definitive answers for management of a given complex patient. Furthermore, the general principles of targeting of the coagulation system for treatment of venous thromboembolic disease and platelet activation for treatment of arterial thrombosis may not suffice as guidance in the complex patient with highly specific features. There can be no clinical trial with a sufficient number of patients to reflect the pivotal aspects of a given complex patient (eg, the duration and severity of components of a complex disorder such as atrial fibrillation in a patient with an ACS, matched for age, gender, comorbidities, who requires a drug-eluting stent and has a history of a bleeding diathesis). Accordingly, the more general the population studied in a clinical trial, the less relevance it may have to a given complex patient. The more specifically the population in a clinical trial is defined, the less the relevance of its results will be for a given patient with complexities that distinguish that patient from those typical of the population studied in the trial.

What is most threatening to a given patient requires particular consideration. The deleterious effects of bleeding, such as the effects of transfusion required for its treatment, can compromise survival. Thus, assessment of the risk of bleeding will often be a primary determinant of the intensity and diversity of the antithrombotic regimen that can be implemented.

Patients will often make a choice regarding the weight of diverse threats. For example, some patients may elect percutaneous coronary intervention rather than surgical coronary revascularization because of the importance they ascribe to preservation of cognitive function that may be compromised by circulatory support provided for cardiopulmonary bypass, despite the fact that they are better suited for the latter on the basis of current clinical criteria.

The relative risks of failure of antithrombotic therapy will obviously vary in relation to the locus of thrombosis and potential additional therapeutic interventions that might be undertaken if recurrent thrombosis should occur. A patient who has sustained massive or multiple MIs and who experiences recurrent coronary thrombosis faces a greater risk of death compared with that of a patient with peripheral arterial disease whose claudication has been relieved and who may sustain recurrent thrombosis that leads to the necessity for medical or surgical limb revascularization. Thus, if both hypothetical patients had experienced a previous bleeding diathesis, a clinician might well be justified in the use of a less intense antithrombotic regimen for the patient with peripheral arterial disease. In essence then, management of a complex patient with an antithrombotic regimen requires assessment of the hierarchy of risks that confront the specific patient; the potential value of the benefits conferred by the antithrombotic regimen with respect to the magnitude of the risks; the qualified guidance that can be acquired by consideration of results in clinical trials with recognition of the limitations of the pertinence of those results to a given complex patient; an understanding of the nature of interactions between multiple components of the prothrombotic system in vivo such as the coagulation cascade, activation of platelets, and the impact of components of the vessel wall; the primary locus targeted by the antithrombotic regimen (prevention of stroke in a patient with atrial fibrillation who also has peripheral arterial disease and in whom the bleeding risk may be judged to be too high to justify combined anticoagulation and antiplatelet therapy); and clinical judgment predicated on thorough understanding of mechanism of disease and pharmacotherapy.

Coping With Specific Clinical Conundrums

Unfortunately, no ironclad recipes are available for guidance for the physician who deals with the complex patient. The principles discussed above and the results of randomized clinical trials are frequently insufficient to provide a basis for specific decisions pertinent to a given complex patient. A biochemical assay that assesses the combined effect of antiplatelet and anticoagulant therapy on thrombosis and hemostasis may ultimately facilitate selection of individualized therapy. Thoughtful clinical judgment that is based on results of available assays and the risks and benefits germane to each patient is necessary. Principles and the results of clinical trials help, but selection of a specific treatment strategy for a specific complex patient cannot be algorithmically driven. The development of novel agents and the completion of ongoing clinical trials will undoubtedly improve therapy, but these factors will also lead to new conundrums.

An approach to a common conundrum that faces clinicians follows. This dilemma surfaces when a patient treated long-term with an oral vitamin K antagonist (eg, for atrial fibrillation) is diagnosed with a condition that requires dual antiplatelet therapy with aspirin plus a P2Y12 antagonist (eg, has an indication for placement of a coronary stent). The risks of both thrombosis and bleeding must be considered. The optimal antithrombotic regimen to prevent thromboembolic complications from the atrial fibrillation is distinct from that necessary to prevent stent thrombosis (combination of aspirin and clopidogrel, a P2Y12 antagonist). However, treatment with aspirin, clopidogrel, and a vitamin K antagonist entails the risk of bleeding. It is not straightforward to balance the risk of thrombosis and the risk of bleeding. Although bleeding appears to be associated with an increased risk of death, the long-term morbidity plus mortality of an embolic stroke is substantial. Accordingly, if the patient were not judged to be at a particularly high risk of bleeding, the combination of all 3 agents would be justified. In such a setting the risk of bleeding may be decreased by the use of a low dose (81 mg) of aspirin.86
A greater risk of bleeding or the perception of a greater risk of morbidity and mortality associated with bleeding may lead the clinician to consider alternatives, such as surgical revascularization, that do not require dual antiplatelet therapy. On occasion, the indication for long-term anticoagulation will be less compelling (ie, prevention of deep vein thrombosis in an individual at increased risk without recurrent episodes of deep vein thrombosis/pulmonary embolism). In such a setting, the risk of cessation of therapy with an oral anticoagulant may be modest and outweighed by the greater risk of bleeding when aspirin, clopidogrel, and an oral vitamin K antagonist are combined.

It is difficult to address such conundrums. Though ambiguity cannot be avoided entirely, judicious assessment of the risks for individual complex patients, knowledge of mechanisms of action of the therapeutic agents considered and of the pathophysiology of the condition(s) that require treatment, and understanding of the interactions of components of the thrombotic system are the foundation for sound decisions.

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References


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