New Antithrombotic Drugs

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Thrombosis, both venous and arterial, is a major cause of morbidity and mortality worldwide. Consequently, there is an ongoing search for new antithrombotic drugs, particularly novel antiplatelet agents and anticoagulants. A better understanding of the biochemical pathways involved in platelet activation and coagulation and of the links between these systems and the impact of thrombosis on inflammation has led to the identification of new targets for antithrombotic drugs. This paper focuses on these new targets and new antiplatelet drugs and anticoagulants and describes the major advances in the continuing search for more potent antithrombotic drugs that have limited effects on hemostasis.

INTRODUCTION

Thromboembolic disorders are a major cause of death and disability worldwide. Thrombosis can occur in either the arterial or venous circulation (Figure 1). With respect to the arteries, most heart attacks and many strokes are triggered by thrombosis secondary to disrupted atherosclerotic plaques. Atrial fibrillation is another cause of stroke. Patients with this common rhythm abnormality have a fivefold greater risk of having a stroke because of their propensity for left atrial thrombosis and subsequent cerebral embolism.1

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism and is the third most common vascular disorder after heart attack and stroke (http://www.vdf.com).2 The importance of VTE is highlighted by the recent US Surgeon General’s Call to Action aimed at raising awareness about this potentially fatal condition (http://www.surgeongeneral.gov/library/calls/index.html). In contrast to what occurs in arterial thrombosis, venous thrombi usually arise in areas where the vein wall is grossly intact. Sluggish blood flow, endothelial cell activation, and hypercoagulability predispose patients to DVT, which often originates in the veins in the calf.3 If calf DVT propagates into the more proximal veins of the leg, some or all of the thrombus can embolize and lodge in the pulmonary arteries to produce pulmonary embolism, which can be fatal.

Arterial and venous thrombi are composed of platelet aggregates, fibrin, and trapped red cells. Because arterial thrombi form under high-shear conditions, platelets are abundant and fibrin is relatively sparse. In contrast, venous thrombi, which form under low-shear conditions, are rich in fibrin and trapped red cells and contain fewer platelets.4 These features have important implications for antithrombotic therapy. Targeting the components of both arterial and venous thrombi, antithrombotic drugs encompass antiplatelet agents, anticoagulants, and fibrinolytic drugs. Because of the preponderance of platelets in arterial thrombi, antiplatelet drugs are the mainstay of their prevention and treatment.5,6 However, anticoagulants are also effective in this setting, although they are not widely used.7 When arterial thrombi are occlusive and rapid restoration of blood flow is required, mechanical or pharmacological methods are employed to extract, compress, or degrade the thrombi.

Anticoagulants are the mainstay in the prevention and treatment of VTE because fibrin predominates in venous thrombi.8,9 Antiplatelet drugs are less efficacious than anticoagulants in reducing the risk of VTE, which is consistent with the scarcity of platelets in venous thrombi.10 Finally, as in the treatment approach for arterial thrombosis, mechanical and/or pharmacological methods can be used for rapid restoration of blood flow in patients with extensive DVT or pulmonary embolism.11

Despite the widespread use of antithrombotic drugs for the prevention and treatment of arterial and venous thrombosis, thrombotic diseases continue to be a major cause of death and disability. Therefore, there remains a need for more effective therapies to combat these disorders. This paper focuses on new antithrombotic drugs and (i) identifies the medical needs that remain unmet with currently available antithrombotic agents, (ii) describes the targets for the new antithrombotic drugs, (iii) reviews the results of emerging clinical trials supporting these drug targets, and (iv) provides perspective on the opportunities and challenges for these new agents.

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MEDICAL NEEDS THAT ARE UNMET WITH EXISTING ANTITHROMBOTIC DRUGS

Why do we need new antithrombotic drugs? They are necessary because, with respect to the arteries, recurrent ischemic events are common despite treatment with aspirin and/or clopidogrel, the most widely prescribed antiplatelet drugs. Breakthrough ischemic events may reflect the inability of these agents to fully suppress the stimulus for platelet activation at sites of plaque disruption, or they may be the result of resistance to the antiplatelet effects of aspirin or clopidogrel. Although resistance to the antiplatelet effects of the drugs can be overcome, at least in part, by designing agents that more efficiently inhibit existing targets, incomplete suppression of the stimulus for platelet activation probably calls for drugs that inhibit new targets. Both types of drugs are in the pipeline.

Stoke prevention in patients with atrial fibrillation and prevention of recurrence in patients with unprovoked VTE require long-term anticoagulant therapy, which is best effected with oral agents. For the past 65 years, the only oral anticoagulants that have been available are the vitamin K antagonists, such as warfarin. Although effective, warfarin has many limitations (Table 1). Warfarin doses differ between patients because commonly occurring genetic polymorphisms affect its metabolism, thereby rendering individuals either more sensitive or less sensitive to the drug. Also, dietary vitamin K intake and multiple drug–drug interactions affect the anticoagulant response to the drug. Consequently, patients require frequent coagulation monitoring and dose adjustments to ensure that a therapeutic level of anticoagulation is maintained. Such monitoring is inconvenient for patients and their physicians and costly for the health-care system. Because of this inconvenience, many patients with atrial fibrillation refuse to take anticoagulant therapy, thereby forgoing an opportunity for stroke prevention. Even when patients do take warfarin, therapeutic levels of anticoagulation are achieved only half the time. These problems highlight the need for more convenient oral anticoagulant drugs that can be given in fixed doses and will produce a predictable anticoagulant response such that little or no monitoring is required.

An overarching problem with antithrombotic therapy is the difficulty of striking the optimal balance between efficacy and safety. In the treatment of arterial thrombosis, particularly, there has been a push toward combining antithrombotic drugs in an attempt to prevent recurrent ischemia in patients with acute coronary syndromes (ACSs). Although this approach has resulted in a declining rate of recurrent ischemia, the incidence of bleeding has increased, to the extent that contemporary registry data indicate that ~4% of such patients experience a major hemorrhage, and up to 14% require a blood transfusion. These findings are worrisome because there is mounting evidence that bleeding is associated with adverse cardiovascular outcomes and carries the same risk of mortality that recurrent ischemia does. The adverse impact of bleeding has prompted an evaluation of antithrombotic regimens that maximize efficacy without increasing the risk of bleeding and highlighted the need for antithrombotic drugs that attenuate thrombosis with minimal effects on hemostasis. Only by identifying new targets are we likely to be able to separate these closely linked biological processes.

NOVEL ANTIPLATELET DRUGS

In healthy vasculature, circulating platelets are maintained in an inactive state by nitric oxide and prostacyclin released by endothelial cells lining the blood vessels. Endothelial cells also express ADPase (adenosine diphosphatase), which degrades ADP released from red blood cells and activated platelets, thereby preventing further activation of ADP. When the vessel wall is damaged, the release of these endogenous antiplatelet substances is impaired and subendothelial matrix is exposed. Platelets adhere to exposed collagen and von Willebrand factor (vWF) through receptors that are constitutively expressed on the platelet surface (Figure 2). Adherent platelets integrate signals from the binding interaction, change their shape, secrete ADP from their dense granules, and synthesize and release thromboxane A₂ (TXA₂). The ADP and TXA₂ that are released serve as platelet agonists by activating ambient platelets and recruiting them to the site of vascular injury.

Disruption of the vessel wall also exposes blood to tissue factor–expressing cells. Tissue factor initiates coagulation. Activated platelets potentiate coagulation by expressing phosphatidylserine on their surface. Clotting factor complexes then assemble on the anionic platelet surface and trigger the generation of thrombin. In addition to converting fibrinogen to fibrin, thrombin also serves as a potent platelet agonist and recruits more platelets to the site of vascular injury.
When platelets are activated, glycoprotein (GP) IIb/IIIa (αIIbβ3), the most abundant receptor on the platelet surface, undergoes a conformational change, which increases its capacity to bind fibrinogen. Divalent fibrinogen molecules bridge adjacent platelets together to form platelet aggregates. Fibrin strands, generated by the action of thrombin, then weave these aggregates together to form a platelet–fibrin mesh.

Antiplatelet agents can be subclassified, on the basis of their site of action, into those that inhibit (i) adhesion, (ii) activation, (iii) aggregation, or (iv) platelet-mediated links with inflammation. Of the currently available agents, aspirin, clopidogrel, dipyridamole, and cilostazol inhibit platelet activation, albeit via different mechanisms, whereas GPIIb/IIIa antagonists block platelet aggregation. Some of the novel antiplatelet drugs inhibit new targets, whereas others have been designed to produce greater inhibition of proven targets (Figure 3).

Inhibitors of platelet adhesion
Platelet adhesion is the first step in platelet plug formation at sites of vessel wall injury. Because this process depends on the interaction between subendothelial proteins and receptors on the platelet surface, this step can be inhibited by blocking the platelet receptors for collagen or vWF, blocking the attachment of vWF to collagen, or by directly binding collagen or vWF and preventing their interactions with platelets. The platelet–collagen interaction has received the most attention because collagen is abundant in atherosclerotic plaques, where it contributes to lesion growth and arterial narrowing. Platelets can bind collagen via α2β1 or GPVI and vWF through GPIb. Collagen receptors may be better targets because their overexpression is associated with stroke and myocardial infarction, whereas their underexpression produces only a modest prolongation in bleeding time. Strategies for inhibiting the collagen–platelet interaction include humanized monoclonal antibodies and aptamers against the receptors, small-molecule peptide inhibitors, and proteins derived from the medicinal leech. Few of these agents have been tested in humans, and none has reached phase III.

Figure 2 Role of platelets in thrombosis. Platelets adhere to collagen and vWF exposed at sites of vascular injury through receptors that are constitutively expressed on their surface. Adherent platelets integrate signals, change their shape, and release ADP and TXA2, which activate ambient platelets and recruit them to the site of injury. Platelet activation triggers signaling pathways that induce a conformational change in GPIIb/IIa (αIIbβ3), the most abundant integrin on the platelet surface, which increases its affinity for fibrinogen. Bound fibrinogen then bridges adjacent platelets to form aggregates. ADP, adenosine diphosphate; TXA2, thromboxane A2; vWF, von Willebrand factor.

Figure 3 Sites of action of antiplatelet drugs. Adhesion antagonists block the binding of subendothelial collagen or vWF to receptors on the platelet surface. Inhibitors of platelet activation include drugs that (i) block the TXA2 pathway by inhibiting TXA2 synthesis or by blocking the TP, (ii) inhibit P2Y12, the ADP receptor, or (iii) block the type 1 PAR-1, the thrombin receptor. Inhibitors of platelet aggregation block GPIIb/IIa, the fibrinogen receptor, thereby preventing fibrinogen-mediated platelet-to-platelet bridging. ADP, adenosine diphosphate; PAR-1, protease activated receptor-1; TP, thromboxane receptor; TXA2, thromboxane A2; vWF, von Willebrand factor.
Inhibitors of platelet activation

New antiplatelet agents designed to block platelet activation target the TXA2 pathway, P2Y12 protease activated receptor-1 (PAR-1), or phosphodiesterase. Drugs against each of these targets will be described separately.

Inhibitors of the TXA2 pathway. Aspirin inhibits TXA2 synthesis by irreversibly acetyling cyclooxygenase 1.24 Although aspirin is widely used, some patients are resistant to its effects. The definition of aspirin resistance varies,25 but incomplete suppression of TXA2 synthesis has been correlated with an increased risk of subsequent cardiovascular events.26 In order to overcome this problem, other strategies to block the TXA2 pathway have been investigated. These include inhibition of thromboxane synthetase—the final step in TXA2 synthesis—and blockade of the thromboxane receptor.27 On their own, thromboxane synthetase inhibitors have limited efficacy because blockade at this step results in accumulation of endoperoxide precursors, which can serve as platelet agonists.28 However, thromboxane synthetase inhibitors or aspirin can be combined with thromboxane receptor antagonists, both to attenuate synthesis and to block the receptor.29,30 To date, in humans, neither strategy has been proven to be more effective than aspirin.

Inhibitors of P2Y12. Clopidogrel is a thienopyridine that irreversibly inhibits P2Y12 on the platelet surface.31 A produrg, clopidogrel must be metabolized in the liver to generate the active metabolites that inhibit the ADP receptor. Consequently, the antiplatelet effects of clopidogrel are both time- and dose-dependent and reach a maximum of ~60% inhibition of ADP-induced platelet aggregation. In addition to this ceiling effect, some patients are resistant to the effects of clopidogrel.32 Such resistance may reflect the presence of commonly occurring polymorphisms in CYP2C19 or 2C9,33,34 which are important for clopidogrel metabolism, or may be caused by concomitant administration of drugs that inhibit CYP3A4.35 which is also involved in clopidogrel metabolism.

New P2Y12 inhibitors include prasugrel,36 cangrelor,37 and ticagrelor.38 Like clopidogrel, prasugrel is a thienopyridine that requires hepatic metabolism to generate active metabolites. However, because the metabolism of prasugrel is more efficient than that of clopidogrel, prasugrel produces more rapid, more consistent, and more potent inhibition of ADP-induced platelet aggregation than clopidogrel does.39 Furthermore, the polymorphisms in CYP2C19 and CYP2C9 that limit the effectiveness of clopidogrel do not affect prasugrel.33

Prasugrel was found to be more effective than clopidogrel in preventing recurrent ischemic events after percutaneous coronary interventions (PCIs), but it caused more bleeding.40 This finding suggests that greater P2Y12 blockade translates into improved efficacy but also increases the risk of bleeding. Patients with a previous history of stroke, those >75 years of age, and those weighing <60 kg had the highest risk of bleeding, including fatal bleeding, when treated with prasugrel. Whether dose reduction in such patients will mitigate this risk is unclear.

Cangrelor and ticagrelor are direct-acting reversible inhibitors of P2Y12. Cangrelor, which is administered intravenously, has a rapid onset and offset of action, which may be advantageous in the PCI setting.37,41 Ongoing phase III trials are comparing cangrelor with clopidogrel in PCI patients. Ticagrelor is an orally active inhibitor of P2Y12 that provides more rapid and complete antiplatelet effect than clopidogrel. Although it is uncertain whether more potent ex vivo platelet inhibition with ticagrelor will translate into better clinical outcomes, the results with prasugrel suggest that this is likely. We will soon have a definitive answer; a large phase III study comparing ticagrelor with clopidogrel in patients with non-ST or ST-elevation ACS has been completed, and the results are forthcoming.42

PAR-1 inhibitors. Thrombin, the most potent platelet agonist, activates platelets via PAR-1 and PAR-2, which are G-protein-coupled receptors. PAR-1 is the higher-affinity receptor and the major effector of thrombin signaling, whereas PAR-4 augments these effects when higher concentrations of thrombin are generated. Although inhibitors of both PAR-1 and PAR-4 have been developed, PAR-1 antagonists, such as SCH530348 and E5555, are in more advanced stages of clinical evaluation.43 SCH530348, an orally active PAR-1 inhibitor, showed promising results in phase II evaluation44 and is now being evaluated against a placebo as an adjunct to aspirin and/or clopidogrel in two large phase III trials. E5555, another orally active PAR-1 antagonist, is currently undergoing extensive phase II evaluation (clinicaltrials.gov/NCT00548587). This class of drugs seemed to exhibit an excellent safety profile in phase II studies—possibly because the higher concentrations of thrombin generated during the hemostatic process engage PAR-4. More work is needed to investigate this possibility.

Phosphodiesterase inhibitors. Cyclic adenosine monophosphate serves as an intracellular signal to suppress platelet activation and subsequent aggregation. By inhibiting phosphodiesterase, dipyridamole and cilostazol increase the levels of cyclic adenosine monophosphate. Because the risk of bleeding with these agents appears to be low, the utility of these and other phosphodiesterase inhibitors is being evaluated for secondary prevention in patients with atherosclerotic diseases, particularly stroke.

Inhibitors of platelet aggregation

GPIIb/IIIa antagonists, which block the final common pathway for platelet aggregation, are potent antiplatelet drugs. Intravenous GPIIb/IIIa antagonists have been shown to reduce ischemic events both in the management of ACS and as adjunctive therapy during PCI. A pooled analysis of data on 32,135 patients from 16 randomized trials revealed a significant reduction, within 48–96 h, in the combined end point of death or myocardial infarction. This reduction persisted at 30 days and at 6 months.45 In contrast, trials with orally administered GPIIb/IIIa inhibitors have failed to demonstrate any benefit. In a pooled analysis of more than 33,000 patients, the use of oral GPIIb/IIIa
inhibitors was associated with a significant increase in mortality.\textsuperscript{46} The explanation for the lack of efficacy of oral GPIIb/IIIa antagonists is unknown, but it may be related to partial agonist activity and/or proinflammatory effects.\textsuperscript{47} Regardless of the mechanism, the disappointing results have halted the development of this class of drugs.

**Inhibitors of platelet-dependent inflammatory pathways**

Inflammation contributes to the progression of atherosclerosis and may be an important determinant of the post-thrombotic syndrome, which complicates DVT.\textsuperscript{48} Platelets contribute to inflammation, at least in part, via the CD40/CD40 ligand pathway and P-selectin.\textsuperscript{49} CD40 is a soluble cell attractant released from activated platelets, which, when bound to CD40 ligand on monocytes, endothelial cells, or T-lymphocytes, elicits a proinflammatory response. CD40 ligand is highly expressed in atheromatous plaques. Consequently, inhibition of the CD40/CD40 ligand axis may represent a novel method for delaying the progression of atherosclerosis.\textsuperscript{50}

P-selectin, a cell-adhesion molecule expressed on activated platelets and endothelial cells, binds a counter-receptor to leukocytes. Such binding results in the formation of platelet-leukocyte aggregates and the tethering of leukocytes to thrombi and to the activated endothelial cell surface. Inhibition of these interactions attenuates thrombosis and reduces inflammation in animal models of DVT.\textsuperscript{51} Whether similar effects occur in humans is unknown.

**NOVEL ANTICOAGULANTS**

The greatest unmet medical need in anticoagulant therapy is the need for a simple and convenient replacement for warfarin to streamline long-term treatment. Most of the attention has focused on the development of oral agents that target thrombin or factor Xa (Figure 4). However, the utility of a long-acting synthetic parenteral pentasaccharide, which also targets factor Xa, is under investigation.\textsuperscript{52}

Why have thrombin and factor Xa been chosen as targets for these new agents, and what are the potential advantages of the new drugs over warfarin? Thrombin is a logical target for new anticoagulants. As the final effector in coagulation, thrombin converts fibrinogen to fibrin. Thrombin also amplifies its own generation by feedback activation of factors V and VIII, key cofactors for the prothrombinase and intrinsic tenase complex, respectively. In addition, as the most potent platelet agonist, thrombin coordinates the process of platelet activation and aggregation with coagulation. Because of its multiple roles in coagulation, the inhibition of thrombin not only blocks fibrin formation but also attenuates thrombin generation and platelet activation.\textsuperscript{53}

The suitability of thrombin as a target was validated by clinical experience with ximelagatran, the first oral, direct thrombin inhibitor. In a large clinical trial program, ximelagatran was shown to be not inferior to conventional anticoagulant strategies for prevention and treatment of VTE and for stroke prevention in atrial fibrillation.\textsuperscript{54} It was launched in some countries and was briefly on the market, but ximelagatran was withdrawn because of potential hepatotoxicity associated with its use.\textsuperscript{55} Nonetheless, the favorable results with this drug confirmed long-term thrombin inhibition as an effective and safe strategy, at least with regard to the hemorrhage problem, and set the stage for other direct thrombin inhibitors.

Factor Xa also is an attractive target.\textsuperscript{56} When factor Xa is assembled along with factor Va on the surface of activated platelets, the resultant prothrombinase complex is a potent activator of prothrombin. Although direct comparisons of inhibitors of factor Xa and of thrombin in animal models have suggested that, for similar antithrombotic efficacy, upstream inhibition at the level of factor Xa causes less bleeding than downstream blockade of thrombin, head-to-head trials in humans have not been performed.\textsuperscript{57} Nonetheless, in phase II trials, dose-dependent increases in the rates of bleeding are observed with inhibitors of either factor Xa or thrombin.\textsuperscript{58–60} Therefore, at this point, there is no evidence that one target is any better than the other.

What are the potential advantages of the new anticoagulants over warfarin? The new agents have been designed to be administered in fixed doses without the need for routine coagulation monitoring.\textsuperscript{52} This is possible because these agents are not affected by any food constituents and the potential for drug-drug interactions is low. Consequently, the new anticoagulants have the potential to simplify long-term anticoagulant therapy. Will they prove superior to warfarin? Promising results with both thrombin and factor Xa antagonists suggest that they will.

**Thrombin inhibitors**

Dabigatran etexilate is an oral, direct thrombin inhibitor that is in the most advanced stages of development (Table 2). A prodrug, dabigatran etexilate has an oral bioavailability of 6%. After oral administration, dabigatran etexilate is rapidly and completely converted by esterases to dabigatran. Plasma levels of dabigatran peak in 2 h, and the drug is cleared via the kidneys with a half-life of 14–17 h, which permits either once-daily or
Apixaban also appears to be a promising drug for thromboprophylaxis after orthopedic surgery, and rivaroxaban and apixaban are both undergoing extensive phase III evaluation for VTE prevention in medical patients, VTE treatment, stroke prevention in atrial fibrillation, and prevention of recurrent ischemic events in ACS patients. The first phase III results comparing rivaroxaban with warfarin in the treatment of VTE are expected in late 2009.

Idrabiotaparinux is a long-acting pentasaccharide that is administered subcutaneously on a once-weekly basis. The drug acts as an anticoagulant by binding to antithrombin and inducing a conformational change that accelerates the rate at which antithrombin inhibits factor Xa. Thus, in contrast to oral factor Xa inhibitors, which bind directly and reversibly to the active site of factor Xa, idrabiotaparinux is an indirect inhibitor of factor Xa that catalyzes the formation of irreversible antithrombin–factor Xa complexes.

A unique aspect of idrabiotaparinux is the presence of a biotin moiety. Should rapid reversal of the anticoagulant effects of idrabiotaparinux be required, intravenous avidin can be administered. Avidin, an egg white–derived protein, binds biotin with high affinity and the avidin–idrabiotaparinux complex is then rapidly cleared. Idrabiotaparinux is thus the only one of the new oral or long-acting parenteral anticoagulants to have a specific antidote. In ongoing phase III trials, idrabiotaparinux is being compared with conventional anticoagulant therapy for treatment of pulmonary embolism and with warfarin for stroke prevention in atrial fibrillation.

### CONCLUSIONS AND FUTURE DIRECTIONS

A large number of new antithrombotic drugs are under development. Designed to inhibit specific targets, several of these agents have already shown advantages over existing drugs. For example, prasugrel and ticagrelor produce more rapid, more predictable, and more potent inhibition of ADP-induced platelet aggregation than clopidogrel does. Likewise, when given in fixed doses, the new oral thrombin and factor Xa inhibitors produce a more predictable anticoagulant response than warfarin does, eliminating the need for routine monitoring and frequent dose adjustments. These drugs therefore have clear benefits with respect to pharmacokinetics and pharmacodynamics as compared with existing agents, but do these properties confer a therapeutic advantage, and, if so, to what extent is enhanced efficacy offset by increased bleeding?

The new oral anticoagulants and idrabiotaparinux were designed to replace warfarin. Because they produce a more predictable anticoagulant response, the new agents have the potential to be both more effective and safer than warfarin. In addition, they will be more convenient to administer because they can be given in fixed doses without routine coagulation monitoring. With the clinical trials nearing completion, we may soon have the first replacements for warfarin in more than 65 years.

In the category of antiplatelet agents, prasugrel has been shown to be more effective than clopidogrel in preventing recurrent cardiovascular events in ACS patients undergoing...
PCI. However, the improvement in efficacy is offset, at least in part, by an increase in bleeding. Ongoing trials will determine whether careful patient selection and appropriate dose reduction will reduce the risk of hemorrhage without compromising efficacy. Likewise, we will soon know whether reversible P2Y12 antagonists such as ticagrelor have a better risk–benefit profile than irreversible inhibitors, such as prasugrel.

Of greater concern is the potential for bleeding when new anticoagulants are used in addition to aspirin plus clopidogrel in ACS patients. Phase II trials suggest that this strategy results in a dose-dependent reduction in recurrent ischemic events but an increase in the risk of bleeding.73 This is problematic, because there is mounting evidence that bleeding in ACS patients is associated with an increased risk of myocardial infarction, stroke, or death.

How might we find a balance between efficacy and safety in the ACS setting? Instead of using the new anticoagulants in addition to aspirin and clopidogrel, they could be used in place of the antplatelet drugs. Warfarin reduces the risk of recurrent cardiovascular events when used for secondary prevention after myocardial infarction.74 Why would the new agents not do the same? The new anticoagulants will be as convenient to administer as antiplatelet drugs are and will produce a more consistent level of anticoagulation than warfarin does.

What is the future of antithrombotic therapy? We now have drugs that have the potential to replace clopidogrel and warfarin. We also have agents that may find the “sweet spot” in the balance between efficacy and safety. In the short term, this includes PAR-1 antagonists, whereas in the future, we may have inhibitors of platelet adhesion or activation, or modulators of links between platelets and inflammation. With new targets and new drugs, antithrombotic therapy is evolving, and our armamentarium of agents to combat thromboembolic disorders is rapidly expanding.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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