New Antithrombotic Drugs*

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This chapter focuses on new antithrombotic drugs that are in phase II or III clinical testing. Development of these new agents was prompted by limitations of existing antiplatelet, anticoagulant, or fibrinolytic drugs. Addressing these unmet needs, this chapter (1) outlines the rationale for development of new antithrombotic agents, (2) describes the new antiplatelet, anticoagulant, and fibrinolytic drugs, and (3) provides clinical perspectives on the opportunities and challenges faced by these novel agents. ***(CHEST 2008; 133:234S–256S)***

Key words: anticoagulants; antiplatelet drugs; antithrombotic drug; fibrinolytic agents

Abbreviations: ACS = acute coronary syndrome; CYP = cytochrome P450; DVT = deep vein thrombosis; factor VIIai = active site-blocked factor VIIa; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NAPc2 = nematode anticoagulant peptide c2; PAI-1 = type 1 plasminogen activator inhibitor; PAR = protease activated receptor; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PF4 = platelet factor 4; TAFI = thrombin activatable fibrinolysis inhibitor; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue-type plasminogen activator; TRAP = thrombin receptor agonist peptide; u-PA = urokinase-type plasminogen activator; VTE = venous thromboembolism

Arterial and venous thrombosis are major causes of morbidity and mortality. Whereas arterial thrombosis is the most common cause of myocardial infarction (MI), ischemic stroke and limb gangrene, deep vein thrombosis (DVT) leads to pulmonary embolism (PE), which can be fatal, and to the postphlebitic syndrome. Arterial thrombi, which form under high shear conditions, consist of platelet aggregates held together by small amounts of fibrin.[1] Because of the predominance of platelets, strategies to inhibit arterial thrombogenesis focus mainly on drugs that block platelet function, but include anticoagulants for prevention of cardioembolic events in patients with atrial fibrillation or mechanical heart valves. Fibrinolytic drugs are used for rapid restoration of antegrade blood flow in patients with acute myocardial infarction who do not undergo a primary percutaneous coronary intervention (PCI) and for treatment of acute ischemic stroke.

Venous thrombi, which form under low shear, are composed mainly of fibrin and trapped red cells, and contain relatively few platelets.[1] With the predominance of fibrin in venous thrombi, anticoagulants are the agents of choice for the prevention and treatment of venous thromboembolism (VTE). Systemic fibrinolytic therapy is used for treatment of massive PE and for management of selected patients with submassive PE, whereas catheter-directed fibrinolytic therapy is used in some patients with extensive iliofemoral DVT.

Limitations of existing antithrombotic drugs have prompted a search for novel agents. Focusing on new drugs for the prevention and treatment of arterial and venous thrombosis, this chapter[1] outlines the rationale for development of new antithrombotic drugs,[2] describes the new antithrombotic drugs, focusing primarily on those in Phase II or III clinical

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testing, and[3] provides perspective on the unmet needs in antithrombotic therapy.

2.0 Rationale for Development of New Antithrombotic Drugs

Better understanding of the molecular mechanisms underlying thrombogenesis, advances in recombinant DNA technology, isolation and characterization of antithrombotic proteins from hematophagous organisms, and improvements in structure-based drug design have accelerated the pace of drug discovery. With these advances, we now have an array of new antithrombotic drugs.

The established efficacy of aspirin and the thienopyridines validates platelet cyclooxygenase-1 and ADP receptors as targets for antiplatelet drugs.[2,3] By irreversibly acetylating cyclooxygenase-1, aspirin inhibits arachidonate-induced platelet aggregation and reduces thromboxane A_2 synthesis by $> 98\%$. Although cheap and effective, breakthrough cardiovascular events occur despite aspirin therapy. Some patients are resistant to usual doses of aspirin as manifested by incomplete inhibition of platelet aggregation and/or ongoing thromboxane A_2 production. Such patients may be more prone to recurrent cardiovascular events.[4–6]

Thromboxane A_2 receptor antagonists were developed, at least in part, to overcome the limitations of aspirin. Thromboxane A_2 induces platelet aggregation by binding to the thromboxane A_2 receptor on platelets. The thromboxane A_2 receptor also binds prostanoids, such as prostaglandin F2α, which can promote platelet aggregation by causing vasoconstriction.

Thromboxane A_2 receptor antagonists block platelet aggregation in response to both thromboxane A_2 and prostanoids. In contrast, aspirin has no effect on prostanoid synthesis and incompletely inhibits thromboxane A_2 synthesis in some patients.[4–6] Therefore, thromboxane A_2 receptor antagonists have the potential to be more effective than aspirin.

The thienopyridines irreversibly inhibit $P2Y_{12}$, a major ADP receptor on the platelet surface. Currently available thienopyridines include ticlopidine and clopidogrel.[7] Clopidogrel has largely replaced ticlopidine because the risk of hematological toxicity is lower and the drug can be given once daily. When given in usual doses, these drugs incompletely inhibit ADP-induced platelet aggregation producing a maximum of 70% inhibition.[7] The extent of inhibition varies between patients and some are resistant to clopidogrel.[8–10]

The thienopyridines have a delayed onset of action because they require metabolic activation.[7] This is problematic in patients undergoing percutaneous coronary interventions (PCI) where rapid platelet inhibition is required. Administration of loading doses of clopidogrel accelerates its antiplatelet effects, but maximum inhibition remains delayed for several hours.[11] Not only do the thienopyridines have a slow onset of action, but their offset of action also is delayed for at least 5 days because the active metabolites of these drugs irreversibly inhibit their target receptor. This causes problems for patients who require urgent surgery because clopidogrel increases the risk of bleeding.[12–14]

The limitations of existing antiplatelet drugs provide opportunities for new agents. Attempts to replace aspirin with other inhibitors of the thromboxane A_2-mediated pathway of platelet aggregation have not yet been successful. Instead, attention has focused on novel ADP receptor antagonists and on drugs that target protease activated receptor (PAR)-1, the major thrombin receptor on platelets. New $P2Y_{12}$ antagonists have been developed to replace clopidogrel. Drugs that produce more predictable inhibition of ADP-induced platelet aggregation may overcome clopidogrel resistance, whereas those with a rapid onset and offset of action may have advantages in the PCI setting. Whether a rapid onset and offset of action is an advantage for long-term administration is uncertain. Although new $P2Y_{12}$ antagonists have the potential to be more efficacious than clopidogrel because they produce more profound inhibition of ADP-induced aggregation, there may be issues with safety. Thus, enhancing the extent of platelet inhibition by adding clopidogrel to aspirin increases the risk of major bleeding,[15,16] and more potent ADP receptor antagonists may further increase this risk. Finally, clinical development of PAR-1 antagonists has started and preliminary results are encouraging. Clinical trials with these agents will help define the role of PAR-1 in atherothrombosis.

Currently available anticoagulants include both parenteral and oral agents. Rapidly acting parenteral anticoagulants are usually used for initial treatment of arterial or venous thromboembolism, whereas oral agents are employed for long-term therapy. For initial treatment, low-molecular-weight heparin (LMWH) has replaced heparin for most indications because LMWH is more convenient to administer and meta-analyses of clinical trials comparing it with heparin indicate that LMWH is at least as effective and safe. More recently, fondaparinux, a synthetic pentasaccharide, has been licensed for VTE prevention in high-risk orthopedic surgery patients and in some countries, in general surgical or medical patients. Fondaparinux also is licensed as an alternative to heparin or LMWH for initial treatment of VTE.