Preface

The past 2 decades have witnessed significant advances in the discovery and development of novel drugs to prevent and treat thromboembolic disorders, such as oral direct anti-Xa and anti-IIa (thrombin) antagonists, as well as oral antiplatelet ADP antagonists with rapid onset and offset. The introduction of direct oral factor Xa and thrombin inhibitors that do not require monitoring and have no significant food or drug interactions represents a significant advance that may lead to the replacement of oral warfarin and injectable heparin or low molecular weight heparin (LMWH) in some, but probably not all, indications. In addition, there has been concentrated effort aimed at identifying novel uses of traditional antithrombotic drugs as well as combinations of agents, such as more than one antiplatelet, or antiplatelet plus anticoagulant. These tremendous achievements have resulted in improved management of arterial and venous thromboembolic-associated disorders. Although the morbidity and mortality resulting from acute coronary disease has been reduced by more than 50% over the past 30 years, it is reasonable to anticipate further reductions of similar magnitude in the decade ahead.

Advances in our understanding of the mechanisms of pathogenesis of venous thromboembolism (VTE), acute coronary syndromes, cerebral vascular ischemia, and diseases associated with thrombotic events have provided critical insight for the development of various therapeutic approaches to control these pathogenic events. The roles of plasmatic proteins, blood cells, vascular endothelium, and target organs in thrombogenesis are becoming more clear. Identification of endogenous inhibitors of thrombogenesis such as antithrombin III, tissue factor pathway inhibitor (TFPI), protein C, prostacyclin, nitric oxide, and physiologic activators of fibrinolysis has led to the development of both direct and indirect modalities to treat thrombosis. Knowledge of the proteases involved in thrombogenesis, as well as tissue factor, coagulation factors, adhesion molecules, and fibrinolytic inhibitors, has provided additional insight into the mechanisms by which thrombogenesis can be pharmacologically controlled. All of these novel strategies could not have happened without the utilization of key in vitro and in vivo clinically relevant experimental models for the screening and evaluation of these novel antiplatelets, anticoagulants, and thrombolytics (discussed in Chapters 1 and 2).

Newly developed anti-Xa agents are characterized by high affinity and selectivity for Xa as compared to other serine proteases. In addition to their inhibitory effects on plasmatic coagulation processes, including thrombin generation, thrombin-mediated platelet reactions, and clot-bound pro-thrombinase complexes, there is evidence that some of these agents might interfere with receptor-mediated intracellular signaling events induced by factor Xa that regulate proliferation of vascular smooth muscle cells and other cells. The current outlook for anti-Xa agents is that they have the potential to become important prophylactic and treatment drugs for various venous thromboembolic disorders as well as adjuvants to other antithrombotic therapies in arterial thrombosis.

Major advances in the development of oral anticoagulants are progressing very well, with the goal of developing safe and effective oral anticoagulants that do not require frequent monitoring or dose adjustment and that have minimal food/drug interactions.
Vitamin K antagonist, with its inherent limitations of multiple food and drug interactions and frequent need for monitoring, remains the only oral anticoagulant currently approved for long-term secondary thromboprophylaxis in VTE. The oral direct thrombin inhibitor ximelagatran was withdrawn from the world market due to safety concerns. Newer anticoagulant drugs such as injectable pentasaccharides (e.g., idraparinux, SSR126517E), oral direct thrombin inhibitors (e.g., dabigatran), oral direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, YM-150, DU-176b), and tissue factor/factor VIIa complex inhibitors are “tailor-made” to target specific pro-coagulant complexes and have the potential to greatly expand oral antithrombotic targets for both acute and long-term treatment of VTE, acute coronary syndromes, and prevention of stroke in atrial fibrillation patients (discussed in Chapter 5).

The oral direct factor Xa inhibitor rivaroxaban represents a potentially attractive alternative to warfarin as it may enable simplified once daily dosing, appears to require no therapeutic monitoring, and has lower potential for drug interactions. At present, the safety and efficacy of rivaroxaban for the prophylaxis and treatment of VTE have been evaluated in phase-II and phase-III trials involving over 24,000 patients. In addition, rivaroxaban is currently being evaluated for the treatment of pulmonary embolism, secondary prevention after acute coronary syndromes, and the prevention of stroke and non-central nervous system embolism in patients with non-valvular atrial fibrillation. Several other oral direct anti-Xa inhibitors are in advanced clinical development, approved in Europe and under FDA review for the prevention and treatment of thromboembolic disorders (discussed in Chapter 6).

Dabigatran is a novel oral direct reversible (fast onset and offset) thrombin inhibitor that binds to both free and clot-bound thrombin with a high affinity and specificity. Dabigatran has predictable and reproducible pharmacokinetics that are not affected by interactions with food. It is not metabolized by CYP450, does not induce nor inhibit CYP450, resulting in low potential for drug interactions, and does not require coagulation or platelet monitoring. The RE-NOVATE trial demonstrated that oral dabigatran etexilate at fixed doses is a well-tolerated alternative to injectable enoxaparin for the prevention of VTE after total knee replacement. The RELY trial demonstrated that oral dabigatran etexilate concurrently reduces both thrombotic and hemorrhagic events at two different doses (150 and 110 mg BID), exhibiting different and complimentary advantages over warfarin. At a dose of 150 mg BID, dabigatran had superior efficacy with similar bleeding, while at a dose of 110 mg BID, there was significantly less bleeding with similar efficacy in patients with atrial fibrillation at risk of stroke. Based on the accumulating clinical evidence, dabigatran represents the future of anticoagulation in the prevention and treatment of venous and arterial thrombosis alone and in conjunction with current antiplatelets and thrombolytics.

Anti-platelet therapies remain a major focus in drug development. While aspirin is still considered the gold standard for antiplatelet therapy because of its high benefit-to-cost and benefit-to-risk ratios, ADP receptor antagonists, including ticlopidine, clopidogrel, and prasugrel, represent significant additions to aspirin in the management of different forms of arterial thromboembolic disorders (Chapter 7). Prasugrel is a novel thienopyridine that inhibits the platelet P2Y12 receptor and provides more rapid and consistent platelet inhibition than clopidogrel (Chapter 8).

It is becoming clear, however, that there is variability in individual responses to antiplatelet agents such as clopidogrel, which may limit their widespread implementation. Various definitions of “non-responders” to antiplatelet therapy (i.e., aspirin resis-
Aspirin resistance refers to aspirin-treated patients that are insensitive to aspirin treatment based on ex vivo tests of platelet activation and who experience recurrent cardiovascular disease. Estimates of aspirin resistance based on these criteria range from 20 to 80%, indicating that ex vivo tests are not an optimal tool for such assessments. In long-term aspirin-treated patients, there is evidence of low level but functionally relevant platelet thromboxane A2 formation, which was responsible for enhanced platelet activation in response to platelet agonists. These studies, however, did not fully exclude aspirin compliance, which could be a factor in such a phenomenon. Two trials performed in patients with coronary artery disease demonstrated that laboratory evidence of aspirin resistance was not detectable when aspirin compliance was accurately monitored. The same phenomenon was reported for other anti-platelet drugs such as clopidogrel. Given the multi-factorial nature of atherothrombosis, recurrence of cardiovascular events in aspirin-treated patients is not necessarily suggestive of drug failure. A cause-effect relationship between platelet insensitivity to aspirin and cardiovascular recurrence has not been defined overall because aspirin compliance has rarely been considered. Until such crucial information is taken into account, it would be prudent to take into consideration the distinction between “clinical resistance” to aspirin and resistance to taking the drug. To carefully define anti-platelet resistance, issues such as dose levels, standardized monitoring parameters, drug-drug interactions, and drug monitoring to document compliance should be addressed in future studies.

The next decade should see considerable attention focused on the vascular endothelium, which occupies a strategic position at the interface between tissue and blood. The normal endothelium releases multiple antiplatelet, anti-inflammatory, thrombolytic and vasodilator molecules, such as prostacyclin and nitric oxide, which are potent inhibitors of platelet and monocyte activation and function as vasodilators. In addition, the normal endothelial surface expresses other protective molecules, including ecto-ADP, which degrades ADP, leading to inhibition of platelet aggregation; thrombomodulin, which activates protein C; and heparin-like molecules, which serve as cofactors for antithrombin III and heparin. The normal endothelium also secretes tissue plasminogen activator, which activates fibrinolysis. Insult or injury to the endothelium is accompanied by loss of these protective molecules and induction of expression of adhesive, pro-coagulant and pro-inflammatory molecules, vasoconstrictors, and mitogenic factors, leading to the development of thrombosis, smooth muscle cell migration and proliferation, and atherosclerosis. Hence, protective mechanisms of endothelial function represent new frontiers in the prevention and treatment of thromboembolic disorders that will have minimal effect on hemostasis.

Improved understanding of the cell biology of plaque instability and endothelial hemostasis will promote a number of novel therapeutic strategies, including passivation of the endothelium, reduction of low-density lipoprotein (LDL) in the vessel wall (through decreasing serum LDL levels or accelerating reverse cholesterol transport), inhibition of LDL oxidation, thereby raising high density lipoprotein (HDL), and inhibition of inflammatory cytokine expression, as well as inhibition of thrombus formation upstream in the coagulation cascade or inhibition of activation of coagulation. The recognition that thrombotic disorders represent a syndrome rather than a disease is of crucial importance in the development of newer drugs. Either a poly-therapeutic approach with drug combinations or a drug with multiple actions will likely be more appropriate for the management of thrombotic disorders.
This second edition of *Anticoagulants, Antiplatelets, and Thrombolytics* provides updates on various strategies in thrombosis, experimental models, and clinical and recent advances in the discovery and development of novel antithrombotics. Future directions in the coming decade should focus on the prevention of thromboembolic disorders and the protection of the vascular endothelium.

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