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Edited by

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Preface

During the past decade, remarkable progress has been made in the development of newer drugs to treat thrombotic and cardiovascular diseases. Over this last 10 years, concentrated efforts were made to discover new drugs and to develop novel uses for such traditional antithrombotic drugs as aspirin, heparin, and oral anticoagulants. Biotechnology, molecular biology, combinatorial approaches, isolation and characterization of natural products with antithrombotic activity, and a reassessment of traditional drugs have been the key factors behind these developments.

Some 1 million Americans die of thrombotic and cardiovascular disorders every year. On a global level, the relative proportion of mortality is even higher. Thus, thrombosis and related disorders represent the number one cause of mortality. The understanding of the mechanisms behind the pathogenesis of venous thromboembolism, acute coronary syndromes, cerebral vascular ischemic and thrombotic events, and diseases associated with thrombotic disorders has provided additional insights toward the development of various therapeutic approaches to control these pathogenic events. The roles of plasmatic proteins, blood cells, vascular endothelium, and target organs in both 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. On the other hand, the knowledge of the proteases involved in thrombogenesis, including tissue factors, coagulation factors, adhesion molecules, and fibrinolytic inhibitors have provided insights into the mechanisms by which thrombogenesis can be pharmacologically controlled.

The pharmaceutical industry has played a key role, not only in the development of new drugs, but also in providing sizable resources to academic institutions to foster the development and clinical validation of the uses of these drugs. Such drugs as low molecular weight heparins, antithrombin agents, the hirudins, such antiplatelet drugs as the GPIIb/IIIa inhibitors, and the ADP receptor antagonists have emerged as improved therapeutic strategies over conventional drugs. The development of these drugs required a major undertaking by the pharmaceutical industry with allocation of sizable resources. Beside fiscal considerations, an objective assessment of the newer drugs at both the preclinical and clinical levels was mandatory for optimal applications.

Anticoagulants, Antiplatelets, and Thrombolytics provides a comprehensive update on many of the critical in vitro and in vivo models of thrombosis and hemostasis. Additionally, this book highlights the novel use of low molecular weight heparins, the newer applications of GPIIb/IIIa antagonists, aspirin, and clopidogrel, and the expanded usage of thrombolytics and polytherapeutic approaches. The recent approval of antiplatelet drugs for intermittent claudication, the aspirin–dipyridamol combination for ischemic stroke, and thrombolytic agents in cerebral ischemia represent some of the

concepts that will be highlighted. Similarly, aspirin combinations with oral anticoagulants and other drugs have been in discussion for improved management of arterial thrombosis.

The recognition of heparin-induced thrombocytopenia as a catastrophic complication of heparin therapy necessitated the development of such alternate anticoagulant drugs as the antithrombin agents. Today, hirudins can be used to achieve comparable anticoagulation in heparin-compromised patients. The variation in aspirin tolerance and increased susceptibility to gastric toxicity from this drug led to the development of such ADP receptor antagonists as ticlopidine and clopidogrel. The oral anticoagulant drugs, however, have remained the only orally bioavailable agents that can be used for an extended period of time despite their inherent limitations. These drugs remain unchallenged by low molecular weight heparins, antithrombin agents, and antifactor Xa drugs. Thus, the impact of new drug development on traditionally used drugs has added a fresh dimension. It is interesting to note that many of the polytherapeutic approaches now combine traditional drugs with newer drugs.

The novel developments in antithrombotic drugs include such monotherapeutic approaches as the antiproteases (factors IIa, Xa, and VIIa), tissue factor targeting, platelet receptor targeting, and antithrombin III modulation. Despite the clear mechanisms of action of some of these agents, the recognition of the modulatory effects of aspirin and heparin has led to the development of a multitarget approach. Interestingly, all of the traditional drugs, such as heparin, aspirin, and warfarin, are multitargeting drugs. The recognition that thrombotic disorders represent a syndrome rather than a disease is of crucial importance in the development of newer drugs. Either a polytherapeutic approach with drug combinations or a drug with multiple actions will likely be more appropriate for the management of thrombotic disorders.

Shaker A. Mousa

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