About the Editor

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Jawed Fareed is a Professor of Pathology & Pharmacology and Director of the Hemostasis & Thrombosis Research Laboratories at Loyola University Medical Center. He also serves as a consultant to the Department of Laboratory Science at Hines Veterans Administration in Hines, IL, USA. He received his initial graduate training at the University of London, England and at the University of Guelph in Ontario, Canada. His doctorate degree was completed at Loyola University Chicago in the areas of Pharmacology and Experimental Therapeutics in 1974 and is currently pursuing research, teaching and service activities. In June 1996, Dr. Fareed received the degree of Doctor Honoris Causa from the University of Bordeaux in France. He has received numerous awards from various national and international organizations. His main area of interest is research in the development of novel anticoagulant and antithrombotic drugs. He has devoted much of his activities to the initial studies on low-molecular-weight heparins and he has contributed to the development of several newer antithrombotic drugs such as hirudin and tissue factor pathway inhibitor. Currently he has embarked upon a program on the objective study of newer antiplatelet drugs such as glycoprotein IIb/IIIa inhibitors and ADP receptor antagonists. In addition he has also initiated a program on molecularly designed drugs with multiple targets. More recently he has initiated the development of an integrated program on molecular hemostasis and thrombosis. His professional affiliations include membership of the expert panel on biologicals for the World Health Organization in Geneva, Switzerland. He acts as an advisor to several regulatory agencies. He is a recipient of several national and international awards, including the Sam Natelson Award of the American Association of Clinical Chemistry and the IUA 2002 Lectureship. He is an elected fellow of the International Union of Angiology and the American College of Angiology. In October 1997 Dr. Fareed received the distinguished services award from the South Asian Society of Thrombosis. He is currently the President of the International South Asian Society of Atherosclerosis (SASAT). Together with Professor Hans Klaus Breddin of Germany, he founded the International Institute of Blood and Vascular Disorders located in Frankfurt, Germany. He also serves at the Chair of the Scientific Committee of the IUA. He also serves as the Vice President of the Academy of Clinical and Applied Thrombosis and Hemostasis in Dallas, Texas. He is also an elected member of the Medical Academy of Erfurt, Germany. He is also active in the educational scientific activities of various professional societies including the International Union of Angiology, American Society of Hematology, International Society of Fibrinolysis and Proteolysis and The American Heart Association.

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Foreword

New oral anticoagulants

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The introduction of newer oral anticoagulant drugs has provided additional pharmacologic approaches to treat thrombotic and cardiovascular disorders and potentially to replace conventional oral anticoagulants, such as warfarin and heparins, in some of the indications. Although warfarin and related anticoagulants are now widely used for the outpatient management of thromboembolic conditions, including atrial fibrillation, ever since their introduction concerns have been raised regarding the need for dosage adjustment, monitoring and bleeding complications. Population-based variations and genetic polymorphism has additional challenges to clinicians using these drugs. The newer oral anticoagulants are claimed to offer certain advantages over the conventional oral anticoagulants. However, the available clinical data are mainly focused on post-surgical deep-vein thrombosis and atrial fibrillation. Very limited information is available in medically ill patients and trauma and surgical populations for the use of these drugs. Even with the low-molecular-weight heparins, the available clinical trial data warrant the need of optimizing the dosage and duration of anticoagulant therapy. This book provides an overview on newer anticoagulant drugs and the ongoing developments in this field. As noted by various authors, newer oral anticoagulants may offer certain advantages over the conventional oral anticoagulant agents and may be useful in qualified indications. However, several issues related to their clinical use remain unresolved and may require additional basic and clinical investigations.

Beside the approved indications, including the prophylaxis of post-orthopedic surgical prophylaxis of DVT and atrial fibrillation, there are several indications where the efficacy and safety of these agents is not validated, such as acute venous thromboembolism (VTE) and cancer, pregnancy-associated acute VTE, patient with either rheumatic heart valve heart disease or artificial heart valves. In an acute care environment, anticoagulant reversibility is critical. In procedures such as interventional cardiology and coronary artery bypass surgery where bleeding risk may result in serious consequences, neutralization is extremely important. Intracranial bleeding has been reported with the use of some of these agents with serious outcomes. Therefore, the development of specific approaches to neutralize bleeding complications is crucial.

Population-based differences in the anticoagulant responses of the newer anticoagulant drugs have not been fully explored. There are almost no data on the use of these agents in pediatric patients. Similarly, other populations, including patients with liver diseases, renal disorders, autoimmune diseases and infections, have not been explored fully. The fixed dosing of these drugs is also of major concern. Because of the wide variations in the absorption of these drugs the fixed dosing in underweight and overweight patients may result in safety and efficacy issues. The use of these agents in patients undergoing hemodialysis is also not clear. Most of the newer oral anticoagulants are dialyzable and can be removed from the circulation. The wide variations in protein binding may also result in wide variations in special populations.

The issue of bleeding, nuisance and major, are also not clearly elucidated in the general population. Nuisance and minor bleeding will impact compliance leading to therapeutic failure; and major or severe bleeding will lead to emergent situations. The lack of readily available monitoring contributes to concern when there is no reversal agent. This can lead to a clinical presentation that will be a problem for the patient and clinician. Drug and food interactions are only known from well-controlled clinical trials and we must be vigilant to determine the extent of these situations in the general community. Questions remain about proper dosing in the aged population, renal-impaired, and multiorgan-compromised patients. Such questions can only be answered in well-designed, dedicated, population-based clinical trials.

In recognition that longer-term anticoagulation for stroke prophylaxis in atrial fibrillation patients and multiple medical conditions for VTE prophylaxis is best served by an oral agent, perhaps by one or more of the newer anti-FIIa or anti-FXa drugs, we should be careful in transitioning the

traditional anticoagulants. While these traditional anticoagulants have their limitations, they are generally known for their safety and efficacy profile, which are manageable.

It is interesting to see the developments in the field of oral anticoagulants. It should be noted that the newer agents were introduced to overcome the challenges and limitations of the traditional agents. It is recommended that each of the newer agents be assessed individually, and only for specific indications. This is imperative because each agent has a distinct pharmacological profile, which translates into a specific safety and efficacy for a given indication. The clinical community should be cautious in using these agents for broader general population until answers to unmet needs have been identified.

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