# PREFACE

One of the most important developments in the field of cardiovascular medicine over the last two decades has been recognition of the key role played by arterial thrombosis in the pathogenesis of acute coronary syndromes, ischemic complications of percutaneous coronary revascularization, and coronary and peripheral atherosclerosis. The pharmacologic armamentarium directed against vascular thrombosis has thus expanded substantially during that time, with development of new fibrinolytic agents, low-molecular-weight heparins, direct thrombin inhibitors, antagonists to platelet activation, and the platelet glycoprotein IIb/IIIa inhibitors. Though clinical investigations of these compounds have been marked by failures as well as successes, there is little doubt that enhanced antithrombotic therapies have markedly improved the outcome of patients undergoing coronary revascularization or with acute coronary syndromes.

Glycoprotein IIb/IIIa receptor antagonists were introduced into clinical practice to overcome the limitations of approaches that inhibit only individual pathways of platelet activation. Multiple mechanisms of platelet activation in response to different agonists converge on the platelet membrane glycoprotein IIb/IIIa complex, the "final common pathway" of platelet aggregation. The clinical hemorrhagic syndrome caused by a rare inherited defect in this receptor (Glanzmann's thrombasthenia), characterized by mucocutaneous and postsurgical bleeding, but infrequent spontaneous organ (particularly central nervous system) bleeding, suggested that therapeutic inhibition of this receptor might be a potent, yet well-tolerated means of treating thrombotic disorders. The first agent directed against the receptor, a monoclonal antibody fragment developed by Coller that blocks the interaction of glycoprotein IIb/IIIa with adhesion molecules, received marketing approval in 1995. On the basis of unequivocal efficacy demonstrated during extensive systematic controlled clinical trial evaluations, three parenteral glycoprotein IIb/IIIa inhibitors are presently available for the management of patients undergoing percutaneous coronary revascularization or with unstable ischemic syndromes.

In 1999, we published the first edition of this text, a comprehensive, definitive, and detailed overview of the preclinical and clinical development of the class of glycoprotein IIb/IIIa receptor antagonists. Since that time, new trials have evaluated the relative efficacy of different agents, expanded our understanding of the roles of these drugs in the management of acute coronary syndromes, critically assessed the efficacy of oral agents, and explored the interaction between glycoprotein IIb/IIIa antagonists and other antithrombotic and mechanical interventional therapies. The goals of this second edition, as with the first, are to elucidate the theoretical basis for inhibition of platelet aggregation in the treatment of coronary syndromes, to synthesize the evidence demonstrating the efficacy of glycoprotein IIb/IIIa blockade in inhibiting ischemic complications of coronary intervention and the acute coronary syndromes, and to provide guidelines for the use of this class of agents in the clinical management of cardiovascular disease. In every case, chapters have been contributed by acknowledged experts in the field, including the pioneers in the discovery and characterization of cell surface adhesion molecules and the glycoprotein IIb/IIIa receptor, as well as the principal investigators of the major clinical trials. The most current data are included, with the intent to provide a comprehensive body of knowledge of the contemporary "state of the art" in this field.

The first section of *Platelet Glycoprotein IIb/IIIa Inhibitors in Cardiovascular Disease, Second Edition* outlines the basic pathophysiology underlying the theoretical usefulness and development of this class of agents. In Chapter 1, the role of thrombosis and platelet activity in the pathophysiology of acute ischemic syndromes or complications of coronary intervention are reviewed, providing the underpinnings for antithrombotic therapy in cardiovascular disease. Platelet adhesion, the essential reaction for the hemostatic function of platelets, is discussed in Chapter 2, followed by a detailed description of the structure and functions of the glycoprotein IIb/IIIa receptor in Chapter 3. The "bench to bedside" development of the first agent directed against this receptor is recounted in Chapter 4, along with a summary of the pharmacologic properties of the other parenteral compounds of this class.

The second section concentrates on the adjunctive use of glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization. The three agents that have been evaluated for this indication (abciximab, eptifibatide, and tirofiban) are discussed in Chapters 5–7, focusing on data derived from the pivotal Phase III and IV studies. A summary overview then follows, integrating the results of the major trials in this setting, comparing the different agents, and providing practical guidelines for clinical use.

The third section focuses on glycoprotein IIb/IIIa blockade in the management of the acute coronary ischemic syndromes. Chapters 9–11 detail the roles of these agents as adjuncts to medical and revascularization therapies for unstable angina. Chapters 12 and 13 discuss the use of glycoprotein IIb/IIIa antagonists with mechanical or pharmacologic (fibrinolytic) reperfusion therapies for ST-segment-elevation myocardial infarction.

The fourth section explores practical issues with the use of these agents and provides a view into future applications in the treatment of vascular disease. Medico-economic aspects are analyzed in Chapter 14. Chapters 15 and 16 describe techniques for monitoring the efficacy of platelet inhibition and provide preliminary data regarding the interaction of glycoprotein IIb/IIIa antagonists with other inhibitors of platelet function or the coagulation cascade. The unexpected failure of chronic oral glycoprotein IIb/IIIa therapy in a series of large-scale trials is discussed in Chapter 17. Chapter 18 speculates on the possibility that clinical benefit may be derived from these agents through mechanisms other than platelet inhibition, such as antiinflammatory effects. The potential efficacy and established risks of glycoprotein IIb/IIIa blockade in relation to cerebrovascular disease are explored in Chapters 19 and 20. Finally, advances made in the management of vascular thrombosis and new directions for progress in this field are summarized in Chapter 21.

I am most appreciative of the superb contributions by the chapter authors of this book, who drew on their considerable expertise, first-hand experience, and perspectives to produce a truly comprehensive discussion of this field. Additionally, the publisher and production staff at Humana Press made exceptional efforts for the timely completion of this project. Marion Tomasko and Robin Moss deserve recognition for their imaginative book cover artwork.

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