INTRODUCTION: CLINICAL STATUS OF ANTIPLATELET AGENTS

Since the 1970s, the role of antiplatelet therapy in patients with coronary artery disease has become established. Aspirin was the first drug to be used as an antiaggregant. Although early trials of aspirin lacked adequate statistical power to detect clinical benefits, two metaanalyses by the antiplatelet trialist group established the place of aspirin in the management of coronary artery disease and provided significant insight into the lack of a documented dose-response effect (1,2). Although the administration of aspirin to suitable patients still lags behind desired targets, most surveys indicate that more than 90% of appropriate patients are treated with it at the time of hospital discharge.

Clinical research in more recent years has highlighted the thienopyridines ticlopidine and clopidogrel. A combination of these drugs, so-called “dual antiplatelet therapy” initially began in patients receiving intracoronary stents (3), and has more recently been shown to reduce a composite of ischemic sequelae in patients hospitalized with an acute coronary syndrome (4), and is now undergoing evaluation in a variety of chronic disease states. Antagonists of platelet (GP)IIb-IIIa provide more potent...
inhibition of platelet aggregation and are currently used in patients undergoing percutaneous coronary intervention (PCI) and in patients presenting with acute coronary syndromes. The evidence supporting the use of these therapies is reviewed elsewhere in this text. The purpose of the current chapter is to outline the role that tests of platelet function have played in the evolution of the clinical trials in which these agents were evaluated.

**Purposes of Testing**

Testing platelet function in preparation for clinical trials has generally been directed at evaluation of individual drug therapies and has served two general purposes. The first aim is to confirm that the selected antiplatelet therapy is physiologically active within a clinical syndrome. The second is to select appropriate drug doses for clinical testing in patients with or at risk for atherosclerosis and its clinical manifestations. In most cases, initial dose selection is derived from experimental studies and is refined in volunteer subjects. However, there are several ways in which patients with atherosclerosis are likely to differ from volunteer subjects. In general, subjects with atherosclerosis are older and have more comorbidities than volunteer subjects. As a result, drug absorption and disposition may be different than seen in volunteer subjects and may also be more variable. Disruption of an atherosclerotic plaque may also increase the proportion of circulating platelets that are in an activated state. Compared with quiescent platelets, activated platelets express greater numbers of GPIIb-IIIa receptors, a greater proportion of GPIIb-IIIa in a ligand binding-permissive state, and a number of surface proteins, such as P-selectin, which mediates adhesion to leukocytes and possibly other platelets (5,6) and CD 40 ligand (CD-154).

The literature is replete with documentation of increased levels of activated platelets (7), platelet-leukocyte complexes (8), increased generation of thrombin (9), and increased levels of circulating markers of thrombotic and inflammatory processes in patients with acute coronary syndromes (10). It has also been recognized for more than a decade that platelet activation follows PCI almost immediately (11). The activity of the disease process itself may therefore enhance resistance to antiplatelet drugs, thereby altering dose requirements. Finally, much attention has been drawn to the fact that patient response to any of the antiplatelet drugs in common use is heterogeneous rather than homogeneous. It is this last observation that argues most strongly for the use of platelet functional testing in clinical trials, so that relationships can be observed between physiologic responses and clinical outcomes. In fact, as the patient population under study shifts from the relatively homogeneous