SUMMARY. Atherosclerotic plaque disruption is the predominant pathogenetic mechanism underlying the acute coronary syndromes. Plaque rupture leads to the exposure of collagen and vessel media, resulting in platelet and clotting activation, and occlusive thrombus formation. While drugs that interfere with platelet activation and function have been available for years, more powerful agents with novel mechanisms of action are being developed. Of the available platelet inhibitor drugs, only aspirin, sulfinpyrazone, and dipyridamole have undergone extensive clinical testing in patients with cardiovascular disease. More recently ticlopidine, a new and potent platelet inhibitor, has been successfully tested in patients with coronary and vascular disease.

In acute myocardial infarction, aspirin significantly reduces cardiovascular mortality and reinfarction. Furthermore, the combination of aspirin and a thrombolytic agent produces maximal benefit. A role for heparin in the prevention of early mortality and reinfarction is emerging. This drug is effective for the prevention of left ventricular thrombosis in patients with anterior myocardial infarction.

In the secondary prevention of reinfarction and cardiovascular mortality, available data support the use of a platelet inhibitor. Trials have shown that aspirin is as effective alone as in combination with dipyridamole, and is probably more effective than sulfinpyrazone. Long-term anticoagulant therapy also appears to be beneficial, but is associated with a high cost, need for extensive monitoring, and potential for hemorrhagic side effects.

The role of aspirin in primary prevention is controversial. It may be indicated for patients at high risk for coronary disease in whom the benefit of therapy may outweigh the potential risk of cerebral bleeding.

Coronary atherosclerotic plaque rupture, associated with thrombus formation, is fundamental to the development of acute myocardial infarction. Based on this concept, the role of antithrombotic therapy for the prevention or treatment of ischemic events in patients with coronary artery disease has stimulated enormous interest among clinicians and basic investigators. In this review we will examine: a) the pathogenesis of coronary thrombosis, b) the pharmacology of platelet-inhibitor agents, and c) their role in the management of patients with acute myocardial infarction and in primary and secondary prevention of cardiovascular disease.

Platelets interact with both the coagulation and fibrinolytic systems in the pathogenesis of thrombosis. While the purpose of this review is to discuss the role of platelets and platelet inhibitors in coronary disease, the use of anticoagulant or thrombolytic agents will be analyzed briefly when pertinent.

KEY WORDS. aspirin, secondary prevention, acute myocardial infarction, plaque rupture, platelet inhibitors, platelet adhesion, aggregation coronary thrombosis
Platelet Aggregation (Figures 1 and 2)

Deeper injury to the vessel wall, such as following rupture of an atherosclerotic plaque, leads to the exposure of fibrillar collagen (type I being more prevalent in disease vessels), which is more abundant in the deeper layers of the vessel wall [3]. This results in activation of platelet metabolism, which leads to the exposure of platelet receptor GPIb-IIIa and subsequent binding of fibrinogen, vWF, and fibronectin. These adhesive macromolecules form links between platelets and are essential to the development of platelet aggregates (Figure 1).

Following platelet activation by different agonists (collagen, thrombin, epinephrine, thromboxane A₂ [TXA₂], calcium is released from the dense tubular system into the cytoplasm, resulting in platelet contraction and secretion of its granular contents [4]. The most important products of platelet secretion include: adenosine diphosphate (ADP), serotonin, TXA₂, fibrinogen, fibronectin, vWF, platelet-derived growth factor (PDGF), and others. The released ADP, serotonin, and TXA₂, in addition to thrombin and collagen, contribute to the activation of neighboring platelets via three metabolic pathways [5] (Figure 2).

The first pathway of platelet activation is mediated by collagen and thrombin, which probably directly stimulate the release of a platelet activating factor, favoring the interaction of fibrinogen and vWF with the receptor GPIb-IIIa. During atherosclerotic plaque rupture, thrombin (generated via the activation of the coagulation system) and exposed collagen, may be more important in promoting platelet aggregation than the physiologically low concentrations of ADP and TXA₂. These powerful platelet agonists may lead to thrombus formation, even in patients treated with platelet inhibitor drugs.

The second pathway is dependent on ADP and serotonin, which are released from the platelet dense granules. In addition, ADP is released from erythrocytes during lysis, particularly in areas of vessel stenoses or bifurcations, where turbulent flow exists. These compounds are potent inducers of platelet aggregation in the presence of fibrinogen and calcium. They promote the exposure of the platelet binding site for fibrinogen and calcium. They may also lead to thrombus formation in patients treated with platelet inhibitory drugs.

The third pathway depends on the release of TXA₂, through the action of cyclooxygenase and thromboxane synthetase on arachidonic acid and prostaglandin endoperoxide intermediates (PGH₂ and PGG₂), respectively. Thromboxane A₂ promotes the mobilization of intracellular calcium and leads to a conformational change in the GPIIb-IIIa receptor, which results in the exposure of previously occult fibrinogen binding sites [7]. Thromboxane A₂ is not only a potent platelet agonist, but induces vasocostriction as well. In addition, cyclooxygenase acts on vessel wall arachidonic acid and on platelet-derived PGG₂, and leads to the generation of PGI₂. Prostaglandin I₂ is a potent inhibitor of platelet aggregation by increasing platelet cyclic adenosine monophosphate (cAMP) and reducing the mobilization of calcium [8] (Figure 2).

Thrombus Formation (Figure 1)

Deep injury to the vessel wall, which occurs during disruption of an atherosclerotic plaque, not only results in platelet adhesion to the exposed surface and their subsequent aggregation, but in marked activation of the coagulation system via the intrinsic (surface-activated) and extrinsic (tissue factor-dependent) pathways (Figure 1). This leads to the generation of thrombin, which, in addition to being a powerful platelet activator, catalyzes the conversion of fibrinogen to fibrin and promotes its polymerization. Consequently, the growing thrombotic mass—composed of platelets, fibrin, and erythrocytes—is able to withstand the force of blood flow [9].