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Platelet Activation in Ischemic Heart Disease: Role of Modulators and New Therapies

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1. Introduction

Ischemic heart disease (IHD) remains the major cause of morbidity and mortality in developed countries, and has joined infectious diseases in developing countries as a leading cause of death (WHO 2008). Decades of research have shown conclusively that a number of determinants operating from early childhood onwards, most of them associated with lifestyle, are responsible for IHD.

IHD results when the oxygen demand of the myocardium cannot be met due to an inadequate blood supply. The most common cause of myocardial ischemia is atherosclerosis of epicardial coronary arteries. The major risk factors for atherosclerosis, and therefore IHD, are dyslipidemia (i.e., elevated low-density lipoprotein (LDL) and/or low high-density lipoprotein (HDL)), diabetes mellitus, hypertension, cigarette smoking, poor dietary habits, and lack of physical activity. These risk factors, particularly when more than one co-exists, can progressively damage the vascular endothelium, causing dysregulation of its anti-inflammatory and anti-thrombotic functions. The associated proliferation of underlying fibroblasts and vascular myocytes, together with the accumulation of extracellular matrix and lipids, result in the formation of what are known as atherosclerotic plaques that lead to a reduction in the luminal diameter. Some of the risk factors for atherosclerosis facilitate the development of atherosclerotic plaques, while others sustain or accelerate their formation, producing the clinical manifestations of IHD (Parthasarathy 2008, Garelnabi 2010).

By reducing the lumen of blood vessels, atherosclerosis causes an absolute decrease in myocardial perfusion in the basal state and hinders the required increase in perfusion when the demand for flow is augmented. As this process progressively worsens, the shear stress associated with blood flow through the reduced arterial lumen can cause plaques to erode or rupture, exposing the intimal layer to the luminal contents and thereby promoting frank thrombosis. Platelet activation, mobilization, and recruitment are central to this process. Luminal thrombi can trap red blood cells and acutely reduce coronary blood flow, producing a sudden myocardial ischemic event referred to as an acute coronary syndrome (ACS) that becomes manifest as either unstable angina or myocardial infarction (MI) if there

is complete occlusion without prompt reperfusion. MI may also occur with embolization of platelet aggregates and/or atherosclerotic debris from a ruptured plaque.

Coronary blood flow can also be limited by vascular spasm, as well as by congenital abnormalities, such as anomalous origin of the left anterior descending coronary artery from the pulmonary artery, which may cause myocardial ischemia and infarction in infancy, but is very rare in adults.

Patients with IHD can be grouped into two broad categories: those having chronic coronary artery disease (CAD), who most commonly present with stable angina, and those who present with ACSs (i.e., unstable angina and MI). Chronic CAD is most commonly caused by slowly progressive coronary artery atherosclerosis, whereby a narrowing of the lumen of the coronary arteries limits their ability to adequately increase perfusion in response to an increase in demand for oxygen (e.g., during exertion). As the disease progresses in severity, perfusion of the myocardium can become compromised even at rest. ACSs, on the other hand, are the result of acute vasoocclusive events secondary to thrombosis at sites of erosion or rupture of atherosclerotic lesions.

2. Role of platelets in the etiology and pathophysiology of IHD

2.1 Structure of platelets

Blood platelets play an essential role in hemostasis, thrombosis, and coagulation of blood. They are engaged in a complex repertoire of biochemical and molecular activities designed to prevent hemorrhage.

On Wright-Giemsa-stained blood smears, platelets appear as small, anucleate, ovoid or round cells with a pale grayish blue cytoplasm that contains homogeneously distributed purple-red granules. After platelet spreading or aggregation, these dispersed granules become concentrated in the middle of the cell.

When platelet morphology is considered under functional subdivisions rather than purely anatomic terms, there are three major structural zones of the platelet, each related to specific aspect of platelet function. The peripheral zone is involved primarily in adhesion, the solgel zone in contraction, and the organelle zone in secretion.

The volumes of circulating platelets from a single individual are heterogeneous and exhibit a log normal size distribution. Circulating platelets have a volume of 7.06 ± 4.85 μm^3 (femtoliters), a diameter of 3.6 ± 0.7 μm (Mean $\pm$ SD), and a thickness of 0.9 ± 0.3 μm (Paulus et al. 1979, Frojmovic et al. 1976). Platelet size varies from one individual to another, although abnormally small or large platelets are present only in certain disease states. By scanning electron microscopy, circulating blood platelets appear as flat discs, with smooth contours and rare spiny filopodia, with random openings of a channel system, which invaginates throughout the platelet and is the conduit by which granule contents exocytose after stimulation. Although the platelet is anucleate, transmission electron microscopy reveals a cytoplasm packed with a number of different organelles essential to maintenance of normal hemostasis. Platelets contain four distinct populations of granules: α-granules, dense bodies, lysosomes, and microperoxisomes. α-granules and dense bodies are distinguished morphologically from one another by their electron density as revealed by electron microscopy.

Phospholipids constitute 80% of the total lipid content of platelets, although smaller amounts of neutral lipids and glycolipids are also present. Evidence suggests that these phospholipids move to the outer membrane leaflet after platelet activation, thereby functioning to promote clot formation. Platelet membrane glycoproteins mediate a wide number of adhesive cellular interactions. These glycoproteins function as receptors that can receive signals from outside the platelet, facilitating cell-cell interactions; binding of specific ligands to these receptors results in distinct platelet responses to the external environment. Several other proteins are unique to the platelet, including platelet factor 4 (PF4), low-affinity PF4, β-thromboglobulin (β-TG), and the calcium-binding proteins thrombospondin, calmodulin, and platelet-derived growth factor (PDGF) (Stenberg et al. 1984).

2.2 Function and biochemistry of platelets

In terms of dry weight, platelets are composed of approximately 60% protein, 15% lipid, and 8% carbohydrate. Platelet minerals include magnesium, calcium, potassium, and zinc. Platelets contain substantial amounts of vitamin B_{12}, folic acid, and ascorbic acid (Weiss et al. 1968). The concentration of sodium and potassium within the platelet are 39 and 138 mEq, respectively, a gradient against plasma that is maintained by active ion pumping, which derives energy from membrane adenosine triphosphatase of the Ouabain-sensitive, Na^+/K^+-dependent type. Potassium apparently is distributed in two discrete metabolic compartments (Cooley and Cohen 1967).

Non-stimulated platelets maintain a low cytoplasmic Ca^{2+} concentration, by limiting Ca^{2+} transport from plasma and promoting active efflux of this ion from the cell. Two pools of calcium are present in platelets: a rapidly-turning over cytosolic pool that is regulated by sodium-calcium antiporter in the plasma membrane, and a more slowly-exchanging pool that is regulated by a calcium-magnesium-ATPase and is sequestered in a dense tubular system. Platelets are therefore able to transport calcium from the cytosol by moving it against a gradient into the extracellular space or by sequestration in the dense tubular system (Brass 1984, Enouf et al. 1987).

There are several similarities between the energy metabolism of platelets and that of skeletal muscle. Both involve active glycolysis and the synthesis and use of large amounts of glycogen, and in both, the major mediator of intracellular energy use is ATP. Platelets, like muscle cells, are metabolically adapted to expend large amounts of energy rapidly during aggregation, the release reaction, and clot retraction (Karpatkin et al. 1970).

The presence of platelets in the hemostatic plugs that form to prevent bleeding suggests that platelets have a physiological role in hemostasis. Their presence in thrombi and emboli, however, suggests that they may have a pathological role as well. Platelets display certain properties that may be relevant to hemostasis and thrombosis. They have the capacity to adhere to foreign surfaces, they can be induced to aggregate, and they can synthesize or release a number of substances.

Platelet adhesion

The only structures with which platelets normally interact are red cells, white cells, and the endothelial lining of blood vessel walls. All other surfaces are thus foreign to them, but platelets have the ability to adhere to such surfaces. Platelets adhere to subendothelial

structures that are exposed when the normal endothelial lining of the blood vessel wall is injured, which causes the deposition of a monolayer of platelets on the surface of the injured vessel. This is followed by the release of pro-coagulation substances, leading to platelet aggregation and formation of a fibrin clot over the adhered layer that results in thrombus formation (Heptinstall and Hanley 1985).

Platelet aggregation

Platelets circulate as disc-shaped cells, but when they come in contact with exposed subendothelium, agonists that activate platelets are exposed, generated, or released. These agonists include collagen, which is present in subendothelium; thrombin, which is generated on the surface of activated platelets and elsewhere; ADP, which is released from damaged red blood cells and secreted from activated platelet-dense granules; circulating epinephrine; and arachidonic acid, which is released from lipid stores in platelets and metabolized to the potent agonist thromboxane A_2 (TXA$_2$). These agonists generally cause platelets to change shape such that they form long pseudopodia, followed by platelet aggregation. Aggregation requires activation of platelet integrin adhesion receptor GP IIb/IIIa so that it can bind fibrinogen or von Willebrand factor (vWF) and link adjacent platelets together in an aggregate. Platelet agonists induce signal transduction events in platelets that cause the above events, although the signal transduction pathways are not completely understood (Leslie et al. 1999).

Platelet release reaction

Platelets store ATP, ADP, Ca^{2+}, and serotonin in dense granules as well as adhesive proteins such as platelet factor 4, β-thromboglobulin, platelet-derived growth factor (PDGF), fibrinogen, fibronectin, thrombospondin, and vWF in α-granules (Siess 1989). Upon activation by agonists, platelets undergo a release reaction, thereby secreting their granular contents. The release reaction is associated with the production of TXA$_2$, and the extent of the secretion depends on the strength of the agonist. Weak agonists (e.g., ADP and epinephrine) require both cyclooxygenase activity and primary aggregation to induce secretion that is observed at low Ca^{2+} concentrations (Smith et al. 1973, Banga et al. 1986). Agonists of intermediate strength (e.g., platelet activating factor, PAF) can induce secretion in the absence of formation of arachidonic acid metabolism and without primary aggregation. Interestingly, when collagen is added at low concentrations to platelet suspensions, secretion of ATP occurs before the onset of shape change. This secretion is not inhibited by cyclooxygenase blockers, but is sensitive to the extracellular Ca^{2+} concentration and is a direct consequence of platelet binding to collagen (Siess et al. 1983, Malmgren 1986).

Platelet activation

Some signaling pathways involved in various platelet activation events are reasonably well understood, whereas others are not. Many, but not all platelet agonists activate platelets by occupying seven transmembrane-spanning, G protein-coupled receptors. Activation of these receptors generally results in activation of phospholipase Cβ (PLC). PLC hydrolyzes phosphatidyl-inositol-4,5-bisphosphate (PIP$_2$), generating inositol-1,4,5-triphosphate (IP$_3$) and diacylglycerol (DAG). Both IP$_3$ and DAG appear to play important roles in pathways leading to various aspects of platelet activation. IP$_3$ is believed to interact with specific receptors to induce intracellular Ca^{2+} release from the dense tubular system, an intracellular

Ca^{2+} storage organelle analogous to the sarcoplasmic reticulum in skeletal muscle. However, the exact mechanism by which this response contributes to platelet aggregation is not entirely clear because IP_3-induced platelet aggregation is also dependent on thromboxane A_2 (TXA_2) production and ADP release (Knezevic et al. 1992). DAG interacts directly with protein kinase C (PKC) and appears to play a crucial role in the pathways of some agonists, leading to the activation of GP IIb/IIIa and fibrinogen binding. Specific inhibitors of PKC block fibrinogen binding and platelet aggregation induced by some agonists. Drivers for platelet activation include the signaling events that occur downstream of receptors for collagen (GP VI and GP Ibα), thrombin (PAR1 and PAR4), adenosine diphosphate (ADP; P2Y1 and P2Y12), and thromboxane A2 (TXA_2; TP) (Brass 2010).

Platelets are activated and stimulated to synthesize or release a number of substances, namely thrombin, arachidonic acid, PAF, and epinephrine which are of functional importance. When platelet ADP is released from platelet-dense granules during platelet activation by numerous agonists, secreted ADP potentiates the activating effects of other agonists (Hourani and Cusack 1991). ADP causes shape change, granular secretion, and aggregation. However, unlike strong agonists such as thrombin and collagen, ADP induces secretion usually only in conjunction with platelet aggregation. Strong agonists generally stimulate phosphoinositide hydrolysis, increase cytosolic free Ca^{2+}, and induce TXA_2 formation.

Platelet receptors and MicroRNA signaling

Platelet receptors are known to interact with external stimuli in the main blood stream leading to the regulation of platelet activation. Platelet adhesion receptors are the key initiators of platelet activation at sites of vascular injury, where platelets become exposed to adhesive proteins in the matrix, or on endothelial cells. Despite significant differences in their functions and signaling pathways, several major platelet adhesion receptors share many similarities in their signal transduction mechanisms (Li et al. 2010). The most studied platelet receptor is platelet integrin GP IIb/IIIa, which is reported to play an essential role in thrombus formation through interactions with adhesive ligands and has emerged as a primary target for the development of anti-thrombotic agents (Hagemeyer and Peter 2010). Successful blockade of this ligand binding has validated GP IIb/IIIa as a therapeutic target in cardiovascular medicine.

MicroRNAs (MiRs) molecules are a novel class of endogenous, small, noncoding RNAs that regulate gene expression via degradation, translational inhibition, or translational activation of their target messenger RNAs (Pan et al. 2010, O'Sullivan et al., 2011). Bioinformatics analysis predicts that each MiR can regulate hundreds of targets, suggesting that they play an essential role in almost every physiological and pathological pathway. Functionally, an individual MiR is important as a transcription factor because it is able to regulate the expression of its multiple target genes. MiRs are short (~20 nucleotides long), single-stranded RNAs initially transcribed by either RNA polymerase II or RNA polymerase III, as a long primary MiR transcript (pre-MiR). It is then cleaved in the nucleus by the microprocessor complex, Drosha-DGCR8, resulting in a precursor hairpin (pre-miRNA) ranging in length from 60 to 110 nucleotides. The pre-MiRNA is exported from the nucleus to the cytoplasm by exportin 5-Ran-GTP. In the cytoplasm, Dicer, a member of the RNase III family, in complex with TRBP, cleaves the pre-MiR hairpin to a 22 base pair MiR duplex.

The mature MiR is incorporated with argonaute (Ago2) proteins into the RNA-induced silencing complex (RISC), where MiR guides the complex to partial complementary binding sites located in the 3′ untranslated region (UTR) of target mRNAs to suppress gene expression. MiRs are able to directly regulate at least 30% of genes in a cell. In addition, other genes may also be regulated indirectly by MiRs. Therefore, MiRs are pivotal regulators in normal development, physiology, and pathology. Recent studies have identified a number of MiRs highly expressed in the vasculature and their expression is dysregulated in diseased vessels (Jamaluddin et al. 2011, Haver et al. 2010, Bonauer et al. 2010, Wierda et al. 2010, Urbich et al. 2008, Fang et al. 2010, Leeper et al. 2011). MiRs are also found to be critical modulators of cell differentiation, contraction, migration, proliferation, and apoptosis. Accordingly, MiRs have emerged as therapeutic targets in disease.

Platelets are also reported to have microRNA population that may regulate its activity. It is well known that platelets have mRNA and mRNA splicing machinery, and translate mRNA into proteins relevant to hemostasis and inflammation (Edelstein and Bray 2011). In silicon analysis work from Edelstein and Bray indicates that each platelet MiR targets an average of 307 distinct mRNAs, concluding in their review that platelet MiRs have ample opportunity to regulate platelet function.

2.3 Role of inflammation and oxidative stress in platelet activation

Involvement of inflammation in cardiovascular disease is well defined. Circulating platelets are affected by this metabolic disruption and by inflammatory mediators synthesized and/or released on contact with inflammatory signals. Platelets are known to play a major role in this process and have been identified as targets and players in inflammation-induced cardiovascular disease (Weksler 1983, Nurden 2011). It has been explicitly established that free radicals can cause metabolic disturbances and cell injury in a variety of ways, including lipid peroxidation, hydroxyl radical-induced modification of proteins and nucleic acids, changes in enzyme activity, and carbohydrate damage. Oxidative modification of lipids can be induced in vitro by a wide array of pro-oxidant agents and occurs in vivo during atherosclerosis and several other disease conditions (Parthasarathy et al. 2008). Alterations in the superoxide and glutathione oxidation-reduction system may lead to depleted antioxidant capacity and may result in oxidative stress. Previous studies have suggested that platelets and vascular endothelial cells could be the central target as well as the origin of oxygen free radicals or its metabolites (Dousset et al. 1983). Measuring the end products of lipid peroxidation is one of the most widely accepted assays for oxidative damage. These aldehydic secondary products of lipid peroxidation are generally accepted markers of oxidative stress.

Several studies suggest that the basal release of NO by the endothelium contributes to regulation of the vascular tone (Antoniades et al. 2008), blood flow, and blood pressure. NO inhibits platelet aggregation and adhesion to vascular endothelium. In addition, NO inhibits leukocyte adhesion to endothelium (Petidis et al. 2008). Alteration of cellular calcium homeostasis is also a critical event in ischemic heart injury. NO released by endothelium or synthesized by platelets participates in the regulation of Ca^{2+} signaling. Elevation of cGMP as a result of the activation of guanylate cyclase by NO stimulates a number of mechanisms that actively decrease calcium levels within the cell (Joseph et al. 1996). Although the NO-cGMP signaling system has been immensely investigated, sparse data is available pertaining

to the role of platelet NO activity in coronary artery (CAD). We and others have studied the NO-cGMP system in patients with CAD, particularly the role of oxidative stress and NO-mediated platelet response in IHD (Garelnabi et al. 2010, Ikeda et al. 2000, Garelnabi et al. 2011). These studies have clearly indicated that lipid peroxidation is augmented in patients with ischemic heart disease. The increased oxidative stress seen in these patients was accompanied by platelet activation and impaired antioxidant enzymes activity. On the other hand, platelet aggregation, NO, cGMP, NO synthase activity, plasma NO, and ionized Ca^{2+} was profoundly increased in CAD. The increases in NO-cGMP components may have resulted as a compensatory response to ameliorate platelet activity and increased Ca^{2+} levels in CAD patients. Another interesting modulator of platelet activity is the recent description of platelet-derived microparticles (PMP) which are known as a heterogeneous population of vesicles (<1 mm) generated from the plasma membrane upon platelet activation by various stimuli. These PMPs have been shown to not only stimulate the response of platelets, but have also been reported to mediate the intercellular transfer of bioactive molecules such as lipids, surface receptors, and even enzymes (Siljander 2010).

3. Classes and mechanism of action of antiplatelet drugs

The main goals of pharmacological intervention in patients with IHD are to reduce the occurrence of anginal attacks by minimizing the rise in blood pressure and heart rate associated with physical activity so that patients can go about their daily activities without ischemic episodes. Given the prominent role that thrombosis plays in IHD, antiplatelet therapy is one of the most important modalities used in its treatment.

Antithrombotic drugs used for prevention and treatment of thrombosis include: (1) antiplatelet drugs, (2) anticoagulants, and (3) fibrinolytic agents. Given the predominance of platelets in arterial thrombi, which are the major source of IHD, the treatment and inhibition of arterial thrombosis focus mainly on antiplatelet agents, although anticoagulants and fibrinolytic drugs are often included in the acute setting.

Under normal conditions, the actions of vascular endothelial cells maintain platelets in the bloodstream in an inactive state, largely by their production of nitric oxide (NO) and prostacyclin, but also by their surface expression of adenosine diphosphatase (ADPase), which breaks down ADP released via degranulation of activated platelets. With the occurrence of injury to the vascular endothelium, production of these substances is compromised and certain components of the subendothelial matrix are exposed (e.g., collagen, von Willebrand factor (vWF), and fibronectin) to which platelets adhere via receptors constitutively expressed on their surface (e.g., GP IIb/IIIa). As discussed above, adhered platelets undergo a morphological change and then release the contents of their dense granules (e.g., ADP) and synthesize and release thromboxane A_2 (TXA_2), both of which serve to recruit and activate surrounding circulating platelets to the site of vascular injury.

Disruption of the vascular wall also exposes underlying cells and matrix that express pro-thrombotic factors to the circulation, which triggers the coagulation cascade. Activated platelets enhance coagulation by binding clotting factors and supporting the assembly of activation complexes that increase thrombin generation, which in addition to converting fibrinogen to fibrin, also acts as a potent platelet agonist and recruits more platelets to the site of vascular injury.

The most abundant receptor on the surface of platelets is GP IIb/IIIa, which undergoes a conformational change upon platelet activation that allows it to bind fibrinogen. Divalent fibrinogen molecules link adjacent platelets together to form aggregates, which are meshed together via fibrin strands generated via the action of thrombin to form a lattice composed of platelets plus fibrin. Antiplatelet drugs target various steps in this process. The most commonly used drugs include cyclooxygenase inhibitors, among which aspirin is the most common, thienopyridines and functionally related drugs, phosphodiesterase inhibitors, adenosine reuptake inhibitors, and GP IIb/IIIa antagonists, all of which are discussed below.

3.1 Cyclooxygenase inhibitors

The cyclooxygenases (COXs) are a family of isoenzymes responsible for the biosynthesis of various important and potent pro-inflammatory and pro-thrombotic mediators called eicosanoids, which include prostaglandins, leukotrienes, and thromboxanes. Non-steroidal anti-inflammatory drugs (NSAIDs), like aspirin and ibuprofen, exert their effects through inhibition of COX, and as such they relieve the symptoms of inflammation (e.g., pain, swelling).

COX converts arachidonic acid (AA, an ω-6 polyunsaturated fatty acid (PUFA)) to prostaglandin H_2 (PGH_2), the parent of the eicosanoids, which can then be converted to the other compounds via further enzymatic action that involves radical chemistry and the consumption of molecular oxygen. To date, three distinct COX isoenzymes have been identified: COX-1, COX-2, and COX-3. COX-1 and COX-3 are products of alternative splicing of the same gene, so COX-3 is referred to by some as COX-1b or COX-1 variant (COX-1v). Different tissues express varying levels of the different COXs, and although the isoenzymes basically catalyze the same transformations, selective inhibition can produce a different side-effect profile. COX-1 is nearly ubiquitous among mammalian cells, but COX-2 is undetectable in most normal tissues and is inducible in macrophages upon their activation, as well in endothelial cells at sites of inflammation, where it serves to produce prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. COX-2 is also upregulated in various types of cancers, so it is believed to play a role in oncogenesis.

Both COX-1 and -2 also oxygenate two other essential fatty acids – dihomo-γ-linolenic acid (DGLA, ω-6) and eicosapentaenoic acid (EPA, ω-3) – to give eicosanoids with less potent pro-inflammatory properties than those derived from AA. Both DGLA and EPA competitively inhibit oxidation of AA by the COXs, which is believed to be the major mechanism by which dietary sources of DGLA and EPA (e.g., fish oil) can reduce inflammation.

The traditional COX inhibitors are not selective for any particular COX, resulting in widespread inhibition of eicosanoid synthesis that ultimately reduces inflammation, as well as providing antipyretic, antithrombotic, and analgesic effects. However, inhibition of the synthesis of gastroprotective prostaglandins can cause gastric irritation and increases the risk of development of peptic ulcer disease.

The development of selective COX-2 inhibitors was originally aimed at blocking the production of pro-inflammatory prostaglandins while minimizing any effects on platelet and gastric function. Selective inhibition of COX-2 has been accomplished with the

"coxibs", which differ in their selectivity for COX-2 relative to COX-1 by selectively binding to a hydrophobic side-pocket on the COX-2 enzyme where a valine takes the place of what is an isoleucine on COX-1, allowing access to an otherwise sterically hindered site that causes inhibition of the enzyme's function. Since COX-2 is largely expressed selectively in inflamed tissue, there is much less gastric irritation and risk of peptic ulceration associated with COX-2 inhibitors. However, the selectivity of COX-2 causes an imbalance between thromboxane and prostacyclin, resulting in an increased risk of thrombosis, MI, and stroke. Thus, by blocking prostacyclin synthesis without concomitant inhibition of thromboxane A_2 (TXA$_2$) production, highly selective inhibitors of COX-2 increase the risk of cardiovascular events. These effects seemed most notable with rofecoxib (Vioxx®) and valdecoxib (Bextra®), which were removed from the market in 2004 and 2005, respectively. Other COX-2 selective NSAIDs, such as celecoxib (Celebrex®), and etoricoxib (Arcoxia®), are still on the market as they continue to be investigated for these adverse effects. Even with short-term use, COX-2 inhibitors have been found to increase the risk of atherothrombosis, most notably manifested as a 2-to-5-fold increased risk of myocardial infarction. Furthermore, high-dose regimens of some traditional NSAIDs such as diclofenac and ibuprofen are associated with a similar increase in risk of vascular events. Thus, although NSAIDs, particularly COX-2 inhibitors, have demonstrated benefits, the risks associated with their use should be seriously considered when prescribing them to a patient having risk factors and/or a personal or family history of IHD.

3.1.1 Aspirin
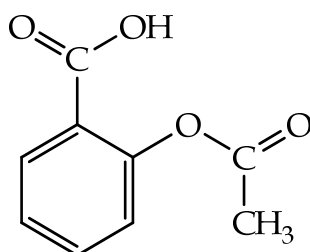
Aspirin (acetylsalicylic acid, ASA), is the oldest and most widely used antiplatelet drug due to its low cost, wide availability, and proven effectiveness. It is a salicylate drug whose mechanism of action serves as the model of most antiplatelet therapeutic strategies.

Mechanism of action

Aspirin, a non-selective COX inhibitor, is one of the most commonly used drugs in IHD that can reduce the development of thrombosis associated with the rupture of atheromatous plaques. Aspirin interferes with the activation of platelets by irreversibly inhibiting COX, thereby interfering with the biosynthetic pathway of thromboxanes. Unlike other NSAIDs, whose antiplatelet action is transient (i.e., in the order of hours), aspirin irreversibly acetylates COX-1 in platelets, thereby inhibiting the biosynthesis of thromboxane A_2 (TXA$_2$) and in that manner producing a long-lived antithrombotic effect (i.e., days, until new platelets are produced by the bone marrow). At higher doses (e.g., 1 g/d), however, aspirin also inhibits COX-2, which can ultimately produce a prothrombotic effect by inhibiting the synthesis of prostacyclin in endothelial cells.

Indications, dosage, and side effects

Aspirin is widely used for the primary prevention of ischemic events in patients at risk, as well as secondary prevention of cardiovascular events in patients with IHD and cerebrovascular and peripheral vascular disease. Aspirin is usually administered once a day at a dose between 75-325 mg, with 75-100 mg being recommended for most indications. When fast platelet inhibition is needed, a dose of at least 160 mg should be given orally. Higher doses of aspirin have not been shown to be more effective than lower doses, and in fact, reduced efficacy has been reported with higher doses. As discussed above, very high doses of aspirin (i.e., 1 g/d) can have a paradoxical prothrombotic effect due to the inhibition of COX-2.

Long-term daily oral enteric-coated aspirin has been demonstrated to reduce (1) the incidence of anginal episodes in patients with chronic stable angina, as well as in survivors of unstable angina and myocardial infarction (MI), and (2) the risk of recurrent infarction, stroke, or cardiovascular mortality by 25% following an MI compared with placebo. It has also been established that low doses of aspirin may be given immediately after an MI to reduce the risk of another MI or of the death of the myocardium.

Aspirin is equally effective in men and women, although in men it mainly reduces the risk of MI, while in women it lowers the risk of stroke. Although aspirin also raises the risk of hemorrhagic stroke and other major bleeds, these events are rare, and are by far outweighed by aspirin's positive effects.

The most common side effects of aspirin use are gastrointestinal, ranging from simple stomach upset, to erosive gastritis, to peptic ulcers with bleeding and perforation, all of which are dose-dependent. For these reasons, aspirin should never be administered to individuals with a history of gastrointestinal bleeding or severe stomach upset. Although the use of enteric-coated or buffered aspirin may relieve some of these symptoms, they do not eliminate the risk of gastrointestinal complications due to the inhibition of gastroprotective prostaglandins as part of the actions of aspirin. The overall risk of major bleeding with aspirin is low, however, estimated at 1-3% per year, but is increased when aspirin is given in conjunction with anticoagulants (e.g., warfarin). In these situations, a lower dose of aspirin should be given (e.g., 75-100 mg/d). In patients with a documented history of peptic ulcer disease caused by Helicobacter pylori infection, treatment of the infection and administration of a proton pump inhibitor (PPI) may reduce the risk of aspirin-induced gastrointestinal bleeding. Aspirin should also never be given to individuals with a history of allergic responses to salicylates, particularly those associated with bronchospasm.
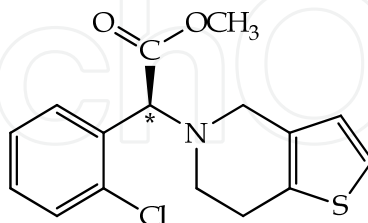
3.2 Thienopyridines

A second class of antiplatelet drugs commonly used in IHD is the thienopyridines. These structurally related drugs have similar benefits as aspirin in patients with stable chronic IHD and may be used instead of aspirin when aspirin is contraindicated. The thienopyridines include clopidogrel (Plavix®), ticlopidine (Ticlid®), and prasugrel (Effient®). A structurally unrelated but functionally similar drug is ticagrelor (Brilinta®).

Mechanism of action

The thienopyridines are prodrugs that must first be metabolized by the hepatic cytochrome P450 enzyme system before they can exert any biological activity, so their onset of action can

be delayed for several days. They interfere with the aggregation of platelets by competitively and irreversibly inhibiting the adenosine diphosphate (ADP) chemoreceptor P2Y12 on the surface of platelets, which is crucial for the conformational change that activates GP IIb/IIIa and ultimately leads to platelet aggregation and cross-linking by fibrin.

3.2.1 Clopidogrel (Plavix®)

Clopidogrel is an oral thienopyridine marketed under the trade name Plavix by Bristol-Myers Squibb and Sanofi-Aventis as 75 mg oral tablets.

Indications, dosage, and side effects

Clopidogrel is indicated for the prevention of vascular ischemic events in patients with symptomatic atherosclerosis, acute coronary syndromes, and MI. When compared with aspirin in patients with recent ischemic stroke, MI, or peripheral arterial disease, clopidogrel further reduced the risk of cardiovascular death, MI, and stroke by nearly 10%. Thus, although clopidogrel is actually more effective than aspirin in reducing morbidity and mortality of IHD, it is also considerably more expensive and not as readily available. It is also used, together with aspirin, for the prevention of thrombotic events after placement of intracoronary stents, or as an alternative to aspirin in patients who have a contraindication for aspirin.

Combination therapy consisting of aspirin and clopidogrel has been shown to reduce morbidity and mortality in patients with angina and it also reduces the risk of thrombosis in patients who have undergone coronary artery stenting (the risk of gastrointestinal bleeding in these patients can be reduced by also prescribing a PPI while on this combination therapy). The combination therapy of clopidogrel and aspirin capitalizes on the capacity of these drugs to inhibit complementary pathways of platelet activation and is associated with a highly statistically significant 20% relative risk reduction when comparing each drug alone.

In patients with a history of acute coronary syndrome, it is standard medical practice to administer aspirin indefinitely, and it is recommended that combination therapy with clopidogrel be given for 1-3 months after the implantation of a bare metal stent. With the use of drug-eluting stents, which deliver antiproliferative drugs locally (e.g., rapamycin or paclitaxel), combination therapy should continue for at least one year because these drugs are associated with delayed endothelial healing that prolongs the window during which there is an increased risk for thrombosis around the area where the stent was placed. Although aspirin and clopidogrel may help prevent coronary thrombosis associated with stenting, there is no evidence that these drugs reduce the occurrence of re-stenosis. However, the use of drug-eluting stents can reduce re-stenosis to near zero within the stent itself and less than 10% at its edges.

There is little evidence of additional benefit of adding clopidogrel to the routine regimen of aspirin in patients with chronic stable IHD that have not undergone stenting. However,

"aspirin resistance" has been noted in up to 10% of patients, more frequently in patients treated with lower doses of aspirin. In these cases, the use of higher doses of aspirin and/or combination therapy with clopidogrel should be considered. Although the routine management of patients with IHD is medical, many patients show greater improvement after undergoing interventional coronary revascularization. These invasive procedures should not take the place of the required ongoing modification of risk factors and medical therapy but rather should be performed in combination with them.

Combination therapy of aspirin and clopidogrel increases the risk of major bleeding to about 2% per year, a risk that will exist even if the daily dose of aspirin is reduced to 100 mg. Thus, the combination of clopidogrel and aspirin should only be used when there is a clear benefit. For example, combination therapy has not been shown to reduce the risk of acute ischemic stroke relative to clopidogrel alone or to reduce the risk of primary cardiovascular events when compared to aspirin alone.

As mentioned above, the onset of action of clopidogrel is slow, so even though platelet inhibition can be seen within a few hours after a single oral dose of the drug, a loading-dose between 300-600 mg is commonly given when prompt inhibition of the ADP receptors is desired, which is continued as a once daily oral dose of 75 mg for maintenance.

The documented adverse effects of clopidogrel include bleeding, severe neutropenia, and thrombotic thrombocytopenic purpura (TTP). Patients with a history of resolved aspirin-related peptic ulcers who received aspirin plus a PPI (e.g., esomeprazole) were shown to have a lower incidence of recurrence of peptic bleeding when compared to patients receiving clopidogrel instead. Another study suggested that prophylaxis with PPIs when undergoing treatment with clopidogrel following an acute coronary syndrome (ACS, i.e., unstable angina or MI) may increase the incidence of adverse cardiac events, perhaps as a result of the inhibition of the cytochrome P450 variant CYP2C19, which is required for the conversion of clopidogrel to its pharmacologically active form. However, even after some government health agencies issued a statement on a potential drug interaction between clopidogrel and PPIs, people within the cardiology community manifested concerns regarding the possible existence of flaws in the studies that served as the basis for these conclusions and subsequent warnings, putting into question the veracity of an adverse drug interaction between clopidogrel and PPIs.

Clopidogrel, was issued a black box warning from the FDA on March 12, 2010 because it is estimated that 2-14% of the US population have low levels of the CYP2C19 liver enzyme needed to activate clopidogrel and, therefore, may not get the full effect from the drug. However, there are tests available to predict if a patient will be susceptible to this reduced pharmacological effect.
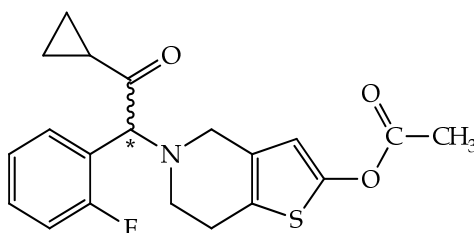
3.2.2 Ticlopidine (Ticlid®)
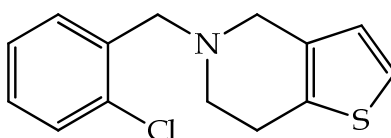
Ticlopidine is an oral thienopyridine marketed under the trade name Ticlid by Roche Pharmaceuticals as 250 mg oral tablets.

Indications, dosage, and side effects

Ticlopidine is typically administered as an oral twice-daily dose of 250 mg. Like aspirin, ticlopidine is more effective than placebo at reducing the risk of cardiovascular death, MI, and stroke in patients with atherosclerotic disease, but due to its delayed onset of action, ticlopidine is not recommended for patients with acute MI. Ticlopidine has been routinely used in addition to aspirin after coronary artery stenting, and as a substitute for aspirin in patients with a contraindication to aspirin. However, because ticlopidine is less potent than clopidogrel and is associated with greater risk of hematologic disorders (e.g., neutropenia, TTP, thrombocytopenia, aplastic anemia), it has largely been replaced by clopidogrel. Due to the known hematologic side effects, which usually become manifest within the first few months of beginning therapy, frequent blood counts must be carefully performed when taking ticlopidine. As with clopidogrel, it is contraindicated in patients having hypersensitivity reactions to thienopyridines, as well as bleeding disorders, active bleeding, and liver disease.

3.2.3 Prasugrel (Effient®)

Prasugrel is an oral thienopyridine marketed under the trade names Effient, Efient, Apagrel, and Prasita. It was developed by Daiichi Sankyo Co. and is currently marketed in the United States in cooperation with Eli Lilly and Co. as 5 mg and 10 mg oral tablets.

Indications, dosage, and side effects

Prasugrel was approved for patients with acute coronary syndrome who will be undergoing a percutaneous coronary intervention (PCI) to reduce the occurrence of cardiovascular thrombotic events. Prasugrel is faster than clopidogrel at inhibiting ADP-induced platelet aggregation and does so to a greater extent than both normal and higher doses of clopidogrel in healthy individuals, as well as in patients with coronary artery disease, including those undergoing PCI. Unlike clopidogrel, prasugrel has not been shown to produce a lesser effect in patients who have a low level of hepatic CYP2C19 enzyme. Prasugrel should be administered as a single 60 mg oral loading dose and then continued at a dose of 10 mg orally once daily. Patients should also take aspirin (75-325 mg) per day.

A study published in the New England Journal of Medicine that compared prasugrel with clopidogrel in patients with acute coronary syndromes, both in combination with aspirin, found that prasugrel was a more potent anti-platelet agent, demonstrating a 1.2-fold reduction in the combined rate of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. However, prasugrel was associated with a 1.6-fold rate of serious bleedings and 4-fold rate of fatal bleedings, even though overall mortality did not differ between the two patient groups.

3.2.4 Ticagrelor (Brilinta®)
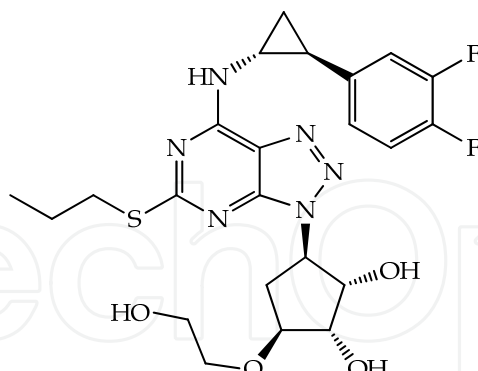
Ticagrelor is an oral cyclopentyltriazolopyrimidine (CPTP) agent marketed under the trade names Brilinta, Brilique, and Possia. The drug was approved for use in the European Union on December 3, 2010 and by the US Food and Drug Administration on July 20, 2011, being marketed in the United States by AstraZeneca as 90 mg oral tablets.

In contrast to the other antiplatelet drugs clopidogrel, ticlopidine, and prasugrel, ticagrelor is a reversible allosteric inhibitor that does not require hepatic activation, making it a better choice for patients with hepatic insufficiency or those carrying low levels or genetic variants of the CYP2C19. Due to its reversible mode of action, ticagrelor is both faster and shorter acting than clopirogrel, making it a easier to discontinue (e.g., surgery, hypersensitivity), but typically requiring more frequent dosing, which can present an issue with compliance.

In a study by AstraZeneca, ticagrelor was associated with ~2% lower mortality rate than clopidogrel in patients with ACS and it was found that taking ticagrelor displayed a lower mortality rate from vascular causes, heart attack, or stroke. However, patients taking ticagrelor was associated with 1.5% higher propensity of non-lethal bleeding.

Indications, dosage, and side effects

Treatment with ticagrelor should be initiated as an oral loading dose of 180 mg, and then continued at 90 mg orally twice daily. Patients should also take aspirin (75-100 mg) daily. Ticagrelor is indicated for the prevention of thrombotic events in patients with ACS or MI, in combination with aspirin unless the latter is contraindicated. Compared with clopidogrel, ticagrelor significantly reduces the mortality rate in patients with ACS. The drug is contraindicated in patients with hepatic insufficiency and a history of pathological bleeding. It also should not be given in combination with other drugs that affect the CYP3A4 liver enzyme, since the drug is metabolized by CYP3A4 and is mainly excreted via bile and feces.

The most common side effects of ticagrelor are dyspnea as well as bleeding (e.g., gastrointestinal, nasal, subcutaneous/dermal). To date, less than 1% of patients taking ticagrelor have reported allergic reactions.

Inhibitors of hepatic CYP3A4 enzyme (e.g., ketoconazole and (?) grapefruit juice), increase blood plasma levels of ticagrelor and can therefore cause bleeding and other adverse effects. Conversely, activators of hepatic CYP3A4 (e.g., rifampicin and (?) St. John's wort), can reduce the effectiveness of ticagrelor. Furthermore, drugs that are also metabolized by CYP3A4 (e.g., simvastatin), will display higher plasma levels, which can result in an increase of the side effects of these drugs when combined with ticagrelor.

3.2.5 Thienopyridine resistance

There is variability among different individuals in the ability of the thienopyridines to inhibit ADP-induced platelet aggregation. To a certain extent this variability reflects genetic polymorphisms in the CYP isoenzymes associated with the metabolic activation of these drugs. For example, individuals carrying the CYP2C19*2 allele have been shown to display a lower responsiveness to clopidogrel, in a similar fashion as those having a lower activity of hepatic CYP3A4. These observations have resulted in the proposal that genetic testing may lead to the identification of individuals that may experience resistance to the effects of thienopyridines.

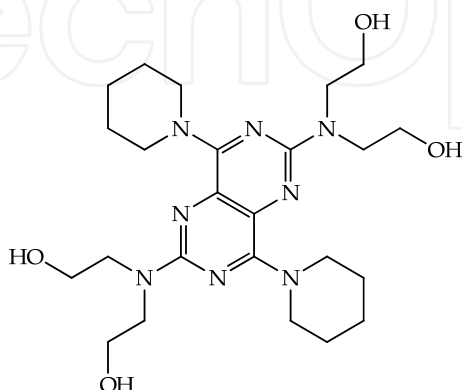### 3.3 Phosphodiesterase inhibitors and adenosine reuptake inhibitors

As the name implies, phosphodiesterase inhibitors interfere with the function of the enzyme phosphodiesterase, which breaks down the intracellular second messenger cyclic adenosine monophosphate (cAMP). This results in increased levels of cAMP, ultimately leading to the inhibition of platelet activation and vasodilation.

3.3.1 Cilostazol (Pletal®)
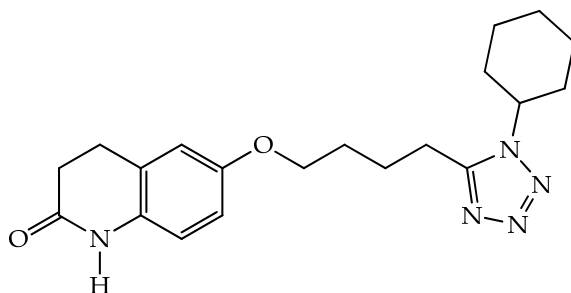
Cilostazol is an oral phosphodiesterase inhibitor marketed under the trade name Pletal. The drug is marketed in the United States by Otsuka Pharmaceutical Co. as 50 and 100 mg oral tablets. Cilostazol is not used in the treatment of ischemic heart disease but rather in the relief of intermittent claudication in patients with peripheral vascular disease.

3.3.2 Dipyridamole (Persantine® and Aggrenox® (in combination with aspirin))

Dypyridamole is an oral phosphodiesterase inhibitor marketed as a single drug under the trade name Persantine, and as an extended-release combination with low-dose aspirin

under the name Aggrenox. Persantine drug is marketed in the United States by Boehringer Ingelheim Pharmaceuticals, Inc. as 25, 50, and 75 mg oral tablets, while Aggrenox contains 200 mg of extended-release dipyridamole and 25 mg of aspirin.

Dypiridamole also inhibits the reuptake of adenosine by platelets, red blood cells, and vascular endothelial cells, as well as the enzyme adenosine deaminase, which metabolizes adenosine into inosine. Both of these effects increase the extracellular concentration of adenosine, which causes smooth muscle relaxation and is, at least in part, responsible for the vasodilatory effects of dipyridamole. Persantine causes vasodilation when given at high doses over a short time and it inhibits thrombosis when given long term by also acting as a thromboxane synthase inhibitor.

Indications, dosage, and side effects

The recommended dose of dipyridamole is 75-100 mg four times daily as an adjunct to warfarin therapy. Dipyridamole is a relatively weak antiplatelet agent on its own and thus is not used for the treatment of IHD. However, dipyridamole has been shown to increase myocardial perfusion and left ventricular function in patients with ischemic cardiomyopathy. In combination with low-dose aspirin (i.e., Aggrenox) it is used for prevention of stroke in patients with a history of transient ischemic attacks given as a twice-daily dose.

When given by intravenous infusion over 3-5 minutes, dipyridamole is associated with a rapid increase in the local concentration of adenosine in the coronary circulation, which has a vasodilatory effect. However, this vasodilation largely occurs in healthy coronary arteries, while those arteries that are stenosed remain so. This results in an imbalance of coronary perfusion that can become clinically manifest by symptoms of chest pain as well as electrocardiographic signs of ischemia.

Dipyridamole combined with aspirin reduces the risk of stroke by 22.1% compared with aspirin and by 24.4% compared with dipyridamole alone in patients with a history of cerebrovascular disease (i.e., TIA and/or stroke). With regard to secondary prevention in patients with a history of ischemic stroke, combination therapy resulted in 13% of patients having vascular death, stroke, or MI as opposed to 16% of those treated with aspirin alone. Based on all this data, Aggrenox is often used for stroke prevention. However, because it has vasodilatory effects, combination therapy of dipyridamole with aspirin (i.e., Aggrenox) should not be used for the prevention of stroke in patients with symptomatic coronary artery disease. A triple therapy of aspirin, clopidogrel, and dipyridamole has been investigated, but an increase in adverse bleeding events was observed with this combination.

The major side effects documented with the use of dipyridamole are gastrointestinal, headache, facial flushing, dizziness, and hypotension, which often disappear with continued use of the drug.

3.4 GP IIb/IIIa receptor antagonists

As a member of the integrin family of adhesion receptors, GP IIb/IIIa is found on the surface of platelets and megakaryocytes. With about 80,000 copies, GP IIb/IIIa is the most abundant receptor on platelets. GP IIb/IIIa consists of a non-covalently linked heterodimer

that is inactive on resting platelets. When platelets are activated, a signal transduction pathway triggers a conformational change on the receptor that leads to its activation. Activated GP IIb/IIIa can bind other adhesion molecules (e.g., fibrinogen, vWF) under conditions of high shear stress. Binding is mediated by an Arg-Gly-Asp (RGD) sequence found on both fibrinogen and vWF, and by a Lys-Gly-Asp (KGD) sequence located within a unique dodecapeptide domain on fibrinogen. Once GP IIb/IIIa is bound to fibrinogen and/or vWF, adjacent platelets can be bridged together and lead to platelet aggregation.

Abciximab, eptifibatide, and tirofiban all target the GP IIb/IIIa receptor, but as described below, they are structurally and pharmacologically distinct. Abciximab has a long half-life and can be detected on the surface of platelets for a couple of weeks, while eptifibatide and tirofiban have shorter half-lives.

All of the GP IIb/IIIa antagonists are administered by intravenous (IV) infusion following an IV bolus. The dosage of eptifibatide and tirofiban must be reduced in patients with renal insufficiency since they are cleared by the kidneys.

The most serious complications of GP IIb/IIIa inhibitors are bleeding and thrombocytopenia, which is immunoglobulin-mediated as a result of antibodies directed against neoantigens on GP IIb/IIIa that form upon binding of the drug.

3.4.1 Abciximab (ReoPro®)

Abciximab is manufactured by Centocor and distributed by Eli Lilly. As with all of the GP IIb/IIIa antagonists, it is administered by intravenous (IV) infusion. It is a humanized murine monoclonal immunoblogulin Fab fragment directed against the activated form of GP IIb/IIIa that binds to the activated receptor with high affinity and blocks the binding of adhesion molecules.

Indications, dosage, and side effects

Abciximab is used in the setting of percutaneous coronary interventions (e.g., angioplasty, with or without stenting) to prevent platelet aggregation and thrombosis. It is administered as an IV bolus at 0.25 mg/kg, 10 to 60 min before PCI followed by continuous infusion of 0.125 µg/kg/min (to a max of 10 µg/min) for 12 h. Its use is associated with a reduction in both the incidence of ischemic complications, as well as the necessity for repeated interventional procedures within the first thirty days. Patients with diabetes and chronic renal insufficiency can be given abciximab, but its use is contraindicated in patients who shall be undergoing an emergent surgical procedure (e.g., coronary artery bypass grafting), since bleeding time may remain elevated for up to 12 hours.

Abciximab has a relatively short half-life (i.e., ~10-30 min), but its pharmacological effects on platelet function persist for up to 48 hours after cessation of IV infusion, followed by a low degree of GP IIb/IIIa receptor blockade that can continue for up to two weeks.

Many of the side effects of abciximab are due to its anti-platelet effects, including an increased risk of bleeding (e.g., gastrointestinal hemorrhage). Thrombocytopenia is a rare but known serious risk that occurs in up to 5% of individuals receiving the drug, which can be severe in ~1% of these patients. Abciximab-induced thrombocytopenia can typically be treated with transfusion of platelets. Abciximab induced thrombocytopenia can last for

seven days after initial drug administration. Transfusing platelets is the only known treatment and may have limited effectiveness as the drug may also bind to the new platelets. Platelet counts, which should average 250,000-400,000, can effectively drop to zero.

In addition to targeting the GP IIb/IIIa receptor, abciximab also inhibits the closely related v3 receptor, which binds vitronectin, and M2, a leukocyte integrin. In contrast, eptifibatide and tirofiban are specific for GP IIb/IIIa. Inhibition of v3 and M2 may impart abciximab with anti-inflammatory and/or antiproliferative properties that extend beyond the inhibition of platelets.

3.4.2 Tirofiban (Aggrastat®)
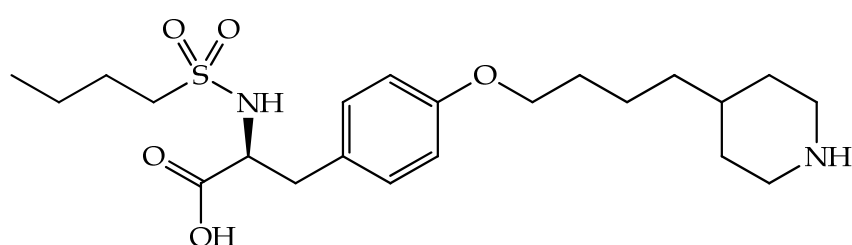
Tirofiban is marketed the United States by Medicure Pharma and the rest of the world by Irokocardio International SARL under the brand name Aggrastat as a parenteral solution for intravenous administration in dosages of forms 5 mg and 12.5 mg. Tirofiban is a non-peptidic tyrosine derivative that mimics the RGD motif found on the ligands of GP IIb/IIIa.

Indications, dosage, and side effects

Tirofiban is administered intravenously with an initial dose of 0.4 µg/kg/min for the first 30 minutes, followed by a maintenance dose of 0.1 µg /kg/min as a constant IV infusion for 12-24 hours following PCI. Tirofiban, in combination with aspirin and heparin, is indicated in the treatment of patients with acute coronary syndromes (i.e., unstable angina or acute MI), including those who may be undergo subsequent percutaneous coronary intervention, to reduce the occurrence of further ischemic damage, new myocardial infarction, and mortality.

Tirofiban has a fast onset and short duration of action, with coagulation parameters returning to normal within 4-8 hours after intravenous infusion is stopped.

The major side effect of tirofiban seen in clinical trials was bleeding, both locally and systemically, with major bleeding occurring in 1.4% of patients and minor bleeding in 10.5%. About 4.0% of patients needed a transfusion to stop intractable bleeding and to improve anemia secondary to it. Thrombocytopenia was seen in patients given tirofiban and heparin at a rate of about 1.5%, compared to only 0.8% in those receiving heparin alone. This side effect was usually reversible within a few days. Positive fecal and urine hemoglobin tests were also seen. After the drug entered the market, there have been reports of intracranial and retroperitoneal bleeding, pulmonary hemorrhage, spinal-epidural hematoma, and hypersensitivity reactions including acute anaphylaxis. Fatal bleedings have been rarely reported.

3.4.3 Eptifibatide (Integrilin®)
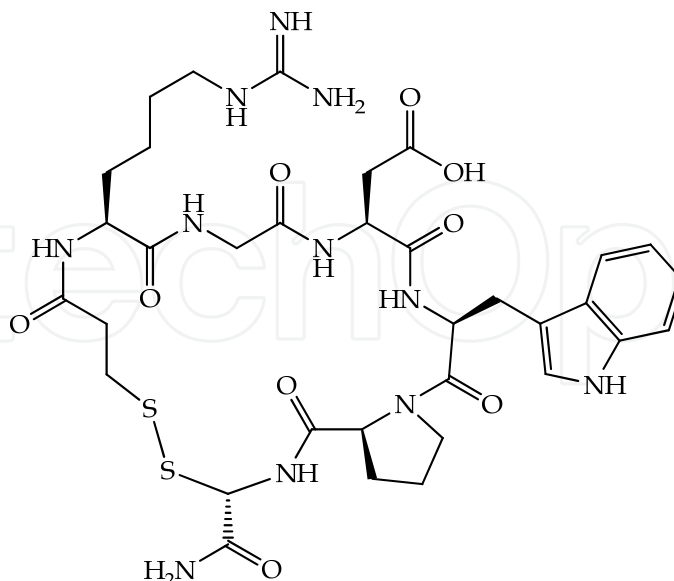
Eptifibatide is a cyclic heptapeptide that binds GP IIb/IIIa because it contains the KGD motif. It is manufactured by Millennium Pharmaceuticals and co-promoted by Schering-Plough/Essex. Eptifibatide is supplied as a sterile solution in 10-mL vials containing 20 mg of the drug, and 100-mL vials containing either 75 mg or 200 mg of eptifibatide.

Indications, Dosage, and Side Effects

The recommended adult dosage of eptifibatide in patients with acute coronary syndrome that have normal renal function is an intravenous bolus of 180 μg/kg as soon as possible following diagnosis, followed by a continuous infusion of 2.0 μg/kg/min for up to 72 hours until hospital discharge or initiation of coronary artery bypass graft (CABG) surgery. For patients who are to undergo a percutaneous coronary intervention (PCI) while receiving eptifibatide, the infusion should be continued up to hospital discharge, or for up to 18 to 24 hours after the procedure, whichever comes first, allowing for up to 96 hours of therapy.

Eptifibatide is used to reduce the risk of acute cardiac ischemic events (i.e., death and/or myocardial infarction) in patients with unstable angina or non-ST-segment elevation (i.e., non-Q-wave) myocardial infarction (i.e., non-ST-segment elevation acute coronary syndromes) both in patients who are to receive non surgery (conservative) medical treatment and those undergoing percutaneous coronary intervention (PCI). The drug is always applied together with aspirin or clopidogrel and (low molecular weight or unfractionated) heparin.

The side effects of eptifibatide are very similar to those of abciximab.

4. Ongoing trials of antiplatelet therapy

According to the International Committee of Medical Journal Editors (ICMJE):

"Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."

Over the past ten years, government agencies and the IMCJE have issued laws and directives on the subject of trial registration. All parties have consistently agreed that the purpose of trial registration is to promote the public good by ensuring that the existence and design of clinically directive trials are publicly available. The registration effort began with the development of a publicly available website, ClinicalTrials.gov, which is a service of the NIH, developed by the National Library of Congress.

In 1997, the FDA/NIH began requiring registration for only a limited number of trials. In September, 2007, the Food and Drug Amendments Act (Title VIII. Sec. 801) significantly expanded the scope of clinical trials that must be registered. Penalties for failing to register "applicable trials" may include civil monetary penalties.

In 2004, the International Committee of Medical Journal Editors (ICMJE) defined trials that must be registered in order to be considered for publication in journals that adhere to ICMJE standards. In 2007 the ICMJE expanded the definition of trials that must be registered. Scores of journals (not limited to medical journals) have adopted the registration policy.

The best way to obtain information about clinical trials in platelet activation in ischemic heart disease is by accessing two renowned sources:

http://clinicaltrials.gov

http://www.clinicaltrialresults.org/

Clinicaltrials.gov is a site organized by US government and their webpage states:

"ClinicalTrials.gov offers up-to-date information for locating federally and privately supported clinical trials for a wide range of diseases and conditions. A clinical trial (also clinical research) is a research study in human volunteers to answer specific health questions."

ClinicalTrials.gov currently contains 112,970 trials sponsored by the National Institutes of Health, other federal agencies, and private industry. Studies listed in the database are conducted in all 50 States and in 175 countries. ClinicalTrials.gov receives over 50 million page views per month and 65,000 visitors daily.

The U.S. National Institutes of Health (NIH), through its National Library of Medicine (NLM), has developed this site in collaboration with the Food and Drug Administration (FDA), as a result of the FDA Modernization Act, which was passed into law in November 1997. See the FDA document - Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions (March 2002).

This site allows for selection of all important characteristics of clinical trial to be displayed. We can choose any combination of next characteristics: condition, intervention, sponsor, gender, age group, phase, number enrolled, funded by, study type, study design, NCT ID, other IDs, first received date, start date, completion date, last updated date, last verified date, acronym, primary completion date, and outcome measure.

The second site, http://www.clinicaltrialresults.org/, can be used as excellent source of slides, movies, reports, and other useful information about clinical trials. The 'cardiology' section contains divisions into subspecialty news, with listing about: acute coronary syndromes, angina, anticoagulants, antiplatelet agents, antithrombins, congestive heart

failure, electrophysiology, imaging, interventional cardiology, prevention, and patient resources. Since access to these sources is in the public domain, we decided not to cite individual trials by other sources although we went deeper and extracted information from from individual trials. We advise our readers to visit these two sites frequently.

A reasonably informative overview of ongoing trials of antiplatelet therapy is supposed to list name and registry number for trial, to describe study population, specify primary end point, and define study arms. This data is presented in table 4.1

Clinical Trial (Registry No.)	Study Population	Primary End Point	Study Arms
ACCOAST (NCT01015287)	4,100 patients with NSTEMI planned to undergo PCI	CV death, MI, stroke, urgent revascularization, or GP IIb/IIIa inhibitor bailout at 7 days	Randomized to pre-treatment with prasugrel (30 mg at time of diagnosis with additional 30 mg atPCI) vs. prasugrel (60 mg) at PCI. Maintenance therapy in both arms will be 10 mg daily with dose reduction to 5 mg in patients >75 yrs and body weight <60 kg
ARCTIC (NCT00827411)	2,500 patients undergoing elective PCI with DES	Death, MI, stroke, urgent coronary revascularization, or stent thrombosis assessed at 1 yr; death, MI, stroke, urgent coronary revascularization, or stent thrombosis at 6–18 months after second randomization	Initial randomization to tailored antiplatelet therapy with VerifyNow P2Y12 vs. standard dual antiplatelet therapy. Subsequent randomization after 12 months of patients who remain eventfree to discontinuation of antiplatelet therapy or continuation of therapy
DANTE Trial (NCT00774475)	442 patients with NSTE-ACS undergoing PCI with stent implantation found to have high residual platelet reactivity with the VerifyNow P2Y12	CV death, MI, or target vessel revascularization at 6 months and 1 yr	Randomized to 75 mg of clopidogrel or 150 mg of clopidogrel
DAPT (NCT00977938)	20,645 subjects undergoing PCI	CV death, MI, and stroke at 33 months; stent thrombosis at 33 months	Subjects in the overall cohort who are free from death, MI, stroke, repeat revascularization, stent thrombosis, or major bleeding at 12 months will be randomized to 18 additional months of dual antiplatelet therapy or aspirin and placebo

Clinical Trial (Registry No.)	Study Population	Primary End Point	Study Arms
GRAVITAS (NCT00645918)	2,783 subjects after DES placement for stable CAD or NSTE-ACS will have platelet function testing done with VerifyNow P2Y12	CV death, MI, and definite/ probable stent thrombosis at 6 months	Patients with high residual platelet reactivity will be randomized to receive standard-dose clopidogrel (75 mg daily) or high-dose clopidogrel (600 mg load, 150 mg daily). A random sample of patients without high residual platelet reactivity will also be enrolled and will receive 75 mg of clopidogrel daily
INNOVATE-PCI (NCT00751231)	Phase II trial in 800 patients undergoing elective PCI	No pre-specified primary end point	Randomized to clopidogrel (300/600 mg load, followed by 75 mg daily) or elinogrel (80 mg IV bolus administered before PCI, followed by twice daily dosing of oral 50 mg, 100 mg, or 150 mg)
LANCELOT 201 (NCT00312052)	Phase II trial of 600 patients with CAD	Safety and tolerability (6 months)	Randomized to E5555 (50 mg, 100 mg, or 200 mg daily) or placebo
LANCELOT 202 (NCT00548587)	Phase II trial of 600 patients with CAD	Safety and tolerability (12 weeks)	Randomized to E5555 (50 mg, 100 mg, or 200 mg daily) or placebo
TRA-CER (NCT00527943)	12,500 subjects with ACS	CV death, MI, stroke, recurrent ischemia with repeat hospital stay, and urgent coronary revascularization at end of study	Randomized to SCH 530348 (40 mg loading dose, 2.5 mg daily) vs. placebo
TRA-2P-TIMI 50 (NCT00526474)	26,450 patients with history of CAD, CVA, or PAD	CV death, MI, stroke, and urgent coronary revascularization at end of study	Randomized to SCH 530348 (2.5 mg daily) vs. placebo
TOPAS-1 (NCT00914368)	Phase II trial of 450 patients who have either had or not had stent thrombosis or MI within 6 months of PCI while on dual antiplatelet therapy	Establish VerifyNow P2Y12 (PRU) and VASP (PRI, %) cutoff level of platelet inhibition in patients with and without clinical events.	All subjects will undergo platelet function testing with both VerifyNow P2Y12 and VASP assays

Clinical Trial (Registry No.)	Study Population	Primary End Point	Study Arms
TRIGGER-PCI (NCT00910299)	2,150 subjects with high residual platelet reactivity with the VerifyNow P2Y12 after elective PCI with DES	CV death or MI at 6 months	Randomized to prasugrel (60 mg load, 10 mg daily) vs. clopidogrel (75 mg daily)
TRILOGY-ACS (NCT00699998)	10,300 patients with NSTE-ACS being initially medically managed	CV death, MI, or stroke at end of study	Randomized to prasugrel (30 mg load ifadministered, followed by 5 mg or 10 mg maintenance) or clopidogrel (300 mg load if administered, followed by 75 mg daily)

Table 4.1

5. Abbreviations

ACCOAST: Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction Trial

ACS: acute coronary syndrome

ARCTIC: Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy Trial

ARMYDA: Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty

CIPAMI: Clopidogrel Administered Prehospital to Improve Primary PCI in Patients with Acute Myocardial Infarction

CAD: coronary artery disease

CLARITY-TIMI: Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction

CREDO: Clopidogrel for the Reduction of Events During Observation

CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events

CURRENT/OASIS: Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions

CV: cardiovascular

CVA: cerebrovascular accident

DANTE: Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition

DAPT: Dual Antiplatelet Therapy

DES: drug-eluting stents

GP IIb/IIIa: glycoprotein IIb/IIa

GRAVITAS: Gauging Responsiveness With A VerifyNow Assay—Impact On Thrombosis And Safety

INNOVATE-PCI: A Phase 2 Safety and Efficacy Study of PRT060128, a Novel Intravenous and Oral P2Y12 Inhibitor, in Non-Urgent PCI

LANCELOT 201: Safety and Tolerability of E5555 and Its Effects on Markers of Intravascular Inflammation in Subjects With Coronary Artery Disease

LANCELOT 202: Safety and Tolerability of E5555 and Its Effects on Markers of Intravascular Inflammation in Subjects With Acute Coronary Syndrome

MI: myocardial infarction

NSTE-ACS: non–ST-segment elevation acute coronary syndrome

NSTEMI: non–ST-segment elevation myocardial infarction

PAD: peripheral artery disease

PCI: percutaneous coronary intervention

PRI: platelet reactivity index

PRINCIPLE: Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation

PRU: platelet reactivity unit

STEMI: ST-segment elevation myocardial infarction

TIMI: Thrombolysis In Myocardial Infarction

TOPAS-1: Tailoring Of Platelet Inhibition to Avoid Stent Thrombosis

TRA-CER: Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome

TRA-2P-TIMI 50: Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis

TRIGGER-PCI: Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel

TRILOGY-ACS: Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects

TRITON: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel

VASP: Vasodilator-stimulated phosphorprotein

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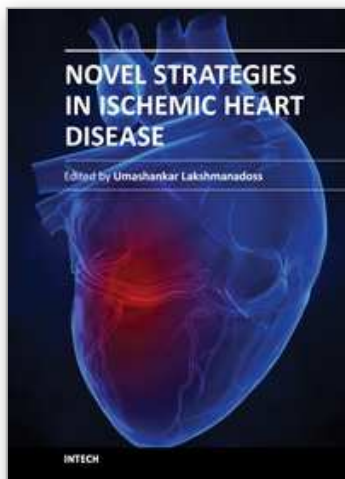
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