1. Introduction

Cardiovascular diseases (CVDs) remain the biggest cause of deaths worldwide, though over the last two decades, cardiovascular mortality rates have declined in many developed countries but have increased at an astonishingly fast rate in developing countries. More than 17.5 million people died from cardiovascular diseases in 2012 representing 30 % of all global deaths.[1] Of these deaths, an estimated 7.3 million are due to coronary heart diseases. If current trends are allowed to continue, by 2015 an estimated 20 million people will die from cardiovascular diseases, mainly from heart attacks and strokes. The number of people, who die from CVDs, mainly from heart disease and stroke, will increase to reach 23.6 million by 2030.[2] CVDs are caused by disorders of the heart and blood vessels, and include coronary heart disease (heart attacks), cerebrovascular disease (stroke), raised blood pressure (hypertension), peripheral arterial disease, rheumatic heart disease, congenital heart disease and heart failure. More people die annually from CVDs than from any other causes. CVDs are projected to remain the single leading cause of deaths. Overall 9.4 million deaths each year, or 16.5 % of all deaths can be attributed to high blood pressure. This includes 51 % of deaths due to strokes and 45 % of deaths due to coronary heart disease. Each year, heart diseases kill more people in developed and developing countries than cancer. In recent years, cardiovascular risk in women has been increasing and has killed more women than breast cancer.

Heart attacks and strokes are usually acute events that are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain.

Thrombosis is the formation of a blood clot within the blood vessel, resulting in occlusion of blood flow.[3] There are two forms of thrombosis, namely

a) Arterial thrombosis and

b) Venous thrombosis.

Hemostasis is a physiological process by which the body stops blood loss whenever a blood vessel is severed or ruptured; thrombosis is a pathological process in which hemostatic mechanisms, i.e., blood coagulation and platelet aggregation, are activated in the absence of bleeding. Therefore, inhibiting coagulation and preventing platelet aggregation at different stages are essential components of most antithrombotic therapeutic strategies. Of the several drug targets in the blood coagulation cascade e.g., thrombin, factor VIIa, and factor Xa, thrombin has

provided the most frequently used strategy for the design of novel anticoagulants over the past decade. The principal physiological role of thrombin, the final enzyme in the blood coagulation cascade, is conversion of soluble fibrinogen into insoluble fibrin, which forms a mechanical matrix for the developing blood clot, and the activation of platelet aggregation.[4]

Since thrombosis involves multiple pathways, a combination of antiplatelet and anticoagulant drugs have been shown to be effective in the clinic. However, these drugs are associated with side effects like bleeding tendencies, adverse drug-drug interactions, and complicated pharmacokinetics.[5]

1.1. Thrombogenesis

In normal healthy nondisrupted vascular endothelium, platelets and blood coagulation factors are not activated. Endothelial cells synthesize several inhibitors of thrombosis- nitric oxide and prostacyclin, plasminogen activators, thrombomodulin and heparin sulfate.[6] These molecules modulate coagulation and promote fibrinolysis. The matrix in the deeper layers of the vessel wall contains thrombogenic elements including adhesive proteins such as collagen and von Willebrand factor (vWF) (both of which promote platelet adhesion) and tissue factor (TF) that triggers the blood coagulation cascade.[7]

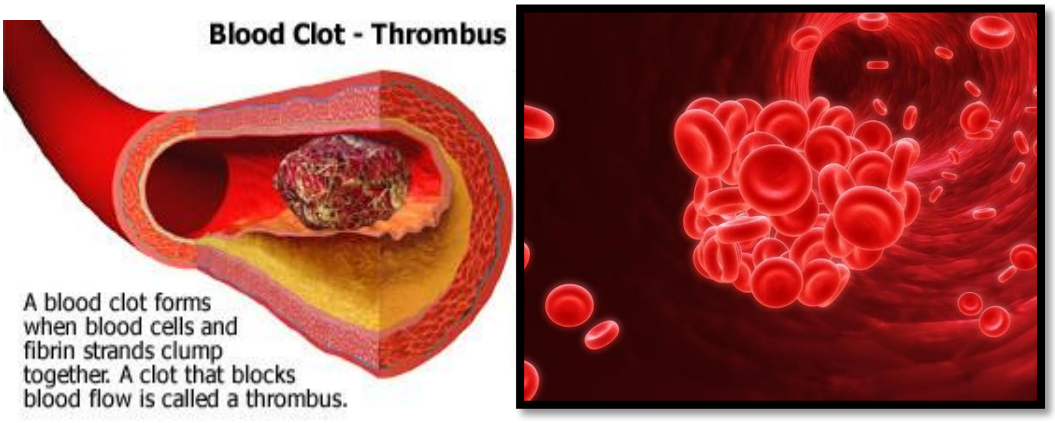


Fig.1. Thrombosis

Thrombosis however may occur if the hemostatic stimulus becomes unregulated. This can occur due to the impairment of the inhibitory pathway or more commonly the overwhelming of the capacity of the natural anticoagulant mechanism due to the intensity of the stimulus (Fig. 1).[8] An example of this is acute stroke associated with deep vein thrombosis (DVT). Important

predisposing conditions to thrombosis are low flow state, disturbed flow[9] and altered endothelial coverage caused by ulceration or endarterectomy.

Injury of the vessel wall also plays a major role in vascular thrombosis.[10] However, it is more important in the pathogenesis of arterial thrombosis than its venous counterpart. Arterial thrombi are predominantly composed of platelets, a small amount of fibrin, and a few red blood cells. Because of the high platelet composition of these thrombi, antiplatelet agents rather than anticoagulants have been used in the treatment and prevention of arterial thrombosis.[11] Venous thrombi are mainly composed of red blood cells in a fibrin mesh[12] and anticoagulant agents are used in the treatment of venous thrombosis (Fig. 2).

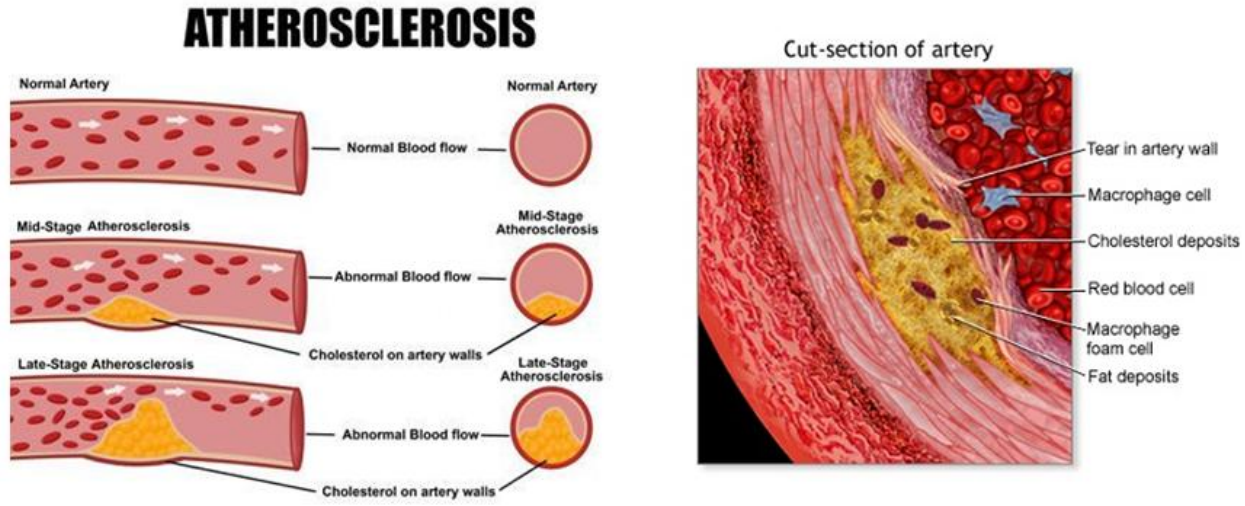


Fig. 2. Atherosclerosis and cut section of artery

1.2. Coagulation cascade

The classic coagulation system is divided into extrinsic and intrinsic pathways (Fig. 3).[13] An intrinsic system that is activated by coagulation factors that is already present in the blood and an extrinsic system that is initiated outside of blood vessels in the presence of injury to a vessel. In the extrinsic system, factor VII, which is present in whole blood, is converted into its activated form factor VIIa, by binding to Tissue factor (TF).

The TF-VIIa complex so formed then converts factor X into its activated form Xa. In turn, this forms a complex with factor Va and so brings about cleavage of prothrombin in order to form thrombin. Thrombin can then cleave fibrinogen to form fibrin, which polymerizes to form fibrin sheets.[14]

When a blood vessel injury occurs, platelets exhibit a sequence of events. These events include (1) adhesion of platelets to the injury site, (2) spreading of adherent platelets over the exposed subendothelial surface, (3) secretion of platelet granule constituents, (4) platelet aggregation and (5) platelet coagulant activity.[13]

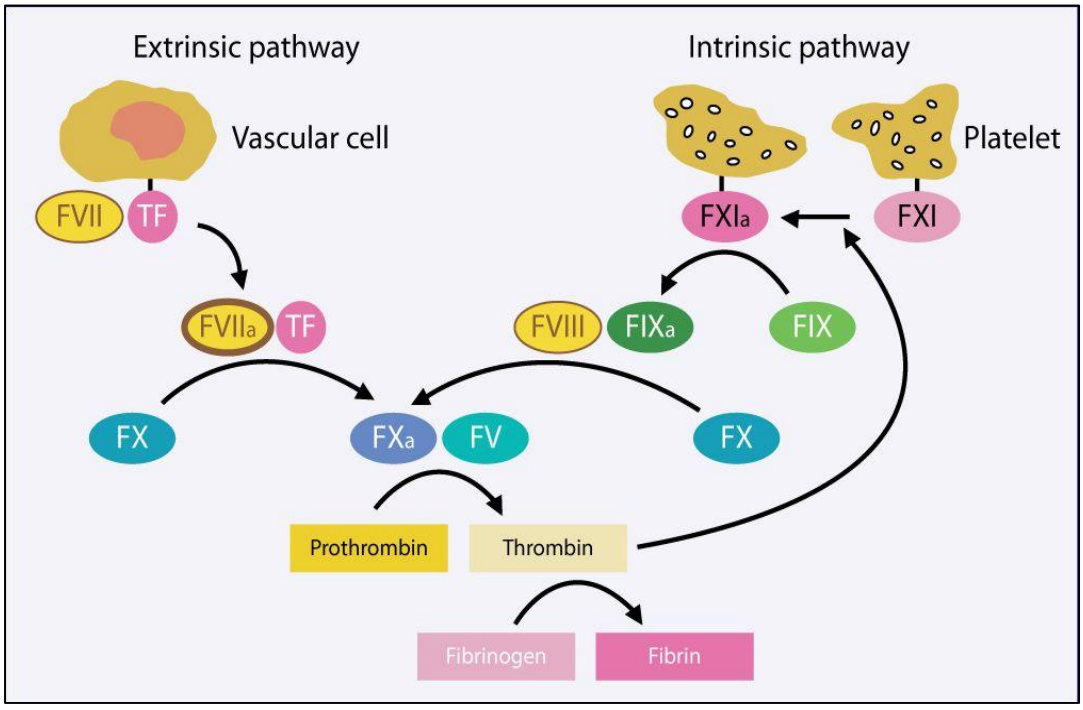


Fig. 3. Simplified schematic representation of blood coagulation cascade

The GPIIb/IIIa receptor (αIIbβ3) belongs to the integrin family of platelet receptors. The receptor consists of two subunits, alpha and beta. The GPIIb/IIIa receptor is the final common pathway by which platelet aggregation takes place; direct inhibition of this receptor is likely to prove superior to blockers of only some of the pathways.[15]

1.3. Platelet aggregation and mechanism of thrombosis

The earliest events in thrombus formation include platelet adhesion, platelet activation, subsequent platelet aggregation and granule release (Fig. 4). These events are inseparable from the initiation of the coagulation cascade principally by tissue factor, thrombin generation and cross-linked fibrin formation. The interactions between platelet and coagulation events during thrombus formation are numerous. Activated platelets provide the physical surface for efficient thrombin formation. In turn, the thrombin generated by activation of the coagulation cascade is a potent platelet aggregating agent. The importance of platelets in thrombus formation is evident

by the therapeutic efficacy of antiplatelet drugs in thromboembolic diseases, especially arterial vascular disease.[16]

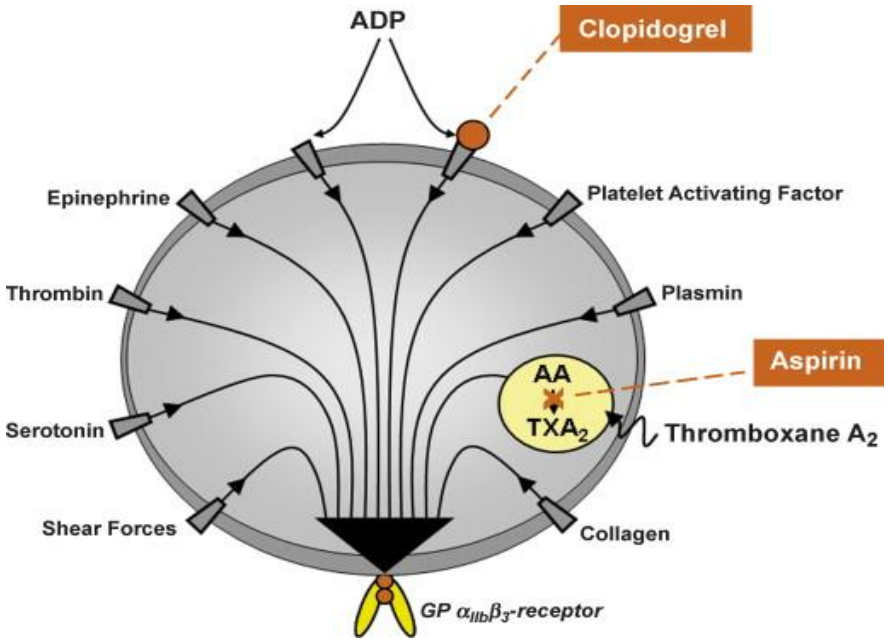


Fig. 4. Mechanism of platelets aggregation in response to blood vessel injury and sites of action of antiplatelet drugs

The biochemistry of platelet adhesion, activation and aggregation is complex. Many of these events are coordinated by surface receptors. Platelets adhere to immobilized von Willebrand Factor (vWF) and also collagen at functional glycoprotein Ib/IX/V and collagen receptors. Adhesion results in initial platelet activation by internal signaling pathways often involving reduced intraplatelet cyclic adenosine monophosphate (Fig. 5). Activated platelets release the contents of stored granules into the blood plasma. The granules include adenosine diphosphate (ADP), serotonin, platelet-activating factor (PAF), vWF, platelet factor 4 [also known as chemokine (c-x-c motif) ligand 4], and thromboxane A_2 (TXA_2), which, in turn, activate additional platelets.[22] Important platelet agonists *in vivo*, including thrombin, ADP, TXA_2 and collagen, all act via specific platelet surface receptors. The final common pathway of platelet aggregation is activation of the glycoprotein IIb/IIIa receptor (GP IIb/IIIa). An aggregate consists of platelets linked together by fibrinogen and vWF bound to multiple GP IIb/IIIa receptors. The activated platelets change shape from spherical to stellate.[17]

Vascular injury triggers a coagulation cascade that ultimately leads to the formation of a fibrin clot, which stabilizes platelet thrombi. The coagulation cascade is a stepwise process of

activation of several proteases in both the extrinsic (tissue factor, factor VIIa) and intrinsic (factor XIIa, XIa, IXa and VIIIa) pathways. These cascades converge upon activation of factor Xa to form a common pathway, in which thrombin plays a central role in catalyzing the production of fibrin.[18]

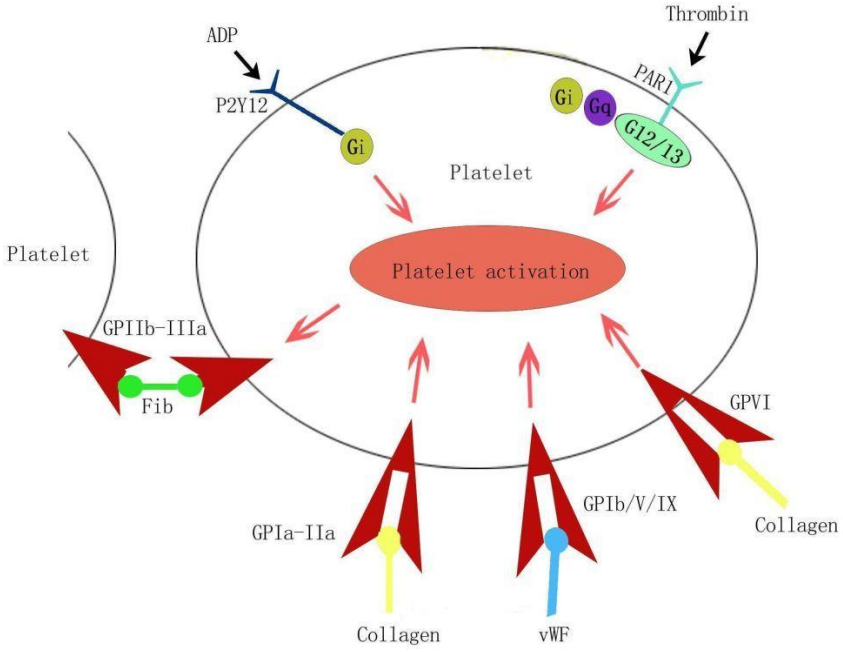


Fig. 5. Platelet activation[23]

1.4. Phases of coagulation cascade and thrombus formation

Phase 1: Platelet adhesion

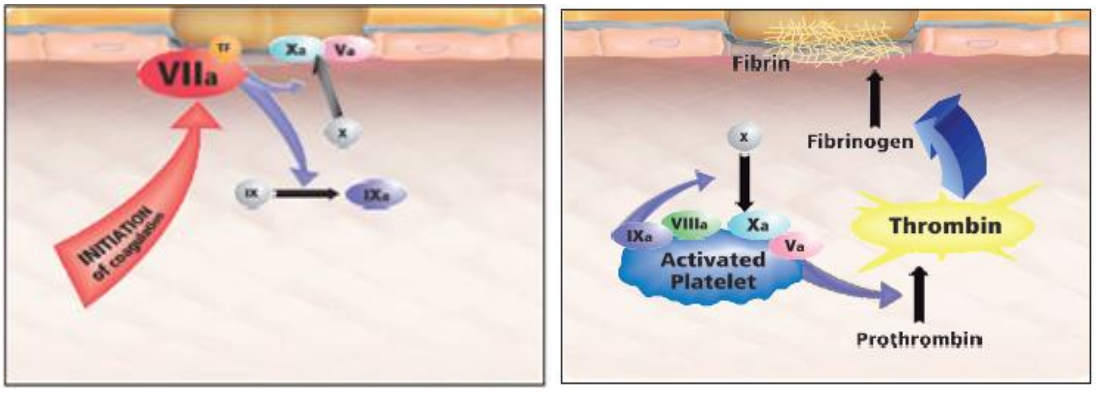
When the vascular endothelium is injured, platelets directly bind to collagen fibres through GP Ia receptors, and GP Ib receptor and GP IIb/IIIa receptors bind to the von Willebrand Factor (vWF), which in turn bind to the collagen fibres. This triggers a complex series of chemical reactions resulting in platelet activation.

Phase 2: Platelet activation

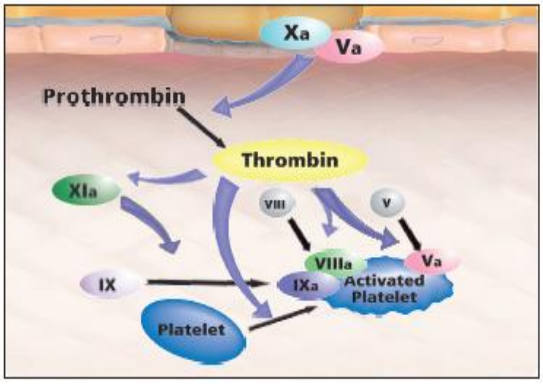
Due to activation, platelets change their shapes and release chemical mediators such as adenosine diphosphate (ADP), TXA_2, serotonin, platelet activating factor and thrombin. The GP IIb-IIIa receptors bind to fibrinogen and tissue factor is released from platelets and arterial wall tissues.

Phase 3: Platelet aggregation

These activated platelets adhere to each other by means of fibrinogen, which bind to the GP IIb/IIIa receptors of platelets. During this process, prothrombin is converted into thrombin. The fibrinogen (soluble) is converted to fibrin (insoluble) by the thrombin, strengthening the thrombus.



Initiation phase Propagation phase



Thrombin amplification phase

Fig. 6. Phases of coagulation cascade

The blood coagulation cascade is usually initiated when subendothelial tissue factor is exposed to the blood flow following either damage or activation of the endothelium. As a result, the hemostatic mechanism is invoked through a complex series of regulated events, involving interactions of blood components and tissue proteins, resulting in a spectrum from hemorrhage, through controlled hemostasis, to thrombosis (Fig. 6).[19]

1.5. Platelet inhibiting agents

The relevance of antiplatelet drugs has been firmly established by clinical trials and experience with drugs such as acetyl salicyclic acid (aspirin). There are several drugs that are used to inhibit platelet aggregation. Of the classes of agents listed below, aspirin, dipyridamole and thienopyridines are the only oral antiplatelet agents currently approved by the Food and Drug Administration (FDA) for use in patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) come in both oral and intravenous (IV) forms. The GPIIb/IIIa agents are currently available only in IV forms. The ideal antiplatelet drug to be used for management of cardiovascular diseases should be orally administrated, rapidly acting, nontoxic, have reasonable antithrombotic efficiency and show minimal side effects especially with regard to bleeding. Recently meta-analysis of randomized clinical trials has shown that antiplatelet therapy (aspirin or other oral antiplatelet drugs) among the high risk patients reduces the combined outcome of any serious vascular event by about one-quarter, nonfatal myocardial infraction by one-third, nonfatal stroke by one-quarter and vascular mortality by one-sixth.[20]

Classification of antiplatelet drugs

Antiplatelet drugs are classified as per their mechanism of action.

(1) Cyclooxygenase (COX) inhibitors

- Aspirin
- Indobufen
- Triflusal

(2) ADP receptor antagonists

- Ticlopidine
- Clopidogrel
- Prasugrel

(3) Phosphodiesterase inhibitors

- Dipyridamole
- Cilostazol
- Triflusal

(4) GP IIb/IIIa Inhibitors

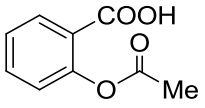
- Tirofiban
- Eptifibatide
- Abciximab

Antiplatelet agents are drugs that interfere with the blood clotting. Antiplatelet drugs are used to prevent blood clots from forming as clots can lead to heart attack/strokes. A blood clot starts forming when platelets in the blood clump together at the site of formation of plaques in the blood vessel. Plaque formation takes place when cholesterol, fat, calcium and other substances build up on the inside walls of the arteries. This process is called atherosclerosis.

1.5.1. Cyclooxygenase (COX) inhibitors

Aspirin and aspirin-like drugs

As a general class NSAIDs such as aspirin **(1.1)**, indomethacin and ibuprofen interfere with the binding of arachidonic acid in the cyclooxygenase active site of the enzyme. Aspirin is the most widely used inhibitor of platelet function. It interferes with platelet aggregation by inhibiting the synthesis of TXA_2 through the irreversible acetylation of cyclooxygenase.[21] Other NSAIDs compete reversibly with arachidonic acid for binding to the cyclooxygenase site.



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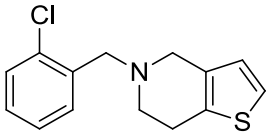
1.5.2. ADP receptor antagonists

Thienopyridine derivatives

Ticlopidine (Ticlid) and its more recently developed analog clopidogrel (Plavix) are thienopyridine derivatives. They inhibit the binding of ADP to its receptor present on the platelets, leading to direct inhibition of the binding of fibrinogen to the GPIIb/IIIa complex.[22] Ticlopidine also interferes with vWF, resulting in reduced binding of vWF factor to the platelet receptors.[23]



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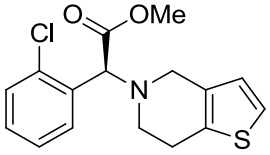

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Ticlopidine **(1.2)** and clopidogrel **(1.3)** can both be administered orally. Both agents are inactive *in vitro*, requiring breakdown to as yet unidentified active metabolites to achieve *in vivo* activity. Ticlopidine **(1.2)** has a number of potentially serious side effects; it has been associated with a low rate of severe neutropaenia which requires the monitoring of white cell counts during

the first few weeks of treatment and more rarely can cause thrombotic thrombocytopenic purpura (TTP).[23,24]

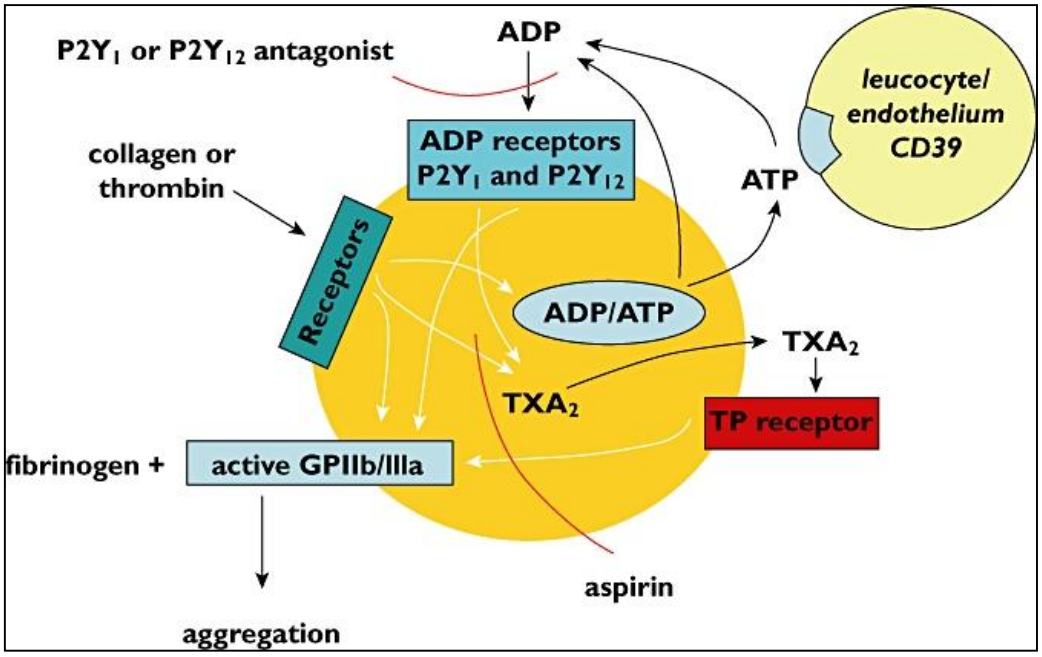


Fig. 7. Some of the receptors and pathways involved in platelet aggregation

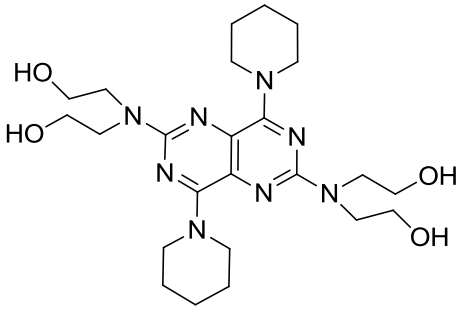
Clopidogrel **(1.3)** is associated with reduction in gastrointestinal hemorrhage making it a valuable therapeutic alternative to aspirin in oral, long-term, prevention of atherothrombotic vascular occlusion (Fig. 7).[25]

1.5.3. Phosphodiesterase inhibitors

Dipyridamole

The pyrimidopyrimidine derivative dipyridamole (Persantin) **(1.4)** is a phosphodiesterase inhibitor that has been used as an antiplatelet agent, almost always concurrently with either aspirin or warfarin. Elevation of intracellular cyclic adenosine monophosphate (cAMP) levels by agents that activate adenylate cyclase or that inhibit the cyclic phosphodiesterases result in the inhibition of platelet responses. Dipyridamole **(1.4)** does not appear to inhibit aggregation responses to collagen, epinephrine, and ADP at usual doses but has a synergistic effect with aspirin in preventing platelet aggregation in thromboembolic disorders. Its phosphodiesterase inhibitory activity potentiates the effect of adenosine on platelets. Dipyridamole may also have an effect on the initial phase of platelet adhesion as well as platelet aggregation. Dipyridamole used concurrently with aspirin increased coronary blood flow and graft patency following

coronary bypass surgery. It was as effective in reducing vascular smooth muscle cells (VSMC) proliferation as the combination of aspirin and dipyridamole. However, in recent meta-analysis of randomized clinical trials, the addition of dipyridamole to aspirin for prevention of death, myocardial infarction (MI) and stroke in high risk patients was found not to be associated with a significant reduction in serious vascular events.[26]



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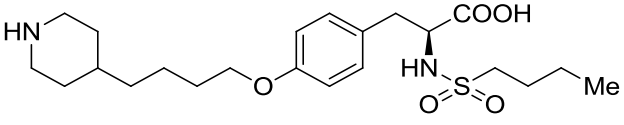
1.5.4. Glycoprotein IIb/IIIa inhibitors

Ligand binding to the GPIIb/IIIa receptors on activated platelets is a prerequisite for platelet aggregation and formation of a platelet thrombus.[27] Therefore, the GPIIb/IIIa receptors have become a target for the development of drugs to inhibit platelet-mediated thrombus formation. Several intravenous medications directed specifically at these receptors (called platelet GPIIb/IIIa receptor antagonists) have emerged. These include the human-murine chimeric monoclonal antibody Fab fragment abciximab, the peptide antagonist eptifibatide and the peptidomimetic tirofiban.



(1.5)

Tirofiban (Aggrastat) **(1.5)** is a tyrosine derivative that inhibits fibrinogen binding to GP IIa/IIIb. This particular drug is an Arg-Gly-Asp (RGD)-based peptidomimetic that effectively blocks the surface glycoprotein GPIIb/IIIa receptor reducing thrombin generation and subsequently platelet aggregation and secretion.[28] The drug is used intravenously together with heparin for coronary applications (unstable angina, non-Q-wave MI, and angioplasty) but not in patients who have hypertension or have had hemorrhagic stroke or suffered trauma. The use of

tirofiban with heparin resulted in a significant decrease in the composite endpoints of death, MI, and refractory ischemia.[29] However, the benefit was short term for patients with acute coronary syndromes. The most common complication with this drug is excessive bleeding, and pelvic pain in 5 % of patients, slowing of the heart rate and dizziness.

1.6. Anticoagulant agents

An anticoagulant is a substance that prevents coagulation (clotting) of blood. Anticoagulant drugs represent a wide group of natural agents, recombinant agents equivalent to some of the naturally occurring proteins and synthetic agents. This group of drugs is characterized by marked structural and functional heterogeneity. Anticoagulants are usually administered to patients with myocardial infarction, venous thrombosis, peripheral arterial emboli and pulmonary emboli. They have been used to prevent transient ischemic attacks and to reduce the risk of recurrent myocardial infarction. Anticoagulant solutions are also used for the preservation of stored whole blood and blood fractions. These anticoagulants include heparin and acid citrate dextrose. Anticoagulants are also used to keep laboratory blood specimens free from clotting.

Classification of anticoagulant agents

Anticoagulant drugs as per their mechanism of action are listed as follows:

(1) Coumarin derivatives

- Warfarin
- Acenocoumarol
- Phenprocoumon
- Atromentin
- Phenindione

(2) Heparin and its derivatives

(3) Hirudin and its derivatives

- Bivalirudin
- Dabigatran

(4) Direct Factor IIa inhibitors

- Argatroban

(5) Direct Factor Xa inhibitors

- Rivaroxaban
- Apixaban

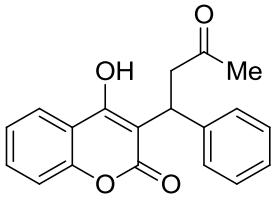
- Betrixaban
- Darexaban

1.6.1. Coumarin derivatives

Coumarin anticoagulants inhibit the release of plasma clotting factor VII by vitamin K in liver slices from vitamin K-deficient animals without inhibition of protein synthesis. When the ratio of vitamin K to coumarin anticoagulant is kept constant, and the concentrations are increased, the inhibition disappears. This suggests that the pharmacological action of coumarin anticoagulants depends on irreversible inhibition of normal vitamin K transport to its site of action. At higher concentrations of vitamin K the inhibition can be surmounted, because vitamin K can enter the cell by an alternate route that is not inhibited by coumarin anticoagulants.[30]

Warfarin

Warfarin **(1.6)** is a synthetic derivative of dicoumarol, a 4-hydroxycoumarin derived mycotoxin anticoagulant originally discovered in spoilt sweet clover-based animal feeds. Dicoumarol, in turn, is derived from coumarin. Warfarin and related 4-hydroxycoumarin-containing molecules decrease blood coagulation by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII.[31] Warfarin is used in atrial fibrillation, in the presence of artificial heart valves, deep venous thrombosis, and pulmonary embolism. Warfarin is also used in antiphospholipid syndrome. It has been used occasionally after heart attacks (myocardial infarctions), but is far less effective at preventing new thromboses in coronary arteries.[32]



(1.6)

In some countries, other coumarins are used instead of warfarin, such as acenocoumarol and phenprocoumon. These have a shorter (acenocoumarol) or longer (phenprocoumon) half-life, and are not completely interchangeable with warfarin. Warfarin has side effects like hemorrhage, warfarin necrosis, osteoporosis and purple toe syndrome. Warfarin is the only orally available

antithrombotic drug. Unfortunately warfarin has a narrow therapeutic window, undesirable interactions with food and drugs and also possesses risk of bleeding.[33]

1.6.2. Heparin and its derivatives

Heparin, a highly-sulfated glycosaminoglycan, is widely used as an injectable anticoagulant. Heparin is usually stored within the secretory granules of mast cells and released only into the vasculature at sites of tissue injury. Heparin is a polymer with a molecular weight ranging from 3 to 30 kDa. Heparin binds to the enzyme inhibitor antithrombin III (AT) causing a conformational change that results in its activation through an increase in the flexibility of its reactive site loop.[34] The activated AT then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa. Heparin and its low molecular weight derivatives (e.g. enoxaparin, dalteparin, tinzaparin) are effective at preventing deep vein thrombosis and pulmonary emboli in patients at risk.[35]

1.6.3. Hirudin and its derivatives

Hirudin is a naturally occurring peptide found in the salivary glands of medicinal leeches (such as *Hirudomedicinalis*) that has a blood anticoagulant property. A key event in the final stages of blood coagulation is the conversion of fibrinogen into fibrin by the serine protease enzyme thrombin. Thrombin is produced from prothrombin, by the action of an enzyme, prothrombinase, in the final states of coagulation. Fibrin is then cross linked by factor XIII to form a blood clot. The principal inhibitor of thrombin in normal blood circulation is antithrombin III. Similar to antithrombin III, the anticoagulatant activity of hirudin is based on its ability to inhibit the procoagulant activity of thrombin. Therefore, hirudin prevents or dissolves the formation of clots and thrombi, and has therapeutic value in blood coagulation disorders, in the treatment of skin hematomas and of superficial varicose veins, either as an injectable or a topical application cream.[36]

Bivalirudin

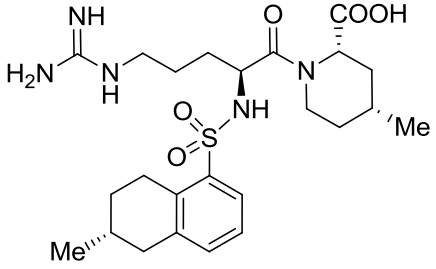
Chemically it is a synthetic congener of the naturally occurring drug hirudin. Bivalirudin a 20 amino acid peptide containing an active site thrombin inhibitor D-Phe-Pro-Arg linked via a Pro-Gly-4 bridge to a dodecapeptide analogue of the carboxy-terminus of hirudin. Bivalirudin is a potent, specific and reversible direct thrombin inhibitor.[54,55] It inhibits both circulating and

clot-bound thrombin, while also inhibiting thrombin-mediated platelet activation and aggregation. It does not bind to plasma proteins (other than thrombin) or to red blood cells. Therefore it has a predictable antithrombotic response. There is no risk for Heparin Induced Thrombocytopenia/Heparin Induced Thrombosis-Thrombocytopenia Syndrome (HIT/HITTS).[37]

1.6.4. Direct Factor IIa inhibitors

Argatroban

Argatroban **(1.7)** is an anticoagulant that is a small molecule direct thrombin inhibitor. Argatroban was licensed (FDA) for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia, Argatroban is given intravenously and drug plasma concentrations reach a steady state in 1-3 hours.



(1.7)

Argatroban is metabolized in the liver and has a half-life of about 50 minutes. Because of its hepatic metabolism, it may be used in patients with renal dysfunction. If warfarin is chosen as a long term anticoagulant, this poses particular challenges due to the falsely elevated prothrombin time and international normalized ratio (INR) caused by argatroban. The safety and efficacy of the drug as an adjunctive treatment is well tolerated in patients with acute MI compared to heparin.[38]

1.6.5. Direct Factor Xa Inhibitors

Factor Xa propagates coagulation by converting prothrombin (Factor II) to thrombin (Factor IIa). One molecule of FXa is responsible for the formation of more than 1000 thrombin molecules.[39] Thus, FXa is a crucial amplifying agent in the coagulation process. Selective inhibition of FXa has no or less bleeding risks because normal pre-existing thrombin level, aggregation and activation of platelets are not affected.[40] The direct FXa inhibitors rivaroxaban

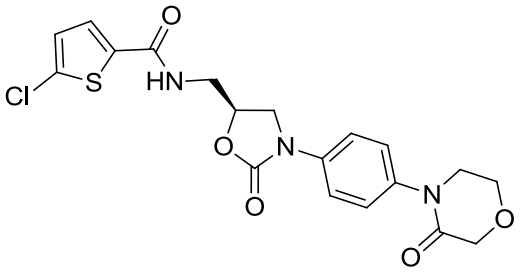
and apixaban have gained U.S. Food and Drug Administration (FDA) approval for antithrombotic therapy.

Rivaroxaban

Rivaroxaban **(1.8)** is the first orally active direct FXa inhibitor having oxazolidinone scaffold with P1 and P4 motifs which reversibly bind with S1 and S4 pockets of FXa respectively. Rivaroxaban showed 10,000 fold more selectivity than other serine proteases that completely inhibited FXa without disturbing antithrombin.[41]

Apixaban

Apixaban **(1.9)** was developed by Bristol-Meyers Squibb and Pfizer as orally active direct FXa inhibitor. Apixaban, sold under the trade name Eliquis, is an anticoagulant for the treatment of venous thromboembolic events.[42]



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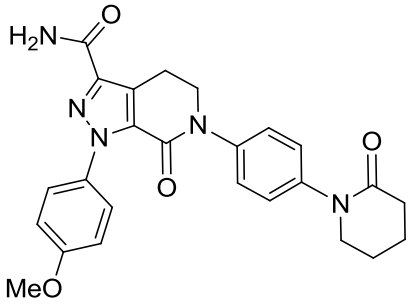

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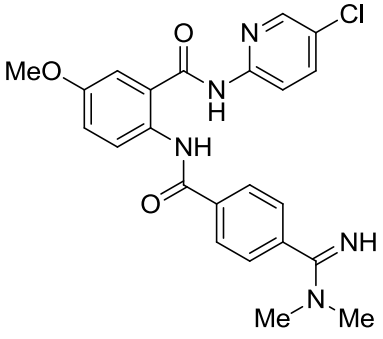
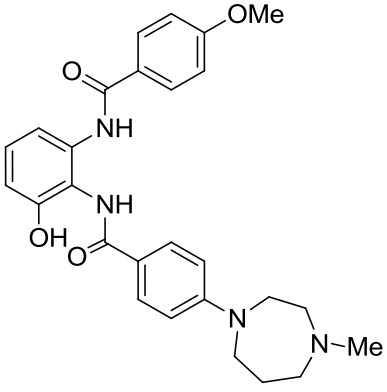


(1.10)



(1.11)

Betrixaban

Betrixaban (INN, codenamed PRT-054,021, **1.10**) is an anticoagulant drug of the anthranilamide class which acts as a direct factor Xa inhibitor. It is potent, orally active and highly selective for factor Xa, being selected from a group of similar compounds for its low

hERG affinity. Betrixaban has undergone human clinical trials for prevention of embolism after knee surgery, and prevention of stroke following atrial fibrillation, with promising results. IC_{50} of batrixaban is 1.5 nM.[43]

Darexaban

Darexaban (*N*-[2-hydroxy-6-(4-methoxybenzamido)phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide) **(1.11)**, a 1,2-dibenzamidobenzene class of compound was under clinical trials as a potent and orally available factor Xa inhibitor for the prevention of venous thromboembolism.[44] The development of darexaban was discontinued in September 2011.

Summary table for antiplatelet and anticoagulant treatment

United States Food and Drug Administration (USFDA) and British National Formulary (BNF) described the uses, doses and indications of anticoagulants. The table summarizes the presently used anticoagulants.

Table 1: Anticoagulant agents clinically used, their mode of action and indication[13]

Anticoagulant Agents	MW (Da)	Half life (h)	Mode of action	Dose[a]	Indication
Warfarin (Coumadin)	308	6	Inhibit synthesis of vitamin-K dependent coagulation factors, factor II, VII, IX and X	2.5-10 mg daily	Treatment of venous thrombosis and prevention of venous thromboembolism in patients with MI
Heparin	15000[b]	1-2	Binds to & activats AT-III to inhibit factor IIa and Xa	5000-10000U IV bolus, followed 15-25U/Kg/h	Prevention and treatment of arterial & venous thrombosis, prophylaxis in general surgery
LMWHs	5000[b]	4-6	Activates AT-III to inhibit factor IIa and Xa		
Enoxeparin				2000-4000U daily	Treatment of DVT, unstable angina & MI
Dalteparin				2500-5000U daily	Prophylaxis of postoperative DVT and pulmonary embolism.
Certoparin				3000U daily	Prophylaxis of postoperative DVT
Hirudin and its derivatives	7000[b]	1-2	Direct thrombin inhibitor that reversibly binds to thrombin active site	0.4 mg/Kg bolus	For the prophylaxis of postoperative DVT in patients undergoing hip replacement
Lepirudin	6980	1.3		0.15 mg/Kg/hr IV	
Bivalirudin	2180	0.5		1.0 mg/Kg bolus followed 2.5 mg/Kg/h daily	Treatment of thromboembolic diseases in patients with HIT
Argatroban	527	0.5-1		2 µg/Kg/min	Prevention of unstable angina, MI and PCI

[a]Drugs doses from BNF; Keys: MW, molecular weight; AT-III, antithrombin; DVT, deep vein thrombosis; MI, myocardial infarction; GPIIb/GPIIIa, glycol protein IIb/IIIa; PCI, percutaneous coronary intervention; HIT, heparin-induced thrombocytopenia. [b]Average molecular weight.

1.7. Drawbacks of current drug therapy

There are some side effects of current drug therapy such as signs of unusual bleeding, blood in the urine or stools, nosebleeds, unusual bruising, heavy bleeding from cuts, black tarry stools, coughing up of blood, unusually heavy menstrual bleeding or unexpected vaginal bleeding, vomiting that looks like coffee grounds, dizziness, severe headache, difficulty in swallowing, shortness of breath, difficulty in breathing or wheezing, tightness in chest, chest pain, fever, chills, sore throat, swelling of face or hands, ringing in the ears, severe stomach pain etc. Thrombosis, however, is a complex process involving multiple pathways. Hence drug acting via multiple pathways would be beneficial. Currently there are very few molecules under advanced development which simultaneously targets both the antiplatelet and the anticoagulant pathways.[45]

Currently available antithrombotic drugs are associated with significant drawbacks that limit their use. Hence there is a real unmet clinical need for developing novel and safer antithrombotic agents. An increasing number of people are vulnerable to the risk factors for thromboembolic events due to the rapidly aging population.

1. Major limitations of current antiplatelet drugs include risk of bleeding, significant inter-individual variability in the response, and extended duration of action that cannot be reversed if the need for hemostasis or emergency surgery arises.[46]
2. Aspirin and clopidogrel represent the cornerstone of treatment for secondary prevention of ischemic events in patients, including those with diabetes and with either stable or unstable atherosclerotic cardiovascular disease. However, a considerable number of patients continue to experience recurrent atherothrombotic events despite the use of these antiplatelet agents. These observations have led in recent years to the development of the concept of antiplatelet drug resistance.[47]
3. Most of the currently developed drugs, with the exception of the heparins, are monotherapeutic agents, targeting single sites such as thrombin, factor Xa or platelet activated receptors. However, in March 2008, major recalls of heparin were announced by pharmaceutical companies due to a suspected and unknown contamination of the raw heparin stock imported from China. The U.S. Food and Drug Administration was quoted as stating that at least 19 deaths were believed linked to a raw heparin ingredient

imported from the People's Republic of China, and that they had also received 785 reports of serious injuries associated with the drug's use.[48]

4. Because of the bleeding risk, the prescribing information contains a "black box warning" not to use prasugrel in patients with a history of transient ischemic attack or stroke or in patients above 75 years of age.[49] Body weight above 60 kg is also a risk factor for bleeding.
5. An oral direct thrombin inhibitor, ximelagatran was generally well tolerated in the trial population, but a small proportion (5-6 %) developed elevated liver enzyme levels, which prompted the FDA to reject an initial application for approval in 2004. Further development was discontinued in 2006 after reports of severe liver damage and heart attacks.[50]
6. Variability in responsiveness to clopidogrelhas also been documented.[51] Inconsistencies in response to clopidogrel may be due to pre-existing variability in platelet response to adenosine diphosphate (ADP), genetic variability (polymorphisms in the hepatic enzymes [*i.e.* CYP_2C_{19}] involved in clopidogrel metabolism or within the platelet P_2Y_{12} receptor) or drug interactions (e.g. proton pump inhibitors).[51]

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