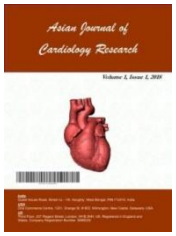

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Drugs Used in Thromboembolic Disorders: An Insight into Their Mechanisms

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Authors' contributions

This work was carried out in collaboration among all authors. Author AMH designed the study, managed the literature searches and wrote the first draft of the manuscript, author PVN managed the literature searches and wrote the second draft, author NF did the proof reading and completed the final draft. All authors read and approved the final manuscript.

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ABSTRACT

In the United States alone, more than 6 million patients receive long-term anti-platelet and anticoagulation therapy. The hemostatic system must maintain a balance between fibrin formation (coagulation) and fibrin dissolution (fibrinolysis). Thrombin and Factor Xa are two of the most important components of the coagulation cascade. Any disruption in this cascade can lead to either thrombosis, hemorrhage or both. The clotting process is a dynamic, highly interwoven array of multiple processes. There are four different phases involved in the response of activated platelets: Adhesion, aggregation, secretion and the procoagulant activity. The coagulation cascade is a coordinated sequence of linked enzymatic reactions in which each reaction product converts the subsequent inactive zymogen into an active serine protease that are responsible for the conversion of soluble plasma fibrinogen into insoluble fibrin. Several antithrombotic factors regulate coagulation and limit the production of thrombin to prevent the perpetuation of coagulation and thrombus formation; these include protein C/protein S, antithrombin, heparin cofactor and tissue factor pathway inhibitor. Antiplatelet agents play a major role in the management of cerebrovascular, peripheral vascular and cardiovascular diseases. Aspirin is a non-steroidal anti-inflammatory drug that works by irreversibly inhibiting cyclo-oxygenase 1 and 2 by covalent

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acetylation. Cilostazol, a specific and strong inhibitor of PDE3 in platelets and smooth muscle cells was approved in the USA in 1999 for the treatment of intermittent claudication. Dipyridamole affects platelet function by inhibiting the reuptake of adenosine by red blood cells, in this way enhancing plasma levels of this vasodilator and platelet inhibitory nucleoside; it acts as an inhibitor of PDE5 and PDE3, thus increasing intraplatelet cAMP and/or cGMP; and it also acts as an antioxidant by scavenging free radicals that inactivate cyclo-oxygenase, thus enhancing PGI2 biosynthesis. Vorapaxar, a first in its class, is an orally available PAR-1 antagonist approved for patients with prior myocardial infarction or peripheral arterial disease with no previous history of stroke or TIA, and is added to standard therapy for long-term secondary prevention of thrombotic CV events. Abciximab, eptifibatide, tirofiban all bind the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation. Warfarin is a Vitamin K antagonist that interferes with γ-carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X, and proteins C and S. Dabigatran is a potent, competitive inhibitor of thrombin, while Apixaban, edoxaban and rivaroxaban all selectively inhibit factor Xa. Heparins, acts indirectly by binding to anti-thrombin (AT) rather than acting directly on the coagulation factors. This interaction converts AT to a rapid inactivator of factor IIa and factor Xa. Unfractionated heparin, LMW heparin (enoxaparin, dalteparin) and fondaparinux all inactivate factor Xa, but unfractionated heparin is a much more efficient inactivator of thrombin. Drugs such as anti-platelet therapy and anti-coagulants are frequently used in clinical settings. It is imperative that the physicians have a thorough understanding of these agents. An insight into the mechanism of how these medications act serves as a prelude to understanding the pharmacology of these drugs.

Keywords: Thromboembolic disorders; drugs used; cardiovascular diseases; fibrinolysis.

1. INTRODUCTION

Cardiovascular diseases like myocardial infarction, stroke, deep-venous thrombosis, and pulmonary embolism are among the leading cause of mortality worldwide [1]. In the United States alone, more than 6 million patients receive long-term anti-platelet and/or anti-coagulation therapy for the prevention of various causes of thromboembolism that include venous thromboembolism, atrial fibrillation or placement of a mechanical heart-valve prosthesis [2].

Venous thromboembolism (VTE) comprising deep venous thrombosis (DVT) and pulmonary embolism (PE) is the third vascular cause of death after myocardial infarction and stroke and is a significant cause of morbidity and mortality. Annual incidence of VTE is estimated to be approximately 1 or 2 cases per 1000 persons in the general population [3]. however, VTE is often misdiagnosed, asymptomatic and unrecognized at death and regular post-mortem examinations are missing. These factors are believed to result in marked underestimations of VTE incidence. Complications that arise after VTE including chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome account for the substantial increase in morbidity and healthcare costs incurred from VTE.

In order to ensure adequate blood perfusion through tissues and to prevent the free flow of blood at sites of injury, the hemostatic system must maintain a balance between fibrin formation (coagulation) and fibrin dissolution (fibrinolysis) [4]. The major structural component of blood clot is fibrin, which is formed by the proteolytic action of thrombin on fibrinogen. Fibrinolysis is a process by which fibrin is degraded (into fibrin degradation products) by the action of plasmin. Thrombin and Factor Xa are two of the most important components of the coagulation cascade [5]. Any disruption in this cascade can lead to either thrombosis, hemorrhage or both.

Anticoagulants include a variety of agents that work by inhibiting one or more steps in the coagulation cascade. Their mechanisms include direct enzymatic inhibition, indirect inhibition by binding to antithrombin, antagonism of vitamin K-dependent coagulation factors by either the modification of their calcium-binding properties or by preventing their synthesis in the liver.

The steadily expanding list of antiplatelet and anticoagulants provide a wide range of agents for prevention and management of thromboembolic diseases. However, the appropriate use of these agents require an understanding of their individual characteristics, benefits and risks. This article provides a review of the recent advances in the use of antiplatelet and anticoagulant

therapy and an insight into their mechanisms in the coagulation cascade.

2. MECHANISMS OF ACTION

2.1 Normal Hemostasis

The hemostatic system provides a balance between procoagulant and anticoagulant forces. When a blood vessel wall is disrupted, the hemostatic response must be quick, localized and carefully regulated. Any disturbances in this pathway may lead to either abnormal bleeding or thrombosis.

The clotting process is a dynamic, highly interwoven array of multiple processes [6]. The phases of the process include:

1. Endothelial injury and formation of the platelet plug
2. Propagation of the clotting process by the coagulation cascade
3. Termination of clotting by antithrombotic control mechanisms.
4. Removal of the clot by fibrinolysis.

2.2 Formation of a Platelet Plug

In order to stop bleeding, the initial hemostatic response is the formation of a platelet plug at the site of vascular injury. Endothelial cell activation and the exposure of the subendothelial elements promote recruitment of platelets, procoagulant factors and other cell types [7].

The activation of platelets is done through a number of physiological stimuli that include adenosine diphosphate (ADP), thrombin, collagen and epinephrine. The summary of all the important steps involved in formation of a platelet plug has been mentioned below in the Fig. 1.

The adherence of platelets is prevented by the secretion of prostacyclin and nitric oxide from the intact endothelium. Endothelial injury impairs this process and leads to the exposure of subendothelial elements such as collagen that activates platelets. The two most important platelet collagen receptors are GPIa/IIa (integrin-α2β1) and GPVI [8].

The principal receptors for thrombin on human platelets are a family of G-protein coupled protease-activated receptors (PAR). PAR-1 is a high-affinity receptor that mediates the effect of thrombin at low concentrations, while PAR-4 is a low-affinity receptor that requires high levels of thrombin for activation. Notably the binding of thrombin to PAR-1, which represents a very potent platelet activation pathway, is necessary for thrombus formation but may not be required for hemostasis [9,10]. Vorapaxar is an oral PAR-1 antagonist developed as an antiplatelet agent [11].

ADP released from damaged red blood cells and vessels activates the integrin GPIIb-IIIa and subsequent binding of fibrinogen that induces platelet aggregation. ADP mediates its action through binding of two purinergic G-protein coupled receptors, P2Y1 and P2Y12 [12]. The P2Y1 receptor couples to Gq and mobilizes intracellular calcium and mediate platelet shape change and rapidly reversible aggregation; P2Y12 is coupled to a Gi that mediates a more stable platelet aggregation [13]. The thienopyridine derivatives, clopidogrel and ticlopidine are antiplatelet agents that inhibit the platelet aggregation induced by ADP, thereby reducing ischemic events [14].

There are four different phases involved in the response of activated platelets:

Adhesion, aggregation, secretion and the procoagulant activity. The first response of activated platelets is the deposition of platelets on the subendothelial matrix followed by aggregation which is mediated via platelet-platelet cohesion and the secretion of platelet granule proteins and finally the enhancement of thrombin generation [15].

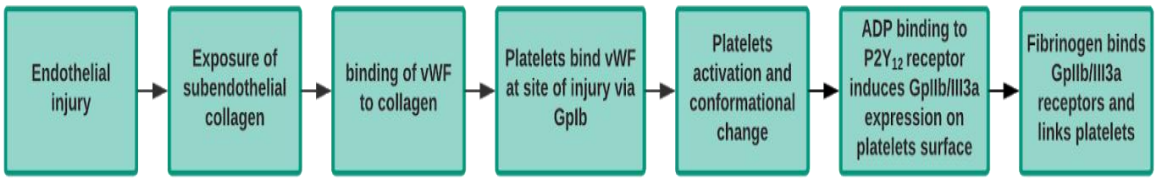

Fig. 1. Summary of all the important steps in the formation of the platelet plug

2.3 The Coagulation Cascade

The coagulation cascade is a coordinated sequence of linked enzymatic reactions in which each reaction product converts the subsequent inactive zymogen into an active serine protease that are responsible for the conversion of soluble plasma fibrinogen into insoluble fibrin [16].

The primary initiating factor for the coagulation cascade is the exposure of tissue factor at areas of endothelial or tissue injury to blood components and the interaction of activated factor VII (FVIIa) with exposed tissue factor (TF). Tissue factor may be found in leukocytes or platelets or in bloodborne cell-derived microparticles. The TF-FVIIa complex then activates factors IX (FIX) and X (FX), leading to the release and activation of factor V (FV) from platelet α-granules. Activated FX (FXa) links with activated FV (FVa) converting factor II (FII, also known as prothrombin) to thrombin (FIIa). Thrombin then converts fibrinogen to fibrin and overlapping fibrin strands are cross-linked and stabilized by activated factor XIII (FXIIIa) [17].

Several antithrombotic factors regulate coagulation and limit the production of thrombin to prevent the perpetuation of coagulation and thrombus formation; these include protein C/protein S, antithrombin, heparin cofactor and tissue factor pathway inhibitor (TFPI) [18].

2.4 The Cell-based Model of Fibrin Formation

The cell-based model of hemostasis replaces the traditional hypothesis of "cascade" and suggests that coagulation takes place in four overlapping steps on distinct cell surfaces: initiation, amplification and propagation [19].

The initiation phase occurs when cells on the site of injury that express TF on their surface are exposed to blood components. It results in a small amount of FIXa and thrombin being generated that diffuses to the platelet from the TF-bearing cell surface.

In The amplification phase, binding of thrombin to platelet surface receptors results in extreme modifications in the platelet surface, leading to changes in shape, release of granules and shuffling of membrane phospholipids to generate procoagulant membrane surface. These modifications result in activation of platelets that release vWF and generate FV, FVIII and FXI.

The propagation phase is characterized by the migration of large numbers of platelets to the injury site. The different enzymes generated in earlier phases assemble to form the tenase complex and the prothrombinase resulting in FXa and thrombin generation [20].

Different anticoagulant agents work on this pathway; these include Heparin, LMWH, direct thrombin inhibitors, direct Xa inhibitors, fondaparinux and thrombolytics such as alteplase. The sites of action of the different anticoagulants is described in the Fig. 2.

3. ANTIPLATELET AGENTS

Antiplatelet agents play a major role in the management of cerebrovascular, peripheral vascular and cardiovascular diseases. Depending on the specific clinical indication and the patient's risk for thromboembolic or bleeding events, these agents can be used as monotherapy or combination therapy. A list of the currently available anti-platelet agents is provided in the Table 1.

Table 1. List of the available anti-platelet medications (generic and brand names)

Drug generic name	Drug brand name
Aspirin / extended-release dipyridamole	Aggrenox
Aspirin / omeprazole	Yosprala
Aspirin extended-release	Durlaza
Cilostazol	Pletaal
Clopidogrel	Plavix
Dipyridamole	Persantine
Ticagrelor	Brilinta
Prasugrel	Effient
Ticlopidine	Ticlid
Vorapaxar	Zontivity
Abciximab	Reopro
Eptifibatide	Integrilin

3.1 Aspirin

Aspirin is a non-steroidal anti inflammatory drug that works by irreversibly inhibiting cyclo-oxygenase 1 and 2 by covalent acetylation. This leads to decreased synthesis of prostaglandins and thromboxane A2 particularly in the platelets. Thromboxane A2 is an important mediator that is essential for platelet aggregation and therefore aspirin acts as an anti-aggregator of the platelets [18]. Mechanism of action of various Antiplatelet agents has been described in the Fig. 3.

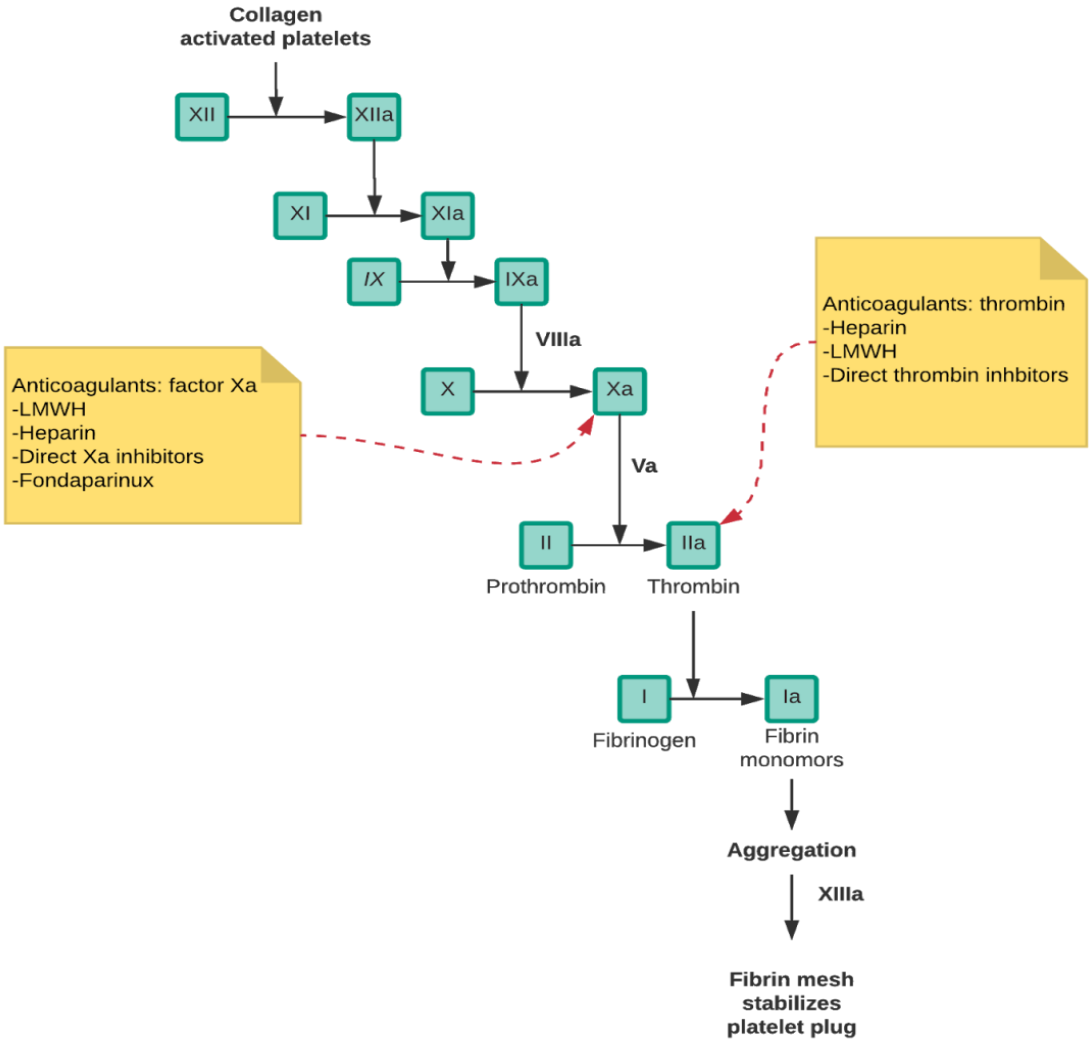

Fig. 2. Illustrates and summarizes the sites of action of different therapeutic agents

The therapeutic effects of aspirin are dose dependent. Antithrombotic effects of aspirin have been reported with low doses (<300 mg/day), antipyretic, analgesic effects are seen with Intermediate doses (300–2400 mg/day) and anti-inflammatory effects are seen at High doses (2400–4000 mg/day) [21].

Potential side effects when aspirin is used as an anti-platelet medication include gastric erosion, gastric and duodenal ulceration. Side effects that are rarely seen when used as anti-platelet medication include nephropathy due to reduced blood flow to the kidneys, interstitial nephritis, hepatotoxicity, asthma, and GI bleeding [22].

3.2 Cilostazol and Dipyridamole

Inhibition of platelet aggregation can be achieved by inhibiting certain intracellular signalling pathways. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are two critical intracellular second messengers with strong inhibitory activity on fundamental platelet functions. These second messengers (cAMP and cGMP) are both metabolized by the class of enzymes known as Phosphodiesterases (PDEs), which catalyzes the hydrolysis of cAMP and cGMP, thus regulating platelet function.

Platelets possess three PDE isoforms (PDE2, PDE3 and PDE5), with different selectivity for cAMP and cGMP. While PDE2 catalyzes the hydrolysis of both cAMP and cGMP (cAMP = cGMP), PDE3 preferentially catalyzes the hydrolysis of cAMP over cGMP (cAMP > cGMP) and PDE5 catalyzes the hydrolysis of cGMP. The inhibition of PDEs may therefore exert a strong platelet inhibitory effect.

Cilostazol, a specific and strong inhibitor of PDE3 in platelets and smooth muscle cells was approved in the USA in 1999 for the treatment of intermittent claudication. The overall effect of the drug is that it diminishes intracellular calcium, causing smooth muscle cell relaxation and inhibition of platelet activation. Cilostazol inhibits adenosine uptake, thus enhancing adenosine levels that in turn enhance intracellular cAMP, resulting in additional increases in cAMP. Cilostazol enhances the antiplatelet effects of the endothelium-derived prostacyclin (PGI2), which inhibits thrombosis in vivo and inhibits shear, stress-induced platelet aggregation in vitro and ex vivo. One potential benefit of the use of cilostazol over conventional antiplatelet therapy is the relatively short recovery time of platelet function. The most common adverse effects of cilostazol are headache, tachycardia, palpitations, soft stools and diarrhea [23-25].

Dipyridamole affects platelet function by acting on the following different targets: it inhibits the reuptake of adenosine by red blood cells, in this way enhancing plasma levels of this vasodilator and platelet inhibitory nucleoside; it acts as an inhibitor of PDE5 and PDE3, thus increasing intraplatelet cAMP and/or cGMP; and it acts as an antioxidant by scavenging free radicals that inactivate cyclo-oxygenase, thus enhancing PGI_2 biosynthesis. Combination therapy of aspirin and dipyridamole is more effective than aspirin alone in the prevention of new serious vascular events in patients after non-disabling cerebral ischemia of presumed arterial origin [24, 26].

3.3 ADP Receptor Inhibitors

Red blood cells, damaged endothelial cells and activated platelets release ADP, which is a potent activator of platelets which induces its adhesion and aggregation. The response of the platelets to ADP is mediated by a family of membrane bound receptors called P2 receptors. ADP binds to the P2Y 1 and P2X 1 receptors leading to platelet aggregation. The binding of ADP to its Gi -coupled $P2Y_{12}$ receptor liberates the Gi protein subunits Gα and Gβγ and this results in stabilisation of platelet aggregation. The subunit Gα leads to inhibition of adenylyl cyclase (AC), which reduces cyclic adenosine monophosphate (cAMP) levels. This is also known to cause glyprotein IIb/IIIa receptor activation resulting in aggregation of platelets. Furthermore, Gβγ is known to independently cause platelet aggregation via phosphatidylinositol 3-kinase pathway, which can cause platelet aggregation.

The thienopyridine compounds ticlopidine and clopidogrel were the first ADP inhibitors to be used clinically as antithrombotic drugs. Other agents in this category include; prasugrel and ticagrelor. These agents inhibit platelet aggregation by blocking the $P2Y_{12}$ receptor thus preventing the expression of glycoprotein IIb/IIIa on platelets surface. Ticlopidine and clopidogrel are effective antiplatelet agents and are useful in the prevention of stroke, myocardial infarction, and vascular death in patients with vascular disease. However, the major concern regarding safety of ticlopidine is severe and sometimes fatal blood dyscrasias which is not observed with Clopidogrel [27,28].

3.4 Vorapaxar

Thrombin is a potent platelet activator which acts via cell-surface protease-activated receptors (PARs) which are widely expressed in human platelets. Platelet activation through PAR-1 signalling results in extracellular ADP release, resulting in activation of platelet ADP receptors, thereby promoting aggregation of platelets. The PAR-1 receptor blockade produces potent antiplatelet effects without affecting the ability of thrombin to generate fibrin and without inhibiting platelet activation by collagen.

Vorapaxar, a first in its class, is an orally available PAR-1 antagonist approved for patients with prior myocardial infarction or peripheral arterial disease and is added to standard therapy for long-term secondary prevention of thrombotic CV events. However, the use of this medication is associated with an increased risk of bleeding, resulting in the accompanying boxed warning. Further, it is contraindicated in patients who have history of stroke, TIA, or intracranial haemorrhage, because of an increased risk for intracranial bleed in this patient populations [29].

3.5 Glycoprotein IIb/IIIa Inhibitors

Abciximab, eptifibatide, tirofiban all bind the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation. Glycoprotein IIb/IIIa inhibitors have been shown to reduce cardiac complications in patients undergoing percutaneous coronary intervention and also to reduce the mortality in patients with acute coronary syndromes who are not routinely scheduled for early revascularization [30].

4. ANTICOAGULANT AGENTS

There are a variety of parenteral and oral anticoagulants available for the management of thromboembolic disease. Parenteral agents such as low molecular weight heparin (LMWH), unfractionated heparin (UFH) and fondaparinux are used for initial, and sometimes longer term, treatment. On the other hand Vitamin K antagonists are used for long-term treatment. The available oral antagonists consist of warfarin, rivaroxaban, dabigatran, edoxaban and apixaban. A list of available anticoagulants has been mentioned in Table 2 [31,32].

5. VITAMIN K ANTAGONISTS (VKA)

Warfarin is the most widely used anticoagulant in the world. It is most commonly used to prevent embolic strokes in patients with atrial fibrillation. Warfarin is a Vitamin K antagonist that interferes with γ-carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X, and proteins C and S. The main adverse effect associated with warfarin is bleeding. The patients on warfarin therapy are monitored regularly by measuring their International Normalized Ratio (INR). The target range for INR in patients is between 2 and 3. An INR over 3 increases the risk for bleeding whereas an INR below the level of 2 increases the risk for thrombosis. Warfarin's narrow therapeutic index makes it difficult to maintain this predefined target range of INR. This problem is additionally compounded by the individual and pharmacogenomic variations that affect warfarin metabolism as well as the drug-drug interactions associated with the therapy. Polymorphisms in the genes encoding CYP2C9, (Hepatic cytochrome that metabolizes warfarin) and VKORC1, (vitamin K epoxide reductase, an enzyme that warfarin inhibits) have been shown to be the major determinants of warfarin dosage. Other determinants of warfarin dosage include dietary vitamin K intake, herbal products and dietary supplements which can have a significant effect on the degree of anticoagulation.

Warfarin also interferes with the formation of γ-carboxyglutamate proteins that is an essential part of osteocalcin, a bone regulating protein. This effect contributes to the teratogenic effects ranging from skeletal to cartilaginous malformations [33,34,35].

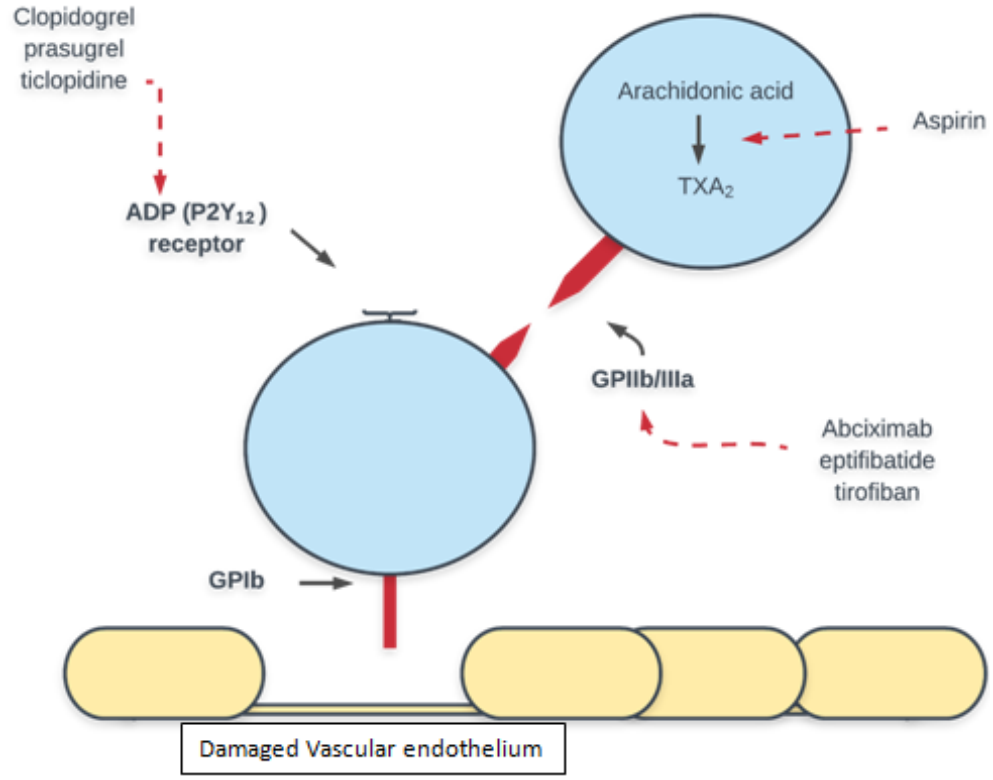

Fig. 3. Illustration of mechanism of action of different anti-platelet agents

Table 2. List of available anti-coagulants, their generic name, brand name and route of administration (ROA)

Drug generic name	Drug brand name	ROA
Heparin		Intravenous/Subcutaneous
Fondaparinux	Arixtra	Intravenous/Subcutaneous
Dalteparin	Fragmin	Intravenous/Subcutaneous
Enoxaparin	Lovenox	Intravenous/Subcutaneous
Warfarin	Coumadin	Oral
Rivaroxaban	Xarelto	Oral
Dabigatran	Pradaxa	Oral
Edoxaban	Savaysa	Oral
Apixaban	Eliquis	Oral

6. DIRECT ORAL ANTICOAGULANTS

The treatment of venous thromboembolism (VTE) traditionally consists of initial low-molecular-weight heparin (LMWH) or unfractionated heparin followed by warfarin for at least 3 months. Recently, the development and introduction of direct oral anticoagulants have proven to be an effective and safe alternative [36]. These agents work by inhibiting factor Xa and IIa (thrombin) in the coagulation cascade leading to inhibition of fibrin formation. Dabigatran is a potent, nonpeptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule, while Apixaban, edoxaban and rivaroxaban all selectively inhibit factor Xa.

Advantages of direct oral anticoagulants, unlike Vitamin K antagonists (VKA) like warfarin is that their therapy does not require frequent laboratory monitoring and subsequent dose adjustments, which represents a major shift from the traditional VKA-based therapies. Direct oral anticoagulants for the treatment and prevention of thromboembolic disorders represent a major shift from the traditional VKA-based therapies. Four direct oral anticoagulants apixaban, dabigatran, edoxaban and rivaroxaban have completed large phase III clinical studies and have been currently approved by the FDA for treatment and prophylaxis of various thromboembolic conditions. These direct oral anticoagulants bind directly to key proteins of the clotting cascade, leading to the inhibition of fibrin formation.

The Thrombin clotting time assay evaluates thrombin activity in a plasma sample directly and thus gives a direct measure of DTI activity. TT tests in many hospital laboratories are readily available. The TT is particularly sensitive to dabigatran effects and shows a linear dose response over therapeutic concentrations [37].

However, with direct oral anticoagulants, severe bleeding may occur. Furthermore, patients taking NOACs may experience trauma and may need urgent surgery or procedures. Therefore, the accessibility of particular reversal agents for NOACs in these emergency scenarios could enhance patient management. Idarucizumab is a monoclonal humanized antibody fragment created as a particular dabigatran reversal agent. Studies in vitro and ex vivo have shown that idarucizumab quickly restores parameters of dabigatran-prolonged coagulation to baseline values [38].

7. HEPARIN AND LMW HEPARIN

Heparins, including unfractionated heparin and a variety of low molecular weight (LMW) heparin products have been used for over eighty years as an anticoagulant in treatment and prophylaxis of venous thromboembolism, Coronary Artery Disease, Unstable Angina and Non–Q-Wave Myocardial infarction, Acute Myocardial infarction, Coronary Thrombolysis, Coronary Angioplasty, Atrial Fibrillation, etc. These agents act indirectly by binding to anti-thrombin (AT) rather than acting directly on the coagulation factors.

This interaction converts AT to a rapid inactivator of factor IIa and factor Xa [39]. The antithrombin-mediated anticoagulant effects of heparin are best described for factors Xa and thrombin, but a third factor, IXa, is an important contributor. Factor XIa, a less important contributor to the

anticoagulant action of heparin / antithrombin, is structurally distinct from other proteases of coagulation, but like factors IXa, Xa and thrombin it is created by a pro-enzyme cleavage and is subject to heparin-bound antithrombin inhibition Although thrombin inhibition is a desirable therapeutic effect of unfractionated heparin, nonspecific interactions with other proteins, such as platelet factor 4, result in side effects that can be life-threatening [40].

Unfractionated heparin, LMW heparin (enoxaparin, dalteparin) and fondaparinux all inactivate factor Xa, but unfractionated heparin is a much more efficient inactivator of thrombin [41,42]. Unfractionated heparin generally is administered intravenously as an initial bolus followed by a continuous infusion using a heparin nomogram while LMW heparin is administered subcutaneously in fixed or weight-based dosing without monitoring [42].

The limitations of heparin use include osteopenia and heparin-induced thrombo-cytopenia (HIT).

HIT is a life-threatening disorder that results from exposure to non-fractionated or (less frequently) low-molecular heparin. Classically patients present with low platelet counts (< 150,000 per cubic millimetre) or a relative decrease from baseline by 50 percent or more. HIT is caused by antibodies against complexes of platelet factor 4 (PF4) and heparin. The risk of thrombosis in patients with HIT is more than 30 times that in control populations. The risk of thrombosis remains high for days to weeks after heparin has been discontinued, even after platelet counts have normalized. HIT occurs more frequently in patients treated with low-molecular-weight heparin who have recently had exposure to unfractionated heparin (within 100 days) than in those who have not had a recent exposure to unfractionated heparin [44].

Osteopenia is caused as a result of binding of heparin to osteoblasts, which releases factors that activate osteoclasts. The dosage regimen of the heparins is calculated based on the body weight and therefore there is a possibility of an inadvertent overexposure. A number of techniques have been published to standardize the management of IV heparin treatment, including nomograms for heparin dose adjustment and computer algorithms. A weight-based nomogram using a starting dose of 18 U/kg/h heparin infusion (1,260 U/h for a 70-kg patient) reduced recurrent thromboembolism in a randomized controlled trial [45].

In case of Unfractionated heparin, Protamine sulfate is used as an antidote for toxicity. However, there are no clear guidelines for management of toxicity of LMW heparins [46,47].

8. CONCLUSION

Cardiovascular events such as myocardial infarction, stroke, deep-venous thrombosis, and pulmonary embolism are the most common life-threatening conditions that are required to be treated on a timely basis and therefore prompt recognition and management is vital. Drugs such as anti-platelet therapy and anti coagulants are frequently used in clinical settings. It is imperative that the physicians have a thorough understanding of these agents. An insight into the mechanism of how these medications act serves as a prelude to understanding to the pharmacology of these drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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