Venous and arterial thrombosis – pathogenesis and the rationale for anticoagulation

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Summary
Thromboembolic disorders are major causes of morbidity and mortality. It is well-recognised that the pathogenesis is different for arterial and venous thrombosis; however, both involve coagulation activation. Anticoagulants are used for the prevention and treatment of a wide variety of thromboembolic and related conditions. Agents with anti-inflammatory properties in addition to anticoagulation may be particularly beneficial. Traditional anticoagulants, although effective, are associated with certain limitations. Understanding the pathological processes associated with thrombosis and the rational target for anticoagulation is essential, not only for the development of safer and more effective agents, but also for better clinical management of patients who require anticoagulation therapy. In recent years, new oral agents that target single enzymes of the coagulation cascade have been developed – some of those are in advanced stages of clinical development. Based on scientific rationale, both factor Xa and thrombin are viable targets for effective anticoagulation.

Keywords
Anticoagulation, arterial thrombosis, factor Xa, thrombin, venous thrombosis

Introduction
Haemostasis is the normal physiological response that prevents significant blood loss after vascular injury. Blood vessel injury triggers a sequence of responses: vessel constriction to reduce blood flow; platelet plug formation at the site of trauma involving platelet adhesion, activation, and aggregation; and blood coagulation involving a complex set of protease reactions. Although haemostasis is essential for survival, inappropriate coagulation can lead to the formation of a thrombus. Thromboembolic disorders are major causes of morbidity and mortality. Anticoagulants are used to prevent or treat a wide variety of conditions that involve arterial or venous thrombosis, including the prevention and treatment of venous thromboembolism (VTE), long-term prevention of ischaemic stroke in patients with atrial fibrillation (AF), and secondary prevention of cardiac events in patients with acute coronary syndrome (ACS) (1–4).

It is well-recognised that the pathogenesis of arterial thrombosis differs from that of venous thrombosis, which is reflected by their different management strategies. Understanding the pathogenic processes that occur in the blood vessel wall and in the blood itself causing thrombosis is crucial, not only for developing more effective and safer antithrombotic agents, but also for better management of patients with thromboembolic disorders. Traditional anticoagulants are associated with limitations such as parenteral administration with the heparins and the requirement for routine coagulation monitoring and dose adjustment with the vitamin K antagonists (5, 6). In recent years, small-molecule, oral agents that target a single enzyme in the coagulation cascade have been developed. Some of these new oral agents (such as direct factor Xa inhibitors and direct thrombin inhibitors) have undergone extensive evaluation for the prevention and treatment of thromboembolic disorders (7).

After a brief description of haemostasis and blood coagulation, this article will provide an overview of the pathogenesis of venous and arterial thrombosis, and the rationale for using anticoagulants in those thromboembolic and related disease conditions. The impact of the protein C pathway on coagulation and inflammation, and the potential role of new oral anticoagulants and other antithrombotic agents in the management of thromboembolic disorders will also be discussed.
Haemostasis and blood coagulation

The endothelium of the blood vessel wall plays a crucial role in maintaining the integrity of the vasculature. When the vessel wall is damaged or the endothelium is disrupted, collagen in the sub-endothelial matrix becomes exposed to the flowing blood. Within seconds, platelets bind to the exposed collagen, which causes platelet activation, degranulation, and aggregation, leading to the formation of a primary platelet plug. In conjunction, coagulation is activated at the site of injury by the exposed subendothelial tissue factor (TF), resulting in fibrin formation, which stabilises the platelet plug (8, 9).

TF is an integral membrane protein that is constitutively expressed on fibroblasts and pericytes in the adventitia and medial smooth muscle cells of the blood vessel wall (8). Under normal conditions, the endothelium acts as a barrier to separate TF from factor VII and factor VIIa in the circulating blood, which prevents the initiation of coagulation in the absence of vessel injury. However, TF is also expressed in many non-vascular cells (such as monocytes) and microparticles in the circulation. This blood-borne TF is thought to participate in the processes of blood coagulation (8, 10). Coagulation reactions occur on specific cell surfaces such as activated platelets and TF-bearing cells.

For decades, the coagulation cascade was conceptualised as having two distinct points of initiation – the extrinsic and intrinsic pathways (11). However, it has become clear that these pathways do not function in the body as independent systems. An increasing understanding of the role of different factors and cells involved in blood coagulation has led to a cell-based model of coagulation. Unlike the older cascade model, the cell-based model represents more accurately the interaction between coagulation enzymes and cellular activity that leads to thrombin generation and clot formation (12).

Initiation phase

The initiation phase is localised to cells that express TF (8, 12). After binding to factor VIIa, the TF–factor VIIa complex activates small amounts of factor IX and factor X. Factor Xa then activates factor V on the TF-bearing cells and forms a complex with factor Va, which then converts a small amount of prothrombin (factor II) to thrombin (factor IIa; Fig. 1) (12, 13).

Amplification phase

The small amount of thrombin generated on TF-bearing cells amplifies coagulation reactions. In addition to activating platelets, the generated thrombin activates factor V and factor VIII on the platelet surface, leading to a burst of thrombin-generating potential. Thrombin also activates platelet-bound factor XI (Fig. 1) (8, 12).

Propagation phase

On the surface of activated platelets, factor Xla activates factor IX. This factor IXa, together with the factor IXa generated by the TF–factor VIIa complex, forms the tenase complex with factor VIIIa. This factor IXa–factor VIIIa complex activates factor X, which forms the prothrombinase complex with factor VA and produces a burst of thrombin generation.

Clot formation

The generated thrombin cleaves soluble fibrinogen to insoluble fibrin. Fibrin monomers polymerise to form the fibrin mesh that is stabilised and cross-linked by thrombin-activated factor XIIIa (Fig. 1) (12, 14).

Recent evidence suggests that cellular injury can release mRNA from the cells, which in turn can activate coagulation by triggering factor XII activation. The physiological relevance of this pathway is demonstrated by the observation that vessel occlusion in the ferric chloride model of arterial thrombosis has been reduced by RNAase treatment (15). Cell injury can also release histones that are cytotoxic to cells and elicit fibrin and platelet deposition along with leucocyte accumulation in the tissues. The trigger for these responses is probably the release of RNA from the cells and the exposure of TF (16). The relevance of these observations is supported by the finding that the blockade of histone toxicity protects animals from the lethal responses to endotoxin.

The role of endothelial cells in the control of blood coagulation

The endothelium of the blood vessel wall plays a crucial role in maintaining the integrity of the vasculature. By releasing substances such as nitric oxide, prostacyclin, and the ectonucleotidase CD39, the endothelium keeps the platelets in their inactivated state and impairs their adhesion in the absence of vessel injury (8, 17). The endothelial cells also produce coagulation inhibitors, including tissue factor pathway inhibitor (TFPI) and heparan sulphate. TFPI inhibits the TF–factor VIIa/factor Xa complex (9), thus eliminating the generation of both factor Xa and factor IXa, and inhibiting the initiation of coagulation. Free thrombin and factor Xa are inhibited by antithrombin (AT), and this inhibitory activity of AT is markedly enhanced by heparan sulphates present on the surface of endothelial cells (18). In addition, free thrombin in the circulation binds to the endothelial surface-bound thrombomodulin (TM) and activates the protein C system – a major negative control mechanism of coagulation (18, 19).

The protein C anticoagulant system is initiated when thrombin binds TM and forms the thrombin–TM complex, which decreases free thrombin levels, thus preventing thrombin from cleaving fibrinogen or activating platelets. Furthermore, this complex masks...
Figure 1: An overview of blood coagulation. TF, tissue factor; TFPI, tissue factor pathway inhibitor; vWF, von Willebrand factor.
the binding sites of thrombin for fibrinogen and the platelet thrombin receptor (20, 21). Protein C is a vitamin K-dependent protein, and is activated after binding to the endothelial cell protein C receptor (EPCR). Activated protein C (APC) binds to protein S (PS) and inactivates factor Va and factor VIIIa.

Activated protein C

Endothelial protection
- Thrombin-induced hyperpermeability
- Vascular integrity by stabilising endothelial cytoskeleton

Anti-apoptosis
- Pro-apoptotic genes
- Anti-apoptotic genes

Anti-inflammation
- Proinflammatory cytokines such as IL-1β, IL-6, IL-8, MCP-1
- Neutrophil adhesion to endothelium
- TF expression on leucocytes
- Anti-inflammatory cytokines

Figure 3: The cytoprotective effects of activated protein C. IL, interleukin; MCP, monocyte chemoattractant protein; TF, tissue factor.

The protein C pathway is particularly sensitive to downregulation by inflammatory responses (22). For example, endotoxin, tumour necrosis factor (TNF)-α and interleukin (IL)-1β can downregulate TM and endothelial protein C receptor – the APC complex co-factors (23, 24). Acquired protein C deficiency is prevalent in the majority of septic patients (>85%) and is associated with increased morbidity and mortality in patients with severe sepsis and septic shock (25). On the other hand, APC exhibits anti-inflammatory activity by decreasing proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, and MCP-1, reducing inflammatory mediator-induced TF expression on leucocytes, inhibiting neutrophil adhesion to the endothelium, and upregulating anti-inflammatory mediators (e.g. IL-10) (21, 24). In addition, APC can also reduce endothelial cell apoptosis and help maintain endothelial cell barrier functions (21, 24). Accumulating evidence suggests that the APC system protectively modulates a variety of disease processes, including diabetic nephropathy (26), stroke (27), tumour metastasis (28), multiple sclerosis (29), reperfusion-induced coronary (30), and renal injury (31). These effects are thought to be attributed to its cytoprotective properties (Fig. 3).

Relationship between coagulation and inflammation, and the role of activated protein C

Thrombosis and inflammation share some pathophysiological processes that involve inflammatory mediators, the activated endothelium, TF expression on monocytes, and circulating TF-bearing microparticles derived from activated platelets and endothelial cells (8, 21). Inflammation can trigger a coagulation response in a number of ways, such as inducing TF synthesis in intravascular cells and stimulating blood-borne TF, increasing platelet numbers and reactivity, causing the exposure of negatively charged phospholipids (22), and downregulating the natural anticoagulant systems.

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Figure 2: The anticoagulant effect of the activated protein C system. Thrombin (IIa) binds to thrombomodulin (TM) and activates protein C (PC), which is reversibly bound to the endothelial cell protein C receptor (EPCR). Activated protein C (APC) binds to protein S (PS) and inactivates factor Va and factor VIIIa.
Venous thrombosis

VTE comprises deep-vein thrombosis (DVT) and pulmonary embolism. DVT occurs most often in the large veins of the legs. When part of the thrombus breaks away, it can travel to the lungs and disrupt or block the blood flow in a pulmonary artery. Over 150 years ago, Rudolph Virchow proposed a triad of causes for venous thrombosis: venous stasis, vascular endothelial injury, and hypercoagulability of blood. This triad still applies, with one or more factors participating in the development of DVT (Fig. 4).

Venous stasis (or reduced blood flow in the veins) can be caused by many medical conditions, including immobility (e.g. hospital or nursing home confinement), major orthopaedic surgery (e.g. during and after surgery), or increased venous pressure (e.g. in heart failure). The majority of venous thrombi form in regions with a slow blood flow and reducing venous stasis in the legs has been found to reduce the risk of VTE (33). Venous stasis promotes thrombus formation by failing to clear activated coagulation factors quickly from the site of vascular injury. In addition, local hypoxia and distension of the vessel wall as a result of venous stasis can activate the endothelium, causing the expression of adhesion molecule selectins on its surface (17). Accumulating evidence suggests that circulating TF-bearing microparticles may play important roles in venous thrombosis (8, 17) – similar to that of platelets in arterial thrombosis (34). These microparticles attach to the activated endothelial cells and transfer TF to them, initiating coagulation reactions and clot formation (17). An increase in endothelial microparticles and leucocyte activation has been found in patients with VTE (35).

It has also been suggested that TF-bearing microparticles may also contribute to the hypercoagulable state associated with disease conditions with an increased risk of DVT (such as cancer, inflammation, and congestive heart failure) (8, 17, 36). Elevated numbers of tumour-derived TF-bearing microparticles in plasma have been found in cancer-associated thrombosis (8). Although surgery or trauma can directly cause vascular wall injury, and coagulation is activated via the exposed subendothelial TF, deep vessel wall injury is not a common feature in non-surgical patients with DVT.

Factors that may allow a small, silent thrombus to enlarge, or a new thrombus to develop, include the prolonged impairment of venous function (37), sustained hypercoagulability (38), and impairment of the endogenous anticoagulant or fibrinolytic systems (39, 40). Venous thrombi consist of mostly red blood cells and large amounts of fibrin. Activation of the coagulation system is the primary cause of venous thrombosis, and precedes platelet activation and aggregation (17). This explains why anticoagulation therapy has become the primary management strategy for VTE, and evidence-based guidelines strongly recommend the use of anticoagulants for the prevention and treatment of VTE (3, 4, 41).

Arterial thrombosis

The primary trigger for arterial thrombosis is the rupture of an atherosclerotic plaque, causing a complete or partial vessel occlusion. When plaque rupture occurs, its lipid core is exposed to the circulating blood in the arterial lumen. The core area of the plaque contains TF and fragments of collagen, which are highly thrombogenic (42, 43). Circulating TF is also increased in patients with cardiovascular disease and might contribute to thrombosis after plaque rupture (44). In the initial stage of plaque rupture, platelets are rapidly recruited to the site, followed by aggregation and the resulting rapid growth of the thrombus. The coagulation cascade is also activated at this stage with the formation of thrombin, which activates platelets. Activated platelets promote further platelet recruitment, adhesion, aggregation, and activation (44). Thus, an arterial thrombus is platelet-rich and exposed to fast flowing blood.
The fibrin component of the thrombus increases as it extends into the arterial lumen, although the surface area of the thrombus that is exposed to the blood in the lumen will be covered by activated platelets. A loose network of fibrin with large numbers of trapped red blood cells also form part of the thrombus in the final stage of thrombosis (43) (Fig. 5).

ACS is usually the outcome of atherosclerosis and thrombosis in the coronary arteries. Most acute myocardial infarctions are caused by thrombosis developed on a culprit coronary atherosclerotic plaque. Thrombosis is also the major initiating factor in unstable angina. Studies have suggested that a new thrombotic coronary event accounts for 50–70% of sudden deaths caused by ischaemic heart disease (43). An arterial thrombus that is rich in fibrin is often fully occlusive and results in ST-elevated myocardial infarction, whereas a platelet-rich arterial thrombus is often partially occlusive, resulting in unstable angina and non-ST-elevated myocardial infarction.

It is now well recognised that inflammation plays a key role in the pathogenesis of coronary artery disease and other manifestations of atherosclerosis. Blood-borne inflammatory and immune cells constitute an important part of an atheroma. Many of these cells are activated, producing several types of molecules (including inflammatory cytokines and proteases), which can destabilise the plaque, resulting in plaque rupture and ACS (45). The levels of C-reactive protein and IL-6, as well as other inflammatory markers, are elevated in patients with unstable angina and myocardial infarction (24, 45, 46). Interestingly, it has been suggested that some beneficial effects of statins may be partly attributed to their anti-inflammatory properties (47–49). However, results from a meta-analysis have indicated that most of the anti-inflammatory effect of statins is related to the magnitude of low-density lipoprotein (LDL) reduction, and the potential non-LDL effects of statins on inflammation are relatively small (50). Nevertheless, it is likely that LDL lowering may be a primary driver for the reduction in inflammation that contributes to lower cardiovascular risk (50).

Cyclooxygenase (COX)-2 is the inducible form of cyclooxygenase and has been shown to be involved in the proinflammatory response of vascular tissue, participating in both atherosclerosis and thrombosis (51). Increased inflammatory activity that involves COX-2 may predispose patients to cardiovascular events. Recent evidence also suggests that altered histone acetylation levels in inflammatory processes are associated with atherosclerosis and restenosis, and histone hyperacetylation may have a protective mechanism in vascular injury and remodelling, possibly by reducing the expression of factors involved in these pathological processes (52).

In acute arterial thrombotic events, drugs that reduce the growth of a thrombus should be administered, with platelets as the main target. Although antiplatelet agents are most commonly used to prevent the incidence of arterial thrombosis and recurrent ischaemic events, coagulation is clearly activated after plaque rupture, which provides a mechanistic rationale for anticoagulation therapy. Clinical evidence has shown that the combination of anti-coagulant and antiplatelet therapy is more effective than either treatment alone (53). In addition, based on the role of inflammation in the pathogenesis of ACS, anti-coagulants with anti-inflammatory properties may be beneficial. It has been shown that the combination of vitamin K antagonists with acetylsalicylic acid causes higher bleeding rates (42). New oral anticoagulants have demonstrated effective anticoagulation in some clinical studies. However, adequate dose-findings studies for the new oral agents to be co-administered with antiplatelet drugs in this setting are necessary to ensure that the potential benefit of the combination therapy is not offset by any increase in bleeding complications.

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Figure 5: Arterial thrombosis. An atherosclerotic plaque develops through the accumulation of lipid deposits and foam cells. The rupture of an atherosclerotic plaque is the primary trigger of arterial thrombosis. The core area of the plaque contains tissue factor and collagen (highly thrombogenic), which are released into the lumen of the blood vessel upon rupture.
Thrombus formation in atrial fibrillation

AF is the most common significant cardiac arrhythmia and it increases the risk of stroke four- to five-fold across all age groups (54). Left atrial thrombus formation in patients with AF fulfills the Virchow’s triad for thrombogenesis, with abnormal blood flow, endothelial dysfunction, and a hypercoagulable state (55, 56). Thrombi associated with AF occur most often in the left atrial appendage, and abnormal blood flow is evident in the left atrium. AF is also associated with markers of coagulation and platelet activation that may reflect a systemic hypercoagulable or prothrombotic state (56). For example, systemic fibrinogen and fibrin D-dimer levels are elevated in patients with persistent and paroxysmal AF, indicating the presence of active intravascular thromboembolism (55). Both von Willebrand factor and TF are overexpressed in the atrial endothelium in patients with AF who have a history of cardiogenic thromboembolism (56). In addition, recent evidence suggests that inflammation and various growth factors may also play a potential role in driving the prothrombotic state in AF (56).

Based on the existing evidence, the pathogenesis of thromboembolism in AF seems to fulfill the Virchow’s triad for thrombogenesis. Thus, the thrombus may be a ‘venous-type clot’. Therefore, anticoagulation therapy is an important part of patient management strategies and is strongly recommended in evidence-based guidelines (41). Numerous clinical studies have demonstrated that anticoagulants can effectively reduce the incidence of ischaemic stroke in patients with AF.

Targets for anticoagulation

The coagulation pathway provides many targets for potential anticoagulants (Fig. 6). Drugs that target the TF–factor VIIa complex inhibit the initiation phase of coagulation, whereas those that target factor IXa or factor Xa, or their co-factors (factor VIIIa and factor Va), inhibit the propagation of coagulation. Thrombin inhibitors inhibit thrombin activities. Direct factor Xa inhibitors and direct thrombin inhibitors are in the most advanced stage of clinical development. These include rivaroxaban, apixaban, edoxaban, betrixaban (oral, direct factor Xa inhibitors), and dabigatran etexilate (an oral, direct thrombin inhibitor). Some of these agents have already shown promise in providing safe, equivalent, or more effective anticoagulation compared with traditional anticoagulants, without the need for routine coagulation monitoring (7, 57, 58).

Direct factor Xa inhibition

Factor X is a key component of coagulation. As part of the prothrombinase complex, factor Xa catalyses the conversion of prothrombin to thrombin – one molecule of factor Xa results in the generation of approximately 1,000 thrombin molecules (59, 60). Whenever there is vessel damage, exposing subendothelial TF, factor Xa is generated after the formation of the TF–factor VIIa complex. Thus, factor Xa inhibition would be desirable in both arterial and venous thrombosis. Moreover, inhibiting factor Xa may also be
important in preventing platelet activation, deposition and recruitment at the sites of vessel injury by preventing thrombin generation. In addition, direct factor Xa inhibition does not affect the activity of preformed thrombin, which may allow the function of the existing thrombin to continue (such as activating protein C) (61–63).

Inhibition of factor Xa with new, oral, direct inhibitors may have potential advantages over indirect factor Xa inhibitors. These include their ability to inhibit factor Xa within the prothrombinase complex, which the AT-dependent, indirect factor Xa inhibitors (such as unfractionated heparin and low-molecular-weight heparin – which have anti-factor Xa activity – and fondaparinux, which is an indirect factor Xa inhibitor) are unable to do. Direct factor Xa inhibitors inhibit free, prothrombinase-bound, and clot-associated factor Xa (61, 64, 65). Clot-associated factor Xa has been shown to be enzymatically active in vitro and is able to activate prothrombin to thrombin (66) thus contributing to clot-associated procoagulant activity (67). Therefore, direct inhibition of clot-associated factor Xa could be an effective and localised approach to prevent thrombus growth. Recent evidence suggests that rivaroxaban, a direct factor Xa inhibitor, also affects clot structure by increasing the permeability and degradability of the clot, thus promoting clot lysis (68).

In addition to coagulation, factor Xa also exhibits proinflammatory and proliferative activities. Factor Xa induces macrophage migration inhibitory factor in endothelial cells and the expression of IL-6, IL-8, and monocyte chemotactic protein, thus contributing to the inflammatory processes (69–71). Recent studies have also indicated a potential role for factor Xa in the progression of tissue fibrosis and wound healing (72). The binding of factor Xa to vascular endothelial cells induces the release of platelet-derived growth factor, which is involved in cell proliferation (73, 74). The migration and proliferation of vascular smooth muscle cells in response to endothelial injury contribute to the development of restenosis and atherosclerosis. Preclinical evidence suggests that factor Xa inhibition could block some of the proinflammatory and proliferative processes, such as the expression of proinflammatory cytokines (75), and the proliferation of vascular smooth muscle cells (76) and, thus, limit restenosis after balloon angioplasty (77, 78).

It has been shown recently that the oral, direct factor Xa inhibitor rivaroxaban concentration-dependently inhibited the procoagulant activity of activated monocytes and macrophages, whereas the indirect factor Xa inhibitor fondaparinux did not display this effect (79). This property could be attributed to the ability of rivaroxaban to inhibit factor Xa bound to monocytes. Interestingly, both rivaroxaban and fondaparinux exhibited anti-inflammatory activity by inhibiting the secretion of inflammatory chemokines – an effect that was thought to be due to the inhibition of thrombin generation (79); it is not yet known to what extent this is attributed to the direct inhibition of factor Xa-mediated proinflammatory activities.

**Direct thrombin inhibition**

Thrombin has multiple effects on coagulation, including the conversion of fibrinogen to fibrin and the activation of factor XIII and platelet-bound factor XI. Thrombin is the most potent activator of platelets, and also induces the synthesis and/or secretion of adenosine diphosphate (ADP), endothelial platelet-activating factor, serotonin, and thromboxane A2 (20). In addition, thrombin amplifies its own generation by activating factor VIII and factor V – key co-factors for the tenase complex and the prothrombinase complex, respectively (80). Moreover, thrombin mediates a number of processes that promote anticoagulation and fibrinolysis, via the thrombin–TM complex and APC system.

Fibrin-bound thrombin is an important potentiator of thrombus growth. Unlike indirect thrombin inhibitors, direct thrombin inhibitors inactivate fibrin-bound thrombin and free thrombin (81). In addition, because direct thrombin inhibitors do not bind to platelet factor 4, their anticoagulant activity is not affected by the large quantities of this chemokine released from activated platelets in platelet-rich thrombi (7).

Thrombin is also involved in many other physiological and pathophysiological processes such as inflammation and wound healing (20). Vascular endothelial growth factor (VEGF) is a specific endothelial mitogen that initiates angiogenesis. It mediates endothelial cell proliferation, cellular migration, and vascular tube formation. Thrombin potentiates the effects of VEGF; clot-bound thrombin, which is resistant to inhibition by AT, contributes to angiogenesis and tissue repair at the sites of injury. The effect of thrombin on vascular permeability contributes to oedema and swelling associated with inflammation (20). Furthermore, thrombin mediates inflammatory processes via increasing monocyte adhesion to selectins (19) and the stimulation of proinflammatory cytokine (e.g. IL-6 and IL-8) and chemokine production (20, 82, 83). These properties also present thrombin as a target for other pharmacological interventions beyond coagulation. However, thrombin also has anti-inflammatory properties via the thrombin–TM complex and the APC system, and the APC system exhibits other cytoprotective functions (such as anti-apoptosis and endothelial barrier protection) (21). While inhibiting thrombin activity may have anti-inflammatory potential by blocking thrombin-mediated proinflammatory activities, it is not known whether long-term inhibition of the APC system (e.g. by thrombin inhibition) would have any adverse consequences.

**Inhibition of platelets**

Platelets play a vital role in haemostasis and are key participants in the pathogenesis of arterial thrombosis (84). When vascular injury occurs (such as the rupture of an atherosclerotic plaque), platelets are rapidly recruited to the site, followed by activation and aggregation. Activated platelets then release the contents of granules, which further promote platelet recruitment, adhesion, aggregation, and activation. This results in the rapid growth of the
thrombus (44). Antiplatelet agents are used for the prevention and acute treatment of arterial thrombosis. The primary targets are molecules involved in platelet activation and aggregation. The commonly used agents include acetylsalicylic acid (a COX-1 inhibitor) and the thienopyridines (ADP receptor antagonists) (84). Although the established efficacy has validated platelet COX-1 and ADP receptors as clinically viable targets for antiplatelet therapy, there are limitations with the use of these agents, such as the incomplete inhibition of platelet aggregation and/or ongoing thromboxane A₂ production with the use of acetylsalicylic acid and the delayed onset and offset of action with the thienopyridines (7). Recent attention has focused on the protease activated receptor-1 inhibitors and novel ADP receptor antagonists (7).

**Other pharmacological agents**

In addition to anticoagulant and antiplatelet therapies, there are also other agents that exhibit antithrombotic activity. For example, statins have been shown to significantly reduce the risk of VTE in recent clinical studies (85–87). The potential mechanisms that mediate the antithrombotic effect of statins include the reduction of TF expression and the attenuation of the APC anticoagulant pathway (89, 90). Thus, the benefits of statins may be attributed not only to their effects on lipid levels and anti-inflammatory properties, but also their potential influence on coagulation (88, 91).

**Conclusions**

The aetiology and pathological mechanisms are different for venous and arterial thrombosis, which are reflected in their different treatment strategies. Both oral, direct factor Xa inhibitors and oral, direct thrombin inhibitors have demonstrated potential in clinical studies to date (92–98), providing further evidence for both factor Xa and thrombin being viable targets of anticoagulant therapy. However, each drug or drug class may behave differently when used in different clinical situations, likely due to the different mechanisms of action of the drugs and differences in the pathogenesis of disease conditions.

Accumulating evidence suggests a strong link between coagulation and inflammation. Inflammatory mediators trigger coagulation responses, and coagulation factors mediate inflammatory processes and cell proliferation. The APC system, which has multiple cytoprotective roles, is downregulated in inflammation. The biological and pathophysiological roles of factor Xa and thrombin are far beyond coagulation. The anti-inflammatory and metastatic inhibitory effects of heparin, for example, are believed to be independent of their anticoagulation property (99). Although there are no clinical data currently available, by directly blocking thrombin generation or activity, the new oral anticoagulants might have potential anti-inflammatory effects, which could contribute to their anti-thrombotic efficacy and the overall clinical benefits. However, it is not yet known whether long-term suppression of the APC pathway (e.g. through inhibiting thrombin activity) could cause adverse consequences. Further studies examining the influence of direct factor Xa inhibitors and direct thrombin inhibitors on the APC system, as well as inflammatory markers, may provide further insight.

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