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REVIEW ARTICLE

# Drug-Induced Thrombosis: An Update

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**Abstract** Drugs may play an important role in development of thrombosis, and in recent years there has been increased attention to the importance of this issue. Although drug-induced thrombosis usually causes venous thrombotic events, arterial events are also noted due to drug administration. Here we review the different mechanisms through which drugs can exert thrombosis. Drugs can cause direct endothelial damage and expose the underlying subendothelium thus leading to platelet adherence and subsequent thrombus formation. Such an effect is seen by contrast media and chemotherapeutic cytotoxic drugs. Drugs may also attenuate the secretion of pro- and anticoagulation mediators by the endothelial cells and may have prothrombotic effects on platelets by increasing adhesion and aggregation, as for example seen after heparin administration in an immune-mediated mechanism. Red and white cells can also be affected by drugs, by increasing their aggregation or adhesion to the endothelial wall. Some drugs, such as oral contraceptive pills, may promote thrombosis by altering the balance between the different coagulation factors, and many drugs can lead to decreased blood flow by increasing blood viscosity, as seen for example after intravenous immunoglobulin administration. Better understanding of the mechanisms through which drugs exert thrombosis may facilitate their safe use in patients. Additionally, awareness of the drugs that are known to induce thrombosis is important in order to stop their administration in case of a thrombotic event. This review further emphasizes the fact that drug administration is a risk factor that should always be considered together with additional known thromboembolic risk factors such as genetic predisposition or cancer.

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## 1 Introduction

The understanding that drugs may play an important role in thrombosis development has gained widespread attention after extensive investigations have been undertaken to elucidate the apparent thrombogenic effects of estrogens contained in oral contraceptives [1]. In recent years there has been a wave of increased attention to drug-induced thrombosis following reports that some selective cyclooxygenase-2 (COX-2) inhibitors may increase the risk of myocardial infarction (MI) and atherothrombotic events, leading to the withdrawal of rofecoxib from global markets [2]. The herbal supplement ephedra, used as a slimming aid, was removed from the US market due to similar concerns [3]. A "black box" warning was added to the package insert for thalidomide, indicating that patients with multiple myeloma who receive thalidomide in combination with dexamethasone or chemotherapy may benefit from concurrent thromboembolism prophylaxis [4]. A "black box" warning was also added by the US Food and Drug Administration (FDA) to the prescribing information of erythropoiesis-stimulating agents in March 2007, among

others because of safety concerns regarding thromboembolic events [5].

Thrombosis may present as either a venous or an arterial event. The most common presentation of drug-induced thrombosis is venous thrombosis, which can present as deep vein thrombosis of the extremities (most common), portal, splenic or renal vein, or cerebral or sinus venous thrombosis. Emboli can be detached from the original thrombus in legs or arms, and reach the lung venules to induce pulmonary embolism. Arterial thrombosis is less common, and can present as a cerebrovascular accident, MI or peripheral vascular event.

Thrombosis is typically multifactorial so that predisposing factors other than prescribed drugs or toxic exposures are to be considered as well. Age, genetic predisposition, surgery, cancer, immobility, indwelling catheters, long flights or acquired antiphospholipid antibodies are among the important risk factors that have been identified to facilitate the development of venous thromboembolism [6].

In 2007 we published a review [7] that for the first time described the different mechanisms through which drugs may exert thrombosis. This review highlighted the importance of performing sufficient preclinical safety testing in order to reveal any possible prothrombotic effects of drugs. This review was also oriented towards histopathology changes observed following drug administration, and emphasized the aetiological changes at a more basic science level. In recent years, more evidence has accumulated on the topic of drug-induced thrombosis, which has led to changes in clinical practice, and initiated examination of better testing methods for prothrombotic effects of drugs [8]. Therefore, the aim of this article is to provide an update on the different mechanisms through which drugs can lead to thrombosis. This review also expands the list of drugs that can cause thrombosis, and thereby highlights additional potential prothrombotic mechanisms of drugs.

This article is organized similarly to the first review published by Ramot and Nyska [7], and drugs are divided according to the mechanisms through which they induce thrombosis, thus emphasizing similarities and differences between different drugs. Since some drugs have several suggested mechanisms for thrombus formation, they are mentioned more than once in the text. Table 1 summarizes the different mechanisms through which a specific drug may exert its thrombogenic risk.

A search of the English literature using the PubMed database was undertaken, using a combination of the keywords “drug” and “thrombosis”. All article types were reviewed, including original basic science research, clinical studies, case series and systematic reviews. Since the aim of the current review is to describe the different mechanisms through which drugs may exert thrombosis, drugs suggested to cause thrombosis, but with an unknown mechanism, were excluded. Additionally, in cases where there was sparse evidence on the ability of a drug to induce thrombosis (e.g., case reports), they were not included in our list of drugs. In addition, in cases where several drugs are known to induce thrombosis via one mechanism, only prominent drug examples were selected (e.g., in the case of thrombotic thrombocytopenic purpura). Included in the review are drugs that are in common use or that were more extensively studied.

## 2 Physiological Mechanisms of Thrombosis: An Outline

### 2.1 The Endothelium

One of the most important components in the pathogenesis of atherosclerotic and thrombotic disease is the endothelium [9]. Adherence of cells and fibrin to intact endothelium is rarely seen [10]. However, when the blood vessel wall is injured, the subendothelium is revealed. Platelets will immediately attach to the subendothelium, become activated and clot. Endothelial cells (ECs) also produce a variety of substances that regulate vessel tone, permeability, coagulation and fibrinolysis [9]. Damage to the endothelium also leads to the release of high levels of prothrombotic von Willebrand factor (vWF) and the loss of the anticoagulant thrombomodulin [11, 12].

### 2.2 Platelets

Platelet activation is achieved by a variety of stimuli, the most important of which is injured endothelium and exposure to subendothelial constituents. Platelets interact with the coagulation system in many ways: one important aspect is that activated platelets provide a negatively charged environment required for optimal activity of the coagulation cascade. Activated platelets also release small membrane vesicles—platelet microparticles—which have a procoagulant activity [13].

### 2.3 Coagulation Cascade

The coagulation process is viewed as a series of proteolytic reactions ultimately resulting in fibrin clot formation [10, 14]. The enzymes involved in these reactions are usually in an inactive state in the plasma. However, when the coagulation cascade is initiated, the activated form of the preceding factor activates the circulating factor next in line, having a propagating effect. The coagulation cascade may be initiated by reactions mediated by endothelial injury activating the extrinsic pathway. Thrombin is generated and further activates the intrinsic pathway and platelets.

**Table 1** Summary of drugs and their suggested mechanisms for inducing thrombosis

| Drug | Thrombotic effects | Prevalence and risk | References |
|---|---|---|---|
| Activated prothrombin complex concentrate | Direct activation of the coagulation cascade | Approximately 7 % | [184] |
| Alcohol | Inhibition of fibrinolytic activity and increased levels of coagulation protein FVIII. In addition, may increase shear stress on platelets leading to their activation and aggregation | Contradicting reports, and possible "U-shaped" association. One study shows that liquor consumption (>3 U/w) increased risk for VTE by 53 % and frequent binge drinking (>1/week) increased risk by 17 % | [185–188] |
| Antipsychotics | Increased serotonin and prolactin levels, inducing platelet activation (both first- and second-generation antipsychotics). Cause elevation of antiphospholipid antibodies level. May also induce arterial hypotony and peripheral vasodilation, leading to blood stasis (mostly first-generation antipsychotics) | *First generation antipsychotics*:<br>RR of 7.1<br>*Second generation antipsychotics*:<br>Hazard ratio for olanzapine: 1.87<br>Hazard ratio for risperidone: 1.98<br>Hazard ratio for clozapine and quetiapine fumarate: 2.68 | [105, 110, 189–192] |
| Carbon nanoparticles | Activation of GPIIb/IIIa, stimulating platelet aggregation | NA | [114] |
| Chemotherapeutic agents | | | |
| 5-FU | Cytolysis of ECs, leading to denudation of endothelial lining and decreased excretion of NO | 3.3 % of cancer outpatients | [29, 30, 193] |
| All-trans-retinoic acid | Increasing adhesion of APL cells to the endothelium | NA | [125] |
| Bleomycin | Morphological damage to lung ECs, leading to pulmonary thrombosis. Additionally increases TNF production | In combination with cisplatin in germ cell cancer patients the risk of thrombosis is estimated to be 8.4 % | [40, 58, 194] |
| Busulfan | Causes damage to ECs, which may lead to hepatic veno-occlusive disease | Veno-occlusive disease risk was 32 % with busulfan plus cyclophosphamide treatment | [39, 195] |
| Cis-platinum | Increased production of TNF inducing EC activation. In addition, induces vasospasm | 12.9 % of transitional cell carcinoma patients treated with multi-agent cis-platin-based therapy | [57, 196, 197] |
| Doxorubicin | Excess levels of free radical metabolites, damaging the ability of ECs to activate protein C | DVT developed in 16 % of multiple myeloma patients treated with doxorubicin-containing regimen | [76, 198] |
| Gemtuzumab ozogamicin | Mechanism not fully elucidated. It is suggested that GO binds to the CD33 surface antigen on sinusoidal endothelial cells resulting in injury and eventually occlusion | 12 % of haematological malignancy patients treated with GO developed hepatic veno-occlusive disease | [37, 199] |
| L-asparaginase | Impairs the synthesis of the naturally occurring anticoagulant proteins | Acute lymphoid leukemia patients treated with L-asparaginase had a 4.9-fold increased risk for thrombosis in comparison with those who did not | [33, 200] |
| Mitomycin C | Inhibits the production of prostacyclin, leading to platelet aggregation and local intravascular coagulation. In addition, direct toxicity of mitomycin C on endothelial function may lead to TTP | NA | [73, 93] |
| Paclitaxel | When administered with drug-eluting stents may lead to hypersensitivity reaction and chronic inflammation, resulting in stent thrombosis | Yearly incidence of 0.2–0.6 % | [42] |

**Table 1** continued

| Drug | Thrombotic effects | Prevalence and risk | References |
|---|---|---|---|
| Tamoxifen | Reduces coagulation inhibitor factors | The risk of tamoxifen-associated thromboembolic events ranges from 1 % to 3 % | [138, 139, 201] |
| Thalidomide | Increases EC and platelet activation, while reducing levels of the anticoagulant thrombomodulin | 10–20 % when associated with dexamethasone therapy. 30 % when associated with chemotherapy | [78, 80, 202] |
| VEGF antagonists | Blocking of VEGF leads to EC apoptosis, followed by arterial and venous thrombosis | Cancer patients treated with bevacizumab had an 11.9 % risk of developing VTE (RR of 1.33) | [32, 203] |
| Cocaine | Platelet activation and vessel vasoconstriction | The risk of MI is increased by 24-fold during 1 h after the use of cocaine | [204–206] |
| Contrast media | Lead to endothelial injury following damage to ECs and also increase platelet adhesiveness. Although under debate, there is evidence suggesting that high-osmolar contrast media are more prone to induce thrombosis than low-osmolar or iso-osmolar contrast media | NA | [22, 97, 207] |
| COX-2 inhibitors | Mediated by the inhibition of prostacyclin | RR for MI with rofecoxib was reported to be 1.25 | [68, 69, 208] |
| ε-aminocaproic acid | Direct inhibition of fibrinolysis | Eightfold increase in DVT incidence with ε-aminocaproic acid | [159, 209] |
| Ephedra | Vasoconstriction that may lead to MI | NA | [173, 174] |
| Erythropoietin | Increased vascular resistance by changing the balance between vasodilatory and vasoconstrictive prostaglandins. Leads to EC and platelet activation. In addition, the increased RBC mass leads to blood viscosity | RR of 1.67 for thromboembolic events | [101, 163, 175, 210] |
| Granulocyte colony-stimulating factor | Increased levels of TF antigen and other endothelial markers | 1.2 % risk for thrombotic events in cancer patients in combination with chemotherapy | [53, 61] |
| Granulocyte macrophage colony-stimulating factor | Increased release of pro-inflammatory cytokines by EC | OR of 1.67 in cancer patients | [53–56] |
| Heparin | May paradoxically induce thrombosis via an auto-immune response to platelet-heparin complex | Heparin-induced thrombocytopenia occurs in about 1–5 %, and thrombosis occurs in 30–50 % of these patients | [89, 211, 212] |
| Hormone replacement therapy | Estrogen leads to imbalance between increased levels of coagulation factors and decreased levels of coagulation inhibitors | Twofold increased risk for VTE. 50 % increased risk for stroke | [131] |
| Immunosuppressive agents | | | |
| Ciclosporin | Changes metabolism of ECs leading to cell detachment. In addition, increases platelet activation | 2.3 % for graft thrombosis in kidney transplantation patients | [52, 112, 113, 213] |
| Glucocorticoids | Increased plasma levels of thrombotic factors and decreased levels of anti-thrombotic factors. Decreases fibrinolytic activity | Preoperative corticosteroid use confers an OR of 1.87 for VTE | [149, 150, 164, 214] |

**Table 1** continued

| Drug | Thrombotic effects | Prevalence and risk | References |
|---|---|---|---|
| Sirolimus | When administered with drug-eluting stents may lead to hypersensitivity reaction and chronic inflammation, resulting in stent thrombosis. By reducing renal VEGF, may lead to renal TMA. Can also up-regulate TF, thus leading to thrombosis | Yearly incidence of 0.2–0.6 % | [35, 43, 63] |
| Interferon-α | By inducing disturbances in microcirculation may lead to thrombosis and TMA | NA | [129, 130] |
| Intravenous immunoglobulin | Stems from contamination with activated coagulation factor XI, arterial vasospasm and increased blood viscosity | Thrombosis incidence of between 1.1 % and 4.5 % in neurological patients and up to 13 % in autoimmune patients | [145, 146, 191–193, 221] |
| Metformin | Leads to hyperhomocysteinaemia, which causes oxidative damage to the ECs | NA | [215] |
| Quinine | May lead to rapid TTP induction in an immune-mediated mechanism | 57 % of drug-associated HUS/TTP are ascribed to quinine | [94, 216] |
| Recombinant factor VIIa | Direct activation of the coagulation cascade | Approximately 7 % of treated patients develop thromboembolic events including MI, stroke and disseminated DIC | [159, 160] |
| Selective serotonin reuptake inhibitors | By increasing serotonin levels adjacent to specific serotonin-receptor subtypes may lead to platelet activation and vasoconstriction of blood vessels | The OR for ischaemic stroke is 1.1 | [104, 168, 217] |
| Sildenafil | Increasing levels of cGMP, thus interfering with the normal functions of ECs. The venodilating effects may lead to blood stasis and venous thrombosis events | Incidence of MI is 1.7/100 patient years (in one study was found to be similar to placebo) | [86, 218] |
| Thienopyridine derivatives | | | |
| Ticlopidine | Induction of an antibody to ADAMTS13 | Incidence of TMA is 0.02–0.06 % | [90, 219, 220] |
| Clopidogrel | Direct endothelial cell injury | The incidence of TTP is 1/1600–1/5000 | [95] |
| t-PA | Causes proteolysis of ECs, leading to matrix exposure. In addition, leads to increased platelet adhesion. May paradoxically lead to thrombotic events | NA | [44] |
| Tranexamic acid | Direct inhibition of fibrinolysis | Uncertain effects on thrombotic events | [159, 221] |

*5-FU* 5-fluorouracil, *APL* acute promyelocytic leukemia, *EC* endothelial cells, *cGMP* cyclic guanosine monophosphate, *DIC* disseminated intravascular coagulation, *DVT* deep vein thrombosis, *EC* endothelial cells, *FVIII* factor VIII, *GO* gemtuzumab ozogamicin, *GPIIb/IIIa* glycoprotein IIb/IIIa, *HUS* haemolytic uraemic syndrome, *MI* myocardial infarction, *NA* not applicable, *NO* nitric oxide, *OR* odds ratio, *RBC* red blood cells, *RR* relative risk, *TF* tissue factor, *TMA* thrombotic microangiopathy, *TNF* tumour necrosis factor, *TTP* thrombotic thrombocytopenic purpura, *VEGF* vascular endothelial growth factor, *VTE* venous thromboembolism

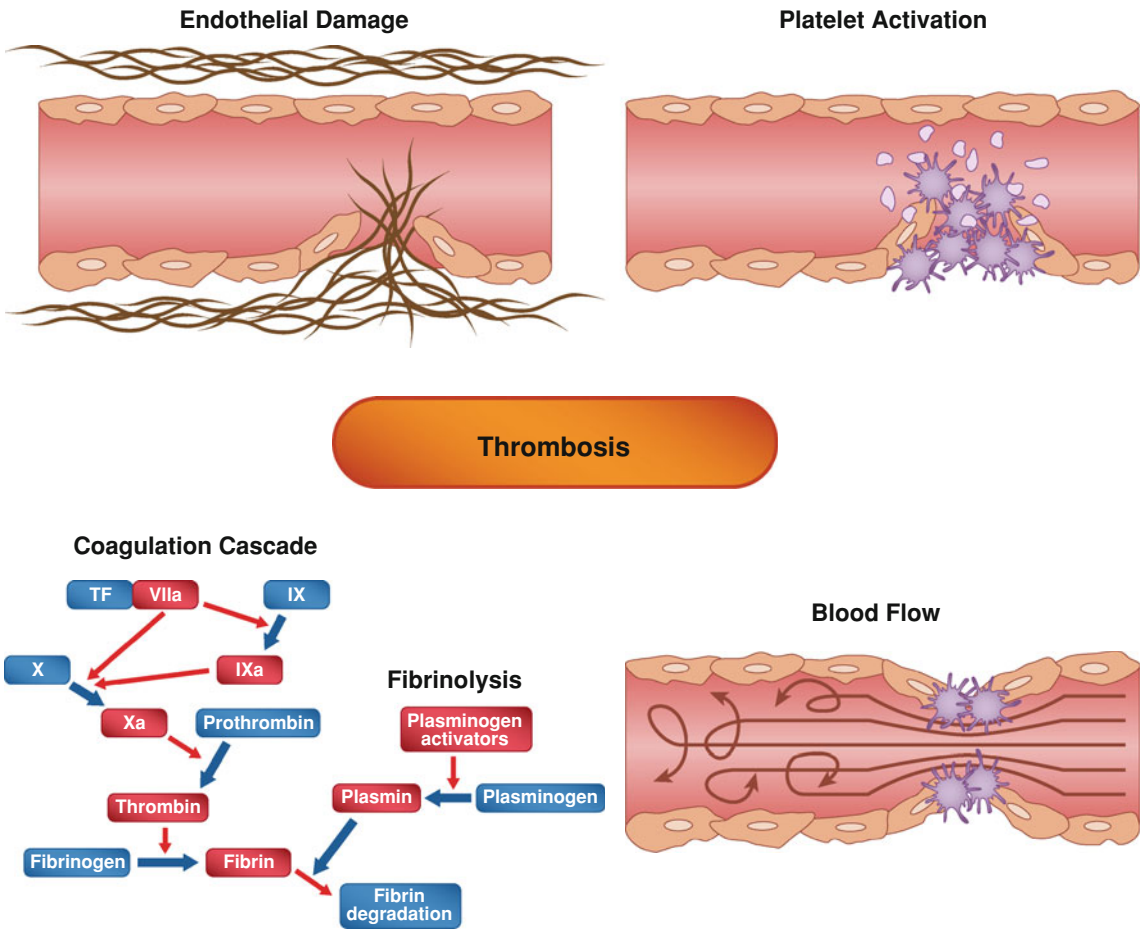


**Fig. 1** The major components involved in the pathogenesis of thrombosis, and which can be affected by drugs. *TF* tissue factor

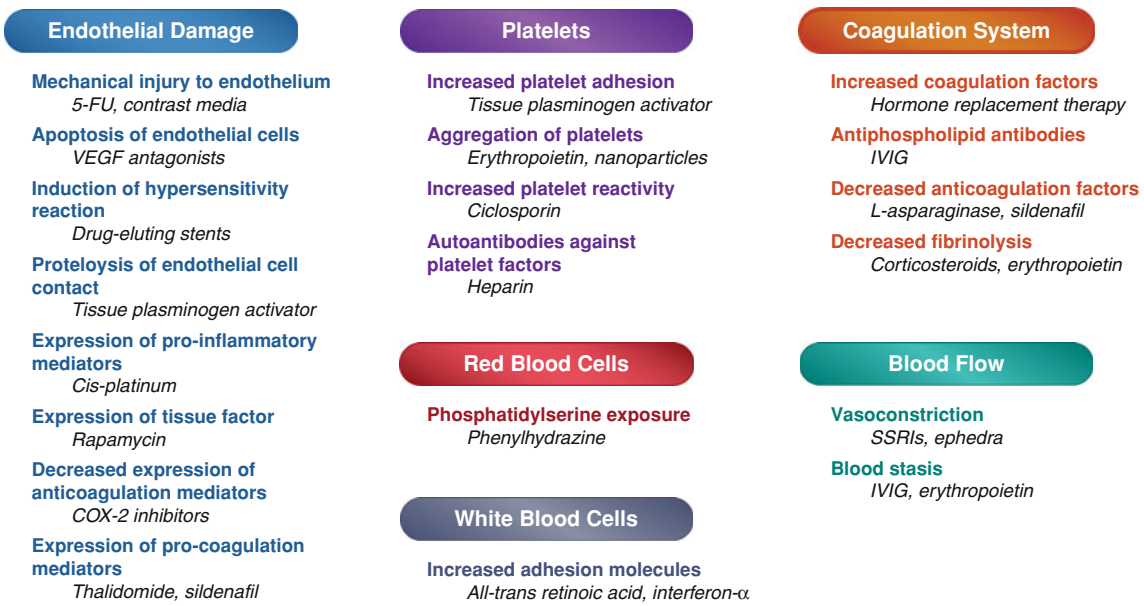


**Fig. 2** A list of the different mechanisms through which drugs can cause thrombosis. Examples of drugs for each mechanism are listed in italics. *5-FU* 5-fluorouracil, *COX-2* cyclo-oxygenase-2, *IVIG* intravenous immunoglobulin, *SSRI* selective serotonin reuptake inhibitor, *VEGF* vascular endothelial growth factor

Ultimately, the two pathways converge to a common pathway of coagulation resulting in thrombin formation. Thrombin, once formed, amplifies the coagulant response in several ways.

### 2.4 Fibrinolysis

Fibrinolysis, the process of dissolution of blood clots, starts when plasminogen activator activates plasminogen to plasmin, which is responsible for fibrin degradation [15]. Its action is limited by a potent plasma inhibitor system.

### 2.5 Blood Flow

Changes in the rheological characteristics of blood may lead to a thrombogenic tendency through two different methods: turbulence and stasis. In laminar flow, shear stress is maximal at the vessel wall, and the ECs align in the direction of flow. Flow regulates endothelium-related vascular reactivity by inducing the release of endothelial defenses, such as nitric oxide, prostacyclin and tissue plasminogen activator [16]. Turbulence disrupts the release of these mediators. In addition, high shear stress may activate platelets and increase their adherence to exposed subendothelium [16].

Blood stasis favours the interaction of thrombogenic blood constituents with the vessel wall. It also prevents the dilution of clotting factors and delays their removal in the liver. It may also lead to hypoxia and further damage to ECs [10, 17]. Blood stasis may be caused by an increase in blood viscosity [18].

A general overview of the mechanisms involved in thrombosis, and which are affected by drugs, is presented in Fig. 1. A summary of the different mechanisms through which drugs can exert thrombosis, with examples of selected drugs for each mechanism, is presented in Fig. 2.

## 3 Endothelial Damage

### 3.1 Primary Mechanical Endothelial Injury

One of the most important functions of normal ECs is to prevent the activation of the intrinsic or extrinsic coagulation pathways or the adherence of platelets or leukocytes [10]. Many drugs can lead to a direct mechanical endothelial injury through various mechanisms.

The injection of contrast media for diagnostic purposes may lead to such an injury [19–21]. The degree of lesion formation by contrast media is dependent on three factors: (1) type of contrast media used, for example hyper- or hypo-osmolar: hyper-osmolar solutions might cause an increased endothelial cell shrinkage, and therefore increase contrast media-mediated cytotoxicity [22, 23]; (2) the dose of contrast media and rate of injection [24, 25]: it is thought that the higher turbulent flow caused by rapid injection induces high shear stress, leading to enhanced thrombosis [26]; and (3) the proliferation rate of ECs: the degree of endothelial damage is correlated with the rate of EC proliferation, as measured using autoradiography to evaluate DNA synthesis [27, 28].

The anticancer agent 5-fluorouracil (5-FU) may cause severe changes in the arterial endothelium including severe and extensive cytolysis and denudation of the underlying internal elastic lamina [29]. This could be the trigger for 5-FU-induced cardiotoxicity, which manifests as arrhythmias, myocardial infarction and sudden cardiac death [30]. 5-FU harms the ability of the cells in antioxidant defence, and affects the production of nitric oxide. Free radical generation by 5-FU causes lipid peroxidation, and damage to the cell membrane. Indeed, the addition of probucol, which has strong antioxidant characteristics, has a protective effect on the endothelium [29].

Vascular endothelial growth factor (VEGF) antagonists are antineoplastic agents that target angiogenesis and thereby deprive tumours of their blood supply. They have been associated with both thrombosis and haemorrhage [31]. VEGF is essential for the preservation of healthy blood vessel endothelium; therefore, blocking VEGF from binding to its related receptor may lead to EC apoptosis [32]. Most reports involve bevacizumab, an anti-VEGF monoclonal antibody [33]. Both venous and arterial thrombotic events have been observed during several clinical trials [33]. Arterial events have also been reported after intravitreal injections for age-related macular degeneration [34].

Disturbances of VEGF function can be induced by drugs other than VEGF inhibitors. Sartelet et al. [35] reported four cases of thrombotic microangiopathy (TMA) in patients on a sirolimus-based immunosuppressive regimen. Renal VEGF expression was reduced, and the authors suggested that altered VEGF podocyte production is one mechanism by which sirolimus increases the risk of renal TMA.

Gemtuzumab ozogamicin (GO) is a semisynthetic derivative of calicheamicin, a potent cytotoxic antibiotic, which is linked to a humanized anti-CD33 monoclonal antibody [36]. Its therapeutic use is associated with the development of the sinusoidal obstructive syndrome, a potentially fatal hepatic vaso-occlusive disease in leukemia patients [37]. It has been suggested that GO binds to the CD33 surface antigen on sinusoidal endothelial cells resulting in injury and eventually occlusion [38].

The alkylating agent busulfan can damage the endothelial lining of the sinusoids and terminal hepatic venules, which contributes to hepatic veno-occlusive disease [39]. Animal studies have shown that bleomycin, an anti-tumour antibiotic, can cause morphological damage to the lung vascular endothelium, which results in pulmonary thrombosis [40].

Drug-eluting stents (DES) release antiproliferative drugs attached via polymers on the stent surface in order to minimize smooth muscle proliferation and to reduce the rate of restenosis in patients undergoing percutaneous coronary interventions. Sirolimus and paclitaxel are the most common drugs included in DES [41]. Stent thrombosis is a major adverse event that usually occurs in the first month after stent implantation and results in acute MI and/or sudden cardiac death. With the increasing use of DES, late stent thrombosis (>1 month to <1 year) was reported with a yearly incidence of 0.2–0.6 % in both types of stents [42]. The exact mechanism of late stent thrombosis is not clear. Virmani et al. [43] reported the first case of a local hypersensitivity reaction with extensive vasculitis affecting the intima, media and adventitia, and predominantly consisting of lymphocytes and eosinophils in a patient suffering from late DES thrombosis. It seems that DES thrombosis is caused by delayed healing and impaired endothelialization, which either alone or in combination with chronic inflammation and hypersensitivity cause incomplete attachment of the stent to the vessel wall and exposure of the stent thrombogenic metallic moiety to the coagulation system [42, 43].

Recombinant tissue-type plasminogen activator (t-PA) can also compromise the antithrombotic abilities of ECs [44]. t-PA is being used for the treatment of MI, ischaemic stroke and DVT [45–47]. Although t-PA was designed to dissolve blood clots, it may paradoxically lead to thrombus formation after treatment [48, 49]. t-PA activates plasminogen and therefore transiently increases blood plasmin levels. The excess of plasmin together with plasminogen activation on the cell surface may lead to proteolysis of cell–cell contacts and cell matrix sites. Consequently, the EC monolayer retracts and the subendothelial matrix is exposed [50]. In addition, plasmin serves as a feedback regulator of the natural fibrinolytic system, and leads to down-regulation of endogenous t-PA excretion [51].

Ciclosporin (CsA), a calcineurin phosphatase inhibitor used as an immunosuppressive agent, induces changes in the metabolism of vascular endothelial cells. Treatment of human umbilical vein endothelial cells (HUVECs) with CsA led to dose-dependent cell detachment and the exposure of subendothelial areas that induces activation of the intrinsic coagulation pathway [52].

## 3.2 Endothelial Expression of Coagulant and Anticoagulant Factors

### *3.2.1 Increased Pro-Inflammatory Cytokines Expression*

As described above, ECs do not merely serve as a passive lining for blood vessels, but they also play a metabolically active part involving both procoagulant and anticoagulant properties [10]. Recombinant granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) are used in cancer patients to shorten neutropenia time [33]. Thrombotic events have been described after G-CSF or GM-CSF administration [53]. Pro-inflammatory cytokines, such as tumour necrosis factor (TNF) and interleukin-1 (IL-1), cause alterations of coagulation via enhanced production of procoagulants by ECs and down-regulation of the anticoagulant thrombomodulin [54]. GM-CSF has been shown to induce the release of these pro-inflammatory cytokines leading to an increased incidence of arterial and venous events in breast cancer women [54–56].

Other drugs may produce inflammatory effects. Cisplatinum, one of the most potent anti-cancer drugs, was shown to induce transcription of the TNF gene [57], whereas bleomycin increased TNF production in tumour-bearing rat spleen cells *in vitro* [58]. Increased TNF production was suggested to be one mechanism for the increased rate of thrombosis associated with the therapeutic use of both drugs [59].

### *3.2.2 Increased Tissue Factor Expression*

Tissue factor (TF) is a transmembrane protein acting as a receptor for factor VIIa, thus initiating the extrinsic coagulation cascade [60]. ECs, by expressing TF, affect the thrombotic cascade. Drugs that influence TF induction may have a significant effect on thrombosis, which is demonstrated with G-CSF that increases both TF antigen level and activity in addition to increased levels of endothelial markers, such as factor VIII and vWF [61]. Rapamycin, an immunosuppressive agent, is another drug that influences TF expression [62]. This drug exerts antiangiogenic properties by blocking VEGF secretion and up-regulating TF secretion. The co-stimulatory effect of rapamycin and local VEGF secretion by tumours results in excessive endothelial TF expression leading to thrombosis in tumour-containing vessels [63]. Therefore, what was initially thought to be an adverse effect of the drug was later exploited to reduce the size of tumours by occluding their blood supply.

### *3.2.3 Decreased Expression of Anticoagulation Mediators by Endothelial Cells*

Prostacyclin ($PGI_2$) is one of the products of ECs that plays an important part in vascular homeostasis. It is produced in small quantities by resting ECs, and can prevent or reverse platelet aggregation and cause vasodilation. Since $PGI_2$ is a derivative of arachidonic acid, it is affected by COX inhibitors [64]. COX-2 inhibitors drew the attention of health authorities after rofecoxib was withdrawn from markets around the world by its manufacturer following

results of the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial showing an increased risk of thrombotic events in patients taking rofecoxib [2, 65]. Platelets contain mainly or solely the COX-1 isoform. The main isomerase that couples to COX-1 is thromboxane ($TxA_2$) synthase [66]. As a result, the main arachidonic acid product resulting from COX activity in platelets is $TxA_2$. In the normal state, the vasculature maintains a strong balance between $PGI_2$ (COX-2 mediated) and $TxA_2$ (COX-1 mediated) [67]. Therefore, COX-2 inhibitors have two potentially negative outcomes on the vasculature system. They do not inhibit $TxA_2$ production by platelets, but they inhibit $PGI_2$ production, thus diverting the homeostatic balance towards platelet aggregation and vasoconstriction [68]. A meta-analysis concluded that use of selective COX-2 inhibitors is associated with a moderate increase in the risk of vascular events [69]. High doses of ibuprofen and diclofenac, non-selective COX inhibitors, i.e. COX-1 and COX-2 inhibitors, are also associated with a moderately increased risk, in contrast to high-dose naproxen, another non-selective COX inhibitor that has a much longer half-life, which was not found to be associated with a higher risk for thrombosis [69]. The functional importance of $PGI_2$ in restraining the response to $TxA_2$ is further supported by the inverse relationship between aspirin (acetylsalicylic acid) dose and clinical benefit. It has been suggested that low doses of aspirin (50–100 mg/day) are more effective in thrombosis prevention than high doses of aspirin (650–1,500 mg/day) due to $PGI_2$ inhibition and the toxic gastric effect of the high dose [70, 71]. This finding is consistent with the dose-dependent inhibition of $PGI_2$ biosynthesis by aspirin in healthy volunteers [72].

Mitomycin C, used as part of aggressive anti-tumour therapy, is another drug that inhibits the production of $PGI_2$ [73]. Similar to COX-2 inhibitors, this effect of mitomycin C may lead to platelet aggregation and local intravascular coagulation.

Erythropoietin (EPO), used to treat anaemia, significantly increases the release of endothelin-1 as well as the vasoconstrictive prostaglandins $PGF_{2\alpha}$ and thromboxane $B_2$, and significantly reduces the release of $PGI_2$ by cultured HUVECs [74]. Thus, EPO may increase vascular resistance by changing the balance between vasodilatory and vasoconstrictive prostaglandins [75].

The EC protein C receptor (EPCR) and thrombomodulin are two receptors located on ECs that are needed for the activation of zymogen protein C. Exposure of HUVECs to doxorubicin, a chemotherapeutic agent, reduces cell surface EPCR levels. This decrease is a result of receptor shedding and down-regulation in EPCR mRNA levels [76]. In contrast, doxorubicin increases cell surface thrombomodulin, which is ascribed to an up-regulation of thrombomodulin mRNA levels. The net effect is a decrease in the capability of HUVECs to convert protein C to activated protein C, which is a natural anticoagulant. These changes are attributed to doxorubicin free radical metabolites.

#### *3.2.4 Increased Expression of Pro-coagulation Mediators by Endothelial Cells*

Thalidomide is an immunomodulatory and anti-angiogenic drug that can induce apoptosis of the established neovasculature, and is mainly used for treating multiple myeloma [77]. DVT has become the most important complication of thalidomide therapy, especially when associated with dexamethasone therapy (10–20 % of patients) or chemotherapy (30 %), particularly doxorubicin [78]. Thalidomide increases EC expression of the thrombin receptor protease-activated receptor-1 (PAR-1), a G-protein-coupled receptor stimulated by thrombin that has an essential function in haemostasis and arterial thrombosis [79]. This leads to EC activation, which results in endothelial dysfunction, platelet activation and thrombosis [80].

Sildenafil is a selective phosphodiesterase type 5 inhibitor (PDE5i) used for the treatment of erectile dysfunction. It was also approved by the FDA for the treatment of pulmonary hypertension due to its local vasodilatory effects mediated by the nitric oxide-guanosine monophosphate (NO–cGMP) pathway [81]. Several reports suggest that sildenafil may rarely cause arterial thrombotic or embolic events in the optic nerve (non-arteritic ischaemic optic neuropathy) [82], retina (retinal artery occlusion) [83], heart (arrhythmia, MI) [84] and brain (transient ischaemic attacks and strokes) [85]. High concentrations of cGMP induced by the long-term use of sildenafil are known to mediate the phosphorylation of several protein kinases (or isoforms), which interfere with normal endothelial function [86]. cGMP also activates $PDE_2$ and $PDE_4$, which may induce cAMP-mediated changes in endothelial permeability [87], promoting platelet adhesion and thrombus formation [86].

Antibodies from patients suffering from heparin-induced thrombocytopenia/thrombosis (HITT), in addition to their activating effects on platelets (which will be described later), have been shown to interact with ECs via their $F(ab')_2$ end (the divalent antigen-binding peptic fragment) and activate them [88, 89]. This activation causes expression of surface adhesion molecules, such as E-selectin and vascular cellular endothelial molecule-1, which may contribute to thrombosis in those patients.

#### *3.2.5 Thrombotic Thrombocytopenic Purpura*

Thrombotic thrombocytopenic purpura (TTP) is a severe, multisystem TMA manifested by thrombocytopenia, microangiopathic haemolytic anaemia, renal dysfunction,

neurological abnormalities and fever [90]. The congenital form of TTP is caused by a deficiency of the circulating zinc metalloproteinase ADAMTS-13 [91], while the acquired form is usually antibody-mediated. When ADAMTS-13 activity is deficient or inhibited, endothelium-derived, ultralarge multimers of vWF are left uncleaved in the circulation and lead to intravascular platelet aggregation and disseminated thrombus formation [92].

About one-fifth of TTP cases are associated with pharmaceuticals [93]. The most commonly reported agents include mitomycin C, quinine, ciclosporin and ticlopidine [94]. The clinical characteristics of TTP associated with these drugs are different, which suggests the involvement of two major mechanisms: a dose-related direct toxicity (e.g., mitomycin C, ciclosporin), and an immune-mediated reaction (quinine, ticlopidine, clopidogrel).

The direct toxicity of mitomycin C on endothelial function plays an important role in the pathogenesis of TTP [95]. Mitomycin C induces direct damage on the renal endothelium and the formation of platelet aggregates that result in the characteristic pathological abnormality of TMA [94]. Mitomycin C also decreased $PGI_2$ production following exposure of human EC cultures, which may exacerbate platelet aggregation [96]. Quinine-associated TTP has a rapid onset and is immune mediated [94]. Consistent with an immune-mediated mechanism, re-exposure to quinine is associated with an immediate recurrence of the signs and symptoms of TTP.

## 4 Platelets

### 4.1 Increased Platelet Adhesion

Although endothelial damage is the main factor that leads to platelet adhesion to vessel walls, the platelets have an adhesive ability of their own [7]. Recombinant t-PA tends to increase platelet adhesion via several possible mechanisms, either directly on platelets by involving cytoskeletal rearrangements, by effects on plasma factors, or through compromised antithrombotic capacity of ECs (as described above) [44]. t-PA causes dramatic changes in platelet morphology with pseudopod and cluster formation that may contribute to increased platelet adhesion [44]. Contrast media were also found to increase platelet adhesiveness [97].

### 4.2 Platelet Aggregation

Erythropoietin (EPO) therapy leads to reticulocytosis by increasing the number of young, metabolically active red blood cells (RBCs) in peripheral blood. Since these fresh RBCs are metabolically active, they enhance platelet reactivity *in vitro* [98]. In the presence of metabolically active RBCs, platelets release increased quantities of the platelet α-granule protein, β-thromboglobulin, and synthesize more thromboxane [99]. The releasates of platelets and RBCs contain more adenosine diphosphatase (ADP) and adenosine triphosphatase (ATP) than releasates of platelets alone. In addition, EPO acts synergistically with the platelet growth factor thrombopoietin and this leads to platelet activation *in vitro* at concentrations that can be achieved pharmacologically *in vivo* [100]. In addition to effects on RBC formation, EPO exerts effects on platelet formation. EPO increases the number of megakaryocytes and platelet counts in mice and humans. Platelet reactivity and endothelial activation markers are also increased [101].

The risk of VTE is increased in psychiatric patients. Antipsychotics, especially of the first-generation, are presumed to induce blood clotting by sedation and reduced mobility [102]. In addition, drugs that increase serotonin blood levels may predispose to thrombotic events, by inducing and amplifying platelet aggregation [103]. Antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), deplete serotonin storage, therefore decreasing the risk of hypercoagulation [103]. However, the immediate and early effect is an increase in serotonin levels adjacent to specific serotonin-receptor subtypes. This immediate increase may lead to augmented risk of thrombosis [104]. Antipsychotics also increase serotonin levels and were suggested to induce platelet aggregation [105, 106]. This direct effect on platelets was found to be mediated mostly by second-generation antipsychotics, and especially clozapine [106]. These *in vitro* effects corresponded to the known increased risk for VTE with these second-generation drugs [107]. Nevertheless, recent *in vitro* studies have actually suggested an inhibitory role on platelet aggregation for second-generation antipsychotics, which leave this issue still in debate [108, 109].

It is well known that antipsychotic drugs act as dopamine antagonists and that some of them cause hyperprolactinaemia. Hyperprolactinaemia may be an important novel risk factor for VTE, mediated through enhanced platelet reactivity via potentiation of ADP-induced platelet stimulation [110], although this finding is still under debate [111]. Nevertheless, hyperprolactinaemia may be an additional acquired risk factor for VTE in patients treated with antipsychotic drugs.

Ciclosporin thrombogenicity has been shown both *in vivo* and *in vitro*. *In vivo* it manifests mostly as DVT and pulmonary embolism [112]. One of the proposed mechanisms of ciclosporin-induced thrombogenesis is increased platelet reactivity, mediated by an altered availability of platelet surface fibrinogen receptors, which are final mediators of platelet activation [113].

Engineered carbon nanoparticles are being increasingly used for selective imaging, sensor tools or drug-delivery

systems [114]. They have been shown to stimulate human platelet aggregation *in vitro* and increase the rate of vascular thrombosis [114, 115]. Nanoparticle-induced platelet aggregation probably results from activation of GPIIb/IIIa, the membrane complex that serves as the fibrinogen receptor. It has also been suggested that the shape of the nanoparticle plays an important role in platelet aggregation. For example, carbon nanotubes mimic molecular bridges and lead to platelet-platelet interaction.

Heparins are commonly used for the treatment of VTE. Type II heparin-induced thrombocytopenia is immune mediated and might paradoxically lead to thrombosis (HITT). Auto-antibodies to platelet factor 4 (PF4)-heparin complexes are produced and lead to platelet activation, and to platelet microparticle release [89].

Stent thrombosis has been found to be mediated by aggregation of platelets, and it is for this reason that treatment with dual antiplatelet therapy with aspirin and a thienopyridine is now advocated for at least 1 year [116, 117].

## 5 Red Blood Cells

Although in the past RBCs have been considered irrelevant to haemostasis and thrombosis, more recent studies showed that RBCs are involved in interactions with ECs, platelets and macrophages [118]. Alterations in the RBC membrane enable RBCs to participate in thrombus formation [119]. Phosphatidylserine exposed on RBCs provides a site for the assembly of the prothrombinase-tenase complex, thus leading to thrombin generation, and clotting [119, 120]. In addition, those RBCs that display phosphatidylserine on their outer surface adhere more strongly to endothelial cells, and contribute to vaso-occlusion [121].

Drugs that cause peroxidation of RBC membranes can induce phosphatidylserine externalization. One example is the haemolytic agent phenylhydrazine, which was formerly used to treat polycythemia vera; it increases phosphatidylserine externalization, leading to vascular thrombosis [122, 123].

## 6 White Blood Cells

All-trans-retinoic acid (ATRA) is used to treat acute promyelocytic leukemia (APL). ATRA results in the resolution of the coagulopathy and bleeding induced by disseminated intravascular coagulation that is often evident at the time of APL presentation, but paradoxically induces thrombosis in a small number of patients [33]. ATRA promotes the differential regulation of adhesion molecules on acute myeloid leukemia blasts, thus assisting cell migration and extravasation, and promoting localized coagulation [124]. Indeed, ATRA treatment increased the adhesion of APL cells to the endothelium [125].

A similar mechanism is involved in interferon-α (IFN-α) treatment. IFN-α exerts antiviral and antiproliferative effects via stimulation of the cytotoxic activity of a variety of immunocompetent cells [126]. IFN-α induces leukocyte adherence to vessel walls and entrapment in the retinal microcirculation of rats [127]. Furthermore, high plasma levels of C5a, a potent intravascular aggregator of granulocytes, were evidenced in patients with IFN-associated retinopathy [128]. IFN-α-induced disturbances of microcirculation may be an important cause of thrombosis and thrombotic microangiopathy in treated patients [129, 130].

## 7 Coagulation System

### 7.1 Changes in Blood Coagulation Factors

For more than 40 years, hormone replacement therapy (HRT) was promoted to improve the quality of life and reduce the incidence of osteoporosis and coronary heart disease in at-risk humans [131]. However, accumulated data showed that HRT actually increased cardiovascular risks. The risk of VTE is increased twofold, and the risk of stroke by 50 % [131]. The risk of early MI is also increased and in the long run there is no protective effect against coronary heart disease.

The risk of VTE associated with exogenous estrogens involves activation of blood coagulation attributed to an imbalance between increased levels of coagulation factors and decreased levels of coagulation inhibitors. Plasma levels of coagulation factors are increased in oral contraceptive users [132–135]. In HRT, factor VII levels are higher, but other coagulation factors are probably not affected. Oral contraceptive use can cause an acquired form of resistance to activated protein C (APC resistance) attributed in part to decreased protein S levels [136]. These effects are most pronounced in gestagen-containing contraceptives (third-generation oral contraceptives) [137]. Antithrombin levels are also reduced, although to a lesser extent. Oral HRT impairs all coagulation inhibition pathways, except protein C [131, 135]. Tamoxifen is an antiestrogen used in the treatment of breast cancer. However, it also exerts weak estrogenic effects and reduces antithrombin and protein C levels [138, 139]. Increased risk for thrombosis may also be evident in men treated with exogenous testosterone, and it has been speculated that after testosterone is aromatized to estradiol, there is an increased thrombosis risk in a similar manner to females [140].

Erythropoietin leads to a significant early increase in thrombin-antithrombin III complex concentrations—a

specific indicator of thrombin generation in blood—reflecting the effect of EPO on microcirculatory factors [141]. This leads to an increased risk of thrombosis in EPO-treated patients.

Intravenous immunoglobulin (IVIG) is mainly used as IgG replacement and anti-inflammatory therapy in a variety of acute and chronic autoimmune diseases [142]. Since the first report of thromboembolic complications associated with IVIG [143] the incidence has been estimated to be up to 13 % in autoimmune patients [144]. Some IVIG preparations have been found to be contaminated with activated coagulation factor XI [145]. Since the addition of small amounts of factor XIa to plasma can lead to the production of significant amounts of thrombin, this might be a possible mechanism for the reported thromboembolic events.

Additionally, high levels of antiphospholipid or anticardiolipin antibodies have been detected in some IVIG preparations [145, 146]. The passive administration of antiphospholipid antibodies via IVIG infusion can cause the antiphospholipid syndrome. Induction of antiphospholipid antibodies has also been suggested to be a potential mechanism of infliximab-induced arterial thrombosis [147].

The chemotherapeutic agent L-asparaginase is used to treat acute lymphoblastic leukemia. L-asparaginase inhibits protein synthesis by hydrolysing the amino acid asparagine, which is essential to lymphoid cells [148]. It also impairs the synthesis of the naturally occurring anticoagulant proteins antithrombin, protein C, protein S and plasminogen [33]. Thus, the balance is tilted further toward a prothrombotic tendency after cessation of L-asparaginase therapy as recovery of the coagulant proteins fibrinogen and factor VII takes place earlier than the recovery of anticoagulant proteins. This imbalance can lead to thrombosis, which is a major complication of L-asparaginase therapy.

A slight reduction in antithrombin III and free protein S levels was also demonstrated following the prolonged use of sildenafil [86]. However, in contrast to L-asparaginase, this reduction is not attributed to a direct effect of the drug, but rather to dehydration and possibly venous stasis.

Patients with Cushing's syndrome have long been known to be at a greater risk of thrombosis [33]. This is likely due to the high plasma levels of glucocorticoids. Early studies revealed that prednisone treatment resulted in decreased plasma levels of fibrinogen and plasminogen, and increased levels of prothrombin, antithrombin and vWF [149, 150]. The probable underlying mechanism for the latter changes is up-regulation of vWF-mRNA transcription [151]. In addition, corticosteroids block the reticuloendothelial clearance of clotting factors in the liver, thus increasing their blood levels [152].

Additional drugs can alter coagulation factors, but the mechanism is less well understood. G-CSF can increase markers of coagulation activation, including FVIII levels, thrombin-antithrombin complexes, and prothrombin fragment F1+2 in normal allogeneic stem-cell donors [153, 154]. Patients treated with cyclophosphamide/methotrexate/5-FU chemotherapy have a decrease in protein C and protein S levels, as well as an increase in PAI-1 [155, 156]. 5-FU infusion alone was also associated with a reduction in protein C levels and an increase in fibrinopeptide A, a split product of fibrinogen [157, 158].

Direct activation of the coagulation cascade may result from the use of clotting factor concentrates, such as recombinant factor VIIa (rVIIa) or activated prothrombin complex concentrate, which are used to control acute bleeding [159]. The frequency of thromboembolic events is approximately 7 % [160].

As described above, t-PA may paradoxically cause hypercoagulability after use, mediated by changes in endothelial cells and activation of platelets. Additionally, t-PA has been found to modify the balance between coagulation and anticoagulation factors, which may persist up to 72 h after its administration [48]. This is evident by an increase in thrombin generation and activity and in the levels of thrombin–antithrombin III complex [49, 161], and is accompanied by activation of plasminogen activator inhibitor-1, which suppresses endogenous fibrinolysis [162].

### 7.2 Inhibition of Fibrinolysis

The fibrinolytic system is the definitive weapon against the adverse results of intravascular coagulation. Inhibition of this system might have very dangerous effects. Patients with end-stage renal disease treated with EPO were found to have chronic inflammation, thus promoting the release of thrombin-activatable fibrinolytic inhibitor with an ensuing deficiency in fibrinolytic capacity and eventually thrombosis [163]. Dexamethasone inhibits fibrinolysis by increasing plasma PAI-1 and decreasing tissue plasminogen activity [164].

Two direct inhibitors of fibrinolysis are in general use, ε-aminocaproic acid and tranexamic acid [159]. Their clinical use was associated with thrombotic adverse events including MI and stroke. The risk is highest when the drug is administered to patients with disseminated intravascular coagulation or in combination with clotting factor concentrates, estrogens or ATRA [165].

### 7.3 Release of Tissue Factor

TF has an important role in the initiation of coagulation. Although it is mainly derived from ECs, it can be excreted from fibroblasts, smooth muscle cells, various types of injured cells and monocytes. Heparin-PF4 antibodies can

bind to monocytes, leading to increased expression of IL-8, a pro-inflammatory cytokine, and eventually to synthesis and expression of TF [89, 166, 167].

## 8 Changes in Blood Flow

### 8.1 Vasoconstriction

Serotonin is a potent vasoactive amine with complex actions on cerebral arteries. It induces vasoconstriction of larger cerebral arteries and vasodilatation of small vessels. The vasoconstrictive effects of serotonin are mediated by 5-$HT_2$ receptors on smooth muscle cells. SSRIs, by increasing serotonin blood levels early after administration, have been implicated in vasoconstrictive and ischaemic strokes [168].

Corticosteroids play an important role in the control of vascular smooth muscle tone by potentiating the vasoactive responses to catecholamines via regulation of $Ca^{2+}$ haemostasis and increased $Ca^{2+}$ sensitivity of myofilaments [169]. Cisplatin can cause renal tubular injury leading to hypomagnesaemia due to decreased magnesium absorption [170]. Hypomagnesaemia can potentiate the contractile response of arteries [171].

The herbal supplement ephedra was recently withdrawn from the US market due to a concern that it may present "an unreasonable risk of illness or injury" [3]. Ma huang, an alkaloid of ephedra, increases the availability of catecholamines, stimulating α- and β-adrenergic receptors [172]. This may lead to vasoconstriction and to MI seen in patients taking this supplement [173, 174].

### 8.2 Blood Stasis

Recombinant human EPO administration results in increased erythrocyte mass with augmented blood viscosity and a higher risk of thrombosis [175]. VEGF inhibition leads to overproduction of EPO, which may increase the risk of thrombosis via elevation of haematocrit and blood viscosity [176, 177].

Ethinyl estradiol/desogestrel combined oral contraceptives (OCs) increase haematocrit and blood viscosity [178]. Thus, thromboembolic events in women taking OCs could be partially due to a drop in blood flow, which at the lower shear rates could increase RBC aggregation and clotting.

High-dose IVIG increases blood viscosity, thus causing a hypercoagulable state [179–181]. In particular, IgGs have been postulated to increase viscosity through molecular interactions between proteins. This effect is dose-dependent with an increased susceptibility to thromboembolism in predisposed patients [182].

Sildenafil has both arterio- and venodilating properties in the periphery, causing a reduction in systolic and diastolic blood pressure [183]. This can be explained by increased cGMP levels in vascular smooth muscles. Vascular insufficiency and stasis are major factors causing the initial formation and progression of venous thrombosis [86].

## 9 Limitations

The aim of the current review was to describe and characterize the different mechanisms through which drugs might cause or predispose to thrombosis. Our approach to this issue was to use an extensive search in Pubmed, utilizing very broad search terms ("drug" and "thrombosis"). Nevertheless, it is possible that a number of manuscripts did not fit these criteria, and therefore were not reviewed. Additionally, databases other than Pubmed, such as Google Scholar or ISI Web of Knowledge were not reviewed. Furthermore, it should also be born in mind that some of the reported mechanisms are based on a limited amount of reports, and not on well-controlled clinical trials.

## 10 Conclusions

A pathological hypercoagulable condition can be induced by drugs as a result of a variety of mechanisms, as exemplified in this extensive review. Moreover, one drug can activate several pathways leading to thrombosis, and even antithrombotic drugs, such as heparin or t-PA, can paradoxically lead to thrombosis. Better understanding of the mechanisms by which drugs exert thrombosis may facilitate their safe use in patients, especially those with predisposing risk factors. Awareness of the drugs that are known to induce thrombosis is also important in order to stop their administration in case of a thrombotic event.

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