

The Threat of Thromboembolism

Addressing unmet need in the prevention
of VTE after major orthopaedic surgery

Foreword by Professor Sylvia Haas



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Foreword



**Professor
Sylvia Haas**

From public health scares about the risk of deep vein thrombosis on long-haul flights to high rates of pulmonary embolism in patients recovering from major surgery, venous thromboembolism (VTE) is a serious health issue frequently in the news. In fact, VTE is the third most common cardiovascular disorder after ischaemic heart disease and stroke, and is a significant cause of morbidity and death. Patients undergoing major orthopaedic surgery are at high risk of developing VTE. The cost of treating VTE in these patients is substantial, placing a considerable burden

on healthcare resources, and it is more appropriate to use effective measures to prevent the development of VTE.

Several strategies are available for prevention of VTE, including use of unfractionated heparin, low molecular weight heparins (LMWHs), an indirect Factor Xa inhibitor, a direct thrombin inhibitor and vitamin K antagonists. Despite the widespread availability of these drugs, many patients do not receive sufficient intervention to prevent and treat VTE. The reasons for this are unclear but may include a lack of awareness among clinicians of the true prevalence of VTE, which is often clinically silent. Perhaps the most significant reason for underuse of anticoagulants, however, is concern among physicians about bleeding complications. For instance, because of their narrow therapeutic window and tendency to interact with food and other drugs, patients receiving vitamin K antagonists are prone to severe fluctuations in bleeding and thromboembolic risk if their treatment is not closely monitored. These fluctuations can lead to maximal risk of bleeding and minimal risk of VTE at one extreme, and minimal risk of bleeding and maximal risk of VTE at the other. Regular coagulation monitoring is inconvenient for patients once they have left hospital, leading to suboptimal adherence to their treatment

regimen. Unfractionated heparin, LMWHs and fondaparinux have more predictable pharmacodynamics than vitamin K antagonists but are administered subcutaneously and therefore are inconvenient to use outside hospital. In fact, none of the anticoagulants widely available for use in clinical practice meets the criteria for an 'ideal' anticoagulant.

The shortcomings of currently available anticoagulants have led to a search for a solution that will address the unmet need in VTE prophylaxis. Conventional anticoagulant therapies exert their pharmacological action by indirect interaction with various proteins in the coagulation cascade, but the past decade has seen the development of new compounds that target single points of the coagulation cascade and do not require cofactors for their antithrombotic effect. In particular, oral drugs that directly target Factor Xa, which acts at a pivotal point of the coagulation cascade where the intrinsic and extrinsic pathways meet, have shown promising pharmacokinetics and pharmacodynamics and are undergoing clinical trials.

I hope that you enjoy reading this booklet and find it informative and helpful.

A handwritten signature in black ink, reading "Sylvia Haas". The script is cursive and fluid, with the first name "Sylvia" and last name "Haas" clearly distinguishable.

Sylvia Haas
Munich, Germany

Executive summary

- ◆ Patients who have undergone major orthopaedic surgery are at high risk of venous thromboembolism (VTE), a life-threatening disorder that can lead to increased morbidity and mortality and a reduced quality of life.
- ◆ Waiting for signs and symptoms of VTE to appear before initiating treatment increases the risk of long-term complications.
- ◆ There is therefore a clear need for primary prevention of VTE in patients undergoing major orthopaedic surgery of the lower limb.
- ◆ The use of effective thromboprophylaxis varies widely between countries. Underuse may result from a lack of confidence among physicians in the safety and effectiveness of available anticoagulants.
- ◆ None of the anticoagulants in common use has all of the characteristics of an ideal anticoagulant. A new agent that meets the criteria of an ideal anticoagulant could facilitate adherence to evidence-based recommendations.
- ◆ Targeted searches for novel compounds that inhibit specific points in the coagulation cascade have led to the development of several new anticoagulants.
- ◆ Factor Xa is a key target for effective anticoagulation and Factor Xa inhibitors under development seem to have many of the properties of an ideal anticoagulant.

Introduction

Patients who have undergone major orthopaedic surgery of the lower limb (e.g. total hip or total knee replacement) are at high risk of developing venous thromboembolism (VTE). VTE after major orthopaedic surgery poses a massive burden on healthcare systems and results in long-term increases in morbidity and mortality and a reduced quality of life (QoL). Many patients who do not receive effective thromboprophylaxis will die from the consequences of VTE once they have left hospital. Anticoagulants in current use for the prevention of VTE after major orthopaedic surgery have several drawbacks, and none meets the criteria of an ideal anticoagulant. This has led to the search for new anticoagulants that meet these criteria.

Patients who have undergone major orthopaedic surgery of the lower limb are at high risk of VTE

This booklet discusses the incidence, pathophysiology, and signs and symptoms of VTE in patients who have undergone major orthopaedic surgery of the lower limb, and highlights the unmet need for effective and convenient thromboprophylaxis in these patients. The latest developments in the search for new anticoagulants that have the potential to meet this need are examined.

What is venous thromboembolism (VTE)?

- ◆ A thrombus is a blood clot that consists of platelets, blood cells and fibrin, and forms within blood vessels. Blood clots can adhere to the vessel wall, potentially causing an obstruction to blood flow.
- ◆ Venous thrombosis is the process whereby a thrombus forms within a vein. Deep vein thrombosis (DVT) is the most common type, usually occurring in the deep veins of the leg (Figure 1).¹
- ◆ Thromboembolism occurs when part or all of a thrombus breaks away from a blood vessel wall and this clot (now called an embolus) enters the bloodstream. Emboli are dangerous as they can cause occlusion or obstruction of blood vessels in vital organs.
- ◆ Patients with DVT are at risk of pulmonary embolism (PE), which occurs when emboli travel through the heart to lodge in an artery in the lungs.²
- ◆ DVT and PE are collectively referred to as VTE.

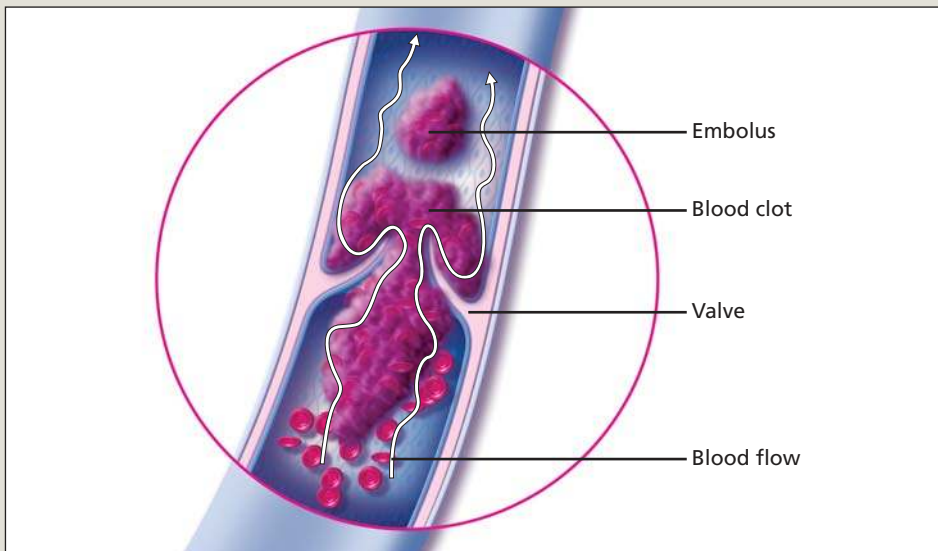


Figure 1. Deep vein thrombosis of the calf, showing the formation of an embolus (detached blood clot).

VTE is a frequent cause of death after major orthopaedic surgery

VTE imposes a large burden on healthcare systems, and is the third most common cardiovascular disorder after ischaemic heart disease and stroke.³ It is a major health problem in the European Union (EU), with over 1 million symptomatic events or deaths every year.⁴ About 12% of venous thromboembolic events in hospital are fatal at the time of the event.^{5,6} However, over the following year, fatalities from hospital-acquired VTEs rise to 29–34%.^{5–7} The number of in-hospital deaths due to VTE is 25 times greater than that from methicillin-resistant *Staphylococcus aureus* (MRSA) and more than five times the total for all hospital-acquired infections.⁸ Furthermore, about 10% of all hospital deaths are attributed to PE.⁵ To put this figure in context, the number of hospital deaths attributed to PE in the UK is greater than the combined total number of deaths from breast cancer, AIDS and traffic accidents.

The number of in-hospital deaths due to VTE is 25 times that from MRSA and more than five times that from hospital-acquired infections

Patients undergoing total hip or total knee replacement surgery are at high risk of developing DVT.⁵ Major orthopaedic surgery is associated with about twice the risk of VTE as major general surgery.⁹ The American College of Chest Physicians (ACCP) reviewed the results of several randomized controlled clinical trials of VTE in patients undergoing major orthopaedic surgery who received no thromboprophylaxis. This review showed that the rates of DVT, as assessed 7–14 days after surgery, were 42–57% in those who underwent total hip replacement and 41–85% in those who underwent total knee replacement. The rates of PE were 0.9–2.8% after total hip replacement and 1.5–10.0% after total knee replacement.⁵

Symptomatic venous thromboembolic events are reported in 1.5–10.0% of patients within 3 months of surgery; most of these events occur after discharge from hospital. The risk of symptomatic VTE after major orthopaedic surgery continues to be higher than that in the general population for at least 2 months after surgery.⁵ However, VTE is often clinically silent, and the first manifestation (which may be a fatal PE) often occurs after discharge from hospital.¹⁰

Major orthopaedic surgery is associated with about twice the risk of VTE as major general surgery

VTE has traditionally been considered a disease of the developed world; however, recent studies of the prevalence of VTE after major orthopaedic surgery in Thailand and Malaysia showed that more than 60% of patients who did not receive preventive therapy developed DVT.^{11,12} These studies suggest that VTE after major orthopaedic surgery is a global healthcare concern.

VTE after major orthopaedic surgery is a global healthcare concern

Cost of VTE after major orthopaedic surgery

The cost burden of VTE after major orthopaedic surgery is substantial. Studies in Europe have shown that the annual cost of treating a venous thromboembolic event after major orthopaedic surgery is approximately €8265.¹³ In the USA, the per-event cost of managing VTE after major orthopaedic surgery has been estimated to be \$17 552. The main cost driver is inpatient care.¹⁴ In addition to the financial burden of VTE, the human cost in terms of suffering, damage to family life because of fatalities, loss of earnings, pain and impaired QoL should be considered.

Need for primary prevention of VTE

There is clearly a need for appropriate steps to be taken to reduce the impact on QoL and cost of VTE after major orthopaedic surgery. It is impractical to

carry out routine screening to identify patients with DVT in order that they may be treated. Hence, primary prevention of VTE is recommended for all patients undergoing major orthopaedic surgery of the lower limb.

Primary prevention of VTE is recommended for all patients undergoing major orthopaedic surgery of the lower limb

Pathophysiology of VTE

Over 150 years ago, Virchow postulated conditions that predispose to thrombus formation.¹⁵ The development and propagation of a thrombus depend on the presence of abnormalities in blood flow, the blood vessel wall and blood clotting components. These factors are known collectively as Virchow's triad (Figure 2).¹⁶

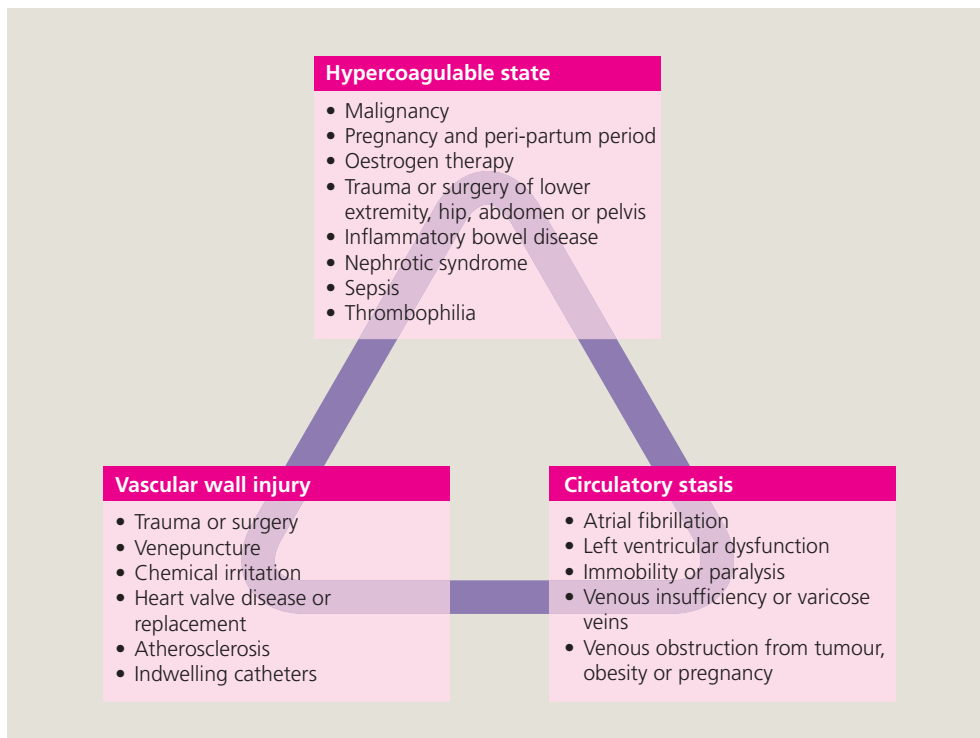


Figure 2. Virchow's triad, showing the interplay between abnormalities of blood flow (circulatory stasis), the blood vessel wall (vascular wall injury) and blood clotting components (hypercoagulable state) in the development of venous thromboembolism.

Table 1. Risk factors for venous thromboembolism.

Predisposing risk factors
◆ History of VTE
◆ Inherited or acquired thrombophilia
◆ Advanced age (exponential increase in risk from the age of 60 years)
◆ Cancer (can also be an exposing risk factor)
◆ Obesity
◆ Pregnancy and the postpartum period
◆ Oestrogen-containing oral contraception or hormone replacement therapy
◆ Immobility or paresis
◆ Myeloproliferative disorders
◆ Nephrotic syndrome
◆ Inflammatory bowel disease (can also be an exposing risk factor)
◆ Chronic heart failure
◆ Varicose veins
Exposing risk factors
◆ Surgery
◆ Trauma
◆ Acute medical illness
◆ Acute heart failure (NYHA classification III and IV)
◆ Acute respiratory failure
◆ Cancer (can also be a predisposing risk factor)
◆ Inflammatory bowel disease (can also be a predisposing risk factor)
◆ Central venous catheterization
NYHA, New York Heart Association; VTE, venous thromboembolism. Information taken from Geerts <i>et al.</i> (2004). ⁵

In light of current medical knowledge, the components of the triad can be further defined:^{17,18}

- ◆ blood flow – abnormalities of haemorheology and turbulence at branch points and narrowed vessels
- ◆ vessel walls – abnormalities in the endothelium, such as atherosclerotic processes leading to inflammation
- ◆ blood clotting components – abnormalities in platelet function and in the coagulation and fibrinolytic pathways.

Risk factors for VTE

There are several factors that contribute to an increased risk of VTE. These can be divided into predisposing risk factors (i.e. a patient's characteristics) and exposing risk factors (i.e. some medical conditions, acute trauma and surgical intervention) (Table 1). Major orthopaedic surgery is an exposing risk factor, with the VTE risk being about twice that associated with major general surgery.⁹

Major orthopaedic surgery is a significant exposing risk factor for VTE

The high risk of VTE associated with major orthopaedic surgery may be due to venous damage and associated increased procoagulant activity (i.e. increased thrombin generation). The advanced age of many patients undergoing such surgery, as well as the reduction in mobility after surgery, also contribute to the increased risk.

Difficulties in diagnosing VTE

Deep vein thrombosis

The classic clinical features of DVT include:

- ◆ pain in the calf
- ◆ unilateral oedema
- ◆ skin discolouration of the affected extremity.¹⁹

Sometimes, it is also possible to discern superficial venous dilation. However, these signs and symptoms can occur in other conditions and therefore have a low predictive value for diagnosing DVT.¹⁹ A wide range of conditions, such as cellulitis, Baker's cyst and haematoma, in which leg swelling is common, should therefore be considered in the differential diagnosis of symptomatic DVT. It should also be noted that DVT is a silent condition in as many as 80% of cases.

There are several methods available for identifying a thrombus in patients with suspected DVT. Clinical judgement continues to be an important factor; however, an objective imaging technique must be used to confirm or rule out the presence of DVT in patients at high risk of VTE. These methods have several drawbacks.

Until recently, the 'gold standard' was contrast venography, and this is still the method most commonly used to diagnose DVT in orthopaedic patients participating in randomized clinical trials of thromboprophylaxis. However, it is not practical to use on a large scale, because it is invasive and may be associated with adverse reactions to the contrast medium. Compression ultrasonography is the most widely used method in clinical practice for evaluating patients with suspected DVT, but it too has limitations. Its accuracy depends on the operator and it is not accurate in detecting DVT of the pelvic vessels or the small veins of the calf. It may not detect DVT in the presence of

Table 2. Wells' clinical prediction tool for deep vein thrombosis.

Clinical feature	Points
Active cancer (treatment within last 6 months, or palliation)	1
Paralysis, paresis or immobilization of lower extremity	1
Bedridden for > 3 days or major surgery within last 12 weeks	1
Localized tenderness along distribution of deep veins	1
Swelling of entire leg	1
Unilateral calf swelling > 3 cm	1
Unilateral pitting oedema	1
Collateral superficial veins	1
Alternative diagnosis as likely or more likely than DVT	-2
Risk score interpretation (probability of DVT): ≥ 3 , high probability (75%); 1–2, moderate probability (17%); ≤ 1 , low probability (3%). DVT, deep vein thrombosis. Adapted with permission from Wells <i>et al.</i> (1997). ²⁰	

obesity or significant oedema, and it does not distinguish between an old clot and a fresh thrombus. Nevertheless, its accuracy is improved when it is used in combination with a clinical probability score (a tool that quantifies the contributions made by components of the history, physical examination and basic laboratory results towards the diagnosis in an individual patient). The most commonly used clinical probability score for DVT has been described by Wells *et al.* (Table 2).²⁰

Pulmonary embolism

The diagnostic evaluation for PE should begin with a careful clinical examination and an assessment of the likelihood that the patient has suffered PE, using a clinical probability score such as described by Wells *et al.* (Table 3).²¹

Table 3. Wells' clinical prediction tool for pulmonary embolism.

Clinical feature	Points
Clinical signs and symptoms of DVT	3
Other diagnosis less likely than PE	3
Heart beat > 100 beats per minute	1.5
Immobilization or surgery within last 4 weeks	1.5
Previous DVT or PE	1.5
Haemoptysis	1
Malignancy	1
Risk score interpretation (probability of DVT): > 6, high probability (78%); 2–6, moderate probability (28%); ≤ 2, low probability (3%). DVT, deep vein thrombosis; PE, pulmonary embolism. Adapted with permission from Wells <i>et al.</i> (2000). ²¹	

Among the imaging techniques used, the ventilation–perfusion scan has for many decades been the first-line study in patients with suspected PE.¹⁹ A ventilation–perfusion scan indicating a high probability of PE provides sufficient evidence for the initiation of treatment. It should be noted, however, that a scan indicating a low probability of PE does not rule out the condition.²² Helical computed tomography has a high sensitivity and specificity for detecting large PEs, but is generally unable to detect small PEs.

Primary prevention is key to managing VTE after major orthopaedic surgery of the lower limb

As the methods for diagnosis of DVT and PE have limitations, it is more appropriate to use thromboprophylaxis to prevent VTE after major orthopaedic surgery than to wait until symptoms of DVT develop before administering treatment.

Need for thromboprophylaxis after major orthopaedic surgery

Randomized controlled clinical trials performed over the past 30 years provide irrefutable evidence that thromboprophylaxis reduces the otherwise high risk of VTE in patients undergoing major orthopaedic surgery.⁵ Waiting for signs and symptoms of VTE to appear before initiating treatment increases the risk of serious thromboembolic events that may lead to long-term sequelae.

Waiting for signs and symptoms of VTE to appear before initiating treatment increases the risk of serious complications

Long-term consequences of VTE

Post-thrombotic syndrome

Approximately 20–50% of patients who develop DVT will go on to develop post-thrombotic syndrome (PTS).²³ Clinical signs and symptoms of this syndrome include chronic pain, swelling, oedema, discolouration, heaviness, cramps, itching, tingling and, in severe cases, venous ulceration and lipodermatosclerosis of the affected limb.²³

The pathophysiology of PTS is not well understood. Most probably, the presence of an acute thrombus, the release of associated mediators of inflammation and the process of vein recanalization in the weeks following DVT-induced damage to venous valves lead to valvular incompetence. It has been suggested that valvular incompetence is associated with the clinical manifestations of PTS.²⁴

PTS has a measurable adverse impact on QoL and the cost of its management is substantial.²⁴ It remains poorly understood, difficult to diagnose and under-recognized. Progression to PTS is not reliably prevented if antithrombotic treatment is initiated after DVT is diagnosed; therefore, it is more appropriate to administer prophylaxis to prevent the formation of DVT.²⁵

 **Post-thrombotic syndrome has a negative impact on quality of life**

Chronic thromboembolic pulmonary hypertension

The embolic hypothesis states that single or recurrent PE can lead to the development of chronic thromboembolic pulmonary hypertension.²⁶ This disorder is characterized by progressive exertional dyspnoea and exercise intolerance. In many cases, the only finding on physical examination is an accentuation of the pulmonic component of the second heart sound, which may be subtle and easily overlooked. The symptoms of chronic thromboembolic pulmonary hypertension may therefore be attributed to other cardiopulmonary disorders. Later in the course of the disorder, a compromised right ventricle may lead to chest pain on exertion, presyncope or syncope.²⁷

Chronic thromboembolic pulmonary hypertension is more common than previously suspected but, because most patients present late in the course of the disease, the early natural history of the disorder is not fully understood.²⁷ Untreated, the rate of survival of patients with chronic thromboembolic pulmonary hypertension is low: one study estimated the survival rate at 5 years for patients with pulmonary artery pressure greater than 40 mmHg at the time of diagnosis to be 30%.²⁸

 **Chronic thromboembolic pulmonary hypertension results in significant morbidity and mortality**

Because chronic thromboembolic pulmonary hypertension is difficult to diagnose and results in significant morbidity and mortality, it is recommended that patients undergoing major orthopaedic surgery receive appropriate prophylaxis to prevent the development of DVT and associated complications.

Current strategies for thromboprophylaxis

Methods of VTE prophylaxis can be divided into two categories: mechanical and pharmaceutical. Guidelines developed by the ACCP in 2004 recommend the routine use of anticoagulants for thromboprophylaxis for surgical patients at highest risk of VTE (e.g. those undergoing major orthopaedic surgery). These guidelines are considered by many to be the 'gold standard' for thromboprophylaxis. They also state that mechanical methods of thromboprophylaxis should be used primarily in patients who are at high risk of bleeding or as an adjunct to anticoagulant-based thromboprophylaxis.⁵

Anticoagulants should be used routinely for VTE prophylaxis after major orthopaedic surgery

Mechanical methods of thromboprophylaxis include graduated compression stockings, intermittent pneumatic compression devices and the venous foot pump. All increase venous outflow and/or reduce stasis within the leg veins.⁵ Mechanical methods have been studied much less intensively than anticoagulant-based options, but they appear to be generally less effective than anticoagulants for the prevention of DVT and have not been shown to reduce the risk of death or PE.⁵ Furthermore, mechanical thromboprophylaxis cannot be used to regulate postoperative changes in haemostasis, which can continue after the patient has left hospital.

Understanding the coagulation cascade

To understand the role of anticoagulants in preventing VTE, the normal physiological response that stops blood loss from damaged blood vessels (haemostasis) needs to be considered. Normally, injury to a blood vessel results in:

- ◆ vasoconstriction to reduce blood flow

- ◆ platelet aggregation (primary haemostasis) – platelets circulating in the blood contact exposed collagen at the site of damage, where they adhere, activate and aggregate
- ◆ activation of the coagulation cascade (secondary haemostasis), during which a stable blood clot forms.^{29,30}

Coagulation is a complex protease cascade involving about thirty interacting proteins (Figure 3). It results in the formation of thrombin (Factor IIa), which catalyses the conversion of fibrinogen, a soluble protein, to insoluble fibrin strands, which form a stable clot in conjunction with platelets.

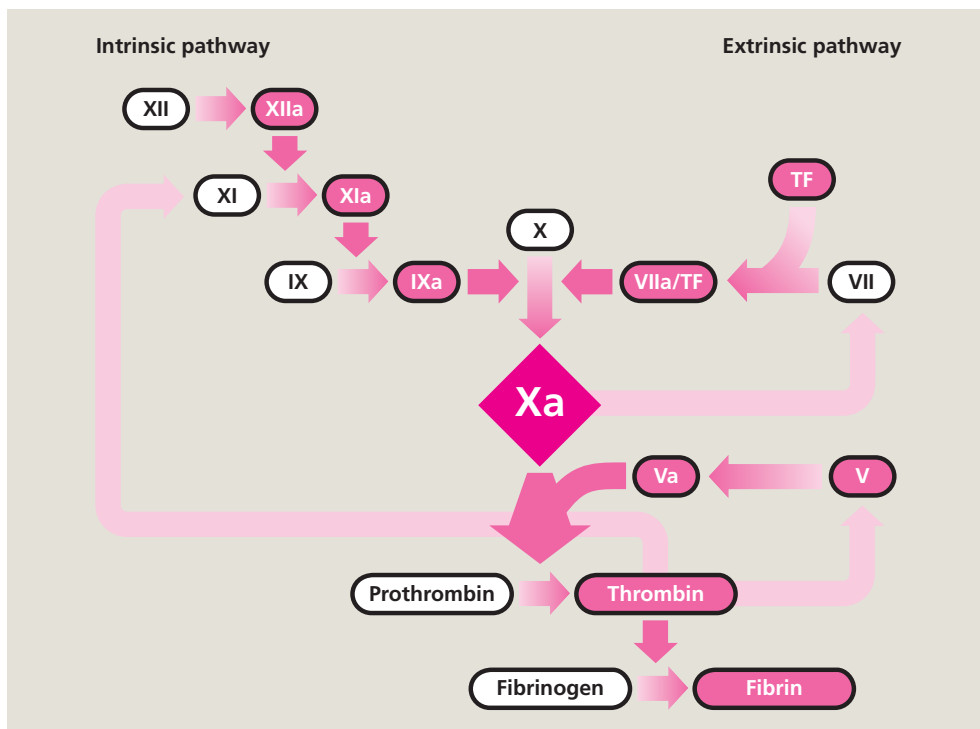


Figure 3. The coagulation cascade: Factor Xa is at the start of the common pathway leading to clot formation and therefore has a central role in the cascade.

The coagulation cascade consists of two distinct parts: the extrinsic and intrinsic pathways, both of which lead to thrombin formation. The extrinsic pathway is the primary pathway for the initiation of coagulation.³¹ The intrinsic pathway leads to the successive activation of Factors IX and X.³² Activated Factor X (Factor Xa) plays a central role in the coagulation cascade owing to its position at the start of the common pathway (Figure 3).³³

Factor Xa plays a central role in the coagulation cascade owing to its position at the start of the common pathway

The coagulation cascade is triggered by the release of tissue factor (TF) from damaged cells.³¹ Factor Xa, with activated Factor V (Factor Va) as a cofactor, propagates the coagulation cascade by catalysing the conversion of prothrombin (Factor II) to thrombin. Factor Xa is the primary site of amplification in the coagulation cascade: one molecule of Factor Xa catalyses the formation of approximately 1000 thrombin molecules.³³

In the final step of the coagulation cascade, thrombin triggers the conversion of fibrinogen to fibrin, and the activation of Factor XIII, which stabilizes the clot by cross-linking the fibrin network.

Current anticoagulants

The four main types of anticoagulants in mainstream use for thromboprophylaxis are unfractionated heparin, LMWHs, fondaparinux and, in the USA, vitamin K antagonists (i.e. warfarin, phenprocoumon and acenocoumarol).*

Unfractionated heparin and low-molecular weight heparins

Heparin and its derivatives target multiple sites in the coagulation cascade and have a rapid anticoagulant effect. They bind to a plasma cofactor,

*In Europe, warfarin is only rarely used for thromboprophylaxis in patients undergoing major orthopaedic surgery of the lower limb; however, it is the most widely used vitamin K antagonist. As such, it is used henceforth in this book as representative of the vitamin K antagonists.

antithrombin, and inactivate several coagulation enzymes, including thrombin and Factors Xa, IXa, XIa and XIIa.³⁴ Thrombin and Factor Xa are most responsive to inhibition.³⁴ Interestingly, the efficacy of heparin-based anticoagulants increases as selectivity for Factor Xa increases (i.e. LMWHs are superior to unfractionated heparin, and fondaparinux is superior to LMWHs).³³

Heparin also interferes with platelet function. This may contribute to its haemorrhagic effects.³⁴ Importantly, because heparin and LMWHs are administered by subcutaneous injection, their use after the patient has left hospital requires patient training or assistance by an experienced health practitioner.

Fondaparinux

Fondaparinux is a recently developed synthetic, indirect, selective inhibitor of Factor Xa, with a structure based on the natural pentasaccharide contained within heparin and LMWHs. It potentiates the rate of neutralization of Factor Xa by antithrombin. However, fondaparinux is unable to inhibit Factor Xa bound in the prothrombinase complex and thus cannot provide complete inhibition of all Factor Xa.¹⁶ Furthermore, there have been rare reports of severe thrombocytopenia associated with the use of fondaparinux.³⁵ Because fondaparinux is administered by subcutaneous injection, duration of prophylaxis is limited.

Warfarin

Warfarin is a vitamin K antagonist. Vitamin K is essential for the synthesis of prothrombin and Factors VII, IX and X in the liver.³⁶ Because warfarin is involved in the synthesis of these factors, onset and offset of its antithrombotic and anticoagulant effects are slow and largely dependent on the half-lives of these coagulation factors.³⁶ Warfarin also inhibits the carboxylation of the natural anticoagulants, protein C and protein S. These proteins have short half-lives; hence, warfarin has the potential to exert a procoagulant effect,³⁶ particularly in the initial phase of administration.

Warfarin has a narrow therapeutic window and interacts with food and other drugs. Frequent coagulation monitoring and dose adjustments are therefore required for patients receiving warfarin.³⁶ In a prospective study of almost 19 000 patients admitted to hospital, nearly 11% (129/1225) of admissions due to adverse drug reactions were patients receiving warfarin.³⁷

Current use of thromboprophylaxis

In 2004, the ACCP published evidence-based consensus guidelines for the prevention of VTE.⁵ Despite strong evidence for the need to prevent VTE, in many countries there is still a low rate of thromboprophylaxis as recommended by these guidelines. A recent study involving 358 hospitals in 32 countries found that, of a total of 19 842 surgical patients who were at risk of VTE, only 60% received ACCP-recommended thromboprophylaxis.³⁸ The proportion of at-risk surgical patients receiving such thromboprophylaxis varied widely between countries, from 0.2% to 92%. In the EU countries included in the study, the proportion of at-risk surgical patients receiving ACCP-recommended thromboprophylaxis varied from 59% (Portugal) to 92% (Germany) (Table 4).

The proportion of at-risk surgical patients receiving ACCP-recommended thromboprophylaxis varies widely between countries

The ACCP recommends VTE prophylaxis for a minimum of 10 days after total hip or total knee replacement (preferably for 28–35 days in patients undergoing total hip replacement). However, a study of over 15 000 patients enrolled in the Global Orthopaedic Registry revealed that although 98% of patients were receiving thromboprophylaxis on the first day after surgery, this was not continued for the minimum recommended period in 26% of patients undergoing total hip replacement and 27% of patients undergoing total knee replacement.³⁹

Reasons for under-use

Clearly, there is evidence that, in some countries, thromboprophylaxis is under-used.⁴⁰ The reasons for this under-use are complex. First, there may be insufficient awareness of the magnitude of the risk because VTE is often

Table 4. Number of at-risk surgical patients receiving ACCP-recommended thromboprophylaxis in some countries of the European Union.

Country	Number of assessable surgical patients	Number of at-risk surgical patients (%)	Number of at-risk surgical patients receiving thromboprophylaxis (%)
France	917	718 (78)	511 (71)
Germany	1210	838 (69)	772 (92)
Greece	947	525 (55)	376 (72)
Hungary	435	253 (58)	219 (87)
Ireland	297	175 (59)	112 (64)
Poland	1092	597 (55)	396 (66)
Portugal	762	525 (69)	310 (59)
Romania	2461	1609 (65)	1011 (63)
Spain	996	738 (74)	605 (82)
UK	2091	1350 (65)	1003 (74)

ACCP, American College of Chest Physicians.
Data taken from Cohen *et al.* (2008).³⁸

clinically silent (80% of DVT cases are subclinical); the first sign of VTE is often a fatal PE occurring after discharge from hospital.⁴¹ Second, physicians' concerns regarding the risk of bleeding associated with anticoagulants play an important part in the decision whether or not to provide thromboprophylaxis. These concerns may result in the use of less effective mechanical methods,⁵ rather than pharmaceutical methods.

A new agent that meets the criteria of an ideal anti-coagulant could facilitate adherence to evidence-based recommendations

Table 5. Characteristics of an ideal anticoagulant.

◆	Once-daily, oral administration
◆	Predictable pharmacokinetic and pharmacodynamic characteristics
◆	Wide therapeutic window
◆	No dose adjustment required
◆	No need for regular coagulation monitoring
◆	No significant interactions with other drugs or food

A lack of confidence among some physicians in the safety and utility of currently available anticoagulants reflects the fact that none of the widely available thromboprophylactic agents has all the characteristics of an ideal anticoagulant (Table 5). A new drug that overcomes the shortcomings of currently available anticoagulants and meets the criteria of an ideal agent could have a significant role in facilitating adherence to evidence-based recommendations regarding the prevention of VTE after major orthopaedic surgery.

New strategies for thromboprophylaxis

It is apparent that none of the anticoagulants in current mainstream use meets the criteria for an ideal anticoagulant. The absence of such an anticoagulant has led to a targeted search for novel compounds that inhibit specific points in the coagulation cascade. These compounds may offer superior safety, efficacy and convenience compared with the current standards of care.

Newly developed anticoagulants can broadly be divided into three categories (Figure 4):⁴²

- ◆ those that interfere with the initiation of coagulation (TF–VIIa complex inhibitors)
- ◆ those that inhibit thrombin activity
- ◆ those that interfere with the propagation of coagulation (indirect and direct inhibitors of Factor Xa or IXa).³¹

TF–VIIa complex inhibitors

The TF–VIIa complex is key to the initiation of coagulation, and therefore potentially an important target.⁴² Inhibitors of TF–VIIa (such as nematode anti-coagulant proteins, TF pathway inhibitors and small molecules that inhibit the active site of Factor VIIa) are in the early stages of development. These inhibitors primarily affect the extrinsic rather than the intrinsic coagulation pathway.

Thrombin inhibitors

Thrombin activity is central to both the intrinsic and extrinsic pathways, and direct thrombin inhibitors are able to inhibit both fibrin-bound and free thrombin. They do not bind to plasma proteins and therefore produce a predictable anticoagulant response. Furthermore, they have the capacity to suppress thrombus growth.

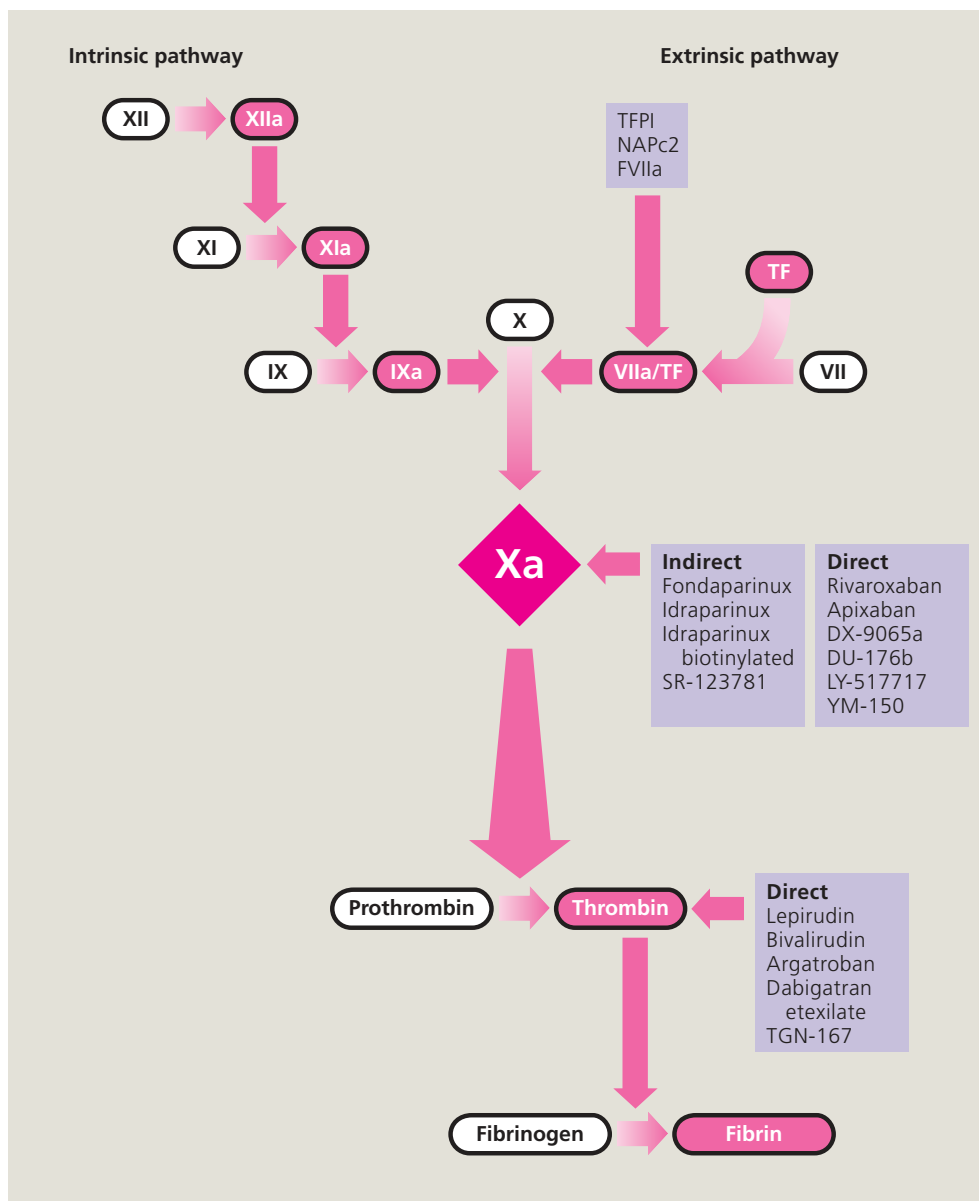


Figure 4. New anticoagulation drugs and their coagulation cascade targets. Adapted from Weitz *et al.* (2004).³¹

Thrombin: a promising target

- ◆ Common to both the extrinsic and intrinsic coagulation pathways
- ◆ Triggers the conversion of fibrinogen to fibrin, resulting in thrombus formation

Several specific inhibitors of thrombin, such as lepirudin, bivalirudin and argatroban, are available for clinical use. However, they require parenteral administration, have limited indications and are expensive.⁴² In addition, it is necessary to monitor coagulation in patients receiving these drugs.⁴² An oral direct thrombin inhibitor, ximelagatran, was discontinued because of severe liver toxicity.

A second oral direct thrombin inhibitor, dabigatran etexilate, has recently received approval from the European Medicines Agency.⁴² Dabigatran etexilate is given once daily in capsule form. Following oral administration, the pro-drug dabigatran etexilate is rapidly converted to its active form, dabigatran.⁴³ It has a rapid onset of action⁴⁴ and, in contrast to other thrombin inhibitors, there are no requirements for routine coagulation monitoring.⁴⁵

It should be noted that thrombin also has a role in anticoagulation and anti-inflammation (via thrombin–thrombomodulin-mediated activation of protein C),³³ which may be disrupted by a thrombin-inhibiting anticoagulant.

Factor Xa inhibitors

The position of Factor X in the coagulation cascade means that it has a critical role in the process of coagulation, making it a very promising target for an anticoagulant. Direct, selective Factor Xa inhibitors should provide effective anticoagulation because Factor Xa is one of only two components of the coagulation cascade common to both the extrinsic and intrinsic coagulation pathways, thrombin being the other one.³³

Factor Xa: a promising target

- ◆ Common to both the extrinsic and intrinsic coagulation pathways
- ◆ Primary site of amplification in the coagulation cascade
- ◆ Only known functions are to promote coagulation and inflammation

The only known functions of Factor Xa are to promote coagulation and inflammation; therefore, disruption of Factor Xa function is less likely to have pleiotropic effects outside coagulation than inhibition of thrombin.³³

Factor Xa is a key target for effective anticoagulation

Inhibition of Factor Xa should achieve effective anticoagulation by inhibiting thrombin generation, while allowing existing thrombin to continue its vital functions in normal haemostasis.³³ Indirect Factor Xa inhibitors require antithrombin as a cofactor and are unable to inhibit Factor Xa bound to the prothrombinase complex. In contrast, direct Factor Xa inhibitors can interact directly with the active centre of the Factor Xa molecule. They do not require cofactors and are able to inhibit both free Factor Xa in plasma and Factor Xa captured in the prothrombinase complex. Direct Factor Xa inhibitors may therefore lead to more complete inhibition of Factor Xa than do indirect Factor Xa inhibitors. It follows from this analysis that direct Factor Xa inhibitors may have many of the properties of an ideal anticoagulant, including oral administration, rapid onset of action, predictable pharmacokinetics and no need for routine coagulation monitoring. The direct Factor Xa inhibitors that are most advanced in clinical development include rivaroxaban and apixaban.⁴²

Direct Factor Xa inhibitors seem to have many of the properties of an ideal anticoagulant

Another advantage of direct Factor Xa inhibitors is that they have a broad therapeutic window (Figure 5). This enables effective anticoagulation to be maintained more easily.³³

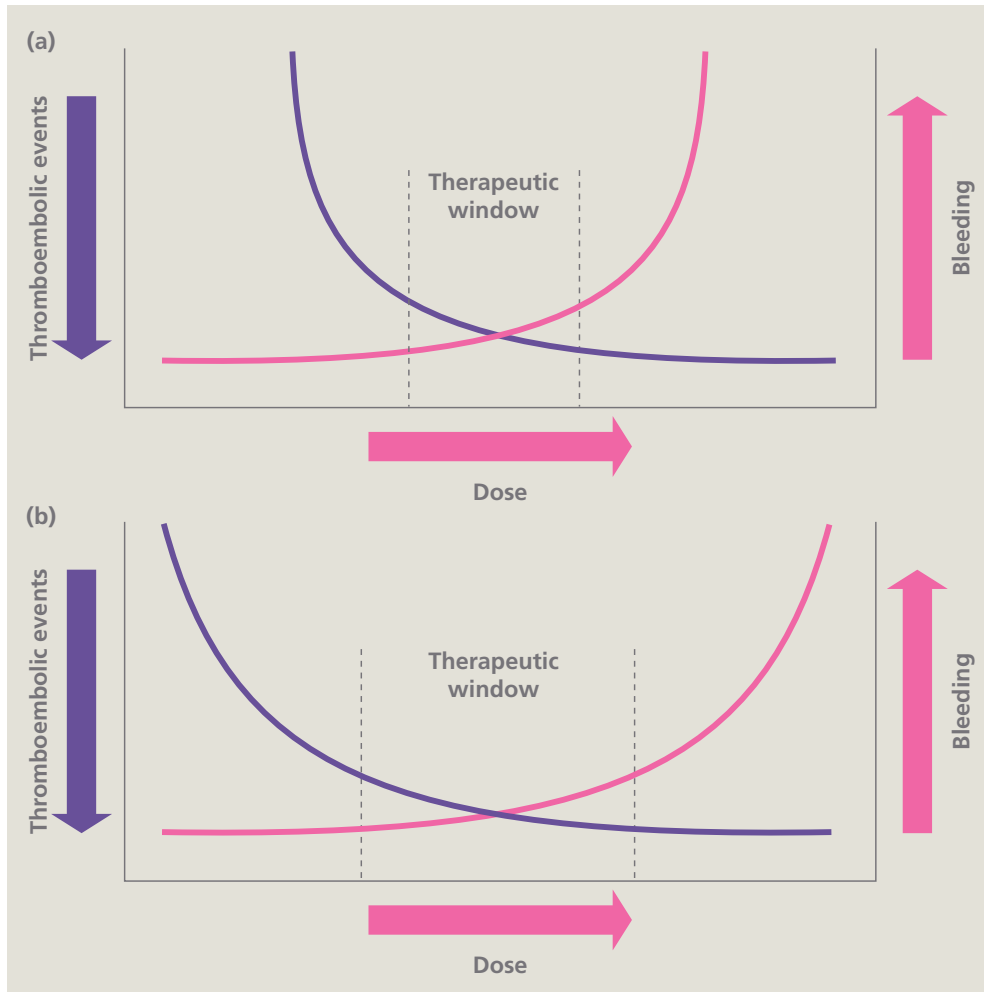


Figure 5. An anticoagulant should ideally have a wide therapeutic window. (a) Vitamin K antagonists have a narrow separation between the dose at which thromboembolic events are significantly reduced (purple line) and the dose at which there is an excessive increased risk of bleeding (pink line). (b) Direct Factor Xa inhibitors that are under development seem to have a wide separation between doses that result in a significant reduction in thromboembolic events (purple line) and those that lead to an excessive increased risk of bleeding (pink line).

Conclusions

VTE after major orthopaedic surgery poses a large burden on healthcare systems, and results in long-term increases in morbidity and mortality and a reduced QoL. DVT and PE are difficult to diagnose, so all patients undergoing major orthopaedic surgery should receive effective thromboprophylaxis to reduce the risk that they will develop VTE.

Anticoagulants in current use for the prevention of VTE after major orthopaedic surgery have several disadvantages. The need for anticoagulants that are convenient for both the patient and the physician has led to the development of novel compounds that target specific points in the coagulation cascade. It is hoped that a new generation of anticoagulants will greatly enhance the prevention of VTE after major orthopaedic surgery.

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