



Pathophysiological Aspects of Coagulation

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SECTION I: NORMAL HAEMOSTASIS

A) Introduction

Haemostasis is a host defence mechanism that protects the integrity of the vascular system after tissue injury. It is responsible for minimising blood loss. It is critical that formation of blood clot in response to a breach in the vascular endothelium occurs rapidly. Systemic activation of the coagulation cascade or extensive local extension of thrombosis resulting in vascular occlusion, however, should not occur. Immediate vasoconstriction of the injured vessel and reflex constriction of adjacent small arteries and arterioles are responsible for an initial slowing of blood flow to the injured area (Fig. 1). The reduced blood flow enables contact activation of platelets and coagulation factors. The vasoactive amines and thromboxane A_2 from platelets and the fibrinopeptides produced during fibrin formation

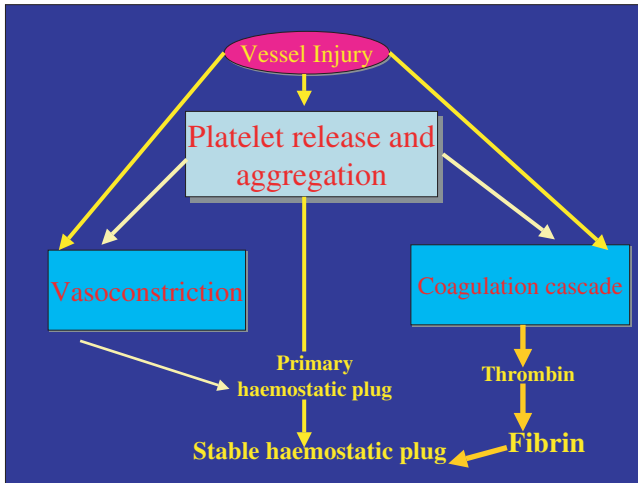


Fig. 1 Scheme of primary haemostatic function.

may also have vasoconstrictive activity.¹ Thrombin generated at the site of injury converts soluble fibrinogen into fibrin and potentiates platelet aggregation and secretion. Thrombin also activates factor XI that amplifies the intrinsic pathway activity. Furthermore, it activates factor XIII that covalently cross-links the fibrin meshwork. A meshwork of fibrin anchors and extends the platelet plug. The fibrin component increases as the fused platelets autolyse, and after a few hours the entire haemostatic plug is transformed into a solid mass of cross-linked fibrin.² During the same time frame, the plug begins to lyse due to the incorporation of plasminogen and tissue plasminogen-activator (t-PA) in the plug, resulting in plasmin generation.³

Role of endothelium and subendothelium

The active role of “endothelial cells” in preserving vascular integrity is well-established. This cell provides the basement membrane, collagen, elastin, and fibronectin of the subendothelial connective tissue. Loss of or damage to the endothelial lining results in both haemorrhage and activation of the coagulation cascade. The endothelial cell has an active role in haemostatic response, including synthesis of tissue factor, prostacyclin (Fig. 3), von Willebrand factor (vWF),

Table 1. Platelet Granule Content and Their Biological Functions

Location	Compound	Function
Alpha granule	Platelet factor 4	Neutralises heparin effect
	α -thromboglobulin	Promotes fibroblast chemotaxis
	Platelet-derived growth factor	Mitogen for fibroblast; chemotaxis for neutrophils, fibroblasts, and smooth muscle
	von Willebrand factor	Adhesion molecule; carrier for factor VIII, protecting it from proteolysis
	Thrombospondin	Promotes platelet-platelet interaction
Dense granule	Fibronectin	Adhesion of platelets and fibroblasts
	ADP	Aggregation of platelets
	ATP	Source of ATP for energy
	Serotonin	Vasoconstriction
	Calcium	Coagulation; platelet function

plasminogen activator, anti-thrombin III, and thrombomodulin (the surface protein responsible for activation of protein C). Furthermore, the endothelium provides agents that are vital to both platelet reaction and blood coagulation.⁴

Role of platelets

Platelets are derived from the cytoplasm of bone marrow megakaryocytes and are the smallest of blood cells. They are disc shaped, anucleate with a relatively complex internal structure, which reflects their specific haemostatic function (Fig. 2). Normal platelet count is $150\text{--}400 \times 10^9/\text{l}$.

The contents of both alpha and dense granules (Table 1) may be released via a system of surface-connecting tubules, during platelet activation.

Platelet reactions and primary haemostatic plug formation

Initial adherence of platelets to exposed connective tissue (Fig. 1) follows endothelial lining breakage. Biochemical pathways for the metabolism of arachidonic acid (Fig. 3) are contained in both platelets and vascular endothelial cells.⁵ The platelet adhesion is

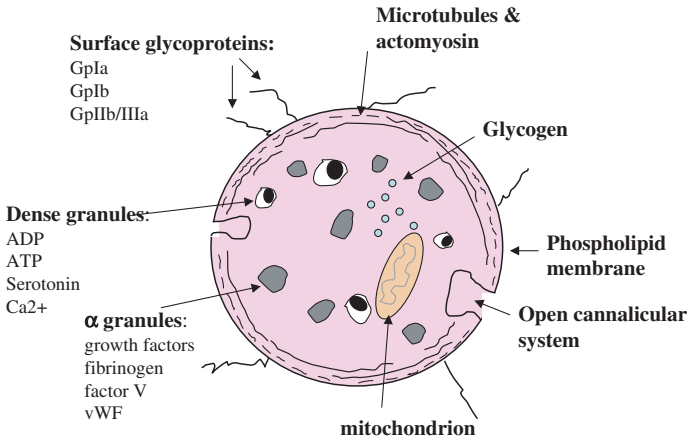


Fig. 2 Platelet electron microscopic ultrastructure (EM × 30,000).

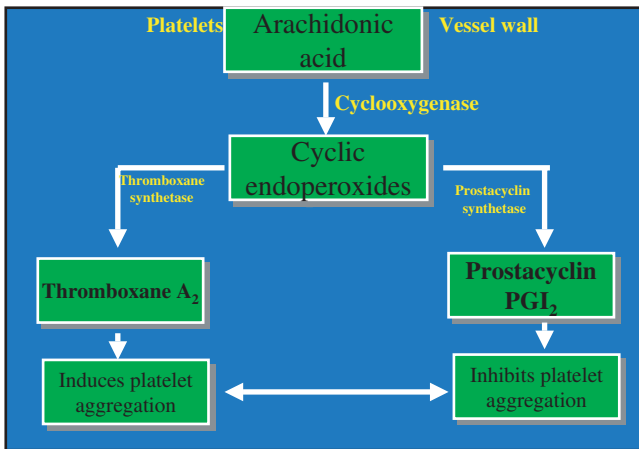


Fig. 3 Arachidonic acid metabolism in vascular endothelium and platelets.

potentiated by von Willebrand factor (vWF).^{6,7} Collagen and thrombin generated at the site of injury cause the adherent platelets to release their granules, including ADP, serotonin, fibrinogen, lysosomal enzymes, and heparin-neutralising factor (PF-4). Collagen and thrombin activate platelet prostaglandin synthesis, leading to the formation of thromboxane A₂, which potentiates platelet release reactions and platelet aggregation. It is also a powerful vasoconstrictor.

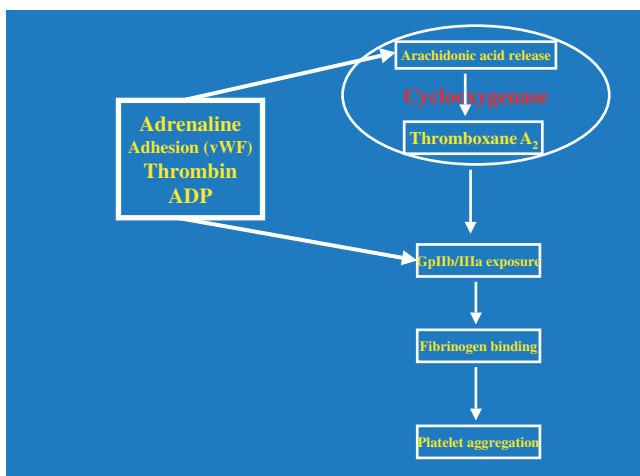


Fig. 4 Main pathways of platelet activation.

Released ADP causes platelets to swell and aggregate (Fig. 4). Additional platelets from the circulating blood are drawn to the area of injury, resulting in growth of the haemostatic plug that soon covers the exposed connective tissue. Released platelet granule enzymes, ADP, and thromboxane A₂ may all contribute to the consolidation of the accumulated platelet plug. Prostacyclin, produced by endothelial and smooth muscle cells in the vessel wall adjacent to the area of damage, is important in limiting the extent of the initial platelet plug. This unstable plug produced is sufficient to provide temporary control of bleeding. Definitive haemostasis is achieved with fibrin formation by blood coagulation and with platelet-induced clot retraction.^{5,7,8}

Role of circulating proteins with procoagulant, anti-coagulant, and fibrinolytic activities

Coagulation

The coagulation cascade involves sequential activation of a number of blood clotting factors, resulting in the formation of fibrin. Figures 5 and 6 show how the coagulation cascade operates *in vitro* (Fig. 5) with the classical waterfall hypothesis, whereas (Fig. 6) is thought to represent the *in vivo* process.

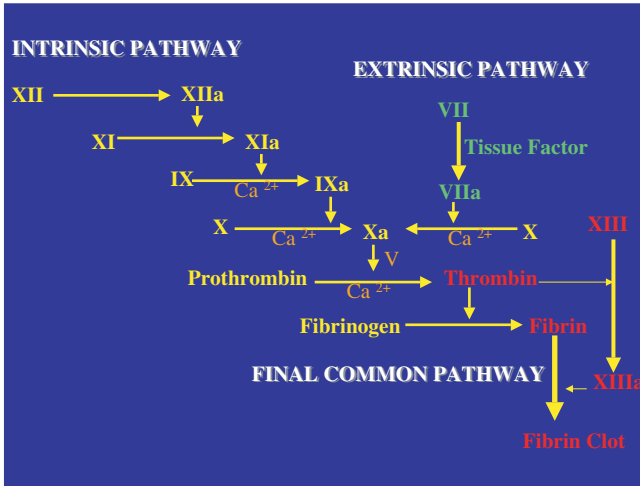


Fig. 5 Classical waterfall hypothesis of coagulation.

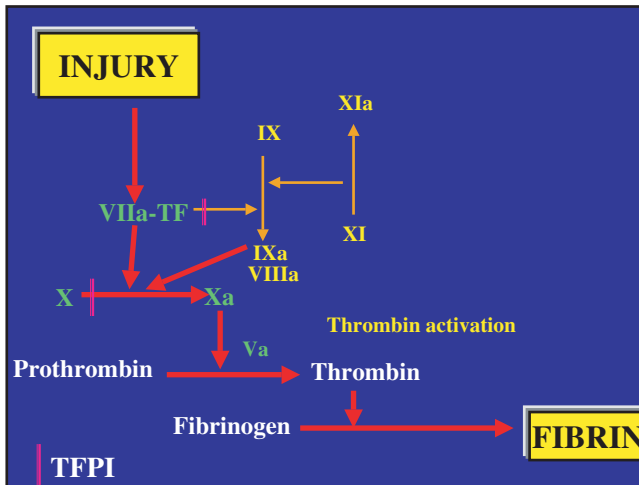


Fig. 6 The revised hypothesis of coagulation.

Conventionally, the coagulation cascade has been divided into intrinsic, extrinsic, and final common pathways. The **intrinsic pathway** ensues when the negatively charged subendothelium activates factor XII which, in turn, leads to activation of factor XI that activates

factor IX. In association with calcium and with factor VIII as a cofactor, activated factor IX activates factor X on the membrane surface provided by platelet phospholipid (platelet factor 3). The intrinsic pathway is mediated via the contact factor system; following limited activation, factor XII activates prekallikrein to kallikrein, which in turn, activates factor XII. High molecular weight kiniogen (HMWK) is a non-enzymatic accelerator of these interactions. In the **extrinsic pathway** tissue factor activates factor VII, which in turn, activates factor X both directly and indirectly via activating factor IX. The **final common pathway** is concluded when activated factor X, in association with cofactor factor V on phospholipid surface and calcium, converts prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin.^{9,10}

***In vivo* versus *in vitro* coagulation: The role of factor VII-tissue factor complex (TF-VII)**

Current evidence indicates that the dominant pathway for blood coagulation is via factor VII and TF, and that the contact system activation plays a little role, if any, *in vivo* coagulation. Mainly, factor VII causes activation of factor IX.^{11,12} Factor XI *in vivo* is activated directly by thrombin and is important only at sites of major trauma or operation.^{11–13}

Therefore, the classical waterfall hypothesis described above, fails to represent accurately *in vivo* haemostasis. This is may be demonstrated by considering the following issues. First, although patients with congenital deficiency of factor XII, prekallikrein, or HMWK have extremely prolonged aPTTs, they do not have any clinical bleeding manifestations. This clinical observation indicates that these proteins are probably not important components of blood coagulation *in vivo*. Similarly, factor XI deficiency is not always associated with bleeding and, therefore, its role is unclear. Patients with factor VII deficiency, however, bleed abnormally, although the intrinsic pathway is largely intact. Third, factor VII-tissue factor is known to activate not only factor X, but also factor IX. In the classical pathway this activation is not required. Tissue factor is a natural constituent of many non-vascular cells. Tissue factor on such cells is able to initiate blood coagulation, supporting a more central role for the TF-VII complex.¹⁴

The revised hypothesis of coagulation

Based on the findings of the direct activation of factor IX by factor VII-tissue factor the coagulation cascade was revised, with factor VII-TF and factor X central to the model. This model also takes into account the newly discovered feedback inhibition of factor VIIa-tissue factor produced by tissue factor pathway inhibitor (TFPI).^{14,15}

The role of vitamin K in blood coagulation

In addition to protein C, protein S, and protein Z coagulation factors II, VII, IX, and X are dependent on vitamin K for their biological activation and, therefore, normal function. These are synthesised in the liver in inactive forms that cannot bind calcium ions. This ability is conferred by a post-translational modification that involves gamma carboxylation of glutamic acid residues. Vitamin K *in vivo* continuously cycles between three forms: vitamin K quinone, vitamin K hydroquinone, and vitamin K epoxide. The gamma carboxylation reaction is coupled to the conversion of vitamin K hydroquinone to the epoxide form. Therefore, in vitamin K deficiency, gamma carboxylation fails and non-carboxylated forms of factors II, VII, IX, X and protein C, protein S, and protein Z are released into the circulation. Although they are immunologically identical to the normal proteins, these proteins induced by vitamin K absence or antagonism (PIVKAs) cannot bind calcium ions. They are non-biologically competent as they cannot bind to phospholipid surfaces.¹⁶

Fibrinolysis

Like coagulation, fibrinolysis is a normal haemostatic response to vascular injury. The deposition of fibrin is coupled by activation of the fibrinolytic pathway (Fig. 7). Fibrinogen and fibrin are substrates for the proteolytic action of plasmin. Unlike the highly specific action of thrombin on fibrinogen, which results in the cleavage of only two pairs of small fibrinopeptides, A and B, plasmin cleaves fibrinogen and fibrin at multiple sites. This produces a variety of split (degradation) products. Plasmin is normally present in its inactive zymogen form, plasminogen, in blood, urine, and tissue fluids. Major activation of the fibrinolytic system follows the release

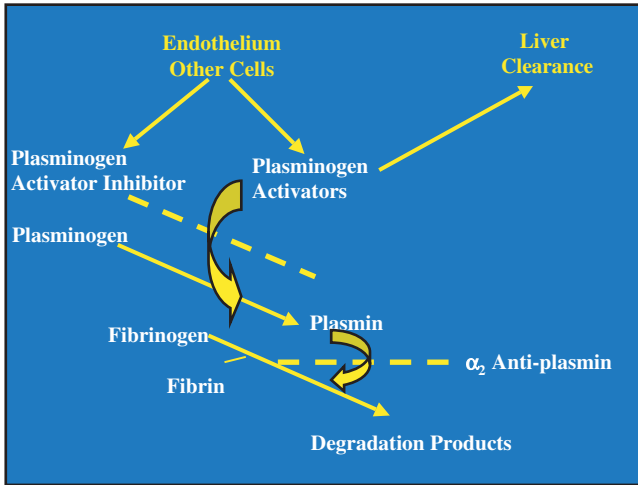


Fig. 7 Fibrinolysis.

of tissue plasminogen activator (t-PA) from endothelial cells. t-PA is a serine protease that binds to fibrin. This enhances its capacity to convert thrombus-bound plasminogen into plasmin. This fibrin dependence of t-PA action strongly localises plasmin generation by t-PA, to the fibrin clot. Release of t-PA occurs after stimuli, such as, trauma, exercise, or emotional stress. Activated protein C stimulates fibrinolysis by destroying plasmin inhibitors of t-PA. Therapeutic t-PA and urokinase are produced by recombinant DNA technology, while the fibrinolytic agent, streptokinase, is a peptide produced by haemolytic streptococci. It forms a complex with plasminogen, which converts other plasminogen molecules to plasmin. Plasmin has a wider range of activity than thrombin, hydrolysing both arginine and lysine peptide bonds in a wider range of substrates. Tissue plasminogen activator is inactivated by plasminogen activator inhibitor-1 (PAI-1). Circulating plasmin is inactivated by potent inhibitors α_2 -antiplasmin and α_2 -macroglobulin. This prevents widespread destruction of fibrinogen and other coagulation factors.¹¹ In addition, thrombin activatable fibrinolysis inhibitor (TAFI) plays a role in limiting the fibrinolytic activity locally. Activated protein C stimulates the release of TAFI.¹²

B) Haemostatic regulation

Natural anti-coagulants

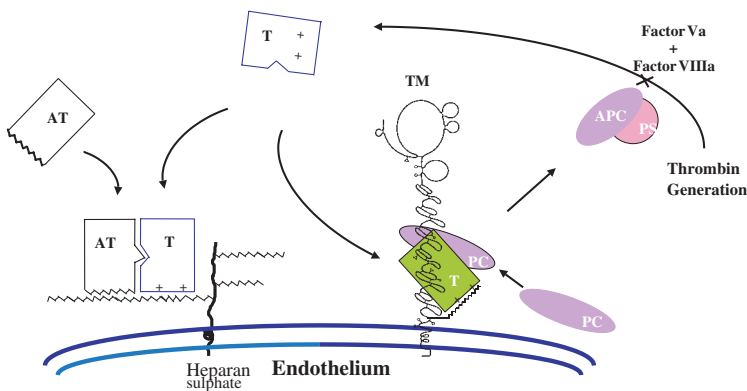
The prevention of unlimited thrombin generation and, therefore, unchecked thrombosis is catalysed by the important, naturally occurring anti-coagulant proteins. These include:

(1) *Anti-thrombin:*

Anti-thrombin (AT) is a single-chain glycoprotein synthesised in the liver and the endothelium. AT is the main physiological inhibitor of activated coagulation serine proteases (Figs. 8 and 9). It inactivates thrombin, factor Xa, IXa, and XIa. Its activity is greatly accelerated (1000- to 2000-fold) by therapeutic heparin and, therefore, it is sometimes known as heparin co-factor I.¹⁷

(2) *Heparin co-factor II:*

This is also a single chain glycoprotein and is of liver origin. It complexes with thrombin in a 1:1 ratio, thereby inactivating it. In contrast to AT, heparin co-factor II is specific for thrombin, having no inhibitory activity against the other serine proteases. Its activity is also greatly amplified, 1000-fold, by therapeutic heparin.



Key: AT, anti-thrombin; T, thrombin; TM, thrombomodulin; PC, protein C; PS, protein S

Fig. 8 Natural anti-coagulant pathways that inhibit thrombin generation.

(3) *Protein C and Protein S pathway:*

Protein C is a vitamin K dependent factor that plays a dual role in haemostasis by inhibiting blood coagulation and stimulating fibrinolysis. Recently, it was shown to have a major anti-inflammatory role. Upon activation by thrombin in the presence of its endothelial cofactor, thrombomodulin (TM) and protein C endothelial receptor (EPCR), activated protein C inhibits the coagulation cascade by inactivating activated factors VIII and V.¹⁸ This reduces the rate of thrombin generation (Figs. 9 and 11). Protein S is required as a non-enzymatic cofactor for protein C activity (Figs. 8 and 10). Thrombomodulin is present in tight association with vascular endothelium. Complexed thrombin

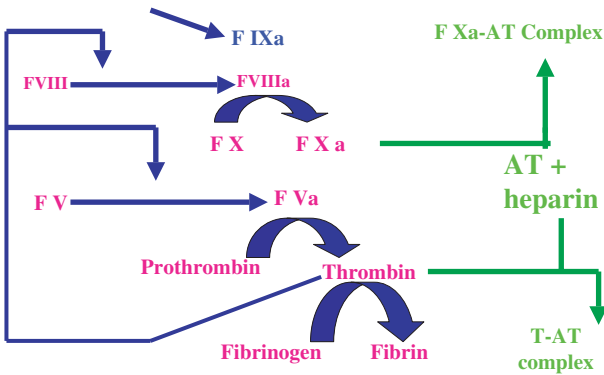


Fig. 9 Anti-thrombin pathway.

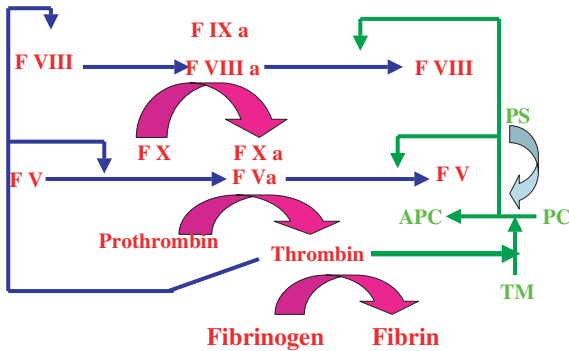


Fig. 10 PC/PS pathway.

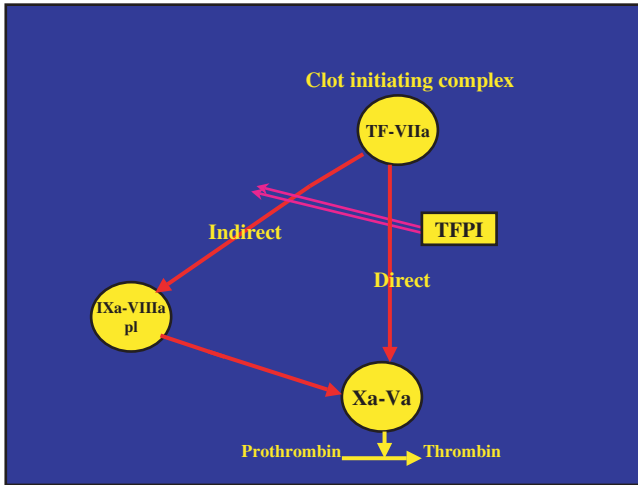


Fig. 11 TFPI.

activates protein C several thousand times faster than unbound thrombin, but does not clot fibrinogen, activate factors V and VIII, or aggregate platelets. Thrombomodulin-bound thrombin can still be inhibited by AT.

Protein S is a single chain glycoprotein synthesised in the liver and the endothelium. It is vitamin K dependent, but is not a serine protease. Activated protein C complexes with protein S and calcium ions on platelets and on the endothelial surface. The inhibitory activity of complexed protein C is greatly amplified.¹⁸ Protein Z is also a vitamin K dependent factor, but its full function is not as yet known.

The two principle anti-coagulant pathways, known to be important in the regulation of coagulation proteinase activity are schematically represented in Figs. 8 and 9. On the left side of each diagram, is a simplified view of the coagulation cascade with its “procoagulant” feedback loops by which thrombin activates factors V and VIII. To the right, are the “anti-coagulant” pathways by which excessive activation of coagulation is prevented. These pathways involve anti-thrombin (which directly inhibits the coagulation proteins, such as, factor Xa and thrombin) and PC-PS (which inactivates factors Va and VIIIa).¹⁸

(4) Tissue factor pathway inhibitor (TFPI):

It is an important inhibitory regulator of *in vivo* coagulation (Fig. 10). TFPI is synthesised by the endothelial cells and circulates in plasma bound to low-density lipoproteins. It is also present in platelets and bound to heparan sulphate on the endothelial surface. TFPI inhibits coagulation by binding to factor Xa-TF-VIIa complex and, therefore, inhibiting its proteolytic activity.^{15,16}

It is the downregulation of tissue factor pathway activity is via a natural plasma component, tissue factor pathway inhibitor (TFPI), which halts continued direct generation of factor Xa. Therefore, continued Xa formation becomes dependent on ongoing activation of factor X by the IXa-VIIIa-phospholipid complex. Neither components of the thrombus initiating complex, TF or VIIa, can be inhibited separately (Fig. 10).^{15,16}

C) Laboratory evaluation of haemostatic function**Global tests of haemostatic function**

Defective haemostasis with abnormal bleeding may result from thrombocytopenia (quantitative platelet defect), platelet function disorder (qualitative platelet defect), or defective blood coagulation. Patients with a variety of vascular disorders may also suffer from a bleeding disorder. In association with the clinical picture, including family history, the haemostatic function may be evaluable using a number of initially simple tests to assess the platelet, vessel wall, and coagulation components of haemostasis.¹⁹

Blood count and blood film examination

As thrombocytopenia is a common cause of abnormal bleeding, patients with suspected bleeding disorders should initially have a blood count, including platelet count and blood film examination to exclude platelet aggregation as a cause of false thrombocytopenia and confirm the presence of thrombocytopenia. The cause of thrombocytopenia may be obvious, e.g., acute leukaemia or DIC.²⁰

Table 2. Screening Tests for Coagulation Disorders

Screening Test	Abnormality Indicated by Prolongation	Most Common Cause of Abnormality
Prothrombin time (PT)	Deficiency or inhibition of one or more of the following coagulation factors: VII, X, V, II, fibrinogen	Liver disease Warfarin therapy or other vitamin K antagonists
Activated partial thromboplastin time (APTT)	Deficiency or inhibition of one or more of the following coagulation factors: XII, XI, IX, VIII, X, V, II, fibrinogen	Haemophilia A Haemophilia B von Willebrand's disease Lupus anti-coagulants Acquired haemophilia and heparin therapy
Thrombin time (TT)	Reduction or abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs	Disseminated intravascular coagulation (DIC) Heparin therapy

Screening tests of blood coagulation

These may provide an assessment of the different components of the extrinsic, intrinsic, and/or common pathway of blood coagulation (Table 2). Generally, a significant prolongation of the respective clotting tests beyond those of normal 'control' plasmas in the test system indicates a defect.

The prothrombin time (PT) measures the extrinsic system (factor VII) and factors common to both systems (factors X, V, prothrombin, and fibrinogen). It may be expressed as the international normalised ratio (INR). *The activated partial thromboplastin time (APTT)* measures the intrinsic system (factors VIII, IX, XI, and XII) in addition to factors common to both systems (factors X, V, prothrombin, and fibrinogen). *The thrombin time (TT)* is sensitive to abnormalities of fibrinogen (quantitative or qualitative) or to inhibition of thrombin.^{19,20}

Mixing equal volumes of the test plasma with normal plasma will correct a prolonged PT or APTT due to factor deficiency. The presence of an inhibitor of coagulation is suspected when there is incomplete or no correction.^{19,20}

Specialised tests that may further delineate abnormal bleeding tendencies

Assessing platelet function

When the platelet count and the blood film examination are normal, the bleeding time is performed to detect abnormal platelet function. The test measures platelet plug formation *in vivo*. Bleeding stops within 3 to 8 minutes and there is a progressive prolongation with platelet counts less than $75 \times 10^9/l$. A prolonged bleeding time is also found in patients with disorders of platelet function. The time-consuming and skill-intensive platelet aggregation studies may be of help in delineating platelet functional defects. In recent years, other less labour-intensive methods may speedily provide objective information on platelet function have become available. These include PFA-100 (platelet function analyser-100). The PFA-100 can be performed on whole blood, and would readily provide the necessary information on platelet competence.²¹

Specific assays for coagulation factors

Assays are available for measuring factors VIII, IX, XI, XII, and VWF. Factor XIII activity can be assessed by testing for clot solubility in urea. Only uncross-linked clots are soluble, suggesting factor XIII deficiency.^{19,21}

Tests for fibrinolysis

Increased levels of circulating plasminogen activator may be detected by a shortened euglobulin clot lysis time. Immunological methods are available for the detection of fibrinogen and fibrin degradation products (FDPs) as well as d-dimers in serum. In patients with enhanced fibrinolysis, low levels of circulating plasminogen may be detected.^{19,21} Specific assays for plasminogen, t-PA, and PAI-1 are also available.

SECTION II: VENOUS THROMBOEMBOLISM

Disregulation of normal regulatory mechanisms of haemostatic function may result in excessive haemorrhage or unchecked thrombosis.

The discussion here, will concentrate on the latter. Securing haemostasis in patients with inherited bleeding defects and those on anti-coagulant therapy will be also covered in this section, but covering bleeding tendency in its entirety is outside the scope of this chapter.

A) Introduction

Venous thromboembolism (VTE) is a common and potentially lethal disease occurring at an incidence of 1 to 3 per 1000, per year.^{22–27} Over 200,000 new cases occurring in the United States annually. It mainly manifests in the deep veins of the leg, but may occur at other sites, such as, the upper limbs, cerebral, intra-abdominal, liver, portal veins or retinal veins. Embolisation occurs when part(s) of the clot dislodge and are transported via the blood flow, usually through the heart to the pulmonary vasculature. VTE is more common with advancing age.

Pulmonary embolism patients face a high risk of death. Estimates of the case fatality rate, however, vary widely. Large natural history studies^{25,26,28} found 12 to 25% of all events of VTE fatal, while recent trials have found much lower figures, around 1 to 3% (5 to 10% for pulmonary embolism).^{28,29} Of these, 30% die within 30 days and one-fifth suffer sudden death due to pulmonary embolism. This wide range may be caused by the inclusion of thrombosis as a secondary cause of death in the studies with a high estimate. The Worcester study also showed that the case fatality rate was highly dependent on age, with a low mortality among those aged forty or less, at the time of thrombosis.²⁵ The post-thrombotic syndrome (PTS) leads to chronic morbidity in a substantial number of patients.²⁶ Despite improved prophylaxis, the incidence of venous thromboembolism has been relatively constant.

Independent risk factors for venous thromboembolism include increasing age, male gender, surgery, trauma, hospital or nursing home confinement, malignancy, neurological disease with limb paralysis, and central venous catheter/transvenous pacemaker, prior superficial vein thrombosis and varicose veins. Among women, risk factors include pregnancy, oestrogen-containing oral contraceptives, and hormone replacement therapy. About 30% of VTE surviving cases develop recurrent venous thromboembolism within 10 years.

Independent predictors for recurrence include increasing age, obesity, active cancer, and limb paralysis.³⁰ About 28% of cases develop venous stasis syndrome within 20 years.

Only a reduction in the incidence of venous thromboembolism can reduce sudden death due to pulmonary embolism. The incidence of venous thromboembolism has been relatively constant since about 1980. Reduction of the incidence of venous thromboembolism will require better recognition of persons at risk, improved estimates of the magnitude of risk, and avoidance of risk exposure where possible. Compared with deep vein thrombosis alone, pulmonary embolism patients have reduced survival for up to 3 months after onset. Improved therapies for pulmonary embolism are needed, especially for patients with chronic heart or lung disease. Venous thromboembolism recurs frequently. While therapeutic oral anti-coagulation prevents recurrence, venous thromboembolism sometimes begins to recur as soon as anti-coagulation is stopped. Therefore, venous thromboembolism should be viewed as a chronic disease with episodic recurrence. Recognition of venous thromboembolism as a multifactorial condition with genetic and genetic-environmental interaction has provided significant insights into the disease epidemiology and has offered the possibility of better identifying those at risk from VTE.

B) Risk factors in venous thromboembolism

Risk factors for thrombosis are usually divided into genetic and acquired. Mechanistically, they fall into three groups of causes, according to Virchow: reduced blood flow, changes in the vessel wall, and changes in the composition of the blood.^{31,32} For venous thrombosis, the first (stasis) and the third group (changes in blood coagulability) appear most prominent. For arterial disease, factors that affect the vessel wall, i.e., promote atherosclerosis are most relevant. The genetic risk factors for venous thrombosis are all associated with changes in the blood composition. Acquired causes are either associated with decreased flow, i.e., immobilisation, paralysis, surgery, or plaster casts or related to hypercoagulability, such as in, the anti-phospholipid antibody syndrome, pregnancy, oral contraception, or cancer. Table 3 lists the main risk factors for venous thrombosis.

Table 3. Risk Factors in VTE

Acquired	Inherited	Mixed/Unknown
Age	Factor V Leiden mutation	Hyperhomocysteinaemia
Malignancy	Prothrombin 20210A	Elevated factor VIII
Previous VTE	Protein S deficiency	Non-Leiden APC-resistance
Immobilisation	AT deficiency	Elevated factor IX
Orthopaedic surgery	Protein C deficiency	Elevated factor XI
Oral contraceptives	Dysfibrinogenaemia	Elevated levels of TAFI
Hormonal replacement therapy		
Anti-phospholipid syndrome		
Myeloproliferative disorders		

The term “thrombophilia” defines situations associated with an increased risk of VTE characterised by hypercoagulability. Inherited coagulation abnormalities predisposing to VTE, such as, deficiencies of the naturally occurring anti-coagulants anti-thrombin, protein C, and protein S and genetic mutations in coagulation factor V (factor V Leiden) and prothrombin^{33–35} define inherited thrombophilia. These two mutations in coagulation factors, together with high factor VIII levels have been identified as risk factors only in the last decade, and their identification has greatly improved our understanding of the aetiology of VTE. Today, inherited thrombophilia may explain more than 50% of cases of VTE.^{33–35} On the other hand, individuals with thrombophilia, particularly with the more common factor V Leiden or prothrombin mutations, frequently remain asymptomatic. This suggests that risk factors for inherited thrombophilia require interactions with other factors to elicit thrombosis. Situations of acquired thrombophilia associated with an increased risk of VTE, i.e., the presence of anti-phospholipid antibodies, cancer, surgery, trauma, prolonged immobilisation, pregnancy/puerperium, and oral contraceptive use have been known for many decades. Some of these acquired conditions, such as, surgery or pregnancy are transient, but others, such as, anti-phospholipid antibodies or cancer may persist over time.

The presence and the interactions of transient or persistent risk factors for VTE, as well as their different strengths in triggering

thrombosis must be taken into account for making decisions on primary and secondary prophylaxis of VTE with anti-thrombotic drugs. While awaiting specially designed controlled clinical trials, decisions concerning anti-thrombotic prophylaxis, particularly secondary prophylaxis, should be based on the identification of different risk profiles of individual cases.

Acquired risk factors for venous thromboembolism

Age

VTE rarely manifests before puberty, after which the annual incidence progressively increases. The estimated annual incidence of VTE is 1 per 10,000 in the young (before age 40) and 1 per 1000 among the elderly (after age 75).^{22–26} Higher incidence of malignancy and frequent orthopaedic surgery in the elderly population may partially explain the high incidence. The thrombotic risk associated with age may be further exacerbated by thrombophilic abnormalities as it has been shown that men heterozygous for factor V Leiden have an age-related increased risk for VTE.^{34,35} Furthermore, three other studies on very elderly people (above 85 years of age and centenarians) have shown a similar prevalence of the factor V Leiden mutations among young people, with no selection effect.^{34,35} In addition, there is no association between age and the plasma levels of anti-thrombin, protein C, protein S, and TFPI as observed in a study of patients over 65 years of age.³³

Malignancy

The procoagulant activity of tumour cells or their products and the administration of chemotherapeutic drugs^{36–40} account for the associated increased risk of thrombosis in cancer patients. VTE is more common with certain types of cancer, such as, pancreatic, gastrointestinal, ovarian, prostatic, or pulmonary neoplasms.^{38,39} VTE usually complicates advanced malignant disease. It may also, however, be the first sign of an underlying cancer that may herald the diagnosis of cancer by several years.⁴¹ In individuals with a first episode of idiopathic VTE, there is a 10 to 20% probability of having cancer at diagnosis or within the following 24 months.³⁸

Therefore, a physical examination together with routine laboratory testing, chest radiograph, and abdominal ultrasonography should be performed in all patients aged over 40 years, presenting with idiopathic VTE. The initiation of more aggressive investigations is controversial, in the absence of any evidence of improved survival or cost effectiveness. Further investigations, such as, CT-scan of the pelvis, abdomen, and chest, however, should be performed routinely in patients aged over 25 years, presenting with idiopathic VTE. These investigations may identify an occult cancer in its early stage in approximately 10% of cases.^{38,40} In addition, a thorough search for occult cancer should be carried out in patients with recurrent thrombosis involving superficial or deep veins, especially if anti-coagulant therapy has been given.

Anti-phospholipid antibodies

This is an acquired condition, sometimes associated with systemic lupus erythematosus or other autoimmune diseases in its secondary form. Lupus anti-coagulant and anti-cardiolipin antibodies together form the anti-phospholipid antibody family.⁴¹ The prevalence of anti-phospholipid antibodies in patients with VTE ranges from 5 to 15%, while the prevalence in the general population is not well established.^{42,43} Clinically, individuals with this acquired thrombophilic state may develop venous or arterial thrombosis and recurrent foetal loss. Placental insufficiency is thought to be the cause of the obstetric complications.^{42,43} It has been shown that the thrombotic risk in individuals with this abnormality is increased 9-fold, and the probability of recurrence may be higher.⁴⁴

History of venous thromboembolism

The history of previous VTE is an independent risk factor for further thrombotic events. Patients who have had VTE have an increased frequency of new episodes.³⁰ The malfunctioning of venous valves, which follows thrombosis of deep veins in the leg, is an important factor contributing to stasis. This, in turn, increases the risk of recurrence.³⁰ As the increased risk does not seem to be attributable

to known thrombophilic factors, a history of previous VTE remains an independent risk factor for recurrence.

Transient risk factors for venous thromboembolism

Surgery and major trauma

Together with malignancy, surgery is a common (and likely to be the strongest) risk factor for VTE. Orthopaedic surgery and neurosurgery are among the most thrombogenic.^{45–47} The risk of deep vein thrombosis after total knee or hip replacement carried out without prophylaxis, ranges from 45 to 70%, with fatal pulmonary embolism complicating up to 3%.⁴⁸ A high risk of thrombosis is also associated with abdominal surgery, urological surgery (particularly open operations of the prostate), and gynaecological surgery.⁴⁹ The risk of thrombosis is not confined to the immediate postoperative period, but continues for several weeks.⁴⁶ Similar to surgery, major traumas, such as, head trauma, spinal injury, and pelvic fracture are frequently complicated by VTE. Nearly 60% of individuals with major trauma had deep vein thrombosis of the legs. This, in most cases, was asymptomatic.⁵⁰ Pulmonary embolism is the third most common cause of death in individuals with trauma, occurring in 2 to 22% of those who survive the first 24 hours.⁵⁰

Pregnancy and the puerperium

Assuming that the incidence of VTE in women of fertile age is 1 per 10,000, pregnancy enhances the risk by 10-fold to up to 1.3 per 1000.^{51,53} The relative risk of VTE during the puerperium, defined as the 6 weeks after delivery, is 10- to 15-fold higher than that during pregnancy.^{51,52} Assuming that the duration of pregnancy is 280 days (40 weeks) and the puerperium is 42 days (6 weeks), the relative distribution of 100 venous thrombotic episodes would be 0.23 and 0.82 per day, respectively.⁵¹ In women heterozygous for the factor V Leiden the risk of pregnancy-related VTE is 1 per 100 pregnancies and in heterozygous women with the prothrombin mutation it is 1 per 500.⁵² The same risk becomes 1 per 25 pregnancies in women with homozygous factor V Leiden.⁵² The reasons for increased thrombogenicity are multifactorial, including hypercoagulability and hypofibrinolysis

due to changes in blood constituents during pregnancy. Obesity and high parity are also contributory factors. The further increase of the risk during the puerperium is only explained partially by caesarean section at delivery and by procoagulant changes. Inherited thrombophilic factors are associated with an increased risk of thrombosis during pregnancy and the puerperium.⁵²

Oral contraceptives and hormone replacement therapy

The increased risk of VTE associated with the use of oral contraceptives has been known since the early 1960s. In women of child-bearing age, oral contraceptives are the most common transient risk factor associated with VTE. The risk of thrombosis is primarily attributed to the oestrogen dose,⁵³ but the type of progestogen is also an important determinant of the risk.⁵⁴ Third generation oral contraceptives, i.e., those containing desogestrel or gestodene as progestogens, are more thrombogenic than the second-generation pill, containing levonorgestrel^{53,54} and are associated with 2- to 3-fold higher risk than that induced by the third generation variety. Initially, these studies attracted a lot of controversy and criticism due to referral bias, diagnostic suspicion bias, recall bias, and reporting bias.^{53,54} Subsequently, it was demonstrated that all these possible biases did not influence the risks and, therefore, the estimated risks were realistic.⁵³ A more pronounced APC resistance has been found with the use of third generation rather than second generation oral contraceptives.⁵⁴ The synergistic effect of oral contraceptive use in association with thrombophilia has been well-recognised, with the risk of thrombosis being increased 20-fold in women with factor V Leiden and 16-fold in those with the prothrombin gene mutation.⁵⁴ Furthermore, a more striking risk amplification between thrombophilia and oral contraceptive use (150-fold increased risk) has been observed for cerebral vein thrombosis.⁵⁵

Compared with oral contraceptives, there have been fewer studies on the relationship between the use of post-menopausal hormone replacement therapy and VTE. The doses of oestrogen used for post-menopausal replacement are much lower than those used for contraception, and the route of administration is sometimes different

(transdermal vs. oral). Yet, several studies have shown a 2- to 4-fold increased risk of thrombosis associated with hormone replacement therapy.^{56,57} Perhaps the lower risk associated with the low oestrogen dose of hormone replacement therapy is neutralised by the higher baseline risk of post-menopausal women due to their older age, in comparison with women of child-bearing age who use oral contraceptives.

Prolonged immobilisation

This refers to any circumstance that contributes to the malfunction of the leg musculature in pumping the blood upstream in the veins. Impaired blood flow is associated with an increased risk of thrombosis. Plaster casts, bed rest, limb paralysis, and prolonged air travel are examples in which stasis plays a major role in the formation of venous thrombi.⁵⁸ Studies on autopsy series of patients confined to bed for longer periods found a prevalence of VTE ranging from 15 to 80%.^{47,59} Although the relative risk of thrombosis during immobilisation is difficult to calculate because of the variety of definitions of immobilisation, it is well established as an independent risk factor for thrombosis.

Inherited risk factors for venous thromboembolism

Deficiencies of naturally occurring anti-coagulant proteins

The role of naturally occurring anti-coagulants in the prevention of VTE was discovered when the association between inherited deficiencies of anti-thrombin,²³ protein C, or protein S^{33–35} and VTE was made between the 1960s and the 1980s. Homozygous deficiencies of protein C or protein S may cause extensive VTE manifestations, such as, neonatal purpura fulminans or warfarin-induced skin necrosis.^{33–35} VTE may manifest at a young age (less than 40 to 45 years) in individuals with heterozygous deficiency of these anti-coagulants, often without environmental triggers and, sometimes, at unusual sites. These sites include cerebral sinuses, abdominal veins, and deep veins of the arms. Tendency to recurrent VTE and positive family history^{34,35} is very common. Among the general population the prevalence of these conditions is low at less than 1%,^{33–35} but

accounts for about 5 to 10% of patients with VTE.^{33–35} The mode of inheritance is autosomal dominant. The reported prevalence of the defects varies significantly among different studies due to the selection criteria (lower in unselected patients and higher in patients referred to specialised centres for thrombophilia screening).³⁵ AT deficiency is the most thrombogenic of these conditions as shown in large family studies, while protein C or protein S deficiency³³ has significantly lower risk.

Factor V Leiden

Dahlbäck *et al.* in 1993 found that the plasma from members of a thrombophilic family failed to prolong the activated partial thromboplastin time after adding APC.⁶⁰ This condition was later called resistance to APC. This was subsequently attributed to the presence of a single amino acid substitution in one of the three cleavage sites of factor V by APC, an Arg instead of Gln at position 506, now best known as factor V Leiden.⁶⁰ This corresponds to a G to A substitution at nucleotide 1691 of the factor V gene. This is the most common cause of genetic thrombophilia, and its discovery has dramatically increased the understanding of the aetiology of VTE. The frequency of factor V Leiden is relatively high among Caucasians ranging between 2 and 15% in the general population^{33–35} and up to 50% in selected patients with VTE.^{33–35} Various studies have confirmed an increased risk of VTE for carriers.^{61,62} The risk for a first episode of VTE as estimated in a large case control study is 7-fold and 80-fold for heterozygous and homozygous factor V Leiden carriers, respectively.^{33–35} Carriers of factor V Leiden often have a mild thrombotic manifestation, such as, superficial vein thrombosis.^{33–35} They rarely develop pulmonary embolism,^{33–35} and may develop the first thrombotic symptoms at a relatively advanced age.³⁵

Prothrombin G20210A mutation

This mutation was discovered in 1996, when candidate genes for thrombosis were investigated in patients with family clustering of VTE.⁶¹ As for factor V Leiden and in contrast with the deficiencies of the naturally occurring anti-coagulants, this mutation causes a “gain

of function” in the coagulation system. Carriers of the mutation have about 30% higher plasma prothrombin levels than non-carriers,⁶¹ associated with an increased potential for thrombin generation.⁶¹ The mutation is present in 2 to 4% of the Caucasian population, and its prevalence in Southern Europe is twice higher than in Northern Europe.^{34,35} This prevalence is the opposite of the geographical prevalence observed for factor V Leiden. In selected patients with VTE the prevalence of the mutation is up to 20%, and the relative risk in carriers is 2 to 4 times higher than in non-carriers.^{34,35,62} Due to the relatively high frequency of the prothrombin mutation and the factor V Leiden in the general Caucasian population, their combined presence is not so rare. Not surprisingly, individuals who carry both mutations have a higher risk of developing a first³⁵ or recurrent⁶² venous thrombotic episode than those with either mutation alone.

Other risk factors for venous thromboembolism

The following factors are of “mixed” inherited and acquired, and their role in determining VTE is usually less well-established.

Hyperhomocysteinaemia

Genetic defects cause an approximately 50% reduction in the activities of the corresponding enzymes, e.g., methylenetetrahydrofolate reductase (MTHFR). Acquired conditions include deficiencies of folate, cobalamine, and pyridoxine deficiencies, which are cofactors for homocysteine metabolism and chronic renal insufficiency. The association between moderate hyperhomocysteinaemia and VTE was made due to the high prevalence of this metabolic abnormality in a series of young patients with VTE in whom other causes of thrombophilia were excluded.⁶³ Since then several case-control studies have consistently demonstrated an increased thrombotic risk among individuals with hyperhomocysteinaemia. Other prospective studies, however, have found no association. Therefore, the causal relationship between hyperhomocysteinaemia and VTE is still unclear. There are also conflicting results on the role of the common homozygous mutation of MTHFR (cytosine to thymine at nucleotide 677), as a risk

factor for VTE. Although the homozygous variant is often associated with mild hyperhomocystaemia (mainly in the presence of low folate concentration), many studies have failed to demonstrate a clear association.⁶⁴

When associated with factor V Leiden, hyperhomocystaemia or homozygosity for MTHFR increases the risk of VTE.^{34,35} Therefore, the inclusion of this in the screening of thrombophilia is doubtful. Hyperhomocystaemia is corrected by vitamin supplementation, a treatment that is effective in the large majority of cases.

High levels of factor VIII

Elevated factor VIII is a risk factor for VTE.⁶⁵ A gradual dose-response relationship between risk of VTE and factor VIII levels has been observed.^{34,35,65} The risk of thrombosis is independent of two major determinants of factor VIII levels, blood group and von Willebrand's factor levels.⁶⁵ The prevalence of high factor VIII levels among patients with thrombosis, taking as a cut-off value the 90th percentile of the distribution of values in a control population, varies from 19 to 25%.⁶⁵ Elevated factor VIII levels persist over time⁶⁵ and confer a high risk of recurrent VTE.⁶⁵ The latter finding may have important implications for the duration of treatment after the first episode of thrombosis.

High levels of factor IX, factor XI, and thrombin activatable fibrinolysis inhibitor (TAFI)

High plasma levels of factor IX or factor XI are associated with an increased risk of VTE.^{34,35} The prevalence of patients with high levels of factor IX or factor XI was 20% and 19%, respectively, with an increased risk of VTE of 2-fold for both factors. A lower prevalence (14%) and increased thrombotic risk (odds ratio 1.7) has been found in association with high TAFI antigen.³⁵ As all of these findings derive from the same population-based case-control study of patients with a first episode of VTE (the Leiden Thrombophilia Study), further investigations are needed to confirm the causal relationship of these abnormalities with the occurrence of thrombosis.

Activated protein C resistance (without factor V Leiden)

Activated protein C (APC) resistance not caused by factor V Leiden may be of genetic or acquired origin. The former has been based on the description of families with APC resistance in the absence of factor V Leiden,⁶⁶ but other mutations are perhaps implicated, such as, the HR2 haplotype of factor V.⁶⁷ Among acquired causes of APC resistance the most common and well-established are pregnancy and the use of oral contraceptives.⁶⁷ A population-based study covering more than 15,000 individuals showed that the risk of thrombosis in the presence of APC resistance (in the absence of factor V Leiden) was nearly doubled.⁶⁷ In the Leiden Thrombophilia Study, a dose-response relationship between the degree of APC resistance and the risk of VTE was observed, with a 4-fold increased risk of VTE.⁶⁷ This study showed that the overall prevalence of APC resistance in patients with thrombosis was 36%, being 24% after the exclusion of factor V Leiden carriers. Therefore, the finding of APC resistance without factor V Leiden is to be expected in one in every 10 unselected patients with VTE, and the functional APC resistance assay should be a part of thrombophilia screening.

Risk stratification in venous thromboembolism

The high-risk (Table 4) category includes patients with the most severe forms of thrombophilia, including anti-thrombin deficiency, homozygous protein C or protein S deficiency, homozygous factor V Leiden, anti-phospholipid syndrome, combined thrombophilic defects, malignancy, and recurrent VTE. The low-risk category (Table 4) includes patients with only one episode of VTE that occurred in the presence of one or more transient risk factors, such as, surgery, immobilisation, pregnancy, oral contraceptive use, or hormone replacement therapy. Generally, patients in the high-risk category should be managed with indefinite anti-coagulant therapy (in case of malignancy, as long as the cancer is active), while short-term prophylaxis (up to 6 months) is an acceptable practice in patients belonging to the low-risk group. Patients who fall in other categories (Table 4), for example, those with mild thrombophilia (such as, heterozygous deficiencies of protein C or protein S, heterozygous factor

Table 4. Risk Stratification of Patients with Venous Thromboembolism

Risk Stratification	Patient Categories	Duration of Anti-coagulant Therapy
Low	Transient risk factors [‡]	Short-term, usually 3 months
Intermediate	Mild thrombophilia [†] Thrombosis in life-threatening sites (portal vein, mesenteric vein, cerebral vein), massive pulmonary embolism	Not well-established, but 6 to 24 months
High	Severe thrombophilia* Malignancy Recurrent VTE	Indefinite

*Includes AT deficiency, homozygous protein C, protein S, and F V Leiden, anti-phospholipid syndrome, and combined thrombophilic defects.

[†]Includes heterozygous protein C, protein S, F V Leiden, and P 20210A.

[‡]Includes immobilisation, surgery, pregnancy/puerperium, oral contraceptive use, and hormone replacement therapy.

V Leiden, or prothrombin mutations) and those with no obvious risk factors who had venous thrombosis in a life-endangering location (for example, portal vein, mesenteric veins, or cerebral veins) or had massive pulmonary embolism, can be grouped in an intermediate-risk category. For this group, there is no consensus about the duration of anti-coagulant therapy.

C) Haemostatic genetic risk factors in arterial thrombosis

Haemostasis plays an integral role in arterial thrombotic disease. Identifying risk factors has, however, proved to be surprisingly difficult.^{68–75} Once established as a risk factor, a genetic polymorphism has the potential to aid selective prophylaxis and therapy of disease. Numerous reports have been published on polymorphisms of coagulation and fibrinolytic factors, of coagulation and fibrinolytic inhibitory proteins, and of platelet membrane glycoprotein receptors.^{76–92} Although many studies have shown an association

between polymorphisms and disease, the collective outcome of these studies has primarily been inconsistent.

Heart disease, diabetes, and many cancers probably arise from the interaction of acquired and genetic factors. For arterial thrombotic diseases, such as, myocardial infarction and stroke a number of environmental risk factors are well-established, including smoking, diet, dyslipidaemia, hypertension, and impaired glucose metabolism. The role of haemostatic disorders in the development of arterial thrombosis is emerging.^{68–75} Arterial thrombogenesis results from atherosclerosis and thrombosis, while atherosclerosis is a disease of the vessel wall resulting from chronic changes in vessel wall cellular components, occurring gradually over many years. The thrombotic event is an acute event thought to be triggered by tissue factor interaction with factor VIIa and almost certainly influenced by haemostatic factors, such as, fibrinogen, fibrinolytic factors, and platelet activation.^{86–88} How the atherosclerotic process might be influenced by haemostatic factors is less clear.^{72,77}

Some of the polymorphisms in coagulation and coagulation inhibitor genes studied include polymorphisms; of fibrinogen, factor VII, factor V/prothrombin, factor XIII, thrombomodulin/endothelial cell protein C receptor, fibrinolytic system genes (PAI-1), platelet glycoprotein receptors (GP IIb/IIIa, GP Ib-IX-V, GP Ia/Iia) and other coagulation proteins.^{78–92}

Knowledge of genetic risk factors may define the pathogenesis of arterial disease and could ultimately help in the rational design of selective therapy. In approaching a large and often contradictory literature, it is helpful to have some basic premises in mind with which to assess the data. For this purpose, two critical premises should be considered. The first is fundamental; for a gene change to have an effect it must be mediated through a phenotype. In studies that report consistent relationships linking polymorphisms, phenotype, and clinical effect there can be some confidence that the genetic variation is influencing disease. In contrast, studies that report only the results of associations between polymorphisms and disease should be considered inadequate. This is because any statistically significant association between polymorphism and disease might well have arisen for reasons unrelated to the effect of its phenotype. Examples of such

confounding factors include play of chance, linkage with another gene locus, and poor study design resulting in bias. The second related premise to be used is whether a polymorphism is making an important contribution to disease and therefore, causing thrombosis.

Adopting the above strategy in analysing the data based on the relation between genotype, phenotype, and clinical outcome reveals that despite extensive investigation, there is still no clear reproducible evidence for the role of any haemostatic polymorphism in arterial thrombosis. This contrasts with the well-defined role of some of the same polymorphisms in VTE.^{33,35} It is worth considering why this might be. There are fundamental differences between arterial and venous disease, with the dominant role of the vessel wall in the former. It can also be assumed that the haemostatic changes will play a crucial role in the thrombotic complications of arterial disease, mediated through atheromatous plaque rupture, fibrin generation, and platelet activation. It is, however, generally thought that arterial occlusion has a multifactorial aetiology, which conspires to undermine the integrity of the vessel wall and promote thrombosis. Some of these processes, which may involve haemostatic factors, will be influenced by genetic variation. Given the large number of factors, together with the lack of penetrance of disease in families, it is highly unlikely that individual haemostatic polymorphisms will have dominant influences on their own. Consequently, studies that focused only on the prevalence of a specific polymorphism in cohorts of patients (and controls), inevitably failed to show in a reproducible manner that the genetic variation is associated with disease. Apart from their lack of power, small studies are particularly prone to bias. The prevalence of polymorphisms in control groups may be underestimated, resulting in apparent, but spurious increased prevalences in case groups (stratification bias). Poor matching of cases and controls due to racial and population genetic heterogeneity is more likely with small numbers (admixture bias). It is certain that such factors have contributed to an over-representation of published studies reporting positive associations between polymorphisms and disease (publication bias).

A key consideration for future work must be the extent to which classical cardiovascular (acquired and genetically determined) risk factors for disease interact with polymorphisms of the haemostatic

system. Gene polymorphisms have existed within populations for thousands of years, while arterial disease has reached epidemic proportions only in the last century. This must have arisen through deleterious gene-environment interactions and suggests that the best means by which the influence of the genetic factor on disease will be reliably detected is by using studies that formally incorporate gene-environment interactions into their design. In retrospect, it is not surprising that so little progress has been made in this area. Fortunately, some studies had been designed at the outset to study interactions. These studies have produced plausible results of increasing risks of disease with increasing interaction, which fit current concepts of the aetiology of arterial disease. As clinical studies of interaction, however, require very large number of patients/controls, the power of most good studies has nevertheless been low. Consequently, there is an urgent need to address the role of haemostatic polymorphisms with well-designed studies that are larger by at least an order of magnitude. An upward scale change in terms of the number of potential risk alleles under evaluation may also be required, which is now possible with the microarray technologies. Such investigations may identify key combinations of polymorphisms that have low individual risks, but together may influence disease.

The prospect is for genetic screening of asymptomatic individuals, to identify their genetic risk profiles. On the basis of a screening programme, lifestyle advice and individualised pharmacological intervention programmes would be given to reduce future risks of disease. Today, it appears that insufficient progress has been made to justify the inclusion of haemostatic gene polymorphisms within such a population genetic screening programme.

SECTION III:

Thromboprophylaxis for high-risk surgical patients

Major orthopaedic surgery

In the absence of prophylaxis, patients undergoing elective THR have a 2 to 5% incidence of symptomatic VTE and 0.1 to 2% fatal PE. Asymptomatic DVT, however, is found in 42 to 57%.^{93,94} Primary

prophylaxis is the only effective method of reducing VTE in this population. Non-invasive screening techniques on discharge or venography are unacceptable alternatives.¹⁰⁵

Non-pharmacological methods of prophylaxis

Physical methods of prophylaxis are designed to reduce stasis in the leg veins. Three types have been evaluated: graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and venous foot pump (VFP). These methods are not associated with increased perioperative bleeding, but their problem is low compliance. Overall experience is also very limited in contrast with the pharmacological agents. These methods, unlike pharmacological agents, have not been shown to reduce mortality or PE and, therefore, appear to be less effective than pharmacological methods. In addition, GCSs are contraindicated in patients with peripheral vascular disease.

All three methods have been evaluated in patients undergoing THR, GCSs,⁹⁵ IPC,^{96–101} and VFP.^{102,103} There is no evidence that GCSs are effective. In two studies, IPC devices were as effective as warfarin.^{97–99} In another study, IPC was less effective than warfarin in preventing proximal DVT.¹⁰⁰ In another randomised study, IPC of the calf and the thigh produced a 50% reduction in both distal and proximal DVT.⁹⁸ VFP is also effective.^{102,103}

Pharmacological prophylaxis

Six different classes of anti-thrombotic agents have been evaluated in patients undergoing major orthopaedic surgery. These include low dose UFH, LMWH, aspirin, vitamin K antagonists, fondaparinux, and ximelagatran.

Aspirin was ineffective in reducing symptomatic VTE in the Pulmonary Embolism Prevention (PEP) Trial of 4088 patients undergoing THR or TKA.¹⁰⁴ Vitamin K antagonists and LMWH are effective and fairly common modalities in prophylaxis in this setting. LMWH is more effective than vitamin K antagonists and low dose UFH.^{105–111} Recent evidence, however, suggests that fondaparinux is more effective than LMWH.¹¹²

Anderson *et al.* compared the relative efficacy of LMWH with that of UFH in six well-conducted trials for DVT prevention after THR.¹⁰⁶ LMWH was found to be significantly more effective than UFH in preventing DVT, as shown by venography, after total hip replacement. Meta-analysis has confirmed that the benefit of LMWH over UFH was only demonstrable for the prevention of proximal-vein thrombosis, while the rates of calf-vein thrombosis were similar in the two groups. The haemorrhagic risk was not significantly different between the two groups. Furthermore, the superiority of LMWH over oral anti-coagulants has emerged in almost all single trials dealing with this issue.^{113–115}

In a recent, large, open-label trial THR patients were randomly assigned to in-hospital prophylaxis with either LMWH (enoxaparin, 30 mg × 2) or adjusted-dose warfarin.¹¹³ Symptomatic, objectively documented VTE developed in a significantly lower proportion of patients treated with enoxaparin (0.3 vs. 1.1%). After three months of follow-up, however, this difference was no longer detectable (3.4 vs. 2.6%). In addition, major bleeding occurred more frequently in the enoxaparin treated group (1.2 vs. 0.6%).

Therefore, present experience consistently supports the view that LMWHs are more effective than UFH for the prevention of proximal DVT, with no additional haemorrhagic risk. They are more effective than oral anti-coagulants for the prevention of in-hospital (mostly distal) DVT, at the price of increased surgical site bleeding and wound haematoma. The choice between LMWH and warfarin should be tailored to the individual patient based on the clinical assessment of postoperative thrombosis and bleeding risk as well as the prophylaxis-specific cost and convenience.

There is still uncertainty about the ideal duration of prophylaxis, despite overwhelming evidence of the efficacy of anti-thrombotics in preventing postoperative VTE after orthopaedic surgery. Concern about the potential risk of pulmonary embolism from symptomless DVT, after hospital discharge, has led to the extension of the duration of prophylaxis for up to a month. Whether thromboprophylaxis should be extended after hospital discharge, however, is controversial.^{116–121} Leclerc *et al.* studied 1984 consecutive patients who underwent hip or knee arthroplasty¹²¹ and who received a mean

of 9 days enoxaparin prophylaxis (30 mg twice daily). The rates of VTE events during and after prophylaxis at 3 months follow-up were 2.1 and 2.1%, respectively. Following elective hip or knee replacement Heit *et al.* randomised 1195 patients to LMWH, to stop at the time of hospital discharge or continued for up to 6 weeks after surgery.¹²² The rate of symptomatic, objectively confirmed VTE after a 3-month follow-up period was similarly low (2 and 1.5%, respectively) in the two groups.

To conclude, the optimal duration of prophylaxis after major orthopaedic surgery remains unclear.

Oncologic surgery

Extensive abdominal or pelvic surgery in cancer patients is associated with a remarkably high risk of developing postoperative VTE. Among pharmacological measures currently utilised for the prevention of postoperative DVT in cancer patients, LMWH have several selective advantage over UFH.^{123–125}

D) Diagnosis of deep-vein thrombosis

Introduction

Many patients develop DVT in the presence of well-known risk factors, such as, immobility and malignancy. DVT can, however, occur unprovoked (idiopathic DVT). An underlying thrombophilia (inherited or acquired) may be present in some patients with idiopathic DVT, while the remainder have no demonstrable thrombophilia. The management of DVT is often straightforward. Problems leading to morbidity and mortality can result from misdiagnosis, treatment failure, and anti-coagulant-related haemorrhage.

Diagnosis of first episode of DVT

Symptoms of DVT vary and may be minimal or atypical. In addition, its diagnostic clinical features can be found in other disorders. DVT confirmed objectively is found in only about 25% of patients who present with such symptoms. As the clinical diagnosis is poor

and non-specific, confirmation with objective testing is paramount. In addition, although anti-coagulant therapy is highly effective, its unnecessary use should be avoided because it can cause serious morbidity and mortality. Despite the limitations of clinical diagnosis, the first step in evaluating a patient with suspected DVT remains history and full clinical examination.¹²⁶

Clinical assessment

A proper clinical evaluation involves a careful assessment of the patient's symptoms, signs, and risk factors for venous thrombosis. Patients with symptomatic DVT can present with painful swelling, tenderness along the distribution of the deep leg veins, and localised erythema consequent to venous obstruction or perivascular inflammation. These signs can also be found in patients with cellulitis, ruptured Baker's cyst, superficial thrombophlebitis, and other musculoskeletal conditions. Therefore, the most important objective of the clinical evaluation is to determine whether the presenting features are more or less likely to be caused by one of these alternative diagnoses. If the patient has no known risk factors for venous thrombosis an alternative diagnosis is considered more likely and, therefore, the likelihood of DVT is significantly reduced. In contrast, if the patient has one or more known risk factors for thrombosis, the likelihood of DVT is increased. Well-established risk factors for venous thrombosis include recent major surgery or trauma, recent hospitalisation, malignancy, prolonged immobilisation, pregnancy and the puerperium, use of combined oral contraceptives or hormonal replacement therapy, and presence of anti-phospholipid syndrome and known heritable thrombophilia. Obesity, smoking, and long distance flights are considered weaker risk factors. Standardisation of the clinical assessment can be achieved by using one of the clinical models available. The first model designed to assess the pretest probability (clinical likelihood) of DVT was developed and validated by Wells and colleagues (Table 5) in outpatients who presented with suspected DVT.^{127,128} Following their clinical presentation, patients are stratified and assigned into low, medium, or high probability category for having DVT. Outpatients with classical findings of DVT and at least one risk factor have 85% probability of having DVT, while those with atypical features and

Table 5. Wells *et al.* Prior Clinical Probability (PCP) for Deep Vein Thrombosis

Clinical Features	Yes	No
Active cancer (on-going treatment or within previous 6 months or palliative)	1	0
Paralysis, paresis, or recent plaster immobilisation of the lower limbs	1	0
Recently bed-ridden for more than 3 days or major surgery, within 4 weeks	1	0
Localised tenderness along the distribution of the deep venous system	1	0
Entire leg swollen	1	0
Calf swelling by more than 3 cm when compared with the asymptomatic leg (10 cm below the tibial tuberosity)	1	0
Pitting oedema (greater in the symptomatic leg)	1	0
Collateral superficial veins (non-varicose)	1	0
Intravenous drug abuse	1	0
Alternative diagnosis as likely or greater than that of DVT	-2	0

High score ≥ 3 ; moderate score 1–2; low score ≤ 0 .

no identifiable risk factors have only about 5% probability of having thrombosis.¹²⁷ Shows a simplified version of the original model.¹²⁸ Although the identification of an alternative diagnosis may prove difficult, the model has been applied successfully to different patient settings, including patients in hospital and patients who present to the Accident and Emergency Department and acute admission and assessment wards.^{129,130}

Wells has further streamlined the diagnostic process more recently by stratifying patients into two broad risk categories: “DVT unlikely” if the clinical score is 1 or less, and “DVT likely” if the score is more than 1.6.¹³¹ Other investigators have adapted the modified model after removing the alternative diagnosis point. Junior medical staff were able to use this modified model without difficulty to triage patients with suspected DVT presenting to the emergency department.¹³²

Initial objective testing

The most useful objective tests for diagnosing DVT are venous compression ultrasonography (CUS) and D-dimer testing. The need for

contrast venography (the reference standard for diagnosing DVT) has been markedly reduced by combining clinical assessment with compression ultrasonography and D-dimer testing. Validation studies have shown that diagnostic strategies incorporating clinical pretest probability, ultrasonography, and D-dimer testing are safe, reliable, and cost-effective in managing patients with suspected DVT.

Compression venous ultrasonograph

Compression venous ultrasonography (CUS) is the first objective test of choice in patients with high or moderate pretest probabilities. Lack of compressibility of the common femoral vein or popliteal vein or both is diagnostic for proximal DVT. Compression B-mode ultrasonography with or without colour duplex has sensitivity of 95% and specificity of up to 98% for diagnosing symptomatic, proximal DVT. It has sensitivity and specificity of 60 to 70% for isolated calf vein thrombosis.¹³³ Therefore, with concordant pretest probability and CUS of the proximal venous system, the accuracy and the predictive values of the positive and the negative combinations approach 100%.¹³⁴ Accordingly, DVT is confirmed when the pretest probability is intermediate or high and the CUS result is positive, while it is safe to exclude a diagnosis of DVT and withhold anti-coagulant therapy when the clinical suspicion is low and the CUS result is negative. In contrast, further objective testing will be required when other combinations occur because DVT is present in a range between 14 and 63%.^{127,128} The major limitation of CUS is its reduced specificity and, therefore, accuracy in diagnosing distal calf thrombosis. Its limited availability outside routine working hours, including weekends and holidays, is also a problem.

D-dimer testing

D-dimer testing is used as the first objective test in patients with suspected DVT and low pretest probability. D-dimer assays were developed about 20 years ago to measure cross-linked fibrin degradation products. Since then many different assays have been evaluated for their accuracy and utility in diagnosing DVT (Table 6). In

Table 6. Performances of D-Dimer Testing in Suspected Venous Thromboembolism

Series	Patients n	Negative Predictive Value (NPV) % (95% CI)
Suspected DVT		
Classical ELISA	1337	96 (93–98)
Vidas-DD	785	98 (95–99)
Classical latex	733	92 (84–91)
Simplified	1108	92 (90–94)

general, a negative result using a sensitive D-dimer test is useful for excluding acute DVT. Conversely, a positive D-dimer result is not useful because the test lacks specificity. Furthermore, D-dimer levels are raised not only in acute thrombosis, but also in other conditions, such as, trauma, postoperative, immobility, pregnancy, infection, and malignancy. In addition, D-dimer levels are raised in elderly patients. Unfortunately, commercially available D-dimer assays vary in their sensitivity and specificity and, therefore, the performance of one assay cannot be extrapolated to another.¹³⁵ The most reliable and extensively evaluated tests are two rapid enzyme-linked immunosorbent assays (ELISAs; Instant-IA D-dimer, Stago, Asnie'res, France and VIDAS DD, bioMe'rieux, Marcy-l'Etoile, France) and a rapid whole blood assay (SimpliRED D-dimer, Agen Biomedical, Brisbane, Australia). The sensitivity of the rapid ELISAs is over 95% and that of the SimpliRED D-dimer assay is approximately 85%.

Earlier studies suggested that DVT can be safely excluded in outpatients who have a low pretest probability on standardised clinical assessment and a negative D-dimer result.^{136,137} This proposed approach has now been validated by management studies that indicate an initial CUS is unnecessary in patients with a low pretest probability and a negative D-dimer result, because less than 2% of these patients will develop symptomatic DVT over the next 3 months.^{132,138} Using this approach, an initial CUS can be avoided in 23 to 40% of patients who present with a suspected first episode of DVT.^{132,138} Furthermore, management studies have also concluded that CUS can be combined with D-dimer testing to reduce serial CUS by about 60%.^{139,140} Even independent of the pretest probability, if the initial

CUS result is negative and normal D-dimer result, further testing with serial CUS is unnecessary and anti-coagulant therapy can be withheld safely.^{139–141} Therefore, D-dimer testing can greatly reduce the number of CUS required to investigate first episode of suspected DVT.

Follow-up testing

Serial CUS or venography is indicated in the presence of disagreement between the clinical assessment and CUS or D-dimer result. If the clinical probability is moderate or high, but the ultrasound is negative, further testing is indicated to detect a calf vein thrombus. Isolated calf vein thrombosis occurs in 15 to 20% of patients with symptomatic, confirmed thrombi and only about 20% of calf thrombi undetectable at initial presentation will extend proximally within 1 to 2 weeks of initial presentation.¹⁴² Therefore, serial CUS (repeat CUS in 5 to 7 days or sooner, if clinically relevant) is a safe approach because it detects thrombus extension into the popliteal vein and because isolated calf vein thrombus that does not extend during the period of testing does not produce serious complications. Systematic review of management studies using serial CUS found a rate of conversion (from a negative to a positive) of only 1 to 2% during the period of testing, and the risk of a patient dying from pulmonary embolism while awaiting serial testing is 0.06% (95% CI, 0.00–0.32%).¹³⁴ Venography is indicated in patients unsuitable for serial CUS or those with severe symptoms and high clinical probability; those with poor cardiorespiratory reserve; and if the CUS result is inconclusive. It is also indicated in patients with unexplained swelling of the entire leg, but a negative CUS, as it is important to exclude an isolated iliac vein thrombus because the iliac veins are not routinely visualised with lower limb CUS. Isolated iliac vein thrombosis is infrequent, but it can occur in pregnancy and in patients who have extensive pelvic malignancy or have undergone recent pelvic surgery. An intraluminal filling defect on venography is considered as evidence of new or recent thrombosis. If the diagnosis is still inconclusive, it is reasonable to treat patients with anti-coagulant therapy and follow patients with abnormalities in distal veins with serial CUS.

Pregnant women with suspected DVT

The diagnosis of venous thrombosis in pregnancy can be challenging because: (1) unilateral left leg swelling can be caused by compression of the left iliac vein by the gravid uterus; (2) leg swelling can be caused by isolated common iliac vein thrombosis that may not be detectable by CUS, and (3) venographic examination of pelvic veins is problematic because of irradiation risk to the foetus. CUS is the initial test of choice in all patients, and the use of venography is limited to patients with suspected isolated iliac vein thrombosis, when the vein cannot be identified by CUS. Although venography exposes the foetus to irradiation, the risk of a fatal pulmonary embolism from a missed iliac thrombus probably outweighs the risk of radiation exposure to the foetus. Examination of the external and common iliac veins is technically feasible in the first two trimesters and can sometimes be done even in the third trimester with appropriate positioning. As in non-pregnant women, patients who have a negative initial ultrasound should be followed up with serial testing.

DVT diagnosis algorithm

This algorithm is based on the balance of evidence, a diagnostic strategy that combines clinical assessment using a standardised model, rapid ELISA D-dimer testing, and CUS. In patients with a low pretest probability, D-dimer testing should be the first investigation. If the D-dimer result is negative, further testing with CUS is unnecessary and DVT can be safely excluded; if the D-dimer result is positive, CUS should be performed. For all patients who have an intermediate or high pretest probability, the first investigation should be a CUS. If the ultrasound result is negative, D-dimer testing is helpful in selecting patients for further evaluation. Follow-up testing is not required if the D-dimer test is negative, while serial CUS or venography is indicated if the D-dimer result is positive (Fig. 14).

This strategy simplifies the diagnostic process and reduces the cost by reducing the number of patients who require both D-dimer testing and CUS examinations. As for all algorithms, there is room for the clinician to exercise their clinical judgment. For example, serial

CUS should be performed earlier than 5 to 7 days if the patient has severe or worsening symptoms, and venography should be considered in a patient with high clinical probability, normal CUS, and severe calf symptoms. Furthermore, if confirmatory tests cannot be performed in a timely manner and the clinical suspicion is high, empiric anti-coagulant therapy should be started before objective testing in the absence of contraindications.

Diagnosis of recurrent DVT

Although establishing a diagnosis of recurrent DVT is difficult because of the lack of a validated clinical model, and residual organised thrombus can complicate the interpretation of CUS, a similar strategy to that used in patients with suspected first episode of DVT is employed. This includes clinical assessment, CUS, and D-dimer testing in all patients who present with suspected recurrent DVT. Two important determinants influence pretest probability of recurrent DVT. These are a history of post-phlebotic syndrome (PPS) and the current use of anti-coagulant therapy. In patients with established PPS, it may be difficult to distinguish between an acute exacerbation of chronic symptoms and an episode of recurrent DVT. In patients already receiving anti-coagulant therapy, the likelihood of recurrence is reduced if the international normalised ratio (INR) is in the therapeutic range. Patients with advanced malignancy or anti-phospholipid syndrome are, however, at increased risk for recurrence despite a therapeutic INR value.^{143,144} Although a new non-compressible segment on CUS is diagnostic of recurrent thrombosis, an earlier test result is needed to make this determination. CUS remains abnormal in up to 50% of patients one year after the initial diagnosis. Therefore, a single abnormal CUS, especially when there is no previous result available for comparison, does not necessarily confirm recurrent DVT.¹⁴⁴ In contrast, an intraluminal filling defect on venography is diagnostic for DVT, and a previous examination is not required for comparison. Venography is, however, technically demanding and invasive. It involves the risk of contrast related complications, is not readily available, and is impractical for repeated use. Although D-dimer testing has not been formally evaluated in

this setting, there is no reason why a negative D-dimer result should not be as reliable for excluding a diagnosis of recurrent DVT as it is for first episode of venous thrombosis. Based on the above considerations, a diagnosis of recurrent DVT is confirmed if there is a new non-compressible segment on CUS. Alternatively, recurrence is ruled out if the patient has a normal CUS and a negative D-dimer result. In patients who have a high clinical suspicion or other combinations of CUS and D-dimer results, venography or serial CUS is indicated.

Cost-effectiveness

The safety and cost-effectiveness of several strategies were compared in a recent decision analysis. For a mortality of untreated deep vein thrombosis of 2.5%, the difference in mortality was only 1 to 2 per 10,000 patients managed by the single ultrasound strategy compared to serial ultrasound.

Performing a single initial diagnostic ultrasound in association with an initial D-dimer reduced the requirement for ultrasound to 70 scans per 100 patients managed compared with 130 to 170 for the serial testing strategy (Table 7).¹⁴⁵ This enabled a cost reduction of 9 to 15% in the single scan compared with the serial ultrasound schemes. Therefore, in a patient with a suspected DVT, clinical probability with an initial ELISA D-dimer test followed by a single

Table 7. Cost-Effectiveness of Various Diagnostic Strategies for Deep Vein Thrombosis¹⁴⁵

Strategy	*Lives Saved/1000 Patients	**Cost per QALY Saved (\$)	Venography or Angiogram/100 Patients
Suspected DVT			
Serial CUS	4.3	15,475	na
+ D-dimer	4.3	14,934	na
PTP + serial CUS	4.4	14,339	19
PTP + D-dimer + single CUS	4.2	13,115	14

*Difference in mortality per 1000 patients compared with “no treatment” strategy in which no investigation or therapy is undertaken.

**Compared with no treatment strategy for a 60-year-old patient considered to have a life expectancy of 20.5 years.

diagnostic ultrasound with venography only in patients with a high clinical probability and a normal ultrasound appears to be safe and is a cost-effective strategy (Table 7).

E) Treatment of acute DVT

Two major advances in the treatment of DVT have been made in the last decade. First, is the introduction of low-molecular-weight heparin (LMWH) as a replacement for un-fractionated heparin (UFH) and, second, is the potential benefit from a longer duration of anti-coagulant therapy. Large meta-analyses have shown that unmonitored, weight-adjusted subcutaneous LMWH is as safe and as effective as UFH administered by continuous infusion guided by the activated partial thromboplastin time (aPTT).^{146,147} As a result, subcutaneous LMWH is replacing intravenous UFH for the initial therapy of acute venous thromboembolism (VTE). Vitamin K antagonists are highly effective for long-term therapy, but they require laboratory monitoring and are problematic in some patients. Several new anti-coagulants with more convenient and potentially safer profiles are now undergoing clinical evaluation in randomised, controlled trials.

Initial anti-coagulant therapy

LMWH is the anti-coagulant of choice for initial therapy in the majority of patients with objectively confirmed DVT. The predictable pharmacokinetic properties enable LMWHs to be given as weight-adjusted subcutaneous injections without the need for laboratory monitoring.¹⁴⁸ Although laboratory monitoring is not usually required for patients receiving LMWHs, checking the 4-hour anti-Xa level is recommended in the following patient groups: advanced renal disease, pregnancy, children, and obese. If necessary, the LMWH dose should be adjusted.¹⁴⁸ In addition to their convenient dosing administration, LMWHs are more cost effective than UFH because the elimination of laboratory monitoring in most patients reduces the length of hospitalisation.¹⁴⁹ Another advantage of LMWHs over UFH is a lower risk of heparin-induced thrombocytopenia.¹⁵⁰ The majority of outpatients with newly diagnosed DVT are treated entirely at home.

This requires appropriate resources and infrastructure, including the ability to be able to teach all suitable patients or family members to administer subcutaneous injections, or arrange for the home support of a district nurse in those who are visually impaired or physically unable to inject themselves. Outpatient treatment requires an organised service with dedicated staff to provide patient support and education. Despite the disadvantages of UFH, it is often used in patients with extensive iliofemoral DVT with circulatory compromise and those who are haemodynamically unstable from associated major pulmonary embolism, because these groups were excluded in clinical trials that compared LMWHs with UFH. The usual intravenous regimen for UFH is a loading dose of 5000 U followed by a continuous infusion of around 1400 U hourly. The dose of UFH is adjusted according to the aPTT by following a validated standard nomogram to maintain a therapeutic heparin level.¹⁴⁸ Alternatively, a weight adjusted loading dose and nomogram can be used.¹⁵¹ If subcutaneous UFH is used, it is given at a starting dose of 17,500 U twice daily, and the dose is adjusted to achieve a therapeutic aPTT at six hours after the initial injection.¹⁴⁸ In patients requiring large doses of UFH ($\geq 35,000$ U/24 h), the heparin level should be monitored by anti-Xa assay. LMWH or UFH should be administered for a minimum of 5 days in patients with uncomplicated thrombosis and for 7 days or longer in patients who have extensive disease (e.g., iliofemoral DVT or massive pulmonary embolism). Oral anti-coagulant therapy can be started on the first day of treatment, and LMWH/UFH should not be stopped until the INR has been at least 2.0 for 2 consecutive days. A baseline platelet count and on days 5 to 7 should be done to check for heparin-induced thrombocytopenia if the patient is receiving UFH.

Long-term anti-coagulant therapy

After an initial course of LMWH or UFH, continuing anti-coagulant therapy with oral vitamin-K antagonists is required to prevent recurrence. Warfarin is the most common agent used in UK. The use of a loading dose is discouraged because it may be associated

with a transient period of excessive anti-coagulation, without a corresponding anti-thrombotic effect.¹⁵² The INR is measured after the first 2 or 3 doses of warfarin, and subsequent doses are adjusted to maintain the INR within the target range. As the therapeutic window for oral anti-coagulant therapy is narrow, frequent monitoring of the INR is essential to reduce the risks of recurrent thrombosis and anti-coagulant-related haemorrhage (ARH). Appropriate adjustments in the dose of warfarin usually require twice-weekly monitoring for the first 1 to 2 weeks, followed by weekly monitoring for the next 4 weeks, then once every 2 weeks for a month and, finally, every 4 weeks if the INRs have remained in the therapeutic range on a stable warfarin dose and the patient has not experienced any adverse effects. It is wise to monitor the INR at 4-week interval even in patients who have maintained a stable warfarin dose because of the potential interactions of warfarin with food or drugs. If there are changes in the patient's medications, more frequent monitoring is needed until a stable dose response is achieved.¹⁵³ Because oral anti-coagulant therapy is inconvenient, LMWH is being evaluated as an alternative for long-term treatment of VTE. LMWH has a number of advantages over warfarin. First, because LMWH does not require INR monitoring, it can be used when laboratory monitoring is problematic (e.g., difficult venous access). Second, LMWH has a more rapid onset and offset of action than warfarin. Therefore, it is more convenient to use in patients who require dental or surgical procedures while anti-coagulated. Third, there is a clinical impression that LMWH is more effective than warfarin in patients with thrombosis and cancer and in those who develop recurrent thrombosis despite therapeutic warfarin therapy. Despite these advantages, however, the routine use of LMWH is not practical or economical because LMWH requires administration by subcutaneous injection and is more expensive than warfarin. LMWHs may be difficult to reverse completely in the event of life-threatening haemorrhage. Randomised controlled trials comparing LMWH with oral anti-coagulant therapy have shown that the rates of recurrent thrombosis and major bleeding between the two treatment groups are similar.^{154,155}

Duration of anti-coagulant therapy

The duration of anti-coagulant therapy is influenced by balancing the risks of recurrence of thrombosis and of anti-coagulant related haemorrhage (ARH), and by the patient preference. The risk of bleeding during the initial period of anti-coagulation with UFH or LMWHs is 2 to 5%, while the estimated risk of major bleeding with oral anti-coagulant therapy is about 3% annually.¹⁵⁶ As 20% of major bleeds are fatal, the annual case fatality rate from ARH is about 0.6%. The risk of bleeding is increased by patient-specific factors, such as, age (65 years or older) and co-morbidity (renal failure, liver disease, diabetes, peptic ulcer disease, cerebrovascular disease, malignancy) and by the concomitant use of anti-platelet agents.^{157,158} Evidence also indicates that the risk of bleeding on anti-coagulant therapy is reduced over time, so the long-term fatality rate is likely to be lower in patients who have tolerated months or years of anti-coagulant treatment without bleeding. On the other hand, the case fatality rate from recurrent VTE is about 5%, with the rate being higher within the first 3 months of an episode of pulmonary embolism. Therefore, at an annual recurrence rate of 12%, the risk of death from recurrent thrombosis is balanced by the risk of death from ARH. In general, patients should be treated with anti-coagulant therapy for a minimum of 3 months. Patients with a reversible risk factor have a low risk of recurrence after 3 months of anti-coagulant therapy. In contrast, patients with idiopathic or unprovoked DVT who are treated for only 3 months have 10 to 27% risk of recurrence in the year after anti-coagulants are discontinued.^{159–161} Recent evidence suggests that extending therapy beyond 6 months in patients with idiopathic thrombosis does not reduce the risk of recurrent thrombosis to less than 10% in the year after discontinuing anti-coagulant therapy. Continuing warfarin after this period protects the patient against future recurrence, but also exposes the patient to the risk of ARH. Based on the results of prospective studies and extrapolation from studies on the risk of recurrence after a first episode of venous thrombosis, patients can be stratified into low, moderate, high, and very high-risk groups for recurrence when anti-coagulants are discontinued. Low-risk patients are those who had an important risk factor for thrombosis (e.g., major surgery, pelvic or leg

trauma, or major medical illness) from which they have fully recovered. Their risk of recurrence when anti-coagulants are discontinued at 3 months is estimated to be less than 5% in the next year and somewhat lesser in subsequent years. These patients should be encouraged to have prophylactic anti-coagulants if exposed to a high-risk state and, in general, should be encouraged to seek alternatives to oestrogens for contraception or post-menopausal use. Moderate-risk patients are those without inherited or acquired thrombophilia who had a thromboembolic event in association with a minor risk factor, such as, oestrogen use or long distance travel. Their risk of recurrent thrombosis after 6 months of anti-coagulants is likely to be less than 10% in the year after stopping anti-coagulants, provided that the precipitating risk factor is avoided; they should be treated with anti-coagulants for 6 months. If, however, the precipitating factor cannot be avoided (e.g., oestrogens) they should be given the option of remaining on anti-coagulants during the period of exposure. High-risk patients are those who have an unprovoked venous thromboembolic event and who either have no demonstrable thrombophilia or are heterozygous for factor V Leiden or the prothrombin G20210A mutation. Their risk of recurrence after 6 months of anti-coagulant therapy is likely to be about 10% per annum. In general, anti-coagulant therapy can be stopped after 6 months in these high-risk patients. If, however, the bleeding risk is low, the INR monitoring is smooth and convenient, and the patient prefers to remain on anti-coagulant therapy, treatment can be continued and the treatment duration reviewed on an annual basis. Very high-risk patients are those with more than one unprovoked thromboembolic event; patients with inherited deficiencies of anti-thrombin, protein C, or protein S; those with anti-phospholipid antibody syndrome or advanced malignancy; and those who are homozygous for factor V Leiden or prothrombin gene mutation or double heterozygotes. The risk of recurrence after a 6-month course of anti-coagulants is likely to be more than 12% annually and, in general, these patients should remain on anti-coagulants indefinitely. Firm evidence for this last recommendation is not available, but because the listed thrombophilic states are strong risk factors for a first episode of VTE, they are also likely to increase the risk of recurrent VTE.

PPS and its prevention

Following an episode of DVT, one-fifth of patients may experience PPS.¹⁶² Leg pain and swelling exacerbated by standing and physical activity and reduced with elevation of the affected leg are typical features. In severe cases, venous ulceration can develop. PPS occurs as a result of venous hypertension, most commonly caused by venous valvular incompetence and less frequently by persistent venous obstruction. Not all patients with valvular incompetence develop the clinical features of PPS.¹⁶³ Two approaches have been proposed to prevent and treat PPS, thrombolytic therapy to reduce the damage to venous valves and graduated compression stockings to counter venous hypertension. Results from clinical trials have, however, not clearly shown beneficial effects with either method.^{162,164,165} The development of PPS is more likely after recurrent episodes of DVT. Therefore, every effort should be made to reduce the likelihood of recurrent thrombosis by using an appropriate course of anti-coagulant therapy for the initial episode and anti-coagulant prophylaxis in subsequent high-risk situations.

Treatment of DVT in pregnancy

UFH was the standard treatment for DVT in pregnant women prior to the introduction of LMWHs. Warfarin is generally avoided because of the risk of warfarin embryopathy and other potential teratogenic effects. UFH has a number of limitations, including heparin-induced osteoporosis, the need for twice-daily subcutaneous injections, and the necessity for aPTT monitoring. These disadvantages are virtually eliminated with LMWH. Although there have been no randomised controlled trials comparing UFH with LMWH in pregnancy, there is no reason to expect that the advantages of LMWH in the non-pregnant population would not apply to pregnant women.¹⁶⁶ In addition to the convenience of once-daily injection without the need for frequent laboratory monitoring, like UFH, LMWH does not cross the placenta. Therefore, it is not teratogenic and is not excreted into breast milk. Pregnant women are treated throughout their pregnancy with LMWH and arrange for a planned induction of labour

in consultation with the obstetrician. The controlled delivery date enables discontinuation of LMWH 24 hours prior to induction, reducing the risk of bleeding during delivery.

Screening for thrombophilia

The indications for screening patients, who present with a first episode of venous thrombosis to identify underlying thrombophilia, are controversial. From a practical viewpoint, screening would be indicated if the results influenced the duration of anti-coagulant therapy or the need for family counseling. The duration of anti-coagulant therapy is influenced by finding deficiencies in anti-thrombin, protein C, or protein S, homozygous factor V Leiden, homozygous prothrombin gene mutation double heterozygosity, and persistently elevated anti-phospholipid antibodies. Family counselling is particularly important for female carriers who are contemplating oestrogen use. Based on these considerations, we think that it is reasonable to perform screening for thrombophilia in the following groups: first episode of idiopathic thrombosis at age 50 or younger; history of two or more episodes of recurrent thrombosis, especially if the events were unprovoked; thrombosis in an unusual site (e.g., cerebral, mesenteric, retinal); positive family history with two or more first-degree relatives with documented venous thrombosis; women who develop pregnancy associated thrombosis or in the setting of a hormonal agent; and women who have unexplained recurrent pregnancy loss. This latter group requires special consideration because anti-coagulant and anti-platelet therapy may improve future pregnancy outcomes if underlying thrombophilia is documented.¹⁶⁷ A standard screening panel includes functional assays for anti-thrombin and protein C, free protein S level, activated protein C resistance assay with DNA testing for factor V Leiden, molecular assay for prothrombin G20210A mutation, a phospholipid-based clotting test for lupus anti-coagulant, ELISAs for anti-cardiolipin antibodies, and a fasting homocysteine level.¹⁶⁸

New anti-thrombotic agents

Several new anti-thrombotic agents that target selectively single molecules in the coagulation cascade are under development. Parenteral

direct inhibitors of thrombin; hirudin and argatroban have been approved for the treatment of HIT. Danaparoid, a heparinoid can be also used for HIT. The synthetic pentasaccharide, fondaparinux (Arixtra) and the oral direct thrombin inhibitor ximelagatran (Mela-gatran) are two potential additional agents.

Synthetic pentasaccharide is administered as a once-daily subcutaneous injection and is being compared with UFH for initial treatment of DVT and pulmonary embolism. This new agent has the advantage of a longer half-life than LMWH and is unlikely to produce heparin-induced thrombocytopenia. A newer form of synthetic pentasaccharide with a longer half-life that enables once-weekly subcutaneous injection is also being evaluated for the out-of-hospital longer-term treatment of patients with VTE. Large randomized controlled trials have shown that pentasaccharide is superior to enoxaparin in thromboprophylaxis after major orthopaedic surgery.^{167,170} Ximelagatran is administered orally and is being compared against standard anti-coagulants for thromboprophylaxis in orthopaedic surgery, atrial fibrillation, as well as initial and long-term treatment of VTE.^{171,172}

Thrombolytic therapy for DVT

The role of thrombolysis in DVT treatment remains ill-defined. Venographic studies, thrombolytic agents can produce rapid lysis of venous thromboemboli and restore venous flow. Consequently, thrombolytic therapy has the potential to provide prompt symptomatic relief and reduce the risk of the PPS.^{173,174} Despite documented improvements on radiologic imaging, however, appropriate studies have not been performed to demonstrate improvements over standard anti-coagulant therapy alone, using clinically relevant outcomes. Thrombolytic therapy increases the risk of major bleeding about 3-fold over that observed with UFH alone, and the observed rate of intracranial haemorrhage is approximately 2%.¹⁷⁵ There is no agreement on whether systemic or catheter-directed thrombolysis is the preferred method of delivery. A recent randomised, controlled trial comparing UFH alone with four regimens of systemic or regional thrombolysis showed greater venographic improvement at 12 months with systemic thrombolytic therapy, but at a cost of substantially higher rates of major bleeding and pulmonary embolism compared with

UFH.¹⁷⁶ Therefore, even if thrombolysis is effective in reducing the risk of recurrent thrombosis or PPS, the cost, the bleeding risk, and the technical expertise required for this aggressive therapy are major obstacles to its routine use. Most clinicians limit thrombolytic therapy to younger patients with massive iliofemoral vein thrombosis, who have limb-threatening circulatory compromise.

Vena caval interruption

In the presence of a contraindication to anti-coagulant therapy, an inferior vena caval filter is placed in patients with iliofemoral DVT. These circumstances include active bleeding, risk of serious bleeding, and failure of therapeutic anti-coagulant therapy. The use of filters remains controversial in other clinical situations, for example, for preventing embolisation of “free-floating” thrombi in iliofemoral territory and as the first-line treatment (alone) in patients with central nervous system malignancy and acute DVT.¹⁷⁷ Only one randomised, controlled trial has evaluated the use of vena caval filters in patients with proximal DVT, all of whom also received anti-coagulant therapy.¹⁷⁸ There was a significant initial reduction in the incidence of pulmonary embolism in the filter group, but this advantage was lost with longer follow-up. In addition, patients with a filter had a higher risk of recurrent DVT and there was no difference in the overall mortality at 2 years following the study. Similar results are reported by a population-based analysis in more than 3600 patients in whom a filter was inserted for DVT.¹⁷⁹ Other potential situations where caval interruption may be indicated include: patients with a newly diagnosed proximal DVT or pulmonary embolism who have to undergo urgent surgery; who have severe thrombocytopenia; or have active and potentially life-threatening bleeding. In all cases, anti-coagulant therapy is restarted when normal haemostasis is achieved.

SECURING HAEMOSTASIS IN HAEMOSTATIC FAILURE

General aspects of anti-coagulant therapy

This is achieved by anti-coagulation initially by heparin and subsequently by warfarin for 3 to 6 months. Anti-coagulants are commonly

used in cardiological practice and in the prevention and the treatment of deep venous thrombosis (DVT) and pulmonary thrombosis (PE). The objective of anti-coagulant treatment is to achieve a level of anti-coagulant at which there is complete anti-thrombotic effect, but no increased risk of bleeding. This ideal is not achieved with current drugs, the main ones in the UK being heparin and warfarin. Careful and regular laboratory control is required to achieve a compromise between efficacy and risk.

Heparin

Unfractionated heparin (UFH) is a naturally occurring strongly anionic mucopolysaccharide, MW 5000–35,000 d. Its main action is to augment the effect of the physiological anti-coagulant, anti-thrombin (AT). Arginine residues on the AT molecule interact with serine residues on certain activated coagulation factors – thrombin, Xa, IXa, XIa, XIIa-forming irreversible complexes, which are removed by reticulo-endothelial cells. Heparin increases the inhibitory action of AT by 1000-fold. Low molecular weight heparin (LMWH) MW 2000–8000 d are prepared from UFH by chemical or enzymatic depolymerisation. Acceleration of inhibition of factor Xa requires only the pentasaccharide sequence, but acceleration of thrombin inhibition requires a minimum total chain length of 18 saccharides (MW 5000 d). Therefore, in all LMWHs the anti-Xa activity is greater than the anti-IIa activity.^{146–149}

The usual routes of administration are by continuous IVI for UFH (half-life about 1 hour); twice daily SC injections have also been used. LMWH is usually given by once or twice daily SC injection.

Laboratory monitoring

The APTT should be measured 4 to 6 hours after starting the IV UFH and, thereafter, once daily aiming to keep the APTT ratio between 1.5–2.5. The platelet count should also be monitored because of the risk (1–2%), of heparin-induced thrombocytopenia (HIT), which may be associated with arterial thrombosis.

No laboratory monitoring is required for LMWH therapy in routine circumstances. For certain patient groups this will be required

and is carried out by measuring anti-Xa levels (see diagnosis and treatment of DVT).

Side effects

Bleeding is the most common side effect.¹⁵⁷ The infusion should be stopped, a clotting screen checked, and blood transfusion may be necessary. Due to its short half-life, heparin may be recommenced after few hours at a lower dose. If bleeding is severe, heparin can be neutralised by IV administration of protamine sulphate. Other side effects include HIT,¹⁸⁰ osteopenia (on prolonged administration), skin necrosis, alopecia, and hypersensitivity reactions.¹⁸⁰

Warfarin

It antagonises vitamin K, required for gamma carboxylation of certain glutamic acid residues that facilitate calcium binding of coagulation factors II, VII, IX, and X and the naturally occurring anti-coagulants proteins C and S. Warfarin takes 3 to 5 days to achieve an anti-coagulant effect which is dependent on achieving a sufficiently low level of factor II (half-life 60 hours). Therefore, heparin and warfarin should be overlapped for at least 72 hours, and heparin should not be stopped until the International Normalised Ratio (INR) is > 2.0 (usually after 5 days of overlap). A number of drugs may interact with warfarin (potentiate or antagonise) and change warfarin requirements, sometimes dramatically.^{153,181,182}

Laboratory monitoring

The INR is a standardised PT. The usual recommended therapeutic range is 2 to 3 or 3 to 4.5 depending upon the indication. The dose of heparin may need to be reduced as the INR rises. The patient should be counselled about warfarin treatment and seen in the anti-coagulant clinic within a week of discharge.

Side effects

Bleeding, usually related to overdosage, is the most common side effect. If the INR is > 4.5 and there is no bleeding, stop the warfarin,

check the INR at 24 to 48 hours, and restart warfarin at a lower dosage. Serious bleeding necessitates treatment with fresh frozen plasma or clotting factor II, IX, X, and VII concentrates. Vitamin K1 given IV slowly acts within a few hours, but may cause problems with reanti-coagulation for unpredictable lengths of time (up to 3 weeks). Small doses are advised (1 to 2 mg) unless further warfarinisation is not required (10 mg). Other side effects include skin necrosis (protein C or S deficiencies), skin rashes, or alopecia.^{156,157,182}

Pregnancy

Warfarin crosses the placenta and is teratogenic, particularly between weeks 6 to 12. Later in pregnancy it may precipitate intracerebral haemorrhage in the fetus. Heparin does not cross the placenta and is the anti-coagulant of choice during pregnancy. Neither heparin nor warfarin is excreted in breast milk.

Advantages of LMWH (Table 8)

1. LMWH have a greater bioavailability at low doses, longer half-life, and more predictable response when administered at fixed doses than UFH.
2. No need for routine laboratory monitoring.

Table 8. Comparison of the Properties of LMWH and UFH

Property	UFH	LMWH
Mean MW (range)	15 (4–30)	4.5 (2.4–15)
Saccharide units (mean)	40–50	13–22
Anti-Xa: Anti-IIa	1:1	2:1–4:1
Inhibited by PF4	Yes	No
Anti-thrombotic effect via anti-IIa	Yes	Yes
Inhibits platelet function	Yes	No
Bioavailability (at low dose)	40%	100%
Elimination	Hepatic and renal	Renal
Half-life of anti-Xa: IV	1 hour	2 hour
SC	2 hour	4 hour
Monitoring required	Yes	No
Frequency of HIT	High	Very low

3. LMWH provide an anti-thrombotic efficacy in the prevention of postoperative DVT and PE, at least as good as UFH in general surgery. This effect may be obtained by once daily SC dose.
4. In orthopaedic surgery, LMWH is superior to UFH as prophylaxis for postoperative DVT, in terms of efficacy without increasing the bleeding risk.
5. SC LMWH is as effective and safe as UFH (IV or SC) for the initial treatment of DVT.
6. LMWH is effective as anti-coagulant in chronic haemodialysis, given as a single bolus injection.
7. LMWH treatment may be associated with a lower incidence of thrombocytopenia and fewer cases of heparin-induced thrombocytopenia and thrombosis.
8. LMWH can be used to treat some patients with DVT and PE as outpatients and at home.
9. LMWH is associated with less osteopenia and heparin-induced osteoporosis related clinical fractures.

Disadvantages of LMWH; cost

Heparin-induced thrombocytopenia

The incidence of heparin-induced thrombocytopenia (HIT) with full dose unfractionated heparin appears to be around 1 to 3%, higher with heparin of bovine than porcine origin, and the incidence is somewhat less with heparin used at prophylactic doses and new LMWHs. HIT has been divided into two groups. Type I is a mild immediate transient thrombocytopenia that occurs soon after heparin exposure. It is seldom associated with a platelet count below $100 \times 10^9/l$ and resolves spontaneously even if treatment is continued. This very seldom, if ever, results in clinical problems. Type II has its onset after greater than 5 days' exposure to heparin. It is associated with a platelet count often below $100 \times 10^9/l$ and is the immune mediated form that is associated with arterial and venous occlusion.¹⁸⁰

Diagnosis remains primarily clinical being based on a fall in the platelet count to less than half the baseline value and usually lower than $100 \times 10^9/l$ with, onset 5 or more days after exposure to

heparin.¹⁸⁰ Other causes of thrombocytopenia, such as, sepsis and ITP should be excluded and the thrombocytopenia will resolve following heparin withdrawal, usually after 5 to 7 days, but this can take up to a month. Clinical diagnosis can be supplemented by positive laboratory tests for the presence of a heparin-dependent antibody.

HIT may be preventable by minimising the duration of heparin exposure and performing regular platelet counts on patients with heparin and ensuring prompt withdrawal of therapy should the platelet count fall.

The treatment of HIT involves the immediate cessation of exposure to heparin. In the majority of cases, particularly where thrombosis has occurred, it will be necessary to commence warfarin. There is often a need for a short acting anti-coagulant to substitute for heparin until warfarin has reached therapeutic levels. Therapy is between the heparanoid Danaparoid, which has only 10% cross-reactivity with unfractionated heparin or hirudin which does not cross-react in HIT. LMWH suffers 40 to 90% incidence of cross-reactivity with unfractionated heparin. Other treatments, such as, ancrod is not used routinely.¹⁸⁰ Fondaparinux is another potential alternative in HIT.¹¹²

As the platelet count seldom falls into single figures, the placement of IVC filters and the use of fibrinolytics and surgery have all been safely performed to alleviate thrombotic complications despite the thrombocytopenia.

The mechanism of HIT is due to the formation of antibodies against the complex of heparin with platelet factor-4, a highly positively charged heparin binding protein released from platelet α -granules. The immune complex with heparin and PF-4 binds to platelet surface FC receptors, and this binding results in *in vivo* platelet activation and subsequent aggregation. The mechanisms of thrombosis are probably multifactorial as in addition to *in vivo* platelet aggregation, there is also evidence of activation of the coagulation cascade with increased levels of markers of thrombin generation and depletion of the proteins of the natural anti-coagulant pathway. Furthermore, endothelial cell immune mediated damage results in the exposure of endothelial cell tissue factor and the formation of a pro-coagulant endothelial surface to favour thrombosis.¹⁸⁰

Table 9. INR Targets for Anti-coagulation

INR (International Randomised Ratio)	Clinical State
2.0–2.5	Prophylaxis of DVT, including high risk surgery
2.0–3.0	Hip surgery, repair of fractures of femur Treatment of DVT and pulmonary embolism Prevention of VTE after myocardial infarction Mitral stenosis with embolism Atrial fibrillation Transient ischaemic attacks
3.0–4.5	Recurrent DVT Recurrent pulmonary embolism Arterial disease including myocardial infarction and grafts Prosthetic valves and grafts

Accepted target INR therapeutic ranges

The current accepted INR targets for anti-coagulation as recommended by the British Committee for Standardisation in Haematology¹⁸² are summarised in Table 9.

Potential factors that interfere with anti-coagulant control

Clinical conditions with potentiating effect on anti-coagulation

- Alcohol excess
- Cardiac failure
- Cholestasis
- Diarrhoea (enteritis)
- Fever
- Gastrocolic fistula
- Hypoalbuminaemia
- Liver damage (*decreased synthesis of vitamin K factors*)
- Malnutrition
- Severe weight reduction regimens
- Renal impairment
- Thyrotoxicosis

Pharmacological agents (Table 10)**Table 10. Drugs that Interfere with the Control of Anti-coagulant Therapy¹⁸²**

Potentialiation of oral anti-coagulants Drugs that increase the effect of coumarins	Inhibition of oral anti-coagulants Drugs that reduce the action of coumarins
<i>Reduced binding to serum albumin</i>	<i>Acceleration of hepatic microsomal degradation</i>
Phenylbutazone Sulphonamides Co-trimoxazole Amidarone	Barbiturates Rifampicin
<i>Inhibition of hepatic microsomal degradation</i>	<i>Enhanced synthesis of clotting factors</i>
Cimetidine Allopurinol Tricyclic anti-depressants Metronidazole Sulphonamides	Oral contraceptives
<i>Alteration of hepatic receptor for drug</i>	
Thyroxine Glucagon Quinidine	
<i>Decreased absorption of vitamin K</i>	
Laxatives	

NB: Patients are also more likely to bleed if taking anti-platelet agents (e.g., NSAIDs, dipyridamole, or aspirin).

Conditions with inhibitory effect on anti-coagulation

- Pregnancy
- Hereditary resistance to warfarin

Managing anti-coagulation in patients undergoing surgery

In patients who are already anti-coagulated and contemplating surgery, it is important to balance the risk of haemorrhage if the INR is not reduced against the risk of thromboembolism if it is reduced too low for too long. The patient should be referred to the anti-coagulant clinic well in advance of any planned surgery to advise patients about their anti-coagulant therapy modification.

Minor surgery. For most minor procedures, e.g., dental work, it is sufficient to simply omit warfarin for 2 days prior to the procedure and restart with the usual maintenance dose immediately afterwards (the same day). Alternatively, warfarin could be stopped for 3 days before the procedure and recommenced the day immediately before the procedure (it takes time for warfarin effect to be established). If any problems are anticipated or there have been problems in the past, then the INR should be checked beforehand. If $\text{INR} < 2.5$ then it is safe to proceed (Fig. 12).¹⁸³

Extreme caution should be exercised with patients who have prosthetic heart valves. The INR should not be allowed to drop too low. If several extractions are required or there is any doubt, then follow the guidelines for major procedures.

Intermediate and major surgery (Fig. 13)

(I) Low risk patients

E.g., Mitral valve disease, atrial fibrillation, cardiomyopathy¹⁸³

Stop warfarin 3 days prior to surgery.

Start heparin 5000 iu s/c 3 times daily or equivalent LMWH dose when $\text{INR} < 2.5$.

Avoid giving heparin < 2 hours before surgery.

Check $\text{INR} < 2$ and $\text{APTT} < 45$ seconds before surgery.

Restart warfarin postoperatively and overlap with heparin until $\text{INR} > 2.5$ for at least 2 consecutive days.

(II) High risk patients

E.g., Mechanical valve replacement, recurrent or acute thromboembolism, known thrombophilia¹⁸³

The management of these patients requires considerable effort and attention. Coordination and communication between the surgeons and the anti-coagulant clinic team is paramount.

Stop warfarin > 3 days before surgery.

When $\text{INR} < 2.5$ start iv heparin at 20,000 iu per 24 hours and adjust to give APTT 1.5–2.5 times control if patient is hospitalised.

Alternatively give LMWH therapeutic dose as an outpatient.

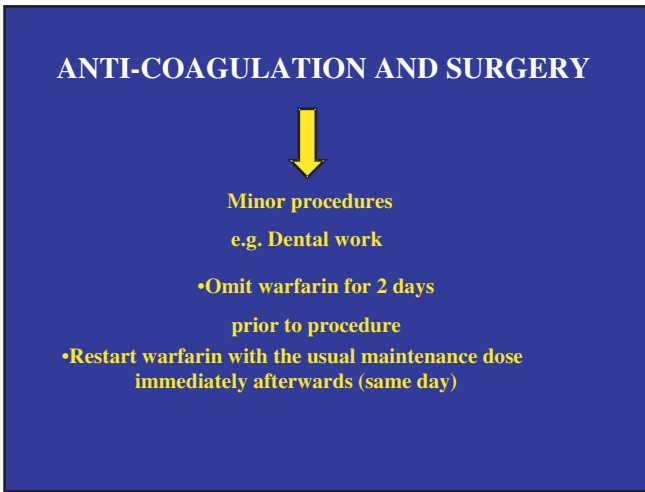


Fig. 12 Flow chart summarising the management of oral anti-coagulation in minor surgical procedures.

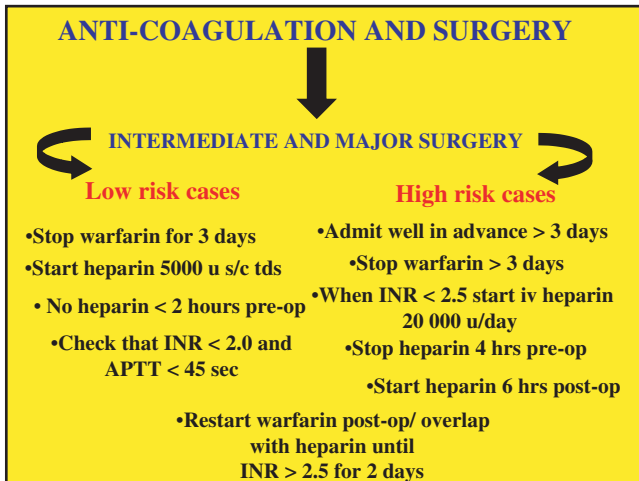


Fig. 13 Flow chart summarising the management of oral anti-coagulation in intermediate and major surgical procedures.

Stop heparin 4 hours (if LMWH, stop it 12–24 hours prior to surgery depending on dose and type of LMWH) prior to surgery and check that INR < 2.0 and APTT < 45 seconds immediately before the procedure. If not, then it will probably be sufficient to wait for 1 to 2 hours and repeat the tests.

Restart heparin 6 hours postoperatively and re-establish therapeutic levels.

When stable restart warfarin and overlap with heparin for at least 2 days.

Do not give a loading dose and remember that the patient is not eating and vitamin K deficiency may be a problem.

Stop heparin when INR > 2.5. If re-operation is possible, continue with heparin.

Reducing the risk of thromboembolism

The risk of thromboembolism and associated morbidity depends on the indication for anti-coagulation: if and how long before patients have had previous episodes of thromboembolism and whether or not surgery increases the risk of thromboembolism. The risk of preoperative bleeding is generally low, but is high following major surgery. As the risk of thromboembolism and bleeding are often influenced by the surgical procedure, anti-coagulant management needs to be considered separately for the pre- and postoperative periods.

Preoperative

Indications for warfarin

To assess the risks associated with temporarily stopping anti-coagulants, the consequences, as well as the absolute risk, of a thromboembolic event need to be considered. Arterial thromboembolism (ATE) often results in death (~40%) or major disability (~20%) whereas venous thromboembolism (VTE) rarely presents as sudden death (~5 to 10%), and major disability is also unusual (<5%) in patients with treated VTE.¹⁸³

(a) Arterial indications for anti-coagulation

Primary prophylaxis of ATE is most commonly undertaken in patients with atrial fibrillation (AF), valvular heart disease, and recent myocardial infarct. Secondary prophylaxis is undertaken after patients (with or without the above conditions), have had an ATE event (usually stroke). Previous thromboembolism is a major risk factor for recurrence.¹⁸³

Previous ATE

These patients have a higher risk of embolism than patients without previous episodes. Therefore, the period of sub-therapeutic anti-coagulation should be kept to a minimum. In patients whose INR is 2.0–3.0, it takes 4 days for it to spontaneously fall to < 1.5 , an intensity of anti-coagulation at which increased intra-operative bleeding is not expected after anti-coagulation is stopped. Therefore, 4 daily doses of warfarin should be withheld preoperatively, and the INR should be measured the day before surgery to determine if a small dose of vitamin K is needed to accelerate the reversal of anti-coagulation:

(1) In general, give 1 mg of vitamin K by slow i.v. injection if the INR is > 1.7 the day before the surgery, repeat the INR the morning of surgery.

(2) If necessary, fresh frozen plasma (FFP) can be given prior to surgery if the INR is still not acceptable (i.e., INR 1.3–1.7, 1 FFP unit, 1.7–2.0, 2 FFP units). Administration of blood products should generally be avoided for elective surgery.

No previous ATE

The risk after discontinuing anti-coagulation is lower in patients who have not had a previous episode. Warfarin can be withheld for 5 doses to ensure that coagulation has returned to normal prior to surgery; however inpatients with prosthetic heart valves have a higher risk of thromboembolism. In these patients, i.v. unfractionated heparin should be substituted while warfarin (alternatively LMWH therapeutic schedules may be used) is withheld till INR < 1.3 , then heparin is withheld 1 to 2 hours (short half-life) prior to surgery. As the usual intensity of anti-coagulation is higher in such patients, a small dose of vitamin K is required more often in these patients on the day before surgery.¹⁸³

Last episode of ATE within 1 month

The risk of recurrent ATE is highest within a month of an acute event (about 0.5% per day). To minimise the possibility of preoperative embolism, i.v. heparin should be administered when INR drops to < 2.0 . Stopping i.v. heparin 6 hours prior to surgery should be adequate for the aPTT to return to normal before surgery.¹⁸³

(b) Venous indications for anti-coagulation

The main indication for anti-coagulation is prevention of recurrent VTE. An exception occurs in selected patients with patients with thrombophilia (e.g., anti-thrombin, protein C, protein S deficiencies, FV Leiden abnormalities, and strong family history of thromboembolism).¹⁸³

Last VTE event within 1 month

The risk of recurrent VTE declines rapidly with duration of anti-coagulation. There is a very high risk of recurrent VTE if anti-coagulants were stopped within 1 month of VTE. Therefore, if feasible, surgery should be deferred until patients have received 1 to 3 months of anti-coagulation. If this is not feasible, preoperative thromboembolic risk should be minimised by administering i.v. heparin when INR is less than 2.0.

Last VTE between 1 to 3 months

These patients have a moderately high risk of recurrent VTE if anti-coagulants are stopped. Warfarin should only be withheld for 4 doses to minimise this period of high risk.

Last VTE > 3 months

These patients have a much lower risk of recurrent VTE than those who have been treated for < 3 months.

Postoperative

Start warfarin as soon as possible

If coagulation has previously returned to normal, there will be 2–3 days delay after warfarin is restarted before the INR begins to increase. Thus warfarin should be restarted as soon as possible after surgery in all patients who do not have additional invasive procedures planned. In patients who are having a minor procedure associated with a low risk of bleeding, warfarin can be restarted shortly before surgery.¹⁸³

Previous ATE within 1 month of minor surgery

The risk of recurrence is sufficiently high within a month of acute ATE that i.v. heparin is warranted until the INR reaches 2.0, provided the risk of bleeding is not very high. Heparin should be started 12 hours after surgery.¹⁸²

Previous ATE within 1 month of major surgery

Despite a high risk of recurrence while the INR sub-therapeutic, heparin should be avoided shortly after major surgery as the risk of bleeding will likely outweigh the anti-thrombotic benefits. Unfractionated heparin or LMWH given in doses recommended for VTE prophylaxis of high risk patients is safe and should be given until the INR reaches 1.8.

No previous ATE within 1 month of surgery

This includes patients without previous ATE and those with ATE that has occurred more than a month previously. S.C Heparin should be given at prophylactic dose.

Postoperative VTE

Surgery is a major risk factor for VTE, and the risk of thrombosis is much higher postoperatively than it is preoperatively. Therefore, the greater need for thromboprophylaxis postoperatively.

Recommendation on the reversal of oral anti-coagulant treatment by the British Committee for Standardisation in Haematology¹⁸² in managing bleeding episodes related to warfarin are:

1. *Life-threatening haemorrhage*

Immediately give vitamin K (5.0 mg) intravenously slowly and either a concentrate of factor II, IX, X with factor VII (if available) or fresh frozen plasma.

2. *Less severe haemorrhage, e.g., epistaxis or haematuria*

Withhold warfarin for one or more days and consider giving vitamin K (0.5–2.0 mg) intravenously slowly.

3. *INR > 4.5 with no haemorrhage*

Withhold warfarin for 1 or 2 days, then review.

4. *Unexplained bleeding at therapeutic levels*

Investigate for underlying cause, e.g., renal or alimentary tract abnormality.

SURGERY IN PATIENTS WITH BLEEDING TENDENCY

Inherited coagulation disorders

von Willebrand's disease

vWD is the most common hereditary haemostatic disorder, this is associated with reduction in von Willebrand factor (vWF) quantity or function resulting in defective platelet adhesion and because vWD is the carrier molecule for VIII, low factor VIII clotting activity. The inheritance is autosomal dominant with varying expression. vWD is usually of mild to moderate severity (easy bruising, mucous membrane bleeding, epistaxis, menorrhagia), prolonged bleeding following minor injury or surgery, but in the rare homozygous form, patients suffer haemarthroses and muscle haematomas.

The condition is diagnosed by a combination of the clinical findings supported by abnormal laboratory tests (depending on the type) including, prolonged bleeding time, prolonged aPTT, low factor VIII clotting activity, defective ristocetin induced platelet aggregation, low vWF antigen, and ristocetin cofactor activity. Patients with a mild phenotype respond to Desmopressin (DDAVP), while more severe ones require factor VIII concentrate, which contains vWF. Specialist input from a haemophilia centre should be sought as early as possible if surgery or other procedures were anticipated.

Haemophilia A (factor VIII deficiency)

Haemophilia A (HA) is inherited as an X-linked recessive disorder, but 33% of cases arise as a result of spontaneous mutation. It affects 1 in every 10,000 males. Patients with severe HA (VIII < 1% of normal) suffer from recurrent spontaneous painful haemarthroses and muscle haematomas with progressive deformity and crippling, if not

adequately treated. Haemophiliac pseudotumours may occur in long bones from repeated sub-periosteal haemorrhage with bone destruction, new bone formation, expansion of the bones and pathological fractures. Patients with moderately severe and mild disease may have severe post-traumatic bleeding.

Diagnosis in suspected patients is established by specific laboratory tests including prolonged aPTT, low factor VIII clotting activity, normal vWF level, and normal bleeding time.

Bleeding episodes are treated with factor VIII concentrates (plasma derived or recombinant) or in milder cases Desmopressin (DDAVP), which lead to a temporary rise in factor VIII due to release from the vascular endothelium. An anti-fibrinolytic agent (e.g., tranexamic acid) should also be given because Desmopressin also induces vascular release of t-PA.¹⁸⁴

Haemophilia B (factor IX deficiency) (Christmas disease)

The inheritance and clinical features of factor IX deficiency are similar to those of Haemophilia A. The incidence is about 1 in every 50,000 males. The diagnosis is established by demonstrating low levels of Factor IX clotting activity in a patient with suspected deficiency and prolonged aPTT, normal bleeding time. Bleeding episodes are treated with factor IX concentrate (plasma derived or recombinant).¹⁸⁴

Haemophilia and surgical procedures

With proper care most procedures can now be carried out on haemophiliacs. The risk of any procedure is, however, greater than for someone with a normal factor VIII level, and the risks and the benefits of the procedure should be carefully evaluated and any alternatives considered. Lack of communication is a source of major problems and steps should be undertaken to prevent this. For this, a written plan should be documented in the patient's notes. This may subsequently be revised and any amendments to the plan should also be documented.¹⁸⁴

For specific therapy and perioperative management, the haematologist in charge of the haemophilia centre should be involved.

Confirm the diagnosis of haemophilia, ascertain if an inhibitor is present or not, and ascertain the previous recovery levels in response to DDAVP. Is this the patient's first exposure to blood products? If so, virological surveillance tests are required. Explain to the patient the risks and the benefits. Has the patient received hepatitis B vaccination? Any additional problems, e.g., thrombocytopenia in HIV infected patients or abnormal liver function tests (and, therefore, prolonged PT).^{184,185}

Intermediate and Major Procedures

Plan of management

Should include:

- Type of concentrate to be used (or DDAVP).

- The initial level required to cover surgery.

- The duration of treatment required (the exact frequency of treatment will have to be managed on an *ad hoc* basis).

- Need for tranexamic acid.

- Frequency of monitoring and exact timing in relation to surgery.

Perioperative management

- Give the FVIII approximately 90 minutes before the planned operation time.

- Take pre- and post-infusion levels.

- Except for minor procedures, take a "fall off" level 4 hours post-operatively to plan further replacement therapy.

Postoperative management

- After major procedures the FVIII level should not be allowed to fall below 50% for at least 10 days.

- Beyond the immediate postoperative period treatment is determined by FVIII half-life (12 hours), therefore, 12-hourly infusions to 100% levels is satisfactory.

- Frequent measurement of levels is very helpful as there is a tendency for them to drift either up or down.

Any postoperative procedures, such as, removal of drains or physiotherapy should be timed to follow shortly after FVIII administration.

A period of once daily treatment, which may be given at home may be necessary in some patients. Its duration should be judged from the nature of the procedure and the need for any further treatment, such as, physiotherapy.

Minor procedures

Some minor procedures require only a single dose of FVIII to approximately 60%, unless problems arise. This can be used in the following procedures:

- Skin biopsy and minor skin surgery
- Endoscopy
- Straightforward dental extraction
- Liver biopsy:

The transjugular approach is the preferred method in patients with bleeding disorders in general.

HAEMOSTATIC ALTERATION IN CARDIOPULMONARY BYPASS SURGERY

Open cardiac surgery produces significant activation of coagulation, fibrinolysis, and platelets, despite the use of heparin. This is due to the presence of the cardiopulmonary bypass circuit. The following are well-documented alterations.¹⁸⁶

1. **Platelet defects during CPB:** A qualitative platelet abnormality exists in virtually 100% of patients during CPB and usually reverses within an hour or so after completion of CPB. The blood-material surface interaction and shear effects of flow through the circuit traumatise platelets. CPB produces thrombocytopenia, platelet fragmentation, and platelet function abnormalities, including a reduced response to aggregation stimuli. This is due to discharge of alpha granules and loss of platelet membrane receptors, such as, GpIb and GpIIb/GpIIIa. As P-selectin is expressed on the inner

surface of α -granules, their release produces increased platelet surface expression of P-selectin. Activated platelets are also able to bind leucocytes forming polymorphonuclear- and monocyte-platelet conjugates. The degree of impairment in platelet function correlates with the duration of CPB and with the level of hypothermia. The defect occasionally persists longer and sometimes results in bleeding. The level of hypothermia used during the procedure and contact with the synthetic surface of the oxygenator contribute to the haemostatic defect. Moderate hypothermia (28–32°C) is used during CPB to reduce tissue ischaemia and preserve the myocardium. This affects platelet number and function. The generation of thrombin-antithrombin (TAT) complexes is greater during and after hypothermic bypass compared to normothermic bypass. Postoperative blood loss and transfusion requirements also appear to be greater in patients undergoing hypothermic CPB.¹⁹⁵

Transfusion of platelet concentrates promptly controls the bleeding. Despite abnormalities in platelet number and function, there is no evidence that routine perioperative transfusion of

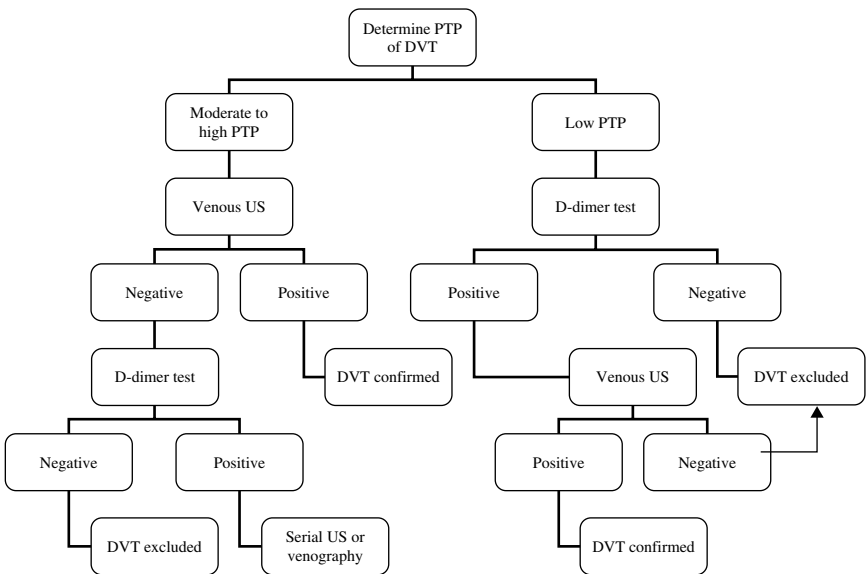


Fig. 14 Algorithm for diagnosing DVT based on clinical assessment of pre-test probability (PTP), venous ultrasonography (US), and d-dimer testing.

platelet concentrates is necessary (Office of Medical Application of Research, National Institute of Health, UK Health Department 1989). Many patients with coronary artery disease may be taking aspirin. Patients taking aspirin before CPB surgery are at risk of excessive blood loss during the procedure. It is, therefore, recommended that aspirin be discontinued 5 to 10 days before CPB surgery.^{186,187}

2. **Thrombocytopenia:** Platelet counts after bypass are generally between 50 and $150 \times 10^9/l$.

Thrombocytopenia itself is rarely a cause for postoperative bleeding.

3. **Failure to neutralise the heparin completely is rarely seen with modern techniques.** Use of thrombin time (TT) and reptilase time quickly clarifies the presence of excessive heparin. Following initial adequate heparin neutralisation, the re-appearance of active heparin in the circulation may occur 2 to 6 hours later. This rebound effect is caused by the delayed return of sequestered extravascular heparin, which occurs when peripheral perfusion improves.¹⁸⁶
4. **DIC:** This does not occur regularly during the CPB procedure. In the postoperative period, DIC occurs uncommonly and usually reflects other problems, such as, poor cardiac output, acidosis, and sepsis.
5. **Fibrinolysis:** Activation of fibrinolysis measured by D-dimer levels has been shown to peak during CPB. There is a wide variation in fibrinolytic response to CPB. The increased fibrinolytic activation is mainly due to an increase in t-PA and to lesser extent by contact activation that is maximal at the first passage of blood through the extracorporeal circuit. Some of the t-PA is released from the coronary circulation after cardioplegic arrest has been performed. During CPB the peak of TAT levels precede high D-dimer levels, suggesting the majority of t-PA released is from the endothelium secondary to thrombin generation. One study showed that peak D-dimer levels correlate with postoperative bleeding. Recent studies indicate that fibrinolysis is much less frequent during bypass than previously believed and probably accounts for bleeding uncommonly. Nonetheless, if the euglobulin clot lysis time is shortened and there is no evidence of DIC, judicious use of tranexamic acid sometimes dramatically halts bleeding.^{186,188,189}

6. **Activation of coagulation during CPB:** Despite systemic heparinisation, CPB produces significant activation of coagulation compared to other thoracic operations not requiring CPB. The thrombogenic effect of the extracorporeal circuit is the main stimulus with surgical cutting playing a lesser role. The time course of activation of coagulation show a significant increase on initiation of CPB and a rapid fall at the end of CPB. CPB surgery is associated with a drop in the plasma levels of most coagulation factors, which is primarily attributable to haemodilution. As with platelet concentrates, it is not necessary to routinely transfuse FFP during CPB. Inappropriate use of FFP in CPB surgery is common and has logistic and economic implications.¹⁹⁰ Selective deficiency of high molecular weight von Willebrand factor multimers and associated prolongation of bleeding time with haemorrhagic tendency have been described in both adults and children with valvular heart disease or congenital cardiac defects. Surgical correction of the defect results in normalisation of the multimer pattern.¹⁸⁶
7. **Haemodilution:** Is a consequence of extracorporeal circulation, but the fall in haematocrit, platelet count, and plasma proteins including coagulation factors is about 25 to 30%. Therefore, it is not sufficient to cause bleeding.

Determinants of haemostasis in CPB

Given differences in bleeding rates and definitions of what is normal, excess bleeding can probably be defined as > 1 litre per procedure. There is twice the risk of bleeding after valve surgery than after CABG, and repeat operations redouble this risk; significantly, 19% of CABG patients need re-grafting within 10 years. Bleeding is usually manifest postoperatively, after protamine reversal of heparin, and shed from the operative field into mediastinal and pleural drains. If aspirin or other anti-platelet therapy has been given, the operation may be “wet” from the start.^{191–193}

Critical rates of blood loss, formulated by Kirklin and Barrett-Boyes,¹⁹⁴ are:

- 500 ml in the first postoperative hour,
- 400 ml/h in the first 2 hours,

300 ml/h in the first 3 hours,
 1 litre in 4 hours, or
 1.2 litre in 5 hours.

If bleeding attains these rates, is acute and massive, or begins again after ceasing, re-sternotomy becomes unavoidable. Volume *per se* can mislead if there is progression from blood to serosanguinous drainage; the haematocrit of the fluid in the drain tubing (not the reservoir) may indicate that blood loss is being overestimated if the patient is otherwise stable.

The need for re-sternotomy entails 30% increase in perioperative mortality and, therefore, is a crucial endpoint in CPB studies. In 67% of cases bleeding vessels are found, often small mediastinal arteries or the aortotomy incision; such vessels might not bleed if haemostasis were normal. In the remainder, general microvascular oozing is seen.¹⁹⁵

Allogeneic RBC transfusion post-CPB shows wide, apparently irrational, variance between centres. Some centres transfuse RBC to fewer than 1/3 of standard risk CPB patients, others to more than 2/3 despite access to evidence-based guidelines, with similar inconsistency in platelet and fresh frozen plasma use.^{196–201}

Withholding RBC unless the systemic haematocrit fell to < 25% (Hb < 8g/dl), post-CPB, had no adverse clinical or physiological impact in standard-risk patients. Observing this threshold is likely to reduce allogeneic transfusion. The role of cardiac surgeons and anaesthetists in UK hospital transfusion committees will be vital as a means of audit and effective guidelines in this area.^{196–201}

Preoperative determinants of haemostasis in CPB:^{191–193}

1. Bleeding increases if aspirin continues up to surgery. This effect is eliminated if aspirin is stopped 7 days before and restarted 1 to 6 hours after surgery. If aspirin cannot be stopped, haemostasis should be enhanced by anti-fibrinolytic therapy.
2. The calcium antagonist nimodipine was associated with excess post-CPB bleeding in one report.
3. Coumarin anti-coagulants (e.g., in transplantation when a donor heart arrives too suddenly to omit warfarin) require replacement

therapy with prothrombin complex concentrate (PCC) containing factor VII if INR > 1.7.

4. Coronary angioplasty/stenting with the hybrid anti-GpIIb/IIIa monoclonal agent abciximab (c7E3, ReoPro) may need urgent conversion to CABG. Intra- and postoperative bleeding occurs, particularly if the interval between abciximab and CPB is < 12 hours or if standard doses of heparin are used for CPB. Reducing heparin (to ACT 400s) with postoperative (\pm preoperative) platelets is one approach. Others suggest aprotinin with platelet transfusion (6 units) given at the end of the bypass. True and pseudo-thrombocytopenia can occur after abciximab therapy and must be distinguished from heparin-induced thrombocytopenia.
5. Patients with congenital heart disease may acquire a deficiency of high-molecular weight von Willebrand's factor, which rarely poses a problem, as it corrects immediately post-surgery. Right-to-left shunts can lead to increased platelet size with misleading automated counts (check the blood film). Children with Noonan syndrome may have coagulation factor deficiencies and can bleed during surgery for heart defects; they need a haemostatic work-up before cardiac surgery.^{191–193}
6. Patients with haemophilia may require CPB; the safest operative cover in all cases is high-purity or recombinant factor VIII:C or IX:C. In von Willebrand's disease a product with a reliably high content of high-molecular-weight multimers should be used. All such patients should be managed at centres with comprehensive expertise in haemophilia.^{191–193}
7. Preoperative thrombocytopenia compounds the bypass-induced platelet function defect. The minimum acceptable preoperative platelet count is $100 \times 10^9/l$. In patients with ITP, administration of steroids and or IVIG might be required.^{191–193}

MODIFYING PERIOPERATIVE BLOOD LOSS

Continued concerns over the risks of using allogeneic blood, especially those of transfusion-transmitted infection, combined with occasional shortage of donor blood and increasing costs (with the

introduction of universal leucodepletion in the wake of variant-CJD), have stimulated interest in perioperative blood conservation. Two broad approaches to blood conservation have been pursued. The first is to accept that blood loss is inevitable and to use measures to conserve patients' blood. Measures, such as, autologous blood pre-deposit have received increasing interest as have the use of autotransfusion, the venesection of one unit prior to CPB and reinfusion of residual oxygenator blood after bypass, the use of cell savers, and the acceptance of a normovolaemic anaemia postoperatively. These measures have been poorly applied in the UK mainly because of the high cost associated with formal programmes. The second approach to blood conservation is to prevent blood loss at the time of surgery by using pharmacological methods.²⁰²

Perioperative bleeding

Excessive bleeding can be due to surgical causes (i.e., suture deficiency) and/or derangement of haemostasis. The most important determinant of surgical blood loss is the surgeon. There is a subset of patients, however, in whom generalised oozing in the surgical field cannot be attributed to demonstrable bleeding vessels.

No consensus exists for the pathogenesis of non-surgical perioperative bleeding. There are several reasons for this: (1) failure to appreciate the limitations of laboratory tests; (2) shortcomings in the current concepts of haemostasis; and (3) lack of reliable laboratory tests for some components of haemostasis, e.g., fibrinolysis.

Pharmacological agents to reduce blood loss

(1) *Anti-fibrinolytics*^{203–219}

Aprotinin: Is a potent anti-fibrinolytic agent. Its molar potency *in vitro* is 100- and 1000-times of tranexamic acid and epsilon amino-caproic acid (EACA). It directly inhibits kallikrein production and, therefore, activation of plasminogen by factor XIIa and indirectly inhibits t-PA release by bradykinin inhibition. Aprotinin can also mop up any plasmin by its direct powerful anti-plasmin action. Aprotinin inhibits activated Protein C, which is formed during CPB. Aprotinin is a bovine protein and, therefore, can provoke an immunological reaction.

The most dramatic reductions in perioperative blood loss have been associated with the administration of aprotinin. Royston *et al.*,^{203,204,208} gave a high dose aprotinin regimen in patients undergoing “repeat” cardiac surgery. Postoperative drainage loss was reduced by 81%, total haemoglobin loss by 89%, and mean blood transfusion requirement was reduced by 91%. Further clinical studies have confirmed that high-dose aprotinin dramatically reduces blood loss after CPB. Shorter operating times are also seen in children, a probable consequence of the fact that the operative fields remain “bone dry”.

It is widely used in Europe including the UK. It is licensed for use in high risk cases, but most cardiac surgeons are reluctant to use it in first time CABG. This is due to the theoretical (but unproven) prothrombotic effects and the potential for the patient to develop anti-aprotinin antibodies that would prohibit their use in future surgery. The use of recombinant protein analogous to human pro-tease nexin II has shown some efficacy in a sheep model.²⁰³ The majority of users of aprotinin in the UK do not use the full high-dose regimen, to reduce cost, and in the recognition that a lower dose does reduce bleeding, although possibly not to the same extent.²⁰⁸

Aprotinin has no effect on the fall in platelet count, but may have a minor effect on preserving platelet function by preserving platelet membrane receptors, possibly by inhibiting plasmin-mediated degradation. All trials have shown that there is a profound inhibition of fibrinolysis, suggesting that its main mechanism of action is through an anti-plasmin effect. The success of other anti-fibrinolytics in reducing bleeding supports this mechanism.²⁰³

(2) *Other anti-fibrinolytic agents*

Lysine Analogues: When plasminogen and plasmin bind to fibrin it is thought their lysine-binding sites. In the presence of lysine analogues epsilon amino-caproic acid (EACA) and tranexamic acid, the binding is reduced and fibrinolysis delayed.^{210–216}

EACA has been used successfully in the control of bleeding due to hyperfibrinolysis following transurethral resection, but others found no significant benefit in patients undergoing cardiac surgery. In one randomised study on patients undergoing CABG, tranexamic acid reduced the blood loss in the first 10 hours by a third.²¹⁵

Desmopressin acetate or DDAVP:

It is a synthetic vasopressin analogue that is relatively devoid of vasoconstrictor activity. It increases the plasma concentration and activity of vWF probably by inducing its release in the endothelium. vWF mediates platelet adhesion to damaged endothelium and also to act as a carrier molecule for factor VIII;C. Plasma levels of vWF increase 2- to 5-fold from the baseline within an hour and are associated with a shortening of the bleeding time in patients with von Willebrand's disease, platelet function defects, and uraemia.¹⁸⁸ Two studies of patients undergoing "re-do" cardiac operations showed that 0.3 mg/kg of DDAVP given after CPB reduced blood loss, elevated vWF levels, and shortened bleeding times.¹⁸⁸ In three trials using DDVAP in doses 0.3 mg/kg after the termination of CPB in uncomplicated CABG, the changes in plasma levels of vWF were studied. In the control group there was a doubling of vWF level and a greater rise in levels of vWF in the DDAVP treated group. This was, however, not accompanied by enhanced platelet aggregation or increased functional activity compared with the placebo treated group. The blood loss was similar. To conclude, it appears that DDAVP is not beneficial in uncomplicated CABG patients.

DDAVP increases the release of t-Pa from the endothelial cell, and this may reduce the beneficial effects of increasing vWF.

(3) *Fibrin sealants*

The sealants mimic the final part of the coagulation cascade in that a source of thrombin is added to the fibrinogen concentrates in the presence of calcium and a clot forms. Fibrin glue has been used to secure haemostasis in patches and suture lines during congenital heart surgery. In one retrospective study, it reduced blood loss significantly. There is no licensed fibrin sealant in the US or UK, but they are available on a named patient basis. Initially, thrombin was of bovine origin, which led to the development of a bleeding diathesis postoperatively, due to the formation of cross-reactive antibodies to bovine thrombin that inhibit factor V. Despite extensive clinical experience with fibrin sealants, the data available is mainly descriptive and randomised clinical trials are needed to fully assess

their contribution to reducing bleeding. The other concern, as with any other product produced from plasma, is transfusion-transmitted diseases. Methods for producing autologous fibrin sealants are, however, being evaluated.²²⁰

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