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REVIEW

Clinical overview of venous thromboembolism

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Abstract

Venous thromboembolism (VTE) encompasses two vascular conditions that are of significant importance, namely deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is also the most common cause of PE. Medical and surgical patients, and individuals who are at increased risk of developing VTE through a variety of factors, require adequate thromboprophylaxis. Primary and secondary prevention, as well as the definitive treatment of VTE, are accomplished through the use of a variety of anticoagulant drugs. This article attempts to provide an overview of VTE, and its prevention and treatment.

Keywords: anticoagulants, deep vein thrombosis, DVT, embolus, NOAC, PE, pulmonary embolism, thromboprophylaxis, thrombus, venous thromboembolism, Virchow's triad, VTE

Introduction

Venous thromboembolism (VTE) is the result of a venous blood clot formation which may manifest itself as deep vein thrombosis (DVT) or pulmonary embolism (PE).[1,2] DVT and PE are part of the same syndrome. However, important distinguishing factors in terms of epidemiology, diagnosis and treatment exist between the two.[3] DVT is a condition in which the clotting of venous blood occurs in a deep vein of an extremity, mostly one of the legs (such as the femoral or saphenous vein) or the pelvis (in the ileofemoral position).[1,4] There is a significant increase in the incidence of DVT after the age of 40 years, with an annual incidence in the region of 108 in 100 000 people, making it the third most common cardiovascular disease. In addition, PE is the third most common cause of cardiovascular mortality, after myocardial infarction and strokes.[3,5] This number is expected to rise since elderly and obese populations are growing. Local damage to the tunica intima, venous stasis and hypercoagulability are major predisposing factors. As a result, conditions that impair venous return lead to endothelial injury or dysfunction, or cause hypercoagulability, might result in DVT.[4-6]

DVT is the primary cause of PE. A venous thrombus usually develops in one of the lower extremities, possibly because of the higher incidence of a clot formation in the legs, from where it also extends more proximally. Should a portion of the clot eventually break free (i.e. an embolus), it will invariably reach the inferior vena cava and the right-sided cardiac chambers, and subsequently become lodged in the pulmonary arterial circulation, causing either partial or complete obstruction of pulmonary blood flow (in 4–13% of DVT cases).[2,4] It is reported that approximately half of all patients with DVT also have occult PE, and at least 30% of patients with PE have demonstrable DVT.[4]

The differences between a thrombus or an embolus, and thrombosis or embolism are explained in Table 1.[7]

Table 1: The differences between a thrombus or an embolus, and thrombosis or embolism[7]

Thrombus	**Thrombosis**
A blood clot in the vascular system which can occlude a blood vessel at the site of its formation	The actual vascular occlusion caused by a thrombus
Embolus	**Embolism**
A blockage or plug, which may be part of a blood clot (i.e. a thrombus) or any other foreign body (including air bubbles, lipid globules or the tip of an indwelling catheter) which has travelled through a section of the cardiovascular system to obstruct the flow of blood through a smaller blood vessel than the one in which it originated	The actual vascular occlusion caused by an embolus

The consecutive stages of VTE (namely DVT in a calf vein, proximal DVT and subsequent PE) may or may not be symptomatic. The degree or severity (i.e. the size and extent of the resultant occlusion, the presence and patency of any collateral veins, and the presence of inflammation) of the thrombosis or embolism determines the development and extent of the symptoms experienced by the patient. The capacity of the patient to tolerate such a thrombosis is an additional factor which influences the

development of the symptomatology. For instance, a moderately sized PE may present with no symptoms in a patient who is in good health otherwise, while it may result in severe symptoms, or even death, in a patient who already suffers from advanced cardiopulmonary disease.[1]

This article provides an overview of VTE and its management.

Pathophysiology

Virchow provided the notion in 1856 that three different pathophysiological events underpin the formation of DVT. These three events, subsequently termed Virchow's triad, are:

- Damage to the vessel wall.
- Alterations to the venous blood flow.
- Hypercoagulability of the blood.

These are still considered to be the main causes of thrombus formation.[8-10]

However, more complex pathophysiological events may be involved as well.[10] It must also be acknowledged while taking these complexities into consideration that early recognition and effective intervention are crucial to achieving satisfactory outcomes in the majority of cases, and that VTE is a highly preventable condition.[10] Once formed, a thrombus may result in, or undergo, any of the following:[2]

- Remain as an asymptomatic phenomenon.
- Undergo spontaneous lysis.
- Cause an obstruction in the venous circulation.
- Spread to more proximal veins.

Table 2: Risk factors for venous thrombosis[4,8]

Active cancer
Acute medical conditions
Advancing age
Cigarette smoking, including passive smoking
Hypercoagulability disorders, e.g. protein C and S deficiency, hereditary fibrinolytic defects and heparin-induced thrombocytopenia
Immobilisation, e.g. prolonged bed rest and long-distance travel
Indwelling venous catheters, especially central venous catheters
Intravenous drug use
Myeloproliferative disorders
Nephrotic syndrome
Obesity
Oral contraceptives, oestrogen therapy and oestrogen-receptor modulators
Other drugs, such as antipsychotics, chemotherapy and thalidomide
Paresis of one or more limbs
Pregnancy and the postpartum period
Prior venous thromboembolism
Sickle cell anaemia
Surgery within the past three months
Trauma
Varicose veins and thrombosis of the superficial veins

- Form an embolus, or
- Act in any combination of the aforementioned ways.

Postthrombotic syndrome (PTS) is a frequent finding following VTE, with an occurrence as high as one half of all patients with ileofemoral DVT who only received anticoagulation therapy. It develops as an outcome of thrombus-related damage to the venous valves, which results in subsequent incompetency and retrograde blood flow, i.e. venous reflux. The combination of reflux, combined with the possibility of residual thrombotic obstruction, results in venous hypertension of the limb. This subsequently results in the symptoms of PTS. Risk factors for the development of PTS include the involvement of a proximal vein, the extent of the thrombus, advancing age, obesity, a history of ipsilateral thrombosis and being of the female gender.[9,10]

Risk factors

Many factors contribute to the development of DVT. These risk factors are listed in alphabetical order in Table 2. Some of them are discussed in this article.

Cancer

Cancer patients, especially those of advanced age and persons with recurrent thrombosis, are at a higher risk of developing DVT.[4]

Acute medical disorders

Patients admitted for acute medical disorders, such as myocardial infarction, acute heart or respiratory failure and acute infections are at a greater risk of thrombosis, even comparable to that of general surgery. This risk is heightened by other contributing factors, such as a history of DVT, advanced age and prolonged bed rest.[8]

Surgery

The type of surgical procedure, as well as the presence of additional risk factors, determines the risk of thrombus formation associated with such procedures. For example, orthopaedic surgery, major vascular surgery, and neurosurgery pose a particularly high risk in the DVT and VTE setting. The risk of thrombosis may also persist over several months following surgical intervention.[8]

Trauma

Major traumatic injuries are associated with a ~50% risk of the formation of DVT, which may be demonstrated by venography. Certain types of injuries are associated with a significantly higher risk of thrombosis, such as:

- *Leg fractures:* 80%.
- *Injuries to the spinal column:* 62%.
- *Pelvis:* 61%.

Others, including plaster casts applied to the lower limb, carry a much lower risk.[8]

A history of deep vein thrombosis

There is a definite risk for the recurrence of DVT once a patient has developed an initial, spontaneous thrombosis. The annual

probability of recurrence is 5–15%. However, the risk is far less in patients with DVT that resulted from a postoperative complication.[8]

Signs and symptoms

The diagnosis of DVT may be quite complex. Some of the more common findings are summarised in Table 3. It is important that a complete history and detailed physical examination are performed during the initial assessment of a patient with suspected VTE. Risk factors may also be identified during the initial assessment. It may also help with the identification of patients requiring further, or more detailed and potentially invasive, assessment.[10] Shortness of breath or dyspnoea and pleuritic chest pain are the most common symptoms that accompany a PE.[4]

Table 3: Common signs and symptoms of deep vein thrombosis[4,10]

Signs	Symptoms	Classic findings
• Protrusion of the veins • Warmth Oedema • Erythema	• Tenderness along the veins • Aching pain	• Pain • Swelling • Tenderness

Complications

Possible complications of DVT include PE, considered to be the most common complication, chronic venous insufficiency and postphlebitic syndrome. The condition may even have a fatal outcome. In addition, there is an increased risk of recurrent episodes in patients who have experienced a first episode of VTE. A number of lesser seen complications also exist.[4,5]

Diagnosis

Findings that are based on the history taking and clinical examination alone are deemed to be unreliable. There is a distinct lack of specificity and sensitivity within the DVT and VTE setting in this regard. Therefore, more reliable diagnostic methods are required. However, the use of recognised scoring systems, such as Well's score or the revised Geneva score, may augment clinical findings in the practice setting, with the former having potential usefulness in predicting both DVT and PE, and the latter PE only. These examples are provided in Tables 4, 5 and 6.[3,5]

Table 4: Well's score for deep vein thrombosis[3]

Criteria	Points*
Cancer	+1
Paralysis or a recent plaster cast	+1
Bed rest > 3 days or surgery < 4 weeks	+1
Pain on palpation of the deep veins	+1
Swelling of the entire leg	+1
Diameter difference on the affected calf > 3 cm	+1
Pitting oedema on the affected side only	+1
Dilated superficial veins on the affected side	+1
Alternative diagnosis, at least as probable as DVT	–2

DVT: deep vein thrombosis
* Patients with a score of 0 are low risk; 1–2 are intermediate risk; and ≥ 3 high risk

Table 5: Well's score for pulmonary embolism[3,11]

Criteria	Points*
Previous PE or DVT	+1.5
Heart rate > 100 beats per minute	+1.5
Recent surgery or immobilisation	+1.5
Clinical signs of DVT	+3.0
An alternative diagnosis less likely than PE	+3.0
Haemoptysis	+1.0
Cancer	+1.0

DVT: deep vein thrombosis, PE: pulmonary embolism
* Patients with a score of 0–1 are low risk; 2–6 are intermediate risk; and ≥ 7 high risk. A so-called dichotomised rule is also applied to this score, whereby it is considered "unlikely" or "likely" for patients to have a pulmonary embolism if a score of ≤ 4 and ≥ 4, respectively, was recorded

Table 6: The revised Geneva score for pulmonary embolism[3]

Criteria	Points*
Age > 65 years	+1
Previous DVT or PE	+3
Surgery (under general anaesthesia) or fracture (of the lower limb) within 1 month	+2
Active malignancy (solid or haematological malignancy, currently active or considered as cured for < 1 year)	+2
Unilateral leg pain	+3
Haemoptysis	+2
Heart rate of 75–94 beats per minute	+3
Heart rate of ≥ 95 beats per minute	+5
Pain on deep vein palpation in the leg and unilateral oedema	+4

DVT: deep vein thrombosis, PE: pulmonary embolism
* Patients with a score < 2 are low risk; 2–6 are intermediate risk; and ≥ 6 high risk

A number of diagnostic tests and procedures may be performed, including the following:[4,5]

- Compression and Doppler ultrasonography.
- Contrast phlebography.
- *D-dimer testing:* D-dimer is a byproduct of fibrinolysis. When levels thereof are elevated, it is indicative of the recent presence and lysis of thrombi.
- Venography.
- Magnetic resonance direct thrombus imaging.

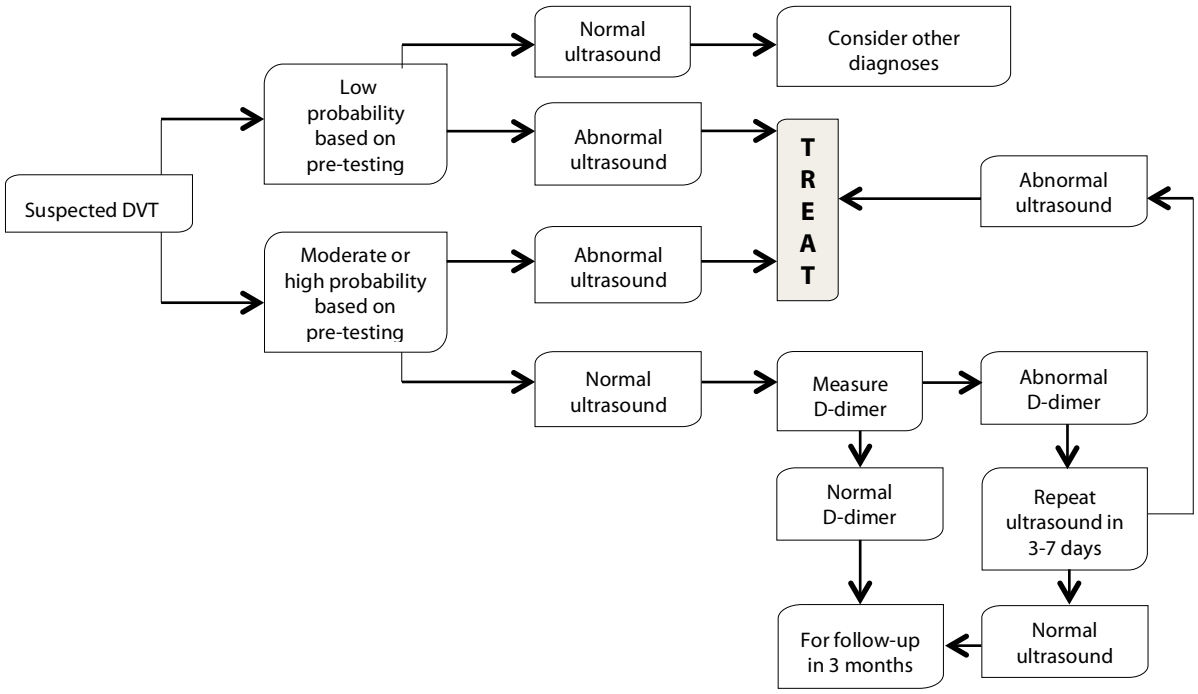
Figure 1 is a suggested algorithm for the diagnosis of DVT, using ultrasonography and D-dimer testing.

Prognosis

In general, the prognosis and risk of recurrence is based on whether the patient has transient risk factors, such as surgery, traumatic injuries or temporary immobility, versus persistent ones. A DVT of the lower extremity, which was treated inadequately, carries a 3% risk of the development of a fatal PE.[4]

The management of venous thromboembolism

The management of DVT and VTE may be divided into primary preventative strategies, aimed at reducing the risk of occurrences,



DVT: deep vein thrombosis

Figure 1: Algorithm for the diagnosis of deep vein thrombosis[4]

and the definitive treatment of established thromboembolism. In addition, the aim of secondary prevention is to reduce the rate of recurrence.

Medical and surgical patients may receive primary prophylaxis, which is effective in reducing the occurrence of DVT. Prophylaxis may be achieved in either one of the following two ways, or by using a combination of both:[3,5,8]

- *Physical (i.e. nonpharmacological) methods:* Interventions include early ambulation, graduated compression stockings or intermittent pneumatic compression. These methods may be used unaided for patients at low risk of DVT, or in cases where definite contraindications to pharmacological agents exist.
- *Anticoagulants (i.e. pharmacological methods):* The range of options now includes unfractionated heparin (UFH), vitamin K antagonists (VKAs), e.g. warfarin, low-molecular-weight heparin (LMWH), fondaparinux (an injectable, indirect factor Xa inhibitor), or one of the novel oral anticoagulant drugs (NOACs). Individuals who are considered to be at a moderate to high risk of thrombosis require effective thromboprophylaxis. The sites of action of warfarin versus the NOACs within the clotting cascade are illustrated in Figure 2.

Definitive treatment typically progresses through three distinct phases, namely an initial or acute phase, an intermediate phase and a chronic phase. However, the NOACs have the potential of providing a much earlier switch in therapy, or even a single-drug approach, as illustrated in Figure 3.[3] The main goal of treatment is to prevent both early and late complications of the condition. The initial treatment regimen commonly includes either UFH or one of the LMWHs. Fondaparinux is an additional treatment option.

Therefore, the backbone of definitive treatment is provided by the array of anticoagulant drugs previously mentioned since the same range of options utilised within the prophylactic setting are also employed during treatment. The advantages of effective anticoagulation lie in the fact that thrombi are effectively stabilised and prevented from undergoing any further thrombus deposition, in addition to the likelihood of recurrence being reduced. This provides for an opportunity for endogenous lysis of the already formed thrombus to take place.[1]

The novel oral anticoagulants and vitamin K antagonists

The NOACs can be classified into two categories:[3,5,12]

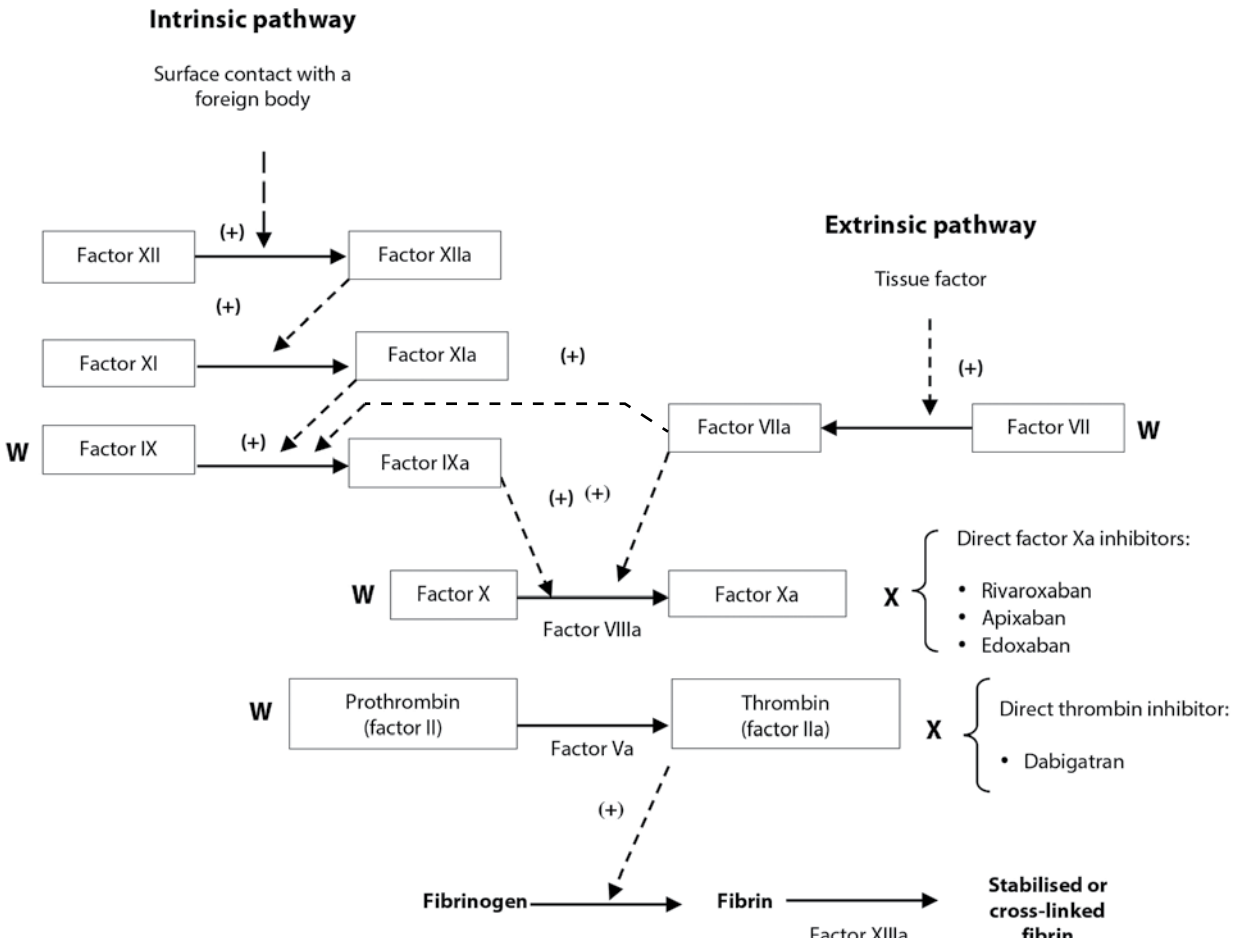
- Oral direct thrombin-inhibitors, e.g. dabigatran.
- Oral direct factor Xa inhibitors, e.g. rivaroxaban, apixaban and edoxaban.

The NOACs block a single step in the coagulation pathway, as opposed to the VKAs which block active vitamin K-dependent coagulation factors (factors II, VII, IX and X). The direct thrombin inhibitors target the thrombin-mediated conversion of fibrinogen to fibrin, and the thrombin-mediated feedback activation of factors V and VIII. The factor Xa inhibitors block the conversion of prothrombin (factor II) to thrombin (factor IIa) by factor Xa (incorporated within the prothrombinase complex).[3,5,12] The sites of action of the oral anticoagulant drugs are depicted in Figure 2.

The older VKAs are compared to the NOACs in Table 7, and aspects that are pertinent to the clinical practice setting highlighted.[5,12]

In a clinical review of the NOACs and DVT, Burgazli *et al.* mention the following eight characteristics of an ideal anticoagulant:[5,12]

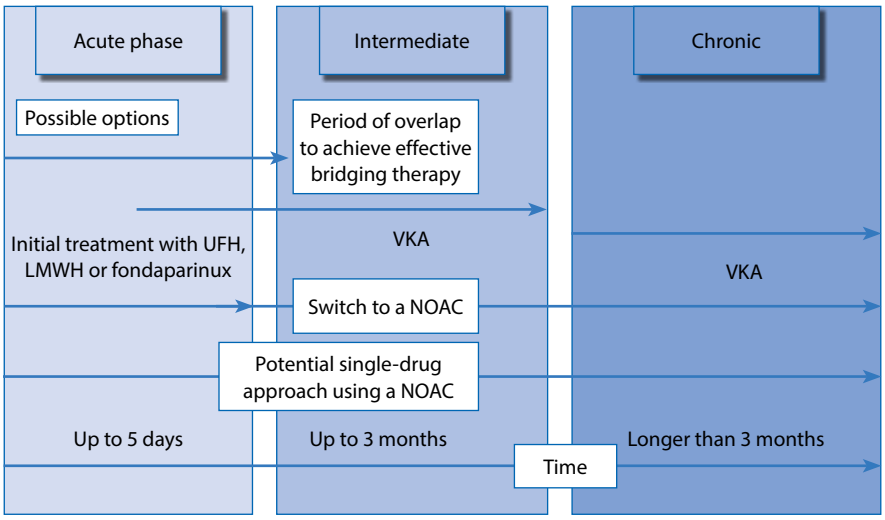
- It should require less monitoring, e.g. compared to heparin and warfarin.



(+): activates
W: factors inhibited by warfarin
X: sites of action of the novel oral anticoagulants

Figure 2: Sites of action of the anticoagulants (vitamin K antagonists, e.g. warfarin, and the novel oral anticoagulant drugs)

- An antidote is available. (Protamine sulphate may be used in cases of a heparin overdose, or vitamin K and fresh frozen plasma for a VKA overdose).
- Fixed dosing, e.g. compared to the notorious international normalised ratio (INR)-based dosing titrations required for effective and safe warfarin therapy.
- Oral administration. (The VKAs are the only other group of oral anticoagulants).
- Rapid onset of action, e.g. warfarin has a very long half-life, and therefore extended onset of action.
- Minimal food and drug interactions.
- A wide therapeutic window.
- Predictable pharmacokinetics. (Warfarin is known to have a significant genetic variation in its rate of metabolism, for example).



LMWH: low-molecular-weight heparin, NOAC: novel oral anticoagulant, UFH: unfractionated heparin, VKA: vitamin K antagonist, e.g. warfarin

Figure 3: Treatment phases in the management of venous thromboembolism[3]

Table 7: Comparison of the pharmacological characteristics of oral anticoagulation therapy in venous thromboembolism[5,12]

Vitamin K antagonists*	New oral anticoagulants**
Slow onset of action (3–4, possibly 5 days)	Rapid onset of action (0.5 or 1–4 hours)
Once-daily dosing	Dosing may be once or twice daily
Genetic variation in metabolism	-
Narrow therapeutic window, requiring frequent anticoagulation monitoring (international normalised ratio)	Predictable anticoagulant effect, meaning that routine anticoagulation monitoring is redundant
Multiple food and drug interactions	Low tendency for interactions with food, alcohol and drugs
Antidote known and available (vitamin K, as well as fresh frozen plasma to replenish clotting factors)	The absence of an antidote. (Haemodialysis may be of benefit in cases of dabigatran overdose. Otherwise supportive treatment needs to be instituted.)
Known and reliable method of monitoring	Underdeveloped method of anticoagulation monitoring
Dosage adjustments not necessary for patients suffering from renal or hepatic disease. However, monitoring is still required because of their altered homeostasis	Potential for toxicity in patients with renal insufficiency
Multiple drug interactions	Interactions are limited to CYP3A4 and/or P-glycoprotein

CYP: cytochrome P450
* warfarin
** dabigatran, apixaban, rivaroxaban and edoxaban

Currently, the NOACs tick all the boxes on this list, with the exception of the availability of a suitable and specific antidote.

Dabigatran

Dabigatran is an oral, direct thrombin inhibitor (Figure 2). Once ingested, it requires activation by plasma esterases and has a half-life of between 14 and 17 hours.[5]

Rivaroxaban

Rivaroxaban has a half-life of between seven and 11 hours, and acts an oral factor Xa inhibitor (Figure 2).[5]

Apixaban

Apixaban also acts as an oral factor Xa inhibitor, and has a half-life of around 12 hours.[5]

Edoxaban

Yet another oral factor Xa inhibitor, edoxaban has a half-life of 8–10 hours.[5]

Warfarin

Warfarin is a well-known and frequently used oral VKA. This drug is renowned for its long list of potential drug (and food) interactions. Also, variation in individual responses to this drug can be substantial. Careful monitoring and good compliance are essential to the success of anticoagulation with warfarin. The INR recommended by the World Health Organization is used for therapeutic drug monitoring.[2,7] Warfarin is contraindicated during pregnancy.[4,7]

Injectable anticoagulant drugs

As already mentioned, the three main classes of injectable anticoagulant drugs are:

- UFH.
- The LMWHs.
- Fondaparinux.

Unfractionated heparin

UFH is derived from animal origin, i.e. porcine intestinal mucosa or bovine lung tissue, and is a so-called heterogeneous mixture of sulphated mucopolysaccharides. UFH is administered through the intravenous route, typically via continuous infusion, although bolus dosages may also be employed. UFH should not be administered via intramuscular injection because of the high risk of haematoma formation. The usefulness of UFH is limited by its pharmacokinetic profile, as well as the potential occurrence of osteoporosis and heparin-induced thrombocytopaenia. Activated partial thromboplastin time is commonly used as the therapeutic monitoring parameter for heparin.[2,3,5,7,8]

Low-molecular-weight heparins

The LMWHs are derived from UFH through a process of depolymerisation, which effective cuts down their molecular weight to approximately one third of the molecular weight of UFH. Therefore, they have the same mechanism of action as UFH.[2,5]

The use of LMWHs has also been shown to substantially reduce the incidence of major bleeding during the initial treatment phase, as well as the overall mortality rate measured during the follow-up phase.[13]

Therefore, the LMWHs are still considered to be a preferred choice. In 2013, Burgazli *et al.* described LMWHs as the standard of care, to be administered daily and in weight-adjusted dosages for the first 5–7 days. However, it should be noted that UFH remains the initial heparin of choice in patients with renal dysfunction, since the LMWHs are predominantly excreted by the kidneys.[5]

Examples of LMWHs include enoxaparin, dalteparin and tinzaparin. They are all administered via subcutaneous injection.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide, which acts as an injectable, selective inhibitor of factor Xa (Figure 2). It is administered via the subcutaneous route and undergoes rapid

and full absorption from its injection site. Fondaparinux displays a terminal elimination half-life of between 17 and 21 hours following its administration.[2,3] Fondaparinux is also administered via subcutaneous injection.

In general, the treatment of VTE should be continued for a period of at least three months, probably up to six months, and possibly for longer.[3,10]

Supportive treatment

In addition to effective anticoagulation, patients will require supportive pharmacotherapeutical interventions. For example, patients with DVT may require the addition of suitable analgesics, with or without short courses of nonsteroidal anti-inflammatory drugs.[4] Patients with PE may require additional respiratory support, among other aspects.

Nonpharmacological interventions

Surgical options may be utilised in the treatment of VTE. Such operative procedures include:[10]

- *Open thrombectomy:* This involves the physical removal of the thrombus through intricate vascular surgery.
- *Catheter-directed thrombolysis:* This is a procedure through which thrombolytic therapy may be delivered locally, as opposed to systemically, to reduce the so-called clot burden.

An additional, albeit rarely used alternative is vena cava interruption, or the so-called inferior vena cava filter. Such a filter may provide short-term protection against PE in patients with lower limb DVT, especially when anticoagulant drugs are absolutely contraindicated, ineffective, or when the risk of a fatal PE is looming.[2]

Conclusion

The phenomenon of VTE and its complications may result in significant morbidity and mortality. Rapid and accurate clinical diagnosis is challenging, making proper patient history taking extremely important. Risk factors need to be identified early on, and suitable prophylaxis needs to be implemented wherever such interventions are warranted. VTE usually manifests as DVT in the lower limb, and if not recognised and managed in time, may progress to PE, which is associated with a significantly greater mortality rate.

The goal of conventional treatment is to halt the progression of thrombus formation and embolisation, and to prevent the recurrence and the development of PE. The NOACs are advantageous as therapeutic monitoring is not required. However, they also do not have an antidote, so patient knowledge of prevention and the early recognition of complications is of paramount importance. Moreover, they produce a more predictable anticoagulant effect, which reduces the likelihood of complications.

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