

# Venous thromboembolism

## — treatment and prophylaxis

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Treatment of venous thromboembolism consists of anticoagulation therapy to reduce clot formation and reduce the risks of mortality and recurrence. This article, the second part of this month's special feature, describes the drugs used and how they are monitored



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Oral therapy with a vitamin K antagonist, usually warfarin, is the treatment of choice for patients with venous thromboembolism

**T**reatment of suspected or confirmed venous thromboembolism (VTE) involves the use of anticoagulant therapy such as heparin, low molecular weight heparin or oral vitamin K antagonists to prevent further clot development and to reduce the risks of mortality and recurrent VTE. For most patients, treatment of deep vein thrombosis (DVT) consists of the same treatment regimens as treatment of pulmonary embolism (PE). In certain circumstances in the management of PE, thrombolytic therapy may be employed to break down the existing clot or interventional procedures may be required (such as thrombectomy or the use of inferior vena cava filters).

The pharmacological agents used in the treatment of VTE are all considered to be "high risk" drugs. The National Patient Safety Agency is undertaking a stakeholder consultation on the safe use of anticoagulants and is due to issue guidance later this year. In the consultation document the NPSA has identified several high-risk areas, including staff competency, training, guidelines, communication and patient information.<sup>1</sup> Pharmacists in both primary and secondary care are in key positions to use their skills to improve patient safety in the management of patients on anticoagulant therapy.

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Prophylaxis of venous thromboembolism (thromboprophylaxis) is an important part of the care of patients at risk. Identification of those who are at risk of developing VTE and implementation of prevention strategies are important and are increasingly being recognised as they can reduce the incidence of VTE and consequent mortality and morbidity.

The House of Commons Health Select Committee recommends that each NHS trust establishes a multidisciplinary thrombosis committee with the aim of reducing the number of patients who die from VTE every year.<sup>2</sup> This is regarded as a high priority within the NHS and pharmacists are ideally placed to become key members of such committees. VTE guidance from the National Institute for Health and Clinical Excellence is due to be published in 2007 and will help support this initiative.

This article, the second part of a special feature on VTE, will outline the main drugs used in the treatment and prevention of the condition.

### Unfractionated heparin

The efficacy and safety of unfractionated heparin (UFH) in the treatment of VTE are well-established and heparin treatment may be started before a diagnosis has been made. UFH binds to antithrombin and these complexes inactivate a number of clotting factors, including thrombin and factor Xa. Heparin, however, is a heterogeneous molecule with respect to its size so binding is

variable. Consequently, inter-patient and intra-patient variability is seen.

**Contraindications and cautions** As with all anticoagulant therapy, contraindications and cautions in use of UFH mainly relate to the risk of bleeding or known hypersensitivity to the product. It is particularly important to identify any history of heparin-induced thrombocytopenia (HIT) because this would contraindicate further use. HIT does not usually develop until after five to 10 days of treatment, and all patients must have their platelet count checked before starting heparin treatment. HIT should be suspected in patients who subsequently develop a skin allergy or a reduction in platelet count of 50 per cent or more, and all heparin products should be discontinued in these patients. If continued anticoagulation is required alternative agents should be used, as described later.

**Dosing and monitoring of UFH** As a treatment dose UFH is started as an intravenous bolus (commonly 5,000 units) followed immediately by a continuous intravenous infusion (often 30,000 units over 24 hours). Careful monitoring of the activated partial thromboplastin time (APTT) or ratio is essential to ensure efficacy and safety of heparin treatment. The APTT ratio should be checked four to six hours after the bolus dose has been administered, with subsequent amendment of the infusion rate to achieve the target APTT ratio of 1.5–2.5.

## — LMW heparins

In recent years, a major advance in the treatment of VTE has been the development of the low molecular weight heparins (LMWHs) bemiparin, dalteparin, enoxaparin, and tinzaparin, which have largely superseded UFH in the treatment of VTE. LMWHs have superior pharmacokinetic parameters allowing for fixed dose subcutaneous administration (calculated by body weight) using a once daily dosage regimen. Furthermore, the therapeutic effects of this regimen are much more predictable so routine monitoring of clotting parameters and consequent dosage adjustment is not required. A number of clinical studies have compared LMWHs with UFH in patients with VTE and a meta-analysis of these studies has demonstrated that subcutaneous LMWHs are safer and more effective than UFH. As a result LMWHs have largely replaced UFH.

There are currently four LMWH products licensed in the UK for the treatment of VTE, and their dosing regimens are outlined in Panel 1. The different products cannot be regarded as interchangeable because of differences in the fractions used to produce them. Whichever LMWH is chosen is continued for five to six days or longer, until adequate anticoagulation with oral agents can be established.

**Difficult patient groups** Although LMWHs have largely replaced UFH there are some patient groups for whom LMWH use can be problematic. This includes patients with renal insufficiency, obese patients and pregnant women, in whom the efficacy and safety of LMWH has not been fully established. In such patients monitoring of factor anti-Xa levels may be used to guide dosing. LMWHs are not thought to cross the placenta, but manufacturers of all LMWHs state that there are no adequate and well-controlled studies in pregnant women and, since animal studies are not always predictive of the human response, the drug should not be used in pregnant patients unless no safer alternative is available. However, LMWHs are increasingly being used in obstetrics practice since the data available suggest that they offer a safe and effective alternative to UFH.<sup>3</sup>

Another situation in which UFH may still be preferred is for patients in whom rapid reversal of effects may be required. UFH has a half-life of 30–60 minutes, so a rapid reduction in effect can be achieved on stopping an infusion. In addition an effective reversal agent, protamine, is available. Although the pharmacokinetics of LMWHs allow for once-daily subcutaneous dosing, the products have a much longer half-life than UFH (three to eight hours) and protamine will only reverse 50–70 per cent of the dose.

### Panel 1: Dosing regimens for low molecular weight heparin products licensed for the treatment of venous thromboembolism

Bemiparin	Dalteparin	Enoxaparin	Tinzaparin
115 IU/kg once a day for 5–9 days	200 IU/kg once a day to a maximum daily dose of 18,000 units	1.5mg/kg once a day (150 IU/kg) for at least 5 days	175 IU/kg once a day for at least 6 days
	Dose can be divided to 100 IU/kg twice a day if high bleeding risk	In patients with renal impairment (creatinine clearance < 30ml/min) reduce dose to 1mg/kg once a day	

#### Inpatient versus outpatient treatment

The introduction of LMWHs has enabled the development of anticoagulation services in the community. Most patients with uncomplicated DVT are now treated entirely at home, as demonstrated by a report from the VERITY registry in 2005 where only 10.4 per cent of patients with DVT were considered unsuitable for home treatment.<sup>4</sup> Increasingly, patients with uncomplicated (submassive) PE are also being treated at home. Successful outpatient treatment requires an organised service with dedicated staff to provide patient support, education and follow-up (this is often a nurse or pharmacist). Good communication between primary and secondary care is key to the success of such services. It is also essential to communicate with local oral anticoagulation services to ensure safe initiation and continuation of warfarin therapy.

**Management of HIT** Heparin-induced thrombocytopenia should be considered in patients receiving any form of heparin who have a decreased platelet count of 50 per cent or greater or develop a skin allergy. The incidence of HIT is higher in surgical patients than in medical or obstetrics patients. The incidence is also higher with UFH than LMWH, but both types of heparin should be avoided in the event of HIT diagnosis. In HIT the platelet count typically falls between days five to 10 of treatment, although this may be more rapid if the patient has received heparin in the preceding three months. Development of HIT is rare after 15 days of treatment or more. Data suggest that the median nadir of the platelet count is  $55 \times 10^9/L$ , with severe thrombocytopenia (platelet count  $<15 \times 10^9/L$ ) being unusual. Skin lesions at the injection site are developed by 10–20 per cent of patients and 50 per cent of patients develop thrombosis.

Recently published guidelines<sup>5</sup> recommend that if HIT is suspected then all heparin preparations must be discontinued,

even before the return of laboratory results. If rapid anticoagulation is still required alternative agents that are recommended are:

- **Lepirudin:** given as a slow intravenous bolus of 400 µg/kg followed by a continuous infusion of 150µg/kg/h (to a maximum dose of 16.5mg/h) with subsequent doses adjusted to an APTT ratio of 1.5–2.5. Because the drug is renally excreted, dose adjustment is required in renal impairment.
- **Danaparoid:** given as an intravenous bolus (weight dependent) followed by an infusion of 400units/h for two hours, then 300units/h for two hours and thereafter 200units/h.

Oral anticoagulation with a vitamin K antagonist such as warfarin can be started once the platelet count has recovered (ie, to above  $100 \times 10^9/L$ ).

## — Vitamin K antagonists

After the initial treatment with LMWH (or less commonly UFH) patients are switched to oral anticoagulation with a vitamin K antagonist (VKA), of which warfarin is the most commonly used agent in the UK. Other oral VKAs are phenindione and acenocoumarol (nicoumalone).

The British Committee for Standards in Haematology published its guidelines on oral anticoagulants in 1998 with a recent update in 2005.<sup>6</sup> These guidelines state that VKAs remain the treatment of choice for the majority of patients with VTE. An exception to this recommendation is in patients with malignancy where continuation with LMWH may be used.

VKAs exert their effects by interfering with the hepatic synthesis of vitamin K-dependent clotting factors. This involves factors II, VII, IX, and X, and the natural anticoagulant proteins C and S. The onset of

action of VKAs is delayed since it depends on the inhibition of production of these clotting factors, and requires the levels of those factors already in circulation to reduce. The half-life of factor VII is only four to six hours, but factors II, IX and X have half-lives of approximately 60, 24, and 36 hours, respectively.

**Warfarin: contraindications** The main contraindications and cautions in use of oral VKAs relate to bleeding risks. Warfarin crosses the placenta so its use in pregnancy requires specialist care. Warfarin treatment must be fully explained to the patient so that they understand the prescribed dosage regimen, and the importance of monitoring. Pharmacists can play a key role in the provision of information both on initiation of treatment, and on an ongoing basis, either in the inpatient setting or in pharmacist-led anticoagulation clinics in primary and secondary care. Care is also required in the assessment of concomitant drug therapy for interactions that alter the response to warfarin. This assessment must include the use of over-the-counter medicines, herbal remedies and vitamin preparations. Dietary advice should also be given.

**Warfarin dosing** Due to the lag time in achieving a therapeutic effect with warfarin in the treatment of VTE, treatment should be initiated while the patient is still receiving LMWH (or UFH) at therapeutic doses. Numerous loading dose schedules exist with the aim of achieving a therapeutic effect within a few days of starting treatment. Whichever schedule is used, it is recommended that the starting dose of warfarin does not exceed 10mg since higher doses tend to exceed the desired effect. Lower doses should be used in the elderly, malnourished or those with liver disease or congestive heart failure since these patients require less warfarin to achieve the desired therapeutic range.

**Drug interactions** There are many factors that can affect the response to warfarin, however, drug interactions are probably the most problematic and should be monitored closely. Panel 2 lists some of the common drugs which interact with warfarin. This list is not exhaustive and readers are advised to refer to recent texts for further information and more detailed explanations of the effects and management. Of note:

- Warfarin is metabolised by the cytochrome P450 enzyme system in the liver. The CYP2C9 isoenzyme, which metabolises S-warfarin, is considered to be most important, primarily because the S-isomer is approximately five times more potent than the R-isomer. The less active R-isomer is metabolised by both the CYP1A2 isoenzyme and the CYP3A4 isoenzyme. Enzyme inducers can substantially reduce the effects of warfarin by increasing its metabolism, necessitating the use of increased doses. These reactions generally take one to two weeks to manifest to their full effect. Conversely there are a number of drugs that have been shown to inhibit warfarin metabolism. The effect of enzyme inhibition is seen shortly after the drug is initiated, usually within the first 24 hours of therapy, although it may take up to a week before the maximal effect is achieved. If the inhibitor is subsequently discontinued, the offset of its effect is also rapid.
- Medicines that inhibit platelet function tend to increase the risk of bleeding in patients concurrently taking warfarin. This is true for drugs such as non-steroidal anti-inflammatory drugs, aspirin and clopidogrel. This effect on platelet function is not reflected in the INR and thus the increased risk of bleeding is not detected by normal monitoring.

- Herbal interactions and dietary interactions are also important. Patients should maintain consistency in their diets with respect to foods high in vitamin K (eg, green leafy vegetables), avoid cranberry juice and cranberry products and restrict the intake of alcohol.

**Monitoring** The effects of warfarin are assessed by monitoring the prothrombin time (PT). This is converted into the international normalised ratio (INR) by comparing the PT with that of a laboratory control. A baseline PT/INR should be measured and the subsequent loading dose regimen started. The PT/INR should then be reassessed to ensure that the INR is in range. The INR should then be monitored twice weekly for the first one to two weeks followed by weekly monitoring for the next month. Dose titration may be necessary to ensure the required INR is maintained. Once stabilisation has occurred, the INR can be performed at extended intervals of up to four weeks.

**Near-patient testing** Warfarin monitoring and consequent dose adjustment have traditionally been carried out by health service providers. However, the availability of self-testing kits now enables patients to monitor and adjust their own treatment. Appropriate patient selection and education are essential to ensure these monitors are used safely.

**Duration of treatment** The duration of anticoagulant therapy is guided by the estimated risks of bleeding and recurrent thrombosis. The risks of recurrent thrombosis vary between patient groups although the risk is highest in the first three months after diagnosis. At one end of the spectrum are those patients at low risk of recurrence such as those who had an important risk factor for thrombosis from which they have now fully recovered (most commonly

## Panel 2: Common drugs that interact with warfarin

Enzyme inducers	Enzyme inhibitors	Drugs that inhibit platelet function	Drugs that interact by other mechanisms	Herbal medicines
Azathioprine	Amiodarone	Aspirin	Bezafibrate	Chondroitin
Barbiturates	Cimetidine	Clopidogrel	Colestipol	Co-enzyme Q10
Carbamazepine	Ciprofloxacin	Cyclo-oxygenase-2 inhibitors	Colestyramine	Dan shen
Phenytoin	Clarithromycin	Non-steroidal anti-inflammatory drugs	Fenofibrate	Dong quai
Primidone	Erythromycin	Ticlopidine	Oestrogens	Garlic
Rifabutin	Fluconazole		Propylthiouracil	Ginger
Rifampicin	Fluoxetine		Thyroid hormones	Ginkgo
	Itraconazole			Ginseng
	Metronidazole			Papain
	Quinidine			St John's wort
	Ritonavir			

### Panel 3: Guidelines for duration of VKA treatment for VTE<sup>6</sup>

Indication	Target INR	Duration
Pulmonary embolus	2.5	At least 3 months At least 6 months if idiopathic or permanent risk factors
Proximal deep vein thrombosis	2.5	At least 3 months At least 6 months if idiopathic or permanent risk factors
Calf vein thrombosis	2.5	At least 6 weeks
Recurrence of VTE — when no longer on VKAs	2.5	6 months to lifelong
Recurrence of VTE — when on VKAs	3.5	Lifelong

surgery or trauma or a major illness). At the other end of the scale are those who have had more than one unprovoked episode of VTE (especially if they were on therapeutic anticoagulation at the time of thrombosis), patients with inherited deficiencies of antithrombin or protein C or S, those with antiphospholipid syndrome and those with advanced malignancy. In such cases the

benefits of long-term treatment may well outweigh the bleeding risks.

The annual risk of major bleeding with anticoagulation therapy is approximately 3 per cent. This risk is increased in the elderly (>65 years) or those with co-morbid factors such as renal impairment, diabetes, peptic ulcer disease and malignancy, and by the concomitant use of antiplatelet agents.

When deciding on duration of therapy the risks versus benefits for the individual need to be established. Panel 3 outlines current guidance on the duration of treatment for VTE. Oral VKA can be discontinued abruptly after this time.

**Intravenous drug users** The management of iliofemoral thrombosis in injecting drug users is often difficult due to poor venous access, non-compliance with treatment and ongoing injection of drugs. Although there have been no controlled trials in this patient group, retrospective data suggest that a satisfactory outcome may be achieved by continuing with LMWHs for the treatment course.

#### Managing excessive anticoagulation

The main adverse effect of all oral anticoagulants is haemorrhage. Checking the INR and omitting doses when appropriate is essential. If the anticoagulant is stopped but not reversed the INR should be measured two to three days later to ensure that it is falling. Panel 4 (p209) outlines the current recommendations based on the result of the INR and whether there is major or minor bleeding, as stated in the British National Formulary. Readers are advised to refer to the British Society for Haematology updated guidelines<sup>6</sup> for the most recent advice.

## — Fondaparinux

Fondaparinux is a pentasaccharide which inhibits factor Xa, has a long half-life and can be given by subcutaneous injection at a fixed once daily dosage. Trials have demonstrated equal efficacy to UFH in the treatment of PE and equal efficacy to LMWHs in the treatment of DVT. Although this recently licensed agent is currently not widely used this may change in the future.

## — Thrombolysis

The effects of PE on right heart function are due to arterial obstruction by the thrombus and may result in circulatory collapse with hypotension and systemic hypoperfusion (massive PE). In such cases mortality is extremely high and thrombolysis may be considered, providing there are no contraindications. The two agents licensed in the UK for thrombolysis are streptokinase and alteplase, the latter being the recommendation of the British Thoracic Society.<sup>8</sup> Use of thrombolysis in more stable patients with clinical evidence of right ventricular dysfunction is more controversial due to the risk of bleeding and it is not routinely used.

Alternative options include surgical thrombectomy or the placement of an inferior vena cava filter. The latter is only

## Panel 4: Management of excessive anticoagulation in patients on oral vitamin K antagonists<sup>7</sup>

- **Major bleeding** Stop warfarin. Administer phytonadione (vitamin K<sub>1</sub>) 5–10mg by slow intravenous injection. Administer prothrombin complex concentrate (factors II, VII, IX and X) 30–50units/kg or (if no concentrate available) fresh frozen plasma 15ml/kg.
- **INR>8.0, no bleeding/minor bleeding** Stop warfarin. Restart when INR<5.0. If there are other risk factors for bleeding administer phytonadione 500µg by slow intravenous injection or give 5mg by mouth. For partial reversal of anticoagulation give smaller oral doses of phytonadione (eg, 0.5–2.5mg) using the intravenous preparation orally. Repeat dose of phytonadione if INR still too high after 24 hours.
- **INR=6.0–8.0, no bleeding/minor bleeding** Stop warfarin. Restart when INR<5.0.
- **INR<6.0 but more than 0.5 units above target value** Reduce dose or stop warfarin. Restart when INR<5.0.
- **Unexpected bleeding at therapeutic levels** Investigate possibility of underlying cause (eg, renal or gastrointestinal tract disease).

generally used if anticoagulation is contraindicated or has been unsuccessful.

## — Prophylaxis

The risk of VTE increases approximately 10-fold in patients in hospital for surgery or trauma, in pregnant and post-partum women and in patients suffering from an immobilising medical illness<sup>9</sup> such as heart

failure, respiratory failure, diabetic coma, inflammatory bowel disease, nephrotic syndrome or patients in intensive care. In many cases the patient will be asymptomatic but in others there may be an increase in morbidity and mortality (due to PE). General measures used to prevent VTE include:

- Early mobilisation and leg exercise
- Adequate hydration

(haemoconcentration results in increased blood viscosity and reduced blood flow, especially in the deep veins of the legs in immobilised patients)

- Compression methods (eg, stockings)
- Pharmacological agents

Pharmacological agents may be used alone or in combination with compression methods for thromboprophylaxis. The most commonly used drugs are low doses of LMWHs (dose varies between agents) or UFH (given as 5,000 units by subcutaneous injection every 8–12 hours). LMWHs and UFH have been shown to be effective in both surgical and medical patients by significantly reducing the incidence of fatal PE. As in the treatment of VTE, LMWHs have largely superseded UFH in VTE prophylaxis.

There are currently five LMWH products licensed in the UK for thromboprophylaxis (bemiparin, dalteparin, enoxaparin, reviparin and tinzaparin). Although all are licensed for surgical prophylaxis only dalteparin and enoxaparin are licensed for prophylaxis in medical patients. Duration of treatment depends on the risk, type of operation and period of immobility.

As with heparin and LMWH, all patients should have a platelet count before starting treatment. However, since HIT is more common in surgical patients, the HIT

guidelines recommend that special care should be taken in these patients and that platelet count is monitored every two to four days for the first two weeks.

### — Newer agents

Fondaparinux is also licensed for prophylaxis of VTE in medical patients and in patients undergoing major orthopaedic surgery of the lower limbs or high risk abdominal surgery. Danaparoid is licensed in the prevention of DVT in patients undergoing general or orthopaedic surgery.

### — Conclusion

Treatment and prophylaxis of VTE involves high-risk drugs, and the pharmacist can have a major input into patient care. Developments in models of service and risk reduction strategies will provide opportunities and challenges in the management of these patients. Pharmacists must ensure that they are at the forefront of improving patient outcomes.

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