MedicineToday PEER REVIEWED ARTICLE POINTS: 2 CPD/2 PDP

Managing the patient with venous thromboembolic disease

Heparin and warfarin remain the mainstay of anticoagulation for venous thromboembolism. The duration of the therapy depends on the estimated risks of thrombosis recurrence and the increased risk of bleeding associated with anticoagulation.

IAN PROSSER
MB BS, PhD, FRACP, FRCPA

PHILIP CRISPIN
MB BS, FRACP, FRCPA

Dr Ian Prosser is a Senior Staff Specialist in Haematology at the Canberra Hospital and also a Clinical Haematologist in private practice. Dr Philip Crispin is a Staff Specialist in Haematology at the Canberra Hospital, Canberra, ACT.

Venous thromboembolism (VTE) is a common clinical problem and is frequently encountered in general practice. Rates are similar in men and women, and the incidence rises steeply with age. Pulmonary embolism (PE), which may prove fatal, will occur in about 50% of patients presenting with symptomatic proximal deep venous thrombosis (DVT) if the DVT is not treated. Early effective treatment is, therefore, essential. It is testament to the efficacy of current anticoagulant therapy that DVT is now seen as a relatively minor and usually benign condition.

Heparin has been used for anticoagulation since the 1940s, and the subsequent development of warfarin in the 1950s enabled long-term oral anticoagulation. The mainstay of management of VTE continues to be anticoagulation with heparin acutely, followed by longer-term use of a vitamin K antagonist, usually warfarin. Although there has been improved understanding of warfarin metabolism over recent years, clinical use remains difficult due to drug interactions, a narrow therapeutic window and the need for monitoring. Warfarin has, however, proven to be difficult to match therapeutically.

This article outlines current recommendations

IN SUMMARY

- **Above knee deep vein thrombosis (DVT) and pulmonary embolism (PE) are increasingly being managed in the ambulatory setting with low molecular weight heparin (LMWH) followed by longer term warfarin therapy.**
- **LMWH or unfractionated heparin (UFH) should always be commenced prior to warfarin, and heparin should be continued for a minimum of five days, and until the INR has been at a therapeutic level for at least two days.**
- **An INR between 2.0 and 3.0 is recommended for DVT and PE treatment.**
- **Anticoagulant duration of at least three months for proximal DVT and PE are recommended, with a longer duration for idiopathic thrombosis and for patients with persisting risk factors, such as active cancer.**
- **Anticoagulation is also recommended for symptomatic below knee DVTs, but as the risk of serious complications is lower, a shorter duration of therapy is recommended. If the risk of bleeding is high, it is safe to withhold anticoagulation and repeat an ultrasound in seven to 10 days.**
- **Ultrasonography may help to predict the likelihood of thrombosis recurrence and assist in determining anticoagulant duration.**

for treatment of venous thrombosis and PE.[1] A practical approach has been adopted, and controversy is indicated where it exists. Highly specialised topics, such as the use of inferior vena caval filters, and the management of complications of therapy, such as heparin-induced thrombocytopenia, are beyond the scope of this brief overview and will not be specifically addressed. The article concludes with an update on the long anticipated replacements for vitamin K antagonists. The investigation of patients with VTE was addressed in an article by the same authors published in the February 2009 issue of *Medicine Today*.[2]

Anticoagulation in above knee DVT and PE

Initiating anticoagulation

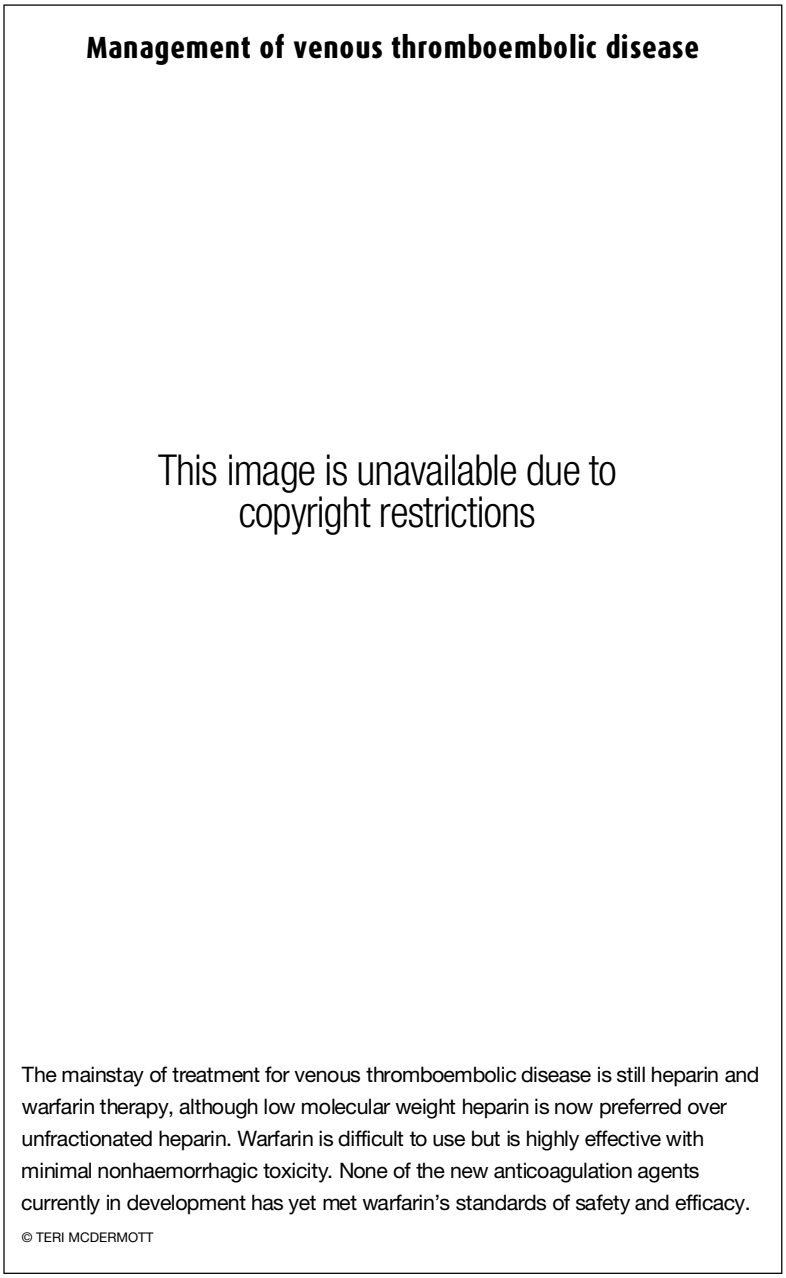
Unfractionated and low molecular weight heparins

There is unquestionable benefit in anticoagulation for above knee (proximal) DVT and pulmonary emboli. Anticoagulation should begin as soon as possible following the diagnosis of VTE, initially with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) in therapeutic doses.

LMWH is now the treatment of choice, particularly as it allows patients to remain ambulant, and in most cases its use may obviate the need for inpatient treatment. Even in hospitalised patients, there are advantages to using LMWH rather than UFH. The LMWHs dalteparin (Fragmin) and enoxaparin (Clexane) and the synthetic heparin-like pentasaccharide fondaparinux (Arixtra) have predictable pharmacokinetics and weight-based dosing, ensuring rapid onset of therapeutic effect within hours of the first dose, and their use generally requires no monitoring of drug levels. They are easier to administer than UFH preparations, in many cases can be given by the patients themselves, and can usually be prescribed as a single daily subcutaneous injection. There appear to be no significant differences in the therapeutic efficacy or safety of the different LMWH preparations, and local availability and familiarity usually determine the choice of agent.

UFH (Heparin Injection BP, Heparin Sodium Injection, Heparinised Saline, Heparinised Saline Injection), in contrast, has unpredictable pharmacokinetics due to its being highly protein-bound, including to a number of acute phase reactants. The resultant marked variability in responses is particularly problematic in acutely ill patients and those with extensive thrombosis. It may take several days for UFH to achieve a stable therapeutic level in a patient, even with careful adherence to dosing protocols. Subtherapeutic levels during anticoagulant initiation may contribute to an increased risk of clot propagation or embolisation.

Management of venous thromboembolic disease



The mainstay of treatment for venous thromboembolic disease is still heparin and warfarin therapy, although low molecular weight heparin is now preferred over unfractionated heparin. Warfarin is difficult to use but is highly effective with minimal nonhaemorrhagic toxicity. None of the new anticoagulation agents currently in development has yet met warfarin's standards of safety and efficacy.

Haemostasis, heparin and vitamin K antagonists

The mechanism of haemostasis involves activated factor X (FXa) initiating conversion of prothrombin to thrombin, leading to the formation of a clot by thrombin converting fibrinogen into fibrin.

Heparin enhances the rate at which antithrombin neutralises thrombin and activated factor X as well as other activated coagulation factors, thereby preventing formation of fibrin. Unfractionated heparin (UFH) targets thrombin and low molecular weight heparin (LMWH) targets activated factor X.

The vitamin K antagonist warfarin acts differently to heparin. It inhibits the synthesis of vitamin K-dependent coagulation factors, with the effect of sequentially depressing factors VII, IX, X and prothrombin, thereby reducing the levels of coagulation factors and preventing formation or further extension of a fibrin clot.

A baseline full blood count should be performed before initiating anticoagulation. However, as the incidence of heparin-induced thrombocytopenia is very low with relatively brief LMWH therapy, routine platelet count monitoring is not recommended unless treatment is prolonged beyond 14 days or the patient has been exposed to UFH in the past 100 days.

UFH may be preferable in patients with severe renal failure (creatinine clearance less than 30 mL/min), in whom LMWH is poorly cleared, and in patients at high risk of haemorrhage.

The action of UFH can be reversed with protamine in an emergency, or alternatively simply stopping the infusion allows complete clearance within hours (due to its short half-life). Protamine has only a limited effect on LMWH, and the long half-life of LMWH can pose serious problems if bleeding occurs. Fresh frozen plasma and prothrombin complex concentrates have no role in reversing the actions of UFH or LMWH. There are no other agents that can reverse LMWH. Although there has been some use of bypassing agents to promote clotting in this circumstance, these agents remain experimental and are prohibitively expensive.

Vitamin K antagonists

An oral vitamin K antagonist should be started immediately after UFH or LMWH therapy is commenced (that is, later on the same day). The two vitamin K antagonists available for therapeutic use in Australia are warfarin (Coumadin, Marevan) and phenindione (Dindevan). Due to its superior pharmacokinetics and tolerability, warfarin is considered the drug of choice, and phenindione should be reserved for patients who are intolerant to warfarin. Coumadin and Marevan do not have equivalent bioavailability, and it is recommended that once patients are stabilised on a particular preparation, it should not be substituted.

Warfarin affects the synthesis and activity of prothrombin and factors VII, IX and X, as well as the natural anticoagulant proteins C and S (see the box on this page). The shorter half-lives of proteins C and S, when compared with prothrombin and factor X, mean that there may be a net prothrombotic tendency when starting warfarin. In addition, the earliest international normalised ratio (INR) response may reflect the effect of warfarin on the level of factor VII rather than on the levels of prothrombin (factor II) and factor X, which may be therapeutically more important targets. This is the rationale for the recommendation to commence heparin prior to vitamin K antagonists and ensuring a minimum of five days overlap of heparin and warfarin, even if a therapeutic INR has been achieved prior to this time.

There are many ways to initiate warfarin. We prefer to avoid the traditional approach of using a higher loading dose, for example '10, 10, 5' (that is, 10 mg on day 1, 10 mg on day 2 and 5 mg on day 3). Although this may be safe in younger patients, it is not suitable for older patients, and may have disastrous results in individuals with genetic sensitivity to warfarin. Patients started on this high-dose regimen are more likely to overshoot with INR results than those started on lower intensity initiation protocols.

The main advantage of a loading dose is achieving an earlier therapeutic INR. Although this may enable earlier cessation of a continuous intravenous infusion of UFH and hospital discharge, there is minimal advantage when initiating treatment with LMWH in an ambulatory care setting. A practical approach to warfarin initiation should take into account the sensitivity to warfarin of older patients, potential interactions of warfarin with medications patients may already be taking and the genetic sensitivity to warfarin of patients with polymorphisms of the genes for cytochrome P450 2C9 (an enzyme involved in warfarin metabolism) or vitamin K epoxide reductase (a key pharmacological target of warfarin).[3]

Several published protocols for warfarin initiation are available,[4] and local clinical guidelines (often those of individual hospitals) should be followed. We prefer a starting dose of warfarin of 3 to 5 mg/day for elderly patients and 7 to 8 mg/day for younger patients. Measuring INR after two doses will ensure that patients highly sensitive to warfarin are detected by the rapidly rising INR, and the dose can be reduced appropriately. Daily monitoring may be required in patients who respond with rapidly rising INRs, until the INR has stabilised. In most patients, the INR can then be monitored every second day. Failure to respond will require the dose to be increased after three to four days. LMWH should be continued until the INR has been more than 2 for two consecutive

days. There is little disadvantage of an extra day or two of LMWH, hence our preference for beginning with conservative warfarin doses and increasing the warfarin dose if the INR is slow to rise.

Once stable anticoagulation has been achieved for one to two weeks, the frequency of INR monitoring can be reduced to every two to four weeks. INR monitoring should, however, be performed more frequently when changing doses or in circumstances where an unpredictable response to warfarin may be more likely (see below).

Ambulatory care is safe and feasible in most patients. Patients with DVT and severely compromised circulation, excessive pain or marked oedema may require inpatient admission. Pulmonary emboli may also be managed in an ambulatory environment provided oxygenation is adequate and patients are haemodynamically stable.

The approach to anticoagulation therapy described above is summarised in the flowchart on page 22.

Maintenance treatment

Warfarin doses should be adjusted to maintain a target INR of 2 to 3 in most patients. Patients who have recurrent VTE while on documented therapeutic levels of warfarin may require a higher INR. For most patients, warfarin therapy is uncomplicated, but a significant minority can prove difficult to stabilise. Age, concurrent medications, genetic susceptibility to vitamin K antagonists and alcohol are the most common causes of difficulties. There may be more than an order of magnitude difference in the doses of warfarin required between patients.

Although it was previously considered that dietary vitamin K intake should be restricted, variations in diet appear to have only a modest effect. A recent study failed to show significant change in INRs following a 400 g meal of spinach or broccoli in normal individuals on stable therapeutic doses of warfarin.[5] Another study has suggested that low-dose supplemental vitamin K (phytomenadione) may help to stabilise INRs and prevent over-anticoagulation.[6] This may be worth considering as a therapeutic trial in patients who are difficult to stabilise on warfarin. However, although low doses of vitamin K are found in some multivitamin preparations in Australia, the lowest vitamin K-only tablet (Konakion Tablets) contains phytomenadione 10 mg – enough to reverse anticoagulation completely. A good diet, including a regular intake of vitamin K-rich green vegetables, should certainly be encouraged.

Management of over-anticoagulation

Over-anticoagulated patients require urgent attention because there is an exponential correlation between high INR and clinically significant bleeding. INR levels of below 5, without bleeding, may require only withholding of warfarin and tracking daily INR estimations until the level declines into the therapeutic range. Higher levels may be treated with low-dose (1 to 3 mg) vitamin K given orally or intravenously, which partially reverses warfarin, enabling continuation of therapy. Unfortunately, the lack of a suitable oral low-dose vitamin K preparation in Australia poses some practical difficulties. We occasionally measure the correct dose from an ampoule of the intravenous vitamin K preparation (Konakion Adult Injection), which contains phytomenadione 10 mg/mL, and give this orally with good effect. (It should be noted that Konakion is not TGA-approved for use in this way: it is indicated for haemorrhage or threatened haemorrhage as a result of severe hyperprothrombinaemia due to, for instance, dicoumarol-type anticoagulant overdose.) Vitamin K should not be given intramuscularly due to the risk of bleeding.

Patients with high INRs and serious clinical bleeding require emergency reversal of anticoagulation with a combination of fresh frozen plasma, prothrombin complex concentrates and intravenous vitamin K. Guidelines for the management of excessive anticoagulation have been published by the Australasian Society of Thrombosis and Haemostasis.[7]

Prevention of post-thrombotic syndrome

Post-thrombotic syndrome (also know as post-phlebitic syndrome) is a cause of significant and long-term morbidity following DVT, leading to pain, dependent oedema and varicose eczema and ulceration in the affected limb. In addition to anticoagulation, venous compression stockings are recommended, as they reduce the incidence of post-thrombotic syndrome by approximately 50%.[8] The commonly available DVT prevention stockings, which exert pressures of about 18 mmHg at the ankle, may help, but only graduated stockings capable of exerting pressures of at least 30 mmHg at the ankle have been proven to be effective in randomised trials, and having these professionally fitted is essential for optimal efficacy. Duration of usage is uncertain, but a minimum of one year is currently recommended. Care needs to be taken to avoid folding of the stocking on itself, causing venous occlusion, and they are relatively contraindicated in patients with peripheral neuropathy or arterial disease.

It is sensible to advise patients to minimise venous stasis by raising their legs when sitting, avoiding crossing their legs and avoiding long periods of immobilisation of the legs, such as during travel. These measures may also be advised for long-term secondary prevention.

Duration of anticoagulation

The history of a thrombosis helps to guide the duration of anticoagulation required (Table 1). A minimum of three months is usually recommended if a lower limb DVT occurs in the context of a known non-recurring precipitating event, such as following lower limb immobilisation, injury or surgery, or post-partum. In the

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A suggested approach to anticoagulation therapy in venous thromboembolic disease

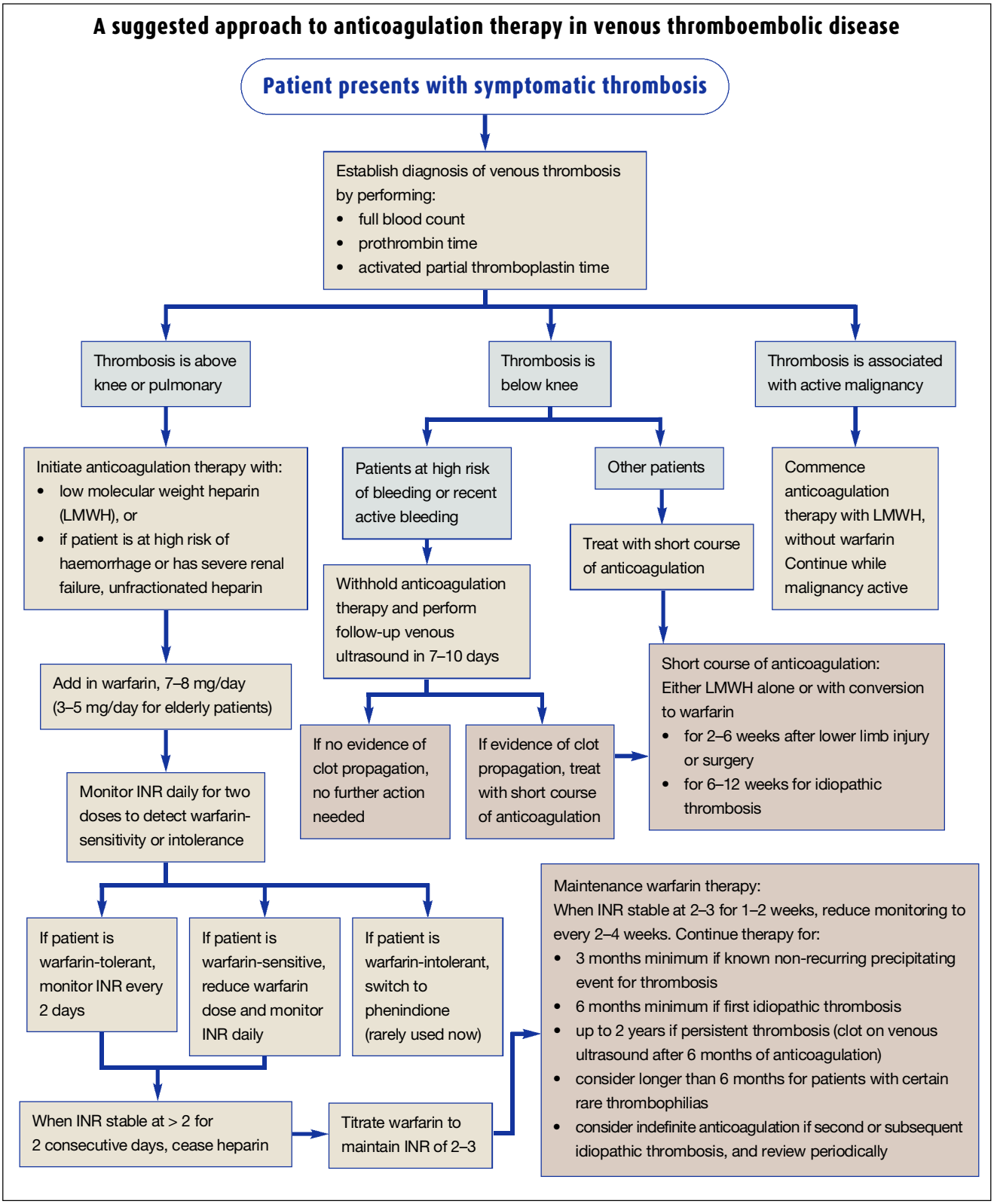

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Table 1. Duration of warfarin anticoagulation for DVT and PE

- Known non-recurring precipitating event – minimum 3 months warfarin therapy
- First idiopathic thrombosis – minimum 6 months warfarin therapy
- Persistent thrombosis (clot on venous ultrasound after 6 months anticoagulation) – up to 2 years warfarin therapy
- Certain rare thrombophilias (e.g. antithrombin deficiency, combined inherited thrombophilias) – consider longer than 6 months warfarin therapy
- Second or subsequent idiopathic thrombosis – consider indefinite warfarin therapy and review periodically

event of idiopathic thrombosis, a minimum of six months of anticoagulation is recommended. Similar anticoagulation durations are recommended for PE, even if there is no ultrasonic evidence of lower limb DVT.

Anticoagulation beyond six months is often advocated, but may not be of benefit to all patients. Persistence of clot on venous ultrasound following six months of anticoagulation is associated with a much higher risk of recurrent thrombosis than is complete resolution of clot during the six months. There may, therefore, be benefit in extending anticoagulation for up to two years for patients with persisting thrombosis. However, it is as yet unknown whether this lowers the longer-term risk of recurrence or simply postpones recurrence until anticoagulation has been ceased.

Extension of anticoagulation has not been shown to be of value for most causes of inherited thrombophilia, including factor V Leiden and the prothrombin gene mutation. Rare thrombophilias, such as antithrombin deficiency and combined inherited thrombophilias, present a particularly high risk of recurrent thrombosis and longer periods of anticoagulation should be considered in patients with these conditions.

For patients with a second or subsequent idiopathic DVT or PE, indefinite anticoagulation is recommended, as the risk of recurrence in these patients is high. However, the risks of recurrence versus the risks of serious haemorrhage need to be considered. Although the risk of severe haemorrhage is relatively constant over time, it may be increased with older age, prior bleeding, poor warfarin control, concurrent antiplatelet therapy and renal or hepatic disease. For this reason, even patients on indefinite anticoagulation should have the continuing appropriateness of this reviewed periodically.

Below knee deep vein thrombosis

The assessment of calf veins by venous duplex ultrasonography is more difficult than similar assessment of the deep veins above the knee, and the assessments are less reproducible. Systematic studies on treatment of below knee DVTs are, therefore, few.

Patients with below knee thromboses are at low risk for PE, so withholding anticoagulation, performing a follow-up venous ultrasound in seven to 10 days and then treating only those patients who show evidence of clot propagation is a safe approach. This approach is recommended in patients at high risk of bleeding, such as those who have had recent neurosurgery or recent active bleeding (see the flowchart on page 22).

The rate of recurrence is also lower in patients with isolated distal venous thrombosis, which impacts on the risk to benefit ratio with extended anticoagulation. However, a short course of anticoagulation often provides rapid symptomatic improvement and alleviates any concerns about proximal extension. We generally prefer this approach in symptomatic patients who are not considered to be at excessive risk of bleeding, either briefly with LMWH alone or with conversion to warfarin for more prolonged periods of anticoagulation (see the flowchart on page 22). We have particular concerns about withholding treatment in patients with immobilised limbs, as proximal extension is more likely in such cases.

The duration of anticoagulation in patients with below knee DVT is uncertain, and we tailor this to the particular patient circumstances. For example, in patients with a transient precipitating factor such as lower limb injury or surgery, brief treatment to cover the period of highest risk (two to six weeks post-event) is offered. In patients with idiopathic thrombosis, a longer period of six to 12 weeks of anticoagulation is more appropriate. Follow-up ultrasound prior to cessation of therapy may be of value in deciding whether to prolong anticoagulation therapy if there are persisting symptoms.

Malignancy

Malignancy (especially adenocarcinoma) is commonly associated with thrombosis because of prothrombotic changes in the blood of cancer patients. It is unwise to cease anticoagulation in the presence of active malignancy due to the risk of recurrence. Treatment with warfarin alone is also associated with more frequent thrombosis recurrence. In patients with cancer, LMWH has been demonstrated to be more efficacious than warfarin, halving the rate of DVT recurrence compared with warfarin over six months of anticoagulation.[9] LMWH, without warfarin, should therefore be considered the treatment of choice for venous thrombosis associated with active malignancy (see the flowchart on page 22).

Use of aspirin in VTE

As an antiplatelet agent, aspirin may have a role in primary or secondary prevention of DVT. There is some evidence that aspirin may be of minor benefit in preventing DVT

following orthopaedic surgery. Whether aspirin has value in secondary prophylaxis after initial adequate anticoagulant therapy for VTE remains the subject of investigation, with a large number of Australasian centres participating in a clinical trial (ASPIRE [Aspirin to Prevent Recurrent Venous Thromboembolism]) aimed at definitively answering this question.

New anticoagulants

The difficulties of warfarin anticoagulation and monitoring, combined with the narrow therapeutic window, make warfarin a drug doctors and patients love to hate. It is metabolised by cytochrome P450, highly protein bound and susceptible to many drug interactions, and genetic variability in patient response makes prediction of dosing difficult, such that dosing has to be tailored to individuals based on regular monitoring.

Pharmaceutical companies have recognised the demand for a safer and more predictable oral anticoagulant, and there are a number of novel agents at various stages of development.[10] These agents also have the potential advantage of not requiring initial overlap therapy with heparin. The thrombin inhibitors and the factor Xa inhibitors are discussed below, and several other agents are beginning early phase clinical trials (Table 2).

With so much development occurring, it is likely that warfarin, and probably heparin, will largely be replaced by one of the newer agents within the foreseeable future. The issues with ximelagatran, however, highlight how difficult it will be for the newer agents to reproduce the proven safety and efficacy of established treatments.

Thrombin inhibitors – ximelagatran and dabigatran

Ximelagatran is an oral small-molecule direct thrombin inhibitor. Efficacy was demonstrated for prophylaxis and treatment of venous thrombosis and prevention of stroke in atrial fibrillation, but clinical use was unfortunately associated with induction of abnormal liver function tests, which although usually minor and transient, occasionally resulted in more severe liver dysfunction. Ximelagatran was registered in Europe briefly, but was withdrawn when several patients developed unexplained liver failure. However, it did provide a proof of concept, and other similar agents have followed.

Dabigatran is another oral direct thrombin inhibitor, and is in advanced stages of clinical trials.

Factor Xa inhibitors – lepirudin, rivaroxaban and idraparinux

Direct factor Xa inhibitors act on activated factor X rather than thrombin, as does LMWH, but are independent of antithrombin. Lepirudin (Refludan) is currently in use to treat heparin-induced thrombocytopenia, and is given by continuous intravenous infusion, similar to heparin.

Several small, orally administered factor Xa inhibitors are in clinical trials. Rivaroxaban (Xarelto) appears the most advanced of these, with a recent series of prophylaxis trials reporting efficacy at least equivalent to LMWH and warfarin.[11] It has recently been approved by the TGA for DVT prevention in joint replacement surgery. Whether this translates into effective treatment of thrombosis and stroke prophylaxis is yet to be demonstrated. Nonhaemorrhagic toxicity appears to be minimal.

Idraparinux is another factor Xa inhibitor, and is given subcutaneously. By modifying fondaparinux to prevent dissociation from antithrombin, a drug with very prolonged activity has been produced, which only needs to be given weekly. Idraparinux has had mixed success in treating patients with DVT and PE. Increased bleeding, in comparison to warfarin, has also been noted in a stroke prevention trial, and further data on safety and efficacy are required. Although the action of idraparinux is irreversible, further modification of the molecule has been undertaken such that an antidote may be administered to remove the modified molecule from the circulation. Further studies are under way into this modified molecule (idrabiotoparinux).

Table 2. Potential warfarin and heparin replacements

Thrombin inhibitors

- Ximelagatran – was registered briefly in Europe but now withdrawn
- Dabigatran – in advanced clinical trials

Factor Xa inhibitors

- Lepirudin (Refludan) – TGA-approved for treatment of acute heparin-induced thrombocytopenia (HIT) type II patients with thrombocytopenia or thromboembolic complications
- Rivaroxaban (Xarelto) – TGA-approved for prevention of VTE in adult patients who have undergone major orthopaedic surgery of the lower limbs
- Idraparinux – further safety and efficacy data required

Conclusion

Heparin and warfarin therapy remains the mainstay of treatment for DVT and PE. Although there has been improved understanding of warfarin over recent years, it remains difficult to use because of drug interactions, a narrow therapeutic window and the need for monitoring. Although warfarin may be disliked by both patients and doctors, it is highly effective with minimal nonhaemorrhagic toxicity, and in over 50 years of usage, no long-term unexpected side effects have emerged. Until new drugs can meet this standard of safety and efficacy, treatment of venous thrombosis in the near future will continue to be based on heparin in conjunction with vitamin K antagonists.

continued

Anticoagulant duration requires the weighing up of estimated risks of thrombosis recurrence and the increased risk of bleeding associated with anticoagulation. A minimum duration of three months is advised for proximal DVT and PE, with a longer duration of at least six months recommended for idiopathic VTE. This may be modified according to patients' specific risk factors for recurrence and bleeding, and indefinite anticoagulation may be required for patients with multiple idiopathic DVTs or PE or persisting risk factors, such as active cancer. For patients with distal venous thrombosis, the need for and duration of anticoagulation is less clear. Although the same principles apply to determining anticoagulant duration for above or below knee DVT, the risk of complications and recurrence is lower in patients with distal clots, so shorter treatment periods are appropriate. MT

References

1. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). Chest 2008; 133 (6 Suppl): 454S-545S.
2. Prosser I, Crispin P. Investigating the patient with venous thromboembolic disease. Medicine Today 2009; 10(2): 50-55.
3. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med 2008; 358: 999-1008.
4. Roberts GW, Druskeit T, Jorgensen LE, et al. Comparison of an age adjusted warfarin loading protocol with empirical dosing and Fennerty's protocol. Aust N Z J Med 1999; 29: 731-736.
5. Schurgers LJ, Shearer MJ, Hamulyak K, Stocklin E, Vermeer C. Effect of vitamin K intake on the stability of oral anticoagulant treatment: dose-response relationships in healthy subjects. Blood 2004; 104: 2682-2689.
6. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 2007; 109: 2419-2423.
7. Baker RI, Coughlin PB, Gallus AS, et al. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. Med J Aust 2004; 181: 492-497.
8. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349: 759-762.
9. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349: 146-153.
10. Gross PL, Weitz JI. New anticoagulants for treatment of venous thromboembolism. Arterioscler Thromb Vasc Biol 2008; 28: 380-386.
11. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008; 358: 2765-2775.

COMPETING INTERESTS: None.