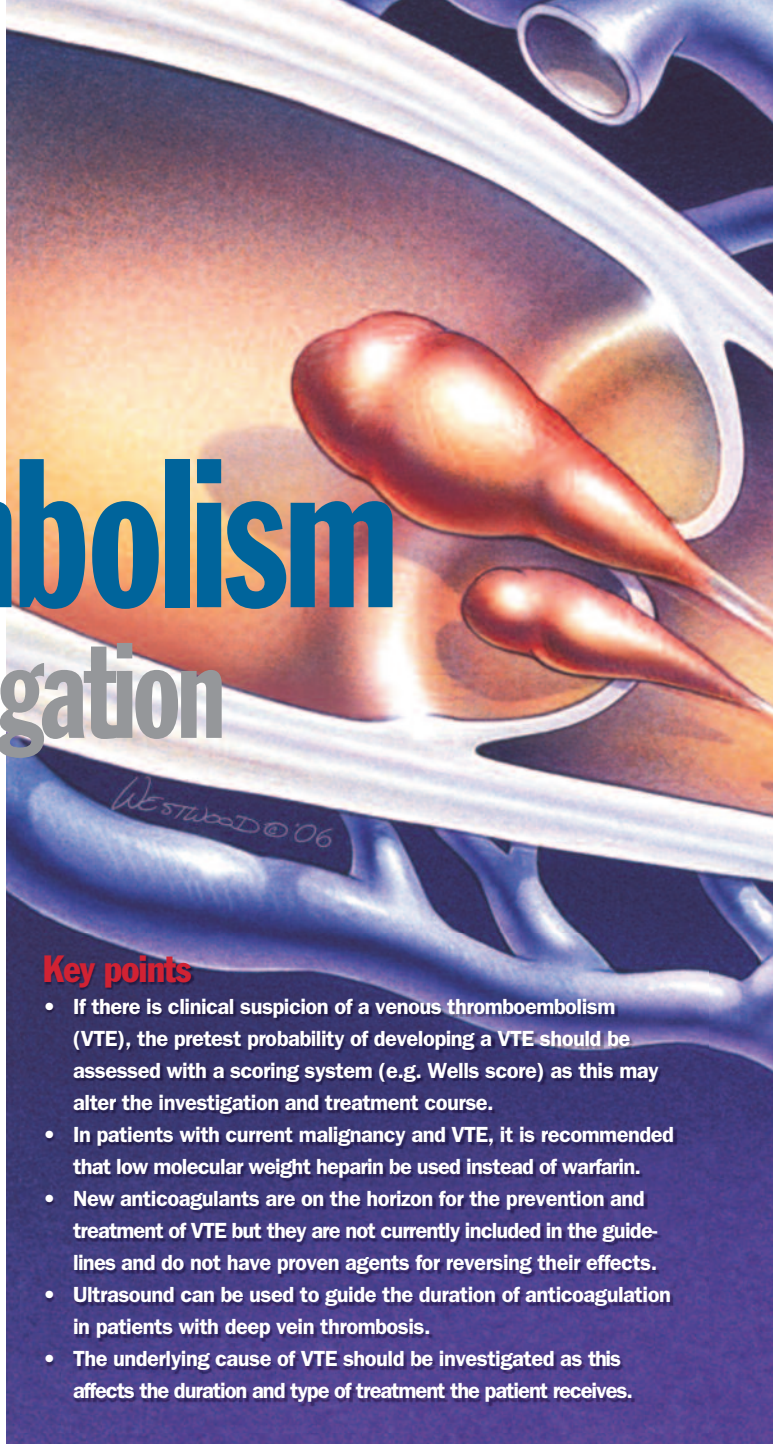
FEATURE

Venous thromboembolism

Prevention, investigation and treatment



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People at risk of developing venous thromboembolism (VTE) need to be identified so that they can commence prophylaxis, which may prevent significant morbidity and mortality. Investigation of the underlying cause of VTE is essential because this affects the duration and type of treatment.

Key points

- If there is clinical suspicion of a venous thromboembolism (VTE), the pretest probability of developing a VTE should be assessed with a scoring system (e.g. Wells score) as this may alter the investigation and treatment course.
- In patients with current malignancy and VTE, it is recommended that low molecular weight heparin be used instead of warfarin.
- New anticoagulants are on the horizon for the prevention and treatment of VTE but they are not currently included in the guidelines and do not have proven agents for reversing their effects.
- Ultrasound can be used to guide the duration of anticoagulation in patients with deep vein thrombosis.
- The underlying cause of VTE should be investigated as this affects the duration and type of treatment the patient receives.

Venous thromboembolism (VTE) is a common and often preventable cause of morbidity and mortality, with approximately one in 1250 people being affected in the USA.[1] Most people who present acutely have one or more risk factors for developing VTE.

In practice, VTE can be divided into pulmonary embolism (PE) and deep vein thrombosis (DVT), with the former posing a much higher mortality risk. It is estimated that about 1.5% of all deaths are a result of PE,[2] and approximately 80% of all unexplained in-hospital deaths were confirmed cases of massive PE on autopsy. A rise in the incidence of VTE has been reported; however, this is probably secondary to the increased awareness of VTE and improved access to ultrasonography and CT scanning.[3,4]

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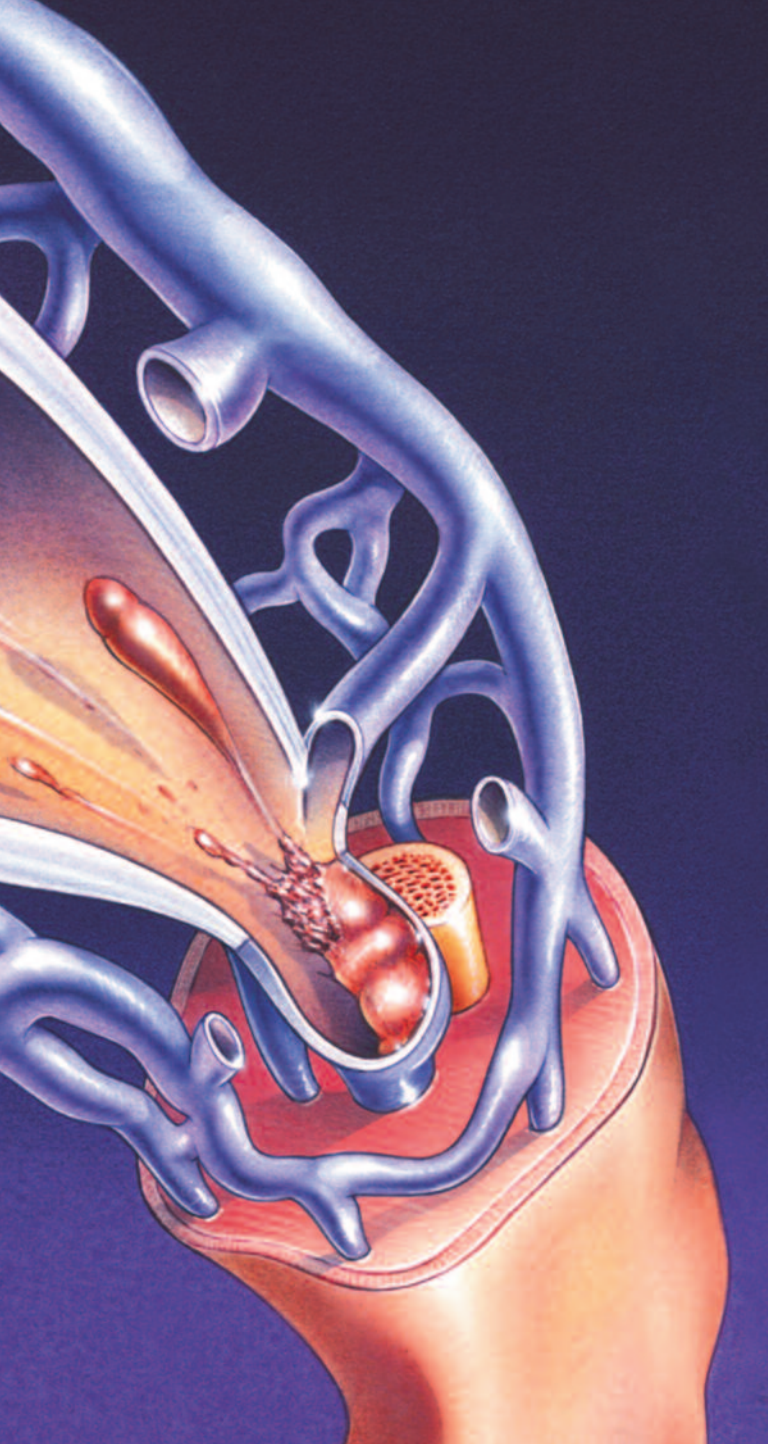
Prevention of DVT and PE

Identifying patients who are at high risk is arguably the most important step in the primary prevention of VTE. Virchov's triad of alterations in blood flow (stasis), vascular endothelial injury and alterations in blood constitution (hypercoagulability) still stands the test of time and helps to explain most of the risks for developing VTE (see the box on page 7).

In general, prophylaxis should be started in patients who are older than 40 years of age, have had limited mobility for more than three days and have one or more risk factors.[5,6] Prophylaxis can be medical with anticoagulation and/or physical with use of compression stockings or intermittent pneumatic compression.

Before starting anticoagulation, the patient's risk of bleeding needs to be carefully considered because this may be higher than the risk



Risk factors for venous thromboembolism

Inherited (thrombophilia)
Factor V Leiden mutation
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Prothrombin gene mutation

Acquired
Mechanical factors
Immobilisation (e.g. after a stroke)
Surgery especially orthopaedic
Trauma
Venous procedures, including implanting of pacemakers

Alterations in blood constituents
Malignancy
Pregnancy
Congestive cardiac failure
Antiphospholipid antibody
Myeloproliferative disorders
Paroxysmal nocturnal haemoglobinuria
Inflammatory bowel disease
Nephrotic syndrome
Acute exacerbation of chronic obstructive pulmonary disease
Sepsis
Prior venous thromboembolism
HIV infection
Intravenous drug use

Medications
Oral contraceptive pill
Tamoxifen, thalidomide, lenalidomide
Hormone replacement therapy

associated with having a VTE. The current options for medical prophylaxis include low molecular weight heparin (LMWH), subcutaneous unfractionated heparin and fondaparinux.

Mechanical prophylaxis with compression stockings has been shown to reduce the incidence of DVT,[7] and when used in conjunction with anticoagulation has been shown to decrease the incidence of DVT even further. In a meta-analysis, the use of compression stockings versus no compression stockings in an at-risk group decreased the rate of DVTs from 27% to 13%.[7] When compression stockings were used in conjunction with anticoagulation, the absolute risk was decreased by 13%.[7]

In regards to anticoagulation, the current data support the use of LMWH. In a meta-analysis of 36 trials comparing subcutaneous unfractionated heparin with LMWH, it was found that LMWH was more effective in preventing DVT and had less injection site haematoma than did unfractionated heparin. Also, using unfractionated heparin 5000 units three times daily was more effective than twice daily.[8] Surprisingly, this study also showed that VTE prophylaxis did not alter the mortality rate.

The role of the new oral anticoagulants in the prevention of DVT and PE in medical patients has not yet been clearly defined. Apixaban, dabigatran and rivaroxaban have all been approved for the prevention of VTE following elective hip and knee surgery (see text below). Rivaroxaban is also approved and PBS funded for the prevention of recurrent DVT and PE.

Specific groups

Pregnancy

During pregnancy, the highest incidence of VTE is usually seen in the postpartum period,[9] especially in patients who have undergone

Table. Wells score for VTE[14]

Clinical features	Score
Active cancer	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for more than 3 days or major surgery within 4 weeks	1
Localised tenderness along the distribution of the deep vein system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (non varicose)	1
Alternative diagnosis to deep vein thrombosis as likely or more likely	-2

High probability = 3 or more; moderate probability = 1 to 2; low probability = 0.

caesarean section.[10] Current guidelines do not advocate VTE prophylaxis in healthy postpartum women. However, if patients have multiple risk factors and are in their postpartum period, LMWH (e.g. enoxaparin) is the treatment of choice for VTE prophylaxis because its use is associated with a decreased risk of bleeding, osteopenia and thrombocytopenia when compared with the use of unfractionated heparin.

Extended travel

The majority of data about DVTs secondary to extended travel are from retrospective studies that are likely to be inaccurate due to the fact that quite a number of events are asymptomatic. In a small prospective randomised study of healthy individuals who travelled for a minimum of eight hours per flight, 10% of them (12/116) developed asymptomatic DVT.[11] The use of below-knee graduated compression stockings in four other people in this trial reduced the risk of DVT from 10% to 0%.[11]

Current guidelines for extended travel recommend the following: regular movement; refraining from smoking, sedatives and constrictive clothing; adequate hydration; and use of below-knee stockings for people who are travelling more than six to eight hours.[12] If patients are at high risk of DVT, a single dose of LMWH can be considered a couple of hours before travel.[13]

Investigation of VTE

If there is clinical suspicion of VTE, it is of the utmost importance that clinicians first assess the patient for PE. If a PE is unlikely, the clinical pretest probability of the patient developing a DVT should be calculated using the well-validated Wells score (see the Table).[14] Further diagnostic testing can then be considered.

D-dimer is a small protein fragment that is present in the blood after a blood clot is degraded by fibrinolysis. The D-dimer test for suspected VTE has a high sensitivity of 93% to 95%, but only modest specificity of 50%;[15] therefore, its main use is for patients with a low-to-moderate probability of having VTE. A negative D-dimer test result is helpful in ruling out VTE.

It is important to note that if a patient has a high pretest probability (i.e. a Wells score of 3 or more) and low risk of bleeding, anticoagulation should be initiated while awaiting confirmation by more definitive diagnostic testing (e.g. CT pulmonary angiography, lower limb ultrasonography). There is no additional diagnostic benefit in carrying out a D-dimer test in these patients.

Patients who have a Wells score of 1 to 2 are at moderate risk and should undergo a D-dimer test. If this is positive they should be anticoagulated while awaiting confirmatory lower limb ultrasound. If the D-dimer test is negative they may be reclassified to low risk and no further assessment is needed as there is an almost 99% negative predictive value in this case.

A score of 0 on the Wells score indicates a low probability of VTE and has a negative predictive value of 96% and the diagnosis of DVT can therefore be essentially ruled out. An algorithm for the diagnosis of DVT is proposed in the flowchart on page 9.

If a PE is suspected, the patient should be referred to hospital for inpatient anticoagulation and investigation. The most prominent symptoms to suggest a PE are shortness of breath and pleuritic chest pain. It is always important to take into account the risk factors of VTE (see the box on page 7). According to one study, patients with proven PE had the following symptoms present: dyspnoea (73%), pleuritic chest pain (66%), cough (37%) and hemoptysis (13%).[16]

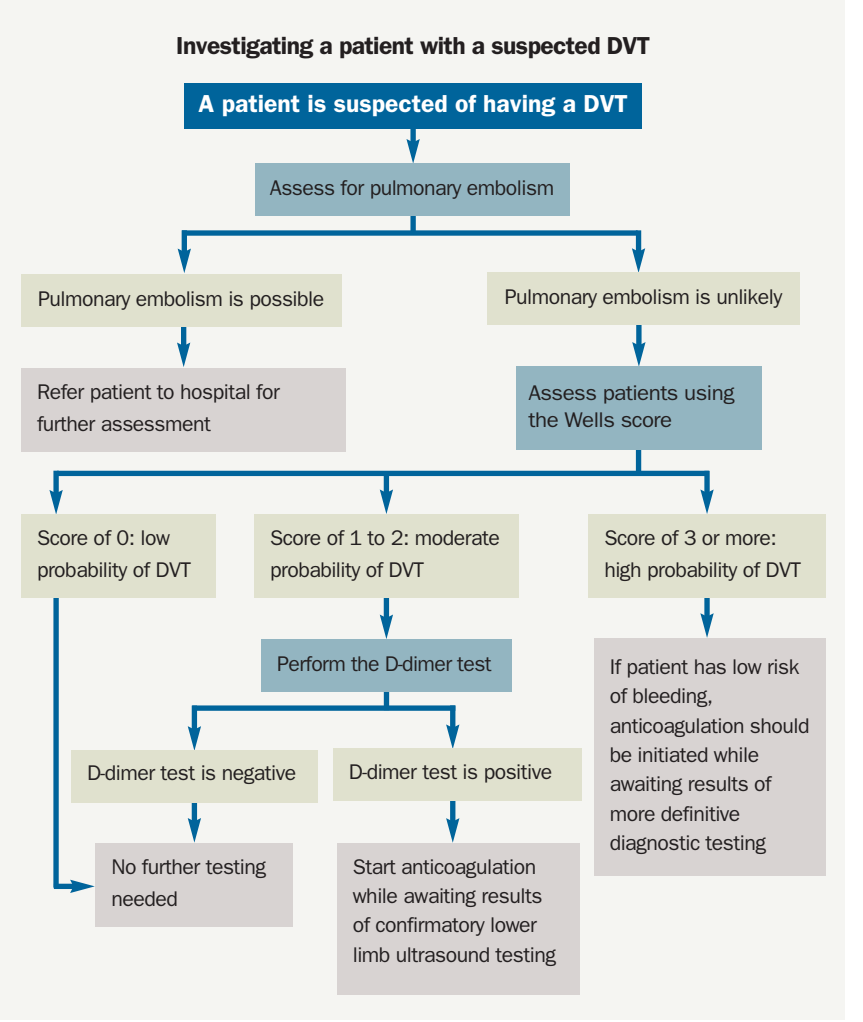
When investigating patients with suspected PE, it is important to consider a few factors. The presence of increased air space or interstitial infiltrates, which is seen in patients with asthma, chronic obstructive pulmonary disease, interstitial lung disease and congestive cardiac failure, make ventilation/perfusion scans harder to interpret and increase the chances of receiving an intermediate probability result. In these situations, therefore, it would be logical to choose CT pulmonary angiography over ventilation/perfusion scans. CT pulmonary angiography is also better at visualising other underlying lung pathology and there is less interobserver variation (see Figure). However, CT scanning has the disadvantage of its high radiation dose and the need for contrast. In young women, higher doses of radiation has potential to increase the risk of breast cancer; hence in this population ventilation/perfusion scanning should be considered because it has a much lower radiation dose.[17] Also patients with renal failure need to be considered for ventilation/perfusion scanning, given the risk of contrast nephropathy.

After the diagnosis of VTE is established, it is also essential to investigate for an underlying precipitant for the VTE. If there is no obvious cause for embolic disease, a hypercoagulation workup should be performed. This includes screening for factor V Leiden, prothrombin gene mutation, antithrombin III deficiency, protein C

or protein S deficiency, lupus anticoagulant, homocystinuria, connective tissue disorders and occult neoplasms. If antiphospholipid syndrome is suspected, anticardiolipin antibodies and beta-2 glycoprotein 1 should also be tested for.

As protein C and protein S levels are affected by use of warfarin and thrombosis, it is recommended that patients have their levels checked at least 10 days post-thrombosis and while they are not taking anticoagulants therapy. This poses a clinical problem as patients are usually started on anticoagulation therapy early. Often the best time to check levels of proteins C and S would be after stopping treatment for VTE.

Screening for occult neoplasms should include a careful history and complete physical examination, including a digital rectal examination, faecal occult blood test and, in women, pelvic examination. Investigations include routine blood tests, including a full blood count, measurement of urea and electrolytes levels, liver function tests, measurement of calcium levels, urinalysis, chest x-ray, and, in men over the age of 50 years, a prostate-specific antigen test.



Management

Treatment of DVT

Patients with DVTs can often be managed as outpatients. The main rationale behind treating DVT is to prevent PE and minimise the risk of developing post-thrombotic syndrome. Currently, medical therapy consists of anticoagulation with both LMWH and warfarin until the international normalised ratio is therapeutic and then stopping the LMWH. The rationale behind this is that, firstly, warfarin has a long half-life of 20 to 60 hours and can therefore take days to reach a therapeutic range. Secondly, warfarin impairs production of proteins C and S and can transiently be paradoxically prothrombotic in the initial few days. By using LMWH at the start of anticoagulation therapy, it is possible to achieve rapid anticoagulation and also cover the patient for the initial prothombotic effects of warfarin.

Anticoagulation therapy can often be managed in an outpatient setting. However, patients should be referred for inpatient management if they have suspected or proven PE, have iliofemoral DVT (because of the risk of embolisation), have familial or inherited disorders of coagulation, are pregnant or morbidly obese, have renal failure or are unable to follow instructions.

Patients should have their platelets monitored at baseline and five to 14 days after starting heparin to identify the possibility of heparin-induced thrombocytopenia developing. If the platelet count falls below 75,000 per μL, LMWH should be discontinued. Fondaparinux 7.5 mg daily by subcutaneous injection is not associated with heparin-induced thrombocytopenia and may be used in place of heparin as it has been shown in trials to have comparable safety and efficacy compared with enoxaparin.[18] Fondaparinux is, however, expensive and is not PBS funded for the treatment of DVT.

Rivaroxaban, an oral direct factor Xa inhibitor, has in the past year been listed on the PBS for the treatment of DVT based on the results from the oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic DVT (EINSTEIN DVT) study. This study showed that rivaroxaban 15 mg twice daily for the first three weeks followed by 20 mg daily was noninferior to enoxaparin plus warfarin for the treatment of DVT.[19] The study also showed that rivaroxaban did not increase major bleeding risk.[19]

For the first episode of DVT, the patient should be treated with anticoagulation for three to six months. For recurrent episodes or in patients with irreversible risk factors (e.g. malignancy) lifelong anticoagulation therapy should be considered.

A recent study has shown that low-dose aspirin given after the discontinuation of anticoagulation after a first episode of unprovoked VTE decreased the incidence of major vascular events and had a net clinical benefit although it did not decrease the rate of recurrence of VTE.[20]

Another study used ultrasonography to guide the duration of anticoagulation, based on the ultrasonographic clearance of the DVT.[21] In this study, after patients were treated for their DVT (three months for provoked and six months for unprovoked DVT) they were randomised to conventional treatment duration or to ultrasound-guided treatment duration. Patients who did not have resolution of their DVT were anticoagulated for a further three months followed by repeat ultrasonography. This study showed that by using ultrasonography, the investigators were able to reduce the rate of recurrent DVT by an absolute risk of 5%.[21] The mean duration of anticoagulation was prolonged by a mean of 3.7 months in those with provoked DVT and a mean of five months in those with unprovoked DVT.[21]

Treatment of VTE in patients with malignancy

About 20% of patients with VTE are found to have a malignancy.[22] Those most commonly found are pancreatic, lung, genitourinary, bowel and breast cancers.[23] Patients with malignancy have a threefold greater risk of VTE and are six times more likely to bleed, compared with patients without malignancy.[24]

The use of long-term LMWH has been shown to be more effective than warfarin in reducing the incidence of recurrent VTE in patients with cancer without significantly increasing the risk of bleeding.[25] In addition, the use of LMWH has been shown in multiple trials to lower mortality in patients with cancer, with its effects lasting after the treatment has stopped.[26-29] This effect is postulated to be secondary to LMWH having some antimalignancy effect.

Treatment of PE

All patients who have been diagnosed with PE should be risk stratified into massive PE (systolic blood pressure <90 mmHg) and nonmassive PE (systolic blood pressure ≥90 mmHg). It is estimated that massive PE accounts for less than 5% of patients with PE.[30]

Patients with massive PE with low bleeding risks should receive thrombolysis because of their risk of irreversible cardiogenic shock.[31] In patients who have high bleeding risks, surgical embolectomy should be considered.

All patients with PE should be started on unfractionated heparin/LMWH and commenced on warfarin. When their international normalised ratio is between 2 and 3 heparin can be ceased.

Patients with a reversible risk factor for PE (e.g. surgery or immobility) should be treated for a minimum of three months. Patients with nonmodifiable risk factors (e.g. malignancy, protein S or C deficiency) should be placed on lifelong anticoagulation if the bleeding risk is acceptable. Patients with an unprovoked PE should be evaluated for underlying thrombophilic disorders and considered for lifelong warfarin if bleeding risk is low.

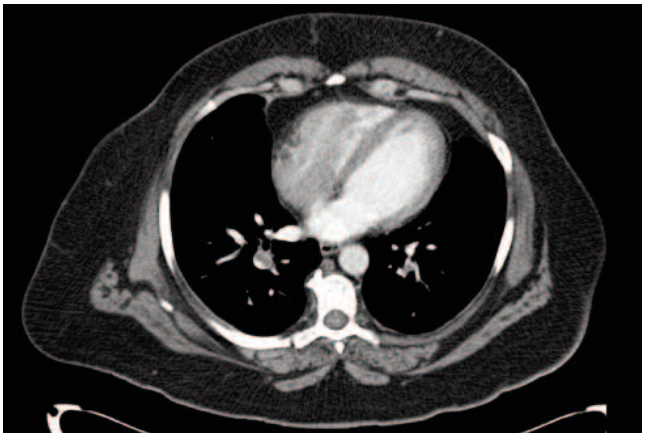


Figure. CT pulmonary angiography showing bilateral pulmonary embolism.

Recent trial data from the EINSTEIN PE study,[32] one of the largest PE studies to date, showed that treatment with rivaroxaban was noninferior to standard therapy with warfarin plus enoxaparin and was associated with fewer major bleeding events (1.1 *vs* 2.2%, p = 0.0032). However, given the lack of an effective antidote and the fact that rivaroxaban is not currently licensed for the treatment of PE, the use of rivaroxaban in PE is not current practice. It may in the future become the standard of care, and may then facilitate outpatient treatment of nonmassive PE.

New oral anticoagulants and VTE

Apixaban

Apixaban, a direct factor Xa inhibitor, is listed on the PBS for the prevention of VTE in patients undergoing elective hip and knee surgery following the publication of the apixaban versus enoxaparin for thromboprophylaxis after knee and hip replacement (ADVANCE-1, -2 and -3) trials.[33-35] These trials demonstrated that treatment of patients with apixaban was superior to treatment with enoxaparin in the prevention of VTE, and did not increase significant bleeding.[33-35]

Unfortunately when use of apixaban was trialled in the prophylaxis of VTE in medically ill patients, apixaban 2.5 mg twice daily for 30 days showed no increased efficacy and had higher bleeding risks compared with enoxaparin 40 mg daily for six to 14 days.[36]

Another interesting trial investigated 2486 patients who had had a VTE and completed a six- to 12-month course of anticoagulation therapy. These patients were randomised to placebo or 12 months of apixaban. The results showed that treating patients with apixaban for a further 12 months reduced rates of symptomatic VTE or death from VTE from 8.8% (in the placebo group) to 1.7% (apixaban 2.5 mg or 5 mg) without increasing the rate of major bleeding.[37]

Apixaban is contraindicated in patients who have active bleeding or are at high risk of bleeding, have severe hepatic impairment or severe renal impairment, or are taking strong inhibitors of CYP3A4 and P-gp inducers.

Dabigatran

Dabigatran is a direct thrombin inhibitor and is listed on the PBS for the prevention of VTE in patients undergoing elective hip and knee surgery on the basis of the dabigatran etexilate versus enoxaparin for prevention of VTE after total hip and knee replacement (RE-NOVATE and RE-MODEL) studies.[38,39] These studies demonstrated that dabigatran was noninferior to standard dose enoxaparin for DVT prophylaxis in patients having elective hip and knee surgery.

Dabigatran is contraindicated in patients who have severe renal impairment (creatinine clearance <30 mL/min), high bleeding risk, hepatic impairment, history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, or a history of gastrointestinal bleeding within the past year.

Case study

Case scenario

Mr FS, a 45-year-old man with a past medical history of hypertension, hypercholesterolaemia and heavy smoking, was recently discharged from the emergency department following an unprovoked lower limb deep vein thrombosis (DVT). He was started on a treatment dose of enoxaparin and warfarin and asked to follow up with his GP for treatment of his lower leg DVT.

Q1. How would you investigate Mr FS?

Q2. How long would you treat his DVT for and what agent would you use?

Answers

You should investigate Mr FS by carrying out laboratory tests, including a full blood count, measurement of urea and electrolyte levels, and testing for factor V Leiden, protein C and S levels, antithrombin III, lupus anticoagulant and prothrombin gene mutation. A history and examination for occult neoplasm and connective tissue disorder screen should also be carried out.

If Mr FS's bleeding risk is low, he should be treated for three to six months with warfarin. Alternatively, he could be treated until his DVT is cleared on ultrasound.

Case continued

At Mr FS's follow-up appointment with you three months later, he informs you that he has lost 4 kg in weight and has been feeling increasing shortness of breath. He was subsequently sent for a chest x-ray, which showed a pulmonary lesion suspicious of lung cancer.

Q3. How does this new diagnosis change your management and why?

Answers

Due to the diagnosis of malignancy, Mr FS would benefit from long-term anticoagulation with low molecular weight heparin as per the CLOT (comparison of low molecular weight heparin vs oral anticoagulant therapy for the prevention of recurrent venous thromboembolism in patients with cancer) study.[25]

The trial of dabigatran versus warfarin in the treatment of acute VTE (RE-COVER) demonstrated that dabigatran 150 mg twice daily was noninferior to warfarin with no increase in major bleeding risk for the treatment of acute VTE.[40] The main drawback with this study was the fact that most patients treated had DVT and therefore it is unclear if the RE-COVER trial data are truly applicable to patients with PE.

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor currently listed on the PBS for the prevention of VTE in patients undergoing hip and knee surgery. This occurred following the release of the regulation of coagulation in orthopaedic surgery to prevent DVT (RECORD) studies, which showed that rivaroxaban had slightly higher efficacy in reducing the incidence of VTE following hip and knee surgery.[41-43]

Rivaroxaban is also licensed for the treatment of DVT and for the prevention of recurrent DVT and PE. It is contraindicated in patients with severe renal or hepatic impairment, with active bleeding or who are at increased risk of clinically significant bleeding, and who are pregnant, breastfeeding or taking strong inhibitors of CYP3A4 and P-gp inducers.

Other trials of note involving rivaroxaban include the EINSTEIN PE study and MAGELLAN study (the multicenter, randomized, parallel group efficacy superiority study in hospitalized medically ill patients comparing rivaroxaban with enoxaparin).[32,44] The MAGELLAN study showed that rivaroxaban 10 mg once daily was more effective than enoxaparin 40 mg once daily for the prevention of VTE in the acutely ill medical patient, but had significantly increased rates of fatal bleeding.[44]

Conclusion

It is important for clinicians to identify patients at risk of developing VTE and commence prophylaxis because this may prevent significant morbidity and mortality. In patients who have had a VTE where no obvious cause is found, it is important to investigate further for underlying precipitating factors.

Although there are newer anticoagulants available, we currently recommend LMWH for prophylaxis of VTE except in patients undergoing hip/knee surgery, in whom one of the new oral anticoagulants may be used.

Treatment of VTE generally consists of LMWH followed by warfarin. Guidelines are likely to change in the near future to include use of the newer anticoagulants. Currently in Australia, rivaroxaban is the only new oral anticoagulant licensed for the treatment of DVT, but not for PE. It is also licensed for the prevention of recurrent DVT and PE. These new anticoagulants currently do not have proven agents for reversing their effects. As such it is prudent to only use them in selected patients with very low risk of bleeding. **CT**

References

A list of references is available on request to the editorial office.

COMPETING INTERESTS: None.

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