Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

NICE guideline

Draft for consultation, October 2011

If you wish to comment on this version of the guideline, please be aware that all the supporting information and evidence is contained in the full version.

Contents

Introduction

Venous thromboembolism (VTE) is a condition in which a blood clot (a thrombus) forms in a vein and then dislodges to travel in the blood (an embolus). A venous thrombus most commonly occurs in the deep veins of the legs or pelvis; this is called deep vein thrombosis (DVT). Blood flow through the affected vein can be limited by the clot, and this can cause swelling and pain in the leg. If the clot dislodges and travels to the pulmonary arteries in the lungs, it is called pulmonary embolism (PE), and can be fatal. Non-fatal VTE is also important because it can cause serious longer-term conditions such as post-thrombotic syndrome and chronic pulmonary hypertension

VTE as a term includes both DVT and PE. Major risk factors for VTE include a history of DVT, age over 60 years, surgery, obesity, prolonged travel, acute medical illness, cancer, immobility, thrombophilia (an abnormal tendency for the blood to clot) and pregnancy.

Failure to diagnose and treat VTE correctly can result in fatal PE. However, diagnosis of VTE is not always straightforward. This guideline includes advice on the use of clinical diagnostic scores such as the Wells score, D-dimer measurement, ultrasound and radiological imaging. It also offers guidance on the management of VTE, investigations for cancer in patients with VTE and thrombophilia testing. The guideline covers adults with suspected or confirmed DVT or PE. It does not cover children or young people aged under 18, or women who are pregnant.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Key to terms

The following terms are used in this guideline.

International normalised ratio (INR) A standardised laboratory measure of blood coagulation used to monitor the adequacy of anticoagulation in patients who are having treatment with a vitamin K antagonist.

Provoked deep vein thrombosis (DVT) or pulmonary embolism (PE) DVT or PE in a patient with an antecedent (within 3 months) and transient major clinical risk factor for VTE – for example surgery, trauma, significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperium – or in a patient who is having hormonal therapy (oral contraceptive or hormone replacement therapy).

Proximal DVT DVT in the popliteal vein (including the trifurcation area) or above.

Renal impairment Reduced renal function that may be acute or chronic. An estimated glomerular filtration rate of less than 90 ml/min/1.73 m^2 indicates a degree of renal impairment in chronic kidney disease[1].

Unprovoked DVT or PE DVT or PE in a patient with no antecedent major clinical risk factor for VTE (see 'Provoked deep vein thrombosis or pulmonary embolism' above) who is not having hormonal therapy (oral contraceptive or hormone replacement therapy).

Wells scores Clinical prediction rules for estimating the probability of DVT and PE. There are a number of versions of Wells scores available. This guideline recommends the two-level DVT Wells score and the two-level PE Wells score.

[1] For NICE guidance on the classification of chronic kidney disease see Chronic kidney disease (NICE clinical guideline 73).

Patient-centred care

This guideline offers best practice advice on the care of adults with VTE.

Treatment and care should take into account patients' needs and preferences. People with VTE should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/en/DH_103643) and the code of practice that accompanies the Mental Capacity Act (available from www.dh.gov.uk/en/SocialCare/Deliveringsocialcare/MentalCapacity). In Wales, healthcare professionals should follow advice on consent from the Welsh Government (available from www.wales.nhs.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Diagnosis

Diagnostic investigations for deep vein thrombosis

- If a patient presents with signs or symptoms of DVT, carry out an assessment of their general medical history and a physical examination to exclude other causes. **[1.1.1]**

- Offer patients with a 'likely' two-level DVT Wells score:
  - a proximal ultrasound scan carried out within 4 hours **and**
  - a D-dimer test if the proximal ultrasound scan is negative **or** (if a proximal ultrasound scan cannot be carried out within 4 hours)
  - a D-dimer test **and** low molecular weight heparin (LMWH) or unfractionated heparin (UFH) **and** a proximal ultrasound scan carried out within 24 hours to avoid the need for a second dose of LMWH or UFH.

  Repeat the proximal ultrasound scan 6–8 days later if the D-dimer test is positive and the proximal ultrasound scan is negative. **[1.1.3]**

- Offer patients with an 'unlikely' two-level DVT Wells score a D-dimer test and if the result is positive offer:
  - a proximal ultrasound scan carried out within 4 hours **or** (if a proximal ultrasound scan cannot be carried out within 4 hours)
  - LMWH or UFH **and** a proximal ultrasound scan carried out within 24 hours to avoid the need for a second dose of LMWH or UFH. **[1.1.4]**

Diagnostic investigations for pulmonary embolism

- Offer patients with a 'likely' two-level PE Wells score:
  - a computed tomography pulmonary angiogram (CTPA) **and**
  - consider a proximal ultrasound scan if the CTPA is negative and DVT is suspected. **[1.1.9]**

- Offer patients with an 'unlikely' two-level PE Wells score:
  - a D-dimer test **and**
  - a CTPA if the D-dimer test is positive. **[1.1.10]**

Treatment

Pharmacological interventions

Deep vein thrombosis or pulmonary embolism

- Offer a choice of LMWH or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:
  - For patients with renal impairment or an unpredictable bleeding risk, consider UFH.
  - For patients with PE and haemodynamic instability, offer UFH.

  Start the LMWH, fondaparinux or UFH as soon as possible and continue it for 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3) is 2 or above for at least 24 hours, whichever is longer. **[1.2.1]**

- Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for at least 6 months[2]. **[1.2.2]**

- Offer a VKA beyond 3 months to patients with an unprovoked PE unless they are at increased risk of bleeding, taking into account the patient's risk of VTE recurrence and of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. **[1.2.4]**

- Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. **[1.2.5]**

[2] At the time of publication some types of LMWH do not have a UK marketing authorisation for extended treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

Thrombolytic therapy

Deep vein thrombosis

- Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:
  - symptoms of less than 14 days' duration **and**
  - good functional status **and**
  - a life expectancy of 1 year or more **and**
  - a low risk of bleeding. **[1.2.6]**

Mechanical interventions

- Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT 1 week after diagnosis if swelling is reduced sufficiently and:
  - advise patients to continue wearing the stockings for at least 2 years
  - ensure that the stockings are replaced two or three times per year. **[1.2.12]**

Investigations for cancer

- For patients aged over 40 years with a first unprovoked VTE – after carrying out a physical examination (guided by the patient's full history), a chest X-ray, blood tests (full blood count, serum calcium and liver function tests) and urinalysis – consider further investigations for cancer with:
  - an abdomino-pelvic CT scan **and**
  - sputum cytology **and**
  - a mammogram for women. **[1.5.2]**

1 Guidance

The following guidance is based on the best available evidence. The full guideline ([hyperlink to be added for final publication]) gives details of the methods and the evidence used to develop the guidance.

To ensure comprehensive management and continuity when developing a programme of care for patients with VTE, users of this guideline are encouraged to refer to NICE guidance on 'Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital' (NICE clinical guideline 92), 'Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults' (NICE technology appraisal guidance 170), 'Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults' (NICE technology appraisal guidance 157) and 'Medicines adherence' (NICE clinical guideline 76) (see also section 6, 'Related NICE guidance').

1.1 Diagnosis

Diagnostic investigations for deep vein thrombosis

1.1.1 If a patient presents with signs or symptoms of DVT, carry out an assessment of their general medical history and a physical examination to exclude other causes.

1.1.2 If DVT is suspected, use the two-level DVT Wells score (see table 1) to estimate the clinical probability of DVT.

Table 1 Two-level DVT Wells score[3]

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for more than 3 days or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	−2
Clinical probability simplified score	
DVT 'likely'	2 points or more
DVT 'unlikely'	Less than 2 points

[3] Adapted with permission from Wells PS et al. (2003) Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. New England Journal of Medicine 349: 1227–35

1.1.3 Offer patients with a ‘likely’ two-level DVT Wells score:

- a proximal ultrasound scan carried out within 4 hours **and**
- a D-dimer test if the proximal ultrasound scan is negative **or** (if a proximal ultrasound scan cannot be carried out within 4 hours)
- a D-dimer test **and** low molecular weight heparin (LMWH) or unfractionated heparin (UFH) **and** a proximal ultrasound scan carried out within 24 hours to avoid the need for a second dose of LMWH or UFH.

Repeat the proximal ultrasound scan 6–8 days later if the D-dimer test is positive and the proximal ultrasound scan is negative.

1.1.4 Offer patients with an ‘unlikely’ two-level DVT Wells score a D-dimer test and if the result is positive offer:

- a proximal ultrasound scan carried out within 4 hours **or** (if a proximal ultrasound scan cannot be carried out within 4 hours)
- LMWH or UFH **and** a proximal ultrasound scan carried out within 24 hours to avoid the need for a second dose of LMWH or UFH.

1.1.5 Diagnose DVT and start treatment in patients with a positive proximal ultrasound scan.

1.1.6 Take into consideration alternative diagnoses in patients with:

- an 'unlikely' two-level DVT Wells score **and**
  - a negative D-dimer test **or**
  - a positive D-dimer test and a negative proximal ultrasound scan.
- a 'likely' two level DVT Wells score **and**
  - a negative D-dimer test and a negative proximal ultrasound scan **or**
  - a positive D-dimer test and a repeat negative proximal ultrasound scan.

Advise patients in these two groups that it is not likely they have DVT, and discuss with them the signs and symptoms of DVT and when and where to seek further medical help.

Diagnostic investigations for pulmonary embolism

1.1.7 If a patient presents with signs or symptoms of PE, carry out an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes.

1.1.8 If PE is suspected, use the two-level PE Wells score (see table 2) to estimate the clinical probability of PE.

Table 2 Two-level PE Wells score[4]

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified scores	
PE 'likely'	More than 4 points
PE 'unlikely'	4 points or less

1.1.9 Offer patients with a 'likely' two-level PE Wells score:

- a computed tomography pulmonary angiogram (CTPA) **and**
- consider a proximal ultrasound scan if the CTPA is negative and DVT is suspected.

1.1.10 Offer patients with an 'unlikely' two-level PE Wells score:

- a D-dimer test **and**
- a CTPA if the D-dimer test is positive.

1.1.11 Offer parenteral anticoagulant therapy to patients with suspected PE who are having imaging and in whom PE cannot be excluded immediately.

[4] Adapted with permission from Wells PS et al. (2000) Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. Thrombosis and Haemostasis 83: 416–20

1.1.12 Consider a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan as an alternative to CTPA for patients with suspected PE who have:

- an allergy to contrast media **or**
- renal impairment.

Take into consideration the patient's age and history of cancer, and the increased risk of exposing dividing cells to radiation.

1.1.13 Diagnose PE and start treatment in patients with a positive CTPA or in whom PE is identified with a V/Q SPECT scan.

1.1.14 Take into consideration alternative diagnoses in patients with:

- an 'unlikely' modified two-level PE Wells score **and**
  - a negative D-dimer test **or**
  - a positive D-dimer test and a negative CTPA.
- a 'likely' modified two-level PE Wells score **and**
  - a negative CTPA **and**
  - no suspected DVT.

Advise these patients that it is not likely they have PE and discuss with them the signs and symptoms of PE, and when and where to seek further medical help.

Patients with signs or symptoms of both deep vein thrombosis and pulmonary embolism

1.1.15 If a patient presents with signs or symptoms of both DVT (for example a swollen and/or painful leg) and PE (for example chest pain, shortness of breath or haemoptysis), carry out diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgement.

1.2 Treatment

Pharmacological interventions

Deep vein thrombosis or pulmonary embolism

1.2.1 Offer a choice of LMWH or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:

- For patients with renal impairment or an unpredictable bleeding risk, consider UFH.
- For patients with PE and haemodynamic instability, offer UFH.

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3) is 2 or above for at least 24 hours, whichever is longer.

1.2.2 Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for at least 6 months[5].

1.2.3 Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for at least 3 months.

1.2.4 Offer a VKA beyond 3 months to patients with an unprovoked PE unless they are at increased risk of bleeding, taking into account the patient's risk of VTE recurrence and of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

1.2.5 Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

[5] At the time of publication some types of LMWH do not have a UK marketing authorisation for extended treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

Thrombolytic therapy

Deep vein thrombosis

1.2.6 Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:

- symptoms of less than 14 days' duration **and**
- good functional status **and**
- a life expectancy of 1 year or more **and**
- a low risk of bleeding.

Pulmonary embolism

1.2.7 Consider pharmacological systemic thrombolytic therapy for patients with PE and haemodynamic instability.

1.2.8 Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability.

Mechanical interventions

Proximal deep vein thrombosis or pulmonary embolism

1.2.9 Offer temporary inferior vena caval filters to patients with proximal DVT or PE who cannot have anticoagulation treatment, and remove the inferior vena caval filter when the patient becomes eligible for anticoagulation treatment.

1.2.10 Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as long-term high-intensity oral anticoagulant therapy (INR 3-4) or LMWH.

1.2.11 Ensure that a strategy for removal of the inferior vena caval filter at the earliest possible opportunity is planned and documented when the filter is placed, and that the strategy is reviewed regularly.

1.2.12 Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT 1 week after diagnosis if swelling is reduced sufficiently and:

- advise patients to continue wearing the stockings for at least 2 years
- ensure that the stockings are replaced two or three times per year.

1.3 Patient information

1.3.1 Give patients having anticoagulation treatment verbal and written information about:

- how to use anticoagulants
- duration of anticoagulation treatment
- possible side effects of anticoagulant treatment and what to do if these occur
- the effects of other medications, foods and alcohol on oral anticoagulation treatment
- monitoring of their anticoagulant treatment
- how anticoagulants may affect their dental treatment
- taking anticoagulants if they are planning pregnancy or become pregnant
- when and how to seek medical help.

1.3.2 Provide patients who are having anticoagulation treatment with an 'anticoagulant alert card' and advise them to carry the card at all times.

1.3.3 Advise patients who need anticoagulation treatment and who have concerns about using animal products in line with NICE guidance on patient information in Venous thromboembolism: reducing the risk (NICE clinical guideline 92).

1.3.4 Advise patients about the correct application and use of below-knee graduated compression stockings, and how long they should be worn.

1.4 Self-management and self-monitoring for patients treated with a vitamin K antagonist

1.4.1 Do not routinely offer self-management or self-monitoring of INR to patients who have had DVT or PE and are having treatment with a VKA.

1.5 Investigations for cancer

1.5.1 Offer all patients diagnosed with unprovoked DVT or PE the following investigations for cancer:

- a physical examination (guided by the patient's full history) **and**
- a chest X-ray **and**
- blood tests (full blood count, serum calcium and liver function tests) **and**
- urinalysis.

1.5.2 For patients aged over 40 years with a first unprovoked VTE – after carrying out a physical examination (guided by the patient's full history), a chest X-ray, blood tests (full blood count, serum calcium and liver function tests) and urinalysis – consider further investigations for cancer with:

- an abdomino-pelvic CT scan **and**
- sputum cytology **and**
- a mammogram for women.

1.6 Thrombophilia testing

1.6.1 Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.

1.6.2 Consider testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.

1.6.3 Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.

1.6.4 Do not offer thrombophilia testing to patients who have had provoked DVT or PE.

1.6.5 Do not offer thrombophilia testing to first-degree relatives of patients with thrombophilia who have had DVT or PE.

2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from http://guidance.nice.org.uk/CG/Wave21/5/Scope/pdf/English

How this guideline was developed

NICE commissioned the National Clinical Guideline Centre to develop this guideline. The Centre established a Guideline Development Group (see appendix A), which reviewed the evidence and developed the recommendations. An independent Guideline Review Panel oversaw the development of the guideline (see appendix B).

There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

3 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG[XX])'.

4 Research recommendations

The Guideline Development Group (GDG) has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The GDG's full set of research recommendations is detailed in the full guideline (see section 5, 'Other versions of this guideline').

4.1 Diagnosis of deep vein thrombosis

What is the clinical and cost effectiveness of a whole-leg ultrasound scan compared with a proximal ultrasound scan in the diagnosis of acute DVT?

Why this is important

The GDG noted that proximal ultrasound scans can miss an isolated calf vein thrombus but that a repeat scan 1 week later will identify the clinically

important thrombi that have extended. If a whole-leg scan is conducted initially, no repeat ultrasound at 1 week is required, but more patients may need anticoagulation therapy. More DVTs are identified by a whole-leg scan but this is more time consuming and the impact on patient outcomes is unknown. Whole-leg scans are also more difficult technically and are subject to variability because there are more veins within the calf and they are considerably smaller; therefore there is still a risk of missing a calf vein thrombus. Repeating the proximal leg ultrasound scan after 1 week necessitates two scans, which is also time-consuming. A randomised controlled trial (RCT) with cost-effectiveness analysis could answer the crucial question of whether full-leg ultrasound improves patient outcomes and allows for more effective use of NHS resources. Primary outcomes should include objectively confirmed 3-month incidence of symptomatic VTE in patients with an initially normal diagnostic work-up, mortality and major bleeding.

4.2 Long-term versus 3-month anticoagulation treatment in subgroups of patients at increased risk of VTE recurrence

What is the clinical and cost effectiveness of long-term anticoagulation treatment in specific subgroups of patients with first unprovoked VTE?

Why this is important

There is evidence that some risk factors are associated with a greater risk of VTE recurrence than others. Although it is thought that subgroups with these risk factors (for example male sex, raised D-dimer, presence of post-thrombotic syndrome, and presentation with PE versus DVT) are at increased risk of VTE recurrence, high-quality evidence on the benefits of extending anticoagulation treatment is lacking in this area. An RCT comparing extended long-term oral anticoagulation with 3 months of oral anticoagulation treatment in patients with first unprovoked VTE is needed to determine the relative benefits and risks for these subgroups. This study should include the following outcomes: all-cause mortality, VTE recurrence, major bleeding and quality of life. Follow-up should be for 5 years. The results of this study would inform the

recommendation in this guideline on continuing anticoagulation therapy beyond 3 months.

4.3 Long-term anticoagulation treatment with low molecular weight heparin versus a vitamin K antagonist in people with VTE and active cancer

In patients with VTE and active cancer who have had 6 months of anticoagulation treatment with LMWH, what is the clinical benefit (in terms of VTE recurrence rates, all-cause mortality and major bleeding) and cost effectiveness of continued anticoagulation treatment with LMWH versus a VKA?

Why this is important

Determining whether LMWH or a VKA should be used for anticoagulation treatment in patients with cancer beyond the initial 6 months of LMWH therapy is critically important. The current recommendation for use of LMWH for the initial 6 months is based on the CLOT study[6] in which anticoagulation was limited to 6 months. Long-term anticoagulation is currently recommended for patients with cancer, based on their continuing high risk of VTE. The relative benefits of LMWH or a VKA beyond the initial 6 months are therefore unknown. An RCT is urgently needed to answer this question. As in the CLOT study, the trial should recruit patients with VTE associated with cancer who have completed 6 months of LMWH treatment and in whom long-term treatment is planned and there is no contraindication to further anticoagulation treatment with either LMWH or a VKA. Patients should be randomised between these two therapeutic options. The primary outcome measure should be VTE recurrence rates. Secondary outcomes should include cost effectiveness and quality of life. Such a trial will provide an evidence-based understanding of the relative benefits and risks of long-term treatment with LMWH versus long-term treatment with a VKA, inform patient and clinician

[6] Lee AY et al. (2003) Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. New England Journal of Medicine 349: 146-53

choice, enable development of clear guidelines to minimise variability in care and maximise use of scarce NHS resources.

4.4 Thrombolytic therapy for DVT

What is the clinical and cost effectiveness of clot removal using catheter-directed thrombolytic therapy or pharmacomechanical thrombolysis compared with standard anticoagulation therapy for the treatment of acute proximal DVT?

Why this is important

Clot removal strategies such as catheter-directed thrombolysis might be more effective than standard anticoagulation treatment in reducing post-thrombotic syndrome. However, there is an increased risk of major bleeding with these strategies. Evidence was identified on outcomes (mortality, major bleeding, post thrombotic syndrome and recurrent DVT) related to clot removal strategies for the treatment of acute (less than 14 days' duration) proximal DVT. However, the studies had important methodological limitations and the follow-up periods were only 6 months. It is important to have longer-term (at least 2 years) and higher-quality evidence from RCTs to inform the decision on whether to use clot removal strategies for the treatment of acute proximal DVT. Catheter-directed or pharmacomechanical thrombolysis should be compared with standard anticoagulation therapy (LMWH or fondaparinux). The primary outcome measures should be mortality, major bleeding, VTE recurrence at 3 months, incidence and severity of post-thrombotic syndrome at 2 years (measured by a validated tool) and quality of life.

4.5 Systemic pharmacological thrombolysis compared with standard anticoagulation treatment in patients with pulmonary embolism and right ventricular dysfunction

What is the clinical and cost effectiveness of systemic pharmacological thrombolysis compared with standard initial anticoagulation therapy in patients with confirmed PE and haemodynamic stability who present with right ventricular dysfunction?

Why this is important

It is unclear from the evidence identified in the review whether there are subgroups of patients with PE and haemodynamic stability who have a significant risk of PE-related mortality and morbidity and would benefit from systemic thrombolysis. No evidence was found in the clinical review for the safety and effectiveness of pharmacological thrombolysis in patients with confirmed PE and haemodynamic stability who present with right ventricular dysfunction. An RCT is needed to compare pharmacological thrombolysis (for example, with alteplase) with standard initial anticoagulation therapy (with LMWH or fondaparinux) in these patients. The important outcomes would be all-cause mortality, VTE-related mortality, cardiopulmonary resuscitation, major bleeding, VTE recurrence and chronic thromboembolic pulmonary hypertension. This could improve early outcomes and survival, and reduce complications such as chronic thromboembolic pulmonary hypertension. The results of this study would inform an update of this guideline. Currently the guideline does not recommend systemic thrombolysis for these patients.

5 Other versions of this guideline

5.1 Full guideline

The full guideline, 'Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing' contains details of the methods and evidence used to develop the guideline. It is published by the National Clinical Guideline Centre, and is available from our website (www.nice.org.uk/guidance/CG[XX]/Guidance). **Note: these details will apply to the published full guideline.**

5.2 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway, which is available from http://pathways.nice.org.uk/pathways/[xxx] **Note: these details will apply when the guideline is published.**

5.3 'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG[XX]/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N[XXXX]). **Note: these details will apply when the guideline is published.**

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about VTE.

6 Related NICE guidance

Published

- Venous thromboembolism: reducing the risk. NICE clinical guideline 92 (2010). Available from www.nice.org.uk/guidance/CG92
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance 170 (2009). Available from www.nice.org.uk/guidance/TA170
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal guidance 157 (2008). Available from www.nice.org.uk/guidance/TA157

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Patient experience in adult NHS services: improving the experience of care for people using NHS services. NICE clinical guideline. Publication expected October 2011.
- Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery. NICE technology appraisal guidance. Publication date to be confirmed.

- Rivaroxaban for the prevention of venous thromboembolism in people hospitalised for acute medical conditions. NICE technology appraisal guidance. Publication date to be confirmed.
- Dabigatran etexilate for the treatment of acute venous thromboembolic events. NICE technology appraisal guidance. Publication date to be confirmed.

7 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

Appendix A: The Guideline Development Group, National Clinical Guideline Centre and NICE project team

Guideline Development Group

Gerard Stansby
Professor of Vascular Surgery, Freeman Hospital and Newcastle University

Roshan Agarwal
Senior Lecturer/Honorary Consultant Medical Oncologist, Imperial College London

Susan Ballard
Patient/carer member

David Berridge
Consultant Vascular Surgeon, Leeds General Infirmary

Christian Clark
Patient and carer member, Member of the Atrial Fibrillation Task Force

Richard Day
Consultant Physician (Geriatrics), Poole Hospital NHS Foundation Trust

Hayley Flavell
Anticoagulant and Thrombosis Consultant Nurse, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust

Scott Harrison
Lead Pharmacist, Oxford Radcliffe Hospital NHS Trust

Beverley Hunt
Professor of Thrombosis and Haemostasis, King's College, London and Medical Director of Lifeblood

David Keeling
Consultant Haematologist, Oxford Radcliffe Hospitals NHS Trust

Nigel Langford

Acute Medical Physician, Sandwell and West Birmingham NHS Trust, City Hospital, Birmingham

Steven Moser

Consultant Radiologist, St Mary's and Charing Cross Hospitals, London

Kat Noble

General Practitioner with a specialist interest in Emergency Care, NHS County Durham

Karen Sheares

Respiratory Consultant with an interest in pulmonary vascular diseases, Papworth Hospital NHS Foundation Trust

Expert Adviser

Richard Graham

Consultant Radiologist, Royal United Hospital Bath

National Clinical Guideline Centre

Joanna Ashe

Senior Information Scientist

Liz Avital

Associate Director

Caroline Blaine

Research Fellow (from January 2011)

Sara Buckner

Research Fellow (from January 2011)

Lee-Yee Chong

Senior Research Fellow

Elisabetta Fenu

Senior Health Economist

Caroline Hatchett

Research Fellow/Project Manager (from March 2011)

Jennifer Hill

Operations Director

Clare Jones

Senior Research Fellow/Project Manager (until March 2011)

Zahra Naqvi

Research Fellow (from January 2011)

Julie Neilson

Senior Research Fellow (until January 2011)

Sarah Riley

Senior Research Fellow/Project Manager (until January 2011)

NICE project team

Sarah Willett

Associate Director

Sarah Dunsdon

Guideline Commissioning Manager

Andrew Gyton

Guideline Coordinator

Judith Thornton

Technical Lead

Prashanth Kandaswamy

Health Economist

Judy McBride

Editor

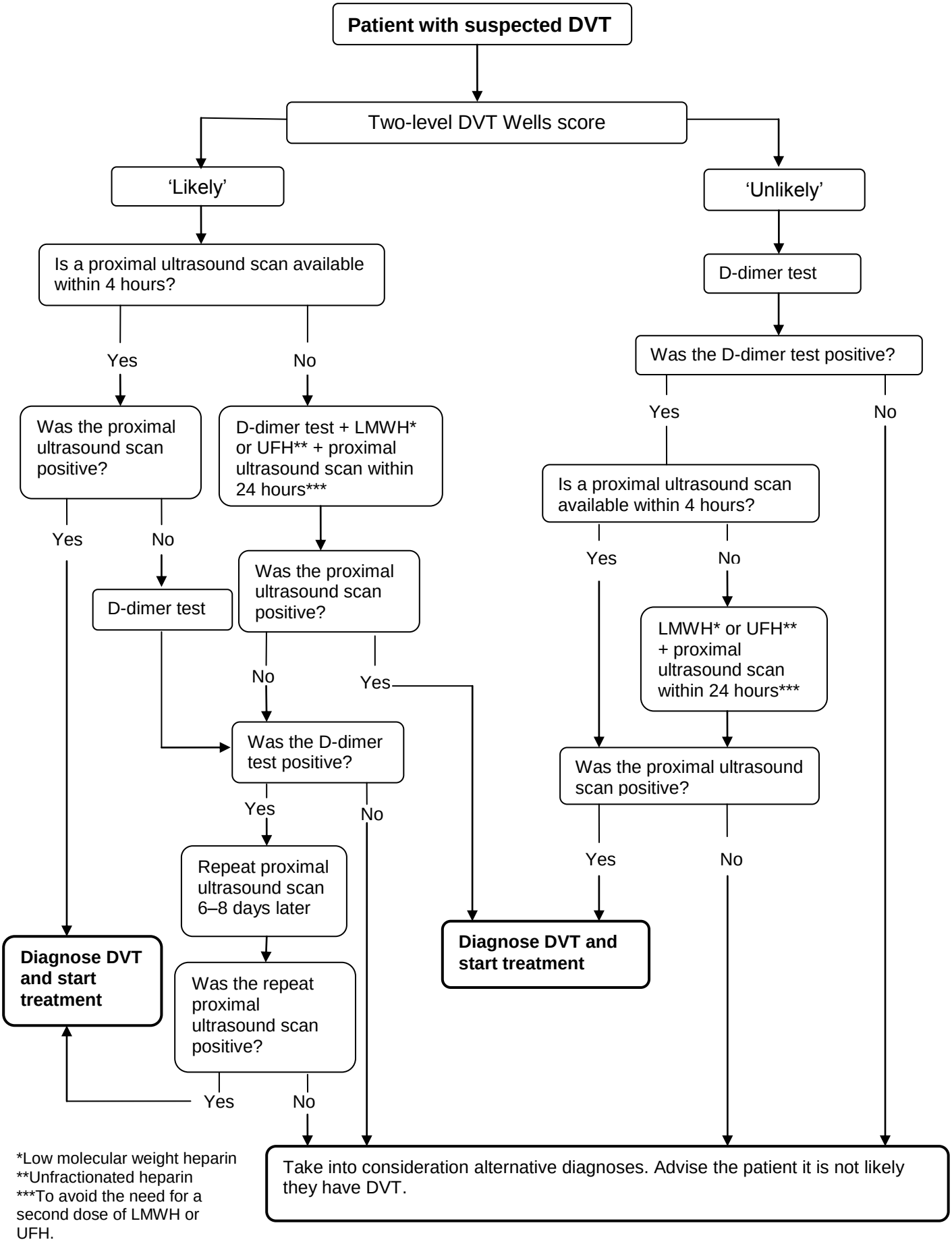
Appendix B: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

NICE to add

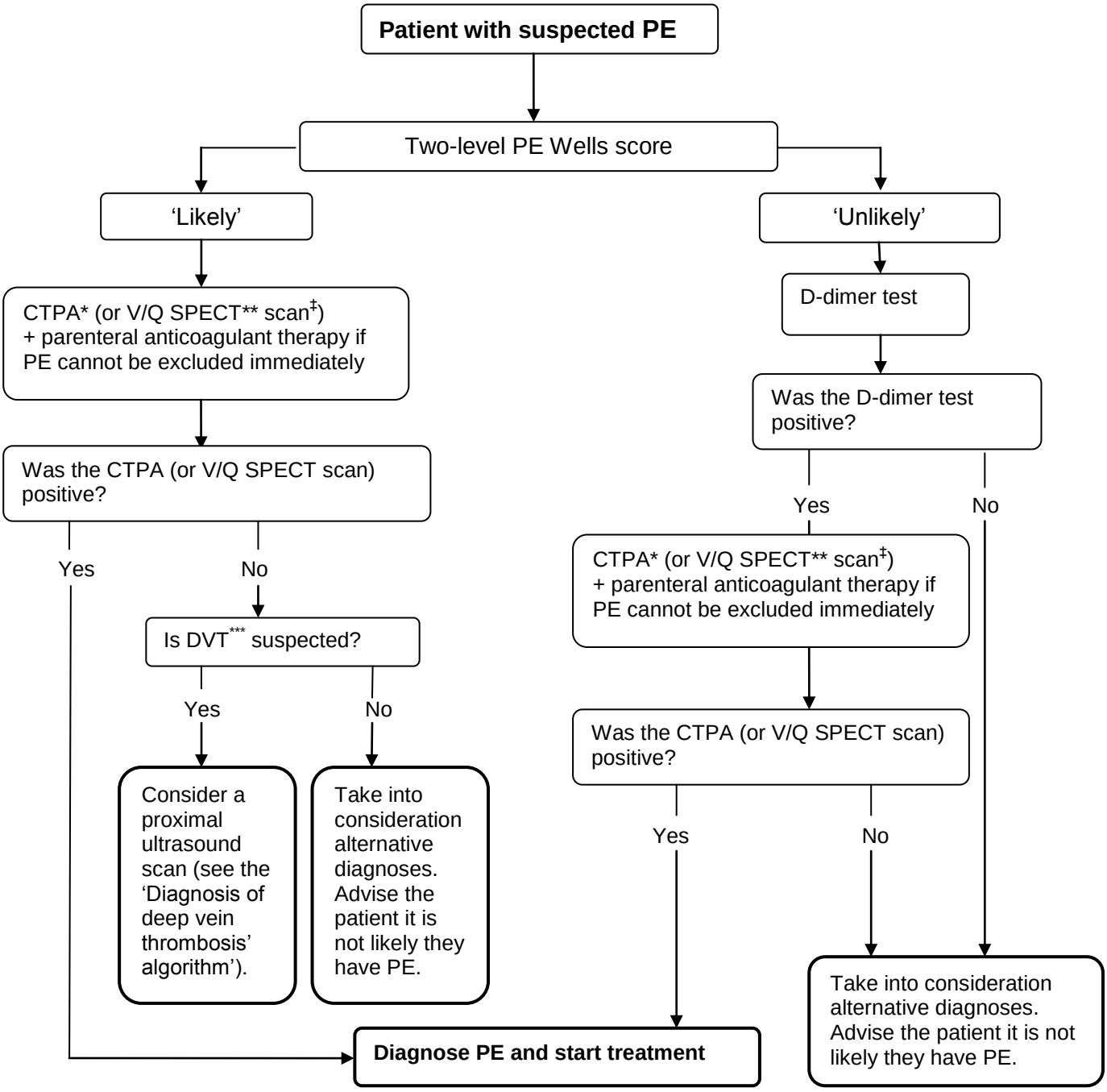
Appendix C: The algorithms

Diagnosis of deep vein thrombosis (DVT)



*Low molecular weight heparin
**Unfractionated heparin
***To avoid the need for a second dose of LMWH or UFH.

Diagnosis of pulmonary embolism (PE)



*Computed tomography pulmonary angiogram
** Ventilation/perfusion single photon emission computed tomography
‡Consider a V/Q SPECT scan as an alternative to CTPA if the patient has:

- an allergy to contrast media **or**
- renal impairment.

Take into account the patient's age and history of cancer, and the increased risk of exposing dividing cells to radiation.

*** Deep vein thrombosis