NICE National Institute for Health and Care Excellence

NICE guideline

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

Clinical guideline

Published: 27 June 2012
nice.org.uk/guidance/cg144

Contents

This guideline is the basis of QS29.

Key priorities for implementation

The following recommendations were identified as priorities for implementation in the 2012 guideline and have not been changed in the 2015 update. The full list of recommendations is in the recommendations section.

Diagnosis

Diagnostic investigations for deep vein thrombosis

- If a patient presents with signs or symptoms of deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes. **[2012]**
- Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score (for the two-level DVT Wells score see table 1 in section 1.1) **either:**
  - a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test **or**
  - a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.

    Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan. **[2012]**
- Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score (for the two-level DVT Wells score see table 1 in section 1.1) a D-dimer test and if the result is positive offer **either:**
  - a proximal leg vein ultrasound scan carried out within 4 hours of being requested **or**
  - an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. **[2012]**

Diagnostic investigations for pulmonary embolism

- Offer patients in whom pulmonary embolism (PE) is suspected and with a *likely* two-level PE Wells score (for the two-level PE Wells score see table 2 in section 1.1) **either:**
  - an immediate computed tomography pulmonary angiogram (CTPA) **or**
  - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.

    Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected. **[2012]**
- Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score (for the two-level PE Wells score see table 2 in section 1.1) a D-dimer test and if the result is positive offer **either:**
  - an immediate CTPA **or**
  - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. **[2012]**

Treatment

Pharmacological interventions

Deep vein thrombosis or pulmonary embolism

- Offer a choice of low molecular weight heparin (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 severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
  - For patients with an increased risk of bleeding consider UFH.
  - For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism).

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal DVT or PE) is 2 or above for at least 24 hours, whichever is longer. [2012]

- Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months[1]. At 6 months, assess the risks and benefits of continuing anticoagulation[2]. [2012]
- Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. [2012]
- 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. [2012]

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. [2012]

Investigations for cancer

- Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 1.5.1 on investigations for cancer). [2012]

[1] At the time of publication (November 2015) some types of LMWH do not have a UK marketing authorisation for 6 months of treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH and make appropriate adjustments for severe renal impairment or established renal failure. Informed consent for off-label use should be obtained and documented.

[2] Although this use is common in UK clinical practice, at the time of publication (November 2015) none of the anticoagulants has a UK marketing authorisation for the treatment of DVT or PE beyond 6 months in patients with cancer. Informed consent for off-label use should be obtained and documented.

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength of our recommendations, and has information about safeguarding, consent and prescribing medicines (including 'off-label' use).

1.1 Diagnosis

Diagnostic investigations for deep vein thrombosis

1.1.1 If a patient presents with signs or symptoms of deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes. [2012]

1.1.2 If DVT is suspected, use the two-level DVT Wells score (see table 1 below) to estimate the clinical probability of DVT. [2012]

Table 1 Two-level DVT Wells score[a]

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 3 days or more 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 at least 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*	1 point or less
[a] Adapted with permission from Wells PS et al. (2003) Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis.	

1.1.3 Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score (see table 1) either:

- a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test
  or
- a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested

  Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan. **[2012]**

1.1.4 Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score (see table 1) a D-dimer test and if the result is positive offer **either**:

- a proximal leg vein ultrasound scan carried out within 4 hours of being requested **or**
- an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. **[2012]**

1.1.5 Diagnose DVT and treat (see the recommendations on treatment in section 1.2) patients with a positive proximal leg vein ultrasound scan. **[2012]**

1.1.6 Take into consideration alternative diagnoses in patients with:

- an *unlikely* two-level DVT Wells score (see table 1) and

  - a negative D-dimer test **or**
  - a positive D-dimer test and a negative proximal leg vein ultrasound scan.
- a *likely* two-level DVT Wells score (see table 1) **and**
  - a negative proximal leg vein ultrasound scan and a negative D-dimer test **or**
  - a repeat negative proximal leg vein 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. **[2012]**

Diagnostic investigations for pulmonary embolism

1.1.7 If a patient presents with signs or symptoms of pulmonary embolism (PE), carry out an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes. **[2012]**

1.1.8 If PE is suspected, use the two-level PE Wells score (see table 2) to estimate the clinical probability of PE. **[2012]**

Table 2 Two-level PE Wells score[a]

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
[a] 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.	

1.1.9 Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score (see table 2) **either**:

- an immediate computed tomography pulmonary angiogram (CTPA) **or**
- immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.

  Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected. **[2012]**

1.1.10 Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score (see table 2) a D-dimer test and if the result is positive offer **either**:

- an immediate CTPA **or**
- immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. **[2012]**

1.1.11 For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high:

- Assess the suitability of a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan or, if a V/Q SPECT scan is not available, a V/Q planar scan, as an alternative to CTPA.
- If offering a V/Q SPECT or planar scan that will not be available immediately, offer immediate interim parenteral anticoagulant therapy. **[2012]**

1.1.12 Diagnose PE and treat (see the recommendations on treatment in section 1.2) patients with a positive CTPA or in whom PE is identified with a V/Q SPECT or planar scan. **[2012]**

1.1.13 Take into consideration alternative diagnoses in the following 2 groups of patients:

- Patients with an *unlikely* two-level PE Wells score (see table 2) and **either**:
  - a negative D-dimer test **or**
  - a positive D-dimer test and a negative CTPA.
- Patients with a *likely* two-level PE Wells score (see table 2) and **both**:
  - 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. **[2012]**

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

1.1.14 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 initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgement. **[2012]**

1.2 Treatment

Pharmacological interventions

Deep vein thrombosis or pulmonary embolism

1.2.1 Offer a choice of low molecular weight heparin (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 severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism).

  Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal DVT or PE) is 2 or above for at least 24 hours, whichever is longer. **[2012]**

1.2.2 Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months[3]. At 6 months, assess the risks and benefits of continuing anticoagulation[4]. **[2012]**

1.2.3 Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 1.2.4 and 1.2.5). **[2012]**

1.2.4 Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. **[2012]**

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. **[2012]**

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. **[2012]**

Pulmonary embolism

1.2.7 Consider pharmacological systemic thrombolytic therapy for patients with PE and haemodynamic **instability** (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE). **[2012]**

1.2.8 Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic **stability** with or without right ventricular dysfunction (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE). If patients develop haemodynamic instability, refer to recommendation 1.2.7. **[new 2015]**

Mechanical interventions

Proximal deep vein thrombosis or pulmonary embolism

1.2.9 Do not offer elastic graduated compression stockings to prevent post-thrombotic syndrome or VTE recurrence after a proximal DVT. This recommendation does not cover the use of elastic stockings for the management of leg symptoms after DVT. **[new 2015]**

1.2.10 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. **[2012]**

1.2.11 Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as:

- increasing target INR to 3–4 for long-term high-intensity oral anticoagulant therapy **or**
- switching treatment to LMWH. [2012]

1.2.12 Ensure that a strategy for removing 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. [2012]

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 their anticoagulant treatment
- how anticoagulants may affect their dental treatment
- taking anticoagulants if they are planning pregnancy or become pregnant
- how anticoagulants may affect activities such as sports and travel
- when and how to seek medical help. [2012]

1.3.2 Provide patients who are having anticoagulation treatment with an 'anticoagulant information booklet' and an 'anticoagulant alert card' and advise them to carry the 'anticoagulant alert card' at all times. [2012]

1.3.3 Be aware that heparins are of animal origin and this may be of concern to some patients (see Religion or belief: a practical guide for the NHS). For patients who have concerns about using animal products, consider offering synthetic

alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient. (This recommendation is from Venous thromboembolism: reducing the risk [NICE guideline CG92]). **[2012]**

1.3.4 Advise patients about the correct application and use of below-knee graduated compression stockings, how long they should be worn and when they should be replaced. **[2012]**

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. **[2012]**

1.5 Investigations for cancer

1.5.1 Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer 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. **[2012]**

1.5.2 Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 1.5.1). **[2012]**

1.6 Thrombophilia testing

1.6.1 Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment. **[2012]**

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. **[2012]**

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. [2012]

1.6.4 Do not offer thrombophilia testing to patients who have had provoked DVT or PE. [2012]

1.6.5 Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia. [2012]

Terms used in this guideline

D-dimer test

D-dimer is a product formed in the body when a blood clot (such as those found in DVT or PE) is broken down. A laboratory or point-of-care test can be done to assess the concentration of D-dimer in a person's blood. The threshold for a positive result varies with the type of D-dimer test used and is determined locally. The result of the D-dimer test can be used as part of probability assessment when DVT or PE is suspected.

Haemodynamically stable PE

When a patient has PE and a normal blood pressure. The haemodynamically stable patient subgroup includes patients with what was previously called normotensive, non-massive, or sub-massive PE. Patients with haemodynamically stable PE, with or without right ventricular dysfunction, may be considered separately by clinicians. See also pulmonary embolism.

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 DVT or 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 or above. Proximal DVT is sometimes referred to as 'above-knee DVT'.

Pulmonary embolism

A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries, causing severe respiratory dysfunction.

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. (For NICE guidance on the classification of chronic kidney disease see chronic kidney disease [NICE guideline CG182]).

Right ventricular dysfunction

Acute PE may lead to right ventricular pressure overload and dysfunction. This can be detected by echocardiography, CT pulmonary angiography (CTPA), or elevated biomarkers because of myocardial stretch (for example brain natriuretic peptide) or transmural right ventricular infarction. Combinations of these indices can be used for risk stratification.

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) who is not having hormonal therapy (oral contraceptive or hormone replacement therapy) or
- active cancer, thrombophilia or a family history of VTE, because these are underlying risks that remain constant in the patient.

Wells score

Clinical prediction rule 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.

You can also see this guideline in the NICE pathway on venous thromboembolism.

To find out what NICE has said on topics related to this guideline, see our web page on embolism and thrombosis.

[3] At the time of publication (November 2015) some types of LMWH do not have a UK marketing authorisation for 6 months of treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH and make appropriate adjustments for severe renal impairment or established renal failure. Informed consent for off-label use should be obtained and documented.

[4] Although this use is common in UK clinical practice, at the time of publication (November 2015) none of the anticoagulants has a UK marketing authorisation for the treatment of DVT or PE beyond 6 months in patients with cancer. Informed consent for off-label use should be obtained and documented.

Context

Venous thromboembolism (VTE) is a condition in which a blood clot (a thrombus) forms in a vein, most commonly in the deep veins of the legs or pelvis. This is known as deep vein thrombosis, or DVT. The thrombus can dislodge and travel in the blood, particularly to the pulmonary arteries. This is known as pulmonary embolism, or PE. The term 'VTE' includes both DVT and PE.

Venous thromboembolic diseases cover a spectrum ranging from asymptomatic calf vein thrombosis to symptomatic DVT. They can be fatal if they lead to PE, in which the blood supply to the lungs is badly blocked by the thrombus. Non-fatal VTE can cause serious long-term conditions such as post-thrombotic syndrome.

Thrombophilia is a major risk factor for VTE. It is an inherited or acquired prothrombotic state that predisposes to VTE. Other major risk factors for VTE include a history of DVT, age over 60 years, surgery, obesity, prolonged travel, acute medical illness, cancer, immobility 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 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.

Recommendations for research

In 2012, the Guideline Development Group made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the full guideline.

1 Diagnosis of deep vein thrombosis

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

Why this is important

The Guideline Development Group noted that proximal leg vein ultrasound scans will not identify 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 vein ultrasound scan after 1 week necessitates 2 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 allow for more effective use of NHS resources. Primary outcomes should include objectively confirmed 3-month incidence of symptomatic venous thromboembolism (VTE) in patients with an initially normal diagnostic work-up, mortality and major bleeding. [2012]

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

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

Why this is important

There is evidence that some risk factors, such as male sex, raised D-dimer or the presence of post-thrombotic syndrome, are associated with a greater risk of VTE recurrence than others. Although it is thought that subgroups with these risk factors are at increased risk of VTE recurrence, high-quality evidence on the benefits of extending anticoagulation treatment in these subgroups is lacking. An RCT comparing long-term oral anticoagulation with 3 months of oral anticoagulation treatment in patients with a first unprovoked VTE is needed to determine the relative benefits and risks of long-term oral anticoagulation treatment in these subgroups. The trial should include initial presentation because, compared with a DVT, a pulmonary embolism (PE) is a stronger predictor of a future PE, and therefore initial presentation is likely to be a factor in the decision to offer long-term oral anticoagulation. The trial should include the following outcomes: all-cause mortality, recurrence of VTE, major bleeding and quality of life. Follow-up should be for 5 years. The results would inform the recommendation in this guideline on continuing oral anticoagulation treatment beyond 3 months. **[2012]**

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

In patients with VTE and active cancer who have had 6 months of anticoagulation treatment with low molecular weight heparin (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 vitamin K antagonist (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 a systematic review that showed LMWH to be advantageous compared with VKA; however, evidence was available only up to 6 months of anticoagulation with VKA. 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. The trial should recruit patients with VTE associated with cancer who have completed 6 months of LMWH treatment, in whom long-term treatment is planned, and who have no contraindications to further anticoagulation treatment with either LMWH or a VKA. Patients should be randomised to treatment with either LMWH or a VKA. 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 choice and enable

development of clear guidelines to minimise variability in care and make the best use of NHS resources. [2012]

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. [2012]

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 who 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 research could improve early outcomes and survival, and reduce complications such as chronic thromboembolic pulmonary hypertension, and would inform an update of this guideline. Currently the guideline does not recommend systemic thrombolysis for these patients. **[2012]**

As part of the 2015 update, the Standing Committee made additional research recommendations on thrombolysis for patients with acute PE and right ventricular dysfunction, and stockings for preventing post-thrombotic syndrome in people with confirmed DVT.

6 Thrombolysis for patients with acute PE and right ventricular dysfunction

Does thrombolysis in patients with acute PE and right ventricular dysfunction improve long-term quality of life and/or reduce the incidence of chronic thromboembolic pulmonary hypertension (CTEPH)?

Why is this important?

PE may affect patients' long-term quality of life and functional capacity. Because of the short timeframes of previous studies, there is currently insufficient evidence to determine whether thrombolysis confers additional longer-term benefits compared with anticoagulation alone in patients with acute PE who are haemodynamically stable with right ventricular dysfunction. **[new 2015]**

7 Lower-dose thrombolysis for patients with acute PE and right ventricular dysfunction

Does lower-dose thrombolysis reduce the risk of major bleeding and improve outcomes in patients with acute PE and right ventricular dysfunction?

Why is this important?

The narrow benefit-to-risk ratio of thrombolysis is due to the associated bleeding risks. Excluding any shunts, the lungs generally receive the entire cardiac output, and a lower dose of thrombolysis may be enough to treat PE with a lower risk of bleeding. **[new 2015]**

8 Stockings for preventing post-thrombotic syndrome in patients with DVT

What is the effectiveness of stockings, when adherence is adequate, for preventing post-thrombotic syndrome in people with confirmed deep vein thrombosis?

Why is this important?

While there have been trials of elastic graduated compression stockings for preventing PTS following proximal DVT, there are aspects of these studies that make it difficult to be certain about the outcomes. In addition, these studies have differed considerably on whether or not the use of these stockings is effective. The Committee noted the importance of ensuring adherence in research on any possible preventative role of elastic compression stockings.

The Committee concluded that the currently available research evidence does not aid decision-making, due to the uncertainty of the output. **[new 2015]**

Update information

This guideline is an update of NICE guideline CG144 (published June 2012).

New recommendations have been added on pharmacological therapy for patients with haemodynamic stability and elastic graduated compression stockings for preventing post-thrombotic syndrome following proximal deep vein thrombosis.

These are marked as:

- **[new 2015]** if the evidence has been reviewed and the recommendation has been added or updated.
- **[2012]** if the evidence has not been reviewed since the original guideline.

ISBN: 978-1-4731-1535-4

Accreditation