

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

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Introduction

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.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients. This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

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](#) and the [code of practice that accompanies the Mental Capacity Act](#). In Wales, healthcare professionals should follow [advice on consent from the Welsh Government](#).

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 deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes.
- 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.

- 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.

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.

- 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.

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.

- 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].
- 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.
- 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.

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.

Mechanical interventions

Proximal deep vein thrombosis or pulmonary embolism

- Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications^[3], 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 or according to the manufacturers' instructions.
 - advise patients that the stockings need to be worn only on the affected leg or legs.

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).

^[1] At the time of publication (June 2012) 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 (June 2012) 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.

^[3] Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.

1 Guidance

The following guidance is based on the best available evidence. The [full guideline](#) 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 who are at risk of or who develop VTE, users of this guideline are encouraged to refer to NICE guidance on [Venous thromboembolism: reducing the risk](#) (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](#)).

Terms used in this guidance

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.

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 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'.

Renal impairment Reduced renal function that may be acute or chronic. An estimated glomerular filtration rate of less than 90 ml/min/1.73 m² 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 clinical guideline 73]).

Unprovoked 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) **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.

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.
- 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.

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 <i>likely</i>	2 points or more

DVT <i>unlikely</i>	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 above) **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.

1.1.4 Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score (see table 1 above) 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.

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.

1.1.6 Take into consideration alternative diagnoses in patients with:

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

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.

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

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 <i>likely</i>	More than 4 points
PE <i>unlikely</i>	4 points or less
<p>^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.</p>	

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

1.1.10 Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score (see table 2 above) 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.

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.

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.

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

- Patients with an *unlikely* two-level PE Wells score (see table 2 above) 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 above) 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.

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.

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 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.

- 1.2.2 Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months^[4]. At 6 months, assess the risks and benefits of continuing anticoagulation^[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 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 1.2.4 and 1.2.5 below).
- 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.

- 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.

Rivaroxaban

NICE is developing technology appraisal guidance on [rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism](#) (publication expected July 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.

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).
- 1.2.8 Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic **stability** (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE).

Mechanical interventions

Proximal deep vein thrombosis or pulmonary embolism

- 1.2.9 Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications^[6], 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 or according to the manufacturer's instructions
 - advise patients that the stockings need to be worn only on the affected leg or legs.
- 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.
- 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.
- 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.

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.

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.

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 clinical guideline 92)].

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.

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 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.

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 above).

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 routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.

^[4] At the time of publication (June 2012) 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.

^[5] Although this use is common in UK clinical practice, at the time of publication (June 2012) 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.

^[6] Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.

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.

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. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is [available](#).

3 Implementation

NICE has developed [tools to help organisations implement this guidance](#).

4 Research recommendations

The Guideline Development Group has 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](#).

4.1 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 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 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.

4.2 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, VTE recurrence of venous thromboembolism (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.

4.3 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.

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 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.

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.

5.2 NICE pathway

The recommendations from this guideline have been incorporated into a [NICE pathway](#).

5.3 'Understanding NICE guidance'

A summary for patients and carers ('[Understanding NICE guidance](#)') is available. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2751). We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about venous thromboembolic diseases.

6 Related NICE guidance

Published

- [Patient experience in adult NHS services](#). NICE clinical guideline 138 (2012).
- [Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults](#). NICE technology appraisal guidance 245 (2012).
- [Venous thromboembolism: reducing the risk](#). NICE clinical guideline 92 (2010).
- [Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults](#). NICE technology appraisal guidance 170 (2009).
- [Medicines adherence](#). NICE clinical guideline 76 (2009).
- [Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults](#). NICE technology appraisal guidance 157 (2008).

Under development

NICE is developing the following guidance (details available from [the NICE website](#)):

- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal guidance. Publication expected July 2012.
- 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

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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.

Dr Graham Archard

GP

Professor Mike Drummond

Professor of Health Economics, University of York

The following members were responsible for reviewing the final guideline.

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Lay member

Appendix C: Two-level Wells score tables and algorithms for diagnosis

These algorithms are available in [a separate file](#).

About this guideline

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

The guideline was developed by the National Clinical Guideline Centre, which is based at the Royal College of Physicians. The Centre worked with a group of healthcare professionals (including consultants, GPs and nurses), patients and carers, and technical staff, who reviewed the evidence and drafted the recommendations. The recommendations were finalised after public consultation.

The methods and processes for developing NICE clinical guidelines are described in [The guidelines manual](#).

The recommendations from this guideline have been incorporated into a [NICE Pathway](#). We have produced a [summary for patients and carers](#). Tools to help you put the guideline into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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