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PRACTICE

GUIDELINES

Management of venous thromboembolic diseases and the role of thrombophilia testing: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Venous thromboembolic diseases range from asymptomatic deep venous thrombosis (DVT) to fatal pulmonary embolism. Non-fatal venous thromboembolic diseases may also cause serious long term conditions such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension. In the United Kingdom, pathways to diagnosis and to decisions on long term treatment or further investigation for thrombophilia and cancer vary, so guidance is needed in these areas. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the management of confirmed or suspected venous thromboembolic diseases in adults (excluding pregnant women).[1]

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Diagnostic investigations for deep venous thrombosis

- If a patient presents with signs or symptoms of DVT, conduct an assessment of his or her general medical history and a physical examination to exclude other causes. [*Based on the experience and opinion of the Guideline Development Group (GDG)*]
- For patients in whom DVT is suspected and who score ≥2 ("DVT likely") on the Wells scoring system (table 1⇓), offer either *(a)* a proximal leg vein ultrasound scan to be done within four hours of being requested and, if the result is negative, a D dimer test; or *(b)* if a proximal leg vein ultrasound scan cannot be done within four hours, a D dimer test and an interim 24 hour dose of a parenteral anticoagulant, with a proximal leg vein ultrasound scan to be done within 24 hours of being requested. Repeat the proximal leg vein ultrasound scan six to eight days later for all patients with a positive D dimer test and a negative proximal leg vein ultrasound scan. [*Based on very low to moderate quality evidence from meta-analysis of diagnostic studies, individual diagnostic studies, and randomised controlled trials and on a published cost effectiveness analysis with potentially serious limitations and partial applicability; the specific time points were based on the GDG's experience and opinion*]
- For patients in whom DVT is suspected and who have a Wells score of ≤1 ("DVT unlikely") (table 1⇓), offer a D dimer test. If the result is positive, offer either *(a)* a proximal leg vein ultrasound scan to be done within four hours of being requested; or *(b)* if a proximal leg vein ultrasound scan cannot be done within four hours, an interim 24 hour dose of a parenteral anticoagulant, with a proximal leg vein ultrasound scan to be done within 24 hours of being requested. [*Based on very low to moderate quality evidence from meta-analysis of diagnostic studies, individual diagnostic studies, and randomised controlled trials, and on a published cost effectiveness analysis with potentially serious limitations and partial applicability; the specific time points were based on GDG's experience and opinion*]

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Diagnostic investigations for pulmonary embolism

- For patients in whom pulmonary embolism is suspected and who have a Wells score of >4 ("pulmonary embolism likely") (table 2⇓), offer immediate computed tomography pulmonary angiography (CT pulmonary angiography) or, if such imaging cannot be done immediately, offer immediate interim parenteral anticoagulant treatment followed by CT pulmonary angiography. Consider a proximal leg vein ultrasound scan if the CT pulmonary angiography is negative and DVT is suspected.
- For patients in whom pulmonary embolism is suspected and who have a Wells score of ≤4 ("pulmonary embolism unlikely"), offer a D dimer test. If the result is positive, offer either immediate CT pulmonary angiography or, if this imaging cannot be done immediately, offer immediate interim parenteral anticoagulant treatment followed by CT pulmonary angiography.

[*Both points above are based on very low to moderate quality evidence from diagnostic studies and randomised controlled trials and on an original economic model with potentially serious limitations and direct applicability*]

Drug interventions for confirmed deep venous thrombosis or pulmonary embolism

- Offer a choice of low molecular weight heparin or fondaparinux, 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 <30 ml/min/1.73 m^2), offer unfractionated heparin with dose adjustments based on the activated partial thromboplastin time, or low molecular weight heparin with dose adjustments based on an anti-factor Xa assay

  -For patients with an increased risk of bleeding, consider unfractionated heparin

  -For patients with pulmonary embolism and haemodynamic instability, offer unfractionated heparin and consider thrombolysis.

Start the low molecular weight heparin, fondaparinux, or unfractionated heparin as soon as possible and continue it for five days or until the international normalised ratio (adjusted by a vitamin K antagonist—see the next recommendation) is ≥2 for at least 24 hours, whichever is longer. [*Based on very low to moderate quality evidence from randomised controlled trials and on cost effectiveness studies with potentially serious limitations and partial applicability for the type of agent; the other aspects were based on the GDG's experience and opinion and on information from marketing authorisation of products*]

- Offer low molecular weight heparin to patients with active cancer and confirmed proximal DVT or pulmonary embolism, and continue the heparin for six months. At six months, assess the risks and benefits of continuing anticoagulation. (From June 2012, not all low molecular weight heparins have a UK marketing authorisation for six months of treatment of DVT or pulmonary embolism in patients with cancer, and none of the anticoagulants has a UK marketing authorisation for treatment beyond six months.) [*Based on very low to moderate quality evidence from randomised controlled trials and on cost effectiveness studies with potentially serious limitations and partial applicability. The reassessment at six months is based on the GDG's opinion*]
- Offer a vitamin K antagonist beyond three months to patients whose pulmonary embolism is "unprovoked" (that is, patients who have no antecedent major clinical risk factor for venous thromboembolic disease and are not taking hormonal therapy (oral contraception or hormone replacement therapy), or patients with active cancer, thrombophilia, or a family history of venous thromboembolic disease, because these are underlying risks that remain constant in patients). Take into account the patient's risk of recurrence of venous thromboembolic disease and whether he or she is at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their treatment with a vitamin K antagonist. [*Based on low quality evidence from randomised controlled trials and on an original economic model with potentially serious limitations and partial applicability*]
- Consider extending the vitamin K antagonist beyond three months for patients whose proximal DVT is unprovoked (same definition as for unprovoked pulmonary embolism) if their risk of recurrence of the disease is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their treatment with a vitamin K antagonist. [*Based on low to moderate quality evidence from randomised controlled trials and on an original economic model with potentially serious limitations and partial applicability*]

Thrombolysis for deep venous thrombosis

- Consider catheter directed thrombolysis for patients with symptomatic iliofemoral DVT who have all of the following: symptoms of less than 14 days' duration, good functional status, a life expectancy of one year or more, and a low risk of bleeding. [*Based on very low to moderate quality randomised controlled trials; criteria for consideration in bullets are based on the GDG's experience and opinion*]

Mechanical interventions

- Offer below-knee, graduated compression stockings with an ankle pressure greater than 23 mm Hg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and there are no contraindications. Advise patients to continue wearing the stockings for at least two years; ensure that the stockings are replaced two or three times a year or according to the manufacturer's instructions; and advise patients that stockings need to be worn only on the affected leg or legs. [*Based on moderate quality evidence from randomised controlled trials and a simple cost analysis; the specific details about pressure are based on the GDG's experience and opinion*]

Investigations for cancer

- Offer all patients with unprovoked DVT or unprovoked pulmonary embolism who are not already known to have cancer the following investigations: a physical examination (guided by the patient's full history), chest radiography, blood tests (full blood count, serum calcium, and liver function tests), and urine analysis. [*Based on low quality evidence from randomised controlled trials*]

- Consider further investigations for cancer with an abdominopelvic CT scan (and mammography for women) in all patients aged over 40 years with a first unprovoked DVT or pulmonary embolism who do not have signs or symptoms of cancer based on the above initial assessment. [*Based on low quality evidence from a randomised controlled trial and on a published cost effectiveness analysis with potentially serious limitations and partial applicability*]

Investigations for thrombophilia

- Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment, or to those who have had "provoked" DVT or pulmonary embolism (that is, patients who in the past three months have had a transient major clinical risk factor for venous thromboembolic disease)—for example, surgery, trauma, prolonged immobility (confined to bed, unable to walk unaided, or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy, or puerperium—or patients who are having hormonal therapy (oral contraception or hormone replacement therapy)).
- Consider testing for antiphospholipid antibodies in patients who have had unprovoked DVT or pulmonary embolism if stopping anticoagulation treatment is planned.
- Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or pulmonary embolism and who have a first degree relative who has had DVT or pulmonary embolism if stopping anticoagulation treatment is planned.
- Do not routinely offer thrombophilia testing to first degree relatives of people with a history of DVT or pulmonary embolism and thrombophilia.

[*All the above recommendations are based on the GDG's experience and opinion*]

Overcoming barriers

Although it is important that the recommended key diagnostic tests are available when required, the Guideline Development Group recognises the potential difficulties and delays in accessing computed tomography pulmonary angiography, ventilation and perfusion scanning, or ultrasonography, especially at weekends and outside normal working hours. It has therefore recommended interim anticoagulation and time limits for accessing these tests. The guideline also recommends catheter directed thrombolysis for some patients; relatively few such interventions are currently undertaken in the NHS, and there may be some resource implications for centres that do not currently offer this treatment, requiring changes to facilities or local referral arrangements for appropriate patients.

Patients with cancer should be offered subcutaneous low molecular weight heparin instead of oral vitamin K antagonist, but patients who cannot self inject may need a carer or district nurse to administer these daily injections. Whenever possible, patients or carers should be trained in injection technique, to limit the numbers needing nurse delivered injections, which would potentially increase costs. The recommendation to assess the risks and benefits of continuing treatment with a vitamin K antagonist at three months may also have clinical, resource, and/or economic implications. Factors associated with risk of recurrence after an unprovoked initial venous thromboembolic event are debated; factors include male sex,[4-6] post-thrombotic syndrome,[6 7] obesity, and a raised D dimer after stopping anticoagulation.[8 9] As there are no simple rules of thumb or validated tools to reliably predict these risks, the decisions will often have to be taken in a secondary care setting.

The members of the Guideline Development Group were Gerard Stansby (chair), Roshan Agarwal, Susan Ballard, David Berridge, Christian Clark, Richard Day, Richard Graham, Hayley Flavell, Scott Harrison, Beverley Hunt, David Keeling, Nigel Langford, Steven Moser, Kat Noble, Karen Sheares. The technical team at the National Clinical Guideline Centre comprised Joanna Ashe, Liz Avital, Caroline Blaine, Sara Buckner, Lee-Yee Chong, Elisabetta Fenu, Caroline Hatchett, Sarah Hodgkinson, Jennifer Hill, Clare Jones, Zahra Naqvi, and Julie Neilson.

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Further information on the guidance

Methods

The Guideline Development Group followed the standard NICE methods in the development of this guideline (www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/developing_nice_clinical_guidelines.jsp).[10] The group developed clinical questions, collected and appraised clinical evidence, and evaluated the cost effectiveness of proposed interventions through literature review and original economic modelling. The draft guideline went through a rigorous reviewing process, in which stakeholder organisations were invited to comment; the group took all comments into consideration when producing the final version of the guideline. Quality ratings of the evidence were based on GRADE methodology (www.gradeworking group.org). These relate to the quality of the available evidence for assessed outcomes rather than the quality of the clinical study.

The GDG comprised two vascular surgeons, two patient representatives, two haematologists, a general practitioner, an oncologist, an acute medical physician, a pharmacist, a nurse, a radiologist, a respiratory consultant, and a geriatrician.

Future research

- 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 venous thrombosis?
- What is the clinical and cost effectiveness of long term oral anticoagulation treatment in specific subgroups of patients with first unprovoked venous thromboembolic disease?
- In patients with venous thromboembolic disease and active cancer who have had six months of anticoagulation treatment with low molecular weight heparin, what is the clinical benefit (in terms of recurrence rates of venous thromboembolic disease, all cause mortality, and major bleeding) and cost effectiveness of continued anticoagulation treatment with low molecular weight heparin versus a vitamin K antagonist?
- What is the clinical and cost effectiveness of clot removal using catheter directed drug thrombolysis or pharmacomechanical thrombolysis compared with standard anticoagulation therapy for the treatment of acute proximal deep venous thrombosis?
- What is the clinical and cost effectiveness of systemic drug thrombolysis compared with standard initial anticoagulation treatment in patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction?

Tables

Table 1| **Wells scoring system for deep venous thrombosis***

Clinical feature	Score
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the leg	1
Recently confined to bed for ≥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 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 deep venous thrombosis	1
An alternative diagnosis at least as likely as deep venous thrombosis	–2
Likelihood of deep venous thrombosis	
Total score of ≥2: likely	
Total score of ≤1: unlikely	

*Adapted from Wells et al.[2]

Table 2| Wells scoring system for pulmonary embolism*

Clinical feature	Score
Clinical signs and symptoms of deep venous thrombosis (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis that is less likely than pulmonary embolism	3
Heart rate >100 beats/min	1.5
Immobilisation for >3 days or surgery in the previous 4 weeks	1.5
Previous deep venous thrombosis or pulmonary embolism	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the past 6 months, or palliative)	1
Likelihood of pulmonary embolism	
Total score of >4: likely	
Total score of ≤4: unlikely	

*Adapted from Wells et al.[3]