NICE guideline: management of venous thromboembolic diseases and role of thrombophilia testing

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ABSTRACT
The National Institute for Health and Clinical Excellence recently published a clinical guideline on the management of venous thromboembolic disease and thrombophilia testing. Several stand-out recommendations are made which may be practice changing for many physicians, such as catheter-directed thrombolysis for ilio-femoral deep venous thrombosis, routine cancer screening and extended duration of anticoagulation for unprovoked events. In this article, we summarise the key points of the guideline and discuss remaining areas of controversy.

INTRODUCTION
In June 2012 the National Institute for Health and Clinical Excellence (NICE) published clinical guideline 144 on the management of venous thromboembolic diseases (VTE) and the role of thrombophilia. This superceded the update planned by the British Thoracic Society (BTS) of the pulmonary embolism guideline, last updated in 2003. The NICE document covers diagnosis of suspected pulmonary embolus (PE) and deep venous thrombosis (DVT) and subsequent acute management, but excludes children and pregnancy. While it does elaborate on the role of thrombophilia testing, it provides no guidance on how to weigh up the risks and benefits of prolonged anticoagulation.

The NICE guideline differs from what readers may normally expect to see in VTE guidelines drafted by national or international bodies, such as those previously produced by the British Thoracic Society, European Society of Cardiology (ESC) or American College of Chest Physicians (ACCP), in that the committee assessed both clinical and cost effectiveness before reaching a recommendation. When there is no evidence for review, no recommendations, for example on the basis of expert opinion, are made, which leaves some areas uncovered and unlicensed indications for novel therapies are also omitted. Furthermore, certain aspects of management, such as risk stratification, follow-up and home treatment are not covered.

The purpose of this article is not to provide a comprehensive summary of the guideline, rather to provide core recommendations and update the reader on new recommendations, while providing the rationale of the NICE guideline development group (GDG). Readers who wish to read a fuller set of recommendations should also refer to the latest ESC and ACCP guidelines.

The full version of the guideline document with shorter summaries can be found at http://guidance.nice.org.uk/CG144.

NEW RECOMMENDATIONS
Diagnosis
The GDG recommended moving from a three-way (low, medium and high probability) to two-way Wells score for DVT and PE and if these are deemed likely then proceeding to diagnostic imaging, with compression Doppler ultrasound of the leg veins being the modality of choice. For DVT, if the first ultrasound scan is negative, then further risk stratification with d-dimer should be undertaken, and if positive, the patient re-scanned. When there is concern about the risk of radiation, contrast allergy or renal impairment, nuclear medicine ventilation-perfusion (VQ) scanning is an alternative, preferably using single photon emission CT (SPECT), but planar if not available. When CTPA or VQ is negative and a DVT is suspected, further imaging of the leg veins with ultrasound is recommended. Ultrasound of the leg veins is not recommended as a first-line imaging investigation in patients presenting with symptoms and/or signs of PE and DVT. In the presence of a low likelihood of DVT or PE using the Wells score, then d-dimer stratification is advised. Positive assays necessitate further imaging, whereas an alternative diagnosis should be sought in patients with negative assays. Previous guidelines have advocated the use of echocardiography to diagnose PE when the patient’s condition is unstable and rapid intervention is required. This issue is not covered by the GDG.

Treatment
Patients should be offered treatment if imaging is not available immediately in the case of PE or within 4 h for suspected DVT. Once the diagnosis has been confirmed then anticoagulation should be commenced with subcutaneous low molecular weight heparin (LMWH) or fondaparinux for at least 5 days or until an international normalised ratio (INR) of >2 is achieved with a vitamin K antagonist (VKA). In the presence of renal impairment (estimated glomerular filtration rate <30 ml/min/1.73 m²), either unfractionated heparin or LMWH with anti-factor Xa monitoring should be used and when there is a risk of bleeding, unfractionated heparin is advised. Patients
In recognising that the presence of thrombophilia does not predict the risk of recurrence following an unprovoked episode of VTE, the GDG were mindful to reduce the rate of unnecessary thrombophilia investigations and provide clear guidance on when it may impact on treatment decisions. As such, the only clear indications to perform thrombophilia testing were when consideration was being given to discontinuing anticoagulation following an unprovoked DVT or PE. Patients with a history of a first-degree relative with VTE should undergo testing for hereditary thrombophilia, but testing should not be extended to relatives, and all patients should undergo testing for antiphospholipid antibodies (detected as a lupus anticoagulant or as antibodies against cardiolipin or β2-glycoprotein I).

Lastly, the GDG stressed the importance of patient information and education relating to lifestyle issues while on anticoagulation, when receiving dental treatment and during pregnancy.

Investigations for cancer

This guideline for the first time recommends routine screening for cancer in patients over the age of 40 following an unprovoked VTE episode. This was based on a single study which showed no statistically significant reduction in cancer-related mortality, but the GDG felt that the non-significant reduction was potentially clinically and economically important, with patients and relatives also being reassured by negative investigations. Despite the lack of good evidence for a reduction in cancer-related mortality, the screening strategy used in the study showed an increased pick-up of cancers (in approximately 1 in 10 patients with 93% sensitivity) and at an earlier stage than in the standard care group. The study used a strategy of abdominal/pelvic CT or abdominal/pelvic ultrasound scan, alone or in combination with other tests (mammography, sputum cytology, tumour markers, faecal occult blood and colonoscopy). The most cost-effective strategy, however, appeared to be abdominal/pelvic CT, mammography and sputum cytology on top of the routine screening using history/examination, chest radiograph, blood tests (including serum calcium and liver function) and urinalysis, all at the time of diagnosis. Sputum cytology was removed from the final recommendation due to its limited role in the diagnosis of lung cancer. The impact of additional radiation was not taken into consideration, since the increased risk of cancer was felt to be very small compared with the increased early detection of cancer.

AREAS FOR RESEARCH

Many areas for research were identified by the GDG, but the following five areas were highlighted as being of high importance:

- The value of whole leg versus proximal leg vein ultrasound in the diagnosis of acute DVT.
- Long-term versus 3-month anticoagulation in patients with a high risk of recurrence.
- Treating with LMWH versus VKA beyond 6 months in patients with VTE in association with active cancer.
- The clinical and cost effectiveness of catheter-directed thrombolytic therapy or pharmacomechanical thrombolysis for the removal of acute proximal DVT versus standard anticoagulation.
- Systemic pharmacological thrombolysis versus standard anticoagulation for the treatment of acute PE with right ventricular dysfunction.
ISSUES NOT COVERED
Certain areas of VTE management were explicitly excluded from the guideline, such as children (aged <18) and women who are pregnant. While recent guidance for these populations has been published by other organisations,4–6 several areas pertaining to the management of PE in particular are left open by the NICE guideline:

- The role of the new oral direct thrombin and anti-Xa inhibitor anticoagulant agents are not covered, and for information on these, the reader is referred to the ACCP guideline published earlier this year4 7 and the subsequent technology appraisal for rivaroxaban in the treatment of DVT and prevention of recurrent VTE.8

- The guideline does not cover risk stratification beyond defining haemodynamic instability for the purposes of consideration of thrombolysis and thus no recommendations are made on who may be considered eligible for home treatment of VTE. This is despite the availability of well validated clinical risk assessment scores, such as the Pulmonary Embolism Severity Index (PESI) score, which allows stratification of immediate risk following PE (30-day mortality).9 This score clearly defines a low-risk population potentially suitable for home management.10 PESI may also be useful to guide physicians in further evaluating haemodynamically stable patients and indentifying who remains at high risk of death,11 even if there can be no clear guidance on which of these patients may benefit from thrombolysis.

- No advice is given on how to follow up patients with VTE with respect to screening for complications, such as post-thrombotic syndrome or chronic thromboembolic disease. This is despite guidance from the British Thoracic Society suggesting follow up at 3–6 months following PE.12

- Also, as outlined above, no guidance is provided on how to balance risk of recurrence versus risk of bleeding in determining whether to continue anticoagulation, and the reader should be referred again to the ACCP guideline.7

IMPLICATIONS FOR SERVICES/RESOURCES
This guideline considered the economic impact of the recommendations and highlights some of the implications for services. In our view, the principal impact of this guideline will be on diagnostic services in trying to move over to VQ SPECT from planar imaging and covering the increased demand for cancer screening, and the increased demand from vascular surgical departments or interventional radiology to perform catheter-directed thrombolysis for ilio-femoral DVT.

The recommendation to consider CT imaging of the abdomen and pelvis in patients with idiopathic VTE is likely to generate a significant increase in requests for such assessments, although the evidence for this approach is still somewhat controversial and not recommended in other guidance.1

Additionally the recent development in England and Wales of a tariff-based payment for the ambulatory management of PE is now left without any standardised assessment of suitability. It is left to individual organisations to determine the criteria by which this approach can be applied.

CONCLUSION
NICE clinical guideline 144 standardises the initial investigation and management of VTE and provides recommendations for the type and duration of anticoagulation based on well established clinical criteria. Several important areas, however, are not addressed and for the physician attending the patient, this guideline leaves some areas of clinical uncertainty in the management of acute PE. We recommend that readers refer to other documents for top-up guidance.4–6

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