



Surveillance report 2016 – Venous thromboembolic diseases (2012) NICE guideline CG144

Surveillance report

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Surveillance decision

We will plan an update of the following sections of the guideline:

- Diagnostic investigations for pulmonary embolism (PE)
- Pharmacological interventions – anticoagulation treatment for deep vein thrombosis (DVT) or PE^[1]
- Investigations for cancer

An extension to the scope will be needed to incorporate outpatient treatment of people with PE.

Reason for the decision

We found 59 new studies through surveillance of this guideline.

New evidence that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated and any new sections added.

Diagnosis for pulmonary embolism (PE)

- In people with suspected PE, can we safely rule out further imaging based on clinical probability score and D-dimer assay?

The current recommendations do not specify a D-dimer threshold to use in patients with an unlikely 2-level PE Wells score. The evidence identified at the 4-year surveillance review on D-dimer thresholds to safely rule out further imaging has a potential impact on [NICE guideline CG144](#). Topic experts highlighted the increase in false positive rates of D-dimer with age when using unadjusted thresholds. An age adjusted D-dimer may increase the proportion of patients, primarily over the age of 50, in whom further imaging can be safely withheld. In turn, this has the potential to reduce impact on resources and reduce the risks of imaging with less radiation exposure and complications from contrast injections. A further consideration of age adjusted D dimer concerns the use of different D-dimer assays with varying cut-off thresholds across services and laboratories. Although some topic experts believe this topic to be relatively low priority, most topic experts agreed that the new evidence suggests the current recommendation ([1.1.10](#)) to offer a D-dimer test may need to be updated to include consideration of the patient's age when setting the threshold to rule out further imaging tests for PE. Some consideration should

be given to the wording of any such new recommendation to suggest that each service validate its own D-dimer assay and this could be influenced by the patient's age.

Decision: This review question should be updated.

Treatment – pharmacological interventions

- What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed DVT?
- What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed PE?

The evidence identified at the 4-year review on pharmacological interventions with non-vitamin K oral anticoagulants (NOACs) to manage DVT or PE has a potential impact on NICE guideline CG144. The 4-year surveillance review identified new evidence for the efficacy and safety of NOACs which have not been previously considered in NICE guideline CG144. The evidence suggests similar rates of efficacy for NOACs compared with current standard treatments for confirmed venous thromboembolism (VTE) and a trend towards reduced risks of bleeding. NICE Technology Appraisals have, since the publication of NICE guideline CG144, approved the use of NOACs for the treatment and prevention of VTE.

Intelligence from topic experts also highlights the common practice for clinicians to use NOACs rather than a low molecular weight heparin (LMWH) for the treatment of suspected DVT prior to diagnosis. However, anticoagulant use may impair the reliability of subsequent D-dimer assay results. Topic experts suggested guidance in this area would be useful.

Topic experts also highlighted that patients who have a negative proximal leg vein ultrasound scan for DVT but need a repeat scan one week later should not be treated. The rationale for the second scan is to determine if any undetected calf vein clots extend off treatment however pharmacotherapy may impair the reliability of subsequent ultrasound scan results. There is also a potential risk of a suppressed calf vein clot extending if treatment is stopped after one week. Topic experts suggested that some clarity for clinicians in this area would be useful.

Topic experts agreed that the new evidence suggests the current recommendations on pharmacological interventions for VTE may need to be updated to include consideration of the use of NOACs as a treatment option and some clarity around treatment during diagnosis of DVT.

Decision: This review question should be updated.

Investigations for cancer

- Do investigations for cancer in patients with spontaneous VTE (DVT or PE) improve patient outcomes (morbidity and mortality)?

The 4-year surveillance review identified new evidence to suggest that CT scans of the abdomen and pelvis in addition to routine or limited screening do not provide a clinically significant benefit in diagnosis or mortality rates for cancer in patients with VTE. Intelligence from topic experts also highlights the lack of benefit in additional cancer screening and the increased risk of radiation from CT scans. This new evidence is inconsistent with the current recommendation to offer further investigations for cancer to all patients with unprovoked DVT or PE. Topic experts agreed that the new evidence suggests the current recommendations on investigations for cancer may need to be updated to reflect the new information on this question. Some consideration should be given to the wording of any such new recommendation to suggest that further screening with CT should be considered if guided by clinical assessment or if other risk factors are present.

Decision: This review question should be updated.

Outpatient treatment of patients with PE

- Which patients with suspected or confirmed PE can be safely discharged and managed within outpatient settings?
- What is the clinical and cost-effectiveness of outpatient treatment for the management of patients with low risk PE?

NICE guideline CG144 does not currently include recommendations regarding outpatient treatment of PE. New evidence from the 4-year surveillance review suggests that patients with PE who are at low risk of adverse events could safely receive anticoagulation treatment on an outpatient basis. Topic experts highlighted the increased use of ambulatory care units as an alternative to hospital care and the use of mortality risk and Pulmonary Embolism Severity Index (PESI) scores to identify patients with a low risk of adverse events who could be safely discharged. Topic experts agreed that there is a need to establish a new area in the guideline to incorporate recommendations on outpatient treatment for PE.

Decision: This review question should be included.

Other clinical areas

Topic experts considered the effectiveness of whole-leg ultrasound scans for the diagnosis of DVT. The 4-year surveillance review did not find any new evidence comparing the effectiveness of a whole-leg ultrasound scan with a proximal leg vein ultrasound scan for the detection of distal DVT. Topic experts suggest that there may be an indication for a whole-leg ultrasound scan in circumstances where a serial ultrasound is not available, when a repeat scan would be very difficult to arrange or in patients receiving an anticoagulant prior to a D-dimer test. However, there remains some uncertainty of the clinical and cost-effectiveness of a whole-leg ultrasound scan in the diagnosis of DVT to impact recommendations at this time. This area will be examined again at the next surveillance review of the guideline.

We also found new evidence that was not thought to have an effect on current recommendations. This evidence related to self-management and self-monitoring for patients treated with a vitamin K antagonist.

We did not find any new evidence related to patient information or thrombophilia testing.

For any new evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all the new evidence and views of topic experts, we decided that a partial update with modified scope is necessary for this guideline.

See [how we made the decision](#) for further information.

^[1] The proposed update to pharmacological interventions is limited to anticoagulant treatments and does not include pharmacological thrombolysis or analgesia.

Commentary on selected new evidence

With advice from topic experts we selected 2 studies for further commentary.

Diagnosis – diagnostic interventions for pulmonary embolism

We selected the [ADJUST-PE](#) prospective diagnostic management outcome study by Righini et al. (2014) for a full commentary because this study potentially provides further information on D-dimer thresholds to inform recommendations on diagnostic tests. Intelligence from the surveillance review highlighted the potential benefit of adjusting the diagnostic strategy for people with suspected pulmonary embolism (PE).

What the guideline recommends

For patients with an unlikely 2-level PE Wells score and positive D-dimer test NICE guideline CG144 recommends offering an immediate computed tomography pulmonary angiogram (CTPA) or interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. NICE guideline CG144 states that the threshold for a positive D-dimer result varies with the type of D-dimer test used and is determined locally.

NICE guideline CG144 also recommends that alternative diagnoses be considered in patients with an unlikely 2-level PE Wells score and either a negative D-dimer test or a positive D-dimer test and a negative CTPA. Alternative diagnoses should also be considered for patients with a likely 2-level PE Wells score and both a negative CTPA and no suspected deep vein thrombosis (DVT).

Methods

The [ADJUST-PE](#) prospective diagnostic management outcome study by Righini et al. (2014) compared an age-adjusted D-dimer threshold to a fixed D-dimer threshold as a diagnostic strategy in 3,324 people with suspected PE. Patients were recruited from hospitals in Belgium, France, the Netherlands and Switzerland. A clinical suspicion of PE was required for patients to be eligible to participate.

Patients were excluded if they met any of the following criteria:

- Suspicion of PE more than 24 hours after being admitted to hospital
- Already taking anticoagulant therapy

- Allergy to contrast medium
- Impaired renal function
- Less than 3-month life expectancy
- Pregnant
- Not available for follow-up

A sequential diagnostic strategy was applied to all patients based initially on the clinical probability of PE from either the simplified, revised Geneva score or the 2-level Wells score. All patients with a high or likely clinical probability from these scores received CTPA as a further diagnostic test and commenced anticoagulant therapy. Patients with a low or unlikely clinical probability of PE underwent a D-dimer test. The study incorporated the use of 6 different D-dimer tests as these were used across the study centres.

The study intervention consisted of an age-adjusted D-dimer threshold for the diagnosis of PE. The threshold was determined by multiplying the patient's age by 10 if they were aged 50 years or over and a threshold of 500 microgram/litre was used for patients younger than 50 years. PE was ruled out in patients with a D-dimer level lower than the values derived according to their age.

A CTPA was conducted in patients with a positive D-dimer result (levels above the relevant age-adjusted threshold) and anticoagulant therapy commenced. Patients with a negative D-dimer result (levels below the relevant age-adjusted threshold) had no further tests and did not receive anticoagulant therapy.

The primary outcome was defined as the rate of symptomatic thromboembolic events during the 3-month follow-up period for patients with an age-adjusted negative D-dimer result. This primary outcome essentially determined the failure rate of the diagnostic strategy used in the study. Secondary outcomes consisted of the thromboembolic risk during the 3-month follow-up of patients with a low or unlikely clinical probability and a D-dimer result between 500 microgram/litre and their age-adjusted value. The value of the age-adjusted D-dimer diagnostic strategy was also analysed in patients aged 75 years and older.

Thromboembolic events were adjudicated by independent experts using the following criteria:

- For DVT
 - abnormal results from proximal compression ultrasonography.

- For PE
 - a high probability pattern on ventilation-perfusion lung scan
 - CTPA
 - angiography.
- For PE-related death
 - confirmed by autopsy
 - if death followed a clinically severe PE.

Results

Of the 3,324 patients completing a clinical probability assessment, 2,898 were determined low or unlikely for PE. From these patients:

- 1154 (39.8%) had a negative D-dimer result according to their age-adjusted cut-off (95% confidence interval [CI] 38.1% to 41.6%)
- 817 (28.2%) had a D-dimer lower than 500 microgram/litre (95% CI 26.6% to 29.9%)
- 337 patients (11.6%) had a D-dimer between 500 microgram/litre and their age-adjusted cut-off (95% CI 10.5% to 12.9%).

For the outcomes during the 3-month follow-up period, 7 patients with a D-dimer lower than 500 microgram/litre and 6 patients with a D-dimer between 500 microgram/litre and their age-adjusted cut-off were excluded from analysis:

- Thromboembolic risk was identified in 1 of 810 patients with a D-dimer result lower than 500 microgram/litre (0.1%, 95% CI 0.0% to 0.7%).
- The failure rate of the age-adjusted cut-off in patients with a D-dimer result between 500 microgram/litre and their age-adjusted cut-off was 1 of 331 patients (0.3%, 95% CI 0.1% to 1.7%).
- Thromboembolic risk was found in 0 of 195 patients (0.0%, 95% CI 0.0% to 1.9%) aged 75 years or older with a low or unlikely clinical probability and a D-dimer result below their age-adjusted cut-off.

Strengths and limitations

Strengths

This study contains a population of direct relevance to the NICE guideline CG144 with the inclusion of patients with suspected PE. The diagnostic strategy, D-dimer test and CTPA, used in the study are recommended in the guideline and addressed within the study's methodology. Further strengths of the study include patient selection using consecutive enrolment and appropriate inclusion and exclusion criteria.

Limitations

A limitation of this study is the low proportion of patients included that were relevant to the diagnostic strategy of interest. Of the 3,324 included patients, only 337 had an age-adjusted D-dimer level. This reduction in the population of interest reduces the potential impact the results would have on the guideline. The study only conducted the reference standard test (CTPA) in a subgroup of patients (those with a likely or high clinical probability of PE and those with a positive D-dimer result) and not in the population of interest. A further limitation of the study is the use of multiple index tests (2 clinical probability tools and 6 different D-dimer tests) across the study centres and the equivalence of these in practice is not known. These limitations in the use of reference and index tests do not allow a calculation of sensitivity, specificity, positive likelihood ratio or negative likelihood ratio statistics. This lack of operating statistics prevents a comparison of age-adjusted D-dimer levels with the conventional D-dimer level. The use of a 3-month follow-up to determine the primary outcome, rate of PE and venous thromboembolism (VTE), rather than confirming diagnosis at presentation leads more towards a prognostic study. Although clinically useful, for the purpose of the guideline question on diagnosing PE the results of a prognostic study may be less applicable. Also, as the study was not an RCT, it is not possible to compare the 3-month thromboembolic risk with a control group managed using the 500 microgram/litre cut-off level.

Impact on guideline

The new evidence indicates that an age-adjusted D-dimer level can increase the number of patients in whom PE is ruled out without the need for further diagnostic tests. This has a potential to impact on NICE guideline CG144 recommendations for the use of D-dimer tests with the consideration of applying age-adjusted levels instead of the conventional level.

Investigations for cancer

We selected a randomised controlled trial by [Carrier et al. \(2015\)](#) for a full commentary because this study potentially challenges the current recommendation to consider further CT investigations for cancer in people with unprovoked DVT or PE. Intelligence from the surveillance review highlighted the lack of benefit from further screening for cancer and raised concerns regarding the potential increase in risk of radiation exposure to patients.

What the guideline recommends

NICE guideline CG144 recommends investigations for cancer with a physical examination (guided by the patient's full history), a chest X-ray, blood tests (full blood count, serum calcium and liver function tests), and urinalysis are offered to all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer.

NICE guideline CG144 also recommends further investigations for cancer are considered with an abdomino-pelvic CT scan (and 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.

Methods

The [Carrier et al. \(2015\)](#) Canadian multicentre, open-label, randomised controlled trial compared a limited cancer screening strategy to a limited cancer screening strategy in combination with a comprehensive CT strategy in people with a first unprovoked VTE.

The trial included 854 patients randomly assigned to a limited cancer screening strategy which consisted of basic blood tests, chest radiography, and screening for breast, cervical and prostate cancer or this strategy with the addition of CT of the abdomen and pelvis. Patients were included if they had a new diagnosis of first unprovoked symptomatic VTE and referred to a thrombosis clinic. Exclusion criteria consisted of:

- age below 18 years
- informed consent not provided
- allergy to contrast media
- lower than 60 ml per minute of creatinine clearance

- claustrophobia or agoraphobia
- weight over 130 kg
- ulcerative colitis
- glaucoma.

Follow-up of patients was conducted over 1 year at fixed intervals to detect the primary outcome of newly diagnosed cancer in patients with a negative screening result for occult cancer. Secondary outcomes consisted of the total number of occult cancers diagnosed and the total number of early cancers diagnosed either at screening or during follow-up, time to cancer diagnosis, 1-year cancer-related mortality and overall mortality, and the incidence of recurrent VTE. A clinician further investigated any abnormal findings identified by either strategy.

Results

From a total of 3,186 patients who were initially screened for eligibility, 854 were randomised and included in the final analysis. The baseline characteristics of the study population indicated that the mean age was 54 years and the majority of patients were male.

A total of 33 from 854 patients were diagnosed with cancer (3.9%, 95% CI 2.8 to 5.4). This included 14 patients in the limited screening strategy (3.2%, 95% CI 1.9 to 5.4) and 19 patients in the limited screening plus CT strategy (4.5%, 95% CI 2.9 to 6.9). The difference between the 2 groups was not significant ($p=0.28$).

The results indicated 4 of 14 occult cancers were missed by the limited screening strategy (29%, 95% CI 8 to 58) and 5 of 19 occult cancers were missed by the limited screening plus CT strategy (26%, 95% CI 9 to 51). The difference between the 2 groups was not significant ($p=1.0$). Also, information from the Kaplan–Meier analysis found that the time to detection of a missed occult cancer over the 1-year follow-up period was not significantly different between the strategies (log-rank chi-square test with 1 degree of freedom, 0.03, $p=0.87$).

For the limited screening strategy, the absolute rate of occult-cancer detection was 0.93% (95% CI 0.36 to 2.36). For the limited screening plus CT strategy, the absolute rate of occult-cancer detection was 1.18% (95% CI 0.51 to 2.74). This results in a 0.25% absolute difference between the strategies (95% CI –1.12 to 1.63).

No significant differences were found between the limited screening and the limited screening plus CT groups in the secondary outcomes of:

- Detection of early cancers (0.23% for the limited screening group and 0.71% for the limited screening plus CT group, $p=0.37$).
- Cancer-related mortality (1.4% for the limited screening group and 0.9% for the limited screening plus CT group, $p=0.75$).
- Overall mortality (1.4% for the limited screening group and 1.2% for the limited screening plus CT group, $p=1.0$).
- Time to cancer diagnosis (4.2 months for the limited screening group and 4.0 months for the limited screening plus CT group, $p=0.88$).
- Incidence of recurrent VTE (3.3% for the limited screening group and 3.4% for the limited screening plus CT group, $p=1.0$).

Strengths and limitations

Strengths

This trial contains a population of patients with a first unprovoked VTE that is directly relevant to NICE guideline CG144. The question investigated by the trial relates directly to the recommendations on screening for cancer in the guideline and all relevant outcomes considered in relation to this population. The trial generally has a robust study design with the use of randomisation, allocation concealment and clear minimisation of bias, although the open-label nature of the trial prevented the use of blinding. However, the impact of this bias may have been minimised with the biopsy-proven cancer outcome.

Limitations

The trial was limited with a follow-up duration of 1 year as longer-term follow-up may provide a better understanding of mortality rates. The authors also note a limitation with their study population potentially having a lower risk for cancer than the general population as only 854 patients were included in the analysis after over 3,000 assessed for eligibility. The low mean age also indicates a low prevalence study population and there is potentially a case for further study in older groups with a higher prevalence.

Impact on guideline

The new evidence indicates that further screening for occult cancer using CT of the abdomen and pelvis in patients with a first unprovoked VTE does not provide a clinically significant benefit. This result is inconsistent with the current recommendation in NICE guideline CG144 to consider a CT

scan for cancer in all patients over 40 years with a first unprovoked VTE. Given the strengths of this trial and the further implications associated with extensive screening for cancer, there is a potential for this trial to impact the recommendations for this population.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of [venous thromboembolic diseases: diagnosis, management and thrombophilia testing \(2012\) NICE guideline CG144](#).

For details of the process and update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in 'Developing NICE guidelines: the manual'.

Previous surveillance [update decisions](#) for the guideline are on our website.

New evidence

We found 37 new studies in a search for randomised controlled trials and systematic reviews published between 11 November 2013 and 26 January 2016. We also considered 8 additional studies identified by members of the guideline committee who originally worked on this guideline. A further 4 studies were identified through post-publication communications.

Evidence identified in previous surveillance 2 years after publication of the guideline was also considered. This included 10 studies identified by search during the 2-year Evidence Update (2014).

From all sources, 59 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See [appendix A](#): summary of new evidence from surveillance for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 4-year surveillance review, and the decision was to update, we did not consult on the decision.

See [ensuring that published guidelines are current and accurate](#) in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

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