



2022 exceptional surveillance of venous thromboembolic diseases: diagnosis, management and thrombophilia testing (NICE guideline NG158)

Surveillance report

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Surveillance decision

We will update [NICE's guideline on venous thromboembolic diseases](#). The update will focus on the diagnosis of pulmonary embolism (PE) in people with COVID-19. We will then cross-refer to this updated section from [NICE's rapid guideline on managing COVID-19](#).

We will also refresh recommendation 1.1.21 to clarify that the action relates to any setting.

Exceptional surveillance review summary

Background: reason for the exceptional review

[Healthcare Safety Investigation Branch \(HSIB\) published a report on clinical decision making: diagnosis and treatment of pulmonary embolism in emergency departments](#) (March 2022) following concerns about safety risk related to delayed or missed diagnosis and treatment of PE across several areas of healthcare. The report made several safety recommendations for healthcare practice and policymakers, including R/2022/189, which recommended that NICE should review the findings of the investigation in relation to its guideline on venous thromboembolic (VTE) diseases, and update it if required.

NICE subsequently reviewed its guideline on VTE to assess any impact of the findings in the report. Although it was not directly mentioned in the report, NICE also reviewed its rapid guideline on managing COVID-19, as the report raises issues about complications in people with COVID-19 and a PE for diagnosis and treatment.

NICE's original guideline on VTE published in 2012, and the [section on diagnosis and initial management of suspected PE](#) includes a combination of tools to support diagnosis such as Wells score, D-dimer blood testing and radiological imaging (scans), which are summarised in a [visual summary](#).

NICE's rapid guideline on managing COVID-19 published in 2021, and covers prevention and management of COVID-19 and any complications, including VTE prophylaxis.

Methods

The exceptional surveillance process consisted of:

- Considering the findings of the HSIB investigation report (2022) that triggered the exceptional review.
- Considering the evidence used to develop NICE's guideline on VTE, specifically the sections that are mentioned in the HSIB report: section 1.1 on diagnosis and initial management and section 1.3 on anticoagulation treatment for suspected or confirmed deep vein thrombosis (DVT) or PE.
- Literature searches to identify relevant evidence on Wells score and D-dimer tests for people with COVID-19 and suspected PE.
- Assessing the new evidence and information against current recommendations to determine whether or not to update sections of the guideline.

For further details about the process and the possible update decisions that are available, see [ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual](#).

Key findings in the HSIB report and related findings of the surveillance check by NICE

There are 4 topics from the HSIB report that are considered in this surveillance review.

Topic 1: PE rule-out criteria (PERC) to help determine whether further tests for PE are needed in NICE's guideline on VTE

Key points from the HSIB report

The HSIB investigation found that emergency department (ED) staff were familiar with NICE's guideline on VTE, but rarely applied the decision-making scores and criteria of the guideline, as outlined by the PERC rule and Wells score. The HSIB report, paragraphs 4.4.7 and 4.4.8, describe implementation barriers to recommendation 1.1.16 and problems using the PERC rule. It mentions that determining a 'less than 15%' likelihood of PE in a patient is challenging and there was uncertainty about application of the PERC rule.

Background to the PERC rule

Diagnosing PE is known to be a challenge because the symptoms and signs are common and not specific. The initial step for patients presenting with signs and symptoms of possible PE is to assess their likelihood of having a PE. Therefore, several clinical prediction scores incorporating predisposing factors, symptoms and clinical signs have been developed to safely rule out the diagnosis of PE in a significant proportion of patients; this in turn means patients could be ruled out for further imaging or tests.

NICE's guideline on VTE was updated in 2020 to include recommendation 1.1.16 and consideration of the PERC rule (which is used in addition to the Wells score):

'If clinical suspicion of PE is low (the clinician estimates the likelihood of PE to be less than 15% based on the overall clinical impression, and other diagnoses are feasible), consider using the pulmonary embolism rule-out criteria (PERC) to help determine whether any further investigations for PE are needed.'

The guideline was updated to include the PERC rule as it has high specificity and can accurately eliminate PE as a possible diagnosis in patients. The recommendation applies where clinical suspicion of PE is low and when discharge of a patient is being considered. The PERC rule could therefore reduce anxiety in those patients and reduce healthcare costs by preventing unnecessary downstream tests, scans and treatment. The evidence for the PERC rule was limited so the committee agreed to recommend that the PERC rule be considered as part of initial assessment.

Impact

During the 2019 stakeholder consultation of the draft guideline update, NICE did not receive any comments to indicate that recommendation 1.1.16 and the PERC rule would be difficult to implement. Further, it would require similar knowledge and skills to implement the PERC rule as required to implement the Wells score, which was already part of the guideline since 2012; the 2-level PE Wells score requires the clinician to judge whether 'an alternative diagnosis less likely than PE'. Regarding both the PERC rule and Wells score, for scoring to be effective, it requires clinical experience and expertise. That may include identifying perceived signs and symptoms, in addition to the tangible features that are listed in the PERC rule.

Recommendation 1.1.16 requires that clinicians categorise patients based on unstructured clinical gestalt assessment using their clinical experience and expertise, notionally into

strata of low, medium and high likelihood of PE. In some studies, these strata have been quantified, such as low (less than 15%), medium (15% to 40%) and high (more than 40%; [Kline et al. 2008](#)). The 15% numeric cut-off was added to the NICE guideline as a helpful guide to support gestalt assessment and as a guide to low likelihood of PE.

The NICE guideline clarifies in the rationale section that the clinician estimates the likelihood of PE to be less than 15% based on the overall clinical impression and where other diagnoses are feasible.

During development of the guideline, it was acknowledged that the experience and expertise of the person doing the scoring is an important consideration that could determine the accuracy of the scoring system.

Paragraph 4.4.8 of the HSIB report states 'the emergency department subject matter advisor told the investigation that they had seen PERC support clinical decision-making and promote evidence-based care. However, both the emergency department and haematology subject matter advisors said that it can be inappropriately applied where staff do not understand its role and there is limited clarity around its use'. Paragraph 4.4.27 also identifies that workforce shortages may be responsible for less experienced staff undertaking initial assessments and they 'may struggle to assess risk'. The HSIB report identifies a need for training to prepare staff for work in emergency departments with a focus on the development of decision-making skills; such training may support the use of the PERC rule, given the mixed pattern of implementation that is reported. There may also be a need for local support through having expert decision makers on-hand at initial assessment (see HSIB paragraph 4.4.30). These issues, which are beyond the scope of the NICE's guideline on VTE and the remit of NICE, are addressed in the HSIB report as safety recommendations for other organisations.

We do not plan to revise the guideline in respect of recommendation 1.1.16 and the PERC rule. Clinical judgement is needed to identify the subgroup of people in whom clinical suspicion of PE is low and for whom discharge is being considered. Where the PERC rule is applied successfully, there will be benefits of using it, including reduced need for D-dimer testing and imaging for people with none of the PERC criteria for PE, leading to some reductions in waiting times in primary care and emergency departments.

The HSIB report highlights issues that stem from staff not having the knowledge and experience to follow the recommendations or senior support to help make relevant assessments, and this would appear to be the main barrier to successfully implementing

the recommendations relating to the PERC rule.

Topic 2: Applying the 2-level Wells score for estimating PE in NICE's guideline on VTE

Key points from the HSIB report

The HSIB report identifies implementation issues with the Wells score in paragraphs 4.4.9 to 4.4.11, 4.4.24 and 4.4.25. As mentioned above, the HSIB investigation found that emergency department staff were familiar with NICE's guideline on VTE, but rarely applied the decision-making scores and criteria described in it. During its observations, the investigation 'did not see staff documenting a Wells score before requesting a D-dimer test and did not hear it being used to support diagnostic decisions for PE', as recommended by the NICE guideline.

Despite feedback that some staff questioned the validity of the Wells score, the report consulted experts that confirmed it was still the most appropriate scoring system to stratify further investigations.

Background to the 2-level PE Wells score

NICE's guideline on VTE includes the following recommendation 1.1.17:

'If PE is suspected, use the 2-level PE Wells score to estimate the clinical probability of PE.'

The Wells score is a clinical prediction rule for estimating the probability of PE. There are a number of versions of Wells scores available including the 2-level PE Wells score as recommended in the NICE guideline. Among the clinical scores, the Wells score was chosen because it safely ruled out PE when used in combination with sensitive D-dimer tests.

Following recommendation 1.1.17, recommendations 1.1.18 to 1.1.21 then go on to describe what actions to take where PE is likely (Wells score more than 4 points) or PE is unlikely (Wells score 4 points or less). The strategy involves managing according to the 2-level PE Wells score: if PE is likely (score of 5 points or more), offer a CT pulmonary angiogram (CTPA); if PE is unlikely (score 4 points or less), offer a D-dimer and a CTPA only if the D-dimer is positive.

Impact

The barriers to implementing the Wells score, as outlined in the HSIB report, are similar to the barriers to implementing the PERC rule, as discussed above.

The Wells score requires experience and expertise of the person doing the scoring, due to the weight of 1 subjective item in the 2-level PE Wells score ('alternative diagnosis less likely than PE'). This is an important consideration that could determine the accuracy of the scoring system.

Also, the NICE guideline recommends that for higher Wells scores (more than 4 points), the patient should be offered a CTPA immediately if possible (following the actions in recommendations 1.1.18 and 1.1.19), rather than wait for a D-dimer test (as indicated in the practices witnessed by the HSIB enquiry).

As stated in relation to the PERC rule above, clinical judgement is needed to successfully apply the Wells score. Where the Wells score is applied successfully, there will be benefits of using it. The use of 2-level Wells score to stratify further investigations in patients with suspected PE is a cost-effective strategy. Calculating a 2-level PE Wells score is associated with low costs while it is helpful to rule out PE together with a D-dimer test; it also helps avoid further costlier tests and radiation exposure.

The HSIB report highlights issues that stem from staff not having the knowledge and experience to follow the recommendations and this would appear to be the main barrier to successfully implementing the recommendations relating to the Wells score. As the barriers to implementation relate directly to staff knowledge and experience, we do not plan to revise the guideline in respect of recommendation 1.1.17 and the PE Wells score.

Topic 3: Starting patients on interim anticoagulation in NICE's guideline on VTE

Key points from the HSIB report

The HSIB report, paragraphs 4.4.12 to 4.4.15, present findings relating to the risk of interim therapeutic anticoagulation and the intended audience of the action.

The HSIB report notes that the risk from a single-dose interim therapeutic anticoagulation (such as low molecular weight heparin) was small unless there were obvious risk factors.

However, staff who engaged with the HSIB investigation identified that 'NICE's recommendation did not consider the risk to patients of taking anticoagulation if their diagnosis turned out to be something other than PE'. In addition, they note that before interim anticoagulation is provided, consideration of patient history is required to identify bleeding risk or other diagnosis, which takes time and may be limited in an emergency department.

The HSIB report also notes that, in relation to the administration of anticoagulation pending a D-dimer result, emergency department staff were often unaware of this NICE recommendation and suspected that it was aimed at primary care. NICE told the investigation that the guidance was for all providers of primary, secondary and tertiary care.

Recommendation 1.1.21, which states when to offer interim therapeutic anticoagulation

NICE's guideline on VTE includes the following recommendation 1.1.21, which covers actions where PE is unlikely, based on a Wells score:

'Offer people with an **unlikely** PE Wells score (4 points or less):

- a D-dimer test with the result available within 4 hours if possible (see the [section on D-dimer testing](#)) **or**
- if the D-dimer test result cannot be obtained within 4 hours, offer interim therapeutic anticoagulation while awaiting the result (see the [section on interim therapeutic anticoagulation for suspected DVT or PE](#)).

If the D-dimer test result is:

- positive, follow the actions in recommendations 1.1.18 and 1.1.19
- negative:
 - stop interim therapeutic anticoagulation (but do not stop long-term anticoagulation if being used for secondary prevention)
 - think about alternative diagnoses

- tell the person that it is not likely they have PE. Discuss with them the signs and symptoms of PE and when and where to seek further medical help. **[2012, amended 2020]**'

Impact

NICE's guideline on VTE (see [evidence review D](#)) acknowledges there is a trade-off between missed PE cases and wrongly diagnosing and starting interim anticoagulation unnecessarily in someone who does not have PE. The NICE diagnostic algorithm tries to achieve this balance, without subjecting patients to too many tests or delay important treatment.

During guideline development, the following considerations were made by the committee: people without PE may undergo unnecessary anticoagulant treatment in the interim if CTPA scans or D-dimer tests are not immediately available; the anticoagulation treatment may have serious side effects including major bleeding. However, the committee agreed in 2020 that the period that people received interim anticoagulant treatment was likely to be short in most cases. A single dose of therapeutic anticoagulant is likely to have an overall benefit to patients who are waiting for D-dimer results or diagnostic imaging to exclude a PE. Given that PE is potentially life threatening, the potential harms from a dose of a therapeutic anticoagulant is less than the potential harms from delay of treatment.

It is acknowledged that where a patient may be presenting for the first time, it will be necessary to take the time to establish any risks associated with taking interim therapeutic anticoagulation. The NICE guideline provides [information on prescribing medicines](#). Healthcare professionals should, therefore, take note of the contraindications, warnings, safety recommendations and any monitoring requirements for the medicine when following recommendations about prescribing.

Regarding the comments that emergency department staff were unaware that recommendation 1.1.21 (to offer interim therapeutic anticoagulation while awaiting the D-dimer test result) was relevant to them, the recommendation will be refreshed to clarify this relates to any setting, as follows by adding the text highlighted in bold:

'if the D-dimer test result cannot be obtained within 4 hours **(in any setting)**, offer interim therapeutic anticoagulation while awaiting the result (see the [section on interim therapeutic anticoagulation for suspected DVT or PE](#)).'

Topic 4: D-dimer result thresholds and the Wells score for patients with COVID-19

Key points from the HSIB report

The HSIB report, paragraphs 1.1.8, 1.1.14 to 1.1.16, 4.4.16 and 4.4.17, present findings relating to the use of D-dimer tests and the Wells score for people with COVID-19 and suspected PE.

The report notes that during the COVID-19 pandemic, it became apparent that the virus affected the formation of blood clots. COVID-19 can lead to people developing PE, and other clots, through immune-related clot formation. The virus can also result in increased D-dimer levels in the blood because of inflammation.

The respondents in the HSIB report highlight that the emergence of COVID-19 may impact some of the recommendations in NICE guidance for diagnosing PE. With the risk of blood clots associated with COVID-19, the report questions whether D-dimer result thresholds and the Wells score are still appropriate.

The pandemic is considered to have increased the risk of missing a PE because the symptoms of COVID-19 and PE may be similar (for example, breathlessness and cough) and people may have COVID-19 and a PE at the same time. Studies have explored the presence of PE in people with COVID-19 with variable results. The HSIB report highlighted that there is limited national guidance to help clinicians identify patients with a PE and COVID-19 (information provided by the British Thoracic Society was acknowledged, including its [Rationale for CTPA in COVID-19 patients](#) and [Guidance on venous thromboembolic disease in patients with COVID-19](#)).

Recommendations which cover D-dimer testing and Wells score for PE in NICE's guideline on VTE

Section 1.1 in the NICE guideline covers diagnosis and initial management of VTE. Within that section, recommendations 1.1.12 to 1.1.14 cover D-dimer testing for suspected PE, as follows:

- 'When offering D-dimer testing for suspected DVT or PE, consider a point-of-care test if laboratory facilities are not immediately available.'

- 'If using a point-of-care D-dimer test, choose a fully quantitative test.'
- 'When using a point-of-care or laboratory D-dimer test, consider an age-adjusted D-dimer test threshold for people aged over 50.'

As mentioned above, the NICE guideline includes the Wells score in the following recommendation 1.1.17:

'If PE is suspected, use the 2-level PE Wells score to estimate the clinical probability of PE.'

These recommendations were published before the COVID-19 pandemic and do not refer to people with COVID-19.

D-dimer testing and Wells score for PE in NICE's rapid guideline on managing COVID-19

The aim of the NICE rapid guideline on COVID-19 is to provide recommendations on the management of acute complications (such as VTE) in COVID-19 patients. The guideline does not include any recommendations on Wells score for estimating the probability of PE or D-dimer tests for diagnosis of PE in patients with COVID-19.

Recommendation 8.3.1 only covers the use of D-dimer to guide prophylactic dosing of heparin:

'Do not base prophylactic dosing of heparin on levels of D-dimer.'

The COVID-19 guideline also provides recommendations on prophylaxis for VTE in COVID-19 patients for a period of time, but it does not provide guidance on diagnosis of suspected PE in COVID-19 patients after the course of prophylaxis.

Search and selection strategy to identify relevant evidence on Wells score and D-dimer tests for patients with COVID-19 and suspected PE

We searched for new diagnostic studies published between March 2020 and June 2022, which related to Wells score or D-dimer tests for patients with COVID-19 and suspected PE. We screened 1,915 studies on title and abstract and we found:

- 8 studies assessing D-dimer tests

- 1 study assessing Wells score combined with a D-dimer test.

Studies were selected in accordance with the inclusion criteria used for NICE's guideline on VTE, with the additional requirement that they related to patients with COVID-19.

See [appendix A for details of all evidence considered, and references](#).

Impact

Five retrospective studies found that a higher threshold for D-dimer were identified in COVID-19 patients with PE, compared with those without COVID-19, and that the use of higher thresholds could reduce unnecessary pulmonary CTPA scans. However, D-dimer thresholds provided by the studies are heterogenous with no definitive threshold to rule in or rule out PE in COVID-19 patients, with values ranging from 900 ng/ml to 2,903 ng/ml.

Three studies, including 2 retrospective and a diagnostic test accuracy study, did not find a significant difference in sensitivity of D-dimer for PE in those with or without a co-occurring COVID-19 infection. This suggests that D-dimer thresholds alone should not be used for the diagnosis of PE in patients with COVID-19.

When looking at combining the standard and age-adjusted D-dimer threshold and the Wells score, 1 retrospective cohort study found that these were not clinically useful tools to identify PE in patients with COVID-19. This was because there was no significant difference detected in Wells scores between COVID-19 patients with and without PE.

Further research is required to determine if PE can be safely excluded based on an increased D-dimer threshold alone or combined with the Wells score in patients with suspected or proven COVID-19. However, although the evidence is not definitive, it does suggest that diagnosing PE in COVID-19 patients requires an elevated D-dimer threshold. This highlights a safety issue, as this is not covered by either of NICE's guidelines on VTE or COVID-19. It is therefore anticipated that there will be an impact on these guidelines.

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

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

We will update NICE's guideline on venous thromboembolic diseases. The update will focus on the diagnosis of pulmonary embolism (PE) in people with COVID-19. We will then cross-refer to this updated section from NICE's rapid guideline on managing COVID-19.

We will also refresh recommendation 1.1.21 to clarify that the action relates to any setting.

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