[1] National Institute for Health and Care Excellence, UK

[2] Hull York Medical School, University of Hull, UK
On behalf of the Clinical Guidelines Committee

Correspondence to S Boyce
sarah.boyce@nice.org.uk

Cite this as: *BMJ* 2023;383:p2204
http://dx.doi.org/10.1136/bmj.p2204
Published: 12 October 2023

GUIDELINES

Diagnosis of venous thromboembolic diseases in people with covid-19: summary of updated NICE guidance

Sarah Boyce, [1] Emma McFarlane, [1] Susan Harrison, Terry McCormack[2]

What you need to know

- The current pathway for diagnosing pulmonary embolism or deep vein thrombosis, including the use of D-dimer testing, is appropriate for people with covid-19
- Prevention of primary venous thromboembolism in people with covid-19 should not be stopped, even if deep vein thrombosis or pulmonary embolism is not confirmed
- Criteria to rule out pulmonary embolism may not be suitable in people with covid-19 because of the increased risk of venous thromboembolism in this population

In venous thromboembolism, a blood clot usually forms in the deep veins of the legs or pelvis. This is known as deep vein thrombosis, and the blood clot can dislodge from these sites, resulting in pulmonary embolism.

In 2020, the National Institute for Health and Care Excellence (NICE) first published guidance on the diagnosis and management of venous thromboembolic disease.[1] Since then, new evidence has emerged which indicates that people with covid-19 have a higher risk of developing venous thromboembolism and elevated D-dimer levels, and that this risk increased with severity of covid-19 infection. In the 2021 British Thoracic Society guidelines on venous thromboembolism in patients with covid-19, one meta-analysis of 49 studies reported an incidence of venous thromboembolism of 17% in people with covid-19, and that the incidence was higher in patients in intensive care (28%) compared with those on a medical ward (7%).[2] D-dimer, a protein fragment that can represent a by-product of blood clotting, is often elevated in severe covid-19 as a result of severe lung inflammation.[2] This can challenge the usefulness of D-dimer testing for predicting the presence of venous thromboembolism.

In addition, the 2020 guidelines recommend using the pulmonary embolism rule-out criteria (PERC) to rule out pulmonary embolism. However, a Healthcare Safety Investigation Branch report identified that some clinicians were reporting difficulty in quantifying risk of pulmonary embolism as a percentage, as required by the tool, thereby limiting its use in practice currently.[3] This article summarises the 2023 recommendations from the NICE guideline, focusing on diagnosis of venous thromboembolic disease in people with covid-19.[1] It includes updated recommendations in relation to diagnosis and initial management of suspected deep vein thrombosis and pulmonary embolism in patients with covid-19 and a refresh of the recommendation on the use of the PERC rule.

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.

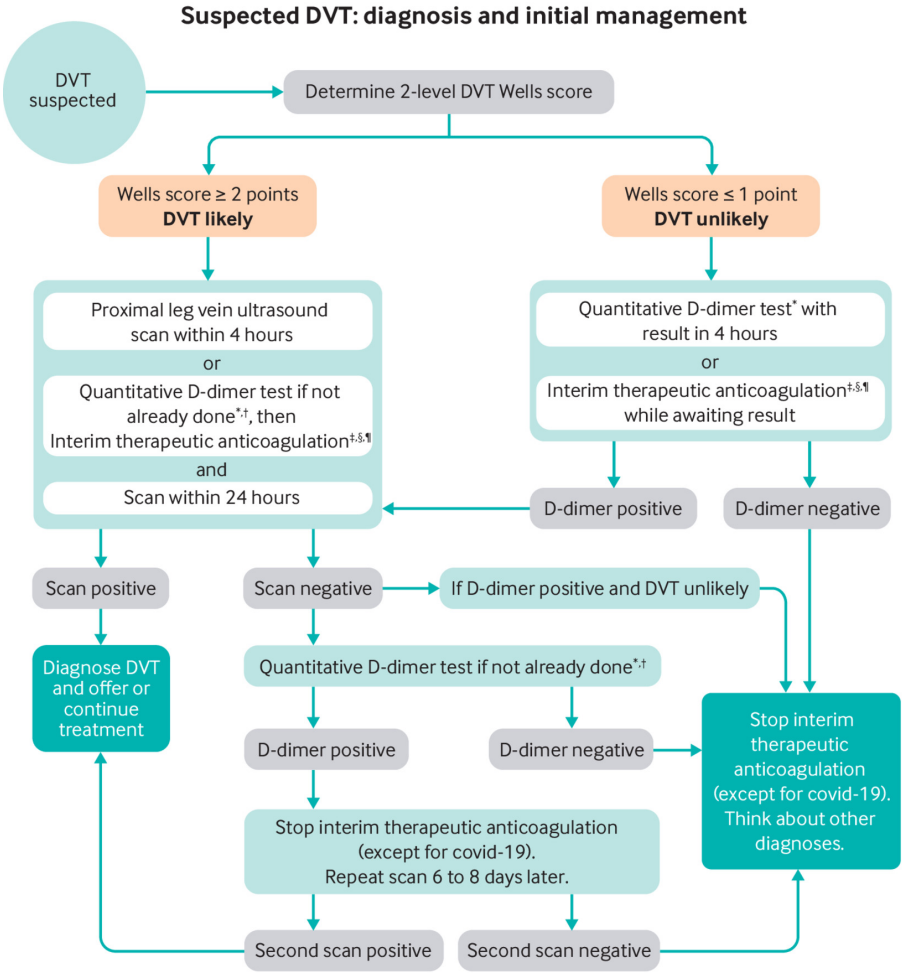
Diagnosis and initial management

Diagnosis of venous thromboembolism in people with covid-19 can be challenging because patients may present similarly, and elevated D-dimer levels can be seen in both deep vein thrombosis and pulmonary embolism. In the current NICE recommended diagnostic pathway for pulmonary embolism and deep vein thrombosis, elevated D-dimers above a specific threshold indicate the need for further imaging.[1] Limited evidence, however, has suggested that raising the D-dimer threshold for people with covid-19 would likely increase the number of missed diagnoses of venous thromboembolism.[1] Fewer cases of covid-19-related venous thromboembolism now occur, in part because most of the population has now had covid-19 or has been vaccinated, and evolution of the SARS-CoV-2 variants has led to a milder disease. Therefore, the current NICE guidance for diagnosing pulmonary embolism or deep vein thrombosis, including the use of D-dimer testing, remains appropriate for people with covid-19.[1] However, the NICE guidance for managing covid-19 recommends that people with covid-19 who are receiving prophylaxis for venous thromboembolism should continue this treatment for 14 days or until discharge.[4] Therefore, a recommendation for continuing venous thromboembolism prophylaxis for people with covid-19 where deep vein thrombosis and pulmonary embolism are ruled out was added to the diagnostic pathway, alongside the existing recommendation for not stopping anticoagulation used for long term secondary prevention.

- People with covid-19 should follow the current pathway for diagnosing deep vein thrombosis or pulmonary embolism (including a two-level Wells score), including the use of D-dimer testing (figs 1, 2). However, short term anticoagulation when used for prevention of primary venous thromboembolism in people with covid-19 should

not be stopped even if deep vein thrombosis or pulmonary embolism is not confirmed.[4]

[Based on low to very low quality evidence and the experience and opinion of the Guideline Committee]



2-level DVT Wells score

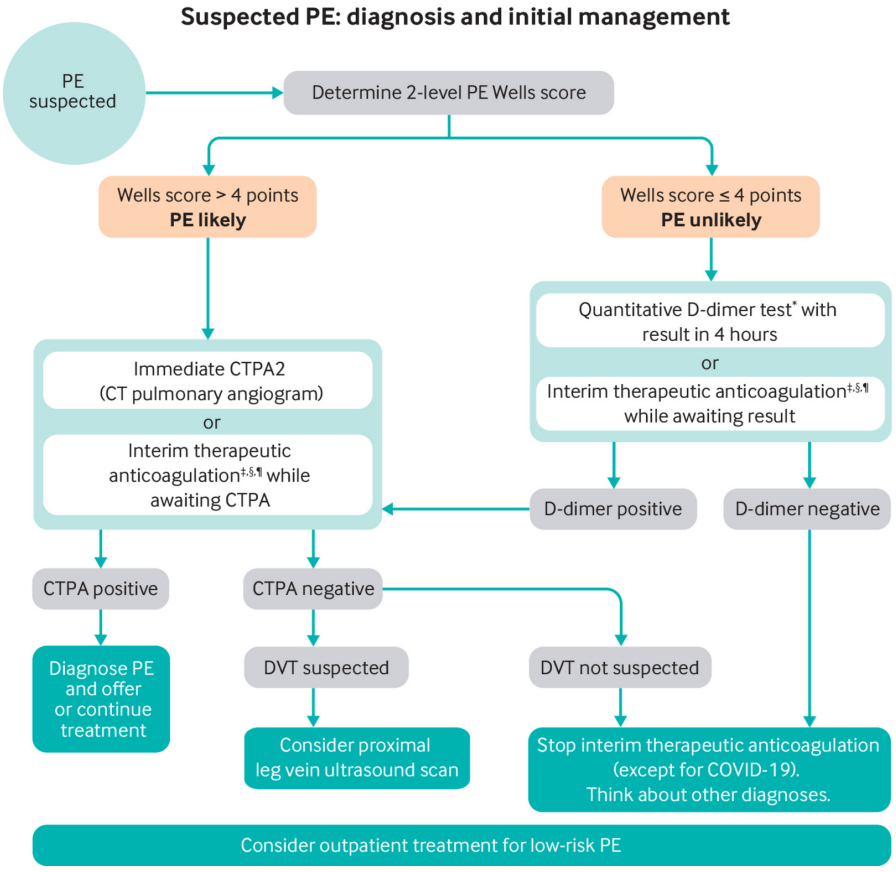
Clinical feature	Points
Active cancer (treatment ongoing within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of lower extremities	1
Recently bedridden for 3 days or more, or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness 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

DVT likely: 2 points or more
DVT unlikely: 1 point or less

Do not stop short-term anticoagulation when used for primary VTE prevention in people with covid-19

See the recommendations on VTE prophylaxis in the NICE guideline on managing covid-19

Fig 1 | Venous thromboembolism: diagnosis and anticoagulation treatment. Suspected deep vein thrombosis (DVT): diagnosis and initial management *Laboratory or point-of-care test. Consider age adjusted threshold for people over 50 †Note that only one D-dimer test is needed during diagnosis ‡Measure baseline blood count, renal, and hepatic function, prothrombin time and activated partial thromboplastin time, but start anticoagulation before results are available and review within 24 hours §If possible, choose an anticoagulant that can be continued if DVT confirmed ¶Direct acting anticoagulants and some low molecular weight heparins are off label for use in suspected DVT. Follow GMC guidance on prescribing unlicensed medicines. 2-level DVT Wells score adapted with permission from Wells et al (2003)



2-level PE Wells score

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 more than 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1

PE likely: More than 4 points
PE unlikely: 4 points or less

Do not stop short-term anticoagulation when used for primary VTE prevention in people with covid-19

See the recommendations on VTE prophylaxis in the NICE guideline on managing covid-19

Fig 2 | Venous thromboembolism: diagnosis and anticoagulation treatment. Suspected pulmonary embolism (PE): diagnosis and initial management *Laboratory or point-of-care test. Consider age adjusted threshold for people over 50 †Computed tomography (CT) pulmonary angiogram. Assess suitability of V/Q SPECT or V/Q planar scan for allergy, severe renal impairment (Creatinine clearance <30 mL/min estimated using the Cockcroft and Gault formula; see BNF) or high irradiation risk ‡Measure baseline blood count, renal and hepatic function, prothrombin time and activated partial thromboplastin time, but start anticoagulation before results are available and review within 24 hours §If possible, choose an anticoagulant that can be continued if PE is confirmed ¶Direct acting anticoagulants and some low molecular weight heparins are off label for use in suspected PE. Follow GMC guidance on prescribing unlicensed medicines. 2-level PE Wells score adapted with permission from Wells et al (2000)

Pulmonary embolism rule-out criteria (the PERC rule)

The PERC rule is a diagnostic tool used to exclude pulmonary embolism in people where clinical suspicion of pulmonary embolism is low (box 1).[5 6] However, it may not be suitable to rule out pulmonary embolism in people with covid-19 because of the increased risk of venous thromboembolism in this population, and because the tool has not been validated in this population. Taken together, the guideline committee wanted to raise awareness around the potential use and limitations of PERC in the covid-19 population.

Box 1: The pulmonary embolism rule out criteria (PERC rule)[5 6]

PERC is a rule out test for people with a low (<15%) pre-test probability of pulmonary embolism based on clinical gestalt. It is used to rule out PE (with a <2% probability) without further testing when all of the following clinical features are absent:

- Age ≥50
- Heart rate ≥100 beats/min
- Oxyhaemoglobin saturation <95%
- Haemoptysis
- Hormone use
- Prior deep vein thrombosis or pulmonary embolism
- Unilateral leg swelling
- Surgery or trauma that required hospital admission within the prior four weeks

- If clinical suspicion of pulmonary embolism is low based on the overall clinical impression (from general medical history, physical examination, and any initial investigations such as electrocardiography or chest x ray), and other diagnoses are feasible, consider using PERC to help determine whether any further investigations for pulmonary embolism are needed.
- Be aware that the PERC rule has not been validated in people with covid-19.

[Based on the experience and opinion of the guideline committee]

Implementation

The PERC rule is not widely used in current practice in the UK. The recommendation from the 2020 NICE guidelines defined low clinical suspicion of pulmonary embolism as likelihood less than 15% based on the evidence.[5 6] However, clinicians have reported difficulty in quantifying this risk as a percentage in practice. Therefore, the Guideline Committee amended the 2020 recommendation by describing that identification of low risk as based on clinical gestalt informed by general medical history, physical examination, and

initial investigations. Adding this additional detail is expected to aid implementation.

The recommendation is expected to increase the use of PERC in a subgroup of people in whom clinical suspicion of pulmonary embolism is low and for whom discharge is being considered. Increased use of PERC can be expected to reduce the need for D-dimer testing and imaging for people with none of the PERC criteria for pulmonary embolism, leading to some reductions in waiting times in primary care and emergency departments. It will also help to avoid unnecessary anticoagulation treatment. The Guideline Committee also expects that this may help with implementation of PERC outside the hospital setting.

Guidelines into practice

- How do you investigate for pulmonary embolism or deep vein thrombosis in patients with covid-19?
- Does your department recommend the use of the PERC tool to rule out pulmonary embolism in patients where clinical suspicion is low?

How patients were involved in the creation of this article

Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

Further information on the guidance

This guidance was developed in accordance with NICE guideline methodology (https://www.nice.org.uk/process/pmg20/chapter/introduction). A Guideline Committee (GC) was established by NICE, which incorporated healthcare professionals (two haematologists, two radiologists, one general practitioner, one general physician, one physician with a special interest in vascular disease, and one vascular nurse) and two lay members.

The guideline is available at https://www.nice.org.uk/guidance/ng158.

The GC identified relevant review questions and collected and appraised clinical and cost effectiveness evidence. Quality ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes or themes rather than the quality of the study. The GC agreed recommendations for clinical practice based on the available evidence or, when evidence was not found, based on their experience and opinion using informal consensus methods.

The draft of the guideline went through a rigorous reviewing process, in which stakeholder organisations were invited to comment; the GC took all comments into consideration when producing the final version of the guideline.

NICE will conduct regular reviews after publication of the guidance, to determine whether the evidence base has progressed significantly enough to alter the current guideline recommendations and require an update.

Funding: No authors received specific funding to write this summary. This guidance was funded by NICE.

Contributorship and the guarantor: All authors contributed to the development of the guideline, the planning, drafting, and revision of this summary, approved the final version, and take responsibility for its accuracy. SB and EMF are guarantors.

The members of the Guideline Committee were (shown alphabetically): Anne Byrne, Colin Church, Deepa Gopalan, Susan Harrison, Dan Horner, Beverley Hunt, Nigel Langford, Graham Lloyd-Jones, Terry McCormack, Lara Roberts, Huw Roswell, Astrid Ullrich-Boereboom.

Competing interests: The declaration of interests is based on NICE's policy on conflicts of interests (https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf). The guideline authors' full statements can be viewed at Project documents | Venous thromboembolic diseases: diagnosis, management and thrombophilia testing | Guidance | NICE

Provenance and peer review: commissioned; not externally peer reviewed.

1 National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (NICE guideline NG158). 2023 https://www.nice.org.uk/guidance/ng158
2 British Thoracic Society. BTS guidance on venous thromboembolic disease in patients with COVID-19. 2021. https://www.brit-thoracic.org.uk/quality-improvement/covid-19/covid-19-information-for-the-respiratory-community
3 Health Safety Investigation Branch. Clinical decision making: diagnosis and treatment of pulmonary embolism in emergency departments. 2022 https://www.hsib.org.uk/investigations-and-reports/timely-recognition-and-treatment-of-suspected-pulmonary-embolism/clinical-decision-making-diagnosis-and-treatment-of-pulmonary-embolism-in-emergency-departments
4 National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19 (NICE Guideline NG191). 2023. https://www.nice.org.uk/guidance/ng191
5 Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost* 2004;2:-55. doi: 10.1111/j.1538-7836.2004.00790.x pmid: 15304025
6 Kline JA, Courtney DM, Kabrhel C, etal. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6:-80.