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PRACTICE

GUIDELINES

Venous thromboembolism in adults: summary of updated NICE guidance on diagnosis, management, and thrombophilia testing

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What's new in this guidance?

- If clinical suspicion of pulmonary embolism is low, consider using the pulmonary embolism rule-out criteria (PERC) to help determine whether any further investigations for pulmonary embolism are needed
- In people over 50, consider using an age-adjusted D-dimer
- Consider outpatient treatment for low risk patients with pulmonary embolism
- Offer apixaban or rivaroxaban as interim treatment for suspected venous thromboembolism (VTE) or substantive treatment for confirmed VTE unless special considerations apply. If neither is suitable (and special considerations do not apply) then offer low molecular weight heparin (LMWH) followed by dabigatran or edoxaban, or LMWH with a vitamin K antagonist
- Consider using direct oral anticoagulants (DOACs) for people with active cancer
- Do not offer further investigations for cancer to people with unprovoked deep vein thrombosis or pulmonary embolism unless they have relevant clinical symptoms or signs.

Venous thromboembolic (VTE) disease is a continuing global health burden with serious mortality, morbidity, and health economic consequences.[1] The one year case fatality rate of definite or probable VTE has been estimated at 23%.[2] Approximately 1 to 2 of every 1000 adults in the worldwide population will be diagnosed with VTE annually, with higher incidence rates in those over 70 (2 to 7/1000) and over 80 (3 to 12/1000).[1 3]

On 26 March 2020, the National Institute for Health and Care Excellence (NICE) published NG158,[4] an updated version of its guideline on the diagnosis and management of VTE (original version 2012, minor update 2015: National Institute for Health and Care Excellence 2020 venous thromboembolism in adults: diagnosis, management and thrombophilia testing. https://www.nice.org.uk/guidance/ng158). This article summarises the new key recommendations, with a focus on those most relevant to primary care and secondary generalist physicians, and includes existing 2012 or 2015 recommendations that have not been updated where they are relevant to the topic discussed.

Why did the guidance need updating?

The key changes include offering direct oral anticoagulants (DOACs) as first line treatment to most people with VTE (including in patients with active cancer), considering the use of outpatient treatment for people with suspected or confirmed pulmonary embolism and low risk for complications, and not routinely carrying out intensive cancer screening investigations for people with unprovoked VTE.

NICE recommendations are based on systematic reviews of the best available evidence and explicit considerations of cost effectiveness. Evidence levels are given in italics in square brackets.

Recommendations

Diagnosing VTE

The committee looked at new evidence on clinical exclusion of VTE, which included the recent PROPER trial.[5] This supported the use of the pulmonary embolism rule-out criteria (PERC) (box 1) in clinical practice because it has high sensitivity, meaning that there would be few false negative results if the test were used in a population with low prevalence, and it could

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be used to reduce unnecessary tests if used as part of a global patient assessment.

Box 1: Pulmonary embolism rule-out criteria (PERC)

If clinical suspicion of pulmonary embolism is low, consider using the pulmonary embolism rule-out criteria (PERC) to help determine whether any further investigations for pulmonary embolism are needed. In patients at low risk of pulmonary embolism, as determined through history, careful examination, and application of physician gestalt, you might consider no further investigation for pulmonary embolism if the following are all absent:

- Age ≥ 50
- Heart rate ≥ 100
- Saturated oxygen on air ≤ 94%
- Previous pulmonary embolism or deep vein thrombosis
- Surgery or trauma requiring general anaesthetic within four weeks
- Haemoptysis
- Use of oestrogen
- Unilateral swollen leg.

A negative PERC reduces the post-test probability to <2%, with validation studies reporting a diagnosis of pulmonary embolism in 1.0% (95% confidence interval 0.6 to 1.6) of patients who are deemed low suspicion by gestalt and are PERC negative (all criteria absent).[6]

• If clinical suspicion of pulmonary embolism is low (the clinician estimates the likelihood of pulmonary embolism to be less than 15% based on the overall clinical impression and other diagnoses are feasible) consider using PERC to help determine whether any further investigations for pulmonary embolism are needed. *[Based on very low to moderate quality evidence from randomised controlled trials, diagnostic accuracy studies and an economic model]*

The committee accepted that the evidence for PERC has limitations in terms of quality and was obtained in emergency departments, but could see no reason why its use should be limited to this setting or why the diagnostic accuracy of PERC would differ in other settings.

The existing recommendations on the diagnosis of VTE were not reviewed for this update, although the wording was refreshed and new visual summaries of the pathways added. The diagnosis of VTE remains primarily based on pre-test probability assessment using the modified deep vein thrombosis and pulmonary embolism Wells Scores.[7] These scores guide further definitive investigation using blood D-dimer assay, compression ultrasonography and/or lung imaging via computed tomography pulmonary angiogram or ventilation/perfusion scan.

Several new recommendations have been added to the guideline regarding the use and interpretation of D-dimer assays. The committee agreed that it is important to receive the results of D-dimer testing rapidly (within four hours) to help inform diagnosis of VTE; however, laboratory facilities may not be available on site to facilitate this. The committee therefore recommended point-of-care testing when certain conditions are met.

- When offering D-dimer testing for suspected deep vein thrombosis or pulmonary embolism, consider a point-of-care test if laboratory facilities are not immediately available. *[Based on very low to high quality evidence from prospective diagnostic accuracy studies]*
- If using a point-of-care D-dimer test, choose a fully quantitative test. *[Based on very low to high quality evidence from prospective diagnostic accuracy studies]*

Quantitative point-of-care tests are quicker and as accurate as laboratory tests and their use may aid faster diagnosis and avoid further investigation or therapeutic intervention. However, as they are more expensive than laboratory testing, the latter should be used where it is immediately available.

For people over 50, the guideline now supports the use of age-adjusted test thresholds when interpreting D-dimer tests. This will reduce the number of people who receive false positive results, thereby avoiding unnecessary imaging and anxiety.

- When using a point-of-care or laboratory D-dimer test, consider an age adjusted D-dimer test threshold for people over 50. *[Based on very low to moderate quality evidence from prospective and retrospective diagnostic test accuracy studies]*

The evidence reviewed by the committee suggests that using an age adjusted test threshold does not decrease the sensitivity of the test. Prospective management studies such as the ADJUST-PE trial also confirm the safety and clinical effectiveness of this strategy.[8]

Interim treatment and outpatient care

When diagnosis cannot be established within four hours (for example, while awaiting imaging results), the guideline recommends using an interim anticoagulation therapy that can be continued if VTE is confirmed, if possible. Although no studies of interim treatment were identified, pragmatism and convenience support treatment as for established diagnosis. The committee recognised that this may not always be possible, for example, if the treatment options for suspected VTE are limited by local policies or availability. This guidance now supports DOAC therapy as an interim treatment in most patients, unless contraindicated.

New recommendations clarify the need for baseline blood tests when using interim therapeutic anticoagulation, but highlight that awaiting these results should not delay initiation of treatment. Blood tests should be reviewed and acted upon, if necessary, within 24 hours.

Until recently, outpatient care has mainly been reserved for investigation and management of deep vein thrombosis. For people with both suspected and confirmed pulmonary embolism, new evidence supports ambulatory care for those at low risk of complication, assessed by validated tools.[9-11]

- Consider outpatient treatment for suspected or confirmed low-risk pulmonary embolism, using a validated risk stratification tool to determine the suitability of outpatient treatment. *[Based on low to high quality evidence from randomised controlled trials with the experience and opinion of the GC]*

The committee did not review the accuracy of risk stratification tools and so was unable to recommend any in particular. The randomised controlled trials included in the evidence review used the Pulmonary Embolism Severity Index (PESI) or the Hestia Criteria.[9 11]

Patients are likely to benefit from being able to stay at home for treatment, rather than being admitted to hospital unnecessarily, and no evidence suggests that this approach increases risks. It is important that rigorous monitoring and follow-up arrangements are put in place and that people know why and who to call at the treatment centre, and out of service hours, if necessary. These recommendations are in agreement with other guidelines.[12 13]

Treating confirmed VTE

Where VTE is confirmed, patients should continue anticoagulation already prescribed for suspected VTE. Switching treatments unnecessarily has associated safety issues and inconvenience; and should be avoided where feasible. Baseline blood tests should be carried out if not already done, but

anticoagulation should not await the results because the risk of not treating VTE is greater than the risk associated with giving a single or couple of doses of anticoagulant to people who do not have VTE. These blood tests should be reviewed, and acted upon, within 24 hours.

This guidance now recommends anticoagulant treatment with apixaban or rivaroxaban in most cases (see box 2 for patients who need special consideration because other recommendations apply).

Box 2: Patients who need special consideration before prescribing an anticoagulant

- Deep vein thrombosis or pulmonary embolism in people at extremes of body weight (<50 kg or >120 kg)
- Pulmonary embolism with haemodynamic instability
- Deep vein thrombosis or pulmonary embolism with renal impairment or established renal failure (estimated creatine clearance between 15 ml/min and 50 ml/min)
- Deep vein thrombosis or pulmonary embolism with active cancer (take into account the tumour site, interactions with other drugs including those used to treat cancer, and the person's bleeding risk)
- Deep vein thrombosis or pulmonary embolism with triple positive antiphospholipid syndrome.

- Offer either apixaban or rivaroxaban to people with confirmed proximal deep vein thrombosis or pulmonary embolism. If neither apixaban nor rivaroxaban is suitable, offer

  o low molecular weight heparin (LMWH) for at least five days followed by dabigatran or edoxaban or

  o LMWH concurrently with a vitamin K antagonist (VKA) for at least five days, or until the international normalised ratio (INR) is at least 2.0 in two consecutive readings, followed by a VKA on its own. *[Based on very low to high quality evidence from randomised controlled trials and health economic modelling]*

The committee made these new recommendations for several reasons. The clinical evidence showed that apixaban and rivaroxaban were effective at reducing the risk of VTE recurrence and carried a lower risk of major bleeding compared with other treatment options. The health economics analysis also showed that apixaban, followed closely by rivaroxaban, was the most cost effective option. However, the committee noted that there were differences between the inclusion criteria of the apixaban trials and the other DOACs and that this led to a degree of uncertainty about the relative effectiveness of apixaban compared with the other treatment options. To account for this uncertainty, the committee recommended both apixaban and rivaroxaban as first line options because it was satisfied that the evidence showed that either apixaban or rivaroxaban was the most cost effective option. Lastly, apixaban and rivaroxaban can be used as single agent strategies without LMWH lead-in; as such, these agents represent the most cost effective and convenient strategies, for suitable patients.

Separate recommendations are made for anticoagulant treatment in people who weigh <50 kg, >120 kg, or those with renal impairment. No DOACs are recommended at creatine clearance <15 ml/min and dabigatran has an even more limited role in kidney dysfunction because it is only recommended for use if creatine clearance is 30 ml/min or above. Note the cautions and requirements for dose adjustment and monitoring in the medicine's summary of product characteristics, and follow locally agreed protocols or advice from a specialist or multidisciplinary team.

Treating VTE in people with active cancer

The guideline now supports using DOAC therapy for people with active cancer for three to six months, when the treatment should be reviewed.

- When choosing anticoagulation treatment for people with active cancer and confirmed proximal deep vein thrombosis or pulmonary embolism, take into account the tumour site, interactions with other drugs (including those used to treat cancer), and the person's bleeding risk. *[Based on the experience and opinion of the GC]*

• Consider a DOAC (box 3) for people with active cancer and confirmed proximal deep vein thrombosis or pulmonary embolism. *[Based on very low to high quality evidence from randomised controlled trials and health economic modelling]*

Box 3: DOACs and licensing

At the time of publication of the NICE guideline (March 2020) most anticoagulants do not have a marketing authorisation for the treatment of deep vein thrombosis or pulmonary embolism in people with active cancer. The prescriber should consult the medicine's summary of product characteristics for details, and follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's prescribing guidance: prescribing unlicensed medicines for further information.

Limited evidence from cancer specific trials shows that rivaroxaban and edoxaban are similarly effective to LMWH in treating patients with active cancer, although the evidence about outcomes is currently limited to six months' duration. The evidence supporting the use of apixaban and dabigatran came from subgroup analyses of people with cancer from the AMPLIFY and RECOVER randomised controlled trials. Taken overall, the evidence was not sufficient to enable the committee to differentiate between the DOACs. This might change in future updates of the guideline as new data supporting the use of apixaban in people with cancer and VTE is incorporated into future guideline reviews.[14 15] The results of the ADAM-VTE and CARAVAGGIO trials support the recommendations within this guideline iteration, but were published after the reviews were completed. Although the risk of gastrointestinal and bladder haemorrhage is higher with DOACs, there was no conclusive evidence to specify avoiding DOACs with particular tumour types.

LMWH has traditionally been used in people with active cancer; however, the health economics model did not support the use of LMWH alone in most cases because of its very high cost relative to DOAC therapy. Therefore, where suitable, a DOAC should be used in place of LMWH. However, this decision needs to be made on a case-by-case basis to ensure that the individual is given the safest and most effective treatment for their individual clinical needs, while supporting the NHS to make the best use of its limited resources.

- If a DOAC is unsuitable, consider LMWH alone or LMWH concurrently with a VKA[2] for at least five days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own. *[Based on very low to high quality evidence from randomised controlled trials and health economic modelling]*

Antiphospholipid syndrome

Based on results from a randomised controlled trial, an alert from the Medicines and Healthcare products Regulatory Agency (MHRA) states that DOACs are not recommended in patients with antiphospholipid syndrome, particularly those who test

positive for all three antiphospholipid tests, citing high risks of thrombosis recurrence.[16 17]

- Offer people with confirmed proximal deep vein thrombosis or pulmonary embolism and an established diagnosis of triple positive antiphospholipid syndrome LMWH concurrently with a VKA for at least five days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own. *[Based on the MHRA alert and the experience and opinion of the GC]*

The committee was aware of the British Society for Haematology guideline on the investigation and management of antiphospholipid syndrome, which provides more guidance on this topic.[18]

Inferior vena caval (IVC) filters

Use of IVC filters is a highly specialist area, largely based on very low quality evidence. The committee therefore made decisions based on consensus to limit use of IVC filters to certain circumstances or clinical studies, which could be used to provide future stronger evidence of benefit.

- Do not offer an IVC filter to people with proximal deep vein thrombosis or pulmonary embolism unless
  - o it is part of a prospective clinical study or
  - o anticoagulation is contraindicated or a pulmonary embolism has occurred during anticoagulation treatment (see recommendations 1.7.2 and 1.7.3). *[Based on very low to high quality evidence from randomised controlled trials and retrospective cohort studies and the experience and opinion of the GC]*
- Before fitting an IVC filter, ensure that there is a strategy in place for it to be removed at the earliest possible opportunity. Document the strategy and review it if the clinical situation changes. *[Based on the experience and opinion of the GC]*

Follow-up

Recent evidence does not support further screening investigations for cancer in people with unprovoked VTE, unless the person has relevant symptoms or signs.

Although there is a known association between cancer and VTE, no evidence supports a wide variety of mandatory tests, which can be harmful and are likely to cause unnecessary anxiety, over and above good clinical history taking and examination.

- Do not offer further investigations for cancer to people with unprovoked deep vein thrombosis or pulmonary embolism unless they have relevant clinical symptoms or signs (for further information see the NICE guideline on suspected cancer). *[Based on very low to moderate quality evidence from randomised controlled trials]*
- After three months of anticoagulation (three to six months for people with active cancer) review treatment options.
- Assess and discuss the benefits and risks of continuing, stopping, or changing the anticoagulant with people who have had anticoagulation treatment for three months (three to six months for people with active cancer) after a proximal deep vein thrombosis or pulmonary embolism. *[Based on the experience and opinion of the GC]*
- Consider stopping anticoagulation treatment at this point following a provoked deep vein thrombosis or pulmonary embolism if the provoking factor is no longer present and the clinical course has been uncomplicated. If the VTE was unprovoked, consider continuing anticoagulation treatment, taking bleeding risk, risk of recurrence, and patient preference into account.
- Explain to people with unprovoked deep vein thrombosis or pulmonary embolism and a low bleeding risk that the benefits of continuing anticoagulation treatment are likely to outweigh the risks. *[Based on the experience and opinion of the GC]*
- For people who do not have renal impairment, active cancer, established triple positive antiphospholipid syndrome, or extreme body weight (less than 50 kg or more than 120 kg)
  - o offer continued treatment with the current anticoagulant if it is well tolerated or
  - o if the current treatment is not well tolerated, or the clinical situation or person's preferences have changed, consider switching to apixaban if the current treatment is a DOAC other than apixaban. *[Based on very low to high quality evidence from randomised controlled trials and health economic modelling with the experience and opinion of the GC].*

The recommendation to consider switching if the current treatment is not well tolerated or the clinical situation or person's preferences have changed was heavily influenced by the human and financial costs of major bleeding in the economic model. The committee had reservations about the level of uncertainty concerning these findings, based on the strict inclusion criteria in apixaban studies (limiting the chance of major bleeding) and the low incidence of major bleeding in any of the studies. Using their experience and expertise, they agreed that it was preferable for an individual to remain on an already established treatment if it continued to suit them, and included the option to switch to apixaban (the most cost effective option) otherwise for people taking a DOAC already.

For people where the risk/benefit balance of continuing anticoagulation therapy is less clear, current prediction tools were not recommended for use in isolation because of the limited prognostic accuracy of the tools under most circumstances.

- Do not rely solely on predictive risk tools to assess the need for long term anticoagulation treatment. *[Based on very low to high quality evidence from a prospective management study and retrospective cohort studies]*

The HAS-BLED bleeding risk score has been validated in VTE patients, but only performs well at extremes of the scale. As such, the evidence appears to support stopping anticoagulation if the HAS-BLED score is ≥4 and cannot be modified, but it is expected that this tool will be used only as a part of the discussion about stopping anticoagulation treatment, including patient values and preferences. The committee made two research recommendations for this topic: the first is aimed at developing a better tool to predict the risk of VTE recurrence and major bleeding, and the second aims to test this tool to determine if its use is an improvement over clinician judgement alone.

- For people who decline continued anticoagulation treatment, consider aspirin (75 mg or 150 mg). *[Based on very low to moderate evidence from randomised controlled trials and health economic modelling]*

This recommendation was made because of recent and ongoing evidence in people with previous VTE showing the superiority of aspirin to placebo, in terms of risk reduction.[19 20] Ideally, people would take an anticoagulant rather than making this choice, but some people with VTE who are at risk of recurrence decide against continuing anticoagulation.

Guidelines into practice

- At diagnosis, do you routinely give patients detailed written information with advice about whom to call with concerns, and a treatment-specific alert card to carry at all times?
- Do you offer all patients an assessment after three months of VTE treatment?
- Do you routinely reassess the anticoagulant used in people with active cancer?
- What decision aids do you use to inform patients properly about long-term recurrence risks, and examine their values to ensure shared decision making?

Further information on the guidance

Methods

This guidance was developed by NICE in accordance with NICE guideline development methods (https://www.nice.org.uk/media/default/about/what-we-do/ourprogrammes/developing-nice-guidelines-the-manual.pdf).

A Guideline Committee was established by NICE, which incorporated healthcare and allied healthcare professionals (one vascular specialist nurse, two radiologists, two general practitioners, one thoracic physician, one emergency medicine and intensive care specialist, one haematologist, one general physician with a specialist interest in VTE, one senior pharmacist, two lay members, and a chair).

Review questions were developed based on key clinical areas of the scope. Systematic literature searches, critical appraisals, evidence reviews, and evaluations of cost effectiveness, where appropriate, were completed for all review questions included within the update. Quality ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org/) or modified GRADE methodology in the case of the diagnostic and prognostic review questions. They also examined the cost effectiveness of interventions where possible, including (in the current update) the use of a novel economic model that was generated for the anticoagulation treatment review and cost-consequence models for the PERC, and point-of-care D-dimer reviews.

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

The evidence reviewed in the 2015 and 2020 updates is available as separate review documents, while the evidence for the sections of the guideline that were not updated is contained in the 2012 full guideline document. The guideline itself contains the recommendations with a new section on the rationale for the 2020 recommendations. The documents are all available at https://www.nice.org.uk/guidance/ng158

Future research

The guideline committee prioritised the following research recommendations:

- What is the short and long term clinical and cost effectiveness of inferior vena caval filters in people with VTE?
- What is the clinical and cost effectiveness of DOACs compared with each other, with LMWH plus a VKA, with LMWH alone, with placebo, and with aspirin for the initial and long term treatment of deep vein thrombosis or pulmonary embolism based on individual patient data from existing trials?
- What is the prognostic accuracy of a tool to predict both VTE recurrence and major bleeding compared with clinical judgement in people with unprovoked proximal deep vein thrombosis or pulmonary embolism?
- Does lower dose thrombolysis reduce the risk of major bleeding and improve outcomes for people with acute pulmonary embolism and right ventricular dysfunction?
- 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 vein thrombosis?

How patients were involved in the creation of this article

Two lay guideline committee members contributed to the formulation of the recommendations, and patient organisations took part in the stakeholder consultation.

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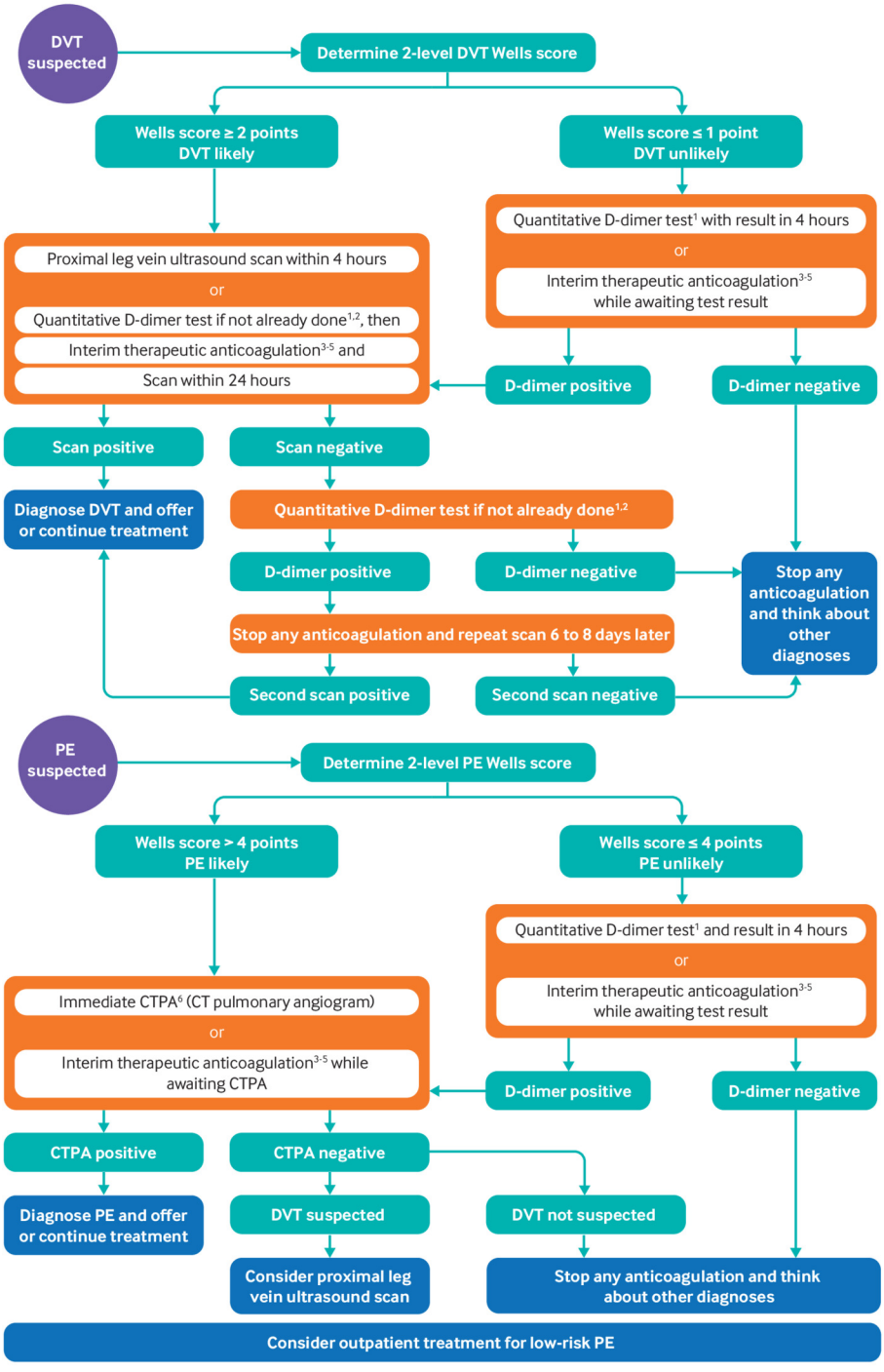
Figure

This is the NICE summary of the recommendations on diagnosis and management from the guideline on venous thromboembolism diseases. See the original guideline at www.nice.org.uk/guidance/NG158



2-level DVT Wells score*

Clinical feature	
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

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

* Adapted from Ref 7, bmj.com

[1] Laboratory or point-of-care test. Consider age-adjusted threshold for people over 50
[2] Note that only one D-dimer test is needed during diagnosis
[3] Measure baseline blood count, renal and hepatic function, PT and APTT but start anticoagulation before results available and review within 24 hours
[4] If possible, choose an anticoagulant that can be continued if DVT or PE confirmed
[5] Direct-acting anticoagulants and some LMWHs are off label for use in suspected DVT. Follow GMC guidance on prescribing unlicensed medicines
[6] CT pulmonary angiogram. Assess suitability of V/A SPECT or V/Q planar scan for allergy, severe renal impairment (CrCl <30 ml/min estimated using the Cockcroft and Gault formula; see the BNF) or high irradiation risk

Adapted from NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (NICE guideline NG158). https://www.nice.org.uk/guidance/ng158