

What the busy GP needs to know about VTE management and the new NICE guidance

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Summary points

- This article summarises the 2020 National Institute for Health and Care Excellence (NICE) venous thromboembolism (VTE) guidelines, which are also covered in [RCGP Essential Knowledge Updates e-learning](#). We focus on rapid detection and treatment, changes in recommendations around anticoagulation and implications for primary care practice.¹
- Direct oral anticoagulants are now the mainstay of treatment for both interim and long-term anticoagulation in people with VTE and can also now be considered in people with active cancer.
- The guideline highlights the need for a treatment decision within four hours for all people with suspected VTE.
- Investigation into a possible diagnosis of cancer in people with VTE is no longer recommended unless there are other symptoms suggestive of malignancy.

What clinical features are particularly important in diagnosis?

Individual signs and symptoms have a low positive predictive value (PPV) for VTE, making the clinical diagnosis difficult. For example, one primary care study found 77.8% of patients with a PE were breathless at time of assessment and 59.8% had chest pain, but only 29.5% were tachycardic and 28% had calf pain.² The PPV of unilateral leg swelling ≥ 2 cm is just 27% for DVT.³ Reassuringly, the absence of any clinical signs suggestive of DVT in low-risk patients has a negative predictive value of 97%.³

PERC scores

To help exclude a PE on clinical grounds, NICE now recommend using the PERC rule (Pulmonary Embolism Rule-Out Criteria) among selected low-risk patients (Table 2).⁴ A patient must score zero to exclude a PE. One external validation study including over 8,000 patients found that a PERC score of 0 had a false negative rate of just 1.0% (95%CI 0.6 to 1.6%) in low-risk patients.⁴ It is important to note that the PERC score was developed in Emergency Departments and is yet to be externally validated among community cohorts, where patients might be expected to present with less severe symptoms. Despite this, PERC may help primary care clinicians identify which patients to investigate for PE. It is limited to younger people without risk factors for VTE where the prevalence of PE is extremely low.

Deciding on further investigation in primary care

Where a clinician suspects a DVT or PE, they should use the Well's score to determine which subsequent investigation is needed. The Well's score alone is not intended to be a VTE rule-out test. Where a Well's score suggests VTE is 'likely', urgent imaging should be arranged via secondary care with either doppler ultrasound for DVT or CT pulmonary angiogram for PE. A D-Dimer should still be collected, as people with a high Well's score and positive D-Dimer but a negative initial imaging result should have a repeat scan after a one-week interval to help exclude false negative results.

All patients with a suspected VTE and a low-risk Well's score (≤ 4 for PE or ≤ 1 for DVT) should have a D-Dimer checked. In primary care, 5% of people with a suspected DVT but Well's score ≤ 1 will still have a proximal DVT.⁵ A negative D-Dimer and low risk Well's score in combination have 99% sensitivity for excluding PE or DVT.⁵ For most primary care clinicians, this means patients with a suspected DVT or PE would be referred urgently to secondary care for further assessment, depending on the agreed local pathway. Importantly, for all patients, a treatment decision should be made within four hours of a patient being assessed, even when the Well's score suggests VTE is 'unlikely'.

Age-adjusted D-Dimer thresholds in people aged ≥ 50 years are now recommended, to reflect the fact that minor D-Dimer elevations are common in older populations and rarely significant. Laboratory D-Dimer testing remains the gold standard, but if this is unavailable or unable to deliver a result within four hours, point-of-care (POC) D-Dimer testing may be helpful. The sensitivity and specificity of POC D-Dimer for VTE is 0.88 (95%CI 0.83 to 0.92) and 0.70 (95%CI 0.62 to 0.77) respectively.⁶ POC testing is likely to incur additional costs for practices, particularly up front e.g. when purchasing analyser equipment and test kit consumables. However, a NICE cost consequence analysis found that quantitative POC testing was still associated with cost savings compared to laboratory testing due to reductions in hospital referrals and interim treatment, particularly where a delay in receiving a laboratory result might be expected.

If a patient has a suspected VTE and it is not possible to establish the diagnosis within four hours, primary care clinicians should start interim anticoagulation with a direct oral anticoagulant (DOAC) immediately. This may be relevant if general practitioners use D-Dimer testing to exclude DVT. Baseline blood tests such as renal function should be collected but waiting for the results should not delay treatment.

VTE treatment

Apixaban or rivaroxaban are now the recommended first line treatment for most patients with suspected or confirmed VTE. This change is informed by randomised trials, which confirmed the DOACs are non-inferior to conventional therapy with low-molecular heparin followed by warfarin (hazard ratio for death or recurrent VTE 1.10, 95% CI: 0.65 to 1.84) and have a better safety profile (relative risk of major bleeding 0.31, 95%CI 0.17 to 0.55).^{7 8}

NICE also now supports the use of DOACs in most people with active cancer, based on subgroup analyses from the AMPLIFY and RECOVER studies, which reported reassuring safety data.^{7 8} Of note, most DOACs do not yet have marketing authorisation for VTE treatment in this group.

Follow-up

It is important to consider whether a confirmed VTE was ‘provoked’ by a secondary cause via close history and examination. One important change is that NICE no longer suggest people with unprovoked VTE should be investigated for cancer, as this is felt to have a low yield and risks causing high levels of patient worry. Cancers associated with a higher risk of DVT include brain, ovary, pancreas, colon, stomach, lung and kidney.

Unprovoked VTE typically needs three months of anticoagulation and provoked VTE six months or longer. Some patients who have a recurrent or provoked VTE will need lifelong anticoagulation, such as people with a long-term malignancy or a clotting disorder. A Haematology outpatient appointment is usually recommended to determine duration of treatment. Thrombophilia testing may be arranged for people who have had an unprovoked VTE, where there is a close family history of the disease or in people with recurrent VTE who will be treated with a DOAC.

Conclusion

The new NICE guideline emphasises the importance of a treatment decision within four hours of assessing a patient. For people with suspected VTE, a Well’s score alone cannot be used to exclude the diagnosis and so urgent referral to secondary care for further testing should be considered. DOACs such as apixaban and rivaroxaban are now the mainstay of anticoagulation treatment.

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Conflicts of Interest

TR is Associate Editor for the BJGP. NJ is a writer for RCGP Essential Knowledge Updates (EKU) e-learning and wrote the EKU 2021.1 module on Venous Thromboembolic disease.

TR is clinical lead for the EKU programme.

References

1. National Institute for Health and Care Excellence. Venous Thromboembolic disease: diagnosis, management and thrombophilia testing. NICE Guideline 158. 2020
2. Walen S, Damoiseaux RA, Uil SM, et al. Diagnostic delay of pulmonary embolism in primary and secondary care: a retrospective cohort study. *Br J Gen Pract* 2016;66(647):e444-50. doi: 10.3399/bjgp16X685201 [published Online First: 2016/04/27]
3. Criado E, Burnham CB. Predictive value of clinical criteria for the diagnosis of deep vein thrombosis. *Surgery* 1997;122(3):578-83. doi: 10.1016/s0039-6060(97)90131-8 [published Online First: 1997/10/06]
4. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6(5):772-80. doi: 10.1111/j.1538-7836.2008.02944.x [published Online First: 2008/03/06]
5. Geersing GJ, Zuithoff NP, Kearon C, et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. *BMJ* 2014;348:g1340. doi: 10.1136/bmj.g1340 [published Online First: 2014/03/13]
6. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ* 2009;339:b2990. doi: 10.1136/bmj.b2990 [published Online First: 2009/08/18]
7. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369(9):799-808. doi: 10.1056/NEJMoa1302507 [published Online First: 2013/07/03]
8. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361(24):2342-52. doi: 10.1056/NEJMoa0906598 [published Online First: 2009/12/08]