

Practical guide to management after an acute pulmonary embolism

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ABSTRACT

Follow-up after acute pulmonary embolism (PE) is important to assess recovery, consider the need for on-going anticoagulation and identify chronic thromboembolic pulmonary hypertension (CTEPH), a rare but serious complication of PE. 16 dilemmas in the follow-up of acute PE were identified by a steering committee of four pulmonologists and a haematologist with interest in PE and/or CTEPH. Current literature was reviewed and a practical approach suggested based on expert consensus. Dilemmas discussed included: (1) how to manage a breathless patient; (2) what to do if CTEPH is suspected; (3) the difference between CTEPH and post-PE syndrome, (4) testing for thrombophilia, (5) when to investigate for cancer, (6) anticoagulation duration and dose, (7) approaches to discussions and decision-making with respect to anticoagulation, (8) use of aspirin and whether antiplatelet therapy should be stopped during anticoagulation and (9) advice for patients on discharge from hospital at 3 months and information for first-degree relatives. Given the occurrence of complications that may require assessment, follow-up of patients post-PE should be systematic and consider the individual needs of the patient.

INTRODUCTION

In the UK, over 69 064 hospital episodes of pulmonary embolism (PE) were reported between 2021 and 2022, resulting in 36 757 admissions.^{1 2} Up to 50% of patients with PE will have residual symptoms,³ with chronic thromboembolic pulmonary hypertension (CTEPH), a serious but uncommon complication, occurring in approximately 2% of patients.^{4 5} The British Thoracic Society (BTS) guideline recommends that all hospitals should have local protocols and pathways in place for follow-up of all patients with PE and follow-up should be performed by clinicians with a special interest in venous thromboembolism (VTE).⁶ The BTS audit of outpatient PE management found that structured follow-up of patients presenting with PE is suboptimal: 87% of UK centres performed follow-up at 3 months, with this occurring in a dedicated PE clinic in 36% of the centres.⁷ In addition, a survey of UK physicians found that

only 46% of respondents reported that ≥75% of patients were offered a 3-month to 6-month follow-up,⁸ and a retrospective, single-centre UK study found that 32% of intermediate-high risk and 37% of patients with intermediate-low risk PE were not followed up.⁹ To address the gap in practical advice for follow-up of PE, a steering committee of four pulmonologists and a haematologist identified sixteen key questions that they are often asked by physicians assessing patients following an acute PE. Authors conducted a non-systematic literature search for each question and drafted a suggested approach for coauthor review and round-table discussion to achieve consensus.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Diagnostic scenarios

What should I do if my patient is breathless following at least 3 months of anticoagulation for an acute PE?

Breathlessness is present in up to half of all patients following an acute PE^{10 11} and is most frequently due to pre-existing cardiac and/or respiratory disease, deconditioning and/or anxiety.^{10 12–15} The assessment of breathlessness should include: (1) an assessment of severity and recovery from the index PE; (2) the temporal relationship to the index PE; (3) features associated with lung disease, such as frequent coughing, wheezing or lung infections and/or cardiac disease such as chest pain, ankle swelling and orthopnoea; (4) identification of known comorbidities and (5) an assessment for risk factors for CTEPH.^{5 16 17} Risk factors for CTEPH include history of/or recurrent VTE, the absence of major transient risk factors for VTE, large clot burden,¹⁸ echocardiographic features of pulmonary hypertension (PH) and/or right ventricle (RV) dysfunction and CT imaging features

suggestive of pre-existing CTEPH on the initial diagnostic scan (dilated bronchial arteries, webs, attenuated vessels, eccentric clot, mosaic perfusion and CT features of PH).^{5 17 19} In the event that no treatable comorbidities are identified, cardiopulmonary rehabilitation may be considered.²⁰

What should I do if I suspect CTEPH?

CTEPH is an uncommon, but serious, complication of PE. Two recent, large prospective multicentre studies, the FOCUS (Follow-up after aCute pulmonary emboliSm) study⁴ and the OSIRIS (feasibility of a screening algorithm for CTEPH) study,²¹ noted a cumulative 2-year incidence of CTEPH of 2.3% and 2.49%, respectively. Untreated CTEPH has a survival rate worse than many common cancers;^{22 23} however, mechanical interventions such as pulmonary endarterectomy (PEA) and balloon pulmonary angioplasty (BPA) improved 3-year survival to ≥88%.²⁴ Additionally, PEA, BPA and PH medical therapy have also been shown to improve symptoms and pulmonary haemodynamics.¹⁵

Recent studies in the UK and mainland Europe support a structured approach to PE follow-up, with one study showing this approach can achieve CTEPH diagnostic rates of 2% in addition to identifying patients earlier and with less severe haemodynamic disease.^{5 25} The 2019 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for PE management proposed a follow-up strategy that involved referring all patients with persistent dyspnoea at the 3-month to 6-month follow-up and/or CTEPH risk factors for an echocardiogram.²⁶ However, this is not seen as feasible for most practices and several prediction scores/algorithms have been developed to identify patients at high risk of CTEPH and reduce the need for echocardiograms. Klok *et al* developed a clinical prediction score to identify patients at high risk of CTEPH following acute PE,²⁷ and a non-invasive diagnostic algorithm for ruling out CTEPH.²⁸ These two approaches were integrated into a stepwise screening algorithm, InShape II.²⁹ Incorporation of a dedicated CT pulmonary angiography (CTPA) reading of the index PE to the InShape II algorithm resulted in the InShape IV algorithm.³⁰ This algorithm starts with CTPA reading of the index PE for six signs of CTEPH, followed by ECG and NT-proBNP measurement to determine if echocardiographic investigation for CTEPH is necessary. Application of this algorithm to the InShape II cohort (N=341) and part of the German FOCUS cohort (N=171) resulted in a need for echocardiography in 20% and 24% of patients, respectively, and no CTEPH cases were missed.³⁰ These results support the 2019 ESC/ERS guideline recommendation to screen for CTEPH based on symptoms combined with the estimation of pretest probability in all PE survivors.²⁶

The InShape III and IV studies also highlight the importance of reviewing the index CTPA at the time of the acute presentation.^{5 15 30 31} This should include an

assessment for webs, attenuated vessels (which may be difficult to appreciate), enlarged bronchial arteries and mosaic perfusion in addition to features of PH (pulmonary artery size ≥30 mm,^{32–34} right ventricular outflow hypertrophy ≥6 mm and right ventricular:left ventricular ratio ≥1).^{5 17 35} An echocardiogram is only required in highly selected patients at the time of acute PE; however, if performed, a systolic pulmonary artery pressure (sPAP) of >50 mm Hg on echocardiography at the time of acute PE is a risk factor for CTEPH.³⁶ This reflects an inability of the RV to generate a sPAP >50 mm Hg in the absence of pre-existing pulmonary vascular disease. While CTPA is an excellent test for delineating proximal CTEPH, subtle abnormalities may be missed by radiologists not used to assessing CTEPH.³⁷

If CTEPH is suspected, an assessment should be made as to whether the patient is likely to benefit from intervention if CTEPH is confirmed, before proceeding with further investigation. Where CTEPH is suspected and further investigation is appropriate, the 2022 ESC/ERS guidelines recommend an assessment of lung perfusion³⁸ (nuclear medicine imaging such as single-photon emission CT (SPECT) imaging, CT imaging using dual-energy CT or lung subtraction iodine mapping, or magnetic resonance (MR) perfusion mapping) in combination with an assessment of the likelihood of PH using echocardiography.¹⁷ If perfusion abnormalities are present and the patient has an intermediate or high echocardiographic probability of PH (ie, either tricuspid regurgitation velocity (TRV) ≥2.9 m/s or TRV ≤2.8 m/s with other echocardiographic signs of PH), referral to a PH centre for further evaluation should be considered.¹⁷

Perfusion abnormalities are common following acute PE and, depending on the patient's symptoms and echocardiographic findings, may not require any further investigation.³⁹ Access to perfusion imaging (eg, ventilation-perfusion (VQ) SPECT) or Q SPECT is not universal,^{7 8} and the presence of chronic lung disease reduces the specificity of such scans.⁴⁰ Perfusion lung maps can also be obtained at the time of CTPA using dual energy CT or using lung subtraction iodine mapping, allowing an assessment of chronic thromboembolic pulmonary disease (CTEPD) and CT features of PH, as well as lung perfusion.⁴⁰

Some patients with breathlessness following an acute PE have a low probability of PH on echocardiogram and have abnormal perfusion scan and/or evidence of chronic, organised fibrotic clot on CTPA. Before considering further assessment, it is important to consider other causes of breathlessness, particularly deconditioning, left heart disease and lung disease. Where deconditioning is suspected, it may be reasonable to advise a graded increase in exercise with review before considering further investigation. Where there is diagnostic doubt, cardiopulmonary exercise testing (CPET) may be helpful.¹⁷ If pulmonary vascular disease is the dominant problem limiting exercise, you would expect CPET to demonstrate inefficient ventilation due to high dead space in the lungs.^{41 42}

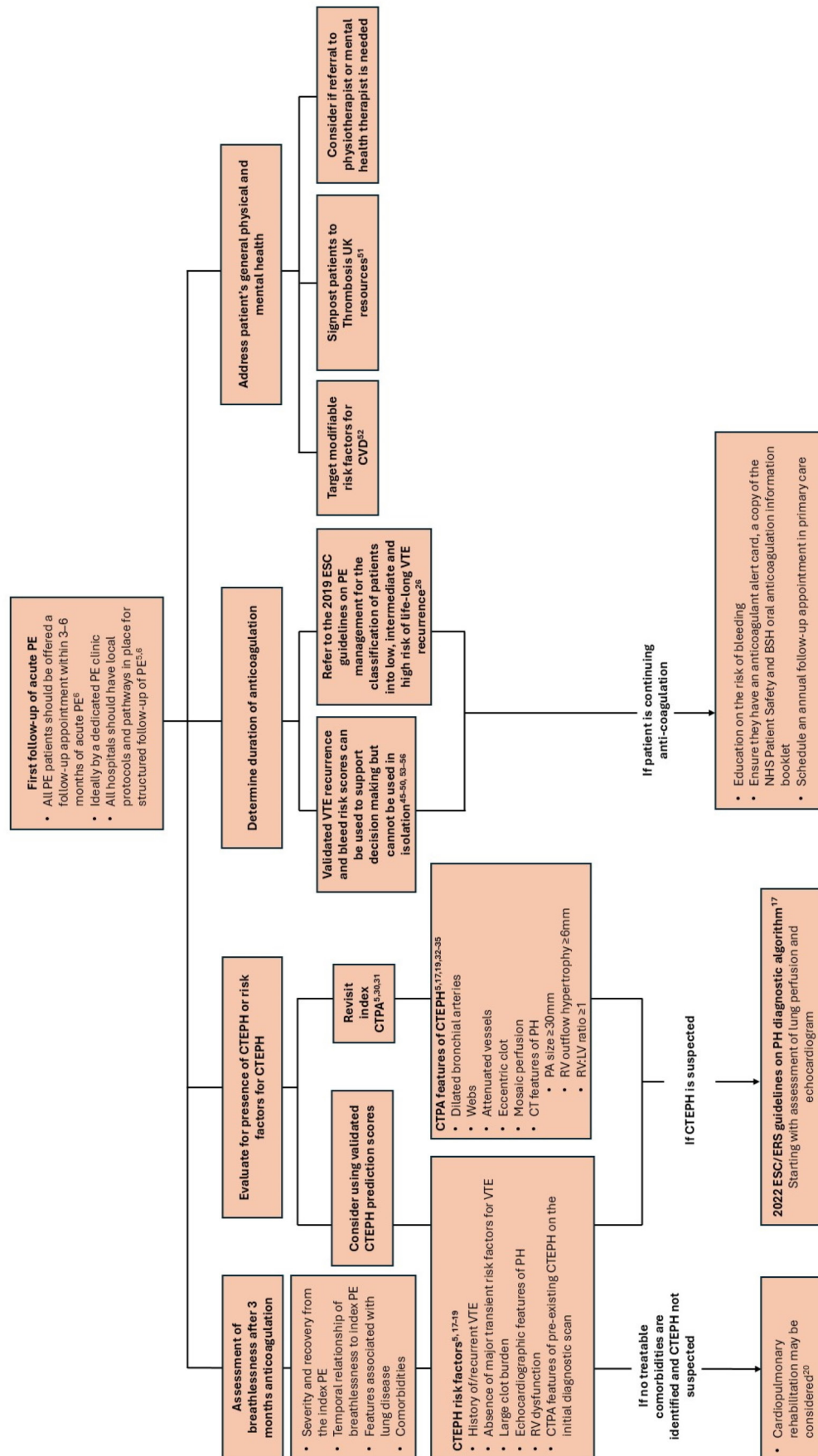


Figure 1 Flow chart summarising the key actions and considerations for the first follow-up visit at 3–6 months following an acute PE. BSH, British Society for Haematology; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, CT pulmonary angiogram; CVD, cardiovascular disease; ERS, European Respiratory Society; ESC, European Society of Cardiology; LV, left ventricle; NHS, National Health Service; PA, pulmonary artery; PE, pulmonary embolism; PH, pulmonary hypertension; RV, right ventricle; VTE, venous thromboembolism.

However, deconditioning is commonly found on CPET in patients with persistent breathlessness following an acute PE.⁴³ Stress echocardiogram is an alternative modality and can demonstrate exercise-induced PH; however, it is not commonly performed in this setting.⁴⁴ NT-proBNP may also help stratify the likelihood of significant PH, although data is limited²⁹ and elevated levels are also frequently seen in left heart disease, which is a common comorbidity.

Patients suspected of CTEPH should be referred to a PH centre given the availability of evidence-based treatments that improve outcomes. Symptomatic patients with CTEPD who have exercise-induced PH may benefit from interventional management, although data are limited.¹⁷

Figure 1 summarises the key actions and points to consider at the first follow-up of an acute PE.^{5 6 17–20 26 30–35 45–56}

What is the difference between CTEPD and post-PE syndrome?

CTEPD was first precisely defined in the ERS statement on chronic thromboembolic disease.¹⁵ The definition was further clarified in the ESC/ERS PH guidelines in 2022.¹⁷ To be present, the following criteria should be met: (1) therapeutic anticoagulation must have been in place for at least 3 months; (2) symptoms of breathlessness must be present; (3) there are mismatched perfusion defects on perfusion imaging (VQ SPECT, MR perfusion maps, CT perfusion maps); (4) features of organised, fibrotic clots seen on CTPA or conventional pulmonary angiography; (5) and the absence of PH. If PH is present, the condition becomes CTEPH (ie, CTEPD with PH). Asymptomatic patients may have chronic, organised, fibrotic clots or perfusion defects, but this is not CTEPD.

The term post-PE syndrome was first proposed in 2014¹⁰ and its definition has changed over time. It is an umbrella term for several conditions directly related to post-acute PE, including CTEPD, due to its broad criteria. An updated definition of the syndrome has been published recently by the International Society on Thrombosis and Haemostasis.⁵⁷ This definition requires ≥3 months of therapeutic anticoagulation following a confirmed acute PE and includes the presence of one or more of the following: (1) post-PE functional impairment; (2) post-PE cardiac impairment; (3) CTEPD with no PH or (4) CTEPH. Post-PE functional impairment requires new or worsening breathlessness post-PE, reduced exercise capacity or other functional limitation without an adequate alternative explanation. This may be related to pulmonary vascular or cardiac sequelae of the PE. More commonly, it is due to deconditioning⁴³ or psychological consequences⁵⁸ of the acute PE event. Post-PE cardiac impairment refers to intermediate or high echocardiographic probability of PH according to ESC/ERS criteria.¹⁷ This may indicate the presence of PH, or simply right heart dysfunction or a combination of both.

Why is it important to revisit the initial presentation with acute PE?

A review of presenting symptoms and imaging to confirm the diagnosis is important, as occasionally patients will be misdiagnosed with acute PE, or scans may be non-diagnostic.⁵⁹ A long history of symptoms prior to diagnosis could indicate the patient has pre-existing CTEPH. An assessment of the early mortality risk as high, intermediate-high, intermediate-low or low risk (based on haemodynamic instability, clinical parameters of PE severity using the Pulmonary Embolism Severity Index (PESI) or simplified PESI, RV dysfunction on echocardiogram or CTPA and troponin levels)²⁶ is important, as patients with more severe acute PE are at greater risk of developing CTEPH. Risk factors for PE are important for determining the likelihood of CTEPH: a meta-analysis demonstrated an OR of 4.1 for the development of CTEPH in patients with no major transient risk factors compared with those with them.^{5 60} In a recent study from the ASPIRE Registry (Assessing the Spectrum of Pulmonary hypertension Identified at a REferral Centre), only 3 of 376 (0.8%) patients seen 3–6 months post PE with a major transient risk factor, compared with 33 of 1139 patients (2.8%) with no major transient risk factors, went on to develop CTEPH.⁵

Which patients should undergo imaging to determine if there are residual perfusion defects or persistent abnormalities?

Residual perfusion defects are common following an acute PE. A meta-analysis of 25 studies reported 52% of patients as having residual perfusion defects at 11 months,⁶¹ although a more recent prospective cohort study reported a prevalence of 29% at a median of 12 months following acute PE.³⁹

When evaluating a patient following an acute PE, the decision to perform further imaging should always include an assessment of breathlessness. In the absence of breathlessness, further imaging is not recommended unless there are risk factors for CTEPH present, and further evaluation will impact on treatment decisions. In symptomatic patients, echocardiography is recommended and patients with an intermediate or high risk of PH should be considered for referral to a PH centre (recognising that other comorbidities such as left heart disease may also cause PH).¹⁷ Patients with a low probability of PH, who have significant symptoms and no other cardiopulmonary comorbidity, but with significant residual defects should also be considered for further evaluation such as CPET and/or referral to a PH centre.¹⁷

Long-term anticoagulation is recommended in patients with PE with no transient risk factor and in CTEPH (irrespective of whether they had a major transient risk factor or not).^{17 26} Not included in these groups are patients who have had a PE associated with a major transient risk factor. Occasionally, these patients may undergo further imaging and be noted to have features of organised thrombus on CTPA or persistent defects on VQ imaging. For patients

with minor residual CTEPD and a low probability of PH, the authors would usually recommend stopping anticoagulation. For patients with more extensive residual thromboembolism following a major transient risk factor and a low probability of PH, there is currently no evidence on the optimal anticoagulation strategy and this decision should be made on a case-by-case basis. However, we would usually favour ongoing anticoagulation in symptomatic patients with CTEPD and no PH if the bleeding risk is low.

For a patient who has undergone CT imaging and has an incidental finding of chronic thromboembolism (webs and/or attenuated vessels), what should I do?

Strictly, CTEPD cannot be diagnosed until after 3 months of therapeutic anticoagulation. If there is an incidental finding of chronic, organised, fibrotic clot and the patient presents with breathlessness, we would recommend therapeutic anticoagulation with reassessment after 3 months. The decision with respect to long-term anticoagulation should be made on an individual basis²⁶ and consider the risk of PE recurrence, the previous history of PE (if any) and the burden of organised clot seen on CTPA against the risk of potential bleed.^{26 62}

Patients who remain symptomatic at 3 months require further assessment. The first step would usually be an echocardiogram. If there is an intermediate or high probability of PH, then referral to a PH centre is recommended.¹⁷ If there is a low probability of PH, a CPET looking for an abnormal pulmonary vascular response pattern^{41 42} should be considered, or, if unfit to perform CPET, the authors suggest echocardiogram surveillance after a year. NT-proBNP can also help to stratify likelihood of having significant PH.^{17 29} Where patients have a low echocardiographic probability of PH and breathlessness is likely due to other factors, it may not be necessary to perform any further assessment. In cases where the probability of PH is unclear, a follow-up echocardiogram after an interval may be helpful.

When should I investigate for cancer in a patient with VTE?

One in 20 patients who present with VTE is diagnosed with cancer within 12 months.⁶³ The multicentre, open-label, randomised controlled 'screening for occult malignancy in patients with idiopathic venous thromboembolism' trial found that routine screening with CT scans of patients with a first unprovoked VTE did not result in a significant improvement in time to cancer diagnosis or cancer-related mortality versus limited occult cancer screening.⁶⁴ Therefore, the updated 2020 National Institute for Health and Care Excellence (NICE) guidelines on the management of VTE do not recommend routine screening of cancer in patients with an unprovoked VTE.⁶⁵ The decision on whether to investigate for cancer should be based on physical examination and medical history of symptoms, as described in the 2015 NICE guidelines for recognition and referral of suspected cancer.⁶⁶ An interactive cancer

screening tool is available from NICE.⁶⁷ Age-specific and gender-specific testing (eg, mammography, cervical smear and prostate specific antigen testing) should be implemented in accordance with national guidelines and local practice. During follow-up after acute PE, the threshold to suspect cancer should be low in patients with a relatively recent history of cured cancer (eg, within 5 years, as VTE can be a sign of recurrent cancer), early VTE progression/recurrence despite anticoagulant treatment and anticoagulant-related bleeding shortly after start of treatment (particularly gastrointestinal bleeding or haematuria).²⁰

When should I test for thrombophilia?

Thrombophilia is defined as the increased tendency to form blood clots and there are heritable and acquired forms. Genetic causes of heritable thrombophilia include Factor V Leiden/prothrombin gene mutations, antithrombin deficiency and protein C and S deficiency.⁶⁸ Antiphospholipid syndrome (APS) is the most common form of acquired thrombophilia.^{68 69}

Heritable thrombophilia

It is not recommended to test for heritable thrombophilia in most patients with a first VTE/PE.⁶⁸ However, there are select patient populations in which testing is indicated:⁷⁰

- Patients with unfractionated heparin/low molecular weight heparin resistance should be tested for antithrombin deficiency.⁷¹
- Patients with skin necrosis associated with vitamin K antagonists (VKAs) should be tested for protein C and S deficiency.⁷⁰

Similarly, case finding among asymptomatic relatives of patients with a history of VTE is not recommended in most cases, as the annual risk of thrombosis in family members is low.⁷⁰ It is not indicated in asymptomatic relatives of those with low risk thrombophilia (such as factor V Leiden) and, in high risk thrombophilia (such as antithrombin deficiency or protein C or S deficiency), case finding should only be considered in families who are prone to thrombosis (one first-degree or two second-degree relatives with VTE).⁷⁰

In those with confirmed deficiency of antithrombin, protein C or protein S, and patients with homozygous factor V Leiden or homozygous prothrombin G20210A mutation, long-term anticoagulation should be considered after a first episode of PE occurring in the absence of a major reversible risk factor.^{26 68} The 2019 ESC guidelines on management of acute PE advise that testing for thrombophilia may also be considered in patients whose PE occurs at a relatively young age (<50 years) in the absence of any provoking risk factors, particularly if they have a strong family history of VTE, as testing in these patients may be helpful for treatment decisions.²⁶ However, it is important to note that thrombophilia testing should not be routinely conducted for unselected patients in order to inform decisions on the duration of anticoagulant

Box 1 Risk factors for antiphospholipid syndrome

- ⇒ History of systemic lupus erythematosus or another autoimmune disease.
- ⇒ Presence of livedo reticularis.
- ⇒ Prolonged activated partial thromboplastin time prior to starting anticoagulation.
- ⇒ Recurrent thrombosis.
- ⇒ Venous thromboembolism at unusual sites.
- ⇒ History of arterial thrombosis without clear risk factors.
- ⇒ Thrombocytopaenia.
- ⇒ Recurrent miscarriages, stillbirth and/or severe pre-eclampsia.
- ⇒ Cardiac valve abnormalities in the absence of other explanations.⁷²

treatment; rather, these decisions should be based on the presence or absence of a provoking risk factor for VTE/PE and the risk of bleeding during treatment.⁷⁰

Antiphospholipid syndrome (acquired thrombophilia)

The following list of risk factors for APS can be used to determine when a diagnosis should be considered and investigated (box 1).⁷²

A diagnosis of APS is given if patients meet at least one clinical criteria and at least one laboratory criteria from the Sapporo classification of APS (box 2).^{72 73} Laboratory testing should only be conducted if the clinical criteria are met.^{72 73} It should be noted that, while all anticoagulants interfere with clotting assays, lupus anticoagulant testing is particularly prone to high rates of false positives in patients treated with VKAs and direct oral anticoagulants (DOACs)^{74–76} and also if tested at the time of the acute VTE.^{77 78}

Box 2 Clinical and laboratory criteria for the diagnosis of antiphospholipid syndrome

Clinical criteria

At least one of the following:

- ⇒ ≥1 episodes of vascular thrombosis.
- ⇒ Recurrent complications during pregnancy:
 - ≥1 unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation.
 - ≥1 preterm births of a morphologically normal fetus before the 34th week of gestation due to eclampsia/severe pre-eclampsia or recognised features of placental insufficiency.
 - ≥3 unexplained consecutive spontaneous miscarriages before the 10th week of gestation.

Laboratory criteria

At least one of the following:

- ⇒ Anticardiolipin antibody of immunoglobulin G (IgG) and/or immunoglobulin M (IgM) isotype present in medium or high titres in serum or plasma, on ≥2 occasions at least 12 weeks apart.
- ⇒ Anti-β₂-glycoprotein I antibody of IgG and/or IgM isotype present in serum or plasma, on ≥2 occasions at least 12 weeks apart.
- ⇒ Lupus anticoagulant present in plasma, on ≥2 occasions at least 12 weeks apart.

Reproduced from Keeling et al.⁷³

The 2023 American College of Rheumatology/EULAR (European Alliance of Associations for Rheumatology) classification criteria for APS were designed as highly specific criteria for use in observational studies and trials and, as such, have higher specificity (but lower sensitivity) than the Sapporo classification criteria.⁷⁹

TREATMENT

How long should I anticoagulate for? And with what dose?

Acute VTE/PE events should be treated for a minimum of 3 months.⁶⁵ Physicians may consider stopping treatment at 3 months if the risk factor associated with the blood clot is no longer present. However, if the associated risk factor persists beyond 3 months, or if the blood clot occurred with no identifiable risk factors, physicians should consider treatment beyond 3 months, with the possibility of long-term anticoagulation.⁶⁵

Over the past decade, there has been a paradigm shift in anticoagulation management with the majority of patients with acute PE being treated with a DOAC. A step-down dose in certain DOACs (apixaban and rivaroxaban) may be considered from 3 to 6 months after starting anticoagulation.^{80–82} Although patients were treated for a minimum of 6 months in randomised controlled trials of DOACs,^{80 83–85} in clinical practice, treatment can be reviewed between 3 and 6 months post-VTE.⁶⁵

Specific exceptions to the use of DOACs in acute PE include some patients with cancer such as gastrointestinal tract, renal system or brain malignancies or those receiving systemic cancer therapies with potential drug interactions.⁸⁶ It is also recommended against initiating DOACs for the treatment or secondary prophylaxis in patients with venous thrombosis and known APS.⁷²

When there is no clear major transient risk factor, how should I approach a discussion and decision on life-long anticoagulation?

Shared decision-making with the patient is vital to support treatment adherence.⁶⁵ Regarding the decision on long-term anticoagulation, physicians should consider the long-term risks of bleeding versus the risk of VTE/PE recurrence and discuss how best to balance these risks with the patient.⁶⁵ This balance may change over time, thus an annual review of patients taking long-term anticoagulation should take place. The risk of VTE recurrence following discontinuation of anticoagulation is related to the presence or absence of provoking risk factors at the time of the acute event.²⁶ Readers should refer to the 2019 ESC guidelines on PE management for the classification of patients into low, intermediate and high risk of life-long VTE recurrence.²⁶ Patients who have had multiple episodes of VTE in the absence of major transient or reversible risk factors are considered as being at high risk of VTE recurrence, per the 2019 ESC guidelines on PE management, and it is recommended to extend anticoagulation indefinitely in these patients.²⁶ Cases in which there is no clear provoking risk factor underpinning a

Table 1 DASH prediction score^{49 50}

DASH score determination based on risk factors		
Factor	Yes	No
D-dimer abnormal (measured 1 month after stopping anticoagulation)	+2	0
Age ≤50 years	+1	0
Male patient	+1	0
Hormone use at VTE onset (if female; select 'No' if male)	-2	0
Risk of recurrence of VTE as by DASH score in learning and validation data sets ⁵⁰		
DASH score	Annualised risk of recurrence (95% CI)	
	Learning data set (used to derive the DASH score)	Validation data set
≤-1	1.2 (1.1 to 1.3)	0.5 (0.4 to 0.6)
0	2.4 (1.4 to 4.2)	3.9 (3.6 to 4.2)
1	3.9 (2.9 to 5.3)	5.3 (5.1 to 5.4)
2	6.4 (5.0 to 8.1)	6.7 (6.5 to 7.0)
3	10.8 (8.7 to 13.4)	6.8 (6.5 to 7.2)
4	19.9 (13.9 to 28.2)	12.1 (10.9 to 13.3)
CI, confidence interval; DASH, D-dimer, age, sex, hormonal therapy; VTE, venous thromboembolism.		

patient's first and only episode of VTE are classified as being at intermediate risk of recurrence, and determining the duration of anticoagulation in these patients may be challenging.²⁶ To inform this decision, several scores for predicting VTE recurrence and bleeding are available to estimate individual patient risk. However, these risk scores should not be used in isolation and cannot be solely relied on.

VTE recurrence scores

Several risk scores for VTE recurrence have been developed and validated in patients who experienced a first VTE with no identifiable risk factors and had completed a minimum of 3 months of anticoagulation treatment. They include:

The D-dimer, age, sex, hormonal therapy (DASH) prediction score (table 1) was developed using pooled data from seven prospective studies on 1818 cases of VTE treated with VKAs.⁴⁹ Patients are classified as low (<5%) or high risk (≥5%) of recurrence according to their score, using a threshold score of 1, with a low score indicating that physicians should consider stopping anticoagulation.⁴⁹ The retrospective validation study in 827 patients confirmed that patients with a DASH score of ≤1 had a

Table 2 HERDOO2 prediction score^{46 47}

HERDOO2 score determination based on risk factors		
Factor	Yes	No
Post-thrombotic signs (eg, hyperpigmentation, oedema or redness on either leg)	+1	0
D-dimer level ≥250 µg/L	+1	0
BMI ≥30 kg/m ²	+1	0
Age ≥65 years	+1	0
Risk of recurrence by HERDOO2 score in learning and validation data sets		
HERDOO2 score	Risk of major* VTE recurrence per 100 patient years, % (95% CI)	
	Learning data set ⁴⁶	Validation data set ⁴⁷
0 or 1	1.6 (0.3 to 4.6)	3.0 (1.8 to 4.8)
2–4	14.1 (10.9 to 17.3)	7.4 (3.0 to 15.2)
*Proximal deep vein thrombosis and segmental or greater pulmonary embolism. BMI, body mass index; HERDOO2, Hyperpigmentation, Edema, Redness, D-dimer, Obesity, Older age; VTE, venous thromboembolism.		

cumulative risk of recurrence at 1 year of <5%.⁵⁰ However, the risk of recurrence remained high (>5%) in patients over 65 years old, irrespective of DASH score; thus, physicians should use caution when interpreting DASH risk score in older patients.⁵⁰ Another group also aimed to externally validate the DASH score as part of the follow-up for a large population-based case-control study; the MEGA, (Multi Environmental and Genetic Assessment), study follow-up of 3750 patients with DVT or PE found that its ability to distinguish risk of recurrence was lower than in the original studies (c-statistic of 0.56–0.66, depending on definition of unprovoked VTE, compared with 0.71 in the original validation study).⁴⁸ Importantly, the DASH score failed to validate in a smaller, single-centre study (n=271 with VTE and no major transient risk factors for VTE and a DASH score); the authors could not find patients with a low DASH score with a VTE recurrence rate below which anticoagulation could be withheld.⁴⁵

The Hyperpigmentation, Edema, Redness, D-dimer, Obesity, Older age (HERDOO2) prediction score (table 2) can be used to aid decisions around discontinuing anticoagulation in women and was developed and validated in the REVERSE (REcurrent VENous thromboembolism Risk Stratification Evaluation) studies.^{46 47} The score is not applicable to men, as the men in this cohort had a 13.7% (95% CI: 10.8% to 17.0%) annual risk, and it was therefore not possible to develop a score that could identify a cohort of men who could safely stop anticoagulation.⁴⁶ Consequently, the score is commonly known

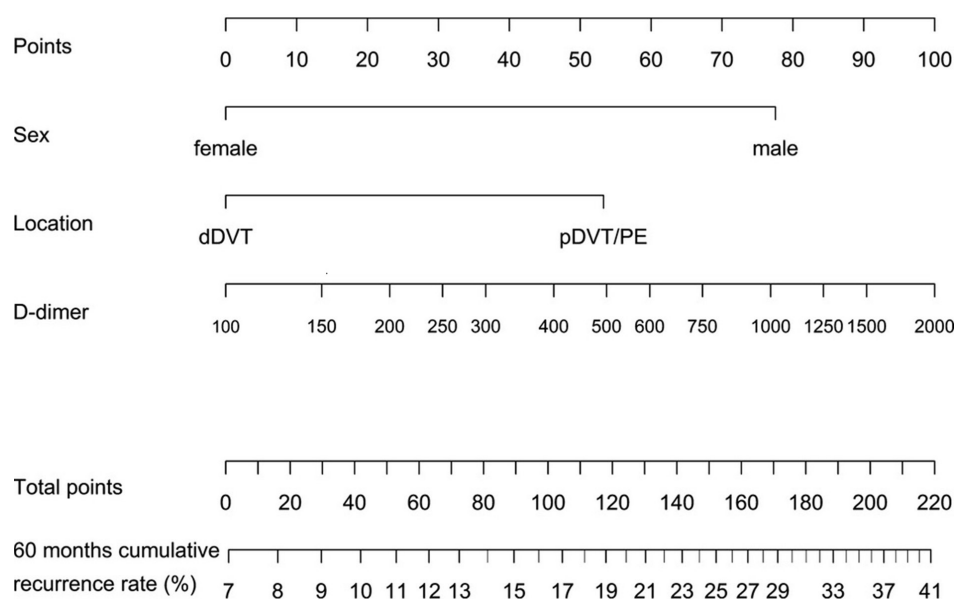


Figure 2 Updated nomogram for the VIENNA prediction score for risk of VTE recurrence (available as an online calculator)⁷⁷ from 3 weeks after the end of anticoagulation. Reproduced with permission from Eichinger *et al*⁵⁵; link to license: <https://creativecommons.org/licenses/by-nc/3.0/>; no changes made. For each value of the associated risk factors, the corresponding 'points' can be read from the top of the nomogram. These scores should then be totalled and read on the 'Total points' score at the bottom. The total points are aligned with their associated 60-month cumulative recurrence rate (%) below. The VIENNA risk score is available as an online calculator.⁷⁷ DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

as the 'MEN continue and HERDOO2' score. Women with none or one of the HERDOO2 criteria are classified as having low risk of recurrent VTE.⁴⁶ HERDOO2 was externally validated in the multinational, prospective REVERSE II study (N=1213), which confirmed that women with none or one of the criteria had a low risk of recurrence (3.0% per patient year; 95% CI 1.8% to 4.8%) and could safely discontinue anticoagulation (with VKAs and the DOACs dabigatran, rivaroxaban, apixaban and edoxaban, in this study).⁴⁷ The D-dimer levels are measured while the patient is anticoagulated for the HERDOO2 score, in contrast to the DASH score, in which the D-dimer is measured after stopping anticoagulation.^{47 50} It is also interesting and important to note that young age portends greater risk of recurrence in the DASH score, whereas the opposite is true for HERDOO2.

The VIENNA prediction score uses a nomogram to determine patients' risk of recurrence based on sex, location of VTE and D-dimer level (figure 2),⁵⁴ and is available as an online calculator.⁵³ The original score was designed for use 3 weeks after discontinuation of anticoagulation⁵⁴ and an update of the model also allows prediction up to 15 months after stopping anticoagulation.⁵⁵ Independent validation in 904 patients pooled from five studies further supports the use of the VIENNA score, although data only covered the first after discontinuation.⁵⁶ As observed for the DASH score, the VIENNA score did not perform as well as part of the MEGA follow-up study, as it did in the original studies (c-statistic of 0.61–0.62, depending on definition of unprovoked

VTE in MEGA follow-up study compared with 0.65 in the original study).⁴⁸

It is important to be aware of these VTE recurrence scores, as well as their limitations. The risk scores can be used to support decision making, depending on the clinical scenario. For example, the DASH score is more suited for use in younger patients, particularly women or those with hormone-associated blood clots, whereas HERDOO2 is more appropriate to use in older women.^{46 47 49 50} Importantly, these scores should not be used in isolation. Patient values and preferences should be taken into account throughout a shared decision-making process.

VTE bleed scores

While there are bleeding scores available, they have poor predictive performance in acute PE.^{87 88} The NICE guidelines of VTE management state that physicians can consider using the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, and Drugs or alcohol use) for estimating the risk of major bleeding events in patients with VTE and no identifiable risk factors, as there is some evidence that it can identify those who are at particularly high risk of major bleeding.⁶⁵ However, the NICE guidelines also recommend research to focus on developing a new prediction tool for recurrence and major bleeding combined, as the current tools cannot be solely relied on.⁶⁵ There is also an unmet need for VTE bleed scores designed for patients with cancer.

In general terms, the risk of having a recurrent VTE following an acute PE is approximately 1 in 10 in the first year, rising to 1 in 3 over 5–19 years once anticoagulation is stopped.^{89 90} For patients presenting with a symptomatic PE rather than a deep vein thrombosis (DVT), the risk of the recurrent VTE event being another PE rather than a DVT is threefold higher than if the patient presented with a DVT.⁹¹ This needs then to be balanced against an overall risk of major bleeding of 1–2 cases in 100 per year.⁹²

Can I prescribe aspirin?

Aspirin should not be used to treat acute VTE. In terms of prevention of future VTE, randomised placebo-controlled trials showed only a moderate benefit (reducing the rate of occurrence by 26% in the ASPIRE (Aspirin to Prevent Recurrent Venous Thromboembolism) and 42% in the WARFASA (WARFarin and ASpirin) study of prophylactic aspirin at a dose of 100 mg daily in patients who had completed several months of therapeutic anticoagulation for a VTE with no provoking factors.^{93 94} Furthermore, recent trial findings suggest that low-dose anticoagulation therapy may be a better option for patients requiring extended treatment.⁸¹ The randomised, double-blind phase 3 EINSTEIN CHOICE trial compared the efficacy and safety of up to 12 months' treatment with 100 mg aspirin with that of either the prophylactic (10 mg) or treatment dose (20 mg) of rivaroxaban, in patients with VTE following 6–12 months of therapeutic anticoagulation.⁸¹ It found that both doses of rivaroxaban resulted in a significant reduction (approximately 70%) in the risk of a recurrent VTE event compared with aspirin, without a significant increase in bleeding events.⁸¹

Aspirin is widely used for the secondary prevention of cardiovascular disease,^{95 96} but, in general, aspirin should be stopped if the patient requires an anticoagulant, due to the increased risk of major bleeding events.⁹⁷ In cases where patients with a cardiac coronary artery bypass graft had aspirin treatment stopped for full-dose DOAC treatment, we advise re-starting aspirin if patients switch to a step-down dose of DOAC, although there is currently no empirical evidence to support this.

Should I stop antiplatelet therapy when my patients start their anticoagulant?

The full answer depends on the indication for the antiplatelet therapy. If the patient is on antiplatelet treatment for a cardiac indication, then you should consider discussing ongoing antiplatelet therapy with a cardiologist. Around 5–15% of patients with atrial fibrillation (AF) will have concurrent indications for anticoagulation and antiplatelet therapy (as a result of percutaneous coronary intervention (PCI), or acute coronary syndrome (ACS)).⁹⁸ Many trials have investigated the best antithrombotic regimens that balance the risk of major bleeding events with that of ischaemic events in these patients. Overall, dual therapy—ideally with a DOAC and clopidogrel—achieves better outcomes than triple therapy.⁹⁹ However, there is

some evidence to suggest that up to 1 week of initial triple therapy (including aspirin) would benefit some patients with post-ACS/PCI AF, particularly those at increased risk of ischaemic events.^{100 101} However, early cessation of aspirin is recommended if the risk of stent thrombosis is low or lower than the bleeding risk.⁹⁷ Regardless of whether patients are initially treated with dual or triple therapy, it is not recommended to discontinue antiplatelet therapy for 6–12 months following ACS.^{97 102} However, antiplatelet therapy may be discontinued in patients with stable coronary disease 12 months postintervention. It is recommended that most patients are transitioned to oral anticoagulation monotherapy after 6 (ACS) or 12 (chronic coronary syndrome) months of dual therapy.⁹⁷

Follow-up

What information is of relevance to first-degree relatives?

First-degree relatives of patients experiencing a PE with no provoking factors should be considered to be at increased risk of VTE, particularly when exposed to VTE risk factors.¹⁰³ Physicians may recommend that family members using the combined contraceptive pill consider switching to progesterone-only treatments if the index case PE occurred in a first-degree relative below the age of 45.^{70 104}

What should I tell a patient when I discharge them at 3 months?

Advice for patients following discharge will depend on ongoing therapy. If anticoagulation is being stopped, clinicians should discuss the risk of VTE recurrence with the patient and educate patients on the symptoms of blood clots and when they should seek urgent medical attention.⁶⁵ Written information should be provided as a reference.⁶⁵

If the patient is continuing anticoagulation, physicians should discuss the associated risks and benefits, explaining that the benefits of anticoagulation are likely to outweigh the risk of bleeding events.⁶⁵ Patients should be educated on such risks, as well as the symptoms of VTE and the importance of medication adherence.⁶⁵ Patients should also be issued with an anticoagulant alert card, a copy of the UK National Health Service Patient Safety and the British Society for Haematology Oral Anticoagulation Information booklet.¹⁰⁵ An annual follow-up appointment in primary care should be scheduled for the patient to assess the ongoing risk:benefit of continuing anticoagulation with advice to refer to a thrombosis expert if concerns arise.⁶⁵

Patients may also have concerns about getting active after a PE, and some patients may have anxiety about having another PE. Advice for physicians and patients on tackling these issues can be found on the Thrombosis UK website,⁵¹ including a video of physiotherapists demonstrating exercises that patients can try at home,¹⁰⁶ and fact sheets on using

active distraction or meditation and mindfulness to cope with their post-PE worries.¹⁰⁷

When should I consider (re-)scanning the legs?

A scan of the legs should be considered if patients exhibit new symptoms of DVT. Rescanning is not recommended for residual vein thrombosis, as it is a poor predictor of risk of recurrence.¹⁰⁸

SHOULD I DO A D-DIMER TEST AT 3 MONTHS?

A D-dimer test can be considered as part of the VTE recurrence risk assessment (HERDOO2 and DASH scores discussed above) if physicians are considering stopping anticoagulation at 3 months.^{46 47 49 50} Caution should be exercised in performing this test if it is not likely to change management, that is, in a patient who wishes to stop anticoagulation regardless. In males, given the higher risk of recurrent VTE following cessation of anticoagulation even if the D-dimer is negative, the annual risk of recurrent VTE will still be higher than the risk of bleeding.

CONCLUSION

The suggested approaches are based on a non-systematic review of the guidelines and literature, and expert consensus. Management in an individual patient should be based on clinical risk–benefit assessment, careful management of coagulation status and effective physician–patient communication. Structured follow-up post-acute PE is important to improve patient outcomes, including diagnosing CTEPH. How best to deliver such care and how best to structure follow-up PE clinics requires further evaluation.

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