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Basics of diagnosis and treatment of venous thromboembolism

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Abstract

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism (PE), is common and associated with significant morbidity and mortality. The symptoms and signs of VTE are nonspecific. Well-established integrated diagnostic strategies combining clinical probability scores and D-dimer are used to identify patients with a low probability of VTE, where the diagnosis can be safely excluded without imaging. In patients with confirmed VTE, anticoagulation is the mainstay of treatment. However, patients with high-risk features at presentation may benefit from advanced reperfusion therapies such as thrombolysis and/or interventional approaches to reduce early mortality and/or long-term morbidity. The advent of direct oral anticoagulants has greatly simplified the treatment of VTE for most patients, with a persisting role for low molecular weight heparin and vitamin K antagonists in select patient groups. Following an initial 3 to 6 months of anticoagulation, those with major transient provoking factors can safely discontinue anticoagulation. Balancing the risk of recurrent VTE and bleeding risk is central to decisions regarding long-term anticoagulation, and patients should be included in shared decision-making. Assessment and recognition of common long-term complications such as postthrombotic syndrome and post-PE syndrome are also essential, given they are associated with significant adverse impact on long-term quality of life, with a significant risk of mortality associated with the less frequent complication of chronic thromboembolic pulmonary hypertension. This review provides a basic overview and framework for the diagnostic approach to deep vein thrombosis and PE, risk stratification of confirmed diagnoses, and management.

KEYWORDS
anticoagulants, pulmonary embolism, venous thrombosis, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT refers to the formation of thrombosis within the deep veins and most commonly involves the lower limb. PE occurs when some or all of the thrombosis breaks away and travels to the lungs via the venous circulation to occlude the pulmonary arterial vasculature. VTE is common, affecting an

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estimated 1 in 12 adults within their lifetime, and more than 10 million events are diagnosed worldwide each year [1,2]. Half of all episodes are associated with recent hospitalization and/or surgery, with most events presenting following hospital discharge. Knowledge of VTE, including its diagnosis and management, is therefore relevant to all clinicians, as a lack of clinical suspicion both during the index admission, at outpatient follow-up, or in primary care may lead to delays in diagnosis and further morbidity [3].

In this review, we provide a basic overview and framework for the diagnostic approach to DVT and PE, risk stratification of confirmed diagnoses, and management. We discuss phases of treatment including estimating the risk of recurrent VTE and secondary prevention, along with a brief overview of the monitoring and management for long-term complications. This review does not cover the pathophysiology of VTE [4], thrombosis at unusual sites [5–9], pregnancy-associated VTE [10], or primary prevention of VTE [11–13], and we direct readers to the cited references for further information. Further topic-specific reviews and guidance are signposted for readers wanting more detail throughout.

2 | EPIDEMIOLOGY

The annual incidence of VTE in adults is estimated at 1 to 2 per 1000 per year [14]. Increasing age is associated with a significant increase in risk, with an annual incidence of 1 per 100, in those over 80 years of age [15]. Females are at greater risk at younger ages owing to the use of combined hormonal contraception and pregnancy, with men having a higher incidence associated with increasing age, as well as increased risk of recurrent VTE [16].

Half of all VTE episodes are associated with hospitalization and/or surgery in the preceding 3 months [17]. Where hospitalization is associated with reduced mobility for ≥3 days, or with surgery requiring general anesthesia for more than 30 minutes, this is considered a major provoking factor for VTE. Guidance on prevention of hospital-associated VTE is discussed elsewhere [11,12,18,19]. Other common risk factors are summarized in Table 1 and include cancer, obesity, and inherited thrombophilia. It is important to recognize that a third or more of patients with VTE may have no apparent provoking risk factor [1,17].

3 | CLINICAL PRESENTATION

The clinical presentation of VTE is varied and largely nonspecific. DVT usually presents with unilateral symptoms with leg pain the most frequent and sometimes the only presenting symptom [20]. Other symptoms include leg swelling, redness, and skin changes, such as dilated superficial veins. PE can present with breathlessness, pleuritic chest pain, cough with or without hemoptysis, dizziness, syncopal episodes, or when severe, cardiac arrest [3,21]. Physical examination may be unremarkable or reveal tachycardia, hypoxia, or hypotension in those with significant thromboembolic burden.

TABLE 1 Risk factors for venous thromboembolism.

Persistent/ transient	Inherited	Acquired
Persistent	Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene polymorphism Non-O blood group Sickle cell disease	Malignancy (until remission) ± chemotherapy Myeloproliferative disorders Paroxysmal nocturnal hemoglobinuria Antiphospholipid syndrome Inflammatory bowel disease Systemic lupus erythematosus Nephrotic syndrome Obesity HIV infection
Transient		**Major** Major surgery/trauma within 3 mo Hospitalization ≥3 d with acute illness within 3 mo Heparin-induced thrombocytopenia **Minor** Combined hormonal contraception Oral estrogen-containing HRT Pregnancy/puerperium Immobilization, eg, in plaster cast Long-haul travel

HRT, hormone replacement therapy.

4 | VTE DIAGNOSIS

All patients with suspected DVT and PE should have a thorough history and examination to consider alternate diagnoses. Where PE is suspected a chest X-ray and electrocardiogram should also be performed to exclude alternate pathology. Where DVT and/or PE remain a significant concern, pretest probability should be assessed. Good practice points for patients with a confirmed diagnosis are summarized in Table 2 [18,22–27].

4.1 | Clinical or pretest probability scores

As the symptoms and signs of VTE are nonspecific, pretest probability scores (Figure 1) have been developed for use in integrated diagnostic strategies. This enables VTE to be excluded without diagnostic imaging using clinical criteria in conjunction with D-dimer testing [28–35]. Less than 5% to 20% of patients with suspected VTE are confirmed to have the condition; therefore, avoiding imaging in those at very low risk improves efficiency, limits unnecessary radiation exposure for suspected PE, and avoids unnecessary utilization of resources [18,28,36].

TABLE 2 Good practice tips at diagnosis of acute venous thromboembolism (VTE).

DO	Rationale
Use simple, reassuring language Examples: "You have a blood clot in your leg" "Most patients do well when diagnosed and treated promptly…"	Word choice, incomplete transfer of information from clinician to patient, and nonverbal cues can lead to an imbalance of fear over reassurance at initial encounters [23] This may contribute to ongoing stress and anxiety.
Take a menstrual history from premenopausal women	Anticoagulation commonly causes HMB. Identifying women with pre-existing HMB can influence the choice of anticoagulation and also enable early intervention to mitigate against increased HMB, identify and manage iron deficiency, and empower women to seek medical help appropriately [22]. Direct women to available online resources, for example: https://thrombosis.org/2023/08/bleeding-bloodthinners-hmb/ www.sciani.com/portfolio/anticoagulants-and-your-periods/
Review modifiable bleeding risk factors [27]	To reduce risk of bleeding. For example, • discontinue antiplatelet agents unless absolute indication to continue (ie recent coronary arterial drug eluting stent) • counsel to avoid NSAIDs for analgesia • reduce alcohol intake • ensure adequate control of hypertension
Offer a single-drug approach to anticoagulation when appropriate	Apixaban and rivaroxaban offer an oral treatment approach upfront, avoiding the need for parenteral LMWH [18]. Improved patient experience, and cost-effectiveness
AVOID	
Stopping combined hormonal contraception at VTE diagnosis	This can precipitate withdrawal bleeding, which may be heavier in the acute phase and lead to a risk of unwanted pregnancy. Continuing combined hormonal contraception while on anticoagulation is safe [22]
Indiscriminate testing to find a cause for unprovoked VTE	Antiphospholipid antibodies should be considered in those <50 years or with other autoimmune conditions. Lupus anticoagulant testing should be avoided at the time of acute thrombosis diagnosis as false results can occur. MPN mutational analysis and PNH screening can be considered in those with a suggestive FBC [24]
• Heritable thrombophilia testing	Heritable thrombophilia tests do not impact acute management. There is a risk of both false negative and positive results due to acute thrombosis±anticoagulation [24]
• Routine whole-body CT scans to look for underlying malignancy	While there is a risk of occult malignancy in unprovoked VTE, studies have shown extensive screening does not improve detection or outcomes [25] Further investigation (ie, endoscopy/imaging) should only be ordered when indicated based on findings of a thorough history, examination, chest X-ray and basic blood tests (FBC, calcium, renal, and liver profile) [18,26]

CT, computed tomography; FBC, full blood count; HMB, heavy menstrual bleeding; LMWH, low molecular weight heparin; MPN, myeloproliferative neoplasm; NSAID, nonsteroidal anti-inflammatory drug; PNH, paroxysmal nocturnal hemoglobinuria; VTE, venous thromboembolism.

The most established pretest probability score for suspected DVT is the Wells score (Figure 1) [28,30]. DVT can be excluded in those with an "unlikely" pretest probability and negative D-dimer, with imaging required for the remainder. The diagnostic pathway for suspected DVT is illustrated in Figure 2. Alternate clinical probability scores have been developed to simplify diagnosis and to reduce the proportion of patients requiring definitive imaging (Figure 1).

Patients with suspected PE should also be assessed with a pretest probability score (Figure 1), after initial assessment to identify alternate causes including a full history, examination, and initial investigations such as electrocardiogram and chest X-ray [18,36]. PE can be excluded in those with an "unlikely" pretest probability and a negative D-dimer without further imaging (Figure 3).

4.2 | D-dimer testing

D-dimers are fibrinogen degradation products, resulting from fibrinolysis of cross-linked fibrin within the thrombus. D-dimer assays are widely available, cheap, and incorporated in integrated diagnostic pathways for VTE, where the clinical probability of DVT/PE is assessed as unlikely (Figures 2 and 3) [18]. A negative D-dimer in combination with a low pretest probability score has a high negative predictive value and can safely exclude VTE without imaging [37].

The threshold at which a D-dimer is considered "positive" varies by manufacturer [38]. D-dimer is a nonspecific marker and will be raised with increasing age, and inflammatory states including the postoperative period, concurrent infection, and malignancy.

Examples of clinical probability scores used in assessment for DVT/PE

DVT

Two-level DVT Wells Score

Clinical Feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, Paresis or recent plaster immobilisation of the 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 3cm 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
Clinical probability simplified score	Total score
DVT likely	≥2
DVT unlikely	≤ 1

PE

Revised Geneva Score

Variable		Points
Risk factors	Age ≥65years	1
	Previous DVT/PE	3
	Recent surgery/fracture (4 weeks)	2
	Active malignancy	2
Symptoms	Unilateral lower-limb pain	3
	Haemoptysis	2
Clinical signs	Heart rate 75-94 beats per minute	3
	Heart rate ≥95 beats per minute	5
	Pain on lower-limb deep venous palpation and unilateral oedema	4
Interpretation		Total score
Low risk		0-3
Moderate risk		4-10
High risk		11-25

Simplified Geneva Score

Variable		Points
Risk factors	Age ≥65years	1
	Previous DVT/PE	1
	Recent surgery/fracture (4 weeks)	1
	Active malignancy	1
Symptoms	Unilateral lower-limb pain	1
	Haemoptysis	1
Clinical signs	Heart rate 75-94 beats per minute	1
	Heart rate ≥95 beats per minute	2
	Pain on lower-limb deep venous palpation and unilateral oedema	1
Interpretation		Total score
Unlikely		≤2
Likely		>2

PE

Two-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 the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified score	Total score
PE likely	>4
PE unlikely	≤ 4

YEARS algorithm

Clinical Feature	Points
Clinical signs of DVT	1
Haemoptysis	1
An alternative diagnosis is less likely than PE	1
Outcome	
0 YEARS items and D-dimer <1000ng/ml	PE excluded
1-3 YEARS items and D-dimer <500ng/ml	
0 YEARS items and D-dimer >1000ng/ml	PE imaging required
1-3 YEARS items and D-dimer >500ng/ml	

Pulmonary embolism rule-out criteria (PERC)

Clinical feature	Points
Age ≥50	1
Heart rate ≥100	1
Oxygen saturations on room air <95%	1
Unilateral leg swelling	1
Haemoptysis	1
Recent surgery or trauma within the last 4 weeks requiring general anaesthesia	1
Prior PE/DVT	1
Hormone use; Oral contraceptive, hormone replacement therapy or estrogenic hormone use	1
Outcome	
0 PERC criteria = v low risk of PE	No further investigation required
≥1 PERC criteria, cannot exclude PE	Further investigation required using an integrated diagnostic strategy (see Fig 3)

FIGURE 1 Examples of available pretest probability scores used in the assessment of suspected deep vein thrombosis (DVT) and pulmonary embolism (PE) including simplified Wells for DVT [30,35], PE [35], revised and simplified Geneva scores [31,32], YEARS algorithm [33,34] and pulmonary embolism rule-out criteria [34].

For this reason, raised D-dimer alone cannot be used to diagnose VTE or as a screening tool [39]. D-dimer can also be normal in those on anticoagulants and therefore should not be used to exclude VTE in this scenario. Adapting D-dimer thresholds by age in those over 50 ("age-adjusted" D-dimer) or by clinical probability (with incremental increases in D-dimer thresholds with reducing pretest probability) have been investigated and are proposed as strategies to further reduce the proportion of patients requiring imaging [40,41].

4.3 | Diagnostic imaging

Access to imaging may be restricted out of hours or limited by capacity. When DVT/PE is suspected and there is an anticipated delay in confirmatory imaging (in England defined as >1 hour for PE, >4 hours for DVT), interim therapeutic anticoagulation should be commenced until the diagnosis is confirmed/excluded [18].

4.3.1 | Imaging for suspected DVT

The current gold standard for DVT diagnosis is compression ultrasound of the lower limb. The inability to compress a vein indicates the presence of thrombosis. Color Doppler is used to visualize blood flow within the vessel and is a useful adjunct, particularly for intra-abdominal/pelvic veins, which cannot easily be compressed [18,36,42]. Ultrasound can be limited to the proximal veins, or extended to include the distal veins (whole leg scan), although this practice varies between centers. If a proximal DVT is diagnosed, then the more time-consuming scanning of the distal veins is not usually required. In centers without access to whole leg scanning, patients with a high/likely pretest probability and positive D-dimer should have a repeat ultrasound at 1 week (following suspension of newly commenced anticoagulation), in the presence of an initially normal proximal leg compression ultrasound. CT venography and MR venography are rarely required for DVT diagnosis but may be considered in those with inadequate views on ultrasound and a strong clinical suspicion of iliac vein thrombosis, eg, patients presenting with buttock pain and/or swelling of the upper thigh.

4.3.2 | Imaging for suspected PE

Patients with suspected PE and a high/likely clinical pretest probability, and those with low to moderate or unlikely probability and a high D-dimer, require further imaging for diagnosis of PE. CT pulmonary angiography is the predominantly used imaging modality for the diagnosis of PE [18,36]. It is widely available and can be rapidly performed in and out of office hours with a high sensitivity and specificity. Additional advantages are the identification of alternate diagnoses and for confirmed PE, evaluation for radiological features of right heart strain [18].

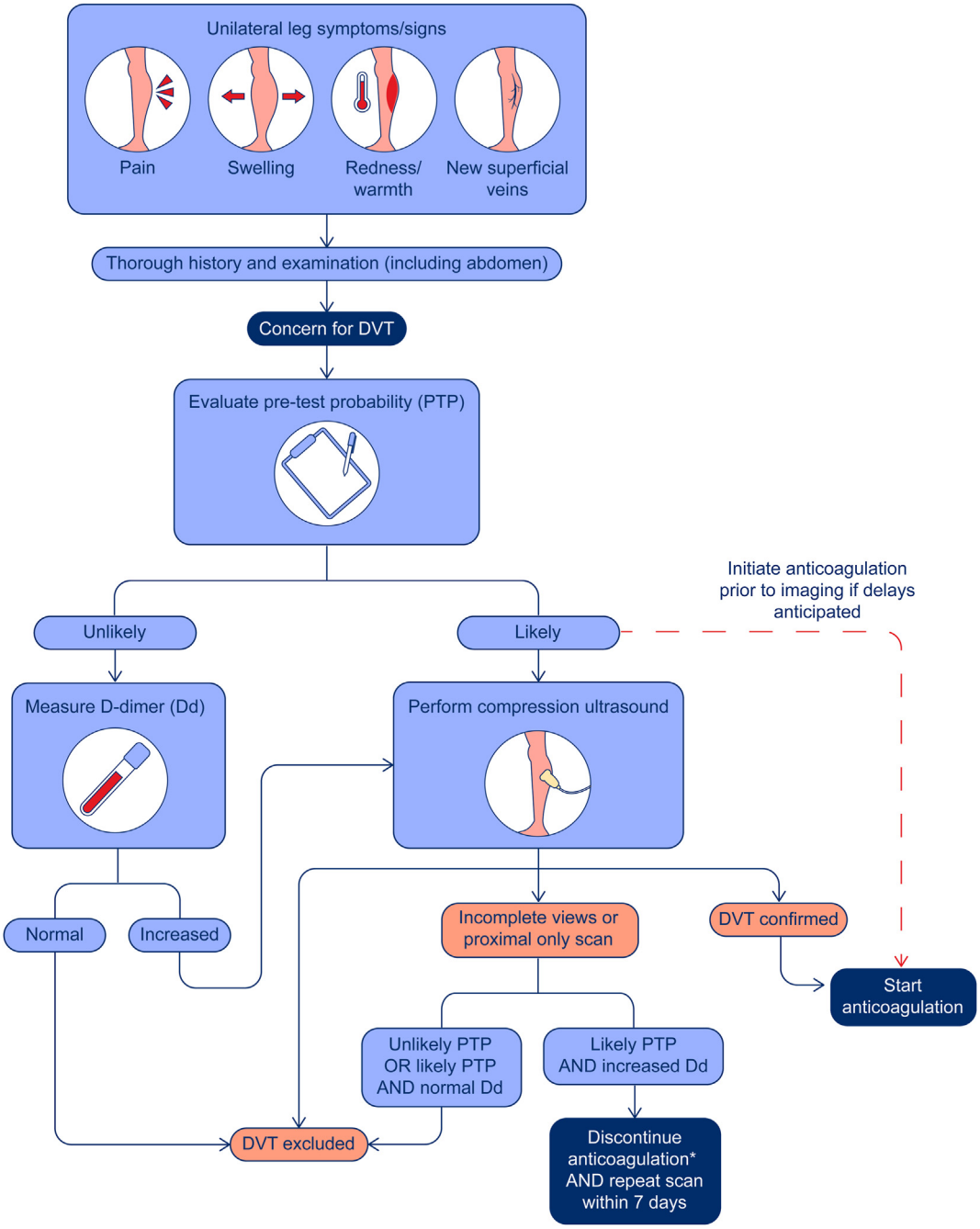


FIGURE 2 Integrated diagnostic strategy for suspected deep vein thrombosis (DVT) using the simplified Wells score [30]. *For patients previously on thromboprophylaxis or long-term anticoagulation, continue prior treatment. PTP, pretest probability.

Ventilation-perfusion (V/Q) scanning is a nuclear medicine imaging technique used in the diagnosis of PE, where radiopharmaceuticals are given intravenously or inhaled to assess lung perfusion and ventilation, respectively. PE is confirmed when a mismatch is identified, ie, absent perfusion with normal ventilation of 2 or more segmental areas. The key advantage is reduced radiation exposure and lack of need for intravenous contrast, which may be preferred in those with renal impairment or contrast allergy. However, it is not as widely available and not suitable for use in patients with lung parenchymal abnormalities where ventilation will be impaired [18]. Other concerns include the availability of radiopharmaceuticals, interobserver variation in interpretation, and reduced sensitivity for subsegmental PE.

5 | RISK STRATIFICATION OF CONFIRMED PE AND MANAGEMENT IMPLICATIONS

Acute PE has variable clinical severity ranging from minimal symptoms to cardiovascular compromise, shock, and early death. PE may

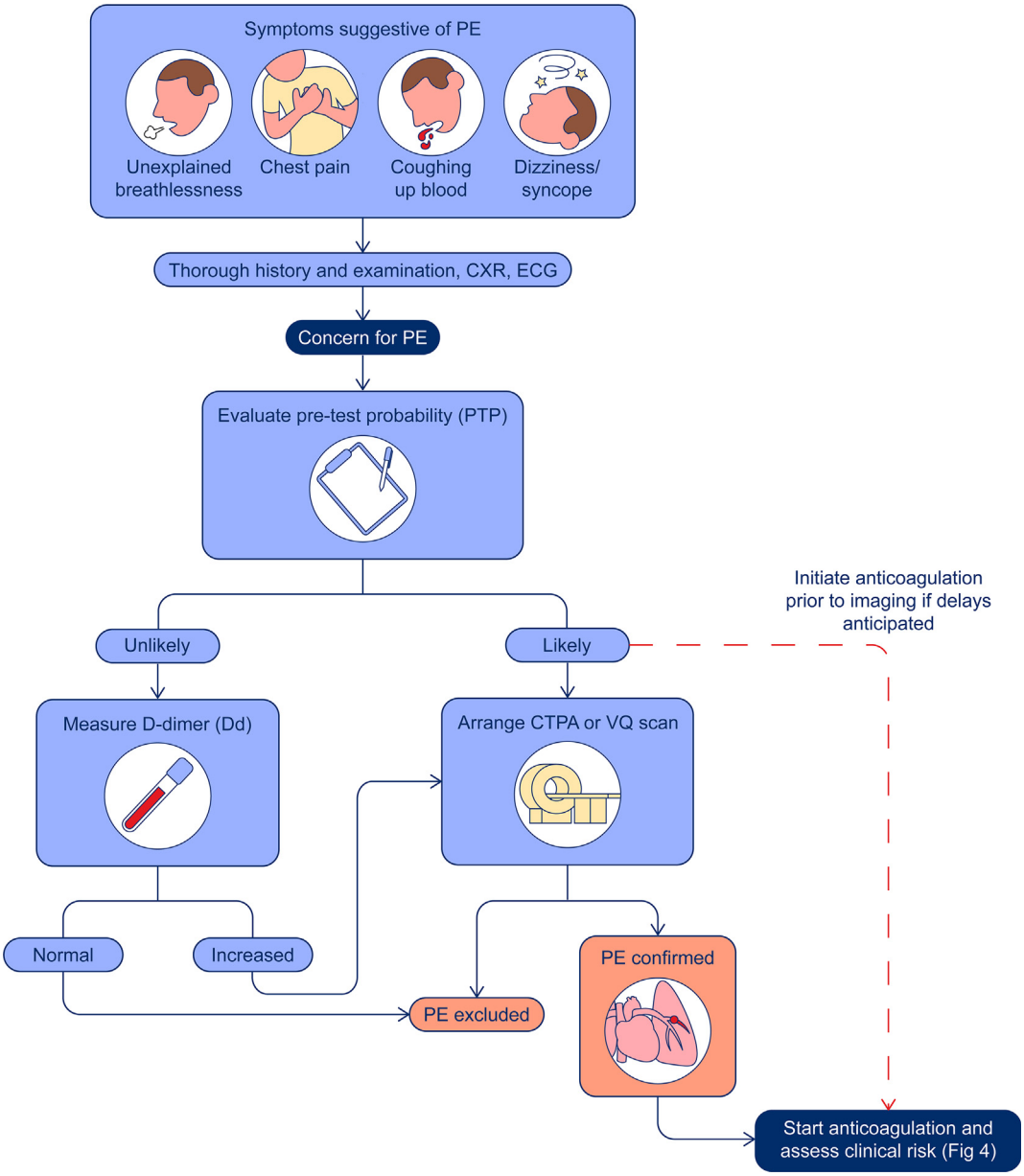
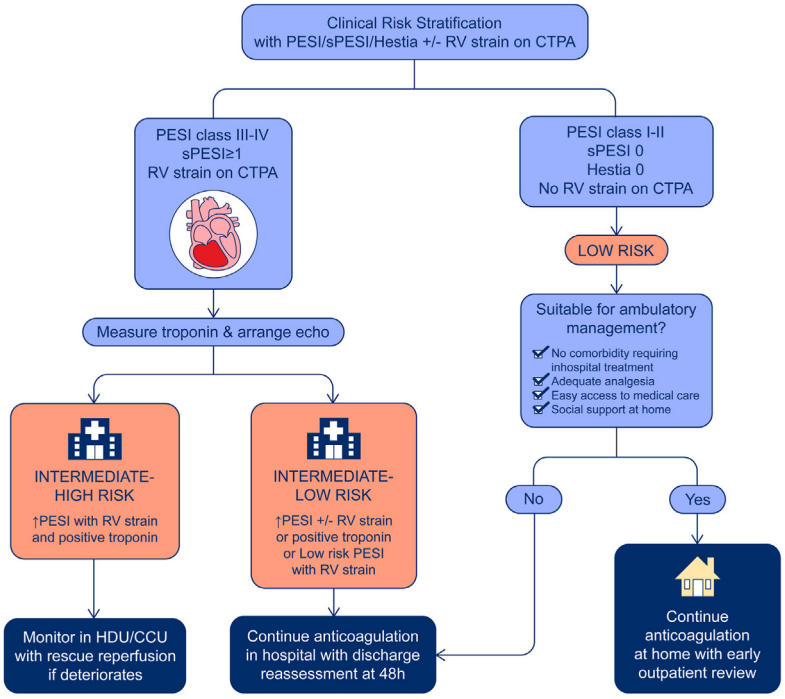


FIGURE 3 Integrated diagnostic strategy for suspected pulmonary embolism (PE) using the simplified Wells score for PE [35]. CTPA, computed tomography pulmonary angiography; CXR, chest X-ray; echo, echocardiogram; ECG, electrocardiogram; VQ, ventilation/perfusion.

compromise both gas exchange and circulation with the latter responsible for most mortality due to pressure overload leading to right ventricular failure [43]. Hemodynamic instability is defined as any of the following conditions: (1) cardiac arrest, (2) obstructive shock (persistent hypotension, systolic blood pressure [SBP] < 90 mmHg, or need for inotropes to maintain SBP with end-organ hypoperfusion); or (3) persistent hypotension (SBP < 90 mmHg despite adequate filling) [44]. It represents a life-threatening emergency, and reperfusion therapy with thrombolysis is recommended. If a patient is too unstable for definitive imaging, a bedside echocardiogram can help confirm right ventricular (RV) strain suggestive of PE. In all other patients, clinical risk stratification tools (PESI score [45], simplified PESI score [46], HESTIA [47,48]), incorporating patient characteristics, comorbidities, clinical observations, and laboratory parameters can be used to identify those patients at low, intermediate, and high risk of mortality (Figure 4). Many patients with low-risk PE, including those with isolated subsegmental PE, can be safely managed in the ambulatory setting [49].

Prognostic markers include the presence or absence of RV strain, assessed radiologically via CTPA or by echocardiogram, and cardiac biomarkers (troponin, NT-proBNP). These markers are only useful to predict mortality in PE when used in conjunction with clinical risk stratification scores [43]. Patients with an intermediate high-risk score on PESI with evidence of RV strain on imaging (ideally echocardiogram) and positive troponin have higher mortality and require close initial monitoring due to a higher risk of clinical deterioration [43].



Pulmonary Embolism Severity Index (PESI) score	
Clinical Features	**Points**
Age	Age (years)
Male sex	10
History of cancer	30
History of heart failure	10
History of chronic lung disease	10
Heart rate ≥ 110	20
Systolic blood pressure < 100 mmHg	30
Respiratory rate ≥ 30	20
Temperature < 36 °C	20
Altered mental state	60
Oxygen saturations < 90%	20
Interpretation	**Total Score**
PESI class I = Very Low Risk	≤65
PESI class II = Low Risk	66-85
PESI class III = Intermediate Risk	86-105
PESI class IV = High Risk	106-125
PESI class V = Very High Risk	>125
Simplified PESI Score	
Clinical Feature	**Points**
Age >80	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Heart rate ≥ 110	1
Systolic blood pressure < 100 mmHg	1
Interpretation	**Total Score**
Low Risk	0
High Risk	≥1
Hestia Score	
Clinical Feature	**Points**
Haemodynamically unstable	1
Thrombolysis or embolectomy needed	1
Active bleeding or high risk for bleeding	1
Supplemental oxygen required to maintain oxygen saturations >90%	1
PE diagnosed whilst on anticoagulation	1
Severe pain requiring iv analgesia for >24hours	1
Medical or social reason for admission >24hours	1
Creatinine clearance <30ml/min	1
Severe liver impairment	1
Pregnant	1
Documented history of heparin induced thrombocytopenia	1
Interpretation	**Total Score**
Low Risk	0
High Risk	≥1

FIGURE 4 Risk stratification for confirmed PE with hemodynamic stability. CCU, critical care unit; CTPA, computed tomography pulmonary angiography; HDU, high dependency unit; PE, pulmonary embolism; PESI, pulmonary embolism severity index; [45] RV, right ventricular.

Clinical decision-making regarding treatment of intermediate-high and high-risk PE can be challenging and timely treatment decisions need to be made. Critical care review should be sought to consider initial observation (48-72 hours) in a high dependency/critical care unit. Given the lack of strong evidence to inform optimal management in this patient group, expert opinion, and experience in making these clinical decisions are invaluable. Many centers now have PE response teams enabling multispecialty discussion in real-time to optimize early decision-making, particularly with regard to reperfusion therapy [50].

6 | ANTICOAGULATION MANAGEMENT

The principal aim of initial and primary treatment is to prevent thrombosis propagation and embolization, thereby reducing associated morbidity and mortality. Anticoagulation remains the mainstay of treatment, with consideration of concomitant reperfusion therapy in selected high-risk patients. Direct oral anticoagulants (DOACs) are now the standard of care for VTE treatment, with low molecular weight heparin (LMWH) and vitamin K antagonists (VKAs) reserved for selected patients. All patients should have their weight measured, along with a full blood count, creatinine, liver profile, and coagulation screen, to aid in the evaluation of bleeding risk and inform the optimal choice and dose of anticoagulant. The vast majority of patients with DVT can be managed in an ambulatory setting, exceptions being those with vascular compromise or comorbidities requiring inpatient management [51]. In the longer term, the focus moves to secondary prevention of recurrent VTE, with assessment and management of complications. Treatment considerations throughout phases of care are summarized in Figure 5.

6.1 | Available anticoagulants

Characteristics of the available anticoagulants for VTE treatment are summarized by class in Table 3 [52].

6.1.1 | Direct oral anticoagulants

DOACs are preferred for the treatment of VTE in most patients. Randomized controlled clinical trials demonstrated noninferior efficacy of both direct oral activated factor X (FXa) inhibitors (apixaban, edoxaban, rivaroxaban) and the oral direct thrombin inhibitor, dabigatran in the treatment of VTE in comparison to LMWH/warfarin, with a reduced risk of fatal and intracranial bleeding [53–58]. The advantages of DOACs compared to VKAs include predictable pharmacokinetics allowing fixed dosing regimens (Table 3) without the need for therapeutic drug monitoring, rapid onset/offset of action, and fewer drug/food interactions. Apixaban and rivaroxaban can be used as a single oral drug approach in the acute phase of VTE treatment, whereas edoxaban and dabigatran require parenteral anticoagulation for at least 5 days prior to initiation. The short half-life of DOACs simplifies management in clinical scenarios such as bleeding, overdose, and

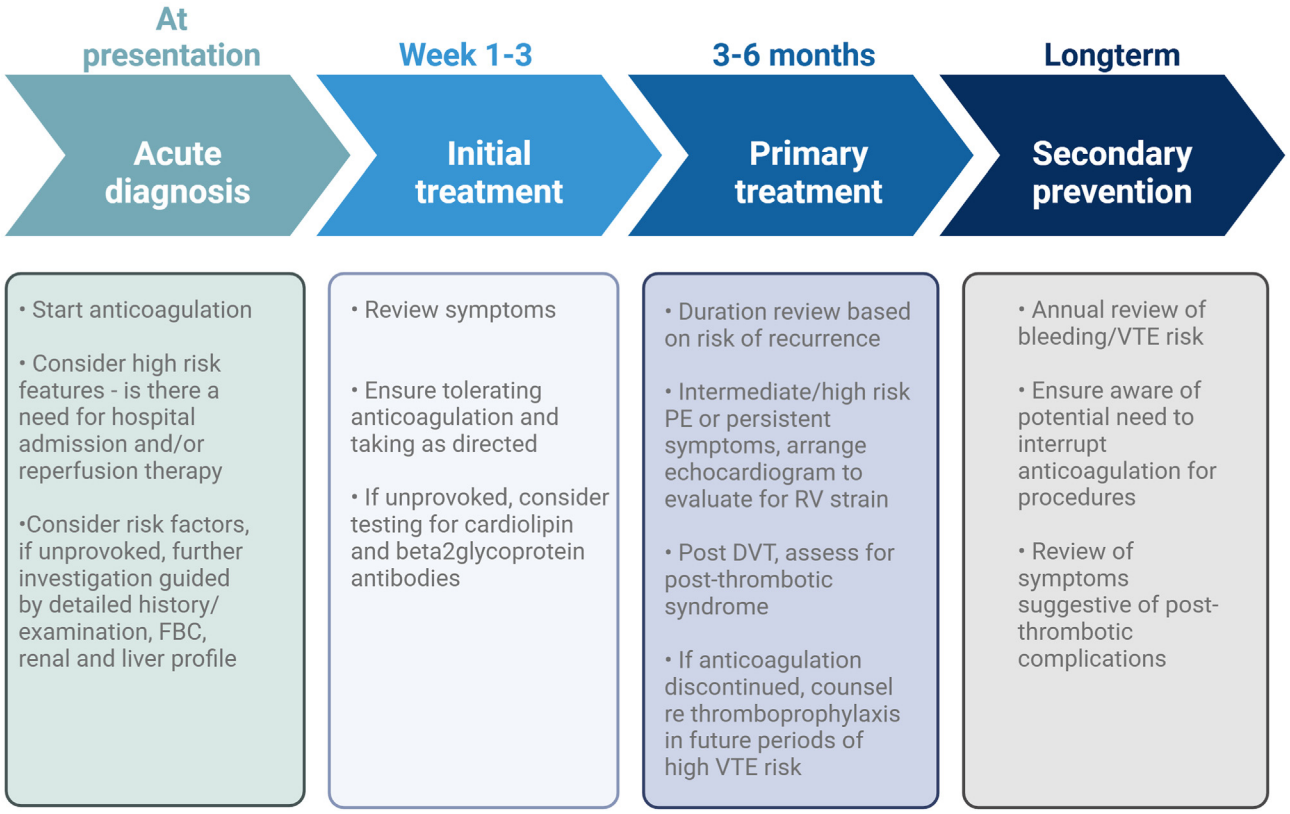


FIGURE 5 Approach to venous thromboembolism (VTE) management throughout phases of care Created with Biorender.com. DVT, deep vein thrombosis; FBC, full blood count; RV, right ventricular; PE, pulmonary embolism.

perioperative management. However, this may be a disadvantage in those with incomplete adherence. Other potential limitations of DOACs include renal and hepatic metabolism, drug–drug interactions (P-gp and CYP3A4 inducers/inhibitors), and limited scope for dose adjustment. While antidotes (idarucizumab and andexanet alpha) are available, there is geographic variation in access and use. There is generally insufficient data to recommend one DOAC over another. Patient characteristics and preferences are important factors when deciding on which anticoagulant to offer.

6.1.2 | LMWH/unfractionated heparin

eparin has been extensively used in the treatment of VTE; it acts indirectly by potentiating the inhibitory action of antithrombin on FX and FII. Both unfractionated heparin (UFH) and LMWH remain treatment options for VTE. UFH is rarely required and generally avoided due to its unfavorable safety profile with unpredictable dose response, increased risk of bleeding, heparin-induced thrombocytopenia, and mortality compared to LMWH [59]. UFH may be preferred for patients under consideration for primary reperfusion therapy. LMWH is administered by subcutaneous injection once or twice daily with the dose determined by body weight. LMWH is available as prefilled syringes, and patients can be taught to self-administer, enabling use in ambulatory settings. LMWH can be used in patients with a creatinine clearance >15 mL/min, with dose adjustments in those with a creatinine clearance of 15 to 30 mL/min. Given the short half-life and potential for once-daily dosing, LMWH is particularly useful in those patients who have an increased risk of bleeding and those undergoing further invasive procedures. LMWH is required as a bridge to VKA and should be continued until the international normalized ratio (INR) >2.0. It may also be used for the initial 5 days prior to initiation of edoxaban or dabigatran in acute VTE.

6.1.3 | Fondaparinux

Fondaparinux is a synthetic pentasaccharide that indirectly inhibits FX via potentiation of antithrombin. It is as effective as LMWH/UFH in the initial treatment of VTE [60,61]. It is preferred for patients requiring parenteral anticoagulation with heparin allergy, previous heparin-induced thrombocytopenia, or with concerns regarding the use of animal products (as heparin is porcine-derived).

6.1.4 | VKAs

VKAs were the first oral anticoagulant available to treat VTE and have been in use for decades. VKAs inhibit vitamin K epoxide reductase

TABLE 3 Characteristics and dosing of available anticoagulants.

Characteristic	Vitamin K antagonist	LMWH	Fondaparinux	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Dosing	Variable once daily, based on INR	Weight-based, Once or twice daily	Weight-based, 7.5 mg once daily	150 mg twice daily	Twice daily	60 mg once daily	Twice daily for 3 wk then once daily
Initiation	Overlap with LMWH until INR >2	Twice daily preferred	Weight-based, once daily	≥ 5 d LMWH then switch to dabigatran	10 mg twice daily for 7 d	≥ 5 d LMWH then switch to edoxaban	15 mg twice daily for 3 wk
Subsequent	Based on INR	Consider switching to once daily if continuing beyond acute phase	No change	Continue same dose	5 mg twice daily from day 8. Consider ↓ to 2.5 mg at 6 mo for secondary prevention	Continue same dose	20 mg daily from day 22. Consider ↓ to 10 mg after 3-6 mo for secondary VTE prevention
Dose modification	Based on INR	Dose reduction if CrCl <30mL/min	<50 kg, 5 mg once daily >100 kg, 10 mg once daily	Y to 110 mg twice daily for selected patients[a]	n/a	Y to 30 mg daily for selected patients[b]	n/a
Drug monitoring	Y	N	N	N	N	N	N
Hepatobiliary and intestinal metabolism	Predominant	Minimal	Minimal	20%	73%	50%	65%
Renal excretion	Minimal	Predominant	Predominant	80%	27%	50%	66%
CKD							
CrCl, 15-30 mL/min	Y	↓dose	Do not use	Do not use	Limited experience	Limited experience	Limited experience
<15 mL/min	Y	Avoid	Do not use	Do not use	Do not use	Do not use	Do not use
Reversal agent	Y	Partial	N	Y	Y, restricted use in some regions	N	Y, restricted use in some regions

CKD, chronic kidney disease, CrCl; creatinine clearance; INR, international normalized ratio; LMWH, low molecular weight heparin; n/a, not applicable; N, no; Y, yes.

Adapted from [52] with permission from Wolters Kluwer Health, Inc.

[a] Dabigatran 110 mg twice daily in patients >80 years of age and those also on verapamil. Consider dose reduction in patients aged 75-80 years, with moderate renal impairment (CrCl 30-50 mL/min), with gastritis, esophagitis, or gastroesophageal reflux, or at increased risk of bleeding.

[b] Edoxaban 30 mg once daily for patients with CrCl 15-50mL/min or <60 kg or taking concomitant PgP inhibitors.

thereby depleting the reduced form of vitamin K required for gamma-carboxylation of vitamin K-dependent coagulation factors (FII, FVII, FIX, FX, protein C, and protein S). Hence, VKAs have slow onset and offset of action, numerous food and drug interactions, and significant intra- and interindividual variability. Therapeutic drug monitoring with the INR is required to guide dosing, with a usual therapeutic range of 2.0 to 3.0 for the treatment of VTE. Given the slow onset of action, there is the requirement to bridge patients with LMWH (or alternatives), until an INR of >2.0 is achieved. Warfarin and acenocoumarin are the most widely prescribed VKAs. As VKAs are not dependent on renal clearance, VKAs can be used in patients with a creatinine clearance <15 mL/min and are therefore preferred in those with end-stage renal disease.

6.2 | Assessment of bleeding risk

Bleeding is the most frequent side effect of anticoagulation, with an overall incidence of 2% to 3% in the initial 3 to 6 months, and ~1% per year in those on extended anticoagulation (with higher bleeding risk with VKAs compared to DOAC) [62,63]. Additionally, bleeding has a higher case fatality rate than recurrent VTE [64,65]. It is rarely appropriate to withhold anticoagulation completely in the absence of active bleeding or very high bleeding risk in patients with acute VTE. For selected patients with isolated distal DVT or subsegmental PE (without concomitant DVT) and a lack of persisting VTE risk factors for extension, surveillance may be appropriate. However, the optimal management approach remains controversial [66–68]. The aim of assessing bleeding risk is to identify and address modifiable bleeding risk factors, such as stopping antiplatelets or NSAIDs if no longer required, reducing alcohol intake, optimizing control of hypertension, assessing and preventing falls, and avoiding interacting medications/herbal remedies where suitable alternatives exist [27]. There are validated risk assessment models to aid in evaluating bleeding risk, however further comparative outcome studies are needed to identify the tool with optimal prediction [27]. Patients should be counseled regarding the risk of bleeding, symptoms, and signs to be aware of and when to seek medical attention.

6.3 | Special patient groups

In this section, we summarize important considerations in these commonly encountered patient populations [69,70]. Of note, there are comprehensive reviews and guidelines dedicated to each of these special populations available, and we direct readers to these for more detailed discussion than possible in this "basics" review.

6.3.1 | Women of childbearing age

Anticoagulation commonly results in or exacerbates, heavy menstrual bleeding with consequent significant morbidity and adverse impact on quality of life [22]. It is important to take a menstrual history to identify pre-existing menorrhagia when commencing anticoagulation to enable preventative measures. All women should be counseled regarding the potential risk of menorrhagia. Apixaban, dabigatran, and LMWH may be associated with a lesser risk of heavy menstrual bleeding and may be preferred for women with pre-existing menorrhagia [22]. Women taking hormonal contraception should not be advised to discontinue abruptly at diagnosis of VTE, as this may precipitate withdrawal bleeding. Estrogen-containing contraception should be reviewed and switched in a controlled manner prior to stopping anticoagulation given the increased recurrence risk associated with continuation. All women of childbearing age should be counseled regarding the limited data supporting the safety of DOACs in pregnancy, the risk of embryopathy where VKAs are continued beyond 6 weeks of pregnancy, and the need to seek further medical advice if planning pregnancy or on positive pregnancy test [71,72].

6.3.2 | Extremes of body weight

VKAs have, until recently, remained the preferred anticoagulation for patients with low (<50 kg) or high (>120 kg) body weight, as such patients were excluded from the seminal DOAC trials. There is increasing evidence to support the use of apixaban and rivaroxaban in those with high body weight, and international guidelines now recommend these agents for the treatment of VTE, without routine drug monitoring [73]. While there is no consensus guideline regarding the use of DOACs in low body weight, there is increasing use of apixaban and edoxaban in patients with low body weight <50 kg with good clinical outcomes [74].

6.3.3 | Cancer

Patients with cancer-associated thrombosis (CAT) have an increased risk of recurrent VTE and bleeding [75,76]. Patients with cancer often have additional bleeding risk factors such as drug interactions with chemotherapy, thrombocytopenia, issues with absorption (as a result of poor appetite, nausea, or vomiting), and renal impairment. Historically, LMWH has been preferred for the treatment of CAT. However, trials have more recently demonstrated that DOACs are associated with a lower risk of recurrent VTE compared to LMWH, but with increased bleeding [77]. Bleeding risk with DOACs is at least partly influenced by site of cancer, with increased risk in patients with genitourinary or intraluminal gastrointestinal tumors. Decisions regarding the choice of anticoagulant should be made following consideration of bleeding risk, site of cancer, suitability of oral therapy, drug interactions, and patient preference [78,79]. LMWH may be preferred at initiation, particularly where a cancer diagnosis/treatment plan has not yet been confirmed [78,79].

6.3.4 | Renal impairment

DOACs, LMWH, and fondaparinux are at least partially renally cleared with consequent implications for patients with low or high creatinine clearance. Patients with renal impairment were excluded from the seminal DOAC trials, and therefore, their use is cautioned against in chronic kidney disease [53–57]. Dabigatran is almost exclusively renally cleared and should not be offered to those with creatinine clearance of < 30mL/min, with a reduced dose for moderate renal impairment (Table 3). Rivaroxaban and edoxaban are not licensed for those with creatinine clearance of < 15mL/min. In the United States, apixaban is licensed for VTE treatment in those with renal impairment including those requiring dialysis but there is limited high-quality data to support this and limited experience in other countries [80,81]. The seminal study of edoxaban for stroke prevention in atrial fibrillation suggested an increased stroke risk in patients with high creatinine clearance receiving edoxaban compared to warfarin; it is therefore suggested that it should be avoided in patients with creatinine clearance >95 mL/min [82].

6.3.5 | Previous GI/bowel resection surgery/ malabsorption

Absorption of DOACs occurs predominantly in the stomach and small intestine. As a result of this, there may be concern regarding the use of DOACs in those patients who have had bariatric or major small bowel resection surgery, percutaneous gastrostomy, or issues with malabsorption [83]. LMWH/fondaparinux remain the anticoagulants of choice in those with true malabsorption and in the acute setting, following bariatric surgery [73]. There is emerging evidence of adequate apixaban absorption following bariatric surgery and apixaban may be considered in selected cases [84]. Apixaban, edoxaban and rivaroxaban are all licensed for administration via percutaneous gastrostomy.

6.3.6 | Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder characterized by arterial and/or venous thrombosis, and/or pregnancy morbidity alongside the presence of persistent antiphospholipid antibodies (one or more β2-glycoprotein, cardiolipin antibodies, and lupus anticoagulant confirmed on repeat testing 12 weeks apart) [85]. Patients with APS have a high risk of recurrent (venous and arterial) thrombosis and long-term anticoagulation is recommended. The risk of thrombotic complications is partially mediated by antibody profile and patients with persistent positivity of all 3 antibodies (so-called triple positive) have the highest risk of thrombotic complications including an increased risk of recurrence despite anticoagulation. Trials investigating rivaroxaban and apixaban in patients with APS were terminated early due to safety concerns, with an increased risk of predominantly arterial thrombosis in those receiving DOAC [86]. Therefore VKAs remain the treatment of choice in those with confirmed APS, particularly in those with triple-positive antibody profiles [85].

7 | INTERVENTIONAL APPROACHES TO VTE MANAGEMENT

7.1 | Catheter-directed thrombolysis for proximal DVT

Most patients with DVT can be safely managed with anticoagulation alone. There has been significant interest in the use of catheter-directed thrombolysis (CDT) to reduce the risk of postthrombotic syndrome (PTS), with conflicting findings in clinical trials [87–89]. The use of CDT necessitates hospitalization for the duration of intervention and carries a risk of bleeding. CDT has not been associated with an improvement in long-term quality of life, and therefore, this should only be considered for highly selected cases. It may be beneficial for those with vascular compromise or without symptomatic improvement with anticoagulation in those with recent symptom onset (<14 days), iliac vein involvement, consequent significantly impaired mobility, and a low risk of bleeding [18]. Such patients should be discussed with a vascular surgeon/interventional radiologist with expertise in this area.

7.2 | Reperfusion therapy for PE

7.2.1 | Systemic thrombolysis for PE with hemodynamic instability

In this patient group, thrombolysis has been shown to significantly reduce mortality and recurrent PE. There is, however, a significant risk of major bleeding and intracranial hemorrhage, particularly in those over 65 years [44,90]. Where there is an absolute contraindication to systemic thrombolysis or an inadequate response to treatment, catheter-directed approaches or surgical embolectomy should be considered [44].

7.2.2 | Intermediate-high risk PE

In the absence of hemodynamic compromise, the evidence for interventional approaches to PE management is weak. A randomized controlled trial of thrombolysis for those with intermediate-risk PE did not demonstrate a net clinical benefit due to the increased bleeding risk [91]. However, a small study suggests reduced-dose thrombolysis may be safe and beneficial [92]. A catheter-directed approach reduces the overall dose of thrombolytic agent and is therefore associated with a lower bleeding risk; emerging evidence suggests catheter-directed thrombectomy may be of benefit in those with a high baseline bleeding risk. There is currently insufficient

evidence for these approaches to be considered routine care and further evidence from ongoing trials is required to guide their use. However, systemic thrombolysis, CDT, and/or thrombectomy should be considered in the event of deterioration despite adequate anticoagulation [44].

7.3 | Vena cava filters

Routine use of inferior vena cava (IVC) filters is not recommended. Anticoagulation is highly effective at preventing progressive thrombosis and embolization [93]. IVC filters may be considered in patients with an acute proximal DVT ± PE (within 4 weeks of diagnosis) and an absolute contraindication to anticoagulation, to reduce the risk of embolization. Of note, IVC filters are associated with an increased risk of DVT in the longer term [94], and early retrieval should be planned at the initiation of anticoagulation when no longer required [18].

8 | DURATION OF ANTICOAGULATION

The minimum treatment duration of anticoagulation in VTE is 3 months, following which a decision is required as to whether to stop or continue anticoagulation [13,51,95]. Long-term anticoagulation is effective at reducing the risk of VTE but is associated with a risk of bleeding [64]. Therefore assessment of VTE recurrence risk, risk of bleeding, patient concerns, and preferences is required when considering extended anticoagulation. Patient characteristics such as male sex, age, extent of thrombosis, and the presence of persistent or transient risk factors all influence recurrence risk [95,96]. When a decision is made in favor of extended anticoagulation, bleeding risk factors should be considered, with a focus on reducing modifiable risk factors (see above) [27]. Of note, the risk of recurrence following a first isolated distal DVT is thought to be low and extended anticoagulation is not usually required in the absence of strong persisting risk factors (eg, cancer) [68].

Review of VTE risk factors for the acute event is the currently recommended strategy for determining the risk of recurrence following proximal DVT or PE (Figure 6) [13,43,51,97]. For example, VTE associated with major surgery is associated with a low risk of recurrence of <1% at 2 years, compared to VTE-associated nonsurgical, transient provoking risk factors with a recurrence risk of approximately 8% at 2 years, and those with unprovoked VTE a recurrence rate of almost 20% at 2 years [97,98]. Patients with persistent provoking factors such as active autoimmune disease and inflammatory disorders may benefit from extended anticoagulation given the increased risk of VTE recurrence [97]. Patients with CAT should continue anticoagulation for a minimum of 6 months, with consideration of extension until the cancer is in remission and cancer treatment is completed [18,78,79].

9 | SECONDARY VTE PREVENTION AFTER WITHDRAWAL OF ANTICOAGULATION

When anticoagulation is discontinued, patients should be carefully counseled about the importance of VTE prevention in future periods of increased VTE risk (such as surgery, hospitalization with acute illness, lower limb immobilization, and pregnancy) and to seek medical attention in the event of new symptoms to suggest recurrence. Women should also be made aware of the increased VTE risk associated with combined hormonal contraception and oral hormone replacement therapy (transdermal preparations are considered safe). Where a decision to discontinue anticoagulation is made, combined hormonal contraception should be switched to a progesterone-only form (if still required) at least 4 weeks prior to discontinuing anticoagulation. Long-haul travel is a weak risk factor for VTE, and patients with major provoking factors should be reassured and advised to remain active while traveling [99]. For patients at higher risk of recurrence (previous unprovoked VTE, persistent risk factors, travel-associated VTE) who are no longer on anticoagulation, prophylactic anticoagulation can be considered for travel >4 hours [99].

10 | LONG-TERM COMPLICATIONS

The major complications of concern following an initial VTE are the risk of VTE recurrence (see above), PTS (following DVT), and chronic thromboembolic pulmonary hypertension (CTEPH) following PE.

10.1 | PTS

PTS is common affecting up to 20% to 50% of patients following the first DVT [100,101]. It is thought to arise due to damage to venous valves with consequent venous hypertension leading to increased capillary permeability and/or inflammation [102]. It is characterized by symptoms of pain, cramps, swelling, pruritis, and paresthesia, which are typically exacerbated during or following activity and relieved by rest or elevation. PTS can lead to skin changes (venous ectasia, erythema, hyperpigmentation, induration) and when severe, ulceration [101]. PTS remains a clinical diagnosis and further imaging is not helpful (unless there is concern for recurrent DVT). Residual vein thrombosis is common, and while this can make diagnosing recurrent DVT in the ipsilateral leg difficult, it is not required for the diagnosis of PTS. There is no specific treatment for PTS, and patients should be reassured that symptoms generally improve with time and simple measures such as exercise, elevating the leg when seated, and emollients to alleviate dry skin, may provide symptomatic benefit [102]. Graduated compression stockings are no longer recommended for the prevention of PTS but may be useful to manage symptoms in selected patients, ie, with significant swelling in the absence of contraindications (particularly arterial disease) [100]. For selected patients with

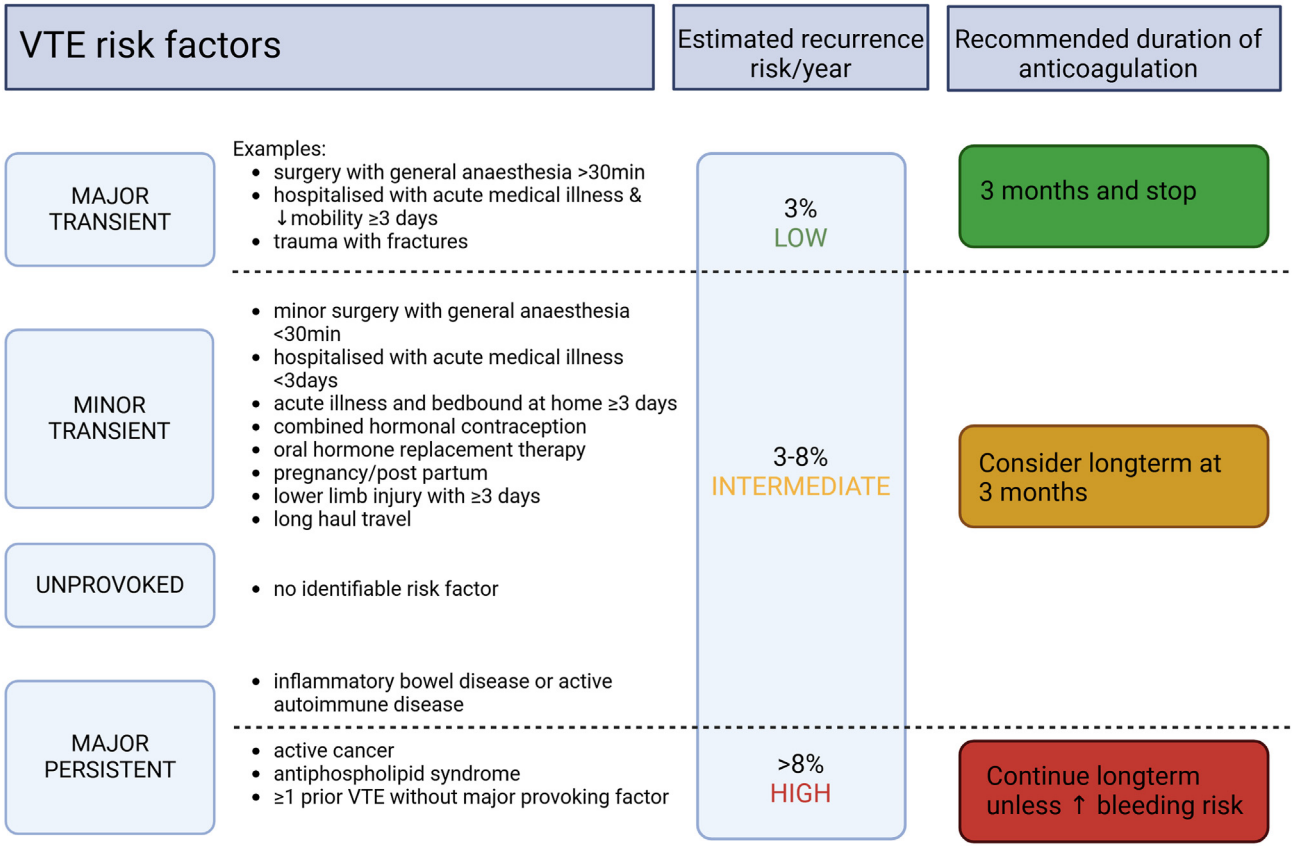


FIGURE 6 Stratification of recurrence risk following proximal deep vein thrombosis or pulmonary embolism and recommended duration of anticoagulation. Created with Biorender.com. VTE, venous thromboembolism. Adapted from [43] with permission from the author.

previous iliac vein thrombosis, persistent venous obstruction, and severe symptoms, there may be a role for endovascular or surgical intervention, and referral to a vascular surgeon with a special interest in DVT is suggested [100]. Prevention of recurrent DVT is key to avoid progression of symptoms.

10.2 | Post-PE syndrome and CTEPH

CTEPH is uncommon affecting 2% to 3% of patients surviving acute PE [103]. Symptoms are nonspecific and most commonly comprise persistent exertional breathlessness. Signs of RV failure (ie, RV heave, raised jugular venous pressure, hepatomegaly, peripheral edema) are only evident at a late stage [104]. Of note, up to half of patients report persistent breathlessness up to 12 months following a PE diagnosis, recently coined "post-PE syndrome" [105]. This is attributed to a combination of deconditioning, anxiety, and/or ventilatory or circulatory impairment secondary to previous PE. Post-PE syndrome has a significant adverse impact on quality of life. Evaluating which patients require further investigation for CTEPH is essential as this condition is associated with high mortality and is frequently a delayed diagnosis [104]. Those with significant thrombosis burden (and RV strain) at presentation and/or persistent symptoms of exertional breathlessness should have an echocardiogram following 3 months of anticoagulation. CTEPH is considered low probability in those with low or undetectable tricuspid regurgitation velocity and the absence of other echocardiographic evidence of RV strain. These patients can be reassured, with consideration of pulmonary rehabilitation/exercise programs to improve exercise tolerance. Where tricuspid regurgitation velocity is increased (>2.8 m/s) or with other echocardiographic features of RV strain, a ventilation/perfusion scan should be performed to look for persistent perfusion defects. Those with persistent perfusion defects should then be referred to a specialist pulmonary hypertension center for further evaluation with right heart catheterization and pulmonary angiography. We direct readers to an excellent illustrated review and the European Respiratory Society statement for further details of CTEPH diagnosis and management [104,106].

11 | CONCLUSION

VTE is common and associated with significant morbidity and mortality. A high degree of clinical suspicion is required to ensure early diagnosis using integrated diagnostic strategies with prompt initiation of anticoagulation. DOACs are the treatment of choice for the majority and have greatly simplified management. All patients should be reviewed before 3 months to consider the optimal duration of anticoagulation, re-evaluate bleeding risk, and monitor for long-term

complications. Extended anticoagulation should be considered for those at high risk of VTE recurrence. Patients should be counseled and involved in decision-making throughout, to minimize later anxiety and optimize treatment adherence.

AUTHOR CONTRIBUTIONS

C.C. and L.N.R. cowrote the manuscript and approved the final submission.

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