New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism

Huyen A Tran[1,2], Harry Gibbs[1,2], Eileen Merriman[3], Jennifer L Curnow[4], Laura Young[5], Ashwini Bennett[6], Tan Chee Wee[7], Sanjeev D Chunilal[8], Chris M Ward[9], Ross Baker[10], Harshal Nandurkar[2,11]

Abstract

Introduction: Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease and, globally, more than an estimated 10 million people have it yearly. It is a chronic and recurrent disease. The symptoms of VTE are non-specific and the diagnosis should actively be sought once considered. The mainstay of VTE treatment is anticoagulation, with few patients requiring additional intervention.

A working group of experts in the area recently completed an evidence-based guideline for the diagnosis and management of DVT and PE on behalf of the Thrombosis and Haemostasis Society of Australia and New Zealand (www.thanz.org.au/resources/thanz-guidelines).

Main recommendations:

- The diagnosis of VTE should be established with imaging; it may be excluded by the use of clinical prediction rules combined with D-dimer testing.
- Proximal DVT or PE caused by a major surgery or trauma that is no longer present should be treated with anticoagulant therapy for 3 months.
- Proximal DVT or PE that is unprovoked or associated with a transient risk factor (non-surgical) should be treated with anticoagulant therapy for 3–6 months.
- Proximal DVT or PE that is recurrent (two or more) and provoked by active cancer or antiphospholipid syndrome should receive extended anticoagulation.
- Distal DVT caused by a major provoking factor that is no longer present should be treated with anticoagulant therapy for 6 weeks.
- For patients continuing with extended anticoagulant therapy, either therapeutic or low dose direct oral anticoagulants can be prescribed and is preferred over warfarin in the absence of contraindications.
- Routine thrombophilia testing is not indicated.
- Thrombolysis or a suitable alternative is indicated for massive (haemodynamically unstable) PE.

Changes in management as a result of the guideline: Most patients with acute VTE should be treated with a factor Xa inhibitor and be assessed for extended anticoagulation.

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease, with an annual incidence of more than 10 million people globally.[1] In Australia, at least 17 000 people develop VTE each year (annual incidence, 0.83 per 1000 population).[2] The lifetime risk of VTE is 8%, with 1% of people aged over 80 years experiencing their first VTE. This disease is a major cause of health-related economic loss for the patient and the community (estimated to be $1.7 billion for Australia in 2008).[3] It is a chronic and frequently recurrent disease.

VTE can be fatal if untreated; long term morbidity includes post-thrombotic syndrome (PTS) and pulmonary hypertension. Symptoms of VTE are non-specific, and the diagnosis should actively be sought once considered. A diagnosis of VTE has an impact on subsequent pregnancies, oestrogen use, surgery, life insurance and, occasionally, long-haul travel.

This guideline summary outlines the recommendations for the diagnosis and management of VTE on behalf the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) (Box 1).

Methods

The VTE Writing Group was established within THANZ and it comprised experts in the field of thromboembolic disorders in Australia and New Zealand. All members undertook a detailed literature review and critically appraised existing evidence on the diagnosis and treatment of VTE. Drafts of evidence-based recommendations, practice points and background manuscript were developed. We then conducted a 2-day face to face meeting on 25–26 February 2018 to draft the guideline. Further revisions were made via emails or face to face meetings. The summary recommendations follow the National Health and Medical Research Council levels of evidence (www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (www.gradeworkinggroup.org) to determine the strength of the recommendations.

Risk factors for venous thromboembolism

There are inherited and acquired VTE risk factors. Multiple risk factors often coexist in an individual, each contributing to the overall VTE risk. While hereditary thrombophilia is associated with an increased VTE risk, there is little clinical benefit of testing for this condition, as its utility in decision making regarding anticoagulation is low.[4]

It is important to delineate whether a VTE event was provoked or unprovoked. Provoking factors can be further classified as surgical (recent major surgery) or non-surgical and transient or persistent (Box 2). Such clinical categorisation is important as it has an impact on the risk of VTE recurrence and duration of anticoagulation (Box 3).[5] VTE occurring within 2 months of a transient provoking risk factor has one-half the risk of recurrent VTE after stopping anticoagulant therapy compared with patients with no transient risk factor.[6]

[1] Alfred Health, Melbourne, VIC. [2] Monash University, Melbourne, VIC. [3] Waitemata District Health Board, Auckland, New Zealand. [4] Haemophilia Treatment Centre, Westmead Hospital, Sydney, NSW. [5] Auckland District Health Board, Auckland, New Zealand. [6] Monash Medical Centre, Melbourne, VIC. [7] Royal Adelaide Hospital, Adelaide, SA. [8] Monash Health, Melbourne, VIC. [9] Royal North Shore Hospital, Sydney, NSW. [10] Perth Blood Institute, Perth, WA. [11] Australian Centre of Blood Diseases, Melbourne, VIC. huyen.tran@monash.edu
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1 Thrombosis and Haemostasis Society of Australia and New Zealand guidelines: evidence-based recommendations for the diagnosis and management of pulmonary embolism (PE) and deep vein thrombosis (DVT)

	Interventions	GRADE*	Evidence†
Diagnosis of PE and DVT	A non-high pre-test probability (Wells or Geneva score) combined with a negative D-dimer result safely excludes VTE without imaging	Strong	High
	A single negative complete ultrasound is sufficient to exclude DVT	Strong	High
	PE can be excluded without D-dimer or radiological testing in selected patients if the PE rule-out criteria (negative PERC rule) are met	Strong	Moderate
	A normal VQ scan or a negative technically adequate CTPA excludes PE and anticoagulation can be safely withheld	Strong	High
Treatment of VTE	Distal DVT caused by a major provoking factor that is no longer present requires OACs for 6 weeks	Strong	Moderate
	Distal DVT that has been unprovoked or with persisting risk factors requires OACs for 3 months	Strong	Moderate
	Proximal DVT or PE caused by major surgery or trauma that is no longer present requires OACs for 3 months	Strong	High
	Proximal DVT or PE that is unprovoked or associated with a transient (non-surgical) risk factor requires OACs for 3–6 months	Strong	High
	For DVT or PE that is provoked by active cancer, treat with therapeutic LMWH for at least 6 months	Strong	High
	For patients continuing with extended anticoagulation, either therapeutic or low dose DOAC is preferred over warfarin in the absence of contraindications	Strong	High
	Aspirin should be avoided unless anticoagulation cannot be used	Strong	High
Thrombophilia testing	Patients with VTE provoked by surgery or major trauma should not be screened for hereditary thrombophilia	Strong	High
Additional interventions			
PE	For patients with massive PE (sustained hypotension) and a low risk of bleeding, administer thrombolytic therapy or an alternative (eg, surgical embolectomy or catheter-based therapy) depending on local availability	Strong	Moderate
	IVC filter insertion may prevent PE in patients with acute VTE and an absolute contraindication to anticoagulation, such as active bleeding, but are not recommended in patients treated with anticoagulants for acute VTE	Strong	High
DVT	CDT may be considered in selected patients with extensive proximal DVT (involves common iliac veins) and low bleeding risk	Strong	Low
	Elastic compression stockings may be useful only to control symptoms of leg swelling and pain following DVT	Strong	Moderate

CDT = catheter-directed thrombolysis. CTPA = computed tomography pulmonary angiography. DOAC = direct oral anticoagulant. IVC = inferior vena cava. LMWH = low molecular weight heparin. OACs = oral anticoagulants. PERC = pulmonary embolism rule-out criteria. VQ = ventilation–perfusion. * Grading of Recommendations Assessment, Development and Evaluation; www.gradeworkinggroup.org. † www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf. ◆

2 Examples of non-surgical transient, or persistent provoking factors for venous thromboembolism (VTE)[5]

Type of VTE risk factor	Examples
Non-surgical transient	• Acute medical illness with immobilisation for at least 3 days • Oestrogen therapy • Pregnancy/post-partum • Leg injury associated with reduced mobility for at least 3 days • Long-haul travel
Persistent provoking	• Active cancer • Ongoing non-malignant condition associated with a twofold or higher increased risk of recurrent VTE after stopping anticoagulant therapy (ie, inflammatory bowel disease and other chronic inflammatory states) • Antiphospholipid syndrome

It is important to consider occult malignancy in unprovoked VTE, as up to 10% of such patients are diagnosed with cancer in the year after a VTE diagnosis.[7] Clinical assessment should include a thorough clinical examination and age-appropriate screening for malignancy (Box 4). In addition, abdominopelvic computed tomography scan does not identify more early stage cancers or improve outcome.[7]

Diagnosis and treatment of pulmonary embolism and deep vein thrombosis

Clinical presentations of VTE are non-specific, and only about 20% of patients with clinically suspected VTE have it objectively confirmed.[10] A misdiagnosis of VTE has significant implications, including needless cessation of effective hormonal contraception in women and unnecessary ante- and post-partum injections of low molecular weight heparin, and in older patients, anticoagulation is associated with higher rates of major and fatal bleeding.[11]

3 Types of venous thromboembolism (VTE) and associated VTE recurrence rates[5]

Type of VTE	Recurrence rate at one year after stopping anticoagulation	Recurrence rate at 5 years after stopping anticoagulation
First VTE provoked by major surgery or major trauma	1%	3%
First VTE provoked by transient risk factor (non-surgical)	5%	15%
Provoked VTE with persistent risk factors (eg, active cancer)	15%	45%
First unprovoked distal DVT	5%	15%
First unprovoked proximal DVT or PE	10%	30%
Second episode of unprovoked VTE	15%	45%

DVT = deep vein thrombosis. PE = pulmonary embolism. ◆

Conversely, failure to diagnose VTE can result in fatal PE. Therefore, objective testing is required to establish the diagnosis of VTE.

The need for imaging can be determined by the use of clinical prediction rules combined with D-dimer testing, avoiding unnecessary radiological investigations that expose patients to radiation and potential nephrotoxic contrast dyes, which are costly and inconvenient.

Clinical prediction rules

The most validated prediction rules for VTE are the Wells and Geneva scores[12] (Box 5). However, they alone cannot safely exclude VTE and must be used in combination with D-dimer testing.[13,15] *GRADE: Strong; Evidence: High.* These algorithms are designed for outpatient or emergency department assessment and are not applicable to hospitalised patients.

The pulmonary embolism rule-out criteria (PERC) is a scoring system for excluding PE.[14] It is only applicable to patients younger than 50 years of age and when the estimated rate of PE is low (< 15%).[16] This rate is seen in most Australian and New Zealand emergency departments and, therefore, PERC can be applied. If used in this way, additional investigations can be avoided in some patients. Patients with a positive PERC score should be assessed further for PE.

D-dimer assay

D-dimer levels are increased in VTE but also in many other conditions, including malignancy, inflammation, infection, trauma and pregnancy.[17]

A negative D-dimer result is a useful rule-out test when combined with an unlikely (non-high) clinical probability, avoiding imaging in many cases (Box 6 and Box 7).[12] A positive D-dimer result alone is not diagnostic of VTE and requires further radiological investigation.

Imaging

Lower extremity duplex ultrasound

Duplex ultrasound is accurate for diagnosing and excluding DVT. In Australia and New Zealand, the entire deep venous system, from ankle to groin, is evaluated with duplex ultrasound. In general, a negative single whole leg ultrasound excludes DVT and anticoagulation can be withheld (Box 6).[18]

4 Good practice points for the diagnosis and management of pulmonary embolism (PE) and deep vein thrombosis (DVT)

Clinical setting	Practice point
Diagnosis of PE and DVT	• In patients with suspected PE and adequate cardiopulmonary reserve, and a non-diagnostic lung scan, we recommend bilateral serial leg ultrasound and withholding anticoagulation if ultrasound remains negative • For patients with suspected VTE awaiting diagnostic imaging, who are considered low risk for bleeding, we recommend a treatment dose of LMWH pending the results of the scan • For pregnant women, VQ scanning is preferred over CTPA for suspected PE • An ultrasound at 3–6 months is useful as a baseline for comparison with future ultrasound for suspected recurrent DVT • For patients with previous DVT with residual venous obstruction on ultrasound, DVT recurrence may be excluded with a combination of negative D-dimer result and unchanged ultrasound appearance
Subsegmental PE	• Patients with isolated subsegmental PE who have adequate cardiopulmonary reserve and low risk of recurrence can have anticoagulation withheld if serial bilateral CUS at Day 1 and Day 7 remains negative[8]
Incidental PE in patients with cancer	• Patients with incidental PE should be treated as for patients with symptomatic cancer-associated PE[9]
Thrombophilia testing	• Young patients (< 45 years) with unprovoked proximal DVT and PE may be tested for antithrombin and protein C and S deficiency if it influences treatment duration • Patients should be counselled regarding the potential significance of thrombophilia screening prior to testing. Testing should be undertaken with specialist advice noting it may be inaccurate in the presence of anticoagulation • Patients with unprovoked proximal DVT and PE should be evaluated for malignancy by a thorough clinical assessment and age- and risk factor-appropriate screening and tested for antiphospholipid syndrome
Complications of VTE	
Chronic thromboembolic pulmonary hypertension	• In patients with prior PE who have ongoing symptoms (eg, decreased exercise tolerance, dyspnoea), perform a VQ scan and TTE to assess for residual pulmonary obstruction and screen for pulmonary hypertension • In patients with prior PE and ongoing significant symptoms with significant residual perfusion defects and pulmonary hypertension, refer to an expert centre for additional investigation and management
Invasive strategies — PE	• Retrieval of an IVC filter should be planned and scheduled at the time of insertion • Establishment of a PE response team may facilitate multidisciplinary evaluation of individual patient risk factors and management selection • Close monitoring is recommended for patients with submassive PE to enable early detection of deterioration

CTPA = computed tomography pulmonary angiography. CUS = compression ultrasonography. DVT = deep vein thrombosis. IVC = inferior vena cava. LMWH = low molecular weight heparin. PE = pulmonary embolism. TTE = transthoracic echocardiography. VQ = ventilation–perfusion. ◆

5 Clinical prediction rules for pulmonary embolism (PE)[12–14] and deep vein thrombosis (DVT)[15]

Simplified Geneva score for PE		Simplified Wells score for PE		Simplified Wells score for DVT		PERC rule*	
Age > 65 years	1	Clinical sign and symptoms of DVT	1	Active cancer (receiving treatment within past 6 months or palliative treatment)	1	Age > 50 years	1
Surgery or fracture previous 4 weeks	1	Immobility/surgery previous 4 weeks	1	Paralysis, paresis or recent plaster immobilisation of the lower extremity	1	Recent trauma/surgery	1
Previous VTE	1	Previous VTE	1	Recently bedridden for 3 days or more, major surgery within 3 months requiring general or regional anaesthesia	1	Prior VTE	1
Haemoptysis	1	Haemoptysis	1	Localised tenderness along distribution of the deep venous system	1	Haemoptysis	1
Active cancer	1	Malignancy	1	Entire leg swollen	1	Oestrogen use	1
Unilateral leg pain	1	Alternative diagnosis less likely than PE	1	Calf swelling at least 3 cm larger than the asymptomatic side	1	Arterial oxygen < 94%	1
Heart rate		Heart rate > 100 beats/min	1	Pitting oedema of the symptomatic leg	1	Heart rate > 100 beats/min	1
75–94 beats/min	1						
> 95 beats/min	2						
Pain on lower leg deep vein palpation or unilateral oedema	1			Previous documented DVT	1	Unilateral leg swelling	1
				Collateral superficial veins (non-varicose)	1		
				Alternative diagnosis at least as likely as deep vein thrombosis	−2	PERC negative	0
						PERC positive	≥ 1
Low	0–1						
Moderate	2–4						
High	≥ 5						
Unlikely	0–2	Unlikely	0–1	Unlikely	< 2		
Likely	≥ 3	Likely	≥ 2	Likely	≥ 2		

PERC = pulmonary embolism rule-out criteria. VTE = venous thromboembolism. * The estimated rate of PE must be low (< 15%). ◆

Diagnosing recurrent ipsilateral DVT is challenging, as incomplete resolution of thrombus occurs in up to 30–50% of patients after DVT.[19] For this reason, many clinicians perform a single repeat duplex ultrasound after 3–6 months if anticoagulation is to be ceased (Box 4). *GRADE: Strong; Evidence: Low.* These images may be compared with future imaging in the event of new symptoms suspicious for DVT. Multiple repeat scans in the absence of symptoms are unhelpful and do not alter management. *GRADE: Strong; Evidence: Low.*

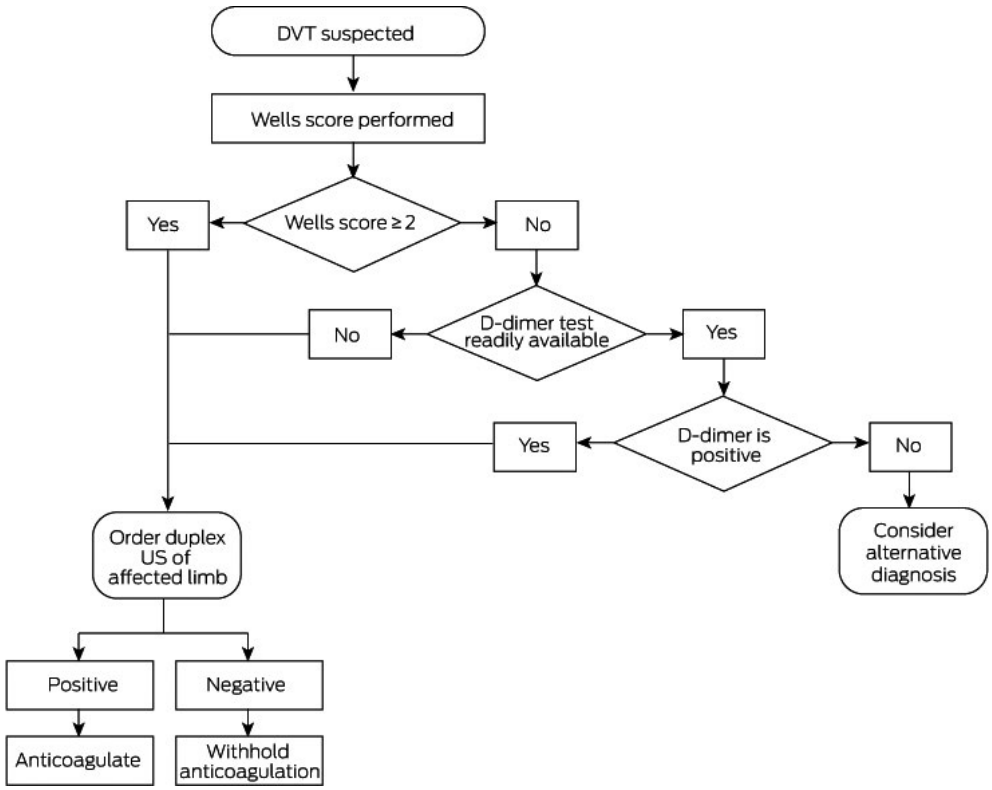
Computed tomography pulmonary angiography

Computed tomography pulmonary angiography (CTPA) is the preferred imaging modality for suspected PE due to its accuracy.[8] *GRADE: Strong; Evidence, High.* However, CTPA involves significant exposure to ionising radiation (3–5 mSv) and requires iodinated contrast, which can cause nephrotoxicity (up to 14%) and allergic reactions (< 1%).[9]

Ventilation–perfusion scanning

Ventilation–perfusion (VQ) scanning does not require radiocontrast, and so is suitable for patients with renal impairment. A normal VQ scan effectively excludes PE, and a high probability scan is diagnostic.[20] However, 27–55% of patients have non-diagnostic lung scans; these patients require testing with serial ultrasound of the legs or CTPA to exclude PE (Box 7).[21] In pregnant women, given the absence of contrast combined with studies showing that

6 Diagnostic algorithm for suspected deep vein thrombosis



DVT = deep vein thrombosis. US = ultrasound. ◆

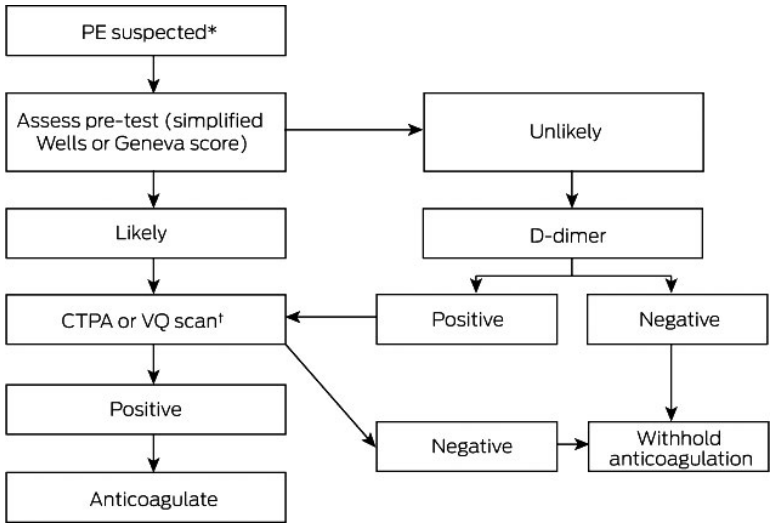
the proportion of diagnostic VQ scans is high, VQ scan is the preferred diagnostic investigation.[22] *GRADE: Strong; Evidence: Low.*

Treatment of venous thromboembolism

The spectrum of VTE ranges from distal DVT, which may not require anticoagulation, through proximal DVT to potentially life-threatening PE requiring additional invasive strategies. The treatment for DVT depends on its anatomical extent: in proximal DVT, thrombus is present in the popliteal (and its trifurcation) or a more proximal vein; in distal DVT, thrombus only occurs in the tibial, peroneal, gastrocnemius and soleal veins.[23]

Anticoagulation is indicated in most cases of VTE because it is highly effective in preventing thrombus extension or recurrence by at least 80%.[5]

7 Diagnostic algorithm for suspected pulmonary embolism



CTPA = computed tomography pulmonary angiography. PE = pulmonary embolism. VQ = ventilation–perfusion. * If PERC is used, the estimated risk for PE should be low (< 15%). † If VQ scan is non-diagnostic: perform CTPA or bilateral duplex ultrasound of lower limbs on Day 1 and Day 7. If negative, withhold anticoagulation. ◆

Anticoagulant therapy for deep vein thrombosis and pulmonary embolism

Direct oral anticoagulants (DOACs) and warfarin are equally effective and can be prescribed to most patients. *GRADE: Strong; Evidence: High.*[5,24] DOACs do not require routine monitoring, have no known food interactions and few drug interactions, and are favoured in most instances. However, DOACs should not be used during pregnancy or breastfeeding, in which case low molecular weight heparin is indicated.[5] Edoxaban and rivaroxaban have been shown to be as efficacious as dalteparin in cancer-related thrombosis, but are associated with an increased risk for major bleeding or clinically relevant non-major bleeding (CRNMB) and, therefore, can be considered when appropriate.[25,26]

Oral factor Xa inhibitors (eg, apixaban, rivaroxaban) are preferred to dabigatran or warfarin to treat proximal DVT and PE because they do not require parenteral anticoagulation for initiation (Box 8). *GRADE: Strong; Evidence: High.*[5]

8 Anticoagulant options for acute venous thromboembolism (VTE)[5,27–29]

Anticoagulant	Initiation dose	Maintenance dose
Apixaban*	• 10 mg oral twice daily for 7 days	• 5 mg oral twice daily; consider 2.5 mg twice daily beyond 6 months
Rivaroxaban†	• 15 mg oral twice daily for 21 days	• 20 mg once daily; consider 10 mg daily beyond 6 months
Dabigatran‡	• Start a parenteral anticoagulant such as a LMWH* for 5 days	• < 75 years and CrCl > 50 mL/min: 150 mg oral twice daily • < 75 years and CrCl 30–50 mL/min: 110 mg oral twice daily • ≥ 75 years and CrCl > 30 mL/min: 110 mg oral twice daily
Warfarin	• Start a parenteral anticoagulant and warfarin simultaneously. Continue LMWH for a minimum of 5 days and until the INR has reached 2 or above on 2 consecutive days then stop the parenteral anticoagulant and continue warfarin alone	• Adjust warfarin dose to target INR 2.0–3.0
LMWH§	• Dalteparin (CrCl ≥ 30 mL/min) 200 units/kg subcutaneously once daily or 100 units/kg twice daily; or • Enoxaparin o CrCl ≥ 30 mL/min: 1.5 mg/kg subcutaneously once daily or 1 mg/kg twice daily; o CrCl ≤ 30 mL/min: 1 mg/kg subcutaneously once daily.	• Continue as for initiation

CrCl = creatinine clearance. INR = international normalised ratio. LMWH = low molecular weight heparin. * Requires CrCl ≥ 25 mL/min; reimbursed for VTE only in Australia. † Requires CrCl ≥ 30 mL/min; reimbursed for VTE in Australia and New Zealand. ‡ Reimbursed for VTE only in New Zealand. § If LMWH is required for a patient with CrCl ≤ 30 mL/min, seek expert advice. Twice-daily dosing of dalteparin and enoxaparin may be preferred for patients at high risk of bleeding, such as patients who are older, are at extremes of weight (eg, ≥ 150 kg) or have a malignancy. ◆

Duration of anticoagulation

Proximal deep vein thrombosis and pulmonary embolism

All patients with proximal DVT and PE should receive anticoagulant therapy for at least 3 months. *GRADE: Strong; Evidence: Strong*. Patients whose proximal DVT or PE were provoked by major surgery or major trauma can cease anticoagulation at this time.[5]

Distal deep vein thrombosis

Uncertainty exists about the value of anticoagulation for distal DVT. In general, anticoagulation is used for proximal DVT and PE, but serial duplex ultrasound (two duplex ultrasound scans over 2 weeks) is reasonable (*GRADE: Strong; Evidence: Moderate*), especially if the risk of bleeding is increased. Most distal DVT can be treated for 6–12 weeks. *GRADE: Strong; Evidence: Moderate*.[30]

Extended anticoagulation for deep vein thrombosis and pulmonary embolism (beyond 3–6 months)

For patients whose events were unprovoked or associated with transient risk factors (non-surgical), decide whether to stop or to continue with extended anticoagulant therapy after 3 months of anticoagulation. Continuing therapy for longer than 3 months reduces the risk of VTE recurrence during therapy by at least 80% but is associated with a major bleeding risk of < 1% per year. Once anticoagulant therapy is stopped, the risk of recurrence is the same as for patients who cease treatment after 3–6months when followed up over time.[27]

The decision to stop or extend anticoagulation beyond 3 months is challenging and depends on the balance between the risks of bleeding and VTE recurrence (see below). Clinical "equipoise" is common and patient preference is important. Box 9 recommends the duration of anticoagulation for different types of VTE based on recurrence rates (Box 8) and risk factors for recurrence (Box 10) while considering patient preference.

Among patients for whom it has been decided to extend anticoagulant therapy, consider low intensity anticoagulation *GRADE Strong; Evidence: High*. The risk of major bleeding and CRNMB on therapeutic anticoagulation (DOACs or warfarin) varies from 2% to 3% per year[34] but is less in patients who have completed 6 months of oral anticoagulants without bleeding.[5] Apixaban 2.5 mg twice daily is as efficacious as 5.0 mg twice daily for preventing VTE recurrence beyond 6 months, with no difference in major bleeding and a trend to have less CRNMB.[28] Likewise, rivaroxaban 10 mg once daily is as efficacious as 20 mg once daily with a trend to have less major bleeding and CRNMB.[29]

Aspirin (100 mg daily) reduces the rate of VTE recurrence to a much lesser extent than oral anticoagulants but is associated with similar rates of bleeding to rivaroxaban 10 mg daily.[29,35] Therefore, aspirin should be avoided, unless anticoagulation cannot be used. *GRADE: Strong; Evidence: High.*

Predictors of venous thromboembolism recurrence

Many risk factors for VTE recurrence have been identified, although few have a major effect (Box 10). Most clinical decisions can be made by assessing the following predictors of recurrence: unprovoked, non-surgical provoking factor and persistent risk factors versus provoked by surgery; PE and proximal DVT versus distal DVT;[36] prior VTE;[5] and male sex.[31]

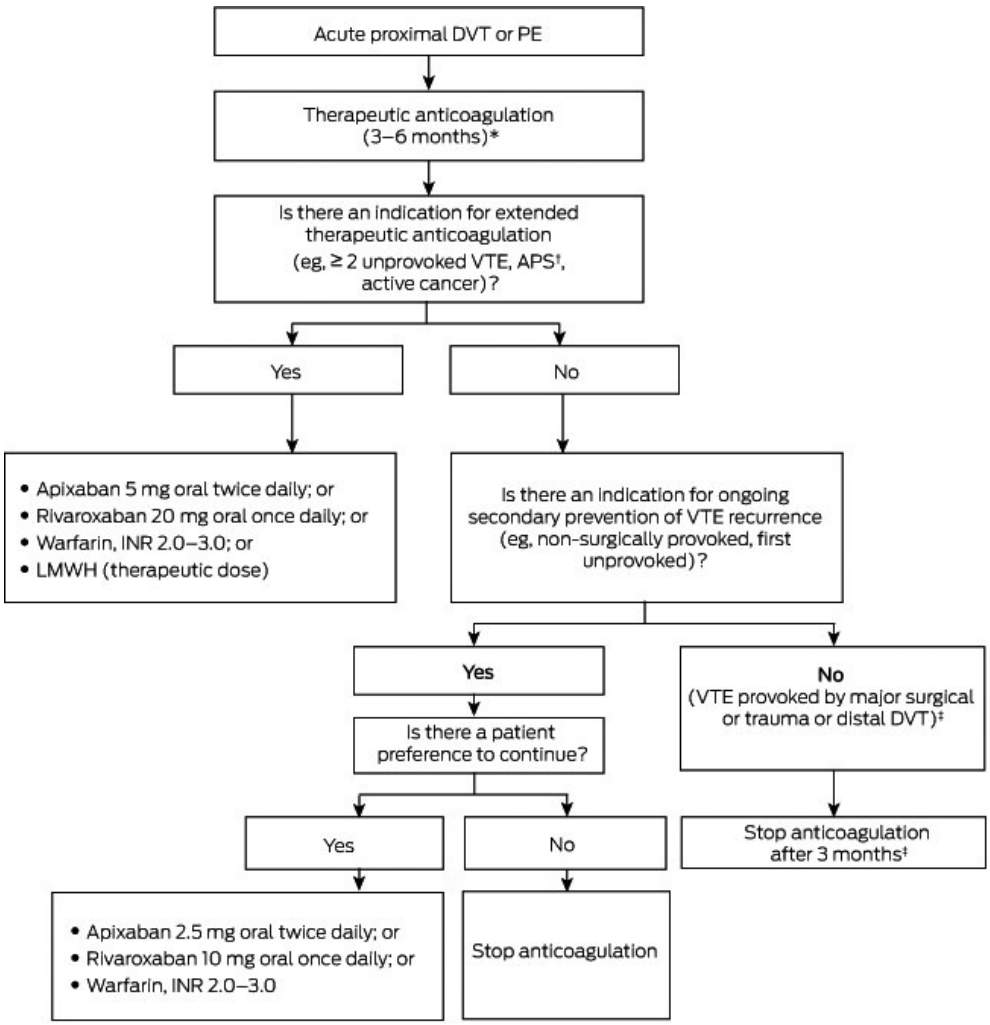
Bleeding risk

The strongest predictor of bleeding is active or recent (< 30 days) bleeding, which usually contraindicates anticoagulant therapy.[37] Other predictors of bleeding include prior history of bleeding (especially while receiving anticoagulation), a potential bleeding lesion (eg, peptic ulceration), recent surgery (within 14 days), severe kidney disease, and active cancer. The decision as to when bleeding risk outweighs the benefit of anticoagulation may be difficult and is often subjective. Importantly, among patients with no bleeding for whom recent therapeutic anticoagulation has been prescribed, the subsequent risk of major bleeding is very low (0.8–1.6% per year), particularly with low intensity DOACs, and similar to patients who are not taking anticoagulants.[5,28]

Thrombophilia testing

The presence of an inherited thrombophilia does not influence initial anticoagulant treatment. Only rare deficiencies of natural inhibitors (antithrombin, protein C or S) significantly increase the

9 Duration of anticoagulation for venous thromboembolism (VTE)



APS = antiphospholipid syndrome. DVT = deep vein thrombosis. INR = international normalised ratio. LMWH = low molecular weight heparin. PE = pulmonary embolism. * Refer to Box 8. † Warfarin is preferred in APS.[24] ‡ For distal DVT without persisting risk, anticoagulation can stop after 6 weeks. ◆

risk of recurrent VTE to warrant extended anticoagulation, and uncertainty remains with homozygous or other compound heterozygosity states.[32,38] Neither factor V Leiden nor prothrombin gene mutation heterozygosity change treatment duration or advice for family members and should not be routinely sought (Box 4).[33]

It is reasonable to test for antiphospholipid syndrome in patients with unprovoked VTE. *GRADE: Strong; Evidence: Moderate.*

Complications of venous thromboembolism

Chronic thromboembolic pulmonary hypertension (CTEPH) is form of pre-capillary pulmonary hypertension which results after pulmonary obstruction with thrombus and organised fibrous tissue, accompanied by pulmonary arteriopathy. The incidence of CTEPH after acute PE is 3.4%.[39] Patients typically report persisting dyspnoea despite anticoagulation over the subsequent 2 years. VQ scan and echocardiography should be performed if CTEPH is suspected (Box 4). If untreated, CTEPH portends a poor prognosis, with a 5-year survival rate of 30%. Treatment ranges from medical therapies aiming to vasodilate the pulmonary vasculature to pulmonary endarterectomy.[40] *GRADE: Low; Evidence: Moderate.*

PTS is characterised by clinical features (eg, swelling, discomfort, hyperpigmentation and lipodermatosclerosis) in a limb with previous DVT.[41] It occurs in one in three patients following DVT.[42] Radiological findings are insufficient to diagnose PTS; the Villalta scale is the most commonly used clinical scale.[43]

Anticoagulation does not prevent PTS.[44] Thrombolysis relieves venous outflow obstruction and has been used to prevent PTS in extensive DVT, although clinical trial results have been mixed.[45,46] Clinical trials evaluating elastic compression stockings among patients with proximal DVT have reported conflicting findings in reducing PTS incidence.[47] Hence, elastic compression stockings may be useful only to control symptoms of leg swelling and pain. *GRADE: Strong; Evidence: Moderate.*

Invasive strategies for venous thromboembolism management

Invasive treatment modalities for acute removal of thrombosis have been investigated, with the goals of rapidly relieving acute right ventricular pressure overload in PE and thereby improving survival or rapidly relieving venous obstruction to prevent vein dysfunction and PTS and reduce VTE recurrence.

10 Risk factors for recurrent venous thromboembolism (VTE)[5,30–33]

	Risk factor
Strong risk factors for recurrence	• Unprovoked VTE • Prior VTE • PE or proximal DVT • Persistent risk factor (eg, active cancer, antiphospholipid syndrome) • Antithrombin, protein C or S deficiency
Moderate risk factors for recurrence	• VTE provoked by non-surgical risk factor • Male sex • Elevated D-dimer level after cessation of anticoagulation
Factors that have little or no effect on recurrence	• Factor V Leiden or prothrombin gene heterozygosity • Residual thrombus on imaging

11 Role of additional interventions in venous thromboembolism (VTE)

	Definition	Intervention	GRADE*	Level of evidence†
Pulmonary embolism				
Massive	Sustained hypotension (systolic BP < 90mmHg for 15 min or requiring inotropic support or pulselessness or sustained HR < 40 beats/min with signs/symptoms of shock)	Thrombolysis or alternative based on local expertise and availability (eg, surgical embolectomy, catheter-based intervention, ECMO)	Strong	Moderate
Submassive	Systolic BP > 90 mmHg and RV dysfunction or myocardial necrosis defined by: • RV dilation (on echocardiography or CT); or • RV systolic dysfunction on echocardiography; or • elevation of BNP or NT-proBNP; or • elevation of troponin	Anticoagulation	Strong	Moderate
		Consider lysis or other invasive therapy if very high thrombus burden, poor cardiorespiratory reserve and low bleeding risk	Low	Moderate
Haemodynamically stable		Anticoagulation	Strong	High
Deep vein thrombosis				
Iliofemoral	Thrombus involving at least the common iliac vein	Consider pharmaco-mechanical thrombus dissolution (phlegmasia cerulea dolens)	Strong	Low
Other (non-iliofemoral)		Anticoagulation	Strong	High

BNP = brain natriuretic peptide. BP = blood pressure. CT = computed tomography. HR = heart rate. ECMO = extracorporeal membrane oxygenation. HR = heart rate. NT-proBNP = N-terminal pro-brain natriuretic peptide. RV = right ventricle. * Grading of Recommendations Assessment, Development and Evaluation; www.gradeworkinggroup.org. † www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf. ◆

The following strategies have been investigated with variable results: systemic administration of thrombolytic agents; catheter-directed thrombolysis, which uses lower thrombolytic doses with or without the addition of mechanical clot disruption; and acute surgical thrombectomy.[46,48–50]

These therapies have a limited role in management of acute VTE (Box 11).

Inferior vena cava filter insertion may prevent PE in patients with acute VTE and who have an absolute contraindication to anticoagulation, such as active bleeding, but are not recommended in patients treated with anticoagulants for acute VTE.[51] *GRADE: Strong; Evidence: Strong.*

Conclusion

The THANZ guideline for the diagnosis and management of VTE has been developed by the VTE Working Group based on up-to-date evidence and using an evidence-based approach. The guideline aims to promote optimal management of VTE. The extended version of the guideline can be found on the THANZ website (www.thanz.org.au/resources/thanz-guidelines).

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