The Diagnosis and Management of Venous thromboembolism – Guidelines of the Thrombosis and Haemostasis Society of Australia and New Zealand

Huyen A Tran\textsuperscript{1,2}, Harry Gibbs\textsuperscript{1,2}, Eileen Merriman\textsuperscript{3}, Jennifer L Curnow\textsuperscript{4}, Laura Young\textsuperscript{5}, Ashwini Bennett\textsuperscript{6}, Tan Chee Wee\textsuperscript{7}, Sanjeev D Chunilal\textsuperscript{8}, Chris M Ward\textsuperscript{9}, Ross Baker\textsuperscript{10}, Harshal Nandurkar\textsuperscript{2,11}
\textsuperscript{1} Alfred Health, Melbourne, VIC.
\textsuperscript{2} Monash University, Melbourne, VIC.
\textsuperscript{3} Waitemata District Health Board, Auckland, New Zealand.
\textsuperscript{4} Haemophilia Treatment Centre, Westmead Hospital, Sydney, NSW.
\textsuperscript{5} Auckland District Health Board, Auckland, New Zealand.
\textsuperscript{6} Monash Medical Centre, Melbourne, VIC.
\textsuperscript{7} Royal Adelaide Hospital, Adelaide, SA.
\textsuperscript{8} Monash Health, Melbourne, VIC.
\textsuperscript{9} Royal North Shore Hospital, Sydney, NSW.
\textsuperscript{10} Perth Blood Institute, Perth, WA.
\textsuperscript{11} Australian Centre of Blood Diseases, Melbourne, VIC.

BACKGROUND

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

VTE can be fatal if untreated; long-term morbidity includes the 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 impacts on subsequent pregnancies, estrogen use, surgery, life insurance and occasionally long-haul travel.

This document outlines the recommendations for the diagnosis and management of VTE on behalf of the Thrombosis & Haemostasis Society of Australia and New Zealand (THANZ).

METHODS

The VTE Writing Group was established within THANZ and comprised of experts in the field of thromboembolic disorders in Australian 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 face-to-face 2-day meeting on February 25-26, 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 (\url{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 VTE**

There are inherited and acquired VTE risk factors. Multiple risk factors often co-exist 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 as its utility in decision making regarding anticoagulation is low.

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 (Table 1). Such clinical categorisation is important as it impacts on the risk of VTE recurrence and duration of anticoagulation (Table 2). VTE occurring within 2 months of a transient provoking risk factor has half the risk of recurrent VTE after stopping anticoagulant therapy compared to those with no transient risk factor.

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 diagnosis. Clinical assessment should include a thorough clinical examination, and age appropriate screening for malignancy (Good Practice Box). Additional abdominopelvic CT does not identify more early stage cancers or improve outcome.

**DIAGNOSIS AND TREATMENT OF PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS**

Clinical presentations of VTE are non-specific and approximately only 20% of patients with clinically suspected VTE have it objectively confirmed. A misdiagnosis of VTE has significant implications, including needless cessation of effective hormonal contraception in young women and unnecessary ante- and post-partum injections of low molecular weight heparin (LMWH), and in older patients, anticoagulation is associated with higher rates of major and fatal bleeding. 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, are costly and inconvenient.
**Clinical Prediction Rules**

The most validated prediction rules for VTE are the Wells and Geneva scores (Table 3). However, they alone cannot safely exclude VTE and must be used in combination with D-dimer testing. 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. It is only applicable to patients younger than 50 years of age, and where the estimated rate of PE is low (<15%). This rate is seen in most Australian and New Zealand (ANZ) 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.

A negative D-dimer test is a useful “rule-out” test when combined with an unlikely (non-high) clinical probability, avoiding imaging in many cases (Figure 1 and Figure 2). A positive D-dimer alone is not diagnostic of VTE and requires further radiological investigation.

**IMAGING**

**Lower Extremity Duplex Ultrasound**

Duplex ultrasound (US) is accurate for diagnosing and excluding DVT. In ANZ, the entire deep venous system is evaluated with US. In general, a negative single whole leg ultrasound excludes DVT and anticoagulation can be withheld (Figure 1).

Diagnosing recurrent ipsilateral DVT is challenging, as incomplete resolution thrombus occurs in up to 30-50% of patients after DVT. For this reason, many clinicians perform a single repeat US after 3-6 months of anticoagulation (Good Practice Box). These images may be compared to 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.
**Computed tomography pulmonary angiography**

Computed tomography pulmonary angiography (CTPA) is the preferred imaging modality for suspected PE due to its accuracy. However, CTPA involves significant exposure to ionising radiation (3-5mSv) and requires iodinated contrast, which can cause nephrotoxicity (up to 14%) and allergic reactions (<1%).

**VQ scanning**

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. 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 (Figure 2). The absence of contrast combined with studies in pregnant women showing that the proportion of diagnostic VQ scans is high, VQ scan is the preferred diagnostic investigation in pregnant women.

**TREATMENT OF VTE**

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. DVT treatment depends on its anatomical extent: in proximal DVT, thrombus is present in the popliteal or a more proximal vein; in distal DVT, thrombus only occurs in the tibial, peroneal, gastrocnemius and soleal veins. Anticoagulation is indicated in most cases of VTE because it is highly effective in preventing thrombus extension or recurrence by at least 80%.

**Anticoagulant therapy for DVT and PE**

The oral anticoagulants, direct oral anticoagulants (DOACs) and warfarin can be prescribed to most patients as both are equally effective. DOAC do not require routine monitoring, have virtually no known food interactions and few drug interactions and are favoured in most instances. However, DOAC should not be used during pregnancy or breast feeding, or severe renal impairment, where LMWH is indicated. Edoxaban and rivaroxaban have been shown to be as efficacious as dalteparin in cancer-related thrombosis, but it is associated with an
increased risk for major bleeding or clinically relevant non-major bleeding (CRNMB) and, therefore, can be considered when appropriate.21-23

**Oral factor Xa inhibitors** (e.g., apixaban, rivaroxaban) are preferred to dabigatran or warfarin to treat proximal DVT and PE because they do not require parenteral anticoagulation for initiation (Table 4).

**DURATION OF ANTICOAGULATION**

**Proximal DVT and PE**

All proximal DVT and PE should receive anticoagulant therapy for at least 3 months. Those provoked by major surgery or major trauma can cease anticoagulation at this time (Figure 3).20

**Distal DVT**

Uncertainty exists about the value of anticoagulation for distal DVT. Generally, anticoagulation is used as for proximal DVT and PE, although serial US (2 US scans over 2 weeks) is reasonable, especially if the risk of bleeding is increased. Most distal DVT can be treated for 6-12 weeks 24.

**Extended anticoagulation for DVT and PE (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 exposes the patient to an increased risk of bleeding of <1% per year. It does not further reduce the recurrence rate once anticoagulant therapy is stopped, that is once anticoagulation is stopped, the risk of recurrence is the same as patients who cease treatment after 3-6 months when followed up over time.25

The decision to stop or extend anticoagulation beyond 3 months depends on the balance between the risks of bleeding and VTE recurrence. Clinical “equipoise” is common and patient preference is important. **Risk factors for VTE recurrence** influence the decision (see Predictors of VTE recurrence). **Figure 3** recommends the duration of anticoagulation for different types of VTE based on recurrence rates (Table 2) and risk factors for recurrence (Table 1) whilst considering patient preference.

Among patients in whom it has been decided to extend anticoagulant therapy, consider low intensity anticoagulation. The risk of major bleeding on therapeutic anticoagulation (DOACs or warfarin) varies from 2%-3% per year 26 but is less in patients who have completed 6 months of oral
anticoagulants without bleeding. Apixaban 2.5mg twice daily is as efficacious as 5.0mg twice daily for preventing VTE recurrence beyond 6 months with no difference in major bleeding and a trend to less clinically relevant non major bleeding (CRNMB).27 Similarly, rivaroxaban 10mg once daily is as efficacious as 20mg once daily with a trend to less major and CRNMB.28 Aspirin reduces the rate of VTE recurrence to a much lesser extent than oral anticoagulants but is associated with similar rates of bleeding to rivaroxaban 10mg daily.28,29 Simes et al., reported that aspirin reduced major vascular events (8.7%/yr versus 5.7%/yr; HR, 0.66; 95% CI, 0.50–0.86; P=0.002).30 Vascular events was defined as the composite of venous thromboembolism, myocardial infarction, stroke, and cardiovascular death. The breakdown of events showed no net benefit of aspirin in arterial events, that is the composite was driven many by reduction in recurrent VTE events. After adjustment for treatment adherence, ASA reduced recurrent VTE by 42% (HR, 0.58; 95% CI, 0.40–0.85; P=0.005) with a major bleeding rate for ASA was 0.5% (placebo, 0.4%). By indirect comparison, the EINSTEIN Choice reported that rivaroxaban 10mg daily was associated with a 74% reduction in recurrent VTE rate in comparison to aspirin, a major bleeding rate of 0.3%. Therefore, aspirin should be avoided, unless anticoagulation cannot be used.

Predictors of VTE recurrence

Many risk factors for VTE recurrence have been identified, although relatively few have a major effect (Table 5). Most clinical decisions can be made by assessing the following predictors of recurrence:

- Unprovoked, non-surgical provoking factor and persistent risk factors vs. provoked by surgery
- PE and proximal DVT vs. distal DVT 31
- Prior VTE32
- Male sex 33

Extended anticoagulation (beyond 3 months) should be considered in patients with PE or proximal DVT which are unprovoked, provoked by a non-surgical transient, or persistent, risk factor, especially among males.

Bleeding risk

The strongest predictor of bleeding is active or recent bleeding (<30 days) which usually contraindicates anticoagulant therapy.34 Other predictors of bleeding include prior bleeding (especially while receiving anticoagulation), a potential bleeding lesion (e.g., 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 in whom recent therapeutic anticoagulation has been prescribed with no bleeding, the subsequent risk of major bleeding is very low (0.8-1.6% per year) particularly with low intensity DOAC, and similar to those not on anticoagulants.37

Role of Thrombophilia Testing

The presence of an inherited thrombophilia does not influence initial anticoagulant treatment or mortality and only the rare deficiencies of natural inhibitors (antithrombin, protein C or S) increases the risk of recurrent VTE sufficiently to warrant extended anticoagulation.35,36 Uncertainty remains with homozygous or other compound heterozygous states.37 Neither Factor V Leiden nor prothrombin gene mutation heterozygosity change treatment duration or advice for family members and should not be routinely sought.38,39

Patients should be counseled about the potential implications of a positive result prior to testing. A family history of VTE is a poor predictor for the presence of thrombophilia.39 It is reasonable to screen patients below 45 years with unprovoked VTE or recurrent events. If testing is undertaken, only natural inhibitor deficiencies might influence advice for relatives in terms of prophylaxis and frequently prophylaxis advice can be informed by the family history alone.40,41

Screening for antiphospholipid syndrome should include lupus anticoagulant, anticardiolipin and anti-beta2 glycoprotein-1, particularly in unprovoked VTE. Lupus anticoagulant and antithrombin, protein C/S results may be affected by anticoagulants and advice should be sought from a specialist.

COMPLICATIONS OF VTE

Chronic thromboembolic pulmonary hypertension (CTEPH) is form of pre-capillary pulmonary hypertension (PH) which results following pulmonary obstruction with thrombus and organized fibrous tissue, accompanied by pulmonary arteriopathy. It is diagnosed when there is persistent pulmonary artery obstruction and a mean pulmonary arterial pressure (mPAP) of 25 mmHg or greater, and pulmonary artery wedge pressure is 15mmHg or less.42 The incidence of CTEPH is approximately four to six per million adults per annum, with an incidence after acute PE of 3.4%.43 If untreated, CTEPH portends a poor prognosis with a 5-year survival of 30%

V/Q scan should be performed if CTEPH is suspected. A normal V/Q scan may exclude treatable CTEPH with a sensitivity of greater than 96%.44,45 Other imaging modalities such as CTPA lack the necessary sensitivity to exclude CTEPH46. A transthoracic echocardiogram (TTE) is useful to estimate
the pulmonary artery pressures but CTEPH cannot be diagnosed nor excluded on this basis alone. Patients with suggestive clinical features, and persistent unmatched perfusion defects on V/Q scan should be referred to an expert centre for further investigation and management of CTEPH (e.g. right heart catheterisation and pulmonary angiography).

Pulmonary endarterectomy is potentially curative surgery. In patients who are unsuitable for surgery or who have persistent PH despite PEA, pharmacological treatments with pulmonary vasodilators (e.g. riociguat) and/or pulmonary balloon angioplasty may be considered.47 Finally, many patients with CTEPH continue long-term anticoagulation to reduce the risk of PE recurrence.

**Post-thrombotic syndrome** (PTS) is characterised by clinical features (e.g., swelling, discomfort, hyperpigmentation and lipodermatosclerosis) in a limb with previous DVT 48. It occurs in approximately one in three patients following DVT 49. Radiological findings are insufficient to diagnose PTS; the Villalta scale is the most commonly used clinical scale 50.

The main risk factors for the development of PTS include DVT location (iliofemoral DVT increased risk compared to distal DVT) and ipsilateral recurrence of DVT.51 Anticoagulation does not prevent PTS. Thrombolysis relieves venous outflow obstruction and has been used to prevent PTS in extensive DVT, although clinical trial results have been mixed. 52,53 Clinical trials evaluating elastic compression stockings (ECS) among patients with proximal DVT have reported conflicting findings in reducing PTS incidence.54 When ECS are used following DVT, the optimal duration of compression therapy is unclear.

Treatment options for established PTS are limited. Graduated ECS may provide symptomatic benefit, although there is a lack of strong evidence as to their efficacy. They can be initiated with a trial of 20-30 mmHg pressure at the ankle 55. Other compression therapies include devices that assist venous return56 and intermittent pneumatic compression 57,58.

Pharmacologic treatments for PTS have been reviewed recently.55 Rutosides appear to offer no additional benefit compared to placebo or ECS.59 Finally, surgical options for treatment of PTS may be considered in very rare select cases, following failure of conservative therapies.60 Venous ulcers are a complication of severe PTS and may be treated by wound specialists, often with the use of compression therapy.
**SITUATIONS**

**Invasive strategies for VTE management**

Invasive treatment modalities for acute removal of thrombosis have been investigated with the goals of a) rapidly relieving acute right ventricular pressure overload in PE and thereby improving survival or b) rapidly relieving venous obstruction to prevent vein dysfunction, PTS and reduce VTE recurrence. The following strategies have been investigated with variable results: 1) systemic administration of thrombolytic agents, 2) catheter-directed thrombolysis, which utilizes lower thrombolytic doses with or without the addition of mechanical clot disruption and 3) acute surgical thrombectomy.\(^5^3,^6^1-^6^3\)

These therapies have a limited role in management of acute VTE (Table 6). 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.\(^6^4\)

**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 summary recommendations are detailed in Box = The extended version of the guideline can be found on the THANZ website (www.thanz.org.au).
References:


#
Table 1. Examples of non-surgical transient, or persistent provoking factors for VTE.\textsuperscript{5}

<table>
<thead>
<tr>
<th>Type of VTE risk factor</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Non-surgical Transient  | • Acute medical illness with immobilisation for at least 3 days  
                          | • Estrogen 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 ≥ 2-fold increased risk of recurrent VTE after stopping anticoagulant therapy, i.e., inflammatory bowel disease and other chronic inflammatory states  
                          | • Antiphospholipid syndrome |

VTE = Venous Thromboembolism
<table>
<thead>
<tr>
<th>Type of VTE</th>
<th>Recurrence rate at one year after stopping anticoagulation</th>
<th>Recurrence rate at five years after stopping anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First VTE provoked by major surgery or major trauma</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>First VTE provoked by transient risk factor (non-surgical)</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>Provoked VTE with persistent risk factors e.g., active cancer</td>
<td>15%</td>
<td>45%</td>
</tr>
<tr>
<td>First unprovoked distal DVT</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>First unprovoked proximal DVT or PE</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td>Second episode of unprovoked VTE</td>
<td>15%</td>
<td>45%</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = Venous Thromboembolism
**Table 3: Clinical prediction rules for PE and DVT.**

<table>
<thead>
<tr>
<th>Simplified Geneva Score For PE</th>
<th>Simplified Wells Score For PE</th>
<th>Simplified Well score for DVT</th>
<th>PERC rule*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>1</td>
<td>Clinical sign and symptoms of DVT</td>
<td>1</td>
</tr>
<tr>
<td>Surgery or fracture previous 4 weeks</td>
<td>1</td>
<td>Immobility/surgery previous 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>1</td>
<td>Previous VTE</td>
<td>1</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1</td>
<td>Haemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral leg pain</td>
<td>1</td>
<td>Alternative diagnosis less likely than PE</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate 75-94/min &gt;95 /min</td>
<td>1</td>
<td>Heart Rate&gt; 100min</td>
<td>1</td>
</tr>
<tr>
<td>Pain on lower leg deep vein palpation or unilateral oedema</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Collateral superficial l veins (non-varicose) | 1 |
- Alternative diagnosis at least as likely as Deep vein thrombosis | -2 |
- PERC negative | 0 |

- Low, 0-1 | Unlikely | 0-1 | Unlikely | <2 | PERC positive | ≥1 |
- Moderate, 2-4 | Unlikely | 0-1 | Unlikely | <2 | |
- High, ≥5 | Likely | ≥2 | Likely | ≥2 | |

*the estimated rate of PE must be low (< 15%)

**DVT = deep vein thrombosis; PE = pulmonary embolism; PERC = Pulmonary Embolism Rule out Criteria; VTE = Venous Thromboembolism**
<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Initiation dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban#</td>
<td>10mg oral twice daily for 7 days</td>
<td>5mg oral twice daily; consider 2.5mg twice daily beyond 6 months</td>
</tr>
<tr>
<td>Rivaroxaban§</td>
<td>15mg oral twice daily for 21 days</td>
<td>20mg once daily; consider 10mg daily beyond 6 months‡</td>
</tr>
<tr>
<td>Dabigatran¶</td>
<td>Start a parenteral anticoagulant such as a LMWH* for 5 days</td>
<td>-younger than 75 years and CrCl &gt;50 mL/min: 150 mg oral twice daily -younger than 75 years and CrCl 30 to 50 mL/min: 110 mg oral twice daily -75 years or older and CrCl &gt; 30 mL/min: 110 mg oral twice daily</td>
</tr>
<tr>
<td>Warfarin</td>
<td>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</td>
<td>Adjust warfarin dose to target INR, 2.0 – 3.0</td>
</tr>
<tr>
<td>LMWH*</td>
<td>Dalteparin: (CrCl ≥30 mL/min) 200 units/kg subcutaneously once daily or 100 units/kg, twice daily OR Enoxaparin: CrCl ≥30 mL/min: 1.5 mg/kg subcutaneously once daily or 1 mg/kg, twice daily; CrCl ≤30 mL/min: 1 mg/kg subcutaneously, once daily.</td>
<td>Continue as for initiation</td>
</tr>
</tbody>
</table>

CrCl = creatinine clearance; INR = international Normalised Ratio; LMWH = low molecular weight heparin

# Requires CrCl≥25ml/min; reimbursed for VTE only in Australia

§ Requires CrCl≥30ml/min; reimbursed for VTE in Australia & New Zealand

¶ Reimbursed for VTE only in New Zealand

† Rivaroxaban 10mg daily yet to receive indication in Australia & 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 (e.g., 150 kg or over) or have a malignancy.
Table 5. Risk Factors for Recurrent VTE.4,26,33,36,37

<table>
<thead>
<tr>
<th>Strong Risk Factors for Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked VTE</td>
</tr>
<tr>
<td>Prior VTE</td>
</tr>
<tr>
<td>PE or proximal DVT</td>
</tr>
<tr>
<td>Persistent risk factor (e.g. active cancer, antiphospholipid syndrome)</td>
</tr>
<tr>
<td>Antithrombin, protein C &amp; S deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate Risk Factors for Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE provoked by non-surgical risk factor</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Elevated D-dimer after cessation of anticoagulation</td>
</tr>
</tbody>
</table>

Factors that have little or no effect on recurrence

| Factor V Leiden or prothrombin gene heterozygosity                      |
| Residual thrombus on imaging                                           |

VTE = Venous Thromboembolism
Table 6: Role of additional interventions in VTE

<table>
<thead>
<tr>
<th>PE</th>
<th>Definition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive</td>
<td>Sustained hypotension (systolic BP&lt;90mmHg for 15 mins or requiring inotropic support or pulselessness or sustained HR &lt; 40 BPM with signs/symptoms of shock)</td>
<td>Thrombolysis or alternative based on local expertise and availability (e.g., surgical embolectomy, catheter-based intervention, ECMO) GRADE*: strong; Evidence: moderate</td>
</tr>
<tr>
<td>Submassive</td>
<td>Systolic BP &gt; 90 mmHg and RV dysfunction or myocardial necrosis defined by: - RV dilation (on ECHO or CT) or RV systolic dysfunction on ECHO or - Elevation of BNP or NT-proBNP or - Elevation of troponin</td>
<td>Anticoagulation GRADE: strong; Evidence: moderate Consider lysis or other invasive therapy if very high thrombus burden, poor cardiorespiratory reserve and low bleeding risk GRADE: low; Evidence: moderate</td>
</tr>
<tr>
<td>Haemodynamically stable</td>
<td></td>
<td>Anticoagulation GRADE: strong; Evidence: high</td>
</tr>
<tr>
<td>DVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ilio-femoral</td>
<td>Thrombus involving at least the common iliac vein</td>
<td>Consider pharmaco-mechanical thrombus dissolution (phlegmasia cerulea dolens) GRADE: strong; Evidence: low</td>
</tr>
<tr>
<td>Other (non-ilio-femoral)</td>
<td></td>
<td>Anticoagulation GRADE: strong; Evidence: high</td>
</tr>
</tbody>
</table>

BNP=brain natriuretic peptide; BP=blood pressure; HR=heart rate; BPM=beats per minute; DVT=deep vein thrombosis; ECHO=echocardiography; ECMO=Extracorporeal Membrane Oxygenation; HR= heart rate; NT pro-BNP=N-terminal pro b-type natriuretic peptide; PE=pulmonary embolism; RV=right ventricle; VTE=Venous Thromboembolism

*Grading of Recommendations Assessment, Development and Evaluation; www.gradeworkinggroup.org
Evidence-based recommendations for the diagnosis and management of pulmonary embolism (PE) and deep vein thrombosis (DVT)

Diagnosis of Pulmonary Embolism and Deep Vein Thrombosis
1. A non-high pre-test probability (Wells or Geneva score) combined with a negative D-dimer safely excludes VTE without imaging. GRADE: Strong; Evidence: High.
2. A single negative complete US is sufficient to exclude DVT. GRADE: Strong; Evidence: High.
3. PE can be excluded without D-dimer or radiological testing in selected patients, if the pulmonary embolism rules out criteria (negative PERC rule) are met GRADE: Strong; Evidence: moderate.
4. A normal VQ scan or a negative technically adequate CTPA excludes PE and anticoagulation can be safely withheld. GRADE: Strong; Evidence: High

Treatment of VTE
1. Distal DVT caused by a major provoking factor that is no longer present, requires OAC for 6 weeks. GRADE: strong; Evidence: moderate.
2. Distal DVT that has been unprovoked or with persisting risk factors, requires OAC for 3 Months. GRADE: strong; Evidence: moderate.
3. Proximal DVT or PE caused by major surgery or trauma that is no longer present, requires OAC for 3 months. GRADE: Strong; Evidence: High
4. Proximal DVT or PE that is unprovoked or associated with a transient (non-surgical) risk factor requires OAC for 3-6 months. GRADE: Strong; Evidence: High
5. DVT or PE that is provoked by active cancer, treat with therapeutic LMWH for at least 6 Months. GRADE: Strong; Evidence: High
6. For patients continuing with extended anticoagulation, either therapeutic or low-dose DOAC is preferred over warfarin in the absence of contraindications. GRADE: Strong; Evidence: High
7. Aspirin should be avoided unless anticoagulation cannot be used. GRADE: strong; Evidence: high

Thrombophilia Testing
1. Patients with VTE provoked by surgery or major trauma should not be screened for hereditary thrombophilia. GRADE: strong; Evidence: high

Additional interventions

Pulmonary Embolism
1. Patients with massive PE (sustained hypotension) and a low risk of bleeding, administer thrombolytic therapy or an alternative (e.g., surgical embolectomy or catheter-based therapy) depending on local availability. GRADE: strong; Evidence: moderate
2. 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. GRADE: strong; Evidence: strong

Deep Vein Thrombosis
1. CDT may be considered in selected patients with extensive proximal DVT (involves common iliac veins) and low bleeding risk. GRADE: strong; Evidence: low
2. Elastic compression stockings may be useful only to control symptoms of leg swelling and pain following DVT. GRADE: strong; Evidence: moderate
### Good practice points for the diagnosis and management of PE and DVT

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Practice point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of PE and DVT</td>
<td>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 and unchanged ultrasound appearance.</td>
</tr>
<tr>
<td>Subsegmental PE</td>
<td>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.</td>
</tr>
<tr>
<td>Incidental PE in patients with cancer</td>
<td>Patients with incidental PE should be treated as for patients with symptomatic cancer-associated PE.</td>
</tr>
<tr>
<td>Thrombophilia testing</td>
<td>Young patients (&lt; 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.</td>
</tr>
<tr>
<td>Complications of VTE</td>
<td></td>
</tr>
<tr>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td>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.</td>
</tr>
<tr>
<td>Invasive strategies — PE</td>
<td>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.</td>
</tr>
</tbody>
</table>

**Figure 1:** Diagnostic algorithm for suspected Deep Vein Thrombosis.

DVT = deep vein thrombosis; US = duplex ultrasound
Figure 2: Diagnostic algorithm for suspected Pulmonary Embolism

CTPA= Computed tomography pulmonary angiography; PE= pulmonary embolism; V/Q= ventilation-perfusion

*If PERC is used, the estimated risk for PE should be low (<15%)

*If V/Q scan is non-diagnostic: 1) perform CTPA or 2) bilateral duplex US of lower limbs day 1 and 7. If negative, withhold anticoagulation
Figure 3. Duration of anticoagulation for VTE

Acute proximal DVT or PE

Therapeutic anticoagulation, 3 – 6 months*

Is there an indication for extended therapeutic anticoagulation? (e.g., ≥2 unprovoked VTE, APS⁷, active cancer)

Yes

Apixaban 5mg oral twice daily or
Rivaroxaban 20mg oral once daily or
Warfarin, INR 2.0 – 3.0 or
LMWH (therapeutic dose)

No

Is there an indication for ongoing secondary prevention of VTE recurrence? (e.g., non-surgically provoked, first unprovoked)

Yes

Is there a patient preference to continue?

Yes

Apixaban 2.5mg oral twice daily or
Rivaroxaban 10mg oral once daily or
Warfarin, INR 2.0 – 3.0

No

Stop anticoagulation

No

(VTE provoked by major surgical or trauma or distal DVT)⁶

Stop anticoagulation after 3 months*⁷

APS= antiphospholipid syndrome; DVT = deep vein thrombosis; INR= international normalised ratio; LMWH= low molecular weight heparin; PE= pulmonary embolism; VTE = Venous Thromboembolism. *For distal DVT without persisting risk, anticoagulation can stop after 6 weeks. †warfarin is preferred in APS ⁵⁷