CASE SIX

Short case number: 3_10_6
Category: Respiratory System
Discipline: Medicine
Setting: General practice
Topic: Deep vein thrombosis and pulmonary embolus

Case

Norman Smith, 65y.o man, presents to your clinic to have his ankle checked. He fractured his tibia and fibula in a motor vehicle accident three weeks ago and he has been treated with an internal wire fixation and back slab. On arrival at the clinic, Norman asks the receptionist if he could be fitted in, as he has not feeling very well since the previous day.

Looking at his file, Norman has no significant medical history apart from hypertension, being on perindopril. He is an ex-smoker who quit >10 yrs ago.

When you see him he tells you he has pain on the left side of his chest which catches when he takes a deep breath. He also noticed that he was a bit short of breath the previous evening. When he coughed up blood that morning, he was alarmed and decided to come to the surgery.
PR 100/min, RR 28/min and BP 100/70, temperature 37.8 degrees.

Questions

1. How would you acutely manage this scenario?
2. Norman has arrived in ED and received the appropriate initial interventions. Pulmonary embolism (PE) is suspected. What further history and examination and investigations would be undertaken?
   Are there any pre-test probability risks scores to guide further investigations?
3. What are the risk factors for Venous Thromboembolism (VTE)?
4. How do you manage VTE acutely and in the longer term?
5. In a table list the appropriate prophylaxis (both mechanical and drug based) against DVT for surgical patients.

REFERENCES:

1. Huyen A Tran et al, New Guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism. MJA 210 (5) March 2019-10-12
2. Ho WK. Deep Vein Thrombosis: Risks and Diagnosis. *Aust Fam Physician* 2010; 39: 468-74.
3. Nick van Es et al, Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 124 (12): 1968-1975, 2014
4. UpToDate: Prevention of venous thromboembolism in adult orthopedic surgical patients
5. UpToDate: Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients

ANSWERS

Deep vein thrombosis and pulmonary embolus

1. **How would you acutely manage this scenario?**

   Check responsiveness, airway, breathing and circulation. Give oxygen (100% preferable) and call for ambulance.

   Differential Diagnoses:
   1) Acute Pulmonary Emboli
   2) Pneumonia/pneumonitis
   3) Although pain/presentation not typical – acute coronary syndrome

   Norman is unwell. For someone who has hypertension, his BP is low and he is borderline tachycardic/tachypnoeic. This is someone who can deteriorate quickly; calling an ambulance for an urgent transfer to ED will be very appropriate

2. **Norman has arrived in ED and received the appropriate initial interventions. Pulmonary embolism (PE) is suspected. What further history and examination and investigations would be undertaken?**
   Are there any pre-test probability risks scores to guide further investigations?

   The varied clinical presentations and non-specific nature of the physical signs can make the diagnosis of Venous thromboembolism (VTE) including DVT and PE difficult. It is often helpful to consider these questions:
   - Is the clinical presentation consistent with PE?
   - Does the patient have risk factors for PE? (E.g. recent surgery, hip fracture, immobility, etc.)
   - Is there any alternative diagnosis that can explain the patient's presentation?

   Taking a good history/examination would provide further information to exclude other causes:
   - Are there any signs/symptoms of infections in the preceding days, any sick contacts?
   - Are there recent risk factors for thrombosis e.g. surgery, long distance flights, immobility, injuries to lower limbs, cancer diagnoses, family history, (in female patients – pregnancy, the use of OCP)?
   - Are there history of cardiovascular disease?
   - Any evidence of uni-lateral swelling in lower limbs, i.e. clinical evidence of DVT

   The clinical features of PE depend largely upon the size of embolism and co-morbidity. They encompass a spectrum from cardiovascular collapse to small emboli with few or no haemodynamic consequences (table 1). Further investigations would usually depend on clinical picture; however, clinical prediction scores could be of benefit to guide the best approach in these patients (diagram 1).

Table 1. Clinical features and investigation findings of PE depending of severity

	Acute massive PE	Acute small/medium PE	Chronic PE
Pathophysiology	Major haemodynamic effects: ↓ cardiac output; acute right heart failure	Occlusion of segmental pulmonary artery → infarction ± effusion	Chronic occlusion of pulmonary microvasculature, right heart failure
Symptoms	Faintness or collapse, central chest pain, apprehension, severe dyspnoea	Pleuritic chest pain, restricted breathing, haemoptysis	Exertional dyspnoea. Late symptoms of pulmonary hypertension or right heart failure
Signs	Major circulatory collapse: tachycardia, hypotension, ↑ JVP, right ventricular gallop rhythm, split P_2 Severe cyanosis ↓ Urinary output	Tachycardia Pleural rub, crackles, effusion Low-grade fever	May be minimal early in disease Later-RV heave, loud, split P_2 Terminal-right heart failure
Chest X-ray	Usually normal. May be subtle oligaemia	Pleuropulmonary opacities, pleural effusion, linear shadows, raised hemidiaphragm	Enlarged pulmonary artery trunk, enlarged heart, prominent RV
ECG	S_1 Q_3 T_3 (which means R axis deviation)anterior T-wave inversion Right bundle branch block (RBBB)	Sinus tachycardia	RV hypertrophy and strain
Arterial blood gases	Markedly abnormal with ↓ PaO_2 and PaCO2 often raised in massive PE, because of great increase in dead space. Metabolic acidosis	May be normal or ↓ *Pa*CO_2	Exertional ↓ *Pa*O_2 or desaturation on formal exercise testing
Alternative diagnoses	Myocardial infarction; pericardial tamponade; aortic dissection	Pneumonia, pneumothorax, musculoskeletal chest pain	Other causes of pulmonary hypertension

All patients with suspected PE should have a chest X-ray, ECG and arterial blood gas analysis. These tests may also help to exclude important differential diagnoses. D-dimer is a specific degradation product released into the circulation when cross-linked fibrin undergoes endogenous fibrinolysis. The presence of a low D-dimer has a high NPV and provides a useful screening test. However, a suggestive clinical picture in a high-risk patient must be investigated further even when the D-dimer level is normal.

The most validated clinical prediction tools for VTE are the Wells and Geneva scores. In combination with D-dimer testing, they can be used safely in outpatient clinics and ED to exclude VTE events. The pulmonary embolism rule-out criteria (PERC) score can be used similarly to exclude PE in younger patients (<50y.o) where the estimated rate of PE is lower (table 2).

Table 2. Clinical Predictions Scores – adapted from Australian Thrombosis Guideline 2019

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%). ◆

Other Confirmatory Testings

CT Pulmonary Angiography

CT pulmonary angiography (CTPA) is the preferred way of diagnosing PE. CTPA may not only exclude PE but highlight an alternative diagnosis. However, CTPA involve significant amount of radiation (therefore contra-indicated in pregnancy), and requires iodinated contrast which can result in nephrotoxicity and allergic reaction in some patients.

VQ Scan

The sensitivity and specificity of V/Q scanning is greatly increased when interpretation is informed by clinical probability. A normal V/Q scan virtually excludes PE and a low probability scan in the presence of a low clinical probability makes PE unlikely. Similarly, the presence of a high probability scan in a patient with a high clinical probability almost certainly establishes the diagnosis of PE. V/Q scans are most useful in patients with normal pulmonary architecture. However, PE often presents as an important differential in patients with pre-existing COPD or congestive cardiac failure and in these cases the majority of scans (70%) are indeterminate. This is the preferred option for scan in pregnant women and those with renal impairment.

Doppler US

Colour Doppler ultrasound of the leg veins remains the investigation of choice in patients with clinical DVT, but may also be applied to patients suspected of PE, particularly if there are clinical signs in a limb, as many will have identifiable proximal thrombus in the leg veins.

Echocardiogram

Bedside echocardiogram is extremely helpful in the differential diagnosis and assessment of acute circulatory collapse. Acute dilatation of the right heart is usually present in massive PE, and thrombus (embolism in transit) may be visible in the pulmonary trunk! Alternative diagnoses including left ventricular failure, aortic dissection and pericardial tamponade can usually be established with confidence. Echocardiography is also useful for patients who present with unexplained pulmonary hypertension.

3. What are the risk factors for Venous Thromboembolism (VTE)?

VTE can be provoked by recent surgery. There are also recognised non-surgical transient risks and more persistent underlying factors that are associated with VTE events such as malignancy, smoking and anti-phospholipid syndrome (Table 3). These should be considered especially in those patients with unprovoked VTE.

With regards to thrombophilia screening, the Australian Thrombosis Guideline recommends:

- Patients with provoked VTE by surgery should not be screened for hereditary thrombophilia
- Young patients (<45y.o) with unprovoked VTE may be tested for some hereditary thrombophilia e.g. protein C&S deficiency or anti-thrombin deficiency
- Patients with unprovoked VTEs should have age-appropriate evaluation for malignancy

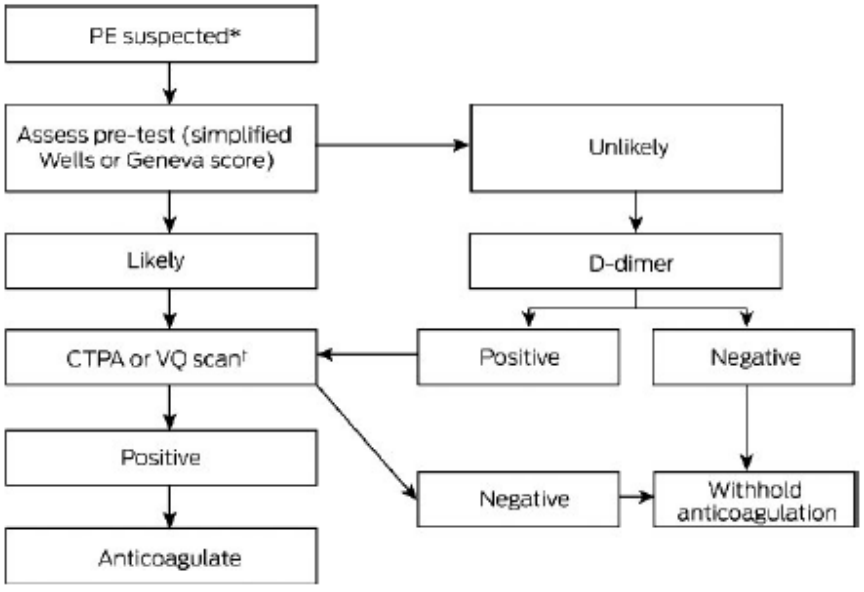
Table 3 – Risk Factors of VTE – adapted from Australian Thrombosis Guideline 2019

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

Diagram 1 – Algorithm for suspected PE – adapted from Australian Thrombosis Guideline 2019

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. ◆

4. How do you manage VTE acutely and in the longer term?

General:
Prompt recognition and treatment is potentially life-saving. Oxygen should be given to all hypoxaemic patients in a concentration necessary to restore arterial oxygen saturation to over 90%. Opiates may be necessary to relieve pain and distress but should be used with great caution in the hypotensive patient. Diuretics and vasodilators should also be avoided; indeed, hypotension should be treated by giving intravenous fluid or plasma expander.

Anticoagulation:
Anticoagulation should be commenced immediately in patients with a high or intermediate probability of PE but can usually be safely withheld from patients with a low clinical probability pending further investigation.

The choice of anti-coagulation has changed considerably in the last decade. Whilst previously low molecular weight heparin/warfarin bridging was considered standard, many landmark trials have shown that Novel Oral Anti-coagulants (NOACs) are not inferior in efficacy, with no increased risks of bleeding compared to this approach. It is standard practice now to commence majority of VTE patients on NOACs (table 4). Rivaroxaban and Apixaban are both available on PBS.

Table 4 – Anti-coagulation options for VTE – Adapted from Australian Thrombosis Guideline 2019

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. ◆

There are certain circumstances where NOACs are not recommended (Clexane/Warfarin will be the choice for treatment)

- Pregnancy (Clexane)
- Reduced CrCl <30ml/min (Warfarin)
- Anti-phospholipid syndrome (Warfarin, although more data are supporting NOACs use for some patients with APS)

Traditionally, low molecular weight heparin (LMWH e.g. Clexane, Dalteparin) has been used for treatment in cancer related thrombosis based on the findings from CLOT trial. However, more recent data has demonstrated that NOACs such as Rivaroxaban are not inferior to LMWH for treatment of cancer related VTE, although they have been associated with increased risks of bleeding in patients with GI malignancy.

Thrombolytic therapy:
Thrombolysis appears to improve outcome when acute massive PE is accompanied by acute shock but it is not clear whether there is any advantage of thrombolysis over anti-coagulation in patients without haemodynamic instability. Patients with PE appear to have a high risk of intracranial haemorrhage and must be screened carefully for haemorrhagic risk. (Note: the dosage and treatment regime is different from that for acute myocardial infarction).

Caval filters:
Patients who experience recurrent PE despite adequate anticoagulation, or those patients in whom anticoagulation is absolutely contraindicated, may benefit from insertion of a filter in the inferior vena cava below the origin of the renal vessels. The introduction of retrievable caval filters has been useful in patients with temporary risk factors.

Other Invasive Strategies:
Pulmonary embolectomy is generally performed only in severe cases with very large PE and in patients where anticoagulation and/or thrombolytic therapy is contraindicated or has not responded adequately to standard treatments. Percutaneous thrombectomy using special catheters (Catheter directed lysis) under X-ray guidance to break up or extract the emboli is an alternative in specialised centres.

Longer term Management of VTE beyond 3-6 months
There are increasing body of evidence in the era of NOACs that patients with moderate to high risk of recurrent thrombosis (table 5), will benefit from longer-term anti-coagulation. These patients may be kept on full dose NOACs or lower dose NOACs depending on the risks.

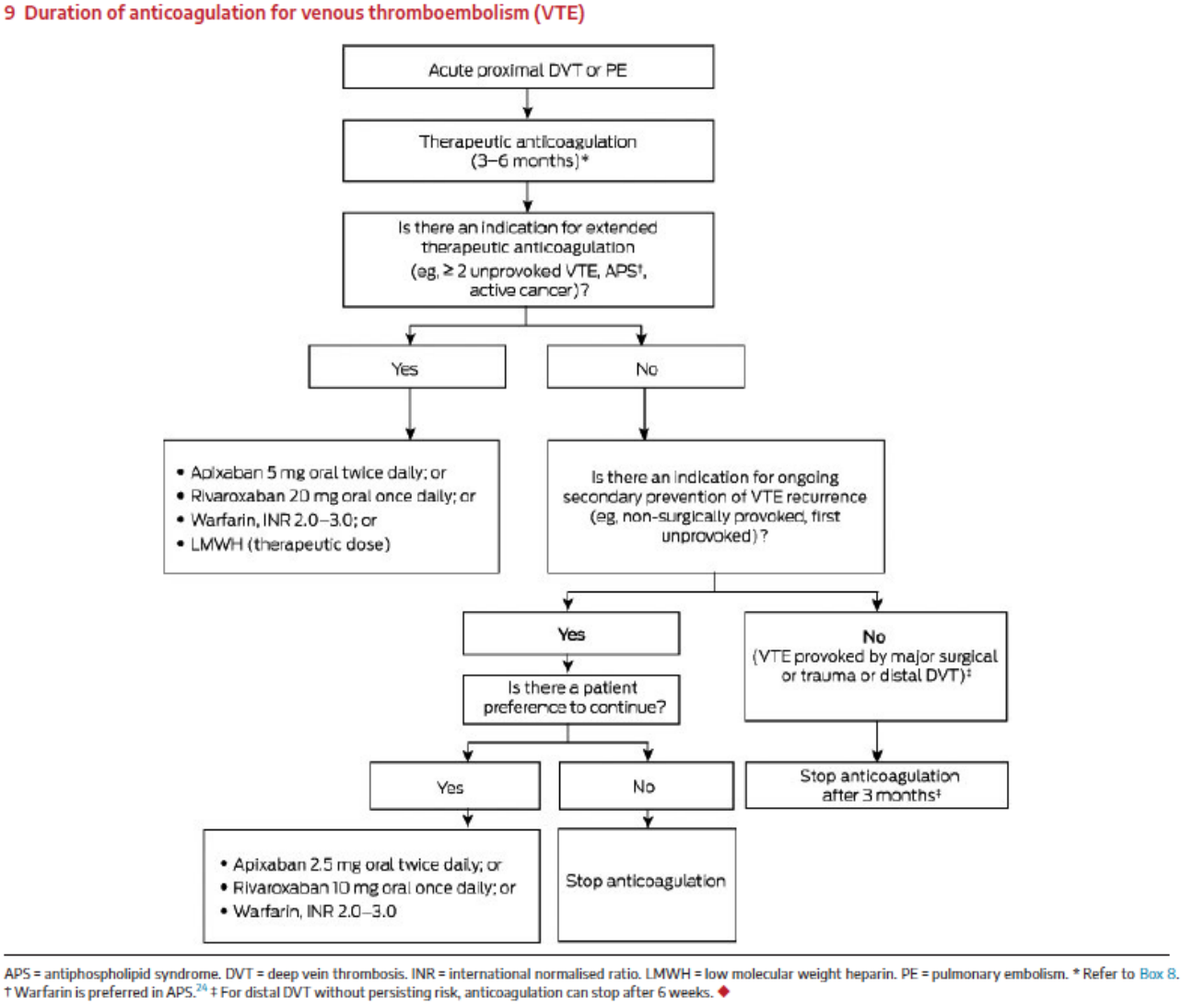
The flow chart below from Australian thrombosis guideline highlights the thought process for decision making re- length of duration of anti-coagulation.

Table 5 – Risks for recurrent thrombosis – Adapted from Australian Thrombosis Guideline 2019

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

Diagram 2 – Algorithm for duration of anti-coagulation – Adapted from Australian Thrombosis Guideline 2019



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.

5. **In a table list the appropriate prophylaxis (both mechanical and drug based) against DVT for surgical patients.**

- Full-length graduated compression stockings
- Intermittent Pneumatic Compression devices
- Early mobilisation
- Standard LMWH or heparin
- Low dose NOACs

Early mobilisation of all patients is important to prevent DVTs. For patients with very low risk of VTE, early mobilisation may be adequate. For patients with low risk of VTE – mechanical prevention may be suitable. Patients at medium or high risk may require additional pharmacological antithrombotic measures.

Table 6 – Patients with moderate/high risks of VTE following surgery

Patients in the following categories should be considered for pharmacological antithrombotic prophylaxis:
Moderate risk of VTE

• Major surgery in patients > 40 years or with other risk factor
• Major medical illness e.g. heart failure
  ○ Chest infection
  ○ Malignancy
  ○ Inflammatory bowel disease

High risk of VTE
• Hip or knee surgery • Major abdominal or pelvic surgery for malignancy or with history of DVT or known thrombophilia