CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF
VENOUS THROMBOEMBOLISM

Ministry of Health Malaysia

**National Heart Association
Of Malaysia**

**Academy of Medicine,
Malaysia**

Statement of Intent

These guidelines are meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management options available locally.

Review of the Guidelines

These guidelines were issued in July 2003 and will be reviewed in July 2005 or sooner if new evidence becomes available.

Foreword

Venous thromboembolism covers a spectrum of disorders characterized by thrombosis in the venous circulation with its often fatal sequelae. It is a disorder which is seen across a spectrum of medical and surgical disciplines.   Like many disorders which crosses specialties, it often gets neglected with no particular specialty claiming 'ownership'. It is therefore pertinent that a multi disciplinary effort be made to guide doctors on various aspects of VTE. The disparate figures on incidence and prevalence of VTE between and within specialties do not make matters any easier. What is worrisome is that without proper guidelines, patients may be under diagnosed and avoidable death not prevented.

In 1999 the Academy of Medicine , College of Surgeons and Ministry of Health released a 'Consensus on Prophylaxis of Venous Thromboembolism'. Two years later, the National Heart Association of Malaysia proposed to the Academy of Medicine that an updated version of the Consensus to include diagnostics and therapeutics aspects be authored. Following approval by the Academy, a committee   comprising of specialists from 13 different specialties was formed. All members from the 1999 Consensus committee were invited. After almost 18 months of endeavour, the Guideline is now ready   for circulation

In view of the scope to be covered .it is inevitable that this current Guideline is somewhat lengthy. It should however be of benefit to a spectrum of specialties. Every effort is made to ensure that references quoted are contemporary and levels of evidence are highlighted close to the text in question. This is also one of the first (if not the first) Guideline which discusses the economics of disease management.. It is hoped that other Guidelines will follow suit.

It is our sincere hope that this Guideline will be of use to doctors in preventing and treating VTE. We pray to the Almighty that we will be successful in putting the latest available knowledge He has bestowed on us for the betterment of our patients.

Prof. Abdul Rashid Abdul Rahman
Chairman VTE CPG Committee

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Guideline Development and Objectives

Guideline Development

Venous thromboembolism covers a spectrum of disorders characterized by thrombosis in the venous circulation with its often fatal sequelae. It is a disorder which is seen across a spectrum of medical and surgical disciplines. Like many disorders which crosses specialties, it often gets neglected with no particular specialty claiming 'ownership'. It is therefore pertinent that a multi disciplinary effort be made to guide doctors on various aspects of VTE.

Objectives

The main objective is to guide practitioners on the various aspects of VTE prophylaxis and management incorporating the latest scientific evidence. Diagnostic aspects are also covered in view of the concern that VTE is not only under treated   but also under diagnosed in Malaysia.

Clinical Question

The clinical questions addressed in this guideline are:
- When and whom VTE prophylaxis should be adopted.

- How to optimize the diagnosis of VTE with currently available methods.

- What are the available options in managing VTE and its sequelae.

- Pharmacoeconomics of prevention and treatment of VTE.

Target Population

This guideline are to be applied to patients who are at risk or have developed VTE.

Target Group

The target group will be mainly doctors working in hospitals, where the majority of VTE occurs. It will also be of use to general practitioners particularly those involved with continuing care of patients once they are discharged from the hospitals. Like most CPGs it is meant to guide doctors in making decisions based on the latest available evidence. It should be used to assist and not replace clinical judgment and decision making.

GRADING RECOMMENDATIONS

A   Based on evidence from one or more randomized clinical trials and/or meta-analyses

B   Based on evidence from non-randomise clinical trials or observational studies. These may include subgroups analyses from randomized clinical trials.

C   Based on expert committee reports and/or clinical experience of respected authorities. Absence of directly applicable clinical studies of good quality.

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1.1   INTRODUCTION

There is an increasing incidence of venous thromboembolism (VTE) among the Asian population partly because of greater awareness among doctors and patients themselves. The incidence of VTE varies in different parts of the world for reasons not completely understood. The worldwide incidence exceeds 1 per 1000.[1,2]

Postoperative deep vein thrombosis (DVT) is believed to be rare in Asians. Studies in the region however, have shown that the incidence ranges from 2.2 – 62.5% [3] (refer to Table 1).

Pulmonary embolism (PE) is the cause of death in 0.9% of all hospital admissions and remains the main cause of maternal death in the United Kingdom.[4] In Malaysia, PE is the third cause of maternal mortality according to the report on Confidential Enquiries into Maternal Deaths from 1991 to 1996.[5]

1.2   PATHOGENESIS AND NATURAL HISTORY OF VTE

Venous thrombosis results from an imbalance between thrombogenic factors and protective mechanisms. Thrombogenic factors include activation or destruction of vascular endothelium, activation of platelets or blood coagulation, inhibition of fibrinolysis and stasis.

Silent DVT usually starts in the venous sinuses of the calf muscles and in 20% it extends to the proximal veins.[6]These patients are at risk of PE. Thromboembolism in hospital patients depends not only on the underlying disease and trauma of surgery but also on patient-related variables (Table 2).

Table 1: **Incidence of post-operative deep vein thrombosis in Asian patients**

Gen. Surg: General surgical patients

Author and Country	Year	Postoperative DVT incidence percentage	Type of patients studied & No.	Method of investigation
Cunningham and Yong (Malaysia)	1974	12.0	Gen. Surg 68	[125]I fibrinogen
Nandi et al (Hong Kong)	1980	2.6	Gen. Surg 150	[125]I fibrinogen
Inada et al (Japan)	1983	15.3	Gen. Surg 256	[125]I fibrinogen
Tun et al (Malaysia)	2001	2.2	Gen. Surg 45	Duplex Ultrasound and Venography
Chumnijarakij and Poshyachinda, (Thailand)	1975	2.4	Gynaecology 169	[125]I fibrinogen
Mok et al (Hong Kong)	1979	53.3	Orthopaedic 53	Ascending venography
Kim and suh (S. Korea)	1988	10.0	Orthopaedic 146	Ascending venography
Atichartakarn et al (Thailand)	1988	4.0	Orthopaedic 50	Ascending venography
Mitra, Khoo and Ngan (Singapore)	1989	9.7	Orthopaedic 72	Ascending venography
Dhillon et al (Malaysia)	1996	62.5	Orthopaedic 88	Ascending venography

1.2.1 Epidemiology of post-operative DVT in general surgical, gynaecological and orthopaedic patients in Asian studies.

In general surgical patients, Western studies report an incidence ranging from 33% to 35%.[8-10] Asian studies revealed a lower incidence ranging from 2.2% to 15.3% [11-14] in general surgical patients and 2.4% in gynaecological patients.[15]

In orthopaedic patients after hip and knee surgery, the incidence ranges from 4% to 62.5%. [3,16-19] This is in contrast to Western figures ranging from 45-84% [20,21]

Table 2:   Risk factors for Thromboembolism from Thromboembolic Risk Factors (THRIFT) Consensus Group, 1992[7]

Patient factors	Disease or surgical procedure
↳ Age	↳ Trauma or surgery especially of pelvis, hip, lower limb
↳ Obesity	↳ Malignancy, especially pelvic, metastatic
↳ Varicose veins	↳ Heart failure
↳ Immobility (bed rest over 4 days)	↳ Recent myocardial infarction
↳ Pregnancy	↳ Paralysis of lower limbs
↳ Puerperium	↳ Infection
↳ High dose oestrogen therapy	↳ Inflammatory bowel disease
↳ Previous DVT or PE	↳ Nephrotic syndrome
↳ Thrombophilia	↳ Polycythaemia
↳ Deficiency of antithrombin, Protein C or Protein S	↳ Paraproteinaemia
↳ Antiphopholipid antibody or Lupus anticoagulant	↳ Paroxysmal noctural haemoglobinuria
	↳ Bechcet's disease, homocystinaemia

1.2.2   Epidemiology of Venous Thromboembolism in medical patients.
In contrast to surgical patients, VTE has been less well studied in hospitalised medical patients. In chronically ill patients such as congestive cardiac failure, chronic obstructive airway disease or infections, the DVT rate in the absence of prophylaxis has been reported to be approximately 16%.[22]

1.2.3 Epidemiology of venous thromboembolism in critically ill patients.

Cross-sectional studies of medical and surgical intensive care unit patients have shown that approximately 10%[23,24] has proximal DVT on admission to the ICU. The prevalence of DVT in patients in the medical-surgical ICU is 25-32%.[25-28]

Patients with multi system or major trauma have a risk for DVT that exceeds 50%[29] and fatal PE occurs in approximately 0.4 to 2.0%. Among trauma subgroups, high rates of DVT were seen in patients with lower extremity (69%) and spine (62%) fractures and in patients with major head injuries (54%).

Table 3: Prevalence on DVT in ICU

Author	Year	DVT prevalence, %	Sample size	Method of investigation
Cade JF[26]	1982	29%	119 medical-surgical ICU pts	[125] I fibrinogen
Fraisse[27]	2000	28%	85 COPD pts on mechanical ventilation	Contrast venography
Hirsh[25]	1995	32%	Medical ICU pts	Doppler ultrasound
Marik[28]	1997	25%	102 medical and surgical ICU pts	Doppler ultrasound

1.2.4 Epidemiology of post-stroke deep venous thrombosis

Most of the available epidemiological data have been collected in Western. There were also different diagnostic modalities used in the studies.

The incidence of DVT after ischaemic stroke ranged from 11-53%.[31-32,34-36,39,40] Significant risk factors were time interval without prophylaxis (ie time from stroke to admission), lower active movement scores for limb movement and artrial fibrillation.[30,31] Prevalence data ranged from 6.3% to 33%. The lower prevalence comes from 2 Asian studies and may reflect the lower prevalence of DVT in Asians.[34,38]

A summary of the related studies is presented below.

Table 4:   Prevalence and incidence of deep vein thrombosis in stroke patients

Author and Country	Year	DVT incidence prevalence* percentage(%)	Sample size	Method of investigation
S.Tongiputn, N.Kunanusont et. al.[38] (Thailand)	1999	6.3*	111	Ultrasound
P.Noel, F.Gregoire et. al.[30] (Belgium)	1991	10.4*	539	Venography
G.Pambianco, T.Orchard, P.Landau [31] (USA)	1995	21	508	Ultrasound
W.J.Oczkowski et. al. [32] (Canada)	1992	11	150	Impedance Plethysmography
ER Sioson et al [33] (USA)	1988	33*	105	Impedance Plethysmography
S.C.Tso [34] (Hong Kong)	1980	17	35	[125] I-fibrinogen
Miyamota AT, Miller LS [35] (USA)	1980	29	150	[125] I-fibrinogen
C.Warlow, D.Ogston, AS Douglas[39] (Scotland)	1976	53	76	[125] I-fibrinogen
F B Gibberd et. al.[40] (England)	1976	50	26	[125] I-fibrinogen
Cope et. al.[35] (England)	1973	33	150	Ascending venography

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2.1 CLINICAL DIAGNOSIS OF VTE

Review of the literature between 1966 and 1997 performed by Anand[1] demonstrated that the sensitivity of clinical assessment in diagnosis of DVT ranged from 60% to 96% while the specificity ranged from 20% to 72%. To diagnose DVT, clinical assessment must be supplemented. This is especially true in pregnancy because leg swelling and pain are physiological consequences of pregnancy.

Clinical models are available for the prediction of both DVT and PE (Tables 1 & 2)

Clinical Assessment of DVT in Lower Limb
Table 1: Clinical Model for Predicting Pretest Probability of Lower Limb DVT [2]

If Present	Score
Risk Factors	
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis or recent immobilization of lower extremities	1
Recently bedridden more than 3 days or major surgery within 4 weeks	1
Clinical Signs	
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting odema confined to symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of DVT	- 2

High Probability	Moderate Probability	Low Probability
>3	1 - 2	<0

In patients with symptoms in both legs, the more symptomatic leg is used.

Clinical Assessment of DVT in Upper Limb
In the upper limbs, DVT is an increasingly common problem but the clinical diagnosis is non-specific with less than 50% being symptomatic.[3]

Clinical Assessment of Pulmonary Embolism (PE)

Table 2:   Clinical Model for Predicting Pretest Probability for Suspected PE [4]

Symptoms & Signs	Score
Clinical signs & symptoms of DVT (minimum of leg swelling & pain with palpation of deep vein)	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate greater than 100 beats/min	1.5
Immobilization or surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1.0
Malignancy (at treatment, treated in the last 6 months or palliative)	1.0

High Probability	Moderate Probability	Low Probability
>6	2 - 6	<2

Classical symptoms and signs of acute PE apart from sudden death not mentioned in the table include chest pain, dyspnoea, hypotension and elevated jugular venous pressure. Routine investigations should include chest x-ray (pruning of pulmonary vessels, atelectasis, wedge shaped opacity). ECG (tachycardia, right heart strain, S1, Q3, T3 pattern) and echocardiogram show right heart strain. Arterial blood gases will show hypoxia.

2.2 DIAGNOSTIC APPROACH FOR VENO-THROMBOEMBOLIC DISEASE

Numerous algorithms have been suggested for the diagnosis of VTE. These will depend on the availability of imaging facilities, the studies used as reference as well as the philosophy of the referring doctor. It must be recognised that the clinical probability of VTE must be a part of any of these algorithms.

2.2.1 First episode of DVT

Figure 1 is a suggested protocol for diagnosis of the first episode of symptomatic acute DVT. The tests along with the advantages, disadvantages and comments are presented in Appendix I.

Clinical assessment is pivotal in providing safe management when radiographic imaging is not routinely available. Those with moderate or high clinical probability should receive unfractionated or low-molecular weight heparin in doses designed to treat acute DVT[5] with imaging which may be delayed until the next day if it is not immediately available. However, for those with low clinical probability, imaging can be delayed 12 to 24 hours without anticoagulant coverage.[5]

Patients should first undergo Duplex ultrasound (US) with manual compression since it has proved to be highly sensitive and specific in symptomatic acute proximal DVT. A positive test is sufficiently predictive that treatment should be continued or initiated. Approximately 10% to 20% of patients have DVT confined to the calf veins where the sensitivity and specificity of the US are definitely less. However, about 20% to 30% of the isolated distal DVT will have proximal propagation. Serial ultrasound testing has evolved to solve this problem. Patients with negative serial US have less than 1% risk of developing symptomatic DVT or PE in a 3-month period.[6] In addition, a single negative ultrasound test in those with low clinical pretest probability safely excludes DVT.[2]

Contrast venography is useful when US results are equivocal or when clinical probability is high despite the negative US study. This also holds true for isolated calf vein thrombosis which can result in chronic venous insufficiency if untreated.[2]

Following spiral CT for suspected PE, CT images of the deep veins can be obtained (indirect CT venography). This is now being used to diagnose both PE and DVT in the same sitting which simplifies and shortens the work-up.[7] The sensitivities and specificities of indirect CT venography range from 97% to 100%. [8-10] It has the added advantage of demonstrating the IVC and iliac veins.

D-dimer may also be used to limit the need for serial testing in patients with suspected DVT where a negative test in the low pre-test probability has a negative predictive value of >99%.[11] A low clinical probability, normal ultrasound and negative d-dimer virtually rules out DVT.[12] However, in those patients with cancer, recent surgery or elevated bilirubin levels, the negative predictive value of D-dimer is less. In pregnancy, low levels of D-dimer make VTE unlikely.

Figure 1: **Algorithm for diagnosing DVT using clinical assessment, venous ultrasonography and D-dimer testing[13]**

Signs or symptoms of suspected DVT

Clinical Probability

Low Clinical Probability

D-dimer test

negative
exclude DVT

positive
venous
ultrasonography

negative
exclude
DVT

positive[#]
diagnose
DVT

Intermediate or High Clinical Probability

Venous ultrasonography

positive
diagnose DVT

negative
D-dimer test

positive

negative
exclude DVT

serial venous
ultrasonography*

positive
diagnose
DVT

negative
exclude
DVT

[#] Re-evaluate history and review ultrasound for features suggestive of old rather than new thrombosis. If ultrasound findings are inconclusive, venography should be considered.

*In patients with a high clinical probability or who cannot return for serial ultrasonography, venography is recommended.

2.2.2   Suspected pulmonary embolism

As with DVT, patients suspected of PE should be stratified into high-, moderate- and low-probability groups (Table 2). Clinical information by itself, however, is inadequate to confirm or exclude the diagnosis of PE.

Patients who are haemodynamically unstable or severely hypoxic should be started on treatment (see Chapter 4, Fig 3) and further investigations may be needed to confirm the diagnosis. Spiral CT allows direct visualization of clot within the pulmonary arteries. Pooled analysis[14] using pulmonary angiography has shown spiral CT to have an overall sensitivity & specificity of 72% and 95% respectively. The sensitivity is higher for central PE (94%). Spiral CT can also be used to make alternative diagnoses that would explain the symptoms and signs.

In stable patients with suspected PE, a DVT demonstrated clinically and confirmed on US support the diagnosis of PE. This can be further confirmed by a ventilation-perfusion (V/Q) scan or a spiral CT. A low level D-dimer concentration (<500 ng/ml), measured by ELISA, has been shown to effectively exclude VTE. [15]

Figure 2:   Algorithm for Suspected Pulmonary Embolism using Lung Scan as Initial Investigation
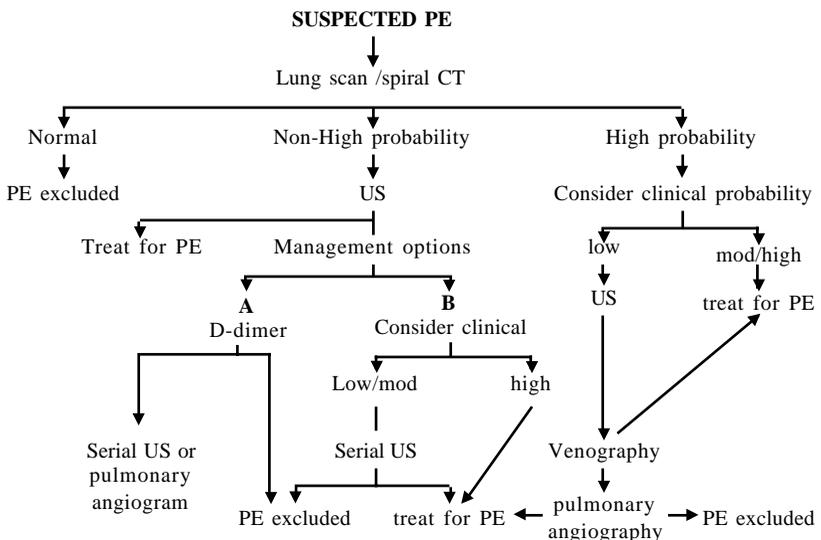
Recurrent symptoms may be due to a variety of non-thrombotic disorders e.g. venous reflux or venous insufficiency/ post-thrombotic syndrome. Up to 70% of patients with non-thrombotic disorders may be incorrectly labelled as having recurrent DVT with the unnecessary course of long-term anticoagulant therapy[16]

Contrast venography is the gold standard for diagnosis of recurrent DVT. Real-time compression ultrasound is of limited value.

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3.1   INTRODUCTION

Deep vein thrombosis (DVT), particularly of the lower limbs, occurs either spontaneously or in patients admitted to hospital either for a surgical or medical problem. The occurrence of DVT in hospitalised patients is dependent upon various risk factors. The reported incidence of DVT varies from 0.45% to 30%. [1] A study done in University Hospital Kuala Lumpur reported an incidence of 76.5% in orthopaedic patients undergoing surgery.[2] Up to 50% of patients with asymptomatic DVT may go on to have pulmonary embolism (PE), and in a significant number of cases, it is fatal.

Hospital patients may be stratified according to VTE risk (Table 1). It is recommended that all hospital patients at moderate or high risk should receive specific prophylaxis.

High-risk groups of hospital patients have an incidence of DVT in screening studies of 40 - 80%, and an above average risk of fatal PE of 1-10% (Table 1). Effective and safe prophylactic measures against VTE are now available for most high-risk patients. There are two approaches to the prevention of PE:

1. Secondary prevention – early detection and prompt treatment of subclinical venous thrombosis by careful screening of post-operative patients using a reliable test.

2. Primary prophylaxis – the use of drugs or mechanical methods that have been proven to be effective in preventing the occurrence of thrombosis.

Primary prophylaxis is naturally preferred in clinical circumstances because prevention is more effective than treatment of these thromboembolic complications. Ideally, the primary prophylactic measure would be effective, safe, easy to administer, cost effective and would encourage good compliance with the patient, nurses and physicians. Currently, the prophylactic measures that are commonly used are low dose UFH, LMWH, oral anticoagulants and intermittent pneumatic leg compression.

Prophylactic measures should be started prior to surgery and then continued until the patient is fully mobile. There is abundant data from meta-analyses and placebo-controlled, double-blind, randomised trials that demonstrate either no increase or small increases in the absolute rates of major bleeding with the use of low dose unfractionated heparin or LMWH.[5-11]

Table 1: Risk Stratification and Prevention Strategies in Medical and Surgical Patients [3-4]

	Incidence of VTE				
	Calf DVT %	Proximal DVT %	Clinical PE %	Fatal PE %	
LOW RISK Minor surgery in patients < 40 yr with no additional risk factors Minor medical illness	2	0.4	0.2	0.002	No specific measures Aggressive mobilisation
MODERATE RISK Minor surgery in patients with additional risk factors Minor surgery in patients aged 40-60 yr with no additional risk factors Major surgery in patients <40 yr with no additional risk factor Immobilised patients with acute medical illness.	10 to 20	2 to 4	1 to 2	0.1 to 0.4	Low dose unfractionated Heparin 5000 – 7500IU bd LMWH (daily dose according to manufacturer) Intermittent pneumatic compression OR Elastic graduated compression stockings
HIGH RISK Minor surgery in patients > 60 yr or with additional risk factors Major surgery in patients > 40 yr or with additional risk factors Fractures or undergoing major orthopaedic surgery of the pelvis, hip, or lower limb.	20 to 40	4 to 8	2 to 4	0.4 to 1.0	Unfractionated heparin 5000 - 7500IU tds LMWH or Intermittent pneumatic compression
VERY HIGH RISK Major surgery in patients > 40 yr plus prior VTE, cancer, or molecular hypercoagulable state Patients with lower limb paralysis	40 to 80	10 to 20	4 to 10	0.2 to 5.0	LMWH Intermittent pneumatic compression/ Elastic graduated stockings+ LMWH / Unfractionated heparin 5000 – 7500IU tds; Oral anticoagulants Target INR 2.0 – 2.5

Minor surgery: duration under 30 minutes.
Major surgery: duration more than 30 minutes.

Although wound haematomas are seen more frequently with these agents, avoidance of an anticoagulant cannot generally be justified on these grounds alone. Alternatively, mechanical methods of prophylaxis may be used as they do not have any risk of bleeding and yet have been efficacious in some groups of patients.[5] If spinal or epidural analgesia is used, prophylaxis may be given after 1 hour of needle placement for unfractionated heparin and 6-8 hours for low molecular weight heparin.

3.2 METHODS OF PROPHYLAXIS FOR MODERATE AND HIGH RISK GROUPS

A) Mechanical methods
These include graduated elastic compression stocking and intermittent pneumatic compression devices. They are effective in preventing DVT in moderate-risk surgical patients. However, there were no methodically sound studies that compared graduated compression stockings alone with another form of prophylaxis.[1]

Graded compression elastic stockings (GCS) reduce the incidence of leg DVT and enhance the protection afforded by low dose heparin. However data on their effect in proximal DVT and PE is lacking. Further clinical trials are needed to assess the effectiveness of this method in high-risk patients. One small disadvantage is that some patients cannot effectively wear these stockings due to unusual limb size or shape.

Mechanical methods may also be combined with pharmacological prophylaxis to increase efficacy in high-risk patients. Unlike pharmacological prophylaxis, trials of mechanical methods have not yet been large enough to establish whether or not they significantly reduce fatal PE. Moreover they have not been evaluated in medical patients. However, it seems reasonable to extrapolate efficacy from studies of DVT in surgical patients. As they do not increase the risk of bleeding, mechanical methods may be preferred in patients at increased risk of bleeding from pharmacological prophylaxis. Graduated elastic stockings are contraindicated in severe leg ischaemia.

B) Pharmacological methods
These include:
- Standard unfractionated heparin (usually in low dosage)
- Low molecular weight heparins or heparinoids
- Oral anticoagulants
- Dextran 70

(i) *Low dose UFH* subcutaneously is effective in preventing DVT and PE in medical patients and in moderate-risk surgical patients.[9] It has less effect on DVT in hip surgery. An international multicentre trial also established the effectiveness of low dose UFH in preventing fatal pulmonary embolism, a significant reduction from 0.7% to 0.1%.[12]

This therapy is administered subcutaneously in a dose of 5000U every 12 hours after the surgery. Meta-analyses have revealed that low dose heparin reduces the incidence of all DVT and PE.

Low dose UFH is easy to administer and relatively inexpensive, and does not require anticoagulant monitoring.

In elective hip surgery, the efficacy of UFH is increased by adjusting the dose, e.g. 3500 IU 8-hourly, starting two days before surgery and adjusting the dose to maintain the activated partial thromboplastin time (APTT) ratio in the upper normal range.[1] Such an adjusted dose regimen is, however, more complicated to use than fixed doses of UFH or LMWH. | Grade A

(ii) *LMWHs and heparinoids* are also given subcutaneously for prophylaxis of VTE. They are effective as once-daily injections. Compared to standard heparins, LMWHs are more effective in orthopaedic surgery and slightly more effective in general surgery without increasing the risk of bleeding. [1,7]

Randomised clinical trials comparing LMWH (given once or twice daily) with UFH have shown that the former is as effective as, or more effective than the latter in preventing thrombosis. Recent meta-analyses also revealed similar findings.[5-11] LMWH is much less likely to produce heparin-induced thrombocytopaenia and osteoporosis than unfractionated heparin.[13, 14] | Grade A

The advantages of LMWH include its ease of administration using pre-filled syringes, non-requirement for monitoring and once-daily injection schedule for most of the preparations. Its main disadvantage is that it is porcine-based and so cannot be routinely administered to Muslim patients. Despite its relatively high cost, studies have uniformly concluded that broad application of prophylaxis is highly cost-effective. [15-22]

(iii) *Oral anticoagulants* may sometimes be used as prophylaxis especially when heparin is contraindicated. The advantages are its ease of administration, low cost and safety. The disadvantages are firstly, they require daily monitoring of the international normalised ratio (INR) or the prothrombin time. The recommended therapeutic range is 2.0 to 2.5 (2.0 to 3.0 in orthopaedic surgery).[1] Secondly, if started at a low dose before surgery, they may reduce the risk of bleeding compared to full anticoagulation at the time of surgery.

In view of these shortcomings and the wide availability of other effective options, there is little rationale for this therapy to be used routinely as prophylaxis.

(iv) *The pentasaccharide fondaparinux sodium* is the first of a new class of synthetic antithrombotic agents that acts through selective inhibition of factor Xa. Fondaparinux contains no animal sourced components and has been designed to bind selectively to a single target in plasma, antithrombin (ATIII), the main endogenous inhibitor of blood coagulation. Clinical trials results using fondaparinux have been encouraging. In these trials, 2.5 mg of fondaparinux sodium given once daily to patients undergoing orthopaedic surgery, starting 6 hours post operatively, showed a major benefit over LMWH, achieving an overall risk reduction of VTE greater than 50% without increasing the risk of clinically relevant bleeding.[23-26]

Grade A

3.3 DURATION OF PROPHYLAXIS

Specific antithrombotic prophylaxis should be continued for at least 5 days (the minimum duration for prophylaxis in clinical trials) or until hospital discharge if this is earlier than 5 days. In high-risk patients, prophylaxis should be continued until illness and immobility have resolved, or until hospital discharge if this is earlier.

After hospital discharge, increased risk of VTE may continue for several weeks in patients with continuing risk factors (See Table 2, Chapter 1). In such patients, consideration should be given by the doctor to continue prophylaxis after discharge, although such practice has not yet been tested in randomised trials. If the hospital team recommends prophylaxis after discharge, they should communicate with the patient prior to discharge. Separate guidelines should be prepared for this and other aspects of antithrombotic therapy.

3.4   SPECIAL CONSIDERATIONS

Acute stroke with paralysis of lower limb
It is well recognised that the risk of DVT in acute stroke correlates with the degree of paralysis[27] and is greater in older patients[28] and those with atrial fibrillation.[29] Numerous recommendations locally and abroad have extrapolated from different patient populations and settings in acute stroke patients. A review of the available evidence to date confined to stroke patients is described below.

Evidence from randomised controlled trials in acute stroke patients does not support the use of Graduated Compression Stockings (GCS) and Intermittent Pneumatic Compression (IPC).[30] A large multicentre trial, Clots in Legs or TED stockings **(CLOTS)** is ongoing to answer the above question conclusively with a larger number of patients.

There is a risk reduction of 29% in thromboembolism with aspirin following ischaemic stroke.[31] The International Stroke Trial (IST) compared UFH initiated within 48 hours of ischaemic stroke and continued for 2 weeks to no heparin.[32] This treatment regime reduced thromboembolism and recurrent stroke but this was offset by an increased risk of haemorrhagic stroke transformation and extracranial haemorrhage. Therefore, routine use of standard heparin such as thromboprophylaxis cannot be recommended.

In the *TAIST* study,[33] treatment with tinzaparin at high dose (175 anti-Xa IU/kg daily) within 48 hours of acute ischaemic stroke was superior to aspirin in preventing VTE but was associated with a higher rate of symptomatic intracranial haemorrhage. More trials are needed before routine use of LMWH can be recommended.

Graduated compression stockings with or without IPC can be used if other concomitant risk factors such as obesity, previous DVT, AF and malignancy are also present.

Acute spinal cord injury or disease causing lower limb paralysis (e.g. Guillain-Barre syndrome)
Intermittent pneumatic compression, with or without subcutaneous LMWH or adjusted dose subcutaneous UFH is recommended.[34-35]

Grade A

Grade B

Critical ischaemia or amputation of the lower limb

- · Subcutaneous low-dose standard heparin (5000 IU, 8 hourly)
- · Adjusted dose warfarin (INR 2.0 - 3.0) [36]

No prevention needed for amputation.

Grade C

3.5 OBSTETRICS AND GYNAECOLOGY HRT AND VTE

Exogenous oestrogens are associated with an increased risk of VTE. [37]

A number of epidemiological case control studies have provided evidence linking HRT and VTE.[38-41] Women suffering from thrombophilic traits are more at risk of VTE.

There is a paucity of similar epidemiological studies in Malaysia. The incidence of VTE in Malaysia is probably less than in the Caucasian population.

Routine screening for thrombophilia is not recommended prior to commencing or continuing HRT.[42-63] It is recommended that the risk of VTE be discussed with the patient in the context of overall benefits of HRT and family history of VTE in first or second degree relatives be obtained. If the above history is positive, selected screening is indicated. The presence of multiple risk factors (Table 2, Chapter 1) may suggest that HRT is best avoided.

In patients whose history is suggestive of VTE but in the absence of objective testing, prophylaxis is recommended.

In the absence of underlying thrombophilic defect or in cases of VTE occurring more than a year earlier, HRT can be prescribed. Transdermal therapy is recommended in such a situation. The patient should be aware of the potential for a venous thrombotic event to develop and the need to report promptly any such symptoms. However, HRT is best avoided in patients in whom thrombophilia has been identified.

With regards to patient on HRT undergoing surgery, appropriate assessment of the thrombotic risk should be made. There is no indication to routinely stop HRT prior to surgery provided appropriate thromboprophylaxis, such as low molecular weight heparin or low dose heparin is employed.

OCP and VTE (Ref: [64])

The combined OCP is associated with changes in the coagulation system, which may be regarded as prothrombotic. These changes correlate with the oestrogen content but even the low dose preparations are associated with changes in the coagulation system.

There is a higher risk of VTE in OCP users due to the higher oestrogen content compared to HRT. In patients undergoing elective surgery, the decision to stop OCP 4-6 weeks before surgery must be balanced against the risk of unwanted pregnancy. These risks (development of VTE & unwanted pregnancy) must be communicated to the patient. Effective alternative method of contraception must be recommended. Progestogen-only contraceptives are not associated with any increased risk of VTE and can be used as an alternative.

In the absence of other risk factors, there is insufficient evidence to support a policy to routinely stop the combined OCP prior to elective surgery. There is insufficient evidence to support routine thromboprophylaxis in these women without additional risk factors.

However in emergency surgery, the risk of VTE is higher. Thromboprophylaxis is recommended for a patient taking the combined OCP undergoing such surgery.

For patients undergoing uncomplicated minor or intermediate procedures (e.g. curettage or laparoscopy) there is no evidence to support stopping the combined pill or the use of thromboprophylaxis.

Precaution

When HRT and OCP's are given in conjunction with coumarins, care must be taken to avoid potentiation of the anticoagulant effect and more frequent monitoring of the INR is required. However, concomitant coumarin usage is not a contraindication to HRT or OCP use.

Caesarian Section

Caesarian section increases the risk of thromboembolism by approximately 10-fold.[65] Patients should have their risk stratified to determine what prophylaxis is needed (table 2).

Table 2:

Risk Assessment Profile for Thromboembolism in Caesarean Section.	
Risk Level	**Prophylaxis**
Low risk · Elective caesarian section-uncomplicated pregnancy and no risk factors	Early mobilisation and hydration
Moderate risk - · Age >35 years · Obesity >80kg. · Para 4 or more · Gross varicose veins · Current infection · Preeclampsia · Immobility prior to surgery>4 days · Major current illness e.g. heart or lung disease, cancer, nephrotic syndrome · Emergency caesarian section in labour	Consider one of a variety of prophylactic measures
High risk- · A patient with 3 or more moderate risk factors from above · Extended major pelvic or abdominal surgery e.g. caesarian hysterectomy · Patients with personal or family history of deep vein thrombosis; pulmonary embolism or thrombophilia; paralysis of lower limbs · Patients with antiphospholipid antibody	heparin / LMWH prophylaxis ± compression stockings

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4.1   INTRODUCTION

The aim of treatment of VTE is to reduce morbidity and mortality. This is achieved by optimal therapy to prevent thrombus extension and embolisation. The mainstay of therapy is pharmacological. Adjunct therapies include mechanical devices like filters and stents.

4.2   INITIAL TREATMENT OF VTE

In clinically suspected VTE, treatment with UFH or LMWH should be given until the diagnosis is excluded by objective testing. Treatment regimens for DVT and PE are similar because the two conditions are manifestations of the same disease process. Anticoagulation remains the standard treatment.

4.2.1   Heparin regimens
Intravenous unfractionated heparin
Intravenous UFH remains the standard treatment in most cases of DVT and PE. The optimal duration of initial iv UFH therapy in patients with VTE is between 5 to 7 days. The regimen for the administration of iv UFH is as follows:

1.   Baseline APTT, PT, FBC, renal profile, liver function test and thrombophilia screen (if indicated).
2.   Initial dose of iv bolus UFH 80 IU/kg followed by maintenance infusion at 18 IU/kg/hr.
3.   Check APTT at 6, 12 and 24 hours. The target APTT ratio is 1.5 to 2.5. This must be achieved in the first 24 hours and maintained thereafter.
4.   Start warfarin therapy at 5 mg on the first 2 days. Thereafter adjust daily dose according to INR.
5.   Check platelet count from day 3 till the end of second week.
6.   Discontinue heparin once target INR (2.0 - 4.0) is achieved on 2 consecutive days.

To standardize the management of iv UFH, a weight-based normogram is used (Table 1).

TABLE 1: MANAGEMENT OF IV UFH

Initial dose	80 IU/kg bolus, then 18 IU/kg/hr
APTT < 35 s (<1.2x control)	80 IU/kg bolus, then increase rate by 4 IU/kg/hr
APTT 35 to 45 s (1.2 to 1.5x control)	40 IU/kg bolus, then increase Infusion rate by 2 IU/kg/hr
APTT 46 to 70 s (1.5 to 2.3x control)	No change
APTT 71 to 90 s (2.3 to 3x control)	Decrease infusion rate by 2 IU/kg/hr
APTT >90 s (>3x control)	Hold infusion for 1 hour, then decrease Infusion rate by 3 IU/kg/hr

The APTT monitoring of UFH is sometimes problematic, particularly in late pregnancy, when an apparent heparin resistance occurs due to increased fibrinogen and factor VIII, which influence the APTT. This can lead to unnecessary high doses of heparin being used with subsequent haemorrhagic problems. In these situations, it is useful to determine the anti-Xa level as a measure of heparin dose (target 0.3-0.7 u/ml).[1] However anti-Xa is not available in most hospitals and switching to LMWH is recommended.

Subcutaneous unfractionated heparin
Subcutaneous UFH is an effective alternative to intravenous UFH for the initial management of DVT. In a meta-analysis, 12 hourly subcutaneous unfractionated heparin has been shown to be as effective, and at least as safe as intravenous unfractionated heparin in the initial management of DVT. The regimen for the administration of subcutaneous, unfractionated heparin includes an initial intravenous bolus of 5000 IU followed by subcutaneous injections of 15,000 to 20,000 IU 12 hourly. This is monitored by the APTT with the mid-interval APTT maintained between 1.5-2.5 times the control.[2]

Grade A

4.2.2   Low molecular weight heparin

LMWH is given subcutaneously and does not require monitoring and is as effective and at least as safe as UFH in the treatment of DVT and PE.[1] Currently available LMWHs and its recommended doses for the treatment of acute VTE are as shown in Table 2).

TABLE 2:   LMWHS AND ITS RECOMMENDED DOSES FOR THE TREATMENT OF ACUTE VTE

LMWH recommended	Treatment
Enoxaparin (Clexane)	1 mg/kg twice daily
Nadroparin (Fraxiparine)	0.1 ml/kg twice daily
Nadroparin (Fraxiparine Forte)	0.1 ml/kg once daily
Tinzaparine (Innohep)	175 units/kg once daily

Recommended duration of treatment is 7 to 14 days for patients who will subsequently be continued on warfarin.

Table 3:   META-ANALYSIS COMPARING LMWHS TO UFH IN THE IN-PATIENT VS OUTPATIENT MANAGEMENT OF VENOUS THROMBOEMBOLISM (VTE)

Outcome	In-patient LMWH vs UFH RR (95% CI)	P value	Outpatient LMWH vs UFH RR (95 % CI)	P value
Recurrent VTE	0.80(0.53-1.19)	NS	0.90(0.63-1.29)	NS
Pulmonary embolism	0.97(0.49-1.94)	NS	1.06(0.56-1.98)	NS
Major bleeding	0.40(0.21-0.76)	<0.01	1.18(0.56-2.49)	NS
Total mortality	0.63(0.42-0.95)	NS	0.85(0.61-1.18)	NS

LMWH= low- molecular weight heparin; UFH = unfractionated heparin; RR = relative risk ; CI = confidence interval ; p value = probability; NS = not significant.

Monitoring of LMWHs with anti-Xa levels is generally not necessary except in renal failure, extreme obesity and late pregnancy. Peak anti-Xa activity (3 hours post-injection) should be measured by a chromogenic substrate assay where facilities are available. The target therapeutic range for LMWH is between 0.6 to 1.0 units/ml.

4.2.3 Adjunct therapy

In the initial management of DVT, adequate analgesia should be given and the leg elevated. A graduated elastic compression stocking should be applied as soon as the patient can tolerate it and mobilisation encouraged.

A temporary caval filter may be required in patients with recurrent PE despite satisfactory anticoagulation or in situations where anticoagulation is contraindicated. Where life-threatening massive PE occurs, cardiorespiratory resuscitation is usually required and intravenous heparin given. Thrombolytic therapy, percutaneous catheter thrombus fragmentation or surgical embolectomy will be required. This will vary with local expertise.

Where DVT threatens leg viability through venous gangrene, the leg should be elevated, anticoagulation commenced and consideration given to venous thrombectomy or thrombolytic therapy. | Grade C

4.2.4 Thrombolysis

Thrombolytic agents used are tissue plasminogen activator (tPA) and streptokinase. They are indicated in massive PE. The dose for streptokinase is 250,000IU iv bolus followed by 100,000IU/hr for 24 hours. The dose for tPA is 100mg iv over 2 hours.[1] | Grade C

4.2.5 Pulmonary embolectomy

Indications are massive PE with failure of thrombolytic therapy or contra-indication to thrombolysis. | Grade C

4.2.6 Thrombolysis and venous thrombectomy

There are ongoing prospective studies of both these treatments to reduce post thrombotic syndrome (PTS) following DVT.

4.2.7 Endovascular stents

Endovascular stents have been used for residual iliac stenosis and result in relief of obstructive venous symptoms and leg oedema. The patency rates when combined with thrombolysis is more than 80% immediately and 60% at 5 years.[3,4,5]

4.3 MAINTENANCE TREATMENT OF VTE

Following initial heparinisation in patients with VTE, maintenance of anticoagulation with oral anticoagulants is recommended. Duration of oral anticoagulation and target INR are shown in Tables 4 & 5.

Following discharge, patiens should be followed up within a week with a repeat INR. If the INR remains within therapeutic range, the same dose is maintained and the next follow-up will be 2 weeks later. If the INR still remains within therapeutic range, then monthly follow-up with INR is advised. More frequent visits are required if therapeutic INR is not achieved. For details of dose adjustment, refer to algorithm. (Figures 1 and 2)

TABLE 4: DURATION OF THERAPY.

Time	Therapy
3 to 6 months	first event with reversible or time-limited risk factor (Surgery, trauma, immobility, oestrogen use)
= 6 months	idiopathic VTE, first event
12 months to lifetime - first event with cancer until resolved	- anticardiolipin antibody - antithrombin deficiency - recurrent event, idiopathic or with thrombophilia

Figure 1: Warfarin Maintenance dosing Protocol for Goal INR 2.0-3.0[6]

```
                          ┌─────────────────┐
                          │ Dose Alteration │
                          │   for goal INR  │
                          │     2.0-3.0     │
                          └─────────────────┘
        ┌───────────────┬──────────┴──────────┬───────────────┐
 ┌──────────────┐ ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
 │  INR <2.0    │ │  INR 3.1-3.5 │ │  INR 3.6-4.0 │ │   INR >4.0   │
 └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
 ┌──────────────┐ ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
 │  Increase    │ │  Decrease    │ │  Withhold 1  │ │  Withhold 2  │
 │  by 5% -15%  │ │  by 5% -15%  │ │    Dose      │ │    Doses     │
 └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
                                   ┌──────────────┐ ┌──────────────┐
                                   │  Decrease    │ │  Decrease    │
                                   │  by 10% -15% │ │  by 10% -15% │
                                   └──────────────┘ └──────────────┘
```
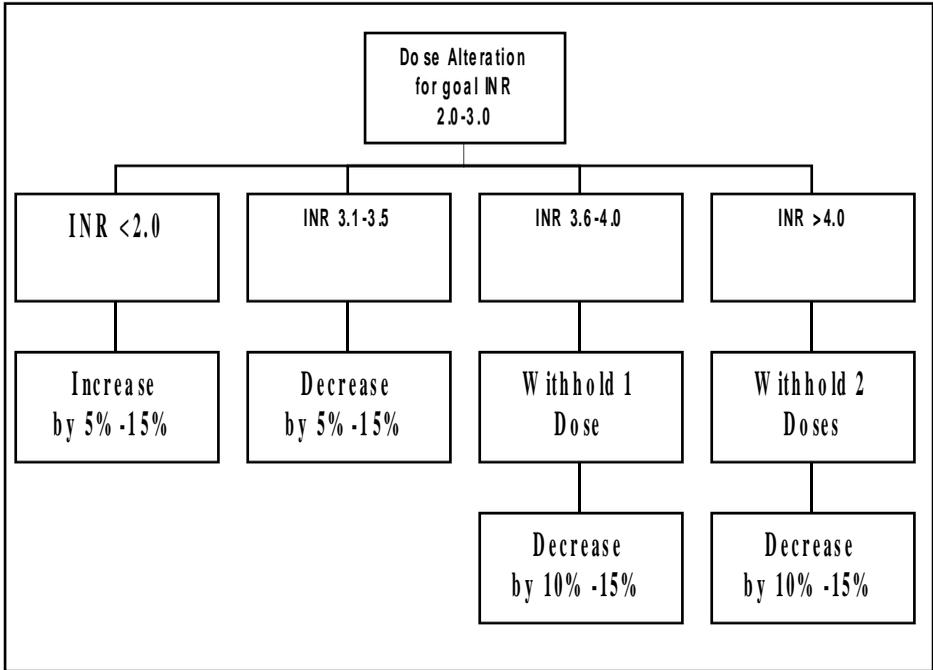
Figure 2: Warfarin Maintenance Dosing Protocol for Goal INR 3.0-4.0[6]

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                          ┌─────────────────┐
                          │ Dose Alteration │
                          │  for Goal INR   │
                          │     3.0-4.0     │
                          └─────────────────┘
        ┌───────────────┬──────────┴──────────┬───────────────┐
 ┌──────────────┐ ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
 │  INR <3.0    │ │ INR 4.1 - 4.5│ │ INR 4.6 – 5.0│ │   INR >5.0   │
 └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
 ┌──────────────┐ ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
 │  Increase    │ │  Decrease    │ │  Withhold 1  │ │  Withhold 2  │
 │  by 5% - 15% │ │  by 5% - 15% │ │    Dose      │ │    Doses     │
 └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
                                   ┌──────────────┐ ┌──────────────┐
                                   │  Decrease    │ │  Decrease    │
                                   │  by 10% - 15%│ │  by 10% - 15%│
                                   └──────────────┘ └──────────────┘
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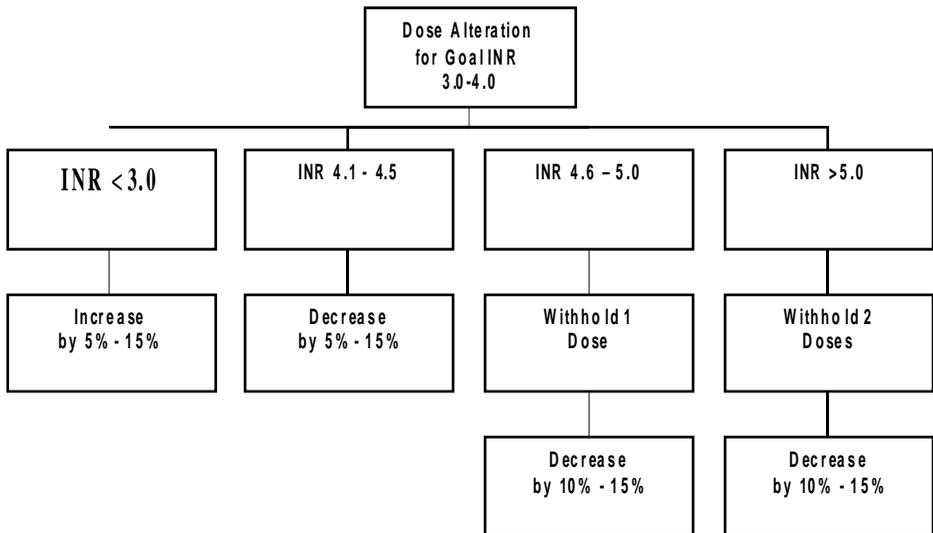
4.4 VENOUS THROMBOEMBOLISM IN PATIENTS UNDERGOING SURGERY/ANAESTHESIA

Elective surgery should be avoided in the first month after an acute episode of venous thromboembolism. There is an estimated risk of recurrent VTE of 40% on stopping anticoagulation in the first month after an acute episode.[7]

If major surgery is unavoidable within two weeks after a PE or a proximal DVT, anticoagulation should be stopped and an inferior vena caval filter should be inserted. Intravenous heparin should be recommenced as soon as it is safe.

For patients on warfarin during the first month after a VTE, warfarin should be stopped for 4 days for the INR to fall below 2.0. Pre-operative intravenous heparin should be administered for 2 days before surgery while the INR is subtherapeutic. If the activated partial thromboplastin time is within the therapeutic range, stopping continuous heparin therapy six hours before surgery should be sufficient for heparin to be cleared before surgery. Post-operative intravenous heparin is indicated and should be started not earlier than 12 hours after major surgery or delayed longer if there is evidence of bleeding from the surgical site. Heparin should be restarted without a bolus.

For patients in the second or third month of warfarin therapy for acute VTE, pre-operative intravenous heparin therapy is not justified unless there are additional risk factors for recurrent VTE (e.g. hospitalisation for acute illness). Post-operative intravenous heparin is recommended for such patients until warfarin therapy is resumed and the INR is above 2.0.

Patients who have been receiving warfarin for more than three months since their last episode of acute VTE do not need pre-operative heparin. They should receive post-operative prophylaxis as recommended for patients at high risk for VTE e.g. with LMWH until warfarin therapy is resumed and the INR is above 2.0. It should be combined with mechanical methods of prophylaxis such as graduated compression stockings or intermittent pneumatic compression.

Grade B

4.5 VTE IN PREGNANCY

Treatment:
Evidence for the management of VTE during pregnancy is lacking and, in general, recommendations for the management of VTE during pregnancy are extrapolated from studies in non-pregnant patients.

Heparin has been widely used for thromboprophylaxis and treatment. Neither unfractionated standard heparin nor low molecular weight heparin crosses the placenta and thus there is no risk of foetal haemorrhage or teratogenicity effect.

In women with features consistent with VTE, anticoagulant treatment should be employed until an objective diagnosis is made (Table 6).

Oral anticoagulant treatment during pregnancy:

Oral anticoagulants cross the placenta readily and are associated with a characteristic embryopathy in the first trimester, central nervous system abnormalities and fetal haemorrhage.[8]

Warfarin embryopathy consists of nasal hypoplasia and/or stippled epiphyses and occurs in approximately 6.4% of patients taking warfarin throughout pregnancy.[8]

Maintenance treatment with heparins

During pregnancy, adjusted-dose subcutaneous, unfractionated heparin or subcutaneous LMWH are suitable for maintenance treatment of VTE.

Women with antenatal VTE can be managed with an adjusted-dose regimen of subcutaneous unfractionated heparin or subcutaneous LMWH for the remainder of the pregnancy. [8 - 12]

The simplified therapeutic regimen for LMWH is convenient for patients and allows outpatient treatment. Women should be taught to self-inject. They can then be managed as outpatients until delivery.

Grade B

Duration of therapy

Peripartum

When VTE occurs in pregnancy, therapeutic anticoagulation should be continued for at least six months.

Postpartum

Following delivery, treatment should continue for at least 6-12 weeks. Warfarin can be used following delivery. Heparin and LMWHs are not secreted into breast milk and can be safely given to nursing mothers.[13]

Warfarin can be commenced on the second or third postnatal day. The international normalised ratio (INR) should be checked on day two and subsequent doses titrated to maintain the INR between 2.0 and 3.0. Background heparin/LMWH treatment should be continued until the INR > 2.0 on two successive days. **Grade C**

TABLE 6: RECOMMENDATIONS FOR ANTICOAGULATION IN PREGNANCY

Clinical Condition	Peripartum	Alternative Strategy	Postpartum
DVT/PE before pregnancy; not currently anticoagulated	UFH 5,000 U sc Q 12 hr	LMWH/ prevention doses	Warfarin to INR 2-3 for 4-6 wk*
DVT/PE before pregnancy; currently anticoagulated	sc UFH/treatment doses	LMWH/ treatment doses	Warfarin to INR 2-3 until full course completed* (minimum, 4-6 wk)
New DVT/PE during pregnancy	IV UFH/treatment doses for 5-10 days, followed by sc UFH/treatment doses	LMWH/ treatment doses	Warfarin to INR 2-3 until full course completed* (minimum, 4-6 wk)
Currently anticoagulated for other reasons (e.g., atrial fibrillation, valve replacement)	sc UFH/treatment doses		Warfarin to appropriate INR density*

DVT = Deep venous thrombosis; LMWH = Low-molecular-weight heparin; PE = Pulmonary embolism; sc = Sub-cutaneous; UFH = Unfractionated heparin.

*Background heparin/LMWH treatment should be continued until the INR > 2.0 on two successive days **Grade C**

Anticoagulant therapy during labour and delivery

The woman should be advised that once she is established in labour or thinks that she is in labour, she should not inject any further heparin.

The dose of heparin should be reduced to its prophylactic dose on the day prior to induction of labour and continued in this dose during labour (for unfractionated heparin, this means a dose of 5000 iu given 12 hourly. For LMWH preparations, a once-daily regimen should be adopted using the following doses: nadroparin: 0.3 ml, enoxaparin: 40 mg).

The treatment dose should be recommenced following delivery. Epidural anaesthesia can be sited only after discussion with a senior anaesthetist, in keeping with local anaesthetic protocols.

For delivery by elective Caesarean section, the woman should receive a prophylactic dose of LMWH on the day prior to delivery. On the day of delivery, the morning dose should be omitted and the operation performed that morning. The prophylactic dose of LMWH should be given three hours post-operatively (or four hours after removal of the epidural catheter) and the treatment dose recommenced that evening. There is an increased risk of wound haematoma following Caesarean section with both unfractionated heparin and LMWH of around 2%.

In patients receiving therapeutic doses of LMWH, wound drains should be considered at Caesarean section and the skin incision should be closed with interrupted sutures to allow drainage of any haematoma.

Any woman who is considered to be at high risk of haemorrhage, and in whom continued heparin treatment is considered essential, should be managed with intravenous, unfractionated heparin until the risk factors for haemorrhage have resolved. These risk factors include major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding and postpartum haemorrhage. Unfractionated heparin has a shorter half-life than LMWH and its activity is more completely reversed with protamine sulphate. If a woman develops a haemorrhagic problem while on LMWH, the treatment should be stopped and expert haematological advice sought.

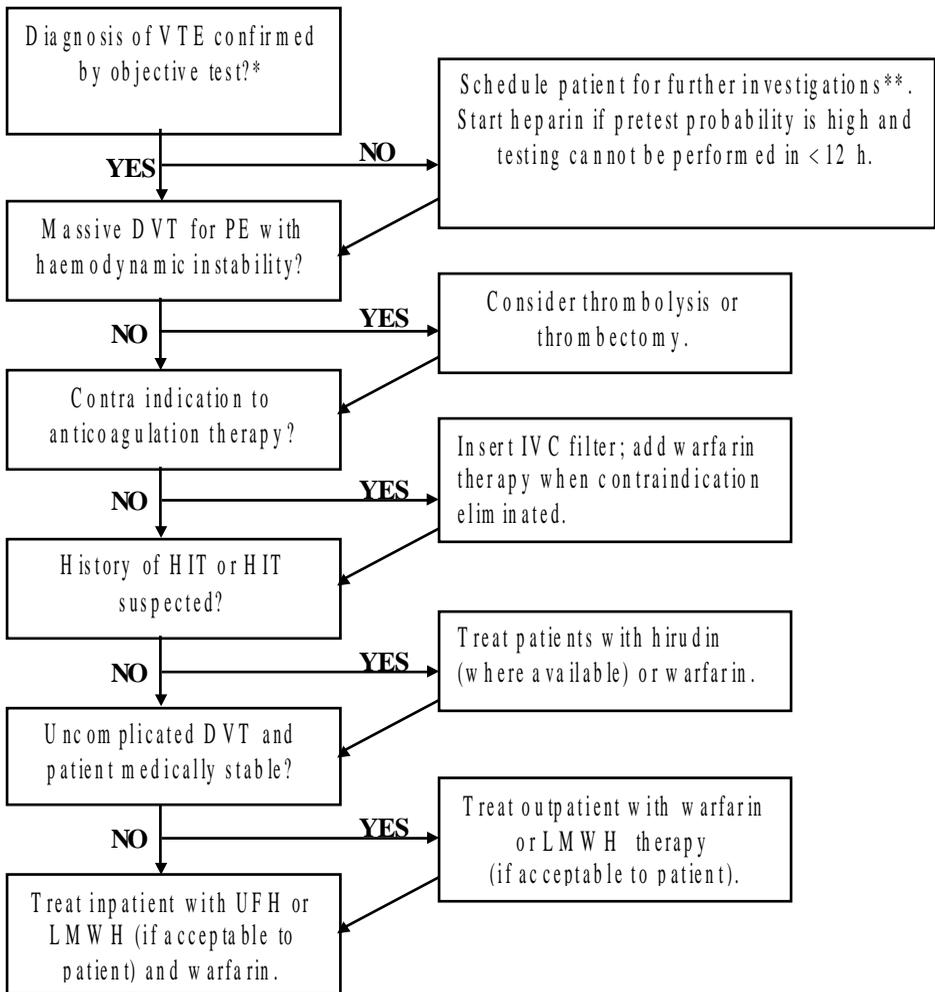Grade C

Prevention of post-thrombotic syndrome

Post-thrombotic syndrome is a severe disabling sequelae of DVT. It is characterized by chronic venous oedema, peripheral vascular insufficiency associated with chronic venous ulcers. Graduated elastic compression stockings should be worn on the affected leg for two years after the acute event to reduce the risk of post-thrombotic syndrome. A RCT in non-pregnant patients has shown that such therapy can reduce the incidence of post thrombotic syndrome from 23% to 11% over this period.[14]

Grade A

4.6   RECOMMENDATIONS FOR ANTICOAGULATION FOR ESTABLISHED VTE IN STROKE PATIENTS.

The greatest risk of haemorrhagic transformation in acute ischaemic stroke is in the first 4 days.[15] From IST[16], where medium and low dose heparin are used, there is an increased risk of haemorrhagic stroke transformation and extracranial haemorrhage with the regime started within 48 hours and continued for 2 weeks. As VTE is usually diagnosed several days after stroke onset, the greatest risk of haemorrhagic transformation has passed. Based on IST data, it may be safe to anticoagulate towards the end of the 2nd week. This must be balanced against risk from the DVT. The clinical decision to anticoagulate is more urgent if the DVT is a proximal one compared with a distal DVT or if the DVT is propagating proximally on repeated imaging. LMWH or UFH followed by 3 months of warfarin is the standard practice.

Figure 3: Algorithm of treatment regime for VTE

```
┌─────────────────────────┐
│ Diagnosis of VTE confirmed
│ by objective test?*      │
└─────────────────────────┘
                    NO ──────► ┌───────────────────────────────────────┐
                               │ Schedule patient for further investigations**.
   YES                         │ Start heparin if pretest probability is high and
                               │ testing cannot be performed in < 12 h. │
                               └───────────────────────────────────────┘
┌─────────────────────────┐
│ Massive DVT for PE with  │
│ haemodynamic instability?│
└─────────────────────────┘
                    YES ─────► ┌───────────────────────────┐
                               │ Consider thrombolysis or
   NO                          │ thrombectomy.             │
                               └───────────────────────────┘
┌─────────────────────────┐
│ Contra indication to     │
│ anticoagulation therapy? │
└─────────────────────────┘
                    YES ─────► ┌───────────────────────────┐
                               │ Insert IVC filter; add warfarin
   NO                          │ therapy when contraindication
                               │ eliminated.               │
                               └───────────────────────────┘
┌─────────────────────────┐
│ History of HIT or HIT    │
│ suspected?               │
└─────────────────────────┘
                    YES ─────► ┌───────────────────────────┐
                               │ Treat patients with hirudin
   NO                          │ (where available) or warfarin.│
                               └───────────────────────────┘
┌─────────────────────────┐
│ Uncomplicated DVT and    │
│ patient medically stable?│
└─────────────────────────┘
                    YES ─────► ┌───────────────────────────┐
                               │ Treat outpatient with warfarin
   NO                          │ or LMWH  therapy
                               │ (if acceptable to patient). │
                               └───────────────────────────┘
┌─────────────────────────┐
│ Treat inpatient with UFH or
│ LMWH (if acceptable to
│ patient) and warfarin.   │
└─────────────────────────┘
```

HIT: Heparin Induced Thrombocytopenia
* In most hospitals without specialized test, the minimum investigation include
ECG, blood gases and chest X-ray are required.

** Refer to centres with appropriate facilities.

4.7 PHARMACOECONOMICS OF VENOUS THROMBOEMBOLISM

All health care systems today are being forced to examine ways in which costs especially drug costs, can be lowered. Antithrombotic agents are no exception. The general approach to pharmacoeconomics of venous thromboembolism requires certain principles of pharmacotherapy. These include evaluation of safety, efficacy and affordability.

Economic analyses must take into account the efficacy of the strategy, treatment complications, and monitoring costs. The determination of the cost-effectiveness of VTE prophylaxis is based on the premise that a reduction in future VTE events will reduce future costs.[17]

Furthermore, the incremental cost per patient will decrease proportionally with an increase in the frequency of VTE in the population. In other words, the cost of providing prophylaxis to 1000 patients will decline as the incidence of VTE in the given population increases. More expensive and effective strategies therefore become more cost-effective in higher risk populations.

Only a handful of studies have formally evaluated the cost-effectiveness of VTE prevention strategies. The acquisition costs of graduated compression stockings, heparin, and warfarin are considerably less than those of the LMWHs, danaparoid, and fondaparinux. However, the acquisition cost for drug therapy is relatively small when compared with the overall cost of care. In population at low risk for VTE, early ambulation appears to be the most cost-effective strategy. In population at moderate risk, the use of graduated compression stockings, the least expensive intervention, results in a lower overall cost when compared with no prophylaxis.[17] The use of low-dose heparin in moderate risk population is favourable when compared with no prophylaxis.[18] Although LMWHs provide a slightly greater reduction in the risk of VTE, the additional cost per 1000 patients is estimated to be double when compared with low dose UFH.[19] Whether universal use of LMWHs in moderate-risk patients is a cost-effective strategy remains controversial. In high-risk patients, the cost effectiveness of prevention is far greater because the incidence of VTE is higher. Following hip replacement surgery, regardless of strategy selected, prophylaxis saves money when compared with no prophylaxis.[20] The LMWHs slightly increase the total mean cost of care after total hip and knee replacement when compared with low dose UFH and warfarin.[21] However, because of their superior effectiveness, the LMWHs have a significantly lower cost per DVT and pulmonary embolism avoided.[21] As

determined by typical drug acquisition cost, the LMWHs appears to be a cost-effective choice in the highest risk patient population. To date no formal pharmacoeconomic analysis has been performed to compare fondaparinux to other pharmacological strategies.

A number of cost-effectiveness analyses using decision-modelling suggest that in the treatment of DVT, LMWH is more cost-effective than UFH.[22, 23] According to these decision models, the LMWHs will reduce overall health care cost if as few as 8 % of patients are treated entirely on an outpatient basis or if 13% of patients are discharged from hospital early. Five practice models for the outpatient management of DVT have been described: (1) anticoagulation clinic, (2) medical day care clinic (ambulatory care clinic), (3) emergency department fast-track program, (4) one visit and self-injection, and (5) physician office follow-up.[24] Each institution must assess which model fits its resources and patient population best.

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GENERAL SURGERY

5.1 ANTITHROMBOTIC THERAPY AND REGIONAL ANAESTHESIA

The decision to perform regional anaesthesia (spinal or epidural anaesthesia) in a patient receiving anti-coagulants should be made on an individual basis, weighing the small, though definite risk of spinal haematoma with the benefits of regional anaesthesia for a specific patient. Although the occurrence of a bloody or difficult regional needle placement may increase the risk, there are no data to support mandatory cancellation of a case.[1]

Grade C

1. For patients on preoperative thromboprophylaxis dose of LMWH, a single-injection spinal anaesthetic may be the safest regional technique. In these patients, needle placement should occur at least 10-12 hours after the LMWH dose. Patients receiving higher doses of LMWH will require delays of at least 24 hours before needle placement.

2. Patients with postoperative initiation of LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. For single daily dosing, the first postoperative LMWH dose should be administered 6-8 hours postoperatively. The second postoperative dose should occur no sooner than 24 hours after the first dose. Indwelling catheters may be safely maintained. However, the catheter should be removed within a minimum of 10-12 hours after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hours after catheter removal

3. During subcutaneous unfractionated heparin for thromboprophylaxis, there is no contraindication to the use of regional techniques. Since heparin-induced thrombocytopenia may occur during heparin administration, patients receiving heparin for greater than four days should have a platelet count assessed prior to regional block. The catheter should be removed 1 hour before any subsequent heparin administration or 2-4 hours after the last heparin dose.

4. Systemic therapeutic anticoagulation appears to increase risk of spinal haematoma formation. Therefore, regional blocks should be avoided in this clinical setting. Whereas, if systemic anticoagulation therapy is begun with an epidural catheter in place, it is recommended to delay catheter removal for 2-4 hours following therapy discontinuation and evaluation of coagulation status.

5. For patients on chronic oral anticoagulation, the anticoagulant therapy must be stopped, (ideally 4-5 days prior to the planned procedure) and the PT/INR measured prior to initiation of regional block. Early after discontinuation of warfarin therapy, the PT/INR reflect predominantly factor VII levels, and in spite of acceptable factor VII levels, factors II and X levels may not be adequate for normal haemostasis. Thus, caution should be used when performing regional techniques in patients recently discontinued from chronic warfarin therapy.

5.2 INFERIOR VENA CAVAL FILTERS

Vena caval filters are recognized treatment modalities to prevent sequelae of DVT. They can be inserted in both the superior and inferior vena cavae. They are usually inserted through the internal jugular vein or femoral vein, and normally placed in the infra-renal inferior vena cava under fluoroscopic or ultrasound guidance.[2]

Major indications for filters are recurrent pulmonary embolism (PE) despite adequate anticoagulation, contraindication for anticoagulation with further risk to bleeding in proximal ilio-femoral DVT and prevention of recurrent PE after pulmonary embolectomy. Other indications include recurrent chronic PE with pulmonary hypertension, ilio-femoral propagating thrombus, floating thrombus in the inferior vena cava and bilateral free floating femoral DVT inspite of effective anticoagulation. Anticoagulation should be resumed after insertion of the caval filters. The long-term patency of IVC filter is 98% in several large series. [2-4]

5.3 PULMONARY EMBOLECTOMY

It is indicated in massive PE with hypotension and rapid deterioration requiring inotropic support. It is done in emergency situations following failed conservative measures in patients with the following criteria:

1. Echocardiographic or angiographically documented large pulmonary embolus.
2. Haemodynamically unstable (shock) inspite of heparin and resuscitation efforts.
3. Failure of thrombolytic therapy or contraindication to its use.

5.4 CATHETER TRANSVENOUS EXTRACTION OR FRAGMENTATION OF PULMONARY EMBOLI

Suction extraction of venous thrombosis for pulmonary embolus has recently been developed. It is done using a double lumen steerable balloon-tipped catheter under fluoroscopic and ECG monitoring.[5]

The embolus can also be fragmented using a high-speed saline jet catheter system. The jet utilizes the Venturi effect to fragment the embolus. It is then evacuated using suction.[6]

5.5 VENOUS THROMBECTOMY

This procedure is done to prevent severe complications of post-thrombotic syndrome. Venous thrombectomy is indicated in impending venous gangrene of the lower limbs due to phlegmasia caerulea dolens (PCD). PCD is associated with considerable morbidity (50% amputation rate and 12-14% PE) and a 20% mortality rate.[7]

5.6 CHRONIC VENOUS INSUFFICIENCY

The most common complication of VTE is chronic venous insufficiency (CVI) due to post thrombotic syndrome (PTS). PTS results in debilitating pain, swelling, ulceration and is a significant cause of loss of working days.[8] It can contribute to an increase in recurrent DVT.[8] One in 5 recurrences present as PE with a mortality of 50%.[9]

PTS occurs in 35 to 69 % of patients within 3 years of DVT.[10] Patients with obstruction, reflux and recurrent DVT are at the highest risk of skin changes and ulcers. Prevention of PTS will significantly reduce the morbidity and late mortality of DVT.

Thrombolysis achieves more rapid lysis and is associated with a much lower rate of PTS (36% vs 80%) when compared to heparin alone.[11] Two other reviews were enthusiastic about the role of thrombolysis[12,13] but in the absence of randomised trial data, we cannot recommend this as standard treatment.

Reduction of venous pressure and reflux can be achieved by external compression, both elastic (single layer) and inelastic (4 layer) bandages. [14] A prospective randomised study has shown that compression stockings significantly reduced mild to moderate PTS (20% vs 47%) and severe PTS (11.5% vs 23%) compared to the control group.[15] Distal DVT once thought to be insignificant can result in PTS and therefore should be treated.[14,16,17]

The strongest factor associated with the development of PTS is recurrent DVT.[9] As such, DVT should be treated optimally. The duration of anticoagulation after DVT varies considerably and can range from 6 weeks to years. A long term follow up study showed the cumulative recurrence rate to be 30% at 8 years.[9] Recurrences were much higher in the group anticoagulated for 6 weeks compared to 6 months at 2 years. This difference was only seen in the first 6 months. Between 6-24 months there was no difference seen.[18] Recurrence rates after 2 years are much lower in patients with transient risk factors eg surgery and trauma as compared to permanent factors like cancer or thrombophilic states.[18] Another study that randomised patients to 2 years of warfarin or placebo after an initial 3 months of warfarin showed a 95% reduction in risk of recurrence in the long term warfarin group. There was however an increased rate of non fatal bleeding in the warfarin group.[19] It would seem reasonable to anticoagulate patients with temporary risk factors for 6 months and to consider longer periods in patients with permanent risk factors.

The most dreaded consequence of PTS is non healing venous ulcer. Only 50% have healed at 4 months and 80% at 2 years. The annual recurrence rate ranges from 6-15%.[10]

Surgery to the veins has a very limited role if any.[20] Debridement and skin grafting can achieve healing rates of 58%. After 2½ years of follow up recurrence rates were 33% but the ulcers were 80-90% smaller.[21] However this study did not compare skin grafting with the best compression therapy.

Compression bandages are the mainstay of treating these ulcers. The efficacy of these bandages in preventing PTS has already been mentioned earlier. The reduction in venous pressure and reflux has been demonstrated.[14] The improvement in healing time compared to other methods of dressing has also been shown.[20] The four layer bandage system[22] provides more sustained compression for periods up to a week and resulted in 75% healing at 12 weeks. The rate of recurrence in patients who continued with graduated compression stockings was 22% compared to 45% in those who did not use compression stockings.[22]

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APPENDIX 1 - Imaging of pulmonary embolism

Imaging modality	Sensitivity & specificity	Advantages	Disadvantages	Comments
Radionuclide lung scintigram	High probability scans usually indicate PE in 85% to 90% patients[1]	Non-invasive	Not readily available. Vast majority of studies of intermediate probability where incidence varies from 10% to 30%. History of PE decreases accuracy of high probability scans. Low-probability with strong clinical suspicion does not exclude PE. Intermediate probability not helpful in making diagnosis V/Q only helped in making diagnosis in minority[1]. Even in high probability or near normal V/Q scan, the likelihood of PE is 88% and 4%	Approx 20% with non-diagnostic scan plus normal lower limb US will have PE[2]. Negative US with low probability V/Q scan does not exclude PE[3]. Chronic obstructive disease results in decreased sensitivity[4]. Consider non-diagnostic all scans that not positive or negative and require further testing[5]. 45% to 66% high probability scans false positive when pretest probability low[6].
Helical (spiral) Computed Tomography	Dependent of the speed of the scanner with multidetector scanner showing best results Diagnosis of PE in 90% compared to 54%[7] Pooled analysis[8] sensitivity 72%, specificity 95%. Central thrombi sensitivity 94% & specificity 94%	Show non-embolic causes of symptoms. More useful than V/Q as first line test in central pulmonary emboli[9]. Discordance with V/Q, spiral CT correct in 92% & intermediate scan CT shows 80% of PE[10]. May allow assessment of the veins of the pelvis and lower limbs May be only available technique in this country for confirmation of PE	Multidetector CT scanners not readily available. High iodinated contrast medium load. Clinicians should not use negative test as diagnostic end point of excluding PE[11]. May be non-diagnostic in the dyspneic especially with single slice scanners. Not really a problem with the multi-detector CT scanners.	Demonstrates anatomy beyond the pulmonary arteries Currently not recommended by American College of Chest Physicians[12] and American Thoracic Society[13] as routine
Pulmonary Angiography		Gold standard test Can identify thrombi in subsegmental pulmonary arterial vessels	Not performed in this country. Invasive with morbidity of arrhythmias, hypotension, etc. Requires skilled radiologist and co-operative patient. Negative study does not exclude PE	American College of Chest Physicians recommend that it may be prudent to select the single most definitive test of conventional pulmonary angiography[12]
Chest radiography		Major value is demonstration of non-embolic pathology and interpretation of radionuclide scan		Classical findings of oligaemia, pleural based density and loss of lung volume[14]
ECG		Main function is demonstration of MI, left bundle branch block		Show findings consistent with but not diagnostic
Echocardiography	Poor sensitivity ranges 51%-67% Specificity 87%- 94%[15-17]	May assist in confirmation in massive PE	No use as a screening modality	Unexplained RV hypokinesis and dilation strongly suggestive but not diagnostic. May detect RA or RV clot

Imaging modality	Sensitivity & specificity	Advantages	Disadvantages	Comments
Venography		Gold standard for diagnosis of symptomatic calf thrombosis that do not extend proximally, recurrent DVT and those with high pretest probability with negative or non-diagnostic non-invasive test. Most accurate method for diagnosis of asymptomatic thrombi following surgical procedures[8] Also good for assessment of the iliac veins and IVC	Require lower venous access and intravenous contrast medium. Greater technical demands Cumbersome and expensive 10% inadequate examination. May not be available in every center in this country	Still required when US clinical features discordant, previous DVT[19]
Ultrasonography	Positive predictive value 97% for non-compression[?]. Full compressibility of femoral and popliteal veins negative predictive value of 98% [20] Isolated calf vein DVT sensitivity 50 to 75% [21] Asymptomatic patients sensitivity 54%, specificity 91%, positive predictive value 83%, negative predictive value 69% [22] Sensitivity & specificity for upper limb not adequately assessed. Sensitivity varies from 50% to 100%	Established as imaging procedure of choice for investigation of suspected DVT Duplex most sensitive and specific of non-invasive routinely non-invasive test May be only available technique in this country for surrogate confirmation of PE Can be performed rapidly and cheap Ideal for evaluation of common femoral vein to popliteal vein	More accurate in symptomatic patients & DVT in thigh then above groin or below knee Asymptomatic patients poor results Assessment of the calf veins more time consuming& technically demanding US of upper limb DVT unable to assess subclavian vein below the clavicle	Normal vein compressible unlike thrombosed When pretest probability high but US non-diagnostic, venography should be performed Calf DVT without more proximal DVT uncommon[23] and subsequent PE only in 1.1% [24]
D-Dimer	ELISA method of assay most sensitive. The negative predictive value varies with clinical probability (99% in those with low pre-test probability, 87.9% in moderate pre-test probability to 64.3% in high pretest probability) [25]	Negative results most helpful in obviating further testing in those with low pretest probability[26] Latex assays more readily available but less sensitive or specific	ELISA is expensive, time-consuming and not widely available.Predictive value increases proportionally with sensitivity but inversely with the prevalence of VTE in population being studied. D-dimer has greater variability of assay performance[27]. Elevated in variety of other illnesses e.g. MI, pneumonia. Limits specificity in those with concomitant disease[28]	Only blood screening test useful for DVT Detects breakdown product of fibrin clots i.e. D-Dimer Variety of different assays available Combination of D-dimer with US or clinical pretest probability best diagnostic accuracy than single examination [21]
Computed tomography		Can detect thrombus in abdomen and pelvis[29]. Superior to venography in identifying intraluminal thrombi, distinguishing old from new thrombi plus adjacent abnormalities		Requires further investigation in detection of calf vein thrombus. Prevalence of unsuspected DVT in CT seen in up to 1%[30]
Magnetic resonance venography	99% sensitivity and more than 91% specificity in proximal DVT [31]	Can differentiate acute from chronic clot Demonstrates surrounding tissues. Less operator dependent than US	Expensive, not readily available and presence of claustrophobia and implants may be contraindication	

Appendix 2:

Clinically Significant Warfarin Drug Interactions		
Mechanism	**Effect on Prothrombin Time**	**Drugs/ Drug Classes**
Increased synthesis of clotting factors	Decreased	Estrogens, vitamin K
Reduced Catabolism of clotting factors	Decreased	Methimazole, propylthiouracil
Induction of warfarin metabolism	Decreased	Barbiturates, carbamazepine, chronic alcohol use, icloxacillin, griseofulvin, nafcillin, phenytoin, primidone, rifampicin
Reduced absorbtion of warfarin	Decreased	Cholestyramine, colestipol, sucralfate
Unexplained mechanisms	Decreased	Azathioprine, cyclophosphamide, cyclosporin, mesalamine
Increased catabolism of clotting factors	Increased	Thyroid hormones
Decreased synthesis of clotting factors	Increased	Cefamandole, cefmetazole, cefoperazone, cegotaxime, moxalactam, vitamin E
Impaired vitamin K production by gastrointestinal flora	Increased	Broad-spectrum antibiotics
Inhibition of warfarin metabolism	Increased	Acute alcohol use, allopurinol, amiodarone,[b] azithromycin, cimetidine,[c] ciprofloxacin,[c]clarithromycin,[a] disulfiram,[b] erythromycin,[b,c]fluconazole,[a,b] fluorouracil, fluoxetine,[a] fluvoxamine,[b] grapefruit juice,[a] isoniazid,[a] itraconazole,[a] ketoconazole, metronidazole,[b] miconazole,[a,b] norfloxacin,[c] afloxacin,omeprazole,[a] phenytoin, propafenone, quinidine, asulfamethoxazole,[b] sulfasoxazole
Unexplained mechanisms	Increased	Acetaminophen, androgens, ascorbic acid, clofibrate, corticosteroids, gemfibrozil, statins
Increased bleeding risk	No effect	Aspirin/acetylated salicylates, clopidrogel, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, ticlopidine

[a] Inhibition of CYP3A4, primary metabolic pathway for (R)-warfarin..
[b] Inhibition of CYP2C9, primary metabolic pathway for (S)-warfarin.
[c] Inhibition of CYP1A2, primary metabolic pathway for (R)-warfarin.

Appendix 3:

Potential Warfarin Interactions with Dietary Supplements			
Presumed Mechanism	**Possible Effect**	**Case Report**	**Potential Interactions**
Inhibition of platelet aggregation	? risk of bleeding	Garlic,[a] Ginkgo[a]	Cassio, clove. Feverfew, ginger
Contains salicylate derivatives	? risk of bleeding		Liquorice, meadowsweet, poplar, willow
Enhanced fibrinolysis	? risk of bleeding		Dehydroepiandrosterone (DHEA)
Procoagulant activity	? risk of thromboembolism		Agrimony, yarrow
Contains warfarin constituents	? PT/INR	Dan Shen (Salvia)	Alfalfa, aniseed, armica, artemesia, celery seed, chamomile, dong quai (angelica), fenugreek horse chestnut, melilot, prickly ash, quassia, red clover, sweet woodruff, tonka beans
Unknown	? PT/INR	Ginseng	
[a] Case reports of bleeding when used alone.			

Appendix 4:

Key Elements of Patient Education Regarding Warfarin
Identification of generic and brand names
Purpose of therapy
Expected duration of therapy
Dosing and administration
Visual recognition of drug and tablet strength
What to do in case a dose is missed
Importance of prothrombin time monitoring
Recognition of signs and symptoms of bleeding
Recognition of signs and symptoms of thromboembolism
What to do in case of bleeding or thromboembolism
Recognition of signs and symptoms of disease states influence warfarin dosing   requirements
Potential for interactions with prescription and over-the-counter medications
Dietary considerations and use of alcohol
Avoidance of pregnancy
Significance of informing other health care providers that warfarin has been prescribed
When, where and with whom follow-up will be provided

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