CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/264.13(GU)

Prevention and Treatment of Venous Thromboembolism

Ministry of Health Malaysia

Malaysian Society of Haematology

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 2013 and will be reviewed in 2017 or sooner if new evidence becomes available.

Electronic version available on the following website:

http://www.haematology.org.my

DISCLOSURE STATEMENT

The panel members had completed disclosure forms. None held shares in pharmaceutical firms or acted as consultants to such firms (details are available upon request from the CPG Secretariat).

SOURCES OF FUNDING

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GUIDELINES DEVELOPMENT

The development group for these guidelines consists of Haematologist, Cardiologist, Neurologist, Obstetrician & Gynaecologist, Vascular Surgeon, Orthopaedic Surgeon, Anaesthesiologist, Pharmacologist and Pharmacist from the Ministry of Health Malaysia, Ministry of Higher Education Malaysia and the Private sector.

Literature search was carried out at the following electronic databases: International Health Technology Assessment website, PUBMED, MEDLINE, Cochrane Database of Systemic Reviews (CDSR), Journal full text via OVID search engine and Science Direct. In addition, the reference lists of studies selected for inclusion were scanned for relevant studies.

The clinical questions were divided into 18 subgroups and members of the development workgroup were assigned individual topics. Literature searched were appraised by workgroup members using Critical Appraisal Skills Programme (CASP) checklist, presented in the form of evidence table and discussed during group meetings. All statements and recommendations formulated were agreed by both the development group and review committee. Where the evidence was insufficient, the recommendations were derived by consensus of the development group and review committee.

The articles were graded by using the National Guidelines Clearinghouse (www.guidelines.gov), Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services, USA, level of evidence while the grading of recommendations in these guidelines was modified from the Scottish Intercollegiate Guidelines Network (SIGN). Refer to Appendix 12 for further details.

These guidelines have been presented to the Technical Advisory Committee for Clinical Practice Guidelines and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVES
GENERAL OBJECTIVES
To provide evidence-based guidance in the management of venous thromboembolism.

SPECIFIC OBJECTIVES
- To provide guidance in preventing venous thromboembolism
- To provide guidance in diagnosing venous thromboembolism
- To provide guidance in treating venous thromboembolism
- To provide guidance in anticoagulation and monitoring
- To provide guidance in managing bleeding complications of anticoagulants
- To provide guidance in managing VTE in special populations
- To provide guidance in managing thrombosis in unusual sites
- To provide guidance in perioperative management of anticoagulation
- To provide guidance in establishing a Medication Therapy Adherence Clinic - Warfarin(MTAC-W)

It is not the objective of these guidelines to cover:
- Management of arterial thrombosis

TARGET POPULATION
All patients with VTE or at risk for VTE

CLINICAL QUESTIONS
Refer to appendix 13

TARGET GROUP/USER
All health care professionals

GUIDELINES DEVELOPMENT GROUP

Chairperson
Professor Dr Abdul Rashid Abdul Rahman
Consultant Physician and Clinical Pharmacologist
Cyberjaya Unviversity College of Medical Sciences and Hospital Pakar An Nur

Co-Chairperson
Dr Jameela Sathar
Consultant Haematologist
Ampang Hospital

Members (alphabetical order)

Chong Chia Chee
Pharmacist
Ampang Hospital

Dr Eeson Sinthamoney
Consultant Obstetrician & Gynaecologist
Pantai Hospital Kuala Lumpur

Dr Hamat Hamdi Che Hassan
Consultant Cardiologist
Hospital Universiti Kebangsaan Malaysia

Assoc Professor Dr Hanafiah Harunarashid
Consultant Vascular Surgeon
Hospital Universiti Kebangsaan Malaysia

Dr Kiren Sidhu
Consultant Obstetrician & Gynaecologist
Pantai Hospital Kuala Lumpur

Assoc Professor Dr Mohammad Hassan Shukur
Consultant Orthopaedic and Trauma Surgeon
Hospital Universiti Kebangsaan Malaysia

Dr Santhi Datuk Puvanarajah
Consultant Neurologist
Hospital Kuala Lumpur

Dr Shanti Rudra Deva
Consultant Intensivist
Hospital Kuala Lumpur

Professor Dr Woo Yin Ling
Consultant Obstetrician & Gynaecologist
University Malaya Medical Center

REVIEW COMMITTEE

The draft of these guidelines are reviewed by a panel of independent expert referees from both public and private sectors, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence supporting the recommendations in the guidelines.

Chairman

Dr Chang Kian Meng
Head of Haematology & Consultant Haematologist
Department of Haematology
Ampang Hospital

Members (in alphabetical order)

Dr Fitzgerald Henry
Head of Surgery & Consultant Surgeon
Department of Surgery
Selayang Hospital

Dr Jay Suriar
Consultant haematologist
Department of Haematology
Ampang Hospital

Dr Kauthaman a/l Mahendran
Head of Medicine
Consultant Physician
Department of Medicine
Malacca Hospital

Dr Liew Nyan Chin
Medical Officer
Department of Obstetrics & Gynaecology
Ampang Hospital

Dr Muralitharan Ganesalingam
Consultant Obstetrics & Gynaecology
Head of Department
Department of Obstetrics & Gynaecology
Ampang Hospital

Dr Salmiah Md Shariff
Family Medicine Specialist
Batu 9, Cheras Health Clinic

Dr Shekhar Krishnan
Consultant Paediatric Haematologist
Department of Paediatrics
University Malaya Medical Center

Dr Wan Hamilton bt Wan Hassan
Head and Consultant Obstetrician & Gynaecologist
Department of Obstetrics & Gynaecology
Serdang Hospital

Dr Wong Jun Ching
Medical Officer
Department of Obstetrics & Gynaecology
Ampang Hospital

Dr Zaharah Musa
Head of Radiology & Consultant Radiologist
Department of Diagnostic Imaging
Hospital Selayang

Dr Zainal Ariffin Azizi
Head of Surgery & Consultant Vascular Surgeon
Department of Surgery
Hospital Kuala Lumpur

EXTERNAL REVIEWERS

The following external reviewers provided feedback on the draft.

Professor Mike A Laffan
Professor of Haemostasis & Thrombosis
Department of Medicine
Imperial College, United Kingdom

Professor John Andrew Murie
Senior Consultant Vascular Surgeon, Royal Infirmary of Edinburgh
Honorary Senior Lecturer University of Edinburgh Medical School
Adjunct Professor, Universiti Kebangsaan Malaysia

Professor Paul Monagle
Head and Consultant Paediatric Haematologist
Department of Paediatrics
The University of Melbourne
Royal Children's Hospital
Victoria, Australia

CLINICAL PATHWAYS

PATHWAY 1: THROMBOPROPHYLAXIS[1]

Thromboprophylaxis in Hospitalised Patients	Ministry of Health Malaysia

Name of Assessor: **Date:**

1. Patient information

NAME:	DOB:	SEX:
HOSPITAL NO.	IC NO.	

2. Assess the risk for VTE and the risk for bleeding

- Assess all patients on admission to identify:
  - those who are at increased risk of VTE
  - those who are at increased risk of bleeding
- Reassess patients' risks of VTE and bleeding within 24 hours of admission and whenever the clinical situation changes
- Weigh the risk of VTE against the risk of bleeding

3. Risk factors for VTE

- Active cancer ☐
- Age >60 years ☐
- Dehydration ☐
- Critical care admission ☐
- Obesity (BMI >30 kg/m^2) ☐
- Use of oestrogen-containing oral contraceptive pill ☐
- Use of Hormone Replacement Therapy ☐
- Post-partum (within 6 weeks) ☐
- Previous VTE ☐
- Family h/o VTE ☐
- One or more significant medical comorbidities:
  - Heart disease ☐

- Metabolic, endocrine or respiratory pathologies ☐
- Acute infectious disease ☐
- Inflammatory conditions ☐
- Sickle cell disease ☐
- Thalassaemia ☐

❖ Varicose veins with phlebitis ☐

4. Risk factors for bleeding

❖ Active bleeding ☐
❖ Acquired bleeding disorders (such as acute liver failure) ☐
❖ Concurrent use of anticoagulants (e.g. warfarin with INR >2.0) ☐
❖ Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours ☐
❖ Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours ☐
❖ Acute stroke ☐
❖ Uncontrolled systolic hypertension (230/120 mmHg or higher) ☐
❖ Untreated inherited bleeding disorder ☐ (e.g. haemophilia or von Willebrand disease)

5. Hospitalised Patients at increased Risk for VTE

Medical patients

❖ Regard medical patients as being at increased risk of VTE if they:
- have had or are expected to have significantly reduced mobility for ≥3 days OR
- are expected to have ongoing reduced mobility relative to their normal state AND
- have one or more of the risk factors for VTE

Surgical & trauma patients

❖ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
- Surgical procedure with a total anaesthetic and surgical time of >90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- Acute surgical admission with inflammatory or intra-abdominal condition
- Expected significant reduction in mobility
- One or more of the risk factors for VTE

6. Methods for VTE prophylaxis

A. Mechanical

- Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure, patient preference and if bleeding risk outweighs the risk of VTE
- Choose any one of:
  - Anti-embolism stockings ☐
  - Foot impulse devices ☐
  - Intermittent pneumatic compression devices ☐

Anti-embolism stockings (thigh or knee length)

- Do not offer anti-embolism stockings to patients who have:
  - Suspected or proven peripheral artery disease
  - Peripheral arterial bypass grafting
  - Peripheral neuropathy
  - Any local conditions in which stockings may cause damage e.g. dermatitis, gangrene, recent skin graft
  - Known allergy to material
  - Cardiac failure
  - Severe leg oedema
  - Unusual leg size
  - Major limb deformity
- Use stockings that provide graduated compression and produce a calf pressure of 14 - 15 mmHg
- Encourage patients to wear their stockings day and night until they no longer have significantly reduced mobility
- Remove stockings daily for hygiene purposes and to inspect skin

Foot impulse devices

- Encourage patient to use foot devices both in bed and when sitting in a chair

Intermittent pneumatic compression devices (thigh or knee length)

- Encourage patient to use IPC devices for as much time as possible both in bed and when sitting in a chair

B. Pharmacological

- Base the choice of pharmacological VTE agents on individual patient factors, including clinical condition and patient preferences

- Choose any one of:
  - Low molecular weight heparin SC ☐
  - Fondaparinux sodium SC ☐
  - Rivaroxaban PO (at present, licensed for THR and TKR) ☐
  - Dabigatran etexilate PO (at present, licensed for THR and TKR) ☐
  - Unfractionated heparin SC ☐

Low molecular weight heparin

- Choose either:
  - Enoxaparin ☐
    - Enoxaparin 40 mg daily or
    - Enoxaparin 20 mg daily (for moderate renal impairment with eGFR 15 - 30 mL/min/1.73/m^2)
  - Tinzaparin ☐
    - Tinzaparin 3500 units daily (lower VTE risk or moderate renal impairment) or
    - Tinzaparin 4500 units daily (higher VTE risk e.g. hip or knee surgery or during pregnancy)

Fondaparinux sodium

- Fondaparinux ☐
  - Starting dose at 2.5 mg (6 hours after surgery) followed by 2.5 mg daily
  - Contraindicated in severe renal impairment (eGFR <30 mL/min/1.73/m^2)

Rivaroxaban

- Rivaroxaban ☐
  - Starting dose at 10 mg (6 - 10 hours after surgery) followed by 10 mg daily
  - No dose adjustment in renal impairment with prophylactic dose

Dabigatran etexilate

- Dabigatran ☐
  - Starting dose at 110 mg (1 - 4 hours after surgery) followed by 220 mg daily
  - For elderly >75 years, moderate renal impairment: 75 mg starting dose, followed by 150 mg daily

Unfractionated heparin

- Choose UFH for patients with severe renal impairment (eGFR <15 mL/min/1.73/m^2)
  - UFH dose is 5000 units bd ☐

7. Monitoring platelet counts

- Patients who are to receive any heparin should have a baseline platelet count
- Post-operative patients, including obstetric cases, receiving UFH should have platelet count monitoring performed every 2 - 3 days from days 4 to 14 until heparin is stopped
- Post-cardiopulmonary bypass patients receiving LMWH should have platelet count monitoring performed every 2 - 3 days from days 4 to 14 until heparin is stopped
- Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring
- Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 days and are receiving any type of heparin should have a platelet count determined 24 hours after starting heparin
- Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring

8. Using VTE prophylaxis in hospitalised patients

General medical patients

- Offer pharmacological VTE prophylaxis
- Start pharmacological VTE prophylaxis as soon as possible after risk assessment
- Continue until patient is no longer at risk of VTE

Patients with stroke

- Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke
- Consider prophylactic-dose LMWH if a haemorrhagic stroke has been excluded and the risk of bleeding is low
- Until the patient can have pharmacological VTE prophylaxis consider a foot impulse or IPC device

Patients with cancer

- Offer pharmacological VTE prophylaxis and continue until the patient is no longer at increased risk of VTE

Patients in palliative care

- Consider pharmacological VTE prophylaxis in patients who have potentially reversible acute pathology
- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care

All surgical patients

- Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery
- Consider regional anaesthesia for individual patients as it carries a lower risk of VTE than general anaesthesia
- If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to 11 inimize the risk of epidural haematoma
- Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5 - 7 days)

Cardiac surgery

- Start mechanical VTE prophylaxis
- Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding

Gastrointestinal, gynaecological, thoracic and urological surgery

- Start mechanical VTE prophylaxis
- Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding
- Extend pharmacological VTE prophylaxis to 28 days post-operatively for patients who have had major cancer surgery in the abdomen or pelvis

Neurological (cranial or spinal) surgery

- Start mechanical VTE prophylaxis
- Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding
- Do not offer pharmacological VTE prophylaxis to patients with
  - ruptured cranial or spinal vascular malformations or
  - acute traumatic or non-traumatic haemorrhage until the lesion has been secured or the condition is stable

Orthopaedic surgery

- ❖ Offer combined VTE prophylaxis with mechanical and pharmacological methods for lower limb surgery
- ❖ Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery

Elective hip replacement

- ➢ Start mechanical VTE prophylaxis at admission and continue until the patient no longer has significantly reduced mobility
- ➢ Start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - LMWH: starting 6 - 12 hours after surgery ☐
  - Fondaparinux: starting 6 hours after surgical closure, provided haemostasis has been established ☐
  - Rivaroxaban: starting 6 - 10 hours after surgery ☐
  - Dabigatran etexilate: starting 1 - 4 hours after surgery ☐
- ➢ Continue pharmacological VTE prophylaxis for 35 days

Elective knee replacement

- ➢ Start mechanical VTE prophylaxis at admission and continue until the patient no longer has significantly reduced mobility
- ➢ Start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - LMWH: starting 6 - 12 hours after surgery ☐
  - Fondaparinux: starting 6 hours after surgical closure, provided haemostasis has been established ☐
  - Rivaroxaban: starting 6 - 10 hours after surgery ☐
  - Dabigatran etexilate: starting 1 - 4 hours after surgery ☐
- ➢ Continue pharmacological VTE prophylaxis for 35 days

Hip fracture

- ➢ Start mechanical VTE prophylaxis at admission
- ➢ Add pharmacological VTE prophylaxis. Choose any one of:
  - LMWH: starting at admission, stopping 12 hours before surgery and restarting 6 - 12 hours after surgery ☐
  - Fondaparinux: starting 6 hours after surgical closure. It is not recommended for use pre-operatively for patients undergoing hip fracture surgery ☐
- ➢ Continue pharmacological VTE prophylaxis for 35 days

Vascular surgery

- Offer VTE prophylaxis to patients undergoing vascular surgery who are not having other anticoagulant therapy and are assessed to be at increased risk of VTE
- Start mechanical VTE prophylaxis
- Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding
- Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility

Major trauma

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with major trauma
- Regularly reassess the patient's risks of VTE and bleeding
- Start mechanical VTE prophylaxis at admission or as early as clinically possible
- Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility
- Add pharmacological VTE prophylaxis if the benefits of reducing the risk of VTE outweighs the risk of bleeding and the bleeding risk has been established as low
- Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility

Spinal injury

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with spinal injury
- Regularly reassess the patient's risks of VTE and bleeding
- Start mechanical VTE prophylaxis at admission or as early as clinically possible
- Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility
- Add pharmacological VTE prophylaxis if the benefits of reducing the risk of VTE outweighs the risk of bleeding and the bleeding risk has been established as low
- Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility

Lower limb plaster casts

- Consider pharmacological VTE prophylaxis to patients with lower limb plaster casts after evaluating the risks and benefits based on clinical discussion with the patient
- Offer pharmacological VTE prophylaxis until lower limb plaster cast removal

Pregnancy and up to 6 weeks post-partum

- All women should be assessed at booking and after delivery and stratified into risk groups according to risk factors and offered thromboprophylaxis with LMWH where appropriate
- This assessment should be repeated if the woman is admitted to the hospital for any reason or develops other intercurrent problems during the antenatal and postpartum period

Critical care

- Assess all patients on admission to the critical care unit for their risks of VTE and bleeding
- Reassess patients' risks of VTE and bleeding daily and more frequently if their clinical condition is changing rapidly
- Offer VTE prophylaxis to patients admitted to the critical care unit according to the reason for admission, taking into account:
  - Any planned interventions
  - The use of other therapies that may increase the risk of complications

Patients taking anti-platelet agents or anticoagulants on admission or needing them for treatment

- Consider additional pharmacological VTE prophylaxis to patients who are taking one but not two anti-platelet agents to treat other conditions and who are assessed to be at increased risk of VTE
- Consider additional mechanical prophylaxis to patients who are taking two anti-platelet agents to treat other conditions and who are assessed to be at increased risk of VTE
- Do not offer additional pharmacological or mechanical VTE prophylaxis to patients who are taking vitamin K antagonists and who are within their therapeutic range, provided anticoagulant therapy is continued
- Do not offer additional pharmacological or mechanical VTE prophylaxis to patients who are having full anticoagulant therapy

9. Timing of regional anaesthesia / analgesia

Unfractionated heparin (subcutaneous)

- Wait at least 4 hours after a dose before block or catheter removal
- Wait at least 1 hour before dosing after procedure (catheter insertion or withdrawal)

Unfractionated heparin (intraveneous)

- Stop infusion 2 - 4 hours before block

- Start infusion >1 hour after block
- Remove epidural catheter no sooner than 2 - 4 hours after discontinuation of infusion

Low Molecular Weight Heparin

- Wait at least 12 hours after a prophylactic dose before block
- Wait at least 24 hours after a therapeutic dose before block
- Wait at least 10 hours after dose before removing catheter
- After catheter removal wait 2 - 4 hours before next dose

Warfarin

- Proceed if INR ≤1.5

Rivaroxaban

Rivaroxaban is started post-operatively

- Wait 12 - 18 hours after dose for epidural catheter removal
- Wait 6 hours before next dose

Dabigatran

Dabigatran is started post-operatively

- Wait 12 - 18 hours after dose for epidural catheter removal
- Wait 6 hours before next dose

Aspirin and NSAIDs

- No issue

Clopidogrel

- Stop 7 days pre-op if possible
- If not, proceed with caution

10. Patient information

- Be aware that heparins are of animal origin and this may be of concern to some patients
- For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement and after discussing their suitability, advantages and disadvantages with the patient
- In specific conditions such as pregnancy, LMWH is the anticoagulant of choice and is superior to UFH in its efficacy with less bleeding complications

- Before starting VTE prophylaxis, offer patients and their families verbal and written information on:
  - The risks and possible consequences of VTE
  - The importance of VTE prophylaxis and its possible side-effects
  - The correct use of VTE prophylaxis
  - How patients can reduce the risk of VTE (keeping well hydrated and mobilizing early)

11. Discharge plan

- As part of the discharge plan, offer patients and their families or carers verbal and written information on:
  - The signs and symptoms of DVT and PE
  - The recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
  - Ensure that patients who are discharged with pharmacological or mechanical VTE prophylaxis are able to use it correctly
  - Know who to contact if DVT, PE or adverse events are suspected

PATHWAY 2: MANAGEMENT OF VTE[2]

Diagnosis and Treatment of Venous Thromboembolism	Ministry of Health Malaysia

Name of Assessor: **Date:**

1. Patient information		
NAME:	**DOB:**	**SEX:**
HOSPITAL NO.	**IC NO.**	

2. Triaging	
➢ Suspected PE ☐ ➢ Suspected DVT ☐ ➢ Suspected PE + DVT ☐	Duration of Symptom(s): Site: ➢ Leg R ☐ L ☐ ➢ Chest R ☐ L ☐

3. Vital Signs					
Temp			Calf circumference (cm)	Peripheral pulses	
Pulse	RR			R	L
BP			R	Popliteal	
O2 sat			L	Pedal	
Wt (kg) Ht (cm)		BMI	Skin: Warm /	Cold	

4. Clinical Probability					
DVT	**Yes**	**No**	**PE**	**Yes**	**No**
Active cancer or cancer within 6 months	1	0	Clinical signs & symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins	3	0
Paralysis or recent leg plaster	1	0	An alternative diagnosis is less likely than PE	3	0
Bedridden >3 days or major surgery <12 weeks	1	0	Heart rate >100 beats/min	1.5	0
Tenderness along deep venous system	1	0	Immobilization >3 days or surgery in the previous 4 weeks	1.5	0
Entire leg swollen	1	0	Previous DVT/PE	1.5	0
Calf swelling >3 cm than asymptomatic leg	1	0	Haemoptysis	1	0
Pitting edema (symptomatic leg)	1	0	Malignancy (on treatment; treated in the last 6 months; or palliative	1	0
Collateral superficial veins	1	0			
Previously documented DVT	1	0			
Alternative diagnosis more likely	-2	0			
DVT likely	**≥2**		**PE likely**	**>4**	
DVT unlikely	**<1**		**PE unlikely**	**≤4**	

5. History	
History of present illness	
Past medical history	
Drug history	Allergies

6. Risk Factors

- ❖ Obesity ☐
- ❖ Smoking ☐
- ❖ Malignancy ☐
- ❖ Anti-phospholipid syndrome ☐
- ❖ OCP ☐
- ❖ HRT ☐
- ❖ Pregnancy ☐
- ❖ Post-partum (within 12 weeks) ☐
- ❖ Previous VTE ☐
- ❖ Family h/o VTE ☐
- ❖ Recent leg trauma or plaster ☐
- ❖ Recent abdominal or pelvic surgery ☐
- ❖ Bedridden >3 days ☐
- ❖ Nephrotic syndrome ☐
- ❖ Sickle cell disease ☐
- ❖ Thalassaemia ☐
- ❖ Inflammatory bowel disease ☐

7. Blood tests	
FBC	
Coagulation profile	
Renal profile	
Liver function	
Urinalysis	

8. DVT likely			
Request for Doppler Ultrasound		Date of US:	
DVT confirmed		DVT not confirmed	
Below knee	Above knee	Suggest repeat scan in 7 days Date:	
Proceed to treatment		Repeat scan negative	
		Discharge patient to Health Clinic	

9. Other investigations	
CXR	ECG

10. PE likely		
Perform immediate computed tomography pulmonary angiogram (CTPA)	Date of CTPA:	
PE confirmed	PE not confirmed	
Full report	Doppler US both legs	
	DVT confirmed	No DVT
Proceed to treatment	Proceed to treatment	No further action
Consider systemic thrombolytic therapy for patients with PE and haemodynamic instability		

11. Initial treatment for confirmed VTE

a. Heparin or Fondaparinux and vitamin K antagonists (VKA)

- Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE taking into account comorbidities, contraindications and drug costs
- Start LMWH (enoxaparin or tinzaparin) or fondaparinux as soon as possible and continue for at least 5 days or until the INR is 2 or above for 2 consecutive days, whichever is longer
  - Tinzaparin dose is 175 IU/kg once daily ☐
  - Enoxaparin dose is 1 mg/kg twice daily ☐
  - Fondaparinux dose is 7.5 mg daily (5 mg if <50 kg; 10 mg if >100 kg) ☐
- Start VKA i.e. warfarin at 5 mg daily within 24 hours of diagnosis and continue for 3 months for provoked VTE or consider long term for unprovoked VTE

- For pregnancy, LMWH is the treatment of choice
- Fondaparinux is not recommended in pregnancy as it may cross the placenta

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- For severe renal impairment or established renal failure (eGFR <30 mL/min/1.73 m^2)
  - offer intravenous unfractionated heparin with dose adjustment based on APTT or
  - LMWH daily with dose adjustments based on anti-Xa assay (Fondaparinux is contraindicated in patients with renal impairment)

- For patients with PE and haemodynamic instability
  - offer IV UFH and consider thrombolytic therapy
  - once patient is haemodynamically stable, switch to LMWH and start warfarin

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- For patients with active cancer and confirmed proximal DVT or PE, continue LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation

b. Rivaroxaban

Rivaroxaban is indicated for the treatment of acute deep vein thrombosis and pulmonary embolism and the prevention of recurrence

- For the initial treatment of acute DVT or PE
  - the recommended dose of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrence ☐

12. Thrombolytic Therapy

Deep vein thrombosis

- Consider catheter-directed thrombolytic therapy for patients with symptomatic ilio-femoral DVT who have:
  - Symptoms of less than 14 days duration AND
  - Good functional status AND
  - A life expectancy of 1 year or more AND
  - A low risk of bleeding

Pulmonary embolism

- Consider systemic thrombolytic therapy for patients with PE and haemodynamic instability (e.g. systolic BP <90 mmHg)
- Do not offer systemic thrombolytic therapy to patients with PE and haemodynamic stability
- The most commonly used agent is t-PA infused at 100 mg over 2 hours followed by continuation of therapeutic heparin infusion
- Consider thoracotomy in critically ill / not suitable for thrombolysis

13. Mechanical Intervention

Compression stockings

- Prescribe below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications
- advice patients to continue wearing the stockings for at least 2 years
- ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions
- advice patients that the stockings need to be worn only on the affected leg or legs

Inferior vena cava filters

- Offer temporary inferior vena cava filters ONLY to patients with proximal DVT or PE who cannot have anticoagulation treatment

- Remove the inferior vena cava filter when the patient becomes eligible for anticoagulation treatment, at the earliest possible opportunity

14. Investigations for Cancer

- All patients diagnosed with unprovoked DVT or PE who are not known to have cancer should be offered:
  - A physical examination (further specific tests are guided by the patient's history)
  - Chest X-ray
  - Blood tests (FBC, LFT, RP, urinalysis)
- Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked VTE who do not have signs and symptoms of cancer based on initial investigation
- Tumour markers are not recommended for cancer screening

15. Thrombophilia testing

- DO NOT offer thrombophilia testing to patients who are continuing anticoagulant treatment
- Consider testing for lupus anticoagulant and anti-phospholipid antibodies in patients who have had an unprovoked DVT or PE if it is planned to stop anticoagulant treatment
- Consider testing for hereditary thrombophilia in patients who have had an unprovoked DVT or PE and who have a first-degree relative who has had a DVT or PE if it is planned to stop anticoagulant treatment
- DO NOT offer thrombophilia testing to patients who have had a provoked DVT or PE
- DO NOT offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia
- DO NOT offer heritable thrombophilia testing to patients who have had an arterial thrombosis (young stroke or myocardial infarction)
- Consider testing for lupus anticoagulant and anti-phospholipid antibodies in the following:
  - in the presence of both arterial and venous thrombosis
  - unexplained arterial thrombosis (young stroke or myocardial infarction with no risk factors)
  - ≥3 unexplained miscarriages <10 weeks gestation
  - a fetal death >10 weeks gestation
  - premature birth <35 weeks gestation due to severe pre-eclampsia or IUGR

16. Duration of anticoagulation therapy

- ❖ Consider extending anticoagulation beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high (e.g. male, family history) and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their treatment
- ❖ Offer anticoagulation beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their treatment
- ❖ Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation
- ❖ Experience with rivaroxaban in extending anticoagulation beyond 12 months is limited
- ❖ DO NOT routinely do D-dimer test and Doppler US on completion of anticoagulation except guided by clinical symptoms and signs

17. Follow up

- ❖ Arrange for follow-up at medical or haematology clinic
- ❖ Arrange for INR monitoring at the anticoagulation clinic (MTAC-Warfarin)

18. Patient information

- ❖ Verbal and written information are given to patients having anticoagulant treatment about:
- Duration of anticoagulation treatment
- Anticoagulation booklet
- Possible side effects and what to do if these occur
- The effects of other medication, food and alcohol on oral anticoagulant
- Monitoring their anticoagulant treatment
- Pregnancy and contraception
- Surgery and dental treatment
- Future risk reduction measures including travel
- Clear advice on long term use of stockings

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1. EPIDEMIOLOGY AND PATHOGENESIS

1.1 EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) is a major health problem. It is the third most common cardiovascular disease after myocardial infarction and stroke.[3] The overall VTE rates are 100 per 100,000 population per year, of which 70% are hospital-acquired.[4]

It is estimated that 25,000 people in the UK die from preventable hospital-acquired VTE every year. In Europe, the annual mortality from VTE surpasses the sum of the mortalities from breast cancer, prostate cancer, AIDS and traffic accidents.[5]

It has long been perceived that VTE is rare in Asia. However, several recent epidemiological studies seem to refute this. The incidences of VTE after major orthopedic surgery, stroke, medically ill and critical care patients approach that of Western countries.[5-18]

Hospital-acquired VTE in Asia is increasing.[14-16] Pulmonary embolism accounts for up to 6% of hospital deaths.[5] Acquired factors such as immobilisation, active cancer, infections, advancing age, heart diseases and major surgeries are associated with an increase risk of VTE.[12-17]

Venous thromboembolism in obstetrics is also on the rise in the East due to several factors such as increasing maternal age, obesity, rising trend for caesarean deliveries, multiple pregnancies and low rate for thromboprophylaxis.[21] Obstetric VTE is now the leading cause of maternal death in Malaysia.[22]

Hence, VTE should no longer be considered a Western disease but a worldwide health crisis. Appropriate measures must be taken to prevent it in the correct setting.

EPIDEMIOLOGY OF VTE

- Venous thromboembolism is a major health problem worldwide
- The overall rate of VTE is 100 per 100,000 population per year
- More than ⅔ of VTEs are hospital-acquired
- About 10% die within the first month of VTE diagnosis
- In Asia, VTE is increasing due to several factors:
  - Aging population
  - Higher rates of major complex surgeries
  - Higher rates of caesarean deliveries
  - Rise in Obesity
  - Rise in Cancer
  - Low rates for thromboprophylaxis

1.2 PATHOGENESIS AND THE NATURAL HISTORY OF VTE

Venous thromboembolism comprises both deep vein thrombosis (DVT) and pulmonary embolism (PE). Three major pathophysiologic determinants of VTE were proposed by Virchow: venous stasis, endothelial injury and hypercoagulability. All risk factors for VTE influence at least one of these 3 mechanisms.

Venous thrombi originate in venous valve pockets at sites of venous stasis or following vessel wall injury.[23,24] The symptoms of VTE are caused by obstruction of venous outflow by thrombi, causing inflammation of the vein wall, inflammation of the tissues surrounding it or embolisation into the pulmonary circulation.[24]

About half of DVT associated with surgery start intra-operatively and many resolve spontaneously.[24,26,27] The risk of progression of post-operative VTE is greater when there are continuing risk factors for thrombosis.[24,27,48]

The risk of VTE differs with the type of surgery: major orthopedic surgery is associated with twice the risk of VTE associated with major general surgery.[32] The risk of symptomatic VTE is highest within 2 weeks of surgery and remains elevated for a further 2 to 3 months.[28,49] The risk of fatal PE is highest 3 to 7 days following surgery.[27,32,33,35]

Most DVT begin in the calf.[23-25] Eighty percent of symptomatic DVT involve the proximal veins.[24] Isolated calf DVT rarely cause leg symptoms or clinically significant PE.[24,25] About 25% of untreated symptomatic calf DVT extend to the proximal veins, mostly within 1 week of presentation.[31,32] Without treatment, 50% of patients with symptomatic proximal DVT or PE have recurrent thrombosis within 3 months.[40,41] Ten percent of symptomatic PE are fatal within one hour of onset of symptoms.[42]

Isolated proximal DVT (without involvement in the calf veins) is more common during pregnancy. Two-thirds of VTE in pregnancy occur during the antepartum period while the occurrence of PE is more common during the post-partum period.[31] The natural course of DVT in pregnancy is less well known.[50-52]

Resolution of proximal DVT is slow and less than half have complete lysis after 6 months of anticoagulation.[37] However, more than 90% will have complete recanalisation with development of collaterals.[37] As for PE, 50% resolution occurs after 2 to 4 weeks of treatment.[40] Eventually, complete resolution of PE occurs in about two-thirds of patients.[42-44]

The risk of recurrence after stopping anticoagulation is similar following proximal DVT and PE.[36,45] However the risk of mortality is 2 to 3-fold higher with recurrent PE. The risk of recurrent VTE is higher in patients with unprovoked VTE or with persisting risk factors for thrombosis (e.g. cancer and anti-phospholipid syndrome) compared to patients with transient risk factors (e.g. recent surgery).[29,30,46,47]

Complications of VTE include post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. Following symptomatic DVT, the incidence of severe post-thrombotic syndrome is 10% after 5 years but is as high as 80% following pregnancy-associated VTE; mostly occurring within the first 2 years.[29,38,39] Chronic thromboembolic pulmonary hypertension occurs in 5% of patients with treated PE.[41]

NATURAL HISTORY OF VTE

- Most DVT begin in the calf. In pregnancy it begins in the proximal and pelvic veins
- The risk factors for VTE influence at least one of Virchow's triad: blood coagulability, vessel integrity and blood flow
- The risk of VTE is highest following major orthopedic surgery where vessel damage and immobility play a major role
- The risk of symptomatic VTE is highest within 2 weeks of surgery and remains elevated for a further 2 to 3 months
- The risk of fatal PE is highest within 1 week of surgery
- Following treatment, the resolution of DVT is slower than for PE with complete resolution being more common with PE than in DVT, where recanalisation is commoner
- The risk of VTE recurrence is higher in unprovoked than in provoked (recent surgery) VTE
- The risk of recurrence remains elevated after a first episode of VTE
- Active cancer and the anti-phospholipid syndrome are risk factors for VTE recurrence
- The risk of mortality is higher with recurrent PE than recurrent DVT
- Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are complications of VTE
- Post-thrombotic syndrome occurs more frequently following pregnancy-associated VTE because the proximal ilio-femoral veins are usually involved

2.0 VTE PROPHYLAXIS

2.1 INTRODUCTION

VTE is an important cause of death in hospital patients and treatment of VTE and its related long-term morbidities are associated with considerable cost to the health service. Efforts should be made to prevent the occurrence of VTE by stratifying hospitalised patients according to risk categories and offering thromboprophylaxis when appropriate.

2.2 METHODS OF PROPHYLAXIS

2.2.1 Mechanical Prophylaxis

Application of Graded Elastic Compression Stockings (GECS), Intermittent Pneumatic Compression (IPC) of the calf or calf and thigh or Venous Foot Pump (VFP) provide a valuable adjunct to pharmacologic methods in patients at high-risk for VTE and serve as the preferred alternative in patients who are ineligible for pharmacologic therapy. Mechanical prophylaxis is also effective when used in combination with early ambulation but less efficacious than pharmacologic methods when used as a stand-alone modality.[55,56,68]

Mechanical prophylaxis are applicable pre- and intra-operatively, and should be continued post-operatively until the patient is fully ambulating. They have no major clinically significant adverse effects, particularly bleeding. The IPC has relative contraindications in patients with severe leg ischemia/ peripheral artery disease, acute superficial and deep vein thrombosis, and congestive heart failure.[55,56,72]

Home use of mechanical prophylaxis is important because VTE is reported to develop between 8 and 21 days after TKA and THA respectively. Portable motorized mechanical compression devices are available and are superior to compression stockings but are expensive.[60,62]

2.2.2 Pharmacological Prophylaxis

Prophylactic drugs include low molecular weight heparin (LMWH), pentasaccharide sodium (fondaparinux), unfractionated heparin (UFH) and the newer oral anticoagulants (dabigatran, rivaroxaban, apixaban).[62,65]

2.2.2.1 Low Molecular Weight Heparins

Low molecular weight heparins have become the standard first line thromboprophylactic agents. Although relatively costly, LMWHs have been widely used for prophylaxis owing to their cost-effectiveness. Studies comparing LMWH (once or twice daily) with UFH have shown that LMWH is more effective than UFH in preventing thrombosis without increasing the risk of bleeding.[60-64] Low molecular weight heparin is less likely to produce haematomas at injection site, heparin-induced thrombocytopenia/ thrombosis (HITT) and osteoporosis than UFH.[67,70]

2.2.2.2 Fondaparinux

Fondaparinux is a synthetic pentasaccharide sodium that selectively binds to antithrombin, inducing a conformational change that increases anti-factor Xa without inhibiting thrombin. It's predictable pharmacokinetic and a long elimination half-life of 17 to 21 hours allows once-daily dosing. It is eliminated unchanged in urine; but its elimination is prolonged in patients aged >75 years and in those weighing <50kg.[57]

Fondaparinux has been shown to be effective in preventing VTE in knee and hip replacement surgeries, hip fracture surgeries, abdominal surgeries and acute medically ill patients. It can be used as an alternative to LMWH. It is licensed for use outside pregnancy. The prophylactic dose is 2.5 mg given no earlier than 6 to 8 hours after surgery.[57,61]

2.2.2.3 Unfractionated Heparin

Unfractionated heparin is no longer the preferred first line agent as it requires complex labor-intensive administration, monitoring and dose adjustment. Major bleeding events, risk of HITT and associated costs favour other newly available agents.[61]

Subcutaneous low-dose UFH administered in a dose of 5000 IU every 12 hours after the surgery reduces the rate of VTE in patients undergoing a moderate risk surgery.[55,56] However, it is less effective than warfarin, adjusted-dose UFH and LMWH when used as prophylaxis in elective hip surgery. In elective hip surgery, the efficacy of UFH is enhanced 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.[58,60,61]

2.2.2.4 Vitamin K Antagonist

Adjusted-dose warfarin, historically the primary agent used peri-operatively and compared with mechanical thromboprophylaxis or placebo, was effective in reducing VTE and its consequences.[62,71]

VTE prophylaxis with warfarin can be commenced pre-operatively (risk of major bleeding event), at the time of surgery or at the early post-operative period (may not prevent small venous thrombi formation during or soon after surgery because anticoagulation effect is not achieved until the third or fourth post-operative day). If started at a low dose before surgery, it may reduce the risk of bleeding compared to full anticoagulation at the time of surgery.[69]

The advantages are its ease of oral administration and low cost. The disadvantages include delayed onset on action, narrow therapeutic range, drug-drug interaction and requirement for daily monitoring of the INR (the recommended therapeutic range is 2.0 to 2.5 in orthopaedic surgery). These shortcomings along with wide availability of other effective options narrow the rationale for warfarin to be used routinely as prophylaxis. It should be reserved for patients who have contraindications to the alternative agents.[62,71]

2.2.2.5 Oral Direct Thrombin Inhibitors

Dabigatran etexilate has been evaluated for VTE prophylaxis in patients undergoing THR and TKR and the results show that it is non-inferior to LMWH with similar bleeding rates. Dabigatran can be considered an alternative to LMWH and fondaprinux for the prevention of VTE following THR and TKR surgeries.[60]

The dose is 110 mg given 1 to 4 hours post-operatively and continued with a dose of 220 mg daily for 10 days after knee replacement and for 35 days after hip replacement. For patients with moderate renal impairment and age >75 years, a reduced dose of 75 mg starting dose and 150 mg continuing dose once daily is recommended.[71,73]

2.2.2.6 Oral Direct Factor Xa Antagonists/Inhibitors

2.2.2.6.1 Rivaroxaban

Rivaroxaban has a rapid onset of action by reaching peak concentration at 3 hours. Bioavailability ranges between 60 to 80% after oral administration. It is mainly metabolized via CYP3A4 and eliminated by both the renal and fecal/ biliary routes. It has an elimination half-life between 5 to 9 hours.[59]

A single dose of rivaroxaban produces pharmacologic effects that persist for 24 hours, making it suitable for once daily administration. It has predictable pharmacokinetics and does not require monitoring.[59,70]

Rivaroxaban has been shown to be superior to enoxaparin in VTE prevention studies during hip and knee replacement surgeries with similar bleeding rates. The dose is 10 mg orally once daily with or without food and the initial dose should be taken at least 6 to 10 hours after surgery once haemostasis has been established.[59,60]

2.2.2.6.2 Apixaban

A small molecular weight agent with bioavailability of 50 to 85% after oral intake reaches peak concentration at 3 hours, and excretes predominantly via the biliary tract.

Apixaban has been found to be superior to enoxaparin in reducing VTE following hip and knee replacement surgeries with no difference in the bleeding rates. The recommended dose is 2.5 mg orally twice daily. The initial dose should be taken 12 to 24 hours after surgery. It is safe to be used in patients with renal impairment.[71]

2.3 RISK ASSESSMENT FOR VTE

2.3.1 Non-surgical/ medical patients

Patients seen in medical wards differ from surgical patients with many having co-morbidities including renal or hepatic impairment, and increased risk of bleeding. The Padua Prediction Score (PPS) is the best available validated prediction for VTE risk in medical patients (table 2.3.1.1) with low-risk patients having a 0.3% rate of developing symptomatic VTE in 90 days and high risk patients having an 11% rate of developing VTE within 90 days.[1] The PPS should not be applied to critically ill patients.

Table 2.3.1.1: Padua Risk Assessment Model for Medical Patients[74] (RAM Score of 4 and above = high risk of VTE)	
Baseline Features	**Score**
An active cancer	3
Previous VTE	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (<1 month) trauma and/or surgery	2
Age 70 years and above	1
Heart and/or respiratory failure	1
AMI or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity BMI >30kg/m^2	1
Ongoing hormonal therapy	1

2.3.1.2 Prophylactic Recommendation For Medical Patients

Based on the risk assessment score, recommendations for VTE prophylaxis can be made for medical patients (Table 2.3.1.2)[74]

Table 2.3.1.2: Risk Stratification of Medical Patients and Prophylactic Recommendation

Category	Recommendations	Grade
Low Risk		
PPS <4	No prophylaxis	B
High Risk		
PPS ≥4	LMWH Fondaparinux	A B
High Risk for bleeding		
IMPROVE score ≥7 (see Table 2.4)	1. Leg Compression Device (IPC or GECS) only 2. Switch to anticoagulant prophylaxis as soon as bleeding risk is considered to be low 3. Early ambulation	C B B
Cancer		
Prior VTE Immobilization Angiogenesis inhibitors-lenalidomide, thalidomide Hormonal therapy	LMWH daily	B
High risk on long-distance flights		
Cancer Previous VTE Severe obesity Pregnancy	1. Encouraged to get up and walk around periodically, flex calf muscles and sit in an aisle seat when possible 2. Consider using below-the-knee compression stockings at 15-30 mmHg 3. Aspirin or anticoagulant is not recommended for the purpose of prophylaxis against VTE on a long-distance flight	B C B

2.3.2 Surgical patients

For surgical patients, the primary prophylactic measures depend on the risk stratification of the individual patient and the clinical situation (Table 2.3.2).[75,76]

Table 2.3.2: Risk Stratification of Surgical Patients and Prophylactic Recommendation

Risk category	Recommended prophylaxis	Grade
Low Risk • Ambulatory patient <40 years without risk factor* • Minor surgery (<30 min) • Knee arthroscopy with no additional risk*	Early aggressive ambulation	A
Moderate Risk • Patient with an extra risk* • Patient 40-60 years without risk* • Major surgery (>30 min) for benign disease	LMWH Fondaparinux LD-UFH, 12 hrly GESC, IPC, VFP	A A B C
High Risk Surgery in patient • >60 years • 40-60 years with an extra risk* • with multiple risk factors* Major surgery for cancer Major trauma, Spinal Cord Injury	LMWH Fondaparinux LD-UFH, 8 hrly Warfarin INR 2-3 plus IPC or GESC	A A B B A
Highest Risk Hip arthroplasty Knee arthroplasty** Hip fracture surgery	LMWH > fondaparinux > warfarin, and IPC** Rivaroxaban	A A

* Risk factors:
  - Active cancer
  - Obesity (BMI >30 kg/m^2)
  - Use of oestrogen-containing oral contraceptive pill
  - Use of Hormone Replacement Therapy
  - Previous VTE
  - Family h/o VTE
  - One or more significant medical comorbidities:
    - Heart disease
    - Metabolic, endocrine or respiratory pathologies
    - Acute infectious disease
    - Inflammatory conditions
    - Sickle cell disease
    - Thalassaemia
    - Varicose veins with phlebitis

2.4 RISK ASSESSMENT FOR BLEEDING

Both the PPS and Wells' Score do not address the risk of bleeding events. To address this issue, some forms of clinical judgments are required when weighing up the risk of thrombosis versus bleeding events with thromboprophylaxis. For this purpose, the IMPROVE Bleeding Risk Score is used (Table 2.4).[77]

Table 2.4: The IMPROVE Bleeding Risk Score

Bleeding Risk Factors	Score
Active gastro-duodenal ulcer	4.5
Bleeding <3 months prior to admission*	4
Platelet count <50x10^9/L**	4
Age >85 years	3.5
Liver failure with PT>1.5x Normal	2.5
Severe renal failure GFR <30 mL/min/1.73m^2	2.5
ICU/CCU admission	2.5
Central line catheter in place	2
Rheumatic/autoimmune disease	2
Current cancer	2
Age 40-84 years	1
Male	1
GFR 30-59 mL/min/1.73m^2	1
High risk	**Risk score: ≥7**
Low risk	**Risk score: <7**

* include previous GI bleeding of irreversible cause, non-cardiac embolic stroke and concomitant use of oral anticoagulant

** include previous history of HITT and concomitant antiplatelet therapy with aspirin or clopidogrel

2.5 TIMING AND INITIATION OF PROPHYLAXIS

Issues related to the optimal timing of initiation and duration of peri-operative thromboprophylaxis in the peri-operative setting and in medical patients remain unsettled. The timing of initiation depends on the clinical situation, specific prophylactic agent of choice and type of anaesthesia used.[78,79,80]

Table 2.5: Timing of Thromboprophylaxis Initiation (Grade B Recommendation)

Clinical Situation	Prophylactic Agent	Timing of Initiation
General Surgery		
	Low Dose UFH	2 hr prior to surgery
	LMWH: Enoxaparin 40 mg OD Tinzaparin 3500 IU	12-24 hr post-op
	Fondaparinux 2.5mg	6 hr post-op
Orthopaedics		
TKR/ THR	LMWH: Enoxaparin 30mg BD or 40 mg OD Tinzaparin 4500 IU OD	12-24 hr post-op
	Fondaparinux 2.5 mg OD	6-24 hr post-op
	Rivaroxaban 10 mg OD	6-10 hr post-op
	Warfarin 2-10 mg OD (INR 2-2.5)	1-12 hr pre-op or early post-op
Hip Fractures	LMWH: Enoxaparin 40 mg OD Tinzaparin 4500 IU OD	12-24 hr post-op
	Fondaparinux 2.5 mg OD	6-24 hr post-op
	Rivaroxaban 10 mg OD	6-10 hr post-op
	Warfarin (INR 2-3)	1-12 hr pre- or early post-op

2.6 ANTI-THROMBOTIC THERAPY AND REGIONAL ANAESTHESIA

The decision to perform spinal or epidural anesthesia/analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy is made on an individual basis, weighing the small, although definite risk of spinal hematoma with the benefits of regional anaesthesia for a specific patient.

Overall, the risk of clinically significant bleeding increases with age, associated abnormalities of the spinal cord or vertebral column, the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation, perhaps in a multifactorial manner.[81] Its been consistently reported that prompt diagnosis and intervention is necessary to optimize neurologic outcome.

2.6.1 Patients receiving unfractionated heparin

The safety of neuraxial blockade in patients receiving daily or more than twice-daily dosing of UFH is not established.[82,83] The risk/benefits of neuroaxial blockade needs to be assessed on an individual basis and implement more frequent neurological monitoring.

Heparin-induced thrombocytopenia may occur during heparin administration, therefore patients receiving heparin for more than 4 days should have a platelet count assessed before neuraxial blockade and catheter removal.[84]

2.6.2 Patients receiving LMWH

Perform neuroaxial techniques at least 10 to 12 hours after a thromboprophylaxis dose and 24 hours after a high or therapeutic dose of LMWH. In patients administered a dose of LMWH 2 hours preoperatively, neuroaxial technique is not recommended because needle placement would occur during peak anticoagulant activity.

Post-operative LMWH twice daily dosing is associated with increased risk of spinal haematoma. The first dose of LMWH is administered no earlier than 24 hours postoperative regardless of the anaesthetic technique and only in the presence of adequate surgical hemostasis. Indwelling catheters should be removed before initiation of twice daily LMWH. The first dose of LMWH is administered 2 hours after catheter removal and 24 hours after needle/catheter placement, whichever is later.[85,86]

With daily dosing, the first dose of LMWH is administered 6 to 8 hrs after needle/catheter placement. Subsequent dosing should occur no sooner than 24 hours later.

2.6.3 Patients receiving Fondaparinux

The actual risk of spinal hematoma with fondaparinux is unknown. Until further clinical experience is available, performance of neuraxial techniques should occur under conditions used in clinical trials (single-needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters). If this is not feasible, an alternate method of prophylaxis should be considered.[87,88]

Table 2.6: Guidelines for Epidural Use With Anticoagulant Therapy

Prophylactic Agent	Timing for Catheter Placement and Removal	Grade
UFH	The safety of neuroaxial blockade in patients receiving daily or more than twice daily dosing of UFH is not well established. The risk and benefits need to be assessed on an individual basis and techniques to facilitate detection of neurological deficit be applied	C
	Heparin administration delayed for 1 hour after needle placement (this is in neuroaxial blocks with intraoperative anticoagulation)	A
	Catheter removal 2 - 4 hours after last heparin dose	A
LMWH	Placement of catheter at least 12 hours after prophylactic LMWH dose or 24 hours after therapeutic LMWH dose	C
	In patients who received LMWH 2 hours before surgery, neuroaxial blockade is not recommended	A
	In single daily dosing: Administer the first dose 6 - 8 hours after needle/catheter placement Remove catheter when LMWH effect is minimum (2 hours before next injection) Delay LMWH at least 2 hours after spinal needle or epidural catheter removal	C
	In twice daily dosing: Administer the first dose of LMWH no earlier than 24 hours after operation, regardless of anesthetic technique, and only in the presence of adequate haemostasis	C
	Indwelling catheters should be removed before initiation of LMWH	C
	The first dose of LMWH is administered 2 hours after catheter removal and 24 h after needle/catheter placement	C
Warfarin	Continuous epidural should not be used more than 1-2 days because of unprotected anticoagulation effect Target INR of <1.5 at time of catheter removal	A
Fondaparinux	Do not use pre-operatively with neuroaxial block or with continuous epidural block (lack of safety data)	C
Rivaroxaban	Do not use pre-operatively with neuroaxial block or with continuous epidural block (lack of safety data)	C

2.7 DURATION OF PROPHYLAXIS

Depending on the clinical situations, standard thromboprophylaxis of 7 to 14 days is usually commenced until the patient is ambulating. It has been shown that the activation of coagulation persists for at least 30 days after THR. For certain high-risk situations especially after major orthopaedic procedures (THR more than TKR and hip fracture repair), extended thromboprophylaxis for up to 35 days is recommended (Table 2.7).[89-91]

Table 2.7: Recommended Duration of VTE Prophylaxis for Various Indications

Indication	Duration	Grade
Major general surgery	Until hospital discharge (7-10 days)	A
Hip fracture repair	35 days with LMWH or fondaparinux or warfarin	A, C, C
Hip arthroplasty	35 days with LMWH or fondaparinux or warfarin IPC	A, C, B B
Knee arthroplasty	35 days with LMWH or fondaparinux or warfarin	C, A, C
Bariatric surgery	21 days	B
Medical prophylaxis	10-14 days	B

2.8 SPECIAL CONSIDERATIONS: STROKE

The immobility that is often associated with stroke (either ischaemic or haemorrhagic) remains an important risk factor for the development of VTE. Advanced age, dehydration and the severity of paralysis are important risk factors. Patients with hemiplegia may develop DVT in up to 60 to 70% of cases, if DVT prophylaxis is not prescribed within 7 to 10 days. In a retrospective cohort study, DVT prophylaxis was identified as one of the three processes of care that was independently associated with an improvement in acute stroke outcomes.

Deep vein thrombosis was initially thought to be uncommon in the Asian stroke population. However more recent data has shown otherwise.[92] In Malaysia, DVT prophylaxis is recommended as one of the nine key performance indicators (KPI) in stroke management.[93]

2.8.1 Non-pharmacological

Non-pharmacological measures commonly utilised in preventing DVT are the use of graduated elastic compression stockings (GECS), either at below-knee or thigh-level, as well as intermittent pneumatic compression (IPC) devices.

In two recent studies, the routine use of GECS after an acute stroke is not supported. Smaller RCTs showed that IPC is associated with a non-significant trend towards lower risk of DVTs and this is currently being evaluated in an on-going RCT.[94]

A retrospective observational study showed that IVC filter used in post stroke patients did not offer significant protection.[95]

2.8.2 Pharmacological

Evidence strongly supports the effectiveness of prophylactic dose LMWH or subcutaneous UFH 5000 IU BD in reducing the incidence of DVT. Despite the fact that over the years, rigorous clinical trials have been published reporting the effectiveness and safety of pharmacological prevention with low, fixed doses of anticoagulant medications, prophylaxis remains underused among in-patients at risk for VTE.[96]

In patients with intracerebral haemorrhage, prophylactic LMWH therapy when given after 48 hours of stroke were not observed to be associated with an increased haematoma growth.[97] A meta-analysis on the efficacy and safety of all anticoagulants in VTE reported early anticoagulation as being associated with a significant reduction in pulmonary embolism and a non-significant reduction in mortality. A non-significant increase in haematoma enlargement was also observed.[98]

2.8.3 Combination Treatment

Eleven studies (including six randomized controlled trials) evaluated the efficacy of combined methods of treatment (IPC + pharmacological prophylaxis) versus single modalities (IPC or pharmacological prophylaxis) in VTE prevention among high-risk patients. The combined modalities when compared with IPC, significantly decreased the incidence of VTE.[99]

Table 2.8: VTE Prophylaxis In Patients With Stroke

Recommendations	Grade
Prophylaxis for VTE should be tailored to the individual patient after cautious assessment of benefits versus risks. Any prophylaxis should be started early and ideally continued for at least a period of 4 weeks	A
Current guidelines recommend that patients with acute stroke, restricted mobility and no contraindications to anticoagulant should be prescribed thromboprophylaxis - prophylactic dose preferably LMWH over low dose UFH	A
In high-risk patients, combined modalities of IPC + pharmacological prophylaxis appear more effective in preventing VTE	A
Evidence from randomized trials is no longer supportive of the routine use of GECS after acute stroke	A
The timing of pharmacological thromboprophylaxis in haemorrhagic stroke is yet to be defined but may be used 72 - 96 hours after onset, if no further volume expansion of the intracranial haematoma is observed	C

3.0 CLINICAL DIAGNOSIS

3.1 CLINICAL PREDICTION MODEL

There are clinical prediction models to help with the diagnosis of VTE. The most widely used is the Wells' score that has been validated for non-pregnant patients.[103-108]

3.1.1 Deep vein thrombosis

Table 3.1.1: DVT Wells' Score

Clinical feature	Points
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
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, greater in the symptomatic leg*	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis** to DVT as likely or more likely	-2

* In patients with symptoms in both legs, use the more symptomatic leg

** An alternative diagnosis may include: superficial phlebitis, post-thrombotic syndrome, cellulitis, muscle strain or tear, leg swelling in paralysed limb, venous insufficiency, oedema due to CCF or cirrhosis, external venous obstruction (eg. due to tumour), lymphangitis or lymphoedema, popliteal (Baker's) cyst, haematoma, pseudoaneurysm or knee abnormality

Clinical probability score	
DVT likely	**≥ 2 points**
DVT unlikely	**≤1 point**

3.1.2 Pulmonary embolism

Table 3.1.2: PE Wells' Score	
Clinical feature	**Points**
Clinical signs & symptoms of DVT (minimum of leg swelling & pain with palpation of deep vein)	3
An alternative diagnosis is less likely than PE	3
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
Malignancy (on treatment, treated in the last 6 months or palliative)	1
Clinical Probability Score	
PE likely	**> 4 points**
PE unlikely	**≤ 4 points**

Patients with PE may also have symptoms of shortness of breath, pleuritic chest pain and cough. Other clinical signs such as hypotension and elevated JVP may be present. The ABG may reveal low PaO2 and low O2 saturation. Chest X-ray would be normal most of the time but sometimes may show the classical findings of atelectasis, wedge shape lesion and pruning of pulmonary vessels.[102,238]

The ECG findings in PE can also be non-specific such as tachycardia but sometimes can have a classical finding of S1, Q3, T3 and right strain pattern including RBBB and RV hypertrophy. Echocardiogram can also be very useful to diagnose PE, which shows right side strain and in severe cases, a blood clot can be seen inside the RA, RV, RVOT and also in pulmonary artery.[96]

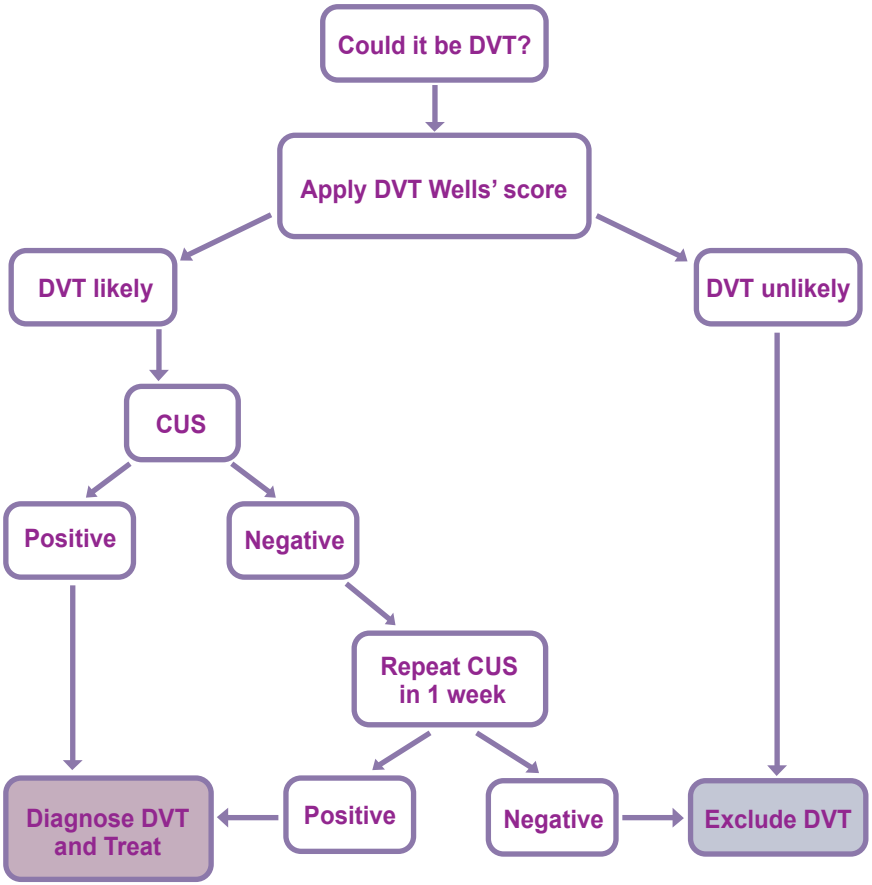
3.2 ALGORITHM FOR DIAGNOSIS OF VTE

3.2.1 Deep Vein Thrombosis

If scoring suggests likely DVT, offer Compression US scan (CUS) on the same day. If the CUS cannot be performed within the same day, commence LMWH and perform CUS in the next 24 hours. If the CUS is normal, repeat within 1 week. If this is normal, patient can be discharged to the health clinic.[100]

If the score suggests that DVT is unlikely, no further investigation is required. The utility of D-dimer in clinical practice has its limitations. There are many commercial D-dimer assays but they lack standardisation and the appropriate cut-off values.[333] The whole blood agglutination method for D-dimer testing that is used in most laboratories in Malaysia is not sensitive in ruling out VTE.[106,108,333] On the other hand, there are many causes for a raised D-dimer (e.g. inflammation, infection, normal pregnancy, cancer, haematoma, disseminated intravascular coagulation, surgery/ trauma, stroke, myocardial infarction, liver failure, renal failure, pre-eclampsia and eclampsia, etc.) which limits its value in the exclusion of VTE in the hospitalised patients.[333]

ALGORITHM FOR DVT DIAGNOSIS



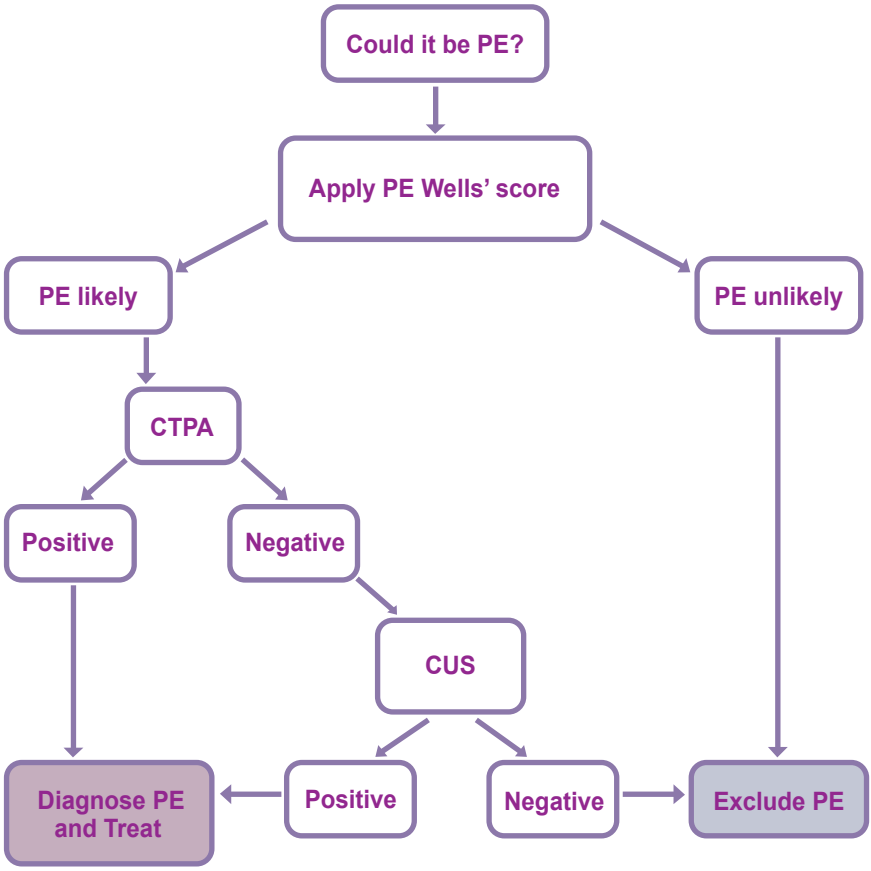
3.2.2 Pulmonary Embolism

Wells' Criteria as described in Table 3.1.2 was well tested in the clinical testing to manage non-pregnant patients with suspected PE.

If the score suggests likely PE, cover patient with LMWH and perform computerized tomography pulmonary angiogram (CTPA) on the same day or within next 24 hours. If CTPA is normal, proceed with bilateral compression US scan (CUS). If these are negative, patient can be discharged to the health clinic.[100,107]

Computerized tomography pulmonary angiogram is now the radiological investigation of choice for PE and has superseded the ventilation-perfusion scan. Ventilation-perfusion scan is limited to very few centres in Malaysia and is not readily available. However V/Q scan still has a role in certain situations such as allergy to ionized contrast and if peripheral PE is suspected.[100,107]

ALGORITHM FOR PE DIAGNOSIS



3.3 INVESTIGATIONS FOR CANCER

All patients diagnosed with unprovoked VTE who are not known to have cancer should be offered a physical examination (further specific tests guided by the patient's history and examination), a chest X-ray and blood tests (FBC, RP, LFT, urinalysis).[110]

Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked VTE. Tumour markers are not recommended for cancer screening.[110]

3.4 THROMBOPHILIA TESTING

Thrombophilia means a predisposition to clot formation. It can either be inherited or acquired. The known heritable thrombophilias are factor V Leiden, prothrombin gene mutation and deficiencies of the natural anticoagulants (protein C, protein S and antithrombin).[111,112] There may be other genetic defects that remain to be identified.

Factor V Leiden and prothrombin gene mutation are disorders of Caucasians and recent studies have shown that they are rare in East Asia.[113,114] Deficiencies of protein C, protein S and antithrombin are very uncommon but seem to be higher in East Asia when compared to Europe.[113,114]

The most common thrombophilia is the acquired antiphospholipid syndrome. It is associated with both arterial and venous thrombosis as well as recurrent pregnancy losses.[115,116] Other rare acquired causes are the myeloproliferative neoplasia and paroxysmal nocturnal haemoglobinuria.

Thrombophilia testing does not influence the initial management of a VTE nor the intensity of anticoagulant therapy.[111,112,117-119] Recurrence of VTE after stopping anticoagulant treatment has not been shown to be predictable by thrombophilia testing except in the presence of the lupus anticoagulant (LA)/ antiphospholipid antibodies (APA).[111-113,115,119-122]

Thrombophilia testing is affected by pre-analytical variables and errors in interpretation are frequent, which results in both reduced sensitivity and specificity for accurate diagnosis. Thus genuine deficiencies and abnormalities may not be detected and false positive diagnoses are common.[111,112]

The other drawbacks of thrombophilia testing are the high costs of testing and its psychosocial impact. Positive tests may cause unnecessary anxiety and carriers of thrombophilia may find it difficult to obtain life or disability insurance, whether symptomatic or not.[123]

There is also no strong evidence linking the heritable thrombophilias to the development of arterial thrombosis and recurrent miscarriages except for the acquired antiphospholipid syndrome.[115,116,122]

Hence, thrombophilia testing has very little clinical utility and should not be performed on a routine basis. Environmental and acquired risk factors play a bigger role in the development of VTE.[111,112]

Table 3.4: Thrombophilia Testing[124,125]	
Recommendations	**Grade**
Do not offer thrombophilia testing during the acute thrombotic event or prior to initiation of anticoagulant therapy	B
Do not offer thrombophilia testing to patients who are continuing anticoagulant treatment	B
Consider testing for APA and LA in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulant treatment	B
Consider testing for hereditary thrombophilia in patients who have unprovoked DVT or PE and who have a first-degree relative who has had a DVT or PE if it is planned to stop anticoagulant treatment	C
Do not offer thrombophilia testing to patients who have had a provoked DVT or PE	A
Do not offer thrombophilia testing in women with a previous VTE associated with pregnancy or the oral contraceptive pill	C
Do not offer thrombophilia testing to first-degree relatives of patients with thrombophilia who have had a DVT or PE	B
Do not offer thrombophilia testing to patients who have had an arterial thrombosis but consider APA and LA if there are no other risk factors	B
Do not offer thrombophilia testing in recurrent miscarriages or pregnancy losses except for APA and LA	B
Neonates and children with purpura fulminans should be tested urgently for protein C or protein S deficiency	A

4.0 TREATMENT OF VTE

4.1 INTRODUCTION

The aim of treatment of VTE is to reduce morbidity and mortality. This is achieved by optimal therapy with anticoagulants to prevent thrombus extension and embolisation. Graduated elastic compression stockings are important to prevent post-thrombotic complications following a proximal DVT.[126,127]

4.2 INITIAL TREATMENT OF VTE

In clinically suspected cases with high probability VTE, treatment with LMWH or fondaparinux should be given until the diagnosis is excluded by objective testing. In patients with confirmed DVT or PE, offer a choice of LMWH, fondaparinux or rivaroxaban, taking into account comorbidities, contraindications and drug costs. Start treatment as soon as possible.[129,130,137] Adequate analegesia should be given and the leg elevated.[136,137]

Offer warfarin within 24 hours of diagnosis in combination with LMWH or fondaparinux. For rivaroxaban, no overlap with LMWH or fondaparinux is needed as rivaroxaban has a rapid onset of action and predictable bioavailability. In patients with severe renal impairment or established renal failure (eGFR <30 mL/min) offer UFH with dose adjustments based on APTT or LMWH with dose adjustments based on anti-Xa assay.[130,134,136] For patients with PE and hemodynamic instability, offer IV UFH and consider systemic thrombolytic therapy.[128,131,132]

4.2.1 Low molecular weight heparin

Low molecular weight heparin is associated with decreased mortality, lower recurrence of VTE and decreased incidence of major bleeding when compared with unfractionated heparin.[133-135,138] It does not require monitoring and it's ease of use makes outpatient treatment feasible.

Currently available LMWHs in Malaysia and recommended doses for the treatment of acute VTE are as shown in Table 4.2.1.[134,139]

Table 4.2.1: LMWHs and the recommended doses for the treatment of acute VTE

LMWH	Treatment dose
Enoxaparin (20, 40, and 60 mg prefilled syringes)	1 mg/kg twice daily
Tinzaparin (0.5 and 0.7 mL of 20,000 anti-Xa IU/mL prefilled syringes)	175 units/kg once daily A simple way to calculate tinzaparin dose: Volume of tinzaparin in mL required = (weight in Kg - 10) ÷ 100 e.g. 60 kg patient = 0.5 mL; 70 kg = 0.6 mL; 45 kg = 0.35 mL tinzaparin)

Low molecular weight heparin is continued for at least 5 days or until the INR is above 2 for at least 24 hours, whichever is longer.[134,136]

4.2.2 Fondaparinux

Fondaparinux is an indirect inhibitor of activated factor X. It does not inhibit thrombin and has no effect on platelets. It is given subcutaneously and the dosing for the treatment of VTE is based on the body weight (Table 4.2.2). Fondaparinux must be used with caution in patients with renal impairment as it is eliminated unchanged in the kidneys.[129,131] Fondaparinux, like LMWH is continued for at least 5 days or until the INR is above 2 for at least 24 hours, whichever is longer.

Table 4.2.2: The recommended doses for fondaparinux in the treatment of acute VTE

Body weight, kg	Dosing, mg
<50	5
50 - 100	7.5
>100	10

4.2.3 Rivaroxaban

Rivaroxaban is a highly selective, direct factor Xa inhibitor that is orally active with a rapid onset of action. The dose used in the treatment of VTE is 15 mg twice a day as the loading dose for 3 weeks followed by 20 mg daily. At these doses, it has been shown to be non-inferior to enoxaparin followed by warfarin with significantly less major bleeding complications.[130,136]

4.2.3.1 Switching heparin to rivaroxaban

For patients currently receiving a parenteral anticoagulant, rivaroxaban should be started 0 to 2 hours before the time of the next scheduled administration of LMWH or at the time of discontinuation of continuous intravenous unfractionated heparin. [309,310]

4.2.3.2 Switching rivaroxaban to heparin

To convert rivaroxaban to LMWH, give the first dose of LMWH at the time the next rivaroxaban dose would be taken or 12 hours after the last dose of rivaroxaban.[309,310]

4.2.3.3 Switching VKAs to rivaroxaban

Stop VKA and allow INR to fall. Rivaroxaban can be given as soon as INR ≤2.5.[309,310]

4.2.3.4 Switching rivaroxaban to VKA

There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR.[309,310]

In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥2.0. For the first 2 days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both rivaroxaban and VKA, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once rivaroxaban is discontinued, INR testing may be done reliably at least 24 hours after the last dose.[309,310]

4.2.4 Dabigatran

At the time of writing this cpg, dabigatran is not licensed for use in the treatment of VTE.

4.2.5 Intravenous unfractionated heparin

Intravenous UFH is no longer the standard treatment in DVT and PE because it has to be given as an infusion with frequent APTT monitoring and may take more than 12 hours to achieve therapeutic level. All patients receiving UFH should have a platelet count performed at baseline but do not necessitate platelet count monitoring unless post-operative.[128,131,133,134]

The duration of initial IV UFH therapy in patients with VTE is between 5 to 7 days. To standardize the management of IV UFH, a weight-based normogram is used (Table 4.2.5).[134,136,138]

Table 4.2.5: Management with IV UFH

Initial dose	**80 IU/kg bolus, then 18 IU/kg/h**	
APTT ratio	Action and Dose change	Next APTT
<1.2 (APTT <35s)	80 IU/kg bolus, then increase rate by 4 IU/kg/h	6 h
1.2 - 1.5 (APTT 35 to 45s)	40 IU/kg bolus, then increase infusion rate by 2 IU/kg/h	6 h
1.5 - 2.5 (APTT 46 to 70s)	No change	24 h
2.5 - 3.0 (APTT 71 to 90s)	Decrease infusion rate by 2 IU/kg/h	6 h
>3.0 (APTT >90s)	Withold infusion for 1 hour, then decrease infusion rate by 3 IU/kg/h	6 h

4.3 MAINTENANCE TREATMENT OF VTE

Following initial heparinisation or fondaparinux in patients with VTE, maintenance of anticoagulation with oral anticoagulants is recommended. Following discharge, those on warfarin 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 (see chapter 10.0: MTAC-W).

Patients on rivaroxaban do not need initial heparinisation or laboratory monitoring. Patients are seen within 1 to 2 weeks of treatment to monitor response and to assess drug tolerability. Thereafter monthly follow-up is advised.

4.3.1 Duration of anticoagulation

The aim of anticoagulant therapy is to prevent extension of the thrombus and recurrence of the disease; however, the optimal duration is still not known. Anticoagulant therapy should be continued until the reduction of recurrent VTE no longer outweighs the increase risk of bleeding.[140-143,146]

4.3.1.1 Risk factors for VTE recurrence

The risk of recurrence after stopping therapy is primarily determined by two factors:

(1) whether the acute episode of VTE has been effectively treated and

(2) the patient's intrinsic risk of having a new episode of VTE (Table 4.3.1.1).[140-143,146]

Table 4.3.1.1: Risk factors for recurrence

- ❖ Unprovoked (idiopathic) VTE
- ❖ Previous VTE
- ❖ Male gender
- ❖ Active cancer
- ❖ Antiphospholipid syndrome
- ❖ Proximal versus distal DVT
- ❖ Post-thrombotic syndrome

The most important factors that influence the risk of recurrence after stopping anticoagulant therapy are the presence of a reversible provoking risk factor, unprovoked (idiopathic) VTE and the presence of active cancer.[140,142,143,147]

Among patients with VTE provoked by a reversible risk factor, the risk of recurrence is much lower if the provoking factor was recent surgery compared with a nonsurgical trigger (e.g. estrogen therapy, pregnancy, long-haul flight).[140,141,143]

4.3.1.2 Risk factors for increased bleeding

The risk factors for increased bleeding in patients on anticoagulation are listed below (Table 4.3.1.2):[143,147]

Table 4.3.1.2: Risk factors for increased bleeding
❖ Uncontrolled hypertension ❖ Age >75 years ❖ Renal impairment ❖ Anaemia ❖ Recent major bleeding

The recommended duration of anticoagulation hence depends on the risk of recurrence and the risk of bleeding (Table 4.3.1).[142,143,145]

Table 4.3.1: Duration of anticoagulation (Grade B Recommendation)

First VTE	Recommended Duration of AC
Provoked by a transient surgical risk factor	3 months
Provoked by a transient nonsurgical risk factor	3 months
Unprovoked VTE	Offer indefinite anticoagulation after taking into account: • Patient's preference • Low bleeding risk • Good anticoagulant monitoring is achievable
Unprovoked VTE and one or more bleeding risk	3 months
Unprovoked VTE in association with active cancer and the anti-phospholipid syndrome	Anticoagulation is continued as long as the risk factor remains

4.3.1.3 Completion of anticoagulation

There is no strong evidence to recommend routine D-dimer testing or US examination upon completion of anticoagulation in order to determine VTE recurrence and the decision to prolong therapy, unless guided by clinical symptoms.[311,312] A high D-dimer does not typically predict recurrence while a normal D-dimer does not exclude recurrence.[141] Ultrasound examination is operator-dependent and an old thrombus with partial recanalization may falsely suggest a recurrrence.[141]

4.4 THROMBOLYTIC THERAPY

4.4.1 Pulmonary embolism

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.[153]

4.4.1.1 Pulmonary embolectomy

This procedure is very rarely done and has a high peri-operative morbidity and mortality rates (30-50%).[157] However, the long-term outcome for survivors is good. It is indicated in massive PE (proven by imaging modalities) with haemodynamic compromise. It is done as an emergency procedure following failed conservative measures including thrombolysis.[156]

Recently, percutaneous cathether-directed embolectomy devices had been developed. These are quicker and easier to perform. This can be augmented by the administration of thrombolytic drugs, which speeds up clot fragmentation.[148,150,151]

4.4.2 Deep Vein Thrombosis

Where DVT threatens leg viability through venous gangrene, the leg should be elevated, anticoagulation commenced and consideration given to venous thrombectomy or thrombolytic therapy. Catheter-directed thrombolysis is preferred to systemic thrombolysis.[152]

4.4.2.1 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. Phlegmasia caerulea dolens is associated with considerable morbidity (50% amputation rate and 12 to 14% PE) and a 20% mortality rate.[148]

A multicentre randomized trial shows significant benefit of surgical venous thrombectomy plus anticoagulation versus anticoagulation alone in iliofemoral DVT.[155]

4.4.3 Thrombolytic agents

Thrombolytic agents used are tissue plasminogen activator (tPA) and streptokinase. They are indicated in massive PE. Tissue plasminogen activator is the agent of choice as it is clot-specific. The dose for streptokinase is 250,000IU IV bolus followed by 100,000 IU/hr for 24 hours. The dose for tPA is 100mg IV over 2 hours followed by therapeutic heparin infusion.[149]

4.5 VENA CAVAL FILTERS

A temporary caval filter may be required in situations where anticoagulation is contraindicated. There is no evidence for the role of prophylactic IVC filters in high risk patients.[158]

4.5.1 Vena Caval Filters

Vena caval filters are recognized treatment modalities to prevent pulmonary embolism secondary to DVT.[158] They can be inserted through the internal jugular or femoral vein, and placed in the IVC under fluoroscopic or ultrasound guidance.

There are two types of filters; temporary and permanent. The current practice is to insert temporary rather than permanent filters because the long-term effect of IVC filters is unproven. Due to lack of long-term data, IVC filters cannot be recommended in young patients.

There is a disturbing trend among interventionists to insert IVC filters even when there is no contraindication to anticoagulation and then forgeting to remove them. This practice is strongly discouraged.

Strict criteria should be applied when assessing patients for caval filter insertion, as there are significant associated risks. The indications for placement of IVC filter and its complications are listed below (Table 4.5).[160] The absolute contraindications to IVC filter insertion are complete IVC thrombosis and lack of vascular access.[158]

Table 4.5: IVC filter insertion

Indications for IVC filter
1. Contraindication to anticoagulation 2. Large free floating iliocaval thrombus
Complications reported with IVC filters
• Procedural complications are reported at 4 to 11% • Known complications include filter migration, venous insufficiency, IVC obstruction, venous access site thrombosis, penetration of IVC, filter fracture and death • Pulmonary embolism due to device failure occurs in 2 to 5% of cases

Anticoagulation should be resumed after insertion of caval filters unless it is contraindicated.[159] The long-term effects of IVC filters are untested, therefore filters should be safely removed once there is no risk of emboli. Most filters can be removed between 14 to 25 days of insertion, however the newer filters can be left in-situ for up to 90 days.

Patients who had IVC filter insertion MUST be given a date for removal of the filter with the stipulated time according to the manufacturer's recommendation. Hence it is the duty of the practitioner to establish a recall system to ensure patient is not lost to follow-up.[158]

4.6 PREVENTION OF POST-THROMBOTIC SYNDROME

The most common complication of VTE is chronic venous insufficiency (CVI) leading to post-thrombotic syndrome (PTS). Post-thrombotic syndrome results in debilitating pain, swelling, and ulceration and is a significant cause of loss of working days. It can contribute to an increase in recurrent DVT and PE.[161] Prevention of PTS will significantly reduce the morbidity and late mortality of DVT.[162]

4.6.1 Thrombo-Embolic Deterent Stockings

Wearing graduated elastic compression stockings with an ankle pressure greater than 23 mmHg following a proximal DVT have been shown to reduce post-thrombotic complications. It should be applied as soon as the patient can tolerate it and mobilisation encouraged.[163,164]

Patients are advised to continue wearing the stockings on the affected leg for at least 2 years and also to ensure that they are replaced 2 to 3 times per year or according to the manufacturer's instructions.[163,164]

5.0 MONITORING ANTICOAGULATION

5.1 INTRODUCTION

Monitoring the intensity of anticoagulants especially in the treatment of acute VTE is considered desirable in an attempt to secure maximal anti-thrombotic effect without excessive risk of bleeding through over-anticoagulation.

Accurate laboratory monitoring has been achieved for warfarin with the standardization of the INR however, it has proven to be difficult to achieve for both unfractionated heparin and low molecular weight heparins.[165,171] Laboratories should determine the APTT range that corresponds to the measured levels of heparin activity given.

5.2 WARFARIN

Prior to initiation of warfarin therapy, samples should be drawn for PT and APTT to establish a baseline. A first sample for INR is taken 2 to 3 days after the initiation of warfarin and monitored every 2 to 4 days until the INR is in the patient's target range, after which it can be monitored weekly.[170,171]

Once therapeutic level is achieved and is consistent for 2 consecutive readings, INR testing is then carried out every 2 weeks, then 4 weekly if the INR remains stable. For patients on long-term anticoagulation with consistently stable INRs, testing can be done every 12 weeks.[170,175]

For most indications, a therapeutic range of 2.0 to 3.0 (target INR 2.5) is recommended except for metallic heart valves and recurrent VTE while on adequate anticoagulation where a higher intensity INR between 2.5 to 3.5 (target INR 3.0) is recommended.[169,170,171]

There is no maximum warfarin dose to maintain a therapeutic range. Dose can be increased as long as the target INR is not achieved.[170,171]

5.3 UNFRACTIONATED HEPARIN

The APTT has been widely used for monitoring therapeutic doses of UFH. A target ratio of 1.5 to 2.5 is based on the apparent efficacy and safety of a plasma heparin concentration by protamine titration of 0.2 to 0.4 IU/mL or by anti-Xa of 0.3 to 0.7 IU/mL.[165,166,169]

Standardization between laboratories in the control of heparin therapy using the APTT has not been achieved because of the considerable reagent and instrument variability employed in the APTT, which results in inconsistency in sensitivity to heparin.[167,168,172] Laboratories are now moving towards anti-Xa for monitoring treatment with UFH.[166,168,172,174,177]

Heparin resistance is common in pregnancy making APTT monitoring unreliable with the danger of over-heparinisation with unfractionated heparin. Furthermore the APTT ratio uses control plasma from normal individuals and not from plasma of pregnant women.[166,167]

5.4 LOW MOLECULAR WEIGHT HEPARIN

Low molecular weight heparin (LMWH) has a highly predictable anticoagulant response because of its excellent bioavailability and hence does not require monitoring. However in some clinical settings such as renal impairment (delayed clearance of LMWH), pregnancy with mechanical heart valves and neonates, monitoring heparin with anti-Xa activity assay by the chromogenic method may be useful if there is a concern of over- or under-coagulation.[165,169,170]

However, the anti-Xa assay has significant limitations. Different LMWH preparations have different anti-IIa activity in relation to anti-Xa activity. The degree of anticoagulation of different LMWHs may not be comparable at the same plasma anti-Xa concentration.[173,176]

Monitoring of LMWH using anti-Xa assay requires careful assay validation, provides an incomplete picture of the anticoagulant effect and is poorly predictive of antithrombotic efficacy and risk of haemorrhage.[173,176]

If LMWH is monitored, the blood sample should be drawn approximately 4 hours after subcutaneous injection. If accumulation of LMWH is suspected, for example in renal failure, a trough level on a sample taken 24 hours after the last dose may be informative. The standard should be a sample of the administered LMWH. Alternatively the WHO standard for LMWH may be used.[165,169,170]

5.5 FONDAPARINUX

Fondaparinux produces a predictable anticoagulant response and does not require monitoring. If required, fondaparinux can be measured using fondaparinux-specific anti-Xa activity.[313]

5.6 RIVAROXABAN

Rivaroxaban has predictable pharmacokinetics and does not require monitoring.[314] If required, rivaroxaban can be measured using rivaroxaban-specific anti-Xa activity.[314]

Table 5.0: Monitoring anticoagulants

Recommendations	Grade
Warfarin	
The International Normalised Ratio (INR) is used to monitor warfarin	A
For most indications, the target INR is 2.5 (therapeutic range between 2.0-3.0)	B
Once therapeutic level is achieved and is consistent for 2 consecutive readings, INR testing is then carried out every 2 weeks, then 4 weekly if INR is stable	B

For patients on long-term anticoagulation with consistently stable INRs, INR testing can be done every 12 weeks	B
There is no maximum warfarin dose to maintain a therapeutic range	A
Unfractionated heparin	
Monitoring prophylactic doses of UFH is not required	A
Monitoring therapeutic doses of UFH can be achieved using the APTT. However local calibration of the test using anti-Xa or protamine titration must be carried out to determine the recommended target APTT ratio of 1.5-2.5	A
APTT monitoring for UFH is not standardised producing unreliable results with the hazards of over- or under-coagulation	A
Heparin resistance is common in pregnancy with the danger of over-heparinisation when APTT is used for monitoring	A
In the absence of proper calibration with factor Xa for APTT test, LMWH is preferred	A
LMWH	
Monitoring of prophylactic & therapeutic doses of LMWH is not required	A
Monitoring with anti-Xa assay may be of value in certain clinical settings where there is a concern of over- or under-coagulation (e.g. renal impairment, neonates, mechanical heart valves in pregnancy)	B
When LMWH is monitored, the blood sample should be obtained 4 hours after subcutaneous injection or 24 hours after the last dose if accumulation in renal failure is suspected	B
A calibrated LMWH should be used to establish the standard curve for the anti-Xa assay	A
Fondaparinux	
Fondaparinux produces a predictable anticoagulant response and does not require monitoring	A
Rivaroxaban	
Rivaroxaban has predictable pharmacokinetics and does not require monitoring	A

5.7 HEPARIN-INDUCED THROMBOCYTOPENIA AND MONITORING PLATELET COUNTS

5.7.1 Introduction

All patients receiving any heparin should have a baseline platelet count as heparin-induced thrombocytopenia and thrombosis (HITT) is a known complication of heparins. HITT is caused by the development of IgG antibodies directed against a complex of platelet factor 4 (PF4) and heparin. The IgG/ PF4/ heparin complexes bind to and activate platelets through their Fc receptors resulting in a prothrombotic condition that is associated with venous and arterial thrombosis.[315,316]

The incidence of HITT is greater with bovine than with procine heparin and greater with unfractionated heparin than with LMWH (5% vs. 0.5%). The frequency of HITT is greater in surgical than medical patients.[315,316]

5.7.2 Platelet monitoring

All post-operative patients on unfractionated heparin should have their platelet counts monitored, while those on LMWH should have their platelet counts monitored only after cardiopulmonary bypass (Table 5.7.2).[315,316]

Table 5.7.2: Monitoring platelet counts during heparin therapy

Rcommendations	Grade
Patients who are to receive any heparin should have a baseline platelet count	C
Post-operative patients, including obstetric cases, receiving UFH should have platelet count monitoring performed every 2-3 days from days 4 to 14 until heparin is stopped	C
Post-cardiopulmonary bypass patients receiving LMWH should have platelet count monitoring performed every 2-3 days from days 4 to 14 until heparin is stopped	C
Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring	C
Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 days and are receiving any type of heparin should have a platelet count determined 24 hours after starting heparin	C
Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring	C

5.7.3 Diagnosis and management of HIT/T

If heparin-induced thrombocytopenia (HIT) develops, the platelet count typically begins to fall 5 to 10 days after starting heparin, although in patients who have received heparin in the previous 3 months it can have a rapid onset due to pre-existing antibodies.[315,316]

If the platelet count falls by 30% or more and/or the patient develops new thrombosis or skin allergy or any of the other rarer manifestations of HITT (Table 5.7.3) between days 4 to 14 of heparin administration, HITT should be considered and heparin should be stopped and an alternative anticoagulant started in full dosage e.g. danaparoid, argatroban or fondaparinux (not licensed for use at present).[315,316]

Table 5.7.3: Manifestations of HITT[1]

- ❖ Deep vein thrombosis*
- ❖ Pulmonary embolism*
- ❖ Arterial thrombosis: stroke, coronary artery syndrome, peripheral arterial disease
- ❖ Skin lesions
- ❖ Adrenal haemorrhage
- ❖ Venous limb gangrene
- ❖ Total global amnesia
- ❖ Acute systemic reactions - chills, rigors
- ❖ Acute onset with collapse and death
- ❖ Warfarin-induced skin necrosis

* more common manifestations

Heparin-induced thrombocytopenia and thrombosis is a clinical diagnosis. Tests for HIT antibodies e.g. platelet activation assays and antigen assays are time consuming and have limited sensitivity and specificity.[315,316]

Patients should be therapeutically anticoagulated for 3 months after HIT with a thrombotic complication and for 4 weeks following HIT without a thrombotic complication.[315,316]

6.0 PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION

6.1 INTRODUCTION

The most common indications for warfarin anticoagulation are atrial fibrillation (AF), mechanical heart valve (MHV) and venous thromboembolism (VTE). Treatment with warfarin presents a problem if these patients need surgery because the interruption of anticoagulant therapy may increase the risk of thromboembolism.[178,179,180]

After warfarin therapy is discontinued, it takes several days for its antithrombotic effect to recede, and when it is resumed, several days are needed to re-establish therapeutic anticoagulation.[181,182,183,195] With the introduction of novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban and apixaban, this will no longer pose a problem as these agents have a quick onset of action and a short half-life.[184]

For emergency surgery, IV vitamin K 2 to 4 mg is given to correct the INR with infusion of 15 to 30 IU/kg of prothrombin complex concentrate or 15 to 20 mL/kg fresh frozen plasma if needed.[185-188]

The risk of recurrence following an episode of VTE is highest during the first 3 months and declines rapidly to about 5% per year. Patients with non-valvular AF who do not receive antithrombotic therapy have an average risk of systemic embolism of 4.5% per year; in patients with previous cerebral embolism it is approximately 12% per year.[179,180,182] In patients with prosthetic valve who are not on anticoagulant therapy, the estimated risk of major thromboembolism is 8% per year.[179,180,182,197]

The risk of bleeding depends on the type of surgery, patient's age, presence of other medical illnesses and bridging therapy with intravenous unfractionated heparin (IV UFH).[178,180,182,188] It is estimated that two days of IV UFH will increase the absolute rate of major postoperative bleeding by about 3%.[179,180,182]

The absolute risk of thromboembolism associated with a few days of perioperative sub-therapeutic anticoagulation is generally very low, and the risk of bleeding associated with postoperative IV UFH therapy is often relatively high.[179,180,182] Low molecular weight heparin may cause less bleeding than IV UH because it does not interfere with platelet aggregation.[183,190,194,196,197]

6.2 THROMBOEMBOLIC RISK

Patients can be stratified into risk groups according to their risks for thromboembolism (Table 6.2).[180-183]

Table 6.2: Risk stratification for perioperative thromboembolism

Thromboembolic risk	Clinical indication for warfarin therapy		
	Atrial fibrillation	**Prosthetic valves**	**Venous thromboembolism**
High	1. $CHADS_2$ score 5 or 6 2. Recent stroke/TIA (<3 months) 3. Rheumatic valvular heart disease	1. Any mechanical mitral valve 2. Older aortic mechanical valve (caged-ball, tilting disk) 3. Recent stroke or TIA (<3 months)	Recent VTE (<3 months)
Moderate	$CHADS_2$ score 3 or 4	Bi-leaflet aortic valve with at least one risk factor	1. VTE within past 3 -12 months 2. Recurrent VTE 3. Active cancer
Low	$CHADS_2$ score 0 to 2 (without previous stroke or TIA)	Bi-leaflet aortic valve without any risk factors	VTE >12 months ago

$CHADS_2$ indicates cardiac failure, hypertension, age, diabetes, stroke
Risk factors: AF, cardiac failure, hypertension, age>75 years, diabetes, stroke or TIA (Use CHA_2DS_2 Vasc: predicts better than $CHADS_2$ score)

6.3 BLEEDING RISK IN SURGERY

Surgeries can be associated with a high or low risk of bleeding (Table 6.3).[180-183,193]

Table 6.3: Surgical bleeding risk

High bleeding risk surgeries		Low bleeding risk surgeries
Major surgeries	**Minor surgeries**	**Minor surgeries**
Heart surgery: Coronary artery bypass, heart valve replacement	Biopsy of prostate or kidney (endogenous urokinase may promote bleeding)	Skin: Small skin excisions

Spinal surgery: Intracranial surgery, intra-spinal surgery	Colon polypectomy (ongoing bleeding from polyp stalk resection site)	Eye: Cataract removal
Vascular surgery: Aortic aneurysm repair, peripheral artery bypass	Cardiac pacemaker implantation (unopposed tissue layers of the pacemaker pocket heal by secondary intent)	Dental: Tooth extraction, endodontic (root canal) procedures
Major orthopaedic surgery, reconstructive plastic surgery		
Urogenital surgery: Prostate and bladder resection		Other procedures: Bone marrow aspiration and trephine biopsy Diagnostic ERCP without sphincterotomy Diagnostic endoscopy
Major cancer surgery		

6.4 MANAGING ANTICOAGULATION IN SURGERY

6.4.1 Warfarin interruption

Warfarin interruption is not required for minor surgical procedures with low risk of bleeding. Warfarin interruption is required for high bleeding risk surgeries. When warfarin is stopped, bridging therapy with LMWH, fondaparinux or IV UFH is indicated for high risk group and case-by-case for moderate risk group for thromboembolism.[181-183]

It takes approximately 5 days after stopping warfarin for the INR to normalize.[192,195] A safe INR for major surgeries is <1.5 and <1.2 for neurosurgeries. Warfarin can be resumed 12 to 24 hours (evening or next morning) after surgery and when adequate haemostasis is achieved.[189-192]

6.4.2 Bridging therapy

Bridging therapy is started on the third day before surgery. On the day before surgery patients should receive only the morning dose if a twice-daily LMWH regimen is used or 50% of the total dose if a once-daily LMWH regimen or fondaparinux is used. If IV UFH is used, this should be stopped 4 to 6 hours before surgery.[178-183]

Resuming therapeutic LMWH or fondaparinux after surgery will depend on whether haemostasis is secured; in general for surgeries with high bleeding risk, LMWH or fondaparinux is resumed after 48 to 72 hours; for surgeries with low bleeding risk, LMWH or fondaparinux is resumed after 24 hours.[178-183,194]

Table 6.4: Managing warfarin anticoagulation in surgery			
Warfarin interruption	**Continue warfarin**	**Bridging**	**No bridging**
High bleeding risk surgeries	Low bleeding risk surgeries	High/moderate thrombo-embolic risk	Low thrombo-embolic risk

Recommendations	Grade
Elective surgery should be avoided in the first month after an acute episode of VTE	C
Warfarin should be stopped at least 5 days before surgery	B
Warfarin should be restarted 12 to 24 hours after surgery once haemostasis is achieved and there is no ongoing bleeding	C
No bridging therapy is required for patients with AF, prosthetic valve or VTE with low risk for thromboembolism	B
Patients at high risk of thromboembolism should receive bridging therapy	B
Patients at moderate risk should be considered on case-by-case basis for bridging therapy according to the risks of surgical bleeding and of thromboembolism	C
Bridging therapy is started on the third day before surgery	C
The last dose of LMWH or fondaparinux is given 24 hours before surgery	C
If IV UFH is used, it should be stopped 4 to 6 hours prior to surgery	C
LMWH or fondaparinux is resumed after 24 hours for surgeries with low bleeding risk and 48 to 72 hours for surgeries with high bleeding risk	C
For emergency surgery, warfarin is stopped and iv vitamin K 2 to 4 mg is given with infusion of prothrombin complex concentrate or fresh frozen plasma if needed	B
A safe INR for major surgeries is <1.5 and <1.2 for neurosurgeries	C
Minor surgeries such as dental extractions, cataract surgeries and small skin excisions do not require interruption of anticoagulation	B

6.4.3 The novel oral anticoagulants

Two novel oral anticoagulants (NOACs), dabigatran and rivaroxaban have recently been approved. Dabigatran is licensed for use in stroke prevention in non-valvular atrial fibrillation and in VTE prevention in hip and knee surgery. Besides stroke and VTE prevention as for dabigatran, rivaroxaban is also licensed for use as an option for the treatment of DVT and PE.

The management of these anticoagulants when transitioning from or back to warfarin, around surgery or in case of major haemorrhage requires knowledge of their pharmacokinetics and mechanism of action.

6.4.3.1 Peri-operative management of dabigatran or rivaroxaban

The principles that are important for the peri-operative management with the new anticoagulants are:

1. The half-life is shorter than with warfarin
2. The onset of effect is within 2 hours, provided that intestinal absorption is normal.

6.4.3.1.1 Pre-operative management

For elective surgery in patients with normal renal function, it is safe to recommend the patient to simply interrupt therapy for 1 to 2 days (depending on the type of procedure) prior to their planned procedure (Table 6.4.3.1.1).[317] With decreasing renal function the period of interruption should be longer. This short period of interruption does not require bridging therapy.[317]

Table 6.4.3.1.1: Timing of interruption of dabigatran or rivaroxaban before surgery or invasive procedures

Calculated creatinine clearance, mL/min	Half-life, hours	Timing of last dose before surgery	
		Low bleeding risk	High bleeding risk
Dabigatran			
>80	13 (11 - 22)	24 hours	2 days
>50 - 80	15 (12 - 34)	24 hours	2 days
>30 - 50	18 (13 - 23)	2 days	4 days
≤30	27 (22 - 35)	4 days	6 days
Rivaroxaban			
>30	12 (11 - 13)	24 hours	2 days
<30	unknown	2 days	4 days

A normal thrombin time rules out the presence of important levels of dabigatran; this test could be used pre-operatively in patients in whom there is a potential for persistent anticoagulant effect, or for those undergoing surgery with a high risk of complications from bleeding, such as spinal or neurosurgery.[317,318] Prothrombin time may be prolonged in rivaroxaban but this does not reliably predict rivaroxaban levels.[317]

6.4.3.2. Post-operative management

The time point for the resumption of dabigatran or rivaroxaban depends almost excusively on the post-operative risk of bleeding. For procedures with good haemostasis shortly after the end of the procedure, resumption of drug is recommended after a minimum of 4 to 6 hours following surgery.[317]

For dabigatran, a half-dose (75 mg) is recommended for the first dose, and thereafter the usual maintenance dose. For rivaroxaban, a 10 mg dose is recommended for the first dose. Patients with bowel paralysis may require bridging with parenteral anticoagulants until they are able to tolerate orally.[317]

7.0 MANAGEMENT OF OVER-ANTICOAGULATION

7.1 WARFARIN AND BLEEDING

Anticoagulation with warfarin is very effective in the prevention and treatment of thromboembolic events. However, major bleeding complications leading to hospitalisation and death has been reported in 1 to 8% of patients during each year of long-term warfarin therapy.[198,203]

The risk for bleeding increases with age, history of past bleeding, specific co-morbid conditions and the level of the INR. Although the bleeding risk increases as the INR increases, 50% of bleeding episodes occur when the INR is less than 4.0.[198,203,204,206]

7.2 WARFARIN REVERSAL

The management for warfarin reversal will depend on the INR and whether or not bleeding is present. There are several options for warfarin reversal: stopping the warfarin, giving vitamin K and replacing the coagulation factors with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP).

7.2.1 Vitamin K

Vitamin K is available as ampoules for intravenous administration but can also be given orally mixed with a glass of juice or water. The ampoules are not recommended for subcutaneous or intramuscular use as the response is unpredictable with a risk of haematoma formation in the latter.[198-200,209]

Oral vitamin K is the treatment of choice unless very rapid reversal of anticoagulation is required. For most patients 1.0 to 2.0 mg of oral vitamin K is sufficient. If the INR is particularly high, 5 mg may be required.[199-201]

The optimal intravenous dose of vitamin K for partial reversal of over-warfarinisation is 0.5 to 1.0 mg. If full correction of the INR is desired, larger doses are needed. The INR can usually be normalized within 24 hours with an intravenous dose of 5 mg.[198,203,206]

7.2.2 Prothrombin Complex Concentrate

Prothrombin complex concentrate is made from pooled donor plasma and has undergone viral inactivation. It contains clotting factors II, IX and X with variability in their factor VII content. Concentrates with little factor VII (3-factor PCC) produce poor correction of the INR and are not recommended.[202,203]

Patients on warfarin have reduced levels of factors II, VII, IX and X and rapid correction involves replacement of these 4 factors. This is achieved with the 4-factor PCC. The 4-factor PCCs that are currently available in Malaysia are octaplex and beriplex.[203,205,206]

Four-factor PCCs are able to completely reverse warfarin-induced anticoagulation within 10 minutes but the infused clotting factors have a finite half-life, the shortest of which is factor VII at 6 hours. For this reason, 5 mg of intravenous vitamin K should be given with the PCC.[205,206]

Recombinant activated factor VII (rFVIIa) has been used in warfarin reversal but all reports have been retrospective, small series or without adequate controls. Although rFVIIa rapidly corrects the INR, its impact on stopping bleeding is unclear and its use cannot be recommended for warfarin reversal.[203,210]

7.2.3 Fresh frozen plasma

Fresh frozen plasma cannot provide a rapid and complete correction of warfarin-induced coagulopathy. At doses of 15 to 20 mL/kg, factor levels rise no more than 30%, hence FFP cannot be recommended for life-threatening bleeding.[205,206]

All hospitals and units responsible for the care of patients on anticoagulant must stock a 4-factor PCC as this will achieve factor levels between 80 to 100% within 10 minutes in life-threatening bleeding.[205,206]

7.3 MANAGEMENT OF OVER-WARFARINISATION

The management of over-warfarinisation and warfarin reversal are summarized in Tables 7.3 and 7.4.

7.3.1 Major bleeding

Major bleeding can be defined as limb or life-threatening bleeding that requires complete reversal of warfarinisation within 6 to 8 hours. Rapid correction is most effectively achieved by the administration of 4-factor PCC and must be combined with intravenous vitamin K 5 mg.[198,203,206]

7.3.2 Non-major bleeding

Patients with non-major bleeding can be managed with vitamin K combined with temporary discontinuation of warfarin. Intravenous vitamin K produces a more rapid correction of the INR than oral vitamin K and should be used in preference in the bleeding patient.[211,212]

7.3.3 INR >8 in non-bleeding patients

The risk of bleeding increases exponentially with increasing INR. Patients with INR more than 8 are at a significantly high risk of bleeding.[203,204]

In the non-bleeding patient, the use of vitamin K results in more rapid reduction in INR than discontinuation of warfarin alone. Oral vitamin K is preferred over the intravenous route as equal correction is achieved at 24 hours.[199,201,203] The recommended dose is between 1 to 5 mg oral vitamin K. At these doses over-correction is infrequent and resistance to re-anticoagulation does not occur.[199,201,211,212]

7.3.4 INR >5 but <8 in non-bleeding patients

The decision to give vitamin K to a non-bleeding patient with INR <8 is more controversial. It is reasonable to consider giving oral vitamin K to patients with an INR between 5.0 to 8.0 if they are judged to be at high risk of bleeding, but it is not necessary to offer this routinely to all patients. Witholding 1 to 2 doses of warfarin and reducing maintenance dose may be all that is required.[198,203,206]

Table 7.3: Management of over-warfarinisation

Clinical Scenarios	Recommendations	Grade
Major Bleeding (Life / Limb Threatening)	For all give:	
	1. IV vitamin K 5 mg	B
	2. PCC as follows:	B
	➢ INR <5.0 give 15 IU/kg	
	➢ INR >5.0 give 30 IU/kg	
	For intracranial haemorrhage, doses of up to 50 IU/kg can be given	B
	If PCC not available, give FFP 15 to 20 mL/kg	C
Non-Major Bleeding	For all consider:	
	Temporary discontinuation or dose reduction of warfarin (depending on clinical scenario)	B
	IV vitamin K: 1 to 3 mg	B
Elevated INR (No bleeding)	For all, the cause for the elevated INR should be investigated	B
1.INR >5.0 <8.0	Withhold 1 to 2 doses of warfarin and reduce maintenance dose	C
2.INR >8.0	Give oral vitamin K 1 to 5 mg and withold warfarin (as above)	C

7.4 SPECIFIC CLINICAL SCENARIOS

7.4.1 Emergency surgery for patients on warfarin

For surgery that requires reversal of warfarin and that can be delayed for 6 to 12 hours, the INR can be corrected by giving intravenous vitamin K. For surgery that requires reversal of warfarin that cannot be delayed, the INR can be corrected with PCC and intravenous vitamin K.[198,203,206]

7.4.2 Head injury in patients on warfarin

Patients on warfarin are more likely to have a cerebral bleed with more minor injury and there should be a lower threshold for CT scanning.[203]

Patients with a strong suspicion of intracerebral haematoma after a head injury should have their INR reversed with PCC immediately before the CT scan and INR results are available.[203,208]

7.4.3 Dengue infection in patients on warfarin

As it is difficult to predict which patient will progress to severe dengue, all patients should discontinue warfarin when platelets fall below 50 x 10^9/L. Bridging with LMWH is carried out only in patients with a high risk for thrombosis e.g. prosthetic heart valve with atrial fibrillation or a history of thromboembolic stroke when the INR falls below therapeutic levels.[207]

Warfarin can be resumed once patient is out of the defervescence phase and is in the recovery phase with a rising platelet count.[207]

Table 7.4: Warfarin reversal in specific clinical scenarios

Clinical Scenarios	Recommendations	Grade
Emergency surgery:		
Can be delayed for 6 to 12 hours	IV vitamin K, 2 mg to 5 mg	C
Immediate	IV vitamin K, 2 mg to 5 mg AND PCC 30 IU/kg	C

Trauma/Head Injury: Strong suspicion of intracranial bleed Intracranial bleed confirmed	Check INR Reverse anticoagulation with PCC before the results of any investigations Add IV vitamin K 5 mg	C C C
Dengue	Withhold warfarin if: • platelet count is <50x10^9/L • bleeding • shock	C

7.5 HEPARIN AND BLEEDING

Over-heparinisation may occur in conditions such as 'heparin resistance' in pregnancy or accidental heparin overdose as a result of drug error, with 5000 units/mL vials being mistaken for 50 units/mL vials.

7.5.1 Heparin reversal

For immediate reversal, protamine sulfate rapidly neutralises UFH activity. In animal models, LMWH-associated bleeding is completely reversed by protamine sulfate although it results in partial neutralisation of anti-Xa activity. The protamine dosage to neutralise heparin is listed in Table 7.5.1. Protamine is made from the sperm of salmon.

Table 7.5.1: Reversal of heparin

Reversal of unfractionated heparin	
Time since last UFH dose, min	**Protamine dose / 100 units UFH received**
<30	1.0 mg
30 - 60	0.5 - 0.75 mg
60 - 120	0.375 - 0.5 mg
>120	0.25 - 0.375 mg

Reversal of low molecular weight heparin	
Time since last LMWH dose	**Protamine dose / 100 anti-Xa units LMWH received**
Within 8 hours	1.0 mg
If bleeding continues	0.5 mg
>8 hours	0.5 mg
Maximum dose of 50 mg. Infusion rate of a 10 mg/mL solution should not exceed 5 mg/min. 1 mg enoxaparin equals approximately 100 anti-Xa units. Hypersensitivity reactions to protamine sulfate may occur in patients with known hypersensitivity reactions to fish or those previously exposed to protamine.	

7.6 FONDAPARINUX AND BLEEDING

Although there is no antidote for fondaparinux, recent studies suggest that rFVIIa may be beneficial in reversing its anticoagulant effects.[319]

7.7 THE NOVEL ORAL ANTICOAGULANTS AND BLEEDING

When bleeding occurs the event should be risk-stratified: minor bleeding (such as epistaxis, ecchymoses or menorrhagia) can be managed with simple withdrawal of the anticoagulant for one or two days. The drug could then be re-started at a lower dose (e.g. dabigatran 75 mg/day or rivaroxaban 10 mg/day) for a short period of time.[322]

Moderate bleeding (e.g. upper or lower gastrointestinal bleeding) should be managed with withdrawal of anticoagulant, close clinical monitoring, interventions to identify and definitely treat the bleeding source and consideration for an extended period of withdrawal of the oral anticoagulant (perhaps with the addition of a parenteral anticoagulant for patients at high risk of thrombosis) to allow healing. Transfusion therapy with red cells may be required to treat symptomatic anaemia.[322]

Major and life-threatening bleeding should be treated with immediate anticoagulant withdrawal, aggressive cinical monitoring, transfusion of packed red cells for anaemia and aggressive interventions to identify and treat the bleeding source. Other blood products such as plasma or cryoprecipitate do not reverse the anticoagulant effect of NOACs. Interventional therapy may be life saving and cannot wait reversal of anticoagulant effect; thus interventionists will be required to provide therapeutic inerventions despite the associated risk of bleeding.[322]

7.7.1 Dabigatran

If detected soon after ingestion the absorption of dabigatran may be reduced by the administration of activated charcoal. There is currently no antidote for the anticoagulant effect of dabigatran. Fresh frozen plasma, PCC or rFVIIa have not been demonstrated to reverse bleeding complications due to dabigatran.[320,321]

In extreme cases, acute hemodialysis should be considered since only 35% of dabigatran is bound to plasma proteins. The thrombin time can be used as a guide to further dialysis.

7.7.2 Rivaroxaban

A ceiling effect with no further increase in average plasma exposure is expected at supra-therapeutic doses of 50 mg rivaroxaban and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

Due to a high degree of albumin binding in plasma (92 to 95%), rivaroxaban is not dialysable. All its measurable anticoagulant effects are, however, reversed by a four-factor PCC, as studied in healthy volunteers. Clinical data is lacking but it seems reasonable to give a dose of between 30 to 50 IU/kg in case of acute, life-threatening bleeding.[320]

8.0 VENOUS THROMBOEMBOLISM IN OBSTETRICS

8.1 INTRODUCTION

Venous thromboembolism complicates between 1 in 500 and 1 in 2000 pregnancies and is more common postpartum than antepartum.[213,214,216,217-222] Obstetric VTE is now the leading cause of maternal death in Malaysia.[244]

8.2 PATHOGENESIS AND RISK FACTORS

The increased incidence of VTE in pregnancy and the puerperium may be related to venous stasis (due to pregnancy-associated changes in venous capacitance and compression of large veins by the gravid uterus), endothelial injury (due to changes at the uteroplacental surface and vascular injury during delivery), and a hypercoagulable state (pregnancy is associated with progressive increases in several coagulation factors, a decrease in protein S, and a progressive increase in resistance to activated protein C).[215,220,222]

The risk of DVT is approximately twice as high after caesarean delivery than vaginal birth. [221,222] In addition, DVT is far more common in the left than the right leg.[223] This striking distribution has been attributed to increased venous stasis in the left leg related to compression of the left iliac vein by the right iliac artery, coupled with compression of the inferior vena cava by the gravid uterus itself.[223,225,226]

8.3 DIAGNOSIS

Diagnosis of VTE during pregnancy can be complicated by physiological changes associated with pregnancy and by the reluctance of parents and clinicians to expose the fetus to even small amounts of ionising radiation.

8.3.1 Clinical examination

The clinical diagnosis of both DVT and PE is notoriously insensitive and nonspecific.[220-222] This problem is heightened in pregnant women since lower extremity swelling and discomfort are common in advanced pregnancy, and women with DVT may present with diffuse pain in the lower abdomen or leg.[218,220,224,225] Dyspnoea, the most frequent symptom of PE, occurs at some point in up to 70 percent of normal pregnancies, often stabilising near term.[228,230] Iliac vein thrombosis is suspected when there is swelling of the entire limb and associated with back-pain.[226]

8.3.2 Laboratory studies

Arterial blood gases are neither sensitive nor specific for the diagnosis of PE, and respiratory alkalosis is a very common feature of both pregnancy and PE. As in the non-pregnant population, a normal PO2, PCO2, or alveolar-arterial difference is common with PE.[234] Elevations in D-dimer are found in uncomplicated pregnancy, increasing with gestational age and peaking at the time of delivery and in the early postpartum period making the utility of this test in pregnancy limited.[232,235]

8.3.3 Radiologic evaluation

There are no systematic differences in the diagnostic strategies for deep venous thrombosis and pulmonary embolism in the pregnant and the non-pregnant patient.[238]

8.3.3.1 Deep vein thrombosis

The accuracy of non-invasive tests for DVT of the lower extremities in the general population approaches that of venography, with the caveat that they are less sensitive for calf vein thrombosis (which is less common in the pregnant population) and pelvic vein thrombosis. Large, direct prospective comparisons between individual diagnostic modalities have not been performed specifically in pregnant patients.[226,229]

8.3.3.1.1 Compression duplex Doppler ultrasound

Compression duplex Doppler ultrasound is the most commonly employed study in this setting; lack of compressibility of a femoral vein with the ultrasound probe is highly sensitive and specific for symptomatic proximal vein thrombosis.[232,233,236] The addition of Doppler analysis of flow variation with respiration in the left lateral decubitus position assists in diagnosing isolated iliac vein thrombosis.[231]

8.3.3.1.2 Magnetic resonance venography

Magnetic resonance venographyis a modality that may find increasing use in the pregnant population. It can detect both femoral and pelvic vein DVT with a sensitivity that approaches 100 percent in the non-pregnant population. Although no comparison studies have been performed in pregnancy, one case series documented the usefulness of MRI, permitting diagnosis of pelvic vein thrombosis or the presence of a patent but extrinsically compressed inferior vena cava in situations where non-invasive examinations were equivocal.[237]

8.3.3.1.3 Ascending contrast venography

Ascending contrast venography is rarely performed because the test requires ionising radiation and percutaneous cannulation of lower extremity veins. Although the delivered radiation to the fetus is small (<500 mcGy) when venography is performed with abdominal-pelvic shielding, shielding renders the test relatively insensitive to isolated ilio-femoral thrombosis.[213,226,231,245]

8.3.3.2 Pulmonary embolism

A patient who presents with respiratory but no lower extremity symptoms, first undergoes a chest X-ray. If this is normal, a bilateral CUS is performed. If both these tests are negative with persistent clinical suspicion of PE, a ventilation-perfusion scan (V/Q scan) or computed tomography pulmonary angiogram (CTPA) should be performed.[227,238,239]

If the clinical suspicion of PE is high at presentation a CTPA or V/Q scan should be performed from the outset.[249]

8.3.3.2.1 Chest X-ray

Chest X-ray may identify other pulmonary disease such as pneumonia, pneumothorax or lobar collapse. Whilst the X-ray is normal in 50% of pregnant women with objectively proven PE, abnormal features caused by PE include atelectasis, effusion, focal opacities, regional oligaemia or pulmonary oedema.[243]

8.3.3.2.2 CT pulmonary angiography

CT pulmonary angiography is the study of choice for the diagnosis of pulmonary embolism in the non-pregnant population. This technique has better sensitivity and specificity with a lower radiation dose to the fetus when compared with a V/Q scan.[240,241] The main disadvantage is the higher radiation dose to the maternal breasts.[242,245]

8.3.3.2.3 Ventilation/ Perfusion (V/Q) scan

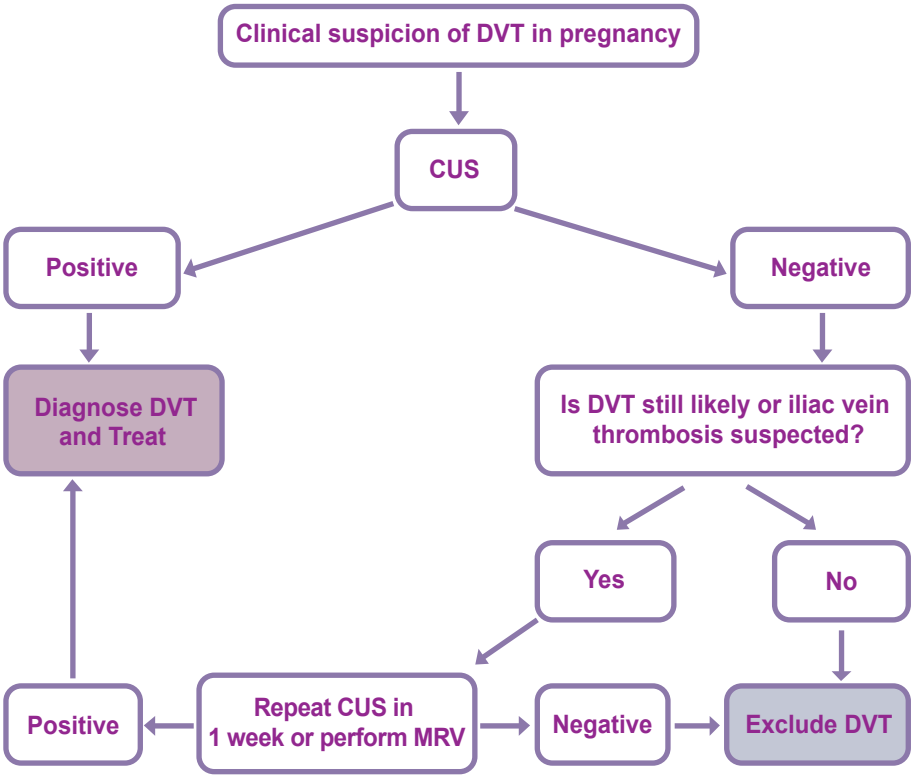
A ventilation/ perfusion scan is limited to very few centres and testing depends on the availability of isotope. It carries a slightly increased risk of childhood cancer compared with CTPA (1/280,000 versus <1/1,000,000) but carries a lower risk of maternal breast cancer.[242,245]

8.4 ALGORITHM FOR DIAGNOSIS OF VTE IN PREGNANCY

8.4.1 Deep vein thrombosis

Compression duplex ultrasound should be undertaken when there is a clinical suspicion of DVT. If this is negative but a high level of clinical suspicion exists, anticoagulation is continued and CUS is repeated in 1 week. If iliac vein thrombosis is suspected (back-pain and swelling entire limb), a magnetic resonance venography (MRV) or contrast venography should be considered.[245]

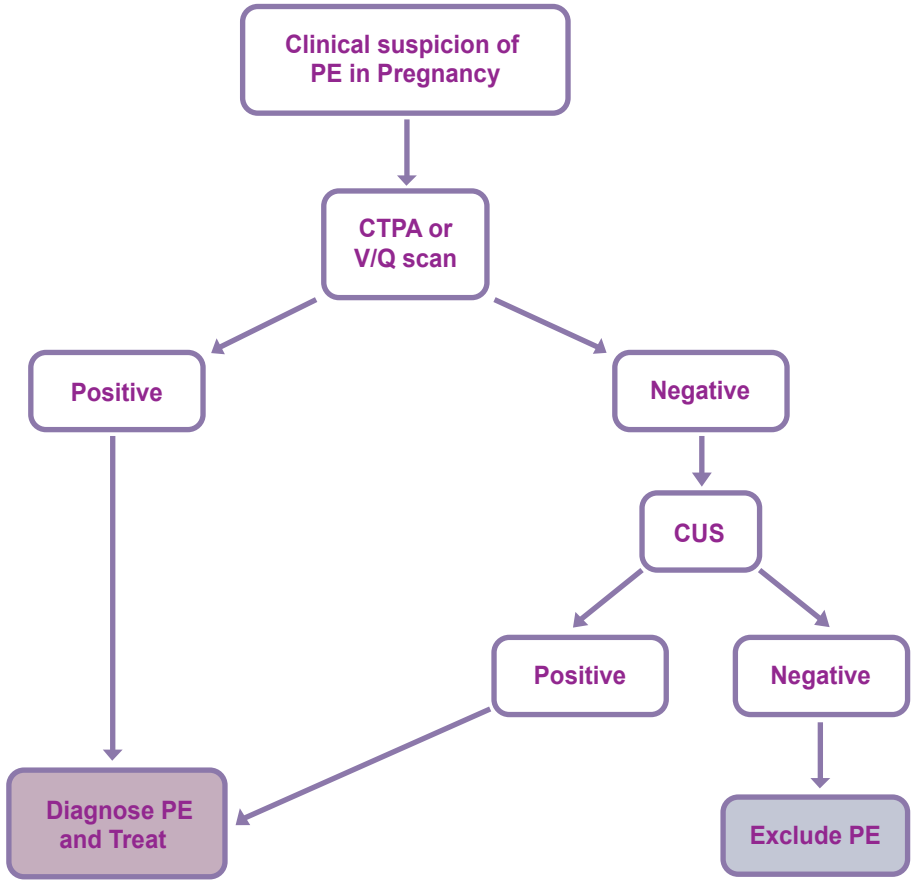
DIAGNOSTIC ALGORITHM FOR SUSPECTED DVT IN PREGNANCY



8.4.2 Pulmonary embolism

If the clinical suspicion of PE is high, a V/Q scan or CTPA should be performed. Where feasible, women should be involved in the decision to undergo CTPA or V/Q scanning. Ideally informed consent should be obtained before the tests are undertaken.[245]

DIAGNOSTIC ALGORITHM FOR SUSPECTED PE IN PREGNANCY



8.5 TREATMENT OF VTE IN PREGNANCY

8.5.1 Initial treatment of VTE

In clinically suspected DVT or PE, treatment with LMWH should be given until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated. Randomised control trials indicate that LMWHs are more effective, are associated with a lower risk of haemorrhagic complications and are associated with lower mortality than UFH in the treatment of VTE.[245]

Treatment with fondaparinux is not recommended in pregnancy as it can cross the placenta. It is licensed outside pregnancy, with very limited experience in pregnancy. No adverse effects have been observed but there is insufficient evidence to conclude safety during pregnancy. It is reserved for women intolerant to heparin.[250]

8.5.2 Dosing of LMWH

LMWH should be given daily with dosage titrated against the woman's booking or most recent weight (Table 8.5.2)

Table 8.5.2: Dosing of LMWH in pregnancy

Initial dose	Pregnancy weight (kg)			
	<50	50 - 69	70 - 89	>90
Enoxaparin	40 mg BD	60 mg BD	80 mg BD	100 mg BD
Tinzaparin (20,000 IU/mL)	175 units/kg once daily Volume of tinzaparin in mL required = (weight in Kg - 10) ÷ 100			

Massive life-threatening PE should be treated with initial intravenous heparin followed by immediate thrombolysis with thrombolytic therapy or surgical embolectomy (see section 4.4).[230,246]

8.5.3 Monitoring LMWH

Routine measurement of peak anti-Xa is not recommended for patients on LMWH for the treatment of VTE in pregnancy except in women of extremes body weight or with other complicating factors (renal impairment or recurrent VTE) putting them at high risk.[245]

8.5.4 Maintenance treatment of VTE

Treatment with LMWH should be continued throughout pregnancy. Warfarin is contraindicated during pregnancy.[247]

8.5.5 Anticoagulant therapy during labour and delivery

Women taking LMWH for maintenance therapy should be advised that once she is in labour, she should not inject any further heparin. Where delivery is planned, LMWH therapy should be discontinued 24 hours before planned delivery.[245,247]

8.5.6 Regional anaesthesia during labour and delivery

Regional anaesthesia should not be undertaken until at least 24 hours after the last dose of therapeutic LMWH. A thromboprophylactic dose of LMWH should be given by 3 hours after a caesarean section (more than 4 hours after removal of the epidural catheter). The epidural catheter should not be removed within 12 hours of the most recent injection.[245,247]

8.5.7 Post-natal anticoagulation

Therapeutic anticoagulation therapy should be continued for the duration of the pregnancy and for at least 6 weeks post-natally and until at least 3 months of treatment has been given in total. Women should be offered the choice of LMWH or warfarin post-natally after discussion about the need for regular blood tests for INR monitoring with warfarin. Both LMWH and warfarin are safe for breastfeeding.[245]

8.5.8 Prevention of post-thrombotic syndrome

Graduated elastic compression stockings should be worn on the affected leg for at least 2 years after the acute event to reduce the risk of PTS.[245,248]

8.6 PREVENTION OF VTE IN PREGNANCY

All women should undergo a documented assessment of risk factors for VTE in early pregnancy or before pregnancy and following delivery. This assessment should be repeated if the woman is admitted to the hospital for any reason or develops other intercurrent problems during the antenatal and postpartum period.

8.6.1 Antenatal Risk Assessment

Women should be assessed at booking and stratified into risk groups according to risk factors and offered thromboprophylaxis with LMWH where appropriate (Table 8.6.1).[249]

Table 8.6.1: Risk groups and indications for antenatal thromboprophylaxis (Grade C Recommendation)

ANTENATAL RISK ASSESSMENT
❖ To be assessed at booking and with every admission into hospital ❖ Can be divided into 3 risk groups ❖ Management will depend on the risk group
These risk groups do not include those who are sufficiently high risk (very high risk) to require anticoagulation when not pregnant (on long-term warfarin): • Previous VTE on warfarin • APLS with previous VTE This group requires therapeutic dose of LMWH antenatally

1. High risk	Recommendations
Risk factors	**Management**
Any one ➢ Single previous VTE with ☐ • Family history or • Unprovoked / estrogen-related ➢ Previous recurrent VTE >1 ☐	Requires antenatal prophylaxis with LMWH ➢ Enoxaparin 1 mg/kg daily ☐ or ➢ Tinzaparin 4500 units daily ☐ (if BW >90kg, to dose at 75 units/kg daily)
2. Intermediate risk	**Recommendations**
A. Risk factors	**Management**
Any one (if admitted into hospital): ➢ Single previous VTE with no family history ☐ ➢ Medical comorbidities e.g. • Heart/lung diseaser ☐ • SLE ☐ • Cancer ☐ • Inflammatory conditions ☐ • Nephrotic syndrome ☐ • Sickle cell disease ☐ • Thalassaemia ☐ • IVDU ☐ ➢ Surgical procedures e.g. • Appendicectomy ☐	Consider antenatal prophylaxis with LMWH ➢ Enoxaparin 1 mg/kg daily ☐ or ➢ Tinzaparin 4500 units daily ☐ (if BW >90kg, to dose at 75 units/kg daily)
B. Patient risk factors (see below)	
➢ Any ≥3 ☐ or ➢ ≥2 (if admitted into hospital) ☐	

3. Low risk	Recommendations
Patient risk factors	**Management**
Any 2 or less (not admitted into hospital): ➢ Age >35 years ☐ ➢ Obesity BMI >30 ☐ ➢ Parity ≥3 ☐ ➢ Smoker ☐ ➢ Gross varicose veins ☐ ➢ Current systemic infection ☐ ➢ Immobility e.g. paraplegia, long-haul travel >4 hours ☐ ➢ Pre-eclampsia ☐ ➢ Dehydration/ hyperemesis/ OHSS ☐ ➢ Multiple pregnancy ☐ ➢ Assisted reproductive treatment ☐	Mobilisation Avoid dehydration

8.6.2 Postnatal risk assessment

All women should be assessed after delivery and stratified into risk groups according to risk factors and offered thromboprophylaxis with LMWH where appropriate (Table 8.6.2).[249]

Table 8.6.2: Risk groups and indications for postnatal thromboprophylaxis (Grade C Recommendation)

POSTNATAL RISK ASSESSMENT	
❖ To be assessed in delivery suite ❖ Can be divided into 3 risk groups	
These risk groups do not include those who are sufficiently high risk (very high risk) to require anticoagulation when not pregnant (on long-term warfarin): • Previous VTE on warfarin • APLS with previous VTE Switch from therapeutic LMWH to long-term warfarin postnatally	
1. High risk	**Recommendations**
Risk factors	**Management**
➢ Any previous VTE ☐ ➢ Anyone requiring antenatal prophylactic LMWH ☐	At least 6 weeks postnatal prophylactic LMWH
2. Intermediate risk	**Recommendations**
A. Risk factors	**Management**
Any one ➢ Caesarean section in labour ☐ ➢ BMI >40 ☐ ➢ Prolonged hospital admission ☐ ➢ Medical comorbidities e.g. ☐ • Heart/lung disease ☐ • SLE ☐ • Cancer ☐ • Inflammatory conditions ☐ • Nephrotic syndrome ☐ • Sickle cell disease ☐ • Thalassaemia ☐ • IVDU ☐	At least 7 days postnatal prophylactic LMWH If persisting or >3 risk factors, consider extending thromboprophylaxis with LMWH
B. Patient risk factors (see below)	
≥2 risk factors ☐	

3. Low risk	Recommendations
Patient risk factors	**Management**
Any 1 risk factor: ➢ Age >35 years ☐ ➢ Obesity BMI >30 ☐ ➢ Parity ≥3 ☐ ➢ Smoker ☐ ➢ Elective CS ☐ ➢ Any surgical procedure in the puerperium ☐ ➢ Gross varicose veins ☐ ➢ Current systemic infection ☐ ➢ Immobility e.g. paraplegia, long-haul travel >4 hours ☐ ➢ Pre-eclampsia ☐ ➢ Mid-cavity rotational operative delivery ☐ ➢ Prolonged labour >24 hours ☐ ➢ Assisted reproductive treatment ☐ ➢ PPH >1 litre or blood transfusion ☐	Mobilisation Avoid dehydration

8.7 MANAGEMENT OF PREGNANT WOMEN WITH THE ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Women with APLS of childbearing age already on established anticoagulation who are contemplating a pregnancy should be commenced on aspirin and be switched from warfarin to therapeutic dose LMWH upon confirmation of pregnancy, which should be continued until delivery, at which point they may recommence warfarin.[323,324]

The management of women with APLS with a history of pregnancy loss in the absence of a history of thrombosis is more controversial because of conflicting data from clinical trials.

Women with recurrent early fetal loss as the predominant manifestation of APLS should be offered aspirin alone or aspirin plus prophylactic dose UFH or LMWH from the time of pregnancy confirmation until delivery;[323,324] the latter option is preferred in women who have predominantly manifested previous late pregnancy loss or placentally mediated pregnancy morbidity (pre-eclampsia or IUGR).[323,324]

Table 8.7: Managing APLS in pregnancy	
Recommendations for Management of Pregnant Women with APLS	**Grade**
Women with APLS of childbearing age already on established anticoagulation who are contemplating a pregnancy should be commenced on aspirin	C
Women with APLS already on established anticoagulation should be switched from warfarin to therapeutic dose LMWH upon confirmation of pregnancy plus aspirin	C
Women with APLS on established anticoagulation should continue therapeutic LMWH until delivery, at which point they may recommence warfarin	C
Women with recurrent early fetal loss as the predominant manifestation of APLS should be offered aspirin alone or aspirin plus prophylactic dose UFH or LMWH from the time of pregnancy confirmation until delivery	C
Aspirin plus prophylactic dose UFH or LMWHis preferred in women who have predominantly manifested previous late pregnancy loss or placentally mediated pregnancy morbidity (pre-eclampsia or IUGR)	C

9.0 THE TREATMENT OF VTE IN SPECIAL POPULATIONS AND IN UNUSUAL SITES

9.1 THE ELDERLY, RENAL IMPAIRMENT AND OBESITY

The occurrence of VTE is not uncommon in patients with renal impairment, morbid obesity and the elderly. However, the optimal treatment of VTE in these patients is controversial and remains a challenge.[251,253,255]

Warfarin with INR monitoring is safe for all patient population as well as in patients with renal impairment. Low molecular weight heparin is however metabolized in the kidneys and must be used with caution in these patients.[253,254,255]

Reducing the dose of LMWH to once daily and monitoring with anti-Xa is necessary. Unfractionated heparin is safe in renal failure and is recommended in patients with creatinine clearance <30 mL/min. Tinzaparin is safe to be used up to a CrCl of <20 mL/min.[255,256,257]

Management of the elderly patients with VTE is similar to the general population however care must be taken as these patients may have renal impairment and are at a higher risk of bleeding.[255]

Studies have shown that the pharmacokinetics of LMWH is similar in obese and non-obese patients with no significant difference in the incidence of haemorrhage or VTE recurrence.[252,257]

It is recommended that in obese patients, LMWH is dosed by actual weight and capping the dose is not recommended as this could lead to sub-therapeutic anticoagulation and increased risk of recurrent VTE.[252,255]

Table 9.1: Treatment of VTE in special populations

Recommendations	Grade
Elderly	
Anticoagulation in the elderly is similar to the general population but it must be noted that these patients may have underlying renal insufficiency	B
Renal impairment	
The elimination half-life of LMWH is increased in renal insufficiency, therefore reducing the dose to 1 mg/kg once daily enoxaparin and monitoring the trough anti-Xa for toxicity and peak anti-Xa to adjust dosage is necessary	B
Tinzaparin is safe to be used up to a Cr Cl of 20 mL/min with no dose adjustment	A

UFH is recommended in patients with a CrCl <30 mL/min with dose adjustments based on the APTT if no anti-Xa testing is available to monitor the effects of LMWH	B
Fondaparinux should not be used in patients with renal impairment	A
Warfarin with INR monitoring is safe in patients with renal failure	B
Obesity	
The pharmacokinetics of LMWH in obese patients are similar to non-obese patients	A
LMWH should be dosed by actual weight and capping the dose is not recommended	B
The dose for fondaparinux is 10 mg daily for body weight >100 kg	B

9.2 ANTICOAGULATION FOR ESTABLISHED VTE IN STROKE PATIENTS

Once the diagnosis of DVT has been confirmed with compression duplex Doppler ultrasound, most patients with venous thromboembolism will respond to anticoagulation.[258] The current practice in ischaemic stroke patients is to commence with subcutaneous LMWH which will continue (usually 5 to 10 days) until warfarin, initiated concurrently, achieves an INR above 2.0 for >24 hours.[259]

The new oral anticoagulant, rivaroxaban although not evaluated in the treatment of VTE in stroke patients seem to be a promising anticoagulant as it causes less intracranial bleeding complications than LMWH/warfarin.

While anticoagulation is recommended for the duration of three months in non-stroke patients, the ideal duration of treatment in established VTE in stroke patients is still unresolved and should be guided by the presence of continuing risk factors in the individual patient or the recurrence of venous thromboembolism.

Table 9.2: Anticoagulation of established VTE in stroke patients

Recommendation	Grade
The duration of anticoagulation for established VTE in stroke patients is at least 3 months but may be extended if the risk of VTE recurrence remains high	C

9.3 ANTITHROMBOTIC THERAPY IN CHILDREN

Venous thromboembolism in paediatrics is rare. The leading contributor of VTE in childhood is the placement of central venous access devices.[260,262] Other conditions associated with the development of VTE in childhood are malignancy, vascular malformations, trauma or surgery.

Anticoagulation poses a significant challenge in the paediatric population. The response, distribution, binding and clearance of antithrombotics are age-dependent which makes dosing and monitoring difficult.[260,261,262]

Limited vascular access reduces the ability to deliver some antithrombotic therapy and to accurately monitor blood anticoagulant levels. The need for general anaesthesia to perform diagnostic studies in paediatric patients has an impact on the ability to investigate and on the confidence in therapeutic decisions.[261,262]

The choice of antithrombotic is also influenced by the unavailability of paediatric formulation as in the case of vitamin K antagonist (VKA; no suspension or liquid formulation) and low molecular weight heparin (LMWH; pre-dosed syringes based on adult weights). Dietary differences also make the use of VKA difficult (breast milk and infant formula have very different vitamin K content).[161,262]

Important issues when considering treatment options include the site, extent and clinical consequences of the thrombosis and the risks of bleeding complications associated with the use of anticoagulant or thrombolytic therapy. The later will vary with gestational age, birth weight and comorbidities such as lung disease, necrotising enterocolitis, sepsis and intraventricular haemorrhage.[260]

Management should be individualised with appropriate consideration of the risk-benefit ratio for each case. Options for treatment include supportive care only, anticoagulant therapy, thrombolytic therapy and surgery.

Table 9.3: Factors that complicate delivery of anti-thrombotic therapy in children

- ❖ Physiologically evolving haemostatic mechanism in children
- ❖ Absence of paediatric-specific formulations
- ❖ Difficulty of frequent sampling in young children (especially the absence of established capillary PT-INR testing)
- ❖ Absence of robust paediatric-specific evidence to guide practice

9.3.1 Unfractionated heparin

9.3.1.1 Monitoring UFH

Despite its difficulties, UFH is commonly used in paediatric patients. The therapeutic APTT range of UFH in neonates or children is not known but is extrapolated from adults.[261,262] Baseline APTT in paediatric patients especially neonates are often increased compared with adults. Therefore the therapeutic ranges represent a reduced relative increment in APTT values and hence underestimate UFH concentration.

Thus there is uncertainty over how best to monitor unfractionated heparin therapy in children, given the non-uniformity and lack of calibration of institutional APTT values to other measures of heparin activity such as anti-Xa activity or protamine neutralisation and the lack of ready availability of the alternative assays.[325]

9.3.1.2 Dosing UFH

One prospective study used weight-based normogram to dose UFH in paediatric population (Table 9.3.1). Bolus doses of 75-100 units/kg resulted in therapeutic APTT values in 90% of children at 4 to 6 hours post-dose, however in recent studies, this dosing has resulted in unrecordable values.[260,261] Thus, there is also uncertainty over the requirement of a loading dose prior to commencing heparin infusion.

Individual risk factors for bleeding and thrombosis especially in premature infants need to be taken into consideration before recommending initial bolus strategy. Maintenance doses are age dependent, with infants having the highest requirements because of faster clearance due to a larger volume of distribution.

Table 9.3.1: Protocol for intravenous unfractionated heparin administration in paediatric patients[260]

I. Loading dose: UFH 75 units/kg over 10 minutes (requirement is uncertain and has to be individualised)

II. Initial maintenance dose: 28 units/ kg per hour for infants <1 year; 20 units/kg for children >1 year

III. Adjust heparin to maintain APTT of 60-85 sec (correlates to anti-Xa level of 0.35-0.70)

APTT, sec	Bolus, units/kg	Hold, min	% rate change	Repeat APTT
<50	50	0	+ 10	4 h
50 - 59	0	0	+ 10	4 h
60 - 85	0	0	0	Next day
86 - 95	0	0	- 10	4 h
96 - 120	0	30	- 10	4 h
>120	0	60	- 15	4 h

IV. Obtain blood for APTT 4 hours after heparin loading dose and 4 hours after every change in the infusion rate

V. When APTT values are therapeutic, do a daily FBC and APTT

There is no data to define optimal prophylactic doses of UFH. The efficacy of using a dose of 10 units/kg per hour as a continuous infusion has not been proven.

9.3.1.3 Side effects of UFH

Bleeding is a known side effect of intravenous UFH with major bleeding rates as high as 24% in one study in paediatric ICU patients who received UFH therapy. A common cause of fatal bleeding is accidental heparin overdose as a result of drug error, with 5000 units/mL vials being mistakenly selected instead of 50 units/mL vials.[260-263]

Other side effects that are uncommon are osteoporosis and alopecia. Heparin-induced thrombocytopenia is a distinct rarity in paediatric thrombosis management. The cases of HIT reported have been exposed to low-dose heparin flushes used in maintaining patency of CVADs and during hemodialysis and to supra-therapeutic doses given during cardiopulmonary bypass.

9.3.2 Low molecular weight heparin

Despite the lack of studies, LMWH has become the anticoagulant of choice in paediatric patients due to its better bioavailability, less need for monitoring and less side effects.[260,262]

There are 3 factors that influence the decision to use LMWH:

1. patient stability (balance between thrombosis and bleeding)
2. renal function
3. need for invasive intervention and rapid reversibility of anticoagulation

When transitioning from UFH to LMWH, LMWH is administered at time of discontinuation of UFH.

9.3.2.1 Monitoring LMWH

Due to its good bioavailability and predictable response, monitoring is not required in paediatric patients on LMWH therapy for VTE prophylaxis and treatment except for premature infants and neonates where higher doses may be needed. The drug should be monitored to achieve a target anti-Xa range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 hours after subcutaneous injection.[260,262]

9.3.2.2 Dosing of LMWH

The therapeutic doses of LMWH required for paediatric patients have been assessed and are listed in Table 9.3.2.

Table 9.3.2: Dosing of LMWH in children[260]			
LMWH	**Age**	**Initial prophylactic dose**	**Initial treatment dose**
Enoxaparin	<2 months >2 months	0.75 mg/kg/dose BD 0.5 mg/kg/dose BD	1.5 mg/kg/dose OD 1.0 mg/kg/dose OD
Tinzaparin	0 - 2 months 2 - 12 months 1 - 5 years 5 - 10 years 10 -1 years	- - - - -	275 u/kg/dose OD 250 u/kg/dose OD 240 u/kg/dose OD 200 u/kg/dose OD 175 u/kg/dose OD

9.3.2.3 Dose adjustment for invasive procedures

For lumbar punctures or invasive procedures, omit 2 doses of enoxaparin (24-hour drug washout) prior to procedure (e.g. scheduled lumbar puncture and intra-thecal therapy on Friday; omit Thursday evening dose and Friday morning dose).

9.3.2.4 Stability of reconstituted LMWH

The stability of reconstituted fixed-dose preparations enables multi-dosing[326] for example, if an infant weighing 6 kg requires enoxaparin at 6 mg 12 hourly, a 20 mg/0.2 mL pre-filled syringe preparation may be reconstituted with sterile 0.9% saline to create a 20 mg/mL solution, from which stock 0.3 mL may be injected subcutaneously twice daily, enabling optimum use of the pre-filled syringe -dispensed volumes.

9.3.3 Heparin reversal

Heparin can be reversed by protamine with partial reversibility for LMWH (see Table 7.5.1).

9.3.4 Warfarin

Warfarin is problematic in neonates for several reasons.

1. Plasma levels of vitamin K-dependent factors are physiologically decreased in newborns to levels that are comparable to adults receiving warfarin with INR of 2.0 to 3.0
2. Infant formula is supplemented with vitamin K to prevent haemorrhagic disease of the newborn
3. Warfarin is only available in tablet form
4. Warfarin requires frequent monitoring
5. Problems with vascular access

Warfarin is the most commonly used oral anticoagulant. The therapeutic ranges are directly extrapolated from adult patients.[260,262]

For the management of warfarin anticoagulation in children, refer to UMMC guidelines 2013 in appendix 11.

9.3.5 Thrombolysis in neonates and children

Thrombolysis, either systemic or catheter-directed is indicated for life-, limb- or organ-threatening thrombosis. Success rates for thrombolysis in paediatric patients vary between 60 to 80%. Tissue plasminogen activator is the agent of choice because of experimental evidence of improved clot lysis, fibrin specificity and low immunogenicity when compared with streptokinase or urokinase.

Table 9.3.5: Thrombolytic therapy with tPA[260]

1. Before thrombolysis is used, concurrent haemostatic problems such as thrombocytopenia and vitamin K deficiency should be corrected
2. Pre-therapy plasminogen replenishment through fresh frozen plasma (10-15 mL/kg) is given
3. UFH is reduced to 10 units/kg/hour throughout the duration of tPA therapy and resumed at previous therapeutic dose subsequently
4. t-PA at 0.5 mg/kg/hour infused over 6 hour

9.3.5.1 Thrombolysis and bleeding

Mild bleeding (such as oozing from wound) can be treated by local pressure and supportive care. Major bleeding may be treated by stopping thrombolytic therapy and administering cryoprecipitate (1 unit/5 kg or 5 to 10 mL/kg dose) and an antifibrinolytic or both.[260]

9.3.6 Surgical thrombectomy

Surgical thrombectomy is rarely used in children and is restricted to the following situations (Table 9.3.6):

Table 9.3.6: Indications for surgical thrombectomy in children[260]

1. IVC thrombosis in association with intravascular extension of Wilms' tumour
2. Acute thrombosis of Blalock-Taussig shunt
3. Life-threatening intracardiac thrombosis immediately after complex cardiac surgery
4. Prosthetic valve thrombosis
5. Septic thrombosis
6. Peripheral artery thrombosis secondary to vascular access in neonates

9.3.7 Specific recommendations

Listed in Table 9.3.7 are the summarised recommendations from the 9th ACCP guidelines 2012 on antithrombotic therapy in neonates and children.[260]

Table 9.3.7: Antithrombotic Therapy and Prevention of Thrombosis in Children	
Recommendations	**Grade**
CVADs and UVCs associated with confirmed thrombosis	
Initial anticoagulation with LMWH or UFH followed by LMWH or supportive care with radiologic monitoring for extension	C
Start anticoagulation if extension occurs	C
Remove after 3 to 5 days of therapeutic anticoagulation rather than left in-situ	C
Total duration of anticoagulation of between 6 weeks and 3 months	C
If either a CVAD or UVC is still in place on completion of anticoagulation, prophylactic dose of anticoagulation should be given until catheter is removed	C
Unilateral renal vein thrombosis without renal impairment or IVC extension	
Initial anticoagulation with LMWH or UFH followed by LMWH or supportive care with radiologic monitoring for extension	C
Start anticoagulation if extension occurs	C
Total duration of anticoagulation of between 6 weeks and 3 months	C
Unilateral renal vein thrombosis with IVC extension	
Anticoagulation with LMWH or UFH/LMWH for 6 weeks to 3 months	C
Bilateral renal vein thrombosis with renal impairment	
UFH/LMWH or initial thrombolytic therapy with t-PA followed by UFH/LMWH	C
Neonates with CVADs	
Maintain patency with continuous infusion of UFH at 0.5 units/kg/h or intermittent local thrombolysis	C
Blocked CVADs	
Local thrombolysis after clinical assessment	C
Acute femoral artery thrombosis	
IV UFH or LMWH for 5 to 7 days	C

Limb-threatening or organ-threatening acute femoral artery thrombosis who fail to respond to initial IV UFH	
Thrombolytic therapy	C
Surgical thrombectomy if contraindication to thrombolytic therapy or limb death is imminent	C
Peripheral arterial catheters in-situ	
UFH continuous infusion at 0.5 units/mL at 1 mL/h	A
Peripheral arterial catheter-related TE	
Immediate removal of catheter	B
UFH or LMWH with or without thrombolysis or surgical thrombectomy	C
Neonates with UAC	
Prophylaxis with low-dose UFH infusion via UAC (heparin concentration 0.25-1 unit/mL, total heparin dose of 25-200 units/kg/day) to maintain patency	A
Cardiac catheterization via an artery	
IV UFH (100 units/kg bolus) as thromboprophylaxis or aspirin	A,B
Cerebral sino-venous thrombosis without significant intracranial haemorrhage	
UFH/LMWH or LMWH for between 6 weeks and 3 months	C
Cerebral sino-venous thrombosis with significant intracranial haemorrhage	
Supportive care with radiologic monitoring at 5 to 7 days	C
Anticoagulation if thrombus extends	C
First arterial ischaemic stroke (AIS) in the absence of documented embolic source	
Supportive care	C
First AIS with a documented embolic source	
Anticoagulation with LMWH or VKA for at least 3 months	C
Recurrent AIS	
Anticoagulant or aspirin	C

Idiopathic first VTE	
LMWH or UFH followed by VKA for 6 to 12 months	B
Provoked VTE	
Anticoagulant therapy for 3 months	C
Life or limb-threatening thrombosis	
Systemic thrombolysis or catheter-directed thrombolysis	C
Life-threatening VTE	
Surgical thrombectomy	C
Long-term home total parenteral nutrition	
Thromboprophylaxis with VKAs	C
Homozygous Protein C deficiency with purpura fulminans	
10 to 20 mL/kg of FFP every 12h or protein C concentrate at 20-60 uints/kg until lesions resolved	A
Long term VKA, LMWH, protein C replacement or liver transplantation	C,C,B,C
CVAD = Central Venous Access Devices UVC = Umbilical Venous Catheters VKA = Vitamin K antagonist	

9.4 FERTILITY TREATMENT AND VENOUS THROMBOEMBOLISM

9.4.1 Introduction

Worldwide, the use of assisted reproductive technology (ART) has increased exponentially over the past three decades and Malaysia has seen a similar trend. While ART is an umbrella term that refers to all fertility procedures, in-vitro fertilization (IVF) with concurrent ovarian stimulation is the most common form of ART that may result in venous thromboembolism.

9.4.2 Complication of ART

A known but rare complication of ART is arterial and venous thromboembolism. The incidence ofarterial and venous thromboembolic complications during IVF is approximately 0.1% of treatment cycles and has primarily been ascribed to the presence of ovarian hyperstimulation syndrome (OHSS).[263,327] This risk is even greater should the IVF cycle be successful.

Among IVF patients who conceived, women with a diagnosis of OHSS were at a 100-fold increased risk of VTE during the first trimester, whereas women without OHSS were at a five-fold increased risk as compared to pregnant women who conceived spontaneously.[328] Up to 31% of thromboembolic events occurred even in women who did not get pregnant.[263]

9.4.2.1 Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially fatal complication and occurs in its mild form in up to 33% of all IVF cycles. However, moderate or severe OHSS may complicate 3 to 8% of successful IVF cycles (see Table 9.4.2.1).[266,268,329]

Table 9.4.2.1: Classification of severity of OHSS[6]

Grade	Symptoms
Mild OHSS	Abdominal bloating Mild abdominal pain Ovarian size usually <8 cm
Moderate OHSS	Moderate abdominal pain Nausea ± vomiting Ultrasound evidence of ascites Ovarian size 8 - 12 cm
Severe OHSS	Clinical ascites (occasionally hydrothorax) Oliguria Haematocrit >45% Hypoproteinemia Ovarian size usually >12 cm
Critical OHSS	Tense ascites or large hydrothorax Haematocrit >55% White cell count >25 x 10^9/L Oliguria/ anuria Thromboembolism Acute respiratory distress syndrome

9.4.2.1.1 Pathogenesis of thrombosis in OHSS

The mechanism by which OHSS creates a prothrombotic state remains uncertain but may involve changes in coagulation factors, markers of fibrinolysis, high localised estrogen and the possible presence of rudimentary brachial cysts.

Venous events occur in approximately 75% of cases.[330] While arterial events usually occur concurrently with the onset of OHSS, at a mean of 10 days after the embryo transfer, venous events occur several weeks later even after the clinical resolution of OHSS, occurring at a mean of 40 to 42 days after the embryo transfer.[263]

9.4.2.1.2 Diagnosis of thrombosis following ART

Arterial thromboses are predominantly cerebrovascular accidents, whereas venous events are mostly reported in unusual sites such as the upper extremities.

In patients who develop unusual symptoms (neurological symptoms or neck pain) following ART, and especially in those who develop OHSS, the presence of arterial and venous thrombotic events should be considered and appropriate investigations carried out.

9.4.2.1.3 Treatment of thrombosis following ART

Patients who develop venous thrombosis should be treated with therapeutic LMWH throughout pregnancy and for up to six weeks postpartum.

All patients who develop venous thrombosis should be monitored closely as approximately 10% of these patients may develop progression of thrombi, within days, even after they have been initiated on therapeutic coagulation.[267] Future studies are needed to determine the appropriate dosage of anticoagulation required.

9.4.3 Thromboprophylaxis in OHSS

There is no evidence to recommend routine use of thromboprophylaxis in all patients undergoing IVF. In patients who develop moderate to severe OHSS, thromboprophylaxis should be initiated. Consideration should be given to continue thromboprophylaxis for a minimum of 4 weeks beyond the resolution of symptomatic OHSS if the cycle is unsuccessful and possibly for up to 13 weeks duration if the patient conceives. It is recommended that this option is discussed with the patient taking into consideration that while the actual risk of thrombosis is small, the consequences may be significant and the use of thromboprohylaxis has cost implications.

Table 9.4.3: Thromboprophylaxis and treatment of VTE following ART

Recommendations	Grade
Thromboprophylaxis should be initiated In patients who develop moderate to severe OHSS	C
Thromboprophylaxis should be continued for a minimum of 4 weeks beyond the resolution of symptomatic OHSS if the cycle is unsuccessful and possibly for up to 13 weeks duration if the patient conceives (option discussed with patient)	C
Patients who develop venous thrombosis following ART should be treated with therapeutic LMWH throughout pregnancy and for up to six weeks postpartum	B

9.5 HORMONAL CONTRACEPTION AND VTE

9.5.1 Introduction

Combined hormonal contraception includes the combined oral contraceptive pills (COC), the combined hormonal patch, the combined hormonal ring and the combined injectable variety. The COC is by far the most commonly utilised form of combined hormonal contraception and therefore most data regarding the use of combined contraceptives are extrapolated from evidence from COC use. In addition to combined hormonal contraception, certain options may contain only a progestogen and is used either orally, an injectable or as an implant.[269-276]

9.5.2 Oral contraception and VTE risk

In women in the reproductive age group who do not use oral contraception, the risk of VTE is approximately 4 to 5/10,000 women-years. The risk of VTE amongst COC users is approximately twice that of non-users (9 to 10/10,000 woman-years – average across all brands studied).[274]

The risk of VTE is greatest in the first few months of starting COC, after which the risk falls although is still higher than among non-users until COC is stopped.[270-274] The risk returns to levels that of non-users within weeks of discontinuation.[274]

Both the estrogen and progestogen content of the combined oral contraceptive pill have been implicated in differences in venous thrombotic risk between products. However, even if these risks are real, the absolute difference in risk between products is small, because the background incidence of venous thromboembolism in young women is essentially low.[274]

Current use of drospirenone or cyproterone oral combined contraceptives increases the risk of VTE compared with second generation pills. In the context of contraceptive use, non-oral route of ethinyl-estradiol administration seems to be more thrombogenic than oral route.[274]

Venous thromboembolism appears to be higher in overweight users while the association with smoking is still controversial (smoking increases the risk of arterial thrombosis by 2 to 4 fold).[331] It is recommended that for women with a body mass index of 35 kg/m^2 or greater, the risks of CHC may outweigh the benefits. For women aged over 35 years who are current smokers or who have stopped smoking less than 1 year ago, the use of CHC is not recommended.[332]

Table 9.5: Combined hormonal contraception	
Recommendations	**Grade**
Healthcare professionals should be aware that when compared to non-users, the risk of VTE with use of Combined Hormonal Contraceptives (CHC) is approximately double. However, the absolute risk is still very low	B
Healthcare professionals who prescribe CHCs should be guided by their individual preferences, risk of VTE, presence of contraindications, likely non-contraceptive benefits and experience with other contraceptive formulations	B
A history of VTE or a known thrombogenic mutation is a contraindication to the use of CHC	B
For women with a family history of VTE, a negative thrombophilia screen does not necessarily exclude all thrombogenic mutations	B
A thrombophilia screen is not recommended routinely before prescribing CHC	C

9.5.3 Medical Eligibility Criteria for Contraceptive Use

The 'Medical eligibility criteria for contraceptive use' is an evidence-based family planning guideline produced by the World Health Organization that provides guidance regarding "who" can use contraceptive methods safely.[276]

Medical Elligibility	Category
A condition for which there is no restriction for the use of the contraceptive method	1
A condition where the advantages of using the method generally outweigh the theoretical or proven risks	2
A condition where the theoretical or proven risks usually outweigh the advantages of using the method	3
A condition which represents an unacceptable health risk if the contraceptive method is used	4

Medical Eligibility Criteria for common hormonal contraceptives					
	COC	POP	DMPA NET-ET	LNG/ETG IMPLANTS	LNG IUD
History of DVT/ PE	4	2	2	2	2
Acute DVT/ PE	4	3	3	3	3
DVT/ PE and established on anti-coagulant therapy	4	2	2	2	2
Family history (first-degree relatives <45 years)	3	1	1	1	1
Family history (first-degree relatives ≥45 years)	2	1	1	1	1
Major surgery with prolonged immobilization	4	2	2	2	2
Major surgery without prolonged immobilization	2	1	1	1	1
Minor surgery without immobilization	1	1	1	1	1
Known thrombogenic mutations	4	2	2	2	2
Varicose veins	1	1	1	1	1
Superficial thrombophlebitis	2	1	1	1	1

Glossary
Combined Hormonal Contraceptives (CHC) includes the combined oral contraceptives (COC), the combined contraceptive patch, the combined contraceptive vaginal ring and the combined injectable contraceptives. All these options other than the COC are relatively new. Therefore only the COC is alluded to.
POP: progestogen-only pills

DMPA NET-EN: depot medroxyprogesterone or acetate norethisterone enantate
LNG/ETG: levonorgestrel and etonogestrel implants
LNG-IUD: levonorgestrel-releasing IUD (20 µg/24 hours)

9.6 VENOUS THROMBOEMBOLISM AND CANCER

9.6.1 Introduction

Venous thromboembolism poses a significant clinical problem in patients with cancer. Nearly all patients with active malignancy demonstrate some degree of activation of coagulation resulting in a hypercoagulable state. Underlying malignancy accounts for one in four symptomatic VTE. More significantly, cancer associated VTE has a high 28-day case-fatality rate of 25%.[280]

VTE is an independent poor prognostic factor for patients with cancer. Patients with cancer diagnosed at the same time of acute VTE have a greater likelihood of distant metastases and lower survival rates. The activated coagulation cascade associated with VTE is thought to promote angiogenesis and metastases. There is now evidence to suggest that LMWH treatment could delay metastases in different tumours and improve survival.[281,282,284]

9.6.2 Pathophysiology of cancer-related thrombosis

The natural history of VTE in cancer patients is different from non-cancer patients. It usually presents with larger and more significant thrombus, greater clinical deterioration despite anticoagulation therapy and a higher recurrence rate. VTE in cancer patients should also not be considered as a 'one off' event but rather, a recurring complication with prognostic implications; the factors that predispose a cancer patient to VTE usually persist till the patient is in remission.[285,287]

The mechanisms of VTE in patients with cancer are summarized in Table 9.6.2.[278]

Table 9.6.2: Mechanisms of VTE in Cancer Patients

Tumour-associated	Non-tumour associated
Extrinsic vascular compression & invasion	Central venous access devices
Tissue factor production	Anti-neoplastic mediated platelet activation
Cancer pro-coagulant production	Anti-neoplastic mediated endothelial cell damage
Accentuated platelet activation	Anti-angiogenesis therapy
Inflammation-mediated increases in factor VIII, vWF and fibrinogen	Anthracycline-induced congestive heart failure
Impaired fibrinolysis due to high PAI-1	Immobility
Acquired deficiencies of natural anticoagulants	

9.6.3 Management of VTE in cancers

Low molecular weight heparin is the treatment of choice for the initial and long-term therapy of patients with cancer.[288,289] Patients with cancer are not only at increased risk of developing VTE but also at significant risk of recurrent VTEs. Therefore, indefinite anticoagulation or until the cancer is resolved is recommended.[279]

Many studies have shown that LMWH has superior efficacy with lower recurrence rate and no increase in bleeding compared to warfarin.[281,282,284,291] Interestingly, in the CLOT study, the majority of recurrent VTE occurred in patients on warfarin with INR of >2.[284]

9.6.4 Gynaecological cancers

9.6.4.1 Thromboprophylaxis

Gynaecological cancer patients undergoing surgery are at significant risk of developing VTE. Post-operatively, extended duration of LMWH (from 7 to 28 days after surgery) has been shown to significantly reduce the incidence of DVT.[277] Consequently, thromboprophylaxis with extended duration LMWH should be considered in all patients undergoing surgery for gynaecological malignancy.[286]

9.6.4.2 Treatment of VTE in patients with gynaecological cancers

Low molecular weight heparin instead of UFH should be used for the treatment of VTE in gynaecological cancers.[283] Tinzaparin has been shown to be effective with a once daily dosing.[290] There is no direct evidence that rivaroxaban is superior to LMWH in patients with cancer but may be an alternative especially in patients who decline regular injections with LMWH.[1]

Table 9.6.4: Prevention and Treatment of VTE in Cancers

Recommendations	Grade
Extended thromboprophylaxis with LMWH should be considered in all patients undergoing gynaecological oncology surgery	A
LMWH instead of UFH should be used for treatment of VTE in patients with cancers	A
In patients with cancers and confirmed VTE, indefinite anticoagulation should be considered or at least until the cancer is resolved	B

9.7 THROMBOSIS IN UNUSUAL SITES

9.7.1 Introduction

Thrombosis in sites such as the upper limb, cerebral venous sinuses or splanchnic veins are uncommon. Management with anticoagulation is important as complications can be life or limb threatening.

9.7.2 Upper Limb DVT

Upper limb DVT is relatively unusual and most cases are secondary to a venous catheter, malignancy, compression of the vein or OHSS. There may also be a history of unaccustomed upper limb exercise.[294]

In patients with upper limb DVT without underlying risk factors (e.g. anti-phospholipid syndrome or cancer), the risk of recurrence is significantly less than lower limb DVT (2% v.s. 19% at 5 years).[295] Prolonged anticoagulation beyond 3 months is generally not indicated for upper limb DVT.[295]

9.7.3 Cerebral Vein Thrombosis

Thrombosis of the cerebral veins and sinuses is uncommon with an estimated annual incidence of 3 to 4 per million. The majority of patients make full recovery although there is an early in-hospital fatality rate of about 5% and an overall mortality rate of approximately 10%.[296]

Anticoagulation with heparin and with or without warfarin results in lower mortality and dependency when compared to no anticoagulation with an absolute reduction in the risk of death of 13%. There was no new or enlarging cerebral haemorrhage with anticoagulation.[298] Clinical use of thrombolytic therapy in cerebral sinus thrombosis cannot be supported as there is insufficient evidence.[297]

Long-term cohort follow-up studies indicate that recurrent cerebral vein thrombosis is uncommon perhaps because many initial events occur in young patients with temporary precipitating factors (e.g. hyperemesis gravidarum).[292,293] Furthermore, the presence of heritable thrombophilia does not influence the recurrence risk. Therefore, long-term anticoagulation should not be necessary in most patients.[297]

9.7.4 Splanchnic Vein Thrombosis

Thrombosis of hepatic, portal and mesenteric veins is rare and most often associated with an underlying myeloproliferative neoplasm (especially for hepatic and portal vein thrombosis) or local or systemic inflammation.[296]

Case series and cohort studies indicate a mortality rate of around 10% and a recurrence rate of 18% at 41 months in non-anticoagulated patients.[296] Approximately 40% of patients with underlying myeloproliferative neoplasms suffered a recurrent thrombosis. Anticoagulation reduces recurrence and was associated with recanalisation in 45% of patients.[297]

The presence of liver cirrhosis and/or portal hypertension with oesophageal varices and hypersplenism with thrombocytopenia, the sequelae to splanchnic vein thrombosis further increase the risk of bleeding should anticoagulation be prescribed.[297]

9.7.5 Incidental thrombosis at imaging

In patients with incidentally detected hepatic or portal vein thrombosis, no anticoagulation is recommended.[170,297] In patients with incidentally detected thrombosis at imaging for the staging of a cancer e.g. subclavian vein thrombosis associated with a mediastinal lymphoma, anticoagulation with LMWH is recommended as long as the cancer is present and is causing the obstruction with a minimum duration of 3 months.[170,295]

Table 9.7: Recommendations in the management of thrombosis in unsual sites[170,297,299]

Recommendations	Grade
Upper limb DVT	
In patients who have upper extremity DVT that is associated with a central venous catheter that is removed, anticoagulation for a duration of 3 months is recommended	B
Patients with upper extremity DVT without underlying risk factors such as anti-phospholipid syndrome or cancer do no require extended anticoagulation beyond 3 months	B
Cerebral sinus thrombosis	
Patients with cerebal sinus thrombosis do no require extended anticoagulation beyond 3 months	B
Splanchnic vein thrombosis	
Patients with acute splanchnic vein thrombosis should have treatment for any underlying disease and be considered for anticoagulation after careful assessment of individual risks and benefits	B
In patients with incidentally detected hepatic or portal vein thrombosis, no anticoagulation is recommended	C

10.0 MEDICATION THERAPY ADHERENCE CLINIC-WARFARIN (MTAC-W)

10.1 INTRODUCTION[300,301]

1. Warfarin therapy for the prevention and treatment of thromboembolic diseases is safe and effective only when it is maintained within a narrow therapeutic window.[300,301]

2. Existing evidence suggests that management of warfarin sodium by pharmacist-managed anticoagulation clinics is more likely to attain the desired patient outcomes in term of percentage of time in therapeutic and expanded range, reduced rates of thromboembolic and bleeding episodes and reduce costs per person-year of follow-up than routine medical care by physicians although both models of care provided very high quality oral anticoagulation management.[301]

3. In Malaysia, pharmacist-managed physician-supported anticoagulation clinic is called Medication Therapy Adherence Clinic-Warfarin (MTAC-W). It was introduced in 2004 in Malaysia as part of clinical pharmacy services in the Ambulatory Clinic System.

4. MTAC-W service is designed to coordinate and optimize the delivery of anticoagulant therapy by determining the appropriateness of therapy, managing warfarin sodium dosing, and providing continuous monitoring of patients' INR results, dietary factors, concomitant medications and interfering disease states.

5. The patients' primary physicians retained responsibility for overall care and were consulted by pharmacists regarding complications of anticoagulation and patient unreliability.

6. Clinical pharmacists in-charged provided patient education, monitored patients for hemorrhagic and thromboembolic complications, and adjusted warfarin sodium dosage to maintain therapeutic INR.

7. This document sets out standardised guidelines for the operation of MTAC-W clinic incorporating MTAC- Warfarin Protocol published by Pharmaceutical Services Division, MOH Malaysia.[302]

10.2 NATIONAL GUIDANCE AND ADDITIONAL RESOURCES

1. Protocol-Medication Therapy Adherence Clinic: Warfarin. Pharmaceutical Services Division, Ministry of Health Malaysia. First Edition 2010.

2. Guidelines on Oral Anticoagulation: Third edition. British Journal of Haematology 3rd edition 1998;101,374-387

10.3 OBJECTIVES

1. To provide continuity and enhance patient care through education, monitoring, and close follow-up to patients who require anticoagulation therapy.

2. To maximize the benefits of antithrombotic therapy and minimize the adverse effect and complications resulting from antithrombotic therapy.

3. Assist physicians in the management of patient prescribed with anticoagulant therapy.

4. Serve as an information resource for patients and family/care provider.

5. Provide consultative and educational services to physicians, dentists, and other healthcare providers on antithrombotic drug management and related issues.

10.4 RESPONSIBILITIES OF THE CLINICAL PHARMACIST IN-CHARGE[302]

1. Ensure patient receive education regarding warfarin at the initial visit and reinforce this education at each visit.

2. Be aware of the potential effects of additional therapy (drug/herbal/supplement/elective procedure) given to a patient on anticoagulants, and arranging earlier INR testing as required.

3. Ensure patient receive appropriate INR monitoring and make dosage recommendation guided by the approved protocol (Appendix 1)

4. Transcribe warfarin prescriptions:
   a. This activity should be done based on the agreement by the hospital management and the doctor in-charge. The doctor must be aware that the final responsibilities for the prescription should be liaised with the doctor. Prescription has to be initiated by the pharmacist and counter-signed by the doctor.

   b. Act promptly to patients with bleeding problems and/or INR >4 or who are otherwise considered to be at risk of bleeding.

5. The patient shall be referred to the physician in the following situations:
   a. Actual or suspected signs and symptoms of severe haemorrhage regardless of the INR value.

   b. Actual or suspected signs and symptoms of thromboembolism.

   c. INR values over 4.0 or values less than 1.0 (INR range at the discretion of the respective hospital)

   d. INR <1.5 for patients with prosthetic valve replacement.

   e. When the duration of therapy has been completed.

   f. When patients consistently miss appointments or remain non-compliant to therapy.

6. Ensure correct dispensing of warfarin tablets in the clinic to the patients/care givers.

7. Ensure all patients have been given warfarin booklet.

8. Ensure at the end of the session, a summary of important information is provided to the patients and their understanding is reassessed.

10.5 MANPOWER REQUIREMENT[302]

At least one pharmacist should be placed in the clinic. The pharmacist should spend an average of 10 to 15 minutes per case but longer time (around 30 minutes) will be needed for newly referred cases.

10.6 APPOINTMENT

All appointment will be scheduled by pharmacists in-charge of the clinic.

10.7 WORK PROCEDURES

The workflow of MTAC Warfarin is as shown in Appendix 2.

10.8 PATIENT SELECTION

1. Adult patients who are currently on warfarin therapy as out-patient from any relevant disciplines (as agreed by the individual institution)

2. All new cases shall be referred by physicians using the standardised referral form (MTAC_Warfarin/F1: Appendix 3). For patient started on warfarin therapy in the ward, referrals should be made prior to the discharge.

3. Patients who are 'stable' and considered appropriate for management at the MTAC-Warfarin.

4. Complex high risk patients need to be identified and assessed for the appropriateness of monitoring at the MTAC-W. Some of these conditions may be referred back to the doctor:[303]

    a. A known hereditary or acquired bleeding disorder (Discuss with Consultant Haematologist)

    b. Alcoholics due to instability in anticoagulation management

    c. Severe malnourishment due to absorption difficulties

    d. Mentally ill with no carer support in the community

    e. Dementia with no carer support in the community

    f. Liver failure

    g. Severe renal impairment

    h. Documented evidence of CNS haemorrhage

i. Severe heart failure

j. Uncontrolled severe hypertension

k. Gastric-intestinal bleeding in the last 6 months

l. Pregnancy (Urgent referral to appropriate Haematologist/Consultant Obstetrician)

m. Those on chemotherapy for malignant tumours (consider LMWH)

n. Homozygous protein C deficiency (high risk of skin necrosis)

10.9 INR TESTING

1. The method for INR monitoring should be determined by individual institution and blood sampling for INR reading should be performed by trained healthcare staff.

2. Two methods available: Point-Of-Care (Fingerstick/Coagucheck XR) or laboratory testing.

3. INR results from 2 methods are said to be in reasonable agreement if the two results are within 0.5 INR units of each other.[304]

4. Certain conditions can interfere with the INR test e.g. anti-phospholipid antibody syndrome which may cause the INR to be falsely high.[304,305] Such interference can wrongly suggest patient being over-warfarinised. Alternative laboratory test called the chromogenic factor X level, which is a measure of warfarin effect that is not altered by the anti-phospholipid antibodies may offer more accurate testing.

10.10 PATIENT COUNSELLING

1. Patient education is imperative to ensure safe and effective use of warfarin therapy. All new patients to MTAC-W should have the warfarin counseling checklist completed and being given a comprehensive warfarin education based on their level of understanding.

2. Each patient should be provided with a MOH-approved warfarin booklet and/or other compliance aids.

3. Existing patients may benefit from PERIODIC educational efforts reinforcing key medication safety information, even after initial education and ongoing monitoring.[306]

4. Incorporating patient anecdotes into physician-patient dialogues or educational materials may increase the effectiveness of the message.[306]

5. Patient education should include the following:
   a. Drug name, strength and description of tablet
   b. Current dosage and administration time
   c. Reason for taking warfarin and how it works
   d. Therapeutic goals and the anticipated length of treatment
   e. How to handle missed doses
   f. Medications/supplements and dietary interactions
   g. Recognition of symptoms of bleeding/thrombosis, adverse reactions and the appropriate procedures to follow
   h. Importance of adherence to drug regimen and clinic appointments
   i. Emphasis on the importance of follow up and documentation
   j. What to do if dental treatment/surgery is required
   k. What to do if surgery is indicated/required
   l. Patient education on the use of warfarin in pregnancy and lactation (if related)
   m. Who to contact regarding any worries or concerns relating to their warfarin therapy.
6. Patient education checklist is provided in Appendix 4.

10.11 MONITORING AND EVALUATION

1. Patient's response to warfarin therapy should be evaluated based on INR results and information gathered from patient's interview.
2. Two documents are used: First Visit Form (MTAC_Warfarin/F2: Appendix 5) or Follow-Up Visit Form (MTAC_Warfarin/F3: Appendix 6).
3. The following criteria should be assessed to check/evaluate patient's response to warfarin therapy and detect any potential problems prior to dosage adjustments:
   a. Signs and symptoms of haemorrhage and thromboembolism
   b. Change in condition(s) requiring warfarin therapy
   c. Recent alterations in diet,medications, tobacco or alcohol intake
   d. Alterations in other medical problems or recent illnesses
   e. Adherence to warfarin therapy
   f. Patient undergoing surgical or dental procedures

10.12 DOSAGE ADJUSTMENT

1. Marked individual inter-variability exists for the metabolism of warfarin. Patient's genetic make up, disease states and other concurrent medications also affect the response of warfarin in different patient. Therefore, the response in individual cannot be reliably predicted.

2. The warfarin dose should be selected to maintain INR within the range according to current guidelines established by the American College of Chest Doctors Consensus Conference on Antithrombotic Therapy (ACCP 2012).

3. Dosage adjustments should be guided by clinically approved protocol and individualized according to clinical judgement.

4. Dose adjustments should be considered in the following instances:
   a. When two consecutive INR values are sub-therapeutic or

   b. Supra-therapeutic when prior control has been good(+/- 0.2 of target INR range)

   c. When patients has just been referred for follow up after the initiation of anticoagulation

   d. When there is indication to adjust the dose due to warfarin-drug/supplement/herbal/diet/disease-state interactions. (List of warfarin-drug interactions in Appendix 7)

5. Compliance and patient satisfaction is highest with whole tablet warfarin regimen.[307,308]{e.g. 5 mg once daily}

6. Higher patient satisfaction is associated with split tablet regimen indicating that alternating dose regimen makes taking their medications more difficult.[307,308]

10.13 DISPENSING

1. Warfarin will be dispensed in the MTAC-W clinic to the patients/care givers.

2. Patients should be dispensed with the correct dose and quantity of warfarin tablets and re-emphasised on the correct dose, route and time of administration.

3. The pharmacist will need to update the MOH warfarin booklet giving dosage instructions to include details of dose, frequency, colour and number of tablets e.g. 7 mg once a day (2 x 3 mg – blue tabletsand 1 x 1 mg - brown tablets).

4. Standardised label as in Appendix 8 isused upon dispensing.

5. Warfarin Dosing Note (Appendix 9) is attached to the patient's Warfarin Booklet to facilitate warfarin administration.

6. At the end of the session, a summary of important information is provided to the patients and their understanding is assessed.

10.14 MISSED APPOINTMENTS

1. Patients who missed the scheduled appointment should be contacted at the end of clinic day or the next working day to reschedule a new appointment. A 'Missed Appointment' sheet (Appendix 10) should be filled and filed in the patient's medical record.

2. Patients who have missed appointment for more than 3 consecutive times or more than 1 month from the scheduled appointment shall be referred back to the respective clinicians.

10.15 DOCUMENTATION

1. MTAC Warfarin Referral Form (MTAC_Warfarin/F1)

2. MTAC Warfarin First Visit Form(MTAC_Warfarin/F2)

3. MTAC Warfarin Follow-up Visit Form(MTAC_Warfarin/F3)

4. Missed Appointment Sheet(MTAC_Warfarin/F4)

10.16 QUALITY ASSURANCE

1. This service should be continuously assessed to ensure patients receive optimal care.

2. Outcome measurement from anticoagulation therapy will include percentage of patients achieving INR goal, response to therapy, adverse events and general evaluation on patients understanding towards therapy.

APPENDICES

Appendix 1

WARFARIN DOSAGE ADJUSTMENT
WARFARIN THERAPY INITIATION GUIDELINES

1.0 Dosing Initiation

1. In patients beginning warfarin therapy, the initiation dose may start with doses between 5 and 10 mg for the first 1 or 2 days for most individuals and subsequent dosing based on the INR response.

2. In elderly patients or in patients who are debilitated, malnourished, have CHF, have liver disease, have had recent major surgery, or are taking medications known to increase the sensitivity to warfarin (e.g. amiodarone), the starting dose should be of <5 mg with subsequent dosing based on the INR response.

2.0 Monitoring

1. Baseline PT/INR/PTT, full blood count (FBC) with platelets and liver function test (LFT) shall be obtained prior to warfarin initiation. If baseline level not available, it should be obtained within 24 hours.

2. In hospitalised patients, INR monitoring is usually performed daily, starting after the second or third dose until the target therapeutic range has been achieved and maintained for at least 2 consecutive days; then two or three times weekly for 1 to 2 weeks; then less often, depending on the stability of INR results.

3. In outpatients starting warfarin therapy, initial monitoring may be reduced to every few days until a stable dose response has been achieved. When the INR response is stable, the frequency of testing can be reduced to intervals as long as every 4 to 8 weeks.

3.0 Suggested algorithm for initiating warfarin (Goal INR 2-3)*

Day	INR	Dose (mg)	
		Age <70 years	Age >70 years
1		5	3
2		5	3
3	<1.2	6-8	4
	1.2 - 1.5	5	3
	1.5 - 2	3	2
	2 - 3	2	1
	>3	Nil	Nil
4	<1.3	6	5
	1.3 - 1.5	5	4
	1.5 - 1.7	4	3
	1.7 - 2	3	2
	2 - 2.5	2.5	1.5
	2.5 - 3	2	1
	3 - 3.5	1.5	Omit 1 day, then 1 mg
	3.5 - 4	Omit 1 day, then 1 mg	Omit 1 day, then 1 mg
	>4	Omit 2 days, then 0.5 mg	Omit 2 days, then 0.5 mg

* Deviation from this algorithm may be necessary for goal INR 2.5 - 3.5

Adapted from:

1. The University of Michigan Cardiovascular Center, Anticoagulation Mnagement Service for Health Professionals Guideline, Revised 10/08/08
2. Singapore General Hospital, Warfarin Treatment Guidelines and Prescription Chart. Revised January 2009

WARFARIN DOSE ADJUSTMENT GUIDELINES

Target INR 2.5 (Range 2.0 - 3.0)						
Patient's INR	**<1.5**	**1.5 - 1.9**	**2.0 - 3.0**	**3.1 - 3.9**	**4.0 - 4.9**	**>5.0**
Dose change	Increase 10 - 20%	Increase 5 - 10%	No change	Decrease 5 - 10%	Hold 0 - 2 days and decrease 10%	Refer to appropriate algorithm
Next INR	3 - 8 days	7 - 14 days	See follow-up algorithm	7 - 14 days	3 - 8 days	

Follow-up Algorithm	
No. of consecutive in-range INRs	**Repeat INR in**
1	5 - 14 days
2	2 - 3 weeks
3	4 - 8 weeks

* If INR 1.8 - 1.9, consider no change with repeat INR in 7 - 14 days
** If INR 3.1 - 3.2, consider no change with repeat INR in 7 - 14 days

Target INR 3.0 (Range 2.5 - 3.5)						
Patient's INR	**<1.5**	**1.5 - 2.4**	**2.5 - 3.5**	**3.6 - 4.4**	**4.5 - 4.9**	**>5.0**
Dose change	Increase 10 - 20% Consider extra dose	Increase 5 - 10%	No change	Decrease 5 - 10% Consider holding 1 dose	Hold 0 - 1 days and decrease 10%	Refer to appropriate algorithm
Next INR	4 - 8 days	7 - 14 days	See follow-up algorithm	7 - 14 days	4 - 7 days	

Follow-up Algorithm	
No. of consecutive in-range INRs	**Repeat INR in**
1	5 - 14 days
2	2 - 3 weeks
3	4 - 8 weeks

* If INR 2.2 - 2.4, consider no change with repeat INR in 7 - 14 days
** If INR 3.6 - 3.8, consider no change with repeat INR in 7 - 14 days

Notes:
1. Always consider trend in INRs when making warfarin management decisions. Exclusion of factors affecting INR must be done prior to dosage adjustment
2. Consider repeating INR same day or next day if observed value markedly different than expected value (Potential for lab errors exist)
3. Dose should be rounded up to nearest 0.5 mg
4. Maximum changes of daily dose is + 1.0 mg

Adapted from:
The University of Michigan Cardiovascular Center, Anticoagulation Management Service For Health Professionals Guideline, Revised 10/08/08

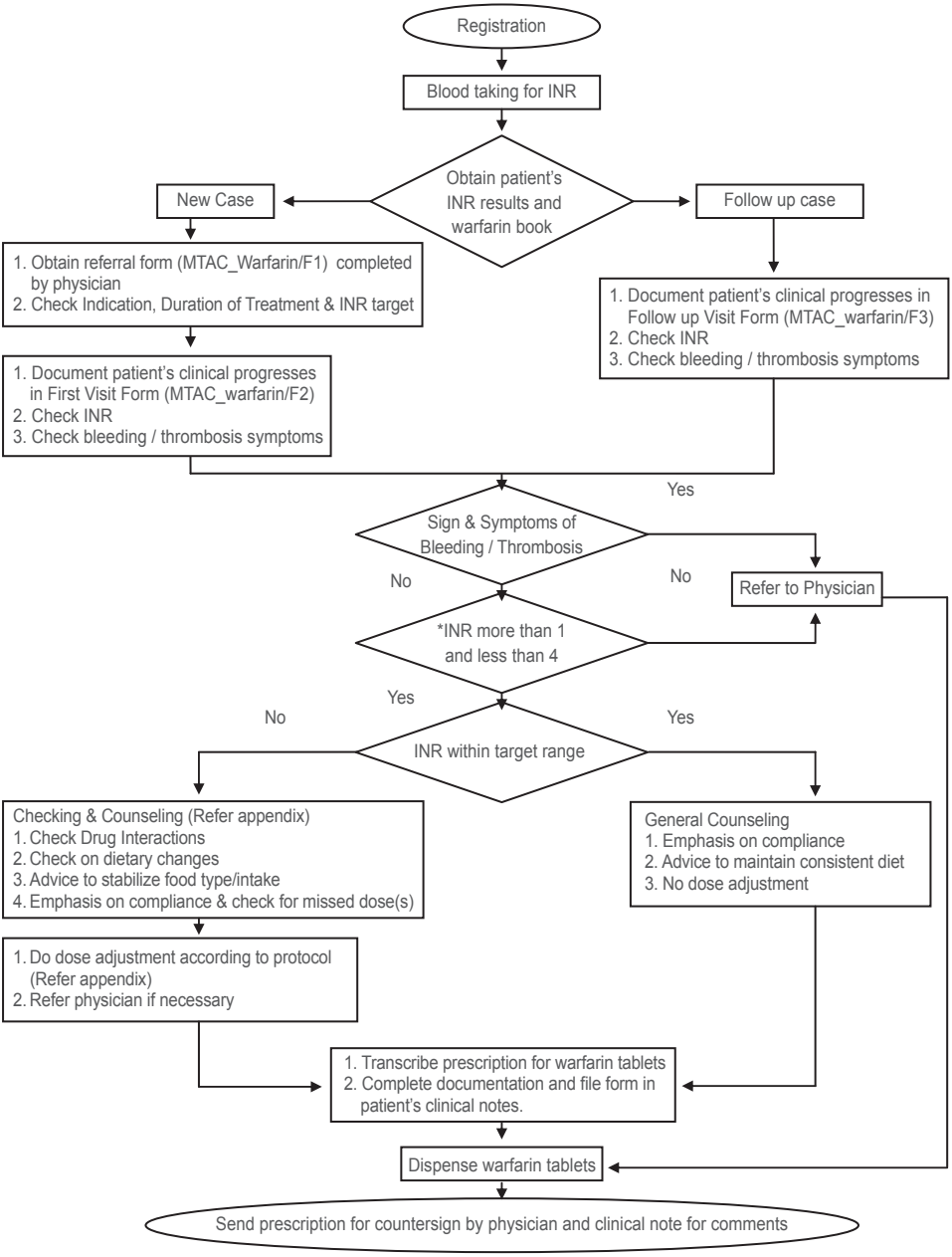
GUIDELINE FOR TREATMENT OF PATIENT OVER-ANTICOAGULATED WITH WARFARIN

INR	Clinical Setting	Recommendations
<5.0	No bleeding	Lower dose or omit dose, monitor more frequently and resume at a lower dose when the INR is therapeutic. If only minimally above therapeutic range, no dose reduction may be required.
	Rapid reversal required	E.g. Patient require urgent surgery. Hold warfarin and give vitamin K 1 mg IV infusion or 2 mg PO.
5-8.9	No bleeding	Omit one or two doses, monitor more frequently and resume warfarin at lower dose when INR is therapeutic. Alternatively, omit dose and give vitamin K (≤5 mg orally), particularly if at increased risk of bleeding.
	Rapid reversal required	Hold warfarin and give Vitamin K 1-2 mg IV infusion or 2-5 mg PO, with the expectation that a reduction of INR will occur in 24h.
>9.0	No bleeding	Hold warfarin until INR in therapeutic range and give vitamin K (2.5-5 mg PO or 1-2 mg IV infusion), with the expectation that the INR will be substantially reduced in 24-48h. Monitor frequently and use additional vitamin K if required. Resume therapy at lower dose when INR therapeutic.
	Rapid reversal required	Hold warfarin and give vitamin K 1-10 mg IV and may repeat 6-24h as necessary.
Any INR	Serious bleeding	Hold warfarin and give vitamin K (10 mg slow IV) and supplement with FFP (fresh frozen plasma) or PPC (prothrombin complex concentrate), depending on the urgency of the situation. Recombinant factor VIIa may be considered as alternative to PCC; vitamin K can be repeated every 12h.
Any INR	Life-threatening bleeding	Hold warfarin and give PPC (prothrombin complex concentrate) supplemented with vitamin K (10 mg slow IV); recombinant factor VIIa may be considered as alternative to PCC; repeat if necessary, depending on INR.

Source: The 8th Edition ACCP Conference on antithrombotic and thrombolytic therapy Evidence-based guidelines. CHEST June 2008.

Appendix 2

MTAC WARFARIN CLINIC WORKFLOW



*INR range is based on agreement between Head of Cardiology/Medical/Hematology and pharmacy department.

Appendix 3

MTAC-WARFARIN: REFERRAL FORM MTAC-W/F1

Date:

Patient Details

Name:			Age:	Race: M / I / C / O
MRN:	IC No:	Gender: M / F	Phone No:	

Warfarin Therapy

Target INR Range

¤ 1.5 - 2.5 ¤ 2.0 - 3.0 ¤ 2.5 - 3.5

¤ Other (please specify):

Date warfarin started:

Anticipated Duration:

Anticipated Stop Date:

Warfarin Indication

¤ Arterial Embolism
¤ Cerebrovascular Accident
¤ Heart Valve Replacement (describe):
¤ Pulmonary Hypertension
¤ Transient Ischaemic Attack
¤ Other (please specify):

¤ Atrial Fibrillation
¤ Deep Vein Thrombosis (describe):
¤ Pulmonary Embolism
¤ Coagulopathy (Derscribe);
¤ Venous Thrombosis of other specific Vein

Clinical Information

Is this patient on Antiplatelet Drugs? Yes / No

o AspirinIs this to continue during anticoagulation: Yes / No
o Clopidogrel
o Other (please specify): ……

Concurrent Illness

¤ CAD ¤ Diabetes ¤ GI bleeds ¤ Heart Failure ¤ Hypertension
¤ Hyper/Hypothyroidism ¤ Liver disease ¤ Peptic Ulcer disease ¤ Renal Impairment ¤ Seizure Disorder
¤ Other (please specify):

Bleeding Risk Factors (Tick all that applies)[1]

1 Age ≥65	(1 point)	4	One/more of the following: (1 point)
2 History of stroke	(1 point)		¤ Recent MI ¤ Cr >133 umol/L
3 History of gastrointestinal bleeding	(1 point)		¤ Hct <30% ¤ Diabetes

Classify Your Patient Overall Bleeding Risk (Total of 1-4)

¤ High Risk (3 - 4 Points) ¤ Intermediate Risk (1 - 2 Points) ¤ Low Risk (0 Point)

Concurrent Drug Therapy

Name	Dose	Freq

Name	Dose	Freq

Comments:

Physician Review & Notes

Referring Physician's Signature and Chop:

1. Beth RJ, Quinn LM, Landefeld SC. Prospective Evaluation of an Index for Predicting the Risk of Major Bleeding in Outpatients Treated with Warfarin..AM J Med.1998;105:91-99

Appendix 4

CHECKLIST FOR WARFARIN COUNSELLING

✔ *Use layman terms throughout; medical terms are in parenthesis.*
✔ *Italicized notes should only be addressed if asked by the patient.*

☐ Introduction

- Name_____
- Pharmacist from……
- " I'm here to educate you a new drug you will be starting soon called warfarin"
- "Have you been told what this drug is for?"

☐ Warfarin is…

- A blood thinner also known as an anticoagulant.
- Decreases formation of blood clots
- Blood clots can cause a stroke, heart attack, or blood clots in the legs *(DVT) or lungs (PE).*
- *MOA: the liver makes clotting factors to help the blood clot and prevents you from bleeding. With some serious conditions, your blood can clot too much. Warfarin blocks the clotting factors made by the liver, preventing your blood from clotting (thins your blood). Formation of clotting factors are dependent on vitamin K. Therefore, taking more vitamin K than usual may decrease the effects of warfarin and may put you at risk for clot formation.*

☐ You are asked to take warfarin because…

- You just experienced _____
  - *A leg clot (DVT)*
  - *A lung clot (PE)*
  - *An arrhythmia (Atrial fibrillation)*
  - *A heart attack (MI)*
  - *The placement of a mechanical or bioprosthetic heart valve.*
- By taking warfarin, it will treat your _____ (current event) and prevent you from having another clotting event *(thromboembolic event)*.
- *OR*
- You are receiving a cancer treatment of thalidomide in combination with chemotherapy and dexamethasone - by taking warfarin, it will help to "to reduce the risk of getting a clot" which is sometimes associated with this group of patients.

☐ Your initial warfarin dose…

- Will be determined by your doctor.
- Your dose may change based on your regular blood tests.
- No matter what the dose, you must take your warfarin everyday and at the same time every day.
- If you miss a dose, take the dose as soon as you remember if within the same day. DO NOT double your dose the next day to make-up for the missed dose.
- Warfarin can be taken with food or on an empty stomach.

☐ Your regular blood tests…

- Will check your response to warfarin (is your blood too thin or not thin enough?; how quickly will you blood clot on the dose your on?)
- This blood test is called an INR test *(International Normalized Ratio)*.
- The goal is to keep your INR between a certain range that will be determined by your doctor. This will assure us that warfarin is effectively working.
  - *VTE (DVT, PE), A fib, post-MI, AVR without risk factors: INR range 2-3*
  - *MVR or AVR with risk factors (AF, low EF, previous embolism, hypercoagulable state): INR range 2.5-3.5.*
- If you fall out of this range, your warfarin dose may change.
- It is very important that you meet all of your appointments so the most effective dose is given to you.
- You may need to have your blood tested more frequently at first; however, once we determine your dose, your scheduled appointments will be less frequent.

☐ Possible side effects of warfarin are…

- Bleeding problems, allergies, liver problems, low BP, swelling, paleness, fever, and rash.
- If any of these side effects or other unusual events occur after the start of warfarin, alert your healthcare provider.
- THESE SIDE EFFECTS CAN BE PREVENTED AS LONG AS REGULAR BLOOD TESTS ARE DONE AND DIET IS CONSISTENT TO ASSURE AN APPROPRIATE DOSE IS GIVEN.
- The most concerning side effect is the bleeding, which is the result of the blood being too thin.
- Alert your healthcare provider if you have signs and symptoms of bleeding.
  - Pain, swelling, or discomfort
  - Headache, dizziness, or weakness
  - Bruising (careful with machinery, sharp object or aggressive sports)
  - Avoid activities that may cause bleeding (acupuncture, massage, cupping/ ‘bekam’)
  - Nosebleeds
  - Bleeding gums (careful when brushing teeth – use soft toothbrush)
  - Pink or brown urine
  - Red or black stools
  - Vomiting blood or material that looks like coffee grinds

☐ *Rare side effect include…*

- *Death of skin (RARE; skin necrosis or gangrene; can occur soon after starting Coumadin (3-8 days) because blood clots form and block blood flow to area of the body(high adipose tissue). Patients may be protein C deficient)*
- *Purple toes syndrome (MORE RARE; painful purple lesions on the toe; occurs 3-8 weeks after starting warfarin. Patients may have vascular atherosclerosis. Warfarin induces bleeding into the cholesterol plague and cholesterol crystal emboli are released and travel to the small arteries of the feet and hands).*

☐ **Many Rx/OTC/herbals/vitamins can interact with warfarin**

- Try to avoid NSAIDs (ibuprofen, naproxen) and aspirin for pain or inflammation as these can increase your risk for bleeding while on warfarin.
- Always alert your healthcare provider before starting or stopping any Rx/OTC/herbal/vitamin agents.

☐ **Many foods can interact with warfarin**

- Do you eat a lot of vegetables or salads?
- Large amounts of green leafy vegetables, which contain high amounts of vitamin K, can lower the effects of warfarin (vitamin K works against or antagonizes warfarin).
  - Kale
  - Parsley
  - Spinach
  - Turnip greens
  - Broccoli
  - Brussels sprouts
- Try to maintain a consistent diet, try to eat the same amount to leafy vegetables every day.
- Avoid cranberry juice or products and alcohol.
- Always alert your healthcare provider before making any changes to your diet.

☐ **Always alert any healthcare provider you interact with that you are on warfarin (surgical, medical, dental)**

☐ **Signs/symptoms of a stroke (for pts. with A.fib., CVA, post-MI, or valve replacements)**

- Facial droop
- Arm drift
- Slurred speech
- Weakness or numbness in extremities (usually unilateral, but may be bilateral)
- Abnormal or loss of vision (usually unilateral, but may be bilateral)
- Abnormal or loss of hearing (usually unilateral, but may be bilateral)
- Difficulty walking (unsteady gait)
- If you experience any of these symptoms go to emergency department immediately

☐ **Sign/symptoms of a DVT and PE (for pts. with either a DVT or PE)**

- DVT
  - Leg swelling
  - Leg pain/tenderness
  - Leg discoloration
  - Leg warm to the touch
  - Call your doctor immediately or go to the emergency room if you have any signs of a DVT

- PE
  - Sudden unexplained difficulty breathing
  - Cough
  - Rapid breathing
  - Rapid heart rate or palpitations
  - Chest pain when you breath in (pleuritic chest pain)
  - Anxiety
  - Go to emergency department immediately if you have any signs of a PE

☐ **Always alert your healthcare provider if you make changes in your diet, exercise, or Rx/OTC/herbals/vitamin use.**

☐ **Final verification of indication, dosing/administration, side effects, drug/food interactions, and appropriate signs/symptoms of VTE.**

Appendix 5

MTAC-WARFARIN: FIRST VISIT FORM MTAC-W/F2

Date of Visit:			
Patient Information			
Name:		Age:	Race: M / I / C / O
MRN:	IC No:		Gender: M / F
Address:		Telephone No Home / Office: Handphone:	
Anticoagulation Plan			
Indication:			
Target INR:		Initiation Date:	
Plan Duration:		Anticipated Stop Date:	
Risk Factors & Co-morbid conditions			
Risk Factors:		Co-morbid Medical Conditions:	

Medications

Current Medications			OTC / Supplement / Traditional Medicines
Name	Dose	Freq	

Objective Information

INR (Laboratory):	Current Warfarin Regimen:
INR (Point of Care):	Total mg / week:

Subjective Information

Signs of bleeding: Y / N (Describe if Yes)	Signs of thrombosis: Y / N (Describe if Yes)
Correct dose taken: Y / N Mon | Tues | Wed | Thurs | Fri | Sat | Sun (| | | | | |)	Missed doses in past 1 week: Y / N (Specify if Yes)
Changes In Medical Status / Illness: Y / N (Describe if Yes)	Medications Changes: Y / N (Describe if Yes)
Change in Physical Activity: Y / N (Specify if Yes)	Diet / Herbal / Supplements changes: Y / N (Specify if Yes)

1. Pregnancy / plan to get pregnant?
   No
   Yes: Is doctor aware? If no, refer to doctor

2. Alcohol consumption?
   No
   Yes: amount & frequency?

3. Smoker?
   No
   Yes: How many sticks/day? Any changes in smoking habit (stop or just started smoking)

Other complain / Patients Plans: Y / N
(Describe if Yes)

Assessment

Is INR therapeutic: Y / N
Describe:

Pharmacist Review / Plan

Pharmacist's Signature and Chop

Physician Review & Notes

Physician's Signature and Chop

Appendix 6

MTAC-WARFARIN: FOLLOW-UP FORM MTAC-W/F3

<table>
<tr><td colspan="2">Date of Visit:</td></tr>
<tr><td colspan="2">Patient Information</td></tr>
<tr><td colspan="2">MRN / IC:</td></tr>
<tr><td colspan="2">Age:</td></tr>
<tr><td colspan="2">Diagnosis / Indication:</td></tr>
<tr><td colspan="2">Missed appointments: Y / N
(Explain if Yes)</td></tr>
<tr><td>Same Indication: Y / N
(Describe if No)</td><td>SameTarget INR: Y / N
(Describe if No)</td></tr>
<tr><td colspan="2">Objective Information</td></tr>
<tr><td>INR (Laboratory):</td><td>Current Warfarin Regimen:</td></tr>
<tr><td>INR (Point of Care):</td><td>Total mg / week:</td></tr>
<tr><td colspan="2">Subjective Information</td></tr>
<tr><td>Signs of bleeding: Y / N
(Describe if Yes)</td><td>Signs of thrombosis: Y / N
(Describe if Yes)</td></tr>
<tr><td>Correct dose taken: Y / N
<table><tr><td>Mon</td><td>Tues</td><td>Wed</td><td>Thurs</td><td>Fri</td><td>Sat</td><td>Sun</td></tr><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table></td><td>Missed doses in past 1 week: Y / N
(Specify if Yes)</td></tr>
<tr><td>Medications Changes: Y / N
(Describe if Yes)</td><td>Changes In Medical Status / Illness: Y / N
(Describe if Yes)</td></tr>
<tr><td>Change in Physical Activity: Y / N
(Specify if Yes)</td><td>Diet / Herbal / Supplements changes: Y / N
(Specify if Yes)</td></tr>
</table>

4. Pregnancy / plan to get pregnant?
   No
   Yes: Is doctor aware? If no, refer to doctor

5. Alcohol consumption?
   No
   Yes: amount & frequency?

6. Smoker?
   No
   Yes: How many sticks/day? Any changes in smoking habit (stop or just started smoking)

Other complain / Patients Plans: Y / N

(Describe if Yes)

Assessment

Is INR therapeutic: Y / N

Describe:

Pharmacist Review / Plan

Pharmacist's Signature and Chop

Physician Review & Notes

Physician's Signature and Chop

Appendix 7

MTAC-WARFARIN: DRUG CHECK LIST

Drugs/Drug Classes	EFFECT ON INR			Level of Causation	Mode of Action
	↑	↓	↔		
Acarbose	✔	✔		III	Unknown.
Alcohol (acute use)	✔			I	Large intermittent doses of alcohol cause some inhibition of warfarin metabolism.
Allopurinol	✔			No evidence found	Increase in the hypoprothrombinemic response.
Amiodarone	✔			I	Amiodarone inhibits metabolism of warfarin, increasing its anticoagulant effect and risk of bleeding; reduce warfarin dose by about one-quarter, monitor INR frequently and adjust dose further as necessary.
Antibiotics					
Broad Spectrum Antibiotics	✔			No evidence found	Inhibition of vitamin K synthesis by intestinal flora.
Cephalosporins • Cefotetan • Cefamandole • Cefoperazone • Cefmetazole	✔			IV	Interfere with vitamin K-producing bacteria in the gut. Use in combination is safe in most situations, provided vitamin K intake is normal. Direct prolongation of prothrombin time affects liver enzyme clotting factors. Cephalosporins with an N-Methylthiotetrazol (N-MTT) side chain have the most pronounced interaction-examples are cefotetan, cefamandole, cefoperazone.
Erythromycin	✔			I	Several case reports of marked increase in hypoprothrombinemic response to warfarin, but studies in healthy subjects suggest smaller interaction. It might occur only in certain predisposed individuals.
Penicillins • Nafcillin • Dicloxacillin		✔		IV	Generally have little effect on INR. Additional monitoring generally not needed unless high doses are used more than 7 day. Nafcillin and dicloxacillin may decrease the INR and require a dose increase of warfarin.
Aspirin			✔	II	Combination increases risk of bleeding. Low-dose aspirin may be justified for some clinical indications for additional anticoagulant effects. Prolongation of prothrombin time may occur at higher doses (>3grams) of aspirin.

Drugs/Drug Classes	EFFECT ON INR			Level of Causation	Mode of Action
	↑	↓	↔		
Azathioprine		✔		II	Unknown.
Barbiturates		✔	✔	I	Induce metabolism of warfarin.
Carbamazepine		✔		I	Carbamazepine may increase warfarin's metabolism.
Cholestyramine		✔		I	Cholestyramine reduces warfarin absorption, reducing its anticoagulant effect; give 1 hour before, or 4-6 hours after, cholestyramine and monitor INR and adjust warfarin dose as needed.
Cimetidine	✔			I	Inhibits warfarin metabolism. Substitute with other H2 antagonists.
Ciprofloxacin	✔			I	Inhibit CYP 1A2, decrease metabolism of warfarin.
Clarithromycin	✔			II	Inhibit warfarin metabolism by inhibiting CYP 3A4.
Clofibrate	✔			I	Unkown. (May alter protein binding, indirect potentiation) Avoid using in combination. Interaction is usually dose related.
Clopidogrel			✔	I	Clopidogrel may enhance the anticoagulant effect of Warfarin.
Colestipol		✔		No evidence found	Binds warfarin in the gut and inhibits total warfarin absorption. Administer warfarin at least 2 hrs prior to colestipol or 6 hours after colestipol.
Corticosteroid	✔	✔		No evidence found	Unexplained mechanism.
Cyclophosphamide		✔		No evidence found	Unexplained mechanism.
Cyclosporine		✔		III	Cyclosporine inhibits warfarin by an unknown mechanism. An increase in dose may be required.
Disulfiram	✔			II	Inhibits metabolism of warfarin. Avoid using in combination if possible, otherwise a decrease in warfarin dose may be required when initiating disulfuram therapy. When stopping disulfuram therapy, an increase in warfarin dose may be required.

Drugs/Drug Classes	EFFECT ON INR			Level of Causation	Mode of Action
	↑	↓	↔		
Estrogen		✔		No evidence found	Estrogens induce coagulant factors. Estrogens increase the risk for clot formation and decrease the effects of warfarin.
Fenofibrates	✔			I	Unexplained metabolism.
Fluconazole	✔			I	Unknown. Alters clearance of warfarin.
Fluoroquinolones	✔			No evidence found	Inhibition of warfarin metabolism.
Fluoxetine	✔			I	Inhibition of warfarin metabolism.
Flurouracil	✔			II	Inhibition of warfarin metabolism.
Fluvoxamine	✔			II	Inhibitor of CYP 1A2, CYP 3A4, and CYP 2C9. Decrease metabolism of warfarin.
Gemfibrozil	✔			III	Unknown mechanism due to poor documentation. Interaction is usually dose related.
Griseofulvin		✔		I	Unknown.
Heparin	✔			IV	Oral anticoagulants may prolong the activated partial thromboplastin time (aPTT) in patients receiving heparin, while heparin may prolong the International Normalized Ratio (INR) in patients receiving warfarin.
Ifosfamide/Mesna	✔			III	Unknown.
Imatinib	✔			No evidence found	Competitive inhibition of isoenzyme CYP3A4 and imatinib-provoked inhibition of CYP2C9 and CYP2D6-mediated warfarin metabolism.
Influenza Vaccine	✔			II	Unknown. Has been associated with altered hypoprothrombinemic response to warfarin in some patients, but the effect appears to be minimal in most cases.
Isoniazid	✔			I	Unknown.
Itraconazole	✔			II	Decreased warfarin metabolism.
Ketoconazole	✔			II	Decreased warfarin metabolism.
Lepirudin	✔			No evidence found	Additive anticoagulation via different mechanism.
Low Molecular Weight Heparin	✔			No evidence found	Additive anticoagulation.

Drugs/Drug Classes	EFFECT ON INR			Level of Causation	Mode of Action
	↑	↓	↔		
Lovastatin	✔			III	Unknown.
Mesalamine		✔		I	Unknown.
Metronidazole	✔			I	Decreased warfarin metabolism.
Miconazole	✔			III	Decreased warfarin intrinsic clearance and increased plasma free fraction; inhibition of cytochrome P450-mediated metabolism of warfarin by miconazole.
Moxalactam	✔			No evidence found	Inhibition of platelet function, decreased clotting factor synthesis.
Nonsteroidal Anti-inflammatory Drugs	✔			No evidence found	All NSAIDs (including selective COX-2 inhibitors) increase the risk of serious GI bleeding. Nonselective agents (antiplatelet effect) and selective COX-2 inhibitors (may increase INR) may further increase the risk of bleeding.
Omeprazole	✔			I	Inhibits warfarin metabolism although moderate clinical significance.
Paracetamol				II	Inhibition of warfarin metabolism or interference with clotting factor formation.
Paroxetine	✔			No evidence found	Inhibitor of CYP 1A2. Decrease metabolism of warfarin.
Phenytoin	✔	✔		II	Displacement of warfarin from protein binding sites, increased warfarin metabolism
Primidone		✔		No evidence found	Induces CYP1A2, 2B6, 2C8/9, 3A4.Induces of warfarin metabolisme.
Propafenone	✔			No evidence found	Inhibit CYP1A2, 2D6. Inhibit of warfarin metabolisme
Propylthiouracil		✔		No evidence found	Reduces catabolisme of clotting factors.
Quetiapine	✔			IV	Inhibit of warfarin metabolisme.
Quinidine	✔			II	Inhibit CYP1 2C8/9, 2D6, 3A4. Inhibit of warfarin metabolisme.
Rifampicin		✔		I	Induces CYP1A2,2A6, 2B6,2C8/9, 2C19. Induces metabolisme of warfarin. Careful monitoring of INR and dose (20%-50%) are required. The interaction is maximal1-2 weeks following additional of rifampicin.

Drugs/Drug Classes	EFFECT ON INR			Level of Causation	Mode of Action
	↑	↓	↔		
Ritonavir	✔	✔		II	Inhibit CYP 2C8/9, 2C19, 2D6,2E1, 3A4. Induces CYP1A2, 2C8/9, 3A4.
Saquinavir	✔			III	Inhibit CYP2C8/9, 2C19, 2D6, 3A4. Inhibit of warfarin metabolism.
Sertraline	✔			I	Inhibit CYP1A2, 2B6, 2C8/9, 2D6, 3A4. Inhibit of warfarin metabolism.
Sildenafil	✔			No evidence found	Inhibit CYP1A2, 2C8/9, 2C19, 2D6, 2E1, 3A4. Inhibit of warfarin metabolism.
Simvastatin	✔			II	Inhibit CYP2C8/9, 2D6. Inhibit of warfarin metabolism.
Sucralfate		✔		I	Altered absorption of warfarin.
Sulfamethoxazole	✔			No evidence found	Inhibit CYP2C8/9. Inhibit of warfarin metabolisme and delays warfarin protein binding. A decrease in warfarin dose maybe required. Monitoring INR 3-5 days of starting,at least weekly during treatment and again one week following.
Tamoxifen	✔			II	Inhibit CYP2B6, 2C8/9, 3A4.
Thyroid hormones	✔			No evidence found	Increase catabolisme of clotting factors.
Ticlopidine			✔	III	Inhibit CYP1A2, 2C8/9, 2C19, 2D6. Inhibit of warfarin metabolisme.
Tricyclic Antidepressants	✔			No evidence found	Increase hypoprothrombinemic response reportedly has occurred, but clinical evidence is minimal.
Vitamin E	✔			I	Alter the effect of vitamin K action on clotting factors resulting in an increase hypoprotrombinemic response to warfarin.
Vitamin K		✔		I	Inhibit effectiveness of warfarin.
Zarfirlukast	✔			No evidence found	Inhibit CYP1A2, 2C8/9, 2C19,2D6,3A4. Inhibit of warfarin metabolisme

EFFECT ON INR	
↑	INCREASE
↓	DECREASE
↔	NO EFFECT (INCREASED RISK OF BLEEDING)

LEVEL OF CAUSATION	
I	HIGHLY PROBABLE
II	PROBABLE
III	POSSIBLE
IV	HIGHLY IMPROBABLE

Appendix 8

WARFARIN LABEL

WARFARIN 1MG/2MG/3MG/5MG

NAMA:_____ TARIKH:_____

MAKAN

____BIJI PADA HARI ISNIN
____BIJI PADA HARI SELASA
____BIJI PADA HARI RABU
____BIJI PADA HARI KHAMIS
____BIJI PADA HARI JUMAAT
____BIJI PADA HARI SABTU
____BIJI PADA HARI AHAD

SEKALI SEHARI SEBELUM MAKAN.
PADA JAM…….
JABATAN FARMASI ,
HOSPITAL…….

Appendix 9

WARFARIN DOSING NOTE

JADUAL PENGAMBILAN UBAT
MTAC-ANTITROMBOSIS
JABATAN FARMASI,
HOSPITAL.....

Nama: _____

Tarikh: _____ INR: _____

Dos Mingguan Warfarin:

Ahad _____ Isnin _____

Selasa _____ Rabu _____

Khamis _____ Jumaat _____

Sabtu _____

Arahan Khas:

_____

_____

Tarikh Temujanji akan datang:

_____

Appendix 10

MISSED APPOINTMENT RECORD

MISSED APPOINTMENT
MTAC WARFARIN
JABATAN FARMASI, HOSPITAL……

Patient Name : _____ R/N: _____

Phone Number : _____

Date	Contact Details	Patient Response	Reschedule Appointment	Initials

Appendix 11

MANAGEMENT OF WARFARIN ANTICOAGULATION IN CHILDREN (UMMC GUIDELINES 2013)

Abbreviationsin this guideline

PT-INR	Prothrombin time, International Normalised Ratio
TWD	Total weekly dose

Challenges of warfarin therapy in children

Challenges in achieving optimal warfarin anticoagulation in children include

- Wide variations in dietary vitamin K intake, especially during infancy
- Intercurrent common childhood illnesses, associated with poor oral intake and use of antibiotics, factors that destabilise warfarin therapy
- Requirement for regular monitoring, including need for regular venous sampling for PT-INR testing
- Adherence to warfarin therapy in adolescents

Indications

Long-term (indefinite duration) anticoagulation in children with

- Some forms of congenital heart surgery (typically, cavopulmonary shunt surgery [e.g. Fontan procedure])
- mechanical heart valve replacement
- dilated cardiomyopathy complicated by dysrythmia or heart failure
- recurrent arterial or venous thromboembolism
- primary pulmonary arterial hypertension

Intermediate-duration anticoagulation (6 months) in children with

- first episode of idiopathic vascular thrombosis

  N.B: Children who experience a first event of provoked vascular thrombosis may be more easily managed with extended low-molecular weight heparin therapy (duration: at least 3 months). Extended low-molecular weight heparin therapy is similarly appropriate for children with venous thrombosis in the context of cancer.

Dosing preparations (University Malaya Medical Centre)

Strength	Colour	Brand
1 mg	Brown	---
2 mg	Purple	Apo-Warfarin
3 mg	Blue	Orfarin
5 mg	Orange	Apo-Warfarin

Dosing principles

- Family education is critical to safe successful long-term warfarin anticoagulation
- Warfarin is best avoided in children less than 2 months old (greater haemorrhagic risk since levels of clotting factors are physiologically lower). Warfarin is typically prescribed in children ≥6 months old.
- Maintain heparin anticoagulation until lower limit of target PT-INR is

achieved with warfarin; this may take between 5 and 10 days.

- Dose warfarin by whole tablets since active warfarin is not evenly distributed within a tablet
- For younger children, warfarin may be administered as solution by crushing/dissolving the tablet extemporaneously in water (Note: the impact of such reconstitution on drug activity has not been systematically ascertained)
- Warfarin is administered daily, usually in the evening (allowing for dose changes following PT-INR tests in the morning)
- Consider a dose as 'missed' if more than 12 hours have elapsed since scheduled intake. Do not substitute with booster doses (risk of overshoot anticoagulation).
- Daily or alternate-day monitoring of PT-INR is required during the initial treatment phase
- During the maintenance phase, dose changes are made based on the total weekly dose
- In patients experiencing wide swings in PT-INR while on warfarin, supplementation with daily oral vitamin K helps minimise the fluctuations in PT-INR

e.g. Daily administration of Konakion MM paediatric (phytomenadione or vitamin K1, 2 mg/0.2 mL), 30 mcg/kg

e.g. Supplementation with 1-2 ounces of formula milk in exclusively breast-fed infants

Target PT-INR

Condition	Target PT-INR (Range)
Congenital heart surgery (cavopulmonary shunts)	2.5 (2.0 - 3.0)
Mechanical heart valve recipients	
All mechanical mitral valves	3.0 (2.5 - 3.5)
Caged-ball or tilting-disk aortic valves	3.0 (2.5 - 3.5)
Bileaflet or Medtronic-Hall aortic valve	2.5 (2.0 - 3.0)
Dilated cardiomyopathy, with complications	2.5 (2.0 - 3.0)
Recurrent vascular thromboembolism	2.5 (2.0 - 3.0)

Pre-treatment checks

Clinical

- Ascertain that child is clinically stable and that oral therapy is feasible
- Ensure no active bleeding
- Obtain diet and drug history, exploring factors that could influence warfarin action
- Explore factors that could increase risk of bleeding (recent surgery, non-steroidal anti-inflammatory drugs, scheduled invasive procedures including intramuscular injections, hepatic dysfunction)
- Consider possibility of pregnancy in older girls (warfarin is teratogenic)

Laboratory

- Ensure safe platelet count (platelet count ≥100 $x10^9$/L)
- Ensure safe baseline PT-INR (PT-INR ≤1.3)

Initial treatment phase

Day 1
- Administer 0.2 mg/kg orally as a single evening dose (maximum, 5 mg)
- In frail patients, patients with liver dysfunction or severe renal impairment, reduce loading dose to 0.1 mg/kg (maximum, 5 mg)
- For young adult patients, commence warfarin at a loading dose of 5 mg

Days 2 - 4

1.1 - 1.3	Repeat initial loading dose
1.4 - 1.9	50% of initial loading dose
2.0 - 3.0	50% of initial loading dose
3.1 - 3.5	25% of initial loading dose
>3.5	Hold until INR ≤3.5; restart at 50% less than previous dose

If the INR is not >1.5 on Day 4, reassess and consider increasing the loading dose

Maintenance treatment phase

Dose adjustments based on total weekly dose (TWD)

e.g. A patient taking 2 mg Warfarin daily on Monday - Friday and 1 mg on Saturday and Sunday will receive a total weekly dose (TWD) of 12 mg. A ~10% increase in TWD would result in a dose change to 2 mg on Mondays to Saturdays and 1 mg on Sunday (TWD of 13 mg)

INR*	Intervention
<1.5	Check patient adherence Increase TWD by 10 - 20% Repeat PT-INR in 1 week
≥1.5 but less than therapeutic range	Check patient adherence Make no dose change; repeat PT-INR in 1 week If repeat PT-INR still below therapeutic range, increase TWD by 5 - 10%
2 - 3	No change
3.1 - 3.5	Decrease TWD by 10% Repeat PT-INR in 1 week
>3.5	Withhold warfarin until INR <3.5 (see section on 'Overanticoagulation') Then restart at a reduced TWD (reduction by 20%) Repeat PT-INR in 1 week

* For patients treated to a target PT-INR of 2 - 3

Monitoring while on warfarin therapy

- Clinical monitoring
  - Assessment for features of thrombosis (including cutaneous vascular thrombosis) and haemorrhage (cutaneous, mucosal and intracranial)
  - Assessment for other complications of warfarin (e.g. alopecia, bone density)

- Assessment of adherence to therapy

- Evaluation of factors that could influence warfarin therapy
  - Dietary changes (e.g. switch from largely breast-feeding to formula milk feeds)
  - Intercurrent infections
  - Medications (e.g. dose change of cardiac drugs or prescription of new drugs [e.g. antibiotics])

COMMONLY PRESCRIBED DRUGS THAT TEND TO INCREASE PT-INR BY PROLONGING WARFARIN EFFECT

- Antimicrobials including cotrimoxazole, metronidazole, azole antifungals (especially fluconazole), macrolides (e.g. erythromycin), quinolones (e.g. ciprofloxacin) and isoniazid. Note: all antibacterials alter gut flora and thus potentially enhance warfarin activity
- Paracetamol, *typically with long-term use*
- Corticosteroids, *typically at high doses*
- Proton pump inhibitors (e.g. omeprazole)
- L-thyroxine, *especially during dose titration*
- Amiodarone

COMMONLY USED DRUGS THAT TEND TO DECREASE PT-INR BY ACCELERATING WARFARIN ELIMINATION

- Anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbitone)
- Rifampicin

COMMONLY PRESCRIBED DRUGS THAT INDEPENDENTLY INCREASE RISK OF BLEEDING

- Non-steroidal anti-inflammatory drugs (e.g. aspirin and ibuprofen)

COMMONLY USED DRUGS THAT ARE PROTHROMBOTIC AND THUS ANTAGONISE WARFARIN EFFECT

- Oestrogen-progesterone medications

- Non-prescription agents that could influence warfarin therapy
  - Herbal supplements (typically through effect on platelet function)
  - Cranberry juice (inhibits warfarin metabolism, prolongs warfarin effect)

- Laboratory monitoring of PT-INR

Treatment context	Frequency of monitoring
Initial treatment phase until therapeutic PT-INR	Daily or every other day
Initiation of total weekly dosing	Within 3 - 5 days
First month of maintenance phase therapy	Weekly
Any dose change during maintenance phase	Within 1 - 2 weeks
Dose withheld due to significant overanticoagulation	Within 1 - 2 days
Routine follow-up, medically stable, reliable	Every 4 - 6 weeks
Routine follow-up, medically unstable or unreliable	Every 1 - 2 weeks

- Maintain a warfarin treatment diary (sample below)

Date	Current warfarin dose	PT-INR	Recommended dose	Date of next blood test

Management of overanticoagulation

Always explore possible explanations for overanticoagulation

HAEMORRHAGE

Not life-threatening
Stop Warfarin
Oral Vitamin K* 0.5 - 2 mg (based on body weight)
Alternatively, intravenous or subcutaneous vitamin K 0.5 - 1 mg
Higher doses (e.g. 2 - 5 mg) of oral vitamin K are appropriate in patients who will not require warfarin again

Life-threatening
Stop Warfarin
Prothrombin complex concentrate** 25 - 50 units/kg
Intravenous (or subcutaneous) Vitamin K 5mg (slow intravenous)
Resuscitate as appropriate
Actively assess for intracranial haemorrhage

NO HAEMORRHAGE

PT-INR <5
Stop Warfarin
Daily or alternate day PT-INR monitoring until PT-INR <3.5
Resume with reduced total weekly dose (reduction by 20%)
Check PT-INR a week later

PT-INR 5 - 9
Stop Warfarin
Consider oral vitamin K at 0.5 - 2.0 mg (based on body weight) in patients at high risk of bleeding
Daily or alternate day PT-INR monitoring until PT-INR <3.5
Resume with reduced total weekly dose (reduction by 10-20%)
Check PT-INR a week later

PT-INR > 9	Stop warfarin Administer oral vitamin K at 0.5 - 2.0 mg (based on body weight) Repeat oral vitamin K if repeat PT-INR remains elevated (>5)
12h later	Daily or alternate day PT-INR monitoring until PT-INR <3.5 Resume with reduced total weekly dose (reduction by 20%) Check PT-INR a week later

* Oral Vitamin K, using the Konakion MM Paediatric preparation (2 mg/0.2 mL)
** Four-factor prothrombin complex concentrate is the most suitable (enriched in Factors II, VII, IX, X). Where not available, fresh frozen plasma (FFP) may be administered (20 mL/kg)

Periprocedure management of warfarin and requirement for bridging heparin therapy

Principles

- Assess thrombotic risk

Low risk	Primary low-risk thromboprophylaxis (e.g. Fontan surgery, stable)
Medium risk	Vascular thromboembolism >3 months from onset Primary thromboprophylaxis for dilated cardiomyopathy, rheumatic valvular heart disease and mechanical heart valves
High risk	Vascular thromboembolism ≤3 months from onset Pulmonary embolism Recurrent thromboembolism Primary thromboprophylaxis for primary pulmonary hypertension Past history of prosthetic valve thrombosis Homozygous protein C deficiency

- Assess risk of periprocedure bleeding
  Patients undergoing procedures with low risk of bleeding do not require interruption of warfarin therapy.
  These procedures include
  - tooth extractions and endodontic (root canal) procedures
  - small skin excisions (e.g. skin biopsy)
- Stop warfarin 5 days prior to the scheduled operative procedure
- Determine strategy for periprocedure bridging therapy based on estimated risk for thrombosis

Risk	Preprocedure bridging	Postprocedure bridging*	Restart of warfarin*
Low	No	No	Usual maintenance dose on night of procedure
Intermediate	Enoxaparin, 1 mg/kg BD when PT-INR <2; continue until AM of day prior to procedure (PM dose on day before and AM dose on day of procedure omitted)	Enoxaparin 1 mg/kg BD, beginning PM of day of procedure (if no bleeding concerns); else begin on AM of day after procedure	Restart warfarin at usual maintenance dose on PM of the day after the procedure provided no contraindications Check PT-INR 3 days later and titrate dose Continue enoxaparin until PT-INR >2
High	Enoxaparin, 1 mg/kg BD when PT-INR <2; continue until AM of day prior to procedure. Commence unfractionated heparin (starting at 20 u/kg/hr) 4 hours after last dose of enoxaparin and continue until 1 hour prior to procedure	Restart unfractionated heparin (UFH) 1 hour postprocedure (if no bleeding concerns) and adjust using APTT (target, 60-80 secs). Maintain on UFH as long as higher bleeding risk. Restart enoxaparin 1 mg/kg BD as soon as bleeding risk low (start at same time of stopping UFH)	Restart Warfarin at usual maintenance dose at Day 5 postprocedure provided no contraindications Check PT-INR 3 days later and titrate dose. Continue enoxaparin until PT-INR >2 (aim for anti-Xa activity of 0.5-1 unit/mL)

* Timing of postprocedure anticoagulation depends on assessment of risk of postprocedure bleeding. Close consultation advised with surgeon/physician performing the procedure

Family education

Education of caregivers on the following aspects of warfarin therapy

- Rationale for warfarin therapy
- Mechanism of action of warfarin
- Importance of adherence to therapy
- Action in the case of missed doses
- Necessity for regular monitoring while on warfarin therapy
- Target PT-INR
- Diet, prescription and non-prescription medications and other factors that could interfere with warfarin action
- Importance of maintaining consistent balanced dietary intake to avoid wide swings in vitamin K intake
- Risk of haemorrhage with warfarin anticoagulation
- Minimising risk of injuries (e.g. avoiding contact sports, wearing bicycle helmets etc)
- Access to advice and care in the event of queries or concerns
- Medic-alert badge or bracelet
- Written anticoagulation advice

Endpoint of successful therapy

Percent time spent in target therapeutic range

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Appendix 12

LEVEL OF EVIDENCE

Levels	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials (RCTs)
Ib	Evidence obtained from at least one RCT
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies e.g. comparative studies, correlation studies, case-control studies
IV	Evidence obtained from expert committee reports or opinions and / or clinical experience of respected authorities, or both

Adapted from the National Guidelines Clearinghouse (www.guidelines.gov), Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services, USA.

Grade	Recommendation
A (evidence levels Ia and Ib)	Requires at least one randomised controlled trial, as part of the body of literature, of overall good quality and consistency addressing the specific recommendation
B (evidence levels IIa, IIb and III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (evidence level IV)	Required evidence obtained from expert committee reports or opinions and / or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality

Adapted from the Scottish Intercollegiate Guidelines Network (SIGN).

Appendix 13

CLINICAL QUESTIONS

1. **What is the epidemiology of VTE in Asia?**

2. **What is the pathogenesis and natural history of VTE?**

3. **How do we prevent VTE?**
   - What are the methods of prophylaxis?
   - Who are the patients at risk of VTE?
   - Who are the patients at risk of bleeding?
   - When is the right timing and initiation of prophylaxis?
   - What is the duration of prophylaxis?
   - How do we use antithrombotic therapy with regional anaesthesia?
   - How do we use antithrombotic prophylaxis in stroke patients?

4. **How do we diagnose VTE?**
   - What are the investigations for VTE?
   - When do we investigate for cancer-related VTE?
   - Is thrombophilia testing useful?

5. **How do we treat VTE?**
   - What are the modalities of treatment?
   - What is the preferred first line treatment for VTE?
   - What is the role of newer and more expensive drugs for the management of VTE
   - When is thrombolytic therapy indicated?
   - What is the indication for IVC filter?
   - How do we prevent post-thrombotic syndrome?

6. **How do we monitor anticoagulation therapy?**

7. **How do we manage a patient on anticoagulant who is going for surgery?**
   - How do we stratify patients at risk of thromboembolism when stopping anticoagulation?
   - How do we stratify bleeding risks according to surgical procedures?

8. **How do we manage over-anticoagulation?**
   - What are the advantages of prothrombin complex concentrate (PCC) over fresh frozen plasma (FFP) in the management of life-threatening haemorrhage due to warfarin?
   - How do we manage bleeding complications in the new anticoagulants?

9. What is the pathogenesis and risk factors for VTE in pregnancy?
- How is VTE diagnosed in pregnancy?
- What is the treatment of VTE in pregnancy?

10. How do we manage pregnant women with the antiphospholipid syndrome?

11. How do we manage anticoagulation in the elderly, obese or renal impaired patients?

12. How do we manage anticoagulation in stroke patients?

13. How do we manage anticoagulation in children?

14. How do we manage VTE following fertility treatment?

15. What is the risk of VTE in a woman who is on combined oral contraception (COC)?
- What is the eligibility criteria for starting COC?

16. How do we manage VTE in cancer patients?

17. How do we manage thrombosis in unsual sites such as upper extremity, cerebral venous sinuses and splanchnic veins?

18. What are the objectives and function of the medication therapy adherence clinic warfarin (MTAC-W)?

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