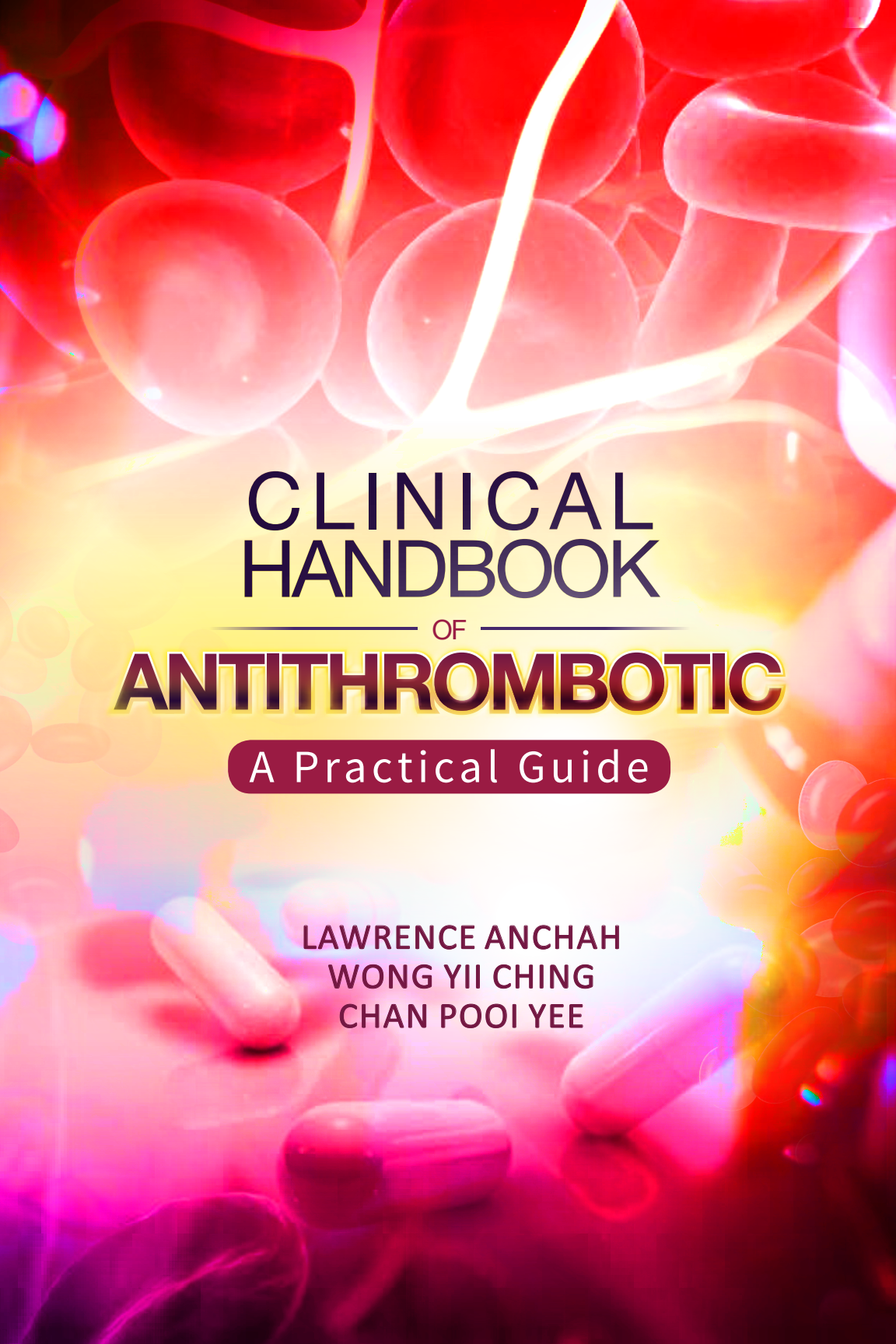
CLINICAL
HANDBOOK
OF
ANTITHROMBOTIC
A Practical Guide
LAWRENCE ANCHAH
WONG YII CHING
CHAN POOI YEE

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UNIVERSITI MALAYSIA SARAWAK

CLINICAL HANDBOOK OF ANTITHROMBOTIC

A Practical Guide

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Contents

List of Contributors

Editors

Dr Lawrence Anak Anchah, PhD
BPharm, MPharm (Clinical Pharmacy) (USM)
Associate Professor,
Faculty of Medicine and Health Sciences,
Universiti Malaysia Sarawak (UNIMAS)

Wong Yii Ching, BCPS
BPharm (IMU), MPharm (Clinical Pharmacy) (USM)
Clinical Pharmacist, Sarawak Heart Centre

Chan Pooi Yee
BPharm (UCSI), MPharm (Clinical Pharmacy) (USM)
Clinical Pharmacist, Raja Permaisuri Bainun Hospital, Ipoh, Perak

Contributors

Dr Melissa Lim Siaw Han, PhD
BPharm (Uni SA), MSc (Pharmacogenetics) (SUTS), (Okayama University)
Clinical Research Centre, Sarawak General Hospital

Ku Ming Ying, BCPS
MPharm (Uni of Strathclyde), MPharm (Clinical Pharmacy) (USM)
Clinical Pharmacist, Sarawak General Hospital

Lum Kah Yee
BPharm (IMU), MSc (Health Economics and Health Policy) (Uni of Birmingham)
Pharmacist, Sarawak Heart Centre

Aaron Chang Chee Ming
MPharm (Uni of Strathclyde)
Pharmacist, Sarawak Heart Centre

Chelfi Chua Zhi Fei
BPharm (Uni of Queensland)
Pharmacist, Sarawak Heart Centre

King Teck Long
BPharm (IMU)
Pharmacist, Sarawak General Hospital

Lee Qian Jin
BPharm (USM)
Pharmacist, Sarawak Heart Centre

Sandra Anak Abi
MPharm (Cardiff University)
Pharmacist, Sarawak Heart Centre

Shirley Tan Siang Ning
BPharm (USM)
Pharmacist, Sarawak General Hospital

Sim Pui Pui
BPharm (USM)
Chief Pharmacist, Tanah Puteh Health Clinic, Kuching, Sarawak

Tiong Lee Len
BPharm (UM)
Administrative Manager and Senior Pharmacist,
Clinical Research Centre, Sarawak General Hospital

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Although every effort has been made to ensure the information and drug doses in the handbook are correct and accurate, the responsibility lies with the prescribers. The authors and the publisher of this work have checked sources believed to be reliable in their effort to provide information that is complete and accepted at the time of publication. The authors cannot be held responsible for errors or any undesirable consequences arising from the use of the information contained in this handbook. Always refer to the manufacturer's prescribing information before prescribing drugs cited in this handbook in particular with new or infrequently used drugs.

Preface

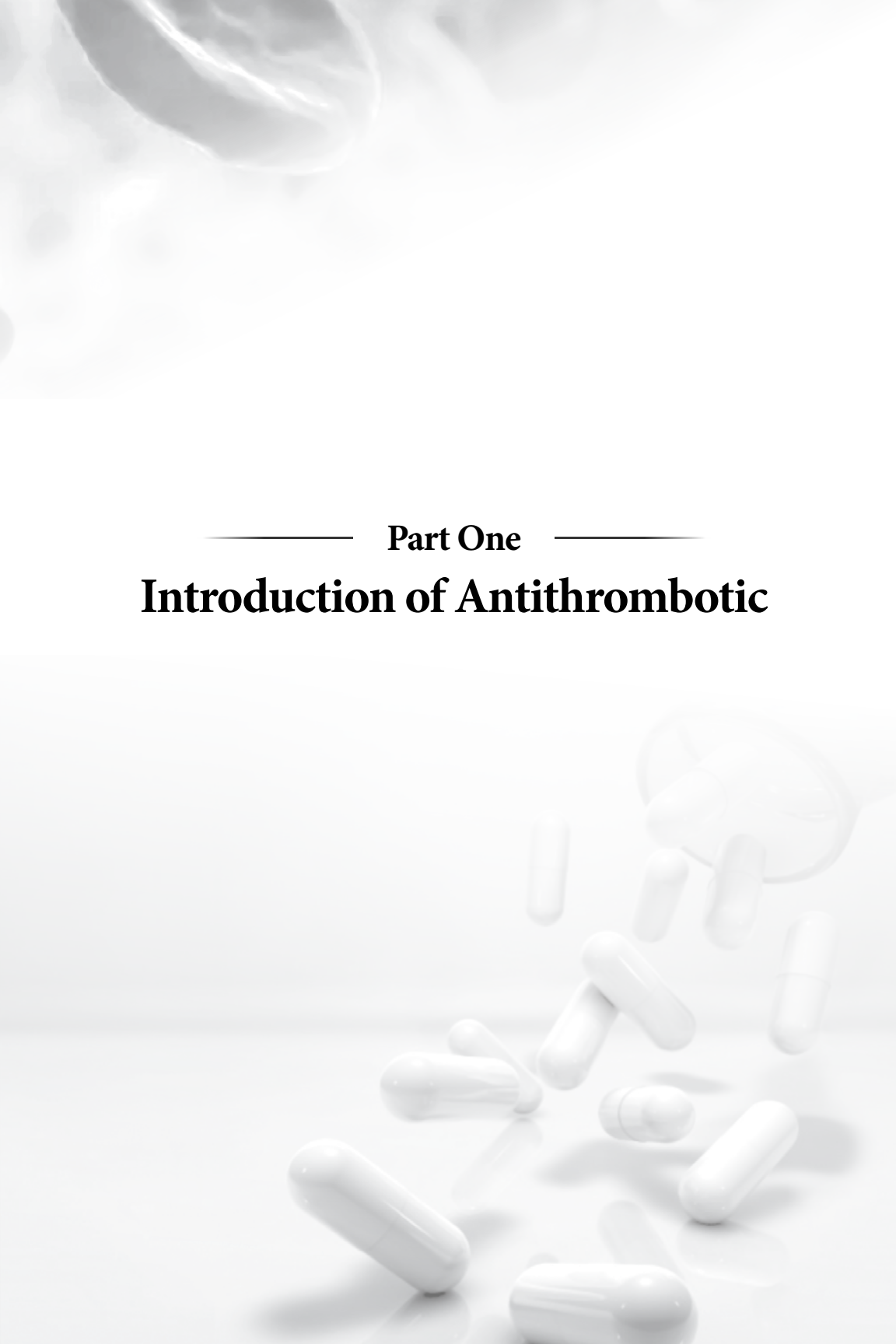
Antithrombotic agents are high risk medications associated with significant rates of medication errors. The use of antithrombotic agents is extensively high in cardiology and medical specialties; thus, a good understanding of antithrombotic agents is essential.

A group of pharmacists has work collectively to come out with this handbook focusing on antithrombotic agents that commonly established in Sarawak Heart Centre. The purpose of this handbook is to serve as a reference material on antithrombotic agents for pharmacists, nurses, medical officers, medical interns, students and other healthcare providers in the medical field. Therefore, additional basic knowledge of pharmacogenetics and pharmacogenomics information of patients' response to certain antithrombotic agents are also highlighted in this handbook.I hope the healthcare providers, trainees and students will find this handbook useful during their course of duties.

Dr Mohd. Asri bin Riffin
Director
Sarawak Heart Centre

Part One

Introduction of Antithrombotic



The coagulation process is a complex chain of reaction that leads to haemostasis. With that, antithrombotic are drugs that manipulate the blood coagulation process by inhibiting the formation of thrombus during haemostasis phase.

Haemostasis

- In event of an injury, a series of processes involving vasoconstriction, platelet activation and blood coagulation occurs to prevent blood loss. This physiological response is called haemostasis.
- Primary haemostasis involves vasoconstriction and platelet activation and aggregation, facilitated by the von Willebrand factor (vWF) and fibrinogen glycoproteins to form a platelet plug.
- Secondary haemostasis involves the coagulation cascade (see figure 1) which converts fibrinogen to fibrin. Fibrin strands reinforce more platelet plug and trap red blood cells to form a blood clot.

Coagulation Cascade

- Coagulation cascade *(see Figure 1)* is a series of biochemical processes in the blood involving the activation of proenzymes, proceeding through a pathway of coagulation to form a fibrin clot.

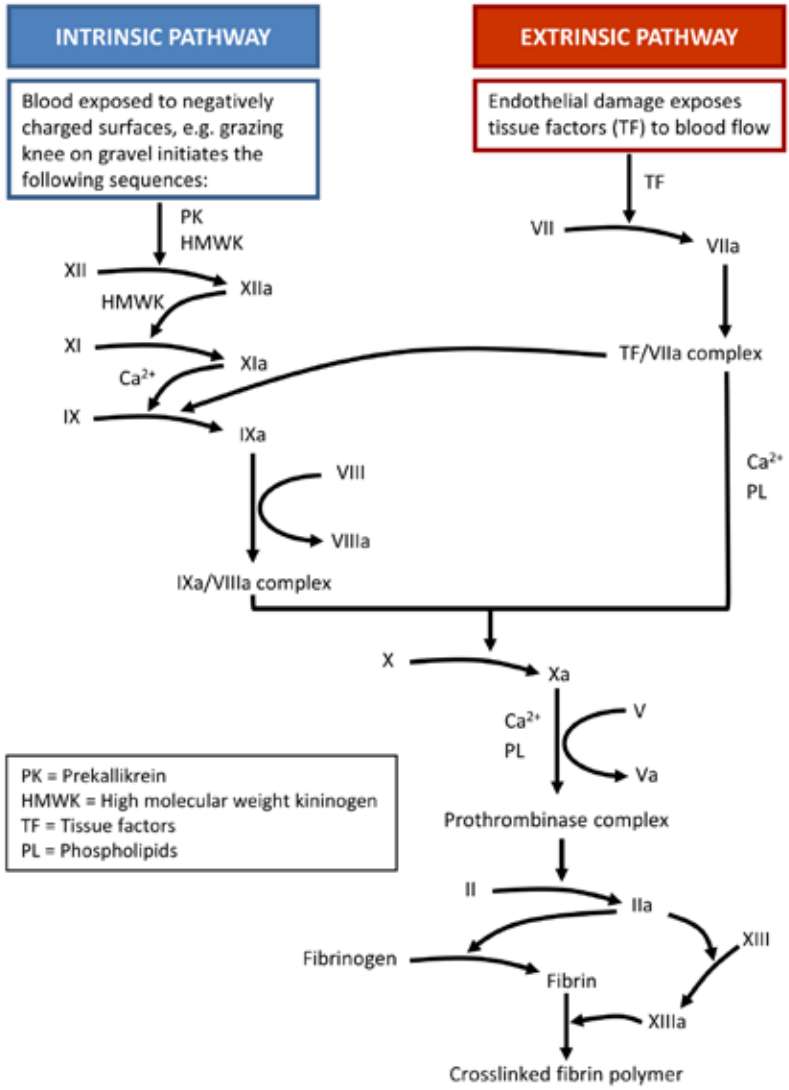


Figure 1: Coagulation cascade

- Extrinsic pathway begins at tissue injury.
- Intrinsic pathway begins in the blood and is triggered by damage to the vascular wall.
- The common pathway begins at the formation of Factor Xa which combines with Factor Va

Virchow's Triad

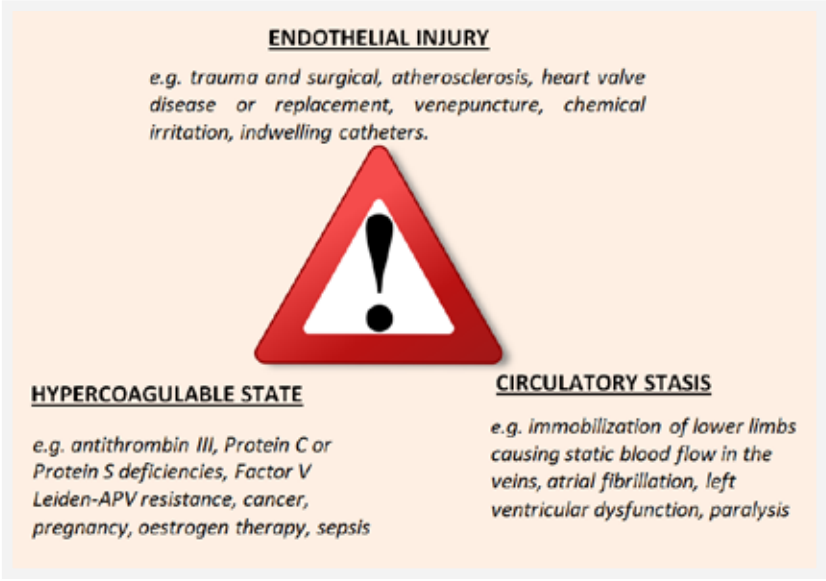


Figure 2: Virchow's triad.

- Virchow's Triad – predisposing factors to venous thrombosis and thromboembolism.
- While one factor may predominate in a given clinical situation, it is likely that more than one factor is involved in the development of venous embolism.

Types of Thrombi

1. **Arterial Thrombus**
    - Arterial thrombus – also known as white thrombus – formed under conditions of high flow.
    - Mainly composed of platelet aggregates bound together by fibrin strands and only few red blood cells.
    - Flat, tightly adherent, and relatively small.
    - Usually occurring in association with pre-existing vascular disease, most commonly atherosclerosis.
    - Clinically manifesting diseases by inducing tissue ischemia such as myocardial infarction (MI) and stroke.

2. **Venous Thrombus**
    - Venous thrombus – also known as red thrombus – formed under conditions of slow flow.
    - Mainly composed of red blood cells with large amount of interspersed fibrin and relatively fewer platelets
    - Venous thrombi are large, friable casts of the venous channel with branching arms that may extend into tributary veins.
    - Very weakly attached to the venous intima and may detach and embolise to occlude downstream vessels.
    - Usually occurring silently in lower limbs, particularly in the deep veins of the calf or thigh.
    - Produces acute symptoms when they cause inflammation of the vessel wall, obstruction to flow, damage venous valves (which cause deep vein thrombosis), or embolise to in the pulmonary circulation (causing pulmonary embolism, (PE))

3. **Mix Thrombus**
    - Mix thrombus – formed in regions of moderate to slow blood flow e.g. within the chambers of the heart or around heart valves.
    - Composed of a mixture of red blood cells, platelets, and fibrin strands and are known as mixed platelet-fibrin thrombi.

Types of Anti-Thrombotic

1. Antiplatelets
    - Cyclooxygenase inhibitor
        - Acetylsalicylic Acid (Aspirin)
    - Adenosine diphosphate (ADP) receptor inhibitors
        - Ticlopidine
        - Clopidogrel
        - Prasugrel
        - Ticagrelor
    - Glycoprotein IIb/IIIa inhibitors
        - Tirofiban

2. Anticoagulants
    - Vitamin K antagonist
        - Warfarin
    - Unfractionated heparin (UFH)
    - Low molecular weight heparin (LMWH)
        - Enoxaparin
    - Synthetic pentasaccharide factor Xa inhibitor
        - Fondaparinux
    - Direct factor Xa inhibitors
        - Rivaroxaban
        - Apixaban
    - Direct thrombin inhibitor
        - Dabigatran

Site of Action of Anti-Thrombotics

Antiplatelets

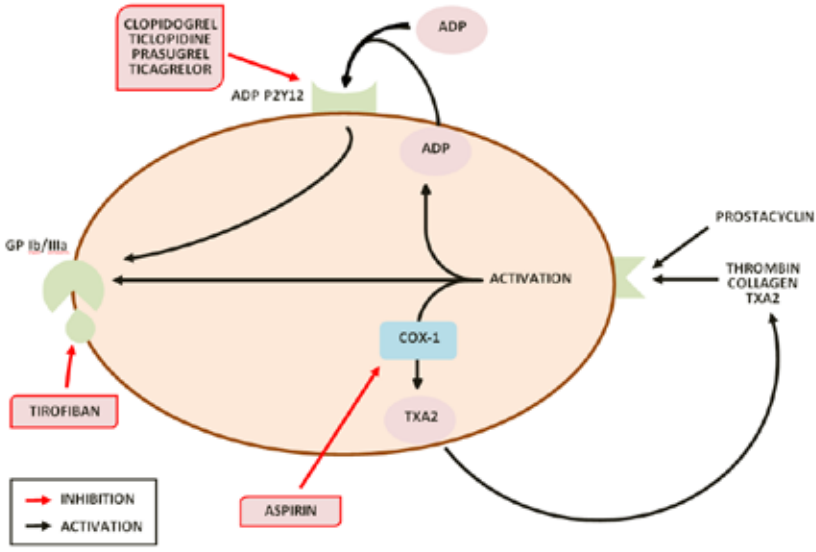


Figure 3: Site of inhibition of antiplatelets

Warfarin

Inhibits vitamin K-dependent clotting factors II, VII, IX, and X.

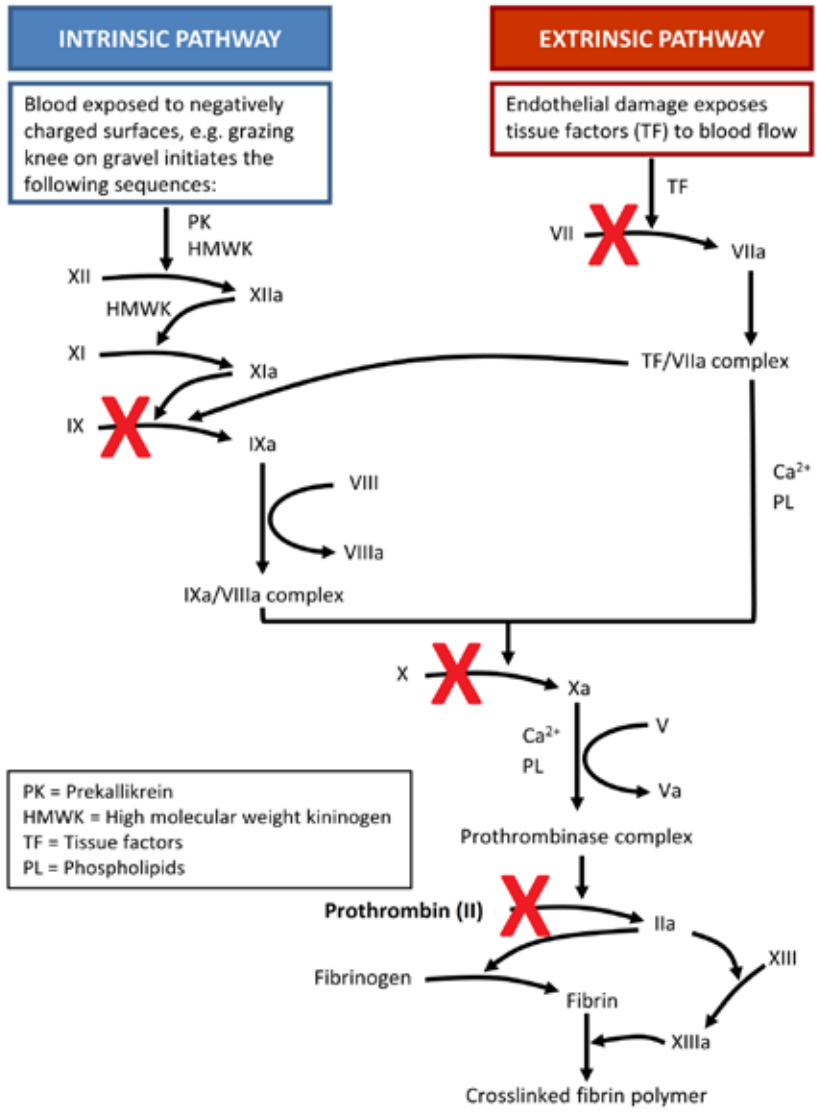


Figure 4: Coagulation cascade with site of inhibition of warfarin

Unfractionated Heparin

Inactivates factor Xa, IX, X, XI and XII and thrombin, and inhibits conversion of fibrinogen to fibrin. Also inhibits conversion of prothrombin to thrombin.

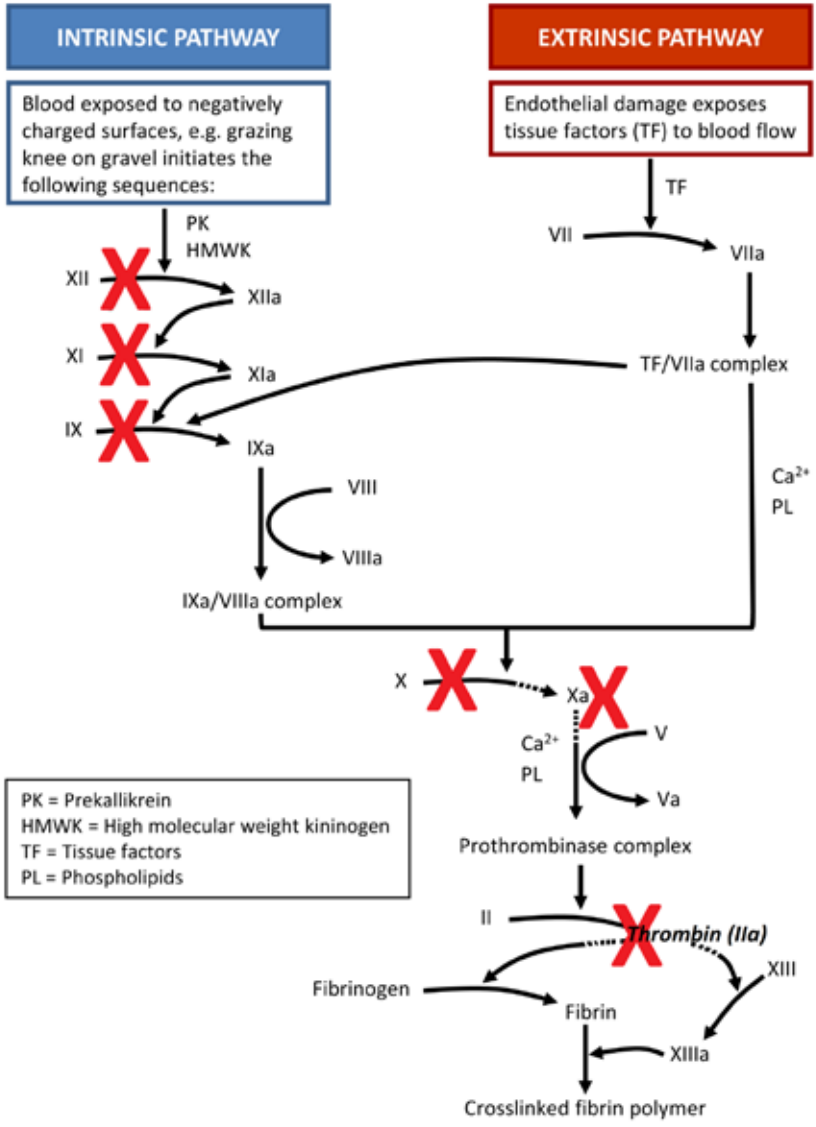


Figure 5: Coagulation cascade with site of inhibition of heparin

Factor Xa Inhibitors

E.g. Low molecular weight heparin (Enoxaparin), synthetic pentasaccharide factor Xa inhibitor (Fondaparinux), direct factor Xa inhibitor (Rivaroxaban, Apixaban).

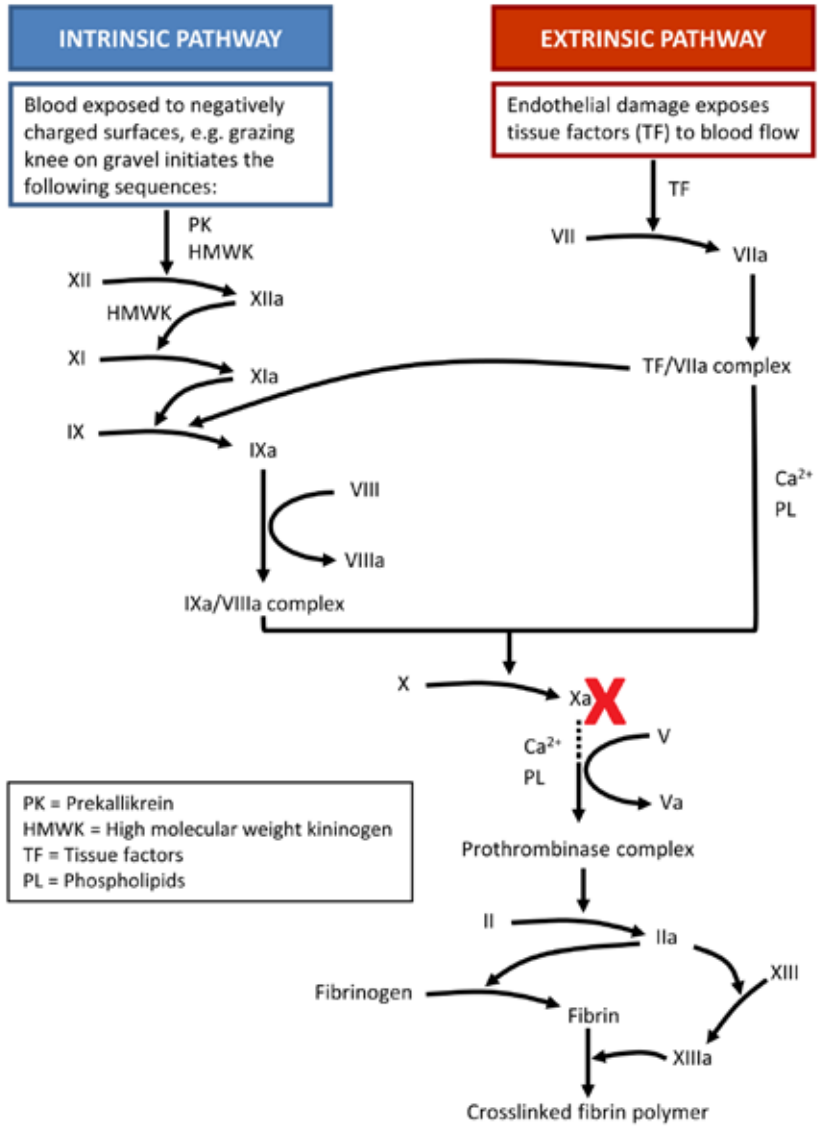


Figure 6: Coagulation cascade with site of inhibition of factor Xa inhibitors

Direct Thrombin Inhibitors

E.g. Dabigatran

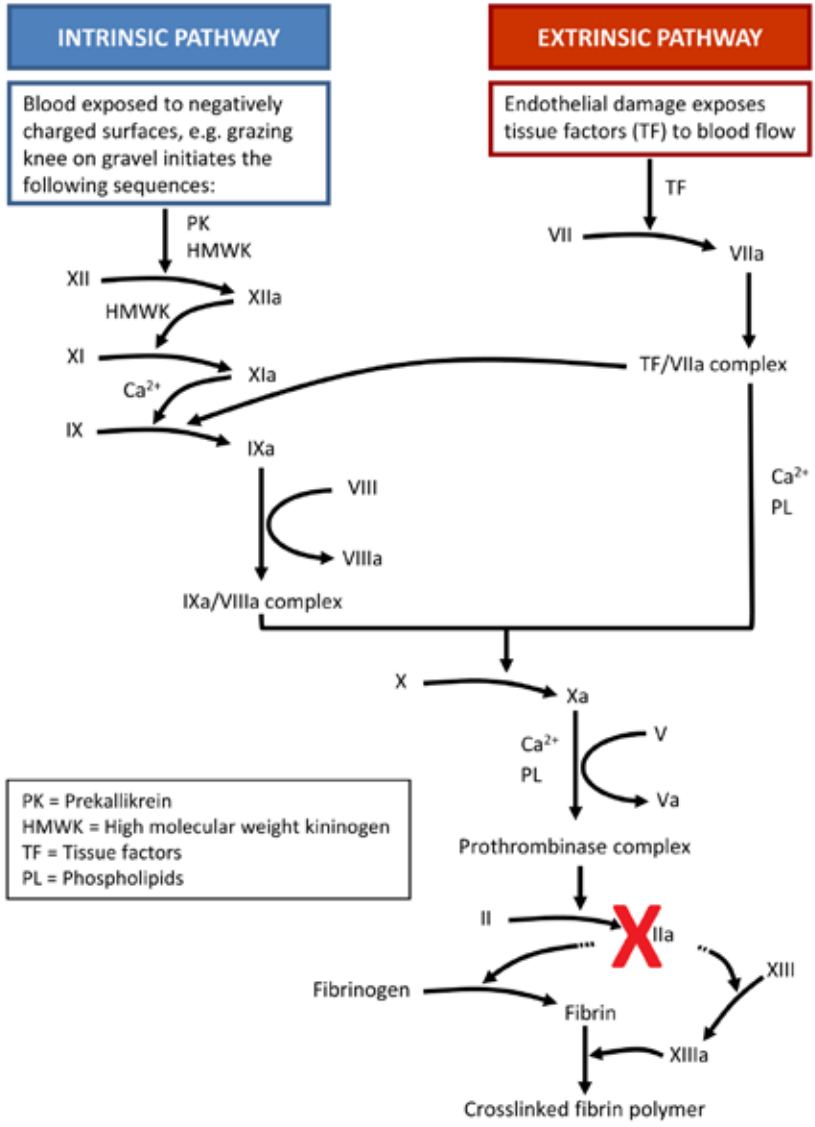
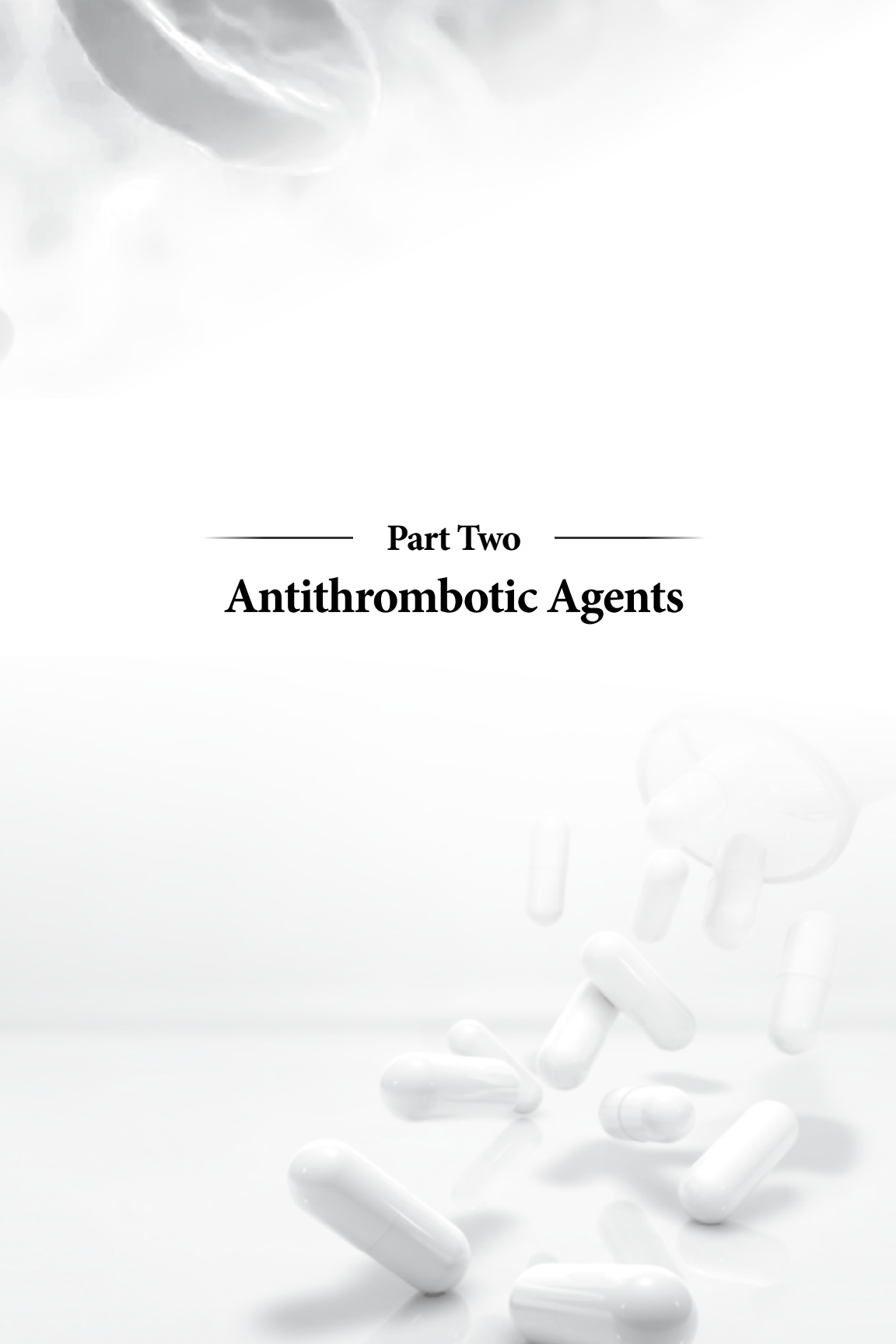


Figure 7: Coagulation cascade with site of direct thrombin inhibitors

Part Two
Antithrombotic Agents



Aspirin

1. Indications (ANTIPLATELET)
    - **Coronary Artery Disease (CAD)**
    - **Acute Coronary Syndrome (ACS)**
    - **Percutaneous Coronary Intervention (PCI)**
    - **Acute Ischemic Stroke and Transient Ischemic Attacks (TIAs)**
    - **Peripheral Artery Disease (PAD)**
    - **Coronary Artery Bypass Grafting (CABG)**
    - **Prosthetic Heart Valves**

2. Dosage
    - **CAD**
        - 75 to 150 mg OD lifelong
    - **ACS**
        - Loading dose 300 mg (non-enteric coated), then 75-150 mg OD; continued indefinitely; given as part of DAPT
    - **Primary PCI**
        - Loading dose 300 mg (non-enteric coated) as early as possible before PCI
        - 75 - 150 mg OD; continued indefinitely; given as part of DAPT
    - **Elective PCI**
        - Continue taking the usual dose for patients on long term aspirin
        - Loading dose 300 mg (non-enteric coated) at least 2 hours, preferably 24 hours before (PCI) procedure for aspirin naïve patients
        - 75 - 150 mg OD; continued indefinitely; given as part of DAPT

- **Acute Ischaemic stroke (non-cardioembolic)** and **TIA**
  - Loading dose 150 mg – 300 mg within 24-48 hours of acute ischaemic stroke onset, followed by 75 to 150 mg OD
  - Do not administer aspirin within 24 hours after administration of alteplase
  - Mild ischaemic stroke *(NIH stroke scale (NIHSS) score ≤ 3)* or TIA *(ABCD score ≥ 4)* as per CHANCE trial: Given in combination with clopidogrel i.e. DAPT. Aspirin and clopidogrel loading dose 300 mg, followed by aspirin and clopidogrel 75 mg OD for 21 days, then clopidogrel 75 mg only OD until 90 days after stroke, then antiplatelet monotherapy (either aspirin or clopidogrel)

- **PAD**
  - 75 to 300 mg OD

- **CABG**
  - 75 to 150 mg OD; continued indefinitely

- **Prosthetic heart valves**
  - 75 to 150 mg OD in addition to warfarin (mechanical heart valve)
  - 75 to 150 mg OD (bioprosthetic heart valve)

3. Dosage Adjustment

- **Renal Impairment**
  - Aspirin should be continued and the recommended dose should not be reduced in any patients with antithrombotic indication.
  - Aspirin is dialyzable and it is recommended to administer the dose after haemodialysis.

- **Hepatic Impairment**
  - Avoid use in severe liver disease

- **Geriatric**
  - ➢ No dosage adjustment
- **Paediatric**
  - ➢ No established evidence.
  - ➢ Empiric low doses of 1 - 5 mg/kg/day have been proposed
- **Pregnancy**
  - ➢ Pregnancy Category: D
- **Breastfeeding**
  - ➢ No aspirin is excreted into breast milk and salicylate levels are low with daily low dose aspirin (75 - 300 mg)
  - ➢ Monitor infant for bruising and bleeding if it is used by the nursing mother.

4. Concomitant drugs issues
   - Avoid using aspirin for 24 hours following administration of alteplase in the case of acute ischaemic stroke to prevent the risk of haemorrhagic transformation.

5. Checklist before starting the medication
   - Hypersensitivity or allergy to aspirin or other NSAIDs
   - Concomitant drug: other NSAIDs, other antiplatelets, anticoagulants
   - Full blood count
   - Bleeding/platelet disorder
   - Gastrointestinal disease
   - Severe hepatic disease
   - Others: asthmatic patient, heavy alcohol drinker (> 3drinks/day)

6. Monitoring parameters

    - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting or coughing out blood)
    - Full blood count
    - Renal function
    - Platelet function test – to measure inhibitory effect of aspirin on platelet aggregation (Optional)

7. Method of administration

    - Immediate-release tablets
        - ➢ administer with food or full glass of water to minimise gastrointestinal distress, or chew the tablet to achieve faster platelet inhibition (within 20 minutes)
        - ➢ Do not crush enteric-coated tablet
    - Extended-release capsules:
        - ➢ Do not cut, crush, or chew
        - ➢ Administer with a full glass of water

8. Counselling points

    - Take the dose at the same time after meal everyday
    - Store at room temperature. Avoid moisture and heat
    - If tablet cutting is needed, cut one tablet at a time
    - Monitor for any bleeding tendency, e.g. gum bleeding, longer than usual bleeding time
    - Inform doctor/pharmacist/dentist before any procedures, taking new medications, traditional product, or supplements

9. Mechanism of action

- Aspirin works by blocking the cyclooxygenase (COX) cascade, which activates the platelet aggregation. It irreversibly acetylates the COX-1 enzyme at a serine residual near its catalytic site, resulting in inhibition of prostaglandin H2 production, which is the precursor of thromboxane A2, a potent vasoconstrictor and platelet activator. As platelets do not have nucleus, platelets have minimal capability to synthesise new COX-1 enzyme. The effect of platelet inhibition by aspirin is therefore maintained throughout the life span of the platelet, approximately 7 - 10 days.

10. Pharmacokinetics

- Absorption
  - Immediate release: Rapidly absorbed in stomach and upper intestine
  - Extended-release capsule: Dependent upon food, alcohol, and gastric pH
- Distribution
  - Volume of distribution (Vd): 10 L; readily into most body fluids and tissues
  - Protein binding: ~ 90% to 94% (to albumin) at concentrations of salicylate ≤ 80 mcg/mL; ~ 30% with concentrations seen in overdose
- Metabolism
  - Hydrolysed to salicylate by esterase in gastrointestinal mucosa, red blood cells, synovial fluid, and blood; metabolism of salicylate occurs primarily by hepatic conjugation; metabolic pathways are saturable.
- Bioavailability
  - 50-70% (immediate release)

- Half-life elimination
  - Parent drug: Plasma concentration: 15 to 20 minutes
  - Salicylates (dose dependent): 3 hours at lower doses (300 to 600 mg), 5 to 6 hours (after 1 g), 10 hours with higher doses
- Time to peak, serum
  - Immediate release: ~ 1 to 2 hours (non-enteric-coated), 3 to 4 hours (enteric-coated);
  - Extended-release capsule: ~ 2 hours.
  - Chewing non-enteric-coated tablets results in a time to peak concentration of 20 minutes. Chewing enteric-coated tablets results in a time to peak concentration of 2 hours.
- Excretion
  - Urine (75% as salicyluric acid, 10% as salicylic acid)
- Onset of action (platelet inhibition)
  - Within 1 hour (non-enteric-coated), 20 minutes if chewed.
- Duration
  - Platelet inhibitory effect last the life time of the platelet (~10 days)

11. Adverse Effect (*Lists are NOT exhaustive)*
    - Gastrointestinal ulcer
    - Bleeding
    - Allergy reaction

Ticlopidine

1. Indication
    - **Prevent stent thrombosis following coronary stent implantation.**
    - **Reduce risk of thrombotic stroke (fatal or non-fatal) in patients who have experienced stroke precursors and in patients who had stroke**

      Note: Ticlopidine is no longer available in the US. Overall, the use of ticlopidine has been replaced by newer P2Y12 Inhibitors (i.e. clopidogrel, prasugrel, ticagrelor). Because of the risk of neutropenia, ticlopidine should only be used in patients with a documented intolerance to other platelet inhibitors.

2. Dosage
    - 250 mg BD

3. Dosage Adjustment
    - **Renal impairment**
        - ➢ No dosage adjustment provided in manufacturer's labelling.
        - ➢ While there were no statistically significant differences in ADP-induced platelet aggregation, AUC increases and clearance decreases were seen in patients with mild to moderate renal impairment. However, bleeding time may be prolonged in patients with moderate renal impairment.
        - ➢ Haemodialysis: not dialyzable
    - **Hepatic impairment**
        - ➢ No dosage adjustment provided in manufacturer's labelling. Use with caution.
        - ➢ Use is contraindicated in severe hepatic impairment.

- **Geriatric**
  - 250 mg BD
  - Dosage in older patients has not been determined. A dosage decrease may be necessary if bleeding develops.

- **Paediatric**
  - No established data on safety and efficacy, use is not recommended

- **Pregnancy**
  - Pregnancy Category: B
  -

- **Breastfeeding**
  - It is not recommended for use in nursing mothers
  - It is not known if ticlopidine is excreted in breastmilk. Due to the potential for serious adverse reactions in the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of treatment to the mother

4. Contraindication (*Lists are NOT exhaustive)*
   - Hypersensitivity to the drug and its excipients
   - Presence of haemopoietic disorders such as neutropenia, agranulocytosis, and thrombocytopenia
   - Presence of active pathological bleeding (e.g. bleeding, peptic ulcer or intracranial bleeding).
   - Patients with severe liver impairment or cholestatic jaundice
   - Elderly patients (>65 years) with renal and/ or hepatic impairment
   - Patients with severe heart failure with hepatic congestion

5. Checklist before starting the medication
   - Full blood counts

6. Monitoring parameters

    - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood).
    - Full blood counts every 2 weeks starting the second week through the third month of treatment. More frequent monitoring is recommended for patients whose absolute neutrophil counts have been consistently declining or are 30% less than baseline values. The peak incidence of thrombotic thrombocytopenic purpura (TTP) occurs between 3-4 weeks, and the incidence of aplastic anaemia peaks after 4-8 weeks of therapy.

7. Method of administration

    - Oral, to take with food

8. Mechanism of Action

    - Ticlopidine requires in vivo biotransformation to an unidentified active metabolite. This active metabolite irreversibly blocks the P2Y12 component of ADP receptors, which prevents activation of the GPIIb/ IIIa receptor complex, thereby reducing platelet aggregation. Platelets blocked by the ticlopidine are affected for the remainder of their lifespan (7-10 days).

9. Pharmacokinetic

    - Absorption:
        - Well absorbed
    - Onset of action
        - 6 hours. Peak effect: 3-5 days; serum levels do not correlate with clinical antiplatelet activity.
    - Distribution
        - Protein binding; parent drug: 98%; < 15% bound to $alpha_1$- acid glycoprotein.

- Metabolism
  - Extensively hepatic; has at least 1 active metabolite.
- Elimination
  - Half -life: 13 hours. Urine (60%); faeces (23%)

10. Adverse Effect (*Lists are NOT exhaustive)*
    - Diarrhoea
    - Nausea, and vomiting
    - Skin rash
    - Neutropenia is the most serious side effect reported with ticlopidine and occurs in 2.1% of ticlopidine-treated patients. This can be severe (<450 neutrophils per mm^3 in 0.9% of patients) and has resulted in several fatalities. Most cases develop within the first 3 months of therapy and initially may be clinically silent. Full blood counts should be performed every 2 weeks during the first 3 months of therapy to identify these potential complications.
    - Bone marrow aplasia and thrombotic thrombocytopenic purpura *(reversible after drug withdrawal)*
    - Cholestatic jaundice

Clopidogrel

1. Indication
    - **Coronary artery disease (CAD)**
    - **Acute coronary syndrome (ACS)**
    - **Percutaneous coronary intervention (PCI)**
    - **Coronary artery bypass graft surgery (secondary prevention)**
    - **Ischemic Stroke (non-cardioembolic)**
    - **Peripheral Arterial Disease (PAD)**

2. Dosage
    - **CAD**
        - 75 mg OD lifelong (monotherapy)
    - **ACS**
        - NSTE-ACS (Unstable Angina (UA)/Non-ST elevation myocardial infarction (NSTEMI))
            - Loading dose: 300 mg or 600 mg
            - Maintenance dose: 75 mg OD up to 1 year, as part of DAPT
        - ST elevation myocardial infarction (STEMI)
            - Primary PCI or not reperfused:
                - Loading dose: 300 mg or 600 mg
                - Maintenance dose: 75 mg OD up to 1 year, as part of DAPT
            - Fibrinolysis:
                - ≤75 years old: 300 mg loading dose, then maintain 75 mg OD up to 1 year, as part of DAPT
                - >75 years old: NO loading dose, then maintain 75 mg OD up to 1 year, as part of DAPT

- PCI
  - Primary PCI
    - Loading dose: 300 mg or 600 mg before PCI or at the time of PCI
    - Maintenance dose: 75 mg OD for up to 12 months in combination with aspirin (bare metal or drug-eluting stent), then continue with aspirin only indefinitely
  - Elective PCI
    - Continue taking the usual dose for patients on long term clopidogrel
    - Loading dose: 300 mg or 600 mg before PCI or at the time of PCI procedure for clopidogrel naïve patients
    - Maintenance dose: 75 mg OD for at least 1 month (bare metal stent) or 6 months (drug-eluting stent) in combination with aspirin, then continue with aspirin only indefinitely *(Duration of DAPT may differ on case-to-case basis)*

- **CABG**
  - 75 mg OD, in combination with aspirin, for 4 weeks – 12 months, then continue with antiplatelet monotherapy lifelong

- **Ischaemic stroke (non-cardioembolic)**
  - 75 mg OD as monotherapy
  - Mild ischaemic stroke *(NIHSS score ≤3)* or TIA *(ABCD score ≥4)* as per CHANCE trial: Given in combination with aspirin i.e. DAPT. Aspirin and clopidogrel loading dose 300 mg, followed by aspirin and clopidogrel 75 mg OD for 21 days, then clopidogrel 75 mg only OD until 90 days after stroke, then antiplatelet monotherapy (either aspirin or clopidogrel).

- **PAD**
  - 75 mg OD

3. Dosage adjustment

- **Renal impairment**
  - No dosage adjustment
  - Non-dialysable
- **Hepatic impairment**
  - No dosage adjustment
- **Geriatric**
  - No dosage adjustment
  - Refer to dosage
- **Paediatric**
  - Safety and efficacy not established in paediatric patients.
- **Pregnancy**
  - Pregnancy Category: B
- **Breastfeeding**
  - No published information. Manufacturer reports no adverse event observed in breastfed infants with maternal clopidogrel use during lactation in small number of post marketing cases.
  - An alternate drug may be preferred. If used, monitor the infant for bruising and bleeding.

4. Concomitant drug use

- Proton pump inhibitors (PPI)
  - Pharmacokinetic and pharmacodynamics studies suggest that concomitant use of PPI reduces the effect of clopidogrel. The strongest evidence of an interaction is between omeprazole and clopidogrel

- Pantoprazole has less effect on the pharmacological activity of clopidogrel than omeprazole

5. Contraindication (*Lists are NOT exhaustive)*
    - Active bleeding such as peptic ulcer and intracranial haemorrhage (ICH)
    - Significant liver impairment or cholestatic jaundice

6. Checklist before start medication
    - Hypersensitivity to clopidogrel or another thienopyridine (ticlopidine or prasugrel) *(cross–sensitivity among thienopyridine has been reported)*
    - Full blood count
    - Bleeding/platelet disorder
    - Concomitant antiplatelet or anticoagulant
    - Gastrointestinal disease

7. Monitoring Parameter
    - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting or coughing out blood)
    - Full blood count
    - Allergy reaction
    - Platelet function test to measure platelet aggregation inhibitory effect of clopidogrel (Optional)
    - Genetic testing – To identify CYP2C19 poor metaboliser of clopidogrel to its active metabolite (Optional)

8. Counselling points
    - Take the dose at the same time every day without regard to meal
    - Store at room temperature. Avoid moisture and heat.
    - Monitor for any bleeding tendency, e.g. gum bleeding, longer than usual bleeding time
    - Inform doctor/pharmacist/dentist before any procedures, taking new medications, traditional product, or supplements

9. Peri-operative management
    - Discontinue clopidogrel 5 to 7 days prior to surgery

10. Mechanism of action
    - Clopidogrel is a prodrug that requires *in vivo* biotransformation into its active metabolites by CYP450 enzymes. The active metabolite of clopidogrel selectively and irreversibly inhibits the binding of adenosine diphosphate to its $P2Y_{12}$ receptor on platelets. This will in turn prevent the activation of the glycoprotein GPIIb/IIIa receptor complex, thereby inhibiting the platelet aggregation.

11. Pharmacokinetics
    - Absorption
        - Rapid, well absorbed
    - Distribution
        - Vd: 12.6 L
        - Protein binding
            - Parent drug: 98%;
            - Inactive metabolite (carboxylic acid derivative): 94%

- Metabolism
  - Extensively hepatic via esterase-mediated hydrolysis to an inactive carboxylic acid derivative (85% of circulating metabolites) and via CYP450-mediated (CYP2C19 primarily) oxidation to 2-oxo-clopidogrel intermediate metabolite then to an active thiol metabolite.

- Half-life elimination
  - Parent drug: ~6 hours
  - Thiol derivative: ~30 minutes
  - Carboxylic acid derivative ~8 hours

- Time to peak, serum
  - ~45 minutes after dosing

- Excretion
  - Urine (50%)
  - Faeces (46%)

- Onset of action
  - 300 mg loading dose – within 2 hours
  - 75 mg daily dose – second day of treatment

- Time to maximal Inhibition of Platelet Aggregation (IPA)
  - 300 mg – 600 mg loading dose
    - 20% – 30% IPA at 6 hours post administration
  - 75 mg daily dose
    - 50% - 60% IPA at 5 – 7 days

- Duration of action
  - Platelet aggregation and bleeding time return to normal after about 5 days of discontinuation

12. Adverse Effect (*Lists are NOT exhaustive)*
    - Gastrointestinal haemorrhage
    - Haematoma
    - Epistaxis
    - Minor or major haemorrhage

Genotyping and platelet function testing for clopidogrel response

Dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor, remains the mainstay for secondary prevention of atherothrombotic events in patients with acute coronary syndromes (ACS), with or without revascularization. In Malaysia, clopidogrel remains as the P2Y12 inhibitor of choice primarily due to economic considerations.

Recurrent thrombotic events are still being reported in a substantial number of revascularized ACS patients who were prescribed DAPT with clopidogrel. Failure of these patients to response adequately to clopidogrel treatment is often described as high on treatment platelet reactivity (HOTPR). Prevalence of clopidogrel HOTPR in our Malaysian population is approximately 30%. However, the prevalence of aspirin HOTPR is relatively low in our population at approximately 10%. Clopidogrel is a prodrug which undergoes a 2-step metabolism by the CYP2C19 enzyme pathway into the active metabolite. The CYP2C19 enzyme is highly polymorphic and therefore, attributed to high interindividual variability in clopidogrel response. Patients who have wild-type allele CYP2C19*1/*1 are associated with normal enzyme activity while those who have loss-of-functional (LOF) alleles e.g. *2 and *3 are associated with suboptimal clopidogrel response. Individuals with one and two reduced-activity or non-functioning CYP2C19 alleles are termed as 'intermediate metabolizers' and 'poor metabolizers'; respectively. Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are *CYP2C19* poor metabolisers. LOF alleles are highly prevalent in our population at approximately up to 50% and 12% for *2 and *3; respectively. These CYP2C19 LOF alleles can now be rapidly determined with point-of-care (POC) instrument, the Spartan RX system that requires minimal laboratory training for its operation.

Besides genotyping, platelet reactivity after clopidogrel treatment can also be determined by readily available POC tools such as the Multiplate® and VerifyNow® system. Platelet function tests (PFT) from different POC devices have different cut-off values to predict response to clopidogrel treatment. However, routine use of these tools is currently not recommended (Class III). The main reasons are: Different assays were used and there was no universal cut off for DAPT HOTPR. Previous RCTs have failed to demonstrate that genotyping or PFT guided therapy and switching clopidogrel to more potent ticagrelor or prasugrel would improve clinical outcome. To date, no conclusive link has been demonstrated between CYP2C19 genotype polymorphism, platelet reactivity, and clinical outcome.

A study conducted by the research team at Sarawak Heart Centre to ascertain the association between CYP2C19*2 genetic polymorphism with platelet reactivity and clinical outcome, was able to demonstrate that having clopidogrel HOTPR, is an independent predictor (adjHR: 3.5 95% CI [1.2, 10.10]) of major adverse cardiovascular events in an elective population implanted with drug eluting stent. This echoed the findings of the most recent ADAPT-DES trial. However, further studies are warranted to explore the use of genotyping and PFT in different subsets of high-risk patients.

Ticagrelor

1. Indication
    - **Acute Coronary Syndrome (UA, NSTEMI, STEMI) managed medically or with PCI or CABG**
      (PLATO)

2. Dosage
    - Loading dose: 180 mg
    - Maintenance dose: 90 mg BD, initiated 12 hours after initial loading dose

3. Dosage Adjustment
    - **Renal impairment**
        - ➢ No dose adjustment
        - ➢ No information is available regarding patients on renal dialysis, not recommended in these patients.
    - **Hepatic impairment**
        - ➢ No dose adjustment for patients with mild hepatic impairment
        - ➢ No information is available for moderate to severe hepatic impairment patient, contraindicated in these patients.
    - **Geriatric**
        - ➢ No dose adjustment
    - **Paediatric**
        - ➢ No data available for children below age of 18
    - **Pregnancy**
        - ➢ Not recommended during pregnancy *(studies in animals have shown reproductive toxicity)*

- **Breastfeeding**
  - Risk to new-borns/infants cannot be excluded *(studies in animals have shown excretion of ticagrelor and its active metabolites in milk)*

4. Contraindication (*Lists are NOT exhaustive)*
   - Active pathological bleeding (e.g. peptic ulcer bleeding, intracranial haemorrhage)
   - History of intracranial haemorrhage *(due to high risk of recurrent intracranial haemorrhage)*
   - Moderate to severe hepatic impairment
   - Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir)
   - Hypersensitivity to ticagrelor or any component of the formulation

5. Checklist before starting the medication
   - Ensure no contraindications to ticagrelor such as active pathological bleeding, history of intracranial haemorrhage
   - Moderate to severe hepatic impairment
   - Co-administration of ticagrelor with strong CYP3A4 inhibitors

6. Monitoring parameters
   - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood)
   - Breathlessness/ dyspnoea *(Ticagrelor increases local endogenous adenosine levels by inhibiting ENT-1. Adenosine has been documented to cause induction of dyspnoea. In PLATO trial, dyspnoea was reported by 13.8% of patients treated with ticagrelor and by 7.8% of patients treated with clopidogrel. It is usually mild to moderate in intensity and often resolves without need for treatment discontinuation)*

- Bradycardiac event (*In earlier clinical study, asymptomatic ventricular pauses have been observed. Therefore, patients with increased risk of bradycardiac events (patients without pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from the main PLATO study evaluating the safety and efficacy of ticagrelor).*
- Check for any abnormalities in laboratory parameters (e.g. liver profile, full blood count)
- Check for uric acid levels *(for patient with gout or at risk of hyperuricemia)*

7. Method of administration
    - Administer orally with or without food
    - Tablets may be crushed to a fine powder and mixed with water to create a suspension for oral or NG use for patients unable to swallow whole tablet
    - If administered via nasogastric (NG) tube (CH8 or greater), flush NG tube through with water after administration

8. Counselling point
    - Avoid premature discontinuation of treatment to prevent increase risk of cardiac events (e.g. stent thrombosis, myocardial infarction, death)
    - To complete the duration of therapy needed, in which the duration is determined by the type of stent placedor the ACS event.
    - Notify healthcare providers promptly if experiences shortness of breath/wheezing, sign and symptoms of bleeding (e.g. blood in urine, blood in stool/black stools)

9. Missed dose
    - Missed dose should be taken at its next scheduled time (should take only one 90 mg tablet)

10. Pre-operative management
    - Discontinue use at least 3 days before any surgery

11. Mechanism of Action
    - Direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$ platelet activation and aggregation
    - Increase local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine has been documented to have vasodilation, cardioprotection, platelet inhibition, modulation of inflammation and induction of dyspnoea

12. Pharmacokinetic
    - Absorption
        - Rapid with a median time of peak concentration (Tmax) of approximately 1.5 hours
    - Distribution
        - Vd: 87.5 L
        - Protein binding: > 99% (parent drug & active metabolite)
    - Metabolism
        - hepatic via CYP3A4/5 to active metabolite (AR-C124910XX)
    - Half-life
        - 7 hours (ticagrelor), 8.5 hours (active metabolite)
    - Elimination
        - Faeces (57.8%)
        - Urine (26.5%)

- Onset of action
  - 41% Inhibition of Platelet Aggregation (IPA) at 0.5 hour after 180 mg loading dose. Maximum IPA effect of 89% by 2-4 hours post dose

13. Adverse Effect (*Lists are NOT exhaustive)*
    - Bleeding
    - Dyspnoea
    - Ventricular pauses and bradycardiac events
    - Hyperuricemia

Prasugrel

1. Indication
   - **Acute Coronary Syndrome (UA, NSTEMI, STEMI) with PCI**
     (Triton-TIMI 38)

2. Dosage
   - Loading dose: 60 mg
   - Maintenance dose: 10 mg OD. Consider 5 mg OD for patients < 60kg

3. Dosage Adjustment
   - **Renal impairment**
     - No dose adjustment
     - There is limited experience in patients with end stage renal disease
   - **Hepatic impairment**
     - No dose adjustment for patients with mild-moderate hepatic impairment (Child-Pugh Class A and B)
     - No information is available for severe hepatic impairment patient, not recommended in these patients
   - **Geriatric**
     - ≥ 75 years old, use not recommended *(increased risk of fatal bleeding)*
     - May be considered in high-risk situations (e.g. patients with diabetes or history of MI) where the effect is greater.
   - **Paediatric**
     - No data available for paediatric patients

- **Pregnancy**
  - Pregnancy Category: B
  - Should be used during pregnancy only if potential benefit to the mother justifies the potential risk to the foetus *(no adequate and well-controlled studies of prasugrel use in pregnant women).*

- **Breastfeeding**
  - Should be used during breastfeeding only if the potential benefit to the mother justifies the potential risk to the infant *(metabolites of prasugrel were found in rat milk)*

- **Low Body Weight**
  - < 60kg: Consider 5 mg OD as maintenance dose
  - Increased risk of bleeding and increased exposure to the active metabolite of prasugrel in this group of patients.

4. Contraindication (*Lists are NOT exhaustive)*
   - Active pathological bleeding (e.g. peptic ulcer bleeding, intracranial haemorrhage)
   - Prior TIA or stroke (*In TRITON-TIMI 38 trial, patients with a history of TIA or ischemic stroke (> 3 months prior to enrolment) had a higher rate of stroke on prasugrel (6.5%; of which 4.2% were thrombotic stroke and 2.3% were intracranial haemorrhage) than on clopidogrel (1.2%; all thrombotic). Patients with history of ischemic stroke within 3 months and patients with history of haemorrhagic stroke at any time were excluded from the trial)*
   - Hypersensitivity to prasugrel or any component of the formulation

5. Checklist before starting the medication
   - Ensure no contraindications to prasugrel such as active pathological bleeding, prior TIA or stroke
   - Patients with ACS who are to be managed by PCI only

- Do not start in patients likely to undergo CABG *(increased risk of bleeding)*
- Generally, not recommended for patients ≥ 75 years old except in high-risk situations (patients with diabetes or history of MI)

6. Monitoring parameters
   - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood)
   - Check for any abnormalities in laboratory parameters (e.g. liver profile, haemoglobin level)

7. Method of administration
   - Administer orally with or without food
   - Tablets may be crushed or mixed in food or water and immediately administered by mouth or gastric tube
   - Administration via enteral tube that bypasses the acidic environment of stomach may result in reduced bioavailability of prasugrel

8. Counselling point
   - Avoid premature discontinuation of treatment to prevent increased risk of cardiac events (e.g. stent thrombosis, myocardial infarction, death)
   - To complete the duration of therapy needed, in which the duration is determined by the type of stent placed
   - Notify healthcare providers promptly if experiences sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood)

9. Pre-operative management
   - Discontinue use at least 7 days before any surgery

10. Mechanism of Action
    - An inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to $P2Y_{12}$ class of ADP receptors on platelet

11. Pharmacokinetic
    - Absorption
        - Rapid
        - Peak plasma concentrations of the active metabolite occurring approximately 30 minutes after dosing
    - Distribution
        - Vd: 44-68 L
        - Protein Binding: 98% active metabolite
    - Metabolism
        - Rapidly hydrolysed in intestine to a thiolactone, which is then converted to active metabolite by a single step, primarily by CYP3A4 and CYP2B6
    - Elimination
        - Urine (68%)
        - Faeces (27%)

12. Adverse Effect (*Lists are NOT exhaustive)*
    - Bleeding
    - Thrombotic thrombocytopenic purpura (TTP)
    - Hypersensitivity (e.g. angioedema)

Double Antiplatelet Duration (DAPT)

1. DAPT in patients with coronary artery disease

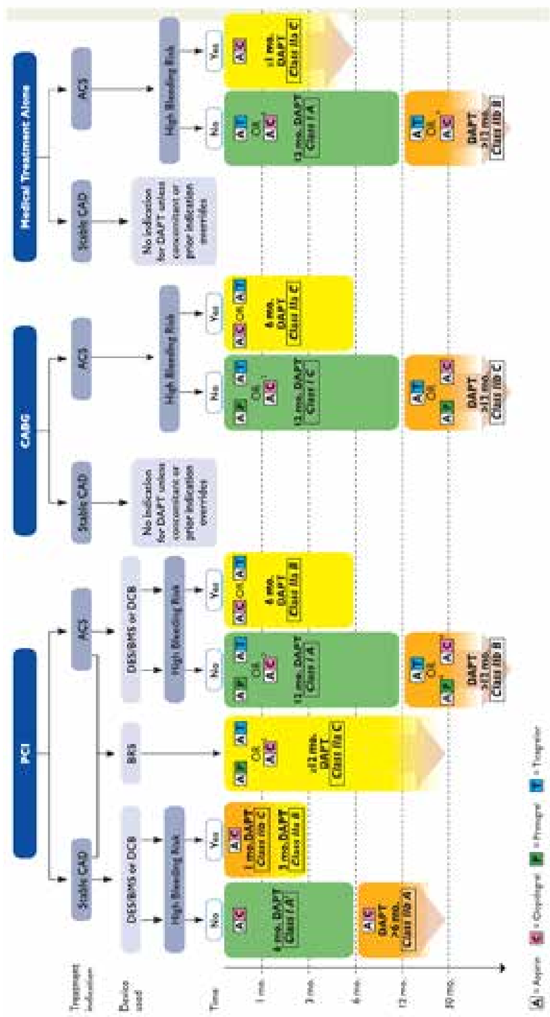


Figure 8: Algorithm for DAPT in Patients with Coronary Artery Disease

ACS = acute coronary syndrome, BMS = bare-metal stent; BRS = bioresorbable vascular scaffold; CABG = Coronary artery bypass graft; DCB = drug-coated balloon; DES: drug-eluting stent; PCI = percutaneous coronary intervention; Stable CAD = stable coronary artery disease. High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).

Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb). Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.

[1]: After PCI with DCB 6 months. DAPT should be considered (Class IIa B).

[2]: If patient presents with Stable CAD or, in case of ACS, is not eligible for a treatment with prasugrel or ticagrelor.

[3]: If patient is not eligible for a treatment with prasugrel or ticagrelor.

[4]: If patient is not eligible for a treatment with ticagrelor.

Source: ESC Clinical Practice Guidelines 2017; Focused update on Dual Antiplatelet Therapy (DAPT)

A. Percutaneous coronary intervention

- Stable CAD
  - 6-month DAPT for patient with stable CAD treated with Coronary stent implantation, irrespective of stent types.
  - Patients with stable CAD treated with drug-coated balloon, DAPT for 6 months should be considered
  - Patients with stable CAD treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.
  - Patients who have high bleeding risk (PRECISE-DAPT ≥25), 3-month DAPT should be considered. 1-month DAPT may be considered if 3-month DAPT poses safety concerns.
  - Continue DAPT with clopidogrel beyond 6 months and ≤ 30 months may be considered for patients with stable CAD (treated with PCI) who have tolerated DAPT without bleeding complications and who are at low bleeding risk but high thrombotic risk.
  - Drug of choice:
    - Aspirin in combination with clopidogrel is indicated in this population.
    - While there are no RCTs on ticagrelor or prasugrel in stable CAD patients undergoing PCI, they can be considered in selected patients in whom the use of clopidogrel is unsatisfactory based on prior clinical outcomes or associated with higher ischaemic risk than bleeding risk.

- ACS
  - 12-month DAPT should be given to patients with ACS treated with coronary stent implantation unless there are contraindication such as high bleeding risk (PRECISE-DAPT ≥25)
  - 6-month DAPT should be considered for patients with ACS who have high bleeding risk (PRECISE-DAPT ≥25)
  - Continue DAPT beyond 12 months (until 30 months) may be considered for patients with ACS who have tolerated DAPT without bleeding complications.

- Drug of choice:
  - Ticagrelor or prasugrel is preferred over clopidogrel in DAPT in patients with ACS

B. CABG

- Stable CAD/Non-emergent surgery
  - ESC (2017) guideline does not recommend DAPT in stable CAD patients undergoing CABG *while ACC/AHA (2016) guideline gives a Class IIb evidence in giving DAPT up to 12 months to stable IHD patients undergoing CABG.*
  - In patients on aspirin who need to undergo non-emergent cardiac surgery, it is recommended to continue aspirin at a low daily regime throughout the perioperative period
  - In patients on P2Y12 inhibitors who need to undergo non-emergent cardiac surgery, postponing surgery for at least 3 days after discontinuation of ticagrelor, at least 5 days after clopidogrel and at least 7 days after prasugrel should be considered

- ACS
  - In patients with ACS (NSTE-ACS or STEMI) treated with DAPT, undergoing CABG, and not requiring long-term OAC therapy, resumption of P2Y12 inhibitor therapy post-operation to complete 12 months of DAPT is recommended.
  - Continue DAPT for longer than 12 months and up to 36 months may be considered for patients with prior MI and CABG who have tolerated DAPT without bleeding complications and who are perceived to have high ischaemic risk.
  - In CABG patients with prior MI who are at high risk of severe bleeding ACS (PRECISE-DAPT ≥25), discontinuation of P2Y12 inhibitor therapy after 6 months should be considered

C. Medical Therapy

- Stable CAD
  - ➢ No indication for DAPT
- ACS
  - ➢ 12-month DAPT should be given to patient with ACS who are given medical therapy alone.
  - ➢ At least 1-month DAPT should be considered for patients with ACS who are treated medically and at high risk of bleeding (PRECISE-DAPT ≥25).
  - ➢ Drug of choice:
    - Ticagrelor or clopidogrel is recommended on top of aspirin in DAPT for medically treated patients with ACS.
    - Ticagrelor is preferred unless bleeding risk outweighs the ischaemic benefit.
    - Prasugrel is not recommended in medically treated patients.

2. DAPT in patients with ischaemic stroke (non-cardioembolic)

- Mild ischaemic stroke *(NIHSS score ≤ 3)* /TIA *(ABCD score ≥ 4)*
  - ➢ CHANCE Trial Protocol: Aspirin and clopidogrel loading dose 300 mg, followed by aspirin and clopidogrel 75 mg OD for 21 days, then clopidogrel 75 mg only OD until 90 days after stroke, then antiplatelet monotherapy (either aspirin or clopidogrel).
- Not recommended for moderate to severe stroke

Risk scores as guidance for the duration of dual antiplatelet therapy

	PRECISE-DAPT score[18]	DAPT score[19]
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)
Score calculation*	HB ≥12 11.5 11 10.5 ≤10 WBC ≤3 8 10 12 14 16 18 ≥20 Age ≤50 60 70 80 ≥90 CrCl ≥100 80 60 40 20 0 Prior Bleeding No Yes Score Points 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	Age ≥75 −2 pt 65 to <75 −1 pt <65 0 pt Cigarette smoking +1 pt Diabetes mellitus +1 pt MI at presentation +1 pt Prior PCI or prior MI +1 pt Paclitaxel-eluting stent +1 pt Stent diameter <3 mm +1 pt CHF or LVEF <30% +2 pt Vein graft stent +2 pt
Score range	0 to 100 points	−2 to 10 points
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT
Calculator	www.precisedaptscore.com	www.daptstudy.org

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Figure 9: Risk Scores Validated for Dual Antiplatelet Therapy Duration Decision-Making
Source: SC Clinical Practice Guidelines 2017; Focused update on Dual Antiplatelet Therapy (DAPT)

- PRECISE-DAPT Score:
  - Prediction algorithm for out of-hospital bleeding in patients treated with DAPT. To decide whether to give short DAPT (3-6 months) or standard/long DAPT (12-24 months)
  - Patient with high bleeding risk (PRECISE-DAPT score ≥ 25), prolonged DAPT (12-24 months) was associated with no ischaemic benefit but a remarkable bleeding burden.
  - Patient without high bleeding risk (PRECISE-DAPT score < 25), prolonged DAPT showed significant reduction in MI risk, stent thrombosis, stroke, and target vessel revascularization without an increase in bleeding risk.
  - However, this score is not tested in RCT. The value in improving patient outcome is still unclear.

- DAPT Score
  - To decide standard 12-months or 30-months long DAPT duration
  - In DAPT trial, **high risk (≥ 2)** score selected patients who showed a reduction in MI/stent thrombosis and cardiovascular or cerebrovascular events risk after given **30-month DAPT** with a modest increase in bleeding risk
  - **Low-risk score (< 2)** selected patients recruited in the DAPT trial **who did not derive any reduction of ischaemic events from prolonging DAPT**, with a significant increase in moderate/major bleeding.
  - The value of DAPT score in guiding duration of therapy has so far only shown for patients recruited in the DAPT trial. Additional validation of the DAPT score to guide DAPT duration is needed.

Tirofiban Hydrochloride

1. Indication

   - **Used in combination with heparin for patients with unstable angina or non-Q-wave myocardial infarction to prevent cardiac ischemic events** (*PRISM, PRISM-PLUS)*
   - **Used in patients with acute coronary syndromes undergoing coronary angioplasty or atherectomy to prevent cardiac ischemic complications related to abrupt closure of the treated coronary artery (***RESTORE)*

2. Dosage

   - **Unstable Angina Pectoris or Non-Q-Wave Myocardial Infarction:**
     - Bolus dose infusion rate: 0.4 μg/kg/min over 30 minutes
     - Maintenance dose infusion rate: 0.1 μg/kg/min

Table 1: Recommended Loading and Maintenance Dosing

Table 1.

Patient Weight (kg)	Most Patients		Severe Renal Insufficiency	
	30-Min Loading Infusion Rate (mL/hr)	Maintenance Infusion Rate (mL/hr)	30-Min Loading Infusion Rate (mL/hr)	Maintenance Infusion Rate (mL/hr)
30-37	16	4	8	2
38-45	20	5	10	3
46-54	24	6	12	3
55-62	28	7	14	4
63-70	32	8	16	4
71-79	36	9	18	5
80-87	40	10	20	5
88-95	44	11	22	6
96-104	48	12	24	6
105-112	52	13	26	7
113-120	56	14	28	7
121-128	60	15	30	8
129-137	64	16	32	8
138-145	68	17	34	9
146-153	72	18	36	9

Source: Adapted *from [package insert] AGGRASTAT® (Tirofiban Hydrochloride) concentrate for infusion Espoo (Finland) 2009*

- **Angioplasty /Atherectomy**
  - In high-risk NSTE-ACS patients who undergo PCI within 4 hours of diagnosis, tirofiban is administered intravenously at the start of PCI utilizing an initial bolus dose of 25 µg/kg given over a 3-minute period, followed by a continuous infusion at a rate of 0.15 µg/kg/min for 12-24 hours.

Table 2: Recommended Loading and Maintenance Dosing

Patient Weight (kg)	Most Patients 25 µg/kg Dose Bolus Regimen		Patients with Severe Kidney Failure 25 µg/kg Dose Bolus Regimen	
	Bolus (ml)	Maintenance Infusion Rate (ml/hr)	Bolus (ml)	Maintenance Infusion Rate (ml/hr)
30-37	17	6	8	3
38-45	21	7	10	4
46-54	25	9	13	5
55-62	29	11	15	5
63-70	33	12	17	6
71-79	38	14	19	7
80-87	42	15	21	8
88-95	46	16	23	8
96-104	50	18	25	9
105-112	54	20	27	10
113-120	58	21	29	10
121-128	62	22	31	11
129-137	67	24	33	12
138-145	71	25	35	13
146-153	75	27	37	13

Source: Adapted from [product monograph] AGGRASTAT® (Tirofiban Hydrochloride Injection) 12.5 µg/ 250ml Infusion (Canada) 2018

3. Dosage Adjustment

- **Renal Impairment**
  - Decrease infusion rate by half for patients with creatinine clearance <30 mL/min *(refer to dosage)*
  - Tirofiban can be removed by haemodialysis

- **Hepatic Impairment**
  - In patients with mild to moderate hepatic insufficiency, plasma clearance of tirofiban is not significantly different from clearance in healthy subjects.

- **Geriatric**
  - No dose adjustment is recommended for the elderly (≥ 65 years) population
  - Plasma clearance is about 19 to 26% lower in elderly (> 65 years) patients with coronary artery disease than in younger (≤ 65 years) patients
  - Elderly patients receiving Tirofiban with heparin or heparin alone had a higher incidence of bleeding complications than younger patients, but the incremental risk of bleeding in patients treated with Tirofiban in combination with heparin compared to the risk in patients treated with heparin alone was similar regardless of age

- **Paediatric**
  - Safety and effectiveness have not been established

- **Pregnancy**
  - Pregnancy Category: B
  - There are no adequate and well-controlled studies in pregnant women.
  - Tirofiban has been shown to cross the placenta in pregnant rats and rabbits. Studies with Tirofiban at intravenous doses up to 5 mg/kg/day (about 5 and 13 times the maximum recommended daily human dose for rat and rabbit, respectively, when compared on a body surface area basis) have revealed no harm to the foetus.

- **Breastfeeding**
  - ➢ It is not known whether Tirofiban is excreted in human milk. However, significant levels of Tirofiban were shown to be present in rat milk. Because many drugs are excreted in human milk, and because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue Tirofiban, considering the importance of the drug to the mother.

4. Contraindication
   - known hypersensitivity to any component of the product
   - active internal bleeding or a history of bleeding diathesis within the previous 30 days
   - a history of intracranial haemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm
   - a history of thrombocytopenia following prior exposure to tirofiban

5. Checklist Before Initiation
   - Platelet counts
   - Haemoglobin
   - Haematocrit
   - Creatinine clearance (CrCl)

6. Monitoring parameters
   - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood).
   - Monitor platelet counts, creatinine clearance, haemoglobin and haematocrit prior to treatment, within 6 hours following the bolus or loading infusion, and at least daily thereafter during therapy with tirofiban (or more frequently if there is evidence of significant decline).
   - If platelet count decreases to <90,000 cells/mm^3, additional platelet counts should be performed to exclude pseudothrombocytopenia.

7. Instruction for Administration

- To administer intravenously using sterile equipment; may be co-administered with heparin through the same line.
- Use calibrated infusion device. Avoid prolonged loading infusion.
- Calculate bolus dose and infusion rate based on patient body weight
- In clinical studies, patients received Aspirin unless contraindicated.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permits.
- It comes as a sterile concentrate, clear and colourless solution in a 50 mL glass vial for intravenous infusion after dilution. It **must be diluted** prior to administration. It contains no antimicrobial agent. Use once only and discard any residue.

- Directions for Preparation of Tirofiban Solution for Infusion
  - Withdraw and discard 50 mL from a 250 mL bag of sterile 0.9% saline or 5% glucose in water and replace it with 50 mL of Tirofiban (from one 50 mL vial) to achieve a final concentration of 50 µg/mL. Mix well before administration. Alternatively, withdraw and discard 100 mL from a 500 mL bag of sterile 0.9% saline or 5% glucose in water and replace it with 100 mL of Tirofiban (from two 50 mL vials) to achieve a final concentration of 50 µg/mL. Mix well before administration.
  - Administer according to the appropriate dosage adjustments by weight above.
  - To reduce microbiological hazard, use as soon as practicable after dilution.
  - Discard any unused intravenous solution after 24 hours following start of infusion. If storage is necessary, hold at 2-8 °C for not more than 24 hours.

8. Compatibility
    - Intravenous (IV) Incompatibilities
        - Y-site: Diazepam
    - Intravenous (IV) Compatibilities
        - Solution: Dextrose 5%, Dextrose 5% in sodium chloride 0.45%, Normal Saline

9. Mechanism of Action
    - Tirofiban is a non-peptide antagonist of the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. Tirofiban prevents binding of fibrinogen to GP IIb/IIIa, thereby blocking the cross-linking of platelets and platelet aggregation

10. Pharmacokinetic
    - Onset
        - > 90% of IPA attained by end of the 30–minute infusion
        - Platelet aggregation inhibition is reversible following discontinuation of the infusion
    - Half-life
        - 1.4-1.8 hours (healthy subjects), 1.9-2.2 hours (patients with coronary artery disease)
    - Distribution
        - Vd: 22-42 L
        - Protein bound: 65%
    - Plasma Clearance
        - 213-314 mL/min (healthy subjects), 152 to 267 mL/min (patients with coronary artery disease)

- Excretion
  - Urine 65% (unchanged)
  - Faeces 25% (unchanged)
- Dialyzable
  - Yes (Haemodialysis)
- Metabolism
  - Limited metabolism. Remains mostly as unchanged tirofiban in urine and faeces

11. Adverse Effect (*Lists are NOT exhaustive)*
    - Bradyarrhythmia
    - Haemorrhage
    - Pain in pelvis
    - Coronary artery dissection
    - Thrombocytopenia
    - Anaphylaxis, Hypersensitivity reaction
    - Intracranial haemorrhage
    - Pulmonary haemorrhage

Warfarin

1. Indication and International normalized ratio (INR) target

Table 3: Indication and INR target

Thromboembolic Disorder	INR range	Duration of warfarin
Venous Thromboembolism (VTE) – Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE)		
First VTE provoked by a transient surgical risk factor and nonsurgical risk factor	2 – 3	3 months
First unprovoked VTE		Offer indefinite anticoagulation after taking into account: • Patient's preference • Low bleeding risk • Good anticoagulant monitoring is achievable
First unprovoked VTE and one or more bleeding risk		3 months
First unprovoked VTE in association with active cancer and the anti-phospholipid syndrome		Anticoagulation is continued as long as the risk factor remains
Atrial Fibrillation (AF) – valvular, non-valvular		
AF with CHA_2DS_2Vacs score ≥ 1 (male), ≥ 2 (female)	2 – 3	Infinite
Rheumatic Mitral Valve Disease		
Rheumatic mitral valve disease with left atrial thrombus	2 – 3	Infinite
Rheumatic mitral valve disease with AF or previous systemic embolism		Infinite
Rheumatic mitral valve disease and normal sinus rhythm with left atrial diameter > 55 mm		Infinite

Table 3: Indication and INR target *(Continue)*

Thromboembolic Disorder	INR range	Duration of warfarin
Venous Thromboembolism (VTE) – Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE)		
Prosthesis heart valve		
Bioprosthetic heart valve, aortic and mitral	2 – 3	At least 3 months and for as long as 6 months in patients with low risk of bleeding ##
Mechanical prosthetic heart valve, aortic	2 – 3	Infinite
Mechanical prosthetic heart valve, mitral ###	2.5 – 3.5	Infinite
Mechanical prosthetic aortic heart valve with older generation valve such as ball-in-cage (Starr-Edwards)		
Transcatheter aortic valve replacement (TAVR)	2 – 3	At least 3 months in patients with low risk of bleeding ####
Others		
Thromboembolic complications while in INR 2 – 3	2.5 – 3.5	Infinite

Danish Registry demonstrated a lower risk of stroke and death with VKA extending up to 6 months, without a significantly increased bleeding risk
Mechanical mitral valve has greater thrombosis and thromboembolic risks than aortic valve due to low forward flow velocity at mitral valve and relative stagnation in left atrium where mitral valve faced.
post-TAVR antithrombotic regimen without warfarin seems to predispose patients to the development of valve thrombosis

2. Dosage

Table 4: Warfarin initiation

	Non-sensitive Patients	Sensitive Patients
Initial Dose	5 mg	3 mg
First INR	3 days	3 days
< 1.5	7.5 mg OD	5 mg OD
1.5 – 1.9	5 mg OD	3 mg OD
2.0 – 3.0	2.5 mg OD	1.5 mg OD
3.1 – 4.0	1.25 mg OD	0.5 mg OD
> 4.0	Hold	Hold
Next INR	2 – 3 days	2 – 3 days
Subsequent dosing and monitoring	Continue dose escalation and frequent monitoring until lower limit of therapeutic range is reached	

This table is served as a guide to initiate warfarin. However, it is not exhaustive.
For warfarin sensitive patients, initiation dose of 2 mg – 3 mg should be considered. Exclusion of factors affecting INR must be done prior to dosage adjustment.

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

Table 5: Factors increase sensitivity to warfarin

Age > 75 years[a]	Clinical congestive heart failure[f]
Clinical Hyperthyroidism[b]	Elevated baseline INR
End stage renal failure[c]	Fever[g]
Malignancy[d]	Diarrhoea[h]
Hepatic disease[e]	Malnutrition
CYP-inhibition drug interaction	Known CYP2C9 variant
Following heart valve replacement	Decreased overall oral intake
Asian Race	Hypoalbuminemia[i]

a Elderly has reduced clearance of warfarin

b D-thyroxine increases affinity of warfarin to receptor sites in the liver, leading to decrease production of vitamin K-dependent clotting factors. Besides that, hyperthyroidism increased catabolism of vitamin K-dependent clotting factors.

c End stage renal failure patients may have decreased hepatic CYP2C9 metabolism of warfarin.

d Use of chemotherapy may cause alterations to INR. Liver metastasis could also increase sensitivity to warfarin.

e Liver disease may cause reduction in production of clotting factors.

f Congestive heart failure induces hepatic congestion, leading to increase PT. Congestive heart failure increases plasma volume, reducing the concentration of clotting factors.

g Fever may cause reduction in warfarin metabolism by cytochrome P450. Fever may increase clearance of vitamin K-dependent clotting factors and reduce albumin-binding affinity.

h Diarrhoea may cause reduced absorption of vitamin K or increased elimination of vitamin K.

i Warfarin is highly protein-bound thus hypoalbuminemia will increase free fraction of warfarin.

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

Table 6: Warfarin Dose Adjustment for Target INR 2.5 (2 – 3)

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 day 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	
# 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*
This table is served as a guide to warfarin dose adjustment. However, it is not exhaustive. Always consider the trend of INRs when making warfarin management decisions. Exclusion of factors affecting INR must be done prior to dosage adjustment.

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

Table 7: Warfarin Dose Adjustment for Target INR 3.0 (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%	Increase 5 – 10% *	No change	Decrease 5 – 10%** consider holding 1 dose	Hold 0 – 1 day 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	
# Consecutive In – range INRs	Repeat INR in
1	5 – 14 days
2	2 – 4 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*
This table is served as a guide to warfarin dose adjustment. However, it is not exhaustive. Always consider the trend of INRs when making warfarin management decisions. Exclusion of factors affecting INR must be done prior to dosage adjustment.

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

3. Dosage adjustment

- **Renal Impairment**
  - Close monitoring of INR is required.
- **Hepatic Impairment**
  - Close monitoring of INR is required.
- **Geriatric**
  - Close monitoring of INR is required.
- **Pregnancy**
  - Pregnancy category: X
    - Warfarin crosses the placenta and causes teratogenic effect following first trimester exposure. Teratogenic effect includes coumarin embryopathy where nasal hypoplasia, stippled epiphyses and limb hypoplasia may be presented. Warfarin exposure at any trimester can cause foetus CNS abnormalities such as ventral and dorsal midline dysplasia. Besides that, spontaneous abortion, foetal bleeding, foetal death can occurred. Therefore, warfarin should be avoided during first trimester and close to delivery whenever possible
      - For the pregnant lady who requires anticoagulation (warfarin), the proposed therapy is to use adjusted-dose low molecular weight heparin (LMWH) or adjusted-dose heparin throughout the pregnancy or until week 13 of gestation when therapy can be changed back to warfarin. At week 36 of gestation, LMWH or heparin should be resumed until delivery
      - Use of Warfarin during first trimester can be considered if the dose required to achieve therapeutic INR is ≤ 5 mg (after full discussion with patients about risks and benefits)
      - Foetal outcomes, maternal outcomes, burden of therapy and maternal preference should be considered when deciding a treatment option

- **Breastfeeding**
  - ➢ Warfarin is not detected in breast milk. Therefore, warfarin is safe to be consumed by the breast-feeding woman

4. Checklist before staring the medication
   - Baseline International Normalised Ratio (INR)
   - Full Blood Count
   - Liver function
   - Renal function
   - Age (Elderly)
   - Possibility of drug-drug interaction
   - Warfarin sensitive patient
   - Logistic issue (availability of INR monitoring service)

5. Monitoring Parameters
   - INR (outpatients, inpatients)
   - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/coughing out blood)

6. Method of administration
   - Take at the same time every day. Usually recommend to take in the evening. *(in case INR is not in range and dosage adjustment is needed)*
   - Taken with or without food

7. Counselling Points
   - Counsel patient regarding high vitamin K diet and interaction between warfarin and high vitamin K diet
   - Counsel patient regarding the drug-herbal, drug-supplement, drug-traditional product interaction

- Counsel patient to monitor sign and symptoms of bleeding
- Inform doctor/pharmacist/dentist before any procedures, taking new medications, traditional product, or supplements

8. When to interrupt warfarin peri-operatively

Table 8: Peri-operative warfarin interruption

INR measurement 5 – 7 days prior to procedures		
Supratherapeutic (>3)	Goal Level (2 – 3)	Subtherapeutic (1.5 – 1.9)
Discontinue ≥ 5 days before procedure depending on the current INR, time to procedure, and desired INR for procedure; recheck INR 24 hours before procedure	Discontinue 5 days before procedure depending on the current INR, time to procedure, and desired INR for procedure; recheck INR 24 hours before procedure	Discontinue 3 – 4 days before procedure; recheck INR 24 hours before procedure if a normal INR is desired

- INR measurement is performed 5 – 7 days prior to procedures to determine the number of days that the warfarin should be stopped prior to procedure.

- For those who on a higher warfarin dose (7.5 mg – 10 mg/day or higher), or for whom the INR is known to normalise quickly, a shorter discontinuation time may be required prior to procedure

9. Mechanism of Action

- Coagulation factors II, VII, IX, and X, require γ-carboxylation of several glutamate residues in these factors to become biologically active. The γ-carboxylation reaction is coupled to the oxidation of reduced form of vitamin K (Vitamin K Hydroquinone) to vitamin K epoxide. Then, vitamin K epoxide must be reduced back to vitamin K hydroquinone by vitamin K epoxide reductase complex 1 (VKORC1), in order to continue the activation of the coagulation factors
- Warfarin competitively inhibits the VKORC1, thus depleting the vitamin K hydroquinone. Hence, there is a reduction in the synthesis of biological active coagulation factors

10. Pharmacokinetics

- Onset of action
  - Anticoagulation: Oral: 24 – 72 hours *(Anticoagulation effect of warfarin is result from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K-dependent clotting factors. The inhibition of coagulation is dependent on clotting factors' degradation half-lives. Their half-lives are 6, 24, 40, 60 hours for factors VII, IX, X, II respectively. Hence, there is an 8 – 12 hours' delay in the action of warfarin.)*

- Peak effect
  - Full Therapeutic effect: 5 – 7 days
  - INR may increase in 36 – 72 hours

- Protein Binding
  - 99%

- Metabolism
  - Hepatic, primarily via CYP2C9, minor pathways includes CYP2C8, 2C18, 2C19, 1A2, and 3A4

- Elimination half-life
  - 20 – 60 hours
  - mean: 40 hours; highly variable among individuals

- Excretion
  - Urine (92%, primarily as metabolites)

- Racemic
  - Equal amount of levorotatory *S*-warfarin and dextrorotatory *R*-warfarin. *S*-warfarin is 4 times more potent than *R*-warfarin

11. Adverse effects (*Lists are NOT exhaustive)*
    - Bleeding
    - Skin necrosis / gangrene
    - "Purple toe" syndrome *(cholesterol microembolisation)*

Warfarin dose prediction in pharmacogenetics studies

VKORC1 (Contribution in warfarin dose prediction)

Warfarin exerts its antithrombotic effects by inhibiting the vitamin K epoxide reductase complex 1 (VKORC1) and hence causing an interruption of the vitamin K redox cycle (Wittkowsky 2003). One of the most common single nucleotide polymorphisms (SNP) that have been extensively studied is the VKORC1 (-1639 G>A) gene polymorphism (King et al. 2008; Rathore et al. 2011; Teh et al. 2012; Wen et al. 2008; Xie et al. 2009; Yuan et al. 2005; Zhu et al. 2007). Individuals who carry the -1639 G>A gene polymorphism are more sensitive to warfarin and require lower doses. Population based studies have demonstrated that Asians usually acquire the VKORC1 -1639A allele and to a lesser extent in white people and those of African descendant.

Patient cohort and other Asian Population

Our recent in-house study consisted of a cohort of 200 patients [60(30.0%) Malay, 87(43.5%) Chinese and 53(26.5%) non-Malay Bumiputeras]. In the state of Sarawak alone, there are over 40 sub-ethnic groups (Iban, Bidayuh, Melanau, Indians, Orang Ulu and others) where we categorised these ethnicities into one group (non-Malay Bumiputeras). The mean (SD) daily warfarin dose was 2.81(1.1) mg which was consistent with the mean dose from other Asian populations such as Japan(Okumura et al. 2011), but not China (3.4 mg), Oman (4.75 mg), Iran (3.79 mg) and India (4.7 mg) (Gaikwad, Ghosh & Shetty 2014). Our mean daily warfarin dose also differs greatly from our Korean counterpart which shows a mean (SD) stable dose requirement of 5.5(1.9) mg(Jeong et al. 2015; Lee et al. 2015).

The mean dose in our population is relatively lower compared to our Caucasian counterpart, which is again a consistency in our findings with the other Asian populations. Of the out-of-range readings, the total INR readings

that were below 2 or subtherapeutic were almost double compared to INR readings above 3 or supratherapeutic (29.1% vs 15.2%). This leads to the impression that the majority of our patients, when poorly controlled, are underwarfarinised. This reason could be due to the clinicians in our settings who are less aggressive when it comes to warfarin dose increment especially in warfarin sensitive patients with a relatively lower warfarin dose. More than half of the patients in this cohort (64%) have received an alternate dosing regimen at least once during the study period. Frequent alternate dosing implementation reflects the warfarin sensitivity nature of our multi-ethnic population as dosing adjustments need to be more stringent and careful to avoid haemorrhagic side effects.

Local profile for VKORC1 gene polymorphism and Clinical Role of VKORC1

The study cohort consisted a majority of 143(71.5%) with the AA genotype, 54(27.0%) was found with the GA genotype and only 3(1.5%) was found with the GG genotype. The A: G allelic frequency according to the Hardy-Weinberg Principle is 0.85:0.15. There was a significant difference in the mean (SD) daily warfarin dose for patients with the AA, GA and GG genotype at 2.49(0.9) mg, 3.53(1.0) mg and 5.26(2.7) mg, respectively ($p<0.001$) which is consistent with previous studies.

The number of patients with AA genotype in Malay, Chinese and non-Malay Bumiputera patients were 49(34.3%), 58(40.5%) and 36(25.2%), respectively. The number of patients with GA genotype in Malay, Chinese and non-Malay Bumiputera patients were 11(20.4%), 29(53.7%) and 14(25.9%), respectively. All three patients with the GG genotype fell under the non-Malay Bumiputera group. The mean (SD) daily warfarin dose for patients with theVKORC1 variant AA, GA and GG were 2.49(0.9) mg, 3.53(1.0) mg and 5.26(2.7) mg, respectively ($p<0.001$).

Multiple linear regression analysis shows that the VKORC1 (-1639G>A) polymorphism, Age, body mass index (BMI) and diabetes mellitus (DM) are independent predictors of average daily warfarin dose (ADWD) in this cohort. **Table 9** shows that all four variables explaining around 41.6% of the variation in ADWD in this study sample with the most contribution from the genetic factor VKORC1 (-1639G>A) polymorphism which alone can explain 25.4% of ADWD variation in this study.

Table 9: Multiple linear regression analysis for factors independently associated with average daily warfarin dose

Variables	SLR[a]		MLR[b]		
	***b*[c](95% CI)**	***P* value**	***Adj.b*[d] (95% CI)**	***t*-stat**	***P* value**
VKORC1	1.12 (0.85,1.38)	<0.001	1.05 (0.81,1.29)	8.59	<0.001
DM	-0.69 (-1.04,-0.35)	<0.001	-0.79(-1.08,-0.50)	-5.39	<0.001
Age	-0.026 (-0.043,-0.008)	0.005	-0.04(-0.05,-0.02)	-4.76	<0.001
BMI	0.053 (0.024,0.082)	<0.001	0.04(0.01,0.06)	2.91	0.004
Gender	-0.49 (-0.78,-0.19)	0.002			
Race	0.24(0.04,0.44)	0.018			
Alt Dose	-0.32(-0.63,-0.01)	0.046			

[a] Simple linear regression
[b]Multiple linear regression
[c] Crude regression coefficient
[d] Adjusted regression coefficient

R^2 = 0.416 meaning that with the 4 significant variables, the model explains 41.6% of variation of average daily warfarin dose in the study sample

Overall, pharmacogenetics plays a vital role in warfarin prediction profile. However, clinical factors alongside with pharmacogenetics may be even stronger predictors of warfarin dose. Studies have shown that genetic polymorphism of CYP2C9 and VKORC1, age and height account for nearly 55% of warfarin daily dose variation (Sconce et al. 2005). However, data differs in different population setting. Therefore, the genetic profile of a population based on geographic region is vital to the local warfarin dose prediction profile.

Although genetic profile may be a general guideline for warfarin dose prediction and warfarin sensitivity, we should not rule out the impact of diet-drug, drug-drug and traditional medicine on erratic warfarin responses. Pharmacogenetics are able to guide us to be more careful when adjusting warfarin doses in warfarin sensitive patients to avoid bleeding and stroke.

Dabigatran Etexilate

1. Indication

   - **Reduction of risk of stroke and systemic embolism in non-valvular AF***(RE-LY)*
   - **Primary prophylaxis of VTE following elective hip or knee replacement surgery**

     RE-MODEL: knee replacement
     RE-NOVATE: hip replacement
     RE-MOBILIZE: knee replacement

   - **Treatment of DVT and PE** (*RE-COVER, RE-COVER II)*
   - **Prevention of recurrent DVT and PE** *(RE-MEDY, RE-SONATE)*

2. Dosage

   - **Reduction of risk of stroke and systemic embolism in non-valvular AF**
     - 150 mg BD
     - For the following groups, 150 mg BD or 110 mg BD should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding.
       - Patients between 75 – 80 years
       - Patients with moderate renal impairment
       - Patients with gastritis, esophagitis, or gastroesophageal reflux
       - Other patients at increased risk of bleeding
     - Duration: life-long
   - **Treatment of DVT and PE, and Prevention of recurrent DVT and PE**
     - 150 mg BD after treatment with parenteral anticoagulant for at least 5 days

- For the following groups, 150 mg BD or 110 mg BD should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding
  - Patients between 75 – 80 years
  - Patients with moderate renal impairment
  - Patients with gastritis, esophagitis, or gastroesophageal reflux
  - Other patients at increased risk of bleeding

- Duration: at least 3 months, should be based on transient risk factors (e.g. recent surgery, trauma, immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE

- **Primary prophylaxis of VTE following elective knee replacement surgery**
  - Start 110 mg within 1 – 4 hours after surgery, followed by 220 mg OD
  - Duration: 10 days
  - If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery, then treatment should be initiated with 220 mg OD

- **Primary prophylaxis of VTE following elective hip replacement surgery**
  - Start 110 mg within 1 – 4 hours after surgery, followed by 220 mg OD
  - Duration: 28 – 35 days
  - If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery, then treatment should be initiated with 220 mg OD

3. Dosage Adjustment

- **Renal Impairment**
  - Discontinue dabigatran for patients who develop acute renal failure
  - Renal impairment increases elimination half-life from average of 12 – 17 hours to 15 – 34.1 hours

Table 10: Renal Adjustment for Dabigatran

Renal function, CrCl (mL/min)	Reduction of risk of stroke and systemic embolism in non-valvular AF	Primary prophylaxis of VTE following hip or knee replacement surgery	Treatment of DVT and PE, and prevention of recurrent DVT or PE
> 50	150 mg BD	220 mg OD	150 mg BD
30 - 50	150 mg BD*	150 mg OD	150 mg BD*
< 30 or dialysis	Not recommended	Not recommended	Not recommended

* Consider 110 mg BD for patients with high bleeding risk

- **Hepatic Impairment**
  - Not recommended in patients with elevated liver enzymes > 2 upper limits of normal (ULN). *(This population of patients were excluded from the main trails)*

- **Geriatric**
  - Reduction of risk of stroke and systemic embolism in patients with non-valvular AF, Treatment of DVT and PE, Prevention of recurrent DVT and PE
    - 110 mg BD for patients aged 80 years old and above due to increased risk of bleeding in this population *(RE-LY showed 31% higher trough concentration for patients above the age of 75 years compared to those between 65-75 years old)*
    - Renal function should be assessed by calculating creatinine clearance (CrCl) prior to initiation of treatment to exclude patients for treatment with severe renal impairment (CrCl <30 ml/min) especially for those > 75 years' old

- Assess renal function at least once a year or if renal function deteriorates (e.g. hypovolemia, dehydration, with certain co-medications, etc.)

➢ Primary prevention of VTE following elective total hip or total knee replacement surgery

- No dose adjustment is necessary
- Renal function should be assessed by calculating creatinine clearance (CrCl) prior to initiation of treatment to exclude patients for treatment with severe renal impairment (CrCl < 30 ml/min) especially for those > 75 years' old

- **Paediatric**

➢ Dabigatran is not recommended for use in patients less than 18 years old *(no clinical experience)*

- **Pregnancy**

➢ Pregnancy Category: C (FDA)

➢ No clinical data on potential risk for humans and exposed pregnancies available

➢ Avoid pregnancy during treatment with dabigatran

➢ When pregnant, women should not be treated with dabigatran unless expected benefit is greater than the risk

- **Breastfeeding**

➢ No clinical data available.

➢ As a precaution, stop breastfeeding

4. Contraindication (*Lists are NOT exhaustive)*

- Hypersensitivity to dabigatran or other any component of the product
- Active clinically significant bleeding
- Prosthetic heart valves requiring anticoagulant treatment / mechanical prosthetic heart valves

- Severe renal impairment (CrCl < 30 ml/min)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone
- Concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when UFH is given to maintain an open central venous or arterial catheter
- Lesions or conditions at risk of clinically significant major bleeding

5. Checklist Before Initiation
   - Renal profile: CrCl *(Cockcroft-gault equation)*
   - Coagulation profile: PT, activated partial thromboplastin time (aPTT), INR
   - Liver function test
   - Full blood count

6. Monitoring Parameters
   - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/coughing out blood)
   - Serum creatinine: recheck several days before surgery
   - Signs or symptoms of blood loss
   - Complete blood count when clinically indicated
   - Renal function when clinically indicated, and at least annually in all patients
   - Thrombin time (TT), aPTT and Ecarin clotting time (ECT) – to detect excessive dabigatran activity *(routine monitoring of coagulation tests not required)*

7. Method of Administration

    - Dabigatran can be taken with or without food. If dyspepsia occurs, consider administration with meals.
    - Swallow the capsule whole with a glass of water *(to facilitate delivery to the stomach)*
    - Do not break, chew or empty contents of capsule *(Oral bioavailability may be increased by about 37%, increase bleeding risk)*
    - Do not serve dabigatran via nasogastric tube
    - Remove dabigatran capsule by tearing off one individual blister along the perforated line.
    - Peel off the backing foil and remove the capsule. Do not pushed the capsule through the blister foil
    - Only remove the capsule from blister foil immediately before use

8. Counselling Points

    - To notify doctor of dabigatran use prior to surgical procedures
    - Immediately report signs and symptoms of bleeding
    - Do not discontinue dabigatran unless directed by doctor
    - To consult healthcare professional prior to new drug use
    - To inform doctor if experiencing any dyspepsia, heartburn, nausea abdominal pain, nausea, or discomfort that bothers them or that does not go away

9. Missed dose

    - Reduction of risk of stroke and systemic embolism in non-valvular AF, Treatment and prevention of recurrence of DVT and PE
        - Take the forgotten dose immediately if it is more than 6 hours before the next scheduled dose
        - If a missed dose cannot be given at least 6 hours before the next scheduled time, the dose should be skipped. Do not double up for a missed dose

- Primary prophylaxis of VTE following knee or hip replacement surgery
  - Take the next dose at the same time. Do not take a double dose to replace missed dose

10. Switching Therapy
    - **Switching from parenteral anticoagulant to dabigatran**
      - Dabigatran should be given 0-2 hours before the next dose of parenteral anticoagulant is due
      - Dabigatran should be given at the time of discontinuation of continuous parenteral anticoagulant
    - **Switching from dabigatran to parenteral anticoagulant**
      - Reduction of risk of stroke and systemic embolism in non-valvular AF, Treatment and prevention of recurrence of DVT and PE
        - Serve parenteral anticoagulant 12 hours after the last dose of dabigatran
      - Primary prophylaxis of VTE following knee or hip replacement surgery
        - Serve parenteral anticoagulant 24 hours after the last dose of dabigatran
    - **Switching from VKA to dabigatran**
      - Stop VKA and initiate dabigatran once INR is less than 2

Table 11: Switching from dabigatran to VKA

Renal function, CrCl (mL/min)	Switching dabigatran to VKA
≥ 50	Start VKA 3 days before discontinuing dabigatran
30-50	Start VKA 2 days before discontinuing dabigatran
15-30	Start VKA 1 days before discontinuing dabigatran
< 15	No recommendation

- Dabigatran can affect INR reading. INR better reflects the actual effect of VKA 2 days after discontinuation of dabigatran

11. Peri-operative Management

- Dabigatran should be withheld temporarily if acute surgery is required. Acute surgery should be postponed if possible until 12 hours after the last dose of dabigatran
- If possible, dabigatran should be discontinued at least 24 hours before any invasive or surgical procedures. For patients at higher risk of bleeding or major surgery where complete haemostasis may be required, consider stopping dabigatran 2 – 4 days before surgery.

Table 12: Peri-Operative Management of Dabigatran

Renal function, CrCl (mL/min)	Estimated elimination half-life (hours)	Time to withhold dabigatran	
		High bleeding risk or major surgery	Standard bleeding risk
≥ 80	13	2 days before	1 day before
≥ 50 - < 80	15	2-3 days before	1-2 days before
≥ 30 - < 50	18	4 days before	2-3 days before (> 48 hours)

- Dabigatran is contraindicated for patients with CrCl less than 30 mL/min. However, in these patients, dabigatran should be withheld at least 5 days before major surgery
- Dabigatran can be resumed post-surgery once haemostasis is secured

12. Mechanism of Action

- Dabigatran Etexilate is a prodrug where it is converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver after absorption.
- Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. It also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

- Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, dabigatran's inhibition prevents the development of thrombus.
- Dabigatran prolongs aPTT, ECT and TT

13. Pharmacokinetic
    - Absorption
        - Tmax: 1- 6 hours
        - Bioavailability: 3 – 7%
        - Bioavailability is not affected by food
        - Food delays Tmax by 2 hours, but does not affect extent of absorption
    - Distribution
        - Vd: 50 – 70 L
        - Protein binding: 35%
    - Metabolism
        - Dabigatran Etexilate is a prodrug that is rapidly and completely hydrolysed to active metabolite by plasma and hepatic esterase.
        - Dabigatran undergoes hepatic glucuronidation to active acyglucuronide isomers.
    - Elimination
        - Elimination half-life: 12 – 17 hours, 15 – 34 hours in renal impairment
        - Primarily excreted through renal route.
        - Dabigatran is dialyzable *(48.8% to 77% over 2 – 5 hours)*

14. Adverse Effect (*Lists are NOT exhaustive)*

- Bleeding
  - Intracranial haemorrhage
  - Hematoma, haemorrhage
  - Epistaxis, haemoptysis
  - Gastrointestinal haemorrhage
  - Skin haemorrhage
  - Hemarthrosis
  - Urogenital haemorrhage
- Blood and lymphatic system disorders
  - Anaemia, thrombocytopenia
- Drug hypersensitivity including pruritus, rash and urticaria, bronchospasm, angioedema, anaphylactic reactions
- Gastrointestinal disorders
  - Abdominal pain, diarrhoea, dyspepsia, nausea, gastrointestinal ulcer, oesophageal ulcer, gastroesophagitis, gastroesophageal reflux disease, vomiting, dysphagia
- Abnormal hepatic function
- General disorders and administration site conditions
  - Injection site haemorrhage, catheter site haemorrhage
- Injury, poisoning and procedural complications
  - Traumatic haemorrhage, incision site haemorrhage

Rivaroxaban

1. Indication
   - **Prevention of stroke and systemic embolism in non-valvular AF** *(ROCKET AF)*
   - **Primary prophylaxis of VTE following hip or knee replacement surgery***(RECORD)*
   - **Treatment of DVT and PE** *(Einstein DVT, Einstein PE)*
   - **Prevention of recurrent of DVT and PE** *(Einstein Extension)*

2. Dosage
   - **Prevention of stroke and systemic embolism in non-valvular AF**
     - 20 mg OD
     - Duration: Life-long
   - **Primary prophylaxis of VTE following knee replacement surgery**
     - 10 mg OD at least 6-10 hours after surgery once haemostasis has been established
     - Duration: 12 days
   - **Primary prophylaxis of VTE following hip replacement surgery**
     - 10 mg OD at least 6-10 hours after surgery once haemostasis has been established
     - Duration: 35 days
   - **Treatment of DVT and PE**
     - 15 mg BD for 3 weeks, followed by 20 mg OD
     - Duration: at least 3 months should be based on transient risk factors (e.g. recent surgery, trauma, immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE

- **Prevention of recurrent DVT and PE**
  - 20 mg OD
  - Duration: life-long

3. Dosage Adjustment
   - **Renal Impairment**
     - In patients with severe renal impairment (CrCl < 30 mL/min), rivaroxaban level maybe increased by 1.6-fold on average, increasing the bleeding risk
     - Use with caution in patients with CrCl 15-29 mL/min.

Table 13: Renal Adjustment for Rivaroxaban

Renal Function, CrCl (mL/min)	**Prevention of stroke and systemic embolism in non-valvular AF**	**Primary prophylaxis of VTE following hip or knee replacement surgery**	**Treatment of DVT and PE, prevention of recurrent DVT and PE**
> 50	20 mg OD	10 mg OD	15 mg BD three weeks, then 20 mg OD
> 30 – 50	15 mg OD	10 mg OD	15 mg BD three weeks, then 20 mg OD
15 – 30	15 mg OD	Not recommended	Not recommended
< 15 or dialysis	Not recommended	Not recommended	Not recommended

     - Use is not recommended in patients with CrCl <15 mL/min and haemodialysis patients *(no safety and clinical data for HD patients)*

   - **Hepatic Impairment**
     - Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

- **Geriatric**
  - No dosage adjustment
  - Concentration of rivaroxaban is approximately 1.5-fold higher in elderly compared to younger patients due to reduced renal clearance

- **Paediatric**
  - Rivaroxaban is not recommended for use in patients less than 18 years old *(no clinical experience)*

- **Pregnancy**
  - Pregnancy Category: C (FDA)
  - Safety and efficacy or rivaroxaban have not been established
  - Rivaroxaban use is contraindicated during pregnancy *(potential reproductive toxicity, intrinsic risk of bleeding and evidence that rivaroxaban crosses placenta)*
  - Women of child-bearing potential should avoid becoming pregnant during rivaroxaban use

- **Breastfeeding**
  - Safety and efficacy have not been established
  - Rivaroxaban use is contraindicated during breastfeeding *(data from animal studies showed rivaroxaban is secreted into milk)*

4. Contraindication (*Lists are NOT exhaustive)*
   - Hypersensitivity to rivaroxaban or any component of the product
   - Clinically significant of active bleeding
   - Prosthetic heart valves *(No safety and efficacy data)*
   - Concomitant treatment with other anticoagulant except under the circumstances of switching therapy or when UFH is given to maintain an open central venous or arterial catheter
   - Hepatic diseases associated with coagulopathy and increased bleeding risk e.g. cirrhosis with Child Pugh B and C

- Hemodynamically unstable PE patients, patients who require thrombolysis or pulmonary embolectomy *(No safety and efficacy data)*

5. Checklist Before Initiation
   - Renal profile: CrCl *(Cockcroft-gault equation)*
   - Coagulation profile: PT, aPTT, INR
   - Liver function test
   - Full blood count

6. Monitoring Parameters
   - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/coughing out blood)
   - Renal function: periodically in patients with pre-existing renal impairment
   - Hepatic function
   - Full blood count when clinically indicated
   - Improvement in symptoms of DVT/PE
   - Signs or symptoms of blood loss

7. Method of Administration
   - To be taken with food at the same time each day
   - For those unable to swallow whole tablet, tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After administration of crushed tablets, the dose should be immediately followed by food
   - Crushed tablet can be administered in small amount of water via gastric tube after which it should be flushed with water. After the administration via gastric tube, the dose should be immediately followed by enteral feeding

8. Counselling Points
    - To notify doctor of rivaroxaban use prior to surgical procedures
    - Immediately report signs and symptoms of bleeding
    - Do not discontinue rivaroxaban unless directed by doctor
    - To consult healthcare professional prior to new drug use

9. Missed dose
    - Once daily dosing
        - Take the forgotten dose immediately if it is more than 12 hours before the next scheduled dose
        - Omit the dose if it is less than 12 hours prior to the next scheduled dose. Take the next dose at the same time. Do not take a double dose to replace missed dose
    - Twice daily dosing (Day 1 – Day 21 of DVT and PE treatment)
        - Take the forgotten dose immediately to ensure total daily dose of 30 mg of rivaroxaban. Two 15 mg rivaroxaban tablets may be taken at once
        - Continue the regular twice daily intake of rivaroxaban the following day

10. Switching Therapy
    - **Switching from parenteral anticoagulant to rivaroxaban**
        - Rivaroxaban should be given 0-2 hours before the next dose of parenteral anticoagulant is due
        - Rivaroxaban should be given at the time of discontinuation of continuous parenteral anticoagulant
    - **Switching from rivaroxaban to parenteral anticoagulant**
        - Serve parenteral anticoagulant at the time the next rivaroxaban dose is due

- **Switching from VKA to rivaroxaban**
  - Prevention of stroke and systemic embolism in non-valvular AF
    - Stop VKA and initiate rivaroxaban once INR is ≤ 3
  - Treatment of DVT and PE and prevention of recurrence of DVT and PE
    - Stop VKA and initiate rivaroxaban once INR is ≤ 2.5

- **Switching from rivaroxaban to VKA**
  - Give VKA concurrently with rivaroxaban until INR is ≥ 2
  - Rivaroxaban can contribute to an elevated INR. Do not check INR 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

11. Peri-operative Management
    - If an invasive procedure or surgical intervention is required, withhold rivaroxaban at least 24 hours before surgical procedure
    - If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention
    - Rivaroxaban can be resumed post-surgery once haemostasis is secured and patient is stable
    - Epidural or spinal hematomas may occur in patients undergoing neuraxial anaesthesia or spinal puncture. Monitor patients for neurological impairment and treat urgently

12. Mechanism of Action
    - Highly selective factor Xa inhibitor
    - Interrupts intrinsic and extrinsic pathway if coagulation cascade, inhibits thrombin formation and development of thrombi

13. Pharmacokinetic

- Absorption
  - Oral Bioavailability: 80 – 100% (2.5 mg and 10 mg tablet dose regardless taken with/without food)
  - Oral Bioavailability: 66% (20 mg tablet dose taken without food). Oral bioavailability increased by 39% for 20 mg tablet when taken with food
  - No difference in bioavailability among patients taking rivaroxaban as whole tablet, crushed tablet or via gastric tube
- Distribution
  - Vd: 50 L
  - Highly protein bound (92 – 95%, primarily bind to albumin)
- Metabolism
  - Primarily metabolised in liver via CYP3A4/5, CYP2J2 and hydrolysis
- Elimination
  - Elimination half-life: 5 – 9 hours in young individuals, 11 – 13 hours in the elderly
  - Primarily excreted in renal: 66%
  - Not dialyzable *(due to high plasma protein binding)*

14. Adverse Effect (*Lists are NOT exhaustive)*

- Bleeding
  - Cerebral and intracranial haemorrhage
  - Hematoma, haemorrhage
  - Epistaxis, haemoptysis
  - Gastrointestinal haemorrhage
  - Skin haemorrhage
  - Hemarthrosis, muscle haemorrhage
  - Urogenital haemorrhage

  - Eye haemorrhage
  - Traumatic haemorrhage, incision site haemorrhage

- Dizziness and headache
- Tachycardia
- Hypotension
- Blood and lymphatic system disorders
  - Anaemia, thrombocytopenia

- Allergic reaction, dermatitis allergic reaction, pruritus, rash, ecchymosis
- Gastrointestinal disorders
  - Abdominal pain, diarrhoea, constipation, dyspepsia, nausea, vomiting

- Abnormal hepatic function, jaundice
- Renal impairment
- General disorders and administration site conditions
  - Injection site haemorrhage, catheter site haemorrhage

- Injury, poisoning and procedural complications

Apixaban

1. Indication

   - **Prevention of stroke and systemic embolism in non-valvular AF**

     ARISTOTLE: apixabanvs warfarin
     AVERROES: apixabanvs aspirin

   - **Primary prophylaxis of VTE following hip and knee replacement surgery**

     ADVANCE-2: total knee replacement
     ADVANCE-3: total hip replacement

   - **Treatment of DVT and PE** *(AMPLIFY)*
   - **DVT and/or PE prophylaxis** *(AMPLIFY-EXT)*

2. Dosage

   - **Prevention of stroke and systemic embolism in non-valvular AF**
     - 5 mg BD
     - Consider 2.5 mg BD in patients with at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 mmol/L)
     - Duration: life-long

   - **Primary prophylaxis of VTE following knee replacement surgery**
     - Start 2.5 mg BD 12 – 24 hours after surgery
     - Duration: 10 – 14 days

   - **Primary prophylaxis of VTE following hip replacement surgery**
     - Start 2.5 mg BD 12 – 24 hours after surgery
     - Duration: 32 - 38 days

- **Treatment of DVT and PE**
  - 10 mg BD for the first 7 days, followed by 5 mg BD
  - Duration: at least 3 months based on transient risk factors (e.g. recent surgery, trauma, immobilisation). Longer duration of treatment should be considered based on risk factors or idiopathic causes of DVT or PE

- **Prevention of recurrent DVT and PE**
  - 2.5 mg BD should be initiated following completion of 6-month treatment dose with 5 mg BD
  - Duration: Life-long

3. Dosage Adjustment
   - **Renal Impairment**

Table 14: Renal Adjustment for Apixaban

Renal Function, CrCl (mL/min)	**Prevention of stroke and systemic embolism in non-valvular AF**	**Primary prophylaxis of VTE following hip or knee replacement surgery**	**Treatment of DVT and PE**	**Prevention of recurrent DVT and PE**
≥ 30	• 5 mg BD • 2.5 mg BD in patients with at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 mmol/L)	2.5 mg BD	10 mg BD for seven days then 5 mg BD	2.5 mg BD
15-29	2.5 mg BD	2.5 mg BD Use with caution	10 mg BD for seven days then 5 mg BD Use with caution	2.5 mg BD Use with caution
< 15 or dialysis	Not recommended	Not recommended	Not recommended	Not recommended

- **Hepatic Impairment**
  - Use Apixaban with caution in patients with:
    - Mild to moderate hepatic impairment (Child-Pugh A or B)
    - Elevated liver enzymes ALT/AST > 2x ULN or total bilirubin ≥ 1.5x ULN *(excluded in clinical trials)*
  - Contraindicated in patients with:
    - Hepatic disease associated with coagulopathy and clinical relevant bleeding risk
    - Severe hepatic impairment
- **Geriatric**
  - Prevention of stroke and systemic embolism in non-valvular AF
    - No dosage adjustment required unless criteria for dose reduction are met *(refer dosage)*
  - Treatment of DVT or PE, prevention of recurrent DVT and PE
    - No dosage adjustment required
- **Paediatric**
  - Apixaban is not recommended for use in patients less than 18 years old *(no clinical experience)*
- **Pregnancy**
  - Pregnancy Category: B (FDA)
  - Safety and efficacy or apixaban have not been established
  - Apixaban is not recommended for pregnant women
- **Breastfeeding**
  - No data on excretion of apixaban or its metabolites in human milk
  - Infant risk cannot be ruled out
  - To discuss whether to discontinue breast feeding or apixaban

4. Contraindication (*Lists are NOT exhaustive)*
    - Hypersensitivity to apixaban or any component of the product
    - Hepatic disease with coagulopathy and clinically relevant bleeding risk
    - Clinically significant active bleeding
    - Lesions or conditions at risk of clinically significant major bleeding
    - Prosthetic heart valves *(No safety and efficacy data)*
    - Concomitant treatment with other anticoagulant except under the circumstances of switching therapy or when UFH is given to maintain an open central venous or arterial catheter

5. Checklist Before Initiation
    - Renal profile: CrCl *(Cockcroft-gault equation)*
    - Coagulation profile: PT, aPTT, INR
    - Liver function test
    - Full blood count
    - Age
    - Body weight

6. Monitoring Parameters
    - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood)
    - PT, INR and aPTT *(Apixaban prolongs PT, INR and aPTT)*
    - Complete blood count when clinically indicated
    - Renal function when clinically indicated, and at least annually in all patients
    - Hepatic function
    - Signs or symptoms of blood loss

7. Method of Administration
    - Tablet can be swallowed whole with or without food
    - Tablet can be crushed and suspended in water, 5% dextrose in water (D5W) or apple juice or mixed with apple puree. Crushed tablets are stable in water, D5W, apple juice and apple puree for up to 4 hours
    - Crushed tablet can be suspended in 60 mL of water and immediately served via nasogastric tube

8. Counselling Points
    - To notify doctor of apixaban use prior to surgical procedures
    - Immediately report signs and symptoms of bleeding
    - Do not discontinue apixaban unless directed by doctor
    - To consult healthcare professional prior to new drug use

9. Missed dose
    - Take apixaban immediately and resume the usual dose

10. Switching Therapy
    - **Switching from parenteral anticoagulant to apixaban**
        - Start apixaban at the next scheduled dose of parenteral anticoagulant
    - **Switching from apixaban to parenteral anticoagulant**
        - Start parenteral anticoagulant at the next scheduled dose of apixaban
    - **Switching from VKA to apixaban**
        - Stop VKA and initiate apixaban once INR is less than 2

- **Switching from apixaban to VKA**
  - Administer apixaban and VKA concurrently for 2 days. Repeat INR after 2 days prior to next scheduled dose of apixaban. Stop apixaban once INR ≥ 2

11. Peri-operative Management
    - Discontinue apixaban at least 48 hours before elective surgery or invasive procedures with moderate or high bleeding risk
    - Discontinue apixaban at least 24 hours before elective surgery or invasive procedures with low bleeding risk
    - If surgery or invasive procedures cannot be delayed, the risk of bleeding should be weighed against the urgency of intervention
    - Apixaban can be resumed post-surgery once haemostasis is secured and patient is stable
    - Indwelling epidural or intrathecal catheters used for neuraxialanesthesia must be removed at least 5 hours before restart apixaban to reduce the risk of epidural or spinal hematoma

12. Mechanism of Action
    - Potent, reversible and highly selective factor Xa inhibitor
    - Inhibits free and clot-bound factor Xa and prothrombinase activity, prevents thrombin formation and thrombus development

13. Pharmacokinetic
    - Absorption
      - Tmax: 3 – 4hours (10 mg), 3.3 hours (5 mg), 1.5 hours (2.5 mg)
      - Bioavailability: 50%
      - Food intake does not affect the absorption and efficacy of apixaban
      - Bioavailability of nasogastric crushed tablet remained unchanged

- Distribution
  - Vd: 21 – 61 L
  - Protein binding: 87%
- Metabolism
  - Primarily metabolised in liver via CYP3A4
- Elimination
  - Mostly excreted via biliary and direct intestinal excretion in faeces
  - 27% excretion via renal route

14. Adverse Effect (*Lists are NOT exhaustive)*
    - Bleeding
      - Cerebral and intracranial haemorrhage
      - Hematoma, haemorrhage
      - Epistaxis, haemoptysis
      - Gastrointestinal haemorrhage
      - Hemarthrosis, muscle haemorrhage
      - Urogenital haemorrhage
      - Eye haemorrhage
      - Intra-abdominal haemorrhage
      - Haematuria
      - Traumatic haemorrhage, incision site haemorrhage
    - Hypotension
    - Blood and lymphatic system disorders
      - Anaemia, thrombocytopenia
    - Allergic reaction, dermatitis allergic reaction, pruritus, rash
    - Abnormal hepatic function, jaundice

Heparin

1. Indication

   - **Treatment of Unstable Angina (UA) and non-ST elevation myocardial infarction (NSTEMI)**
   - **Treatment of ST elevation myocardial infarction (STEMI)**
   - **Prophylaxis of Venous Thromboembolism**
   - **Treatment of Venous Thromboembolism**

2. Dosage

   - **Treatment of Unstable Angina (UA) or non-ST elevation myocardial infarction (NSTEMI)**
     - Initial IV bolus of 60 units/kg (max 4000 units)
     - Infusion of 12 units/kg/hour (max 1000 units/hour) adjusted to maintain aPTT 1.5 – 2.0 ratio
     - Duration: ≥ 48 hours or until management changes to an invasive strategy (e.g. PCI)

   - **Treatment of ST elevation myocardial infarction (STEMI)**
     - Adjunct to PCI
     - *No planned GP IIb/IIIa inhibitor used*: Bolus 70 to 100 units/kg to achieve Activated Clotting Time (ACT) of 250 to 300 seconds (goal may vary depending on point of care device); re-dose as needed to maintain goal ACT throughout procedure.

       Planned GP IIb/IIIa inhibitor used: Bolus 50 to 70 units/kg to achieve ACT of 200 to 250 seconds (regardless of point of care device); re-dose as needed to maintain goal ACT throughout procedure

- Adjunct to fibrinolysis: Bolus of 60 units/ kg (max 4000 units), follow by infusion 12 unit /kg/h (max 1000 units/hour) adjusted to maintain aPPT 1.5 - 2.5 times control.
  - Duration: ≥ 48 hours or until revascularization (if performed)

- Treatment of VTE
  - IV: Loading dose 80 units/kg (aPTT ratio of 1.5-2.5) followed by IV infusion of 18 units/kg/hour (or alternatively 1000 units/hour).
  - Subcutaneous: Initial dose of 333 units/kg, followed by 250 units /kg every 12 hours
  - Long term anticoagulation is not recommended

- **Prophylaxis of VTE**
  - 5000 units BD or TDS to be injected subcutaneously
  - Duration: until fully ambulatory

3. Dosage Adjustments
   - **Renal impairment**
     - Use with caution because of risk of haemorrhage
   - **Hepatic impairment**
     - Use with caution because of risk of haemorrhage
   - **Geriatric**
     - A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Clinical studies indicate that lower doses of heparin may be indicated in these patients.
   - **Paediatric**
     - There are no adequate and well controlled studies on heparin use in paediatric patients (< 16 years of age).
     - Dosing recommendations are based on clinical experiences.
     - Use preservative free heparin

- **Pregnancy**
  - Pregnancy Category: C
  - Use if the potential benefit justifies the potential risk to the foetus.*

- **Breastfeeding**
  - Preservative-free Heparin Sodium is recommended
  - Heparin is not likely to be excreted in human milk due to its large molecular weight. Benzyl alcohol present in the maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant

**LMWH is more effective and associated with lower risk of haemorrhagic complication and lower mortality than UFH in the treatment of VTE in pregnancy.*

4. Contraindications (*Lists are NOT exhaustive)*
   - Severe thrombocytopenia or a history of heparin-induced thrombocytopenia and thrombosis**
   - Known hypersensitivity to heparin or bovine products or to any ingredient in the formulation
   - Uncontrolled active bleeding state, except when this is due to disseminated intravascular coagulation (DIC).
   - In whom, suitable blood coagulation tests (e.g., the whole blood clotting time, partial thromboplastin time) cannot be performed at appropriated intervals when the test are required.

***Heparin-induced Thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thrombosis, a condition known as Heparin-induced Thrombocytopenia and Thrombosis (HITT). Thrombotic events may also be the initial presentation for the HITT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death.*

5. Checklist before starting the medication
    - Baseline Full Blood Count, aPTT and prothrombin time (PT)
    - Body weight

6. Monitoring parameters
    - Sign and symptoms of bleeding (e.g.: blood in urine, blood in stool/ black stools, vomiting/ coughing out blood)
    - Coagulation Testing
    - Periodic platelet counts
    - Haematocrits
    - Electrolytes

7. Method of administration
    - Intravenous (IV)
    - Subcutaneous (SC)
    - Not for intramuscular (IM) injection

8. IV Compatibility
    - Solutions: Normal saline, D5W

9. Mechanism of Action
    - Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin.
    - Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin.

- Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of Factor XIII, the fibrin stabilizing factor. Heparin does not have fibrinolytic activity.

10. Pharmacokinetic
    - Absorption
        - Bioavailability: 22 - 40%
        - Onset: Immediate (IV)
        - Duration: 20 - 60 minutes
    - Distribution
        - Protein bound: Extensive
    - Metabolism
        - Metabolized in the liver (partial) and reticuloendothelial system (partial)
    - Elimination
        - Half-life: 60 – 90 minutes (longer at higher doses)

11. Adverse Effects (*Lists are NOT exhaustive)*
    - Haemorrhage
    - Thrombocytopenia (Heparin Induced Thrombocytopenia, Heparin Induced Thrombocytopenia and Thrombosis)
    - Osteoporosis. Therapeutic doses of heparin administered for longer than 3 months have been associated with osteoporosis and spontaneous vertebral fractures.

Enoxaparin

1. Indication

   - **Acute Coronary Syndrome**
     - Unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) administered concurrently with aspirin.
     - Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) as an adjunctive to thrombolytic treatment.
   - **Treatment of Venous thromboembolism**
   - **Prophylaxis of Venous thromboembolism**
     - Following orthopaedic and general surgery
     - Bedridden medical patients due to acute illness

2. Dosage

   - **Treatment of Unstable Angina (UA) and Non-ST-elevation Myocardial Infarction (NSTEMI)**
     - 1 mg/kg BD
     - Duration: 2 – 8 days
   - **Treatment of Acute ST-segment Elevation Myocardial Infarction (STEMI)**
     - In patients receiving thrombolytic, initiate enoxaparin between 15 minutes before and 30 minutes after fibrinolytic therapy.
     - A single IV bolus of 30 mg plus 1 mg/kg subcutaneously, followed by 1 mg/kg BD
     - Duration: up to 8 days or until hospital discharge or revascularization, whichever comes first
   - **Prophylaxis of Venous thromboembolism**
     - 40 mg OD for all indications, except for Bariatric Surgery which require individualised dosing based on BMI

- For Bariatric Surgery, use standard prophylaxis dose for BMI 30 to 39 kg/$m^{2.}$ Increase standard prophylaxis dose by 30% for BMI ≥ 40 kg/m^2

- **Treatment of Venous Thromboembolism**
  - 1 mg/kg BD or 1.5 mg/kg OD
  - Duration: 3 months for provoked VTE and more than 3 months for unprovoked VTE depending on the risk of recurrence and bleeding.

3. Dosage adjustment

- **Renal Impairment**
  - CrCl < 30 ml/min
  - Treatment of Acute Coronary Syndrome (ACS) or Venous Thromboembolism (VTE)
    - 1 mg/kg OD
  - Prevention of Venous Thromboembolism (VTE)
    - 20 mg OD

- **Hepatic Impairment**
  - No dosage adjustment, use with cautions

- **Geriatric**
  - Age ≥ 75
  - Acute ST-segment Elevation Myocardial Infarction
    - No IV bolus is required, initiate dose at 0.75 mg/kg 12 hourly
    - In patients receiving thrombolytic, initiate enoxaparin between 15 minutes before and 30 minutes after fibrinolytic therapy.

- Prophylaxis and treatment of venous thromboembolism and Unstable Angina or Non-ST Elevation
  - Follow the usual adult dosing unless kidney function is impaired

- **Paediatric**
  - The safety and efficacy of enoxaparin sodium in children has not been established

- **Pregnancy**
  - Pregnancy category: C

Table 15: Dosage for Pregnant Women

For Venous Thromboembolism				
Initial dose	**Pregnancy Weight (kg)**			
	< 50	50 - 69	70 – 89	> 90
Enoxaparin	40 mg BD	60 mg BD	80 mg BD	100 mg BD

- **Breastfeeding**
  - It is unknown whether enoxaparin is excreted into the breast milk of humans. As a precaution, women should be advised not to breast feed while using enoxaparin

4. Contraindications (*Lists are NOT exhaustive)*
   - Allergy to enoxaparin, heparin or its derivatives including other low molecular weight heparins as well as pork products.
   - Acute bacterial endocarditis.
   - Conditions with a high risk of uncontrolled haemorrhage including major bleeding disorders, focal lesions, haemorrhagic stroke, active ulcerative conditions showing a tendency to haemorrhage (e.g. peptic ulcer, ulcerative colitis).
   - Thrombocytopenia associated with a positive in vitro test for antiplatelet antibody in the presence of enoxaparin sodium.

5. Checklist before starting the medication
    - Renal profile
    - Body Weight
    - Allergy history

6. Monitoring parameters
    - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood)
    - Full blood count
    - Coagulation parameters
    - Renal profile

7. Method of administration
    - Subcutaneously (SC)
    - IV bolus for the first treatment dose for STEMI

8. Special consideration
    - Enoxaparin is obtained by alkaline depolymerisation of heparin benzyl ester derived from porcine intestinal mucosa
    - Prescriber need to explain and get consent of patient on the use of non-halal product for treatment

9. Mechanism of Action
    - Enoxaparin inhibits factor Xa by increasing inhibition rate of clotting proteases that are activated by antithrombin III

10. Pharmacokinetic
    - Absorption
        - Bioavailability: ~100%

- Onset: 1 to 4 hours (peak effect)
- Duration (AntifactorXa activity): 12 hours (40 mg)

- Distribution
  - Vd: 4.3 L

- Metabolism
  - Metabolized by liver via desulfation and depolymerisation.

- Elimination
  - Urine
  - Half-life: 4.5-7 hours

- Clearance
  - Decreased by 30% in patients with CrCl < 30 mL/min

11. Adverse Effects (*Lists are NOT exhaustive)*
    - Haemorrhage
    - Thrombocytosis
    - Thrombocytopenia
    - Asymptomatic and reversible increases in the levels of liver enzymes
    - Nausea
    - Diarrhoea
    - Peripheral oedema
    - Fever
    - Confusion
    - Allergic reaction
    - Urticaria, pruritus, erythema
    - Injection site hematoma, injection site pain, and other injection site reactions (such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain or reaction)

Fondaparinux

1. Indication
    - **Treatment of Unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI)**
    - **Treatment of ST elevation myocardial infarction (STEMI).** *Should not be used if primary PCI is the planned reperfusion therapy, due to the risk of catheter thrombosis during PCI*
    - **Treatment of Venous thromboembolism**
    - **Prophylaxis of venous thromboembolism**

2. Dosage
    - **Treatment of Unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI)**
        - 2.5 mg OD by subcutaneous injection.
        - Duration: up to 8 days or until hospital discharge
    - **Treatment of ST elevation myocardial infarction (STEMI)**
        - 2.5 mg OD
        - To be given as soon as possible after fibrinolysis if indicated
        - First dose is administered intravenously and subsequent dose is administered by subcutaneous injection
        - Duration: up to 8 days or until hospital discharge
    - **Treatment of Venous thromboembolism, by subcutaneous injection once daily**
        - 5 mg (body weight < 50 kg)
        - 7.5 mg (body weight 50 – 100 kg)
        - 10 mg (body weight > 100 kg)
        - Duration: at least 5 days and until a therapeutic oral anticoagulant effect is established

- **Prophylaxis of Venous thromboembolism**
  - 2.5 mg OD subcutaneously
  - Contraindicated in body weight < 50 kg due to increased risk of bleeding

3. Dosage Adjustment

- **Renal Impairment**
  - Avoid in patients with severe renal impairment **(CrCl < 30 mL/min)**
  -
- **Hepatic Impairment**
  - No dose adjustment is recommended in patients with mild to moderate (Child-Pugh Category B) hepatic impairment.
  - Use with care in patients with severe hepatic insufficiency because of increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic insufficiency.

- **Geriatric**
  - Use with caution in elderly due to the risk of haemorrhage.

- **Paediatric**
  - The safety and effectiveness in children (< 17 years of age) has not been established.

- **Pregnancy**
  - Limited clinical data available on the use of fondaparinux in pregnant women
  - Fondaparinux should not be prescribed to pregnant women unless potential benefit outweighs the risk.

- **Breastfeeding**
  - Breastfeeding is not recommended during treatment with fondaparinux.

4. Contraindications (*Lists are NOT exhaustive)*
    - Patients who are hypersensitive to fondaparinux sodium injection or to any ingredient in the formulation.
    - Thrombocytopenia associated with a positive in vitro test for anti-platelet antibody in the presence of fondaparinux sodium.
    - Active clinically significant bleeding.
    - Acute bacterial endocarditis due to the risk of haemorrhagic complications
    - Body weight < 50 kg in patients requiring prophylaxis for venous thromboembolism

5. Checklist before starting the medication
    - Renal profile
    - Body weight
    - Allergy history

6. Monitoring parameters
    - Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/ coughing out blood)
    - Full blood count
    - Coagulation parameters
    - Renal profile
    - Liver Function Test (Transient elevation of liver transaminases (Aspartate aminotransferase, AST and Alanine aminotransferase, ALT) to > 3 times the upper limit of laboratory range)

7. Method of administration
    - Subcutaneous (SC)
    - Intravenous (IV) (first dose in the treatment for STEMI)

8. Mechanism of Action
    - Potentiating of antithrombin III (ATIII) which selectively inhibits Factor Xa

9. Pharmacokinetic
    - Absorption
        - Bioavailability: 100%
    - Distribution
        - Vd: 7 – 11 L
    - Metabolism
        - Not metabolized. Eliminated unchanged in the urine.
    - Excretion
        - Half-life: 17 – 21 hours

10. Adverse Effects (*Lists are NOT exhaustive)*
    - Haemorrhage
    - Thrombocytopenia
    - Elevations of Serum Aminotransferases
    - Anaemia
    - Fever
    - Nausea
    - Oedema
    - Constipation
    - Rash
    - Vomiting
    - Insomniav

Part Three
Reversal Agents

Vitamin K1 / Phytomenadione

1. Indication
    - **Serotherapeutic INR secondary to warfarin**
    - **Bleeding secondary from warfarin**

2. Dosage
    - Dosing: refer to Management of Overwarfarinisation
      (Administer a dose that will quickly lower the INR into a safe range without causing resistance to warfarin.[1]Use of high dose of vitamin K1 (≥ 10 mg) may cause warfarin resistance for ≥ 1 week)

3. Route of administration
    - Oral route (PO): elevated INRs without significant bleeding
        - Predictable effects, safe, convenient
        - Parenteral Vitamin K1 can be given orally
    - Intravenous route (IV): life-threatening bleeding / urgent reversal / oral route not feasible
        - Rate of administration: not exceeding 1 mg per minute
    - Subcutaneous route (SC)
        - Bioavailability is erratic, thus the effect is variable and less predictable

      (Oral or intravenous route are preferred for warfarin reversal. However, the efficacy in terms of control bleeding or decrease in INR is delayed regardless of route of administration. Therefore, other form of treatments to control the bleeding should be used concurrently)

4. Dosage Adjustment

- **Renal impairment**
  - ➢ No dosage adjustment
- **Hepatic impairment**
  - ➢ No dosage adjustment
- **Geriatric**
  - ➢ No dosage adjustment
- **Paediatric**
  - ➢ No dosage available for the above mentioned indication
- **Pregnancy**
  - ➢ No specific evidence regarding the safety of Vitamin K1 in pregnancy. Administration during pregnancy should only occur if the benefits outweigh the risks
- **Breastfeeding**
  - ➢ Infant risk cannot be ruled out

5. Contraindication

- Hypersensitivity to vitamin K1 or any component of the product used

6. Monitoring Parameters

- Sign and symptoms of bleeding (e.g. blood in urine, blood in stool/ black stools, vomiting/coughing out blood)
- Anaphylactic reaction (when Vitamin K1 given IV/SC)
- Infusion rate (not exceeding than 1 mg per minute)
- INR

7. Method of Administration

    - **Oral route (PO)**: Oral vitamin K preparations are not available in Malaysia. Thus, correct volume of injectable preparation, corresponding to the required vitamin K needed, may be added to water/orange juice to mask the unpleasant taste and consumed orally by the patient
    - **Intravenous route (IV):** slow injection with the rate not exceeding **1 mg/min**

8. Mechanism of Action

    - Promotes liver synthesis of clotting factors II, VII, IX, X

9. Pharmacokinetic

    - Onset of action
        - Oral: 6 – 10 hours
        - IV: 1 – 2 hours
    - Peak effect (INR value return to normal)
        - Oral: 24 – 48 hours
        - IV: 12 – 24 hours
    - Metabolism: Hepatic
    - Elimination half-life: 1.5 – 3 hours
    - Excretion: Urine (10% unchanged), bile

10. Adverse effect (*Lists are NOT exhaustive)*

- **Intravenous route (IV)**
  - Hypersensitivity or anaphylactic reaction *(frequency of anaphylactic reaction is about three per 10,000 doses administered. Therefore, the IV route should be restricted to those situations where another route is not feasible, greater urgency to reverse anticoagulation and the increase risk involved is considered justified)*
  - Anaphylactic reaction can occur due to administration of large IV doses rapidly with the formulation containing polyethoxylated castor oil

- **Subcutaneous Route (SC)**
  - Allergy reaction

- **Intramuscular Route (IM)**
  - Should be avoided
  - Local pain, tenderness, haematoma at the injection site
  - Allergic reaction

Management of Overwarfarinisation

- When patients are overwarfarinised or when INRs are supratherapeutic, the management can be to:
  - Withhold warfarin dose
  - Lower warfarin dose
  - Administer phytomenadione (vitamin K)
  - Transfuse coagulation factors such as:
    - Fresh frozen plasma (FFP): immediate replacement of vitamin K dependent coagulation factors but correction of the coagulopathy is partial or
    - Prothrombin concentrate complex (PCC): immediate replacement of vitamin K dependent coagulation factors

- The choice of management is based on the potential risk of bleeding, the presence of active bleeding and the level of INR. Table 16 shows the recommendations for managing elevated INRs or bleeding in patients receiving warfarin.

Table 16: Recommendations for managing elevated INRs or bleeding in patients receiving warfarin

INR	Therapeutic Options
More than therapeutic range but < 5.0; no significant bleeding	- Lower dose or omit dose - Monitor more frequently and - Resume at appropriately adjusted dose when INR in therapeutic level - If INR only minimally above therapeutic level or associated with a transient causative factor, no dose reduction may be required
≥ 5 but < 9; no significant bleeding	- Omit 1-2 doses - Monitor more frequently and - Resume at appropriately adjusted dose when INR in therapeutic level OR **IF at increased risk of bleeding** - Omit dose and give PO Vitamin K 1 - 2.5 mg OR **IF rapid reversal is required (e.g. patient requires urgent surgery)** - Omit dose and give PO Vitamin K ≤ 5 mg, expect INR to drop in 24 hour - If INR still high, additional PO Vitamin K 1 - 2 mg can be given
≥ 9; no significant bleeding	- Withhold dose and give PO vitamin K 2.5 - 5 mg, expect INR to drop substantially in 24 - 48 hour; - Monitor more frequently and use additional vitamin K if necessary - Resume at appropriately adjusted dose when INR in therapeutic level
Serious bleeding or life threatening bleeding (e.g. intracranial haemorrhage) regardless at ANY INR value (URGENT reversal required)	- Withhold warfarin - Administer Vitamin K 10 mg by slow IV infusion - Supplement with fresh frozen plasma, prothrombin complex concentrate (PCC), or recombinant factor VIIa (NovoSeven) - Vitamin K can be administered every 12H if necessary, depending on the INR

Source: CHEST 2008; The 8th editon ACCP Conference On Antithrombotic and Thrombolytic Therapy: Evidence Based Clinical Practiced Guidelines.

PROTAMINE SULPHATE

1. Indication

   - **Reversal of heparin effect**; if excessive bleeding occurs and when an overdose happened.

2. Dosage

   - Protamine dose is determined by dosage of heparin. 1 mg of protamine neutralizes ~100 unit of heparin
   - Maximum dose: 50 mg

Reversal of unfractionated heparin (UFH)

- **Heparin over dosage following IV administration**

Table 17: Adjust protamine dosage according to duration of time heparin being administered

Time since last UFH dose, min	Protamine dose/100 units of 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

- **Heparin over dosage following subcutaneous injection**
  - IV: 1 to 1.5 mg protamine per 100 units of heparin; a portion of the dose (25-50 mg) may be given slowly IV followed by the remainder portion as continuous infusion over 8 to 16 hours

- **Heparin overdose following continuous infusion**
  - If heparin is being administered as continuous infusion, only heparin given in the **preceding 2-3 hours** should be considered when administering protamine

Reversal of low molecular weight heparin

Table 18: LMWH neutralisation

Time since last LMWH dose	Protamine dose/100 units anti-Xa LMWH received
Within 8 hours	1.0 mg
If bleeding continues	0.5 mg
> 8 hours	0.5 mg

Note: Anti-Xa activity is never completely neutralized (maximum: ~60-75% of LMWH is neutralized). Maximum dose of 50 mg. 1 mg enoxaparin equals approximately 100 units anti-Xa units.

3. Contraindication (*Lists are NOT exhaustive)*
   - Hypersensitivity to protamine or any of the components

4. Warning and Precautions
   - Too rapid administration may cause hypotension and anaphylactic reactions.
   - Caution is warranted when protamine is administered to these group of patients due to increased risk of allergic reaction
     - Previously undergone procedures such as coronary angioplasty or cardio-pulmonary by-pass which may include use of protamine
     - Diabetics treated with protamine insulin
     - Allergic to fish
     - Men who had a vasectomy or are infertile and may have antibodies to protamine.
   - A rebound bleeding effect may occur up to 18 hours post operatively which responds to further doses of protamine especially in patients with prolonged procedures with repeated doses of protamine which required close monitoring of clotting parameters.

5. Monitoring parameters
    - Coagulation test
    - aPTT or ACT
    - cardiac monitor and blood pressure monitor required during administration

6. Method of administration
    - For IV use only. Administer slowly over 10 minutes
    - Maximum 50 mg in any 10-minute period
    - Normally given undiluted. Compatible with 0.9% Sodium chloride or Dextrose 5% if dilution is necessary

7. IVcompatibility
    - IV Incompatibility
        - Cephalosporin and penicillin
    - IV Compatibility
        - NaCl 0.9%, Dextrose 5%

8. Mechanism of Action
    - Combines with heparin to form a stable inactive complex to reverse the anticoagulant effect.

9. Pharmacokinetic
    - Onset of action
        - IV Heparin neutralization: ~ 5 minutes
    - Half-life elimination: ~ 7 minutes

10. Adverse Effect (*Lists are NOT exhaustive)*
    - Hypotension
    - Bradycardia
    - Dyspnoea

Fresh Frozen Plasma (FFP)

1. Indications

   - **Multiple coagulation factor deficiencies and disseminated intravascular coagulation (DIC) with evidence of bleeding**
   - **Thrombotic thrombocytopenic purpura (TTP)**
   - **Reversal of warfarin effect in the presence of potentially life-threatening bleeding when used in addition to vitamin K.**
   - **In the presence of bleeding and abnormal coagulation parameters following massive transfusion or cardiac bypass surgery or in patient with liver disease.**
   - **Replacement of single inherited clotting factor deficiencies where specific or combined factor concentrate is not available**
   - **For the treatment of inherited deficiencies of coagulation inhibitors in patients undergoing high risk procedures where specific factor concentrate is unavailable**

     The use of FFP is generally not considered appropriate in cases of hypovolaemia, plasma exchanges procedures or treatment of immunodeficiency state.

2. Usual dose

   - 10-15 ml of plasma/kg body weight (may have to be exceeded in the event of massive bleeding)

3. Contraindication

   - Avoid use as a volume expander
   - IgA deficiency with confirmed antibodies to IgA

4. Description

   - FFP is plasma prepared from whole blood either through centrifugation of whole blood into red cells or plasma or via secondary centrifugation of platelet rich plasma. It contains normal plasma levels of stable clotting factors, albumin, immunoglobulin and factor VIII at a level at least 70% of normal fresh plasma

5. Method of administration
    - Before use, the fresh frozen plasma must be thawed in a circulating water bath at 37°C
    - Infuse within 30 minutes of thawing
    - Use within 6 hours of thawing due to rapid degradation of labile coagulation factors

6. Storage
    - 36 months at or below -25°C (≤-25°C)
    - 3 months at -18°C to -25°C

7. Adverse Effects (*Lists are NOT exhaustive)*
    - Allergic reaction
    - Anaphylaxis
    - Transfusion-related lung injury (TRALI)
    - Infection
    - Theoretical risk of vCJD (variant Creutxfeld Jacob Disease)

Idarucizumab

1. Indication

   - **For specific reversal of dabigatran and in situations whereby urgent reversal is warranted** *(emergency surgery or urgent procedures and in life threatening or uncontrolled bleeding)*

2. Dosage

   - 5 g (2 vials of 2.5 g/50 ml idarucizumab).
   - **Second dose of 5 g** may be considered in the following situations
     - Recurrence of clinically relevant bleeding with prolonged clotting times
     - Or if potential re-bleeding would be life threatening and prolonged clotting times are observed
     - Patients require second emergency surgery/urgent procedure with prolonged clotting times

3. Dosage Adjustment

   - **Renal Impairment**
     - No dosage adjustment
   - **Hepatic Impairment**
     - No dosage adjustment
   - **Geriatric**
     - No dosage adjustment
   - **Paediatric**
     - Use not recommended

- **Pregnancy**
  - ➢ No information available for pregnancy category *(Animal reproduction study have not been conducted)*

- **Breastfeeding**
  - ➢ It is not known if idarucizumab is present in breast milk. The manufacturer recommends that caution be exercised when administering idarucizumab to breastfeeding women

4. Contraindication
   - None

5. Checklist before starting the medication
   - Confirm the presence of dabigatran (patient records and prescriptions)
   - Verify time of last dose (degree of anticoagulation)*
   - aPTT and/or diluted thrombin time (dTT)

   **If the timing of the last dose of dabigatran > 48 hours have elapsed in patients with normal renal function or > 72 hours in those with impaired renal function, dabigatran is unlikely to be a major contributor to the bleeding*

6. Warning & Precautions
   - Thromboembolic risk
     - ➢ Patients treated with dabigatran have underlying diseases that predispose them to thromboembolic risk. Dabigatran can be resumed 24 hours after idarucizumab infusion
   - Hypersensitivity
   - Hereditary fructose intolerance
     - ➢ The recommended dose of idarucizumab contains 4 g of sorbitol as an excipient.

- When being prescribed in patients with hereditary fructose intolerance, parenteral administration of sorbitol has been associated with hypoglycaemia, hypophosphatemia, metabolic acidosis, increased in uric acid, acute liver failure and death

7. Monitoring parameters
    - aPTT *(Obtain baseline aPTT, repeat at 2 hours and then every 12 hours until aPTT return to normal)*
    - dTT
    - Ecarin Clotting Time (ECT)
    - Signs and symptoms of clinically relevant bleeding and thromboembolic events

8. Method of administration
    - Intravenous line must be flushed with 0.9% NS prior to and at the end of infusion
    - Administered dose undiluted as IV bolus or infusion
    - Infusion of each vial should be more than 5 to 10 minutes with the second vial of 2.5 g administered no later than 15 minutes after the end of first 2.5 g vial.
    - Idarucizumab must not be mixed with other medications. No other infusion should be administered via the same intravenous access.
    - Once solution has been removed from vial, must be used promptly or within 1 hour

9. Mechanism of Action
    - It is a humanized monoclonal antibody fragment (Fab) that forms a stable complex with dabigatran with rapid on-rate and extremely slow-off rate. It specifically binds to dabigatran and its metabolites thus neutralizing their anticoagulant effect

10. Pharmacokinetic
    - Onset
        - Within minutes and haemostasis is restored at a median of 11.4 hours
    - Duration
        - Usually 24 hours
    - Half-life elimination
        - 47 minutes (initially); 10.3 hours (terminal)

11. Adverse Effect (*Lists are NOT exhaustive)*
    - ≥ 5% of idarucizumab treated healthy volunteers: Headache
    - ≥ 5% of patients: Hypokalaemia, delirium, constipation, pyrexia and pneumonia

Appendix

Non-Vitamin K Antagonist (VKA) Oral Anticoagulants (NOACs) in patients with Valvular Atrial Fibrillation (AF)

Appendix 1: Definition of Non-Valvular AF

	Definition of Non-Valvular AF
European Heart Rhythm Association-Practice Guide on the Use of NOACs in Non-Valvular AF (2015)	AF in the absence of mechanical prosthetic heart valves and moderate to severe mitral stenosis.
AHA/ACC/HRS Atrial Fibrillation Guideline (2014)	AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair
A Joint Consensus document of EHRA/EAPCI/ACCA/HRS and APHRS-Management of antithrombotic therapy in AF patients (2014)	AF in the absence of prosthetic mechanical heart valves or haemodynamically significant valve disease, referring to a valve lesion severe enough to warrant surgical or percutaneous intervention or that would have an impact on survival or well-being.

- lack of consistency regarding the definitions of “valvular” and “non-valvular” in various guidelines
- general agreement that the risk of thromboembolism is particularly high in AF accompanying moderate-to-severe mitral stenosis and mechanical prosthetic valves

- Patients with mechanical prosthetic heart valves and moderate or severe mitral stenosis were excluded from all 3 major trials (RE-LY, ROCKET AF and ARISTOTLE)
- AF in patients with biological valves or after valve repair constitutes a grey area, and was included in some trials on "non-valvular AF"
- Anticoagulation with a VKA to achieve an INR of 2.5 for at least 3 months after transcatheter aortic valve replacement (TAVR) may be reasonable in patients at low risk of bleeding. Studies have shown that valve thrombosis may develop in patients after TAVR, as assessed by multidetector computerized tomographic scanning. This valve thrombosis occurs in patients who received antiplatelet therapy alone but not in patients who were treated with VKA. The utility of the NOACs in this population is unknown at this time.

Appendix 2: Valvular Indications and Contraindications for NOAC Therapy in AF Patients

	Eligible	**Contraindicated**
Mechanical prosthetic valve		√
Moderate to severe mitral stenosis (usually of rheumatic origin)		√
Mild to moderate other native valvular disease	√	
Severe aortic stenosis	√ Limited data. Most will undergo intervention	
Bioprostheticvalve[a]	√ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	√ (except for the first 3-6 months post-operatively)	

[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair

Source: ESC Guidelines 2015: Valvular indications and contraindications for NOAC therapy in AF patients.

Appendix 3: Comparison of Clopidogrel, Ticagrelor and Prasugrel

Properties	Clopidogrel	Ticagrelor	Prasugrel
Indication	ACS managed medically or with PCI or CABG Ischemic stroke (non-cardioembolic)	ACS managed medically or with PCI or CABG	ACS with PCI
Onset of inhibition of platelet aggregation (IPA)	300 mg loading dose – 6 hours 600 mg loading dose – 2 hours	180 mg loading dose – 41% IPA at 30 minutes (similar to clopidogrel 600 mg at 8 hours) Maximal IPA: 2-4 hours post dose	60 mg load - ~50% IPA by 1 hour Maximal IPA: ~ 4 hours post loading dose
Dosing	LD: 300-600 mg MD: 75 mg OD (General dosing guide)	LD: 180 mg MD: 90 mg BD	LD: 60 mg MD: 10 mg OD (5 mg if < 60kg)
Duration	Refer to section DAPT duration		
Renal Impairment	• No dosage adjustment • Non dialyzable	• No dosage adjustment • No information is available regarding patients on renal dialysis, not recommended in these patients	• No dose adjustment • There is limited experience in patients with end stage renal disease
Geriatric	STEMI (Fibrinolysis) • ≤ 75 years old: loading dose 300 mg, followed by 75 mg OD daily up to 1 year • 75 years old: no loading dose, 75 mg OD up to 1 year	No dosage adjustment	• ≥ 75 years old, use not recommended *(increased risk of fatal bleeding)* • Maybe consider in high-risk situation (e.g. patients with diabetes or history of MI) where the its effect appears to be greater and its use may be considered

Appendix 3: Comparison of Clopidogrel, Ticagrelor and Prasugrel (*Continue*)

Properties	Clopidogrel	Ticagrelor	Prasugrel
FDA Pregnancy Category	B	Not recommended during pregnancy *(studies in animals have shown reproductive toxicity)*	B ➢ Should be used during pregnancy only if potential benefit to the mother justifies the potential risk to the foetus *(no adequate and well-controlled studies of prasugrel use in pregnant women)*
Mechanism	• Clopidogrel is a prodrug that requires *in vivo* biotransformation into its active metabolites by CYP450 enzymes. • The active metabolite of clopidogrel selectively and irreversibly inhibits the binding of adenosine diphosphate to its $P2Y_{12}$ receptor on platelets. This will in turn prevent the activation of the glycoproteinGPIIb/IIIa receptor complex, thereby inhibiting the platelet aggregation	• Direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$ platelet activation and aggregation • Increase local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine has been documented to have vasodilation, cardio protection, platelet inhibition, modulation of inflammation and induction of dyspnoea	An inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to $P2Y_{12}$ class of ADP receptors on platelet

Appendix 3: Comparison of Clopidogrel, Ticagrelor and Prasugrel (*Continue*)

Properties	Clopidogrel	Ticagrelor	Prasugrel
Prodrug	Prodrug, converted to active metabolite by 2 steps process	Not prodrug	Prodrug, converted to active metabolite by 1 step process
Absorption	Rapid, well absorbed	Rapid with a median Tmax of approximately 1.5 hours	Rapid with peak plasma concentrations of the active metabolite occurring approximately 30 minutes after dosing
Distribution	• Vd: 12.6 L • Protein binding ➢ Parent drug: 98%; ➢ Inactive metabolite (carboxylic acid derivative): 94%	• Vd: 87.5 L • Protein binding: >99% (parent drug & active metabolite)	• Vd: 44-68 L • Protein binding: 98% active metabolites
Metabolism	Extensively hepatic via esterase-mediated hydrolysis to an inactive carboxylic acid derivative (85% of circulating metabolites) and via CYP450-mediated (CYP2C19 primarily) oxidation to 2-oxo-clopidogrel intermediate metabolite then to an active thiol metabolite.	Hepatic via CYP3A4/5 to active metabolite (AR-C124910XX)	Rapidly hydrolysed in intestine to a thiolactone, which is then converted to active metabolite by a single step, primarily by CYP3A4 and CYP2B6

Appendix 3: Comparison of Clopidogrel, Ticagrelor and Prasugrel (*Continue*)

Properties	**Clopidogrel**	**Ticagrelor**	**Prasugrel**
Elimination	• Urine (50%) • Faeces (46%)	➢ Faeces (57.8%) ➢ Urine (26.5%)	➢ Urine (68%) ➢ Faeces (27%)
Contraindications	• Active bleeding such as peptic ulcer and intracranial haemorrhage (ICH) • Significant liver impairment or cholestatic jaundice	• Active bleeding • History of intracranial haemorrhage • Moderate to severe hepatic impairment • Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g.: ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir)	• Active pathological bleeding (e.g.: peptic ulcer bleeding, intracranial haemorrhage) • Prior TIA or stroke
Perioperative management	Discontinue 5 – 7 days prior to surgery	Discontinue at least 3 days prior to surgery	Discontinue 7 days prior to surgery

Appendix 4: Comparison of Dabigatran, Rivaroxaban, and Apixaban

Properties		Dabigatran	Rivaroxaban	Apixaban
Dosage	**Reduction of risk of stroke in AF**	150 mg BD	20 mg OD	5 mg BD
	Primary VTE prophylaxis	Start 110 mg 1 – 4 hours after surgery, followed by 220 mg OD • Duration of 10 days following knee replacement surgery • Duration of 28 – 35 days following hip replacement surgery	Start 10 mg OD 6 – 10 hours after surgery • Duration of 12 days following knee replacement surgery • Duration of 35 days following hip replacement surgery	Start 2.5 mg BD 12 – 24 hours after surgery • Duration of 10 – 14 days following knee replacement surgery • Duration of 32 – 38 days following hip replacement surgery
	Treatment of DVT and PE	150 mg BD after treatment with parenteral anticoagulant for at least 5 days	15 mg BD for 3 weeks, then 20 mg OD for at least 3 months	10 mg BD for 1 week, followed by 5 mg BD for at least 3 months
	Prevention of recurrent DVT and PE	20 mg OD	Complete at least 6 months of 5 mg BD (treatment phase), followed by 2.5 mg BD	

Appendix 4: Comparison of Dabigatran, Rivaroxaban, and Apixaban *(Continue)*

Properties		Dabigatran		Rivaroxaban		Apixaban	
Renal function **CrCl (mL/ min**	**> 50**	Reduction of risk of stroke and systemic embolism in non-valvular AF	150 mg BD	Prevention of stroke and systemic embolism in non-valvular AF	20 mg OD	Prevention of stroke and systemic embolism in non-valvular AF	5 mg BD
		Primary prophylaxis of VTE following hip and knee replacement surgery	220 mg OD	Primary prophylaxis of VTE following hip and knee replacement surgery	10 mg OD	Primary prophylaxis of VTE following hip and knee replacement surgery	2.5 mg BD
		Treatment of DVT and PE	150 mg BD	Treatment of DVT and PE	15 mg BD for 3 weeks, then 20 mg OD	Treatment of DVT and PE	10 mg BD for 1 week, then 5 mg BD
		Prevention of recurrent DVT and PE	150 mg BD	Prevention of recurrent DVT and PE	20 mg OD	Prevention of recurrent DVT and PE	2.5 mg BD

Renal function **CrCl (mL/min**	**30 - 50**	Reduction of risk of stroke and systemic embolism in non-valvular AF	• 150 mg BD • Consider 110 mg BD in patient with high bleeding risk	Prevention of stroke and systemic embolism in non-valvular AF	15 mg OD	Prevention of stroke and systemic embolism in non-valvular AF	• 5 mg BD • 2.5 mg BD in patients with at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 mmol/L)
		Primary prophylaxis of VTE following hip and knee replacement surgery	150 mg OD	Primary prophylaxis of VTE following hip and knee replacement surgery	10 mg OD, with caution	Primary prophylaxis of VTE following hip and knee replacement surgery	2.5 mg BD
		Treatment of DVT and PE	• 150 mg BD • Consider 110 mg BD in patient with high bleeding risk	Treatment of DVT and PE	15 mg BD for 3 weeks, then 20 mg OD	Treatment of DVT and PE	10 mg BD for 1 week, then 5 mg BD
		Prevention of recurrent DVT and PE	• 150 mg BD • Consider 110 mg BD in patient with high bleeding risk	Prevention of recurrent DVT and PE	20 mg OD	Prevention of recurrent DVT and PE	2.5 mg BD

Appendix 4: Comparison of Dabigatran, Rivaroxaban, and Apixaban *(Continue)*

Properties		Dabigatran	Rivaroxaban		Apixaban	
	15-30	Not recommended Primary prophylaxis of VTE following hip and knee replacement surgery Treatment of DVT and PE Prevention of recurrent DVT and PE	Prevention of stroke and systemic embolism in non-valvular AF	15 mg OD	Prevention of stroke and systemic embolism in non-valvular AF	2.5 mg BD
			Not recommended	Primary prophylaxis of VTE following hip and knee replacement surgery	2.5 mg BD, with caution	
			Not recommended	Treatment of DVT and PE	10 mg BD for 1 week, then 5 mg BD Use with caution	
			Not recommended	Prevention of recurrent DVT and PE	2.5 mg BD, with caution	
	< 15 or dialysis	Not recommended	Not recommended		Not recommended	

Geriatric	110 mg BD for patients aged 80 years old or older	No dosage adjustment	• Prevention of stroke or systemic embolism in non-valvular AF ➢ Consider 2.5 mg BD in patients with at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, **OR** serum creatinine ≥ 1.5 mg/dL (133 mmol/L)
FDA Pregnancy Category	C	C	B
Mechanism of Action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Prodrug	Prodrug	Active drug	Active drug
Absorption	• Bioavailability is not affected by food • Food only delays Tmax by 2 hours, but does not affect bioavailability	• Absorption of 2.5 and 5 mg tablet is not affected by food • Food enhances absorption and oral bioavailability of 15 and 20 mg tablet • No difference in bioavailability among patients taking rivaroxaban as whole tablet, crushed tablet or via gastric tube	• Bioavailability: 50% • Food intake does not affect the absorption and efficacy of apixaban • Bioavailability of nasogastric tube and crushed tablet remained unchanged
Distribution	• Vd: 50 – 70 L • Protein binding: 35%	• Vd: 50 L • Protein binding: 92 – 95%	• Vd: 21 – 61 L • Protein binding: 87%

Appendix 4: Comparison of Dabigatran, Rivaroxaban, and Apixaban *(Continue)*

Properties	Dabigatran	Rivaroxaban	Apixaban
Metabolism	Dabigatran etexilate is a prodrug that is rapidly and completely hydrolysed to active metabolite, dabigatran by plasma and hepatic esterase in plasma and liver	Primarily metabolised in liver via CYP3A4/5, CYP2J2	Primarily metabolised in liver via CYP3A4
Elimination	• Primarily through renal route • Dialyzable	• Primarily through renal route: 66% • Non dialyzable	• Mostly excreted via biliary and direct intestinal excretion in faeces • Non dialyzable
Administration	• Swallow whole with a glass of water • Do not break, chew or empty contents of capsule • Remove capsule by tearing off one individual blister along the perforated line • Peel off the backing foil and remove the capsule. Do not pushed the capsule through the blister foil • Only remove capsule from blister foil immediately before use	• To be taken with food (15 and 20 mg tablet) at the same time each day • For those unable to swallow whole tablet, tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After administration of crushed tablets, the dose should be immediately followed by food • Crushed tablet can be administered in small amount of water via gastric tube after which it should be flushed with water. After the administration via gastric tube, the dose should be immediately followed by enteral feeding	• Tablet can be swallowed whole with or without food • Tablet can be crushed and suspended in water, 5% dextrose in water (D5W) or apple juice or mixed with apple puree. Crushed tablets are stable in water, D5W, apple juice and apple puree for up to 4 hours • Crushed tablet can be suspended in 60 mL of water or and immediately served via gastric tube

Abbreviation

ACS	-	Acute Coronary Syndrome
ACT	-	Activated Clotting Time
ADP	-	Adenosine diphosphate
AF	-	Atrial Fibrillation
ALT	-	Alanine aminotransferase
aPTT	-	Activated partial thromboplastin time
AST	-	Aspartate aminotransferase
CABG	-	Coronary Artery Bypass Grafting
CrCl	-	Creatinine Clearance
D5W	-	5% dextrose in water
DAPT	-	Double Anti-Platelet Therapy
DIC	-	Disseminated Intravascular Coagulation
dTT	-	Diluted Thrombin Time
DVT	-	Deep Vein Thrombosis
ECT	-	Ecarin clotting time
ENT-1	-	Equilibrative Nucleoside Transporter-1
FFP	-	Fresh frozen plasma
ICH	-	Intracranial haemorrhage
INR	-	International normalized ratio
IPA	-	Inhibition of Platelet Activity
IV	-	Intravenous
LMWH	-	Low Molecular Weight Heparin
MI	-	Myocardial Infarction
NG	-	Nasogastric
NIHSS	-	NIH stroke scale
NOACs	-	Non-vitamin K antagonist oral anticoagulants
NSAIDs	-	Non-steroidal anti-inflammatory drug
NSTEMI	-	Non-ST Elevation Myocardial Infarction

PCC	-	Prothrombin concentrate complex
PCI	-	Percutaneous Coronary Intervention
PE	-	Pulmonary Embolism
PT	-	Prothrombin time
SC	-	Subcutaneous
STEMI	-	ST Elevation Myocardial Infarction
TIA	-	Transient Ischemic Attack
Tmax	-	Time of peak concentration
TT	-	Thrombin time
TTP	-	Thrombotic Thrombocytopenic Purpura
UA	-	Unstable Angina
UFH	-	Unfractionated Heparin
Vd	-	Volume of distribution
VKA	-	Vitamin K antagonist
VKORC 1	-	Vitamin K epoxide reductase complex 1
VTE	-	Venous thromboembolism
vWF	-	von Willebrand factor

Equation

Cockcroft-gault formula for creatinine clearance:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \times 0.85 \text{ (if female)}$$

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Lawrence Anchah is an Associate Professor in Faculty of Medicine and Health Sciences at Universiti Malaysia Sarawak, Malaysia. He has been in clinical pharmacy steering committee, research and development (R&D) committee, and various position at national level of pharmacy division in Ministry of Health. After attaining his PhD degree in 2011, he initiated the clinical pharmacy service; specialised in ward pharmacy and phase I cardiac rehabilitation along with other pharmacists during the initial establishment of Sarawak Heart Centre. He also has several publications in clinical pharmacy field to his credit and currently embarking in pharmacoeconomic research.

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