



PHARMACEUTICAL SERVICE PROGRAM
MINISTRY OF HEALTH MALAYSIA

ANTICOAGULATION MTAC (AC-MTAC) PROTOCOL

2nd EDITION (2020)

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FOREWORD



This Anticoagulation Medication Therapy Adherence Clinic (AC-MTAC) Protocol 2nd Edition is a commitment and collective hard work of the Clinical Pharmacy Working Committee (Cardiology Subspecialty). It is a rebranding of Warfarin MTAC (WMTAC) where the 1st edition of protocol was published in year 2010.

Warfarin MTAC (WMTAC) is one of the most established MTAC service in Malaysia. Until now, there are 82 hospitals and 12 health clinics from Ministry of Health Malaysia currently offering this service. Over the year, the treatment options for anticoagulation therapy has evolved and advanced due to new discoveries of direct oral anticoagulants (DOACs) such as Dabigatran, Rivaroxaban and Apixaban. Hence, the pharmacy service on monitoring anticoagulation therapy should also be improved and expanded.

This protocol serves as a guidance to all existing or new facilities that offer Anticoagulant MTAC services. It has outlined the entire standard operating procedures and documentations needed for implementation of AC-MTAC in MOH facilities. It also includes several checklists for DOACs counselling, guidance on medication dosage adjustments together with monitoring and evaluation procedures.

In short, I am glad that the committee members have taken the initiative to upgrade and improve the Warfarin MTAC Protocol to Anticoagulation MTAC (AC-MTAC) Protocol. I would like to congratulate the Cardiology Pharmacy Committee for their contribution and commitment of this publication. I hope that the pharmacists can utilise this protocol as a reference during the implementation of AC-MTAC.

Thank you.

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INTRODUCTION

Anticoagulation Medication Therapy Adherence Clinic (ACMTAC) is a part of Medication Therapy Adherence Clinic (MTAC) services provided by the Pharmacy Practice and Development Division, Ministry of Health collaborate with doctors in the management of patients on anticoagulation therapy. It was formerly known as Warfarin MTAC (WMTAC). Due to the discovery of direct oral anticoagulants (DOACs) such as Dabigatran, Rivaroxaban and Apixaban in recent years¹ prompted the Clinical Pharmacy Working Committee (Cardiology Subspecialty) to revise and come up with AC-MTAC Protocol.

Proper anticoagulation therapy is essential to patients in order to minimise risk of thrombotic events or haemorrhagic events.² Anticoagulation therapy with warfarin has evolved from doctor-managed clinic to the collaboration with pharmacist to improve patient's time in therapeutic range (TTR).³ Maximum benefits of warfarin therapy is evident when TTR is $\geq 70\%$.⁴

The availability of DOACs either targeting Factor IIa/thrombin (Dabigatran) or Factor Xa (Rivaroxaban and Apixaban) reduce the need for frequent monitoring as compared to warfarin.⁵ It has fewer drug interactions and predictable pharmacokinetics.⁶ Nevertheless, proper monitoring of patients on DOAC is still required to ensure patients' adherence towards DOACs and to prevent risk of bleeding.⁷

This protocol was developed to serve as a guide to provide standardised practice in all ACMTAC in Ministry of Health's (MOH). This protocol needs to be discussed with the relevant heads of departments and subsequently endorsed by Hospital Director before implementation in the facility.

This protocol is only applicable to drugs registered under Malaysia Drug Formulary (*FUKKM*). This should in no way be used to replace clinical judgment. Physician, cardiologist, or haematologist can always be consulted for specific patients with more complex regimens.

OBJECTIVES

General Objective

To provide a comprehensive guide on the implementation of anticoagulation MTAC (ACMTAC).

Specific Objectives

1. To provide adequate knowledge and understanding on the pathophysiology of thromboembolism in diseases which require anticoagulation therapy.
2. To provide knowledge on anticoagulation therapy that can be used to prevent thromboembolism.
3. To provide continuity and enhance patient care through education, monitoring, and close follow-up to patients who require anticoagulation therapy.
4. To maximize the benefits of anticoagulation therapy and minimize the adverse effect and complications resulting from anticoagulation therapy.
5. To provide consultative and educational services to other healthcare providers on anticoagulant drug management and related issues.
6. To conduct research regarding anticoagulation therapy and related areas.

SCOPE OF SERVICE

1. The clinic shall operate based on agreed hospital clinic day in the respective departments.
2. Approach of teamwork practice shall be adopted consisting of doctors, pharmacists, and other relevant health care providers.
3. Follow up of patients in the clinic shall be based on ACMTAC schedule.
4. Activities in the clinic includes medication history taking for drugs, OTC, traditional or herbal medicine, and supplements, counselling, dosage adjustment of warfarin based on International Normalized Ratio (INR), renal and/or liver profile, signs and symptoms of bleeding and thromboembolic event, therapy during elective procedure and dispensing of anticoagulation medications.

MANPOWER REQUIREMENT

1. The number of pharmacists shall be based on the number of patients scheduled per day. (Recommended pharmacist:patient ratio is 1:10).
2. Minimum two (2) trained pharmacists in ACMTAC team where at least one (1) pharmacist will be on duty during each ACMTAC session.
3. Pharmacist spends at average of 10 to 15 minutes per case while longer time might be needed for new cases (around 30 minutes).

APPOINTMENT

All appointments are scheduled by the pharmacists or with the help of other health care providers in the clinic.

DISPENSING

Anticoagulation medication shall be dispensed during ACMTAC to the patients/care giver.

OUTCOMES MEASUREMENT

1. This service shall be continuously assessed to ensure that patients are receiving optimal care.
2. The time to therapeutic range (TTR) for warfarin treatment in ACMTAC has to achieve a targeted TTR of $\geq 70\%$.

DOCUMENTATION

Individual clinical notes including the anticoagulation therapy dosing changes, INR and laboratory (renal or liver function) results shall be noted in patients' medical records. The relevant documents also shall be maintained in the patients' medical records:

1. ACMTAC Referral Form (ACMTAC/F1) – **Appendix 1**
2. ACMTAC First Visit Form (ACMTAC/F2) – **Appendix 2**
3. ACMTAC Follow-up Visit Form (ACMTAC/F3) – **Appendix 3**
4. Missed Appointment Sheet (ACMTAC/F4) – **Appendix 4**
5. Prescriber Checklist for DOACs – **Appendix 5**
6. Pharmacist Checklist for DOACs – **Appendix 6**

STANDARD OPERATING PROCEDURES

The workflow of ACMTAC is as shown in Figure 1. Ten main stages involved are:

1. Selection of patient
2. Registration

3. Blood test
4. Clinic operation
5. Patient education
6. Monitoring and evaluation
7. Dosage adjustments
8. Responsibilities of pharmacist
9. Dispensing
10. Missed appointment

Selection of Patient

1. All out-patient on anticoagulation therapy in relevant disciplines.
2. For patient who started on anticoagulation therapy in the ward, referrals should be made prior to discharge to allow adequate time for case review and patient education. A standardised referral form (ACMTAC/F1) – **Appendix 1** can be used.
3. All new cases from other clinics or institutions and any initiation of anticoagulants need to be discussed with prescriber (depends on the hospital/health centre).
4. The pharmacist shall obtain the Prescriber Checklist for DOACs (**Appendix 5**) and Pharmacist Checklist of DOACs (**Appendix 6**) for all new patients started with DOACs and complete the form.

Registration

1. Patients shall follow the general policies and procedures concerning registration.
2. Registry of patients attending ACMTAC shall be kept and updated at all time.

Blood Test

1. For warfarin patients, INR can be determined through point of care testing (POCT) or central laboratory test. All blood samplings for INR reading should be performed by relevant trained healthcare providers.
2. Renal and/or liver profile should be taken prior to scheduled appointment when needed.

Clinic Operation

1. A designated area with minimal interruptions to ensure patient's privacy and confidentiality.
2. Storage area for relevant documents and necessary items shall be made available.
3. For all scheduled patients, the case notes need to be reviewed for better understanding of the therapy.

Patient Education

1. Education of the patient is an important process of ensuring safe and effective use of anticoagulant therapy.
2. Education should be individualised and based on patient's understanding.
3. Each patient shall be provided with a *Buku Rawatan Antikoagulasi* (available in Bahasa Malaysia, Mandarin and Tamil) or other relevant material such as leaflet/pamphlets.
4. Patient education should include the following:
 - Name, strength, and description of anticoagulant tablet.
 - Frequency of dose and administration time.
 - How to handle missed doses.
 - Purpose of anticoagulation therapy and how it works.
 - Medications/supplements and dietary interactions.
 - Recognition of symptoms of bleeding/thrombosis, adverse reactions and the appropriate procedures to follow.
 - Importance of compliance with anticoagulants and clinic appointments.
 - Emphasis on the importance of follow up and documentation.
 - Educate patients on the use of anticoagulants in pregnancy or breast feeding if necessary.
5. Checklist for patients education as listed below:-
 - Checklist for Warfarin Education - **Appendix 7**
 - Checklist for Dabigatran Education - **Appendix 8**
 - Checklist for Rivaroxaban Education - **Appendix 9**
 - Checklist for Apixaban Education - **Appendix 10**

Monitoring and Evaluation

1. Patient's response to anticoagulation therapy shall be evaluated through INR or renal profile and information gathered from patient's interview using ACMTAC/F2 (**Appendix 2**) or ACMTAC/F3 (**Appendix 3**) or Pharmacist Checklist For DOACs (**Appendix 6**).
2. The following criteria shall be used to assess patient's response to anticoagulation therapy and detect any potential problems prior to dosage adjustments:
 - Signs and symptoms of haemorrhage or thromboembolism
 - Change in condition(s) or disease state
 - Recent alterations in diet, medications, tobacco or alcohol intake
 - Alterations in other medical problems or recent illnesses
 - Compliance with warfarin or DOAC therapy
 - Upcoming surgery or dental procedures.

Dosage Adjustments

A. Warfarin

1. The warfarin dose shall be adjusted to maintain INR within range. (Refer **Warfarin Therapy Guide - Appendix 11**).
2. The workflow for warfarin dose adjustment as in **Figure 2**.
3. The weekly dosing chart as in the **Appendix 12**.
4. The exact target range must be used for all valve replacements, acute or recent VTE. Otherwise, extended target range (± 0.2 of target INR range) can be applied.
5. Dose adjustment shall be considered in the following instances:
 - When two consecutive INR values are sub-therapeutic or supra-therapeutic despite prior control being good
 - When patient referred for follow up after initiation of anticoagulation.
 - When there is warfarin-drugs/supplements/herbal/diet interactions (Refer **Warfarin Interaction - Appendix 13**).

B. DOACs

1. The DOACs dose shall be maintained as Dosing Guide.
2. Dosing information are as listed below:-
 - Prescribing Information for Dabigatran (**Appendix 14**)

- Prescribing Information for Rivaroxaban (**Appendix 15**)
 - Prescribing Information for Apixaban (**Appendix 16**)
3. Dose adjustment shall be considered in the following instances:
 - Creatinine clearance $\leq 30\text{ml/min}$
 - Older age
 - Higher bleeding risk

C. Triple Therapy

1. The use of triple anti-thrombotic therapy after ACS and PCI in patients on chronic oral anti-coagulation will lead to high risk of bleeding.
2. Triple therapy beyond 6 months after PCI is not recommended.
3. Dosing guide can refer to Triple Therapy Guideline (**Appendix 17**).

D. Conversion from One Anticoagulant to Another

1. The conversion from Warfarin, LMWH or UFH to DOACs or vice versa shall be done according to Conversion of Anticoagulant Guide (**Appendix 18**).

Managing Bleeding In Anticoagulation Patients

1. Reversal of anticoagulation with Warfarin or DOACs should be done based on bleeding events or/and INR value (Refer **Appendix 19**).

Responsibilities of Pharmacist

1. The pharmacist will educate the patient on anticoagulation therapy at the initial visit and reinforce this education at each visit.
2. The pharmacist will monitor:
 - INR values (Refer **Appendix 11**).
 - risk of bleeding
 - stop the antiplatelet (Refer **Appendix 11**)
 - renal or liver profile (Refer **Appendix 14 – 16**)
3. The pharmacist is authorised to transcribe warfarin prescriptions as needed where the prescription for warfarin will be counter-signed by the appointed doctor for medico-legal requirements (based on local policy/ approval).
4. The patient shall be referred to the doctor in the following situations:

- Actual or suspected signs and symptoms of severe haemorrhage regardless of INR value.
- Actual or suspected signs and symptoms of thromboembolism.
- INR values over 4.0 or any INR value at the discretion of the respective hospital.
- When patients need to overlap with low molecular weight heparin (LMWH) during warfarin initiation or sub-therapeutic INR.
- When the duration of therapy has been completed.
- When patients consistently miss appointments or remain non-compliant to therapy.
- Patient who requires re-initiation for warfarin.
- Patient who requires conversion from one anticoagulant to another
- Patients who need to reduce DOACs dose.

Dispensing

1. Pharmacist must ensure correct dose, quantity of warfarin or DOAC tablets be dispensed.
2. Upon dispensing, pharmacist shall emphasized on the correct dose, frequency and time of administration.
3. Standardised label (**Appendix 19**) is recommended when dispensing warfarin.
4. Patient shall be provided with a summary of important information at the end of each ACMTAC session.
5. Patients' understanding and expectations shall be reassessed when necessary.

Missed appointment

1. Contact patient as soon as possible and reschedule a new appointment (for facilities that offer ACMTAC or WMTAC once a week).
2. Allow patient to walk-in during the next ACMTAC day (for facilities that offer ACMTAC or WMTAC twice a week).
3. Reasons of missed appointment should be documented in Missed Appointment Sheet (**Appendix 4**)

Figure 1 - ACMTAC Work Flow

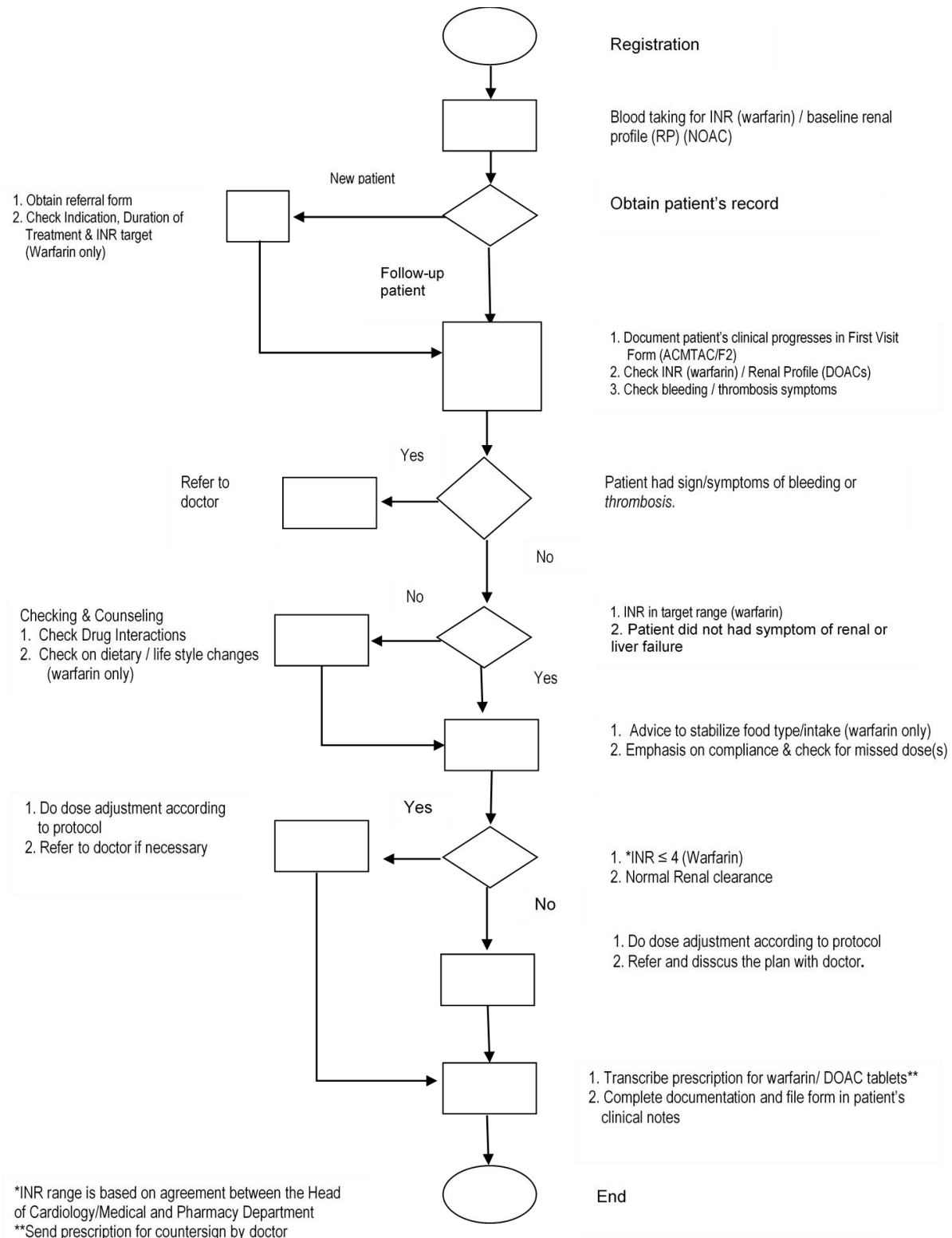
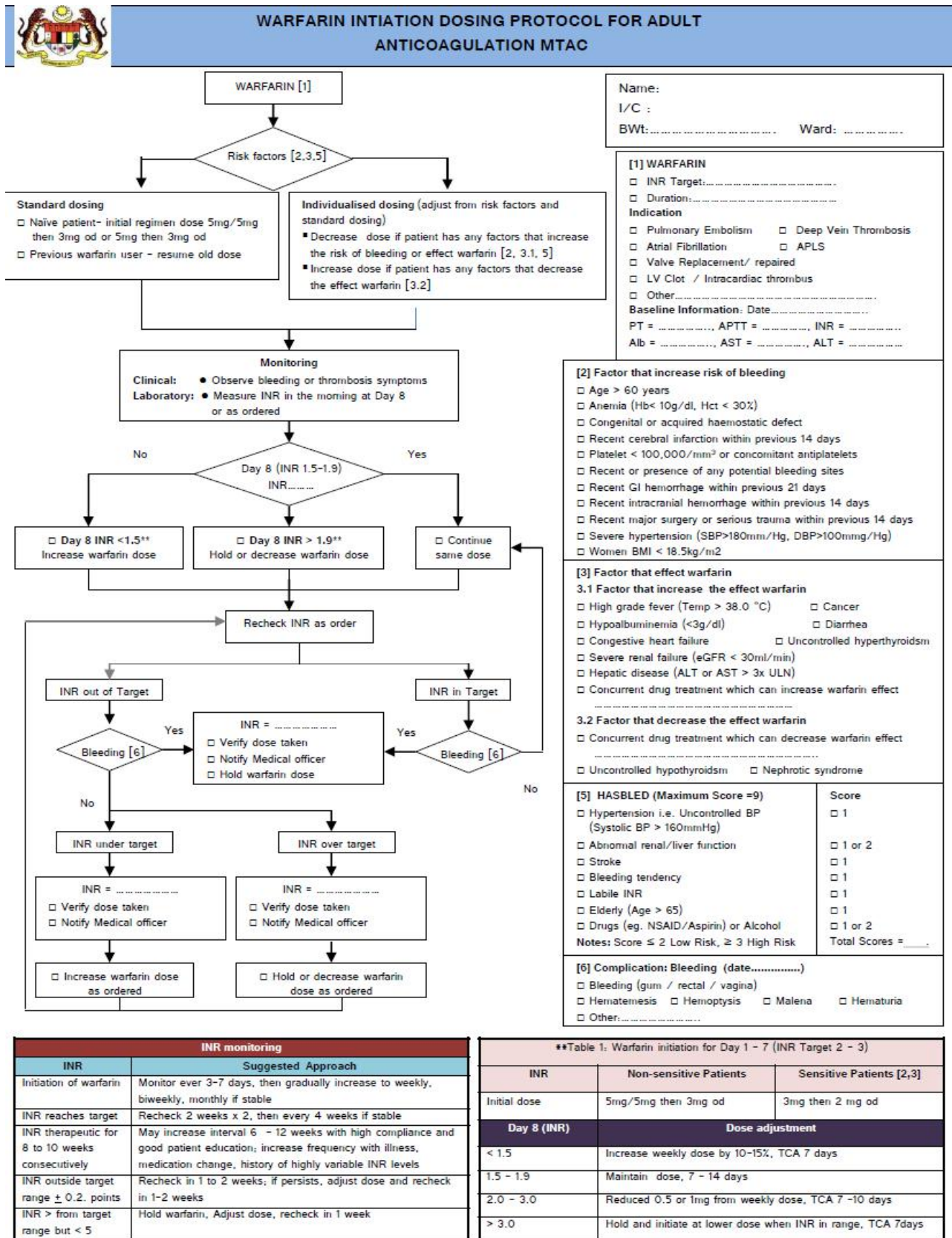


Figure 2 - Warfarin Dose Adjustment Work Flow



1st Version Jan 2019

Appendices

Appendix 1	ACMTAC Referral Form (ACMTAC/F1)
Appendix 2	ACMTAC 1 st Visit Form (ACMTAC/F2)
Appendix 3	ACMTAC Follow-Up Visit Form (ACMTAC/F3)
Appendix 4	Missed Appointment Sheet (ACMTAC/F4)
Appendix 5	Prescriber Checklist For DOACs
Appendix 6	Pharmacist Checklist For DOACs
Appendix 7	Checklist for Warfarin Education
Appendix 8	Checklist for Dabigatran Education
Appendix 9	Checklist for Rivoraxaban Education
Appendix 10	Checklist for Apixaban Education
Appendix 11	Warfarin Therapy Guide
Appendix 12	Weekly Dosing Chart
Appendix 13	Warfarin Interaction
Appendix 14	Prescribing Information for Dabigatran
Appendix 15	Prescribing Information for Rivaroxaban
Appendix 16	Prescribing Information for Apixaban
Appendix 17	Triple Therapy Guide
Appendix 18	Conversion of Anticoagulant Guide
Appendix 19	Guideline for Treatment of Bleeding in Anticoagulation Patients
Appendix 20	Recommended Dispensing label

Appendix 1- ACMTAC/F1

**ANTICOAGULATION MEDICATION THERAPY ADHERENCE CLINIC
REFERRAL FORM
PHARMACY DEPARTMENT, HOSPITAL.....**

Date			
Patient Details			
Name:		Age:	Race: M / I / C / O
MRN:	IC No:	Gender: M / F	Phone No:
Oral Anticoagulant Therapy			
Type of Oral Anticoagulant		Date of oral anticoagulant started:	
<input type="checkbox"/> Warfarin: <u>Target INR Range</u> <input type="checkbox"/> 1.5 – 2.5 <input type="checkbox"/> 2.0 – 3.0 <input type="checkbox"/> 2.5 – 3.5 <input type="checkbox"/> Other (please specify):.....		<input type="checkbox"/> Dabigatran _____ mg <input type="checkbox"/> Apixaban _____ mg <input type="checkbox"/> Rivaroxaban _____ mg Anticipated Duration: Anticipated Stop Date:	
Oral Anticoagulant Indication			
<u>Warfarin therapy</u> <input type="checkbox"/> Arterial Embolism <input type="checkbox"/> Atrial Fibrillation <input type="checkbox"/> Deep Vein Thrombosis <input type="checkbox"/> Pulmonary Embolism <input type="checkbox"/> Heart Valve Replacement <input type="checkbox"/> Coagulopathy state (describe): _____ <input type="checkbox"/> Pulmonary Hypertension <input type="checkbox"/> Left Ventricular Clot <input type="checkbox"/> Venous Thrombosis of other specific Vein <input type="checkbox"/> Other (please specify): _____		<u>Dabigatran/ Rivaroxaban/Apixaban therapy</u> <input type="checkbox"/> Non-valvular atrial fibrillation <input type="checkbox"/> Prevention of venous thromboembolism in total knee/ hip replacement surgery <input type="checkbox"/> Treatment of Deep Vein Thrombosis (DVT) <input type="checkbox"/> Prevention of Recurrent DVT/ Pulmonary Embolism	
Clinical Information			
Is this patient on Triple Therapy? Yes / No			
<input type="checkbox"/> Duration for Triple Therapy _____ Date to stop: _____ Drug to Discontinue _____ <input type="checkbox"/> Duration for Double Therapy _____ Date to stop : _____ Drug to Discontinue _____			
Concurrent Illness			
<input type="checkbox"/> CAD <input type="checkbox"/> Diabetes <input type="checkbox"/> Liver disease <input type="checkbox"/> GI bleeds <input type="checkbox"/> Heart Failure <input type="checkbox"/> Hypertension <input type="checkbox"/> Hyper/Hypothyroidism <input type="checkbox"/> Peptic Ulcer Disease <input type="checkbox"/> Renal Impairment <input type="checkbox"/> Seizure Disorder <input type="checkbox"/> Other (please specify):			

Bleeding Risk Factors (Tick all that applies) ¹

- ☐ Hypertension i.e. Uncontrolled BP (Systolic BP > 160mmHg) - 1 point
- ☐ Abnormal renal/liver function – 2 point
- ☐ Stroke - 1 point
- ☐ Bleeding tendency - 1 point
- ☐ Labile INR - 1 point
- ☐ Elderly (Age > 65) - 1 point
- ☐ Drugs (eg. NSAID/Aspirin) or Alcohol - 2 point

Notes: Maximum score=9, Score ≤ 2 Low Risk, ≥ 3 High Risk

Concurrent Drug Therapy

Name/Dose/Frequency	Interaction

Comments:

Pharmacist's Signature and Stamp

Physician Review & Notes

Referring Physician's Signature and Stamp

Appendix 2- ACMTAC/F2

ANTICOAGULATION MEDICATION THERAPY ADHERENCE CLINIC
1ST VISIT FORM
PHARMACY DEPARTMENT, HOSPITAL.....

Date of Visit :													
Patient Information													
Name :					Age :		Race : M / C / I / Others:_____						
MRN :			IC NO :				Gender : M / F						
Address:							Telephone No						
Anticoagulation Plan (Please Choose One)													
Warfarin		Dabigatran*		Rivaroxaban*		Apixaban*							
Indication :													
Initiation Date:				Anticipated Stop Date:			*Dose (DOAC) :						
Plan Duration:							INR Target (for warfarin only) :						
Baseline Readings													
Serum Creatinine (μmol/L) :					Total Bilirubin (g/L) :								
Creatinine Clearance (mL/min) :					Albumin (g/L) :								
					ALT (μ/L) :		AST (μ/L) :						
Co-morbid conditions													
Co-morbid Medical Conditions :													
Concurrent Medications					Interaction								
Name/Dose/Frequency					Yes / No		Effect						
					Yes / No								
					Yes / No								
					Yes / No								
					Yes / No								
					Yes / No								
Objective Information													
Current dose (Warfarin) :							Correct dose taken : Y / N						
Mon	Tue	Wed	Thur	Fri	Sat	Sun	Mon	Tue	Wed	Thur	Fri	Sat	Sun
Subjective Information													

Compliance <input type="checkbox"/> Good <input type="checkbox"/> Poor _____ Missed doses in past 1 week : <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Bleeding <input type="checkbox"/> No <input type="checkbox"/> Yes _____ Thrombosis <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Drug Interaction <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Food / Herbs/ supplement Interaction <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Alcohol consumption? <input type="checkbox"/> No <input type="checkbox"/> Yes _____ Smoker? <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Change in Medical Status/ Illness <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Change in Physical Activity : <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Pregnancy / plan to get pregnant? <input type="checkbox"/> No <input type="checkbox"/> Yes _____																												
Other complain / Patients Plans : Y / N (Describe if Yes)																												
Assessment																												
INR Value		Sub-therapeutic		Within Range		Supra-therapeutic																						
INR (Laboratory) / (Point of Care)																												
Pharmacist Review / Plan																												
Plan <input type="checkbox"/> Maintain dose <input type="checkbox"/> Loading dose _____ Withhold ____ day(s) <input type="checkbox"/> Increase dose _____ <input type="checkbox"/> Reduce dose _____ <input type="checkbox"/> S/C Enoxaparin _____ TCA _____ Date _____ <input type="checkbox"/> Advice patient to go to ED if had bleeding/thrombosis symptoms or any problems																												
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="7">Warfarin dose recommended:</td> </tr> <tr> <td>Mon</td> <td>Tue</td> <td>Wed</td> <td>Thur</td> <td>Fri</td> <td>Sat</td> <td>Sun</td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </table> <div style="text-align: right; margin-top: 10px;">Pharmacist's Signature and Stamp</div>								Warfarin dose recommended:							Mon	Tue	Wed	Thur	Fri	Sat	Sun							
Warfarin dose recommended:																												
Mon	Tue	Wed	Thur	Fri	Sat	Sun																						
Doctor Review & Notes (If applicable)																												
Physician's Signature and Stamp																												

Appendix 3 - ACMTAC/F3

**ANTICOAGULATION MEDICATION THERAPY ADHERENCE CLINIC
FOLLOW-UP VISIT FORM
PHARMACY DEPARTMENT, HOSPITAL.....**

Date of Visit :													
Patient Information													
Name:													
MRN / IC:													
Age:							Weight :						
Indication:							INR Target :						
Drug:													
Warfarin				Dabigatran				Rivaroxaban				Apixaban	
Missed appointments : Y / N (Reason for missed appointment)													
Objective Information													
Current dose							Correct dose taken :						
a. DOAC_____							<input type="checkbox"/> Yes <input type="checkbox"/> No (DOAC) _____						
b. Warfarin:							<input type="checkbox"/> No (Warfarin):						
Mon	Tue	Wed	Thur	Fri	Sat	Sun	Mon	Tue	Wed	Thur	Fri	Sat	Sun
Subjective Information													
Compliance <input type="checkbox"/> Good <input type="checkbox"/> Poor_____ Missed doses in past 1 week : <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Bleeding <input type="checkbox"/> No <input type="checkbox"/> Yes _____ Thrombosis <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Drug Interaction <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Food / Herbs/ supplement Interaction <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Alcohol consumption? <input type="checkbox"/> No <input type="checkbox"/> Yes _____ Smoker? <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Change in Medical Status/ Illness <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Change in Physical Activity : <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Pregnancy / plan to get pregnant? <input type="checkbox"/> No <input type="checkbox"/> Yes _____													
Other complain / Patients Plans : Y / N (Describe if Yes)													

Assessment																												
INR Value			Sub-therapeutic		Within Range		Supra-therapeutic																					
INR (Laboratory) / (Point of Care)																												
Pharmacist Review / Plan																												
<p>Plan <input type="checkbox"/> Maintain dose <input type="checkbox"/> Loading dose _____ Withhold ____ day(s)</p> <p> <input type="checkbox"/> Increase dose _____ <input type="checkbox"/> Reduce dose _____</p> <p> <input type="checkbox"/> S/C Enoxaparin _____</p> <p>TCA _____ Date _____</p> <p><input type="checkbox"/> Advice patient to go to ED if had bleeding/thrombosis symptoms or any problems</p>																												
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="7" style="padding: 5px;">Warfarin dose recommended:</td> </tr> <tr> <td style="padding: 5px;">Mon</td> <td style="padding: 5px;">Tue</td> <td style="padding: 5px;">Wed</td> <td style="padding: 5px;">Thur</td> <td style="padding: 5px;">Fri</td> <td style="padding: 5px;">Sat</td> <td style="padding: 5px;">Sun</td> </tr> <tr> <td style="height: 30px;"></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>							Warfarin dose recommended:							Mon	Tue	Wed	Thur	Fri	Sat	Sun								Pharmacist's Signature and Stamp
Warfarin dose recommended:																												
Mon	Tue	Wed	Thur	Fri	Sat	Sun																						
Doctor Review & Notes (If applicable)																												
Physician's Signature and Stamp																												

Appendix 4 - ACMTAC/F4**MISSED APPOINTMENT SHEET**

MISSED APPOINTMENT ANTICOAGULATION MTAC Pharmacy Department, Hospital.....				
Date	Patient's details	Miss Appointment (Date)	New Appointment (date)	Initials

Appendix 5 - Prescriber Checklist For DOACs

**PRESCRIBER CHECKLIST FOR DOACS
(DABIGATRAN / RIVAROXABAN / APIXABAN)**

PATIENTS DEMOGRAPHIC		
Patient's Name:	IC No & RN:	
INR Value & Date:	Age (Years):	Weight (Kg):
Serum Creatinine & Date (Baseline)	ClCr (ml/Min)	
Liver Function & Date (Baseline)		
CHOICE OF ANTICOAGULANT		
Please tick (✓) at the relevant box		
<input type="checkbox"/> Dabigatran , Dose _____mg		
<input type="checkbox"/> Rivaroxaban, Dose _____mg		
<input type="checkbox"/> Apixaban, Dose _____mg		
STATUS OF ANTICOAGULANT THERAPY		
<input type="checkbox"/> New Case		
<input type="checkbox"/> Change from Warfarin to Dabigatran / Rivaroxaban/ Apixaban		
Please state reason:		
INDICATION		
<input type="checkbox"/> Prevention of Stroke and Systemic Embolism in Non-Valvular Atrial Fibrillation <i>(Indicated for Dabigatran 110mg & Dabigatran 150mg, Rivaroxaban 15mg & Rivaroxaban 20mg, Apixaban 2.5mg & Apixaban 5mg)</i>		
<input type="checkbox"/> Prevention of VTE events in total knee replacement or total hip replacement surgery patient <i>(Indicated for Dabigatran 75mg & Dabigatran 110mg, Rivaroxaban 10mg)</i>		
<input type="checkbox"/> Prevention and Treatment of Recurrent DVT / PE in Acute DVT <i>(Indicated for Dabigatran 110mg & Dabigatran 150mg, Rivaroxaban 15mg & Rivaroxaban 20mg)</i>		

CONTRAINDICATION**DO NOT start anticoagulant agent if patient has condition(s) as stated below :-**

- ☐ Insufficiency renal function
- ☐ Abnormal hepatic function
- ☐ CrCl <30ml/min : Dabigatran/Rivaroxaban (DVT)
- ☐ Child-Pugh B & C : Rivaroxaban ☐ Child-Pugh C : Apixaban
- ☐ CrCl <15ml/min : Rivaroxaban/Apixaban
- ☐ Active bleeding (< 6 months) (e.g: intracranial hemorrhage, Recent GI bleed)
- ☐ Pregnancy or Lactation
- ☐ Elevated liver enzymes >3 times ULN : Dabigatran
- ☐ Planned for neuraxial anesthesia or spinal puncture

SPECIAL WARNINGS & PRECAUTIONS

- ☐ Active ulcerative GI disease
- ☐ Congenital or acquired coagulation disorder
- ☐ Bacterial endocarditis
- ☐ Recent biopsy or major trauma (< 6 months)
- ☐ Brain, spinal or ophthalmic surgery
- ☐ Extreme body weight: >110 kg
- ☐ Low body weight: <50 kg
- ☐ Thrombocytopenia or function platelet defect

Checklist when Switching patient from warfarin to Dabigatran or Rivaroxaban or Apixaban:

1. Indication	Dabigatran	Rivaroxaban	Apixaban
a. Treatment and Recurrent of DVT	<input type="checkbox"/> INR must be < 2	<input type="checkbox"/> INR must be ≤ 2.5	
b. Prevention of Stroke and Systemic Embolism in Non-Valvular Atrial Fibrillation	<input type="checkbox"/> INR must be < 2	<input type="checkbox"/> INR must be < 3	<input type="checkbox"/> INR must be < 2

2. Patient has been informed to discontinue warfarin immediately ☐3. The bleeding risk and symptoms has been informed to the patient including the necessity for frequent renal function monitoring ☐

(Specialist's signature)

Date:

B. RIVAROXABAN⁹				
Visit no.:				
Date:				
Advise patients to take Rivaroxaban exactly as prescribed. Take the tablet about the same time every day (advisable with the evening meal)				
Remind patients not to discontinue Rivaroxaban without informing the health provider who prescribe it.				
The 15 mg and 20 mg Rivaroxaban tablets should be taken with food, while the 10 mg tablet can be taken with or without food.				
<p>If a dose of Rivaroxaban is not taken at the schedule time, administer the dose as soon as possible on the same day as follows;</p> <ol style="list-style-type: none"> 1. For patients receiving 15 mg twice daily: The patient should take the dose immediately to ensure intake of 30 mg daily, two 15 mg tablets may be taken at once. 2. For patients receiving 20 mg, 15 mg or 10 mg once daily: 3. The patient should take the missed dose immediately on the same day (by 12 midnight). 				
Do not run out of Rivaroxaban. Refill the prescription before it finished.				
Inform healthcare provider if there is new drugs prescribed, procedures planned or pregnancy.				
Please explain the possible side effects (Refer to D,E & F)				
C. APIXABAN¹⁰				
Visit no.:				
Date:				
Advise patients to take Apixaban exactly as prescribed. Take the tablet about the same time every day				
Remind patients not to discontinue Apixaban without informing the health provider who prescribe it.				
If a dose of Apixaban is not taken at the scheduled time, take it as soon as possible on the same day.				
Do not double dose to make up for the missed dose.				
Do not run out of Apixaban. Refill the prescription before it finished.				
Inform healthcare provider if there is new drugs prescribed, procedures planned or pregnancy.				
Please explain the possible side effects (Refer to D,E & F)				

<i>For initial visit, pharmacist has to counsel based on these points. For 2nd visit onwards, pharmacist has to assess patient's knowledge.</i>				
Visit no.:				
Date:				
D. Symptoms of bleeding				
Bruises				
Gum, nose bleed				
Headaches, dizziness or weakness				
Haemoptysis				
Haematuria				
Melaena				
Red or black, tarry stools				
E. Symptoms of renal failure				
Excessive or rapid weight gain				
Oedema				
Dehydration				
Nausea & vomiting				
Pruritus				
F. Gastrointestinal adverse reaction (if applicable)				
Dyspepsia, burning or nausea				
Abdominal pain or discomfort				
Epigastric discomfort, GERD				
G. Comment				
Visit no. / Date				
Sign & stamp				
Visit no. / Date				
Sign & stamp				
Visit no. / Date				
Sign & stamp				
Visit no. / Date				
Sign & stamp				

Appendix 7- Checklist For Warfarin Education**CHECKLIST FOR WARFARIN EDUCATION¹¹**

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

☐ **Introduction**

- Name _____
- Pharmacist from _____
- “ I’m here to educate you a new drug you will be starting soon called warfarin”
- “Have you been told what this drug is for?”

☐ **Warfarin is...**

- A blood thinner also known as an anticoagulant.
- Decreases formation of blood clots
- Blood clots can cause a stroke, heart attack, or blood clots in the legs (DVT) or lungs (PE).

☐ **You are asked to take warfarin because...**

- You just experienced _____
 - *A leg clot (DVT)*
 - *A lung clot (PE)*
 - *An arrhythmia (Atrial fibrillation)*
 - *A heart attack (MI)*
 - *The placement of a mechanical or bioprosthetic heart valve.*
- By taking warfarin, it will treat your _____ (current event) and prevent you from having another clotting event (thromboembolic event).

☐ **Your initial warfarin dose...**

- Will be determined by your doctor or pharmacist.
- Your dose may change based on your regular blood tests.

- No matter what the dose, you must take your warfarin everyday and at the same time every day (evening).
- If you miss a dose, take the dose as soon as you remember or before 12 midnight. DO NOT double your dose the next day to make-up for the missed dose.
- **WARFARIN CAN BE TAKEN WITH OR WITHOUT FOOD**

☐ **Your regular blood tests...**

- Will check your response to warfarin (is your blood too thin or not thin enough?; how quickly will you blood clot on the dose your on?)
- This blood test is called an INR test (International Normalized Ratio).
- The goal is to keep your INR between a certain range that will be determined by your doctor. This will assure us that warfarin is effectively working.
 - *VTE (DVT, PE), AF: INR range 2-3*
 - *MVR or AVR with risk factors (AF, low EF, previous embolism, hypercoagulable state): INR range 2.5-3.5.*
- If you fall out of this range, your warfarin dose may change.
- It is very important that you meet all of your appointments so the most effective dose is given to you.
- You may need to have your blood tested more frequently at first; however, once we determine your dose, your scheduled appointments will be less frequent.

☐ **Possible side effects of warfarin are...**

- Bleeding problems, allergies, liver problems, low BP, swelling, paleness, fever, and rash.
- If any of these side effects or other unusual event occurs after the start of warfarin, alert your healthcare provider.
- These side effects can be prevented as long as regular blood tests are done and diet is consistent to assure an appropriate dose is given.
- The most concerning side effect is the bleeding, which the result of the blood is being too thin.
- Alert your healthcare provider if you any of these signs and symptoms:-

- *Nose bleeds*
- *Headache, dizziness, or weakness*
- *Bruising (careful with machinery, sharp object or aggressive sports)*
- *Bleeding gums (careful when brushing teeth – use soft toothbrush)*
- *Pink or brown urine*
- *Red or black stools*
- *Vomiting blood or material that looks like coffee grinds*
- *Pain, swelling, or discomfort*
- Avoid activities that may cause bleeding (acupuncture, massage, cupping/'bekam')

☐ ***Rare side effect include...***

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

☐ **Many drug/Over the counter medicine (OTC)/herbals/vitamins can interact with warfarin**

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

☐ **Many foods can interact with warfarin**

- Do you eat a lot of vegetables or salads?
- Large amounts of green leafy vegetables, which contain high amounts of vitamin K, can lower the effects of warfarin (vitamin K works against or antagonizes warfarin).
- Try to maintain a consistent diet, try to eat the same amount to leafy vegetables every day.
- Avoid cranberry juice or products and alcohol.

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

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

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

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

- DVT
 - *Leg swelling*
 - *Leg pain/tenderness*
 - *Leg discoloration*
 - *Leg warm to the touch*

- PE
 - *Sudden unexplained difficulty breathing*
 - *Cough*
 - *Rapid breathing*
 - *Rapid heart rate or palpitations*
 - *Chest pain when you breath in (pleuritic chest pain)*

- ☐ **Call your doctor immediately or go to the emergency room if you have any signs of a DVT / PE**

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

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

Appendix 8- Checklist For Dabigatran Education

CHECKLIST FOR DABIGATRAN EDUCATION⁸

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

☐ Introduction

- Name _____
- Pharmacist from.....
- “ I’m here to educate you a new drug you will be starting soon called dabigatran”
- “Have you been told what this drug is for?”

☐ Dabigatran is...

- A blood thinner also known as an anticoagulant. “ANTI” means against and “COAGULANT” refers to the clotting of blood
- Decreases formation of blood clots
- Blood clots can cause a stroke, heart attack, or blood clots in the legs (DVT) or lungs (PE).

☐ You are asked to take dabigatran because...

- You just experienced _____
 - *Atrial fibrillation, DVT or PE*
- People with a heart rhythm problem called atrial fibrillation are at increased risk of a clot forming in the heart. A clot in the heart can dislodge and cause a stroke. The role of dabigatran in patients with atrial fibrillation is to prevent formation of a clot in the heart and lower the risk of stroke.
- Dabigatran is also used to prevent clots after hip or knee surgery.

☐ **How should this drug be taken?**

- Keep Dabigatran in the original blister pack to protect from moisture. Do not put Dabigatran in pill boxes. **(Dabigatran deteriorates immediately when exposed to humidity)**
- Remove only one capsule from the blister pack at the time of use.
- Do not chew or break the capsule before swallowing. Swallow capsules whole with water with or without food.
- For **atrial fibrillation**: Take dabigatran twice daily about the same time every day.
- For **hip or knee surgery**: Take dabigatran once daily.
- NEVER stop taking dabigatran unless told to do so by your doctor.
- You might be at higher risk for stroke or other clot formation for a short time after stopping this medicine.
- Ask your doctor or pharmacist, to explain anything that you do not understand.

☐ **What should you do if you forget to take a dose?**

- If you forget to take a dose, take it as soon as you remember on the same day.
- If taking dabigatran twice daily and you have less than 6 hours before the next dose is due, skip the missed dose.
- NEVER take a double dose to make up for the missed dose

☐ **Possible side effects of dabigatran are...**

- The most concerning side effect is the bleeding, which the result of the blood is being too thin.
- Alert your healthcare provider if you have signs and symptoms of bleeding.
 - Pain, swelling, or discomfort
 - Headache, dizziness, or weakness
 - Bruising (careful with machinery, sharp object or aggressive sports)

- Avoid activities that may cause bleeding (acupuncture, massage, cupping/'bekam')
- Nosebleeds
- Bleeding gums (careful when brushing teeth – use soft toothbrush)
- Pink or brown urine
- Red or black stools
- Vomiting blood or material that looks like coffee ground
- Or allergic reaction.
 - Itching or hives
 - Swelling in your face, hands, mouth, or throat
 - Difficulty breathing or chest tightness
 - Skin rash

□ Drug/OTC/herbals/vitamins can interact with dabigatran

- Always alert your healthcare provider before starting or stopping any Rx/OTC/herbal/vitamin agents.
- Make sure your doctor knows if you take any of these medicines:
 - Fluconazole, Itraconazole, Ketoconazole
 - St. John's Wort
 - Carbamazepine
 - Clarithromycin / Erythromycin
 - Rifampicin
 - Medicines for HIV/AIDS including: indinavir, lopinavir, ritonavir
- Unless instructed by your doctor, do not take dabigatran with:
 - Warfarin / Rivaroxaban /Apixaban
- You may be at increased risk of bleeding if you take dabigatran with:
 - Clopidogrel / Prasugrel / Ticagrelor / Ticlopidine
 - Dipyridamole
 - Drugs that dissolve clots including: alteplase, reteplase, streptokinase, tenecteplase

- Prescription and non-prescription pain and arthritis medicines:
 - Aspirin (your doctor may approve of once daily aspirin with dabigatran)
 - NSAIDS: ibuprofen, naproxen, celecoxib, diclofenac, indomethacin, ketoprofen, piroxicam, sulindac

☐ **What other precautions should I follow while using this drug?**

- Serious, life-threatening bleeding can occur with dabigatran use.
- There is an antidote to reverse the effects of dabigatran which is Idarucizumab
- Make sure your doctor knows if you are pregnant or breastfeeding. Dabigatran may cause harm to the unborn baby and may be harmful to breastfed babies.
- Make sure your doctor knows if you have kidney disease, liver disease, a stomach ulcer, or any other medical problems.
- You may bleed and bruise more easily while you take dabigatran. Avoid activities such as rough sports or other situations that could cause bruising, cuts, or serious bleeding. Report any falls or blows to the head to your doctor right away. Brush and floss your teeth gently.
- Do not allow anyone else to take your medicine

☐ **Always alert your healthcare provider that you are on dabigatran**

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

- Facial droop
- Arm drift
- Slurred speech
- Weakness or numbness in extremities (*usually unilateral, but may be bilateral*)
- Abnormal or loss of vision / hearing (*usually unilateral, but may be bilateral*)
- Difficulty walking (*unsteady gait*)

- If you experience any of these symptoms go to emergency department immediately
- ☐ **Sign/symptoms of a DVT and PE (for patients with either a DVT or PE)**
- DVT
 - Leg swelling
 - Leg pain/tenderness
 - Leg discoloration
 - Leg warm to the touch
 - PE
 - Sudden unexplained difficulty breathing
 - Cough
 - Rapid breathing
 - Rapid heart rate or palpitations
 - Chest pain when you breath in (*pleuritic chest pain*)
- ☐ **Go to emergency department immediately if you have any signs of DVT/ PE.**
- ☐ **Always alert your healthcare provider if you make changes to your drug / OTC / herbals / vitamin use.**
- ☐ **Final verification of indication, dosing/administration, side effects, drug/food interactions, and appropriate signs/symptoms of VTE.**

Appendix 9- Checklist For Rivaroxaban Education

CHECKLIST FOR RIVAROXABAN EDUCATION⁹

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

☐ Introduction

- Name _____
- Pharmacist from.....
- “ I’m here to educate you a new drug you will be starting soon called rivaroxaban”
- “Have you been told what this drug is for?”

☐ Rivaroxaban is...

- A blood thinner also known as an anticoagulant. “ANTI” means against and “COAGULANT” refers to the clotting of blood
- Decreases formation of blood clots
- Blood clots can cause a stroke, heart attack, or blood clots in the legs (*DVT*) or lungs (*PE*).

☐ You are asked to take rivaroxaban because...

- You just experienced _____
 - *An arrhythmia (Atrial fibrillation)*
 - *A leg clot (DVT)*
 - *A lung clot (PE)*
- People with a heart rhythm problem called **atrial fibrillation** are at increased risk of a clot forming in the heart. A clot in the heart can dislodge and cause a stroke. The role of rivaroxaban in patients with atrial fibrillation is to prevent formation of a clot in the heart and lower the risk of stroke.

- Rivaroxaban is also used to treat people who have **clots in blood vessels**, usually in the legs, arms, or lungs. While it does not dissolve a clot that already exists, rivaroxaban can stop the clot from getting worse and prevent new clots from forming (your body naturally dissolves clots).
- Rivaroxaban is also used to **prevent clots after hip or knee surgery**.

☐ **How should this drug be taken?**

- Rivaroxaban comes in oral tablets.
- For **atrial fibrillation**: Take rivaroxaban by mouth once daily with the evening meal.
- For **clots in blood vessels**: Take rivaroxaban by mouth twice daily with meals for 3 weeks then once daily with the evening meal as directed by your doctor
- For **hip or knee surgery**: Take rivaroxaban by mouth once daily with or without food
- NEVER stop taking rivaroxaban unless told to do so by your doctor.
- You might be at higher risk for stroke or other clot formation for a short time after stopping this medicine.
- Ask your doctor, pharmacist, or nurse to explain anything that you do not understand.

☐ **What should you do if you forget to take a dose?**

- If you forget to take a dose, take it as soon as you remember on the same day.
- If taking rivaroxaban twice daily and you have less than 6 hours to go before the next dose is due, skip the missed dose.
- NEVER take a double dose to make up for the missed dose

☐ **Possible side effects of rivaroxaban are...**

- The most concerning side effect is the bleeding, which the result of the blood is being too thin.
- Alert your healthcare provider if you have signs and symptoms of bleeding.

- Pain, swelling, or discomfort
- Headache, dizziness, or weakness
- Bruising (careful with machinery, sharp object or aggressive sports)
- Avoid activities that may cause bleeding (acupuncture, massage, cupping/'bekam')
- Nosebleeds
- Bleeding gums (careful when brushing teeth – use soft toothbrush)
- Pink or brown urine
- Red or black stools
- Vomiting blood or material that looks like coffee grounds
- Or allergic reaction.
 - Itching or hives
 - Swelling in your face, hands, mouth, or throat
 - Difficulty breathing or chest tightness
 - Skin rash

☐ Drug/OTC/herbals/vitamins can interact with rivaroxaban

- Always alert your healthcare provider before starting or stopping any drug/OTC/herbal/vitamin agents.
- Make sure your doctor knows if you take any of these medicines:
 - Fluconazole / Itraconazole / Ketoconazole
 - St. John's Wort
 - Carbamazepine
 - Clarithromycin /Erythromycin
 - Rifampicin
 - Medicines for HIV/AIDS including: indinavir, lopinavir, ritonavir
- Unless instructed by your doctor, do not take rivaroxaban with:
 - Warfarin / Dabigatran

- You may be at increased risk of bleeding if you take rivaroxaban with:
 - Clopidogrel / Prasugrel / Ticagrelor / Ticlopidine
 - Dipyridamole
 - Drugs that dissolve clots including: alteplase, reteplase, streptokinase, tenecteplase
 - Prescription and non-prescription pain and arthritis medicines:
 - Aspirin (your doctor may approve of once daily aspirin with rivaroxaban)
 - NSAIDS: ibuprofen, naproxen, celecoxib, diclofenac, indomethacin, ketoprofen, piroxicam, sulindac

☐ **What other precautions should I follow while using this drug?**

- Serious, life-threatening bleeding can occur with rivaroxaban use.
- There is no antidote to reverse the effects of rivaroxaban.
- Make sure your doctor knows if you are pregnant or breastfeeding. Rivaroxaban may cause harm to the unborn baby and may be harmful to breastfed babies.
- Make sure your doctor knows if you have kidney disease, liver disease, a stomach ulcer, or any other medical problems.
- You may bleed and bruise more easily while you take rivaroxaban. Avoid activities such as rough sports or other situations that could cause bruising, cuts, or serious bleeding. Report any falls or blows to the head to your doctor right away. Brush and floss your teeth gently.
- Do not allow anyone else to take your medicine

☐ **Always alert your healthcare provider that you are on rivaroxaban.**

☐ **Signs/symptoms of a stroke (for patients with AF, CVA, post-MI, or valve replacements)**

- Facial droop
- Arm drift
- Slurred speech

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

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

- DVT
 - Leg swelling
 - Leg pain/tenderness
 - Leg discoloration
 - Leg warm to the touch
- PE
 - Sudden unexplained difficulty breathing
 - Cough
 - Rapid breathing
 - Rapid heart rate or palpitations
 - Chest pain when you breath in (*pleuritic chest pain*)
 - Anxiety

☐ **Go to emergency department immediately if you have any signs of DVT/ PE.**

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

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

Appendix 10 – Checklist For Apixaban Education

CHECKLIST FOR APIXABAN EDUCATION¹⁰

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

☐ Introduction

- Name _____
- Pharmacist from.....
- “ I’m here to educate you a new drug you will be starting soon called apixaban”
- “Have you been told what this drug is for?”

☐ Apixaban is...

- A blood thinner also known as an anticoagulant. “ANTI” means against and “COAGULANT” refers to the clotting of blood
- Decreases formation of blood clots
- Blood clots can cause a stroke, heart attack, or blood clots in the legs (*DVT*) or lungs (*PE*).

☐ You are asked to take apixaban because...

- You just experienced _____
 - *An arrhythmia (Atrial fibrillation)*
- People with a heart rhythm problem called **atrial fibrillation** are at increased risk of a clot forming in the heart. A clot in the heart can dislodge and cause a stroke. The role of apixaban in patients with atrial fibrillation is to prevent formation of a clot in the heart and lower the risk of stroke.
- Apixaban is also used to **prevent clots after hip or knee surgery**.

☐ **How should this drug be taken?**

- Apixaban comes in oral tablets.
- For **atrial fibrillation, hip or knee surgery**: Take apixaban by mouth twice about the same time every day.
- NEVER stop taking apixaban unless told to do so by your doctor.
- You might be at higher risk for stroke or other clot formation for a short time after stopping this medicine.
- Ask your doctor, pharmacist, or nurse to explain anything that you do not understand.

☐ **What should you do if you forget to take a dose?**

- If you forget to take a dose, take it as soon as you remember on the same day.
- If taking apixaban twice daily and you have less than 6 hours to go before the next dose is due, skip the missed dose.
- NEVER take a double dose to make up for the missed dose

☐ **Possible side effects of apixaban are...**

- The most concerning side effect is the bleeding, which the result of the blood is being too thin.
- Alert your healthcare provider if you have signs and symptoms of bleeding.
 - Pain, swelling, or discomfort
 - Headache, dizziness, or weakness
 - Bruising (careful with machinery, sharp object or aggressive sports)
 - Avoid activities that may cause bleeding (acupuncture, massage, cupping/'bekam')
 - Nosebleeds
 - Bleeding gums (careful when brushing teeth – use soft toothbrush)
 - Pink or brown urine
 - Red or black stools
 - Vomiting blood or material that looks like coffee grounds

- Or allergic reaction.
 - Itching or hives
 - Swelling in your face, hands, mouth, or throat
 - Difficulty breathing or chest tightness
 - Skin rash

□ Drug/OTC/herbals/vitamins can interact with apixaban

- Always alert your healthcare provider before starting or stopping any drug/OTC/herbal/vitamin agents.
- Make sure your doctor knows if you take any of these medicines:
 - Voriconazole
 - Itraconazole
 - Ketoconazole
 - Posaconazole
 - Phenytoin
 - Carbamazepine
 - Phenobarbital
 - Rifampicin
 - Medicines for HIV/AIDS including: ritonavir
- Unless instructed by your doctor, do not take apixaban with:
 - Warfarin
 - Dabigatran
 - Rivaroxaban
- You may be at increased risk of bleeding if you take apixaban with:
 - Clopidogrel
 - Prasugrel
 - Ticagrelor
 - Ticlopidine
 - Dipyridamole
 - Drugs that dissolve clots including: alteplase, reteplase, streptokinase, tenecteplase
 - Prescription and non-prescription pain and arthritis medicines:

- Aspirin (your doctor may approve of once daily aspirin with apixaban)
- NSAIDS: ibuprofen, naproxen, celecoxib, diclofenac, indomethacin, ketoprofen, piroxicam, sulindac

☐ **What other precautions should I follow while using this drug?**

- Serious, life-threatening bleeding can occur with apixaban use.
- There is no antidote to reverse the effects of apixaban.
- Make sure your doctor knows if you are pregnant or breastfeeding. Apixaban may cause harm to the unborn baby and may be harmful to breastfed babies.
- Make sure your doctor knows if you have kidney disease, liver disease, a stomach ulcer, or any other medical problems.
- Tell your doctors, dentists, or pharmacists that you are on apixaban.
- You may bleed and bruise more easily while you take apixaban.
- Avoid activities such as rough sports or other situations that could cause bruising, cuts, or serious bleeding.
- Report any falls or blows to the head to your doctor right away. Brush and floss your teeth gently.
- Do not allow anyone else to take your medicine

☐ **Always alert your healthcare provider that you are on apixaban.**

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

- Facial droop
- Arm drift
- Slurred speech
- Weakness or numbness in extremities (*usually unilateral, but may be bilateral*)
- Abnormal or loss of vision (*usually unilateral, but may be bilateral*)
- Abnormal or loss of hearing (*usually unilateral, but may be bilateral*)
- Difficulty walking (*unsteady gait*)

- If you experience any of these symptoms go to emergency department immediately

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

- DVT
 - Leg swelling
 - Leg pain/tenderness
 - Leg discoloration
 - Leg warm to the touch
 - Call your doctor immediately or go to the emergency room if you have any signs of a DVT
- PE
 - Sudden unexplained difficulty breathing
 - Cough
 - Rapid breathing
 - Rapid heart rate or palpitations
 - Chest pain when you breath in (*pleuritic chest pain*)
 - Anxiety
 - Go to emergency department immediately if you have any signs of a PE.

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

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

Appendix 11 – Warfarin Therapy Guide

WARFARIN THERAPY GUIDE¹³

A. WARFARIN DOSING

1. Warfarin dosing should be calculated using weekly dosing.
2. Dose can be increase or decrease up to 15% of weekly dosing.
3. According to ICSI guideline¹⁴, increase of 15% weekly dose, would correspond to increase in INR of 1.0. Locally, for simplicity, we use 1% increase in warfarin dose correspond to increase in INR of 0.1
4. The dosing of warfarin can be divided into two phases:
 - a. **Initiation** (with frequent INR testing) and
 - b. **Maintenance** (with less frequent INR testing)
5. When treatment is initiated, frequent INR monitoring is conducted until a stable dose-response relationship is achieved. Thereafter, the frequency of INR testing is reduced.

a. Initiation Phase

- A baseline INR should be obtained prior to initiating warfarin therapy
- All patients initiated on warfarin must have an INR measurement within 7 days of initiation
- The initiation dose may start with doses between 3 to 5 mg for the first three days and subsequent dosing based on the INR response. Administering a loading dose (≥ 10 mg) during initiation of warfarin is not recommended.
- For patients who may be sensitive to warfarin such as in elderly patients or in patients who are debilitated, malnourished, have CHF, have liver disease, have had recent major surgery, or are taking medications known to increase the sensitivity to warfarin (eg, amiodarone), the starting dose should be less than or equal to 3 mg/day .
- An initial effect on the INR usually occurs within the first 2–3 days. A therapeutic INR can usually be achieved within 5 –10 days.
- Initiation of warfarin can be guided as Table 1 and 2
- In situations where a rapid effect is required, low-molecular-weight heparin (LMWH) should be administered concurrently with warfarin. LMWH usually can be discontinued in 5–6 days or after two consecutive therapeutic INR values are achieved.

Table 1: Warfarin initiation for 1 – 14 days (INR Target 2 – 3)

**Table 1: Warfarin initiation for Day 1 – 7 (INR Target 2 – 3)		
INR	Non-sensitive Patients	Sensitive Patients [2,3]
Initial dose	5mg/5mg then 3mg od	3mg then 2 mg od
Day 8 (INR)	Dose adjustment	
< 1.5	Increase weekly dose by 10-15%, TCA 7 days	
1.5 – 1.9	Maintain dose, 7 – 14 days	
2.0 – 3.0	Reduced 0.5 or 1mg from weekly dose, TCA 7 –10 days	
> 3.0	Hold and initiate at lower dose when INR in range, TCA 7days	

Table 2: Frequency of INR monitoring

INR monitoring	
INR	Suggested Approach
Initiation of warfarin	Monitor ever 3-7 days, then gradually increase to weekly, biweekly, monthly if stable
INR reaches target	Recheck 2 weeks x 2, then every 4 weeks if stable
INR therapeutic for 8 to 10 weeks consecutively	May increase interval 6 – 12 weeks with high compliance and good patient education; increase frequency with illness, medication change, history of highly variable INR levels
INR outside target range \pm 0.2. points	Recheck in 1 to 2 weeks; if persists, adjust dose and recheck in 1-2 weeks
INR > from target range but < 5	Hold warfarin, Adjust dose, recheck in 1 week

Notes:

- 1. All dosage adjustment in Table 1 and 2 are recommendation only.**
- 2. Exclusion of factors affecting INR must be done prior to dosage adjustment.**
 - Always consider trend in INRs when making warfarin management decisions.
 - Consider repeating INR same day or next day if observed value markedly different than expected value (Potential for lab errors exist)
 - Maximum changes of daily dose is \pm 1mg.

b. Maintenance Phase

- This only can be considered when INR achieved target ranged.
- Patients who had stable INR (INR in range > 6 months) can had longer duration of INR monitoring (up to 12 weeks).
- However dose adjustment must be done accordingly when INR not in target ranged.
- Dose adjustment and INR monitoring can be guided as Table 1 and 2
- Weekly dose can be guide as in Appendix 19

B. Laboratory Monitoring

- Baseline PT/INR/PTTT, full blood count (FBC) with platelets and liver function test (LFT) shall be obtained prior to warfarin initiation. If baseline level not available, it should be obtained within 24 hours.
- In hospitalized patients, PT monitoring is usually performed daily, starting after the second or third dose until the target therapeutic range has been achieved and maintained for at least 2 consecutive days; then two or three times weekly for 1 to 2 weeks; then less often, depending on the stability of INR results.
- In outpatients starting warfarin therapy, initial monitoring may be reduced to every few days until a stable dose response has been achieved. When the INR response is stable, the frequency of testing can be reduced to intervals as long as every 4-8 weeks.

Appendix 12 – Weekly Dosing Chart

WEEKLY DOSING CHART

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	- 5	- 10	- 15
0.5	0	0	0	0	0	0	0.5	0.5	0.6	0.6	0.6	0.5	0.5	0.4
1	0	0	0	0	0	0	1.0	1.1	1.1	1.2	1.2	1.0	0.9	0.9
0.5	0	0.5	0	0.5	0	0	1.5	1.6	1.7	1.7	1.8	1.4	1.4	1.3
0.5	0	0.5	0	0.5	0	0.5	2.0	2.1	2.2	2.3	2.4	1.9	1.8	1.7
0.5	0.5	0	0.5	0.5	0	0.5	2.5	2.6	2.8	2.9	3.0	2.4	2.3	2.1
0.5	0.5	0.5	0.5	0.5	0.5	0	3.0	3.2	3.3	3.5	3.6	2.9	2.7	2.6
0.5	0.5	0.5	0.5	0.5	0.5	0.5	3.5	3.7	3.9	4.0	4.2	3.3	3.2	3.0
0.5	0.5	0.5	0.5	0.5	0.5	1	4.0	4.2	4.4	4.6	4.8	3.8	3.6	3.4
0.5	0.5	0.5	0.5	0.5	1	1	4.5	4.7	5.0	5.2	5.4	4.3	4.1	3.8
0.5	0.5	0.5	0.5	1	1	1	5.0	5	5.5	6	6	4.8	4.5	4.3
1	1	1	1	0.5	0.5	0.5	5.5	6	6	6	7	5.2	5.0	4.7
1	1	1	1	1	0.5	0.5	6.0	6	6.5	7	7	5.7	5.4	5.1
1	1	1	1	1	1	0.5	6.5	7	7	7.5	8	6.2	5.9	5.5
1	1	1	1	1	1	1	7.0	7.4	7.7	8.1	8.4	6.7	6.3	6.0
1	1	1	1	1	1	1.5	7.5	7.9	8.3	8.6	9.0	7.1	6.8	6.4
1	1	1	1	1	1.5	1.5	8.0	8.4	8.8	9.2	9.6	7.6	7.2	6.8
1	1	1	1	1.5	1.5	1.5	8.5	8.9	9.4	9.8	10.2	8.1	7.7	7.2
1.5	1.5	1.5	1.5	1	1	1	9.0	9.5	9.9	10.4	10.8	8.6	8.1	7.7
1.5	1.5	1.5	1.5	1.5	1	1	9.5	10.0	10.5	10.9	11.4	9.0	8.6	8.1
1.5	1.5	1.5	1.5	1.5	1.5	1	10.0	10.5	11.0	11.5	12.0	9.5	9.0	8.5
1.5	1.5	1.5	1.5	1.5	1.5	1.5	10.5	11.0	11.6	12.1	12.6	10.0	9.5	8.9
1.5	1.5	1.5	1.5	1.5	1.5	2	11.0	11.6	12.1	12.7	13.2	10.5	9.9	9.4
1.5	1.5	1.5	1.5	1.5	2	2	11.5	12.1	12.7	13.2	13.8	10.9	10.4	9.8
1.5	1.5	1.5	1.5	2	2	2	12.0	12.6	13.2	13.8	14.4	11.4	10.8	10.2
2	2	2	2	1.5	1.5	1.5	12.5	13.1	13.8	14.4	15.0	11.9	11.3	10.6
2	2	2	2	2	1.5	1.5	13.0	13.7	14.3	15.0	15.6	12.4	11.7	11.1
2	2	2	2	2	2	1.5	13.5	14.2	14.9	15.5	16.2	12.8	12.2	11.5
2	2	2	2	2	2	2	14.0	14.7	15.4	16.1	16.8	13.3	12.6	11.9

ANTICOAGULATION MTAC (ACMTAC) PROTOCOL

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	-5	-10	-15
2	2	2	2	2	2	2.5	14.5	15.2	16.0	16.7	17.4	13.8	13.1	12.3
2	2	2	2	2	2.5	2.5	15.0	15.8	16.5	17.3	18.0	14.3	13.5	12.8
2	2	2	2	2.5	2.5	2.5	15.5	16.3	17.1	17.8	18.6	14.7	14.0	13.2
2.5	2.5	2.5	2.5	2	2	2	16.0	16.8	17.6	18.4	19.2	15.2	14.4	13.6
2.5	2.5	2.5	2.5	2.5	2	2	16.5	17.3	18.2	19.0	19.8	15.7	14.9	14.0
2.5	2.5	2.5	2.5	2.5	2.5	2	17.0	17.9	18.7	19.6	20.4	16.2	15.3	14.5
2.5	2.5	2.5	2.5	2.5	2.5	2.5	17.5	18.4	19.3	20.1	21.0	16.6	15.8	14.9
2.5	2.5	2.5	2.5	2.5	2.5	3	18.0	18.9	19.8	20.7	21.6	17.1	16.2	15.3
2.5	2.5	2.5	2.5	2.5	3	3	18.5	19.4	20.4	21.3	22.2	17.6	16.7	15.7
2.5	2.5	2.5	2.5	3	3	3	19.0	20.0	20.9	21.9	22.8	18.1	17.1	16.2
3	3	3	3	2.5	2.5	2.5	19.5	20.5	21.5	22.4	23.4	18.5	17.6	16.6
3	3	3	3	3	2.5	2.5	20.0	21.0	22.0	23.0	24.0	19.0	18.0	17.0
3	3	3	3	3	3	2.5	20.5	21.5	22.6	23.6	24.6	19.5	18.5	17.4
3	3	3	3	3	3	3	21.0	22.1	23.1	24.2	25.2	20.0	18.9	17.9
3	3	3	3	3	3	3.5	21.5	22.6	23.7	24.7	25.8	20.4	19.4	18.3
3	3	3	3	3	3.5	3.5	22.0	23.1	24.2	25.3	26.4	20.9	19.8	18.7
3	3	3	3	3.5	3.5	3.5	22.5	23.6	24.8	25.9	27.0	21.4	20.3	19.1
3.5	3.5	3.5	3.5	3	3	3	23.0	24.2	25.3	26.5	27.6	21.9	20.7	19.6
3.5	3.5	3.5	3.5	3.5	3	3	23.5	24.7	25.9	27.0	28.2	22.3	21.2	20.0
3.5	3.5	3.5	3.5	3.5	3.5	3	24.0	25.2	26.4	27.6	28.8	22.8	21.6	20.4
3.5	3.5	3.5	3.5	3.5	3.5	3.5	24.5	25.7	27.0	28.2	29.4	23.3	22.1	20.8
3.5	3.5	3.5	3.5	3.5	3.5	4	25.0	26.3	27.5	28.8	30.0	23.8	22.5	21.3
3.5	3.5	3.5	3.5	3.5	4	4	25.5	26.8	28.1	29.3	30.6	24.2	23.0	21.7
3.5	3.5	3.5	3.5	4	4	4	26.0	27.3	28.6	29.9	31.2	24.7	23.4	22.1
4	4	4	4	3.5	3.5	3.5	26.5	27.8	29.2	30.5	31.8	25.2	23.9	22.5
4	4	4	4	4	3.5	3.5	27.0	28.4	29.7	31.1	32.4	25.7	24.3	23.0
4	4	4	4	4	4	3.5	27.5	28.9	30.3	31.6	33.0	26.1	24.8	23.4
4	4	4	4	4	4	4	28.0	29.4	30.8	32.2	33.6	26.6	25.2	23.8

ANTICOAGULATION MTAC (ACMTAC) PROTOCOL

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	- 5	- 10	- 15
4	4	4	4	4	4	4.5	28.5	29.9	31.4	32.8	34.2	27.1	25.7	24.2
4	4	4	4	4	4.5	4.5	29.0	30.5	31.9	33.4	34.8	27.6	26.1	24.7
4	4	4	4	4.5	4.5	4.5	29.5	31.0	32.5	33.9	35.4	28.0	26.6	25.1
4.5	4.5	4.5	4.5	4	4	4	30.0	31.5	33.0	34.5	36.0	28.5	27.0	25.5
4.5	4.5	4.5	4.5	4.5	4	4	30.5	32.0	33.6	35.1	36.6	29.0	27.5	25.9
4.5	4.5	4.5	4.5	4.5	4.5	4	31.0	32.6	34.1	35.7	37.2	29.5	27.9	26.4
4.5	4.5	4.5	4.5	4.5	4.5	4.5	31.5	33.1	34.7	36.2	37.8	29.9	28.4	26.8
4.5	4.5	4.5	4.5	4.5	4.5	5	32.0	33.6	35.2	36.8	38.4	30.4	28.8	27.2
4.5	4.5	4.5	4.5	4.5	5	5	32.5	34.1	35.8	37.4	39.0	30.9	29.3	27.6
4.5	4.5	4.5	4.5	5	5	5	33.0	34.7	36.3	38.0	39.6	31.4	29.7	28.1
5	5	5	5	4.5	4.5	4.5	33.5	35.2	36.9	38.5	40.2	31.8	30.2	28.5
5	5	5	5	5	4.5	4.5	34.0	35.7	37.4	39.1	40.8	32.3	30.6	28.9
5	5	5	5	5	5	4.5	34.5	36.2	38.0	39.7	41.4	32.8	31.1	29.3
5	5	5	5	5	5	5	35.0	36.8	38.5	40.3	42.0	33.3	31.5	29.8
5	5	5	5	5	5	5.5	35.5	37.3	39.1	40.8	42.6	33.7	32.0	30.2
5	5	5	5	5	5.5	5.5	36.0	37.8	39.6	41.4	43.2	34.2	32.4	30.6
5	5	5	5	5.5	5.5	5.5	36.5	38.3	40.2	42.0	43.8	34.7	32.9	31.0
5.5	5.5	5.5	5.5	5	5	5	37.0	38.9	40.7	42.6	44.4	35.2	33.3	31.5
5.5	5.5	5.5	5.5	5.5	5	5	37.5	39.4	41.3	43.1	45.0	35.6	33.8	31.9
5.5	5.5	5.5	5.5	5.5	5.5	5	38.0	39.9	41.8	43.7	45.6	36.1	34.2	32.3
5.5	5.5	5.5	5.5	5.5	5.5	5.5	38.5	40.4	42.4	44.3	46.2	36.6	34.7	32.7
5.5	5.5	5.5	5.5	5.5	5.5	6	39.0	41.0	42.9	44.9	46.8	37.1	35.1	33.2
5.5	5.5	5.5	5.5	5.5	6	6	39.5	41.5	43.5	45.4	47.4	37.5	35.6	33.6
5.5	5.5	5.5	5.5	6	6	6	40.0	42.0	44.0	46.0	48.0	38.0	36.0	34.0
6	6	6	6	5.5	5.5	5.5	40.5	42.5	44.6	46.6	48.6	38.5	36.5	34.4
6	6	6	6	6	5.5	5.5	41.0	43.1	45.1	47.2	49.2	39.0	36.9	34.9
6	6	6	6	6	6	5.5	41.5	43.6	45.7	47.7	49.8	39.4	37.4	35.3
6	6	6	6	6	6	6	42.0	44.1	46.2	48.3	50.4	39.9	37.8	35.7

ANTICOAGULATION MTAC (ACMTAC) PROTOCOL

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	- 5	- 10	- 15
6	6	6	6	6	6	6.5	42.5	44.6	46.8	48.9	51.0	40.4	38.3	36.1
6	6	6	6	6	6.5	6.5	43.0	45.2	47.3	49.5	51.6	40.9	38.7	36.6
6	6	6	6	6.5	6.5	6.5	43.5	45.7	47.9	50.0	52.2	41.3	39.2	37.0
6.5	6.5	6.5	6.5	6	6	6	44.0	46.2	48.4	50.6	52.8	41.8	39.6	37.4
6.5	6.5	6.5	6.5	6.5	6	6	44.5	46.7	49.0	51.2	53.4	42.3	40.1	37.8
6.5	6.5	6.5	6.5	6.5	6.5	6	45.0	47.3	49.5	51.8	54.0	42.8	40.5	38.3
6.5	6.5	6.5	6.5	6.5	6.5	6.5	45.5	47.8	50.1	52.3	54.6	43.2	41.0	38.7
6.5	6.5	6.5	6.5	6.5	6.5	7	46.0	48.3	50.6	52.9	55.2	43.7	41.4	39.1
6.5	6.5	6.5	6.5	6.5	7	7	46.5	48.8	51.2	53.5	55.8	44.2	41.9	39.5
6.5	6.5	6.5	6.5	7	7	7	47.0	49.4	51.7	54.1	56.4	44.7	42.3	40.0
7	7	7	7	6.5	6.5	6.5	47.5	49.9	52.3	54.6	57.0	45.1	42.8	40.4
7	7	7	7	7	6.5	6.5	48.0	50.4	52.8	55.2	57.6	45.6	43.2	40.8
7	7	7	7	7	7	6.5	48.5	50.9	53.4	55.8	58.2	46.1	43.7	41.2
7	7	7	7	7	7	7	49.0	51.5	53.9	56.4	58.8	46.6	44.1	41.7
7	7	7	7	7	7	7.5	49.5	52.0	54.5	56.9	59.4	47.0	44.6	42.1
7	7	7	7	7	7.5	7.5	50.0	52.5	55.0	57.5	60.0	47.5	45.0	42.5

ANTICOAGULATION MTAC (ACMTAC) PROTOCOL

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	- 5	- 10	- 15
7	7	7	7	7.5	7.5	7.5	50.5	53.0	55.6	58.1	60.6	48.0	45.5	42.9
7.5	7.5	7.5	7.5	7	7	7	51.0	53.6	56.1	58.7	61.2	48.5	45.9	43.4
7.5	7.5	7.5	7.5	7.5	7	7	51.5	54.1	56.7	59.2	61.8	48.9	46.4	43.8
7.5	7.5	7.5	7.5	7.5	7.5	7	52.0	54.6	57.2	59.8	62.4	49.4	46.8	44.2
7.5	7.5	7.5	7.5	7.5	7.5	7.5	52.5	55.1	57.8	60.4	63.0	49.9	47.3	44.6
7.5	7.5	7.5	7.5	7.5	7.5	8	53.0	55.7	58.3	61.0	63.6	50.4	47.7	45.1
7.5	7.5	7.5	7.5	7.5	8	8	53.5	56.2	58.9	61.5	64.2	50.8	48.2	45.5
7.5	7.5	7.5	7.5	8	8	8	54.0	56.7	59.4	62.1	64.8	51.3	48.6	45.9
8	8	8	8	7.5	7.5	7.5	54.5	57.2	60.0	62.7	65.4	51.8	49.1	46.3
8	8	8	8	8	7.5	7.5	55.0	57.8	60.5	63.3	66.0	52.3	49.5	46.8
8	8	8	8	8	8	7.5	55.5	58.3	61.1	63.8	66.6	52.7	50.0	47.2
8	8	8	8	8	8	8	56.0	58.8	61.6	64.4	67.2	53.2	50.4	47.6
8	8	8	8	8	8	8.5	56.5	59.3	62.2	65.0	67.8	53.7	50.9	48.0
8	8	8	8	8	8.5	8.5	57.0	59.9	62.7	65.6	68.4	54.2	51.3	48.5
8	8	8	8	8.5	8.5	8.5	57.5	60.4	63.3	66.1	69.0	54.6	51.8	48.9
8.5	8.5	8.5	8.5	8	8	8	58.0	60.9	63.8	66.7	69.6	55.1	52.2	49.3
8.5	8.5	8.5	8.5	8.5	8	8	58.5	61.4	64.4	67.3	70.2	55.6	52.7	49.7
8.5	8.5	8.5	8.5	8.5	8.5	8	59.0	62.0	64.9	67.9	70.8	56.1	53.1	50.2
8.5	8.5	8.5	8.5	8.5	8.5	8.5	59.5	62.5	65.5	68.4	71.4	56.5	53.6	50.6
8.5	8.5	8.5	8.5	8.5	8.5	9	60.0	63.0	66.0	69.0	72.0	57.0	54.0	51.0
8.5	8.5	8.5	8.5	8.5	9	9	60.5	63.5	66.6	69.6	72.6	57.5	54.5	51.4
8.5	8.5	8.5	8.5	9	9	9	61.0	64.1	67.1	70.2	73.2	58.0	54.9	51.9
9	9	9	9	8.5	8.5	8.5	61.5	64.6	67.7	70.7	73.8	58.4	55.4	52.3
9	9	9	9	9	8.5	8.5	62.0	65.1	68.2	71.3	74.4	58.9	55.8	52.7
9	9	9	9	9	9	8.5	62.5	65.6	68.8	71.9	75.0	59.4	56.3	53.1
9	9	9	9	9	9	9	63.0	66.2	69.3	72.5	75.6	59.9	56.7	53.6
9	9	9	9	9	9	9.5	63.5	66.7	69.9	73.0	76.2	60.3	57.2	54.0
9	9	9	9	9	9.5	9.5	64.0	67.2	70.4	73.6	76.8	60.8	57.6	54.4

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	- 5	- 10	- 15
9	9	9	9	9.5	9.5	9.5	64.5	67.7	71.0	74.2	77.4	61.3	58.1	54.8
9.5	9.5	9.5	9.5	9	9	9	65.0	68.3	71.5	74.8	78.0	61.8	58.5	55.3
9.5	9.5	9.5	9.5	9.5	9	9	65.5	68.8	72.1	75.3	78.6	62.2	59.0	55.7
9.5	9.5	9.5	9.5	9.5	9.5	9	66.0	69.3	72.6	75.9	79.2	62.7	59.4	56.1
9.5	9.5	9.5	9.5	9.5	9.5	9.5	66.5	69.8	73.2	76.5	79.8	63.2	59.9	56.5
9.5	9.5	9.5	9.5	9.5	9.5	10	67.0	70.4	73.7	77.1	80.4	63.7	60.3	57.0
9.5	9.5	9.5	9.5	9.5	10	10	67.5	70.9	74.3	77.6	81.0	64.1	60.8	57.4
9.5	9.5	9.5	9.5	10	10	10	68.0	71.4	74.8	78.2	81.6	64.6	61.2	57.8
10	10	10	10	9.5	9.5	9.5	68.5	71.9	75.4	78.8	82.2	65.1	61.7	58.2
10	10	10	10	10	9.5	9.5	69.0	72.5	75.9	79.4	82.8	65.6	62.1	58.7
10	10	10	10	10	10	9.5	69.5	73.0	76.5	79.9	83.4	66.0	62.6	59.1
10	10	10	10	10	10	10	70.0	73.5	77.0	80.5	84.0	66.5	63.0	59.5
10	10	10	10	10	10	10.5	70.5	74.0	77.6	81.1	84.6	67.0	63.5	59.9
10	10	10	10	10	10.5	10.5	71.0	74.6	78.1	81.7	85.2	67.5	63.9	60.4
10	10	10	10	10.5	10.5	10.5	71.5	75.1	78.7	82.2	85.8	67.9	64.4	60.8
10.5	10.5	10.5	10.5	10	10	10	72.0	75.6	79.2	82.8	86.4	68.4	64.8	61.2
10.5	10.5	10.5	10.5	10.5	10	10	72.5	76.1	79.8	83.4	87.0	68.9	65.3	61.6
10.5	10.5	10.5	10.5	10.5	10.5	10	73.0	76.7	80.3	84.0	87.6	69.4	65.7	62.1
10.5	10.5	10.5	10.5	10.5	10.5	10.5	73.5	77.2	80.9	84.5	88.2	69.8	66.2	62.5
10.5	10.5	10.5	10.5	10.5	10.5	11	74.0	77.7	81.4	85.1	88.8	70.3	66.6	62.9
10.5	10.5	10.5	10.5	10.5	11	11	74.5	78.2	82.0	85.7	89.4	70.8	67.1	63.3
10.5	10.5	10.5	10.5	11	11	11	75.0	78.8	82.5	86.3	90.0	71.3	67.5	63.8
11	11	11	11	10.5	10.5	10.5	75.5	79.3	83.1	86.8	90.6	71.7	68.0	64.2
11	11	11	11	11	10.5	10.5	76.0	79.8	83.6	87.4	91.2	72.2	68.4	64.6
11	11	11	11	11	11	10.5	76.5	80.3	84.2	88.0	91.8	72.7	68.9	65.0
11	11	11	11	11	11	11	77.0	80.9	84.7	88.6	92.4	73.2	69.3	65.5
11	11	11	11	11	11	11.5	77.5	81.4	85.3	89.1	93.0	73.6	69.8	65.9
11	11	11	11	11	11.5	11.5	78.0	81.9	85.8	89.7	93.6	74.1	70.2	66.3

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	- 5	- 10	- 15
11	11	11	11	11.5	11.5	11.5	78.5	82.4	86.4	90.3	94.2	74.6	70.7	66.7
11.5	11.5	11.5	11.5	11	11	11	79.0	83.0	86.9	90.9	94.8	75.1	71.1	67.2
11.5	11.5	11.5	11.5	11.5	11	11	79.5	83.5	87.5	91.4	95.4	75.5	71.6	67.6
11.5	11.5	11.5	11.5	11.5	11.5	11	80.0	84.0	88.0	92.0	96.0	76.0	72.0	68.0
11.5	11.5	11.5	11.5	11.5	11.5	11.5	80.5	84.5	88.6	92.6	96.6	76.5	72.5	68.4
11.5	11.5	11.5	11.5	11.5	11.5	12	81.0	85.1	89.1	93.2	97.2	77.0	72.9	68.9
11.5	11.5	11.5	11.5	11.5	12	12	81.5	85.6	89.7	93.7	97.8	77.4	73.4	69.3
11.5	11.5	11.5	11.5	12	12	12	82.0	86.1	90.2	94.3	98.4	77.9	73.8	69.7
12	12	12	12	11.5	11.5	11.5	82.5	86.6	90.8	94.9	99.0	78.4	74.3	70.1
12	12	12	12	12	11.5	11.5	83.0	87.2	91.3	95.5	99.6	78.9	74.7	70.6
12	12	12	12	12	12	11.5	83.5	87.7	91.9	96.0	100.2	79.3	75.2	71.0
12	12	12	12	12	12	12	84.0	88.2	92.4	96.6	100.8	79.8	75.6	71.4
12	12	12	12	12	12	12.5	84.5	88.7	93.0	97.2	101.4	80.3	76.1	71.8
12	12	12	12	12	12.5	12.5	85.0	89.3	93.5	97.8	102.0	80.8	76.5	72.3
12	12	12	12	12.5	12.5	12.5	85.5	89.8	94.1	98.3	102.6	81.2	77.0	72.7
12.5	12.5	12.5	12.5	12	12	12	86.0	90.3	94.6	98.9	103.2	81.7	77.4	73.1
12.5	12.5	12.5	12.5	12.5	12	12	86.5	90.8	95.2	99.5	103.8	82.2	77.9	73.5
12.5	12.5	12.5	12.5	12.5	12.5	12	87.0	91.4	95.7	100.1	104.4	82.7	78.3	74.0
12.5	12.5	12.5	12.5	12.5	12.5	12.5	87.5	91.9	96.3	100.6	105.0	83.1	78.8	74.4
13	13	13	13	12	12	12	88.0	92.4	96.8	101.2	105.6	83.6	79.2	74.8
12.5	12.5	12.5	12.5	12.5	13	13	88.5	92.9	97.4	101.8	106.2	84.1	79.7	75.2
13	13	13	13	13	12	12	89.0	93.5	97.9	102.4	106.8	84.6	80.1	75.7
13	13	13	13	12.5	12.5	12.5	89.5	94.0	98.5	102.9	107.4	85.0	80.6	76.1
13	13	13	13	13	12.5	12.5	90.0	94.5	99.0	103.5	108.0	85.5	81.0	76.5
13	13	13	13	13	13	12.5	90.5	95.0	99.6	104.1	108.6	86.0	81.5	76.9
13	13	13	13	13	13	13	91.0	95.6	100.1	104.7	109.2	86.5	81.9	77.4
13	13	13	13	13	13	13.5	91.5	96.1	100.7	105.2	109.8	86.9	82.4	77.8
13	13	13	13	13	13.5	13.5	92.0	96.6	101.2	105.8	110.4	87.4	82.8	78.2

Days							Total/ week	Increase dose				Decrease Dose		
Mon (mg)	Tue (mg)	Wed (mg)	Thur (mg)	Fri (mg)	Sat (mg)	Sun (mg)		5	10	15	20	-5	-10	-15
13	13	13	13	13.5	13.5	13.5	92.5	97.1	101.8	106.4	111.0	87.9	83.3	78.6
13	13	13	13	13	14	14	93.0	97.7	102.3	107.0	111.6	88.4	83.7	79.1
13.5	13.5	13.5	13.5	13.5	13	13	93.5	98.2	102.9	107.5	112.2	88.8	84.2	79.5
13	13	13	13	14	14	14	94.0	98.7	103.4	108.1	112.8	89.3	84.6	79.9
13.5	13.5	13.5	13.5	13.5	13.5	13.5	94.5	99.2	104.0	108.7	113.4	89.8	85.1	80.3
14	14	14	14	13	13	13	95.0	99.8	104.5	109.3	114.0	90.3	85.5	80.8
13.5	13.5	13.5	13.5	13.5	14	14	95.5	100.3	105.1	109.8	114.6	90.7	86.0	81.2
14	14	14	14	14	13	13	96.0	100.8	105.6	110.4	115.2	91.2	86.4	81.6
14	14	14	14	13.5	13.5	13.5	96.5	101.3	106.2	111.0	115.8	91.7	86.9	82.0
14	14	14	14	14	13.5	13.5	97.0	101.9	106.7	111.6	116.4	92.2	87.3	82.5
14	14	14	14	14	14	13.5	97.5	102.4	107.3	112.1	117.0	92.6	87.8	82.9
14	14	14	14	14	14	14	98.0	102.9	107.8	112.7	117.6	93.1	88.2	83.3
14	14	14	14	14	14	14.5	98.5	103.4	108.4	113.3	118.2	93.6	88.7	83.7
14	14	14	14	14	14.5	14.5	99.0	104.0	108.9	113.9	118.8	94.1	89.1	84.2
14	14	14	14	14.5	14.5	14.5	99.5	104.5	109.5	114.4	119.4	94.5	89.6	84.6
14	14	14	14	14	15	15	100.0	105.0	110.0	115.0	120.0	95.0	90.0	85.0
14.5	14.5	14.5	14.5	14.5	14	14	100.5	105.5	110.6	115.6	120.6	95.5	90.5	85.4
14	14	14	14	15	15	15	101.0	106.1	111.1	116.2	121.2	96.0	90.9	85.9
14.5	14.5	14.5	14.5	14.5	14.5	14.5	101.5	106.6	111.7	116.7	121.8	96.4	91.4	86.3
15	15	15	15	14	14	14	102.0	107.1	112.2	117.3	122.4	96.9	91.8	86.7

Appendix 13 – Warfarin Interactions

WARFARIN INTERACTIONS

A. Interactions of Warfarin

1. Numerous medications, foods, and health conditions can either potentiate or inhibit warfarin effects.
2. Instruct patients to report any changes in diet, medications, or health status.
3. Below is a general description of some interactions with warfarin. Please Refer to Warfarin Interactions handbook¹² for further list.

B. Diet

1. Foods that interact with warfarin are mostly the ones that are high in vitamin K, especially green leafy vegetables.
2. Patients should be advised to take such foods consistent amount to avoid large fluctuations in INR.

C. Medication

1. Numerous drugs interact with warfarin, either increasing or decreasing anticoagulant effect.
2. It is therefore recommended that the INR should be checked whenever any new drug or herbal medicine is added or withdrawn from a patient's regimen.
3. Below is some specific guidance:
 - a. **Antibiotics** : Patients started on antibiotics that interact with warfarin (i.e., erythromycin, metronidazole, ciprofloxacin, sulfamethoxazole-trimethoprim, fluconazole, ketoconazole, rifampin, dicloxacillin) should be instructed to return in 3 days to assess the effect on their INR, unless warfarin dose adjustment can be made on the basis of a patient's prior INR response history.
 - b. **Amiodarone** : Patients started on amiodarone should generally be instructed to return in 3 days to assess the effect on their INR. The warfarin dose should be reduced empirically by about one-third to one-half. The INR should be followed closely, *once or twice weekly*, with dosage adjustments until the INR is stable.

D. Health Condition

1. Table 1 showed the health conditions that cause warfarin sensitivity

Table 1: Health Conditions

DISEASE	↑ INR	DISEASE	↓ INR
Cancer	√	Edema	√
Heart Failure	√	Nephrotic syndrome	√
Liver dysfunction	√		
Hyperthyroidism	√		
Fever	√		
Poor nutritional state	√		
Severe or prolonged diarrhea	√		
Renal Disease- end stage	√		

Appendix 14 – Prescribing Information for Dabigatran**PRESCRIBING INFORMATION FOR DABIGATRAN⁸****A. Indication and dose**

- Direct thrombin inhibitor
- Indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation and for the prevention of VTE in patients who have undergone elective total hip replacement or total knee replacement surgery.
- Treatment of AF. Dose in atrial fibrillation is 150 mg twice daily.
- Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following and acute DVT in adults. The recommended daily dose is 300 mg taken as one 150 mg capsule twice daily.
- Prevention of venous thromboembolic events in patients who have undergone total knee replacement or total hip replacement surgery. Initiate orally within 1–4 hours of completed surgery as a single capsule (110 mg). Thereafter,
 - Hip replacement: 110mg twice daily for 28 - 35 days
 - Knee replacement: 110mg twice daily for 10 days

B. Dosing Modification and Consideration

- Special patient populations with a reduced daily dose (220 mg taken as one 110 mg capsule twice daily):
 - Patients aged 80 years or above
 - Concomitant use of verapamil or amiodarone or quinidine
- For the following groups, the daily dose of 300 mg or 220 mg 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 (CrCL 30-50 ml/min)
 - Patients with gastritis, esophagitis or gastroesophageal reflux
 - Other patients at increased risk of bleeding
- Prophylaxis of DVT following hip or knee replacement surgery: Special patient populations with a reduced daily dose:
 - Patients aged 75 years or older

- Moderate renal impairment (creatinine clearance 30–50 mL/min)
- Concomitant use of verapamil or amiodarone or quinidine
- Dose recommendation for special patient populations:
- Initiate orally within 1–4 hours of completed surgery as a single capsule (75 mg). Thereafter,
 - Hip replacement: 150mg once daily for 28 - 35 days
 - Knee replacement: 150mg once daily for 10 days

C. Cautions/ Special warning

- Use in renal impairment:
 - Clearance of dabigatran in patients with renal insufficiency may take longer.
 - Please make sure patients have done renal function test prior to initiation of treatment with Dabigatran.
 - Close clinical surveillance is recommended in patients with renal impairment.
- Use in hepatic impairment:
 - Patients with elevated liver enzymes > 2 ULN should not be prescribed dabigatran.

D. Risk of bleeding:

- Use with caution in conditions with an increased risk of bleeding.
- Bleeding may occur at any site during therapy with Dabigatran.
- An unexplained fall in haemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. When clinically relevant bleeding occurs, treatment should be interrupted.

E. Contraindication

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCL < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis

- Hepatic impairment or liver expected to have any impact survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus

F. Monitoring

- As warfarin patients need to monitor for signs of bleeding and anaemia (no clinical monitoring available – INR not able to be used as different pathway of action)
- Monitoring of creatinine clearance should be done at least
 - Once or twice a year for patients who had CrCl \geq 50ml/min
 - Every 6 months for patients who had CrCl \leq 50ml/min

G. Drug interactions

- Generally, interactions lead to an increase bleeding risk– patients should be monitored closely for signs of bleeding and anaemia.
- Caution with concomitant other anticoagulants
- Systemic azoleantimycotics e.g.ketoconazole, ciclosporin, itraconazole, tacrolimus are contraindicated
- Caution with concomitant strong P-gp inhibitors e.g. amiodarone, quinidine, verapamil
- Caution concomitant use of amiodarone (amiodarone has a long half-life and interaction may exist for weeks after discontinuation, especially in patients with mild-moderate renal impairment)
- Caution concomitant use of quinidine especially in patients with mild to moderate renal impairment
- Caution concomitant use of verapamil
- Caution concomitant use of clarithromycin, especially in patients with mild-moderate renal impairment.
- Protease inhibitors (e.g. ritonavir containing products) should not be prescribed concomitantly (due to lack of available safety data for this combination)
- Interactions below lead to a decrease in anticoagulant concentration therefore treatment may be suboptimal
- Caution concomitant use of strong CYP3A4 inducers e.g. rifampicin, St. John's Wort, carbamazepine, phenytoin

Appendix 15 – Prescribing Information for Rivaroxaban**PRESCRIBING INFORMATION FOR RIVAROXABAN⁹****A. Indication and dose**

- Inhibits Factor Xa
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factor, such as congestive heart failure, hypertension, age \geq 75 yrs, diabetes mellitus, prior stroke or transient ischaemic attack.
- Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following and acute DVT in adults: Dose: 15 mg twice daily with food, for first 21 days on day 22, transition to 20mg once daily with food, for remaining treatment. Dose: 20 mg OD with the evening meal. Therapy should be continued long term.
- Prevention of venous thromboembolism in patients undergoing elective hip or knee replacement surgery.
 - Hip replacement: Dose: 10 mg once daily for 35 days
 - Knee replacement: Dose: 10 mg once daily for 12 days (with or without food)

B. Dosing Modification and Consideration

- Non-valvular Atrial Fibrillation:
 - Renal impairment:
 - CrCl 15 to 50 mL/min: 15 mg once daily with the evening meal
 - CrCl <15 mL/min: Avoid use
- Periodically assess renal function as clinically indicated (i.e. more frequently in situations in which renal function may decline) and adjust therapy accordingly.
- Treatment DVT, and prevention of recurrent DVT and PE following an acute DVT in adults
 - Renal impairment
 - CrCl <30 mL/min: Avoid use

- Prophylaxis of DVT following hip or knee replacement surgery:
 - Renal impairment
 - CrCl<30 mL/min: Avoid use
- Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min.
- Discontinue rivaroxaban in patients who develop acute renal failure while on rivaroxaban.

C. Cautions/ Special warning

- Increased risk of thrombotic events after Premature Discontinuation:
 - An increased rate of stroke was observed during the transition from Rivaroxaban to warfarin in clinical trials in atrial fibrillation patients.
 - If Rivaroxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant

D. Risk of bleeding:

- Rivaroxaban can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss.

E. Spinal/ epidural anesthesia or Puncture:

- When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.
- An epidural catheter should not be removed earlier than 18 hours after the last administration of Rivaroxaban.
- The next Rivaroxaban dose is not to be administered earlier than 6 hours after the removal of the catheter.
- If traumatic puncture occurs, the administration of Rivaroxaban is to be delayed for 24 hours

F. Pregnancy and Nursing mothers:

- Use Rivaroxaban with caution in pregnant women due to the potential for obstetric haemorrhage and/or emergent delivery.
- Promptly evaluate signs and symptoms of blood loss.
- Discontinue drug or discontinue nursing

G. Prosthetic heart valves:

- Rivaroxaban use not recommended

H. Contraindication

- Hypersensitivity to the active substance or to any of the excipients.
- Clinically significant active bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- Patients with severe renal impairment (refer dosing consideration)
- Pregnancy and breastfeeding
- Lesion or condition at significant risk of major bleeding
- Concomitant treatment with any other anticoagulant agent except under the circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.

I. Monitoring

- As warfarin patients need to monitor for signs of bleeding and anaemia (no clinical monitoring available – INR not able to be used as different pathway of action)
- Monitoring of creatinine clearance should be done at least
 - Once or twice a year for patients who had CrCl \geq 50ml/min
 - Every 6 months for patients who had CrCl \leq 50ml/min

J. Drug interactions

- Interactions below lead to an increase bleeding risk – patients should be monitored closely for signs of bleeding and anaemia.
- Concomitant use of systemic azoleantimycotics e.g. ketoconazole, itraconazole, voriconazole, posaconazole,
- HIV protease inhibitors
- Concomitant use of dronedarone should be avoided
- Caution with concomitant anticoagulants, NSAIDs and platelet aggregation inhibitors (e.g. clopidogrel)
- Interactions below lead to a decrease in anticoagulant concentration therefore treatment may be suboptimal
- Caution concomitant use strong CYP3A4 inducers e.g. phenytoin, carbamazepine, phenobarbital, St. John's Wort

Appendix 16 - Prescribing Information for Apixaban

PREScribing INFORMATION FOR APIXABAN¹⁰

A. Indication and dose

- Inhibits Factor Xa
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAf), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class \geq II). Restriction: Only for renal patients.
 - Dose: 5mg BD.
 - Dose reduction: 2.5mg taken orally BD in NVAf patients with at least two of the following characteristics: age ≥ 80 years old, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

B. Dosing Modification and Consideration

- Non-valvular Atrial Fibrillation:
 - Renal impairment:
 - CrCl < 15 -29 mL/min: 2.5mg twice daily
 - Patients with serum creatinine ≥ 1.5 mg/dL (133micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should also receive the lower dose of apixaban 2.5mg twice daily.
- In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore, apixaban is not recommended.

C. Cautions/ Special warning

- As with other anticoagulants, patients taking Apixaban are to be carefully observed for sign of bleeding.
- It is recommended to be used in caution in conditions with increased risk of haemorrhage. Apixaban administration should be discontinued if severe haemorrhage occurs.

D. Spinal/epidural anaesthesia or puncture:

- When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis.
- The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting homeostasis.
- Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Apixaban.
- The risk may also be increased by traumatic or repeated epidural or spinal puncture.
- Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction).
- Prior to neuraxial intervention, the physician should consider the potential benefit versus risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.
- There is no clinical experience with the use of apixaban with indwelling intrathecal or epidural catheters.
- In case there is such need and based on the general PK characteristics of apixaban, a time interval of 20 to 30 hours (i.e., 2 x half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal.
- The next dose of apixaban may be given at least 5 hours after catheter removal.

E. Prosthetic heart valves:

- Use of Apixaban is not recommended.

F. Hepatic impairment:

- Not recommended in patients with severe hepatic impairment (see Contraindications).
- To be used with caution in patients with mild to moderate hepatic impairment (Child Pugh A or B).

G. Hip fracture surgery:

- Use of Apixaban is not recommended.

H. Contraindication

- Hypersensitivity to the active substance or to any of the excipients.
- Active clinically significant active bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition at significant risk of major bleeding, such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agent, except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.

I. Monitoring

- As warfarin patients need to monitor for signs of bleeding and anaemia (no clinical monitoring available – INR not able to be used as different pathway of action)
- Monitoring of creatinine clearance should be done at least
 - Once or twice a year for patients who had CrCl \geq 50ml/min
 - Every 6 months for patients who had CrCl \leq 50ml/min

J. Drug interactions

- Interactions below lead to an increase bleeding risk – patients should be monitored closely for signs of bleeding and anaemia.
- Concomitant use of systemic azole antimycotics e.g. ketoconazole, itraconazole, voriconazole, posaconazole,
- HIV protease inhibitors

- Caution with concomitant anticoagulants
- Caution with concomitant NSAIDs and platelet aggregation inhibitors (e.g. clopidogrel)
- Interactions below lead to a decrease in anticoagulant concentration therefore treatment may be suboptimal
- Caution concomitant use strong CYP3A4 inducers e.g. phenytoin, carbamazepine, phenobarbital, St. John's Wort

Appendix 17 - Triple Therapy Guide

TRIPLE THERAPY GUIDE^{15,16}

A. Duration of Triple Therapy

- The cornerstone of chronic antithrombotic prophylaxis in patients undergoing percutaneous coronary intervention (PCI), presenting with or without an acute coronary syndrome (ACS), is dual antiplatelet therapy (DAPT) with low-dose aspirin and a P2Y₁₂ inhibitor.
- Coronary artery disease (CAD) coexist in 20%–30% of patients with AF, and approximately 5%–7% of PCI patients present with AF or other indications for chronic anticoagulation therapy..
- When indications for DAPT and anticoagulation therapy coexist, the suggestion for optimal management of triple therapy as in Table 1, 2 and Table 3.

Table 1: Antithrombotic Therapy After ACS¹⁶

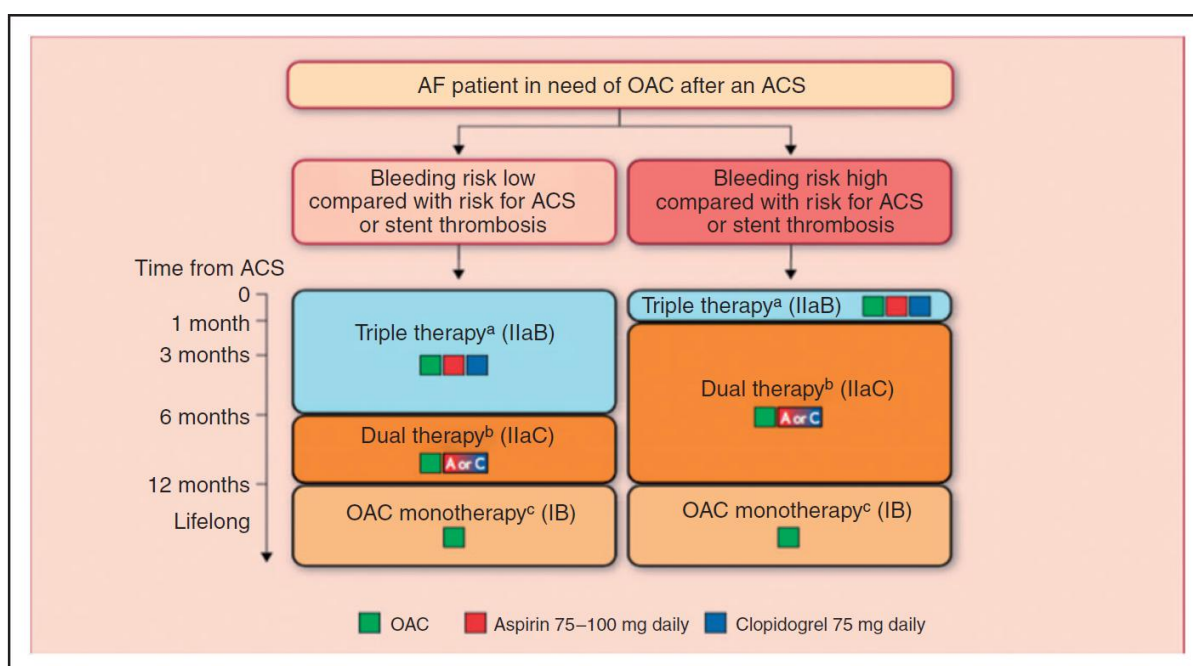
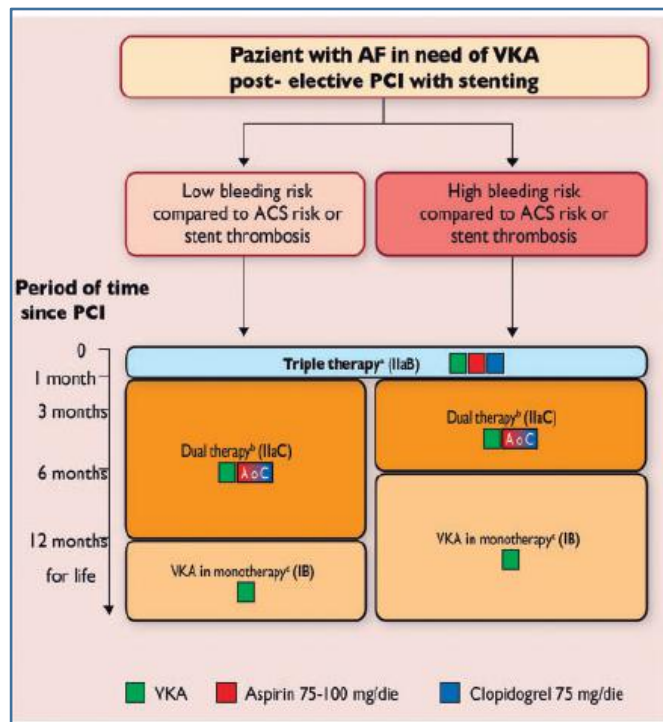
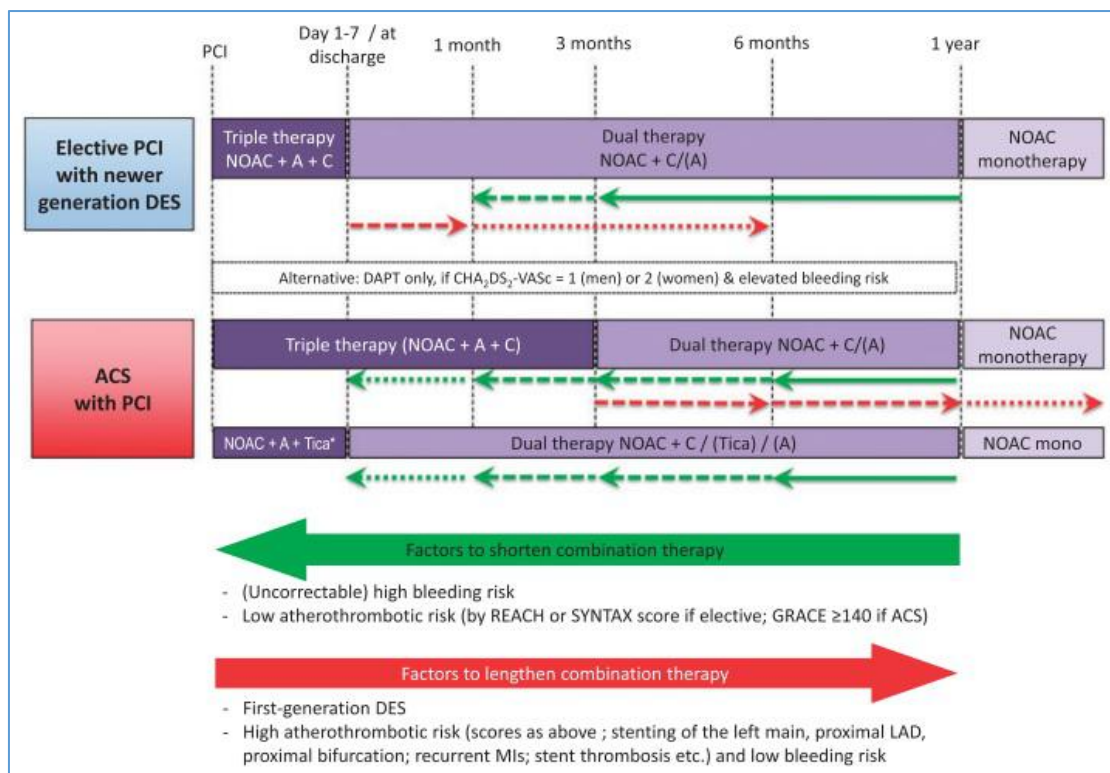


Table 2: Antithrombotic Therapy After PCI¹⁶

Table 3: Guide to shorten Triple Therapy After ACS or PCI¹⁷


B. Strategies to avoid bleeding complications in patients treated with Triple Therapy

- Assess ischemic and bleeding risks using validated risk predictors (eg. CHA₂DS₂VASc, HAS-BLED) with focus on modifiable risk factors.
- Keep triple therapy duration as short as possible; dual therapy after PCI (anticoagulation and clopidogrel) to be considered instead of triple therapy
- Consider a target INR in the lower part of the recommended target range and maximise time in therapeutic range (TTR) (> 65-70%) when warfarin is used
- Clopidogrel as the P2Y₁₂ inhibitor of choice
- Consider the lower DOAC regimen tested in approval studies and apply other DOAC regimen based on drug-specific criteria for drug accumulation
 - *Rivaroxaban 15mg od instead of 20mg od*¹⁸
 - *Dabigatran 110mg twice daily instead of 150mg twice daily*¹⁶
- Use low dose (< 100mg daily) aspirin
- Routine use of PPIs

Appendix 18- Conversion of Anticoagulants Guide

CONVERSION OF ANTICOAGULANTS GUIDE

	TO Dabigatran	TO Rivaroxaban	TO Apixaban
Warfarin	Stop Warfarin and start Dabigatran when INR < 2.	<ul style="list-style-type: none"> • AF - Stop warfarin and start Rivaroxaban when INR ≤ 3.0 • DVT or PE - Stop warfarin and start Rivaroxaban when INR ≤ 2.5 	Stop warfarin and start Apixaban when INR < 2.0
LMWH	Start dabigatran 0 to 2 hours prior to the time of the next dose of LMWH	DVT or PE <ul style="list-style-type: none"> • Start rivaroxaban 0 to 2 hours prior to the next dose of LMWH. • If patient in the initial phase (first 21 days), continue rivaroxaban 15 mg twice daily for first 21 days, then switch to 20mg once daily • If patients on LMWH for more than 21 days, start rivaroxaban 20mg od 0 to 2 hours before the next dose of LMWH. Orthopedic Surgery Start rivaroxaban 0 to 2 hours prior to the next the next dose of LMWH	
UFH	Start Dabigatran at the time of discontinuation of the continuous UFH		To be done at next scheduled dose
	From Dabigatran	From Rivaroxaban	From Apixaban
Warfarin	<ul style="list-style-type: none"> • CrCl ≥ 50 mL/min: Start warfarin 3 days before discontinuing • CrCl 30-50 mL/min: Start warfarin 2 days before discontinuing • CrCl 15-30 mL/min: Start warfarin 1 days before discontinuing 	<ul style="list-style-type: none"> • No data available. • One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time of the next dose of rivaroxaban would have been taken 	<ul style="list-style-type: none"> • Continue Apixaban for at least 2 days after beginning Warfarin • Check INR on day 2. • Continue Apixaban and VKA therapy until the INR ≥ 2.0
LMWH	Start LMWH 12 hours after the last dose of dabigatran		
UFH	If CrCl ≥ 30 - wait 12 hours, if CrCl < 30 - wait 24 hours after last dose of dabigatran before initiating parenteral		

Appendix 19 - Anticoagulation Reversal Guide

GUIDE FOR TREATMENT OF BLEEDING IN ANTICOAGULATION PATIENTS

1. In the anticoagulated patient who presents with clinically relevant bleeding or needs an urgent unplanned procedure, measurement of anticoagulant activity is a key step in the evaluation.
2. A prothrombin time (PT) and/or an activated partial thromboplastin time (aPTT) should be requested in all such patients.
3. Interpretation of the PT and aPTT as well as the potential need to request specialized coagulation tests will depend on the clinical situation, the anticoagulant, and test availability.
4. Unless a concomitant defect in coagulation (e.g., disseminated intravascular coagulation) is suspected, patients taking warfarin may be evaluated with the PT/International Normalized Ratio (INR).
5. The INR may be used to guide perioperative or bleeding management.

A. REVERSAL OF WARFARIN^{19,20}**Table 1- Management of warfarin associated bleeding or supra-therapeutic INR**²¹

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

B. REVERSAL OF DOACS^{19,22,23}

1. Laboratory measurement of the anticoagulant activity of the DOACs is more complex. The best assays are specialized and are not widely available. More accessible tests such as the PT and aPTT have important limitations.
2. Specific measures are directly targeting the anticoagulant agent, by means of (Fab fragments of) monoclonal antibodies (dabigatran) or activated Factor X (FXa) molecules that competitively bind to the rivaroxaban/apixaban are not available in Malaysia.
3. Nonspecific test such as the activated partial thromboplastin time (aPTT), diluted thrombin time (dTT), ecarin clotting time (ECT), prothrombin time (PT) can be used to monitor the effect of anticoagulation effect as in Tables 2.
4. The suggestions of clinical relevant for laboratory measurement of the DOACs based on specialized assay availability is summarized in Table 3.
5. Time of last DOACs dose should always be considered when interpreting test results. Table 4 showed how to interpret the test results.
6. Dependent on the severity of the clinical situation and in view of the relatively short half-life of the direct factor Xa inhibitors (5–15 h), cessation of DOACs may often be sufficient to reverse the anticoagulant effect in case of bleeding.
7. The INR is not a suitable test to quantitate the (residual) anticoagulant effect by DOACs.
8. In severe or life-threatening hemorrhage, or emergency procedures on therapy, reversal of dabigatran anticoagulant effect with 5 grams of idarucizumab as a fixed-dose (intravenous infusion of two 2.5-gram) is recommended.
9. If idarucizumab is unavailable, then either PCC or activated prothrombin complex concentrate (aPCC) at 50 U/kg (max dose 4,000 U) may be used
10. Since dabigatran is mostly not bound to proteins in the serum (>85%), hemodialysis has been suggested if the drug level is very high, especially in patients with impaired renal function. Activated charcoal (50 g) may also be used if the drug was ingested within last 2 to 4 hours
11. There are currently no specific antidotes clinically available for reversal of Rivaroxaban / apixaban anticoagulant effect. Coagulation factor supplementation with PCC or aPCC has been suggested as a potential nonspecific reversal strategy for the direct FXa inhibitors.
12. Table 4 presented the recommended reversal agent for DOACs.

13. Practical guide for how to manage bleeding complications in patients on DOACs is showed in Table 5.

Table 2 – The recommended test to monitor the anticoagulant effect in patients receiving DOACs

Suggestion Tests	Dabigatran	Rivaroxaban	Apixaban
aPTT	✓	✗	✗
TT	✓	✗	✗
dTT, ECT	✓	✗	✗
Anti-FXa	✗	✓	✓
PT	✗	✓	✗
INR	✗	✗	✗

Note : Activated Partial Thromboplastin Time (aPTT), Diluted Thrombin Time (dTT), Ecarin Clotting Time (ECT), Prothrombin Time (PT), Factor-Xa (FXa),

Table 3: Suggestions for Laboratory Assays for “Emergency Situation”²³

Test	Apixaban	Dabigatran	Rivaroxaban
Prothrombin Time (PT)	✓	-/+	✓
Activated Partial Thromboplastin Time (aPTT)	-/+	✓	-/+
Thrombin Time (TT)	✗	-/+	✗
Anti Factor Xa	✓	x	✓
Fibrinogen	-	Falsely low	-
D-dimer	Low	Low	Low

- A normal PT or aPTT does not exclude the possibility of residual anticoagulant effect
- New oral anticoagulants do not cause thrombocytopenia and the D-dimer level is likely to be low
- TT not available locally
- -/+ Not ideal but widely available
- ✓ Requires calibration with required drug.
- ✗ Not locally available

Table 4 - Available Reversal Agents and Suggested Use

Reversal Agent	Factor IIa Inhibitor (Dabigatran)	Factor Xa Inhibitor (Apixaban, and Rivaroxaban)
PCC (3F/4F)	Second line	First line
aPCC	Second line	Second line
Idarucizumab	First line	Not indicated
Plasma	Not indicated	Not indicated

PCC = prothrombin complex concentrate;
aPCC = activated prothrombin complex concentrate.

Table 5 - Management of bleeding in patients receiving DOACs

Dabigatran	Rivaroxaban/apixaban
None life-threatening bleeding	
<ul style="list-style-type: none"> Check last intake; restoration of normal coagulation to be expected at 12–24 h (in case of creatinine clearance > 80 ml/min) or 24–36 h (in case of creatinine clearance 50–80 ml/min) 	
Local hemostatic interventions, fluid management, transfusion	
Consider Activated Charcoal	
Life-threatening bleeding	
All of the above	All of the above
Idarucizumab <ul style="list-style-type: none"> 5 grams as a fixed dose (intravenous infusion of two 2.5 gram) 	Prothrombin complex concentrate <ul style="list-style-type: none"> Dose 50 U/kg (max dose 4,000 U)
Prothrombin complex concentrate <ul style="list-style-type: none"> Dose 50U/kg (max dose 4,000 U) 	

Appendix 20 – Recommended Dispensing Label

RECOMMENDED DISPENSING LABEL

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

NAMA : _____

TARIKH : _____

KUANTITI : _____

MAKAN _____ BIJI PADA HARI ISNIN

_____ BIJI PADA HARI SELASA

_____ BIJI PADA HARI RABU

_____ BIJI PADA HARI KHAMIS

_____ BIJI PADA HARI JUMAAT

_____ BIJI PADA HARI SABTU

_____ BIJI PADA HARI AHAD

SEKALI SEHARI

JABATAN FARMASI , HOSPITAL

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

LOADING DOSE

NAMA : _____

TARIKH : _____

KUANTITI : _____

MAKAN _____ BIJI PADA _____

JABATAN FARMASI , HOSPITAL

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

NAMA : _____

TARIKH : _____

KUANTITI : _____

MAKAN _____ BIJI PADA _____

JABATAN FARMASI , HOSPITAL

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