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Deep vein thrombosis (DVT) Treatment protocol for adult patients

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT), and pulmonary embolism (PE) contributes to significant morbidity and mortality. Anticoagulants are drugs that alter the biochemical processes of blood clotting resulting in the prevention or reduction of blood coagulation. They are the mainstay of pharmacotherapy for thrombosis prevention and treatment.

Purpose:

To help MOH hospital during the establishment of the Anticoagulants Stewardship Program in a hospital setting.

Aim and scope:

This protocol is intended to provide guidance on the safe and cost-effective treatment of DVT.

Targeted population:

Hospitalized and ambulatory adult patients who are diagnosed with DVT.

Targeted end users:

Physicians, Pharmacists, Clinical Pharmacists, and Nurses.

Setup:

In-patient and outpatient setting

Conflict of interest:

This protocol was developed based on valid scientific evidence, critical assessment of this evidence, and objective clinical judgment that relates the evidence to the needs of practitioners and patients. No financial relationships with pharmaceutical, medical device, and biotechnology companies.

Funding:

No fund was provided.

Abbreviations

- VTE: Venous thromboembolism
- DVT: Deep vein thrombosis
- PE: Pulmonary Embolism
- AF: Atrial Fibrillation
- VKA: Vitamin K antagonist
- LMWH: Low molecular weight Heparin
- UFH: Unfractionated Heparin
- INR: International Normalized Ratio
- IVC: inferior vena cava
- HIT: Heparin-induced thrombocytopenia
- DOAC: direct oral anticoagulant

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Initiating anticoagulant:

To start anticoagulation (while awaiting test results), consider the following:	
The higher the clinical suspicion for VTE, the shorter the acceptable interval without treatment.	The higher the risk of bleeding*, the longer the acceptable interval without treatment.

*Risk factors for bleeding: age >65 years, previous bleeding, cancer, renal/ liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, recent surgery, frequent falls.

- **Start anticoagulant** if there is high clinical suspicion of acute VTE, or if intermediate clinical suspicion and test results could be delayed >4 hours, or low suspicion and test results could be delayed >24 hours.

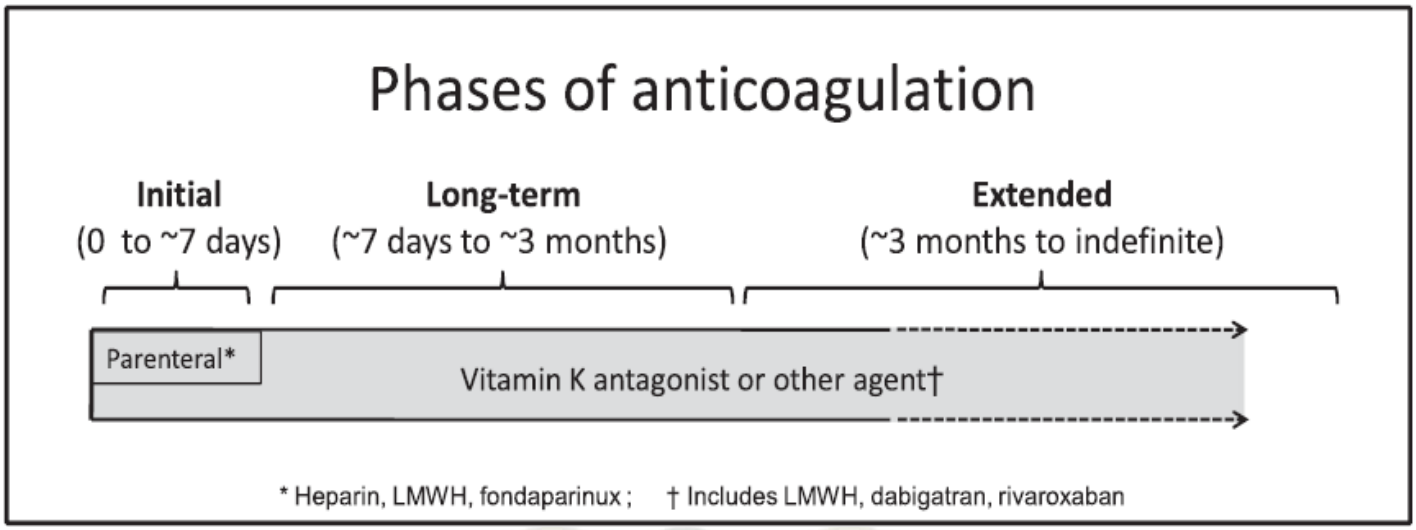
Initial management acute DVT of the leg:

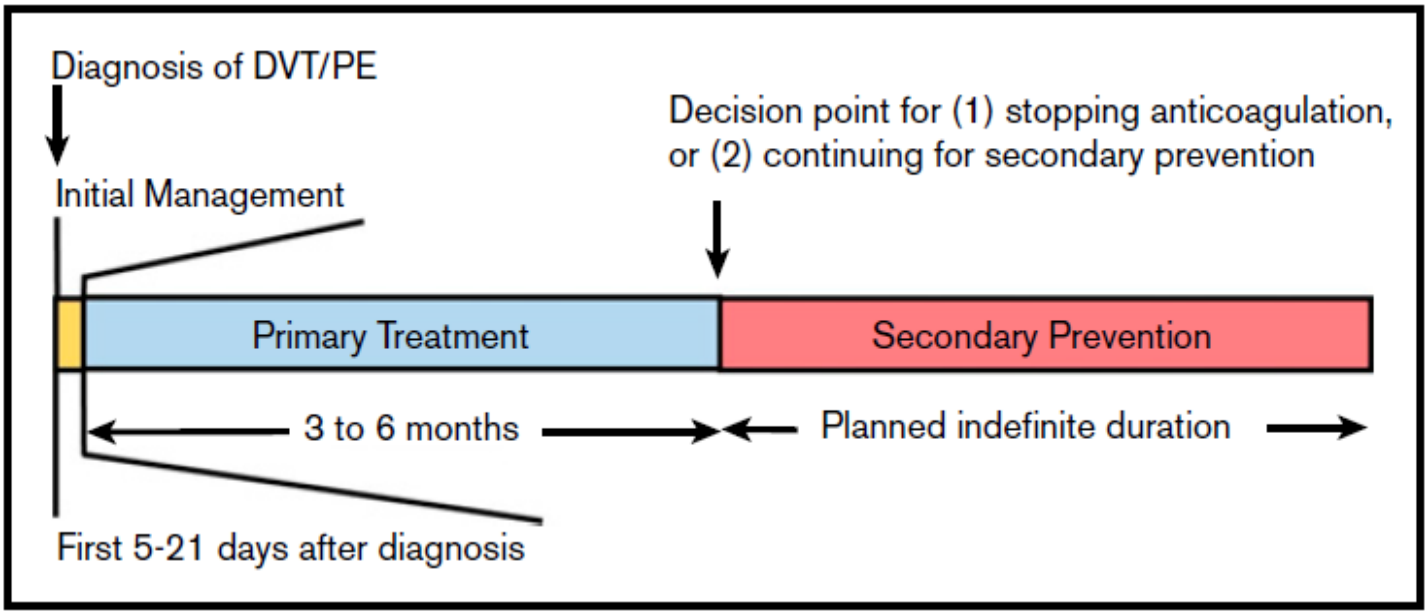
-For patients with uncomplicated deep vein thrombosis (DVT)	Home treatment over hospital treatment
-For patients who Have limited or no support at home and cannot afford medications or have a history of poor compliance. Patients with limb-threatening DVT or a high risk for bleeding and those requiring IV analgesics	May benefit from initial treatment in the hospital.

	Distal DVT	**Proximal DVT**
Management	-If no severe symptoms or no risk of extension*: Serial imaging for 2 weeks with no anticoagulation. -If severe symptoms or risk of extension*: Start anticoagulation. 6/52 -If extended but remained in distal or extended to proximal vein: Start anticoagulant 3/12	-if no contraindication** to anticoagulants, start anticoagulant. -If a contraindication to anticoagulants, use an IVC filter, once the risk of bleeding resolves covert to anticoagulant

*Risk factors of extension: positive D dimer, thrombosis > 5cm in length or > 7 mm in diameter, involves multiple veins, irreversible provoking factor, active cancer, history of VTE, inpatient status.
** Absolute contraindications to anticoagulation include active bleeding, severe bleeding diathesis, platelet count <50,000/microL (sometimes lower depending upon the strength of the indication), recent, planned, or emergent high bleeding-risk surgery/procedure, major trauma, history of intracranial hemorrhage (ICH) particularly recent ICH

Relative contraindications to anticoagulation include recurrent bleeding from multiple gastrointestinal telangiectasias, intracranial or spinal tumors, platelet count <100,000/micro, large abdominal aortic aneurysm with concurrent severe hypertension, stable aortic dissection, recent, planned, or emergent low bleeding-risk surgery/procedure.


Phases of anticoagulation
Initial
(0 to ~7 days)
Long-term
(~7 days to ~3 months)
Extended
(~3 months to indefinite)
Parenteral*
Vitamin K antagonist or other agent†
* Heparin, LMWH, fondaparinux ; † Includes LMWH, dabigatran, rivaroxaban


Diagnosis of DVT/PE
Initial Management
Decision point for (1) stopping anticoagulation, or (2) continuing for secondary prevention
Primary Treatment
Secondary Prevention
3 to 6 months
Planned indefinite duration
First 5-21 days after diagnosis

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Anticoagulants used for initial treatment of acute DVT of the leg:

Anticoagulant	Dose	Monitoring
Oral VKA (warfarin): started the same day as a parenteral anticoagulant	Day 1-2: Normal adult: 10mg or 5 mg Malnourished, elderly, liver disease: 2.5 mg. Dosing is then adjusted until the INR is within the therapeutic range (2 to 3) for 2 consecutive days or 2.5 - 3.5 for Mitral Valve.	INR
Parenteral anticoagulant: SC LMWH (**preferred in cancer/pregnancy)**	1 mg/kg/dose BID	No
SC Fondaparinux **(preferred in HIT)**	Weight-based: <50 kg: 5mg q24 hours 50-100 kg: 7.5 mg q24 hour >100 kg: 10 mg q24 hours (For renal dose adjustment refer to MOH formulary)	No
IV UFH (preferred in hemodynamically unstable patients/ in severe renal impairment)	Initial dose: 80 units/ kg bolus (max: 1000 units), followed by 18 units/kg/hr.	aPTT
SC UFH	Initial: 333 units/kg then 250 units/kg SC every 12 hours	Any option
Apixaban	10 mg twice daily (for first seven days)	No

10 mg Warfarin Initiation Monogram			
Day 3 INR	Warfarin dose , mg on day 3,4	Day 5 INR	Warfarin dose, mg on day 6,7,8
-	-	<2	15,15,15
<1.3	15,15	2-3	7.5, 7.5, 7.5
1.3-1.4	10,10	3.1-3.5	0,5,5
-	-	>3.5	0,0,2,5
-	-	<2	7.5, 7.5, 7.5
1.5-1.6	10,5	2-3	5,5,5
1.7-1.9	5,5	3.1-3.5	2.5, 2.5, 2.5
-	-	>3.5	0,2.5,0
-	-	<2	5,5,5
2-2.2	10,5	2-3	2.5,5,2.5
2.3-3	5,5	3.1-3.5	0,2.5,0
-	-	>3.5	0,0,2.5
-	-	<2	2.5, 2.5, 2.5
>3	0	2-3	2.5, 0, 2.5
-	-	3.1-4	0,2.5,0
-	-	>4	0,0,2.5

5 mg Warfarin Initiation Monogram		
Day	INR	Warfarin Dose,mg
1		5
2		5
3	<1.5	10
	1.5-1.9	5
	2-3	2.5
	>3	0
4	<1.5	10
	1.5-1.9	7.5
	2-3	5
	>3	0
5	<2	10
	2-3	5
	>3	0
6	<1.5	12.5
	1.5-1.9	10
	2-3	7.5
	>3	0

- **Thrombus removal by catheter-directed, systemic thrombolysis, or operative are not recommended.**

I. Long-term Anticoagulation of Acute DVT of the Leg

All patients with acute VTE who are treated initially with anticoagulants are recommended to receive long-term therapy rather than stopping after 1 week of the anticoagulant.

Duration of Therapy
Long-term (3-6 months) proximal or isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor. first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk. first VTE that is an unprovoked isolated distal DVT with low, moderate, or high bleeding risk. second unprovoked VTE who has a high bleeding risk
Extended (>3-6 months to indefinite) first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk. second unprovoked VTE and have a low to moderate bleeding risk. DVT of the leg and active cancer with risk of bleeding not high, or high
In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

Anticoagulants used for long-term anticoagulation for acute DVT.

Anticoagulants	Doses
VKA **Warfarin:** recommended if no cancer Should be used for at least 5 days with heparin or till **Target INR: 2-3** for 2 consecutive days.	Warfarin is initiated with initial parenteral anticoagulant.
Parenteral anticoagulant **LMWH:** recommended if cancer, recommended for pregnancy	1 mg/kg q12 hour
DOAC: **Dabigatran:** requires parenteral anticoagulant initially for at least 5 days.	150 mg twice daily
Apixaban	10 mg twice daily for seven days followed by 5 mg twice daily (2.5 mg twice daily for extended treatment beyond six months)

- **Choice of Anticoagulant Regimen for Extended Therapy (after 3 months):**
If no contraindication arises, continue the same anticoagulant chosen for the first 3 months.
- **Asymptomatic DVT of the leg:**
Same initial and long-term anticoagulation as for comparable patients with symptomatic DVT

II. Pregnancy

- **In pregnant women with acute VTE,** apply the same principle for initiating anticoagulant and for contraindications.
- **In pregnant women with acute DVT,** LMWH is the preferred anticoagulant for both initial and long-term therapy. Multi-dose syringes (contain preservatives) are contraindicated in pregnancy, use prefilled single-dose syringes.
- Intravenous and subcutaneous UFH are alternatives to LMWH in case of severe renal failure (CrCl <30 ml/min) as an initial anticoagulant.
- VKA, warfarin crosses the placenta and is known to be teratogenic when given in the first trimester. So, any woman who plans to be pregnant/ not using contraception and was on VKA should be converted to LMWH if the dose is more than 5mg.
- Fondaparinux is recommended in the case of HIT (limited safety data).
- Rivaroxaban and apixaban have not been adequately tested in pregnant women with acute DVT and as such should not be administered. Women on such anticoagulants are advised to convert to LMWH when becoming pregnant.

Labor and delivery:

- LMWH should be discontinued at least 24 hours prior to delivery if the delivery time is predictable.
- Pregnant women with acute DVT within the last month are recommended to convert to IV UFH as it can be discontinued 4-6 hours before delivery.
- If labor begins unexpectedly and the patient was on full anticoagulation, neuraxial anesthesia should not be administered due to the risk of spinal hematoma.
- In case of preterm delivery, discontinue LMWH at 36 weeks and convert to IV UFH.

After delivery:

- Low-molecular-weight heparin should be restarted 12 hours after a cesarean delivery or 6 hours after a vaginal birth, given no significant bleeding has occurred.
- If acute VTE events occurred during lactation, Fondaparinux, Rivaroxaban, or Apixaban should not be used. Options include LMWH and UFH (not for outpatient treatment). Warfarin is considered safe during lactation. Same recommendations for VKA as for the general population.

Long-term anticoagulation:

- Same general principles applied to pregnant women.
- Warfarin and LMWH are considered safe during lactation.
- Dabigatran, Rivaroxaban and apixaban should not be used by breastfeeding mothers.

Duration of therapy:

- Same principles applied.

III. SWITCHING ANTICOAGULANTS DURING THERAPY:

Original anticoagulant	New anticoagulant	Administration
LMWH	Warfarin	Warfarin and heparin are simultaneously administered for 4-5 days until the INR is 2-3 for two consecutive days.
	DOACs	administering the oral agent within 6 to 12 hours after the last scheduled dose of a twice-daily LMWH regimen.
Warfarin	LMWH	administering LMW heparin two hours prior to the last scheduled dose of warfarin, which is then omitted.
	DOACs	not well established. For patients with VTE, we prefer starting these agents when the INR is within the therapeutic range of 2 to 3. For Rivaroxaban, a maintenance dose of 20 mg daily, Apixaban 5 mg twice daily, Edoxaban 60 mg daily, and dabigatran 150 mg twice daily should be sufficient to maintain an effective anticoagulant. Warfarin can be stopped after the first dose.
DOACs	LMWH	administering LMWH 24 hours after the last dose of the user agent.
	Warfarin	Co-administering warfarin with the newer anticoagulant for at least two (Rivaroxaban, Edoxaban, and Apixaban) to three (dabigatran) days prior to stopping these agents when renal function is normal; one to two days overlap may be reasonable for patients on dabigatran with a CrCl <30 mL/minute.

References:

1-Antithrombotic Therapy for VTE Disease Second Update of the CHEST Guideline and Expert Panel Report 2016

2-Antithrombotic Therapy and Prevention of Thrombosis,9th ed: American College of Chest Physicians

3-Evidence-Based Clinical Practice Guidelines 2012

4-Uptodate

5-American College of Clinical Pharmacy (ACCP) 2022

6-MOH formulary

7-Micromedex 8-ASH