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Committee for practice Guidelines
To improve the quality of clinical practice and
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Guidelines for the Management of
Venous Thrombo-Embolism



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♥ Introduction

Venous thrombo-embolic disorders (VTE) are one of the common causes of morbidity and mortality in hospitalized patients. VTE is usually underestimated since approximately 50% of patients with proximal deep venous thrombosis (DVT) of the leg have asymptomatic pulmonary embolism (PE) and 80% of patients with pulmonary embolism have silent DVT. Even those who had autopsy proven PE, only 50% were clinically suspected to have PE before their death. Acquired risk factors for thrombosis represent the majority of cases of VTE and include immobilization, surgery, trauma, plaster casts, pregnancy, puerperium, lupus anticoagulant, malignancies, and female hormones. Inherited thrombophilic states also play a major role in inducing thrombosis especially in young patients and contribute to the higher risk of VTE for those patients with acquired risk factors.

It is perceived among health care providers that VTE incidence is low in hospitalized patient especially those with medical disorders. However, recent epidemiological surveys have clearly shown that most of the VTE events occur in the medical patients.

This booklet has adopted the most recent recommendations in preventing and managing VTE in hospitalized patients. It is meant to be a companion to a busy house officer facing a variety of medical and surgical conditions providing general guidelines in instituting the appropriate prophylactic modalities based on VTE risk assessment.



♥ Heparin and Low-Molecular- Weight Heparin

- Unfractionated Heparin (UFH) is a heterogeneous mixture of glycosaminoglycans that bind to antithrombin via a pentasaccharide, catalyzing the inactivation of thrombin and other clotting factors.
- UFH also binds endothelial cells, platelet factor 4, and platelets, leading to rather unpredictable pharmacokinetic and pharmacodynamic properties.
- Variability in activated partial thromboplastin time (aPTT) reagents necessitates site-specific validation of the aPTT therapeutic range in order to properly monitor UFH therapy. Lack of validation has been an oversight in many clinical trials comparing UFH to LMWH.
- In patients with apparent heparin resistance, anti-factor Xa monitoring may be superior to measurement of aPTT. LMWHs lack the nonspecific binding affinities of UFH, and, as a result, LMWH preparations have more predictable pharmacokinetic and pharmacodynamic properties.
- LMWHs have replaced UFH for most clinical indications for the following reasons:
 - (1) their properties allow LMWHs to be administered subcutaneously, once daily without laboratory monitoring.
 - (2) the evidence from clinical trials that LMWH is at least as effective as and is safer than UFH.
- Several clinical issues regarding the use of LMWHs remain unanswered. These relate to :
 - the need for monitoring with an anti-factor Xa assay in patients with severe obesity or renal insufficiency.
 - The therapeutic range for anti-factor Xa activity depends on the dosing interval. Anti-factor Xa monitoring is prudent when administering weight-based doses of LMWH to patients who weigh > 150 kg.

- It has been determined that UFH infusion is preferable to LMWH injection in patients with creatinine clearance of < 25 mL/min, until further data on therapeutic dosing of LMWHs in renal failure have been published. However, when administered in low doses prophylactically, LMWH is safe for therapy in patients with renal failure.
- Protamine may help to reverse bleeding related to LMWH, although anti-factor Xa activity is not fully normalized by protamine.

Table 1 - Weight Based adjustment of aPTT[†]

aPTT	Dose
Initial Dose	80 U/kg _____, then 18 U/kg/h
< 35	80U/kg _____, then 4 U/kg/h
35 - 45	40 U/kg _____, then 2 U/kg/h
45 - 70	No change
71- 90	Decrease infusion rate by 2 U/kg/h
>90	Hold infusion 1 hr then decrease infusion rate by 3 U/kg/h

[†] Therapeutical aPTT range of 46 to 70a corresponded to anti-factor Xa activity of 0.3 to 0.7 U/ml at the time the study was performed. The therapeutic range at any institution should be established by correlation with anti-factor Xa levels in the range



♥ Prevention of Venous Thromboembolism

Risk factors for VTE are illustrated in the following table

Table 2 – Risk Factors for VTE

Surgery	
Trauma (major or lower extremity)	
Immobility, paresis	
Malignancy	
Cancer therapy (hormonal, chemotherapy, or radiotherapy)	
Previous VTE	
Increasing age	
Pregnancy and postpartum period	
Estrogen-containing oral contraception or hormone replacement therapy	
Selective estrogen receptor modulators	
Acute medical illness	Successful Prevention Strategies
Heart or respiratory failure	No specific prophylaxis early and "aggressive" mobilization
Inflammatory bowel disease	
Nephrotic syndrome	
Myeloproliferative disorders	LDUH (q12h) LMWH (< 3400 U daily), GCS, or IPC
Paroxysmal nocturnal hemoglobinuria	
Obesity	
Smoking	LDUH (q8h) LMWH (> 3400 U daily), or IPC
Varicose veins	
Central venous catheterization	
Inherited or acquired thrombophilia	LMWH (> 3400 U daily), VKAs (INR, 2-3, or IPC/GCS + LDUH / LMWH

- Aspirin alone is not an appropriate thromboprophylaxis for any patient group.

LDUH: Low Dose Unfractionated heparin

LMWH: Low Molecular Weight Heparin

GCS: Graduated Compression Stockings

IPC: Intermittent Pneumatic Compression

VKAs: Vitamin K Antagonists

General surgery patients

- It is advised to risk stratify surgical patients before instituting the appropriate prophylaxis (Table 3)

Table3: Risk stratification of surgical patients

Level Of Risk

Low risk

- Minor Surgery in patients < 40 yr with no additional risk factors

Moderate risk

- Minor surgery in patients with additional risk factors
- Surgery in patients aged 40-60 yr. with no additional risk factors

High risk

- Surgery in patients > 60 yr. of age 40-60 with additional risk factors prior VTE cancer

Highest risk

- Surgery in patients with multiple risk factor (age > 40 yr. Cancer prior VTE)
- Hip or Knees arthroplasty, Hip Fracture Surgery Major trauma; Spinal Cord

Injury



Recommendations

Low risk surgical patients:

- No specific prophylaxis, early and aggressive mobilization.

Moderate-risk

- Low-dose unfractionated heparin (LDUH-5,000 U bid)
- Or low-molecular-weight heparin (LMWH- < or equal 3,400 U once daily eg. Enoxaparin 20 mg (2000 I.U)

High risk

- LDUH (5,000 U tid)
- Or LMWH (> 3,400 U daily) eg. Enoxaparin 40 mg (4000 Anti - Xa IU).
- Or IPC

Highest risk,

- LMWH > 3,400 U daily alone or in combination with graduated compression stockings and/or intermittent pneumatic compression devices.

Major gynecological surgery

Recommendation

For those patients with benign diseases with no additional risk factors

- LDUH twice daily.
- Or Once daily with LMWH < 3,400 U.
- Or intra-operative IPC continued for at least several days after surgery.

For higher-risk patients e.g. extensive surgery for malignancy:

- LDUH three times /day + ES (Elastic Stocking) or IPC,
- Or LMWH given in daily doses of at least 3,400 U. (e.g. Enoxaparin 40 mg).

Orthopedic Surgery

For patients undergoing elective total hip or knee arthroplasty

- LMWH (using a dose > 3.400 U) e.g. Enoxaparin 40mg
- Or adjusted-dose Warfarin [international normalized ratio (INR) target, 2.5; range, 2.0 to 3.0] .
- Or fondaparinux 2.5 mg daily

For patients undergoing hip fracture surgery (HFS)

- LMWH (> 3.400 U) e.g. Enoxaparin 40mg
- Or Warfarin (target INR, 2.5; range, 2.0 to 3.0)
- Or LDUH 3 times daily
- Or fondaparinux 2.5 mg daily

Duration of Thromboprophylaxis

- Patients undergoing hip or knee arthroplasty, or HFS should receive thromboprophylaxis for at least 10 days.
- Patients undergoing THR or HFS should be given extended prophylaxis up to 28 to 35 days. The recommended options for THR include LMWH (Enoxaparin 40 mg QID) OR Warfarin (target INR, 2.5; range, 2.0 to 3.0)
- Trauma patients with at least one risk factor for VTE should receive thromboprophylaxis with LMWH (Enoxaparin 4000 IU) or mechanical prophylaxis with GCS (Graduated Compression Stockings) until hospital discharge, and to be extended beyond hospital discharge with LMWH or VKA in patients with major impaired mobility.



VTE prophylaxis in acutely ill medical patient

Patients who have been admitted to the hospital with

- Congestive heart failure
- Severe respiratory disease
- Or who are confined to bed and have one or more additional risk factors.

Recommendations

- LDUH or LMWH (e.g. Enoxaparin 40mg Once Daily).
- On admission to the intensive care unit, all patients should be assessed for their risk of VTE. Accordingly, most patients should receive thromboprophylaxis.

VTE prophylaxis in cancer patients

- Cancer patients undergoing surgical procedures receive prophylaxis that is appropriate for their current risk state, refer to the recommendations in the relevant surgical subsections.
- Hospitalized cancer patients who are bedridden with an acute medical illness should receive prophylaxis that is appropriate for their current risk state refer to recommendations in the section dealing with medical patients.



♥ *Treatment of DVT*

In acute DVT,

Initial treatment with LMWH or UFH for at least 5 days, initiation of vitamin K antagonist (VKA) together with LMWH or UFH on the first treatment day, and discontinuation of heparin when the international normalized ratio (INR) is stable and > 2.0 (Grade 1A).

For the duration and intensity of treatment for acute VTE, the recommendations include the following:

For patients with a first episode of DVT secondary to a transient (reversible) risk factor, long-term treatment with a VKA for 3 months is recommended over treatment for shorter periods.

For patients with a first episode of idiopathic DVT, we recommend treatment with a VKA for at least 6 to 12 months. The dose of VKA should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations.

For the prevention of the post-thrombotic syndrome, the use of an elastic compression stocking is recommended.

For patients with objectively confirmed non-massive PE, we recommend acute treatment with SC LMWH or, alternatively, IV UFH.

For most patients with pulmonary embolism (PE), we recommend clinicians not use systemic thrombolytic therapy.

For the duration and intensity of treatment for PE, the recommendations are similar to those for DVT.

Reference

"Adapted from the 7th ACCP Conference on Antithrombotic and Thrombolytic therapy. Chest 2004,126:163S-696S."

