UMassMemorial

PRINTABLE VERSION

Guidelines For Antithrombotic Therapy

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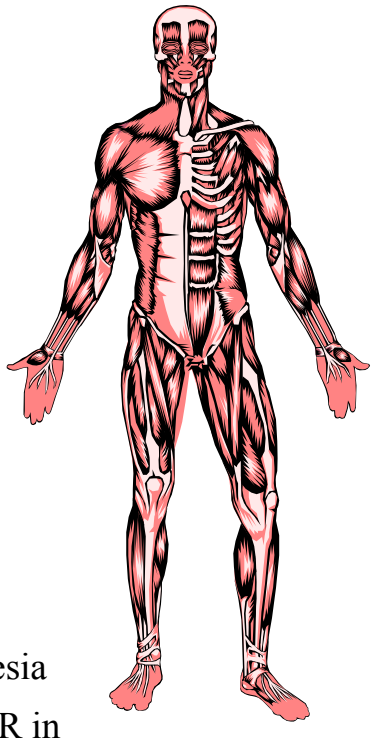

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The guidelines for antithrombotic therapy in adults and children were developed by an experienced group of clinicians through careful review of current literature and consensus statements from recognized experts in the field. Our objective is to optimize the management of patients at risk for and those with thromboembolic disorders of the venous and arterial circulatory systems through evidence-based laboratory testing, drug selection and treatment strategies**.** These guidelines and subsequent updates are posted on the UMass Memorial Intranet under Clinical Practice Guidelines.

I. INITIATION OF ANTICOAGULANT THERAPY

A. Fractionated, Low Molecular Weight Heparin (LMWH) (SC Administration)

- Lovenox 1 mg/kg (maximum dose 150 mg) every 12h (unstable angina, non-ST elevation MI).
- Lovenox 1 mg/kg (maximum dose 150 mg) every 12h (venous thromboembolism) (outpatient or inpatient Rx).
- Lovenox 1.5 mg/kg (maximum dose 225 mg) qd (venous thromboembolism) (inpatient Rx).
- Lovenox 1 mg/kg (maximum dose 120 mg) every 12h (ST elevation MI Rx with TNK-tPA)*.
- LMWH does not prolong aPTT; minimal prolongation of ACT may be observed.
- Routine coagulation monitoring is not required; however, an anti-Xa level may be useful in the following situations: bleeding complications, extremes of body weight (<50 kg, >150 kg), renal insufficiency (creatinine clearance <40 ml/min)*, pregnancy, acute burns, and recurrent thrombosis despite drug treatment. Dosing adjustments and anti-Xa monitoring may be required in these patients, therefore, consider consulting Anticoagulation Service. During treatment the peak anti-Xa level (not to exceed 1.5 Units/ml) is determined 4 hours after the 3rd dose. The trough level (≥0.5 Units/ml) is determined before the 4th dose. The test is performed in the UMass-Memorial laboratory.

** Rx may be initiated with Lovenox 30 mg IV bolus. Dose modifications are required with creatinine clearance < 40 ml/min and experience is limited. Contact Anticoagulation Service for recommendations.*

B. Unfractionated Heparin (IV Administration)

- **Initial bolus** 60 Units/kg (not to exceed 5000 Units; 4000 Units MAX with tPA and related fibrinolytics).
- **Initial infusion**

	Dose	**Initial MAX rate**
Low intensity (e.g. ACS)	15 Units/kg/hr	1200 units/hr
and tPA or GPIIb/IIIa receptor antagonist	12 Units/kg/hr	1000 units/hr
High Intensity (e.g. Acute Venous Thromboembolism)	18 Units/kg/hr	1800 units/hr

- Target aPTT 50-70 sec for acute coronary syndromes (including concomitant tPA or platelet GPIIb/IIIa antagonist therapy).
- Target aPTT 60-85 sec for venous thromboembolism.
- If 2 consecutive aPTT values are < 50 sec or > 90 sec, notify MD.
- If infusion rate reaches or exceeds 2200 units/hour (44cc/hr), call MD.

C. Candidates for Anticoagulant Therapy

- Obtain baseline aPTT, PT (INR), CBC with platelet count.
- Screen for contraindications; assess bleeding risk.
- Heme test stool.

- Check platelet count every 3 to 5 days during therapy (daily if decrease is observed) to evaluate for possible heparin-induced thrombocytopenia (HIT).

Unfractionated Heparin-Dosing Nomogram
For Adult Patients Requiring Lower Intensity Anticoagulation
(e.g. Acute Coronary Syndromes)

aPTT (Sec)	Repeat Bolus* (Units)	Stop Infusion (min)	Rate Change (Units/h)	Repeat aPTT 2,+ (h)
<35	Repeat bolus	0	+150 (3cc/hr)	4
35-49	Half bolus	0	+100 (2cc/hr)	6
50-70	**0**	**0**	**No change**	**6 hours x 1; then q 7 am**
71-90	0	0	- 100 (2cc/hr)	6
91-120	0	0	- 150 (3cc/hr)	4
121-150	0	0	- 200 (4cc/hr), call HO	4
>150	0	Y	HOLD, call HO	4

* maximum dose for repeat bolus 3000 Units (avoid repeat bolus dosing with fibrinolytic Rx).
~ aPTT should be checked every 4-6 h until target achieved, then at least daily.
+ a PTT should be checked every 4-6 h for at least 24 h after tPA and related fibrinolytics.

Unfractionated Heparin Dosing Nomogram
For Patients Requiring Higher Intensity Anticoagulation
(e.g. Acute Venous Thromboembolism)

aPTT (Sec)	Repeat Bolus (Units)	Stop Infusion (min)	Rate Change (Units/h)	Repeat aPTT 2,+ (h)
<35	Repeat initial bolus	0	+200 (4cc/hr)	4
35-59	Half initial bolus	0	+150 (3cc/hr)	6
60-85	**0**	**0**	**No change**	**Next AM**
86-100	0	0	- 100 (2cc/hr)	6
101-120	0	0	- 150 (3cc/hr)	4
121-150	0	0	- 200 (4cc/hr), call HO	4
>150	0	Y	HOLD, call HO	4

- Aspirin (81 to 162 mg qd) or clopidogrel (75 mg qd) can be used as an adjunct to warfarin in high-risk patients; however, the risk of bleeding is increased with combination therapy.

D. Non-Acute Indications for Unfractionated Heparin

- Unfractionated heparin may be used as bridging anticoagulation in hospitalized patients with chronic conditions requiring temporary discontinuation of warfarin. Such conditions include:
    - Chronic A-fib, cardiomyopathy/LV aneurysm
    - Prosthetic heart valves
    - Prior DVT/PE
    - Prior arterial embolic events
- Such patients rarely require rapid achievement of therapeutic PTTs and often have increased bleeding risks (as they are hospitalized). Therefore consider:

- Using the nomogram for lower intensity anticoagulation
- Avoiding or decreasing boluses of unfractionated heparin
- Check PTTs no more frequently than q 6 h

E. Patients with Increased Bleeding Risk

- On occasion, patients with increased bleeding risk will require unfractionated heparin (AVMS/prior GI bleed, recent stroke, recent surgery, etc.) For these patients, consider:
  - Individualized dosing (do not use nomogram)
  - Avoiding or decreasing boluses of unfractionated heparin
  - Slow titration upward to target PTT
  - Daily assessment for signs/symptoms of bleeding, daily CBC
  - Anticoagulation Services consult

II. WARFARIN ANTICOAGULATION

Indication	Target INR	Range
• Prophylaxis of venous thrombosis (high-risk patients)	2.5	(2-3)
• Treatment of venous thrombosis (after heparin)	2.5	(2-3)
• Treatment of pulmonary embolism (after heparin)	2.5	(2-3)
• Prevention of systemic embolism*	2.5	(2-3)
• Bioprosthetic heart valves (particularly in the first 3 months)	2.5	(2-3)
• Atrial fibrillation	2.5	(2-3)
Recurrent systemic embolism	3	(2.5-3.5)
• Mechanical prosthetic valves **	3	(2.5-3.5)
• Post-myocardial infarction (secondary prevention) ***	3	(2.5-3.5)
• Antiphospholipid antibody syndrome (with prior thrombosis)	3.5	(2.5-3.5)
• Long-term indwelling catheters (prophylaxis)	warfarin 1 mg daily	

* Aspirin (81 to 162 mg PO qd) or clopidogrel (75 mg PO qd) can be used as an adjunct to warfarin in high-risk patients; however, the risk of bleeding is increased with combination therapy.

** A target INR of 2.5 (range 2.0-3.0) is acceptable for bileaflet mechanical values (eg. St. Jude Valve) in the aortic position.

*** A target INR of 2.5 (range 2.0-3.0) plus aspirin (81 mg) is also acceptable.

III. INITIATION OF ORAL ANTICOAGULATION WITH WARFARIN

The dosing of warfarin must be individualized according to patient need and anticoagulant response as reflected by the INR. Large initial doses (>10 mg for several days) increase the risk of hemorrhage and other complications, do not offer more rapid protection against thrombotic events, and are not recommended. Lower doses (less than 5 mg) are recommended among elderly and/or debilitated patients, following mechanical heart valve surgery and when sensitivity (increased anticoagulant response) to warfarin is anticipated. interactions on page 7).

Step-Wise Approach

DAY 1: Obtain Baseline INR.

Begin therapy with warfarin at a dose of 5 mg (or less) per day with dosage adjustments based on serial INR determinations.

For Patients on Heparin (unfractionated or low molecular weight): Because the anticoagulant effect of warfarin is delayed, heparin is administered for rapid anticoagulation. When clinically indicated, conversion to warfarin should begin concomitantly with initiation of heparin therapy. After an overlap of three to five days, heparin can be discontinued when a therapeutic INR has been documented on two consecutive days.

DAY 2: Check INR Daily. Adjust Warfarin Dose Based on Serial INR Determinations.

Patients Stabilized in the Target Range: Intervals between subsequent INR determinations should be based upon patient reliability, concomitant medications, and response to warfarin. Acceptable intervals for INR determinations are normally one to four weeks after a stable dosage has been determined. In general, the INR should be checked within 1 to 3 days of hospital discharge. Most patients are satisfactorily maintained on 2.5 to 5 mg warfarin daily; however, the requirements vary widely.

Reminder

* Be aware of potential drug interactions, medical illnesses and other factors (diet) that may affect the INR and /or warfarin response, particularly after hospital discharge.
* Patient education is an important part of therapy. Safe and effective treatment is most often achieved among cooperative and well-instructed patients who communicate with their health care team.

Drug Interactions with Warfarin

Numerous factors, including travel, changes in diet, environment, physical state and medications may influence a patient's response to warfarin therapy. It is considered good practice to monitor the patient's response with additional INR determinations in the period immediately after hospital discharge, and when other medications are initiated, discontinued or taken irregularly. The following factors are listed for reference; however other factors may also affect the anticoagulant response. The degree of interaction is indicated by *. The following factors, alone or in combination, may be responsible for **INCREASED** INR response (potentiate anticoagulant effect of warfarin):

Acetaminophen*
Alcohol*+
Allopurinol*
Amiodarone*
Anabolic steroids**
Anesthetics* (inhalational)
Antibiotics*
Aspirin*
Black willow*
Diuretics*+
Disulfiram**
Feverfew(Tanacetum parthenium)*
Fluconazole*
Fluroquinolone antibiotics*
Garlic*
Ginkgo biloba**
Glucagon*
Hawthorn*
Herbal products*
Narcotics * (prolonged use)
NSAIDS**
Phenylbutazone
Phenytoin*
Propafenone*
Ranitidine*+
Red clover*
Quinidine*
Salicylates**
Sulfonamides*

Celebrex*
Chemotherapy
Cinnbar root
(Salvia multorrhizae)*
Chloral hydrate*+
Cimetidine*
Clofibrate**
Danazol**
Dan-shen
(Salvia miltiorrhiza)**
Dong quai*
Dextran*
Dextrothyroxine**
Ifosfamide/mesna*
Influenza virus vaccine*
Lovastatin*
Metronidazole**
Miconazole*
Monoamine oxidase inhibitors*
Moricizine*+
Nalidixic acid*
Tea berry*
Thyroid drugs*
Trimethoprim/ sulfamethoxazole**
Vitamin E*
Wintergreen*
Zafirlukast*

The following factors, alone or in combinations, may **DECREASE** INR (decrease anticoagulant effect of warfarin)

Adrenocortical steroids*
Alcohol*+
Alfalfa
(Medicago sativa)*
Aminoglutethimide*
Azathioprine*
Barbiturates**
Carbamazepine*
Chloral hydrate*+
Cholestyramine*
Diuretics*+
Ginseng*
Glutethimide**
Griseofulvin*
Mercaptopurine*
Moricizine*+
Nafcillin*
Oral contraceptives*
Propylthiouracil*
Ranitidine*+
Rifampin**
Sucralfate*
Vitamin C*
Vitamin K*

* Minimal risk: take necessary action to reduce the risk.
** Generally avoid combination; use combination only if benefit outweighs risk.
\+ Increased and decreased INR responses have been reported.

Conditions That
Potentiate Warfarin Effect

* Low vitamin K intake
* Poor nutritional state
* Low serum albumin
* Diarrhea, steatorrhea
* Liver disease
* Congestive heart failure
* Febrile states
* Hyperthyroidism

Conditions That
Attenuate Warfarin Effect

* High vitamin K intake
* Hypothyroidism
* Nephrotic syndrome
* Hyperlipidemia

Warfarin is contraindicated in:

Patients in whom the risk of hemorrhage outweighs the potential clinical benefit of therapy.

* Pregnancy (particularly first trimester)
* Alcoholism, drug abuse, high risk for non-compliance
* Unsupervised dementia/psychosis/ major depression
* Allergy to coumarin derivatives

IV. MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION *

High Risk	**Moderate Risk**	**Low Risk**
· 1 or more high risk features · 2 or more moderate risk features	· 1 moderate risk feature	
Treatment	**Treatment**	**Treatment**
Warfarin (target INR 2.5)	Warfarin (target INR 2.5)	No antithrombotic Rx
	or	
Aspirin (325 mg qd) (if warfarin contraindicated)	Aspirin (325 mg/qd)	Close follow-up

High Risk: Age >75 years, prior stroke/TIA or systemic embolism, history of hypertension, poor LV systolic function, rheumatic mitral valve disease, prosthetic heart valve.

Moderate Risk: Age 65 to 75 years, diabetes mellitus, coronary artery disease (with preserved LV function).

Low Risk: Age <65 years with no clinical or echocardiographic evidence of cardiovascular disease.

* Initial management (prior to achieving target INR with warfarin) may include heparin, particularly in high risk patients. If UFH is used target aPTT of 60 seconds is recommended (according to Venous Thromboembolism Dosing Algorithm).

Anticoagulation for Elective Cardioversion

- Warfarin (target INR 2.5) for 3 weeks before and 4 weeks after DC cardioversion for atrial fibrillation
- If TEE performed and does not reveal thrombus, anticoagulation with heparin followed by warfarin (target INR 2.5) for at least 4 weeks after cardioversion for atrial fibrillation.

V. PREVENTION OF VENOUS THROMBOEMBOLISM

Prophylaxis should be selected according to each patient's condition (level of risk) and continued until full ambulation is resumed.

Risk factors for Venous Thromboembolism

- Increasing Age (>40 years)
- Prolonged immobility (>3 days)
- Stroke

- Paralysis
- Malignancy
- Major surgery (particularly operations involving the chest, abdomen, pelvis or lower extremities)
- Trauma (particularly fractures of the pelvis, hip, or lower extremities)
- Obesity
- Congestive Heart Failure
- Pregnancy
- Estrogen use
- Inflammatory Bowel Disease
- Nephrotic Syndrome
- Severe lung disease
- Acute infections
- Previous venous thromboembolism
- Varicose veins
- Recent myocardial infarction
- Indwelling central venous catheters
- Known thrombophilia

Relative Contraindications for Inpatient Anticoagulant Prophylaxis

- Active, uncontrollable bleeding
- Cerebrovascular hemorrhage (not hx)
- Dissecting or cerebral aneurysm
- Bacterial endocarditis
- Active peptic ulcer disease, ulcerative GI lesions (not hx)
- Hypertension: severe, uncontrollable; malignant; hypertensive crisis
- Severe head trauma

- PT or PTT 1.5 x control at baseline
- Hemorrhagic blood dyscrasias
- Threatened abortion
- Severe thrombocytopenia (platelet count 30,000)
- Recent TURP (within several weeks)
- Eye, brain, or spinal cord surgery within the pat 48 hours
- For **warfarin**: pregnancy
- For **heparin** and LMWH: History of HIT

Venous Thromboembolism Prophylaxis

Condition	Recommended Prophylaxis
Acute Myocardial Infarction	• UFH 5000 Units SC q 8 h or IPC if anticoagulant therapy contraindicated
Ischemic Stroke	• UFH 5000 Units SC q 8 - 12 h or • Lovenox 30mg SC Q 12 h or • Elastic stocking plus IPC if anticoagulation contraindicated
Spinal Cord Injury	• Lovenox 30 mg SC q 12 h or • Elastic stocking plus IPC if anticoagulant therapy contraindicated
Trauma	• Lovenox 30 mg SC q 12 h or • Elastic stocking plus IPC if LMWH prophylaxis delayed or anticoagulation therapy contraindicated
Low Risk Surgical Patients (no risk factors)	• Early Ambulation
Moderate Risk Surgical Patients (>40 years, no other risk factors)	• Elastic stockings or • UFH 5000 Units SC q 8 h or • IPC

High Risk Surgical Patients (>40 years, ≤ 2 risk factors)	• UFH 5000 Units SC q 8 h or • Lovenox 30 mg SC q 12 h or • Lovenox 40 mg SC daily
Very High Risk Surgical Patients (>40 years, > 2 risk factors)	• Lovenox 30 mg SC q 12 h plus IPC or • Lovenox 40 mg SC daily plus IPC

Orthopedic Surgery

THA	• Lovenox 30 mg SC q 12 h or • Lovenox 40 mg SC daily or • Adjusted dose heparin or • Warfarin (INR 2.0-2.5)
TKA	• Lovenox 30 mg SC q 12 h or • Lovenox 40 mg SC daily or • Warfarin (INR 2.0-2.5)
General Medical Conditions with risk factors	• UFH 5000 Units SC q 8 h or • Lovenox 40 mg SC daily *The addition of IPC to anticoagulant therapy may offer further protection in high risk patients (3 or* more *concomitant risk factors)* *Lovenox may be preferable to UFH among patients with malignancy*

+ aPTT maintained at upper limit of normal; UFH, unfractionated heparin; IPC, intermittent pneumatic compression.

Contraindications for IPC boots include local ulcers, cellulitis, advanced arterial insufficiency.

Primary Prophylaxis in Children

Not recommended routinely for children with central venous lines, trauma, surgery or immobility given the absence of published data. Consider on a case-by-case basis.

VI. APPROACH TO SUSPECTED THROMBOPHILIA

Thrombophilic (hypercoagulable) states should be suspected with one or more of the following:

- Venous thromboembolism before age 55
- Arterial thromboembolism before age 45
- Recurrent spontaneous venous thrombosis
- Thrombosis in unusual site, e.g. mesenteric vein, cerebral sinus
- Family history of thromboembolism
- Relatives of patients with thrombophilic condition
- Skin necrosis, particularly if secondary to warfarin
- Unexplained neonatal thrombosis
- Recurrent fetal loss
- Unexplained prolongation of aPTT

First Line Laboratory Evaluation (for Venous Thrombosis)

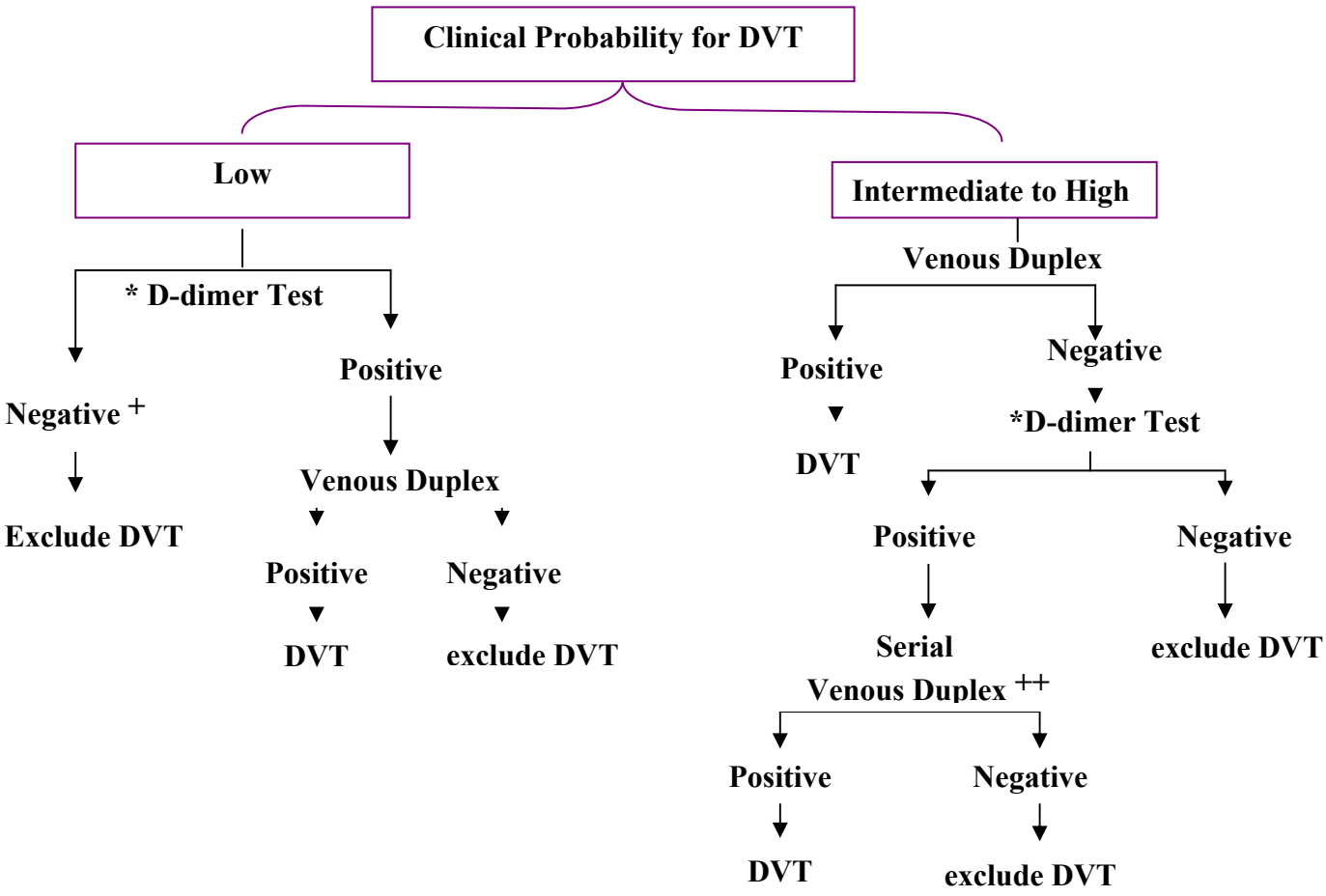
• Activated Protein C (APC) Resistance	Functional (screening)Test
• Factor V Leiden Mutation	Genetic Test (if APC resistance screening test abnormal)
• Prothrombin G20210A Mutation	Genetic Test
• Anticardiolipin antibodies (IgG, IgM)	Immunologic Test
• Lupus Anticoagulant	Functional Test (multi-step)
• Homocysteine	Direct Measurement
• Protein C Activity	Functional Test
• Protein S (Total/Free)	Direct Measurement
• Antithrombin Activity	Functional Test

First Line Laboratory Evaluation (for Arterial Thrombosis)

- Anticardiolipin Antibodies (IgG, IgM)
- Lupus Anticoagulant
- Homocysteine
- Activated Protein C resistance (followed by factor V Leiden genotype if abnormal) (in pediatric stroke)

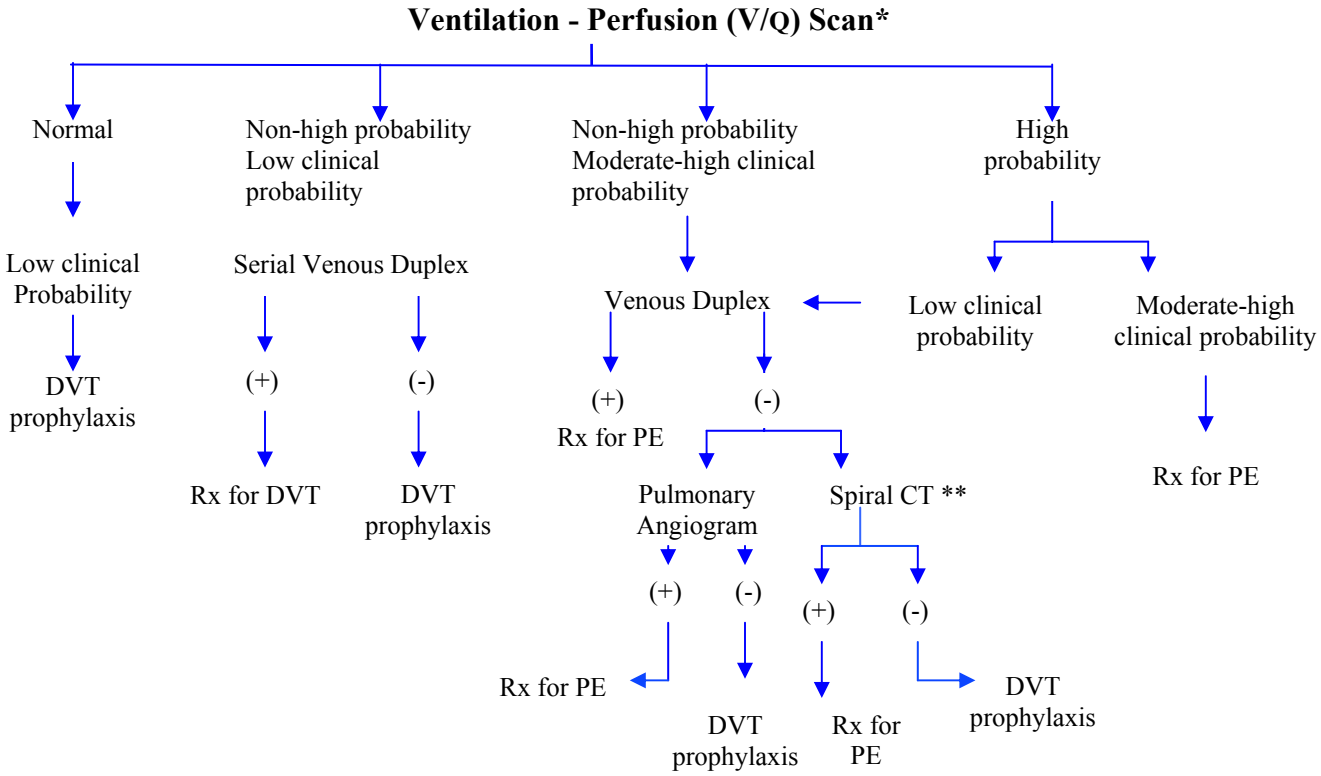
* The ideal time to perform a comprehensive evaluation is 6 months after the event (particularly for laboratory tests such as protein C, Protein S, and Antithrombin). Protein C and S levels are decreased by warfarin. The antithrombin level is decreased by heparin (UFH, LMWH).

VIIa. Approach to Suspected DVT



* D-dimer (DVT/PE D-dimer Assay)
\+ less than 400 ng/mL
++ every 5 days (or sooner if symptoms)

VIIb. APPROACH TO SUSPECTED PULMONARY EMBOLISM



* In patients with low clinical probability, a negative DVT/PE D-dimer assay may exclude PE

* * Spiral CT of chest with contrast (specify PE protocol).

The utilization of contrast CT and venography as a first line diagnostic strategy is under investigation and may, with time, replace V/Q scanning.

- Clinical probability (increased with):
  - Respiratory: dyspnea, pleuritic chest pain:
  - O_2 saturation <92% (on room air with suboptimal correction with supplemental O_2), hemoptysis, pleural-rub.
  - Risk Factors: Surgery <12 weeks, immobilization (for 3 or more days), prior DVT/PE, malignancy, trauma, post-partum, family history of DVT/PE, stroke, spinal cord injury, obesity.

VIII. ANTICOAGULATION IN CHILDREN

Systemic Heparin Administration and Adjustment for Pediatric Patients

Loading Dose: 75 Units/kg IV over 10 minutes (not to exceed 5000 Units)

Initial Maintenance Infusion Dose: <1yr 28 Units/kg/h, >1yr 20 Units/kg/h (not to exceed 1200 Units/h)

Maintenance Monitoring: Adjust heparin to maintain aPTT 60-85 seconds.
(assumes a corresponding anti-Xa level of 0.3 to 0.7 U/ml)

aPTT	Range Dosing/Monitoring
<50 sec	Rebolus with 50 Units/kg. Increase maintenance infusion 10%. Repeat aPTT in 4 hrs.
50-59 sec	Increase maintenance infusion 10%. Repeat aPTT in 4 hrs.
60-85 sec	No dosing change. Repeat aPTT daily.
86-95 sec	Decrease maintenance infusion 10%. Repeat aPTT in 4 hrs.
96-120 sec	Hold infusion x 30 minutes. Decrease maintenance infusion 10%. Repeat aPTT in 4 hrs.
>120 sec	Hold infusion x 60 minutes. Decrease maintenance infusion 15%. Repeat aPTT in 4 hrs.

Obtain blood for a aPTT 4 hours after administration of a heparin loading dose and 4 hours after every change in the infusion rate. When aPTT value is within target range, obtain CBC and aPTT daily.

LMWH Administration*

	< 2 Months	≥ 2 Months
Treatment	1.5 mg/kg q 12h **	1 mg/kg q 12h**
Prophylaxis	0.75 mg/kg q 12h	0.5 mg/kg q 12h

* Normal renal function
** Consider anti-Xa level monitoring

Pediatric Warfarin Dosing Protocol for Maintaining an INR of 2-3

DAY 1: If the baseline INR is <1.3, DOSE = 0.2 mg/kg (Maximum 10 mg).

INR	DAY 2 – 4	Day 5+: Maintenance
1.1 - 1.4	Repeat DAY 1 dose	Increase by 20% of dose
1.5 - 1.9	Give 50% of DAY 1 dose	Increase by 10% of dose
2 - 3	**Give 50% of DAY 1 dose**	**No change**
3.1 - 3.5	Give 25% of DAY 1 dose	Decrease by 10% of dose
>3.5	Hold until INR <3.5, then start at 50% less than the previous dose	Hold until INR <3.5, then start at 20% less than the previous dose

IX. ANTICOAGULATION AND NEURAXIAL ANESTHESIA AND ANALGESIA

The recommendations in this policy are based on the Consensus Statement published by the American Society of Regional Anesthesia on Neuraxial Anesthesia and Anticoagulation.

Oral Anticoagulants and Neuraxial Block

- Patients on chronic oral anticoagulation must have their therapy stopped and the prothrombin time (INR) measured prior to initiation of neuraxial block.
- The PT and INR should be checked before neuraxial block or epidural catheter removal if a dose of warfarin has been administered within the prior 24 hours.

Antiplatelet Drugs and Neuraxial Block

Antiplatelet drugs such as aspirin, and other NSAIDs, by themselves, pose no added risk for the development of spinal hematoma in patients having epidural or spinal anesthesia.

The potential risk of other antiplatelet agents such as ticlopidine (Ticlid®) and clopidogrel (Plavix®) have not been determined.

Heparin Preparations and Neuraxial Block

- There is no contraindication to neuraxial techniques during subcutaneous prophylaxis. It may be best to delay the heparin injection until after the block is placed whenever possible.
- There are currently insufficient data and experience to determine if the risk for neuraxial hematoma development is increased when combining neuraxial techniques with full anticoagulation in cardiac surgery.
- Combining neuraxial techniques and intraoperative anticoagulation with heparin for vascular surgery appears acceptable with the following cautions:
  - Avoid the technique in patients with coexisting coagulopathies.
  - Delay heparin administration for 1 hour after placement.
  - Remove the catheter 1 hour before any subsequent heparin administration or 2-4 hours after the last heparin dose.
  - Monitor the patient postoperatively to assure early detection of motor weakening and consider use of minimal concentration of local anesthetics to enhance the early detection of spinal hematoma.
- Prolonged heparin infusions may increase the risk of spinal hematoma formation, especially if combined with other anticoagulants or thrombolytics. Therefore, neuraxial blocks should be avoided in this clinical setting whenever possible. If a heparin infusion is begun with an epidural catheter in place, careful neurologic monitoring is warranted. Catheter removal should be delayed for 2-4 hours following therapy discontinuation and after determination of the coagulation status.

Low Molecular Weight Heparin and Neuraxial Block

- Patients with postoperative initiation of low molecular weight heparin (LMWH) thrombophylaxis may safely undergo single dose or continuous catheter techniques. It is recommended that indwelling catheters be removed 2 hours prior to initiation of LMWH thrombophylaxis.

- Antiplatelet or oral anticoagulant medications administered in combination with LMWH may increase the risk of spinal hematoma. Concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin or dextran represent an additional risk.
- The presence of blood during needle and catheter placement does not necessitate postponement of surgery; however, initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively.
- Neuraxial techniques are not the technique of choice for patients receiving preoperative LMWH. For patients receiving preoperative LMWH where a neuraxial technique is felt to offer a particular advantage, a single dose spinal technique is recommended. Needle placement should occur at least 12 hours after the LMWH dose. Patients receiving treatment doses of LMWH (eg. enoxaparin 1mg/kg BID) require longer delays (24 hours). Vigilance in monitoring the patients neurologic status postoperatively is required.

X. RECOMMENDED STRATEGIES FOR MANAGING PROLONGED INR IN PATIENTS RECEIVING WARFARIN

1. Above therapeutic but <5, patient is not bleeding, and rapid reversal is not indicated for reasons of surgical intervention: warfarin dose can be decreased or the dose can be omitted and therapy with warfarin can be re-instituted at a lower dose when the INR approaches the therapeutic range.

2. INR 5 – 9 and patient is not bleeding. The next one or two doses can be omitted and warfarin therapy can be resumed at a lower dose when the INR is in the desired range;

   OR

   Omit the next dose of warfarin and administer vitamin K 2.5 mg orally or 1 to 2.5 mg SC (use this strategy if the patient is at an increased risk for bleeding);

   OR

   If rapid reversal is necessary because the patient is undergoing an invasive procedure, vitamin K 2.5 to 5 mg can be administered orally or 2 to 4 mg SC. If the INR remains >5 after 24 hours of administering the first dose of vitamin K, then repeat vitamin K 1 to 2 mg.

3. INR >9 and the patient does not exhibit clinically significant bleeding: Vitamin K 2.5 to 5.0 mg orally or SC should be administered; a second dose can be given if the INR is not reduced within 6 to 12 hours of administering the first dose of Vitamin K.

4. If rapid reversal is necessary because of serious bleeding or INR >20 (calculated), vitamin K 5 to 10 mg slow IV infusion (<1 mg/min) plus fresh frozen plasma should be administered. Vitamin K administration can be repeated every 12 hours.

   In case of a life-threatening bleed or serious warfarin overdose, fresh frozen plasma (10-15 ml/kg) in addition to administration of vitamin K by slow IV infusion (<1mg/min) is indicated; repeat if necessary.

5. If warfarin therapy after the administration of vitamin K is warranted, unfractionated or LMWH can be given until the INR is within the therapeutic range on two consecutive days.

** Administration of vitamin K will result in warfarin resistance for two to three days (or longer depending on the total dose). Vitamin K is available as 5 mg tablets and injection (2 mg/ml, 10 mg/ml).

XI. ALTERNATIVE ANTICOAGULANTS*

Agent	Dosing
Lepirudin (Refludan®)+	0.4 mg/kg IV bolus (up to 110 kg) 0.15 mg/kg/hr to target (up to 110 kg) aPTT 60 – 85 seconds
Argatroban** (Argatroban®)	2 mcg/kg/min (not to exceed 10 mcg/kg/min) to target aPTT 60 – 85 seconds
Bivalirudin (Angiomax®)+	1 mg/kg bolus, 0.2 mg/kg/h (dosing during PCI includes a 2.5 mg/kg/h infusion for 4 hours following initial bolus following a continuous infusion for up to 20 hours)

\+ Dose adjustment required for patients with renal insufficiency.

* Requires clearance from Hematology Service or Anticoagulation Service for use. Most common indication is heparin-induced thrombocytopenia.

** Dose adjustment required for hepatic insufficiency.

XII. PLATELET GPIIb/IIIa RECEPTOR ANTAGONISTS

Agent	Dose	Duration of Platelet Inhibition	Indication(s)	Cost
Abciximab (ReoPro®)	0.25 mg/kg/IV bolus, 0.125 mcg/kg/min (max 10 mcg/min) for ≤ 12h	long	PCI Refractory	$1400.00 (12h infusion) ACS
Eptifibatide* (Integrilin®)	180 mcg/kg bolus,** 2 mcg/kg/min for 18-48h	short	PCI ACS	$325.00 per 24 hr
Tirofiban (Aggrastat®)* NONFORMULARY	0.4 mcg/kg/min x 30 min; 0.1 mcg/kg/min for 18-48 hrs	short	ACS	$350.00 per 24 hr

ACS = acute coronary syndromes; PCI = percutaneous coronary intervention

* Dose adjustment required for patients with renal insufficiency

** A second 180 mg/kg bolus (10 minutes following the first) is recommended during PCI

XIII. COMPARATIVE COSTS AT UMMHC FOR THROMBOEMBOLISM PROPHYLAXIS AND ANTITHROMBOTIC AGENTS

• LDH 5000 Units SC q8hr-q12hr	$ 0.58-0.87
• UFH 25,000 Units/day	$ 5.04
• warfarin 4 mg po/IV	$ 0.04/$3.13
• enoxaparin (Lovenox®)30 mg SC BID	$ 21.88
• enoxaparin (Lovenox®)80 mg sc q12h	$ 31.30 (for each dose)
• Pneumatic compression stockings	$ 25.00 (1x charge)
• EC ASA 325 mg	$ 0.02
• Lepirudin (Refludan®)	$ 833.41*
• Bivalirudin (Angiomax®)	$2,093.75*
• Clopidogrel (Plavix®)	$ 3.08
• ASA/Dipyridamole (Aggrenox®)	$ 1.39
• Argatroban	$ 748.80*

* 24-hour treatment for 70 kg patient

XIV. PATIENT SELECTION FOR HOME DVT MANAGEMENT

Minimal Requirement for Early Discharge or Outpatient Therapy with LMWH

A.

- Patient in stable condition with normal vital signs
- Low bleeding risk
- Absence of severe renal insufficiency (CrCl < 40 ml/min).
- System and follow-up in place for administration of LMWH and warfarin monitoring
- System in place for surveillance and treatment of recurrent VTE and bleeding complications

B. Anticoagulation *

- Lovenox® 1 mg/kg SC q 12h (max 300 mg per 24 hr)
- overlap with warfarin for 3 to 5 days

C. Baseline Laboratory Requirements

- CBC with platelet count
- Serum creatinine (calculate creatinine clearance)
- PT/INR

- Notify Anticoagulation Service of **all** patients being discharged on Lovenox therapy.

XV. ANTITHROMBOTIC THERAPY IN PERIPHERAL VASCULAR DISEASE

Condition	ASA	Clopidogrel	Pentoxifylline	Cilostazol	Aggrenox	Heparin
PVD (Asymptomatic)	+++	++	0	-	-	-
with Claudication	+++	++	0	++	-	-
Vascular Bypass	+++	++	0	0	-	Intraop
Acute Occlusion	+++	-	0	0	-	+++
CVD	+++	++	0	0	++	-

+++	Indicated
++	Indicated in most cases (data modest)
-	Unknown benefit
0	questionable benefit

PVD (peripheral vascular disease); CVD (cerebrovascular disease)

XVI. APPROACH TO HEMORRHAGIC COMPLICATIONS
Associated with Antithrombotic Therapy

Agent	Category	Mechanism of Action	Antidote	Available substrate for attenuating effects
Aspirin	Platelet Antagonist	Cycloxygenase inhibition	DDAVP	Platelet Transfusion
Clopidogrel	Platelet antagonist	ADP-Receptor inhibition	None	Platelet Transfusion
Ticlopidine	Platelet antagonist	ADP-Receptor inhibition	None	Platelet Transfusion
Abciximab	Platelet antagonist	GPIIb/IIIa receptor inhibition	None	Platelet Transfusion FFP, cryoprecipitate
Tirofiban	Platelet Antagonist	GPIIb/IIIa receptor inhibition	None	Cryoprecipitate FFP, Platelet transfusion
Eptifibatide	Platelet Antagonist	GPIIb/IIIa receptor inhibition	None	Cryoprecipitate FFP, Platelet transfusion
UFH	Anticoagulant	Thrombin inhibition (indirect)	Protamine	FFP
LMWH	Anticoagulant	Thrombin inhibition (indirect)	Protamine (60%)	? Factor VIIa (recombinant)
Lepirudin	Anticoagulant	Thrombin inhibition (direct)	None	FFP, Plasmapheresis
Argatroban	Anticoagulant	Thrombin inhibition (direct)	None	FFP, Plasmapheresis
Bivalirudin	Anticoagulant	Thrombin inhibition (direct)	None	FFP, Plasmapheresis
Warfarin	Anticoagulant	Clotting factor inhibitor	Vitamin K	FFP

UFH, Unfractionated heparin; LMWH, low-molecular-weight-heparin; FFP, fresh frozen plasma
DDAVP (Desmopressin)

XVII. ANCILLARY PHONE NUMBERS

Hematology (Coagulation) Lab	Univ. (508) 856-2863	Memorial (508) 334-6080
Pharmacy	Univ. (508) 856-2775	Memorial (508) 334-6356
Anticoagulation Clinic	Univ. (508) 856-2418	
Hematology Office	Univ. (508) 856-2113	Memorial (508) 334-6276
Thrombophilia Clinic	Univ. (508) 856-3453	
Home DVT Program	Univ. (508) 856-2418	

This guideline is **not** intended to represent the sole acceptable or best practice for all patients. After assessing the individual features of a specific case, the patient's physician is in the best position to decide on the most appropriate therapeutic strategy.