

Ronald Reagan UCLA Medical Center

Anticoagulant
Management Program
and Guidelines

2008

Anticoagulant Management Program and Guidelines

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Introduction

The use of anticoagulants for acute inpatients introduces challenges not only because these agents are known to have a narrow therapeutic range, but also because there are patient variables and potential drug–drug interactions that can complicate its management. This guideline was developed to provide the clinician with a standardized protocol for these patients who require anticoagulation. The Pharmacy and Therapeutic Committee along with other stakeholders at the Ronald Reagan UCLA Medical Center have reviewed and approved the use of these guidelines. The guidelines are based on recommendations from the 2008 ACCP Evidence Based Clinical Practice Guidelines 8th ed.

These Anticoagulation Management Guidelines should be used as a guide by all clinicians who are responsible for dosing and monitoring these anticoagulant agents. If the physician orders “Warfarin Dosing per Pharmacy”, the pharmacist shall also manage the warfarin therapy based on these standard guidelines.

Warfarin

I. Mechanism of Action

- a. Inhibits reduction of vitamin K epoxide, thereby limiting activation of vitamin K dependent clotting factors: II (prothrombin), VII, IX, X. *Antithrombotic effect primarily due to reduction in prothrombin.*
- b. Inhibits synthesis of anticoagulant proteins C and S (potential procoagulant effects).

II. Pharmacokinetics

- a. Warfarin is a racemic mixture of two active isomers, R and S. The S-isomer is approximately five times more potent than the R-isomer.
- b. Oral Administration
 - i. Absorption: rapid and complete
- c. Distribution: primarily intravascular, highly protein bound (>98%) primarily to albumin; only free drug is pharmacologically active.
- d. Half-life: 36-42 hours
- e. Time to steady state = approximately 10 days
Half-lives of Clotting Factors:
 - Factor II = 60 hrs
 - Factor VII = 6 hrs
 - Factor IX = 24 hrs
 - Factor X = 40 hrs

NOTE: Anticoagulation may be seen within 24 hours due to inhibition of Factor VII, but peak anticoagulant activity is delayed for 72-96 hours due to Factor II inhibition (2-3 days after 1st therapeutic INR)

- f. Metabolism: Hepatic microsomal enzymes to inactive metabolites
 - S-isomer is metabolized primarily by cytochrome P450 (CYP) 2C9
 - R-isomer is metabolized by CYP 1A2 and CYP 3A4

*Of note: Since S-isomer is much more potent than R-isomer, medications that inhibit or induce P450 2C9 lead to the most significant drug interactions.

 - Reduce dose with hepatic dysfunction and with hypermetabolic states (increased catabolism of vitamin-K dependent factors)
 - Not significantly affected by dialysis

III. Optimal Therapeutic INR Goals by Indication and Duration of Anticoagulation

Indication	Target INR (range)	Duration/Comments
Atrial Fibrillation (AF)/ Atrial Flutter Age <75 with no risk factors With 1 risk factor With 2 or more risk factors (risk factors: age>75; HTN, diabetes, CHF or LV dysfxn) With prior history of stroke/TIA/systemic embolism Following open heart surgery (in NSR) Pre-cardioversion (afib/aflutter > 48h) Post- cardioversion (in NSR)	None 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0)	Use Aspirin 81-325mg daily alone Chronic/ or use aspirin Chronic Chronic 4 weeks 3 weeks 4 weeks
Ischemic Stroke Non-cardioembolic stroke or TIA Cause of stroke or TIA: Afib/Cardiomyopathy With contraindications to warfarin	none 2.5 (2.0 – 3.0) none	Use antiplatelet therapy Chronic Use aspirin 81-325 mg daily
Myocardial Infarction (MI) Following myocardial infarction Following myocardial infarction in high risk patients (High risk: ant. MI, sign. HF, intracardiac thrombus, or hx of thromboembolic event)	2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0)	Up to 4 years (with aspirin) Or INR 3-4 if alone. At least 3 months + aspirin 81 mg daily
Thromboembolism (DVT/PE) ** with concurrent UFH/LMWH/Fondaparinux for at least 5 days and until INR > 2 for ≥24h Treatment/prevention of recurrence Transient risk factors Unprovoked/first event - proximal DVT or PE - distal DVT Unprovoked/ second event With malignancy Chronic thromboembolic pulmonary hypertension Cerebral venous sinus thrombosis Spontaneous superficial vein thrombosis	2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0)	3 months Chronic 3 months (consider chronic) Chronic Chronic Chronic Up to 12 months 4 weeks
Valvular Disease Mitral valve prolapse With TIAs or ischemic stroke With recurrent TIA despite aspirin therapy Mitral annular calcification with AF Rheumatic mitral valve disease With AF, hx systemic emb, LA thrombus, LA >55mm s/p thromboembolic event despite anticoagulation	None 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0)	Use aspirin 81 mg daily Chronic Chronic Chronic Chronic
Valve Replacement – Bioprosthetic Aortic Mitral With LA thrombus With prior hx systemic embolism With additional risk factors for thromboembolism (AF, hypercoagulable condition, low EF)	None 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0)	Aspirin 81 mg daily 3 months, followed w/ Aspirin 81 mg Until resolution At least 3 months Chronic (+/- aspirin 81 mg daily)
Valve Replacement – Mechanical Aortic Bileaflet in NSR w/ nl LA size Medtronic Hall tilting disk in NSR w/ nl LA size Following prosthetic valve thrombosis Mitral Bileaflet or tilting disk Following prosthetic valve thrombosis Caged ball or caged disk (aortic or mitral) With additional risk factors for thromboembolism (AF, LA enlargement, hypercoagulable condition, low EF)	2.5 (2.0 – 3.0) 2.5 (2.0 – 3.0) 3.5 (3.0 – 4.0) 2.5 (2.0 – 3.0) 4.0 (3.5 – 4.5) 3.0 (2.5 – 3.5) 3.0 (2.5 – 3.5)	Chronic Chronic Chronic (+ aspirin 81 mg daily) Chronic Chronic (+ aspirin 81 mg daily) Chronic Chronic (+/- aspirin 81 mg if low bleeding risk)

Reference: Antithrombotic and Thrombolytic Therapy: ACCP Evidence Based Clinical Practice Guidelines, 8th ed. 2008

IV. Dosing

The warfarin dose that is required is variable and dependent on a number of patient-specific and environmental factors. Evaluate patient to determine warfarin sensitivity* and use guidelines below for initial dosing.

a. Initial Warfarin Dosing Guidelines

Day	INR	Warfarin High Sensitivity*	Warfarin Moderate Sensitivity*	Warfarin Low Sensitivity*
Day 1	Baseline INR	2 – 5 mg	5 mg	7.5 mg
Day 2	< 1.5	2 – 5 mg	5 mg	5 – 7.5 mg
	1.5 – 1.9	2 mg	2.5 mg	2.5 – 5 mg
	2 – 2.5	1 – 2 mg	1- 2.5 mg	1 -2.5 mg
	>2.5	none	None	None
Continue below for all patients				
Day 3	< 1.5	5 – 10 mg		
	1.5 – 1.9	2.5 mg – 5 mg		
	2 – 2.5	0 – 2.5 mg		
	2.6 - 3	0 – 2.5 mg		
	>3	NONE		
Day 4	< 1.5	10 mg		
	1.5 – 1.9	5 – 7.5 mg		
	2 – 3	2.5 – 5 mg		
	>3	0 – 2.5 mg		
Day 5	< 1.5	10 mg		
	1.5 – 1.9	5 – 7.5 mg		
	2 – 3	2.5 – 5 mg		
	>3	0 – 2.5 mg		
Day 6	< 1.5	7.5 – 12.5 mg		
	1.5 – 1.9	5 – 10 mg		
	2 – 3	2.5 – 5 mg		
	>3	0 – 2.5 mg		
Day 7	Make adjustment based on total weekly dose (increase or decrease) by 5-20% depending on current INR and target INR			
*High warfarin sensitivity		*Moderate warfarin sensitivity		*Low warfarin sensitivity
Baseline INR > 1.5 Age > 65 Significant hepatic disease Decompensated CHF Malnourished Malabsorption syndrome/ chronic diarrhea Cancer Hypoalbuminemia (<2) Thyrotoxicosis Genetic polymorphism of CYP450 2C9		Baseline INR 1.2 – 1.5 Age 50-65 Concurrent CYP-450 enzyme inhibitor		Baseline INR < 1.2 Age < 50 and no other risk factors

b. Maintenance Warfarin Dosing Guidelines

The following chart should be used as a guideline to adjust therapy for patients already receiving warfarin.

For Target INR 2.0 – 3.0	
INR < 2.0	Increase Weekly dose by 10-15%
INR 2.0 – 3.0	No Change
INR 3.1 – 3.5	Decrease Weekly dose by 5-15%
INR 3.6 – 4.0	Hold 0 -1 dose; then decrease weekly dose by 10-15%
INR >4.0	Hold dose until INR therapeutic; assess bleeding risk, +/- Vitamin K administration; decrease weekly dose by 10-20% - See chart*

* Guidelines on Vitamin K₁ Administration for Reversal of Warfarin

For Target INR 2.5 – 3.5	
INR < 2.5	Increase Weekly dose by 10-15%
INR 2.5 – 3.5	No Change
INR 3.6 – 4.0	Decrease Weekly dose by 5-15%
INR 4.1 – 5.0	Hold 0 -1 dose; then decrease weekly dose by 10-15%
INR > 5.0	Hold dose until INR therapeutic; assess bleeding risk, +/- Vitamin K administration;; decrease weekly dose by 10-20% - See chart*

* Guidelines on Vitamin K₁ Administration for Reversal of Warfarin

V. Monitoring

- a. Baseline INR is recommended prior to initiating warfarin therapy to assess sensitivity.
- b. An INR within the last 48 hours is acceptable as a current baseline INR.
- c. Patients shall be carefully monitored with each dose and adjustments in dose are required based on INR values.
- d. With initial dosing, the INR will usually increase within 24- 36 hours.
- e. Daily INR should be obtained in hospitalized patients being initiated on warfarin until INR is within the desired therapeutic range, then INR can be evaluated twice weekly.
- f. Potential drug-drug and drug-disease state interactions shall be monitored and assessed with warfarin dose adjustments as needed.

VI. Potential Warfarin Drug Interactions

Clinically Significant Interactions with Warfarin by Drug Class and Level of Causation

Potential of Warfarin Effects

Level of Causation	Anti-Infectives	Cardiovascular Drugs	Analgesics, Anti-inflammatory, Immunologics	CNS Drugs	GI Drugs and Food	Herbal Supplements	Other Drugs
I Highly probable	Ciprofloxacin Cotrimoxazole Erythromycin Fluconazole Isoniazid (600mg/d) Metronidazole Miconazole oral gel Miconazole vaginal suppositories Voriconazole	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfinpyrazone (biphasic with later inhibition)	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Entacapone Sertraline	Cimetidine Fish Oil Mango Omeprazole	Boldo-fenugreek Quilinggao	Anabolic steroids Zileuton
II Probable	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Fluvastatin Quinidine Ropinirole Simvastatin	Acetaminophen Acetylsalicylic acid Celecoxib Dextropropoxyphene Interferon Tramadol	Disulfiram Choral Hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)	Grapefruit juice	Danshen Dongquai Lycium barbarum L PC-SPES	Fluorouracil Gemcitabine Levamisole/fluorouracil Paclitaxel Tamoxifen Tolterodine
III Possible	Amoxicillin Amoxicillin/tranexamic rinse Chloramphenicol Gatifloxacin Miconazole topical gel Nalidixic acid Norfloxacin Ofloxacin Saquinavir Terbinafine	Amiodarone-induced toxicosis Disopyramide Gemfibrozil Metolazone	Indomethacin Leflunomide Propoxyphene Rofecoxib Sulindac Tolmetin Topical Salicylates	Felbamate	Cranberry juice Orlistat	Danshen/methylsalicylate	Acarbose CMF (cyclophosphamide/methotrexate/fluorouracil) Curbicin Danazol Ifosfamide Trastuzumab

Reference: Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005; 165; 1095-1106.

Inhibition of Warfarin Effects

I Highly probable	Griseofulvin Nafcillin Ribavirin Rifampin	Cholestyramine	Mesalamine	Barbiturates Carbamazepine	High Vitamin K Content foods/ enteral feeds Avocado (large amounts)		Mercaptopurine
II Probable	Dicloxacillin Ritonavir	Bosentan	Azathioprine	Chlordiazepoxide	Soy milk Sucralfate	Ginseng	Chelation therapy Influenza vaccine MVI supplement Raloxifene HCL
III Possible	Terbinafine	Telmisartan	Sulfasalazine				Cyclosporine Etreinate Ubidecarenone

Reference: Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Inter Med. 2005; 165; 1095-106.

VII. Guidelines on Vitamin K Administration for Reversal of Warfarin

- a. The peak effect of vitamin K on reversing warfarin anticoagulation occurs after 24 hours although initial effects will be noted within 6-12 hours of vitamin K dose.
- b. FFP replaces depleted clotting factors and therefore begins to work immediately with a full effect in 6 hours.
- c. If rapid reversal of an elevated INR is needed for emergent invasive procedures (i.e. surgery), administration of vitamin K and/or FFP may be required. INR should be rechecked in 12 hours. If still not at goal INR, repeat doses of Vitamin K and FFP may be required.
- d. Consider the patient’s future anticoagulation needs when planning the reversal of warfarin anticoagulation.

Guidelines on Vitamin K₁ Administration for Reversal of Warfarin

<u>INR</u>	<u>Action/Recommendation</u>
INR above target, but <5 with no significant bleeding	Continue with lower warfarin dose, OR omit a dose and resume therapy at a lower dose
5-9 (no significant bleeding)	Omit 1 or 2 doses, monitor INR and resume therapy at a lower dose when INR therapeutic
If patient at risk⁺ for bleeding	Omit a dose and administer vitamin K 1.25 – 2.5mg po
5-9 (rapid reversal required for urgent surgery*)	Administer vitamin K 2.5 mg po (INR to normalize in 24hrs); if INR still elevated, administer additional vitamin K 1.25 – 2.5 mg., consider giving FFP If NPO, may give Vitamin K 1mg IVPB over 30mins
>9 (no significant bleeding)	Hold warfarin therapy AND administer vitamin K 5-10 mg PO, administer additional vitamin K in 24-48 hours if necessary; resume therapy at a lower dose when INR therapeutic
Serious bleeding at any INR value	Hold warfarin therapy AND administer vitamin K 10 mg by slow IV infusion over 30mins. diluted in D5W or NS; may repeat every 12 hours if needed. (Supplement with FFP, rFactor VIIa, Prothrombin Complex Concentrate, depending on urgency)
Life threatening bleeding	Hold warfarin therapy AND supplement with FFP, rFactor VIIa, Prothrombin Complex Concentrate AND administer vitamin K 10 mg by slow IV infusion (1mg/min) diluted in D5W or NS.
+ Risk factors for bleeding: history of GI bleed, hypertension, cerebrovascular disease, ischemic stroke, congestive heart failure, renal insufficiency, concurrent aspirin, age >75, and recent major surgery	
*Note if INR >1.5 but < 5 requiring reversal for urgent surgery, administer vitamin K 1.25 mg – 2.5mg PO, or for patients NPO, 1mg IV over 30mins.	

VIII. Warfarin Per Pharmacy Protocol

- a. Pharmacists who have been trained for warfarin per pharmacy and have passed the appropriate competency tests may assume the responsibility of dosing and monitoring warfarin therapy if the physician orders “warfarin per pharmacy”.
- b. Baseline and daily INRs shall be ordered and monitored by the pharmacists.
- c. Pharmacists utilize the Pharmacy and Therapeutics Committee approved “Anticoagulation Guidelines” for daily warfarin dosing.
- d. Doses shall be adjusted per RRUCLA standard warfarin dosing guidelines to achieve the target INR goal.
- e. Pharmacists shall notify the physician if any of the following occur:
 - (1) the INR > 5
 - (2) for any clinically significant signs of thrombosis or bleeding are being reported
 - (3) if they need clarification of the patient’s clinical status.
- f. Orders shall be written on the Anticoagulant Order form which will indicate the current INR, the target INR and the order for the warfarin dose.

IX. Quality Assurance and Performance Improvement

Clinical patient outcomes shall be measured and documented to ensure the safe and effective use of anticoagulants under this anticoagulant management protocol. The following indicators shall be reviewed and tracked at least quarterly. Data shall be reported to the Medication Event and P&T Committee quarterly.

- a. Average time to therapeutic INRs
- b. % of INRs > 5
- c. Adverse Events
- d. Documentation of Patient Education

Heparin – Unfractionated (UFH)

I. Mechanism of Action

- a. Binds to and causes conformational change in anti-thrombin III thereby accelerating inactivation of activated clotting factors IIa (thrombin), IXa, Xa, XIa and XIIa, subsequently halting coagulation.
- b. Low dose predominantly affects factor Xa (prophylaxis)
- c. Full dose predominantly affects factor IIa (thrombin) (established clot)

II. Pharmacokinetics

- a. Unfractionated Heparin (IV or SQ):
Absorption (SQ): completely absorbed (at treatment doses); peak concentrations at 2-4 hrs
- b. Distribution: primarily intravascular
- c. Half-life: 90 minutes (range 0.5-2 hours)
- d. Mean time to steady state = 6 hours (3-5 half-lives)
 - i. Increases with larger doses (non-linear)
 - ii. Decreases with PE, massive thrombus, or new clot (increased clearance)
- e. Metabolism: degraded by reticuloendothelial system
- f. No dose adjustment necessary for hepatic

III. Treatment (initial dosing)

- a. Initial doses based on using actual body weight
- b. Use weight-based heparin protocol for dosing adjustments and monitoring guidelines. Titrate dose to goal aPTT
- c. Indications
 - i. Venous Thromboembolus (VTE)/Pulmonary embolism (PE)
 1. UFH 80 units/kg (bolus), not to exceed 10,000 units
 2. UFH 18 units/kg/hr (maintenance), max initial infusion rate 2,000 units/hr, titrate to goal aPTT.
 - ii. Acute Coronary Syndrome (ACS)
 1. UFH 70 units/kg (bolus), not to exceed 5,000 units
 2. UFH 15 units/kg/hr infusion (maintenance), max initial infusion rate of 1,000 units/hr, and titrate per protocol

IV. Monitoring

- a. Activated partial thromboplastin time (aPTT)
- b. Collect 6 hours after initiation or rate change of heparin infusion, adjust per protocol
- c. CBC with platelets daily

V. Use of Protamine – Reversal of heparin

- a. Binds to heparin forming a stable complex devoid of anticoagulant activity.
- b. Reserved for patients with clinically significant bleeding episodes while receiving heparin therapy. The drug is not indicated in cases of minor bleeding as withdrawal of heparin will generally result in correction of bleeding within several hours.
- c. Use with supportive care of the patient and possible transfusion therapy.
- d. Dosing - 1 mg of protamine will reverse approximately 100 units of heparin
- e. Initial doses rarely exceed 50 mg
- f. Infusion related adverse effects including hypotension and bradycardia can be minimized by extending the infusion time (10 minutes)

- g. Follow-up aPTT should be drawn 15 min post-dose to assess response

Enoxaparin (LMWH)

I. Mechanism of Action

- a. Low molecular weight heparin (LMWH) derived from porcine heparin with an average molecular weight of 4500 daltons. Both heparin and LMWH binds to and causes a conformational change in anti-thrombin III thereby accelerating inactivation of activated clotting factors. Due to its smaller size, enoxaparin preferentially inhibits factor Xa, with an anti-Xa:anti-IIa ratio of 3.6:1.

II. Pharmacokinetics

- a. Absorption (SQ): 90% absorbed by subcutaneous route
- b. Peak anti-factor Xa activity 3-5 hours after injection
- c. Distribution: Similar to intravascular volume
- d. Elimination is primarily renal
- e. Half-Life (based on anti-factor Xa activity): 6 hours (multiple doses)
- f. Prolonged in patients with renal insufficiency due to decreased clearance

III. Dosing

- a. Prophylaxis: 40 mg SQ daily
 - i. General Surgery / Medicine patients
 - ii. Orthopedic hip replacement
- b. Prophylaxis: 30 mg SQ bid
 - i. Orthopedic Trauma patients
 - ii. Orthopedic knee replacement
- c. Treatment Dosing: 1 mg/kg SQ bid* (Actual body weight)
 - i. DVT/PE treatment
 - ii. Unstable angina and NSTEMI
 - iii. Bridge therapy to warfarin
- d. Treatment Dosing: 1.5 mg/kg SQ daily
 - i. DVT/PE treatment
 - ii. Cerebral Ischemia/TIA
- e. Renal dysfunction (Clcr<30ml/min)
 - i. Prophylaxis dosing: Enoxaparin 30mg SQ daily
 - ii. Treatment dosing: Enoxaparin 1mg/kg SQ daily

NOTE: * 1 mg/kg SQ BID is preferred in following patients: proximal DVT, obese patients, hypercoagulable state, patients with increased bleeding risk

IV. Monitoring

- a. Serum Creatinine– as dose adjustments required with renal insufficiency. Use in patients with severe renal dysfunction will prolong elimination half-life and may increase bleeding risk. UFH is recommended for patients on dialysis or renal impairment patients with high risk for bleeding.
- b. Platelet counts – daily CBC with platelets while on enoxaparin
- c. Anti-factor Xa levels (LMWH level) not generally necessary, however may be considered in special populations such as obese or renal insufficiency (defined as Clcr < 30 ml/min) patients. Limited data are available that correlate a specific anti-factor Xa range to antithrombotic activity or bleeding risk.
 - i. Collect peak concentration 3-5 hours after the subcutaneous dose

- ii. Enoxaparin should be at steady state to account for accumulation, typically prior to third dose
- iii. Therapeutic Range (peak concentration): 0.6-1 Unit/ml (1 mg/kg dosing)

V. Reversal of Anticoagulant Effect

- a. Protamine may be used although it will only partially (approximately 60%) reverse the effects of enoxaparin.

Fondaparinux

- I. Fondaparinux is the synthetic anticoagulant that selectively inhibits factor Xa activity.
- II. It is well absorbed and peak plasma concentrations are achieved within 2-3 hours.
- III. Elimination half-life is 17-21 hours, which allows for once daily dosing. Note: anticoagulant effect can persist from 2 to 4 days after discontinuation of the drug
- IV. Fondaparinux is contraindicated in patient's with severe renal dysfunction (Clcr <30ml/min).

- V. **Dosing** is based on indication and patient weight.

Prophylaxis: Fondaparinux 2.5 mg SC q24

Treatment of VTE:

- a. Fondaparinux 5 mg SC q24h if patient weight <50kg
- b. Fondaparinux 7.5 mg SC q24h if patient weight 50 – 100kg
- c. Fondaparinux 10 mg SC q24h if patient weight >100kg

Unstable angina/Non Q wave MI/ Cerebral Ischemia: Fondaparinux 2.5 mg SC q24h

VI. Monitoring

- a. Routine monitoring of coagulation parameters is not required due to its predictable dose-response.
- b. Fondaparinux does not affect aPTT, or prothrombin time (PT).
- c. In high risk circumstances, monitor Factor Xa activity
- d. Renal function should be documented at baseline and then closely monitored during the course of therapy. If CrCl is less than 30ml/min, fondaparinux should be stopped.
- e. Monitor for signs and symptoms of bleeding. CBC should be monitored periodically to screen for occult bleeding.

VII. Reversal of Anticoagulant Effect

- a. Fondaparinux is not reversed by protamine and at this time no specific antidote is available to reverse its antithrombotic activity.
- b. Fresh Frozen plasma and factor concentrates should be given in the event of a major bleed.

Perioperative Management of Antithrombotic Therapy

Management of anticoagulation before and after invasive procedures requires careful, patient-specific evaluation of patient's risk for bleeding associated with the surgical procedure as well as the risk of thromboembolism associated with the discontinuation of the anticoagulation. The following chart provides a guideline for managing the anticoagulation therapy during the perioperative period.

Thromboembolic Risk	Bridge Therapy <i>For patients who require temporary interruption of warfarin therapy before surgery or a procedure and require normalization of INR for surgery/procedure.</i>
High	<p><u>Pre-Procedure</u></p> <ol style="list-style-type: none"> 1. Stop warfarin 5 days pre-op 2. Consider vitamin K 1 -2 mg orally if INR is still elevated (i.e. ≥ 1.5) 1-2 days prior to surgery 3. Start <u>full dose enoxaparin</u>¹ 36 hours after last warfarin dose (≥ 2 days pre-op) (or Unfractionated heparin) 4. Stop enoxaparin 12 – 24 hrs prior to procedure (if on heparin can stop UFH 4-6 hrs prior to procedure). <p><u>Post – Procedure:</u></p> <ol style="list-style-type: none"> 5. Restart warfarin evening of procedure or post-op day 1 and when there is adequate hemostasis (based on physician/surgeon recommendations) 6. Consider Procedural Bleeding Risk <ol style="list-style-type: none"> a. High bleeding risk –start <u>full dose enoxaparin</u>¹ 24 hours after procedure b. Low bleeding risk– start <u>full dose enoxaparin</u>¹ 12-24hrs after procedure
Moderate	<p><u>Pre-Procedure</u></p> <ol style="list-style-type: none"> 1. Stop warfarin 5 days pre-op 2. Consider vitamin K 1 -2 mg orally if INR is still elevated (i.e. ≥ 1.5) 1-2 days prior to surgery 3. Start <u>low dose enoxaparin</u>² SC 36 hours after last warfarin dose (≥ 2 days pre-op) 4. Stop enoxaparin 12 – 24 hours prior to procedure <p><u>Post – Procedure</u></p> <ol style="list-style-type: none"> 5. Restart warfarin evening of procedure or post-op day 1 and when there is adequate hemostasis (based on physician/surgeon recommendations) 6. Consider Procedural Bleeding Risk <ol style="list-style-type: none"> a. High bleeding risk – no bridging OR start <u>low dose enoxaparin</u>² 12-24h after procedure b. Low bleeding risk– start <u>low dose enoxaparin</u>² SC 12- 24hrs after procedure (consider <u>full dose enoxaparin</u>¹)
Low	<p><u>Pre-Procedure</u></p> <ol style="list-style-type: none"> 1. Stop warfarin 5 days pre-op AND bridging not necessary (however, MD may consider low dose enoxaparin SC 36 hours after last warfarin dose) <p><u>Post-Procedure</u></p> <ol style="list-style-type: none"> 2. Restart warfarin evening of procedure or post-op day 1 and when there is adequate hemostasis (based on physician/surgeon recommendations) 3. Consider low dose enoxaparin as a bridge
<p>¹ Full dose enoxaparin: 1 mg/kg SC BID or 1.5 mg/kg SC daily</p> <p>² Low dose enoxaparin: 30mg SC BID or 40mg SC daily</p>	

Reference: ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2008; 133; (suppl).

Patient and Staff Education Materials