CLEVELAND CLINIC ANTICOAGULATION MANAGEMENT PROGRAM (C-CAMP)

Table of Contents

List of Tables and Figures

I. Executive Summary

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a common, lethal disease that is the third most common cause of hospital-related death and the most common preventable cause of hospital associated-death in the United States.

The National Quality Forum (NQF) in response to National Patient Safety Goal 03.05.01 has mandated that each organization implement a formalized anticoagulation management program to reduce the likelihood of patient harm associated with the use of anticoagulation therapy.

Every hospitalized patient over the age of 18 must be evaluated for their risk of developing VTE on admission and regularly thereafter during their hospital stay. The NQF also recommends that appropriate prophylaxis (mechanical or pharmacological) be given to each patient unless contraindicated. Exceptions include patients with behavior disorders, obstetrical patients and those receiving comfort measures only. The choice of anticoagulants can be limited by a contraindication to anticoagulation including but not limited to: active bleeding, and thrombocytopenia defined as a platelet count under 50,000 mm^3. Certain patient specific characteristic will dictate the medication one can choose. Patients with a history of heparin-induced thrombocytopenia (HIT) should not receive heparin or low molecular weight heparin and patients with impaired renal function will either have a contraindication to medications or need to have doses adjusted based on creatinine clearance. For example a patient with a creatinine clearance < 30 mL/min would not be a candidate for fondaparinux, but the LMWHs may be used if the dose is adjusted. Also, patients on dialysis should not receive fondaparinux, LMWHs, dabigatran or rivaroxaban. Other patient characteristics that deserve attention include pregnancy (do not use warfarin) or if active or a history of warfarin-induced skin necrosis (do not use warfarin unless consulting Hematology or Vascular Medicine first). Contraindications for the use of dabigatran include an allergy to the agent or for patients with a creatinine clearance less than 15 mL/min. Contraindications for the use of rivaroxaban include an allergy to this agent, a creatinine clearance of less than 15 mL/min if the indication is for stroke prevention in atrial fibrillation or < 30 ml/min when used for patients after hip or knee replacement surgery. Contraindications for the use of intermittent pneumatic compression or graduated compression stockings may include acute cellulitis, acute DVT of the affected limb or severe peripheral arterial disease (PAD) of the affected limb.

The National Quality Forum also recommends that each organization develop a standard of care based on best evidence or consensus practice for all inpatient and/or outpatients receiving anticoagulation therapy. The current anticoagulant and thrombolytic agents available at Cleveland Clinic include: unfractionated heparin, the low molecular weight heparin preparations including: enoxaparin/Lovenox®, dalteparin/Fragmin® and tinzaparin/Innohep® (note that dalteparin/Fragmin® and tinzaparin/Innohep® are not currently on formulary at all Cleveland Clinic Health System Pharmacies but may be obtained through the non-formulary request process); the factor Xa inhibitors fondaparinux/Arixtra® and rivaroxaban/Xarelto®; the oral vitamin K antagonist warfarin/Coumadin® and the direct thrombin inhibitors lepirudin/Refludan®, argatroban/Argatroban®, bivalirudin/Angiomax®, dabigatran/Pradaxa®), desirudin/Iprivask® (note that desirudin/Iprivask® is not currently on formulary at all Cleveland Clinic Health System Pharmacies) the thrombolytic agents: alteplase/Activase® or tenecteplase TNKase.®

Table 1. Available Anticoagulants at Cleveland Clinic Hospitals

Anticoagulant	Method of administration	Availability at CCHS Pharmacies
Heparin	IV or SC	Yes
LMWH		
a) Enoxaparin/Lovenox®	SC	Yes
b) Dalteparin/Fragmin®*	SC	No
c) Tinzaparin/Innohep®*	SC	No
Factor Xa inhibitors		
a) Fondaparinux/Arixtra®	SC	Yes
b) Rivaroxaban/Xarelto®	PO	Yes
c) Apixaban/Eliquis®*	PO	Yes
Warfarin/Coumadin®	Oral or IV	Yes
Direct thrombin inhibitors		
a) Argatroban/Argatroban®	IV	Yes
b) Bivalirudin/Angiomax®	IV	Yes
c) Dabigatran/Pradaxa®	PO	Yes
d) Desirudin/Iprivask®*	SC	No
Thrombolytic Agents		
a) Alteplase/Activase®	IV	Yes
b) Tenecteplase/TNKase®	IV	Yes

*May be available on request to pharmacy as medication is a non-CCHS formulary product

The following information outlines the Cleveland Clinic Anticoagulation Management Program also known as C-CAMP. All Cleveland Clinic licensed independent practitioners (LIPs) are expected to use this program if questions arise when prescribing mechanical devices, anticoagulation or thrombolytic therapy for patients requiring: prophylaxis or treatment of VTE, treatment or use during acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), atrial fibrillation, prosthetic heart valves or acute ischemic stroke. In addition this guideline reviews treatment options for select adverse events of anticoagulation including: bleeding and heparin-induced thrombocytopenia (HIT). Additional recommendations for perioperative management and outpatient treatment of individuals requiring anticoagulants are also included. Please note, however, this program is not meant to replace the LIP's clinical judgment. For more detailed information the clinician should consult Vascular Medicine, Hematology or Clinical Pharmacy or review the American College of Chest Physicians guidelines (CHEST); 2008; 133: Number 6 (SUPPL) pages 67S-968S and/or the American College Chest Physicians guidelines (CHEST); 2012; 141:Number 2 (SUPPL) pages 1S-801S; doi:10.1378/Chest.1412S3

II. Venous Thromboembolism Risk Assessment and Prophylaxis

The National Quality Forum as part of the National Patient Safety Goal 03.05.01, mandates that all adult patients 18 years of age and older (exceptions include patients with behavior disorders, obstetrical patients and those receiving comfort measures only) shall receive venous thromboembolism (VTE) risk assessment and prophylaxis orders upon admission, or for a change in their level of care.

Oversight and Responsibility

The Licensed Independent Practitioner (LIP) is responsible for the VTE risk assessment and prophylaxis order.

The VTE Task force will update the risk assessment and order set as needed to reflect current best evidence.

Procedure:

1) Identify all adult patients 18 years of age and older (exceptions include patients with behavior disorders, obstetrical patients and those receiving comfort measures only) and perform a VTE risk assessment and prescribe prophylaxis orders at admission.
2) An additional VTE risk assessment and prophylaxis assessment is to be performed with any change in the patients level of care.
3) Document and sign the VTE prophylaxis order.
4) Enter any hospital acquired VTE event(s) in the Safety Event Reporting System (SERS).

III. Recommended Prophylaxis Options for the Prevention of Venous Thromboembolism - General

Table 2. Summary of Venous Thromboembolism Prophylaxis Options

AGENT	INDICATION(S)	DOSING OPTIONS	MONITORING
A) Unfractionated Heparin (UFH)	• Medical patients • Major surgical patients • Major gynecologic surgery • Major, open urologic procedures • Thoracic surgery • Spinal surgery	• 5,000 units of UFH subcutaneously every 8 or every 12 hours	• Obtain baseline CBC. • Monitor platelet count at least every 2-3 days from day 4 to 14 or until UFH is stopped to prevent or identify patients at risk of HIT. • If the patient has received UFH or LMWH within the previous 100 days, monitor the platelet count within 24 hours of starting therapy and then every 2-3 days from day 4 to 14 or until UFH is stopped to prevent or identify patients at risk of HIT.
B) Low molecular weight heparin (LMWH) enoxaparin/ Lovenox® (Check with pharmacy for additional information on alternative LMWH preparations)	• Medical patients • Major general surgery • Major gynecologic surgery • Major, open urologic procedures • Orthopedic surgery (knee or hip arthroplasty) • Thoracic surgery • Spinal surgery	• 40 mg of enoxaparin/Lovenox® subcutaneously every 24 hours for medical and surgical and THR orthopedic surgical patients OR • 30 mg of enoxaparin/Lovenox® subcutaneously every 12 hours for orthopedic TKR surgical patients • 30 mg of enoxaparin/Lovenox® subcutaneously every 24 hours if creatinine clearance <30 mL/min • Contraindicated if the patient is on dialysis. • Orthopedic surgical patients should have prophylaxis for 10 – 14 days minimum and consider extended prophylaxis up to 35 days. IPC devices should also be used during hospital stay • For patients at high risk for VTE undergoing abdominal or pelvic surgery for cancer, recommend extended-duration, postoperative, pharmacologic prophylaxis (28 days)	• Obtain baseline CBC and serum creatinine and consider renal function when using LMWH due to its renal metabolism. An alternative agent or reduced dose should be used if the creatinine clearance is <30 mL/min and LMWH is contraindicated if the patient is on dialysis. • Monitor platelet count at least every 2-3 days from day 4 to day 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in postoperative patients and medical/obstetrical patients who first receive UFH. • If patient has received UFH or LMWH within the previous 100 days, monitor platelet count within 24 hours of starting LMWH therapy and then every 2-3 days day from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT.
C) Fondaparinux/Arixtra®	• Hip fracture surgery) • Orthopedic surgery (knee or hip) • General or abdominal pelvic surgery • Medical Patients	• 2.5 mg of fondaparinux/Arixtra® subcutaneously every 24 hours. • Avoid use in patient with creatinine clearance < 30 ml/min • Orthopedic surgical patients should have prophylaxis for 10 – 14 days minimum and consider extended prophylaxis up to 35 days	• Obtain baseline CBC and serum creatinine and consider renal function when using fondaparinux due to its renal metabolism. An alternative agent should be use if the creatinine clearance is < 30 mL/min or if the patient is on dialysis**.**
D) Rivaroxaban/Xarelto®	• Prophylaxis for hip and knee arthroplasty	• 10 mg orally once daily of rivaroxaban/Xarelto® beginning 6 to 10 hours after surgery. • TKR surgical patients should have prophylaxis for 12 – 14 days minimum and consider extended prophylaxis up to 35 days • THR surgical patients should have extended prophylaxis up to 35 days.	• Obtain baseline renal function studies and avoid if the creatinine clearance is <30 mL/min or the patient is on hemodialysis • No monitoring required

E) Desirudin Iprivask®	• Prophylaxis for hip replacement surgery	• 15 mg twice daily subcutaneously	• Obtain baseline CBC and serum creatinine. Check aPTT • Adjustments are necessary in patients with renal impairment • This agent is **NON-FORMULARY** at the Cleveland Clinic
F) Warfarin/ Coumadin®	• Hip or knee arthroplasty	• Warfarin/Coumadin® oral doses are: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg. • 10 mg dose is dye-free	• Obtain baseline CBC, and PT/INR • Target INR 2- 3
G) Aspirin	• Orthopedic surgery use only. The prophylaxis indication is for knee or hip arthroplasty only to be used in conjunction with the use of intermittent pneumatic compression devices	• 325 mg PO BID	• No monitoring required
H) Intermittent pneumatic compression	• Medical and surgical patients with a contraindication to pharmacological therapy or in combination with pharmacological therapy in select high risk patients		• Avoid placing on affected leg if patient has an acute DVT, active cellulitis or severe peripheral arterial disease
I) Graduated compression stockings	• Medical and surgical patients with a contraindication to pharmacological therapy or in combination with pharmacological therapy in select high risk patients		• Avoid if patient has active cellulitis
J) Early Ambulation	• Surgical and medical patients <40 years of age hospitalized less than 24 hours with no additional risk factors for VTE		

This table is intended as a guideline and does not replace the physician's clinical judgment/ decision making. For more specific information related to medical or surgical patients not specified above, please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) and/or consult Vascular Medicine, Hematology, Internal Medicine or Clinical Pharmacy for assistance or refer to CHEST 2008; 133:381S-453S "Prevention of Venous Thromboembolism" Guidelines. Or The American College Chest Physicians Guidelines ***CHEST February 2012 141:2 suppl :195S-325s***.

IIIa. Recommended prophylaxis options for the prevention of Venous Thromboembolism based on Risk Factor Assessment

Table 3. Recommended Prophylaxis Options for Prevention of VTE based on Risk Factor Assessment

LEVEL OF RISK	***VTE PROPHYLAXIS OPTIONS***
Low risk: *Minor surgery in mobile patients* *Medical patients who are fully mobile without additional VTE risk factors*	*No specific prophylaxis options* ***Early ambulation***
Moderate risk: *Most general surgery, open gynecologic or urologic surgery patients* *Acutely ill medical patients at increased risk for thrombosis*	LMWH (enoxaparin/Lovenox®) 40 mg* subcutaneously every 24 hours **or** UFH 5,000 units subcutaneously every 12 hours LMWH*, UFH q 8 or q12 hours or fondaparinux*
Moderate risk surgical or medical patients: plus high bleeding risk	Intermittent pneumatic compression or graduated compression stockings
High risk: Non-orthopedic surgical patients Abdominal or pelvic surgery for cancer Hip or knee arthroplasty, hip fracture surgery (HFS), major trauma Critically ill medical patients	LMWH (enoxaparin/Lovenox®) 40 mg* subcutaneously every 24 hours or UFH 5,000 units subcutaneously every 8 to 12 hours plus IPC or elastic stockings Extended LWMH* prophylaxis for 4 weeks or IPC if bleeding risk prohibitive. Initiate LMWH* as soon as bleeding risk diminishes LMWH (enoxaparin/Lovenox®) 30 mg* subcutaneously every 12 hours (TKR, THR) or 40 mg every 24 hours (THR) or fondaparinux/Arixtra2.5 mg subcutaneously every 24 hours ** or® Rivaroxaban/Xarelto® 10 mg orally every 24 hours ** or Oral vitamin K antagonist warfarin/Coumadin® maintain an INR 2-3 or Aspirin plus IPC Prophylaxis should be maintained for 10 – 14 days and consider up to 35 days. LMWH* or UFH
High risk surgical or medical patients: plus high bleeding risk	Intermittent pneumatic compression or graduated compression stockings until bleeding risk diminishes, than consider the use of LMWH* or UFH or fondaparinux**

**Doses need to be adjusted for renal insufficiency*

*** Avoid use in patients with creatinine clearance < 30 ml/min*

This table is intended as a guideline and does not replace the physician's clinical judgment/ decision making. For more specific information related to medical or surgical patients not specified above, please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) and/or consult Vascular Medicine, Hematology, Internal Medicine or Clinical Pharmacy for assistance or refer to CHEST 2008; 133:381S-453S "Prevention of Venous Thromboembolism" Guidelines American College Chest Physicians guidelines ***CHEST February 2012 141:2 suppl :195S-325s; doi:10.1378/Chest.1412S3***

a) Unfractionated Heparin (UFH)

1) Unfractionated heparin for prophylaxis of VTE should be administered at 5,000 units every 12 hours subcutaneously for medical and surgical patients and continued until the risk of VTE has diminished. Medical oncology patients, general surgery patients with multiple risk factors for VTE who are thought to be at particularly high risk, and patients undergoing a surgical procedure for cancer should receive 5,000 units of subcutaneous UFH every 8 hours. Unfractionated heparin is generally **not** advised for orthopedic patients undergoing total hip or total knee replacement or for hip fracture patients.
2) Unfractionated heparin is contraindicated in patients with active bleeding, a heparin allergy or a history of heparin-induced thrombocytopenia (HIT). Adverse reactions to UFH are rare but may include hypersensitivity, fever, urticaria, rhinitis, hyperkalemia, hypoaldosteronism and an elevation in transaminases (ALT/AST).
3) Obtain baseline laboratory studies including a complete blood count prior to initiation. Pharmacists verifying or entering orders for UFH will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory work has not been obtained or ordered, the pharmacist will place an order to obtain these studies.
4) Platelet count monitoring is advised while the patient is on prophylactic doses of UFH. Monitor every 2-3 days from day 4 through day 14 or until UFH is stopped to identify or prevent HIT. If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of initiating therapy and then every 2-3 days from day 4 to 14 or until UFH is discontinued to avoid rapid-onset HIT. Notify Vascular Medicine or Hematology if the patient's platelet count drops 50% from its baseline or under 150,000 mm^3, or if new thrombosis or skin necrosis develops while on UFH.

b) Low Molecular Weight Heparin (LMWH) Enoxaparin (Lovenox®)

1) Low Molecular Weight Heparin for prophylaxis of VTE should be administered as 40 mg daily of enoxaparin/Lovenox® subcutaneously for medical and general surgical patients (including major gynecological surgery and major or open urological surgical procedures) and continued until the risk of VTE has diminished. Extended use (up to 28 days) has also been suggested for select high risk general surgery

patients (those that have undergone major abdominal or pelvic cancer surgery or had previous VTE). Extended use of LMWH (up to 35 days) may be appropriate in patients undergoing total hip or knee replacement or hip fracture surgery.

2) Enoxaparin/Lovenox® is given at 30 mg every 12 hours for total hip and total knee replacement surgery with the first dose administered 12 to 24 hours after surgery or ½ of this dose (15 mg) given 4 to 6 hours following surgery and then increased to 30 mg of enoxaparin/Lovenox® the next day. Alternatively, a dose of 40 mg daily of enoxaparin/Lovenox® may be used for prophylaxis in total hip replacement surgery.

3) Dalteparin/Fragmin® and tinzaparin/Innohep® are LMWH preparations not currently available at all Cleveland Clinic Health System formularies but may be available on special request. Recommend consulting Pharmacy for additional information on these agents.

4) Low molecular weight heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions may include but are not limited to: fever, nausea, elevation in the transaminases (ALT/AST), hematoma at the injection site or easy bruising, hyperkalemia and hypoaldosteronism.

5) Baseline laboratory studies must be obtained including a complete blood count and serum creatinine. Calculation of the creatinine clearance should also be done. Pharmacists verifying or entering orders for enoxaparin/Lovenox® will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline lab work has not been obtained or ordered the pharmacist will place an order to obtain the baseline laboratory studies.

6) The dose of enoxaparin/Lovenox® (and other LMWHs) should be adjusted downward for patients with renal insufficiency (creatinine clearance <30 mL/min). Low molecular weight heparins are contraindicated in patients on dialysis. Refer to table 2.

7) Monitor the platelet count every every 2-3 days from day 4 through day 14 or until the LMWH is stopped. Monitoring platelet count is necessary to identify patients who may develop HIT. If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of initiating LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is discontinued to avoid rapid-onset HIT. Notify Vascular Medicine or Hematology if the patient's platelet count drops 50% from its baseline or under 150,000 mm^3, or if new thrombosis or skin necrosis develops while on LMWH.

c) Fondaparinux/Arixtra®

1) Fondaparinux is recommended for prophylaxis in hip fracture patients undergoing surgery, and has approval for prevention of VTE for total hip and knee replacement, and major abdominal surgical patients. It is also recommended by the American College of Chest Physicians' for prophylaxis in medical patients, general surgical, major gynecological and major or open urological surgical patients.
2) Fondaparinux/Arixtra® prophylaxis is contraindicated if there is an allergy to fondaparinux or active bleeding and if the patient weighs ≤ 50 kg. It is contraindicated if the creatinine clearance is < 30 mL/min or if the patient is on dialysis and only used with caution in the elderly patient.
3) Adverse reactions include but are not limited to: fever, nausea, bleeding, and anemia.
4) Baseline laboratory studies must be obtained and include a complete blood count and serum creatinine. Calculation of the creatinine clearance should also be done. Pharmacists verifying or entering orders for fondaparinux/Arixtra® will check that baseline laboratory values have been obtained or ordered. Laboratories obtained in the previous 48 hours may be considered baseline. If baseline laboratory studies have not been obtained or ordered, the pharmacist will place an order to obtain these studies.

d) Rivaroxaban/Xarelto®

1) Rivaroxaban/Xarelto® is recommended for prophylaxis of VTE in the setting of elective hip or knee arthroplasty. The recommended dose is 10 mg daily given orally. Rivaroxaban should be started 6 to 10 hours after surgery once hemostasis is achieved. The duration of therapy for TKR is 12 -14 days minimum and up to 35 days and for THR rivaroxaban should be continued for up to 35 days following surgery.
2) Prior to initiation of rivaroxaban, laboratories should include a serum creatinine and complete blood count.
3) Contraindications include bleeding or severe hypersensitivity reaction to rivaroxaban. Avoid use with P-glycoprotein and strong CYP3A4 inhibitor such as :ketoconazole, ritonavir, and conivaptan and concomitant use with other anticoagulants and NSAIDs/aspirin, clopidogrel, prasugrel and ticagrelor as these may cause an increased bleeding risk. Use with erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone and felodipine may increase bleeding risk and rivaroxaban's use is recommended only if the potential benefit justifies the risk. Also, avoid use with carbamazepine, phenytoin, rifampin, St. John's wort or consider increasing the

dose of rivaroxaban if they must be co-administered. Avoid use with moderate hepatic impairment (Childs-Pugh classes B and C) and in patients with a creatinine clearance less than 30 mL/min. If the creatinine clearance is between 30 to 50 mL/min monitoring is recommended. Its use in pregnancy and lactation should be avoided.

4) No monitoring is required as the prothrombin time and INR are not reliable. There is some evidence that an anti-factor Xa assay that uses rivaroxaban containing plasma calibrators may provide the optimal method for determining plasma rivaroxaban concentrations. As of this writing this lab is unavailable at the Cleveland Clinic.
5) There is a black box warning for its use with spinal or epidural catheters. Because of a risk for an epidural or spinal hematoma, the catheter should not be removed for at least 18 hours after the last rivaroxaban dose. The next dose should not be given for at least 6 hours after the catheter is removed

e) Desirudin/Iprivask®

1) Desirudin/Iprivask® is recommended for prophylaxis of VTE in patients undergoing hip replacement surgery. It is not currently available on the Cleveland Clinic Health System formulary at the main campus but is FDA approved for this indication. Consult pharmacy for availability.

f) Warfarin/Coumadin®

1) Warfarin/Coumadin® is recommended for prophylaxis of VTE in the setting of elective hip or knee arthroplasty.
2) Contraindications to warfarin/Coumadin® may include but are not limited to an allergy to warfarin, active bleeding (gastrointestinal or other), hypersensitivity, during pregnancy or in patients of childbearing potential not using contraception, a history of a major bleeding disorder, recent major surgery, trauma or stroke, or a history of heparin-induced thrombocytopenia (HIT) during the acute event until the platelet count and patient are recovering. Other contraindications include a history of noncompliance, language barriers or unsuitable home environment or patient at risk of falling.

3) Prior to initiation of warfarin/Coumadin® baseline laboratories must be obtained and include a complete blood count and the prothrombin time/international normalized ratio (PT/INR). Pharmacists verifying or entering orders for warfarin/Coumadin® will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory studies have not been obtained or ordered the pharmacist will place an order to obtain these tests.

4) An INR target of between 2 and 3 is recommended.

g) Aspirin

1) Aspirin is restricted for use by the Orthopedics Department for prophylaxis of VTE in patients undergoing elective hip or knee arthroplasty only for those patients who are considered at increased risk of bleeding from the anticoagulants LMWH, fondaparinux or rivaroxaban. It must be used in conjunction with intermittent pneumatic compression stockings at a dose of 325 mg PO BID. It is not recommended for VTE prophylaxis for other surgical or medical patients. Contraindications for it use include an allergy to the medication or active bleeding. In most cases conversion to pharmacologic prophylaxis is advised once hemostasis is achieved.

h) Intermittent Pneumatic Compression Devices (IPCD'S)

1) Intermittent pneumatic compression devices are indicated if there is a contraindication to pharmacological therapy (high risk of bleeding) or as an adjunct to anticoagulant agents. Intermittent pneumatic compression is contraindicated (on the affected limb) if the patient has an acute DVT, cellulitis or severe peripheral arterial disease. Intermittent pneumatic compression devices must be properly fit for each patient and must be worn continuously for optimal benefit (except during bathing and ambulation unless they are ambulatory friendly). An effort should be made to achieve 18-20 hours of daily compliance. For patients undergoing major orthopedic surgery (THA, TKA, HFS) only portable, battery-powered IPCD's capable of recording/reporting wear time are recommended.

I) Graduated Compression Stockings

Graduated compression stockings are indicated if there is a contraindication to pharmacological therapy (high risk of bleeding) or as an adjunct to anticoagulant agents. Compression stockings are contraindicated if a patient has cellulitis or severe peripheral arterial disease. Graduated compression stockings must be properly fit for each patient and it must be stressed that for optimal benefit they be worn continuously (except during bathing). In most patients conversion to pharmacological prophylaxis is advised once hemostasis is achieved.

j) Early Ambulation

Early ambulation is acceptable as the sole means of prophylaxis for selected surgical and medical patients (less than 40 years of age) who are hospitalized less than 24 hours who do not have additional risk factors for VTE and/or considered at low risk for thrombosis.

IV. Diagnosis of Venous Thromboembolism

Patients with suspected VTE should have appropriate testing to confirm the diagnosis. Acceptable methods include the use of clinical decision rules (CDR's) to establish a pretest probability for DVT and PE. There are a number of available clinical decision rules and the tables and figures below are the ones most commonly used. In addition, all patients should have additional testing which may include any of the following: d-dimer (to help exclude VTE due to its high negative predictive value) and venous ultrasound of the lower and/or upper extremity to confirm acute DVT or CTPA of the pulmonary arteries or ventilation perfusion lung scan to confirm or exclude acute PE. A CT of the abdomen and pelvis and/or MRI/MRV of the abdomen, pelvis or head may be indicated for venous thrombosis suspected in other anatomical locations (mesenteric, hepatic, renal, splenic, or cerebral portal veins).

Table 4. Clinical Decision Rule (CDR) to Help Determine the Pretest Probability for DVT

Clinical Features	**Score**
1) Active cancer (treatment on-going or w/in the previous 6 months or palliative treatment)	1
2) Paralysis, paresis or recent plaster immobilization of the lower extremities	1
3) Recently bedridden for more than 3 days or major surgery within 12 weeks requiring general or regional anesthesia	1
4) Local tenderness along the distribution of the deep venous system	1
5) Entire leg swelling	1
6) Calf swelling (more than 3 cms greater than the asymptomatic side) measured 10 cm below the tibial tuberosity	1
7) Pitting edema confined to the symptomatic leg	1
8) Collateral superficial veins (non varicose)	1
9) Previously documented DVT	1
10) Alternative diagnosis at least as likely	-2

Clinical probability:

High: (3 or more points)

Intermediate or Moderate: (1 to 2 points)

Low: (0 points)

JAMA 2006; 295(2) 199-207.

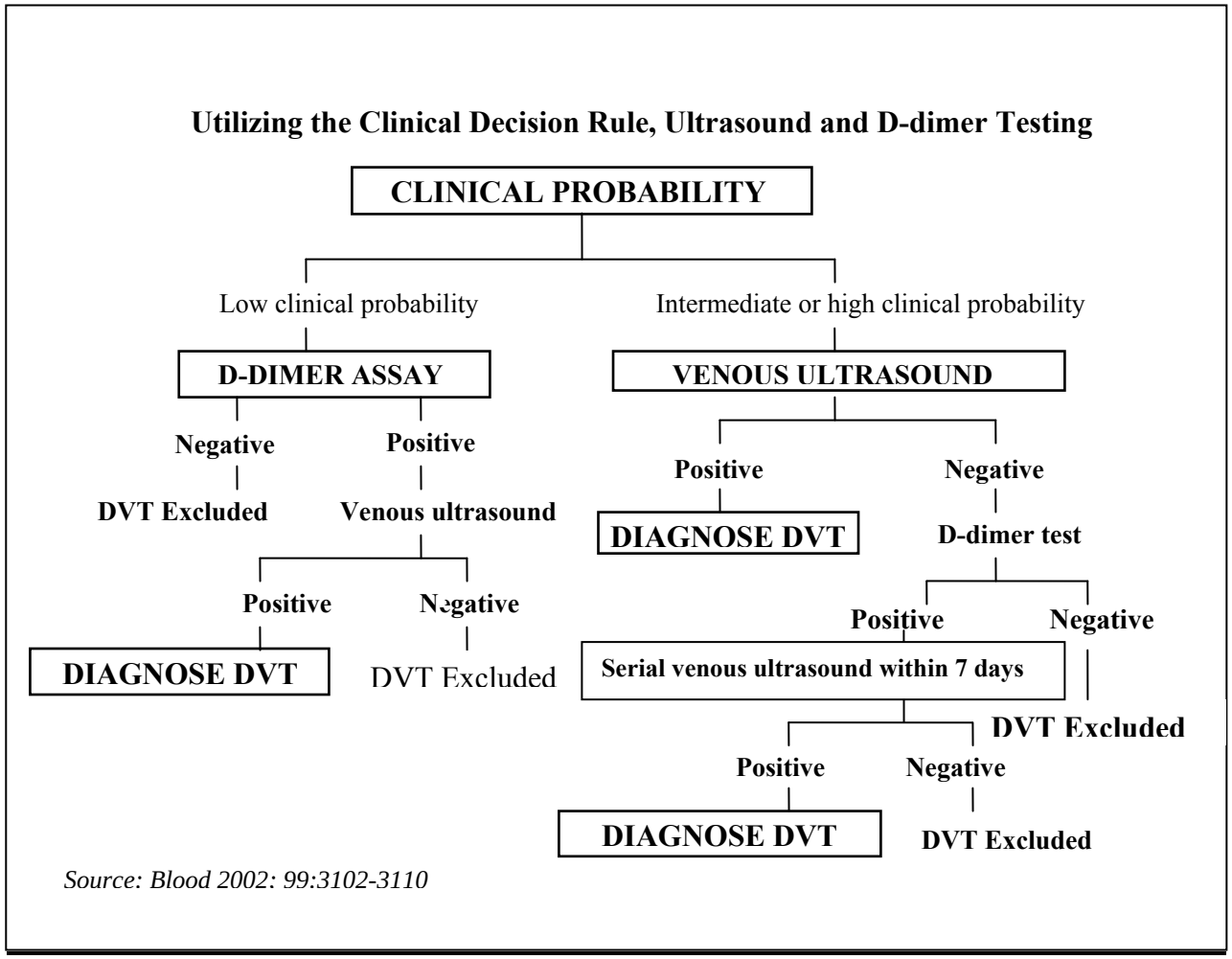

Figure 1. Algorithm for Diagnosing DVT

Table 5. Clinical Decision Rule (CDR) to Determine the Pretest Probability of PE

Clinical Decision	**Score**
1. Clinical signs and symptoms of DVT	3
2. PE as likely as or more likely than an alternative diagnosis	3
3. Heart rate > 100/minute	1.5
4. Immobilization (>3d) or surgery in the previous week	1.5
5. Previous pulmonary embolism or deep vein thrombosis	1.5
6. Hemoptysis	1
7. Cancer (receiving treatment or treated in the last 6 months or palliative treatment)	1

Clinical probability of PE unlikely (4 or less points)

Clinical probability of PE likely (more than 4 points)

Adapted from Thromb Haemost 2007; 195-201.

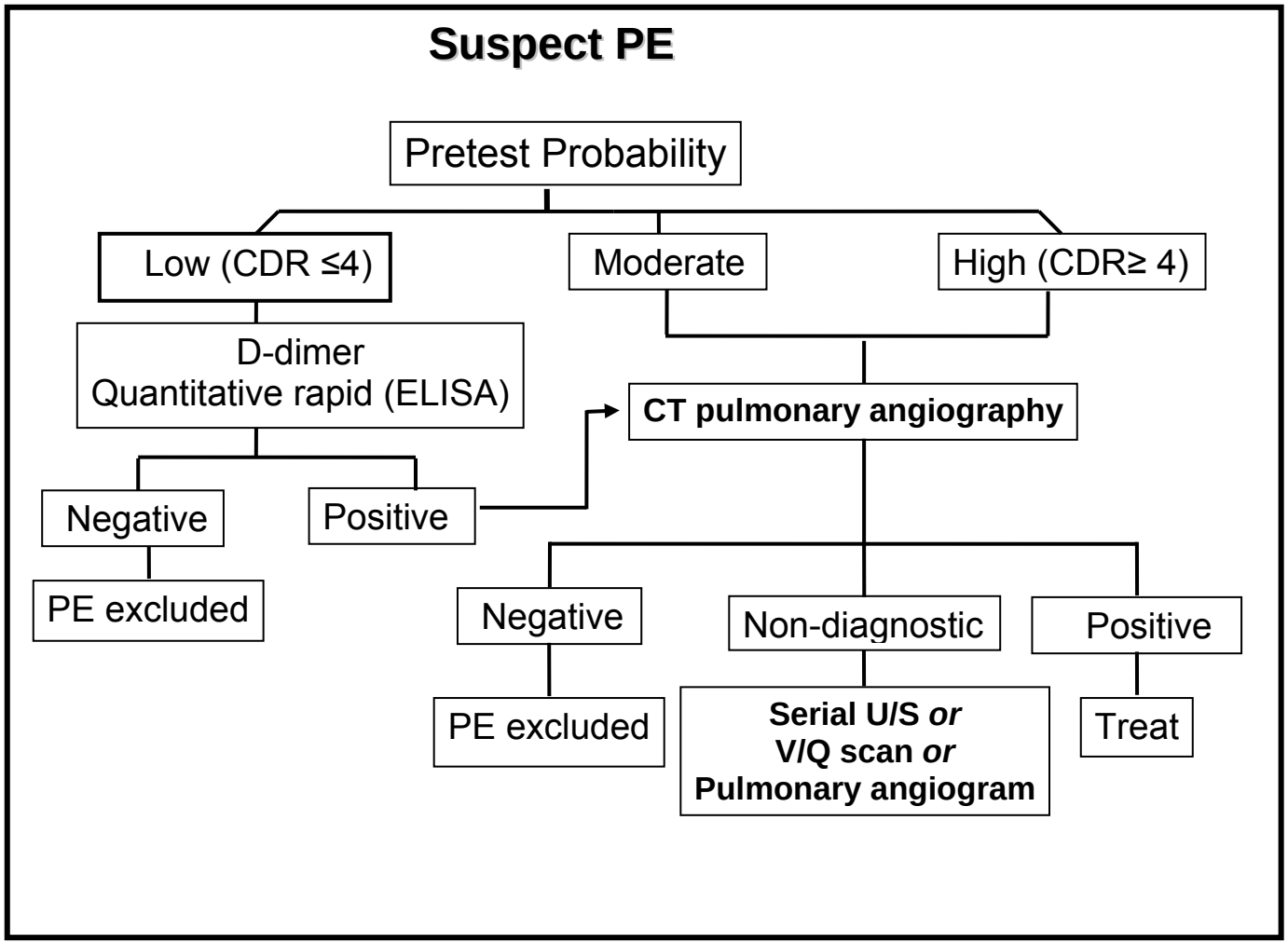

Figure 2. Algorithm for Diagnosing PE- NEMJ 2006; 254: 2317

V. Treatment of Venous Thromboembolism

Patients must be advised of the risks and benefits of Anticoagulation.

*Table 6: Summary Table of Pharmaceutical Agents, Dosing Guidelines for Treatment of VTE**

Agent	Required Baseline labs	Recommended Dosing Guidelines	Monitoring guidelines
A) Intravenous or subcutaneous Heparin (UFH)	CBC, aPTT PT/INR if patient to be converted to Warfarin	• 80 units/kg of UFH is given by an intravenous bolus followed by 18 units/kg/ hour of UFH infusion **OR** **Alternative regimens:** • 5,000 units intravenous bolus of UFH followed by 17,500 units subcutaneously every 12 hours **OR** • 333 units/kg bolus of UFH given subcutaneously followed by 250 units/kg every 12 hours	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • FOLLOW STANDARD UFH NOMOGRAM (see table 6) • Therapeutic levels of anticoagulation for UFH include an aPTT target of 60 to 85 seconds or an anti-Xa level of 0.3 to 0.7 units/mL. The target aPTT is subject to change by the laboratory and dependent on reagents used. If changes required, clinicians will be notified of new targets by the laboratory. • Monitor platelet count at least every 2-3 days from day 4 to 14 or until UFH is stopped to prevent or identify patients at risk of HIT. • If the patient has received UFH within the previous 100 days, monitor platelet count within 24 hours of starting therapy and then every 2-3 days from day 4 to 14 or until UFH is stopped to prevent or identify patients at risk of HIT • In outpatients receiving UFH, informed consent should include HIT and its complications.
B) LMWH (Enoxaparin/ Lovenox® See below for additional information on other LMWH preparations	CBC, creatinine PT/INR if patient to be converted to Warfarin	• Enoxaparin/Lovenox® is given as 1 mg/kg every 12 hr subcutaneously or 1.5 mg/kg subcutaneously every 24 hrs for patients with normal renal function up to a maximum dose of 150 mg total every 12 hr. • Recommend contacting Clinical Pharmacy or Vascular Medicine for recommendations if higher doses needed. • If the creatinine clearance is <30 mL/min, administer 1 mg/kg subcutaneously of enoxaparin/Lovenox® daily. • LMWH is contraindicated if the patient is on dialysis.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • Monitoring is not necessary unless patient has renal insufficiency, is obese, pregnant or a pediatric patient. • If indicated, use an anti-Xa level to LMWH as standard. Target levels (0.5 to 1 IU/mL) for every 12 hour dosing and >1 IU/mL for once daily administration. • Levels should be drawn 4 hours after subcutaneous dose (when applicable). • If the patient has received UFH within the previous 100 days, obtain a baseline platelet count and monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT • Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. • In medical patients on LMWH, platelet count monitoring is not recommended.
C) Fondaparinux (Arixtra®)	CBC, creatinine PT/INR if patient to be converted to Warfarin	• Contraindicated if the creatinine clearance is <30 mL/min or the patient is on dialysis • Dosing for fondaparinux/Arixtra® is: - 5 mg subcutaneously daily for patients <50 kg; - 7.5 mg subcutaneously daily for patients 50 to 100 kg; - 10 mg subcutaneously daily for patients >100 kg	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • No monitoring necessary

*Continued Table 6: Summary Table of Pharmaceutical Agents, Dosing Guidelines for Treatment of VTE**

D) Alteplase Activase® (Tissue plasminogen) activator or (rt-PA)	CBC, PT/INR, aPTT, fibrinogen	• Consult Vascular Medicine and/or the Medical Intensive Care Unit Service if thrombolytic therapy felt to be indicated for acute pulmonary embolism. • For PE: 100 mg of alteplase/Activase® is given intravenously administered per peripheral vein over 2 hours (indications: hemodynamic instability and at the discretion of the physician if there is significant right heart failure) • Consult Vascular Medicine or Vascular Surgery or Interventional Cardiology or Interventional Radiology for assistance if thrombolytic therapy felt to be indicated for an acute DVT. • For acute iliofemoral or extensive proximal DVT with symptoms (swelling/pain) alteplase/Activase® is administered via catheter directed therapy and only considered for patients at low risk for bleeding	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • Intensive care unit is recommended for patients receiving thrombolytic therapy.
E) Rivaroxaban Xalerto®	CBC, BMP	• Contraindicated when creatinine clearance is less than 30 ml/min or if the patient is on dialysis • Initial dose: 15 mg two times daily for 21 days • Maintenance dose: 20 mg daily	• Obtain baseline renal function studies and avoid if the creatinine clearance is <30 mL/min or the patient is on hemodialysis • No monitoring required
F) Warfarin (Coumadin®)	CBC, PT/INR	• Oral doses of warfarin/Coumadin® include the following sizes: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg. The 10 mg dose is dye-free.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • Should be used in conjunction with UFH, LMWH or fondaparinux (Arixtra®) • PT/INR (Target 2-3)
G) IVC filters	CBC, creatinine	• Temporary versus permanent IVC filters	• Consult Interventional Radiology, Interventional Cardiology or Vascular Surgery if an IVC filter placement is needed. Consult Vascular Medicine service if uncertain if the patient meets criteria for an IVC filter
H) Compression Stockings		• Recommend 30 to 40 mmHg below the knee compression stocking for all patients with acute DVT (if patient unable to apply and/or remove this amount of compression a lower compression stocking may be substituted)	•

**This table is intended as a guideline and does not replace the physicians' clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below or the CHEST guidelines (CHEST 2008; 133:454S-545S* or *Treatment of Venous Thromboembolism) or consult Vascular Medicine, Hematology, Internal Medicine or Clinical Pharmacy for assistance. American College Chest Physicians Guidelines Chest February 2012 141:2 suppl :419S-494s; doi:10.1378/Chest.1412S3*

A) Unfractionated Heparin (UFH)

1) Review the risks and benefits and alternatives of anticoagulation with the patient and/or family members.
2) If there is a high clinical suspicion for VTE, begin treatment immediately while awaiting the outcome of diagnostic tests (unless anticoagulation contraindicated).
3) Unfractionated heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions to UFH include: bleeding, hypersensitivity, fever, urticaria and rhinitis. Hyperkalemia, hypoaldosteronism and elevation in transaminases (ALT/AST) have also been reported.
4) Discontinue VTE prophylaxis medication prior to starting full dose anticoagulation.
5) Obtain complete blood count, aPTT, and if warfarin/Coumadin® is to be used a PT/INR. Pharmacists verifying or entering orders for UFH will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory studies have not been obtained or ordered, the pharmacist will place an order to obtain these baseline studies.
6) If the baseline laboratory studies are abnormal, consult Vascular Medicine or Hematology for assistance.
7) Select the Standard UFH nomogram (See *Table 7 below for patients with VTE*) for intravenous bolus and continuous infusion dosing recommendations using programmable infusion pumps. Begin with an intravenous bolus of 80 units/kg followed by 18 units/kg/hour continuously.

Table 7. Heparin Nomogram Orders for the Treatment of Acute Venous Thromboembolism

Cleveland Clinic **Standard Unfractionated Heparin Adult Patients (only)** ***Note: This nomogram is NOT designed for patients receiving thrombolytics, glycoprotein IIb/IIIa antagonists or any anticoagulant other than unfractionated heparin.***		
Weight-based heparin dosing for Bolus and Infusion rates: **(based on 80 units/ kg bolus and 18 units/ kg/ hour infusion)** **GOAL PTTAC = 60 - 85 SECONDS** **(Target Heparin level: 0.3- 0.7 anti-Xa units / ml)**		
Heparin Nomogram Dosing Adjustments		
Laboratory PTTAC Result (seconds)		**Repeat PTTAC in**
Less than 32	Use dosing calculator found on the MAR for dosing adjustments	6 Hours
32 – 59.9		6 Hours
60 –85.9		6 Hours
86 – 106.9		6 Hours
107 – 150		6 Hours
Greater than 150	**Hold heparin infusion and notify physician**	

- **Check first PTTAC 6 hours after infusion started, then follow dosing calculator for heparin adjustments.**
- **Once 2 consecutive PTTACs are within therapeutic range, repeat PTTACs in a.m. and then daily.***
- **Notify the physician for 2 consecutive PTTACs < 60 or > 85 seconds**
- **PTTAC values > 150 sec consider holding the infusion for 1 hour and decreasing the infusion by 3 units/kg/hour and notify the physician.**

8) Unfractionated heparin may also be administered at full dose subcutaneously. There are two recommended regimens:
   a) Initial bolus of 5,000 units intravenously followed by 17,500 units subcutaneously every 12 hours.
   b) Initial bolus of 333 units/kg subcutaneously, followed by a fixed dose of 250 units/kg subcutaneously every 12 hours.
9) Monitor UFH using the aPTT or anti-Xa heparin assay. Once therapy is started, obtain an aPTT every 6 hours until the patient reaches a targeted therapeutic level, then daily (or for dosing changes). The target for the aPTT is subject to the laboratory and dependent on the reagents used. Currently the Cleveland Clinic main campus target is 60 to 85 seconds and is based on the anti-Xa level. If changes are needed for this target, clinicians will be notified by the laboratory. The

anti-Xa heparin assay is an alternative method for monitoring heparin (target is 0.3 to 0.7 IU/mL) which corresponds currently to an aPTT of 60 to 85 seconds. The anti-Xa heparin assay (may be used for routine monitoring) but should be considered if the patient requires large daily doses of UFH without achieving a therapeutic aPTT (i.e. heparin resistance) or if the patient has a lupus anticoagulant. Consult Vascular Medicine or Hematology for assistance if there is difficulty with anticoagulation. If the patient is receiving full dose subcutaneous UFH, an aPTT should be monitored 6 hours after the morning administration.

10) A flow sheet should be used to monitor laboratory tests. EPIC report Anticoagulation Therapy Accordion is available to help with patient monitoring. Data should include the date heparin is started, dose, aPTT and/or an anti-Xa heparin assay and CBC with platelet count. If the patient is to be converted to Warfarin, the dose and a PT/INR should be included.
11) The platelet count should be monitored at least every 2-3 days while on intravenous or subcutaneous heparin therapy (beginning day 4 to 14 or until discontinued) to identify or prevent the adverse complication of HIT. If the patient has had UFH or LMWH within the previous 100 days, a baseline platelet count should be obtained and repeated within 24 hours to monitor for rapid-onset HIT. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% from the pretreatment UFH level; if the platelet count drops below 150,000 mm^3; or if the patient experiences new thrombosis or skin necrosis while on UFH.
12) Start warfarin/Coumadin® therapy once the patient is therapeutic on UFH; see the Warfarin section for further guidelines.
13) Overlap UFH a minimum of 5 days with warfarin/Coumadin® and the INR must be $\geq$2 for 24 hours prior to and discontinuing UFH. If the patient is scheduled for discharge before the INR reaches the targeted goal, the patient will require the addition of a parenteral anticoagulant (full dose subcutaneous UFH, LMWH or fondaparinux) to ensure that both the overlap time and targeted INR are attained.
14) Discontinue heparin 6 hours prior to any surgical or interventional procedure including but not limited to: the placement of CVP lines, pacemaker wires, chest tubes OR removal of epidural catheters. One should consider checking the aPTT before any new invasive procedure to ensure that the patient no longer exhibits a "heparin anticoagulant" effect. Patients who have an epidural or spinal anesthesia, or who receive a spinal puncture are at risk of developing an epidural or spinal hematoma. This can result in long-term or permanent paralysis. The drugs' black box

warns that these patients should be monitored frequently for signs of neurological impairment and if neurologic compromise is noted, urgent treatment is required.

15) Notify the appropriate service immediately if bleeding, new thrombosis or any complications from UFH therapy develop.

16) Heparin can be reversed rapidly by infusion of protamine sulfate. This should be reserved for major bleeding because of risk of anaphylaxis to protamine. Protamine is administered intravenously over 10 minutes at a dose of 1 mg/100 units of circulating heparin. No more than 50 mg should be given over any 10 minute period. A general rule for dosing protamine is to calculate the dose based on the previous 2-3 hours of heparin received by continuous infusion (example: a patient receiving 1200 units/hour should receive about 30 mg of protamine (1200 X 2.5 hours = 3000 units then divide 3000 units by 100 units/mg to get 30 mg)). If a patient bleeds on heparin within 30 minutes of a bolus of heparin use the entire bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin should receive about 50 mg of protamine(5000 units divided by 100units/mg to get 50 mg)). If the bolus was greater than 30 minutes but less than 60 minutes use ½ of the bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin 60 minutes ago and an infusion of 1000 units/hour should receive about 35 mg of protamine (Since the bolus was 60 minutes ago use ½ of the bolus dose which is 2500 units then add 1000 units for the infusion which equates to 3500 units divide this number by 100 units/mg to get the 35 mg of protamine. The appropriate dose of protamine is dependent upon the dose of heparin given. Recommend consulting Clinical Pharmacy, Vascular Medicine or Hematology for assistance.

Example of Protamine Dosing for UFH reversal

Patient Scenario	General Dosing Rule	Example: Calculating Protamine Dose	
		Patient's current heparin dose	Calculation
Heparin continuous infusion for > 2 hours	Calculate dose based on the previous 2-3 hours of heparin administered as a continuous infusion	1200 units/hr for 2.5 hours	1. 1200 units X 2.5 hours = 3000 units 2. 3000 units ÷ 100 units/1mg** = **30mg of Protamine**
Heparin bolus within the past 30 minutes	Use entire bolus dose to calculate reversal	5000 unit bolus	1. 5000 units ÷ 100 units/1mg** = **50mg of Protamine**
Heparin bolus within 30-60 minutes plus initiated on a continuous infusion	Use ½ of the bolus dose and include current infusion dose	5000 unit bolus, then 1000 units/hr for one hour	1. To reverse bolus, use 2500 units since bolus was 60 minutes. Add infusion portion of 1000 units for the past hour. Therefore total heparin to be reversed is 2500 units + 1000 units = 3500 units 2. 3500 units ÷ 100 units/1mg** = **35mg of Protamine**

B) Low Molecular Weight Heparin (LMWH) or Enoxaparin/Lovenox®

1) Enoxaparin/Lovenox® is currently the only LMWH preparation on formulary for the treatment of VTE at the Cleveland Clinic Health System Hospitals. The LMWH preparations dalteparin/Fragmin® and Tinzaparin/Innohep® are also FDA approved for VTE treatment but are not currently available on the Cleveland Clinic formulary. Recommend consulting Pharmacy for additional information on these agents.

2) Review the risks and benefits and alternatives to anticoagulation to the patient and or family members.

3) Low molecular weight heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions may include but are not limited to: bleeding, fever, nausea, elevation in the transaminases (ALT/AST), hematoma at the injection site or easy bruising, hyperkalemia or hypoaldosteronism.

4) Discontinue VTE prophylaxis medication when converting to full dose anticoagulation.

5) If there is a high clinical suspicion of VTE, begin treatment immediately while awaiting the outcome of diagnostic tests (unless anticoagulation contraindicated).

6) Obtain CBC, aPTT, and serum creatinine baseline laboratory studies. Obtain a PT/INR if Warfarin is to be used. Pharmacists verifying or entering orders for enoxaparin/Lovenox® will check that baseline laboratory values have been obtained or ordered. Calculation of the creatinine clearance should also be done to assess renal function. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory studies have not been obtained or ordered, the pharmacist will place an order to obtain these studies.

7) Use weight-based subcutaneous dosing for LMWH (enoxaparin/Lovenox® at 1 mg/kg/every 12 hours or 1.5 mg/kg/every 24 hours). Be certain the patient's weight is accurate, calculated in kilograms and that the creatinine clearance is known.

8) Adjust the dose of the LMWH (enoxaparin/Lovenox®) per the patient's creatinine clearance. If the creatinine clearance is below 30 mL/minute, the dose of enoxaparin/Lovenox® should be reduced to 1 mg/kg/day for VTE treatment. Low molecular weight heparin preparations are contraindicated for patients on dialysis.

9) If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is

stopped to prevent or identify patients at risk of rapid-onset HIT. Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% from the pretreatment level; if the platelet count drops below 150,000 mm^3; or if the patient experiences new thrombosis or skin necrosis while on LMWH. Recent *Chest 2012 Guidelines* indicate patients receiving LMWH with medical problems only do not need platelet count monitoring.

10) Use a flow sheet to monitor appropriate laboratory tests. Epic Report Anticoagulation Therapy Accordion is available to help with patient monitoring. including the dose of LMWH, serum creatinine, anti-Xa level and CBC with platelet count. If warfarin/Coumadin® is to be given, include the dose and a PT/INR.

11) Monitoring LMWH is generally not necessary, however, may be indicated if the patient has renal insufficiency; is obese; pregnant or for pediatric patients. An anti-Xa level with LMWH (enoxaparin/Lovenox®) as the reference standard should be obtained and drawn 4 hours after the subcutaneous dose is administered. Therapeutic levels of anti-Xa to LMWH are 0.5 to 1 IU/mL for every 12 hour dosing and >1 IU/mL for every 24 hour dosing. EPIC report Anticoagulation Therapy Accordion is available to help with patient monitoring.

12) Begin warfarin/Coumadin® after the first dose of LMWH. When converting to warfarin/Coumadin®, ensure a minimum of 5 days overlap and that the INR is ≥2 for 24 hours before LMWH is discontinued.

13) Discontinue the LMWH preparation (enoxaparin/Lovenox®) 24 hours prior to any surgical or interventional procedure including but not limited to the placement of CVP lines, chest tubes, pacemaker wires, or epidural catheter removal.

14) Notify the primary service immediately if bleeding, thrombosis or any other adverse reactions including skin necrosis develop while on LMWH.

15) LMWH is not completely neutralized (reversed) by protamine sulfate unlike UFH and should not be the only agent used to reverse the anticoagulant activity. Protamine sulfate will reverse the antithrombin activity of LMWH however will only reverse up to 60% of the anti-factor Xa activity. One mg of enoxaparin/Lovenox equals approximately 100 anti-Xa units. Protamine Sulfate may be given as 1 mg per 100 anti-Xa units of LMWH (enoxaparin/Lovenox®) when given within 8 hours of last administered dose. Protamine sulfate at a dose of 0.5 mg / 100 anti-

Xa units of LMWH should be administered when the dose was administered between 8 and 12 hours ago or if the aPTT measured 2-4 hours after the first dose of protamine is still prolonged. Protamine sulfate may not necessary when the last dose of LMWH was administered greater than 12 hours earlier. There may be some situations that may require assistance and we recommend consulting Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

16) For Outpatient Management of VTE using LMWH, the patient and/or caregiver must be given proper instructions by the physician and/or nursing staff prior to discharge. Patients should receive an enoxaparin/Lovenox® (or equivalent LMWH discharge kit) including instructions, record of daily injections, sterile alcohol swabs and sharps collector. The patient and or caregiver must demonstrate an ability to self administer subcutaneous injections.

17) Patients must be able to state the purpose of the LMWH (enoxaparin/Lovenox®), when to notify the physician if problems develop and are aware of the signs and symptoms of bleeding and/or new thrombosis.

18) Outpatient routine platelet count monitoring is not recommended for medical patients on LMWH. Patients should be advised of the risks and complications of HIT and seek medical advice if such events develop.

C) Fondaparinux or Arixtra®

1) Review the risks and benefits and alternatives of anticoagulation with the patient and/or family members.
2) Fondaparinux /Arixtra® is contraindicated if there is an allergy to this medication or if there is active bleeding. It is also contraindicated if the creatinine clearance is < 30 mL/min or if the patient is on dialysis. It should be used with caution in the elderly patient.
3) Adverse reactions include but are not limited to bleeding, fever, nausea, and anemia.
4) Discontinue VTE prophylaxis medication prior to converting to full dose anticoagulation.
5) Obtain baseline complete blood count, serum creatinine and a PT/INR if warfarin/Coumadin® is to be used. Calculation of the creatinine clearance should be done to assess renal function. Pharmacists verifying or entering orders for fondaparinux/Arixtra® will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory tests have not been obtained or ordered the pharmacist will place an order to obtain these studies.
6) Dosing of fondaparinux/Arixtra ® for the treatment of VTE is weight-based:

a) Administer 5 mg/subcutaneously q 24 hours for patients <50 kg.

b) Administer 7.5 mg/subcutaneously q 24 hours for patients 50 to 99 kg.

c) Administer 10 mg for patients q 24 hours over 100 kg.

7) No monitoring is necessary, but use a flow sheet for appropriate laboratory tests and includes the date, dose of fondaparinux/Arixtra®, serum creatinine and complete blood count with platelet count. If warfarin/Coumadin® is to be used, add a PT/INR and the dose of warfarin/Coumadin®. EPIC report Anticoagulation Therapy Accordion is available to help with patient monitoring.

8) The half life of fondaparinux is 17 to 21 hours. Prior to surgical or invasive procedures, the drug must be discontinued at least 48 – 72 hours in advance. Recommend consulting Vascular Medicine, Hematology or Clinical Pharmacy for assistance.

9) Notify the primary service if complications develop including bleeding or new thrombosis.

10) No antidote is available. Recommend consulting Hematology, Vascular Medicine or Clinical Pharmacy for assistance if bleeding or other complications occur.

11) Outpatient Management of VTE using fondaparinux/Arixtra®: It may be used in the outpatient management of VTE. The patient and/or caregiver must be given proper instruction by the physician and/or nursing staff prior to discharge. Patients should receive discharge instructions on how to administer and record daily injections and receive alcohol swabs and a sharps collector. The patient and or caregiver must also demonstrate an ability to self administer subcutaneous injections.

12) Patient must be able to state the purpose of fondaparinux/Arixtra®, when to notify the physician if problems develop and be aware of signs and symptoms of bleeding and/or new thrombosis.

D) Alteplase/Activase® (rt-PA)

1) Review the risks and benefits and alternatives with the patient and/or family members.

2) Alteplase/Activase® should only be used for acute pulmonary embolism if the patient is hemodynamically unstable and/or at the discretion of the physician if significant right heart failure is present. It may also be used for acute iliofemoral or extensive proximal DVT with symptoms (swelling/pain). In this situation it should be administered via catheter directed therapy and only considered for those patients at low risk for bleeding

3) Alteplase/Activase® is contraindicated if there is active internal bleeding, recent intracranial or intraspinal surgery, intracranial neoplasm or aneurysm, known bleeding diathesis, significant

trauma, severe uncontrolled hypertension (>185 mmHg systolic or >110 mmHg diastolic) or current use of warfarin/Coumadin® with an INR >1.7.

4) Obtain baseline complete blood count, PT/INR, aPTT and fibrinogen level. Pharmacists verifying or entering orders will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory studies have not been obtained or ordered the pharmacist will place an order to obtain these tests.

5) Discontinue the VTE prophylaxis and/or other anticoagulants if applicable.

6) The dose for alteplase/Activase® for an acute pulmonary embolism is 100 mg given intravenously through a peripheral vein over 2 hours. Following thrombolysis, the patient should be converted to a full dose anticoagulant (UFH, LMWH or fondaparinux). Consider consulting Vascular Medicine and/or the Medical Intensive Care Unit staff for assistance.

7) The dose for alteplase/Activase® for acute iliofemoral or extensive proximal DVT (with symptoms) ranges from 0.25 mg – 1 mg per hour for 12 to 24 hours and should be administered via catheter-directed therapy. Following thrombolysis, the patient should be converted to a full dose anticoagulant (UFH, LMWH or fondaparinux). Continuous infusion UFH (heparin) is generally given concomitantly with alteplase to maintain patency of the intravenous lines. Consult Vascular Medicine, Vascular Surgery, Interventional Cardiology or Interventional Radiology for assistance.

8) An intensive care unit setting is necessary for the management and monitoring of alteplase/Activase®.

E) Rivaroxaban (Xarelto®)

1) Rivaroxaban/Xarelto® is now recommended for the treatment of VTE. The recommended dose is 15 mg twice daily given orally for 3 weeks and then the dose is decreased to 20 mg daily until treatment is completed.

2) Prior to initiation of rivaroxaban, laboratories should include a serum creatinine and complete blood count.

3) Contraindications include bleeding or severe hypersensitivity reaction to rivaroxaban. Avoid use with P-glycoprotein and strong CYP3A4 inhibitor such as :ketoconazole, ritonavir, and conivaptan and concomitant use with other anticoagulants and NSAIDs/aspirin, clopidogrel, prasugrel and ticagrelor as these may cause an increased bleeding risk. Use with erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone and felodipine may increase

bleeding risk and rivaroxaban's use is recommended only if the potential benefit justifies the risk. Also, avoid use with carbamazepine, phenytoin, rifampin, St. John's wort or consider increasing the dose of rivaroxaban if they must be co-administered. Avoid use with moderate hepatic impairment (Childs-Pugh classes B and C) and in patients with a creatinine clearance less than 30 mL/min. If the creatinine clearance is between 30 to 50 mL/min monitoring is recommended. Its use in pregnancy and lactation should be avoided.

4) No monitoring is required as the prothrombin time and INR are not reliable. There is some evidence that an anti-factor Xa assay that uses rivaroxaban containing plasma calibrators may provide the optimal method for determining plasma rivaroxaban concentrations. As of this writing this lab is unavailable at the Cleveland Clinic.

F) Warfarin (Coumadin®)

Table 8: Target INR for the Treatment of acute VTE

INDICATION	INR
Treatment of deep vein thrombosis/pulmonary embolism	2 TO 3
Presence of the Antiphospholipid Syndrome (lupus anticoagulant or antiphospholipid antibodies)	2 TO 3
American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy 2008	

1) Determine the need for long-term anticoagulation with warfarin/Coumadin®.
2) Explain the risks and benefits of anticoagulation and alternatives to the patient and/or family members.
3) Contraindications to the use of warfarin/Coumadin® may include but are not limited to active bleeding (gastrointestinal or other), hypersensitivity or an allergy to warfarin/Coumadin®, pregnancy or childbearing potential w/o contraception protection, history of a major bleeding disorder, major surgery, trauma or a stroke within the past two weeks, acute heparin-induced thrombocytopenia and a history of noncompliance, language barriers or unsuitable home environment or at risk of falling.
4) Obtain a complete blood count and PT/INR as baseline laboratory studies. Pharmacists verifying or entering orders for warfarin/Coumadin® will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline lab work has not been obtained or ordered the pharmacist will place an order to obtain these studies.

5) Recommend starting warfarin/Coumadin® doses of between 5 mg and 10 mg for the first 1 to 2 days for most patients. Subsequent dosing will be based on the international normalized ratio (INR). For elderly patients, those malnourished, with congestive heart failure or liver disease or recent major surgery or on medications known to increase sensitivity to warfarin/Coumadin® begin lower doses (less than 5 mg) with subsequent dosing based on the INR. If the patient has HIT do not begin warfarin/Coumadin® during the acute event and until the platelet count is > 150,000 mm^3 and the patient is recovering.
6) Overlap with a parenteral anticoagulant (UFH, LMWH, or fondaparinux). The INR should be ≥ 2 for > 24 hours before discontinuing the parenteral anticoagulant after a minimum 5 day overlap. If the patient has HIT, overlap with a DTI for a minimum of 5 days , however, the INR must be ≥ 2 for 2 consecutive days after this overlap before discontinuing the parenteral anticoagulant.
7) Recognize Genomics – the genetic variants of the enzymes that metabolize warfarin/Coumadin® contribute to differences in patients responses to various warfarin/Coumadin® doses. Patients with one of the genetic defects (CYP2C9 or VKORC1) require lower doses. This molecular testing is available through Laboratory Medicine. This testing is not necessary for all patients and should be ordered at the discretion of the ordering physician. Consult Vascular Medicine, Hematology, Clinical Pharmacy or Laboratory Medicine for recommendations.
8) Administer warfarin/Coumadin® the same time each day, preferably in the evening
9) Use a flow sheet listing the date, parenteral anticoagulant, serum creatinine, and aPTT or anti-Xa level to UFH or LMWH, complete blood count with platelets, PT/INR and warfarin dose. EPIC report anticoagulation therapy accordion is available to help with patient monitoring. 10) Notify dietary services that the patient is receiving warfarin/Coumadin® while in the hospital.
11) Prior to discharge, assure the following:
    a) Determine who will monitor the patient.
    b) Determine the target INR range and when the next INR is to be ordered.
    c) Determine the length of therapy and/or a review date.
12) Patient Education must include the following:
    a) Patient has access to the warfarin/Coumadin® book and/or has viewed the video.
    b) Patient has received: "***General warfarin***/Coumadin® ***Instructions for the Patient".*** (See below). Additional information is available in section XV.
    c) Evidence that the patient understands the potential for drug-drug interactions and drug-food interactions.

d) Explain that warfarin and Coumadin® are the same drug. warfarin is the generic name for Coumadin®.

.

G) Inferior Vena Cava Filters (Permanent or Temporary)

1) Review the risks and benefits of inferior vena cava (IVC) filter insertion. Instruct the patient that inferior vena cava filters do not treat VTE but help to prevent pulmonary embolism.
2) Indications for IVC filter placement include:
   a) patients who are unable to be fully anticoagulated
   b) those individuals with a complication of anticoagulation
   c) patients with failure of therapeutic anticoagulation (i.e., develop new thrombosis despite therapeutic anticoagulation).
   d) Patients undergoing pulmonary thromboendarterectomy for chronic pulmonary thromboembolic disease.
3) Complications of IVC filters may include but are not limited to: filter migration or thrombus formation within and above the filter. Patients can also develop thrombosis at the filter insertion site.
4) Check baseline laboratory studies for placement including complete blood count, serum creatinine, PT/INR if on warfarin/Coumadin® or an aPTT if on heparin or one of the direct thrombin inhibitors.
5) Contact the appropriate service for placement of the IVC filter as listed in table 5.
6) If a temporary IVC filter is placed, be certain to schedule a follow up time for consideration of removal. An IVC filter retrieval clinic is available by contacting 216-444-4420.
7) Resume anticoagulation as soon as possible when appropriate to do so.

H) Compression Stockings - Prevention of Post-Thrombotic Syndrome

1) **All patients should be given a prescription** for a 30 to 40 mmHg below the knee compression stockings within one month of their diagnosis of DVT and advised they need to wear these for the next one to two years to prevent the post thrombotic syndrome (PTS). Patient's ability to put these stockings on must be taken into consideration, however, when determining the strength of the compression stocking prescribed. Not all patients will be able to wear the 30 to 40 mmHg stockings therefore, prescribe a lower compression stocking (20 to 30 mmHg) in those individuals unable to tolerate the heavier compression stockings on, and/or put them on or take them off.

I) Dietary Role in the Management of VTE

1) Warfarin/Coumadin® is affected by changes in vitamin K levels. The goal is to keep the vitamin K level as stable as possible.
2) Warfarin/Coumadin® appearing on the daily pharmacy report requires dietary attention/intervention due to the food and medication interactions of this anticoagulant.
3) Pharmacy, Nursing, and the Nutrition staff will work responsibly and collaboratively to provide comprehensive care to the patients who is receiving warfarin/Coumadin®. Relevant findings and recommendations will be communicated amongst the Pharmacy, Nursing and Nutrition Therapy team members.
4) Patients on warfarin/Coumadin® therapy must receive initial education from the unit nursing staff (or designated personnel) which includes the booklet titled "Understanding the Anticoagulant medication warfarin." When the patient has additional dietary questions, a consult is placed to dietary in Epic by the nursing unit to see the patient.
5) Patients on warfarin/Coumadin® are evaluated and educated (as needed) by the dietetic technicians who also monitor menu selections.
6) The dietetic technician (DT) or registered dietitian (RD) is responsible for providing an adjusted diet for the patient and the appropriate education when needed. A copy of Your Guide to Food and Drug Interactions created by Pharmacy and Nutrition Therapy is available on-line by accessing the intranet. Type Food and Drug in the search box and click on the document.
7) The dietitians action: Monitor orders for double portions of green leafy vegetables including broccoli, raw cabbage (coleslaw), spinach and green salads with endive, Boston, bib, romaine and head lettuces. For a vegetarian restriction, review food selections daily for excessive amounts of broccoli or spinach. If these are noted, discuss usual eating patterns with the patient and document the interaction with the patient in the medical record. The menu may need to be locked daily to ensure compliance depending on the outcome of the discussion with the patient.

VI. Treatment of Patients with Acute Coronary Syndromes* STEMI

Patients must be advised of their risks and benefits of Anticoagulation.

Table 9. Summary Table of Pharmacological Agents, Dosing Guidelines for ACS

Agent	Baseline labs	Dosing	Monitoring
A) Intravenous Heparin (UFH)	CBC, aPTT PT/INR if warfarin to be used.	• 60 units/kg of UFH intravenous bolus (4000 unit maximum) followed by 12 units/kg/hour of UFH (1000 unit maximum) infusion • **See LOW RANGE/ACS NOMOGRAM below**	• If baseline laboratory studies abnormal or difficulty is encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • Follow standard UFH ACS nomogram (see table 11 below) • The therapeutic aPTT target is **53 to 71** seconds or an anti-Xa level of 0.2 to 0.5 units/mL. • Monitor the platelet count at least every 2-3 days from days 4-14 of therapy or until UFH is discontinued to prevent or identify patients at risk of HIT. • If the patient has received UFH within the previous 100 days, monitor the platelet count at baseline and within 24 hours of starting therapy and at least every 2-3 days from days 4 -14 of therapy or until UFH is discontinued to prevent or recognize patients at risk of HIT.
B) LMWH (Enoxaparin/ Lovenox®	CBC, creatinine PT/INR if warfarin to be used	• Dose adjustments are necessary if the creatinine clearance is less than 30 mL/min and LMWH preparations are contraindicated if the patient is on dialysis. • **For *Patients <75 years of age:*** Initial: give 30 mg of Lovenox/enoxaparin® as a single intravenous bolus plus 1 mg/kg of Lovenox/Enoxaparin® (maximum 100 mg for the first 2 doses only) subcutaneously every 12 hours. The first subcutaneous dose should be administered within 15 minutes of the intravenous bolus. • **Maintenance:** After the first 2 doses, administer 1 mg/kg of Lovenox/Enoxaparin® subcutaneously every 12 hours. • ***For Patients ≥75 years of age:*** Initial: Give a subcutaneous dose of: 0.75 mg/kg o**f Eno**xaparin/Lovenox® every 12 hours (**Note:** No intravenous bolus is administered in this population); a maximum dose of 75 mg of enoxaparin/Lovenox ® is recommended for the first 2 doses. • **Maintenance:** After the first 2 doses, administer 0.75 mg/kg subcutaneously of enoxaparin/Lovenox ® every 12 hours up. • Consider contacting Clinical Pharmacy or Vascular Medicine or Hematology for recommendations on higher doses.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • Monitoring not necessary unless patient has renal insufficiency, obese, pregnant or a pediatric patient • Use an anti-Xa level to LMWH as the standard. • Optimal target levels are not well defined but should be at least >0.5 IU/mL) for every 12 hour dosing. A level (if applicable) should be drawn 4 hours after a subcutaneous dose. • Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. • If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT.
E) Tenecteplase (TNKase®	CBC, PT/INR, aPTT, fibrinogen	• Tenecteplase (TNKase®) is weight dependent:	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology

		Weight (kg) Dose (mg) <60 30 ≥60 to <70 35 ≥70 to <80 40 ≥80 to <90 45 ≥90 50	or Clinical Pharmacy for assistance. • Advise intensive care setting for monitoring.

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) or the CHEST guidelines: (2008; 708S-775S or Chest 2012;637S-668S for Acute ST-Segment Elevation Myocardial Infarction (STEMI) above or consult Vascular Medicine, Hematology, Clinical Pharmacy for assistance.

VII. Treatment of Patients with Acute Coronary Syndromes* NSTEMI

Patients must be advised of their risks and benefits of Anticoagulation.

Table 10. Summary Table of Pharmacological Agents, Dosing Guidelines for ACS.

Agent	Baseline labs	Dosing	Monitoring
A) Intravenous Heparin (UFH)	CBC, aPTT PT/INR if warfarin to be used.	• 60 units/kg IV bolus of UFH (4000 unit maximum) followed by 12 units/kg/hour of UFH (1000 unit maximum) infusion (**See LOW RANGE/ACS NOMOGRAM below**)	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • Follow standard UFH ACS nomogram (table 11 below) • Therapeutic aPTT target is 53 to 71 seconds or an anti-Xa level of 0.2 to 0.5 units/mL. • Monitor the platelet count at least every 2-3 days from days 4-14 of therapy or until UFH is discontinued to prevent or identify patients at risk of HIT. • If the patient has received UFH within the previous 100 days, monitor the platelet count at baseline and within 24 hours of starting therapy and every 2-3 days from day 4 to 14 or until UFH is discontinued to prevent or recognize patients at risk of HIT.
B) LMWH (Enoxaparin/ Lovenox® .	CBC, creatinine PT/INR if warfarin to be used	• Dose adjustments are necessary if the creatinine clearance is less than 30 mL/min and LMWH preparations are contraindicated if the patient is on dialysis. • Give Enoxaparin/Lovenox® at 1 mg/kg every 12 hours subcutaneously daily for patients with normal renal function. Administer enoxaparin/ Lovenox® at 1 mg/kg subcutaneously daily of if the creatinine clearance is <30 mL/min • Recommend contacting Clinical Pharmacy, Hematology or Vascular Medicine for recommendations on higher doses. • Avoid LMWH if the patient is on dialysis.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • Monitoring not necessary unless the patient has renal insufficiency, is obese, pregnant or a pediatric patient • Use an anti-Xa level to LMWH as the standard • Optimal target levels are not well defined but should be at least > 0.5 IU/mL) for every 12 hour dosing. A level (if applicable) should be drawn 4 hours after a subcutaneous dose. • Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. • If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT.
D) Bivalirudin (Angiomax®)	CBC, aPTT, creatinine	• Pre-cardiac catheterization give Bivalirudin at a 0.1mg/kg bolus intravenously then 0.25 mg/kg/hour infusion. • Patients with creatinine clearance < 30 ml/min were excluded from receiving Bivalirudin for NSTEMI trials.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • No monitoring is necessary. However ACT may be use to monitor during PCI

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below or CHEST guidelines (CHEST 2008; 133:670S-707S for Non ST-Segment Elevation Myocardial Infarction (NSTEMI) or consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. Chest 2012;637S-668S

VIII. Treatment of Patients Undergoing Percutaneous Coronary Intervention

Patients must be advised of their risks and benefits of Anticoagulation.

Table 11. Summary Table of Patients undergoing Percutaneous Coronary Intervention

Agent	Baseline labs	Dosing	Monitoring
A) Intravenous Heparin (UFH)	CBC, aPTT PT/INR if warfarin to be used.	**Patients on heparin pre-coronary intervention:** • ***No glycoprotein IIb/IIIa inhibitors:*** • Give additional UFH boluses to maintain an ACT (activated clotting time) between 250 and 300 seconds • ***Concurrent glycoprotein IIb/IIIa inhibitor administration:*** • If patients are on a glycoprotein IIb/IIIa inhibitor or if there is planned glycoprotein IIb/IIIa inhibitor use, give additional UFH boluses to maintain an ACT > 200 seconds. **Patients NOT on heparin pre-coronary intervention:** • ***No glycoprotein IIb/IIIa inhibitors*** • Administer an initial UFH bolus of 60-100 units/kg and maintain an ACT of 250-300 seconds. • ***Planned GP IIb/IIIa inhibitor use:*** • Administer an initial UFH bolus of 50-70 units/kg with planned glycoprotein IIb/IIIa inhibitor to maintain an ACT > 200 seconds.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • ACT (Activated clotting time) • Monitor the platelet count at least every 2-3 days from days 4-14 of therapy or until UFH is discontinued to prevent or identify patients at risk of HIT. • If the patient has received UFH within the previous 100 days, monitor the platelet count at baseline and within 24 hours and at least every 2-3 days from days 4 -14 of therapy or until UFH is discontinued to prevent or recognize patients at risk of HIT.
B) LMWH (Enoxaparin/ Lovenox® .	CBC, creatinine PT/INR if warfarin to be used	• Dose adjustments are necessary if the creatinine clearance is less than 30 mL/min and LMWH preparations are contraindicated if the patient is on dialysis. • **PCI Dosing:** Patients on subcutaneous Enoxaparin/Lovenox® pre-percutaneous coronary intervention (PCI) may require additional boluses of Enoxaparin/Lovenox® immediately prior to intervention: • If the last administered subcutaneous Enoxaparin/Lovenox® dose was ≤ 8 hours no additional Enoxaparin/Lovenox® in required • If the last administered subcutaneous Enoxaparin/Lovenox® dose was > 8 hours administer Enoxaparin/Lovenox® 0.3 mg/kg	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • Monitoring not necessary unless patient has renal insufficiency, obese, pregnant or a pediatric patient • Use an anti-Xa level to LMWH as the standard. • Optimal target levels are not well defined but should be at least >0.5 IU/mL) for every 12 hour dosing. A level (if applicable) should be drawn 4 hours after a subcutaneous dose • Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients

		intravenously	receiving LMWH but who received UFH first. • If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT
D) Bivalirudin (Angiomax®)	CBC, aPTT, creatinine	• **PCI dosing: Give Bivalirudin** 0.75 mg/kg bolus intravenously then infuse 1.75 mg/kg/hr during the intervention • **PCI dosing in patients already receiving Bivalirudin:** • Patients on Bivalirudin pre-percutaneous coronary intervention (PCI) will require a re-bolus with 0.5 mg/kg intravenously and their infusion should be increased to 1.75 mg/kg/hour.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • No monitoring is necessary. However ACT may be use to monitor during PCI • Adjustments may be considered in patients with renal dysfunction

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below or CHEST guidelines (CHEST 2008; 708S-775S or Chest 2012;637S-668S) for Acute ST-Segment Elevation Myocardial Infarction (STEMI) or consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance.

A) Unfractionated Heparin (UFH)

1) Review the risks and benefits and alternatives of anticoagulation with the patient.
2) Begin treatment immediately unless there is a contraindication to its use.
3) Unfractionated heparin is contraindicated in patients with a heparin allergy or a history of Heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions to UFH are rare but may include hypersensitivity, fever, urticaria and rhinitis. Hyperkalemia, hypoaldosteronism and elevation in transaminases (ALT/AST) have also been reported. Sudden severe anaphylactoid-type reactions resulting in hypertension, respiratory distress and/or chest pain are associated with HIT as is skin necrosis at the site of a subcutaneous heparin injection. Prior to initiation of UFH a baseline CBC should be obtained.
4) Obtain baseline laboratory studies including a CBC, aPTT, and if warfarin/Coumadin® is to be used, a PT/INR. Pharmacists verifying or entering orders for UFH will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory work has not been obtained or ordered, the pharmacist will contact the provider to place an order to obtain these baseline studies. The pharmacist will document in an i-Vent within EPIC the baseline lab values or if not available the prescriber whom they contacted to obtain these values.
5) Discontinue the VTE prophylaxis medication (if applicable) prior to starting full dose Heparin. anticoagulation.
6) Select the proper UFH nomogram (**LOW RANGE/ACS**) (Table 12) for intravenous bolus and continuous infusion dosing using programmable infusion pumps. Use a 60 units/kg intravenous bolus of UFH (4000 unit maximum) followed by 12 units/kg/hour continuous infusion of UFH (1000 unit maximum). Patients undergoing PCI will have UFH dosages adjusted in the cardiac catheterization laboratory based on the activated clotting time (ACT).

Table 12: UFH Physician's order for Acute Coronary Syndrome Patients

Cleveland Clinic Low Dose/ACS Unfractionated Heparin Adult Patients (only) *PTTAC Nomogram for all ACS Patients with or without Thrombolytics and/or glycoprotein IIb/IIIa Agents and when a Lower Range Anticoagulation is desired*

Weight-Based Heparin Nomogram for *Initial* Bolus and *Initial* Infusion rates only: (based on 60 units/ kg bolus and 12 units/ kg/ hour infusion) **GOAL PTTAC = 51-73 SECONDS** **(Target Heparin: 0.2 - 0.5 anti-Xa units / ml)**		
Heparin Nomogram Dosing Adjustments		
Laboratory PTTAC Result (seconds)		**Repeat PTTAC in**
Less than 32.4	Use dosing calculator found on the MAR for dosing adjustments	6 Hours
32.4 – 54		6 Hours
55 – 79		6 Hours
80 – 101		6 Hours
102 – 118		6 Hours
119-150		4 Hours
Greater than 150	Hold heparin infusion and notify physician	

- **Check first PTTAC 6 hours after infusion started, then follow dosing calculator for heparin adjustments.**
- **Once 2 consecutive PTTACs are within therapeutic range, repeat PTTACs in a.m. and then daily.**
- **Notify MD for 2 consecutive PTTACs < 51 or > 73 seconds**
- **PTTAC values >150 sec consider holding the infusion for 1 hour and decreasing the infusion by 3 units/kg/hour**

7) An aPTT should be performed every 6 hours until the patient reaches a targeted therapeutic level, then daily (or for dosing changes). The target for the aPTT is subject to the laboratory and dependent on the reagents used. Currently the CCF target is **53 to 71** seconds for patients with acute coronary syndrome (ACS); however, when changes are needed, clinicians will be notified of the new aPTT target by the laboratory. The anti-Xa heparin assay is an alternative method for monitoring heparin and the optimal target (although not well defined) should be 0.2 - 0.5 IU/mL. The anti-Xa heparin assay may be considered for routine monitoring, but should be used if the patient requires large daily doses of UFH without achieving a therapeutic aPTT (heparin resistance) or if the patient has a lupus anticoagulant. Causes of heparin resistance include: increased heparin clearance, increased heparin-binding proteins, elevation of factor VIII or fibrinogen levels, certain medications and antithrombin deficiency.

8) Monitor the platelet count at least every 2-3 days from day 4 to day 14 of therapy or until UFH is discontinued to identify or prevent HIT. In addition, if the patient has received UFH or LMWH within the previous 100 days, monitor the platelet count at baseline and within 24 hours and from day 4 to 14 or until UFH is discontinued to identify rapid-onset HIT. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% while on UFH from the pretreatment level or if the platelet count drops below 150,000 mm^3; or if the patient experiences new thrombosis or skin necrosis while on UFH.

9) A flow sheet should be used to monitor laboratory tests include: Epic report anticoagulation therapy accordion is available to help with the patient monitoring, the date, heparin dose, aPTT or anti-Xa heparin assay and a complete blood count with platelet count. If warfarin/Coumadin® is to be used, a PT/INR and warfarin/Coumadin® dose should be included in the flow sheet.10) Start warfarin/Coumadin® therapy (if indicated) once the patient is therapeutic on UFH; see the warfarin section (XI) below for further guidelines.

11) Overlap UFH a minimum of 5 days with warfarin/Coumadin® (if applicable). The INR should be ≥2.0 for >24 hours prior to discontinuing UFH. If the patient is scheduled for discharge before the INR reaches the targeted INR, the patient may require a parenteral anticoagulant (UFH, LMWH or fondaparinux) to ensure both the overlap time frame and the targeted INR.

12) Discontinue heparin 6 hours prior to any surgical or interventional procedure including but not limited to: CVP lines, pacemaker wires, chest tubes OR removal of epidural catheters. One should consider checking an aPTT before any new procedure to ensure that the patient no longer exhibits a heparin anticoagulant effect. Patients who have an epidural or spinal anesthesia, or who receive a spinal puncture are at risk of developing an epidural or spinal hematoma. This can result in long-term or permanent paralysis. The drugs black box warns that these patients should be frequently

monitored for signs of neurological impairment and if Neurologic compromise is noted, urgent treatment is needed.

13) Notify the appropriate service immediately if bleeding, new thrombosis or any complications from UFH therapy develop.

14) Heparin can be reversed rapidly by infusion of protamine sulfate. This should be reserved for major bleeding because of risk of anaphylaxis to protamine. Protamine is administered intravenously over 10 minutes at a dose of 1 mg/100 units of circulating heparin. No more than 50 mg should be given over any 10 minute period. A general rule for dosing protamine is to calculate the dose based on the previous 2-3 hours of heparin received by continuous infusion (example: a patient receiving 1200 units/hour should receive about 30 mg of protamine (1200 X 2.5 hours = 3000 units then divide 3000 units by 100 units/mg to get 30 mg)). If a patient bleeds on heparin within 30 minutes of a bolus of heparin use the entire bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin should receive about 50 mg of protamine(5000 units divided by 100units/mg to get 50 mg)). If the bolus was greater than 30 minutes but less than 60 minutes use ½ of the bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin 60 minutes ago and an infusion of 1000 units/hour should receive about 35 mg of protamine (Since the bolus was 60 minutes ago use ½ of the bolus dose which is 2500 units then add 1000 units for the infusion which equates to 3500 units divide this number by 100 units/mg to get the 35 mg of protamine. The appropriate dose of protamine is dependent upon the dose of heparin given. Recommend consulting Clinical Pharmacy, Vascular Medicine or Hematology for assistance.

Example of Protamine Dosing for UFH reversal

Patient Scenario	General Dosing Rule	Example: Calculating Protamine Dose	
		Patient's current heparin dose	Calculation
Heparin continuous infusion for > 2 hours	Calculate dose based on the previous 2-3 hours of heparin administered as a continuous infusion	1200 units/hr for 2.5 hours	1. 1200 units X 2.5 hours = 3000 units 2. 3000 units ÷ 100 units/1mg** = **30mg of Protamine**
Heparin bolus within the past 30 minutes	Use entire bolus dose to calculate reversal	5000 unit bolus	1. 5000 units ÷ 100 units/1mg** = **50mg of Protamine**
Heparin bolus within 30-60 minutes plus initiated on a continuous infusion	Use ½ of the bolus dose and include current infusion dose	5000 unit bolus, then 1000 units/hr for one hour	1. To reverse bolus, use 2500 units since bolus was 60 minutes. Add infusion portion of 1000 units for the past hour. Therefore total heparin to be reversed is 2500 units + 1000 units = 3500 units 2. 3500 units ÷ 100 units/1mg** = **35mg of Protamine**

B) Low Molecular Weight Heparin (LMWH) Enoxaparin/Lovenox®

1) Review the risks and benefits and alternatives to anticoagulation to the patient and/or family members.
2) Low molecular weight heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions may include but are not limited to: fever, nausea, elevation in the transaminases (ALT/AST), hematoma at the injection site or easy bruising, hyperkalemia and hypoaldosteronism.
3) Begin treatment immediately unless there is a contraindication to its use.
4) Discontinue VTE prophylaxis medication if applicable.
5) Obtain baseline laboratory studies including a complete blood count, PT/INR and serum creatinine. Pharmacists verifying or entering orders for enoxaparin/Lovenox® will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory work has not been obtained or ordered, the pharmacist will contact the provider to place an order to obtain these baseline studies. The pharmacist will document in an iVENT with in EPIC the baseline lab values or if not available the prescriber whom they contacted to obtain these values. Calculation of the creatinine clearance should also be done to assess renal function. Dose adjustments are necessary if the creatinine clearance is less than 30 mL/min and LMWH preparations are contraindicated if the patient is on dialysis.
6) Use weight-based subcutaneous dosing for LMWH (enoxaparin/Lovenox®). Be certain the patient's weight is accurate, calculated in kilograms and that the creatinine clearance is known.
7) Dosing of the LMWH - enoxaparin/Lovenox®
    a) **FOR STEMI: Patients <75 years of age**: Initial: Give 30 mg of enoxaparin/Lovenox® intravenously as a single bolus plus 1 mg/kg of enoxaparin/Lovenox® (maximum 100 mg for the first 2 doses only) subcutaneously every 12 hours. The first subcutaneous dose should be administered with the intravenous bolus. Maintenance: After the first 2 doses, administer 1 mg/kg subcutaneously of enoxaparin/Lovenox® every 12 hours. If the creatinine clearance is < 30ml/min then the maintenance dose should be 1 mg/kg of enoxaparin/Lovenox® once daily. Low molecular weight heparin is not recommended for patients on dialysis.

b) **FOR STEMI Patient's ≥75 years of age:** Initial subcutaneous dose of: 0.75 mg/kg of enoxaparin/Lovenox® every 12 hours (**Note: NO** intravenous bolus is administered in this population); a maximum dose of 75 mg of enoxaparin/Lovenox® is recommended for the first 2 doses. Maintenance: After the first 2 doses, administer 0.75 mg/kg of enoxaparin/Lovenox® subcutaneously every 12 hours. If the creatinine clearance is < 30ml/min then the maintenance dose should be 1 mg/kg of enoxaparin/Lovenox® once daily. Low molecular weight heparin is contraindicated for patients on dialysis.

c) **FOR NSTEMI:** Administer 1 mg/kg of enoxaparin/Lovenox® every 12 hours subcutaneously daily for patients with normal renal function. If the creatinine clearance is < 30 ml/min then the maintenance dose should be 1 mg/kg of enoxaparin/Lovenox® once daily. Low molecular weight heparin is contraindicated for patients on dialysis.

8) If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT. Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% from the baseline or if the platelet count drops below 150,000 mm^3, or if the patient develops new thrombosis or skin necrosis while on LMWH.
9) Use a flow sheet to monitor appropriate laboratory tests include: Epic Report Anticoagulation Therapy Accordion is available to help with the patient monitoring, the date, dose of LMWH, serum creatinine, anti-Xa level to LMWH (if applicable) CBC with platelet count and a PT/INR and warfarin dose (if warfarin is to be used).
10) Monitoring LMWH is generally not necessary, however, may be indicated if the patient has renal insufficiency; is obese; pregnant or for pediatric patients. An anti-Xa level with LMWH (enoxaparin/Lovenox®) as the reference standard should be drawn 4 hours after a subcutaneous dose is administered. Optimal target levels are not well defined but should be at least > 0.5 IU/mL) for every 12 hour dosing. A level (if applicable) should be drawn 4 hours after a subcutaneous dose.
11) Begin warfarin/Coumadin® after the first dose of LMWH (if indicated). When converting to warfarin/Coumadin®, ensure a minimum 5 days overlap and until the INR is ≥ 2 for >24 hours when applicable**.**

12) Discontinue the LMWH preparation (Enoxaparin/Lovenox®) 24 hours prior to any surgical or interventional procedure including but not limited to CVP lines, chest tube insertion, pacemaker wires, or epidural catheter removal. The manufacturers' recommendation for enoxaparin/Lovenox® and epidural catheters is to not use this agent within 2 hours of removal of these devices.

13) If bleeding, thrombosis or other adverse reactions including skin necrosis develop, notify the primary service immediately.

14) LMWH is not completely neutralized (reversed) by protamine sulfate unlike UFH and should not be the only agent used to reverse the anticoagulant activity. Protamine sulfate will reverse the antithrombin activity of LMWH however will only reverse up to 60% of the anti-factor Xa activity. One mg of enoxaparin/Lovenox equals approximately 100 anti-Xa units. Protamine Sulfate may be given as 1 mg per 100 anti-Xa units of LMWH (enoxaparin/Lovenox®) when given within 8 hours of last administered dose. Protamine sulfate at a dose of 0.5 mg / 100 anti-Xa units of LMWH should be administered when the dose was administered between 8 and 12 hours ago or if the aPTT measured 2-4 hours after the first dose of protamine is still prolonged. Protamine sulfate may not necessary when the last dose of LMWH was administered greater than 12 hours earlier. There may be some situations that may require assistance and we recommend consulting Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

C) Bivalirudin (Angiomax®)

1) Review the risks and benefits and alternatives to anticoagulation to the patient and/or family members.
2) Contraindications to its use include but are not limited to: allergy to hirudin derivatives, active bleeding or a history of a bleeding diathesis, recent stroke or intracerebral surgery, uncontrolled hypertension or recent major surgery.
3) Discontinue VTE prophylaxis medication if applicable.
4) Obtain baseline laboratory studies including a complete blood count with platelet count, PT/INR, aPTT and serum creatinine.
5) Dosing guidelines **for NSTEMI pre-cardiac catheterization lab: Initiate therapy with** 0.1 mg/kg bolus intravenously of bivalirudin/Angiomax® then 0.25 mg/kg/hour continuous infusion. Patients pre-treated with bivalirudin/Angiomax® who then go on to PCI should be given a re-bolus with 0.5 mg/kg of bivalirudin/Angiomax® and their infusion increased to 1.75 mg/kg/hour. This dosing regimen has not been adequately studied in patients with a creatinine clearance < 30 ml/min.

For PCI Dosing administer a 0.75 mg/kg bolus of Bivalirudin/Angiomax® then infuse 1.75 mg/kg/hr during the intervention. Dosing adjustment need to be considered in patients with renal dysfunction.

6) No monitoring is necessary, but use of a flow sheet for appropriate laboratory tests including the date, dose of Bivalirudin, serum creatinine, complete blood count with platelet count and if warfarin is to be used a PT/INR and dose of warfarin.
7) No monitoring is necessary; however, the ACT may be used during PCI.
8) Use with caution if the patients creatinine clearance is <30 ml/min.

D) Tenecteplase (TNKase®)

1) Review the risks and benefits and alternatives to anticoagulation to the patient.
2) Contraindications to its use include: hypersensitivity to Tenecteplase, active internal bleeding, history of stroke, intracranial or intraspinal surgery or trauma within 2 months, intracranial neoplasm, arteriovenous malformation or bleeding diathesis or uncontrolled hypertension defined as >185 mmHg systolic or >110 mmHg diastolic) or current use of warfarin with an INR >1.7.
3) Discontinue the DVT prophylaxis medication if applicable.
4) Obtain baseline laboratory studies including a complete blood count, PT/INR, aPTT and fibrinogen level.
5) Dosing guidelines: Tenecteplase (TNKase®) for acute MI is weight dependent.

Weight (kg)	Dose (mg) of Tenecteplase/TNKase®
<60	30
≥60 to <70	35
≥70 to <80	40
≥80 to <90	45
≥90	50

FIGURE 3. DOSING GUIDELINES FOR TENECTELASE

6) Advise intensive care setting for monitoring.

IX. Treatment of Patients with Atrial Fibrillation

Patients must be advised of the risks and benefits of Anticoagulation.

Table 13: Summary of Pharmaceutical Treatment Options for Atrial Fibrillation.

Agent	Baseline labs	Dosing	Monitoring
A) Intravenous Heparin (UFH)	CBC, aPTT PT/INR if warfarin to be used	• Give 60 units/kg bolus of UFH intravenously followed by 12 units/kg/hour intravenously	• If baseline laboratory studies are abnormal or their is difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • Follow the Low Range ACS UFH Nomogram • Monitor the platelet count at least every 2-3 days from day 4 until day 14 of therapy or until UFH is discontinued to prevent or recognize patients at risk of HIT. • If the patient has received UFH within the previous 100 days, a baseline platelet count and one within 24 hours should also be obtained and from day 4 to 14 or until UFH is discontinued to prevent or recognize patients at risk of HIT.
B) LMWH Enoxaparin/ Lovenox®	CBC, creatinine PT/INR if warfarin to be used	• Give 1mg/kg subcutaneously every 12 hours of enoxaparin/Lovenox® up to a maximum dose of 150 mg. • Consider contacting Clinical Pharmacy or Vascular Medicine for recommendations on higher doses. • Adjust the dose based on renal function. If the creatinine clearance < 30 mL/min use 1 mg/kg of enoxaparin/Lovenox® subcutaneously daily. The LMWH preparations are contraindicated if the	• If baseline laboratory studies are abnormal or their is difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • Monitoring is not necessary unless the patient has renal insufficiency, is obese, pregnant or is a pediatric patient. • Use an anti-Xa level to LMWH as the standard. Target levels are 0.5 to 1 IU/mL for every 12 hour dosing and >1 IU/mL for every 24 hour administration. The level (when applicable) should be drawn 4 hours after a subcutaneous dose. • Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or

		patient is on dialysis	identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. • If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT.
E) Warfarin/ Coumadin®	CBC, PT/INR	• Warfarin/Coumadin® oral doses: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg. • The 10 mg dose is dye-free	• If baseline laboratory studies are abnormal or there is difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • PT/INR (Target 2-3)
F) Dabigatran /Pradaxa®	CBC, BMP	• 150 mgs PO every 12 hours for patients with creatinine clearance >30 mL/min or 75mg PO every 12 hours for patients with creatinine clearance of 15 to 30 mL/min • Avoid if creatinine clearance < 15mL/min.	• No monitoring required although, close monitoring of renal function should be done routinely to avoid over anticoagulation
Rivaroxaban/ Xarelto®	CBC, BMP	• 20 mg PO once daily with evening meals for creatinine clearance >50 mL/min. • For creatinine clearance 15 to 50 mL/min, 15 mg PO once daily. • Avoid if creatinine clearance less than 15 mL/min	• No monitoring required although monitoring of the renal function should be done routinely to avoid over-anticoagulation

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below or CHEST guidelines (CHEST 2008; 133: 546s-592S Antithrombotic Therapy in Atrial Fibrillation or consult Vascular Medicine, Internal Medicine, Chest 2012;141:No.2, e531S-e575S or Hematology or Clinical Pharmacy for assistance.

A) Unfractionated Heparin

1) Review the risks and benefits and alternatives of anticoagulation with the patient.
2) Begin treatment immediately unless there is a contraindication to its use.
3) Unfractionated heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions to UFH are rare but may include hypersensitivity, fever, urticaria and rhinitis. Hyperkalemia, hypoaldosteronism and elevation in transaminases (ALT/AST) have also been reported. Sudden severe anaphylactoid-type reactions resulting in hypertension, respiratory distress and/or chest pain are associated with HIT as is skin necrosis at the site of a subcutaneous heparin injection.
4) Obtain baseline laboratory studies including complete blood count, aPTT, and if warfarin/Coumadin® is to be used a PT/INR. Pharmacists verifying or entering orders for UFH will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory work has not been obtained or ordered, the pharmacist will place an order to obtain these baseline studies.
5) Ensure the prophylaxis medication (if applicable) is discontinued prior to starting full dose anticoagulation.
6) Select the proper UFH nomogram for atrial fibrillation (see Table 14) for intravenous bolus and continuous infusion dosing using programmable infusion pumps. Use an intravenous bolus of 60 units/kg of UFH followed by 12 units/kg/hour of UFH as a continuous infusion. Patients on warfarin/Coumadin® as an outpatient who are hospitalized should have UFH initiated when their INR drops below < 2.

Table 14. Heparin Nomogram Orders for Atrial Fibrillation

Cleveland Clinic Low Dose/ACS Unfractionated Heparin Adult Patients (only) *PTTAC Nomogram for all ACS Patients with or without Thrombolytics and/or glycoprotein IIb/IIIa Agents and when a Lower Range Anticoagulation is desired*

Weight-Based Heparin Nomogram for *Initial* Bolus and *Initial* Infusion rates only: (based on 60 units/ kg bolus and 12 units/ kg/ hour infusion) GOAL PTTAC = 53-71 SECONDS (Target Heparin: 0.2 - 0.5 anti-Xa units / ml)		
Heparin Nomogram Dosing Adjustments		
Laboratory PTTAC Result (seconds)		**Repeat PTTAC in**
Less than 32.4	Use dosing calculator found on the MAR for dosing adjustments	6 Hours
32.4 – 54		6 Hours
55 – 79		6 Hours
80 – 101		6 Hours
102 – 118		6 Hours
119-150		4 Hours
Greater than 150	Hold heparin infusion and notify physician	

- **Check first PTTAC 6 hours after infusion started, then follow dosing calculator for heparin adjustments.**
- **Once 2 consecutive PTTACs are within therapeutic range, repeat PTTACs in a.m. and then daily.**
- **Notify MD for 2 consecutive PTTACs < 53 or > 71 seconds**
- **PTTAC values >150 sec consider holding the infusion for 1 hour and decreasing the infusion by 3 units/kg/hour**

7) An aPTT should be performed every 6 hours until the patient reaches a targeted therapeutic level, then daily (or for dosing changes). The target for the aPTT is subject to the laboratory and dependent on the reagents used. Currently the CCF target is 53 to 71 seconds; however, when changes are needed; clinicians will be notified of new targets by the laboratory. The anti-Xa heparin assay is an alternative and the target is 0.2 to 0.5 IU/ml. The anti-Xa heparin assay may be considered for routine monitoring, but should be used if the patient requires large daily doses of UFH without achieving a therapeutic aPTT (heparin resistance) or if the patient has a lupus anticoagulant. Causes of heparin resistance include: increased heparin clearance, increased heparin-binding proteins, elevation of factor VIII or fibrinogen levels, certain medications and antithrombin deficiency.

8) A flow sheet should be used to monitor laboratory tests, including the date, heparin dose, aPTT or an anti-Xa heparin assay and complete blood count with platelet count. If warfarin is to be used, a PT/INR and warfarin dose should be added. EPIC Report on Anticoagulation Therapy Accordion is available to help with patient monitoring9) The platelet count should be monitored at least every 2-3 days while on intravenous heparin therapy from day 4 up until day 14 or UFH is discontinued to identify or prevent the development of HIT. If there has been recent UFH administration (within 100 days), check the platelet count at baseline and within 24 hours and from days 4 to 14 or until UFH is discontinued to monitor for rapid-onset HIT. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% while on UFH from the pretreatment level or if the platelet count drops below 150,000 mm^3; or if the patient experiences new thrombosis or skin necrosis. Start warfarin therapy once the patient is therapeutic on UFH; see the Warfarin section for further guidelines.

10) Overlap UFH a minimum of 5 days with warfarin (if applicable) and the INR should be ≥ 2 for >24 hours after the appropriate overlap prior to discontinuing UFH in patients at high risk of stroke. If the patient is scheduled for discharge before reaching the targeted INR, the patient may require bridging with a parenteral anticoagulant (UFH, LMWH or fondaparinux) to ensure that both the overlap time and targeted INR are attained. Patients with a low stroke risk may be discharged with a sub-therapeutic INR without parenteral anticoagulation provided that the patient does not have left atrial thrombus or other risks for thromboembolism.

11) Discontinue heparin 6 hours prior to any surgical or interventional procedure including but not limited to: CVP lines, pacemaker wires, chest tubes OR removal of epidural catheters. One should consider checking an aPTT before any new procedure to ensure that the patient no longer exhibits a heparin anticoagulant effect. Patients who have an epidural or spinal anesthesia, or who receive a spinal puncture are at risk of developing an epidural or spinal hematoma. This can result in long-term or permanent paralysis. The drugs black box warns that these patients should be frequently monitored for signs of neurological impairment and if neurologic compromise is noted, urgent treatment is needed.

12) Notify the appropriate service immediately if bleeding, new thrombosis or any complications from UFH therapy develop.

13) Heparin can be reversed rapidly by infusion of protamine sulfate. This should be reserved for major bleeding because of risk of anaphylaxis to protamine. Protamine is administered intravenously over 10 minutes at a dose of 1 mg/100 units of circulating heparin. No more than 50 mg should be given over any 10 minute period. A general rule for dosing protamine is to calculate the dose based on

the previous 2-3 hours of heparin received by continuous infusion (example: a patient receiving 1200 units/hour should receive about 30 mg of protamine (1200 X 2.5 hours = 3000 units then divide 3000 units by 100 units/mg to get 30 mg)). If a patient bleeds on heparin within 30 minutes of a bolus of heparin use the entire bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin should receive about 50 mg of protamine(5000 units divided by 100units/mg to get 50 mg)). If the bolus was greater than 30 minutes but less than 60 minutes use ½ of the bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin 60 minutes ago and an infusion of 1000 units/hour should receive about 35 mg of protamine (Since the bolus was 60 minutes ago use ½ of the bolus dose which is 2500 units then add 1000 units for the infusion which equates to 3500 units divide this number by 100 units/mg to get the 35 mg of protamine. The appropriate dose of protamine is dependent upon the dose of heparin given. Recommend consulting Clinical Pharmacy, Vascular Medicine or Hematology for assistance.

Example of Protamine Dosing for UFH reversal

Patient Scenario	General Dosing Rule	Example: Calculating Protamine Dose	
		Patient's current heparin dose	Calculation
Heparin continuous infusion for > 2 hours	Calculate dose based on the previous 2-3 hours of heparin administered as a continuous infusion	1200 units/hr for 2.5 hours	1. 1200 units X 2.5 hours = 3000 units 2. 3000 units ÷ 100 units/1mg** = **30mg of Protamine**
Heparin bolus within the past 30 minutes	Use entire bolus dose to calculate reversal	5000 unit bolus	1. 5000 units ÷ 100 units/1mg** = **50mg of Protamine**
Heparin bolus within 30-60 minutes plus initiated on a continuous infusion	Use ½ of the bolus dose and include current infusion dose	5000 unit bolus, then 1000 units/hr for one hour	1. To reverse bolus, use 2500 units since bolus was 60 minutes. Add infusion portion of 1000 units for the past hour. Therefore total heparin to be reversed is 2500 units + 1000 units = 3500 units 2. 3500 units ÷ 100 units/1mg** = **35mg of Protamine**

B) Low Molecular Weight Heparin (LMWH) Enoxaparin (Lovenox®)

1) Review the risks and benefits and alternatives to anticoagulation to the patient. Low molecular weight heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions include but are not limited to: fever, nausea, elevation in the transaminases (ALT/AST), hematoma at the injection site or easy bruising, hyperkalemia and hypoaldosteronism.
2) Discontinue the DVT prophylaxis medication if applicable.
3) Obtain baseline laboratory studies including complete blood count, PT/INR and serum creatinine. Laboratory studies obtained in the previous 48 hours may be considered baseline. Pharmacists verifying or entering orders for enoxaparin/Lovenox® will check that baseline laboratory values have been obtained or ordered. Calculation of the creatinine clearance should also be done to assess renal function. If baseline lab work has not been obtained or ordered the pharmacist will place an order to obtain the baseline lab work.
4) Use weight-based subcutaneous dosing for enoxaparin/Lovenox® administering 1 mg/kg/every 12 hours or at a daily dose of 1.5 mg/kg. If the creatinine clearance is <30 ml/minute use the 1mg/kg/day dosing of enoxaparin/Lovenox®. Be certain the patient's weight is accurate, calculated in kilograms and that the creatinine clearance is known.
5) Low molecular weight heparins are contraindicated for patients on dialysis.
6) If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT. Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% from the baseline or if the platelet count drops below 150,000 mm^3, or if the patient develops new thrombosis or skin necrosis while on LMWH**.**
7) Use a flow sheet to monitor appropriate laboratory tests including date, dose of LMWH, serum creatinine, anti-Xa to LMWH level, complete blood count with platelet count and if warfarin to be used, a PT/INR and dose of warfarin. EPIC Report on Anticoagulation Therapy Accordion is available to help with patient monitoring.

8) Monitoring LMWH is generally not necessary, however, may be indicated if the patient has renal insufficiency, is obese; pregnant or for the pediatric patient. An anti-Xa level with LMWH (enoxaparin/Lovenox®) as the reference should be drawn 4 hours after a subcutaneous dose is administered. Therapeutic levels of anti-Xa to LMWH are 0.5 to 1 IU/mL for every 12 hour dosing and >1 IU/mL for every 24 hour dosing.
9) Begin warfarin after the first dose of LMWH (if indicated). Overlap enoxaparin/Lovenox® a minimum of 5 days with warfarin (when applicable) and until the INR is ≥ 2 for > 24 hours prior to discontinuing the LMWH in patients at high risk of stroke. If the patient is scheduled for discharge before the INR reaches the target, the patient may require a parenteral anticoagulant (UFH, LMWH or fondaparinux) to ensure both the overlap time frame and the targeted INR are reached. Patients with a low stroke risk may be discharged with a sub-therapeutic INR without parenteral anticoagulation provided that the patient does not have a left atrial thrombus or other risks of thromboembolism.
10) Discontinue the LMWH preparation (enoxaparin/Lovenox®) 24 hours prior to any surgical or interventional procedure including but not limited to CVP lines, chest tubes, pacemaker wires, or epidural catheter removal. The manufacturers' recommendation for enoxaparin/Lovenox® and epidural catheters is to not use this agent for at least 2 hours after removal of these devices.
11) If bleeding, thrombosis or other adverse reactions including skin necrosis develop, notify the primary service immediately.
12) LMWH is not completely neutralized (reversed) by protamine sulfate unlike UFH and should not be the only agent used to reverse the anticoagulant activity. Protamine sulfate will reverse the antithrombin activity of LMWH however will only reverse up to 60% of the anti-factor Xa activity. One mg of enoxaparin/Lovenox equals approximately 100 anti-Xa units. Protamine Sulfate may be given as 1 mg per 100 anti-Xa units of LMWH (enoxaparin/Lovenox®) when given within 8 hours of last administered dose. Protamine sulfate at a dose of 0.5 mg / 100 anti-Xa units of LMWH should be administered when the dose was administered between 8 and 12 hours ago or if the aPTT measured 2-4 hours after the first dose of protamine is still prolonged. Protamine sulfate may not necessary when the last dose of LMWH was administered greater than 12 hours earlier. There may be some situations that may require assistance and we recommend consulting Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

C) Warfarin (Coumadin®)

1) Determine the need for long-term anticoagulation with warfarin/Coumadin®

2) Explain the risks and benefits of anticoagulation and alternatives to the patient and/or family members.
3) Contraindications to the use of warfarin use may include but are not limited to active bleeding (gastrointestinal or other), hypersensitivity or an allergy to warfarin, pregnancy or childbearing potential w/o contraception, history of a major bleeding disorder, major surgery, trauma or a stroke within the past two weeks, a history of heparin-induced thrombocytopenia (HIT) and a history of noncompliance, language barriers or unsuitable home environment or at risk of falling.
4) Obtain a complete blood count and PT/INR as baseline laboratory studies. Pharmacists verifying or entering orders for warfarin/Coumadin® will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline lab work has not been obtained or ordered the pharmacist will place an order to obtain these studies.
5) Recommend starting warfarin/Coumadin® doses of between 5 mg and 10 mg for the first 1 to 2 days for most patients. Subsequent dosing will be based on the international normalized ratio (INR). For elderly patients, those malnourished, with congestive heart failure or liver disease or recent major surgery or on medications known to increase sensitivity to warfarin, begin lower doses (less than 5 mg) with subsequent dosing based on the INR. If the patient has HIT do not begin warfarin/Coumadin® during the acute event and until the platelet count is > 100,000 mm^3 and preferably to 150,000 mm^3 and the patient is recovering.
6) Recognize Genomics – the genetic variants of the enzymes that metabolize warfarin/Coumadin® contribute to differences in patients responses to various warfarin/Coumadin® doses. Patients with one of the genetic defects (CYP2C9 or VKORC1) require lower doses. Molecular testing is available through Laboratory Medicine. This testing is not necessary for all patients however. Consult Vascular Medicine, Hematology, Clinical Pharmacy or Laboratory Medicine for recommendations.
7) Administer warfarin/Coumadin® the same time each day, preferably in the evening.
8) Notify dietary services that the patient is receiving warfarin/Coumadin® while in the hospital.
9) Prior to discharge, assure the following:
    a) Determine who will monitor the patient.
    b) Determine the target INR range.
    c) Determine the length of therapy and/or a review date.
10) Patient Education must include the following:
    a) Patient has access to the warfarin/Coumadin® book and/or has viewed the video.

b) Patient has received "***General Warfarin***/Coumadin® ***Instructions for the Patient".*** (See below). Additional information is available in section XV.

c) Evidence that the patient understands the potential for drug-drug interactions.

d) Explain that warfarin and Coumadin® are the same drug. Warfarin is the generic name for Coumadin®.

D) Dabigatran (Pradaxa®)

1) Determine the need for long-term anticoagulation.
2) Explain the risks and benefits of anticoagulation. Contraindications to dabigatran/Pradaxa® use may include but are not limited to active bleeding (gastrointestinal or other), hypersensitivity or an allergy to dabigatran/Pradaxa®, a history of a major bleeding disorder, a history of noncompliance, language barriers or unsuitable home environment or risk of falling and severe renal dysfunction. It is also contraindicated in patients with mechanical heart valves.
3) Obtain baseline BMP and complete blood count.
4) Recommend doses of 150 mg every 12 hours for patients with normal renal function. For patients with a creatinine clearance of 15 to 30 mL/min, a dose of 75 mg PO every 12 hours is recommended. Dabigatran/Pradaxa® is contraindicated in patients on dialysis or if the creatinine clearance is less than 15 mL/min.
5) Conversion from warfarin/Coumadin® to dabigatran:

    a. Discontinue warfarin and monitor the INR and once the INR falls below 2 initiate dabigatran.

    b. Conversion from a parenteral anticoagulant (UFH, LMWH, fondaparinux) to dabigatran/Pradaxa®:i. Start dabigatran/Pradaxa® 0 to 2 hours before the next dose of the parenteral agent LMWH or fondaparinux OR

    ii. At the time of discontinuation of a continuously infusing parenteral drug (UFH)

6) Discontinue Dabigatran/Pradaxa:

Table 15. Peri-procedural Recommendations for Dabigatran based on the Renal Function and Interventional or Surgical Procedure

Creatinine clearance, mL/min	Half-life, hours	Standard risk of bleeding	High risk of bleeding
>80	13 (11-22)	24 h	2 days
50 ≤ 80	15 (12-34)	24 h	2 days
30 ≤ 50	18 (13-23)	2 days	4 days
≤30	27 (22-35)	4 days	6 days

Standard risk of bleeding: card cath, colonoscopy without removal of polyps, uncomplicated laparoscopic procedures (gall bladder)

References: Blood 2012; 119:3016-3023 and Thromb Haemostasis; 2010: 103: 1-12

7) Dabigatran/Pradaxa cannot be reversed. If clinical bleeding, discontinue dabigatran/Pradaxa® immediately, give supportive therapy. Dabigatran can be dialyzed. Recombinant factor VIIa may be considered. Consult vascular medicine or hematology for management of the major bleed.

8) Take dabigatran/Pradaxa® at the same time each day. Dabigatran/Pradaxa® is an oral capsule and can NOT be opened. It should be swallowed whole without alteration. For a missed dose, if not taken at the scheduled time it should be given as soon as possible on the same day.

9) Prior to discharge, determine the length of therapy and/or a review date for its discontinuation orcontinuation.

10) Ensure patient understands the use of dabigatran/Pradaxa®. Patient should also have written discharge instructions that include: compliance issues, side effects of the drug.

E) Rivaroxaban (Xarelto®)

1) Determine the need for long term anticoagulation and explain the risks and benefits of anticoagulation.

2) Contraindications to rivaroxaban/Xarelto® use may include but are not limited to active bleeding or hypersensitivity to rivaroxaban. Avoid concomitant use with NSAIDs/Aspirin and P2Y12 inhibitors (ie clopidogrel) as well as with combined P-gp and strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, lopinavir/ritonavir, indinavir/ritonavir and conivaptan as these may cause an increase bleeding risk. Use with erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone and felodipine may increase bleeding

risk and rivaroxaban/Xarelto® use is recommended only if the potential benefit justifies the risk. Also, avoid use with carbamazepine, phenytoin, rifampin, St. John's wort or consider increasing the dose of rivaroxaban/Xarelto® if they must be co-administered. Avoid use with moderate hepatic impairment and in patients with a creatinine clearance less than 30 mL/min. If the creatinine clearance is between 30 to 50 mL/min monitoring of renal function is recommended. Its use in pregnancy and lactation should be avoided.

3) Obtain baseline BMP and complete blood count.
4) Recommend dose of 20 mg PO daily with evening meal for creatinine clearance greater than 50 mL/min and 15mg PO daily for creatinine clearance of 15 to 50 mL/min. Avoid use if the creatinine clearance is less than 15 mL/min.
5) Missed dose (if not taken at the scheduled time) should be given as soon as possible on the same day
6) Discontinue rivaroxaban/Xarelto® at least 24 hours before any surgical procedure depending on bleeding risk and renal function (see table 16 below).

Table 16. Peri-procedural Recommendations for Rivaroxaban based on the Renal Function and Interventional or Surgical Procedure

Creatinine clearance, mL/min	Half-life, hours	Standard risk of bleeding	High risk of bleeding
>30	12 (11-13)	24 h	2 days
<30	unknown	2 days	4 days

High risk of bleeding includes cardiac and neurosurgery, abdominal surgery, spinal anesthesia

References: Blood 2012; 119:3016-3023 and Thromb Haemostasis; 2010: 103: 1-12

7) Prior to discharge, determine the length of therapy and/or a review date for its discontinuation or continue.
8) Ensure patient understands the use of Rivaroxaban/Xarelto®. Patient should also have written discharge instructions that include: compliance issues.
9) There is an increased risk for thrombotic events in patients with non-valvular atrial fibrillation if discontinuing rivaroxaban/Xarelto® in the absence of adequate alternative anticoagulation. An increased rate of stroke was observed during transition from rivaroxaban/Xarelto® to warfarin in clinical trials in atrial fibrillation patients. If rivaroxaban/Xarelto® must be discontinued for a reason other than bleeding, consider bridging with another anticoagulant starting 24 hours after the last dose. 10) There is no antidote for rivaroxaban/Xarelto®. If bleeding occurs, discontinue rivaroxaban/Xarelto immediately. The use of activated charcoal

to reduce absorption of rivaroxaban may be considered. It is not dialyzable. Prothrombin complex concentrates may be considered if bleeding is serious or life threatening. Contact vascular medicine, hematology or pharmacy for additional advice.

X. Treatment of Patients with Prosthetic Heart Valves

Patients must be advised of the risks and benefits of Anticoagulation

Table 17: Summary of Pharmaceutical Treatment Options for Mechanical Heart Valves

Agent	Baseline labs	Dosing	Monitoring
A) Heparin (UFH)	CBC, aPTT PT/INR if warfarin to be used	**Post operative**: • Therapeutic anticoagulation as dictated by the risks of post-operative bleeding. Initiate low dose therapeutic UFH anticoagulation typically without a bolus. • **Patients with existing mechanical heart valve/s:** Initiate UFH as soon as the INR decreases to subtherapeutic levels unless not clinically feasible.	• If baseline laboratory studies are abnormal or there is difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • Target an aPTT of 53 to 71 seconds or an anti-Xa level of 0.2 to 0.5 anti-Xa IU/mL if therapeutic levels desired. • Monitor the platelet count at least every 2-3 days from day 4 to 14 or until UFH is discontinued to prevent or identify patients at risk of HIT. • If the patient has received UFH within the previous 100 days, a baseline platelet count and one within 24 hours should also be obtained to prevent or identify patients at risk of HIT and then every other day until UFH is discontinued.
B) LMWH Enoxaparin/ Lovenox®	CBC, creatinine PT/INR if warfarin to be used.	• Give 1mg/kg enoxaparin/Lovenox® subcutaneously every 12 hours up to a maximum dose of 150 mg total. • Recommend contacting Clinical Pharmacy or Vascular Medicine for recommendations on higher doses. • Adjust LMWH dose based on renal function. If the creatinine clearance is < 30 mL/min use 1 mg/kg enoxaparin/Lovenox® subcutaneously daily. • LMWH preparations are contraindicated if the patient is on dialysis.	• If baseline laboratory studies are abnormal or there is difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • Monitoring is not necessary unless the patient has renal insufficiency, obese, pregnant or is a pediatric patient • Use an anti-Xa level to LMWH as the standard to get. • Levels are 0.5 to 1 IU/mL for every 12 hour dosing and >1 IU/mL for every 24 hour administration. • Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. • If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT.
E) Warfarin	CBC, PT/INR	• Oral doses: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg. • 10 mg dose is dye-free.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • PT/INR (range dictated by valve type, position, and co-morbid conditions

This is intended as a guideline and does not replace your clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below or CHEST

guidelines CHEST 2008; 133: 593S-629S, Valvular and Structural Heart Disease or consult Vascular Medicine, Hematology, Internal Medicine, Chest 2012;141:e576S-e600S. or Clinical Pharmacy for assistance.

A) Anticoagulation Post Mechanical Valve Replacement Surgery

1) Anticoagulation with UFH or LMWH (enoxaparin/Lovenox®) should be initiated as dictated by clinical concerns regarding postoperative bleeding.
2) Parenteral anticoagulation should be followed by warfarin and continued until the INR is > 2.5 for 2 consecutive days. Warfarin should be continued indefinitely.
3) The intensity of warfarin therapy should be dictated by the valve type, valve location and additional risk factors for thromboembolism.
4) For more specific information recommend checking the CHEST guidelines *CHEST 2008; 133: 593S-629S, Valvular and Structural Heart Disease* or *Chest* 2012: 141,e576S-e600S.

B) Pregnancy and Mechanical Heart Valves

1) The risks and benefits of UFH and LMWH must be discussed with the patient and/or family members.
2) When using an anticoagulant in pregnant women with mechanical heart valves, one of the following anticoagulant regimens is advised in preference to no anticoagulation:
   a) Adjusted-dose bid LMWH throughout pregnancy. The dose should be adjusted to achieve a peak anti-Xa level to LMWH level of 0.5 to 1.0 IU/mL obtained 4 hours after a subcutaneous injection.
   b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 hours in doses adjusted to keep the mid-interval aPTT at least twice the control or attain an anti-Xa heparin level of 0.3 to 0.7 IU/mL.
   c) UFH or LMWH (as above) until the thirteenth week with warfarin substitution until close to delivery when UFH or LMWH is resumed.
3) For more specific information recommend consulting Vascular Medicine or Hematology and/or checking the CHEST guidelines or *CHEST 2012; 141: 576S-6014S, Valvular and Structural Heart Disease.*

C) Anticoagulation Post Bioprosthetic Valve Replacement Surgery

1) Bioprosthetic valves in the mitral position require anticoagulation. Bioprosthetic valves in the aortic position do not require anticoagulation unless there is another compelling indication (atrial fibrillation, left atrial thrombus, etc).
2) Anticoagulation with UFH or LMWH (enoxaparin/Lovenox®) should be initiated as dictated by clinical concerns regarding postoperative bleeding.
3) Parenteral anticoagulation (UFH, LMWH (enoxaparin/Lovenox) should be followed by warfarin and continued until the INR is > 2 for 2 consecutive days.
4) After the first 3 months of anticoagulation (in patients who are in normal sinus rhythm and have no other indication for anticoagulation) it is recommended that aspirin be initiated and the warfarin discontinued.
5) For more specific information recommend checking the CHEST guidelines ***CHEST 2008; 133: 593S-629S, Valvular and Structural Heart Disease*** **or** ***Chest 2012;141:e576S-e600S..***

D) Unfractionated Heparin

1) Review the risks and benefits and alternatives of anticoagulation with the patient.
2) Unfractionated heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions to UFH are rare but may include hypersensitivity, fever, urticaria and rhinitis. Hyperkalemia, hypoaldosteronism and elevation in transaminases (ALT/AST) have also been reported. Sudden severe anaphylactoid-type reactions resulting in hypertension, respiratory distress and/or chest pain are associated with HIT as is skin necrosis at the site of a subcutaneous heparin injection.
3) Ensure any VTE prophylaxis medication is discontinued prior to starting full dose anticoagulation.
4) Obtain a complete blood count, aPTT, and if warfarin is to be used a PT/INR. Pharmacists verifying or entering orders for UFH will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory work has not been obtained or ordered, the pharmacist will place an order to obtain these baseline studies.
5) Though there is no specific nomogram for patients with mechanical heart valves one may select the UFH LOW RANGE/ACS nomogram for intravenous bolus and continuous infusion dosing using programmable infusion pumps. Use an intravenous UFH bolus of 60 units/kg followed by 12 units/kg/hour continuous UFH infusion. If the patient is postoperative, **DO NOT** use a bolus.

Table 18. Heparin Nomogram Orders for Heart Valves

Cleveland Clinic Low Dose/ACS Unfractionated Heparin Adult Patients (only) *PTTAC Nomogram for all ACS Patients with or without Thrombolytics and/or glycoprotein IIb/IIIa Agents and when a Lower Range Anticoagulation is desired*

Weight-Based Heparin Nomogram for *Initial* Bolus and *Initial* Infusion rates only: (based on 60 units/ kg bolus and 12 units/ kg/ hour infusion) GOAL PTTAC = 51-73 SECONDS (Target Heparin: 0.2 - 0.5 anti-Xa units / ml)		
Heparin Nomogram Dosing Adjustments		
Laboratory PTTAC Result (seconds)		**Repeat PTTAC in**
Less than 32.4	Use dosing calculator found on the MAR for dosing adjustments	6 Hours
32.4 – 54		6 Hours
55 – 79		6 Hours
80 – 101		6 Hours
102 – 118		6 Hours
119-150		4 Hours
Greater than 150	Hold heparin infusion and notify physician	

- **Check first PTTAC 6 hours after infusion started, then follow dosing calculator for heparin adjustments.**
- **Once 2 consecutive PTTACs are within therapeutic range, repeat PTTACs in a.m. and then daily.**
- **Notify MD for 2 consecutive PTTACs < 51 or > 73 seconds**
- **PTTAC values >150 sec consider holding the infusion for 1 hour and decreasing the infusion by 3 units/kg/hour**

6) An aPTT should be performed every 6 hours until the patient reaches a targeted therapeutic level, then daily (or for dosing changes). The target for the aPTT is subject to the laboratory and dependent on the reagents used. Currently the main CC laboratory target is 53 to 71 seconds; however, when changes are implemented; clinicians will be notified of the new aPTT targets by the laboratory. The anti-Xa heparin assay is an alternative to the aPTT and the target is 0.2 to 0.5 IU/mL. The anti-Xa heparin assay may be considered for routine monitoring, but should be used if the patient requires larger daily doses of UFH without achieving a therapeutic aPTT (heparin resistance) or if the patient has a lupus anticoagulant. Causes of heparin resistance include: increased heparin clearance, increased heparin-binding proteins, elevation of factor VIII or fibrinogen levels, certain medications and antithrombin deficiency.

7) A flow sheet should be used to monitor laboratory tests, including the date, heparin dose, aPTT or an anti-Xa heparin assay and CBC with platelet count. If warfarin is to be used include the PT/INR and warfarin dose. See EPIC Report Anticoagulation Therapy Accordion is available to help with patient monitoring.

8) The platelet count should be monitored at least every 2-3 days while on intravenous heparin therapy from day 4 up until day 14 or UFH is discontinued to identify or prevent HIT. If recent UFH or LMWH administration within the previous 100 days checks the platelet count at baseline and within 24 hours and then from day 4 to 14 or until UFH is discontinued to monitor for rapid-onset HIT. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% while on UFH from the pretreatment level or if the platelet count drops below 150,000 mm^3; or if the patient experiences new thrombosis or skin necrosis. Start warfarin therapy once the patient is therapeutic on UFH; see the Warfarin section for further guidelines.

9) The INR should be ≥2 for >24 hours after appropriate overlap prior to discontinuing UFH. If the patient is scheduled for discharge before the INR reaches the targeted INR, the patient may require a parenteral anticoagulant (UFH or LMWH or fondaparinux) to ensure both the overlap time frame and the targeted INR are reached.

10) Discontinue heparin 6 hours prior to any surgical or interventional procedure including but not limited to: CVP lines, pacemaker wires, chest tubes OR removal of epidural catheters. One should consider checking an aPTT before any new procedure to ensure that the patient no longer exhibits a heparin anticoagulant effect. Patients who have an epidural or spinal anesthesia, or who receive a spinal puncture are at risk of developing an epidural or spinal hematoma. This can result in long-term or permanent paralysis. The drugs black box warns that these patients should be frequently monitored for signs of neurological impairment and if neurologic compromise is noted, urgent treatment is needed.

11) Notify the appropriate service immediately if bleeding, new thrombosis or any complications from UFH therapy develop.

12) Heparin can be reversed rapidly by infusion of protamine sulfate. This should be reserved for major bleeding because of risk of anaphylaxis to protamine. Protamine is administered intravenously over 10 minutes at a dose of 1 mg/100 units of circulating heparin. No more than 50 mg should be given over any 10 minute period. A general rule for dosing protamine is to calculate the dose based on the previous 2-3 hours of heparin received by continuous infusion (example: a patient receiving 1200 units/hour should receive about 30 mg of protamine (1200 X 2.5 hours =

3000 units then divide 3000 units by 100 units/mg to get 30 mg)). If a patient bleeds on heparin within 30 minutes of a bolus of heparin use the entire bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin should receive about 50 mg of protamine(5000 units divided by 100units/mg to get 50 mg)). If the bolus was greater than 30 minutes but less than 60 minutes use ½ of the bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin 60 minutes ago and an infusion of 1000 units/hour should receive about 35 mg of protamine (Since the bolus was 60 minutes ago use ½ of the bolus dose which is 2500 units then add 1000 units for the infusion which equates to 3500 units divide this number by 100 units/mg to get the 35 mg of protamine. The appropriate dose of protamine is dependent upon the dose of heparin given. Recommend consulting Clinical Pharmacy, Vascular Medicine or Hematology for assistance.

Example of Protamine Dosing for UFH reversal

Patient Scenario	General Dosing Rule	Example: Calculating Protamine Dose	
		Patient's current heparin dose	Calculation
Heparin continuous infusion for > 2 hours	Calculate dose based on the previous 2-3 hours of heparin administered as a continuous infusion	1200 units/hr for 2.5 hours	1. 1200 units X 2.5 hours = 3000 units 2. 3000 units ÷ 100 units/1mg** = **30mg of Protamine**
Heparin bolus within the past 30 minutes	Use entire bolus dose to calculate reversal	5000 unit bolus	1. 5000 units ÷ 100 units/1mg** = **50mg of Protamine**
Heparin bolus within 30-60 minutes plus initiated on a continuous infusion	Use ½ of the bolus dose and include current infusion dose	5000 unit bolus, then 1000 units/hr for one hour	1. To reverse bolus, use 2500 units since bolus was 60 minutes. Add infusion portion of 1000 units for the past hour. Therefore total heparin to be reversed is 2500 units + 1000 units = 3500 units 2. 3500 units ÷ 100 units/1mg** = **35mg of Protamine**

E) Low Molecular Weight Heparin (LMWH) ***Enoxaparin (Lovenox®)***

1) Review the risks and benefits and alternatives to anticoagulation to the patient.
2) Low molecular weight heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions include but are not limited to: fever, nausea, elevation in the transaminases (ALT/AST), hematoma at the injection site or easy bruising, hyperkalemia and hypoaldosteronism.
3) Discontinue the VTE prophylaxis medication if applicable.

4) Obtain baseline laboratory studies including complete blood count, PT/INR and serum creatinine. Laboratory studies obtained in the previous 48 hours may be considered baseline. Pharmacists verifying or entering orders for enoxaparin/Lovenox® will check that baseline laboratory values have been obtained or ordered. Calculation of the creatinine clearance should also be done to assess renal function. If baseline lab work has not been obtained or ordered the pharmacist will place an order to obtain the baseline lab work.
5) Use weight-based subcutaneous dosing for enoxaparin/Lovenox® at 1 mg/kg/every 12 hours or 1.5mg/kg for once a day dosing). If the creatinine clearance is ≤ 30 ml/minute, use 1 mg/kg/day dosing of enoxaparin/Lovenox®. Be certain the patient's weight is accurate, calculated in kilograms and that the creatinine clearance is known.
6) Low molecular weight heparins are contraindicated for patients on dialysis.
7) If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT. Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% from the baseline or if the platelet count drops below 150,000 mm^3, or if the patient develops new thrombosis or skin necrosis while on LMWH**.**
8) Use a flow sheet to monitor appropriate laboratory tests including date, dose of the LMWH, serum creatinine, anti-Xa to LMWH (if applicable), a complete blood count with platelets and if warfarin to be used, a PT/INR and dose of warfarin. See EPIC Report on Anticoagulation Therapy Accordion is available. to help patient monitoring.
9) Monitoring LMWH is generally not necessary, however, may be indicated if the patient has renal insufficiency; obese; pregnant or for pediatric patients. An anti-Xa level with LMWH (Enoxaparin/Lovenox®) as the reference should be drawn 4 hours after a subcutaneous dose is administered. Therapeutic levels of anti-Xa to LMWH are 0.5 to 1 IU/mL for twice daily dosing and >1 IU/mL for every 24 hour dosing.
10) Begin warfarin after the first dose of LMWH (if indicated). When converting to warfarin, ensure that the INR is ≥ 2 for > 24 hours after appropriate overlap prior to discontinuing parenteral anticoagulation (if applicable).
11) Discontinue enoxaparin/Lovenox® 24 hours prior to any surgical or interventional procedure including but not limited to CVP lines, chest tubes, pacemaker wires, or epidural catheter removal.

The manufacturers' recommendation for Enoxaparin/Lovenox® and epidural catheters is to not use this agent for at least 2 hours after removal of these devices.

12) If bleeding, thrombosis or other adverse reactions including skin necrosis develop, notify the primary service immediately.
13) LMWH is not completely neutralized (reversed) by protamine sulfate unlike UFH and should not be the only agent used to reverse the anticoagulant activity. Protamine sulfate will reverse the antithrombin activity of LMWH however will only reverse up to 60% of the anti-factor Xa activity. One mg of enoxaparin/Lovenox equals approximately 100 anti-Xa units. Protamine Sulfate may be given as 1 mg per 100 anti-Xa units of LMWH (enoxaparin/Lovenox®) when given within 8 hours of last administered dose. Protamine sulfate at a dose of 0.5 mg / 100 anti-Xa units of LMWH should be administered when the dose was administered between 8 and 12 hours ago or if the aPTT measured 2-4 hours after the first dose of protamine is still prolonged. Protamine sulfate may not necessary when the last dose of LMWH was administered greater than 12 hours earlier. There may be some situations that may require assistance and we recommend consulting Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

XI. Target INR for ACS, Atrial Fibrillation, Prosthetic Heart Valves

Patients must be advised of the risks and benefits of Anticoagulation

Table 19: Target INR for ACS, Atrial Fibrillation and Prosthetic Heart Valves.

INDICATION	**INR**
Tissue Heart Valves	2 TO 3
Acute Myocardial Infarction (To Prevent Systemic Embolism)	2 TO 3
Acute Myocardial Infarction (To Prevent Recurrent MI)	2 TO 3
Valvular Heart Disease	2 TO 3
Atrial Fibrillation	2 TO 3
Bileaflet Mechanical Valve In Aortic Position	2 TO 3
Mechanical Prosthetic Valves (High Risk)	2.5 TO 3.5
AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP) CONSENSUS CONFERENCE ON ANTITHROMBOTIC THERAPY 2008	

FOR SPECIFIC DETAILS SEE CHEST 2008; 133: 160S -198S TREATMENT with Vitamin K **2012 reference 141:e576-e600.** Antagonist or refer to the Cleveland Clinic Anticoagulation Management Program (C-CAMP) or consult Vascular Medicine, Hematology, Internal Medicine or Clinical Pharmacy for assistance.

1) Determine the need for long-term anticoagulation.
2) Explain the risks and benefits of anticoagulation. Contraindications to warfarin/Coumadin® use may include but are not limited to active bleeding (gastrointestinal or other), hypersensitivity or an allergy to warfarin/Coumadin®, during pregnancy or in patients of childbearing potential w/o contraception, a history of a major bleeding disorder, major surgery, trauma or stroke within the

past two weeks, or during acute heparin-induced thrombocytopenia (HIT) and a history of noncompliance, language barriers or unsuitable home environment or risk of falling.

3) Obtain baseline PT/INR and complete blood count.
4) Recommend starting doses of between 5 mg and 10 mg of warfarin/Coumadin® for the first 1 to 2 days for most patients. Subsequent dosing will be based on the international normalized ratio (INR). For elderly patients, those malnourished, congestive heart failure, liver disease or recent major surgery or on medications known to increase the sensitivity to warfarin/Coumadin®, begin lower doses (less than 5 mg) with subsequent dosing based on the INR. If the patient has HIT, do not begin warfarin/Coumadin® until the platelet count has recovered (to at least 150,000 mm^3).
5) Overlap a minimum of 5 days with a parenteral anticoagulant (UFH, LMWH, or fondaparinux). The INR should be ≥ 2 for 24 hours before discontinuing the parenteral anticoagulant after a minimum 5 day overlap. If the patient has acute HIT, do not begin warfarin Coumadin® until the platelet count has recovered to 100,000 mm^3 to 150,000 mm^3 and the patient is recovering and overlap with a DTI for a minimum of 5 days and until the INR is ≥ 2 for 2 consecutive days.
6) The target INR should be ≥ 2 to 3 or higher for select patients as noted in table 13 above.
7) Recognize Genomics – the genetic variants of the enzyme that metabolizes warfarin/Coumadin® contributes to differences in patients responses to various warfarin/Coumadin® doses. Patients with one of the genetic defects (CYP2C9 or VKORC1) require lower doses. Molecular testing is available through Laboratory Medicine. This testing is not necessary for all patients however. Consult Vascular Medicine, Hematology, Clinical Pharmacy or Laboratory Medicine for recommendations.
8) Take warfarin/Coumadin® the same time each day, preferably in the evening up until midnight.
9) Use a flow sheet listing the date, and if overlapping with a parenteral anticoagulant include the anticoagulant, the serum creatinine, aPTT or anti-Xa level to UFH or LMWH (where applicable), complete blood count with platelet count and PT/INR and warfarin/Coumadin® dose.
10) Notify dietary services that patient is receiving warfarin/Coumadin while in the hospital.
11) Prior to discharge, determine who will monitor the patient.
12) Prior to discharge, determine the target INR range.
13) Prior to discharge, determine the length of therapy and/or a review date for its discontinuation or continuation.
14) Ensure patient understands the intricacies of warfarin/Coumadin®, has access to the warfarin/Coumadin® book and/or has viewed the warfarin video. Patient should also have written

discharge instructions that include: compliance issues, dietary restrictions (especially food rich in vitamin K), potential for adverse drug-drug interactions and follow-up monitoring.

15) Make certain the patient understands the potential for drug-drug interactions.

16) Explain that warfarin and Coumadin® are the same drug. Warfarin is the generic name for Coumadin.

XII. Treatment of Acute Ischemic Stroke

Patients must be advised of the risks and benefits of Anticoagulation.

*Table 20. Summary Table of Pharmaceutical Agents for Ischemic Stroke**

Agent	Required Baseline Labs	Dosing per Neurology Protocol	Monitoring
A) Alteplase/ Activase®	CBC, aPTT, fibrinogen	• A dose of 0.9 mg/kg (not to exceed 90 mg) of Alteplase/Activase® with 10% of the total dose administered as an initial intravenous bolus over 1 minute and the rest infused over 60 minutes.	• If baseline laboratory studies are abnormal or difficulty is encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance. • Must monitor in an ICU setting for ≥ 24 hours after administration. • Must be ordered in conjunction with Stroke Neurology Service.
B) Intravenous Heparin (UFH)	CBC, aPTT PT/INR if warfarin is to be used	• No bolus of UFH is given. Start intravenous UFH at 12 units/kg/hour.	• If baseline laboratory studies are abnormal or difficulty is encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • The therapeutic aPTT target is 53-71 seconds for acute ischemic stroke. • Monitor the platelet count at least every 2-3 days from day 4 to 14 or until UFH is stopped to prevent or recognize patients at risk of HIT. • If the patient has received UFH within the previous 100 days, monitor platelet count within 24 hrs. of starting therapy and then every 2-3 days from day 4 to 14 or until UFH is stopped to prevent or recognize patients at risk of HIT
C) LMWH (Enoxaparin/ Lovenox®	CBC, creatinine PT/INR if warfarin is to be used	• Use LMWH only if transitioning to warfarin and/or the patient is to be discharged. The recommended dose is 1 mg/kg every 12 hours subcutaneously of enoxaparin/Lovenox® or 1.5 mg/kg subcutaneously daily for patients with normal renal function up to a	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • Monitoring is not necessary unless the patient has renal insufficiency, is obese, pregnant or is a pediatric patient. • Use an anti-Xa level to LMWH as the standard. Target levels are 0.5 to 1 IU/mL for 12 hour dosing and

		maximum dose of 150 mg total. • Consider contacting Clinical Pharmacy or Vascular Medicine for recommendations on higher doses. • Administer 1 mg/kg subcutaneously daily of enoxaparin/Lovenox® if the creatinine clearance is <30 mL/min. • LWMH preparations are contraindicated if the patient is on dialysis.	>1 IU/mL for daily administration. • Levels should be drawn 4 hours after a subcutaneous injection. • Monitor the platelet count every other day from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. • If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every other day from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT.
D) Warfarin/Coumadin®	CBC, PT/INR	• Warfarin oral doses: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg. • The 10 mg dose is dye-free.	• If baseline laboratory studies abnormal or difficulty encountered with anticoagulation, consult Vascular Medicine, Hematology or Clinical Pharmacy for assistance • PT/INR (target 2-3)

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown above, or reference the CHEST guidelines (CHEST 2008; 133: 630S-669S Antithrombotic and Thrombolytic Therapy for Ischemic Stroke) or consult Vascular Medicine, Hematology, Chest 2012;141:601S-636S. or Clinical Pharmacy for assistance.

A) Alteplase/Activase® (rt-PA)

1) Review the risks and benefits and alternatives of Alteplase with the patient.

2) Consult the Neurology Stroke Service immediately for acute ischemic stroke and the use of rt-PA.

3) Alteplase/Activase ® is contraindicated if there is active internal bleeding, recent intracranial or intraspinal surgery, intracranial neoplasm or aneurysm, known bleeding diathesis, significant trauma, severe uncontrolled hypertension (185 mmHg systolic or >110 mmHg diastolic) or current use of warfarin with an INR >1.7.

4) Obtain baseline complete blood count with platelet count, PT/INR, aPTT, and fibrinogen.

5) Discontinue the VTE prophylaxis medication if applicable.

6) Intravenous Alteplase/Activase® for eligible acute stroke patients is recommended at a dose of 0.9 mg/kg (not to exceed 90 mg) with 10% of the total dose administered as an initial bolus and the rest infused over 60 minutes. **It must be ordered in conjunction with Stroke Neurology Service**.

7) Intensive care unit setting is required for monitoring for ≥ 24 hours after administering Alteplase/Activase®.

B) Unfractionated Heparin

1) Review the risks and benefits and alternatives of anticoagulation with the patient.
2) Unfractionated heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions to UFH are rare but may include hypersensitivity, fever, urticaria and rhinitis. Hyperkalemia, hypoaldosteronism and elevation in transaminases (ALT/AST) have also been reported. Sudden severe anaphylactoid-type reactions resulting in hypertension, respiratory distress and/or chest pain are associated with HIT as is skin necrosis at the site of a subcutaneous heparin injection.
3) Ensure any VTE prophylaxis medication is discontinued prior to starting full dose anticoagulation.
4) Obtain baseline laboratory studies including a complete blood count with platelet count, aPTT, and if warfarin is to be used a PT/INR. Pharmacists verifying or entering orders for UFH will check that baseline laboratory values have been obtained or ordered. Laboratory studies obtained in the previous 48 hours may be considered baseline. If baseline laboratory work has not been obtained or ordered, the pharmacist will place an order to obtain these baseline studies.
5) Full dose UFH should only be reserved for specific clinical situations (i.e., hypercoagulable states). For other patients start UFH at 12 units/kg/hour without a bolus and target an aPTT of 53 to 71 seconds. This nomogram is designed without any boluses.

Table 21. Heparin Nomogram Orders for stroke patients requiring anticoagulation.

Cleveland Clinic Stroke Unfractionated Heparin Adult Patients (only)

Weight-Based Heparin Nomogram for *Initial* Infusion rates only: (based on 12 units/ kg/ hour infusion) GOAL PTTAC = 53-71 SECONDS (Target Heparin: 0.2- 0.5 anti-Xa units / ml)		
Heparin Nomogram Dosing Adjustments		
Laboratory PTTAC Result (seconds)		**Repeat PTTAC in**
Less than 32.4	Use dosing calculator found on the MAR for dosing adjustments	6 Hours
32.4 – 54		6 Hours
55 – 79		6 Hours
80 – 101		6 Hours
102 – 118		6 Hours
119-150		4 Hours
Greater than 150	Hold heparin infusion and notify physician	

- **Check first PTTAC 6 hours after infusion started, then follow dosing calculator for heparin adjustments.**
- **Once 2 consecutive PTTACs are within therapeutic range, repeat PTTACs in a.m. and then daily.**
- **Notify MD for 2 consecutive PTTACs < 51 or > 73 seconds**
- **PTTAC values >150 sec consider holding the infusion for 1 hour and decreasing the infusion by 3 units/kg/hour**

6) Use programmable infusion pumps.

7) Monitor UFH using the aPTT or anti-Xa heparin assay. Once therapy is started, obtain an aPTT every 6 hours until the patient reaches a targeted therapeutic level, then daily (or for dosing changes). The target for the aPTT is subject to the laboratory and dependent on the reagents used. Currently the Cleveland Clinic main campus target is 53 to 71 seconds for acute ischemic stroke. If changes are needed for this target, clinicians will be notified by the laboratory. The anti-Xa heparin assay is an alternative method for monitoring heparin. The anti-Xa heparin assay may be considered for routine monitoring, but should be used if the patient requires large daily doses of UFH without achieving a therapeutic aPTT (heparin resistance) or if the patient has a lupus anticoagulant. Causes of heparin resistance include: increased heparin clearance, increased heparin-binding proteins, elevation of factor VIII or fibrinogen levels, certain medications and

antithrombin deficiency. Recommend consulting Vascular Medicine, Hematology or Clinical Pharmacy for assistance if there is difficulty monitoring UFH.

8) A flow sheet should be used to monitor laboratory tests, including the date, heparin dose, aPTT or an anti-Xa heparin assay and complete blood count with platelet count. If warfarin is to be used, add a PT/INR and warfarin dose. See EPIC Report Anticoagulation Therapy Accordion is available to help with patient monitoring.

9) The platelet count should be monitored at least every 2-3 days while on intravenous or subcutaneous heparin therapy (beginning day 4 to 14 or until discontinued) to identify or prevent HIT. If the patient has received UFH or LMWH within the previous 100 days, a baseline platelet count should be obtained and repeated within 24 hours and then every 2-3 days from day 4 to 14 to monitor for rapid-onset HIT. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient 's platelet count drops 50% while on UFH from the pretreatment level or if the platelet count drops below 150,000 mm^3; or if the patient experiences new thrombosis or skin necrosis while on UFH.

10) Start warfarin therapy (if applicable) once the patient is therapeutic on UFH; see the warfarin section for further guidelines.

11) If UFH is to be used, it should be overlapped a minimum of 5 days with warfarin. The INR should be ≥2.0 for 24 hours prior to discontinuing UFH after the appropriate overlap. If the patient is scheduled for discharge before the INR reaches the targeted goal, the patient may require a parenteral anticoagulant (full dose UFH, LMWH or fondaparinux) to ensure that both the overlap time frame and the targeted INR are attained.

12) Discontinue heparin 6 hours prior to any surgical or interventional procedure including but not limited to: CVP lines, pacemaker wires, chest tubes OR removal of epidural catheters. One should consider checking an aPTT before any new procedure to ensure that the patient no longer exhibits a heparin anticoagulant effect. Patients who have an epidural or spinal anesthesia, or who receive a spinal puncture are at risk of developing an epidural or spinal hematoma. This can result in long-term or permanent paralysis. The drugs black box warns that these patients should be frequently monitored for signs of neurological impairment and if neurologic compromise is noted, urgent treatment is needed.

13) Notify the appropriate service immediately if bleeding, new thrombosis or any complications from UFH therapy develop.

14) Heparin can be reversed rapidly by infusion of protamine sulfate. This should be reserved for major bleeding because of risk of anaphylaxis to protamine. Protamine is administered intravenously over 10 minutes at a dose of 1 mg/100 units of circulating heparin. No more than 50 mg should be given over any 10 minute period. A general rule for dosing protamine is to calculate the dose based on the previous 2-3 hours of heparin received by continuous infusion (example: a patient receiving 1200 units/hour should receive about 30 mg of protamine (1200 X 2.5 hours = 3000 units then divide 3000 units by 100 units/mg to get 30 mg)). If a patient bleeds on heparin within 30 minutes of a bolus of heparin use the entire bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin should receive about 50 mg of protamine(5000 units divided by 100units/mg to get 50 mg)). If the bolus was greater than 30 minutes but less than 60 minutes use ½ of the bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin 60 minutes ago and an infusion of 1000 units/hour should receive about 35 mg of protamine (Since the bolus was 60 minutes ago use ½ of the bolus dose which is 2500 units then add 1000 units for the infusion which equates to 3500 units divide this number by 100 units/mg to get the 35 mg of protamine. The appropriate dose of protamine is dependent upon the dose of heparin given. Recommend consulting Clinical Pharmacy, Vascular Medicine or Hematology for assistance.

Example of Protamine Dosing for UFH reversal

Patient Scenario	General Dosing Rule	Example: Calculating Protamine Dose	
		Patient's current heparin dose	Calculation
Heparin continuous infusion for > 2 hours	Calculate dose based on the previous 2-3 hours of heparin administered as a continuous infusion	1200 units/hr for 2.5 hours	1. 1200 units X 2.5 hours = 3000 units 2. 3000 units ÷ 100 units/1mg** = **30mg of Protamine**
Heparin bolus within the past 30 minutes	Use entire bolus dose to calculate reversal	5000 unit bolus	1. 5000 units ÷ 100 units/1mg** = **50mg of Protamine**
Heparin bolus within 30-60 minutes plus initiated on a continuous infusion	Use ½ of the bolus dose and include current infusion dose	5000 unit bolus, then 1000 units/hr for one hour	1. To reverse bolus, use 2500 units since bolus was 60 minutes. Add infusion portion of 1000 units for the past hour. Therefore total heparin to be reversed is 2500 units + 1000 units = 3500 units 2. 3500 units ÷ 100 units/1mg** = **35mg of Protamine**

C) Low Molecular Weight Heparin (Enoxaparin/Lovenox®)

1) Review the risks and benefits and alternatives of anticoagulation with the patient. Low molecular weight heparin is contraindicated in patients with a heparin allergy or a history of heparin-induced thrombocytopenia (HIT) or in patients with active bleeding. Adverse reactions may include but are not limited to: fever, nausea, elevation in the transaminases (ALT/AST), hematoma at the injection site or easy bruising, hyperkalemia and hypoaldosteronism.
2) Use enoxaparin/Lovenox® at full dose only if the patient is being transitioned to warfarin and/or at discharge as indicated.
3) Discontinue the VTE prophylaxis medication if applicable.
4) Obtain a complete blood count, aPTT, and serum creatinine baseline laboratory studies. Obtain a PT/INR if warfarin is to be used.
5) Use weight-based subcutaneous dosing for enoxaparin/Lovenox® at 1 mg/kg/every 12 hours or 1.5 mg/kg/for every 24 hour dosing. Be certain the patient's weight is accurate, calculated in kilograms and that the creatinine clearance is known.
6) Adjust the dose of the enoxaparin/Lovenox® per the patient's creatinine clearance. If the creatinine clearance is below 30 ml/minute, the dose should be reduced to 1.0 mg/kg/day of enoxaparin/Lovenox® for VTE treatment. Low molecular weight heparin preparations are contraindicated for patients on dialysis.
7) If the patient has received UFH within the previous 100 days, monitor the platelet count within 24 hours of starting LMWH therapy and then every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of rapid-onset HIT. Monitor the platelet count every 2-3 days from day 4 to 14 or until LMWH is stopped to prevent or identify patients at risk of HIT in any postoperative patient receiving LMWH or medical/obstetrical patients receiving LMWH but who received UFH first. Consult the appropriate service (Vascular Medicine or Hematology) to rule out HIT if the patient's platelet count drops 50% while on UFH from the pretreatment level or if the platelet count drops below 150,000 mm^3; or if the patient experiences new thrombosis or skin necrosis while on UFH.
8) Use a flow sheet to monitor appropriate laboratory tests including: date, dose of LMWH, serum creatinine, anti-Xa level to LMWH (if applicable) and a complete blood count with platelet count. If warfarin is to be used, add a PT/INR and dose of warfarin.
9) Monitoring LMWH is generally not necessary, however, may be indicated if the patient has renal insufficiency; is obese; pregnant or for pediatric patients. An anti-Xa level with LMWH (enoxaparin/Lovenox®) as the reference should be obtained and drawn 4 hours after a

subcutaneous dose is administered. Therapeutic levels of anti-Xa to LMWH are 0.5 to 1 IU/mL for twice daily dosing and >1 IU/mL for every 24 hour dosing.

10) Begin warfarin after the first dose of LMWH where applicable. When converting to warfarin, ensure a minimum of 5 days overlap and until the INR is ≥ 2 for 24 hours.

11) Discontinue the LMWH preparation (Enoxaparin/Lovenox®) 24 hours prior to any surgical or interventional procedure including but not limited to CVP lines, chest tubes, pacemaker wires, or epidural catheter removal. The manufacturer's recommendation for Enoxaparin/Lovenox® and epidural catheters is to not use this agent within 2 hours of removal of these devices.

12) Notify the primary service immediately if bleeding, thrombosis or other adverse reactions including skin necrosis develop.

13) LMWH is not completely neutralized (reversed) by protamine sulfate unlike UFH and should not be the only agent used to reverse the anticoagulant activity. Protamine sulfate will reverse the antithrombin activity of LMWH however will only reverse up to 60% of the anti-factor Xa activity. One mg of enoxaparin/Lovenox equals approximately 100 anti-Xa units. Protamine Sulfate may be given as 1 mg per 100 anti-Xa units of LMWH (enoxaparin/Lovenox®) when given within 8 hours of last administered dose. Protamine sulfate at a dose of 0.5 mg / 100 anti-Xa units of LMWH should be administered when the dose was administered between 8 and 12 hours ago or if the aPTT measured 2-4 hours after the first dose of protamine is still prolonged. Protamine sulfate may not necessary when the last dose of LMWH was administered greater than 12 hours earlier. There may be some situations that may require assistance and we recommend consulting Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

14) Outpatient Management using LMWH. The patient and/or caregiver must be given proper instructions by the physician and/or nursing staff prior to discharge. Patients should receive a Enoxaparin/Lovenox® (or equivalent) discharge kit including instructions, record of daily injections, sterile alcohol swabs and sharps collector. The patient and or caregiver must demonstrate an ability to self administer subcutaneous injections.

15) Patient must be able to state the purpose of the LMWH or enoxaparin/Lovenox®, when to notify physician if problems develop including: signs and symptoms of bleeding and/or new thrombosis.

D) Warfarin/Coumadin®

1) Explain the risks and benefits of warfarin anticoagulation.

2) Warfarin is recommended for patients with atrial fibrillation and a recent stroke or TIA as long-term anticoagulation targeting an INR of 2-3. For patients with cryptogenic stroke associated with mobile aortic arch thrombi, use warfarin (or antiplatelet agents).

3) Contraindications to its use may include but are not limited to active bleeding (gastrointestinal or other), history of a major bleeding disorder, major surgery, trauma or stroke within the past two weeks, hypersensitivity or an allergy to warfarin, pregnancy or in patients at risk of falling or non compliance pregnancy or childbearing potential w/o contraception, during acute heparin-induced thrombocytopenia, a history of noncompliance, language barriers or unsuitable home environment or at risk of falling

4) Obtain a complete blood count and PT/INR baseline laboratory studies.

5) Recommend starting doses of warfarin between 5 mg and 10 mg for the first 1 to 2 days for most patients. Subsequent dosing will be based on the international normalized ratio (INR). For elderly patients, those malnourished, congestive heart failure, liver disease or recent major surgery or on medications known to increase sensitivity to warfarin, begin lower doses (less than 5 mg) with subsequent dosing based on the INR. If the patient has HIT, do not begin warfarin until the patient is recovering and the platelet count has recovered to at least 150,000 mm^3.

6) Overlap a minimum of 5 days with a parenteral anticoagulant (UFH, LMWH, or fondaparinux) where applicable. The INR should be ≥ 2 for ≥ 24 hours before discontinuing the parenteral anticoagulant after a minimum 5 day overlap. If the patient has HIT, overlap with a DTI for a minimum of 5 days and until the INR is ≥ 2 for 2 consecutive days.

7) Recognize Genomics – the genetic variants of the enzymes that metabolizes warfarin contribute to differences in patients responses to various warfarin doses. Patients with one of the genetic defects (CYP2C9 or VKORC1) require lower doses. Molecular testing is available through Laboratory Medicine. This testing is not necessary for all patients and should be ordered at the discretion of the oredering physician. Consult Vascular Medicine, Hematology, Clinical Pharmacy or Laboratory Medicine for recommendations.

8) Administer warfarin the same time each day, preferably in the evening up until midnight.

9) Use a flow sheet listing the date, name of parenteral anticoagulant, serum creatinine, and aPTT or anti-Xa level to UFH or LMWH (where applicable), a complete blood count with platelet count and PT/INR and warfarin dose.

10) Notify dietary services that patient is receiving warfarin while in the hospital.

11) Prior to discharge, assure the following:

    a) Determine who will monitor the patient.

b) Determine the target INR range.

c) Determine length of therapy and/or a review date.

12) Patient Education must include the following:

a) Patient has access to the warfarin book and/or has viewed the video.

b) Patient has received ***General Warfarin Instructions for the Patient.*** *(see below)*

c) Evidence the patient understands the potential for drug-drug interactions.

d) Explain that warfarin and Coumadin® are the same drug. Warfarin is the generic name for Coumadin®.

XIII. Complications of Anticoagulation

A) Elevated INR and/or Bleeding in Patients Receiving Warfarin/Coumadin®

Table 22: Warfarin/Coumadin® Reversal Protocol

	INR greater than the upper limits of normal, but <4.5	**INR ≥4.5 - 10**	**INR >10**
No Bleeding	• Monitor more frequently • Hold warfarin (or lower the dose) until INR is in therapeutic range. • If only minimally elevated, no dose reduction may be needed • Restart warfarin at original or lower dose once INR in therapeutic range.	• Hold Warfarin 1 to 2 doses and monitor more often until the INR is in therapeutic range OR • Omit 1 dose and give vitamin K (1 to 2.5 mg) orally. Latest *CHEST* guidelines suggest to not give Vitamin K. • Restart warfarin at an adjusted dose downward once the INR is in therapeutic range.	• Hold Warfarin until the INR is in the therapeutic range. • Give vitamin K (2.5 to 5 mg) orally. Monitor more frequently. • Restart warfarin at an adjusted lower dose once INR is in a therapeutic range.
Rapid Reversal Required	• Discontinue warfarin. • Give vitamin K (2.5 mg orally). • Restart warfarin once the INR is in therapeutic range.	• Discontinue warfarin. • Give vitamin K (≤ 5 mg) orally once. Expect an INR reduction within 24 hours.	• Discontinue warfarin. • Give vitamin K 10 mg by slow intravenous infusion. • Repeat an INR in 8 hours and give vitamin K based on the INR value and this protocol.
Serious Life Threatening Bleeding	• Discontinue warfarin. • Give vitamin K 5-10 mg by slow intravenous infusion. once. • Repeat vitamin K administration if needed in 12 hours. • Supplement with fresh frozen plasma (FFP) or prothrombin complex (PCC). • Consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance	• Discontinue warfarin. • Give vitamin K 10 mg by slow intravenous infusion once. • Repeat vitamin K administration if needed in 12 hours. • Supplement with fresh frozen plasma (FFP) or prothrombin complex (PCC). • Consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance	• Discontinue warfarin. • Give vitamin K 10 mg by slow intravenous infusion once. • Repeat vitamin K administration if needed in 12 hours. • Supplement with fresh frozen plasma (FFP) or prothrombin complex (PCC). • Consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below or CHEST guidelines (CHEST 2008; 133: 160S-198S or 708S-775 Pharmacology and Management of Vitamin K Antagonists or consult Hematology, Chest 2012,141:e152S-e184S Vascular Medicine or Clinical Pharmacy for assistance.

XIV)Reversal guidelines of Parenteral and Oral Anticoagulants

A) Heparin Reversal

Heparin can be reversed rapidly by infusion of protamine sulfate. This should be reserved for major bleeding because of risk of anaphylaxis to protamine. Protamine is administered intravenously over 10 minutes at a dose of 1 mg/100 units of circulating heparin. No more than 50 mg should be given over any 10 minute period. A general rule for dosing protamine is to calculate the dose based on the previous 2-3 hours of heparin received by continuous infusion (example: a patient receiving 1200 units/hour should receive about 30 mg of protamine (1200 X 2.5 hours = 3000 units then divide 3000 units by 100 units/mg to get 30 mg)). If a patient bleeds on heparin within 30 minutes of a bolus of heparin use the entire bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin should receive about 50 mg of protamine(5000 units divided by 100units/mg to get 50 mg)). If the bolus was greater than 30 minutes but less than 60 minutes use ½ of the bolus dose when calculating the protamine dose (example: a patient receives a 5000 unit bolus of heparin 60 minutes ago and an infusion of 1000 units/hour should receive about 35 mg of protamine (Since the bolus was 60 minutes ago use ½ of the bolus dose which is 2500 units then add 1000 units for the infusion which equates to 3500 units divide this number by 100 units/mg to get the 35 mg of protamine. The appropriate dose of protamine is dependent upon the dose of heparin given. Recommend consulting Clinical Pharmacy, Vascular Medicine or Hematology for assistance.

Example of Protamine Dosing for UFH reversal

Patient Scenario	General Dosing Rule	Example: Calculating Protamine Dose	
		Patient's current heparin dose	Calculation
Heparin continuous infusion for > 2 hours	Calculate dose based on the previous 2-3 hours of heparin administered as a continuous infusion	1200 units/hr for 2.5 hours	1. 1200 units X 2.5 hours = 3000 units 2. 3000 units ÷ 100 units/1mg** = **30mg of Protamine**

Heparin bolus within the past 30 minutes	Use entire bolus dose to calculate reversal	5000 unit bolus	1. 5000 units ÷ 100 units/1mg** = **50mg of Protamine**
Heparin bolus within 30-60 minutes plus initiated on a continuous infusion	Use ½ of the bolus dose and include current infusion dose	5000 unit bolus, then 1000 units/hr for one hour	1. To reverse bolus, use 2500 units since bolus was 60 minutes. Add infusion portion of 1000 units for the past hour. Therefore total heparin to be reversed is 2500 units + 1000 units = 3500 units 2. 3500 units ÷ 100 units/1mg** = **35mg of Protamine**

B) LMWH (Enoxaparin/Lovenox®) Reversal

LMWH is not completely neutralized (reversed) by protamine sulfate unlike UFH and should not be the only agent used to reverse the anticoagulant activity. Protamine sulfate will reverse the antithrombin activity of LMWH however will only reverse up to 60% of the anti-factor Xa activity. One mg of enoxaparin/Lovenox equals approximately 100 anti-Xa units. Protamine Sulfate may be given as 1 mg per 100 anti-Xa units of LMWH (enoxaparin/Lovenox®) when given within 8 hours of last administered dose. Protamine sulfate at a dose of 0.5 mg / 100 anti-Xa units of LMWH should be administered when the dose was administered between 8 and 12 hours ago or if the aPTT measured 2-4 hours after the first dose of protamine is still prolonged. Protamine sulfate may not necessary when the last dose of LMWH was administered greater than 12 hours earlier. There may be some situations that may require assistance and we recommend consulting Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

C) Anti-Xa Inhibitor

A) Fondaparinux

There are no reversal agents for fondaparinux. Fondaparinux does not bind to protamine sulfate. Recombinant factor VIIa has been used in select cases fresh frozen plasma as well as PCC have also been used. If bleeding complications develop, consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

B) Rivaroxaban

There is no antidote for rivaroxaban/Xarelto®. If bleeding occurs, discontinue rivaroxaban/Xarelto immediately. The use of oral activated charcoal to reduce absorption of rivaroxaban may be considered. It is not expected to be dialyzable. Prothrombin complex concentrates may be considered. If bleeding is serious or life threatening, contact vascular medicine, hematology or pharmacy for additional advice.

D) Direct Thrombin Inhibitors (DTIs) Reversal Argatroban, Bivalirudin/ Angiomax®, Desirudin, (Dabigatran/Pradaxa).

There are no reversal agents for the DTIs. Fresh frozen plasma and cryoprecipitate, PCC's or recombinant Factor VIIa may be tried. Hemodialysis or hemoperfusion has been used for bivalirudin and Argatroban . If bleeding develops consult Hematology, Vascular Medicine or Clinical Pharmacy for assistance.

A) Heparin Induced Thrombocytopenia

Mandatory Consultation to Vascular Medicine or Hematology for the use of these Agents
Patients must be advised of the risks and benefits of the Direct Thrombin Inhibitors.

Table 23. Summary of Pharmaceutical Agents for Heparin-Induced Thrombocytopenia.

Agent	Baseline labs	Dosing	Monitoring	Indications	Contra-indications
Argatroban/ Argatroban®	CBC, PT/INR, aPTT	• Begin 2 *u*g/kg/minute intravenously of Argatroban. Consider lower doses in patients with multi-organ dysfunction, CHF or total serum bilirubin >1.5. In these instances, administer 0.5 to 1.2 *u*g/kg/minute of Argatroban.	• aPTT target is 1.5 to 3 times the baseline. • Check an aPTT 2 hours after initiation and with all dose adjustments	• Treatment of acute HIT. • Treatment of patients requiring (PCI) with HIT.	• Liver disease. (dose adjustment required) • Active bleeding
Bivalirudin/ Angiomax®	CBC, PT/INR, aPTT	• Begin 0.1 to 0.15 mg/kg/hour of Bivalirudin intravenously. • Lower doses are required in patients with moderate to severe renal dysfunction or requiring dialysis.	• aPTT target 1.5 to 2.0 times the baseline. • Check an aPTT 2 hours after initiation and with all dose adjustments	• Treatment of patients requiring (PCI) with HIT. • Not FDA approved for other HIT patients	• Moderate to severe renal failure (dose adjustment required) • Active bleeding
Fondaparinux/ Arixtra®	CBC, PT/INR, creatinine	• Begin: 5 mg subcutaneously of fondaparinux daily for patients <50 kg; • 7.5 mg subcutaneously daily for patients 50 to 100 kg; • 10 mg subcutaneously daily for patients >100 kg	• No monitoring required	• Not approved by the FDA for HIT. • Has been used off label in this situation	• Allergy to fondaparinux • Active bleeding, • Creatinine clearance <30 mL/minute. • Bacterial endocarditis

This is intended as a guideline and does not replace the physician's clinical judgment/decision making. Mandatory consultation with Vascular Medicine or Hematology required. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below,CHEST guidelines (CHEST 2008; 133: 340S-380S Treatment and Prevention of Heparin-Induced Thrombocytopenia or Chest 2012;141:e419S-e530S.

B) Direct Thrombin Inhibitors

1) Explain the indications for using the direct thrombin inhibitor (DTI) to the patient and the risks and benefits.

2) Obtain baseline laboratory studies including a complete blood count with platelets, PT/INR, aPTT, serum creatinine and liver function tests.
3) Mandatory consultation of Vascular Medicine or Hematology is necessary for the dosing and monitoring of the DTIs.
4) Begin warfarin only after the patient's platelet count is recovering (> 150,000 $mm^{3)}$ and the patient is recovering.
5) Overlap a minimum of 5 days with warfarin and a DTI and continue until the INR is > 2 for 2 consecutive days.
6) Use a flow sheet including the date, dose of the DTI, serum creatinine, and aPTT, complete blood count with platelet count, PT/INR and dose of warfarin.

XV. Bridging Therapy

Recommendations for the Perioperative Management of Anticoagulation.

*TABLE 24. Perioperative Management of Patients on Anticoagulation**

	Low Risk:	Moderate Risk:	High: Risk:
Mechanical Heart Valve(s)	• Newer (bileaflet) aortic valve without risk factors	• Newer (bileaflet) aortic valve WITH any of the following factors: atrial fibrillation - Diabetes mellitus - Hypertension - Stroke/TIA - Age ≥75 years	• Recent TIA/CVA within 6 months • Mitral valve • Older Aortic valve
Recommendations for Mechanical Heart Valves	• Low dose subcutaneous LMWH or no bridging over full dose LMWH or intravenous UFH	• Therapeutic subcutaneous LMWH or therapeutic intravenous UFH or low-dose subcutaneous LMWH over no bridging	• Therapeutic subcutaneous LMWH or therapeutic intravenous UFH
Atrial fibrillation	• $CHADS_2$ score 0 to 2 with no history of TIA or CVA	• $CHADS_2$* score 3 or 4	• Recent (within 3 months) CVA or TIA • Rheumatic heart disease • $CHADS_2$* score 5 or 6
Recommendations for Atrial Fibrillation	• Low dose subcutaneous LMWH or no bridging over full dose LMWH or intravenous UFH • **Dabigatran/Pradaxa®** • **Rivaroxaban/Xarelto®**	• Therapeutic subcutaneous LMWH or therapeutic intravenous UFH or low dose subcutaneous LMWH over no bridging	• Therapeutic subcutaneous LMWH or therapeutic intravenous UFH
Venous thromboembolism	• Single VTE more than one year ago with no risk factors	• Heterozygous for Factor V Leiden or Prothrombin gene mutation • VTE within 3 to 12 months • Recurrent VTE • Active cancer (palliative treatment within 6 months	• Recent VTE within 3 months • Severe thrombophilia (protein C or S, antithrombin deficiency, antiphospholipid syndrome, doubly heterozygous for Factor V Leiden and Prothrombin gene mutation or homozygous for Factor V Leiden
Recommendations for Venous Thromboembolism	• Low-dose subcutaneous LMWH or no bridging over full dose LMWH or intravenous UFH	• Therapeutic subcutaneous LMWH or therapeutic intravenous UFH full dose or low-dose subcutaneous LMWH over no bridging	• Therapeutic subcutaneous LMWH or therapeutic intravenous UFH

*__$CHADS_2$ Score__= **Congestive heart failure, Hypertension, Age, Diabetes and Stroke.**

This table is intended as a guideline and does not replace the physician's clinical judgment/decision making. For more information please reference the full Cleveland Clinic Anticoagulation Management Program document (C-CAMP) as shown below or CHEST guidelines CHEST 2008; 299S-339S Perioperative Management of Anticoagulation or consult Hematology, Internal Medicine, Impact Center, Vascular Medicine, Clinical Pharmacy for assistance or Chest 2012:141;e326-e3505.

Table 25. Atrial fibrillation and bridging

Low risk	CHADs score 0-2	Low SC LMWH or no bridging • New guidelines • No bridging 2012
Moderate risk	CHADs score 3 or 4	Low dose SC LMWH
High risk	• Chads score 5 or 6 • Recent CVA or TIA within • 3 months • Rheum heart disease	Full dose SC LMWH or IV heparin

Table 26. Mechanical heart valve and bridging

Low risk • Newer bileaflet (aortic valve	Low dose subcutaneous LMWH or no bridging • No bridging 2012
Moderate risk with any of the following • Diabetes mellitus • HTN • Stroke/TIA • Age >75 years	Low dose SC LMWH or full dose LMWH or UFH
High risk • Recent TIA/CVA with ??? 6 months • Mitral valve • Older aortic valves	Full dose LMWH and IV UFH

A) LMWH as a Perioperative Bridging Agent

1) Discontinue warfarin 5 days before.

2) Begin full dose LMWH (Enoxaparin/Lovenox®) 36 hours after stopping the last warfarin/Coumadin® dose. Adjust the dose of the Enoxaparin/Lovenox® per the patient's creatinine clearance. If the creatinine clearance is below 30 ml/minute, the dose should be reduced to 1 mg/kg/day of Enoxaparin/Lovenox®. Low molecular weight heparin preparations are contraindicated for patients on dialysis. 3) Discontinue LMWH (Enoxaparin/Lovenox®) 24 hours before any surgery or invasive procedure.

4) If the INR is ≥ 1.5 (1 to 2 days before the surgery) give oral vitamin K 1 to 2 mg.

5) Resume LMWH (Enoxaparin/Lovenox®) (at full dose if hemostasis achieved) 24 hours after the procedure if the bleeding risk is low and if postoperative anticoagulation is necessary.

6) Resume LMWH (Enoxaparin/Lovenox®) (at full dose if hemostasis is a concern/bleeding risk high) 48 to 72 hours after the procedure if postoperative anticoagulation is necessary.

7) Resume LMWH (enoxaparin/lovenox® at prophylactic dose after hemostasis is attained and bridge back to warfarin/coumadin if bleeding risk too high for full dose LMWH anticoagulation.

8) Resume warfarin/Coumadin® on postoperative day 1 if postoperative anticoagulation is necessary.

9) For more information please reference the CHEST guidelines *CHEST 2008; 299S-339S* or *CHEST* 2012;141:e326S-e3250S. *Perioperative Management of Anticoagulation* or consult Hematology, Internal Medicine, Impact Center, Vascular Medicine or Clinical Pharmacy for assistance.

B) Unfractionated Heparin as a Perioperative Bridging Agent

1) Discontinue warfarin/Coumadin® 5 days before surgery.

2) Start full dose UFH (intravenous or subcutaneous) 36 hours after stopping the last dose of warfarin/Coumadin®.

3) Discontinue UFH 6 hours before any surgery or invasive procedure.

4) If the INR is ≥ 1.5 (1 to 2 days before the surgery) give oral vitamin K 1 to 2 mg.

5) Resume UFH (at full dose if hemostasis achieved) 24 hours after the procedure if the bleeding risk is low if postoperative anticoagulation is necessary.

6) Resume UFH (at full dose if hemostasis is a concern/bleeding risk high) 48 to 72 hours after the procedure if postoperative anticoagulation is necessary.

7) Resume UFH at prophylactic dose after hemostasis is attained and bridge back to warfarin/coumadin® if bleeding risk too high for full dose UFH

8) Resume warfarin/Coumadin® on postoperative day 1 if postoperative anticoagulation is necessary.

9) For more information please reference the CHEST guidelines *CHEST 2008; 299S-339S Perioperative Management of Anticoagulation* or consult Hematology, Internal Medicine, Impact Center, Vascular Medicine or Clinical Pharmacy for assistance.

C) Dabigatran/Pradaxa® as a Perioperative Bridging Agent

1) Discontinue dabigatran/Pradaxa®:

a) Discontinue 1 to 2 days before surgery or invasive/interventional procedures if the creatinine clearance is ≥ 50 mL/min

b) Discontinue 3 to 5 days of the creatinine clearance is <50 mL/min

c) Consider discontinuing dabigatran for longer durations for patients undergoing major surgery, spinal puncture or placement of a spinal or epidural catheter

d) Resume dabigatran/Pradaxa® following surgery once hemostasis is attained.

D) Rivaroxaban/Xarelto® as a Perioperative Bridging Agent

1) Discontinue Rivaroxaban/Xarelto®:

a) The product literature for rivaroxaban/Xarelto® contains the following black box warning:

"Discontinuing XARELTO® places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following XARELTO® discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with XARELTO® must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant."

b) Discontinue at least 24 hours prior to procedure

c) Consider discontinuing rivaroxaban/Xarelto® for more than 24 hours in patients who will undergo major surgery, spinal puncture or placement of a spinal or epidural catheter.

d) In high bleeding risk patients with a creatinine clearance ≥ 50 ml/min consider discontinuing rivaroxaban/Xarelto® 3 days prior to surgery and if creatinine clearance < 50 ml/min consider discontinuing rivaroxaban/Xarelto® 5 days prior to surgery.

(Wysokinski WE, McBane II RD. Periprocedural Bridging Management of Anticoagulation. *Circulation*. 2012;126:486-490.)

e) Resume rivaroxaban/Xarelto® dollowin surgery once hemostasis is attained.

XVI. General warfarin/Coumadin® Instructions for the Patient at Discharge

A) Contraindications

- During pregnancy or childbearing potential w/o contraception
- Gastrointestinal or active bleeding in the past 10 days
- Recent history of a major bleeding disorder
- Recent history of intracranial hemorrhage
- Recent major surgery, trauma, or stroke
- Hypersensitivity or an allergy to warfarin
- Acute heparin-induced thrombocytopenia (HIT) (until the platelet count has recovered to 100,000 mm^3 to 150,000 mm^3 and the patient is recovering.
- History of noncompliance, language barriers or unsuitable home environment or at risk of falling

B) Risk and Benefits of warfarin/Coumadin® Therapy

- Discussed with patient and additional information provided
- Viewing the video and a handout
- Patient was provided emergency numbers
- Patient will follow up in clinic in 1 weeks time

C) Patient Instructions for Understanding warfarin/Coumadin®

Your doctor has put you on an anticoagulant medication. "Anti" means against and "coagulant" means causing blood to clot. Therefore an anticoagulant medication controls the way your blood clots inside your blood vessels.

This handout contains information about the anticoagulant medication warfarin also known as Coumadin®. Your understanding of this information will help make your anticoagulant therapy as successful as possible and reduce the chance of complications. Be sure to talk with your doctor if you have any questions.

1) What anticoagulants do:

- An anticoagulant helps your body control how fast your blood clots; therefore, it prevents clots from forming inside your arteries, veins or heart during certain medical conditions.

- If you have a blood clot, an anticoagulant may prevent the clot from getting larger. It also may prevent a piece of the clot from breaking off and traveling to your lungs, brain or heart. The anticoagulant medication does not dissolve the blood clot. With time, however, this clot may dissolve on its own.

2) Blood tests you will need:

The blood tests for clotting time while on warfarin/Coumadin® are called prothrombin time (Protime, PT) and international normalized ratio (INR). These tests help determine if your medication is working. The tests are performed at a laboratory, usually once a week to once a month, as directed by your doctor or health care provider. Your doctor will help you decide which laboratory you will go to for these tests. The test results help the doctor or health care provider decide the dose of warfarin/Coumadin® that you should take to keep a balance between clotting and bleeding.

3) Important things to keep in mind regarding blood tests include:

- Have your INR checked when scheduled.
- Go to the same laboratory each time (there can be a difference in results between laboratories).
- If you are planning a trip, talk with your doctor or health care provider about using another laboratory while traveling.
- Be sure your care provider knows when you have your blood test results.

4) Dosage:

- Warfarin or Coumadin® comes in different doses (1 mg, 2mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg. The doctor or health care provider will prescribe one strength and change the dose as needed (your dose may be adjusted with each INR).
- The tablet is scored and breaks in half easily. For example: If your doctor or health care provider prescribes a 5 mg tablet and then changes the dose to 2.5 mg (2½ mg), which is half the strength, you should break one of the 5 mg tablets in half and take the half-tablet. If you have any questions about your dose, talk with your doctor or pharmacist.

5) What warfarin/Coumadin® tablets look like:

Warfarin/Coumadin® is made by several different drug manufacturers and is available in many different shapes. Each color represents a different strength, measured in milligrams (mg). Each

tablet has the strength imprinted on one side and is scored so you can break it in half easily to adjust your dose, as your doctor instructed.

6) How to take warfarin/Coumadin®:

- Take the dose as instructed once a day.
- Take the dose at the same time each day. We recommend 5 p.m.
- The medication can be taken before or after food.
- If you forget to take your dose and remember within 8 hours, take the dose. If it is past 8 hours, wait until the next day and take only the prescribed dose for that day. **DO NOT TAKE A DOUBLE DOSE**.
- If you forget two or more days in a row, call your doctor. The dose may need to be changed.
- When you take the dose, check off the day on your home calendar.
- Refill your prescription 1 week before the end of your supply to avoid missing a dose.
- Continue to take warfarin/Coumadin® as long as your doctor prescribes it.

7) Where to store warfarin (Coumadin®):

- Store the medicine at room temperature, away from extreme cold, heat, light or dampness. **Note:** Bathroom cabinets usually are not suitable for storing medications because of the dampness.
- Always keep medications out of the reach of children.

8) Precautions when taking warfarin/Coumadin®:

- It is important that you follow these precautions when taking this anticoagulant medication. Other medications and vitamin supplements.
- **Many medications and vitamins can have an effect on the action of warfarin/Coumadin®. These may include:**
    - Prescription medications
    - Non-prescription medications such as acetaminophen, aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), cold and cough medicines, antacids, laxatives, or other medications for pain or discomfort Vitamin preparations containing Vitamin K (phytonadione) or large amounts of vitamins E or C.

- Remember to talk with the doctor or pharmacist before you take any medications or vitamins, whether from the drugstore or from another doctor or dentist. This is very important because you may need some of these medications for another medical condition, and your doctor will regulate them with warfarin/Coumadin®. Remember, do not stop or start any medications without first talking to your doctor or health care provider.

9) Exercise:

- Check with your doctor before starting any exercise or sports program.
- Be sure to talk with your doctor if you are planning any major diet changes, such as a weight-reducing diet, of if you plan to add any nutritional supplements. Vitamin K is needed for normal blood clotting. When you are taking an oral anti-coagulant medication such as warfarin/Coumadin®, Vitamin K can work against the medication. The following guidelines will help control the amount of Vitamin K you are getting from the foods you eat. To help the medicine perform well, you should follow these guidelines:
  - Avoid grapefruit and cranberry products.
  - If you eat spinach, turnip greens, other leafy greens, broccoli, Brussels sprouts, kale, parsley (except as a garnish or minor ingredient), natto (a Japanese dish), liver, or green tea, be sure to **eat a consistent amount week to week**.
  - Eat all other foods as you normally would.
- Tell your doctor if you are thinking about changing your current eating habits. Tell your doctor if you are planning to:
  - Eat more or less vegetables.
  - Change to a vegetarian style of eating.
  - Follow a special meal plan to lose or gain weight.
- Changing your eating habits may mean that you will be getting more or less Vitamin K in the foods you eat. If you change your eating habits, your doctor may want to check your blood more frequently to see how the warfarin/Coumadin® therapy is working.
- Do not take any herbal supplements that may keep your blood from clotting. The following supplements should **NOT** be used when taking anticoagulant medications prior to surgery:
  - Garlic

- Ginger
- Gingko Biloba
- Ginseng
- Feverfew
- Fish oil
- Turmeric
- St. Johns Wort
- Chondroitin sulfate

- Also, tell your doctor if you are currently taking any herbal supplements.
- Do not take any vitamin supplements that provide more than 100 percent of the Recommended Daily Allowance (RDA). Tell your doctor if you are currently taking more than the RDA of any vitamins (especially vitamins A, C or E).
- Avoid chronic, heavy drinking of beverages containing alcohol (heavy drinking is more than two ounces of liquor, 10 ounces of wine, or 24 ounces of beer per day).
- If you drink tea, black tea is recommended because it is not high in Vitamin K. An example of black tea is orange pekoe tea.
- If you want more servings of vegetables in your daily meal plan, choose vegetables that are not high in Vitamin K, such as corn, squash, potatoes, onions, carrots, cucumbers, celery, peppers, pumpkin and tomatoes.

10) Daily activities:

- Be careful when using razors. We suggest an electric razor or hair-removing creams to minimize the chance of cuts.
- Use a soft toothbrush. Brush and floss gently to prevent bleeding from the gums.

11) Illness and emergencies:

- Keep your doctor's phone number close by in the event of an emergency.
- Call your doctor if you have any symptoms of illness, such as vomiting, diarrhea, infection or fever. Illness can change the way warfarin/Coumadin® works.

- Always carry or wear identification that states you are taking warfarin/Coumadin®). In an emergency, you may not be able to speak for yourself.
- Avoid situations where you may get hurt at home or at work. Even minor injuries must be watched for bleeding because warfarin/Coumadin® affects clotting.
- Falls that cause bruising (bleeding under the skin) and cuts from sharp objects are more serious when you are taking warfarin/Coumadin®.
- Call your doctor if you have any injuries that involve falls or blows to the body or head.
- If you do cut yourself and the cut is small, apply constant pressure over the cut until the bleeding stops. This may take up to 20 minutes. If the bleeding does not stop, continue to apply pressure and go to the nearest emergency room. If the cut is large, apply constant pressure and get help immediately either by phone or by going to the nearest emergency room.

12) Pregnancy, surgery and dental work:

- It is important to avoid pregnancy while taking warfarin. Use at least two methods of birth control while taking warfarin/Coumadin®.
- If you are a woman who is taking warfarin/Coumadin® and you are planning to become pregnant, talk with your doctor about the possible risks and ways to reduce those risks. Tell your doctor right away if you become pregnant.
- Tell all your doctors and dentists before treatment that you are taking warfarin (Coumadin®). You may need to have a blood test and may have to stop taking this anticoagulant for a few days before having a surgical or dental procedure. Check with your doctor before any procedures.

13) Travel:

- Check with your doctor before you travel. You may need to have a blood test and the dose adjusted before you leave.
- While you travel, carry your medications with you at all times (do not put medications in checked baggage and do not leave them in the car).

14) Side-effects: Changes to watch for:

Bleeding is the most common side-effect of warfarin/Coumadin® and can appear as any of several different symptoms. Call your doctor if you notice any of the following signs of bleeding:

- Bleeding from the nose, gums or ears.
- Bruises that appear without reason or become swollen or larger after time.
- Purplish spots on your skin.
- Vomiting blood (which may look like coffee grounds).
- Coughing up blood.
- Stomach or abdominal pain.
- Bowel movements that look bright red or black and tarry.
- Unusual hemorrhoid bleeding.
- Reddish or rusty colored urine.
- Menstrual bleeding that is heavier or longer than normal.
- Unusual pain or swelling, especially in the joints.
- Feeling tired or looking pale (symptoms of anemia).
- Unusual headache.
- Sudden changes in speech or vision.
- Numbness/tingling in one side of face or arm.
- Bleeding from cuts that won't stop after applying pressure for 20 minutes.
- If you have any of these symptoms, your doctor may want to do a blood test, change your dose, stop the medication or give you medicine to stop the bleeding.