WMC PHARMACY ANTICOAGULATION PROTOCOL

Current Revision: July 2017

GENERAL ORDER PROCESSING AND MANAGEMENT

- Entering orders for anticoagulation in Cerner
    - Providers will enter individual orders (oneoffs) for apixaban, dabigatran, enoxaparin, fondaparinux,subcutaneous heparin and rivaroxaban (or order from powerplans).
    - Providers will order IV heparin drips as heparin protocol. THEY MUST SPECIFY A PROTOCOL. NURSING IS TO CLARIFY IF NOT SPECIFIED.
    - Providers will have the following options for warfarin ordering. An indication will be required when ordering warfarin.
        - Warfarin Pharmacy to Dose
        - Warfarin (one-off orders), with the provider managing dosing according to a WMC P&T committee approved protocol.

- Pharmacy will enter or modify the "Pharmacy Use Only WMC Anticoagulation Protocol Supplement Orders" powerplan into Cerner each time an anticoagulant drug is ordered. Pharmacy will discontinue or modify the "Pharmacy Use Only WMC Anticoagulation Protocol Supplement Orders" each time an anticoagulant drug is discontinued.

- Pharmacy will be able to adjust enoxaparin based on renal function.

- Pharmacy will be able to order anti-Xa levels and adjust enoxaparin dosing based on levels per protocol.

- Pharmacy will ASSIST with monitoring ALL therapeutic and prophylactic anticoagulation (by using the specific criteria listed below), with the exception of therapeutic heparin drips which are managed by nursing per protocols.

-- Lab monitoring:

--Baseline for all anticoagulant agents: PT/INR, CBC, SCr (done within 48 hrs).

In the case of elective surgery, omit PT/INR unless the patient will receive warfarin. Baseline labs are not required when post-op patients receive anticoagulation for DVT prophylaxis. Initial CBC and SCr will be drawn the morning following an elective surgery.

--Monitoring, drug specific:

- Enoxaparin, Fondaparinux: CBC and SCr Q72Hr x 4 draws.
- Heparin: CBC Q72Hr x 4 draws.
- Dabigatran, Apixaban, Rivaroxaban, Edoxaban: weekly CBC and Scr

    - Warfarin: daily INR, if stable after 7 days, may decrease INR monitoring to twice weekly
    -

- Monitoring of all anticoagulants to include:
    - Renal Function
        - Estimated CrCL under 30, and changes in CrCL from below 30 to above 30
        - Estimated creatinine clearance will be calculated by using CockcroftGault
    - Plts under 125,000/mcL and patient on heparin or enoxaparin
    - Hgb under 7 G/dL and pt on any anticoagulant
    - INRs and patient on warfarin
    - Drug Interactions as detailed in the protocol.

ANTICOAGULANT DRUGS

APIXABAN

- Nonvalvular atrial fibrillation:
  - 5 mg orally twice daily
  - If patient has 2 or more of the following then reduce dose to 2.5 mg twice daily
    - Age ≥80 years
    - Body weight ≤60 kg
    - Serum creatinine ≥1.5 mg/dL
  - Dual strong CYP3A4 and P-glycoprotein inhibitors (eg, clarithromycin, itraconazole, oral ketoconazole, ritonavir): 2.5 mg twice daily
    - Avoid use if patient meets 2 of the above criteria (age, weight, Scr) and is on these interacting drugs.
- **Deep venous thrombosis / PE:**
  - *Treatment:* 10 mg twice daily for 7 days followed by 5 mg twice daily x 6 months
  - *Reduction in the risk of recurrence:* 2.5 mg twice daily after at least 6 months of treatment for DVT
- **Postoperative venous thromboprophylaxis:**
  - Hip replacement surgery: 2.5 mg twice daily beginning 12 to 24 hours postoperatively; duration: 35 days
  - Knee replacement surgery: 2.5 mg twice daily beginning 12 to 24 hours postoperatively; duration: 12 days

DABIGATRAN

- Nonvalvular atrial fibrillation:
  - 150 mg orally twice daily
  - Est CrCl = 15-30 then 75 mg twice daily
  - Est CrCl less than 15, call prescriber to change to another agent.
  - Est CrCl = 30-50 **and** pt on dronedarone or oral ketaconazole, then 75 mg orally twice daily
  - Est CrCl = 15-30 **and** pt on dronedarone or oral ketaconazole, call prescriber to change to another agent.
- **DVT and pulmonary embolism (treatment and prevention):**
  - 150 mg twice daily (after 5 to 10 days of parenteral anticoagulation)
  - Est CrCl under 30, avoid use

EDOXABAN

- Treatment of deep vein thrombosis and pulmonary embolism:
  - CrCl ≥51 mL/minute: 60 mg orally once daily after 5 to 10 days of initial therapy with a parenteral anticoagulant.
  - CrCL 15 to 50 mL/min: 30 mg orally once daily
  - Patient weight ≤60 kg: 30 mg orally once daily
  - Concomitant therapy with specific P-gp inhibitors (ie, verapamil, quinidine; the short-term use of azithromycin, clarithromycin, erythromycin, oral itraconazole, oral ketoconazole): 30 mg orally once daily
  - CrCl <15 mL/minute: Use is not recommended.

- Nonvalvular atrial fibrillation (NVAF) (to prevent stroke and systemic embolism):
    - For patients with nonvalvular atrial fibrillation, do **not** use edoxaban if CrCl is >95 mL/minute using the Cockcroft-Gault equation.
    - CrCl ≥51 mL/min **and** less than 95 mL/min: 60 mg orally once daily.
    - CrCl 15 to 50 mL/minute: 30 mg once daily
    - CrCl <15 mL/minute: Use is not recommended.

May want to consider alternate recommendations for geriatric patients ≥65 years (Beers Criteria [AGS 2015]):

CrCl 30 to 50 mL/minute: Dose should be reduced (specific dosage adjustment not provided although the manufacturer's labeling recommends 30 mg once daily for adults).
CrCl <30 mL/minute: Avoid use due to increased risk of bleeding.

ENOXAPARIN PROPHYLAXIS DOSING:

- 40 mg subcutaneously daily. If ordered for post-op day one, first dose is to be within 21 hours **POST** surgery.
- Est. CrCl is less than 30, then 30 mg subcutaneously daily.
- Dialysis patient. Call prescriber and recommend heparin SubQ

ENOXAPARIN PROPHYLAXIS DOSING FOR OBESE OR LOW WEIGHT, ELDERLY PATIENTS:

- There is no FDA-approved dosing for obese patients beyond 40 mg once daily. However, studies indicate that 0.5 mg/kg once daily in medical patients WHO HAVE A CRCL OVER 30 is more likely to produce anti-Xa levels near or within prophylactic range for patients with a BMI of 35 or more. For obese patients with CrCL under 30, dose at 30 mg SC daily.
- There are no dosage adjustment recommendations for DVT prophylaxis in low weight, elderly patients. However, in clinical trials, the risk of enoxaparin associated bleeding increased with age and low weights. Monitoring of anti-Xa levels in elderly patients with low body weight (<45 kg for females and <57 kg for males) and those predisposed to decreased renal function may be considered, particularly if these patients will receive a week or more of therapy.
- PLEASE CALL MD TO APPROVE ANY WEIGHT-BASED CHANGES FOR PROPHYLACTIC ENOXAPARIN DOSING.

ENOXAPARIN THERAPEUTIC DOSING:

- Est CrCl greater than or equal to 30 mL/min
    - 1 mg/kg sub-q every 12 hours rounded to the nearest 10 mg dose or calibrated syringe size
- Est. CrCl is less than 30 mL/min
    - 1 mg/kg sub-q every 24 hours rounded to the nearest 10 mg dose or calibrated syringe size
- Dialysis patient
    - Call prescriber and recommend heparin infusion

Weight (in Kg)	Dose	Syringe Size
≤100	Round to nearest 10mg	

100-103	100mg	100mg
104-112	105mg	120mg
113-127	120mg	120mg
128-142	135mg	150mg
143-155	150mg	150mg
>156	Round as appropriate	Round as appropriate with 2 syringes

ANTI-XA LEVEL MONITORING

Anti-Xa levels should be NOT be routinely ordered for patient receiving enoxaparin. They may be considered for subgroups of patients to assure therapeutic and non-toxic levels.

Underweight patient (less than 45 kg)

- BMI 35 or more
- Pregnant
- Child
- CrCl < 30
- CrCl is difficult to estimate due to age, wt, or SCr factors

Dosing	**When to Draw**	**Target Level**
Therapeutic, BID or once daily due to renal adjustment	4-6 hrs after 2nd-3rd dose	0.5-1 units/mL
Therapeutic, once daily (1.5 mg/kg dose)	4-6 hrs after 2nd-3rd dose	1-2 units/mL
Prophylactic	4-6 hours after 2nd-3rd dose	0.2-0.5 units/mL

ADJUSTING ENOXAPARIN BASED ON ANTI-XA LEVEL

FOR 1 MG/KG TREATMENT DOSES, TARGET 0.6-1 UNITS/ML

Anti-Xa activity	**Hold Next Dose**	**Dosage Change**	**Next Anti-Xa Level**
< 0.35 units/mL	No	↑ 25%	4-6 hrs after 2nd-3rd dose
0.35-0.49 units/mL	No	↑ 10%	4-6 hrs after 2nd-3rd dose
0.5-1.0 units/mL	No	No	Consider next day to verify, then weekly
1.1-1.5 units/mL	Until Anti-Xa level is under 0.5	↓ 20%	Every 12 hrs until anti-Xa level is under 0.5.

			Then 4-6 hrs after 2nd "new" dose
1.6-2 units/mL	Until Anti-Xa level is under 0.5	↓ 30%	Every 12 hrs until anti-Xa level is under 0.5. Then 4-6 hrs after 2nd "new" dose
Over 2 units/mL	Until Anti-Xa level is under 0.5	↓ 40% OR change frequency to Q24H dosing if receiving Q12H dosing	Every 12 hrs until anti-Xa level is under 0.5. Then 4-6 hrs after 2nd "new" dose

FOR PROPHYLAXIS DOSING, TARGET 0.2-0.5 UNITS/ML

Anti-Xa activity	**Hold Next Dose**	**Dosage Change**	**Next Anti-Xa Level**
< 0.2 units/mL	No	↑ 25%	4-6 hrs after 2nd-3rd dose
0.2-0.5 units/mL	No	No	Weekly
0.51-0.69 units/mL	No	↓ 20%	4-6 hrs after 2nd-3rd dose
0.7-1 units/mL	No	↓ 30%	4-6 hrs after 2nd-3rd dose
Over 1 units/mL	Until Anti-Xa level is under 0.2	↓ 40%	Every 12 hrs until anti-Xa level is under 0.2. Then 4-6 hrs after 2nd "new" dose

FONDAPARINUX PROPHYLAXIS DOSING:

- Est. CrCl greater than 50 mL/min
    - 2.5 mg subcutaneously daily. If ordered for post-op day one, first dose is to be within 21 hours **POST** surgery.
- Est CrCl is 30-50 mL/minute: Use caution; total clearance ~40% lower compared to patients with normal renal function. When used for thromboprophylaxis, the American College of Chest Physicians suggests a 50% reduction in dose or use of low-dose heparin instead of fondaparinux. PLEASE SUGGEST ENOXAPARIN OR LOW DOSE HEPARIN. THERE ARE NO DOSING LINES ON THE ARIXTRA SYRINGES, SO 1.25 MG DOSES MUST BE DISPENSED FROM THE PHARMACY.
- Est. CrCl is less than 30
    - Fondaparinux is contraindicated. Call prescriber to change order.
- Pt weighs less than 50 Kg.
    - Call prescriber and recommend subcutaneous Enoxaparin or Heparin.

FONDAPARINUX THERAPEUTIC DOSING

***** Est. CrCl less than 30, call prescriber and recommend heparin infusion or therapeutic enoxaparin as appropriate.*****

- Weight under 50 kg = 5 mg subcutaneously daily

- Weight 50-100 kg = 7.5 mg subcutaneously daily
- Weight greater than 100 kg = 10 mg subcutaneously daily

HEPARIN PROPHYLAXIS DOSING:

- 5,000 units subcutaneously every 8-12 hours
- Consider Q12H dosing for low weight pts (<60kg) and Q8H dosing for higher weights.
- If ordered for post-op day one, first dose is to be within 21 hours **POST** surgery.

RIVAROXABAN

***Doses of 15mg or greater should be taken with food, preferably with evening meal.

- Acute DVT/PE
    - 15 mg orally twice daily for three weeks then 20 mg orally once daily with evening meal
    - Est CrCl less than 30 - call prescriber to change to another agent
- Reduction in risk of recurrent DVT/PE
    - 20 mg PO once daily with evening meal
    - Est CrCl less than 30 - call prescriber to change to another agent
- Nonvalvular atrial fibrillation
    - Est CrCl greater than 50 - 20 mg orally once daily with evening meal
    - Est CrCl 15-50 - 15 mg orally once daily with evening meal
    - CrCl less than 15 call prescriber to change to another agent
- Postoperative prophylaxis

  If ordered for post-op day one, first dose is to be within 21 hours **POST** surgery.
    - Hip replacement surgery – 10 mg PO daily for 35 days.
    - Knee replacement surgery – 10 mg PO daily for 12 days
    - CrCl less than 30 - call prescriber to change to another agent

WARFARIN

Every patient on warfarin will be followed by a pharmacist. Pharmacy will dose warfarin with a physician order for pharmacy to dose. Should a physician choose to manage a patient's warfarin dosing, all doses must be calculated by using a WMC P&T committee approved protocol.

<u>Clinical Pearls</u>

- For treatment of VTE, therapeutic heparin, enoxaparin or fondaparinux MUST continue a minimum of 5 days AND until 2 consecutive INR measurements drawn 24 hours apart are within therapeutic range.
- Today's INR is the result of the last 2 to 3 warfarin doses.
- To achieve a stable anticoagulant effect it takes approximately 4 to 7 days of warfarin therapy, but an observable effect can be seen in 2 days depending on the dose given.
- After vitamin K, higher doses of warfarin may be needed. Initiate warfarin at patient's maintenance dose, and increase the dose if there is no or little increase in INR after 1 or 2 days. Back off dose when INR starts moving.
- If the patient was on warfarin prior to admission try to utilize their outpatient regimen.

Warfarin Indications and Target INR Ranges

Indication	Target INR (range)	Indication	Target INR (range)
Mechanical Heart Valve (Aortic)		**TIA/Stroke**	
St Jude Medical Bileaflet	2.5 (2.0-3.0)	+ Atrial Fibrillation	2.5 (2.0-3.0)
CarboMedics Bileaflet	2.5 (2.0-3.0)	Venous Sinus Syndrome	2.5 (2.0-3.0)
Medtronic Hall Tilting Disk	2.5 (2.0-3.0)	**Atrial Fibrillation**	
Caged Ball or Caged Disk	3.0 (2.5-3.5)	+ High Risk Factor**	2.5 (2.0-3.0)
Mechanical Heart Valve (Mitral)		**DVT/PE**	
Tilting Disk or St. Jude Bileaflet	3.0 (2.5-3.5)	First + Reversible Risk Factor	2.5 (2.0-3.0)
Mechanical Valve + Risk Factor*	3.0 (2.5-3.5)	First + Idiopathic	2.5 (2.0-3.0)
Mechanical Valve + Embolism	3.0 (2.5-3.5)	+ Cancer	2.5 (2.0-3.0)
Bioprosthetic Heart Valve		+ Anti-phosphlipid Syndrome	2.5 (2.0-3.0)
Aortic Position	2.5 (2.0-3.0)	+ Thrombophilic Condition	2.5 (2.0-3.0)
Mitral Position	2.5 (2.0-3.0)	Two or More Episodes	2.5 (2.0-3.0)
+ History of Embolism	2.5 (2.0-3.0)	**Acute Myocardial Infarction**	
+ Left Atrial Thrombosis	2.5 (2.0-3.0)	High or Low Risk (no aspirin)	3.0 (2.5-3.5)
+ Atrial Fibrillation	2.5 (2.0-3.0)	High or Low Risk (+ aspirin)	2.5 (2.0-3.0)
		Miscellaneous	
		Elective Hip or Knee	2.5 (2.0-3.0)
		Spinal Injury + Impaired Mobility	2.5 (2.0-3.0)

* Risk Factor = Atrial Fibrillation, Acute Myocardial Infarction, Atrial Enlargement, Endocardial Damage, Low Ejection Fraction

**High Risk Factor = Prior Stroke, Systemic Embolism, Transient Ischemic Attack, Age greater than 75, Impaired LV and/or CHF, diabetes

Warfarin Dosing Guidelines

Initiation of Warfarin for INR target of 2.5 (range 2.0-3.0)

Day	INR	Dose	Day	INR	Dose
1	Less than 1.5	2.5mg-7.5mg*	**4**	Less than 1.5	10mg
	Greater than 1.5	**Call Prescriber**		1.5-1.9	5-7.5 mg**
2	Less than 1.5	Same Dose as #1		2.0-3.0	0-5 mg***
	1.5-1.9	2.5 mg		Greater than 3.0	0 mg
	2.0-3.0	1-2.5 mg	**5**	Less than 1.5	10 mg
	Greater than 3.0	0 mg		1.5-1.9	7.5-10 mg**
3	Less than 1.5	5-10 mg		2.0-3.0	0-5 mg or Same as Previous day***
	1.5-1.9	2.5-5mg**		Greater than 3.0	0 mg****
	2.0-3.0	0-2.5mg***	**6+**	Less than 1.5	7.5-12.5 mg
	Greater than 3.0	0mg		1.5-1.9	5-10 mg
				2.0-3.0	0-7.5mg or same as previous day***
				Greater than 3.0	0 mg****

*Consider lower initial doses (i.e. 2.5 mg Daily) in the following patient types: Elderly, Malnourished, Liver disease, High bleeding risk, CHF, and/or on Interacting Drugs (i.e. amiodarone, fluconazole, sulfamethoxazole, voriconazole, etc). Use patient's home dose if admission INR was in therapeutic range or patient was previously stable on home dosage.

** If INR increases greater than 0.5 from previous day, then decrease the recommended protocol dose by 2.5 mg (minimum dose of 1 – 2 mg).

***Base a decision to hold dose on patient specific information (i.e. INR trend) and clinical judgment Instead of holding, small doses of 0.5 – 1 mg may be useful.

**** For INR is 3-3.5, consider small doses of 0.5-2.5 mg if INR is dropping. Hold dose if INR is on an upward trend or the trend is unknown.

Warfarin Dosing Guidelines

Initiation of Warfarin for INR target of 3.0 (range 2.5-3.5)

Day	INR	Dose	Day	INR	Dose
1	Less than 1.5	5-10 mg*	**4**	Less than 1.5	10 mg
	Greater than 1.5	Call Prescriber		1.5-1.9	5-7.5 mg
2	Less than 1.5	Same Dose as Day 1		2.0-2.9	5 mg **
	1.5-1.9	2.5mg		3.0-3.5	2.5 mg **
	2.0-2.9	1-2.5 mg		3.6-5.9	0-2.5 mg ***
	3.0-3.5	0-1 mg (use clinical judgement)		greater than 6.0	Hold Dose and Call Prescriber
	3.6-5.9	Hold dose	**5+**	Less than 1.5	Increase Dose by 2.5-5 mg
	greater than 6.0	Hold Dose and Call Prescriber		1.5-2.4	Increase Dose by 1-2.5 mg**
3	Less than 1.5	5-10 mg**		2.5-3.6	Same Dose as Previous Day (minimum 1-2 mg)**
	1.5-1.9	5-10 mg**		3.7-5.9	0-2.5 mg***
	2.0-2.9	2.5-5 mg**		greater than 6.0	Hold Dose and Call Prescriber
	3.0-3.5	0-2.5 mg			
	3.6-5.9	0-2.5 mg***			
	greater than 6.0	Hold Dose and Call Prescriber			

*Consider lower initial doses (i.e. 2.5 mg Daily) in the following patient types: Elderly, Malnourished, Liver disease, High bleeding risk, CHF, and/or on Interacting Drugs (i.e. amiodarone, etc).

** If INR increases greater than 0.5 from previous day, then decrease the recommended protocol dose by 2.5 mg (minimum dose of 1 – 2 mg).

***Base a decision to hold dose on pt specific information (i.e. INR trend) and clinical judgement. For INR greater than 3.5, consider small doses of 0.5-2.5 mg if INR is dropping. Hold dose if INR is on an upward trend or the trend is unknown.

MONITORING FOR HIT

- HIT (Heparin-induced thrombocytopenia) is an immune-mediated disorder characterized by the formation of antibodies against the heparin-platelet factor 4 complex, which can lead to the formation of platelet-rich arterial clots.
- Platelet counts are to be obtained no less often than every 48 hrs for all patients receiving heparin or enoxaparin.
- HIT should be considered when the platelet count fall by about 50% in a patient on heparin or enoxaparin. To assess the probability of HIT, calculate the 4T score using the chart below.

Category	2 points	1 point	0 point
Thrombocytopenia	> 50% fall, or nadir ≥ 20 x 10^9/L	30–50% fall, or nadir 10-19 x 10^9/L	< 30% fall, or nadir < 10 x 10^9/L
Timing of the decrease in platelet count	Days 5 to 10, or ≤ day 1 with recent heparin (past 30 days)	> Day 10 or timing unclear, or < day 1 if heparin exposure within past 30-100 days	< Day 4 (no recent heparin)
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
Other causes of thrombocytopenia	None evident	Possible	Definite

4T Score 0-3 = low probability HIT

4T Score 4-5 = intermediate probability, ORDER HIT Panel

4T Score 6 or more = high probability, ORDER HIT Panel

If the patient has an intermediate or high probability of HIT, discussion about HIT management should be had with the provider. If HIT is highly suspected, all heparin products should be stopped, 10 mg vitamin K should be given if patient is on warfarin, and argatroban should be considered (see Management of HIT below). If HIT is less likely, stop heparin products, obtain HIT panel, and consider using fondaparinux if patient has a CrCl of 30 mL/min or more. Anticoagulation in patients with suspected HIT who have an estimated CrCl under 30 mL/min are very limited (argatroban, fondaparinux on discussion with nephrology.)

MANAGEMENT OF HIT

Please use the Argatroban for Heparin-Induced Thrombocytopenia (HIT) in Adults Protocol available under Forms and Documents/ Preprinted Order Sets on the Intranet.

References:

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 suppl):1S-e737S.

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