Ventura County Medical Center/Santa Paula Hospital (VCMC/SPH)

Policy 100.087 Anticoagulation Management

Attachment C: Low Molecular Weight Heparin (Enoxaparin) Protocol

Low molecular weight heparin (LMWH) is an anticoagulant that inhibits factor Xa and IIa (thrombin) activity in the coagulation pathway. Unlike unfractionated heparin (UFH), it does not require frequent monitoring for efficacy and is 10 times less likely to cause heparin induced thrombocytopenia (HIT).[1] It also has highest ratio of anti-Xa to anti-IIa activity compared to heparin and other LMWH. Higher ratio of anti-Xa to anti-IIa activity may be related to decrease tendency to cause bleeding. [2,15] Because of this difference in anti-Xa to anti-IIa activity ratio, one LMWH cannot be interchanged for another LMWH.[2] Refer to Table 3 at the end of the document for further drug information.

Initiating enoxaparin therapy:

1. Obtain basic metabolic panel (BMP) and complete blood count (CBC) at least 48 hours prior to initiation of therapy to assess for renal function and baseline platelet levels. Note: May initiate enoxaparin without BMP and CBC within past 48 hours for post-surgical patient if pre-op labs within 30-days reveal normal renal function and platelet levels and there has been no change in clinical status.
2. Use approved powerplan or form (in case of electronic health record (EHR) downtime) for all enoxaparin orders.
3. For use of enoxaparin surrounding procedure/surgery refer to clinical practice guideline (CPG) "Elective perioperative management of anticoagulants and antiplatelet agents".
4. Rounding of the dose for ease of administration will be done at the time of ordering by physician and/or at the time of verification by the pharmacist under this protocol.
    a. For doses less than 100 mg, round total dose to the nearest 5 mg (0.05 mL increments) using enoxaparin concentration 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL prefilled syringe.
    b. For doses greater than 100 mg, round total dose to the nearest 2.5 mg (0.025 mL increments) using enoxaparin concentration 120 mg/0.8 mL or 150 mg/1 mL prefilled syringe.

Exclusion criteria:

1. **Do not initiate on patients with history of HIT.**
2. Do not initiate on patients with platelets ≤ 50,000, international normalized ratio (INR) > 1.5 unless approved by attending physician.
3. Do not initiate on patients with creatinine clearance (CrCL) < 20 mL/min.[1]
4. Discontinue (DC) all intramuscular (IM) injections when using therapeutic dose.
5. Aspirin dose should not exceed 162 mg per day when using therapeutic dose.

Dosing guideline:

1. Venous Thromboembolism (VTE) **Prophylaxis**
    a. If patient has epidural, then use ONCE daily dosing. Also, refer to VCMC Clinical Practice Guideline for Anticoagulation Management Around Epidural/Intrathecal/Lumbar Puncture.

Venous Thromboembolism (VTE) Prophylaxis	
Patient population	**Dose, Route, Frequency**
Medicine patients with CrCL ≥30 mL/min	40 mg SQ* q 24 hours
Trauma patients with CrCL ≥30 mL/min	30 mg SQ q 12 hours[A]
ǂObese BMI ≥ 30 kg/m^2	0.5 mg/kg SQ Q 24 hrs. No dose capping is necessary [4, 5]
ǂMorbidly obese BMI ≥ 40 kg/m^2	
¥Low body weight: Women <45 kg, Men <57 kg	30 mg SQ daily
Post-Op Bariatric surgery patient with CrCL ≥ 30 mL/min	40 mg SQ q 12 hours[6,7] (May start 4 hours post-op)
Hip/Knee replacement surgery with CrCL ≥ 30 mL/min	30 mg SQ q 12 hours (May start 12-24 hours post-op)
¥Pregnancy	40 mg SQ q 24 hours [8,9]
CrCL 20 – 30 mL/min	30 mg SQ q 24 hours [3]
CrCL < 20 mL/min	Not recommended [3]
Note: *SQ = Subcutaneously. ǂ Defined by US National Institute of Health [A]Avoid if epidural – use q24hr dosing. BMI: Body mass index. **¥May monitor anti-Xa LMWH levels as needed.**	

2. **Treatment**: ST-elevation myocardial infarction (STEMI), Non-ST-elevation myocardial infarction (NSTEMI)/Unstable angina (UA), Venous thromboembolism (VTE)

Indication	**Dose, Route, Frequency**		
STEMI	Age < 75 years old	Initial	30 mg **IV** bolus then 1 mg/kg **SQ** q 12 hours starting 15 minutes after initial bolus dose. Maximum of 100 mg total for the first two doses (bolus + first 1 mg/kg dose)
		Maintenance	1 mg/kg SQ q 12 hours
	Age ≥ 75 years old	Initial	NO bolus, give 0.75 mg/kg SQ q 12 hours. Maximum dose of 75 mg for the first two doses
		Maintenance	0.75 mg/kg SQ q 12 hours
	Obesity	Initial	Use weight based dosing with maximum dose of 100 mg for the first two doses [3,10]
		Maintenance	No dosage capping is necessary
	Renal insufficiency	CrCL 20-30 mL/min	Regardless of age, 1 mg/kg SQ q 24 hours[16]
		CrCL < 20 mL/min	Do NOT use
STEMI: Primary PCI [16]	• Use of enoxaparin has not been studied extensively in this setting • 2013 ACCF/AHA guideline recommends the use of UFH ± bivalirudin		
STEMI: To support PCI post fibrinolytic therapy [16]	• Continue enoxaparin through PCI • No additional dose if last dose was given within previous 8-12 hours • 0.3 mg/kg **IV** bolus if last dose was 8-12 hours earlier		

STEMI: Adjunctive with fibrinolytic therapy[16]		• Administer enoxaparin based on age, renal function, weight • Give either 15 min before or 30 min after thrombolytic
NSTEMI/ UA	Normal dosing	1 mg/kg SQ q 12 hours
	Obesity	1 mg/kg SQ q 12 hours based on actual body weight Dose capping is not recommended [1,11]
	Renal insufficiency	CrCL 20-30 mL/min: 1 mg/kg SQ q 24 hours
		CrCL < 20 mL/min: Do NOT use
VTE/PE	Normal dosing	1 mg/kg SQ q12 hours 1.5 mg/kg SQ q 24 hours
	Obesity	• 1 mg/kg SQ q 12 hours based on actual body weight • Once a day dosing is not recommended [1,3] • Dose capping is not recommended [1,3,12,13] • May consider obtaining anti-Xa level for patients who weight > 190 kg [1]
	Renal impairment	CrCL 20-30 mL/min: 1 mg/kg SQ q 24 hours
		CrCL < 20 mL/min: Do not use
Abbreviations: PCI = percutaneous coronary intervention, PE = pulmonary embolism, IV = intravenous		

Monitoring

1. Obtain **BMP** and **CBC** at baseline and a minimum of every other day while inpatient then periodically at primary care provider's (PCP) discretion if therapy needs to continue in outpatient setting.
    - Use Cockcroft-Gault equation to calculate patient's estimated renal function.[3]

      $$\frac{(140 - \text{age}) * \text{weight in kg}}{72 * \text{Scr}} * 0.85(\text{for female})$$

      Use Ideal Body weight: Male = 2.3* height over 60 inches in inches + 50
      (unless underweight) Female = 2.3* height over 60 inches in inches + 45.5
    - Although it is rare, monitor for possible HIT by obtaining/trending platelets for unexplained reduction by 50% or more from baseline or any sign/symptoms of thrombosis within 5-14 days after initiation of therapy or sooner if patient was exposed to any heparin products within the past 3-4 months.[1]
2. Anti-Xa level
    - PATIENT POPULATION
        i. It has been suggested anti-Xa level *may* be used to examine the safety and efficacy of enoxaparin use in these following populations.[3]
            1. **Renal impairment**
            2. **Pregnancy**
            3. **Morbid obesity** (BMI > 40 kg/m^2) or **low body weight**
                a. Anti-Xa monitoring *can be considered* in patients with morbid obesity (BMI > 40 mg/m^2)[3] or if patient weigh ≥ 190 kg.[1]
                b. In patients with total body weight >190kg, start enoxaparin using total body weight and dose adjust according to either anti-Xa level or if bleeding complications occur.[1, 3]
            4. **Coronary interventional procedures**

5. **LMWH for prolonged periods**
6. **Neonates and children**
7. **Recurrent thrombosis despite LMWH therapy**

- HOW TO ORDER
  - i. Anti-Xa level may be ordered through Cerner as "Anti-Xa LMWH"
  - ii. Obtain level at least 2 days into therapy to reach steady state.[13]
  - iii. Peak level must be drawn at 4 hours post subcutaneous dose.[3]
  - iv. There is no consensus on target anti-Xa level.[3] See Table 1.
  - v. See nomogram on Table 2. for dose adjustments when using enoxaparin as treatment.

    NOTE: This nomogram is for goal peak concentration of 0.5 – 1 IU/mL used for every 12 hour dosing for VTE treatment. Sample needs to be adjusted if indication or goal peak concentration is different.

Table 1. Suggested target anti-Xa levels [3]

Indication	Peak Concentration IU/mL (draw 4 hours after subcutaneous dose)
VTE Prophylaxis	0.2-0.4
VTE Treatment – every 12 hour dosing	0.5-1
VTE Treatment – Once daily dosing	1-2
Acute coronary syndrome (ACS) Treatment	0.5-1.5
Trough < 0.5 IU/mL – to evaluate accumulation at the end of dosing interval in severe renal impairment. Unknown clinical significance.	

Table 2. Suggested LMWH dosing nomogram for TREATMENT doses of enoxaparin with goal anti-Xa level 0.5 – 1 IU/mL [3]

Anti-Xa Level (U/mL)	Hold Next Dose	Dose change	Next Anti-Xa level
<0.35	No	Inc by 25%	4 hours after next dose
0.35-0.49	No	Inc by 10%	4 hours after next dose
0.5-1	**No**	**No**	**Next day, then in 1 week, then monthly**
1.1-1.5	No	Dec by 20%	1 hour before next dose*
1.6-2	3 h	Dec by 30%	1 hour before next dose* and 4 hours after next dose
>2	Until anti-Xa <0.5 U/mL	Dec by 40%	1 hour before next dose* and q12h until anti-Xa <0.5 U/mL
*Obtaining trough to check for accumulation			

Reversal [14]

1. See CPG.56 management of Bleeding Associated with Anticoagulants and Antiplatelet Therapies.

Conversion [10]

Drug From	Drug To	Actions
Heparin infusion	Enoxaparin	Wait 2 hours after discontinuation of heparin infusion to start enoxaparin.
Enoxaparin	Heparin infusion	From therapeutic enoxaparin doses: Initiate heparin infusion when next enoxaparin dose is expected to be given. Consider NOT giving heparin loading dose. From prophylaxis enoxaparin doses: Initiate heparin infusion as clinically needed irrespective of time of enoxaparin dose.
Enoxaparin	Oral anticoagulants	VCMC CPG Guideline for the Prescribing of Direct Oral Anticoagulants (DOACs)

Perioperative management [Coming soon: NEW perioperative management CPG]

1. Stop therapeutic dose 24 hours before surgery.
2. High-bleeding risk surgery + therapeutic dose: Resume 48-72 hours after surgery.

Neuraxial anesthesia management

1. See VCMC CPG for Anticoagulant Management Around Epidural/Intrathecal/Lumbar Puncture.

Table 3. Enoxaparin Drug Info [10]	
Food and Drug Administration (FDA) Approved Indication	• Acute Coronary Syndromes: UA, NSTEMI, STEMI • Deep vein thrombosis (DVT) prophylaxis: Post hip or knee replacement surgery, abdominal surgery, or medical patients with severely-restricted mobility during acute illness • DVT treatment (acute)
Mechanism of action	Strongly inhibit factor Xa while small effect on the activated partial thromboplastin time (aPTT). Average molecular weight of enoxaparin is 4500 daltons compared to 16,000 daltons in heparin.
Pharmacokinetics/dynamics	• Onset of action: peak effect after subcutaneous injection = 3-5 hours [measured by anti –Xa level] • Linearly absorbed after subcutaneous injection[2] • Volume of distribution: 5-7 L • Metabolism: Hepatic • Half-life elimination: 4.5 – 7 hours • Excretion: Urine • Hydrophilic – majority in intravascular compartment [13]
Contraindications/precautions	Hypersensitivity to enoxaparin, heparin, pork products, thrombocytopenia, active major bleeding, heparin-induced thrombocytopenia (HIT)

Reference:

1. Phillips, K., et al. Considerations in using anticoagulant therapy in special patient population. Am J Health-Syst Pharm. 2008; 65(suppl 7):s13-21.

2. Fareed, J., et al. Pharmacodynamic and Pharmacokinetic Properties of Enoxaparin. Clin Pharmacokinet 2003; 42(12):1043-1057.

3. Nutescu, E. et al. Low-Molecular-Weight Heparins in Renal Impairment and Obesity: Available Evidence and Clinical Practice Recommendations Across Medical and Surgical Settings. The Annals of Pharmacotherapy 2009; 43:1064-83

4. Rondina, M., et al. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-ill patients. ThromRes 2010 March; 125(3): 220-223

5. Freeman, A., et al. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. American Journal of hematology. 2012 April Online publication. 740-743

6. Parker, S. G., et al. "Enoxaparin venous thromboembolism prophylaxis in bariatric surgery: a best evidence topic." *International Journal of Surgery* 23 (2015): 52-56.
7. Brunetti, Luigi, et al. "Anticoagulant activity of enoxaparin and unfractionated heparin for venous thromboembolism prophylaxis in obese patients undergoing sleeve gastrectomy." *Surgery for Obesity and Related Diseases* 15.3 (2019): 363-373.
8. Hameed, A. B., et al. "Improving health care response to maternal venous thromboembolism." (2018).
9. Kotaska, A. (2018). Postpartum venous thromboembolism prophylaxis may cause more harm than benefit: a critical analysis of international guidelines through an evidence-based lens. *BJOG: An International Journal of Obstetrics & Gynaecology*, *125*(9), 1109-1116.
10. Lexi/Package insert – Enoxaparin.
11. Mahaffey, K., et al. Obesity in patients with non-ST-segment elevation acute coronary syndromes: Results from the SYNERGY trial. International Journal of Cardiology 139(2010):123-133
12. Medico, C., et al. Pharmacotherapy in the Critically Ill Obese Patient. Crit Care Clin 26 (2006) 679-688.
13. Sanderink, G., et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther 2002; 72:308-18.
14. Package insert – Protamine sulfate.
15. Antithrombotic therapy and prevention of thrombosis, 9th Ed. ACCP guidelines 2012. Chest 2012; 141(2)(suppl):e195S-e226S
16. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Circulation. 2013;127:e362-e425.
17. Kearon et al. Antithrombotic Therapy for VTE disease. CHEST guideline and expert panel report. CHEST 2016; 149(2);315-352.