Heparin/Low Molecular Weight Heparin and Fondaparinux Pharmacology and Pharmacotherapy

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Personal Disclosure

- There are no actual or potential conflicts of interest associated with this presentation.

Learning Objectives

- At the conclusion of this activity, participants will be able to:
  - Discuss the pharmacology of heparin, low molecular weight heparin, and fondaparinux
  - Discuss the indications and contraindications for heparin, low molecular weight heparin, and fondaparinux

Hemostasis

- Complex process where multiple components of the coagulation system are activated in result to control bleeding

1. Primary hemostasis
2. Secondary hemostasis
3. Fibrin clot formation and stabilization
4. Inhibition of coagulation

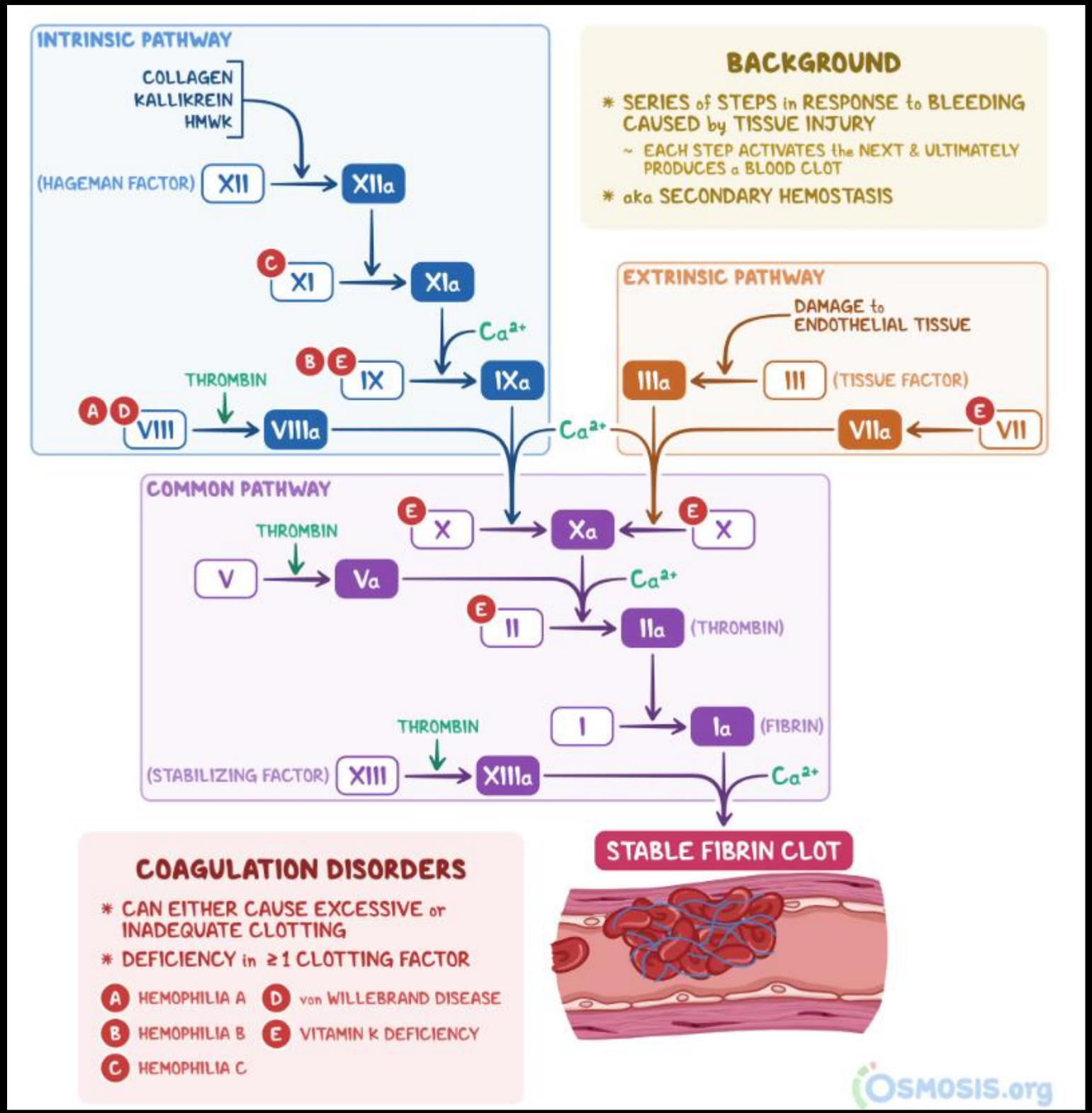
Primary Hemostasis

- Triggered by injury to the vessel wall or other factor
- Formation of a platelet plug
- Results in:
  - Vasoconstriction
  - Adhesion
  - Aggregation

Secondary Hemostasis

- Initiation of coagulation
  - ‘The coagulation clotting cascade’
- Reinforces the platelet plug with protein mesh

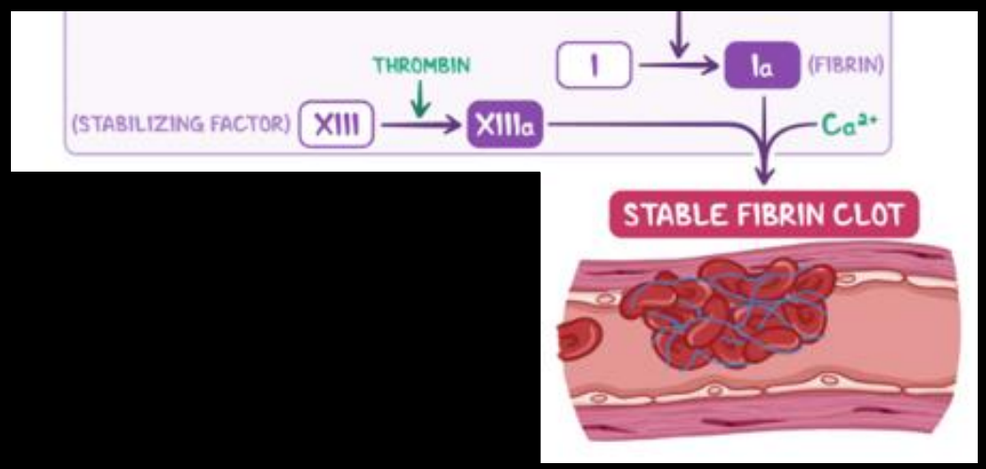
Secondary Hemostasis



Tarantino. 2022.

Stable Fibrin Clot

1. Primary hemostasis
2. Secondary hemostasis
3. Fibrin clot formation and stabilization
4. Inhibition of coagulation



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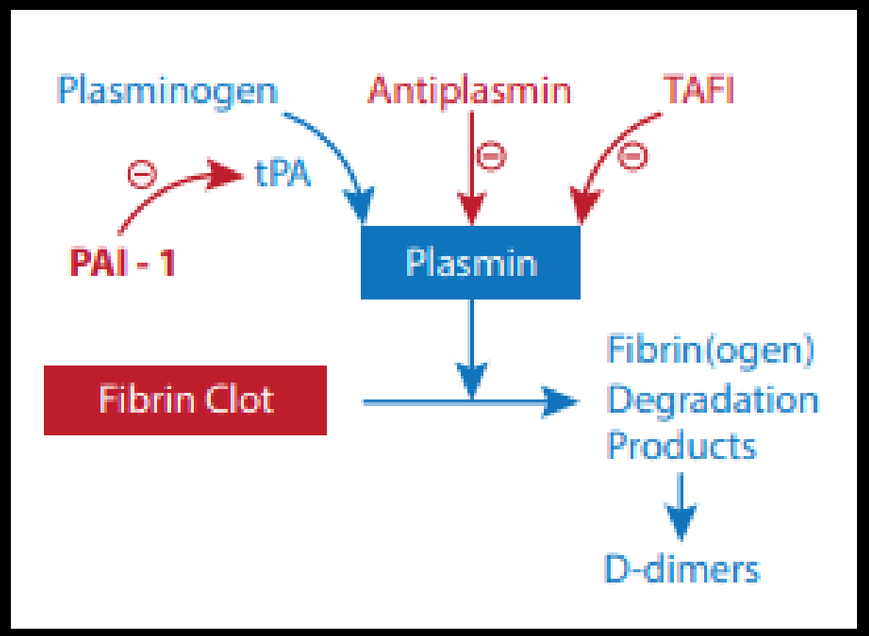
Inhibition of Coagulation

- Inhibition of thrombin generation
  - Thrombin binds to thrombomodulin and activates Protein C
  - Protein C binds with Protein S to slow the coagulation process
  - Thrombin bound thrombomodulin becomes inactive
- Fibrinolysis



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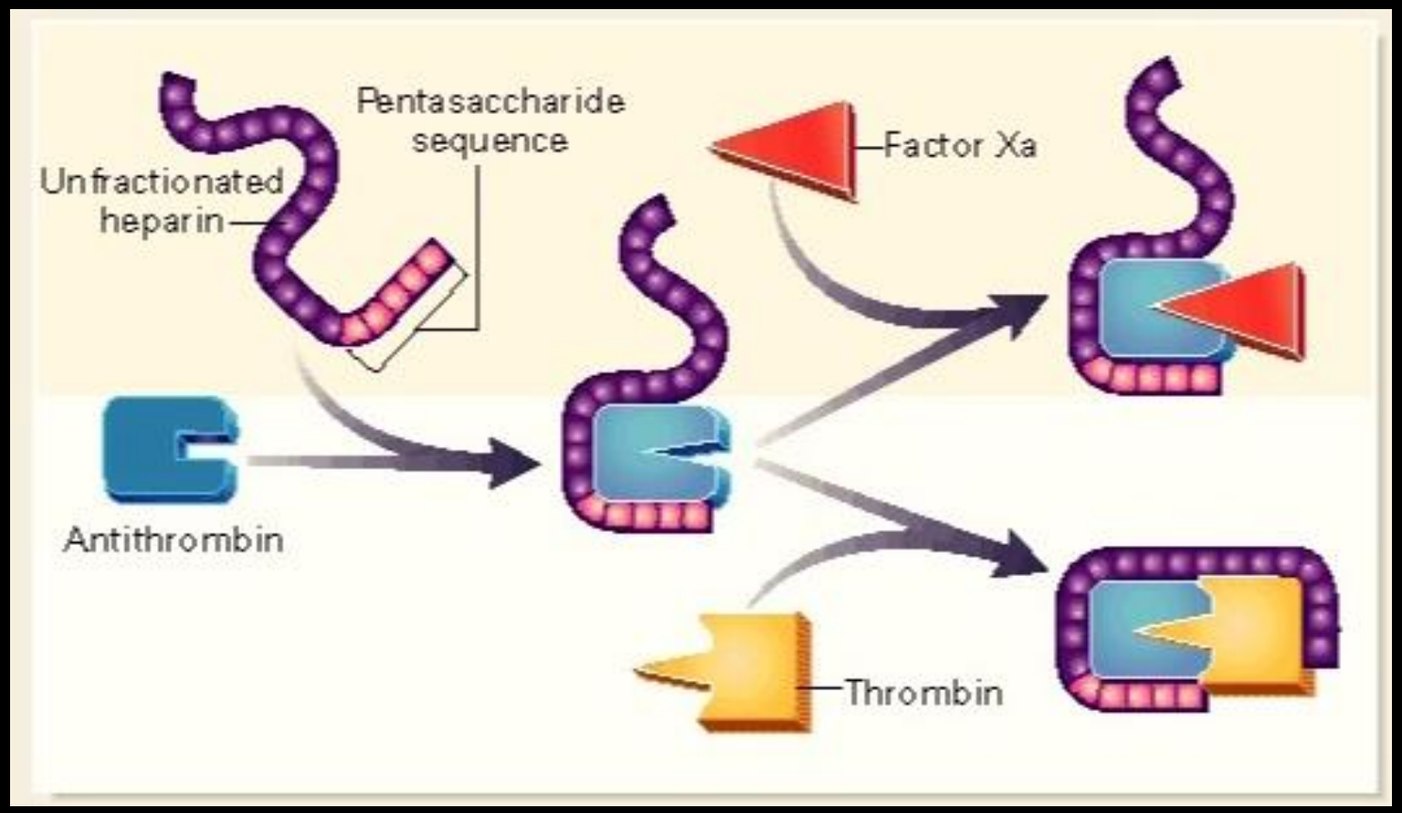
Unfractionated Heparin (UFH): Mechanism of Action

- Heparin is an electronegative polysaccharide found endogenously in mast cells of the lung, liver, and intestines
- Binds directly to Antithrombin (AT), a natural anticoagulant
- UFH is an indirect thrombin (Factor IIa) inhibitor
- Converts AT to a rapid inactivator of thrombin and Factor Xa
- Also inactivates XIIa, XIa, IXa (minor)
- Binding mediated by specific pentasaccharide sequence
- AT/heparin complex boosts AT function four fold, interrupts intrinsic pathway, specifically conversion of fibrinogen to fibrin

Heparin: Mechanism of Action

- Most heparin chains can bind both AT and thrombin molecule
- Can only form when pentasaccharide chain ≥ 18 saccharides long
- Mean molecular weight of UFH = 15,000 daltons (ranges from 6,000-20,000 daltons)



Weitz. 1997.

Heparin: Pharmacokinetics

- Onset of action:
  - Subcutaneous: ~ 30 minutes
  - IV: Immediate
- Absorption:
  - IV: Rapid and complete
  - SC: Erratic
- Distribution:
  - Binds extensively to LDL, globulins (i.e.: AT), and fibrinogen
  - Confined to intravascular space
  - Does not cross placenta or enter breast milk: considered compatible with pregnancy and lactation

Heparin: Pharmacokinetics

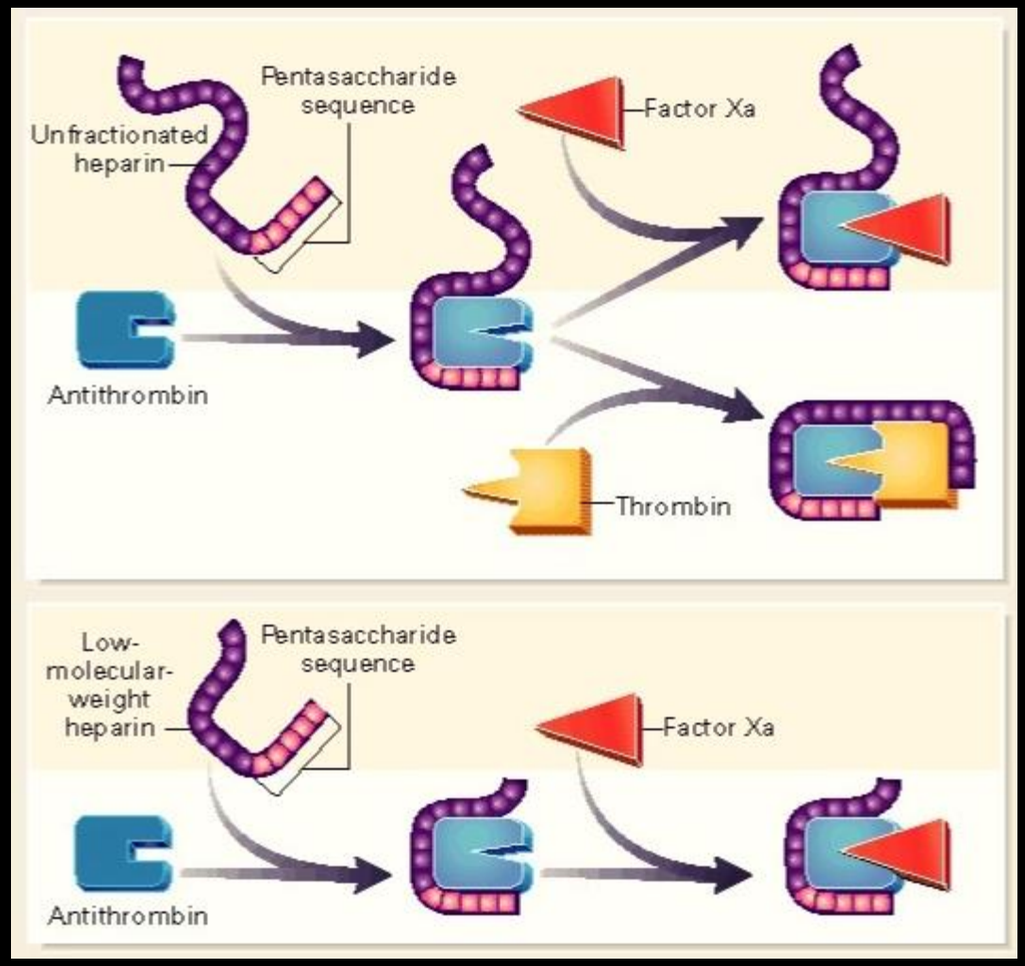
- Metabolism
  - Primarily hepatic
  - Possible reticuloendothelial system involvement
  - Preferred vs. LMWH/fondaparinux for use in renal insufficiency as no dosing adjustment needed
- Elimination $t_{1/2}$
  - 3 measures: bioassayed concentration, clotting time, extension of clotting time
  - Rule of thumb: 1-2 hours
- Elimination:
  - Unchanged in urine
  - Not dialyzable

Low Molecular Weight Heparin

- Similar mechanism of action as heparin, but is a “fractionated” form of UFH
- Primarily binds AT which increases inhibition of Factor Xa
- Mean MW = 4,500 daltons
- Shorter pentasaccharide sequence = less direct anti-thrombin activity

LMWH vs. UFH

- "5" denotes native pentasaccharide sequence common to UFH and LMWH
- Both bind AT which potentiates anti-Factor IIa activity
- Must be >6000 daltons (≥18 monosaccharides) to bind both AT and thrombin
- LMWH is too short to concomitantly bind AT and thrombin



Weitz. 1997.

LWMH: Pharmacokinetics

- Bioavailability: Subcutaneous- 80-95%, but may be affected by high/low body weight
- Time to peak: approximately 4 hours
- Distribution: Large Vd, average 3-5 liters
- Metabolism: Primarily hepatic
- Elimination Half life: ranges from 3-7 hours, but may be extended in patients with renal failure

LMWH vs. Heparin

LMWH	UFH
Increased bioavailability via SC injection route	Erratic absorption via SC route: IV route preferred
Duration of action is longer = once or twice daily dosing	Short half life of 1-2 hours during IV administration = need for continuous IV infusion
Lower risk of heparin induced thrombocytopenia (HIT)	0.2-5% incidence of HIT in patients exposed to heparin > 4 days
Anti Xa testing not usually necessary	Anti Xa or aPTT needed on at least a daily basis
Outpatient treatment feasible	Inpatient treatment usually necessary
Protamine will not completely reverse effects (~50-60% reversal)	Protamine rapidly binds to and neutralizes acidic heparin molecules
Serum creatinine monitoring and dose adjustments for CrCl <30ml/min	No adjustment for poor renal function needed
Monitoring of platelet count, H/H, and signs/symptoms of bleeding necessary	Monitoring of platelet count, H/H, and signs/symptoms of bleeding necessary

Fondaparinux

- Synthetic pentasaccharide sequence
- Causes AT inhibition of Factor Xa
- Similar in size and activity to LMWH

Fondaparinux: Pharmacokinetics

- Absorption: Rapid with 100% bioavailability
- Time to peak: Subcutaneous
  - 2-3 hours
- Distribution: Vd = 7-11 Liters
- Elimination half life: 17-21 hours, prolonged in renal dysfunction
- Excretion: Unchanged in urine

Fondaparinux vs. LMWH

LMWH	Fondaparinux
Good bioavailability via SC injection route	Good bioavailability via SC injection route
Long duration = once or twice daily dosing	Long duration of action = once daily dosing
Lower risk of heparin induced thrombocytopenia (HIT) than UFH	Lower risk of HIT than LMWH
Anti Xa testing not usually necessary	Anti Xa testing not usually necessary
Outpatient treatment feasible	Outpatient treatment feasible
Protamine will only partially reverse effects	Protamine will not reverse, no antidote available
Serum creatinine monitoring and dose adjustment for CrCl < 30ml/min necessary	Contraindicated in CrCl < 30ml/min
Monitoring of platelet count, H/H, and signs/symptoms of bleeding necessary	Monitoring H/H and signs/symptoms of bleeding necessary
$t_{1/2}$ = 3-7 hours	$t_{1/2}$ = 17-21 hours

Heparin: FDA Approved Indications

- Venous Thromboembolism Prophylaxis/Treatment
- Acute Coronary Syndromes
  - Includes: PCI, STEMI, USA/NSTEMI

Heparin: Dosing

- Intravenous dosing based on hospital derived nomograms
- Weight based initial dosing
- Dose adjustments based on aPTT or Anti factor Xa levels

LOW DOSE HEPARIN ORDER FORM

Anti-Xa monitoring

(Suggested for acute MI patients receiving thrombolytics, patients receiving GPIIb/IIIa inhibitors, or selected cerebrovascular disease patients)

1. Lab: Baseline PTT, PT/INR, CBC+PLTs; then CBC+PLTs every 3 days while receiving heparin
2. Bolus dose: IV heparin 26 units/kg; Max 4,000 units (see chart below)

Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)
35-38	950		56-60	1500		81-85	2150		106-110	2800		131-135	3450
39-44	1100		61-65	1650		86-90	2300		111-115	2900		136-140	3600
45-50	1250		66-70	1750		91-95	2400		116-120	3050		141-145	3700
51-55	1350		71-75	1900		96-100	2550		121-125	3200		146-150	3850
			76-80	2050		101-105	2700		126-130	3350		>150	4000

2. Initial IV infusion rate per chart below, Max 1,000 units/hr
25,000 units heparin in 500ml of Dextrose 5% (50 units/mL) Use IV pump setting: **HEPARIN LOWDOSE**

Weight (Kg)	Dose (Units/Hr)		Weight (Kg)	Dose (Units/Hr)		Weight (Kg)	Dose (Units/Hr)		Weight (Kg)	Dose (Units/Hr)		Weight (Kg)	Dose (Units/Hr)
35-38	440		45-50	570		56-60	700		66-70	820		76-80	940
39-44	500		51-55	640		61-65	750		71-75	880		>80	1000

3. Stat Anti-Xa level 6 hours after infusion begun or after each rate change and again 6 hours later until two consecutive levels are within therapeutic range (0.2-0.5 units/ml), then every 24 hours. Adjust infusion based on the following nomogram:

Anti-Xa level (units/ml)	Bolus Dose	Hold infusion (minutes)	Infusion Rate Change mL/hr (units/hr)
<0.1	26 units/kg (rounded to nearest 50 units)	No	INcrease 100 units/hr
0.1-0.19	None	No	INcrease 50 units/hr
0.2-0.5	None	No	No change
0.51-0.6	None	No	DEcrease 50 units/hr
0.61-0.7	None	30 minutes	DEcrease 100 units/hr
0.71-0.8	None	60 minutes	DEcrease 150 units/hr
>0.81	None	60 minutes	DEcrease 300 units/hr

Thromboembolic Heparin/Warfarin Order Form

Anti-Xa monitoring

1. Lab: Baseline PTT, PT/INR, CBC+PLTs; then CBC+PLTs every 3 days while receiving heparin

2. Intravenous bolus dose of heparin 26 units/kg based on actual body weight (see chart below)

Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)		Weight (Kg)	Dose (Units)
35-38	950		66-70	1750		96-100	2550		126-130	3350		156-160	4100
39-44	1100		71-75	1900		101-105	2700		131-135	3450		161-165	4250
45-50	1250		76-80	2050		106-110	2800		136-140	3600		166-170	4350
51-55	1350		81-85	2150		111-115	2900		141-145	3700		171-175	4500
56-60	1500		86-90	2300		116-120	3050		146-150	3850		176-180	4650
61-65	1650		91-95	2400		121-125	3200		150-155	4000		181-185	4750

If >185 kg, continue to calculate 26 units/kg (rounded to nearest 50 units)

3. Begin continuous intravenous infusion at **15 units/kg/hr**.
(25,000 units heparin in 500 ml of D5W = 50 units/ml) Use IV pump drug library setting for **HEPARIN REG**

4. Stat Anti-Xa level 6 hours after infusion begun or after each rate change and again 6 hours later until two consecutive levels are within therapeutic range (0.3-0.7 units/ml), then every 24 hours.

5. Adjust heparin infusion based on the following nomogram:

Anti-Xa level (units/ml)	Bolus	Infusion
<0.2	26 units/kg (rounded to nearest 50 units)	Increase by 4 units/kg/hr
0.2-0.29	NO	Increase by 2 units/kg/hr
0.3-0.7	NO	NO CHANGE
0.71-0.8	NO	Decrease by 1 unit/kg/hr
0.81-0.99	NO	Decrease by 2 units/kg/hr
>1	NO	HOLD 1 HOUR than decrease by 3 units/kg/hr

6. Warfarin_____mg PO X one dose, Call MD daily for dose if not ordered by 2pm,
daily PT/INR labs when warfarin is ordered.

THROMBOEMBOLIC HEPARIN/WARFA

Heparin Dosing: Special Populations

- Heparin Resistance
  - Patients requiring extremely large doses of heparin to achieve and maintain therapeutic levels
  - Possible Causes: accelerated heparin clearance, increased heparin binding proteins (e.g.: LDL, fibrinogen), AT deficiency
- AT deficiency
  - Cause of most heparin resistance
  - Mutation in heparin binding site and/or thrombin binding site
  - First AT product in US approved Feb 2009
  - May be beneficial in some high risk patients

LMWH: FDA Approved Indications

- **Dalteparin**
  - Venous thromboembolism prevention (medical illness, hip, abdominal surgery)
  - Venous thromboembolism treatment/prevention of recurrence in cancer patients
  - Unstable angina (USA) or non Q-wave myocardial infarction
- **Tinzaparin**
  - Venous thromboembolism treatment
    - *Preliminary data from IRIS (Innohep® in Renal Insufficiency) study prompted FDA to issue warning advising alternative drugs in elderly patient with renal failure*
- **Enoxaparin**
  - Venous thromboembolism prophylaxis (medical, hip, knee, abdominal surgery)/treatment
  - Acute Coronary Syndromes
    - Includes PCI, STEMI, USA/NSTEMI

LWMH: Dosing

- **Dalteparin**
  - DVT prophylaxis
    - 5000 units SC daily
- **Tinzaparin**
  - DVT +/- PE treatment: 175 Anti Xa international units/kg SC daily
- **Enoxaparin**
  - DVT/PE treatment: 1 mg/kg SC BID or 1.5mg/kg SC daily, 1 mg/kg SC daily for CrCl <30ml/min
  - DVT/PE medical prophylaxis: 40 mg SC daily, 30 mg SC daily for CrCl <30ml/min

Fondaparinux: FDA Approved Indications

- Venous thromboembolism prophylaxis/treatment

Fondaparinux: Dosing

- DVT/PE prophylaxis (adults at least 50 kg): 2.5mg SC daily
- DVT/PE treatment
  - <50 kg = 5 mg SC daily
  - 50-100 kg = 7.5mg SC daily
  - >100 kg = 10 mg SC daily

Heparin: Contraindications

- Hypersensitivity to heparin or any component of the formulation (including pork products)
- Severe thrombocytopenia, HIT
- Uncontrolled active bleeding (except when due to disseminated intravascular coagulation - DIC)
- Suspected intracranial hemorrhage (ICH)
- Inadequate laboratory monitoring available

LMWH: Contraindications

- Hypersensitivity to heparin or LMWH products and components (includes pork allergies)
- Active HIT or history of HIT
- Active bleeding
- ***Boxed Warning: Patients undergoing epidural or spinal anesthesia are at increased risk of spinal hematoma and paralysis***

Fondaparinux: Contraindications

- Hypersensitivity to fondaparinux
- CrCl < 30ml/min
- Prophylaxis doses in patients weighing < 50 kg
- Active bleeding
- Bacterial endocarditis
- Thrombocytopenia in vitro positive for antiplatelet antibodies in the presence of fondaparinux
- ***Boxed Warning: Patients undergoing epidural or spinal anesthesia are at increased risk of spinal hematoma and paralysis***

CHEST Guidelines: Thromboprophylaxis

- In patients admitted to hospital with **acute medical illness**, thromboprophylaxis with LMWH, low dose UH (LDUH), or fondaparinux is recommended (Grade 1A)
- **On admission to ICU**, it is recommended all patients be assessed for VTE risk and that most receive thromboprophylaxis (Grade 1A)

CHEST guidelines: Treatment of DVT/PE

- **Objectively confirmed DVT** = LMWH, IV UFH, monitored SC UFH, fixed-dose SC UFH, or SC fondaparinux (all Grade 1A)
- **High clinical suspicion of DVT** = treat with anticoagulants while awaiting test outcomes (Grade 1C)
- **Acute DVT** = LWMH as an outpatient if possible, rather than treatment with IV UFH (Grade 1C)
- **Patients with acute DVT and renal failure** = UFH suggested over LMWH (Grade 2C)

CHEST Guidelines: Treatment of DVT/PE

- **Objectively confirmed PE** = LMWH, IV UFH, monitored SC UFH, fixed-dose SC UFH, or SC fondaparinux (all Grade 1A)
- **High clinical suspicion of PE** = treat with anticoagulants while awaiting test outcomes (Grade 1C)
- **Acute non-massive PE** = initial treatment with LMWH over IV UFH (Grade 1A)
- **Massive PE, concerns about SC absorption, thrombolysis planned, severe renal failure** = IV UFH preferred (Grade 2C)

CHEST Guidelines: ACS/NSTEMI

- In addition to other recommended anticoagulant measures (i.e.: aspirin, clopidogrel, GPIIb/IIIa inhibitors):
  - **All patients:** recommend starting UFH, LMWH, bivalirudin, or fondaparinux (Grade 1A)
  - For patients undergoing an **early invasive strategy**: recommend UFH (and GPIIb/IIIa inhibitor) over LMWH or fondaparinux (Grade 1B)
  - For patients undergoing **conservative or delayed invasive strategy:** recommend fondaparinux over enoxaparin (Grade 1A) and LMWH over UFH (Grade 1B)

CHEST guidelines: Acute STEMI

- In addition to aspirin and antiplatelet therapies, recommend UFH, enoxaparin, or fondaparinux (including patients receiving fibrinolysis, primary PCI, or patients not receiving reperfusion therapy) (Grade 1A)

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Heparin/Low Molecular Weight Heparin and Fondaparinux Pharmacology and Pharmacotherapy

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