CARDIOVASCULAR PHARMACOLOGY

HEPARIN

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Heparin | Mechanism of action, Indications, ADR's, Contraindications

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OUTLINE

I) MECHANISM OF ACTION

HEMOSTASIS & COAGULATION CASCADE

(1) Platelet Plug Formation

- **Factors the Increase Thrombi Formation**
- (Recall: Virchow's Triad)
  - Damage to blood vessels/ Injury to endothelial cells
  - Hypercoagulable condition
  - Stasis of blood flow

- **Steps:**

1) **Damaged endothelium → exposed collagen**
2) **Von Willebrand Factor (VWF)** attaches to exposed collagen network
3) **Platelets attach** to VWF
4) **Degranulation** of granules in platelets, releasing platelet aggregation agents - **ADP, TXA_2, Serotonin**
5) Nearby platelets come to injured site and stick to one another forming **platelet plug**
6) **Activated platelet** develop a **negatively charged surface**, which will trigger the **activation of the intrinsic pathway** of the coagulation cascade

(2) Coagulation Cascade

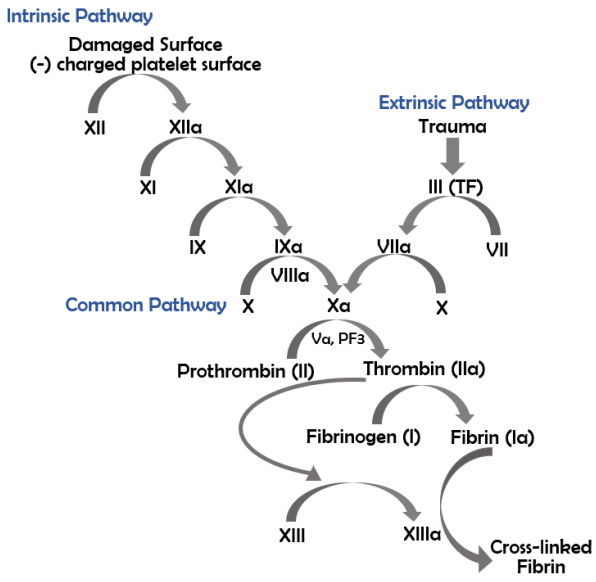

Figure 1. Coagulation Cascade

Intrinsic Pathway

- Platelet plug forms **negatively charged surface** on platelet that activates Factor XII
- Factor XIIa activates Factor XI
- Factor XIa activates Factor IX
- Factor IXa and VIIIa activate Factor X
  - Factor VIII is activated by thrombin

Common Pathway

- Factor X is activated via clotting factors produced by the extrinsic/ intrinsic pathway (Factors VII, VIII, IX)
- Factor Xa combine with Factor Va and Platelet Factor3 (PF3) to convert Factor II (Prothrombin) into the activated Thrombin (Factor IIa)
  - Factor V is also activated by thrombin
- **Thrombin**
  - Activates Factor V and Factor VIII
  - Activates soluble fibrinogen (Factor I) into the insoluble fibrin (Factor Ia)
    - Fibrin: formed by polymerization of fibrinogen
  - Activates Factor XIII into XIIIa that crosslinks fibrin strands producing fibrin mesh that stabilize platelet plug

Extrinsic pathway

- Trauma or injury outside blood vessel releases Tissue Factor or Factor III
- Factor III activates Factor VII into VIIa.
- Factor VIIa and Factor III converts Factor X into Xa →→→ common pathway

Recall:

Warfarin

- *Mnemonic: WEPT*
- **W**arfarin
- **E**xtrinsic Pathway
  - Mainly affect Factor VII since it has the shortest half-life
- **PT**/INR
  - Prothrombin Time/ International Normalized Ratio
  - Monitor extrinsic pathway

Heparin

- *Mnemonic: HAI*
- **H**eparin
- **a**PTT
  - activated Partial Thromboplastin Time
  - monitor intrinsic pathway
- **I**ntrinsic pathway
  - Affect intrinsic and common pathway

HEPARIN

- From bovine (cow) or porcine (pig) source
- **Glycosaminoglycan (GAG) + Pentasaccharide** (five monosaccharides) **= Heparin**
- **MOA:**
  - Binds **Antithrombin III (AT III)**
    - accelerate AT III activities
  - **Inhibit Thrombin**
  - **Inhibit Factor Xa**
  - Amplified effect since inhibiting Factor Xa inhibits activation of prothrombin

(1) Unfractionated Heparin (UFH)

- Considered to be the **High-Molecular Weight Heparin**
- **Longer GAG** + Pentasaccharide
  - Pentasaccharide bind to AT III
  - GAG loop around AT III
  - Activated AT III binds to Factor Xa
  - Longer GAG loops around AT III, inhibiting thrombin
  - Inhibit both Thrombin and Factor Xa
  - Inhibition of thrombin requires binding to both thrombin and AT III [Malloy, Rimsans, Rhoten, Sylvester, Fanikos, 2018]
    - Longer GAG allows this
  - Factor Xa can be inhibited even if heparin binds to AT III only [Malloy, Rimsans, Rhoten, Sylvester, Fanikos, 2018]

(2) Low-Molecular Weight Heparin (LMWH)

- **Shorter GAG** + Pentasaccharide
  - Bind to AT III
  - Inhibit Factor Xa only
  - Shorter GAG cannot reach thrombin to inhibit it
- EnoxaPARIN
- DaltePARIN

(3) FondaPARINux

- Synthetic form of HePARIN
- **Pentasaccharide only, No GAG**
- Bind to AT III
- Inhibit Factor Xa

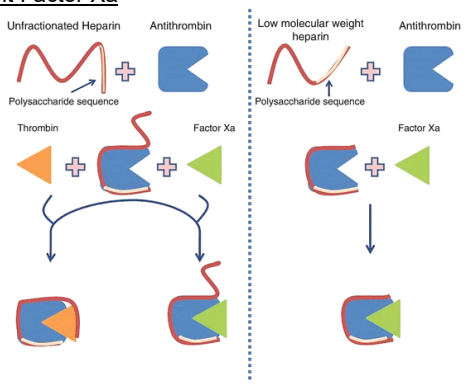

Figure 2. Mechanism of Action of UFH and LMWH

[Malloy, Rimsans, Rhoten, Sylvester, Fanikos, 2018, p. 33, Fig. 3.1]

Factors Affecting Heparin Efficacy

- Heparin's MOA depends on its binding to AT III
- Conditions that ↓**AT III** leading to ↓**Heparin efficacy**
  - **Liver Failure:** ↓AT III production
  - **Nephrotic Syndrome:** proteinuria (↑AT III excretion via urine)

Nephrotic Syndrome
- Lose protein and lipids in urine
- Retain water in body → edema, hypertension

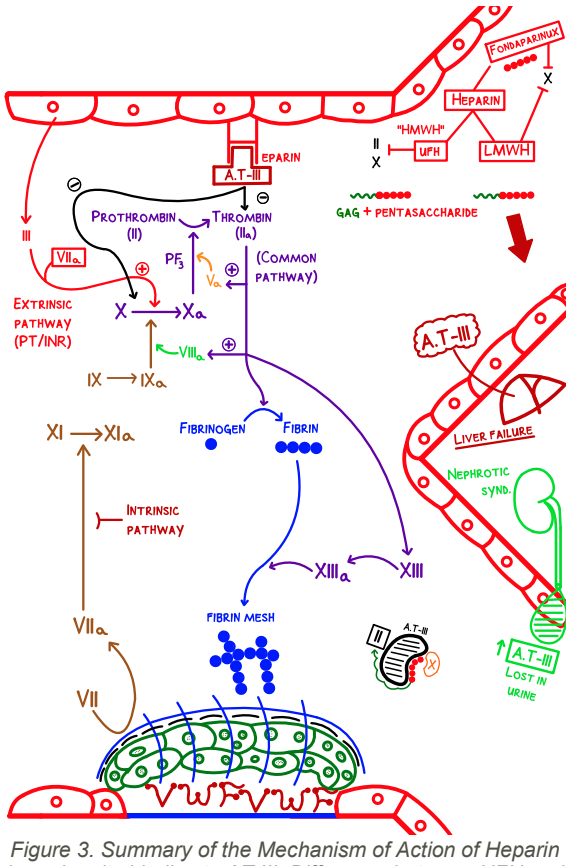

Figure 3. Summary of the Mechanism of Action of Heparin based on its binding to AT III, Difference between UFH and LMWH, and the Effects of Different Conditions to AT III Levels and Heparin Efficacy

II) INDICATIONS

- **Heparin**- used more commonly in **acute** onset conditions
  - Quick onset, short-acting
  - **vs. Warfarin**- used as **prophylaxis/ prevention**

(A) ACUTE DEEP VEIN THROMBOSIS

- **Unfractionated Heparin**
  - Emergencies
  - Bolus, then continuous infusion
- **LMW Heparin**
  - Outpatient
  - Sub-Q injection
  - Types:
    - Enoxaparin (Lovenox)
    - Dalteparin
- **Deep Vein Thrombosis (DVT)**
  - clot forms in deep vein, usually legs

(B) ACUTE PULMONARY EMBOLISM

- **Pulmonary Embolism (PE)**
  - Blood clot, usually from DVT break off and travel to the inferior vena cava → right atrium → right ventricle → pulmonary arteries → hypoxia
- **Unfractionated Heparin**
  - more commonly used since PE poses serious danger
- **LMW Heparin**

(C) PROPHYLAXIS OF DVT/ PE

- **Low dose** heparin, usually LMW Heparin
- Especially for patients that undergo surgical procedures that causes them to be bedridden
- **LMW Heparin**
  - Sub-Q
  - Longer half-life
  - Less side effects (but be cautious in giving to patients with kidney failure or ↓Glomerular Filtration Rate)

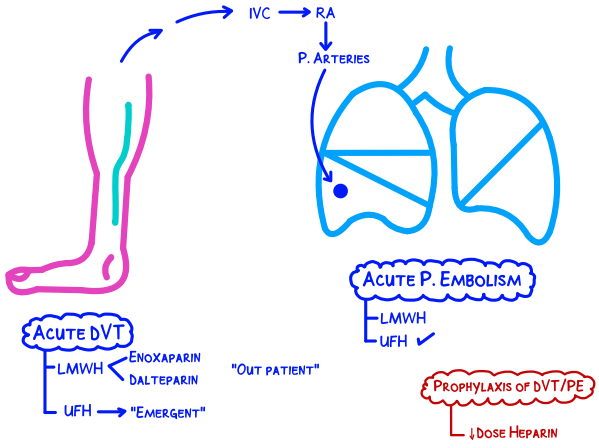

Figure 4. Role of Heparin in the Management of DVT and PE

(D) STEMI/ NSTEMI

- **Clot in the coronary circulation**
- Coronary artery disease
- Atherosclerotic plaques develop in patients that are hypertensive
- **Unfractionated Heparin**
  - Bolus, then continuous infusion
  - Monitor PTT
- **STEMI**
  - go to Cath lab
  - undergo Percutaneous Coronary Intervention (PCI)
- **NSTEMI**
  - no need for PCI
  - not high-risk
  - treat with heparin to prevent complications

(E) NON- VALVULAR ATRIAL FIBRILLATION

- Reentrant circuits/ multiple ectopic foci
- Weak atrial contractions
  - Stasis → clot formation in mitral valve
- **Non-Valvular Atrial Fibrillation**
  - not due to mitral valve disease or prosthetic heart valve
  - can be due to:
    - hypoxia
    - excessive catechol
    - methamphetamine
    - electrolyte imbalances
- **Warfarin**
  - Mainly used in AFib
  - Valvular and Non-Valvular Atrial Fibrillation
- **Heparin** and other direct factor inhibitors
  - only used for Non-Valvular AFib

When to use Heparin?

Severe AFib

- Severe palpitations, chest pain, chest pain
- EKG: rapid ventricular rate (RVR)
- **Treatment Strategy** (reduce heart rate)

1) **Rate control**
   - Medications that block AV node and decrease heart rate to decrease contractions of ventricles
     - Beta blockers
     - Calcium channel blockers
     - Digoxin
   - If rate control fails, do rhythm control
2) **Rhythm control**
   - Sodium channel blockers (i.e., Ibutilide)
     - Not commonly used
     - risk of *Torsades de pointes*
   - Cardioversion: shock
     - Preferred
     - Reset atrial circuitry
       → SA node fires normally
       → normal atrial contractions
     - If patient has pre-existing clot
       - contractions of the atrium can break the pre-existing clots
       - clot travel to systemic circulation → embolism

- **Heparin** is given to AFib patients that have failed rate control and need to undergo cardioversion
- Prior to cardioversion
  - check for clot via transesophageal ECG
    - pre-existing clots can break off when the patient is cardioverted
  - If there is clot, give heparin
    - Reduce thrombus formation and embolization
    - Make sure that there is no clot before cardioversion
- After cardioversion
  - give anticoagulants for 3-6 months.
- **Preventing embolism due to AFib** will prevent:
  - Cerebrovascular accident (CVA)
  - Renal infarcts
  - Splenic infarcts
  - Mesenteric ischemia
    - Superior mesenteric artery blockade
  - Ischemic colitis
    - Inferior Mesenteric Artery blockade
  - Limb gangrene
    - acute arterial embolism in leg
    - necrosis of tissues

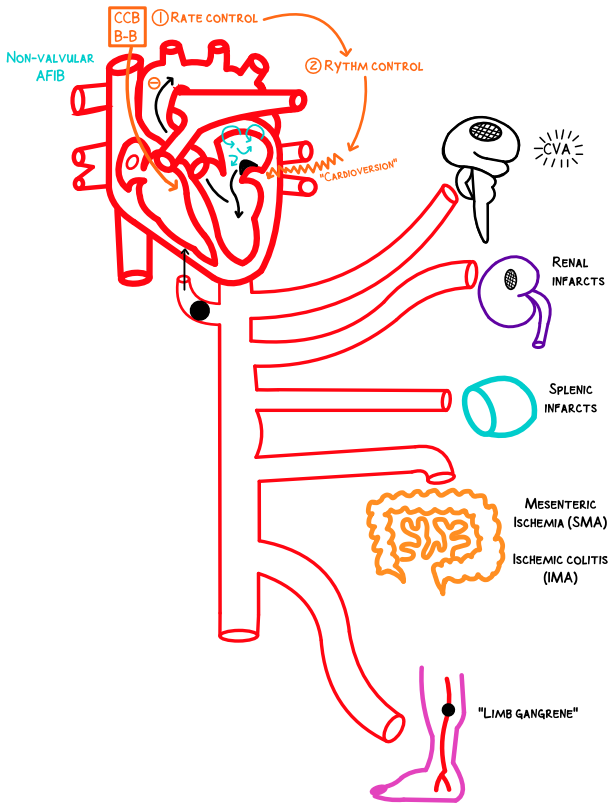

Figure 5. Role of Heparin in Preventing Embolization due to Non-Valvular AFIB

III) ADVERSE DRUG REACTIONS (ADRS)

(A) BLEEDING

1) **Gingival Bleeding**
2) **Anterior Epistaxis** – nosebleed
3) **Bleeding indications on skin**
   a. Petechiae – pinpoint hemorrhage on skin
   b. Purpura – larger pinpoint hemorrhaging
   c. Ecchymosis – large bruising
4) **Hematuria** – blood in urine
5) **Melena** – upper GI bleed – dark or black feces
6) **Hematochezia** – lower GI bleed – red stool
7) **Hematemesis** – vomiting blood
8) **Iron Deficiency Anemia**
   - Fecal occult blood test
     - check blood in feces that is not visibly apparent
   - CBC
     - check MCV and Hemoglobin
9) **Heavy Vaginal bleeding/ Heavy Menstruation**

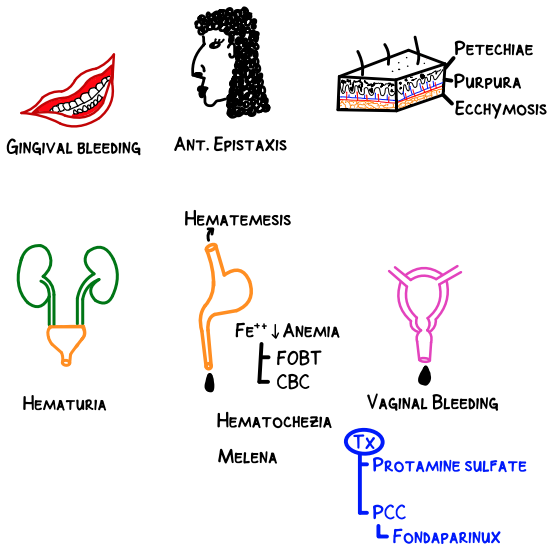

Figure 6. Bleeding as Adverse Reaction of Heparin and Antidotes for Heparin Overdose

Antidote for Heparin Overdose (bleeding):
- Protamine Sulfate
  - More effective in unfractionated heparin
  - Less effective in LMW heparins
  - Not effective for Fondaparinux

Antidote for Fondaparinux Overdose:
- Prothrombin Complex Concentrate (PCC)

(B) HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

Mechanism of HIT

- Heparin binds to **platelet factor 4 (PF4)** of inactivated platelet
- Produce **Heparin + PF4 complex** that is **immunogenic**
  - immune cells will react to it
- Plasma cells produce IgG antibodies against the complex
- **IgG Antibodies bind to the complex**
  1) Tag the platelet for destruction by the macrophages in the spleen, or
  2) Activate platelet
     - Other platelets start binding, forming clot
- **Thrombocytopenia**
  - Platelets are destroyed by spleen or consumed in the formation of clots → **↓platelets (thrombocytopenia)**
- Clots formed can travel to different areas
  - Veins of leg → **DVT** → can break of and travel to lungs → **PE**
  - Myocardium → **Myocardial Infarctions**
  - Central Nervous System → **Cerebrovascular Accident (CVA)** & **Cerebral Venous Thrombosis (CVT)**
  - Arteries of leg → **Acute Arterial Occlusion** → **Limb gangrene**
- For patients taking heparin for the first time
  - reaction manifests after 1-2 weeks since antibodies need to be produced first
- If patient had received heparin in the past
  - antibodies have already been formed
  - exposure to heparin will lead to immediate (within a day) immune response
  - HIT: ↓platelets & paradoxical clotting

Diagnosis: Serotonin Release Assay

- Gold standard test
- **Patient's Serum** (contain IgG, assuming the patient has HIT) + **donor platelets** (contain PF4 and heparin)
- **Activated platelet** release ADP, TXA_2, and **5-HT (Serotonin)**
- **↑5-HT → (+) HIT**

Treatment

- **Discontinue heparin**
  - Switch to **Direct Factor II Inhibitor** (ex. Argatroban)

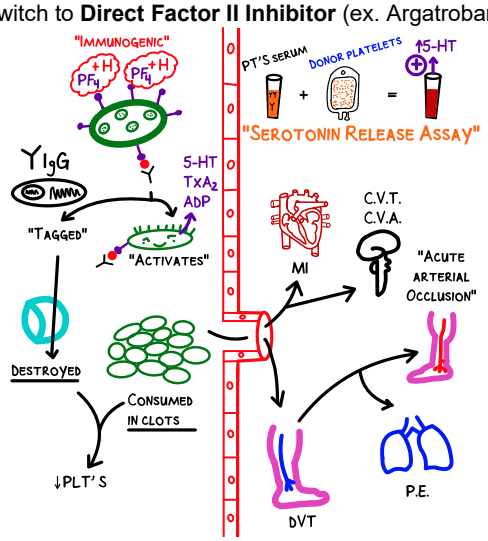

Figure 7. Mechanism, Manifestations, and Diagnosis of HIT

IV) CONTRAINDICATIONS

(A) BLEEDING RISKS

- **Uncontrollable bleeding**
- **Recent CVA**
  - Giving heparin can convert ischemic stroke to hemorrhagic transformation
- **Uncontrolled BP**
  - Increased risk of aortic dissection and aneurysm → bleeding

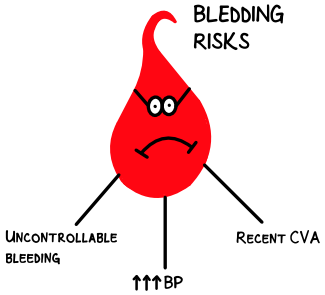

Figure 8. Heparin is Contraindicated in Conditions that Increase Bleeding Risks

(B) RENAL FAILURE

- **LMW heparin** is **contraindicated** in patients with **Creatinine Clearance <30mL/min (Renal Failure)**
  - Bad for kidneys
  - Can do dose adjustments, but kidney failure is a relative contraindication
- Unfractionated heparin can be given instead for Renal Failure since it is nice to the kidneys.

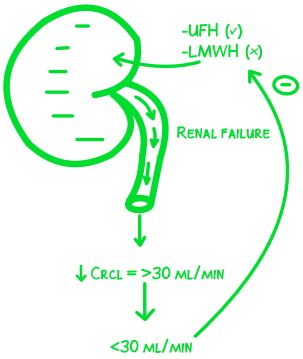

Figure 9. LMWH is Contraindicated in Patients with Renal Failure (CrCl <30mL/min), but UFH can be given

Monitoring Unfractionated Heparin

aPTT (Partial Thromboplastin Time)

- time it takes for **intrinsic and common pathway** to occur and form a clot
  - Factor XII activates XI → activate IX → combine w/ VIII → activate X → convert prothrombin to thrombin → activate fibrinogen and form fibrin → clot
- longer than PT (Prothrombin Time), which measures extrinsic and common pathway
- **Procedure**
  - Activator is added to patient's plasma
    - PTT and aPTT are the same, except that for aPTT, an activator (silica) is added to trigger activation of Factor XII
  - Measure the time it takes for blood to clot after adding the activator

Table 1. aPTT Target Values

Condition	aPTT (sec)
Normal (no Heparin)	30-40 sec
w/ Heparin	1.5 to 2.5 x (Normal Range) 45-100 sec

- **Unfractionated Heparin**

- affect Thrombin, Factor VIII, and Factor X
- affect intrinsic and common pathway, prolong aPTT
- aPTT < 45: insufficient heparin → ↑clotting risk
- aPTT > 100: too much heparin → ↑bleeding risk

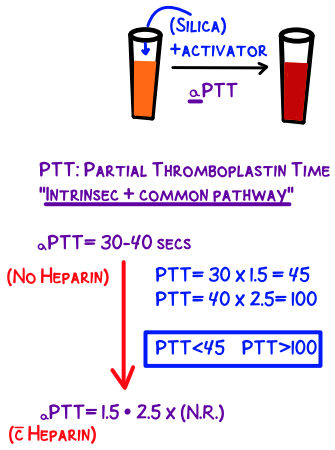

Figure 10. Procedure and Calculation of PTT

Table 2. Comparison of Unfractionated Heparin (UFH) and LMW Heparin (LMWH)

UFH	LMWH
IV/ SQ	SQ
↓half-life (4x less than LMWH)	↑half-life (Longer duration, no need to take as often, good for outpatients)
Nice to kidneys Can be administered in patients w/ renal failure	Rough on kidneys Contraindicated in renal failure (CrCl <30mL/min)
↑bleeding risk	↓bleeding risk
↑HIT	↓HIT
Monitored by aPTT (inhibit Factors II and X)	Monitored by Factor Xa activity (not aPTT since LMWH only inhibits Factor X and indirectly Factor II)

V) REVIEW QUESTIONS

1) **What pathway/s is/ are inhibited by unfractionated heparin?**
   a. Intrinsic pathway
   b. Extrinsic pathway
   c. Common pathway
   d. a and c

2) **What is used to monitor Fondaparinux**
   a. aPTT
   b. PT-INR
   c. Factor Xa activity
   d. PT

3) **Which of the following is composed of a long GAG and pentasaccharide?**
   a. Unfractionated Heparin
   b. LMW Heparin
   c. Fondaparinux
   d. Dalteparin

4) **Which is the following is composed of a pentasaccharide only?**
   a. Unfractionated Heparin
   b. LMW Heparin
   c. Fondaparinux
   d. Dalteparin

5) **True or False: Unfractionated heparin cannot be given to patients with renal failure.**
   a. True
   b. False

6) **Antidote for Heparin:**
   a. Protamine Sulfate
   b. PCC
   c. Fresh Frozen Plasma
   d. Vitamin K

7) **Antidote for Fondaparinux**
   a. Protamine Sulfate
   b. PCC
   c. Fresh Frozen Plasma
   d. Vitamin K

8) **True or False: Heparin should be given to patients who recently suffered from CVA**
   a. True
   b. False

9) **What is usually given in emergency situations, such as PE?**
   a. Unfractionated Heparin
   b. LMW Heparin
   c. Dalteparin
   d. Enoxaparin

CHECK YOUR ANSWERS

VI) REFERENCES

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