Al-Mustaqbal University
College of Pharmacy
5th Stage
Applied therapeutics I
Lecture: 3

Venous Thromboembolism

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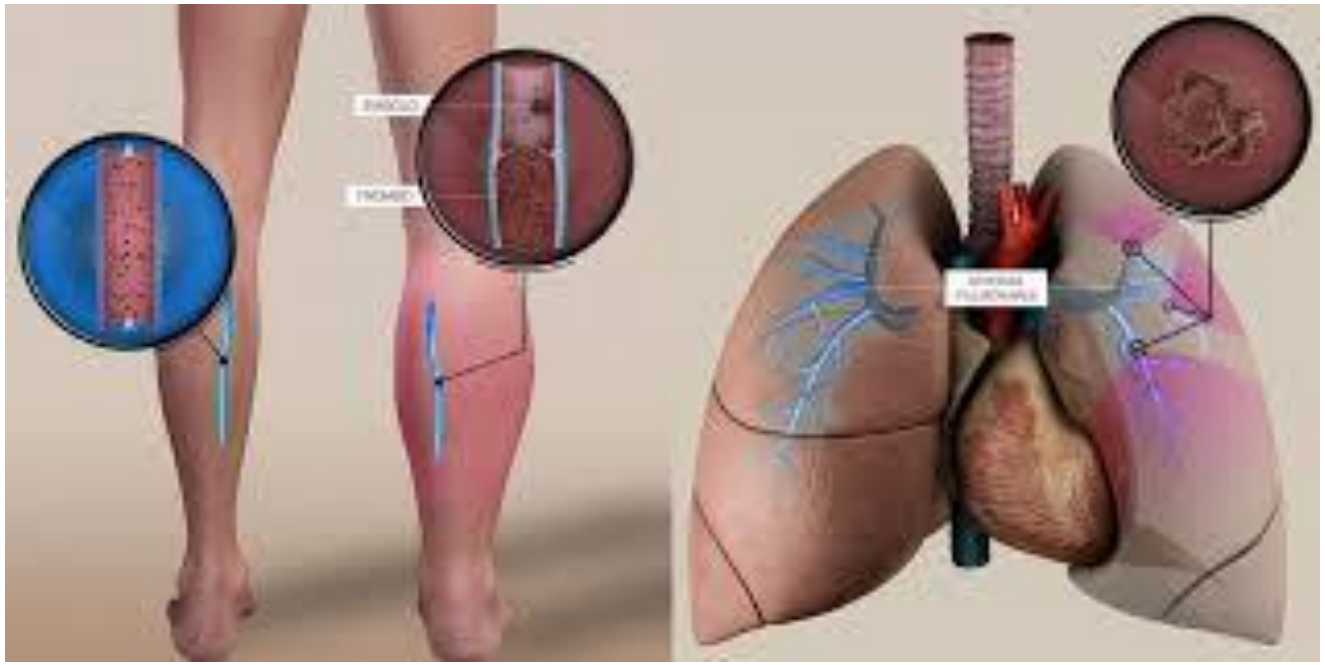
Venous Thromboembolism (VTE)

- Venous thromboembolism (VTE) **results from clot formation** in the **venous circulation** and is manifested as **deep vein thrombosis (DVT)** and **pulmonary embolism (PE).**



Pathophysiology of VTE

- Risk factors for VTE include **increasing age**, **history** of VTE, and aspects related to **Virchow's triad**:

✓(1) blood stasis (eg, immobility and obesity)

✓(2) vascular injury (eg, surgery, trauma, venous catheters)

✓(3) hypercoagulability (eg, malignancy, coagulation factor abnormalities, antiphospholipid antibodies, certain drugs).

- **Inherited deficiencies of protein C, protein S, and antithrombin** occur **in <1%** of the population and may increase the lifetime VTE risk by as much as **sevenfold**.

Pathophysiology of VTE

- **Exposure** of **blood** to **damaged** vessel endothelium causes **platelets** to become **activated** after binding to adhesion proteins (eg, von Willebrand factor, collagen).
- Activated platelets **recruit additional platelets**, causing growth of the **platelet thrombus**.
- Activated platelets **change shape and release components** that sustain **further thrombus formation** at the site.
- Activated platelets express the **adhesion molecule P-selectin**, which facilitates **capture of TF-bearing microparticles**, resulting in **fibrin clot formation** via the coagulation cascade.

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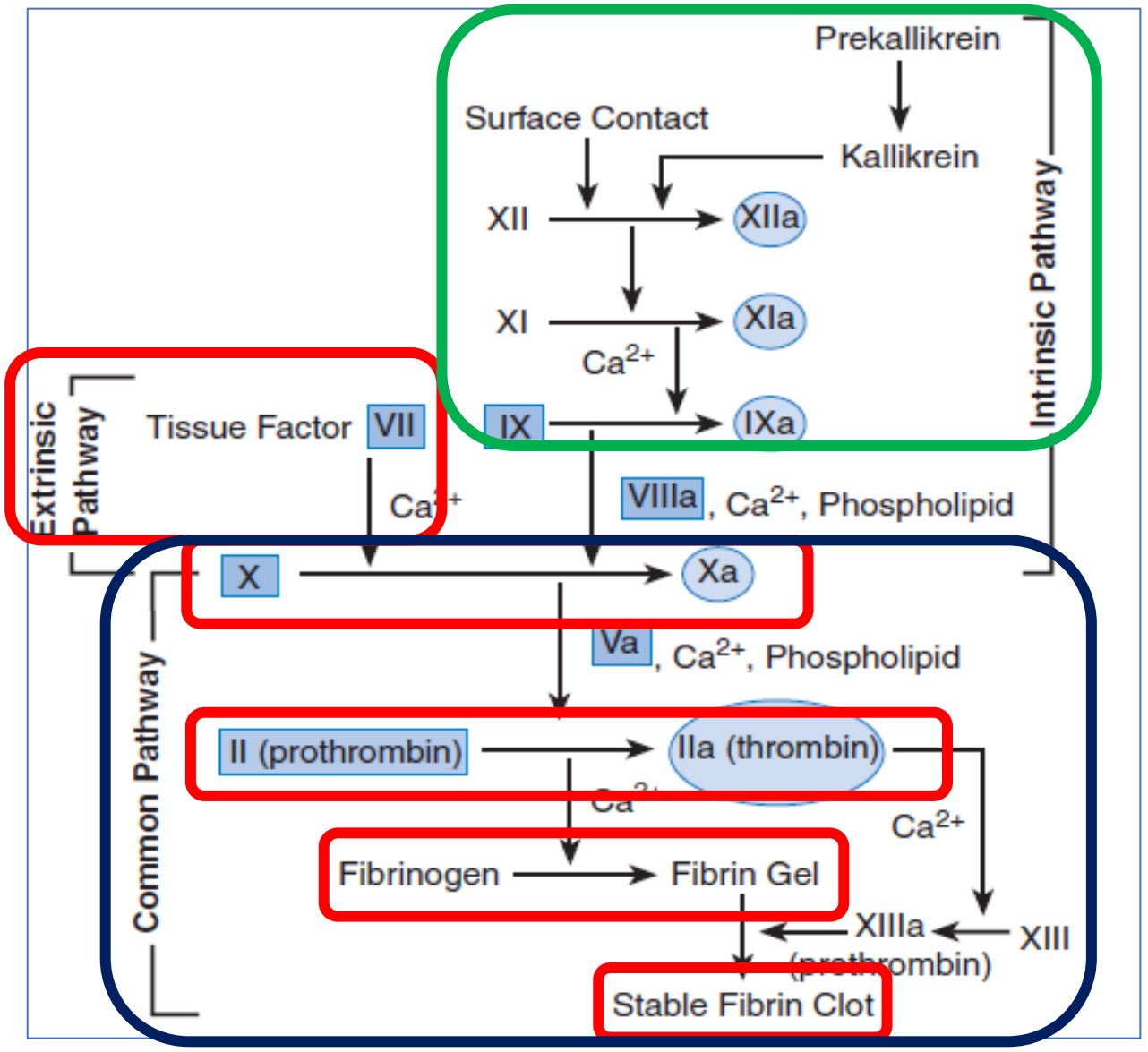
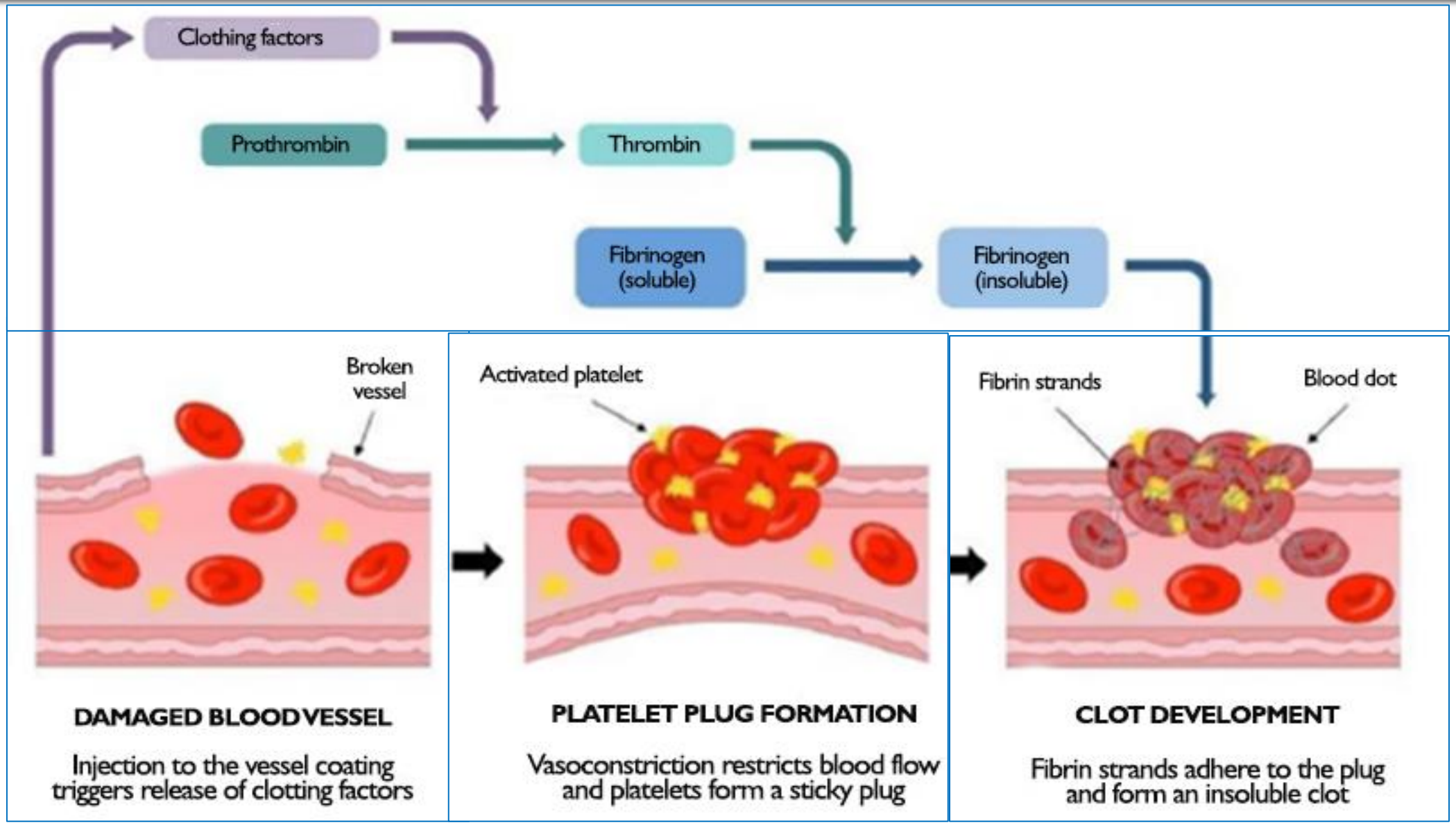
CLOTTING CASCADE

- **Endothelial damage** results in **activation** of the clotting cascade.



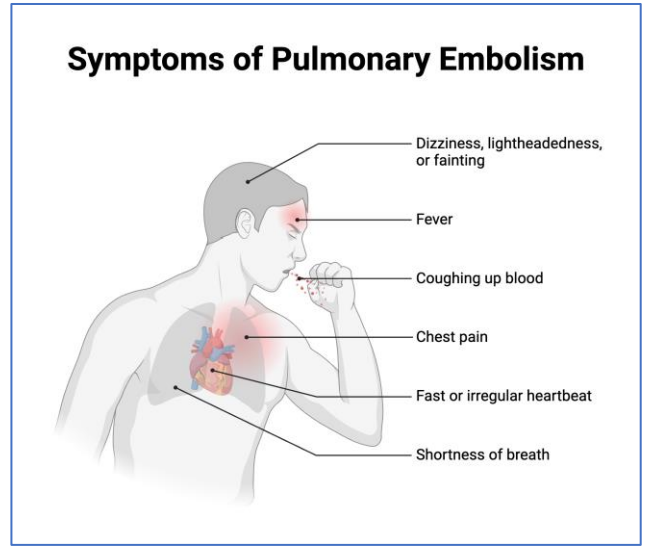
FIBRIN BLOOD CLOT FORMATION



FIBRIN BLOOD CLOT FORMATION

CLINICAL PRESENTATION

- **Some** patients with **DVT are asymptomatic**.
- **Symptoms** may include **unilateral leg swelling, pain, tenderness, erythema, and warmth**.
- **Symptoms of PE** may include **cough, chest pain or tightness, shortness of breath, palpitations, hemoptysis, dizziness, or lightheadedness.**
- **Signs of PE** include **tachypnea, tachycardia, diaphoresis, cyanosis, hypotension, shock, and cardiovascular collapse.**



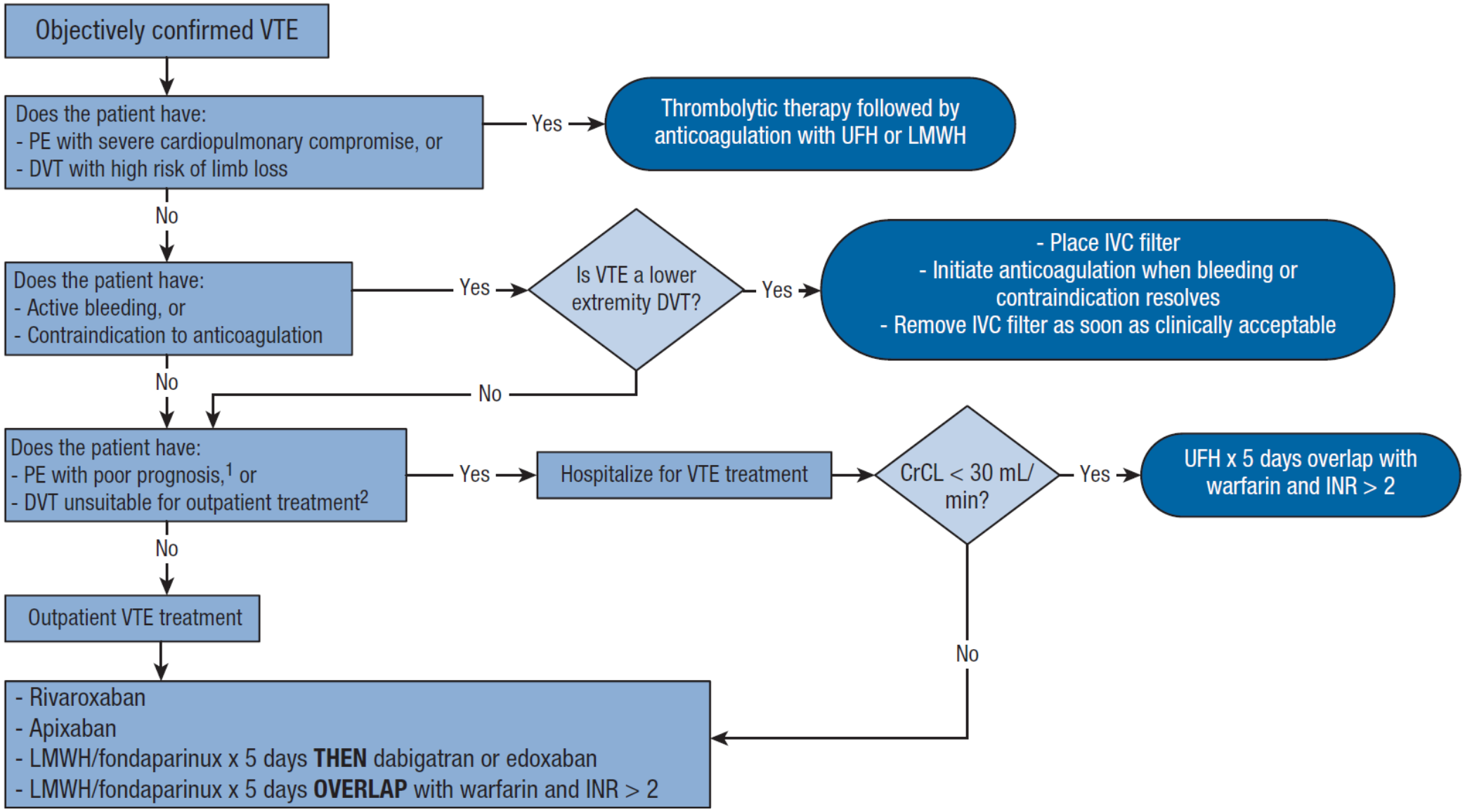
DIAGNOSIS

- Assessment should focus on **identifying risk factors**
- Compression ultrasound (**CUS**) and computed tomography pulmonary angiography (**CTPA**) are used most often for **initial evaluation of suspected VTE**.
- **Radiographic contrast studies** (venography, pulmonary angiography) are the most accurate and reliable diagnostic methods.
- Serum conc. of **d-dimer** is nearly always elevated; values <500 ng/mL (mcg/L) combined with clinical probability scores are useful in ruling out VTE.
- Clinical **assessment checklists** (eg, **Wells score**) can be used to determine whether a patient is likely or unlikely to have DVT or PE.

PREVENTION OF VTE

- **Hospitalized** and acutely ill medical patients at **high VTE risk** and low bleeding risk **should receive pharmacologic prophylaxis** with
  - ✓low-dose unfractionated heparin (LDUH),
  - ✓low-molecular-weight heparin (LMWH),
  - ✓fondaparinux, or betrixaban during hospitalization or until fully ambulatory.
- **Non-orthopedic surgery** patients at **high VTE risk but low bleeding risk** should receive **LDUH or LMWH** prophylaxis **plus** graduated **compression stockings**.
- Recommended VTE prophylaxis following **joint replacement surgery** may include aspirin, adjusted-dose warfarin, LDUH, LMWH, fondaparinux, dabigatran, apixaban, or rivaroxaban for at **least 10 days postsurgery**.

GENERAL APPROACH TO TREATMENT OF VTE



NONPHARMACOLOGIC THERAPY

- Encourage patients to **ambulate** as much as symptoms permit.
- **Ambulation in conjunction with graduated compression stockings** results in faster reduction in pain and swelling than strict bedrest with no increase in embolization rate.
- **Inferior vena cava filters** should **only** be used when **anticoagulants** are **contraindicated** due to active bleeding.
- Elimination of the obstructing thrombus via **thrombolysis or thrombectomy** may be warranted in **life- or limb-threatening DVT**.

PHARMACOLOGIC THERAPY

Pharmacologic therapy of VTE include:

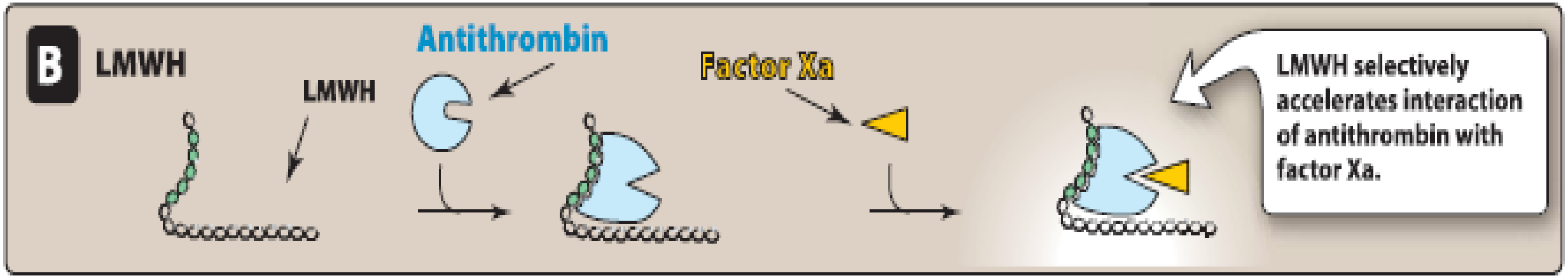
1. **Direct Oral Anticoagulants (DOACs)**
2. **Low-Molecular-Weight Heparin**
3. **Fondaparinux**
4. **Unfractionated Heparin**
5. **Warfarin**
6. **Thrombolytics**

Direct Oral Anticoagulants (DOACs)

- They include **Rivaroxaban, apixaban, edoxaban, and betrixaban.**
- They are **oral selective inhibitors** of **both free and clot-bound factor Xa** and do **not require antithrombin** to exert their anticoagulant effect.
- **Dabigatran** is an **oral selective, reversible, direct factor IIa inhibitor**.
- **Edoxaban and dabigatran** must be given only **after at least 5 days** of subcutaneous (SC) anticoagulation with **UFH, LMWH, or fondaparinux**.
- **Bleeding** is the most common adverse effect with DOAC therapy.
- Patients experiencing significant bleeding should **receive routine supportive care and discontinuation** of anticoagulant therapy.
- **Idarucizumab** (Praxbind) 5 g IV rapidly **reverses** the dabigatran anticoagulant.

Low-Molecular-Weight Heparin

- Like **Dalteparin, Enoxaparin, and Tinzaparin**.
- The **anti-Xa properties** of LMWH are **more significant** than their **anti-IIa properties**, so **aPTT** is **not prolonged**.
- **Monitoring** of therapy is **not** routinely required.
- LMWH has **better SC bioavailability** over UFH, resulting in a **predictable dose response** and a **longer pharmacodynamic effect**, making it a good choice when the goal is to treat **patients at home**.

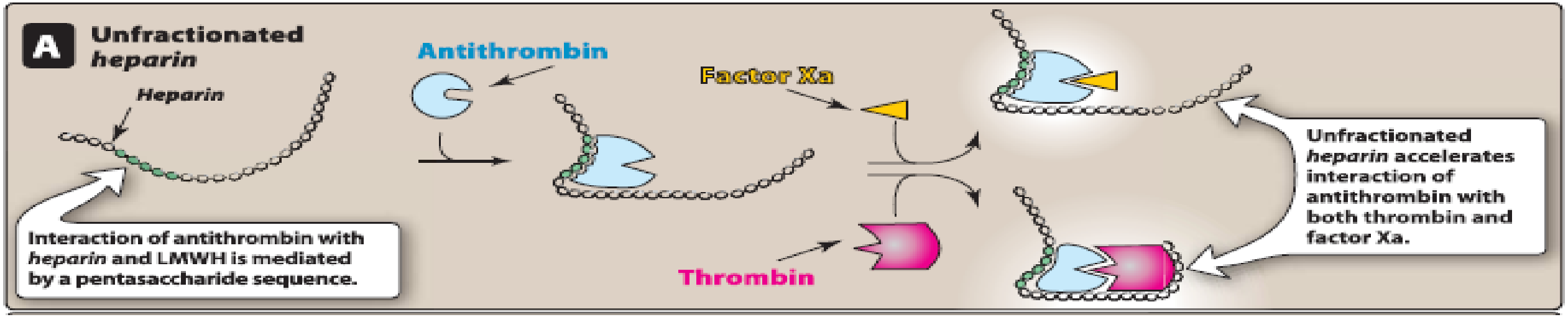


Fondaparinux

- **Fondaparinux** acts as a **selective factor Xa inhibitor**.
- It has a **long elimination half-life** allowing for **once-daily** SC dosing .
- Like LMWH, there is **no need for routine monitoring**.
- It is **eliminated** in the **urine** mainly as unchanged drug with an **elimination half-life of 17 to 21 hours**.
- It is **contraindicated** in patients with **severe renal impairment**.
- **Bleeding** is the major side effect of fondaparinux.

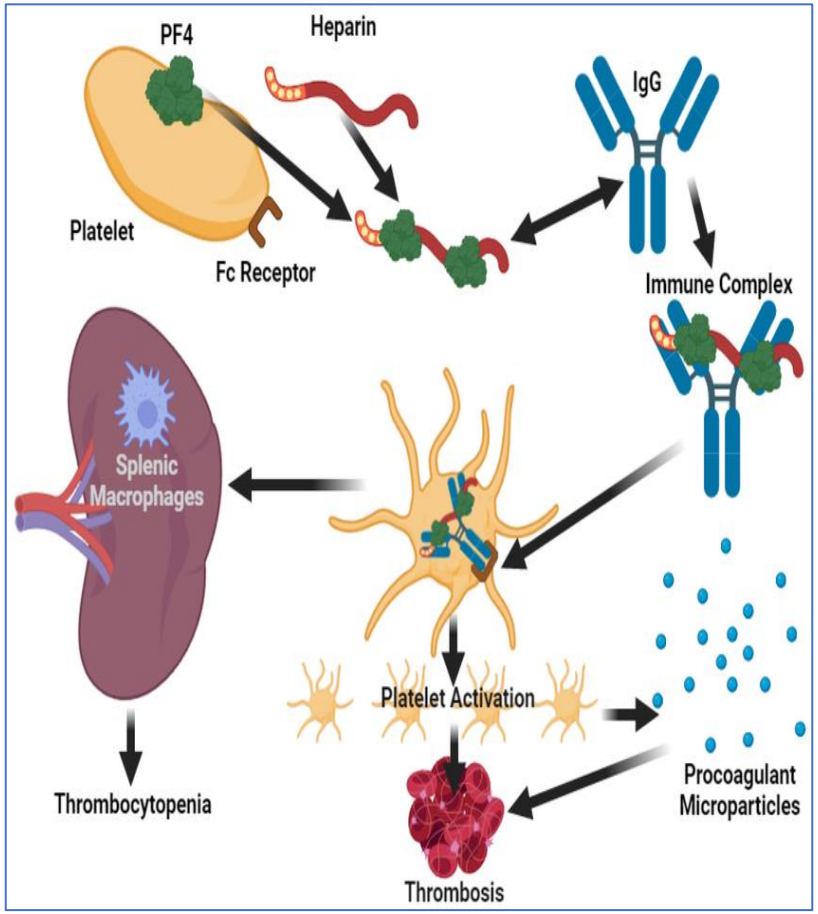
Unfractionated Heparin

- A **rapid acting** anticoagulant that attaches to and **irreversibly inactivates factor IIa** (thrombin) and **factor Xa**.
- In addition to **anticoagulant effects**, it also **inhibits platelet function** and **increases vascular permeability**.
- UFH can be **administered IV and SC**, although **bioavailability** is greatly **reduced with SC** administration.
- **IM** administration should be **avoided** due to **risk for hematoma formation**.



Unfractionated Heparin

- **Side effects** include **thrombocytopenia**, **bleeding** (typically in soft tissue, GI, and urinary tracts), and **osteoporosis** (with long-term use of doses >20,000 units/day).
- Reductions in **platelet counts of >50%** from **baseline** suggest possibility of **heparin induced thrombocytopenia (HIT)**.
- **HIT** occurs in **3%** of patients after **5 days of UFH** and in up to **6%** of patients after **14 days** of continuous UFH therapy.
- Heparin therapy should be **discontinued** in patients who develop **HIT**.
- **Treatment alternatives** include **direct thrombin inhibitors** like **lepirudin** and **argatroban.**
- **LMWH** use is **contraindicated** in patients with **HIT**.



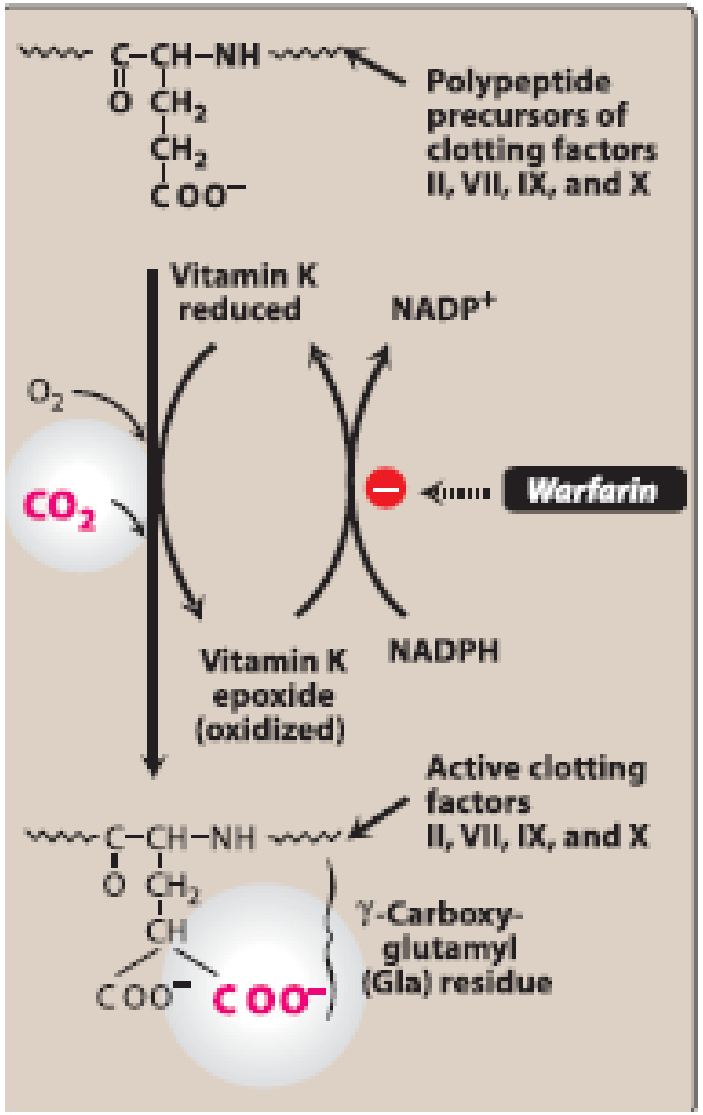
Pathophysiology of HIT

Warfarin

- Warfarin acts as **a vitamin K antagonist**.
- Concentrations of **clotting factors II, VII, IX, and X** are gradually **diminished** in accordance with their elimination half-lives.
- The **onset of effect** of warfarin is **delayed**, typically taking **5 to 7 days** to reach a steady state of anticoagulation.

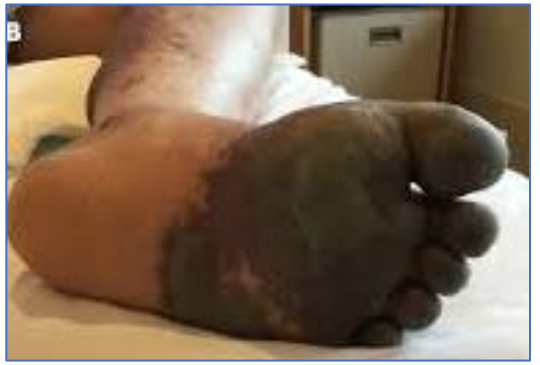
Clotting Factor	Half-Life (hours)
II	42–72
VII	4–6
IX	21–30
X	27–48

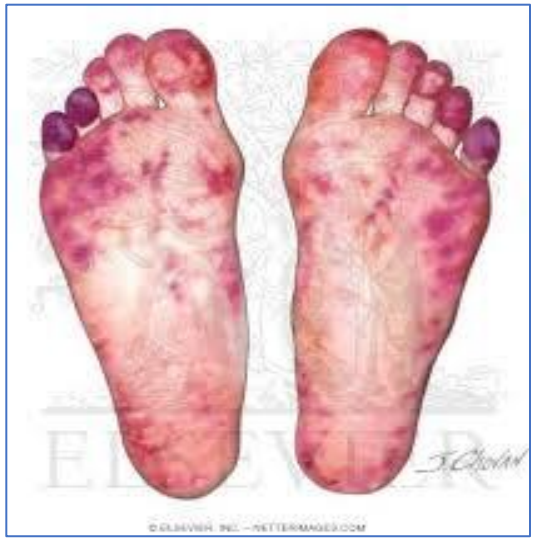
- **Heparin therapy** should be **continued** for **at least 5 days after initiating warfarin**, **because** of the time required for adequate elimination of factors II and X by warfarin.



Warfarin

- **Patients** who are **more sensitive** to warfarin are expected to **require lower doses**.
- **Successful** warfarin therapy depends on **active participation by the patient**.
- Therapy is **monitored** using **prothrombin time** or, more commonly, the **INR**.
- **Side effects** include **bleeding** (commonly in the nose, oral pharynx, soft tissue, and GI and urinary tracts), **skin necrosis** (rare, but serious side effect), and **purple toe syndrome** (rare).
- **Vitamin K** is used for **reversal** of an elevated INR caused by warfarin.





Thrombolytics

- Thrombolytic agents are **proteolytic enzymes** that enhance conversion of **plasminogen to plasmin**, which subsequently **degrades the fibrin matrix**.
- Patients with massive **PE and evidence of hemodynamic compromise** (hypotension or shock) should **receive thrombolytic therapy** unless contraindicated by bleeding risk.
- **Alteplase** (Activase) **100 mg by IV infusion over 2 hours** is the most commonly used thrombolytic therapy for **patients with PE**.
- **Before** giving thrombolytic therapy for PE, **IV UFH should be administered in full therapeutic doses**.
- **During** thrombolytic therapy, IV UFH may be either **continued** or **suspended**; the most common practice in the United States is to suspend UFH.
- Measure the **aPTT** after completion of thrombolytic therapy.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients for **resolution of symptoms, development of recurrent thrombosis, and adverse anticoagulant effects**.
- **Monitor hemoglobin, hematocrit, and blood pressure** carefully to detect bleeding from anticoagulant therapy.
- Perform **coagulation tests (aPTT, PT, INR)** prior to initiating therapy to establish the patient's baseline values and guide later anticoagulation.
- **Ask outpatients taking warfarin** about **medication adherence** to prior dosing instructions, other medication use, changes in health status, and symptoms related to bleeding and thromboembolic complications.

THANK YOU FOR YOUR ATTENTION