Thrombo-Embolic Disease

Definition

- **Thrombosis** is the process involved in the formation of a **fibrin blood clot**. Both platelets and a series of coagulant proteins (clotting factors) contribute to clot formation.
- An **embolus** is a small part of a clot that breaks off and travels to another part of the vascular system. Damage is caused when the embolus becomes trapped in a small vessel, causing occlusion and leading to **ischemia** or **infarction** of the surrounding tissue.

Types of thromboembolic diseases

- **Deep venous thrombosis (DVT)** and its primary complication.
  - **Pulmonary embolism (PE).**
  - **Stroke**
  - **Cardiogenic Thromboembolism** --other systemic manifestations of embolization of clots that form within the heart.

Etiology of Thromboembolism

Three primary factors influence the formation of pathological clots:

- **First**, **abnormalities of blood flow** that ***venous stasis*** can result in **DVT**, which can **progress to PE**. ***Intracardiac stasis*** of blood can also result in **stroke or other systemic manifestations**.

- **Second**, **<u>abnormalities of blood vessel walls</u>**, such as **injury** or **trauma** to the vasculature, the presence of artificial **heart valves** and central **venous catheters**.

- **Third**, **<u>hypercoagulability</u>** resulting from alterations in the availability or the integrity of **blood-clotting components** or **naturally occurring anticoagulants** also represents a significant risk factor for thromboembolic disease.

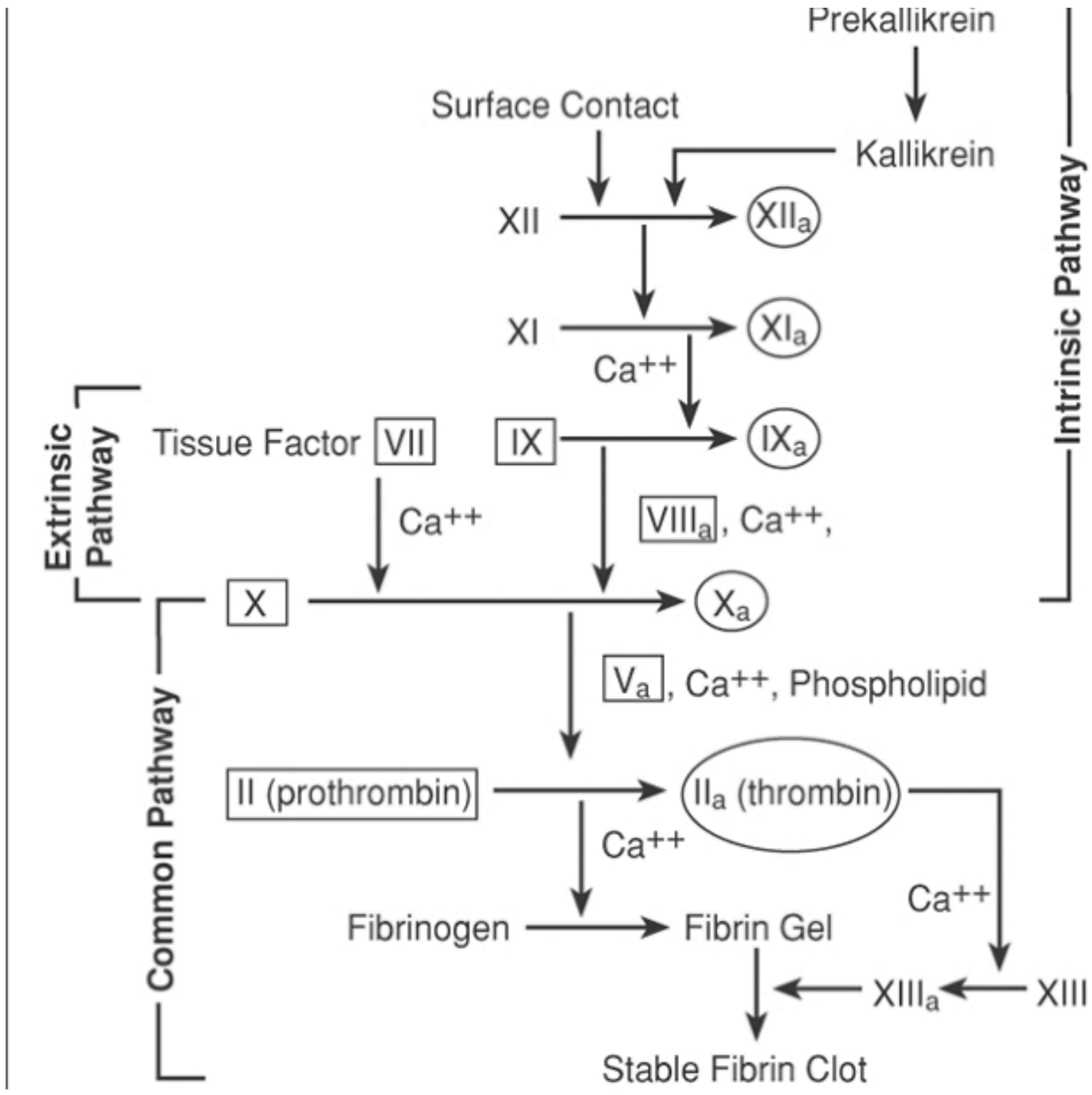
Clot Formation

1. <u>Platelet Adhesion, Activation, and Aggregation</u>

- **Endothelial damage** leads to exposure of blood to sub-endothelial collagen and phospholipids, resulting in **platelet adhesion** to the surface via the **glycoprotein I** (GPI) receptor on the platelet surface.
- Adhered platelets become activated and release numerous compounds, including **adenosine diphosphate** and **thromboxane A_2**, which stimulate **platelet aggregation**.
- **Fibrinogen serves as the binding ligand for platelet aggregation, via the GPIIb/IIIa receptor on the platelet surface.**

2. <u>Clotting Cascade</u>

- Figure below- Simplified clotting cascade. Components in ovals are influenced by **heparin**; components in boxes are influenced by **warfarin.**



Pathological Thrombi

Classified according to location and composition:

Arterial thrombi:

- Are composed primarily of **platelets**, **fibrin** and occasional **leukocytes**.
- Arterial thrombi generally occur in areas of **rapid blood flow** (i.e., arteries)
- Initiated by **spontaneous or mechanical rupture** of atherosclerotic plaques.

Venous thrombi

- Composed almost entirely of **fibrin** and **erythrocytes**, have a **small platelet head**
- Generally formed in response to either venous **stasis** or vascular **injury** after surgery or trauma.
- **The areas of stasis prevent dilution of activated coagulation factors by normal blood flow.**

Antithrombotic Agents:

The selection of an antithrombotic agent may be influenced by the type of thrombus to be treated.

- ***Anticoagulants***

Heparin, (unfractionated heparin [UFH])

Low-molecular-weight heparins, (LMWHs)

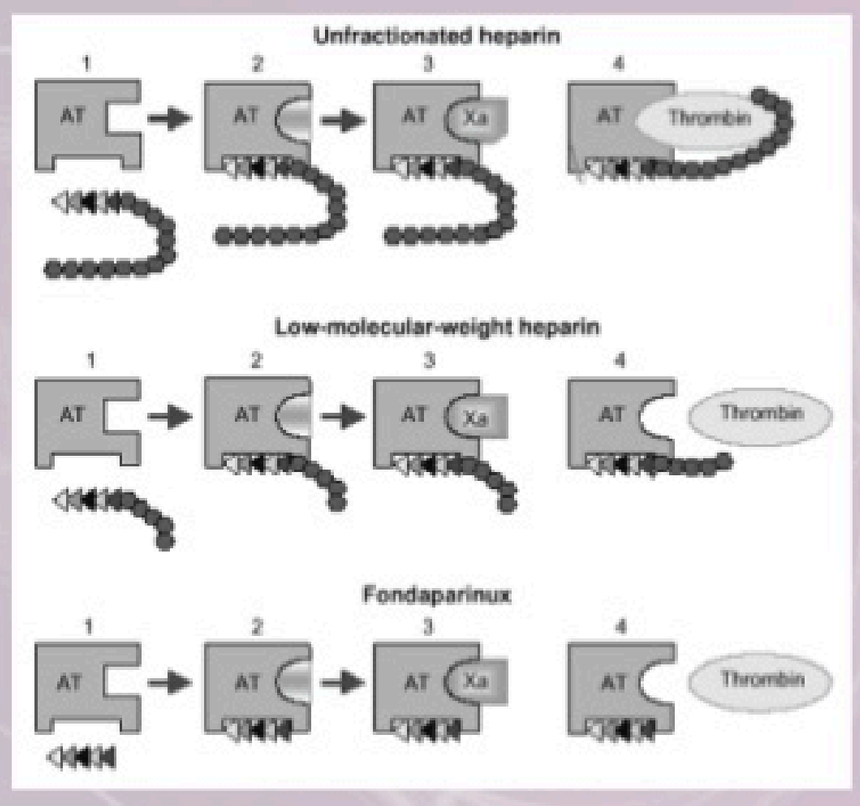
Factor X_a inhibitors (Fondaparinux)

Direct Thrombin Inhibitors (Argatroban, lepirudin and bivalirudin))

Warfarin is used in the treatment and prevention of **both arterial and venous** thrombi.

Antithrombin (AT) Enhancers: Heparin, LMWH, Fondaparinux

- Antithrombin (AT) inhibits factor Xa and thrombin (natural anticoagulant)
- UFH, LMWH, and Fondaparinux bind to AT, causing a conformational change.
- Activated complex increases Factor Xa inactivation by several fold over endogenous AT
- Longer chain polysaccharides:AT complexes irreversibly binds to an inhibits the active site of thrombin
  - –UFH>>>LMH
  - –Fondaparinux does not bind thrombin



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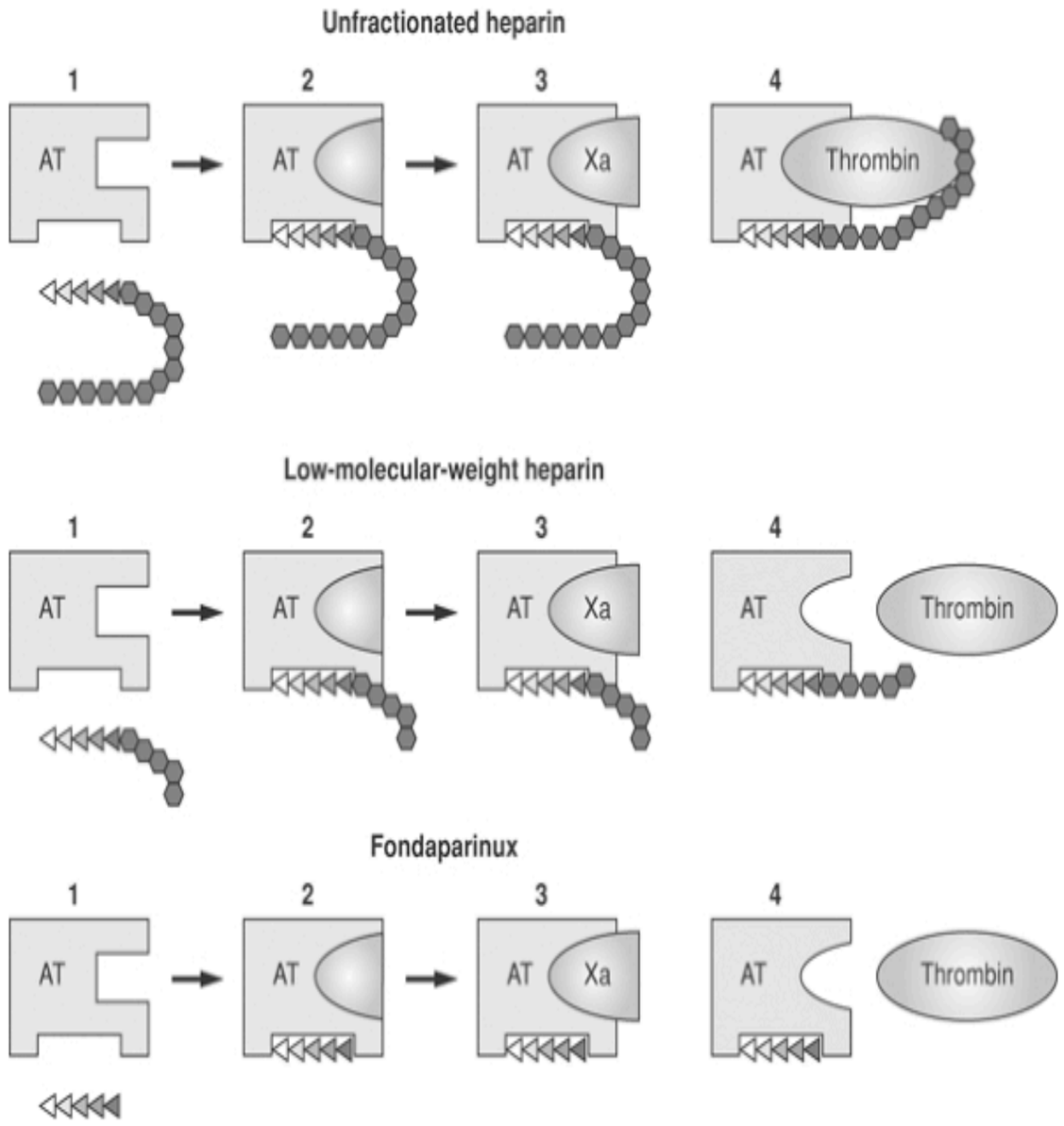

Figure 15-3 Mechanism of action of heparin, low-molecular-weight heparins, and fondaparinux (see text for details). Reprinted from reference 5, with permission.

- ***Antiplatelet Drugs*** **that alter platelet function**:

Aspirin: alone and in combination with anticoagulants, are used in the prevention of **arterial thrombi**.

Clopidogrel: is a pro-drug that is metabolized in part to an active thiol derivative. The latter inhibits platelet aggregation.

Dipyridamole: is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves.

Glycoprotein IIb/IIIa inhibitors: prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets.

- **Abciximab**: is a monoclonal antibody which binds to coronary glycoprotein IIb/IIIa receptors and to other related sites.

- *Eptifibatide and tirofiban*: they inhibit glycoprotein IIb/IIIa receptors; they are licensed for use with heparin and aspirin to prevent early myocardial infarction in patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI).

- ***Fibrinolytic agents*** are used for rapid dissolution of thromboemboli, during **myocardial infarction** (MI).

Streptokinase: Streptokinase was the first agent available in this class.

Alteplase: Tissue plasminogen activator (rt-PA) was developed using recombinant DNA technology.

Reteplase and tenectaplase: are also fibrin-specific agents and so heparin is required to prevent rebound thrombosis.

Urokinase: like alteplase and streptokinase, can be used for the treatment of deep vein thrombosis and PE.

Endogenous Antithrombotic:

Inhibitors of Clotting Mechanisms	
Target	***Inhibitor***
Inhibits factors IIa, IXa, and Xa	Antithrombin
Cofactor for activation of protein C	Protein S
Inactivates factors Va and VIIIa	Protein C
Inhibits activity of factor VIIa	Tissue factor pathway inhibitor
Converted to plasmin via tissue plasminogen activator	Plasminogen
Lyses fibrin into fibrin degradation products	Plasmin

Tests Used to Monitor Antithrombotic Therapy

1. ProthrombinTime PT/International Normalized Ratio INR

To evaluate the extrinsic pathway of coagulation

The PT is prolonged by:

- **Deficiencies of clotting factors** II, V, VII, and X,
- **Low levels of fibrinogen** and **very high levels of heparin**.
- Alterations in the **extrinsic and common pathways**
- **Monitor warfarin** therapy.

2. ***Activated Partial Thromboplastin Time APTT***

- The aPTT reflects alterations in the **intrinsic pathway**
- **Monitor heparin** therapy.

3. **Anti-X_a Activity**

- Because these agents are eliminated renally, patients with **severe renal failure** may **accumulate LMWHs**, leading to an increased risk of **hemorrhagic complications**

Deep Venous Thrombosis (DVT)

Clinical Presentation

- Physical finding of DVT is **unilateral leg swelling** that often is accompanied by **warmth** and **local tenderness** or **pain**.
- A **tender, palpated, cordlike entity** caused by venous obstruction
- **Discoloration of the affected limb**, including **pallor from arterial spasm**, **cyanosis from venous obstruction**, or a **reddish color from perivascular inflammation**, may also occur.
- (>50%) can present with **asymptomatic disease**,
- Patients can have **long-term complications** such as **recurrent DVT** or **post-thrombotic syndrome** (mainly in elderly with recurrent DVT).
- Because **symptoms of DVT are non-specific, the diagnosis must be confirmed by objective testing.**

Risk Factors

- Those related to blood flow

- Those related to Abnormalities of clotting component
- Those related to Abnormalities of surface contact with blood

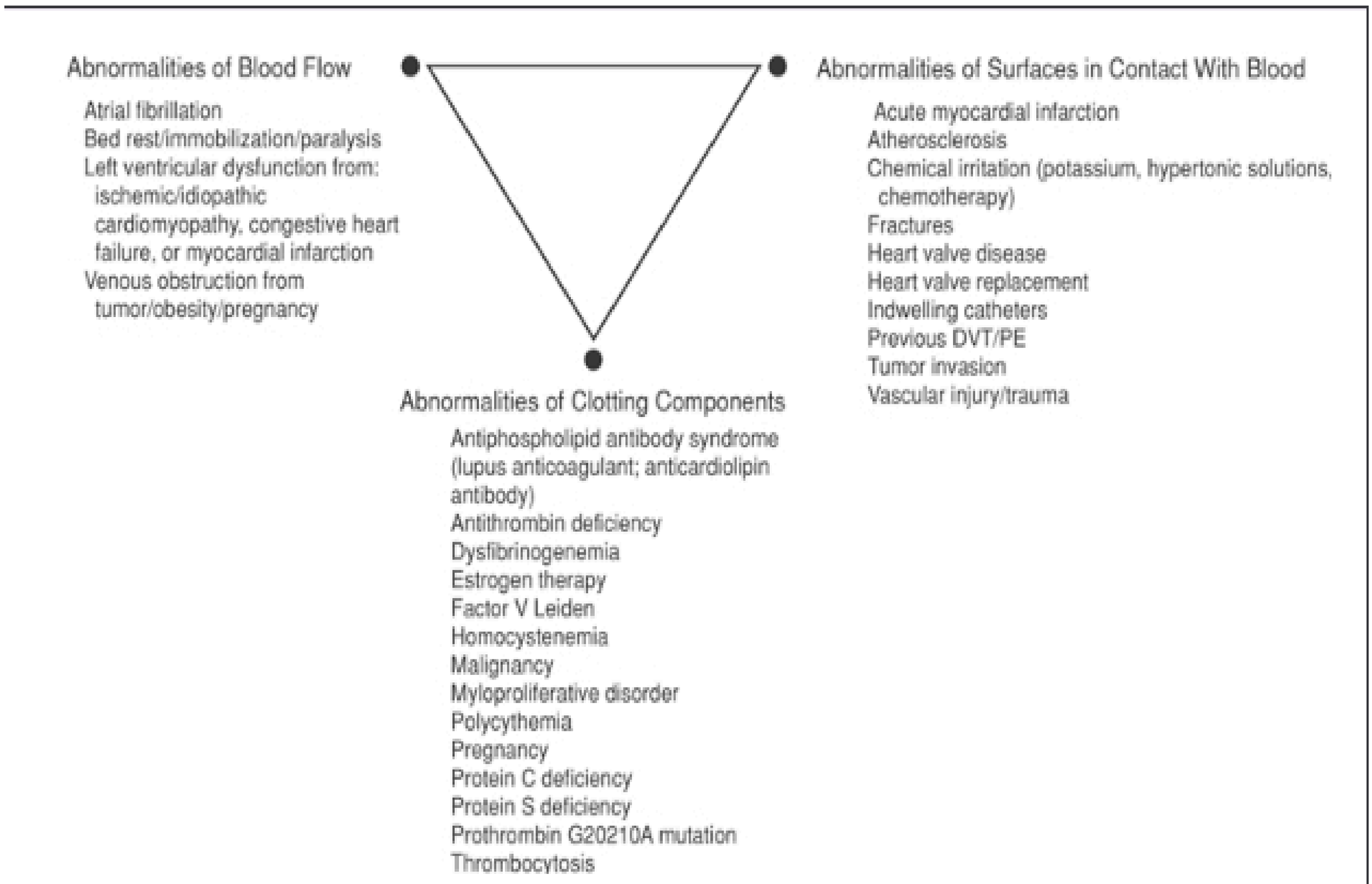

Figure 15-1 Risk factors for thromboembolism. DVT, deep venous thrombosis; PE, pulmonary embolism.

Diagnosis

1. The most common non-invasive test is **Doppler ultrasonography** to visualize veins and thrombi while investigating flow patterns.
2. Other non-invasive testing options include **^{125}I-fibrinogen leg scanning** (injection of radiolabeled fibrinogen followed by scanning to detect areas of accumulation corresponding to thrombosis),

3. **D-dimer** (an evaluation of the presence of fibrin degradation products, indicative of clot formation).

Treatment

Optimal Therapeutic Range and Duration of Anticoagulation

Indication	Target INR (Range)	Duration	Comment
<u>Thromboembolism (DVT, PE)</u>			
Treatment/prevention of recurrence (including calf vein and upper extremity DVT)			
•Transient risk factors	2.5 (2.0–3.0)	3 months	
•Idiopathic/first episode	2.5 (2.0–3.0)	6–12 months	Consider chronic therapy
•Recurrent VTE	2.5 (2.0–3.0)	Chronic	Preceded by LMWH × 3–6 months
•With malignancy	2.5 (2.0–3.0)	Chronic	
•Hypercoagulable state	2.5 (2.0–3.0)	6–12 months	Consider chronic therapy
•Two or more thrombophilic conditions	2.5 (2.0–3.0)	12 months	Consider chronic therapy

			•Antiphospholipid antibody syndrome
Consider chronic therapy	12 months	2.5 (2.0–3.0)	•With recurrent VTE or other risk factors
Consider chronic therapy	12 months	2.5 (2.0–3.0)	Chronic thromboembolic pulmonary hypertension
	Chronic	2.5 (2.0–3.0)	
	3–6 months	2.5 (2.0–3.0)	Cerebral venous sinus thrombosis

Initiation of Therapy:

- **Optimal anticoagulant therapy** is indicated to minimize **thrombus extension** and its **vascular complications, prevent PE.**
- **Treatment options** include **IV UFH therapy** initiated with a **loading dose** followed by a **continuous infusion**,

adjusted-dose SC for UFH, or LMWH or fondaparinux administered by SC injection.

Heparin

- **Loading Dose:** A loading dose of heparin is required for ***several reasons***:
    1. **Therapeutic serum level will be achieved more quickly**; to help prevent progression of clot will occur rapidly.
    2. Second, **a relative resistance to anticoagulation** exists during the active clotting process. Therefore, a larger initial dose generally is necessary to achieve a therapeutic effect.

- ***Initial heparin loading doses of 70 to 100 U/kg followed by an infusion rate of 15 to 25 U/kg/hour are commonly recommended.***
- To ensure accuracy, the clinician should ***obtain aPTT values no sooner than 6 hours after a bolus dose or any change in the infusion rate.***
- **Adherence of a thrombus to the vessel wall and subsequent endothelialization usually takes 7 to 10 days**. Anticoagulation therapy must generally **continue for 3 to 6 months** to prevent recurrent thrombosis.
- ***Warfarin*** is preferred for this **long-term anticoagulation because it can be administered orally, and it is generally initiated on the same day as heparin.**
- **Shortening the duration** of heparin therapy is associated with **an increased risk** of recurrent thrombosis.

Adverse Effects

- **Thrombocytopenia**:

1. Heparin-associated thrombocytopenia (HAT)
2. Heparin-induced thrombocytopenia (HIT),

- **Hemorrhage**
- **Osteoporosis**
- **Hyperkalemia**
- **Hypersensitivity Reactions**

Low-Molecular-Weight Heparin (LMWH)

- Based on these advantages, outpatient use of LMWH has become the most common **approach to treatment of uncomplicated DVT.**

Fondaparinux

- Considered as an alternative treatment option to the LMWHs
- Fondaparinux has **the benefit that HIT has not been associated with its use**.

Prevention:

Non-pharmacologic Measures

- **Mechanical interventions** e.g: **elastic compression stockings**, as well as **leg elevation**, leg **exercises**, and **early postoperative ambulation**.
- **Intermittent pneumatic compression (IPC)** of the leg muscles, using **inflatable cuffs**

Pharmacologic Measures

- **Fixed, low-dose unfractionated heparin (LDUFH)**, administered as 5,000 U SC Q 8 to 12 hr depending on the indication,
- **Fixed-dose SC LMWH and fondaparinux** are alternative approaches for preventing DVT

Pulmonary Embolism:

Clinical Presentation

The **non-specificity** of symptoms:

- **Subjective symptoms** are **dyspnea**, **pleuritic chest pain**, **apprehension** (anxiety or a feeling of impending doom), and **cough**, **hemoptysis** occurs occasionally.
- The **objective signs** are **tachypnea at a rate of ≥20 breaths**/minute, **tachycardia of ≥100** beats/minute, **second heart sound (P_2).**
- **DVT precedes PE in 80% or more of patients**.

- A combination of these signs and symptoms provides further evidence for **acute PE**.

Diagnosis

- **Chest radiograph, ECG**, and **arterial blood gases.**
- **Pulmonary angiography** has been considered the gold standard for diagnosis of PE.
- **Spiral computed tomography (CT**) scans are useful and the most frequently used.
- **V/Q scans** (ventilation/perfusion lung scan) diagnostic procedures to document the presence of PE.

Treatment

PE should not be treated on an outpatient basis.

- **Treatment options** for PE include **IV UFH therapy initiated with a loading dose** followed by a **continuous infusion**.
- UFH therapy could be started with a loading dose of 7,200 U (80 U/kg × 90 kg), followed by continuous infusion of 1,600 U/hour (18 U/kg/hour × 90 kg).
- **Monitoring of the aPTT** would be used to adjust dosing to maintain treatment within the therapeutic range.
- **The alternative** a **SC LMWH** or SC **fondaparinux**.
- **Thrombolytic therapy** should be reserved for patients with **acute massive embolism**, who are **hemodynamically unstable** and at **low risk for bleeding**.

Warfarin initiates therapy in **ambulatory patients**;

- **Heparin or LMWH/fondaparinux therapy should be continued for at least 5 days** in the setting of PE**, and until warfarin therapy is therapeutic and stable**.
- **Warfarin** should be started on the **first day** of hospitalization and continued for a minimum of **3 to 6 months or longer**, if indicated.

Initiation of Therapy

- **Two methods** for initiation of warfarin therapy have been developed.

1. **The average daily dosing method**, patients are typically **started at 4 to 5 mg daily**, with dosing adjustments as necessary until the therapeutic goal is reached.
2. Another **popular dosing algorithm** used a 10-mg initiation dose for the first 2 days, with the **INR on day 3** used to guide dosing on days 3 and 4, and the INR on day 5 used to guide the **next three doses.**

Duration of Therapy

1. Patients with (**idiopathic**) DVT or PE, should be treated for **at least 6 to 12 months**, as their likelihood of having a recurrent event as 30% over 5 years.
2. Patients with DVT or PE associated with **transient or reversible risk** factors are usually **treated for 3 to 6 months**, as the risk of recurrence is lower (approximately 10% over 5 years).
3. Patients with **recurrent** DVT/PE and **persistent risk** factors, **warfarin treatment should be continued indefinitely**.

Adverse Effects

- **Hemorrhage, Menstrual blood flow**
- **Older patients** are more sensitive to the effects of warfarin and, therefore, require **lower dosages** than younger patients.
- **Skin Necrosis**
- **Purple Toe Syndrome (cholesterol crystal embolism)**

Factors Influencing Dosing

1. **Dietary Vitamin K**
2. **Alcohol Ingestion**
3. **Underlying Disease States:**

- **Diarrhea-associated** alterations in intestinal flora can reduce vitamin K absorption.
- **Fever** enhances the catabolism of clotting factors
- **Heart failure, hepatic congestion,** and **liver disease** can also cause significant reduction in warfarin metabolism.
- **End-stage renal** disease is associated with decreased CYP2C9 activity.
- **Hypothyroidism** decreases the catabolism of certain clotting factors, Conversely,
- **hyperthyroidism** increases the catabolism of clotting factors, leading to an increased sensitivity to warfarin..

4. **Genetic Factors**
5. **Other Factors** Acute physical or psychological stress, Smoking.

Prevention of Cardiogenic Thromboembolism

1. Atrial Fibrillation

Anticoagulation before cardioversion

In atrial fibrillation, **compromised atrial activity** and **atrial enlargement** causes **stasis of blood** within the atria and the left atrial appendage, often resulting in atrial **thrombus formation**.

Atrial thrombus formation increases the risk of **systemic embolization**;

1. arterial embolization of the extremities
2. or embolization of the splenic, renal.
3. or abdominal arteries.
4. the cerebral arterial system, resulting in transient ischemic attack or stroke.

Anticoagulation with warfarin is indicated along with scheduled monitoring.

Anticoagulation after cardioversion

- Despite **normalization of atrial electrical** activity, **restoration of effective atrial** mechanical activity after cardioversion can be **delayed for up to 3 weeks**.
- Anticoagulation with warfarin should be continued after cardioversion for a minimum of 4 weeks.

Anticoagulation for Paroxysmal, Permanent, or Persistent Atrial Fibrillation

Anticoagulation in Valvular Atrial Fibrillation

- Atrial fibrillation secondary to **valvular heart** disease has historically been recognized as a significant risk factor for **stroke.**
- Patients **require long-term**, **regular-intensity** anticoagulation to a target INR of 2.5 (range, 2.0–3.0) to prevent thromboembolism and stroke.

Anticoagulation in Non-valvular Atrial Fibrillation

- Non-valvular heart disease is also a common cause of atrial fibrillation and, like valvular heart disease, represents a significant risk for **stroke** in patients with atrial fibrillation.

2. Cardiac Valve Replacement

Mechanical Prosthetic Valves

- Valvular thrombosis can impair the integrity of **valve function** and can lead to **embolization** with systemic manifestations, including stroke.
- The **incidence of thromboembolic** complications depends on the **type** of artificial valve as well as **position** of the replacement (dual valve replacement > mitral > aortic).
- **Long-term anticoagulation is required** in patients with mechanical valve replacement.
- **Chronic warfarin therapy** with a target INR of 3.0 (range, 2.5–3.5) is recommended.
- The **concurrent use of low-dose aspirin** (81 mg daily) is recommended for patients with additional risk factors for systemic embolization.

Bioprosthetic Valves

- **Prosthetic heart valves** extracted from **mammalian** sources are significantly **less** thrombogenic than mechanical prosthetic valves.
- The period of greatest thromboembolic risk appears to be during the first 3 months after implantation.

- **Short-term, regular-intensity**, preventive anticoagulation to an INR of 2.5 (range, 2.0–3.0) is recommended.
- After this period, **long-term aspirin therapy** (minimum dose, 162 mg/day) is indicated.
- However, oral anticoagulation should be continued long term in patients with concurrent atrial fibrillation, a history of systemic embolism, or evidence of atrial thrombus at surgery.