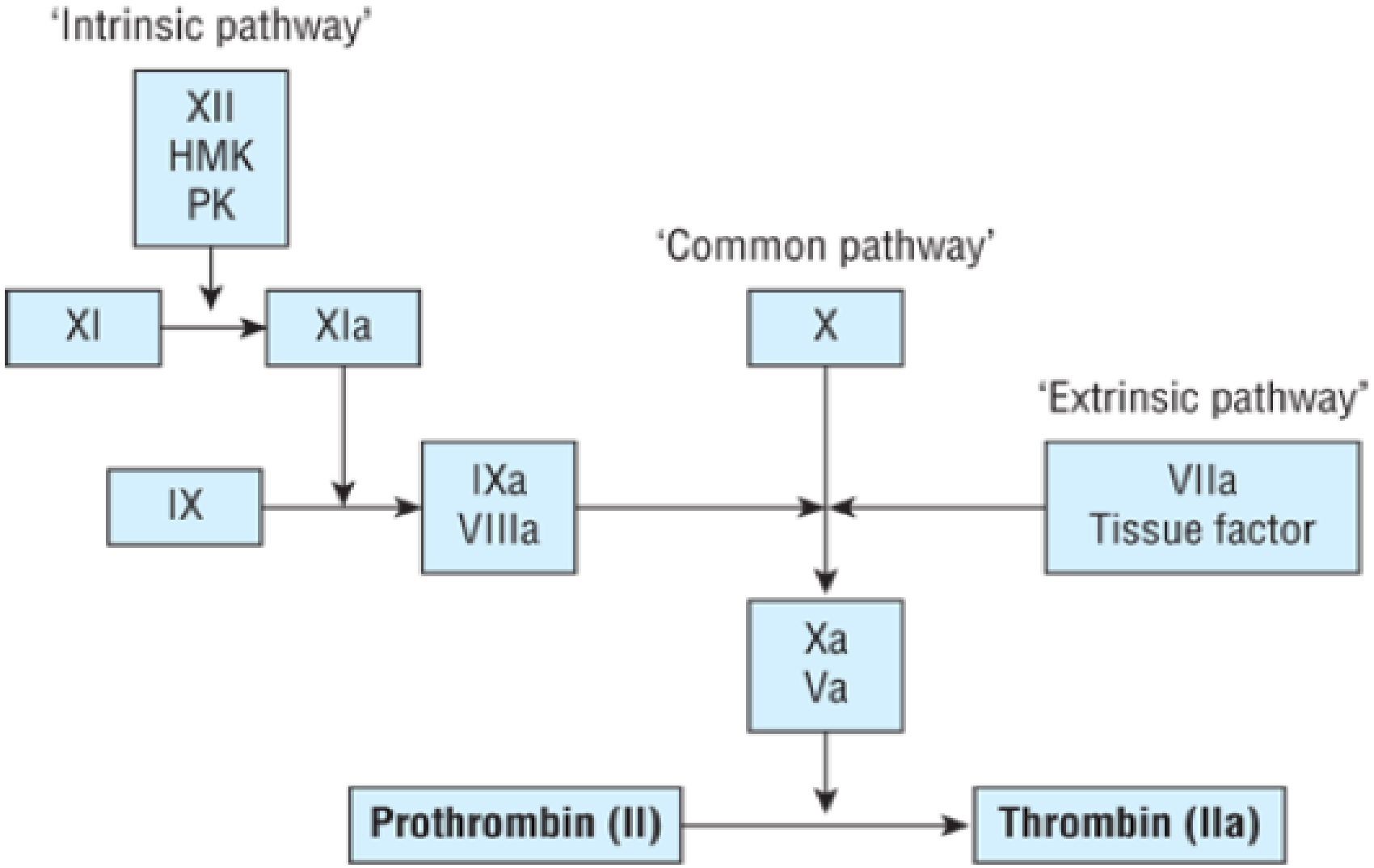
Therapy of Venous Thromboembolism

Therapy of Venous Thromboembolism

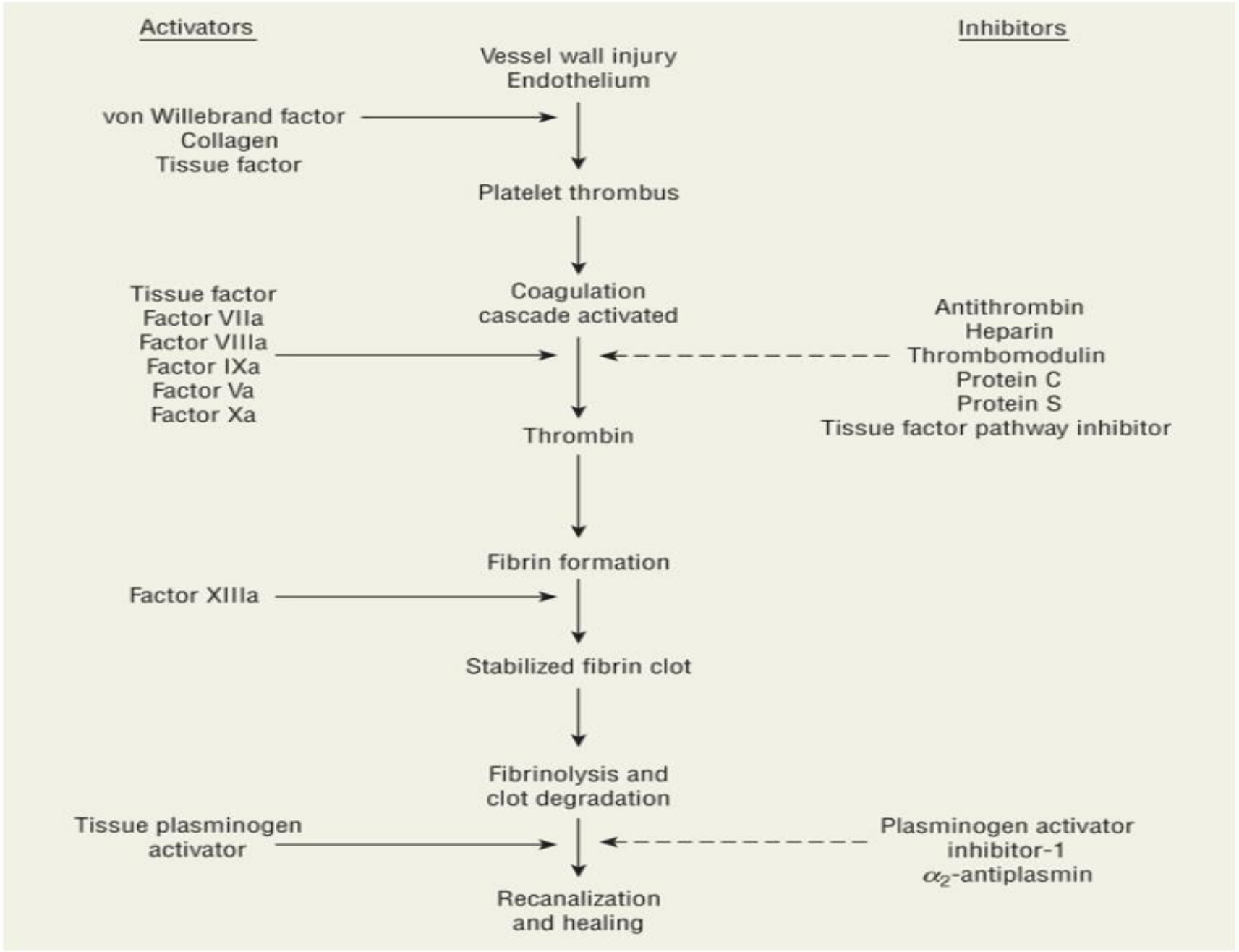
- **Venous thromboembolism (VTE) is a significant health problem and a potentially fatal disorder.**
- **VTE results from clot formation within the venous circulation and is manifested as deep vein thrombosis (DVT) and/or pulmonary embolism (PE).**

Classic depiction of the coagulation cascade.



HMK = high molecular weight kininogen; PK = prekallikrein

Overview of hemostasis.



Venous Thromboembolism Prophylaxis

Pharmacologic Prophylaxis:

- **Pharmacologic options for preventing VTE significantly reduce the risk of VTE following hip and knee replacement, hip fracture repair, general surgery, myocardial infarction, ischemic stroke, and in selected hospitalized medical patients.**

Venous Thromboembolism Prophylaxis

Medical Patients:

- **Hospitalized and acutely ill medical patients at high VTE risk and low bleeding risk should receive pharmacologic prophylaxis with low dose UFH, LMWH, or fondaparinux during hospitalization or until fully ambulatory.**
- **Routine pharmacologic prophylaxis is NOT indicated in low-VTE-risk medical patients.**

Venous Thromboembolism Prophylaxis

Surgical Patients:

Preventing VTE following non-orthopedic surgery:

- **Patients at high VTE risk but low bleeding risk should receive low dose UFH or LMWH.**

Preventing VTE following high risk orthopedic surgery such as joint replacement surgery:

- **Aspirin, adjusted-dose warfarin, UFH, LMWH, fondaparinux, dabigatran, apixaban, or rivaroxaban for at least 10 days postsurgery.**

Therapy of Venous Thromboembolism

Treatment of Venous Thromboembolism:

- **Anticoagulation therapies is the mainstay of VTE (DVT & PE) treatment.**
- **Establish an accurate diagnosis to avoid bleeding.**
- **Then, anticoagulation therapy with a rapid-acting anticoagulant should be instituted as soon as possible.**

Therapy of Venous Thromboembolism

- **Traditionally, therapy is started with warfarin overlapped with LMWH for 5 days.**
- **Early initiation of warfarin (same day as parenteral therapy); or delayed initiation but with continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is ≥2 for at least 24 hours.**

Therapy of Venous Thromboembolism

- **The appropriate initial duration of therapy to effectively treat an acute first episode of VTE for all patients is 3 months.**
- **Circumstances surrounding the initial thromboembolic event, the presence of ongoing thromboembolic risk factors, bleeding risk, and patient preference determine extending anticoagulation therapy beyond 3 months.**

Clinically important bleeding risk factors

1. Age more than 75 years
2. Previous noncardioembolic stroke
3. History of gastrointestinal bleeding
4. Renal or hepatic impairment
5. Anemia
6. Thrombocytopenia
7. Concurrent antiplatelet use
8. Noncompliance
9. Poor anticoagulant control (for patients on warfarin)
10. Serious acute or chronic illness
11. The presence of structural lesions (tumor, recent surgery) that could bleed.

Therapy of Venous Thromboembolism

Unfractionated Heparin:

- **It may be administered by SC injection, or by continuous intravenous infusion.**
- **Response to UFH is highly variable, therefore, dose should be adjusted based on activated partial thromboplastin time (aPTT).**
- **Either weight-based, or fixed UFH dosing (5,000 unit bolus followed by 1,000 units/h continuous infusion) produces similar clinical outcomes.**

Therapy of Venous Thromboembolism

- **Intravenous UFH requires hospitalization with frequent aPTT monitoring and dose adjustment.**
- **Traditional intravenous UFH in the acute treatment of VTE may be replaced by LMWH or fondaparinux.**
- **As elimination clearance of LMWH and fondaparinux is dependent on renal function, UFH will continue to have a role for acute VTE treatment in patients with CrCL < 30 mL/min.**

Therapy of Venous Thromboembolism

Low-Molecular-Weight Heparin:

- **Replaced UFH for initial VTE treatment due to improved pharmacokinetic and pharmacodynamic profiles and ease of use.**
- **LMWH given subcutaneously in fixed, weight-based doses is at least as effective as UFH given intravenously for the treatment of VTE.**

Therapy of Venous Thromboembolism

- LMWHs have reduced need for laboratory monitoring.
- Monitoring is indicated in obesity, pregnancy, & children by anti-Xa activity (goal anti–factor Xa levels 0.5 - 1.0 unit/mL, 4 - 6 hours following subcutaneous injection).
- Can be used on an outpatient basis for stable low-risk patients.

Therapy of Venous Thromboembolism

- **Rapidly reversible UFH is preferred if thrombolytic therapy or embolectomy is anticipated.**
- **In patients without cancer, acute treatment with LMWH is generally transitioned to long-term warfarin therapy after about 5 - 10 days.**

Therapy of Venous Thromboembolism

Fondaparinux:

- **It is safe and effective alternative to LMWH for acute VTE treatment.**
- **It is dosed once daily via weight-based SC injection.**
- **Fondaparinux is contraindicated if CrCL < 30 mL/min.**

Therapy of Venous Thromboembolism

Warfarin:

- **Warfarin monotherapy is unacceptable for acute VTE treatment because the slow onset of action is associated with high incidence of recurrent thromboembolism.**
- **It is effective in the long-term VTE management provided it is started concurrently with rapid-acting parenteral anticoagulant.**

Therapy of Venous Thromboembolism

- **Injectable anticoagulation should overlap with warfarin therapy for at least 5 days and until an INR ≥2 has been achieved for at least 24 hours.**
- **The initial dose of warfarin should be 5 to 10 mg for most patients and periodically adjusted to achieve and maintain an INR between 2 - 3.**

Therapy of Venous Thromboembolism

Direct Oral Anticoagulants:

- **Can be started as single-drug therapy with rivaroxaban or apixaban.**
- **Neither drug requires routine coagulation monitoring.**
- **Dabigatran and edoxaban can be used, but require prior parenteral anticoagulation.**
- **Patients with CrCL < 30 mL/min should NOT receive dabigatran, but can receive edoxaban at half the dose.**

Therapy of Venous Thromboembolism

Thrombolytic therapy:

- **Most VTE cases require only anticoagulation therapy.**
- **In rare cases the thrombus should be removed by pharmacologic or surgical means.**
- **Thrombolytic agents are proteolytic enzymes that enhance conversion of plasminogen to plasmin, which lyses the thrombus.**

Therapy of Venous Thromboembolism

- **Thrombolytic therapy improves early venous patency, but does not improve long-term outcomes.**
- **The same anticoagulation therapy duration and intensity is recommended as for patients with DVT NOT receiving thrombolysis.**
- **Patients with DVT involving the iliac and common femoral veins are at highest risk for post-thrombotic syndrome and may benefit from thrombus removal.**

Therapy of Venous Thromboembolism

- **In acute PE management successful clot dissolution with thrombolytic therapy reduces elevated pulmonary artery pressure and improves right ventricular dysfunction.**
- **The risk of death from PE should outweigh the risk of serious bleeding from thrombolytic therapy.**
- **Patients should be screened carefully for contraindications related to bleeding risk.**

Therapy of Venous Thromboembolism in Special Populations

Pregnancy

- **Anticoagulation therapy is needed for the prevention and treatment of VTE during pregnancy.**
- **UFH and LMWH do NOT cross the placenta and are the preferred drugs.**
- **Warfarin crosses the placenta, and may produce fetal bleeding, central nervous system abnormalities, and embryopathy and should NOT be used.**
- **Pregnant women with a history of VTE should receive VTE prophylaxis for 6 to 12 weeks after delivery.**
- **Warfarin, UFH, and LMWH are safe during breast-feeding.**

Pediatric Patients

- **Venous thromboembolism in pediatric patients is increasing secondary to prematurity, cancer, trauma, surgery, congenital heart disease, and systemic lupus erythematosus.**
- **Pediatric patients rarely experience unprovoked VTE, but often develop DVTs associated with indwelling central venous catheters.**

Pediatric Patients

- **Anticoagulation with UFH and warfarin is similar to that of adults.**
- **Obtaining blood for coagulation monitoring tests is problematic because many have poor venous access.**
- **LMWH is an alternative for pediatric patients due to low drug interaction potential and less frequent laboratory testing.**

Pediatric Patients

- **LMWHs should be monitored by anti-Xa activity (goal anti–factor Xa levels 0.5 - 1.0 unit/mL, 4 to 6 hours following subcutaneous injection).**
- **Warfarin can be started with UFH or LMWH therapy, which should be overlapped for 5 days and until the INR is therapeutic.**

Pediatric Patients

- **Warfarin should be continued for at least 3 months for provoked VTE and 6 months for unprovoked VTE.**
- **Routine use of thrombolysis and thrombectomy is NOT recommended in children.**

Patients with Cancer

- **Cancer-related VTE is associated with 3-fold higher rates of recurrent VTE, (2.5 – 6)-fold higher rates of bleeding, and more resistance to standard warfarin-based therapy compared to patients without cancer.**
- **Warfarin therapy in cancer patients is often complicated by drug interactions (chemotherapy and antibiotics) and the need to interrupt therapy for invasive procedures.**
- **Maintaining stable INR control is also more difficult in these patients because of nausea, anorexia, and vomiting.**

Patients with Cancer

- **Long-term LMWH monotherapy for cancer-related VTE decreases recurrent VTE rates without increasing bleeding risks compared with warfarin-based therapy.**
- **LMWH therapy should be used for at least the first 3 - 6 months of long-term treatment, at which time LMWH can be continued or warfarin therapy substituted.**
- **Anticoagulation therapy should continue for as long as the cancer is "active" and while the patient is receiving antitumor therapy.**

Patients with Renal Insufficiency

- **UFH is preferred for acute VTE treatment in renal dysfunction.**
- **LMWH, fondaparinux, and direct-acting anticoagulants (DOACs) accumulate in renal dysfunction.**
- **LMWHs should be used with caution in patients with CrCL < 30 mL/min.**
- **DOACs require dose adjustment in renal impairment, and should be avoided in patients with CrCL < 30 mL/min (less than 25 mL/min for apixaban).**
- **Patients with chronic kidney disease are at increased risk of bleeding from other causes.**

Anticoagulant Drug Classes

Unfractionated Heparin

Pharmacology/Mechanism of Action:

- **Unfractionated heparin is a heterogeneous mixture of sulfated mucopolysaccharides of variable lengths.**
- **The anticoagulant effect of UFH is mediated through a specific pentasaccharide sequence that binds to antithrombin.**

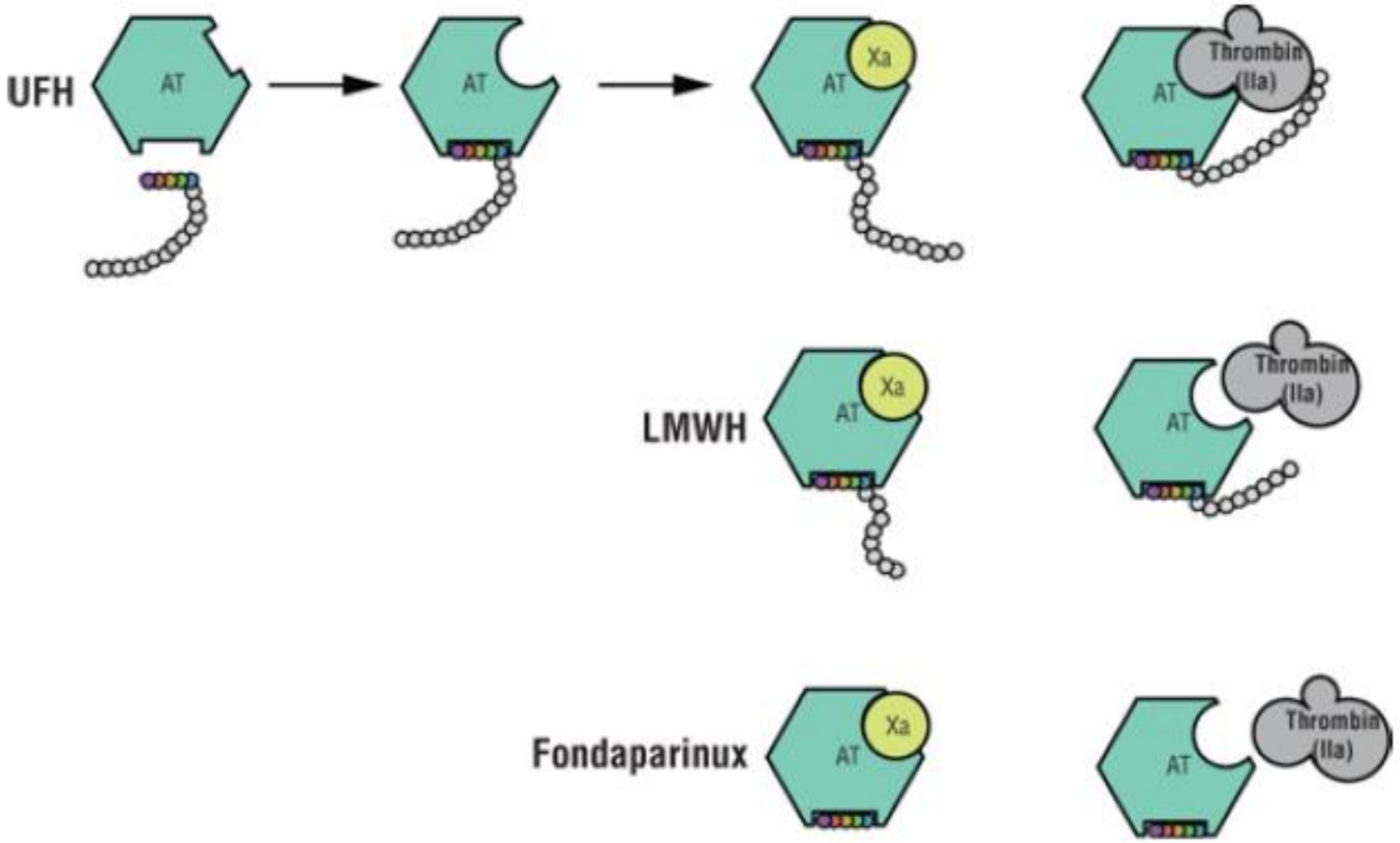
Unfractionated Heparin

- UFH accelerates the anticoagulant action of antithrombin 100 - 1,000 times.
- Antithrombin inhibits factor IIa, IXa, Xa, and XIIa activity.
- UFH prevents thrombus growth and propagation allowing endogenous thrombolytic systems to dissolve the clot.
- Thrombin (IIa) and Xa are most sensitive to UFH–antithrombin complex inhibition.

Unfractionated Heparin

- **To inactivate thrombin (IIa), the heparin molecule must form a ternary complex bridging between antithrombin and thrombin.**
- **The inactivation of factor Xa does NOT require UFH to form a bridge with antithrombin, but requires only UFH binding to antithrombin via the specific pentasaccharide sequence.**

Pharmacologic activity of unfractionated heparin, low-molecular-weight heparins (LMWHs), and fondaparinux



Unfractionated Heparin

- **The onset of action of UFH after SC injection is 1 - 2 hours, peaking at 3 hours.**
- **Continuous intravenous infusion is preferred for intravenous UFH administration.**
- **Intramuscular administration should NOT be used because of the risk of bleeding & hematomas.**
- **UFH has a dose-dependent half-life of ~ 30 - 90 minutes, because its elimination follows zero-order kinetics.**

Unfractionated Heparin

Adverse Effects:

1. **bleeding:**

- **Protamine sulfate in a dose of 1 mg per 100 units of UFH (maximum of 50 mg) can be administered via slow intravenous infusion to reverse the anticoagulant effects of UFH. Protamine sulfate neutralizes UFH in 5 minutes, and action persists for 2 hours.**

2. **Heparin-induced thrombocytopenia (HIT):**

- **Due to formation of heparin-induced antiplatelet antibodies.**

Unfractionated Heparin

- Leads to arterial thromboembolic events.
- Occur in 5 - 10 days after initiation of UFH.
- Alternative anticoagulation: a direct thrombin inhibitor.

3. Significant bone loss and osteoporosis when used for more than 6 months (pregnancy).
4. Drug–drug and Drug–food Interactions:

- Concurrent use with other anticoagulant, thrombolytic, and antiplatelet agents increases bleeding risk.

Low-Molecular-Weight Heparins (LMWHs)

(Enoxaparin, Dalteparin):

- **LMWH is produced by depolymerization of UFH.**
- **Have ~ one-third the mean UFH molecular weight.**
- **Advantages include:**

a) **predictable anticoagulation dose response.**
b) **improved subcutaneous bioavailability.**
c) **dose-independent elimination (first-order).**
d) **longer half-life.**
e) **reduced need for routine laboratory monitoring.**

LMWHs

Pharmacology/Mechanism of Action:

- **Low-molecular-weight heparin prevents thrombus growth and propagation by enhancing and accelerating the activity of antithrombin similar to UFH at factor Xa.**
- **Because of smaller chain lengths, LMWH has limited activity against thrombin (IIa).**

LMWHs

Pharmacokinetics:

- **The bioavailability of LMWH is ~ 90% after SC injection.**
- **The peak anticoagulation at 3 - 5 hours.**
- **Mainly eliminated by renal excretion.**
- **Half-life may be prolonged in patients with renal impairment.**
- **The half-life of LMWHs is ~ 3 - 6 hours.**

LMWHs

Adverse Effects:

1. **Bleeding.**

- **IV protamine sulfate can be administered as antidote.**

2. **HIT is three times lower than that observed with UFH.**

- **LMWH should be avoided in patients with HIT, because of cross reactivity with antibodies.**

3. **Osteoporosis and osteopenia.**

LMWHs

Drug–drug Interactions:

- **Drugs enhancing bleeding risk should be avoided during LMWH therapy.**
- **Such drugs include aspirin, NSAIDs, dipyridamole, or sulfinpyrazone.**

Fondaparinux

- **Fondaparinux is a synthetic molecule consisting of the active pentasaccharide units that bind reversibly to antithrombin.**
- **It inhibits only factor Xa activity.**
- **It is effective in prevention of VTE.**

Fondaparinux

Pharmacokinetics:

- **It is rapidly and completely absorbed following SC administration, peak concentrations ~ 2 hours after a single dose and 3 hours with repeated once-daily dosing.**
- **It is eliminated unchanged in the urine, elimination half-life is ~19 hours.**
- **The anticoagulant effect of fondaparinux persists for 2 to 4 days following discontinuation of the drug in patients with normal renal function.**

Fondaparinux

Adverse Effects:

1. **Bleeding.**
2. **Rare cause of HIT.**

- **No antidote to reverse its antithrombotic activity.**

Drug–drug Interactions:

- **Other drugs with anticoagulant, fibrinolytic, or antiplatelet activity increase the risk of bleeding.**

Lepirudin

- **Hirudin** is derived from Leech.
- **Lepirudin** is from recombinant DNA technology.
- **Irreversible inhibitor, inactivates fibrin-bound thrombin.**
- **Used IV or SC.**
- **Administered parenterally, monitored by aPTT.**
- **Eliminated by hepatic metabolism and renal excretion, accumulate in RF.**
- **Used for thrombosis related to HIT.**
- **No antidote is available.**

Bivalirudin

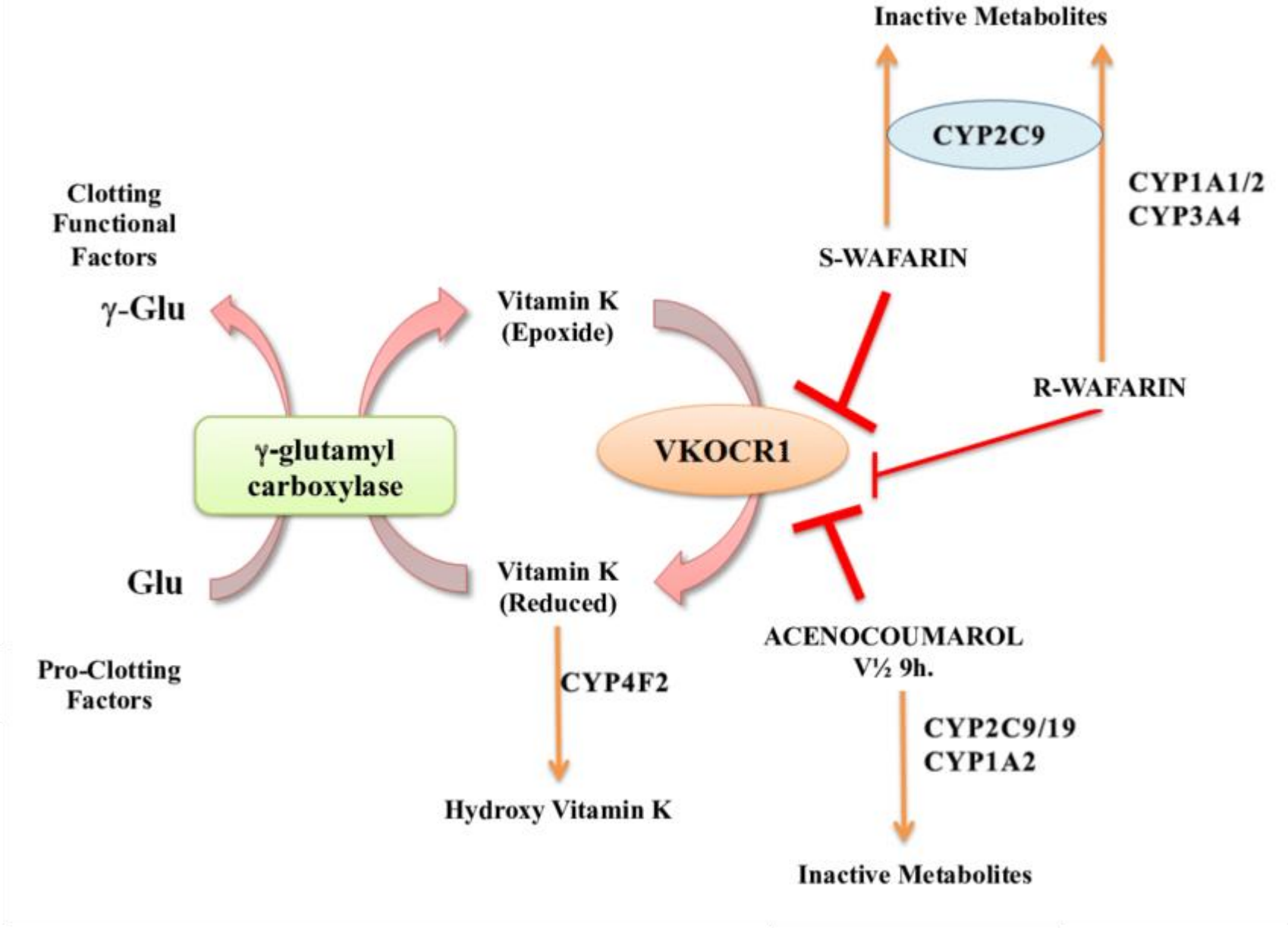
- **Bivalirudin is a direct thrombin inhibitor.**
- **It is a synthetic congener of the naturally occurring drug hirudin.**
- **Used IV.**
- **Elimination half-life is ~ 25 min.**
- **Cleared by hepatic and renal elimination and proteolytic cleavage.**
- **It inhibits both circulating and clot-bound thrombin, reversibly.**
- **Thus, it has less bleeding risk than other r-hirudins.**

Bivalirudin

- It also inhibits thrombin-mediated platelet activation and aggregation.
- Used in PCI and for HIT.
- Monitored by thrombin inhibitor assay which is better than aPTT because it is NOT affected by antiphospholipid antibodies.
- It is contraindicated in severe renal impairment.

Warfarin

- **Vitamin K in its reduced form is a required cofactor for vitamin K-dependent carboxylation of factors II, VII, IX, and X, as well as the endogenous anticoagulant proteins C and S; which is required for their biologic activity.**
- **It inhibits the reduction of vitamin K epoxide, reducing the formation of complete functioning clotting factors.**
- **It has NO effect on preformed clotting factors, thus, full antithrombotic effect is NOT achieved for at least 6 days after warfarin therapy initiation.**


Inactive Metabolites
CYP2C9
CYP1A1/2
CYP3A4
Clotting
Functional
Factors
γ-Glu
S-WAFARIN
Vitamin K
(Epoxide)
R-WAFARIN
γ-glutamyl
carboxylase
VKOCR1
Glu
Vitamin K
(Reduced)
ACENOCOUMAROL
V½ 9h.
Pro-Clotting
Factors
CYP4F2
CYP2C9/19
CYP1A2
Hydroxy Vitamin K
Inactive Metabolites

Warfarin

- **The time required for warfarin to achieve its pharmacologic effect is dependent on coagulation protein elimination half-lives (6 hours for factor VII and 72 hours for prothrombin).**
- **Because of its narrow therapeutic index, predisposition to drug and food interactions, and exacerbation of bleeding, warfarin requires continuous patient monitoring and education to achieve optimal outcomes.**

Half-Lives

Factor	Half-life (~ hours)
II	72
VII	6
IX	24
X	40
Protein C	8
Protein S	30

Warfarin

Adverse Effects:

1. **Bleeding (mild to life threatening).**

- **Vitamin K is the antidote, can be given parenterally or orally; the oral route is preferred in the absence of serious bleeding.**
- **In case of bleeding, warfarin should be temporarily stopped or the dose reduced.**

Warfarin

2. **“Purple toe syndrome” is thought to be the result of cholesterol microembolization into the arterial circulation of the toes.**
3. **Warfarin-induced skin necrosis in the first week of therapy (starts as a painful maculopapular rash and ecchymosis or purpura that progresses to necrotic gangrene).**

- **Areas of the body rich in subcutaneous fat are most commonly affected (breasts, thighs, buttocks, and abdomen).**

Warfarin Drug–drug and Drug–food Interactions

Pharmacodynamic Interaction	Mechanism
ASA/NSAIDs	Antiplatelet, GI injury
Clopidogrel/TIclopidine	Antiplatelet
Tramadol	INR elevation (mech. Unknown)
Levothyroxine	Increased catabolism of clotting factors
Vitamin K containing food/Supplements	INR reduction (reverse warfarin mechanism of action)

INR Elevation	INR Reduction
Amiodarone	Rifampin
Fluoroquinolones	Barbiturates
Trimethoprim/sulfamethoxazole	Carbamazepine
Metronidazole	Phenytoin
Azole antifungals	St John's wort
Statins	Cigarette smoking
Isoniazid	Charcoal broiled food
NSAIDs	Cholestyramine (Bile acid binding resins)
Sertraline Gemfibrozil	Oral contraceptives (Estrogens)
Ethanol	Ginseng
Macrolides	Green tea
Cimetidine	Avocado
Omeprazole	Spinach & leafy green vegs.
Fluorouracil	Brocolli, Cabbage, Brussels sprouts, Red-leaf lettuce
Garlic	
Ginkgo	
Vitamin E	

Open this site or link to see tables for more comprehensive descriptiono f drug and food interactions with warfarin

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/486574

Direct Oral Anticoagulants

(DOACs):

- **Rivaroxaban, apixaban, and edoxaban are potent and selective inhibitors of both free and clot-bound factor Xa.**
- **They do not require antithrombin to exert their anticoagulant effect.**
- **Dabigatran (prodrug) is a selective, reversible, direct factor IIa inhibitor.**

Direct Oral Anticoagulants

- These drugs are partially eliminated by the kidney to various extent, and should be used with caution in patients with renal dysfunction.
- Terminal half-lives ~10 hours for the Factor Xa inhibitors, and 16 hours for dabigatran.
- Rivaroxaban and apixaban are substrates of cytochrome CYP3A4, and P-glycoprotein.

Direct Oral Anticoagulants

Indications:

1. **The Xa inhibitors rivaroxaban and apixaban can prevent VTE following hip or knee replacement surgery.**
2. **Dabigatran, rivaroxaban and apixaban can be used for extended VTE treatment after the first 6 months of anticoagulant therapy.**

Direct Oral Anticoagulants

Adverse Effects:

1. **Bleeding which ranges from minor – severe & fatal.**
- **Discontinuation of therapy and supportive management.**
- **Activated charcoal may provide some benefits if drug intake occurred within 2 hours of presentation, and dabigatran is hemodializable.**
- **Idarucizumab rapidly reverses the dabigatran anticoagulant effect following IV administration.**
- **It is used in life-threatening bleeding and when there is need for urgent surgical intervention.**

2. **Gastrointestinal complaints.**

Direct Oral Anticoagulants

Drug–drug and Drug–food Interactions:

- **DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers.**
- **Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP 3A4.**

Direct Oral Anticoagulants

Renal Function:

- **Periodic renal function assessment is important during long-term DOAC therapy, especially for patients with CrCL < 50 mL/min.**
- **DOACs should NOT be used in patients with CrCL less than 25 mL/min (apixaban) or 30 mL/min (rivaroxaban and dabigatran).**
- **Edoxaban dosing should be reduced in patients with CrCL 15 - 50 mL/min**

Pharmacogenomics

- **CYP2C9 is the hepatic microsomal enzyme responsible for metabolism of the more potent S-enantionmer of warfarin.**
- **Polymorphisms in CYP2C9 and the gene coding for VKOR (Vitamin K Epoxide Reductase) explain a substantial proportion of warfarin dose variability between patients.**
- **For individualized warfarin dosing consult (www.warfarindosing.org).**
- **Poor metabolizer subtypes have been associated with increased risk of bleeding.**
- **Warfarin resistance can be due to mutations in the receptor gene.**