Therapy of Venous Thromboembolism

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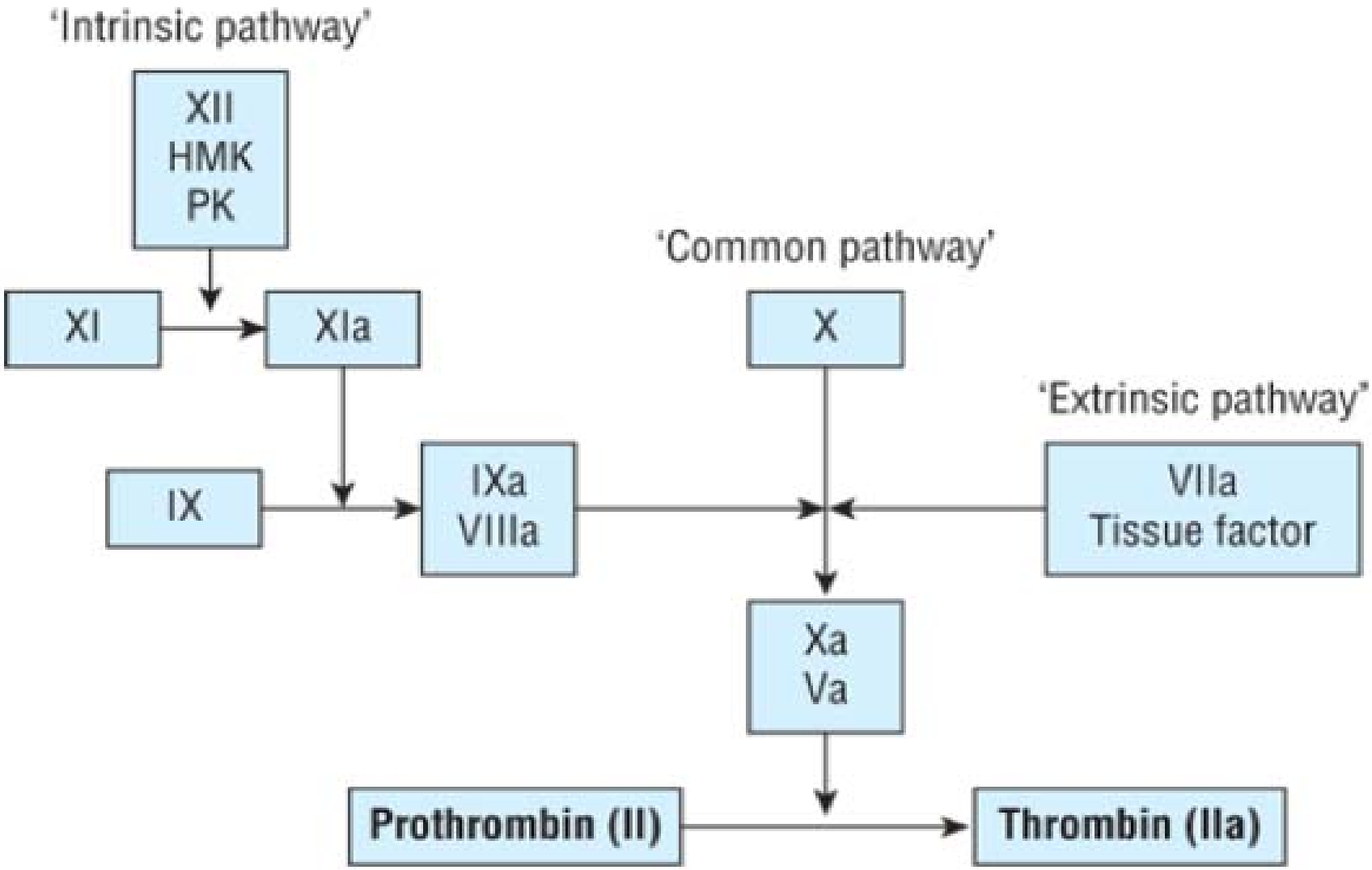
Therapy of Venous Thromboembolism

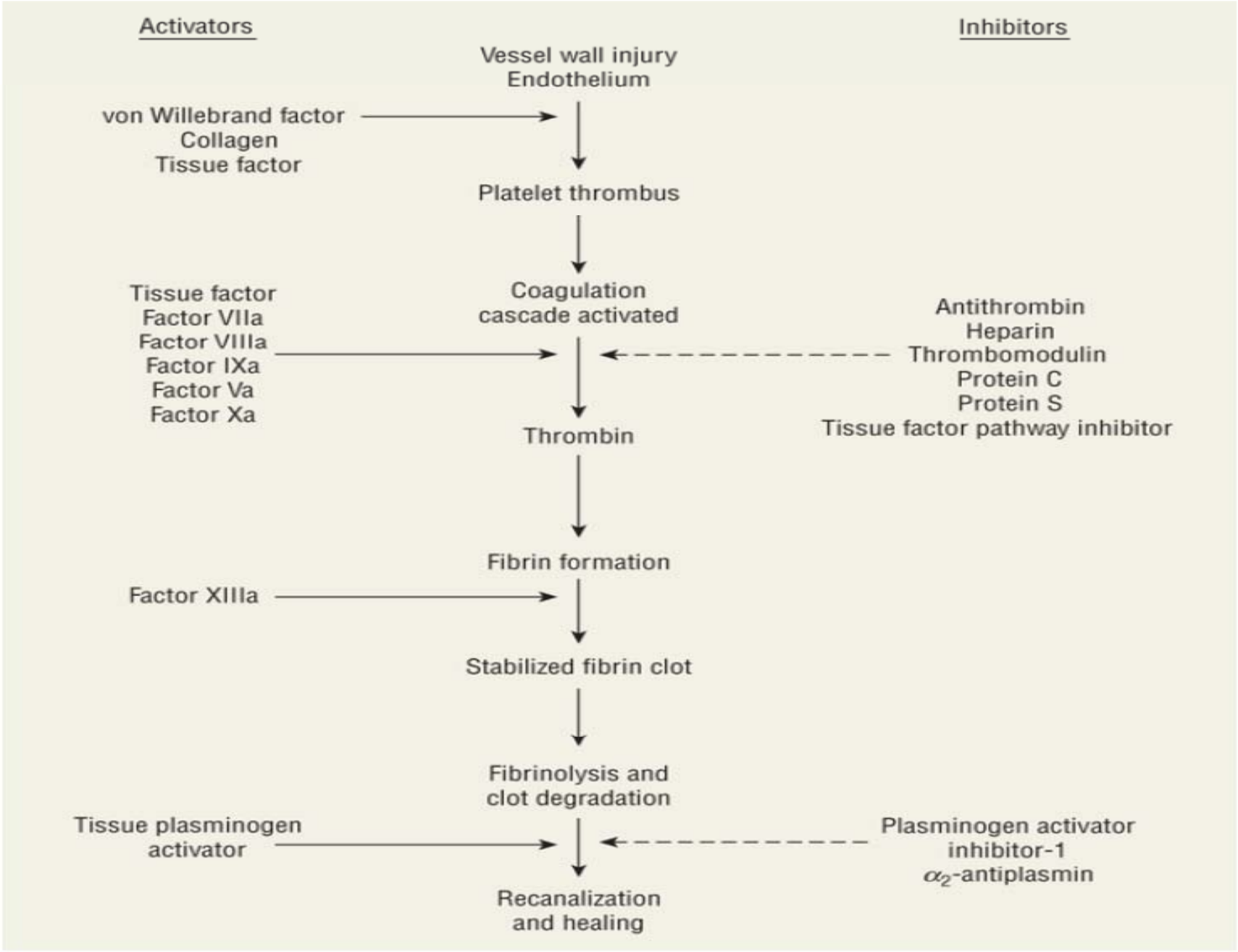
- **Venous thromboembolism (VTE) is a potentially fatal disorder and a significant health problem.**
- **VTE results from clot formation within the venous circulation and is manifested as deep vein thrombosis (DVT) and/or pulmonary embolism (PE).**

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 <u>NOT</u> 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 prophylaxis.**

Preventing VTE following high risk orthopedic surgery (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.**
- **Before prescribing anticoagulation therapy for VTE, establishing an accurate diagnosis is important in avoiding unnecessary bleeding.**
- **Once the diagnosis of VTE has been confirmed, anticoagulant 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.**
- **Early initiation of warfarin (same day as parenteral therapy) or delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2 or above for at least 24 hours is recommended.**

Therapy of Venous Thromboembolism

- **The appropriate initial duration of anticoagulation 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.**

Therapy of Venous Thromboembolism

- **Clinically important bleeding risk factors include:** age more than 75 years, previous noncardioembolic stroke, history of gastrointestinal bleeding, renal or hepatic impairment, anemia, thrombocytopenia, concurrent antiplatelet use, noncompliance, poor anticoagulant control (for patients on warfarin), serious acute or chronic illness, and the presence of structural lesions (tumor, recent surgery) that could bleed.

Therapy of Venous Thromboembolism

Unfractionated Heparin:

- **Unfractionated heparin may be administered subcutaneously or by continuous intravenous infusion.**
- **Anticoagulant 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.**
- **Some patients still fail to achieve an adequate response to UFH therapy.**
- **Traditional intravenous UFH in the acute treatment of VTE may be replaced by LMWH or fondaparinux.**
- **As 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:

- **Low-molecular-weight heparin has largely 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

- **They have reduced need for laboratory monitoring. (obese, pregnancy, children). By anti-Xa activity (goal anti–factor Xa levels 0.5 - 1.0 unit/mL, 4 to 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 to 10 days.**

Therapy of Venous Thromboembolism

Fondaparinux:

- **Fondaparinux 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.**
- **However, warfarin 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 more than or equal to 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 and 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 removing the occluding thrombus by pharmacologic or surgical means may be indicated.**
- **Thrombolytic agents are proteolytic enzymes that enhance conversion of plasminogen to plasmin.**

Therapy of Venous Thromboembolism

- **Thrombolytic therapy for DVT 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 normalizes right ventricular dysfunction.**
- **However, the risk of death from PE should outweigh the risk of serious bleeding associated with thrombolytic therapy.**
- **Patients being considered for thrombolytic therapy should be screened carefully for contraindications related to bleeding risk.**

Therapy of Venous Thromboembolism

Special Populations:

Pregnancy:

- Anticoagulation therapy is commonly used for the prevention and treatment of VTE during pregnancy.
- UFH and LMWH do not cross the placenta and are preferred during pregnancy.
- Warfarin crosses the placenta and can result in fetal bleeding, central nervous system abnormalities, and embryopathy and should not be used for VTE treatment during pregnancy.
- 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.

Therapy of Venous Thromboembolism

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.**

Therapy of Venous Thromboembolism

- **Anticoagulation with UFH and warfarin remains the most frequently used approach for VTE treatment in pediatric patients and the recommended target aPTT and INR ranges as well as the duration of therapy are extrapolated from adults.**
- **Frequent INR monitoring and warfarin dose adjustments are typically required.**

Therapy of Venous Thromboembolism

- **Obtaining blood for coagulation monitoring tests is problematic because many have poor venous access.**
- **Despite need for daily injections, LMWH is an alternative for pediatric patients due to low drug interaction potential and less frequent laboratory testing.**
- **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).**

Therapy of Venous Thromboembolism

- **Warfarin can be initiated concurrently with UFH or LMWH therapy. Therapy should be overlapped for a minimum of 5 days and until the INR is therapeutic.**
- **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.**

Therapy of Venous Thromboembolism

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 this patient population because of nausea, anorexia, and vomiting.**

Therapy of Venous Thromboembolism

- **Long-term LMWH monotherapy for cancer-related VTE decreases recurrent VTE rates without increasing bleeding risks compared with warfarin-based therapy.**
- **LMWH therapy should continue 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.**

Therapy of Venous Thromboembolism

Patients with Renal Insufficiency:

- **UFH is preferred for acute VTE treatment in renal dysfunction.**
- **LMWH, fondaparinux, and DOACs accumulate in renal dysfunction.**
- **LMWHs should be used with caution in patients with severe renal impairment (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:

- **Unfractionated heparin has been used for VTE prevention and treatment for decades.**

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.**

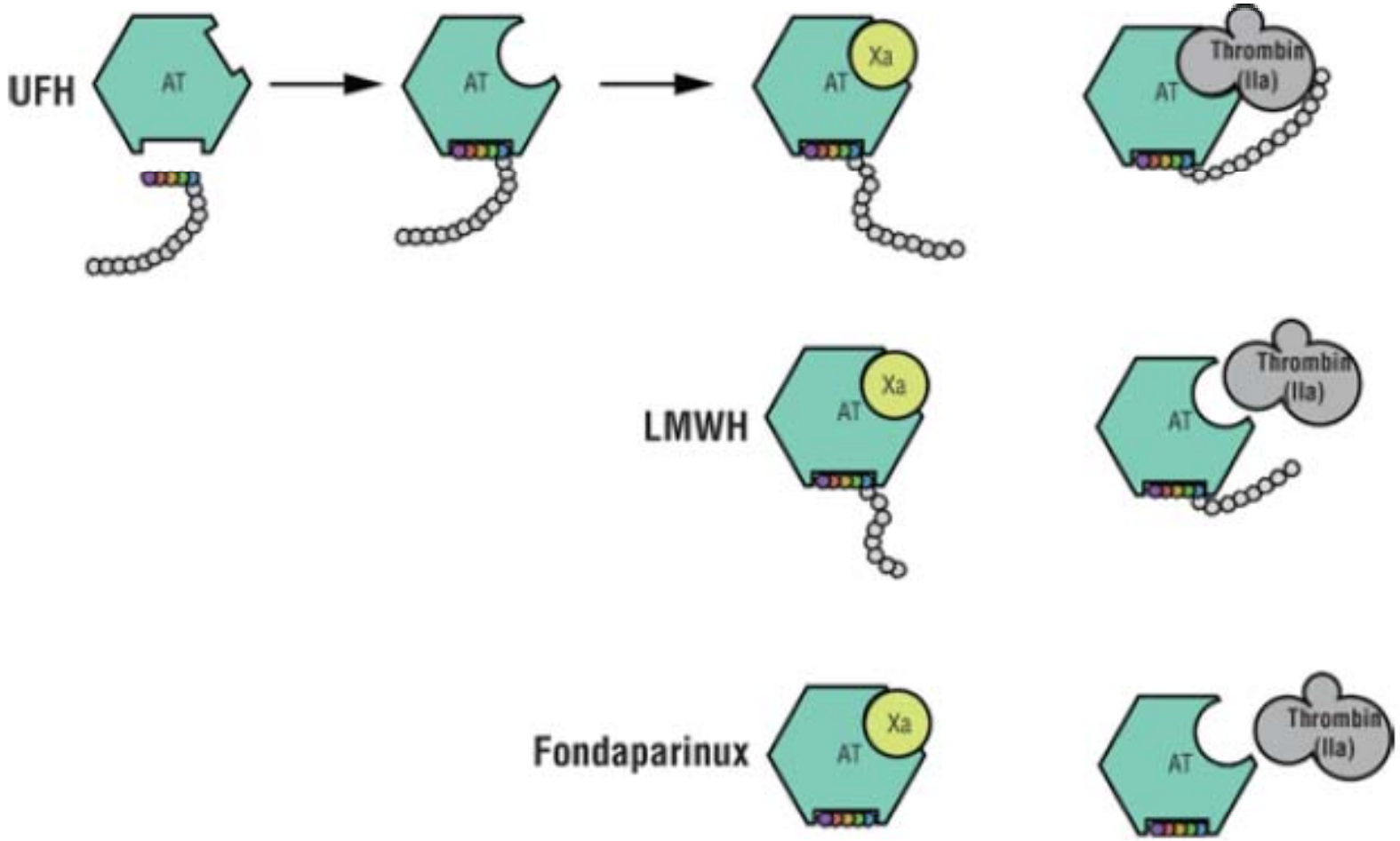
Anticoagulant Drug Classes

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

Anticoagulant Drug Classes

- **To inactivate thrombin, 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



Anticoagulant Drug Classes

- **The onset of action of UFH after SQ injection is 1 - 2 hours, peaking at 3 hours.**
- **Continuous 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.**
- **UFH elimination follows zero-order kinetics.**

Anticoagulant Drug Classes

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 persists for 2 hours.**

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

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

Anticoagulant Drug Classes

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

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

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

Anticoagulant Drug Classes

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.**

Anticoagulant Drug Classes

Pharmacology/Mechanism of Action:

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

Anticoagulant Drug Classes

Pharmacokinetics:

- **The bioavailability of LMWH is about 90% when administered subcutaneously.**
- **The peak anticoagulation effect is seen in 3 - 5 hours.**
- **The predominant mode of elimination for LMWH is renal.**
- **Half-life may be prolonged in patients with renal impairment.**
- **The plasma half-life of LMWHs is ~ 3 - 6 hours.**

Anticoagulant Drug Classes

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.**

Anticoagulant Drug Classes

Drug–drug Interactions:

- **Drugs enhancing bleeding risk should be avoided during LMWH therapy, if possible.**
- **This includes aspirin, non-steroidal anti-inflammatory drugs, dipyridamole, or sulfinpyrazone.**

Anticoagulant Drug Classes

Fondaparinux:

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

Efficacy:

- **The efficacy of fondaparinux for prevention of VTE is established.**

Anticoagulant Drug Classes

Pharmacokinetics:

- **It is rapidly and completely absorbed following SQ 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.**

Anticoagulant Drug Classes

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.**

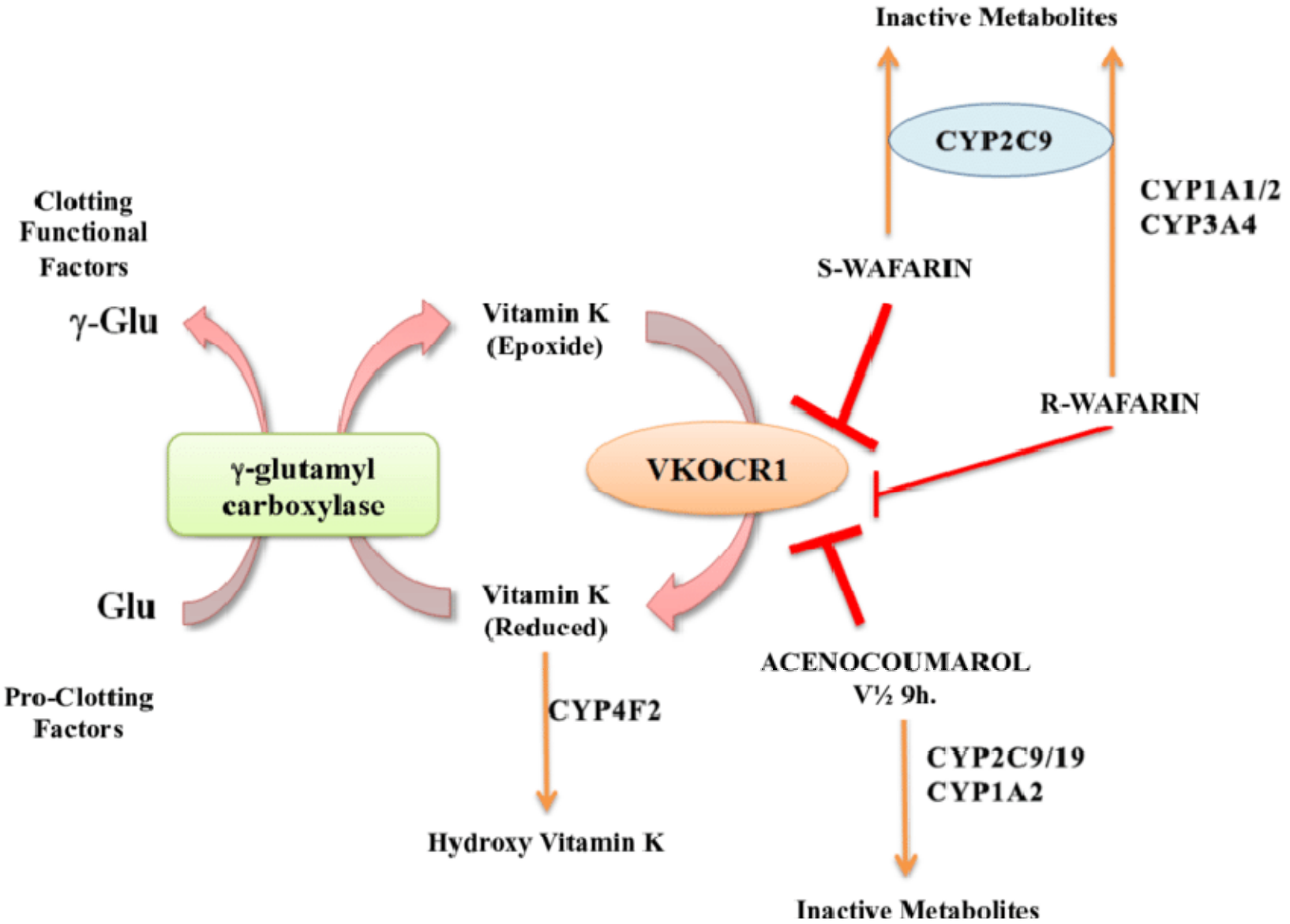
Anticoagulant Drug Classes

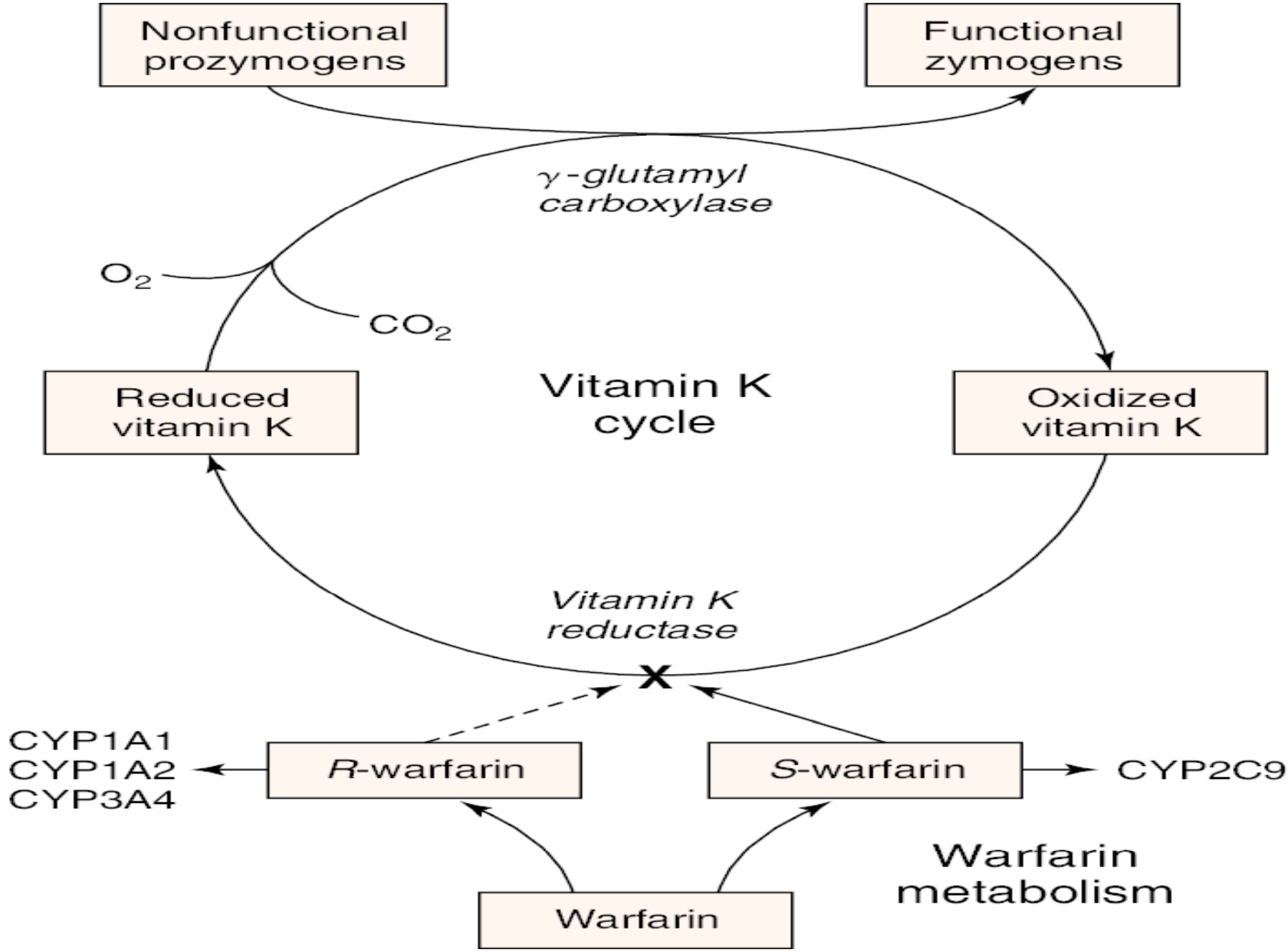
- **Hirudin** is derived from Leech.
- **Lepirudin** is from recombinant DNA technology.
- Irreversible inhibitor, inactivates fibrin-bound thrombin.
- Administered parenterally, monitored by aPTT.
- Eliminated by hepatic metabolism and renal excretion, accumulate in RF.
- Used for thrombosis related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

Anticoagulant Drug Classes

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.**
- **Warfarin inhibits the reduction of vitamin K epoxide, therefore, it reduces the formation of complete functioning clotting factors.**
- **Warfarin 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
S-WAFARIN
γ-Glu
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


Nonfunctional prozymogens
Functional zymogens
γ-glutamyl carboxylase
O2
CO2
Reduced vitamin K
Vitamin K cycle
Oxidized vitamin K
Vitamin K reductase
X
CYP1A1
CYP1A2
CYP3A4
R-warfarin
S-warfarin
CYP2C9
Warfarin
Warfarin metabolism

Anticoagulant Drug Classes

- **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 propensity to exacerbate bleeding, warfarin requires continuous patient monitoring and education to achieve optimal outcomes.**

Anticoagulant Drug Classes

Adverse Effects:

1. **Bleeding that can range from 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.**

Anticoagulant Drug Classes

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 as a painful maculopapular rash and ecchymosis or purpura that subsequently progresses to necrotic gangrene.**

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

Warfarin Drug–drug and Drug–food Interactions

Medscape® www.medscape.com

Pharmacodynamic interactions	Mechanism
ASA/NSAIDs	Antiplatelet, gastrointestinal injury
Clopidogrel/Ticlopidine	Antiplatelet
Tramadol	INR elevation (unclear mechanism)[33]
Levothyroxine	Increased catabolism of clotting factors
Vitamin K-containing food/supplements	INR depression (circumvent warfarin mechanism of action)

Source: Geriatrics Aging © 2007 1453987 Ontario, Ltd.

Medscape® www.medscape.com

INR Elevation	*INR Depression
Amiodarone (2C9)	Rifampin (2C9)
Ciprofloxacin (1A2/3A4)	Secobarbital (2C9)
TMP/SMX (2C9)	Carbamazepine (2C9)
Metronidazole (2C9/3A4)	Phenytoin (2C9)
Fluconazole (2C9/3A4)	Phenobarbital (2C9)
Fluvastatin (2C9)	Primidone (2C9)
Fluvoxamine (2C9)	St John's wort (2C9)
Isoniazid (2C9)	Cigarette smoking (1A2)
Lovastatin (2C9)	Charbroiled food (1A2)
Phenylbutazone (2C9)	
Sertraline (2C9)	
Gemfibrozil (2C9)	
Ethanol (1A2)	
Clarithromycin (3A4)	
Erythromycin (3A4)	
Voriconazole (3A4)	

*mechanism for all agents listed, thought to be due to liver enzyme induction

Source: Adapted from Holbrook AM, et al., 2005[30]; Badyal DK , et al., 2004[31]; Stading JA, et al., 2007.[32]

Table 2. Select Food, Drug, Herbal, and Dietary Supplement Interactions With Warfarin

Increase Anticoagulation Effect (↑ INR)	Decrease Anticoagulation Effect (↓ INR)
Amiodarone	Barbiturates
Azole antifungals	Carbamazepine
Capecitabine	Cholestyramine
Cimetidine	Estrogens
Dan shen	Ginseng
Fluoroquinolones	Green tea
Fluorouracil (5-FU)	Phenytoin
Garlic	St. John's wort
Ginkgo	Vitamin K (e.g., leafy green vegetables such as broccoli, brussels sprouts, cabbage, collard greens, kale, red leaf lettuce, spinach)
Levothyroxine	
Macrolides	
Metronidazole	
Omeprazole	
Trimethoprim/sulfamethoxazole	
Vitamin E	

INR: international normalized ratio.
Sources: References 6, 8, 11. Please refer to these references for a complete list and description of interactions.

Warfarin: Food and drug interactions

	Increase anticoagulation		Decrease anticoagulation
Foods	St. John's Wort Ginseng Garlic		Gingko biloba Avocado Spinach Brocolli
Drugs	Acetaminophen Amiodarone Androgens Allopurinol Aspirin (high dose) Cimetidine Clofibrate Chloramphenicol Disulfiram Dipyridamole Erythromycin Fluconazole Fluoxetine HCl Glucagon	Indomethacin Liquid paraffin Metronidazole Phenylbutazone Phenytoin Probenecid Phenformin Quinidine Sulfinpyrazone Tamoxifen Tolbutamide Thyroid hormone Trimethoprim-sulfamethoxazole	Antithyroid drugs Barbiturates Carbamazepine Cholestyramine Gluthimide Griseofulvin Oral contraceptive Rifampicin Sucralfate

Gogna A, Arun S. Oral Anticoagulation in Clinical Practice. JIACM 2005;6(1):53-66

Anticoagulant Drug Classes

Direct Oral Anticoagulants (DOACs):

- **Rivaroxaban, apixaban, and edoxaban are potent and selective inhibitors of both free and clot-bound factor Xa and do not require antithrombin to exert their anticoagulant effect.**
- **Dabigatran is a selective, reversible, direct factor IIa inhibitor. It is a prodrug.**
- **These drugs are partially eliminated by the kidney to various extent.**

Anticoagulant Drug Classes

- They 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.

Anticoagulant Drug Classes

Efficacy:

- **Direct oral anticoagulants can reduce recurrence during VTE treatment.**
- **The Xa inhibitors rivaroxaban and apixaban can prevent VTE following hip or knee replacement surgery.**
- **Dabigatran, rivaroxaban and apixaban can be used for extended VTE treatment after the first 6 months of anticoagulant therapy.**

Anticoagulant Drug Classes

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 hemodialisable.**
- **Idarucizumab rapidly reverses the dabigatran anticoagulant effect following IV administration.**
- **Used in life-threatening bleeding and when there is need for urgent surgical intervention.**

2. **Gastrointestinal complaints.**

Anticoagulant Drug Classes

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.**

Personalized Pharmacotherapy

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**
- **LMWHs also rely upon renal elimination and UFH remains preferred in patients with severe renal compromise (CrCL < 30 mL/min).**

Personalized Pharmacotherapy

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.**