Therapy of Venous Thromboembolism

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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).**

Venous Thromboembolism Prophylaxis

Pharmacologic Prophylaxis:

- **Pharmacologic prevention significantly reduces the risk of VTE following:**

1. **Hip and knee replacement**
2. **Hip fracture repair**
3. **Major general surgery**
4. **Myocardial infarction**
5. **Ischemic stroke**
6. **Others.**

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 unfractionated heparin (UFH), low molecular weight heparin (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:

A. Preventing VTE following non-orthopedic surgery:

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

B. 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 therapy 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 LMWH or UFH overlapped with warfarin for 5 days, then the patient is maintained on warfarin:**

A. **Early initiation of warfarin (same day as parenteral therapy) for 5 days, or**
B. **Delayed initiation but with continuation of parenteral anticoagulation (UFH or LMWH) 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 administration
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).**
- **Both weight-based, and fixed-UFH-dosing (5,000 unit bolus followed by 1,000 units/h continuous infusion) produce 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 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 or 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

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

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

- **The initial dose of warfarin is 5-10 mg for most patients and periodically adjusted to achieve and maintain an INR between 2 - 3.**

Therapy of Venous Thromboembolism

Direct Oral Anticoagulants:

- **Rivaroxaban or apixaban can be started as single-drug therapy with.**
- **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.**

Therapy of Venous Thromboembolism

- **Patients with DVT involving the iliac and common femoral veins are at highest risk of post-thrombotic syndrome and may benefit from thrombus removal.**
- **In acute PE management, successful clot dissolution with thrombolytic therapy reduces elevated pulmonary artery pressure and improves right ventricular dysfunction.**

Therapy of Venous Thromboembolism

- **For thrombolytic therapy to be used, 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 Pregnancy

- **Anticoagulation therapy may be 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.**

Therapy of Venous Thromboembolism in Pregnancy

- **Pregnant women with a history of VTE should receive VTE prophylaxis for 6 - 12 weeks after delivery.**

- **[Warfarin, UFH, and LMWH are safe during breast-feeding].**

Therapy of Venous Thromboembolism in Pediatric Patients

- **VTE 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 DVT associated with indwelling central venous catheters.**

Therapy of Venous Thromboembolism in Pediatric Patients

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

Therapy of Venous Thromboembolism in Pediatric Patients

- **LMWHs should be monitored by anti-Xa activity (0.5 - 1.0 unit/mL), 4 - 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.**

Therapy of Venous Thromboembolism in 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.**

Therapy of Venous Thromboembolism in 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.**

Therapy of Venous Thromboembolism in Patients with Cancer

- **Maintaining stable INR control is also more difficult in these patients because of nausea, anorexia, and vomiting.**
- **Long-term LMWH monotherapy for cancer-related VTE decreases recurrent VTE rates without increasing bleeding risks compared with warfarin-based therapy.**

Therapy of Venous Thromboembolism in Patients with Cancer

- **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 chemotherapy.**
- **Because of the diversity of cancer, the above recommendations may vary.**

Therapy of Venous Thromboembolism in Patients with Cancer

- **Go to this if you are interested.**

https://www.acc.org/latest-in-cardiology/articles/2020/05/05/08/31/treatment-of-malignancy-associated-venous-thromboembolism

Therapy of Venous Thromboembolism in 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.**

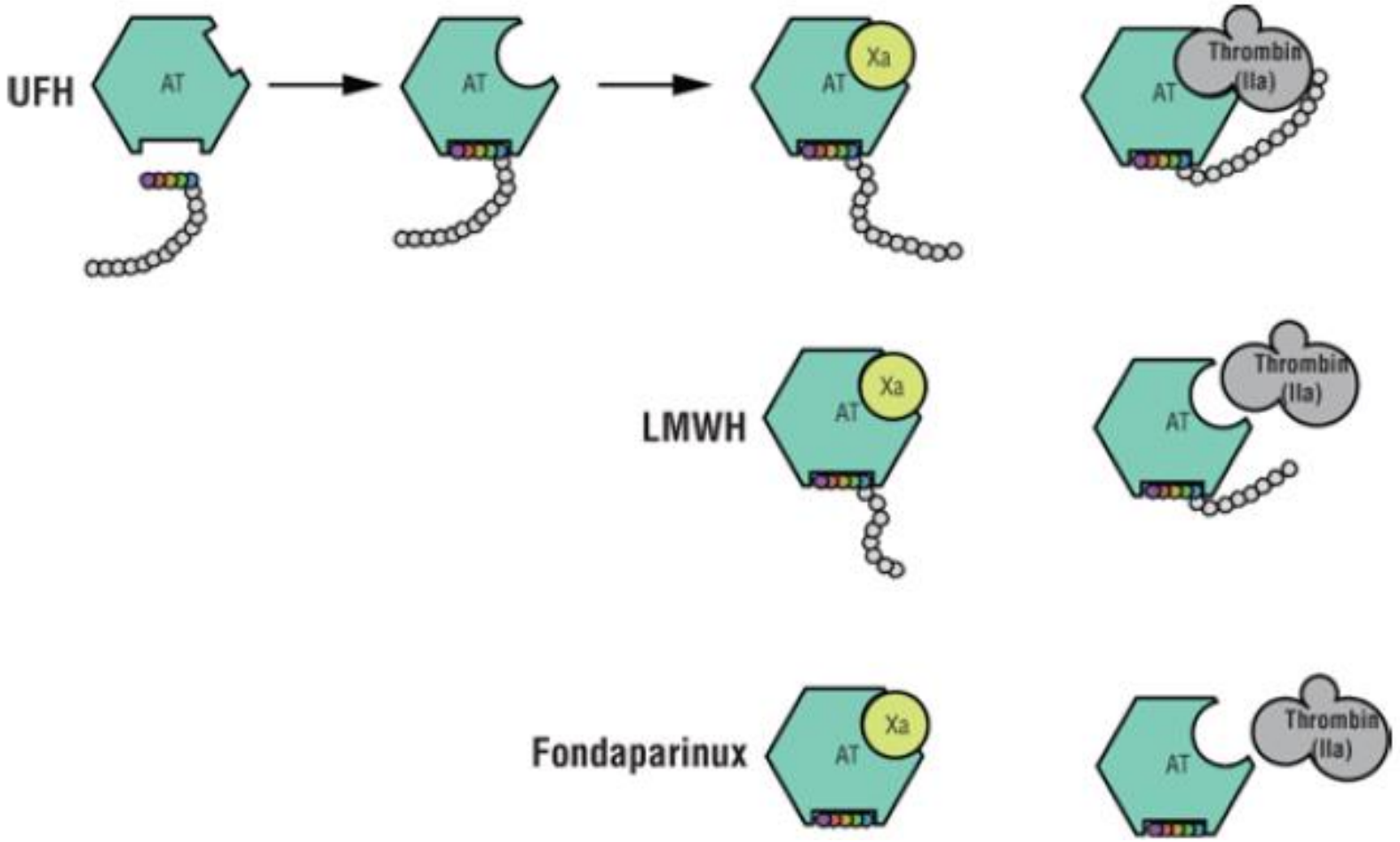
Unfractionated Heparin

- **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

- **It is preferred to administer UFH by continuous intravenous infusion.**
- **The onset of action of UFH after SC injection is 1 - 2 hours, peaking at 3 hours.**
- **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.**

Unfractionated Heparin

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

- **It is caused by antibodies that bind to complexes of heparin and platelet factor 4 (PF4). These antibodies are prothrombotic and activate platelets.**
- **Leads to arterial thromboembolic events.**
- **Occur in 5 - 10 days after initiation of UFH.**
- **Alternative anticoagulation: direct thrombin inhibitors.**

Unfractionated Heparin

- **[Thrombosis seen with some *Covid*-19 vaccines is similar to HIT. It is mediated by antibodies to platelet factor 4-polyanion complexes. It represents vaccine-related variant of HIT. It is called "vaccine-induced immune thrombotic thrombocytopenia"].**

Unfractionated Heparin

3. **Significant bone loss and osteoporosis when used for more than 6 months (pregnancy).**

Drug–drug Interactions:

- **Concurrent use with other anticoagulant, thrombolytic, antiplatelet agents, aspirin and NSAIDs 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

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

LMWHs

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

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:

- **Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.**

Fondaparinux

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

Fondaparinux

Pharmacokinetics:

- **It is rapidly and completely absorbed following SC administration, peak concentrations at ~ 2 hours after a single dose and at 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.**
- **Monitored by aPTT.**
- **Eliminated by hepatic metabolism and renal excretion, accumulates 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 anticoagulant hirudin.**
- **Used IV bolus followed by infusion.**
- **Elimination half-life is ~ 25 min in normal renal function; and 60 min if CLcr < 30ml/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 r-hirudins.**

Bivalirudin

- **It also inhibits thrombin-mediated platelet activation and aggregation.**
- **Used in percutaneous coronary intervention (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.**

Warfarin

- **Warfarin inhibits the reduction of vitamin K epoxide, which impairs 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.**

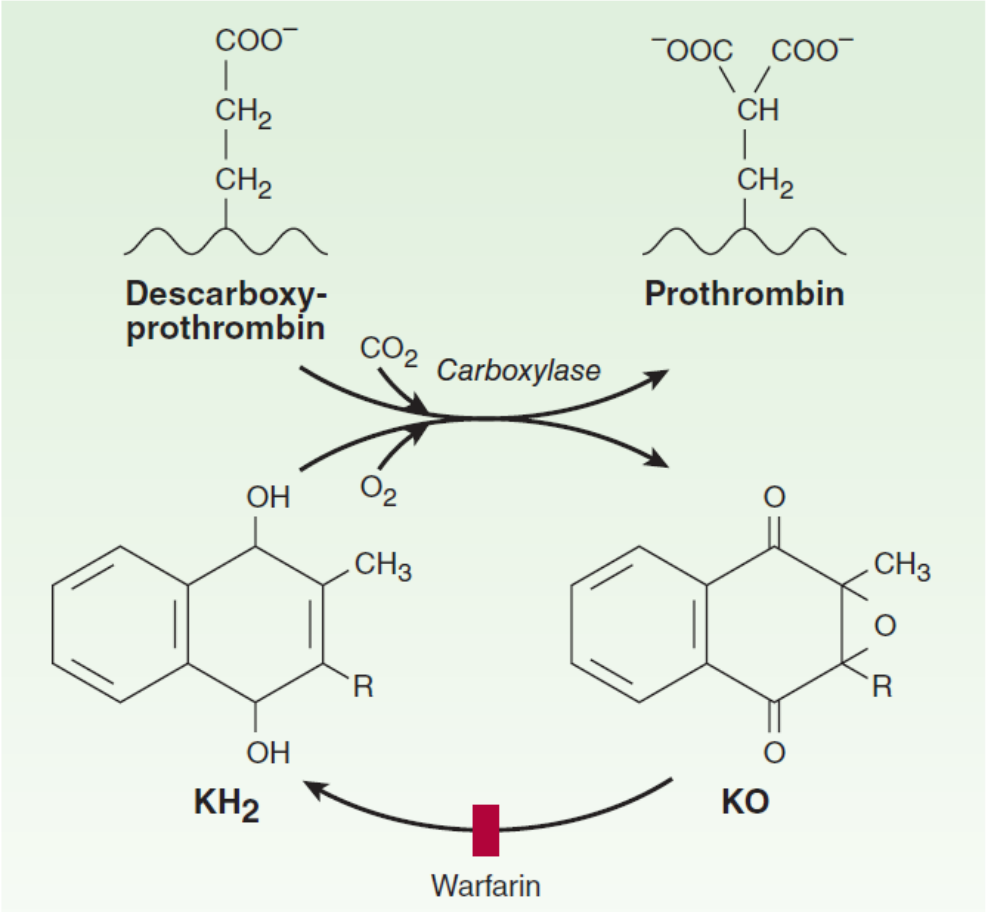


FIGURE 34–6 Vitamin K cycle–metabolic interconversions of vitamin K associated with the synthesis of vitamin K–dependent clotting factors. Vitamin K_1 or K_2 is activated by reduction to the hydroquinone form (KH_2). Stepwise oxidation to vitamin K epoxide (KO) is coupled to prothrombin carboxylation by the enzyme carboxylase. The reactivation of vitamin K epoxide is the warfarin-sensitive step (warfarin). The R on the vitamin K molecule represents a 20-carbon phytyl side chain in vitamin K_1 and a 30- to 65-carbon polyprenyl side chain in vitamin K_2.

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).**

Half-Lives

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

Warfarin

- **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.**

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 (due to thrombosis) in the first week of therapy.**

- **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 description of drug and food interactions with warfarin

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

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.**
- **Poor metabolizer subtypes have been associated with increased risk of bleeding.**
- **Warfarin resistance can be due to mutations in the receptor gene.**
- **For individualized warfarin dosing consult (www.warfarindosing.org).**

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. **Gastrointestinal complaints.**
2. **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.**

Direct Oral Anticoagulants

- **Idarucizumab rapidly reverses the dabigatran anticoagulant effect following IV administration.**
- **It binds to dabigatran and its acylglucuronide with higher affinity than that of dabigatran to thrombin.**
- **It is used in life-threatening bleeding and when there is need for urgent surgical intervention.**

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 CYP3A4.**

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 < 25 mL/min (apixaban) or < 30 mL/min (rivaroxaban and dabigatran).**
- **Edoxaban dosing should be reduced in patients with CrCL 15 - 50 mL/min**