بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 5

Anticoagulants pt.2



Written by : Bushra Aldaboubi
Rawan Okour

Reviewed by : Rawan Okour



Warfarin

- Oral drug.
- Vitamin K antagonist – not in the literal sense.

- **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, reducing the formation of complete functioning clotting factors.**
- Warfarin inhibits the enzyme responsible for converting vitamin K epoxide back to its reduced form.

Warfarin

- **It has NO effect on preformed clotting factors, thus, full antithrombotic effect is NOT achieved for at least 6 days after warfarin therapy initiation,** delayed onset of action.

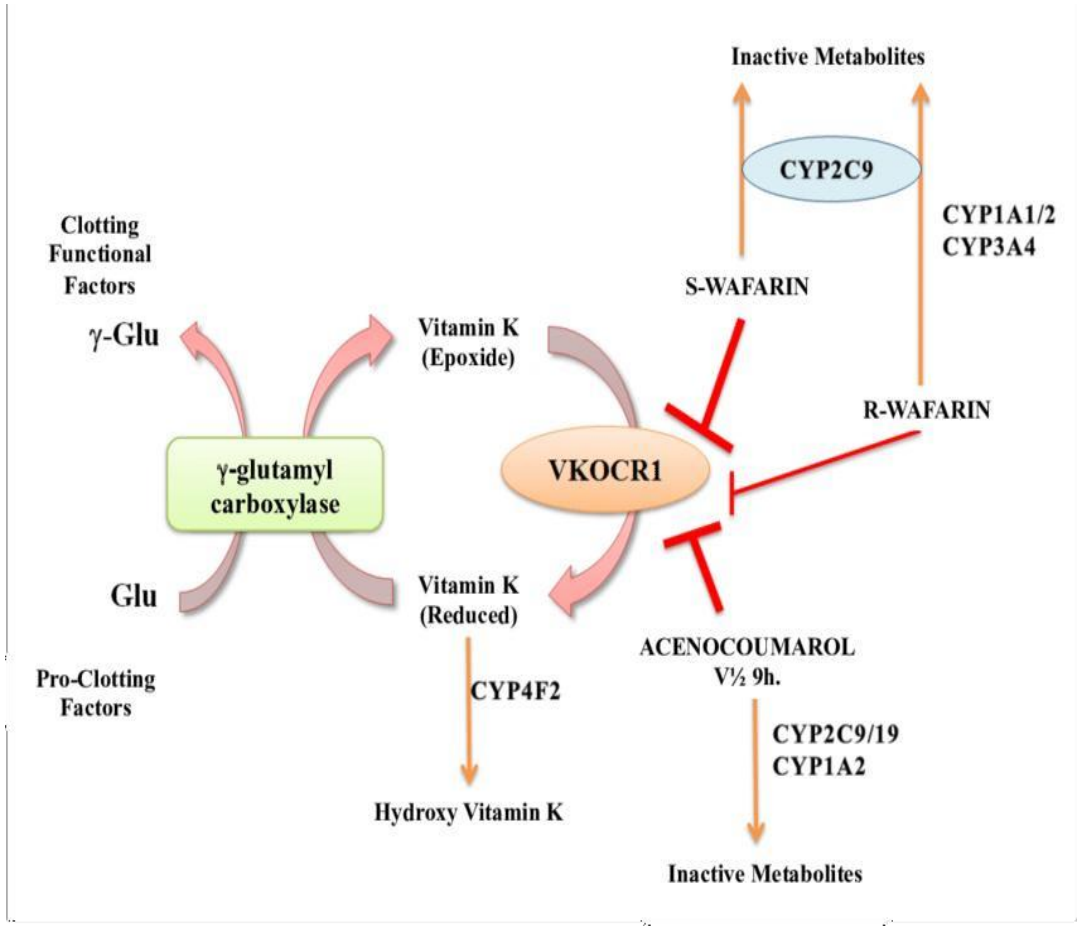
- Not used alone for acute thrombosis.
- Heparin is used initially until warfarin produces its anticoagulant effect.



Vitamin K is an essential cofactor for the synthesis of functional coagulation factors II, VII, IX, and X.
These clotting factors require an additional post-translational modification known as γ-carboxylation, during which an additional carboxyl group is added to specific glutamate residues, allowing them to bind calcium ions (Ca^{2+}).
The negatively charged carboxyl groups facilitate calcium binding, which is essential for the normal function of these coagulation factors.

Vitamin K Cycle

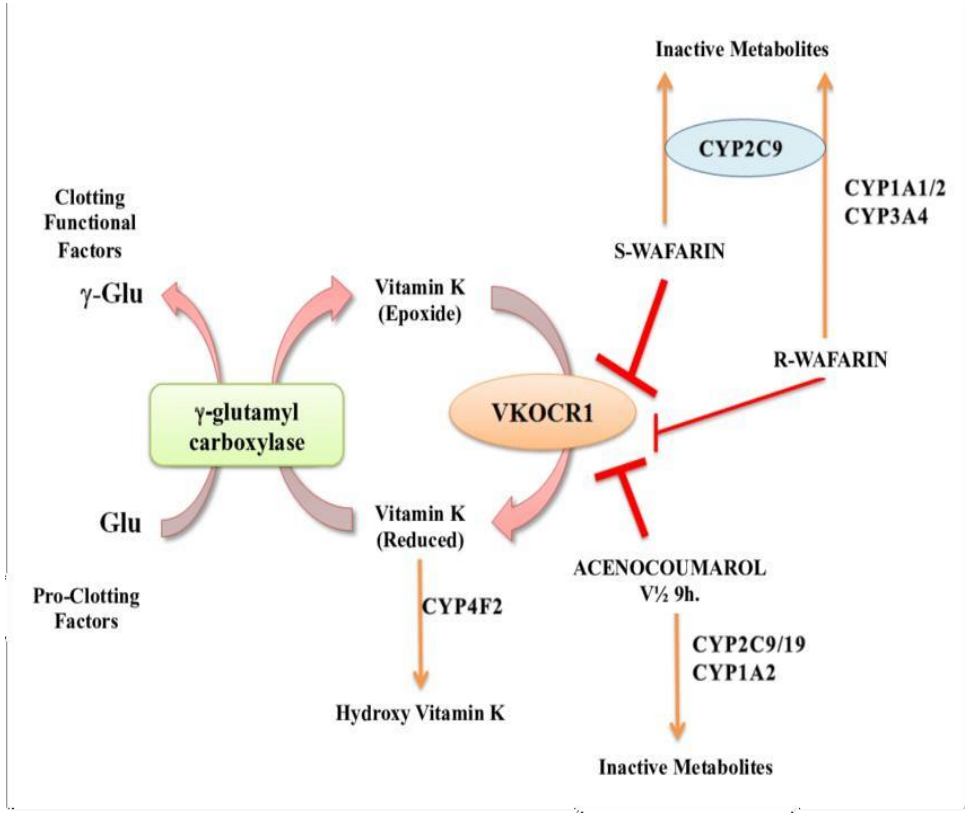
- Reduced vitamin K is the active form required as a cofactor for γ-carboxylation.
- During the carboxylation reaction, reduced vitamin K is oxidized to vitamin K epoxide, an inactive form.
- Vitamin K epoxide must be recycled back to its reduced, active form by the vitamin K epoxide reductase complex (VKORC1).
- This recycling process ensures the continuous availability of active vitamin K for the γ-carboxylation of clotting factors.



Mechanism of Action of Warfarin

Warfarin is an oral anticoagulant belonging to the coumarin anticoagulants.

- Warfarin inhibits the vitamin K epoxide reductase complex (VKORC1).
- This inhibition prevents the efficient recycling of vitamin K epoxide into reduced vitamin K.
- Consequently, the availability of active vitamin K decreases, leading to impaired γ-carboxylation of coagulation factors II, VII, IX, and X.
- As a result, the liver produces clotting factors with reduced biological activity, leading to an anticoagulant effect.



Coumarin Anticoagulants

- Warfarin: The most commonly used coumarin anticoagulant. It exists as two enantiomers, R-warfarin and S-warfarin.
- Acenocoumarol: Another coumarin anticoagulant that acts through inhibition of vitamin K epoxide reductase.

Summary of the Mechanism

Warfarin → Inhibition of VKORC1 → Decreased reduced vitamin K → Decreased γ-carboxylation → Decreased functional clotting factors (II, VII, IX, X) → Anticoagulation.

Warfarin

- Warfarin does not produce an immediate effect, unlike heparin and cant be used instead of heparin.
- **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 (hours)

Clotting Factor	
II	72
VII	6
IX	24
X	40
Protein C	8
Protein S	30

Four half-lives are needed for a factor to become almost completely inactive.

- Factor II: 72 × 4= 288 hours= 12 days
- Factor IX: 24 × 4 = 96 hours = 4 days.
- Factor VII: 6 × 4= 24 hour= 1 day
- Protein C has a shorter half-life than Protein S, not that important because it works as Co-factor for protein C WITHOUT protein C there won't be anticoagulant effect .
- Protein C disappears earlier than Protein S.

Warfarin

- **Because of its narrow therapeutic index (the difference between thearapuetic dose and toxic does is narrow), predisposition to drug and food interactions, and exacerbation of bleeding, warfarin requires continuous patient monitoring and education to achieve optimal outcomes.**

Narrow therapeutic index
Toxic dose is close to the therapeutic dose.
Therapeutic Index = TD50 / ED50.
TD50: Toxic dose for 50% of individuals.
ED50: Therapeutic dose for 50% of individuals.
Ratio less than 4 indicates a narrow therapeutic index any small mistake it will be toxic.

- Warfarin has tremendous food and drug interactions; these interactions can increase the risk of bleeding or alter warfarin's anticoagulant effect.

PT / INR is used for monitoring.
PT is **affected by the reagents** used in different laboratories.
INR provides a **standardized result.**

Warfarin

Adverse Effects:

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

- **Vitamin K is the antidote, can be given parenteraly or orally** (depending on the severity of bleeding)**; the oral route is preferred in the absence of serious bleeding.**
- **In case of bleeding, warfarin should be temporarily stopped or the dose reduced.**
- You may need clotting factor transfusion in cases of severe bleeding. Plasma-derived clotting factor concentrates are obtained from human donors and may carry a risk of transmitting blood-borne infections, particularly HIV and hepatitis viruses.

2. **"Purple toe**(Fingers and toes contain end arteries. These arteries have limited anastomoses; so if the crystal entered and obstruct the artery there won't be another way)**syndrome" is thought to be the result of cholesterol microembolization into the arterial circulation of the toes.**

Warfarin

3. **Warfarin-induced skin necrosis (due to thrombosis) 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).**

- **Monitored using the International Normalized Ratio (INR), a standardized Prothrombin Time (PT). Target 2-3.**

Warfarin Drug–drug 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)

Increase bleeding

Pharmacokinetics interactions

INR elevators: Most of them inhibit the metabolism of warfarin, increases its half-life and anticoagulant effect.

INR Elevation
Amiodarone
Fluoroquinolones
Trimethoprim/sulfamethoxazole
Metronidazole
Azole antifungals
Statins
Isoniazid
NSAIDs Bleeding; antiplatelets
Sertraline Gemfibrozil
Ethanol
Macrolides
Cimetidine
Omeprazole
Fluorouracil

Statins and gemfibrozil have slight anticoagulant effect

The ones who reduce the INR they accelerate the metabolism of warfarin; associated with a reduced anticoagulant effect.

INR Reduction	
Rifampin	
Barbiturates	
Carbamazepine	
Phenytoin	
St John's wort	herbal product used as alternative medicine for depression
Cigarette smoking	
Charcoal broiled food	الطعام المشوي على الفحم
Cholestyramine (Bile acid binding resins)	
Oral contraceptives (Estrogens)	

Used for hypercholesterolemia they bind warfarin and prevent its action and prevent its absorption

High vit. K containing food

Grilled meat; high incidence of stomach cancer
Smoking leads to Increased incidence of pulmonary-related cancer and urinary bladder cancer.

Open this site or link to see tables for more comprehensive description of drug and food interactions with warfarin, if you like.

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.**
- Genetic mutations may increase, decrease, or have no effect on enzyme activity.
- **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).**

Individualized Drug Therapy and Dose Optimization

Individualized drug therapy, also known as personalized dosing, involves adjusting the drug dose according to individual patient characteristics, particularly variations in drug metabolism and genetic factors (pharmacogenetics).

For example, if the recommended dose of a certain drug is 250–500 mg, this does not mean that 500 mg is necessarily more effective or better than 250 mg. Rather, this range represents the dosing requirements observed across the population during drug development and clinical trials. Some patients respond adequately to 250 mg, others require 500 mg, and some may require an intermediate dose.

Therefore, administering 500 mg to a patient who responds adequately to 250 mg may result in unnecessary drug exposure and an increased risk of toxicity. It may also increase the financial cost of treatment without providing additional therapeutic benefits. Thus, a higher dose does not necessarily mean a better therapeutic outcome.

To facilitate individualized dosing, computer-based dosing programs have been developed. These programs consider several patient-specific characteristics, including:

* Age, height, and body weight, Liver and kidney function, Other medications the patient is taking (potential drug interactions),Genetic variations and mutations affecting the activity of drug-metabolizing enzymes.

Based on these variables, the program estimates the most appropriate dose for each individual patient.

However, the use of such programs does not eliminate the need for clinical monitoring. Continuous monitoring remains essential because the information entered into the program may be inaccurate or incomplete, and errors or unexpected patient responses may occur. Therefore, the recommended dose should always be evaluated alongside the patient's clinical condition and therapeutic response.

Key concept: The goal of individualized dosing is to achieve the optimal therapeutic effect with the lowest appropriate dose while minimizing adverse effects, unnecessary drug exposure, and treatment costs.

Direct Oral Anticoagulants

Oral warfarin alternative.
Direct anticoagulant action, can be used instead of heparin too.

(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.**
- **These drugs are partially eliminated by the kidney to various extent, and should be used with caution in patients with renal dysfunction.**

Direct Oral Anticoagulants

- **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** is drug efflux transporter.

Indications:

1. **The Xa inhibitors rivaroxaban and apixaban can prevent venous thromboembolism (VTE) following hip or knee replacement surgery** patients may remain immobile for a prolonged period, increasing the risk of thrombosis**.**
2. **Dabigatran, rivaroxaban and apixaban can be used for extended VTE treatment after the first 6 months of anticoagulant therapy.**

- Initial treatment: Heparin → Warfarin.
- Heparin and warfarin overlap initially.
- After the first 3–6 months, extended anticoagulant treatment may be continued with these drugs

Direct Oral Anticoagulants

Adverse Effects:

1. **Gastrointestinal complaints; significant, recognized but not serious.**
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(more severe).**

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.**

Management of bleeding:

1. Stop the drug.
2. Activated charcoal.
3. Hemodialysis.
4. Monoclonal antibody.

Management depends on the severity of bleeding.

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

P-gp acts as an efflux transporter, helping drugs escape from cells and preventing foreign substances from entering or accumulating inside them. CYP3A4 is involved in drug metabolism in the intestine. Both P-gp and CYP3A4 act as protective mechanisms against toxins and foreign substances. Inhibitors or inducers of P-gp and CYP3A4 can alter drug concentrations and consequently affect their anticoagulant effects.

Additional Resources:

رسالة من الفريق العلمي:



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			