# WARFARIN

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[Warfarin | Mechanism of Action, Indications, Adverse Reactions, Contraindications]

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## OUTLINE



## I) MECHANISM OF ACTION

### CLOTTING PROTEINS PRODUCTION

- Site: **Hepatocytes**

#### Vitamin K Cycle

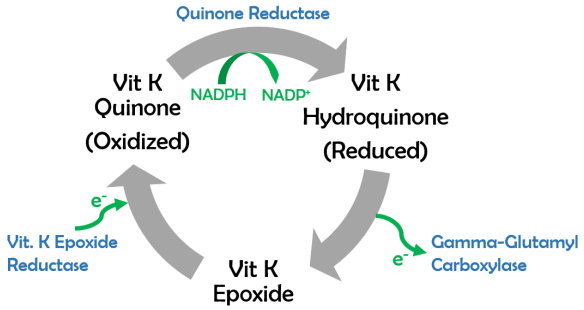


*Figure 1. Vitamin K Cycle*

- **Vitamin K Quinone** (oxidized form) is transformed into **Vitamin K Hydroquinone** (reduced form) via the enzyme **Quinone Reductase** and in the process the coenzyme **NADPH** is oxidized to $NADP^+$
- **Vitamin K Hydroquinone** (reduced) gives the enzyme **Gamma-Glutamyl Carboxylase** (ɣ-GC) electrons, forming **Vitamin K Epoxide** (oxidized)
- The **thiol** group of **Vitamin K Epoxide Reductase** (VKOR) donates electrons to **Vitamin K Epoxide** to convert it back to **Vitamin K Quinone**

#### Functionalization of Clotting Proteins

- **Gamma-Glutamyl Carboxylase** (ɣ-GC) carboxylates clotting proteins to convert them into their functional form
- Clotting Proteins Carboxylated by ɣ-GC
  - **Procoagulants** (Mnemonic- "1972: 9, 10, 7, 2")
    - Factor II
    - Factor VII
    - Factor IX
    - Factor X
  - **Anticoagulants**
    - Protein C
    - Protein S

### WARFARIN MECHANISM OF ACTION

#### Inhibition of Vitamin K Epoxide Reductase

- Warfarin inhibits Vitamin K Epoxide Reductase
  - Vitamin K Epoxide can't get converted into Vit K Quinone → no Vit K Quinone to be reduced into Vit K Hydroquinone → no Vit K Hydroquinone to give $e^-$ to ɣ-GC → ɣ-GC will not be able to carboxylate clotting proteins → non-functional clotting proteins (both procoagulants and anticoagulants)

#### Coagulation Cascade

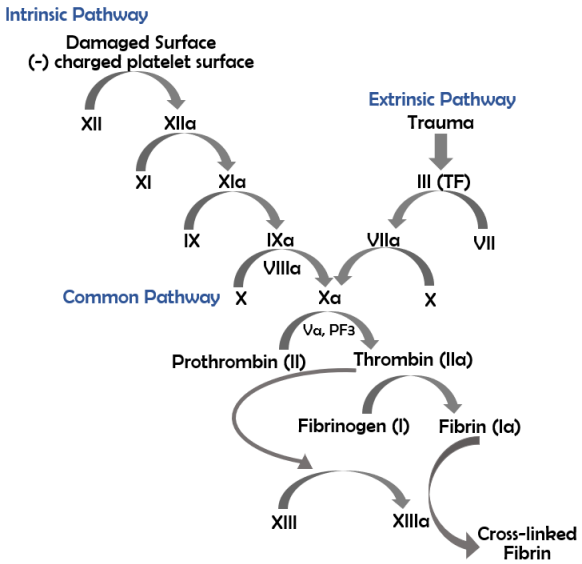


*Figure 2. Coagulation Cascade*

**Intrinsic Pathway**
- Platelet plug forms negatively charged surface on platelet that activates Factor XII into XIIa
- Factor XIIa activates Factor XI into XIa
- Factor XIa activates Factor IX into IXa
- Factor IXa and VIIIa activate Factor X into Xa

**Common Pathway**
- Factor Xa combine with Factor Va and Platelet Factor3 (PF3) to convert Factor II (Prothrombin) into the activated Thrombin (Factor IIa)
- Thrombin activates soluble fibrinogen (Factor I) into the insoluble fibrin (Factor Ia)
- Thrombin also activates Factor XIII into XIIIa that crosslinks fibrin strands producing a stable clot.

**Extrinsic pathway**
- Trauma or injury outside blood vessel releases Tissue Factor or Factor III that activates Factor VII into VIIa.
- Factor VIIa converts Factor X into Xa →→→ common pathway

#### Anticoagulant Action of Warfarin

- Warfarin inhibit production of functional procoagulant clotting factors
  - Inhibition of Factor II → inhibit formation of fibrin and Factor XIIIa that crosslinks fibrin mesh
  - Inhibition of Factor VII → inhibit extrinsic pathway
  - Inhibition of Factor IX → inhibit intrinsic pathway
  - Inhibition of Factor X → inhibit common pathway

#### Procoagulant Effect of Early Dose Warfarin

**Protein C and Protein S**

- Endogenous anticoagulants
- Protein S: cofactor of Protein C
- Normal Physiology:
  - Thrombin binds to Thrombomodulin in the endothelial cells, activating Protein C
  - Activated Protein C inhibits Factor V and VIII → ↓coagulation (anticoagulant)

**Recall:**
- Factor Va is important in activation of Prothrombin to Thrombin
- Factor VIIIa reacts with IXa to activate Factor X

- **First few days of Warfarin** intake: **procoagulant** activity
  - Protein C and S will be the first clotting proteins affected since they have shorter half-lives.
  - ↓protein C and S → ↓inhibition of Factor V and VIII → ↑Factor V and VIII → hypercoagulable state
- **After a few days** of Warfarin: **anticoagulant**
  - hypercoagulable effect of inhibiting protein C and S will be overtaken by the inhibition of procoagulant clotting factors (II, VII, IX, X)
  - by this time, pre-formed procoagulant clotting factors before warfarin intake would have already been excreted

## WARFARIN DRUG INTERACTIONS

### Metabolism of Warfarin

- Catalyzed by **CYP 450 Oxidase** producing its metabolite that will be excreted

### (1) Drugs that INCREASE Warfarin concentration

- Increase risk of bleeding
- **CYP 450 Oxidase INHIBITORS**
  - inhibit Warfarin breakdown (Mnemonic: "O DEVICES")
  - **O**meprazole (Proton Pump Inhibitor)
  - **D**isulfiram (Alcoholism)
  - **E**thanol- acute use
  - **V**alproate (Anti-epileptic, bipolar disorder)
  - **I**soniazid (Anti-TB)
  - **C**iprofloxacin (Antibiotic)/ **C**imetidine (Antihistamine)
  - **E**rythromycin (Macrolide antibiotic)
  - **S**ulfa Drugs

### (2) Drugs that decrease warfarin concentration

- Increase risk for blood clots
- **CYP 450 Oxidase INDUCERS** (Mnemonic: "CP BARS")
  - **C**arbamazepine (Trigeminal neuralgia, Anti-Epileptic)
  - **P**henytoin (Anti-epileptic)
  - **B**arbiturates (Sedative-hypnotic)
  - **A**lcohol- chronic use
  - **R**ifampin (Anti-TB)
  - **S**t. John's Wort

## MONITORING VITAMIN K LEVELS

- MOA of Warfarin involves Vit K Epoxide reductase → affects the Vit K cycle
- Conditions that ↓Vitamin K
  - Celiac disease → damaged small intestine → ↓Vit. K absorption
  - Chronic Pancreatitis → ↓pancreatic enzyme → ↓nutrient absorption
  - Antibiotics → kill bacterial flora that produce Vitamin K and B
- **↓Vitamin K** → ↓Functionalization of Procoagulants → **↑bleeding risk**

**Remember:**
**Warfarin**
- inhibits Vitamin K Epoxide Reductase (VKOR)
- inhibits both procoagulants (Clotting Factor II, VII, IX, X) and anticoagulants (Protein C and S)
- Early dose Warfarin: Procoagulant Effect
- After few days: Anticoagulant
- Monitoring: PT-INR

**Vitamin K Level Monitoring**
- High Vit K: increased risk of clotting
- Low Vit K: increased risk of bleeding

## II) INDICATIONS

### Warfarin

- Route: Oral
- Takes 2-3 days to achieve maximum effect
- Half-life: ≈40 hours
- Prevent clot formation → prevent thromboembolism

### (A) PROPHYLAXIS OF DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE)

- Warfarin
  - chronic prophylaxis treatment for patients that previously had DVT and PE
  - prophylaxis for DVT and PE for patients recovering from a surgery that causes them to be bedridden (i.e., total hip replacement, knee replacement surgery)

**Nice to Know**
- **Acute** DVT and PE Treatment: **Heparin**

### Deep Vein Thrombosis

- blood clot that forms in one or more of the deep veins in the body, usually in the legs

### Pulmonary Embolism

- blood clot from other parts of the body moves through the bloodstream and lodge into the pulmonary arteries, blocking blood flow to lungs
- **Symptoms**
  - Tachypnea
  - Hemoptysis
  - Chest pain
- **Diagnosis**: Helical CT scan

**Virchow's triad**
- factors that increase risk of thrombosis

1) stasis
   - interruption of blood flow
   - Ex: long surgical operations, prolonged immobility
2) hypercoagulable
3) endothelial dysfunction/ injury

### (B) REDUCE INCIDENCE OF EMBOLISM & ISCHEMIC STROKE IN PATIENTS W/ ATRIAL FIBRILLATION

**Atrial Fibrillation**
- Atria do not contract properly → ↓blood flow to ventricles → blood pools up in the atria and stagnate → stasis →clots in the valves
- Acute stressful event can cause the thrombi to break off and go to:
  - Coronary vessels → **Myocardial Infarction**
  - Aorta → Carotid Artery → Brain → **Ischemic Stroke**
  - Aorta → **intestinal vessels**
    - Superior Mesenteric Artery (SMA) → **Mesenteric Ischemia**
    - Inferior Mesenteric Artery (IMA) → **Ischemic colitis**
  - **Kidneys**
  - **Spleen**

### (C) POST-MYOCARDIAL INFARCTION

- Can cause cardiac muscles to be fibrous → ↓contractility (fibrous tissue cannot contract) → blood pool in the area → thrombus (**Left ventricular thrombus**)

### (D) CONGESTIVE HEART FAILURE

- ↓contractility of heart
- ↓Stroke Volume
- ↑End-systolic volume (blood stagnates in the heart)

### Monitoring Warfarin Therapy

**PT/ INR**

- Monitor **Extrinsic Pathway**
- Procedure:
  - Plasma is separated from the patient's blood
  - Tissue Factor (Factor III) is added to patient's plasma
  - Time for blood to clot is measured
- **Prothrombin Time (PT):** Time it takes for blood to clot
- **International Normalized Ratio (INR):** Ratio of Patient's PT to the Control PT
  - $INR = \frac{Patient's\ PT}{Control\ PT}$
  - Different test kits have different control PT

*Table 1. Target INR Base on Indication*

| Indication | Target INR |
|---|---|
| Normal (not on Warfarin) | ≤ 1 |
| Warfarin Therapy | 2-3 |
| Prosthetic heart valve (thrombogenic) | Up to 4 |

- ↑INR (increased risk of bleeding)
  - Too much Warfarin → inhibit Factor VII → inhibit extrinsic pathway → inhibit clotting → ↑PT →↑INR ↑risk of bleeding
- ↓INR (increased risk of clotting)
  - Insufficient Warfarin

## III) ADVERSE DRUG REACTIONS (ADRS)

### (A) BLEEDING

1) Gingival Bleeding
2) Anterior Epistaxis – nosebleed
3) Melena – upper GI bleed – dark or black feces
4) Hematochezia – lower GI bleed – red stool
5) Hematemesis – vomiting blood
6) Bleeding indications on skin
   a. Petechiae – pinpoint hemorrhage on skin
   b. Purpura – larger pinpoint hemorrhaging
   c. Ecchymosis – large bruising
7) Hematuria – blood in urine

#### Monitoring patients

- Look for signs of bleeding (physical exam)
- CBC to check for anemia
- Hemoccult to check for GI bleed

### (B) WARFARIN-INDUCED SKIN NECROSIS

#### Mechanism

- Warfarin (first 2-3days)
  - ↓Protein C and Protein S → ↑Factor Va and VIIIa → ↑Thrombus formation
- Thrombus form in the vessels of skin → ↓blood flow → ischemia → necrotic tissues
- Body parts commonly affected
  - Limbs
  - Breasts
  - Penis

#### Prevention

- Bridging Therapy
  - During first few days of Warfarin initiation, give Heparin with Warfarin to counteract the paradoxical procoagulant effect of early Warfarin doses
  - Heparin
    - Inhibit Factor X and II → inhibit thrombus formation

### Antidote for Warfarin Overdose

1) Slow infusion of Vitamin K
   - Will take a few hours before taking effect
   - Vitamin K will oversaturate VKOR → ↓inhibition of procoagulants
2) Choose between the two:
   a. Prothrombin Complex Concentrate (PCC)
      - Superior
      - Complex of Factor II, VII, IX, X
   b. Fresh Frozen Plasma (FFP)
      - All clotting proteins

## IV) CONTRAINDICATIONS

### (A) LIVER FAILURE

- Liver
  - Main site of production of clotting proteins
  - Liver failure → ↓clotting proteins
  - Warfarin → ↓production of clotting proteins
  - Be cautious in giving Warfarin to patients with liver failure since there is a high risk of bleeding

### (B) PREGNANCY

- Warfarin is Teratogenic

#### (1) Congenital Heart Defects

a. Patent Ductus Arteriosus (PDA)
b. Coarctation of Aorta

#### (2) Central Nervous System Malformations

a. Changes in corpus callosum that connects the two hemispheres of the brain
b. Fluid build-up in subarachnoid space

#### (3) Facial Features / Respiratory Distress

a. Nasal hypoplasia
b. Choanal atresia – narrowing/ block at the back of nasal passage
c. Cleft palate
d. Laryngomalacia

### (C) BLEEDING RISKS

- Actively Bleeding
- ↑BP → Aortic Dissection
- Aortic Aneurysm

## V) REVIEW QUESTIONS

1) **Which of the following increases the risk of bleeding when taken with Warfarin?**
   a. Sulfa Drugs
   b. St. John's Wort
   c. Chronic Alcoholism
   d. Rifampin

2) **What enzyme catalyzes the post-translational modification of clotting proteins to make them functional?**
   a. Quinone Reductase
   b. Vitamin K Epoxide Reductase
   c. Gamma-Glutamyl Carboxylase
   d. CYP450 Oxidase

3) **Which is an endogenous anticoagulant?**
   a. Factor VII
   b. Factor X
   c. Protein C
   d. Factor IX

4) **Which clotting factor converts fibrinogen to fibrin?**
   a. Thrombin
   b. Prothrombin
   c. Factor XIIIa
   d. Factor XIII

5) **Which increases clotting risks?**
   a. High Vitamin K
   b. Low Vitamin K
   c. Liver failure
   d. Taking warfarin with Isoniazid

6) **What is used to treat acute DVT and PE?**
   a. Warfarin
   b. Heparin
   c. Fresh Frozen Plasma
   d. Vitamin K

7) **Contraindications of Warfarin, except:**
   a. Liver Failure
   b. Post-myocardial infarction
   c. Pregnancy
   d. Bleeding

8) **True or False: In the first few days of Warfarin therapy, it produces a procoagulant effect.**
   a. True
   b. False

9) **Which clotting factor/s is/are inhibited by Protein C?**
   a. Va
   b. VIIIa
   c. Thrombin
   d. a & b

10) **What activates Clotting Factor VII?**
   a. Tissue Factor
   b. Factor III
   c. a & b
   d. Factor X

**CHECK YOUR ANSWERS**

## VI) REFERENCES