VITAMIN K ANTAGONIST PHARMACOLOGY, PHARMACOTHERAPY, AND PHARMACOGENOMICS

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PERSONAL DISCLOSURE

Daniel Majerczyk has no relationships with ineligible companies

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LEARNING OBJECTIVES

At the conclusion of this activity, participants will be able to:

- Describe the physiology and pharmacology of vitamin K antagonists
- Identify key indications, contraindications, and adverse effects
- Explain the impact of genetics on warfarin dosing
- Examine anticoagulation needs in atrial fibrillation and valve disorders
- Outline INR goals, monitoring strategies, and patient counseling points

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PHYSIOLOGY OF COAGULATION

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THROMBOSIS → BLOOD CLOT

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Virchow's Triad

HYPERCOAGULABLE STATE
- Malignancy
- Pregnancy
- Hormone (estrogen) therapy
- Sepsis
- Smoking
- Thrombophilias (e.g.: Factor V Leiden, Protein C Deficiency, Lupus, etc.)

VASCULAR WALL INJURY
- Trauma/Surgery
- Venipuncture
- Chemical irritation
- Heart valve disease/replacement
- Atherosclerosis
- Indwelling catheters

CIRCULATORY STASIS
- Atrial Fibrillation
- Left Ventricular Dysfunction
- Immobility/Paralysis
- Venous Insufficiency
- Venous Obstruction

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HEMOSTASIS

- Complex process where multiple components of the coagulation system are activated in result to control bleeding

- Primary hemostasis
- Secondary hemostasis
- Fibrin clot formation and stabilization
- Inhibition of coagulation

Black, et al. 2011.

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COAGULATION CASCADE

"Waterfall" Sequence

or

Enzyme Cascade?

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COAGULATION PHYSIOLOGY

- The process of coagulation is mediated by the presence of tissue factor, negatively charged phospholipid surfaces, and collagen
- Under normal conditions, these compounds are not in contact with blood
- Endothelial damage, exposure to toxins, and inflammation expose these components to intravascular blood flow
- The extrinsic and early intrinsic coagulation pathways begin upon this exposure

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TISSUE FACTOR

- Injury occurs
- Tissue factor (TF) is expressed by damaged endothelium
- TF complexes with circulating activated factor VII (VIIa)
- The extrinsic pathway of the coagulation cascade is catalyzed

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PHOSPHOLIPID SURFACES

- Injury occurs
- Endothelial cells expose negatively charged phospholipid surfaces to blood
- Activated platelet surfaces also expose negatively charged phospholipid surfaces
- Vitamin K dependent clotting factors bind to these surfaces

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COLLAGEN

- Injury occurs
- Collagen is exposed
- Collagen binds von Willebrand factor (VWF)
- Platelets bind VWF via glycoprotein Ia
- Platelets are activated, secrete adenosine diphosphate (ADP) and thromboxane A2 (TXA2), and aggregate

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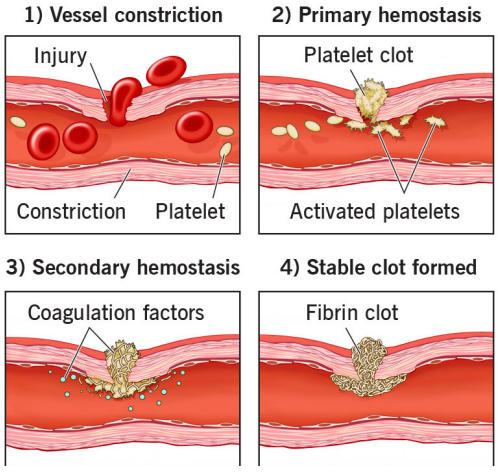

Black, et al. 2011.

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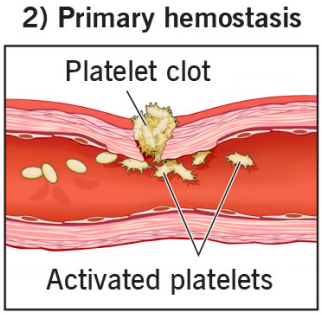
PRIMARY HEMOSTASIS

- Triggered by injury to the vessel wall or other factor
- Formation of a platelet plug
- Results in:
  - Vasoconstriction
  - Adhesion
  - Aggregation



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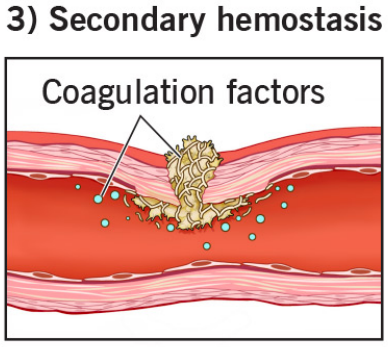
SECONDARY HEMOSTASIS

- Initiation of coagulation
  - ‘The coagulation clotting cascade’
- Reinforces the platelet plug with protein mesh



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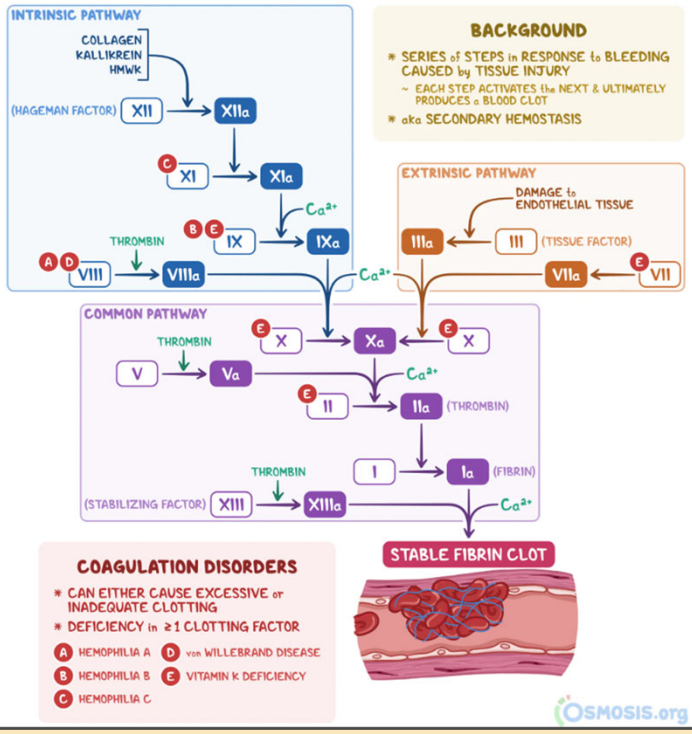
SECONDARY HEOSTASIS



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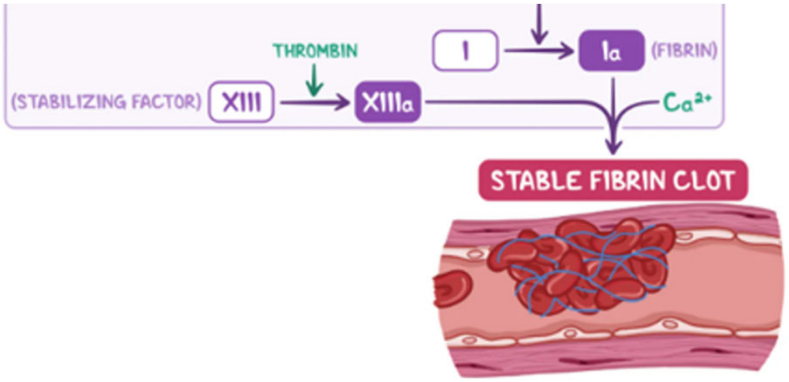
STABLE FIBRIN CLOT

- Primary hemostasis
- Secondary hemostasis
- Fibrin clot formation and stabilization
- Inhibition of coagulation



Tarantino. 2022.

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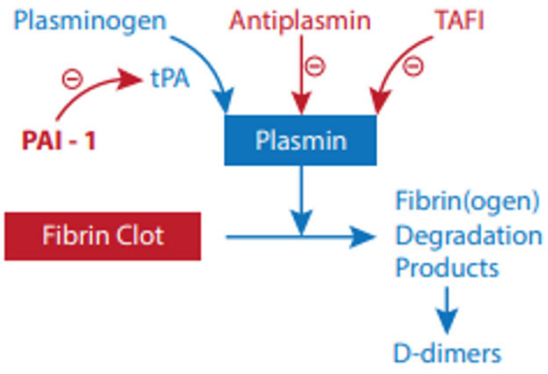
INHIBITION OF COAGULATION

- Inhibition of thrombin generation
  - Thrombin binds to thrombomodulin and activates Protein C
  - Protein C binds with Protein S to slow the coagulation process
  - Thrombin bound thrombomodulin becomes inactive
- Fibrinolysis



Tarantino. 2022.

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KNOWLEDGE CHECK

Which of the following is responsible for initiating the extrinsic pathway of the coagulation cascade?

A. Tissue factor
B. Collagen
C. Negatively charged phospholipid surfaces

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KNOWLEDGE CHECK

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VITAMIN K

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VITAMIN K

- Fat soluble vitamin
- Found in diet and synthesized by bacteria
- Regulates blood coagulation
- Helps convert coagulation factors into mature forms
- Example:
  - Prothrombin (IIa) → Thrombin (II)

Vitamin K hydroquinone

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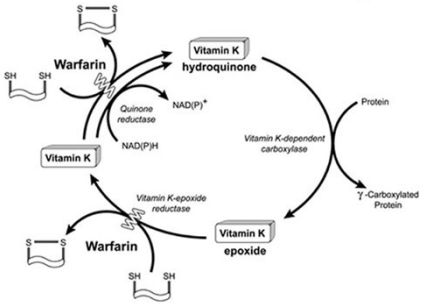
VITAMIN K DEPENDENT CLOTTING FACTOR PHYSIOLOGY

- Clotting factors II, VII, IX, and X and endogenous anticoagulants Protein C and Protein S are synthesized in the liver
- Dietary Vitamin K in quinone form is activated by a quinone reductase to active vitamin K hydroquinone.
- Vitamin K hydroquinone serves as cofactor for carboxylation of clotting factor precursors
  - γ-carboxylation of glutamic acid (glu) residues at N-terminal region of clotting factor precursors and are coverted to γ-carboxyglutamic acid (gla)
- Clotting factors can now complex with negatively charged phospholipid membranes in the presence of calcium



Higdon, et al. 2022.

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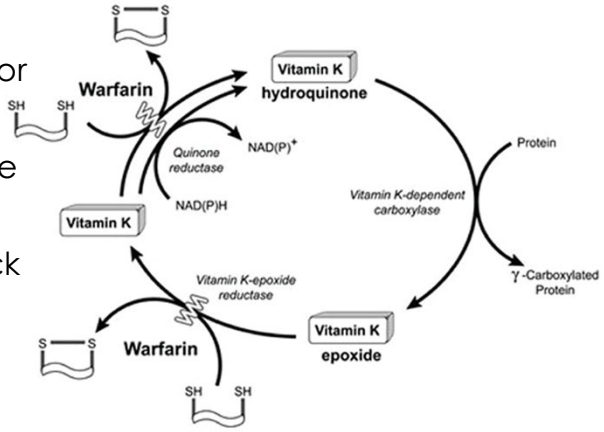
VITAMIN K EPOXIDE REDUCTASE (VKOR)

- Dietary vitamin K must be reduced to hydroquinone form to serve as cofactor for carboxylase
- Vitamin K epoxide reductase (VKOR) is the enzyme "recycles" vitamin K epoxide (a byproduct of gamma carboxylation) back to active vitamin KH2
- Warfarin's mechanism of action targets the VKOR



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KNOWLEDGE CHECK

What is the role of VKOR in the vitamin K cycle?

A. It converts vitamin K epoxide back to its active hydroquinone form
B. It carboxylates clotting factors using vitamin K
C. It enhances calcium binding to clotting factor complexes

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What is the role of VKOR in the vitamin K cycle?

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WARFARIN

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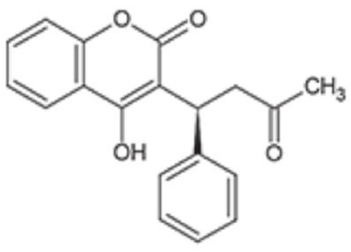
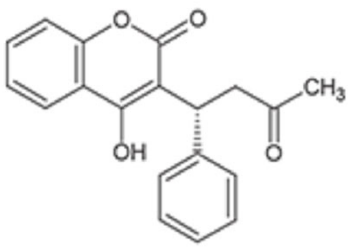
WARFARIN STRUCTURE

- Molecular Formula $C_{19}H_{16}O_4$
- 4-hydroxycoumarin nucleus
- Commercially available as a racemic mixture of optical isomers
- R and S enantiomers have similar mechanisms but different kinetic and dynamic properties



(R)-(+)-Warfarin



(S)-(-)-Warfarin

Higdon, et al. 2022.

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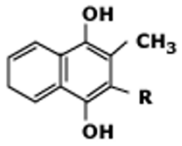
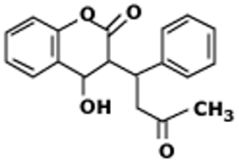
MECHANISM OF ACTION

- Warfarin shares a common ring structure with vitamin K
- Warfarin inhibits VKOR = lower yield of hydroquinone
- With less active cofactor, carboxylation of vitamin K dependent proteins is hindered
- Vitamin K dependent proteins cannot function normally



Vitamin KH2
Hydroquinone form



Warfarin

Higdon, et al. 2022.

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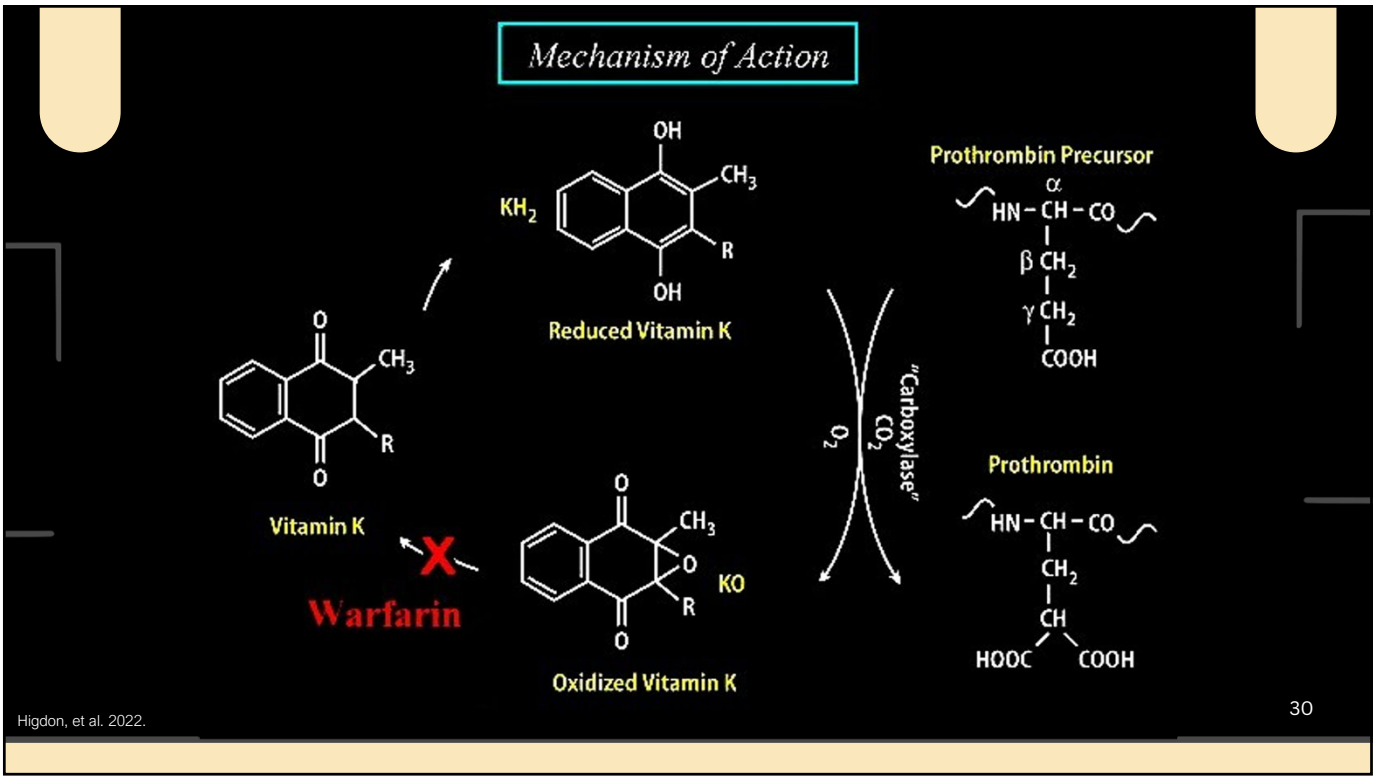

Higdon, et al. 2022.

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PHARMACOKINETICS

- **Absorption**
  - Rapid absorption from GI tract with high bioavailability
  - Highly water soluble
  - Food has no effect on absorption
  - Absorption likely occurs in proximal small bowel

Ansel, et al. 2008.

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PHARMACOKINETICS

- **Distribution**
  - 99% protein bound (mainly albumin)
  - Volume of distribution = 0.11 to 0.2 L/kg
  - Specific disease states (i.e.: cancer, uremia) and use of other highly albumin bound medications (i.e.: phenytoin, ibuprofen) may affect warfarin binding to proteins and alter free fraction of circulating warfarin

Ansel, et al. 2008.

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PHARMACOKINETICS

- **Metabolism**
  - R and S isomers are metabolized by the liver
  - S-warfarin is principally metabolized by CYP2C9 enzyme
  - R-warfarin is principally metabolized by CYP3A4 and CYP1A2 enzyme enzymes
  - Genetic variability in CYP2C9 enzyme may pose additional risk to patients
  - S-warfarin has 2-5 times the anticoagulant activity of its optical isomer, R-warfarin

Ansel, et al. 2008.

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PHARMACOKINETICS

- **Excretion**
  - Elimination $t_{1/2}$ = 20-60 hours
    - S-warfarin =18-43 hours
    - R-warfarin = 20-89 hours
  - Excreted as inactive metabolites in bile, then urine
  - Excreted as inactive metabolites in breast milk (considered compatible with breast feeding with appropriate monitoring)

Ansel, et al. 2008.

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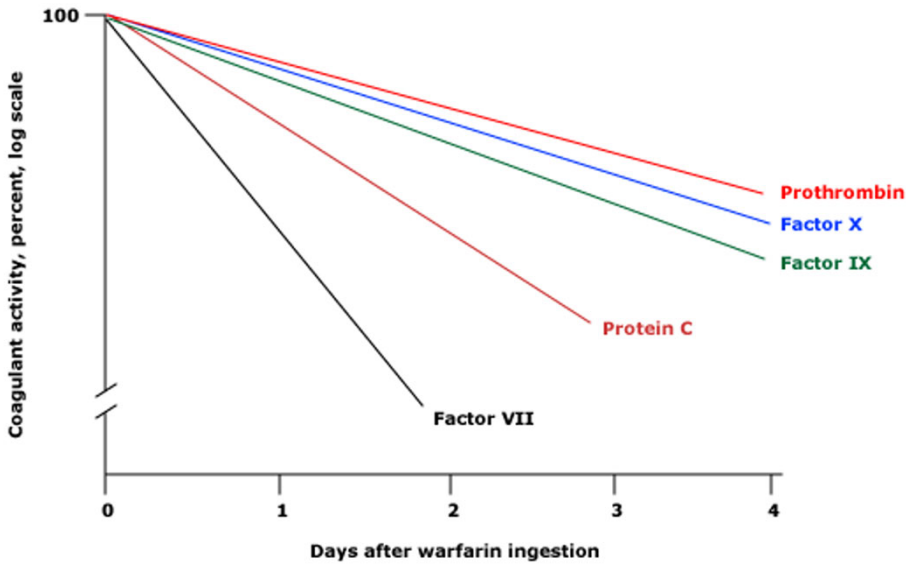
LIFESPAN OF VITAMIN K DEPENDENT PROTEINS



Ansel, et al. 2008.

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LIFESPAN OF VITAMIN K DEPENDENT PROTEINS

- Prothrombin time is most sensitive to factor VII inhibition
- Anticoagulation is not complete until factors IX, X and prothrombin are reduced
- Transient coagulable state occurs when protein C is depleted before clotting factors
- Loading doses of warfarin should never be used

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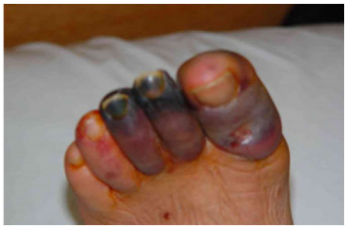
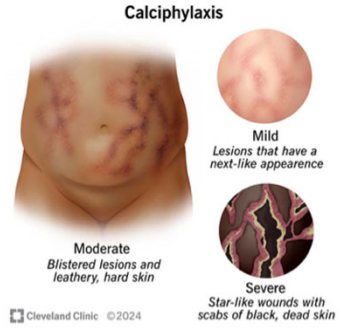
ADVERSE EVENTS OF WARFARIN

- Hemorrhage (e.g., bruising, epistaxis, bleeding gums)
- Hepatitis, elevated LFTs
- GI: Abdominal pain, N/V/D, bloating
- Reduced bone mineral density
  - Mostly seen in younger populations on long-term warfarin therapy
- Serious/rare ADEs: Skin necrosis/gangrene, calciphylaxis, alopecia





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CONTRAINDICATIONS

- Hypersensitivity to warfarin or its components
- Hemorrhagic tendencies
- Pregnancy (except in women w/ mechanical heart valves at high risk for VTE)
- History of falls
- Malignant hypertension
- Major surgery or trauma
- Spinal puncture
- Bacterial endocarditis
- Pericarditis and pericardial effusion
- Blood dyscrasias
- Eclampsia/preeclampsia
- Unreliable, non-adherent patients (i.e.: alcohol abusers, unsupervised/uncooperative patients with dementia or psychosis)

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FDA APPROVED INDICATIONS

- Treatment and/or prophylaxis of pulmonary embolism (PE) and venous thrombosis
- Prophylaxis and/or treatment of thromboembolism associated with atrial fibrillation and/or cardiac valve replacement
- Reduce risk of death, recurrent myocardial infarction (MI), and thrombotic events such as stroke after MI

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VENOUS THROMBOSIS AND PE

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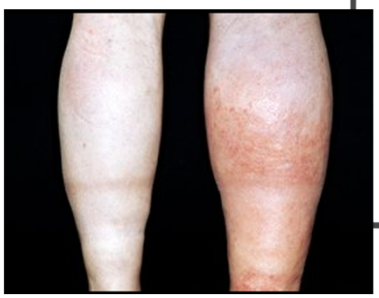
VENOUS THROMBOSIS AND PE

- Treatment
- For patients with DVT and/or PE suggests using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (moderate certainty in the evidence)
- This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency, moderate to severe liver disease, or antiphospholipid syndrome.



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VENOUS THROMBOSIS AND PE

Factor	Recommended Duration	Level of Evidence
Transient/reversible risk factor	3 months	Very low certainty
1st unprovoked/idiopathic	3 months - Indefinite	Moderate certainty
2nd unprovoked/idiopathic	Indefinite	Moderate certainty

The anticoagulation team should periodically reassess the risk/benefit ratio of long-term anticoagulation

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VENOUS THROMBOSIS AND PE

- Intensity of VKA treatment
  - Target INR of 2.5, with range of 2.0 through 3.0
  - For patients who will be treated with a VKA, initiation must be overlapped with UFH or LMWH for a minimum of 5 days and a therapeutic INR is achieved for 24 hours, at which time the heparin is discontinued.

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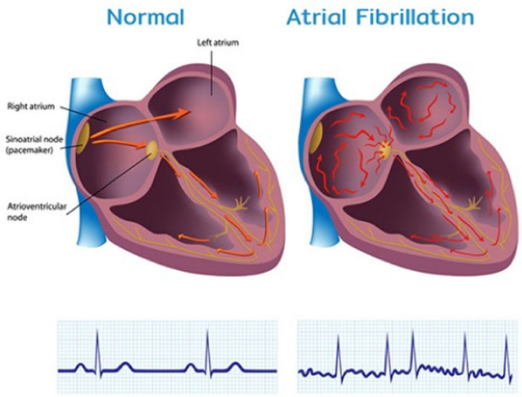
ATRIAL FIBRILLATION



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CHA_2DS_2-VASc RISK STRATIFICATION

CHA2DS2-VASc Risk	Score
CHF or LVEF < 40%	1
Hypertension	1
Age > 75	2
Diabetes	1
Stroke TIA/ Thromboembolism	2
Vascular Disease	1
Age 65-74	1
Female	1

CHA2DS2 -VASc Score	Anticoagulation Recommendation	Level of Evidence
2 men Or > 3 women	Oral anticoagulation	Grade 1A
1 men Or 2 women	Oral anticoagulation may be considered	Grade 2B
0 men Or 1 women	Omit anticoagulation	Grade 2A

CHA2DS2-VASc Score	Adjusted Stroke rate (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

January, et al. 2019.

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ATRIAL FIBRILLATION

- DOACs are recommended over warfarin in DOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (Grade 1A)
- VKA Management:
  - A target INR of 2.5 (range of 2.0 to 3.0) is recommended (Grade 1A)
  - Among patients treated with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable (Grade 1A)

January, et al. 2019.

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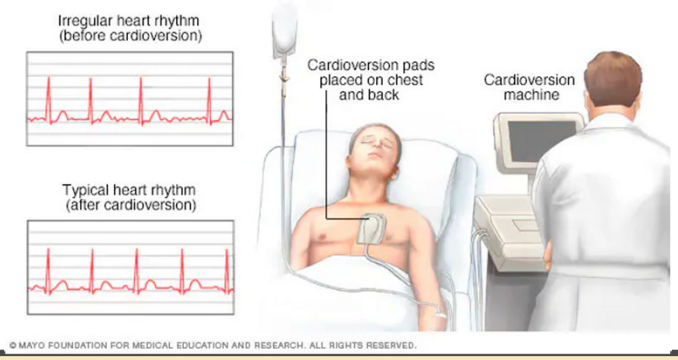
ATRIAL FIBRILLATION

- Special populations: AFib and Cardioversion
  - AFib for ≥ 48 hours or unknown duration: INR 2-3 for 3 weeks prior to procedure and at least 4 weeks after sinus rhythm maintained (Grade 1B)



January, et al. 2019.

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KNOWLEDGE CHECK

Which of the following patients would be an appropriate candidate for warfarin therapy over a direct oral anticoagulant (DOAC)?

A. A 74-year-old male with new-onset atrial fibrillation and no history of valve disease or renal impairment.
B. A 65-year-old female with atrial fibrillation and a mechanical mitral valve.
C. A 58-year-old male with a history of non-valvular atrial fibrillation, normal renal and liver function, and CHA_2DS_2-VASc score of 1.

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Which of the following patients would be an appropriate candidate for warfarin therapy over a direct oral anticoagulant (DOAC)?

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C. A 58-year-old male with a history of non-valvular atrial fibrillation, normal renal and liver function, and CHA_2DS_2-VASc score of 1.

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KNOWLEDGE CHECK

DE is a 60-year-old male with new-onset atrial fibrillation and a history of hypertension, diabetes, hyperlipidemia, and rheumatoid arthritis. Based on CHEST guidelines, what is the recommended duration of warfarin therapy?

A. 3 months to indefinite, CHA_2DS_2-VASc score of 3
B. Indefinite, CHA_2DS_2-VASc score of 4
C. Indefinite, CHA_2DS_2-VASc score of 2

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A. 3 months to indefinite, CHA_2DS_2-VASc score of 3

B. Indefinite, CHA_2DS_2-VASc score of 4

C. Indefinite, CHA_2DS_2-VASc score of 2

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HEART VALVES

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HEART VALVE DISORDERS

- Stenosis: valve narrows → decreased blood flow
- Regurgitation: valve leaks → backflow of blood
- Prolapse: two valve flaps don't close evenly → bulge

Disorder	Treatment Options
Aortic Stenosis	AVR, TAVR, watch & wait
Aortic Regurgitation	AVR, watch & wait
Bicuspid Aortic Valve & Aortopathy	Repair or replacement of aorta
Mitral Stenosis	Percutaneous mitral balloon commissurotomy, MVR or repair, watch & wait
Mitral Regurgitation	MV repair, MVR is failed repair, watch & wait
Tricuspid Valve Disease (stenosis or regurgitation)	TV repair, Percutaneous tricuspid balloon commissurotomy
Pulmonic Valve Disease	Treat elevated pulmonary artery pressure, surgery, watch & wait
Mixed Valve Disease	Focus on predominant valve lesion
Infective Endocarditis	Antibiotic therapy

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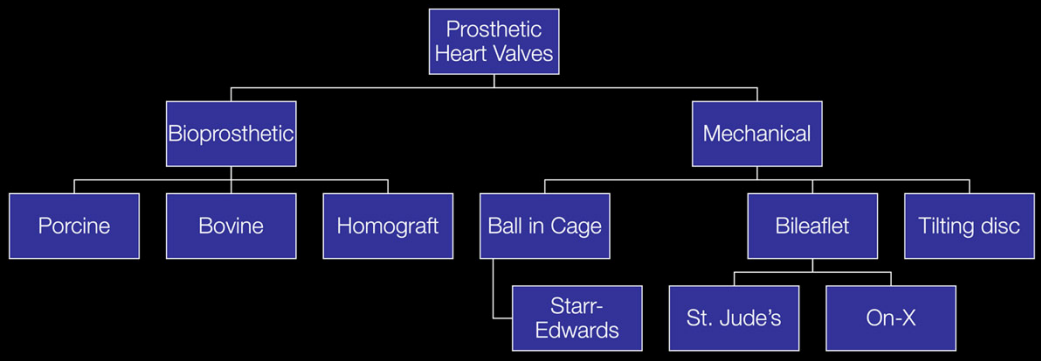
HEART VALVES



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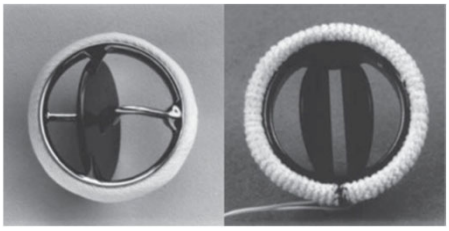
MECHANICAL VALVE

Advantages	Disadvantages
Greater durability (20-30 years)	High sheer stresses
	Higher platelet activation and thrombosis risk
Lower reoperation rate	Lifelong anticoagulation
	Bleeding risk

Tissue valve



Mechanical valve

Tillquist M, et al. 2011.

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BIOPROSTHETIC VALVE

Advantages	Disadvantages
No lifelong anticoagulation	Less durable
Lower thrombotic risk	Accumulate calcium and lipids on surface
Decreased risk of bleeding	Structural valve deterioration (5 years post-op)

Tillquist M, et al. 2011.

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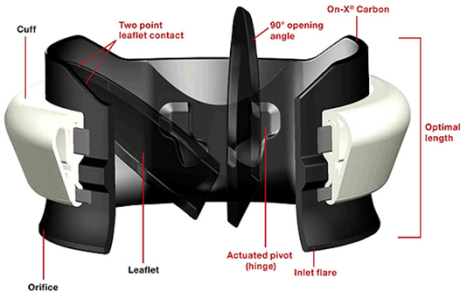
ON-X MECHANICAL VALVE

- Only aortic mechanical valve approved with less warfarin (INR goal 1.5-2)
- >60% reduction in bleeding
- No increase in thromboembolism
- Lower risk of reoperation
- Made from pyrolytic carbon



The unique features of the On-X® Prosthetic Heart Valve are highlighted in red.

Puskas, et al. 2018.

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HEART VALVE INR GOALS

Valve Type	INR Goal	Duration
Mechanical AVR	2.0-3.0*	Lifelong
Mechanical MVR	2.5-3.5	Lifelong
Bioprosthetic AVR/MVR	2.0-3.0	3-6 months
On-X AVR	2.5 (3 months) → 1.5-2.0	Lifelong
TAVR	2.0-3.0	≥ 3 months

*Goal of 2.5-3.5 reasonable with additional risk factors: AF, previous TE, LV dysfunction, hypercoagulable condition, older-gen. (ball-in-cage)

Nishimura RA, et al. 2017.

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KNOWLEDGE CHECK

ML is a 65-year-old female recently diagnosed with a mechanical mitral valve. What is the recommended INR goal and duration of warfarin therapy?

A. INR 2.0–3.0; 3–6 months
B. INR 2.5–3.5; Indefinite therapy
C. INR 1.5–2.0; Indefinite therapy

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KNOWLEDGE CHECK

ML is a 65-year-old female recently diagnosed with a mechanical mitral valve. What is the recommended INR goal and duration of warfarin therapy?

A. INR 2.0–3.0; 3–6 months
B. INR 2.5–3.5; Indefinite therapy
C. INR 1.5–2.0; Indefinite therapy

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WARFARIN DOSING

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INITIAL DOSING

- Doses 5-10 mg are recommended for the 1st 1 or 2 days and then dosed based on INR response (Grade 1B)
- Suggest against the use of pharmacogenetic based initial dosing to individualize warfarin dosing (Grade 2C)
- Recommended starting dose is ≤ 5 mg for specific patient populations (i.e.: elderly, debilitated, malnourished, CHF, liver disease, recent major surgery, on medications like amiodarone, metronidazole, fluconazole, sulfamethoxazole/trimethoprim) (Grade 1C)

Ansel, et al. 2008.

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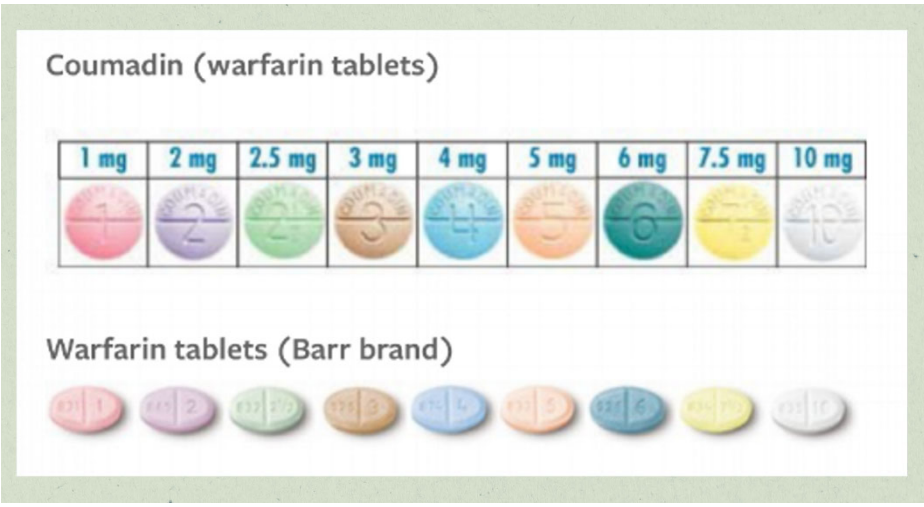
WARFARIN DOSAGE FORMS



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MAINTENANCE DOSING

- Dose adjustments for out of range INR ~5-20% of total weekly dose
- May choose to monitor INR more frequently, rather than change dose if INR slightly out of range
- Suggest monitoring interval of 4 weeks or less (Grade 2C)

Ansel, et al. 2008.

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MAINTENANCE DOSING

- Patient specific factors will influence dosing: medications, OTC and herbal products, dietary vitamin K intake, activity level, alcohol intake, smoking, stress, non-adherence, acute illness, genetic polymorphisms
- Patients with variable INR without known cause for fluctuations may benefit from a trial of daily low dose vitamin K (100 mcg- 200 mcg) with close monitoring of INR (Grade 2B)

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MAINTENANCE DOSING

Assess problems or changes with patient to guide dosing and follow-up:

- Adverse events, specifically bleeding/bruising
- Changes in medications, OTC products, herbals, or diet
- Medication adherence
- Changes in health/acute illnesses

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WARFARIN MONITORING

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INR TESTING

- International Normalized Ratio (INR)
  - Developed to standardize the PT to allow for monitoring of VKA across different labs
- Time in Therapeutic Range (TTR %)
  - The percentage of time the patients INR is in the target range
- Clinic specific procedures are common

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KNOWLEDGE CHECK

Which of the following patient-specific factors is most important to consider when adjusting a warfarin dose?

A. Newly started amiodarone
B. Upcoming dental procedure
C. Dietary sodium intake

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KNOWLEDGE CHECK

Which of the following patient-specific factors is most important to consider when adjusting a warfarin dose?

A. Newly started amiodarone
B. Upcoming dental procedure
C. Dietary sodium intake

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KNOWLEDGE CHECK

AL is a 48-year-old female on warfarin for a mechanical aortic valve. Her INR goal is 2–3, but today's INR is 1.6. She reports no changes to her routine. Her current dosing is 7.5 mg on Mondays and 5 mg on all other days. What is the most appropriate next step?

A. Continue current dosing; no change is needed
B. Increase dose to 7.5 mg on Mondays and Fridays, and 5 mg on all other days
C. Switch to a flat dose of 10 mg daily

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KNOWLEDGE CHECK

AL is a 48-year-old female on warfarin for a mechanical aortic valve. Her INR goal is 2–3, but today's INR is 1.6. She reports no changes to her routine. Her current dosing is 7.5 mg on Mondays and 5 mg on all other days. What is the most appropriate next step?

A. Continue current dosing; no change is needed
B. Increase dose to 7.5 mg on Mondays and Fridays, and 5 mg on all other days
C. Switch to a flat dose of 10 mg daily

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WARFARIN COUNSELING CONSIDERATIONS

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WARFARIN COUNSELING

- Indication and mechanism of action
- Benefits/Importance of medication
- Signs of a blood clot
- Dosing Instructions
- Importance of monitoring INR and patient's INR goal
- Administration instructions
  - Variable dosing
  - Color of tablets
- Missed dose instructions
- Side effects and signs of bleeding
- Instructions for procedures
- Drug & supplement interactions/ Starting new medications
- Food interactions
- Alcohol use
- Tobacco use
- Clinic Contact

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SIGNS AND SYMPTOMS

Thrombosis	Hemorrhage
Pain or swelling in leg or arm	Bleeding from the gums
Skin that is red or warm to the touch	Nosebleed that is not easily stopped
Shortness of breath or difficulty breathing	Blood in stool or urine
Chest pain	Unusual bruising
Unexplained fever	Coughing or vomiting blood
Dizziness, sudden trouble walking, or loss of balance	Cut that does not stop bleeding within 10 minutes
Trouble seeing or a sudden change in vision.	Subconjuctival hemorrhage
Sudden weakness or numbness of the face or drooping to one side	Abnormal back pain
Numbness	Sudden, severe headache
Slurred speech	

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COMMON WARFARIN-DRUG INTERACTIONS

Instruct the patient to contact clinic if they start any new medication including over the counter supplements

Drug	Effect on INR
amiodarone	↑↑
trimethoprim/sulfamethoxazole	↑↑
metronidazole	↑↑
fluconazole	↑↑
levofloxacin	↑
barbiturates	↓
phenytoin	↑
sucralfate	↓
levothyroxine	↑
allopurinol	↑
oral contraceptives	↓

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Very high in vitamin K (more than 800 mcg per serving)

Food	Portion Size
Kale (frozen, cooked, boiled)	1 cup
Spinach (frozen, cooked, boiled)	1 cup
Collards (frozen, cooked, boiled)	1 cup
Turnip greens (frozen, cooked, boiled)	1 cup

High in vitamin K (400 to 800 mcg per serving)

Food	Portion Size
Beet greens	1 cup
Dandelion greens	1 cup
Mustard greens	1 cup

Medium in vitamin K (80 to 400 mcg per serving)

Food	Portion Size
Spinach (raw, leaf)	1 cup
Brussel sprouts	1 cup
Broccoli	1 cup
Onions (springs or scallions, tops and bulb)	1 cup
Lettuce (iceberg)	1 head
Lettuce (green leaf)	1 cup
Cabbage	1 cup
Asparagus	1 cup
Endive	1cup
Parsley	10 sprigs
Okra	1 cup

Tables were adapted from the USDA National Nutrient database for Standard Reference

USDA National Nutrient Database

COMMON WARFARIN-FOOD INTERACTIONS

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REFERENCES

1. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Erratum to: Pharmacology of anticoagulants used in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;42(2):296-311. doi:10.1007/s11239-016-1363-2
2. Black L, Selby R, Brnjac E, et al. "Bloody Easy Coagulation Simplified," Orbcon, 2011.
3. BounameauxH, Perrier A. Duration of anticoagulation therapy for venous thromboembolism. Hematology. Jan 2008;2008: 252-258
4. Coumadin® [package insert]. Princeton, NJ:Bristol-Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(5):629-658. doi:10.1016/j.jacc.2020.09.011
5. Myers Squibb Pharma Company; rev 2009.
6. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S-e184S. doi:10.1378/chest.11-2295
7. Higdon J, Drake V, Delage B, et al. "Vitamin K," Linus Pauling Institute, 2022.
8. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2024 Jan 2;149(1):e167. doi: 10.1161/CIR.0000000000001207] [published correction appears in Circulation. 2024 Feb 27;149(9):e936. doi: 10.1161/CIR.0000000000001218] [published correction appears in Circulation. 2024 Jun 11;149(24):e1413. doi: 10.1161/CIR.0000000000001263]. Circulation. 2024;149(1):e1-e156. doi:10.1161/CIR.0000000000001193
9. LutomskiDM, LaFrance RJ, Bower RH, Fischer JE. Warfarin absorption after massive small bowel resection. Am J Gastroenterol. 1985 Feb;80(2): 99-102.
10. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2021 Feb 2;143(5):e228. doi: 10.1161/CIR.0000000000000960] [published correction appears in Circulation. 2021 Mar 9;143(10):e784. doi: 10.1161/CIR.0000000000000966]. Circulation. 2021;143(5):e35-e71. doi:10.1161/CIR.0000000000000932
11. OrtelTL, Neumann I, Ageno W, et al, American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism." Blood Advances, 2020 (4).
12. Otto C, et al. "2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease." Circulation. 2021;143:e72–e227.
13. Puskas JD, Gerdisch M, Nichols D, et al. Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement. J Am CollCardiol. 2018;71(24):2717-2726
14. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e576S-e600S. doi:10.1378/chest.11-2305
15. Schulman S, Beyth R J, Kearon C, et al, "Hemorrhagic Complications of Anticoagulant and Thrombolytic Treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)." Chest, 2008, 133 (6 Suppl): 257-98.
16. Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. Blood. 2019;133(5):425-435. doi:10.1182/blood-2018-06-820746
17. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e601S-e636S. doi:10.1378/chest.11-2302
18. Tarantino C. "Coagulation Cascade: What Is It, Steps, and More," Osmosis, 2022.
19. Tillquist, M, Maddox TM. Cardiac crossroads: deciding between mechanical or bioprosthetic heart valve replacement. Patient preference and adherence. 2011;5:91.
20. Warfarin. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2010.
21. "Warfarin." In DRUGDEX® System. Intranet database. Version 2.0. Greenwood Village, Colo:Thomson Reuters (Healthcare) Inc.
22. UpToDate. Uptodate.com. Published 2025. Accessed January 24, 2025. https://online.lexi.com/lco/action/doc/warfarin
23. Prescribing information for Warfarin. Warfarin. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf

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VITAMIN K ANTAGONIST PHARMACOLOGY, PHARMACOTHERAPY, AND PHARMACOGENOMICS

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