#### Vitamin K Antagonist Pharmacology, Pharmacotherapy, and Pharmacogenomics

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## Personal Disclosure

• Dr. Lee has no relationships with ineligible companies.

#### Learning Objectives

- At the conclusion of this activity, participants will be able to:
  - Discuss the basic physiology of coagulation
  - Discuss the pharmacology of the vitamin K antagonist
  - Discuss the indications and contraindications for the vitamin K antagonist
  - . Discuss the roles genetics plays in the dosing of warfarin

# Physiology of Coagulation

## Thrombosis -> Blood Clot

#### 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

#### Hemostasis

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



#### Coagulation Cascades

#### "Waterfall" Sequence or Enzyme Cascade?



### Coagulation Physiology

- The process of coagulation is mediated by the presence of <u>tissue factor, negatively charged phospholipid surfaces, and</u> <u>collagen</u>
- 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

#### **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

#### 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

## Collagen

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

#### Hemostasis

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



#### Primary Hemostasis

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

#### Secondary Hemostasis

- Initiation of coagulation
  - · 'The coagulation clotting cascade'
- Reinforces the platelet plug with protein mesh

#### Secondary Hemostasis



#### Stable Fibrin Clot





### 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



#### Knowledge Check

Which of the following is **NOT** a catalyst for the coagulation cascade?

- A. Tissue Factor
- B. Collagen
- C. Negatively charged phospholipid surfaces
- D. Positively charged phospholipid surfaces

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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:



#### 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
  - v-carboxylation of glutamic acid (glu) residues at N-terminal region of clotting factor precursors and are coverted to vcarboxyglutamic acid (gla)
- Clotting factors can now complex with negatively charged phospholipid membranes in the presence of calcium



## 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



The following is true regarding VKOR, except:

- A. It is an enzyme
- B. It is the target of warfarin's mechanism of action
- C. It binds to negatively charged phospholipids in the presence of calcium
- D. It recycles vitamin K epoxide to active vitamin KH2

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# Warfarin

## 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



## 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





- 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

- 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

- 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

- 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)

#### Lifespan of Vitamin K Dependent Proteins



## 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
- Warfarin induced skin necrosis may occur
- Loading doses of warfarin should never be used


#### Contraindications

- Hypersensitivity to warfarin or its components
- Hemorrhagic tendencies
- Pregnancy
- History of falls
- Malignant hypertension
- Major surgery or trauma
- Spinal puncture
- · Bacterial endocarditis
- · Pericarditis and pericardial effusion
- Blood dyscrasias
- Unreliable, non-adherent patients (i.e.: alcohol abusers, unsupervised/uncooperative patients with dementia or psychosis)

#### 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 after MI

#### 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.



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

 Assessing risk/benefit ratio of long term anticoagulation should be periodically reassessed

- 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.

# Atrial Fibrillation

#### CHA<sub>2</sub>DS<sub>2</sub>-VASc Risk Stratification

CHA <sub>2</sub> DS <sub>2</sub> -VASc Risk	Score	0
CHF or LVEF < 40%	1	1
Hypertension	1	2
Age > 75	2	3
Diabetes	1	4
Stroke TIA/	2	5
Thromboembolism		6
Vascular Disease	1	7
Age 65-74	1	8
Female	1	9

CHA <sub>2</sub> DS <sub>2</sub> -V Score	ASc 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

CHA <sub>2</sub> DS <sub>2</sub> -VASc Score	Anticoagulation Recommendation	Level of Evidence
$\geq$ 2 men or $\geq$ 3 women	Oral anticoagulation	Grade 1A
1 men or 2 women	Oral anticoagulation <i>may</i> be considered	Grade 2B
0 men or 1 women	Omit anticoagulation	Grade 2A

#### 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)

#### 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)

### Atrial Fibrillation - Bridging



CrCl = creatinine clearance; DOAC = direct oral anticoagulent; DTl = direct thrombin inhibitor FXa = factor Xa; INR = international normalized ratio; VKA = vitamin K antagonist

Doherty, et al. 2017.

Which if the following is not a contraindication for warfarin therapy?

- A. Pregnancy
- B. Major surgery or trauma
- C. Active bleeding
- D. Spinal puncture
- E. Asymptomatic PE

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DE is a 60 year old male being referred to your anticoagulation clinic with a diagnosis of new onset atrial fibrillation. DE's past medical history is significant for hypertension, hypercholesterolemia, rheumatoid arthritis, and type 2 diabetes mellitus. Based on the CHEST guidelines, what duration of warfarin therapy do you recommend for DE? Why?

- A. 3 months to indefinite, CHADS score of 2
- B. Indefinite, CHADS score of 4
- C. Indefinite, CHADS score of 2
- D. Aspirin therapy preferred over warfarin in this patient
- E. None of the above

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# Heart Valves

#### Heart Valve Disorders

- $_{\circ}$  Stenosis: valve narrows  $\rightarrow$  decreased blood flow
- $_{\circ}$  Regurgitation: valve leaks  $\rightarrow$  backflow of blood
- $_{\circ}$  Prolapse: two valve flaps don't close evenly  $\rightarrow$  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

#### Heart Valves



#### Mechanical Valve

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



#### **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)



#### On-X Mechanical Valve

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



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

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	<u>&gt;</u> 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)

ML is a 65 year old female being referred to your anticoagulation clinic with a s/w new mechanical heart valve in the mitral position. What duration of warfarin therapy and INR goal do you recommend for ML?

- A. 2-3; Indefinite therapy
- B. 2-3; 3-6 months
- C. 2.5-3.5; Indefinite therapy
- D. 2.5-3.5; 3-6 months
- E. 1.5-2; Indefinite therapy
- F. Warfarin is not recommended

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# Warfarin Dosing

#### 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)

# Warfarin Dosage Forms

- 1 mg
- · 2 mg
- 2.5 mg
- . 3 mg
- 4 mg
- 5 mg
- 6 mg
- 7.5 mg
- 10 mg



#### 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)

#### 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)

#### 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

# Warfarin Monitoring

### 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

When considering warfarin dosage adjustments, which of the following patient specific factors is important to consider?

- A. Dietary vitamin K intake
- B. Upcoming dental procedure
- C. Newly started amiodarone
- D. History of patient non-adherence
- E. All of the above

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AL is a 48 year old female who is on warfarin therapy with an indication of mechanical heart valve in the aortic position. Her INR goal is 2-3. Today AL's INR returned at 1.6. She reports no pertinent findings. The patient take 7.5 mg on Monday and 5 mg on all other days. What are your next steps for this patient?

- A. No Change. Continue current warfarin dosing.
- B. Instruct the patient to take warfarin 5 mg daily
- C. Instruct the patient to take warfarin 7.5 mg on M/F and 5 mg on all other days
- D. Instruct the patient to take warfarin 10 mg daily
- E. Contact the clinician. The patient's INR goal is incorrect

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Warfarin Counseling Considerations

# 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

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Clinic Contact

## 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	

## Common Warfarin-Drug Interactions

Drug	Effect on INR	
amiodarone	$\uparrow \uparrow$	
trimethoprim/sulfamethoxazole	$\uparrow \uparrow$	
metronidazole	$\uparrow\uparrow$	
fluconazole	$\uparrow \uparrow$	
levofloxacin	$\checkmark$	
barbiturates	$\rightarrow$	
phenytoin	$\uparrow$	
sucralfate	$\downarrow$	
levothyroxine	$\mathbf{\uparrow}$	
allopurinol	$\checkmark$	
oral contraceptives	$\downarrow$	

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

## Common Warfarin-Food Interactions

### 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 databas



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