Vitamin K Antagonist Pharmacology, Pharmacotherapy, and Pharmacogenomics
Mary Jane E. Mattern, PharmD
Pharmacist
William W. Backus Hospital

Personal Disclosure
- There are no actual or potential conflicts of interest associated with this presentation.

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
- Discuss the utility of how genetic testing will affect initial dosing of warfarin

Virchow's Triad
- HYPERCOAGULABLE STATE
  - Malignancy
  - Pregnancy
  - Hormonal/steroidal Therapy
  - Infection
  - Thrombophilias (e.g., Factor V Leiden, Protein C Deficiency, Lupus, etc.)
- CIRCULATORY STASIS
  - Atrial Fibrillation
  - Left Ventricular Dysfunction
  - Heart valve disease
  - Venous insufficiency
  - Venous obstruction
- VASCULAR WALL INJURY
  - Trauma/Surgery
  - Venipuncture
  - Chemical irritation
  - Heart valve disease
  - Atherosclerosis
  - Indwelling catheter

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

Take a moment to reflect...
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

The Clotting Cascade

Take a moment to reflect...

Which of the following is NOT a catalyst for the coagulation cascade?
- Tissue Factor
- Plasminogen
- Collagen
- Negatively charged phospholipid surfaces

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
Vitamin K Epoxide Reductase (VKOR) enzyme reduces vitamin K in quinone form (vitamin K1) to active vitamin KH2
Vitamin KH2 serves as cofactor for carboxylation of clotting factor precursors
-carboxylation of glutamic acid (glu) residues at N-terminal region of clotting factor precursors yield -carboxyglutamic acid (gla) residues
Clotting factors can now complex with negatively charged phospholipid membranes in the presence of calcium
Vitamin K Epoxide Reductase (VKOR)

Vitamin K1 occurs naturally in quinone oxidized state
Vitamin K1 must be reduced to hydroquinone form (vitamin KH2) to serve as cofactor for carboxylase
Vitamin K epoxide reductase (VKOR) is the enzyme responsible for conversion from the inactive vitamin K1 quinone to the active vitamin KH2
VKOR also “recycles” vitamin K epoxide (a byproduct of gamma carboxylation) back to active vitamin KH2
Warfarin’s mechanism of action targets VKOR

DT-diaphorase

An NAD(P)H dehydrogenase
Reduces quinone form of vitamin K1 to vitamin KH2
Has no effect on vitamin K epoxide
Likely has little role in vitamin K recycling process
May have a role in vitamin K reversal of warfarin overdose

Take a moment to reflect...

The following is true regarding VKOR, except:

a) It converts vitamin K1 to active vitamin KH2
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

Warfarin Structure

Molecular Formula
C19H16O4
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 are hindered
Glu residues on vitamin K dependent proteins are not as easily carboxylated to gla residues
Vitamin K dependent proteins cannot function normally

Mechanism of Action
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

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

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

Pharmacokinetics

Excretion
Elimination t1/2 = 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

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
Take a moment to reflect...

The following are true regarding warfarin kinetics, except:

a) S-warfarin is metabolized by CYP3A4
b) S-warfarin is up to 5x more potent than R-warfarin
c) Anticoagulation is not achieved until 4-5 days after initiation of warfarin
d) Warfarin is highly protein bound, up to 99%, mostly by albumin

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

CHEST Guidelines Grading System

All recommendations are based on benefit vs. risks

Strength of recommendations based on degree of uncertainty in the balance of benefits and risks

- Grade 1 = “recommended,” confidence that benefits do/don’t outweigh risks
- Grade 2 = “suggested,” less certain of the balance between benefits and risks
- Grade 1 can be applied to most patients, Grade 2 requires more patient-specific decisions

Quality of methodology is based on available trials and design on such trials

- “A” = Highest quality evidence: RCTs begin here, but can be demoted for poor design, poorly conducted, bias, etc.
- “B” = Moderate quality evidence
- “C” = Low quality evidence: Observational studies begin here, but can be upgraded for large treatment effects

Venous Thrombosis and PE

Treatment

Start vitamin K antagonist (VKA) on day 1 + low molecular weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux (Grade 1A)

Discontinue LMWH, UFH, or fondaparinux after at least 5 days of crossover and when INR = 2 or greater for 24 hours (Grade 1C)

Duration of VKA Therapy

- Transient/reversible risk factor = 3 months (Grade 1A)
- 1st unprovoked/idiopathic = 3 months to indefinite (Grades 1C and 1A)
- 2nd unprovoked/idiopathic = Indefinite (Grade 1A)

Assessing risk/benefit ratio of long term anticoagulation should be periodically reassessed (Grade 1C)
**Venous Thrombosis and PE**

**Intensity of VKA treatment**
- Target INR of 2.5, with range of 2.0 through 3.0 (Grade 1A)
- In patients with unprovoked event with strong preference for less frequent INR testing, low intensity therapy with INR range 1.5-1.9 is preferred over stopping treatment (Grade 1A)
- High intensity therapy (INR range of 3.1-4.0) is not recommended over standard intensity therapy (Grade 1C)

**Special populations: DVT/PE and cancer**
- LMWH treatment is recommended for the first for 3-6 months (Grade 1A)
- Anticoagulation with LMWH or VKA is recommended after initial LMWH treatment indefinitely, or until cancer has resolved (Grade 1C)
- Special populations: Asymptomatic PE
  - The same recommendations for anticoagulation for symptomatic PE are followed (Grade 1C)

**Special populations: Lupus Inhibitor**
- In patients with no additional risk factors and no lack of response to therapy a goal INR of 2.5 (range of 2-3) is recommended (Grade 1A)

**Special populations: Warfarin failure**
- In patients who have recurrent thromboembolic events despite a therapeutic INR, a goal INR of 3 (range of 2.5-3.5) is suggested (Grade 2C)

**Atrial Fibrillation**

**Intensity of VKA treatment**
- A target INR of 2.5 (range of 2.0 to 3.0) is recommended (Grade 1A)

**CHADS2 Risk Stratification**
Atrial Fibrillation

Afib and prior ischemic stroke, TIA or systemic embolism = Indefinite (Grade 1A)
Afib and CHADS2 score of 2 or more = Indefinite (Grade 1A)
Afib and CHADS2 score of 1 = Indefinite VKA (Grade 1A) or low dose aspirin (Grade 1B)
Afib and CHADS2 score of 0 = Indefinite low dose aspirin (Grade 1B)

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 1C)

Take a moment to reflect...

Focus on:
- CHADS2 scoring and its effects on treatment options
- Duration and intensity of therapy
- Elective cardioversion

Bioprosthetic Heart Valves

<table>
<thead>
<tr>
<th>Indication</th>
<th>Goal INR Range (+ additional recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioprosthetic valve (mitral position)</td>
<td>INR 2-3 for 3 months, then low dose aspirin if no other VKA indications (Grade 1B)</td>
</tr>
<tr>
<td>Bioprosthetic valve (aortic position)</td>
<td>Low dose aspirin therapy if no other indication for VKA (Grade 1B)</td>
</tr>
<tr>
<td>Bioprosthetic valve + history of systemic embolism</td>
<td>Goal INR range is 2-3 for at least 3 months, then reassess (Grade 1C)</td>
</tr>
</tbody>
</table>

Mechanical Heart Valves

<table>
<thead>
<tr>
<th>Indication</th>
<th>Goal INR Range (+ additional recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tilting disk or bileaflet mechanical valve (mitral position)</td>
<td>2.5-3.5 (Grade 1B)</td>
</tr>
<tr>
<td>Bileaflet mechanical valve (aortic position)</td>
<td>2.0-3.0 (Grade 1B)</td>
</tr>
<tr>
<td>Mechanical heart valve + AFib, anterior aortic (STEMI), left atrial enlargement, low EF, or a hypercoagulable state</td>
<td>2.5-3.5 (Grade 1B)</td>
</tr>
<tr>
<td>Mechanical heart valve + AFib, hypercoagulable state, or low EF with atherosclerotic disease</td>
<td>Add low dose aspirin to long term VKA therapy (Grade 1B)</td>
</tr>
<tr>
<td>Mechanical heart valve + systemic embolism despite therapeutic INR</td>
<td>Add low dose aspirin and/or increase goal INR range (Grade 2C)</td>
</tr>
</tbody>
</table>

Take a moment to reflect...

For which of the following indications for VKA is the recommended intensity goal INR 2.5-3.5?
- a) Bioprosthetic valve in mitral position
- b) Mechanical valve in aortic position
- c) Atrial fibrillation
- d) Mechanical valve in mitral position
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

Take a moment to reflect...

A 55 year old male presents for an initial visit at your clinic. The patient has not yet started warfarin, and needs initial dosing. The patient was recently diagnosed with atrial fibrillation. What questions do you need to ask? What other factors need to be assessed before dosing this patient?
Common Warfarin-Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>amiodarone</td>
<td>↑↑</td>
</tr>
<tr>
<td>trimethoprim/sulfamethoxazole</td>
<td>↑↑</td>
</tr>
<tr>
<td>metronidazole</td>
<td>↑↑</td>
</tr>
<tr>
<td>fluconazole</td>
<td>↑↑</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>↑</td>
</tr>
<tr>
<td>barbiturates</td>
<td>↓</td>
</tr>
<tr>
<td>phenytoin</td>
<td>↑</td>
</tr>
<tr>
<td>sulfadiazine</td>
<td>↑</td>
</tr>
<tr>
<td>allopurinil</td>
<td>↑</td>
</tr>
<tr>
<td>oral contraceptives</td>
<td>↓</td>
</tr>
</tbody>
</table>

The HEMORR2HAGES Bleeding Risk Score

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Major Bleed</td>
<td>2 points</td>
</tr>
<tr>
<td>Hepatic or Renal Disease</td>
<td>1 point</td>
</tr>
<tr>
<td>Alcohol Abuse</td>
<td>1 point</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1 point</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1 point</td>
</tr>
<tr>
<td>Uncontrolled Hypertension</td>
<td>1 point</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 point</td>
</tr>
<tr>
<td>Excessive Fall Risk</td>
<td>1 point</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>1 point</td>
</tr>
<tr>
<td>Reduced Platelet Count or Function</td>
<td>1 point</td>
</tr>
</tbody>
</table>

The HEMORR2HAGES Bleeding Risk Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td>10.4</td>
</tr>
<tr>
<td>≥ 5</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Take a moment to reflect...

Consider the following scenarios, think about how you would handle each situation:

- A patient presents with report of black tarry stools
- A patient presents with new prescription for fluconazole
- A patient presents with an INR of 6.2

Genetic Effects on Dosing Requirements

The hypothesis: Specific genetic variants may result in more adverse bleeding events and incur more cost on the healthcare system
Cytochrome P450 2C9

Genetic polymorphisms in CYP2C9 lead to decreased metabolism of S enantiomer of warfarin and lower dose requirements

Multiple variants of CYP2C9: CYP2C9*2 and CYP2C9*3 most common

Mutation prevalence varies by ethnicities

Frequency of mutation can vary anywhere from 0.5% to 20% of certain populations

This “warfarin sensitivity” often results in initial overdosing of the patient, and possibly a higher risk of bleeding events

Vitamin K Epoxide Reductase Complex 1

VKORC1 is the target of warfarin’s mechanism of action

VKORC1 is also responsible for the recycling and regeneration of vitamin KH2

Mutations in VKORC1 vary by ethnicity

Results in enzymes with varying sensitivities to warfarin

May be cause of “warfarin resistance” in some patients

Genetic Testing: Yes or No?

Anderson et al performed best designed randomized control trial to date

Primary endpoint: Reduction in out of range INRs

Trend of fewer dose changes, fewer out of range INRs, more therapeutic INRs by day 5, and less serious adverse events

None of the outcomes showed a statistical significance

Not designed around primary endpoint of clinical outcomes

Genetic Testing: Yes or No?

Cost effectiveness trial by Eckman et al

Better outcomes, but at high cost of $170,000 per QALY

For cost effectiveness, <$50,000 per QALY is needed

Very stringent criteria for testing and/or very “optimistic” changes (cost <$200, 24 hour results, reduce major bleeding by at least 32%) must take place for cost effectiveness

Take a moment to reflect...

Based on this information, at this point in time, would you use pharmacogenetic testing to guide warfarin dosing? Why or why not?

Genetic Testing: Yes or No?

ACCP guidelines: “At the present time, for patients beginning VKA therapy without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing.” (Grade 2C)

The future: NIH/NHLBI trial data to come

Cost, bleeding events, and thromboembolic events all are included in outcomes

Hopefully, these results will answer more questions in this debate
References


UpToDate. Warfarin. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2010.
