Warfarin: A Comprehensive Review

Jay M Patel, PharmD
Objectives

• Explain the important pharmacodynamic and pharmacokinetic properties of warfarin
• Describe the role of warfarin in the inpatient setting
• Identify factors that may contribute to variability in the INR with warfarin use
• Discuss warfarin initiation and dose adjustments based on a comprehensive review of the patient
Disclaimer

Dr. Patel has no actual or potential conflict of interest associated with this presentation
Coumadin® (Warfarin)

• Clinical Pharmacology
  – Inhibit synthesis of Vitamin K dependent clotting factors
    • II, VII, IX and X
    • Protein C and S

• Mechanism of Action
  – “Vitamin K antagonist” (VKA)
  – Inhibit C1 subunit of vitamin K epoxide reductase (VKORC1) enzyme complex
**Coumadin® (Warfarin)**

- Elimination half-lives of vitamin K-dependent proteins

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>42-72 hours</td>
</tr>
<tr>
<td>VII</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>IX</td>
<td>21-30 hours</td>
</tr>
<tr>
<td>X</td>
<td>27-48 hours</td>
</tr>
<tr>
<td>Protein C</td>
<td>8 hours</td>
</tr>
<tr>
<td>Protein S</td>
<td>60 hours</td>
</tr>
</tbody>
</table>
How Warfarin Affects Blood Clotting

Vitamin K, produced by the body, helps form blood-clotting proteins

Blood-clotting proteins hold blood cells together to form clots

Warfarin reduces the body’s ability to make Vitamin K which interferes with protein creation

Lower levels of clotting protein makes blood cells less likely to clot

Date Accessed May 14, 2015.
Question 1

• Warfarin, through the inhibition of VKOR, inhibits the production of which factors?
  A. II, VIII, XII, Protein C and Protein S
  B. I, II, III, and X
  C. XI, Protein C and Protein S
  D. II, VII, IX, X, Protein C and Protein S
Pharmacokinetics

• Racemic mixture of R- and S- enantiomers
  – S- 2 to 5 times more anticoagulant activity
• Completely absorbed after oral administration
• Small volume of distribution
  – ~0.14 L/Kg
Pharmacokinetics

• Approximately 99% protein bound
• Extensive hepatic metabolization
  – CYP2C9, 2C19, 2C8, 2C18, 1A2 and 3A4
    • S- enantiomer 2C9
    • R- enantiomer 1A2/3A4
  – Minimally active metabolites excreted mainly in urine and lesser extent in bile
• Singe dose terminal half-life ~ 1 week
• Effective half life 20-60 hours
Question 2

• Which entantiomer is a more potent anticoagulant and is primarily metabolized by CYP2C9?
  A. R-enantiomer
  B. S-enantiomer
## Warfarin Initiation – CHADS2

### Table-2a: CHADS2.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C  Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H  Blood pressure consistently above 140/90mmHg</td>
<td>1</td>
</tr>
<tr>
<td>(or treated hypertension on medication)</td>
<td></td>
</tr>
<tr>
<td>A  Age $\geq 75$ years</td>
<td>1</td>
</tr>
<tr>
<td>D  Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S2 Prior Stroke or Transient Ischaemic Attack or Thromboembolism</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table-2b:

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Risk</th>
<th>Anticoagulation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>None or ASA</td>
</tr>
<tr>
<td>1</td>
<td>Moderate</td>
<td>ASA or warfarin</td>
</tr>
<tr>
<td>2 or more</td>
<td>High</td>
<td>Warfarin with INR 2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASA daily</td>
</tr>
</tbody>
</table>

ASA: Acetylsalicylic Acid or Aspirin.
INR: International Normalised Ratio.
FDA Approved Indications

• Prophylaxis and/or treatment of
  – Venous thrombosis and its extension, and pulmonary embolism
  – Thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement

• Reduce risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolism after MI
Other Uses of Warfarin

• Orthopedic, general or urological surgery
  – Hip or knee arthroplasty
  – Hip fracture surgery
  – Abdominal or pelvic surgery
  – Prevention of transient ischemic attacks
Warfarin Dosing Inpatient

• Initiation overlap for heparin/low molecular weight heparin (LMWH) and VKA

  – Historically
    • Unfractionated heparin (UFH) 5-7 days then co-administer VKA

  – Contemporary practice
    • VKA therapy initiated day 1 or 2 UFH/LMWH
Warfarin Dosing Inpatient

• Initial dose selection
  – Doses should be individualized based on a comprehensive review of the patient
  – General recommendations
    • 5 mg daily for healthy individuals
    • 2.5 mg daily for individuals with concomitant factors
Patient Factors

- Increased age
- Varying size
- Nutritional status
- Drug-drug interactions
- Chronic heart failure
- Elevated baseline INR
- Diarrhea
- Thyroid disorders
- Hepatic/renal dysfunction
- Genomic variants*
  - CYP2C9 (*2 or *3 alleles)
  - VKORC1 polymorphism

*The American College of Chest Physicians recommends against the use of routine pharmacogenomic testing to guide dosing
Question 3

- Which of the following patient factors can influence initial warfarin dosing and INR variability?
  
  A. Age
  B. Diarrhea
  C. Nutritional status
  D. Chronic heart failure exacerbation
  E. All of the above
Target INR

• International normalized ratio (INR)
  – (Patient PT/Mean normal PT)^ISI
  – ISI = International Sensitivity Index
    • Responsiveness of given thromboplastin to reduction of the vitamin K-dependent coagulation factors
    • More responsive agent ➔ low ISI
## Recommended Target INR

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiphospholipid Syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No additional risk factors</td>
<td>2 to 3</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Recurrent events with therapeutic INRs</td>
<td>2.5 to 3.5</td>
<td>Indefinite</td>
</tr>
<tr>
<td><strong>DVT and PE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient/reversible risk factor</td>
<td>2 to 3</td>
<td>3 Months</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>2 to 3</td>
<td>3 Months</td>
</tr>
<tr>
<td>Second episode unprovoked</td>
<td>2 to 3</td>
<td>Long-term</td>
</tr>
<tr>
<td>With active cancer or LMWH for 3-6 months</td>
<td>2 to 3</td>
<td>Indefinite</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With prior CVA or TIA or systemic embolism</td>
<td>2 to 3</td>
<td>Long-term</td>
</tr>
<tr>
<td>With mitral stenosis</td>
<td>2 to 3</td>
<td>Long-term</td>
</tr>
<tr>
<td>Following open heart surgery</td>
<td>2 to 3</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

PPX = prophylaxis; VT = venous thrombosis
# Recommended Target INR

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical Heart Valve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic bileaflet or tilting disk</td>
<td>2 to 3</td>
<td>Long-term</td>
</tr>
<tr>
<td>Mitral bileaflet or tilting disk</td>
<td>2.5 to 3.5</td>
<td>Long-term</td>
</tr>
<tr>
<td>Aortic or mitral caged ball or caged disk</td>
<td>2.5 to 3.5</td>
<td>Long-term</td>
</tr>
<tr>
<td>Any valve with additional risk factor</td>
<td>2.5 to 3.5</td>
<td>Long-term</td>
</tr>
<tr>
<td><strong>Bioprosthetic Heart Valve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>N/A</td>
<td>Aspirin 50-100mg</td>
</tr>
<tr>
<td>Mitral</td>
<td>2 to 3</td>
<td>3 months</td>
</tr>
<tr>
<td>W/ prior history of systemic embolism</td>
<td>2 to 3</td>
<td>3 months</td>
</tr>
<tr>
<td>W/ left atrial thrombus</td>
<td>2 to 3</td>
<td>Until resolves</td>
</tr>
<tr>
<td><strong>Cardioembolic Ischemic Stroke</strong></td>
<td>2 to 3</td>
<td>Long-term</td>
</tr>
</tbody>
</table>
Factors Influencing INR Variability

- Other medications
  - Antibiotics
  - CYP450 inducers/inhibitors
- Diet
- Increased/decreased activity
- Increased/decreased weight
Factors Influencing INR Variability

• Antibiotics
  – Disrupt vitamin K-producing intestinal flora
    • Increased effect of warfarin
• Inhibit metabolism of warfarin
  – Generally within one week
Factors Influencing INR Variability

- CYP450 Inducers
  - Rifampin
  - Phenobarbital
  - Phenytoin
  - Prednisone
  - St. John’s Wort
  - Ritonavir
  - Smoking

- CYP450 Inhibitors
  - Antifungals
  - Macrolides
  - Fluoroquinolones
  - Antiretrovirals
  - Amiodarone
  - Propafenone
  - Isoniazid
  - Fluvastatin
  - Grapefruit
Factors Influencing INR Variability

• Other medications
  – Amiodarone
  – Ascorbic acid
  – Acetaminophen
  – Corticosteroids
  – Sucralfate
  – Statins
Factors Influencing INR Variability

• Foods high in vitamin K
  – Leafy, green vegetables
    • Kale
    • Spinach
    • Brussel sprouts
    • Asparagus
    • Basil

• Malnutrition

• Diet ordered in house
  – NPO
## Dose Adjustments

<table>
<thead>
<tr>
<th>Day</th>
<th>Warfarin Starting Dose (mg)</th>
<th>INR Value</th>
<th>Warfarin Increased Sensitivity Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>&lt; 1.5</td>
<td>2.5 mg</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>&lt; 1.5</td>
<td>2.5 mg</td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>1.5 – 1.9</td>
<td>1 – 1.5 mg</td>
</tr>
<tr>
<td></td>
<td>1 – 2.5 mg</td>
<td>2 – 2.5</td>
<td>0.5 – 1 mg</td>
</tr>
<tr>
<td></td>
<td>0 mg</td>
<td>&gt; 2.5</td>
<td>0 mg</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 – 10 mg</td>
<td>&lt; 1.5</td>
<td>2.5 – 5 mg</td>
</tr>
<tr>
<td></td>
<td>2.5 – 5 mg</td>
<td>1.5 – 1.9</td>
<td>1 – 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>0 – 2.5 mg</td>
<td>2 – 3</td>
<td>0 – 1 mg</td>
</tr>
<tr>
<td></td>
<td>0 mg</td>
<td>&gt; 3</td>
<td>0 mg</td>
</tr>
</tbody>
</table>
## Dose Adjustments

<table>
<thead>
<tr>
<th></th>
<th>Warfarin Starting Dose</th>
<th>INR Value</th>
<th>Warfarin Increased Sensitivity Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>&lt; 1.5</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>5 – 7.5 mg</td>
<td>1.5 – 1.9</td>
<td>3 – 5 mg</td>
</tr>
<tr>
<td></td>
<td>0 – 5 mg</td>
<td>2 – 3</td>
<td>0 – 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>0 mg</td>
<td>&gt; 3</td>
<td>0 mg</td>
</tr>
<tr>
<td><strong>Day 5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>&lt; 1.5</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>7.5 – 10 mg</td>
<td>1.5 – 1.9</td>
<td>3 – 5 mg</td>
</tr>
<tr>
<td></td>
<td>0 – 5 mg</td>
<td>2 – 3</td>
<td>0 – 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>0 mg</td>
<td>&gt; 3</td>
<td>0 mg</td>
</tr>
<tr>
<td><strong>Day 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 – 12.5 mg</td>
<td>&lt; 1.5</td>
<td>3 – 7.5 mg</td>
</tr>
<tr>
<td></td>
<td>5 – 10 mg</td>
<td>1.5 – 1.9</td>
<td>2.5 – 5 mg</td>
</tr>
<tr>
<td></td>
<td>0 – 7.5 mg</td>
<td>2 – 3</td>
<td>0 – 4 mg</td>
</tr>
<tr>
<td></td>
<td>0 mg</td>
<td>&gt; 3</td>
<td>0 mg</td>
</tr>
</tbody>
</table>
Increased Bleeding Risk

- Current antiplatelet therapy
- Elevated PT
  - Normal: 9.4 – 12.5 seconds
- Thrombocytopenia
  - Platelet <75 K/uL
- Significant hepatic disease
  - Cirrhosis or total bilirubin >2.4 mg/dL
- Alcohol abuse history

- End stage renal disease
- GI bleed w/in past 30 days
- Surgery w/in past 2 weeks
- Intracranial bleed w/in past 30 days
- Medications
Signs and Symptoms of Bleeding

- Low hemoglobin/hematocrit
- Blood in urine, stool, or sputum
- Intracranial bleeding
  - Confusion
  - Weakness
  - Loss of vision
- Lightheadedness
- Weakness
- Black, tarry stools
- Bleeding gums
- Severe abdominal pains
Warfarin Reversal

Elevated INR, a, b No Significant Bleeding

INR above therapeutic range but <4.5
- Reduce or skip warfarin dose.
- Monitor INR.
- Resume warfarin when INR therapeutic.
- Dose reduction may not be needed if only slightly above therapeutic range.

INR 4.5 to 10
- Hold 1 to 2 doses of warfarin.
- Monitor INR.
- Resume warfarin at lower dose when INR therapeutic.
- Vitamin K not routinely recommended if no evidence of bleeding.
- Vitamin K can be used if urgent surgery needed (≤5 mg, with additional 1 to 2 mg in 24 hrs if needed) or bleeding risk is high (1 to 2.5 mg).

INR >10
- Hold warfarin and give vitamin K 2.5 to 5 mg PO, even if not bleeding.
- Monitor INR.
- Resume warfarin at lower dose when INR therapeutic.
- Can give IV formulation of vitamin K orally. Mix with orange juice to improve taste.

Warfarin-Associated Major Bleeding

- PCC suggested over FFP. (FFP disadvantages: slower onset, risks of allergic reaction and infection transmission, longer preparation time, higher volume.)
- Addition of vitamin K 5 to 10 mg by slow IV infusion suggested.

FFP = fresh frozen plasma, PCC = prothrombin complex concentrate concentrate

a, b, 1, 3, 4
Warfarin Reversal

• **Kcentra®** (prothrombin complex concentrate)
  – Factors II, VII, IX, and X
  – Proteins C and S

• Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K Antagonist therapy in adults with:
  – Acute major bleeding
  – Need for an urgent surgery/invasive procedure
**Warfarin Reversal**

- **Kcentra® Dosing**
  - Administer with Vitamin K concurrently

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2 – &lt;4</th>
<th>4 – 6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Dose</em> of Kcentra (Units of Factor IX) / kg body weight</em>*</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td><strong>Maximum dose (units of Factor IX)</strong></td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>

* Dose based on actual potency as stated on the carton
Pharmacy Resources

- American College of Chest Physicians (CHEST Journal)
- Pharmacy.uchc.edu – Inpatient collaborative practice protocol
- Warfarindosing.org
- Global RPh
Conclusion

Initial dose selection
• Target INR
• New start versus continuing maintenance
• Drug, disease, dietary interactions
• Laboratory findings
  – Hepatic/renal function
  – Nutritional status
  – PT/INR
  – Hemoglobin/hematocrit
Case 1

• A 75 year old female patient is being bridged to warfarin therapy following a pulmonary embolism. She has a past medical history of hypothyroidism, type 2 diabetes, and hypertension.

• Her baseline INR is 1.4.

• Her renal and hepatic function are normal.
Case 1

• Home Medication list
  – Lisinopril 5 mg QD
  – Levothyroxine 50 mcg QD
  – Metformin 500mg BID

• Inpatient Medication List
  – Lisinopril 2.5mg QD
  – Insulin sliding scale
Case 1

• What initial dose of warfarin would you recommend for this patient?
  A. 1 mg
  B. 2.5 mg
  C. 5 mg
  D. 7.5 mg
  E. 10 mg
Case 1

• The medical team disagrees with your recommendation and gives the patient a 5 mg dose for 2 days. The INR is found to be 7.9 after the patient received the warfarin 5 mg. The patient has no evidence and is not expressing any symptoms of bleeding.
Case 1

• The medical resident contacts you and asks what the next step should be regarding this patient’s therapy. What would you suggest?

A. Administer 5 mg vitamin K PO
B. Administer 5 mg vitamin K IV
C. Hold warfarin until INR is therapeutic
References

- Wittkowsky, A. Warfarin. *AHFS* 20:12.04