Vitamin K Antagonist Pharmacology, Pharmacotherapy, and Pharmacogenomics

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Personal Disclosure

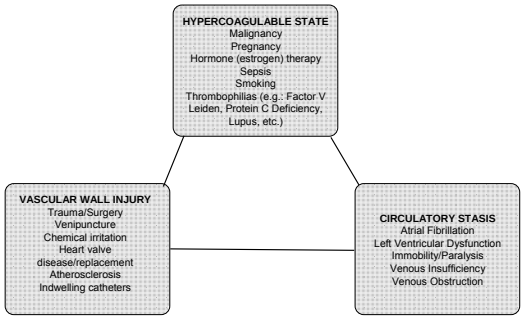
There are no actual or potential conflicts of interest associated with this presentation.

Learning Objectives

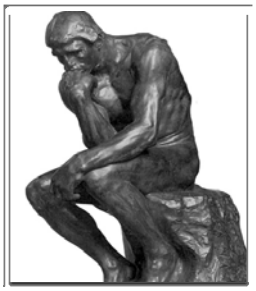
At the conclusion of this activity, participants will be able to:

- 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



Take a moment to reflect...



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

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

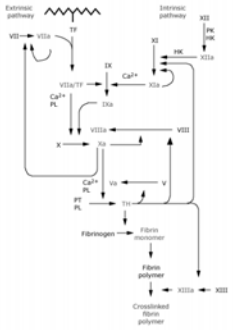
Phospholipid Surfaces

- 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

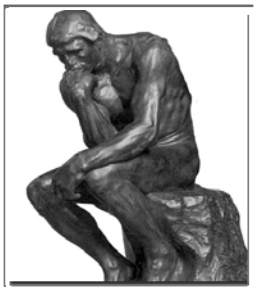
- Injury occurs
- Collagen is exposed
- Collagen binds von Willebrand factor (VWF)
- Platelets bind VWF via glycoprotein Ia
- Platelets are activated, secrete adenosine diphosphate (ADP) and thromboxane A2 (TXA2), and aggregate

The Clotting Cascade



Take a moment to reflect...

- **Which of the following is NOT a catalyst for the coagulation cascade?**
  - a) Tissue Factor
  - b) Plasminogen
  - c) Collagen
  - d) 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)

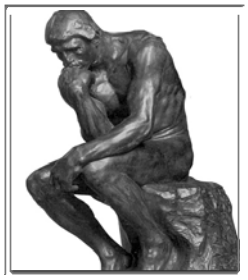
- Vitamin K1 occurs naturally in quinone oxidated state
- Vitamin K1 must be reduced to hydroquinone form (vitamin KH2) to serve as cofactor for carboxylase
- Vitamin K epoxide reductase (VKOR) is the enzyme responsible for conversion from the inactive vitamin K1 quinone to the active vitamin KH2
- VKOR 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

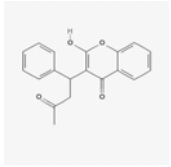
Take a moment to reflect...

- **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



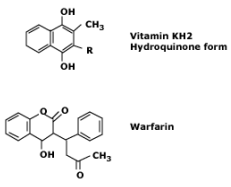
Warfarin Structure

- Molecular Formula $C_{19}H_{16}O_4$
- 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

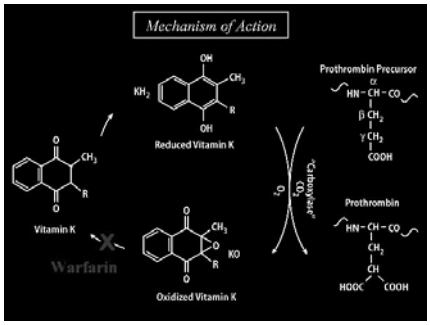


Mechanism of Action

- 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 in 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

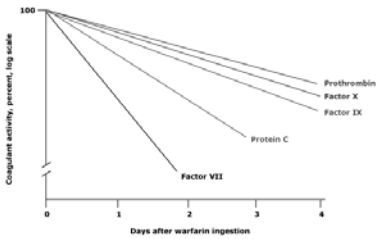
- R and S isomers are metabolized by the liver
- S-warfarin is principally metabolized by CYP2C9 enzyme
- R-warfarin is principally metabolized by CYP3A4 and CYP1A2 enzyme enzymes
- Genetic variability in CYP2C9 enzyme may pose additional risk to patients
- S-warfarin has 2-5 times the anticoagulant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

Pharmacokinetics

Excretion

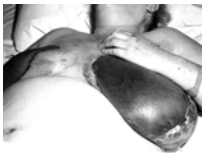
- Elimination $t_{1/2}$ = 20-60 hours
  - S-warfarin =18-43 hours
  - R-warfarin = 20-89 hours
- Excreted as inactive metabolites in bile, then urine
- Excreted as inactive metabolites in breast milk (considered compatible with breast feeding with appropriate monitoring)

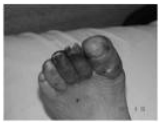
Lifespan of Vitamin K Dependent Proteins



Lifespan of Vitamin K Dependent Proteins

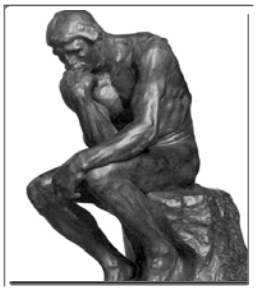
- Prothrombin time is most sensitive to Factor VII inhibition
- Anticoagulation is not complete until factors IX, X and prothrombin are reduced
- Transient coagulable state occurs when protein C is depleted before clotting factors
- Warfarin induced skin necrosis may occur
- Loading doses of warfarin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





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).

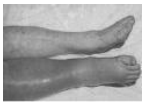
FDA Approved Indications

- 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 benefits vs. risks**
- **Strength of recommendations based on degree of uncertainty in the balance of benefits and risks**
  - Grade 1= "recommended," confidence that benefits do/do not 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)

Venous Thrombosis and PE

- 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)

Venous Thrombosis and PE

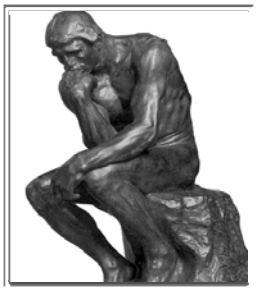
- Special populations: DVT/PE and cancer
  - LMWH treatment is recommended for the first for 3-6 months (Grade 1A)
  - Anticoagulation with LMWH or VKA is recommended after initial LMWH treatment indefinitely, or until cancer has resolved (Grade 1C)
- Special populations: Asymptomatic PE
  - The same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

Venous Thrombosis and PE

- 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)

Take a moment to reflect...

- Focus on:
  - Duration of therapy
  - Target INR range
  - Special populations



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

CHADS2 score, thromboembolic risk, and effect of warfarin in 11,526 patients with nonvalvular atrial fibrillation and no contraindications to warfarin therapy

Clinical parameter	Points
Congestive heart failure (any history)	1
Hypertension (prior history)	1
Age ≥75 years	1
Diabetes mellitus	1
Secondary prevention in patients with a prior ischemic stroke or a transient ischemic attack; most experts also include patients with a systemic embolic event	2

CHADS2 score	Events per 100 person-years*		
	Warfarin	No warfarin	NNT
0	0.25	0.49	417
1	0.72	1.53	125
2	1.27	2.50	81
3	2.20	5.27	33
4	2.35	6.02	27
5 or 6	4.60	6.88	44

NNT, number needed to treat to prevent one stroke per year with warfarin.
* The CHADS2 score estimates the risk of stroke, which is defined as focal neurologic signs or symptoms that persist for more than 24 hours and that cannot be explained by hemorrhage, trauma, or other factors, or peripheral embolization, which is much less common. Transient ischemic attacks are not included. All differences between warfarin and no warfarin groups are statistically significant except for a trend with a CHADS2 score of 0. Patients are considered to be at low risk with a score of 0, at intermediate risk with a score of 1 or 2, and at high risk with a score ≥3. One exception is that most experts would consider patients with a prior ischemic stroke, transient ischemic attack, or systemic embolic event to be at high risk even if they had no other risk factors and therefore a score of 2. However, the great majority of these patients have some other risk factor and a score of at least 3.

Data from Go, AS, Hylek, EM, Chang, Y, et al, JAMA 2003; 290:2685; and CHADS2 score from Gage, BF, Waterman, AD, Shannon, W, JAMA 2001; 285:2864.

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)

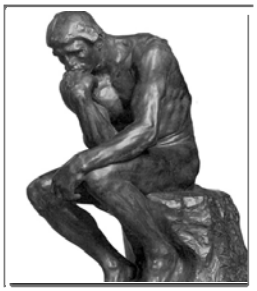
Atrial Fibrillation

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 1C)

Take a moment to reflect...

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



Mechanical Heart Valves

Indication  	**Goal INR Range (+ additional recommendations)**
Tilting disk or bileaflet mechanical valve (mitral position)	2.5-3.5 (Grade 1B)
Bileaflet mechanical valve (aortic position)	2-3 (Grade 1B)
Mechanical heart valve + AFib, anterior apical STEMI, left atrial enlargement, low EF, or a hypercoagulable state	2.5-3.5 (Grade 1B)
Mechanical heart valve + Afib, hypercoagulable state, or low EF with atherosclerotic disease	Add low dose aspirin to long term VKA therapy (Grade 1B)
Mechanical heart valve with systemic embolism despite therapeutic INR	Add low dose aspirin and/or increase goal INR range (Grade 2C)

Bioprosthetic Heart Valves

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

Take a moment to reflect...

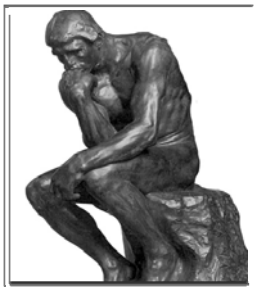
For which of the following indications for VKA is the recommended intensity goal INR 2.5-3.5?

a) Bioprosthetic valve in mitral position

b) Mechanical valve in aortic position

c) Atrial fibrillation

c) 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)

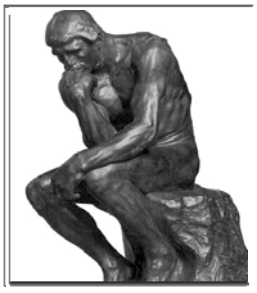
Maintenance Dosing

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

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

The HEMORR2HAGES Bleeding Risk Score

Risk Factors	Score
Prior Major Bleed	2 points
Hepatic or Renal Disease	1 point
Alcohol Abuse	1 point
Malignancy	1 point
Age > 75 years	1 point
Uncontrolled Hypertension	1 point
Anemia	1 point
Excessive Fall Risk	1 point
Prior Stroke	1 point
Reduced Platelet Count or Function	1 point

The HEMORR2HAGES Bleeding Risk Score

Rate of Major Bleeding Per 100 Patient Years

Score	0	1	2	3	4	≥ 5
Rate	1.9	2.5	5.3	8.4	10.4	12.3

Attachment 1

Recommendations for Managing Bleeding or INRs Outside of the Therapeutic Range

Condition	Recommendation
INR below therapeutic range; no signs of thrombosis	Increase dose in increments of 5 to 20% based on the cumulative weekly dose or monitor more frequently; a one-time larger dose may be given followed by more frequent monitoring; if only minimally below therapeutic range, no dose increase may be required
INR above therapeutic range but < 5.0; no significant bleeding	Lower dose in increments of 5 to 20%, based on the cumulative weekly dose or omit dose, monitor more frequently, and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required
INR ≥5.0 but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently and resume at lower dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K1 (1-5 mg orally), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 (2 to 4 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K1 (1 to 2 mg orally) can be given
INR ≥9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K1 (5–10 mg orally) with the expectation that the INR will be reduced substantially in 24–48 h. Monitor more frequently and use additional vitamin K1 if necessary. Resume therapy at lower dose when INR therapeutic
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K1 (10 mg by slow IV infusion), supplemented with fresh plasma or prothrombin complex concentrate, depending on the urgency of the situation; recombinant factor VIIa may be considered as alternative to prothrombin complex concentrate; vitamin K1 can be repeated every 12 h
Life-threatening bleeding	Hold warfarin therapy and give prothrombin complex concentrate supplemented with vitamin K1 (10 mg by slow IV infusion); recombinant factor VIIa may be considered as alternative to prothrombin complex concentrate; repeat if necessary, depending on INR

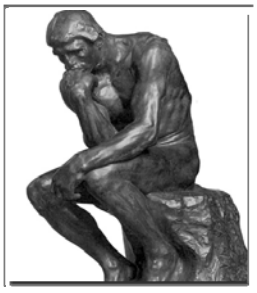
* If continuing warfarin therapy is indicated after high doses of vitamin K1, then heparin or LMWH can be given until the effects of vitamin K1 have been reversed and the patient becomes responsive to warfarin therapy. It should be noted that INR values > 4.5 are less reliable than values in or near the therapeutic range. Thus, these guidelines represent an approximate guide for high INRs.

Adapted from: Ansell J et al. The pharmacology and management of the vitamin k antagonists: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:204-233

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?

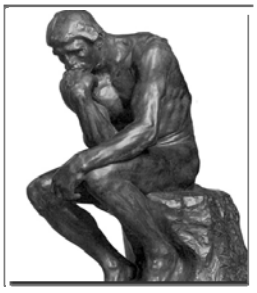
- Anderson et al performed best designed randomized control trial to date
  - Primary endpoint: Reduction in out of range INRs
  - Trend of fewer dose changes, fewer out of range INRs, more therapeutic INRs by day 5, and less serious adverse events
  - None of the outcomes showed a statistical significance
  - 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

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