Assessing the Economics of Genomic Medicine: A Workshop

Institute of Medicine

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Scenario Two

- **Patient is a 40 year old smoker/former smoker found to harbor a prothrombin gene mutation, as well as variations in CYP2C9 and VKORC indicating that she is likely to be “highly sensitive to warfarin” anticoagulation.**

- **She presents with progressive left lower extremity swelling and pain. Evaluation reveals an “unprovoked” deep vein thrombosis in her left lower extremity.**

- **She will be managed as an outpatient with low molecular weight heparin and warfarin. Targeted testing includes CYP2C9 and VKORC gene analysis.**

“Unprovoked DVT” in a 40 year old woman

- ***DVT Provocations***
  - Smoking
  - Pregnancy
  - OBC
  - Immobility
  - long travel
  - Surgery
  - Obesity
  - HTN
  - Cancer
  - Age

- ***“Genetic Provocations”?***
  - Prothrombin mutation (G20210A)
  - Factor 5 Lieden
  - others

Risks for DVT over the Lifetime

GENETICS AND GENOMICS

- **Prothrombin 3X**
- **Factor V L 3-8X**
- **Anticoagulant deficiencies**
  - **Protein S 10X**
  - **Protein C 10X**
  - **Antithrombin 20X RR**

Environmental Triggers

- **Estrogens**
- **Pregnancy**
- **Surgery**
- **Immobilization**

ACQUIRED RISKS

- **Age**
- **Obesity**

Warfarin

Warfarin Mechanism of Action

- **Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide.**

- **Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.**

FDA Label - Coumadin

Warfarin Mechanism of Action

- **An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours.**
- **The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of COUMADIN may become more pronounced as effects of daily maintenance doses overlap.**
- **Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.**

FDA Label - Coumadin

Pharmacogenomics of Warfarin

- A meta-analysis of 9 qualified studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in warfarin-treated patients.
- In this meta-analysis, 3 studies assessed bleeding risks and 8 studies assessed daily dose requirements. The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles. Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele. For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele.
- In an observational study, the risk of achieving INR >3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype. The relative risk of overanticoagulation as measured by INR >3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who were homozygous for the *1 allele.

FDA Label - Coumadin

Pharmacogenomics of Warfarin

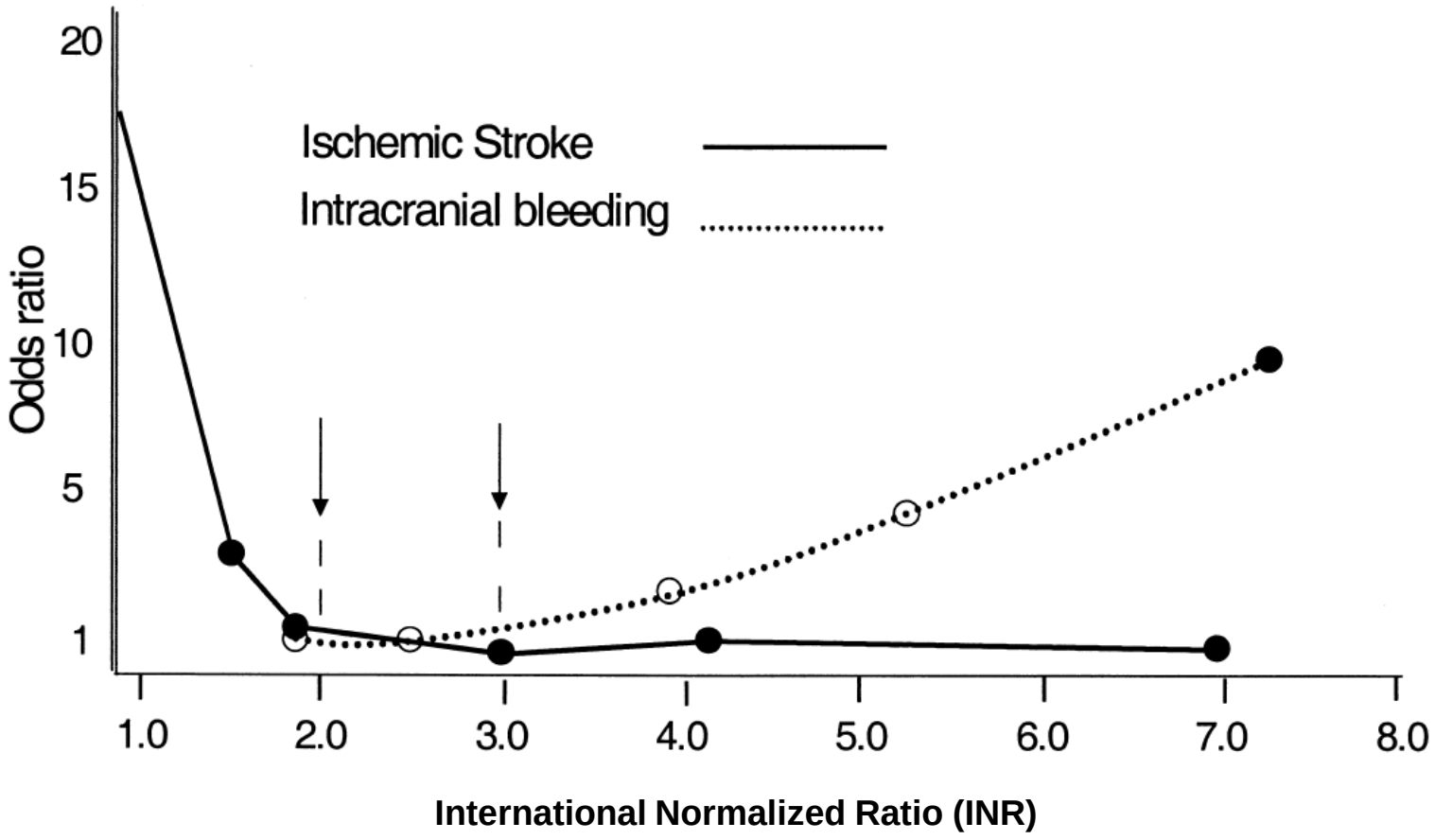
- Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle, through inhibition of vitamin K epoxide reductase (VKOR), a multiprotein enzyme complex.
- Certain single nucleotide polymorphisms in the VKORC1 gene (especially the –1639G>A allele) have been associated with lower dose requirements for warfarin. In 201 Caucasian patients treated with stable warfarin doses, genetic variations in the VKORC1 gene were associated with lower warfarin doses.
- In this study, about 30% of the variance in warfarin dose could be attributed to variations in the VKORC1 gene alone; about 40% of the variance in warfarin dose could be attributed to variations in VKORC1 and CYP2C9 genes combined.
- About 55% of the variability in warfarin dose could be explained by the combination of VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients. Similar observations have been reported in Asian patients.

FDA Label - Coumadin

Pharmacogenomics of Warfarin

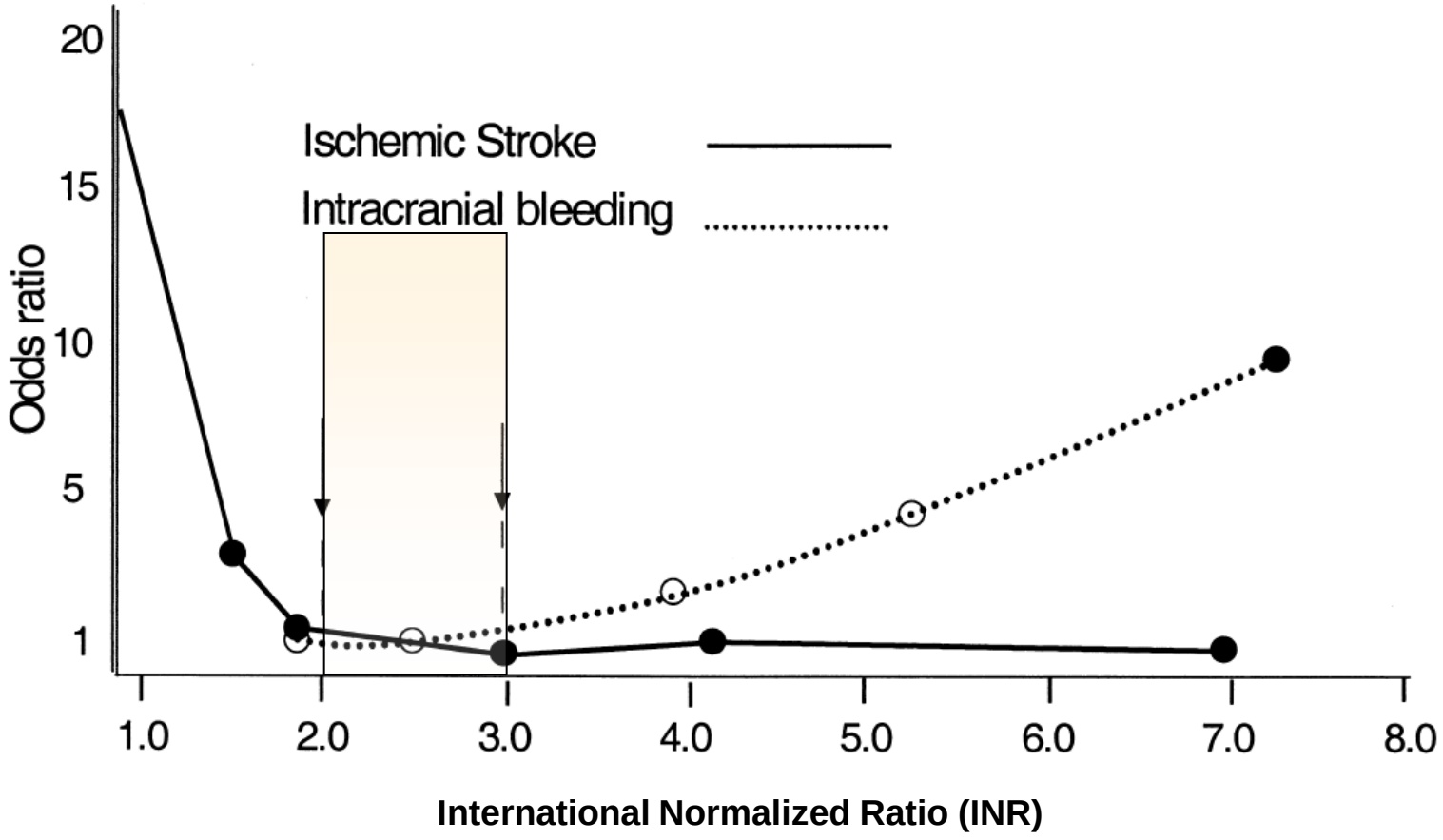
Gene	Variant	Effect	Sensitivity to Warfarin	Dose Recommendation
VKORC1	WT	--	--	--
VKORC1	-1639A	Decreased enzyme	Increased	Decreased
CYPC9	WT	--	--	--
CYP2C9	*2	Slower warfarin metabolism	Increased	Decrease
CYP2C9	*3	Slower warfarin metabolism	Increase	Decrease

Warfarin's Narrow Therapeutic Range



Fuster et al. J Am Coll Cardiol. 2001; 38:1231-1266

Warfarin's Narrow Therapeutic Range



Fuster et al. J Am Coll Cardiol. 2001; 38:1231-1266

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Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

Decision Memo for Pharmacogenomic Testing for Warfarin Response (CAG-00400N)

Decision Summary

CMS believes that the available evidence does not demonstrate that pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries. Therefore, we have determined that pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. However, we do believe the available evidence supports that Coverage with Evidence Development (CED) under §1862(a)(1)(E) of the Social Security Act is appropriate. Thus, we are making the following decision:

Pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who

1. have not been previously tested for *CYP2C9* or *VKORC1* alleles; and
2. have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
3. are enrolled in a prospective, randomized, controlled clinical study when that study meets the following standards:

http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=224&fromdb=true

Warfarin Genotyping Reduces Hospitalization Rates

Table 1 Phenotype Characteristics of Intervention Group Patients

Warfarin Sensitivity	Genotype Combination		Prevalence	Clinical Considerations*
	VKORC1	*CYP2C9*		
Very high	A/A G/A	*1/*3, *2/*2, *2/*3, *3/*3 *3/*3	23 (2.6%)	Dose decrease and frequent INR monitoring
High	A/A G/A G/G	*1/*2 *2/*3 *3/*3	36 (4.0%)	Dose decrease and frequent INR monitoring
Moderate	A/A G/A G/G	*1/*1 *1/*2, *1/*3, *2/*2 *2/*3	238 (26.6%)	Dose decrease and frequent INR monitoring
Mild	G/G	*1/*2, *1/*3, *2/*2	109 (12.2%)	Frequent INR monitoring
Normal	G/A	*1/*1	262 (29.2%)	Likely to experience normal response to warfarin
Less than normal	G/G	*1/*1	228 (25.4%)	Dose increase may be required to maintain optimal INR
Total			896 (100%)	

Values are n (%). Genotype is defined by the combination of measured allelic variations in *CYP2C9* and *VKORC1*. Phenotype is the expected warfarin sensitivity based on genotype. *Complete wording as it appeared in laboratory report is provided in online supplement (Online Table 2).

INR = international normalized ratio.

Interval between initiation of warfarin and genotype results 32 days [range 11-60]

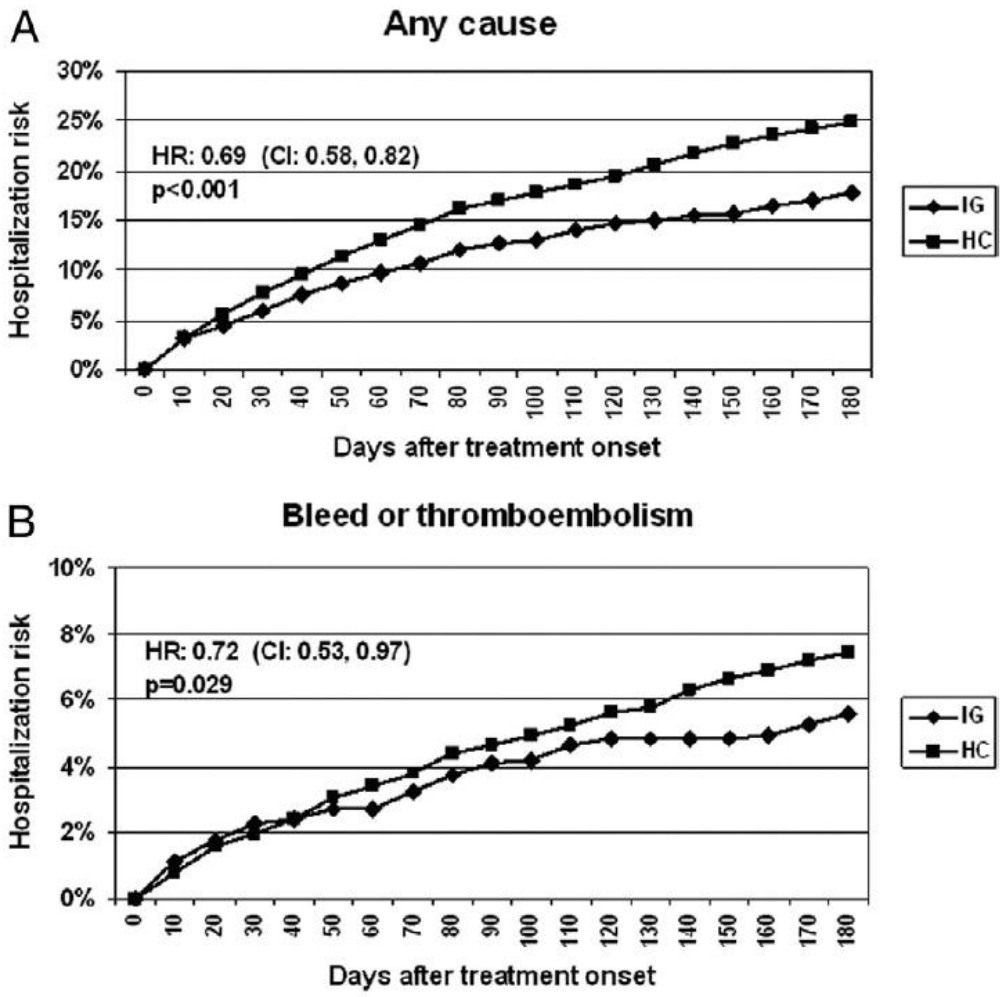
Medco-Mayo Warfarin Effectiveness Study. R.S. Epstein et al. 2010

Warfarin Genotyping Reduces Hospitalization Rates

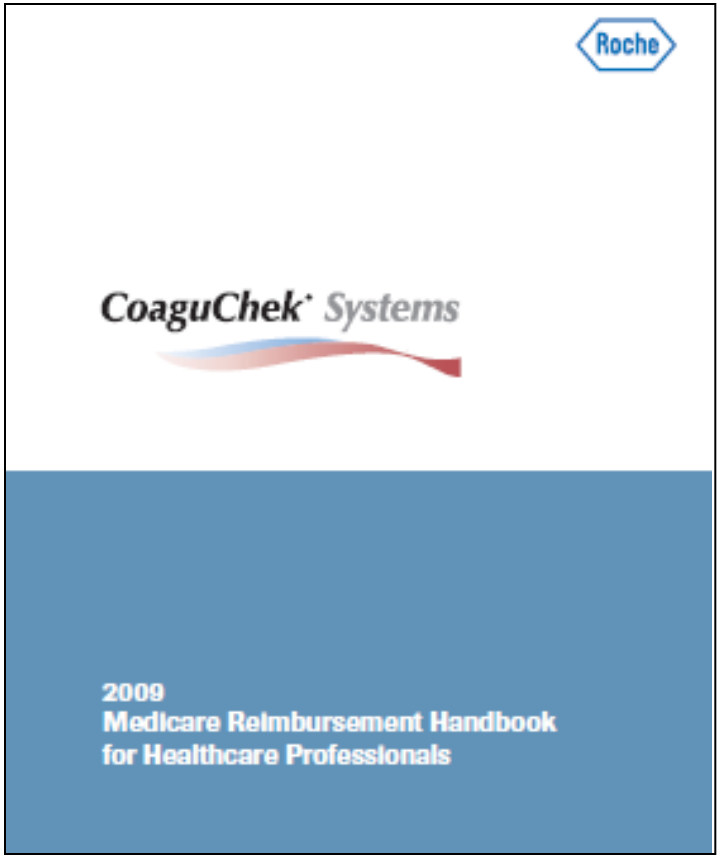
Hawthorne Effect ?

changes in participants' behavior during the course of a study may be "related only to the special social situation and social treatment they received

[source Wikipedia]



The Infrastructure of Warfarin Care



http://www.poc.roche.com/en_US/pdf/44156_Coag2009Handbook_FINAL_APPROVED.pdf

Clarification of Optimal Anticoagulation through Genetics (COAG) trial

- COAG trial is to conduct a 1,238 participant, multicenter, double-blind, randomized trial comparing two approaches to guiding warfarin therapy initiation:
- 1) initiation of warfarin therapy based on algorithms using clinical information and an individual's genotype using genes known to influence warfarin response ("genotype-guided dosing"), and
- 2) initiation of warfarin therapy based on algorithms using only clinical information ("clinical-guided dosing").
- The study hypothesis is that the use of genetic and clinical information for selecting the dose of warfarin during the initial dosing period will lead to improvement in stability of AC relative to a strategy that incorporates only clinical information (without genetics) for initial dosing. Each study arm will include a baseline dose initiation algorithm and a dose revision algorithm applied over the first 4 to 5 doses of warfarin therapy. By comparing the two strategies in this trial, the study will be able to determine if genetic information provides added benefit above and beyond what can be gleaned simply with clinical information. This study is a proof-of-concept efficacy trial. Efficacy is defined as a measure of whether, under optimal application, dosing algorithms will lead to improvement in care.
- The trial will thus answer the question: "can the use of clinical plus genetic information lead to an improvement in anticoagulation control above and beyond the use of only clinical information during the initiation of warfarin, when applied in a uniform and optimal manner to all patients?"
- Because efficacy has not yet been established for genotype-guided dosing of warfarin, it is important to first test whether this approach can, indeed, improve anticoagulation outcomes under controlled conditions.

ClinicalTrials.gov Identifier: NCT00839657

Scenario Two

CLINICAL ASSESSMENT AND PLAN

- **stop smoking**
- **prothrombin gene mutation gives insight into predisposition but does not guide therapy.**
- **variations in CYP2C9 and VKORC lead to lower initial dosing of warfarin, and expectation of lower daily dosing.**
- **duration of warfarin 6+ months**