Regulatory Perspective on Warfarin Relabeling With Genetic Information

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A Bit of Background

The Honorable
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As you may know, we've identified Personalized Health Care as one of the top priorities at HHS. We're making a growing investment in our Department. Personalized health care will increasingly give us the ability to deliver the right treatment to the right patient at the right time – every time.

Personalized Health Care Is More than Pharmacogenetics

"Teaching at the Bedside"

"The good physician treats the disease; the great physician treats the patient who has the disease."

Sir William Osler, M.D.
1849 - 1919

21st century medicine remains both an art and a science although genetics has shifted the ratio

Pharmacogenetics Is a Touchstone to Help Inform Dosing Decisions

- Many patients will share a common illness but not share its medical treatment because of their unique biology

- Important differences in benefit/risk are frequently observed despite patients receiving the same dose of a given drug

- Major role of pharmacogenetics is to predict these differences in advance and allow adjustments of the dose accordingly

This Is Not a New Concept But It Has New Name: Safety Pharmacogenetics

Paracelsus (1493-1542)
Swiss Physician

Poison is in everything, and no thing is without poison.

The dosage makes it either a poison or a remedy.

What Patients Most Want to Know: Will This Drug Hurt Me?

"Most of the patients I have encountered who refuse to take their medicines do so because they are so focused on the side effects."

Dr. Jerome Groopman in *How Doctors Think*

How Can Pharmacogenetics Help With Warfarin?

- Tests such as 2C9 and VKORC1 are *dose predictor tests.*
- They do not predict one's risk of getting a disease
- They do not prevent warfarin from being administered
- They do not cause harm to patients until the drug is administered
- *They are intended to help select the optimal dose and avoid harm to patients*

Congratulations: Anticoagulation Clinics Have Standardized Care and Improved Quality

600 patients receiving warfarin were selected from 3 different anticoagulation clinics and followed for one year.

Patients were within the recommended INR range 62% of the time. 25% of time was below range and 13% were above range.

This study highlights the quality and costs associated with anticoagulation clinic services

Menzin et al, Ann Pharmacother 2005, 39, 446-451

But, There Still Appears to Be Room for Improvement

52 patients attending two anticoagulation clinics were surveyed and INRs were determined from charts.

Only 14% of patients met criteria for good anticoagulation control, i.e., > 70% of INR values between 2-3.

This study suggests that factors such as drug interactions, genetic variability in metabolism or frequent dosing adjustments contributed to poor anticoagulation control.

Davis et al, Ann Pharmacother 2005, 39, 632-636

The Legal Basis of Prescribing Is The Medical Product Label

If evidence is available to support the safety and effectiveness of the drug only in selected <u>subgroups</u> of the larger population with a disease, *the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug.*

- 21 CFR 201.57

General Process of Updating a Label With Genetic Information

- Start with label "claims" – must have evidence
- Decide what section of label to put information
- Construct language that is accurate and precise
- Negotiate internally and with NDA holder

- *D/A section is highly visible vs. clinical pharmacology section*
- *Specific doses are not required vs. lower doses for at-risk patients*
- *FDA-approved tests are not required but are desirable*
- *PGx tests are not mandatory unless co-developed with the drug*
- *Approved tests are required for black box warnings*
- *Cost-benefit analysis does not enter into regulatory label decision*

Relabeling Drugs With PGx Information Is Part of Personalized Health Care Goal

Drug	Enzyme	Goal	Year	Status
6-MP	TPMT	Safety	2003	Complete
Azathioprine	TPMT	Safety	2003	Complete
Irinotecan	UGT	Safety	2004	Complete
Warfarin	2C9 and VKORC1	Safety	2005	Pending
Tamoxifen	2D6	Efficacy	2006	Pending

Inclusion of genetic information in labels endorsed by FDA Advisory Committees comprised of experts in clinical pharmacology, medicine and pharmacogenetics

Interest in Warfarin Driven by Extensive Reports of Safety Issues
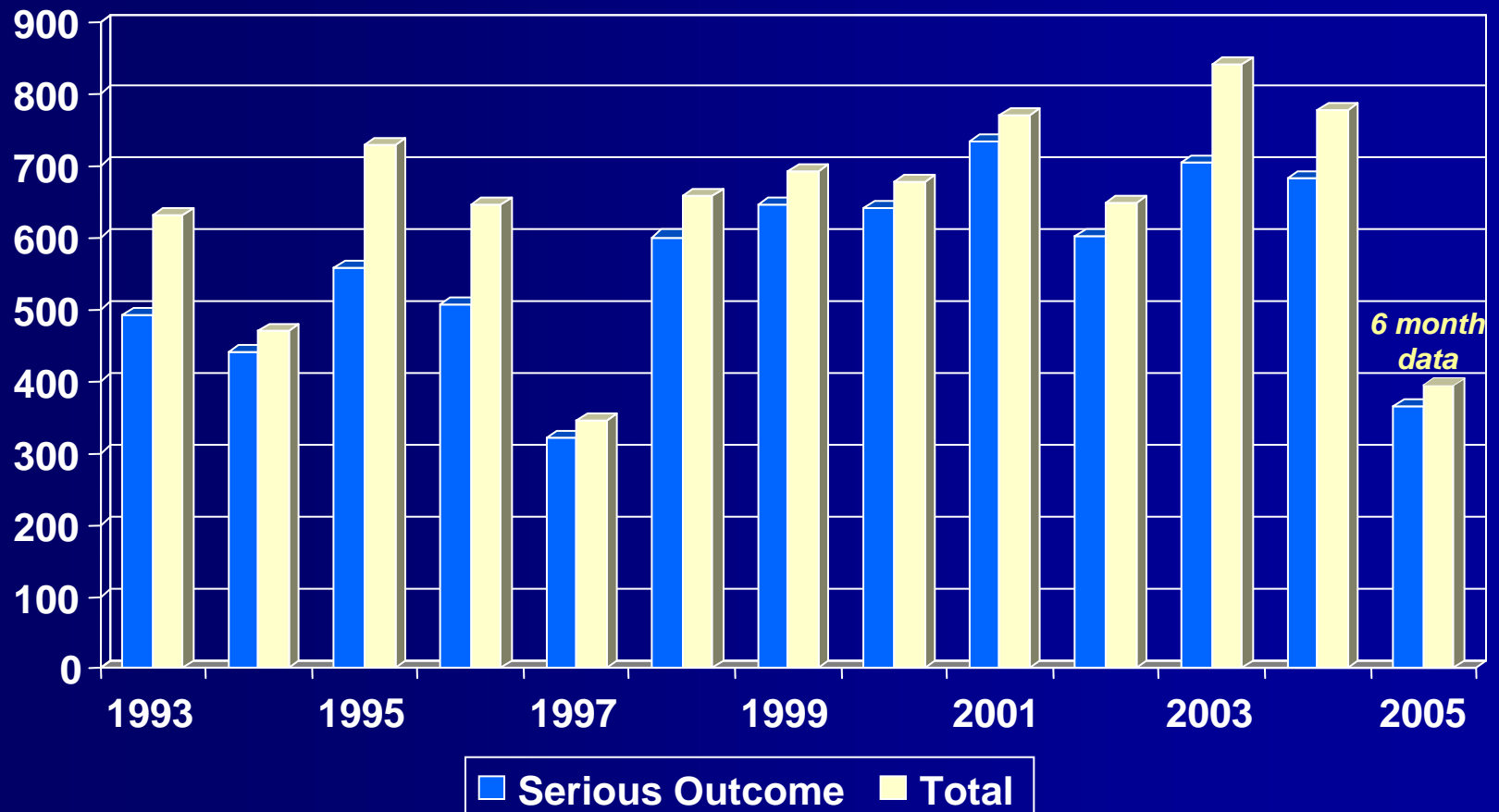
AERS Data from the FDA Division of Drug Risk Evaluation. Note data entry from 1997 is incomplete.

Risks of Warfarin Around The World Confirmed in Scientific Literature

- Over 2,000 bleeding events were reported during a 30 month period (1/1/2003 to 7/1/05)
  - More than 80% (1,749) resulted in hospitalization, disability, life-threatening sequelae and/or death
- Warfarin was ranked in the top ten of all drugs with serious AEs over a 5 year period (2000 to 2005) with more than 6000 reported cases
- Account for 3.6% of all drug-induced AEs and 15.1% of all severe drug-induced AEs

Safety Reports Coupled with Rx Trends Signaled Serious Public Health Issue

Part of the Problem: Warfarin Has Been Dosed by Trial and Error for Over 50 Years

| Initial Dose | → | Estimated Maintenance Dose |

Adjust the initial dose (2-10 mg) based on medical need and *factors we believe will alter the PK or PD of warfarin*

- demographics

- environmental

- drugs

Adjust the maintenance dose by X% up or down based on INR and caution about *factors we believe will alter the PK and PD of warfarin*
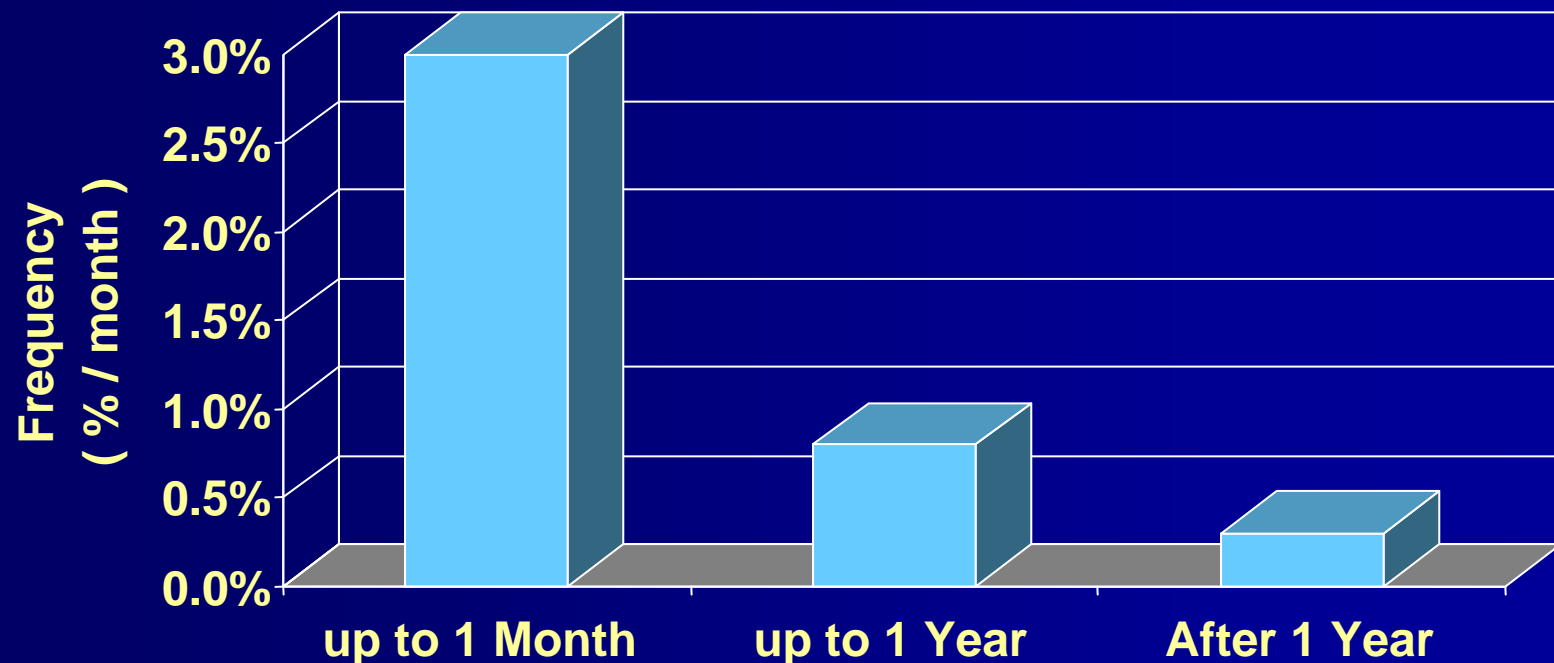
- green leafy vegetables

- cranberry juice

- OTC products

Net Result Is a Wide Range of Individualized Doses by Trial And Error

Reynolds KK et al. Personalized Medicine 2007;4:11-31
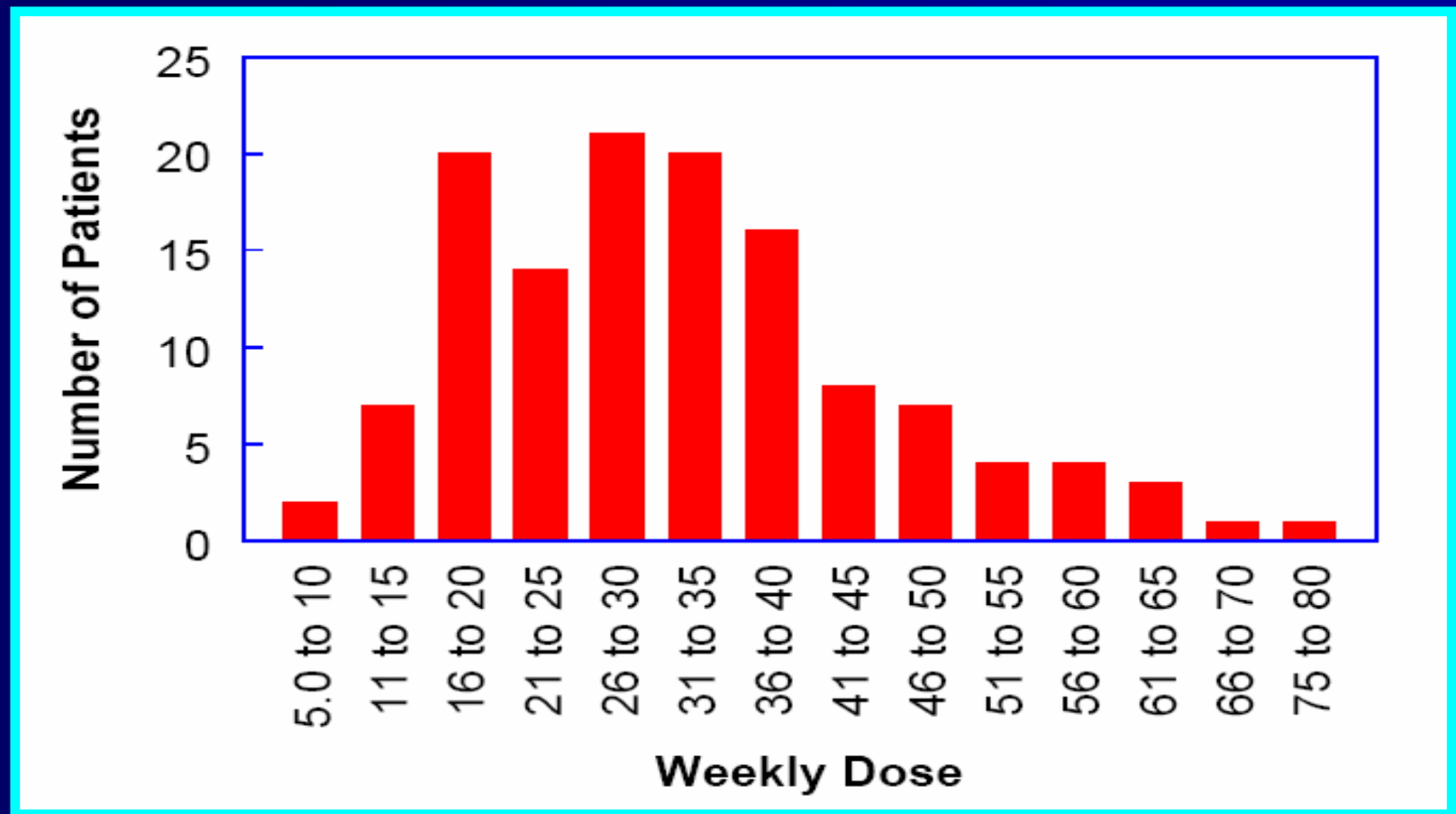
Not Getting Initial Dose "Right" Leads to Greater Risk of AEs During Induction

Major Bleeding with Outpatient Warfarin

Landefeld, Am J Med 1989:87:144-52
CPSC Advisory Committee Meeting, 11/14/05

Adverse Events May Impact Physician Use of Warfarin in Eligible Patients

- 530 physicians of 116,200 patients with AF who were admitted to hospital for either excess bleeding or strokes

- 3.4% of patients had upper GI or intracranial hemorrhage while on warfarin

- Patients treated in the 3 months after a bleeding event were 21% less likely to receive warfarin from physicians having a patient with a bleed in the prior 3 months

- *Conclusion that AEs result in underuse of warfarin*

Choudhry et al, Brit Med J, January 10, 2006

All of This Is Summarized in the Black Box Warning in Warfarin Label

WARNING: BLEEDING RISK

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see **PRECAUTIONS**), and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see **PRECAUTIONS: Information for Patients**).

As of October 4, 2006

Ex: Precautions Section of Warfarin Label

Drug Interactions. PK mechanisms are mainly enzyme induction, enzyme inhibition and reduced plasma protein binding.

- Scientific basis for many – not all – of the precautions and warnings in the warfarin label is the *Exposure Principle*, i.e., intrinsic and extrinsic factors will increase or decrease systemic exposure to warfarin and require <u>initial dose selection</u> to achieve a Cmax and AUC similar to a normal, not at-risk patient

- Initial doses of 2-5 (up to 10) mg are recommended in the D/A section of the label

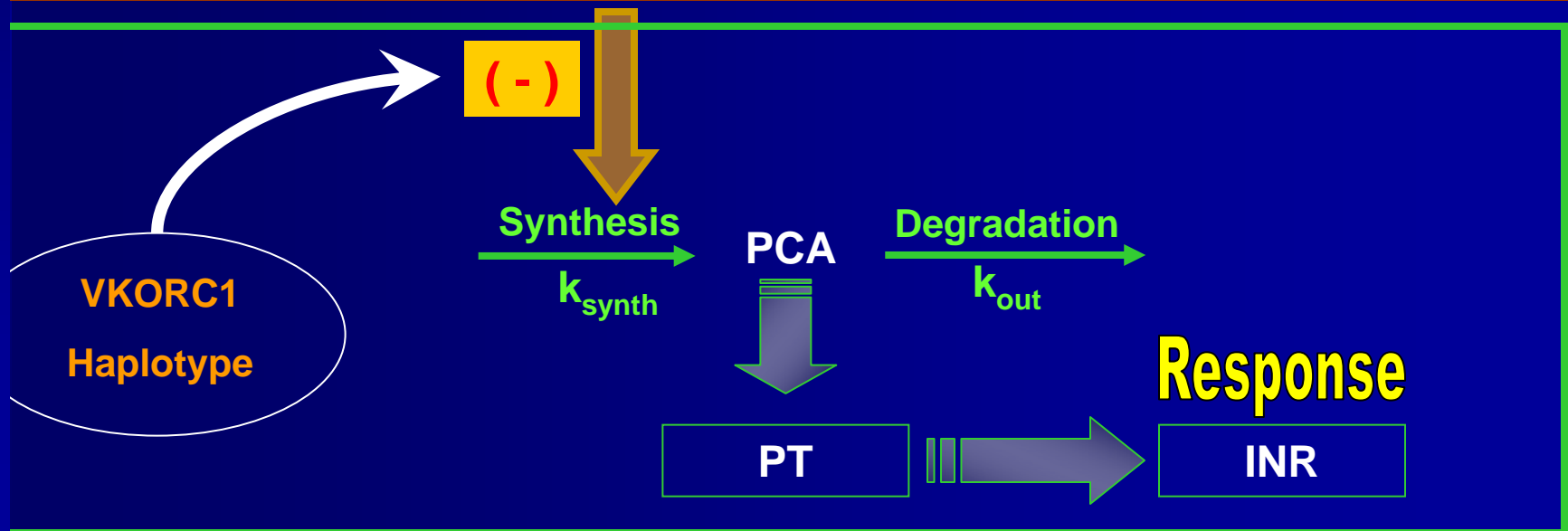- Specific doses cannot be recommended but qualitative changes in dose are possible based on risk factors
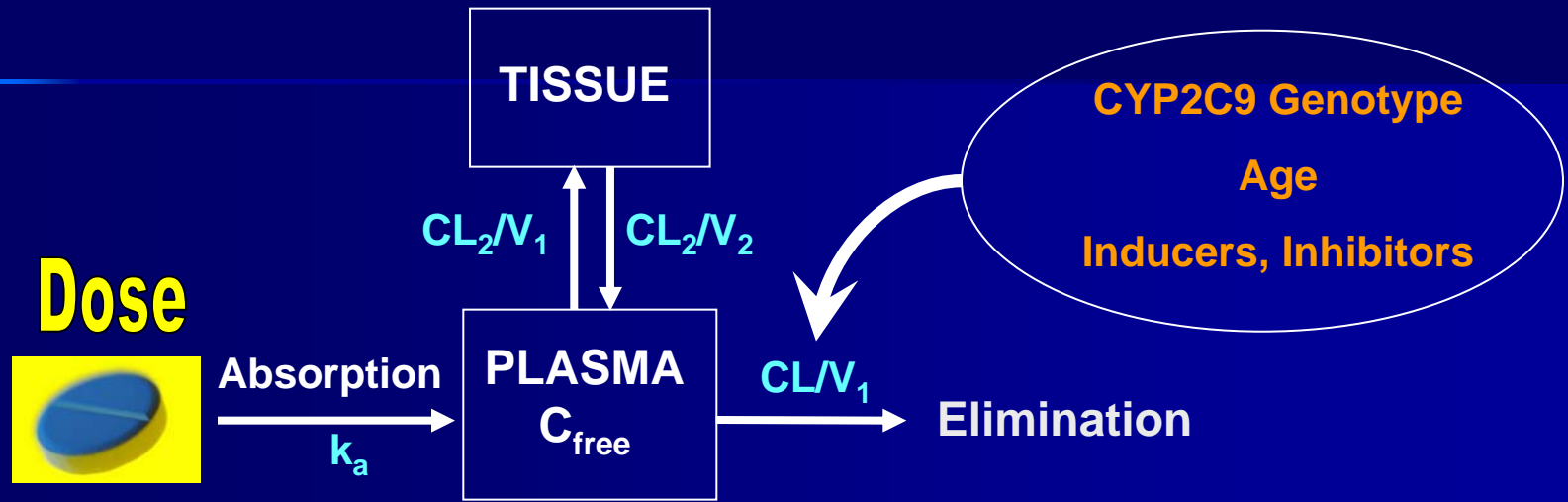
Amiodarone - Warfarin Interaction: Effects on PK (Exposure) and PD (Response)
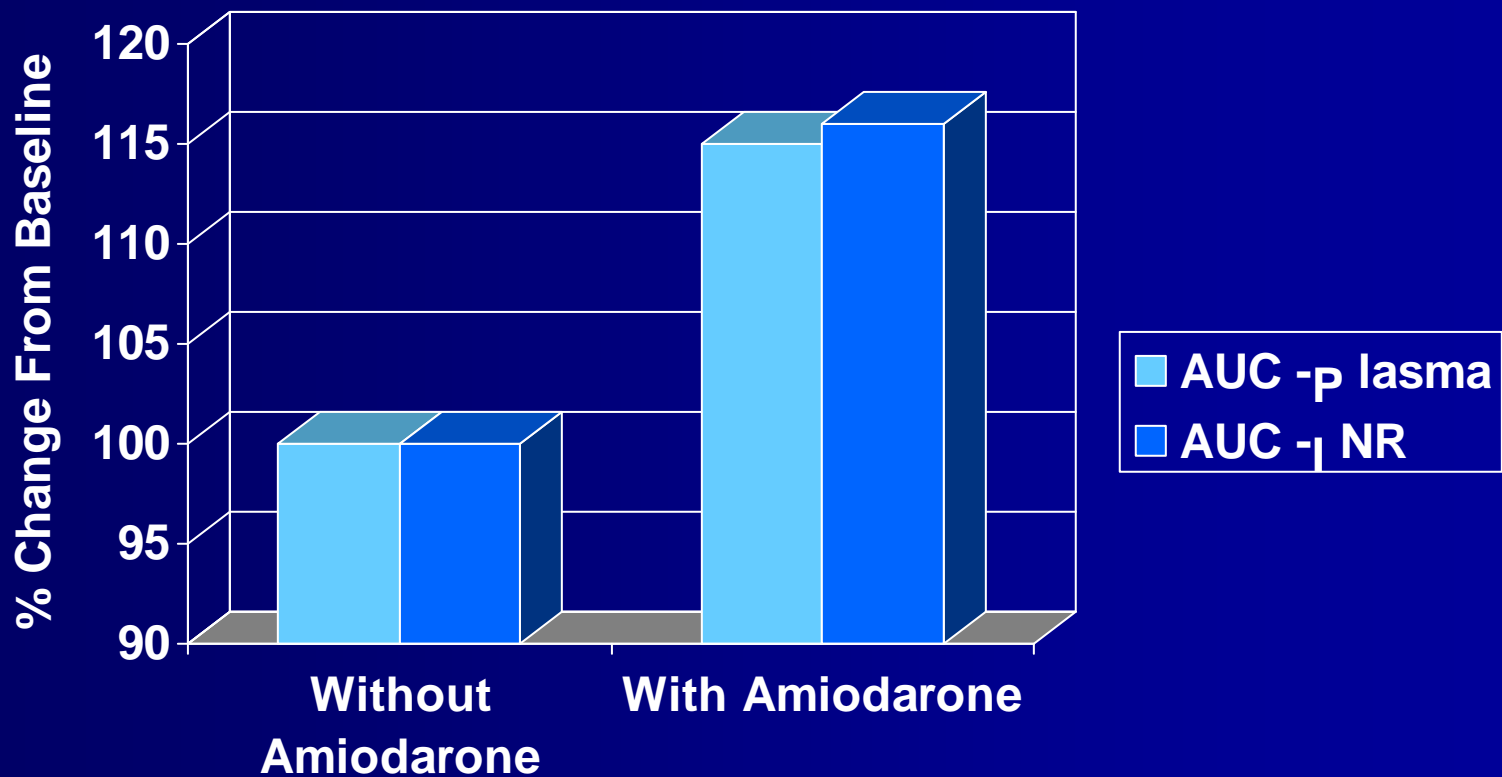
Data from Hamer et al, Circulation 65, 1025-1029, 1982;
Heimark et al, Clin Pharmacol Ther 51, 398-407, 1991

PK of Warfarin: Reduced Clearance As a Function of CYP2C9 Genotype

Genotype (N = 188)	Prevalence	% Enzyme Activity	Clearance/LBW (ml/min/kg)	Daily Dose (mg/day)
2C9 *1/*1 (N=118)	63%	100%	0.065 (0.025)	4.88 (2.78)
2C9 *1/*X (N=59)	31%	50-70%	0.041 (0.021)	2.71 (1.54)
2C9 *X/*X (N=11)	6%	10%	0.020 (0.011)	1.64 (1.03)

Herman et al, Pharmacogenomics J 2005; 4:1-10
Lesko LJ. CPSC Advisory Committee Meeting, November 14, 2005

Higashi et al, JAMA 2002;287:1690-8
Linder et al, J Thrombosis Thrombolysis, 2002:14, 227-232

PD of Warfarin: Different Sensitivity As a Function of VKORC1 Genotype

| Genotype (-1639 G>A)	Prevalence	Relative Sensitivity	Daily Dose (mg/day)
AA	16%	0.64	2.7 (1.2)
AG	47%	1.0	4.2 (2.2)
GG	37%	1.61	6.7 (3.3)

Sconce et al, Blood 2005, Rieder MJ et al NEJM 2005, Wadelius M et al Pharmacogenomics 2005

Subgroup Analyses: Accounting for Sources of Interpatient Variability

Ex: Intrinsic Factors	Ex: Extrinsic Factors
Age	Medical Practice
Sex	Diet
Concomitant Disease	Concomitant Drugs
Organ Function	Adherence
Genetic Polymorphisms	Smoking

Steady State INR is Predicted by Plasma Warfarin Levels and Sensitivity - Not Dose
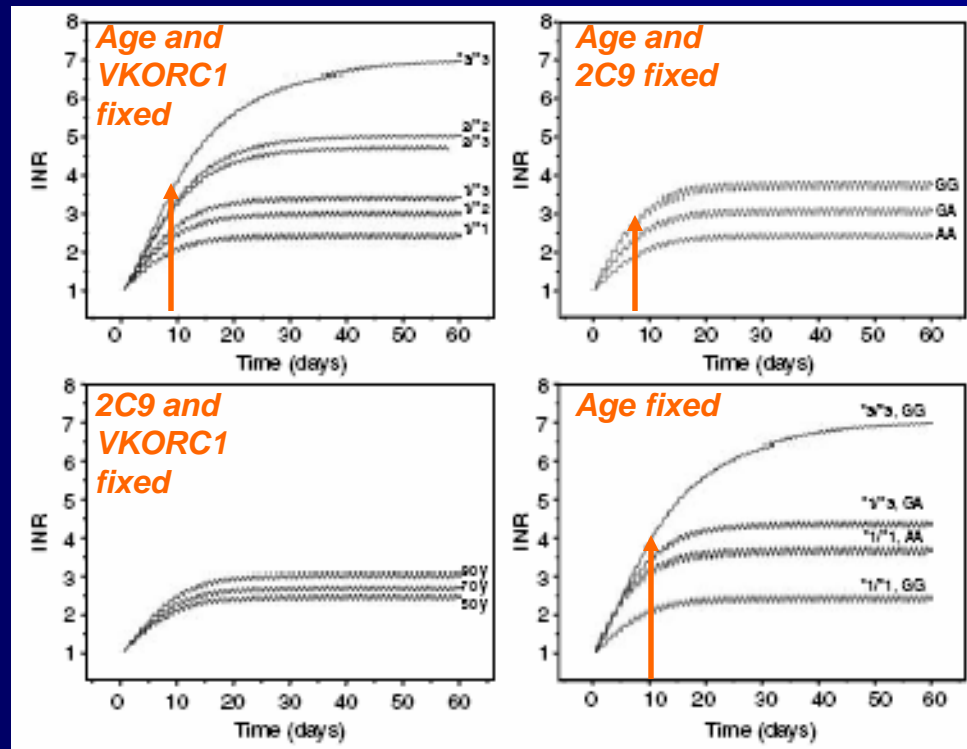
Predicted INR response during induction phase after a fixed dose to individuals with different combinations of age, 2C9 and VKORC1 genotypes

Hamberg et al, Clin Pharmacol Ther, February 2007

- *PK-PD model based on warfarin plasma levels, INR, age, 2C9 and VKORC1 genotypes from 150 patients*

- *INR best described by inhibitory Emax model with warfarin plasma levels, not dose, predicting response*

- *Steady state response curves (left) show early INR measurements alone do not predict differences between patients*

- *Differences in dose requirement evident by day 4*

- *Optimal time to measure INR varies with subgroup*

It's So Easy to Figure Out an Initial Dose That a Machine Can Do It

- **Google search:**

93,900 hits for "warfarin calculators"; 722 hits for "computerized warfarin calculators"

1. Online web site established by Dr. Brian Gage

2. Automated PK-PD software developed by Dr. Roland Valdes and Dr. Mark Linder

Is INR an Acceptable Surrogate for Clinical Outcome?

INR Range	Benefit of Stroke Protection	Risk of Intracranial Hemorrhage
< 2	1.75 – 4.94	---
2 to 3	1.00 (base)	1.00 (base)
3 to 4	---	2.40
4 to 6	---	16
➤6	---	27

Analysis of data from the Anticoagulation and Risk Factors in Atrial Fibrillation Study by Dr. Elaine Hylek; comparison of INRs from 169 patients with stroke and 55 patients with hemorrhage.
http://www.neurologyrerviews.com/march02/atrila.html

Are RCTs a Requirement for Dose Recommendations?

Criterion	Result
Consistency across studies	Yes, different populations and different countries, thus credible
Consistency within studies	Yes, small RCT comparing SOC vs. genotyping provide similar findings
A priori hypothesis	Yes, conceptual approach based on exposure principle for subgroups
Small number of hypothesis	Yes, reducing probability that findings occurred by change
Indirect causal evidence	Yes, current knowledge of mechanistic PK model predicts INR
Difference between genotypes was statistically significant	Yes, at level of $p < 0.5$
Magnitude of difference between genotypes clinically important	Yes, initial and maintenance doses differ by maximum of 70%

Why RCT Are Not Necessary for Defining Doses in Subgroups: FDA Guidances
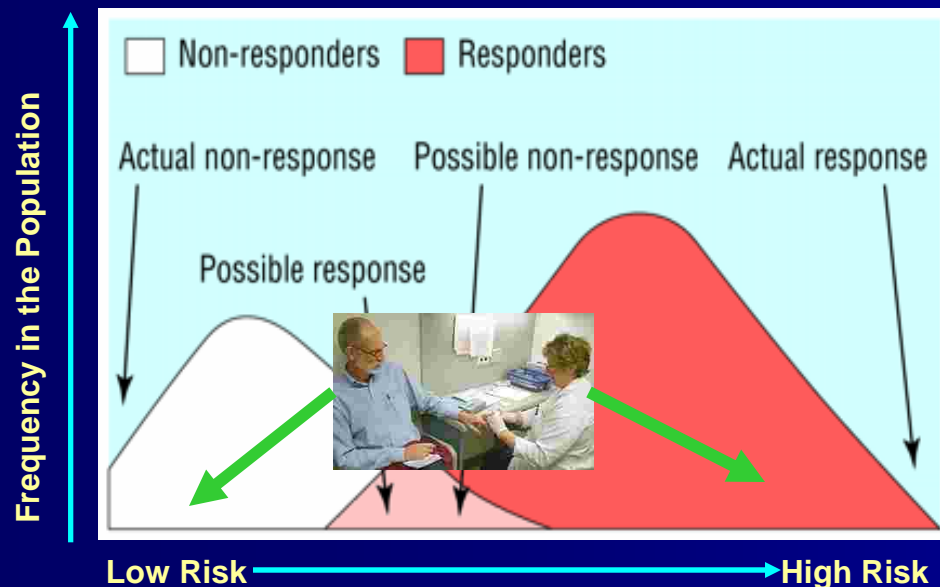
- RCT are 'gold standard' powered for providing evidence of efficacy at a fixed dose; safety is observational – hypothesis driven, confirmatory
  - Analysis of RCT looks at *population differences* between treatment and control arms, not *individual differences*
- Prospective observational PK(PD) studies are done in subgroups with expected changes in PK(PD)
  - Learning trials, how to use drug optimally in *individuals*
  - Renal and hepatic function, elderly, food, drug interactions, gender, pediatrics, different severity of disease
  - Changes in Cmax and AUC relative to controls (healthy volunteers) are used to adjust RCT fixed doses
- Many guidances lay out principles of study design, data analysis and label recommendations

http://www.fda.gov/cder/guidance/

Other Personal Perspectives on Need for RCT for Genotype-Phenotype Associations

- Pragmatism – there are too many questions and too many genotype-phenotype associations to rely on large, expensive and time-consuming RCTs
- Equivocal Results - hypothesis, design and analysis of RCT influence outcomes, *generalizability*
  - Ex: NIMH CATIE trial, NHLBI WHI research, vitamin E and risk of coronary disease, radical prostatectomy vs. watchful waiting in early prostate cancer
- Clinical Uptake and Reimbursement – criteria influencing update is complex but RCT are compelling to practitioners and third party payers
  - Ex: compare drug/test co-development to tests for previously approved drugs

Probabilistic Nature of Pharmacogenetic Tests for Individual Patients

Frequency in the Population

Non-responders   Responders

Actual non-response   Possible non-response   Actual response

Possible response

Low Risk ⟶ High Risk

Responder: patient likely to experience toxicity at usual drug doses

Nonresponder: patient not likely to experience toxicity at usual drug doses

Sensitivity and specificy: attributes of tests to estimate likely of response or non-response

PGx is not the end-all and be-all answer to warfarin variability: but, taken together with patient information, clinical judgment and INR it provides an improved predictor of induction doses maintenance doses and anticoagulation control (INR).

Goal of Genetic Testing

To <u>rule out</u> a potentially clinically significant effect of 2C9 and/or VKORC1 polymorphism on the D/R relationship for warfarin and inform initial dose decisions without significantly delaying the initiation of warfarin therapy

A genetic test is like a seat belt for drugs – it protects the patient from 'accidents' in the form of serious adverse events
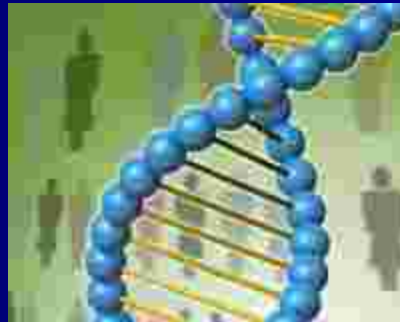
Mystery Question

What are the barriers to getting genetic tests integrated into clinical decision-making?

1. Warfarin is widely prescribed to millions of patients

2. It is among the most hazardous drugs prescribed

3. Excessively high and low anticoagulation is common

4. Many adverse events occur in first month of therapy

5. Establishing optimal induction doses is a problem

Concluding Thought: How Can FDA and Anticoagulation Clinics Work Together?

■ Founding principles of FDA's Critical Path Initiative

– To create collaborations with academia, industry and private sector enterprises

– To build opportunities to share existing knowledge and databases

– To partner in scholarly and critical review of evidence to enable standards for innovations in drug development and clinical practice

Thank you for the opportunity to present and for your attention

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