Warfarin Pharmacogenomics: Translation Into Clinical Practice

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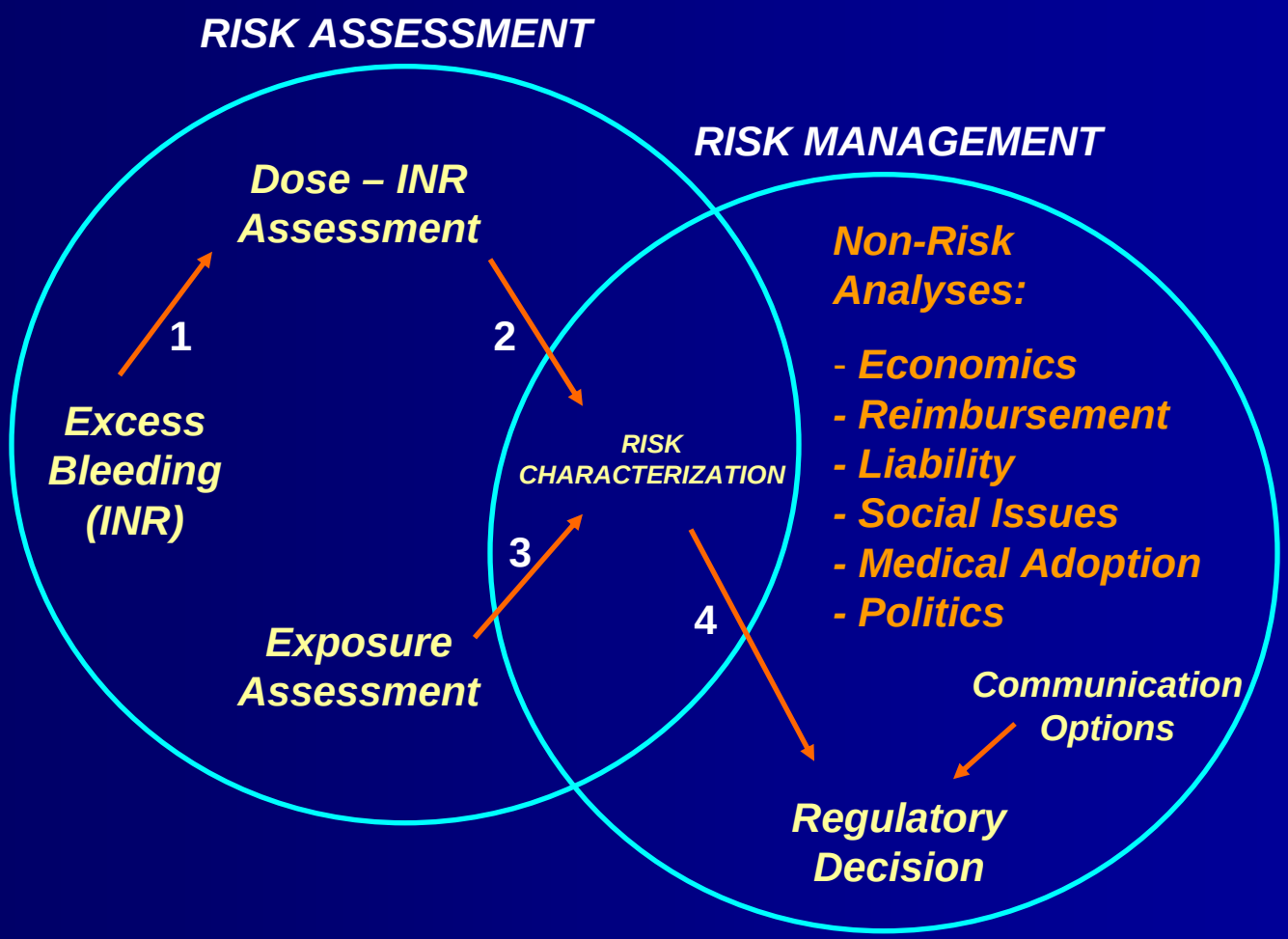
Comparison of Risk Assessment vs Risk Management: Distinctly Different Processes



Considerations In Risk Assessment

Important to weigh:

1. **Magnitude of relative and absolute risk**
2. **Clinical importance of risk**
3. **Public health implications of risk**
4. **Uncertainty of risk factors**

Magnitude of Risk: Vast Amount of Clinical Data on Bleeding Complications

- Warfarin ranks #1 in total mentions of deaths for drugs causing AEs from death certificates
- Warfarin ranks among the top drugs associated hospital emergency room visits for bleeding
- Overall frequency of major bleeding has been 10% to 16% (versus 0.1% for most drugs)
- Minor bleeding event rates in RCT of new anticoagulants has been as high as 25-27%

Wysowksi et al, Arch Int Med 2007 and SPORTIF III Trial 2003 (Exanta, Astra-Zeneca)

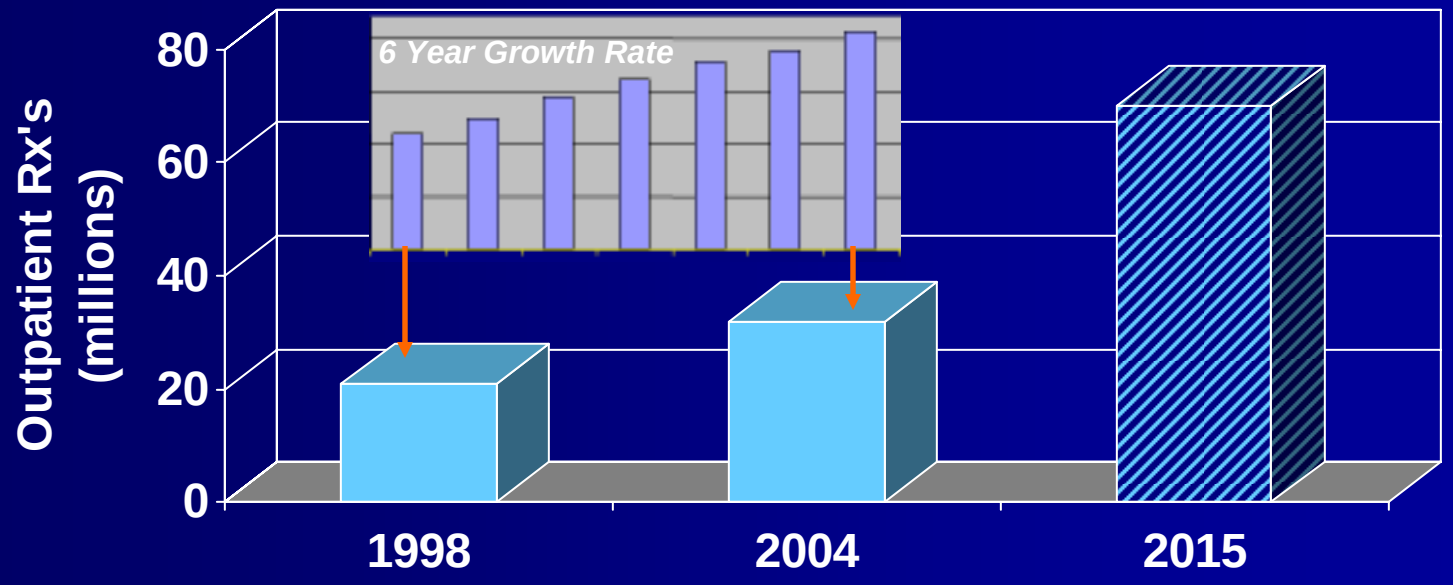
Clinical Importance of Risk: Warfarin Eludes Patients Who Need It the Most

- Risk of stroke in A Fib increases by 40% in elderly while warfarin use decreases by 60%
- New patients with A Fib (1:130 over 65 yo) treated by physicians who had a patient with a bleeding event were 21% less likely to receive warfarin
- Other reasons for not starting warfarin treatment in A Fib patients (n = 300)
  - 28% prefer treatments without INR monitoring
  - 20% fear of bleeding
  - 18% would have difficulty to get INR monitored

Choudhry et al, Br Med J, 2006; Patient Record Review on File at Astra-Zeneca; White et al, Am J Med 1999; Wolf, Arch Int Med 1987

Public Health Implications of Risk: Most Widely Used Anticoagulant Worldwide

Real and Projected Growth in Anticoagulant Market: 600,000 New Patients Per Year



Note: Anticoagulant market projected to increase 3 to 4-fold between 2004 and 2015
Sources include National Rx Audit, IMS Health Forecast (MIDAS)

Added New Black Box Warning About Bleeding to US Product 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**).

Label as of October 2006

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"Does This Mean I have Cancer?" – "Well, No, We Have to Do Further Tests!"

Mammograms

- 30 million mammograms are done each year in the US
- Additional tests will be ordered for 1 in every 3000 women
- 1 woman out of 1000 will benefit from mammogram screening

Prostate Specific Antigen

- Virtually every man over 50 years of age is screened for PSA
- 25% to 85% of men get biopsies following PSA screening
- In 2007 it is still unknown how many men benefit from screening

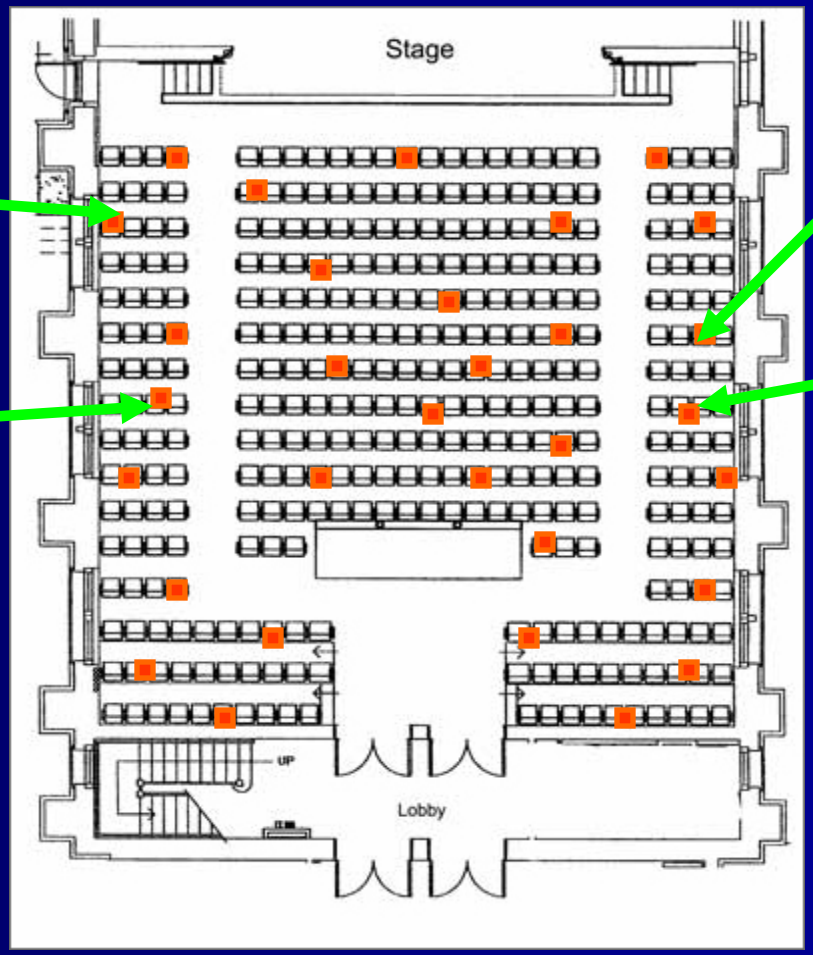
There is no evidence from prospective RCT that mammograms or PSA screening leads to a survival benefit as a result of early detection of cancer. Are they useful? Maybe but nobody knows for sure!

Warfarin Risk Characterization
Theater: All Cause Bleeding Events

70 year old Caucasian male with Afib

75 year old Caucasian women with prior stroke

50 year old healthy male undergoing knee replacement ???

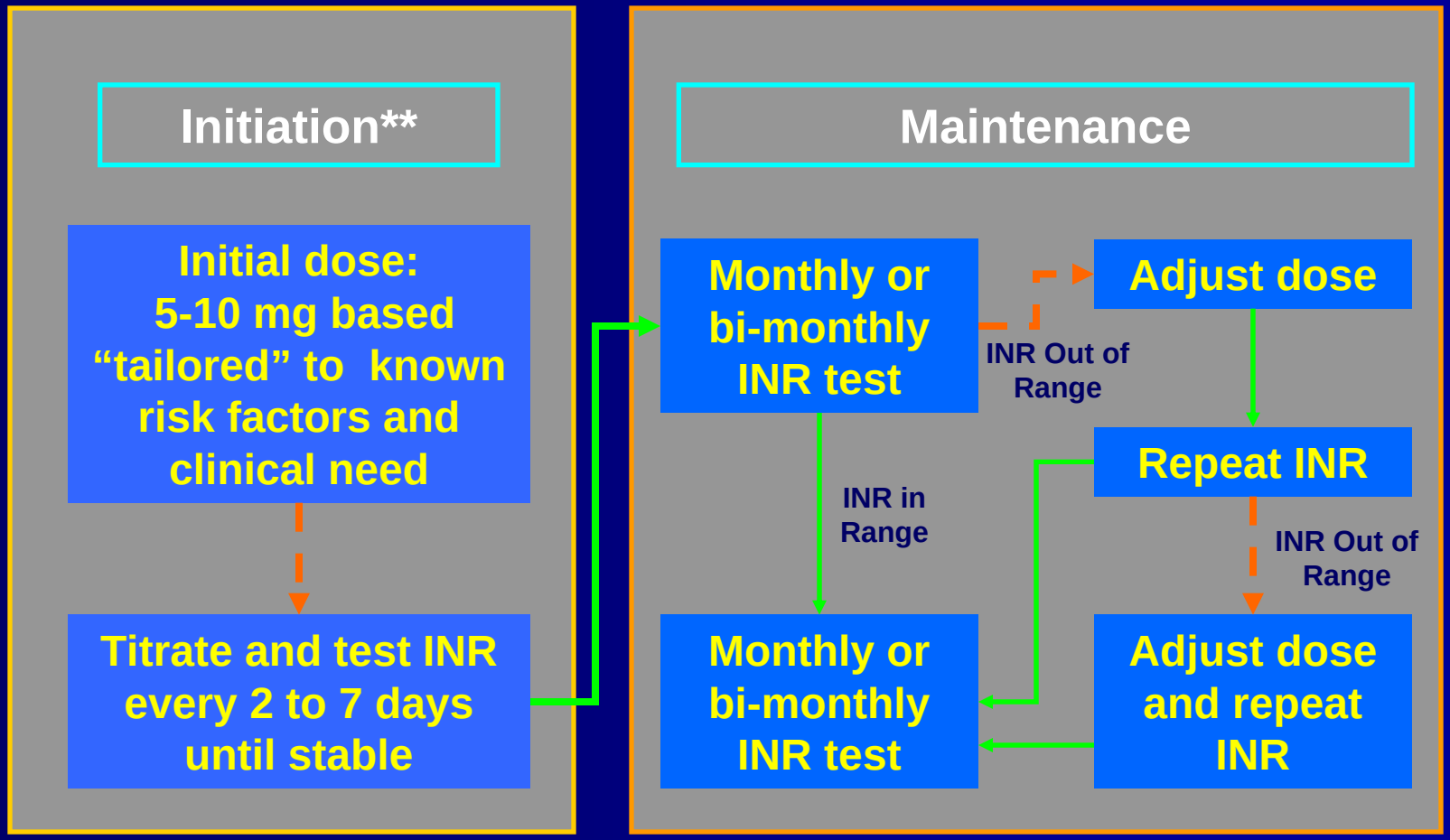


60 year old African-American man with Afib and INR over 4

65 year old Asian female with Afib

23 year old healthy female smoker who had a VTE while taking OC ???

Managing Risk: Steps Required to Maintain Therapeutic Anticoagulation May Not Be Feasible

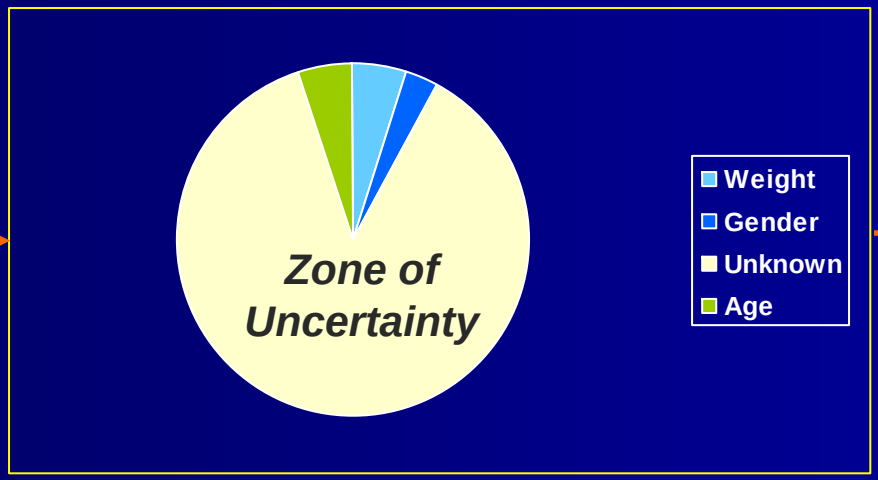


*** Note: Standards of care conflict with how to adjust doses based on observed INRs*

Estimating Warfarin Maintenance Doses Is Difficult: Basically "Act and React"

Fixed Initial Dose:

5 mg



Target Stable INR:

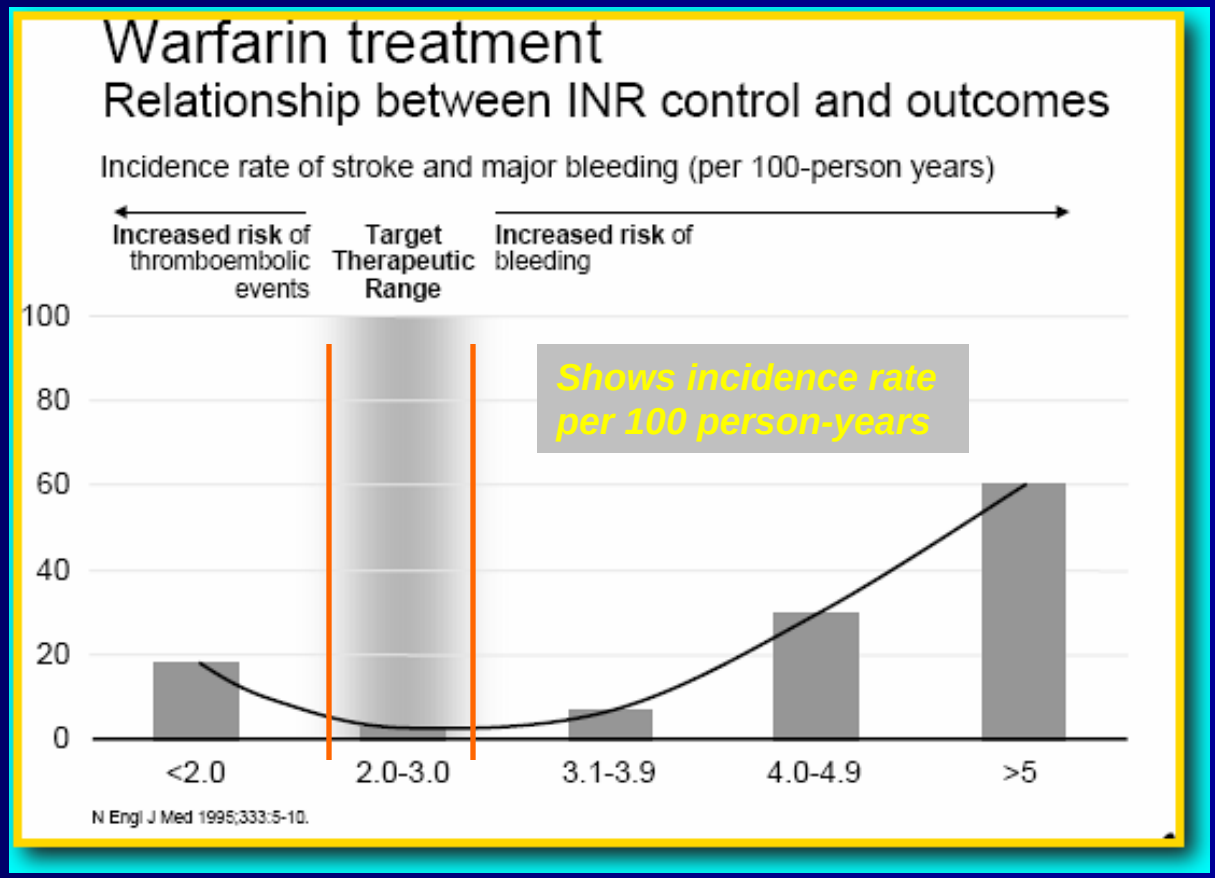
2 to 3

Most frequent initial dose is 5 mg <u>adjusted for risk actors</u> thought to affect warfarin PK and clinical situation

Initial dose attempts to estimate maintenance dose

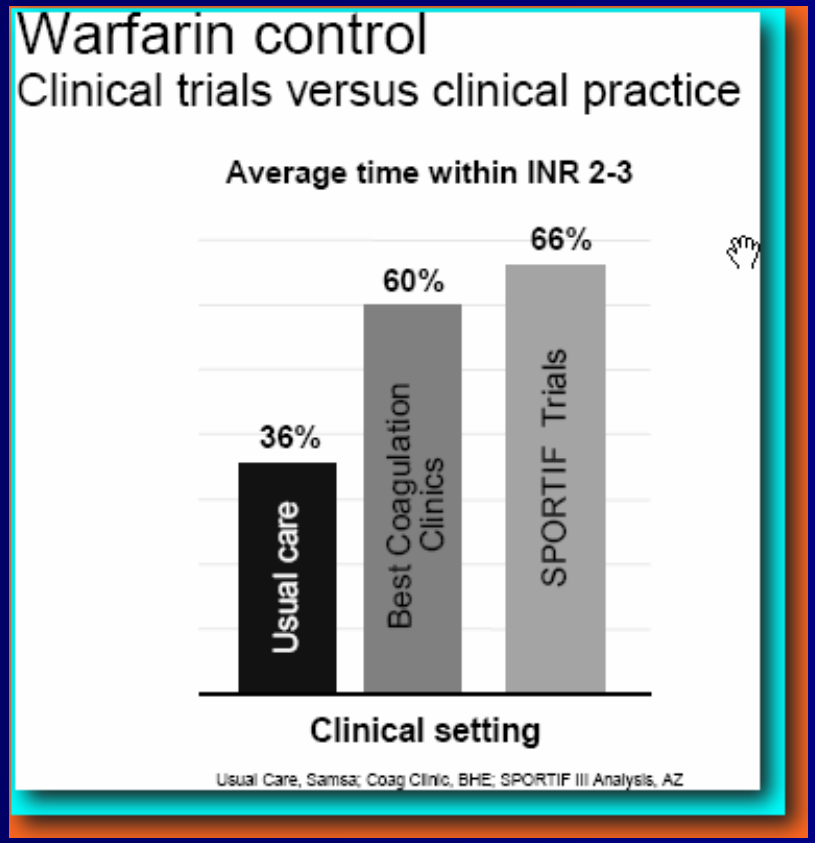
How to adjust dose for known patient risk factors is not clear

Control of INR (Surrogate) Is Critical to Maintaining Therapeutic Anticoagulation



Adapted from http://www.astrazeneca.se/download/2003/2003Cameron.pdf

INR Values in Clinical Practice Are Difficult to Monitor and Maintain

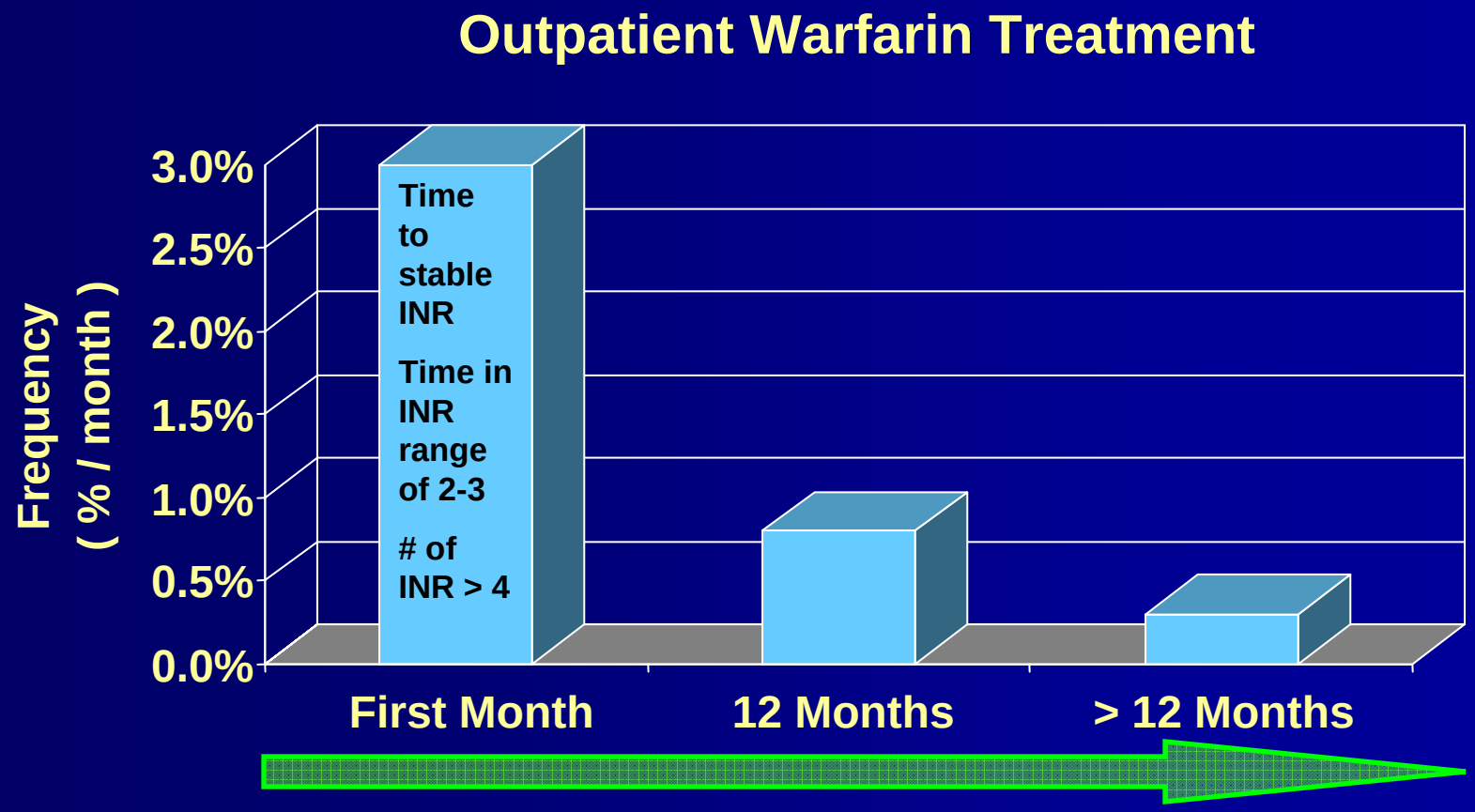


- INR values are less than 2.0-3.0 twice as often as they are more than 2.0-3.0

- Less than 50% of patients achieve target INR range on a starting dose of 5 mg

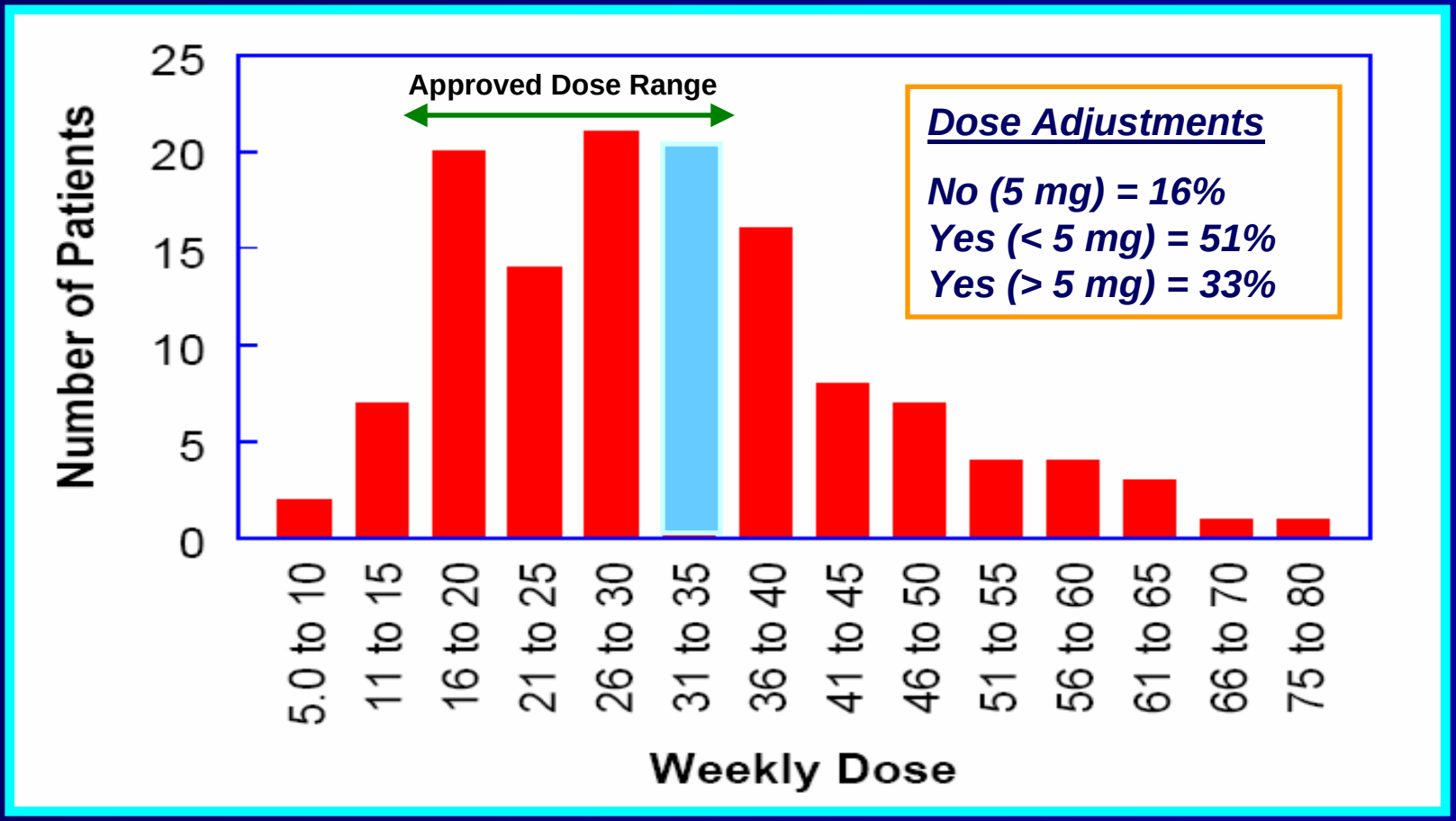
From http://www.astrazeneca.se/download/2003/2003Cameron.pdf
Matchar et al, Am J Med 2002

Result: High % of Major Bleeding Events During Dosing Initiation Phase



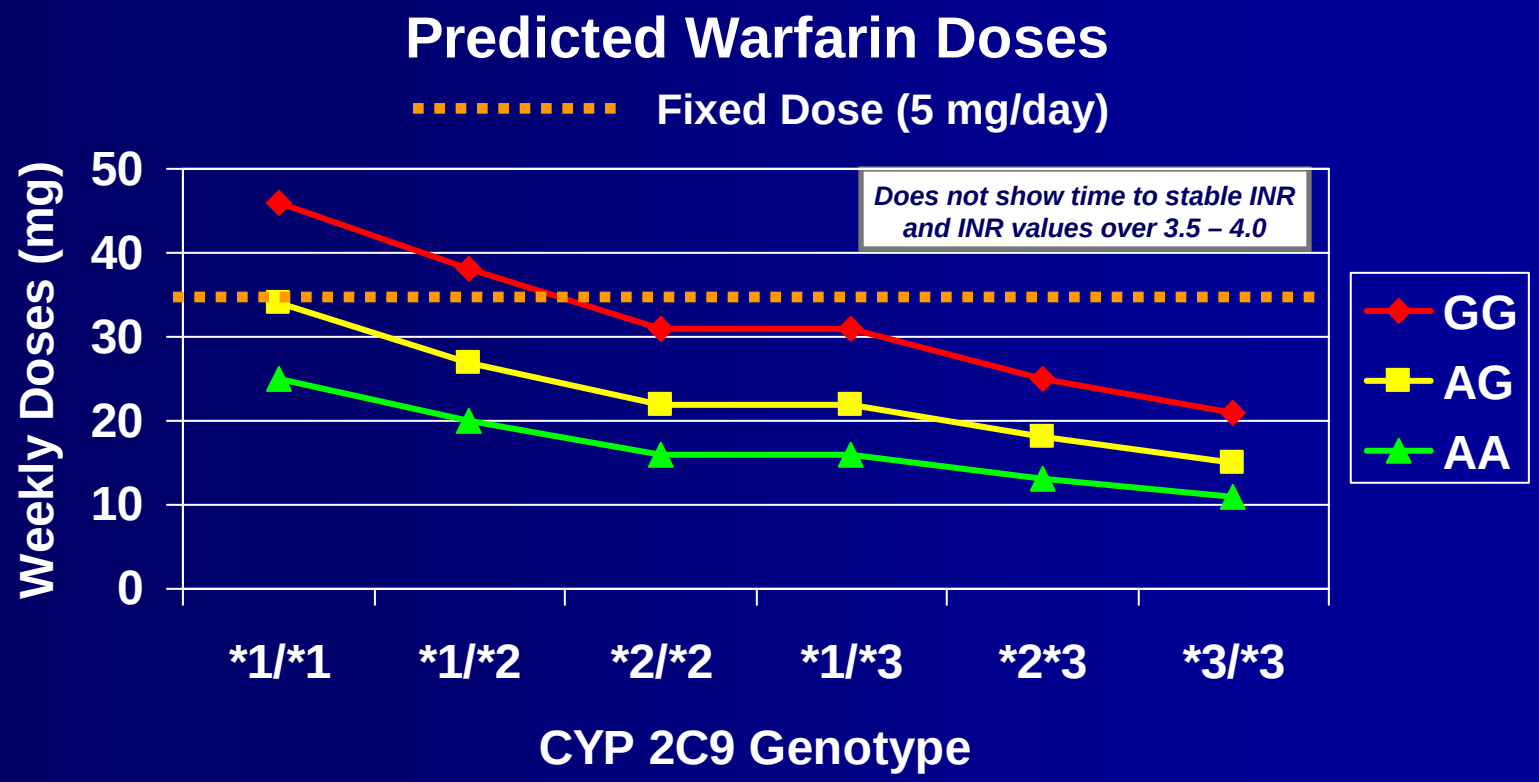
Landefeld et al Am J Med 1989, White et al, Am J Med 1999, Ezekowitz et al, J Cardiovasc Pharmacol Ther, 1999, Higashi, et al, JAMA 2002, Hirsh et al, Circulation 2003

Finding Doses to Maintain Therapeutic Anticoagulation is Largely Trial and Error



Reynolds KK et al. Personalized Medicine 2007

Ex: 50 Yr, Male, NS, 180 lbs, 5'10", A Fib, Normal Hepatic Function, No Drug Interactions From Warfarin Risk Theater



Loading dose recommended for each genotype with a variant 2C9 allele depending on VKORC1 haplotype: 6.6 mg (GG), 4.8 mg (AG) and 3.5 mg (AA)

Here Is The Urgent Clinical Consideration Related to Risk Management

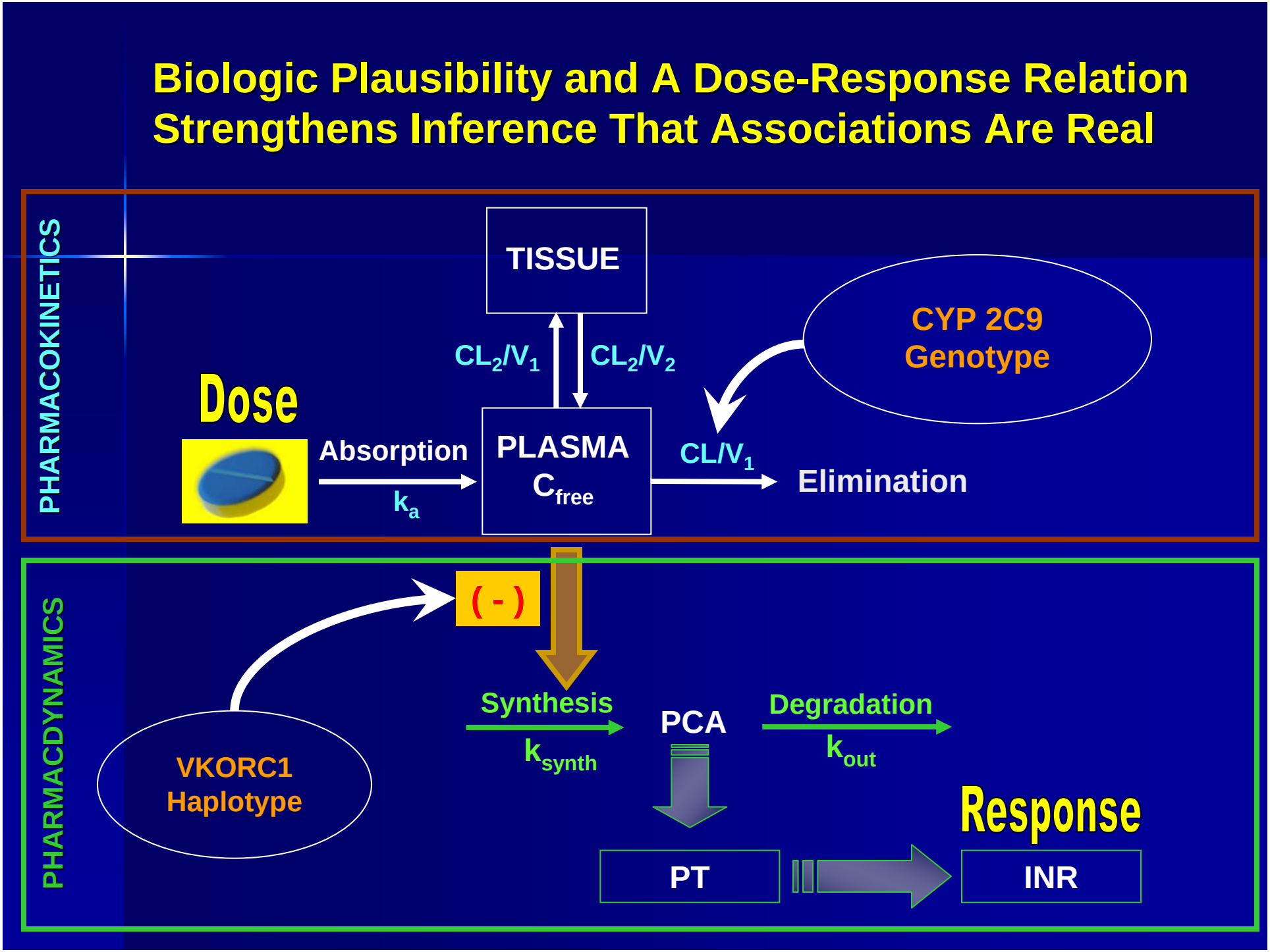
Is the overall increased risk of poor INR control, and bleeding episodes, explained by a particularly elevated risk in an identifiable subgroup of patients, or whether the risk is uniform across all patients?

Extensive amount of clinical data suggesting that risk is particularly high in patients with gene variants in CYP2C9 and/or VKORC1.

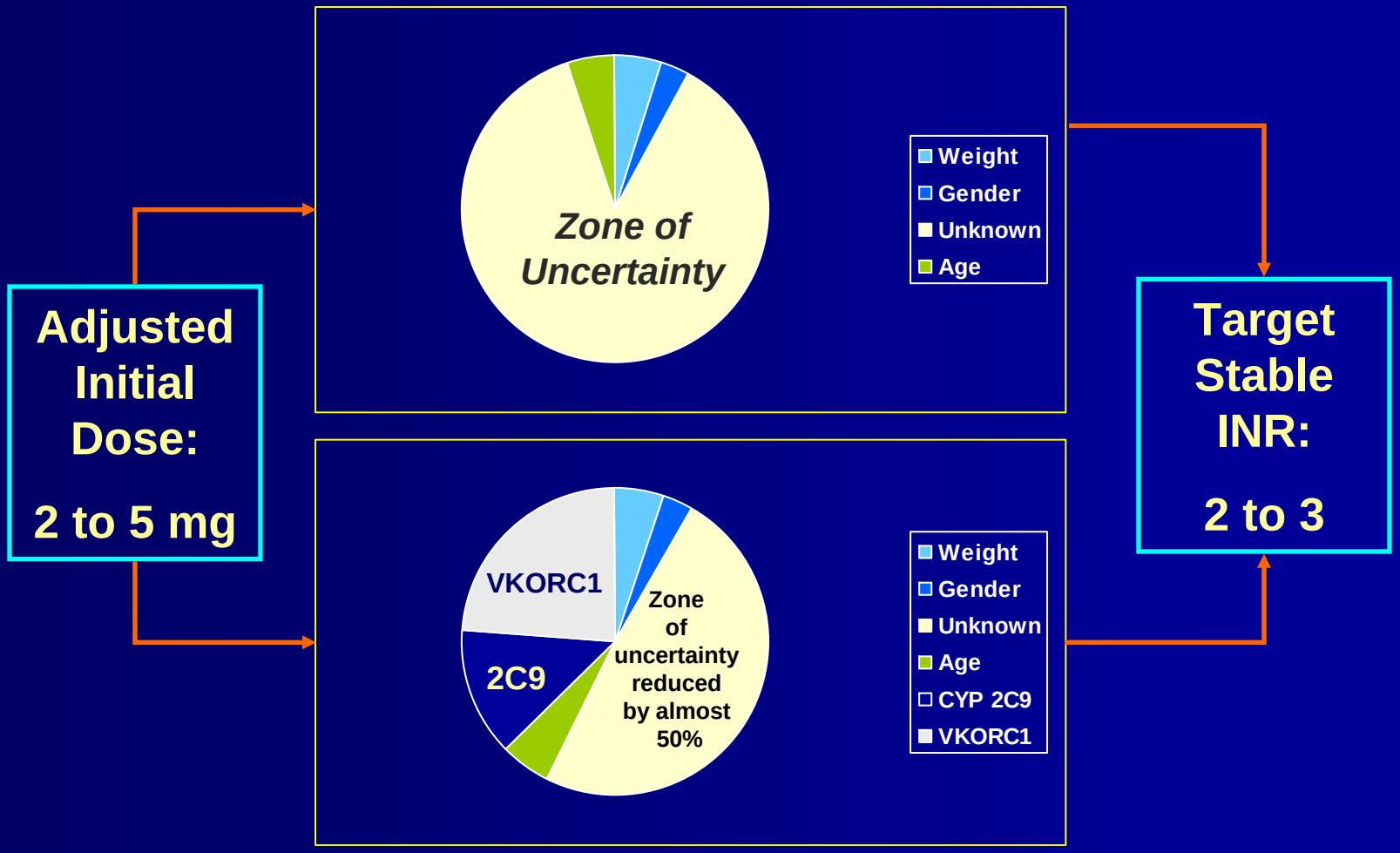
Clinical Data Sources: Strength and Weight of Evidence Supporting Relabeling

- Nine population-based observational studies of matched cases and controls (1999-2006)
  - Historically prospective, i.e., DNA collection, pre-specified protocols for INR collection, warfarin doses, other drugs and data analysis, in over 1800 patients
  - 8 studies found strong associations between lower dose requirements and 2C9 gene variants
  - 3 studies showed strong associations between poor INR control, bleeding and 2C9 and VKORC1 alleles
  - Potential sampling bias reduced by using studies from different clinical sites from three continents
  - Results representative of real world, convergent and extrapolatable to other patients

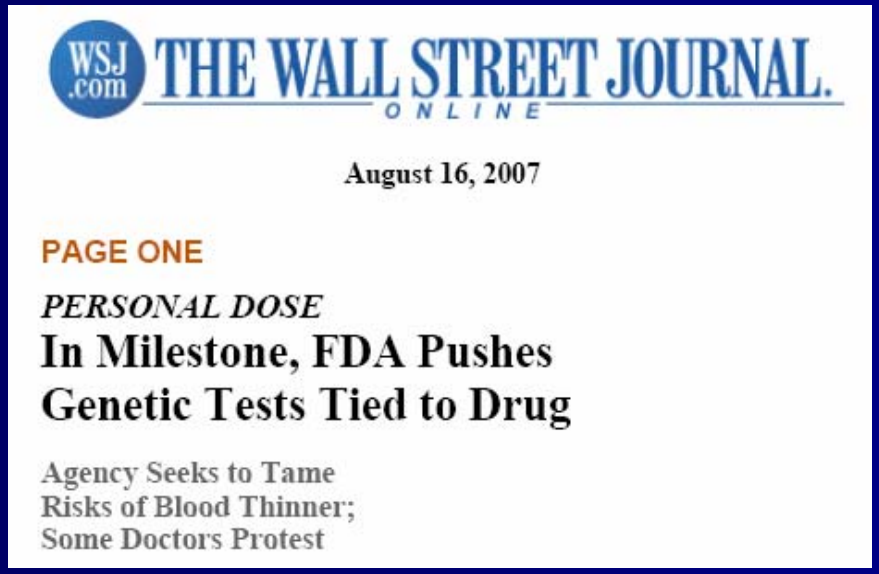
Biologic Plausibility and A Dose-Response Relation Strengthens Inference That Associations Are Real



Initial Warfarin Dosing: PART of the Solution is Reducing the Zone of Uncertainty



Press Release Regarding Genetic Information in New Warfarin Label



WSJ.com THE WALL STREET JOURNAL. ONLINE

August 16, 2007

PAGE ONE

PERSONAL DOSE

In Milestone, FDA Pushes Genetic Tests Tied to Drug

Agency Seeks to Tame Risks of Blood Thinner; Some Doctors Protest

- ***Genetic tests not required***
- ***Encourage doctors to consider genetics in initial warfarin doses***
- ***Genetic tests are available***
- ***Prevalence of genetic variants in different ethnic/racial groups***
- ***Non-genetic factors also important***
- ***INR monitoring is still essential***

Initial Dosage

day with dosage adjustments based on the results of PT/INR determinations.[17,18] The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to COUMADIN (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

http://www.fda.gov/cder/foi/label/2007/009218s105lblv2.pdf

Public Reaction

"I fully support the FDA's stance on the value of genetic information in dosing of warfarin. It is a major step in the right direction of individualized medicine in the future. While it will take years before the final, definitive proof that genotyping the two genes--CYP2C9 and VKORC1--will change the outcomes of bleeding via randomized trials, getting this information today is remarkably inexpensive and harmless, and, at the very least, can accelerate the time it takes for a patient to be properly anticoagulated and markedly improves the convenience features."

Dr. Eric Topol, Scripps
Medscape Medical News, 20 August 2007

"It would be irresponsible and potentially harmful to suggest that testing be used, or even mentioned, in the label for warfarin."

Dr. Ann Wittkowsky, U of Washington
WSJ, 16 August 2007

Announcement of First FDA-Approved Genetic Test for Warfarin

U.S.News & WORLD REPORT

Saturday, September 29, 2007

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Genetic Test Approved for Sensitivity to Blood Thinner

Some people who take Coumadin at higher risk of bleeding

Physician adoption of test will be challenging since a genetic screening test represents deviation from established practices

Prospective Clinical Trial with Bleeding Outcomes

Limdi et al, Clin Pharmacol Ther, July 2007

- Prospective clinical cohort study in 446 (88 with 1 or more gene variants) outpatients eligible for warfarin treatment
- Mean age of 60.5 yrs, 50% men, 50% African-American followed for average of approximately 15 months
- Clinical endpoints of major and minor hemorrhage stratified by INR range and time to stabilization of target INR
- *A variant 2C9 genotype yielded a HR of 3.0 for increased risk of major hemorrhage*
- *Risk of major hemorrhage was 5.3-fold higher before stabilization of INR, and 2.2-fold higher after stabilization*

Prospective Clinical Trial with INR and Bleeding Endpoints

Caraco et al, Clin Pharmacol Ther, September 2007

- Prospective clinical cohort study in 191 (95 2C9 genotyped cases vs. 96 controls) outpatients eligible for warfarin
- Matched for mean age of 58 yrs, 46% men, followed to time of stable anticoagulation up to 3 months (no VKORC1 measures)
- Clinical endpoints of time to stable anticoagulation, time spent in therapeutic range (INR 2-3) and % minor bleeding
- *Cases achieved stable anticoagulation (initiation) 18 days earlier and stayed between INR 2-3 twice as long (45% vs. 24%)*
- *Minor bleeding in the cases was ¼ that observed in the control group (3.4 vs. 12.5%)*

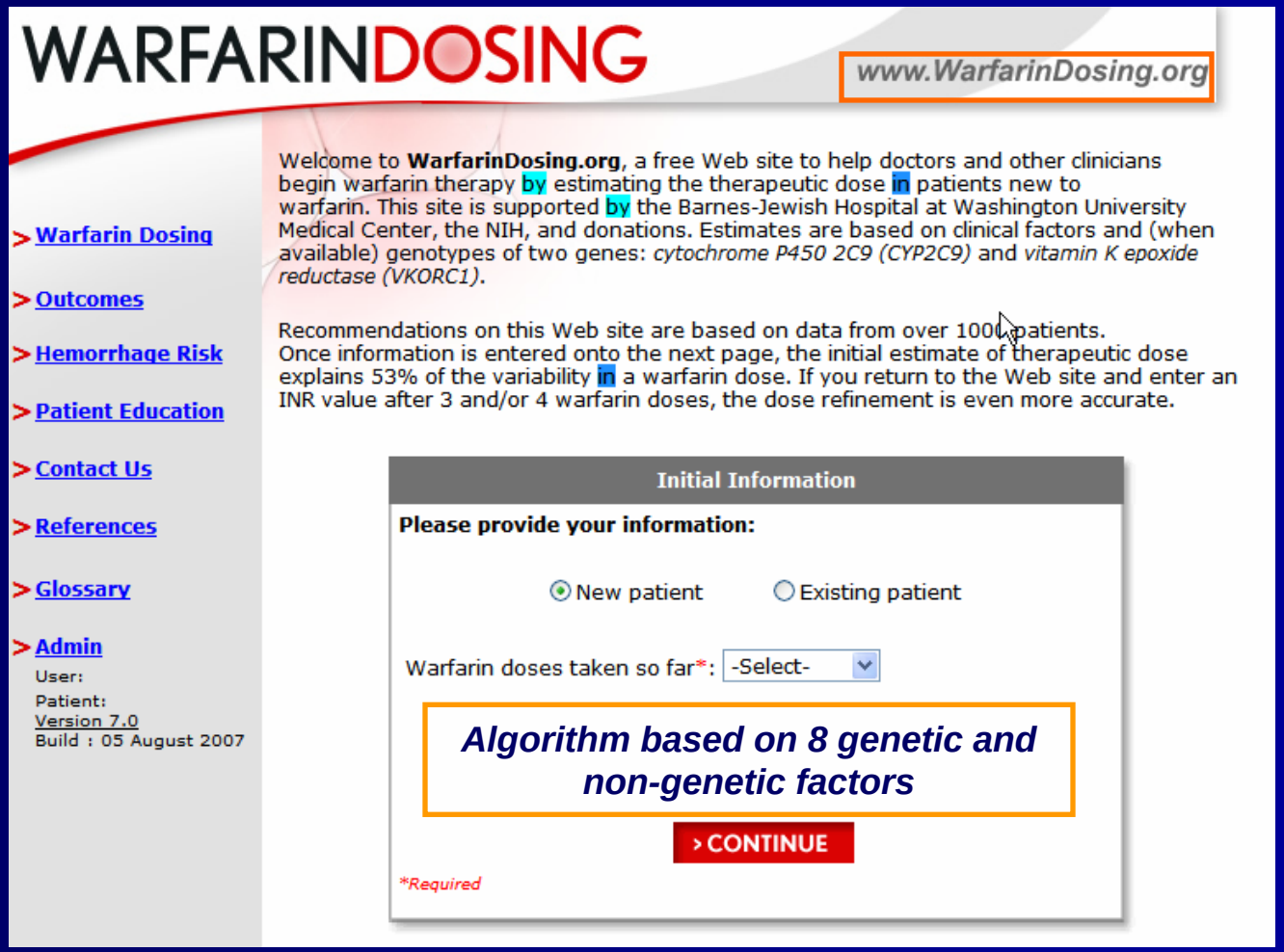
Genetic-Based Dosing Algorithm in Orthopedic Patients Starting Warfarin Therapy

Millican et al, Blood, September 2007

- Retrospective (historically prospective) clinical cohort study in knee or hip replacement patients (CYP 2C9 and VKORC1)
- Matched for mean age of 58 yrs, 56% men, 13% African-American
- Clinical endpoint was the stable maintenance warfarin dose (INR in therapeutic range of 2-3)
- Genetic-based dosing model explained 79% of the variability in warfarin dose (note: r^2 = 64% in 59 non-surgical patients**)
- Significant predictors of dose were 2C9 genotype, VKORC1 haplotype, INR after 3rd dose, first warfarin dose, smoking, EBL

***** Personal communication, Dr. Brian Gage, Oct 1, 2007***

Clinical Decision Support Tool: Algorithm to Estimate Dose With and Without Genetic Information and/or INR Values

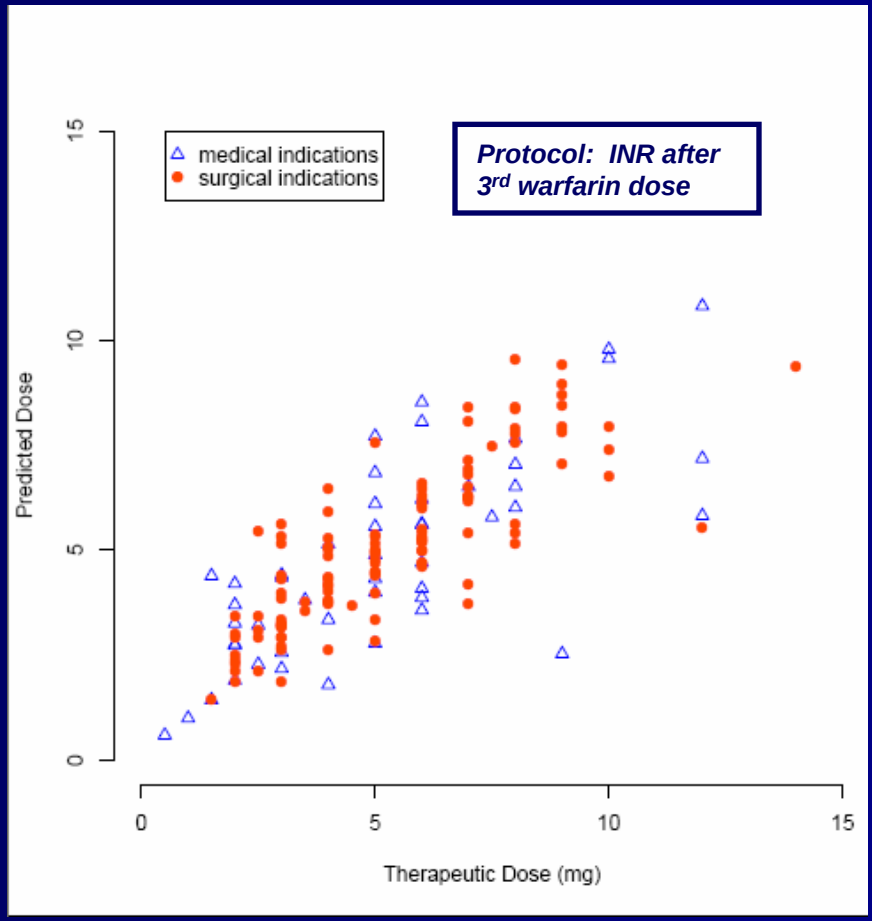


Algorithm-Predicted Warfarin Daily Doses Using the Label-Approved Dose Range

	2 mg/day	2.5 mg/day	3 mg/day	4 mg/day	5 mg/day
3/3 AG	X				
2/3 AA	X				
3/3 AA	X				
2/3 AG		X			
2/2 AA		X			
1/3 AA		X			
3/3 GG			X		
2/2 AG			X		
1/3 AG			X		
1/2 AA			X		
2/2 GG				X	
1/3 GG				X	
2/3 GG				X	
1/2 AG				X	
1/1 AA				X	
1/1 GG					X
1/2 GG					X
1/1 AG					X

Dose reduction of 15-20% per 2C9 and VKORC1 allele

Performance of Dosing Algorithm: Matched Actual Dose by Nearly 80%



With Genetic Factors

Surgical R^2 (n = 119) = 79%
Median Absolute Error = 0.6 mg

Medical R^2 (n = 49) = 64%
Median Absolute Error = 1.1 mg

Clinical Factors Alone

Surgical R^2 (n = 353) = 53%
Median Absolute Error = 0.9mg

"…..We rarely get an INR over 4 using this dosing algorithm."

Data courtesy of Dr. Brian Gage and Petra Jacobsen, Washington University School of Medicine (9 Oct 2007)

Petra et al, Ann of Pharmacotherapy, published online 2 October 2007

Sources of Apprehension About Translation Into Clinical Practice

How to generate the evidence

How much evidence is sufficient

Strength of evidence of "clinical utility"

Problem of cost and coverage

Preparedness of providers

Readiness of delivery system

Challenges

- **Perception**: excess bleeding is worth the risk, given the benefit, and absence of clear and safer alternatives
- **Education**: less than 1 in 10 physicians have been educated in molecular medicine and pharmacogenetics
- **Infrastructure**: unclear availability of test, and needed turn-around-time, who pays, and lack of clear instructions to use results
- **Public Health Value**: Routine genetic screening would not benefit 70% of population with *average risk*
- **Evidence Standards**: Absence of RCT demonstrating significant effect on major bleeding rates

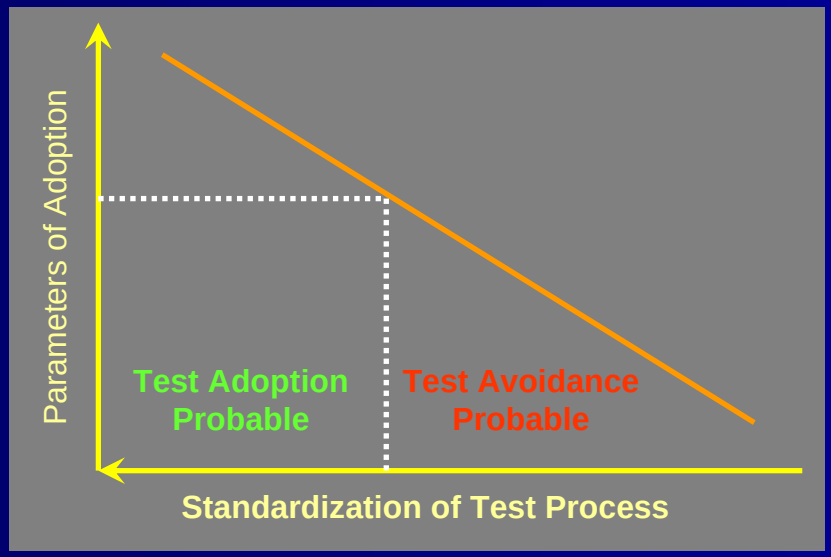
Overcoming the Challenges

- There is always a learning curve
- Clinicians exist in state of information overload
- Do not desire genomics tutorial in patient setting

Unambiguous statements about clinical implications of results

When and how should dosing be adjusted quantitatively

Actionable results important to patient care



No complexities from blood draw to sample handling to test results

Proximal availability of laboratory assay and rapid turn-around-time

Straightforward billing and reimbursement

Adapted from presentation by Peter Keeling, Diaceutics,2007

Summary

- Relatively large number of patients are exposed to warfarin and the number will get larger
- Poor INR control and bleeding events are a major safety problem for patients taking warfarin
- INR monitoring is essential but it has not adequately improved the safety of warfarin
- Vast amounts of evidence suggests that genetic factors play a major role in warfarin risks
- Using genetics to guide initial dosing improves INR control and reduces bleeding events