Warfarin Pharmacogenetics Debate
AACC Annual Meeting
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Warfarin Pharmacogenetic Testing is now Ready for Prime Time

Shiew-Mei Huang, Ph.D.
Deputy Director
Office of Clinical Pharmacology
CDER, FDA
shiewmei.huang@fda.hhs.gov

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FDA Labeling Regulations

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

‹ CFR 201.57›

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"The FDA has been struggling for three decades with serious adverse reactions to drugs"

"if drugs are dosed to fit individual metabolisms and responses, some patients may require less"

"because the science has become much easier to do, you can develop tests very expeditiously"

Janet Woodcock
- October 2007-

< http://www.drugdiscoverynews.com/index.php?newsarticle=1707>

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FDA U.S. Food and Drug Administration — U.S. Department of Health and Human Services

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FDA News

FOR IMMEDIATE RELEASE
August 16, 2007

Media Inquiries:
Karen Riley, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Approves Updated Warfarin (Coumadin) Prescribing Information
New Genetic Information May Help Providers Improve Initial Dosing Estimates of the Anticoagulant for Individual Patients

"Today's approved labeling change is one step in our commitment to personalized medicine. By using modern science to get the right drug in the right dose for the right patient, FDA will further enhance the safety and effectiveness of the medicines Americans depend on."

-FDA Commissioner,
Andrew C. von Eschenbach, M.D.

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Warfarin: Significant Problems for Rats!

First Commercial Product, 1948

An Advertisement from a 1958 Farm Magazine

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Warfarin: Significant Problems for Humans!

- Ranks #1 in total mentions of deaths for drugs causing AEs from death certificates
- Ranks among the top drugs associated hospital emergency room visits for bleeding
- Overall frequency of major bleeding range from [0-2%] to [10-16%] (versus 0.1% for most drugs)
- Minor bleeding event rates in RCT of new anticoagulants has been as high as 29% (% per year)

Ansell Chest 2001; Wysowksi et al, Arch Int Med 2007 ; SPORTIF III Trial 2003 (Exanta, Astra-Zeneca, http://www.astrazeneca.se/download/2003/2003Cameron.pdf)

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Case Report July 2, 2008

- Company director dies of brain haemorrhage after heading a football
- Consultant neurosurgeon told the Macclesfield inquest the warfarin effect was probably the cause of the death
- It can happen to anyone!

http://www.dailymail.co.uk/news/article-1031124/Company-director-dies-brain-haemorrhage-heading-football.html

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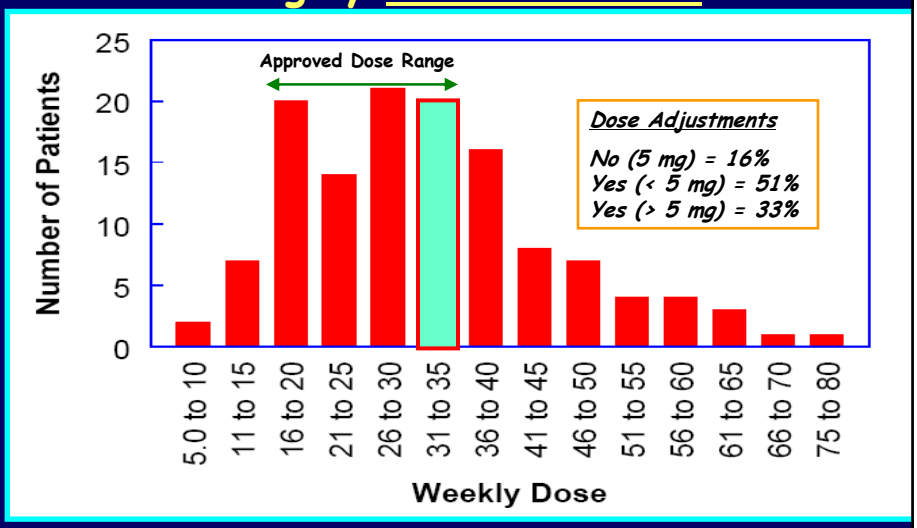
Finding Doses to Maintain Therapeutic Anticoagulation is Largely *Trial and Error*



Reynolds KK et al. Personalized Medicine 2007

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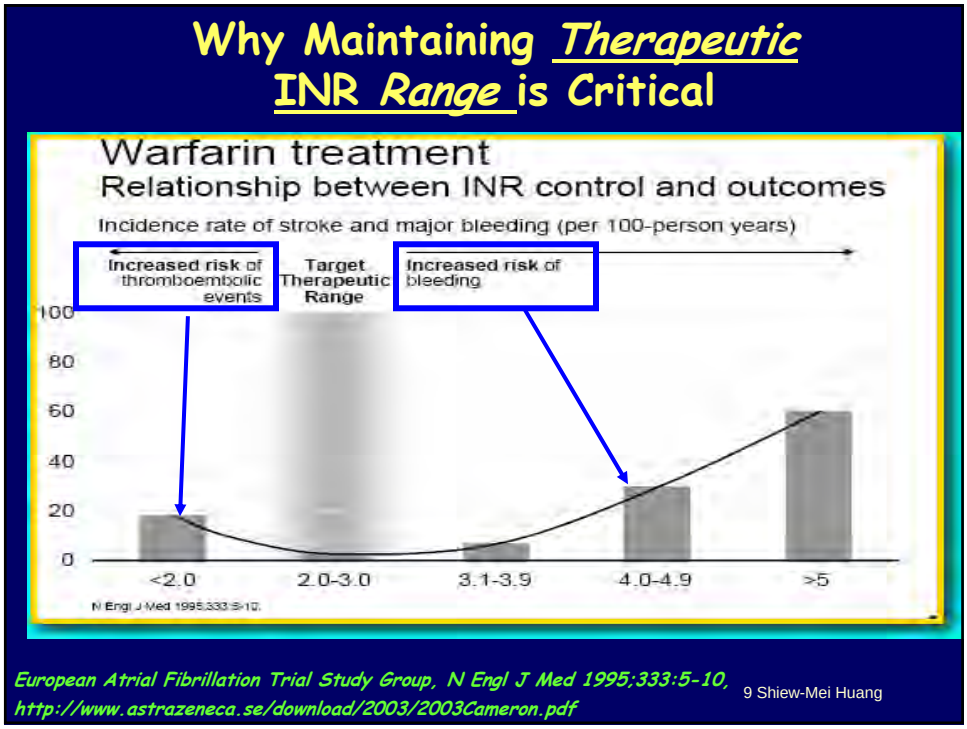
Why Maintaining Therapeutic INR Range is Critical
Warfarin treatment
Relationship between INR control and outcomes
Incidence rate of stroke and major bleeding (per 100-person years)
Increased risk of thromboembolic events
Target Therapeutic Range
Increased risk of bleeding
100
80
60
40
20
0
<2.0
2.0-3.0
3.1-3.9
4.0-4.9
>5
European Atrial Fibrillation Trial Study Group, N Engl J Med 1995;333:5-10,
http://www.astrazeneca.se/download/2003/2003Cameron.pdf
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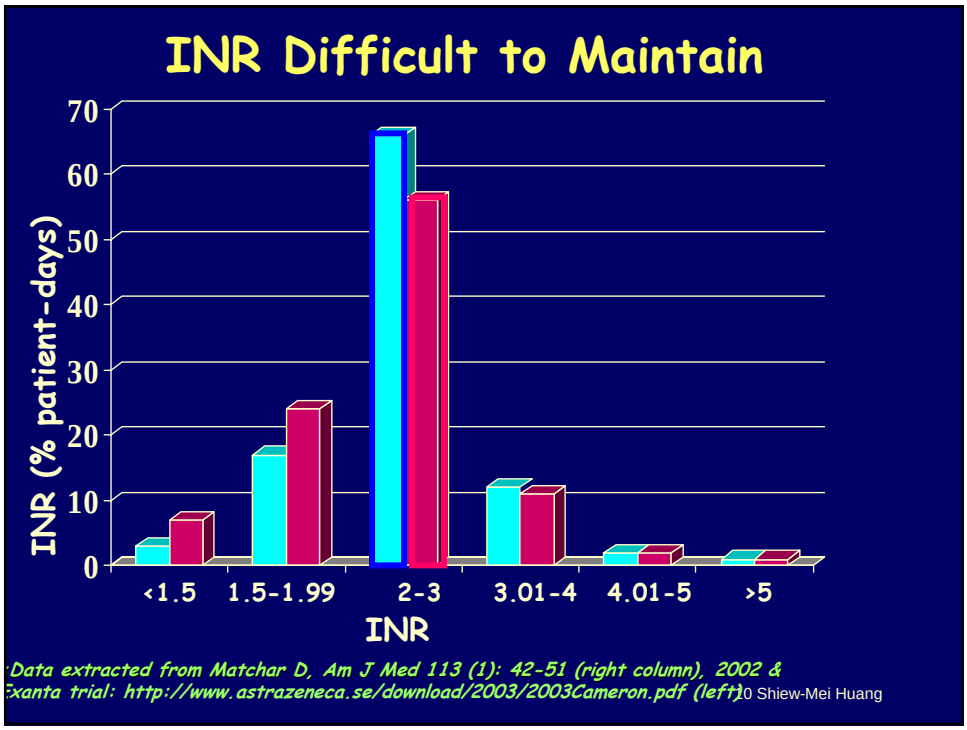
INR Difficult to Maintain
INR (% patient-days)
70
60
50
40
30
20
10
0
<1.5
1.5-1.99
2-3
3.01-4
4.01-5
>5
INR
Data extracted from Matchar D, Am J Med 113 (1): 42-51 (right column), 2002 &
Exanta trial: http://www.astrazeneca.se/download/2003/2003Cameron.pdf (left)
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How can we control the variability in response?

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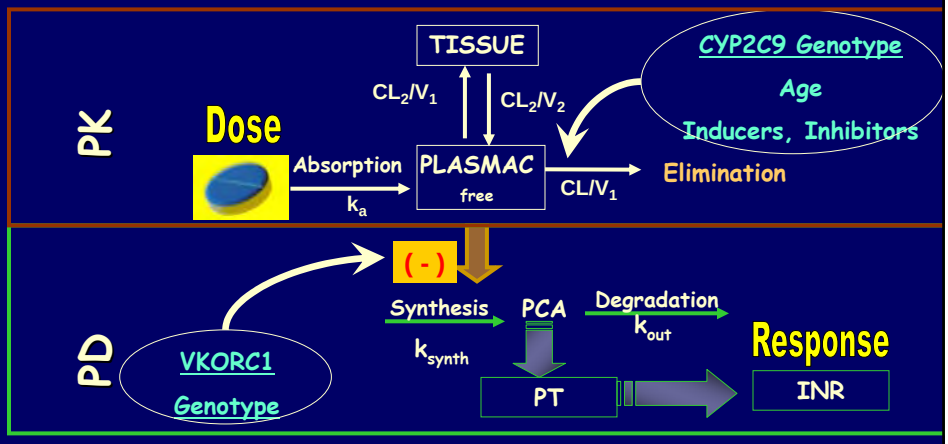
Warfarin Pharmacokinetics (PK) & Pharmacodynamics (PD)



< Lee JY , Madabushi R, Lesko LJ, Huang S-M, Schoenfeld D, Goldhaber SZ, Singer D, Kim M-J, Rahman NA, Frueh F, Gobburu J, *Leveraging Prior Quantitative Knowledge Demonstrates the Importance of Genotype-based Dosing of Warfarin*, American Conference on Pharmacometrics, Tuscon, AZ, March 2008>

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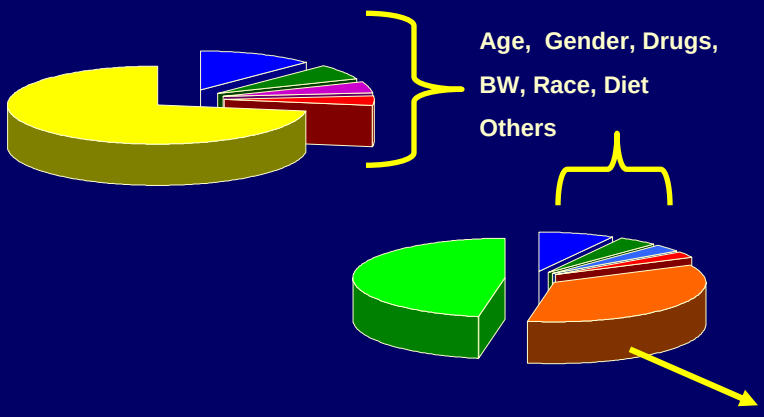
Predicting the Warfarin Stable Dose



<Modified from Caldwell M., CPSC Advisory Committee Meeting, November 14, 2005>
http://www.fda.gov/ohrms/dockets/ac/05/slides/8>

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CHEST guideline suggests against pharmacogenetic-based dosing until randomized data indicate that it is beneficial (Grade 2C)

< Ansell J, et al, Pharmacology and Management of the Vitamin K Antagonists*, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), Chest 133: 60-198, June 2008>

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Are there prospective studies to show "hard" clinical outcome?

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Recent developments

Voora et al, Thromb Haemost 93: 700-705 , 2005 (2C9)
Anderson et al, Circulation 116: 2563-2570, 2007 (2C9+VKORC1)
Gage et al, Clin Pharmacol Ther, Epub Feb 27, 2008 (2C9+VKORC1)
Caraco et al, Clin Pharmacol Ther 83: 460-470, 2008 (2C9) (PRC)
Wen et al, Clin Pharmacol Ther 84: 83-89, 2008 (2C9+VKORC1)

17-22% vs. 53-54%
clinical only vs. clinical + genetics

Prospective studies in different populations strongly suggest that pharmacogenetic-based dosing improves time to therapeutic INR and reduces ADRs

Results of large prospective studies within the *International Warfarin Pharmacogenetics Consortium* are forthcoming

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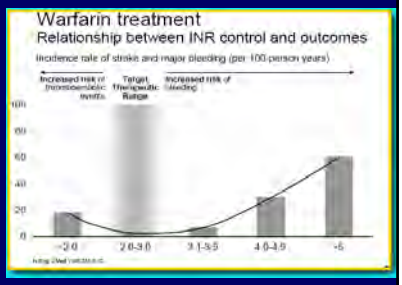
Where are "hard" clinical trial data with bleeding as the endpoint?

- It is long-standing practice to use INR as a surrogate for appropriate anticoagulation

- Association of INR with *CYP2C9* & *VKORC1* genotypes



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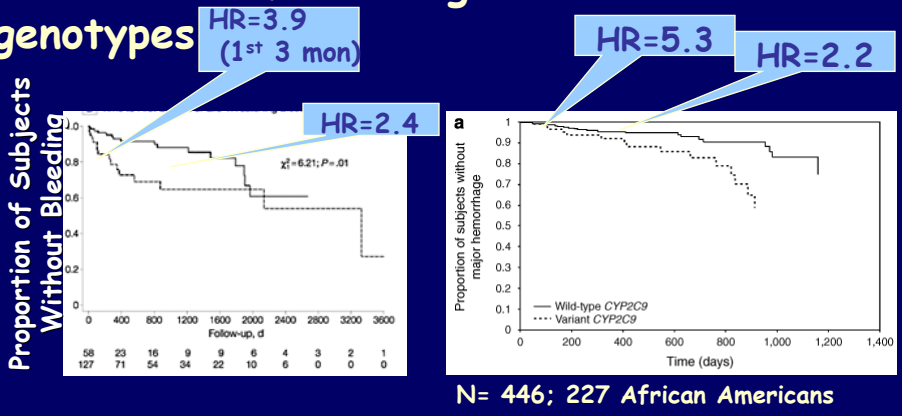
Where are "hard" clinical trial data with bleeding as the endpoint?

Association of bleeding with *CYP2C9* genotypes



N= 446; 227 African Americans

<Data from Higashi JAMA 2002 and Limdi Clin Pharmacol Ther 2008>

How do we dose patients with *CYP2C9* and *VKORC1* info?

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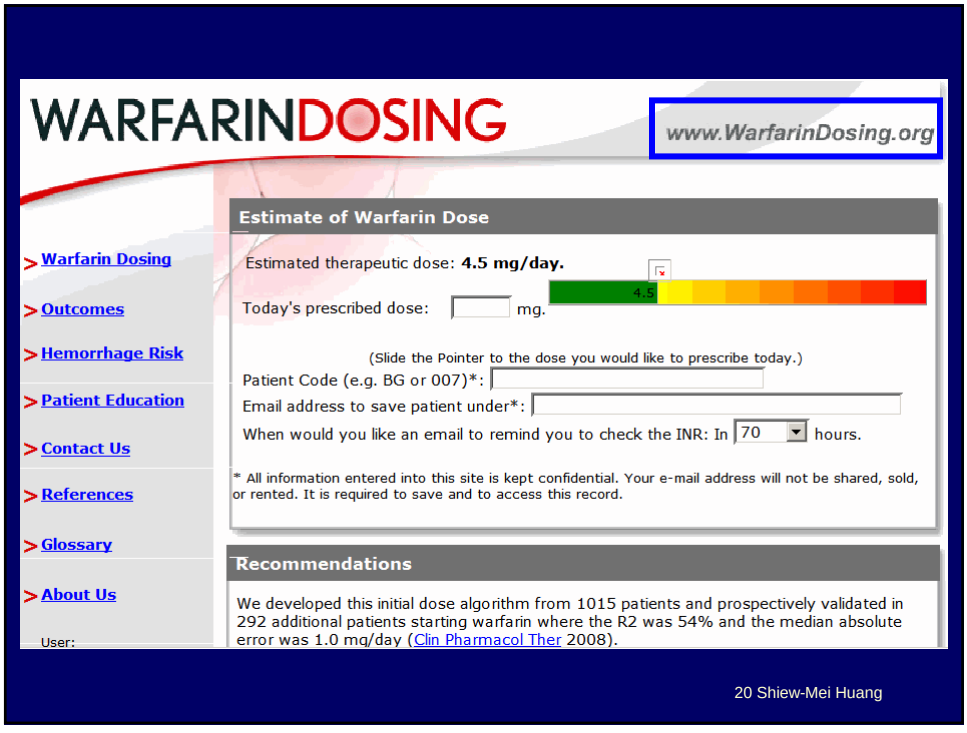

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Estimated dose of warfarin (mg/day) according to genotype for an "average" patient (65y.o., male, Caucasian, BSA 2.0, nonsmoker, no other drugs, Dx atrial fibrillation, target INR 2.5

CYP2C9 genotype

VKORC1 genotype	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	6	5	4	4	3.5	3
GA	5	4	3	3	2.5	2
AA	3	2.5	2	2	2	1.5

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Can the dosing algorithms be applied to various ethnic groups?

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Comparative dosing algorithms applied to different ethnic groups

Algorithm (#variables)	R2 White	R2 AA	%Dose (±1mg) White	%Dose (±1mg) AA
Empirical	-	-	29	34
CYP2C9-- Hill (12) Gage (9)	6-21	18-28	33-42	29-38
CYP2C9+VKOR- Sconce (5) Gage (?) Anderson (10)	38-43	23-34	42-48	33-41
Schelleman-Kimmel (16)	31-37	23-31	47-48	34

->All algorithms performed better than empirical

<Data derived from Schelleman et al, Clin Pharmacol Ther 2008; September (in press)>

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Frequency of VKORC1

-1639 G>A	AA	AG	GG
Caucasians (N=297)	19%	56%	25%
Spanish (N=105)	32%	40%	28%
Chinese (N=104)	80%	18%	2%
African Americans (N=159)	0%	21%	79%

Asians may need a lower dose

<Sconce et al. Blood 2005, Yuan et al. Human Mol Genetics 2005, Schelleman et al. Clin Pharmacol Ther 2007, Montes et al Br J Haemat 2006>

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Are tests readily available?

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- There are three FDA approved tests (2 additional ones in review*) and numerous laboratory developed tests on the market
  [Approved: Nanosphere; Autogenomics; ParagonDx]
  →Available tests providing results within 1 hour

- As the use increased, so would the availability of tests at POC

*<*Personal communication- Steve Gutman; Courtney Harper; Lakshman Ramamurthy >*

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What are potential issues for NOT genotyping?

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- Takes longer to reach therapeutic INR, stable dose
- Poor prediction of dose based on clinical data alone
- 70-75%* of patients not being treated in anticoagulation centers (daily INR not feasible, impractical & costly in private practice)
- 4,500-22,000 additional serious bleeding events annually

<Higashi JAMA, April 2002; Gage Clin Pharmacol Ther, September 2008; *estimate from Garcia- Anticoagulation Forum; McWilliams Pharmacogenomics, May 2008>

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Minimize/Eliminate the uncertainties!!

How can it NOT help by incorporating additional information?

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Summary

- FDA has updated the warfarin label and approved/cleared genetic tests- some with rapid turnaround time

- More than a dozen publications showed value of genetic testing

- More tests being reimbursed by insurance

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Summary (2)

- We have sufficient data to act and recommend genotyping at the initiation of warfarin

- We should move from the present "trial & error" to more "educated prediction of individual dose"

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Acknowledgement

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References

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