AMCP's 21st Annual Meeting & Showcase

Pharmacogenomics and Warfarin Testing: The Case for Personalized Medicine

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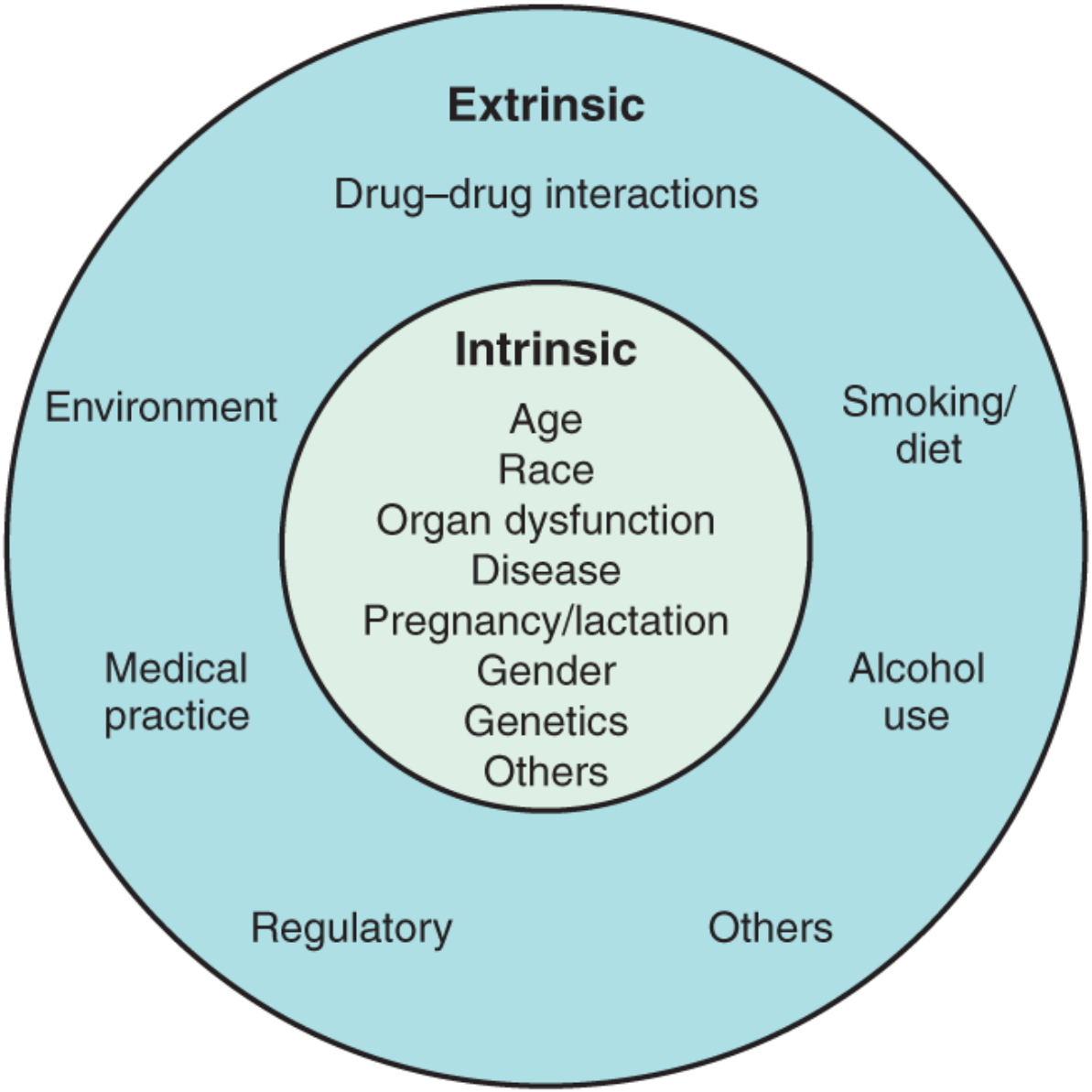
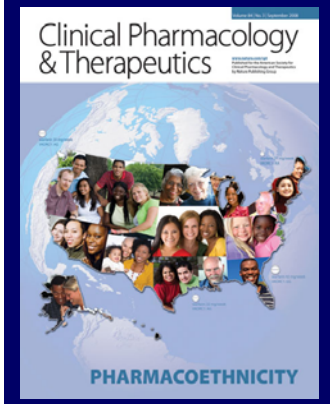
Conflict of Interest Statement

I, Shiew-Mei Huang, PhD, declare no conflicts of interest or financial interests with any pharmaceutical manufacturers, medical device company, or in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.





<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>

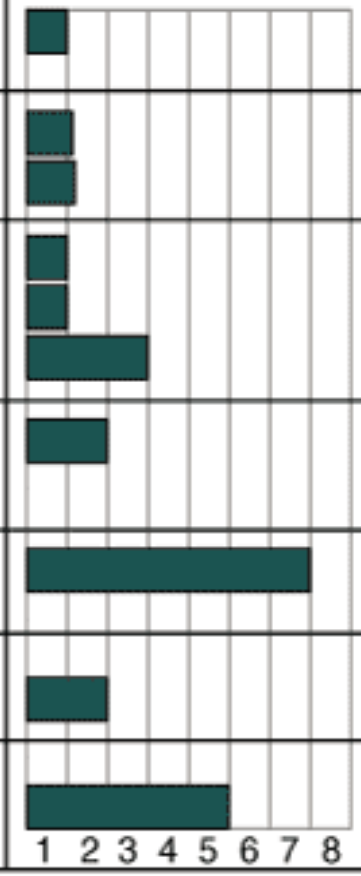
FDA Labeling Regulations

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>

Comparative exposure and dose recommendation in subgroups with various patient factors

Group	Ethnic factor	Fold change in exposure (AUC)	Initial dose (mg)	Daily dose (mg)
1	Control	1-fold	10–20	5–40
2	Hepatic impairment	1.1-fold (mild) 1.2-fold (moderate)	10–20 10–20	5–40 5–40
3	Renal impairment	1-fold (mild) 1-fold (moderate) 3-fold (severe)	10–20 10–20 5	5–40 5–40 ≤10
4	Race	2-fold (Asians)	5	5–20
5	Cyclosporine	7-fold		5
6	Gemfibrozil	1.9-fold		10
7	Lopinavir/ ritonavir	5-fold		10



(Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); Labeling from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.); **November 2007 labeling**

<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>

Recent Example

Dosage & Administration Tetrabenazine

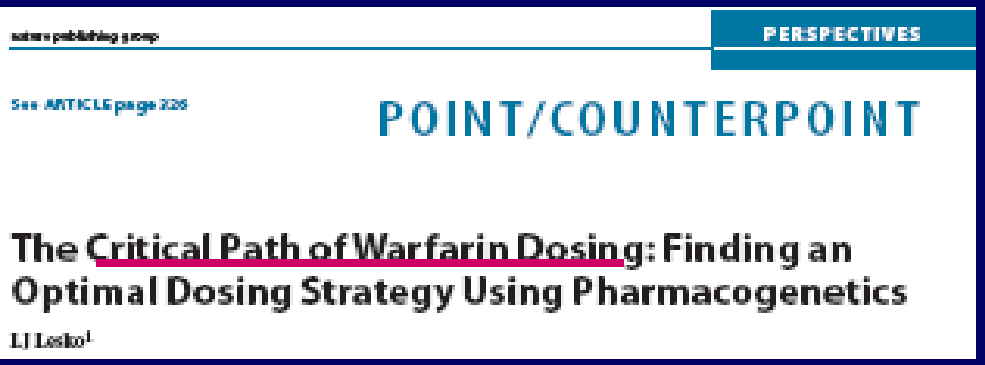
Dosing Recommendations above 50 mg per day Patients who appear to require doses greater than 50 mg per day should be *genotyped for CYP2D6*.

The dose of XENAZINE should be individualized.

Xenazine (Prestwick, tetrabenazine) labeling approved August 15, 2008
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory

Post-marketing Labeling Changes

Public Debates


PERSPECTIVES

See ARTICLE page 226

POINT/COUNTERPOINT

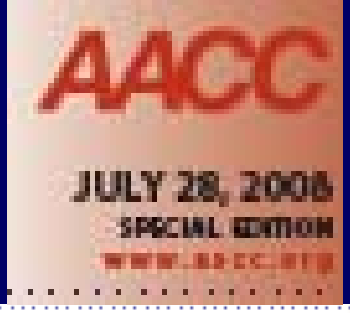
The Critical Path of Warfarin Dosing: Finding an Optimal Dosing Strategy Using Pharmacogenetics

LJ Lesko[1]


Warfarin and Pharmacogenomic Testing: The Case for Restraint

DA Garcia[1]

LJ Lesko, Clin Pharmacol & Ther, September 2008
DA Garcia, Clin Pharmacol & Ther, September 2008




Is Warfarin Pharmacogenomic Testing Ready for Prime Time?

Today's Debate to Focus on Implementation Issues


Opponents Want More Data

Warfarin Debate, from page 1



Proponents Emphasize Potential

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)

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

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FDA News

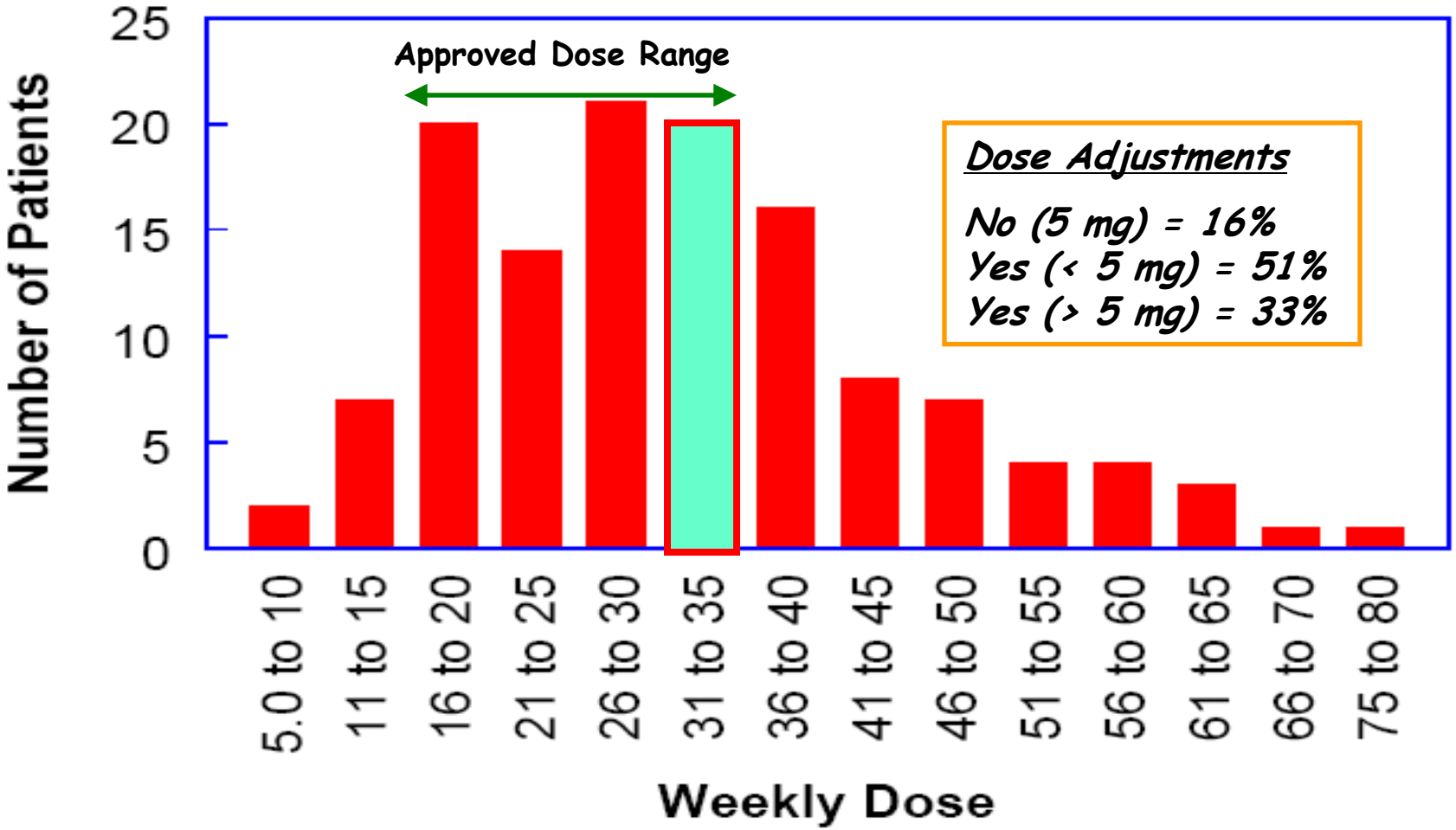
FOR IMMEDIATE RELEASE
August 16, 2007

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

FDA Approves Updated Warfarin (Coumadin) Prescribing Information

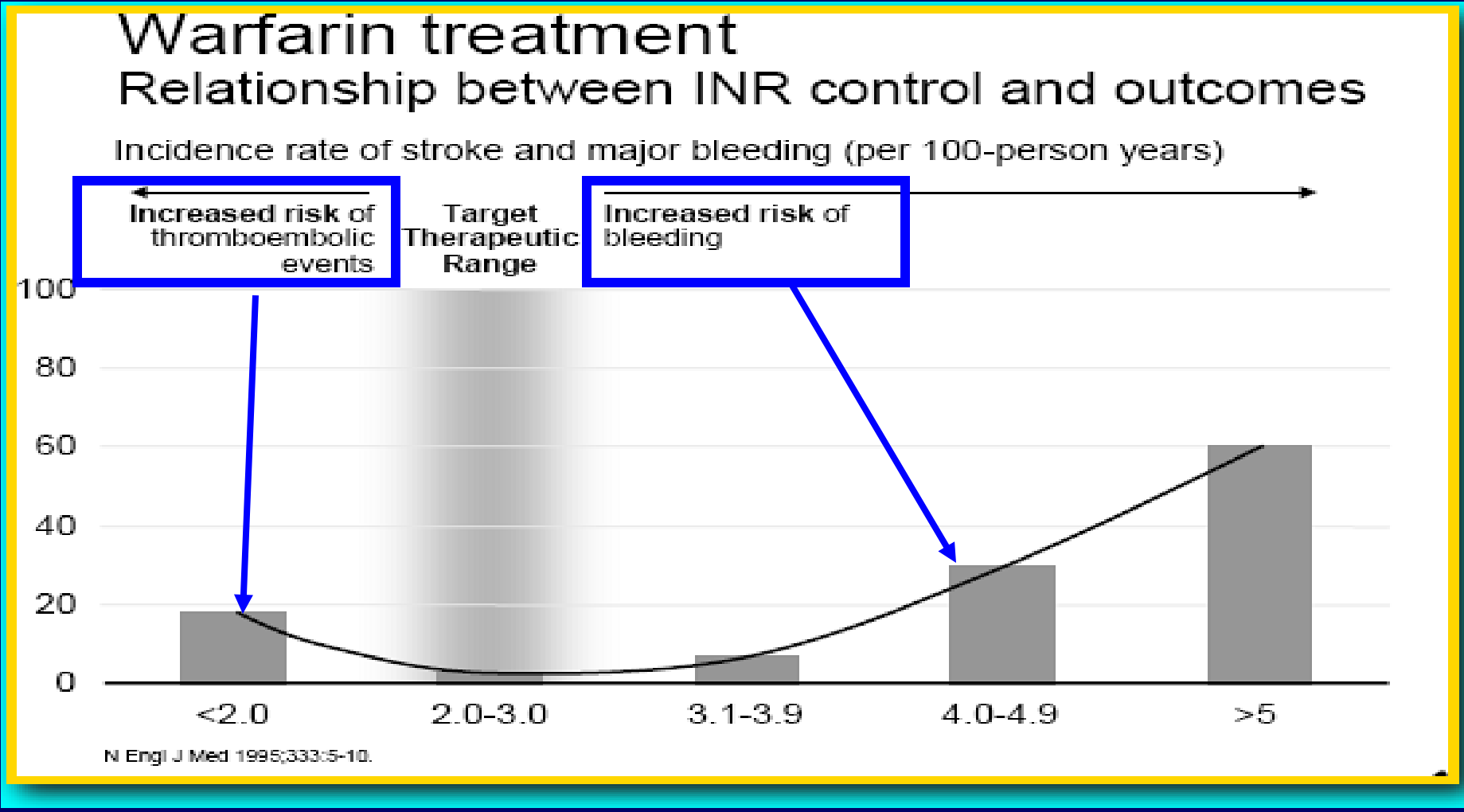
New Genetic Information May Help Providers Improve Initial Dosing Estimates of the Anticoagulant for Individual Patients

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



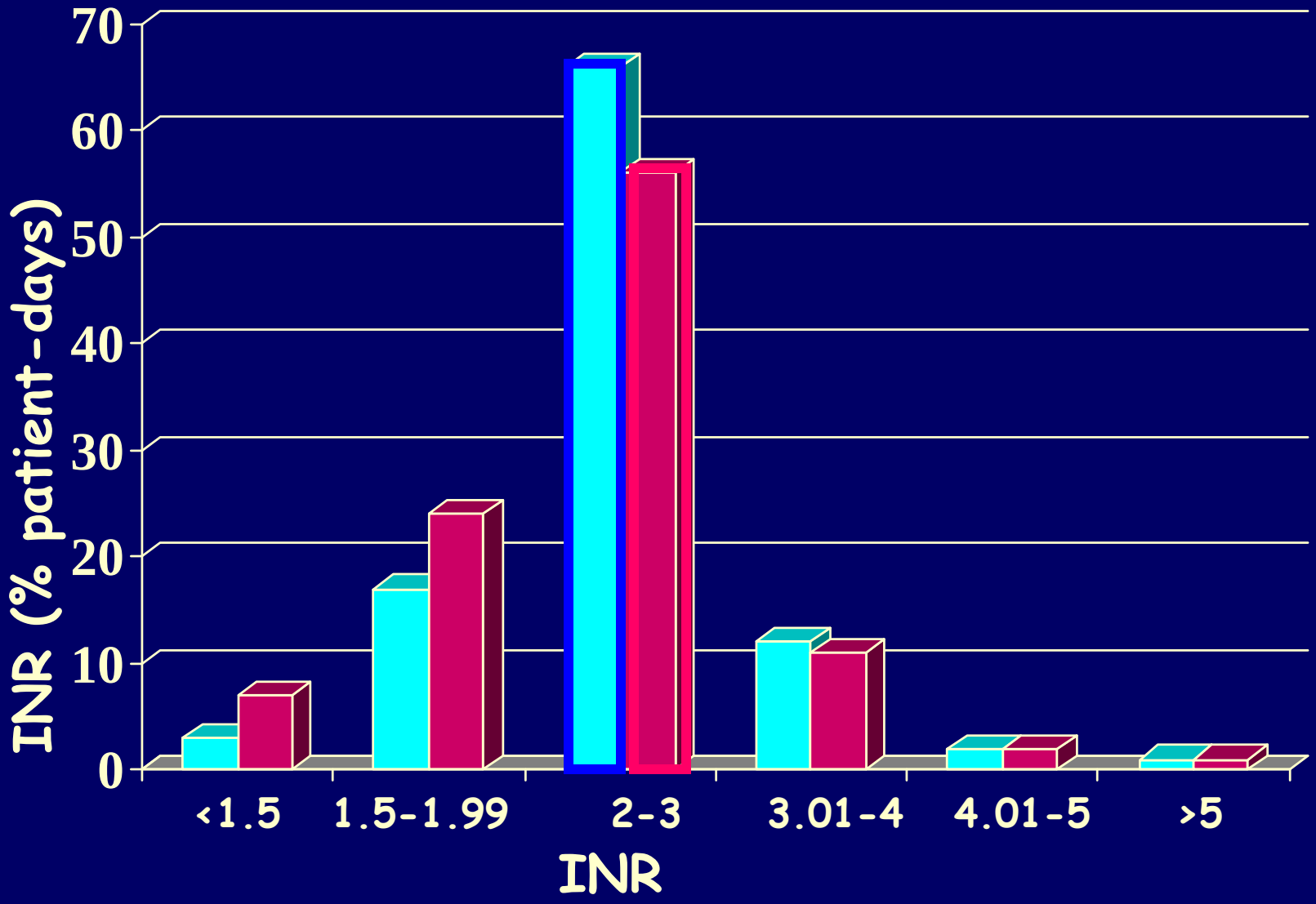
Reynolds KK et al. Personalized Medicine 2007

Why Maintaining *Therapeutic* INR *Range* is Critical



European Atrial Fibrillation Trial Study Group, N Engl J Med 1995;333:5-10,
http://www.astrazeneca.se/download/2003/2003Cameron.pdf

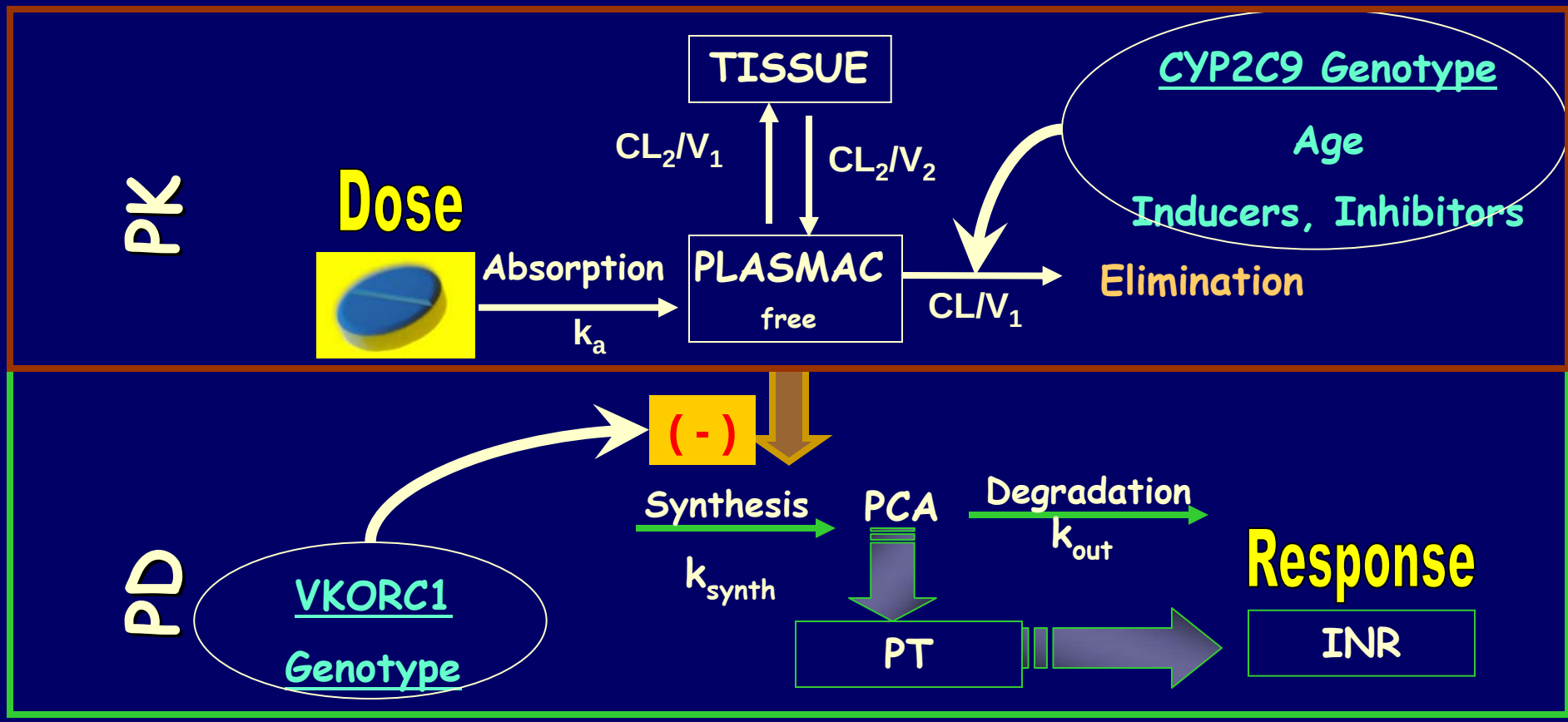
INR Difficult to Maintain



<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)

How can we control the variability in response?

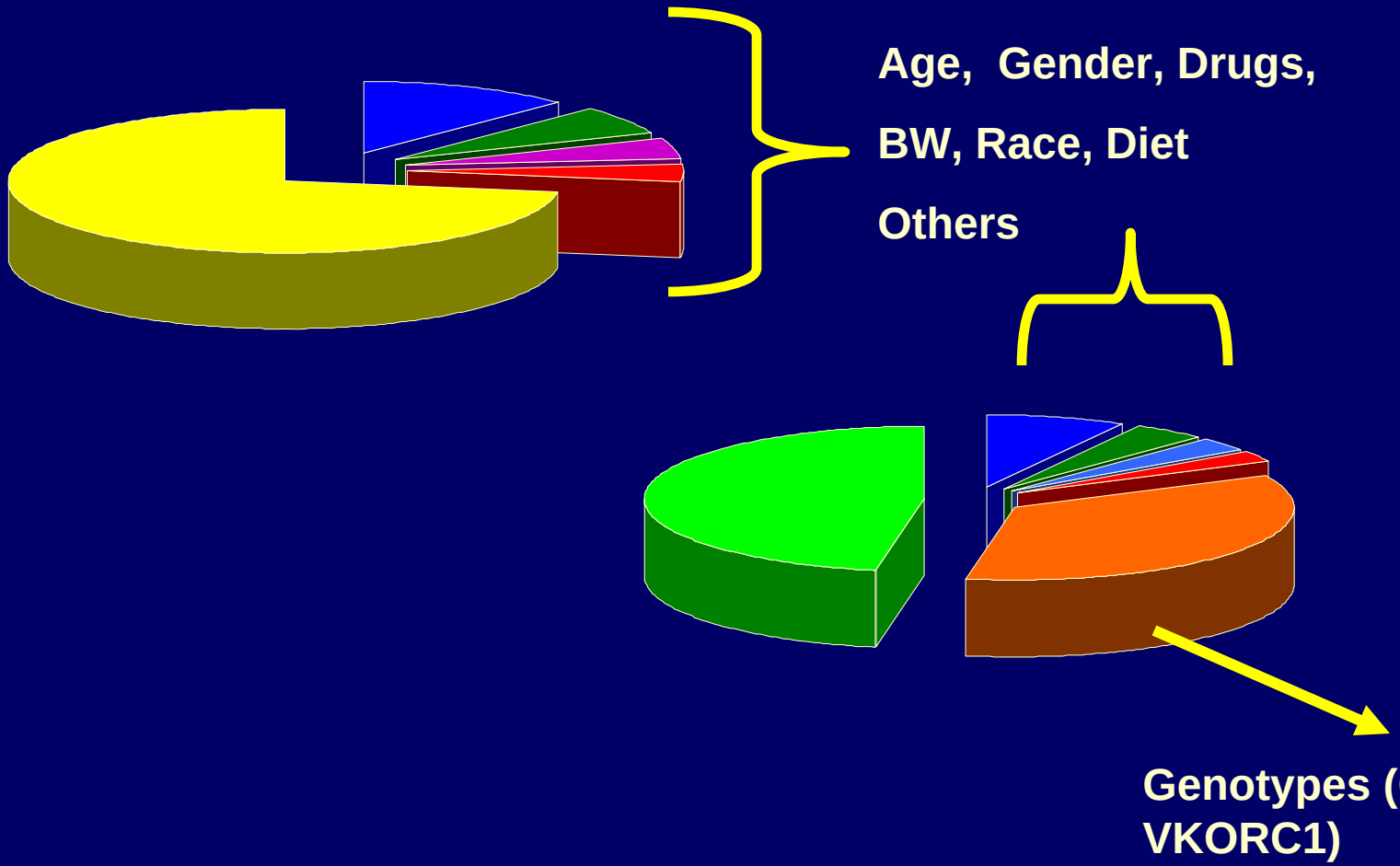
Warfarin Pharmacokinetics (PK) & Pharmacodynamics (PD)



< 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>

<Kim MJ, Huang S-M, Meyer UA, Rahman A, Lesko LJ, J Clin Pharmacol (in press)

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>

Recent Development

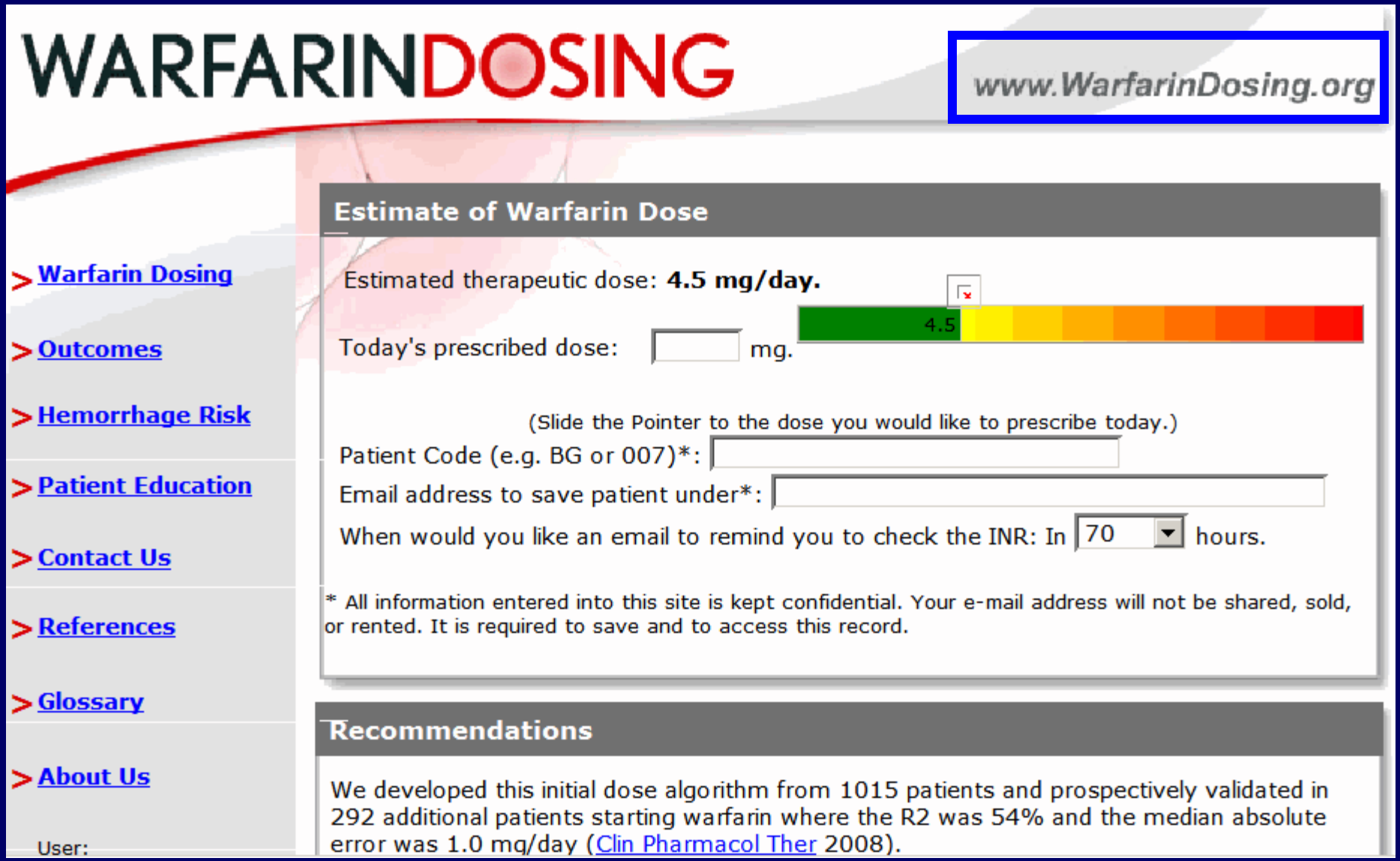
Voora et al, Thromb Haemost 93: 700-705 , 2005 (2C9)
Anderson et al, Circulation 116: 2563-2570, 2007 (2C9+VKORC1)
Gage et al, Clin Pharmacol Ther, Epub Feb 27, 2008 (2C9+VKORC1)
Caraco et al, Clin Pharmacol Ther 83: 460-470, 2008 (2C9) (PRC)
Wen et al, Clin Pharmacol Ther 84: 83-89, 2008 (2C9+VKORC1)
IWPC, NEJM, 360(6): 753-764, 2009 (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

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


WARFARINDOSING
www.WarfarinDosing.org
Warfarin Dosing
Outcomes
Hemorrhage Risk
Patient Education
Contact Us
References
Glossary
About Us
User:
Estimate of Warfarin Dose
Estimated therapeutic dose: 4.5 mg/day.
4.5
Today's prescribed dose: mg.
(Slide the Pointer to the dose you would like to prescribe today.)
Patient Code (e.g. BG or 007)*:
Email address to save patient under*:
When would you like an email to remind you to check the INR: In 70 hours.
* All information entered into this site is kept confidential. Your e-mail address will not be shared, sold, or rented. It is required to save and to access this record.
Recommendations
We developed this initial dose algorithm from 1015 patients and prospectively validated in 292 additional patients starting warfarin where the R2 was 54% and the median absolute error was 1.0 mg/day (Clin Pharmacol Ther 2008).

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

<Kim MJ, Huang S-M, Meyer U, Rahman, A, Lesko LJ, J Clin Pharmacol (in press)>

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>

Are tests readily available?

- There are four FDA approved tests (additional ones in review*) and numerous laboratory developed tests on the market
  [*Approved: Nanosphere, Autogenomics, ParagonDx, Osmetech*]

  →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 >*

- 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>

Minimize/Eliminate the uncertainties!!

How can it <u>NOT</u> help by incorporating additional information?

Therapeutic area	Drug products: generic (brand) names	Ethnicity information	Genetics information
Cardiorenal	Isosorbide dinitrate–hydralazine (BiDil)	Indicated for self-identified blacks	
	Angiotensin II antagonists and ACE inhibitors	Smaller effects in blacks[a]	
Metabolic	Rosuvastatin (Crestor)	Lower dose for Asians	
Transplant	Azathioprine (Imuran)		Dose adjustments for TPMT variants
	Tacrolimus (Protopic)	Higher dose for blacks	
Oncology	Trastuzumab (Herceptin)		Indicated for HER2 overexpression
	Irinotecan (Camptosar)		Dose reduction for *UGT1A1*28*
	6-Mercaptopurine (Purinethol)		Dose adjustments for TPMT variants
	Erlotinib (Tarceva)		Different survival and tumor response in EGFR-positive and -negative patients reported
Antiviral	Maraviroc (Selzentry)		Indicated for CCR5-positive patients
	Oseltamivir (Tamiflu)	Neuropsychiatric events mostly reported in Japan	
	Abacavir (Ziagen)		Boxed warning for HLA-B*5701 allele
Pain	Codeine		Warnings for nursing mothers that CYP2D6 UM metabolized codeine to morphine more rapidly and completely[b]
Hematology	Warfarin (Coumadin)	Lower dose for Asians	Lower initial dose for CYP2C9- and VKORC1-sensitive variants
Psychopharmacological	Thioridazine (Mellaril)		Contraindication for CYP2D6 PM
	Atomoxetine (Strattera)		Dosage adjustments for CYP2D6 PM; no drug interactions with strong CYP2D6 inhibitors expected for PM
Neuropharmacological	Carbamazepine (Tegretol)	Box warning for Asians with variant alleles of *HLA-B*1502*	Box warning for Asians with variant alleles of *HLA-B*1502*

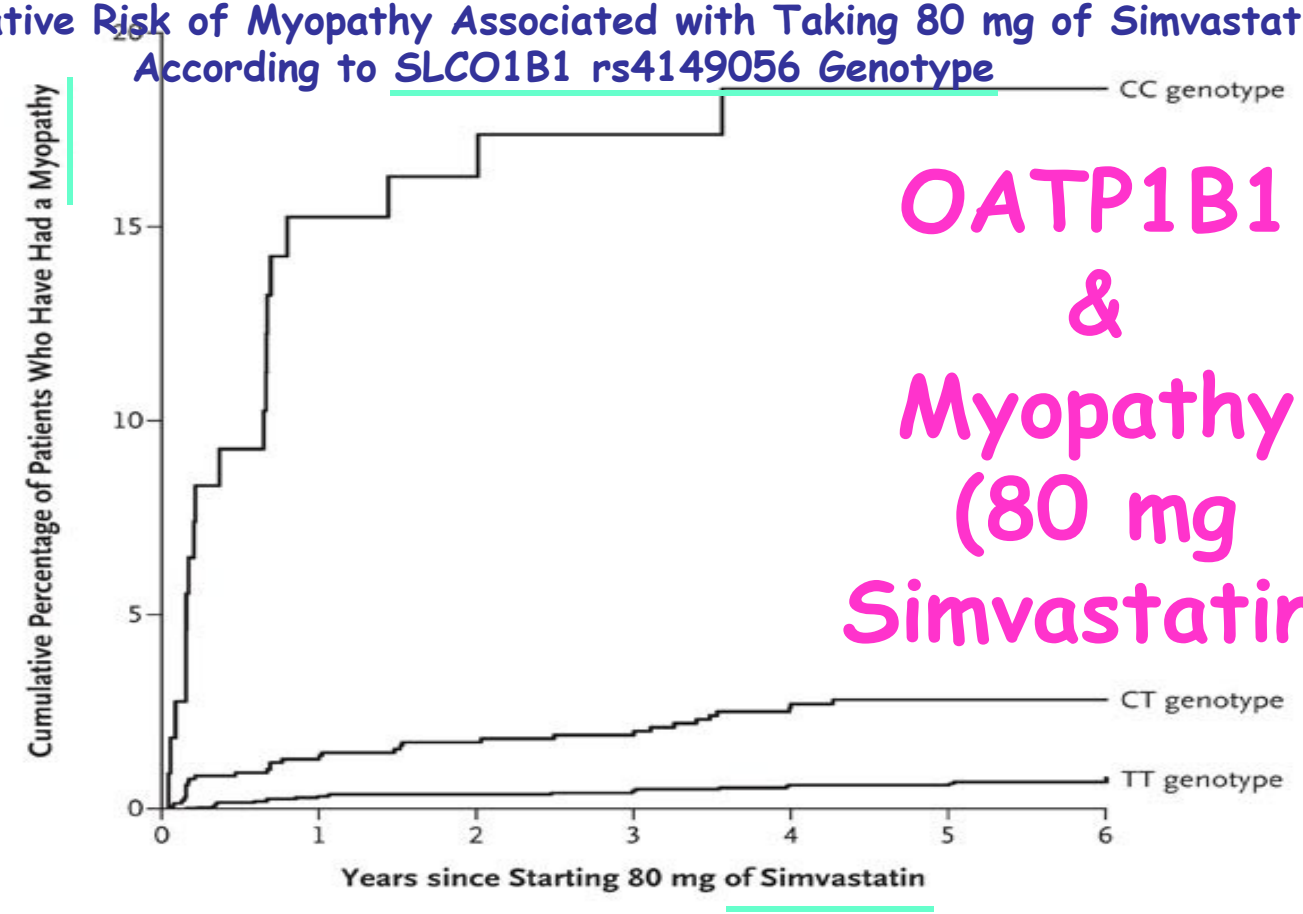
ACE, angiotensin-converting enzyme; CCR5, chemokine (C-C motif) receptor 5; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; PM, poor metabolizer; TPMT, thiopurine methyl transferase; UGT, uridine diphosphate glucuronosyl transferase; UM, ultra-rapid metabolizer; VKORC, vitamin K reductase complex. Data from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

[a]A general statement in the candesartan (Atacand) labeling. [b]http://www.fda.gov/cder/drug/infopage/codeine/default.htm.

<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>

Additional Opportunities

Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype



OATP1B1 & Myopathy (80 mg Simvastatin)

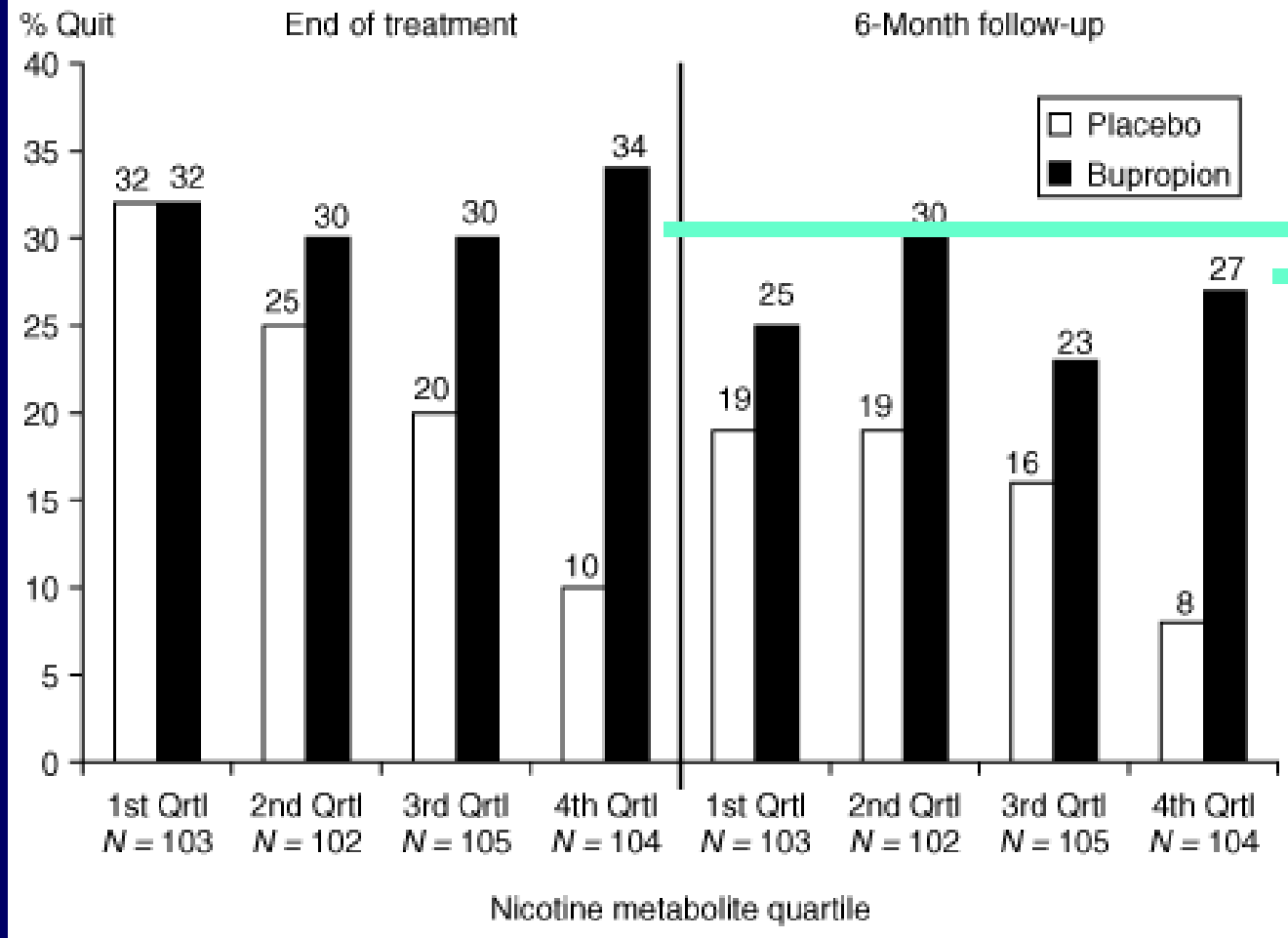
Cumulative No. and Percentages with Myopathy

Genotype	Population Frequency	Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

The SEARCH Collaborative Group. N Engl J Med 2008;10.1056/NEJMoa0801936

Toward Personalized Therapy for Smoking Cessation: A Randomized Placebo-controlled Trial of Bupropion

F Patterson[1], RA Schnoll[1], EP Wileyto[1], A Pinto[1], LH Epstein[2], PG Shields[3], LW Hawk[4], RF Tyndale[5,6], N Benowitz[7–9] and C Lerman[1]

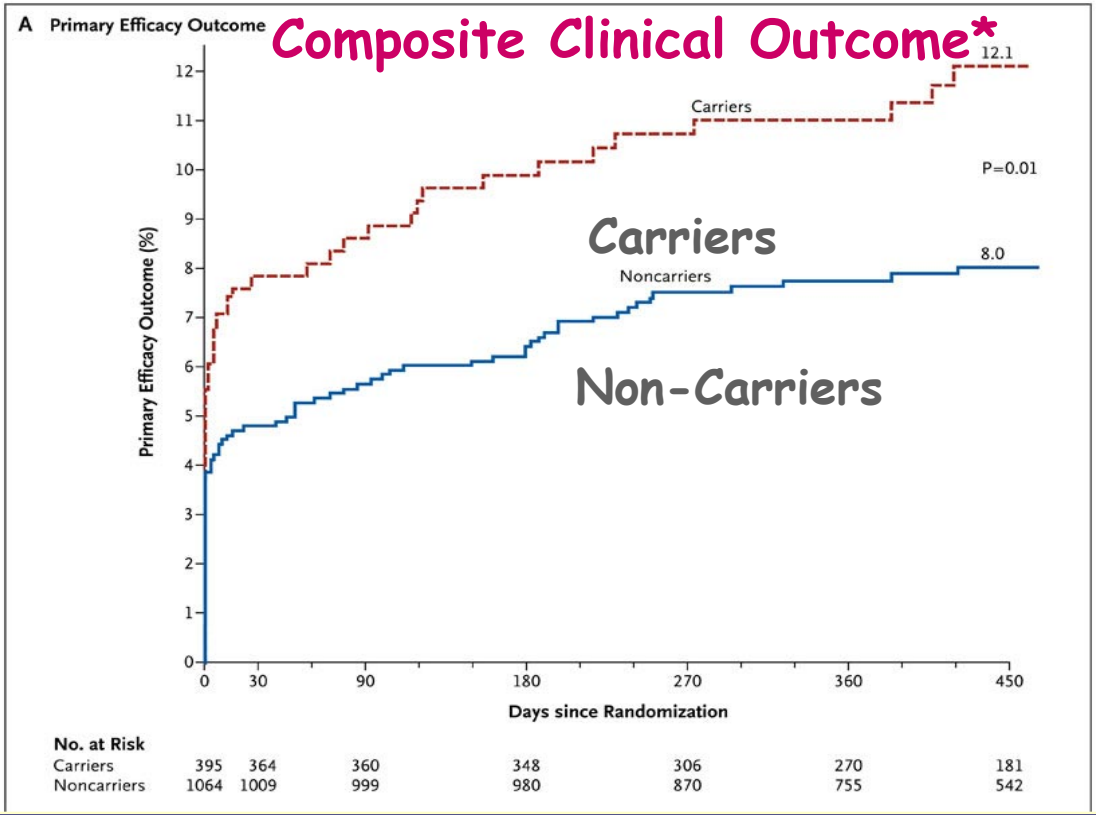


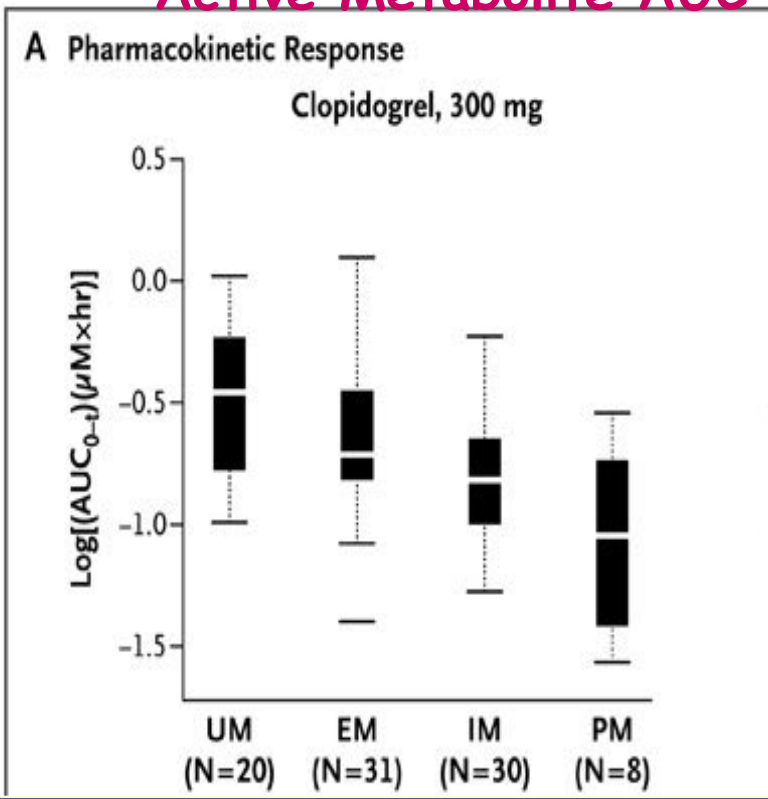
Faster Metabolizers of nicotine benefit from bupropion

CYP2A6 genotype

<Patterson et al, Clin Pharmacol Ther. 84(3): 320-325, 2008>

CYP2C19 and Clopidogrel





Carriers: with at least one variant alleles, *2, 3, 4, 5, 8 (IM+PM);

***Outcome:** a composite of death from cardiovascular causes, myocardial infarction, or stroke

PM: with two reduced function alleles
IM: one reduced function allele
EM: no variant alleles;
UM: one or two *17

<Mega J et al. N Engl J Med 2008;10.1056/NEJMoa0809171 >

Summary

- Variations in drug response may be attributed to various intrinsic and extrinsic factors

- It is important to assess safety, effectiveness and dose-exposure response in various subgroups during drug development and apply the results of exposure-response to better define optimum individual dosing regimens

Summary (2)

- FDA encourages early communications (e.g., FDA/industry early meetings, voluntary genomic submissions, guidances, best practices)

- As the pharmacogenetics/ pharmacogenomics information becomes available; its association with the safe and effective use of drugs has been incorporated in the drug label

Summary (3)

- 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

Summary (4)

- 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"