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This speaker has nothing to disclose.

Optimizing Warfarin Dose: Tools and Strategies for Today and Tomorrow

Pathology Grand Rounds
December 19, 2008

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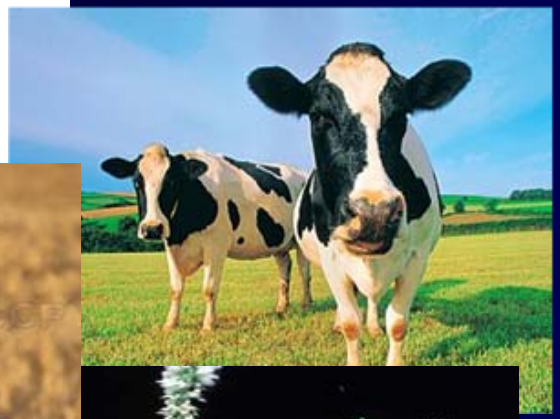
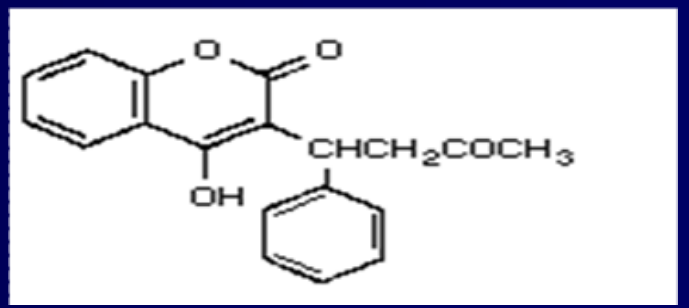
Objectives

- *Become familiar with clinical challenges of warfarin dosing*
- *Learn about laboratory and clinical tools available to guide selection of warfarin dose*
- *Understand strengths and limitations of algorithms designed to optimize warfarin dose through consideration of both clinical and laboratory data.*

The Storied History of Warfarin



WARF




KILL RATS!
STOP
THIS ROBB
Rat Killers
WARFARIN

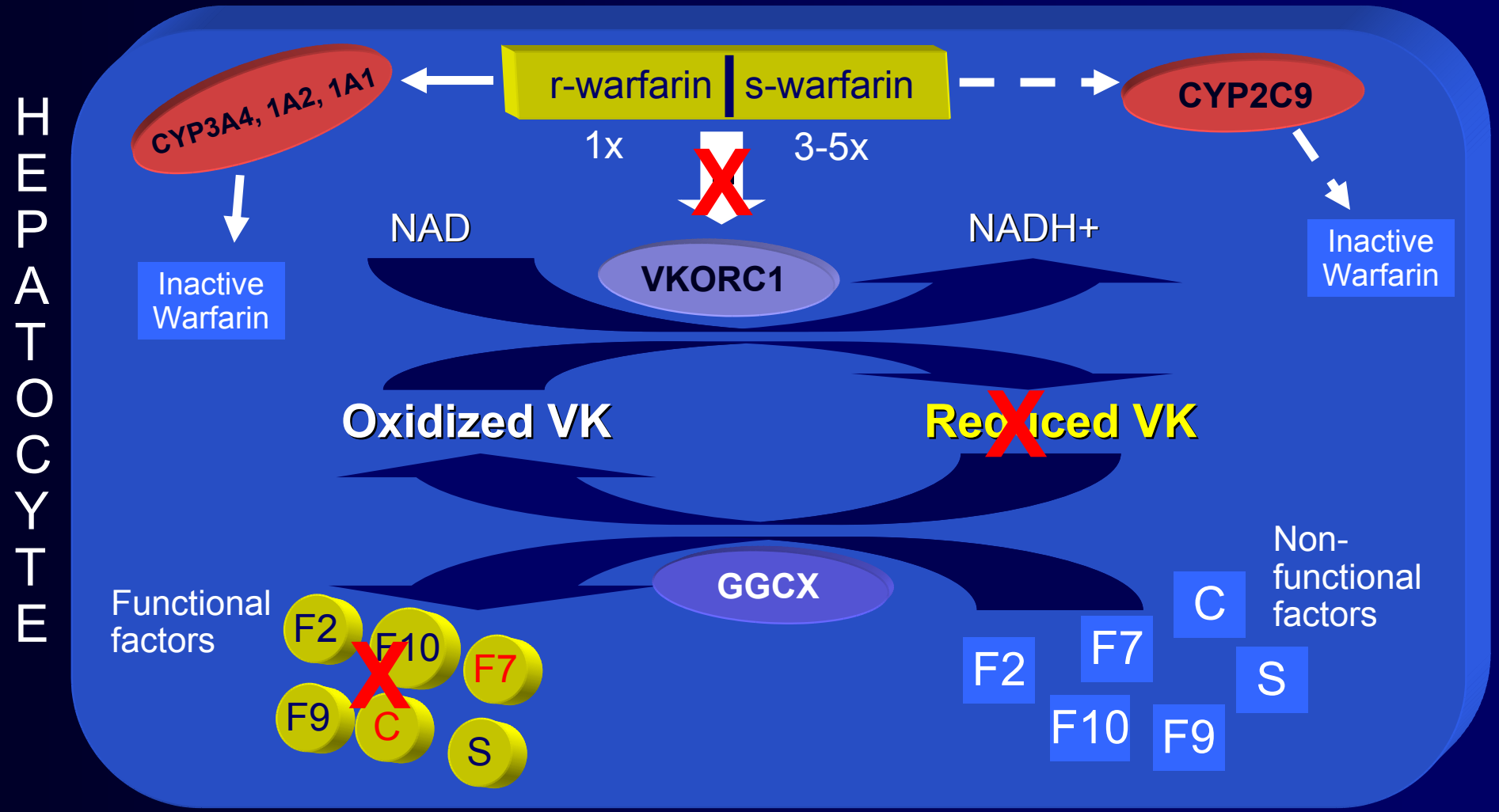
Warfarin / Anticoagulant (AC) Facts

- Over 31 million warfarin prescriptions in U.S. in 2004
  - Atrial fibrillation
  - Venous thromboembolism
  - Mechanical heart valve
  - Other

- With aging population use is increasing:
  - 45% ↑ in warfarin RX 1998-2004

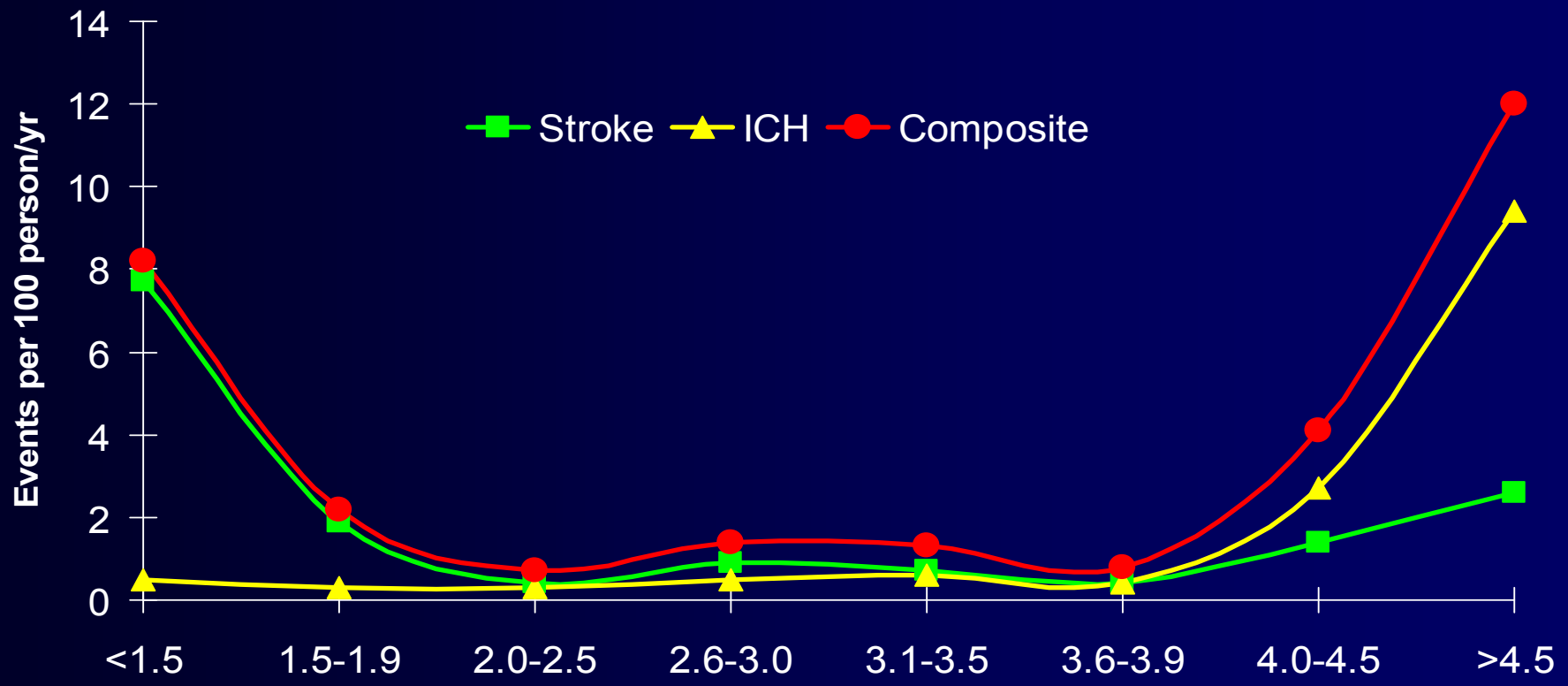
Wysowski et al. *Arch Int Med* 2007; 167(13): 1414-1419
Budnitz et al. *JAMA* 2006; 296(15): 1858-1866

Warfarin: Mechanism of Action



Warfarin: Narrow Therapeutic Range

- Effect assessed by international normalized ratio (INR)
- Dosing titrated to INR target range (usual INR range 2-3)



Hylek et al. *NEJM* 2003; 349: 1019-1026

Warfarin: Time in Therapeutic Range (TTR)

(Indirect comparative data)

	TTR (%)	Above (%)	Below (%)
Usual Care	33-64	8-30	20-50
AC service	59-92	6-16	7-31
Clinical Trial	48-83	1-24	8-40

30-60% NOT Therapeutic

Ansell et al. *CHEST* 2004; 126: 204s-233s

Warfarin Bleeding

	1st 3 mos.	>3mos
Major Bleed	2%	2.7%/yr
ICH	1.5%	0.7%/yr
Fatal Bleed	0.4%	0.6%/yr

Over 30,000 major bleeds/yr
Over 3,500 intracranial bleeds/yr

Linkins et al. *Annal Int Med* 2003; 139: 893- 900
Fang et al. *J Am Geri Society* 2006; 54: 1231-1236

Warfarin Initiation

- Individual dose response is highly variable:
  - Maintenance dose may range from **1-40 mg/day**

- Standard initiation schemes better than usual care:

- INR therapeutic by warfarin day#5 = **45-85%**
- INR $\geq$ 4.0 during initiation = **5-30%**

- Limited translation to daily practice

A Case of Mr. A

A 32yo, 135kg, male presents with L Leg pain & swelling. PMHX: HTN

Exam: pitting edema of L leg to thigh.

Ultrasound: L Common femoral DVT

Labs: Normal PT and PTT. NI CBC. NI CMP

A Case of Mr. A (continued)

Acute DVT Diagnosed

Started on Fondaparinux 10mg SC daily &

Warfarin 5mg daily:

Day	Dose	INR
1	5	-
2	5	1.2
3	7.5	-
4	7.5	1.9
5	5	-
6	7.5	-
7		4.8

A Case of Mrs. L

A 77yo, 52kg, female presents with acute severe abdominal pain. PMHX: afib

Exam: Abdomen with peritoneal signs

CTA: SMA thrombosis + ischemic bowel

Labs: NI PT and PTT. NI CBC. Albumin 2.9

A Case of Mrs. L (continued)

Patient went to OR for emergent thrombectomy and partial small bowel resection.

Post-op begun on heparin gtt.

Warfarin 5mg x2 begun→ INR >15

Rectus hematoma developed. Given 5mg Vit K. Stabilized.

A Case of Mrs. L (continued)

INR 1.7 → warfarin 2mg x1

→ warfarin 1mg x1

INR 9.0 → warfarin held x3, Vit k 5mg

INR 2.3 → warfarin 1mg q Tues and Sat

INR 2.6 → warfarin 1mg q Tues and Sat

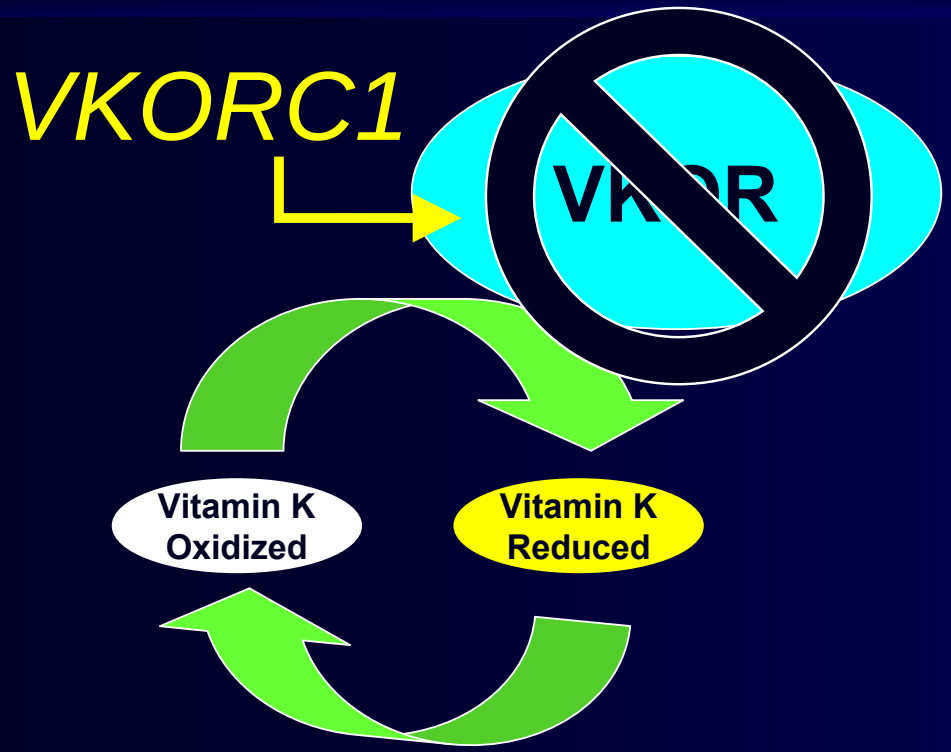
INR 2.4

Can pharmacogenetics take the "*guessing*" out of warfarin initiation and improve outcomes?

Coumadin® label (Bristol-Myers Squibb Company) was revised August, 2007

- Suggests lower doses may be required for individuals with
  - *VKORC1* variants (especially the -1639G>A)
  - *CYP2C9*2 and *3*
- Questions
  - What are these variants?
  - How should genetic results be used?
  - Will the testing improve patient care?
  - Should this testing be routine? How? When? Where?

Warfarin acts via VKOR



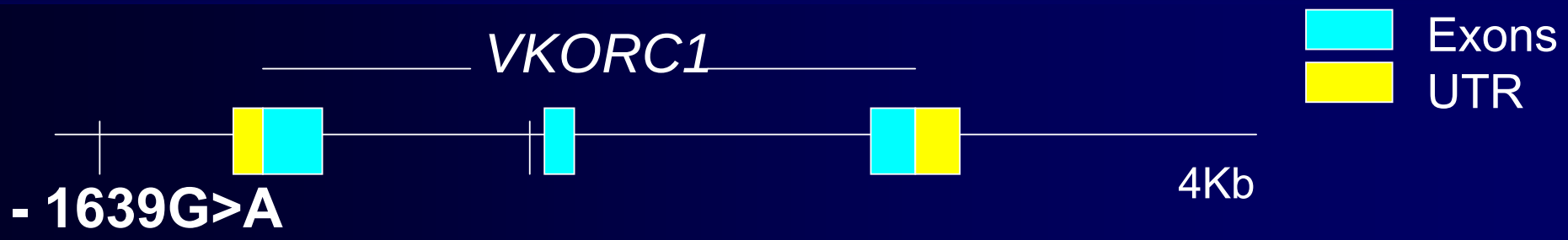
r,s-warfarin

Drug response =

sensitive (low dose)
typical (~5mg/d)
resistant (high dose)

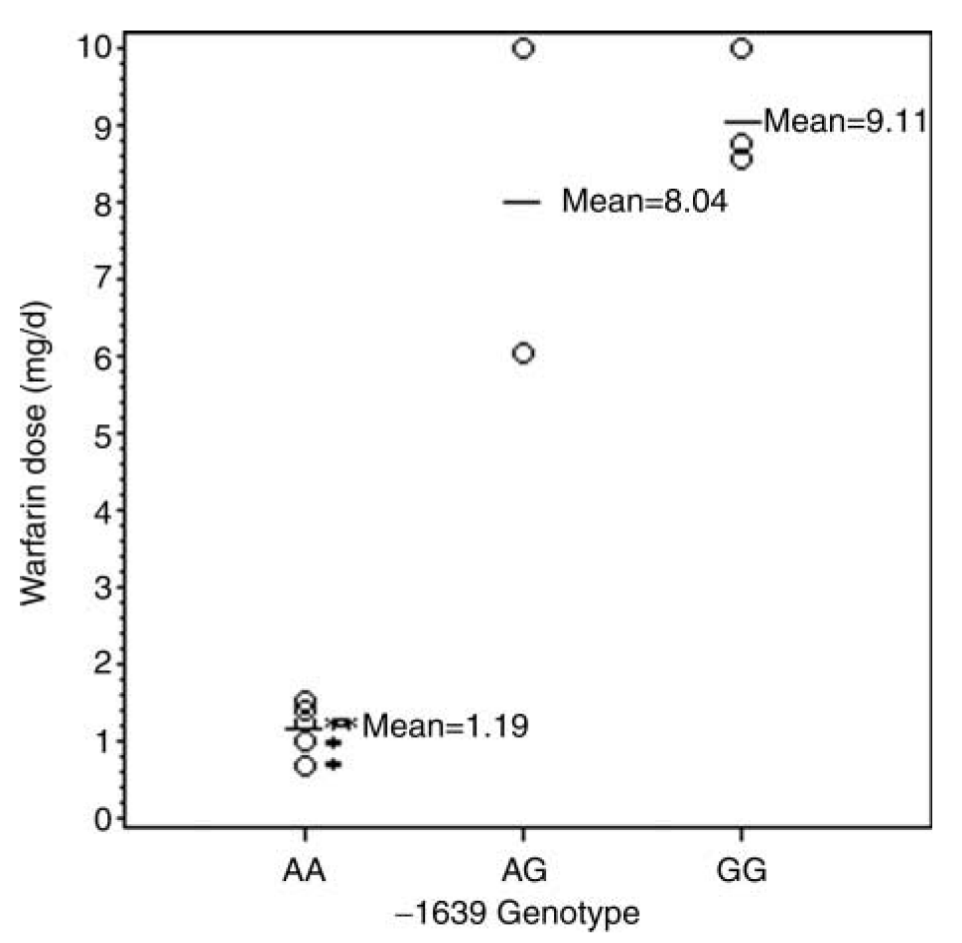
Coagulation factors
II, VII, IX, X, etc.

VKORC1



- Chromosome 16
- Highly polymorphic, >30 SNPs known
- Associated with
  - Multiple coagulation factor deficiency Type 2
  - Warfarin sensitivity and resistance
- Haplotypes for warfarin sensitivity were defined: *2, Group A
- Promoter SNP appears causitive due to effects of expression

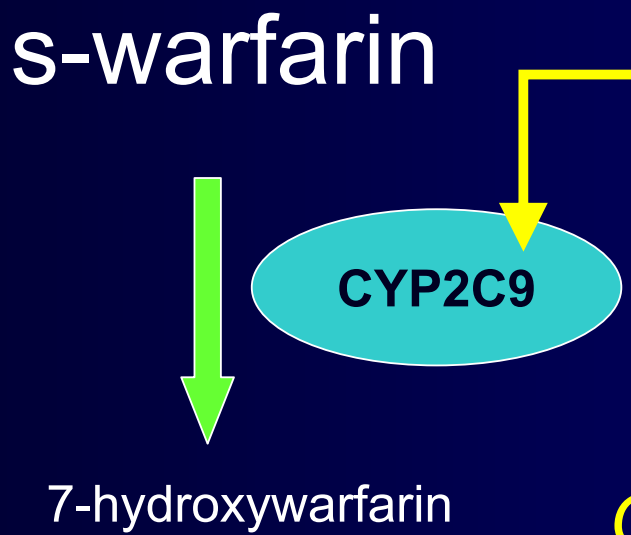
Effect of *VKORC1* -1639 genotype on warfarin dose



VKORC1 promoter variant affects expression and accounts for ~30% of warfarin dose requirement

Yuan et al. Human Mol Genetics, 14(13):1745-51, 2005

s-Warfarin is inactivated by CYP2C9



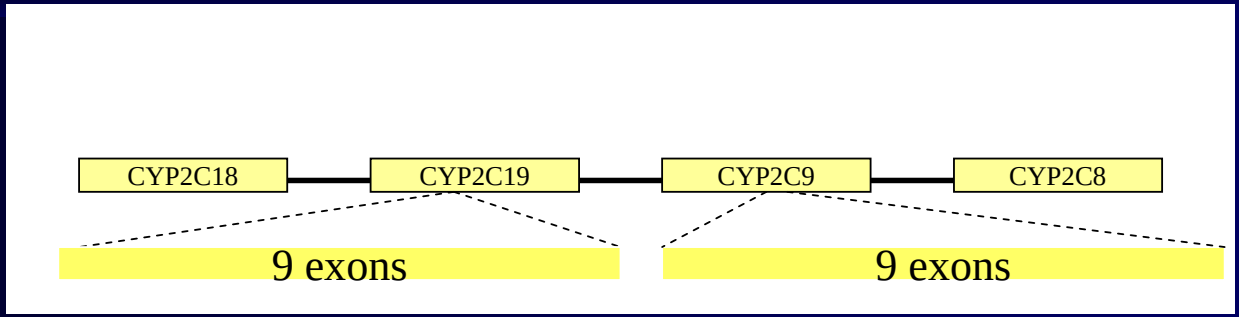
CYP2C9

Drug-drug interactions

CYP2C9 status affects

- *drug clearance, $t_{1/2}$*
- *time to steady state*

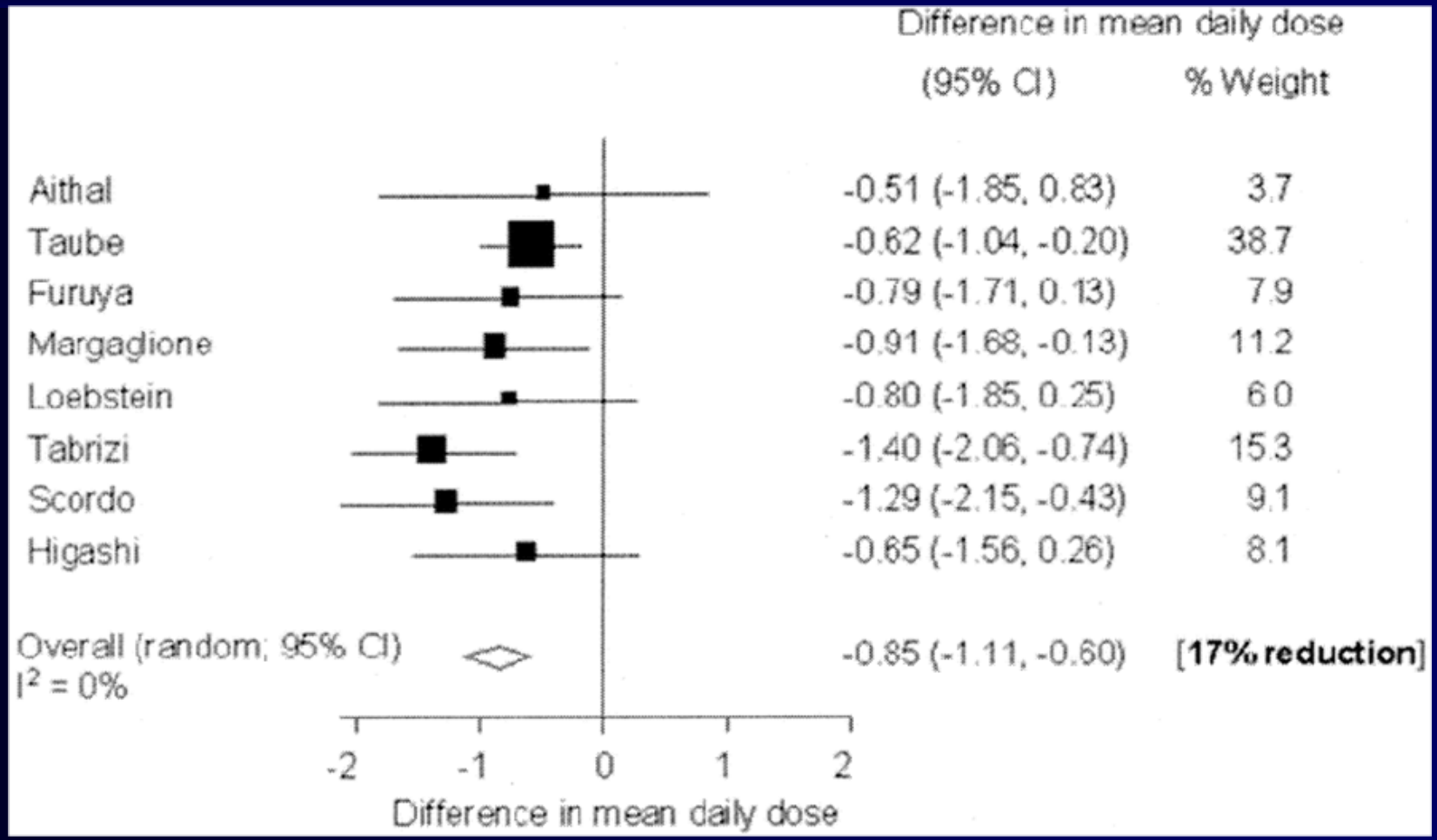
CYP2C9



- Chromosome 10
- Enzyme catalyzes many drug metabolizing reactions for substrates such as: s-warfarin, phenytoin, NSAIDs, and tolbutamide
- Highly polymorphic, >30 alleles described, many other SNPs with unknown significance
- Most common alleles in Caucasians are the *2 and *3 alleles
- Other alleles may be important to other ethnic groups:

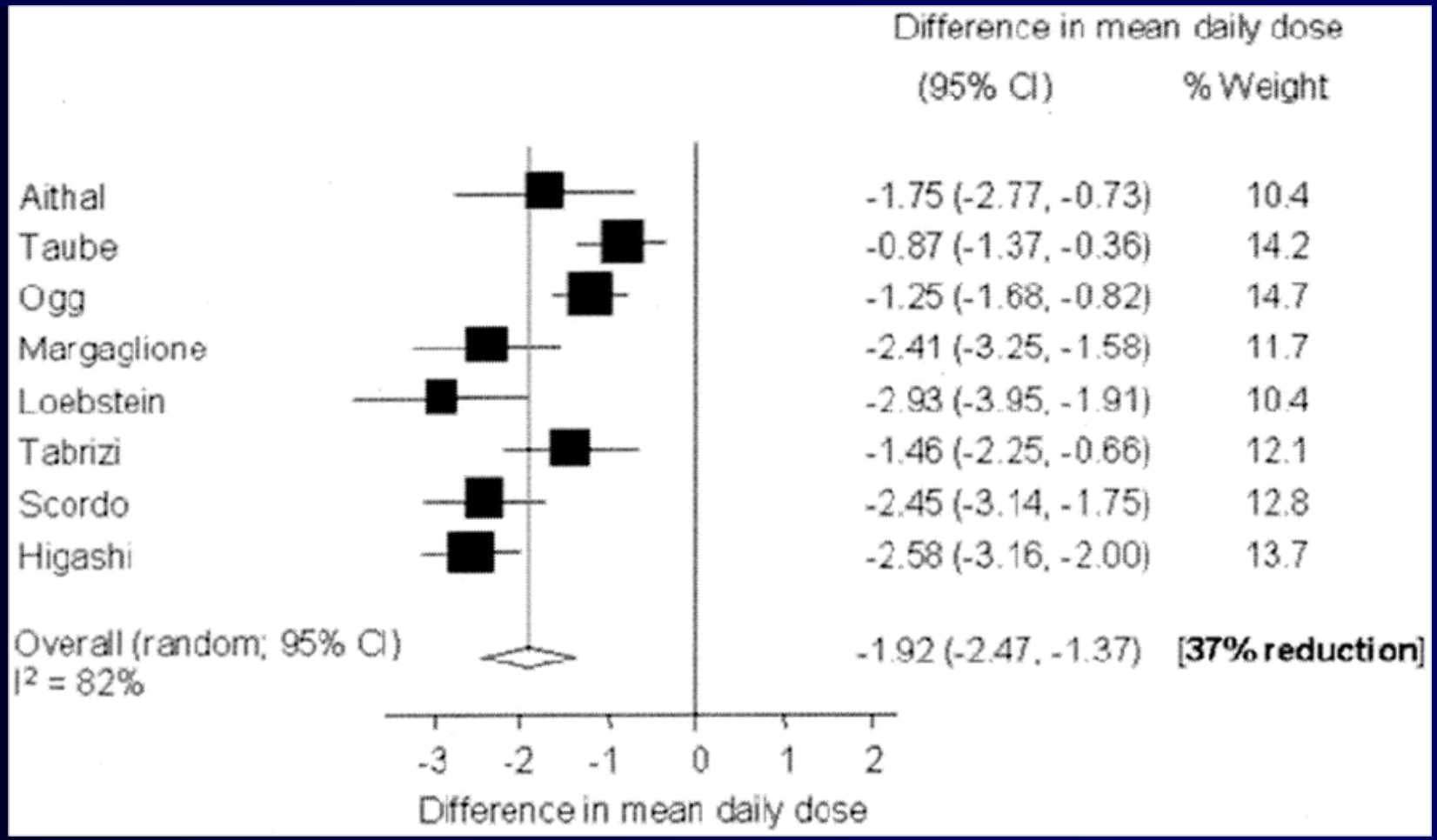
  *4 (Asians), *5 (African), *6 (non-functional but rare)

*CYP2C9*2* and warfarin dose



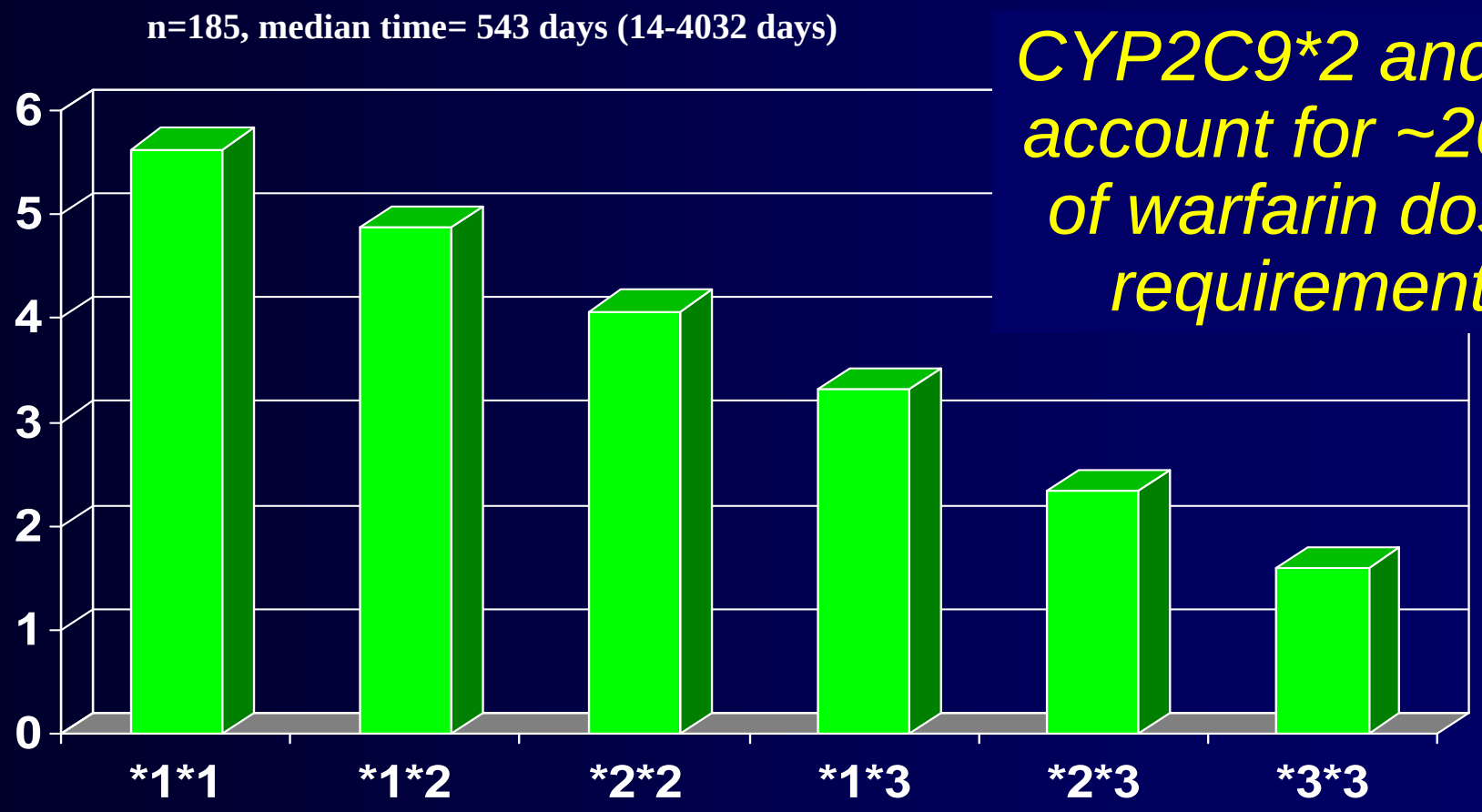
S. Sanderson et al. Genet Med. 2005 Feb;97-104

*CYP2C9*3* and warfarin dose



S. Sanderson et al. Genet Med. 2005 Feb;97-104

Effective warfarin doses by *CYP2C9* genotype



*CYP2C9*2 and *3 account for ~20% of warfarin dose requirement*

Higashi MK et al, JAMA 2002; 287:1690

More than just the dose…

Clearance (mL/min/kg)

from drug label, mean (s)

~0.065 (0.025) with 0 variants

~0.041 (0.021) with 1

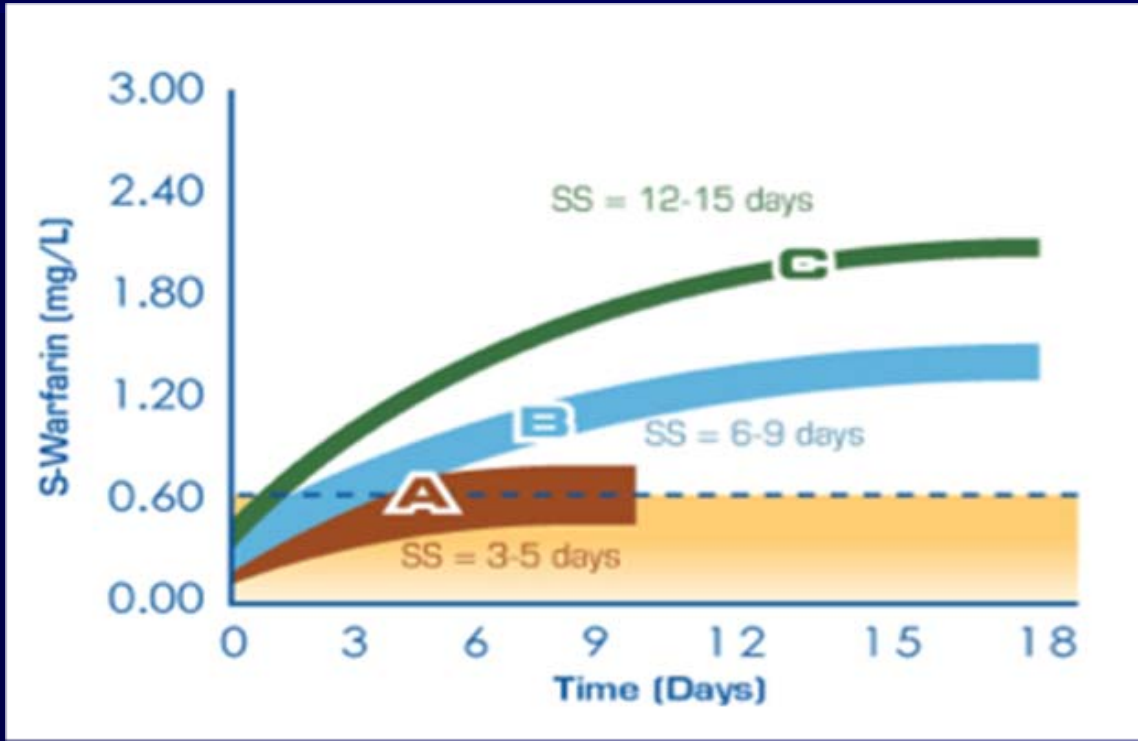
~0.020 (0.011) with 2

Time to steady-state:

~3-5 days with 0 variants

~6-9 days with 1

~12-15 days with 2



Impacts dose equilibration, time to interpret INRs and making dose adjustments = risk to patient

Summary of common *CYP2C9* and *VKORC1* variants associated with warfarin sensitivity

Gene	Variant (nucleotide)	* Allele	Protein change	Effect	Allele frequency (Caucasian)
VKORC1	c.-1639			Decreased	0.42
CYP2C9	c.430 C>T			Modest	0.08-0.13
				enzyme	0.06-0.10

Dose selection

Dose management, predict maintenance dose

Genotype-based dosing

Estimated to account for ~ 60% of variability in warfarin dose

$$\text{Sqrt(Dose)} = 0.628 - 0.0135(\text{Age}) - 0.240(\text{CYP2C9*2}) - 0.370(\text{CYP2C9*3}) - 0.241(\text{VKORC1}) + 0.0162(\text{Height})$$

- Age: input years
- CYP2C9: input 0, 1, or 2 based on # of variant alleles
- VKORC1 -1639G>A : input 1 for GG, 2 for GA, and 3 for AA
- Height: input cms

Sconce et al. Blood 106(7):2329-33, 2005

Genotype-based warfarin doses

55 yr old, 6' tall man

warfarin (mg/d)

CYP2C9 variants	VKORC1 GG calculated initial dose	% reduced from 6.8	VKORC1 AG calculated initial dose	% reduced from 6.8	VKORC1 AA calculated initial dose	% reduced from 6.8
None	7		6	18%	5	34%
CYP2C9*2	6	18%	5	34%	4	47%
CYP2C9*3	5	26%	4	41%	3	54%
CYP2C9*2/*2	5	34%	4	47%	3	60%
CYP2C9*2/3	4	41%	3	56%	2	66%
CYP2C9*3/*3	4	49%	3	62%	2	72%

WARFARINDOSING

www.WarfarinDosing.org

- Warfarin Dosing
- Clinical Prediction Rule
- Patient Education Links
- Contact Us
- **Online Resources**
- Admin

Doc:
Pat :
Version 3.3
Build : 01 Mar 2007

Welcome to **WarfarinDosing.org**, a free Web site to help doctors and other clinicians begin warfarin therapy by estimating the therapeutic dose in patients new to warfarin. This site is supported by the Barnes-Jewish Hospital at Washington University Medical Center, the NIH, and donations. Estimates are based on clinical factors and (when available) genotypes of two genes: *cytochrome P450 2C9 (CYP2C9)* and *vitamin K epoxide reductase (VKORC1)*.

Recommendations on this Web site are based on data from over 1000 patients. Once information is entered onto the next page, the initial estimate of therapeutic dose explains 53% of the variability in a warfarin dose. If you return to the Web site and enter an INR value after 3 and/or 4 warfarin doses, the dose refinement is even more accurate.

Initial Information

Please provide your information:

(•) New patient ( ) Existing patient

Warfarin doses taken so far*: -Select-

> CONTINUE

*Required

Shared with permission from Dr Brian Gage

Estimate of Warfarin Dose

Estimated therapeutic dose: **2.8 mg/day.** ← User gets dose, but has to round

Today's prescribed dose: 3.0 mg. ← Automatic check for agreement w/ estimate

Patient number*: WU-001-JD

Caution

You should not decrease the frequency of INR monitoring based on the above estimate. We check the INR after 3 warfarin doses and modify the dose when clinically indicated.

Additional Information

Email the results to*: WelbyM@GeneralHospital.edu ← Emails doctor or pharmacist

Address email to: Dr. First Name: Marcus Last Name: Welby

Email copy to: Florence Nightingale ← Emails study nurse with all info.

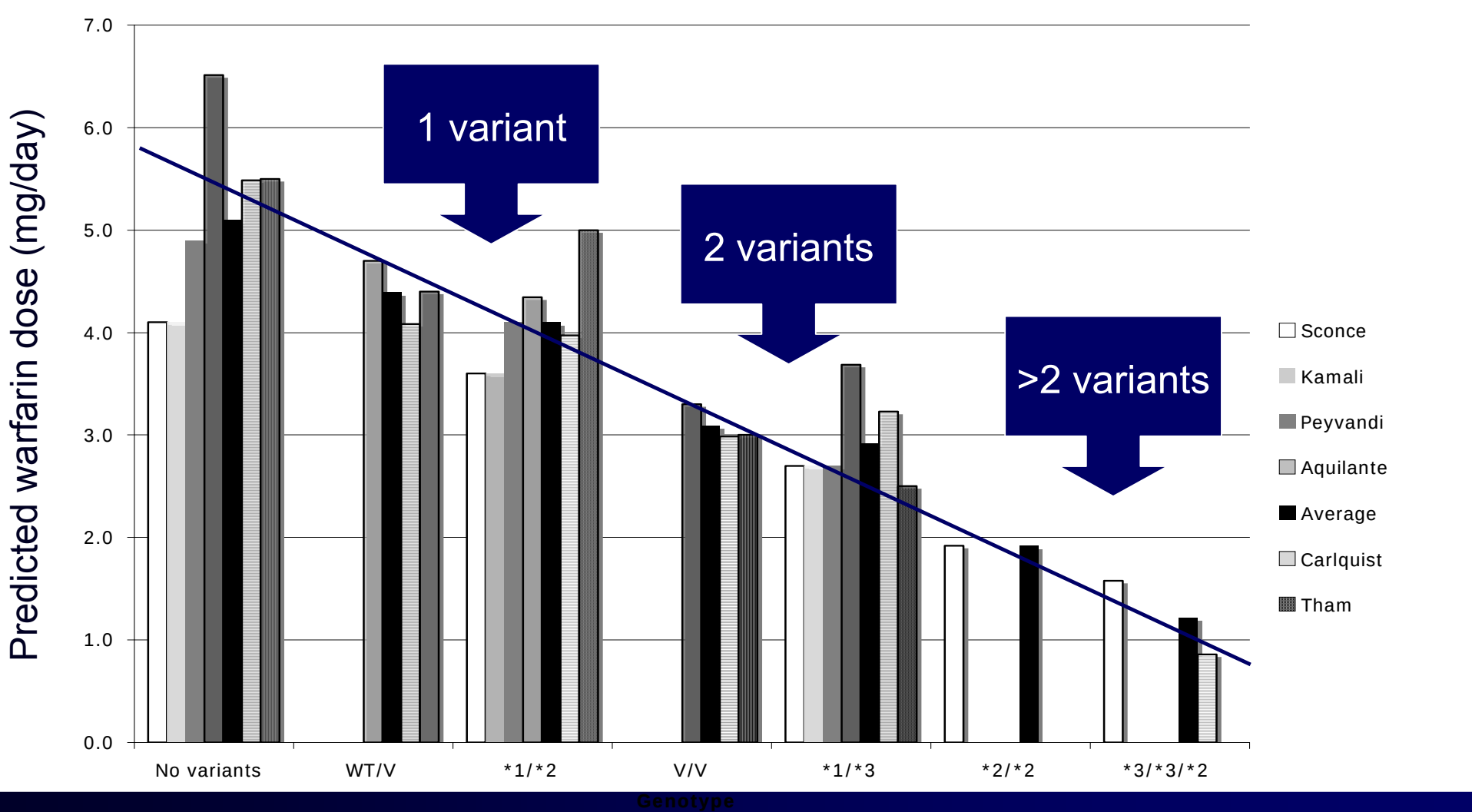
Text to accompany email: John Doe is in bed 7340 ← Private text is not stored in database

When would you like an email to remind you to check the INR: In 70 hours.

** This email address is required to save and to access this record. Information entered into this site will not be disclosed to any 3rd party nor used for commercial purposes.*

> SAVE AND EMAIL RESULTS

Comparison of published algorithms



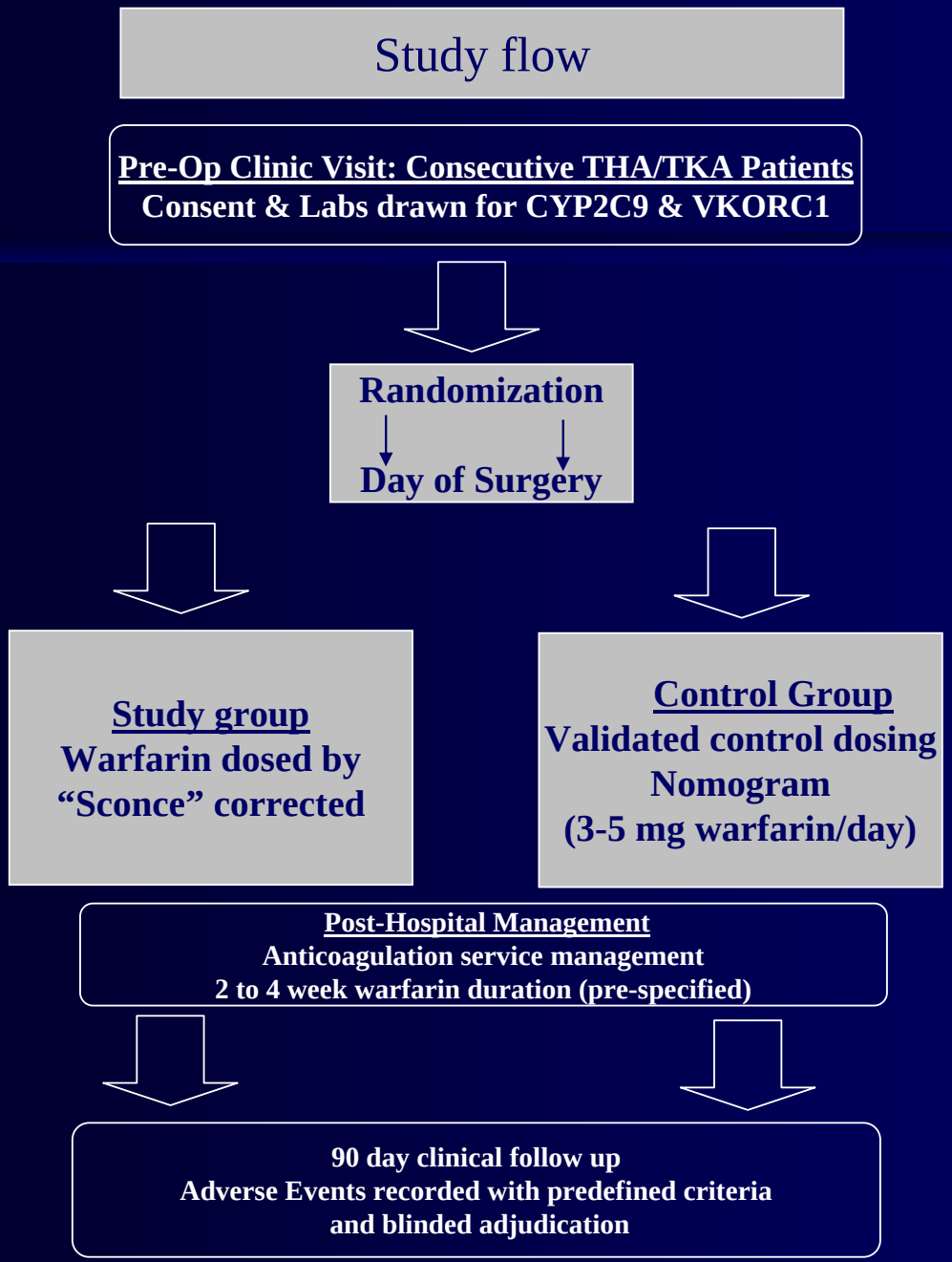
Grice et al. JCOM 2008;14(4):183-90

Limitations of algorithms

- Don’t predict warfarin resistance
- Origin
  Retrospective (i.e., maintenance doses) analysis of specific populations (i.e., Caucasians) using various statistical tools
- Not standardized
- Don’t consider dosing vs. pill size available for Rx
- Don’t account for, or address management of kinetic differences
  - Frequency of INRs
  - Frequency of dosing/adjustments

Does application of warfarin genotyping to dose selection improve patient care?

- Let's see!
- Investigators from ARUP (Dept of Pathology), Dept of Internal Medicine, and the University Orthopaedic Center
- Vendor support from Third Wave, Tm Biosciences, Idaho Technology, and Autogenomics
- Protocol approved and active August, 2006-2008



263 patients enrolled

229 patients underwent surgery & VKA used

Complete follow-up

Pharmacogenetic Warfarin Initiation Trial

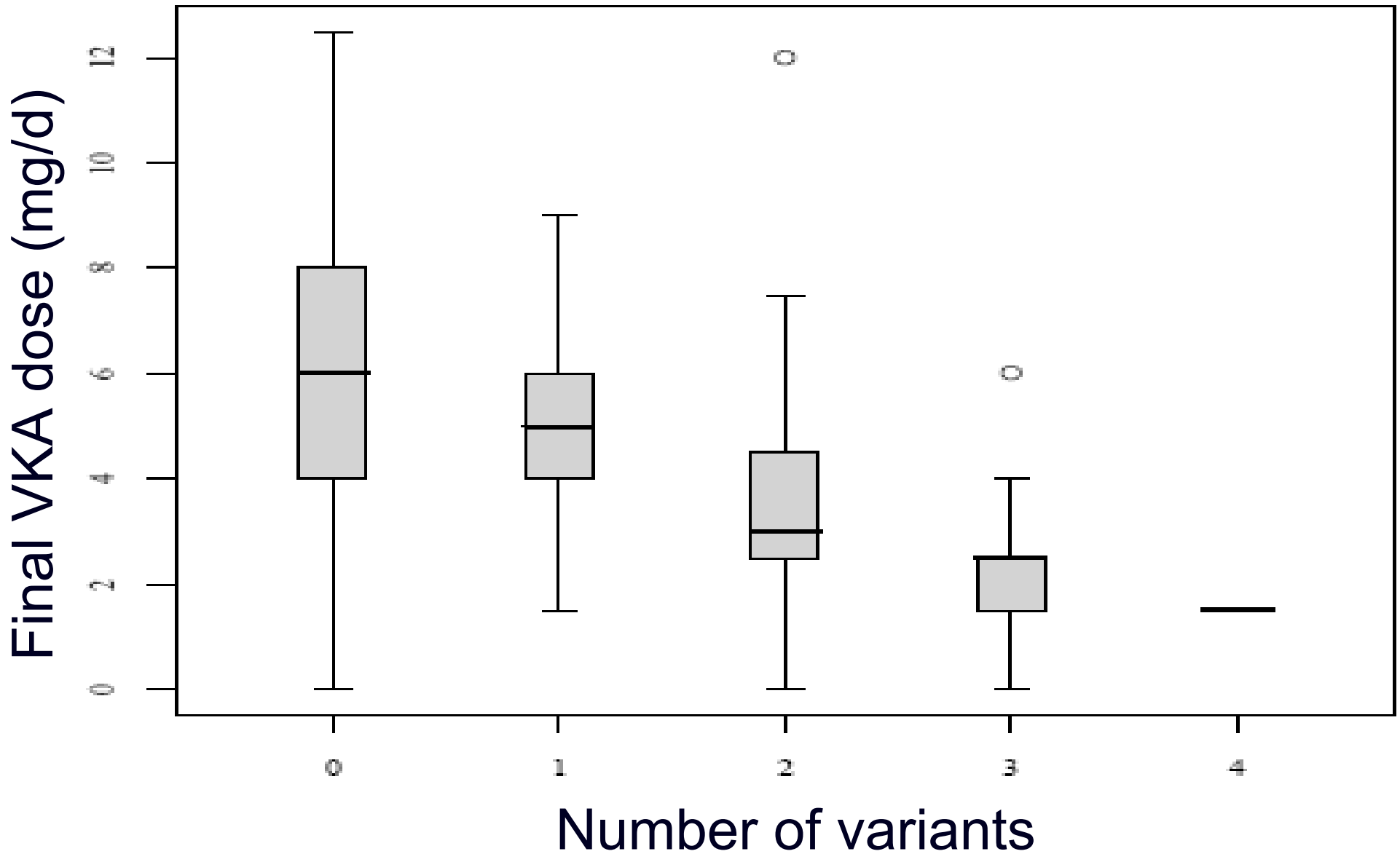
UHOSP Orthopedic Joint Replacement Patients

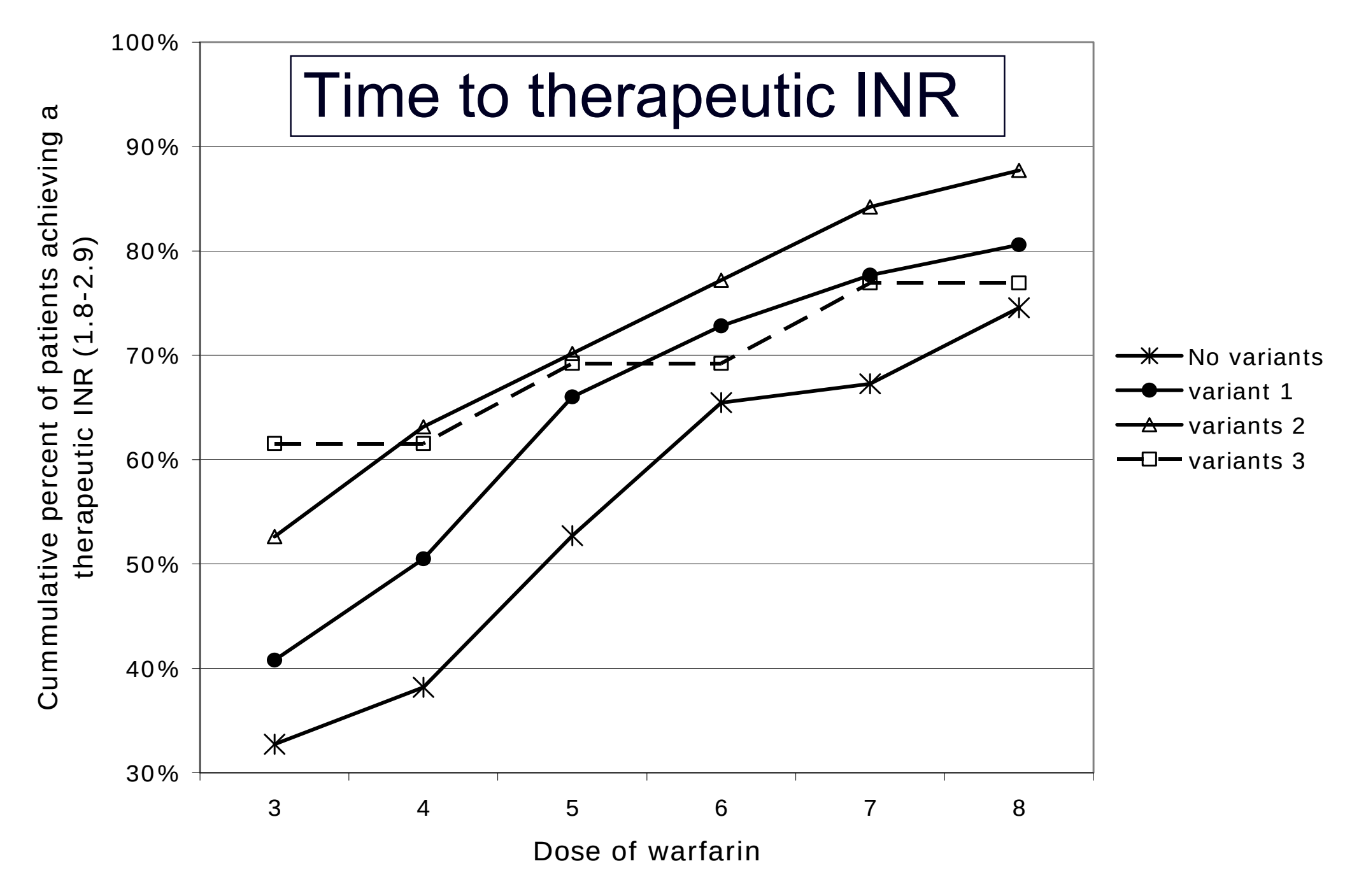
229 patients undergoing joint replacement surgery:
Pharmacogenetics dosing versus Standard initiation protocol

	Genetic	Standard	p
Age, y, mean	59	60	NS
Weight, kg, mean	87.3	91.1	NS
Any allele variant	79%	74%	NS
Doses to INR goal	3.7	3.4	NS
INR >2.9 d14	45.6%	43%	NS
Mean dose adjustments	8.4	7.0	NS
VTE (n)	0	4	NS
Major Bleed (n)	2	0	NS
Minor Bleed (n)	1	6	NS

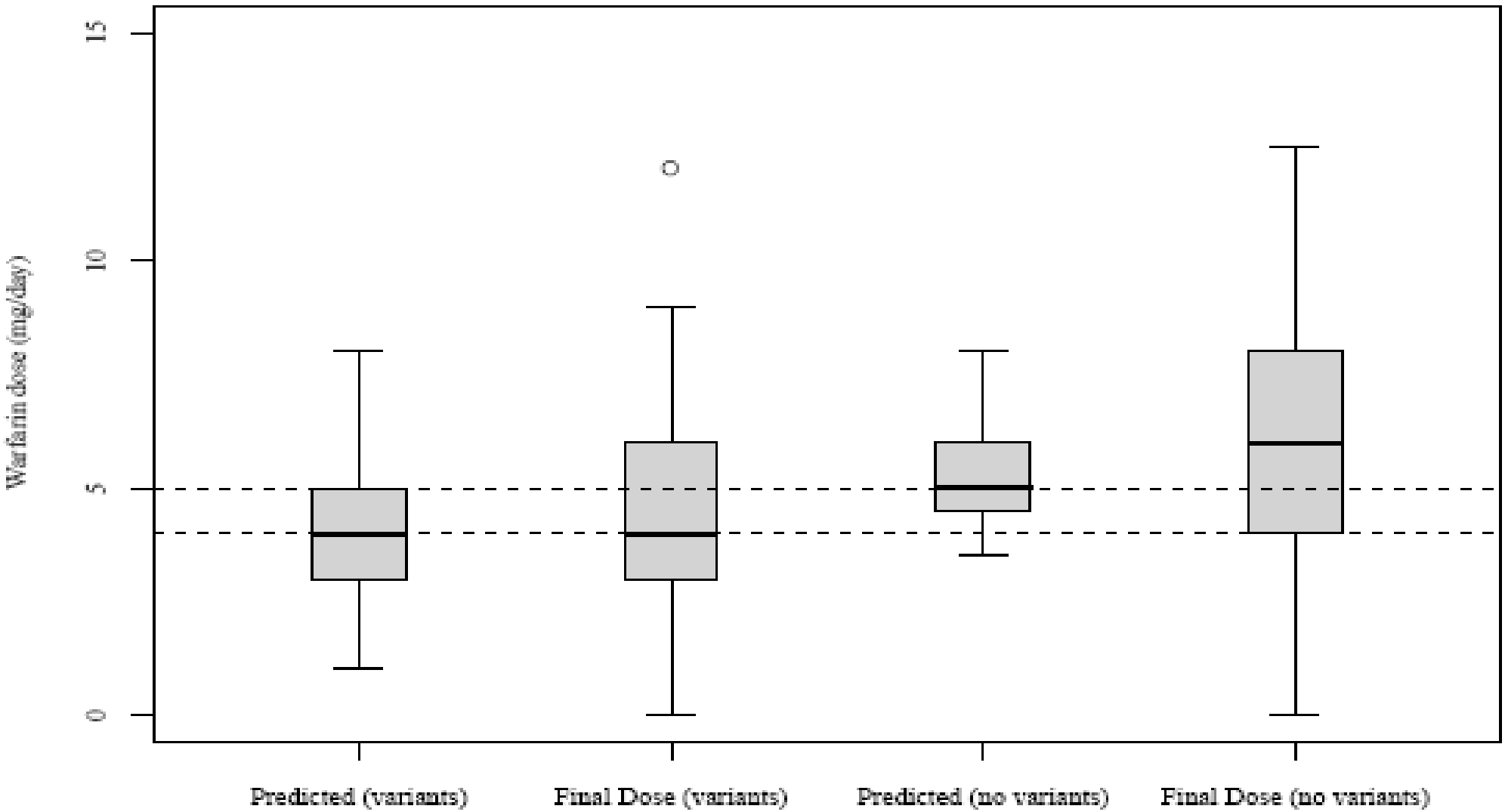
McMillin et al. Data on File

Variant –Dose Relationship




Time to therapeutic INR
Cummulative percent of patients achieving a therapeutic INR (1.8-2.9)
100%
90%
80%
70%
60%
50%
40%
30%
3
4
5
6
7
8
Dose of warfarin
No variants
variant 1
variants 2
variants 3

Accuracy of Algorithm Predicted Dose



Pharmacogenetic Warfarin Initiation Trial

(Couma-Gen Investigators)

- Pharmacogenetic (n=101) vs. Nomogram/Anticoag service (n=99)
- Excluded: Advanced age, Cr >2.5 mg/dL, hepatic insufficiency

	Genetic	Standard	p
Age, y, mean	63.2	56.6	<0.02
Weight, kg, mean	92.1	94.7	-
Any allele variant	61.0%	79.6%	<0.01
INR out of range	30.7%	33.1%	0.47
Therapeutic INR d8	68.8%	63%	0.41
Adverse event*	34.7%	42.4%	0.26

Anderson et al, Circulation 116, 2007

* Clinical event + INR $\geq$ 4.0

Pharmacogenetic Warfarin Initiation Trial
(Couma-Gen Investigators)

- Gene-based dosing
  - Predicted actual dose requirements more accurately than standard dosing protocols
  - Resulted in fewer and smaller dose changes (3.0 vs. 3.6)
  - Resulted in fewer INR test requests (7.2 vs. 8.1)

- Those patients with no variants or multiple variants showed promising reductions in the number of out-of-range INRs, but the effects were not statistically significant

Anderson et al, Circulation 116, 2007

Warfarin gene-based dosing
(The Caraco Study)

- N=191 warfarin-naïve inpatients treated for AFIB, DVT, or PE at the Hadassah University Hospital (Israel)
- Target INR was 2-3
- Dosing: validated computer predicted dosing model first 8 days versus pharmacogenetic modeled dosing
- Primary endpoints: time to first INR>2, and time for stable anticoagulation

Caraco et al Clin Pharmacol Ther 83, 2008

Warfarin gene-based dosing
(The Caraco Study)

- Findings:
  - Time to first therapeutic INR was 2.7 days earlier in the study group
  - Stable anticoagulation was attained 18.1 days earlier in the study group
  - The study group was therapeutic 80% of the time, versus 63% of the time in the control group
  - Incidence of minor bleeding was lower (3.2%) in the study group than in the control group (12.5%)

- Conclusions:
  - Dosing based on CYP2C9 improves patient care

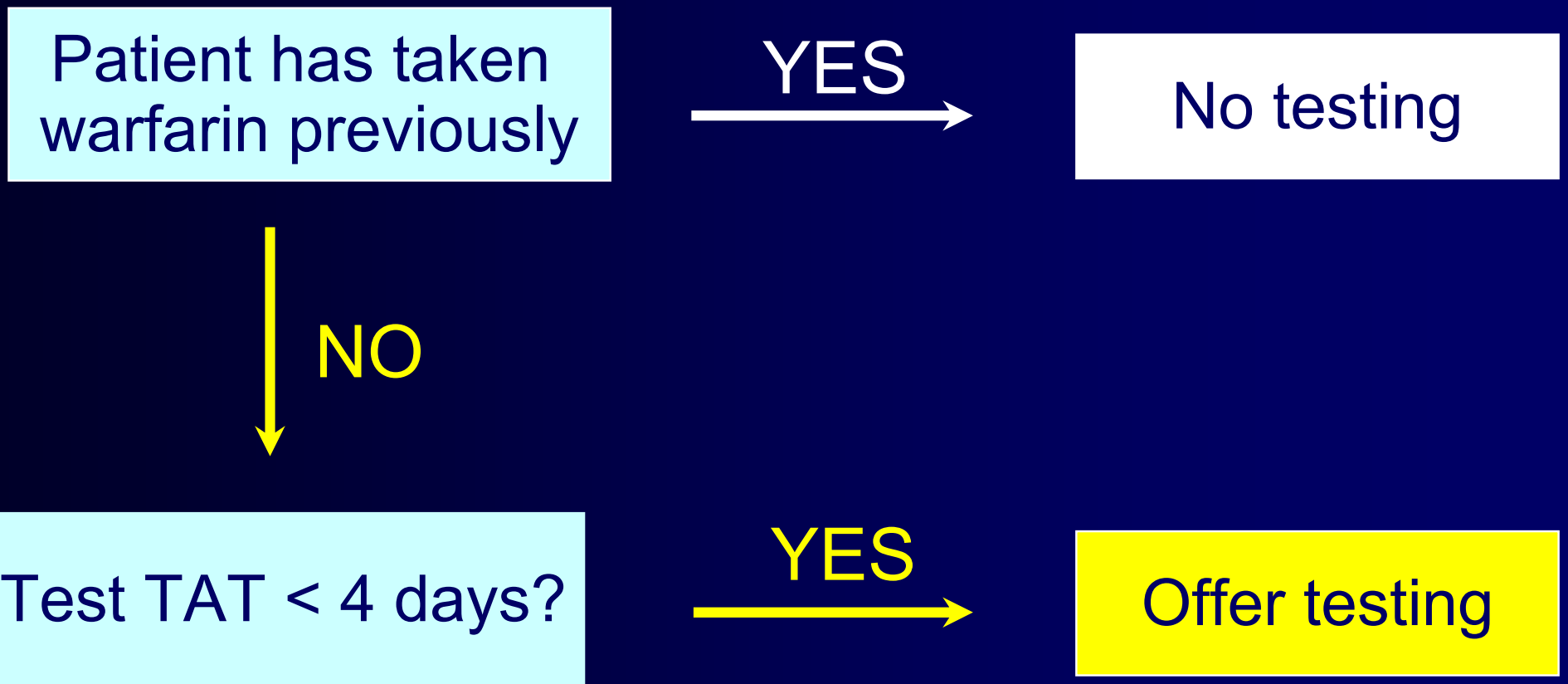
Caraco et al Clin Pharmacol Ther 83, 2008

Perspective: Pharmacogenetic Warfarin Dosing

- Genetics explains 30-50% of warfarin dose variability
- Clinical features explain 20-30%
- >20% of dose variability remains unexplained

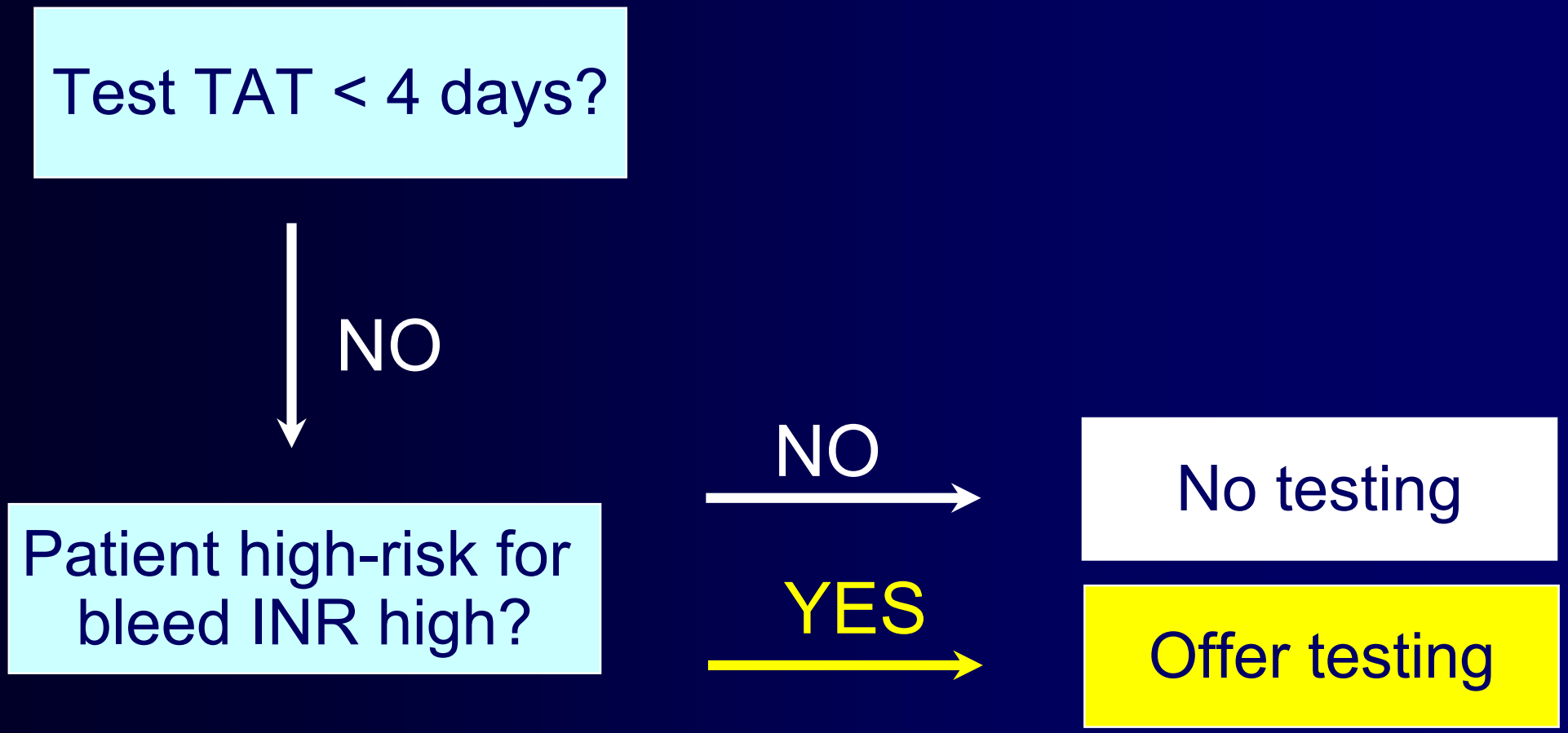
- The gene-dose relationship is clear & convincing.
- Improving outcomes remains to be proven
- Well-designed, large prospective RCTs are needed
- Validated tools needed to help apply to busy clinical practice

Proposed clinical algorithm for today



Modified from Thacker et al., J Thromb Haemost 6:1445-9, 2008

Proposed algorithm for today



Modified from Thacker et al., J Thromb Haemost 6:1445-9, 2008

Commercially available reagents

Gene variants	Nucleotide position	Nucleotide exchange	Third Wave	Luminex	Idaho Technology	Autogenomics	Nanogen	Osmetech
CYP2C9								
***2**	430	C>T	■	■	■	■	■	■
***3**	1075	A>C	■	■	■	■	■	■
*4	1076	T>C		■		■		
*5	1080	C>G		■		■	■	■
*6	818	delA		■		■	■	■
*11	1003	C>T				■	■	■
*14	374	G>A						■
*15	485	C>A						■
*16	895	A>G						■
CYP4F2								
	1347	G>A						■
VKORC1								
3673	(-) 1639G>A	G>A	■	■	■	■	■	■
5808	173+324	T>G				■		
6009	173+525	C>T				■		
6484	173+1000	C>T				■		
6853	283+124	G>C				■		
7566	283+837 C	C>T				■		
8773	358	C>T				■		
9041	492+134	G>A				■		
85	85	G>T		■				
121	121	G>T		■				
134	134	T>C		■				
172	172	A>G		■				
1331	1331	G>A		■				
3487	3487	T>G		■				

Idaho Technology, Inc. ASRs

- DNA extracted from whole blood
- PCR set up
  - Primers
  - Probes (SimpleProbe® with fluorophore hybridization specific to point mutations)
  - Mastermix
- PCR and Melting
  - 35 minutes, single protocol for all 3 assays
- Data analysis

CYP2C9 *2

WT Tm = 54°

Mut Tm = 61°

CYP2C9 *3

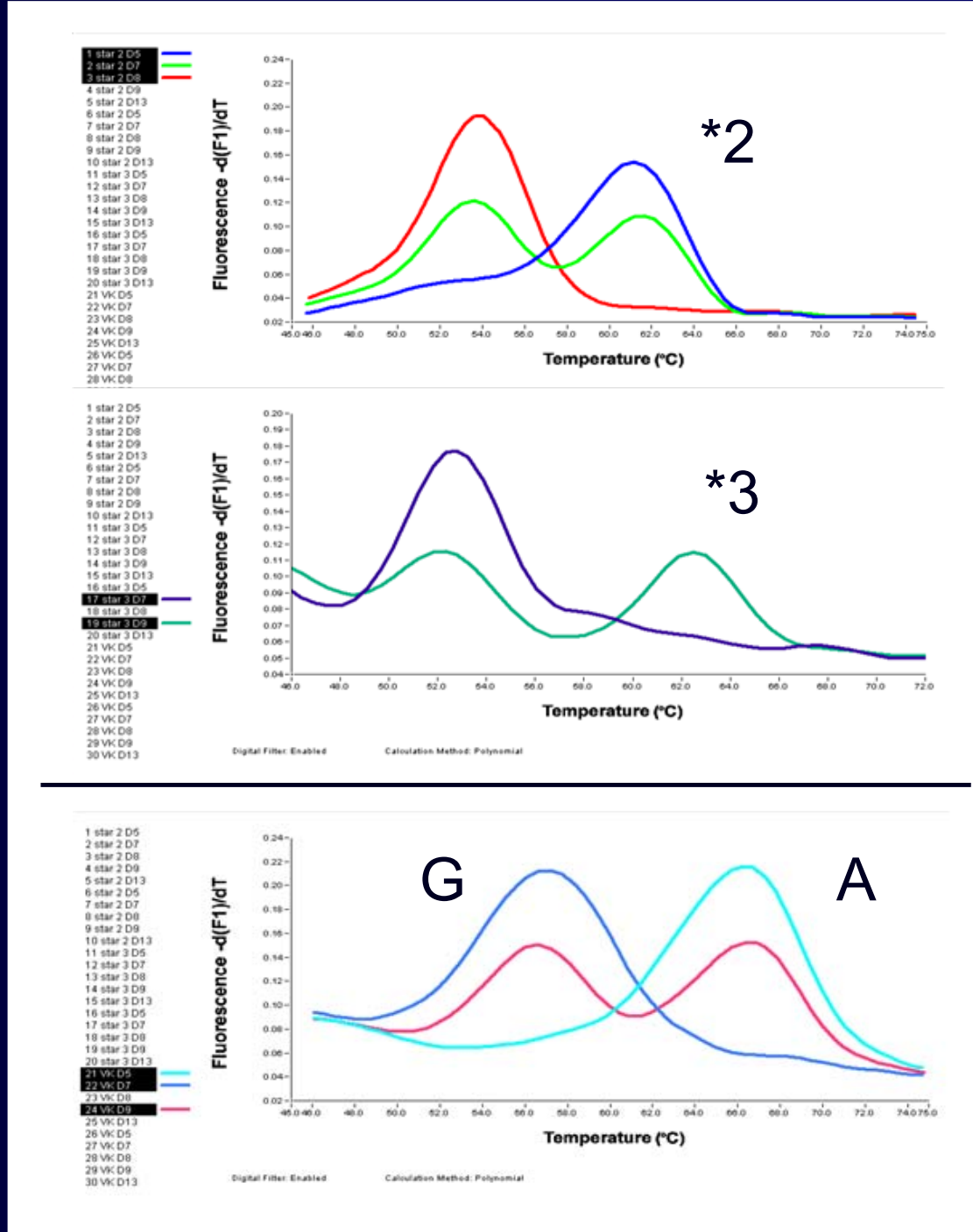
WT Tm = 53°

Mut Tm = 63°

VKORC1-1639

WT Tm = 57°

Mut Tm = 66°



Laboratory issues related to implementation of warfarin pharmacogenetic testing

- TAT
- $$$
- Interpretation?
- Application tools?
  - Dose initiation
  - Dose revision
  - Dosing regimen

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Name: Transition | MR Number | Start Date: 10/18/2007 | Interval(hrs): 24
Age: 65 | Weight(lbs): 145 | Sex: Female | VK Genotype: AA | CYP2C9 Genotype: *1*3

Dose Control
Fill: following
INR: none

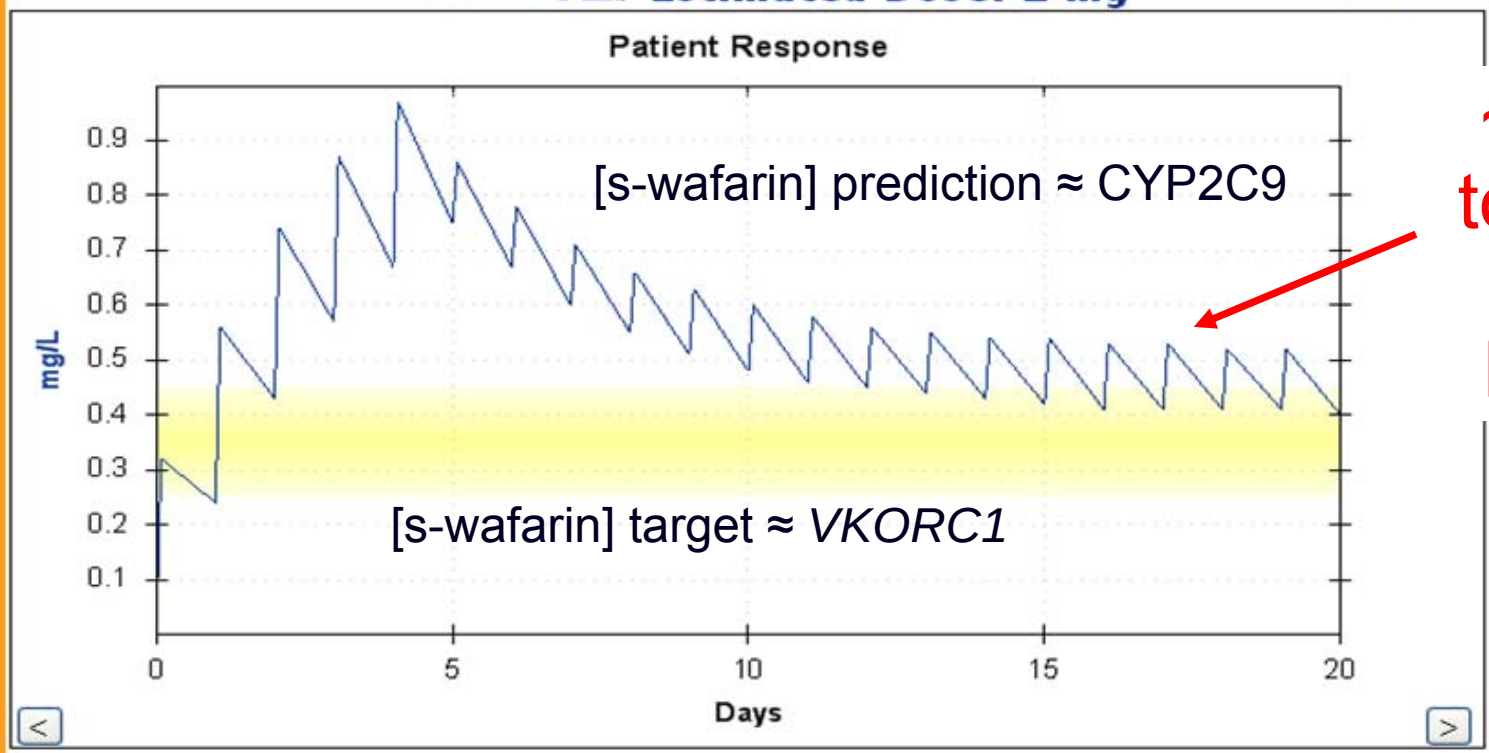
New Save Load Update

Half life: 59 graph

Drug: Warfarin

PGxL Estimated Dose: 2 mg

Day	Dose	INR
0	5	
1	5	
2	5	
3	5	
4	5	
5	2	
6	2	
7	2	
8	2	
9	2	
10	2	
11	2	
12	2	
13	2	
14	2	
15	2	
16	2	
17	2	
18	2	
19	2	
20	2	
21	2	
22	2	
23	2	
24	2	
25	2	



~10 d to Css, too high?

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PGxL laboratories
individually focused

Name: Transition | MR Number: | Start Date: 10/18/2007 | Interval(hrs): 24

Age: 65 | Weight(lbs): 145 | Sex: Female | VK Genotype: AA | CYP2C9 Genotype: *1*3

Dose Control

Fill: quick

INR: none

New | Save | Load | Update

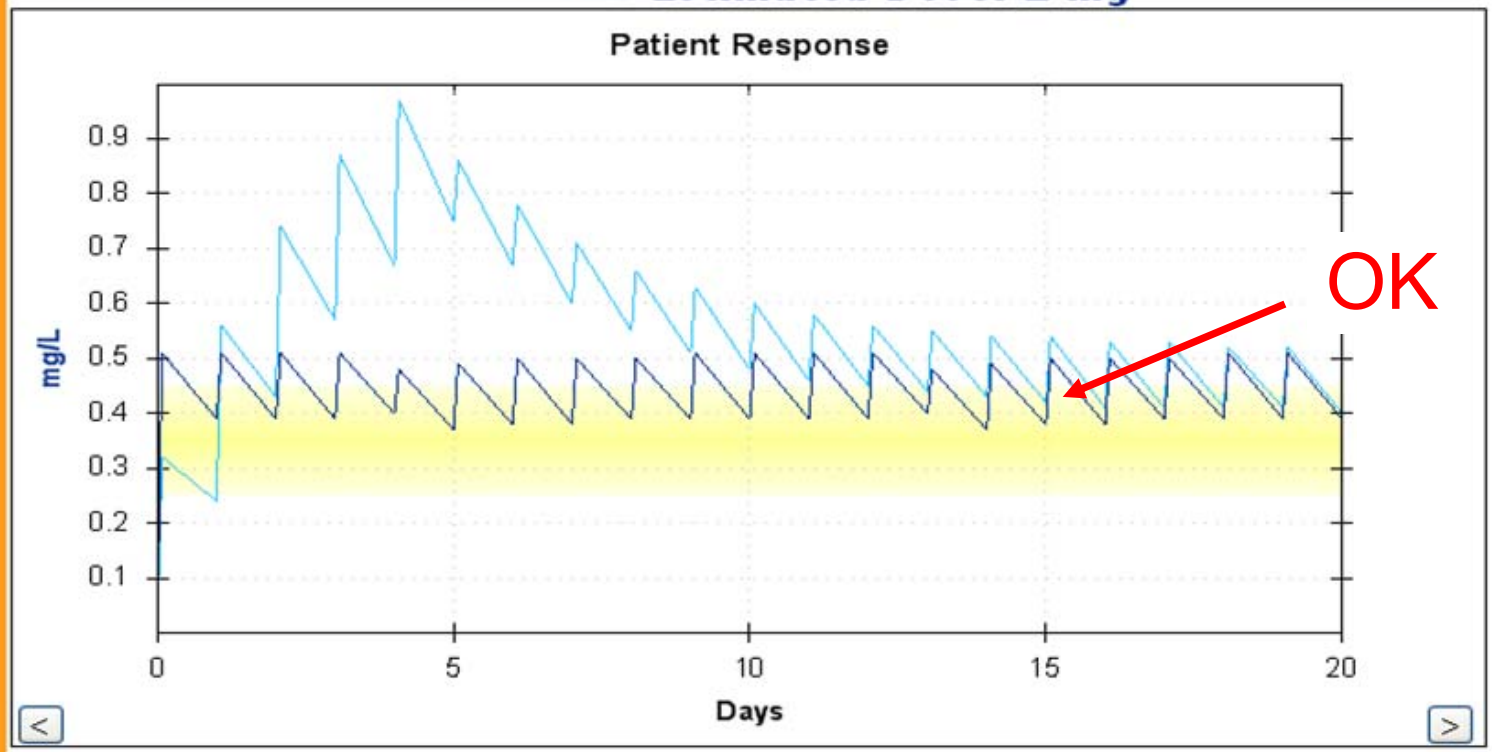
Half life: 59

Drug: Warfarin

PGxL Estimated Dose: 2 mg

graph

Day	Dose	INR
0	8	
1	2	
2	2	
3	2	
4	1.5	
5	2	
6	2	
7	2	
8	2	
9	2	
10	2	
11	2	
12	2	
13	1.5	
14	2	
15	2	
16	2	
17	2	
18	2	
19	2	
20	2	
21	2	
22	1.5	
23	2	
24	2	
25	2	



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Dose revision tools

- Adding INR information and more clinical information after initial dosing should improve accuracy of dose recommendations (account for ~80% of warfarin dose)

- INR_3 dose revision algorithm:

Warfarin dose (mg/day) =

EXP[1.453 – 1.657 x ln(INR_3) + 0.093 x ln(EBL) x ln(INR_3) – 1.62 x statin + 0.070 x first warfarin dose + 0.061 x second warfarin dose]

Lenzini P. et al. Annals of Pharmacotherapy 41:1798-1804, 2007

- INR_4 in press, INR_7 in development

Conclusions

- Gene-dose relationships for warfarin are well established
- Combining genotypes with clinical information accounts for 20-80% of the warfarin dose
- Genotyping may improve safety of warfarin, if used to *select and manage* the dose
- Algorithms may not be useful for patients that do not possess variants in *CYP2C9* and *VKORC1*
- Validated, easy to use tools are needed

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