Terapie Anticoagulanti
EVIDENZE ED OPINIONI A CONFRONTO

Cremona, 4 marzo 2016

Influenza delle variabili genetiche sulle terapie anticoagulanti orali

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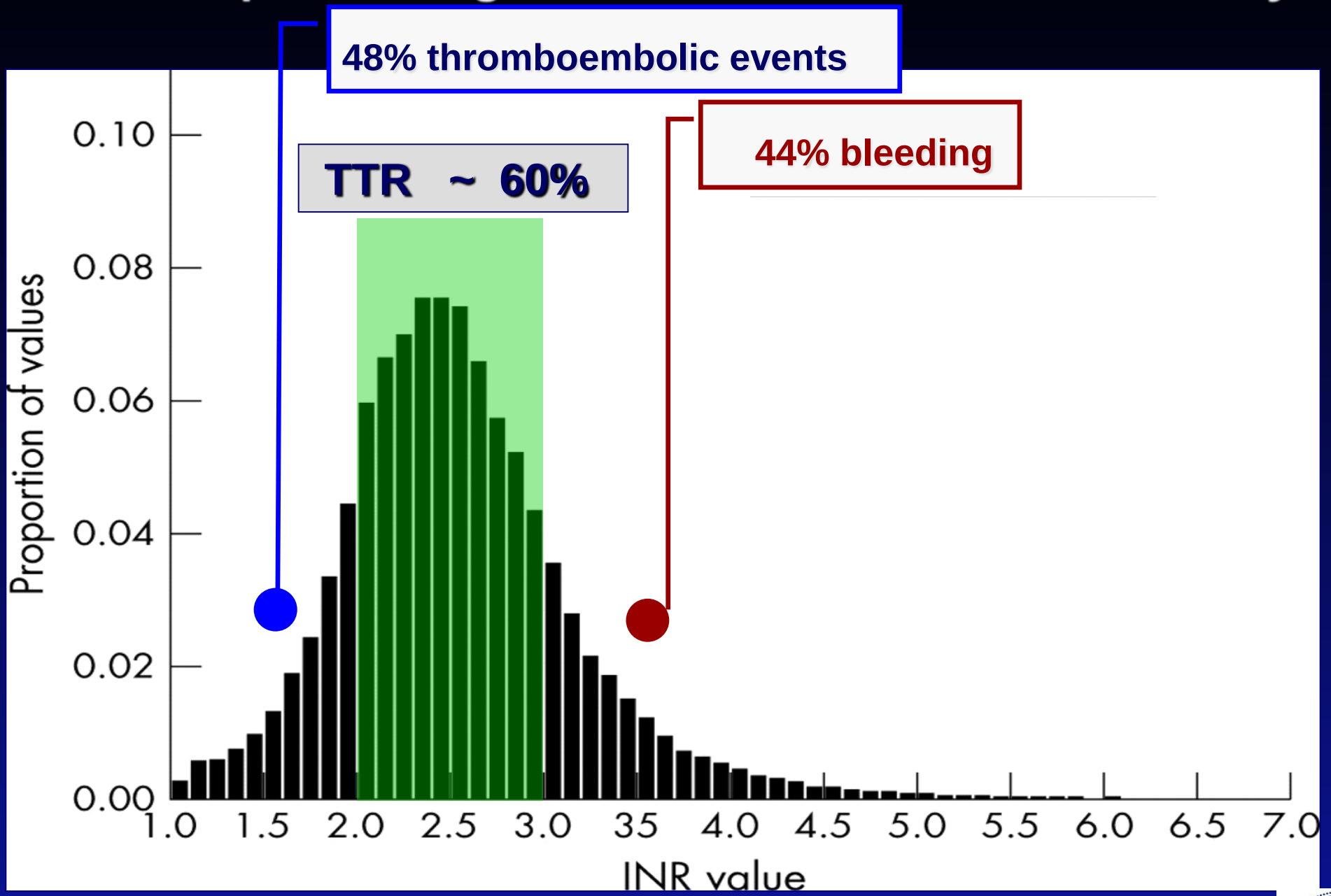
Time in therapeutic range and adverse effets: a meta-analysis



Oake N et al. CMAJ 2007;176:1589-94

Vitamin K antagonists – major drawbacks

Unpredictable response

Narrow therapeutic window (INR range 2-3)

Routine coagulation monitoring

Frequent dose adjustments

Warfarin therapy has several limitations that make it difficult to use in practice

Slow onset/offset of action

Numerous food-drug interactions

Numerous drug-drug interactions

Risk of Bleeding Complications

5 mg/d

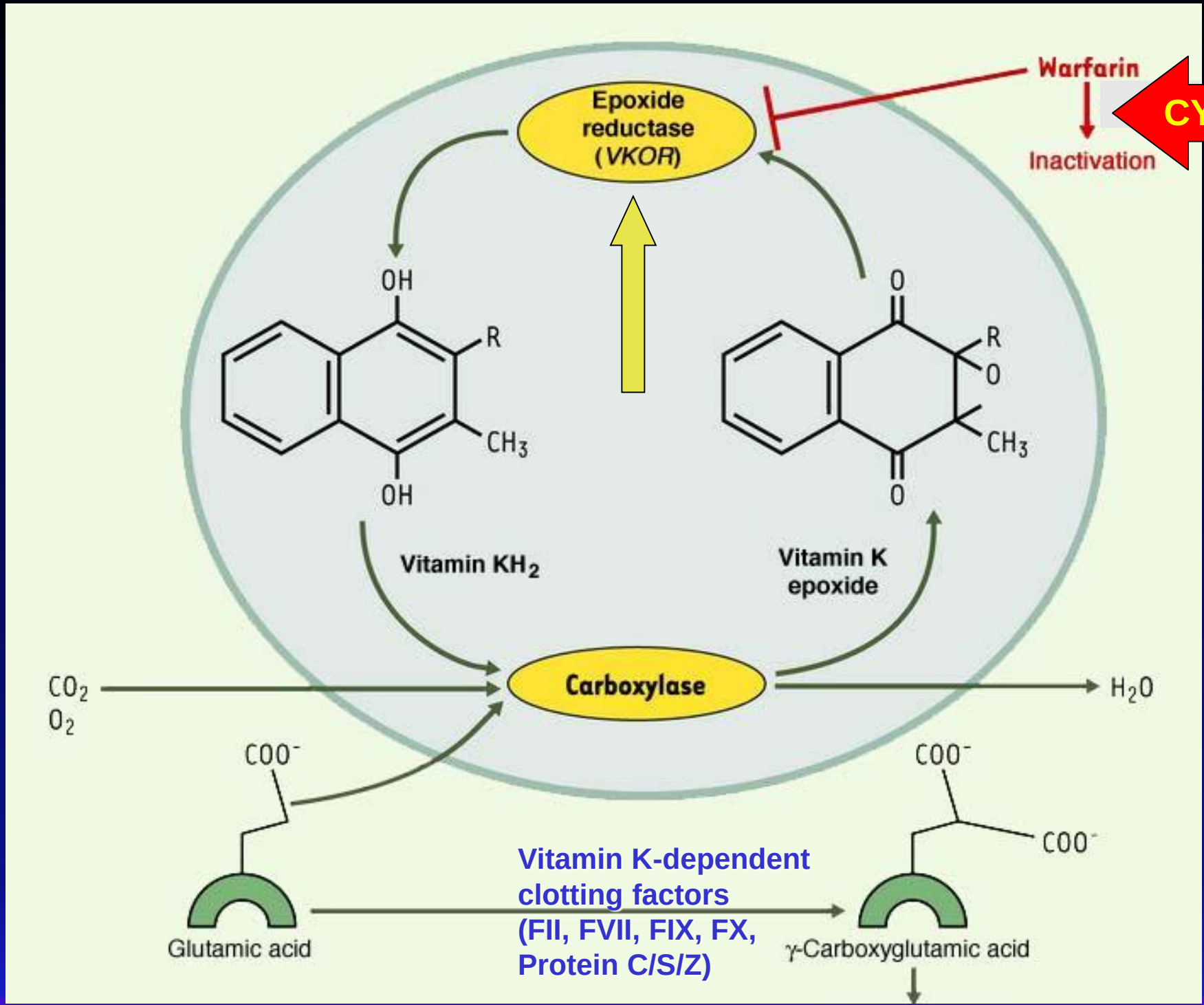
3.0-3.5 mg/d

6.0-7.0 mg/d

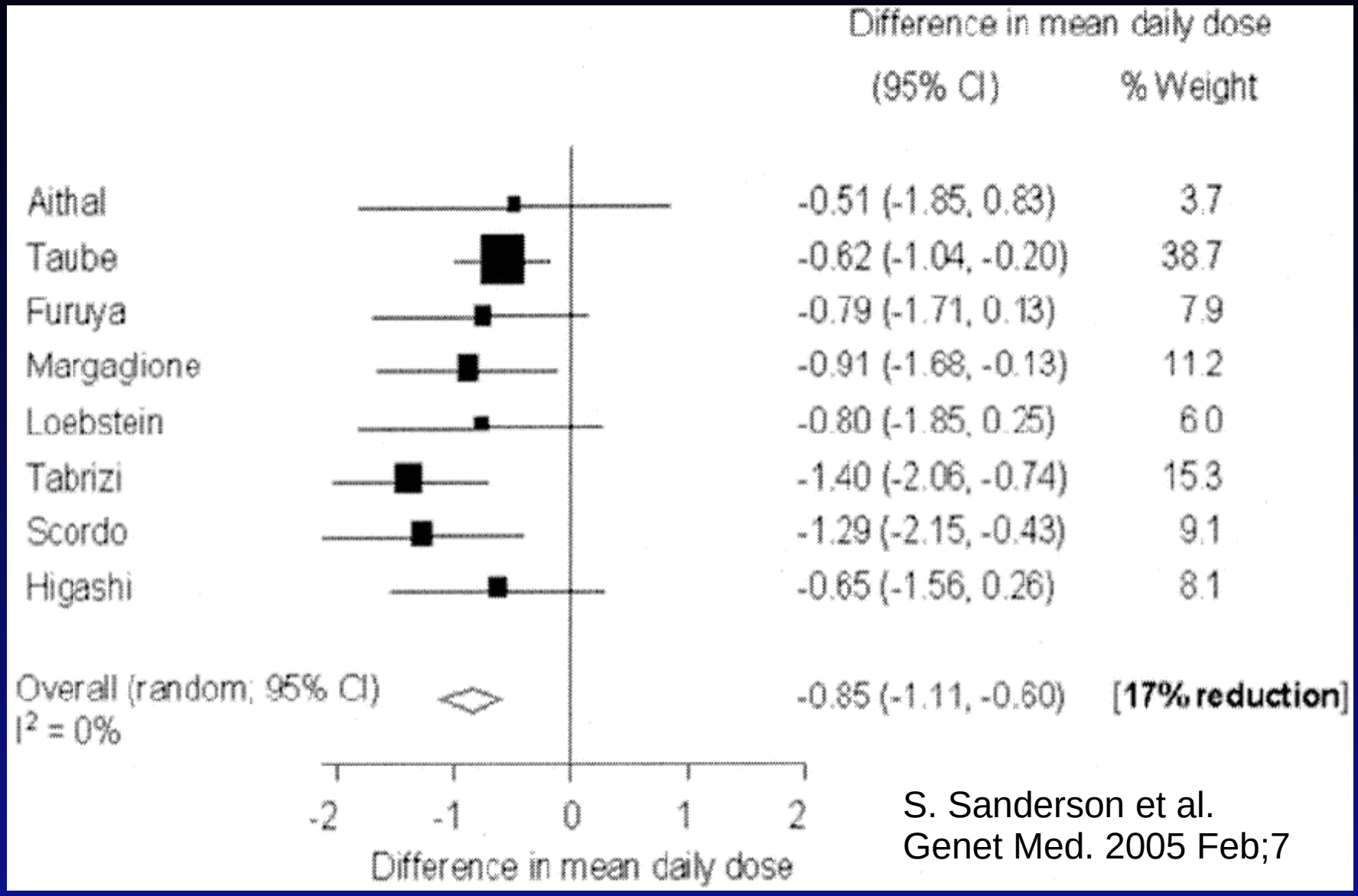
Japanese Caucasians Africans

Chinese Indians

Warfarin inhibits the vitamin K cycle

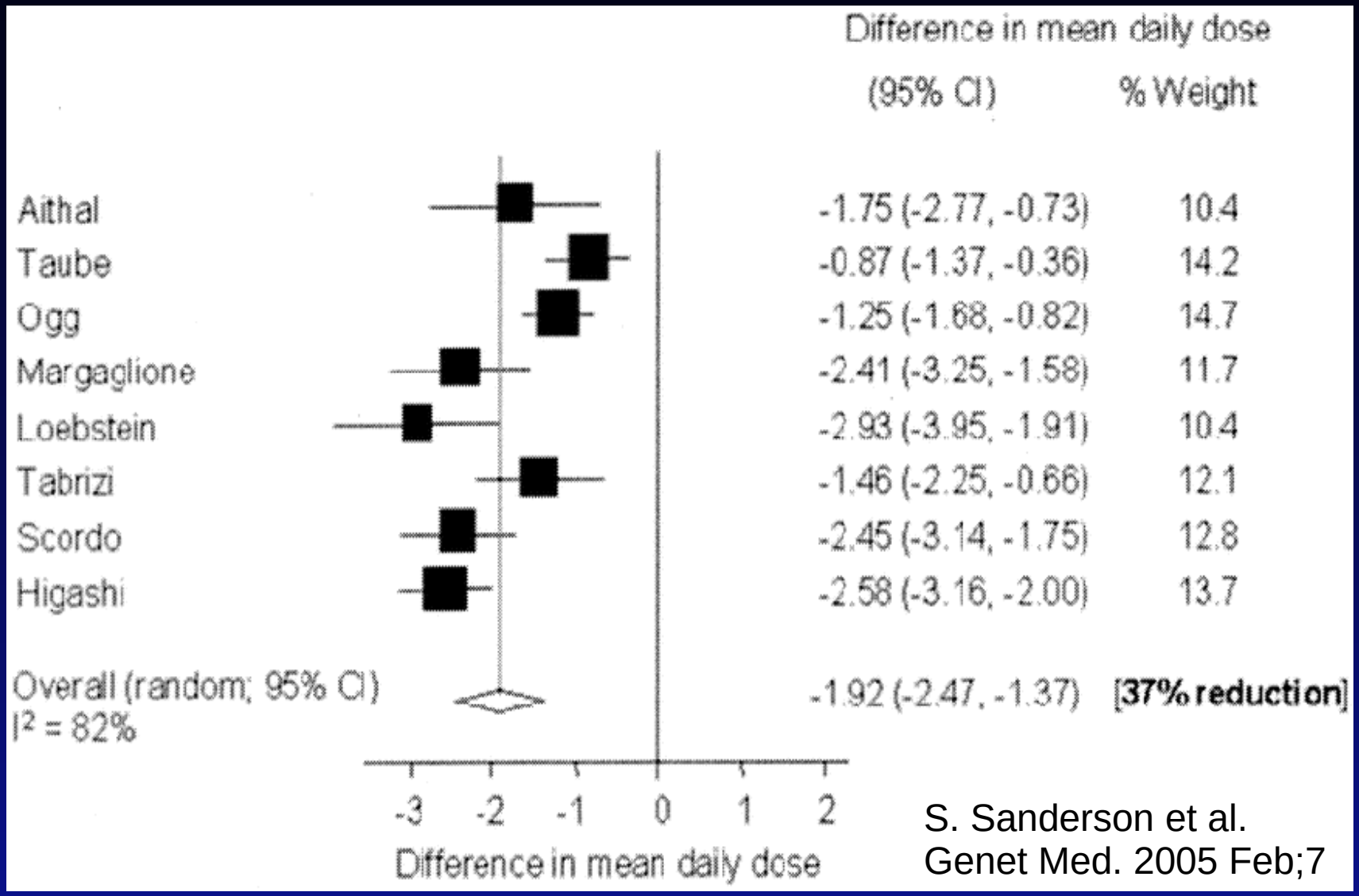


Effect of CYP2C9*2 on Warfarin Dose



S. Sanderson et al.
Genet Med. 2005 Feb;7

Effect of CYP2C9*3 on Warfarin Dose



S. Sanderson et al.
Genet Med. 2005 Feb;7

5 mg/d

*2: 10.7% *3: 8.5 %

3.0-3.5 mg/d

*2: 0% *3: 1-2%

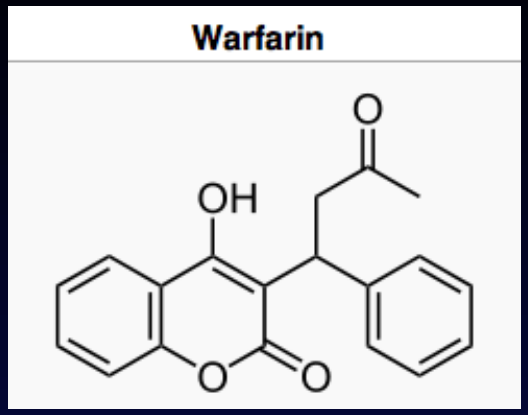
6.0-7.0 mg/d

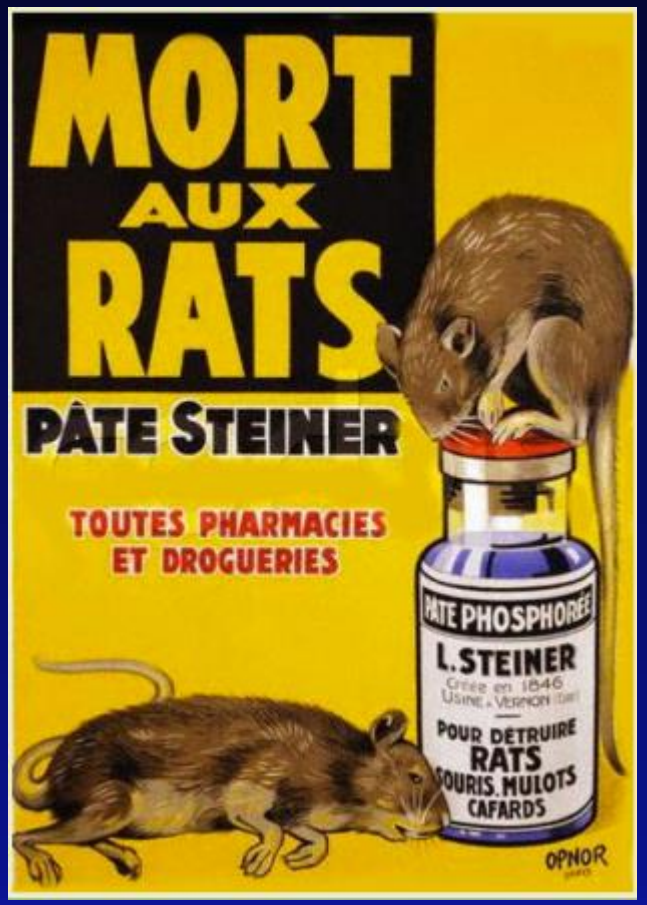
*2: 2.9% *3: 0.8%

Japanese Caucasians Africans

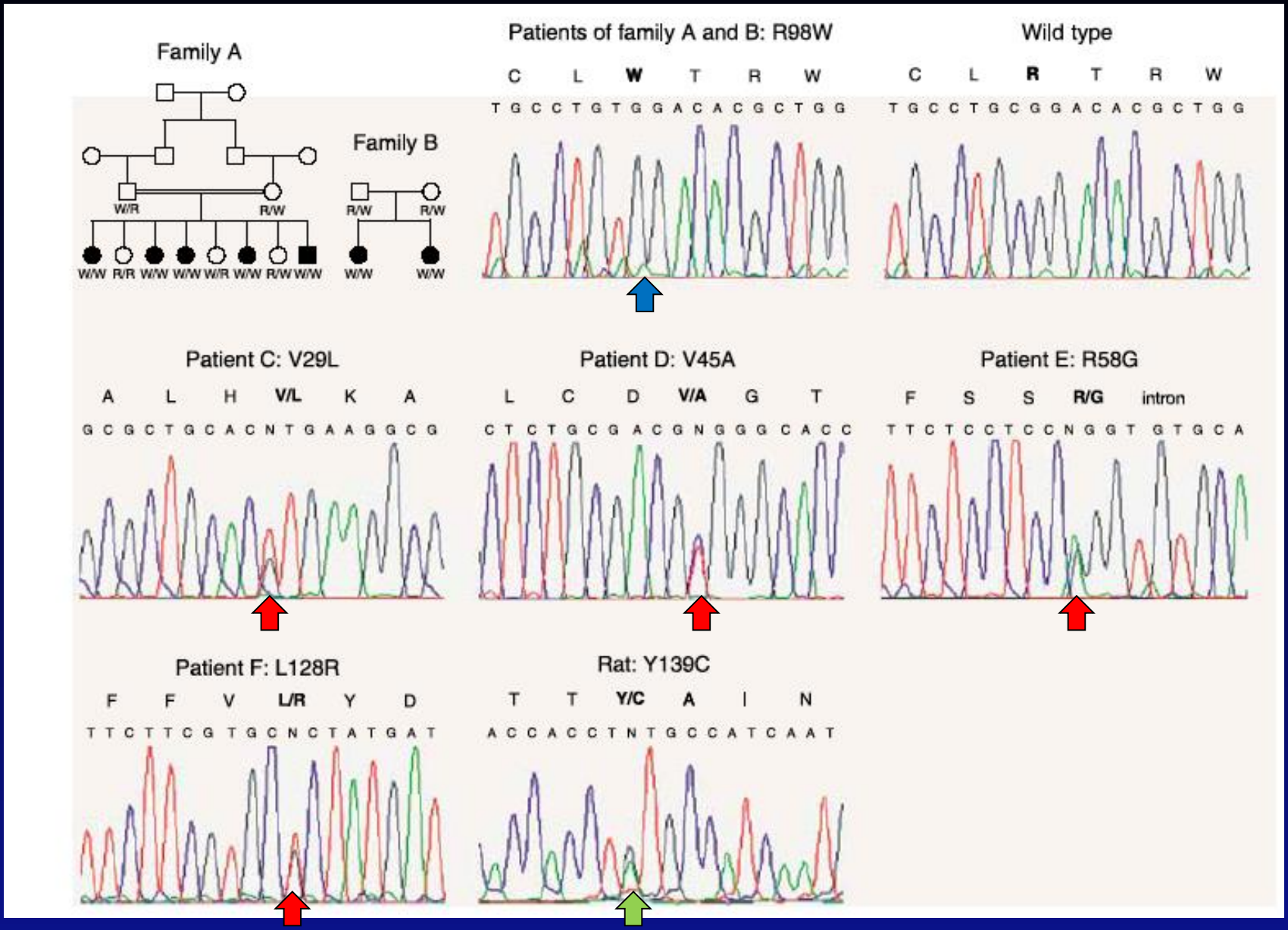
Chinese Indians

Warfarin: Significant Problems for Rats!





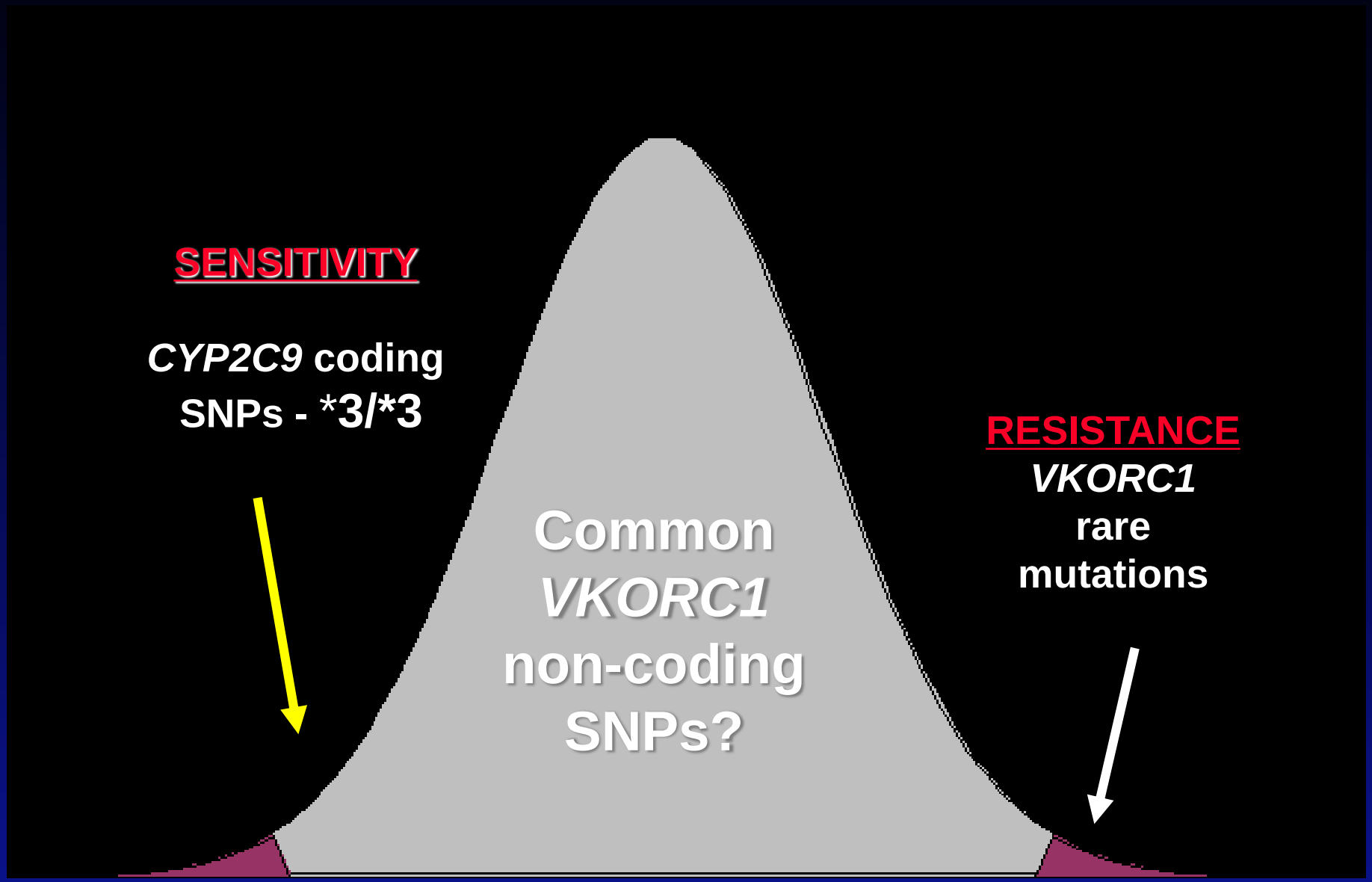
Warfarin Resistance and the VKORC1 gene



- Rare non-synonymous mutations in *VKORC1* causative for warfarin resistance (15-35 mg/d)
- NO non-synonymous mutations found in 'control' chromosomes (n = ~400)

Rost, et. al. Nature (2004)

Inter-Individual Variability in Warfarin Dose: Genetic Liabilities



VKORC1 common mutations

Table 3. Clinical characteristics of patients carrying different genotypes

	Sex, (m/f)	Indication, v/a/o	Mean age when OAT started, y (SD)	Mean time in OAT, y (SD)	Warfarin mean daily dose, mg (SD)	Mean INR (SD)	Patients taking other drugs, % (n)	Visits, n (SD)
VKORC1								
1173C>T (6484)								
CC, n = 54, 36.8%	32/22	42/8/4	42.8 (16.5)	1.9 (2.9)	7.0 (3.0)*	2.45 (0.39)	35.2 (19)	28.4 (24.0)
CT, n = 69, 46.9%	34/35	55/8/6	43.4 (16.0)	1.5 (1.4)	5.1 (2.5)*	2.56 (0.39)	37.7 (26)	27.3 (23.7)
TT, n = 24, 16.3%	14/10	15/5/4	49.6 (18.4)	1.3 (1.2)	3.7 (1.6)	2.53 (0.37)	45.8 (11)	25.2 (20.1)
3730G>A (9041)								
GG, n = 67, 45.5%	31/36	49/11/7	44.2 (18.0)	1.5 (1.3)	5.2 (2.6)†	2.52 (0.35)	42.7 (23)	26.6 (21.9)
GA, n = 58, 39.5%	35/23	42/11/5	46.2 (15.1)	1.7 (2.8)	5.3 (2.2)	2.60 (0.45)	24.3 (25)	25.5 (21.6)
AA, n = 22, 15.0%	14/8	21/1/0	44.3 (16.5)	1.6 (1.6)	6.9 (4.0)	2.38 (0.31)	36.6 (7)	28.9 (26.6)
CYP2C9								
Allele*1, n = 74, 50.3%	44/30	56/11/7	41.9 (15.3)‡	1.8 (2.5)	6.6 (2.9)	2.47 (0.36)	36.5 (27)	27.7 (22.3)
Allele*2, n = 48, 32.0%	25/23	37/6/5	44.5 (17.6)	1.7 (1.5)	5.1 (2.2)§	2.58 (0.41)	37.5 (18)	28.2 (23.2)
Allele*3, n = 23, 16.3%	11/12	18/4/1	47.9 (16.7)	1.2 (1.3)	3.5 (1.9)§	2.63 (0.44)	39.1 (9)	22.3 (22.2)
Allele*2 + Allele*3, n = 2, 1.4%	0/2	1/0/1	76.5 (9.2)	2.3 (2.7)	1.8 (0.1)§	3.00 (0.21)	100.0 (2)	55.0 (58.0)

v/a/o indicates patients with previous venous (v) or arterial (a) thrombosis, or other (o) disease requiring oral anticoagulation; OAT, oral anticoagulant therapy.
*$P < .001$ vs TT carriers (Scheffé test).
†$P < .05$ vs AA carriers (Mann-Whitney *U* test).
‡$P < .05$ vs CYP2C9*2 + CYP2C9*3 carriers (Scheffé test).
§$P < .05$ vs CYP2C9*1 carriers (Scheffé test).

D'Andrea, et al., Blood (2005)

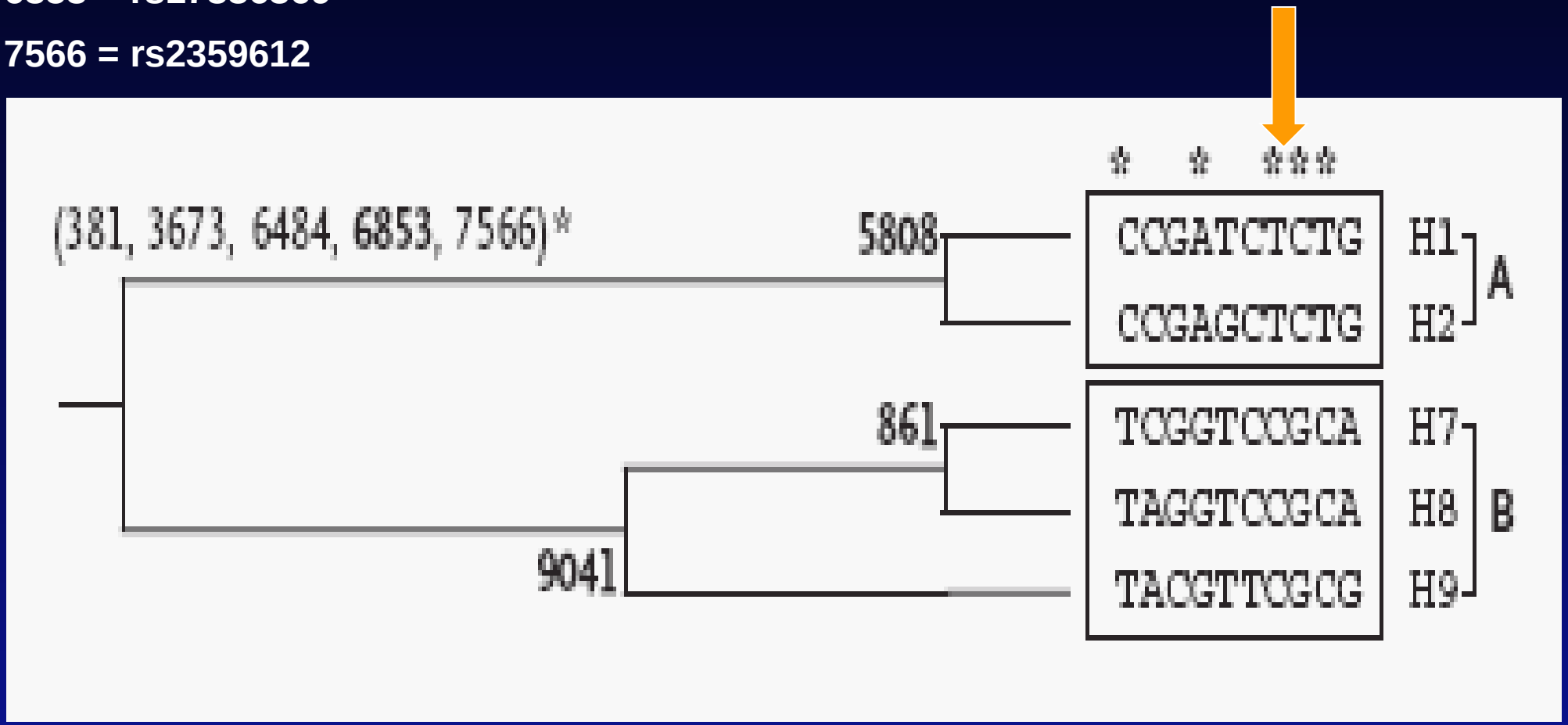
Effect of VKORC1 Inferred Haplotype on Warfarin Dose

3673 = rs9923231 aka -1639, a promoter SNP (M. Wadelius; H. Yuan; E. Sconce)

6484 = rs9934438 aka C1173T, (M. Wadelius; H. Yuan; L. Bodin; D'Andrea);

6853 = rs17886369

7566 = rs2359612



Rieder MJ, Reiner AP, Gage BF et al.
Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose.
N Engl J Med. Jun 2005.

VKORC1 Haplotypes Associate with Dose

Haplotype Identification Code	Haplotype Sequence	Frequency of Haplotype in Primary Patient Sample (n)	Average Maintenance Dose for Homozygous Patients (mg/d)*	p-value
H1	CCGATCTCTG	0.12 (43)	2.9 (2.2 – 3.7)	0.0001
H2	CCGAGCTCTG	0.24 (88)	3.0 (2.5 – 3.6)	0.001
H3	CCGGTCCCCG	0.01 (2)	NA	NS
H4	CCGGTCCGTG	0.00 (1)	NA	NS
H5	TCGAGCTCTG	0.00 (1)	NA	NS
H6	TCGGTCCGCG	0.00 (0)	NA	NS
H7	TCGGTCCGCA	0.35 (132)	6.0 (5.2 – 6.9)	0.0001
H8	TAGGTCCGCA	0.08 (28)	4.8 (3.4 – 6.7)	0.76
H9	TACGTTCGCG	0.21 (77)	5.5 (4.5 – 6.7)	0.05

Adjusted for all significant covariates: age, sex, amiodarone, CYP2C9 genotype

25% variance in dose explained

5 mg/d

*2: 10.7% *3: 8.5 %

A: 37% B: 58%

3.0-3.5 mg/d

*2: 0% *3: 1-2%

A: 89% B: 10%

6.0-7.0 mg/d

*2: 2.9% *3: 0.8%

A: 49% B: 14%

Japanese Caucasians Africans

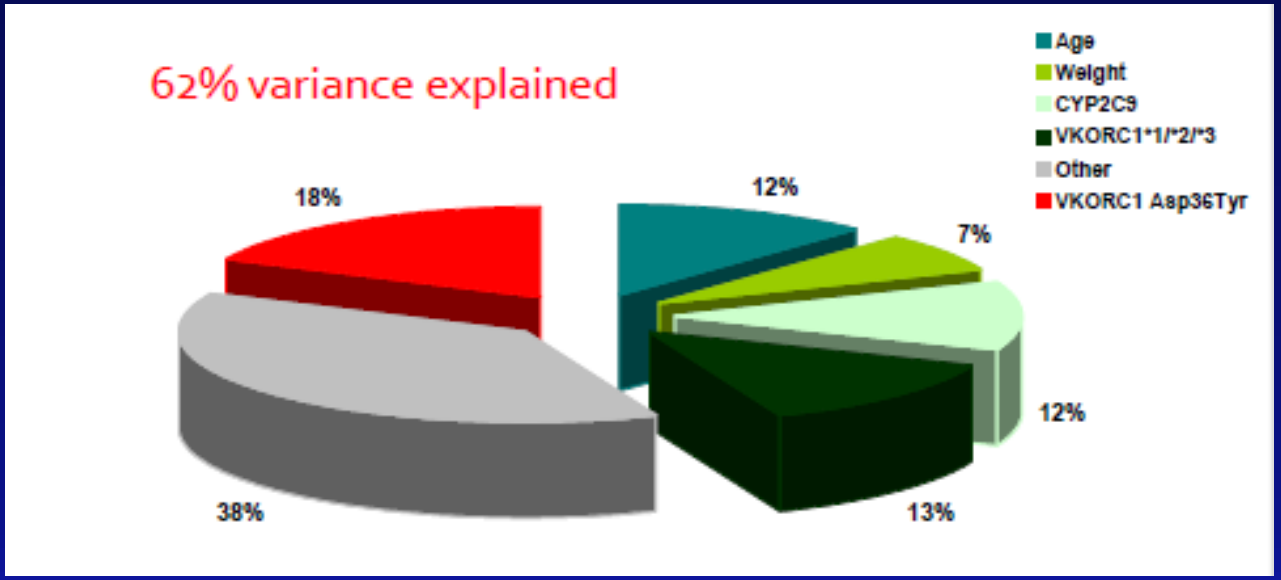
Chinese Indians

VKORC1: more haplotypes

Table 2. Association of dose requirements with constitutional and genetic determinants

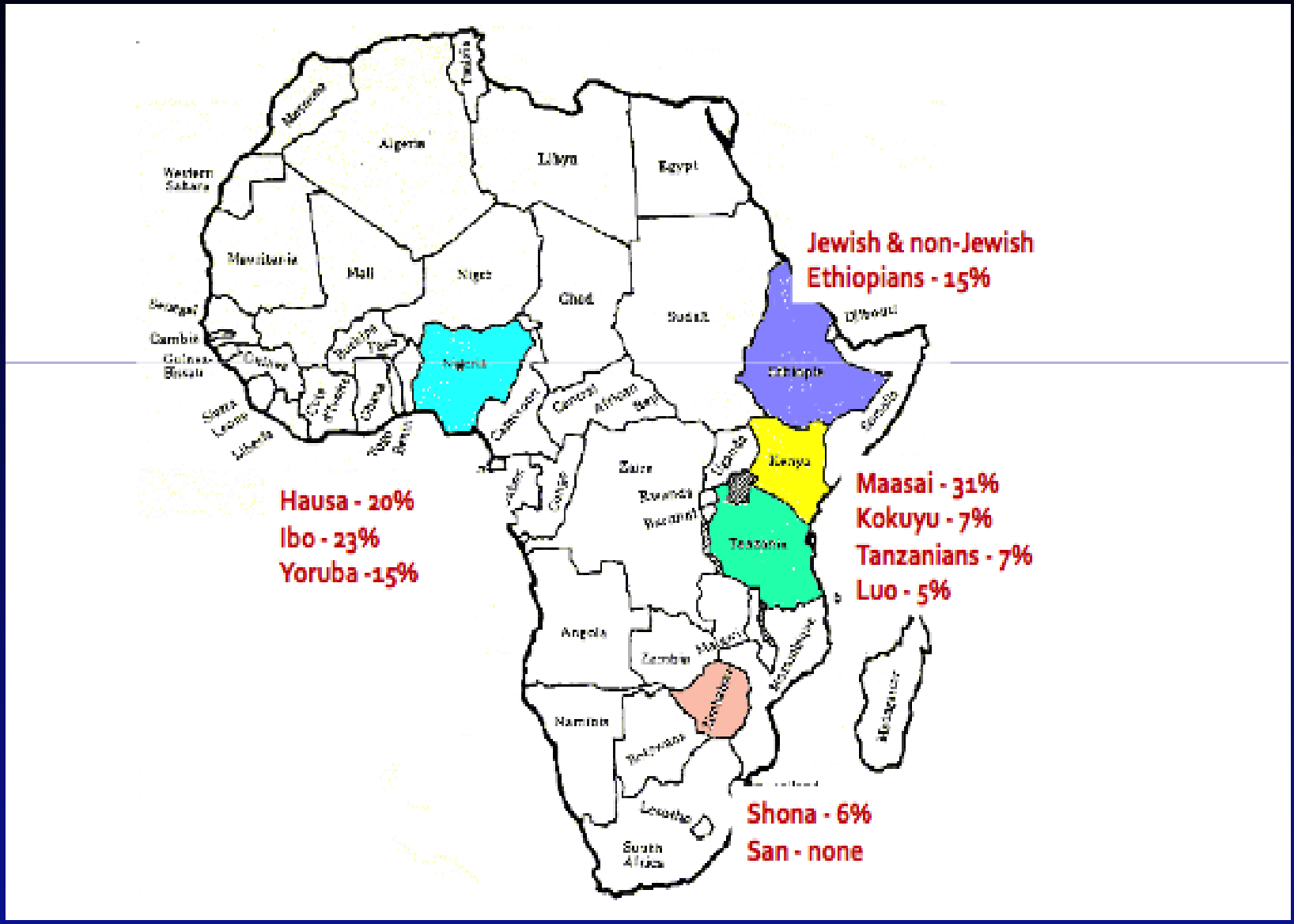
	Less than 20 mg/wk, OR (CL)	More than 70 mg/wk, OR (CL)
Age	1.05 (1.02-1.14)	0.93 (0.87-0.98)
Weight	NS	NS
CYP2C9*2 and *3	2.4 (1.3-4.6)	NS
VKORC1*2	NS	NS
VKORC1 Asp36Tyr	NS	13.0 (1.3-124.2)

Dose requirements in the control group categorized as high (> 70 mg/wk) and low (< 20 mg/wk) are analyzed by the logistic regression.
NS indicates nonsignificant.

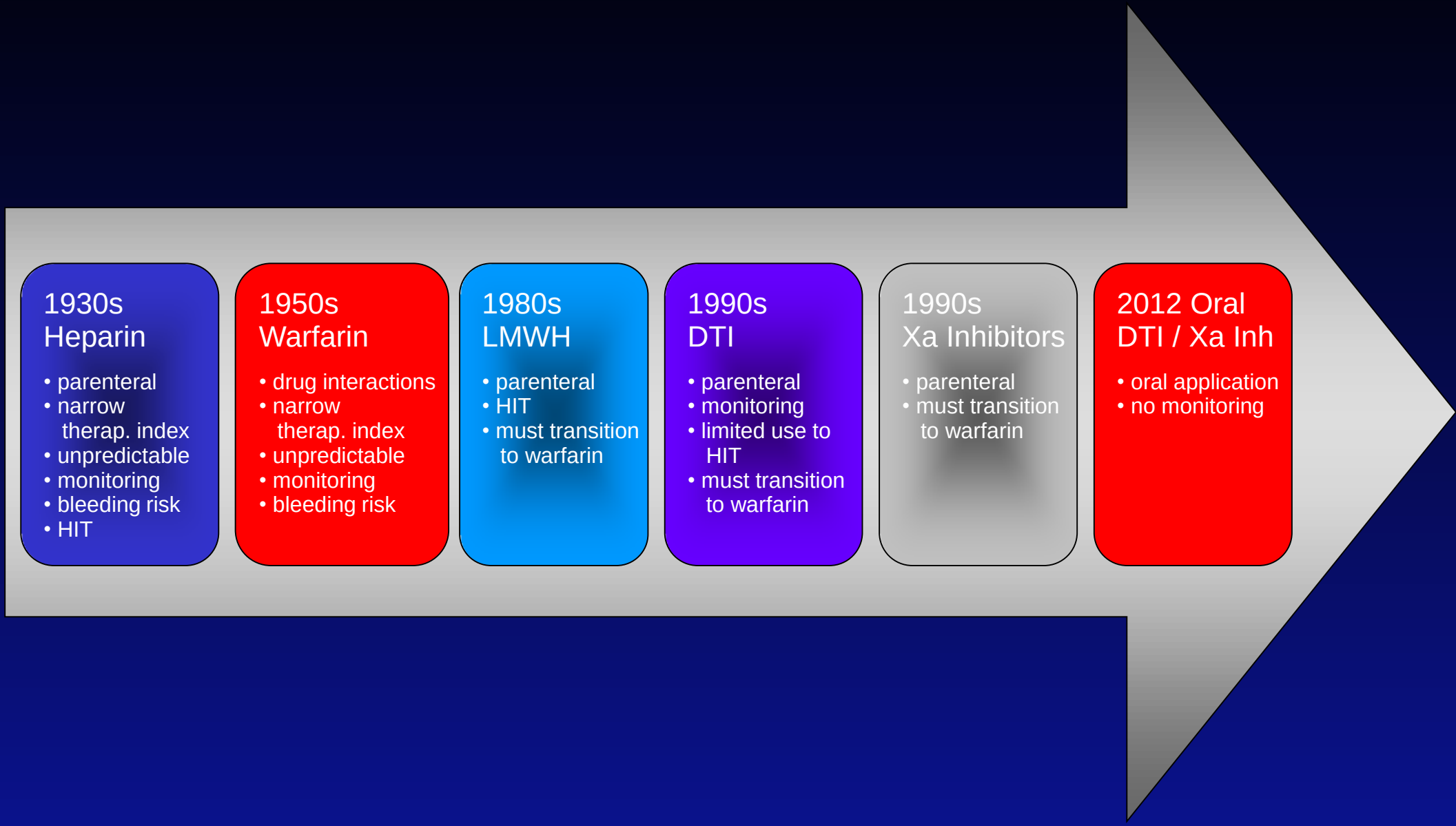


Aklillu et al, Blood 2008

Asp36Tyr is significant & dominant marker of warfarin resistance



Evolution of Anticoagulation

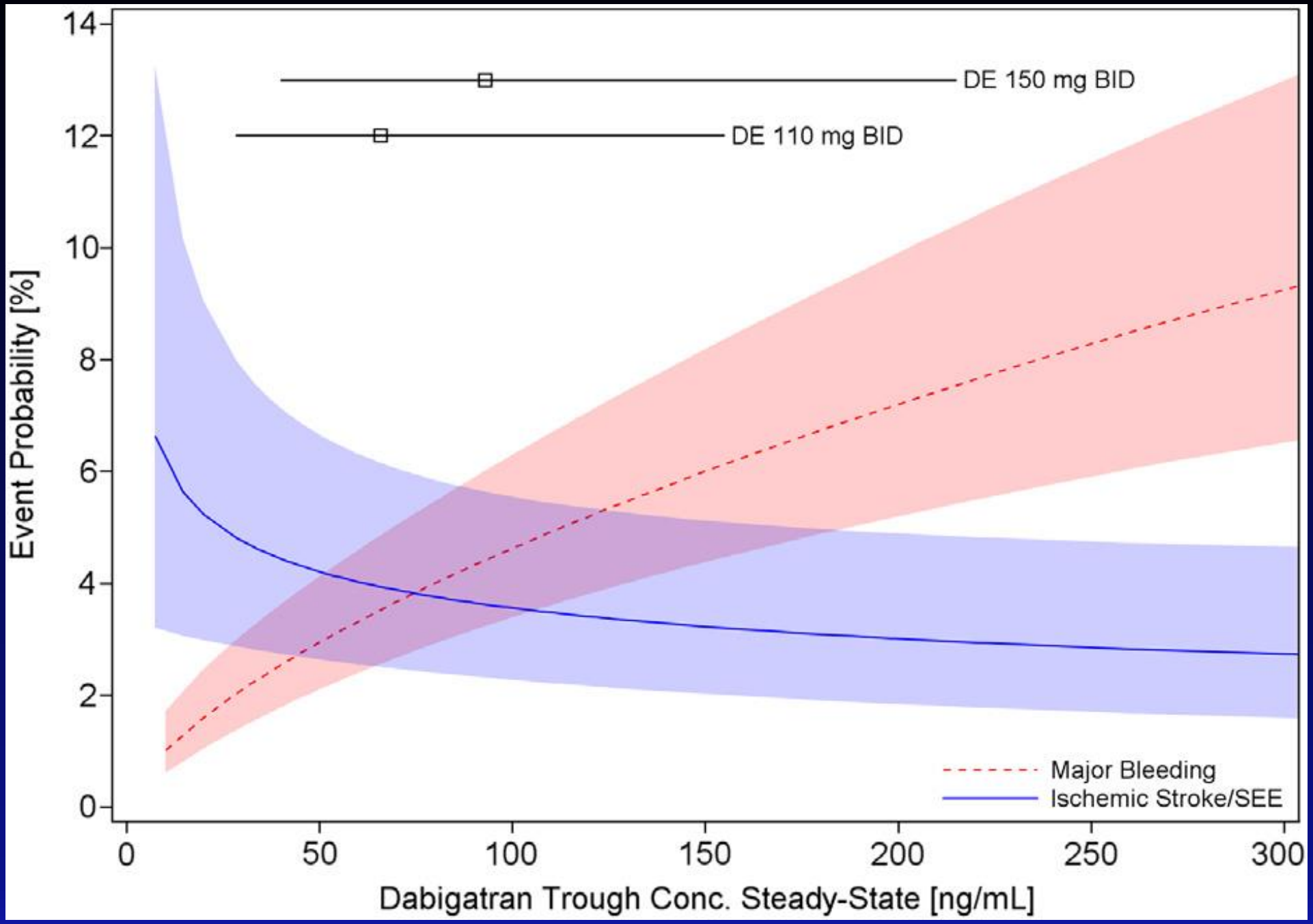


Benchmarks of new oral Anticoagulants

	Dabigatran Pradaxa®	Rivaroxaban Xarelto®	Apixaban Eliquis®	Edoxaban Lixana®
molecular mass [g/mol]	628 / 472 prodrug / drug	436	460	548
protein binding [%]	34-35	92-95	ca. 87	40-60
bioavailability [%]	6.5	80-100	>50	45-50
T(max) [h]	1-2	2-4	3-4	1-2
half-live [h]	14-17	7-11	10-14	9-11
Metabolism CYP450 dependent P-gp substrate	~ 15% (liver) (No) 2% CYP3A4 Yes	~ 60% (liver) Yes, ~ 32% CYP3A4 CYP3A5 CYP2J2 Yes	25% (liver) Yes, minor CYP3A4 (CYP3A5) Yes	27% (liver) Yes CYP3A4 (CYP3A5) Yes
excretion urine excretion faeces	~ 85% (77% active) ~ 15% (8% active)	~ 67% (~ 33% active) ~ 33% (inactive)	~ 30% (~ 24% active) ~ 70% (majority active)	~ 35% (~ 24% active) ~ 65% (~ 49% active)

Weinz et al. 2009, Blech et al. 2008, Raghavan et al. 2009, Eriksson et al. 2009

Dabigatran: Probability of Major Bleeding Event and Ischemic Stroke



Reilly et al. Analysis from the RE-LY trial JACC Vol. 63, No. 4, 2014

Approximate Incidence of the Major Pathways of Drug Elimination

Pathway	Incidence
	%
Renal unchanged	25
P450 metabolism	
CYP3A4	30
CYP2D6	20
CYP2C9/19	10
Glucuronidation	10
Other [a]	5

[a] Other includes acetylation, thiopurine methyltransferase, and dihydropyrimidine dehydrogenase.

Gardiner & Begg, *Pharmacol Rev* 2006; **58**(3): 521-590

Table 2. Common Drug Substrates, Inhibitors, and Inducers of CYP3A, According to Drug Class.*

CYP3A Substrates	CYP3A Inhibitors	CYP3A Inducers
Calcium-channel blockers	Calcium-channel blockers	Rifamycins
Diltiazem	Diltiazem	Rifabutin
Felodipine	Verapamil	Rifampin
Nifedipine	Azole antifungal agents	Rifapentine
Verapamil	Itraconazole	Anticonvulsant agents
Immunosuppressant agents	Ketoconazole	Carbamazepine
Cyclosporine	Macrolide antibiotics	Phenobarbital
Tacrolimus	Clarithromycin	Phenytoin
Benzodiazepines	Erythromycin	Anti-HIV agents
Alprazolam	Troleandomycin (Not azithromycin)	Efavirenz
Midazolam	Anti-HIV agents	Nevirapine
Triazolam	Delavirdine	Others
Statins	Indinavir	St. John's wort
Atorvastatin	Ritonavir	
Lovastatin (Not pravastatin)	Saquinavir	
Macrolide antibiotics	Others	
Clarithromycin	Grapefruit juice	
Erythromycin	Mifepristone	
Anti-HIV agents	Nefazodone	
Indinavir		
Nelfinavir		
Ritonavir		
Saquinavir		
Others		
Losartan		
Sildenafil		

* These inhibitors and inducers can interact with any CYP3A substrate and may have important clinical consequences. HIV denotes human immunodeficiency virus.

Polymorphisms in CYP3A4

42 alleles (to date)

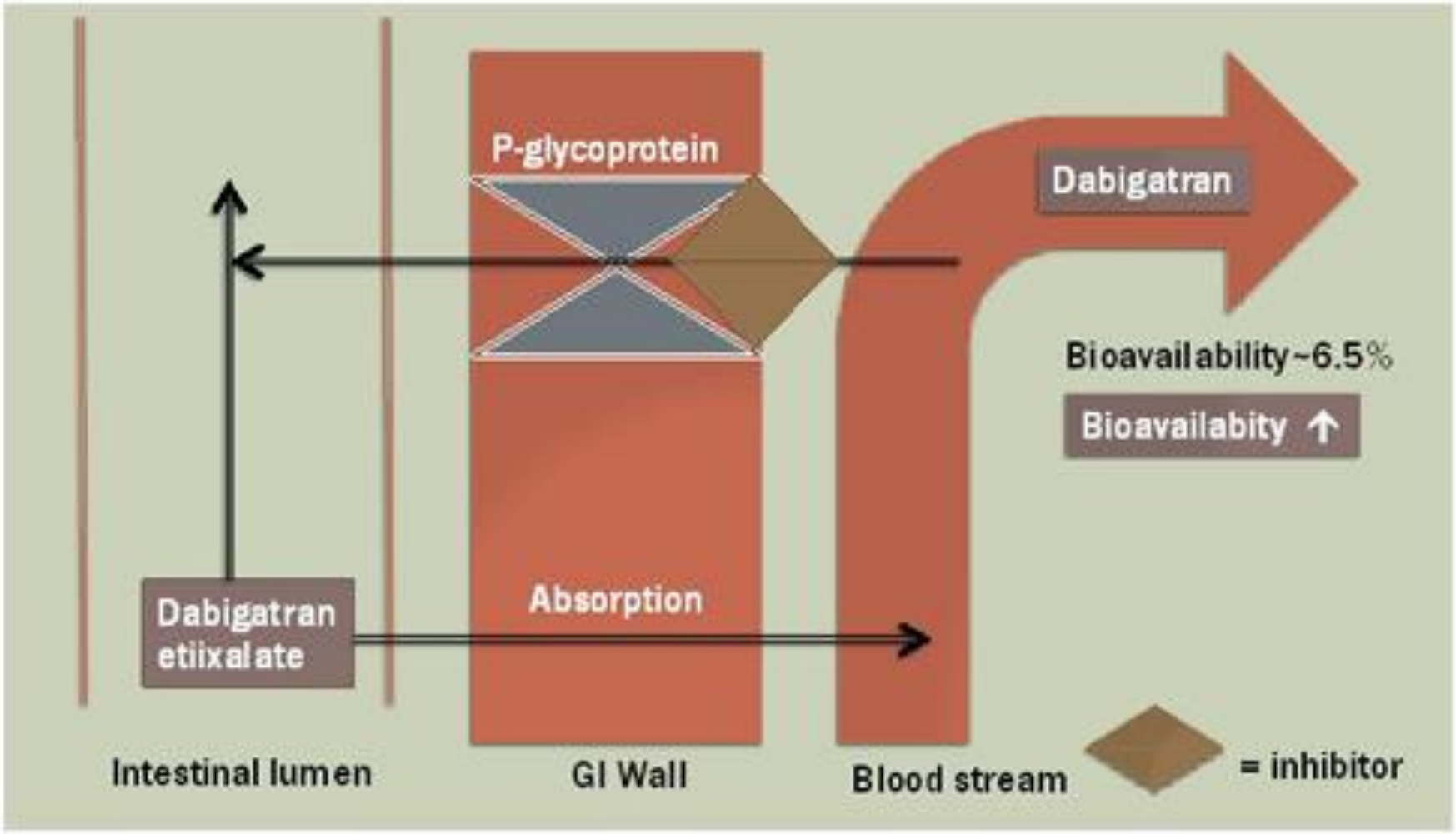
Several alleles associated with increased / reduced / missing enzymatic activity or reduced transcription levels have been described

CYP 3A4*1B and CYP 3A4*20 alter CYP function

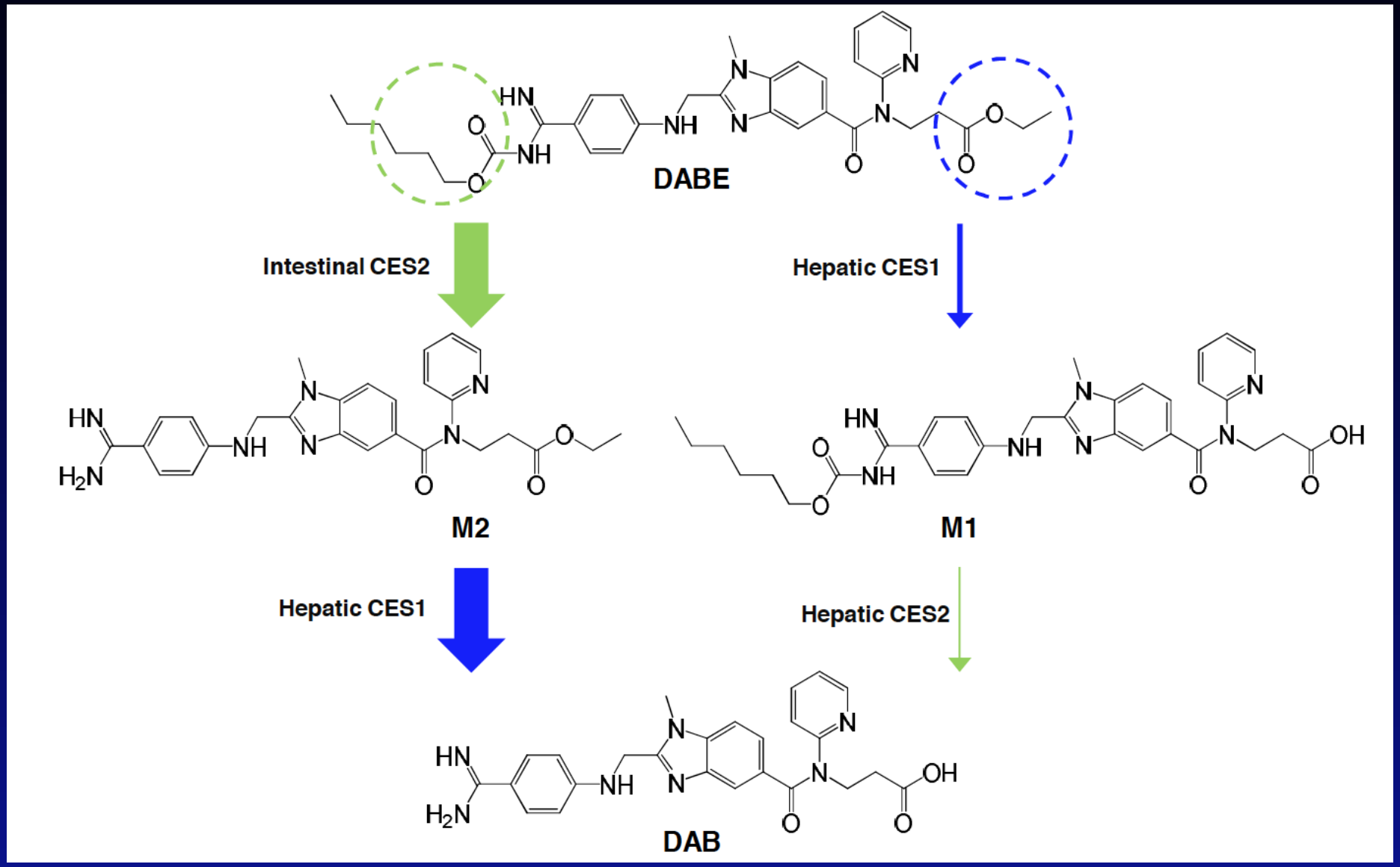
CYP 3A4*1B – 4% in Caucasians, 67% in Black sub.

Eiselt 2001 Pharmacogenetics, Westlind-Johnsson 2006 Clin Pharmacol Ther, Kang 2009 Clin Pharmacol Ther, Wang 2011 Pharmacogenetics

DABIGATRAN AND P-GLYCOPROTEIN

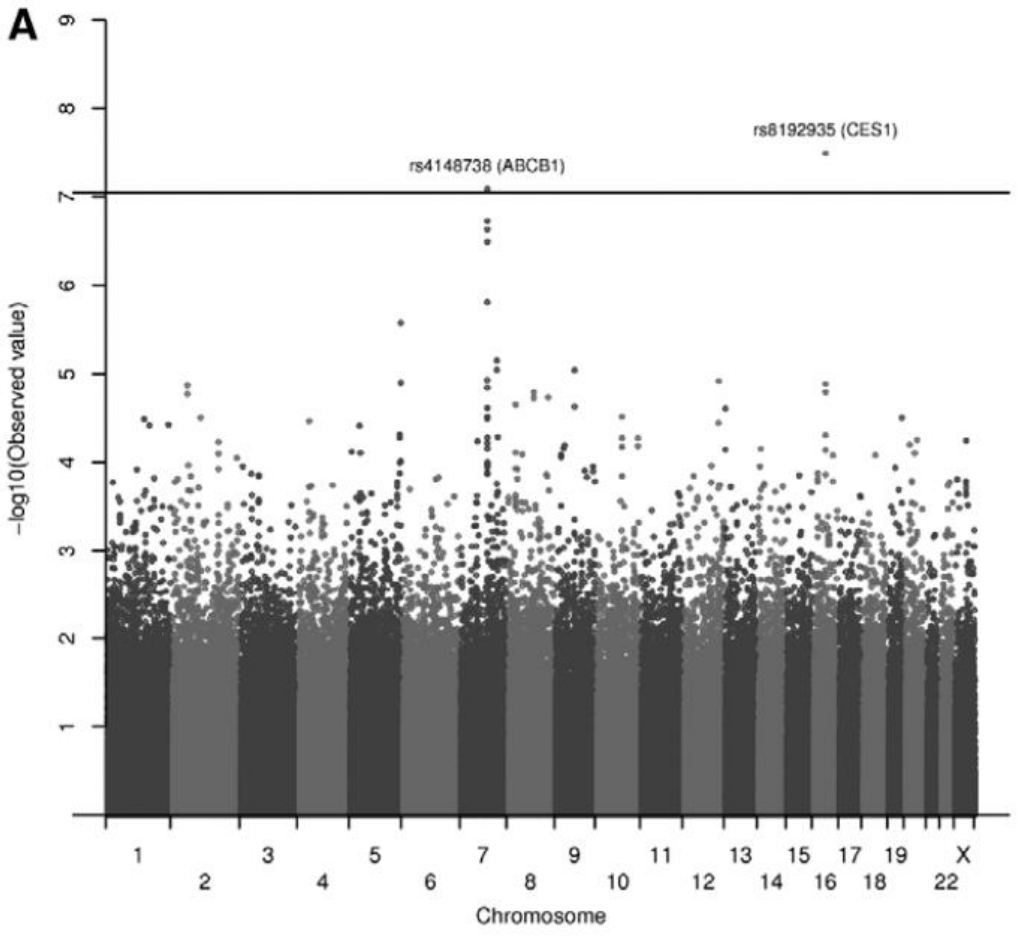


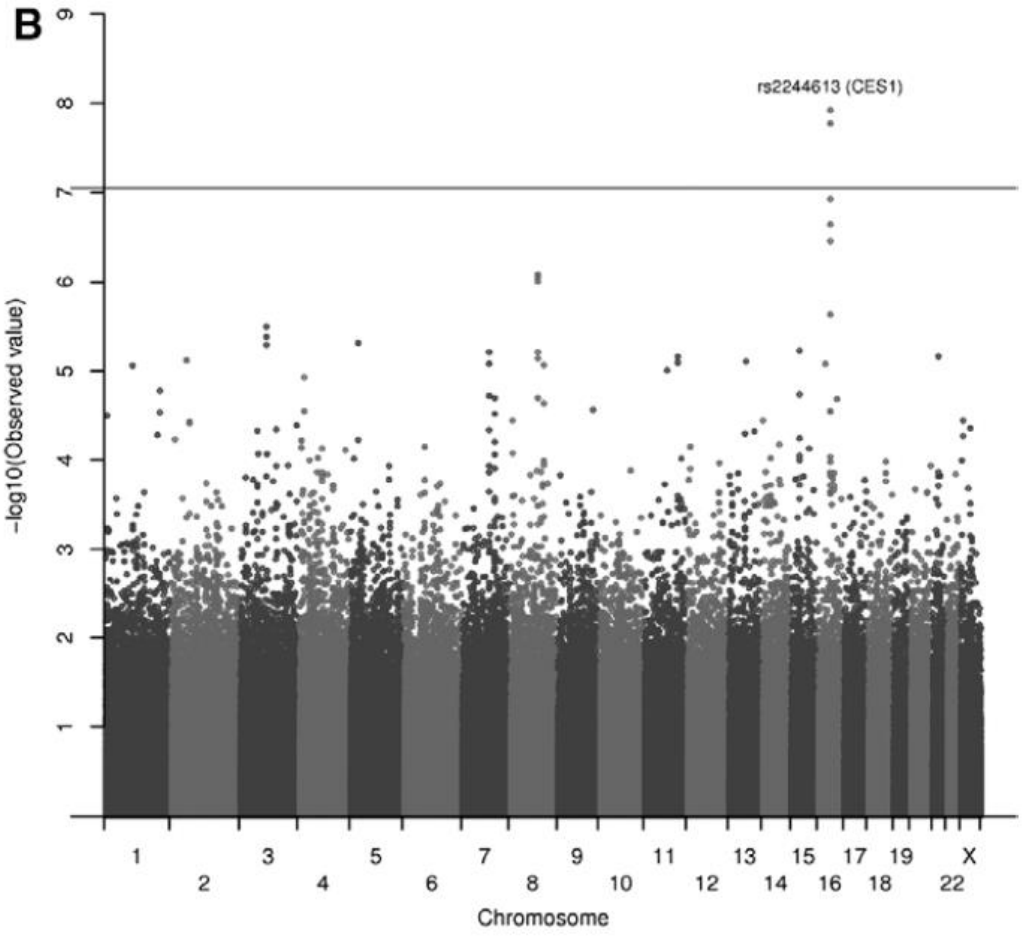
Dabigatran and carboxyl esterase



Laizure SC et al. Drug Metab Dispos. 2014

Genetic Determinants of Dabigatran Plasma Levels





Paré et al. Circulation 2013;127:1404-1412

Genetic Determinants of Dabigatran Plasma Levels

Table 3. Association of Lead SNPs With Bleeding and Ischemic Events in Dabigatran-Treated Participants

	rs4148738* (*ABCB1*; Peak Concentration)		rs8192935* (*CES1*; Peak Concentration)		rs2244613* (*CES1*; Trough Concentration)	
Event	OR (95% CI) †	*P*	OR (95% CI) †	*P*	OR (95% CI) †	*P*
Ischemic stroke or systemic embolism	0.88 (0.53–1.46)	0.62	0.76 (0.43–1.34)	0.34	0.70 (0.33–1.47)	0.34
Any ischemic event	0.98 (0.69–1.40)	0.92	1.04 (0.72–1.51)	0.84	0.95 (0.59–1.51)	0.82
Any bleeding	0.94 (0.82–1.09)	0.44	0.89 (0.76–1.03)	0.13	0.67 (0.55–0.82)	7×10^{-5}‡
Major bleeding	1.14 (0.85–1.52)	0.40	0.88 (0.64–1.21)	0.44	0.66 (0.43–1.01)	0.06
Minor bleeding	0.94 (0.81–1.09)	0.38	0.89 (0.76–1.05)	0.17	0.70 (0.57–0.85)	4×10^{-4}‡

Paré et al. Circulation 2013;127:1404-1412

Genetic Determinants of Dabigatran Plasma Levels

CES1 rs2244613

Coefficienti[a]

Modello		Coefficienti non standardizzati		Coefficienti standardizzati	t	Sign.
		T	Errore std	Beta		
1	(Costante)	2,083	,130		16,046	,000
	clearance	-,004	,002	-,239	-2,158	,034
2	(Costante)	2,200	,139		15,841	,000
	clearance	-,004	,002	-,278	-2,527	,014
	ces1_1	-,107	,051	-,230	-2,089	,040

a. Variabile dipendente: logpre

Riepilogo del modello

Modello	R	R-quadrato	R-quadrato adattato	Errore standard della stima
1	,239[a]	,057	,045	,29593
2	,329[b]	,108	,085	,28966

a. Predittori: (costante), clearance

b. Predittori: (costante), clearance, ces1_1

D'Andrea, Testa, Margaglione *submitted*

Genetic Determinants of Apixaban Plasma Levels

ABCB1 rs4148738

Coefficienti[a]

Modello		Coefficienti non standardizzati		Coefficienti standardizzati	t	Sign.
		T	Errore std	Beta		
1	(Costante)	274,476	18,618		14,742	,000
	SESSO	-53,743	22,710	-,294	-2,366	,021
2	(Costante)	236,008	26,331		8,963	,000
	SESSO	-56,557	22,186	-,310	-2,549	,013
	abcb1_2	51,291	25,432	,245	2,017	,048

a. Variabile dipendente: POST

Riepilogo del modello

Modello	R	R-quadrato	R-quadrato adattato	Errore standard della stima
1	,294[a]	,087	,071	83,26373
2	,383[b]	,147	,117	81,18025

a. Predittori: (costante), SESSO

b. Predittori: (costante), SESSO, abcb1_2

D'Andrea, Testa, Margaglione *unpublished*

Conclusions – New oral Anticoagulants

- Less clear characterisation of pharmacogenetic factors
- It is likely that there is no influence of direct pharmocogenetic factors in the majority of patients
- All new oral anticoagulants are interacting with P-gp
- For Dabigatran there is a dependency on CES genes
- For Rivaroxaban there is a dependency on the CYP450 genes affecting drug levels in both directions
- As monitoring is not intended, accumulation of pharmacogenetic effects (<1% of patients) will be seen only by the respective phenotypes (bleeding or thrombosis)

Rob Rogers / Pittsburgh Post-Gazette