Introduction à la pharmacogénomique

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Institut de cardiologie de Montréal

Faculté de pharmacie
Université de Montréal

5 mai 2010

INSTITUT DE CARDIOLOGIE DE MONTRÉAL

« *Prediction is very difficult, especially about the future.* »
Niels Bohr, physicien danois.


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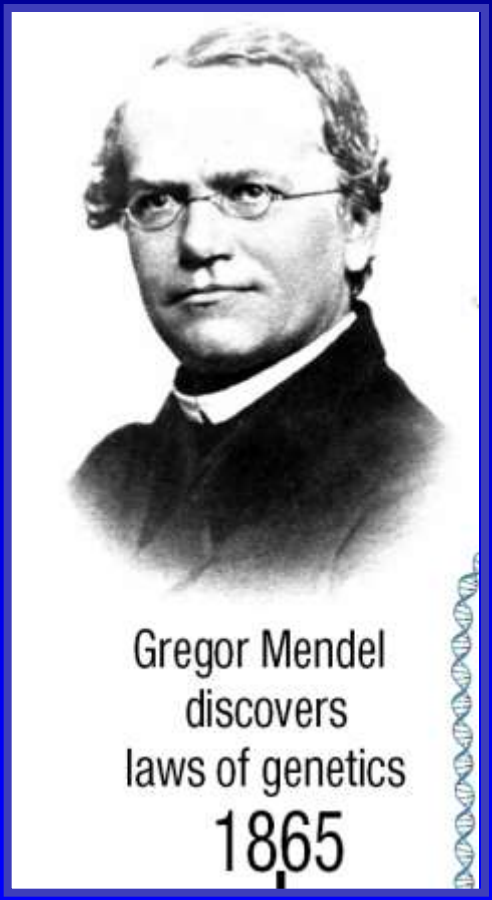
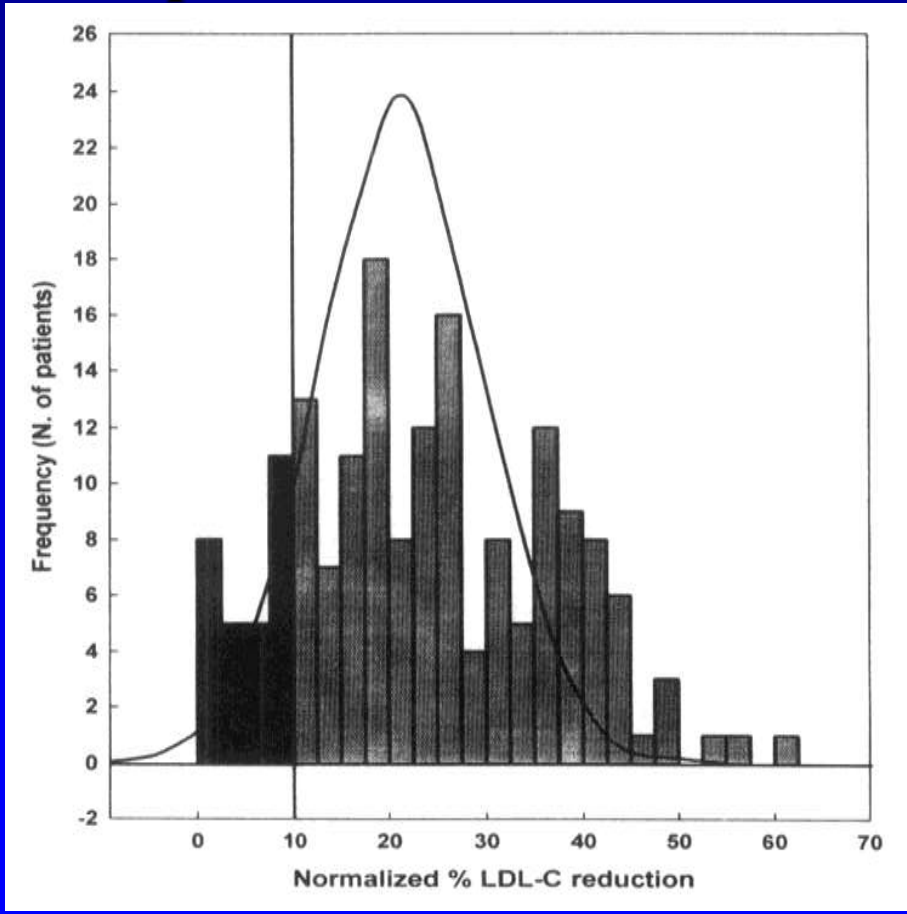


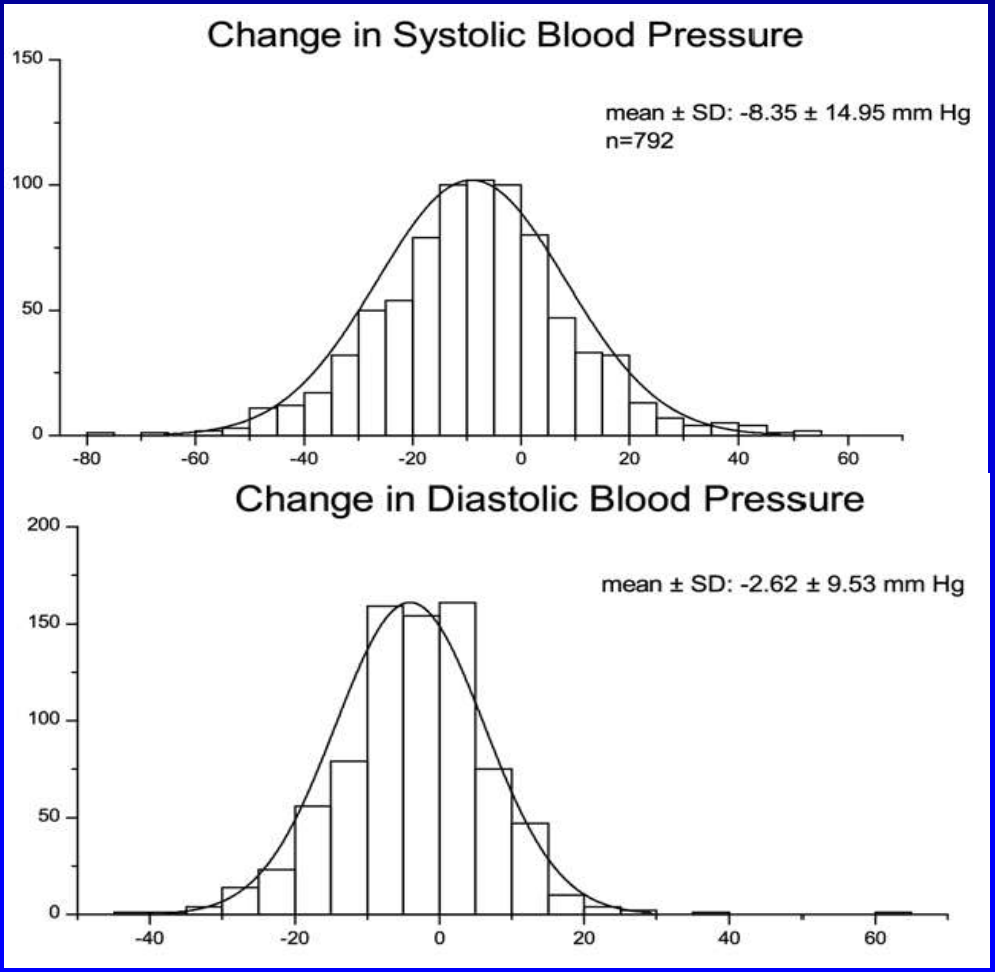
Watson et Crick, 1953

La pharmacogénomique… pourquoi?

- **Réponse très variable aux médicaments**



Pazzucconi F, et al. Atherosclerosis. 1995;117:189-98.



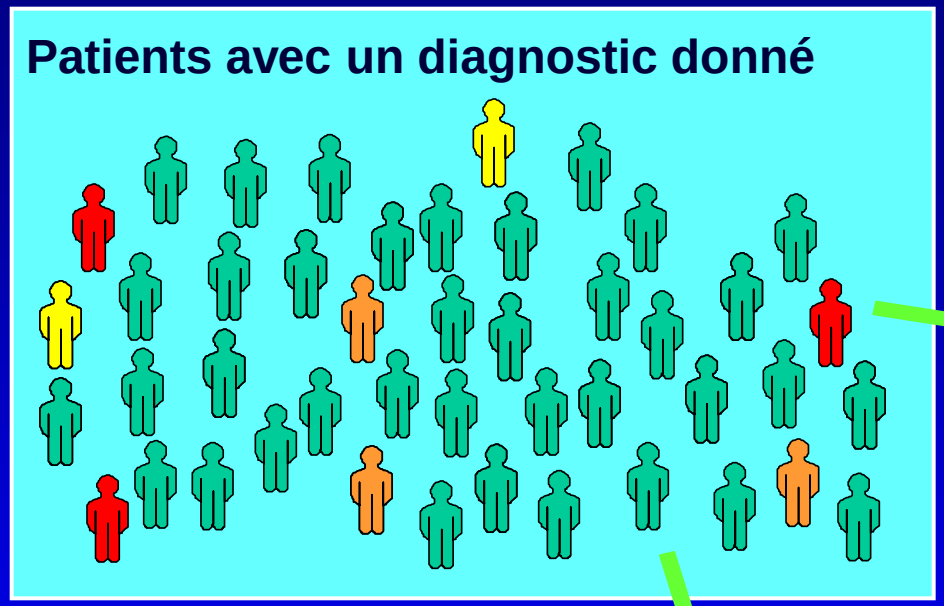
Brunner M, et al. Am J Cardiol. 2007;99:1549-54.

Problématique

- Effets indésirables aux médicaments
  - Données américaines
    - 4 à 6^{e} cause de décès
    - 2 millions d'hospitalisations
    - Jusqu'à 160 milliards dollars/année
- 20 à 95% de la variabilité des effets des médicaments seraient attribuables à des facteurs génétiques.

Gandhi TK, et al. NEJM 2003;348:1556-64. Lazarou J, et al. JAMA. 1998;279:1200-05.
Evans WE, McLeod HL. NEJM 2003;348:538-49.

Potentiel de la pharmacogénomique

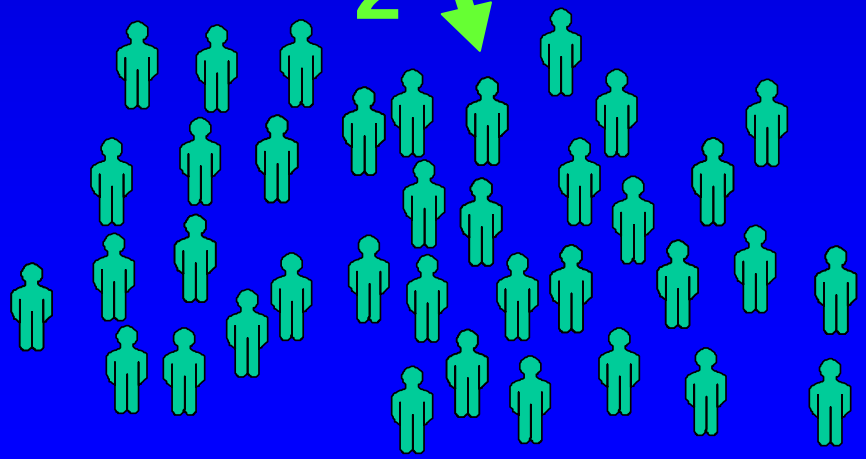


1

Non-répondeurs,
hyper-répondeurs
et répondeurs
"toxiques"

Traiter avec autre Rx ou autre dose

2



Répondeurs sans prédisposition à un effet indésirable

Rx/dose habituels

Quelques chiffres…

- 23 paires de chromosomes
  - 22 paires d'autosomes
  - 1 paire de chromosomes sexuels
- 20 000 à 25 000 gènes codant pour 100 000 protéines
- 3 164 700 000 paires de base (A, T, C, G)
- Le code génétique est identique à 99,9%
- La différence entre l'homme et le chimpanzé est approximativement de 2%

Phénotype

Le phénotype est le trait observable chez une personne résultant de l'expression des allèles.

Ex: couleur des yeux, taille, diabète, TA, réponse à un médicament…

L'influence de l'environnement peut également être conjuguée à celle du génotype dans la pleine expression du phénotype.

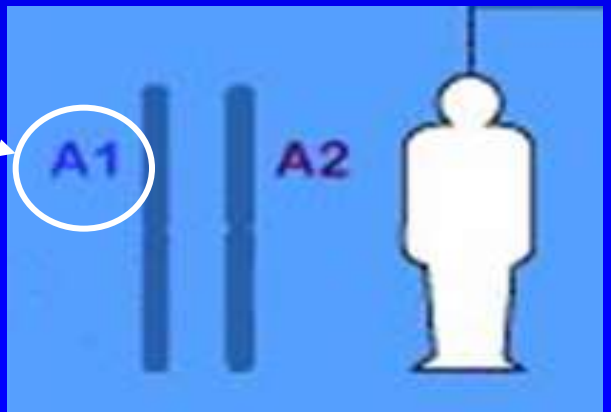
UN Allèle

On nomme **allèle** une variante donnée à un gène.

Les allèles d'un même gène occupent le même **locus** sur un même chromosome.

Exemple : le gène déterminant le groupe sanguin **ABO**, situé sur le chromosome 9 humain, l'un des **allèles** code le groupe **A**, un autre pour le groupe **B**, et un troisième allèle détermine le groupe **O**.

Allèle



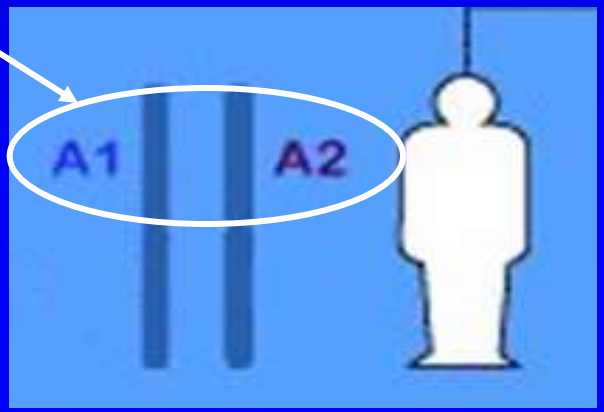
Population

Génotype

1. Le **génotype** est l’ensemble des constituants génétiques d'un organisme, qu'ils soient exprimés ou non.

2. C’est plus communément utilisé pour représenter la constitution d’une paire d’allèles.

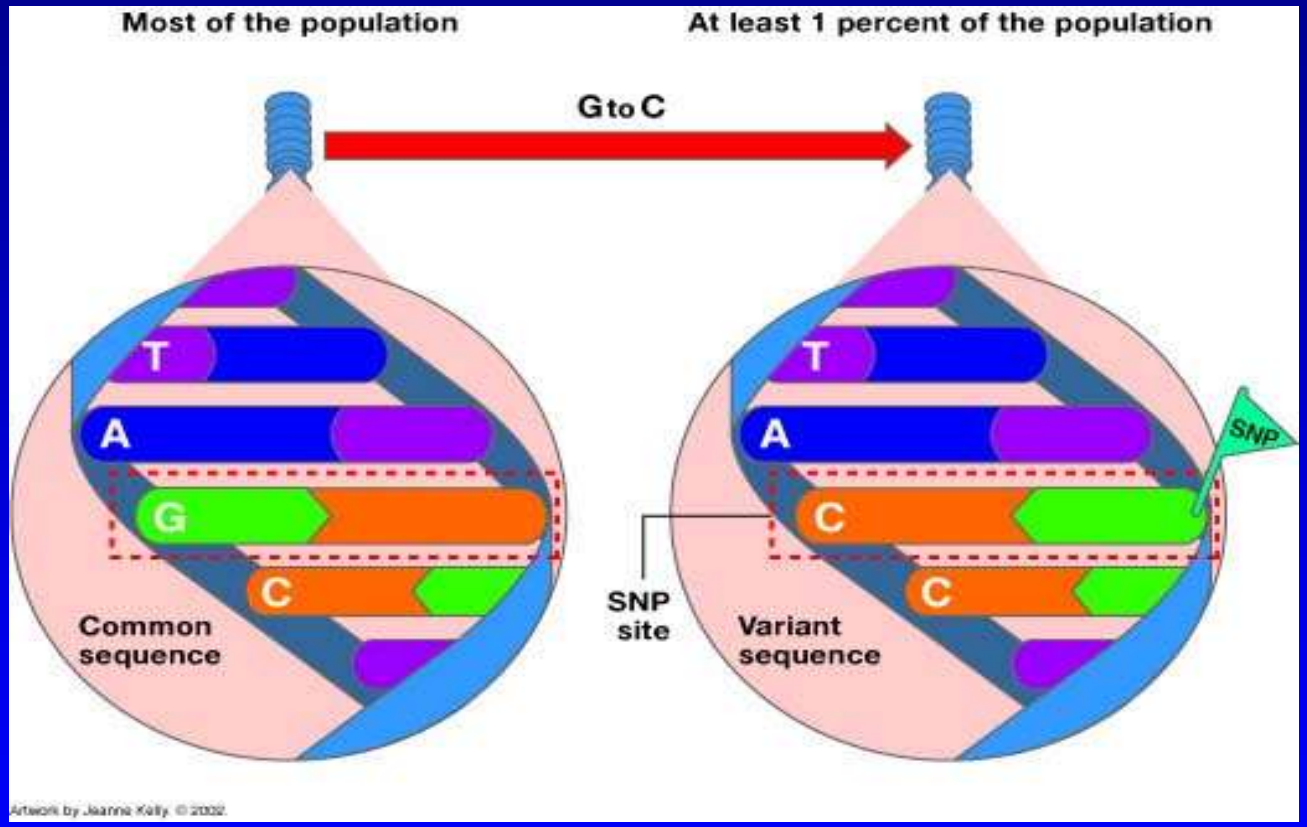
génotype



Quelques termes…

- **Exon: Région codante du gène (1% du génome humain)**
- **Intron: Région non codante du gène (24% du génome humain)**
- **Pénétrance: Probabilité qu'un phénotype particulier soit exprimé chez un individu avec un génotype donné.**

SNPs : Single Nucleotide Polymorphisms ou polymorphismes nucléotidiques simples



TAGC

TACC

- Environ 10 millions de SNPs dans le génome

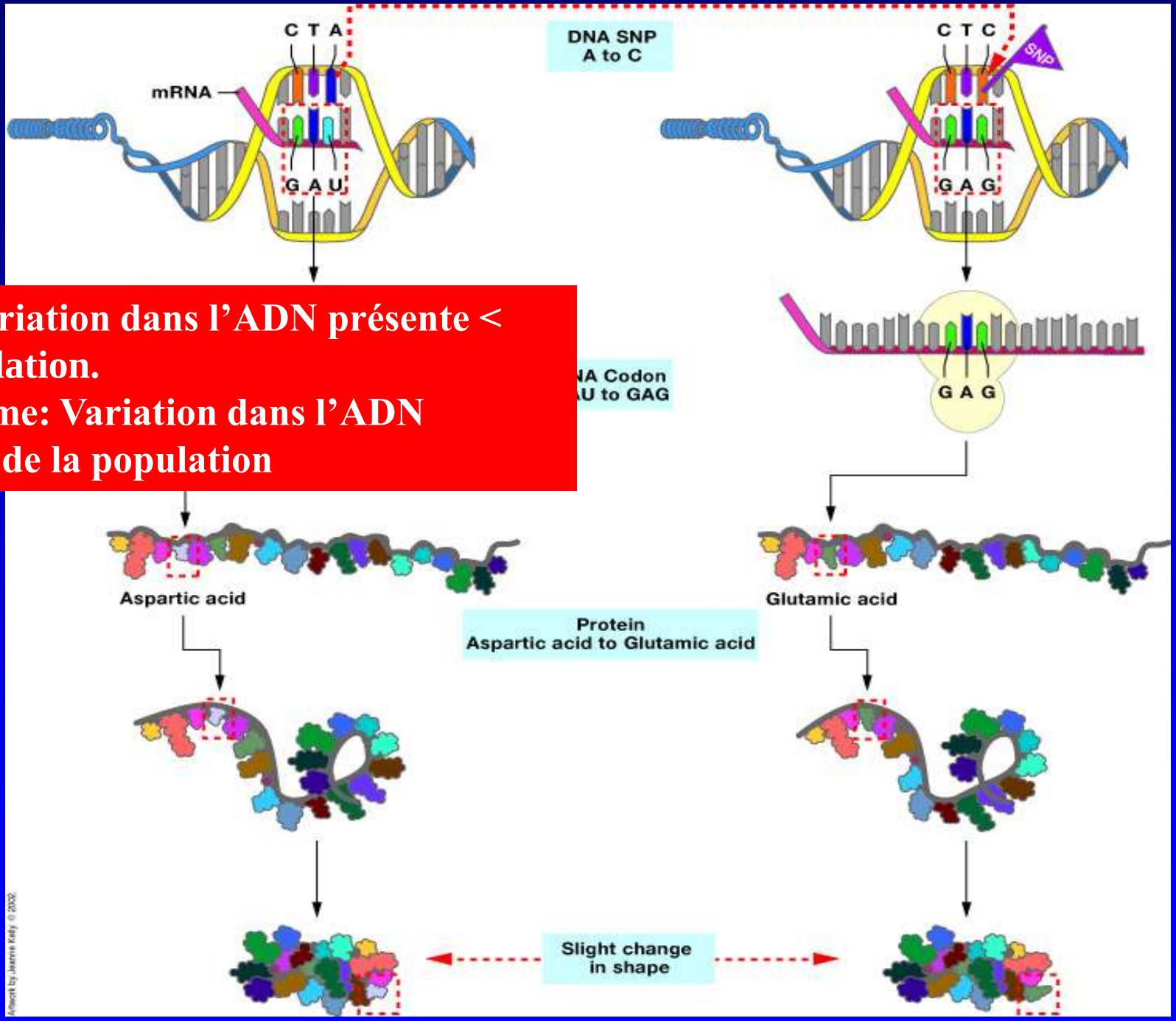
SNP

Transcription

- **Mutation: Variation dans l'ADN présente < 1% de la population.**
- **Polymorphisme: Variation dans l'ADN présente ≥ 1% de la population**

Traduction

Protéine

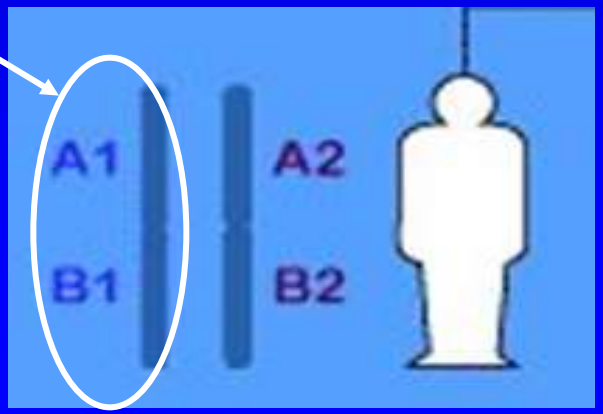


Haplotype

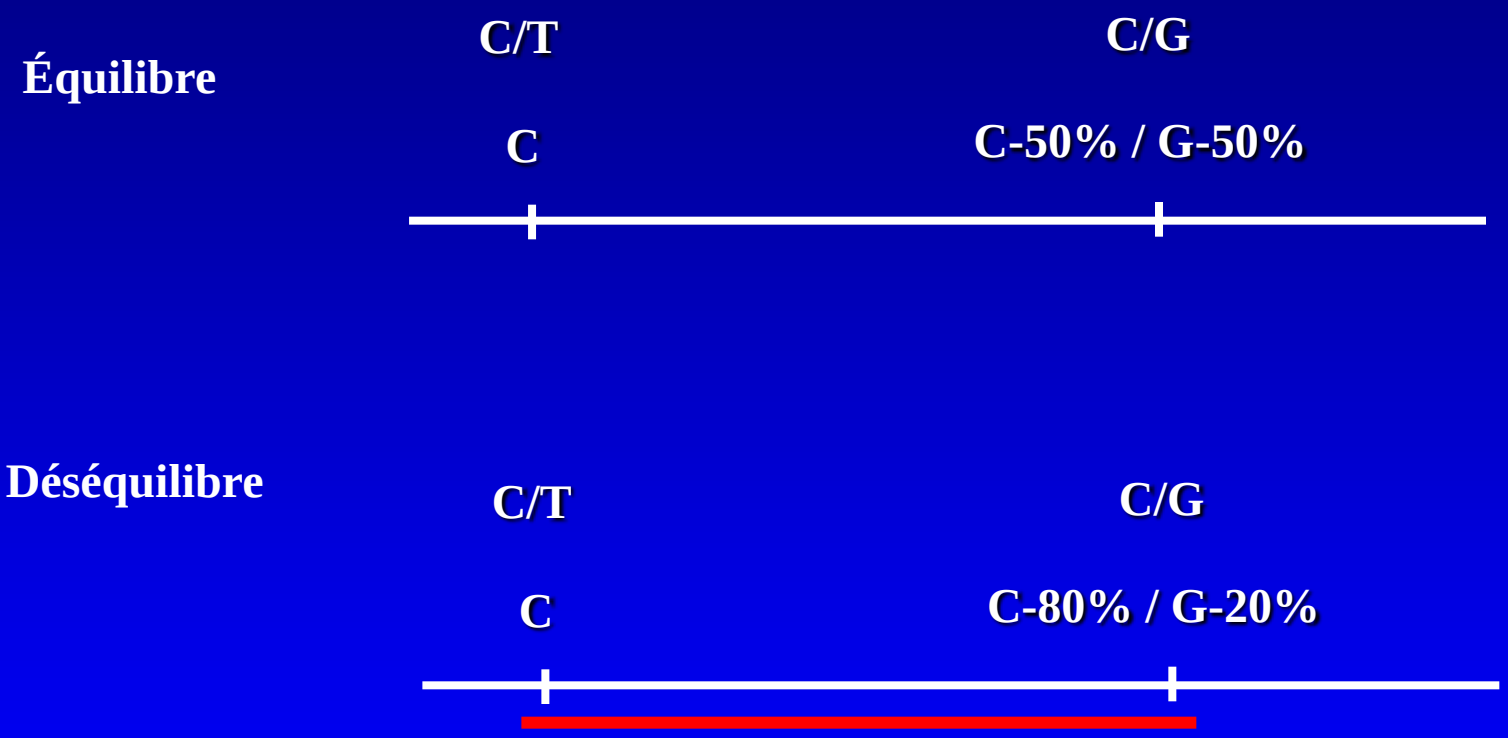
L'**haplotype** est formé de séquence d'ADN (d'allèles) situés sur un seul brin d'ADN, donc un seul chromosome.

C'est l'ensemble des gènes présent sur un des chromosomes d'une paire.

haplotype



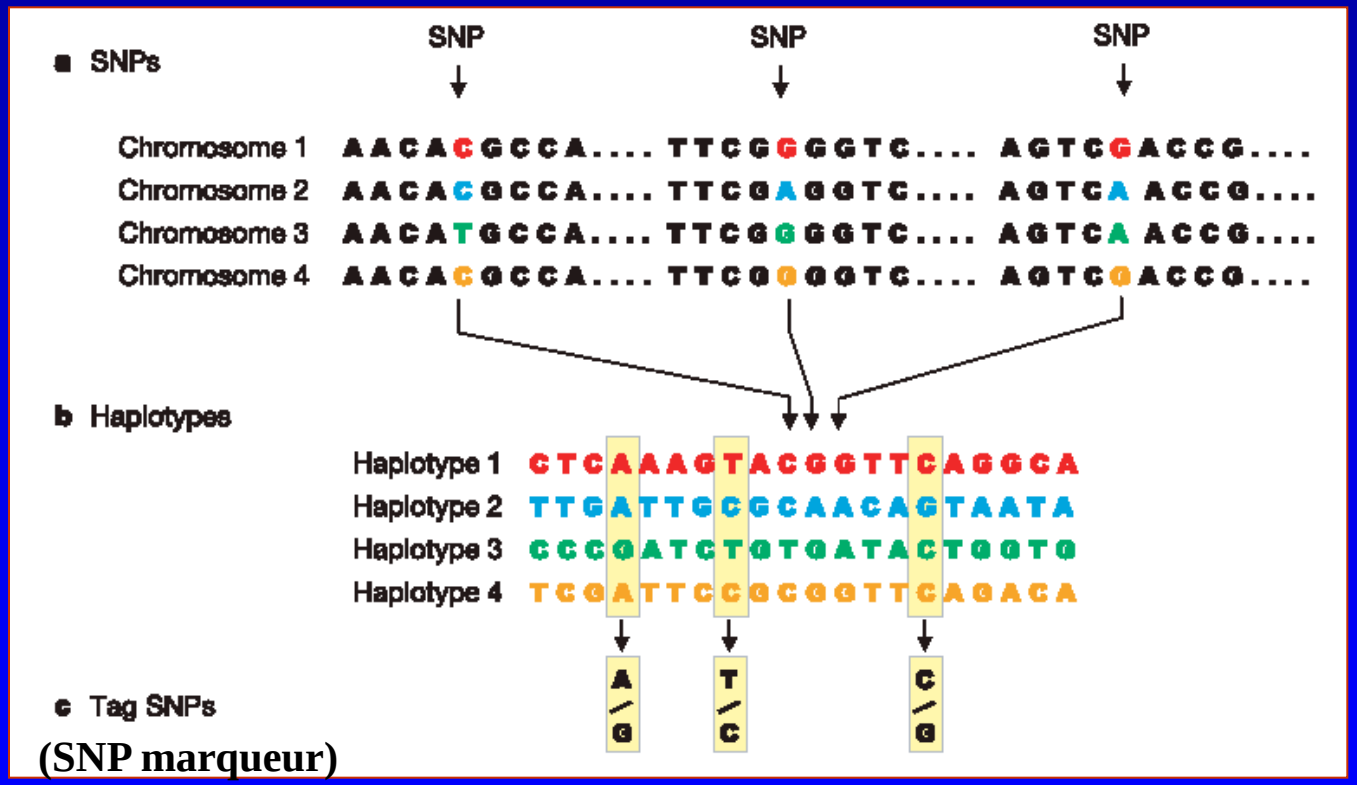
Déséquilibre de liaison



Le DL est proportionnel à la distance entre les marqueurs et est déterminé par le patrimoine génétique

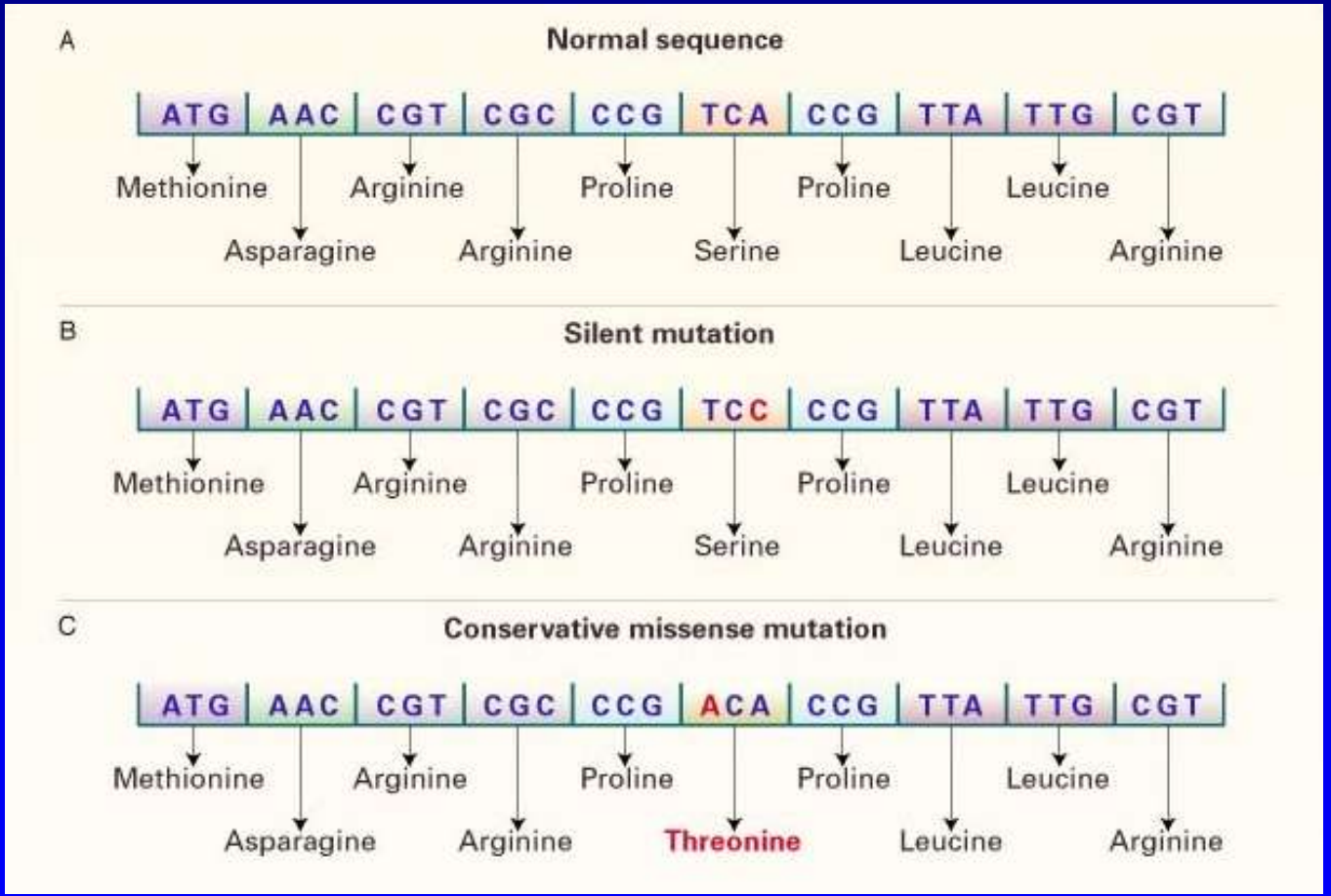
Quelques termes…

- **Haplotypes:**



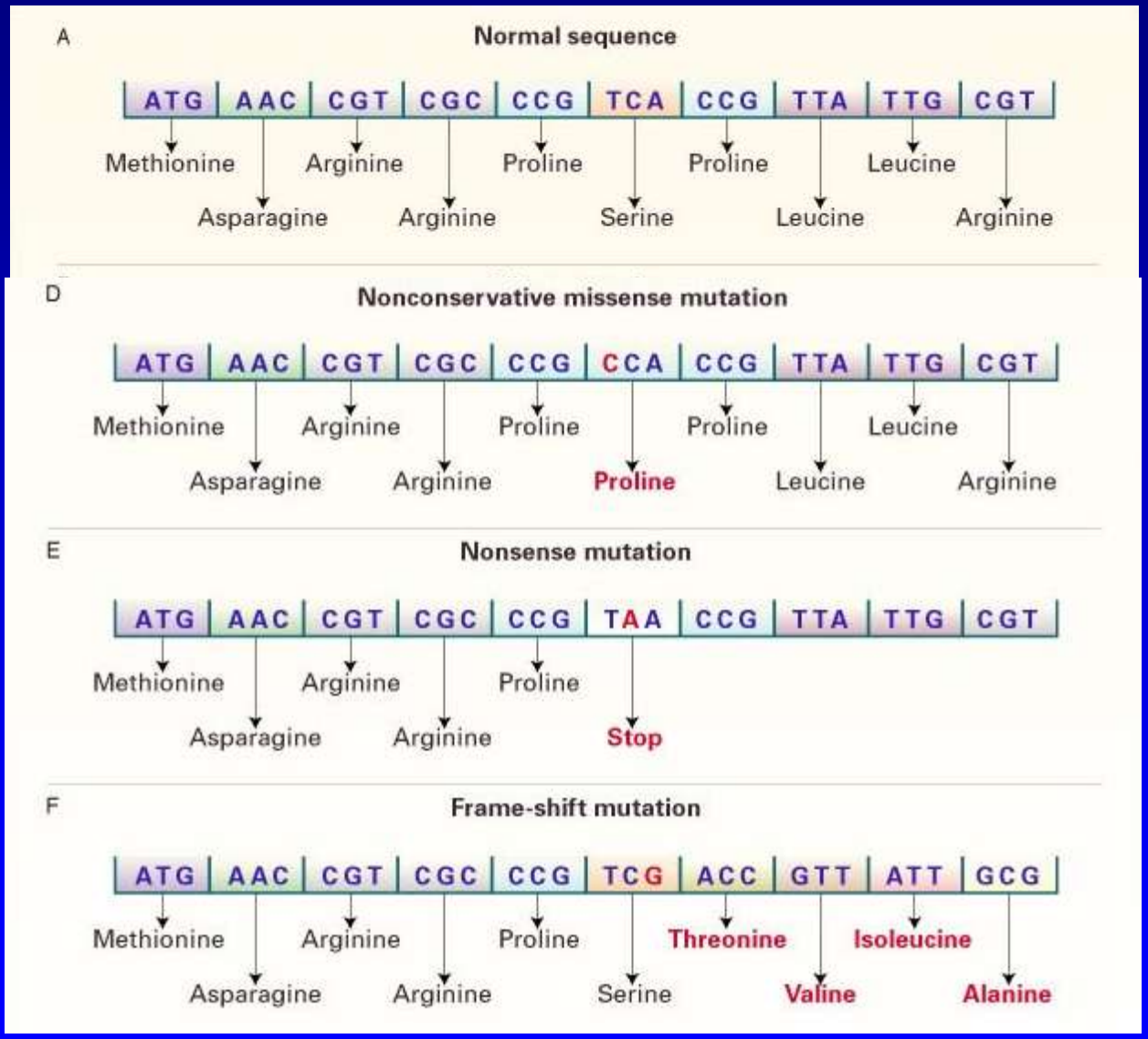
(SNP marqueur)

Types de variations génétiques



Guttmacher AE, et al. N Engl J Med. 2002;347:1512-20.

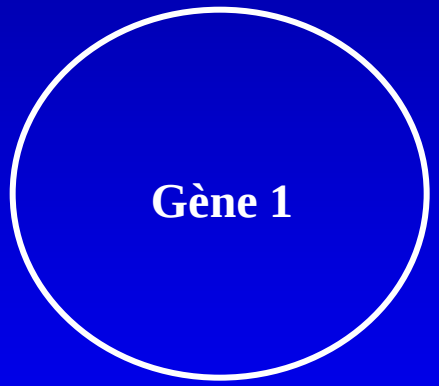
Types de variations génétiques



Guttmacher AE, et al. N Engl J Med. 2002;347:1512-20.

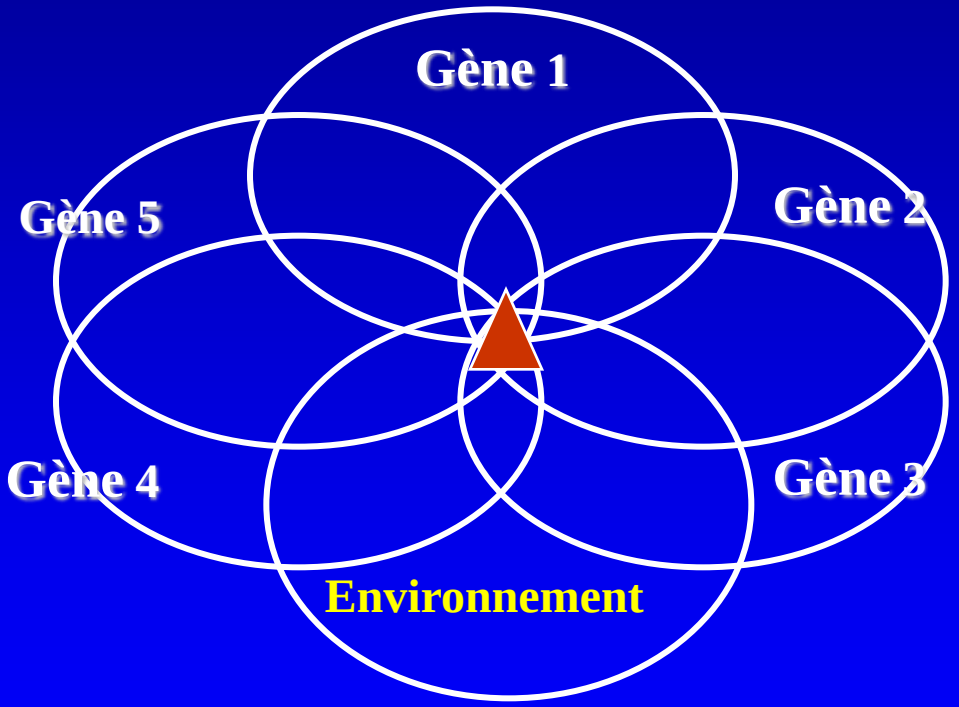
Maladies mendéliennes vs maladies complexes

Maladies mendéliennes
(ex: Fibrose kystique)



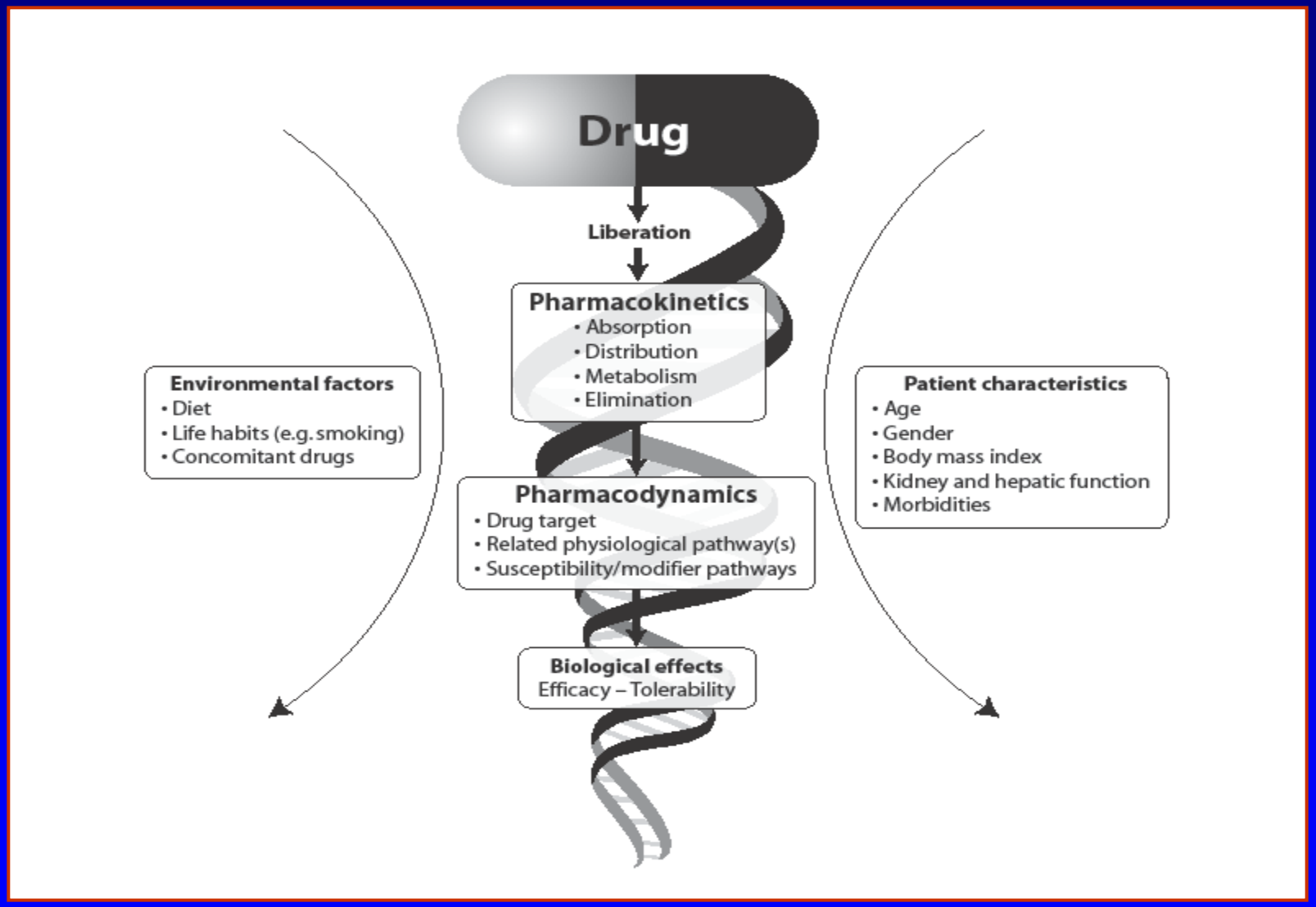
L'expression de la maladie est sous le contrôle d'un gène à forte pénétrance

Maladies complexes
(ex: hypertension)



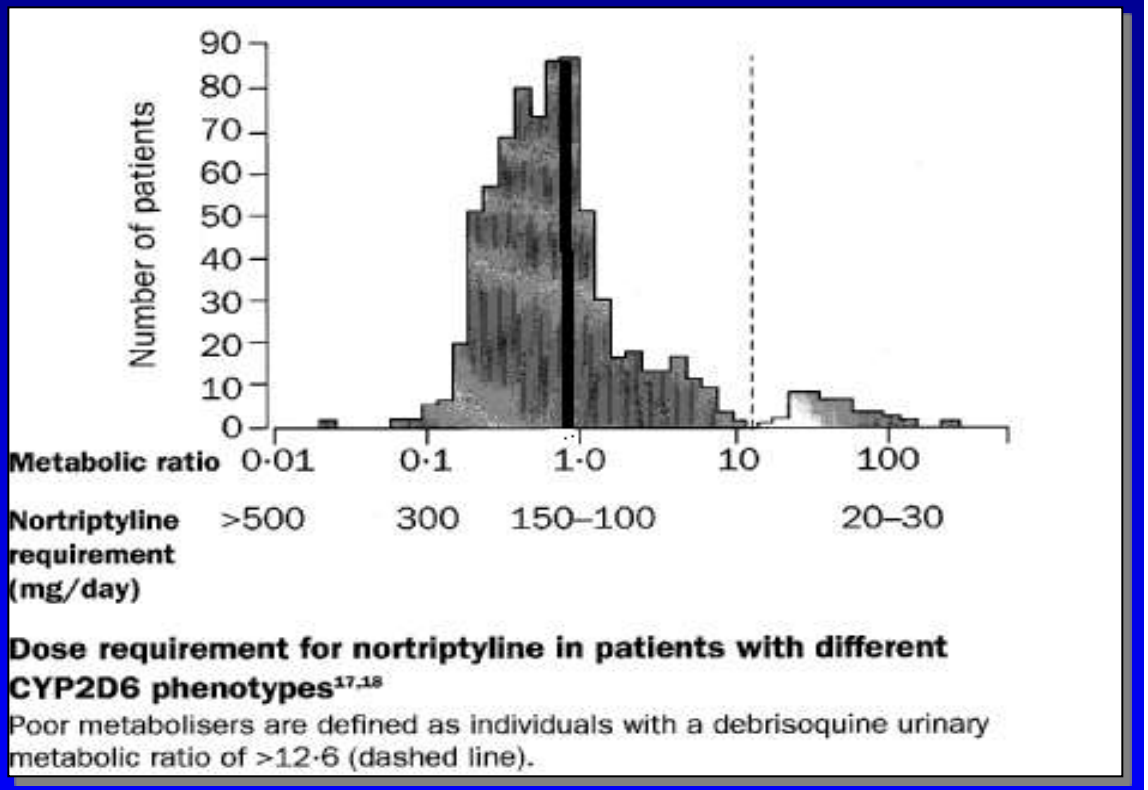
Plusieurs facteurs génétiques et environnementaux conférant un faible risque sont impliqués.

La pharmacogénomique: de la génétique complexe…très complexe



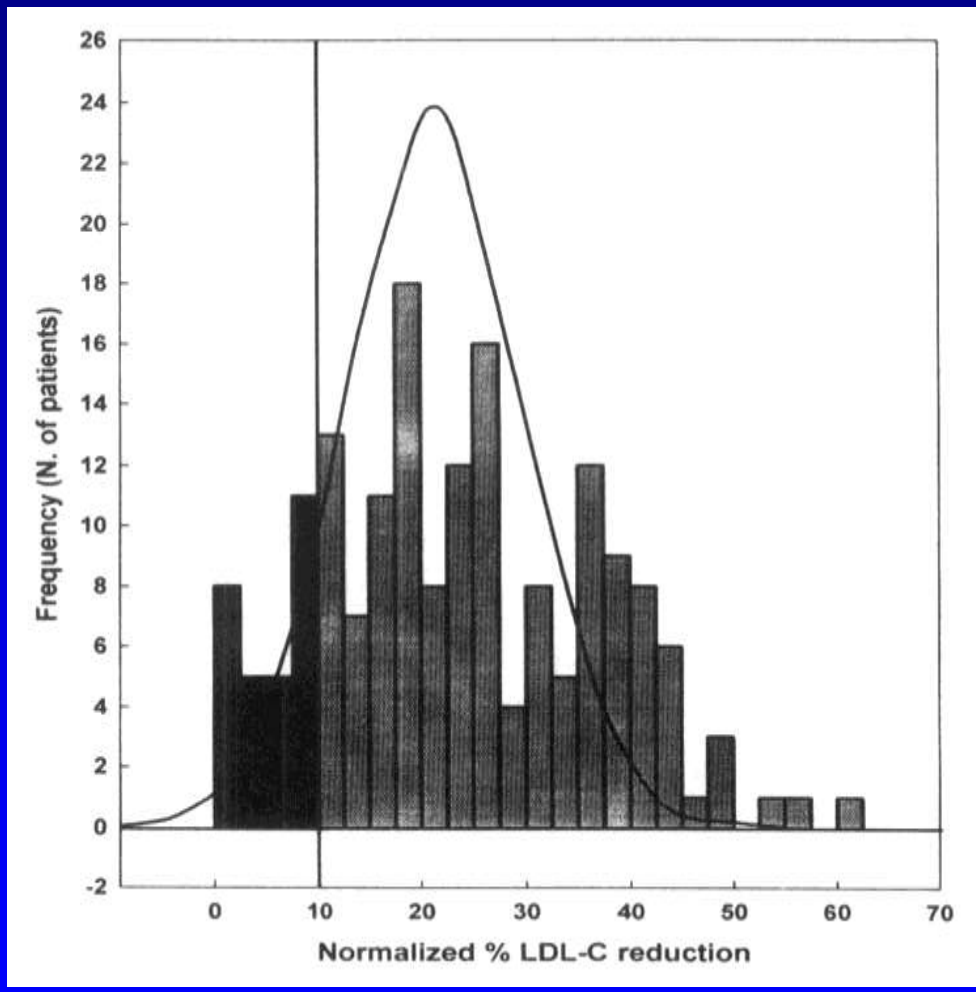
de Denus S, Phillips MS, Tardif JC. Pharmacogenomics. Dans: Clinical approach to sudden cardiac death syndromes.2010:273-287.

Phénotypes avec distribution bimodale vs normale



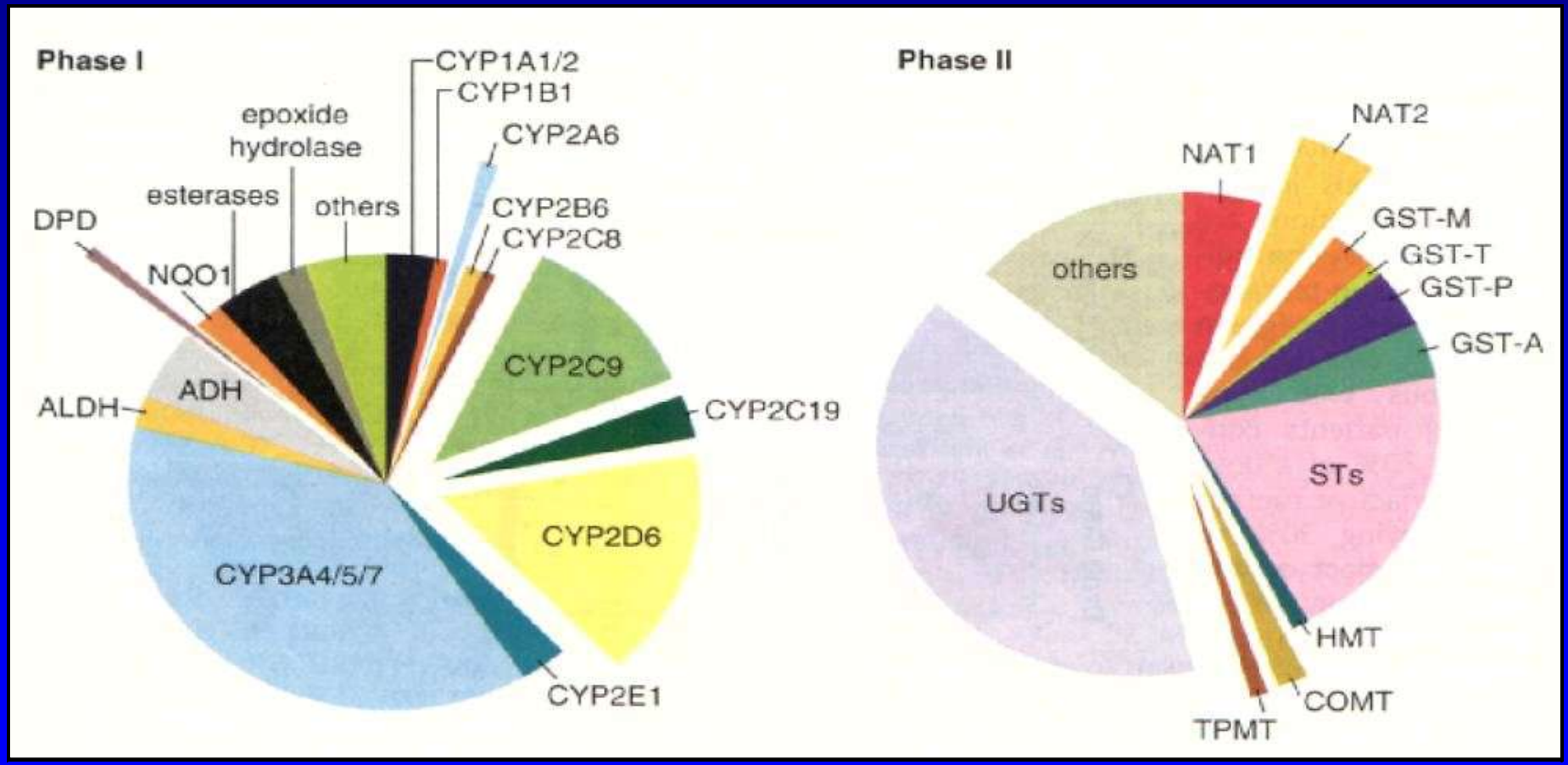
Dose requirement for nortriptyline in patients with different CYP2D6 phenotypes[17,18]

Poor metabolisers are defined as individuals with a debrisoquine urinary metabolic ratio of >12·6 (dashed line).



Pazzucconi F, et al. Atherosclerosis. 1995;117:189-98.

Drug Metabolism Enzymes



From: Evans and Relling, Science 286:487-491, 1999

Quelques exemples

Succinylcholine

- Bloqueur neuromusculaire
- Durée de la curarisation: 4 à 6 minutes
- Métabolisés rapidement par la butyrylcholinestérase (gène codant: BCHE)
  - Chez 25% des patients, réduction de l'activité de la BCHE → effet prolongé (ad 300 minutes).
  - Plus de 70 variations génétiques identifiées.

Pharmacogenetics and genomics 2007;17:995-9
Pharmacogenomics 2005;6: 849-56.

Hyperthermie maligne

- Trouble de l'homéostasie calcique dans la cellule musculaire caractérisé par une acidose respiratoire et métabolique, de la rigidité musculaire, de l'hyperthermie et potentiellement de la rhabdomyolyse.
- Rx impliqués: halothane, sévoflurane, desflurane, enflurane, isoflurane, (succinylcholine).
- Rare~ 1/15000 à 1/50 000
- Transmission autosomale dominante.
- Gène le plus souvent impliqué: RYR1 (canal calcique)
  - Près de 200 variations génétiques identifiées

Stowell KM, et al. Pharmacogenomcis 2008; 9:1657-72

Opiacés

Pharmacogenetic Variation in Drug Metabolism

Polymorphic cytochrome P450 2D6 (CYP2D6)

- CYP2D6 metabolizes drugs from many therapeutic classes.
- 5-8% of Caucasians are phenotypically 'poor metabolizers' (PMs) homozygous for defective CYP2D6 function.
- Multiple SNPs in the *CYP2D6* gene produce allelic variants that impair enzyme activity, > 100 alleles to date.

Examples of Pharmacogenetic Variation in Drug Metabolism

Polymorphic cytochrome P450 2D6 (CYP2D6)
- poor activity of protein

Example #1

- **PMs cannot activate codeine to its analgesic metabolite morphine – lack of efficacy in pain relief.**

Il n'y a pas que les métabolisateurs lents!

	Substrates	Variant alleles	Alteration in function	Allele frequencies (%)				
				White	Black	Asian	Chinese	Japanese
CYP2C8 (refs. 21,22)	Repaglinide Paclitaxel	*2	Reduced	0.4	18	—	—	0
		*3	Reduced	13; 15	2	—	—	0
		*4	Reduced	7.5	—	—	—	0
CYP2C9 (refs. 22–24)	Warfarin Phenytoin Tolbutamide	*2	Reduced	10; 13.3; 8–14.9	3; 1–3.6	Absent or rare	0	0
		*3	More reduced	5.6; 8; 3.3–15.3	1; 0.5–2	—	2.5; 1.7–4.9	3.5[b]; 1.1–6.8
		*5	Reduced	0	3	0[a]	—	—
CYP2C19 (refs. 23,24)	Omeprazole Diazepam	*2	Nonfunctional	13.6; 15	17	—	29.7	34.5[b]
		*3	Nonfunctional	0; <1	<1	—	3.5	9[b]
		*17	Increased	20.1	—	—	0.5	0.5[b]
CYP2D6[c] (ref. 25)	Atomoxetine Codeine	PM	Nonfunctional	7.7	1.9–7.3	0–4.8	<1.0	0
		IM	Decreased	1–2	—	51	—	—
		UM	Increased	4.3	4.9	—	0.9	—

Yasuda, et al. Clin Pharmacol Ther. 2008 ;84:417-23.

Il n'y a pas que les métabolisateurs lents!

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

TO THE EDITOR: Obstructive sleep apnea is not rare in children with hypertrophic tonsils, and the common curative procedure is adenotonsillectomy.[1] Codeine is commonly prescribed for pain after adenotonsillectomy.[2] The respiratory depres-

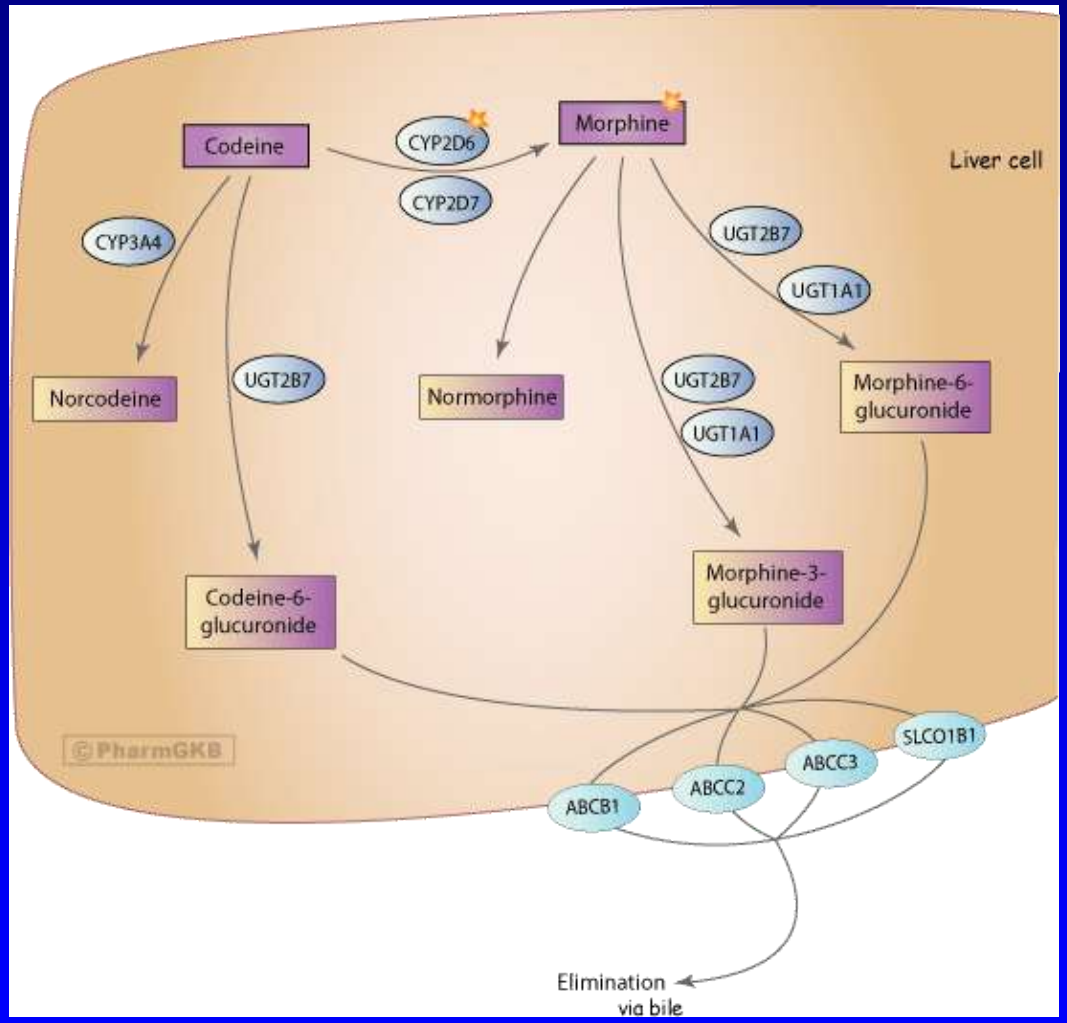
detected in the femoral blood by means of gas chromatography–mass spectrometry; there was no evidence of other drugs or metabolites. Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the *CYP2D6* allele, result-

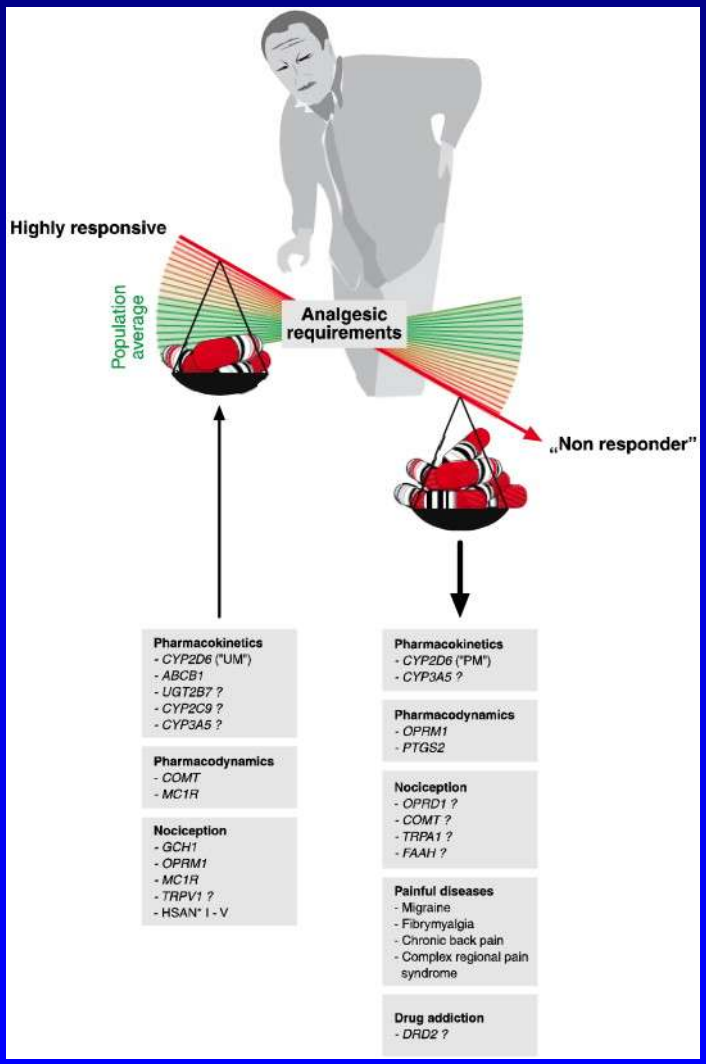
Tramadol

- **Exerce en partie son effet analgésique via l'effet de son métabolite actif M1 (*O*-demethyl tramadol) au niveau du récepteur *μ*.**
  - **Nécessite conversion par CYP2D6**
  - **Données actuelles suggèrent que les métabolisateurs lents nécessitent des doses supérieures de tramadol pour obtenir une analgésie similaire.**

Searle R, et al. Br J Anaesth 2009;103:1425.

Pgx de la codéine



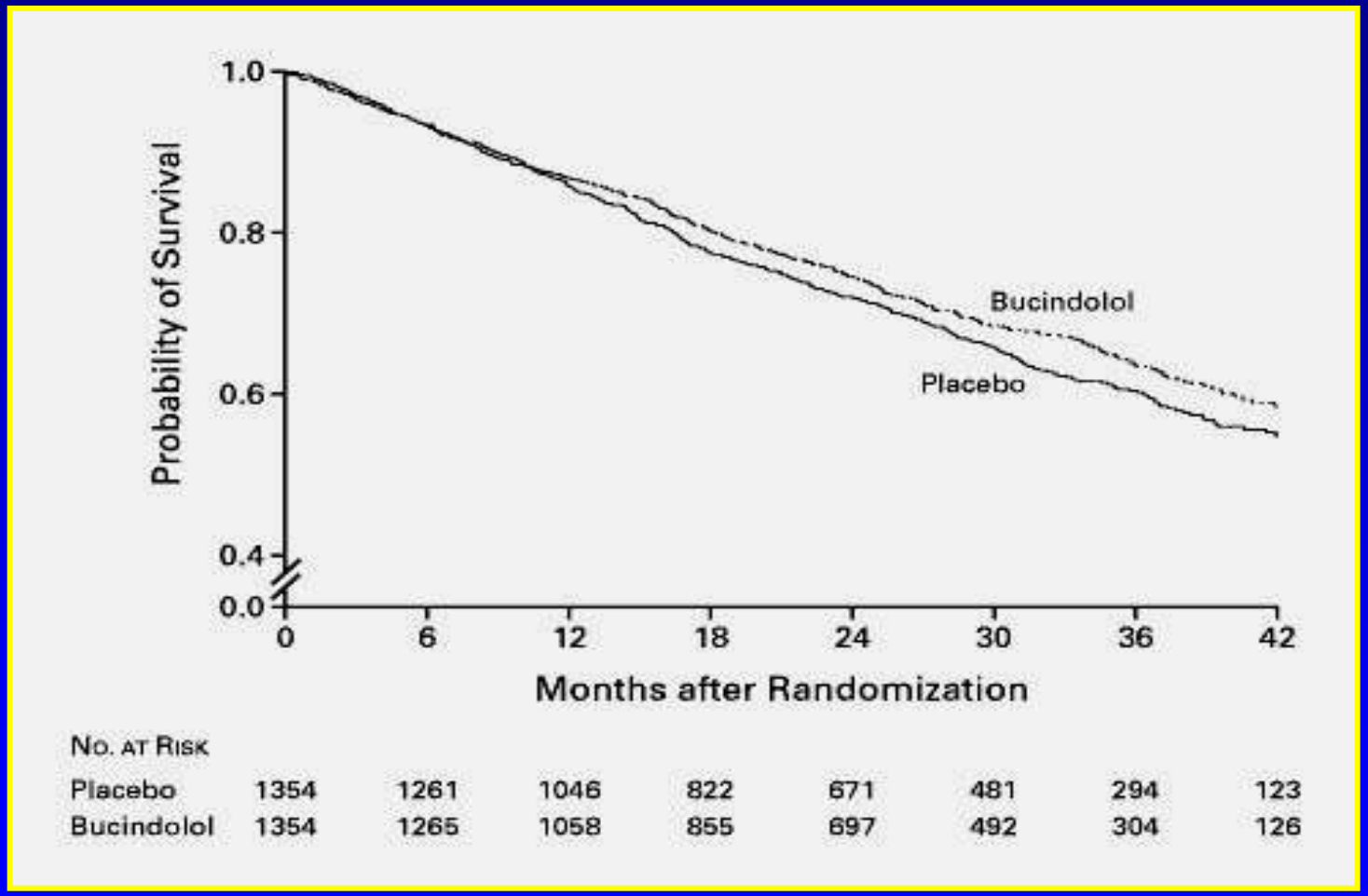


www.pharmgkb.org

Curr Opin Anaesthesiol. 2009;22:476-82.

Autres exemples en cardiologie

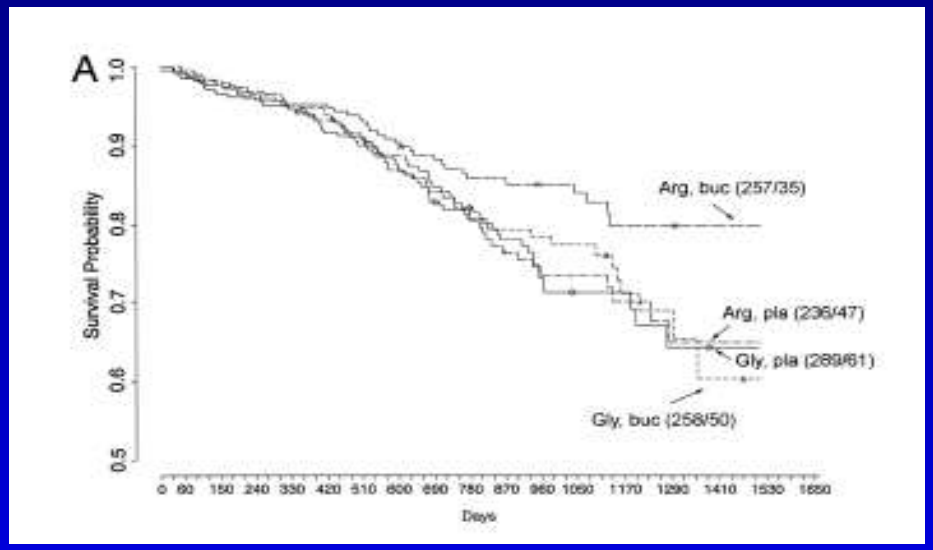
Bucindolol in Survival Trial (BEST)

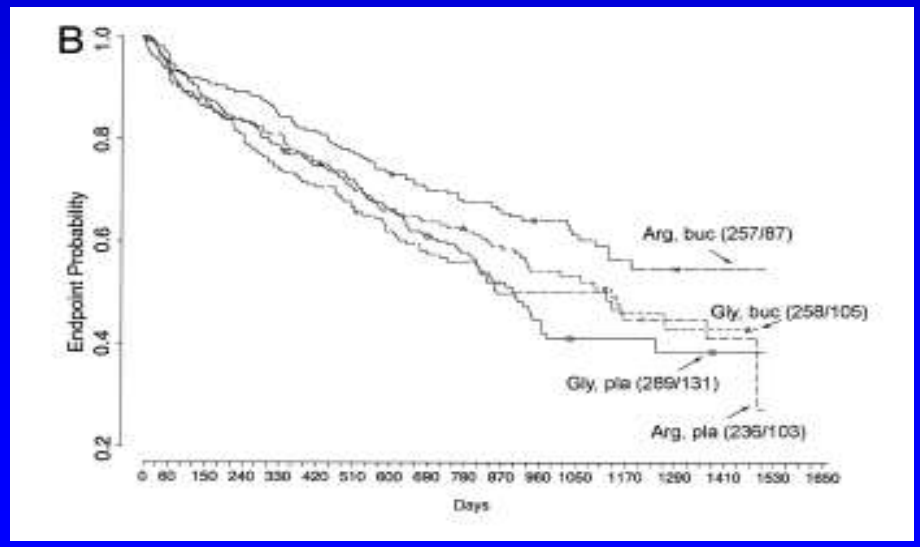


No. at Risk								
Placebo	1354	1261	1046	822	671	481	294	123
Bucindolol	1354	1265	1058	855	697	492	304	126

NEJM 2001

ADRB1 Arg389Gly and outcomes in BEST





Death*

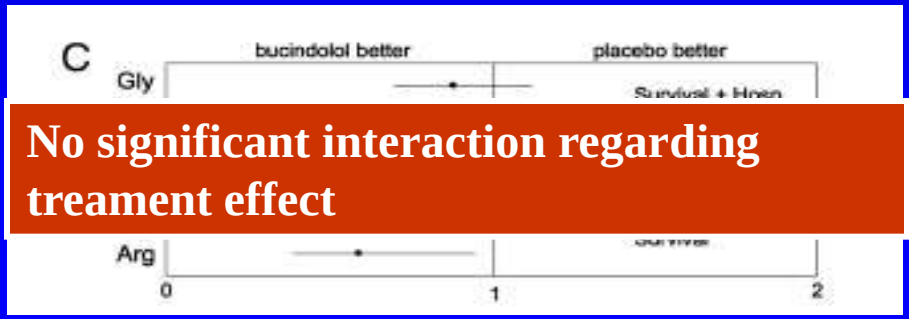
Arg homozygotes: HR 0.62, 95% C.I. 0.40–0.96, *P* 0.03.

Gly-389 carriers: 0.90, 95% C.I. 0.62–1.30, *P* 0.57.

Death or HF hospitalization*

Arg homozygotes: HR 0.66, 95% C.I. 0.50–0.88, *P* 0.004.

Gly-389 carriers: HR : 0.87, 95% C.I. 0.67–1.11, *P* 0.25.

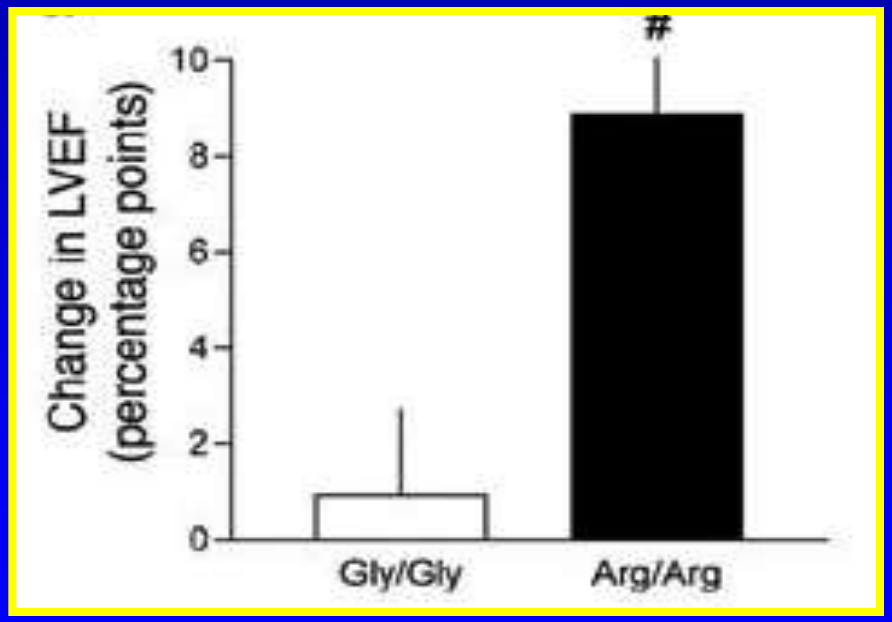


No significant interaction regarding treament effect

Adjusted for sex, race, gender

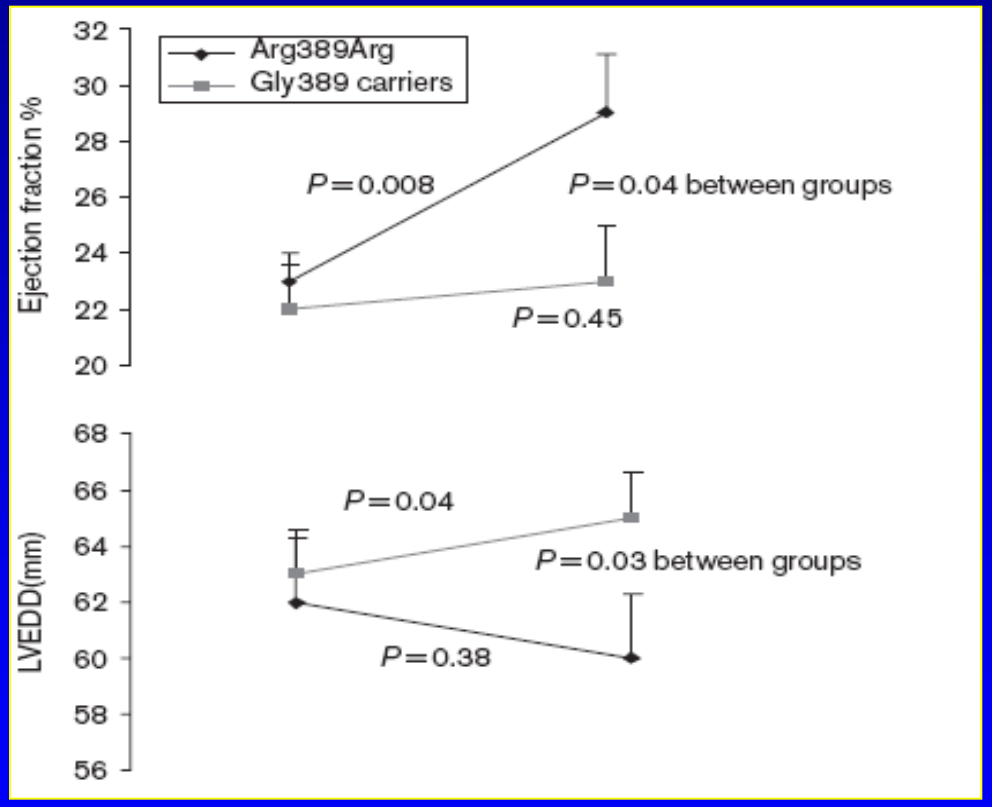
ADRB1 Arg389Gly in other studies

- Improvement in LVEF in 224 patients treated with carvedilol; p < 0.02



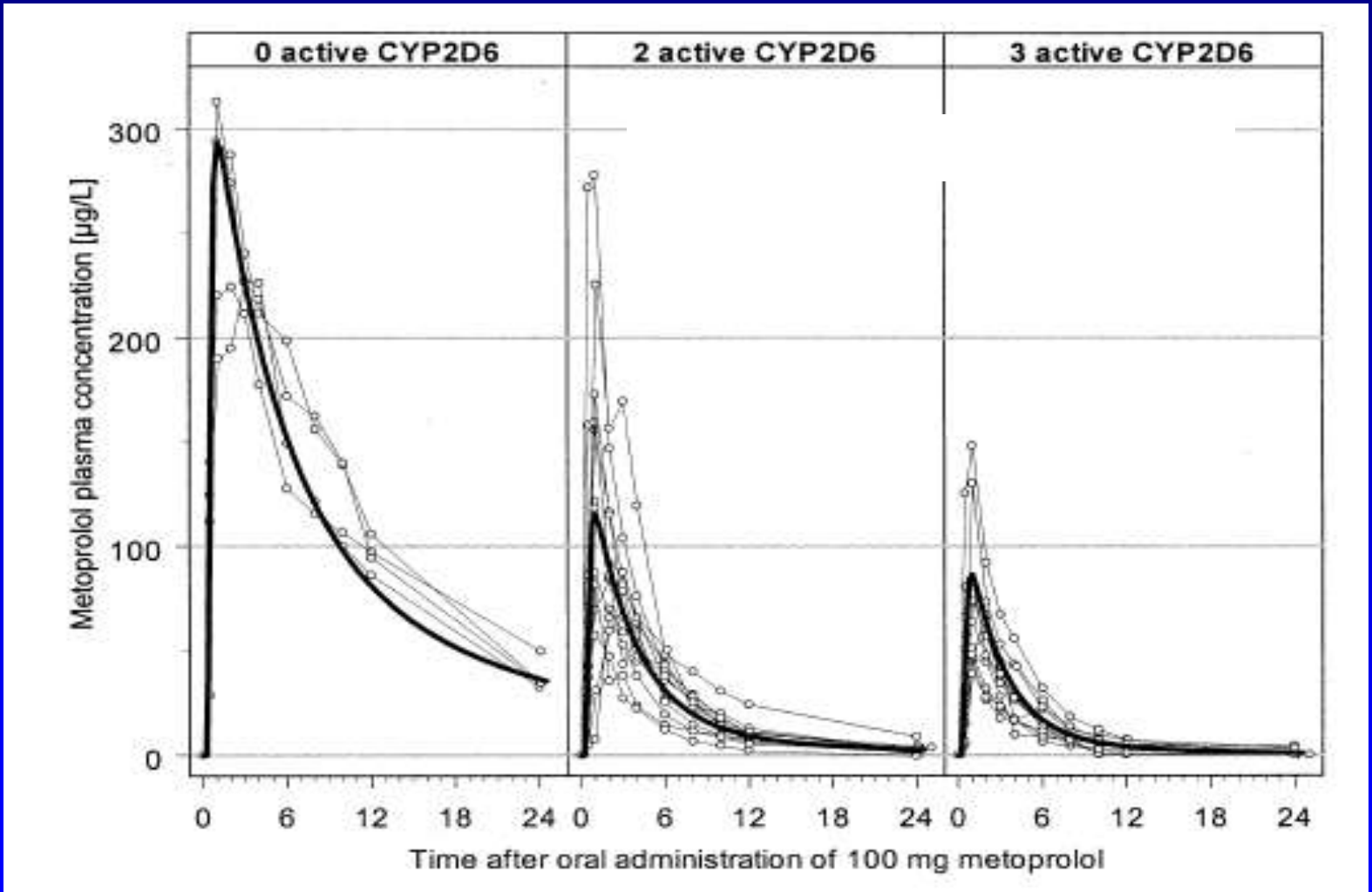
Perez et al. Nat Med 2003;9:1300

- A prospective study using metoprolol succinate (N = 61).



Pharmacogenet Genomics. 2005 Apr;15(4):227-34.

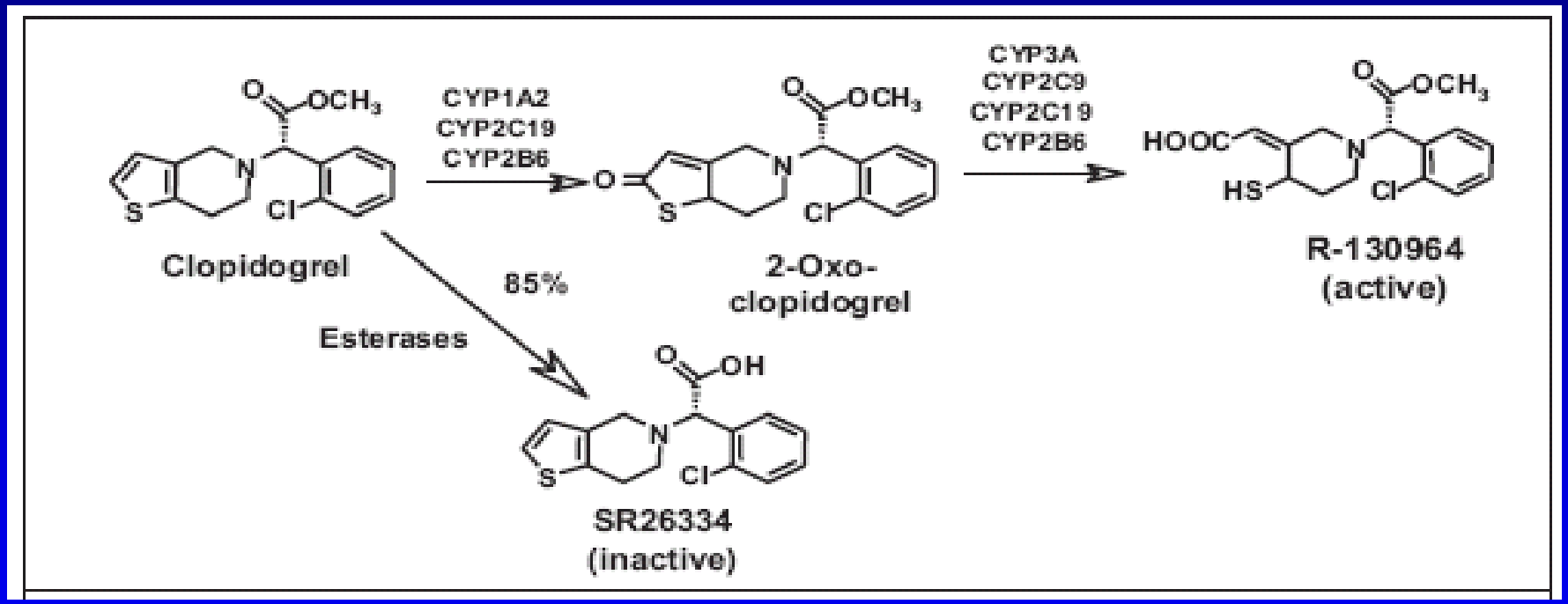
CYP2D6 and HF



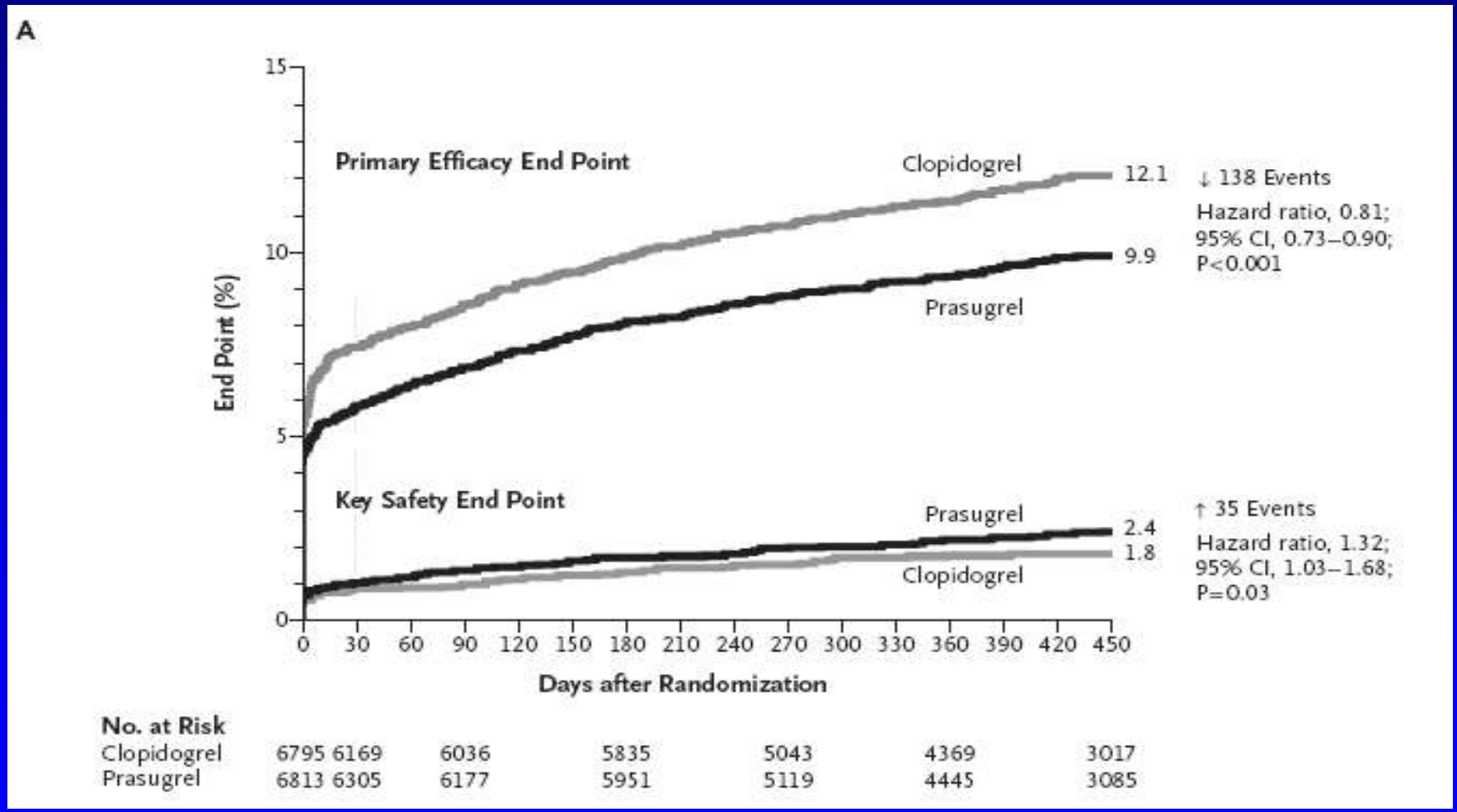
Kirchheiner J, et al. Clin Pharmacol Ther 2004;76:302-12.

Clopidogrel

Background


CYP1A2
CYP2C19
CYP2B6
CYP3A
CYP2C9
CYP2C19
CYP2B6
Clopidogrel
2-Oxo-
clopidogrel
R-130964
(active)
85%
Esterases
SR26334
(inactive)

TRITON-TIMI 38



N Engl J Med. 2007 Nov 15;357:2001-15.

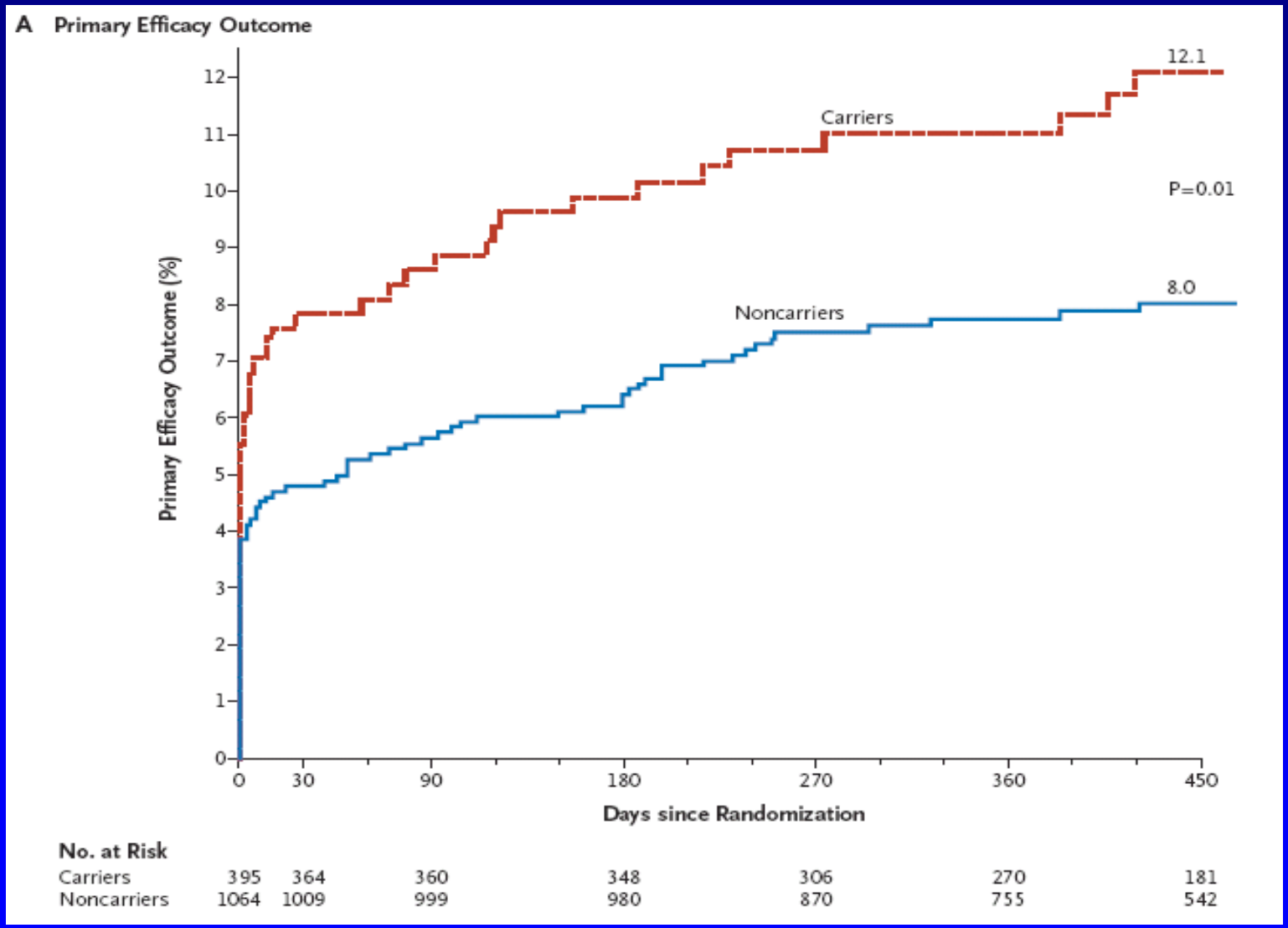
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

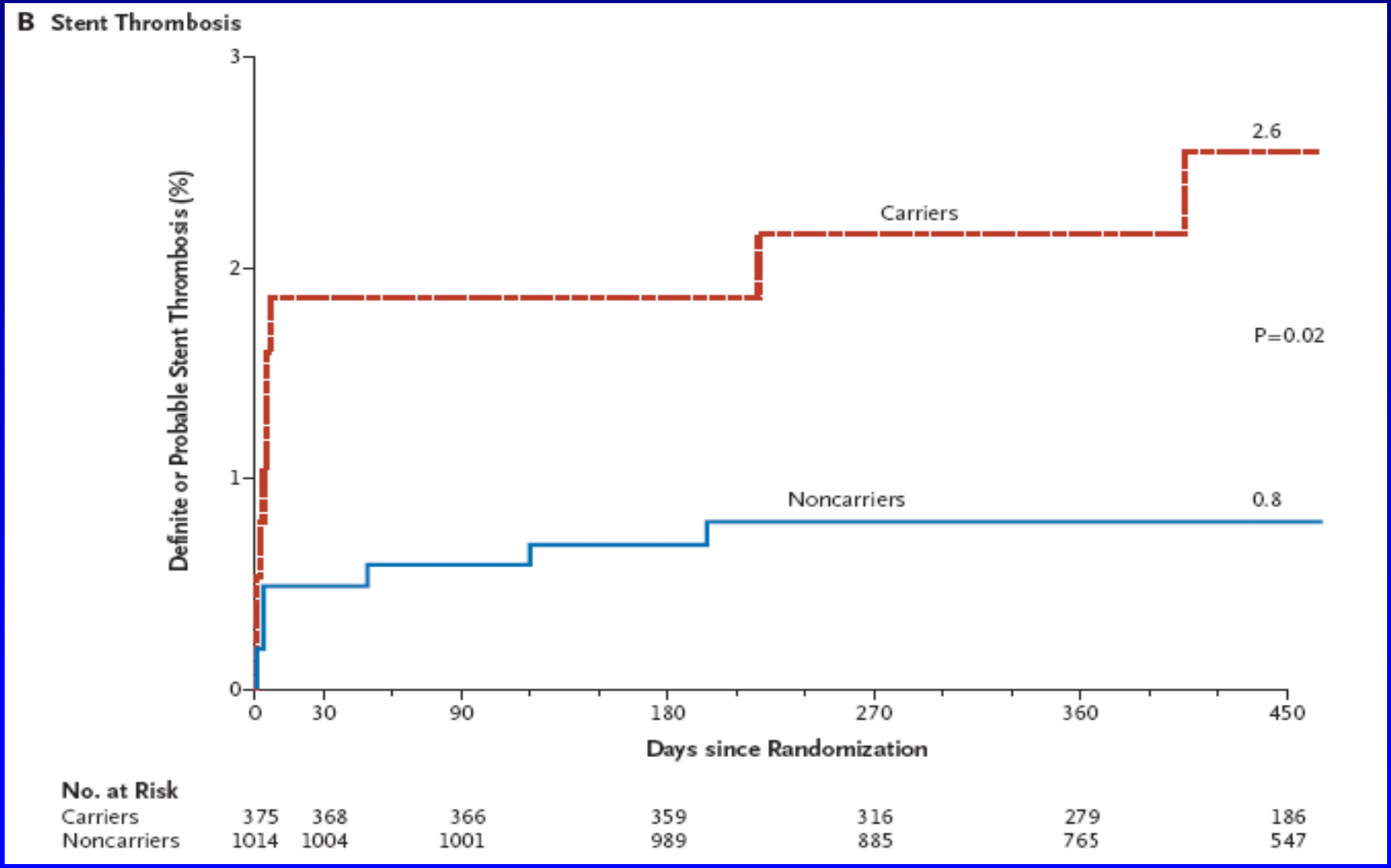
Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Jessica L. Mega, M.D., M.P.H., Sandra L. Close, Ph.D., Stephen D. Wiviott, M.D., Lei Shen, Ph.D., Richard D. Hockett, M.D., John T. Brandt, M.D., Joseph R. Walker, Pharm.D., Elliott M. Antman, M.D., William Macias, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H.

Results


A Primary Efficacy Outcome
Primary Efficacy Outcome (%)
12.1
Carriers
P=0.01
8.0
Noncarriers
0
1
2
3
4
5
6
7
8
9
10
11
12
0
30
90
180
270
360
450
Days since Randomization
No. at Risk
Carriers 395 364 360 348 306 270 181
Noncarriers 1064 1009 999 980 870 755 542

Results


B Stent Thrombosis
Definite or Probable Stent Thrombosis (%)
3
2
1
0
2.6
Carriers
P=0.02
Noncarriers
0.8
0
30
90
180
270
360
450
Days since Randomization
No. at Risk
Carriers 375 368 366 359 316 279 186
Noncarriers 1014 1004 1001 989 885 765 547

Replication???

Replication!!!

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 51, No. 20, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.12.056

CLINICAL RESEARCH — Interventional Cardiology

Cytochrome
Polymorphis
Platelet
Clinical
Interven

Dietmar Trenk
Andreas Pahl,
Hans-Peter Be
Bad Krozinger

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

Tabassome Simon, M.D., Ph.D., Céline Verstuyft, Pharm.D., Ph.D., Murielle Mary-Krause, Ph.D., Lina Quteineh, M.D., Elodie Drouet, M.Sc., Nicolas Méneveau, M.D., P. Gabriel Steg, M.D., Ph.D., Jean Ferrières, M.D., Nicolas Danchin, M.D., Ph.D., and Laurent Becquemont, M.D., Ph.D., for the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators

ABSTRACT

Department of Cardiology, Deutsches Herzzentrum and 1. Medizinische Klinik rechts der Isar, Technische Universität München, Munich, Germany

Received 3 October 2008; revised 16 December 2008; accepted 12 January 2009; online publish-ahead-of-print 4 February 2009

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AL RESEARCH
diology and angiology

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Mehilli,
and

Is this clinically relevant?

European Heart Journal
doi:10.1093/eurheartj/ehp157

CLINICAL RESEARCH

Genetic variation of *CYP2C19* affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease

Christoph Varenhorst[1]*, Stefan James[1], David Erlinge[2], John T. Brandt[3], Oscar Ö. Braun[2], Michael Man[3], Agneta Siegbahn[4], Joseph Walker[5], Lars Wallentin[1], Kenneth J. Winters[3], and Sandra L. Close[3]

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Received 26 September 2008; revised 12 March 2009; accepted 19 March 2009

Is this clinically relevant?

Genetics

Cytochrome P450 Genetic Polymorphisms and the Response to Prasugrel

Relationship to Pharmacokinetic, Pharmacodynamic, and Clinical Outcomes

Jessica L. Mega, MD, MPH; Sandra L. Close, PhD; Stephen D. Wiviott, MD; Lei Shen, PhD; Richard D. Hockett, MD; John T. Brandt, MD; Joseph R. Walker, PharmD; Elliott M. Antman, MD; William L. Macias, MD, PhD; Eugene Braunwald, MD; Marc S. Sabatine, MD, MPH

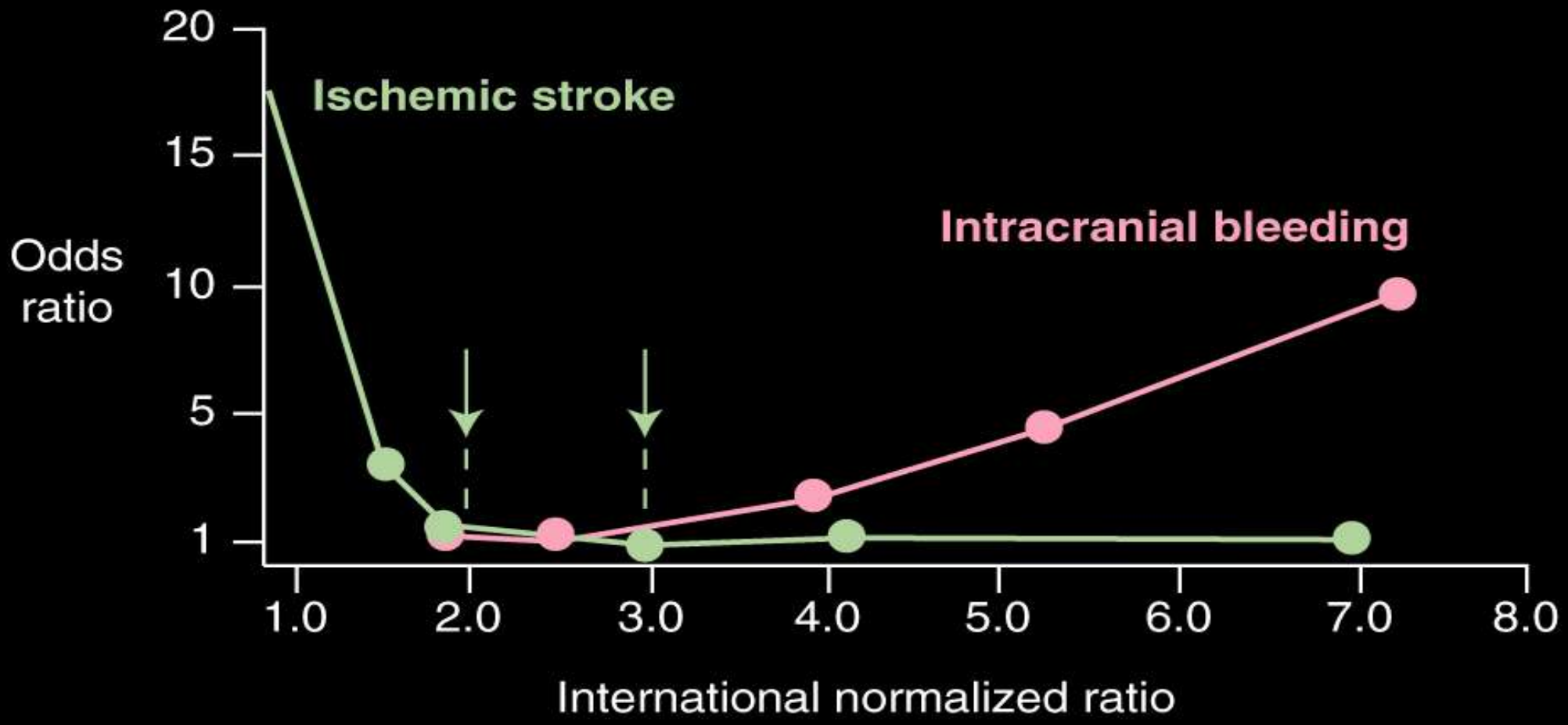
Background—Both clopidogrel and prasugrel require biotransformation to active metabolites by cytochrome P450 (CYP) enzymes. Among persons treated with clopidogrel, carriers of reduced-function *CYP2C19* alleles have significantly lower levels of active metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events. The effect of CYP polymorphisms on the clinical outcomes in patients treated with prasugrel remains unknown.

Methods and Results—The associations between functional variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to prasugrel were tested in 238 healthy subjects. We then examined the association of these genetic variants with cardiovascular outcomes in a cohort of 1466 patients with acute coronary syndromes allocated to treatment with prasugrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 trial. Among the healthy subjects, no significant attenuation of the pharmacokinetic or the pharmacodynamic response to prasugrel was observed in carriers versus noncarriers of at least 1 reduced-function allele for any of the CYP genes tested (*CYP2C19*, *CYP2C9*, *CYP2B6*, *CYP3A5*, and *CYP1A2*). Consistent with these findings, in subjects with acute coronary syndromes treated with prasugrel, no significant associations were found between any of the tested CYP genotypes and risk of cardiovascular death, myocardial infarction, or stroke.

Conclusions—Common functional CYP genetic variants do not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovascular event rates in persons treated with prasugrel. These pharmacogenetic findings are in contrast to observations with clopidogrel, which may explain, in part, the different pharmacological and clinical responses to the 2 medications. (***Circulation***. **2009;119:2553-2560.**)

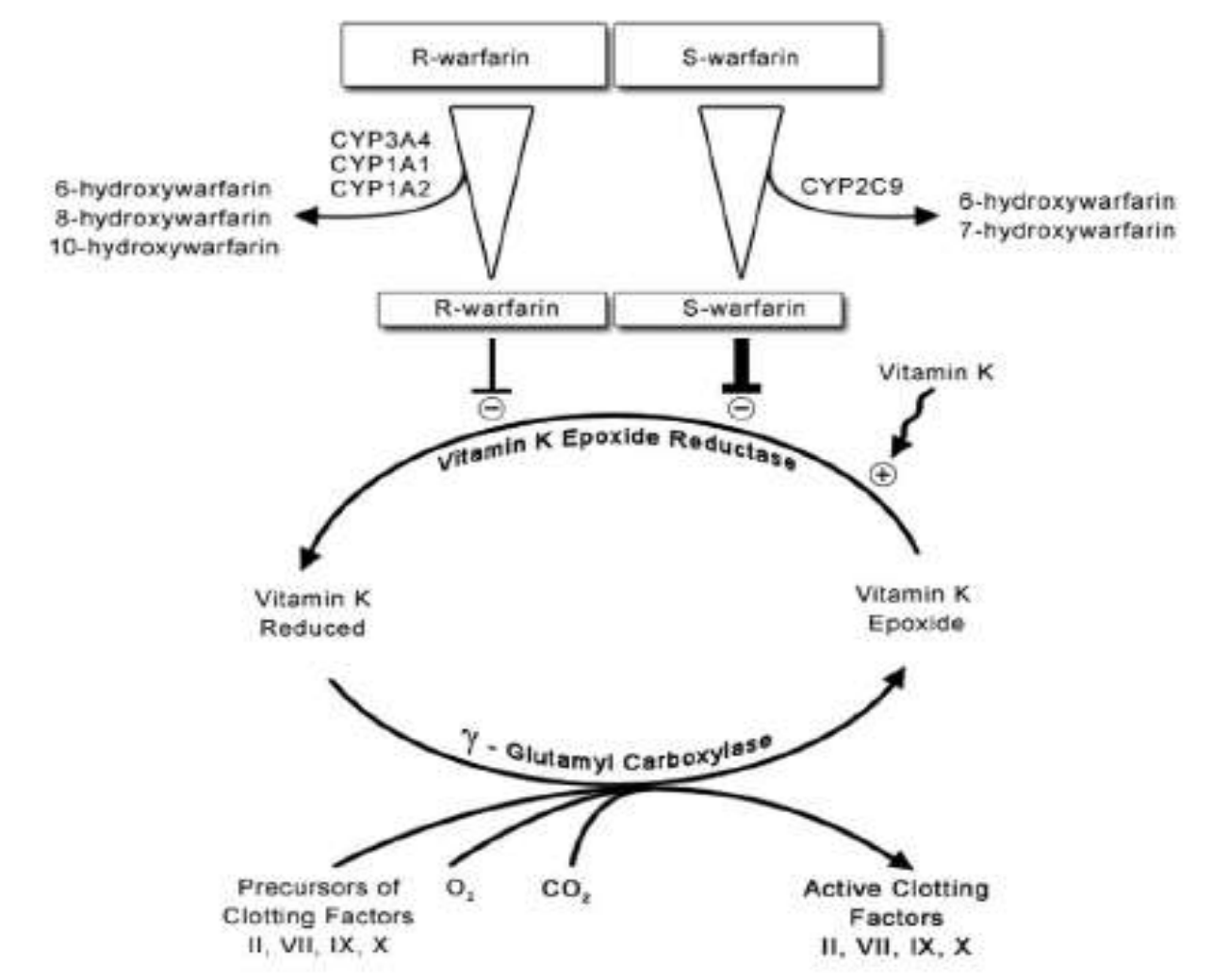
Warfarine

Warfarin: Narrow therapeutic window



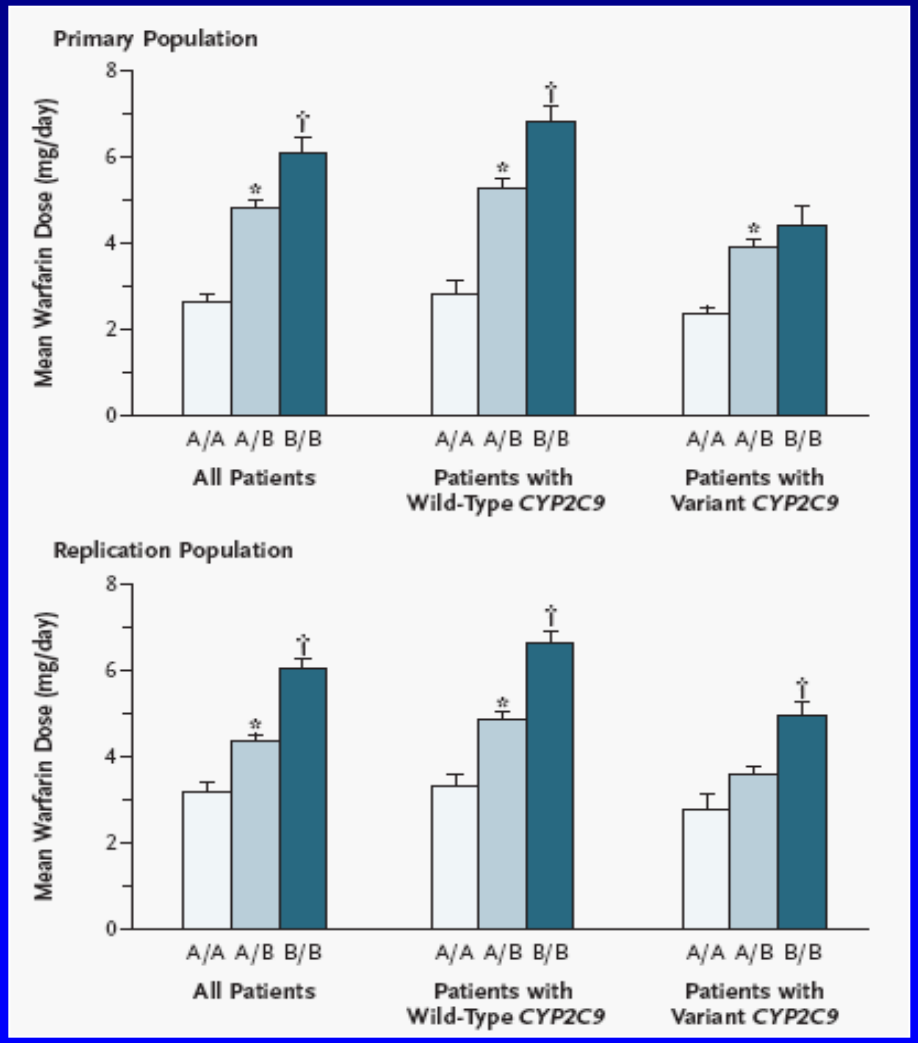
Fuster V, et al. *J Am Coll Cardiol.* 2001;38:1231-1265.

Warfarine et gènes candidats potentiels

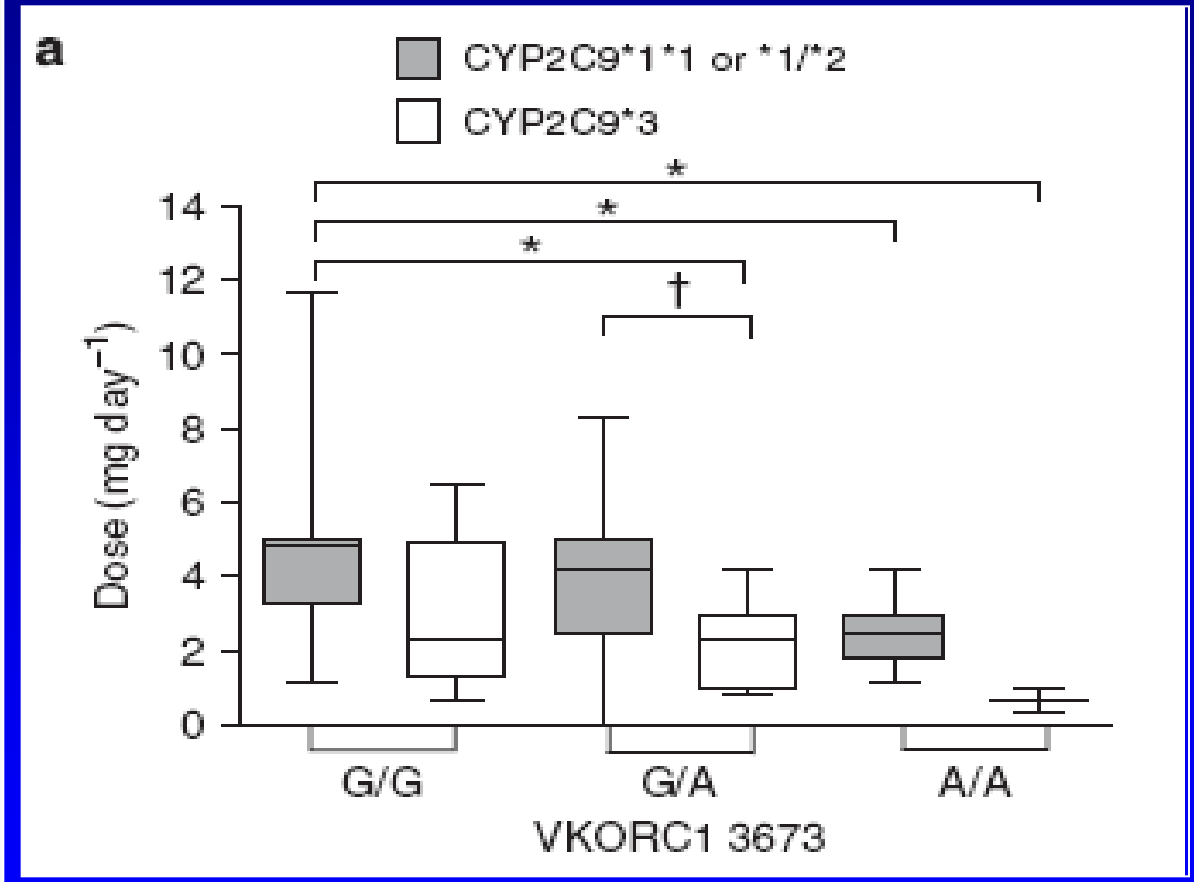


Schwarz and Stein. Clin pharmacol ther 2006;80:7-12

Warfarine et *VKORC1*

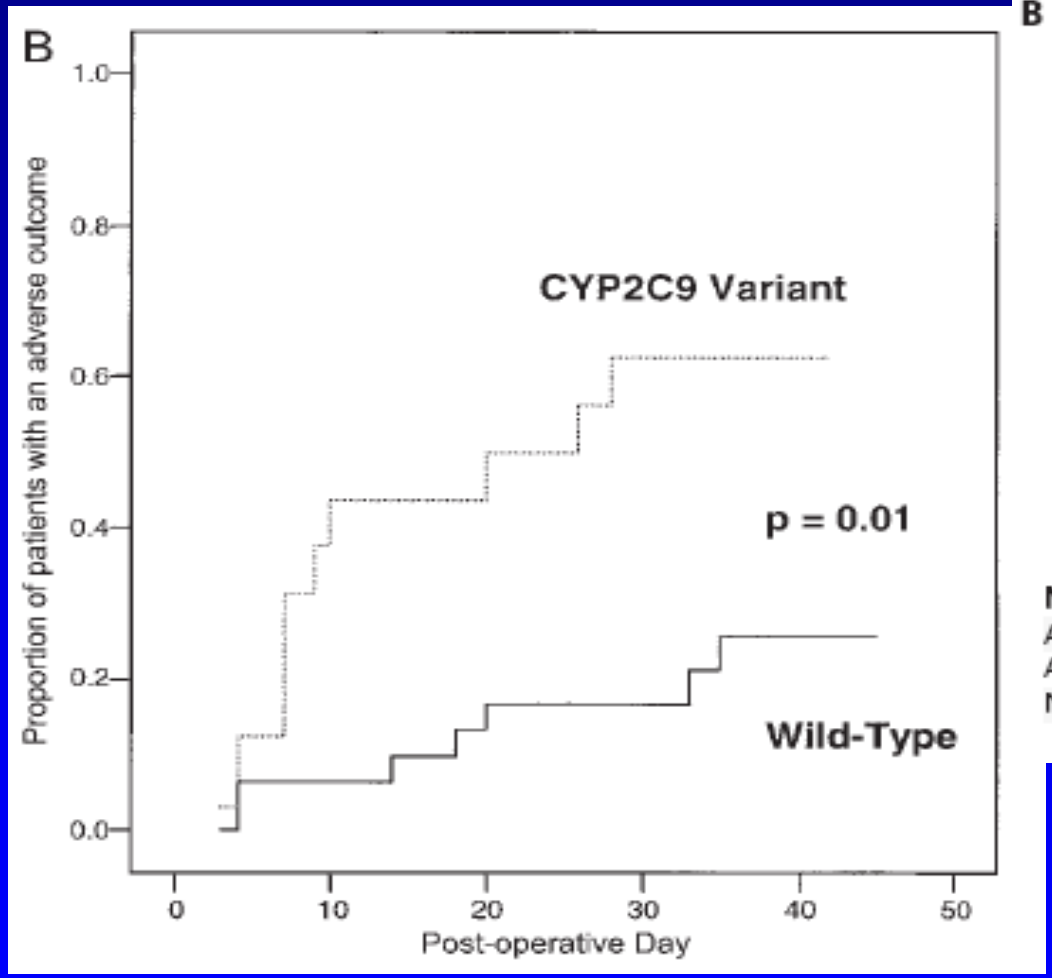


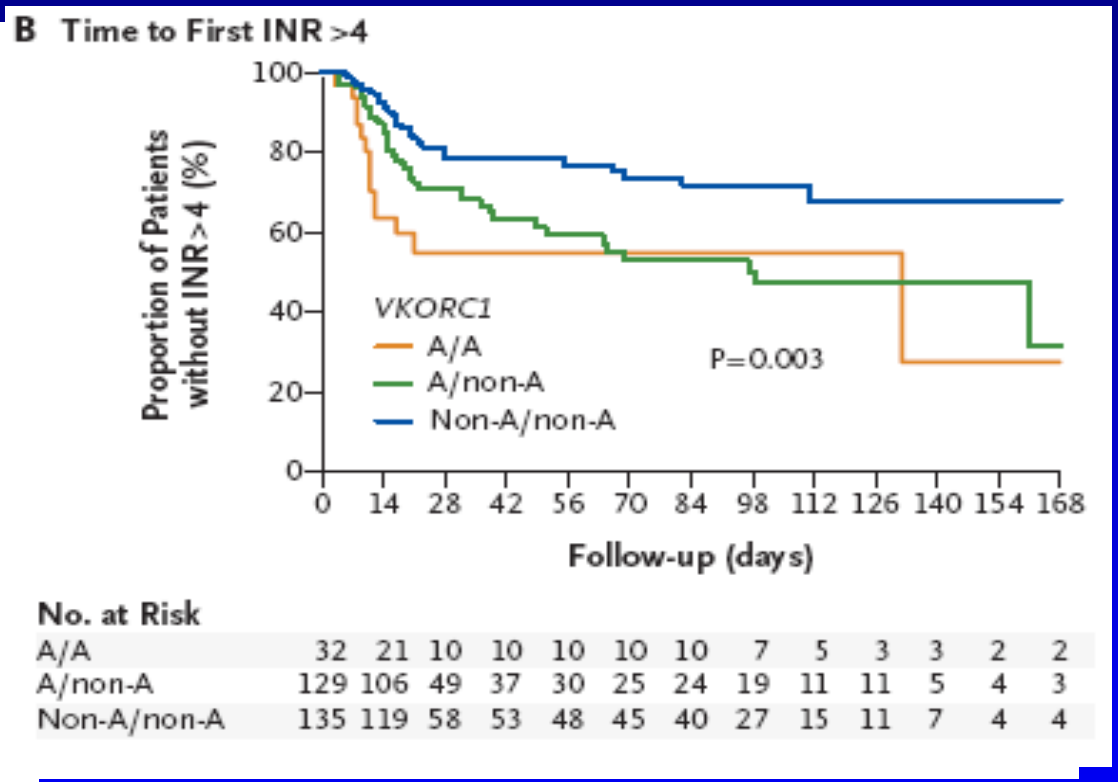
Rieder, MG, et al. N Engl J Med 2005;352:2285-93



Michaud V, et al. Clin Pharmacol Ther. 2008;83:740-8.

Dérivés coumariniques et anticoagulation excessive

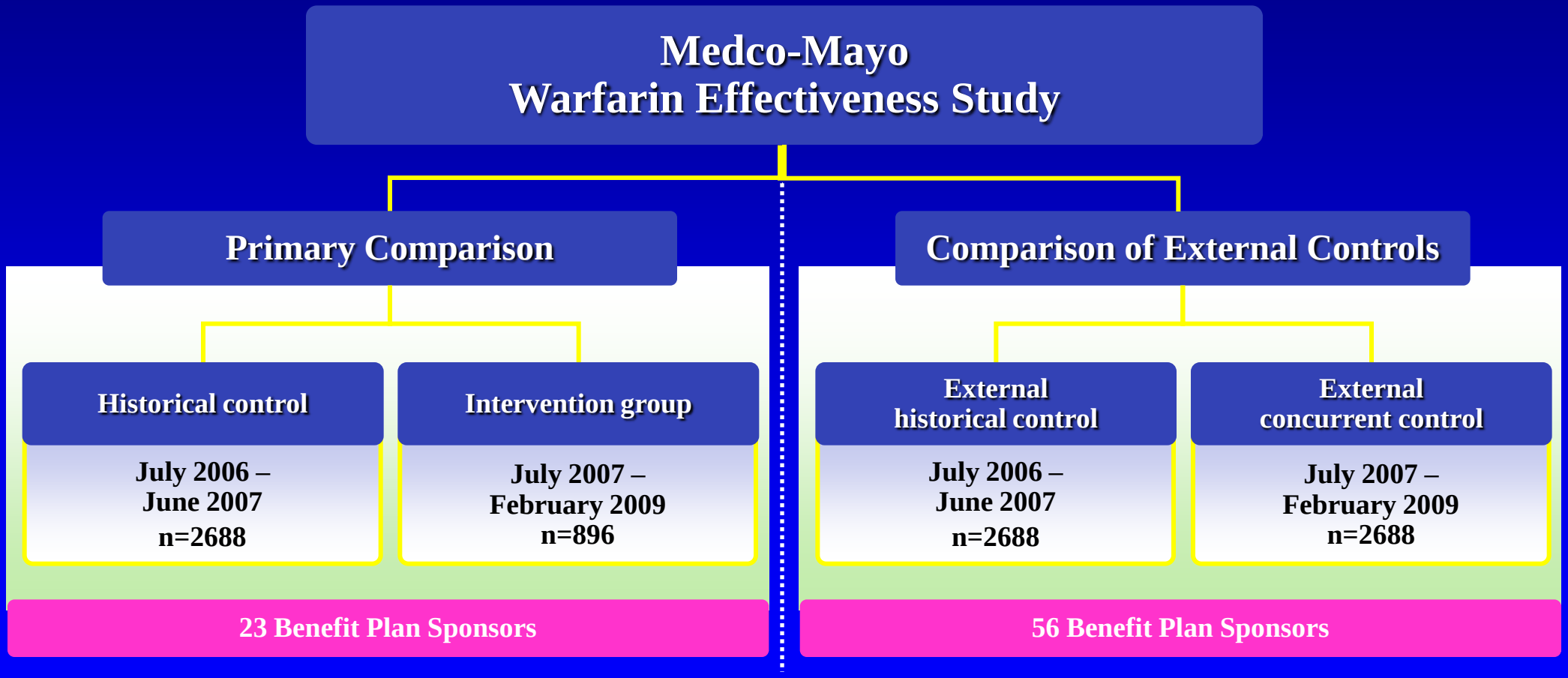




Voora L, et al. Thromb Haemost 2005; 93: 700-5

Schwarz UI, et al. N Engl J Med 2008;358:999-1008.

Study groups*



*6 month follow-up on all patients initiating warfarin in all groups

Sample Mayo Clinic Laboratory Report

Sample Lab Report: Warfarin Genotype Results

Medco Health Solutions
Mayo/Medco Warfarin Protocol
Attn: Accounts Payable
100 Parsons Pond Drive
Franklin Lakes, NJ 07417

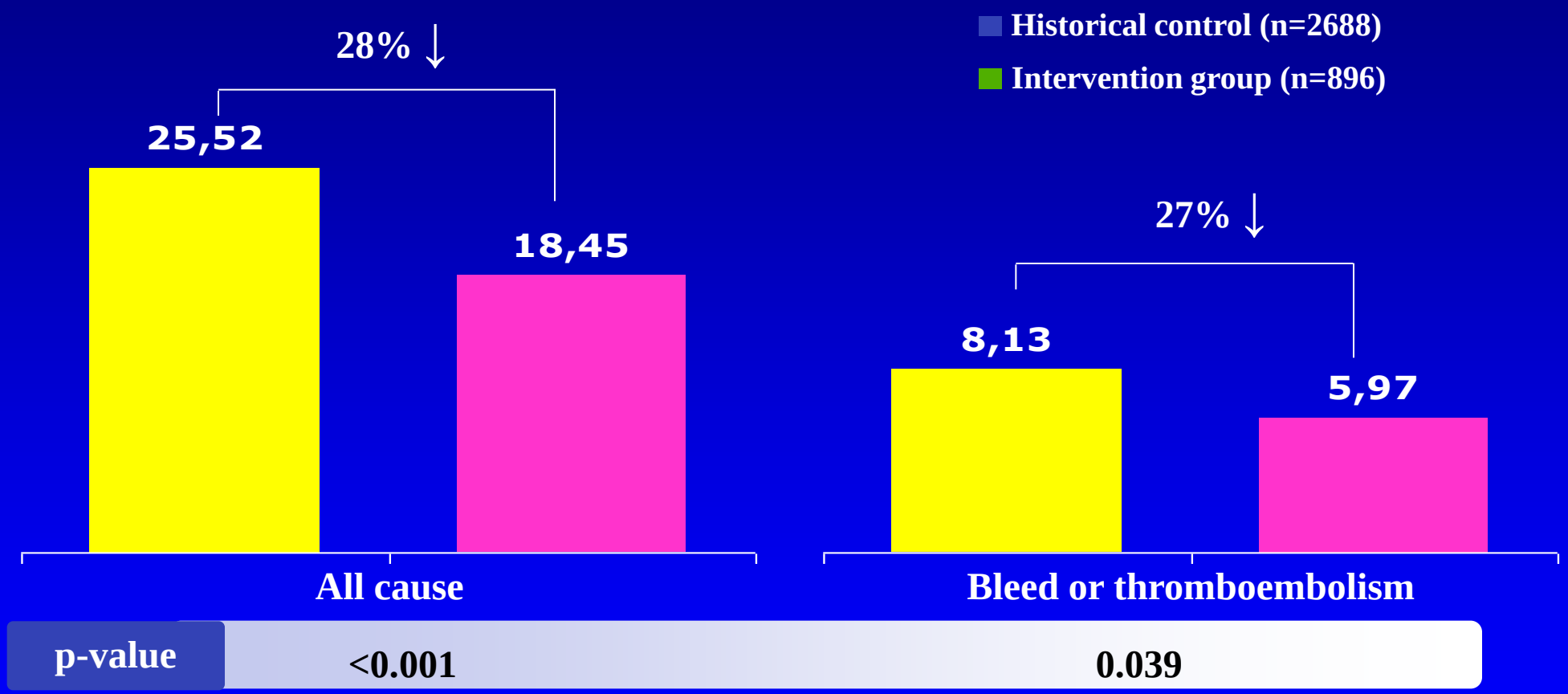
Patient Name: DOE, JANE
Accession #: A1234567
Birth Date: 09/13/1942 Age:65 Gender:F
Medical Rec #: 1234
Client Accn #: 123456789
Ordering Phys: SMITH, JOHN
Collect Date: 11/07/2007 10:40 AM
Received Date: 11/08/2007 7:19 AM

Test Requested	Result	Units	Ref Range	Perform Site *
Rapid DNA Extraction				
Comment	Genomic DNA was extracted.		MCR	
CYP2C9 + VKORC1 Genotype, Warfarin				
CYP2C9 430C>T(*2)	C/T		MCR	
CYP2C9 1075A>C(*3)	A/C		MCR	
CYP2C9 1076T>C(*4)	T/T		MCR	
CYP2C9 1080C>G(*5)	C/C		MCR	
CYP2C9 818delA(*6)	A/A		MCR	
VKORC1 -1639G>A	A/A		MCR	

Interpretation:

This genotype is rare and has very high sensitivity to warfarin. Warfarin dose decrease and frequent INR monitoring should be considered.

Results: Unadjusted 6 mo. hospitalization rates >=1 hospitalization per 100 patients/6months



Intention to treat (ITT)

Le futur

Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Summary

Background The cost of genomic information has fallen steeply, but the clinical translation of genetic risk estimates remains unclear. We aimed to undertake an integrated analysis of a complete human genome in a clinical context.

Methods We assessed a patient with a family history of vascular disease and early sudden death. Clinical assessment included analysis of this patient's full genome sequence, risk prediction for coronary artery disease, screening for causes of sudden cardiac death, and genetic counselling. Genetic analysis included the development of novel methods for the integration of whole genome and clinical risk. Disease and risk analysis focused on prediction of genetic risk of variants associated with mendelian disease, recognised drug responses, and pathogenicity for novel variants. We queried disease-specific mutation databases and pharmacogenomics databases to identify genes and mutations with known associations with disease and drug response. We estimated post-test probabilities of disease by applying likelihood ratios derived from integration of multiple common variants to age-appropriate and sex-appropriate pre-test probabilities. We also accounted for gene-environment interactions and conditionally dependent risks.

Findings Analysis of 2·6 million single nucleotide polymorphisms and 752 copy number variations showed increased genetic risk for myocardial infarction, type 2 diabetes, and some cancers. We discovered rare variants in three genes that are clinically associated with sudden cardiac death—*TMEM43*, *DSP*, and *MYBPC3*. A variant in *LPA* was consistent with a family history of coronary artery disease. The patient had a heterozygous null mutation in *CYP2C19* suggesting probable clopidogrel resistance, several variants associated with a positive response to lipid-lowering therapy, and variants in *CYP4F2* and *VKORC1* that suggest he might have a low initial dosing requirement for warfarin. Many variants of uncertain importance were reported.