# Cardiovascular pharmacogenomics: ready for prime time?

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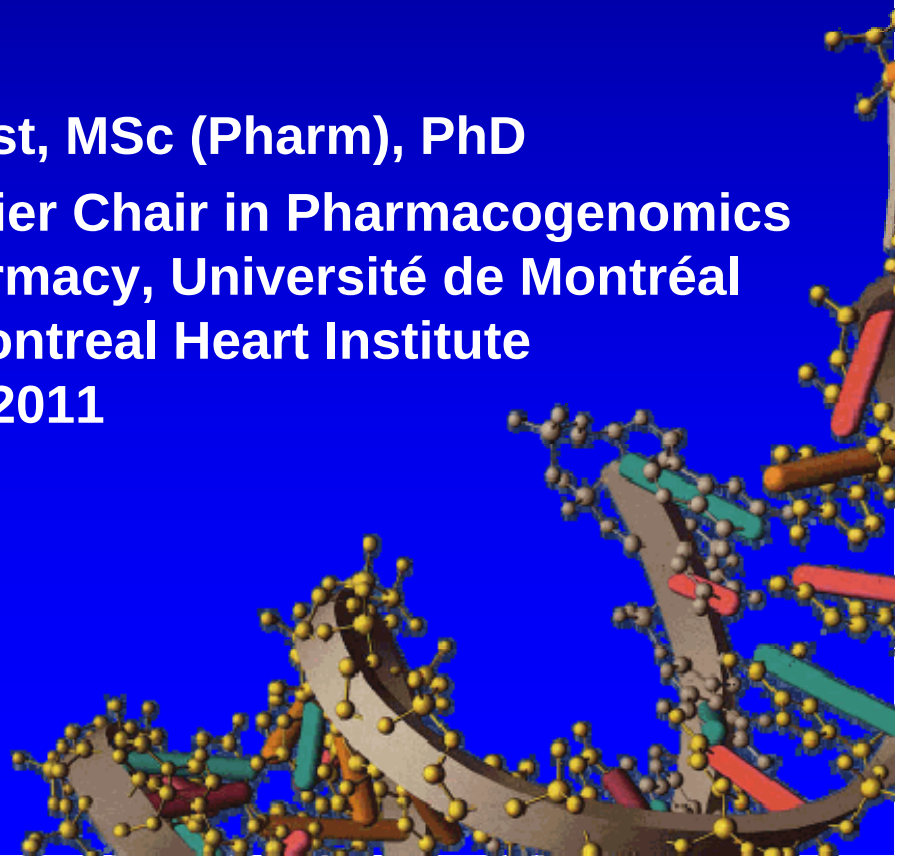
**April 17th 2011**



Faculté de pharmacie
Université de Montréal

INSTITUT DE CARDIOLOGIE DE MONTRÉAL

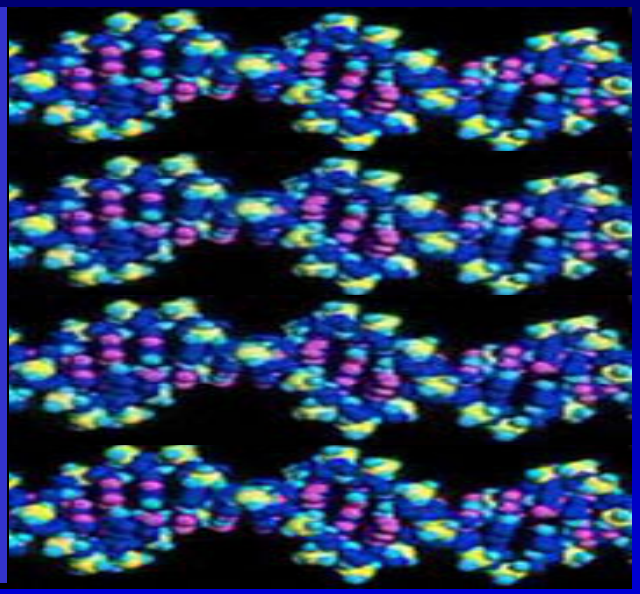
# Genetic Variation

Patient 1

Patient 2

Patient 3

Patient 4



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Patient 1 | A | C | T | G | A | C | T | G |
| Patient 2 | A | C | T | G | C | C | T | G |
| Patient 3 | A | C | T | G | A | C | T | G |
| Patient 4 | A | C | T | G | A | C | T | G |

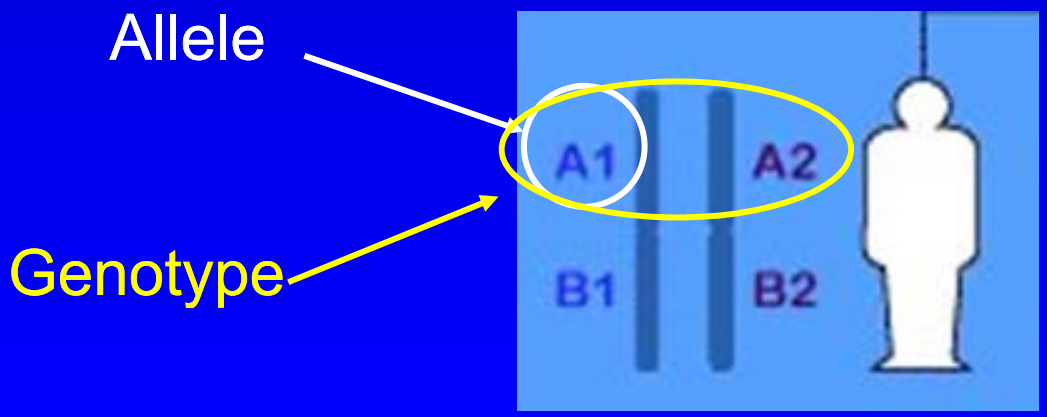
## What is a SNP?

**Single Nucleotide Polymorphism**

**- can be rare or common in specific populations**

# Allele to Genotype

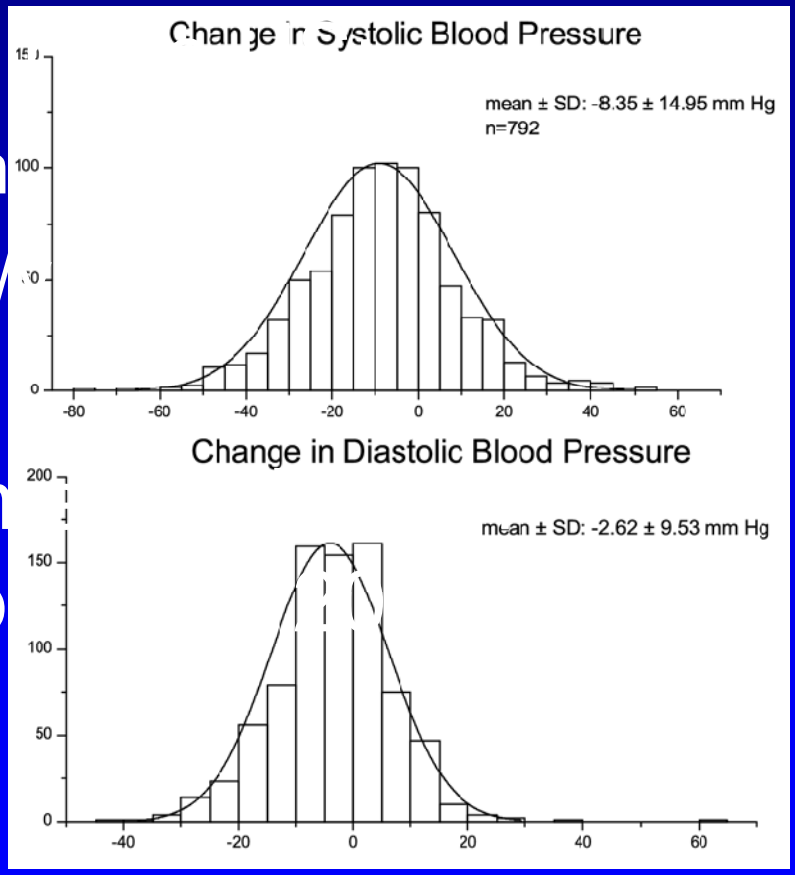
- An allele represents one of two or more versions of a genetic sequence at a particular location in the genome.
- The term **genotype** refers to the two **alleles** inherited for a particular gene.




N Engl J Med 2010;362:2001-11.

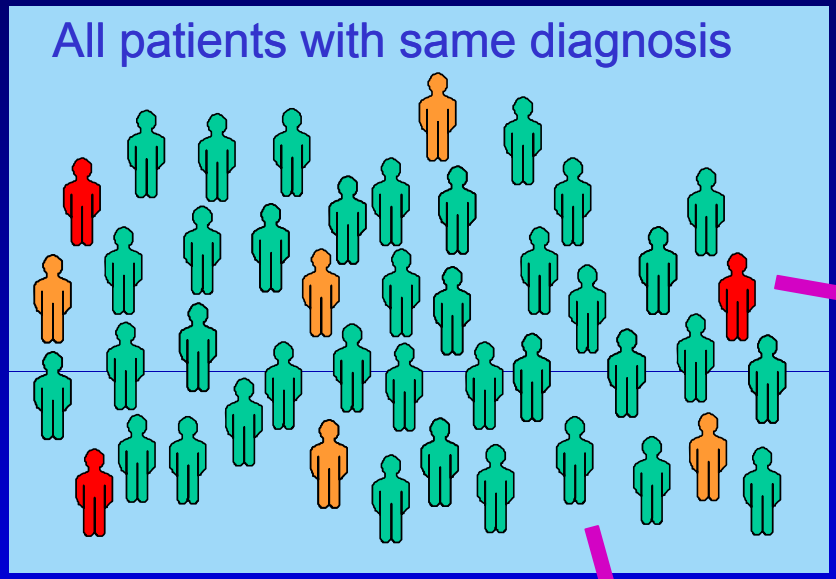
# Why personalized medicine?

- Variable response to CV drugs
- Adverse drug reactions
  - 4th to 6th cause of death
  - 2 million hospitalisations/
  - Up to $160 billion/year
- The annual cost of CV n
  Canada surpassed $5 b




Brunner M, et al. Am J Cardiol. 2007;99:1549-54. 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. Jackevicius, C. A. et al. CMAJ 2009;181:E19-E28

# Potential of Pharmacogenomics




1

Non-responders and toxic responders

*Treat with alternative dose*

2

Responders and patients not predisposed to toxicity

*Treat with conventional drug or dose*

PLAVIX®

Prescribing Information

(clopidogrel bisulfate) tablets

**Rx only**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use PLAVIX safely and effectively. See full prescribing information for**

The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants. Consider these ranges in choosing the initial dose.

In all patients, subsequent dosage adjustments must be made based on the results of PT/INR determinations.[17,18]

**Table 5:** Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

| VKORC1 | CYP2C9 | | | | | |
|---|---|---|---|---|---|---|
| | *1/*1 | *1/*2 | *1/*3 | *2/*2 | *2/*3 | *3/*3 |
| GG | 5-7 mg | 5-7 mg | 3-4 mg | 3-4 mg | 3-4 mg | 0.5-2 mg |
| AG | 5-7 mg | 3-4 mg | 3-4 mg | 3-4 mg | 0.5-2 mg | 0.5-2 mg |
| AA | 3-4 mg | 3-4 mg | 0.5-2 mg | 0.5-2 mg | 0.5-2 mg | 0.5-2 mg |

†Ranges are derived from multiple published clinical studies. Other clinical factors (eg, age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

**CYP2C19 poor metabolizers. (2.3, 5.1)**

http://v

011.

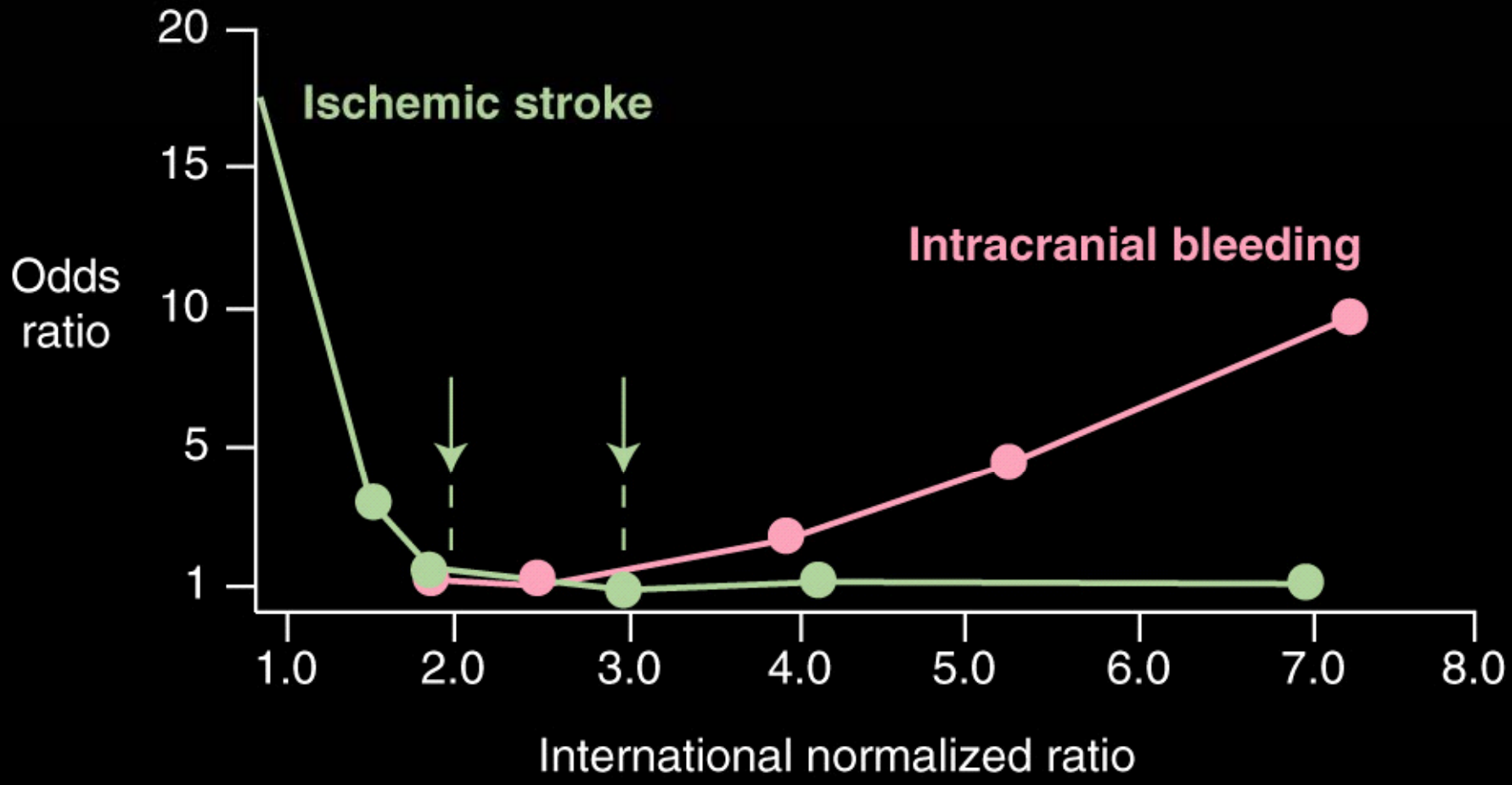
# Pgx of clopidogrel and warfarin, ready for prime time?

- It all depends on the evidence!

# Warfarin

VBWG

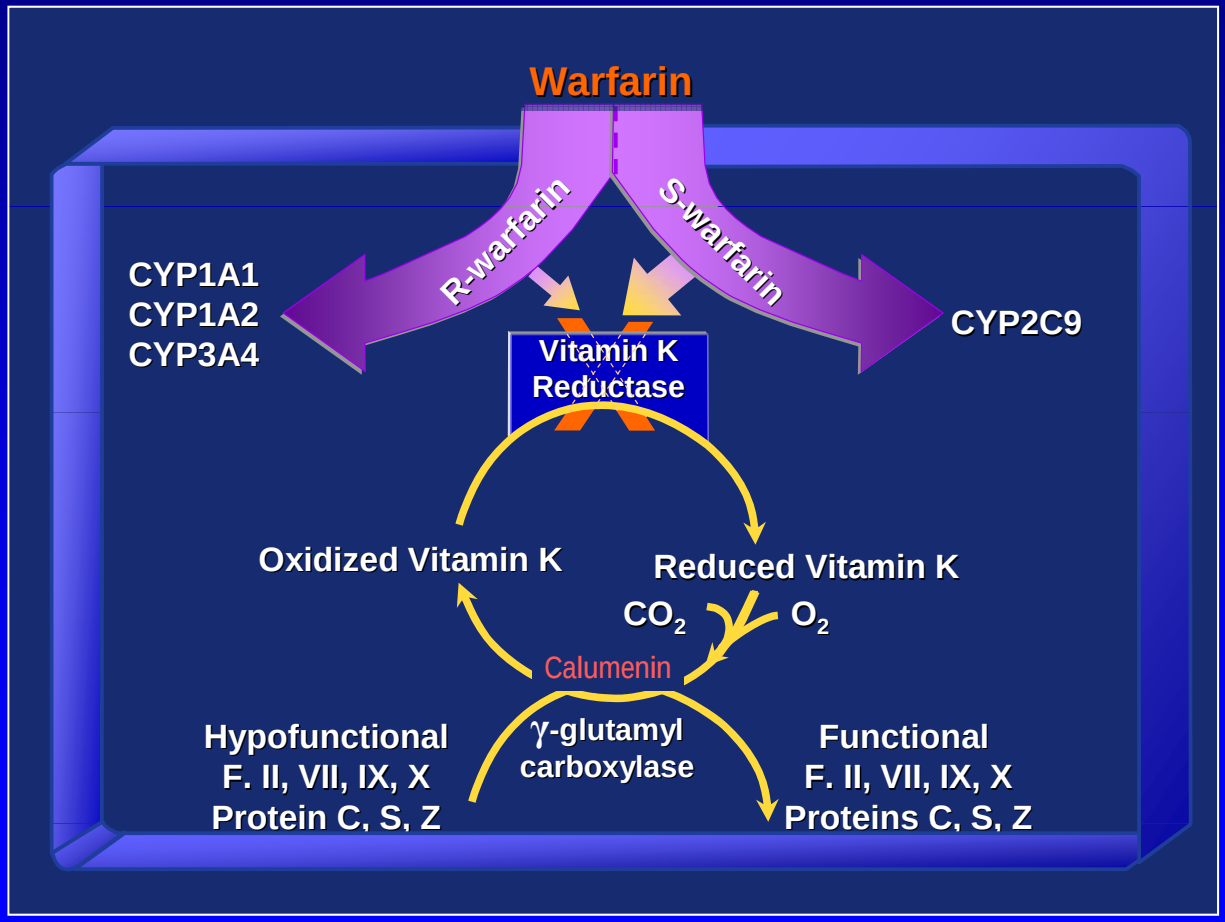
# Warfarin: Narrow therapeutic window




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

# Warfarin Metabolism and Activation Pathway

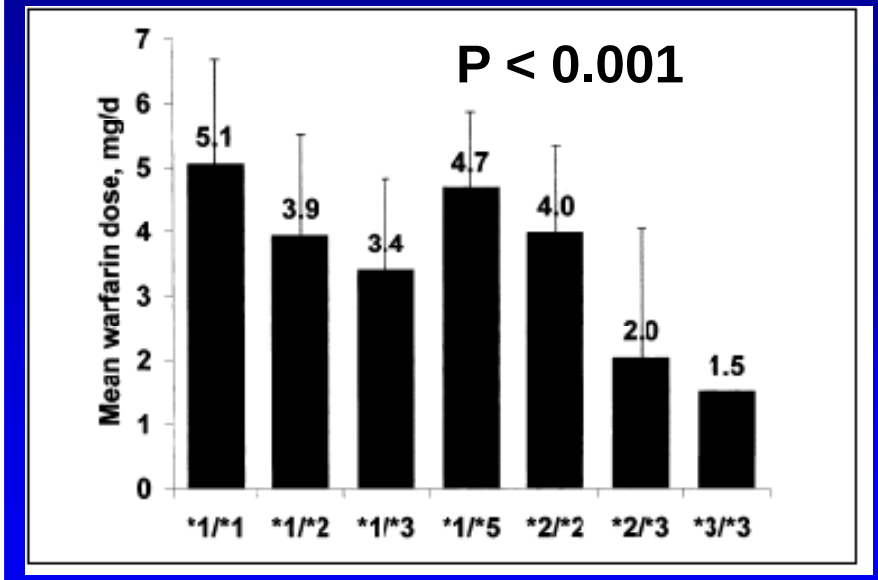
## Candidate proteins in the pathway




Gage et al. 2005

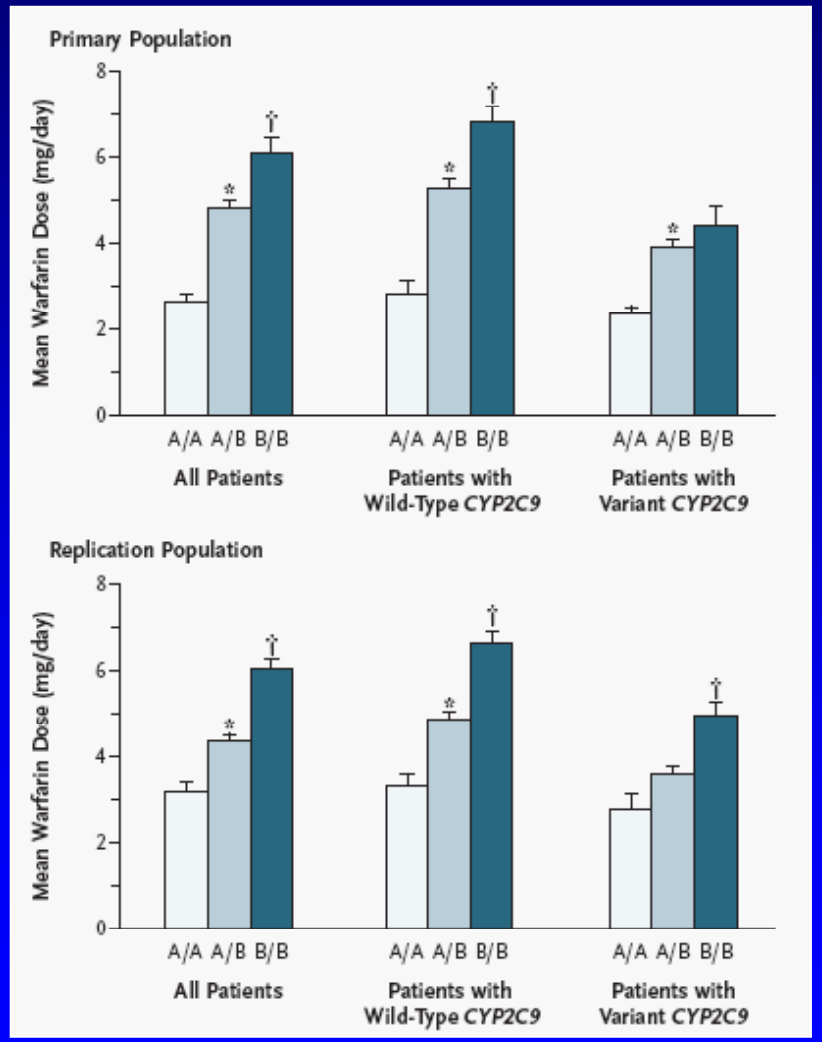
# Association of *CYP2C9 and VKORC1* and warfarin dosing

N = 369



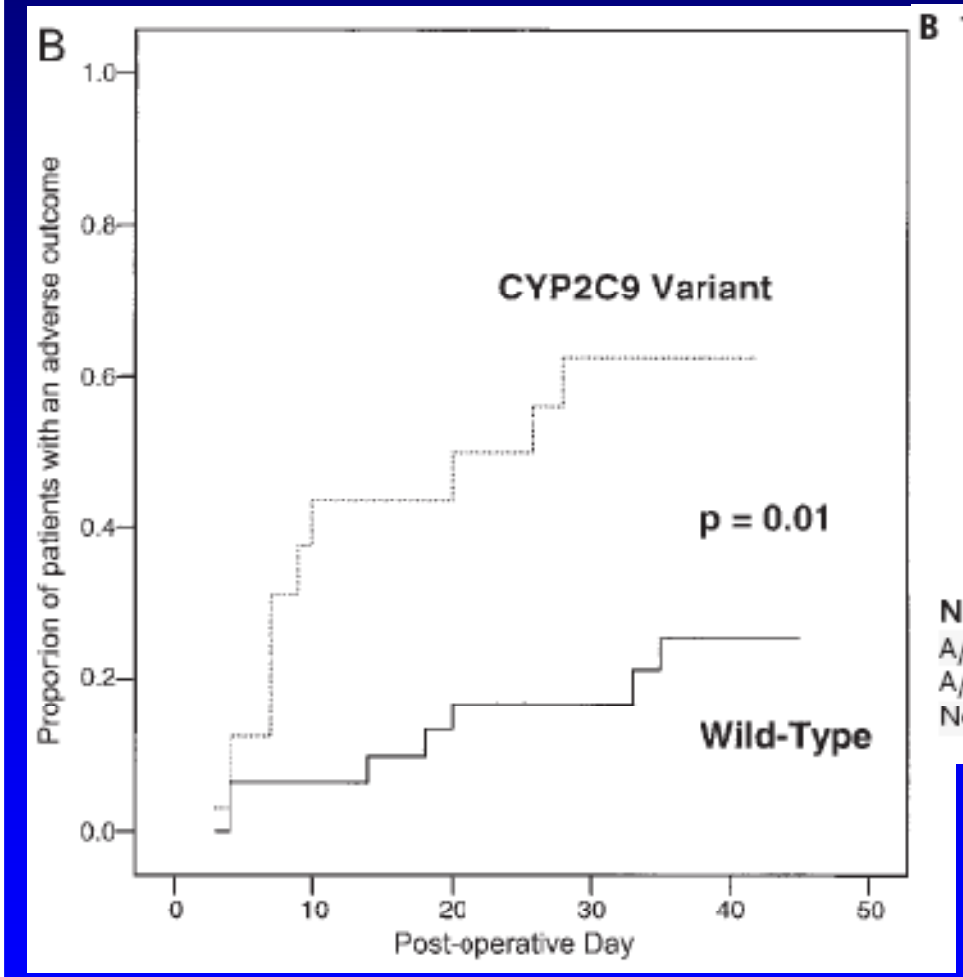

*CYP2C9*

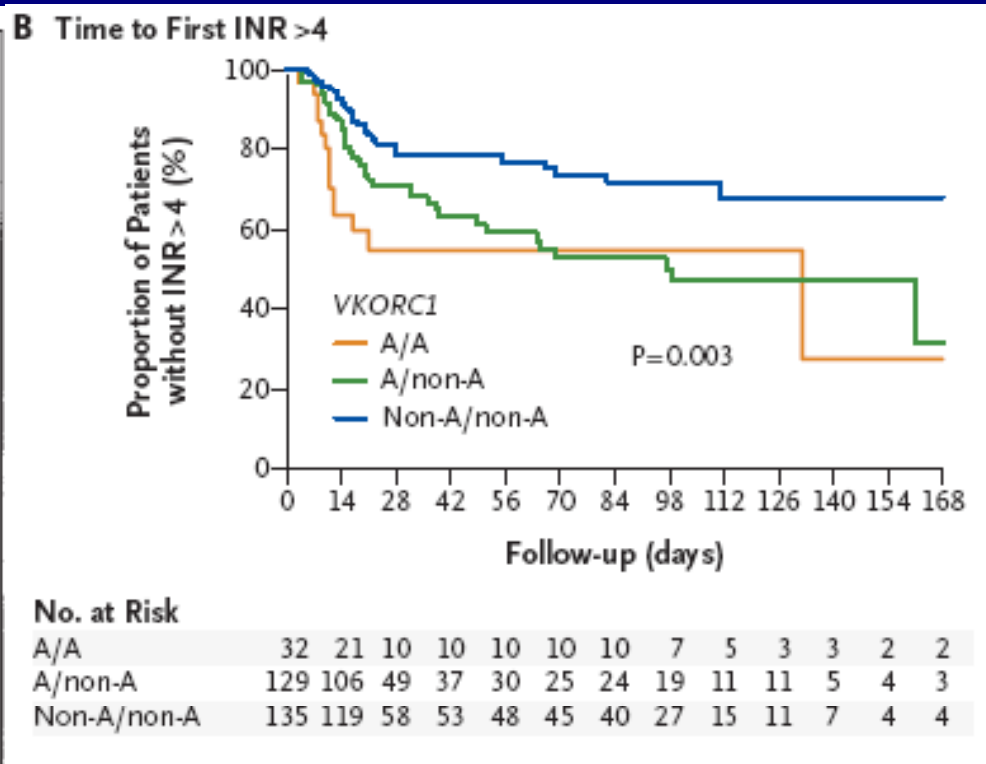
Thromb Haemost 2004; 91: 87–94




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

# Coumarin derivatives and excessive anticoagulation




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

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

# WARFARINDOSING

www.WarfarinDosing.org

- > Warfarin Dosing
- > Clinical Trial
- > Outcomes
- > Hemorrhage Risk
- > Patient Education
- > Contact Us
- > References
- > Glossary
- > About Us

User:
Patient:
Version 2.20
Build : April 06, 2011

## Required Patient Information

**Age:** [ ] **Sex:** -Select- **Ethnicity:** -Select-

**Race:** -Select-

**Weight:** [ ] lbs **or** [ ] kgs

**Height:** ( [ ] feet and [ ] inches) **or** ( [ ] cms)

**Smokes:** -Select- **Liver Disease:** -Select-

**Indication:** -Select-

**Baseline INR:** [ ] **Target INR:** [ ] ☐ Randomize & Blind

**Amiodarone/Cordarone® Dose:** [ ] mg/day

**Statin/HMG CoA Reductase Inhibitor:**
-Select-

**Any azole** (eg. Fluconazole): -Select-

**Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim:** -Select-

## Genetic Information

**VKORC1-1639/3673:** Not available/pending

**CYP4F2 V433M:** Not available/pending

**GGCX rs11676382:** Not available/pending

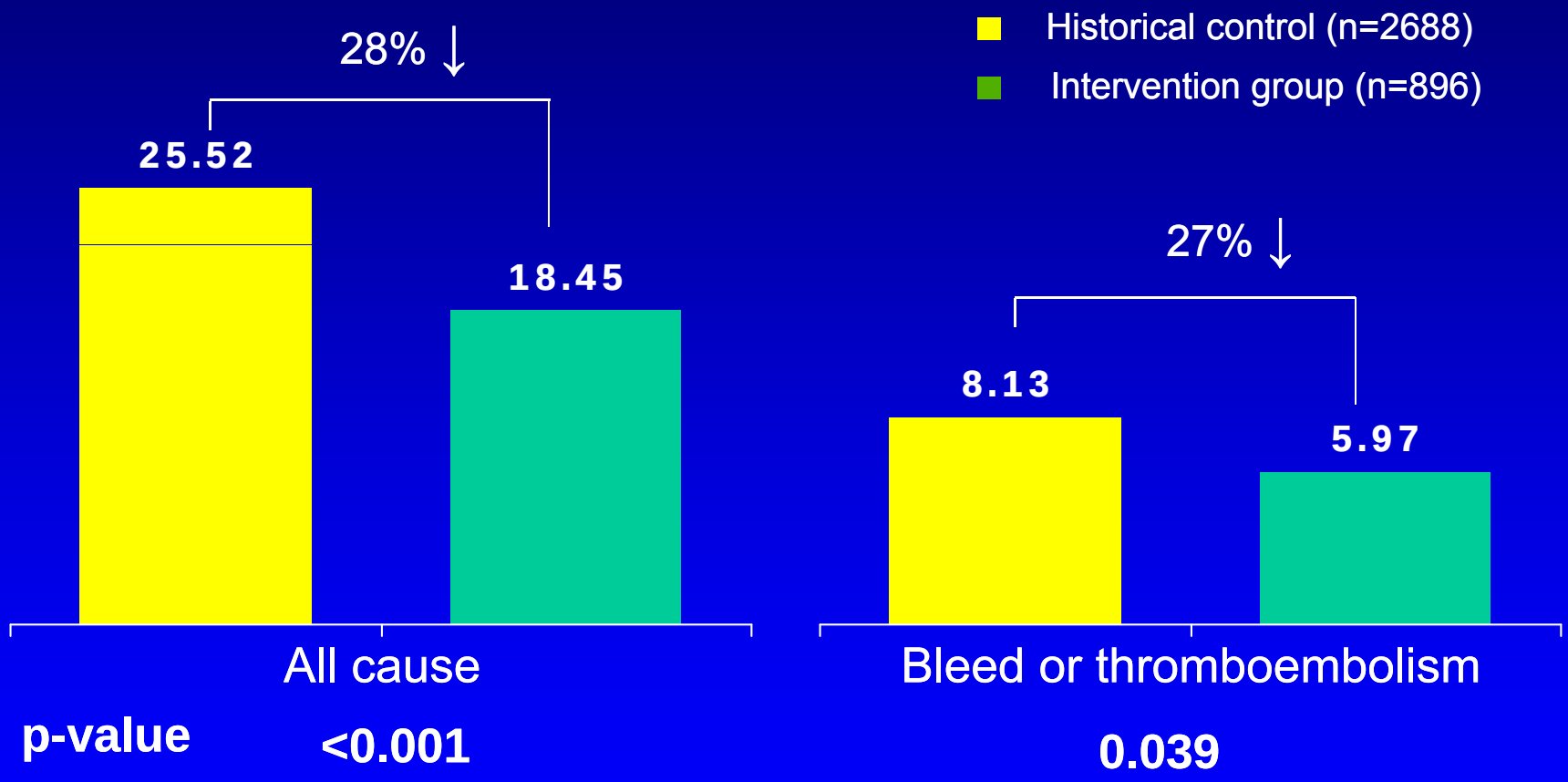
**CYP2C9*2:** Not available/pending

**CYP2C9*3:** Not available/pending

**CYP2C9*5:** Not available/pending

**CYP2C9*6:** Not available/pending

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




**Intention to treat (ITT)**

Epstein RS, et al. J Am Coll Cardiol 2010:2804-12.

# Randomized Trial of Genotype-Guided Versus Standard Warfarin Dosing in Patients Initiating Oral Anticoagulation

Jeffrey L. Anderson, MD; Benjamin D. Horne, PhD, MPH; Scott M. Stevens, MD; Amanda S. Grove, BS; Stephanie Barton, PharmD; Zachery P. Nicholas, BS; Samera F.S. Kahn, BS; Heidi T. May, MSPH; Kent M. Samuelson, MD; Joseph B. Muhlestein, MD; John F. Carlquist, PhD; for the Couma-Gen Investigators

***Background***—Pharmacogenetic-guided dosing of warfarin is a promising application of "personalized medicine" but has not been adequately tested in randomized trials.

***Methods and Results***—Consenting patients (n=206) being initiated on warfarin were randomized to pharmacogenetic-guided or standard dosing. Buccal swab DNA was genotyped for *CYP2C9* *2 and *CYP2C9* *3 and *VKORC1* C1173T with a rapid assay. Standard dosing followed an empirical protocol, whereas pharmacogenetic-guided dosing followed a regression equation including the 3 genetic variants and age, sex, and weight. Prothrombin time international normalized ratio (INR) was measured routinely on days 0, 3, 5, 8, 21, 60, and 90. A research pharmacist unblinded to treatment strategy managed dose adjustments. Patients were followed up for up to 3 months. Pharmacogenetic-guided predicted doses more accurately approximated stable doses ($P<0.001$), resulting in smaller ($P=0.002$) and fewer ($P=0.03$) dosing changes and INRs ($P=0.06$). However, percent out-of-range INRs (pharmacogenetic=30.7%, standard=33.1%), the primary end point, did not differ significantly between arms. Despite this, when restricted to wild-type patients (who required larger doses; $P=0.001$) and multiple variant carriers (who required smaller doses; $P<0.001$) in exploratory analyses, results (pharmacogenetic=29%, standard=39%) achieved nominal significance ($P=0.03$). Multiple variant allele carriers were at increased risk of an INR of ≥4 ($P=0.03$).

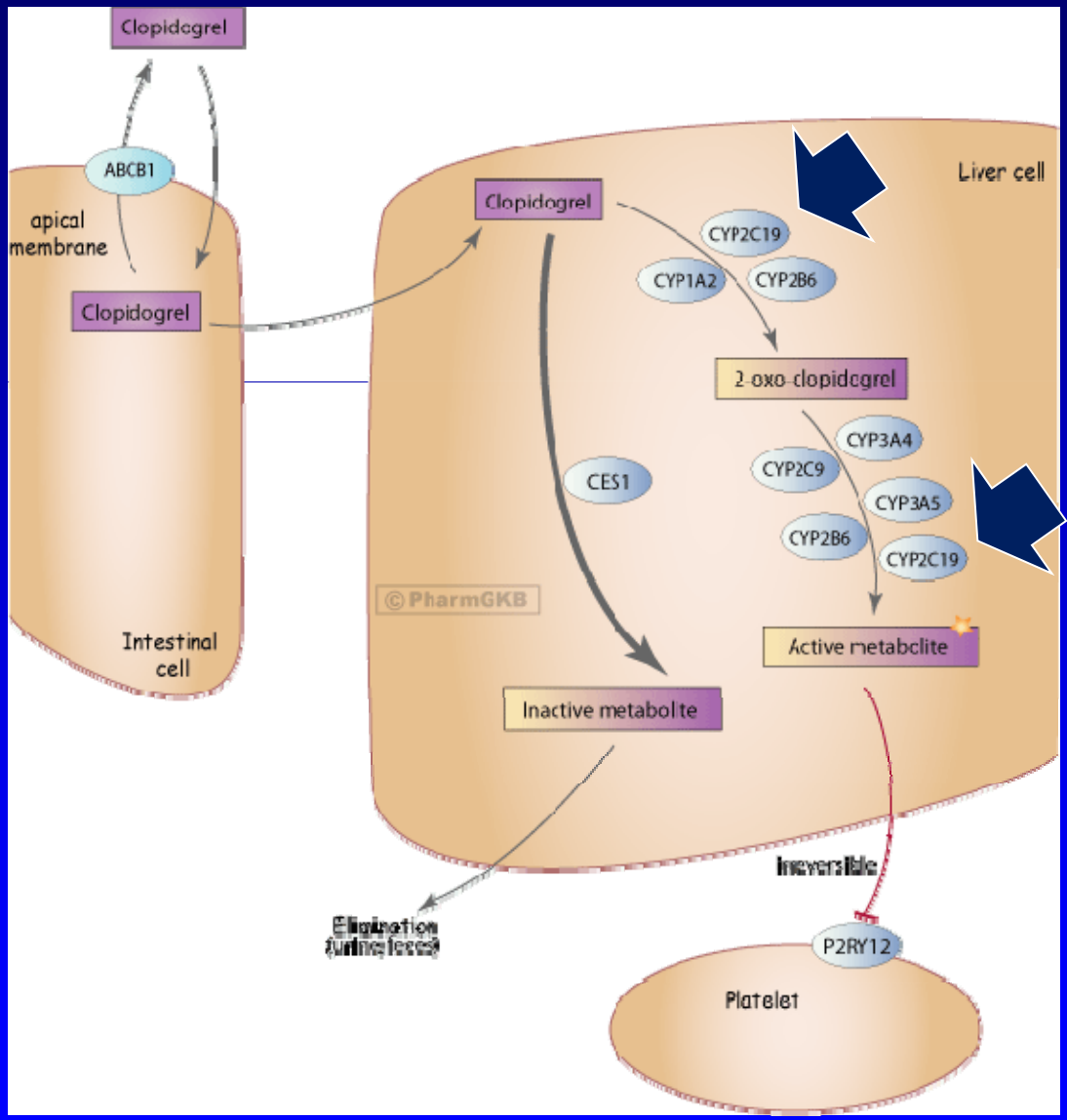
***Conclusions***—An algorithm guided by pharmacogenetic and clinical factors improved the accuracy and efficiency of warfarin dose initiation. Despite this, the primary end point of a reduction in out-of-range INRs was not achieved. In subset analyses, pharmacogenetic guidance showed promise for wild-type and multiple variant genotypes. (***Circulation.*** **2007;116:2563-2570.)**

**Key Words:** anticoagulation ■ clinical trial ■ genetics ■ pharmacogenetics ■ warfarin

**Circulation. 2007;116:2563-2570.**

# Clopidogrel

# Clopidogrel pharmacokinetics




http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway

The NEW ENGLAND JOURNAL of MEDICINE

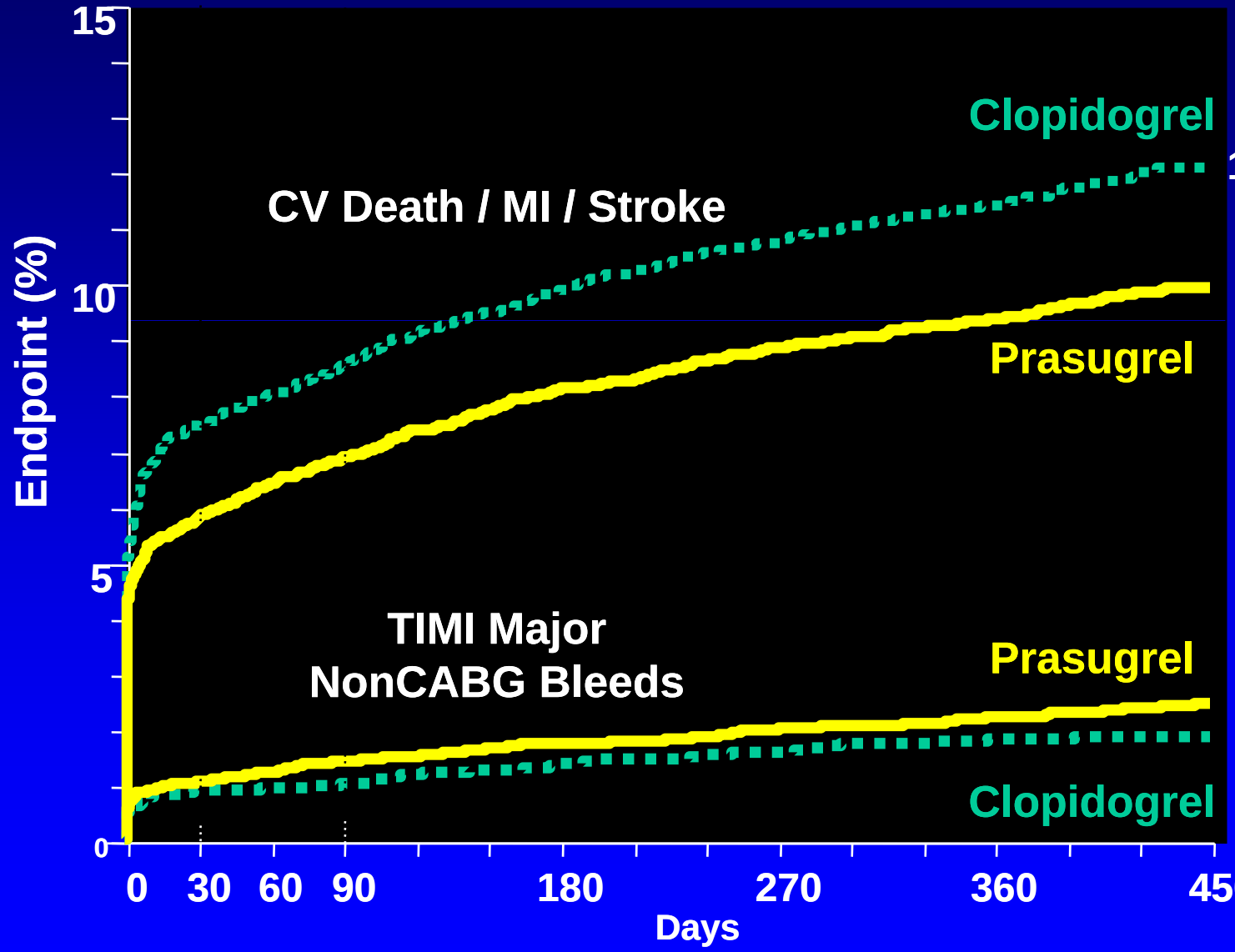
ORIGINAL ARTICLE

# 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.

Mega JL, et al. N Engl J Med. 2009;360:354-62.

# Balance of Efficacy and Safety




↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

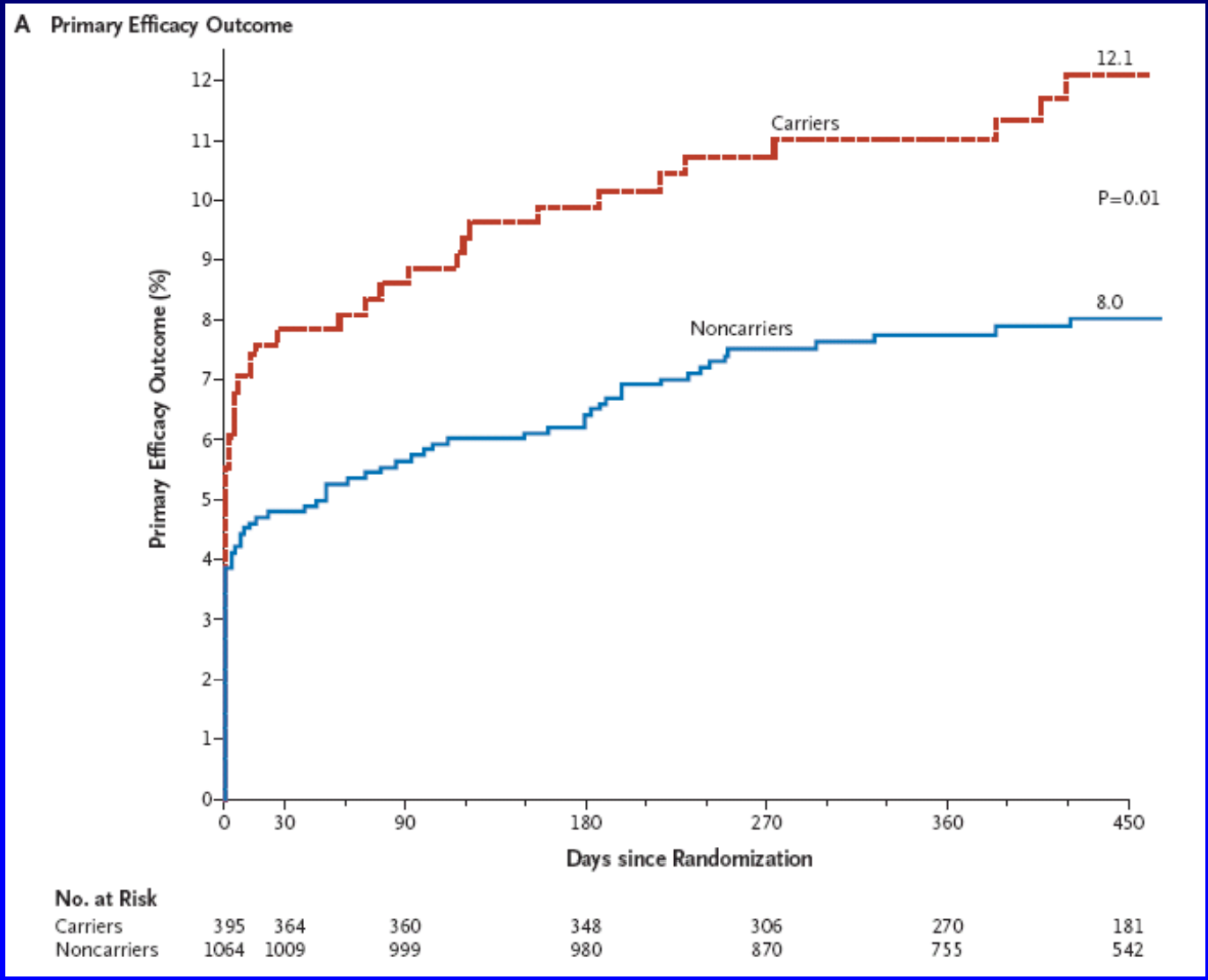
↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

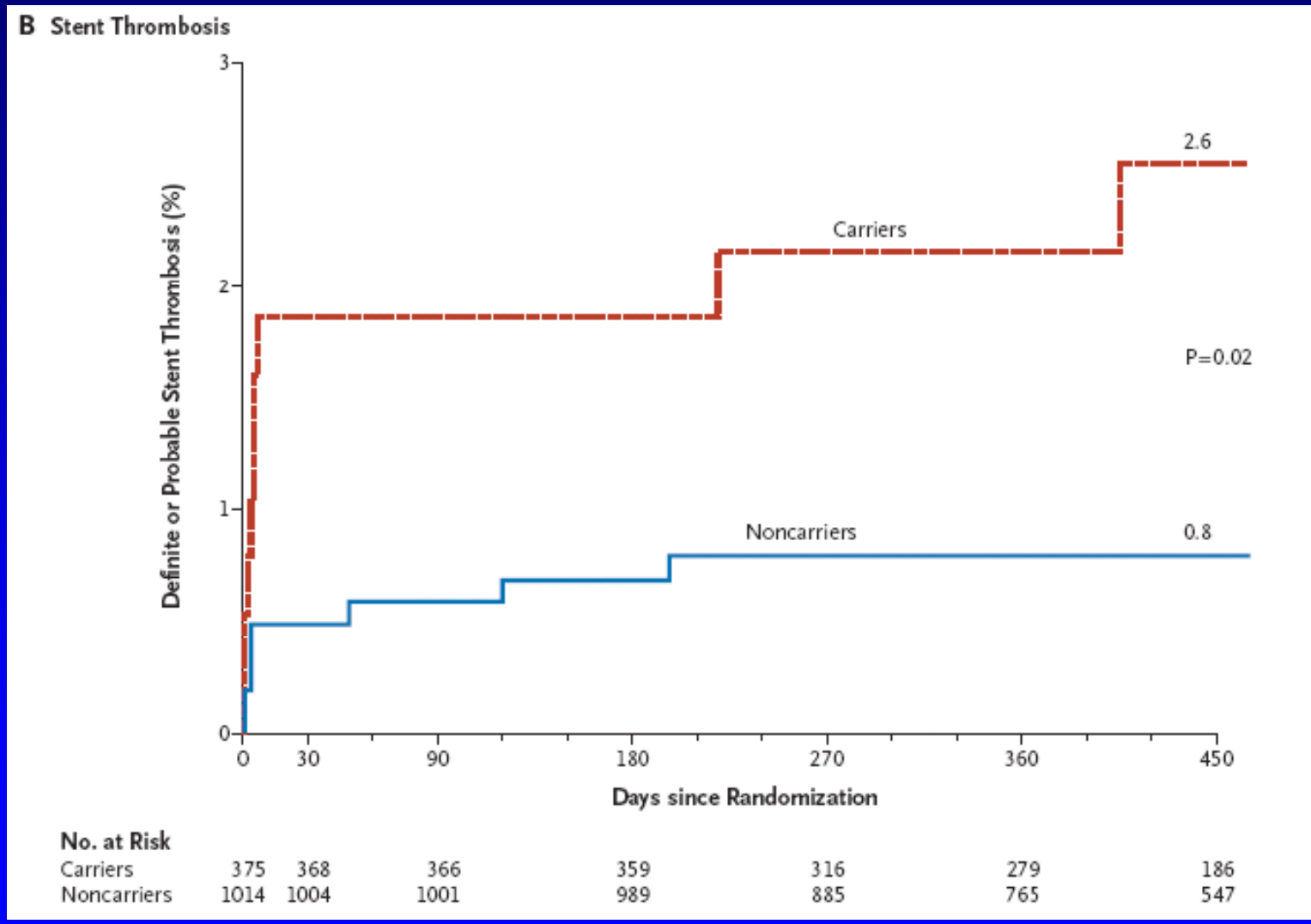
Wiviott SD, et al. N Engl J Med. 2007;357:2001-15.

# Primary end point according to *CYP2C19* genotype in patients receiving clopidogrel




Mega JL, et al. N Engl J Med. 2009;360:354-62.

# Risk of stent thrombosis according to *CYP2C19* genotype in patients receiving clopidogrel




Mega JL, et al. N Engl J Med. 2009;360:354-62.

# Replication???

# Replication!!!

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

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ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.12.056

REVIEW

# Reduced-Function *CYP2C19* Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI

## A Meta-analysis

*JAMA. 2010;304(16):1821-1830*

Dir
Kat
Nic
Mehilli,
and

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*

# Can we do anything about this?

- Use of high-dose clopidogrel?
  - No Pgx data available from CURRENT-OASIS 7
  - Limited data from GRAVITAS study.
    - No improvement in reduced function *CYP2C19* alleles
- Alternatives?
  - The effects of prasugrel and ticagrelor are independent of *CYP2C19* genotype.
    - Genotype-guided use vs unselected use of these new agents in all patients?

Price AJ, et al. JAMA. 2011;305(11):1097-1105. CURRENT-OASIS 7 Investigators. N Engl J Med. 2010 ;363:930-42. Mehta SR, et al. Lancet 2010; 376: 1233–43. Wallentin L, et al. Lancet 2010; 376: 1320–28. Mega JL, et al. Circulation 2009;119:2553-60

# Pgx of clopidogrel and warfarin, ready for prime time?

- It all depends on the evidence!
- … and your definition of “evidence”

# « Evidence » - based medicine

- Marked differences in the evaluation of the "evidence"
  - American Heart Association, American College of Chest Physician
    - RCTs are at the center of the evaluation process.
  - Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
    - One (Level 2) or two (level 1) RCTs are required to provide convincing evidence of clinical utility
  - Clinical Pharmacogenetics Implementation Consortium of the NIH's Pharmacogenomics Research Network:
    - Level 1 evidence: the evidence includes consistent results from well-designed, well-conducted studies.

# Cardiovascular drugs with Pgx

## Pharmacology and Management of the Vitamin K Antagonists*

### American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

*Jack Ansell, MD; Jack Hirsh, MD; Elaine Hylek, MD, MPH; Alan Jacobson, MD; Mark Crowther, MD; and Gualtiero Palareti, MD*

*(CHEST 2008; 133:160S–198S)*

Clinical Expert Cor

*Endorsed by the Soci*

Quinidine

Timolol

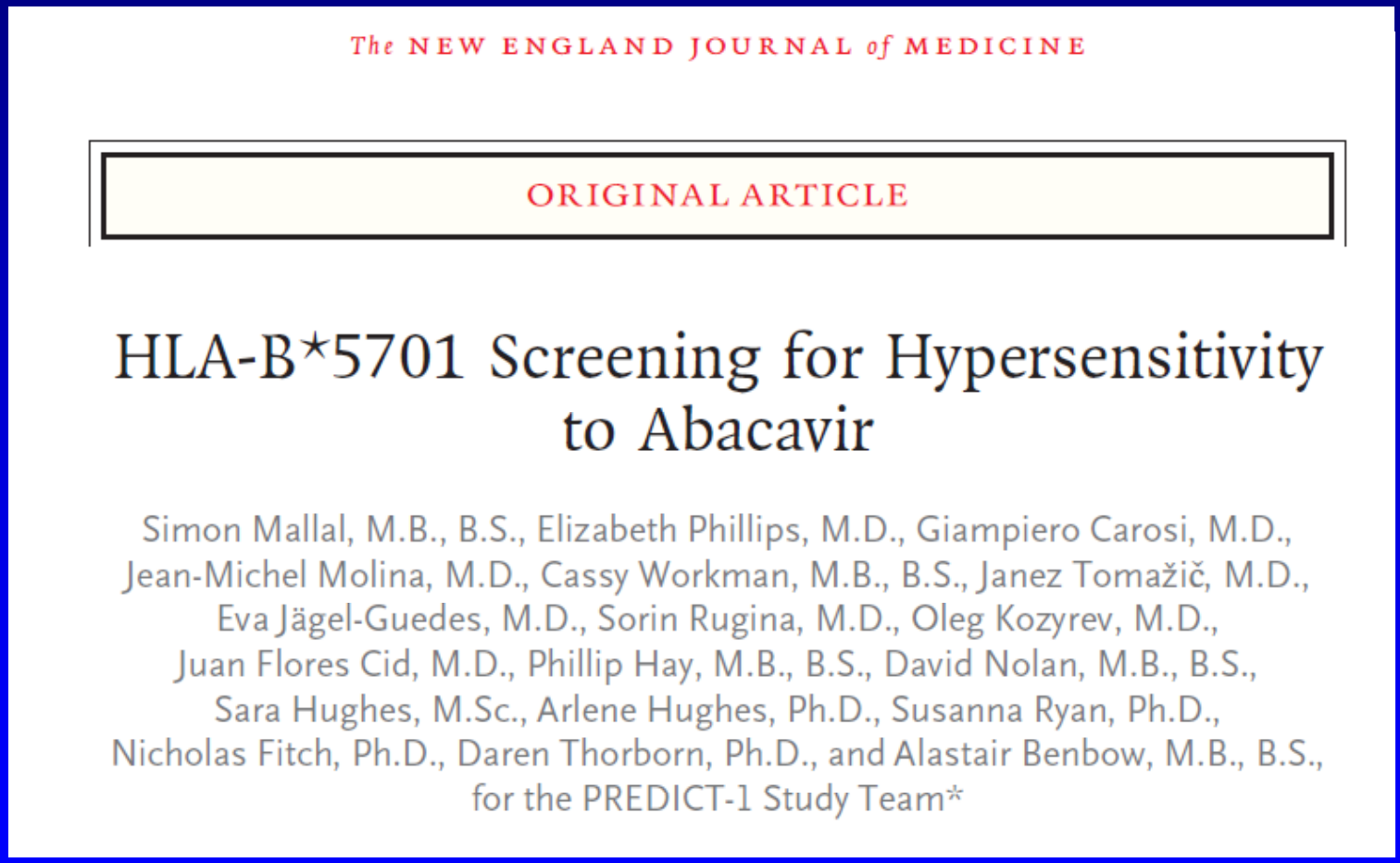
Warfarin

**At the present time, for patients beginning VKA therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing** (Grade 2C).

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. Accessed on April 7th 2011.

# Can RCTs of Pgx markers be performed?

- Yes!



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

Mallal S, et al. N Engl J Med. 2008;358:568-79.

# Are they always necessary?

- No, not always.
- We use « markers » to personalize our selection of drugs, in the absence of RCTs:
  - Choice of an antibiotic in a patient treated with digoxin or warfarin (clarithromycin vs cefuroxime)
  - Choice of a beta-blocker in a patient with severe renal dysfunction (atenolol vs metoprolol)

# Are they always necessary?

- Clopidogrel
  - RCT
  - How
  - Bed
    - W

Class I

3. Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected should receive dual-antiplatelet therapy on presentation.[13,15–17] (*Level of Evidence: A*) ASA should be initiated on presentation.[3–8,10] (*Level of Evidence: A*) The choice of a second antiplatelet

Class IIb

e added to ASA on presentation includes 1 of the following:

2. Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management.[78–84] *(Level of Evidence: C)*

At the time of PCI:

- Clopidogrel if not started before PCI[13,17] *(Level of Evidence: A)*; or
- Prasugrel†[22] *(Level of Evidence: B)*; or
- An IV GP IIb/IIIa inhibitor.[18,21,23,24] *(Level of Evidence: A)*

Pgx

ble

ased

**2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non–ST-Elevation Myocardial Infarction Circulation – online before print**

# Are they always necessary?

- Different paradigms:
  - An alternative for personalizing the therapy is available
    - Monitoring of warfarin using the INR

French et al. Trials 2010, 11:108
http://www.trialsjournal.com/content/11/1/108


METHODOLOGY Open Access

## Statistical design of personalized medicine interventions: The Clarification of Optimal Anticoagulation through Genetics (COAG) trial

Benjamin French[1*†], Jungnam Joo[2†], Nancy L Geller[2], Stephen E Kimmel[1], Yves Rosenberg[3], Jeffrey L Anderson[4], Brian F Gage[5], Julie A Johnson[6], Jonas H Ellenberg[1],
the COAG (Clarification of Optimal Anticoagulation through Genetics) Investigators

# Cardiovascular pharmacogenomics: ready for prime time?

- For most CV drugs, no.
- Warfarin
  - Extensive data
  - RCTs are required to determine whether genotype-guided therapy is superior to INR-guided
- Clopidogrel
  - Testing for *CYP2C19* should be considered for specific indications where alternatives are available
    - Cost-effectiveness?
    - Availability of point-of-care tests?

# The future…

## 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*

Ashley EA, et al. Lancet. 2010;375:1525-35.

*« Prediction is very difficult, especially about the future. »*

Niels Bohr, Danish physicist.

# Summary

- Many Pgx associations reported in CV diseases
  - Few replicated associations with clinical outcomes (clopidogrel and warfarin)
  - The definition of « Evidence-based practice » in Pgx remains an issue of discussion
    - “Personalized evaluation of the evidence”

# Is this clinically relevant?

European Heart Journal
doi:10.1093/eurheartj/ehp157

CLINICAL RESEARCH

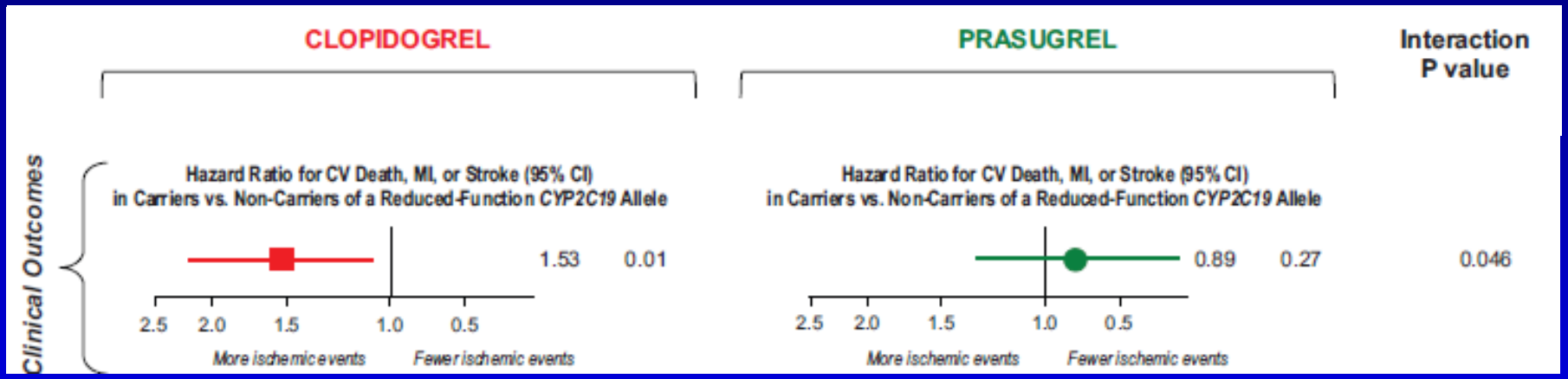
## Genetic variation of *CYP2C19* affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease

**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]**

[1]Uppsala Clinical Research Center and Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden; [2]Department of Cardiology, Lund University, Lund, Sweden; [3]Eli Lilly and Company, Indianapolis, IN, USA; [4]Coagulation Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden; and [5]Daiichi Sankyo, Inc., Parsippany, NJ, USA

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

# TRITON – TIMI 38 Genex treatment interaction




Mega ML, et al. Circulation 2009;119:2553-60.

# TRITON-TIMI 38 - Pgx of clopidogrel

**Table 1. Efficacy and Safety Outcomes at 15 Months in Subjects Treated with Clopidogrel, According to Genotype Status.***

| Gene | Carriers of Reduced-Function Allele | Noncarriers of Reduced-Function Allele | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Composite primary efficacy outcome† | | | | |
| *CYP2C19* | 46/395 (12.1) | 83/1064 (8.0) | 1.53 (1.07–2.19) | 0.01 |
| *CYP2C9* | 22/230 (10.0) | 107/1226 (9.0) | 1.09 (0.69–1.73) | 0.41 |
| *CYP2B6* | 36/370 (10.0) | 68/777 (9.0) | 1.11 (0.74–1.67) | 0.78 |
| *CYP3A5* | 95/1130 (8.7) | 14/151 (9.5) | 0.89 (0.51–1.57) | 0.69 |
| *CYP1A2* | 5/59 (8.5) | 95/1099 (8.9) | 0.97 (0.40–2.39) | 0.96 |
| Major or minor bleeding‡ | | | | |
| *CYP2C19* | 11/393 (2.9) | 30/1061 (3.0) | 1.01 (0.51–2.01) | 0.98 |
| *CYP2C9* | 7/229 (3.4) | 34/1222 (2.9) | 1.07 (0.47–2.40) | 0.88 |
| *CYP2B6* | 12/370 (3.3) | 22/773 (3.1) | 1.08 (0.53–2.18) | 0.84 |
| *CYP3A5* | 31/1125 (3.0) | 5/151 (3.3) | 0.77 (0.30–1.97) | 0.58 |
| *CYP1A2* | 2/59 (3.4) | 31/1094 (3.0) | 1.29 (0.31–5.38) | 0.73 |

Mega ML, et al. N Engl J Med. 2009;360:354-62.

# Other biomarkers in CV diseases

- B-type natriuretic peptide (BNP) and NT-proBNP
  - Established  diagnostic and prognostic markers of heart failure
    - Commonly used to enrich clinical
      - Others: Left ventricular ejection fraction, QRS duration
    - Cannot distinguish « responders » from « non responders », only *low* vs *high*-risk
  - Still no convincing data regarding BNP-guided therapy.

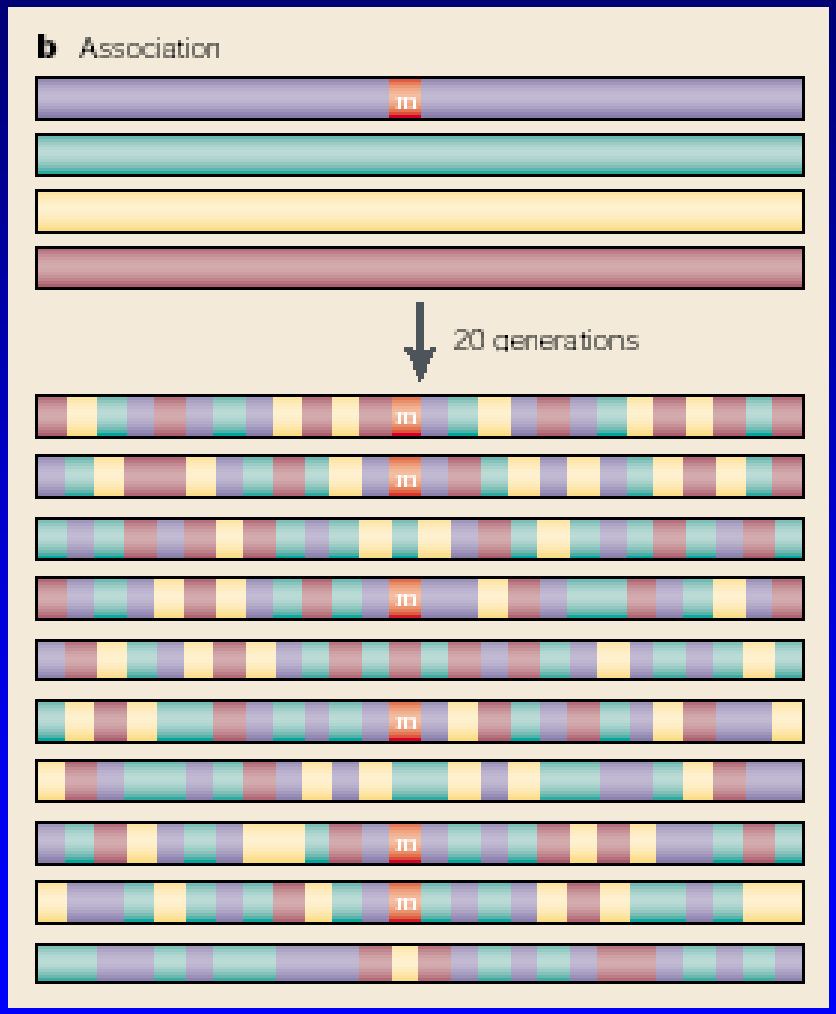
# *SNP* (pronounce snip!), *is…*

A) One of the 3 Rice Krispies® characters (SNP, Crackle et Pop!)

B) A rap band from the 90's

C) The abbreviation of *Single Nucleotide Polymorphisms*

# Association Studies




**Uses:**

- **Unrelated individuals**
- **Case and Controls**
- **Reconstruct ancestral haplotypes**

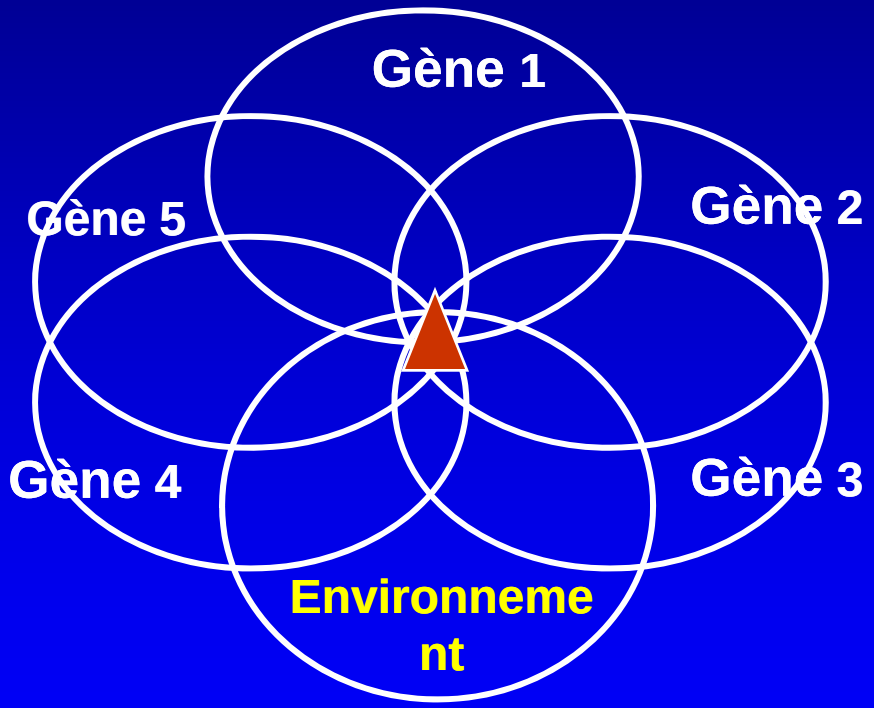
Cardon and Bell, *Nature Reviews: Genetics*, 2001

# 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**

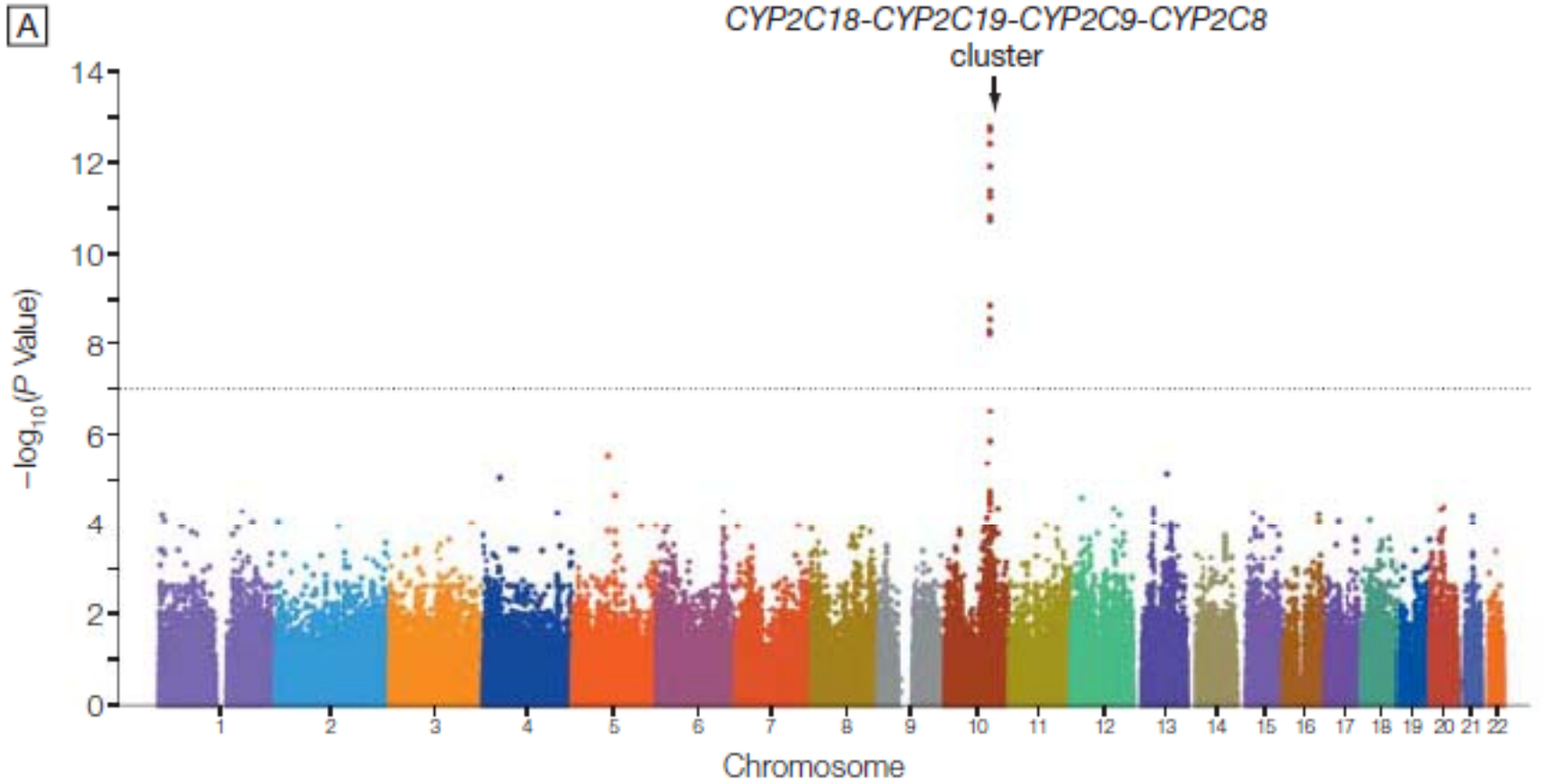
Maladies complexes (ex: hypertension)




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

# GWAS of clopidogrel PD

**Figure 2.** Genome-Wide Association Study of Adenosine Diphosphate–Stimulated Platelet Aggregation in Response to Clopidogrel



# Is this clinically relevant?

**Genetics**

## Cytochrome P450 Genetic Polymorphisms and the Response to Prasugrel

### Relationship to Pharmacokinetic, Pharmacodynamic, and Clinical Outcomes

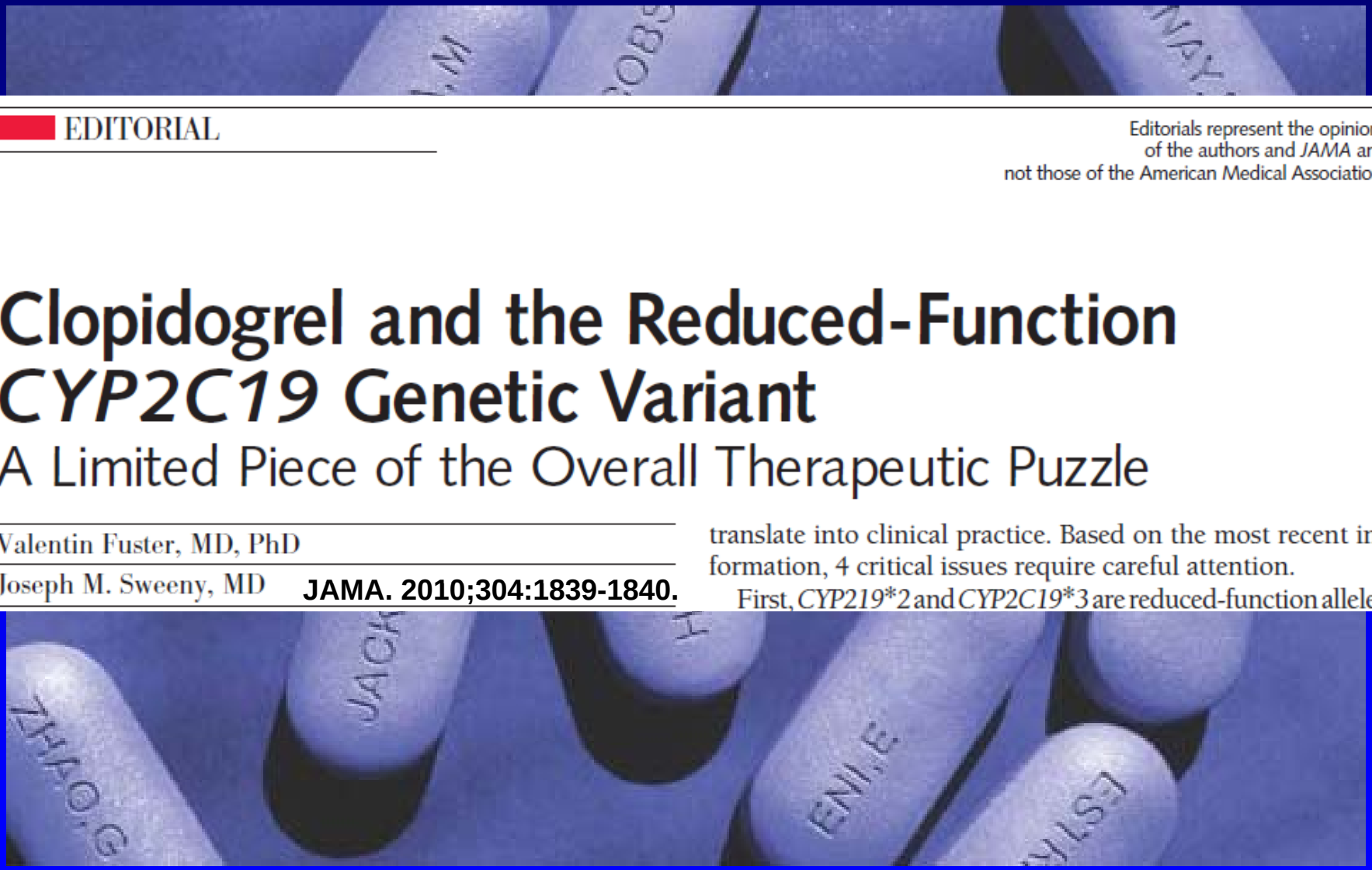
Jessica L. Mega, MD, MPH; Sandra L. Close, PhD; Stephen D. Wiviott, MD; Lei Shen, PhD; Richard D. Hockett, MD; John T. Brandt, MD; Joseph R. Walker, PharmD; Elliott M. Antman, MD; William L. Macias, MD, PhD; Eugene Braunwald, MD; Marc S. Sabatine, MD, MPH

***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.**)

# Too much hype???



EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

## Clopidogrel and the Reduced-Function *CYP2C19* Genetic Variant

### A Limited Piece of the Overall Therapeutic Puzzle

Valentin Fuster, MD, PhD
Joseph M. Sweeny, MD

**JAMA. 2010;304:1839-1840.**

translate into clinical practice. Based on the most recent information, 4 critical issues require careful attention.

First, *CYP219*2* and *CYP2C19*3* are reduced-function alleles

# Plan of the presentation

- Genetics 101
- Do we need personalized medicine?
- Selected examples:
  - Warfarin
  - Clopidogrel
- Ready for prime time?
- Summary and conclusions


*"Oh, I forgot,….*
*here's my genome …"*

# Variant alleles frequencies differ significantly between populations

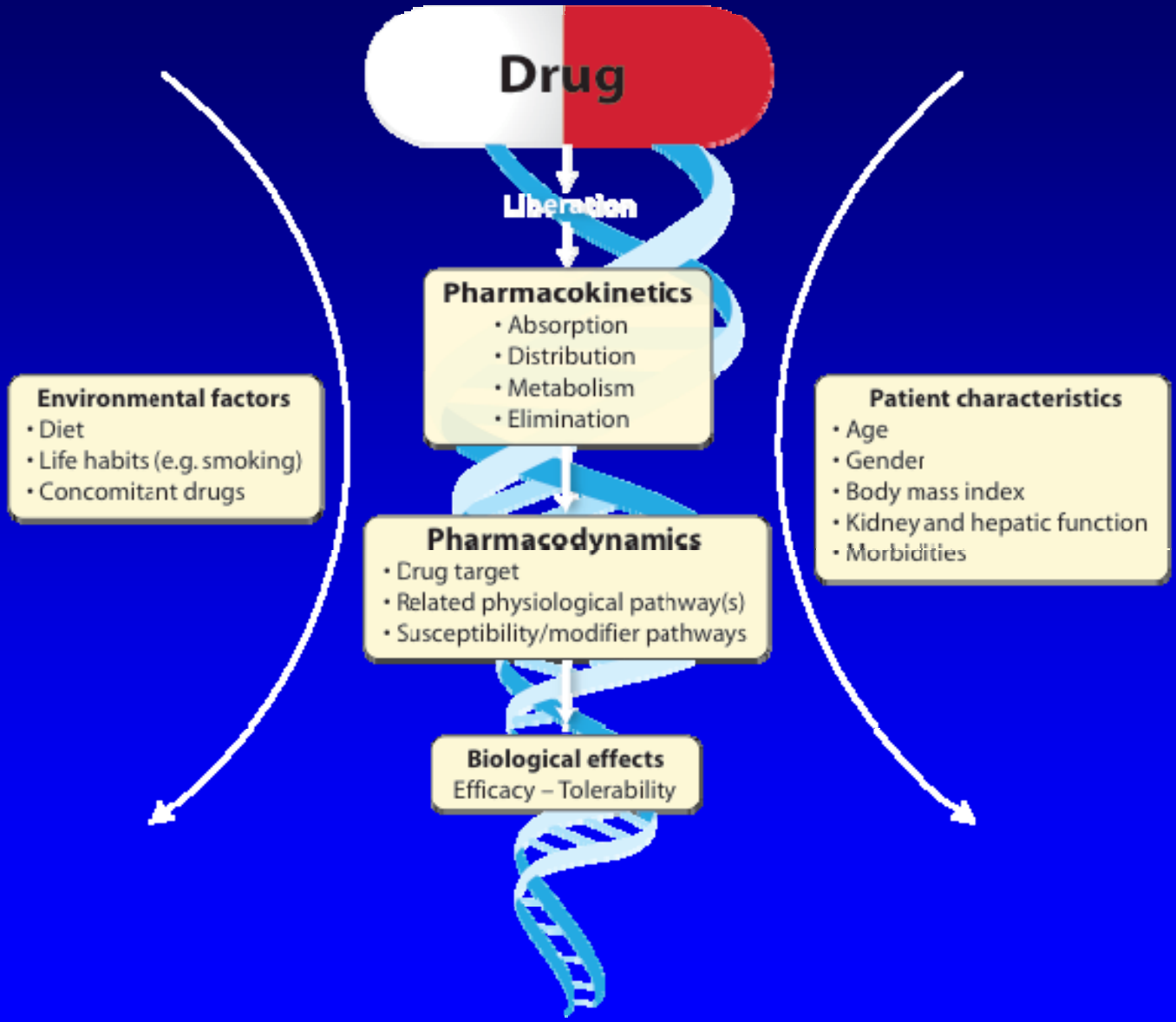
| | Substrates | Variant alleles | Alteration in function | Allele frequencies (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | White | Black | Asian | Chinese | Japanese |
| CYP2C8 (refs. 21,22) | Repaglinide Paclitaxel | *2 | Reduced | 0.4 | 18 | — | — | 0 |
| | | *3 | Reduced | 13; 15 | 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) | [illegible]meprazole 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.

# The Treatment of CV diseases; "A One Size Fits All Approach "

- **The efficacy and safety of drugs are established in populations.**
- **In practice, we treat individuals.**

# Pharmacogenomics is complex (genetics)




de Denus S, et al. Pharmacogenomics. In : Clinical approach to cardiac death syndromes. R Brugada, ed. Spinger; 2010:273-287.