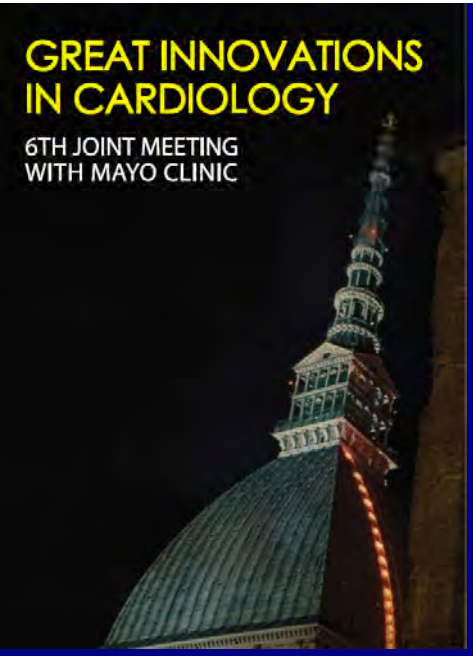

Clopidogrel: are pharmacogenetics and drug interactions clinically relevant?

Leonardo Bolognese
Cardiovascular Department, Arezzo, Italy

ISO 9001

Doctors give drugs of which they know little, into bodies, of which they know less, for diseases of which they know nothing at all

Voltaire

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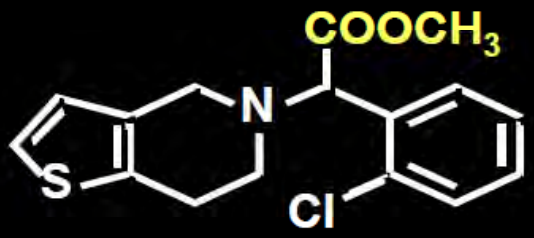
ISO 9001

Is clopidogrel pharmacogenetics clinically relevant?

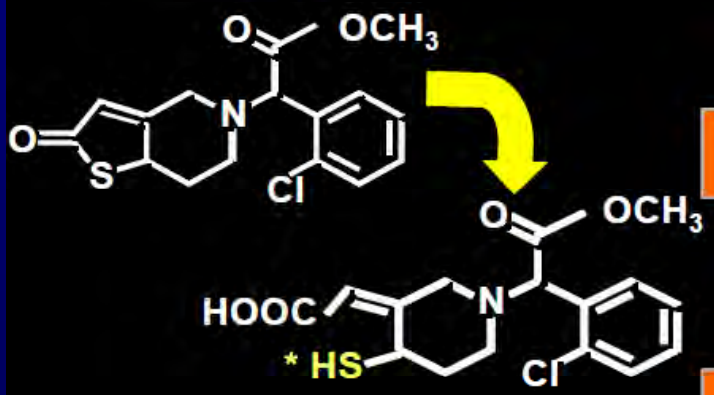
What is Known. What is uncertain. Why is it so confusing?

- **Clopidogrel response is variable and is a PK problem affected by genotype**

Genetic targets potentially modulating Clopidogrel induced antiplatelet effects



Clopidogrel



Pro-drug

Pre-hepatic metabolism
Esterases in blood (Small Intestine)

MDR-1

Hepatic Metabolism

1 step:
CYP1A2
CYP2C19
CYP2B6

2 step:
CYP3A
CYP2C9
CYP2C19
CYP2B6

Platelet inhibition

Platelet membrane receptors
P2Y12, GP IIb/IIIa, GPIa

Marin et al, JACC 2009, 54: 1041-1057

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Full Genotype of CYP2C19

CYP2C19 variant	Effect	Allelic frequency	Carrier frequency
*2	Loss of function/co-dominant	15%	25%
*3	Loss of function	<1%	Very rare
*4	Loss of function/recessive	1%	2%
*5	Loss of function	<1%	Very rare
*6	Loss of function	<1%	Very rare
*17	Increased function	20%	35%

Frequency in European population, *2 more prevalent in African and Asian populations

Is clopidogrel pharmacogenetics clinically relevant?

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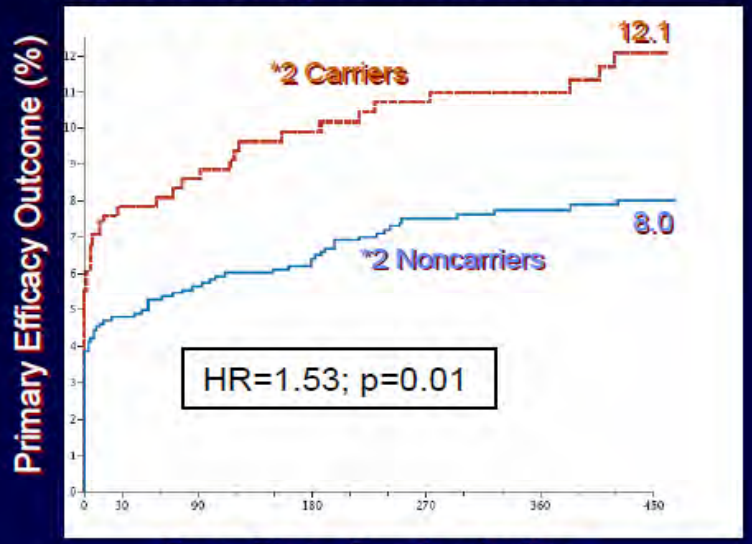
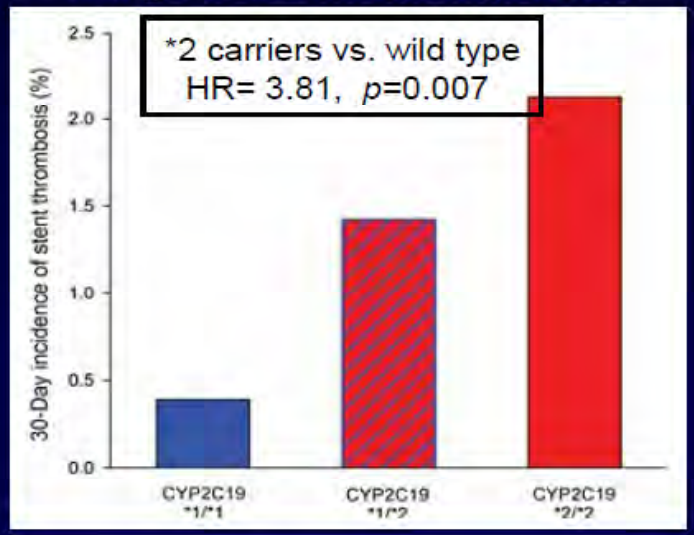
- Clopidogrel response is variable and is a PK problem affected by genotype
- Retrospective studies suggest that CYP2C19 *2 carriers may have an adverse outcome

Reduced Function CYP2C19 SNP is A Risk Factor for Post-PCI Ischemic Events in Patients Treated with Clopidogrel

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

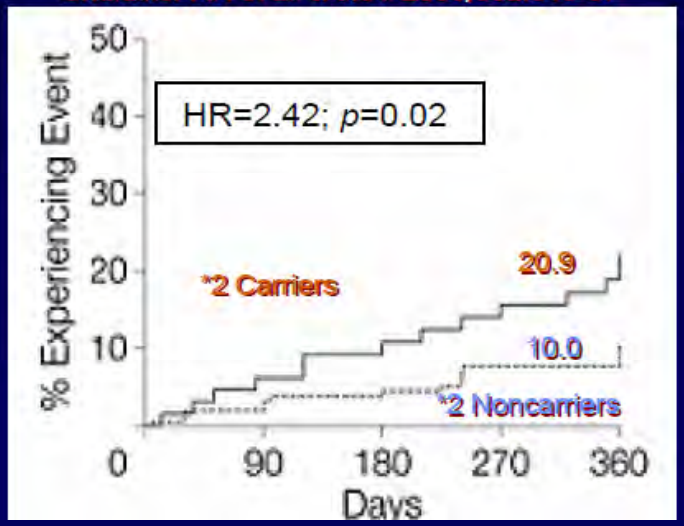


Sibbing D et al. *Eur Heart J.* 2009;30:916-22



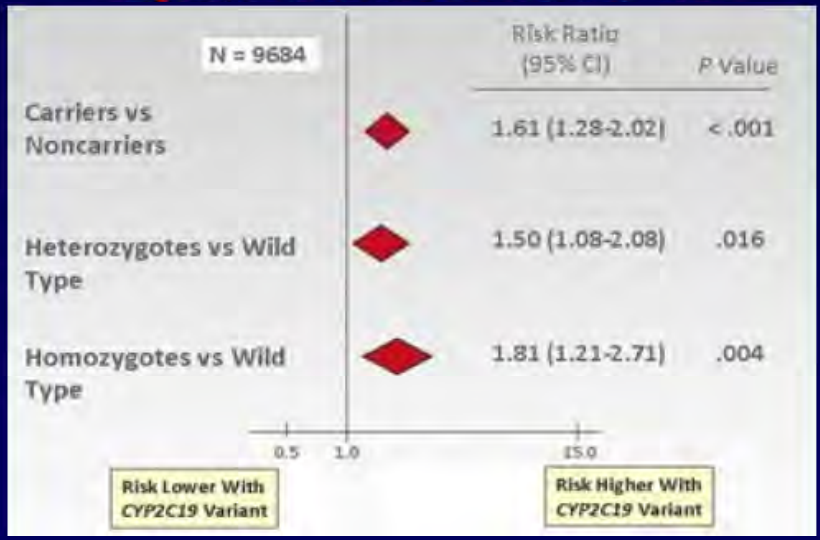
PCI-Elective Stenting

Shuldiner AR et al. *JAMA.* 2009;302:849-57



Collaborative Metaanalysis:2C19 and MACE

Mega JL, AHA November 2009:Orlando, Florida



Pifalls of available evidence

- None of the studies were randomized, the possibility of bias and confounding variables cannot be excluded
- Clopidogrel nonresponders may have been preselected and overrepresented in some studies
- Observational analyses do not include untreated controls
- The data on positive and predictive risk in specific patient populations are incomplete

Clopidogrel Poor Metabolizers

FDA Statement

- FDA, March 2010 (clopidogrel boxed warning)

  "Clopidogrel may be less effective in people who are unable to metabolize the drug because of low CYP2C19 activity"

  "Be aware that tests are available to determine CYP2C19 genotype"

  "Consider use of other antiplatelet meds or alternative dosing strategies for clopidogrel"

Is clopidogrel pharmacogenetics clinically relevant?

What is Known. What is uncertain. Why is it so confusing?

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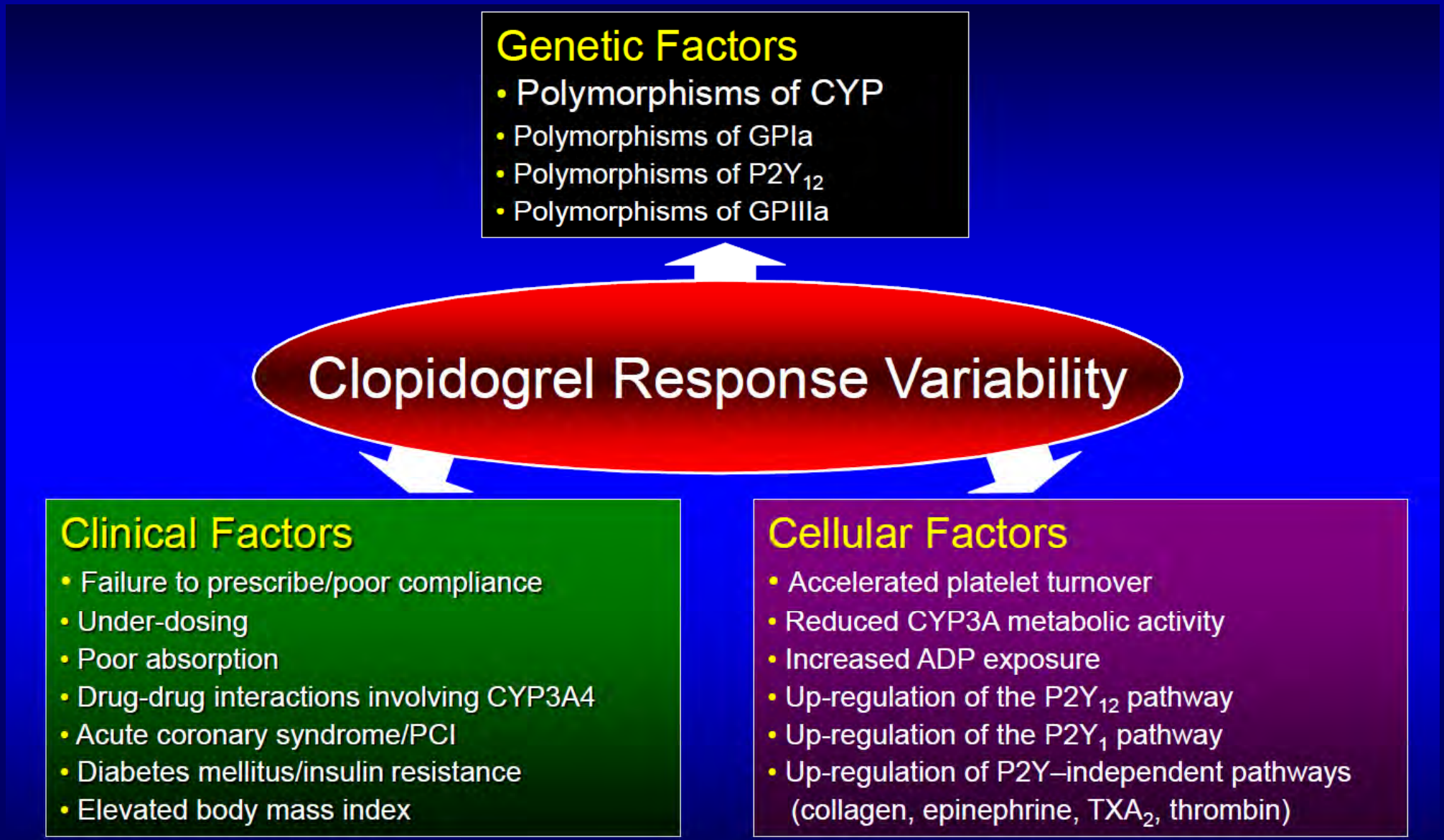
- **The variability in clopidogrel response is multifactorial**



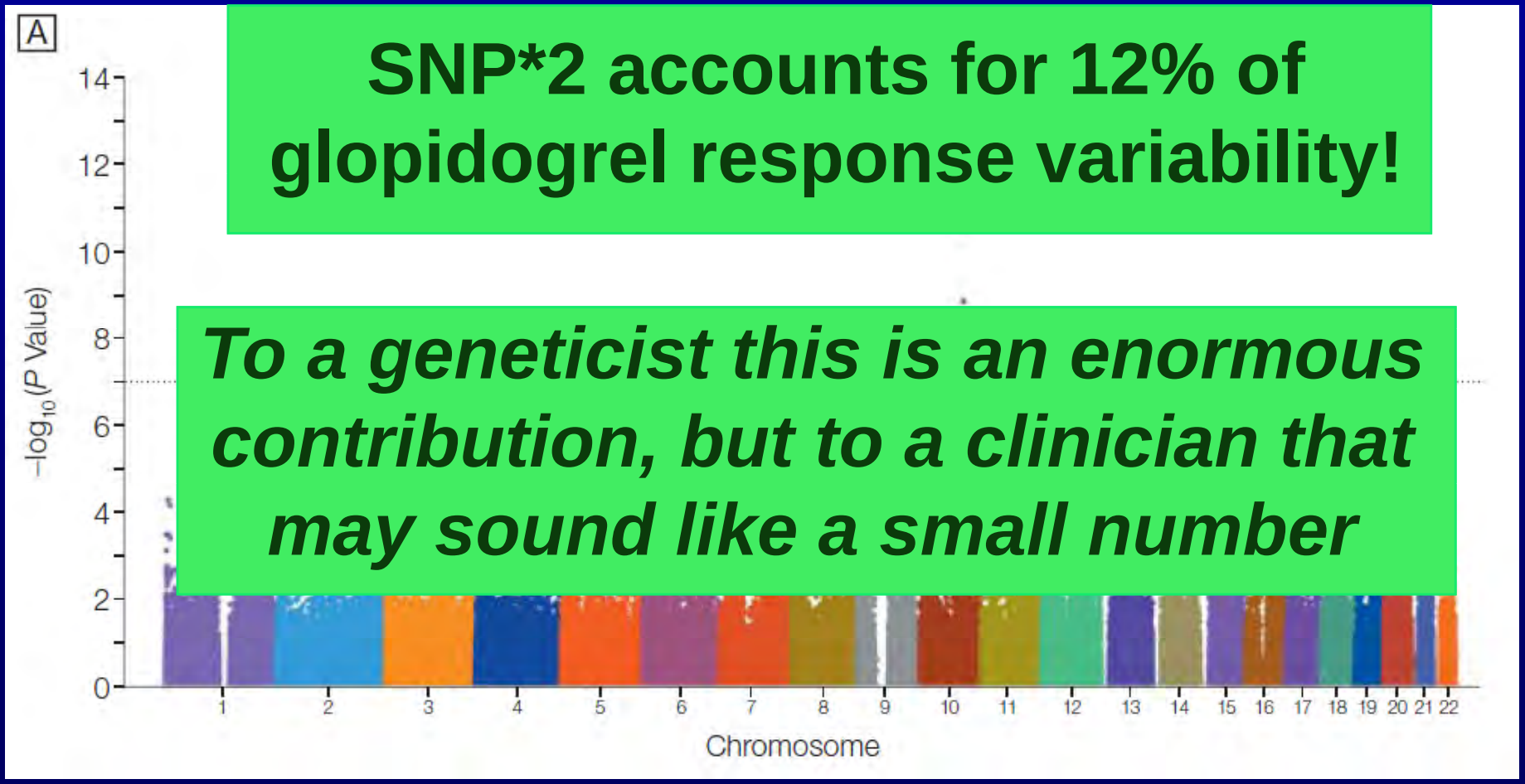
Angiolillo Dj et al. J Am Coll Cardiol 2007; 49:1505

Genome-wide Association Study Demonstrated that CYP 2C19*2 is the Sole SNP Associated with Clopidogrel Response Variability

How Much Does Carrier Status Matter?

SNP*2 accounts for 12% of glopidogrel response variability!

To a geneticist this is an enormous contribution, but to a clinician that may sound like a small number



Sculdiner AR et al. JAMA 2009; 302: 849

How Much Does Carrier Status Matter?

	partial η^2	P
*CYP2C19*2* polymorphism	0.052	<0.001
Age (per year)	0.010	0.006
Arterial hypertension	0.001	0.386
Diabetes mellitus	0.012	0.003
Body mass index (kg/m^2)	0.010	0.008
Platelets (x10^9/L)	0.010	0.006
ACE inhibitors	0.001	0.403
Nitrates	<0.001	0.890
Verapamil/Diltiazem	0.010	0.006
Previous balloon angioplasty	0.007	0.026
Previous CABG	0.001	0.435
Impaired LV function	<0.001	0.945
CCS Angina class III or IV	0.004	0.081

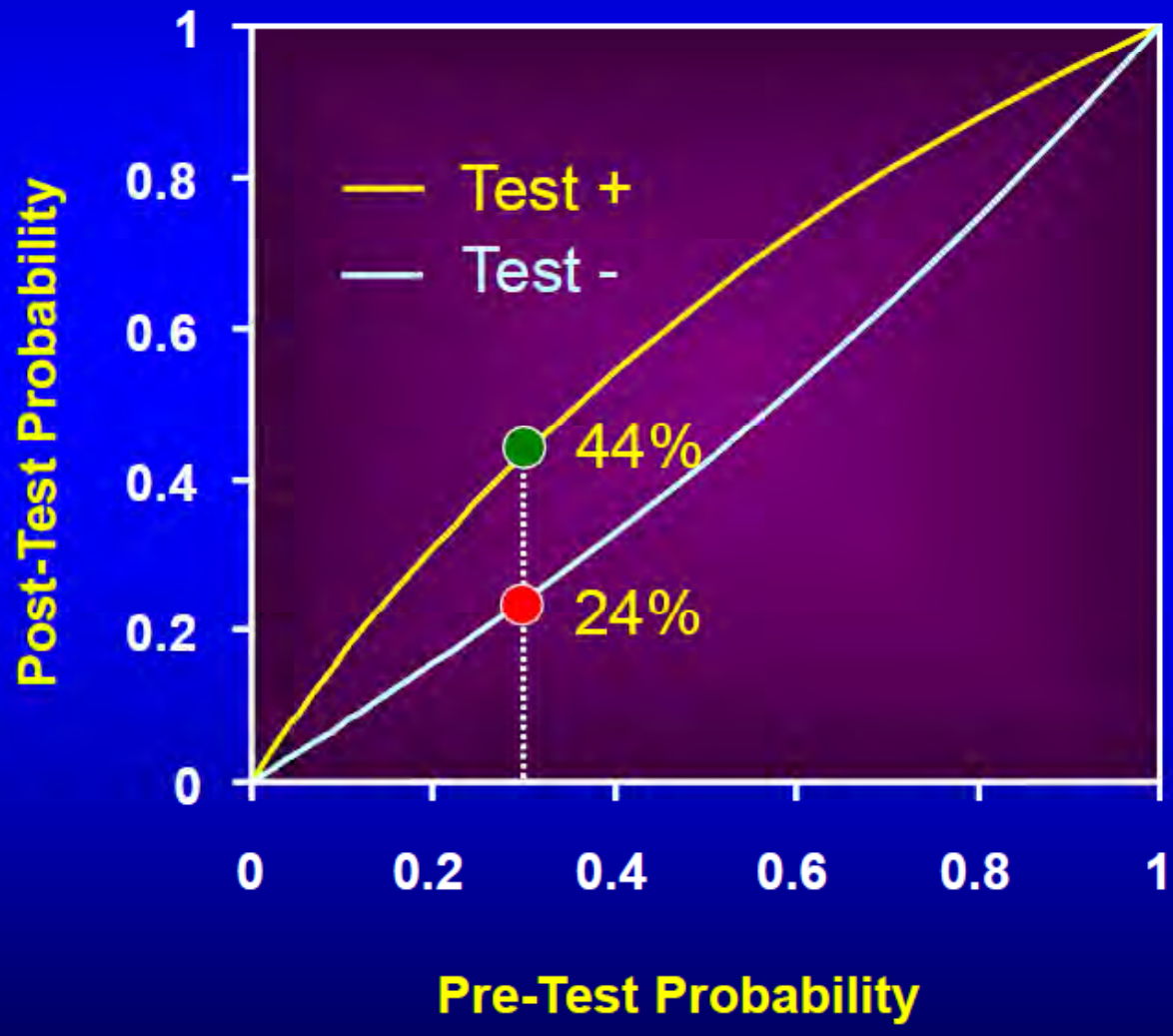
11.5% of variability in RPA explained by the whole model (5.2% by CYP2C19)

Sensitivity 45%
Specificity 75%

Hochholzer, et al. J Am Coll Cardiol 2010

EXCELSIOR: CYP2C19 and High Platelet Reactivity

How Good is the Test?

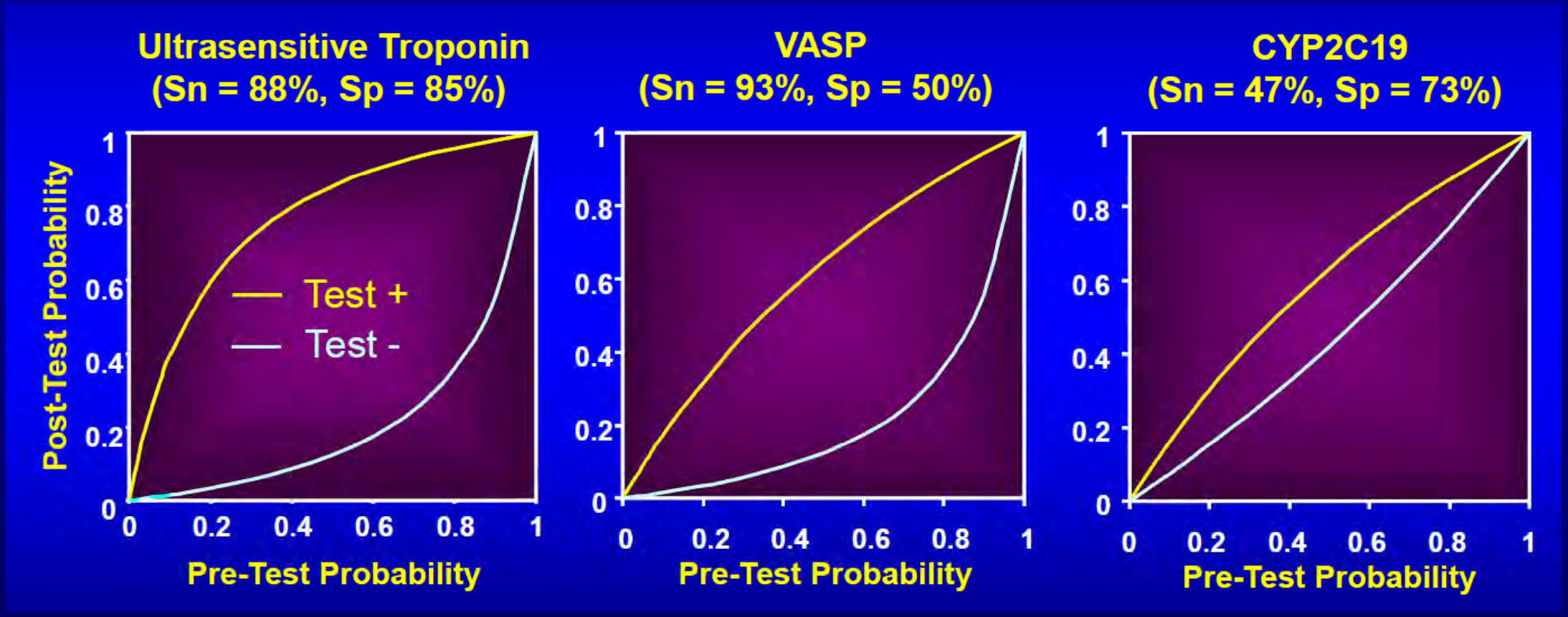


Sn=45%
Sp=75%
LR+ = 1.8
LR- = 0.7
AUC=0.65

Hochholzer W et al. J. Am. Coll. Cardiol. 2010;55;2427

Predicitve Performance of Prognostic Tests

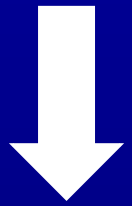
Football, Banana, or a Carrot



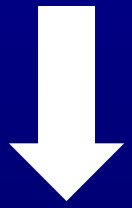
Football >> banana > carrot

Is clopidogrel response pathway so simple?

Clopidogrel



Bioactivation (by a single gene product)



Effect

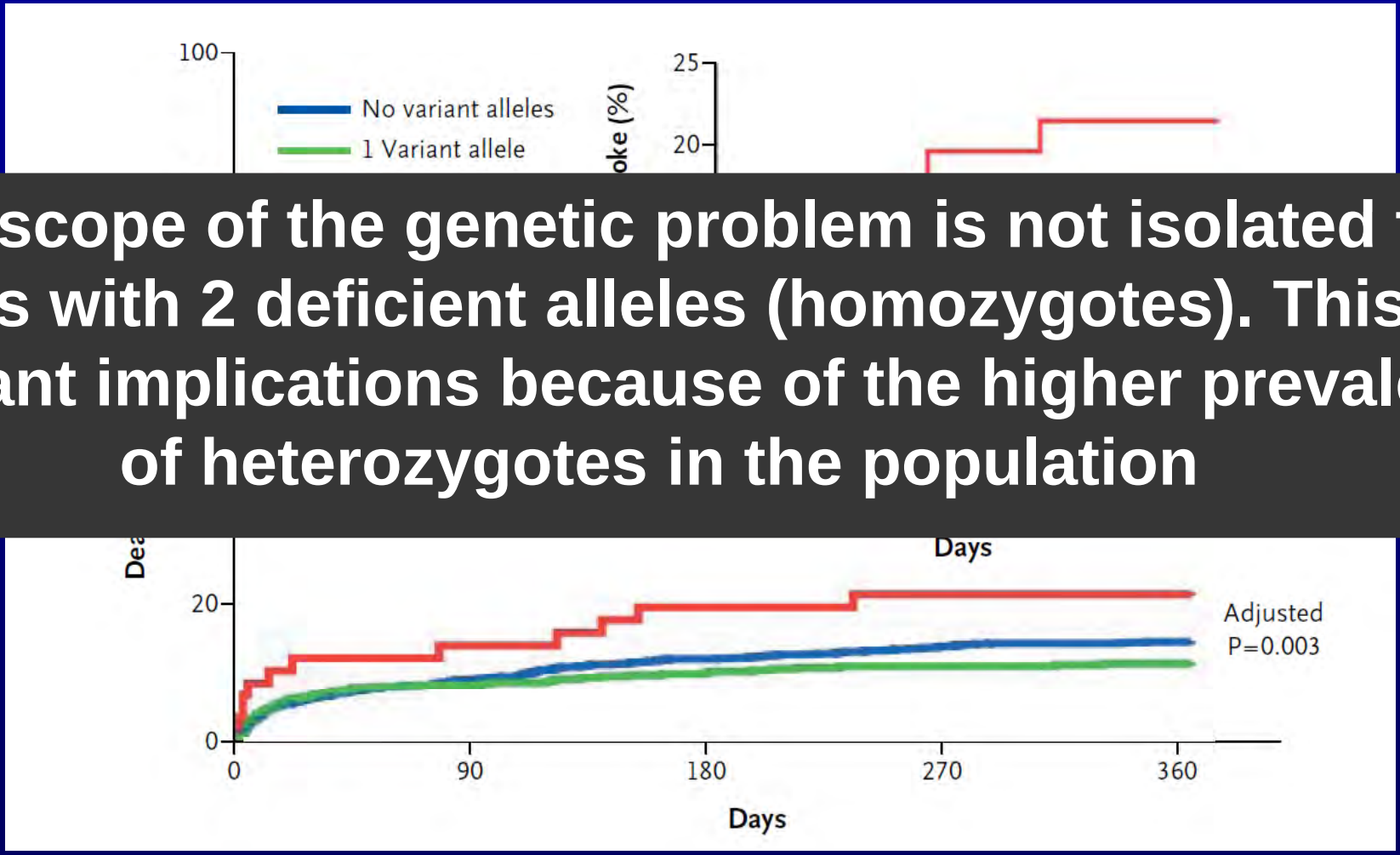
The reality is that biology is often much more complicated than a few arrows on a simple linear drug response pathway!

Is clopidogrel pharmacogenetics clinically relevant?

What is Known. What is uncertain. Why is it so confusing?

- Clopidogrel response is variable and is a PK problem affected by genotype
- Retrospective studies suggest that CYP2C19 *2 carriers may have an adverse outcome
- The variability in clopidogrel response is multifactorial
- **Homozygotes vs heterozygotes**

Estimated Rates of Death, Nonfatal MI, or Stroke, According to Characteristics of Variant-Allele Polymorphisms: The FAST-MI Registry



The scope of the genetic problem is not isolated to patients with 2 deficient alleles (homozygotes). This has important implications because of the higher prevalence of heterozygotes in the population

Simon T et al. N Engl J Med 2009;360:363-75

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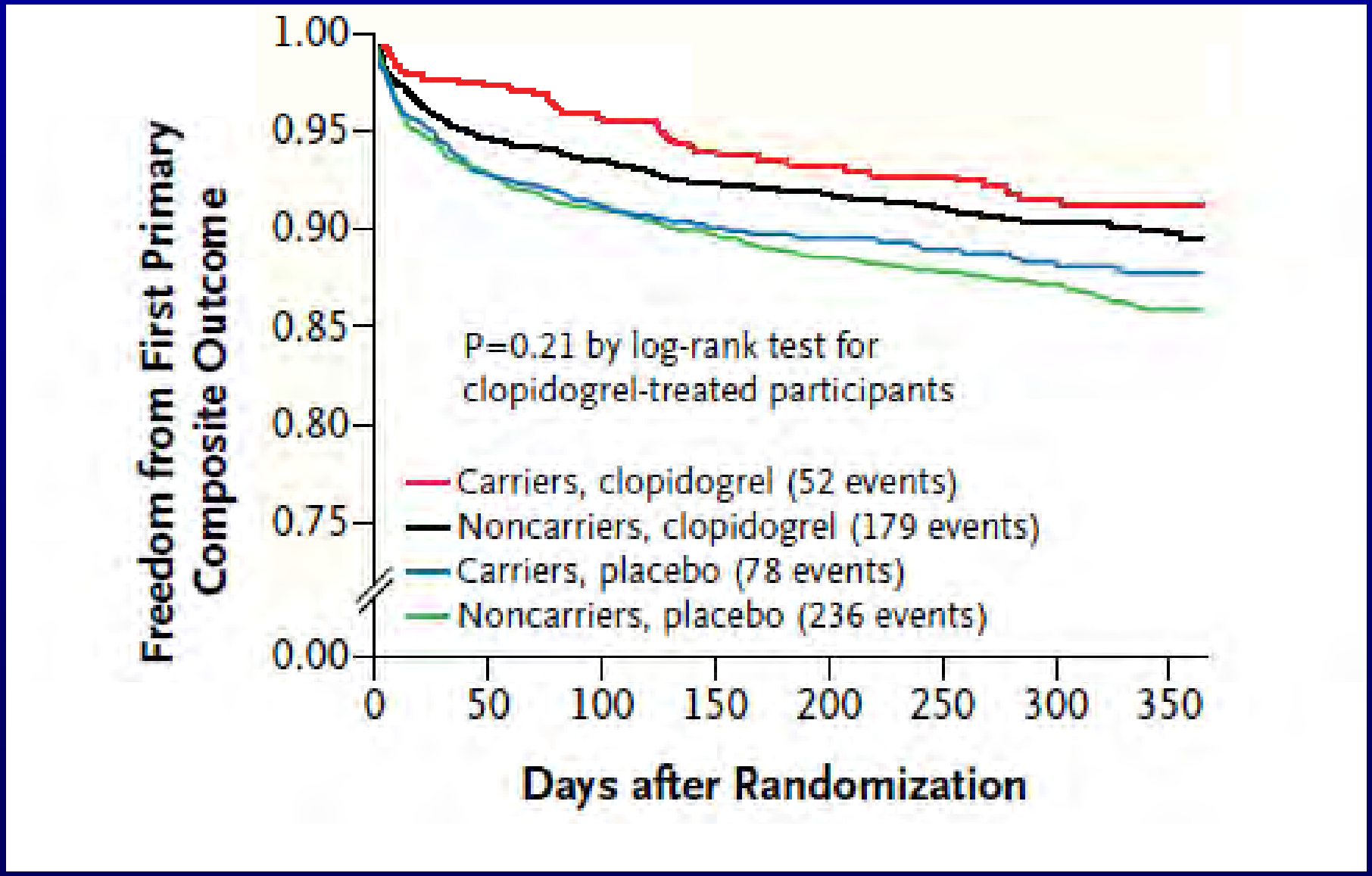
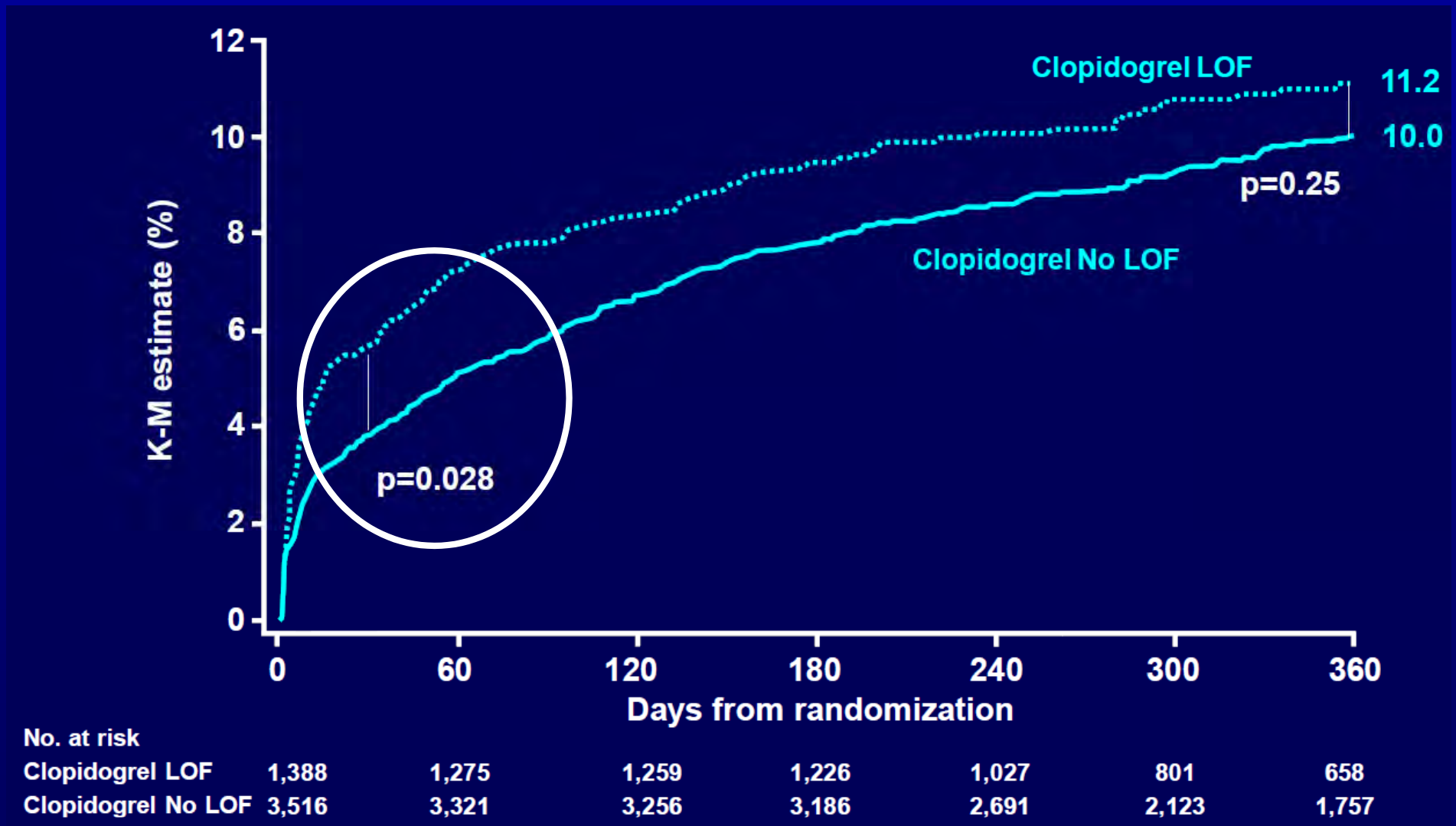
- Retrospective studies suggest that CYP2C19 *2 carriers may have an adverse outcome
- The variability in clopidogrel response is multifactorial
- Homozygotes vs heterozygotes
- ***CYP2C19 LOF*** **variants do not modify the efficacy and safety of clopidogrel in the chronic phase of treatment**

First Primary Composite Outcome According to Loss-of-Function Allele Carrier Status in the CURE Trial



Parè G et al. N Engl J Med August 2010 (online)

Primary endpoint in the clopidogrel group in relation to any CYP2C19 LOF allele



No. at risk							
Clopidogrel LOF	1,388	1,275	1,259	1,226	1,027	801	658
Clopidogrel No LOF	3,516	3,321	3,256	3,186	2,691	2,123	1,757

Wallentin L et al. Lancet 2010:376, Online August 29, 2010

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- The variability in clopidogrel response is multifactorial
- Homozygotes vs heterozygotes
- *CYP2C19 LOF* variants do not modify the efficacy and safety of clopidogrel in the chronic phase of treatment
- **Ischemic events not predicted consistently, low PPV**

Predictive Performance of Platelet Genotyping

Effect	Sn	Sp	PPV	NPV	LR+	LR-	AUC
CYP2C19 for MACE							
CURE	0.27	0.67	8%	89%	0.81	1.10	0.45
ACTIVE A	0.39	0.67	22%	83%	1.20	0.90	0.55
TRITON	0.36	0.74	12%	92%	1.36	0.87	0.57
PLATO	0.31	0.72	11%	91%	1.11	0.96	0.52
Hulot meta-analysis	0.33	0.72	10%	92%	1.17	0.93	0.54

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- The variability in clopidogrel response is multifactorial
- Homozygotes vs heterozygotes
- *CYP2C19 LOF* variants do not modify the efficacy and safety of clopidogrel in the chronic phase of treatment
- Ischemic events not predicted consistently, low PPV
- **No studies have been published to define a clinical strategy that would exploit this pharmacogenetic information to optimize outcomes with clopidogrel**

Strategies to Improve Clopidogrel Response

- Increase clopidogrel dose
- Change to ticlopidine
- Give CYP inducers (rifampin, St Johns Wort, etc.)
- Give Triple antiplatelet regimen (Cilostazol)
- Give tailored peroprocedural GPI (HPR pre or post-procedure?)
- New pharmacologic agents (Prasugrel,Ticaglegor)

CLINICAL ALERT

ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning"

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association

Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

Writing Committee Members

David R. Holmes, Jr, MD, FACC, FSCAI, *Chair**
Gregory J. Dehmer, MD, FACC, FAHA, FSCAI, FACP*
Sanjay Kaul, MBBS, FACC, FAHA*
Dana Leifer, MD, FAHA†
Patrick T. O'Gara, MD, FACC, FAHA†
C. Michael Stein, MD†

*American College of Cardiology Foundation Representative;
†American Heart Association Representative

"The evidence base is insufficient to recommend either genetic testing or platelet function testing at the present time"

Holmes DR et al. J. Am. Coll. Cardiol. 2010;56;321-341

J. Am. Coll. Cardiol. 2010;56;919-933

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JACC White Paper

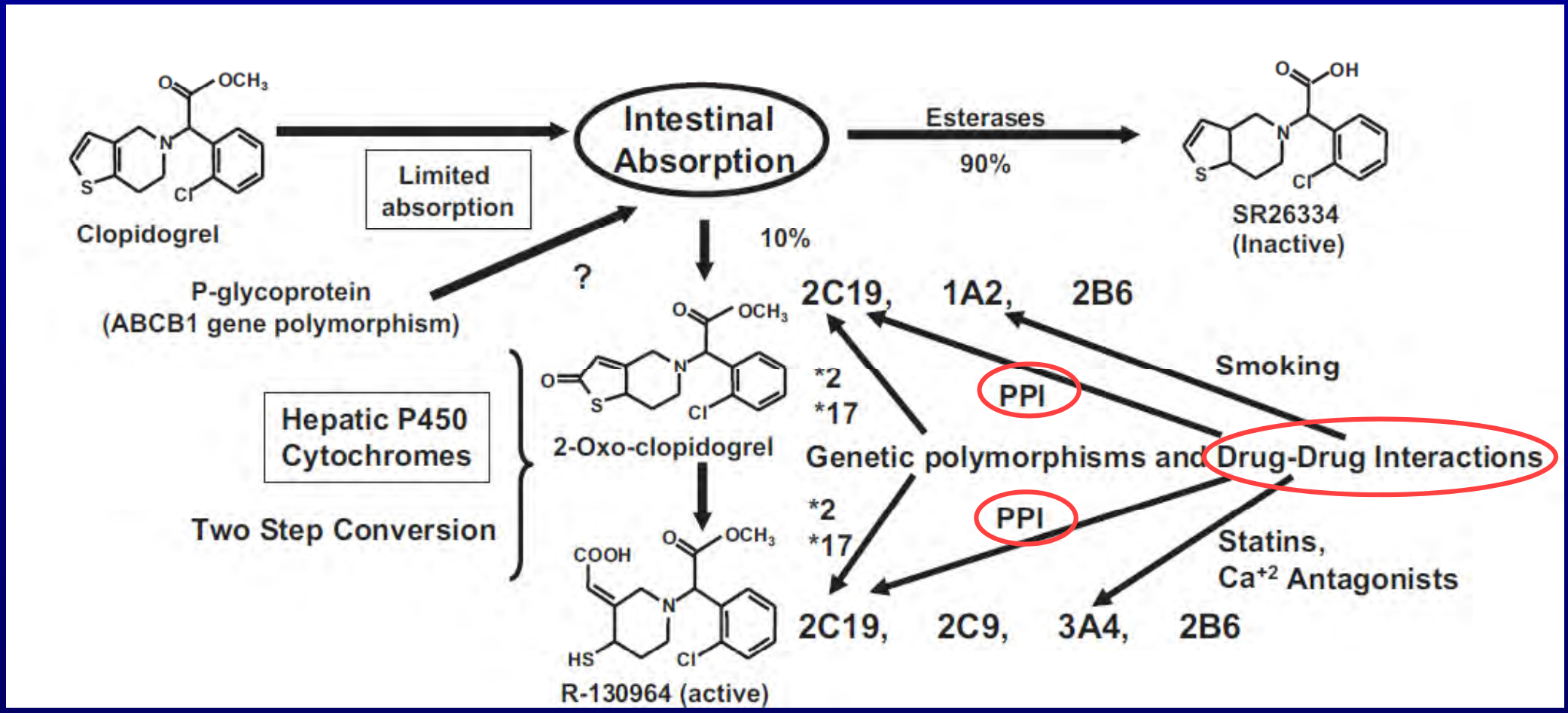
Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate

Laurent Bonello, MD,* Udaya S. Tantry, PHD,§§ Rossella Marcucci, MD, PHD,‖ Ruediger Blindt, MD,# Dominick J. Angiolillo, MD, PHD,‖‖ Richard Becker, MD,¶¶ Deepak L. Bhatt, MD, MPH,## Marco Cattaneo, MD,¶ Jean Philippe Collet, MD, PHD,‡ Thomas Cuisset, MD,† Christian Gachet, MD, PHD,§ Gilles Montalescot, MD, PHD,‡ Lisa K. Jennings, PHD,*** Dean Kereiakes, MD,††† Dirk Sibbing, MD,** Dietmar Trenk, PHD,†† Jochem W. Van Werkum, MD, PHD,‡‡ Franck Paganelli, MD,* Matthew J. Price, MD,‡‡‡ Ron Waksman, MD,§§§ Paul A. Gurbel, MD,§§
for the Working Group on High On-Treatment Platelet Reactivity

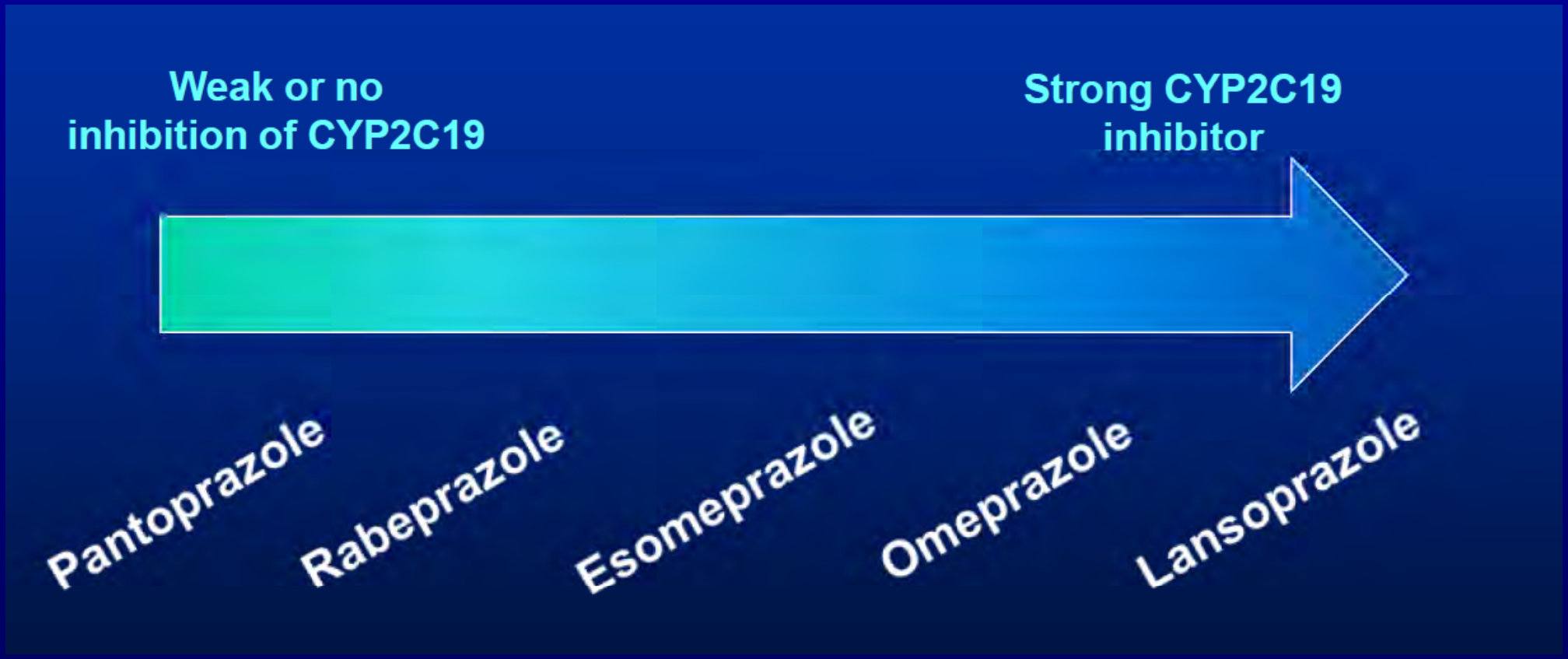
Marseille, Paris, and Strasbourg, France; Florence, and Milano, Italy; Aachen, Munich, and Bad Krozingen, Germany; Nieuwegein, the Netherlands; Baltimore, Maryland; Jacksonville, Florida; Durham, North Carolina; Boston, Massachusetts; Memphis, Tennessee; Cincinnati, Ohio; La Jolla, California; and Washington, DC

Until the results of large-scale trials of personalized antiplatelet therapy are available, the routine use of platelet function measurements in the care of patients with cardiovascular disease cannot be recommended

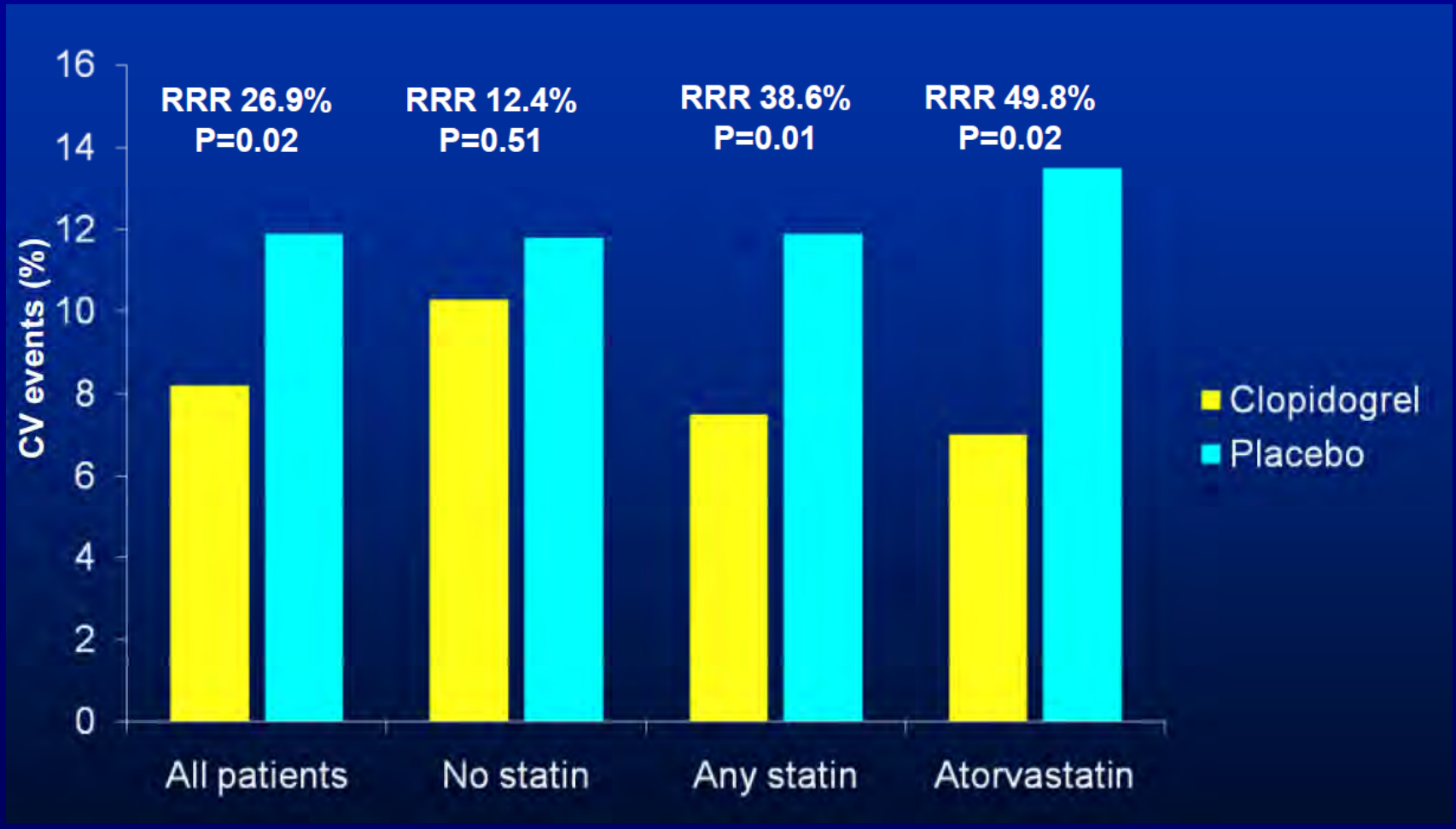
Clopidogrel response variability; the role of drug-drug interactions



Degree of CYP2C19 Inhibition



Déjà vu all over again?



Saw et al. Circulation 2003

Why a so much attention to the recently postulated drug interaction between PPIs and clopidogrel?

- **The blockbuster status of the implicated drugs**
- **A theoretically at-risk population in the tens of millions**
- **Guidelines that recommend near-universal use of PPIs in patients taking clopidogrel, most of whom will also be taking aspirin**
- **Skepticism about the clinical importance of this drug interaction**

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ISO 9001

Independent predictors of increased risk of GI bleeding in high risk survivors of MI: the VALIANT Trial

	Hazard ratio	95% Confidence interval	Z-score	*P*-value
Dual antiplatelet therapy	3.18	1.91–5.29	4.44	<0.001
Non-white race	3.26	1.89–5.61	4.26	<0.001
History of alcohol abuse	4.71	2.02–11.01	3.58	<0.001
Age (10 year increment)	1.51	1.21–1.90	3.57	<0.001
NYHA class 3 or 4	2.27	1.41–3.64	3.39	0.001
Anticoagulant therapy	2.13	1.28–3.52	2.93	0.003
Diabetes	1.76	1.13–2.74	2.48	0.013
eGFR (10 mL/min/ 1.73 m^2 decrement)	1.18	1.03–1.34	2.44	0.015
Male sex	1.82	1.10–3.01	2.32	0.021

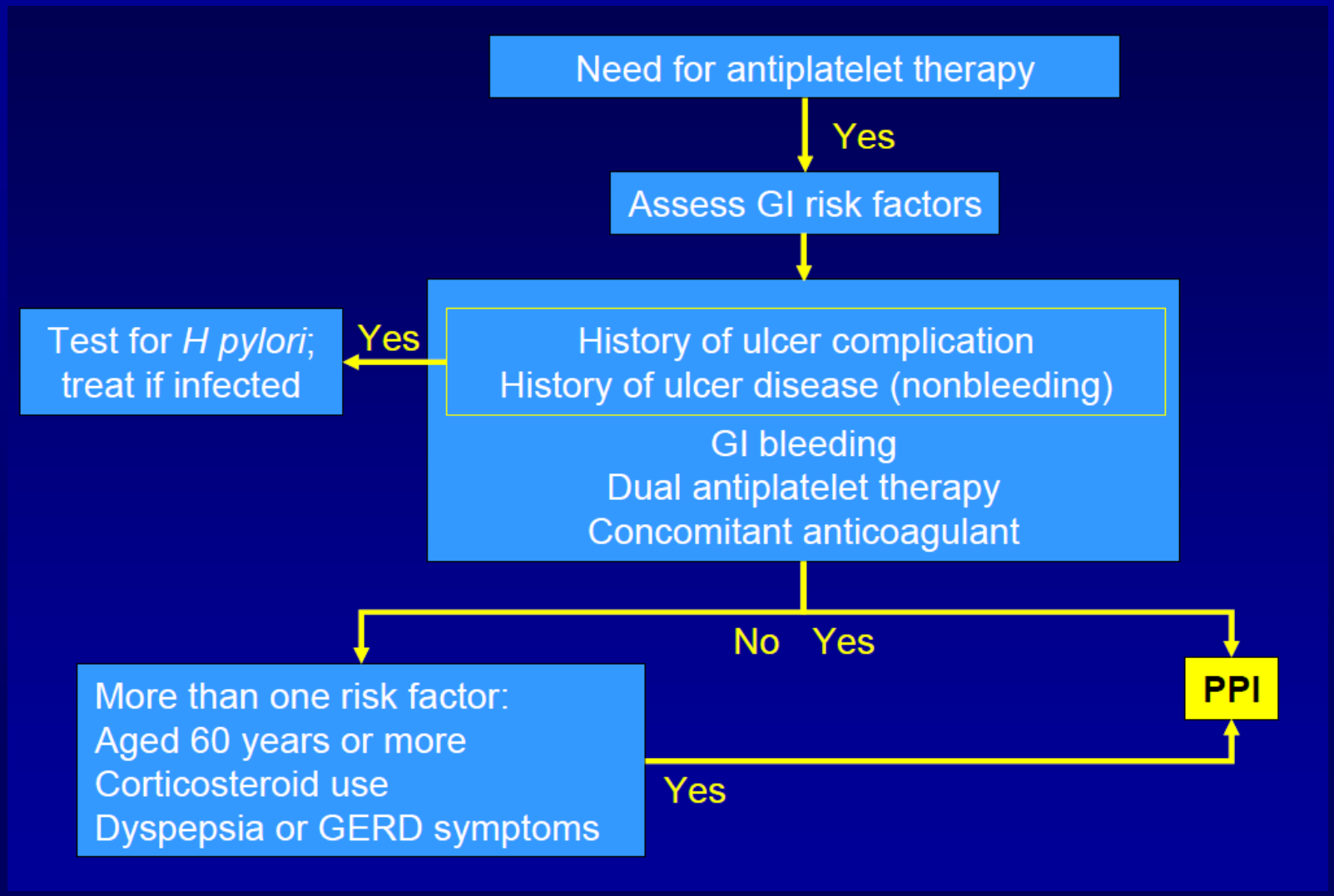
Moukarbel GV et al. Eur Heart J 2009; 30; 2226–2232

EXPERT CONSENSUS DOCUMENT

ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents

Bhatt DL et al. JACC 2008;52:1502



EMEA and FDA statements May 2009

EMEA

"The product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPIs unless absolutely necessary"

FDA

"Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole."

Where is then evidence of clopidogrel/PPIs interaction?

- ✓Ex-vivo studies
- ✓Observational studies
- ✓Metanalyses
- ✓Randomized studies

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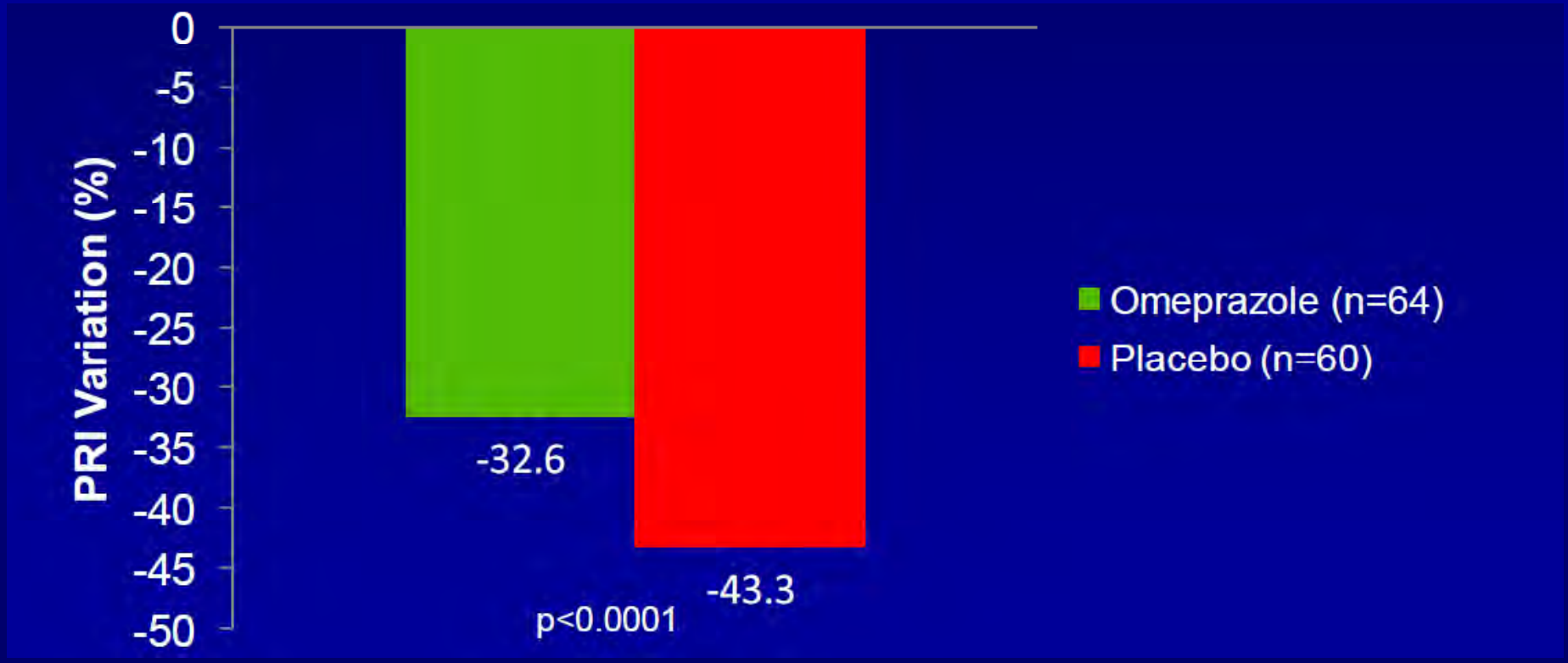
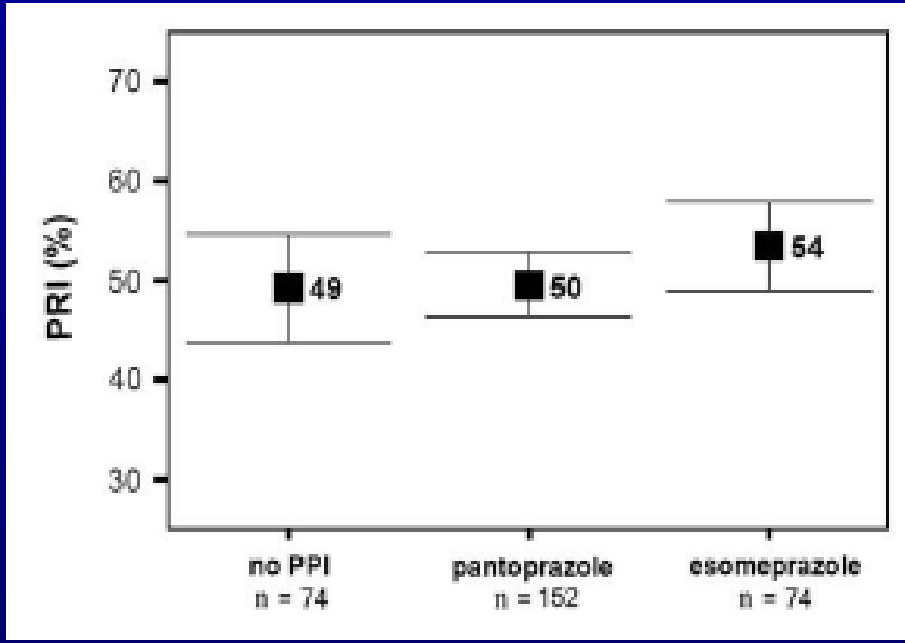
Clopidogrel and PPIs – The OCLA study

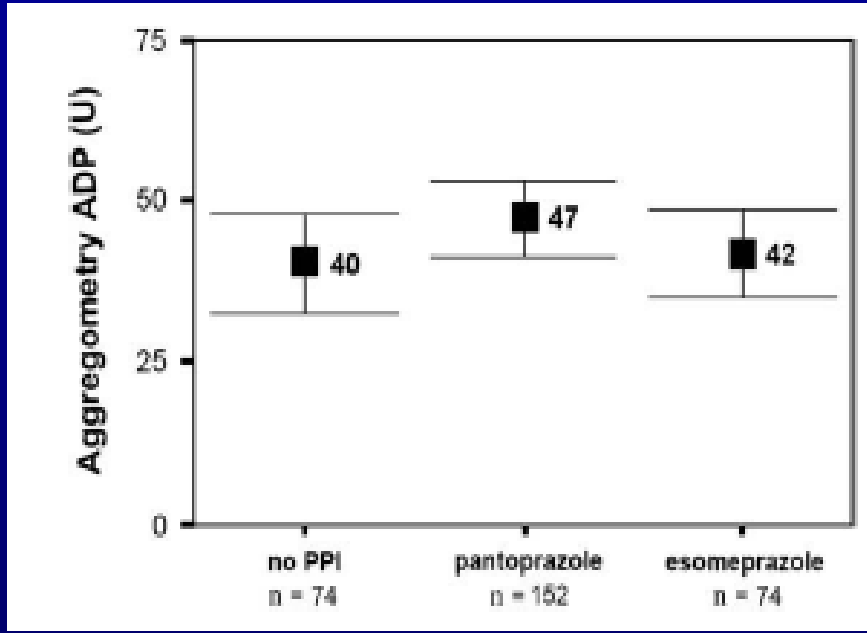


Gillard et al. JACC 2008;51:256

Intake of PPIs Not Associated With Impaired Response to Clopidogrel



Platelet reactivity index in the VASP phosphorylation assay in patients on clopidogrel with or without PPI: pantoprazole or esomeprazole.

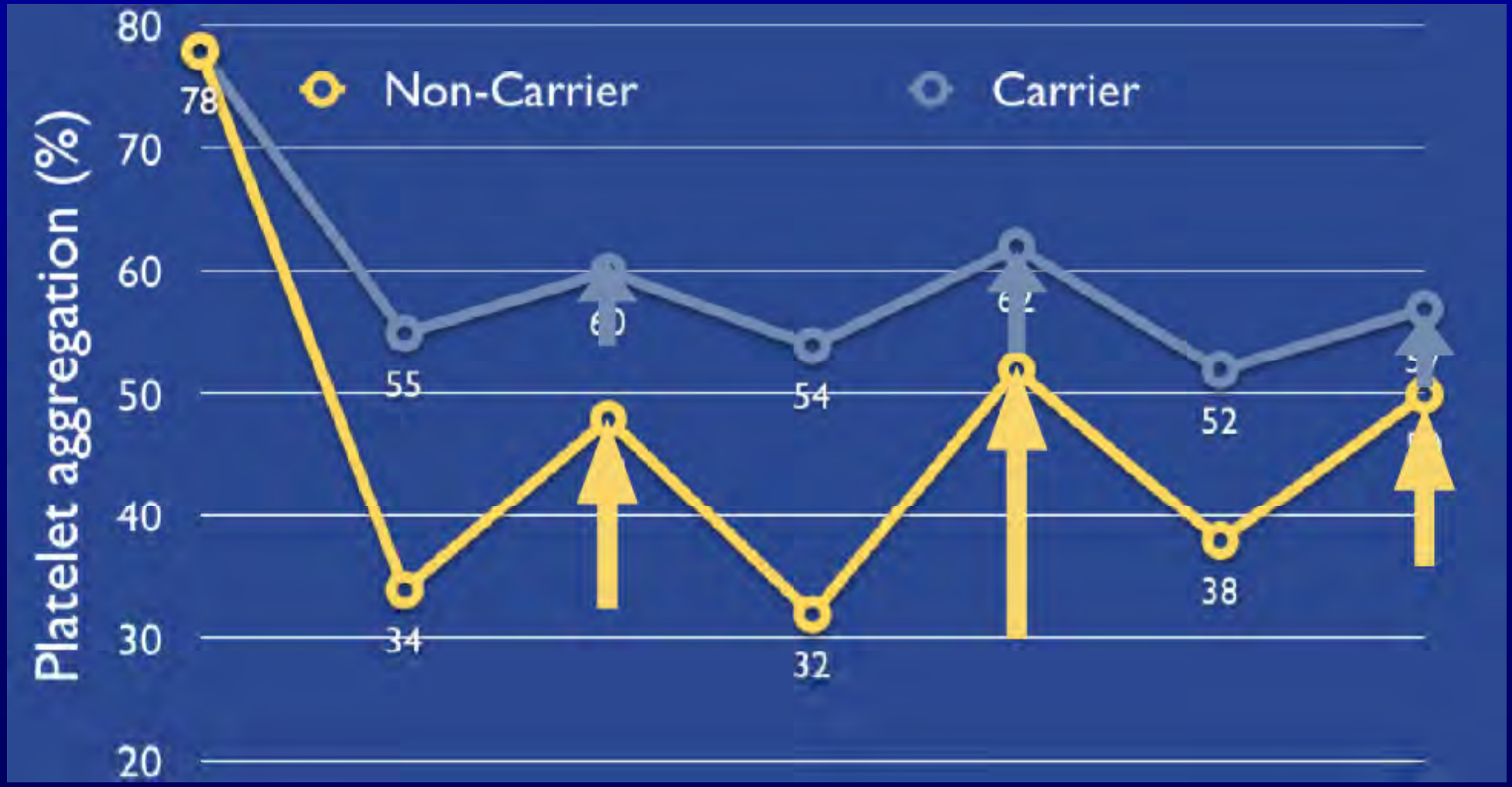


Adenosine diphosphate–induced platelet aggregation in patients on clopidogrel with or without PPI: pantoprazole or esomeprazole.

Siller-Matula JM, et al. Am Heart J. 2009;157:148.e1-148.e5.

ISO 9001

Clopidogrel-PPI interaction more relevant in noncarriers of *CYP2C19* loss-of-function gene

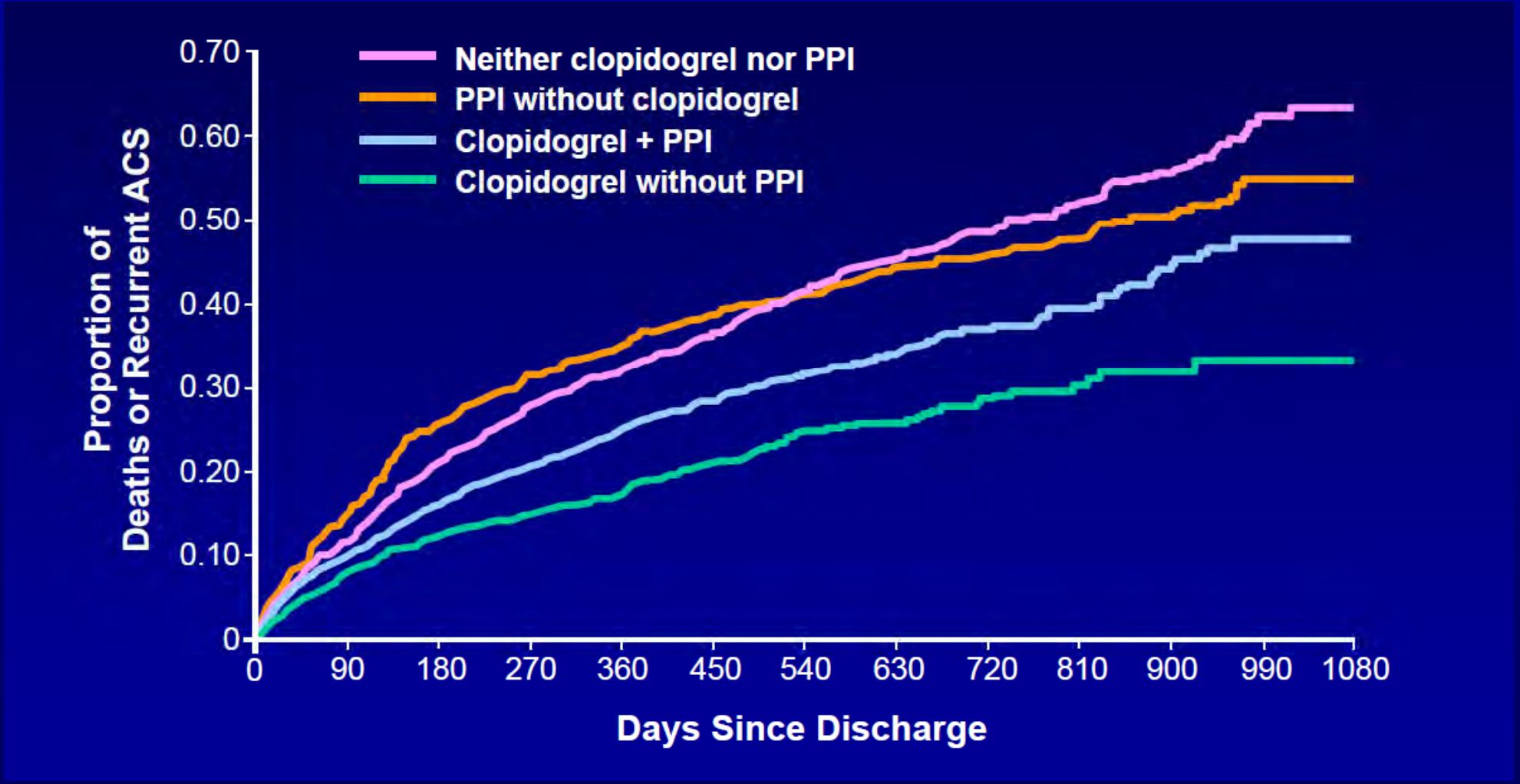


Lee JK ESC 2010

Where is then evidence of clopidogrel/PPIs interaction?

- ✓Ex-vivo studies
- ✓Observational studies
- ✓Metanalyses
- ✓Randomized studies

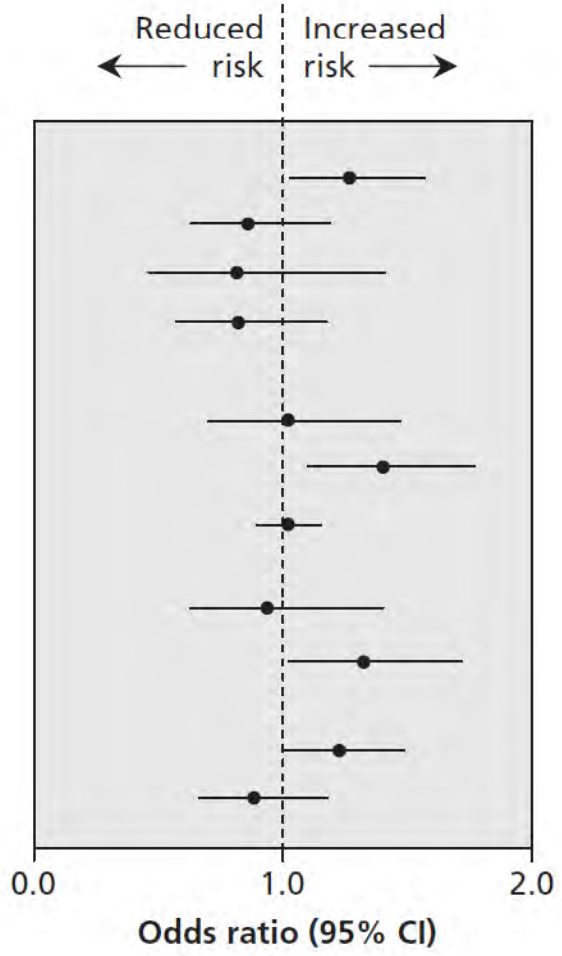
Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI



Ho PM et al. JAMA 2009; 301:937

A population-based study of the drug interaction between proton pump inhibitors and clopidogrel

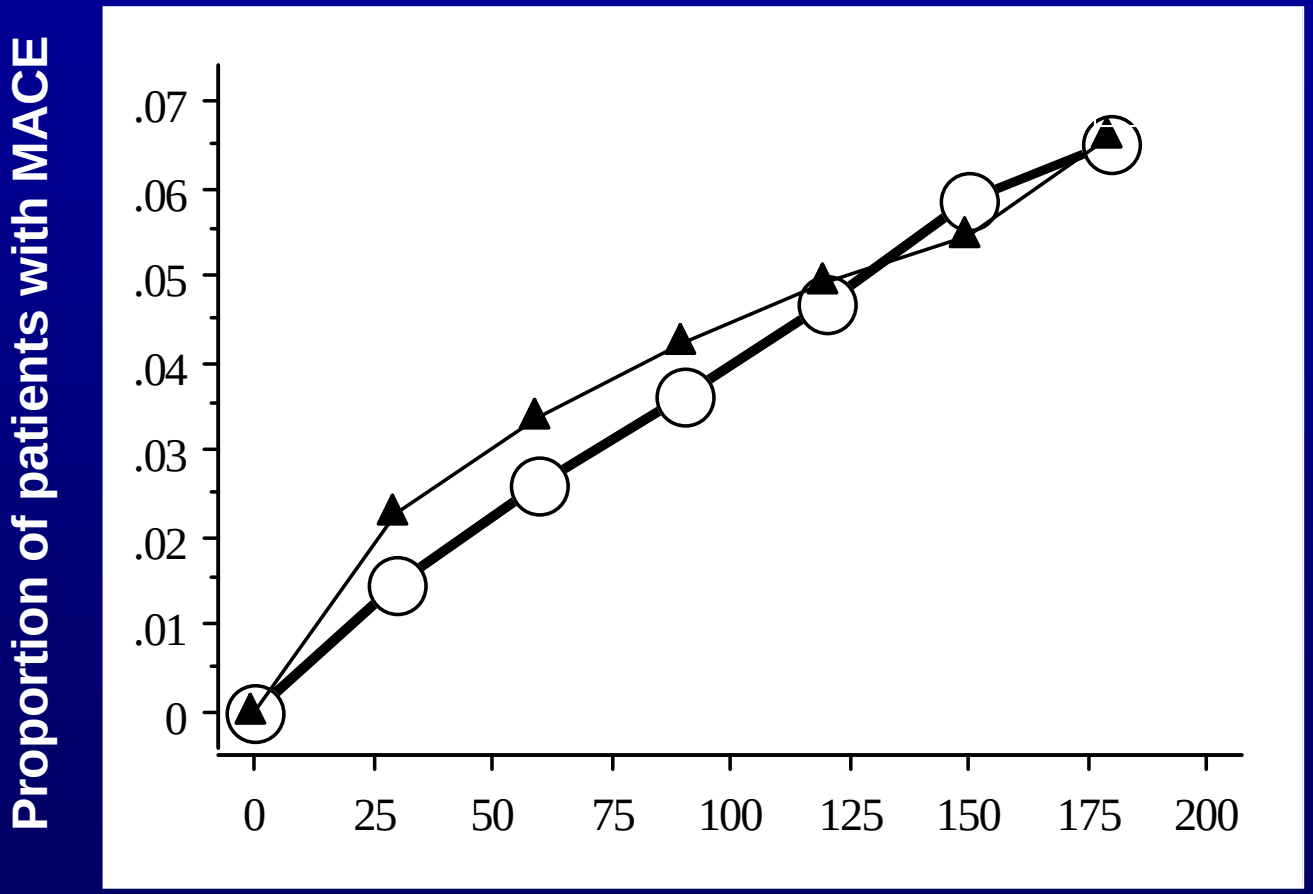
Analysis*	Cases n/N	Controls n/N	Odds ratio (95% CI)
Recurrent MI < 90 days			
Current	194/734	424/2 057	1.27 (1.03–1.57)
Previous	63/734	195/2 057	0.86 (0.63–1.19)
Remote	17/734	68/2 057	0.81 (0.46–1.41)
Death < 90 days	71/323	188/916	0.82 (0.57–1.18)
Proton pump inhibitor			
Pantoprazole	46/734	125/2 057	1.02 (0.70–1.47)
Other	148/734	299/2 057	1.40 (1.10–1.77)
Patients not receiving clopidogrel	438/6 277	1 300/17 291	1.02 (0.90–1.15)
Histamine-H_2 antagonists	37/734	106/2 057	0.94 (0.63–1.40)
Patients with no history of heart failure	134/525	319/1 638	1.33 (1.02–1.72)
Recurrent MI < 1 year	240/982	497/2 626	1.23 (1.01–1.49)
Death < 1 year	116/531	269/1 407	0.89 (0.67–1.18)



Juurlink DN et al. CMAJ 2009;180:713-8

The Influence of PPIs on Clinical Outcomes After Successful PCI insights from the Guthrie PCI Registry

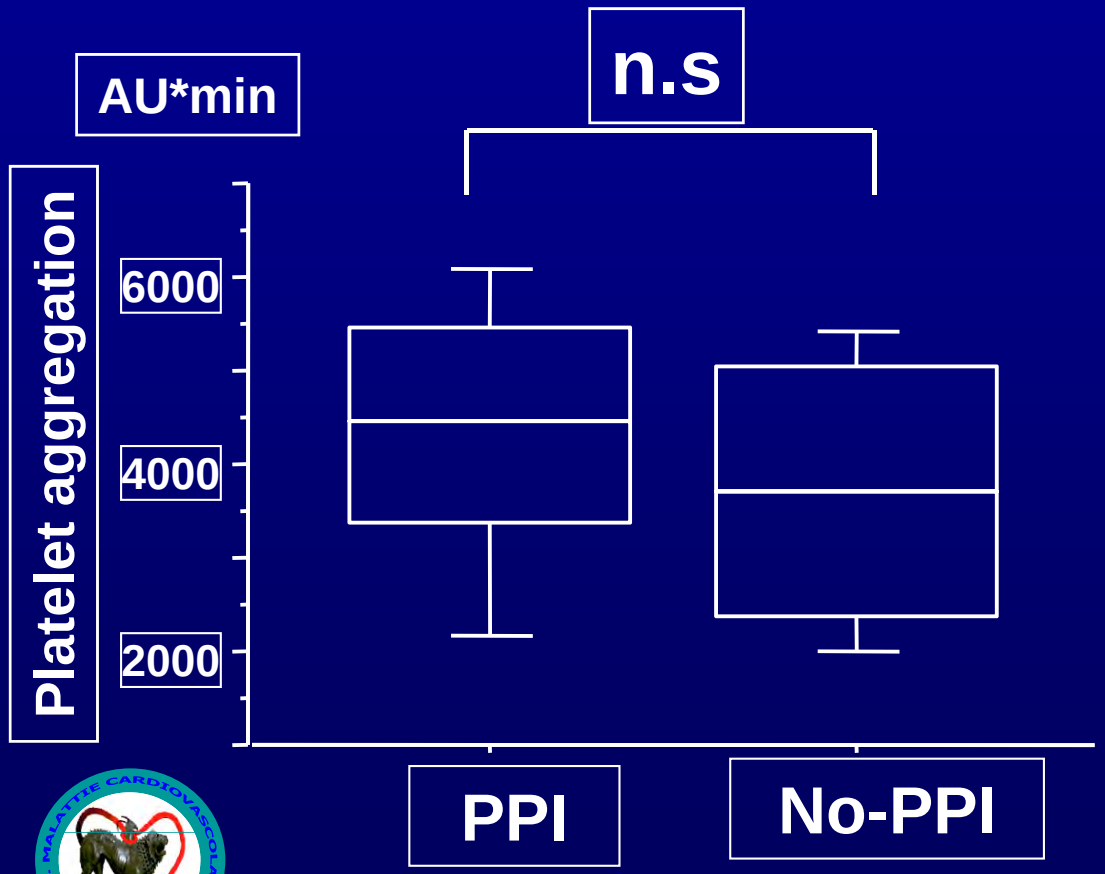
MACE: Cumulative Hazard Curves



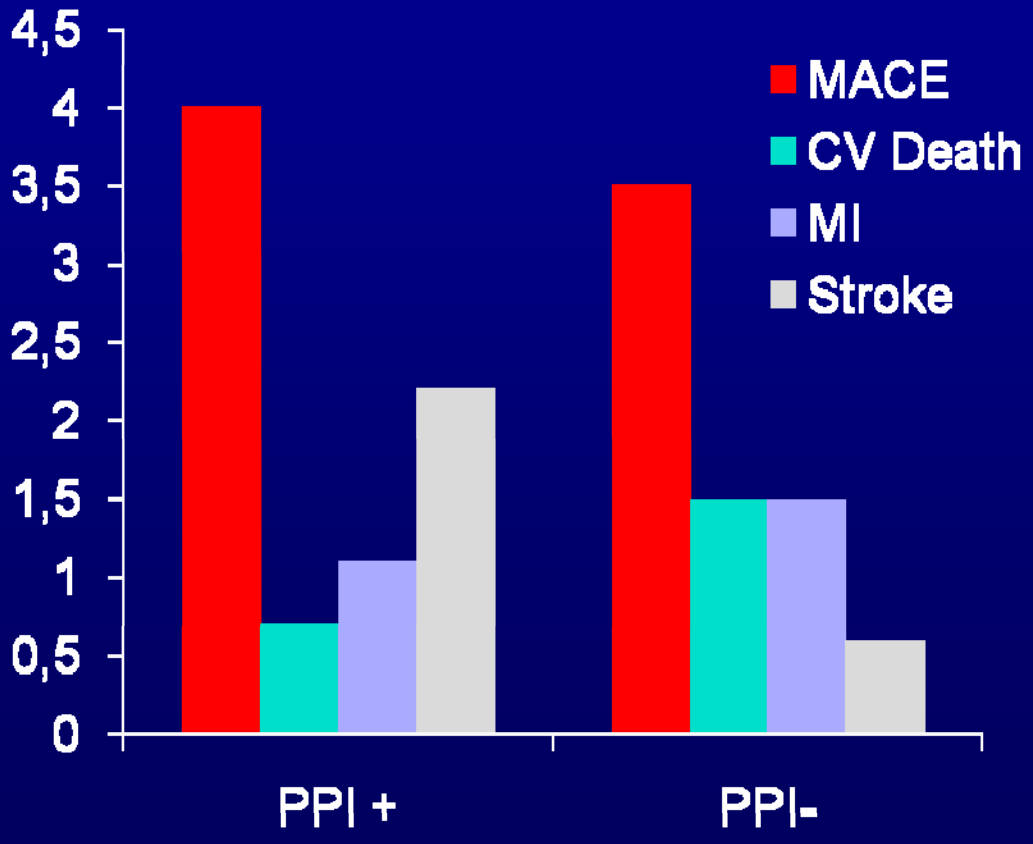
Harjai KJ et al. ACC 2010

Clinical Outcomes Following Coronary Stenting in Japanese Patients with and without PPI: the KICS Trial

Comparison of platelet aggregation between patients with or without PPI



Clinical Outcomes

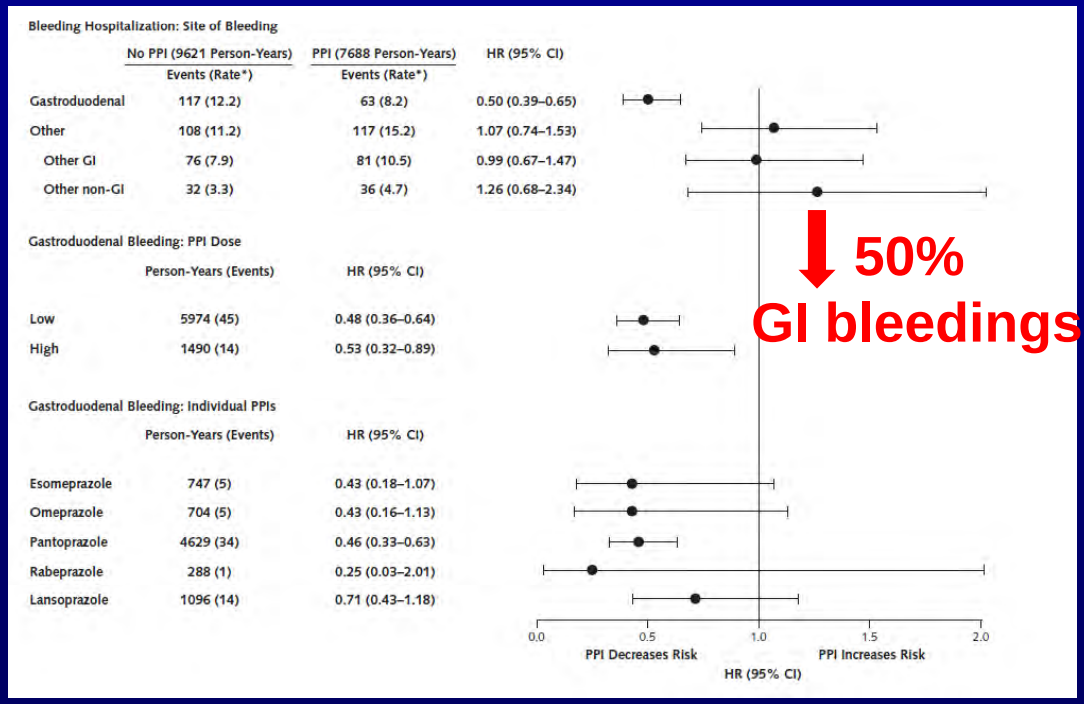


Shimomura H et al. ACC 2010

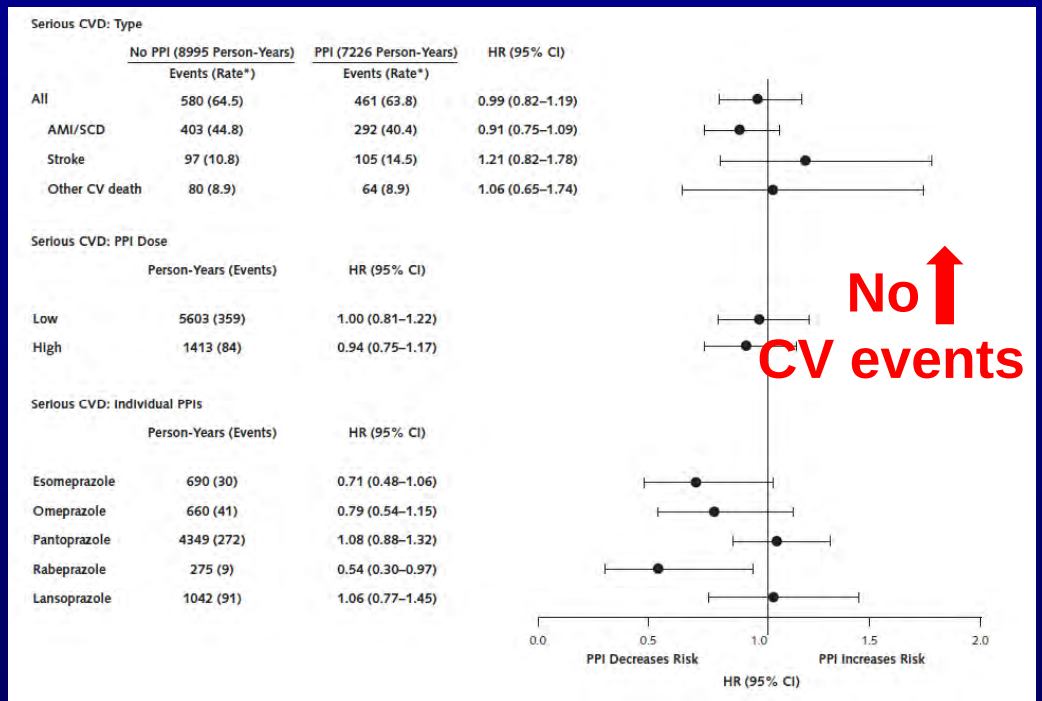
Outcomes With Concurrent Use of Clopidogrel and PPI

A cohort study of 20,596 pts

HRs for gastroduodenal and other bleeding, according to PPI use.



HRs for serious CVD, according to PPI use.



Ray WA et al. Ann Intern Med. 2010;152:337-345.

Pitfalls of Observational Studies

- Results are not in the same direction
- The harmful effect of a PPI appear to be more than the beneficial effect of clopidogrel
- Patients initially prescribed clopidogrel may no longer be exposed, yet events would still be attributed to the clopidogrel-PPI group. An analysis based on person-time would have avoided these potential biases.
- Substantial differences in baseline characteristics
- The presence of significant heterogeneity indicates that the evidence is at best,inconsistent, and at worst, potentially biased or confounded

Where is then evidence of clopidogrel/PPIs interaction?

- ✓Ex-vivo studies
- ✓Observational studies
- ✓**Metanalyses**
- ✓Randomized studies

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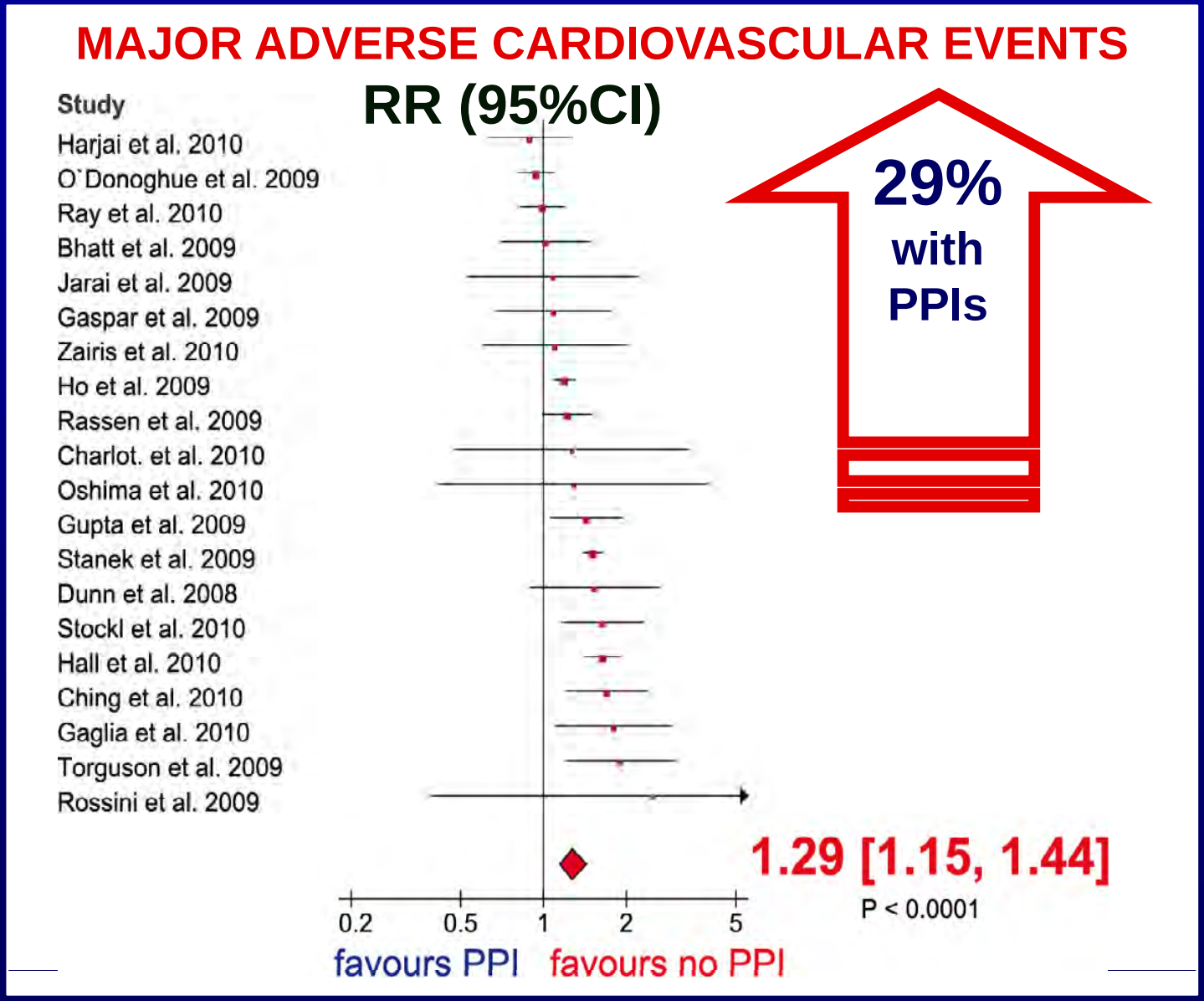
Clopidogrel/PPIs Interaction: a Systematic Review and Meta-analysis



Siller-Matula JM et al. J Thromb Haemost. 2010 Sep 10

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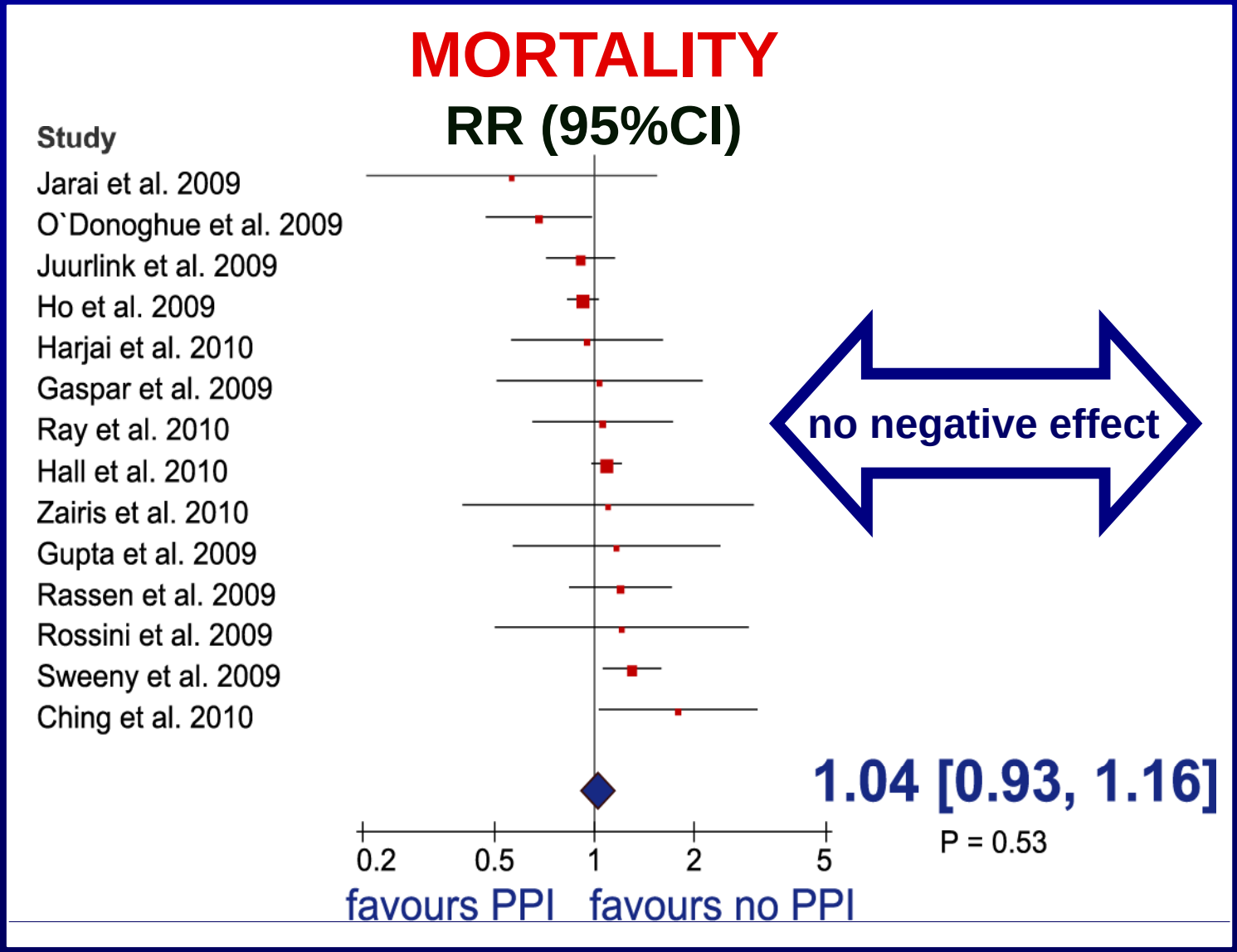
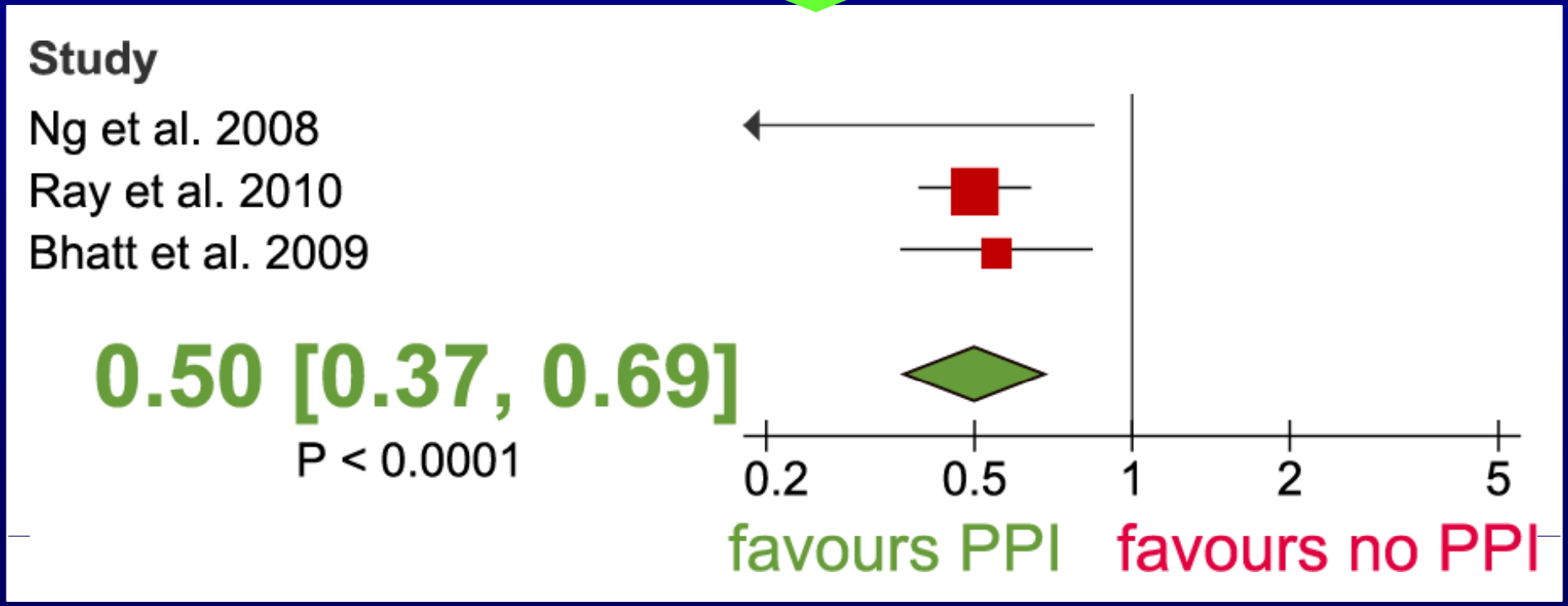


Siller-Matula JM et al. J Thromb Haemost. 2010 Sep 10

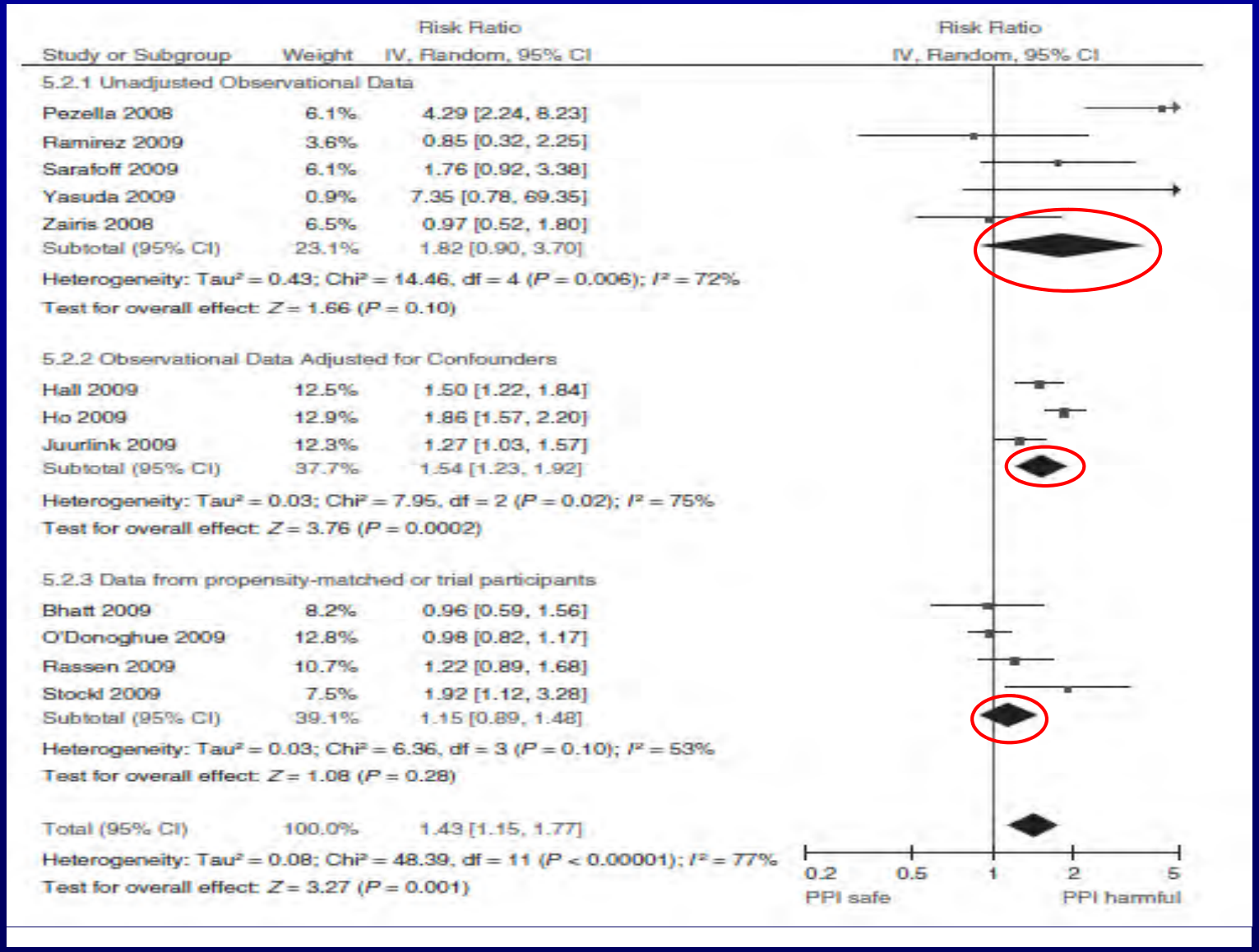
GASTROINTESTINAL BLEEDING

50%
with
PPIs

RR (95%CI)

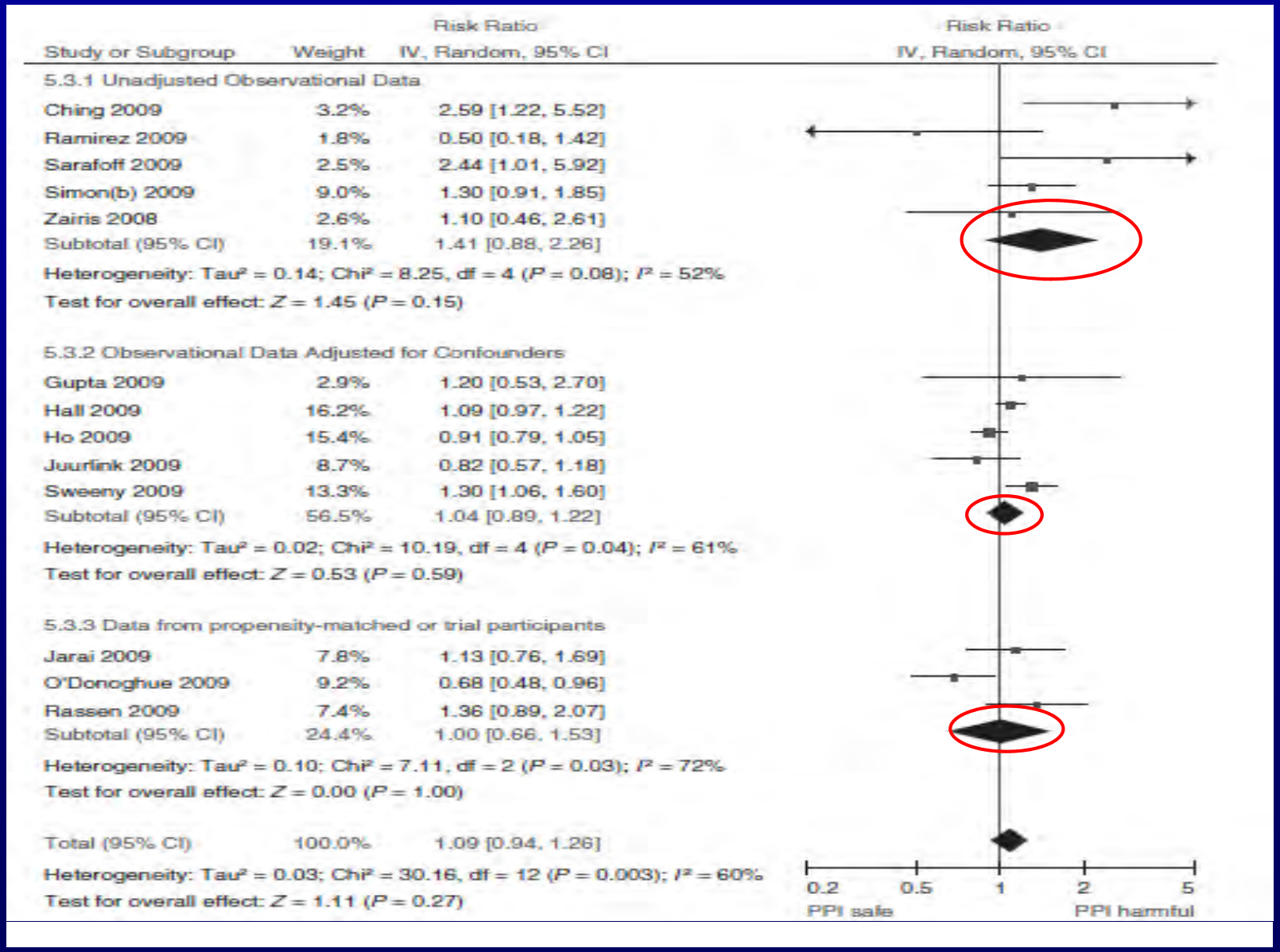


Meta-analysis of MI/ACS with clopidogrel and PPIs use



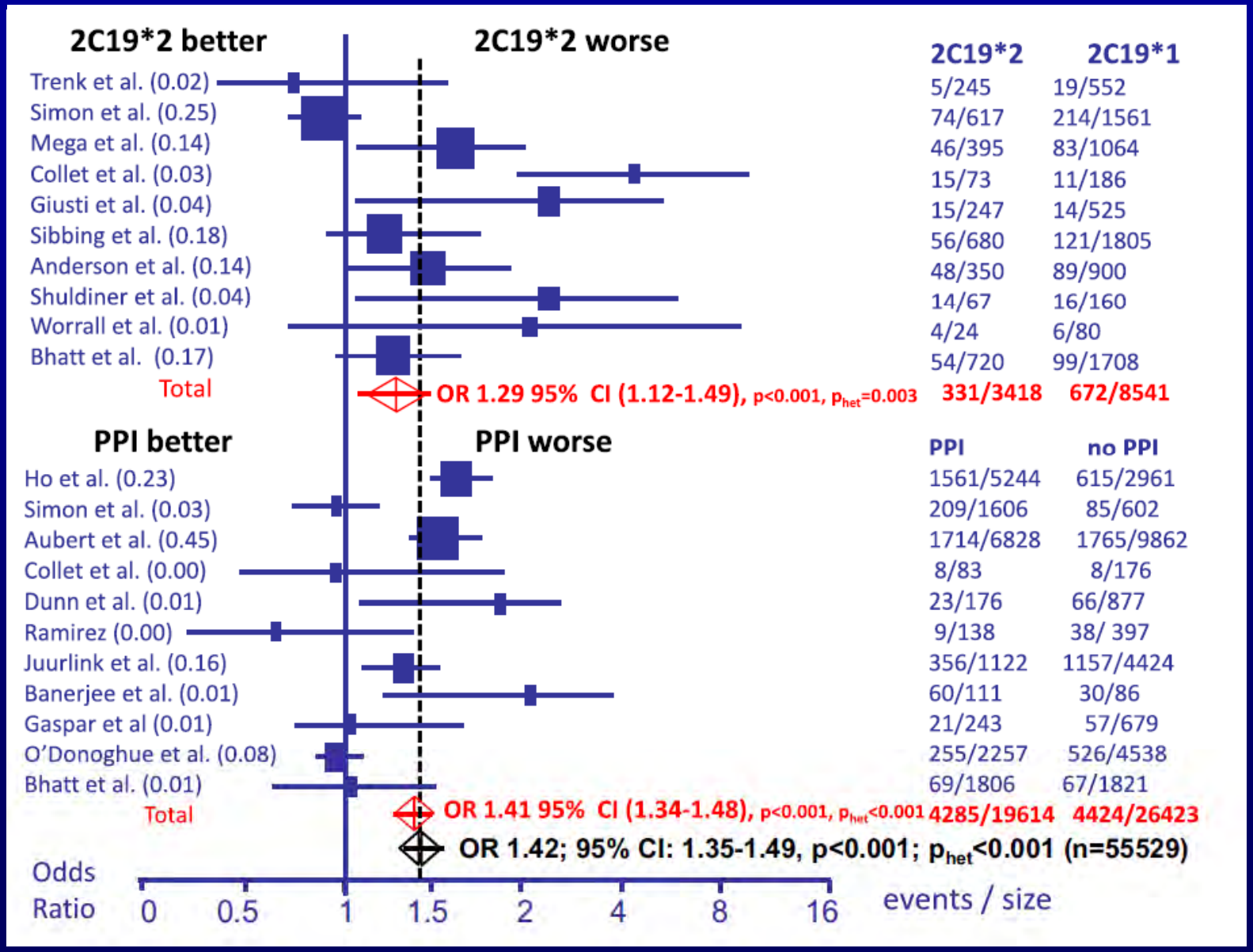
Kwok CS, Loke YK Aliment Pharmacol Ther 2010, 31: 810–823

Meta-analysis of Death with clopidogrel and PPIs use



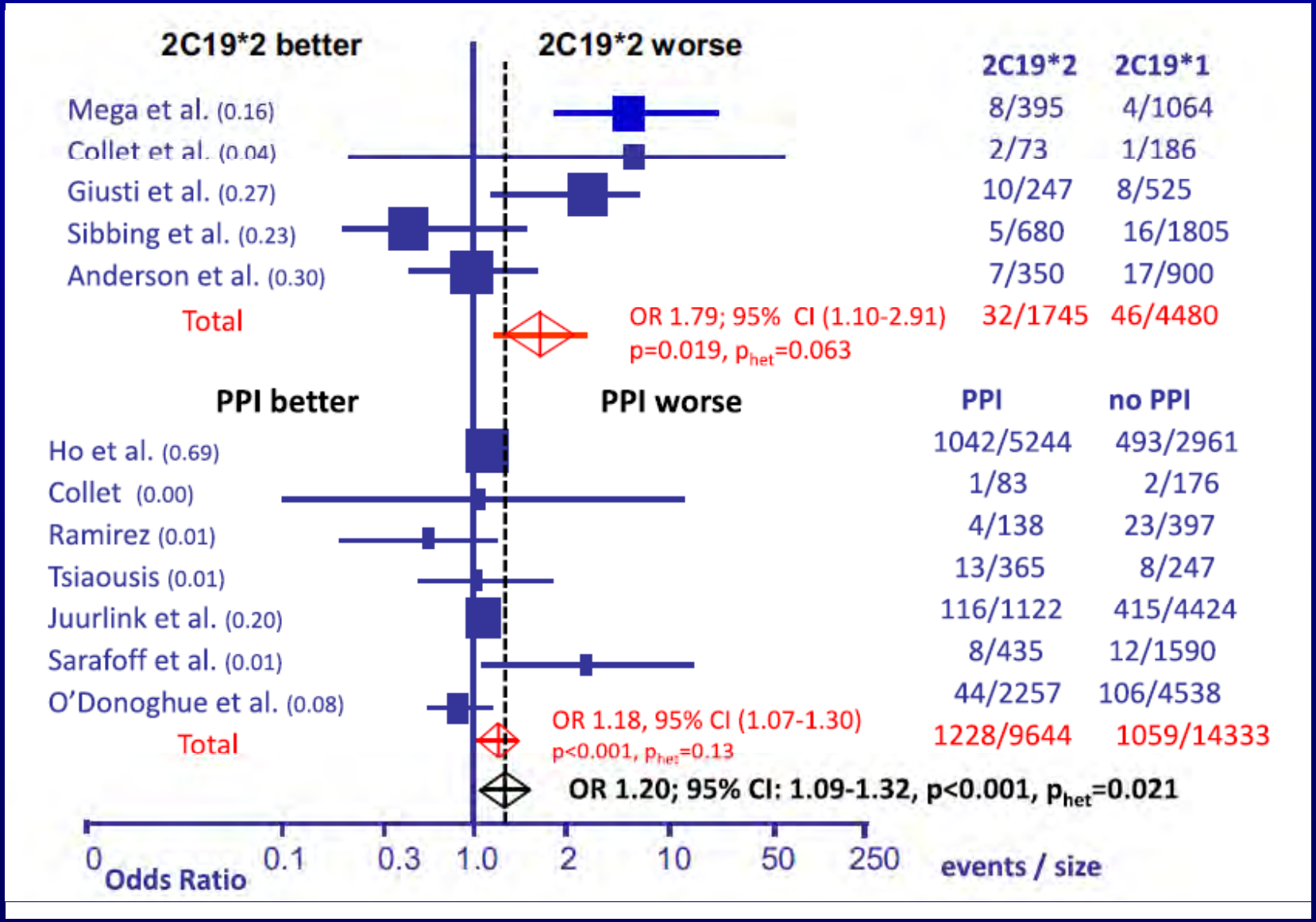
Kwok CS, Loke YK Aliment Pharmacol Ther 2010, 31: 810–823

CV Risk According to CP450 2C19*2 Loss-of-Function Allele or PPI+
A Systematic Meta-Analysis



Hulot JS et al. J. Am. Coll. Cardiol. 2010;56:134

ORs for Death According to CYP2C19*2 Allele and PPI Use



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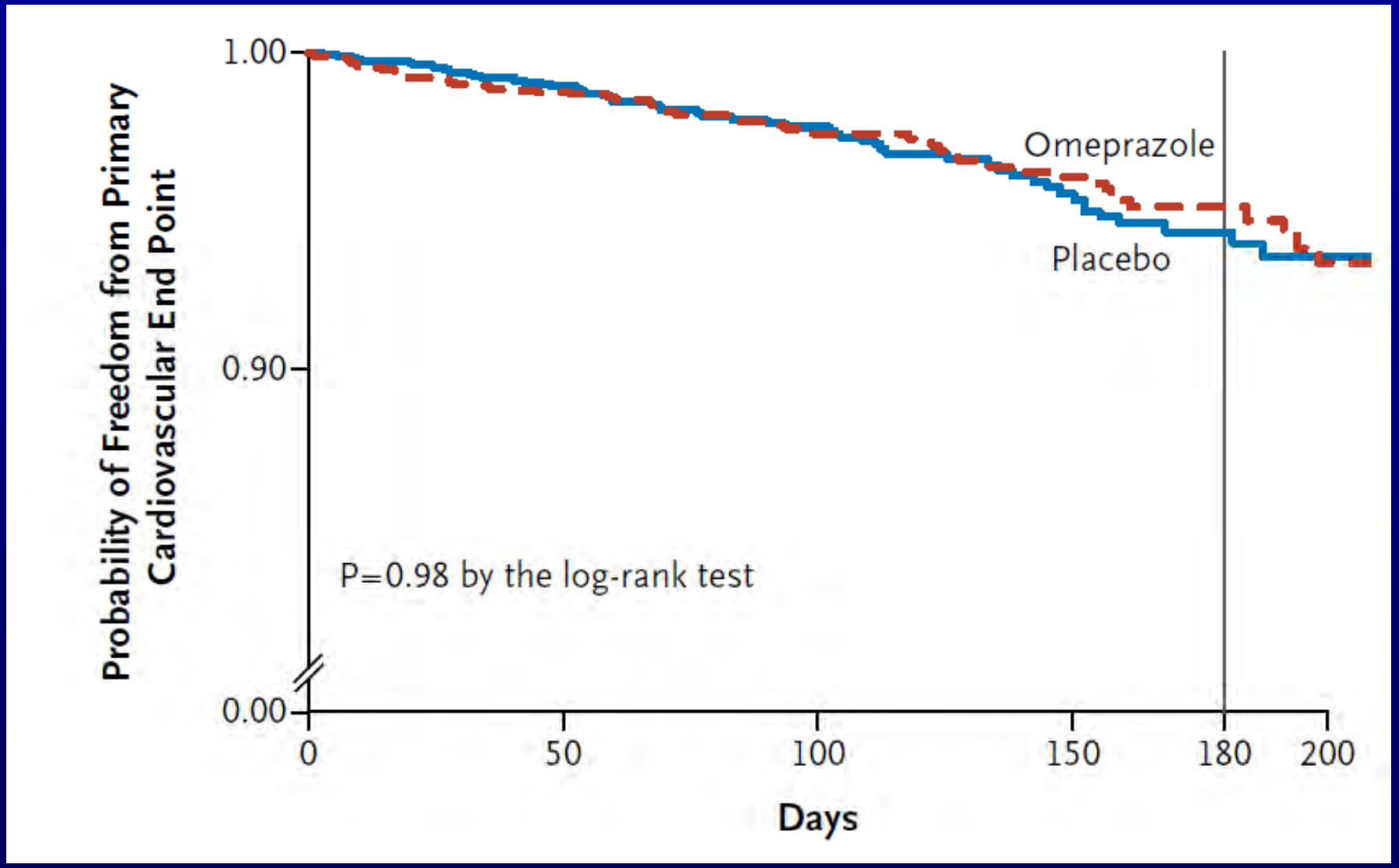
The COGENT Trail: Survival Curves for PPI Treated vs Placebo

Primary Cardiovascular Events



Bhatt DL et al. New Engl J Med Online October 6 2010

The COGENT Trial: Survival Curves for PPI Treated vs Placebo

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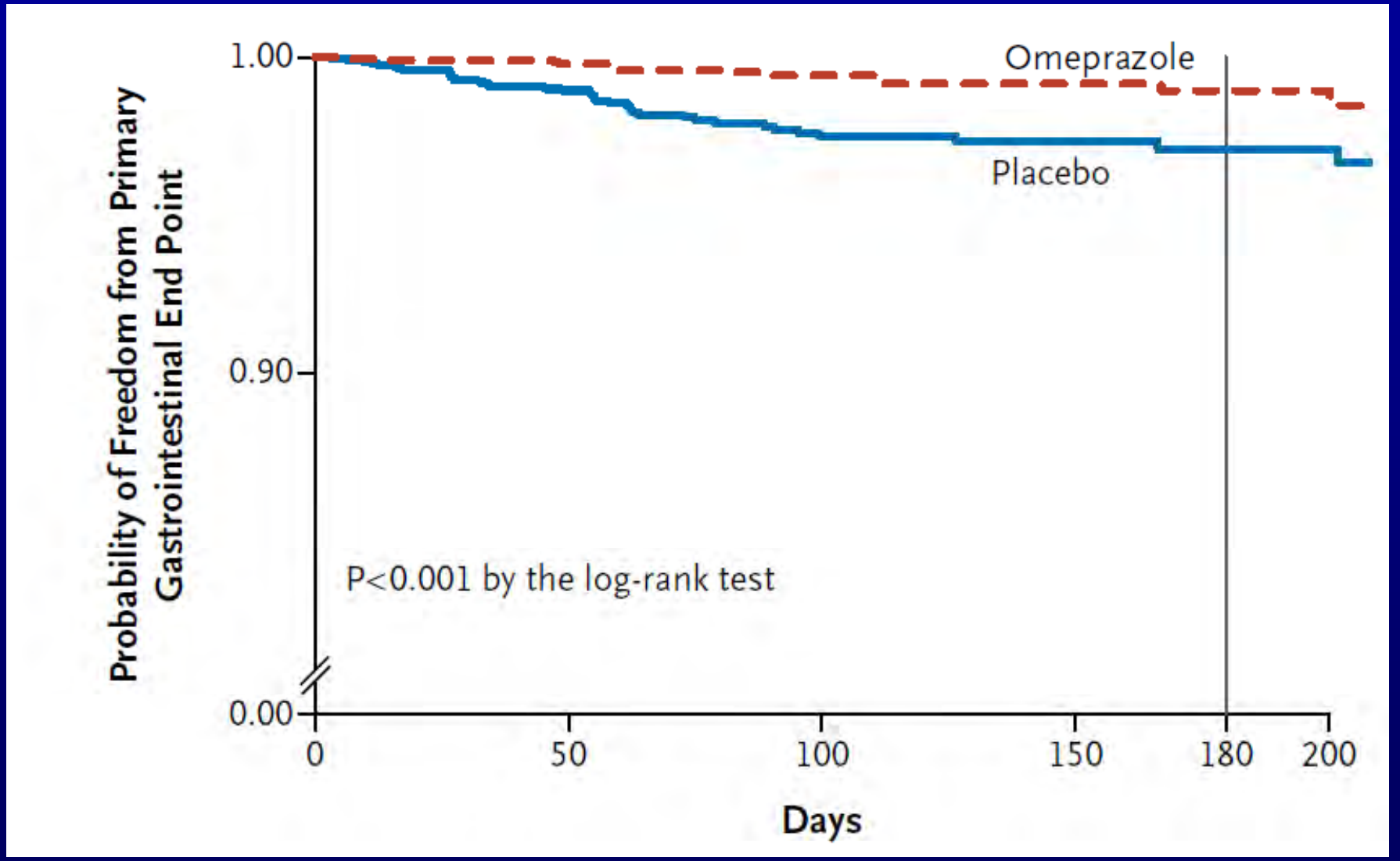

Bhatt DL et al. New Engl J Med Online October 6 2010

Variability in Clopidogrel Response
What Response Might a Clinician Adopt?

- Adherence to existing evidence-based guidelines
- Careful clinical judgement, including weighing the risks and benefits
- Reasonable to modify clopidogrel dose or use alternative therapies in high-risk pts (high-risk PCIs or adverse events on clopidogrel)
- PPI-clopidogrel interaction: mostly a PK/PD issue with less certainty around clinical outcomes. For the majority of pts, the interaction likely poses no seriorus threat