Science Fact or Simply a Good Start: What We Learn from Controlled Studies and Clinical Trials

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Objectives

Upon paying a reasonable amount of attention to this presentation, the learner should be able to:

- Understand the historical reasons for FDA-required clinical studies
- Discuss why clinical trial results may not represent outcomes in all patient populations
- Apply knowledge of laboratory information obtained from limited studies to varied patient populations

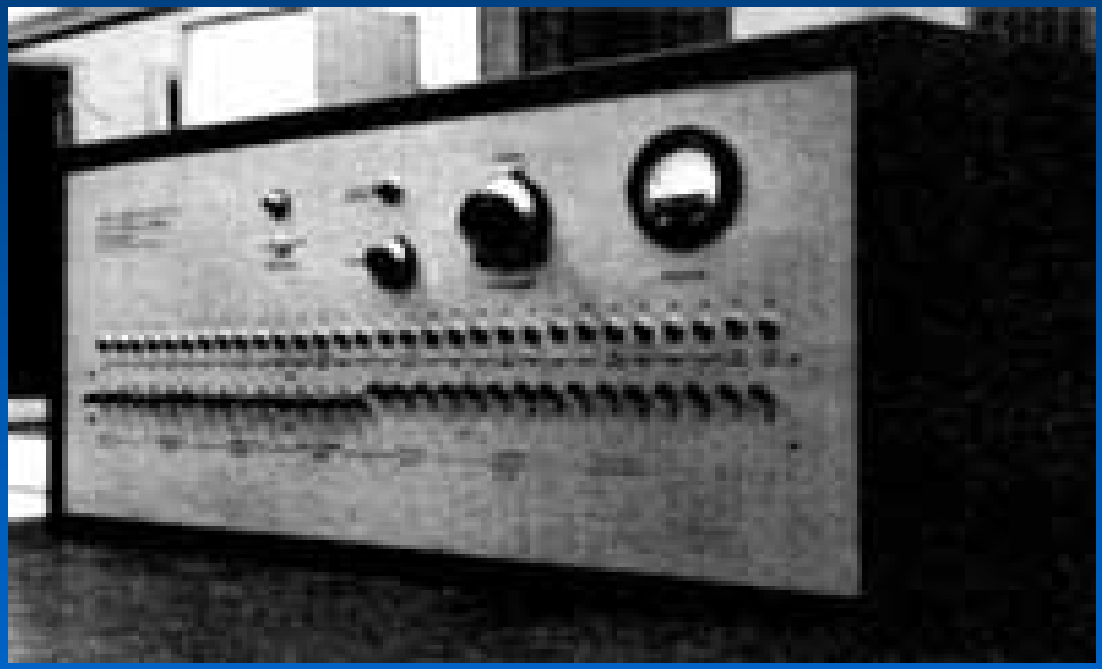
The first century physician Celsus justified experiments on condemned criminals in Egypt using wording that became a classic defense for hazardous experimentation: "It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries." Both the ethics and regulation of human subjects research have changed considerably since Celsus' time.

At the end of World War II, 23 Nazi doctors and scientists were put on trial for the inhumane treatment and murder of concentration camp inmates who were used as research subjects. In the absence of a legal standard for the conduct of research, the court wrote a standard into its legal judgment. This new standard included ten points describing required elements for conducting research with humans. These points became known as the Nuremberg Code.

Summary of Nuremberg Code

- Informed Consent is Essential
- Research on human subjects should be based on prior animal work.
- The risks should be justified by the anticipated benefits.
- Only qualified scientists should be allowed to conduct research with human subjects.
- Physical and mental suffering must be avoided. Research in which death or disabling injury is expected should not be conducted.

Milgram's "Obedience to Authority Study" (1963)



The Public Health Service Syphilis Study (1932-1972)
"Tuskegee Study of Untreated Syphilis in the Negro Male"

Not providing penicillin once it was deemed safe and effective may have been responsible for 28 deaths, 100 cases of disability, and 19 cases of congenital syphilis.

Belmont Report

- US Congress held hearings on "Quality of Health Care - Human Experimentation" in 1973
- National Research Act of 1974 which led to "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research“
- In 1979, motivated by the Public Health Service's Syphilis Study and others, and after several years of deliberations, the National Commission published the *Belmont Report*
- The Belmont Principles are respect for persons, beneficence, and justice

1996- Death of a Normal Volunteer

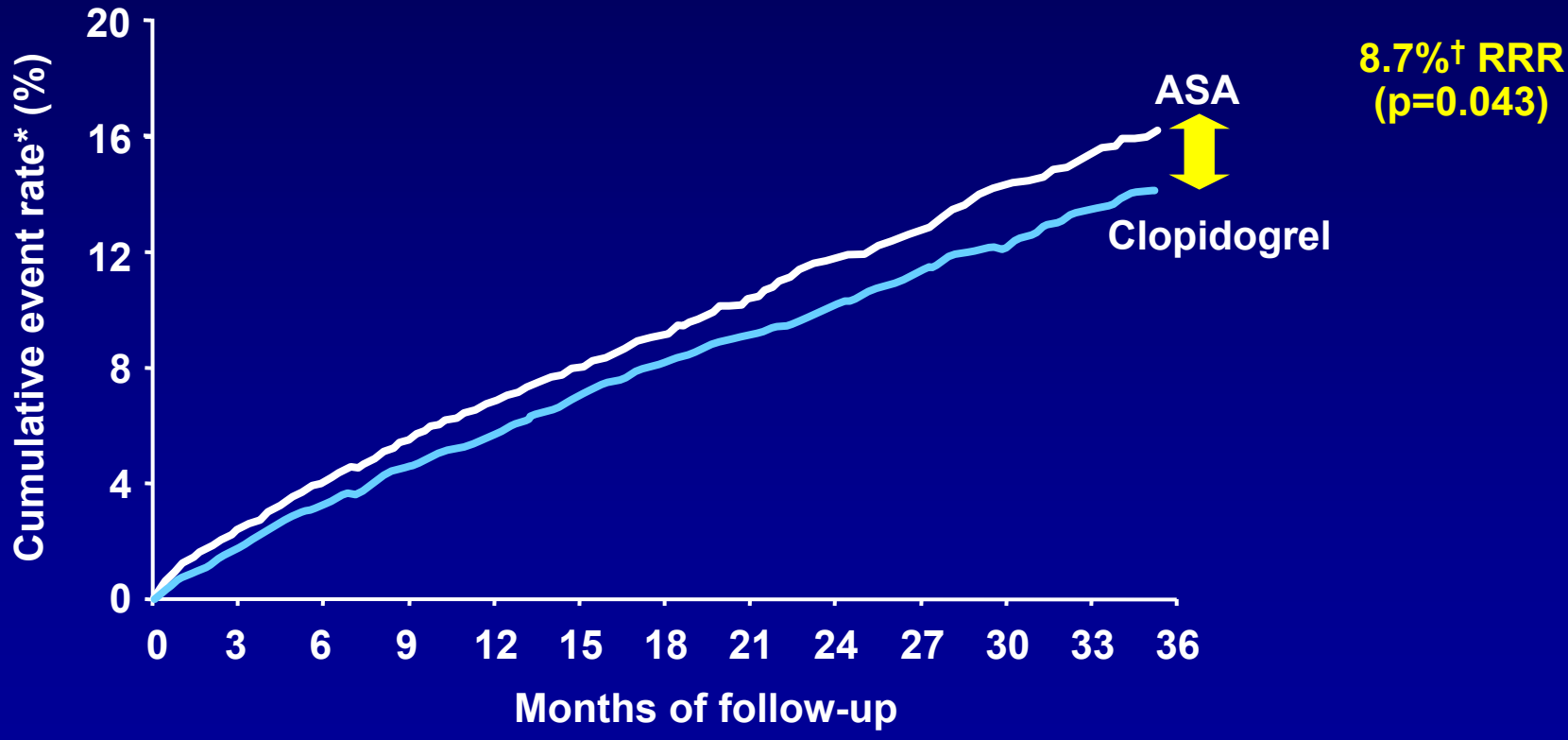
- 19 year old female at University of Rochester
- Volunteered for bronchoscopy to harvest alveolar macrophages
- Proved to be difficult procedure requiring multiple doses of lidocaine
- She was repeatedly question if she wanted to continue, and continued to nod head “yes”. Study completed
- She later suffered lidocaine-induced cardiac arrest and died
- Protocol did not specify number of Lidocaine doses, doses were not documented, subject was not observed post-procedure, lidocaine concentration increased without IRB approval

5th Grade Science

- Formulate a question (hypothesis)
- Design experiments
- Conduct experiments
- Record results
- Report results
- Repeatable

CAPRIE: Superior Efficacy of Clopidogrel versus ASA

Patients with recent ischemic stroke, recent MI or symptomatic PAD

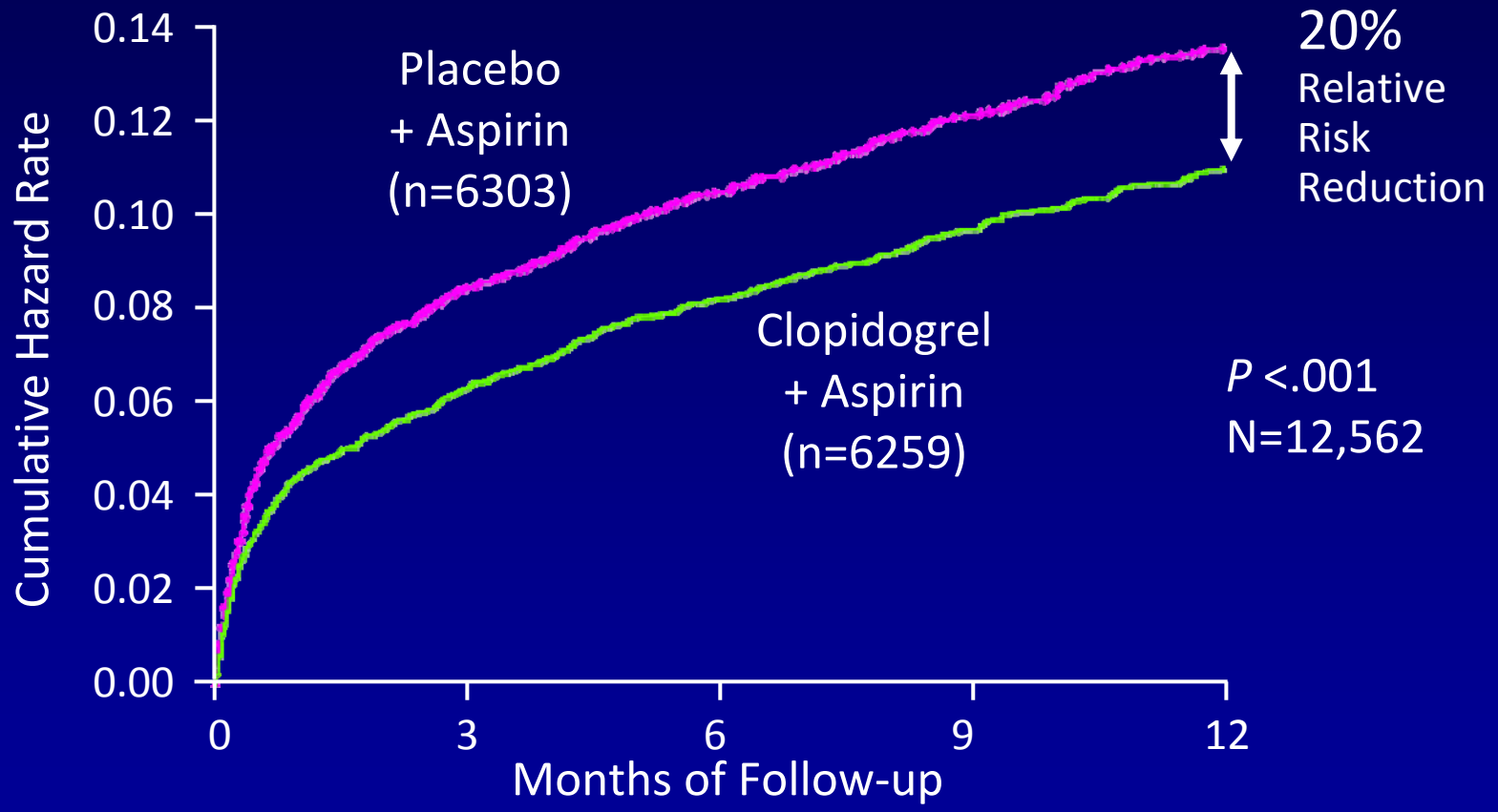


*MI, ischemic stroke or vascular death

†Intent-to-treat analysis (n=19,185) MI within 35 days, ischemic stroke within 6 mo, PAD

CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–1339.

CURE Study:
Primary End Point: MI/Stroke/CV Death

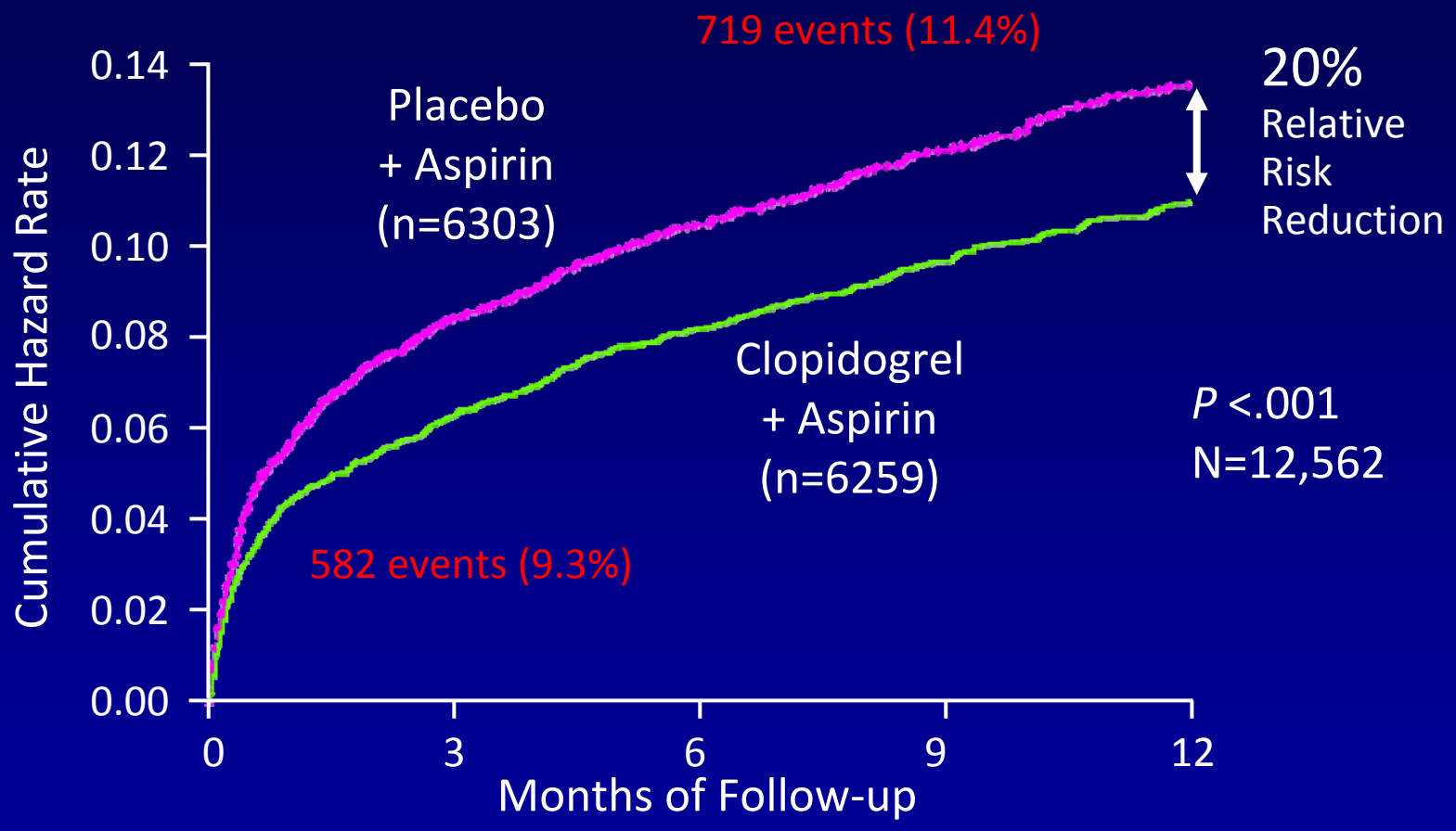


Yusuf S, et al. *N Engl J Med.* 2001;345:494-502. 12,562 ACS non-STEMI patients presenting within 24 hours of of onset of most recent chest pain episode or symptons consistent with ischemia

Relative Risk Reduction

20% - does this mean that 20% of the study group had better outcomes?

CURE Study:
Primary End Point: MI/Stroke/CV Death



Yusuf S, et al. *N Engl J Med.* 2001;345:494-502. 12,562 ACS non-STEMI patients presenting within 24 hours of of onset of most recent chest pain episode or symptons consistent with ischemia

Absolute Risk Reduction

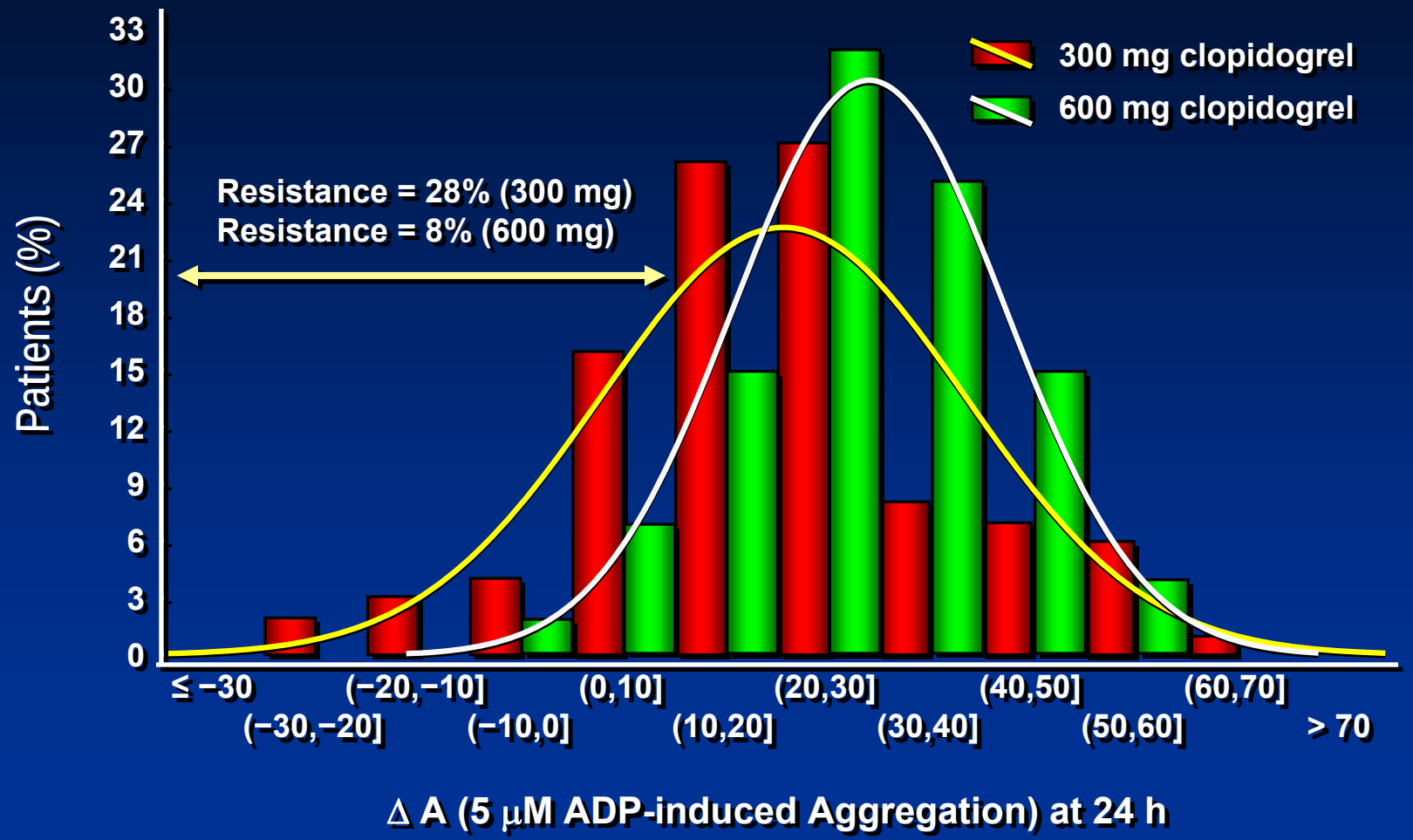
- Placebo + Aspirin = 719 events or 11.4%
- Clopidogrel (Plavix) + Aspirin = 582 events, or 9.3%
- Absolute Risk Reduction = 137, or 1.1%

So now we are in 2011 – that's even a different century!

Plavix is the #2 selling prescribed drug worldwide

Events are catastrophic

Clopidogrel Response Variability (300 vs. 600 mg):
Importance of Dose (n = 190)



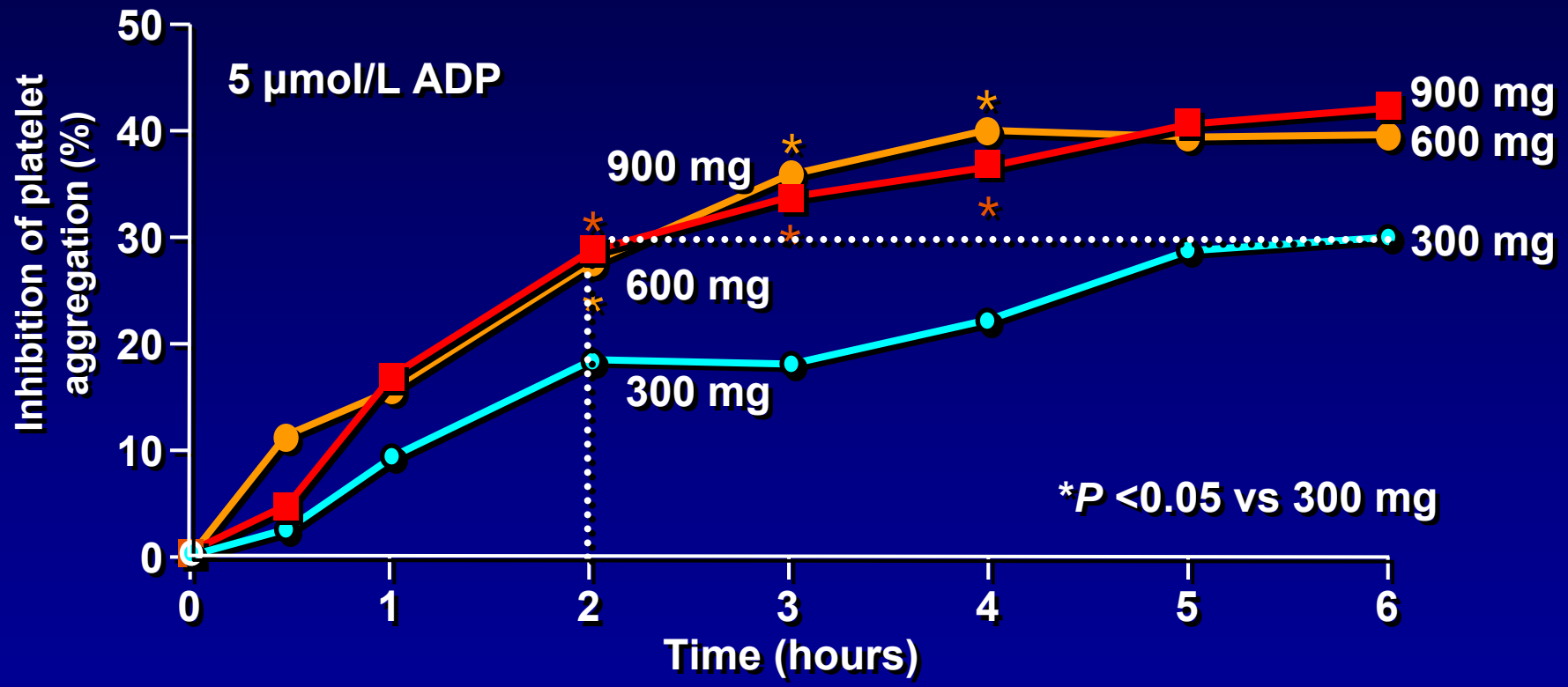
Gurbel PA et al. *J Am Coll Cardiol*. 2005;45:1392

Kong 04/08

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

ALBION: Clopidogrel 600 mg provides more rapid inhibition of platelet aggregation

103 NSTE ACS pts randomized to 300, 600 or 900 mg clopidogrel



Greater loading doses are associated with a significantly faster onset of inhibition

ADP, adenosine diphosphate; NSTE ACS, non-ST-elevation acute coronary syndromes.

Montalescot G *et al. JACC* 2006;48:931–8.

Kong 09/09

Duke Clinical Research Institute
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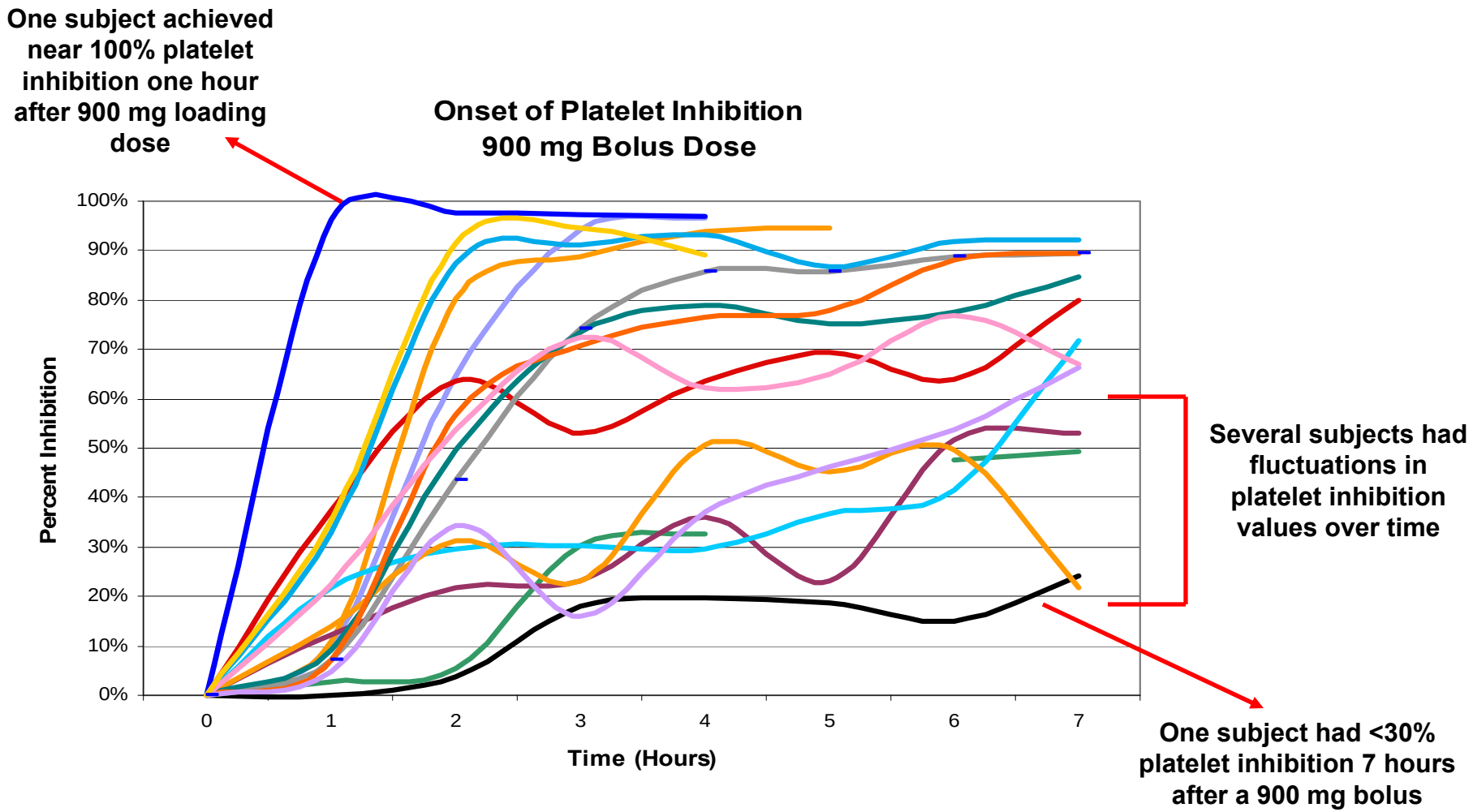
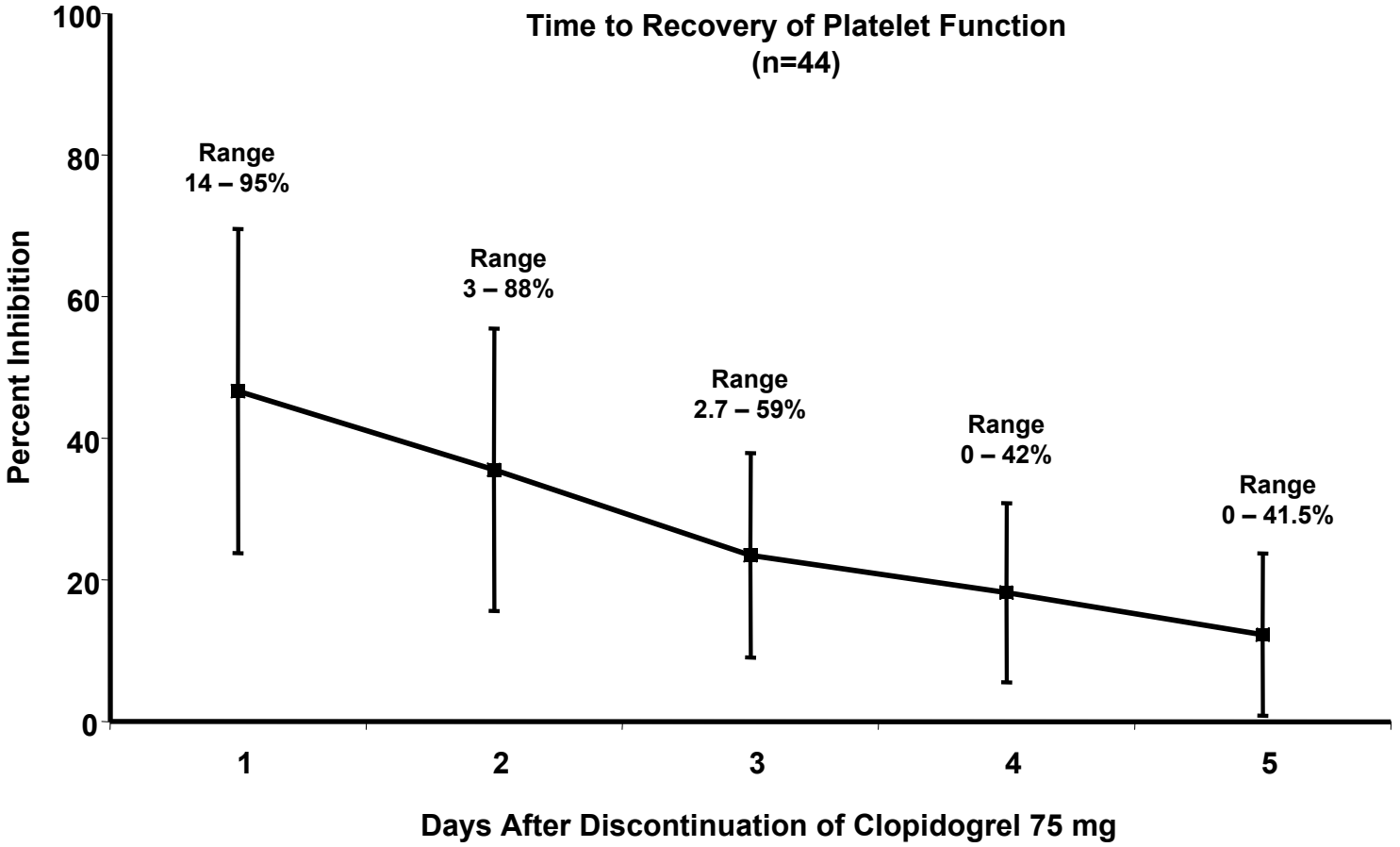
Platelet inhibition varied considerably in all clopidogrel dose groups



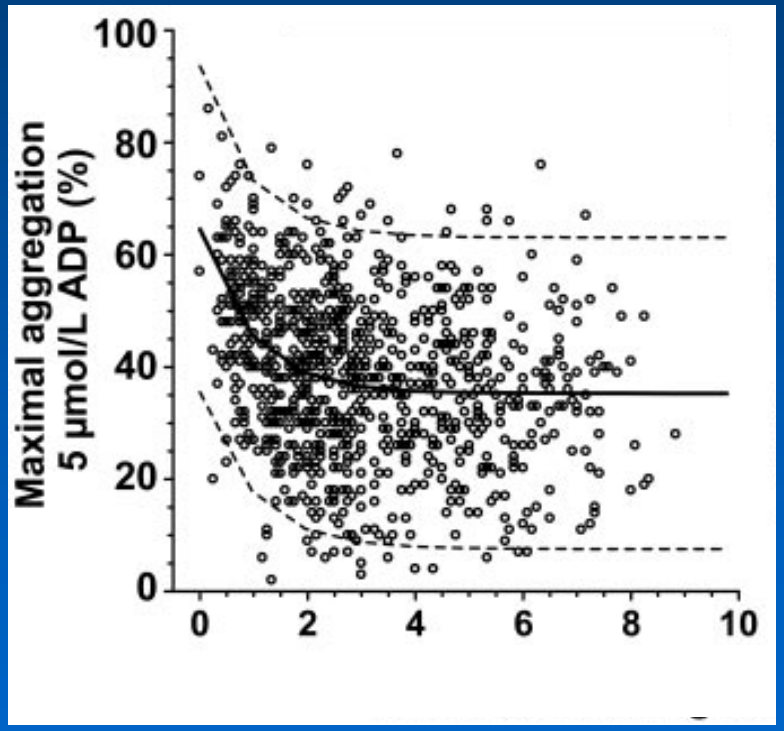
While platelet inhibition decreased significantly on each day of recovery, there were wide ranges at each time point



Inter-individual Variability in Clopidogrel Response

Loading Dose: 600mg
Maximal aggregation 5 µmol/L ADP (%)

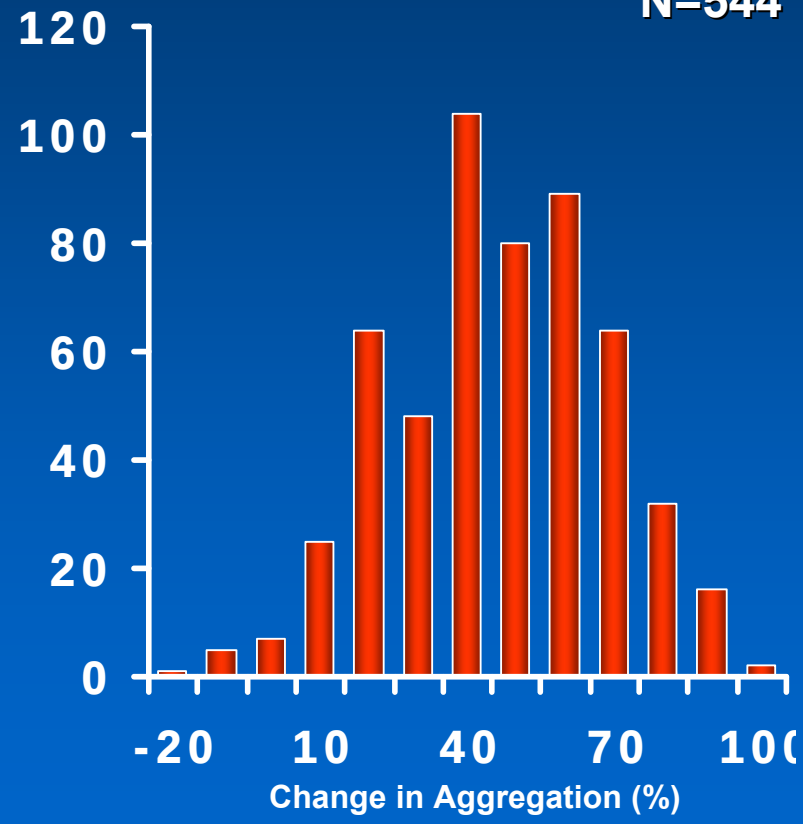
N=1001



Hochholzer W, et al., Circulation 2005;111

Maintenance Dose: 75mg
Change in ADP-Induced Platelet Aggregation

N=544



Serebruany. J Am Coll Cardiol. 2005;45:246.

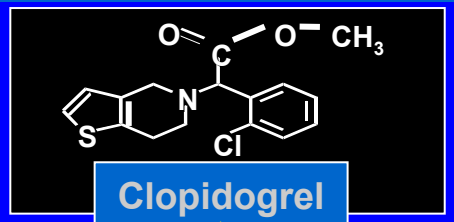
Omeprazole reduces antiplatelet effect of clopidogrel

Gilard M, Arnaud B, Cornily J-C, et al

Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study.

J Am Coll Cardiol 2008;51:256–60.

Thienopyridines: Formation of Active Metabolite

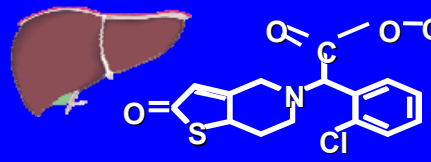


Clopidogrel

85% Inactive Metabolites

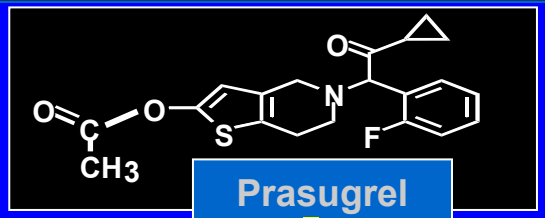
CYPs:
1A2
2C19
2B6

Oxidation (Cytochrome P450)



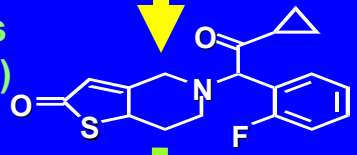
CYPs:
3A
2C19
2C9
2B6

Active Metabolite



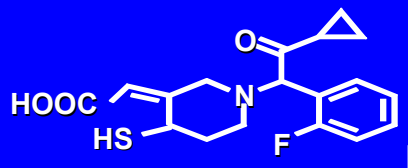
Prasugrel

Hydrolysis (Esterases)



CYPs:
3A
2B6
2C9
2C19

Oxidation (Cytochrome P450)



Active Metabolite

FDA Change to Plavix Package Insert March 2010 – Addition of Boxed Warning

Warning: Diminished Effectiveness In Poor Metabolizers

See full prescribing information for complete boxed warning

Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19

Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function

Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy

Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

Wait – Don't Leave Me Yet!

- What tests? Where are they available? What is the turnaround time? Cost?
- Do I test all Plavix candidates?
- Do I wait for the results prior to loading Plavix? What if I can't?
- How does one define "poor metabolizer"
- What "alternative treatment or treatment strategies" do I consider?

Impact of CYP2C19 Loss-of-Function Polymorphism and of Major Demographic Characteristics on Residual Platelet Function After Loading and Maintenance Treatment With Clopidogrel in Patients Undergoing Elective Coronary Stent Placement

William Hochholzer,[1,2] Dietmar Trenk,[1] Martin F. Fromm,[3] Christian M. Valina,[1] Christian Stratz, [1] Hans-Peter Bestehorn, [1] Heinz Joachim Büttner, [1] and Franz-Josef Neumann,[1]

[1]Herz-Zentrum Bad Krozingen Germany

[2]TIMI Study Group, Boston

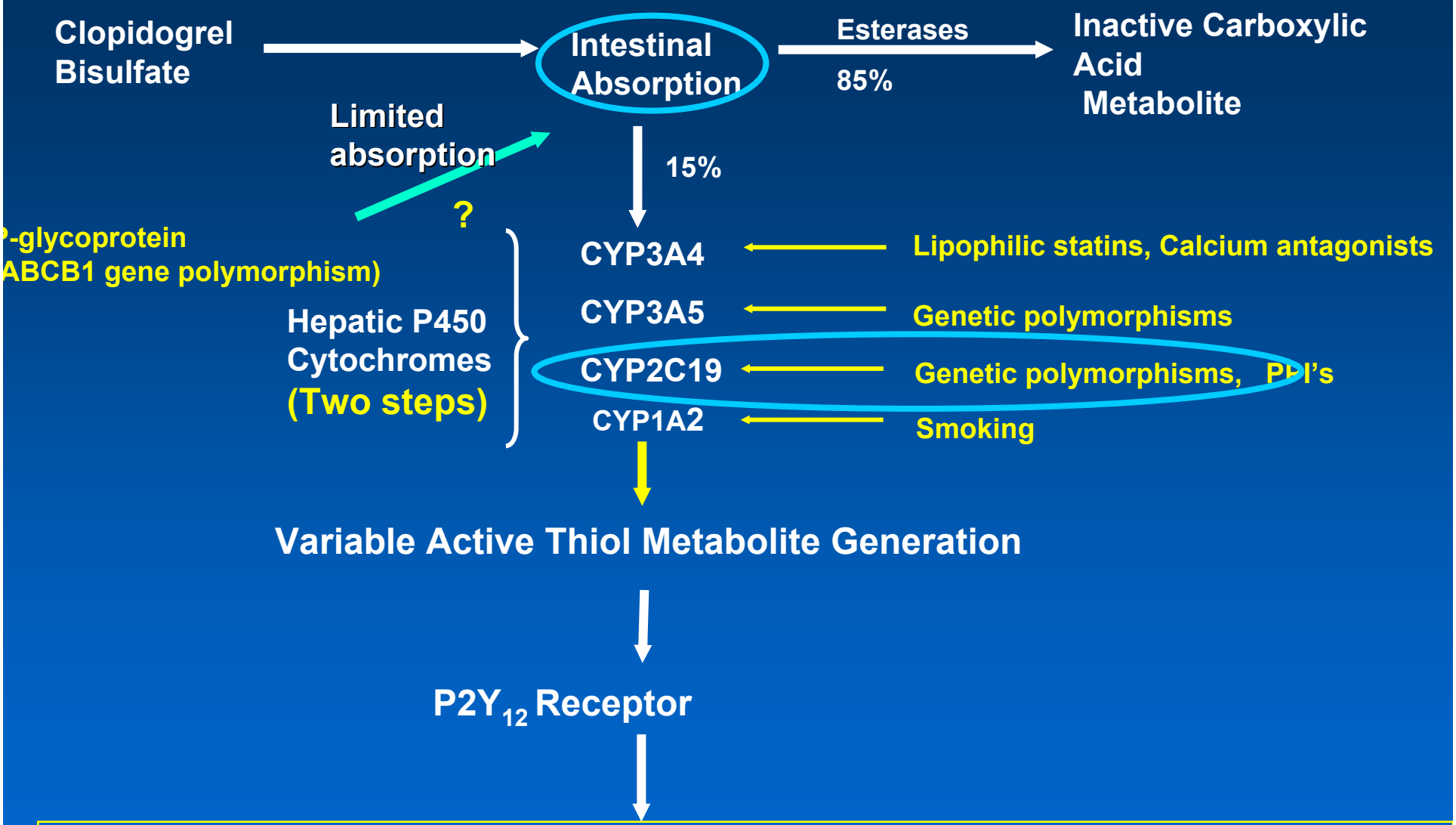
[3]University of Erlangen-Nuremberg Germany

Herz-Zentrum Bad Krozingen, Germany

Conclusions

- The CYP2C19*2 loss-of-function polymorphism is the strongest predictor of high on-clopidogrel platelet reactivity
- The clinical characteristics strongly associated with low response to clopidogrel are age, diabetes mellitus, and BMI
- CYP2C19 carrier status together with all demographic and clinical predictors impacting on response to clopidogrel can only explain 11.5% of variability in RPA
- Thus, in patients critically dependent on adequate platelet inhibition, genotyping alone or in combination with clinical factors cannot replace phenotyping of platelet function

Poor Response to Clopidogrel is a Pharmacokinetic Problem



Gurbel et al. Expert Opin Drug Metab Toxicol. 2009;5:989-1004. Slide provided courtesy of Dr. Gurbel

Paraoxonase-1 is a major determinant of clopidogrel efficacy

Bouman HJ, Schomig E, van Werkum JW, Velder J, Hackeng CM, Hirschhauser C, Waldmann C, Schmalz HG, ten Berg JM, Taubert D

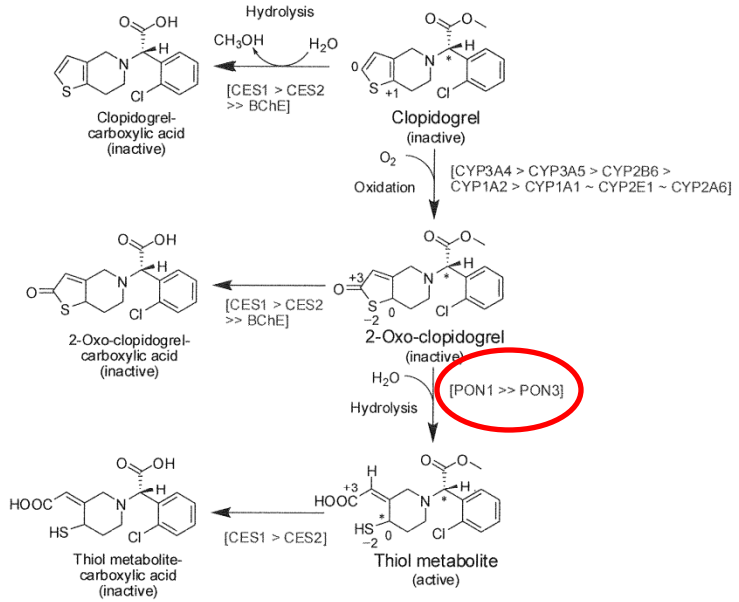
Nature Medicine

Published online 19 December 2010

Study

- Determined that PON1 and PON3 catalyzed the second step hydrolytic cleavage of clopiodgrel metabolism (shown in subsequent slide)
- Study looks at patients with PON 1 variants
- In cohort of 7,719 subjects after 18 months follow-up, compared 41 incident cases with nonfatal stent thrombosis and 71 randomly selected subjects without stent thrombosis

Supplementary Figure 2.

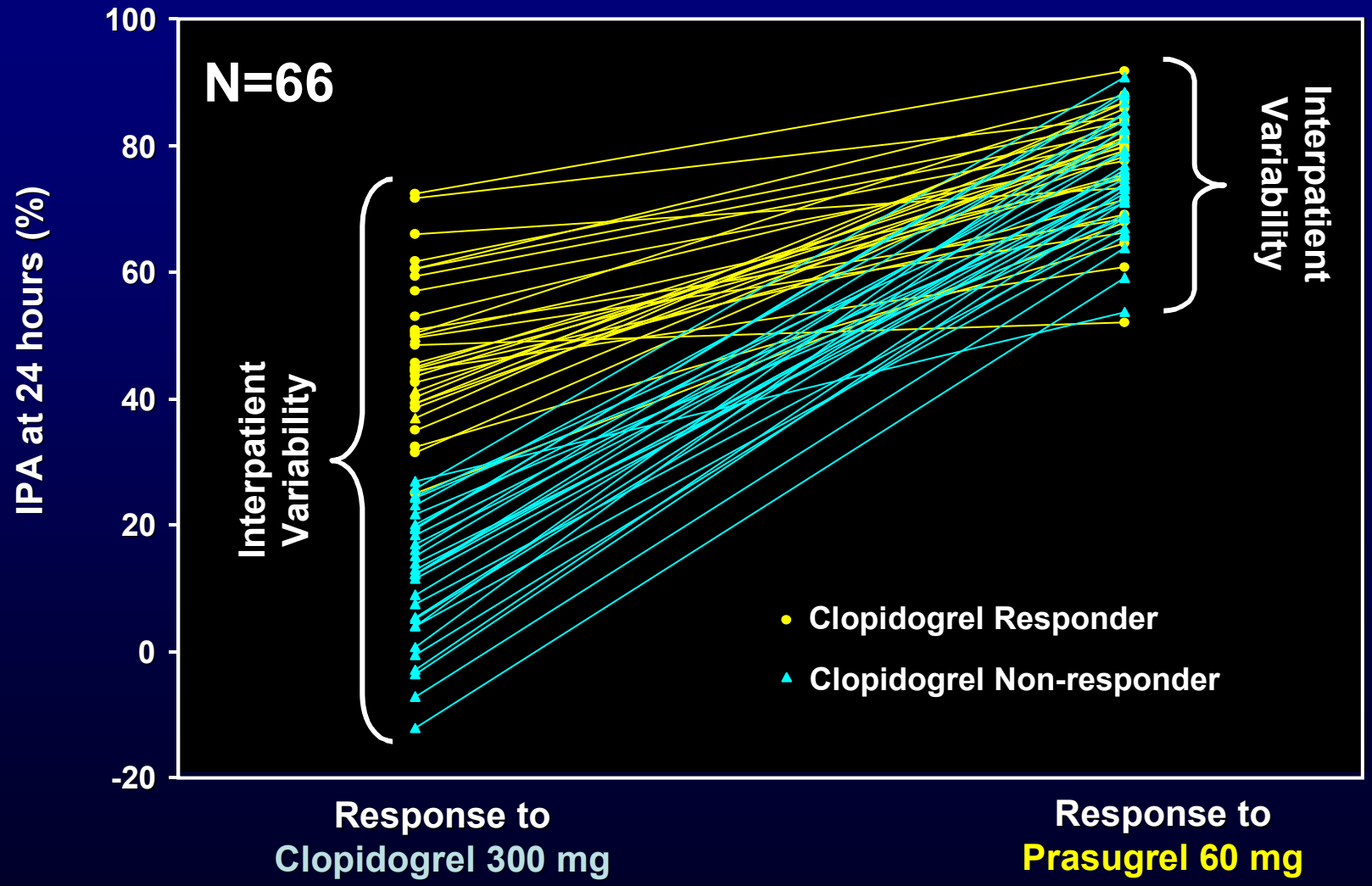


Supplementary Figure 2. Scheme of clopidogrel metabolism and involved enzymes.
Numbers in the formulas indicate formal oxidation state of sulfur and carbon atoms. Stars indicate chiral carbon atoms. Absolute configurations of clopidogrel and 2-oxo-clopidogrel with one chiral center at C-7 (7S) and of the active thiol metabolite with chiral centers at C-7 (7S) and C-4 (4S or 4R) and a geometric center at C-3 (ethylene bond, 3Z) are displayed. Relative catalytic efficiencies of enzymes are shown.
BChE denotes butyrylcholinesterase; CES1,2 carboxylesterase-1,-2; CYP cytochrome P450 isozyme; PON1,3 paraoxonase-1,-3.

- QQ192 PON1 homozygotes more frequent in ST group (OR 3.6). Early ST more frequent than late or very late ST (OR 3.3) compared with heterozygones or wild types
- Considering not only the occurrence of events but also the time of occurrences after PCI, the HR of ST for QR192 heterozygotes was considerably higher than for wild type and increased in log-additive fashion in homozygotes
- The PON1 Q192R genotype was the only significant factor that was independently associated with the occurrence of ST.

TRÎTON TIMI·38

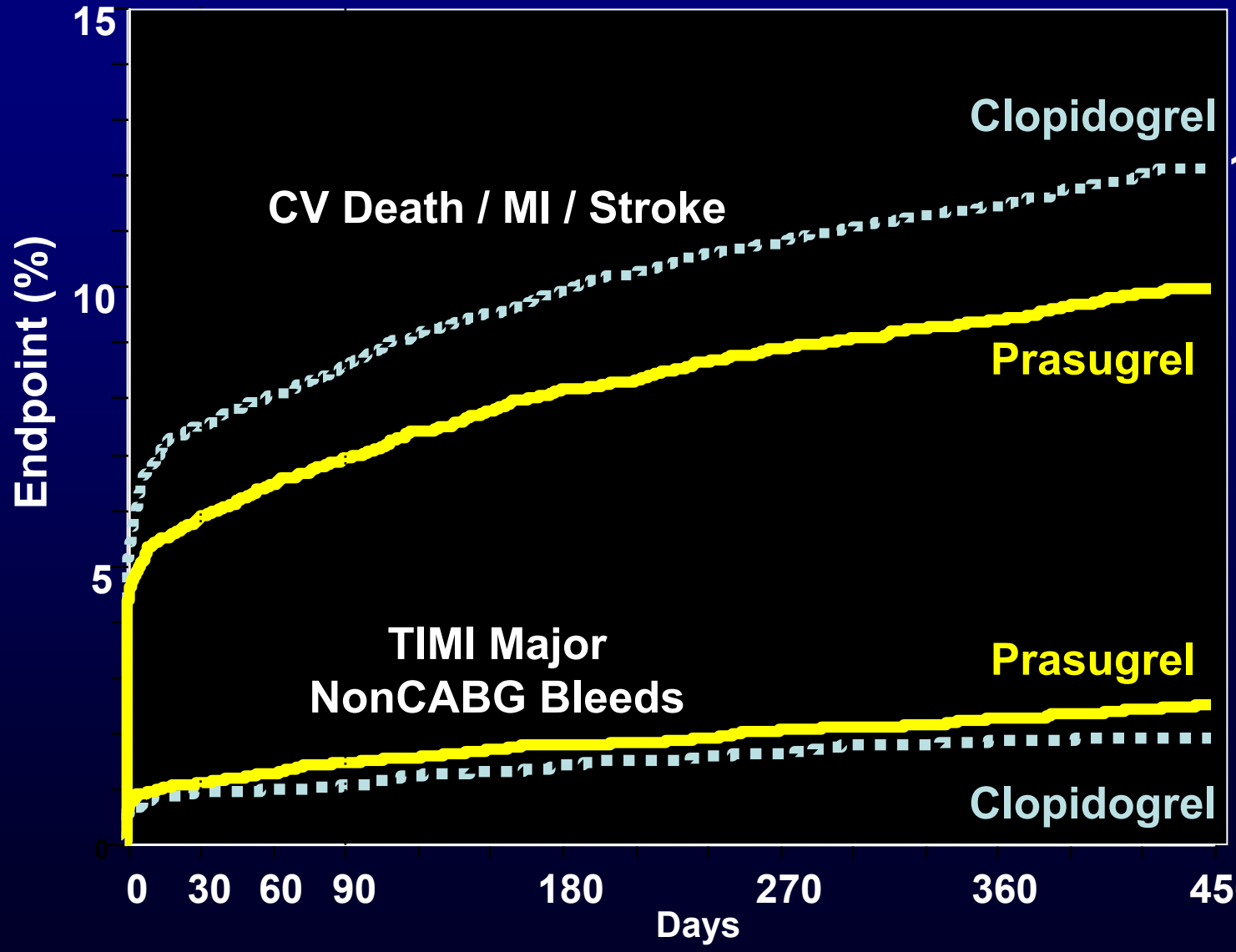
Healthy Volunteer Crossover Study



From Brandt JT AHJ 153: 66e9,2007

TRÎTON TIMI-38

Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

↑ 35 events

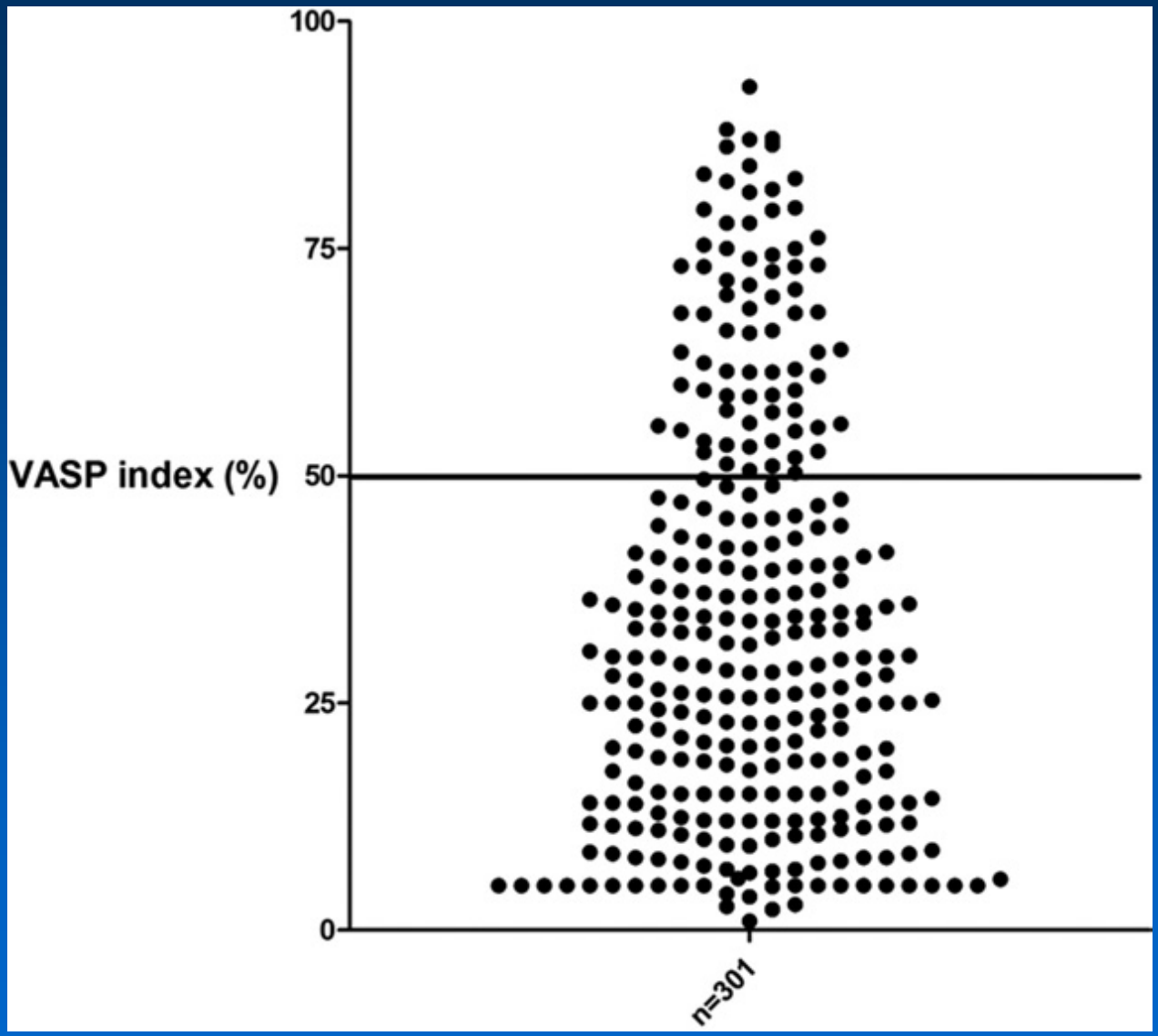
HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

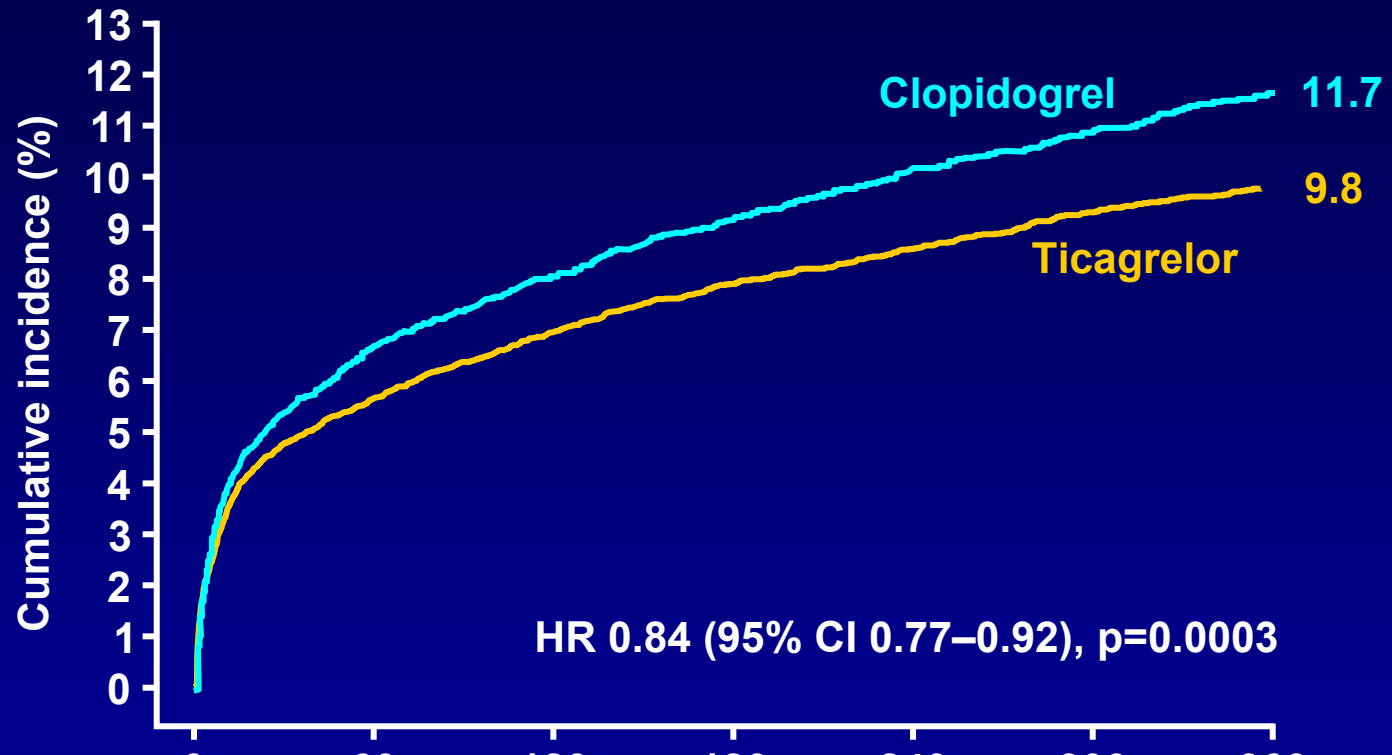
High On-Treatment Platelet Reactivity After Prasugrel Loading Dose and Cardiovascular Events After Percutaneous Coronary Intervention in Acute Coronary Syndromes

Laurent Bonello, MD,*† Michel Pansieri, MD,‡ Julien Mancini, MD et al

J Am Coll Cardiol 2011;58:467–73)


VASP index (%)
100
75
50
25
0
n=301

CV Death, MI, or Stroke



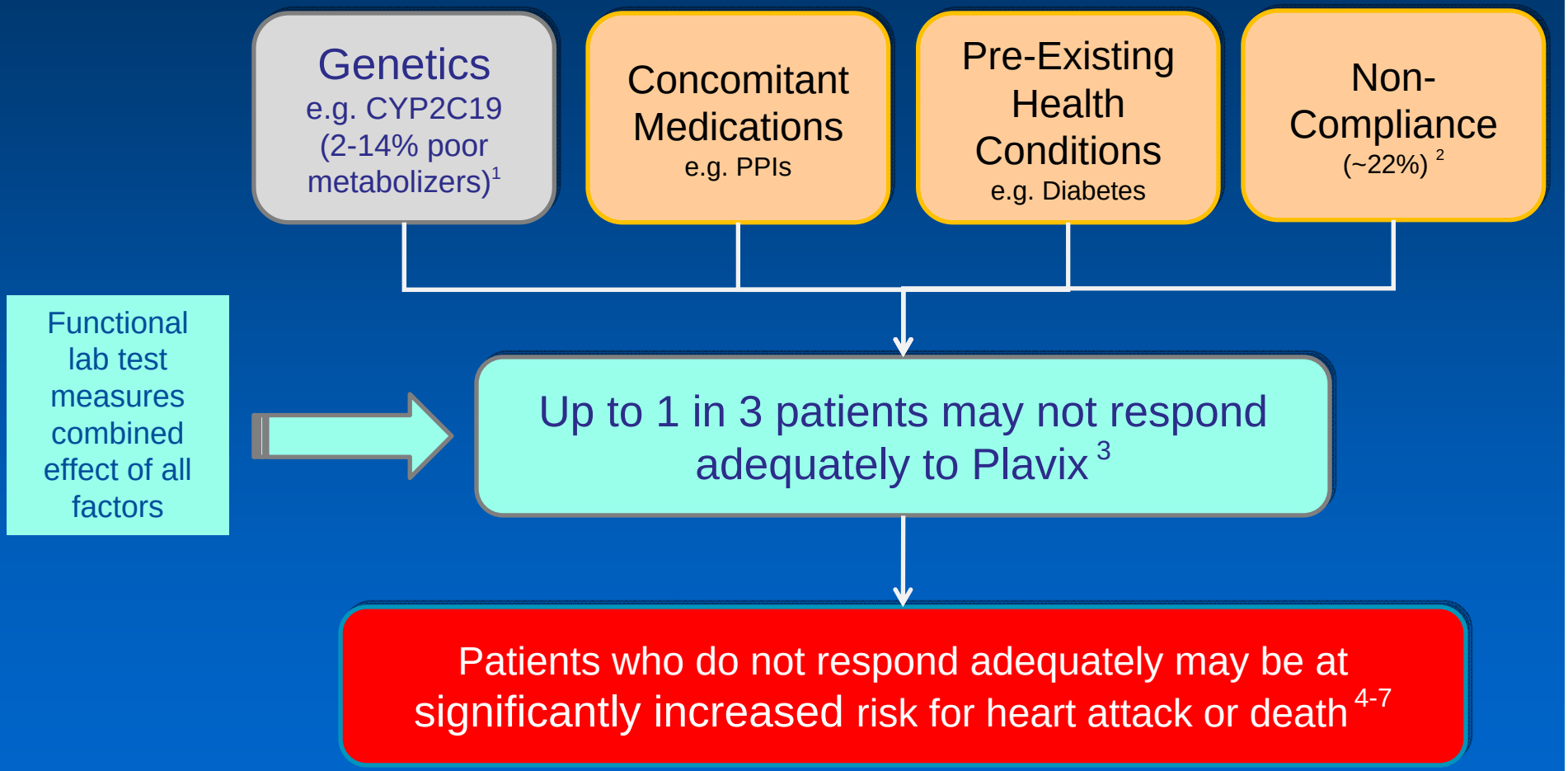
No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin L, et al. N Engl J Med. 2009.

P2Y12 Treatment Regimes

- Clopidogrel 75 mg daily or 300 mg bolus with maintenance dose of 75 mg daily. (CAPRIE, CURE) Note: This is the FDA approved dosing for clopidogrel. Discussion of other regimes is off-label.
- Clopidogrel 600 mg bolus with maintenance dose of 75 mg daily (Most common current practice)
- Clopidogrel 600 mg bolus followed by 150 mg for 7 days then 75 mg daily (OASIS-7 presented at ESC 2009, TCT 2009)
- Prasugrel, 60 mg loading dose followed by 10 mg daily. Note Black Box Warning. (Triton TIMI-38 and 44)
- Prasugrel, 60 mg loading dose followed by 5 mg daily (patient <60 kg). Per package insert, t*he effectiveness and safety of the 5 mg dose have not been prospectively studied.*
- Ticlopidine (STARS) (used if clopidogrel option required)
- Ticagrelor (Brilinta) – just approved by FDA
- Refer to Surgeon
- Combination

Inadequate Response to Antiplatelet Medications: Many Factors Can Contribute



References
1. US FDA at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm Accessed 3-13-10.
2. Serebruany, V. et al. *Am Heart J. 2009;158:925–932.*
3. Dupont, AG. et al. *Thrombosis Research. 2009 May;124(1):6-13.*
4. Patti, G. et al. *J Am Coll Cardiol. 2008; 52:1128–33.*
5. Marcucci, R. et al. *Circulation. 2009;119(2):237-42*
6. Cuisset, T. et al. *Am J Cardiol. 2008 Jun 15;101(12):1700-3*
7. Price, MJ. et al. *Eur Heart J. 2008 Apr;29(8):992-1000*

PN JCPPT1079.A