Anti-Platelet Therapy in Primary Coronary Intervention

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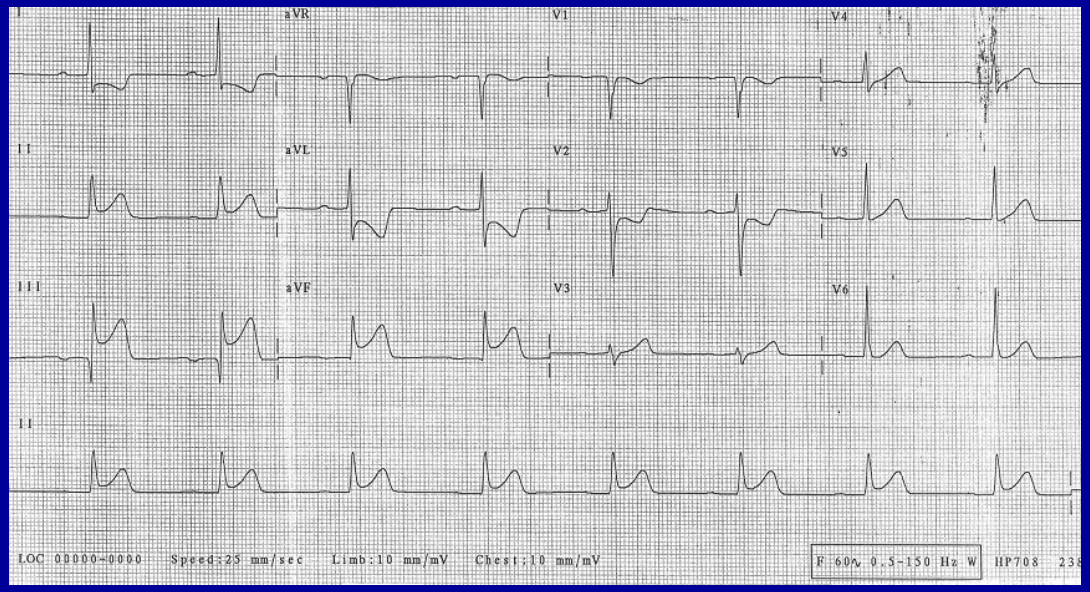
Eli Lilly

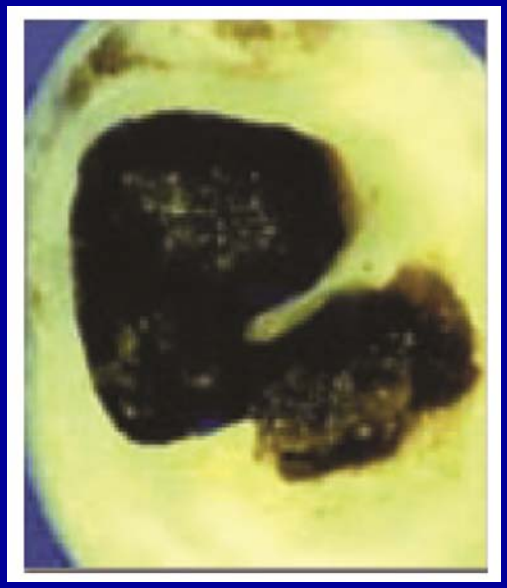
Sanofi

Accumetrics

Bristol Meyers

Treatment of STEMI





Primary PCI with stenting is the preferred treatment to establish reperfusion and improve outcome

Drug eluting stents are safe and have improved late outcomes c/w bare metal stents (mainly lower TVR and TVF)

ANTITHROMBOTIC DRUGS USED IN STEMI

I. ANTIPLATELET DRUGS

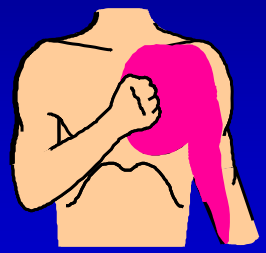
ORAL

- COX-1 inhibitor (aspirin)
- ADP $P2Y_{12}$ receptor inhibitors (ticlopidine; clopidogrel; prasugrel)
- Glycoprotein IIb/IIIa inhibitors (abciximab; eptifibatide; tirofiban)

II. ANTICOAGULANT DRUGS

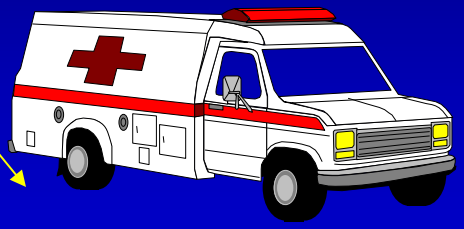
- Anti-Factor II (anti-thrombins)
  - Indirect Thrombin Inhibitors (UFH & LMWH)
  - Direct Thrombin Inhibitors (Bivalirudin)

Options for Transport of Patients With STEMI and Initial Reperfusion Treatment



Aspirin 325 mg

Call 9-1-1
Call fast



Onset of symptoms of STEMI

9-1-1 EMS Dispatch

EMS on-scene

- Encourage 12-lead ECGs.
- Consider prehospital fibrinolytic if capable and EMS-to-needle within 30 min.

EMS Triage Plan

Hospital fibrinolysis: Door-to-Needle within 30 min.

Not PCI capable

Inter-Hospital Transfer

PCI capable

GOALS

5 min. | 8 min. | EMS Transport

Patient

EMS

Dispatch
1 min.

Prehospital fibrinolysis
EMS-to-needle within 30 min.

EMS transport
EMS-to-balloon within 90 min.

Patient self-transport
Hospital door-to-balloon within 90 min.

Golden Hour = first 60 min.

Total ischemic time: within 120 min.

Antman EM, et al. *J Am Coll Cardiol 2008.* Published ahead of print on December 10, 2007. Available at http://content.onlinejacc.org/cgi/content/full/j.jacc.2007.10.001. Figure 1.

Aspirin post-PCI

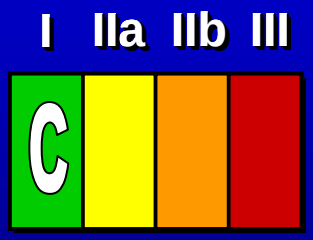
After the PCI procedure, in patients without allergy or increased risk of bleeding, ASA 162-325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after drug-eluting stent implantation, *after* which daily chronic ASA use should be continued indefinitely at a dose of 75 to 162 mg.

Those with an increased risk of bleeding:

ASA 81 mg a day indefinitely

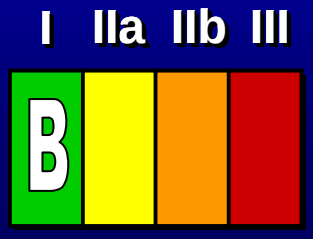
Recommendations for the use of Thienopyridines

A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:



Clopidogrel at least 300 mg to 600mg† should be given as early as possible before or at the time of primary or non-primary PCI.

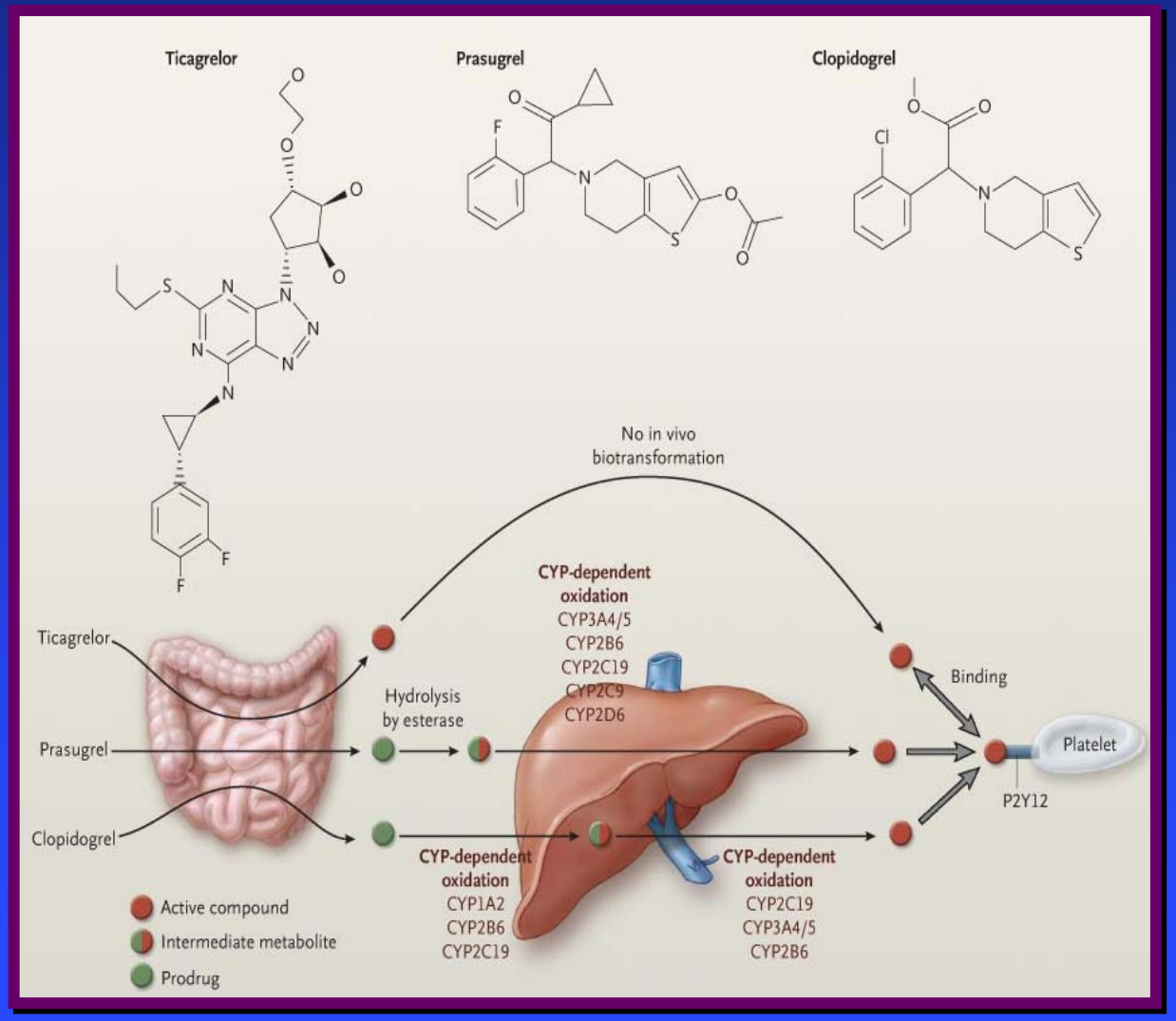
or



Prasugrel 60 mg should be given as soon as possible for primary PCI.

Platelet ADP P_2Y_{12} Receptor Inhibitors

Clopidogrel, Prasugrel, and Ticagrelor: Biotransformation and Mode of Action

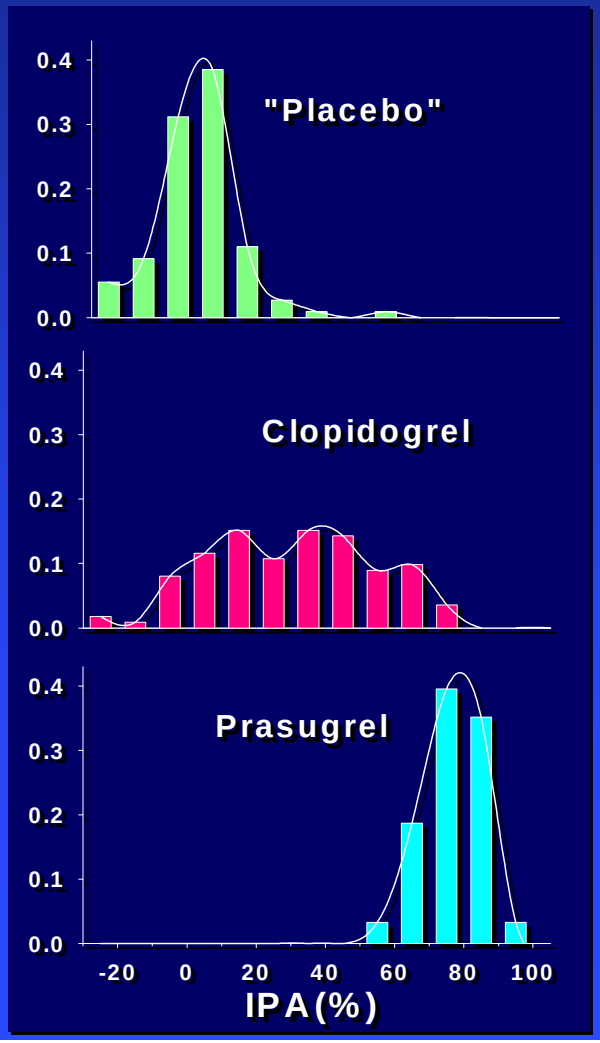


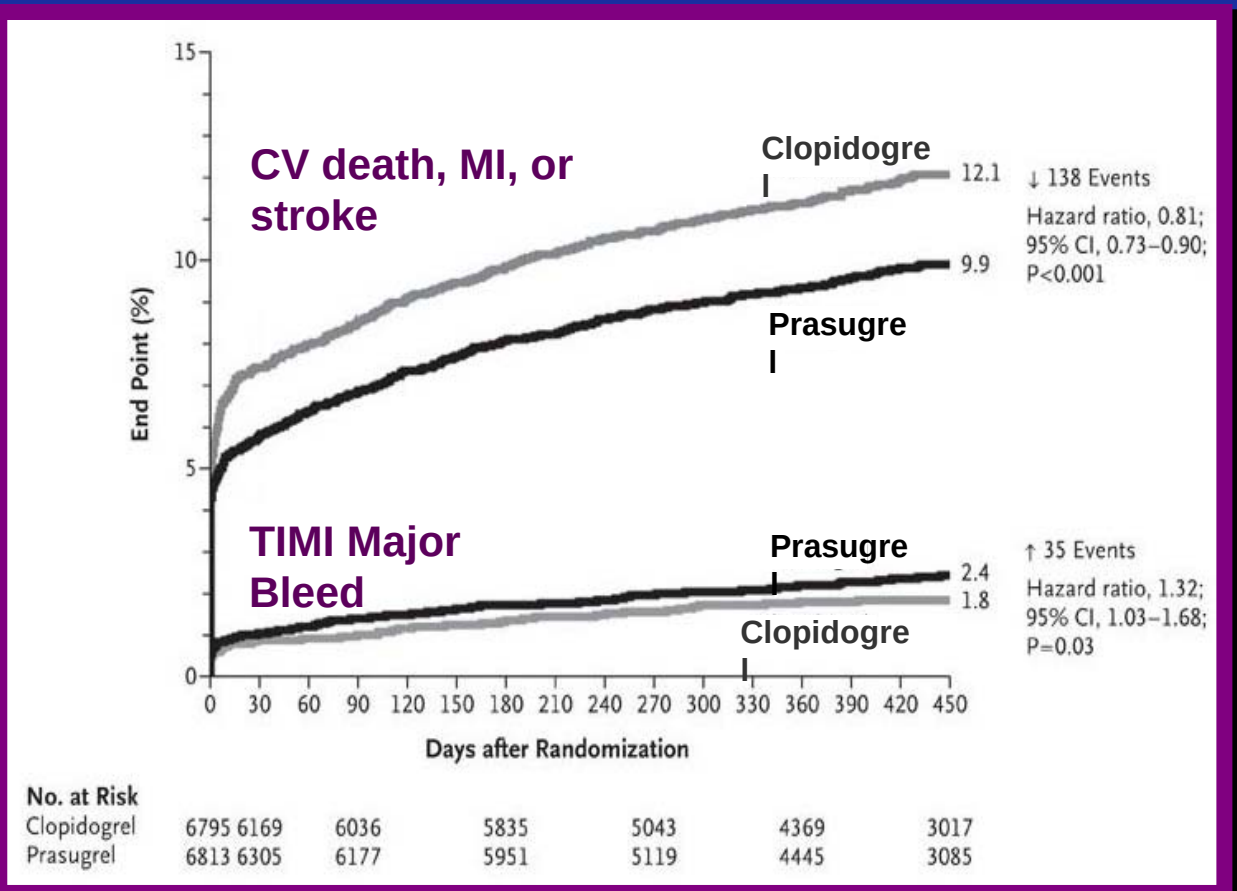
Schomig A. NEJM 2009;361:1108.

Prasugrel

TRITON – TIMI 38 Trial: Prasugrel vs Clopidogrel

13,608 Patients - ACS and PCI

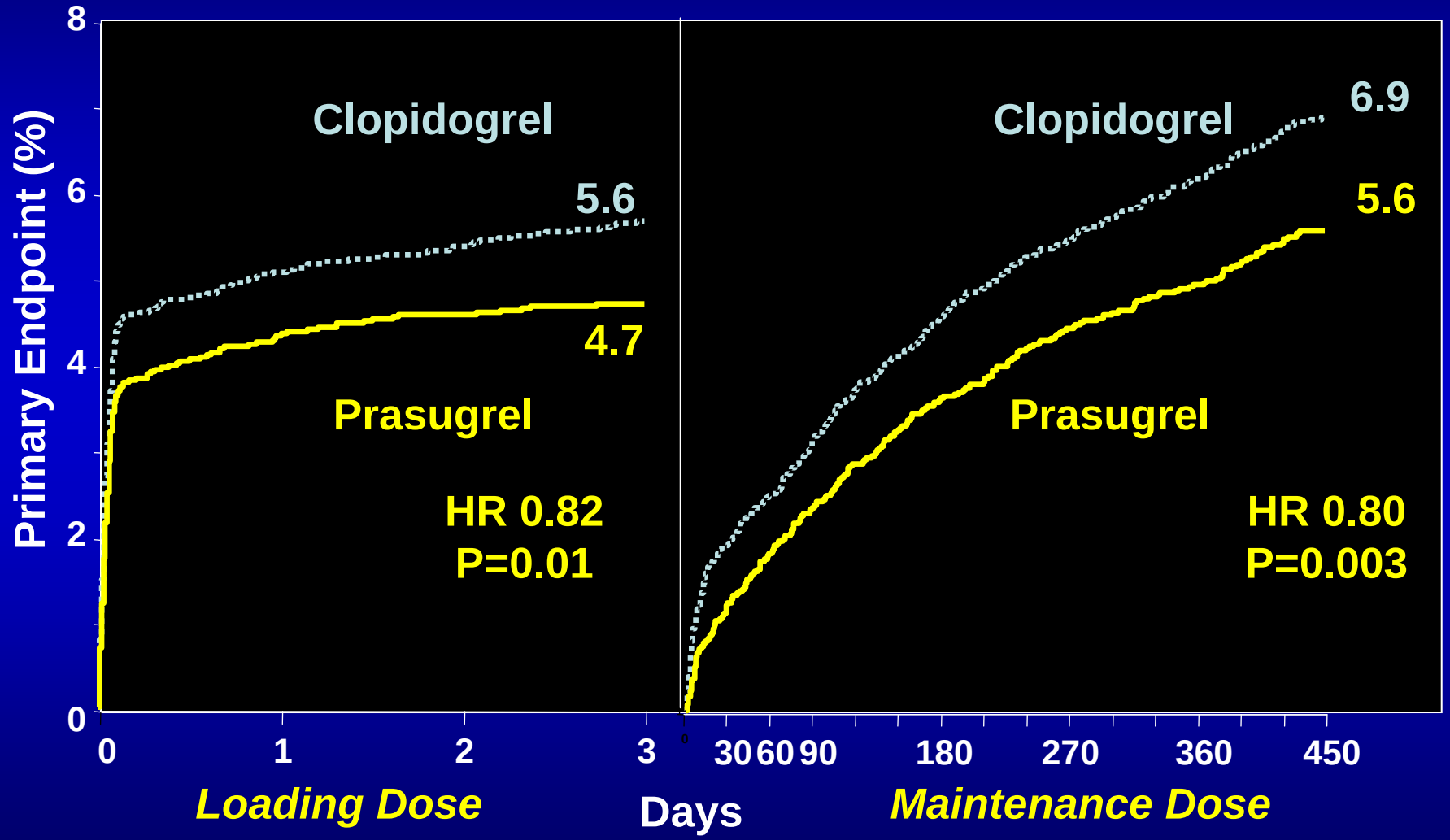




Wiviott S et al. NEJM 2007;357:2001.

TRITON TIMI-38

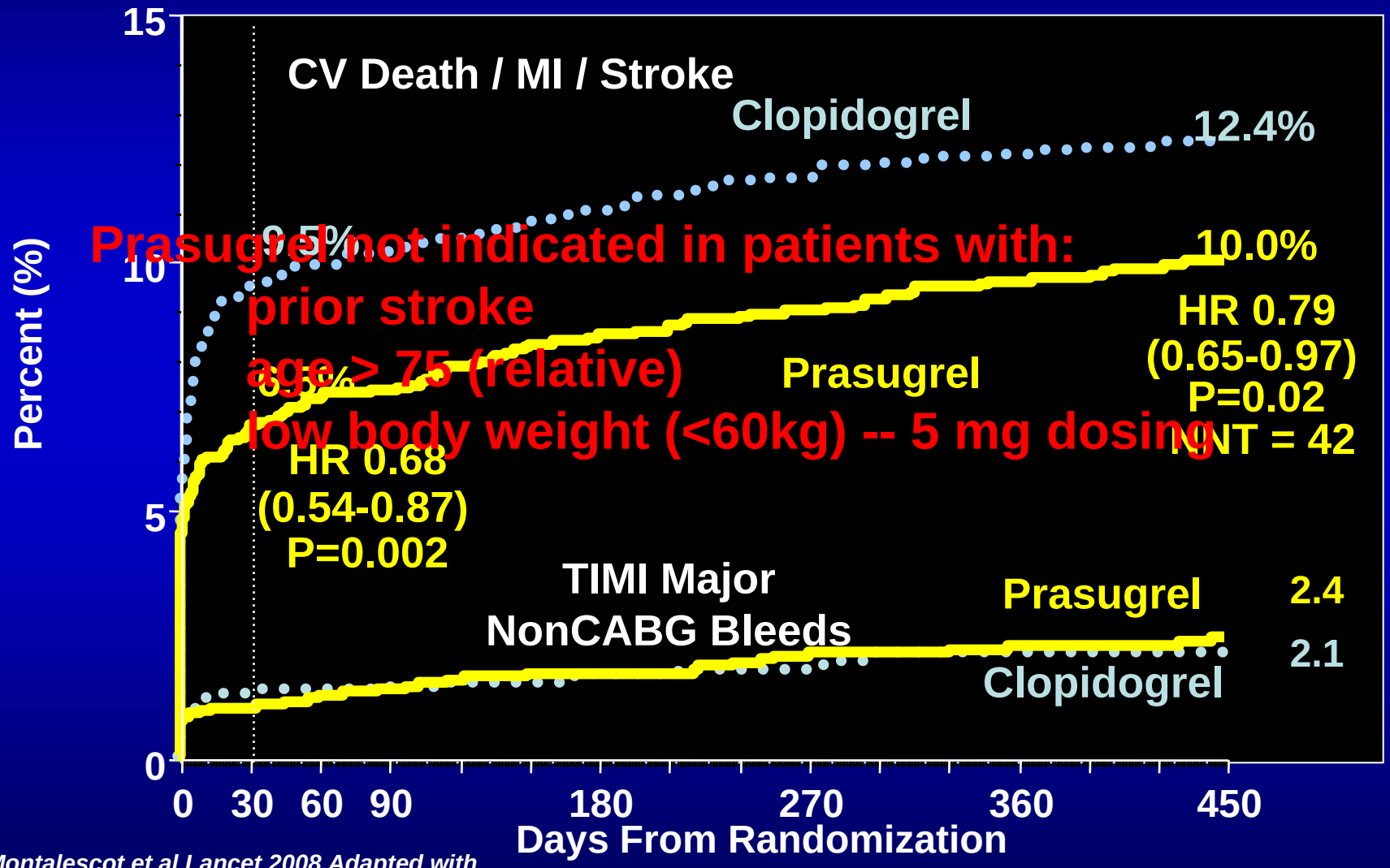
Timing of Benefit (Landmark Analysis - 3 days)



Adapted with permission from Antman EM JACC 2008.

TRITON TIMI-38

STEMI Cohort N=3534

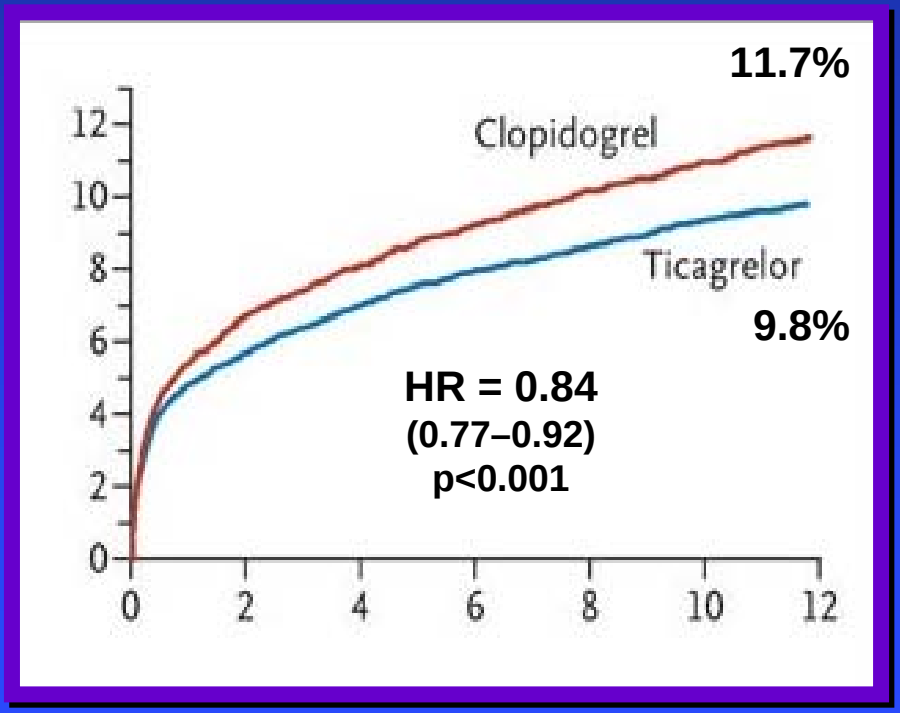


Montalescot et al Lancet 2008.Adapted with permission from Antman EM.

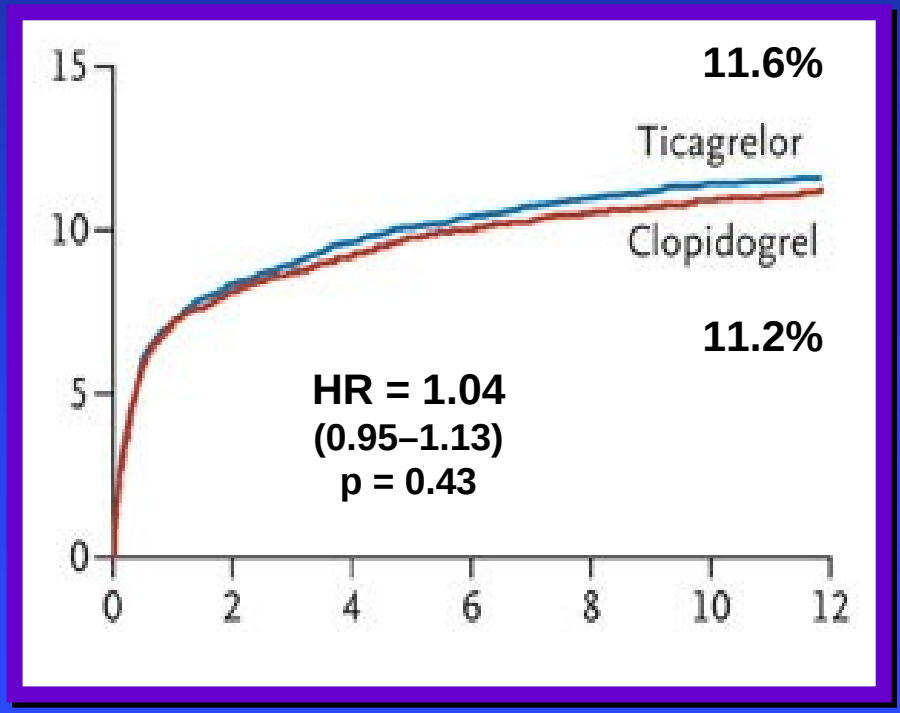
PLATO Trial

Ticagrelor vs Clopidogrel in ACS

Ischemic Endpoint



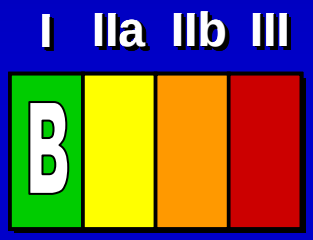
Bleeding Endpoint



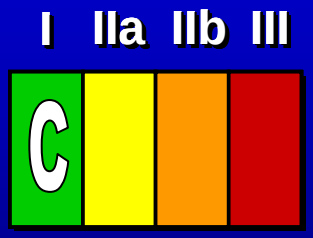
Wallentin L et al. NEJM 2009;361:1045

Thienopyridines

The duration of thienopyridine therapy should be as follows:



a. In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily or prasugrel 10 mg daily should be given for at least 12 months;



b. If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered.

Urgent Non-cardiac Surgery

If possible, operate on ASA 81 mg a day

BMS: 4 weeks of DAPT, then operate week 5-6

DES: 3-6 months of DAPT

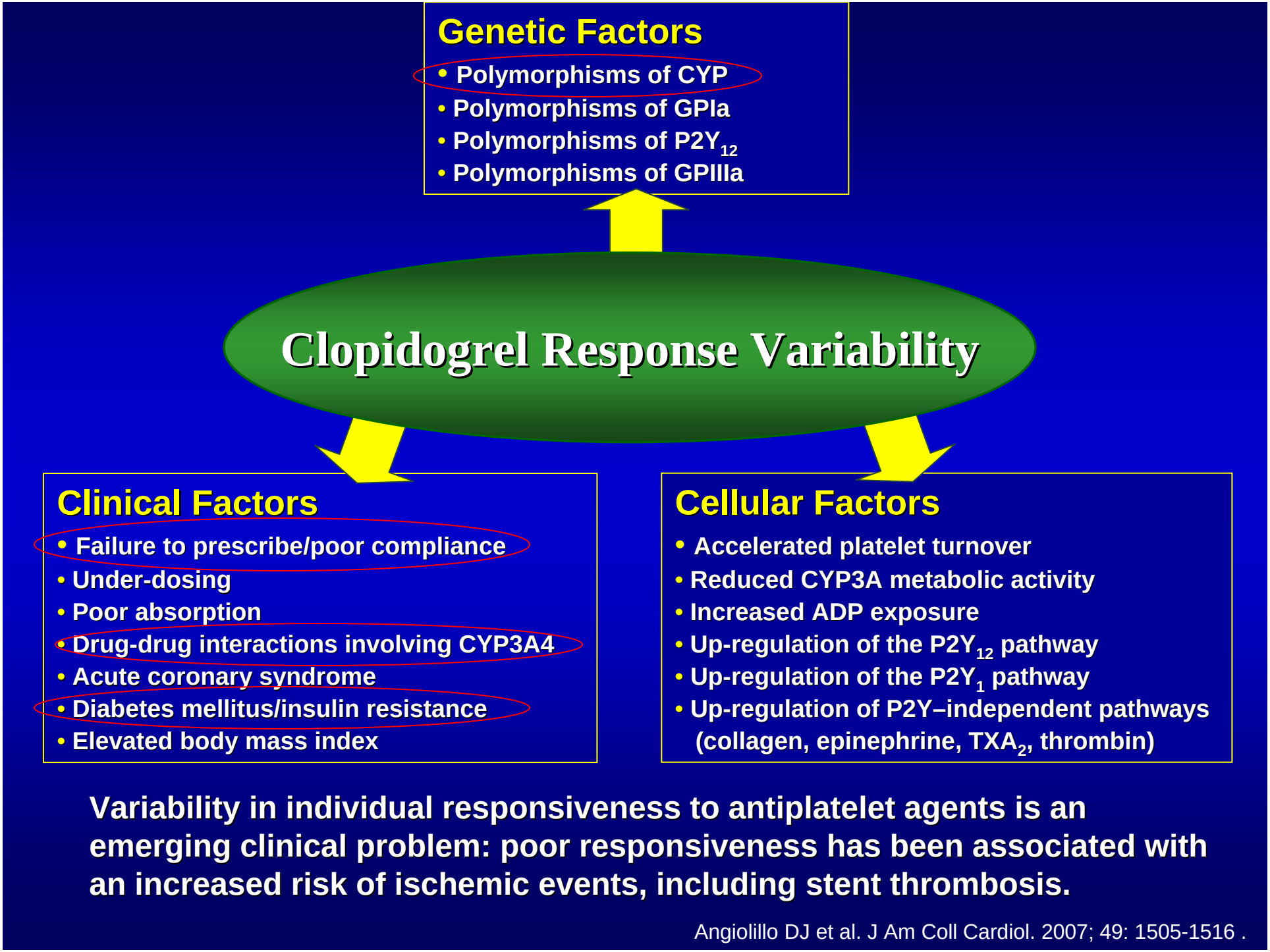
hold thienopyridine 5-7 days (daily PRA testing)

resume thienopyridine as soon as possible post-op

Elective surgery: wait 1 year

Bleeding: tailored treatment to individual

ECASA 81mg a day vs thienopyridine alone



Variability in individual responsiveness to antiplatelet agents is an emerging clinical problem: poor responsiveness has been associated with an increased risk of ischemic events, including stent thrombosis.

Angiolillo DJ et al. J Am Coll Cardiol. 2007; 49: 1505-1516 .

Clopidogrel - Pharmacogenetic Information

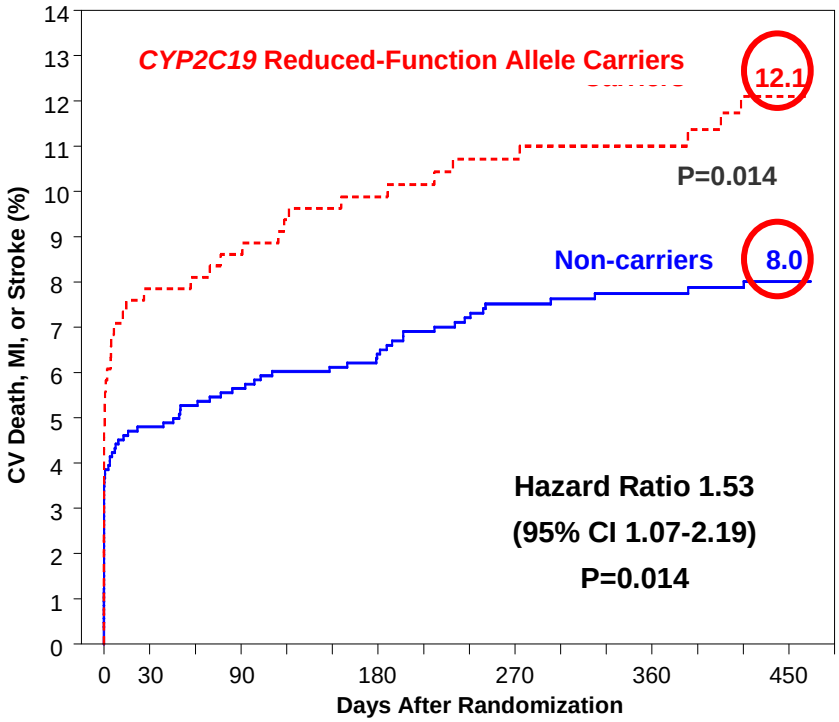
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Clopidogrel product information. Revised March 2010

CYP2C19 and Outcomes: Prasugrel and Clopidogrel, N=2,933

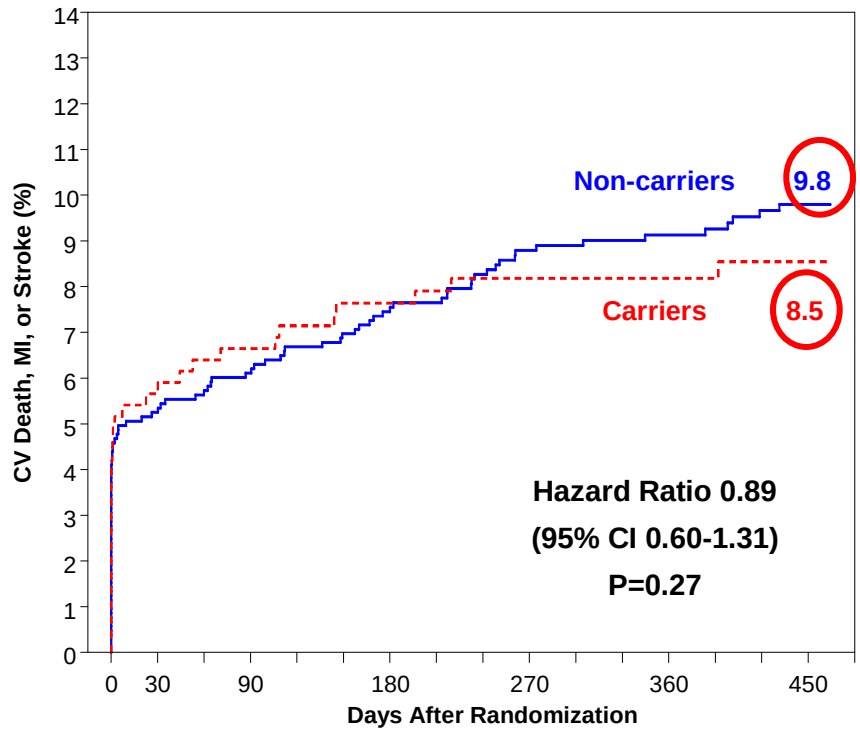
Clopidogrel



Number at Risk:

Non-Carrier	1064	1009	999	980	870	755	542
Carrier	395	364	360	348	306	270	181

Prasugrel



Number at Risk:

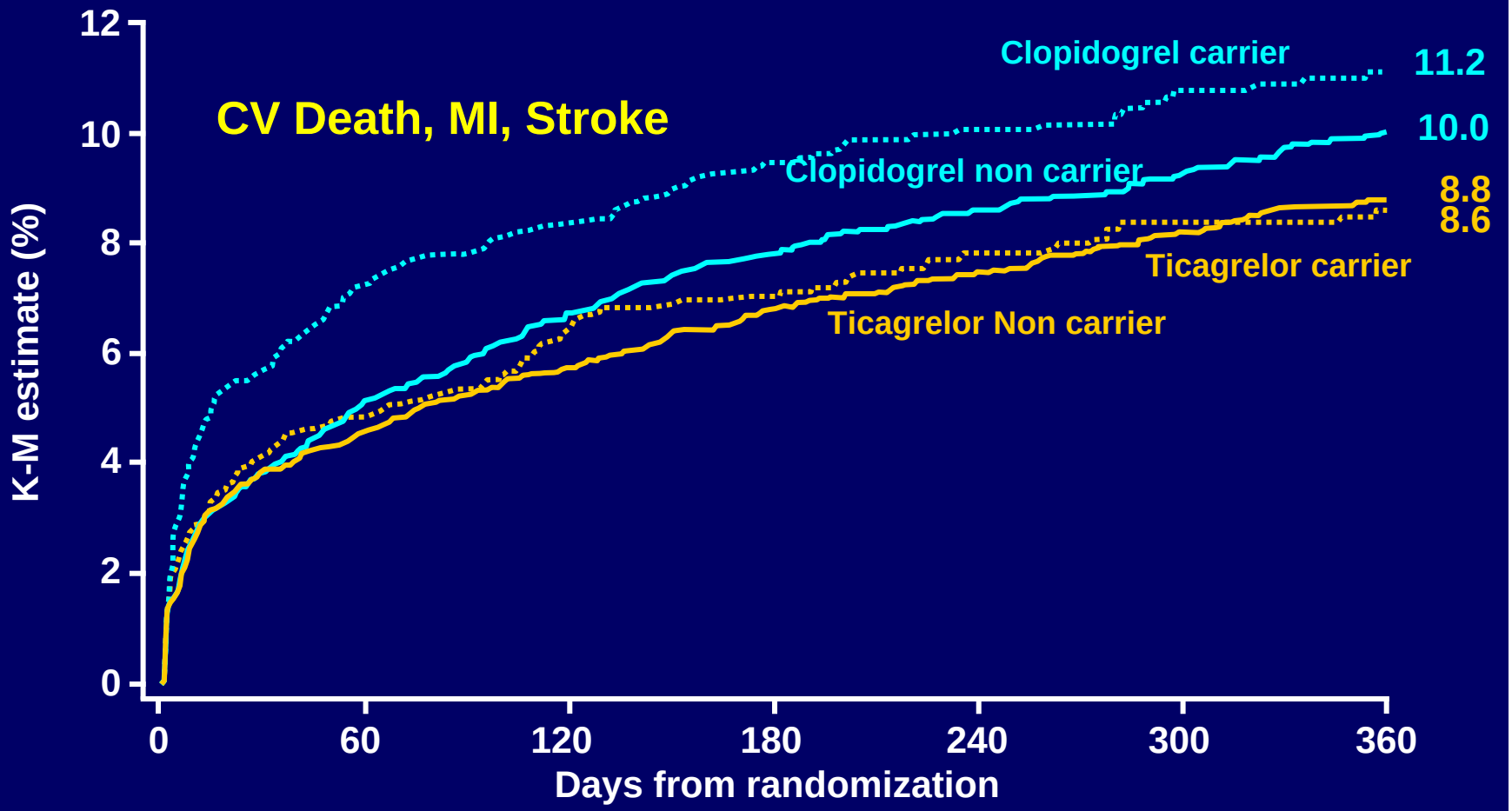
Non-Carrier	1048	991	982	951	849	750	541
Carrier	407	383	376	364	320	276	188

*** Carriers ~30% of the population**

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

***Mega et al Circulation*. 2009;119**

CYP2C19 and Outcomes: Clopidogrel and Ticagrelor, N=10,285



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
Ticagrelor LOF	1,384	1,305	1,274	1,250	1,053	834	683
Ticagrelor No LOF	3,554	3,352	3,301	3,222	2,718	2,127	1,761

Wallentin et al. *Lancet.* 2010; O**nline, 2010 DOI:10.1016/S0140-6736(10)61274-3**

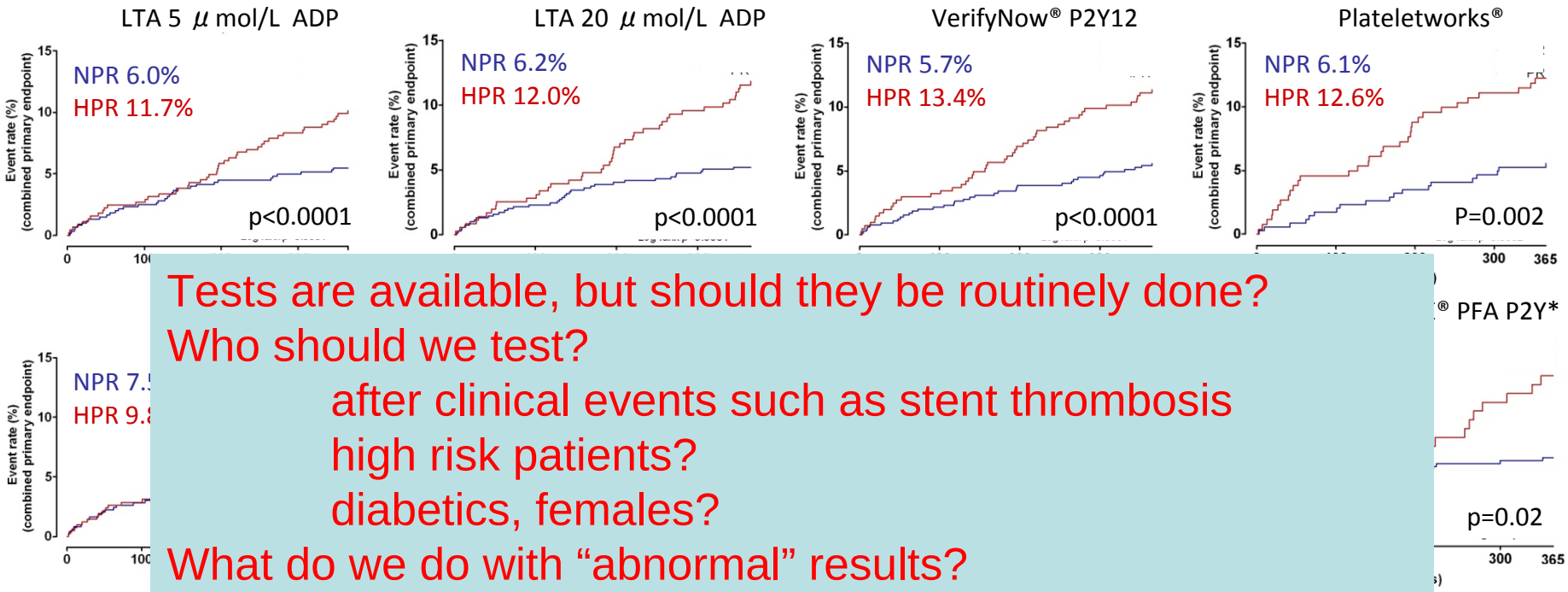
Genetic Testing

- Predictor of adverse events including stent thrombosis, but
- Expensive test
  - Upward of $500
  - Not readily available
- Variable phenotypic response when checking platelet function testing:
  - Patients with LOF alelles may have variable plt reactivity when functional testing performed

Composite of death, non-fatal myocardial infarction, definite stent thrombosis and stroke

HPR = high-on treatment platelet reactivity

NPR = non-HPR



Tests are available, but should they be routinely done?

Who should we test?

after clinical events such as stent thrombosis

high risk patients?

diabetics, females?

What do we do with “abnormal” results?

– more clopidogrel (reload, double dose?)

-- switch to prasugrel?

Platelet Function Tests

- **Platelet Aggregation**
  - Light transmittance aggregometry (LTA) ← *gold standard*
  - Impedance platelet aggregation
- **Flow Cytometry**
  - GPIIb/IIIa receptor activation
  - P-selectin expression
  - Monocyte-platelet aggregates
  - Vasodilator-associated stimulated phosphoprotein (VASP)
- **Point-of-care**
  - Ultegra rapid platelet function analyzer (VerifyNow)
  - Thromboelastagraph (TEG)
  - Plateletworks
  - Cone and plate(let) analyzer (IMPACT)
- **Genetic testing**

adapted from Angiolillo DJ et al. J *Am Coll Cardiol.* 2007.

GRAVITAS

Successful PCI with DES (with 600mg clopidogrel load) without major complication or GPIIb/IIIa use

VerifyNow P2Y12 Assay 12-24 hours post-PCI

PRU ≥ 230?

Yes → **Non-Responder**

R ACS

- **A** N = 1100 → ***"Tailored Therapy"*** clopidogrel 600-mg*, then clopidogrel 150-mg/day
- **B** N = 1100 → **"Standard Therapy"** placebo loading dose, then clopidogrel 75mg +placebo/day

No → **Responder** → Random Selection

- **C** N = 583 → **"Standard Therapy"** placebo loading dose clopidogrel 75mg +placebo/day

Clinical Follow-up And Platelet Function Assessment at 30 days, 6M

Primary Endpoint: 6 month CV Death, Non-Fatal MI, ARC definite/prob ST

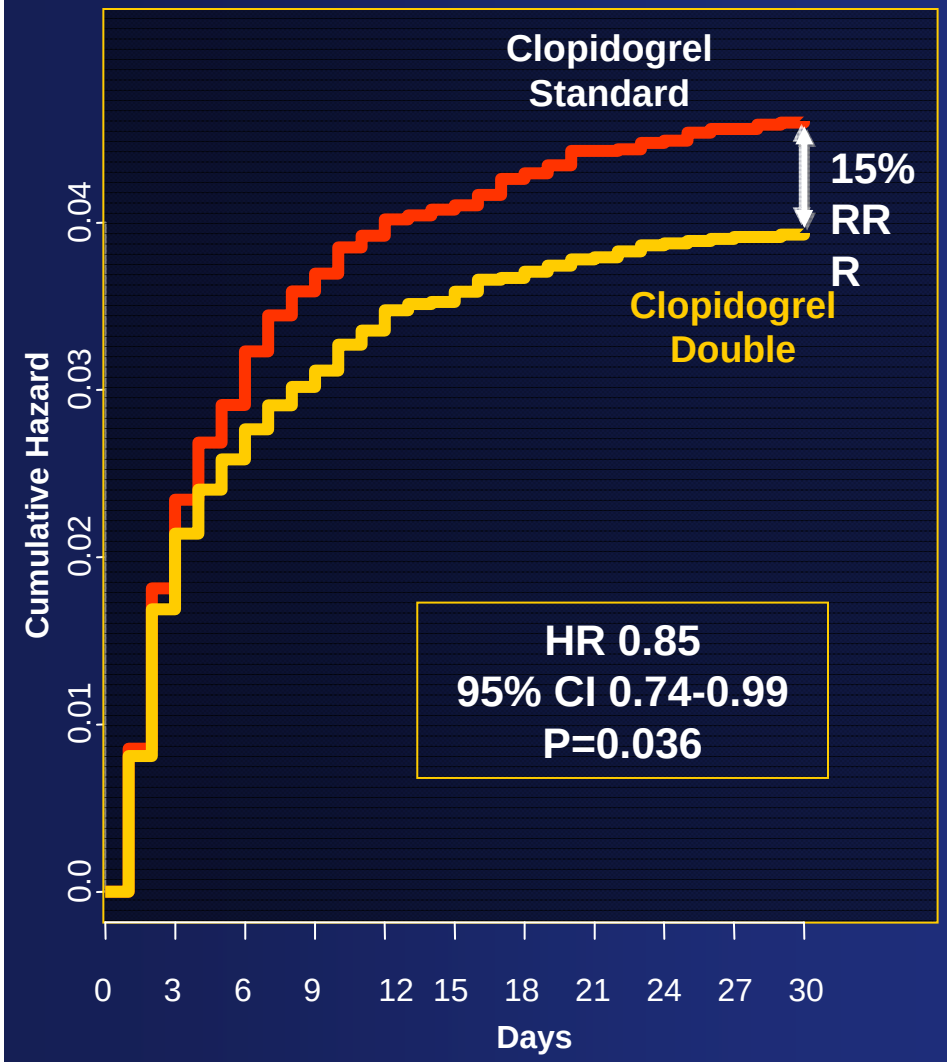
Safety Endpoint: GUSTO Moderate or Severe Bleeding

*total first day dose

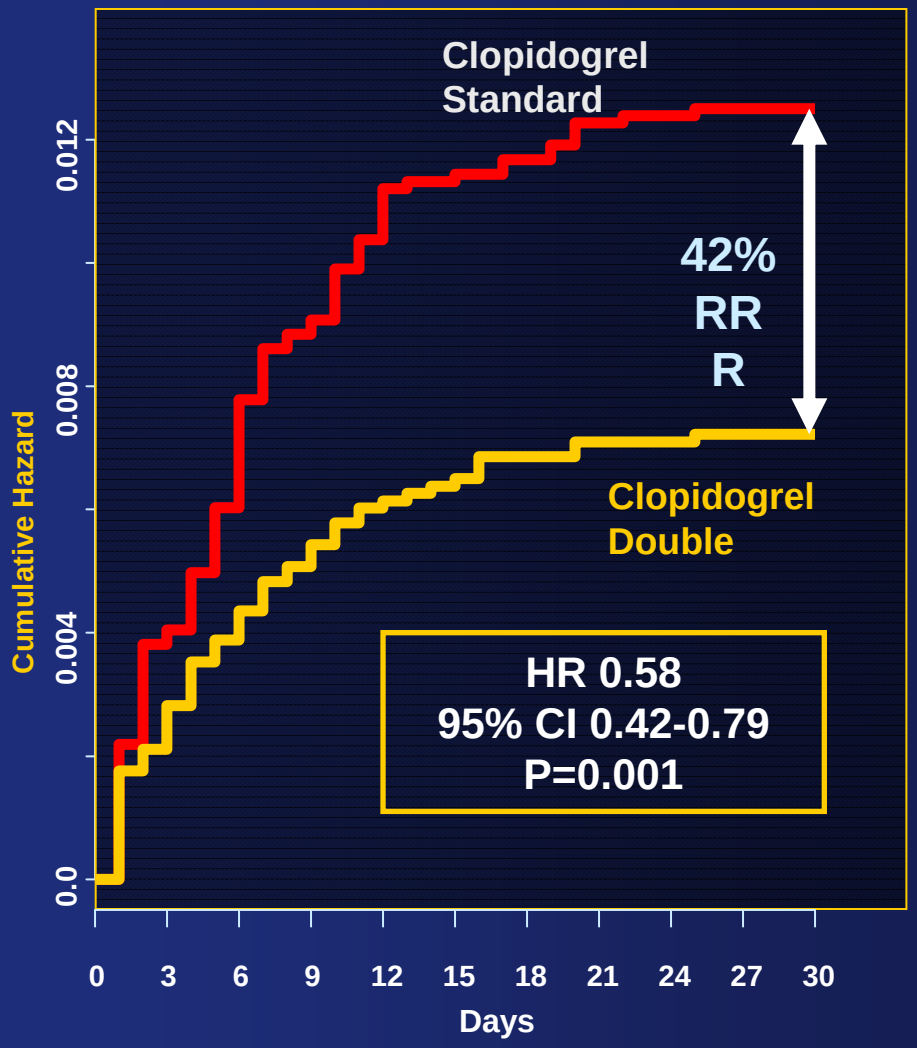
Price MJ et al, Am Heart J 2009

CURRENT Efficacy Outcomes: PCI Patients

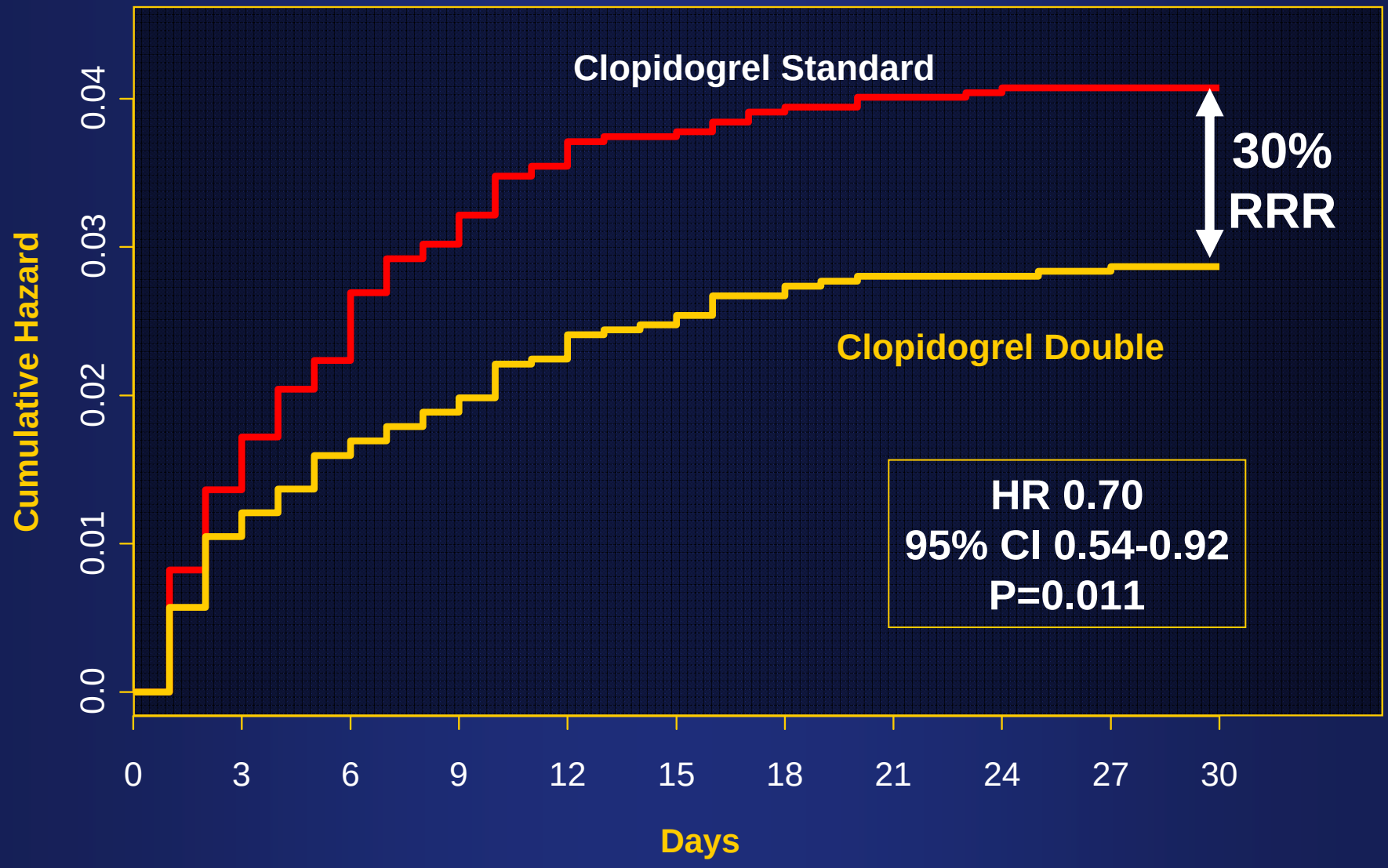
CV Death, MI, Stroke



Definite Stent Thrombosis



STEMI-PCI: Myocardial Infarction or All Stent Thrombosis



2009 Updated Labeling for Clopidogrel–PPI Interaction

- FDA-required label changes:[2]
  - Warning: "Co-administration of Plavix with omeprazole, a proton pump inhibitor that is an inhibitor of *CYP2C19*, reduces the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart"
  - Drug-Drug Interactions: "Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine"
  - Based on PK/PD studies showing concomitant omeprazole reduced clopidogrel active metabolite and effect on platelets[1]
    - Did not include COGENT study data[2]
- EMEA warning extends to discourage concomitant use of all PPIs[3]
  - Concomitant use of drugs that inhibit CYP2C19 discouraged; concomitant use of <u>any</u> PPI "should be avoided unless absolutely necessary"[4]

EMEA=European Medicines Agency; FDA=Food and Drug Administration; PD=pharmacodynamic; PK=pharmacokinetic.

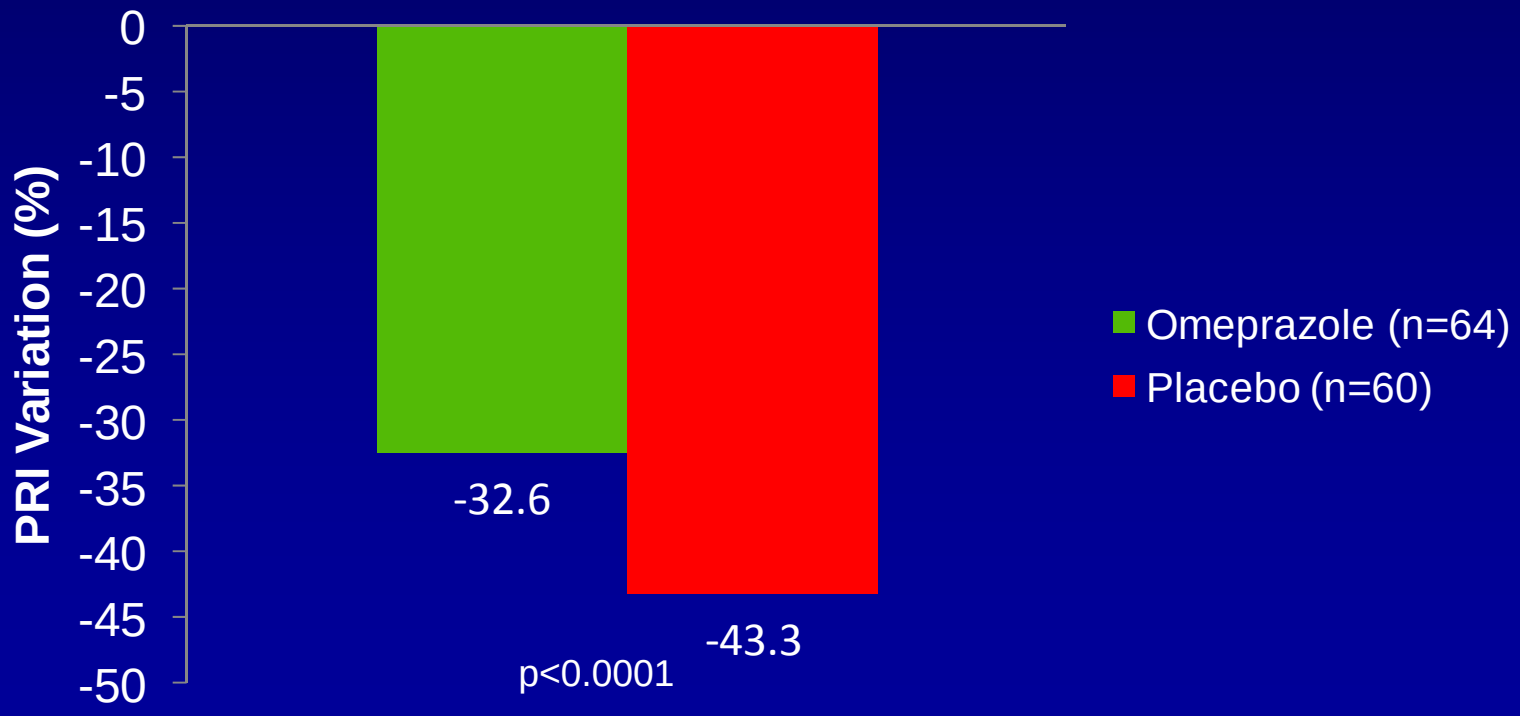
[1]Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafety InformationforHeathcareProfessionals/ucm190787.htm. Published November 17, 2009. Accessed January 22, 2010. [2]Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2009. [3]Wathion N. http://www.emea.europa.eu/humandocs/PDFs/ EPAR/Plavix/32895609en.pdf. Published May 29, 2009. Accessed January 22, 2010. [4]Plavix [summary of product characteristics]. Paris, France: Sanofi Pharma Bristol-Myers Squibb SNC; 2009.

Clopidogrel and PPIs – The OCLA study

Clopidogrel is a prodrug; requires conversion by the liver primarily via CYP3A4 and CYP2C19 to an active metabolite

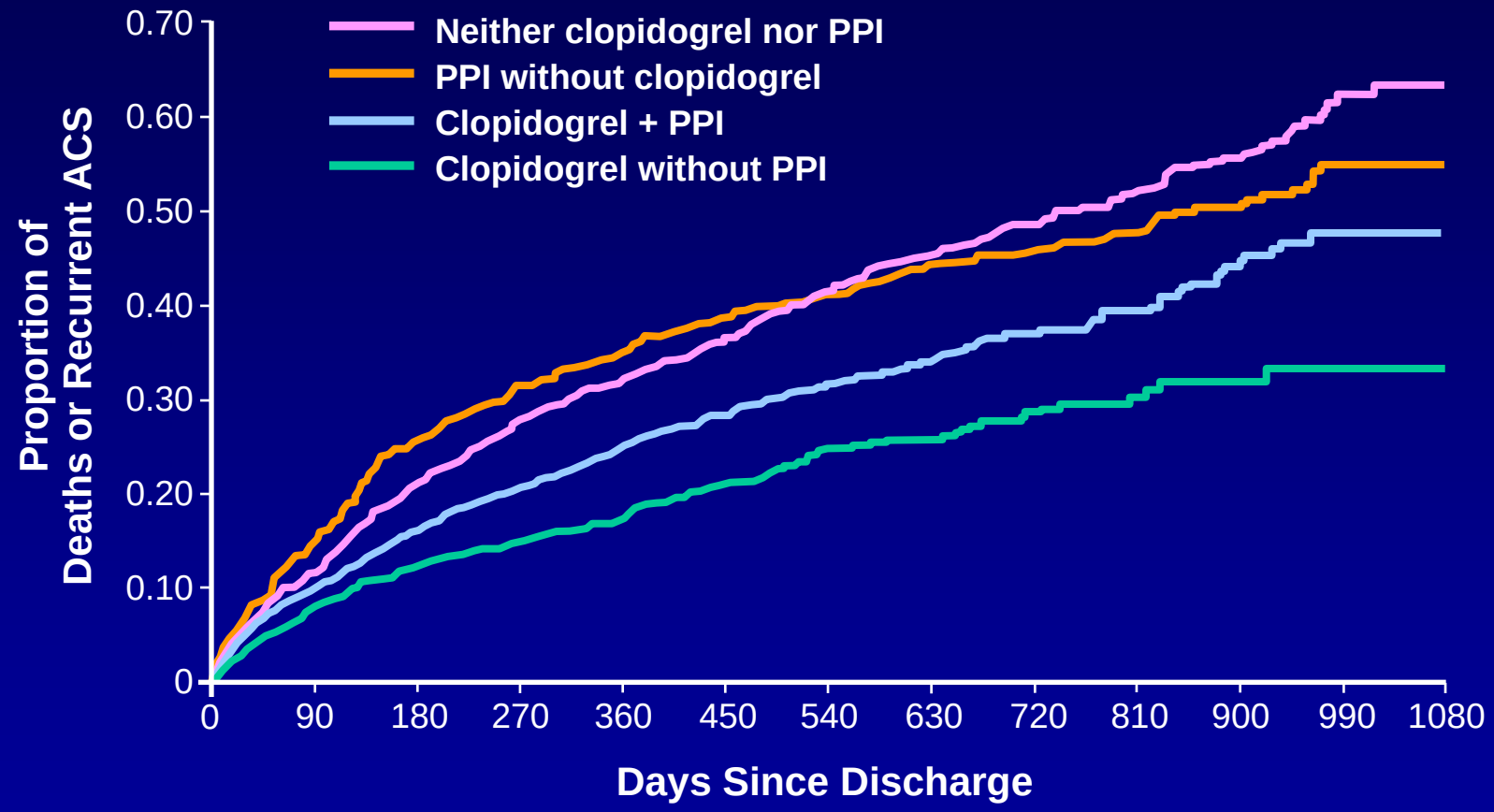
PPIs are strong inhibitors of CYP2C19 activity

PRI: Platelet Reactivity Index as measured by vasodilator stimulated phosphoprotein (VASP)



Gilard et al. J Am Coll Cardiol 2008;51:256-60.

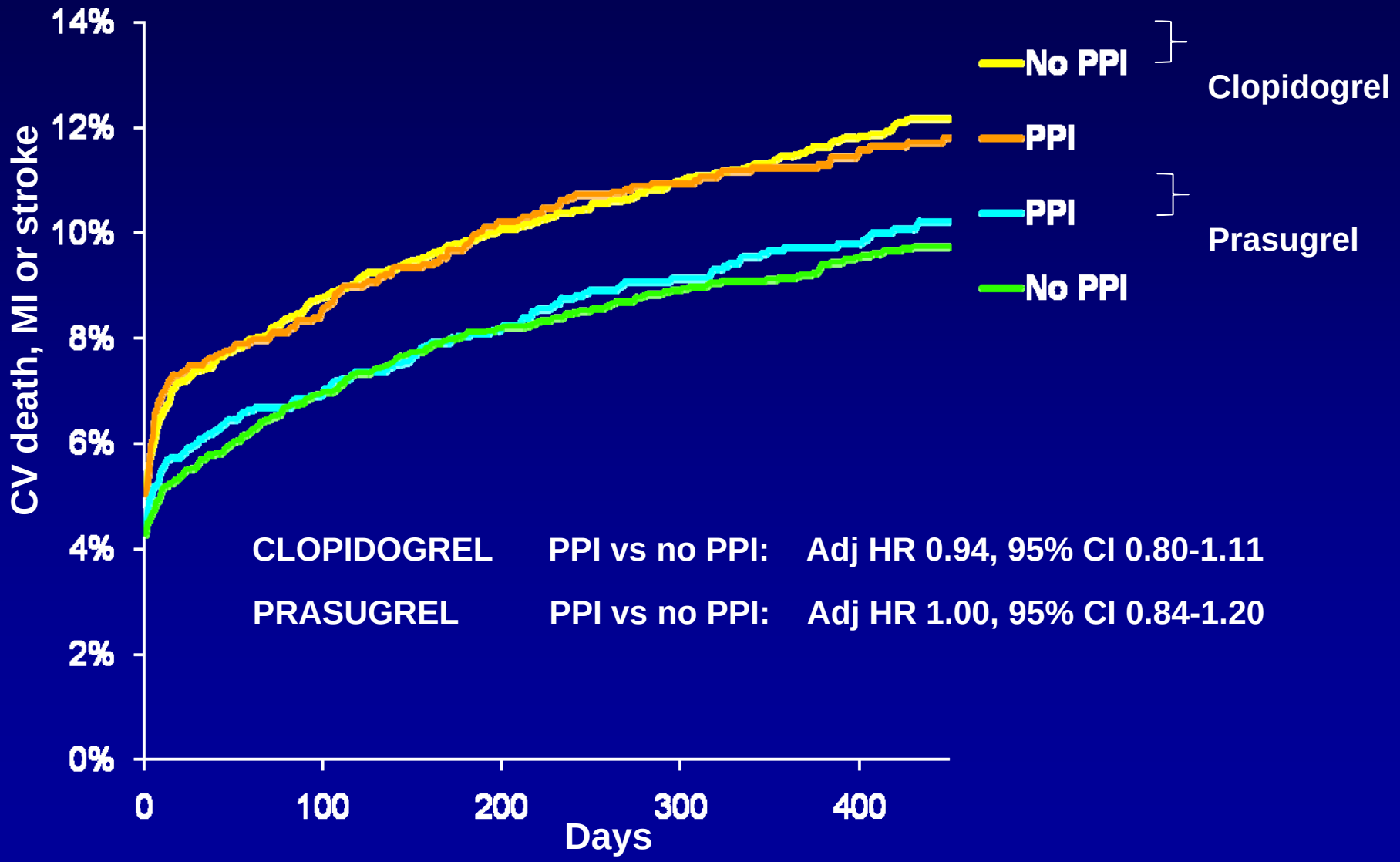
Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI



Ho PM, Maddox TM, Wang L, et al. JAMA. 2009;301(9):937-944.

Primary endpoint stratified by use of a PPI

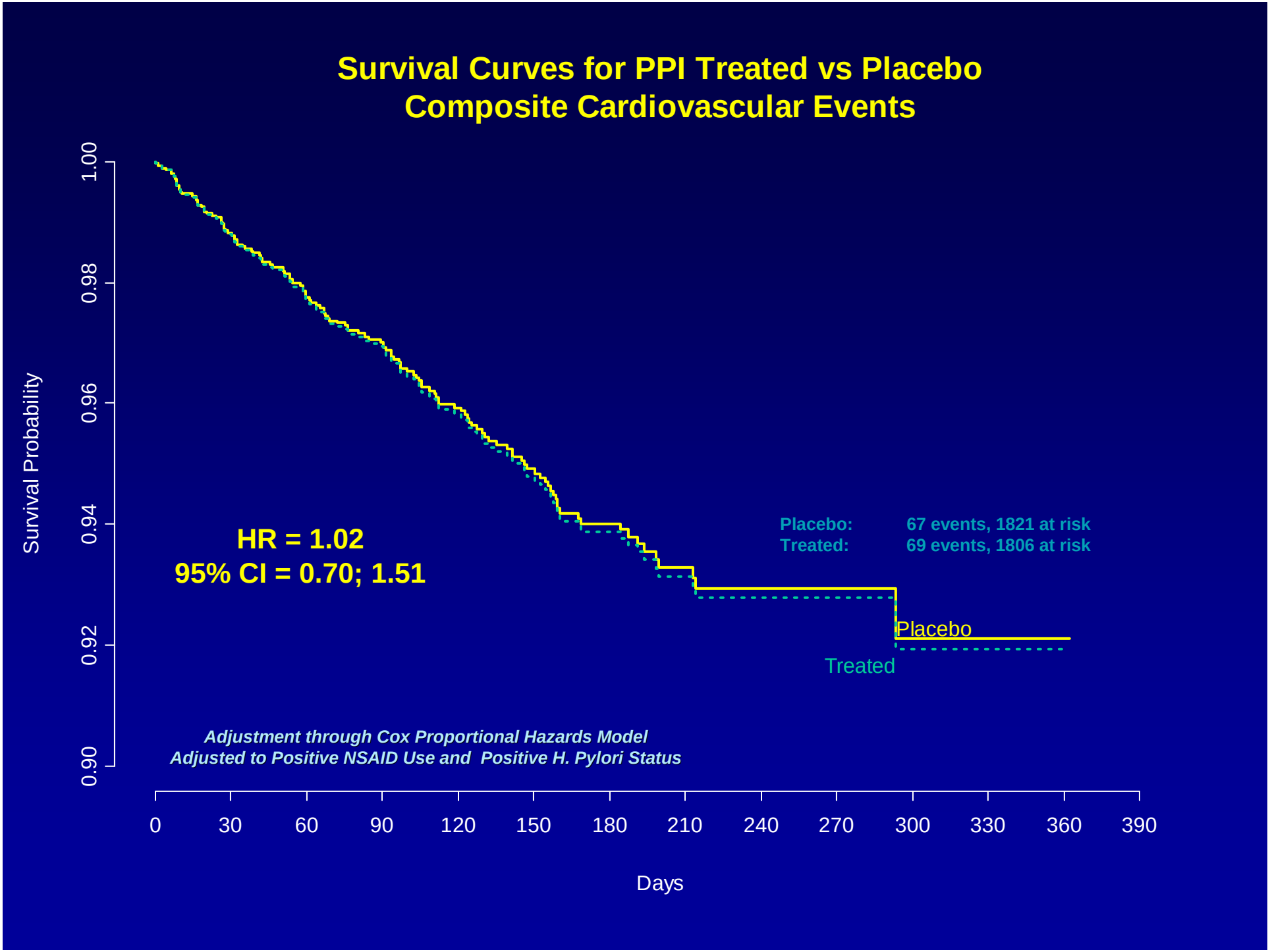
PPI use at randomization (n= 4529)



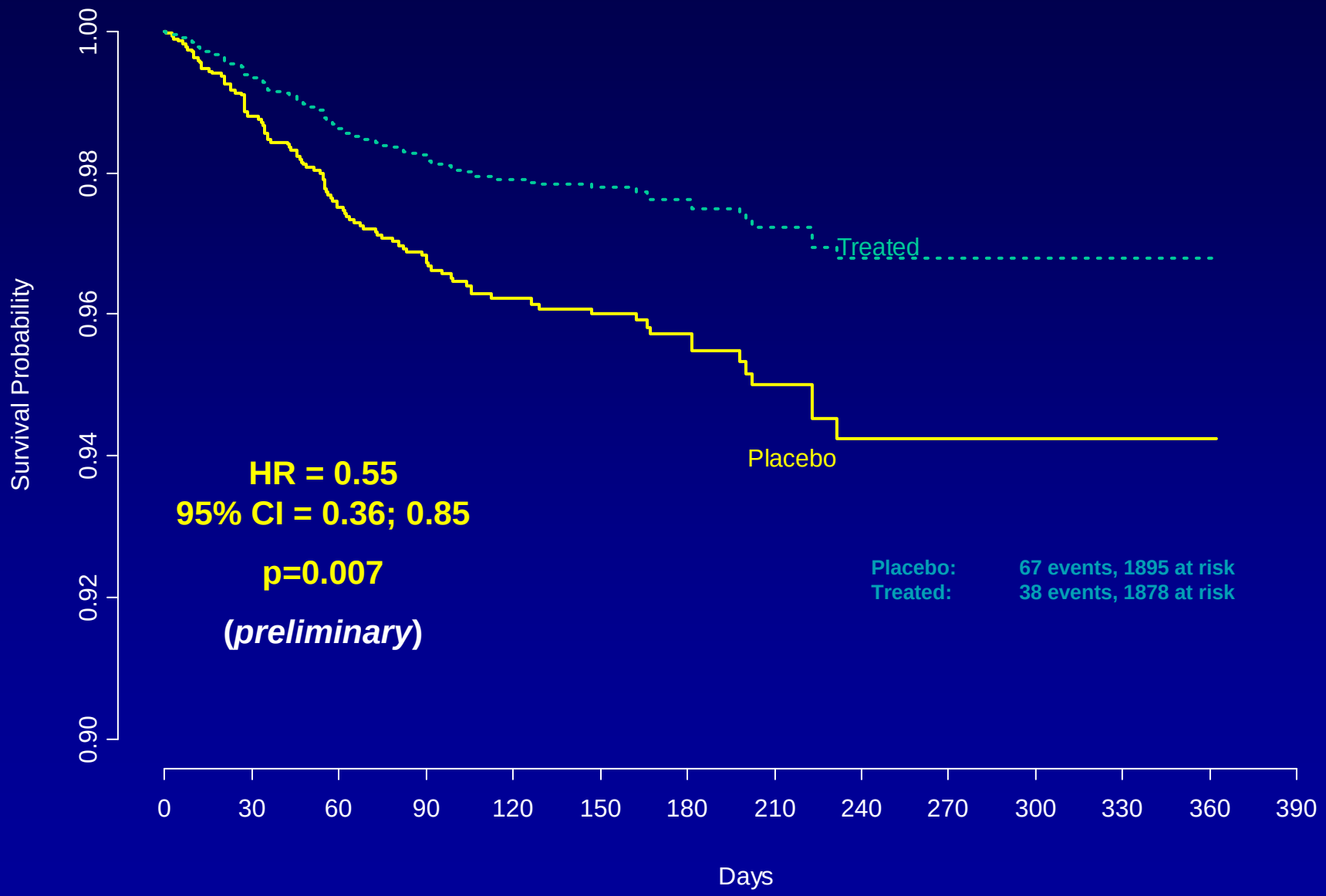
CLOPIDOGREL **PPI vs no PPI:** **Adj HR 0.94, 95% CI 0.80-1.11**

PRASUGREL **PPI vs no PPI:** **Adj HR 1.00, 95% CI 0.84-1.20**

O'Donoghue ML, Braunwald E, Antman EM, et al. *Lancet*. 2009.


Survival Curves for PPI Treated vs Placebo
Composite Cardiovascular Events
Survival Probability
1.00
0.98
0.96
0.94
0.92
0.90
HR = 1.02
95% CI = 0.70; 1.51
Placebo: 67 events, 1821 at risk
Treated: 69 events, 1806 at risk
Placebo
Treated
Adjustment through Cox Proportional Hazards Model
Adjusted to Positive NSAID Use and Positive H. Pylori Status
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Days

Survival Curves for PPI Treated vs Placebo
Composite GI Events



Thienopyridines after 1 year?

Very Late Stent Thrombosis

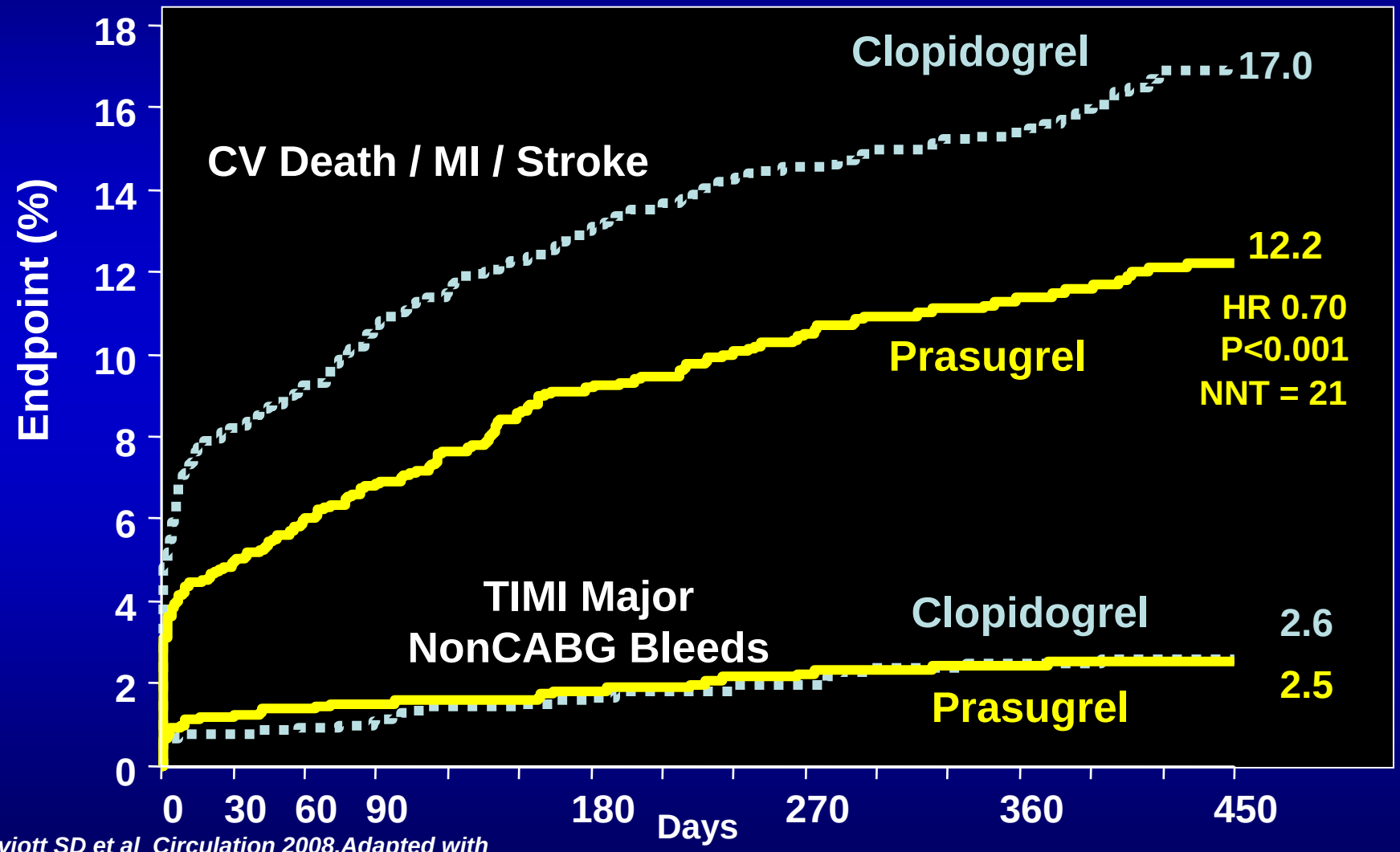
To be answered in “near future” by several large scale *DAPT* Trials

Event free patients at 12 months randomized to thienopyridine vs placebo along with daily aspirin

TRITON TIMI-38

Diabetic Subgroup

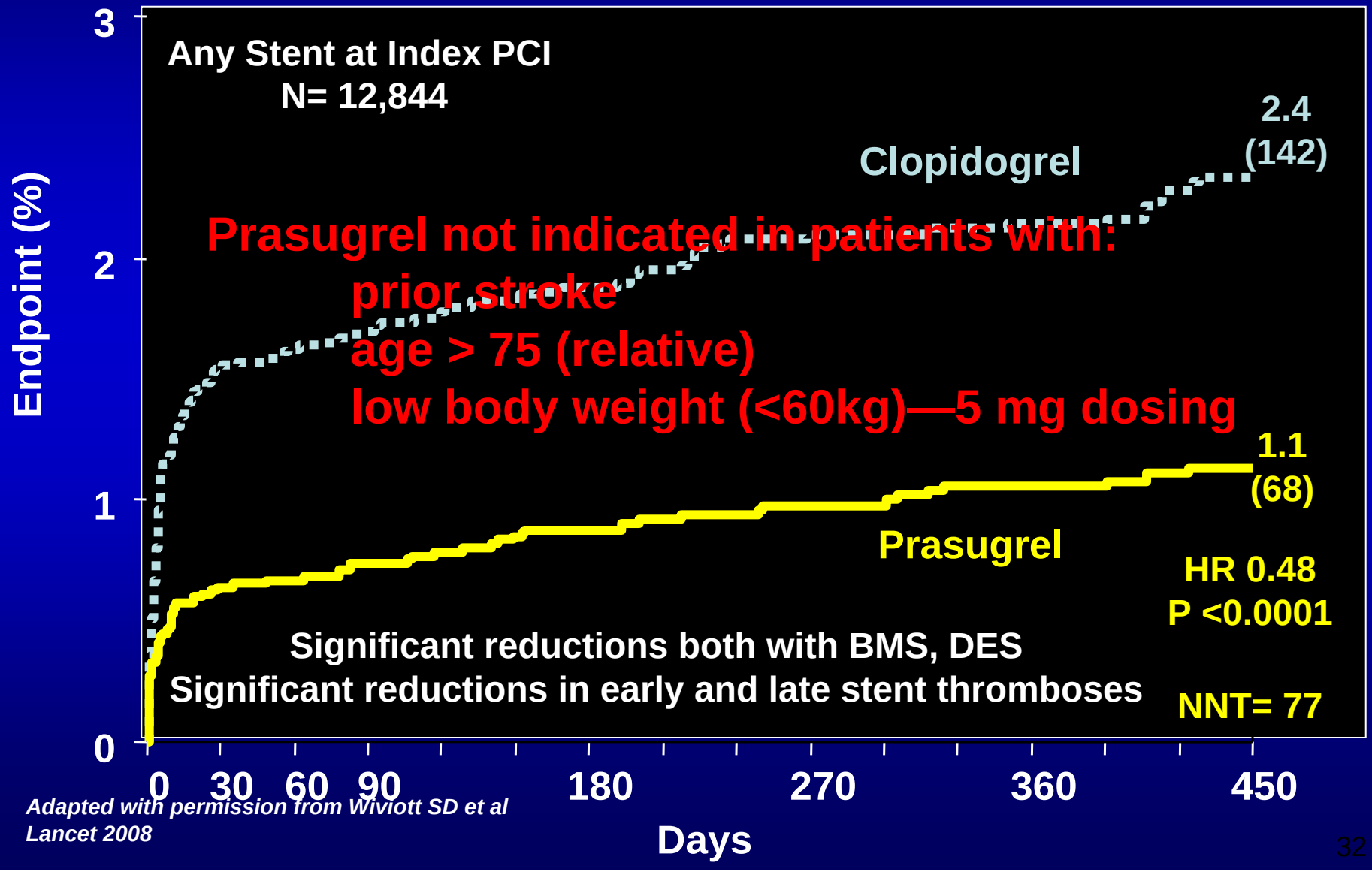
N=3146



Wiviott SD et al Circulation 2008.Adapted with permission from Antman EM.

TRITON TIMI-38

Stent Thrombosis (ARC Definite + Probable)



Adapted with permission from Wiviott SD et al Lancet 2008