

Clopidogrel Use in ACS and PCI: Clinical Trial Update

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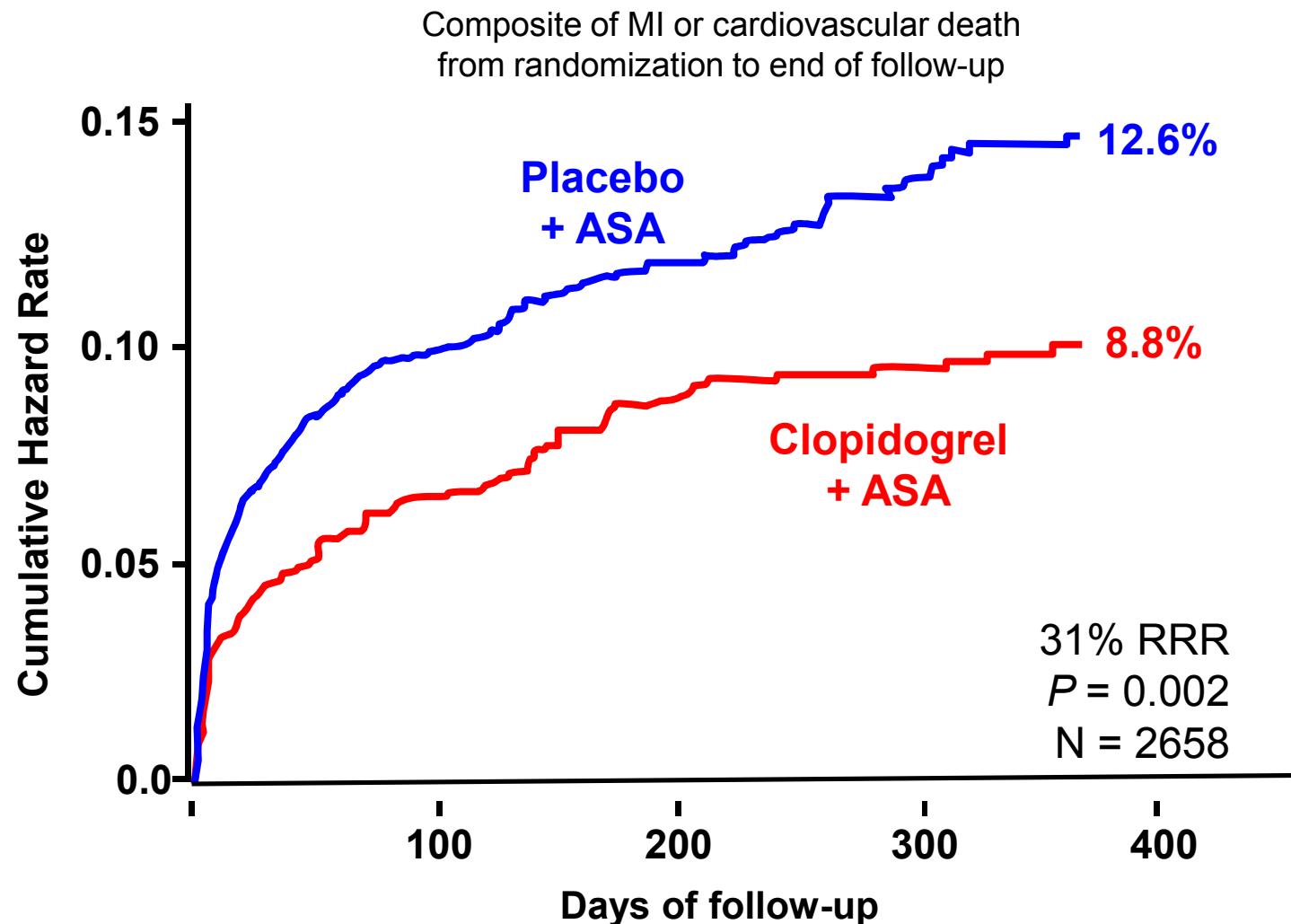
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 **SCRIPPS CLINIC**

PCI-CURE: Clopidogrel vs placebo + aspirin in patients with ACS undergoing PCI



OASIS 7- CURRENT

Randomizing patients to low vs. high-dose clop + ASA

25,807 ACS patients
Intended PCI \leq 24 hrs
No restriction on GP IIb/IIIa inhibitors

Clopidogrel 600 mg
150 mg from Day 2 to Day 7
75mg from Day 8 to 30

Clopidogrel 300 mg
75 mg from Day 2 to 30

ASA 300 mg Day 1
75–100 mg
from Day 2 to 30

ASA 300 mg Day 1
300 mg–325 mg
from Day 2 to 30

ASA 300 mg Day 1
75–100 mg
from Day 2 to 30

ASA 300 mg Day 1
300 mg–325 mg
from Day 2 to 30

1° Outcome: Death / MI /stroke, 30 Days; 2° outcome: CURRENT bleeding

ClinicalTrials.gov Identifier: NCT00335452.

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	Standard	Double	HR	95% CI	P	Intn P
CV Death/MI/Stroke						
PCI (2N=17,232)	4.5	3.9	0.85	0.74-0.99	0.036	0.016
No PCI (2N=7855)	4.2	4.9	1.17	0.95-1.44	0.14	
Overall (2N=25,087)	4.4	4.2	0.95	0.84-1.07	0.370	
MI						
PCI (2N=17,232)	2.6	2.0	0.78	0.64-0.95	0.012	0.025
No PCI (2N=7855)	1.4	1.7	1.25	0.87-1.79	0.23	
Overall (2N=25,087)	2.2	1.9	0.86	0.73-1.03	0.097	
CV Death						
PCI (2N=17,232)	1.9	1.9	0.96	0.77-1.19	0.68	1.0
No PCI (2N=7855)	2.8	2.7	0.96	0.74-1.26	0.77	
Overall (2N=25,087)	2.2	2.1	0.96	0.81-1.14	0.628	
Stroke						
PCI (2N=17,232)	0.4	0.4	0.88	0.55-1.41	0.59	0.50
No PCI (2N=7855)	0.8	0.9	1.11	0.68-1.82	0.67	
Overall (2N=25,087)	0.5	0.5	0.99	0.70-1.39	0.950	



Clopidogrel Double vs Standard Dose Bleeding Overall Population

	Clopidogrel		Hazard Ratio	95% CI	P
	Standard N=12579	Double N=12508			
TIMI Major ¹	0.95	1.04	1.09	0.85-1.40	0.50
CURRENT Major ²	2.0	2.5	1.25	1.05-1.47	0.01
CURRENT Severe ³	1.5	1.9	1.23	1.02-1.49	0.03
Fatal	0.11	0.13	1.15	0.56-2.35	0.71
ICH	0.05	0.03	0.67	0.19-2.37	0.53
RBC transfusion \geq 2U	1.76	2.21	1.26	1.06-1.51	0.01
CABG-related Major	0.9	1.0	1.10	0.85-1.42	0.48

¹ICH, Hb drop \geq 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal

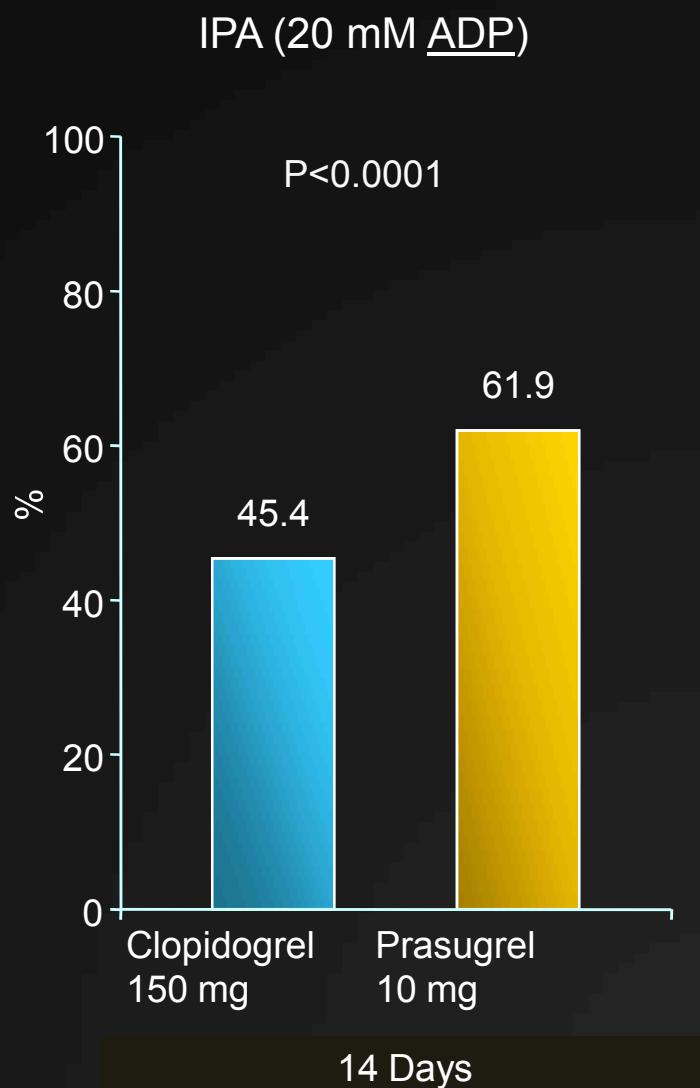
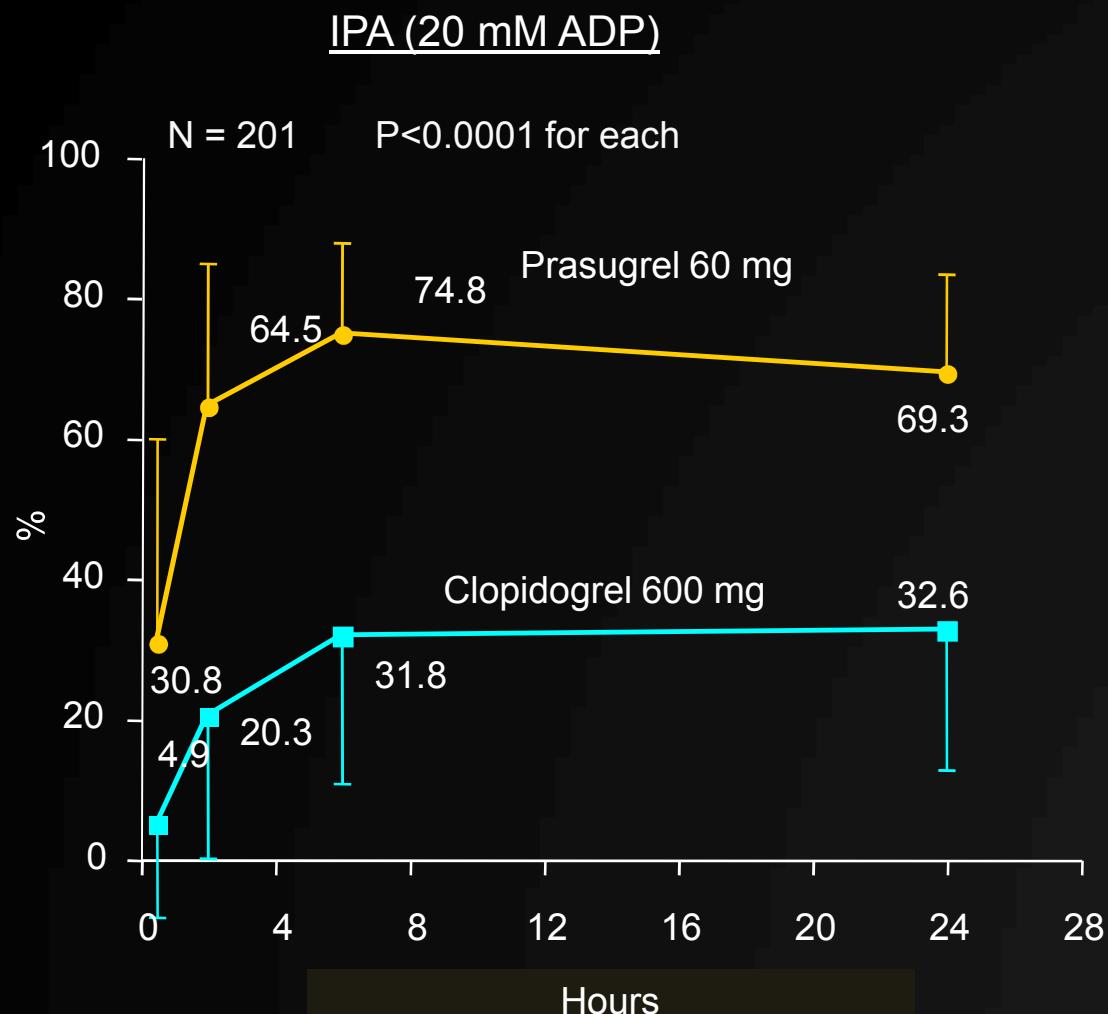
²Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units

³Fatal or \downarrow Hb \geq 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of \geq 4 units

SDW1

PRINCIPLE TIMI-44:

Comparative Pharmacodynamics of Prasugrel and High-Dose Clopidogrel

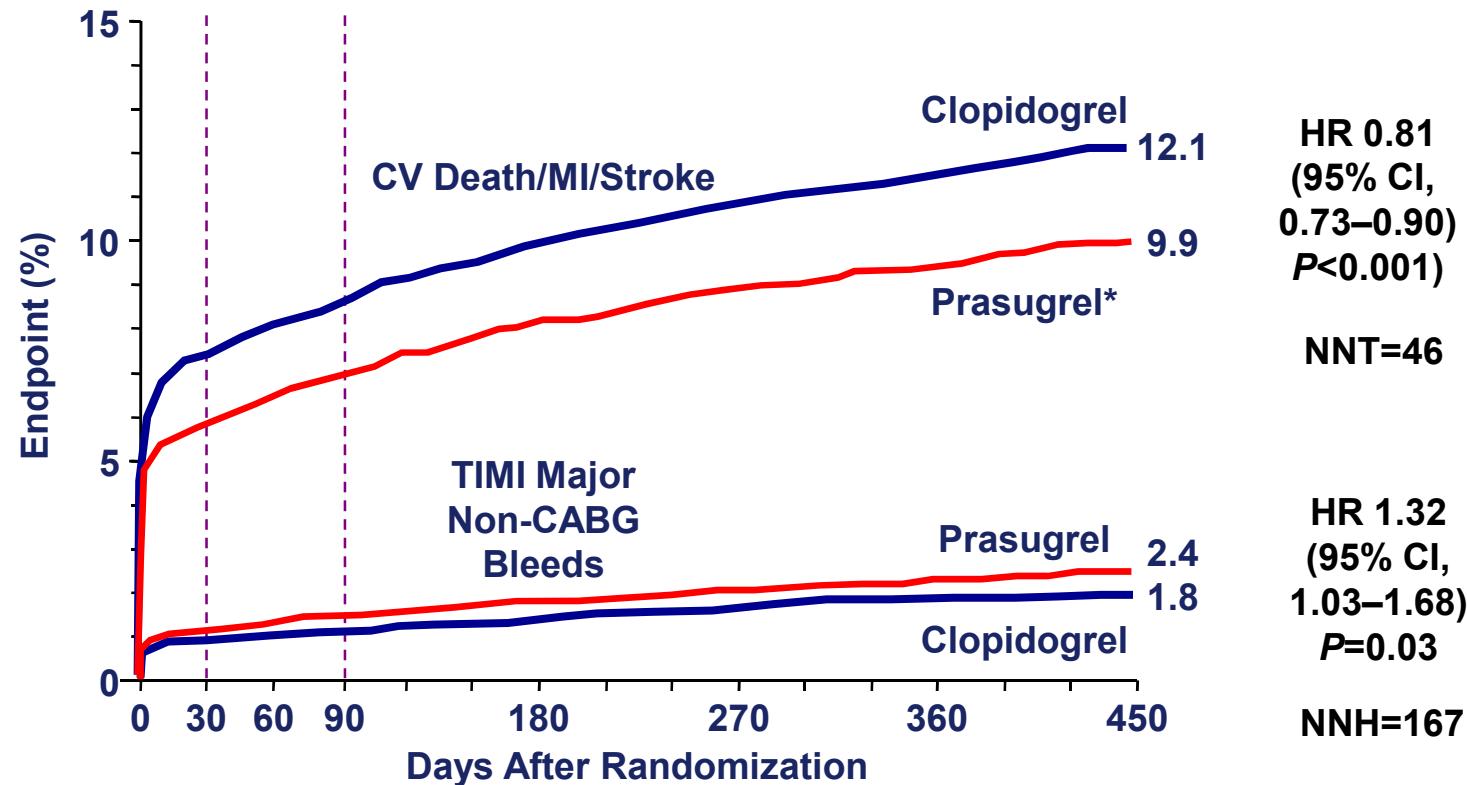


Slide 6

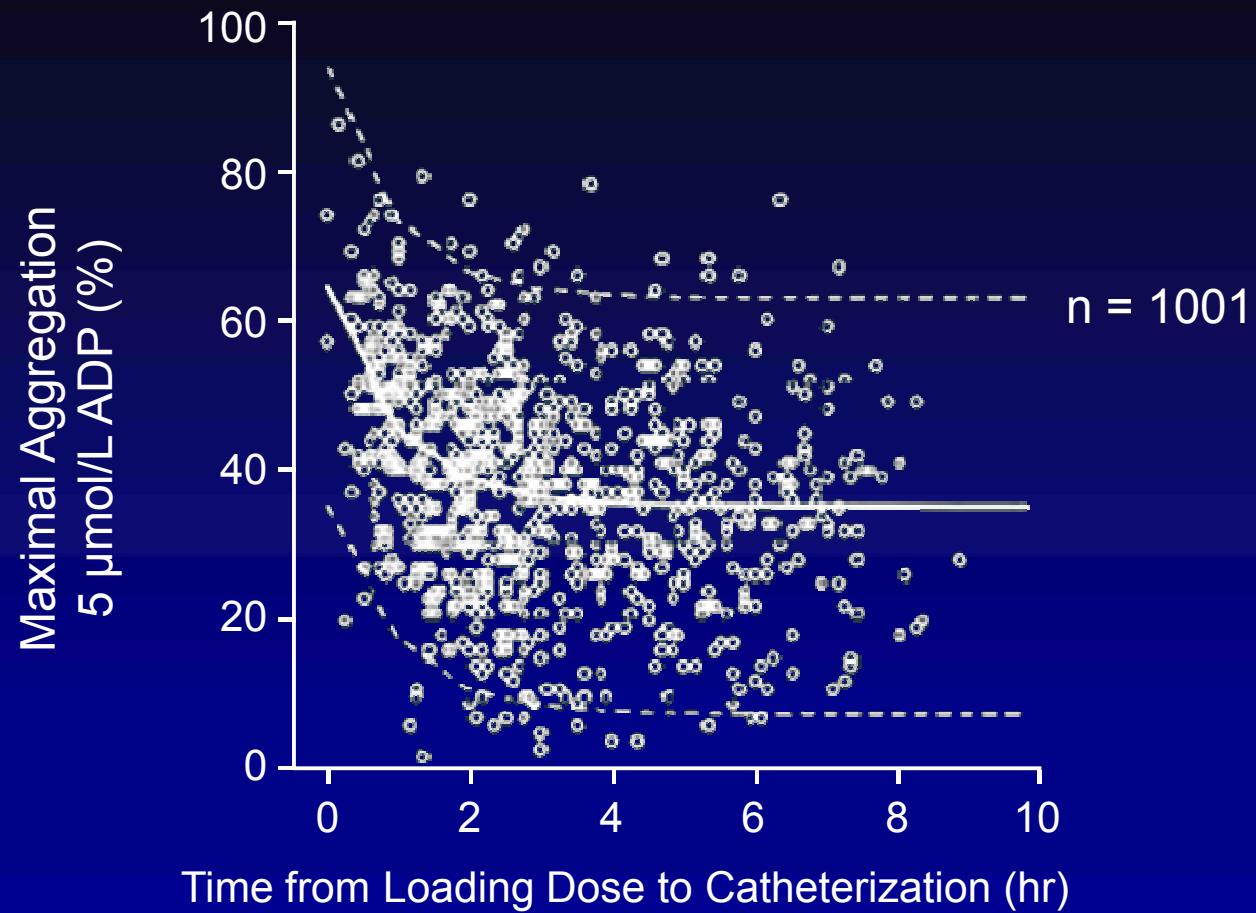
SDW1 Could just move this up to before TRITON RESULTS
, 2008-04-22

TRITON-TIMI 38:

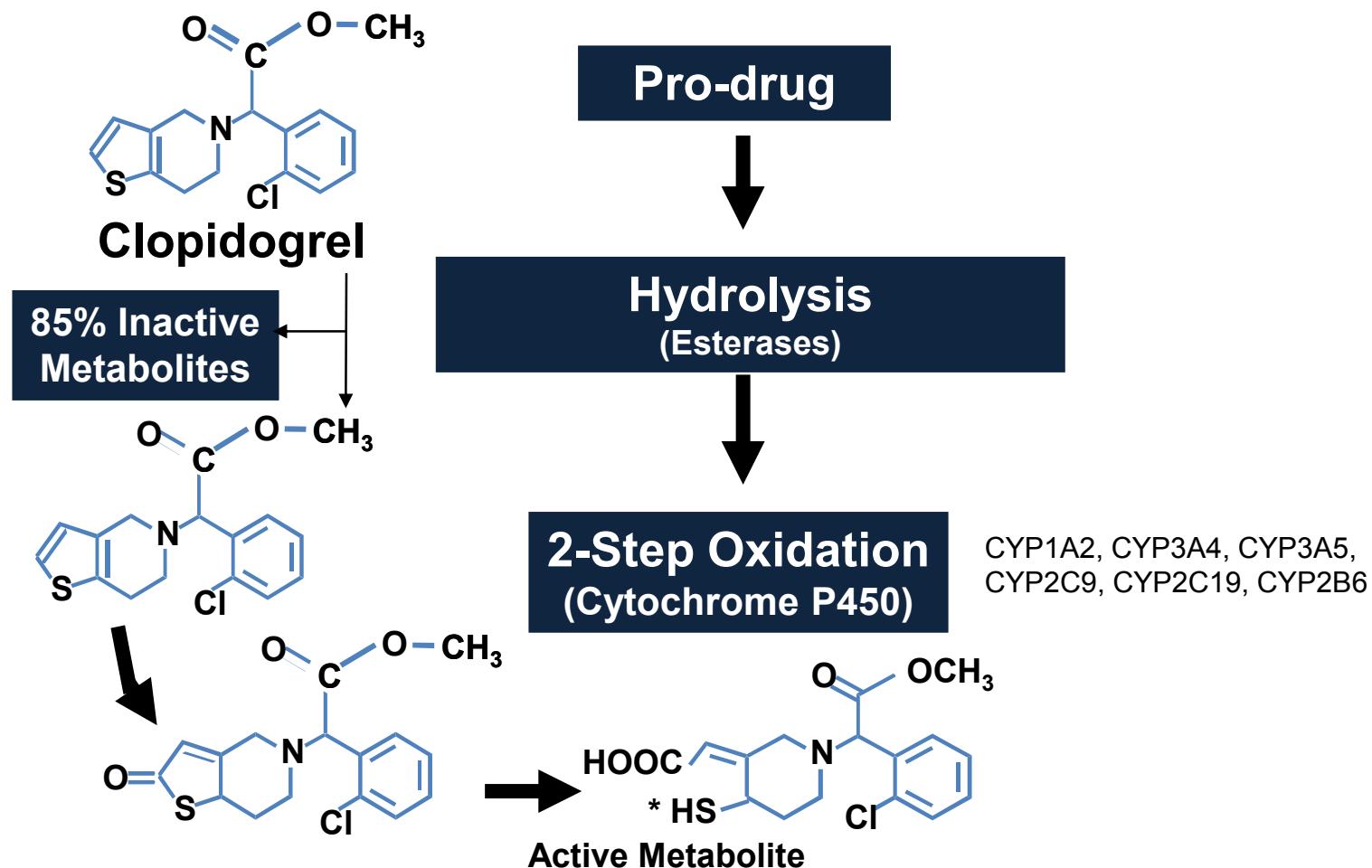
Balance of Efficacy and Safety



ADP-induced Platelet Reactivity on Clopidogrel Therapy Varies Widely Among Individuals



The Generation of Clopidogrel's Active Metabolite is Inefficient and CYP450-Dependent



Herbert JM, Savi P. *Semin Vasc Med* 2003;3(2):113-122.

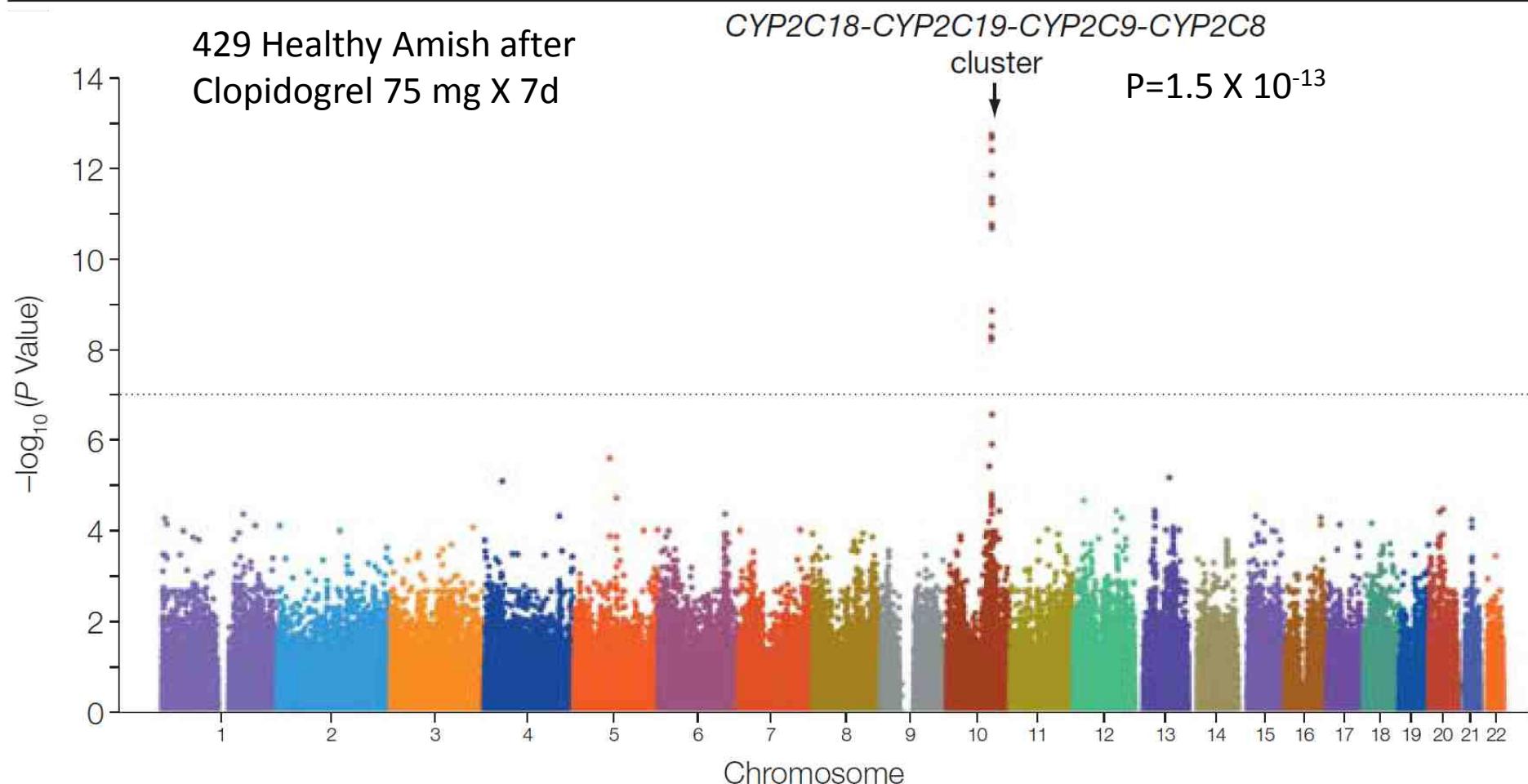


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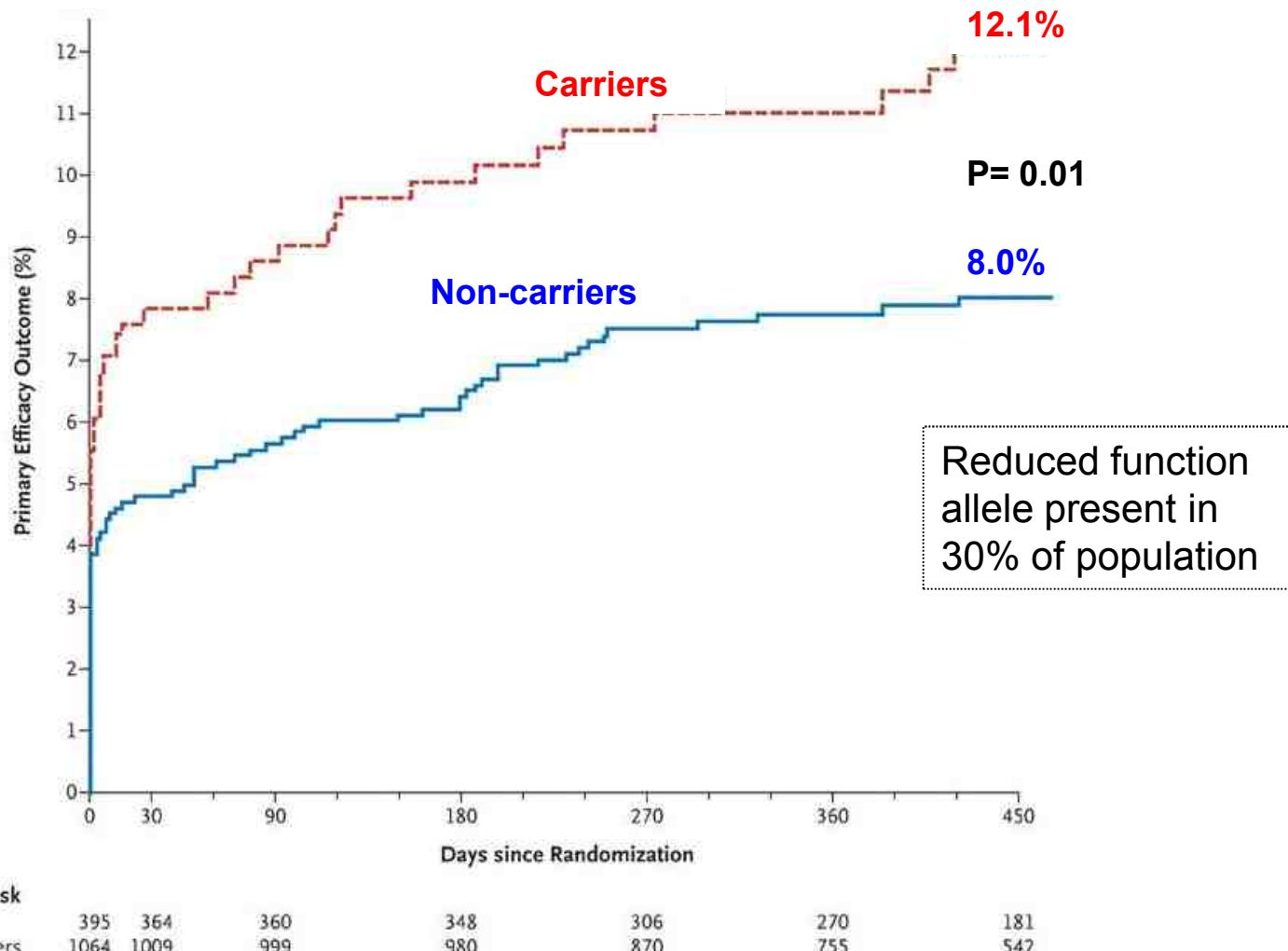
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Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy

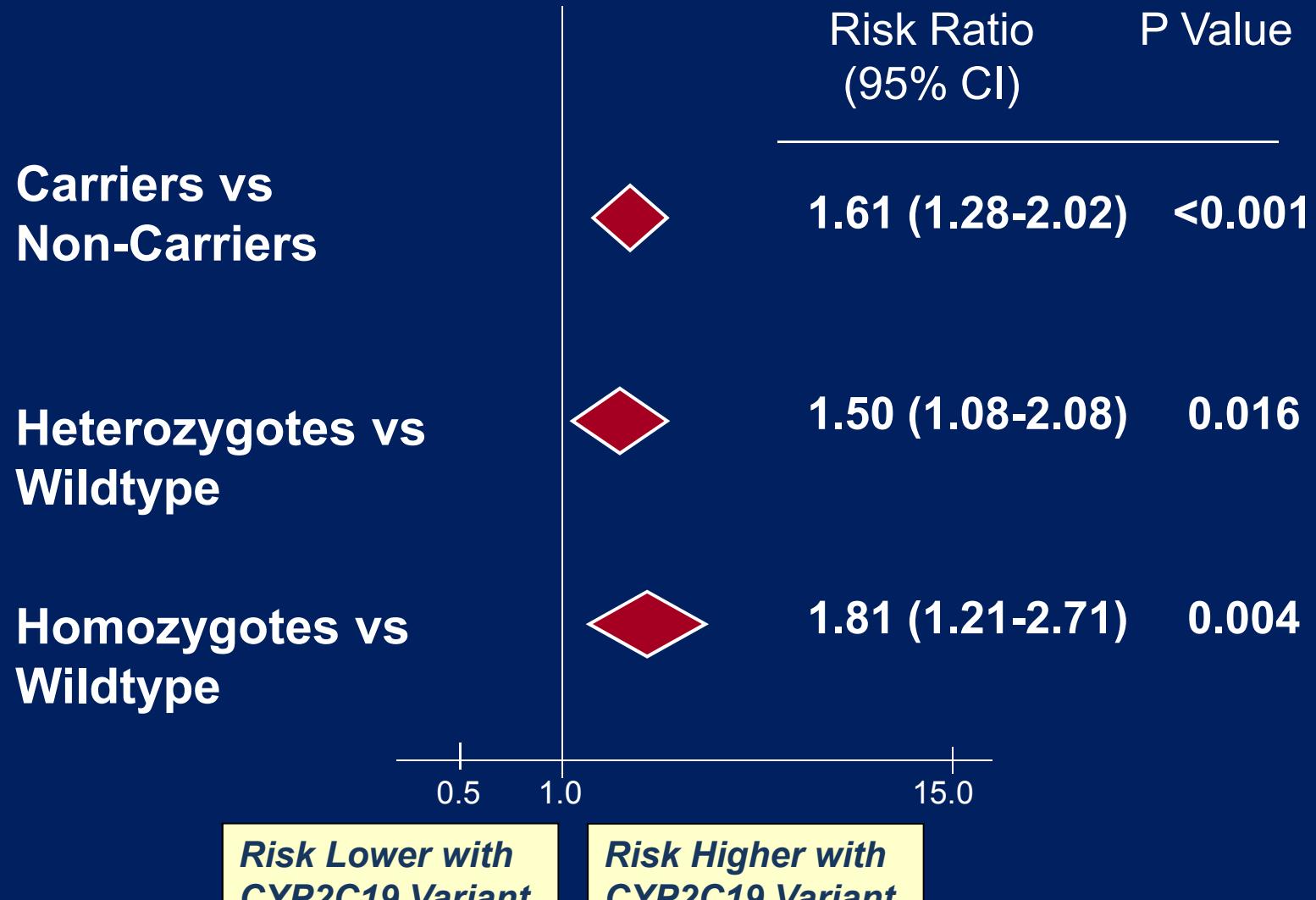


Influence of CYP2C19*2 In Clopidogrel-Treated Patients

TRITON Results According to Carriage of Reduced Function CYP2C19 Allele



CYP2C19 and MACE: A Collaborative Meta-analysis



N=9,684

Mega JL et al, AHA 2009

CYP2C19 and Stent Thrombosis: A Collaborative Meta-analysis

Carriers vs Non-Carriers
Heterozygotes vs Wildtype
Homozygotes vs Wildtype



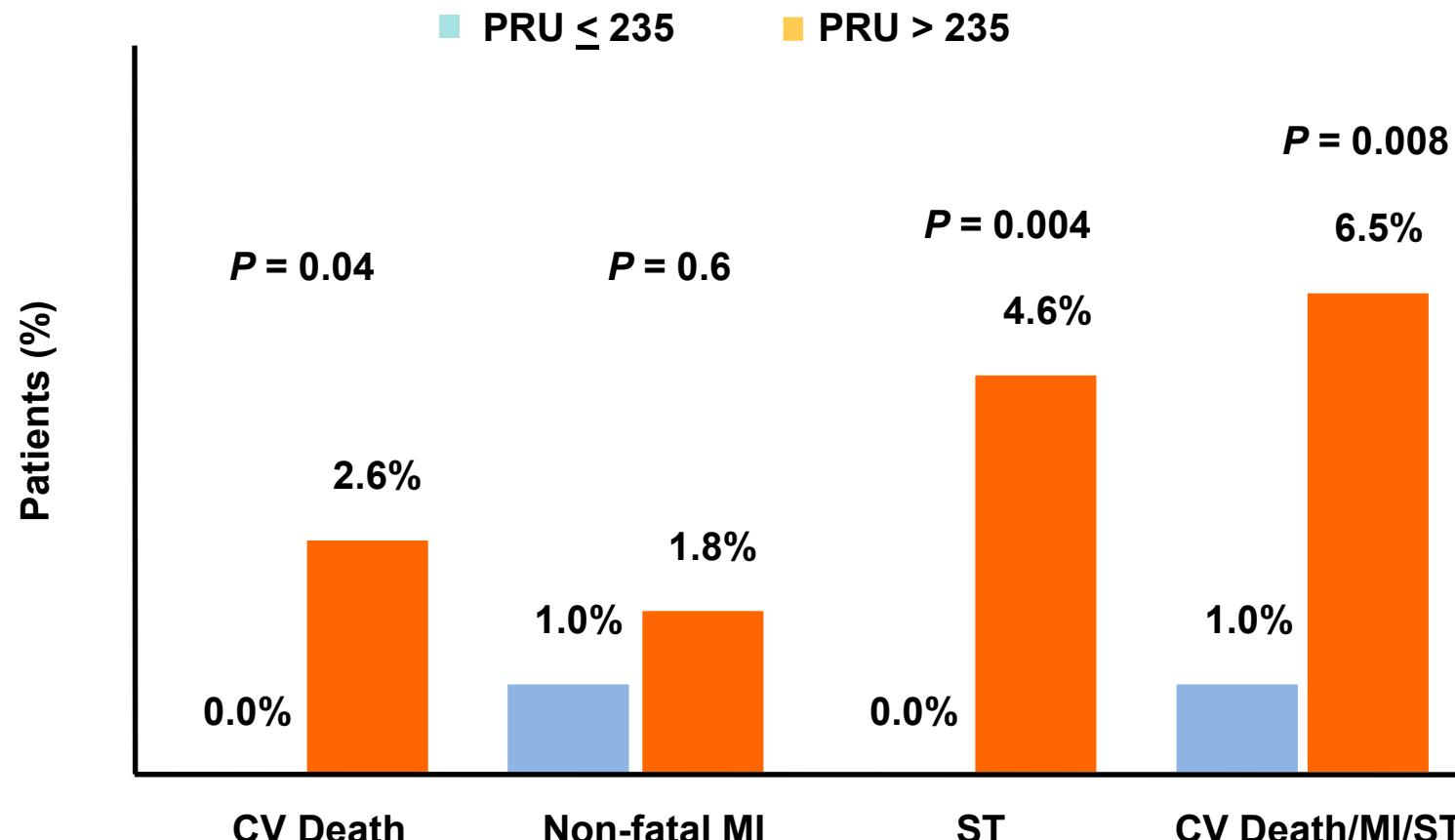
Risk Lower with CYP2C19 Variant

Risk Higher with CYP2C19 Variant

N=5,772

Mega JL et al, AHA 2009

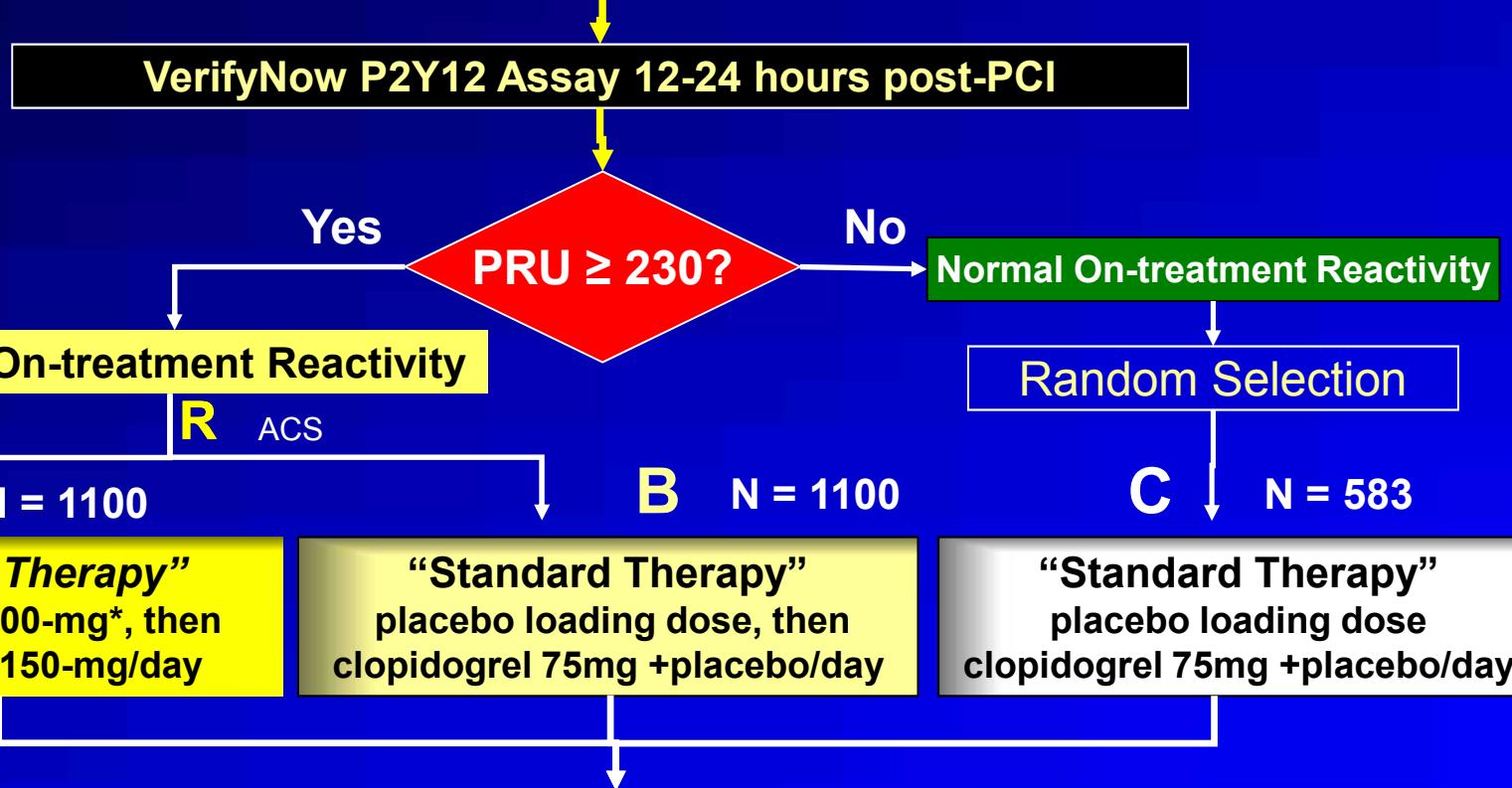
Out-of-hospital 6-Month Outcomes Post-PCI Stratified by Reactivity in Patients on Consistent Clopidogrel Therapy at 6 Months



*On clopidogrel at 30 day & 6-month FU or reached an endpoint on clopidogrel by 6-month FU

GRAVITAS

Successful PCI with DES without major complication or GPIIb/IIIa use



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

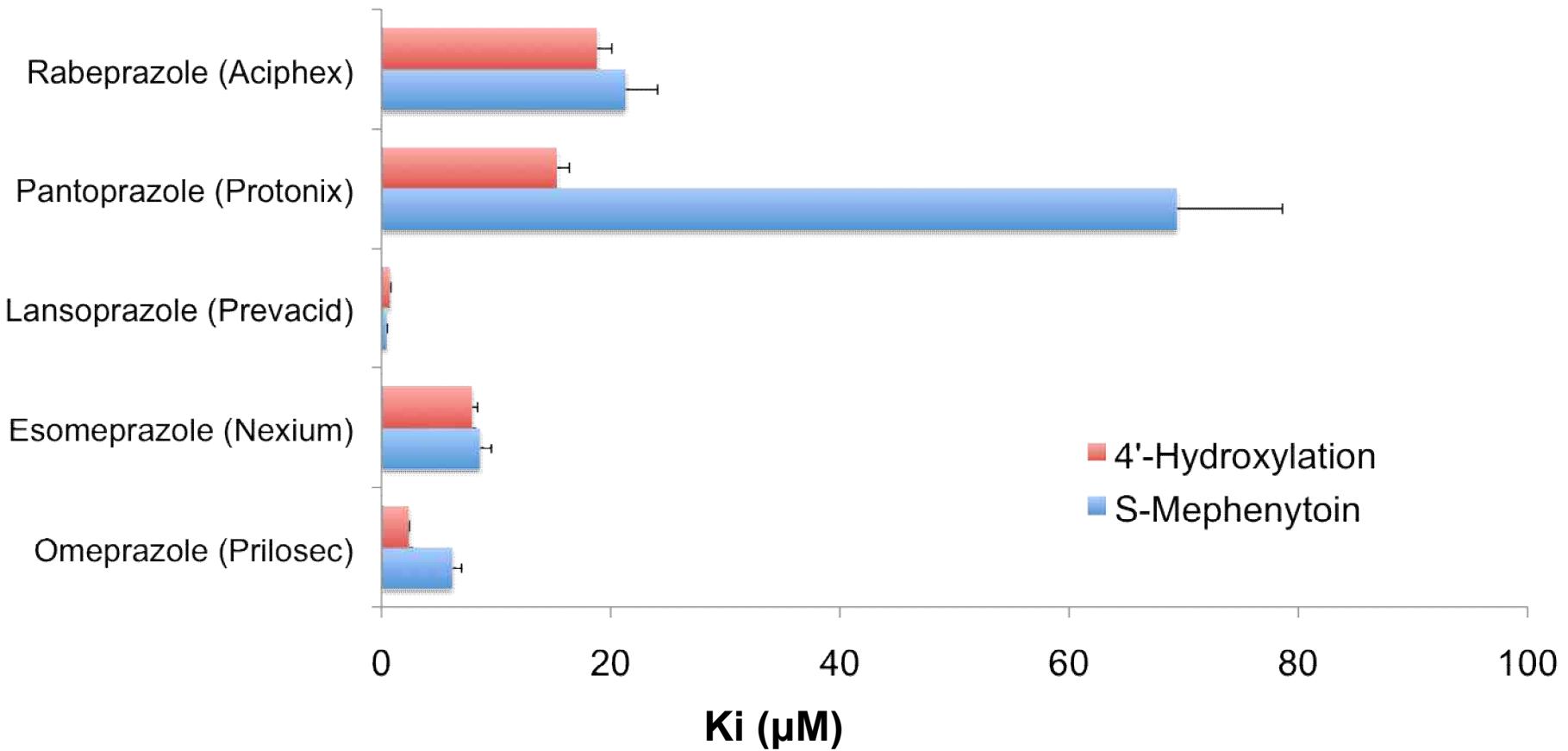
Primary Endpoint: 6 month CV Death, Non-Fatal MI, ARC definite/prob ST

Safety Endpoint: GUSTO Moderate or Severe Bleeding

*total first day dose

Price MJ et al, Am Heart J 2009

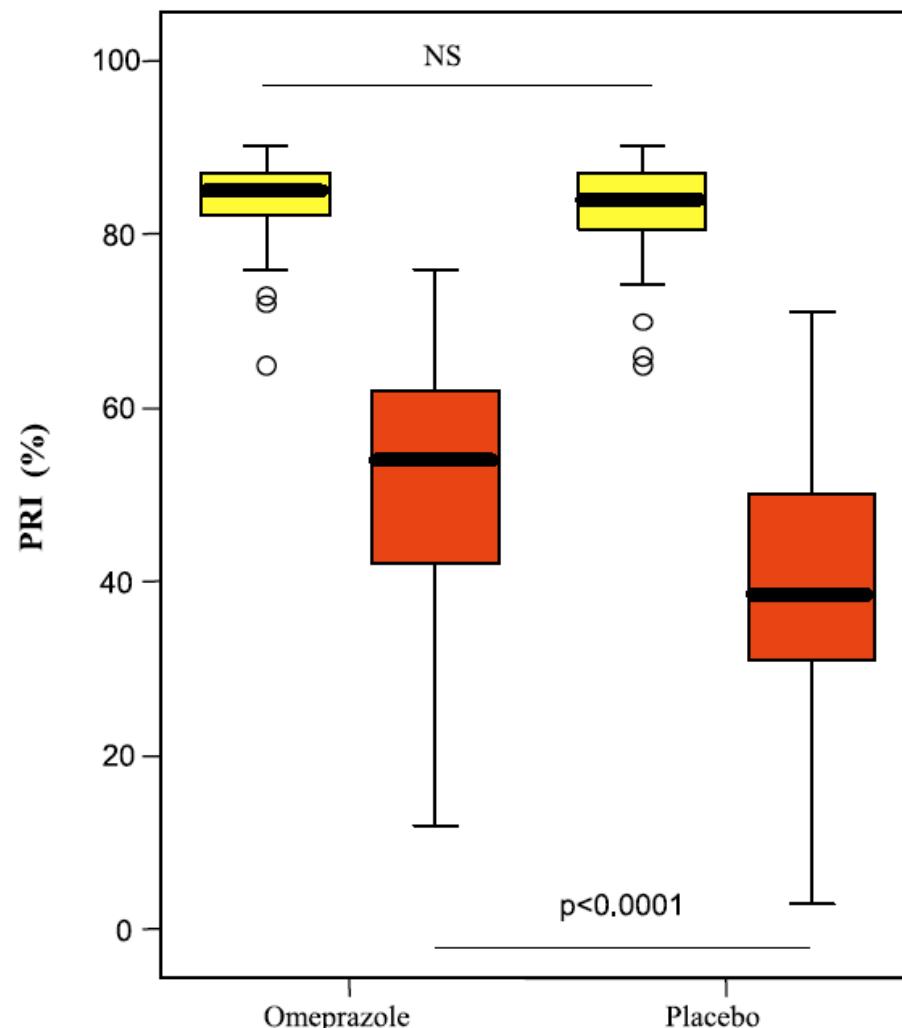
The Degree of CYP2C19 Inhibition Differs Among The Proton Pump Inhibitors



Ki = concentration required to decrease metabolic activity by 50%

Omeprazole CLopidogrel Aspirin (OCLA) Study:

A randomized, placebo controlled trial of the influence of omeprazole on the PD effect of clopidogrel

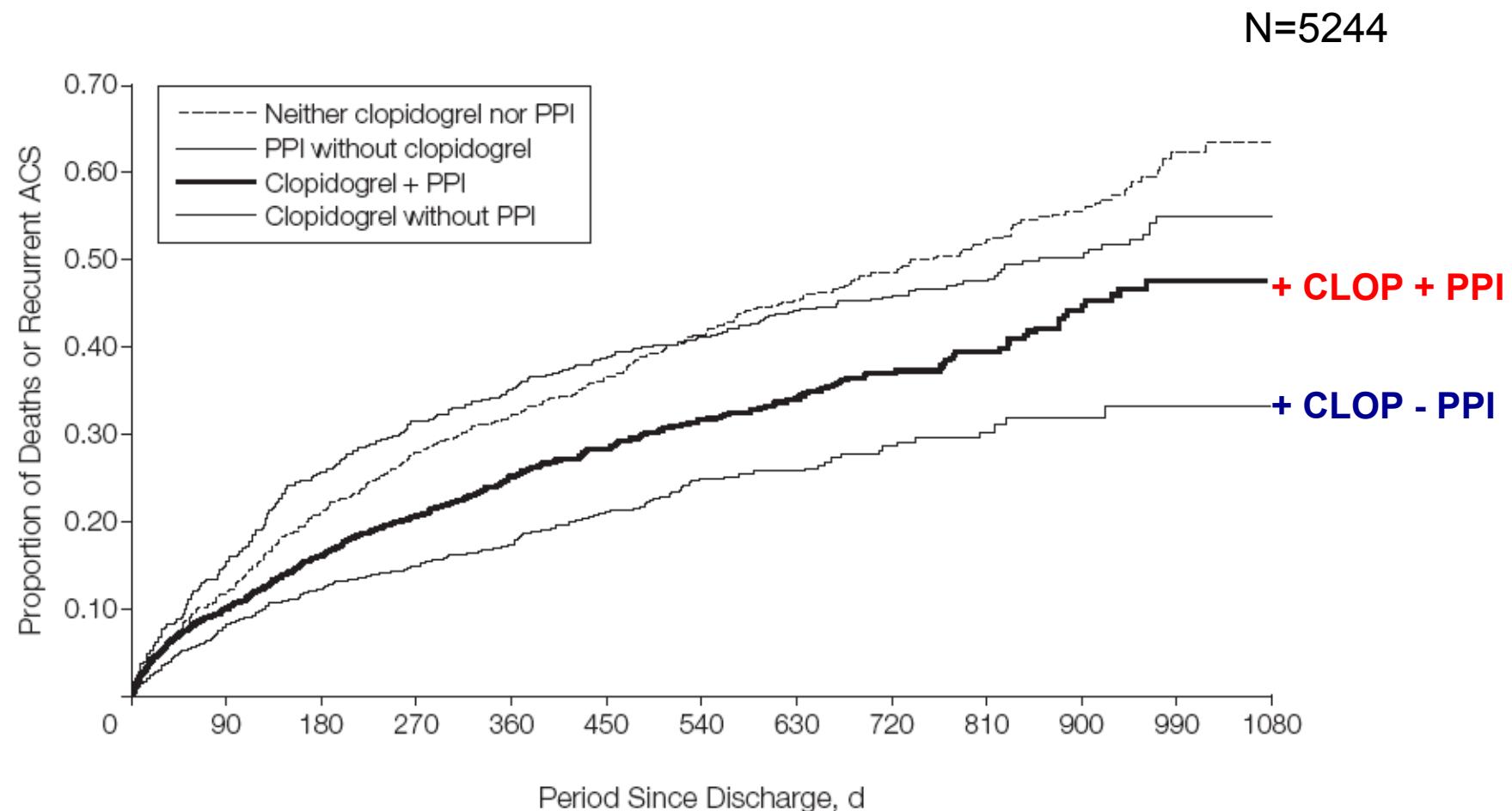


N=120 (60 each group)

- Yellow box: VASP PRI (%) day 1
- Red box: VASP PRI (%) day 7

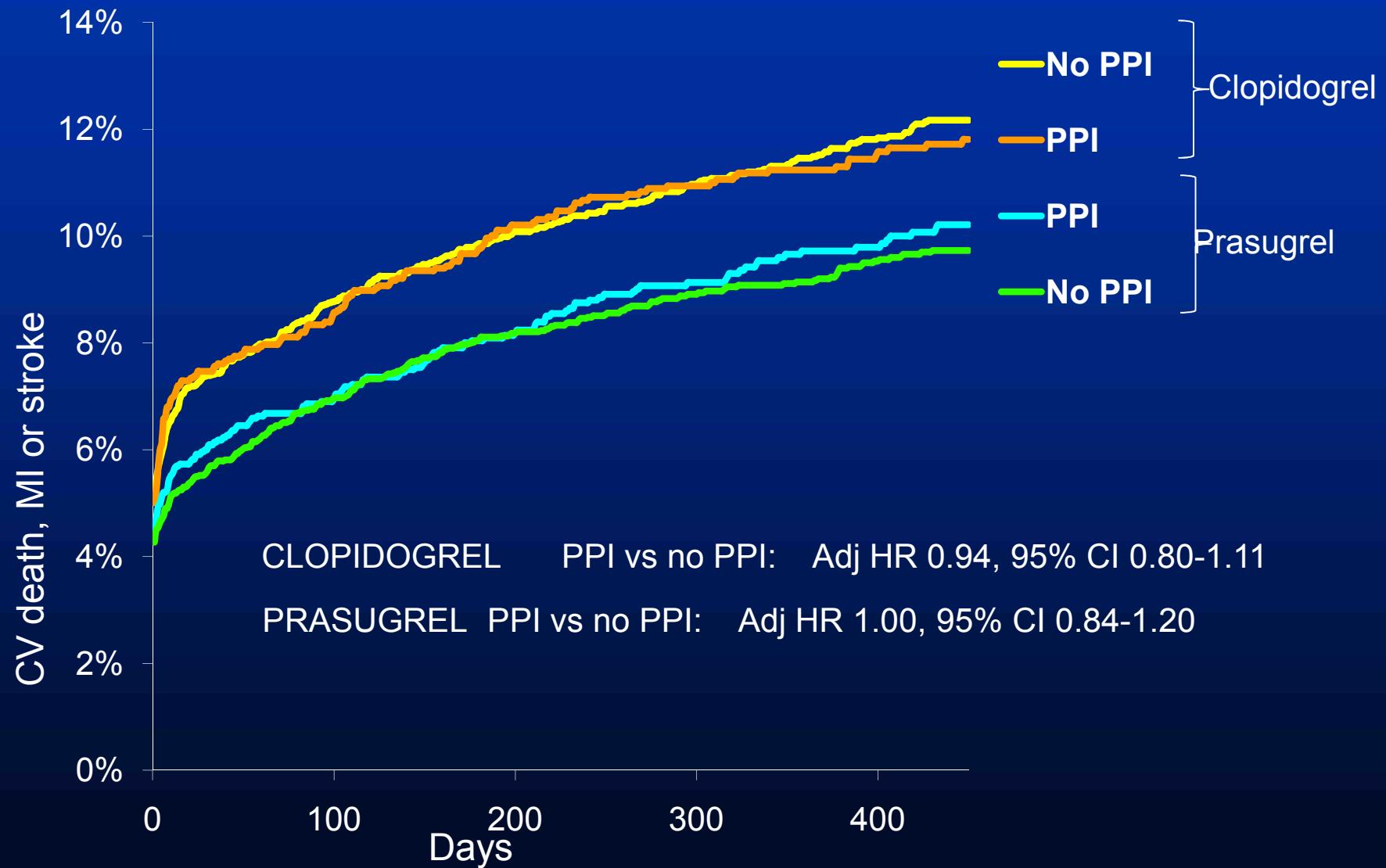
Lower PRI means greater platelet inhibitory effect

Influence of PPI Therapy on Outcome After ACS in Clopidogrel Treated Patients – A Retrospective Analysis



TRITON: Primary endpoint stratified by use of a PPI

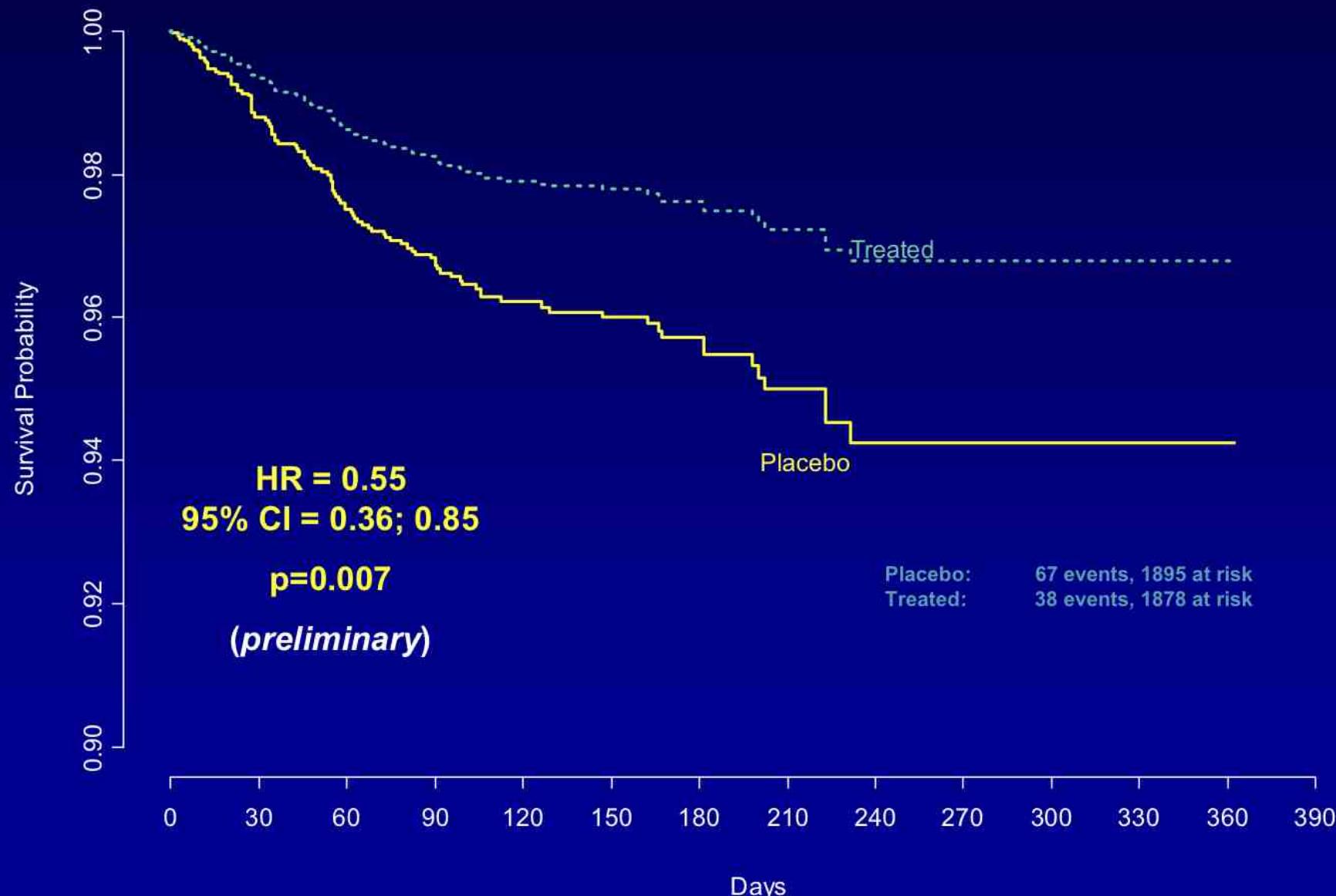
PPI use at randomization (n= 4529)



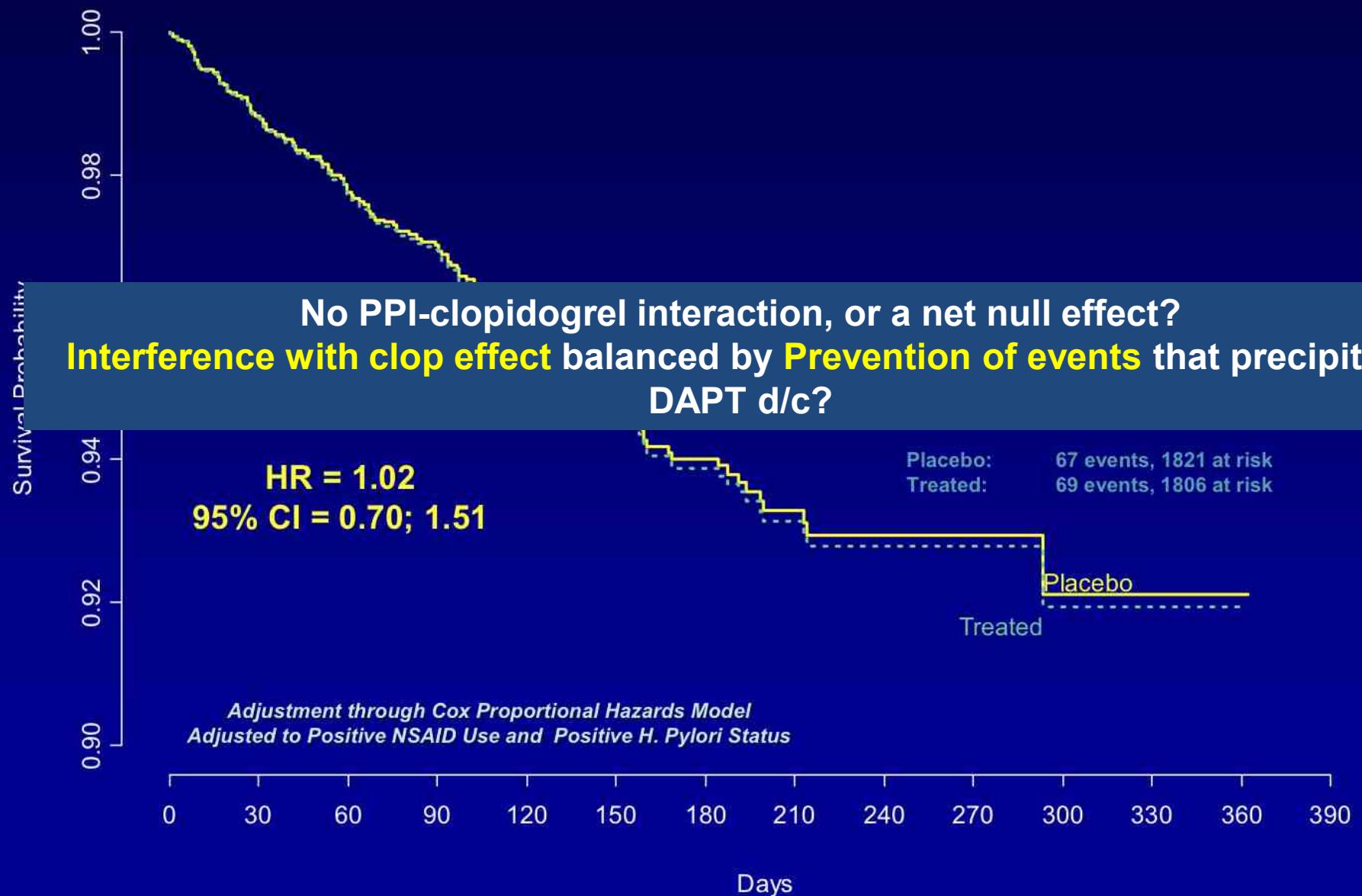
O'Donoghue et al, Lancet. 2009;374(9694):989-97

COGENT

Survival Curves for PPI Treated vs Placebo Composite GI Events

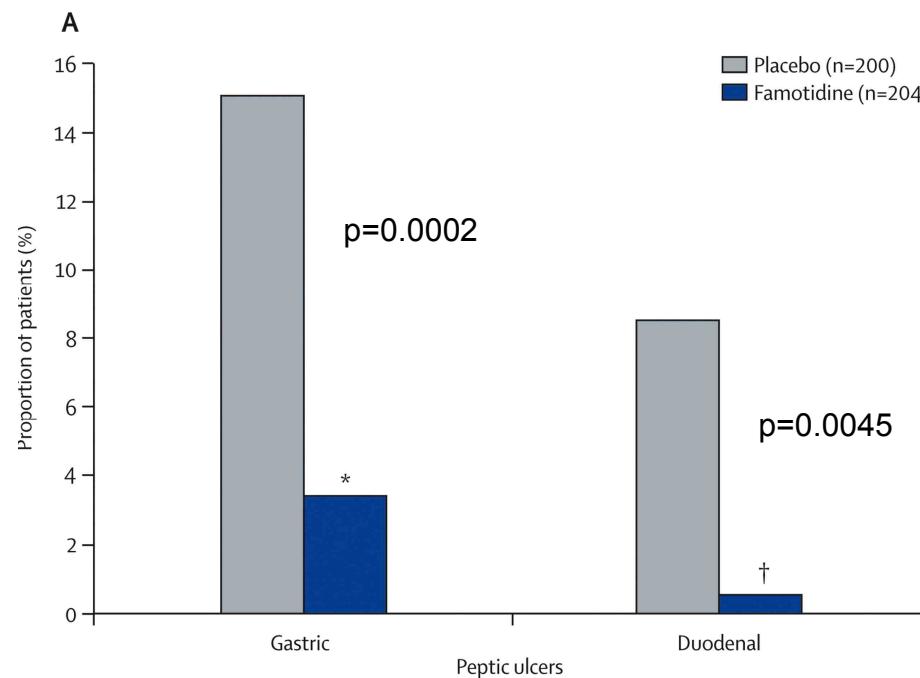


Survival Curves for PPI Treated vs Placebo Composite Cardiovascular Events

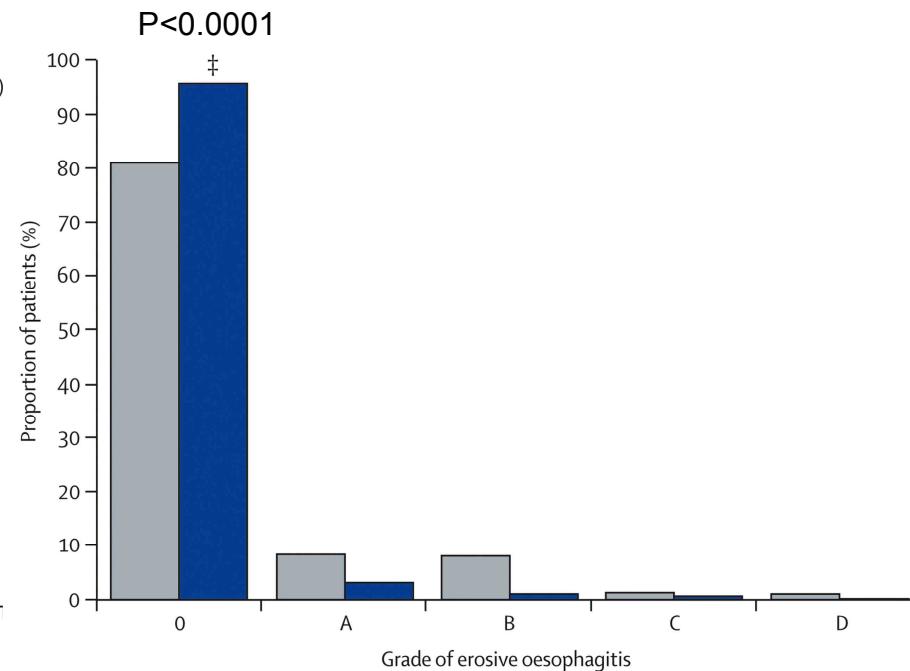


FAMOUS: Famotidine 20-mg Bid for the Prevention of Esophagitis in Patients Taking Low-Dose Aspirin

Incidence of peptic ulcers



Grades of erosive esophagitis



Summary

- CURRENT-OASIS 7: *no* ischemic benefit of short course of high-dose clopidogrel in ACS patients undergoing an invasive management strategy, with higher rates of major bleeding.
 - Sub-group analysis of the PCI population appears to show ischemic benefit with high-dose therapy.
- Carriage of a CYP2C19 loss-of-function allele, which decreases clopidogrel AM generation and reduces its antiplatelet effect, has been associated with MACE in TRITON and in other trials.
 - Homozygosity (poor metabolizers substantially higher risk)

Summary (2)

- CYP2C19 genotype explains only a portion of the variability of clopidogrel's antiplatelet effect.
- Randomized trials of “tailored” antiplatelet therapy based on platelet function testing (phenotype), such as GRAVITAS, are ongoing.
- The “PPI story” is still not finished. If GI treatment is necessary, consider pantoprazole, rabeprazole, or, famotidine.