Prasugrel

Studies in Risk, Benefit and the Evolution of Individualized Medicine

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott Vascular, Cordis Corporation, Medtronic CardioVascular
Consulting Fees/Honoraria	Abbott Vascular, Cordis Corporation, Medtronic CardioVascular, Micell Technologies, Terumo Medical
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

Dilemmas in Antiplatelet Therapy
Considerations for Clinical Practice

- Does high residual ('on-treatment') platelet reactivity correlate with increased risk of adverse events?
- Does altering or adjusting therapy change outcome in patients with high residual platelet reactivity (HRPR)? Is 'resistance' overcome at a safety cost?
- Is there a potential for drug-drug interactions that may influence clinical outcome among patients taking thienopyridine therapy?
- Among clopidogrel users, is there a purpose for reloading at time of PCI?
- What is the optimal duration of dual antiplatelet therapy following DES revascularization?

Concern for Drug Interaction?

FDA Public Health Advisory, 17 November 2009

- The concomitant use of omeprazole and clopidogrel should be avoided. Omeprazole…reduces the anti-blood clotting effect of clopidogrel by almost half when these two medicines are taken by the same patient.
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.
- Esomeprazole and cimetidine should also be avoided; H2 antagonists and antacids are acceptable alternatives
- At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations

http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm190825.htm

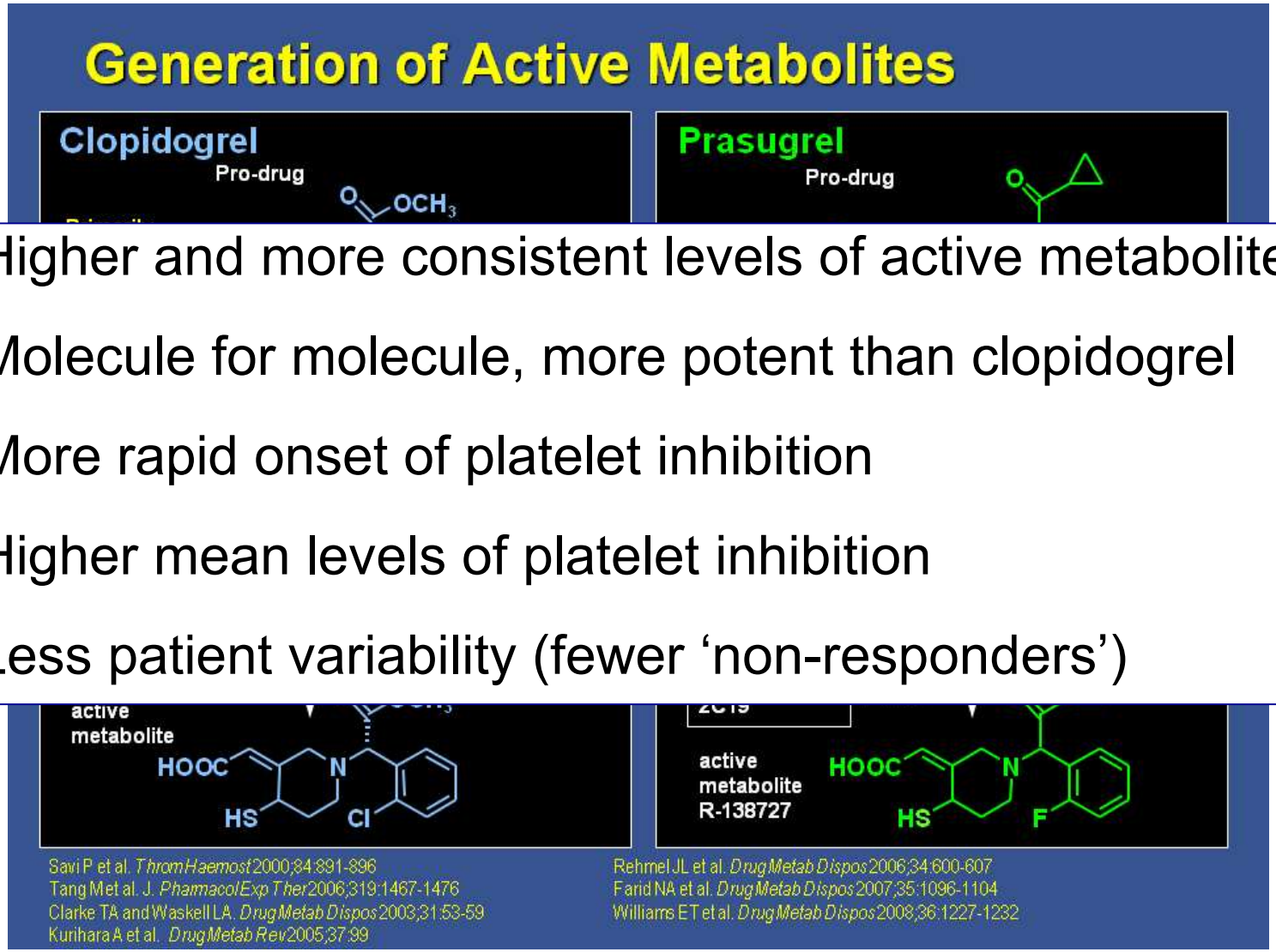
Reduced Clopidogrel Effectiveness and Genotype

FDA Boxed Warning, 12 March 2010

- The CYP2C19*2 and *3 alleles have no functional metabolism of Plavix. A patient with two loss-of-function alleles will have poor metabolizer status.
- Tests are available to determine patients' CYP2C19 status. Consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients who have been identified as poor metabolizers.
- Be aware that although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response, an appropriate dose regimen for poor metabolizers has not been established in a clinical outcome trial.
- Patients should not stop taking Plavix unless told to do so by their healthcare professional.

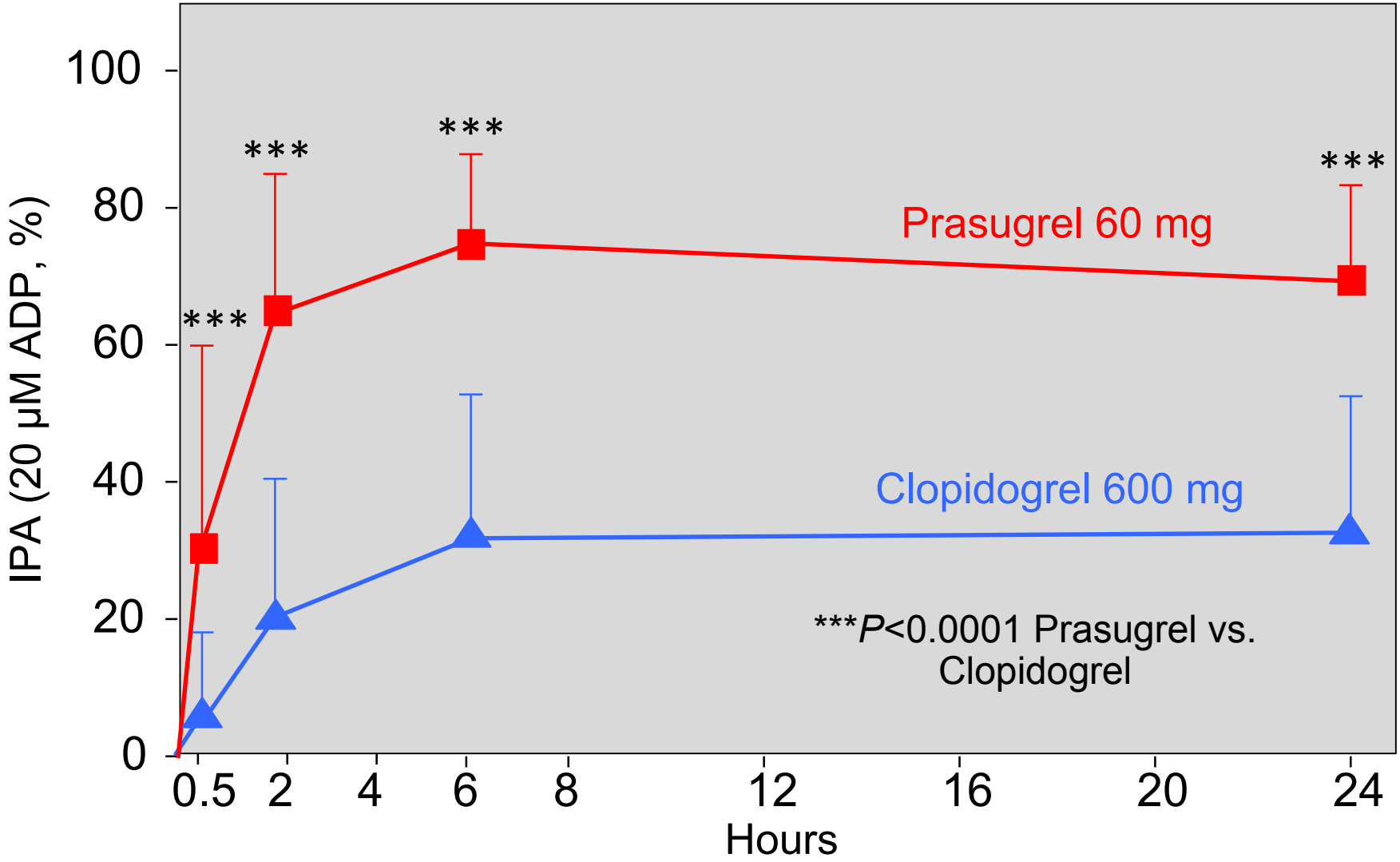
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm#ds

Prasugrel: A Novel Thienopyridine



- Higher and more consistent levels of active metabolite
- Molecule for molecule, more potent than clopidogrel
- More rapid onset of platelet inhibition
- Higher mean levels of platelet inhibition
- Less patient variability (fewer ‘non-responders’)

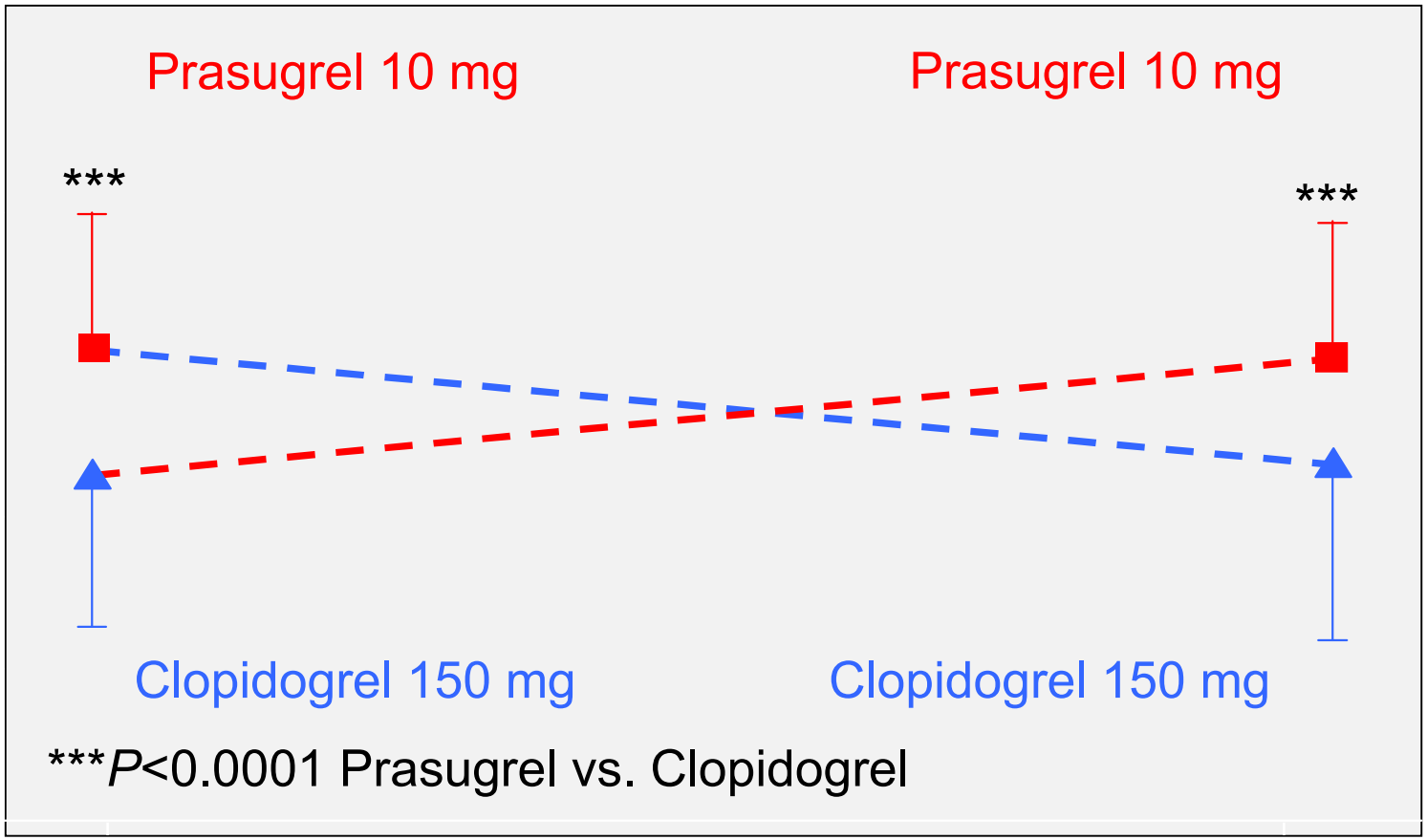
PRINCIPLE-TIMI 44 Primary Endpoint: Loading Dose Phase Inhibition of Platelet Aggregation (20 µM ADP)



IPA=inhibition of platelet aggregation

Wiviott SD et al. *Circulation* 2007;116(25):2923-2932

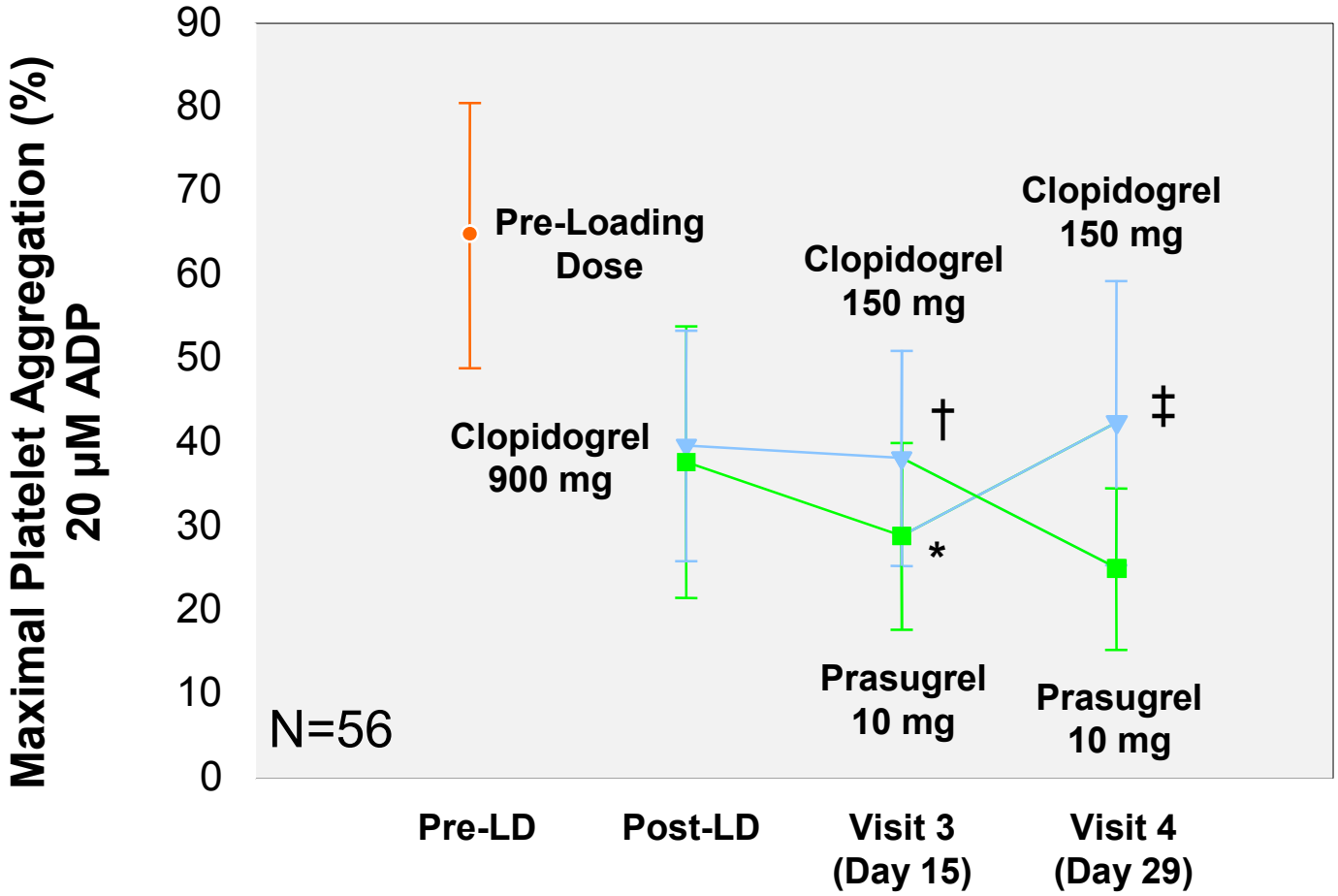
PRINCIPLE-TIMI 44 Second Primary Endpoint: Maintenance Dose Phase IPA (20 µM ADP)



Least square mean (LSM) + standard deviation; IPA=inhibition of platelet aggregation

Wiviott SD et al. *Circulation* 2007;116(25):2923-2932

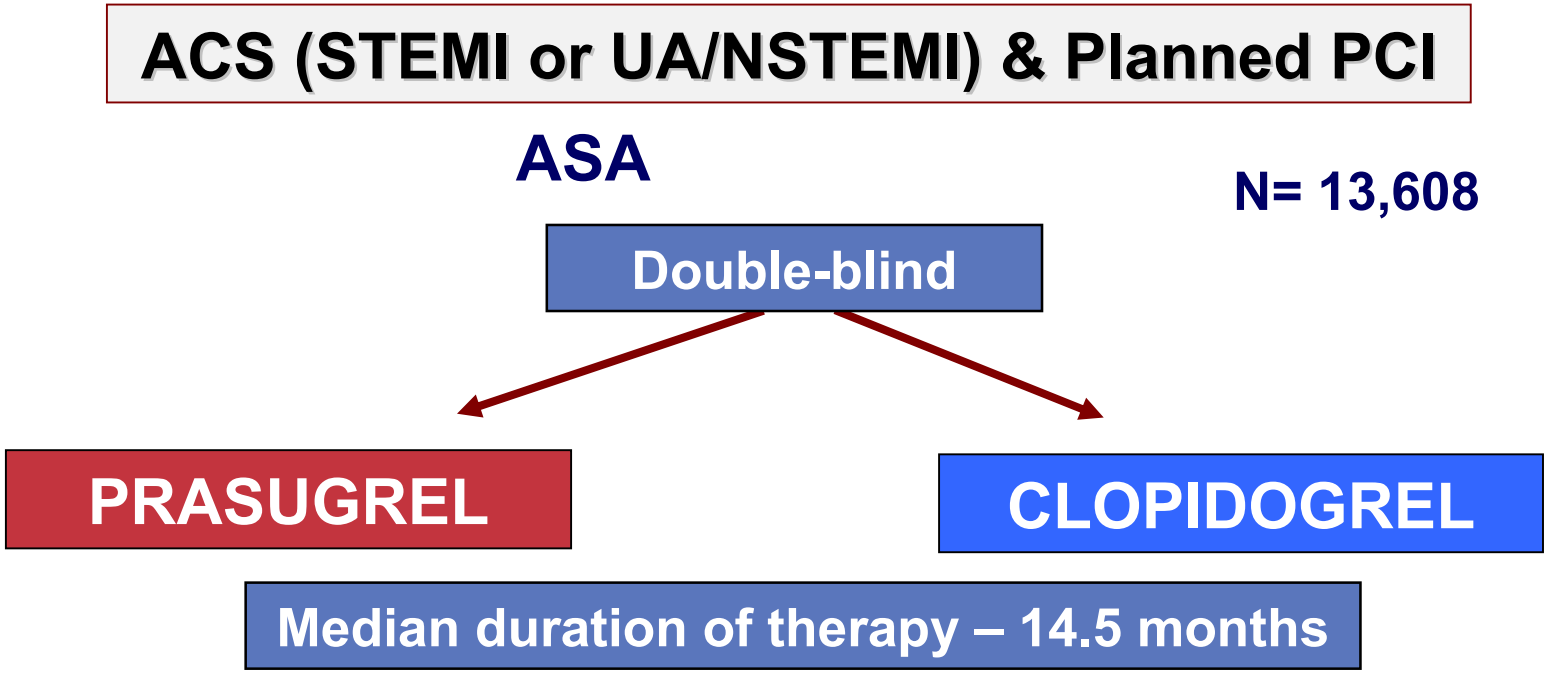
ACAPULCO
Maximum Platelet Aggregation by Treatment Sequence



*Comparison of prasugrel 10 mg at day 15 vs. the clopidogrel 900 mg loading dose, p=0.011 †Comparison of clopidogrel 150 mg versus prasugrel 10 mg at day 15, p=0.008; ‡Comparison of clopidogrel 150 mg vs. prasugrel 10 mg at day 29, p<0.001; ADP=adenosine diphosphate

Montelescot G, et al. Thromb Haemost 2010;103(1):213-223

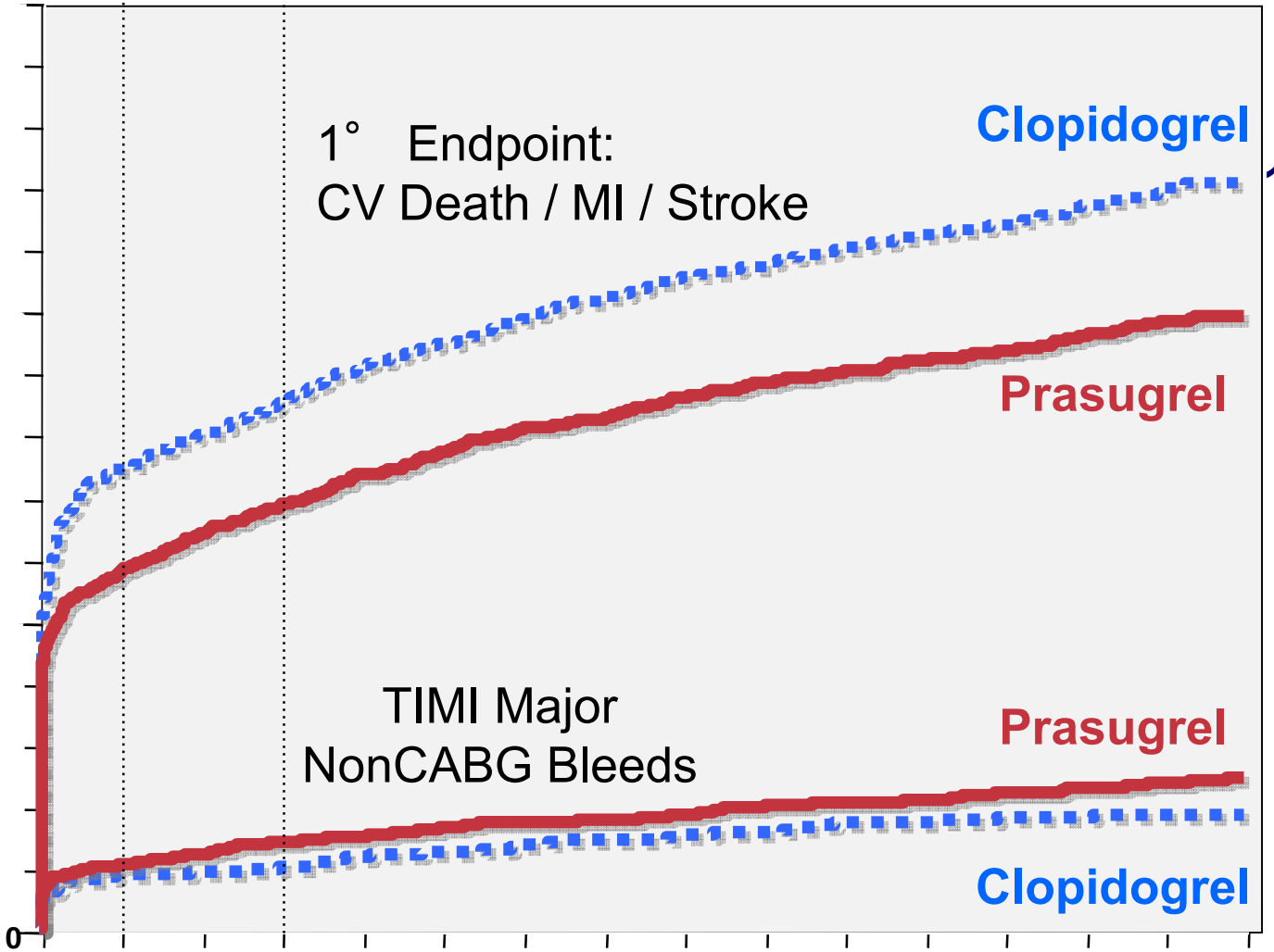
TRITON–TIMI 38
Study Design



1º end point:	CV death, MI, stroke
2º end points:	CV death, MI, stroke, re-ischemia
	CV death, MI, UTVR

TIMI, thrombolysis in myocardial infarction; ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; UTVR, urgent target vessel revascularization

TRITON TIMI 38
Balance of Efficacy and Safety



12.1
9.9
2.4
1.8

↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

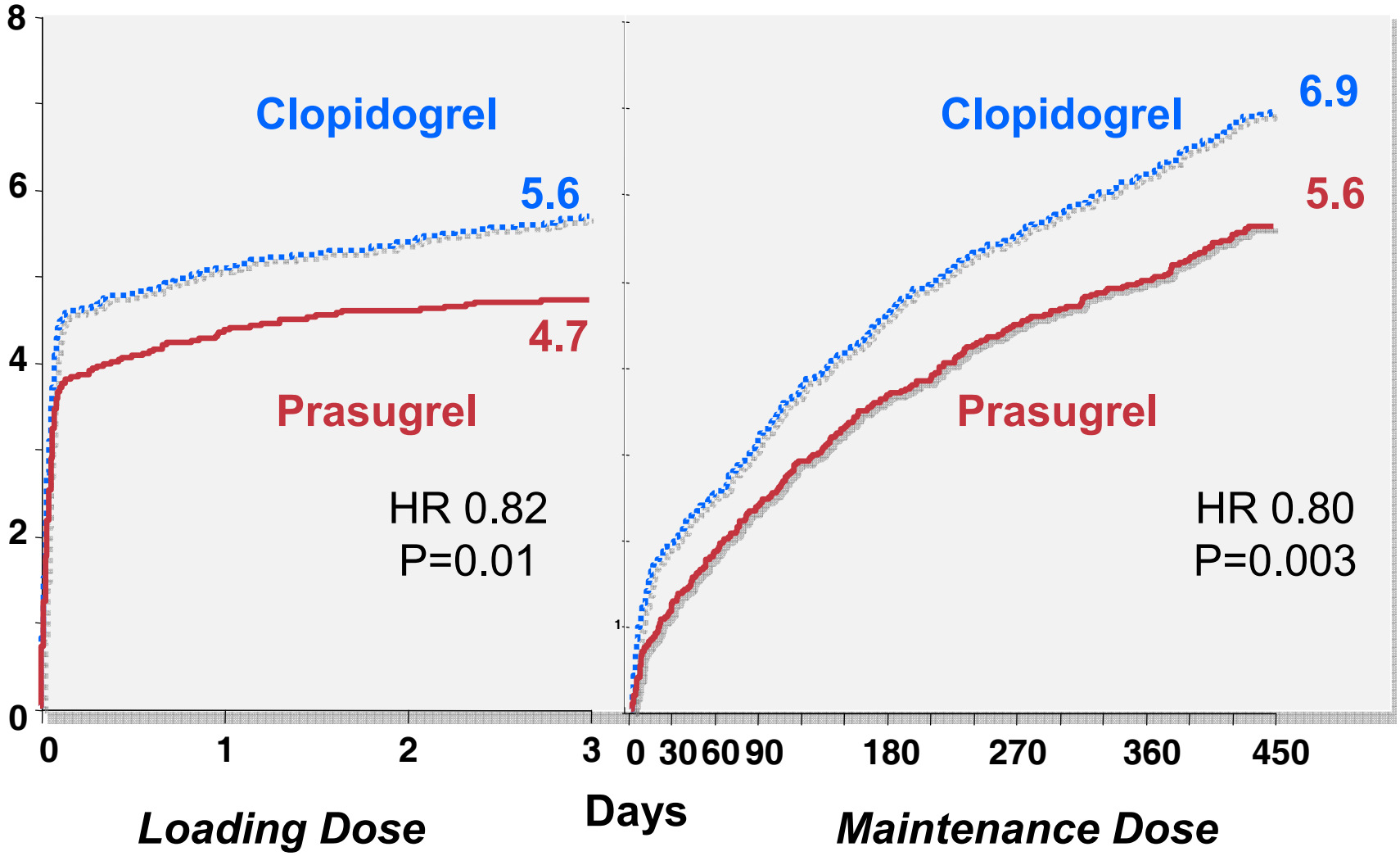
↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

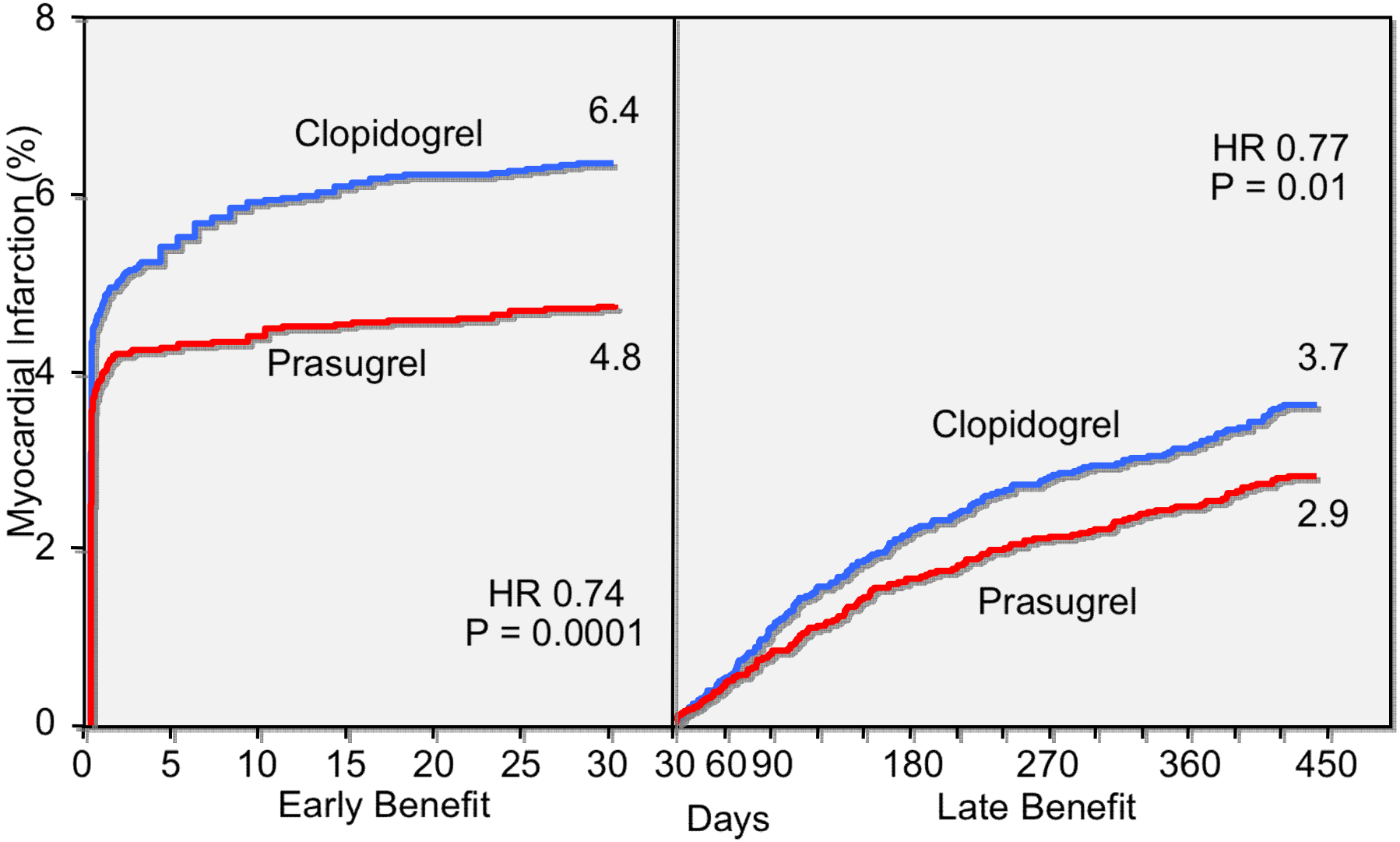
Wiviott et al. NEJM 2007

TRITON TIMI 38
Timing of Benefit (Landmark Analysis)

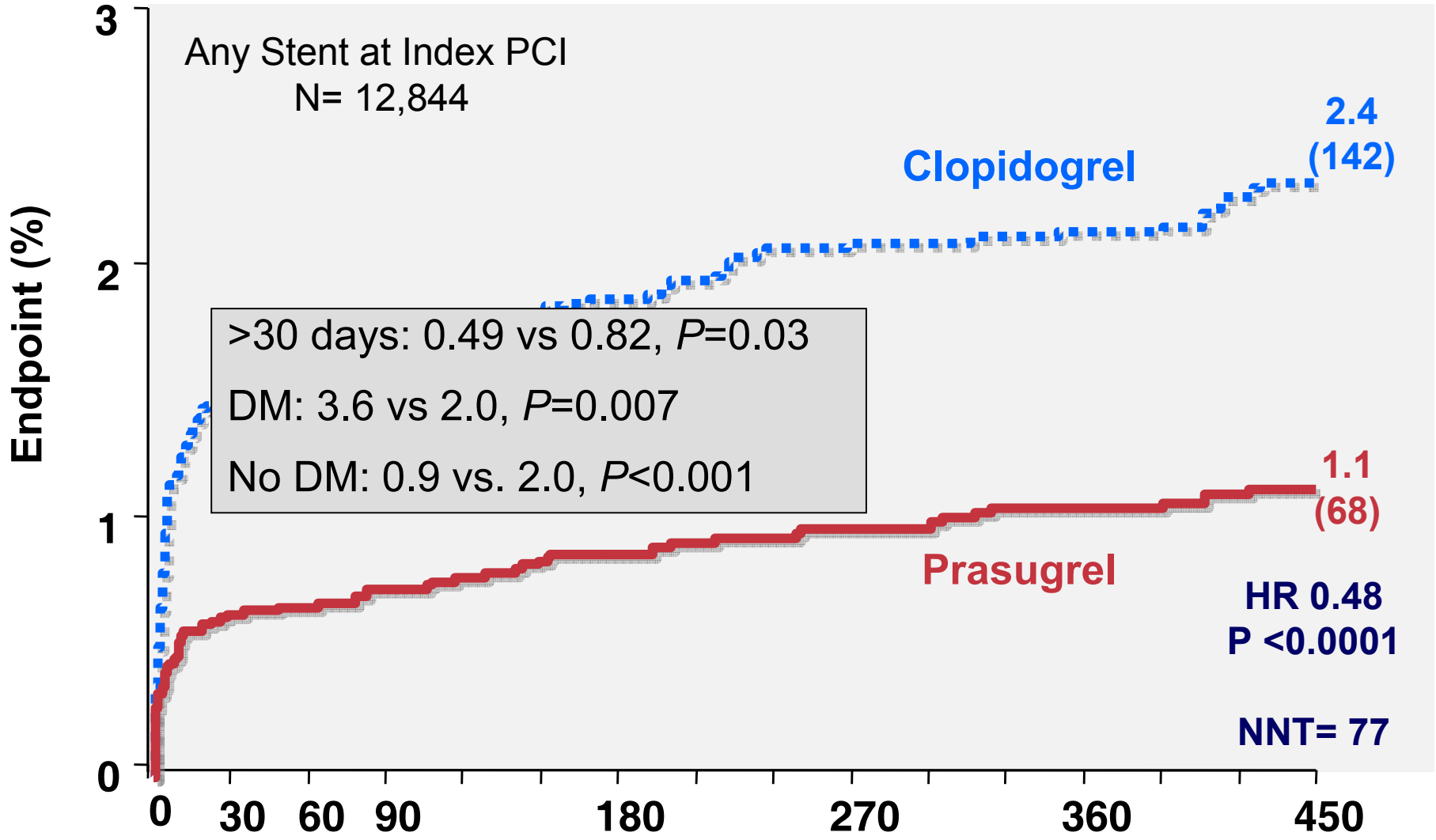


Wiviott et al. NEJM 2007

TRITON: Myocardial Infarction



TRITON TIMI 38
Stent Thrombosis (ARC Definite + Probable)



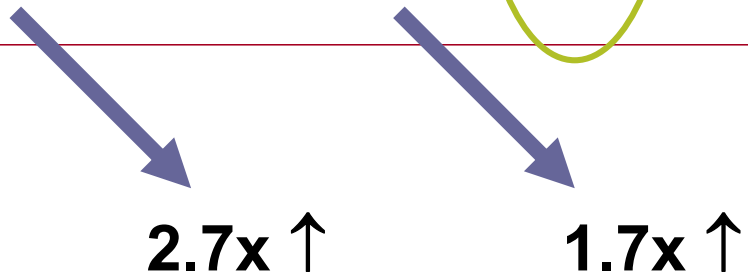
Wiviott et al. NEJM 2007

Influence of Trial Conduct and Definitions

What is Meaningful to a Doctor May Differ to a Trial Committee

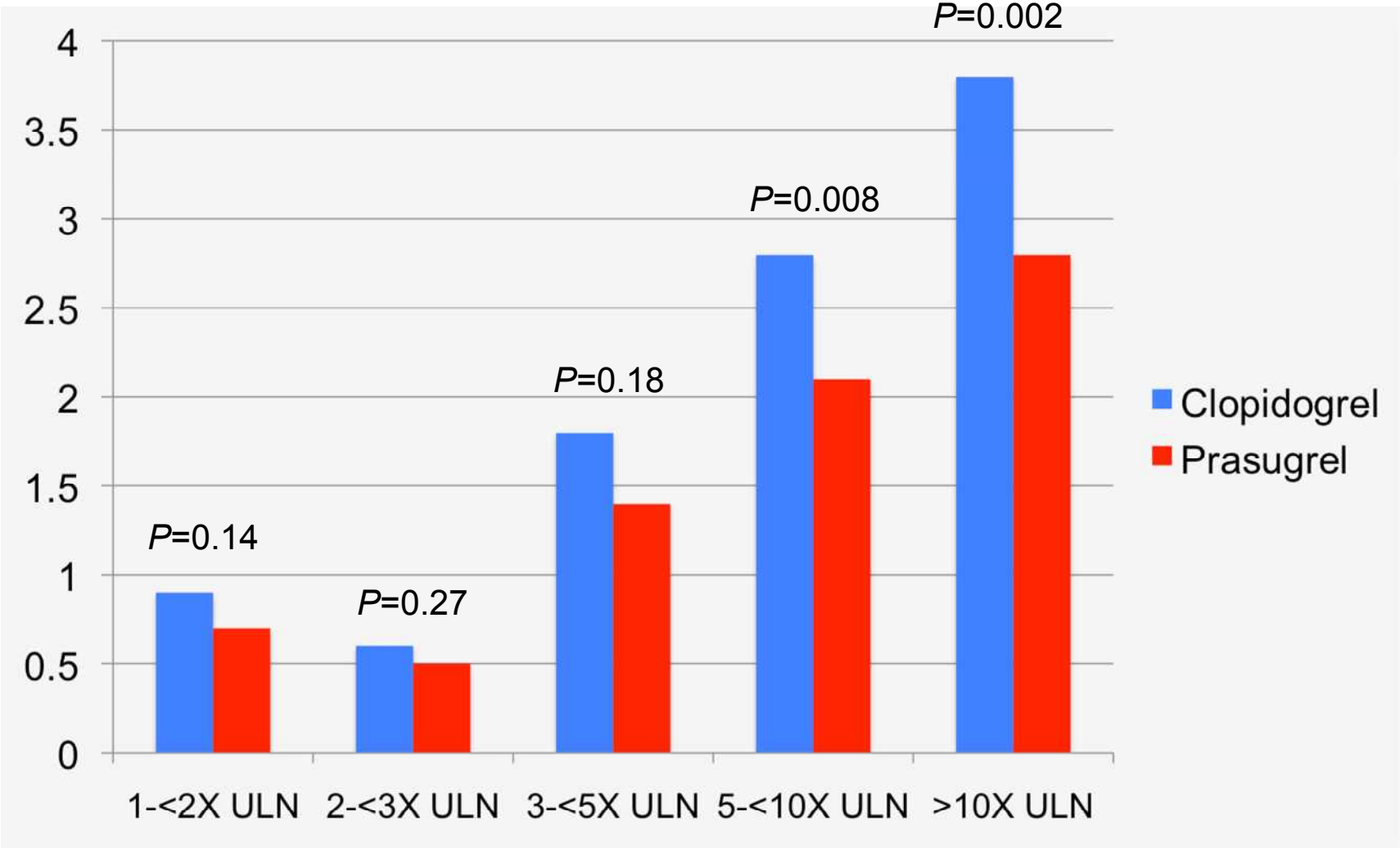
Definite Stent Thrombosis

	Prasugrel	Clopidogrel	RR	*P* Value
CEC adjudicated	52	122	0.42	<0.001



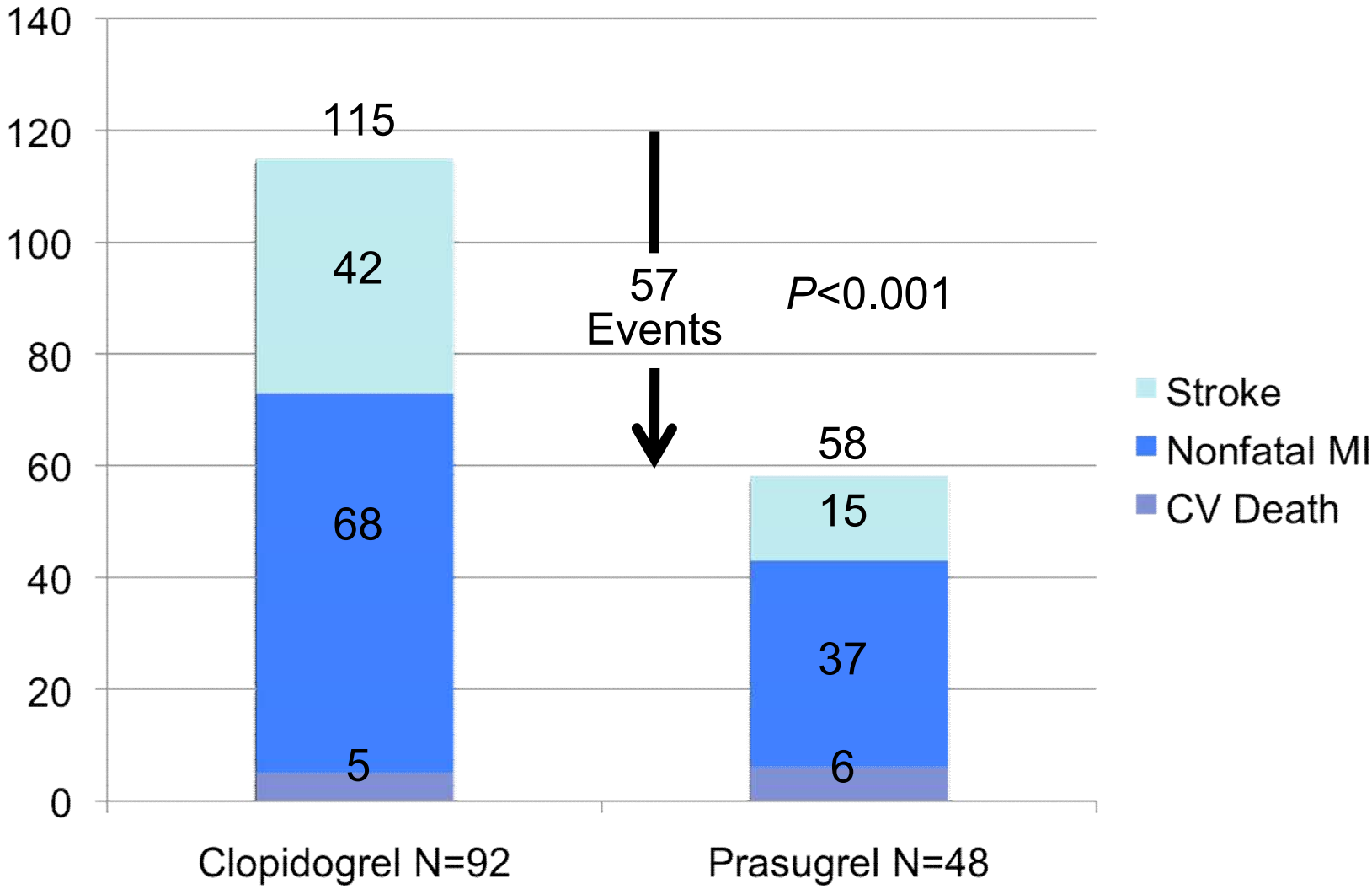
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022307s000_MedR_P23.pdf

TRITON
Efficacy Analysis by Biomarker Elevation



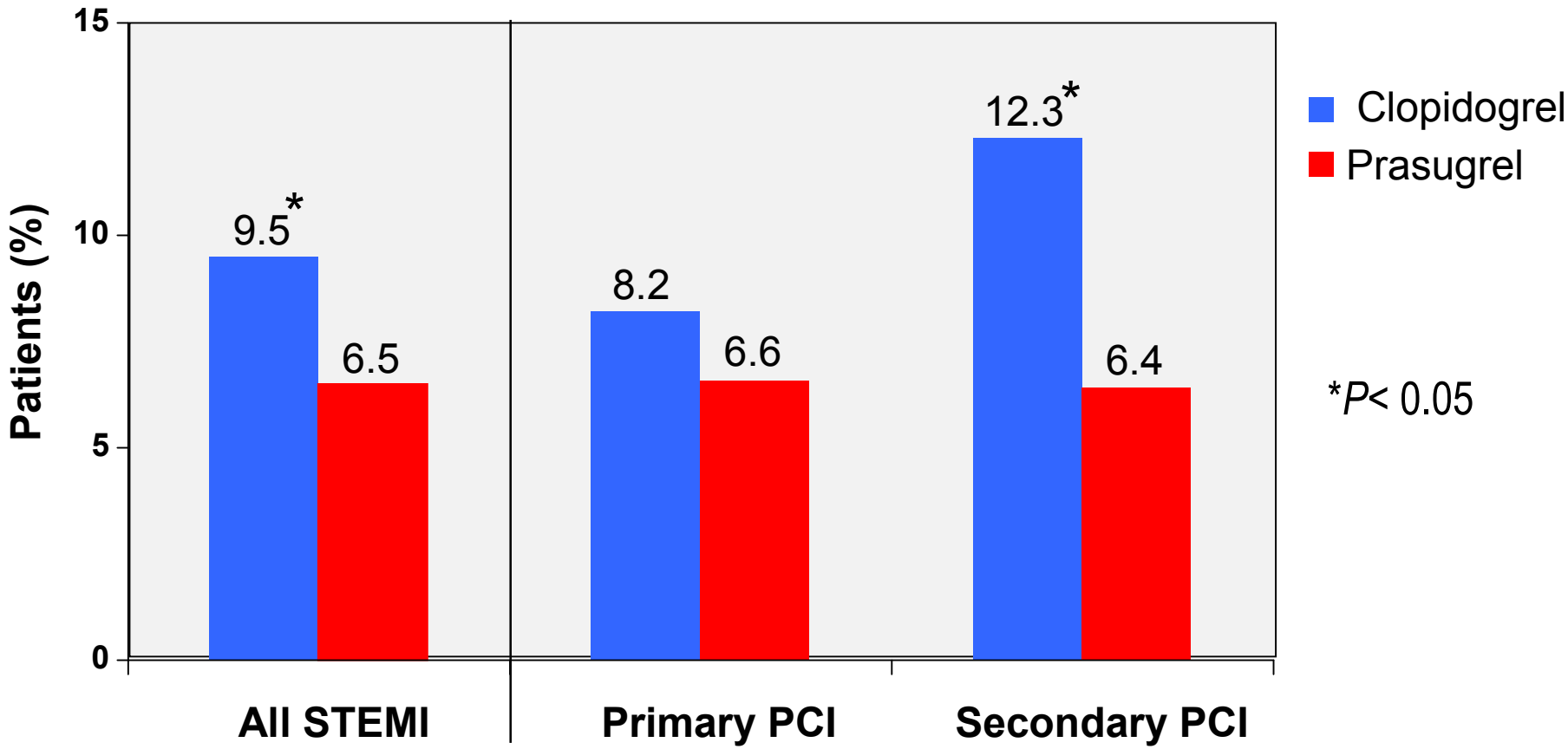
Morrow et al. Circulation 2009

TRITON
Impact on Recurrent Events



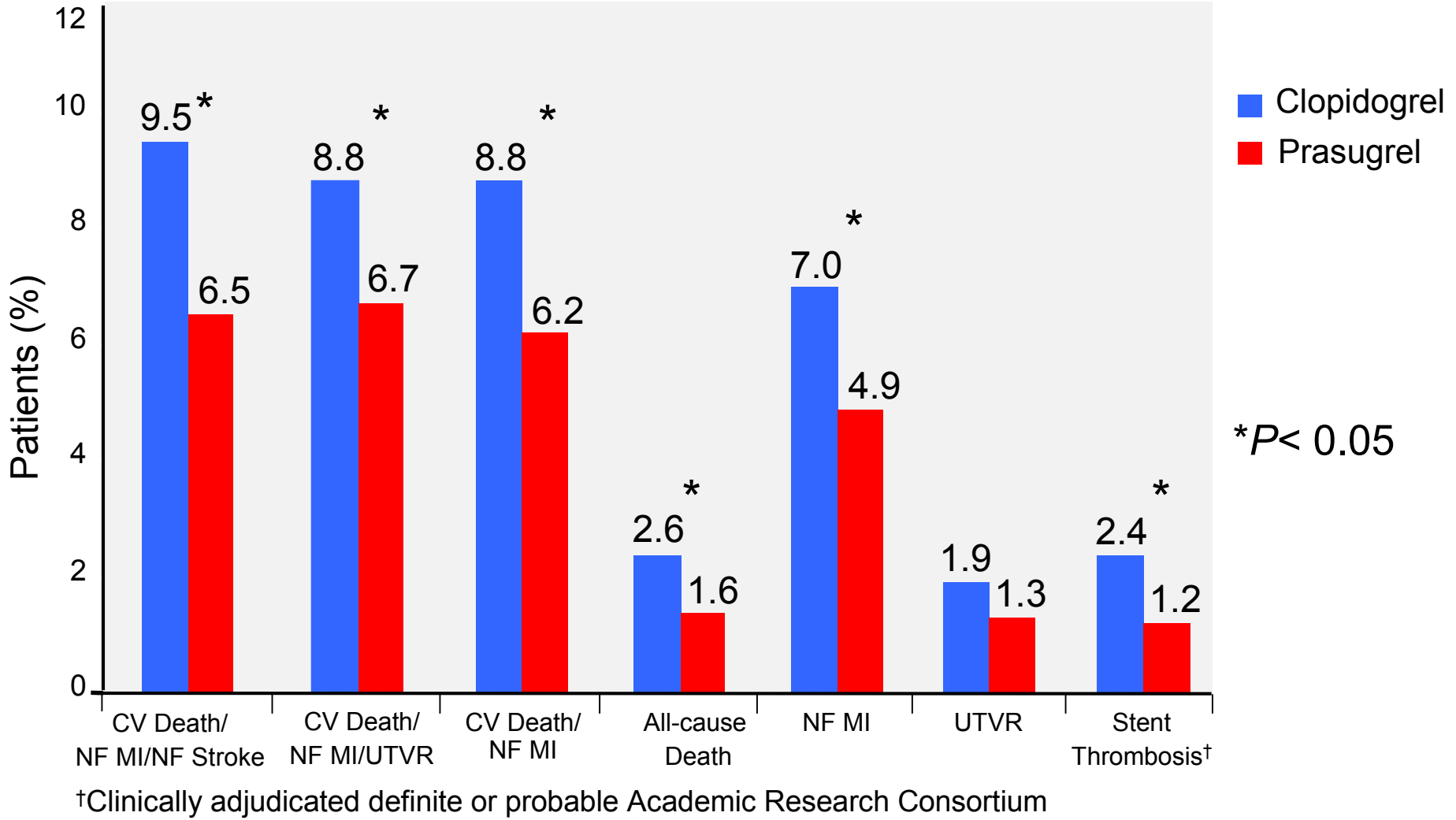
Murphy et al. Eur Heart J 2008

TRITON-TIMI 38: STEMI Cohort Primary Efficacy Endpoint at 30 Days (CV Death, NF MI, NF Stroke)



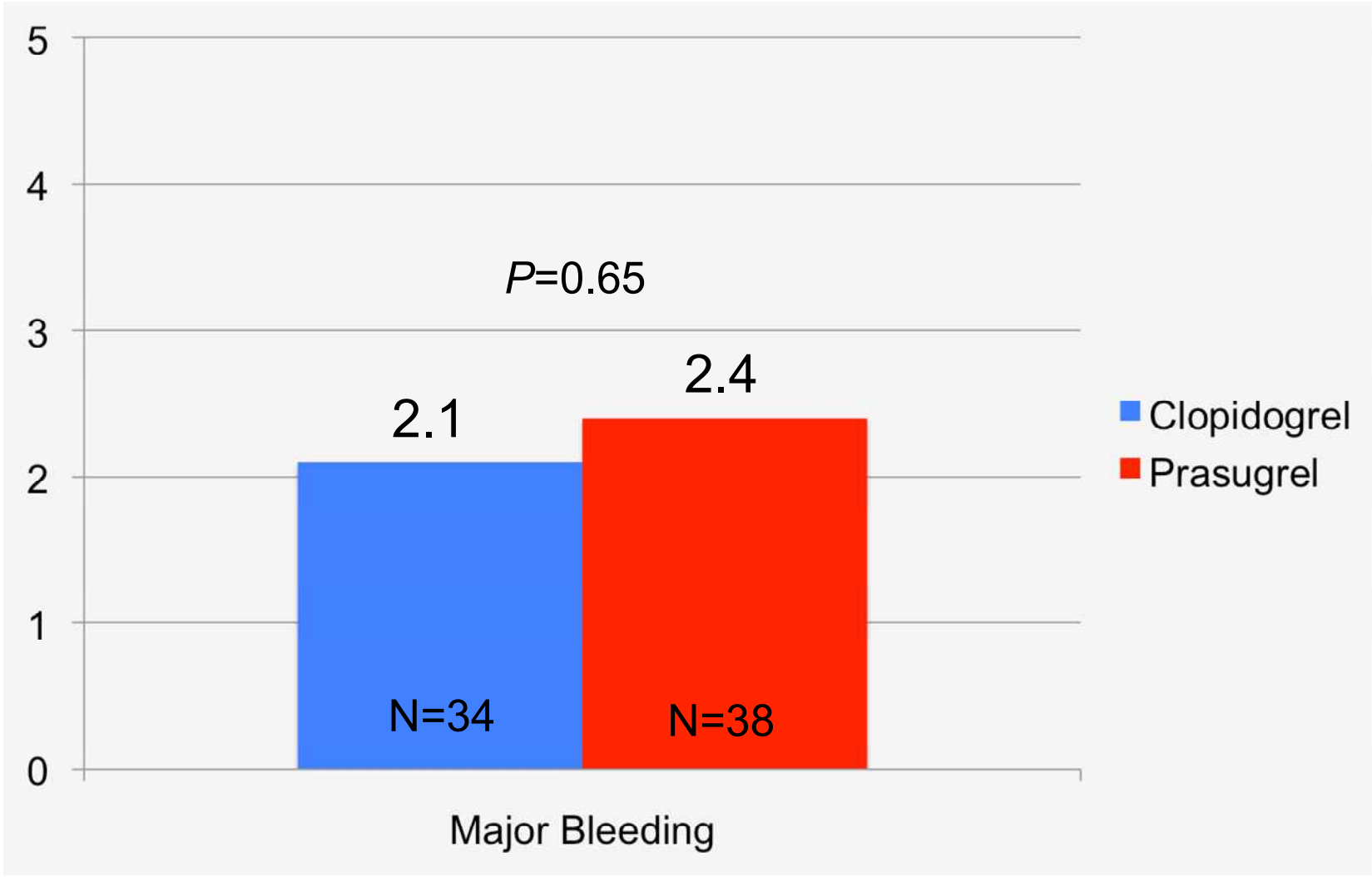
Montalescot G et al. *Lancet* 2009;373(9665):723-731

TRITON-TIMI 38
STEMI Cohort Efficacy Endpoints at 30 Days

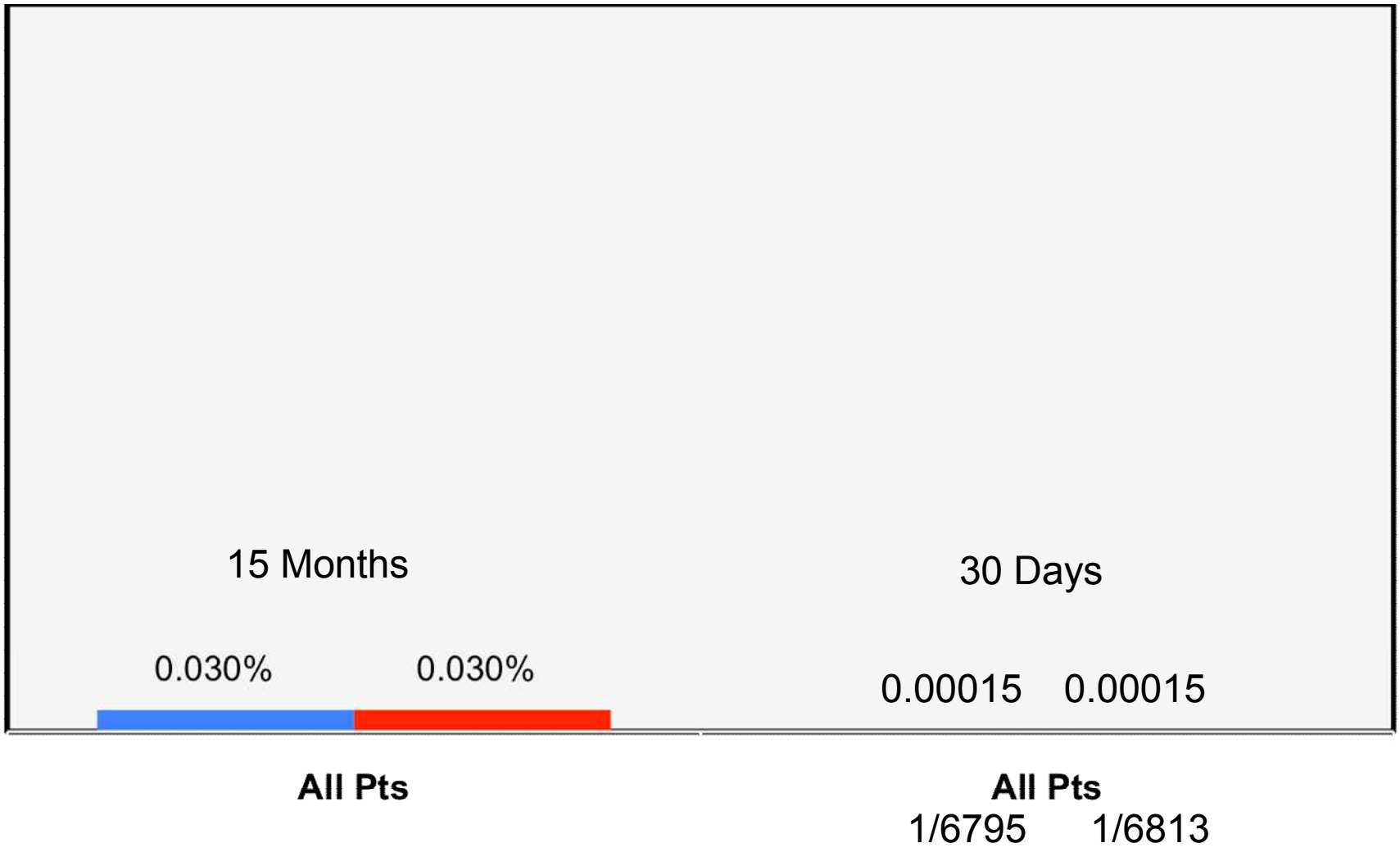


Montalescot G et al. Lancet 2009;373(9665):723-731

STEMI Cohort
Non-CABG TIMI Major Bleeding

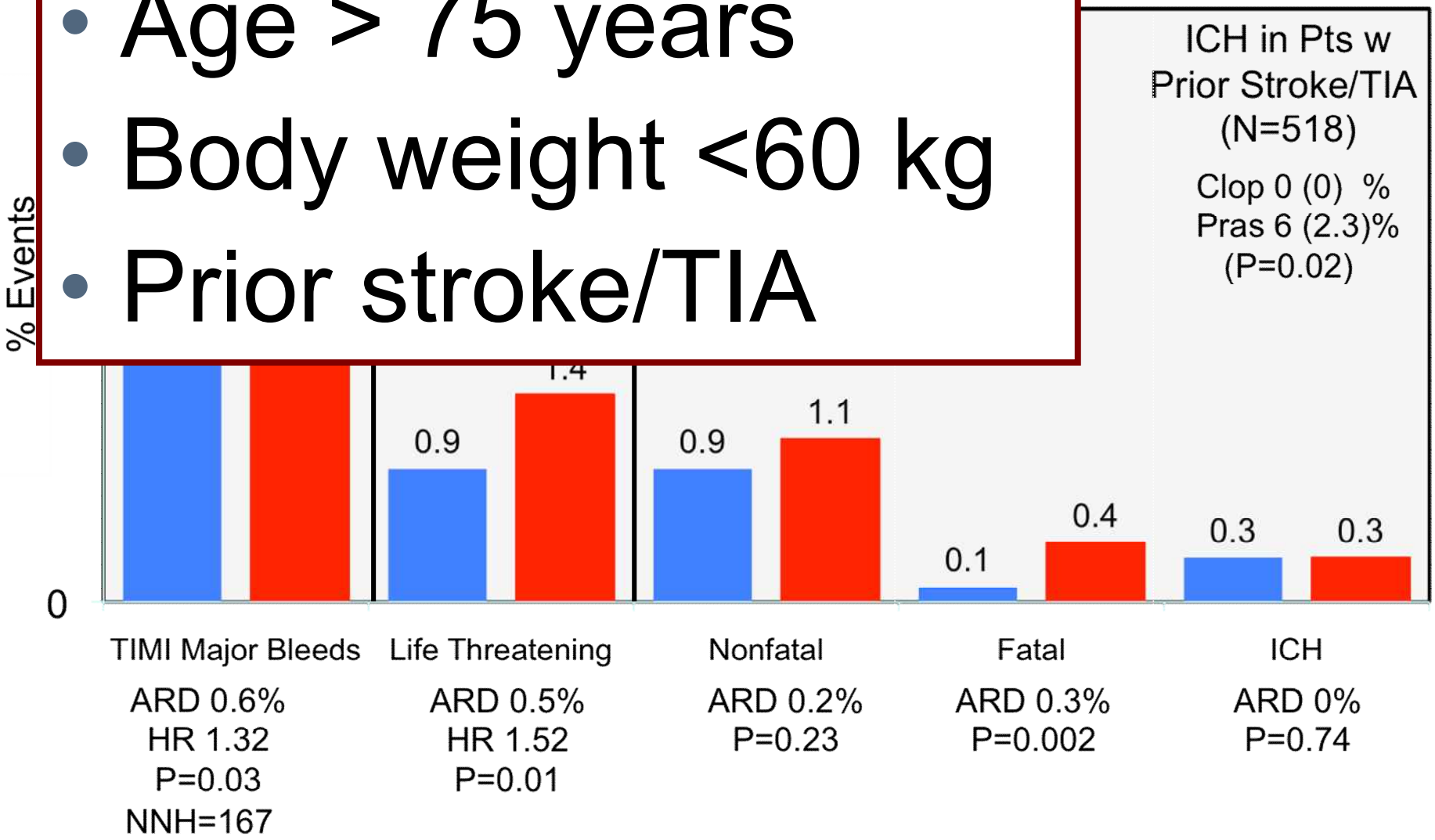


Intracranial Hemorrhage
Non-CABG TIMI Major Bleeding



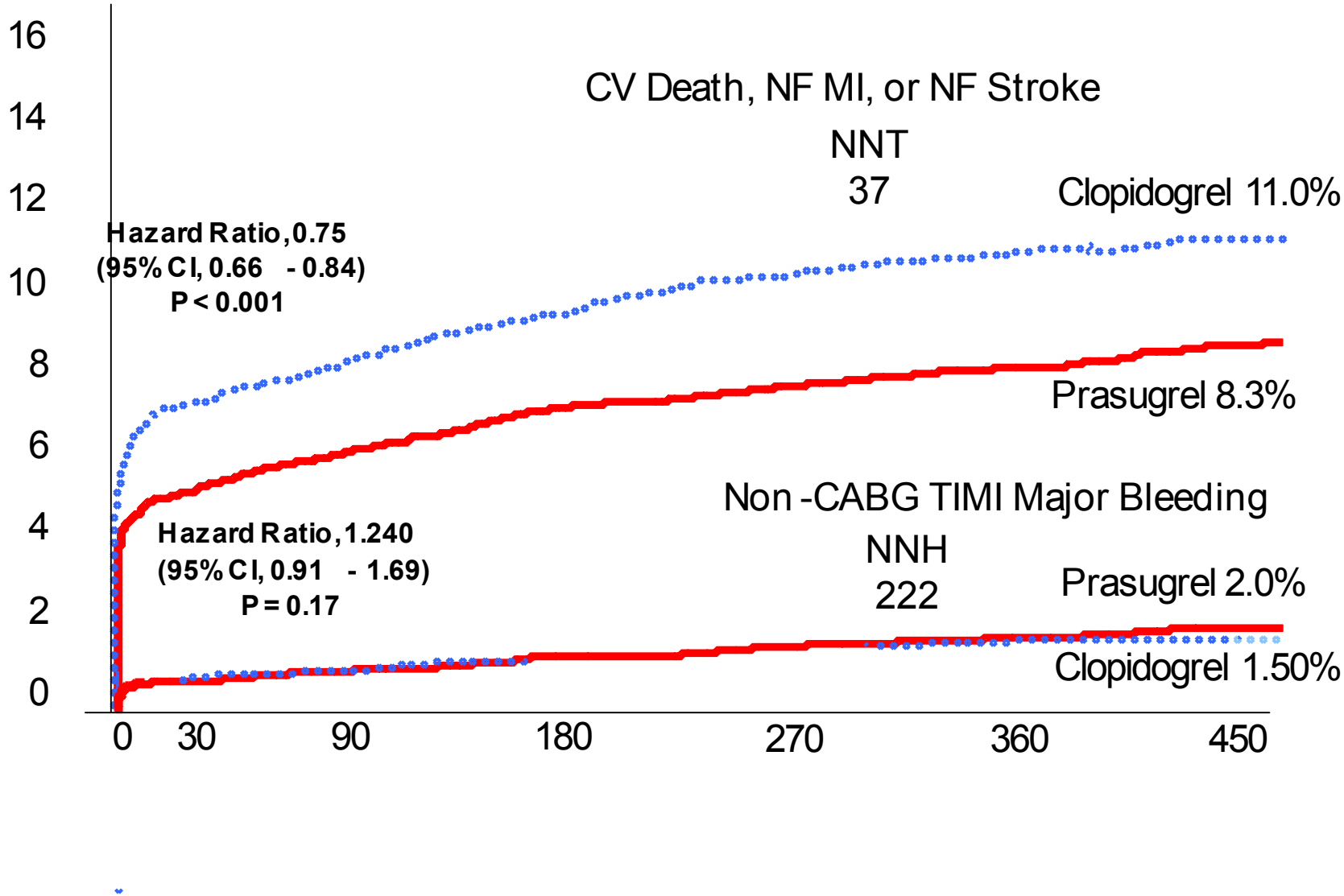
Bleeding Events
Safety Cohort (N=13,457)

- Age > 75 years
- Body weight <60 kg
- Prior stroke/TIA

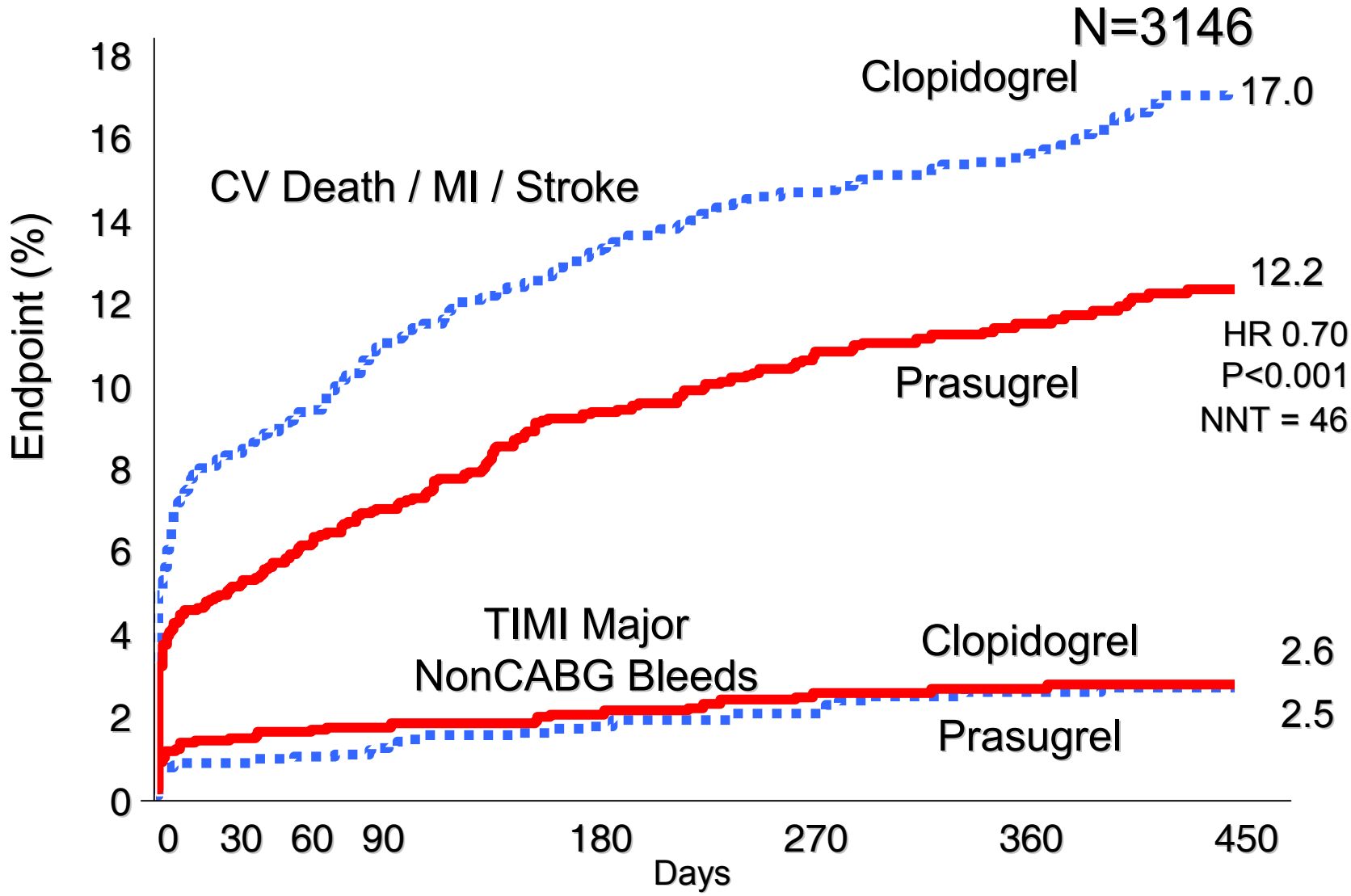


Prasugrel: Balance of Risk and Benefit

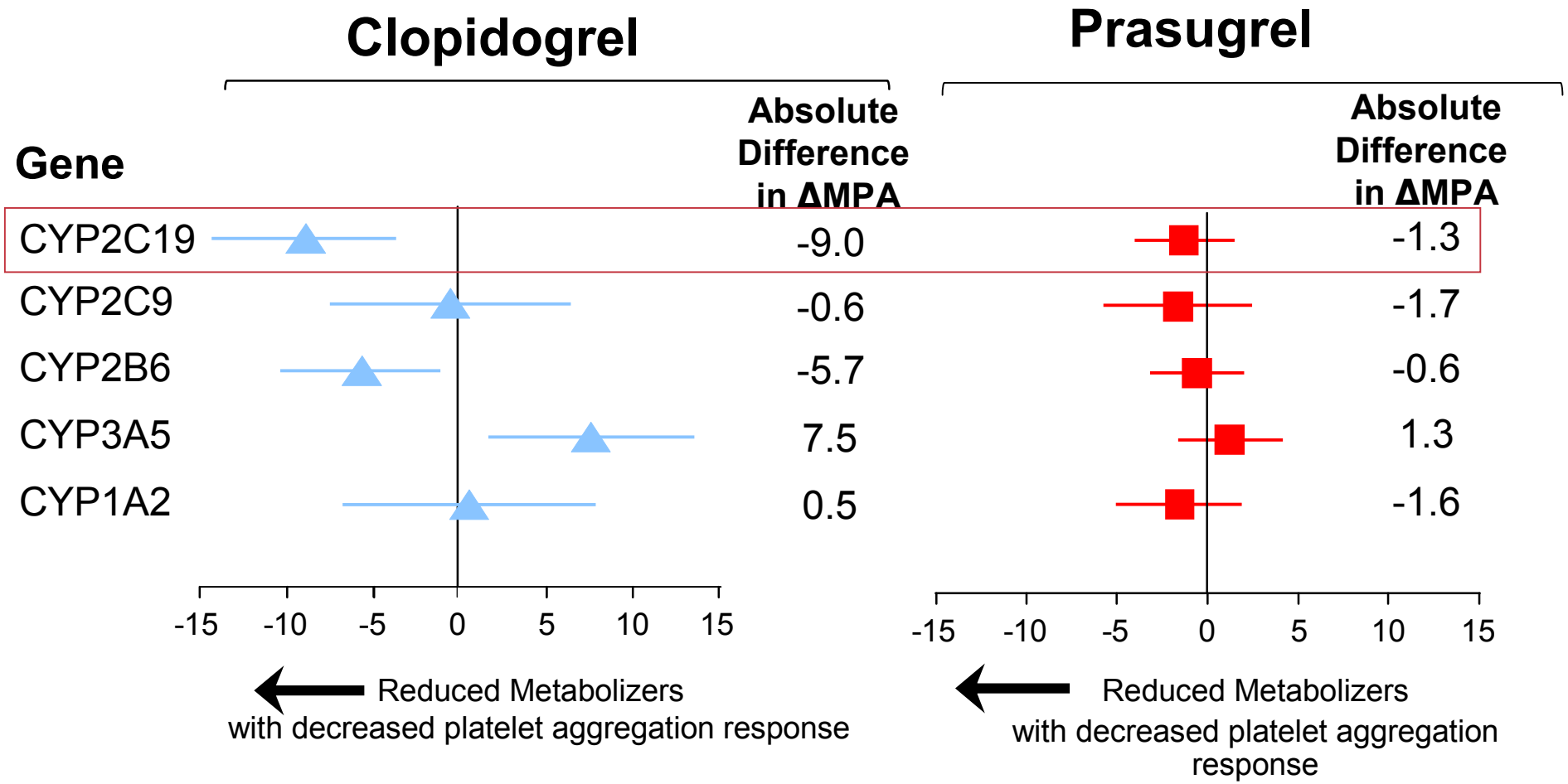
Patients <75 y, >60 kg and without prior stroke/TIA



Prasugrel: Balance of Risk and Benefit
Diabetic Subgroup



Genomic Effects on Thienopyridine Pharmacodynamics



Mega JL, et al. *N Engl J Med* 2009;360(4):354-362
Mega JL, et al. *Circulation* 2009;119:19:2553-2560

Genetic Determinants of Antiplatelet Therapy Response

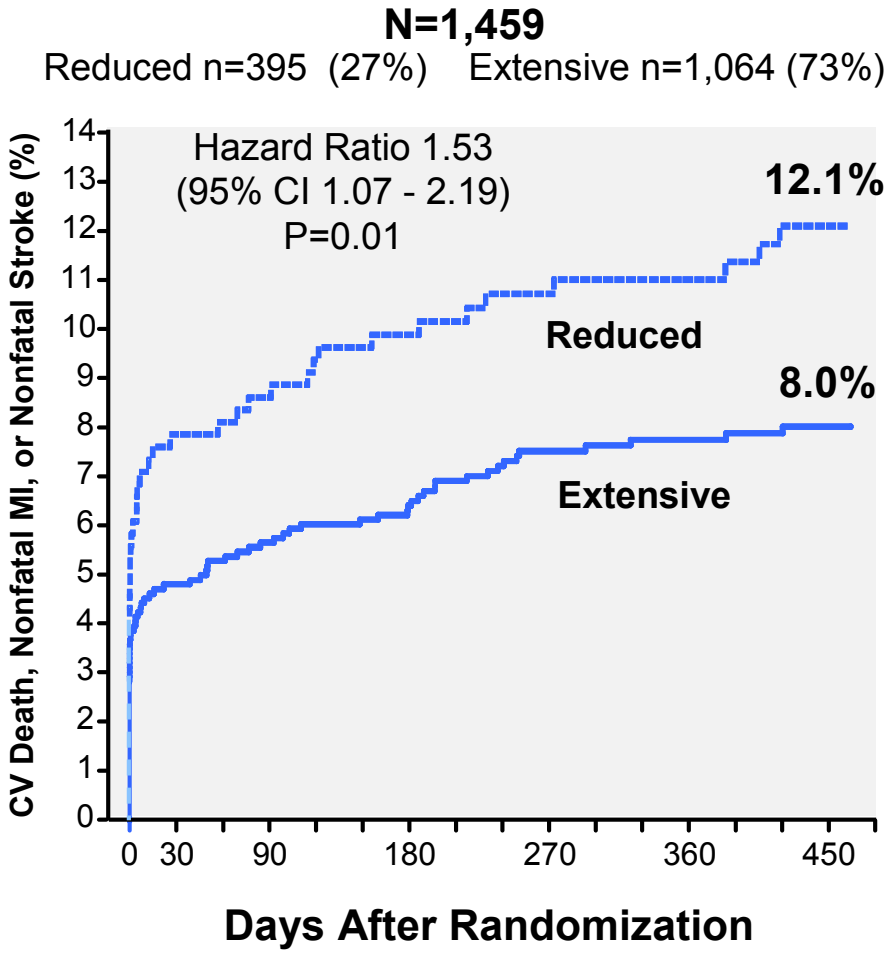
CYP2C19 Polymorphisms and Clinical Outcomes

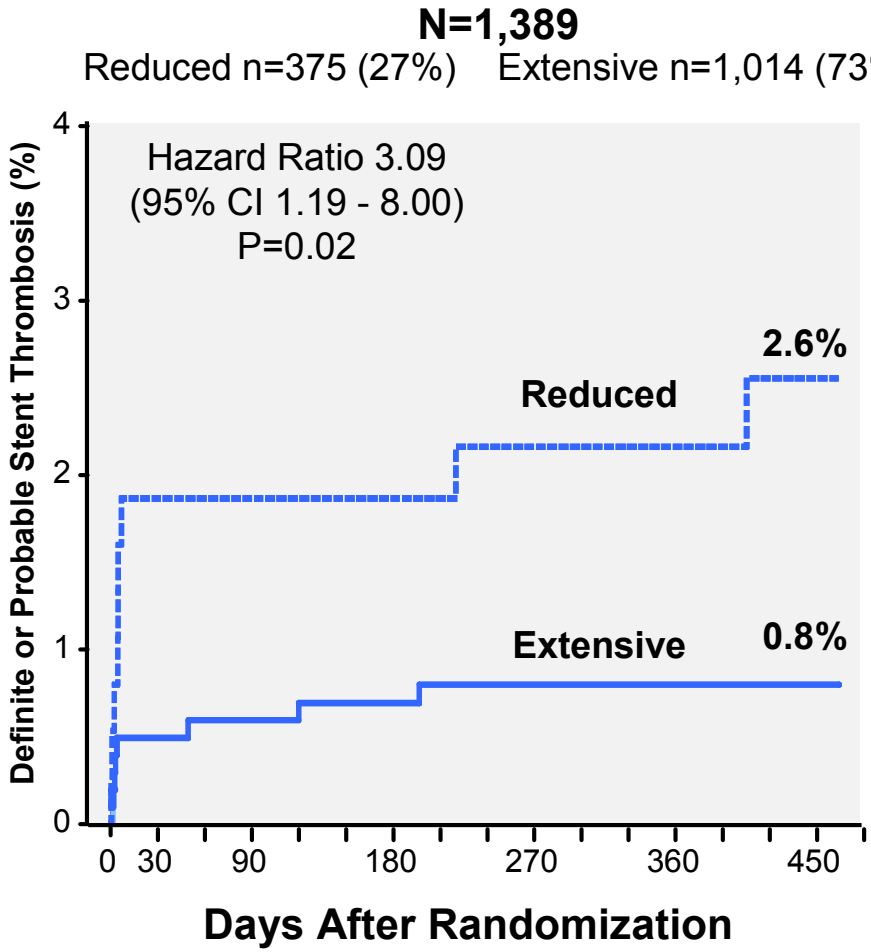
FAST-MI: Predictors of All-Cause Death, Non-fatal MI, Stroke

Any loss-of-function CYP2C19 allele (*2, *3, *4, *5)	All patients (N=2,208)	*P* value	Patients who underwent PCI (N=1,535)	*P* value
0 variant allele	1.00	0.003	1.00	0.005
1 variant allele	0.69 (0.51-0.93)		0.78 (0.50-1.21)	
2 variant alleles	1.98 (1.10-3.58)		3.58 (1.71-7.51)	

Simon et al. NEJM 2008

Adverse Events Relative to Inherited Reduced Metabolism Variant of CYP2C19: *Clopidogrel Cohort* TRITON-TIMI 38



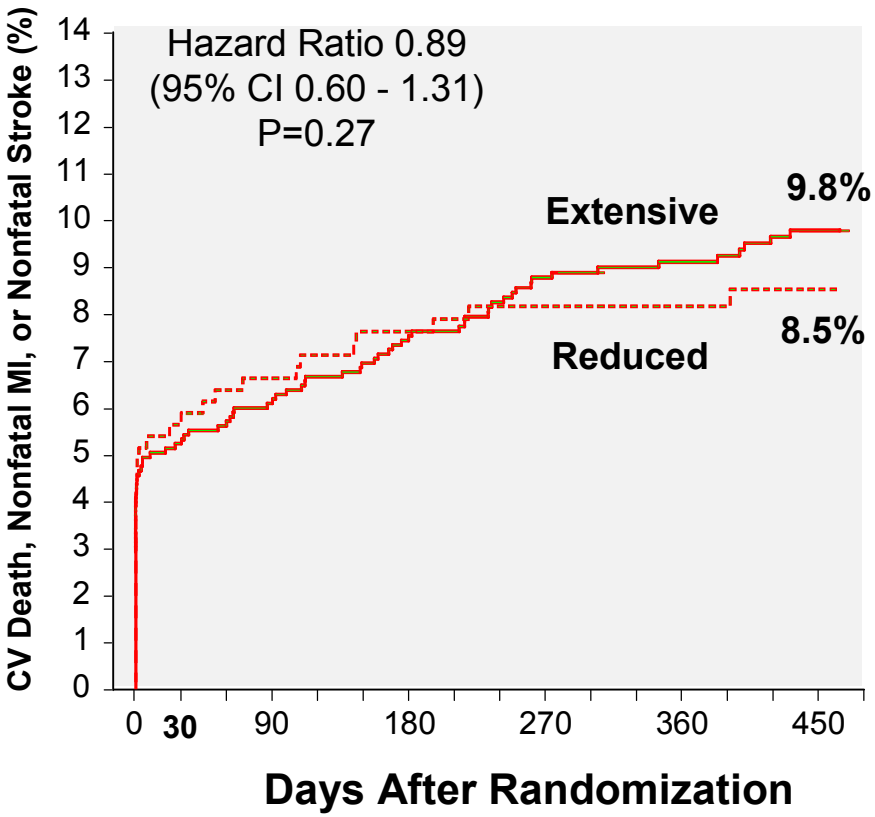


Mega JL, et al. *New Engl J Med* 2009;360(4):354-362

Adverse Events Relative to Inherited Reduced Metabolism Variant of CYP2C19: *Prasugrel Cohort* TRITON-TIMI 38

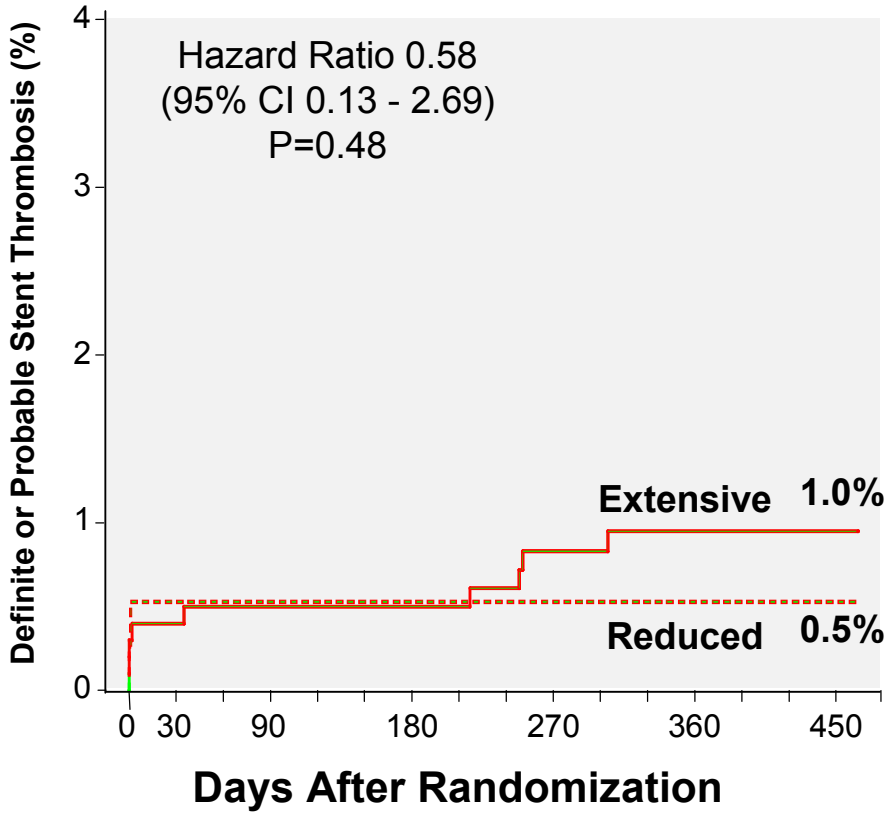
N=1,455

Reduced n=407 (28%) Extensive n=1,048 (72%)



N=1,379

Reduced n=379 (27%) Extensive n=1,000 (73%)



Mega et al. *Circulation.* 2009;119:2553-2560.

From Clinical Trials to Clinical Practice

"A p-value is no substitute for a brain."

— Anonymous

Stone, Pocock. JACC 2010

Prasugrel
From Clinical Trials to Clinical Practice

Who is a suitable candidate for Prasugrel?

- ACS patients (both NSTEMI and STEMI) intended to undergo PCI, not for those with expectation of CABG
  - STEMI patients (consider as initial therapy for most patients)
  - Diabetes
- High-risk PCI anatomy (eg, UPLM, bifurcation disease)
- PCI in patients not adequately pre-treated with thienopyridine therapy
- Clopidogrel non-responsiveness by platelet aggregation/genomic testing

Who is not a Prasugrel candidate?

- Patients for whom CABG may be a consideration
- Prior stroke/TIA
- Uncertainty regarding elderly (≥75 years), body weight <60 kg

Prasugrel

From Clinical Trials to Clinical Practice

- Compared with Clopiodgrel, Prasugrel is associated with more rapid, complete and consistent platelet inhibition
- In ACS patients (both NSTEMI and STEMI), treatment with prasugrel is associated with significant reductions in the composite of cardiovascular mortality, MI, and stroke, in addition to stent thrombosis
- Prasugrel is associated with a modest but significant increased bleeding risk for whom the benefit/risk is particularly decreased among patients ≥75 years age, with prior stroke/TIA or body weight <60 kg
  - 5 mg maintenance dose may preserve efficacy and reduce bleeding risk, although not formally studied for patient level outcomes
- Experience with Prasugrel has exposed the opportunity and potential for individualized medicine
- Role of Prasugrel in medical management of ACS, clopidogrel non-responsiveness presently under investigation (TRIGGER PCI, TRILOGY)