

**Prasugrel (LY640315; CS-747) as an  
anti-thrombotic therapy in patients with  
acute coronary syndromes (ACS)**

**NDA 22-307  
EFFIENT™ (prasugrel)**

**Presentation to the  
Cardiovascular and Renal Drugs Advisory Committee  
03 February 2009**

**Daiichi Sankyo, Inc.  
and  
Eli Lilly and Company**

# **Prasugrel**

## **Introduction and Overview**

**J. Anthony Ware, M.D.**

**Vice President Lilly Research Laboratories  
Global Brand Development Platform Leader  
Cardiovascular, Diabetes, and Acute Care  
Eli Lilly and Company**

# Proposed Indication

## Acute Coronary Syndromes (ACS)

**EFFIENT (prasugrel) is indicated for the reduction of cardiovascular events in patients with ACS as follows**

- ◆ **Unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) when managed with percutaneous coronary intervention (PCI)**
- ◆ **ST-segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI**

**EFFIENT has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction, or nonfatal stroke, and to prevent stent thrombosis**

# Prasugrel Clinical Development Program (1)

- ◆ **The TIMI Group and the Sponsors conducted a clinical testing program in response to needs expressed by the cardiovascular community**
  - **Extensive program**
    - **13,608 patients in the pivotal clinical trial (TRITON-TIMI 38)**
    - **Nearly 9000 people have received at least 1 dose of prasugrel**

# Prasugrel Clinical Development Program (2)

- ◆ **Relevant to U.S. clinical practice: Nearly one third of the patients in TRITON-TIMI 38 were from the U.S.**
- ◆ **Provides information important to practitioners**
  - **Critically ill patients with an unmet need**
  - **Head-to-head comparison with the standard of care**
  - **Meaningful endpoints- cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, stent thrombosis**

# Prasugrel Clinical Development Program (3)

- ◆ The entire clinical program was developed in close consultation with the FDA, who concurred with the design and statistical analysis plan for TRITON-TIMI 38
- ◆ The database and adjudication procedures were of very high quality and we and our colleagues at TIMI are confident in their integrity
- ◆ The comprehensive efficacy, safety, and benefit-risk analyses of our extensive database are compelling and this application was granted a priority review by the FDA

# Central Hypothesis of Prasugrel Research Program

- ◆ A new thienopyridine (prasugrel) with a faster, higher and more consistent (ie, with fewer poor responders) inhibition of platelet function will produce important clinical benefits for the ACS patient

# External Consultants

## Eugene Braunwald, MD

Hersey Distinguished Professor of Theory and Practice of Medicine, Harvard Medical School  
Chairman, TIMI Study Group, Brigham and Women's Hospital

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## Elliott M. Antman, MD

Professor of Medicine, Harvard Medical School  
Senior Investigator, TIMI Study Group  
Director of Samuel A. Levine Cardiac Unit, Brigham and Women's Hospital

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## Jeffrey S. Barrett, PhD, FCP

Research Associate Professor, Pediatrics  
University of Pennsylvania, School of Medicine  
Director, Laboratory for Applied PK/PD, The Children's Hospital of Philadelphia

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## Robert F. Ozols, MD, PhD

Senior Vice President Medical Science Division  
Fox Chase Cancer Center

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## Philip S. Schein, MD

Visiting Professor in Cancer Pharmacology  
Oxford University

# Agenda: Sponsor's Presentation

**Unmet Medical Need**

**Eugene Braunwald, MD**

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**Dosing Considerations**

**Jeffrey Riesmeyer, MD**

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**Benefit-Risk  
(TRITON-TIMI 38)**

**Elliott M. Antman, MD**

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**Special Topics**

**William Macias, MD, PhD**

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**Closing Remarks**

**Eugene Braunwald, MD**

# Summary Points

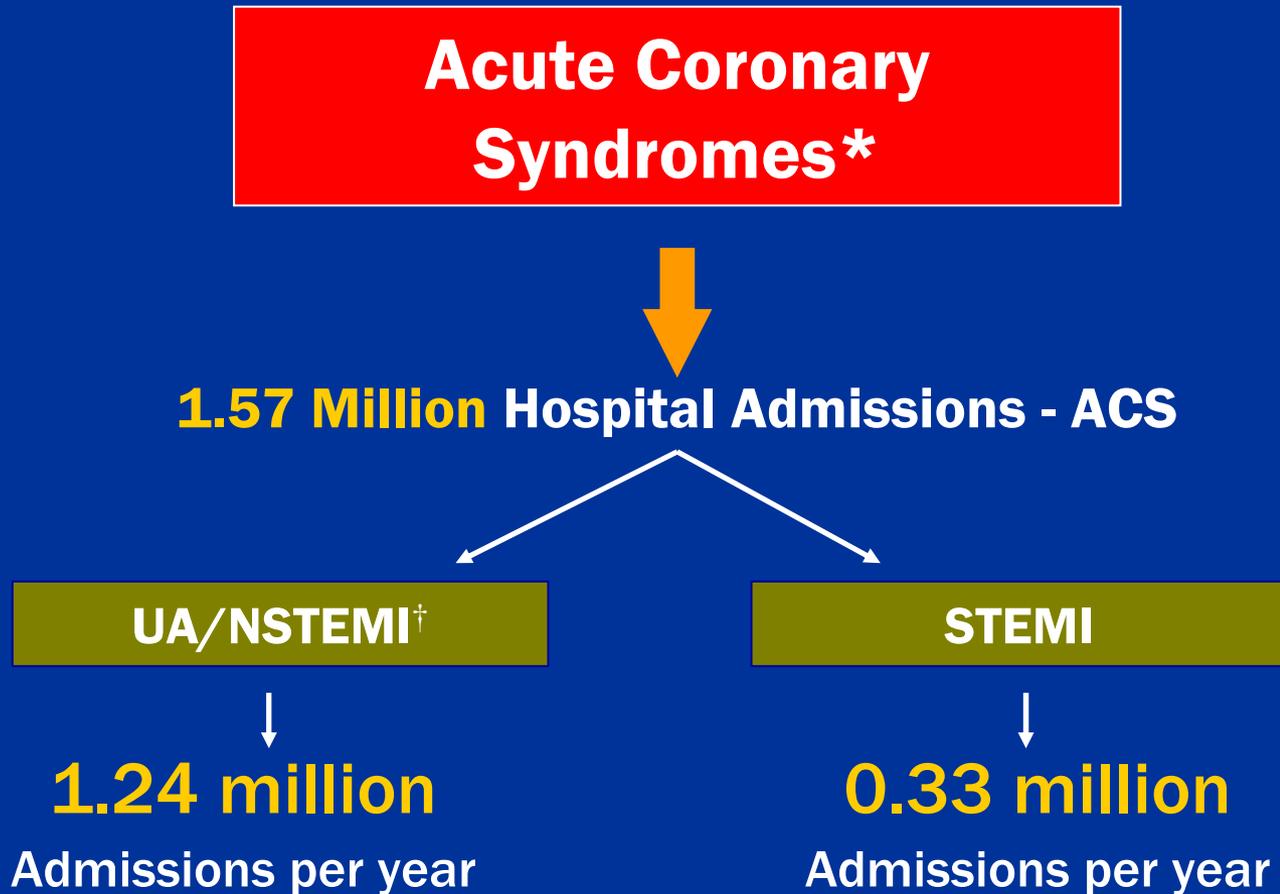
- 1. A substantial unmet need exists in ACS patients because of shortcomings in current standard of care**
- 2. Prasugrel is superior to clopidogrel in preventing cardiovascular events, including stent thrombosis**
- 3. No credible evidence exists that prasugrel is carcinogenic or promotes the growth of tumors**
- 4. The benefit-risk profile for prasugrel is favorable and we have developed a plan to effectively manage the risk of bleeding in the appropriate patients**

# **Acute Coronary Syndromes: Unmet Medical Need**

**Eugene Braunwald, MD**

**Hersey Distinguished Professor of Theory and  
Practice of Medicine, Harvard Medical School  
Chairman, TIMI Study Group, Brigham and Women's  
Hospital**

# Hospitalizations in the US Due to ACS

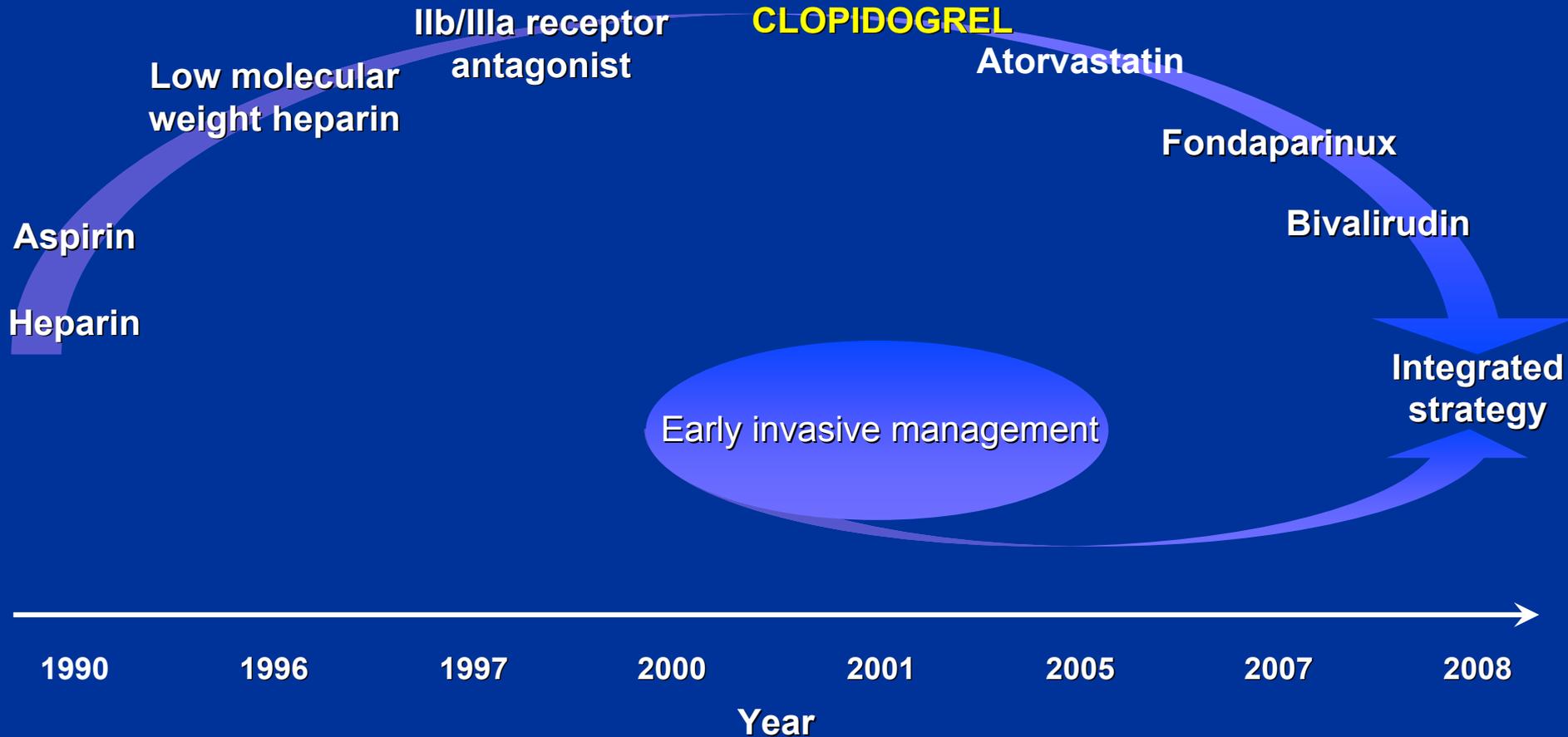


\*Primary and secondary diagnoses.

†About 0.57 million NSTEMI and 0.67 million UA.

Heart Disease and Stroke Statistics – 2007 Update. *Circulation* 2007; 115:69–171

# Evolution of ACS Therapies

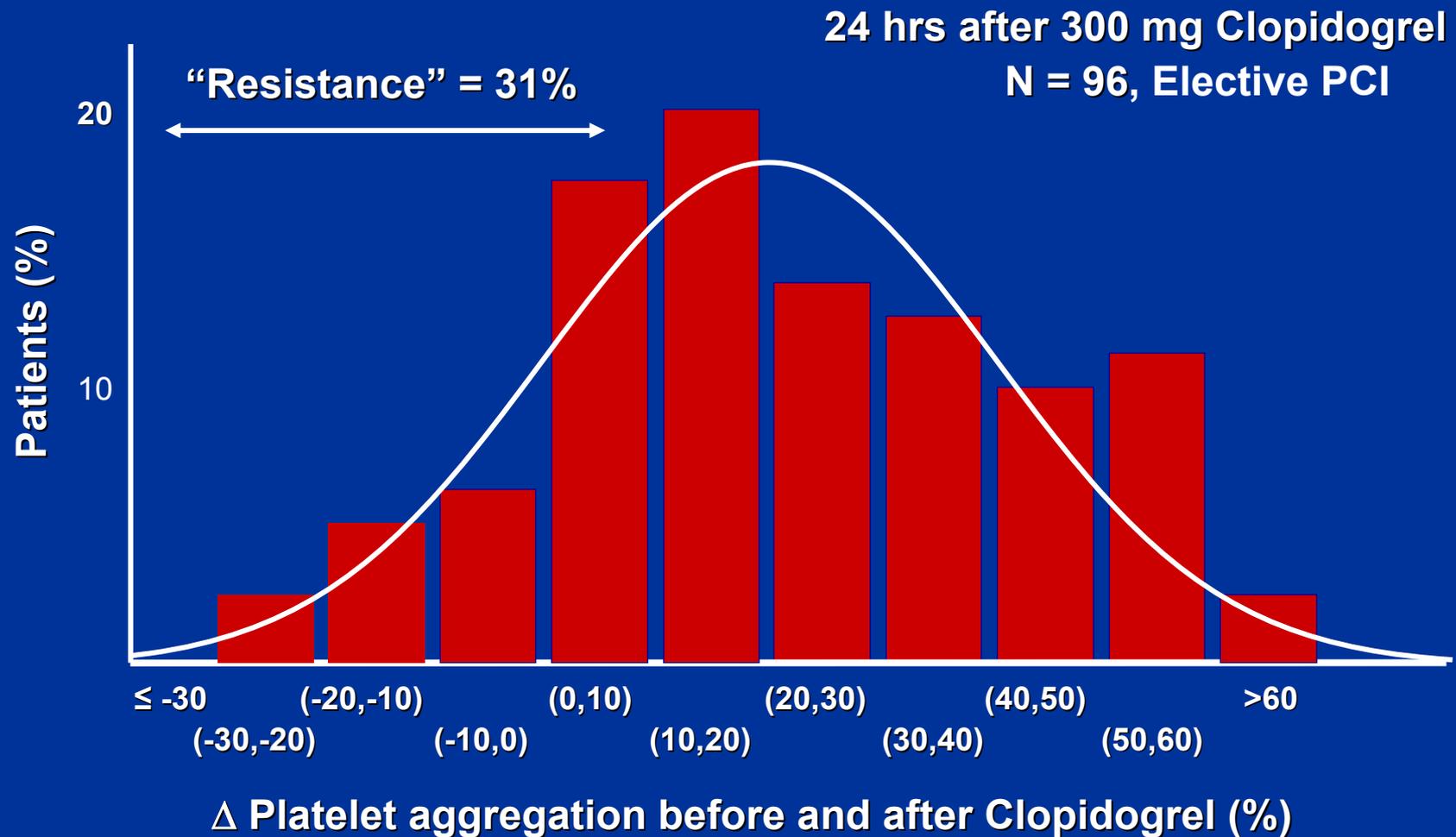


# Prevention of Recurrent Ischemic Events with Dual Antiplatelet Therapy

## ◆ Limitations of clopidogrel

- Modest antiplatelet effect with high interpatient variability
- Delayed onset of action
- In multiple small clinical studies, lesser pharmacologic response to clopidogrel may increase risk for myocardial infarction (MI) and coronary stent thrombosis

# Variable and Unpredictable Response to Clopidogrel

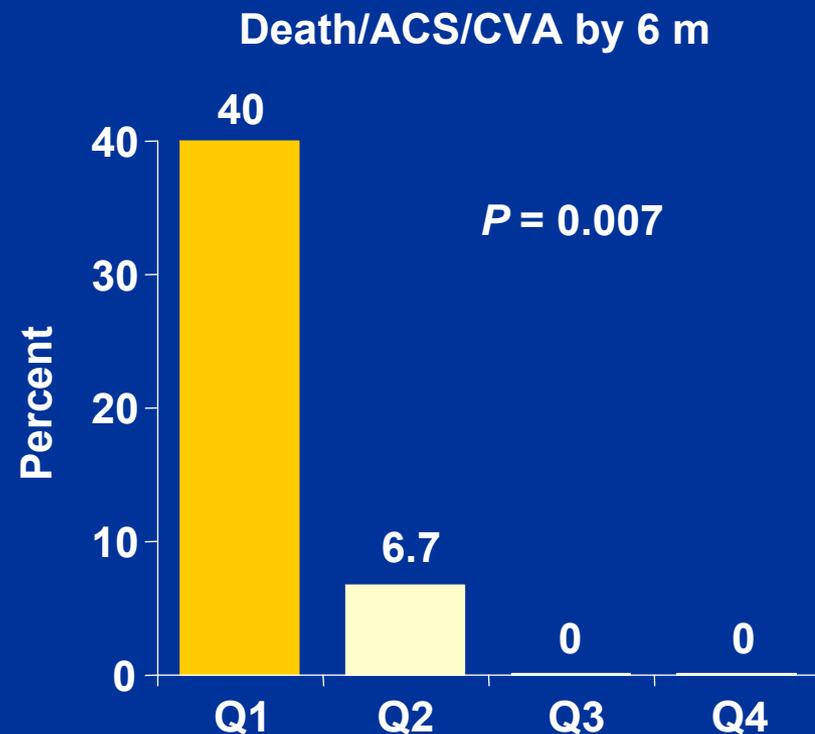
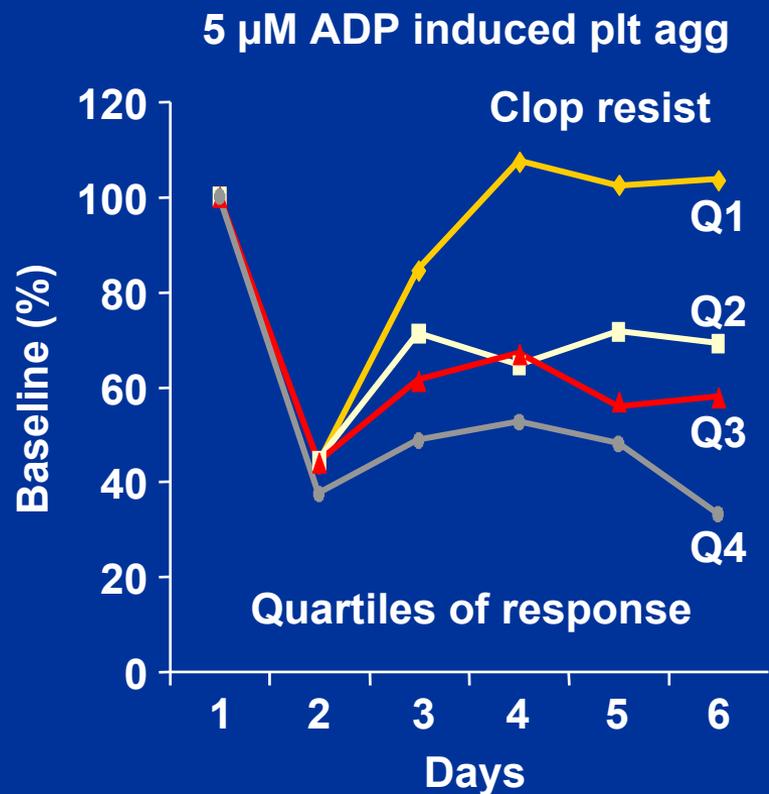


“Resistance” =  $\leq 10\%$   $\Delta$  platelet aggregation

Gurbel PA et al. *Circulation* 2003; 107: 2908-2913

# Clopidogrel Response Variability and Increased Risk of Ischemic Events

Primary PCI for STEMI (N = 60)



Matetzky S, et al. *Circulation*. 2004;109:3171-3175.  
Wiviott SD, Antman EM. *Circulation*. 2004 109:3064-3067.

# Clinical Relevance of Clopidogrel Response Variability Post-Stent Ischemic Events and Periprocedural Infarction

	<b>N</b>	<b>Functional Parameter</b>	<b>Clinical Relevance</b>
Matezky et al. Circulation 2004	60	↑ platelet aggregation (4 <sup>th</sup> quartile)	Post-primary PCI ischemic events (6 months)
Gurbel et al. JACC 2005	192	↑ periprocedural platelet aggregation	Post-PCI ischemic events (6 months)
Gurbel et al. Circulation 2005	120	↑ periprocedural platelet aggregation	Myonecrosis and inflammation marker release
Cuisset et al. J Thromb Haemost 2006	106	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Lev et al. JACC 2006	150	↑ clopidogrel/aspirin-resistant patients	Post PCI-myonecrosis
Cuisset et al. JACC 2006	292	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Hocholzer et al. JACC 2006	802	↑ platelet aggregation (3 <sup>rd</sup> & 4 <sup>th</sup> quartiles)	Post-PCI ischemic events (30 days)
Geisler et al. Eur Heart J 2006	379	↓ platelet inhibition	Post-PCI ischemic events (3 months)
Bliden et al. JACC 2007	100	↑ platelet aggregation	Post-PCI ischemic events (12 months)

# Recent Trials Reporting Clinical Outcomes at 1 Yr for Patients with ACS Undergoing PCI

	Patients, n (%)				
	Total N	D/MI/TVR	Death	MI	TVR
<b>ACUITY*</b>	<b>7789<sup>a</sup></b>	<b>1465 (18.8)</b>	<b>247 (3.2)</b>	<b>682 (8.8)</b>	<b>928 (11.9)<sup>b</sup></b>
<b>ISAR-REACT 2*</b>	<b>2022</b>	<b>515 (25.5)</b>	<b>94 (4.6)</b>	<b>202 (10.0)</b>	<b>301 (14.9)<sup>c</sup></b>

\* Clopidogrel plus ASA

<sup>a</sup> Subset of patients in the ACUITY trial who underwent PCI

<sup>b</sup> Unplanned revascularization for ischemia.

<sup>c</sup> Target vessel revascularization = CABG or repeat PCI for symptoms or ischemia.

White HD et al. *JACC* 2008; 52: 807-814  
Ndrepepa G et al. *EHJ* 2008; 29: 455-461

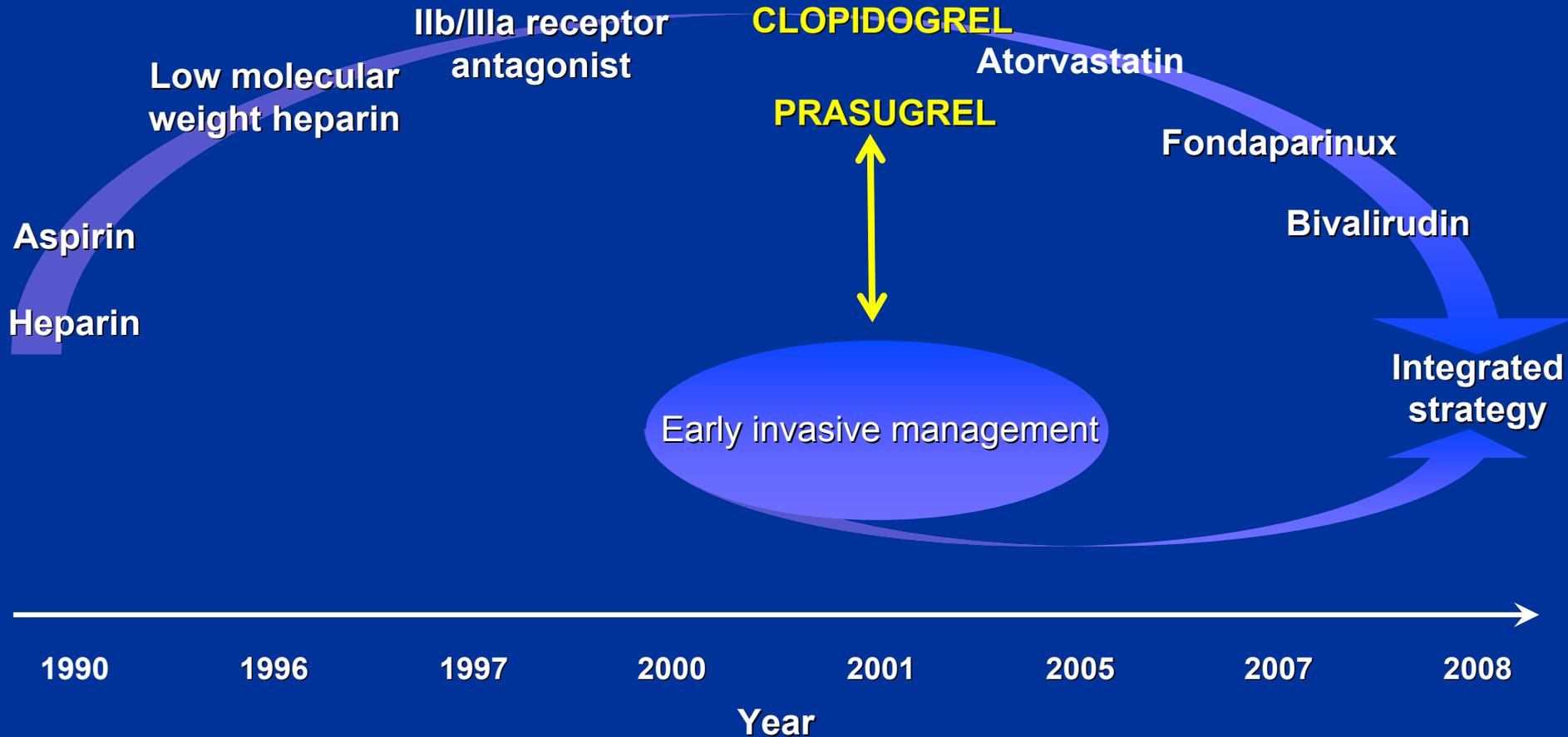
**ACS Managed with PCI**  
*Dual Antiplatelet Therapy*

**High Risk Clinical  
Features**

**Genetic Polymorphisms  
Drug-Drug Interactions**

**Continued Ischemic Events**

# Evolution of ACS Therapies



# Clinical Pharmacology and Dose Selection

**Jeffrey S. Riesmeyer, MD**

**Medical Fellow I**

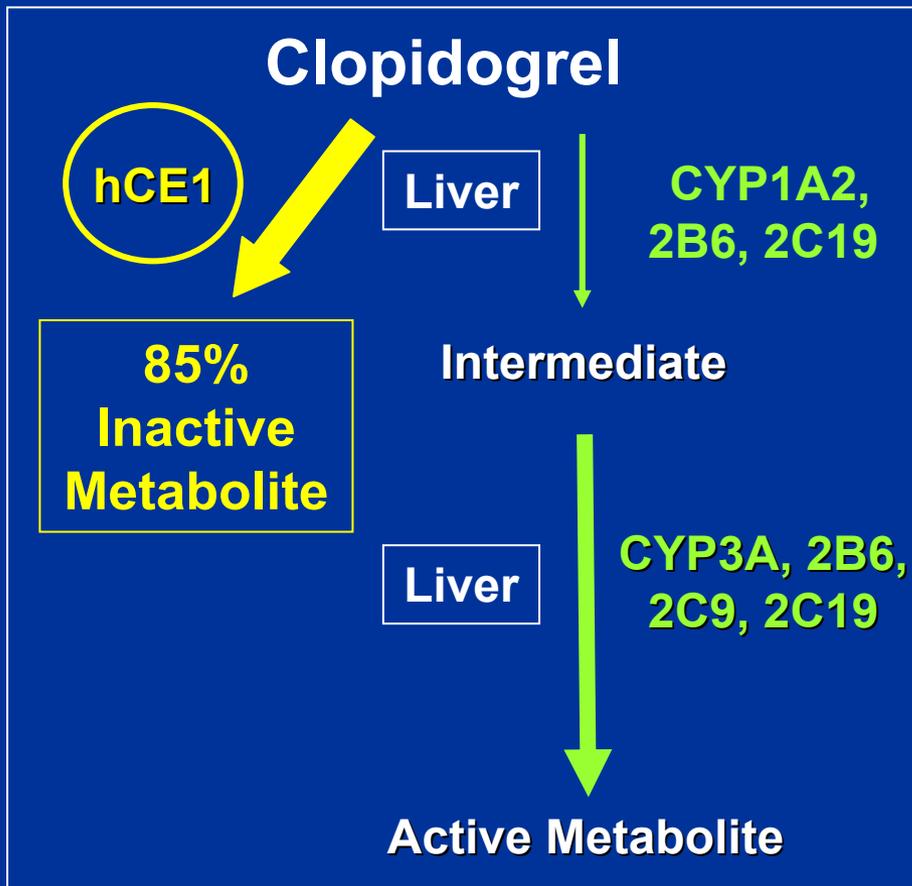
**Prasugrel Product Team**

**Eli Lilly and Company**

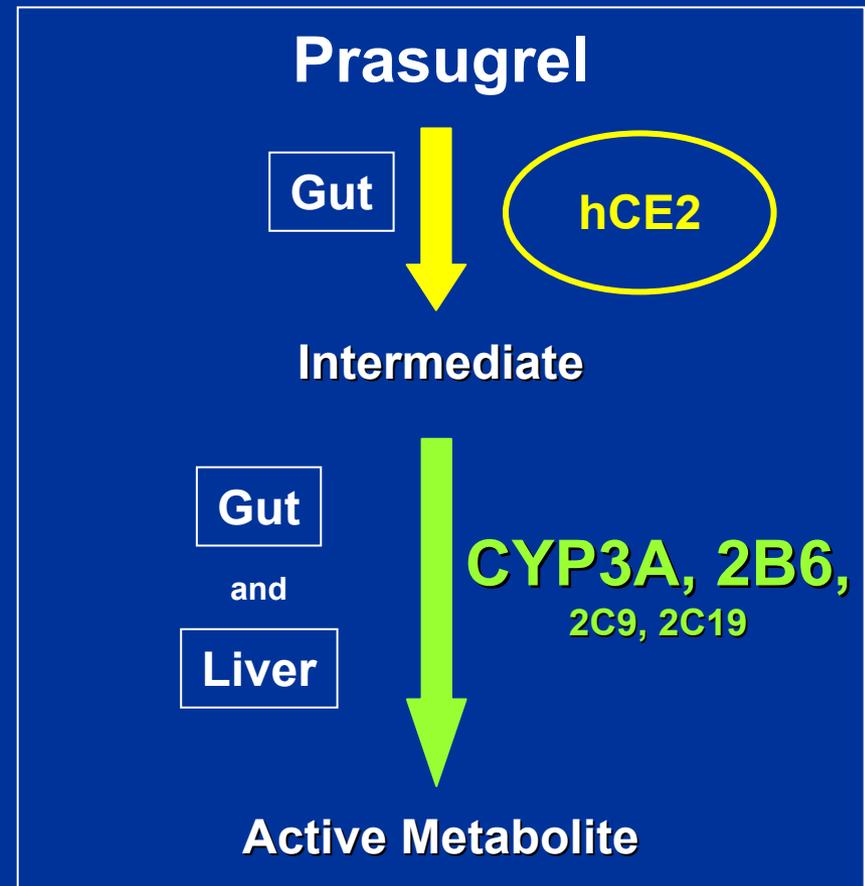
# Metabolism is a Key Difference Between Prasugrel and Clopidogrel

- ◆ Prodrugs - metabolized *in vivo* to active metabolites
- ◆ Irreversibly bind to the platelet P2Y<sub>12</sub> receptor
  - Inhibit ADP-induced platelet activation and aggregation
  - Inhibition persists for the life of the platelet
- ◆ *In vitro*, at equimolar concentrations, active metabolites show similar levels of platelet inhibition
- ◆ Prasugrel has a more efficient metabolic pathway compared to clopidogrel

# More Efficient and Less Variable Activation of Prasugrel Compared to Clopidogrel

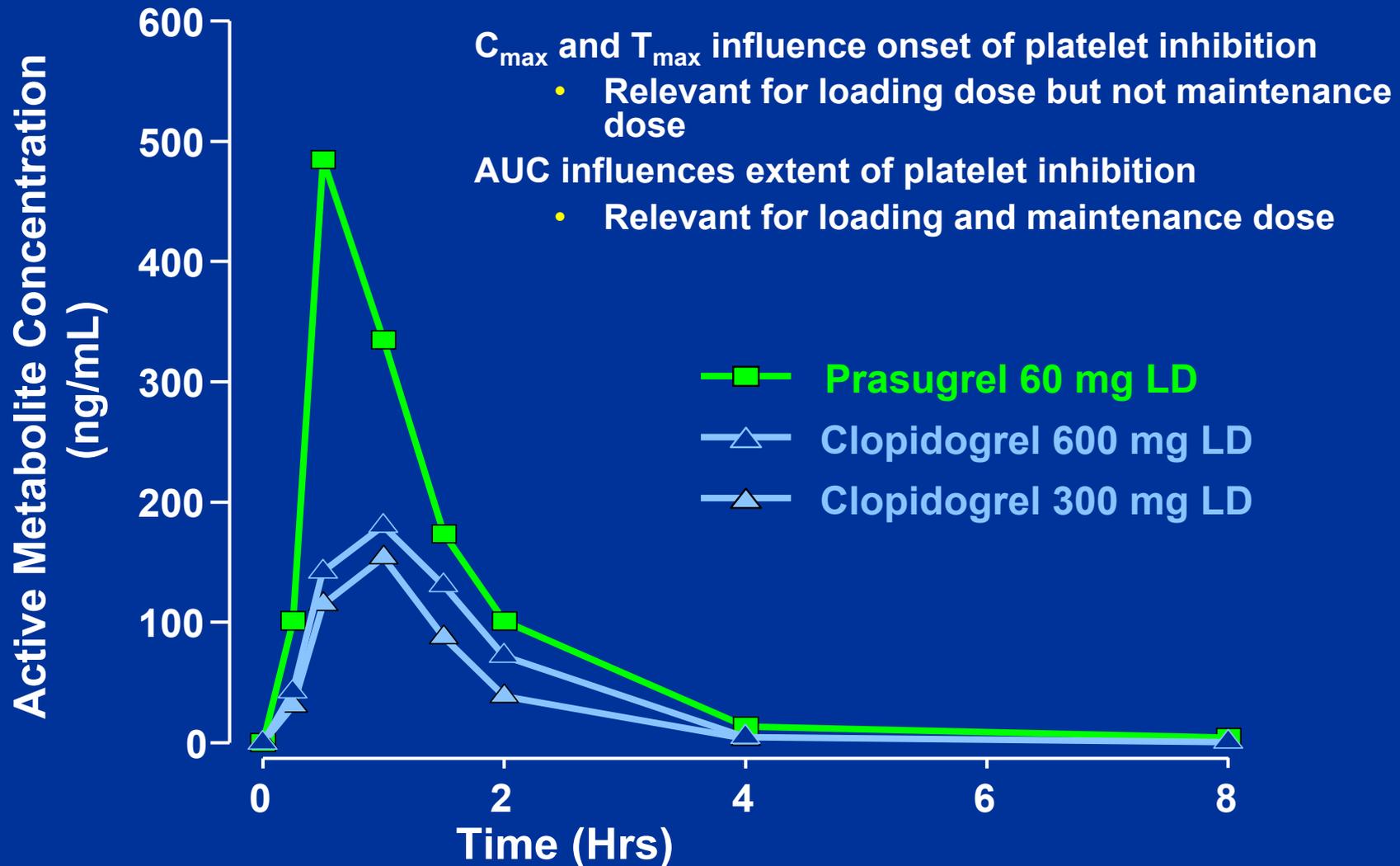


CYP2C19 variants and inhibitors affect the PK and PD of clopidogrel

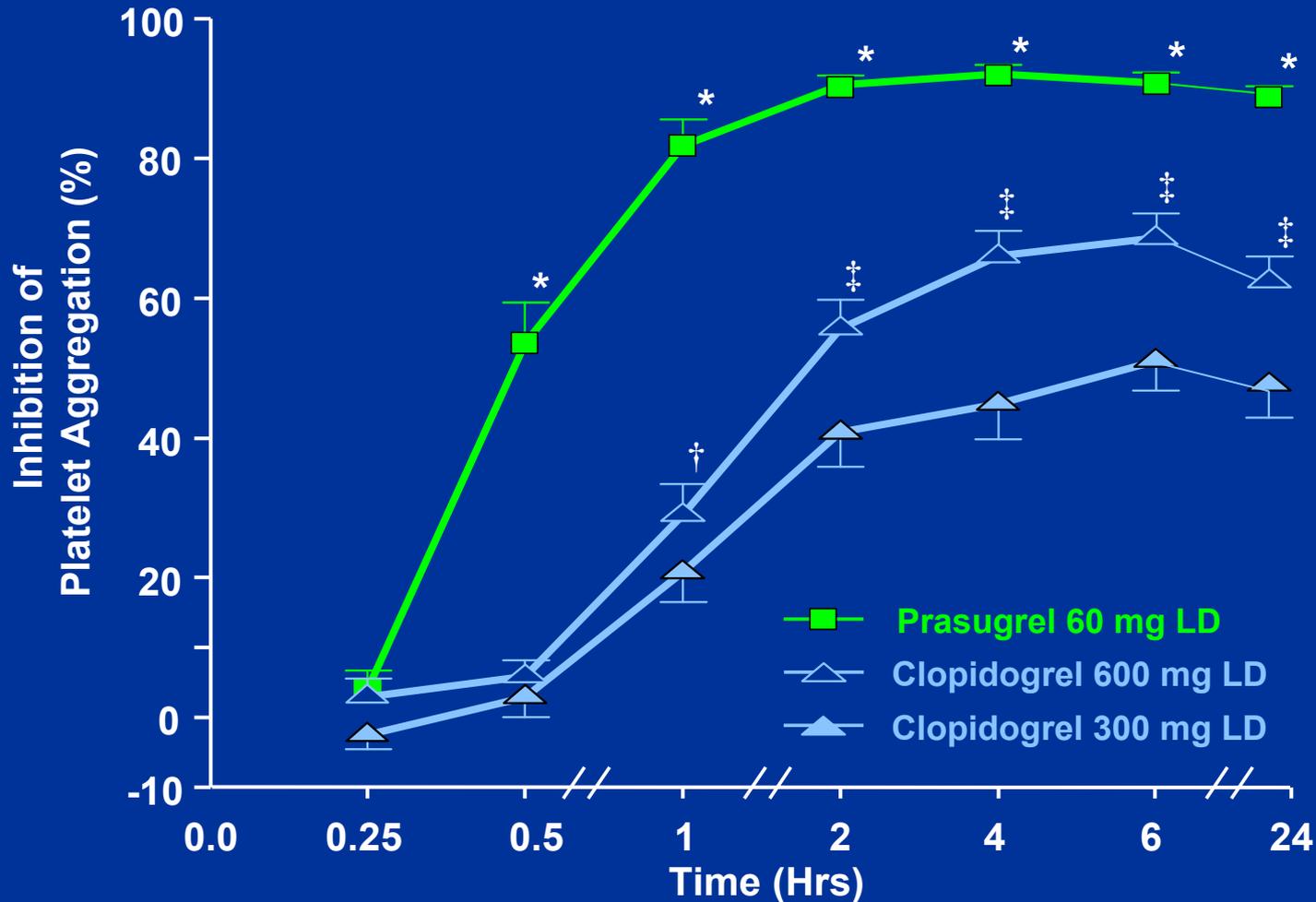


Prasugrel has no clinically relevant interactions with CYP2C19 variants or inhibitors

# Higher Active Metabolite Concentrations of Prasugrel After Loading Dose



# Prasugrel 60 mg LD Achieves More Effective Platelet Inhibition than Clopidogrel

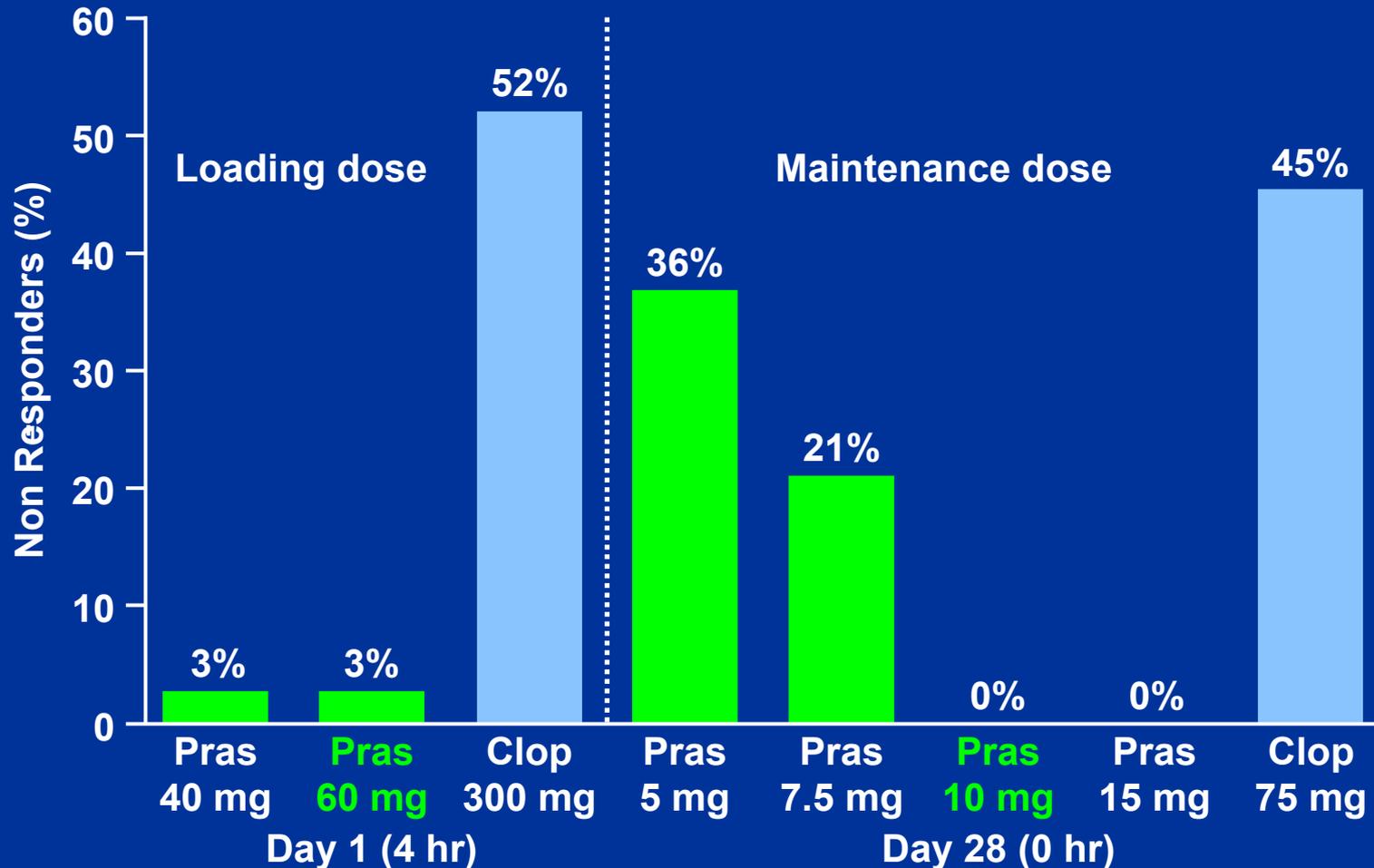


\*; p < 0.001 vs. clop 300 mg/75 mg 600 mg/75 mg;

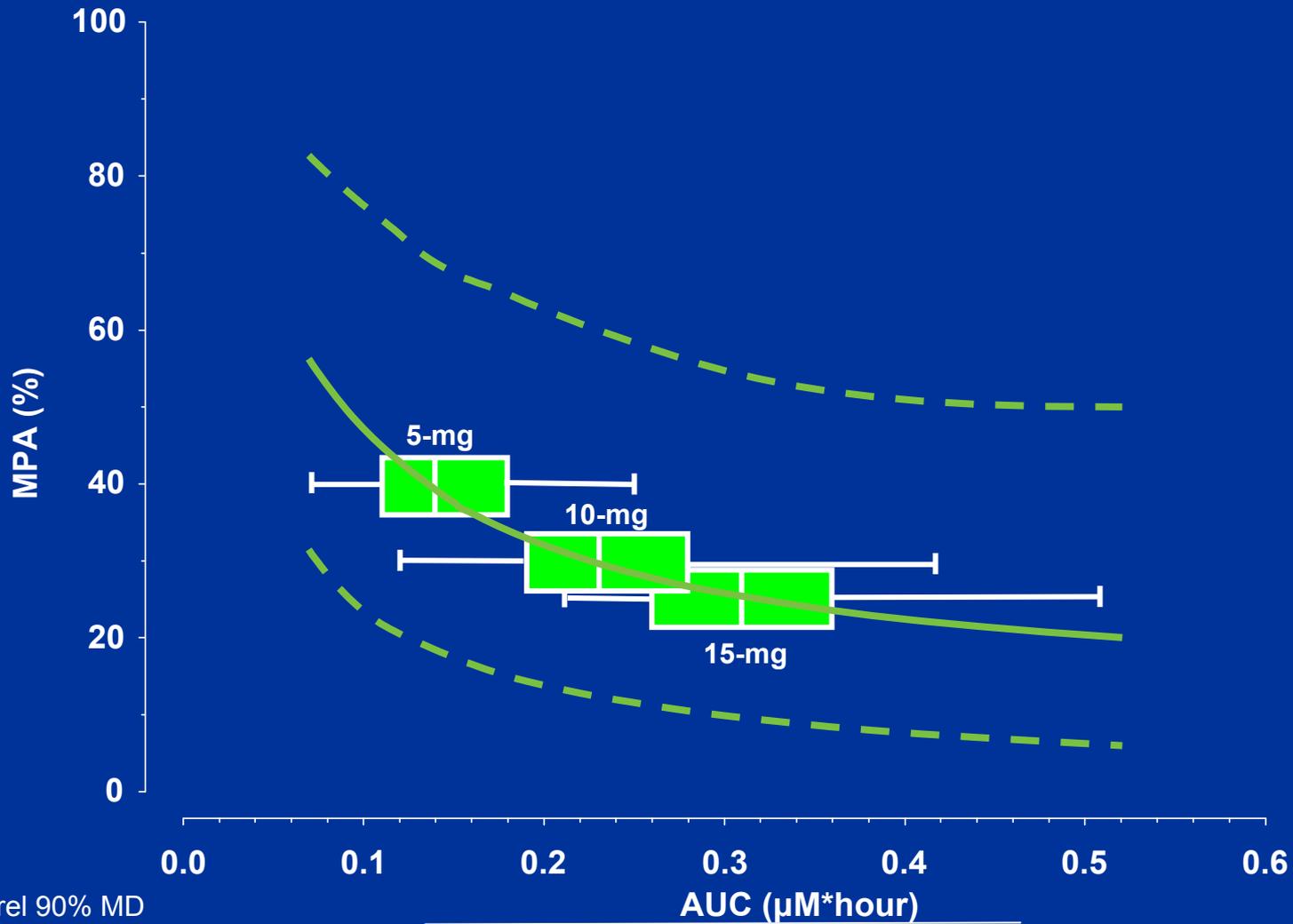
†; p < 0.05 vs. clop 300 mg/75 mg;

‡; p < 0.001 vs. clop 300 mg/75 mg

# Prasugrel 60 mg LD with 10 mg MD Demonstrates Superior Response Compared to Clopidogrel



# Predictable Relationship between Prasugrel<sup>27</sup> Active Metabolite PK and PD



Prasugrel 90% MD  
Prediction Interval

3134.01

# Summary of Prasugrel Clinical Pharmacology

- ◆ Prasugrel metabolism more efficient and less variable compared to clopidogrel
- ◆ Prasugrel 60 mg LD more effective platelet inhibition than clopidogrel
- ◆ Prasugrel 10 mg MD superior PD response rate compared to clopidogrel
- ◆ Predictable PK/PD relationship allows targeted PK
- ◆ No clinically relevant impact of
  - Drug-drug interactions
  - CYP genetic variants

# TRITON-TIMI 38

## **Dr. Elliott Antman**

Professor of Medicine, Harvard Medical School,  
Senior Investigator, TIMI Study Group,  
Director of Samuel A. Levine Cardiac Unit  
Brigham and Women's Hospital, Boston, MA

# TRITON-TIMI 38 Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ N = 13,608

Double-blind

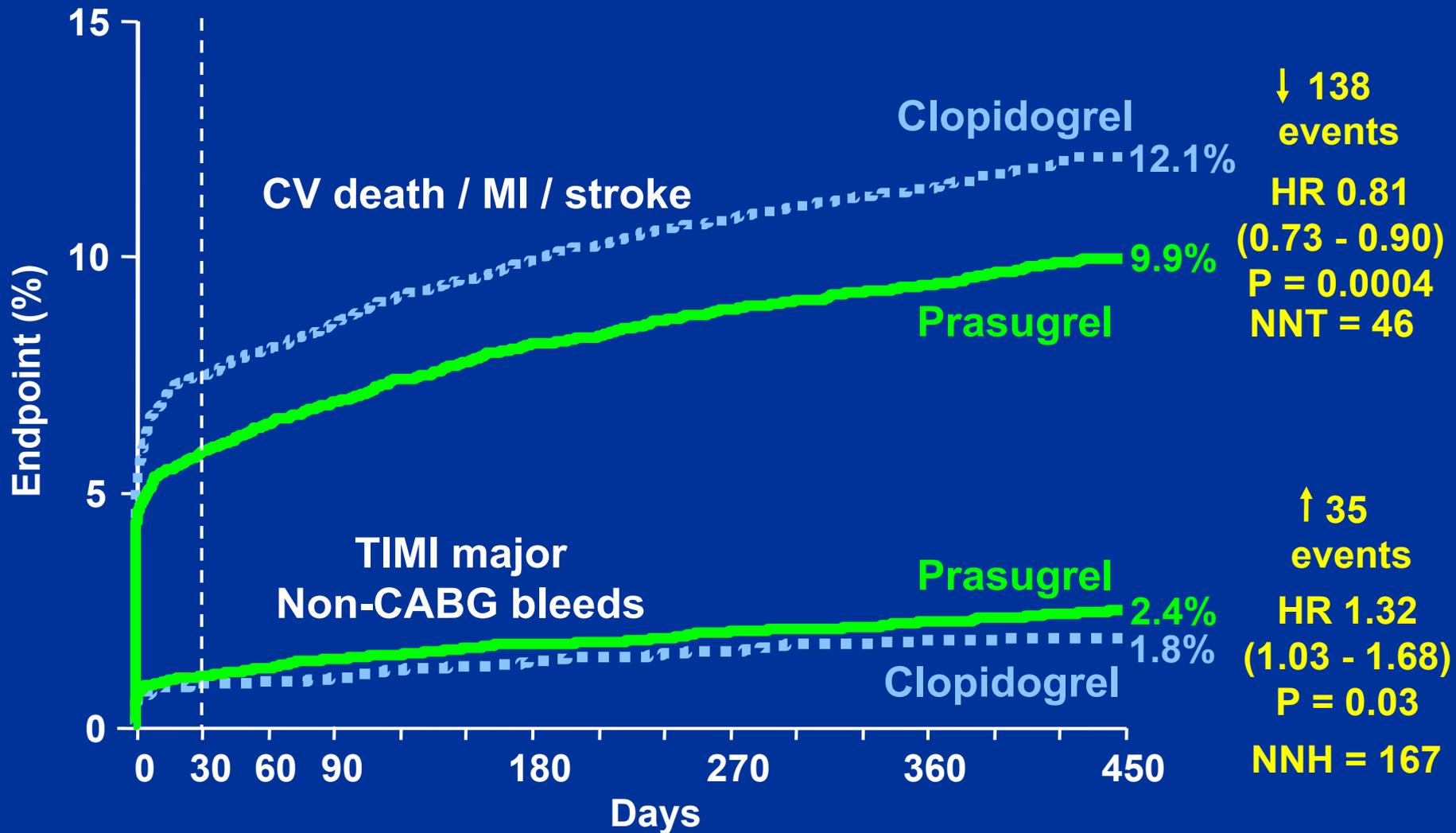
**CLOPIDOGREL**  
300 mg LD/ 75 mg MD

**PRASUGREL**  
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1° endpoint: CV death, MI, stroke  
 2° endpoints: CV death, MI, stroke, re hosp-Rec Isch  
 CV death, MI, UTVR  
 Stent thrombosis (ARC definite/prob.)  
 Safety endpoints: TIMI major bleeds, life-threatening bleeds  
 Key substudies: Pharmacokinetic, genomic

# Balance of Efficacy and Safety: All ACS



Wiviott SD et al. *NEJM* 2007; 357: 2001-2015

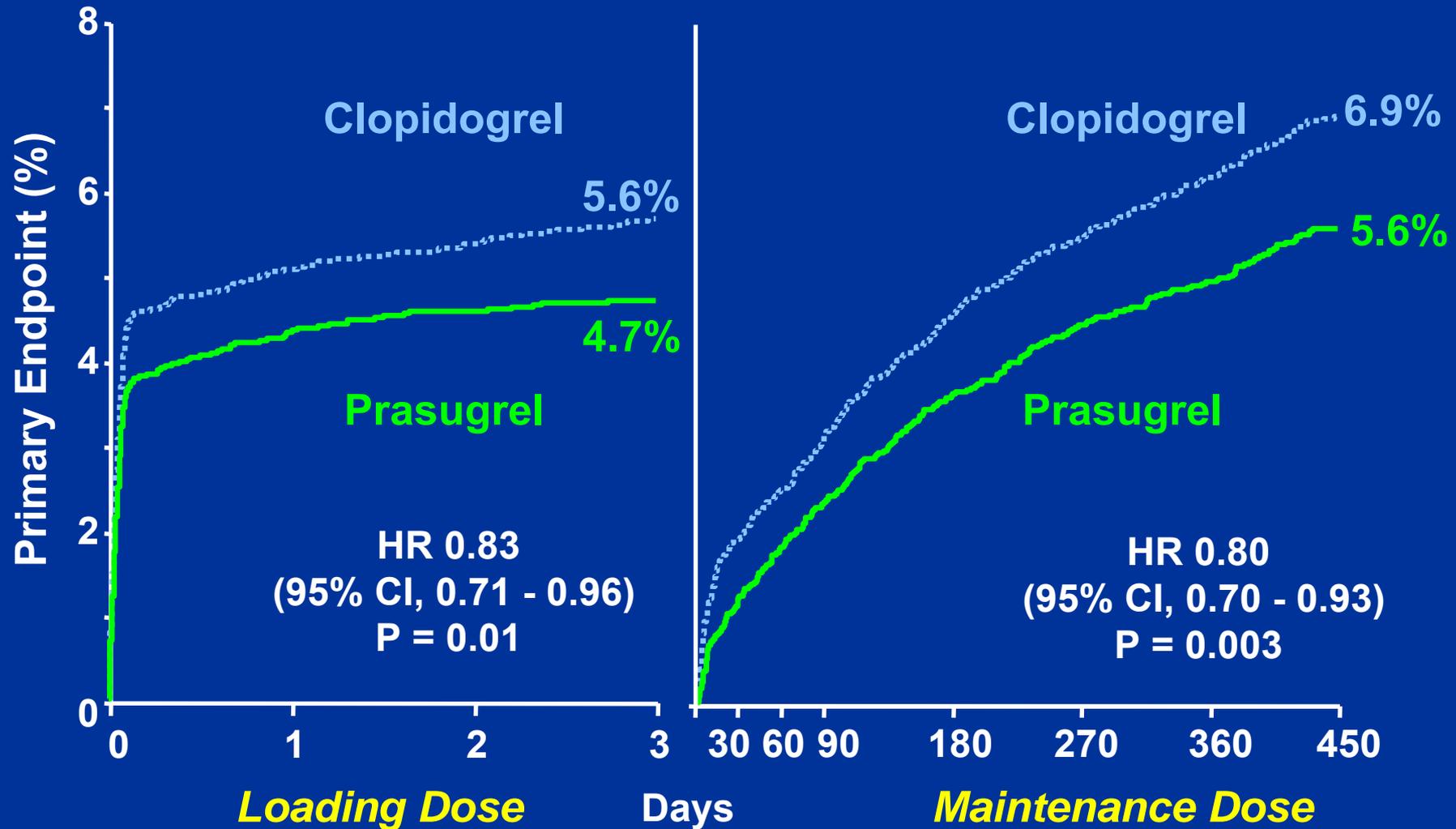
# TRITON Endpoint Testing



Endpoint		UA/NSTEMI	All ACS	STEMI
CVD / MI / stroke	30 days	✓	✓	✓
	90 days	✓	✓	✓
CVD / MI / UTVR	30 days	✓	✓	✓
	90 days	✓	✓	✓
All cause death / MI / stroke at study end		✓	✓	✓
CVD / MI / rehospitalization for CIE at study end		✓	✓	✓
Definite or probable stent thrombosis at study end		✓	✓	✓

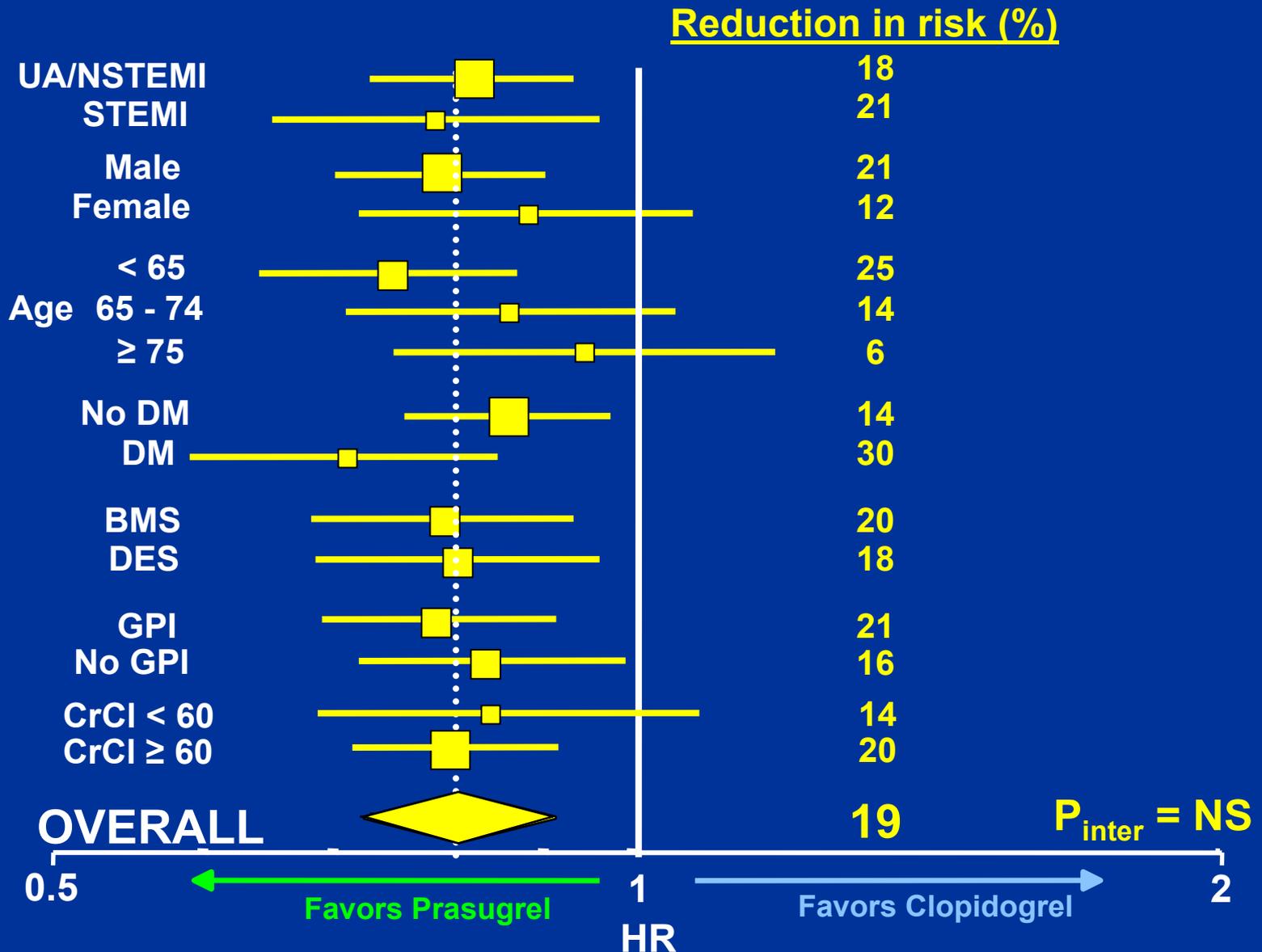
p-values ranged from 0.023 to 0.0000003

# Timing of Benefit (Prospectively Defined) Landmark Analysis - 3 days

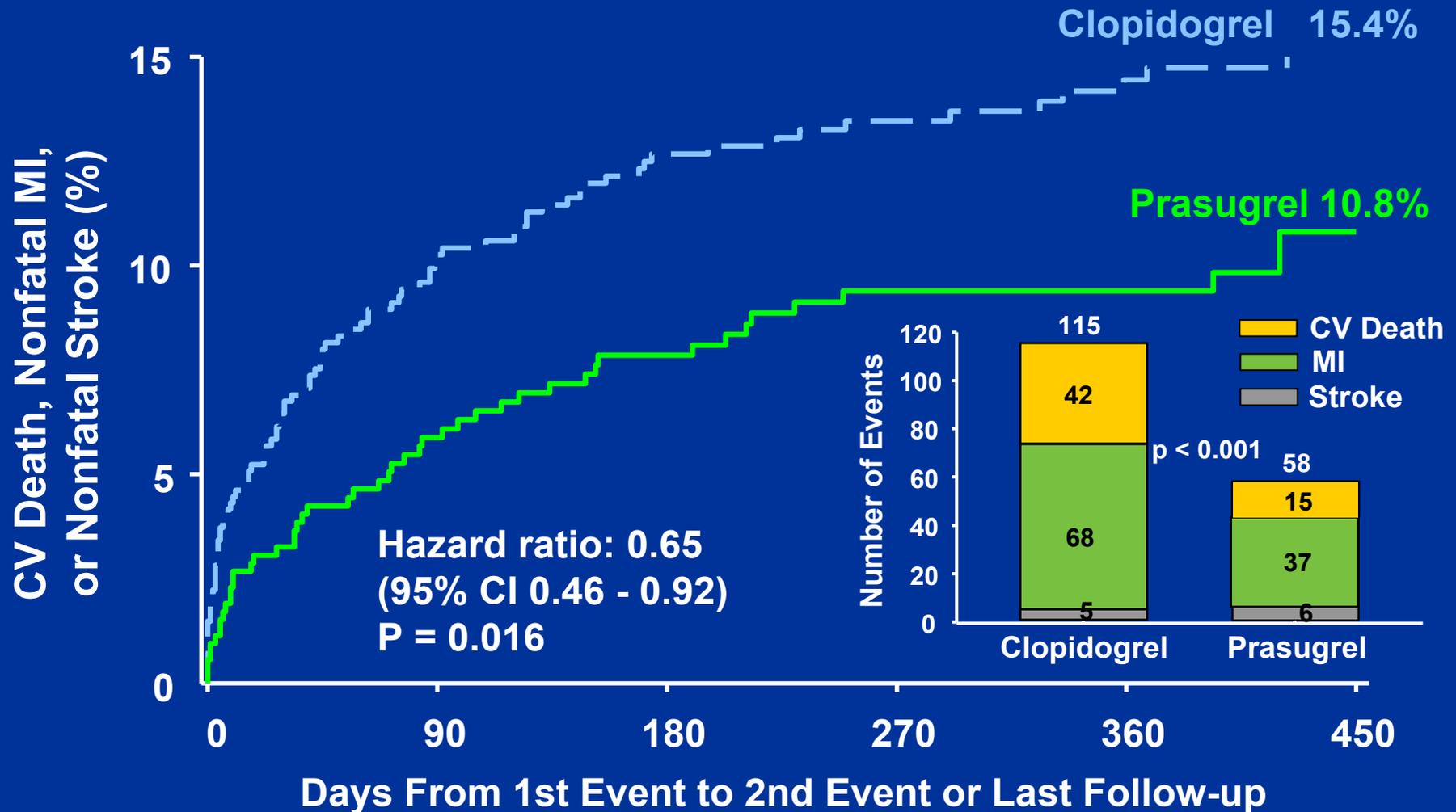


Wiviott SD et al. *NEJM* 2007; 357: 2001-2015

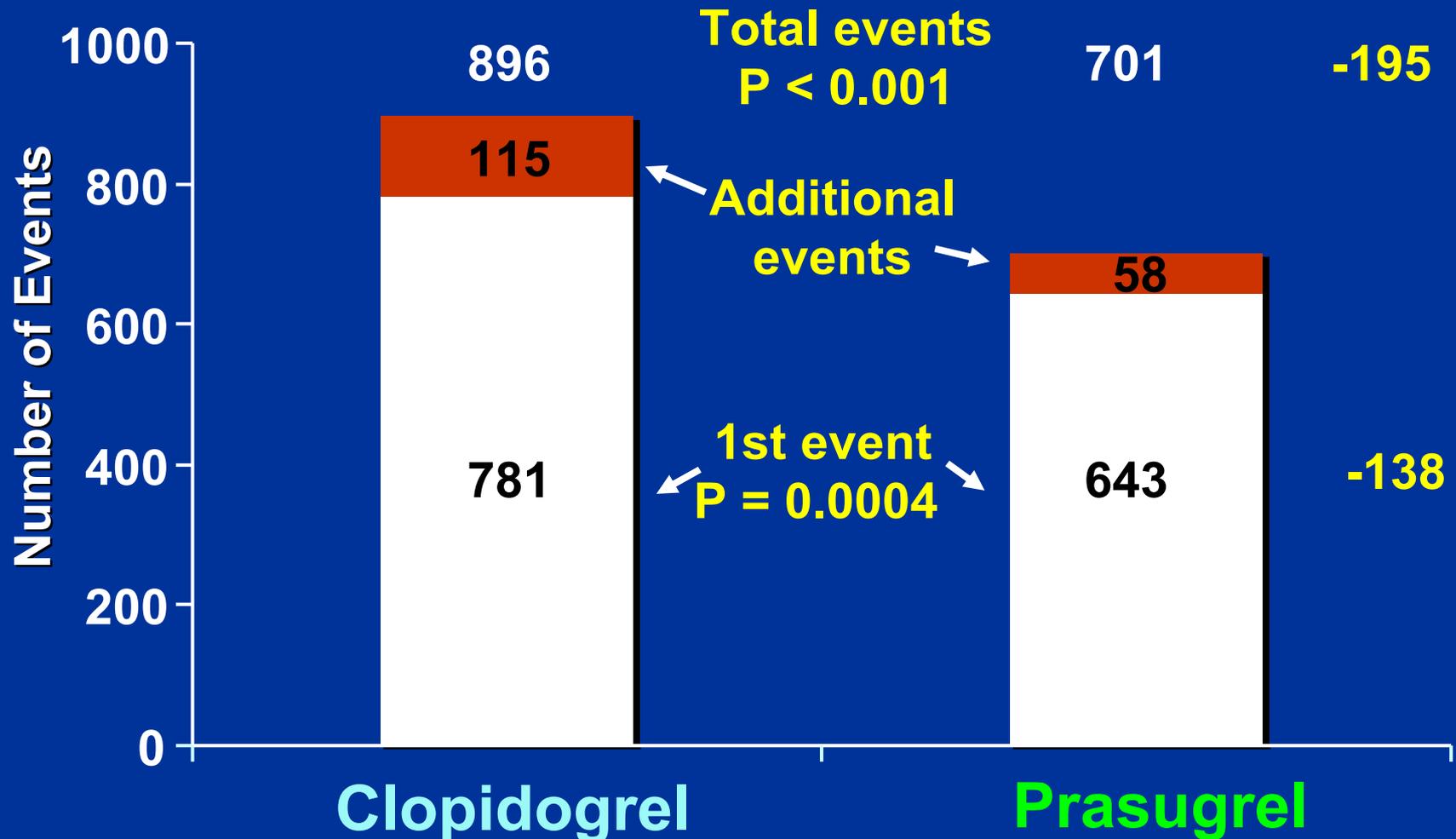
# CV Death, MI, Stroke (Major Subgroups)



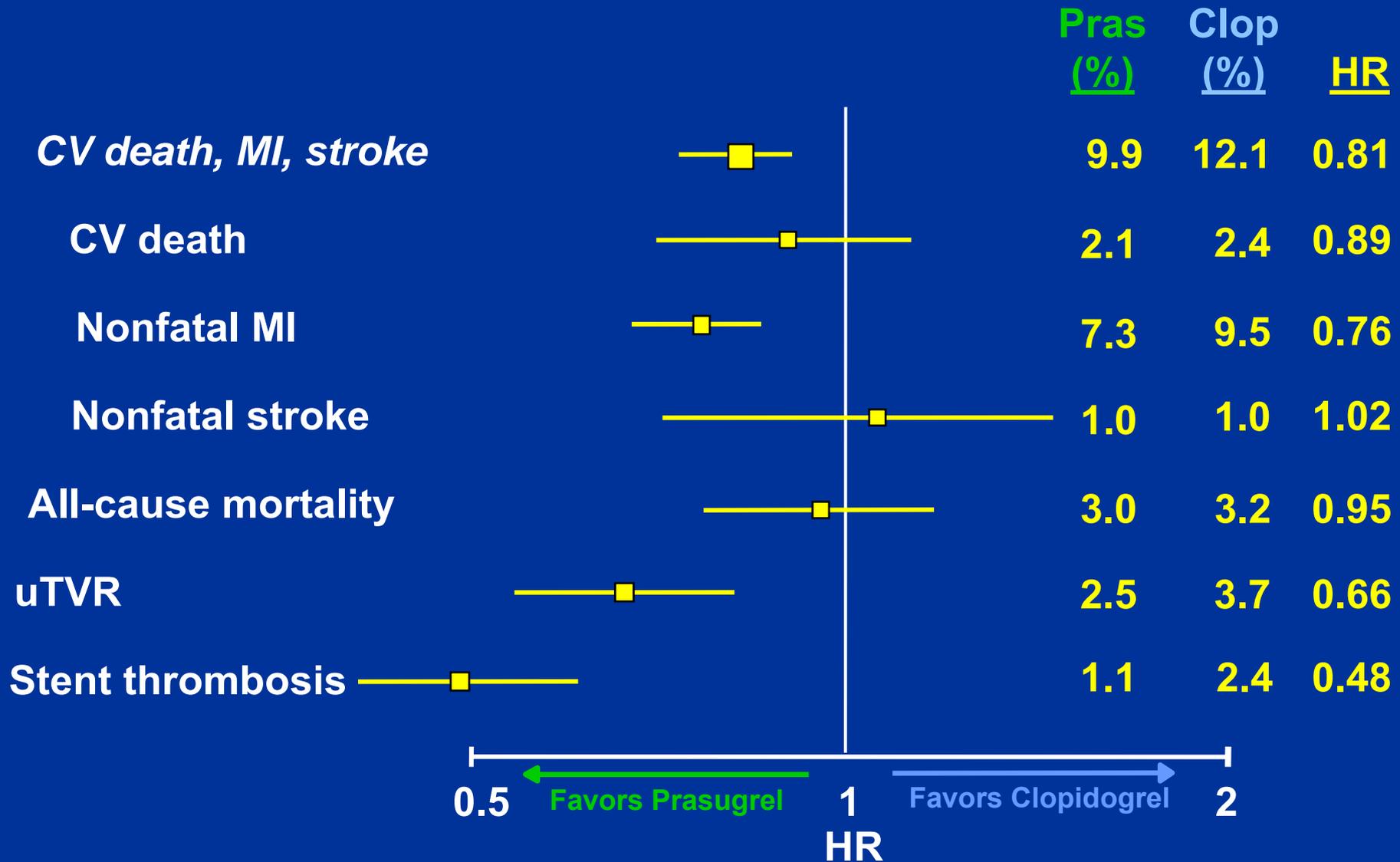
# Recurrence of Primary Composite Endpoint



# Total Primary Endpoint Events Prevented With Prasugrel

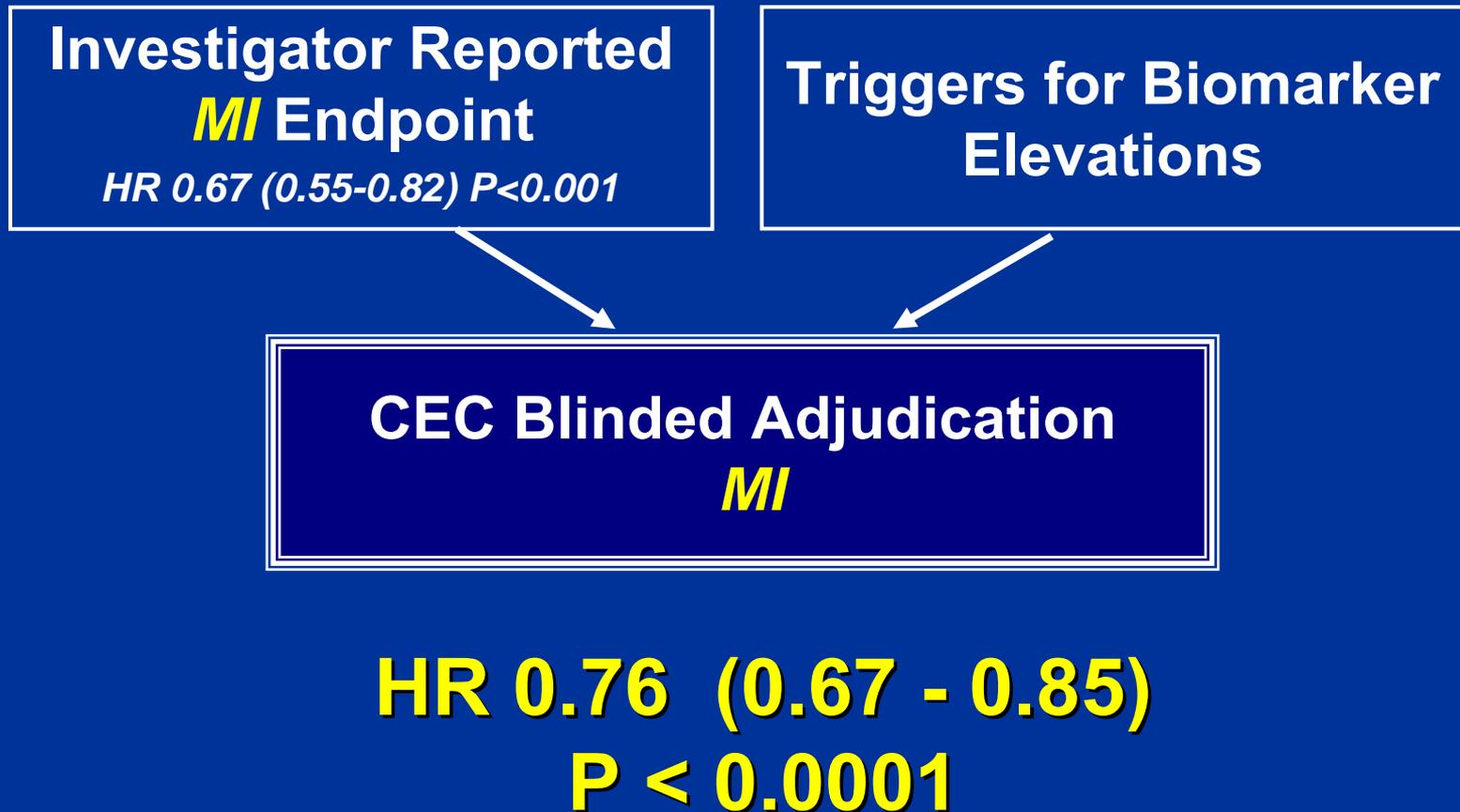


# Components of Endpoints

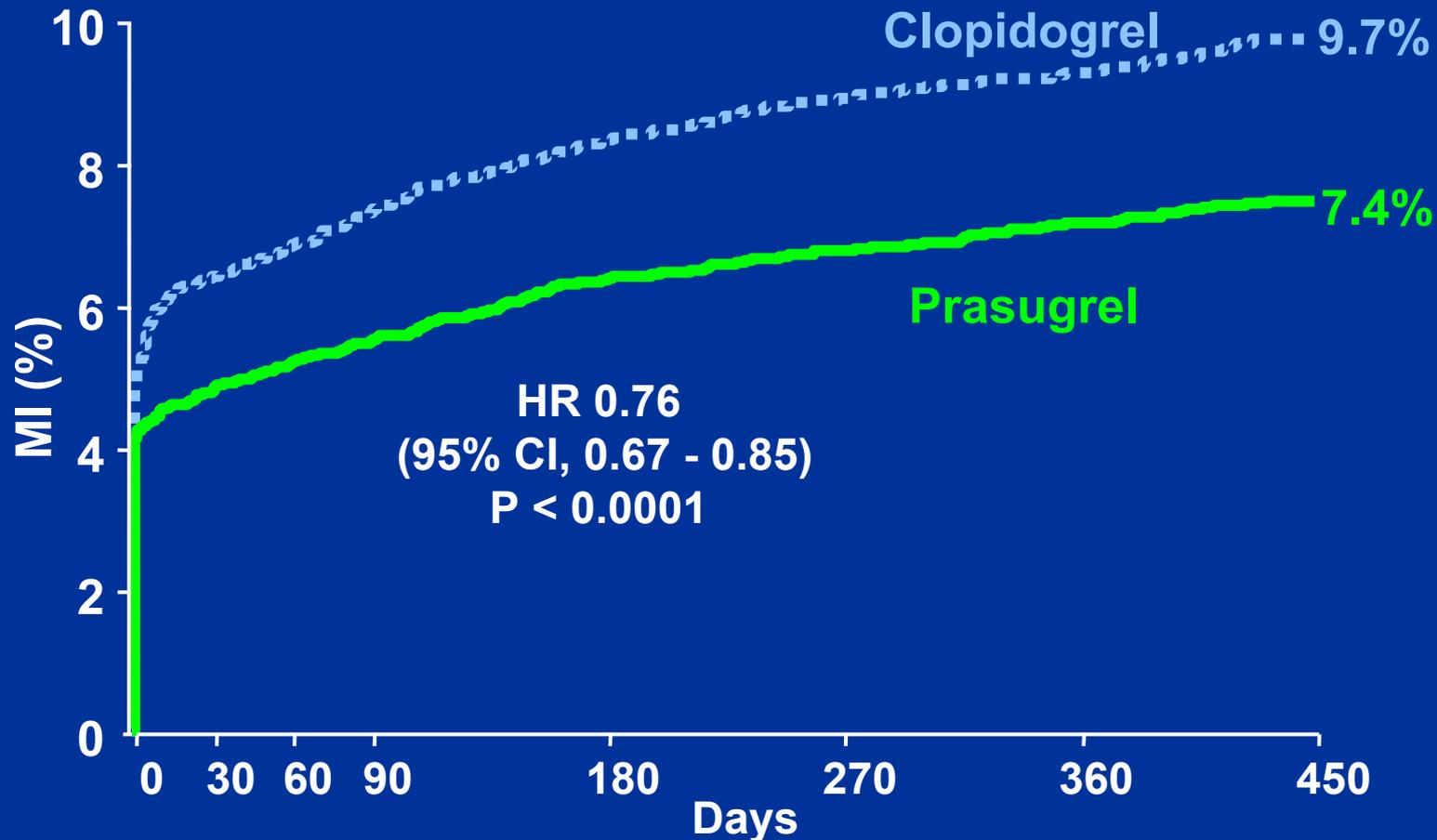


Wiviott SD, et al. *NEJM*. 2007;357:2001-2015.

# Process for Adjudication of MI



# Myocardial Infarction (0 - 450 days)\*



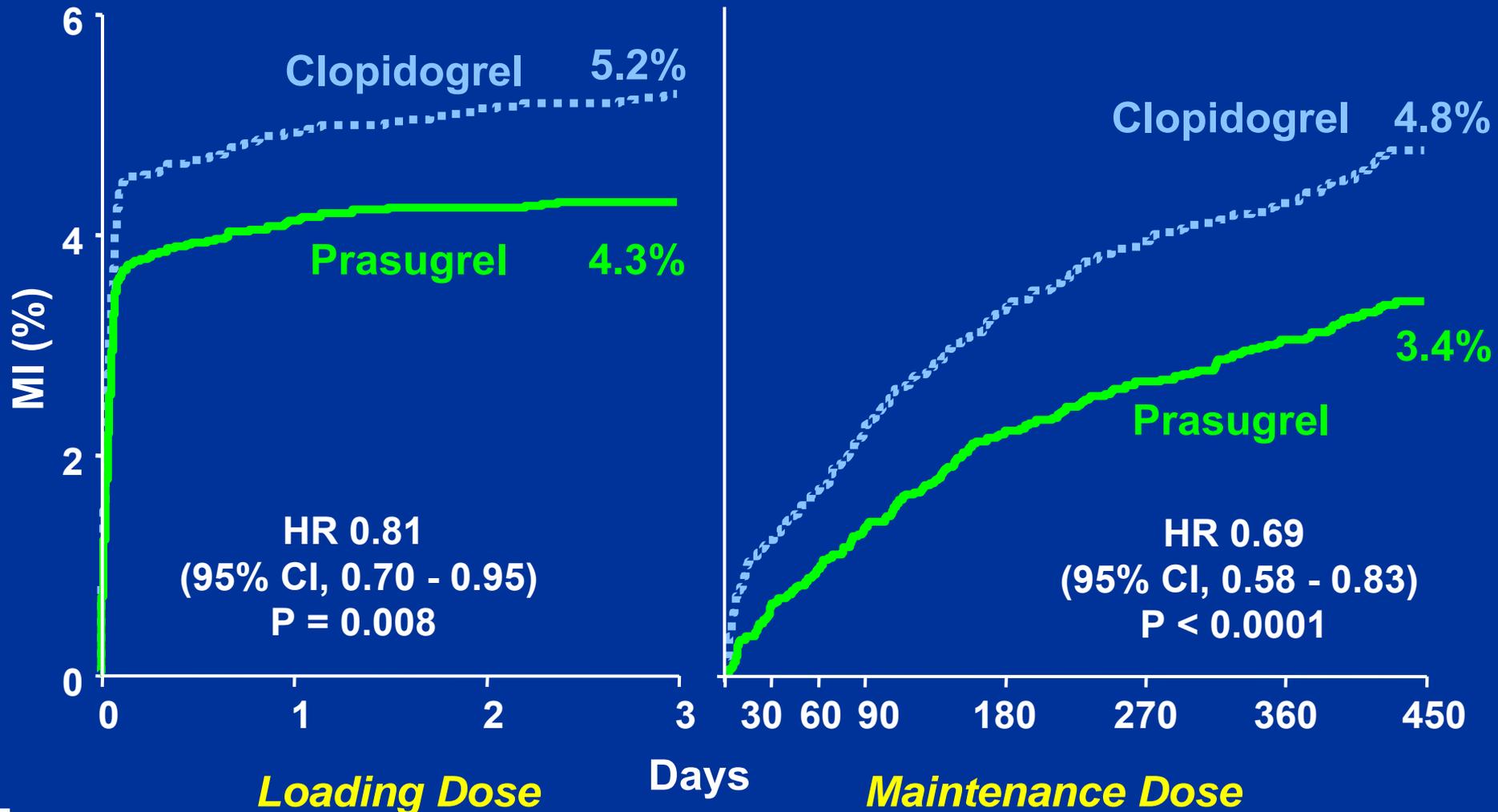
	Clopidogrel, %	Prasugrel, %	HR	p-value
CV death after MI	0.7	0.4	0.58	0.02

\*Fatal and nonfatal MIs

Wiviott SD et al. *NEJM* 2007; 357: 2001-2015

# Myocardial Infarction\*

## Landmark Analysis - 3 Days

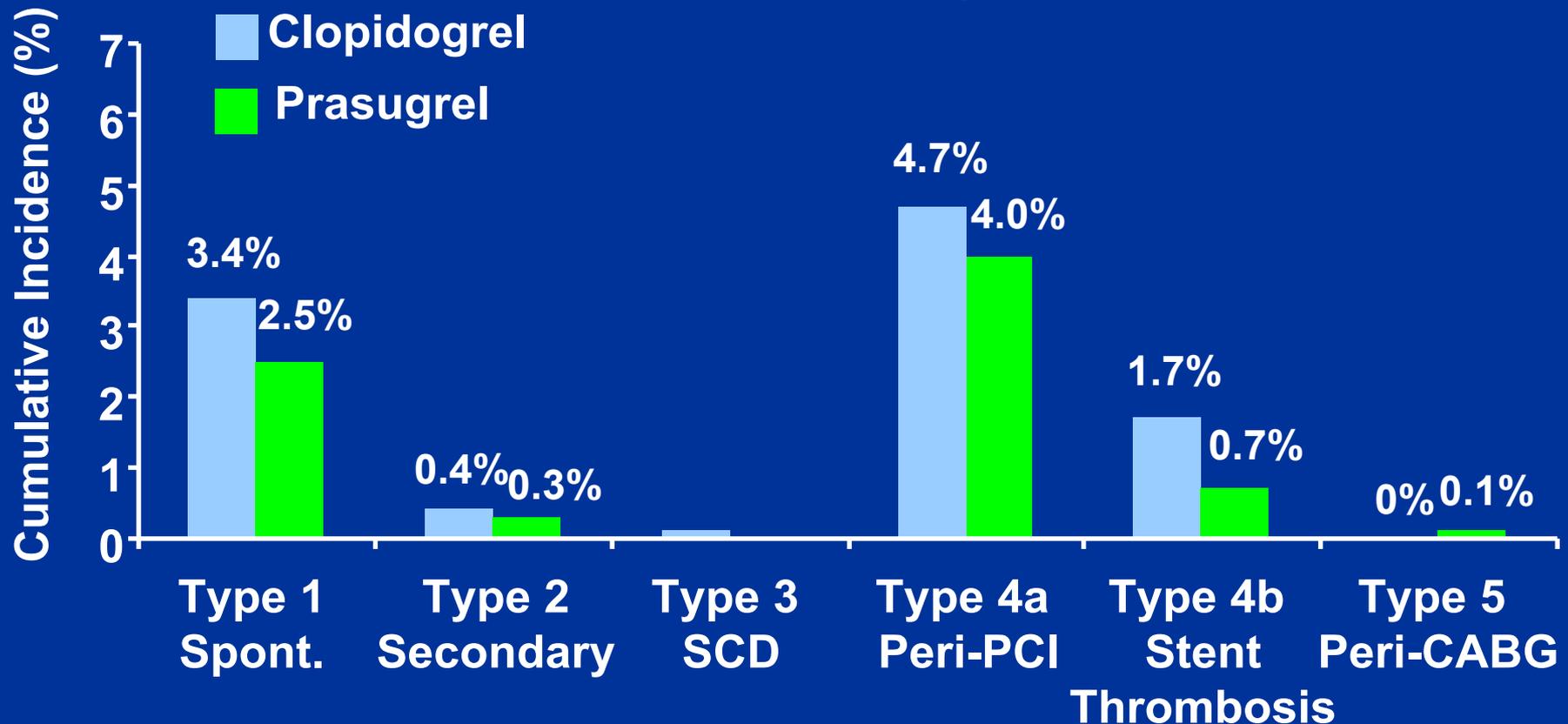


\*Fatal and nonfatal MIs

Antman et al. *JACC* 2008; 51(S21):2028-2033.

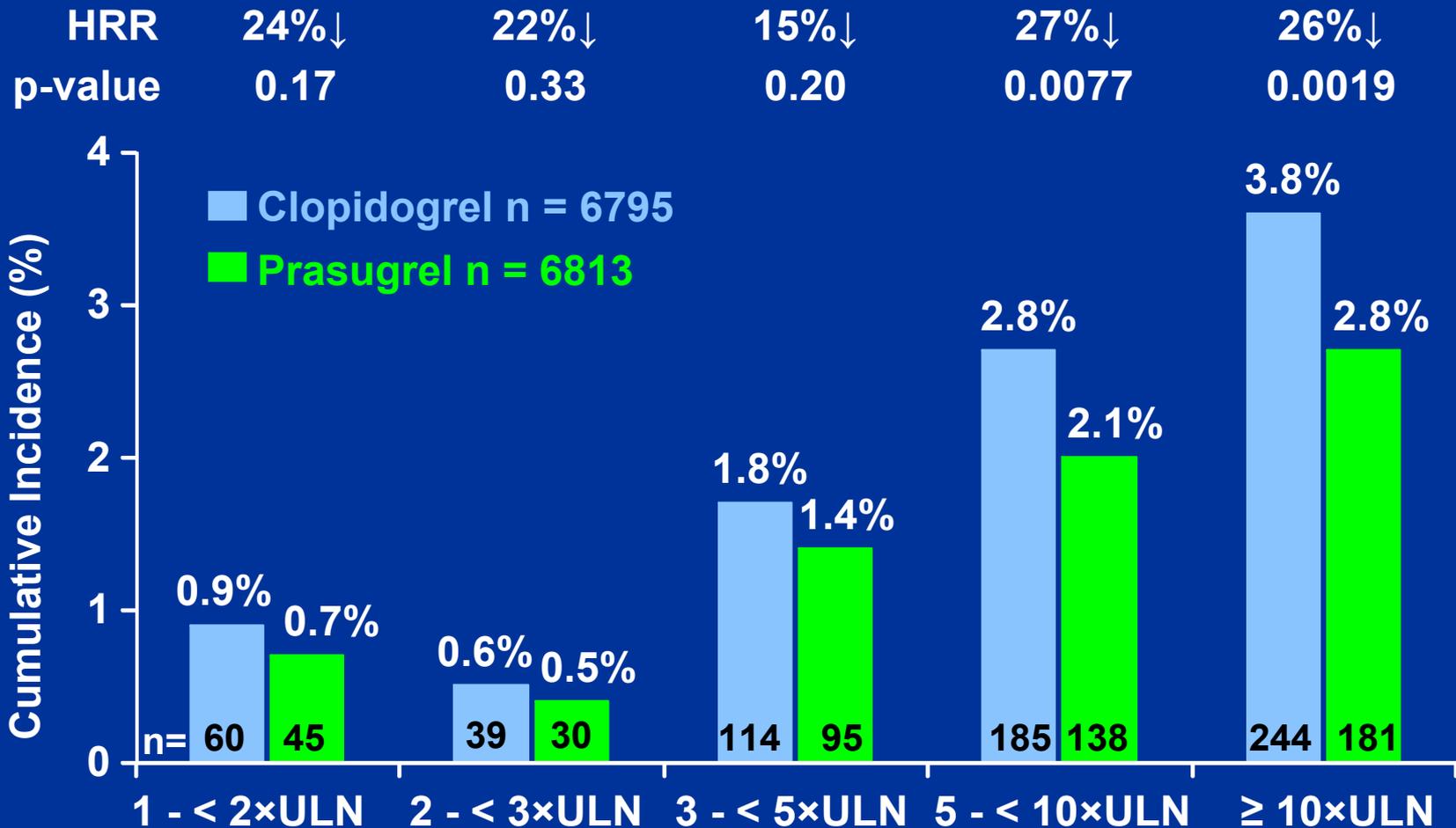
# Efficacy Analysis (Universal MI Classification)

HRR	29%↓	18%↓	—	24%↓	—
p-value	0.0015	0.53		< 0.0001	



# Efficacy Analysis Peak Biomarker

MI size using ESC / ACC / AHA / WHF categorization



# Impact of Prasugrel on MI

Significant reductions in:

Type of MI

Spontaneous

Peri-procedural

Stent thrombosis

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Number of MIs

24% decrease

P < 0.0001

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Large MIs  
( $\geq 5 \times$  ULN)

26% decrease

P = 0.0001

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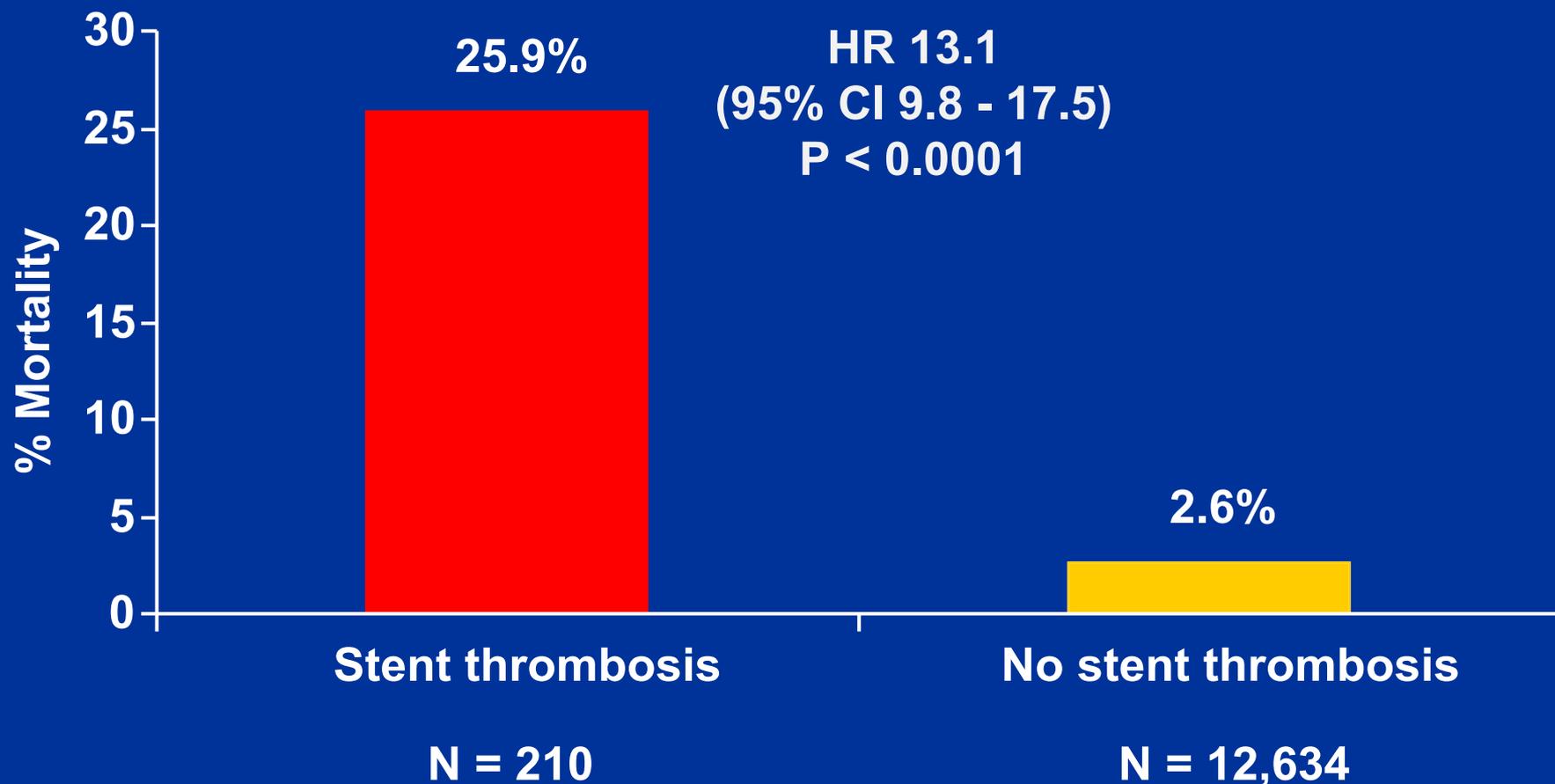
CV death after MI

42% decrease

P = 0.02

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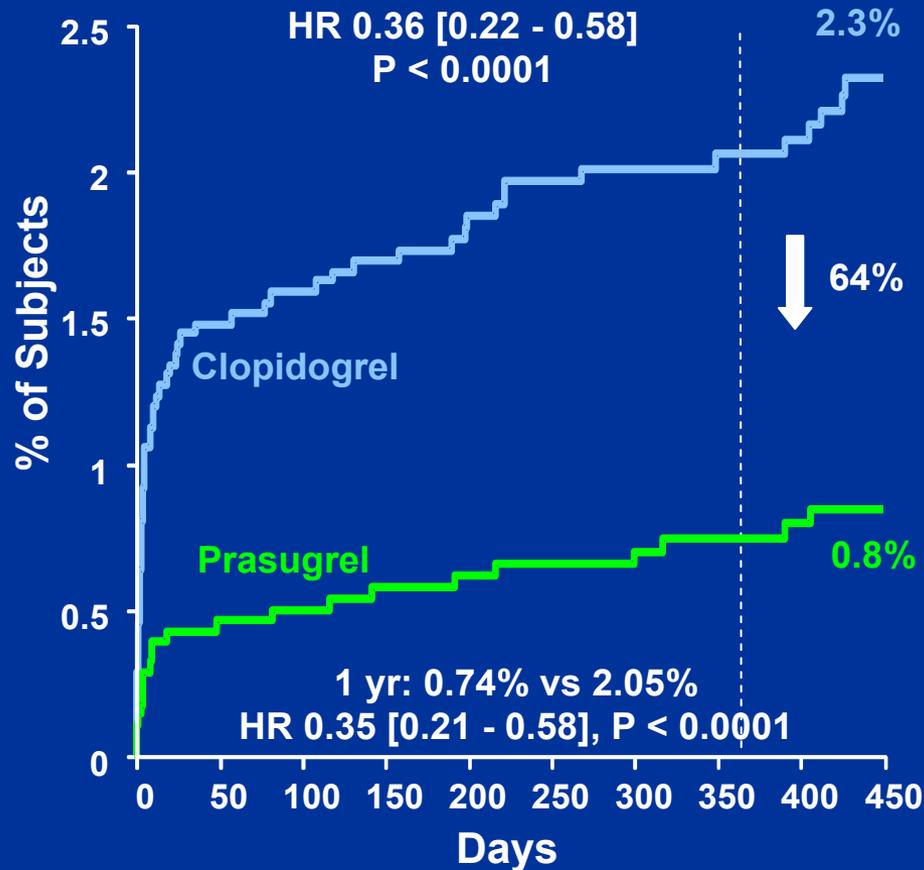
# Mortality Following Stent Thrombosis\*



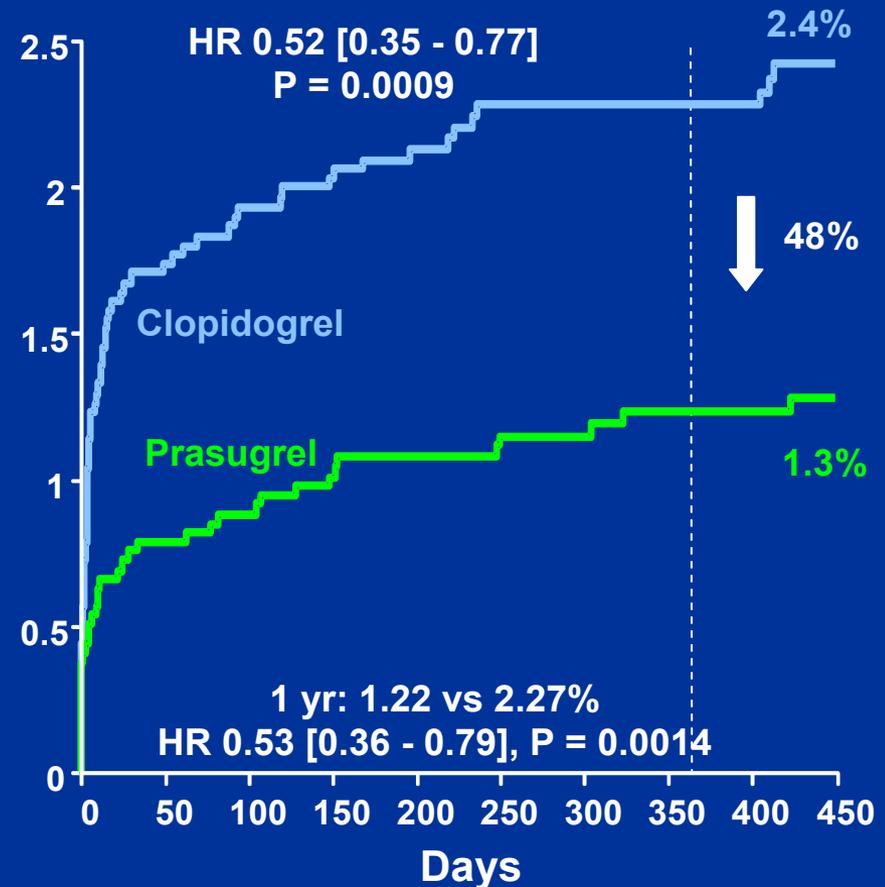
\* ARC Definite + Probable

# CEC Adjudicated Stent Thrombosis: Definite/Probable

**DES Only (N = 5743)**

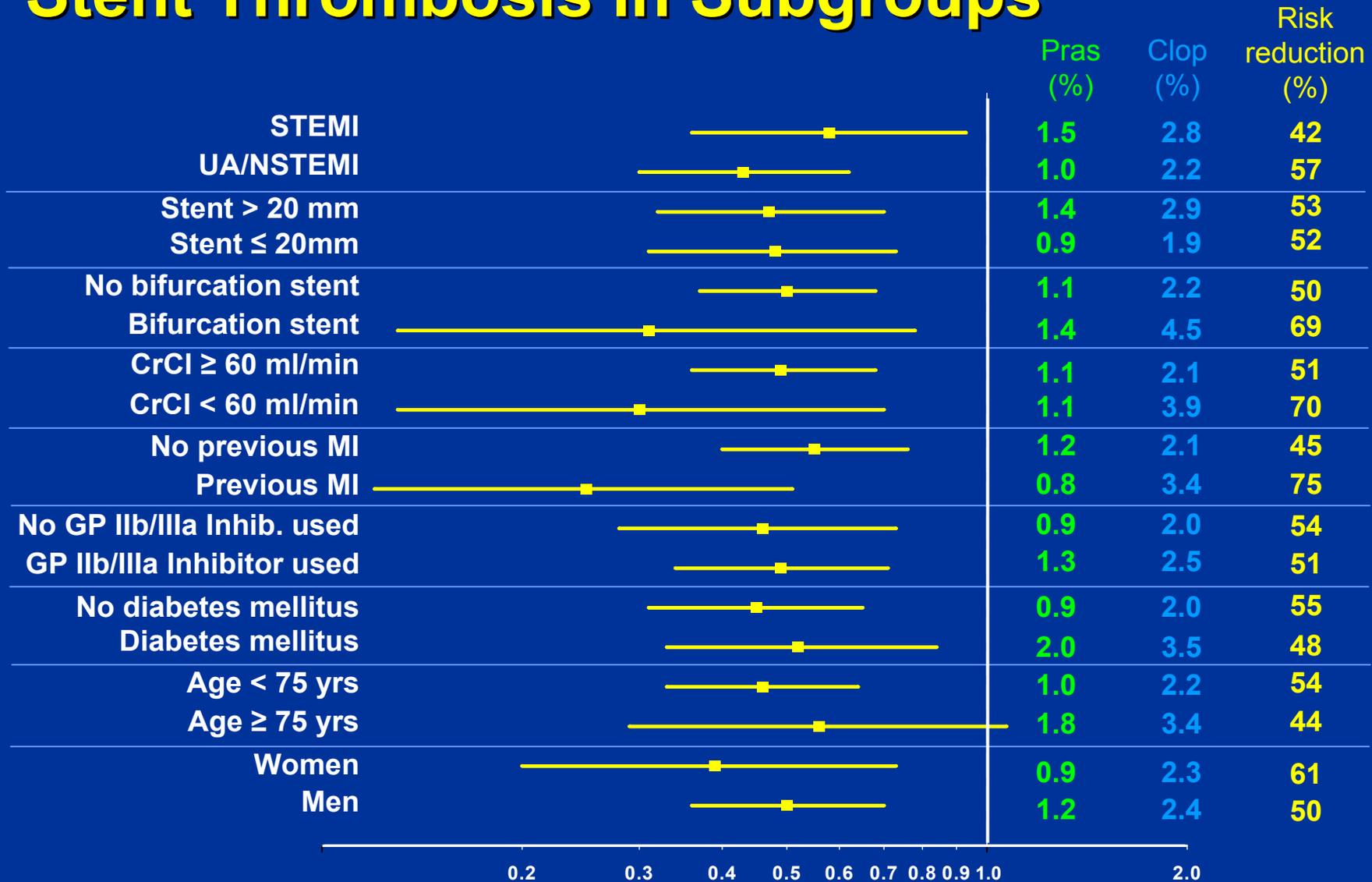


**BMS Only (N = 6461)**



**Significant reductions in early and late stent thromboses**

# Stent Thrombosis in Subgroups\*



← Prasugrel better Hazard Ratio Clopidogrel better →

# Impact of Prasugrel on Stent Thrombosis

## Process

**Pre-specified**

**Discussed with FDA**

**Blinded CEC (unbiased)**

## Results

**Substantial reductions (approximately 50%)**

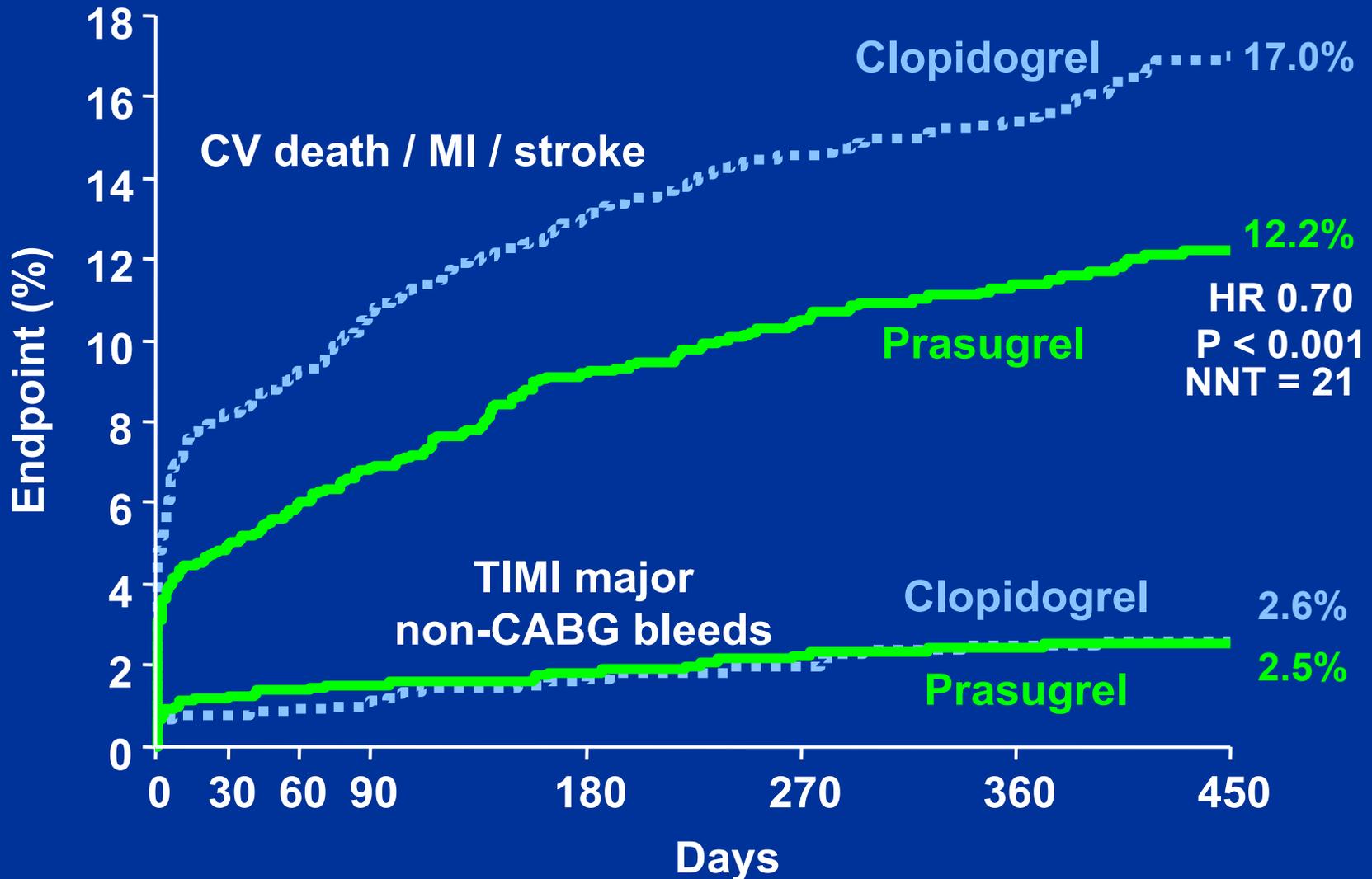
**Robust: definitions, patient types, stent types, subgroups**

## Implications

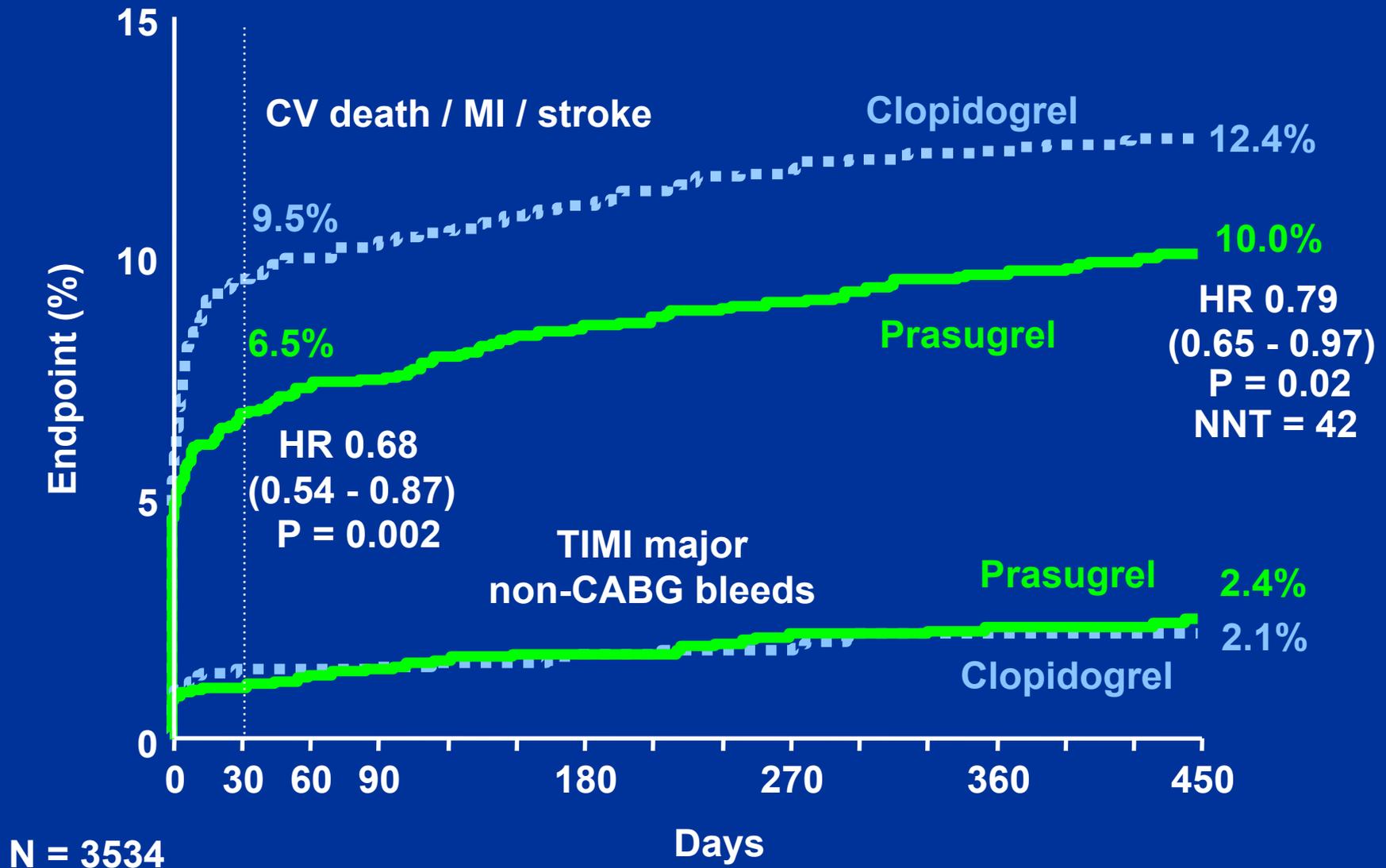
**Benefit of long-term treatment with prasugrel**

**Critically important information for clinicians**

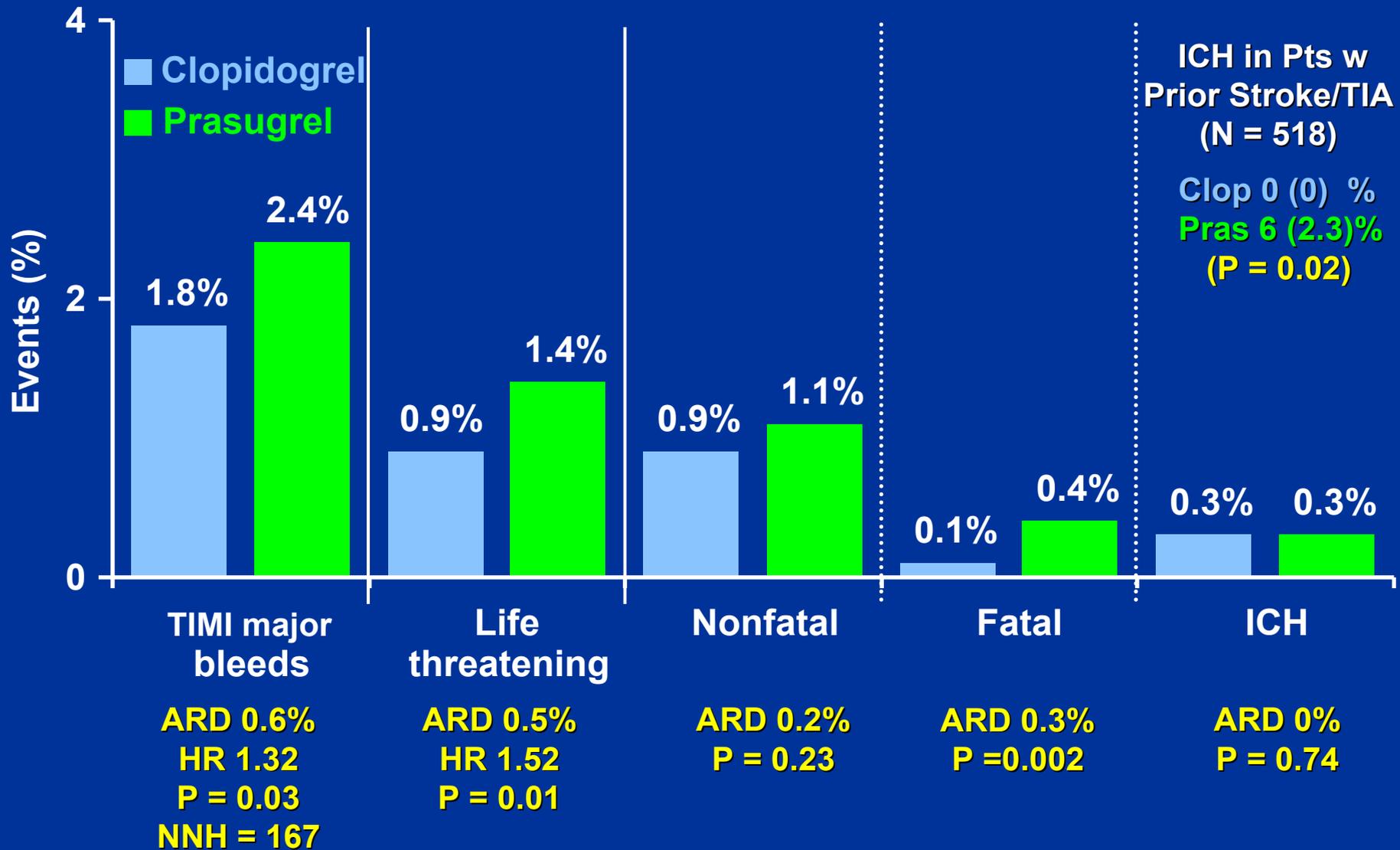
# Diabetic Subgroup - (N=3146)



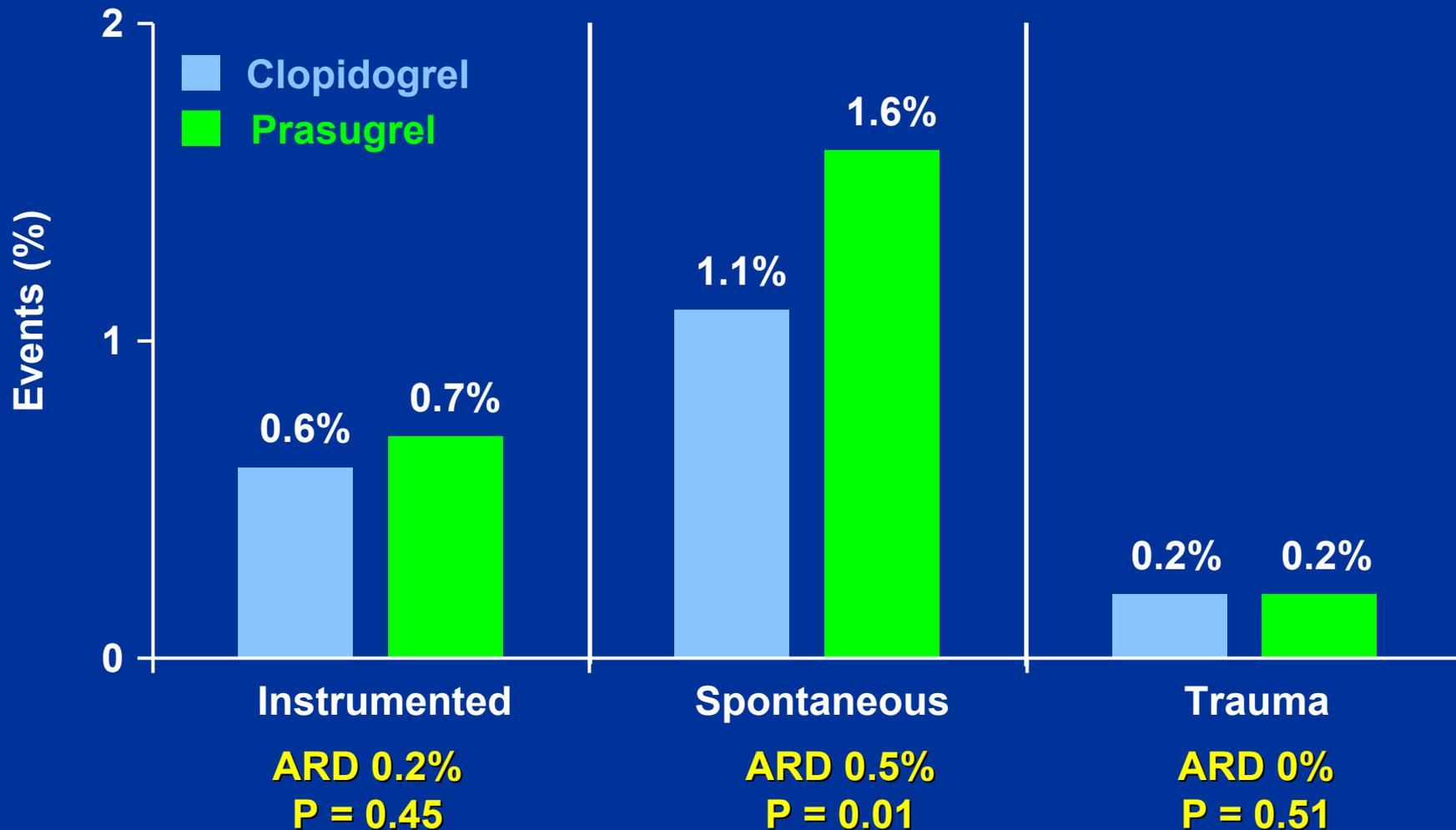
# STEMI Cohort (N= 3534)



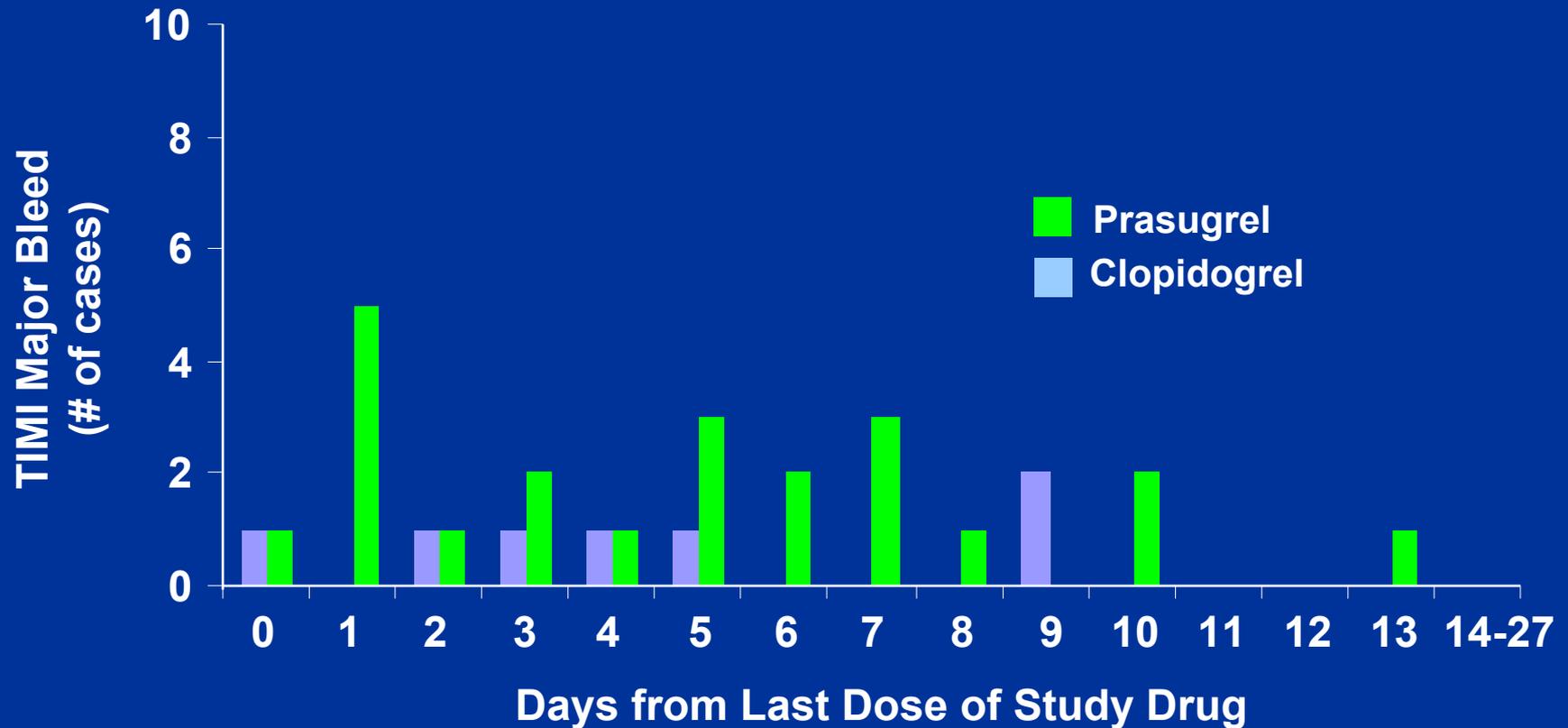
# Bleeding Events Safety Cohort



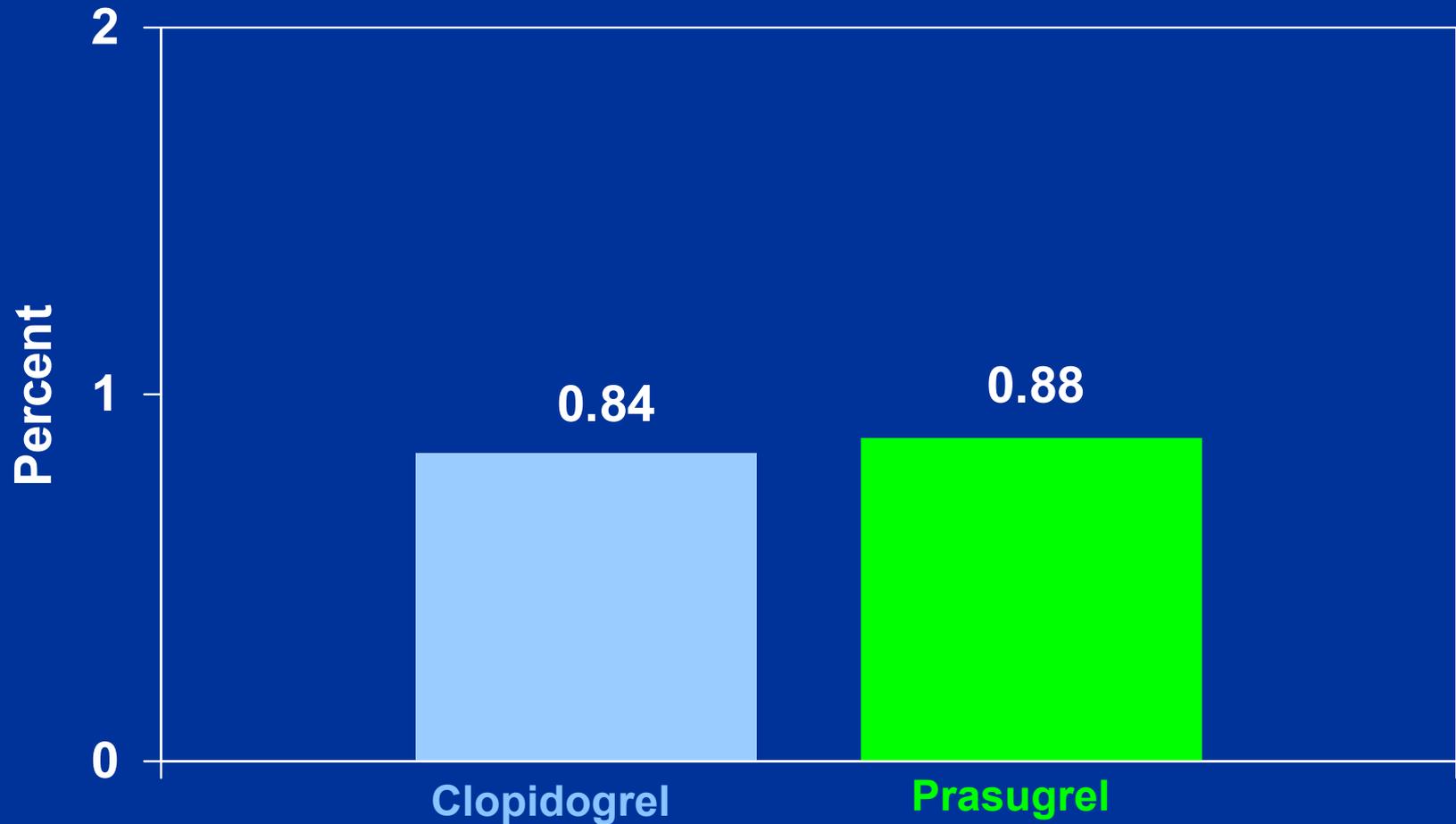
# Types of Major Bleeds



# CABG Surgery and TIMI Major Bleeding— Days from Last Dose of Study Drug (All ACS)

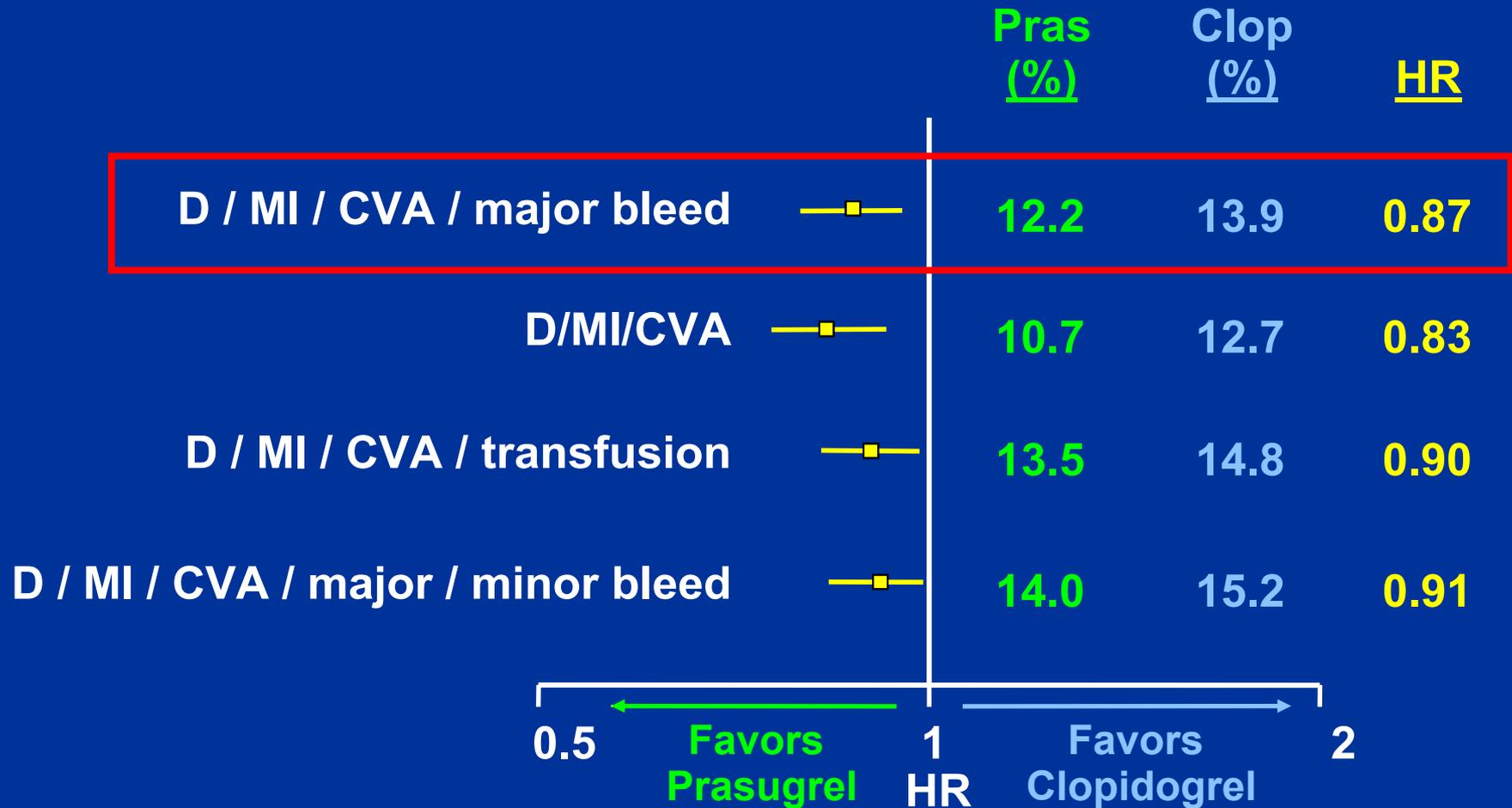


# Non-CABG TIMI Major Bleeding Through 3 Days With GPIIb/IIIa Use\* - All ACS

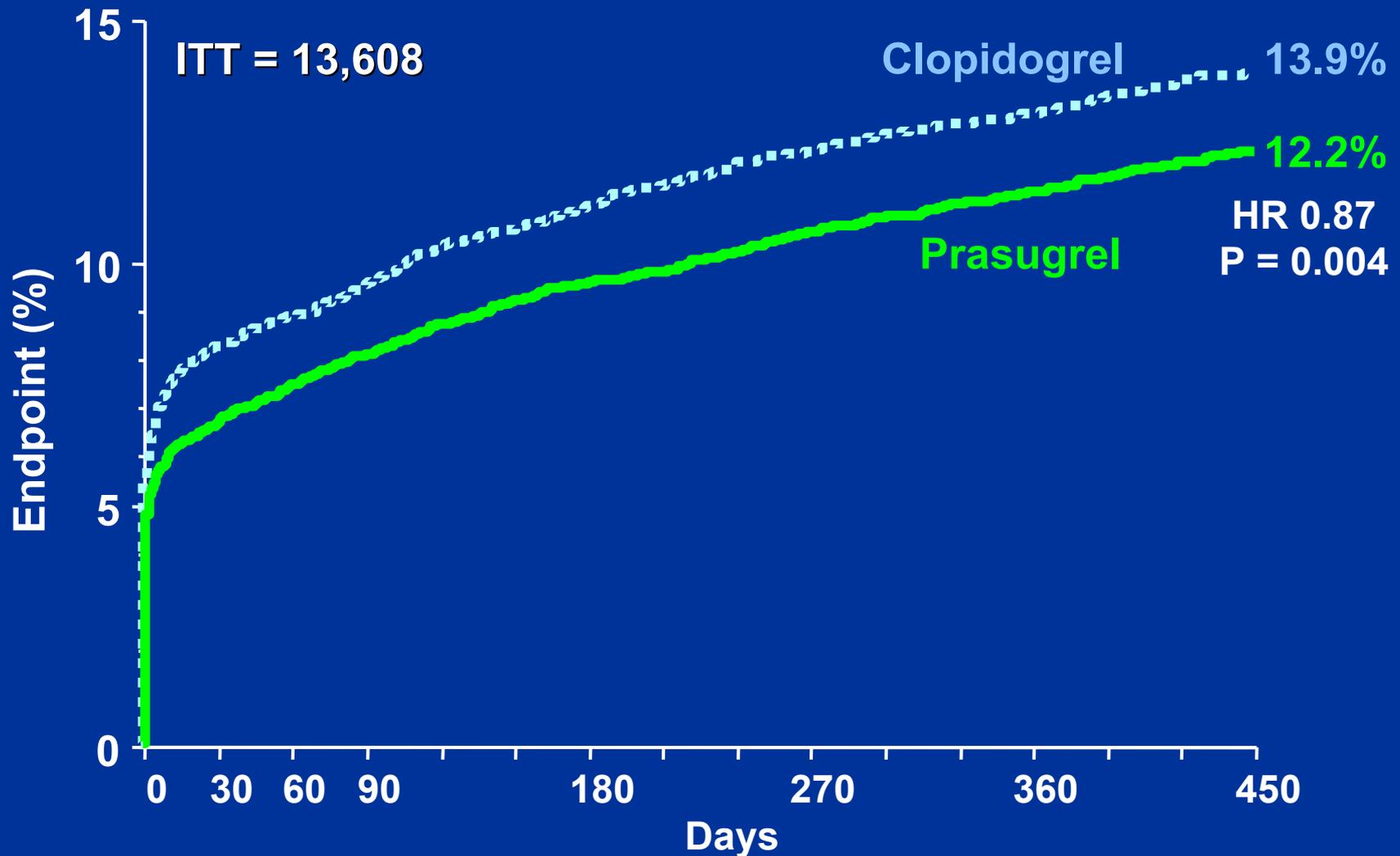


\* Any GPIIb/IIIa use from symptom onset through 3 days after randomization

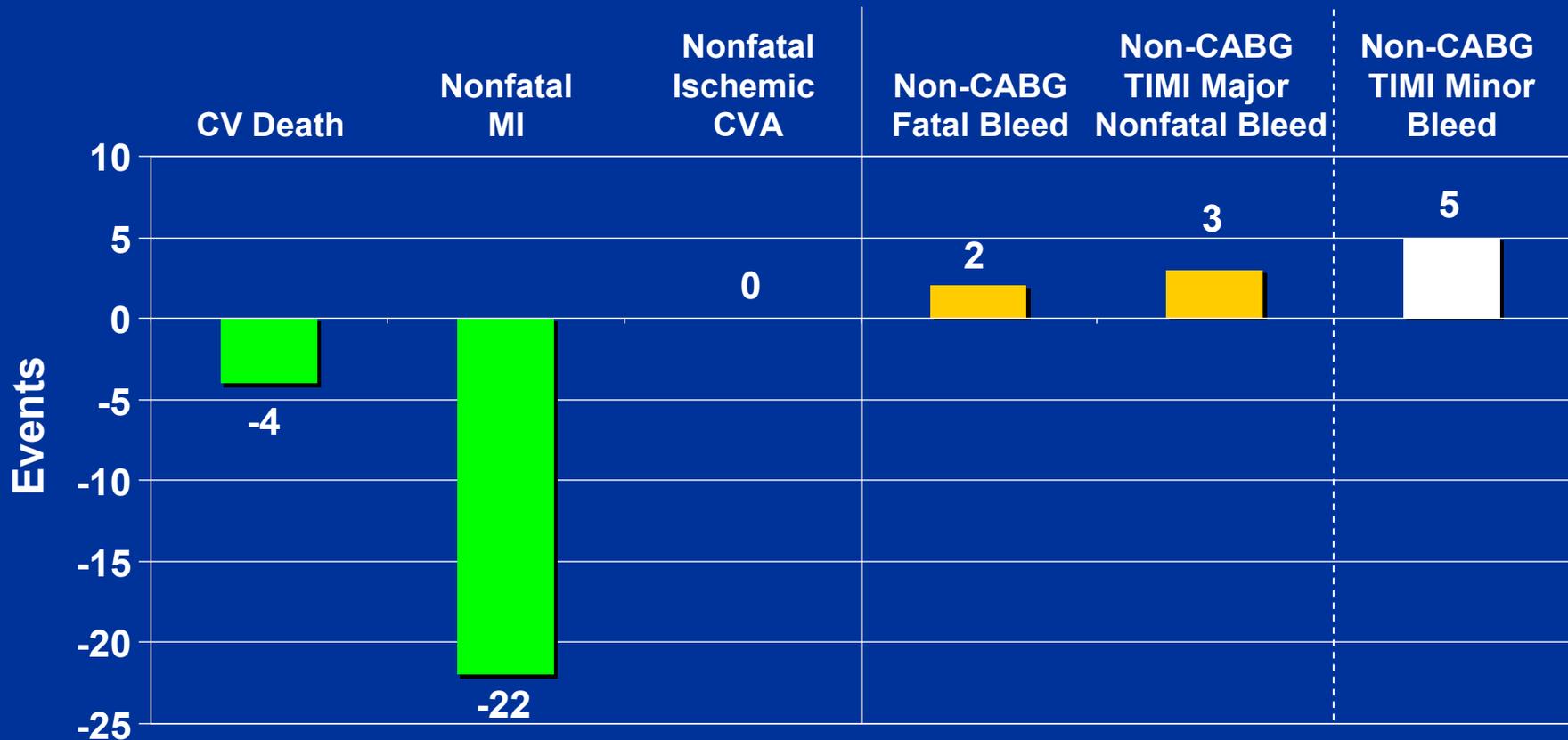
# Net Benefit Endpoints in TRITON-TIMI 38



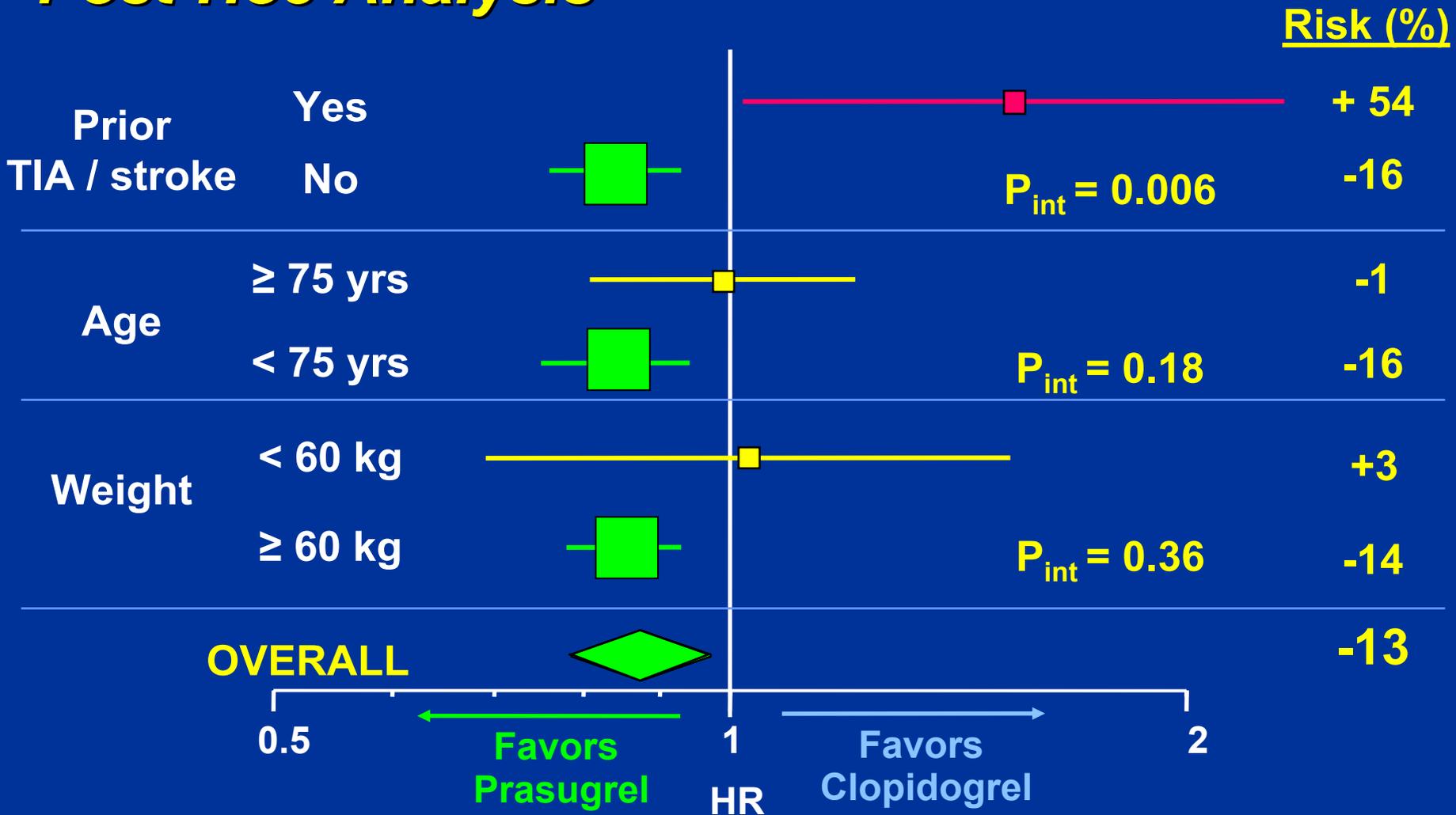
# Net Clinical Benefit – Death, MI, Stroke, TIMI Major Bleeding



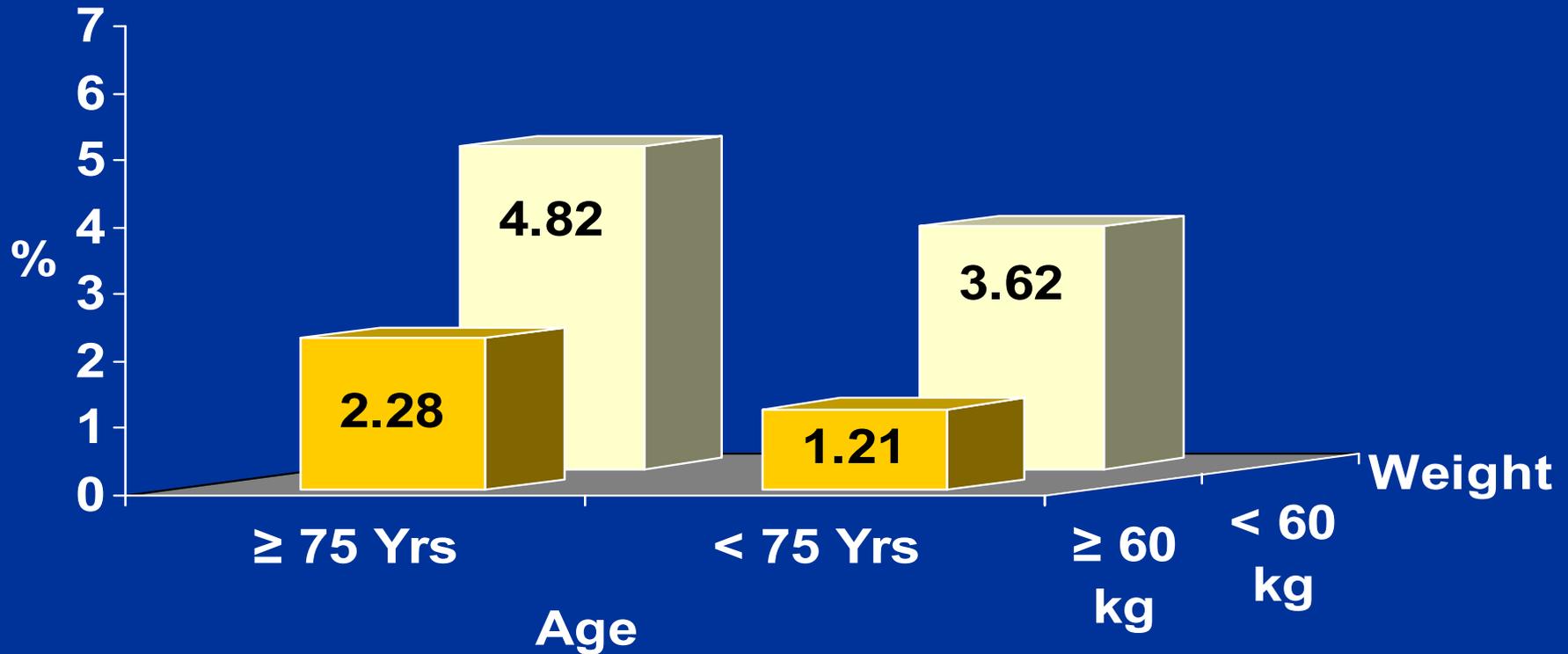
# Events Per 1000 Patients - All ACS



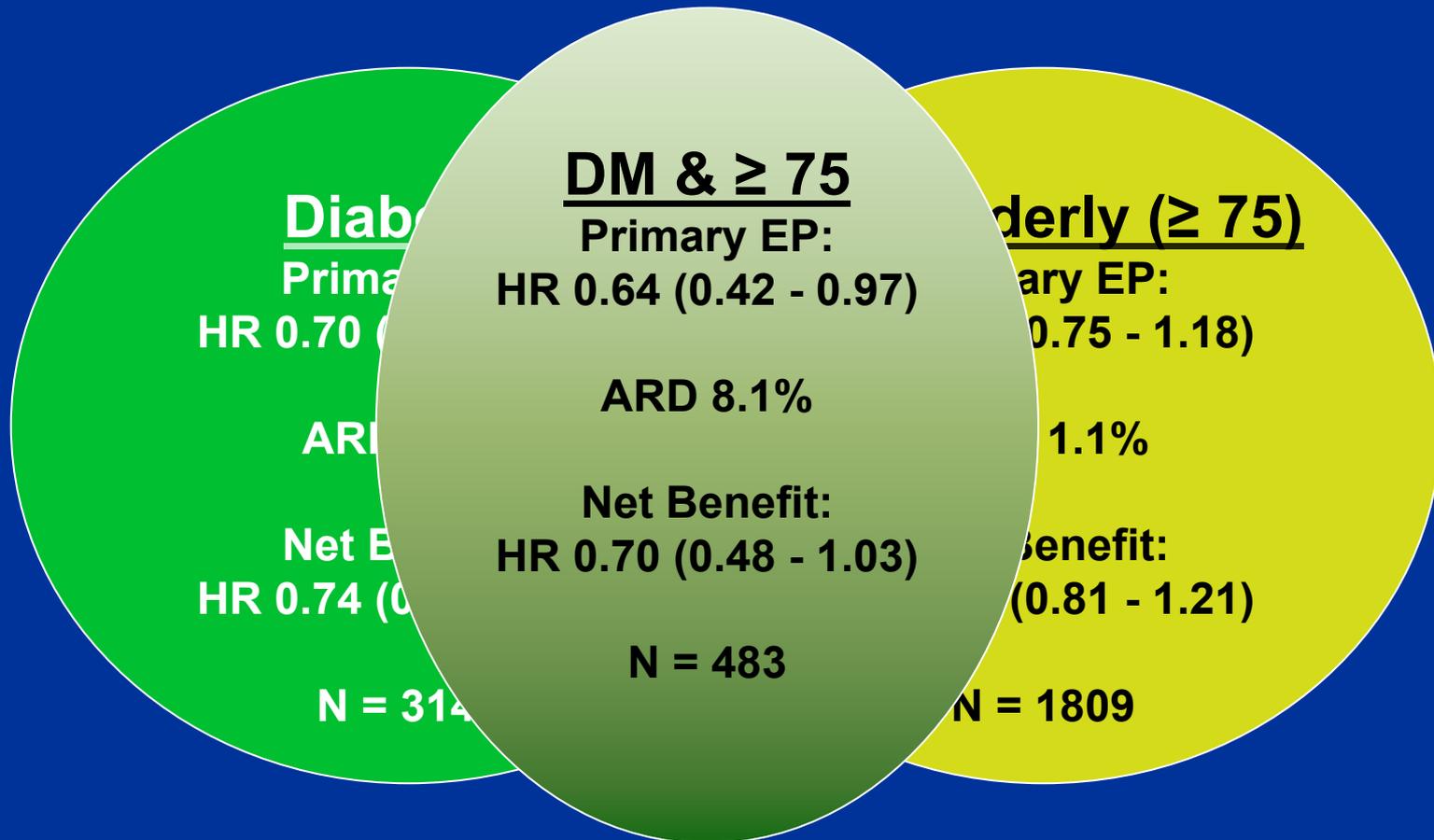
# Net Clinical Benefit in Subgroups: Death / MI / CVA / Major Bleed *Post-Hoc Analysis*



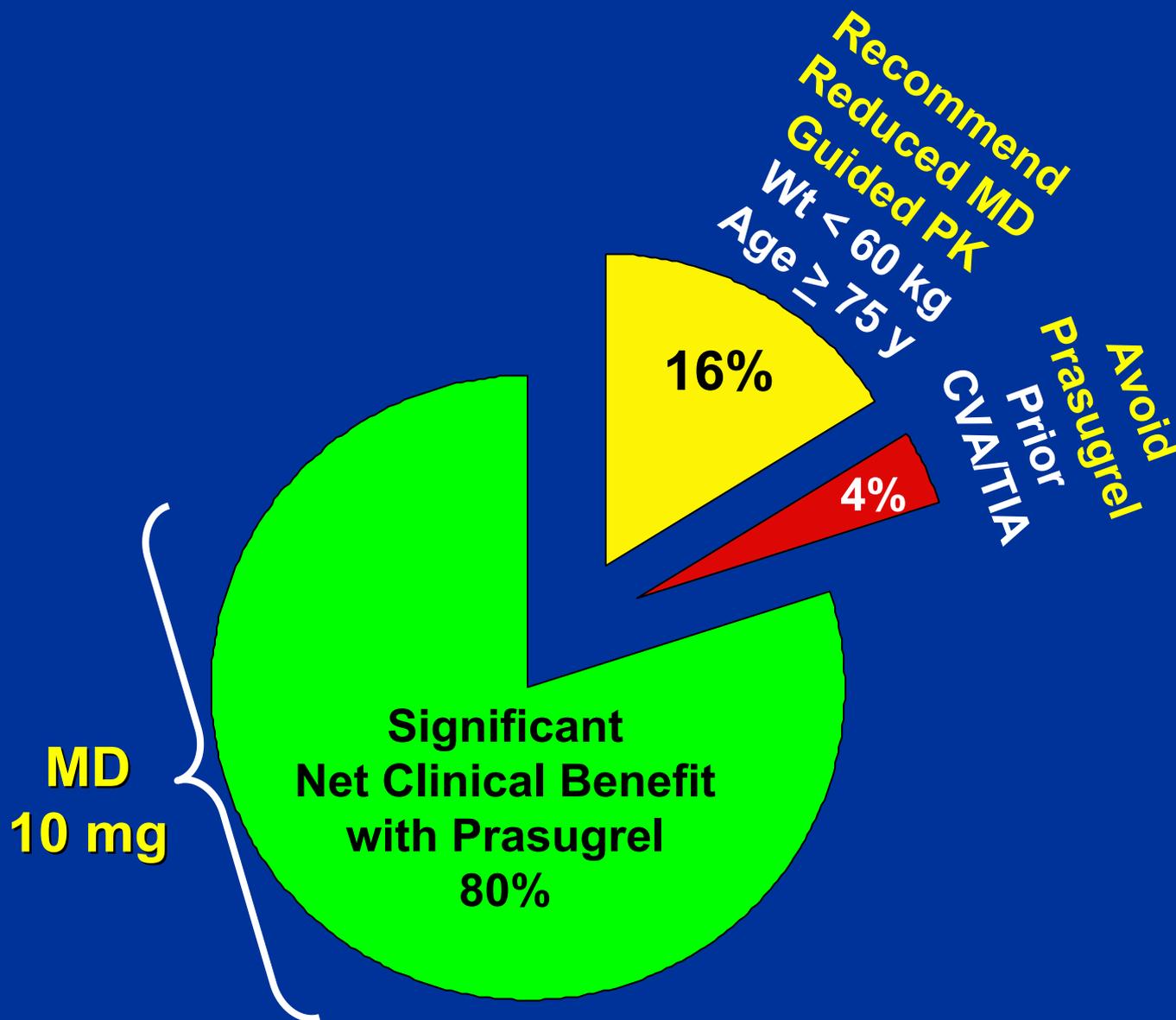
# Non-CABG TIMI Major Bleeding (After 3 days) for Prasugrel Group Impact of Weight and Age



# Influence of Age and Diabetes on Efficacy



# Therapeutic Considerations



ACS Managed with PCI  
*Dual Antiplatelet Therapy*

High Risk Clinical  
Features

Genetic Polymorphisms  
Drug-Drug Interactions

Inhibition of Platelet Aggregation  
Faster, Greater, More Consistent

Continued Ischemic Events

**2.2% ARD in CVD/MI/Stroke (HR = 0.81; NNT = 45)**

**2.3% ARD in MI (HR = 0.76; NNT = 43)**

**1.22 % ARD in stent thrombosis (HR = 0.48; NNT = 82)**

**ACS Managed with PCI**  
*Dual Antiplatelet Therapy*

**High Risk Clinical  
Features**

**Genetic Polymorphisms  
Drug-Drug Interactions**

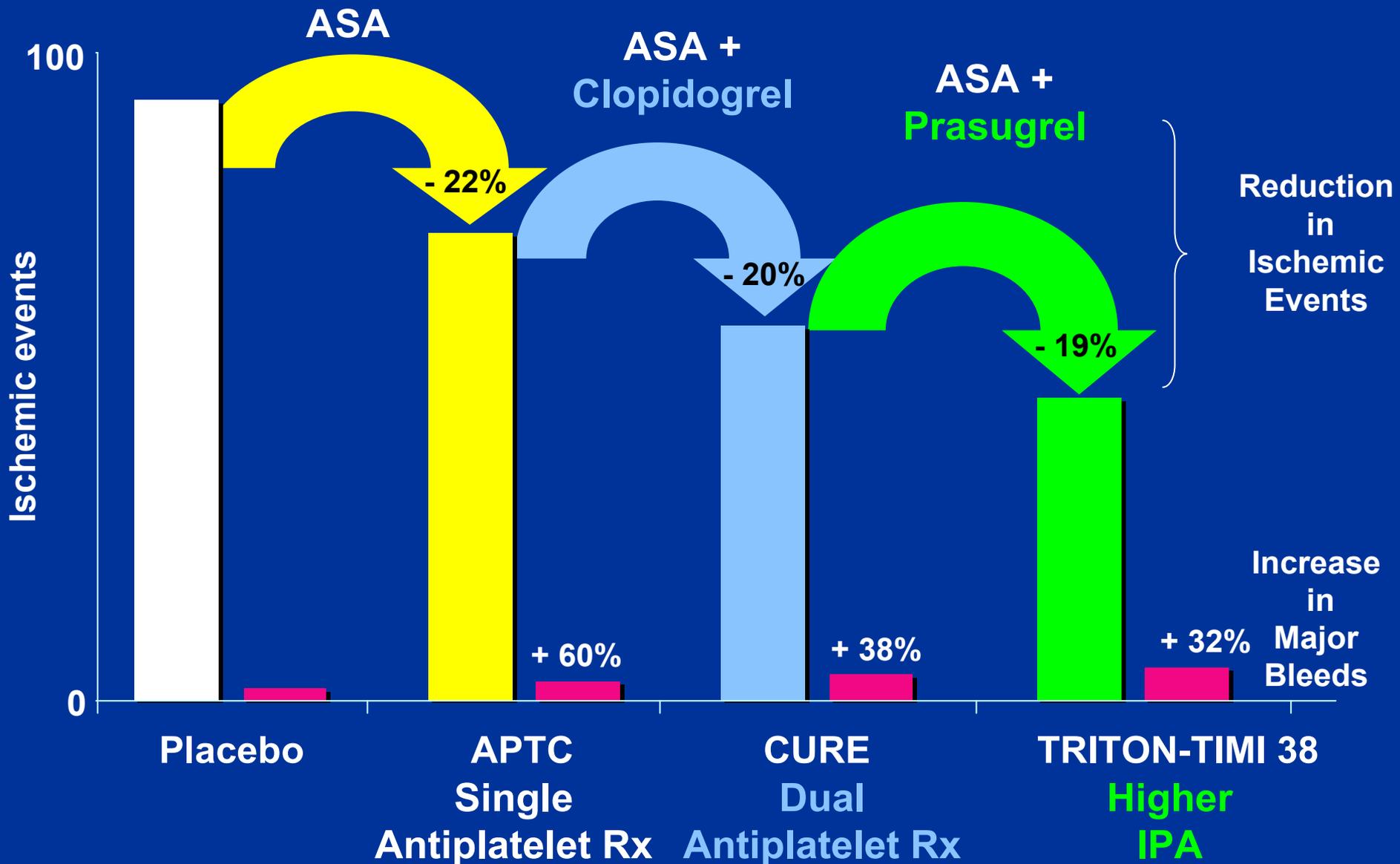
**Inhibition of Platelet Aggregation**  
**Faster, Greater, More Consistent**

***0.6% ARD in non-CABG TIMI Major Bleeding (HR = 1.32; NNH = 167)***

**Potential Mitigation of Bleeding Risk:**

**Access site selection (radial vs femoral)**  
**Contraindication for prior TIA/Stroke**  
**Dose ↓ in patients ≥75 yrs, or <60 kg**

# Antiplatelet Therapy in ACS



# Special Topics

**William Macias, MD, PhD**

**Senior Medical Director  
Cardiovascular and Acute Care  
Eli Lilly and Company**

# Regulatory Review Topics

- ◆ Incidence of neoplasms in TRITON-TIMI 38
- ◆ Sponsor's recommendation for reduced maintenance dose in patients  $< 60$  kg or  $\geq 75$  yrs
- ◆ Salt to base conversion
- ◆ Proposed risk management plan

# Possible Signal of Risk for Neoplasm with Prasugrel

# TRITON-TIMI 38 Not Designed to Ask or Answer Questions Related to Cancer Risk

- ◆ Inclusion/exclusion criteria:
  - Did not exclude patients with cancer
  - Did not exclude patients based on known risk factors for cancer
- ◆ Did not prospectively collect data on:
  - Risk factors for cancer
  - Cancer history, recurrent cancers, new cancers
  - Tumor burden, metastasis, or treatment
- ◆ No protocol defined analytical plan for cancer

# Original Dataset: Neoplasms Reported as Adverse Events

	<b>Prasugrel n/N, (%)</b>	<b>Clopidogrel n/N, (%)</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
<b>Neoplasm benign, malignant, and unspecified (including cysts and polyps)</b>	<b>175 / 6741 (2.60)</b>	<b>138 / 6716 (2.05)</b>	<b>1.26 (1.01 - 1.57)</b>	<b>0.043</b>
<b>New non-benign neoplasm</b>	<b>135 / 6741 (2.00)</b>	<b>115 / 6716 (1.71)</b>	<b>1.18 (0.91, 1.50)</b>	<b>0.212</b>
<b>Malignancy related deaths</b>	<b>21 / 6741 (0.31)</b>	<b>17 / 6716 (0.25)</b>	<b>1.24 (0.65, 2.35)</b>	<b>0.63</b>

# Sponsor Agrees with FDA's Division of Oncology Drug Products\*

- ◆ There are no data in TRITON to support a belief that prasugrel is a “promoter” in humans
- ◆ Cancers diagnosed in TRITON are likely incidental and the finding is probably spurious
- ◆ No neoplasm analyses based on TAAL (TRITON-TIMI 38) can be conclusive

\* Revised Secondary CDTL Review; page 67 of 77.

# Possible Signal of Risk for Neoplasm with Prasugrel

## Assessment of Carcinogenicity

Review:  
Toxicology data

## Assessment of Tumor Stimulation

Review:  
Toxicology data  
↓  
Outcomes for patients with pre-existing cancers  
↓  
Outcomes for patients with new cancers  
↓  
Outcomes for patients with prolonged exposure to prasugrel

## Assessment of Bleeding Leading To Detection of Tumors

Review:  
Number of cancers diagnosed during evaluation of bleeding  
↓  
Analysis excluding colorectal cancers

## Chance Finding

Review:  
Historical rates of new cancers  
↓  
Historical rates of colorectal cancers

# Assessment of Carcinogenicity

- ◆ Prasugrel not genotoxic in in-vitro and in in-vivo tests
- ◆ Two-year toxicology studies in rodents show no increased development of any malignant cell type
  - FDA statement- “Two-year chronic bioassays in two rodent species are the current “gold standard” for assessing carcinogenicity of new drugs as well as other products. Results from these studies have been shown to identify virtually all known human carcinogens.”
- ◆ Benign hepatocellular adenoma noted in mice
  - FDA statement - “These tumors are common in mice and are most likely related to chronic enzyme induction and are not considered relevant to human risk.”

**Both Sponsor and FDA agree prasugrel not a carcinogen.**

# Assessment of Tumor Stimulation

Review:

Toxicology data



Outcomes for patients with pre-existing cancers



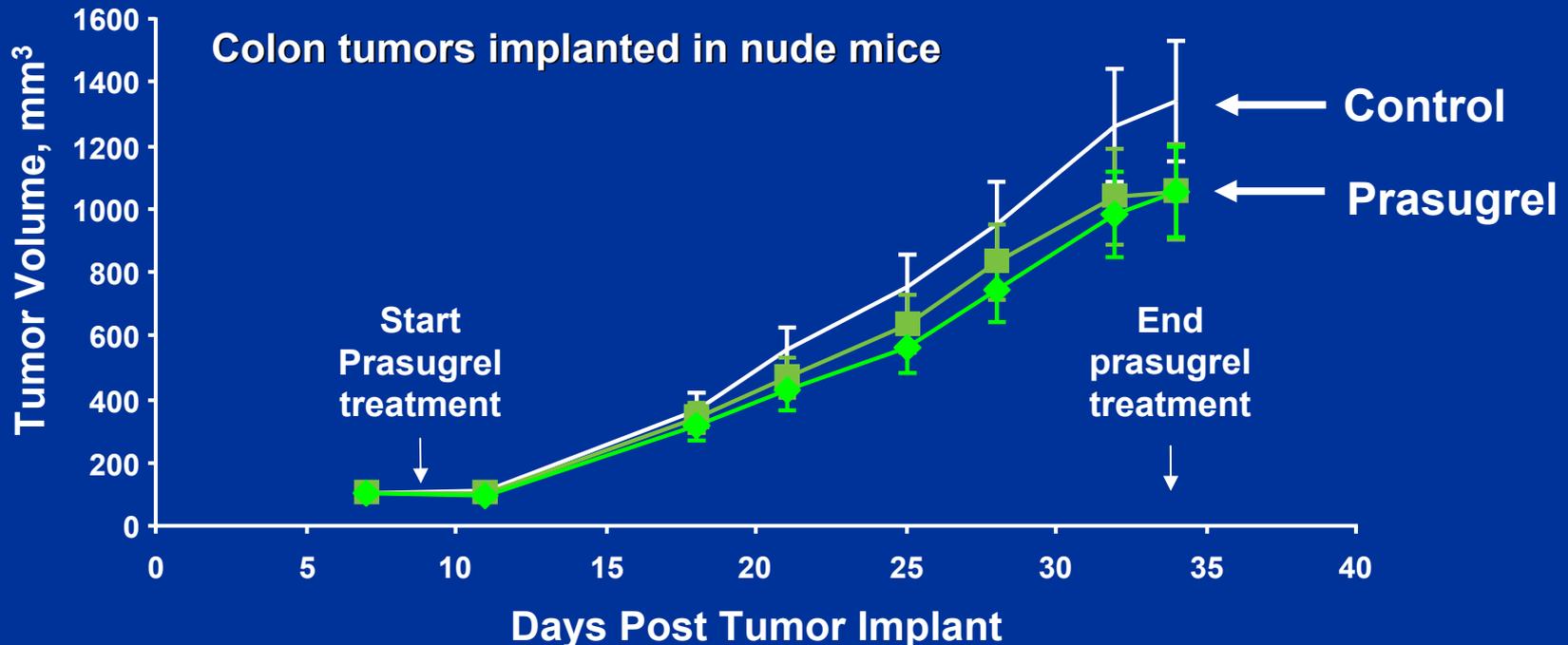
Outcomes for patients with new cancers



Outcomes for patients with prolonged exposure to prasugrel

# Additional Studies Requested by FDA Show Prasugrel Does Not Stimulate Tumor Growth

- ◆ Prasugrel did not stimulate growth of lung, colon, or prostate tumor cells in culture
- ◆ Prasugrel did not stimulate growth of lung, colon, or prostate tumors implanted in nude mice



# Comparable Mortality Rates at Study End for Patients with Pre-existing Non-benign Neoplasm\*

Outcome at database lock	Patients, n (%)	
	Prasugrel N = 137	Clopidogrel N = 132
Malignancy deaths (CEC)	4 (2.9)	3 (2.3)
Use of anti-neoplastic agents	7 (5.1)	8 (6.1)

\*Reported at baseline or reported post baseline as pre-existing neoplasm (excludes non-melanotic skin cancer)

# Number of Newly Diagnosed Cancers

Original dataset  
(Database Lock- Sept. 2007)

Extended follow-up  
of non-randomized cohort  
of subjects with neoplasm AE

Data collected:

- tumor type
- pre-existing or new
- benign, malignant, unknown
- what led to diagnosis
- vital status

Follow-up dataset  
(Data lock March 2008)

New non-benign neoplasms  
(reconciled with FDA\*)

**Prasugrel = 94**

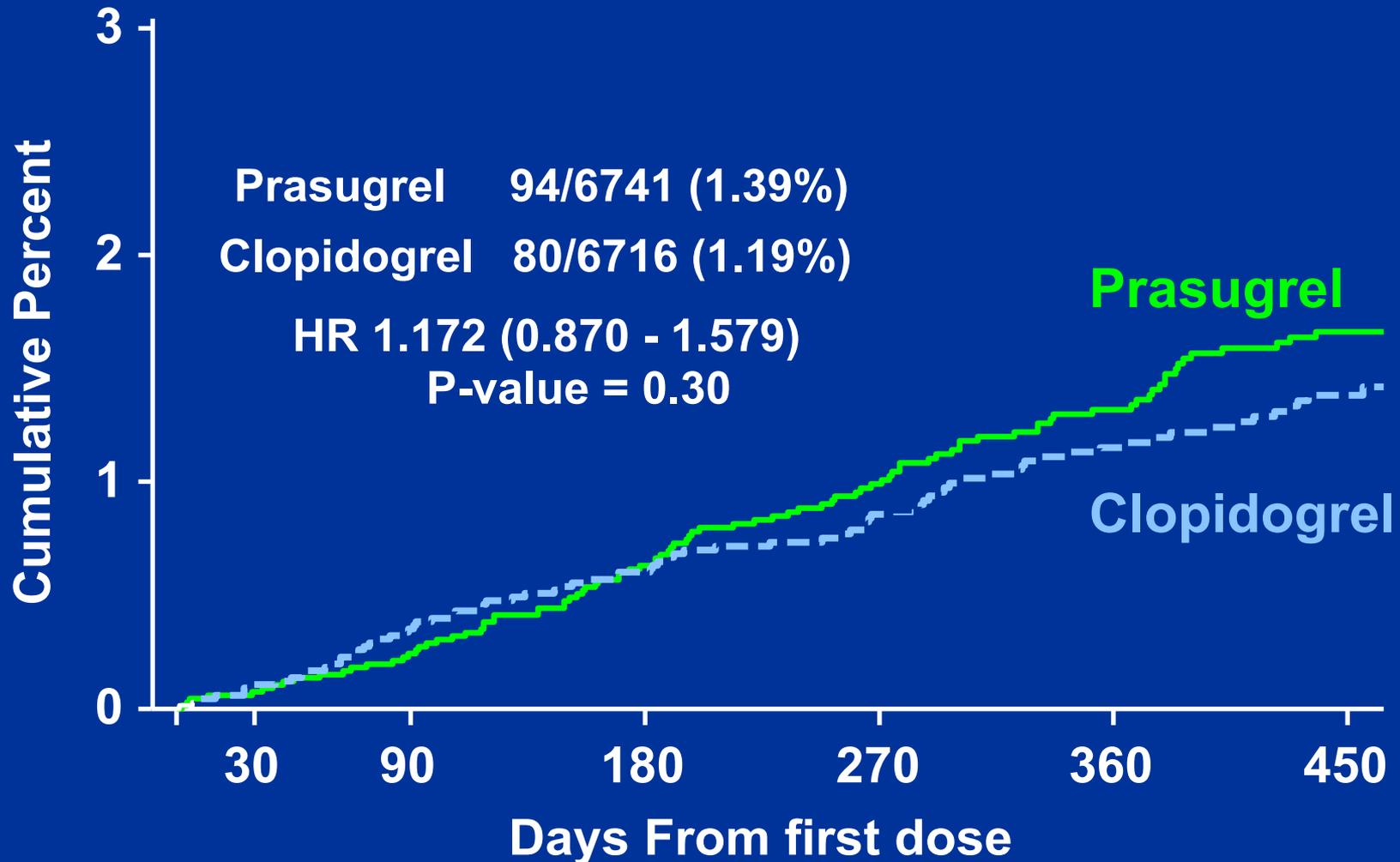
**Clopidogrel = 80**

**Analyses presented based on  
reconciled dataset**

# Rationale for Including Non-melanotic Tumors

- ◆ Pre-clinical data do not support exclusion of any tumor type
- ◆ Exclusion of any tumor type is post hoc and subject to bias
- ◆ Detecting signal for tumor promotion should assess wide variety of tumors
- ◆ Biology of skin cancer is similar to other cancers
- ◆ Systemic exposure to some carcinogens result in skin cancers (eg, arsenical poisoning)
- ◆ Skin tumors are sensitive to known tumor promoters – Most common laboratory model of tumor promotion

# Incidence of Newly Diagnosed Cancers (Non-benign Neoplasms)



# Comparable Mortality Rates for Patients with Newly Diagnosed Cancers who Received Extended Follow-up

Outcome at end of extended follow-up	Patients, n (%)		Relative Risk (95% CI)
	Prasugrel N = 94	Clopidogrel N = 80	
Malignancy deaths (CEC and Investigator reported)	30 (31.9)	23 (28.8)	1.11 (0.70-1.75)

- ◆ Results differ from FDA's analysis due to:
  - Sponsor's use of reconciled database
  - Sponsor's use of only patients with new cancers as at risk population
  - FDA's use of all treated patients as at risk population

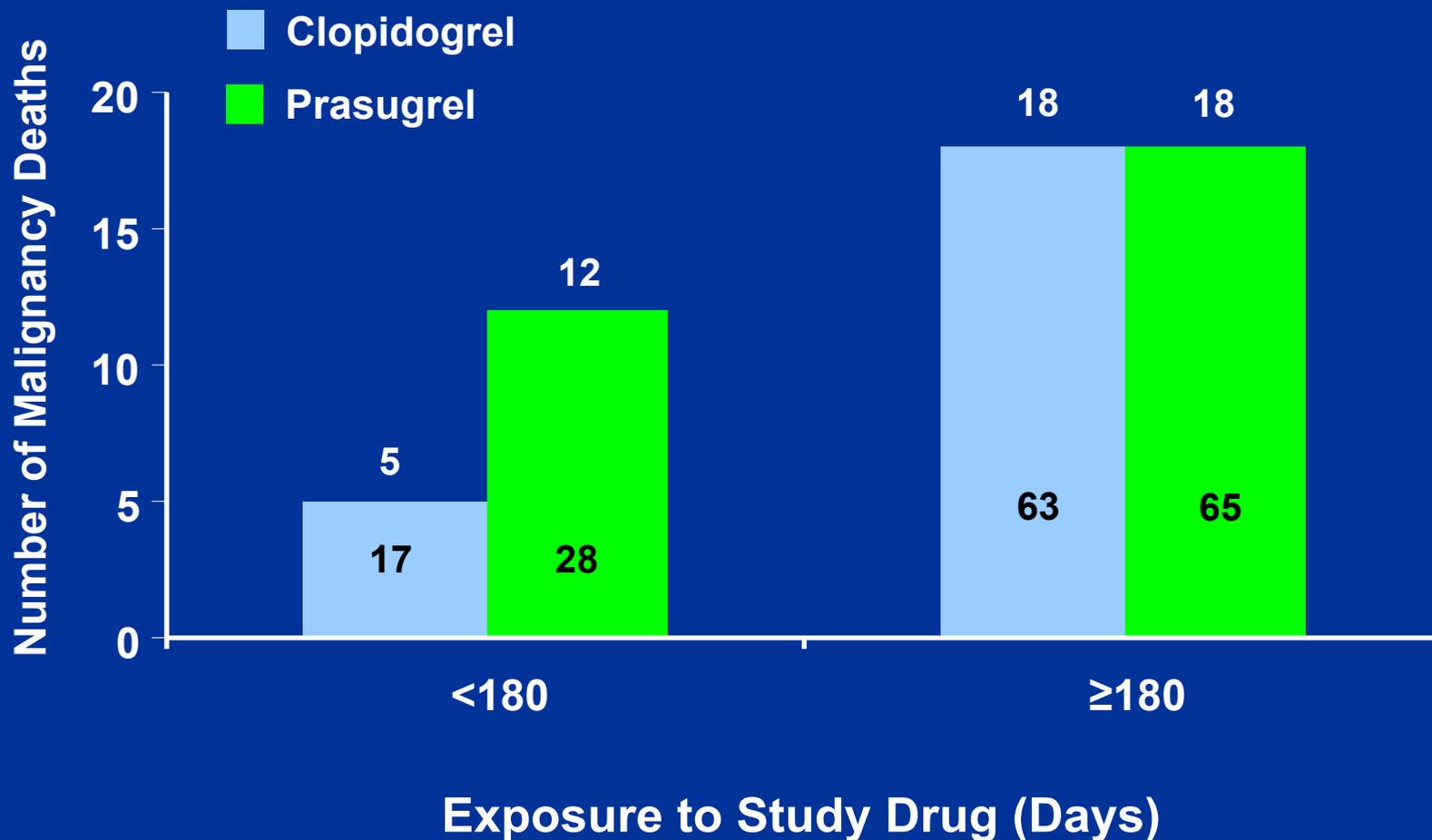
# Comparison of Sponsor's and FDA's Calculation of Relative Risk for Malignancy-related Deaths in Patients with New Cancers (Through Extended Follow-up)

	Patients, n (%)		
<b>FDA's Analysis of Follow-up Data</b>	<b>Prasugrel N = 6741</b>	<b>Clopidogrel N = 6716</b>	<b>Relative Risk (95% CI)</b>
Malignancy deaths (CEC and Investigator reported)	27 (0.40)	19 (0.28)	1.42* (0.79-2.54)
<b>Sponsor's Analysis of Follow-up Data</b>	<b>Prasugrel N = 100</b>	<b>Clopidogrel N = 84</b>	<b>Relative Risk (95% CI)</b>
Malignancy deaths (CEC and Investigator reported)	27 (27.0)	19 (22.6)	1.19 (0.72-1.99)

**Follow-up was only obtained on patients with newly diagnosed cancers. Therefore, not appropriate to use all-treated patients as the at risk population.**

\* Revised Secondary CDTL Review; page 64 of 77.

# Prolonged Exposure to Prasugrel Not Associated with Higher Malignancy Death (Relative to Clopidogrel)



# No Evidence that Prasugrel Worsened Outcomes for Patients with Cancer

- ◆ Similar mortality rates between treatment groups for patients with prior (2.9% vs 2.3%) or newly diagnosed cancers (31.9% vs 28.8%)
- ◆ Observed difference in number of deaths in patients treated with prasugrel related to:
  - Non-randomized cohort defined by post-baseline event of new neoplasm
  - Extended follow-up for only this cohort (all randomized patients not followed post study end)
  - Unequal number of patients followed-up
- ◆ Prolonged exposure to prasugrel did not worsen outcomes for patients with cancer (relative to clopidogrel)

# Consult from the FDA's Division of Oncology Drug Products\*

- ◆ No neoplasm analyses from TRITON-TIMI 38 can be conclusive
  - Study not designed to compare cancer incidence between treatment groups
    - Did not include cancer screening at baseline
  - Clinical significance obtained by combining different cancers hard to interpret
- ◆ “There are no data in TRITON-TIMI 38 to support a belief that prasugrel is a “promoter” in humans”
  - Short drug exposure to the study drugs
  - No specified follow-up to detect specific cancers
  - Cancers diagnosed likely to be incidental

\* Revised Secondary CDTL Review; page 67 of 77.

# Assessment of Bleeding Leading to Detection of New Cancers

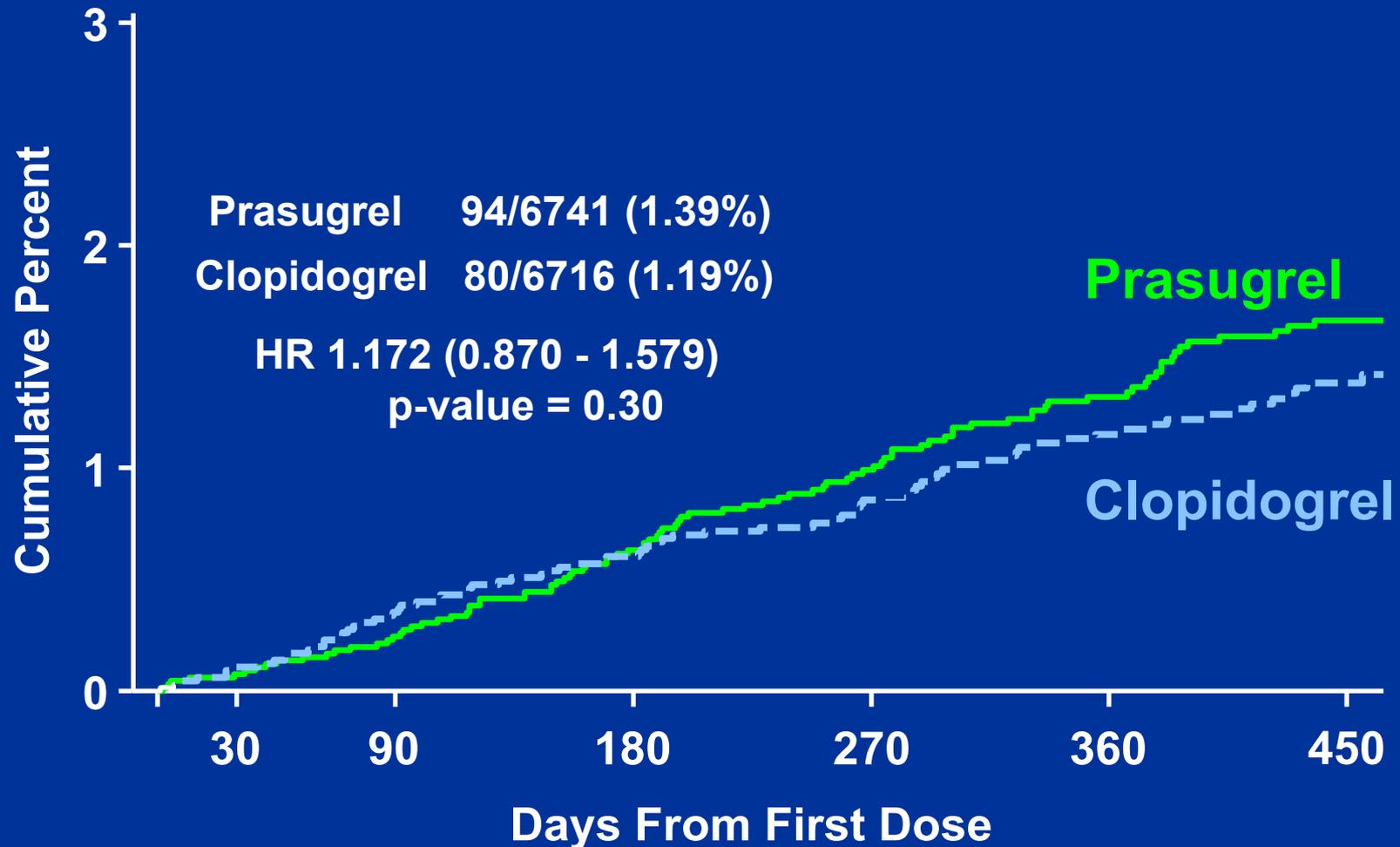
Review:

Number of cancers diagnosed during evaluation of bleeding



Analysis excluding colorectal cancers

# Incidence of New Non-benign Neoplasms in TRITON-TIMI 38



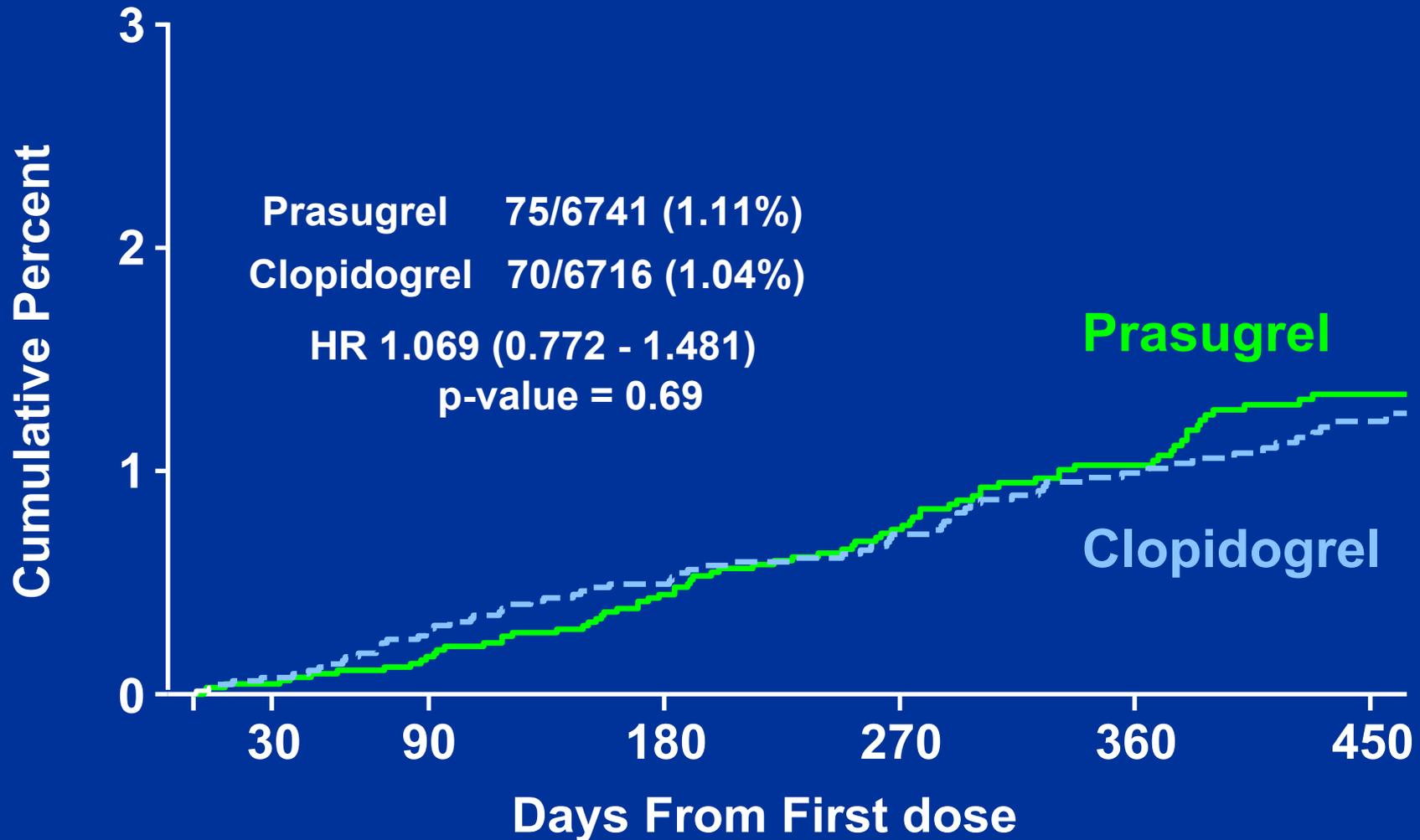
# Colorectal Neoplasms Frequently Diagnosed During Evaluation of Bleeding or Anemia

Evaluation of anemia or bleeding led to diagnosis*	Diagnosis of colorectal neoplasm	
	Prasugrel	Clopidogrel
Yes	16	8
No	3	2
Total	19	10

- ◆ Approximately 80% of colorectal cancers diagnosed during evaluation of bleeding or anemia
  - Similar percentage in both treatment groups

\* As reported by the investigator

# Incidence of New Non-benign Neoplasms Excluding Colorectal Cancers



# Chance Finding

**Review:**

**Historical rates of new  
cancers**



**Historical rates of  
colorectal cancers**

# Rates of Colorectal Cancers in CURE and TRITON

Name of study	Number cancers	Patient-yrs
<b>CURE</b>		
ASA	8 (11*)	4728
ASA + clopidogrel	16 (22*)	4694
<b>TRITON</b>		
ASA + clopidogrel	10	6503
ASA + prasugrel	19	6464

\* Projected number for 6500 patient-yrs

# Summary: Sponsor Agrees with FDA's Division of Oncology Drug Products\*

- ◆ There are no data in TRITON to support a belief that prasugrel is a “promoter” in humans
- ◆ Cancers diagnosed in TRITON are likely incidental and the finding is probably spurious
- ◆ No neoplasm analyses based on TAAL (TRITON-TIMI 38) can be conclusive
  - **Sponsor plans to prospectively collect additional data in TRILOGY-ACS**
    - **Oncology experts providing guidance on data collection and analytical plan**

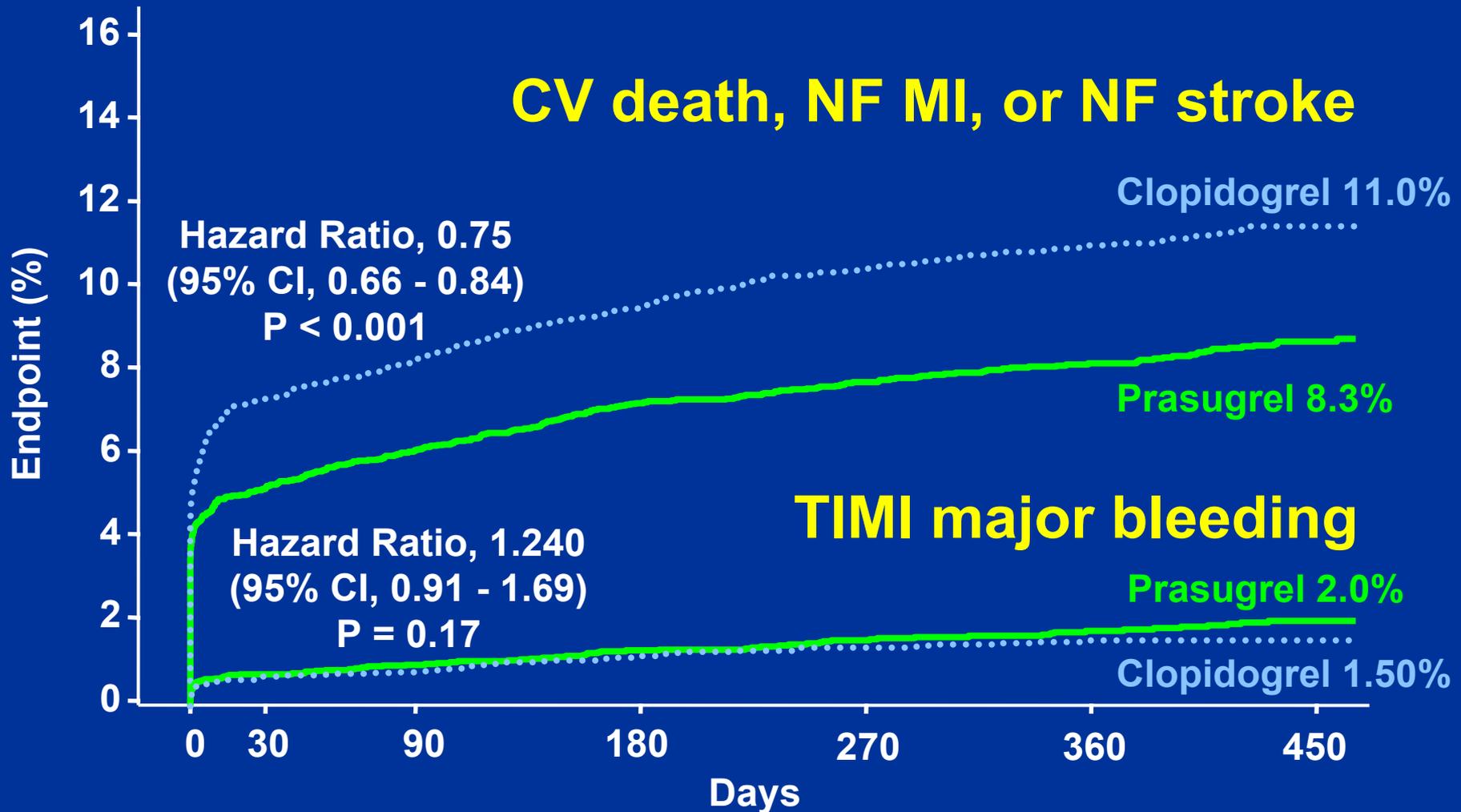
\* Revised Secondary CDTL Review; 67 of 77.

# Sponsor's Recommendation on Labeling Specific to Neoplasms

- ◆ Neoplasm information included in labeling
  - Should reflect uncertainty of the observation
  - Should be useful to prescriber
  - Should not create unfounded alarm for physicians or patients
  - Should not have equal prominence to risk of bleeding
    - Evaluation of GI bleeding should be undertaken because it may unmask previously undiagnosed cancers comparable to warfarin
- ◆ Specific labeling language should
  - Be included in the adverse event section listing
  - Not restrict treatment duration

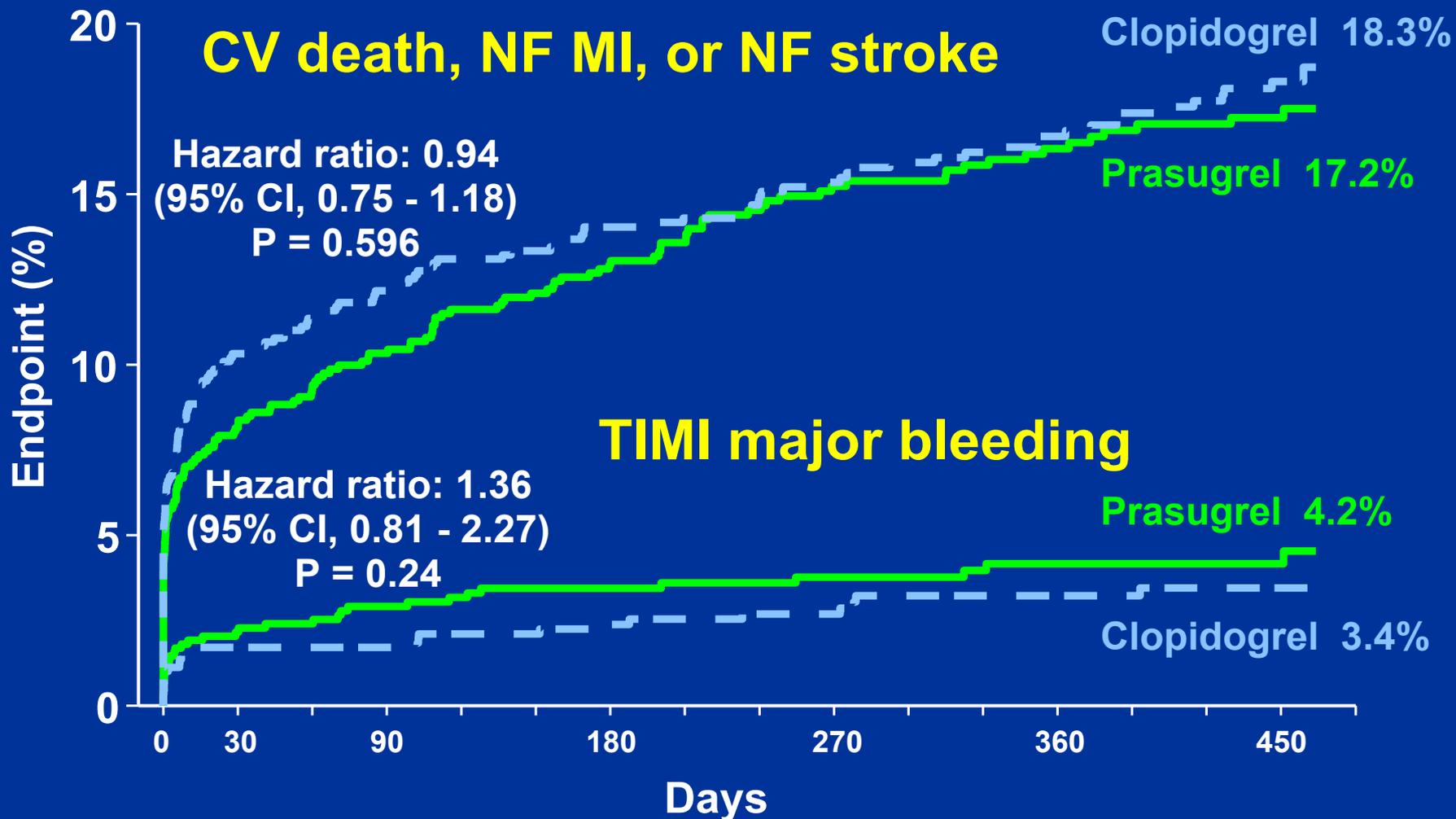
# **Rationale for Dose Adjustment in Patients $< 60$ kg or $\geq 75$ yrs**

# Balance of Efficacy and Safety in Patients < 75 Yrs, $\geq$ 60 kg, and without Prior TIA/Stroke

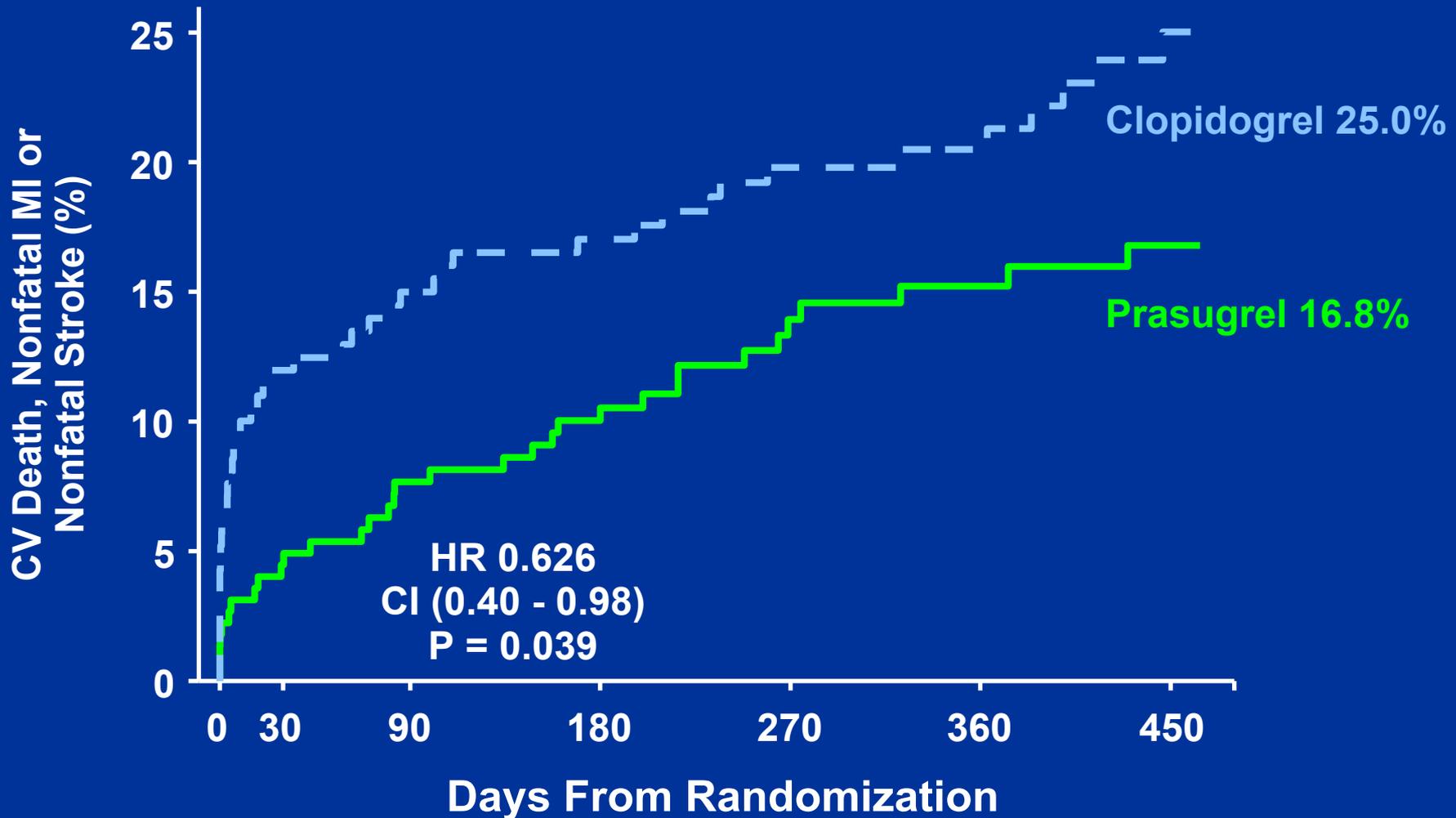


Modified from Wiviott SD et al. *NEJM* 2007; 357: 2001-2015

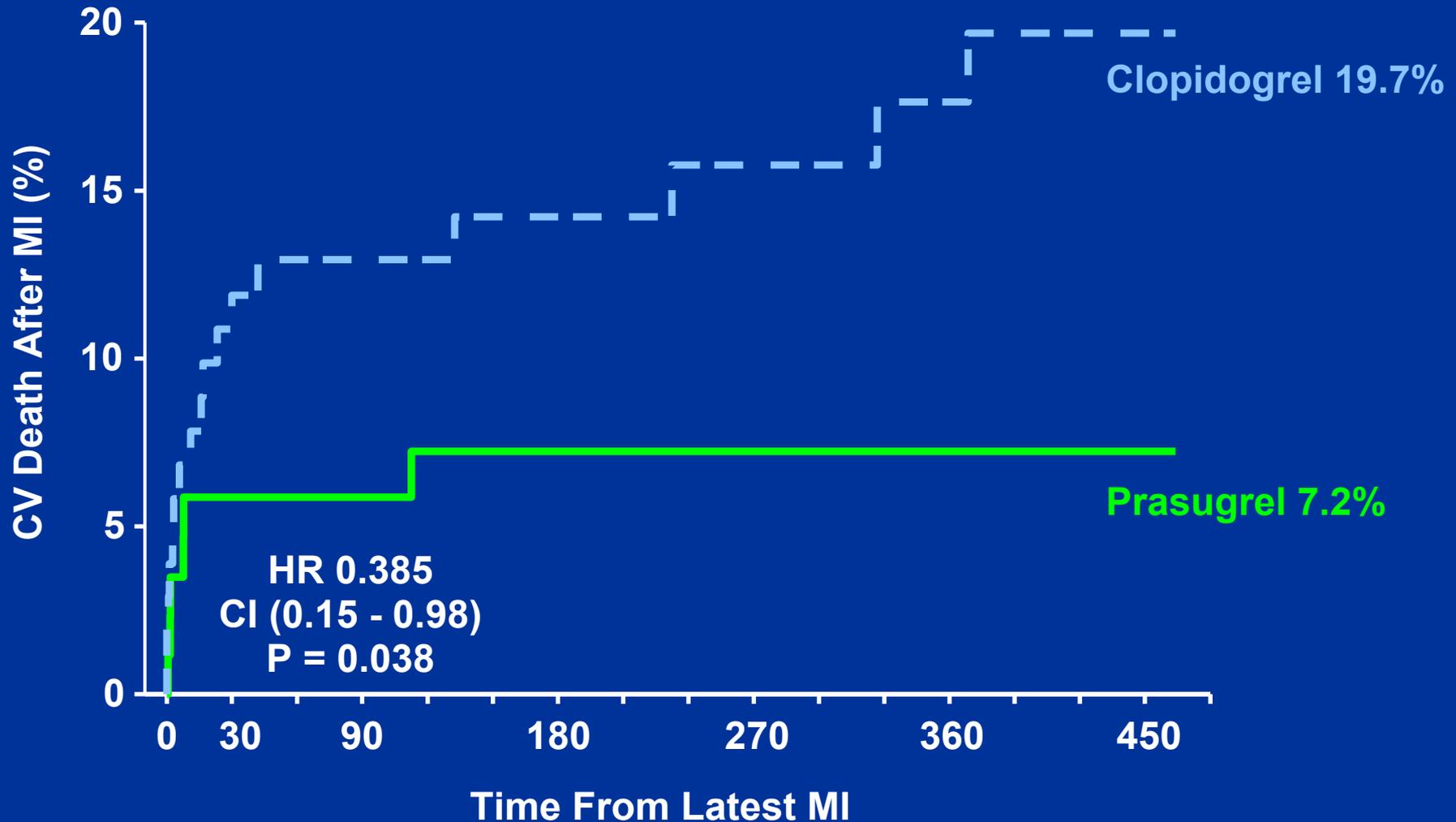
# Balance of Efficacy and Safety in Patients $\geq 75$ Yrs (All ACS)



# Primary Composite Efficacy Endpoint in Patients $\geq 75$ Yrs with Diabetes (All ACS)



# Cardiovascular Death Following MI in Patients $\geq 75$ Yrs Without TIA/Stroke (All ACS)



# Dose Adjustment

## ◆ Recommendation

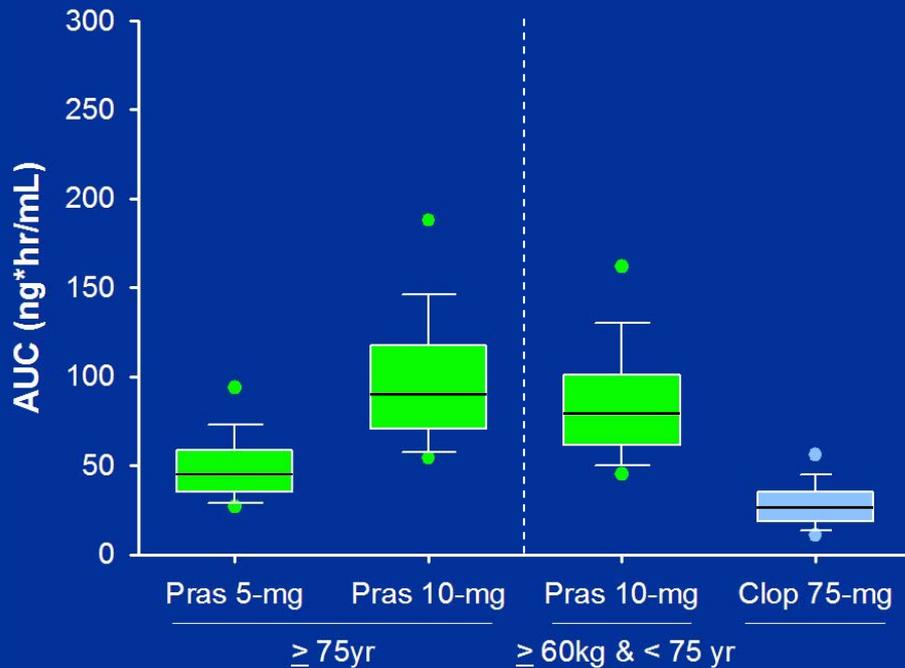
- Reduced maintenance dose of 5 mg in
  - Patients < 60 kg
  - Patients  $\geq$  75 yrs

## ◆ Rationale

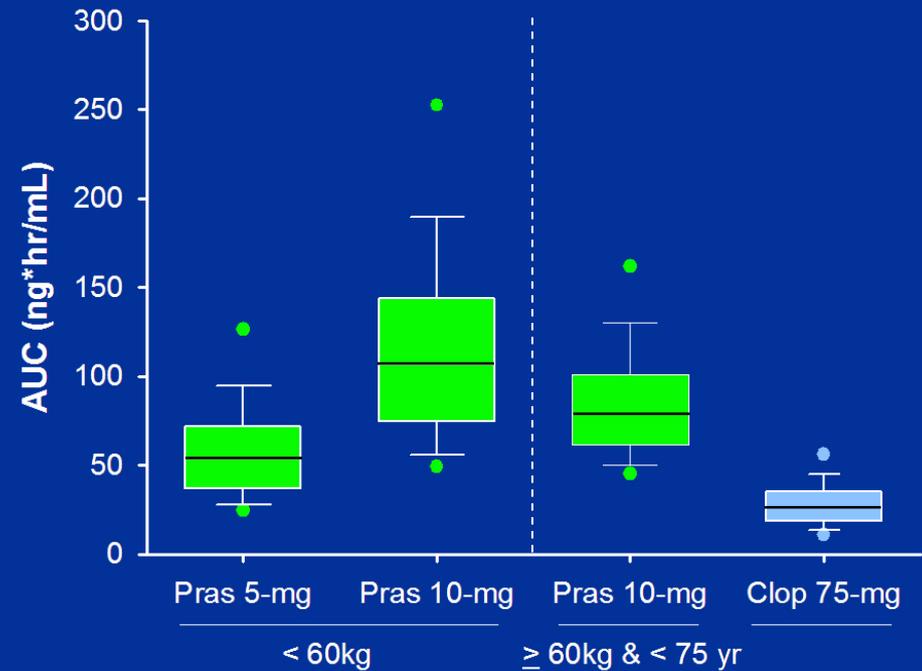
- Patients < 60 kg or  $\geq$  75 yrs had higher exposure to prasugrel active metabolite
- Increased exposure associated with increased bleeding during the maintenance phase
- Reduction in dose would maintain estimated exposure similar to general population and reduced risk of bleeding
- Reduction in dose should maintain efficacy

# Predicted Exposure During 5 mg MD in Patients $\geq 75$ Yrs or $< 60$ kg

## Patients $\geq 75$ Yrs



## Patients $< 60$ kg



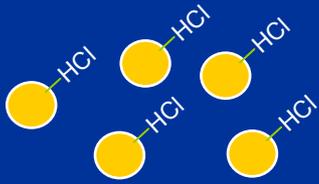
## **CHMP\* Dosing Recommendation for Patients < 60 kg or ≥ 75 Yrs of Age**

**Prasugrel is administered as a loading dose of 60 mg and a once daily maintenance dose of 10 mg**

**However, for patients at special risk (≥ 75 yrs, < 60 kg), a dose reduction is strongly recommended. Following the administration of a loading dose of 60 mg, the 5 mg once daily maintenance dose is to be given.**

# Salt to Base Conversion

Tablet manufacture with  
Prasugrel HCl

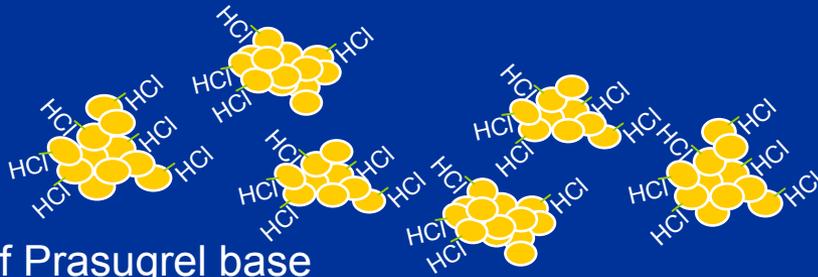


During manufacture and  
storage some conversion to  
Prasugrel base.

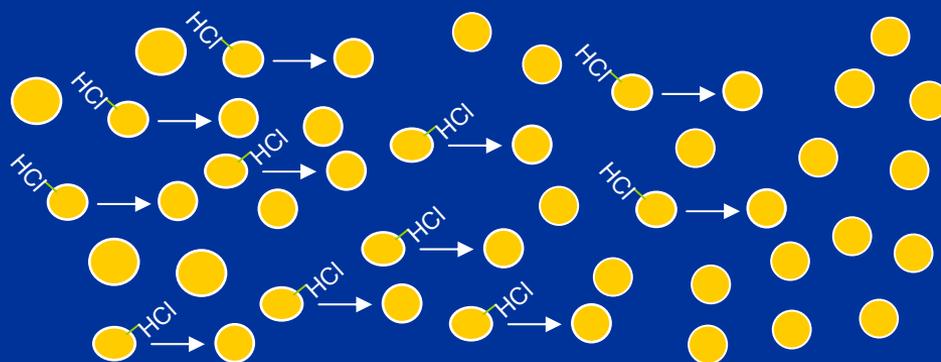


Ingestion

Particles of Prasugrel base  
and salt



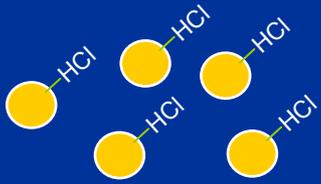
Dissolution



**Low gastric pH:**  
rate of dissolution,  
extent of dissolution, and  
absorption unaffected by  
base/salt ratio

Only Base  
Absorbed

Tablet manufacture with  
Prasugrel HCl

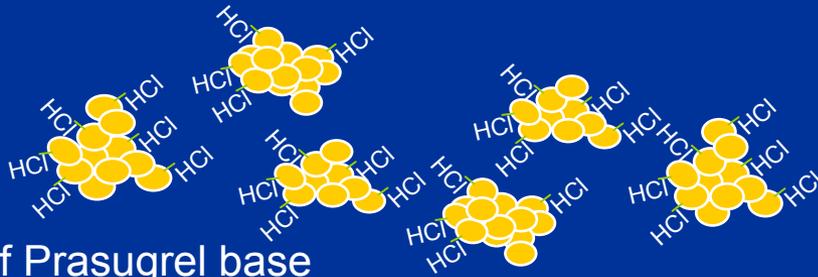


During manufacture and  
storage some conversion to  
Prasugrel base.

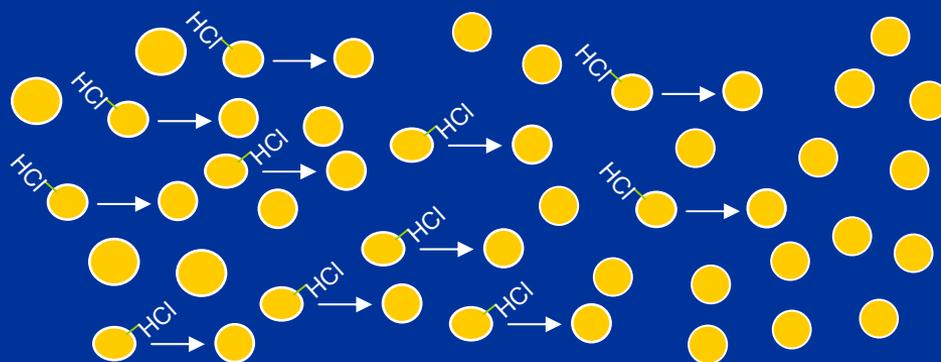


Ingestion

Particles of Prasugrel base  
and salt



Dissolution

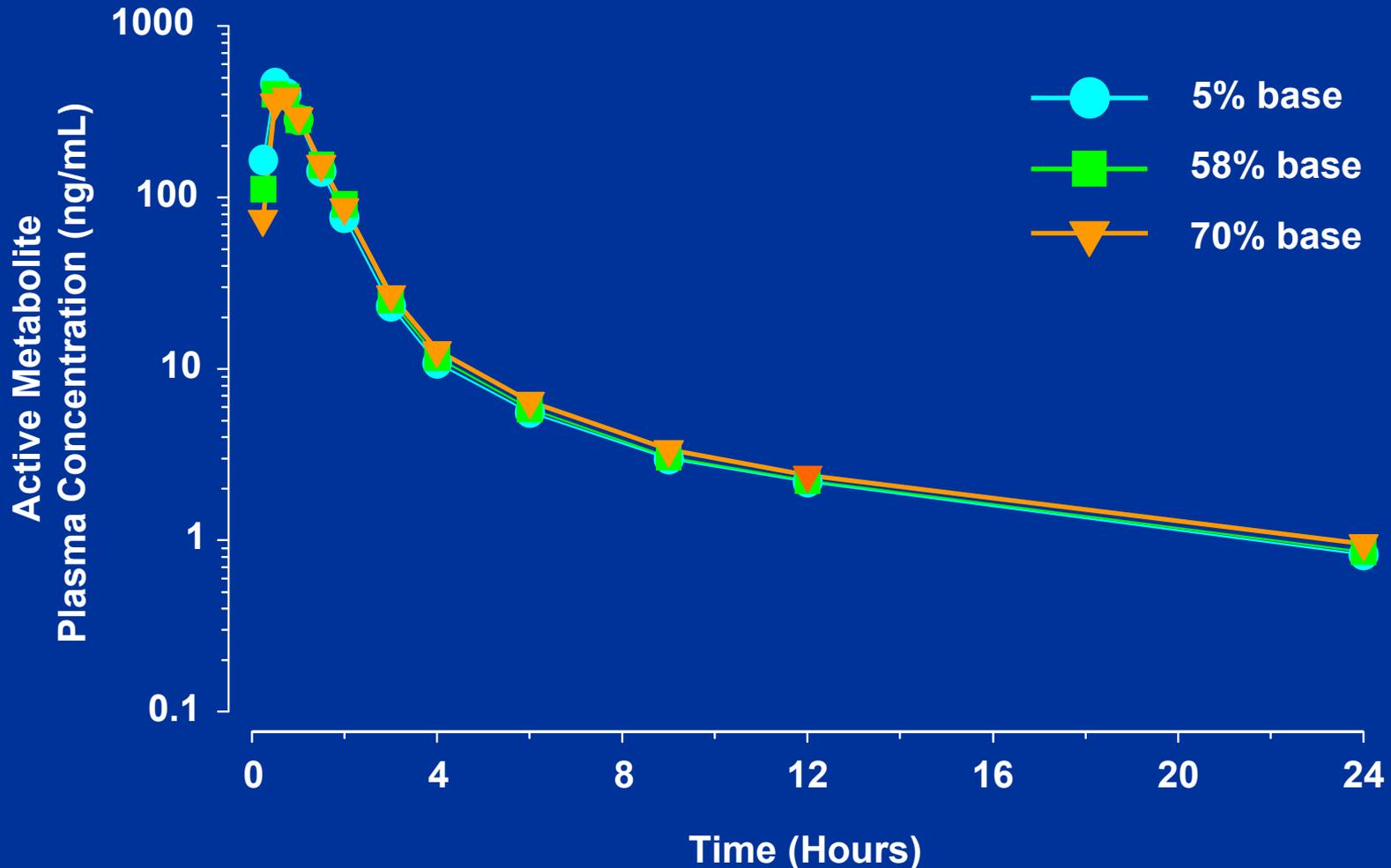


**High gastric pH:**  
rate of dissolution is  
reduced but extent of  
dissolution and  
absorption unaffected by  
base/salt ratio

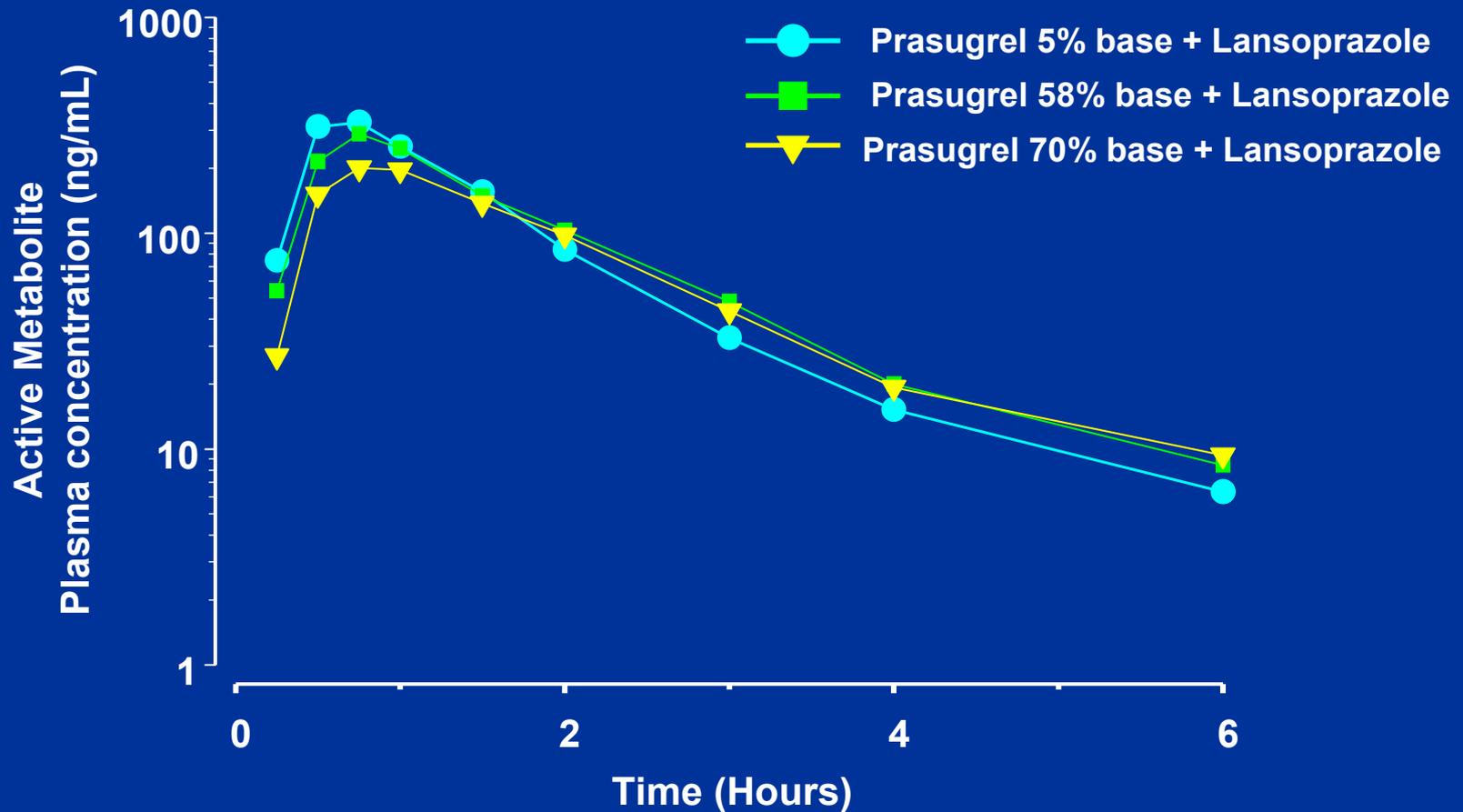
Only Base  
Absorbed



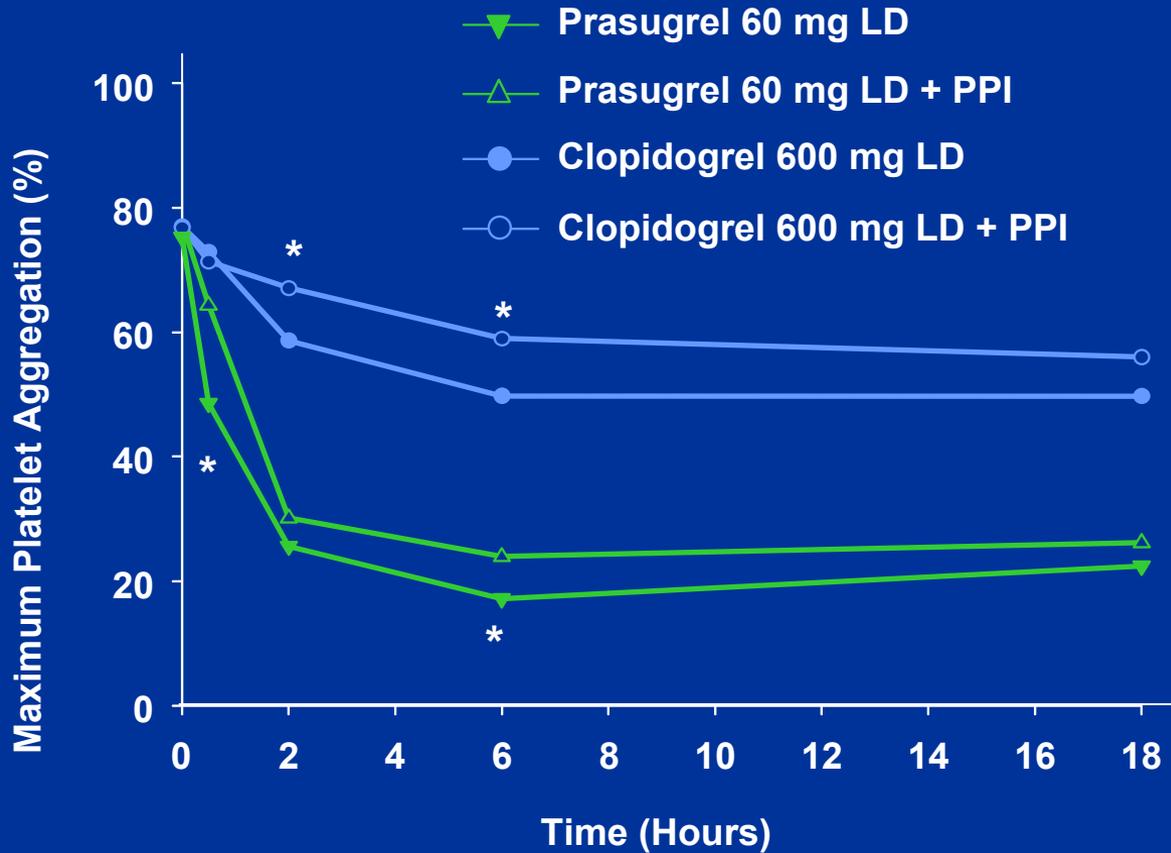
# No Effect of Partial Conversion on Absorption of a 60-mg Prasugrel LD at Normal Gastric pH



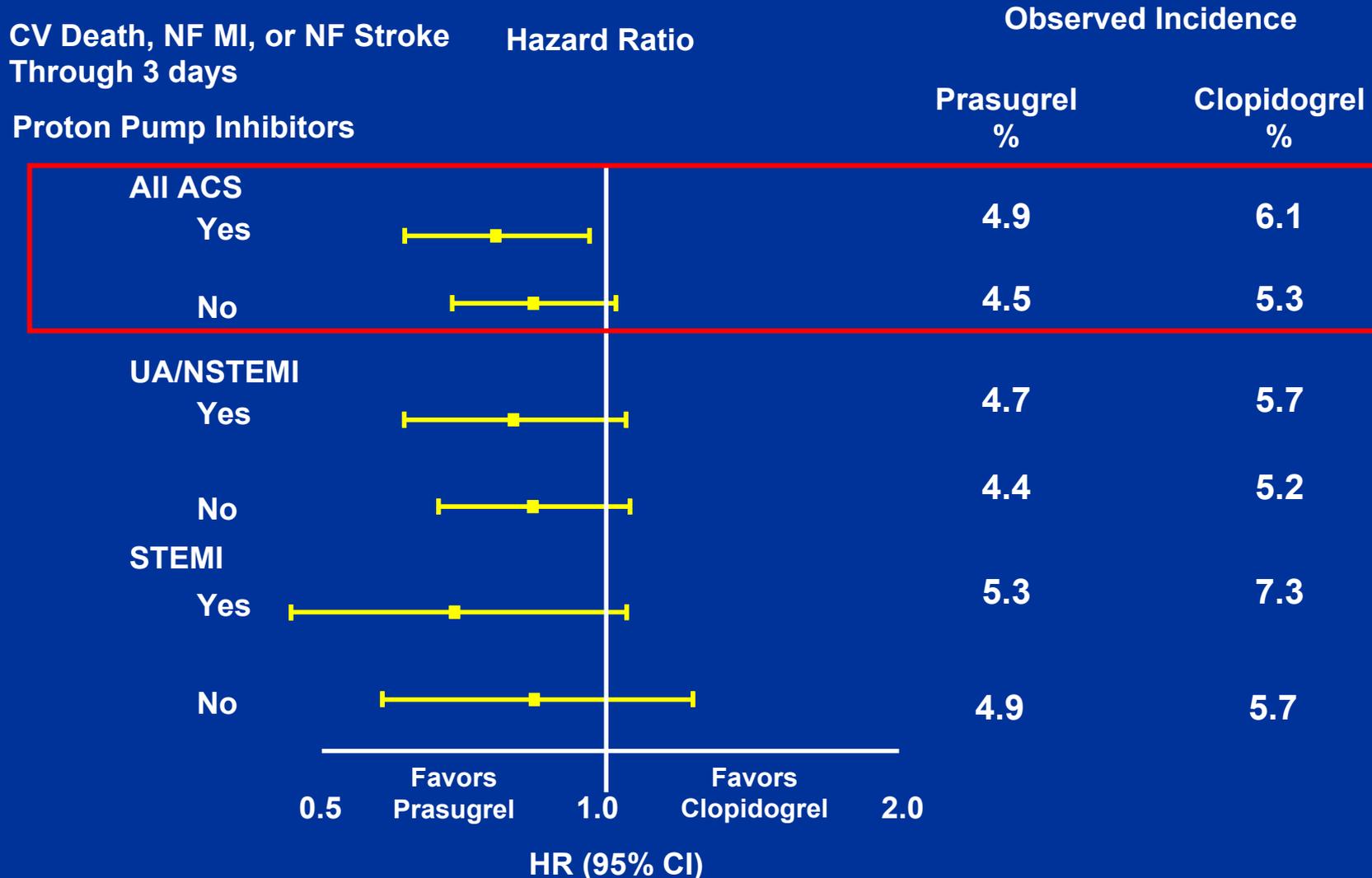
# Effect of Partial Conversion on Absorption of a 60-mg Prasugrel LD with Lansoprazole



# Pharmacodynamic Responses Following 60 mg Prasugrel or 600 mg Clopidogrel LDs With and Without PPI – PRINCIPLE-TIMI 44



# Primary Endpoint Through 3 days With and Without PPI Use – TRITON-TIMI 38

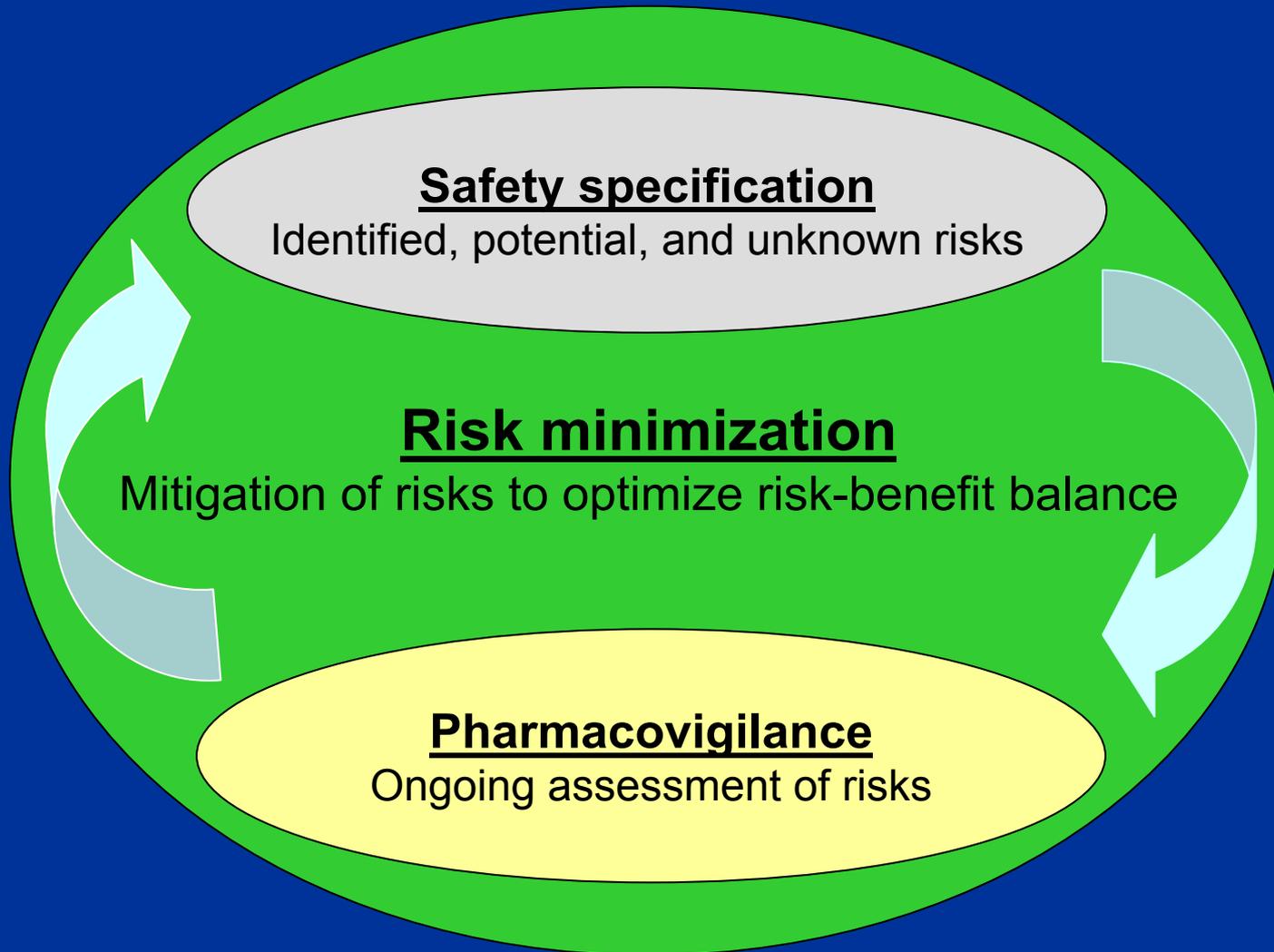


# Proposed Product Attributes

- ◆ PK/PD demonstrated equivalent extents of absorption between tablets with low base content and those with base content within the range used in TRITON-TIMI 38
- ◆ To-be-marketed tablets will have controlled base content
- ◆ The dose, purity, stability, and appearance is not affected by the base content
- ◆ Proposed label statement:
  - Section 11. Description; “During manufacture and storage, partial conversion from salt to base may occur.”
  - Section 16.2 Storage and Handling; “Dispense product in original container.”

# Risk Management for Prasugrel

# Components of Risk Management



# Safety Specification

- ◆ **Identified risks: bleeding, with increased risk in subgroups**
  - **History of TIA/stroke**
  - **Very elderly**
  - **Low body weight**
  - **Undergoing urgent surgery including CABG**
  - **Concomitant medications leading to increased bleeding risk**
- ◆ **Other events for focused follow up**
  - **Neoplasm**
  - **Thrombocytopenia including thrombotic thrombocytopenic purpura (TTP)**
  - **Leukopenia/ neutropenia/ agranulocytosis**
  - **Photosensitivity**

# Risk Minimization - Communication Plan

- ◆ **Content defined by safety specification**
  - **US Package Insert**
  - **Patient Medication Guide**
  - **HCP communications**
- ◆ **Targeted HCP groups defined by windows of risk**
  - **Cardiologists – treatment initiation and maintenance**
  - **PCPs and other HCPs – treatment maintenance**

# Risk Minimization - Letter to Healthcare Professionals at Launch

- ◆ **Broad coverage to HCPs who treat ACS PCI patients or assist in risk communication**
  - **Interventional and clinical cardiologists (> 10,000)**
  - **Primary care physicians (> 25,000)**
  - **Hospitals with cath labs (> 800)**
  - **Commercial/trade pharmacists (> 30,000).**
- ◆ **Emphasizing**
  - **Indicated population**
  - **Contraindications and warnings**
  - **Benefit-risk in subpopulations**
  - **Management of bleeding risks**

# Prescriber Brochure

- ◆ **Emphasizing risk management**
- ◆ **Distributed to prescribers during first contact within the initial post-launch period**
- ◆ **Broad coverage to HCPs who treat ACS PCI patients or assist in risk communication**

# Pharmacovigilance Plan

- ◆ **Assessment of spontaneous and clinical trial adverse event reports**
- ◆ **Automated Signal Detection in spontaneous report databases (eg, FDA Adverse Event Reporting System)**
- ◆ **Aggregate data reviews and periodic safety reporting to agencies**
- ◆ **Pharmacoepidemiology studies in US and EU**
- ◆ **Information from prospective clinical research**

# Prospective Clinical Research

- ◆ **Randomized controlled trial TRILOGY**
  - Prasugrel vs clopidogrel for medically managed ACS
  - > 10,000 patients globally, treated for up to 30 month
  - 5 mg used in very elderly and low body weight
  - Neoplasm focused data collection
- ◆ **US prospective observational study**
  - Standardized prospective capture of patient level effectiveness and safety outcomes in a large naturalistic study
  - Link from inpatient to outpatient data (up to 18 month)

# Closing Remarks

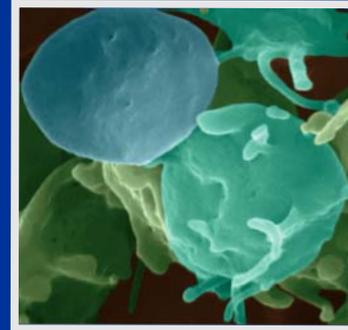
**Eugene Braunwald, M.D.**

**Hersey Distinguished Professor of Theory and Practice  
of Medicine, Harvard Medical School  
Chairman, TIMI Study Group, Brigham and Women's  
Hospital**

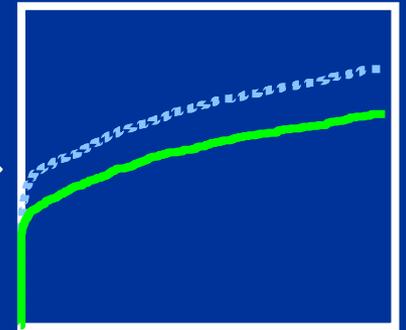
# Response to Thienopyridines



**Prodrug**



**Platelet  
response  
(PD)**



**Clinical  
response**

**Conversion  
to active  
metabolite  
(PK)**



**PK/PD substudies**

**CYP  
Genotypes**

# Public Health Implications

1.6 Million ACS admissions per year in US



850,000 PCIs for ACS per year

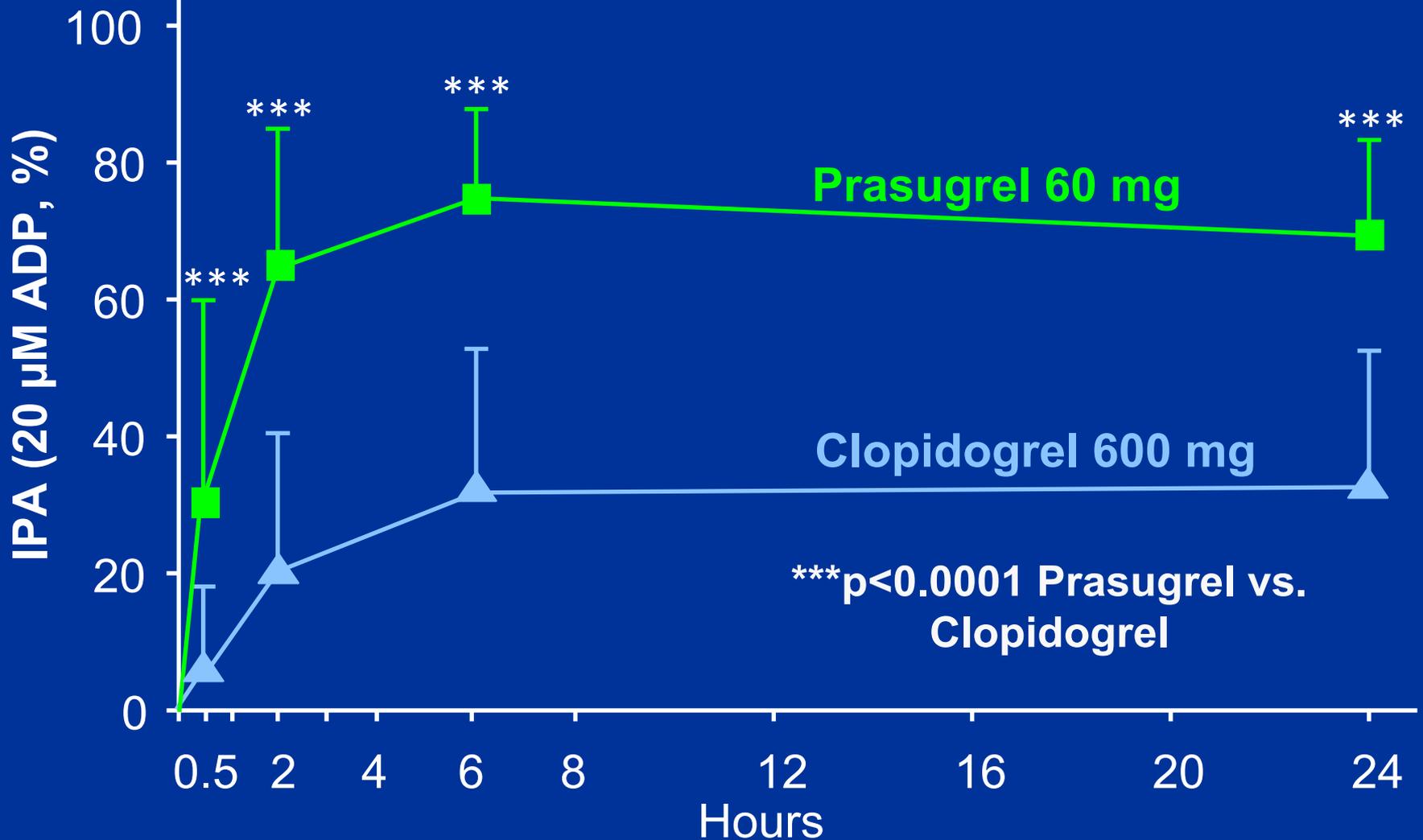


<u>Benefit</u>	<u>Events Per Year</u>	<u>US Cohort</u>
	Myocardial infarctions	23,000
	Urgent target vessel revascularizations	8600
	Stent Thrombosis	7400
	Deaths	4000
<u>Risk</u>		
	Nonfatal major bleed (non CABG)	2300

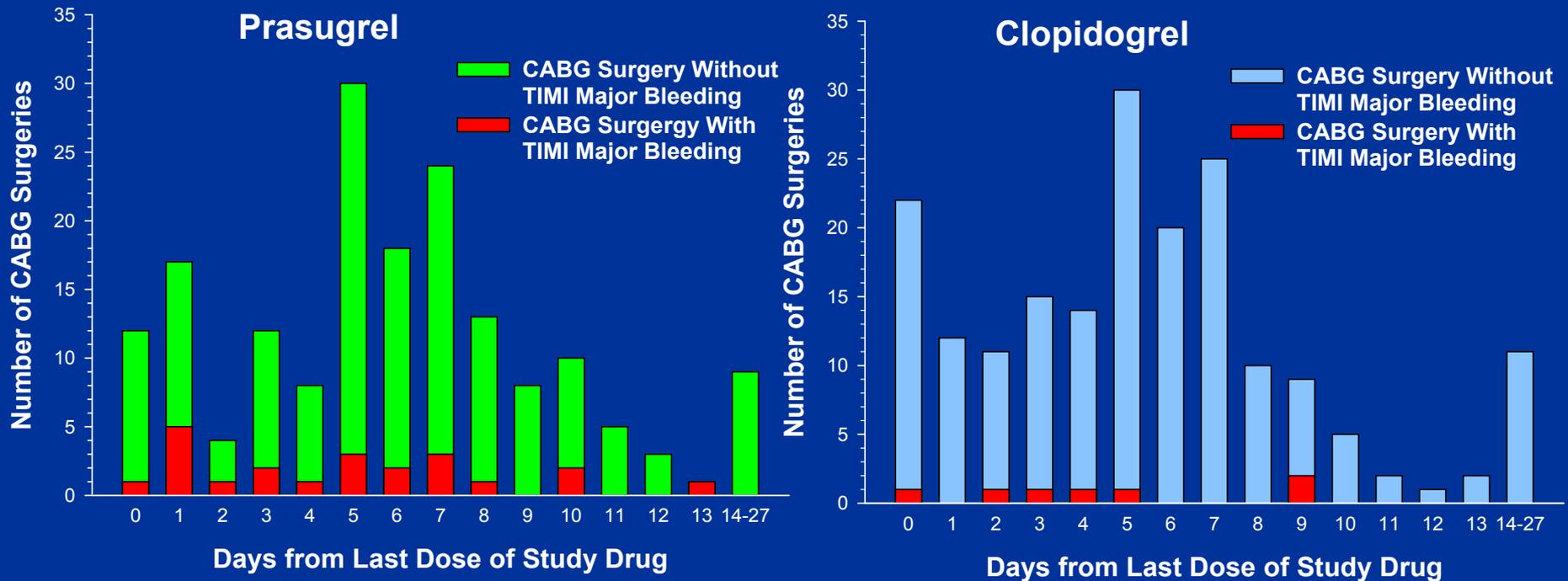
**Back up slides shown**



# Figure 5.5 Loading dose phase inhibition of platelet aggregation (20 $\mu$ M ADP) – PRINCIPLE-TIMI 44.



# Figure 6.29 CABG-related TIMI major bleeding.

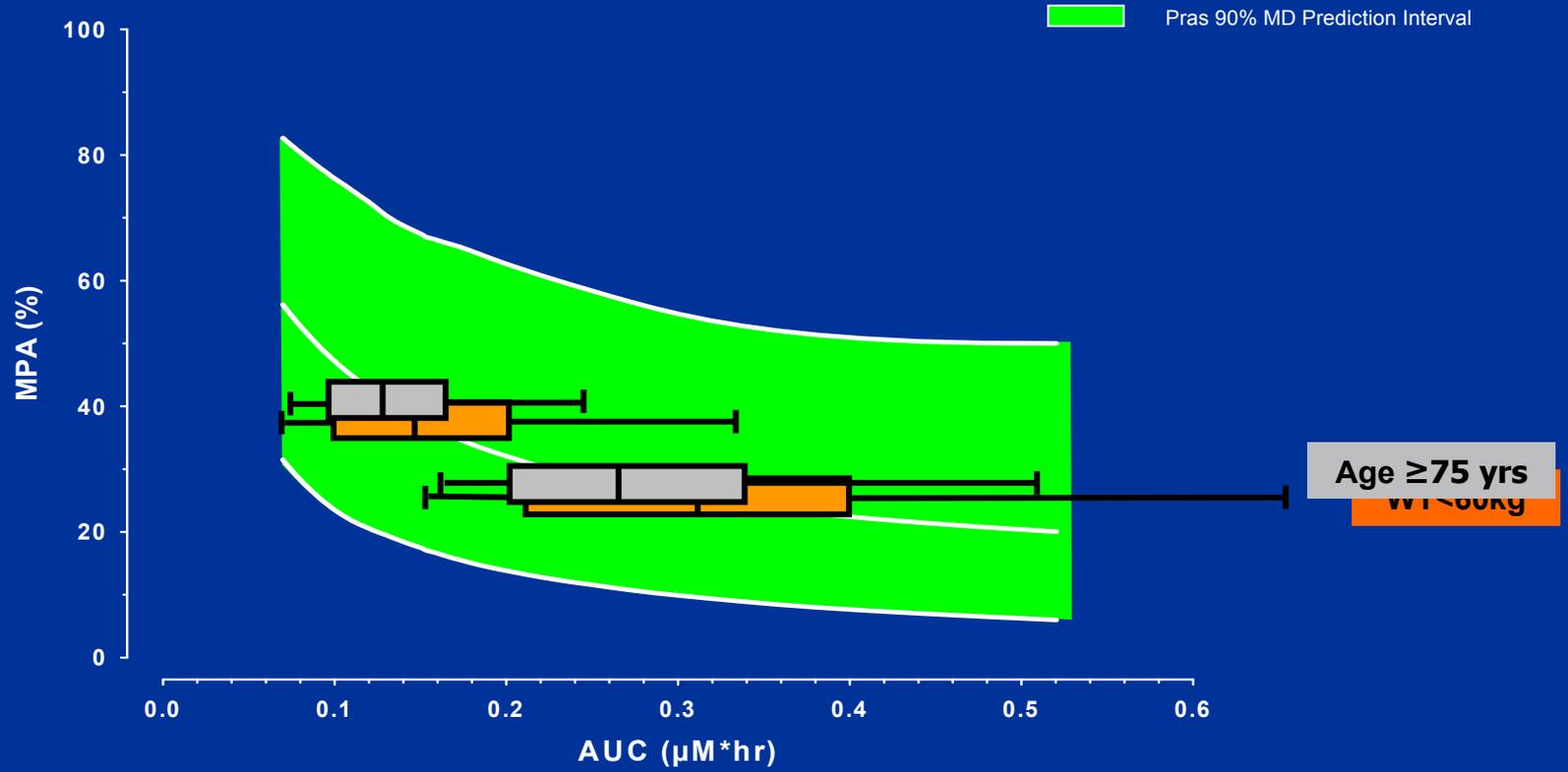


°N = 437 All treated CABG patients. A patient (not included in the graphs below) who was assigned to prasugrel experienced a CABG-related TIMI Major bleeding event 28 days after the last dose of study drug. However, the patient was treated with open-label clopidogrel after discontinuation of study drug until 4 days prior to CABG.

## Table 6.26 CABG All-Cause Mortality CEC Adjudicated – All Treated Patients who Underwent CABG

	Prasugrel % (n/N)	Clopidogrel % (n/N)
Death in patients after CABG	3.3 (7/213)	7.6 (17/224)
Death within 30 days of CABG	1.9 (4/213)	5.8 (13/224)
Death more than 30 days after CABG	1.4 (3/213)	1.8 (4/224)
Death in patients who had CABG within 7 days of last dose of study drug	3.7 (5/134)	9.0 (14/156)

# Relationship Between MPA and Exposure Following Maintenance Dose Administration of Prasugrel

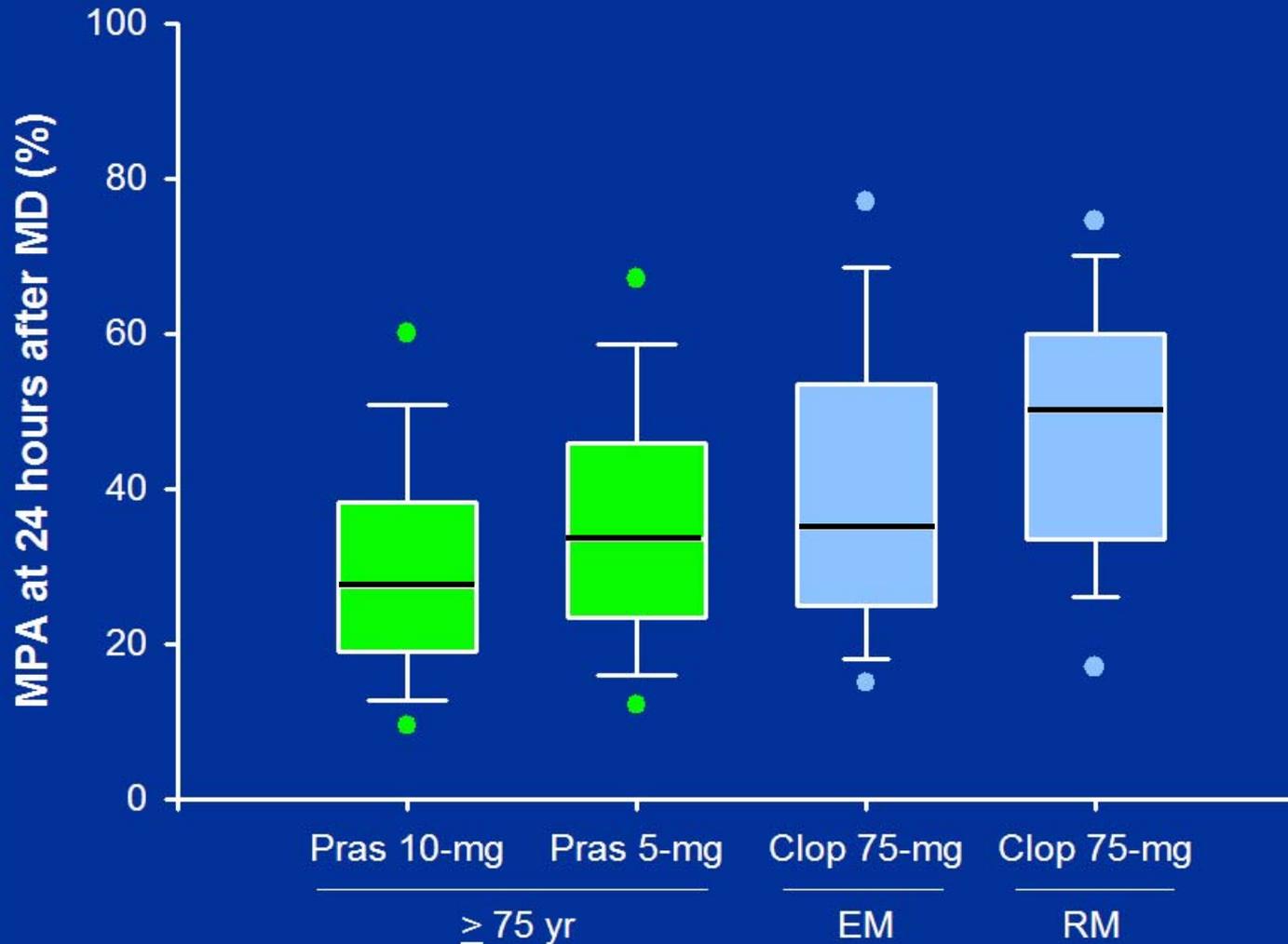


# Percentage of Non-responders with 5-mg Exposure – Dose Adjustment for Elderly

TABR Observed % Non-Responders (<20% IPA)		Predicted* Mean (90% Prediction Interval) % Non-Responders (<20% IPA)		
>60 kg & ≤75 y	>50 kg & <75 y	≥60 kg & <75 y	≥60 kg & ≥ 75 y	≥60 kg & ≥ 75 y
Clopidogrel 75 mg	Prasugrel 10 mg	Prasugrel 10 mg	Prasugrel 10 mg	Prasugrel 5 mg
N=55	N=55	N=996	N=110	N=110
43.0%	4.0%	5.8% (4.6-7.2)	4.8% (1.8-8.2)	8.8% (4.5-13.6)

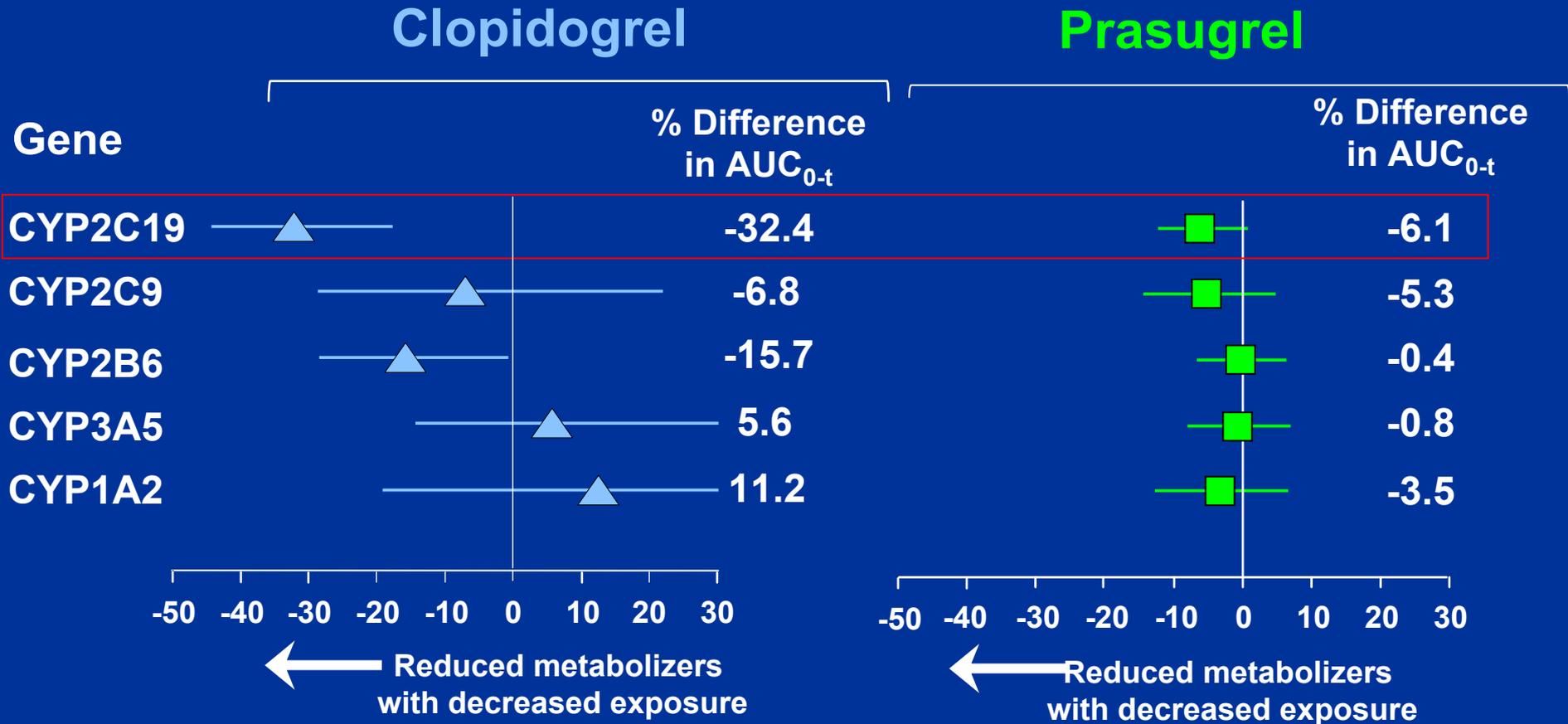
\* Based on 200 simulations

# Predicted MPA During 5 mg MD in Subjects $\geq 75$ Years



EM = extensive metabolizers  
RM = reduced metabolizers

# No Genetic Effect on Pharmacokinetics for Prasugrel



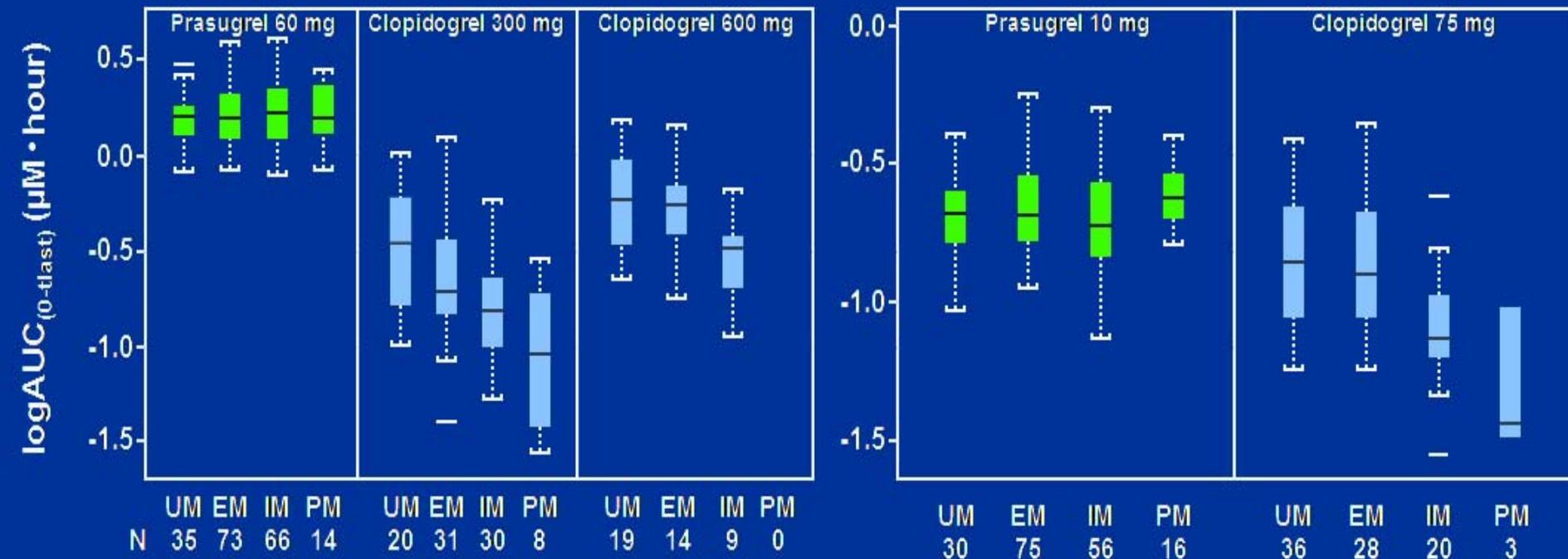
Mega J et al. *NEJM* 2009; 360(4):354-362

Mega JL et al. *Circulation* 2008;118:18(Suppl 2):325-326

# Relationship Between CYP2C19 and Exposure to Active Metabolite

## Loading Doses

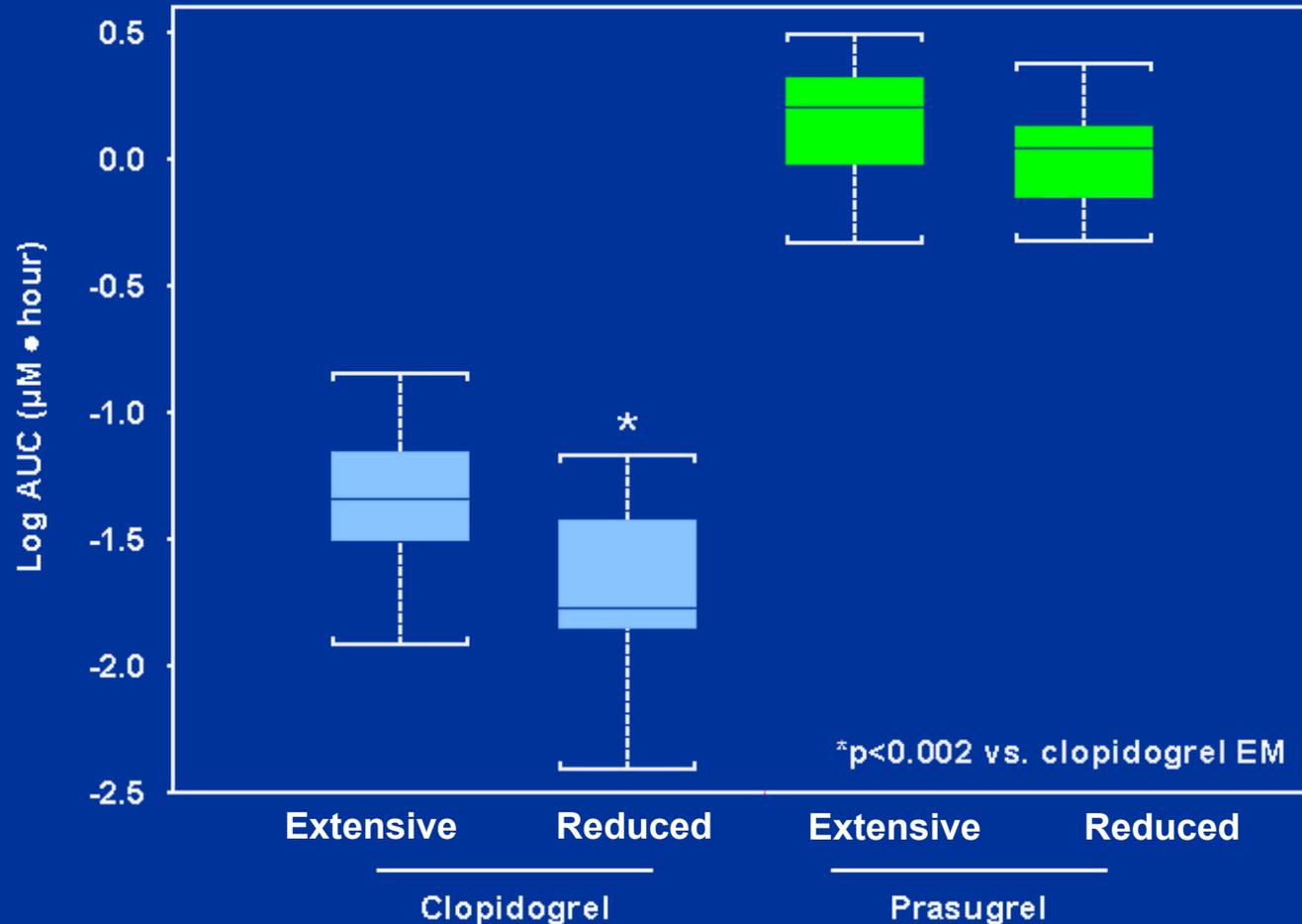
## Maintenance Doses



Box represents median, 25th, and 75th percentiles; whiskers represent the most extreme values within 1.5 times inter-quartile range of the box and individual lines represent outlying values

Close SL et al. *Eur Heart J* 2008;29 (Abstract Supplement):759

# TABR: Active Metabolite Exposure to Prasugrel 60 mg and Clopidogrel 600 mg LD by CYP2C19

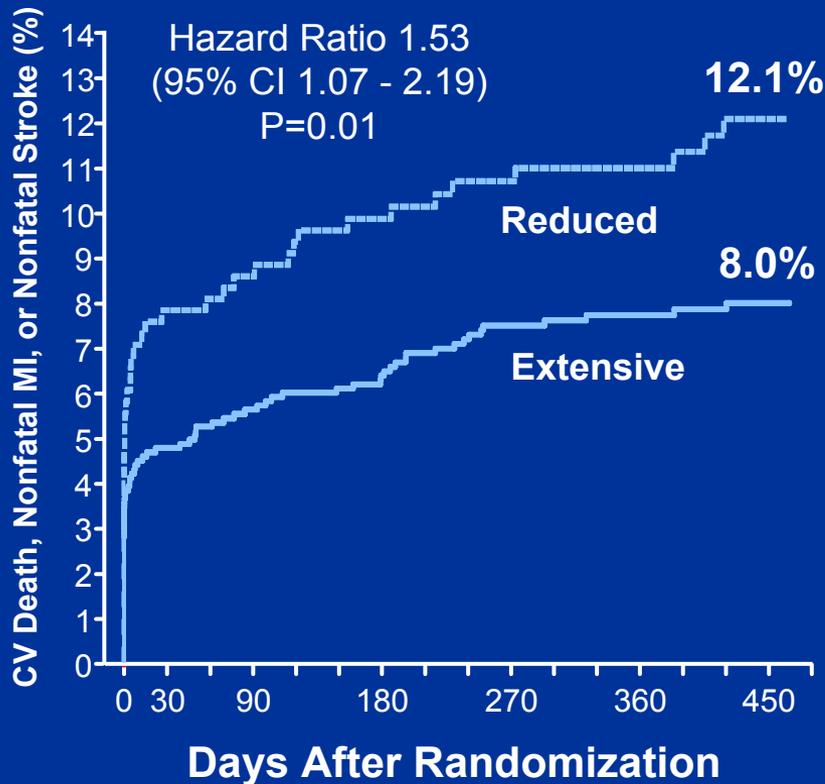


Box represents median, 25th, and 75th percentiles; whiskers represent the most extreme values within 1.5 times inter-quartile range of the box  
 Extensive = patients with genotype predicted to confer normal metabolic function;  
 Reduced = patients with genotype predicted to confer reduced metabolic function

# CYP2C19 Effect on Clinical Outcomes in ACS Patients for Clopidogrel: TRITON-TIMI 38

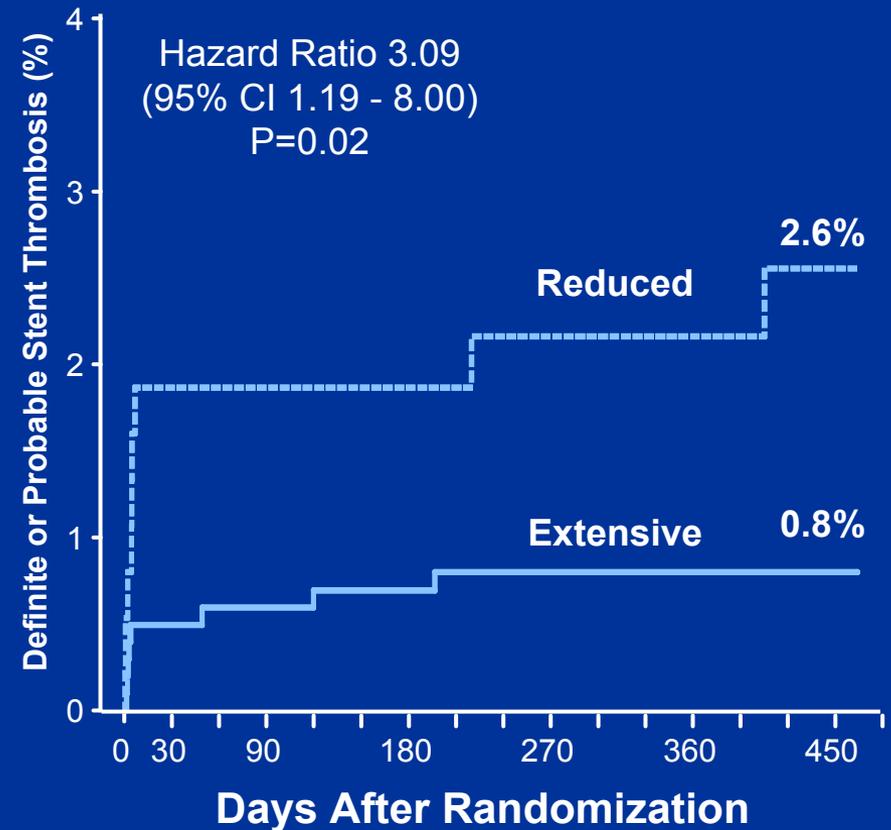
**N=1,459**

Reduced n=395 (27%) Extensive n=1,064 (73%)



**N=1,389**

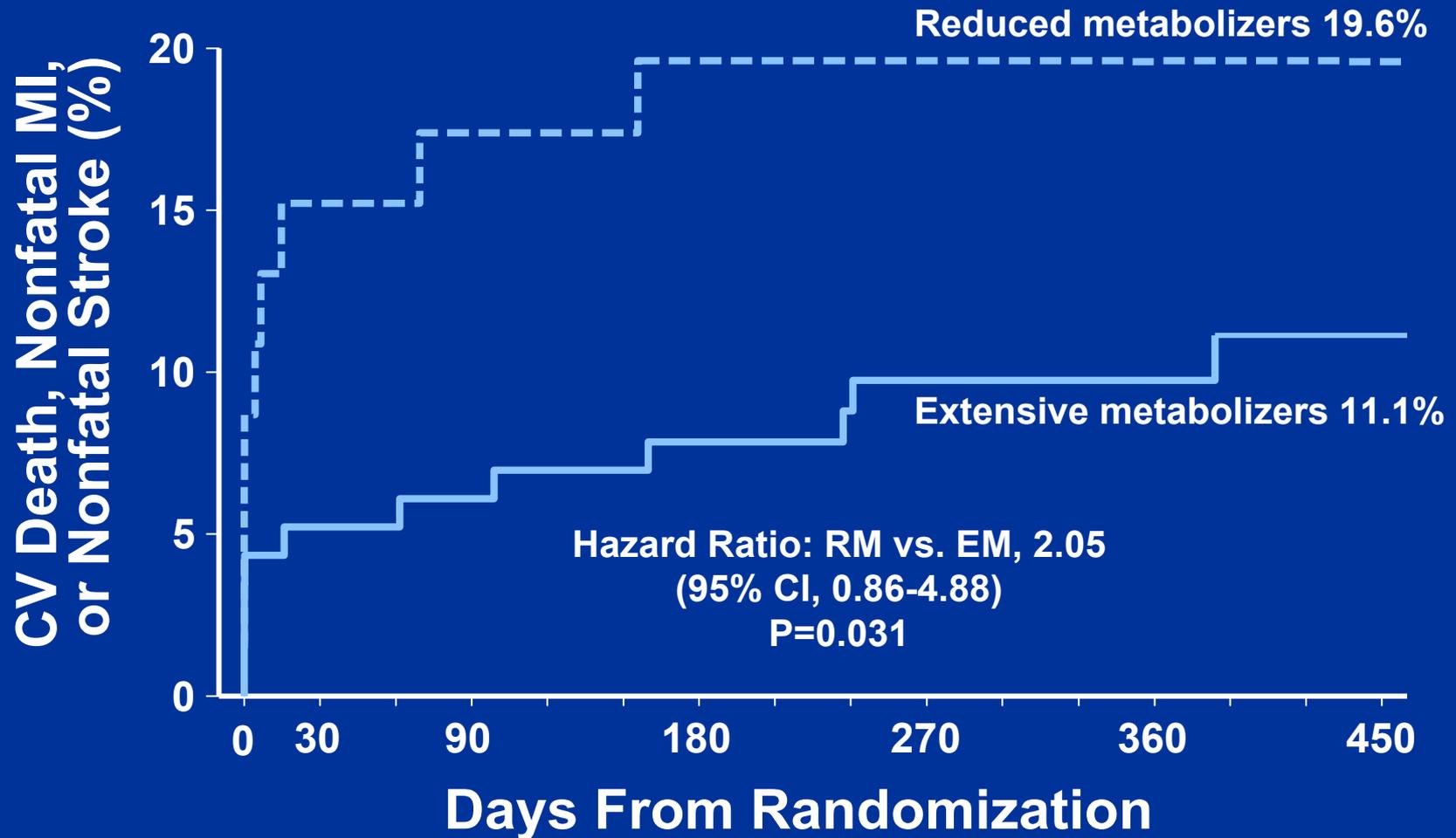
Reduced n=375 (27%) Extensive n=1,014 (73%)



Mega J et al. *NEJM* 2009;360(4):354-362

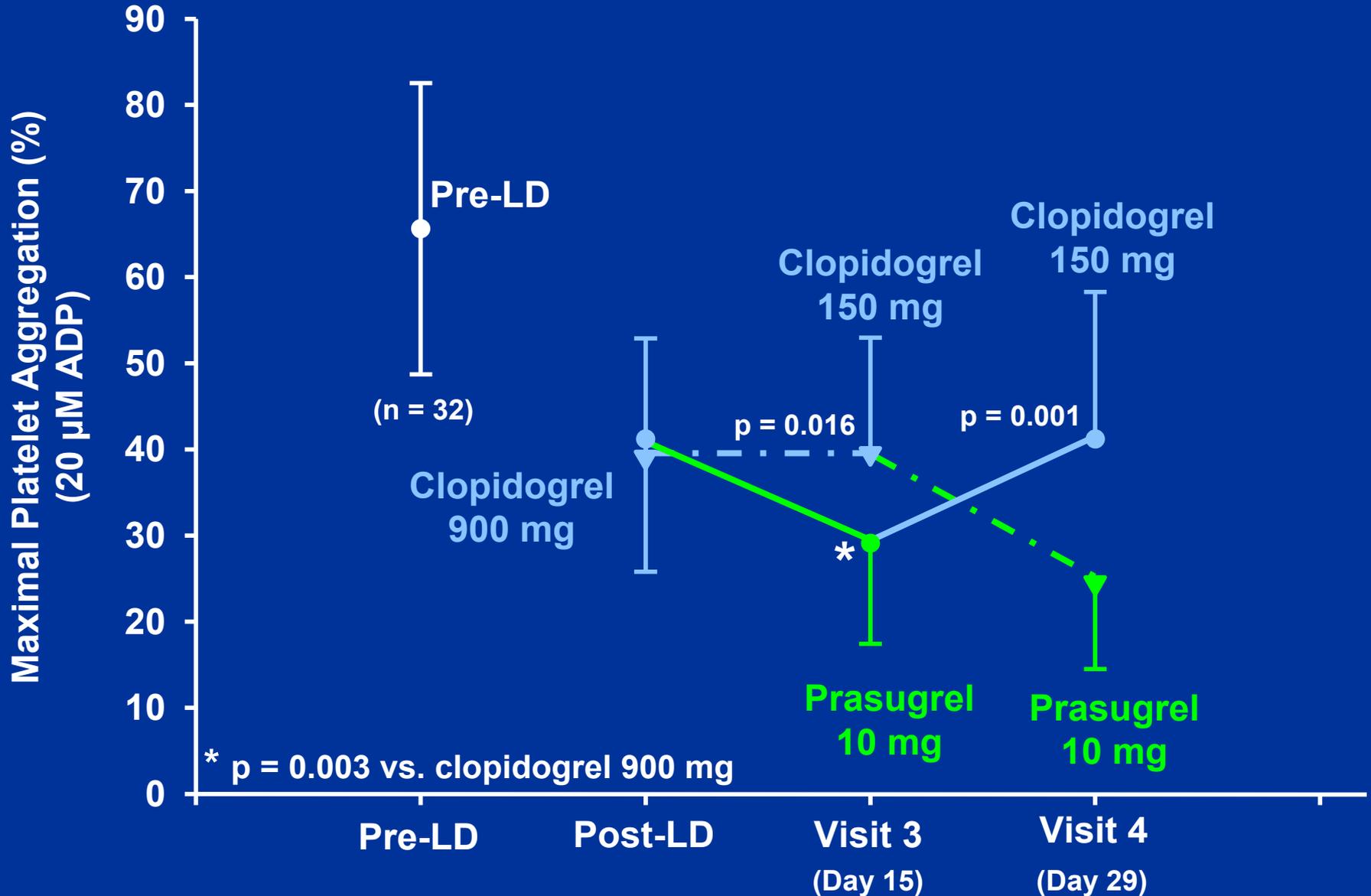
Mega JL et al. *Circulation* 2008;118:18(Suppl 2):S325-S326

# Primary Composite Efficacy Endpoint in Patients $\geq 75$ Years by CYP2C19 for Clopidogrel

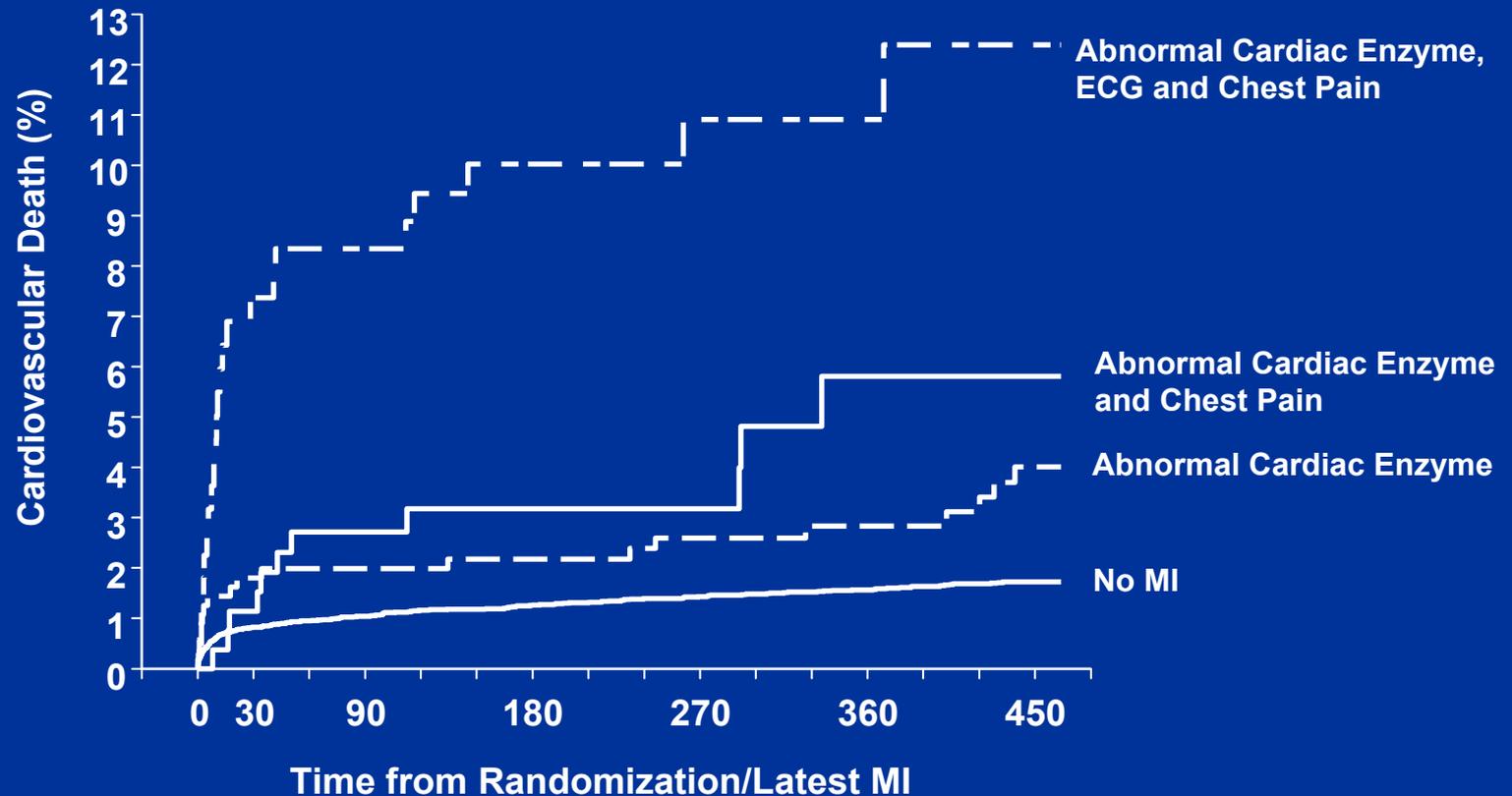


Extensive = patients with genotype predicted to confer normal metabolic function  
 Reduced = patients with genotype predicted to confer reduced metabolic function

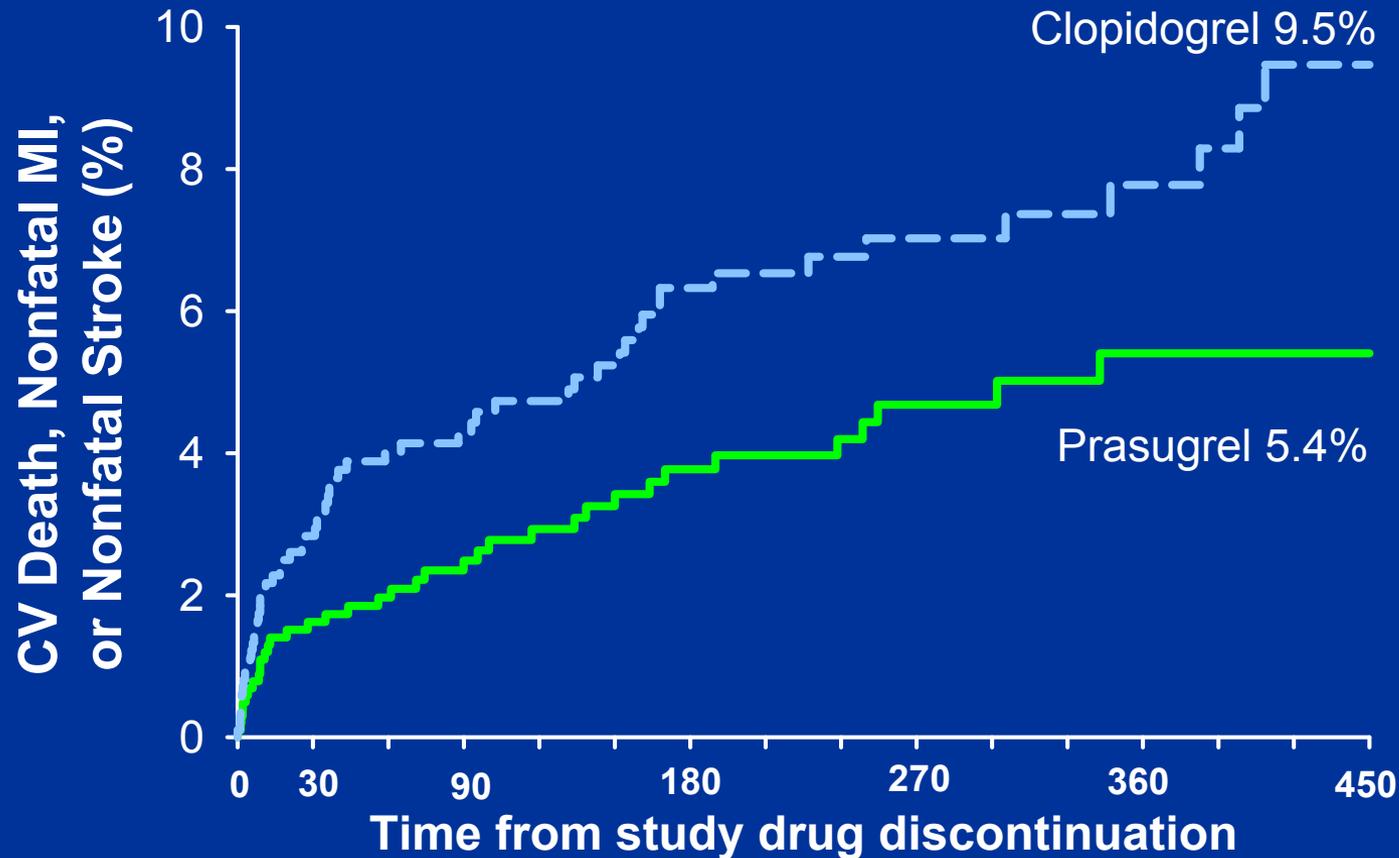
# ACAPULCO Study Results



# Cardiovascular Death by Myocardial Infarction Characteristics: TRITON All ACS



# Primary Endpoint: Time From Study Drug Discontinuation: TRITON – All ACS



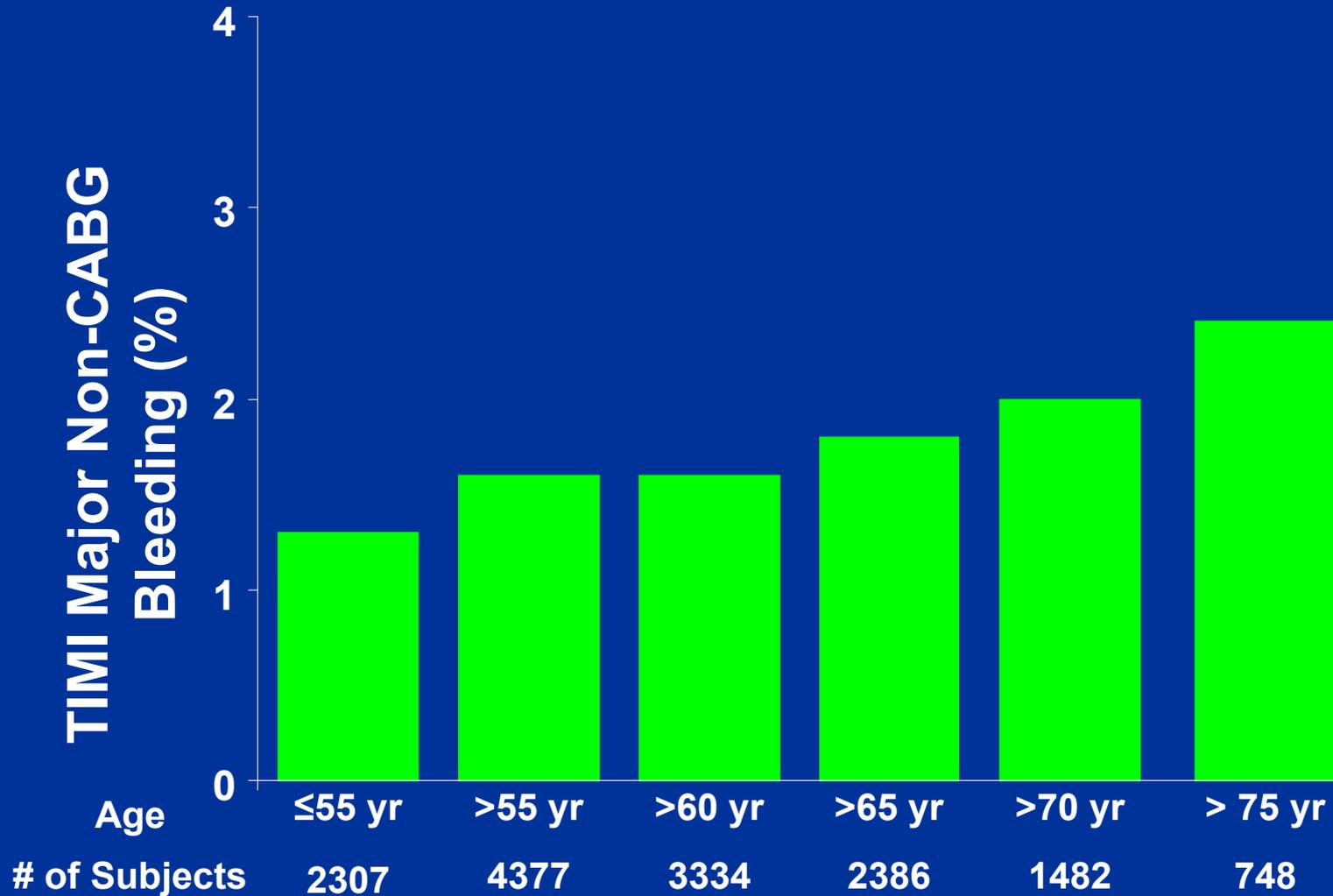
Number at Risk:

	Day 2	Day 4	Day 6	Day 8	Day 10
Prasugrel —	1031	1017	1006	993	977
Clopidogrel - -	995	974	962	950	939

# Odds Ratio for Statistically Significant Risk Factors of Non-CABG-Related TIMI Major Bleeding with Prasugrel

	Prasugrel		
	Point estimate	95% Wald Confidence Limits	p-value
Weight <60 kg	2.768	1.652, 4.640	0.0001
Age ≥75 years	1.805	1.205, 2.704	0.0042
Prior TIA/Stroke	2.623	1.480, 4.649	0.0010

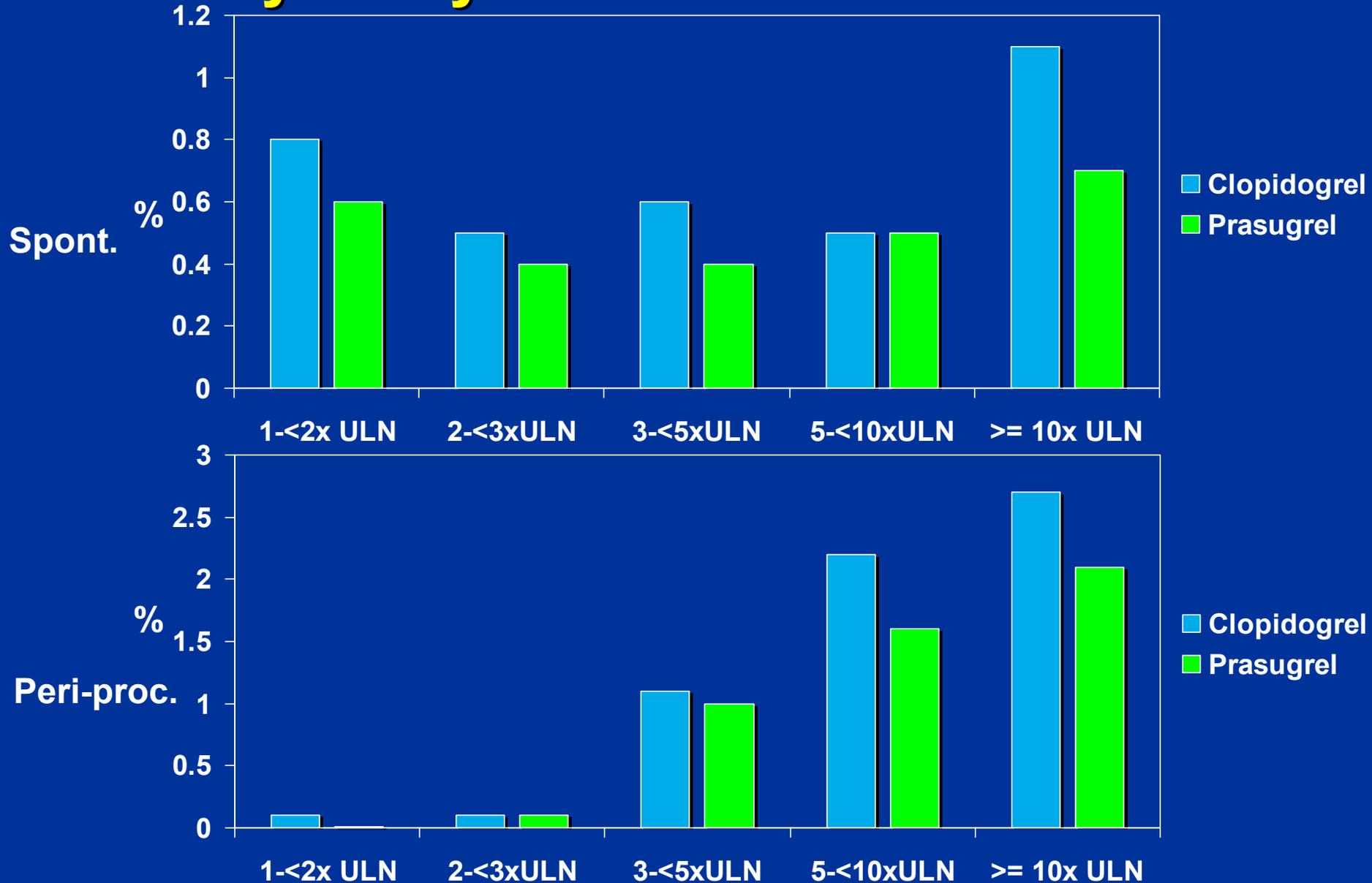
# TIMI Major Non-CABG Bleeding After 3 Day for Prasugrel by Age



# TIMI Major Non-CABG Bleeding After 3 Day for Prasugrel by Weight

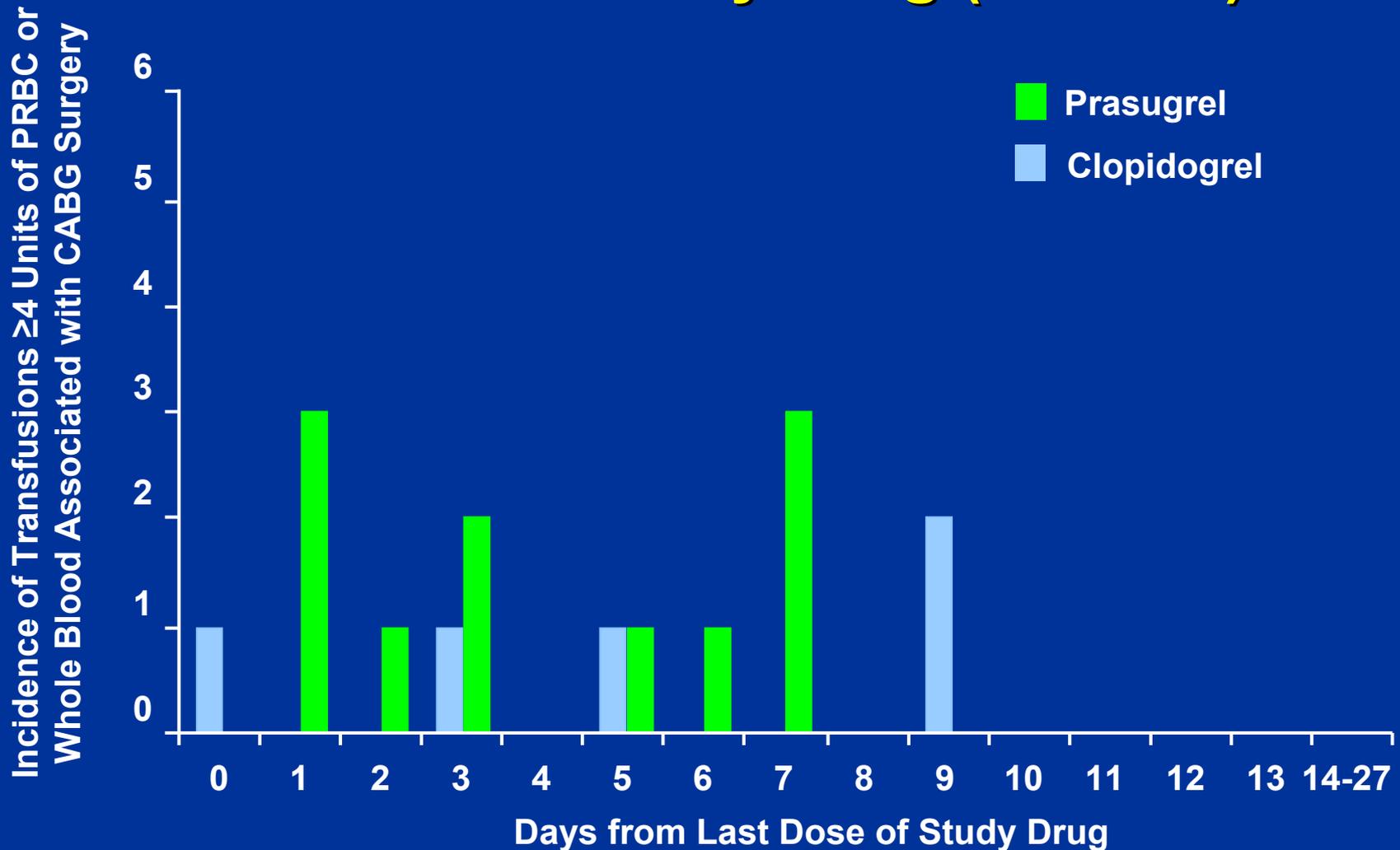


# Efficacy Analysis Peak Biomarker

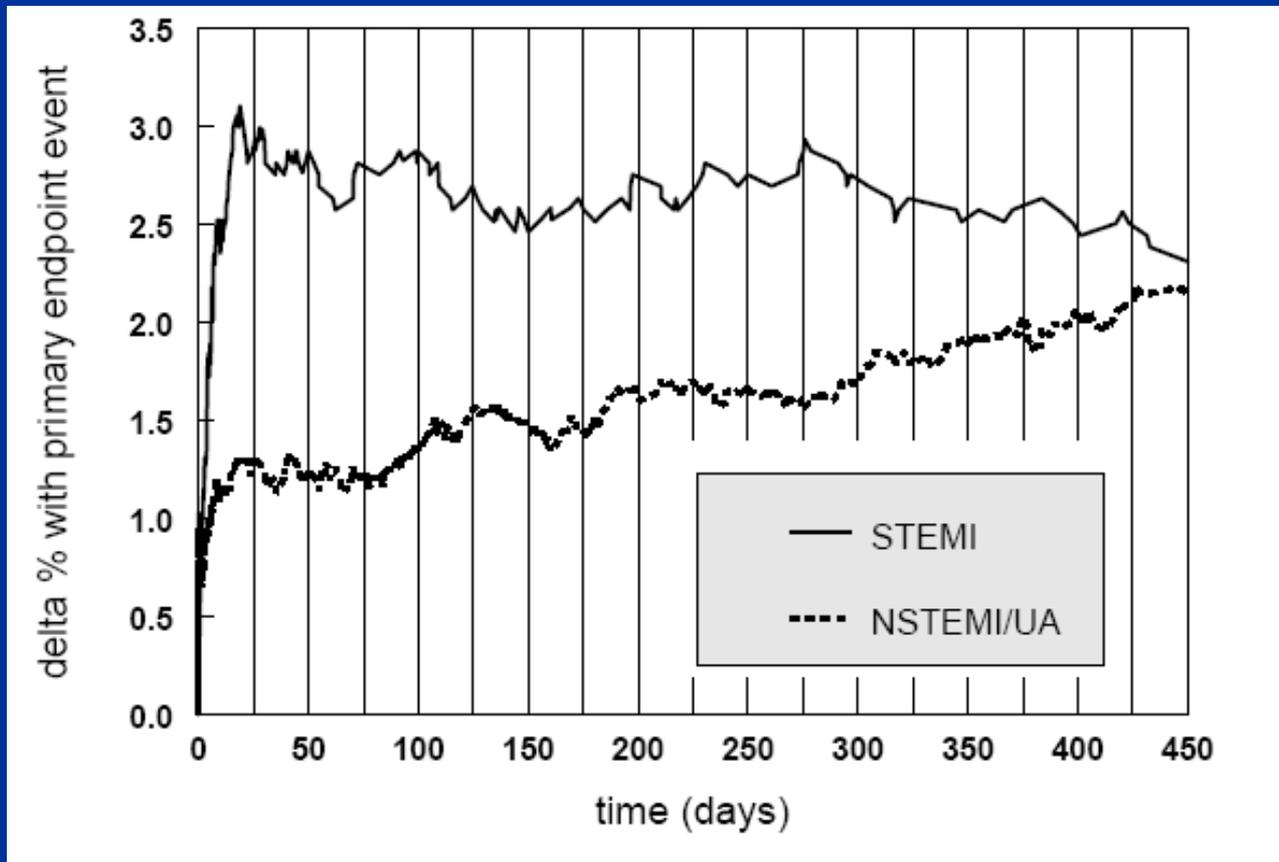


# CABG Surgery and Transfusions

## ≥ 4 Units of PRBC or Whole Blood – Days from Last Dose of Study Drug (All ACS)



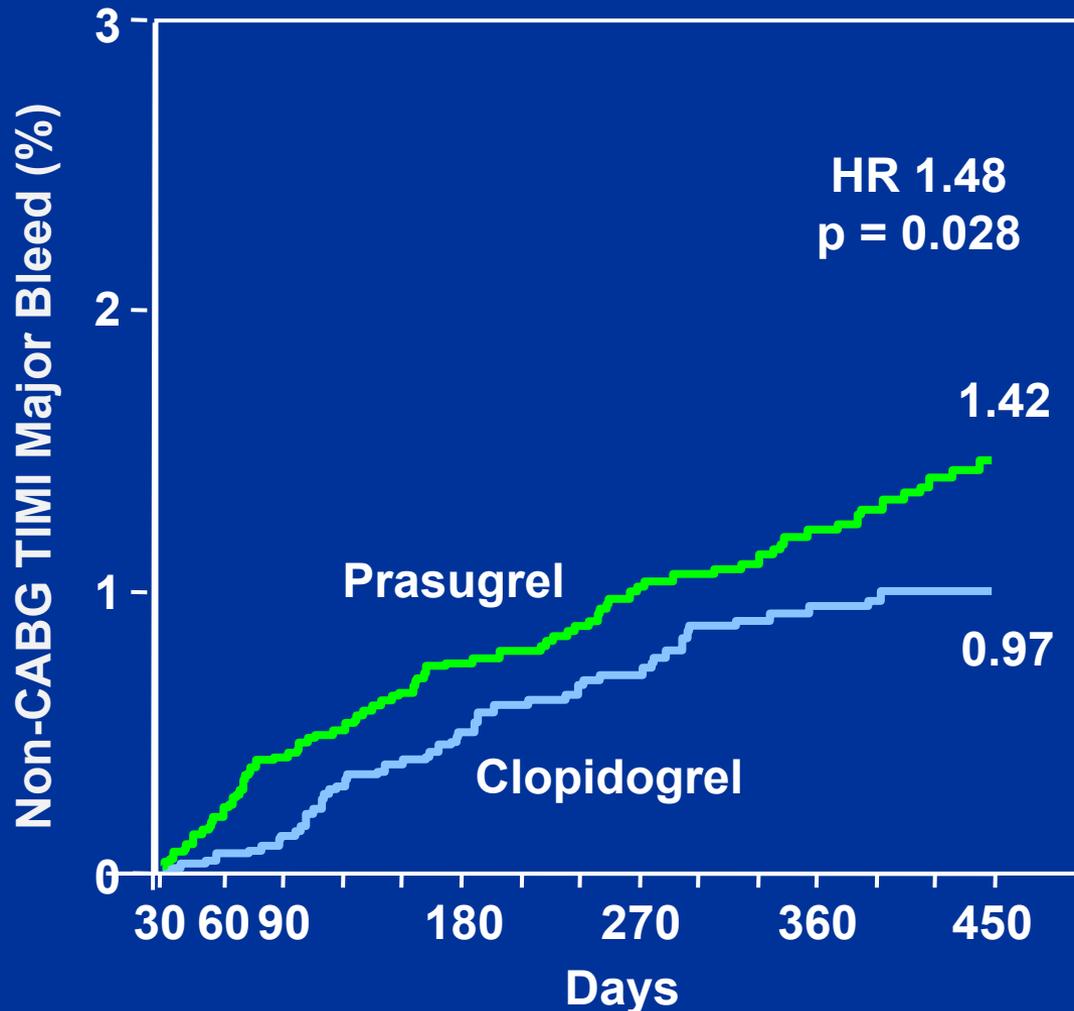
# Figure 7: Kaplan-Meier Estimates of the 1° Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations



# Advantages of Contemporary Therapy

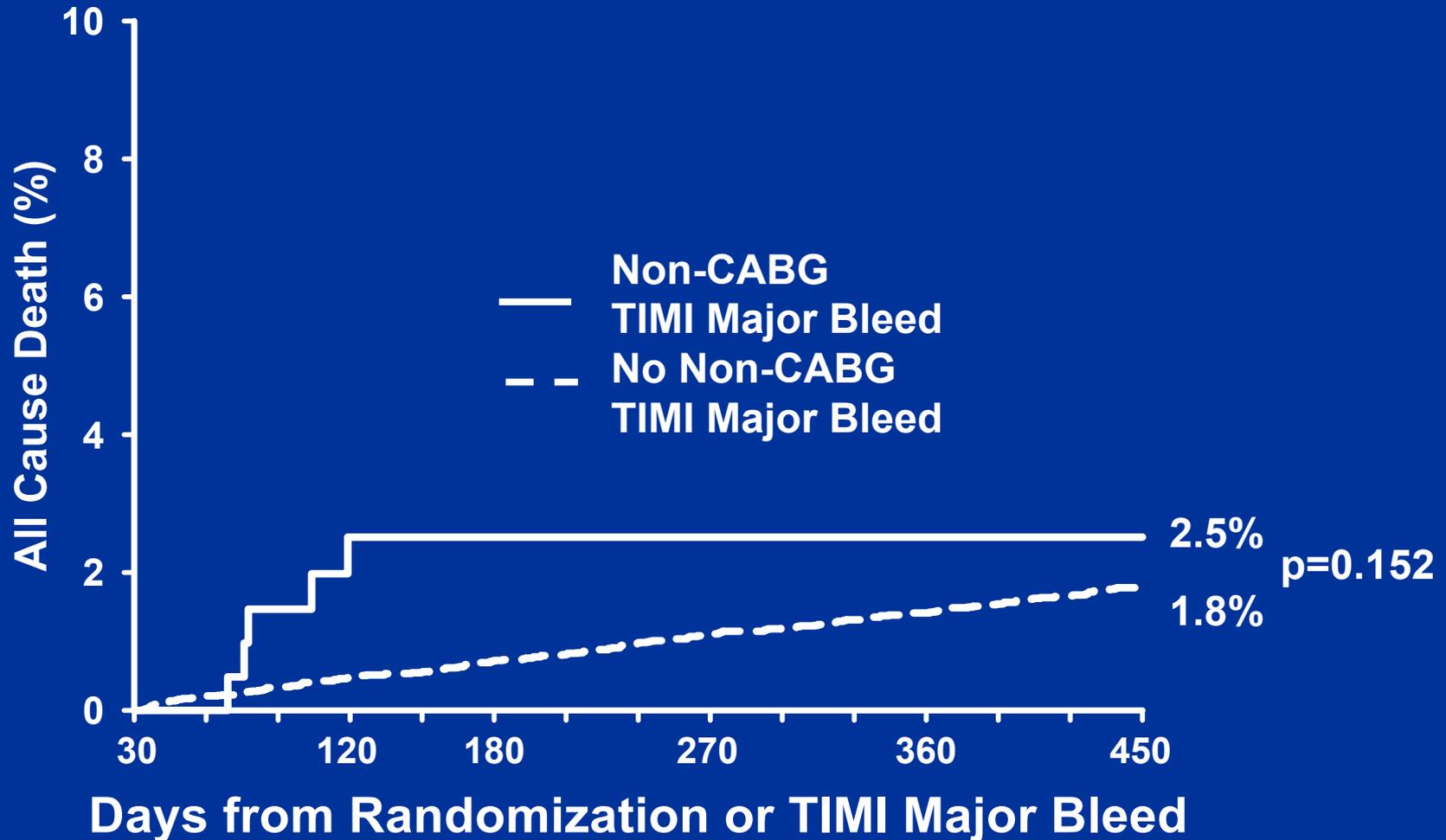
	Prasugrel	Clopidogrel
Loading Dose Practice	Pre-Treatment Not Necessary	Pre-Treatment Recommended Guidance
Wash Out	7-day	5-day Recommended Guidance

# Non-CABG TIMI Major Bleeding 30-Day Landmark – All ACS

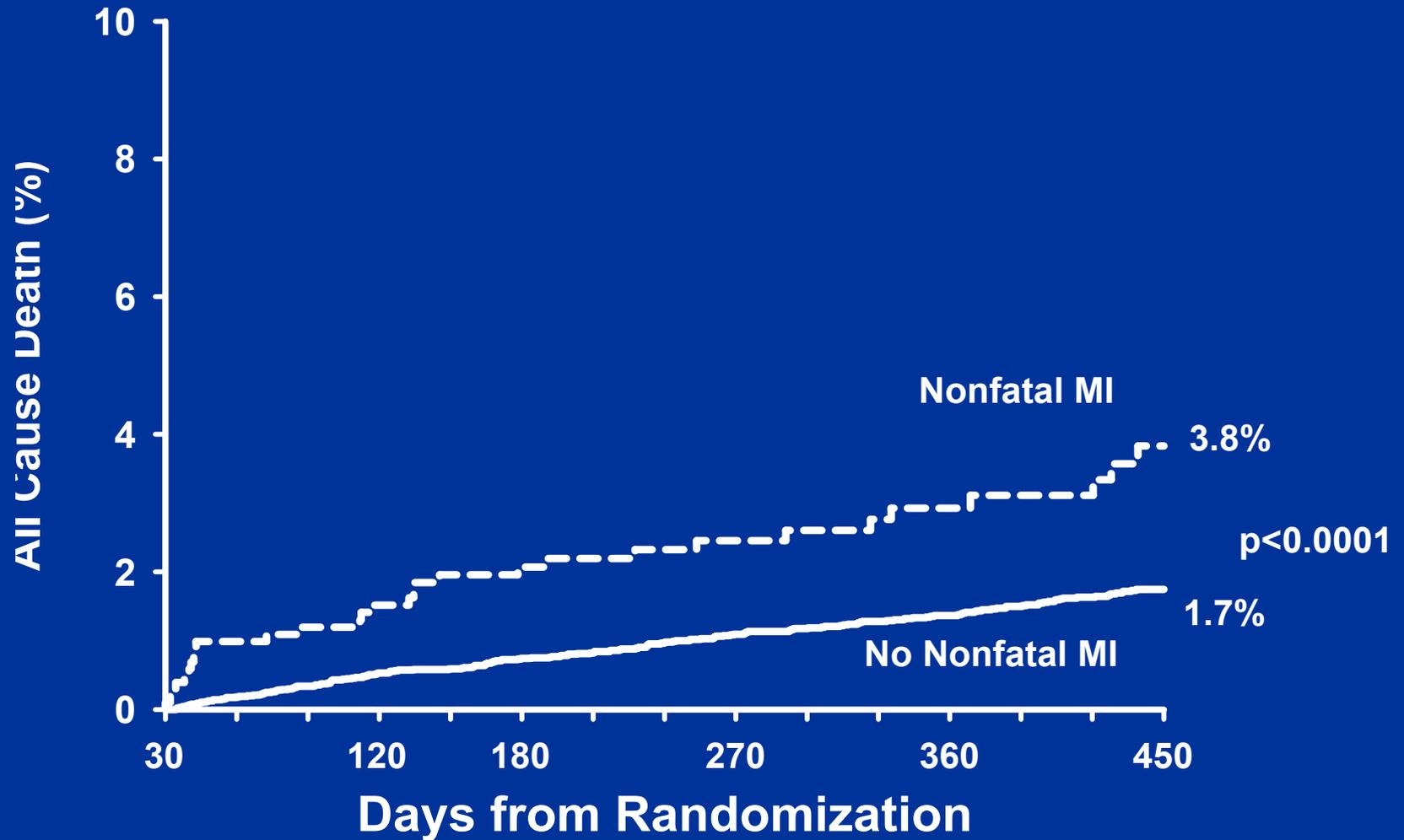


Cumulative Kaplan-Meier estimates of the rates of key study end points during the follow-up period. Trial was not powered for the 30-day landmark analyses.

# All-Cause Death After Non-CABG TIMI Major Bleed – Landmark Analysis (30 Days)

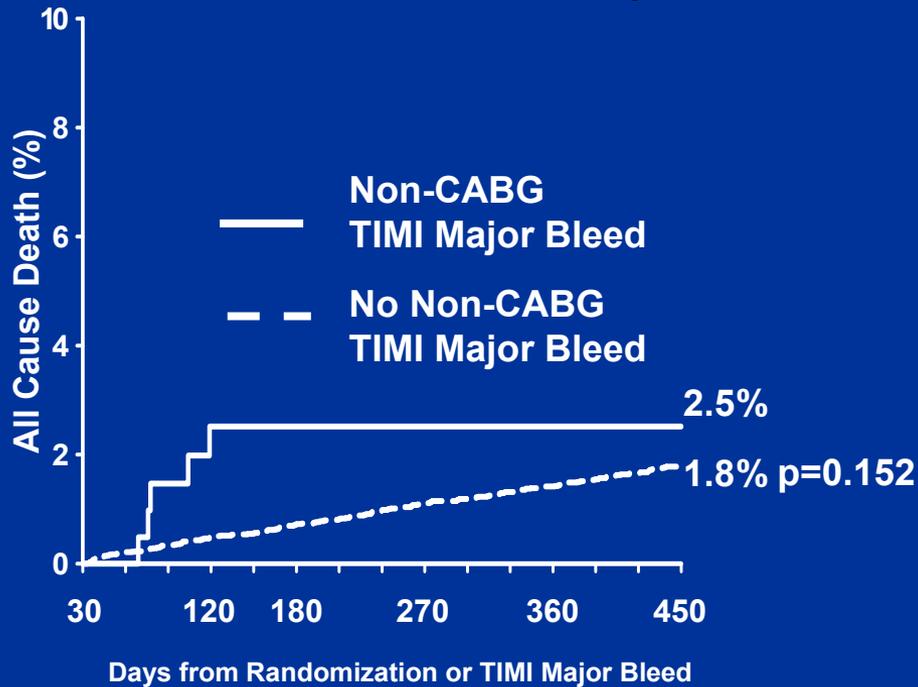


# All-Cause Death After Nonfatal MI – Landmark Analysis (30 Days)

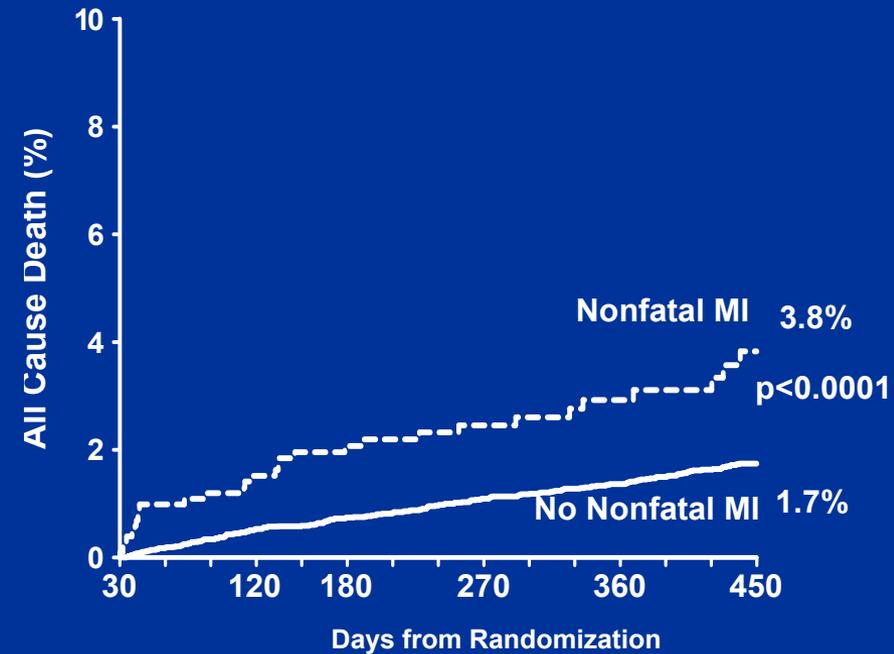


# All-Cause Death Landmark Analysis (30 Days)

## After Non-CABG TIMI Major Bleed



## After Nonfatal MI



# Predicted Exposure and IPA During 5 mg MD in Subjects $\geq 75$ Yrs

