Emerging Approaches to Antiplatelet Therapy for PCI: Prasugrel

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Disclosures

Grant Support/Drugs

- Eli Lilly/Daiichi-Sankyo - Merck/Schering Plough
- Eisai Pharmaceuticals

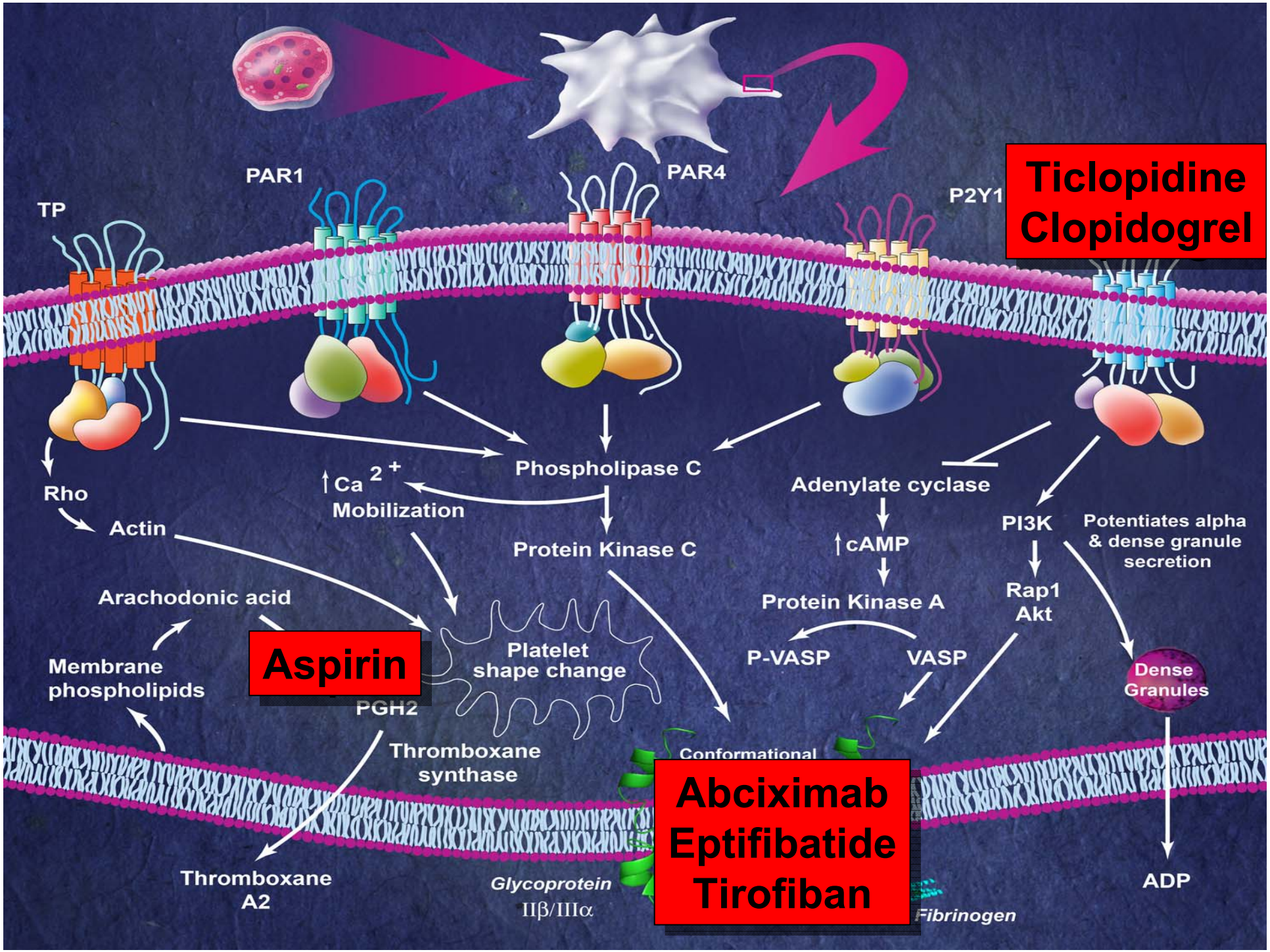
Grant Support/Devices

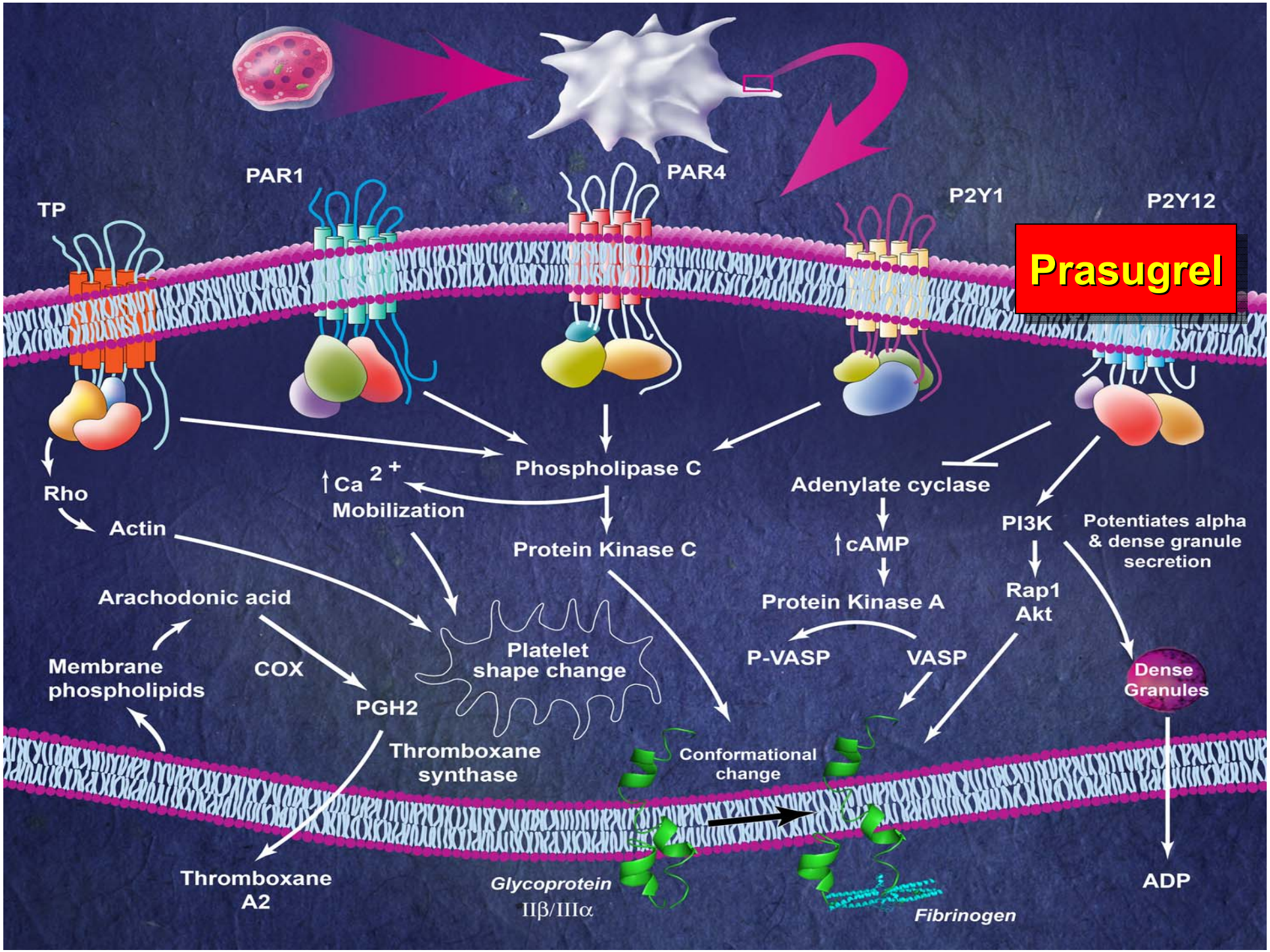
- MedRAD - Boston Scientific
- Edwards Lifesciences - Abbott Vascular
- Medtronic

Consulting/Advisory Boards

- Medtronic - Eli Lilly/Daiichi-Sankyo
- Cordis - Boehringer-Ingelheim

DJC: 4/11


PAR1
PAR4
P2Y1
TP
Ticlopidine
Clopidogrel
Rho
Actin
↑Ca 2 +
Mobilization
Phospholipase C
Protein Kinase C
Adenylate cyclase
↑cAMP
Protein Kinase A
PI3K
Rap1
Akt
Potentiates alpha
& dense granule
secretion
Arachodonic acid
Aspirin
Membrane
phospholipids
PGH2
Platelet
shape change
P-VASP
VASP
Dense
Granules
Thromboxane
synthase
Conformational
Abciximab
Eptifibatide
Tirofiban
Thromboxane
A2
Glycoprotein
IIβ/IIIα
Fibrinogen
ADP


PAR1
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TP
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Prasugrel
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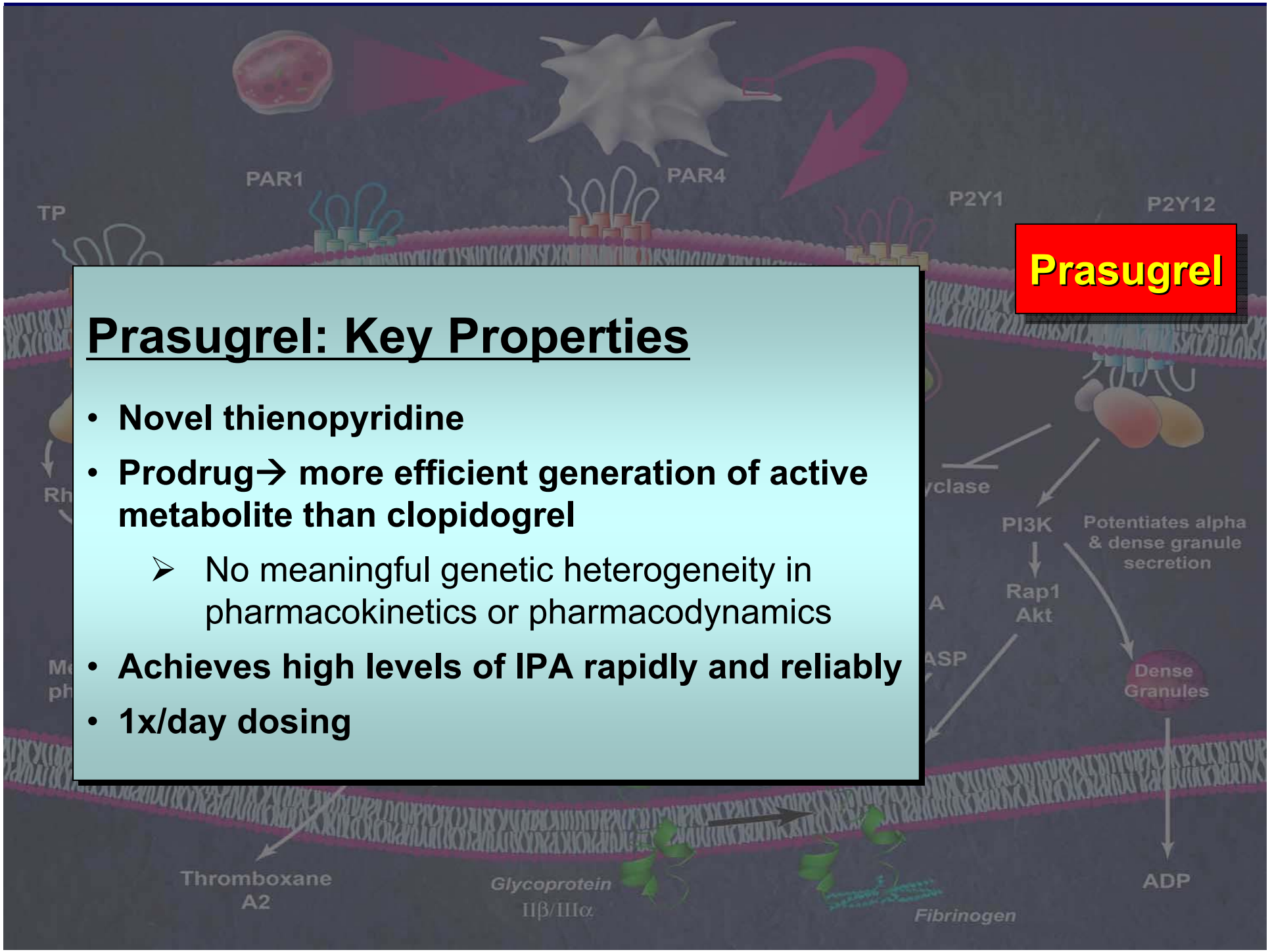
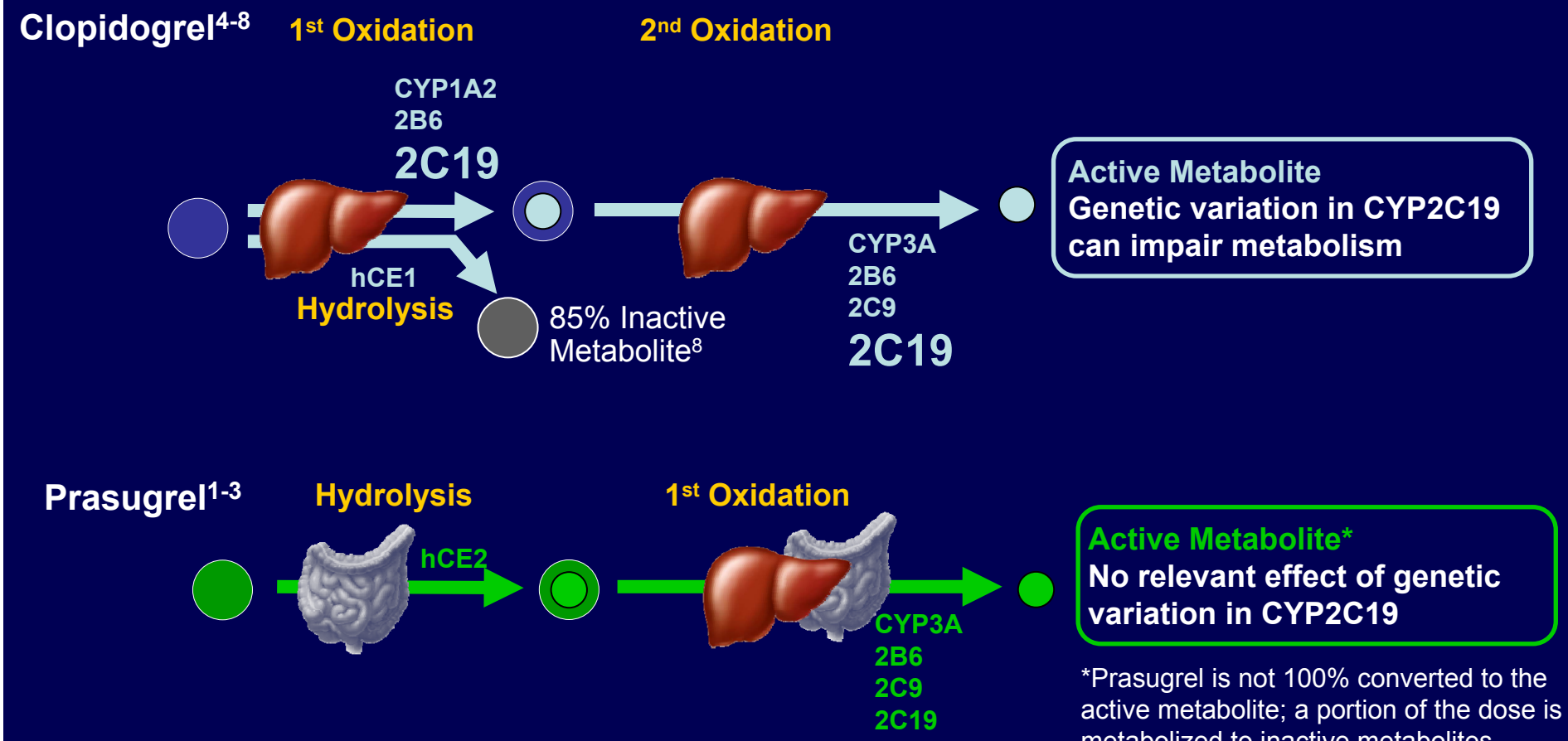


Prasugrel: Key Properties

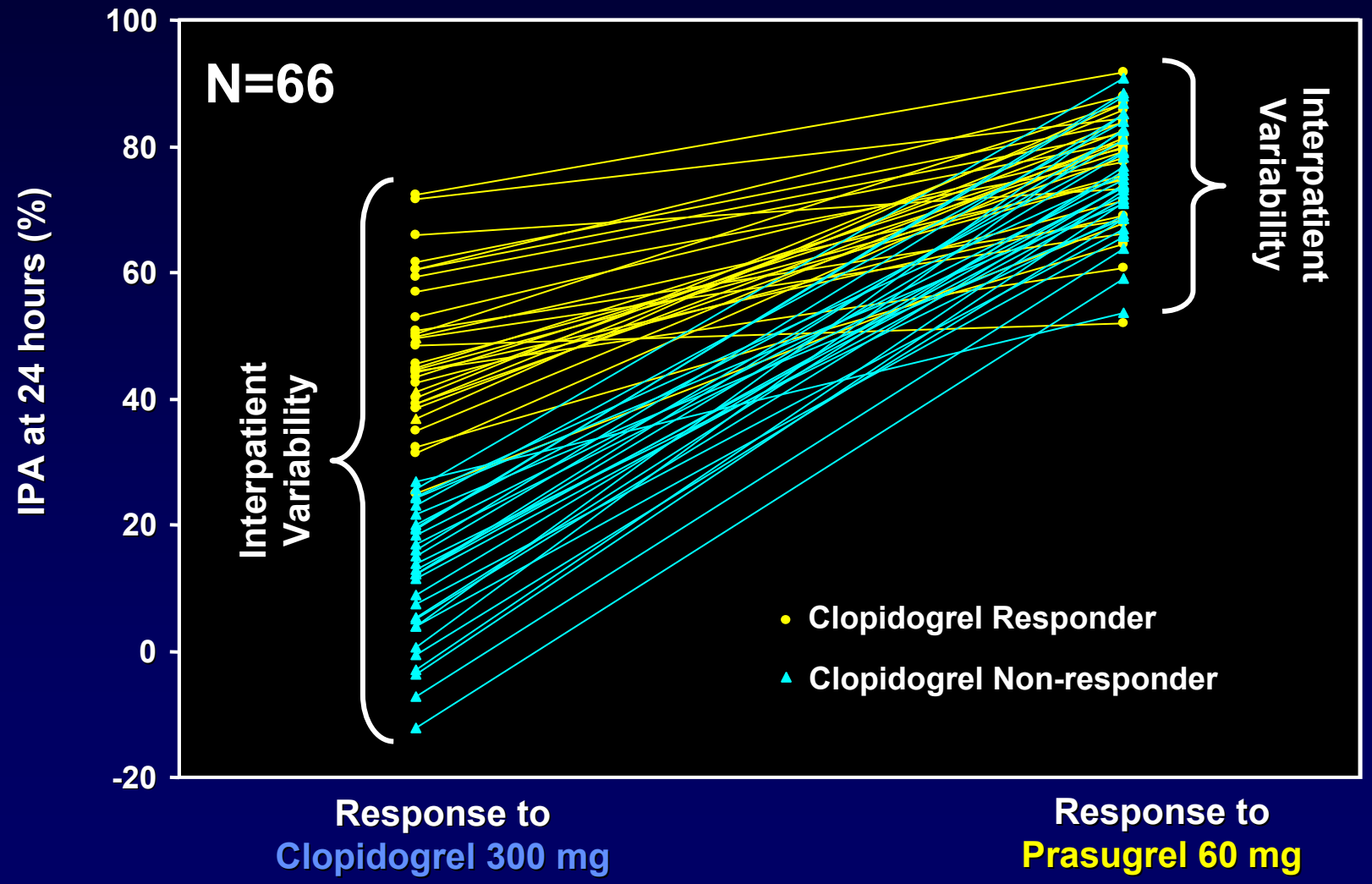
- **Novel thienopyridine**
- **Prodrug→ more efficient generation of active metabolite than clopidogrel**
  - ➢ No meaningful genetic heterogeneity in pharmacokinetics or pharmacodynamics
- **Achieves high levels of IPA rapidly and reliably**
- **1x/day dosing**

Prasugrel vs. Clopidogrel: Active Metabolite Formation



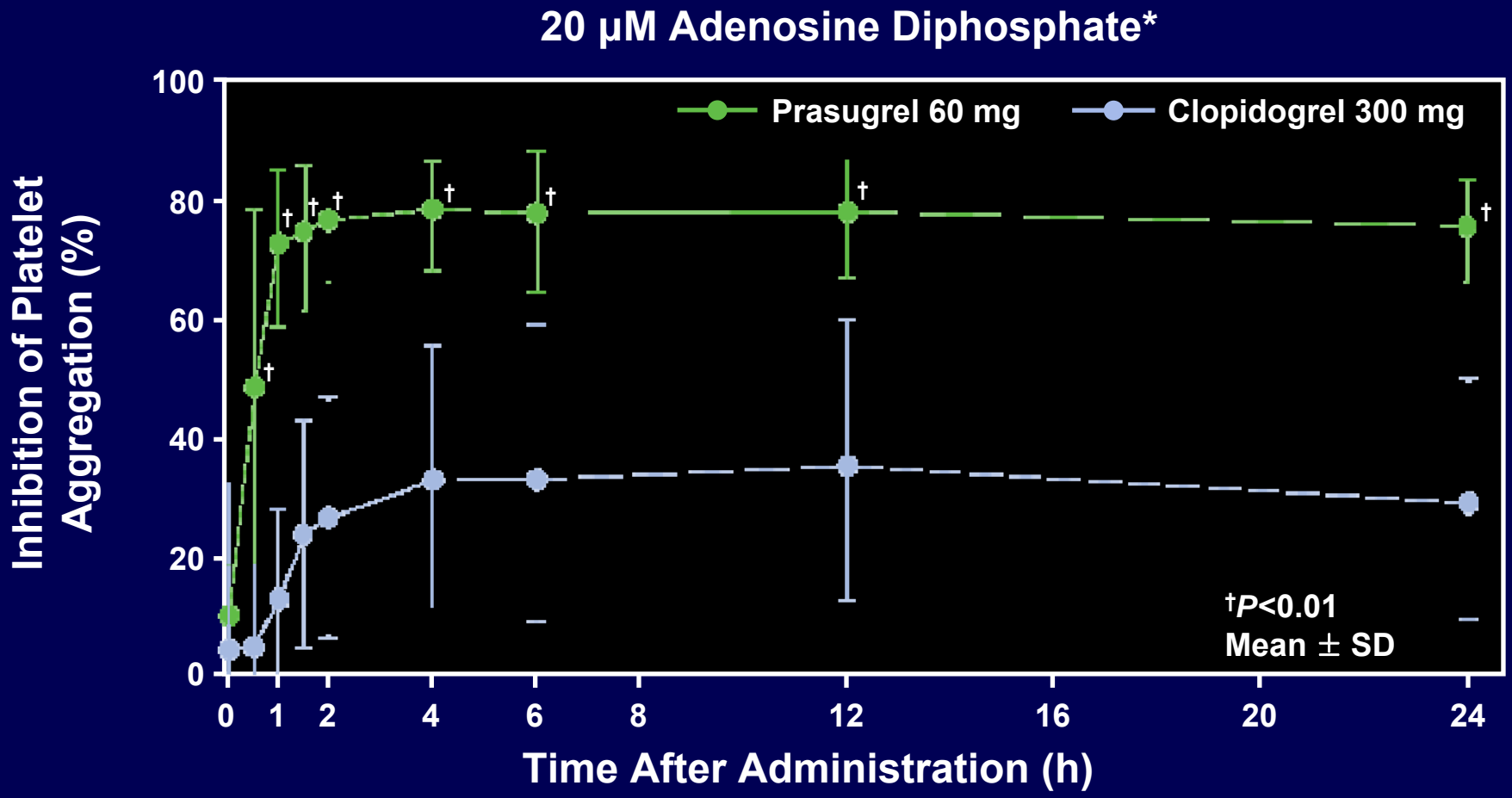
*Prasugrel is not 100% converted to the active metabolite; a portion of the dose is metabolized to inactive metabolites.

Prasugrel vs. Clopidogrel: Healthy Volunteer Crossover Study



From Brandt JT AHJ 153: 66e9,2007

Inhibition of Platelet Aggregation (IPA): Prasugrel and Clopidogrel Loading Dose



The relationship between IPA and clinical activity has not been established.

*Represents healthy subjects in a crossover study who were not on concurrent ASA therapy (n=64).

1. Brandt et al. *Am Heart J.* 2007;153:66.e9-16.
2. Effient Full Prescribing Information.

TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN With Prasugrel (TRITON)-TIMI 38

TRITON-TIMI 38

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 = 14.5 months

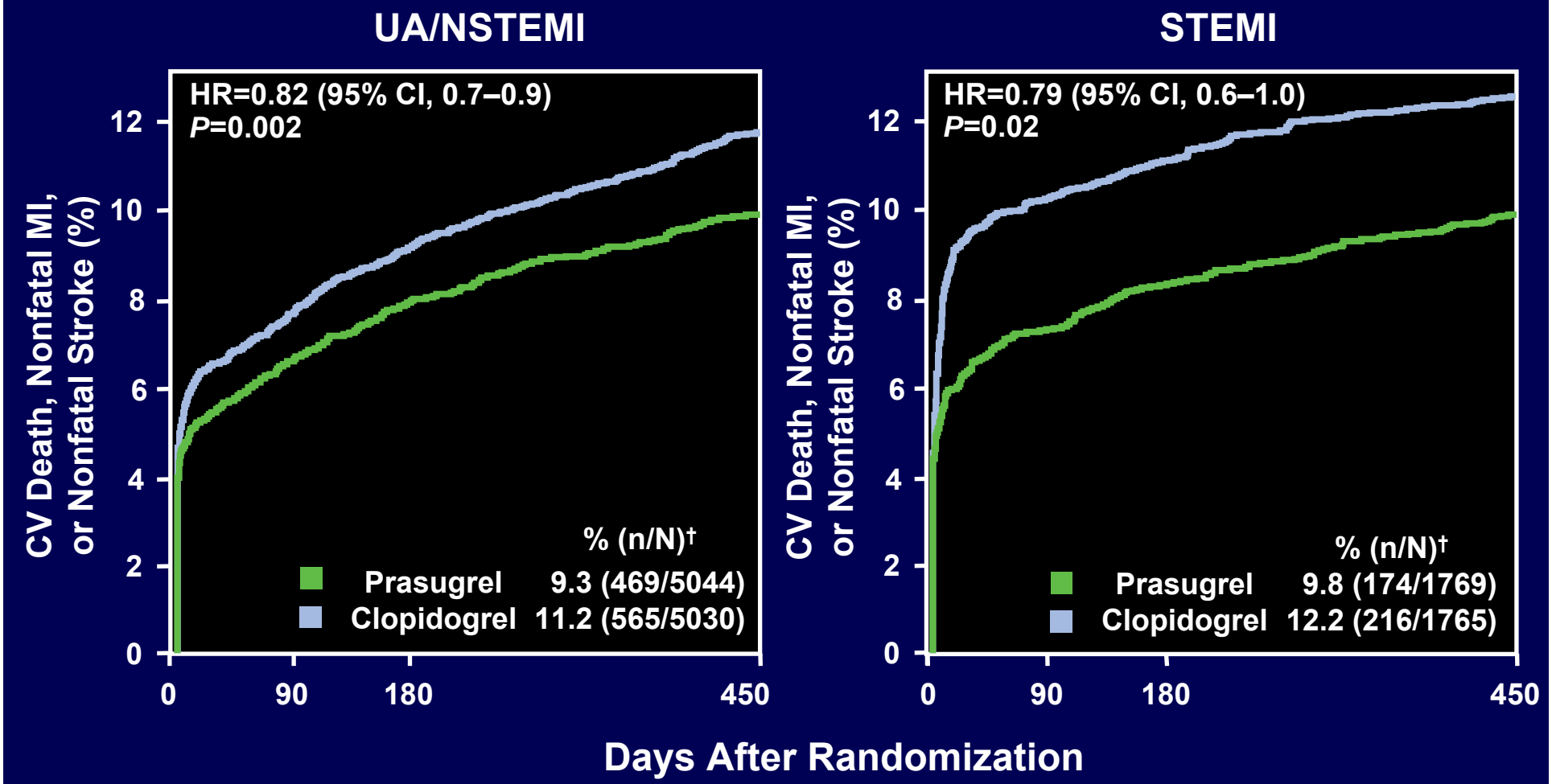
1º endpoint: CV death, MI, Stroke

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

Primary Composite Endpoint* Through End of Study

TRITON-TIMI 38

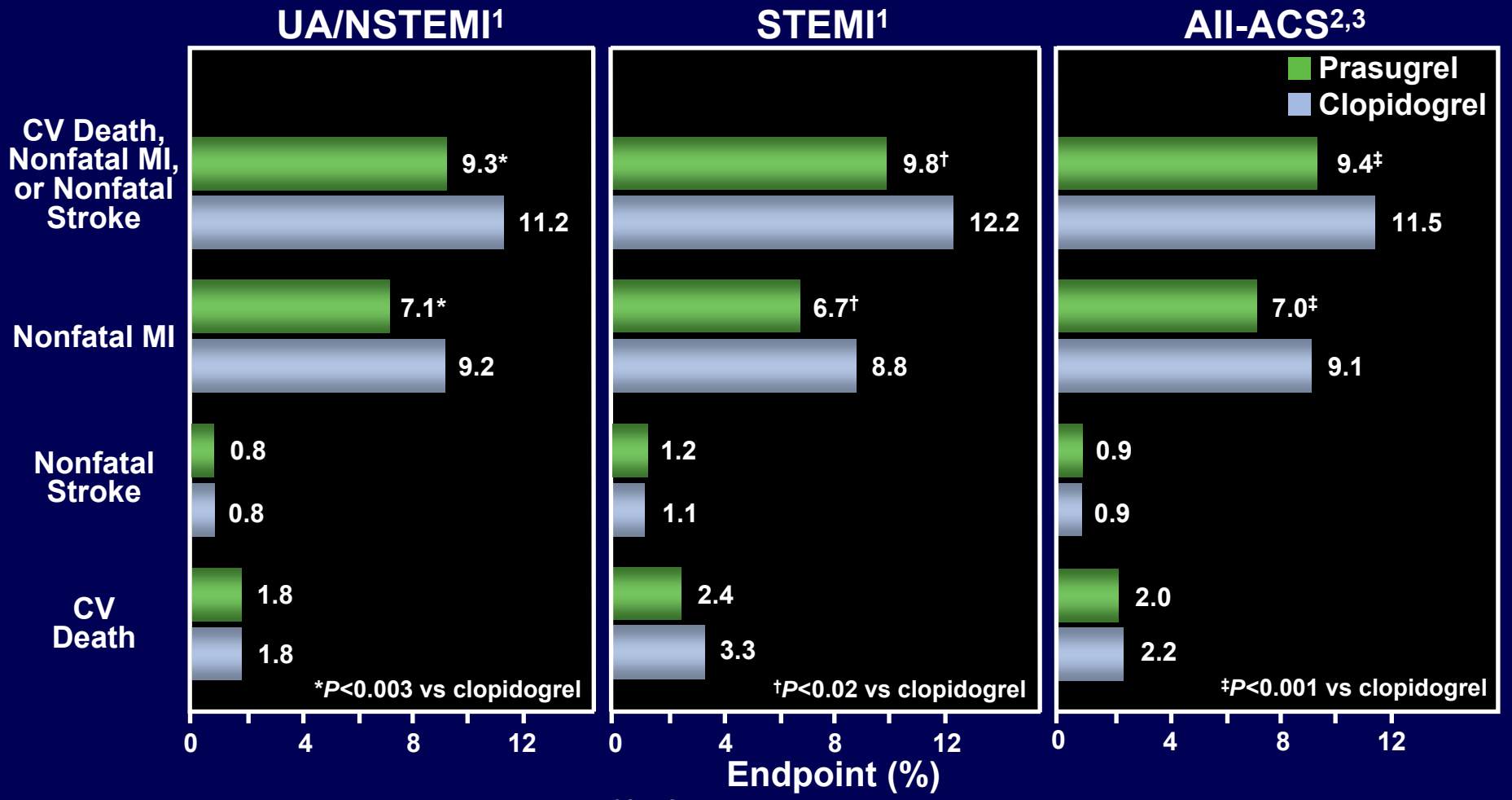


*Composite of CV death, nonfatal MI, or nonfatal stroke.
†Observed data.

1. Effient Full Prescribing Information.
2. Data on file: #EFF20091204a: DSI/Lilly.

Primary Composite Endpoint* and Components

TRITON-TIMI 38



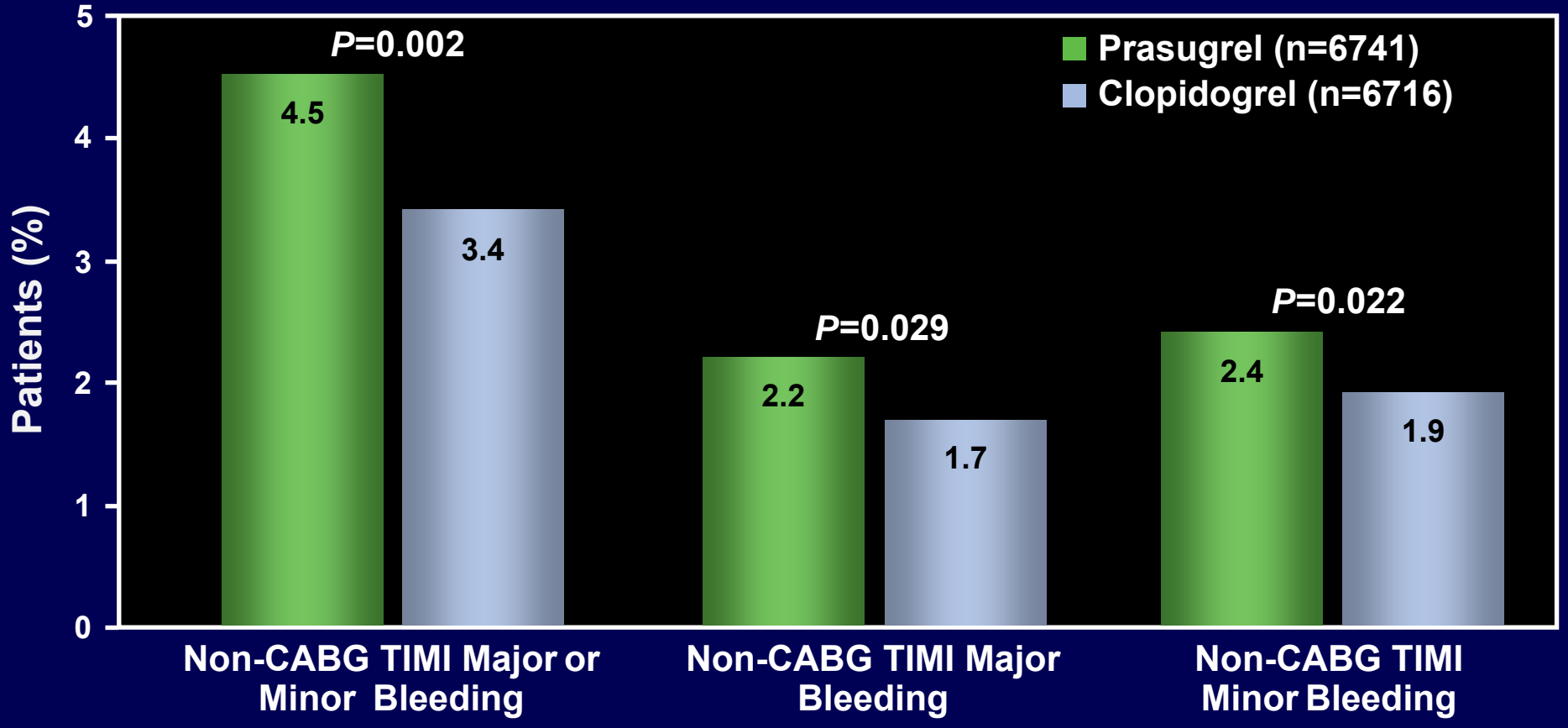
In the overall study, approximately 40% of MIs occurred periprocedurally and were detected solely by changes in CK-MB.

*Composite of CV death, nonfatal MI, or nonfatal stroke.

1. Effient Full Prescribing Information. 2. Data on file: #EFF20091204a: DSI/Lilly. 3. Data on file: #EFF20091204e: DSI/Lilly.

Non-CABG TIMI Bleeding

TRITON-TIMI 38

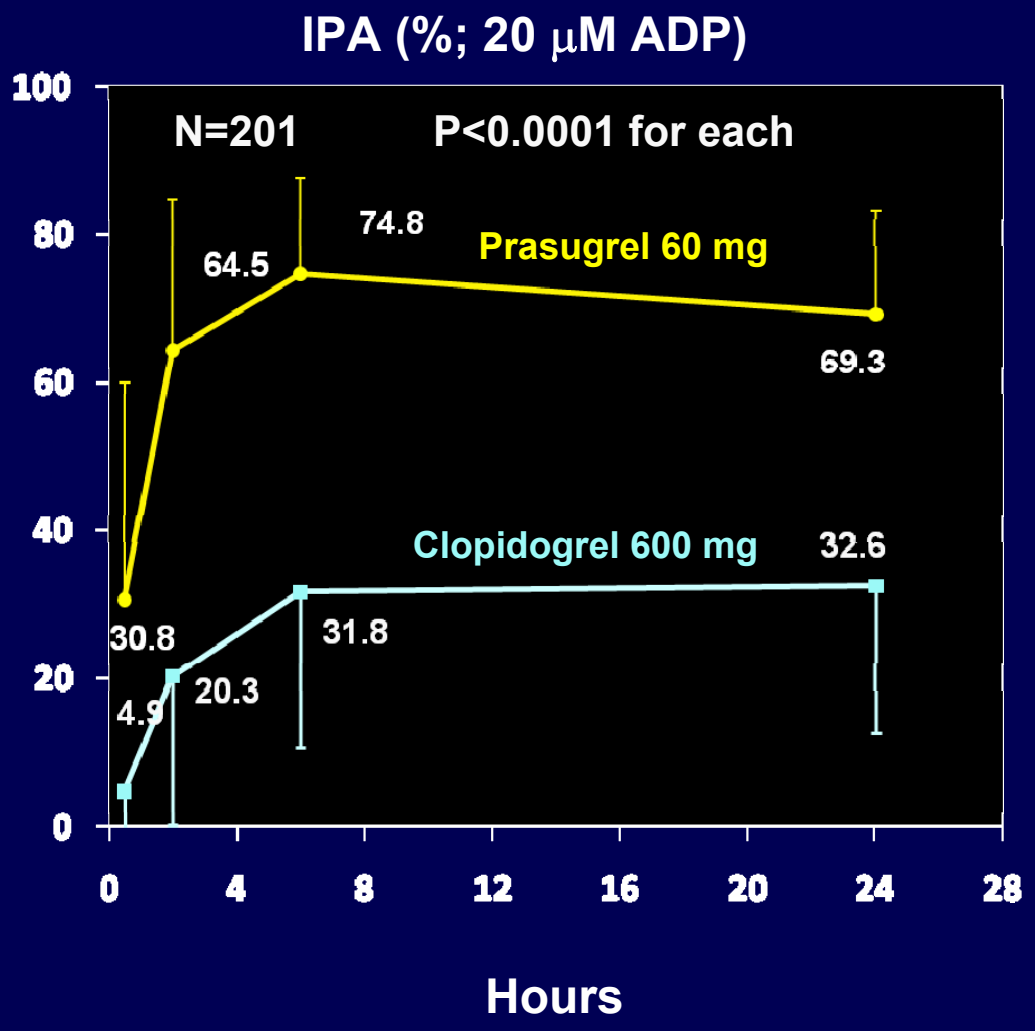


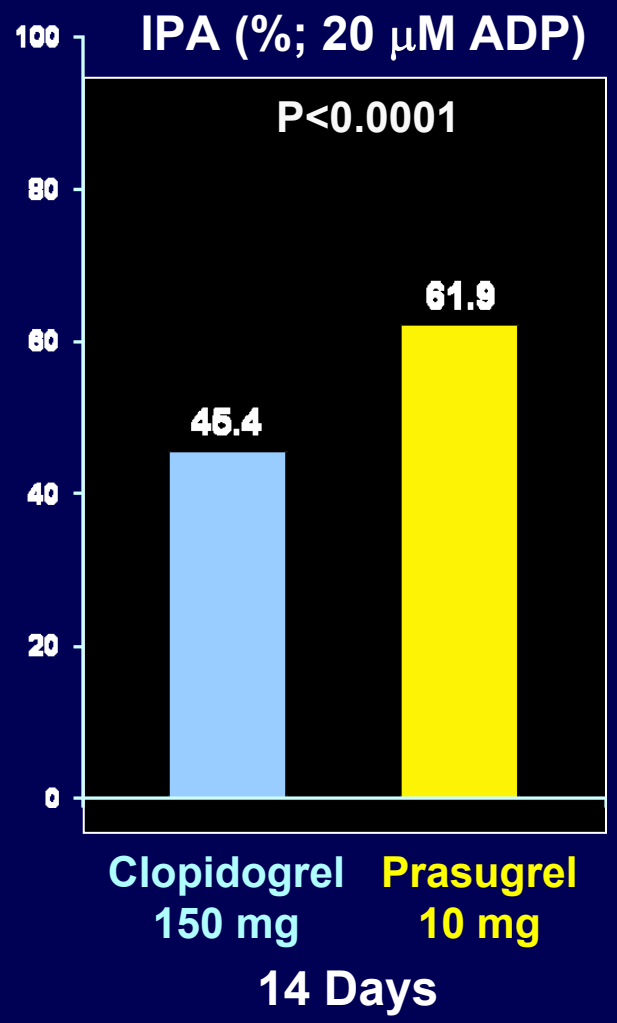
Observed rates of fatal bleeding were 0.3% with prasugrel + ASA vs 0.1% with clopidogrel + ASA

Issues with Prasugrel/TRITON-TIMI 38

The trial only used a 300 mg loading dose of clopidogrel– we generally use 600 mg these days

PRINCIPLE-TIMI 44: Comparison of Prasugrel with Higher Dose Clopidogrel

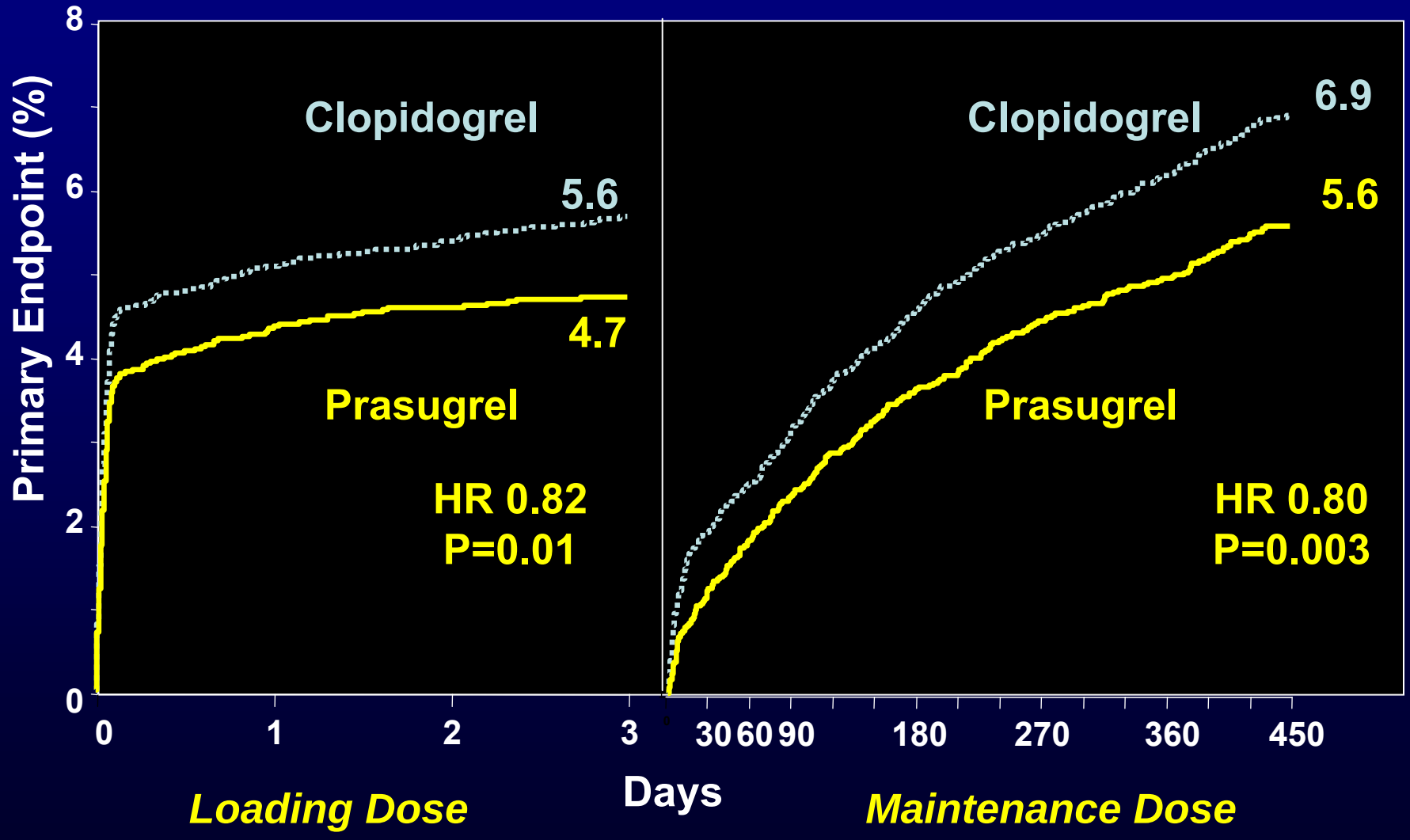




Wiviott S, et al. Circulation 2007

TRITON TIMI-38

Timing of Benefit (Landmark Analysis)



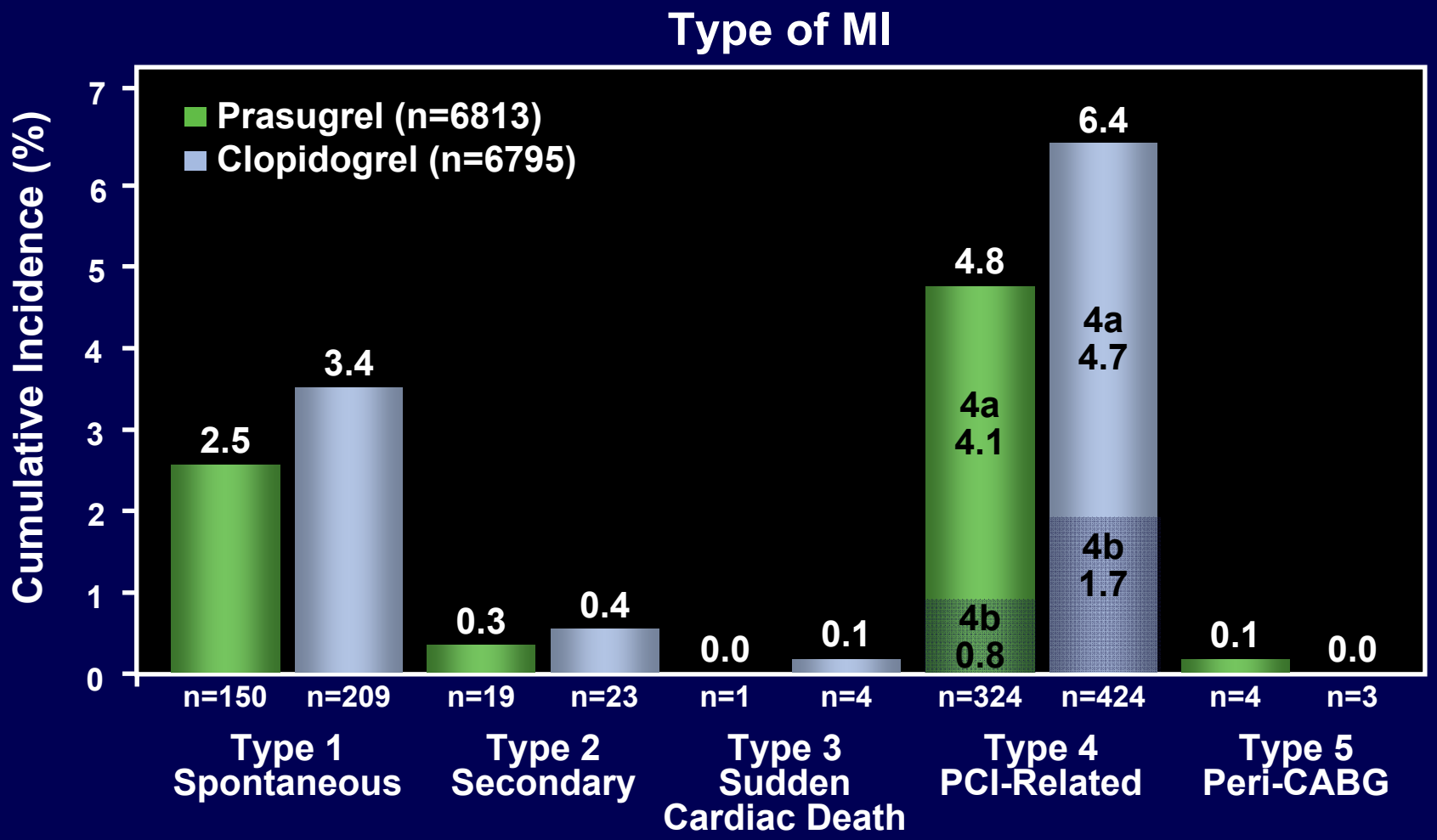
Wiviott SD et al. NEJM 2007;357:2001-15

Issues with Prasugrel/TRITON-TIMI 38

The benefit of prasugrel was driven entirely by a reduction in non-fatal MI

Application of Universal MI Classification to TRITON-TIMI 38 MI Events

TRITON-TIMI 38

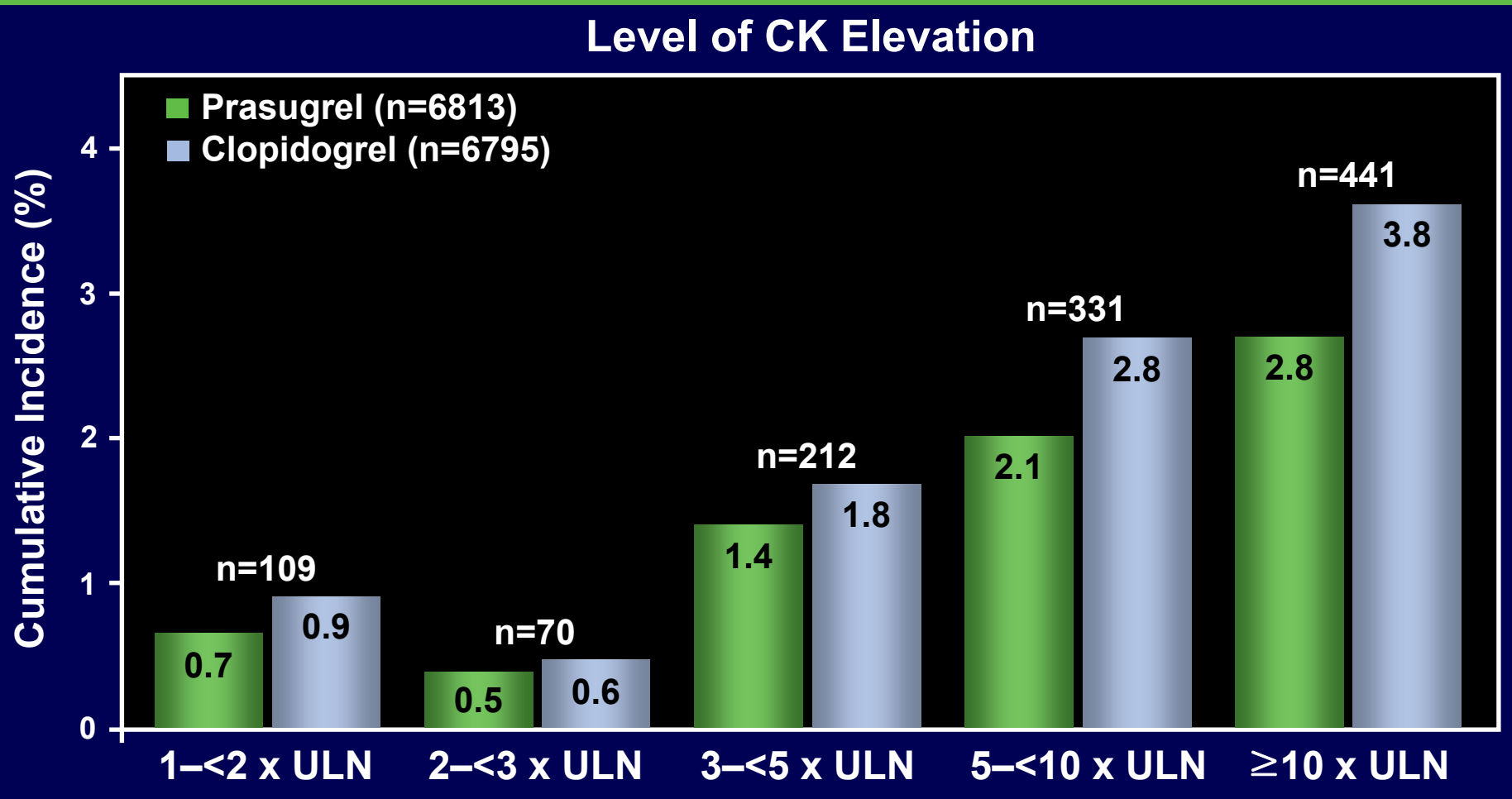


In the TRITON-TIMI 38 trial, there were a total of 1218 MIs. This retrospective analysis classified these MIs using the newly developed classification system from the universal definition of MI, which was developed after the study protocol was complete.

Morrow et al. *Circulation*. 2009;119:2758-2764.

Application of Universal MI Classification to TRITON-TIMI 38 MI Events

TRITON-TIMI 38



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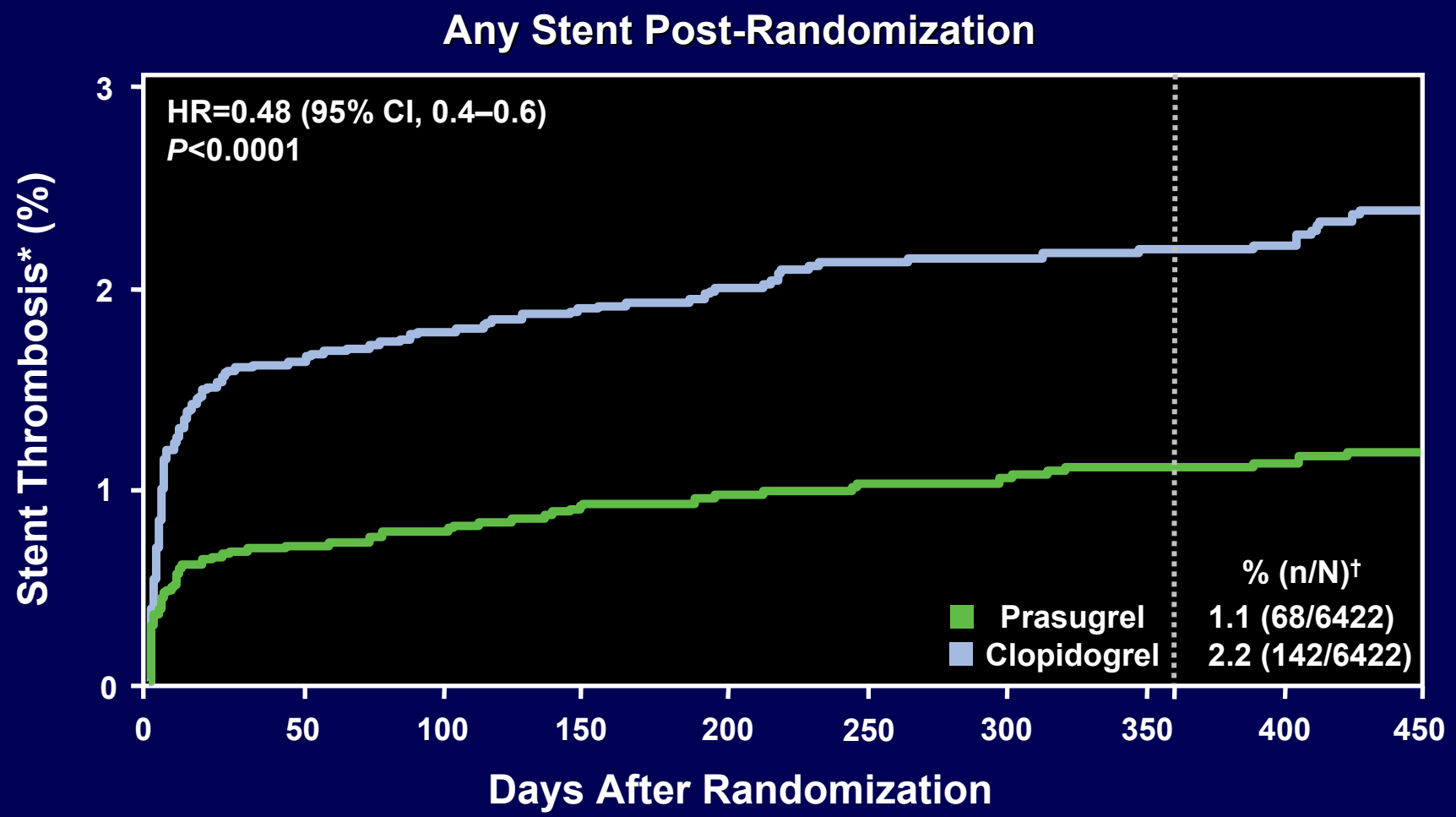
Morrow et al. *Circulation*. 2009;119:2758-2764.

Issues with Prasugrel/TRITON-TIMI 38

The stent thrombosis rates in TRITON seem very high– we don't see anything like this in our practice

Stent Thrombosis: All ACS

TRITON-TIMI 38

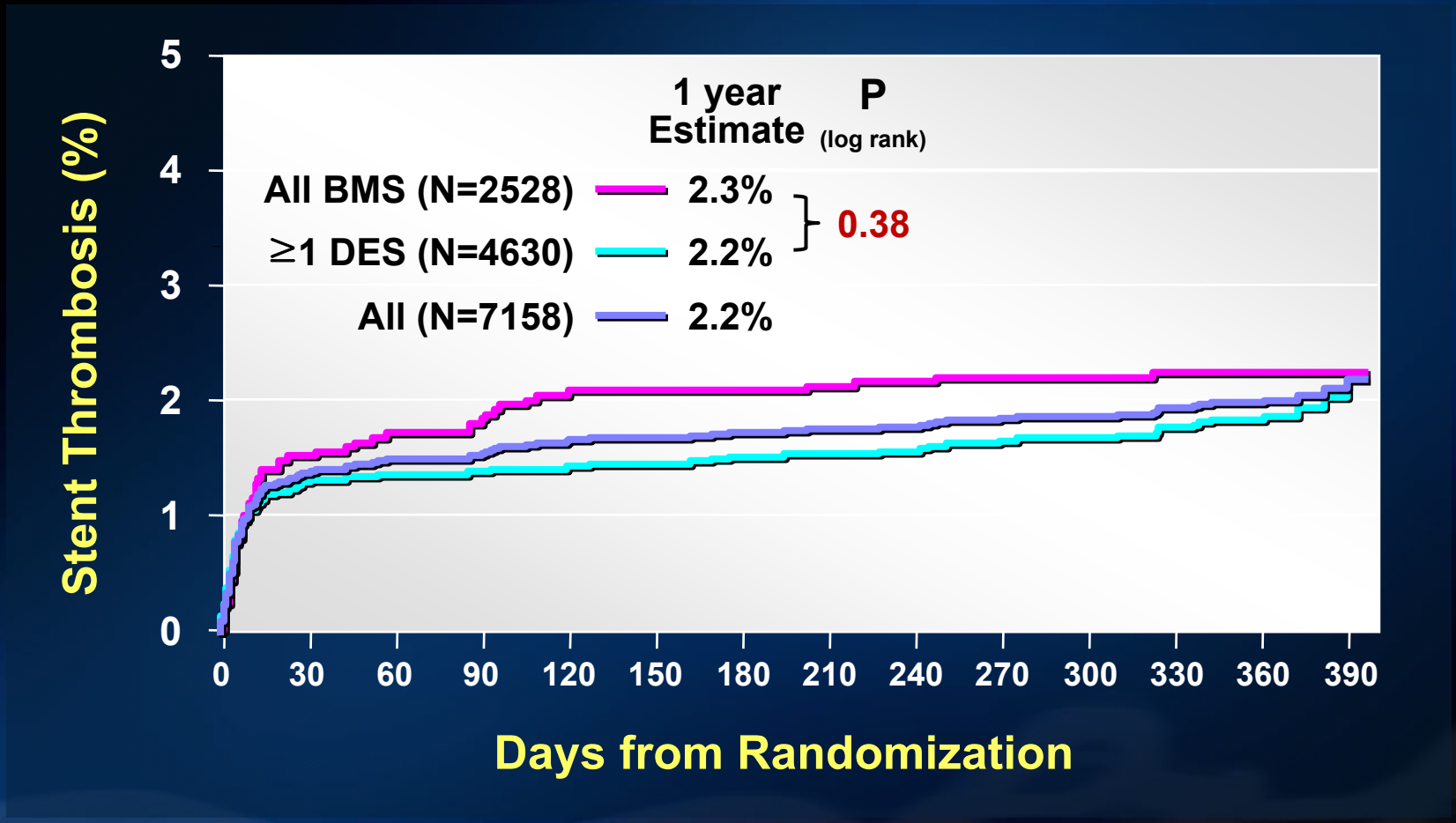


*Stent thrombosis defined as Academic Research Consortium definite or probable.
†Observed data.

1. Wiviott et al. *Lancet.* 2008;371:1353-1363. 2. Data on file: #EFF20091204b: DSI/Lilly.

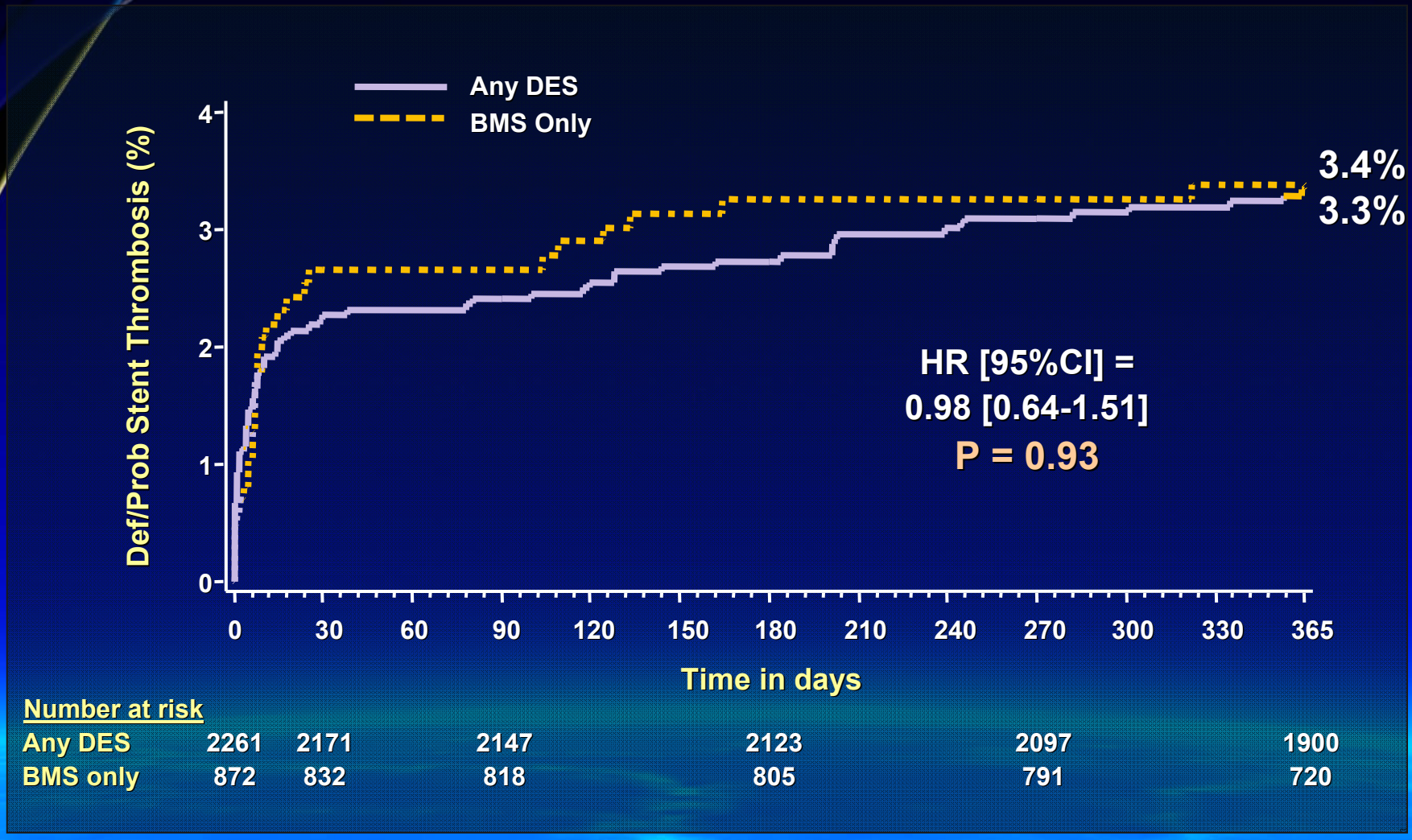
Stent Thrombosis (Protocol Defn.)

Drug-eluting Stents (DES) vs. Bare Metal Stents (BMS)



ACUITY

1-Year Stent Thrombosis: Impact of Implanted Stent Type



HORIZONS AMI

Stent thrombosis

PLATO Invasive

	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)	HR for ticagrelor (95% CI)	p value*
Stent thrombosis, %				
Definite	1.0	1.6	0.62 (0.45–0.85)	0.003
Probable or definite	1.7	2.3	0.72 (0.56–0.93)	0.01
Possible, probable, or definite	2.2	3.1	0.72 (0.58–0.90)	0.003

¶ Evaluated in patients with any stent during the study

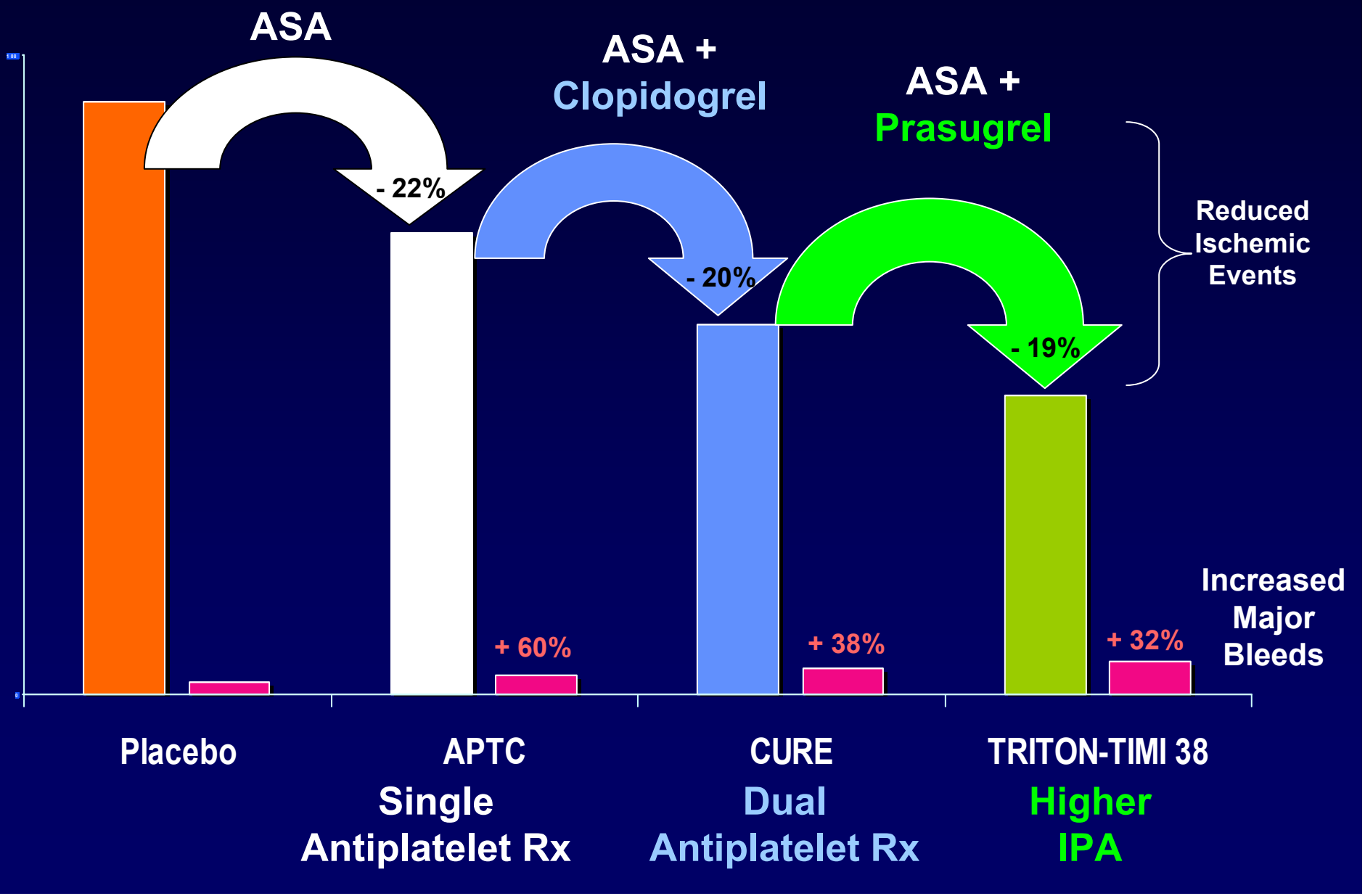
Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

* By univariate Cox model

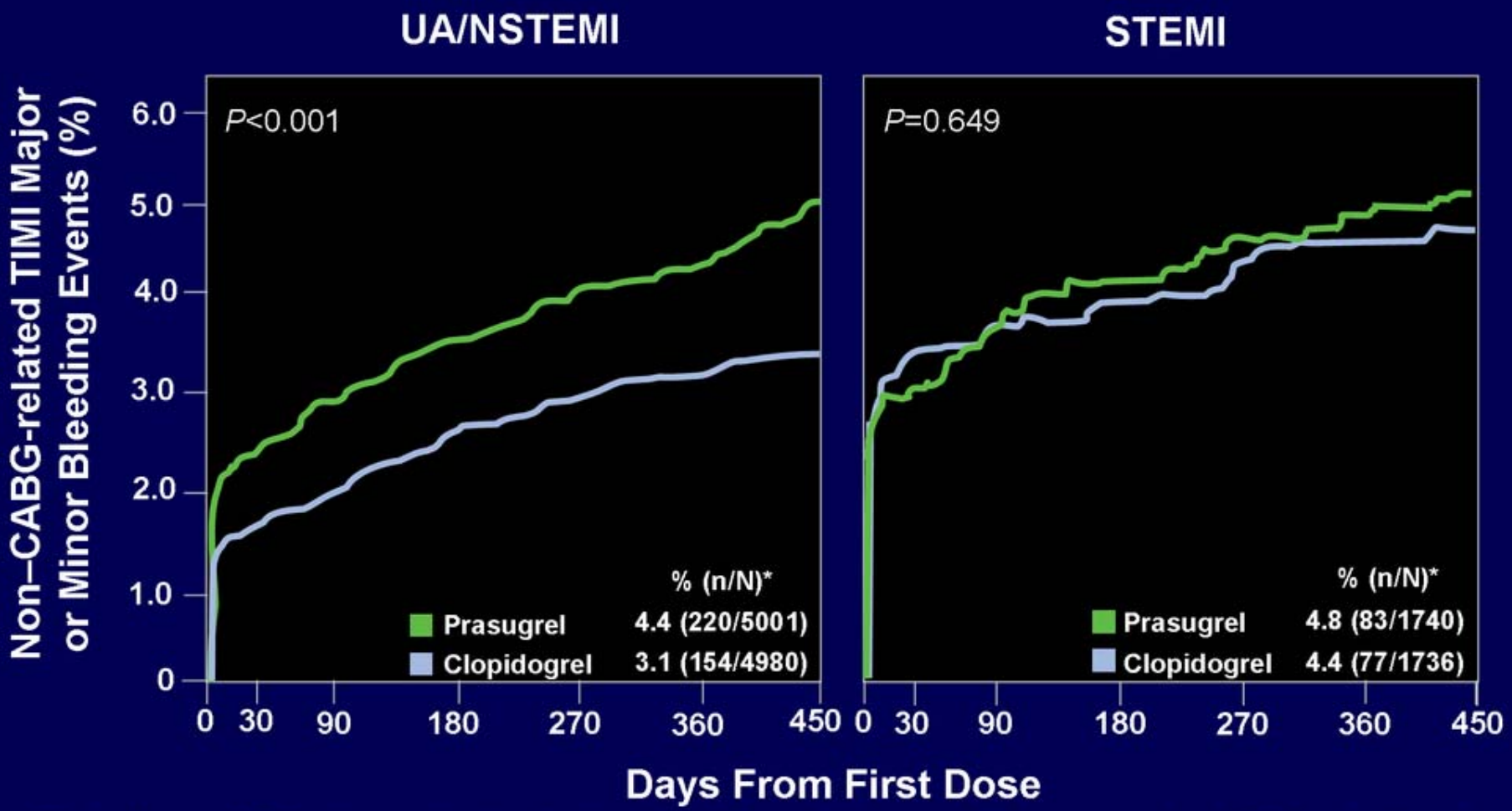
Issues with Prasugrel/TRITON-TIMI 38

The increased risk of bleeding outweighs any benefit in reduced MI and stent thrombosis

Antiplatelet Therapy in ACS



Major or Minor Bleeding in UA/NSTEMI and STEMI Populations



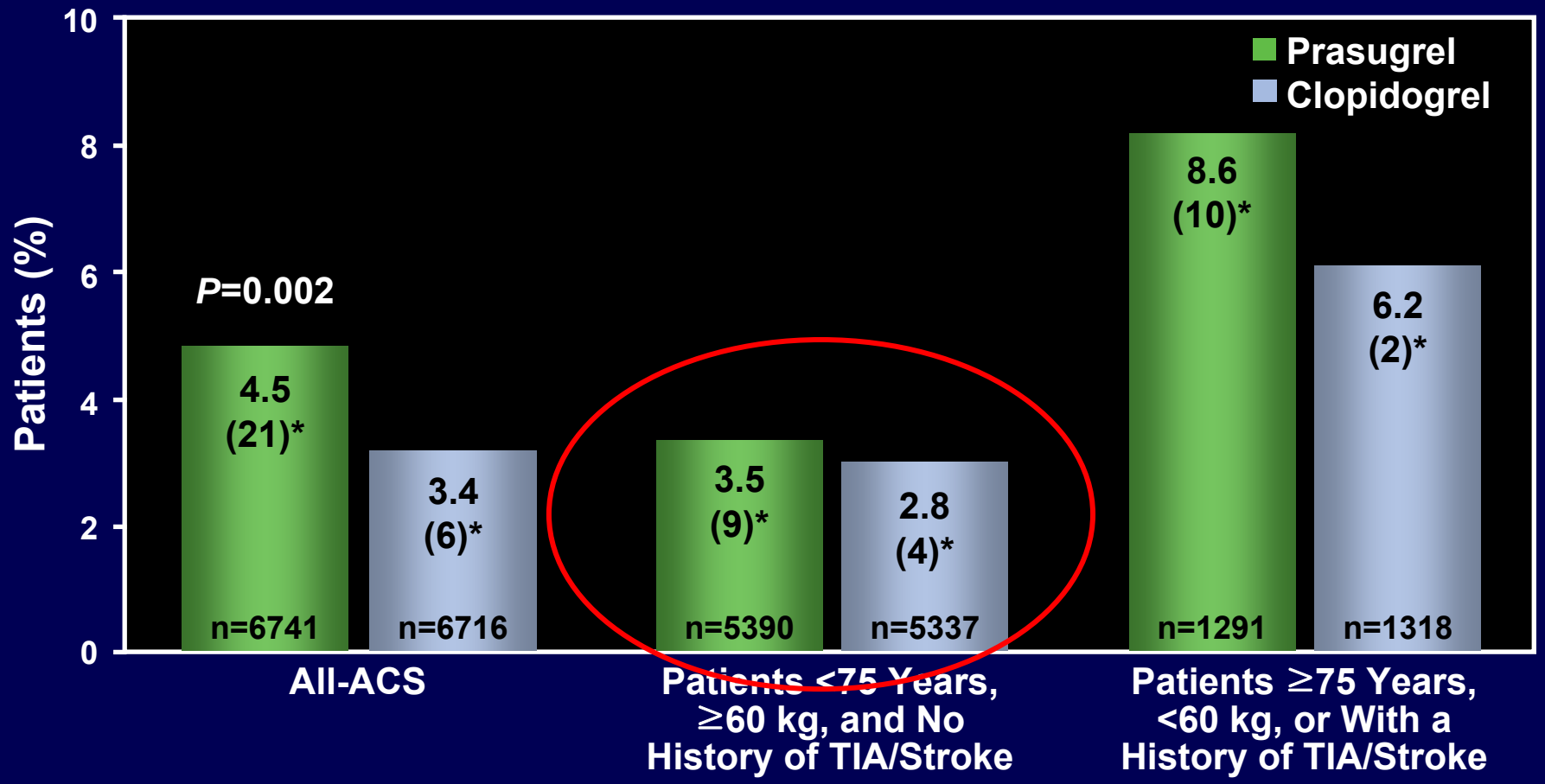
The incidence of TIMI major or minor bleeding in the All ACS population was 4.5% for prasugrel and 3.4% for clopidogrel (P=0.002). *Observed data.

Data on File: #EFF20091207e, DSI/Lilly.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Non-CABG TIMI Major or Minor Bleeding by Age, Weight, and History of TIA/Stroke

TRITON-TIMI 38



The TRITON-TIMI 38 trial was not designed or powered to demonstrate independent efficacy or safety in patients <75 or ≥75 years, and <60 or ≥ 60 kg and with or without a history of TIA/stroke.

*Number of patients with a fatal bleed.

1. Wiviott et al *N Engl J Med*. 2007;357:2001-2015.
2. Data on file: #EFF20091204h: DSI/Lilly.

Conclusions: Emerging Platelet Inhibitors

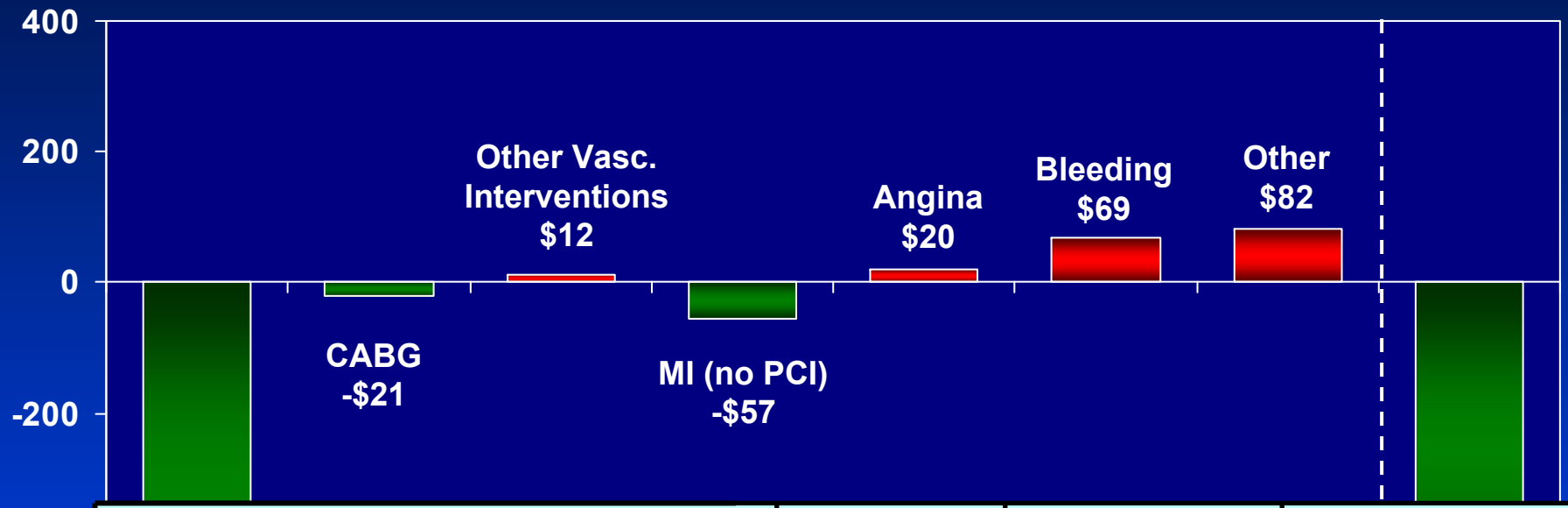
- While current antiplatelet therapies are efficacious, there is substantial room for improvement– particularly in the ACS setting
- Prasugrel is the first agent to demonstrate that greater, more rapid, and more uniform platelet inhibition can further reduce ischemic events, but it does come at the price of greater major bleeding.
- Careful patient selection is critical to optimizing the risk-benefit profile of prasugrel
  - *Clinical Factors: Age, Weight, ACS type, diabetes*
  - *Novel Factors: Genetics, Platelet function testing*

Issues with Prasugrel/TRITON-TIMI 38

Prasugrel is just too expensive– especially compared with generic clopidogrel

TRÎTON TIMI·38

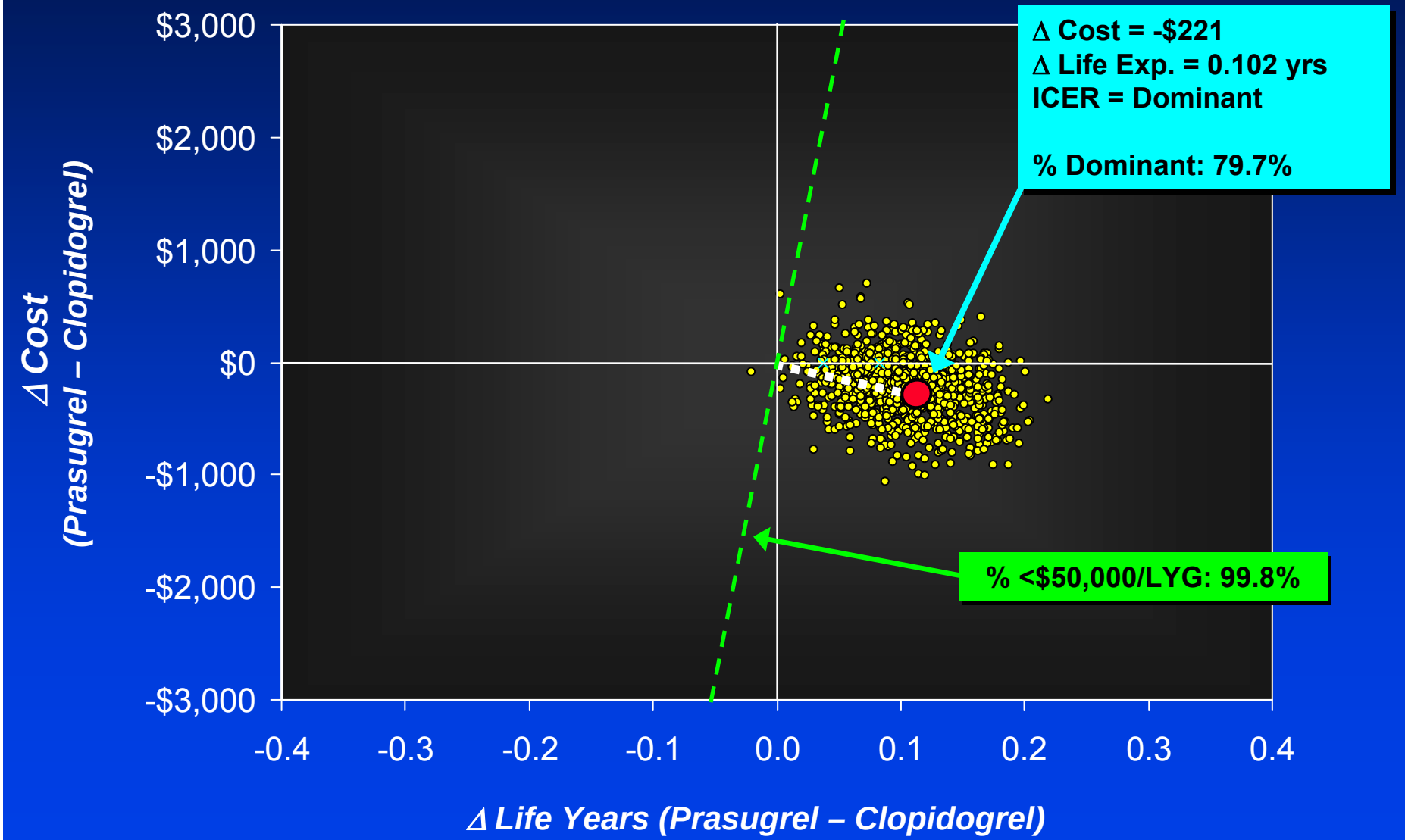
Incremental Costs/Cost Offsets with Prasugrel*



	Prasugrel	Clopidogrel	Difference (P-C)
Index Hospitalization Costs	$19,740	$19,752	-$12
Rehospitalization Costs	$4,465	$4,982	-$517
Study Drug Costs	$1,862	$1,554	$308
TOTAL COSTS	**$26,067**	**$26,288**	**-$221**

TRITON TIMI-38

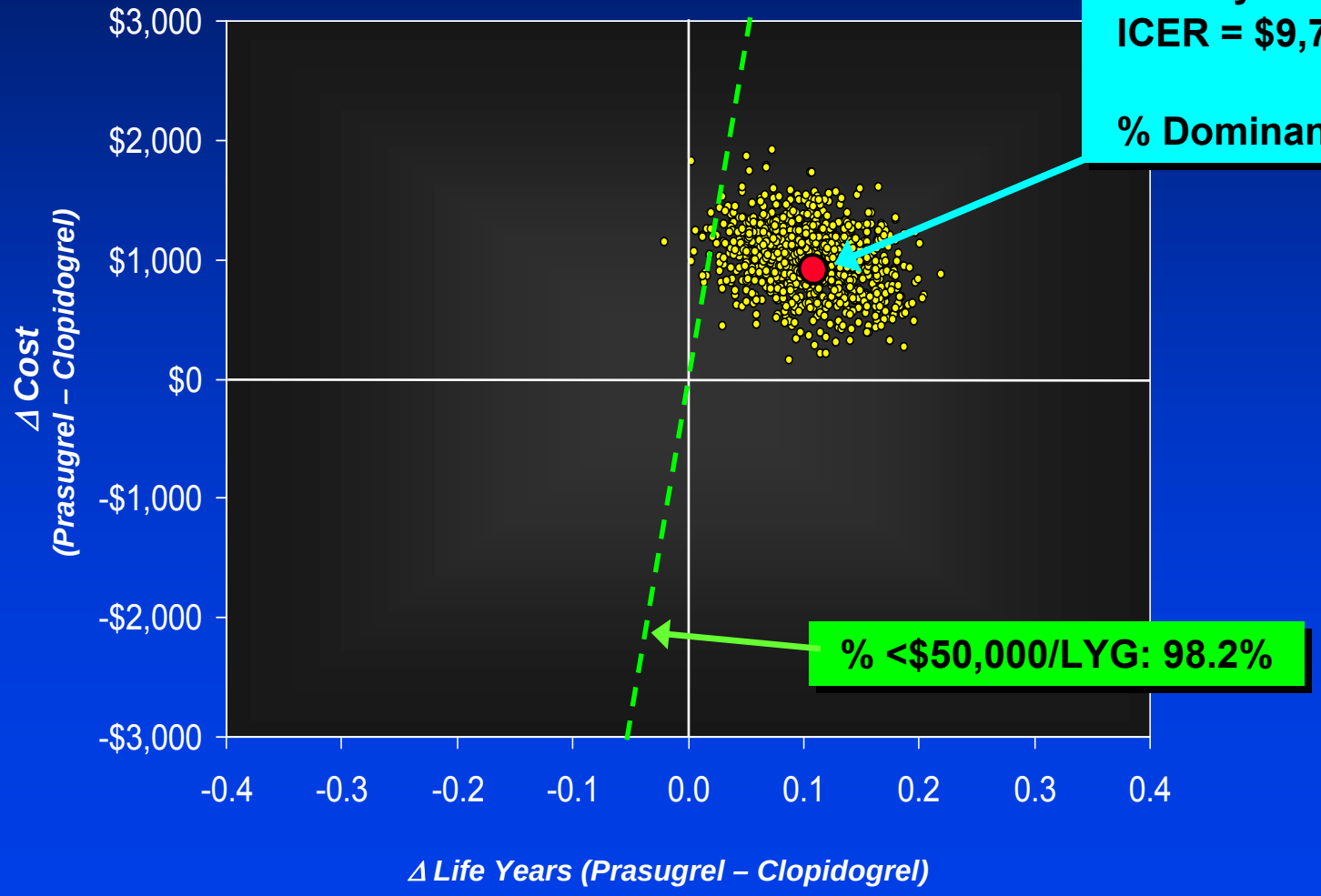
Cost-Effectiveness: *Base Case*



TRITON TIMI-38

Impact of Generic Clopidogrel

Treatment Over Full Trial Duration
Cost of Generic Clopidogrel = $1/day



Δ Cost = +$996
Δ Life-years= 0.102
ICER = $9,727/LYG

% Dominant: 0%

% <$50,000/LYG: 98.2%