New and Emerging Approaches to Antiplatelet Therapy for PCI

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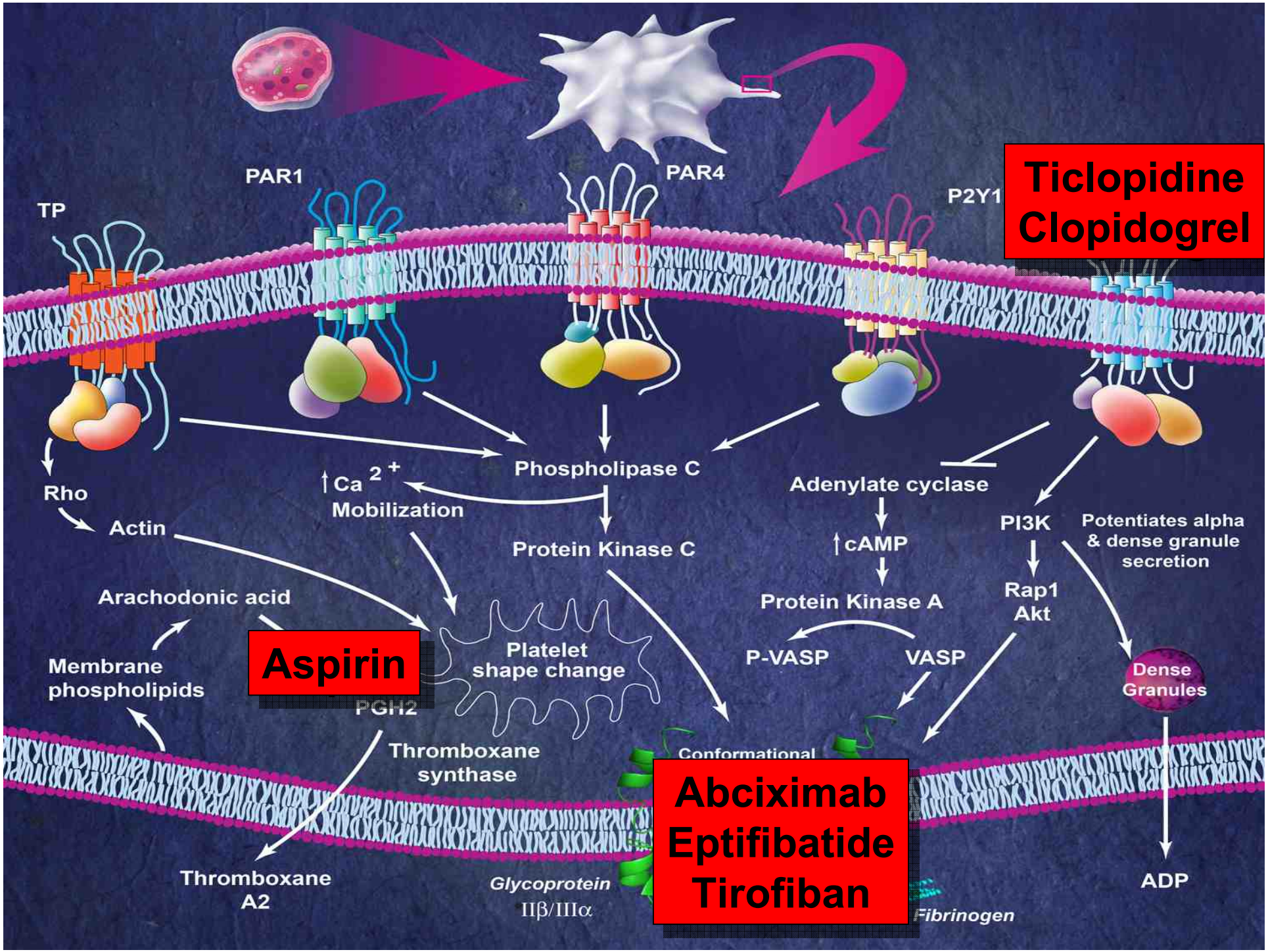
- Medtronic

Consulting/Advisory Boards

- Medtronic
- Cordis

DJC: 2/10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PAR4
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P2Y1
Ticlopidine
Clopidogrel
Rho
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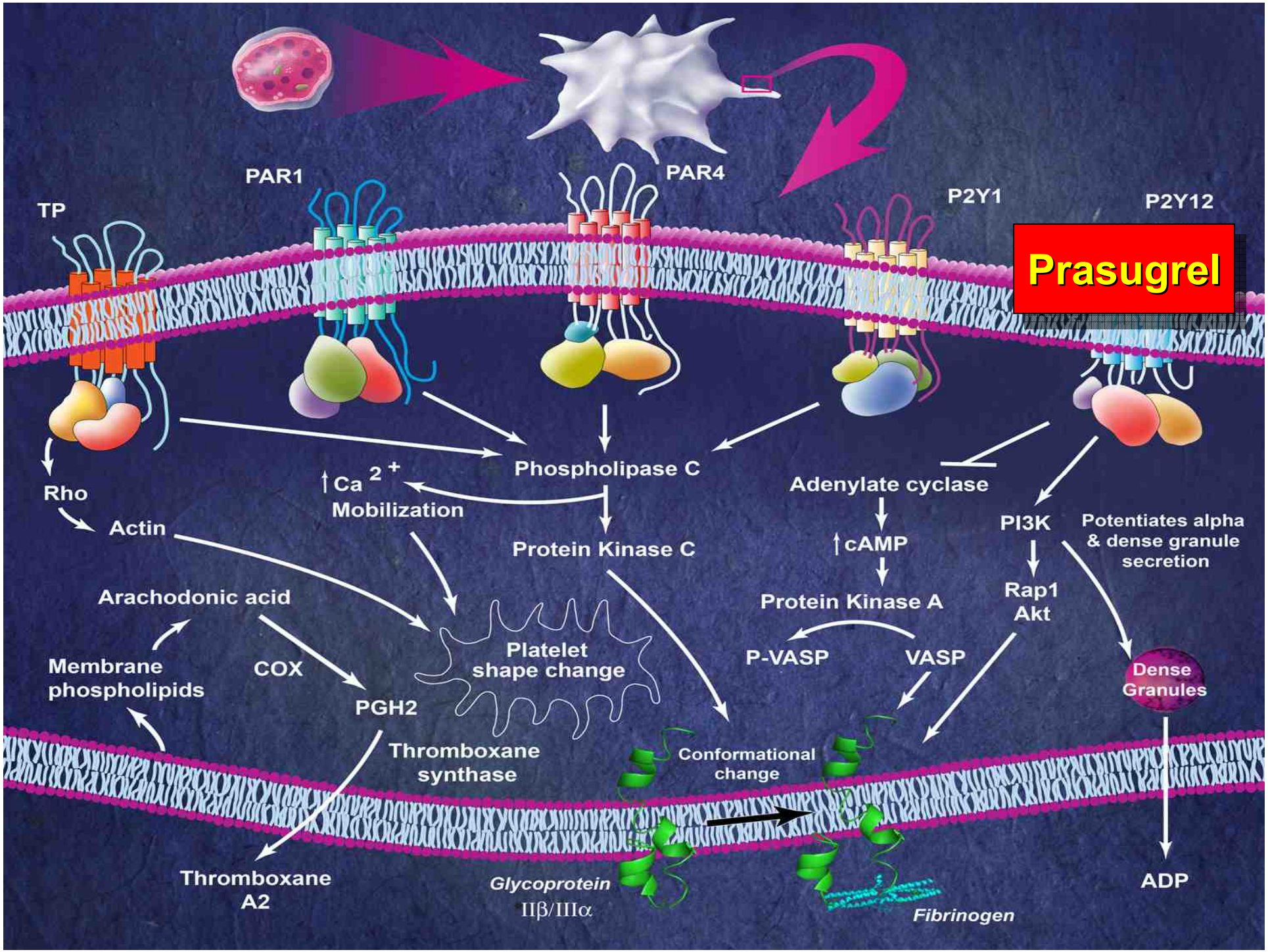
Mobilization
Phospholipase C
Adenylate cyclase
PI3K
Potentiates alpha
& dense granule
secretion
↑cAMP
Protein Kinase C
Protein Kinase A
Rap1
Akt
Arachodonic acid
Aspirin
Platelet
shape change
P-VASP
VASP
Dense
Granules
Membrane
phospholipids
PGH2
Thromboxane
synthase
Conformational
Abciximab
Eptifibatide
Tirofiban
Thromboxane
A2
Glycoprotein
IIβ/IIIα
Fibrinogen
ADP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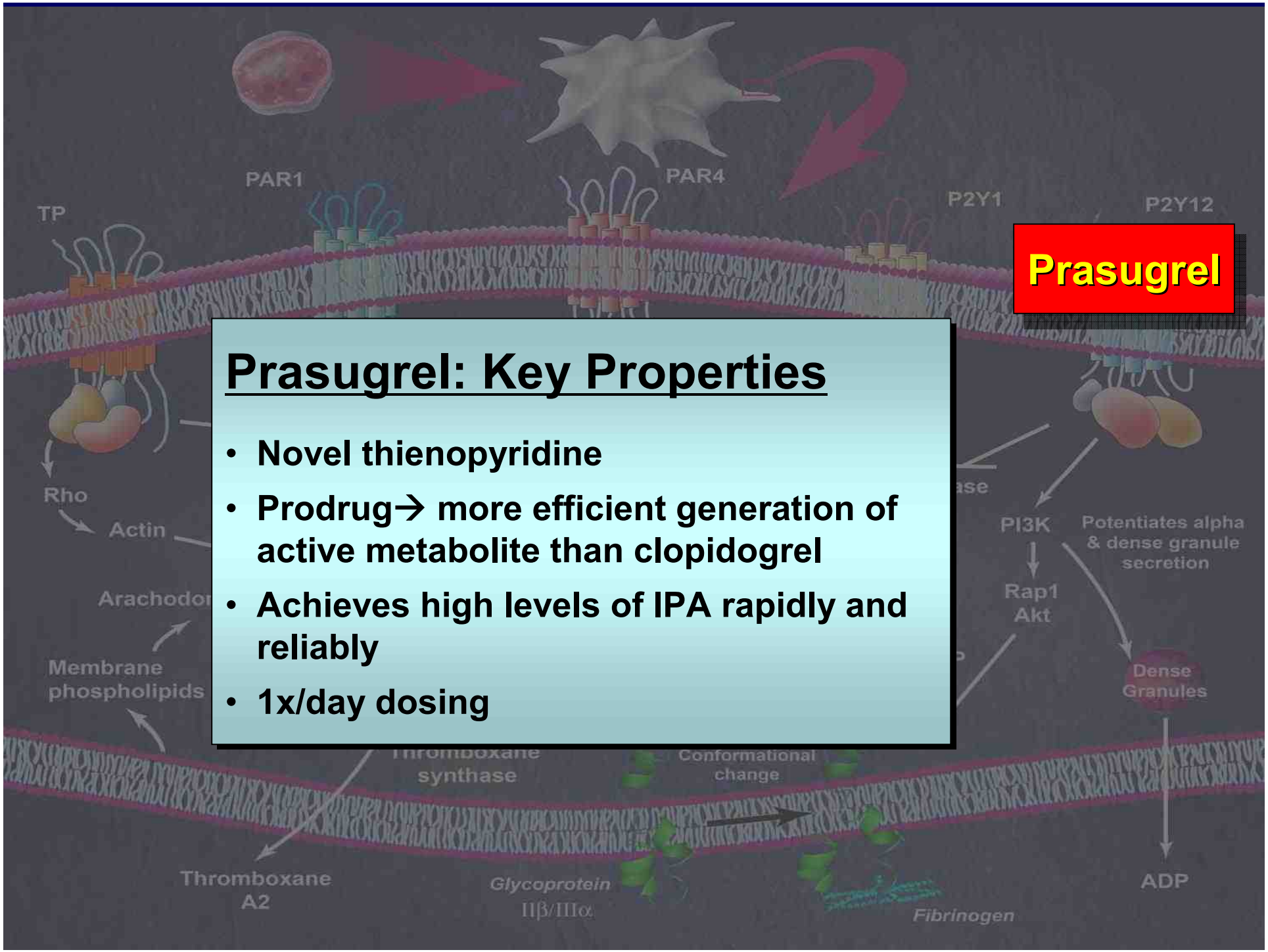
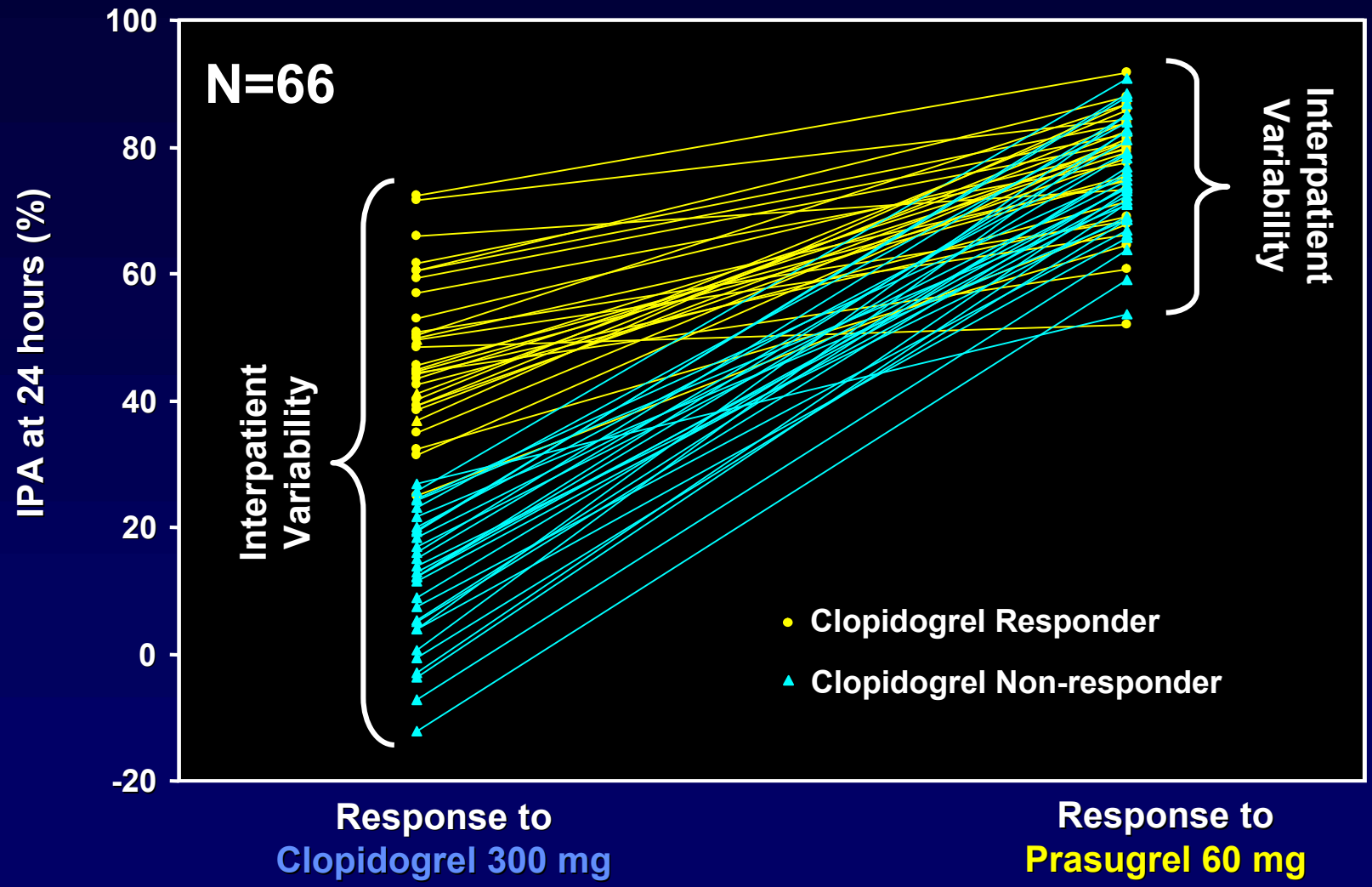


Prasugrel: Key Properties

- Novel thienopyridine
- Prodrug→ more efficient generation of active metabolite than clopidogrel
- Achieves high levels of IPA rapidly and reliably
- 1x/day dosing

Prasugrel vs. Clopidogrel: Healthy Volunteer Crossover Study



From Brandt JT AHJ 153: 66e9,2007

TRITON TIMI-38

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ **N= 13,600**

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

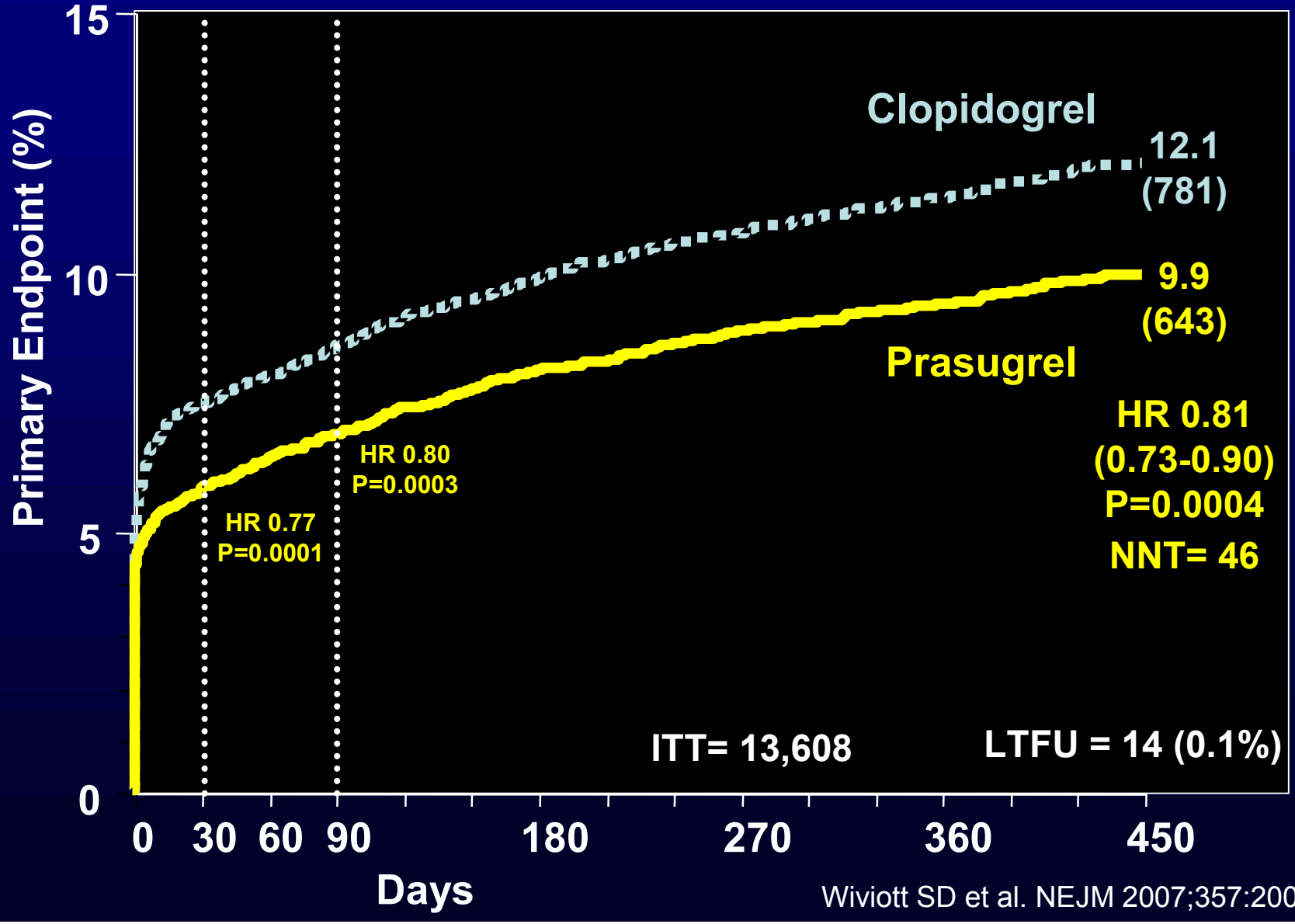
Median duration of therapy ~ 15 months

1º endpoint: CV death, MI, Stroke

Safety endpoints: TIMI major bleeds, Life-threatening bleeds
Key Substudies: Pharmacokinetic, Genomic

TRITON TIMI-38

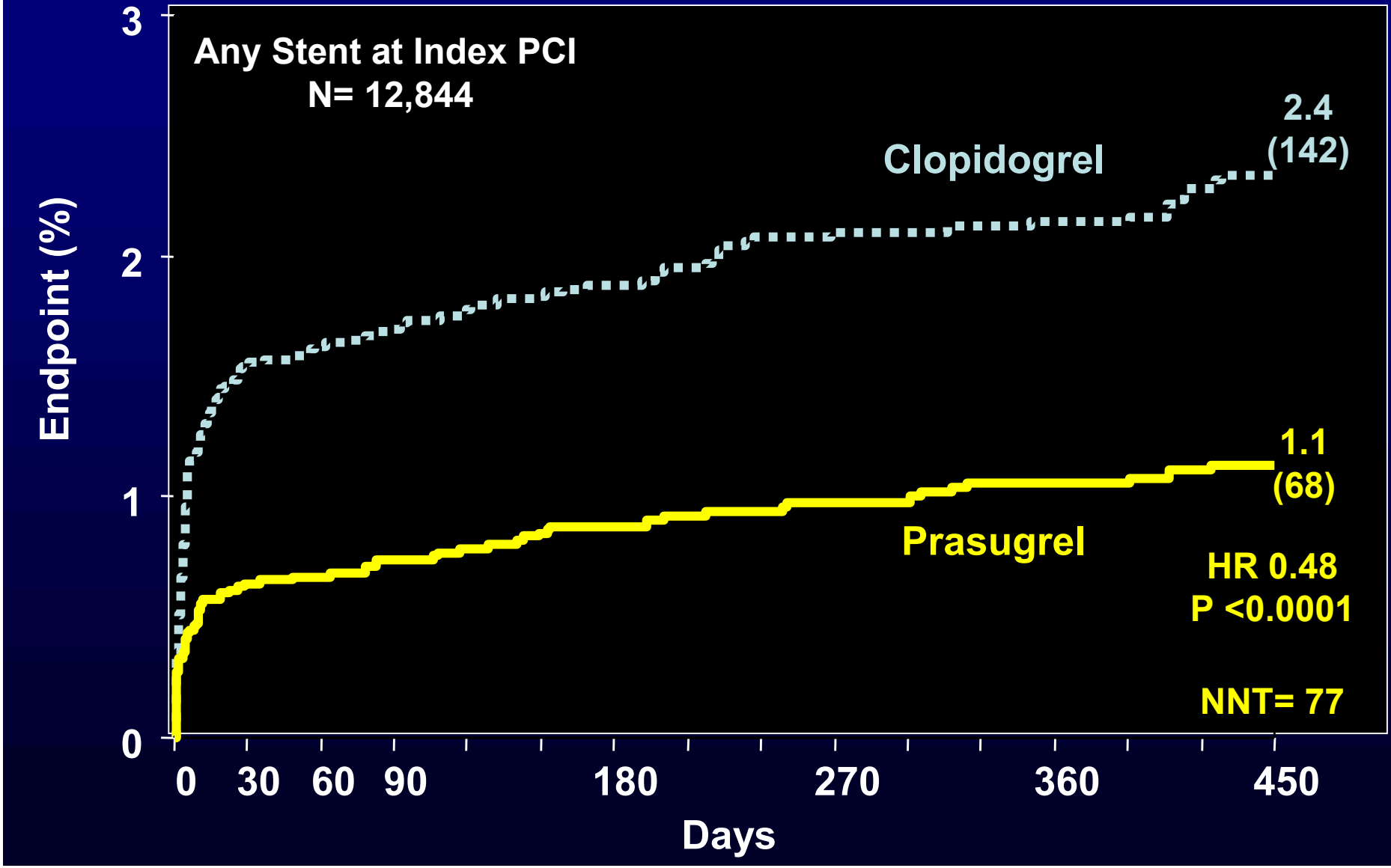
Primary Endpoint
CV Death,MI,Stroke



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

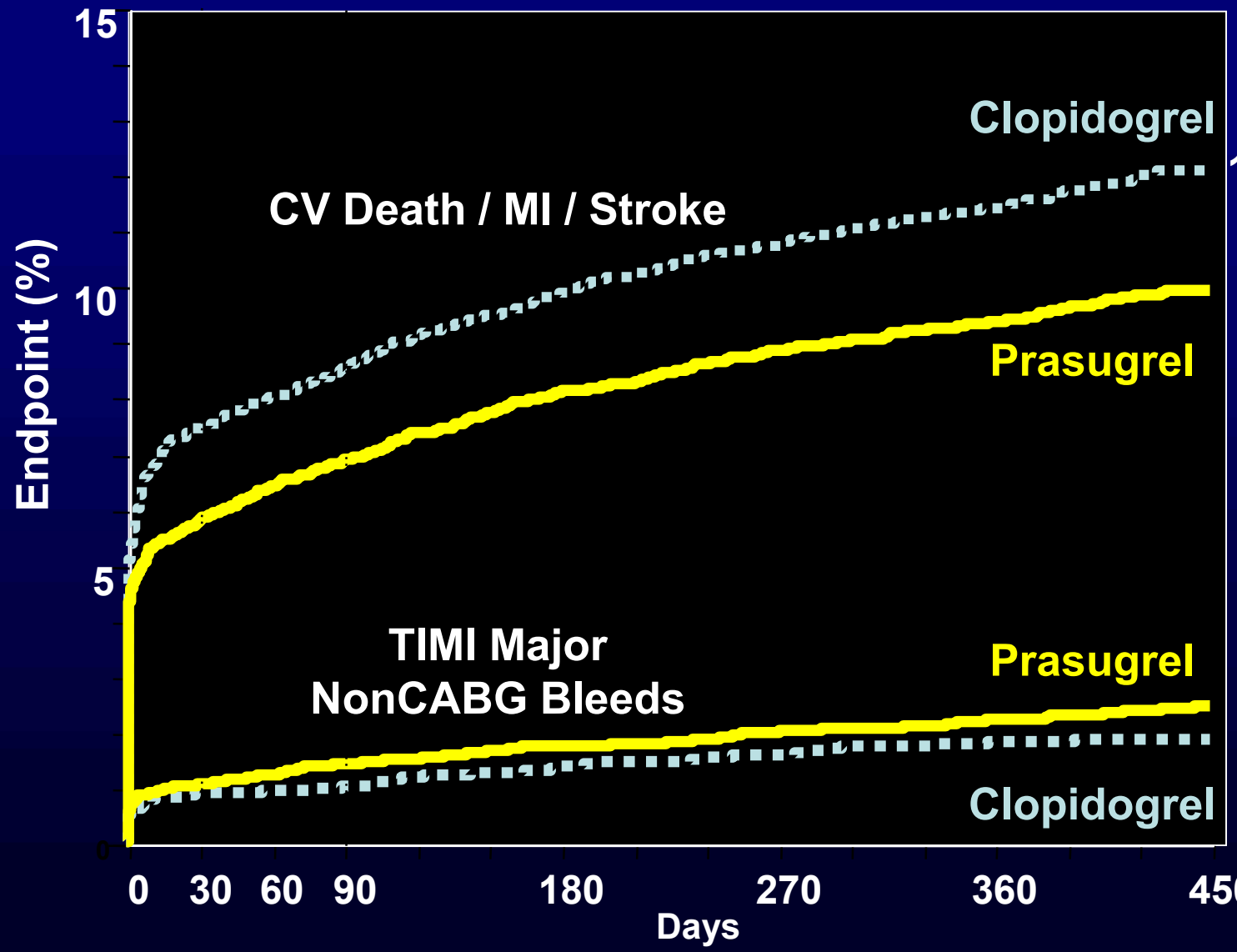
TRÎTON TIMI·38

Stent Thrombosis
(ARC Definite + Probable)



TRITON TIMI-38

Balance of Efficacy and Safety



↓ 138 events

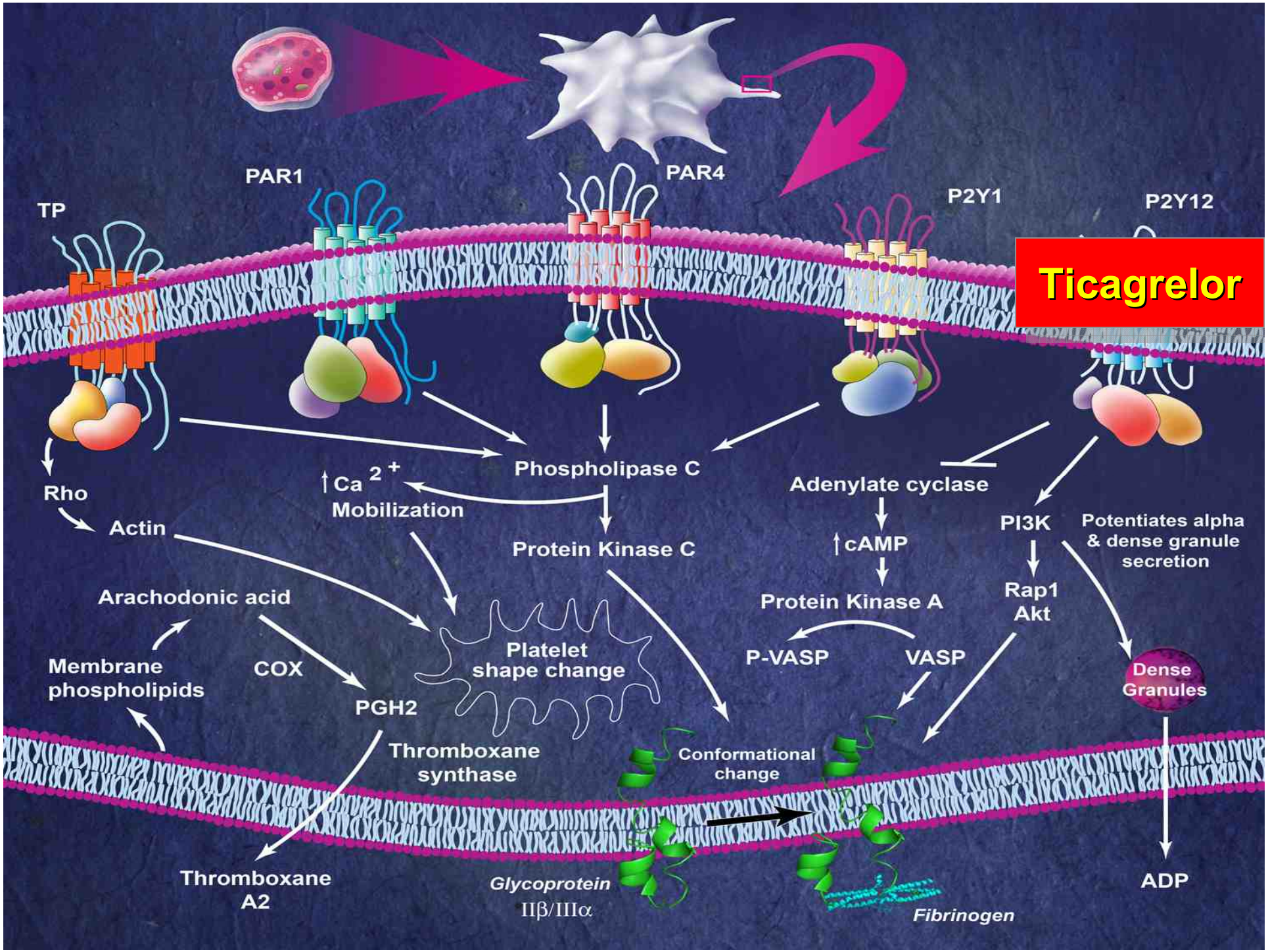
HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167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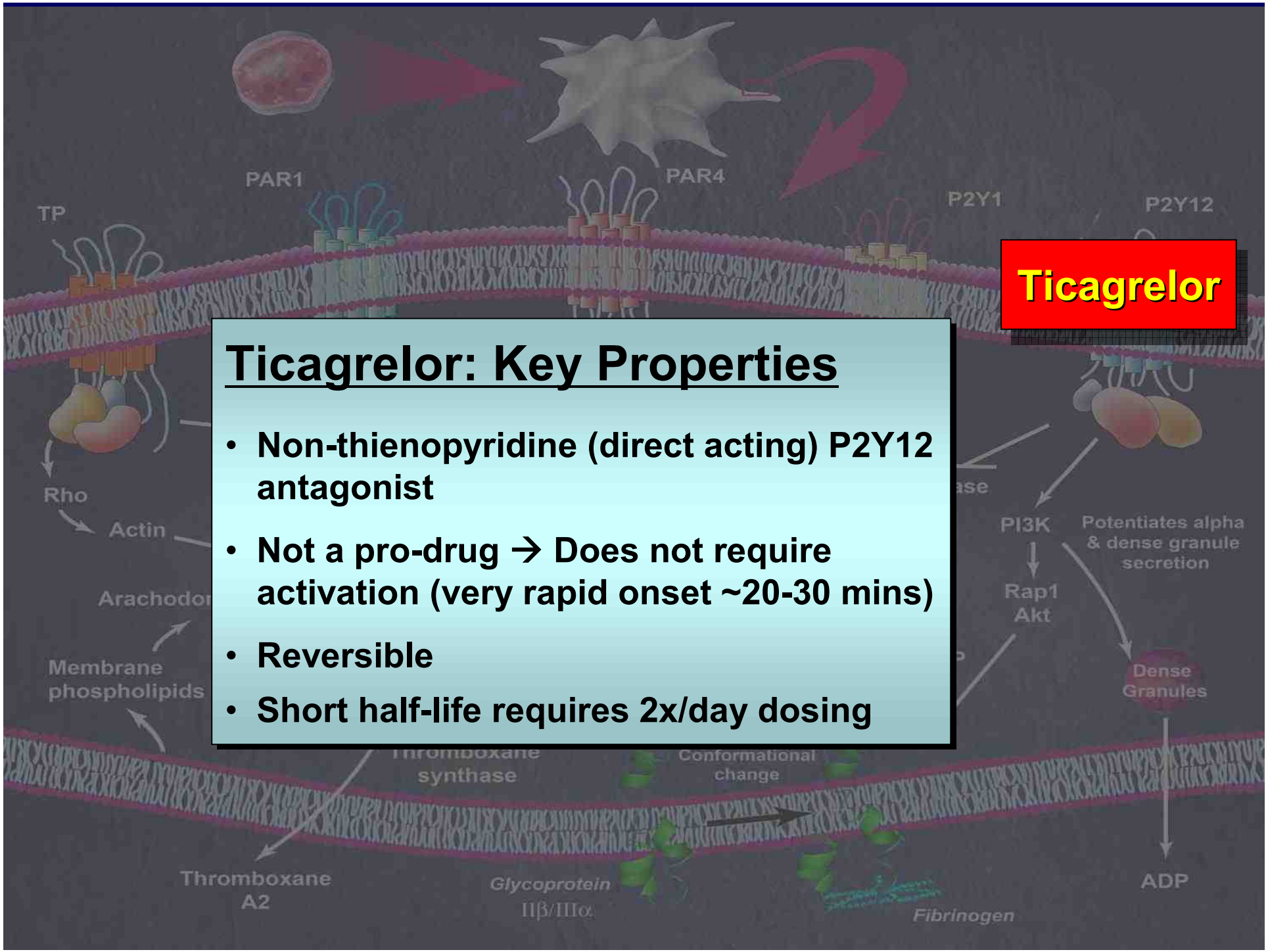


Ticagrelor: Key Properties

- Non-thienopyridine (direct acting) P2Y12 antagonist
- Not a pro-drug → Does not require activation (very rapid onset ~20-30 mins)
- Reversible
- Short half-life requires 2x/day dosing

PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

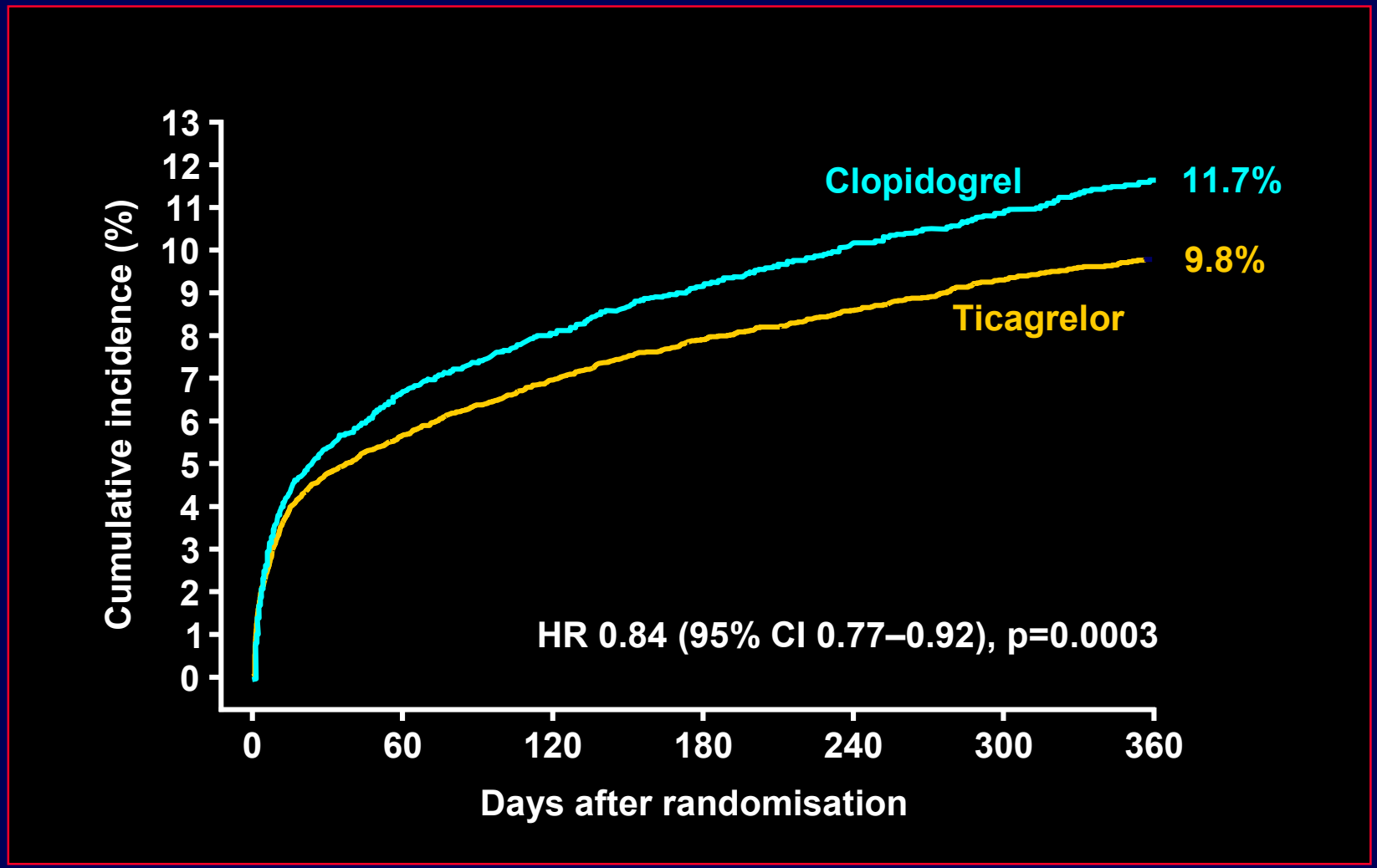
Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

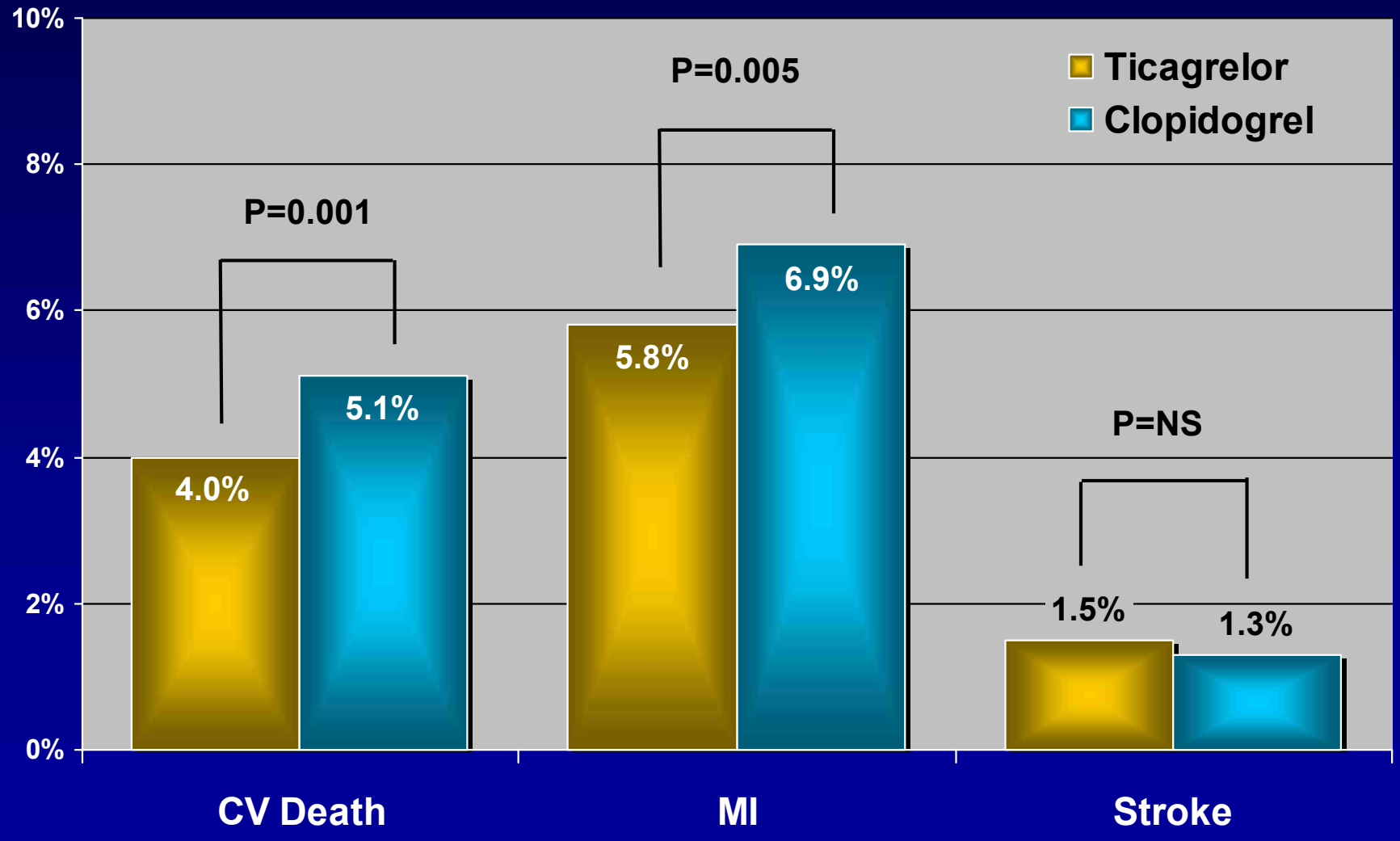
Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

Primary Endpoint: CV death/MI/Stroke

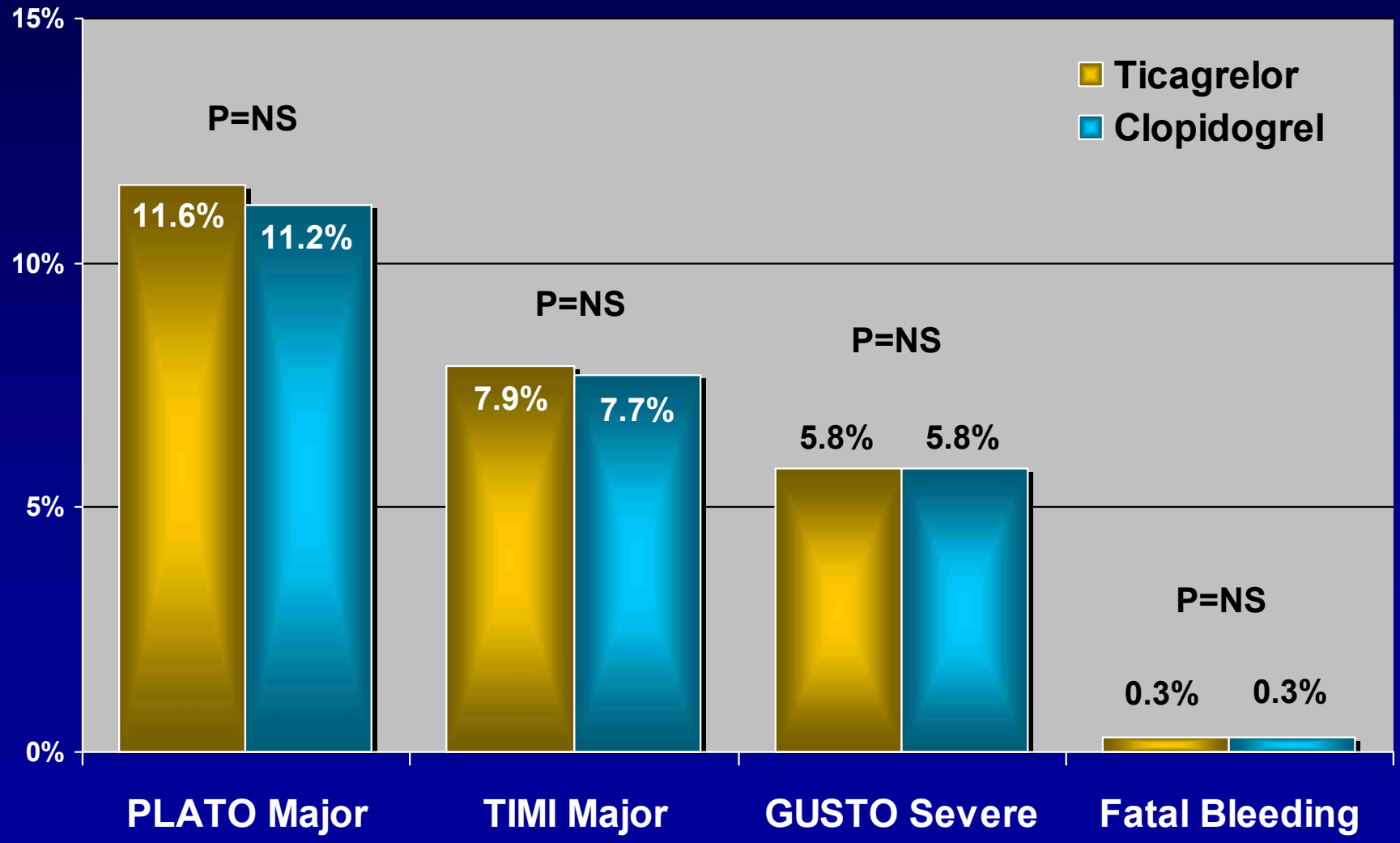
PLATO



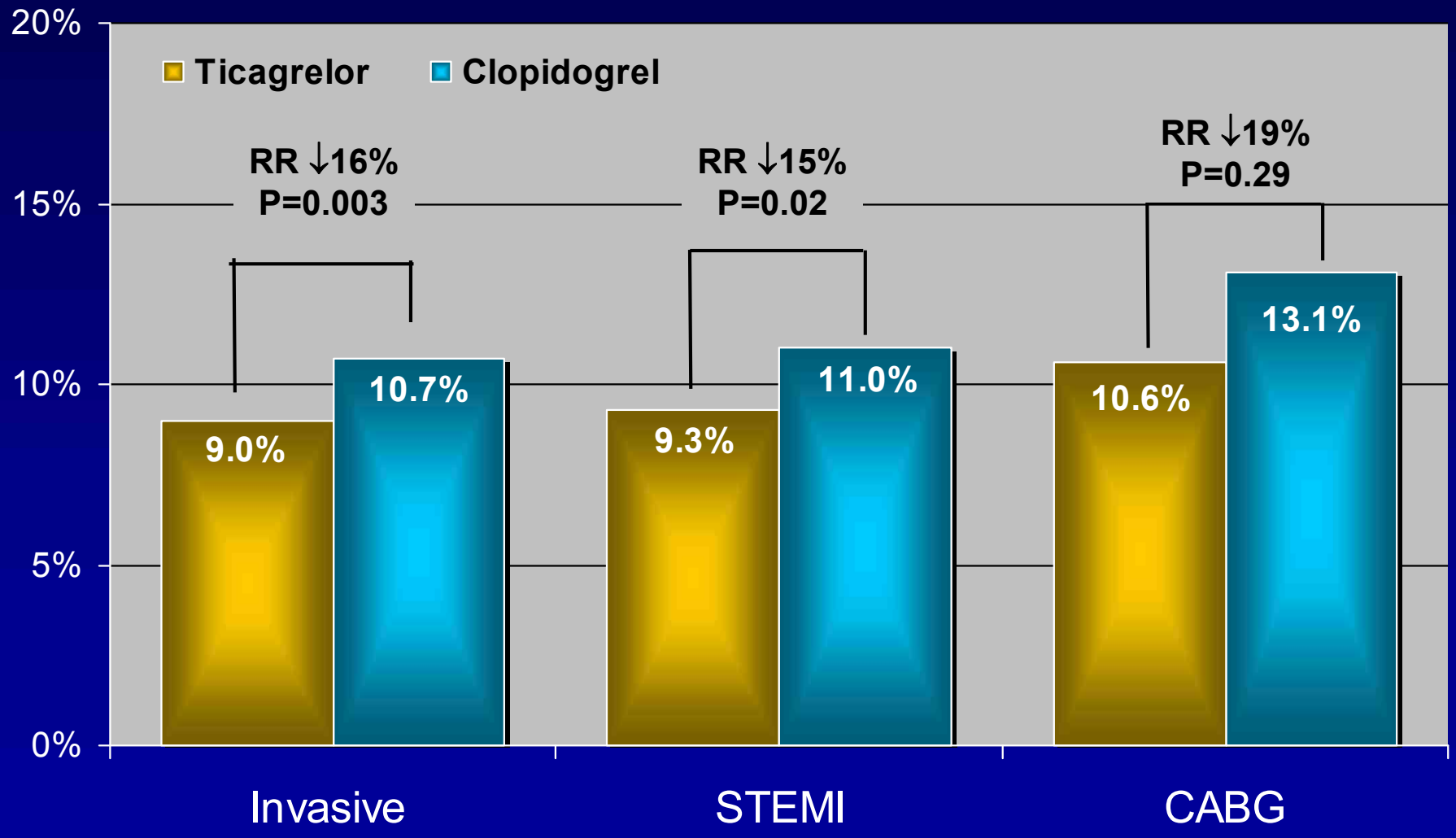
Endpoint Components



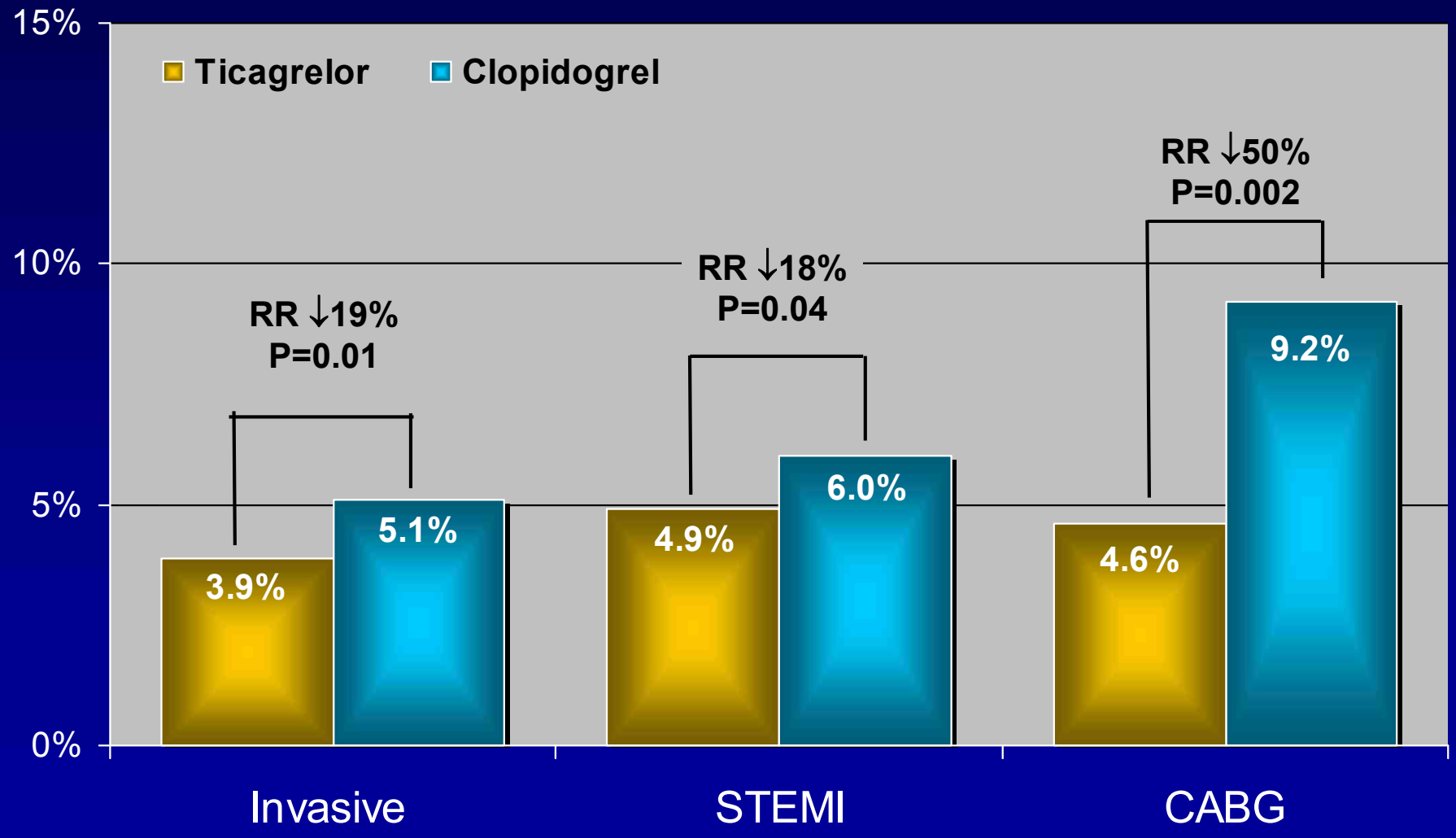
Bleeding Events



Key Subgroups: Primary Endpoint



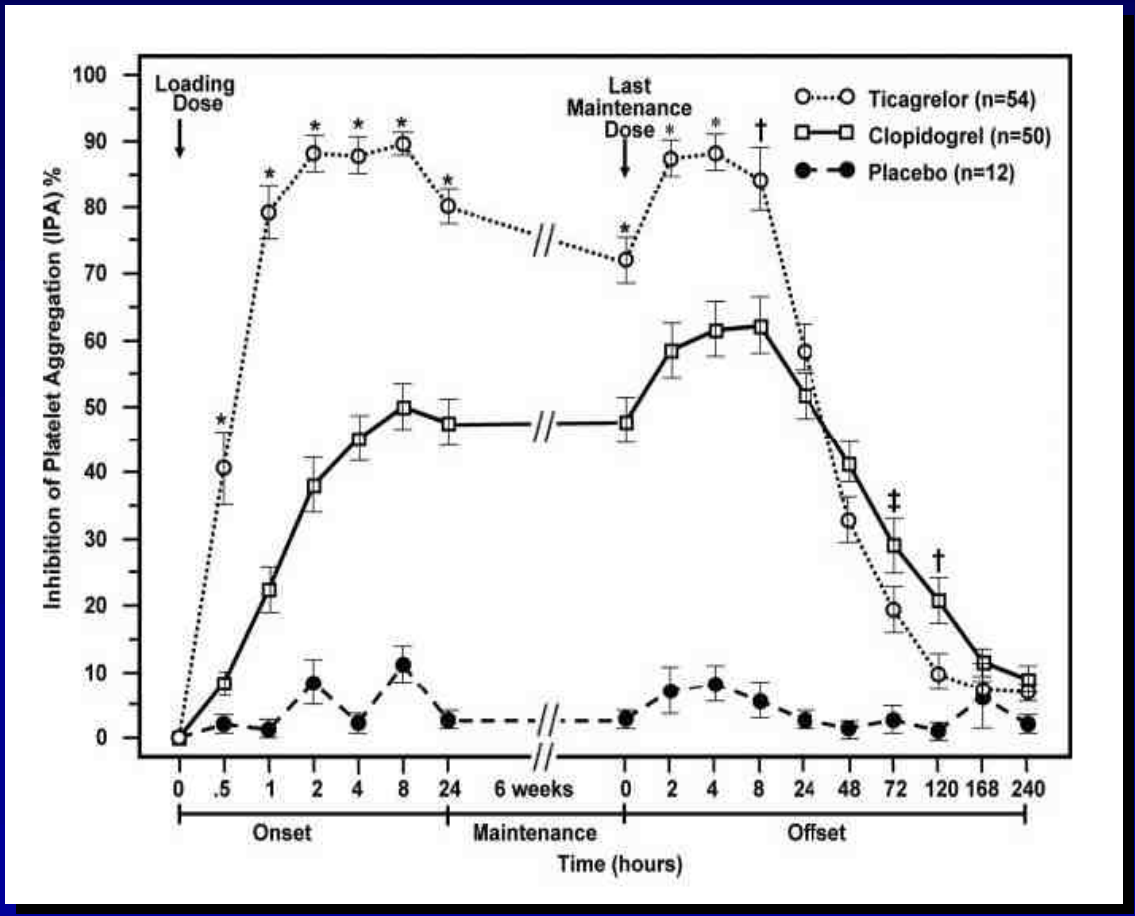
Key Subgroups: All-Cause Mortality



Why was ticagrelor so beneficial?

Ticagrelor: Onset/Offset vs. Clopidogrel

IPA (20 μM ADP)



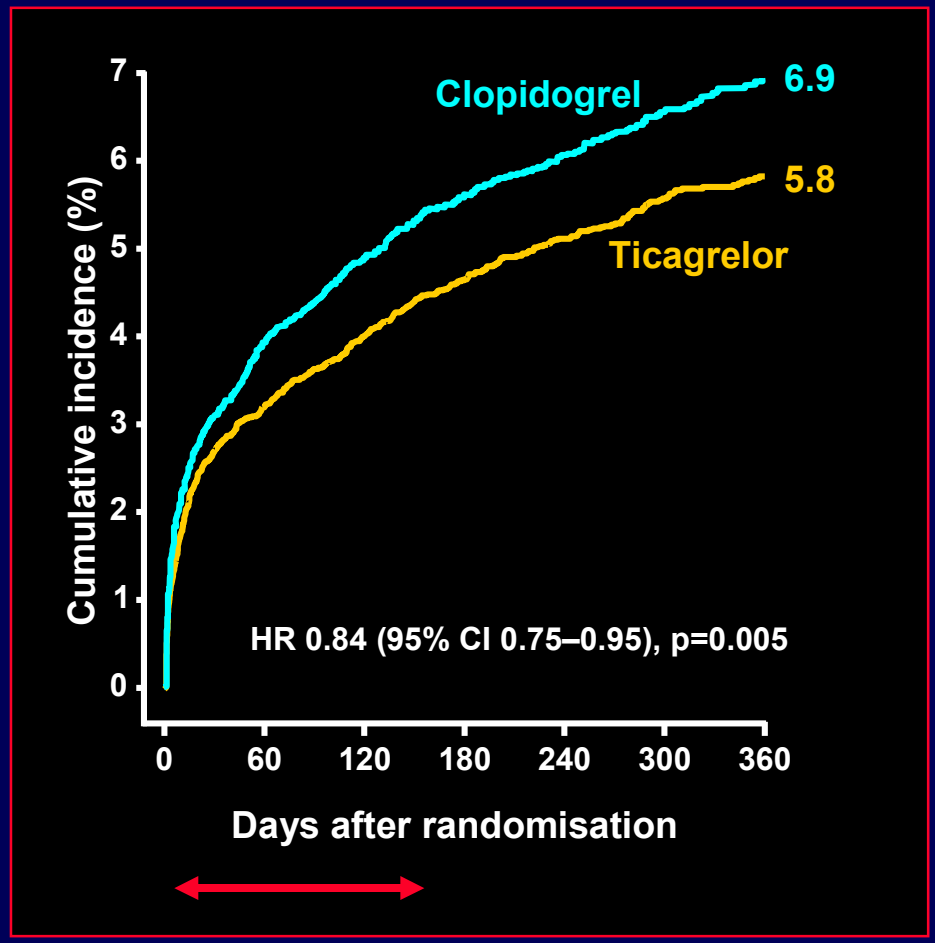
Onset/Offset Trial

- 123 pts with CAD randomized to ticagrelor (180/90), clopidogrel (600/75), or placebo
- By 2 hrs, >50% IPA achieved in 98% of ticagrelor vs. 31% clopidogrel
- Offset of ticagrelor ~ 2 days quicker than clopidogrel for any level of platelet inhbition

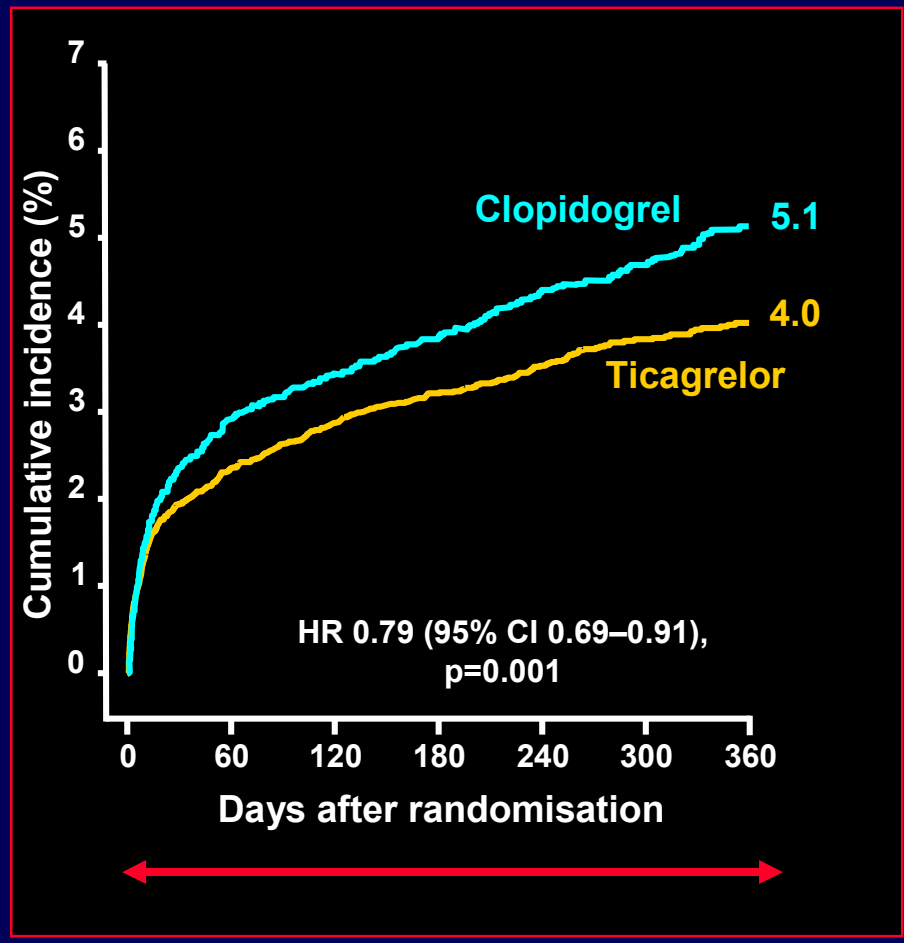
Gurbel PA et al. Circulation 2009;120

Timing of Benefit: MI vs. CV Death

Myocardial Infarction

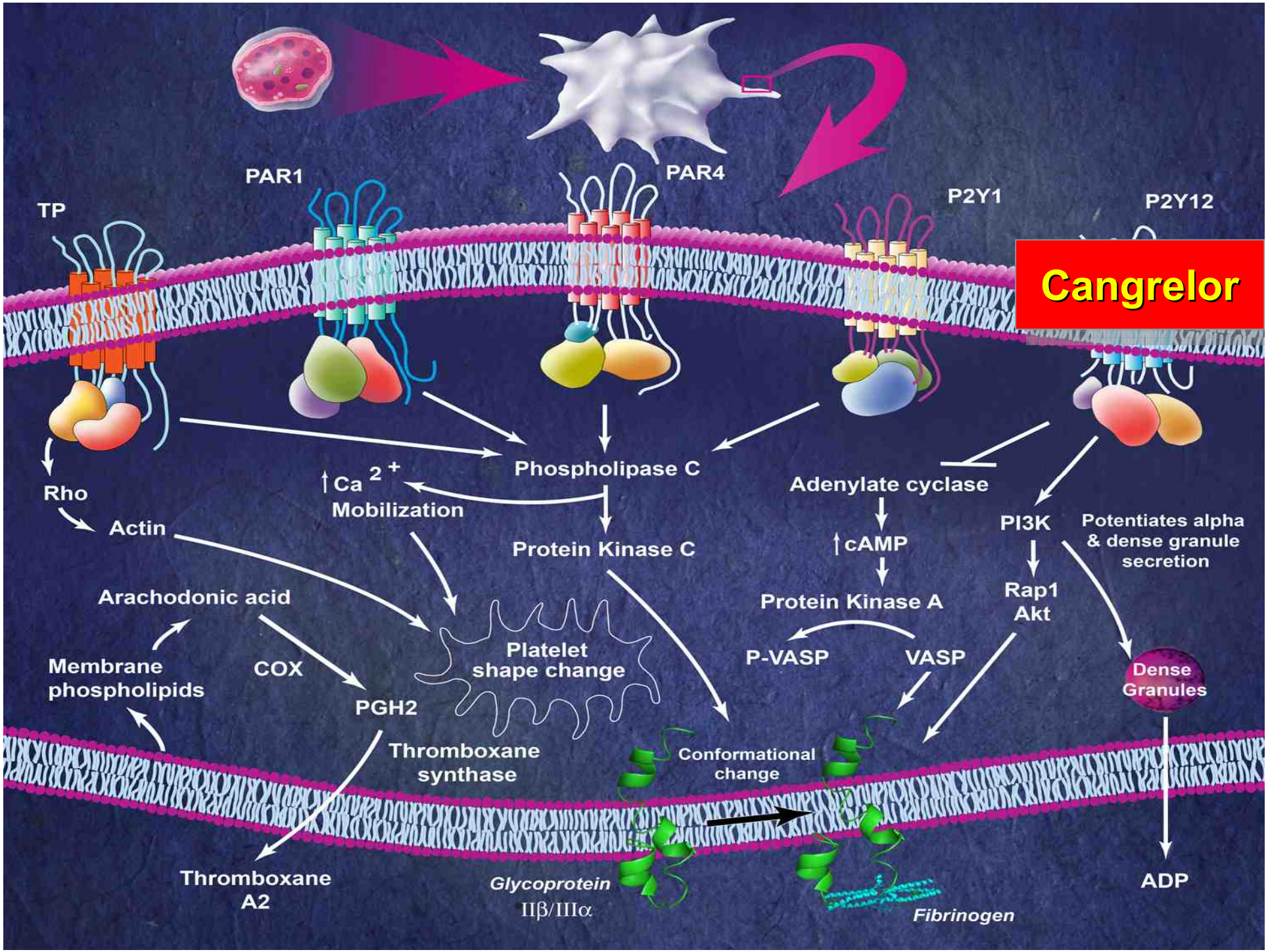


CV Death



Alternative Mechanisms

- "Decoupling" of ischemic protection from bleeding
  - *Do "non life-threatening bleeds" actually lead to increased long-term mortality?*
  - *But non-CABG TIMI major bleeding actually increased to a similar degree with ticagrelor as with prasugrel*
- Higher-risk population than TRITON
  - *1-year mortality in clopidogrel group 5.0% vs. 2.2%*
  - *40% STEMI vs. 25% STEMI*
- Is there an "off-target" effect related to adenosine production?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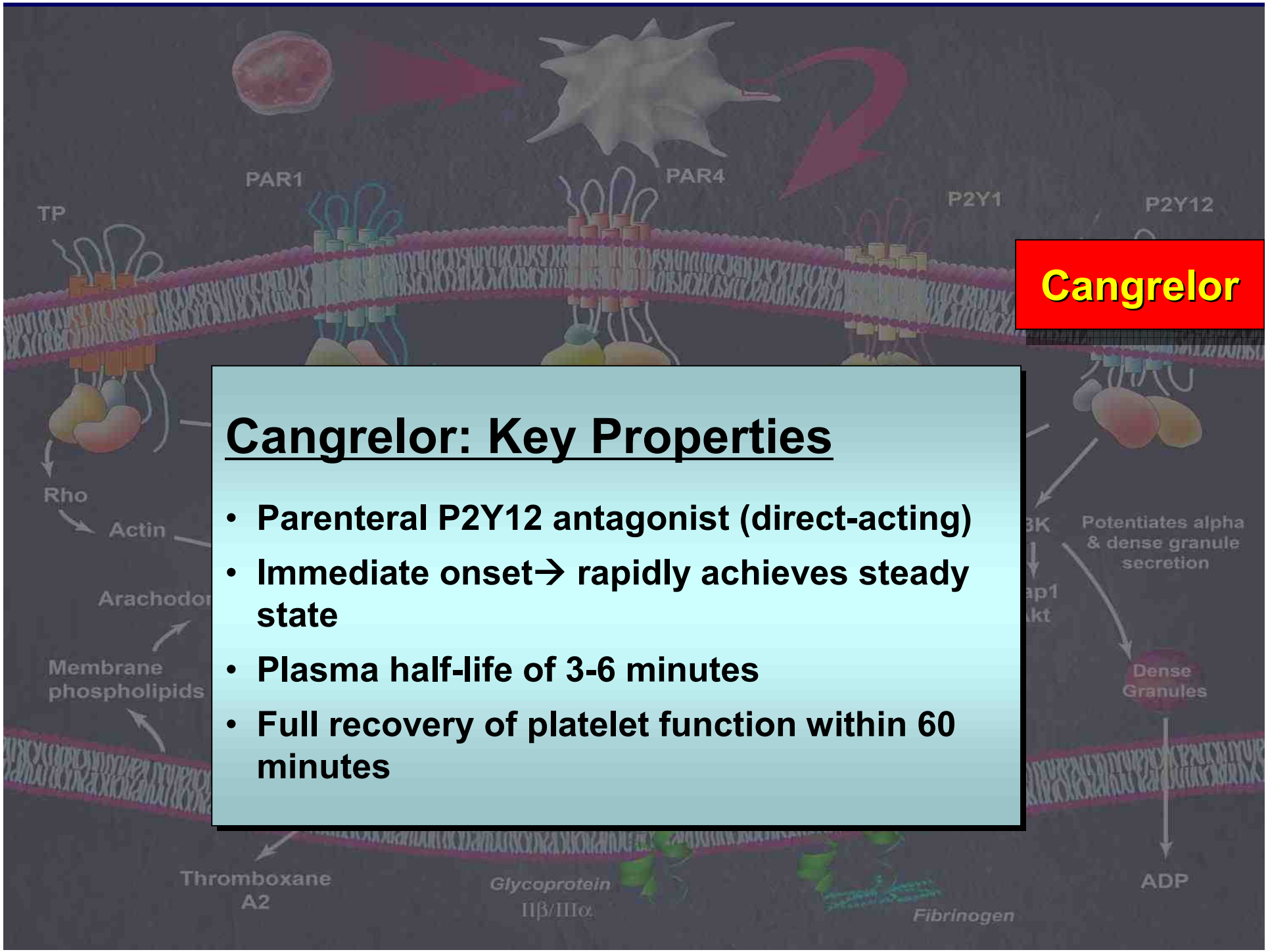
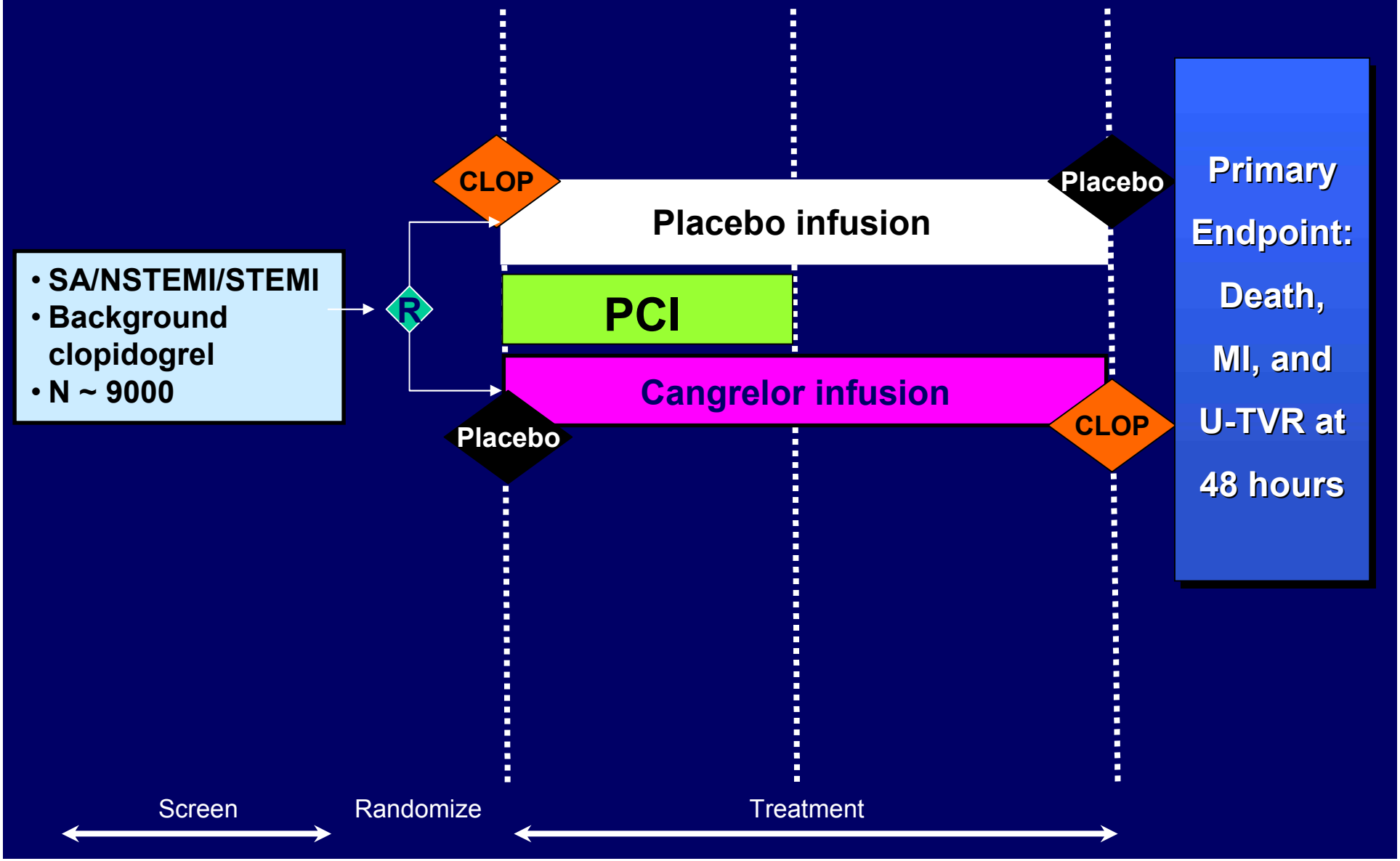


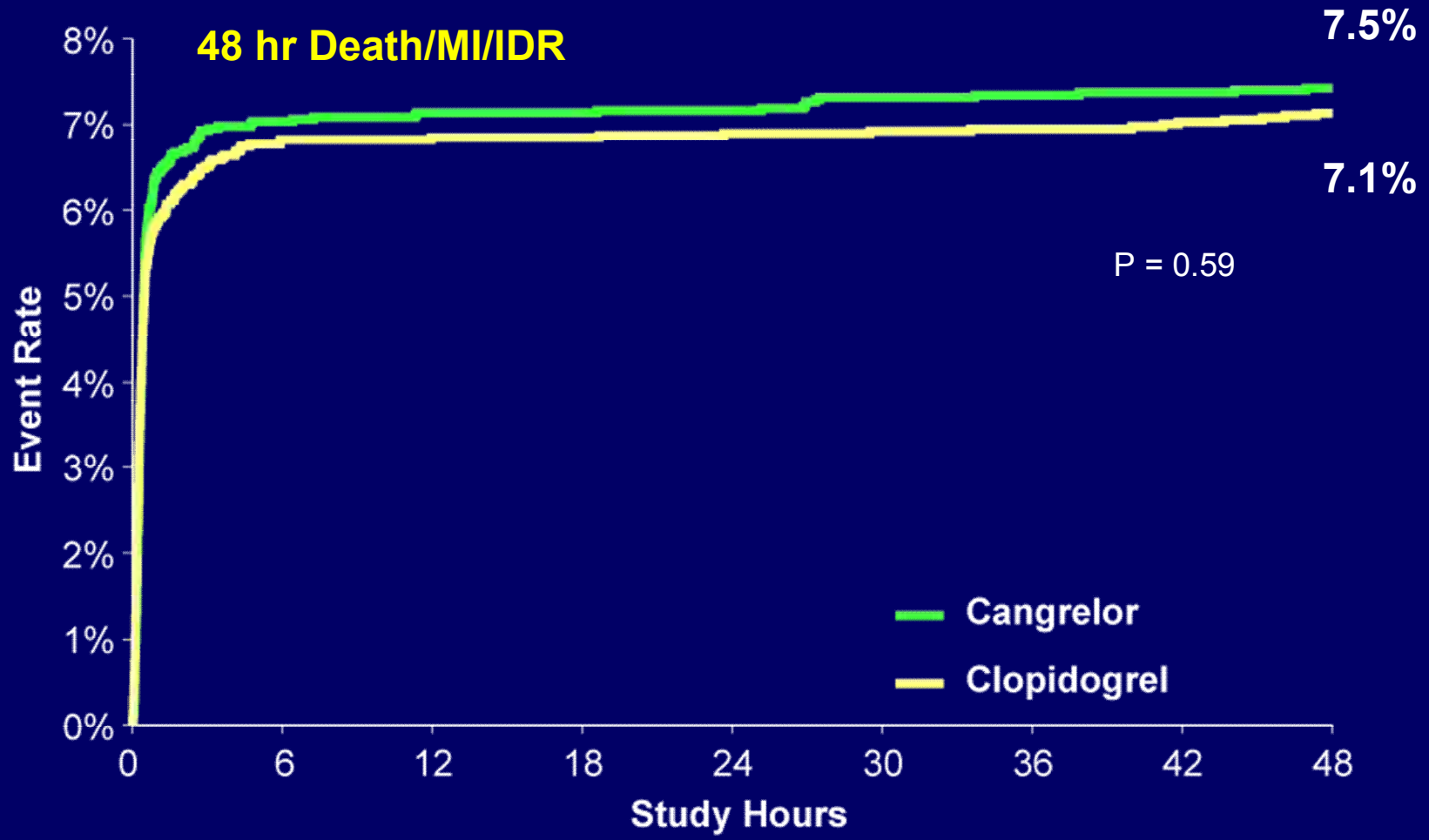
Cangrelor: Key Properties

- Parenteral P2Y12 antagonist (direct-acting)
- Immediate onset→ rapidly achieves steady state
- Plasma half-life of 3-6 minutes
- Full recovery of platelet function within 60 minutes

CHAMPION-PCI

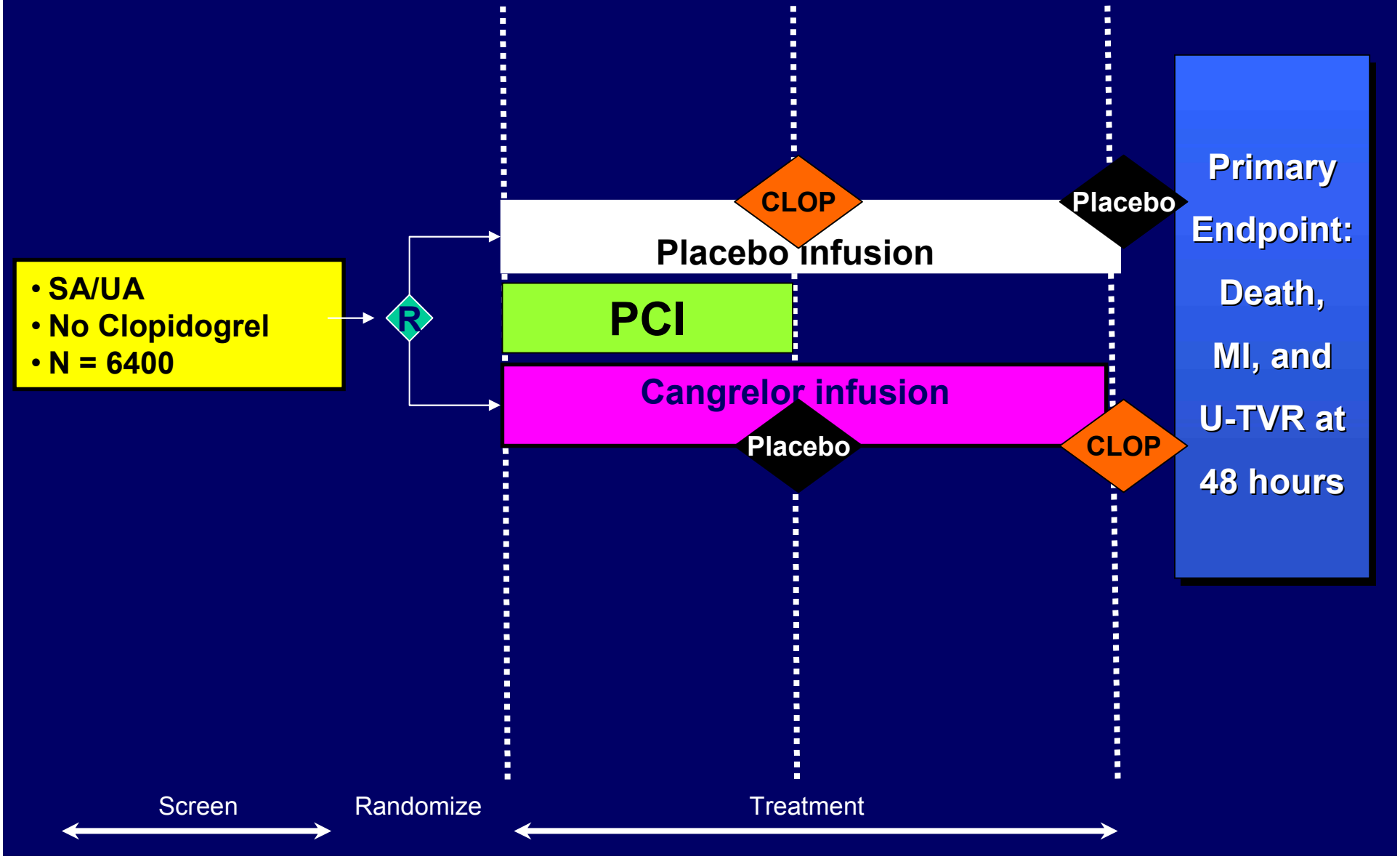


CHAMPION PCI: Primary Endpoint

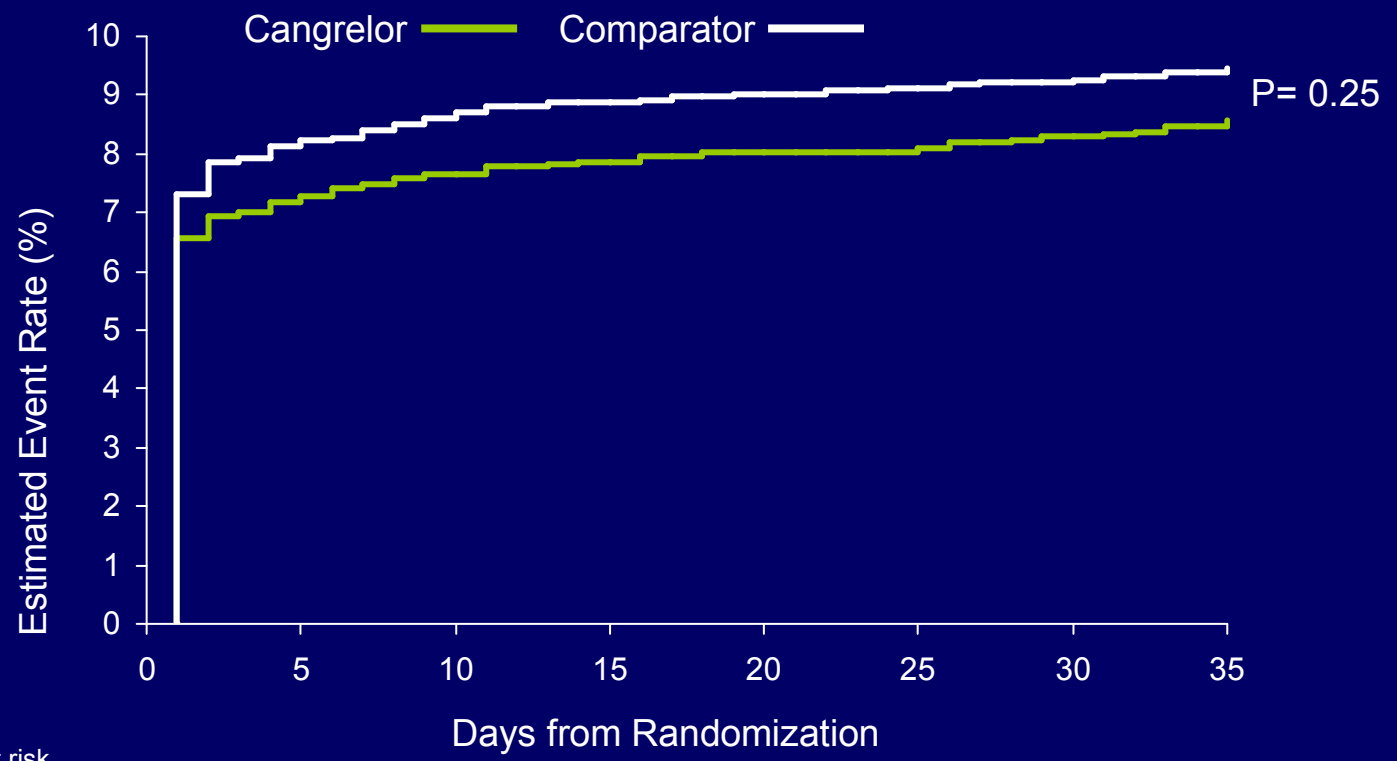


Cangrelor:	3897	3623	3619	3619	3614	3606	3604	3603	3599
Clopidogrel:	3871	3607	3606	3606	3602	3599	3598	3595	3588

CHAMPION-PLATFORM



CHAMPION PLATFORM: 30-day Death/MI/IDR



Patients at risk

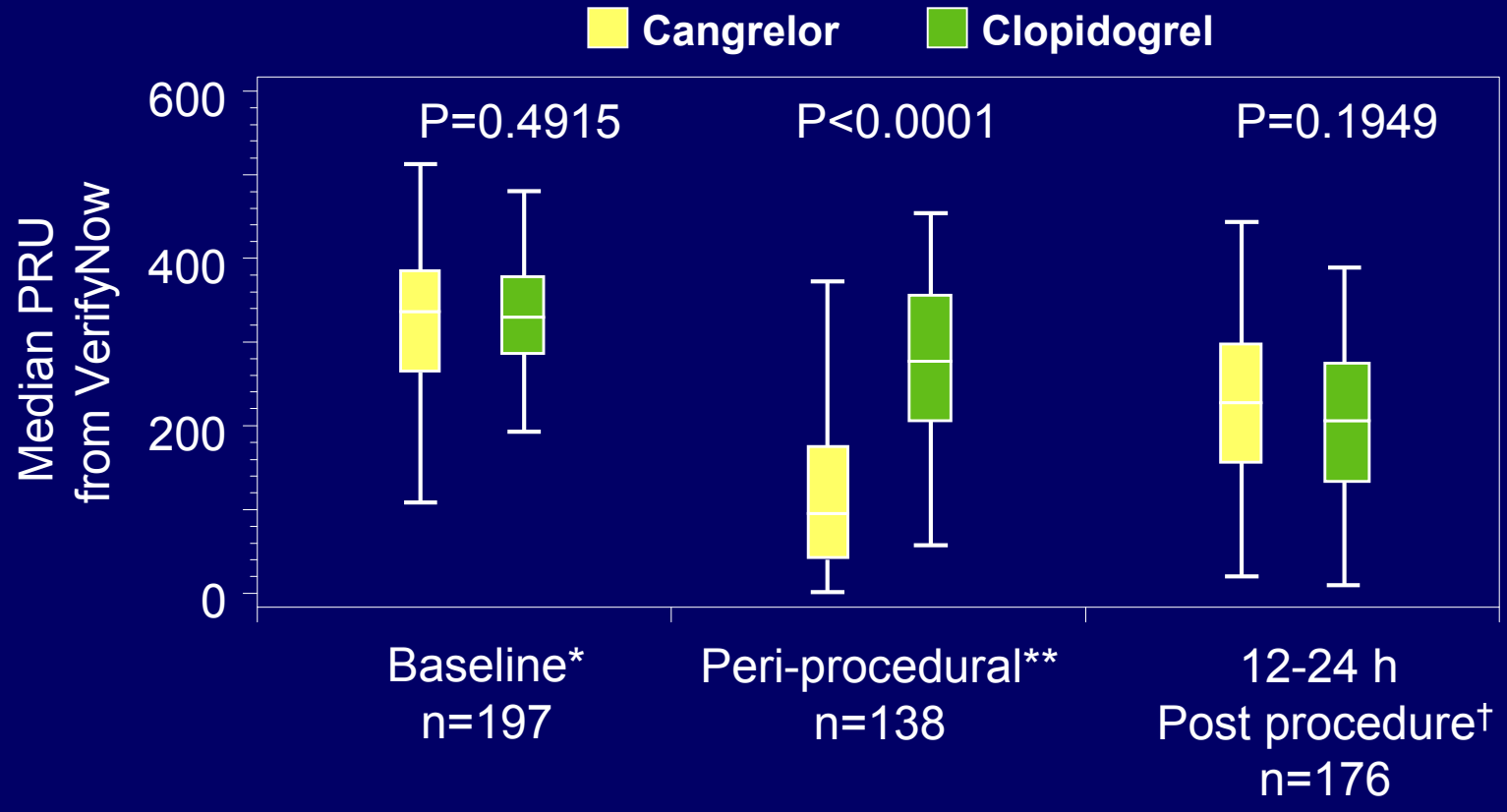
Cangrelor	2656	2461	2448	2441	2437	2437	2425	1557
Comparator	2645	2427	2409	2402	2399	2396	2389	1552

Why did it fail?

- Cangrelor-Clopidogrel interaction
  - *Circulating cangrelor may have prevented clopidogrel from achieving its full antiplatelet effect*

Platelet Substudy Results

- More robust platelet inhibition with cangrelor during infusion
- No evidence of attenuation of clopidogrel effect at 12-24 hours



**Baseline-Before the first infusion,
**Peri-procedural- During study drug/placebo infusion
† Post procedure - 1st sample within 12 to 24 hours relative to 1st Infusion.

Why did it fail?

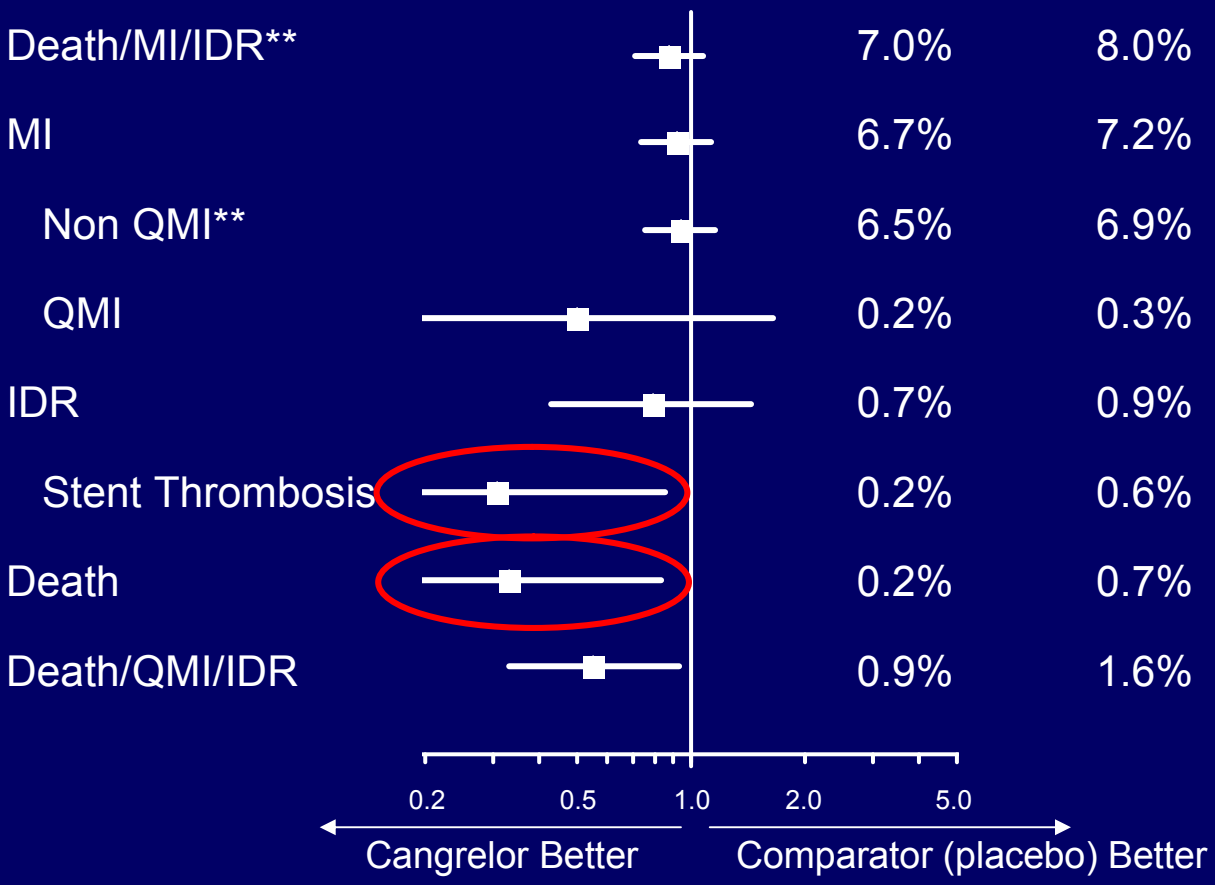
- Competitive inhibition of P2Y12 receptor
  - *Circulating cangrelor may have prevented clopidogrel from achieving its full antiplatelet effect*
- Periprocedural MI may actually occur several hours post-PCI (after cangrelor is turned off)

Why did it fail?

- Competitive inhibition of P2Y12 receptor
  - *Circulating cangrelor may have prevented clopidogrel from achieving its full antiplatelet effect*
- Periprocedural MI may actually occur several hours post-PCI (after cangrelor is turned off)
- Difficult to diagnose periprocedural MI in the ACS setting, particularly when time from presentation to PCI is very brief

CHAMPION PLATFORM: Efficacy Endpoints at 48 Hours

Efficacy mITT* (SA/UA/NSTEMI)	Cangrelor N=2654	Comparator N=2641	OR [95% CI]	P value
Death/MI/IDR**	7.0%	8.0%	0.87 (0.71,1.07)	0.17
MI	6.7%	7.2%	0.92 (0.74,1.13)	0.42
Non QMI**	6.5%	6.9%	0.94 (0.76,1.16)	0.55
QMI	0.2%	0.3%	0.50 (0.15,1.65)	0.25
IDR	0.7%	0.9%	0.79 (0.43,1.44)	0.44
Stent Thrombosis	0.2%	0.6%	0.31 (0.11,0.85)	0.02
Death	0.2%	0.7%	0.33 (0.13,0.83)	0.02
Death/QMI/IDR	0.9%	1.6%	0.55 (0.33,0.93)	0.02



* *Primary Analysis

** mITT= modified intent to treat population (patients with PCI and study drug), QMI= Q-wave myocardial infarction

Why did it fail?

- Competitive inhibition of P2Y12 receptor
  - *Circulating cangrelor may have prevented clopidogrel from achieving its full antiplatelet effect*
- Periprocedural MI may actually occur several hours post-PCI (after cangrelor is turned off)
- Difficult to diagnose periprocedural MI in the ACS setting, particularly when time from presentation to PCI is very brief
- Clopidogrel 600mg is a pretty tough competitor

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.
- Over the next several years, several other novel antiplatelet agents will likely be approved and are likely to have a profound impact on the practice and outcomes of PCI

Emerging Platelet Inhibitors for PCI/ACS

- While current antiplatelet therapies are efficacious, there is substantial room for improvement– particularly in the ACS setting
- The TRITON trial is the first to demonstrate that greater, more rapid, and more uniform platelet inhibition improves antithrombotic efficacy, but it does come at the price of greater major bleeding.
- Over the next several years, several other novel antiplatelet agents will likely be approved and are likely to have a profound impact on the practice and outcomes of PCI