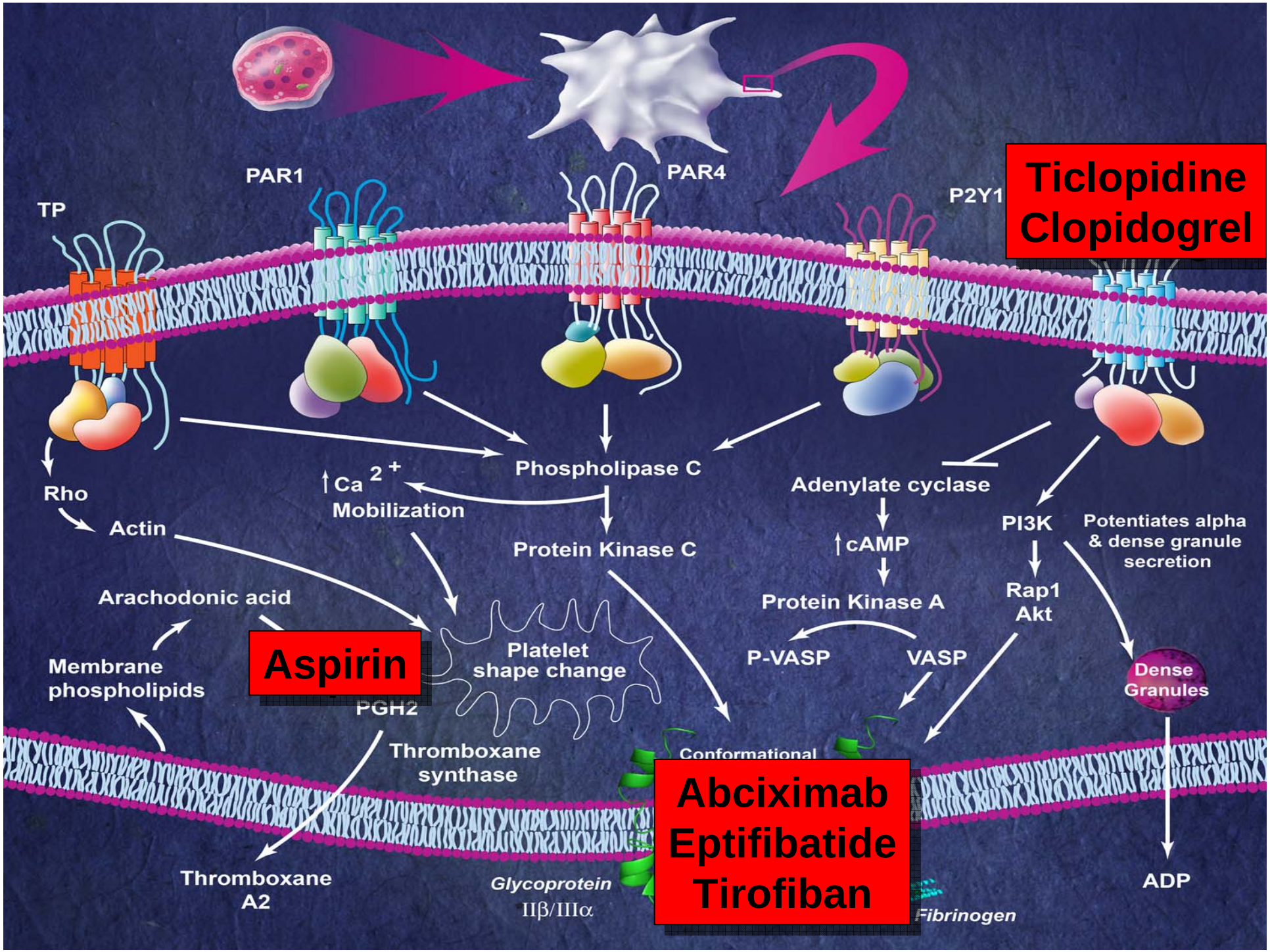
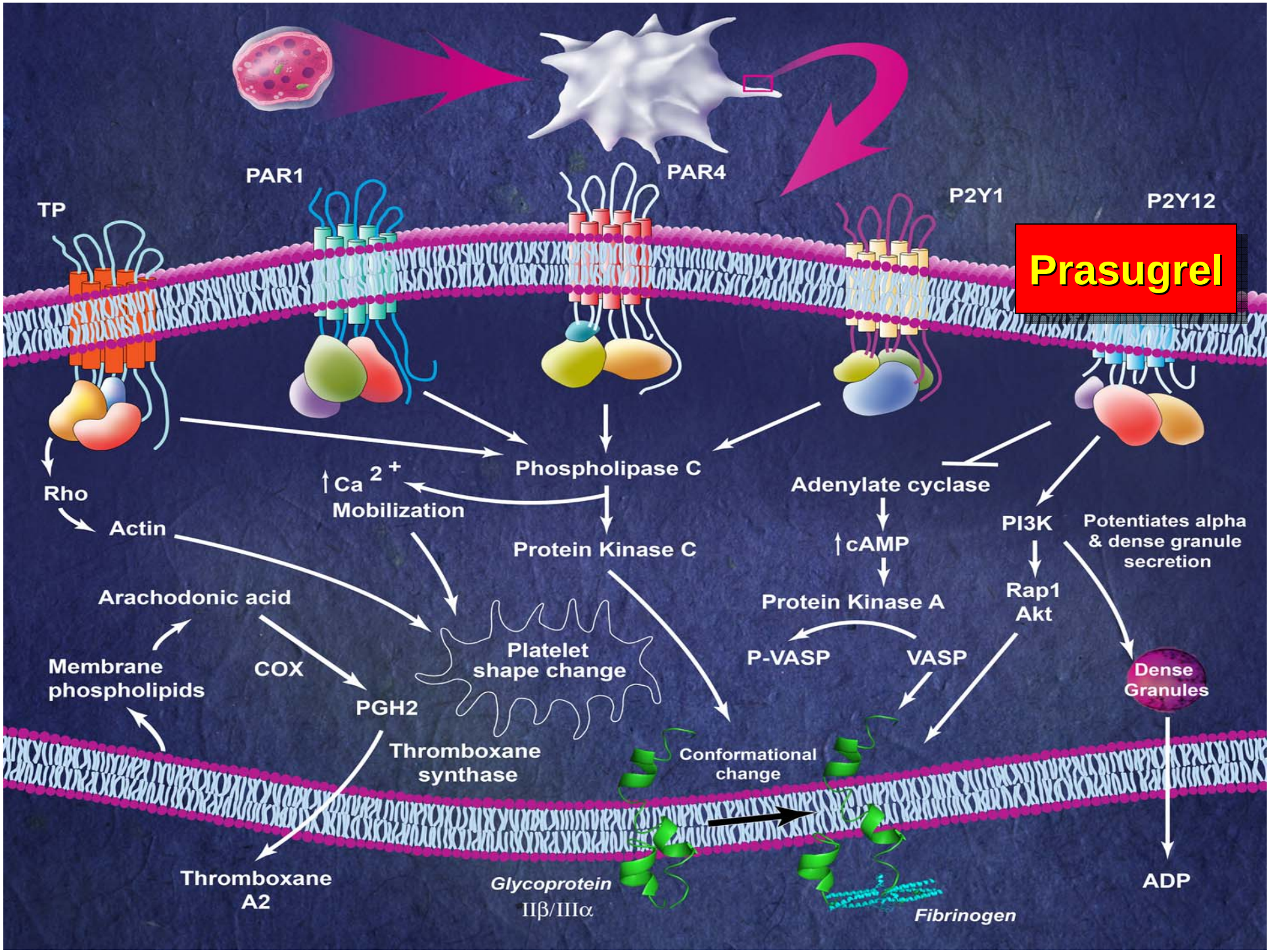
New and Emerging Approaches to Antiplatelet Therapy for PCI

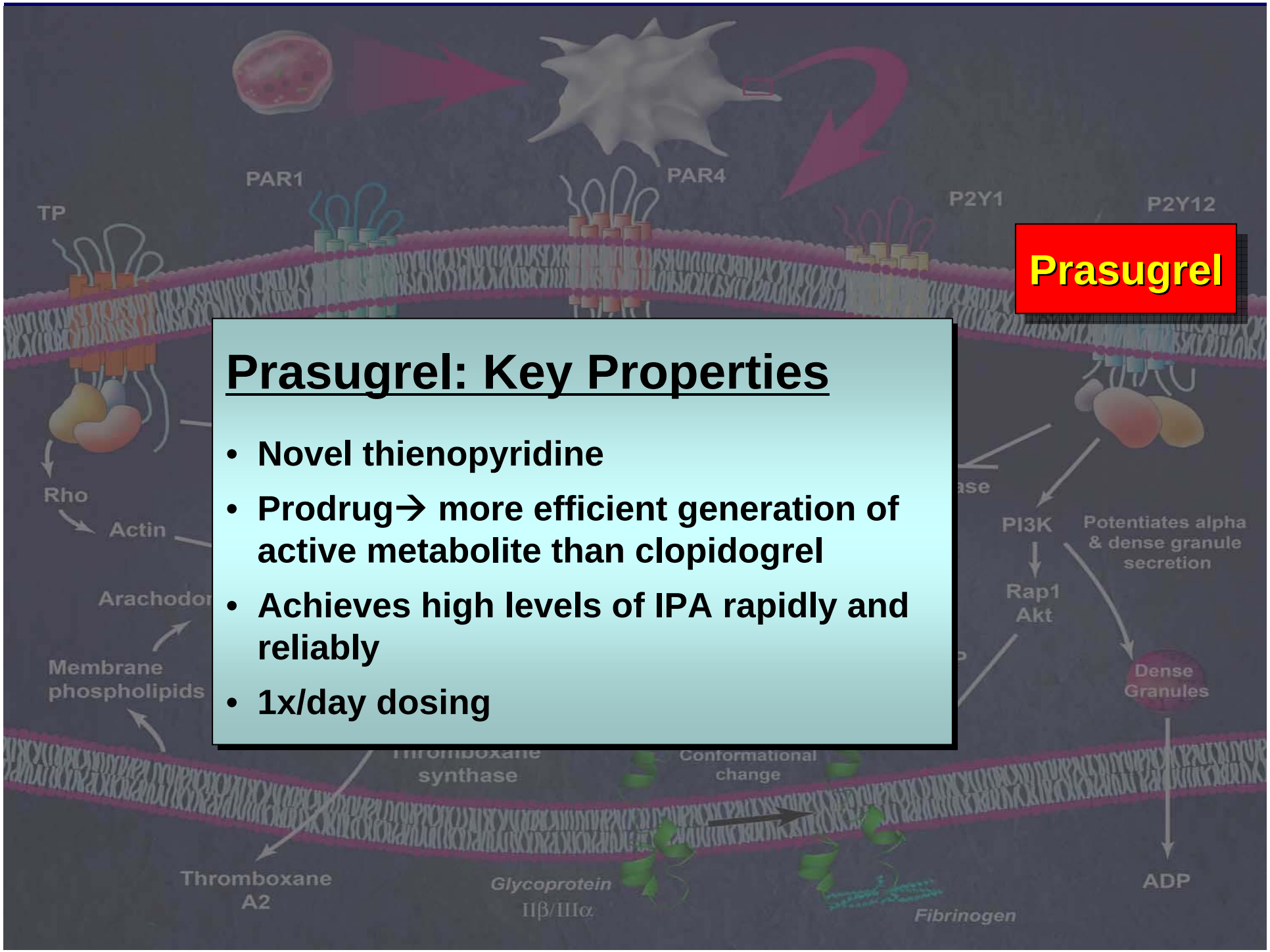
David J. Cohen, M.D., M.Sc.

Director, Cardiovascular Research
Saint-Luke's Mid America Heart Institute

Professor of Medicine
University of Missouri-Kansas City


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

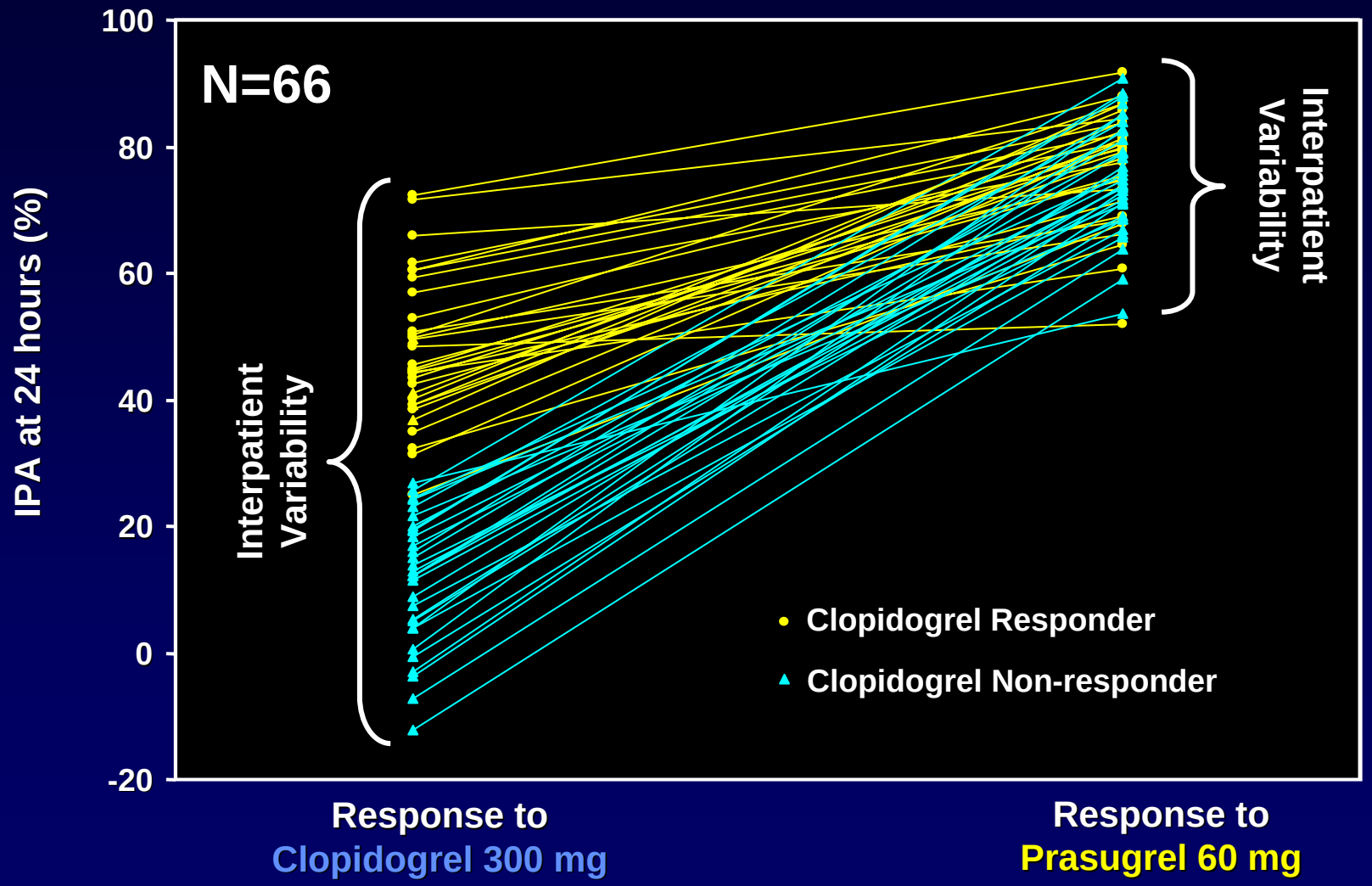

PAR1
PAR4
TP
P2Y1
P2Y12
Prasugrel
Rho
Actin
↑Ca 2 +
Mobilization
Phospholipase C
Protein Kinase C
Adenylate cyclase
↑cAMP
Protein Kinase A
PI3K
Rap1
Akt
Potentiates alpha
& dense granule
secretion
Arachodonic acid
Membrane
phospholipids
COX
PGH2
Thromboxane
synthase
Platelet
shape change
P-VASP
VASP
Dense
Granules
Conformational
change
Thromboxane
A2
Glycoprotein
IIβ/IIIα
Fibrinogen
ADP



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

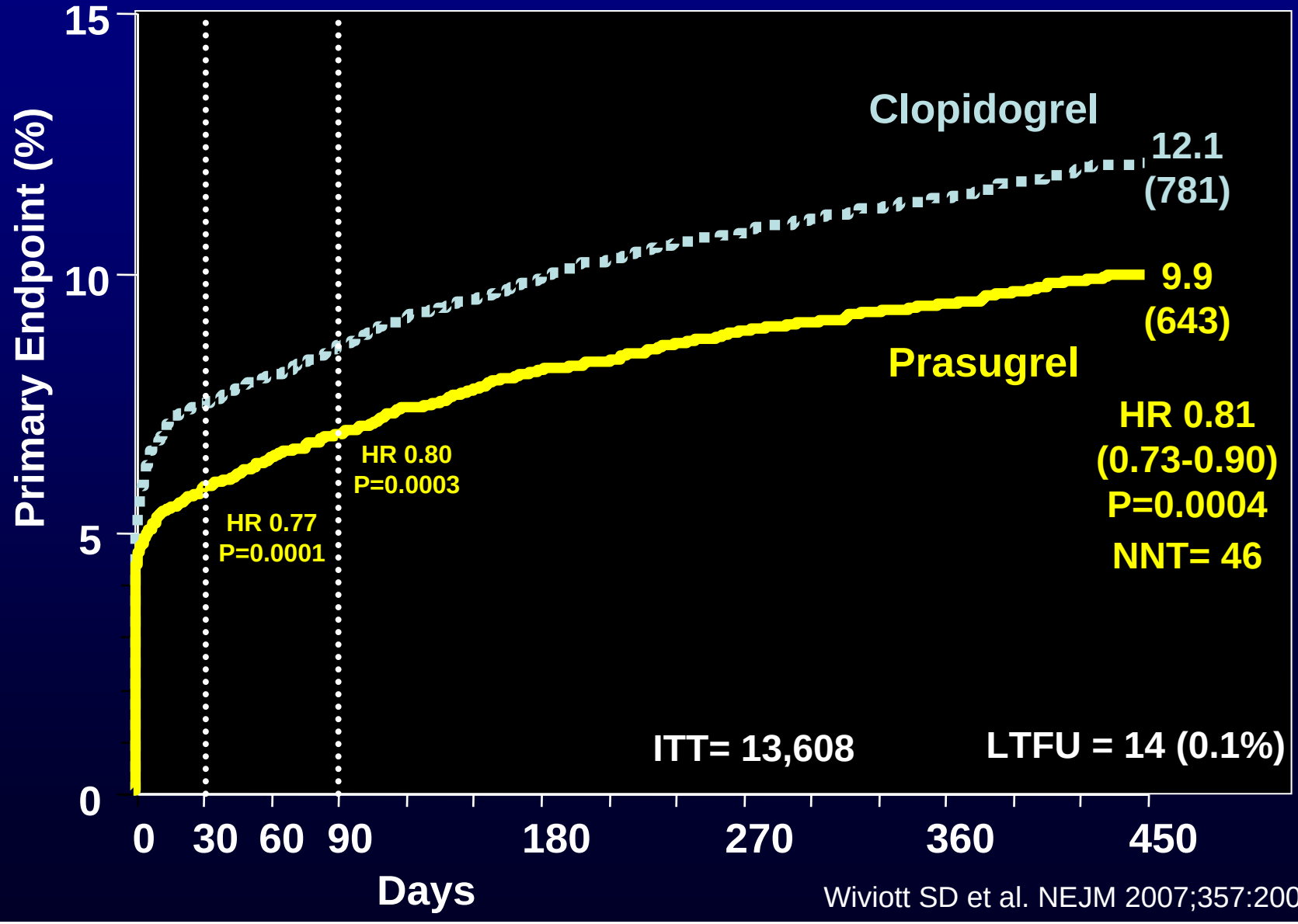
Median duration of therapy ~ 12 months

1º endpoint: CV death, MI, Stroke

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

TRITON TIMI-38

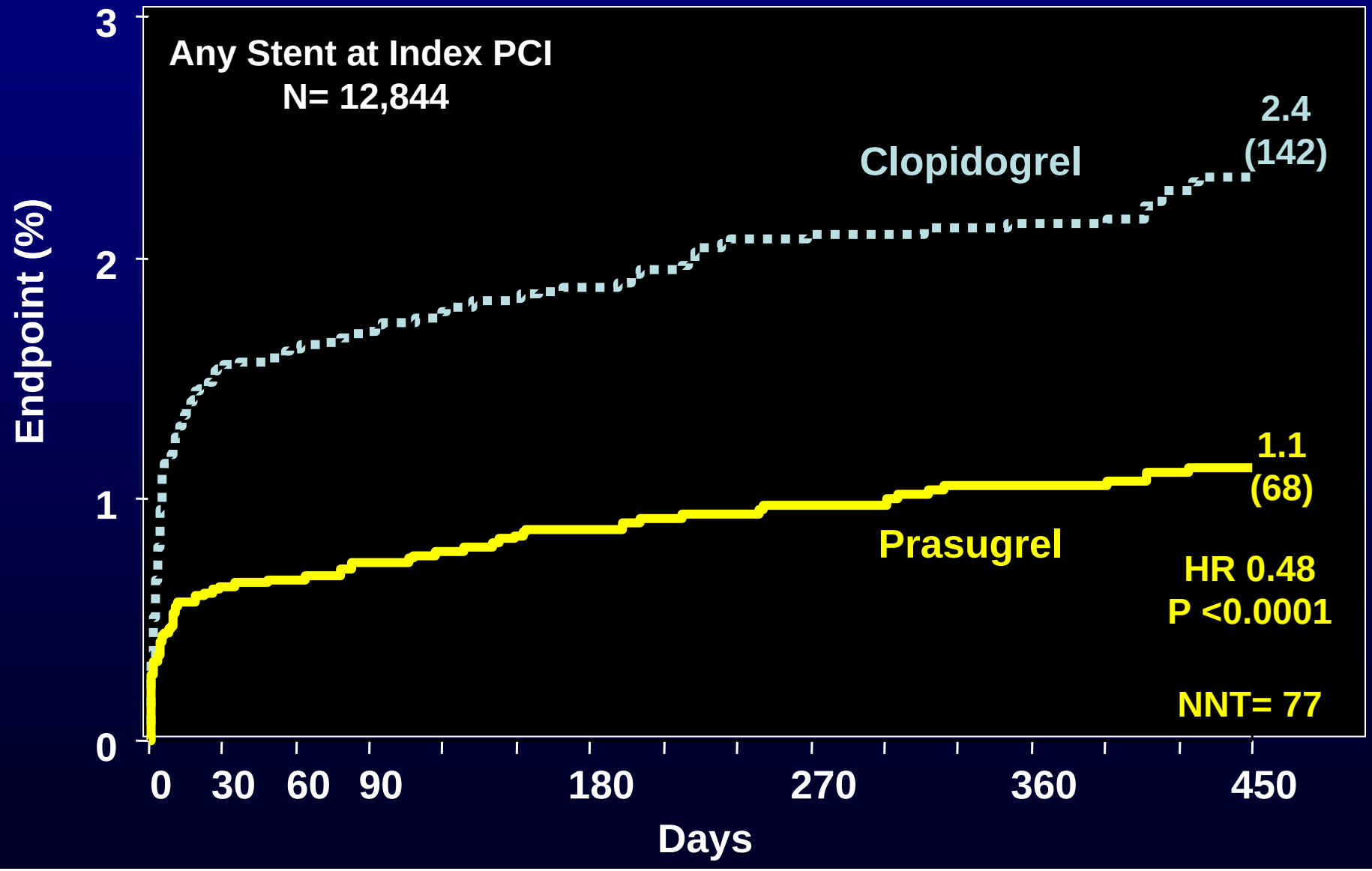
Primary Endpoint
CV Death,MI,Stroke



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

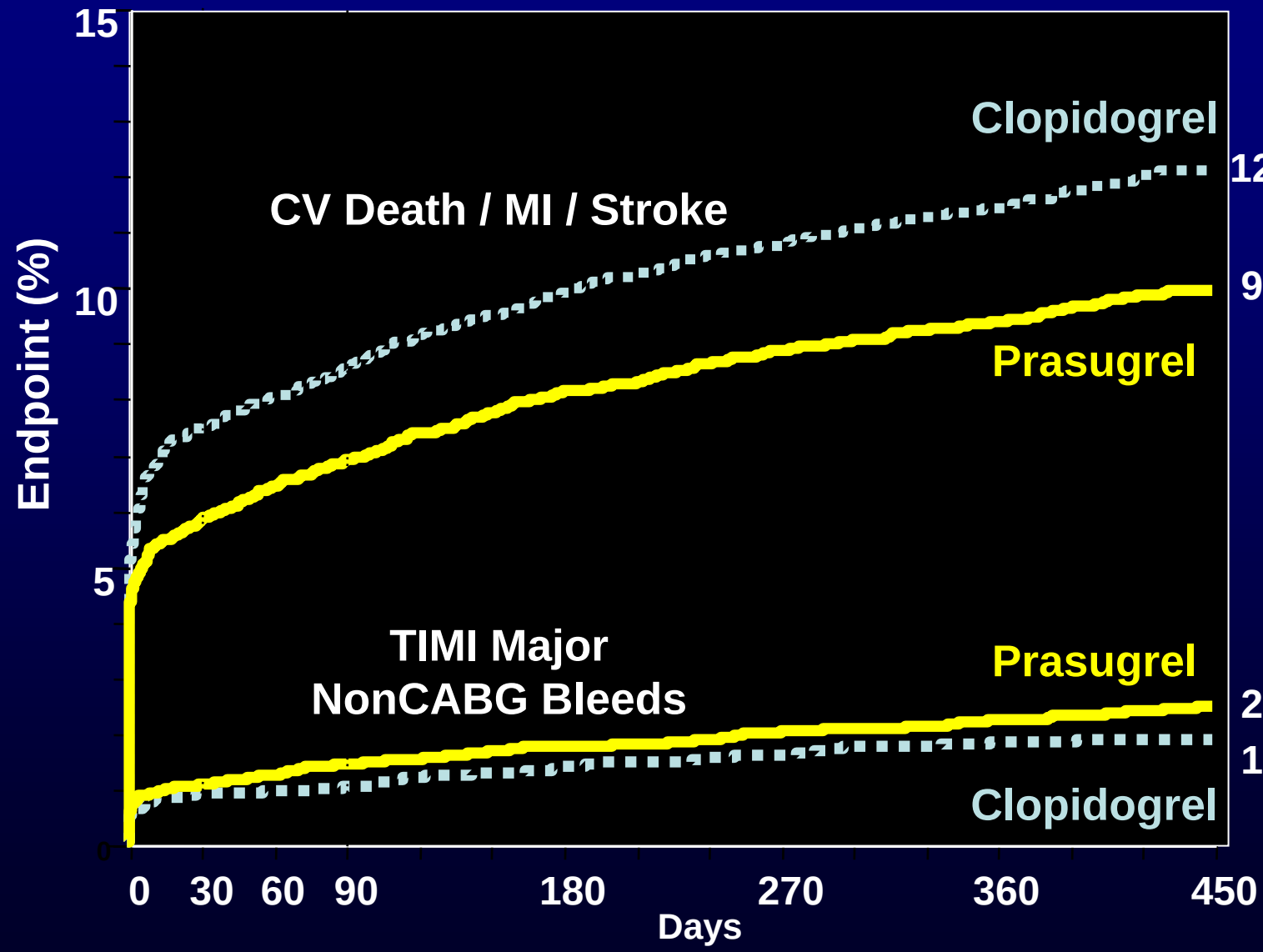
TRITON TIMI-38

Stent Thrombosis
(ARC Definite + Probable)



TRITON TIMI-38

Balance of Efficacy and Safety



↓ 138 events

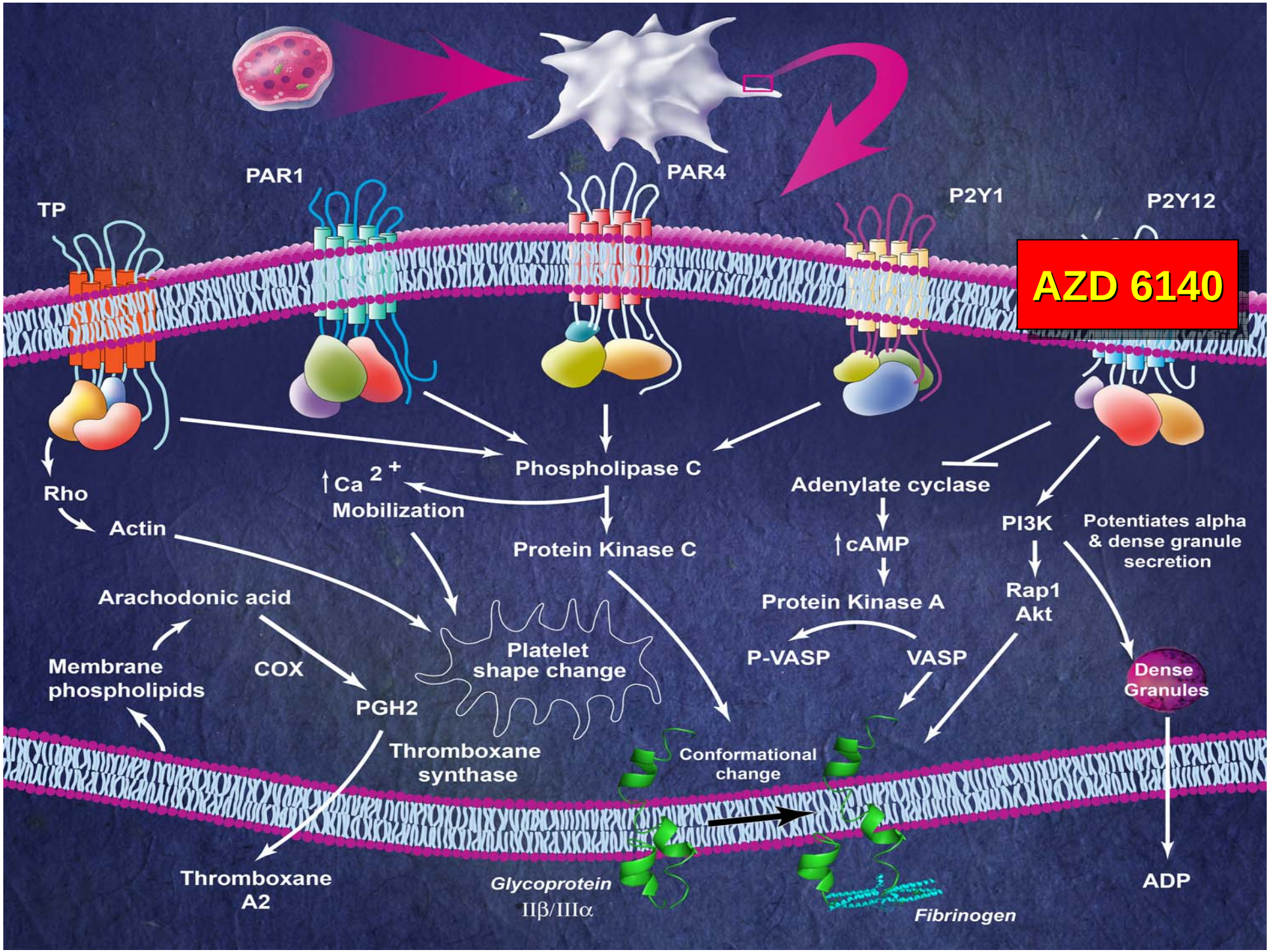
HR 0.81
(0.73-0.90)
P=0.0004

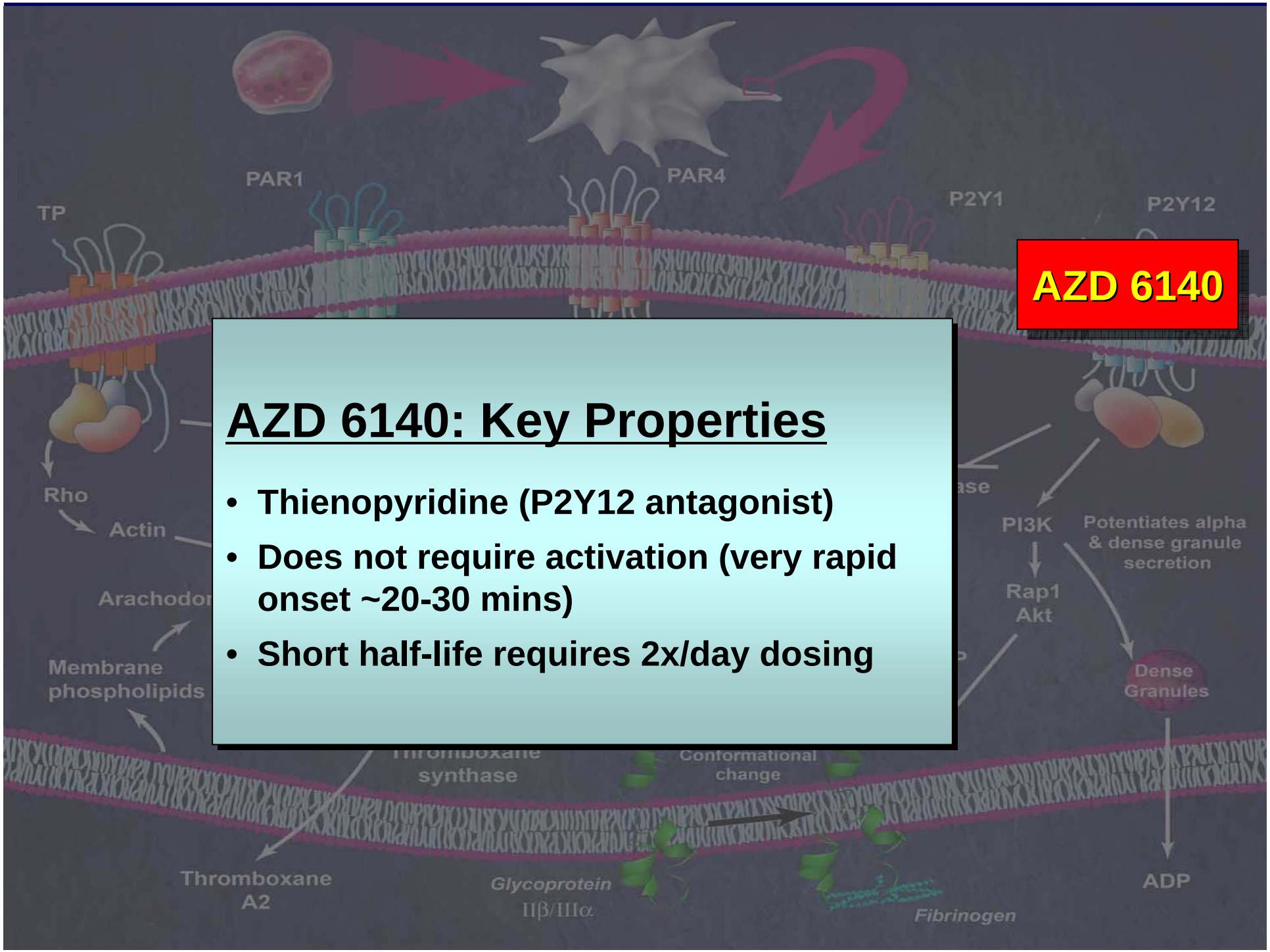
NNT = 46

↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167


PAR1
PAR4
TP
P2Y1
P2Y12
AZD 6140
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
Membrane
phospholipids
COX
PGH2
Thromboxane
synthase
Platelet
shape change
P-VASP
VASP
Dense
Granules
Conformational
change
Thromboxane
A2
Glycoprotein
IIβ/IIIα
Fibrinogen
ADP



AZD 6140: Key Properties

- Thienopyridine (P2Y12 antagonist)
- Does not require activation (very rapid onset ~20-30 mins)
- Short half-life requires 2x/day dosing

PLATO

Can PLATelet Inhibition be Optimized to Prevent Vascular Events

~16,000 patients within 24 hours of an index ACS (STEMI or NSTEMI)

ASA 75 -100mg QD

AZD6140 BID

Clopidogrel 75 mg QD

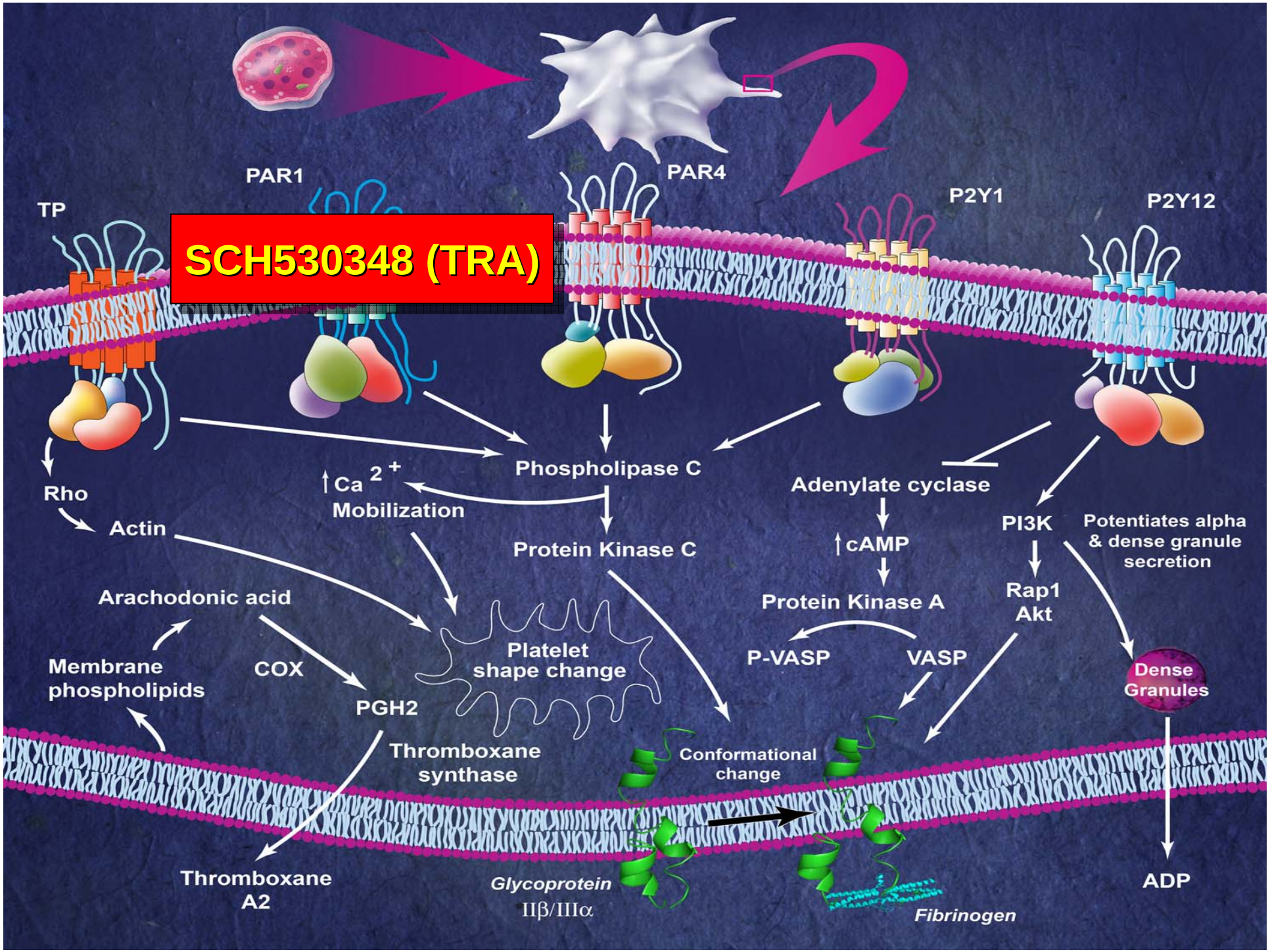
At least 2 inclusion criteria:

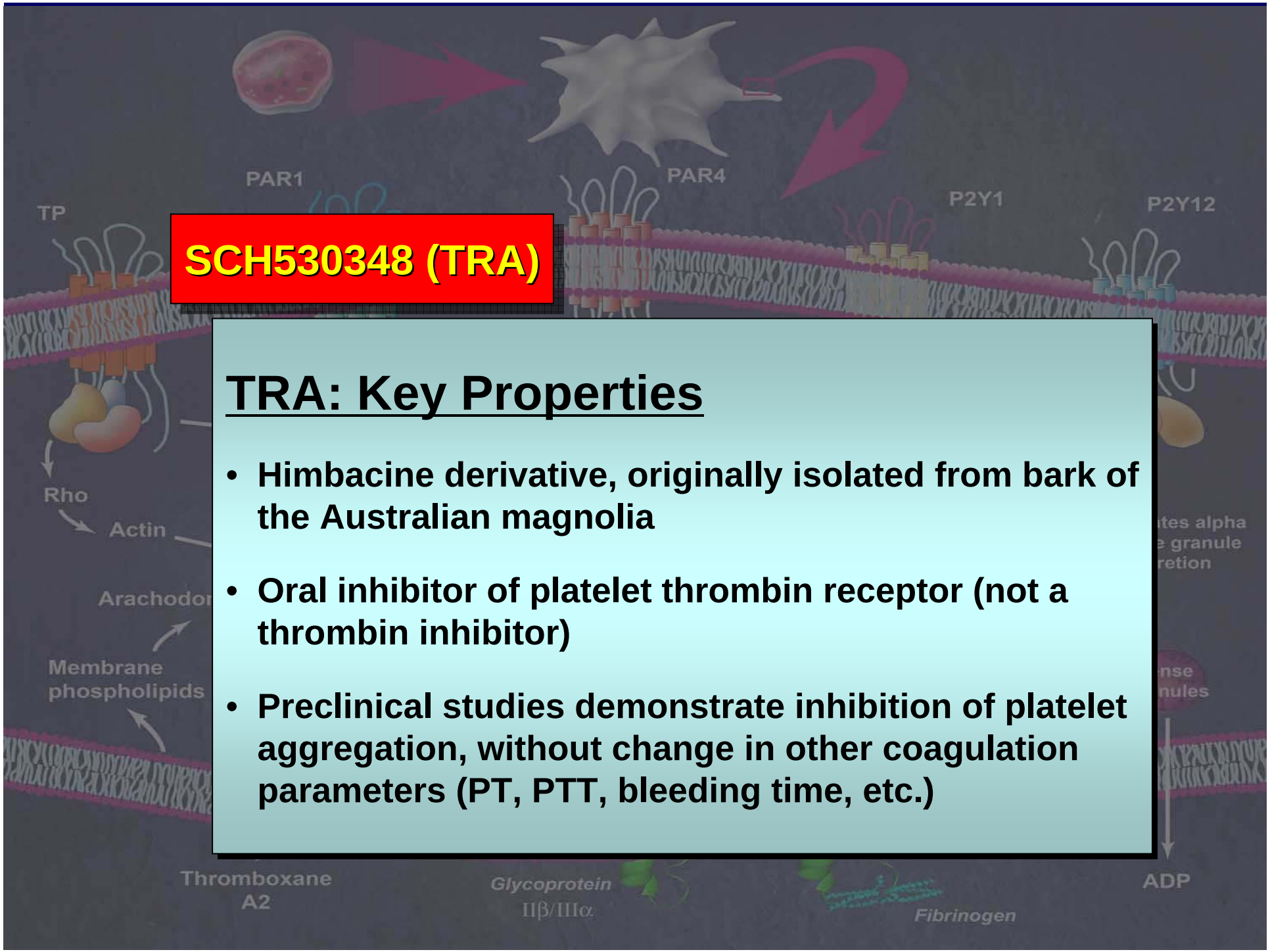
1. ST segment changes
2. + biomarkers
3. At least 1 high risk condition:
   - > 60 y.o.
   - Previous MI/CABG
   - Known > 1V CAD
   - AODM
   - PVD
   - Renal dysfxn

Double-blind, double-dummy
Mean f/u ~12.5 months. Range 6-24

Primary Endpoint: Time to first occurrence of the composite of death, MI or stroke.

Primary Safety Endpoint: Major bleeding


SCH530348 (TRA)
PAR1
PAR4
TP
P2Y1
P2Y12
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
Membrane
phospholipids
COX
PGH2
Thromboxane
synthase
Platelet
shape change
P-VASP
VASP
Dense
Granules
Conformational
change
Thromboxane
A2
Glycoprotein
IIβ/IIIα
Fibrinogen
ADP



SCH530348 (TRA)

TRA: Key Properties

- **Himbacine derivative, originally isolated from bark of the Australian magnolia**
- **Oral inhibitor of platelet thrombin receptor (not a thrombin inhibitor)**
- **Preclinical studies demonstrate inhibition of platelet aggregation, without change in other coagulation parameters (PT, PTT, bleeding time, etc.)**

T·R·A-PCI Study Design

Non-Urgent PCI or Cath possible PCI (All Receive Aspirin)
Randomization #1 — 3:1 SCH530348:Placebo (Single Loading Dose)
Sequential Groups: 1=10 mg; 2=20 mg; 3=40 mg, or Placebo

Cardiac Catheterization
Planned PCI (All Receive ASA, Clopidogrel, and Antithrombin)

Randomization #2 1:1:1
Maintenance Therapy Once Daily for ~ 60 days
SCH 530348 Loading Dose → SCH 530348
Or Placebo Loading Dose → Placebo

SCH 530348

0.5 mg n~100	1 mg n~100	2.5 mg n~100	Placebo n~100

Safety: TIMI Major plus Minor Bleeding
Efficacy: Death/MACE

**** Primary Evaluable Cohort***

No PCI**

CABG

Medical Management

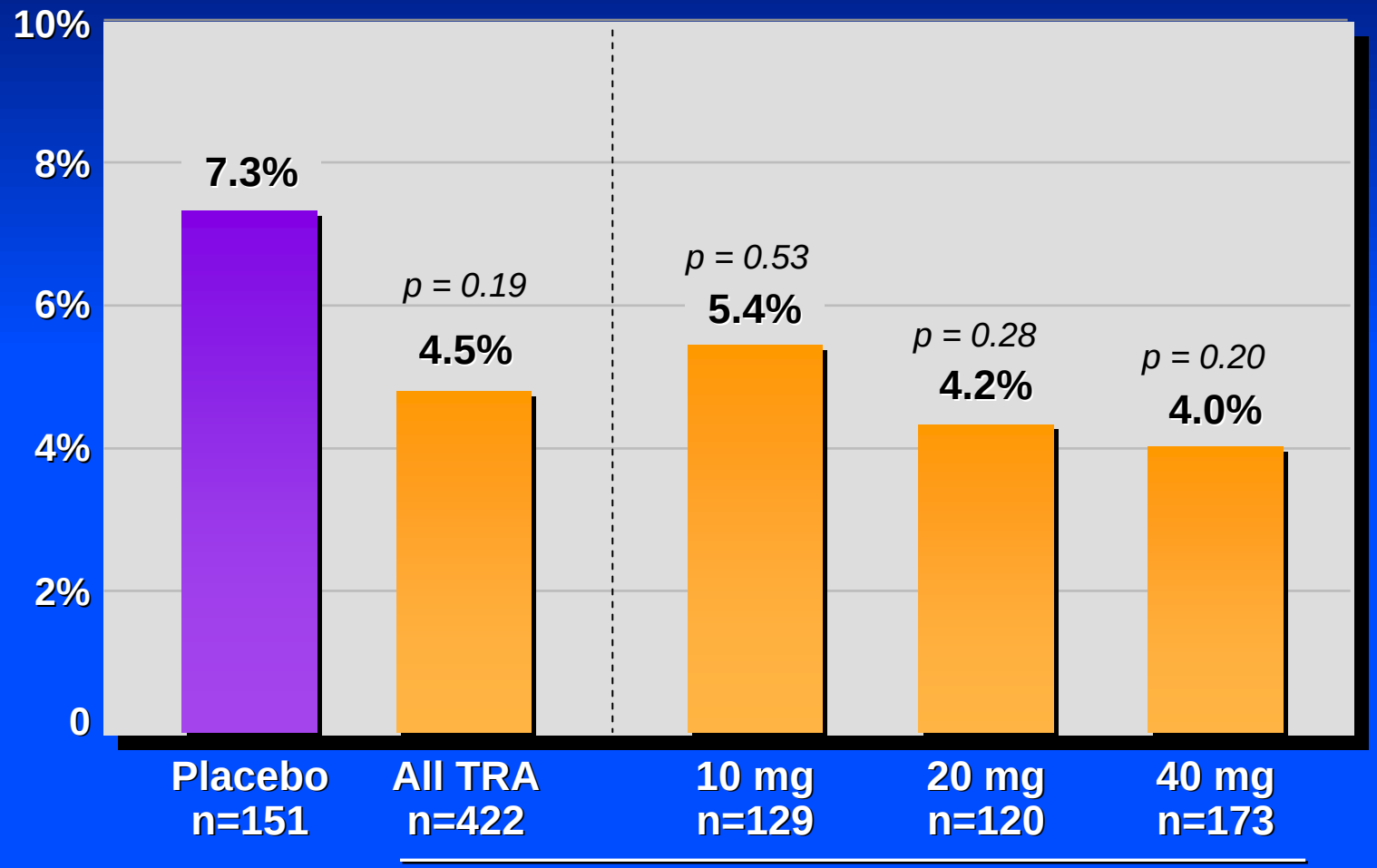
Quantify Postoperative Chest-Tube Drainage, Transfusions, and Re-exploration

Safety: TIMI Major plus Minor Bleeding

*****Secondary Evaluable Cohort***

Ischemic Events

60-Day Death or MI

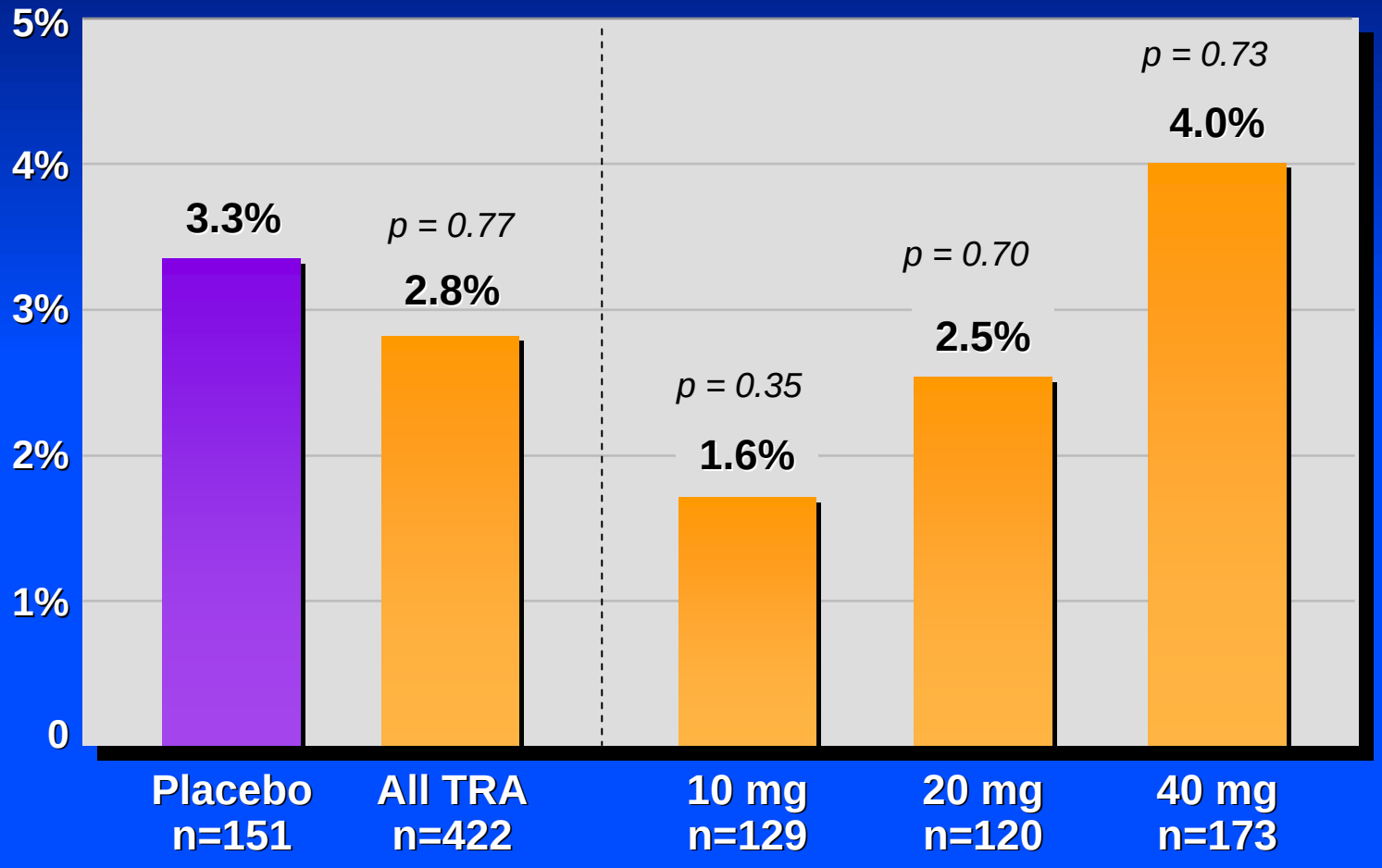


p- value relative to placebo

T·R·A-PCI

Bleeding Events

TIMI Major/Minor Bleeding



p- value relative to placebo

T·R·A-PCI

TRA Phase III Trials

TRA-ACS

10,000 Patients with ACS

- TRA 40mg Load, 2.5mg QD
- Placebo

1° Endpoint:
CV death, MI, rehosp for ACS, urgent revasc, stroke.
Minimum 1 year f/u

In addition to std. tx, including ASA and clopidogrel

TRA 2P – TIMI 50

19,500 Patients with prior MI, stroke or PVD

- TRA 2.5mg QD
- Placebo

1° Endpoint:
CV death, MI, urgent revasc, stroke.
Minimum 1 year f/u

Emerging Platelet Inhibitors for PCI/ACS

- While current antiplatelet therapies are efficacious, there is substantial room for improvement.
- 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, the results of multiple large scale clinical trials involving at least half a dozen novel antiplatelet agents and nearly 100,000 patients will have a major impact on our ability to better treat the ACS and PCI patient.