

# Reshaping the Guidelines

## Clopidogrel Classic vs. New Therapies: PLATO and More



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# Presenter Disclosure Information

Name: Dominick J Angiolillo

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Received payment as an individual for:

- a) Consulting fee or honorarium from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca, Merck, Evolva, Abbott Vascular and PLx Pharma;
- b) Participation in review activities from Johnson & Johnson, St. Jude, and Sunovion.

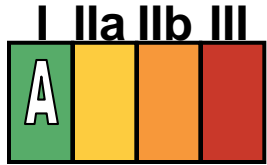
Institutional payments for grants from Bristol Myers Squibb, Sanofi-Aventis, Glaxo Smith Kline, Otsuka, Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca, Evolva; and has other financial relationships with Esther and King Biomedical Research Grant.

# Current Controversies on DAPT in PCI

- Which drug?
- When to start?
- Which dose?
- How long?

# 2011 ACCF/AHA/SCAI Guideline for PCI

## Oral Antiplatelet Therapy



A loading dose of a P2Y<sub>12</sub> receptor inhibitor should be given to patients undergoing PCI with stenting. Options include:

- a. Clopidogrel 600 mg (ACS and non-ACS patients).
- b. Prasugrel 60 mg (ACS patients).
- c. Ticagrelor 180 mg (ACS patients).

**Not very practical!**



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# ESC Guidelines for NSTEMI-ACS

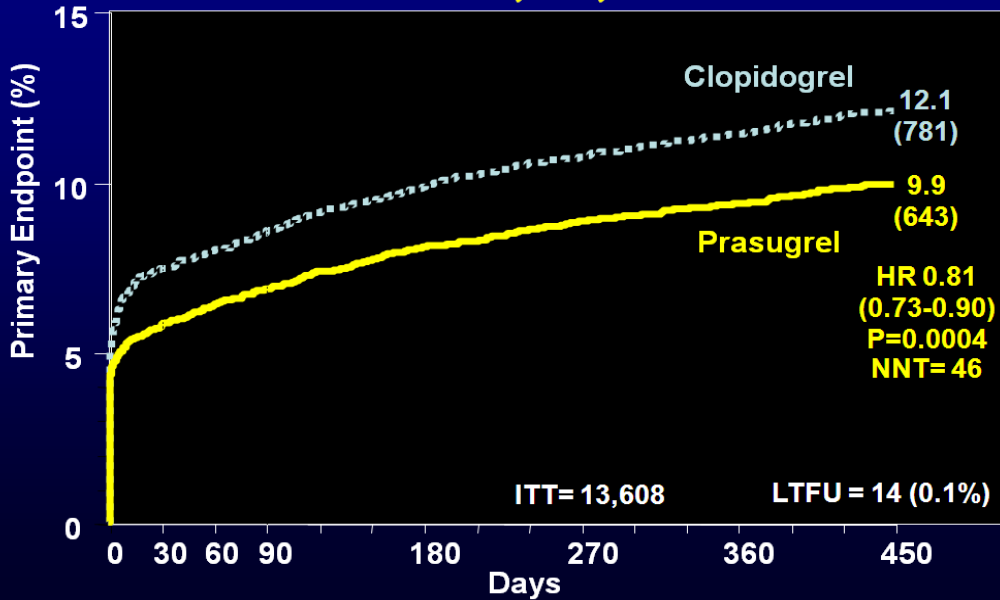
## Clopidogrel

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
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## New P2Y<sub>12</sub> receptor antagonists

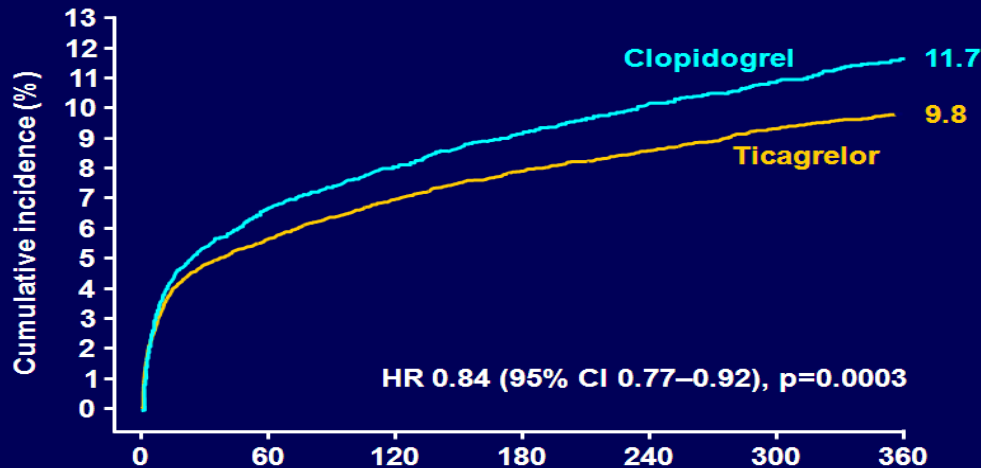
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y <sub>12</sub> -inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications. <sup>d</sup>	I	B

## Primary Endpoint CV Death, MI, Stroke



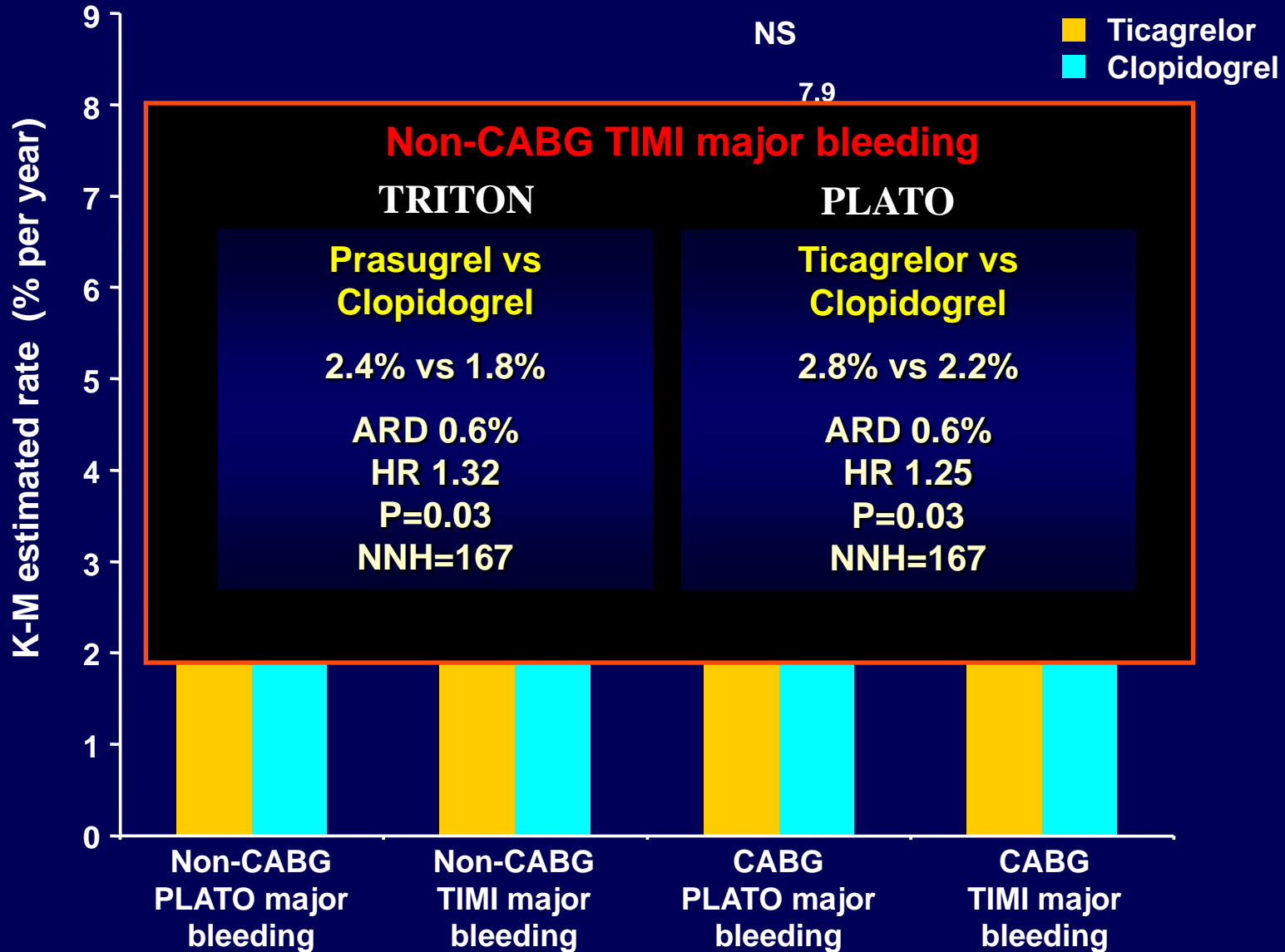
## TRITON TIMI 38 (prasugrel vs clopidogrel)

## K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



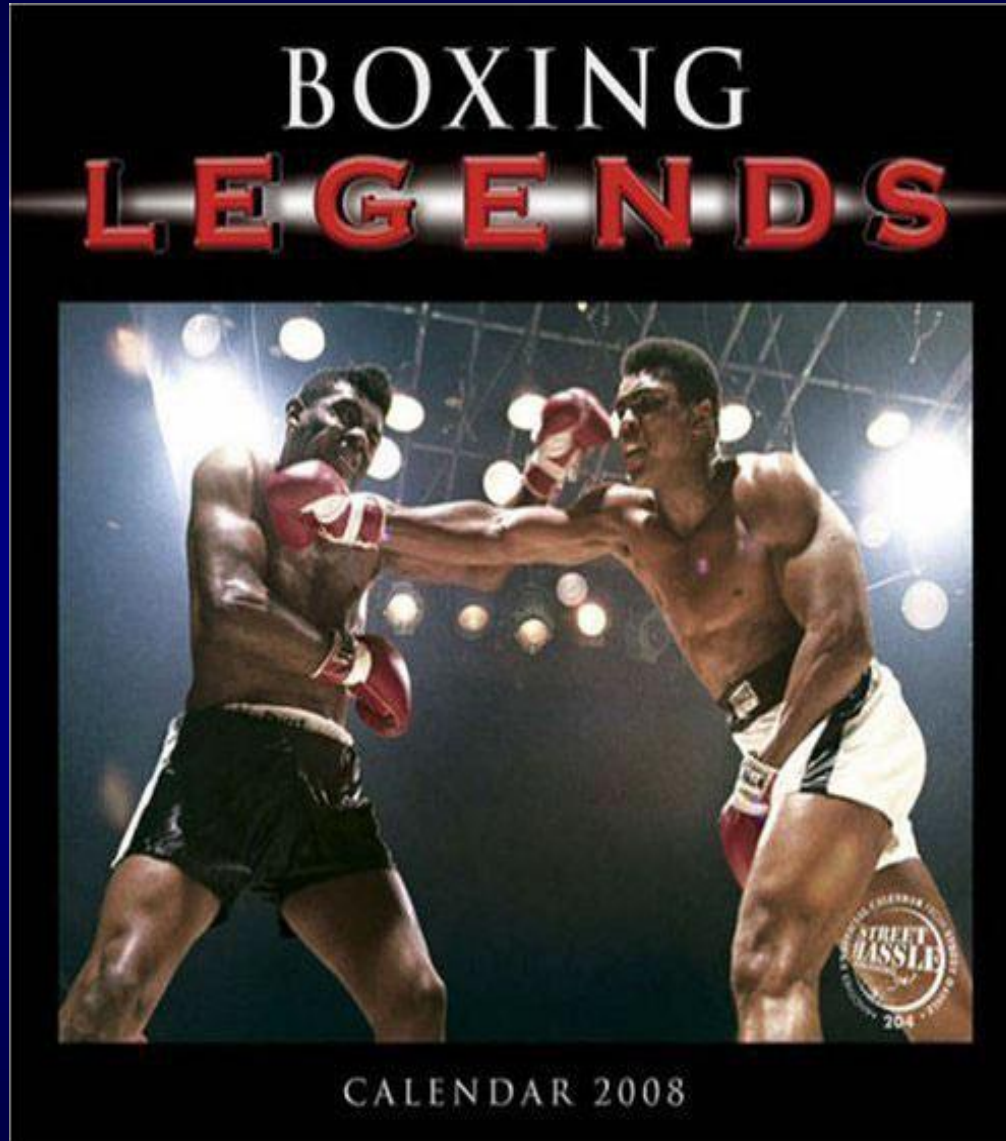
## PLATO (ticagrelor vs clopidogrel)

# Non-CABG and CABG-related major bleeding





# TRITON vs PLATO: *Is there a winner?*





# TRITON vs PLATO

## *Proof of concept: Higher IPA to Support ACS*

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### Differences between trials

#### 1. Patient Population

TRITON: ACS undergoing PCI

PLATO: Full spectrum ACS

#### 2. Pretreatment

TRITON: No pretreatment (except STEMI)

PLATO: Pretreatment

#### 3. Clopidogrel Loading Dose

TRITON: 300mg

PLATO: 300-600mg

#### 4. Duration of trial (median)

TRITON: 14.5 months

PLATO: 9 months

# TRITON vs PLATO: *Is there a winner?*

Prasugrel and ticagrelor both showed favorable efficacy and safety profiles in their respective trials and only a head-to-head comparison will be able to define *the winner*. Subgroup analysis will allow to define the best niche for each drug.

## Prasugrel.

Pro's: Particularly efficacious in reducing stent thrombosis, MI, uTVR  
great benefit in diabetics and STEMI.

Contraindicated: high-risk bleeding; prior TIA/stroke; hypersensitivity

Precautions: elderly, low-weight; CABG/surgery (7days).

## Ticagrelor.

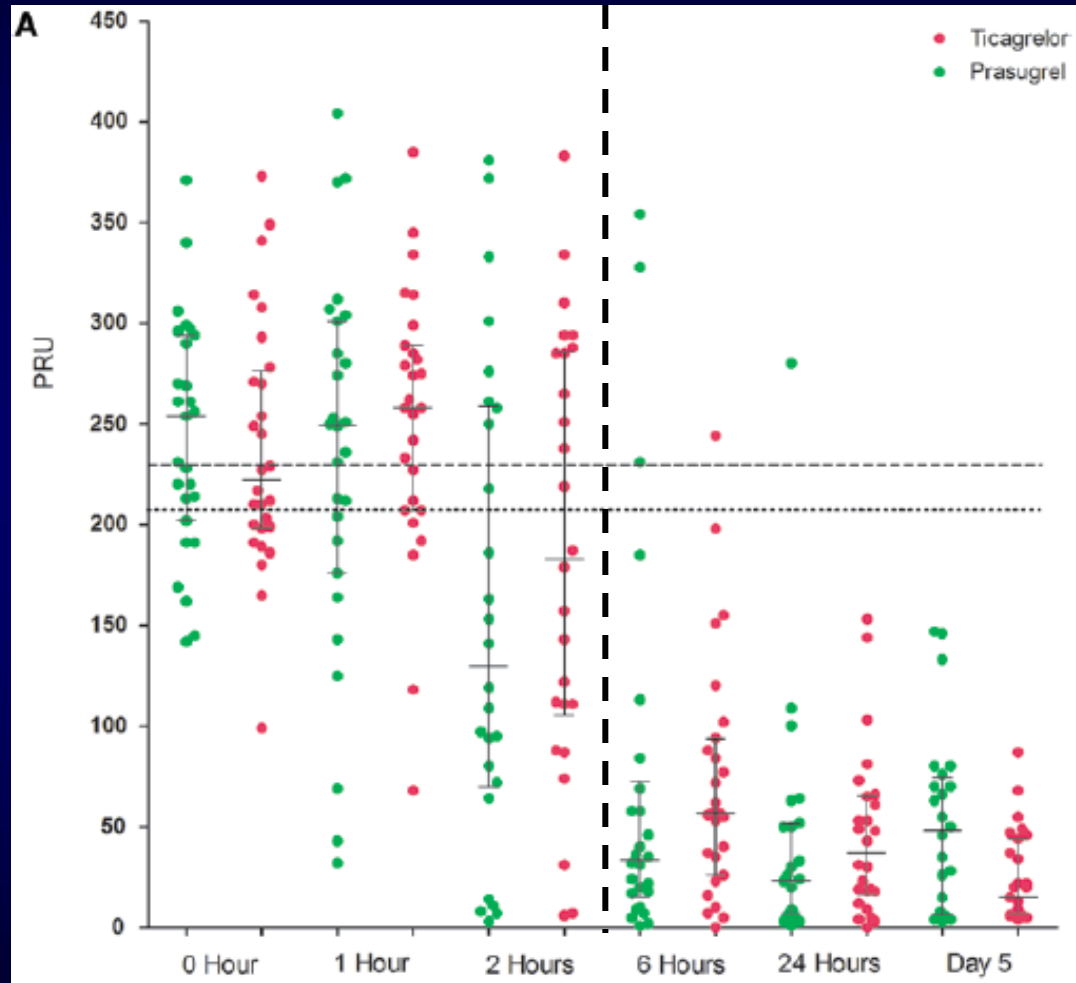
Pro's: Particularly efficacious in reducing mortality (*off-target effects*),  
attractive for upstream use even if CABG is required, OK for patients  
with prior TIA/stroke.

Contraindicated: high-risk bleeding; prior hemorrhagic stroke; severe  
hepatic dysfunction ; hypersensitivity

Precautions: COPD/asthma, bradyarrhythmia without pacemaker,  
compliance (b.i.d. administration), drug interactions (CYP 3A4  
interfering agents); aspirin dose (<100mg), CABG/surgery (5-7days).

# Novel Oral P2Y<sub>12</sub> effects in STEMI patients

55 patients undergoing primary PCI  
randomized to prasugrel or ticagrelor



Alexopoulos D. et al *Circ Cardiovasc Interv.* 2012;5:00-00 .

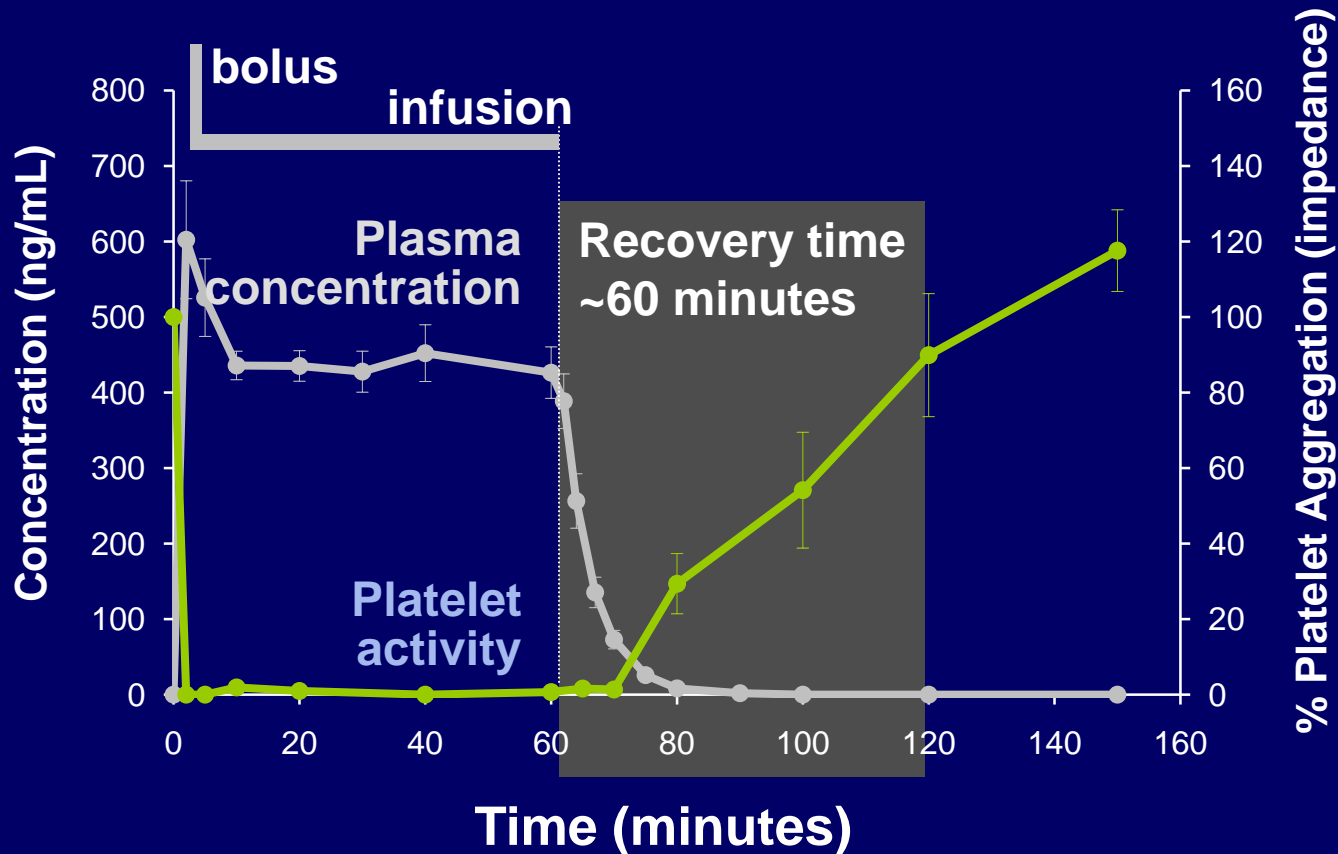
# Is it game over for GPI's in STEMI?

*The search for a niche:  
bolus only / intracoronary infusion*

- **FABOLUS PRO** (M. Valgimigli)
- **INFUSE – AMI** (M. Gibson/ G. Stone)

# Cangrelor : Phase I Human PK/PD

- Rationale for Use

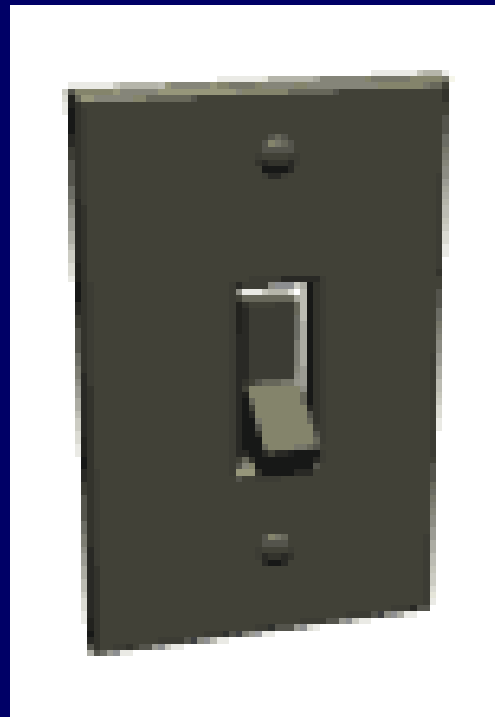


dose 30ug/kg bolus + 4ug/kg/min infusion

# Cangrelor: *“ON/OFF Switch” PD Effects*

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**ON**



**OFF**

# Primary Efficacy Outcomes at 48 Hours, MITT



	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P-value
Primary Analysis Adjusted <sup>1</sup>				
Death/MI/IDR/ST	257/5470 (4.7%)	322/5469 (5.9%)	0.78 (0.66, 0.93)	0.005











## Secondary Efficacy Outcomes at 48 Hours, MITT

Stent thrombosis (key secondary endpoint)	46/5470 (0.8%)	74/5469 (1.4%)	0.62 (0.43,0.90)	0.01
MI	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67,0.97)	0.02
Q-wave MI	11/5470 (0.2)	18/5469 (0.3)	0.61 (0.29,1.29)	0.19
IDR	28/5470 (0.5)	38/5469 ( 0.7)	0.74 (0.45,1.20)	0.22
Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99
CV Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99

<sup>1</sup> The logistic model was adjusted for baseline status and clopidogrel dose. P value of 0.006 shown on the KM curve is log rank p value.



# Cangrelor vs GPI: Key PK/PD differences

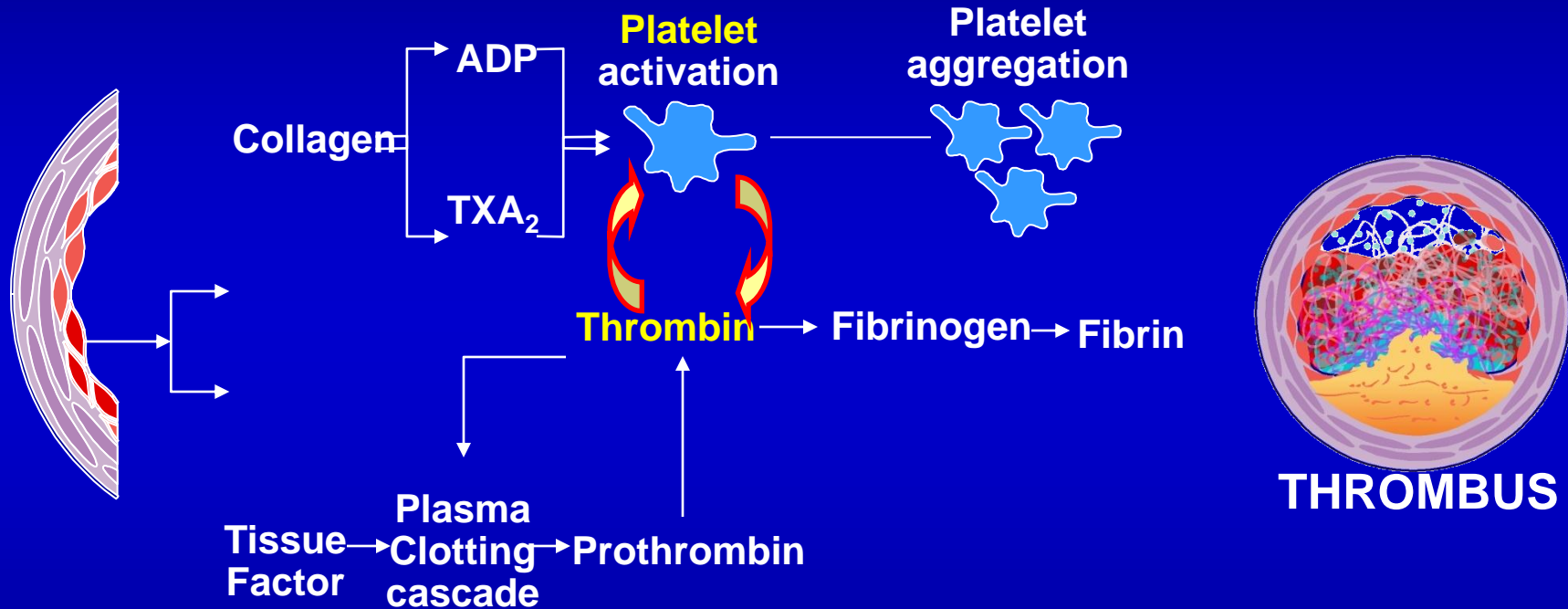
	<b>GPI</b>	<b>CANGRELOR</b>
<b>Fast onset (minutes)</b>		
<b>Potent platelet Inhibition</b>		
<b>Rapid offset (&lt;1 hour)</b>		
<b>P2Y12-specific (Natural Bridge)</b>		
<b>“Targeted” Inhibition (thienopyridine-like)</b>		

Adapted from Angiolillo DJ et al. JAMA. 2012;307:265-74

# Is there still room for ischemic improvement?

# Thrombus Formation

Two key elements: cellular (platelets) and plasmatic (coagulation factors)



# How to Modulate Thrombin Effects

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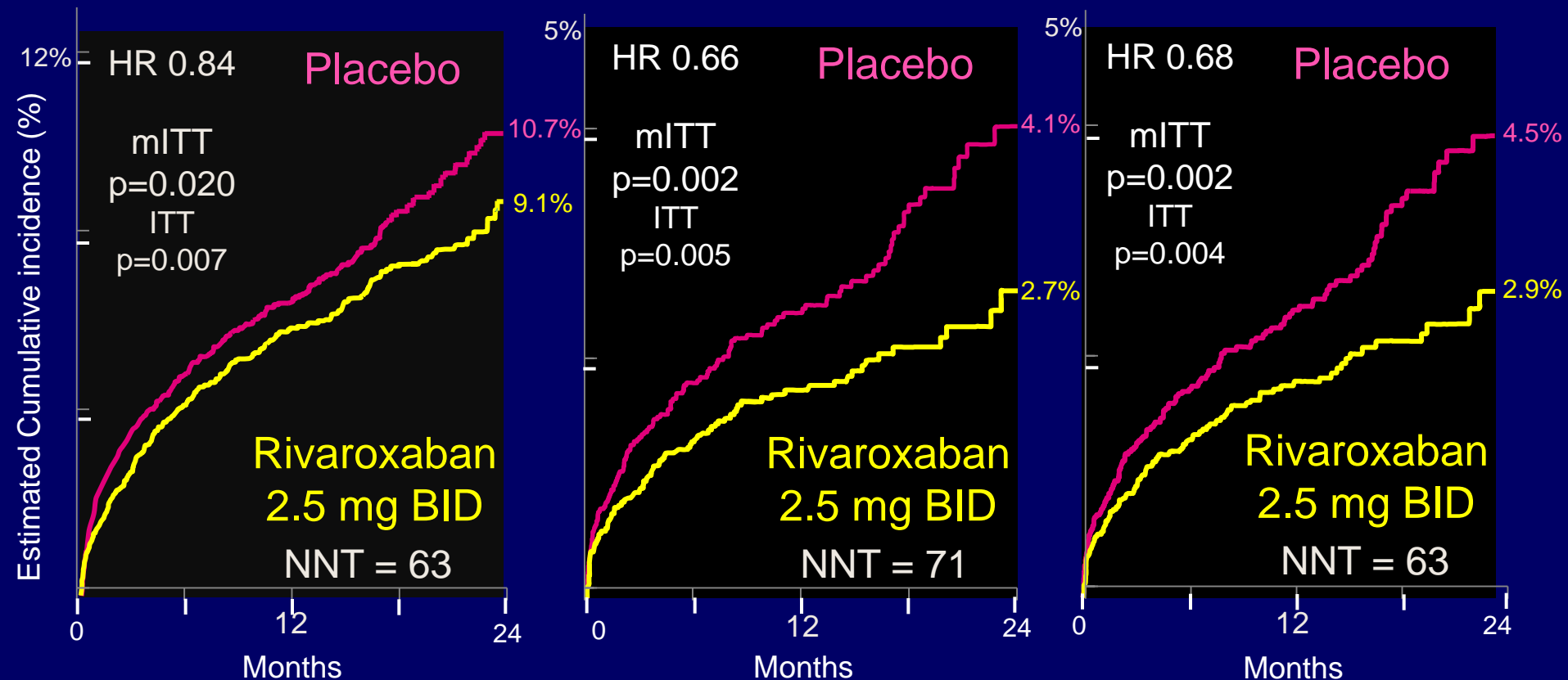
- **Thrombin receptors on platelets**
  - PAR-1 receptor antagonists (vorapaxar)
- **Circulating (plasma) thrombin**
  - Oral anticoagulants (anti-II and anti-X)

# Efficacy Endpoints: Very Low Dose 2.5 mg BID

CV Death / MI / Stroke

Cardiovascular Death

All Cause Death



# Antithrombotic Therapies

COMPARATOR

Aspirin

+

Clopidogrel  
Standard  
Dose

TRITON  
TIMI 38

Aspirin

+

Prasugrel  


PLATO

~~Aspirin~~

+

Ticagrelor  



ATLAS ACS 2  
TIMI 51

~~Aspirin~~

+

Clopidogrel  
Standard  
Dose

+

Rivaroxaban  
(Very Low Dose  
2.5 mg BID)\*  


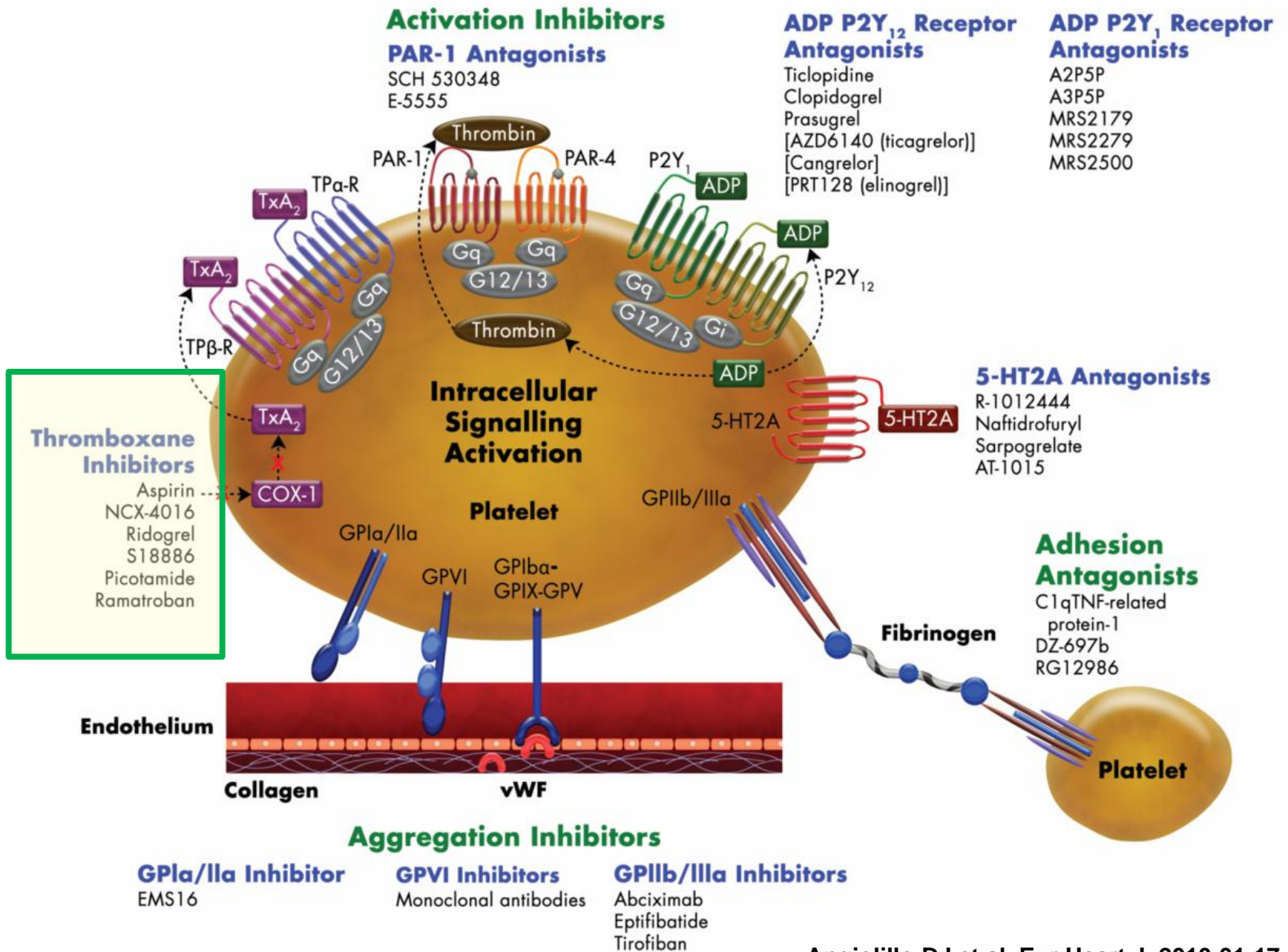
Antithrombotic Therapy



CV  
Endpoints



# Sites of action of current and emerging antiplatelet agents







# Balancing Safety and Efficacy

