

# $P_2Y_{12}$ Receptor Inhibitors

*Clopidogrel, Prasugrel and Ticagrelor*

Which Drug and for Whom?

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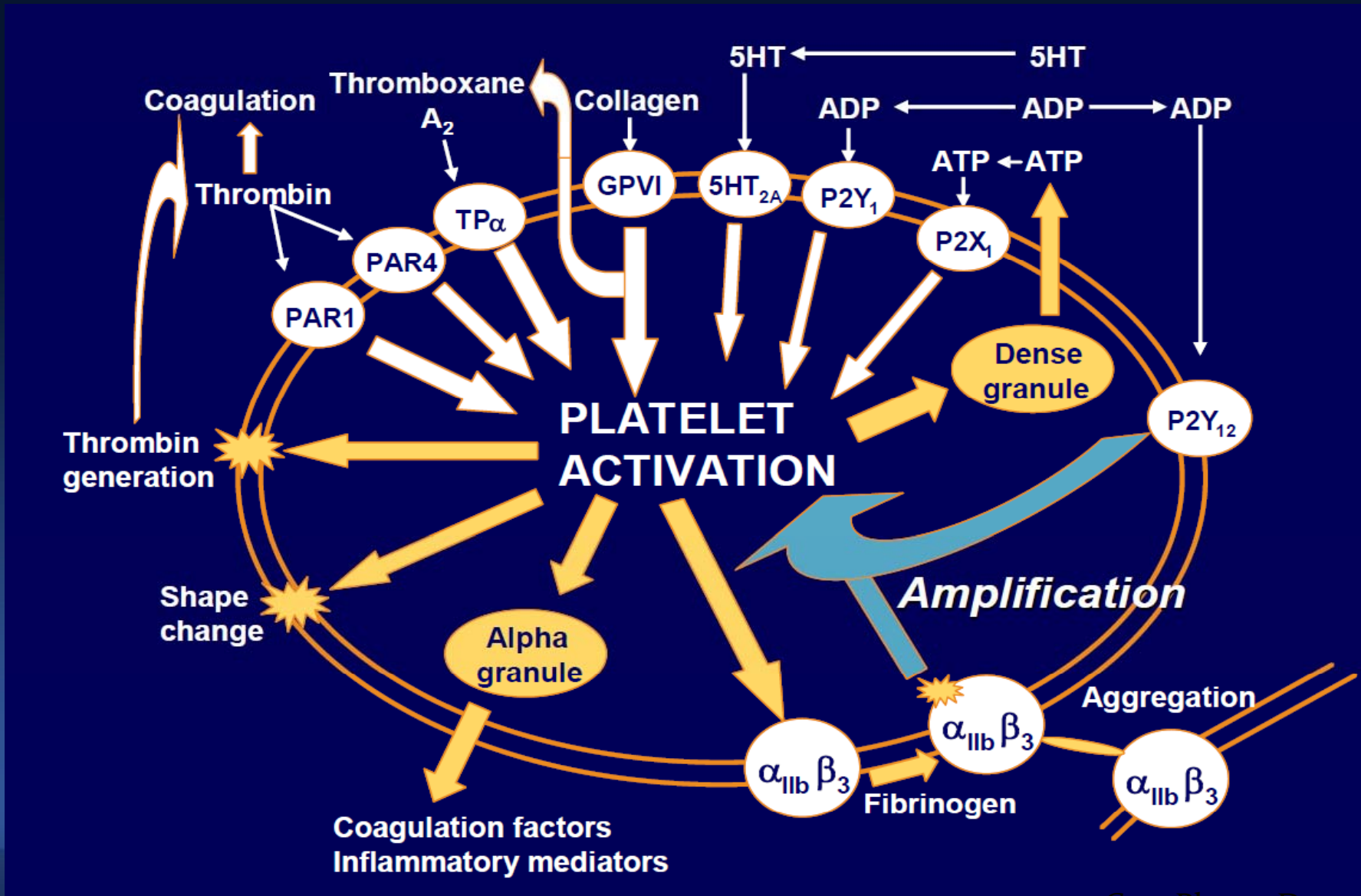
A **M**iracle **D**rug!

*The* **G**reat **J**ourney

P<sub>2</sub>Y<sub>12</sub> Receptor Blockers



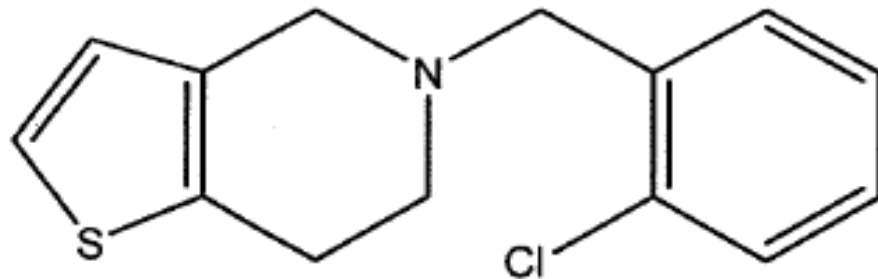
# P2Y<sub>12</sub> Receptor: *A Key Player*



# The Inventor of Ticlopidine

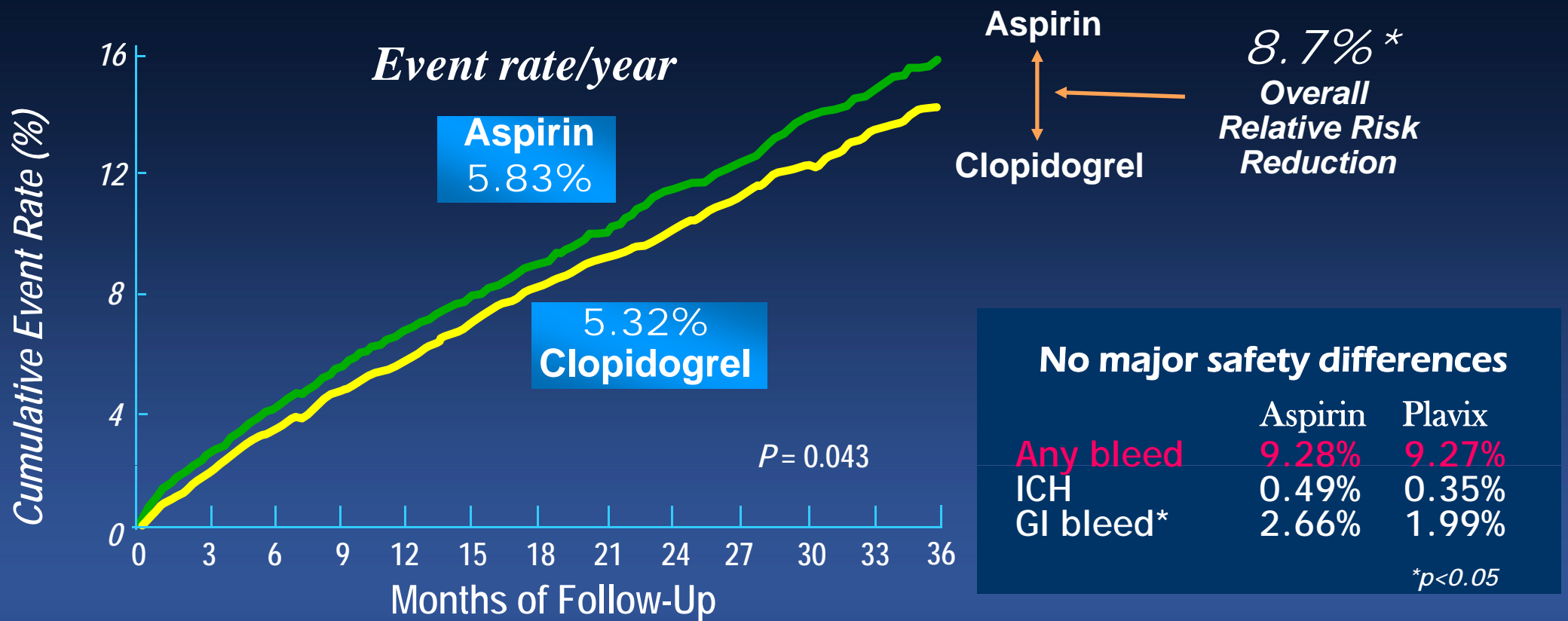
Jean-Pierre Maffrand, 1972 (retire 2008)

In the early 1970's Sanofi's predecessor company (which will be referred to as "Sanofi" for simplicity) invented a "thienopyridine" compound named ticlopidine which was shown to have anti-thrombotic therapeutic benefit in that it inhibited blood platelet aggregation. The Sanofi inventor was Jean Pierre Maffrand, Ph.D. Ticlopidine, in the form of a hydrochloride salt, was marketed as a pharmaceutical in Europe beginning in 1978, and has the following structure (shown as a base, without any salt anion):

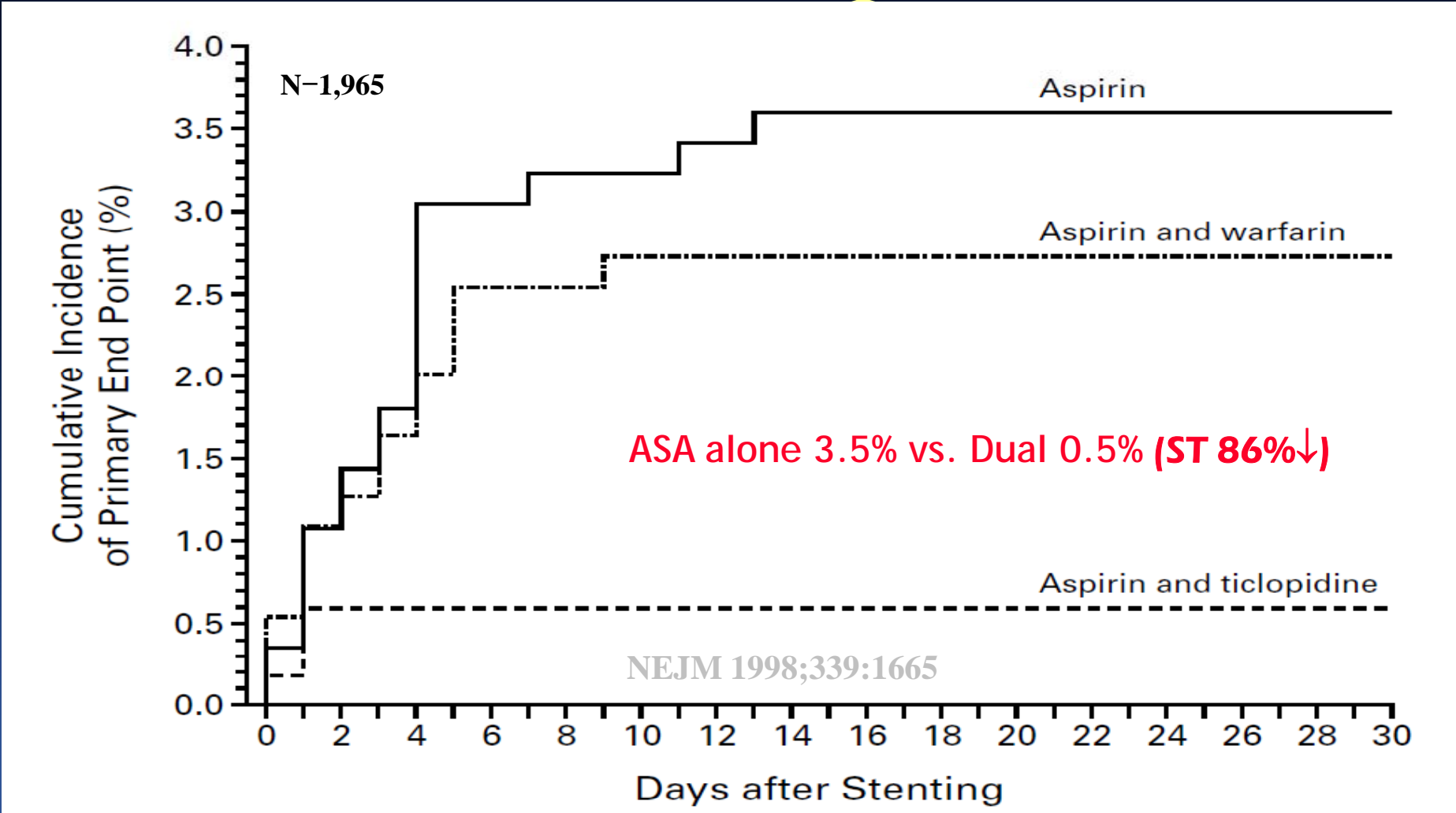


# Cumulative Risk of Stroke, MI or Vascular Death in Patients in the CAPRIE Trial

19,185 patients with atherosclerotic disease



# STARS: P<sub>2</sub>Y<sub>12</sub> Receptor Inhibitor



After coronary stenting, aspirin & ticlopidine should be considered for the prevention of the serious complication of stent thrombosis.

# Superior Efficacy of ADP Receptor Antagonists in Coronary Stenting

## Clopidogrel

- **Dual therapy (aspirin & clopidogrel)**
  - PCI: BMS (1 month), DES (12 months)
  - ACS: 12 months

A P2Y<sub>12</sub> inhibitor should be added to aspirin as soon as possible and maintained over 12 months in ACS patients unless contraindication (IA, ESC2011)

- **An alternative to aspirin**

... Further Drama

# The Challenge

## Which one is better?

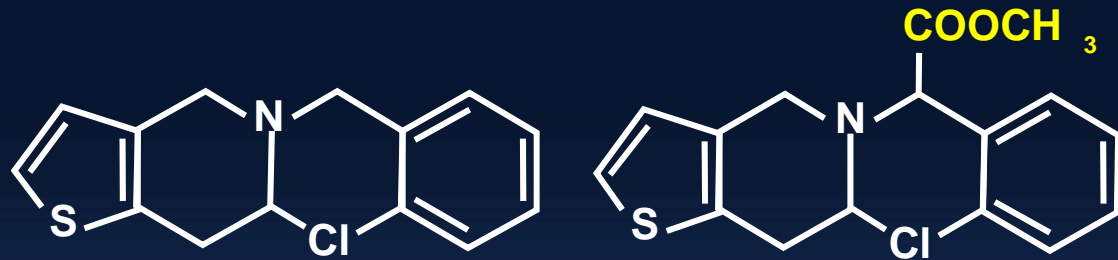




# P2Y<sub>12</sub> Antagonists

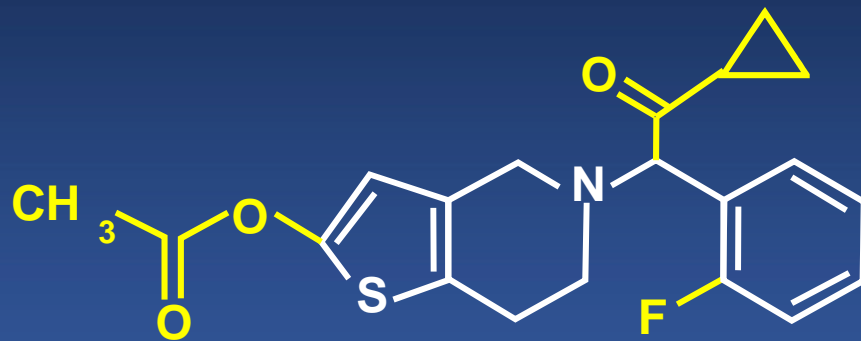
Form follows function!

## Evolution



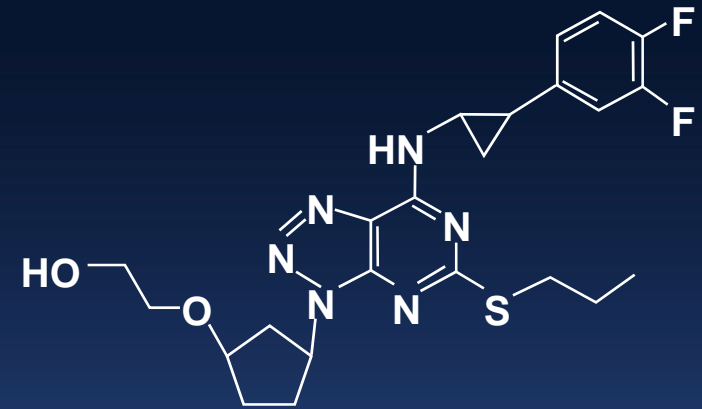
Ticlopidine

Clopidogrel



Prasugrel

## Revolution



HO OH

**AZD6140**

(CPTP: Cyclo-Pentyl-Triazolo-Pyrimidine;  
orally active)

# TRITON – TIMI 38

ACS (STEMI or UA/NSTEMI) & Planned PCI (99%)

ASA



N = 13,000

Double-blind

PRASUGREL

CLOPIDOGREL

Median duration of therapy – 12 months

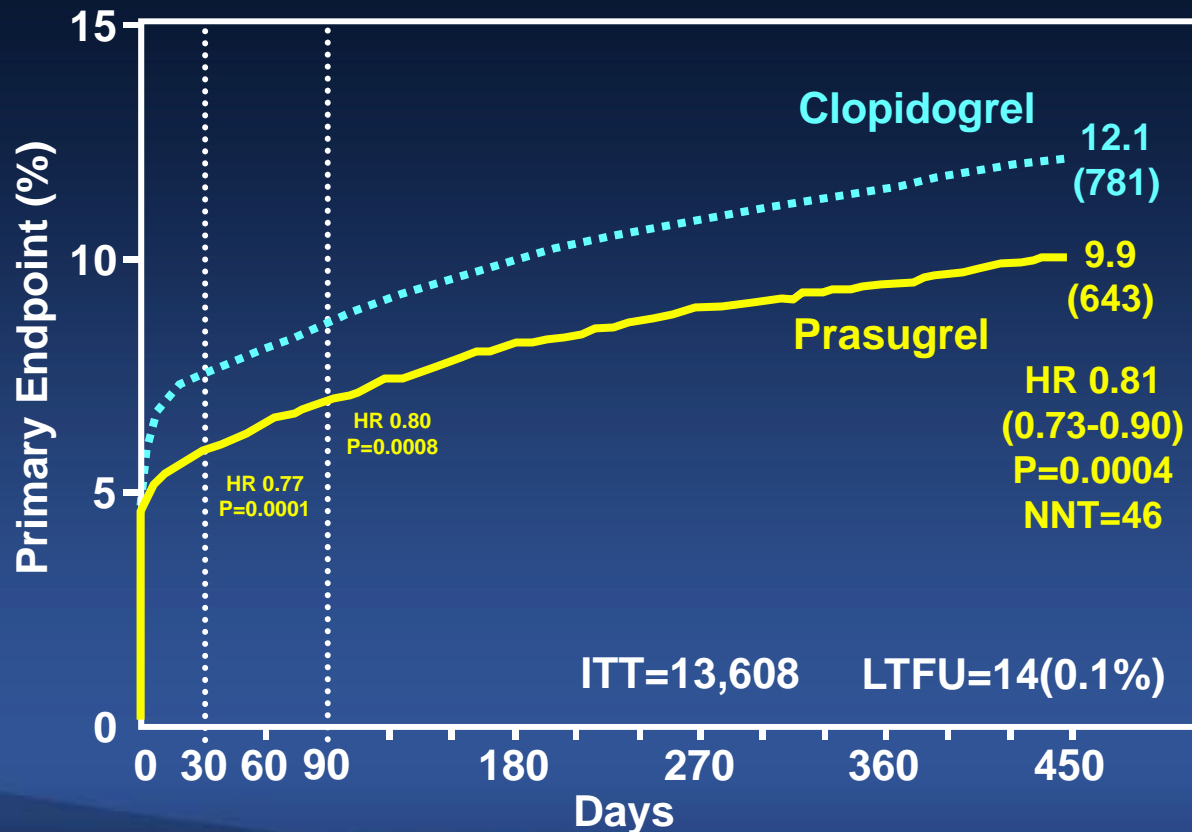
1° endpoint: CV death, MI, Stroke

2° endpoints: CV death, MI, Stroke,

Rehosp Re-isch CV death, MI, UTVR

# TRITON-TIMI 38 Prasugrel Lowers Events but Ups Bleeding versus Clopidogrel in ACS

13,608 ACS patients scheduled for PCI (**STEMI 26%**)



**Cardiovascular death/MI/stroke**  
HR 0.81 (0.73 - 0.90), p<0.001

**Nonfatal MI**

HR 0.76 (0.67 - 0.85), p<0.001

**Stent thrombosis (1.1% vs. 2.4%)**

HR 0.48 (0.36 - 0.64), p<0.001

**Fatal bleeding (0.4% vs 0.1%)**

HR 4.19 (1.58 - 11.11), p=0.002

**TIMI major/minor bleeding**

HR 1.31 (1.11 - 1.56), p=0.002

**Risk groups: age>75 & lean<60kg  
or history of stroke/TIA**

# TRITON: Study Limitations

## Prasugrel in ACS

NSTE-ACS, ACCF/AHA Guideline 2011

It is not our recommendation that prasugrel be administered routinely before angiography, such as in an emergency department, or be used in patients who have not undergone PCI.

*Circulation* 2011;123:2022-60

ACS, ESC Guideline 2011

*Prasugrel in, Clopidogrel out for STEMI*

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>

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B

# TRILOGY – ACS

Medically Managed NSTEMI-ACS

Low-dose ASA

N = 10,300 (<75y: ~7800)

Randomization within 10 days of index event  
*Stratified by age (75y), BWt (60kg), clopidogrel treatment (300mg LD within 72h of index event & daily MD; or MD ≥ 5 days)*

**PRASUGREL**  
*5 or 10mg/day*

**CLOPIDOGREL**  
*75mg/day*

Duration of therapy : minimum 6m, maximum 30m

**1° endpoint: CV death, MI, Stroke**

# PLATO

A Study of PLATelet  
Inhibition & Patient Outcomes

ACS (STEMI/NSTEMI) (<24 h after chest pain)

ASA



N = 18,624

Double-blind

IIb/IIIa 27%

Ticagrelor

Clopidogrel

Median duration of therapy: 6-12 months

1° endpoint: CV death, MI, Stroke (15%RRR)

2° endpoints: Death, CV death, MI, stroke,  
recurrent ischemia, arterial thrombotic events

# Major Outcomes

7

**In 1000 ACS patients, replacing clopidogrel with ticagrelor for 12 months,**

- 14 fewer deaths  
(absolute risk reduction 1.4%)
- 11 fewer MI
- 6~8 fewer cases of stent thrombosis
- no increase in bleeding requiring transfusion.

# Major Bleeding

## Ticagrelor **in ACS**

**ESC2011**

*Ticagrelor in, clopidogrel out*

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).

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Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.

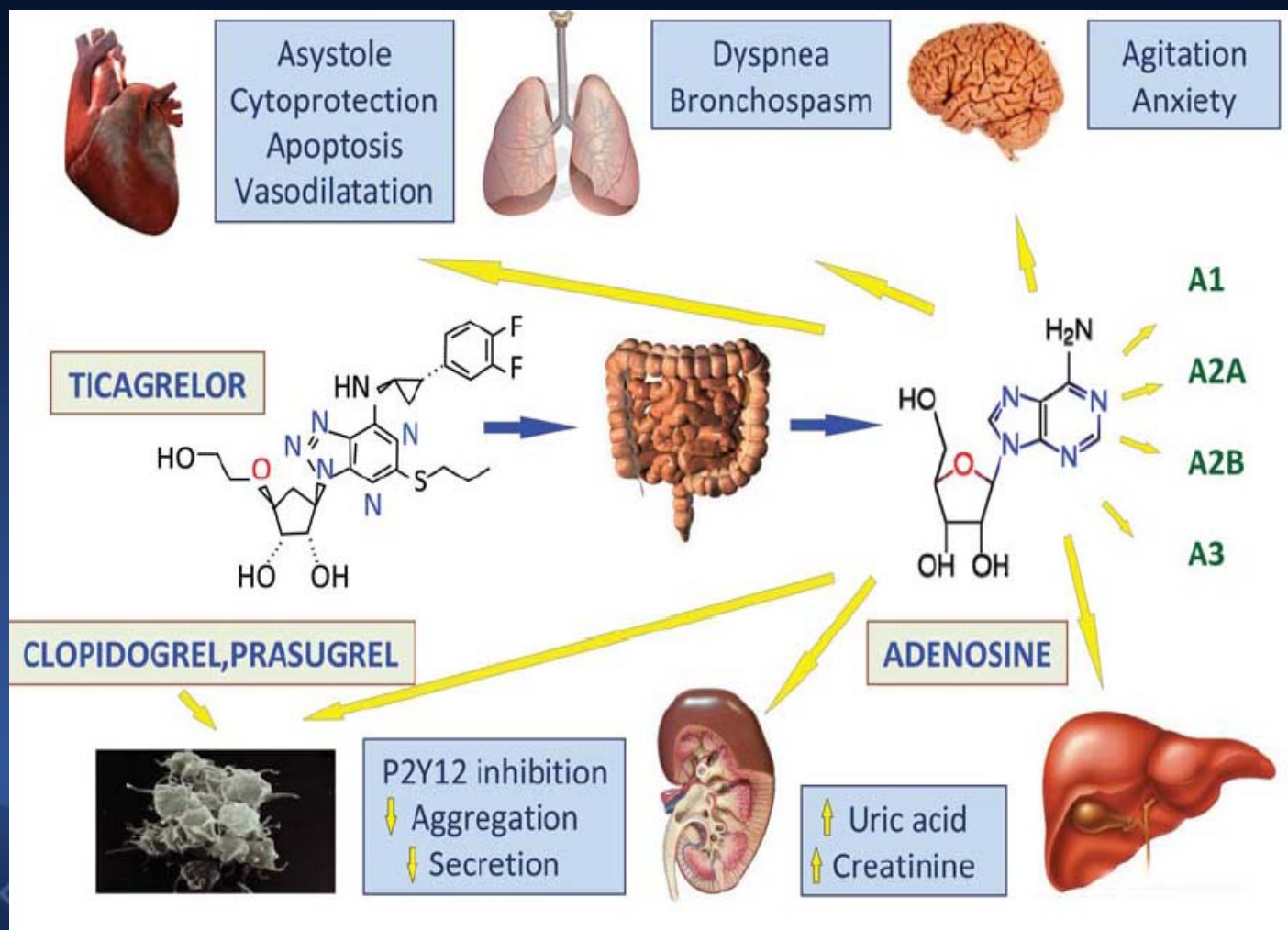
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# The PLATO trial: do you believe in magic?

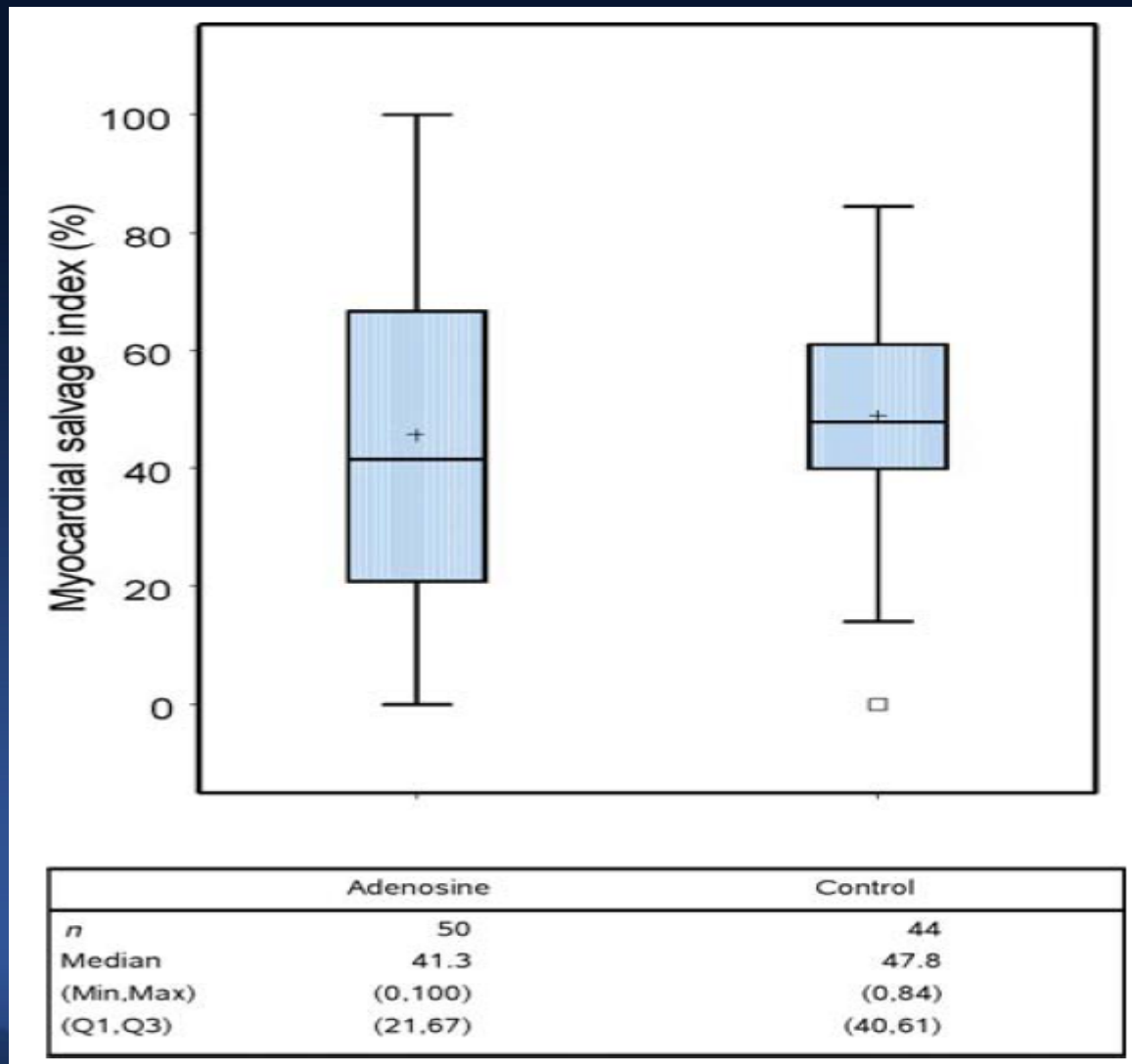
Victor L. Serebruany<sup>1\*</sup> and Dan Atar<sup>2</sup>



## Adenosine Hypothesis ?

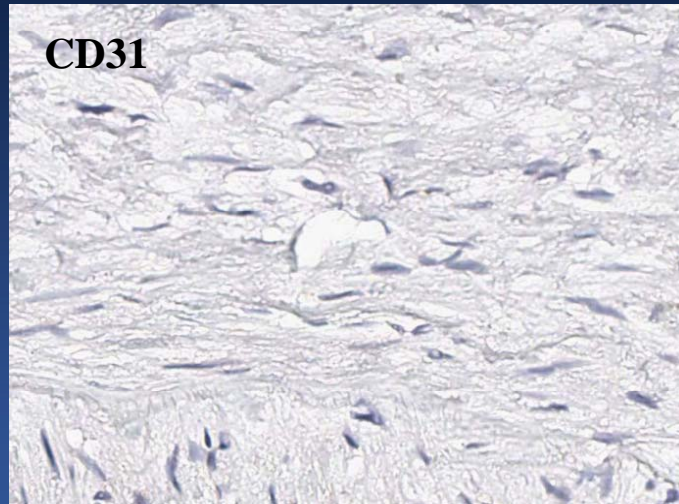
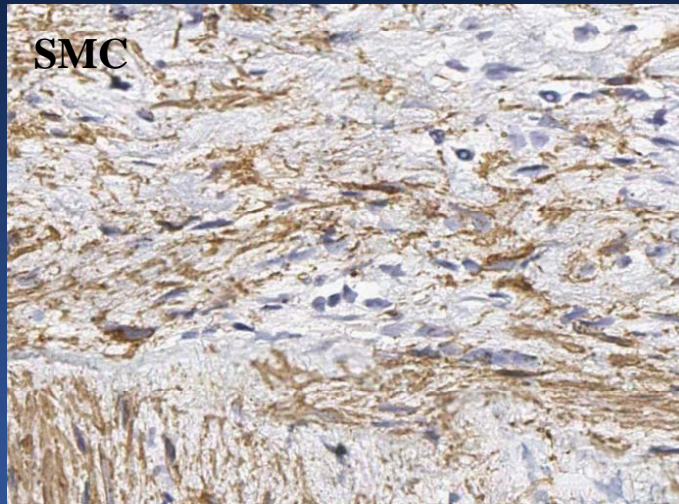
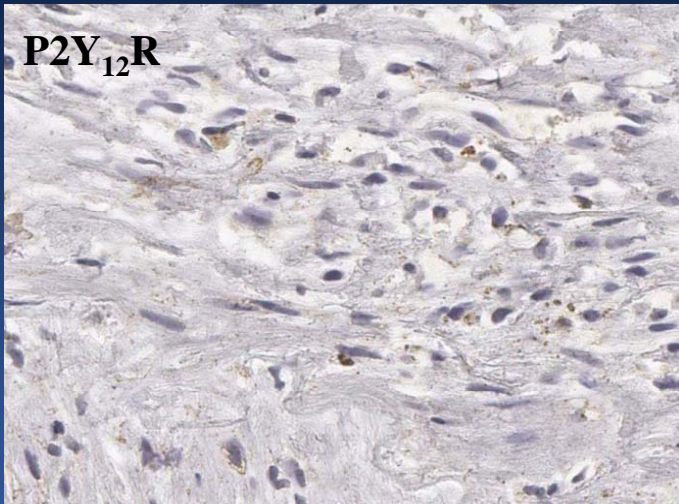
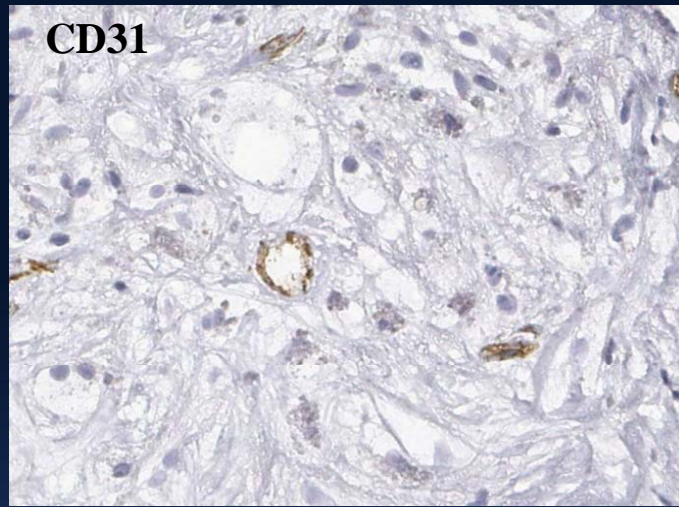
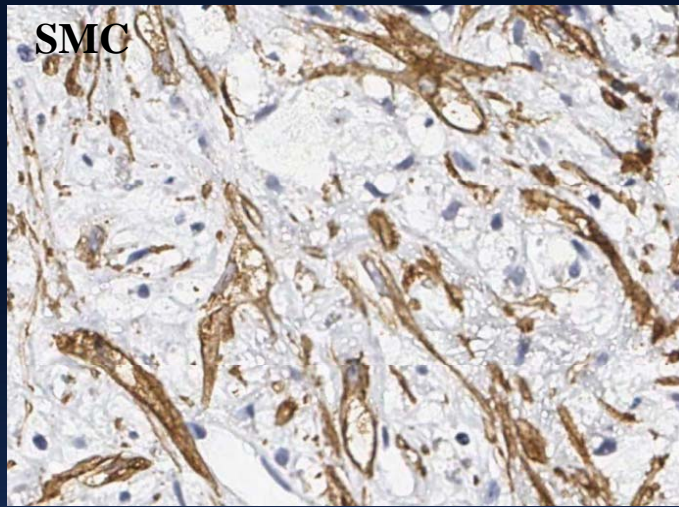
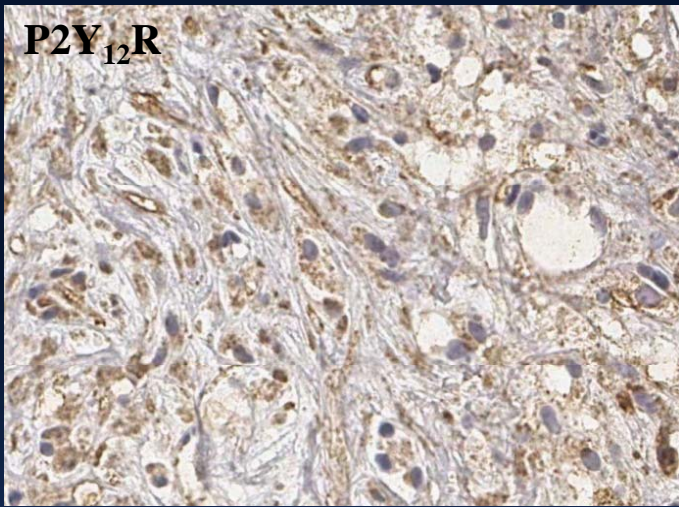
- vasodilation
- preconditioning
- immunomodulation
- dyspnea
- heart block
- renal funtion

# IC Adenosine for Myocardial Salvage in Patients With STEMI



- Adenosine 4mg
- CMRI on day 2-3
- Salvage index =  
necrotic area/  
risk area

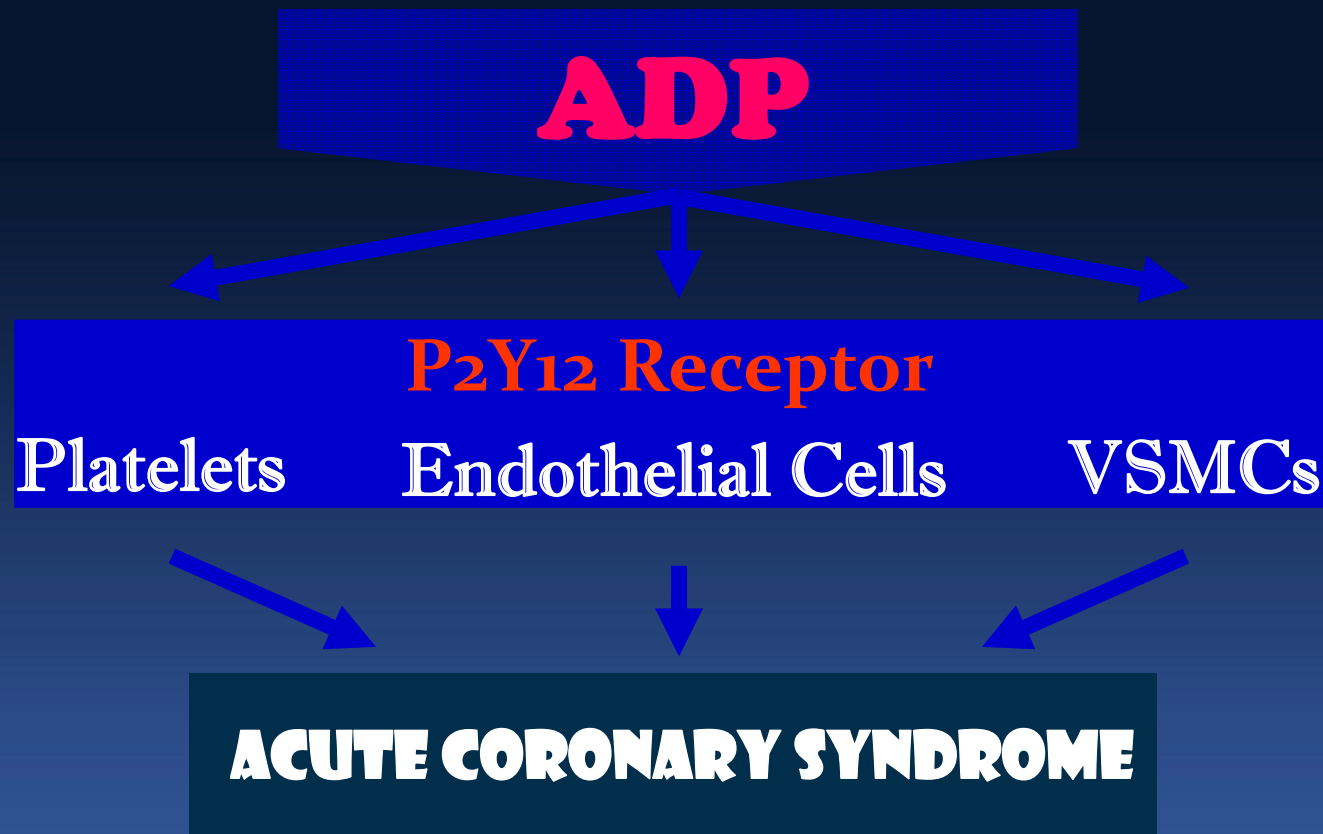
# AMI



# Stable angina



# Beyond Platelets



P<sub>2</sub>Y<sub>12</sub> receptor inhibitors may have a dual anti-ischemic effect by inhibiting both platelet activation and plaque destabilization.

## P2Y<sub>12</sub> Receptor Inhibitors

Type	Clopidogrel Thienopyridine	Prasugrel Thienopyridine	Ticagrelor Cyclopentyltriazolopyrimidine
Prodrug	Yes	Yes	No
Oral administration	Yes	Yes	Yes
Loading dose (mg)	300	60	180
Maintenance dose (mg)	75	10	90
Frequency of administration	Once daily	Once daily	Twice daily
Onset of action	Delayed	Rapid	Rapid
Offset of action	Delayed	Delayed	Rapid
Individual variability	Large	Small	Small
CYP-450 activation	Yes (twice)	Yes	No
Irreversible P2Y <sub>12</sub> inhibition	Yes	Yes	No
Relative potency	Low	High	High
Mean platelet inhibition	~50%	~70%	~95%
Time to peak inhibition (h)	~12*	2	2
Half-life	Life of platelet	Life of platelet	7–12 h
Days to hold before CABG surgery	>5	>7	>3

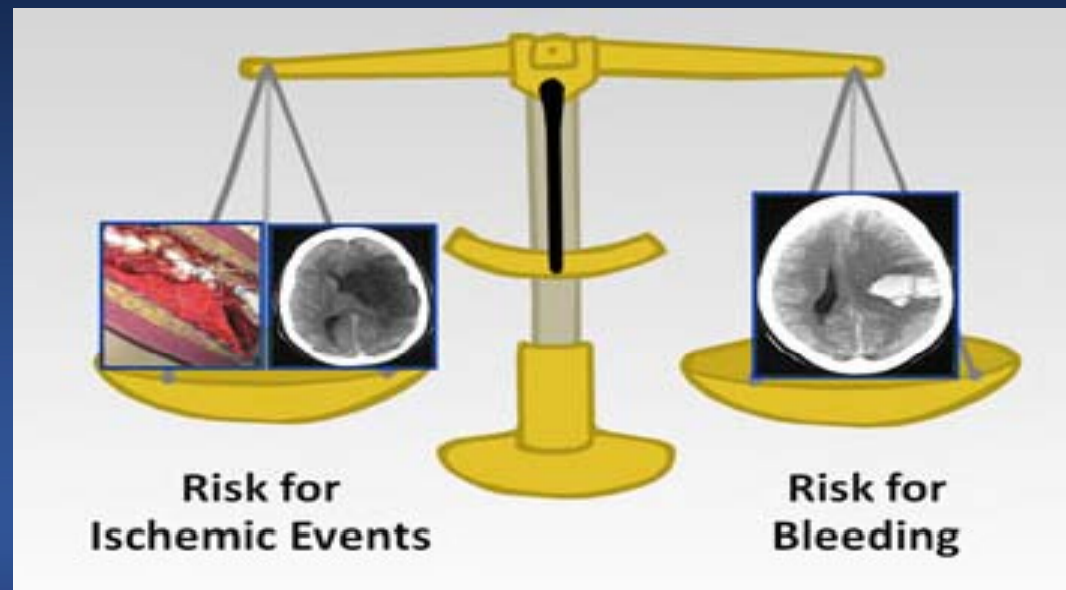
\*With 300 mg loading dose.

# Unanswered Questions

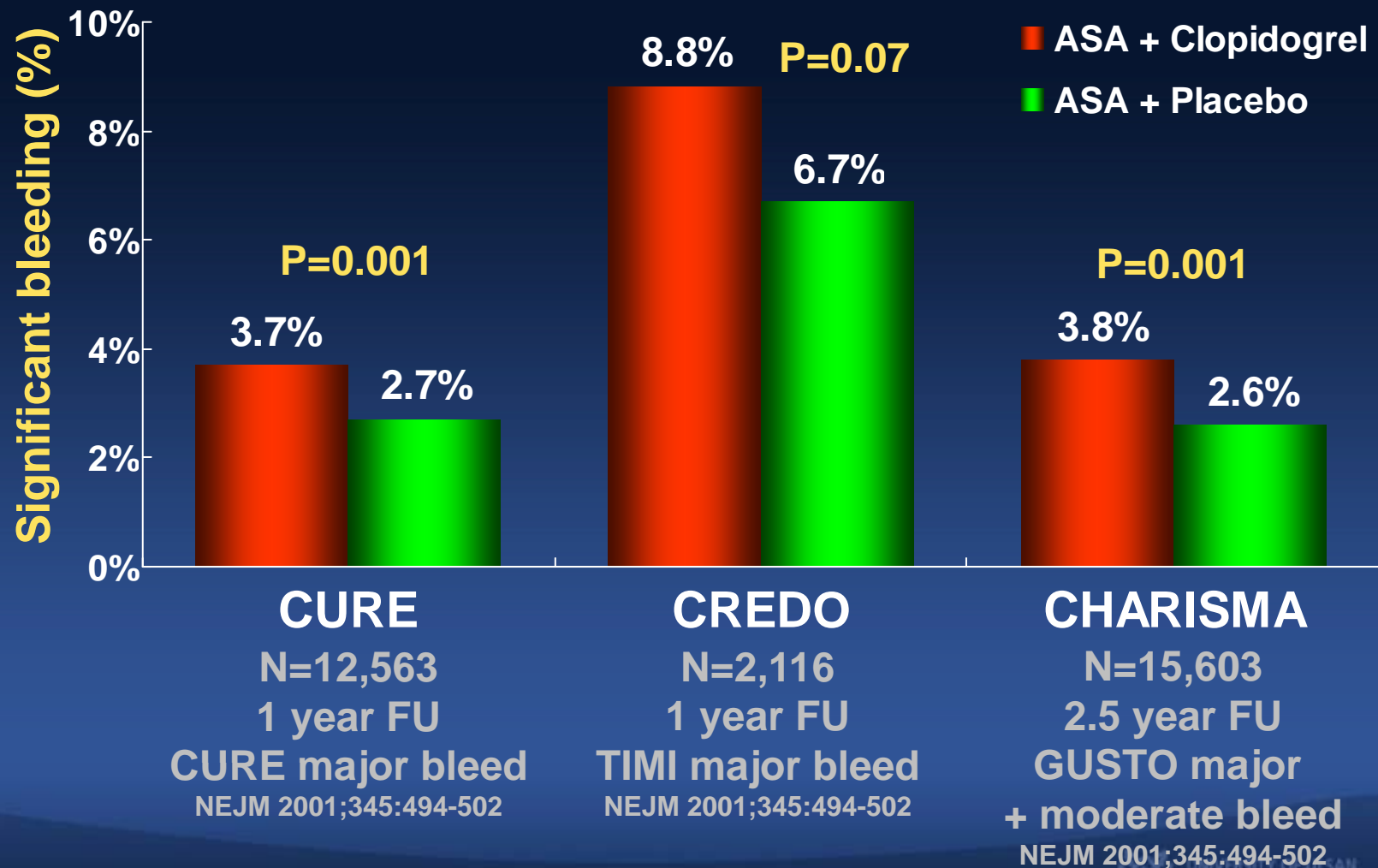
- **STEMI: thrombolytic or medical therapy**
- **AMI: 1 year after AMI (PEGASUS)**
- **Stable angina: after DES**
- **Ischemic stroke**
- **Primary prevention**

## The Dilemma

Bleeding is the key!



# Safety: More Potent, More Bleeding!





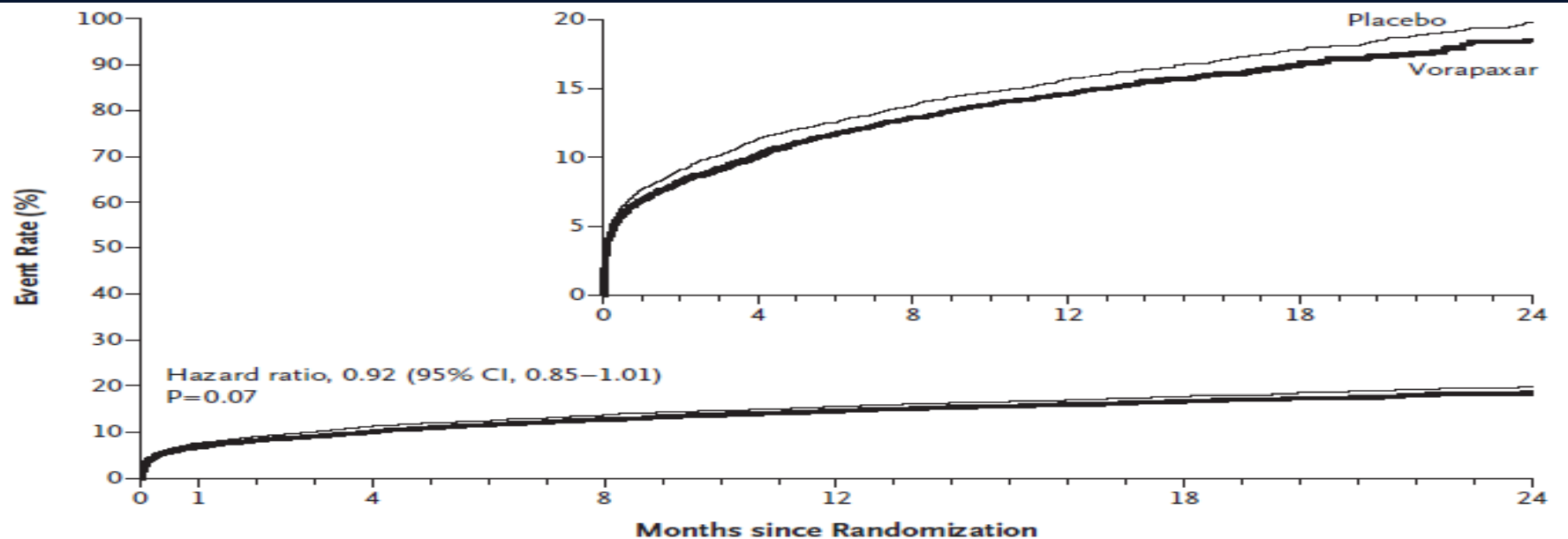
# Intracranial Bleeding

- Patient history of stroke or TIA
- TRITON-TIMI 38: incidence of stroke in patients with a history of prior TIA or stroke greater with prasugrel + ASA (6.5% total: 4.2% thrombotic, 2.3% ICH) vs clopidogrel + ASA (1.2% total, all thrombotic)
- PLATO: Fatal ICH higher in ticagrelor vs clopidogrel (0.1 vs 0.01;  $P=.02$ )

# TRACER, Gone without Any Trace

ORIGINAL ARTICLE

## Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes



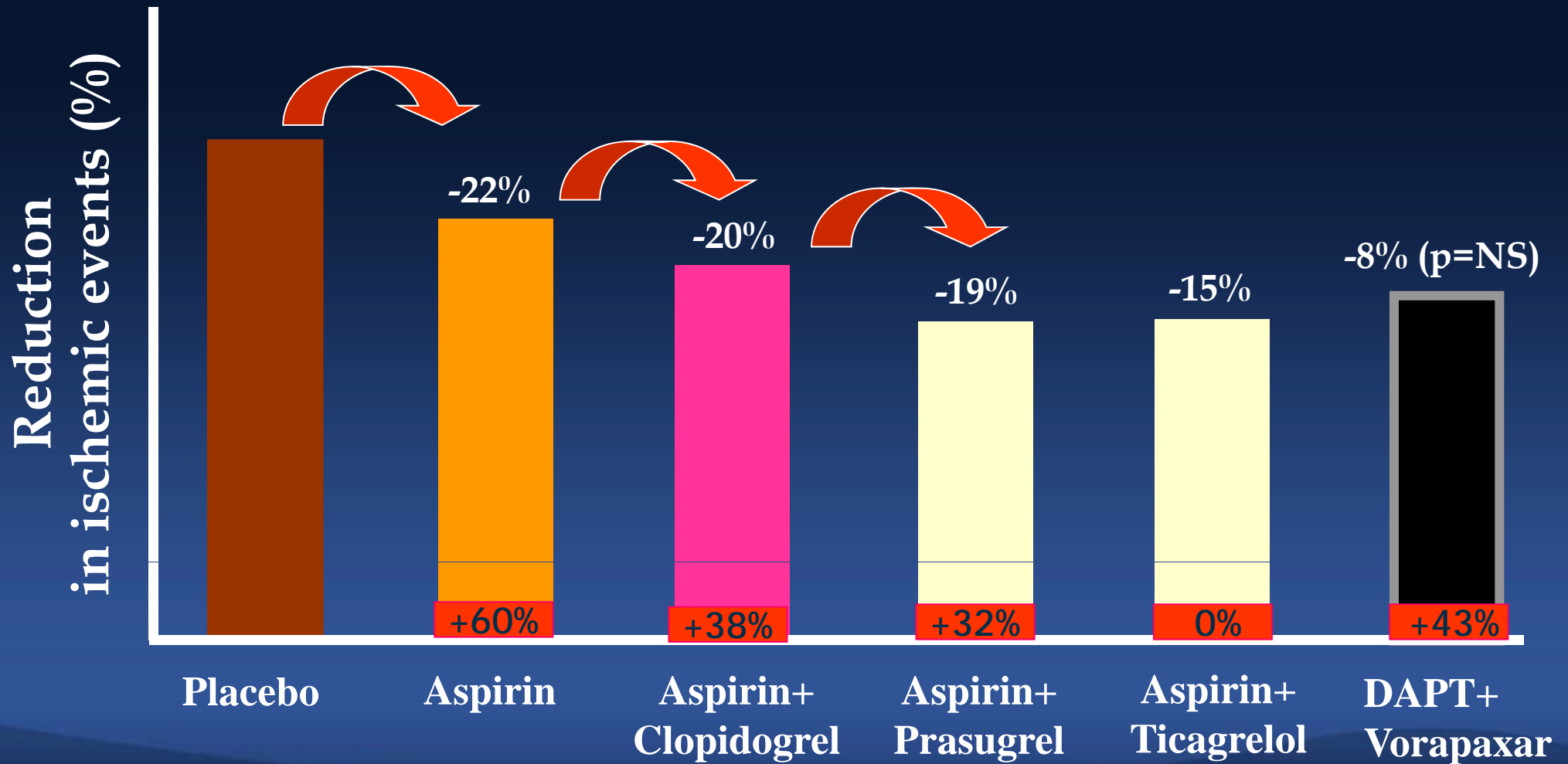
No. at Risk								
Placebo	6471	5844	5468	5121	3794	2291	795	
Vorapaxar	6473	5897	5570	5199	3881	2318	832	

Bleeding ( $p < 0.001$ ): GUSTO severe (HR 1.66), TMIMI major (HR 1.53), ICH (HR 3.39)

Total death: HR 1.05 (P=0.52)

In pts with ACS, the addition of vorapaxar to standard therapy did not significantly reduce the primary endpoint but significantly increased the risk of major bleeding.

# Evolution of Anti-platelet Therapy



... largely replaced  
by Newer Ones

Small bleed becomes a big bleed!  
Old Soldiers Never Die.

New  $P_2Y_{12}$  receptor inhibitors  
will be the key players in CV medicine.

감사합니다.