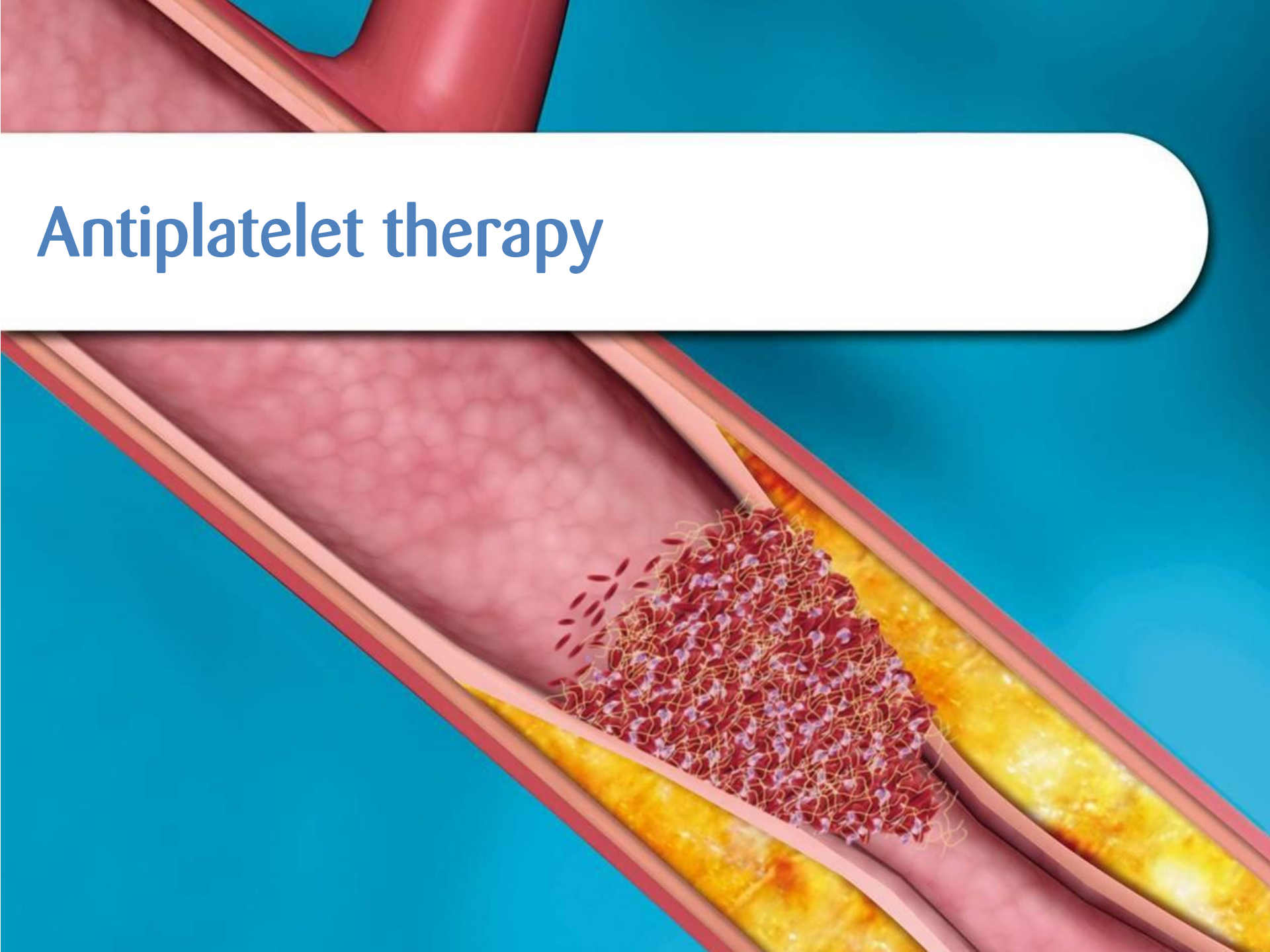
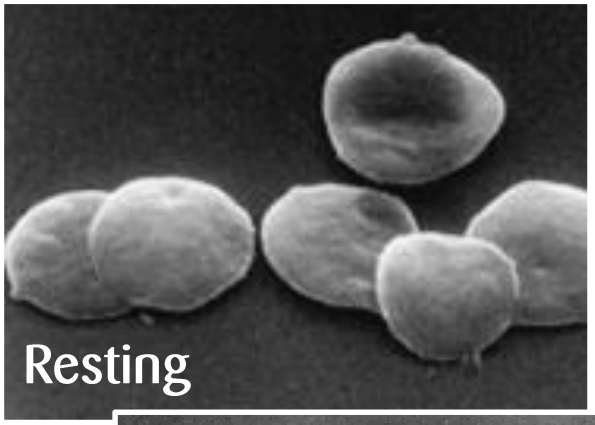
Antiplatelet therapy

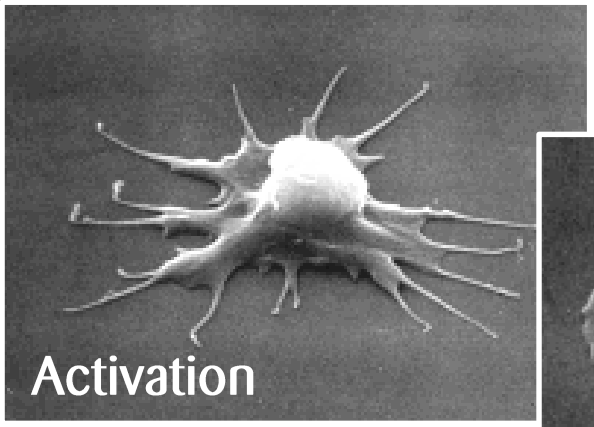


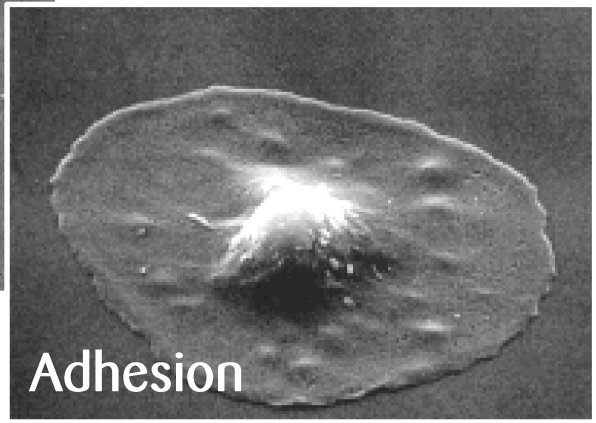
Platelet Pathophysiology

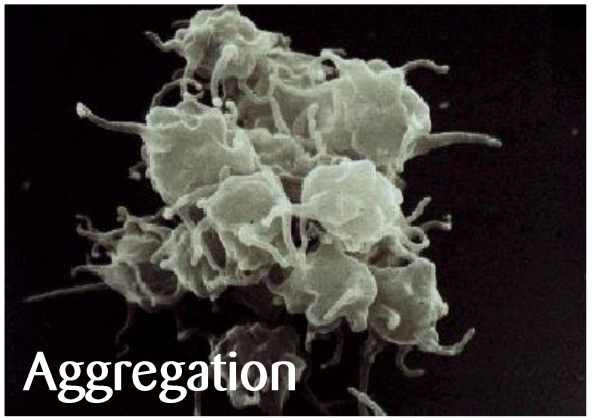
Reminder

4 different states:





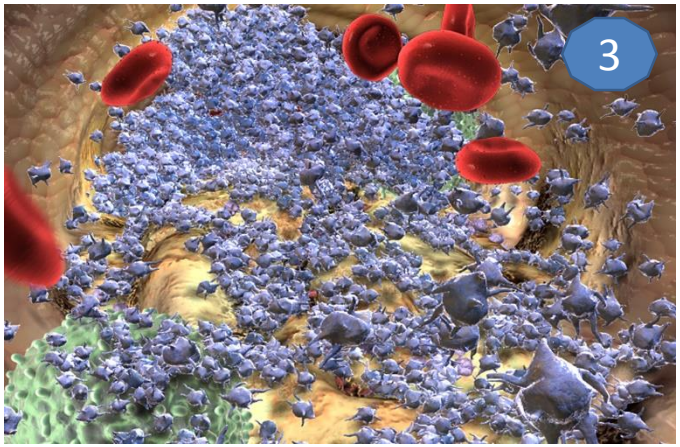




- Small, disk shaped clear cell fragments
- Derived from megakaryocytes fragmentation in bone marrow
- 2 – 3 µm diameter
- 5% of blood total volume
- Normal range: 150,000 – 400,000 G/L
- Lifespan 5-9 days

Platelet Pathophysiology

Atherosclerosis

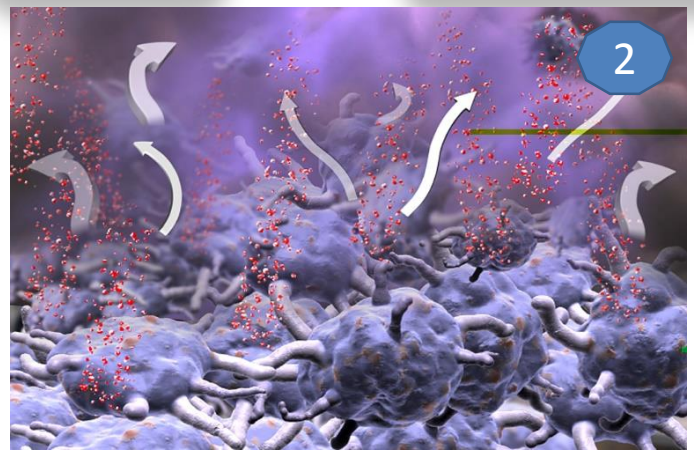


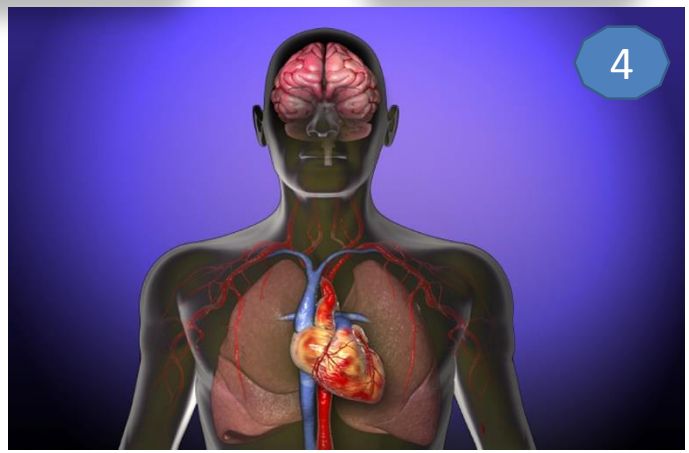
1 **Activation**

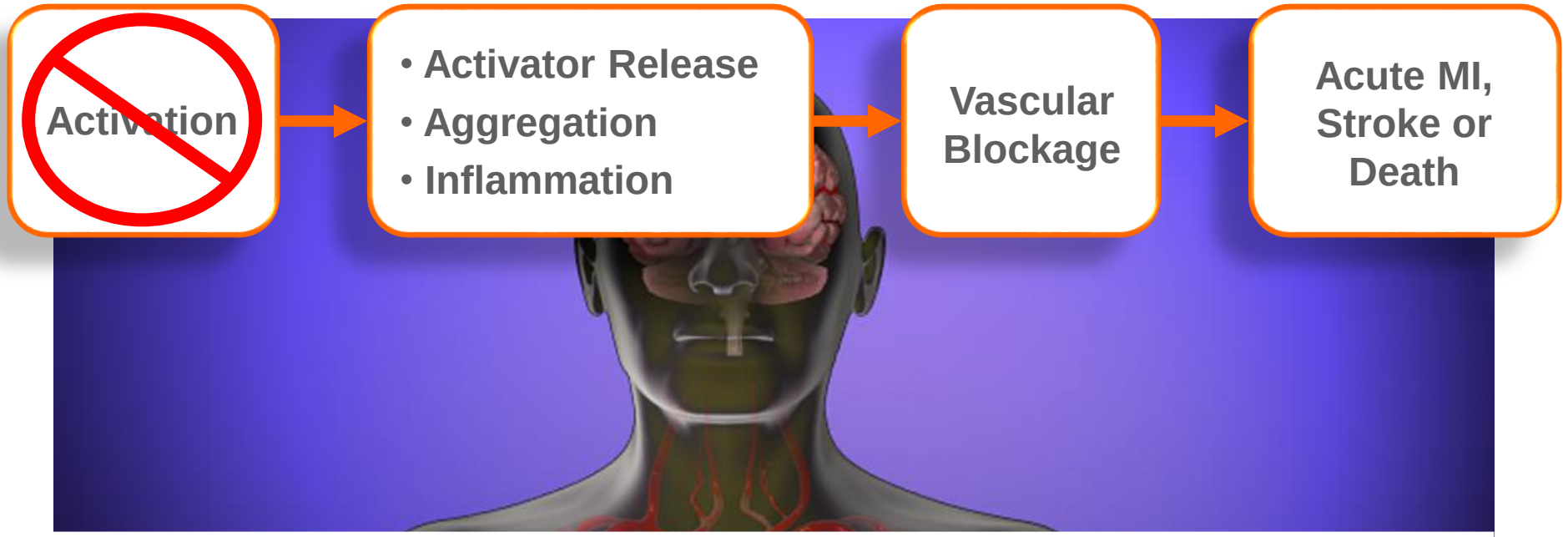
2
- **Activator Release**
- **Aggregation**
- **Inflammation**

3 **Vascular Blockage**

4 **Acute MI, Stroke or Death**







Effective management of platelet aggregation over time

Antiplatelet Therapy

Indications

Why prescribe antiplatelet drugs?

Antiplatelet agents reduce incidence of Major Adverse Cardiovascular Events* in a variety of atherothrombotic situations:

- Acute Coronary Syndrome (ACS)
- Percutaneous Coronary Intervention (PCI)
- Peripheral Arterial Disease (PAD)
- Secondary prevention after Ischemic Stroke

Aspirin

Anti-P2Y12 drugs

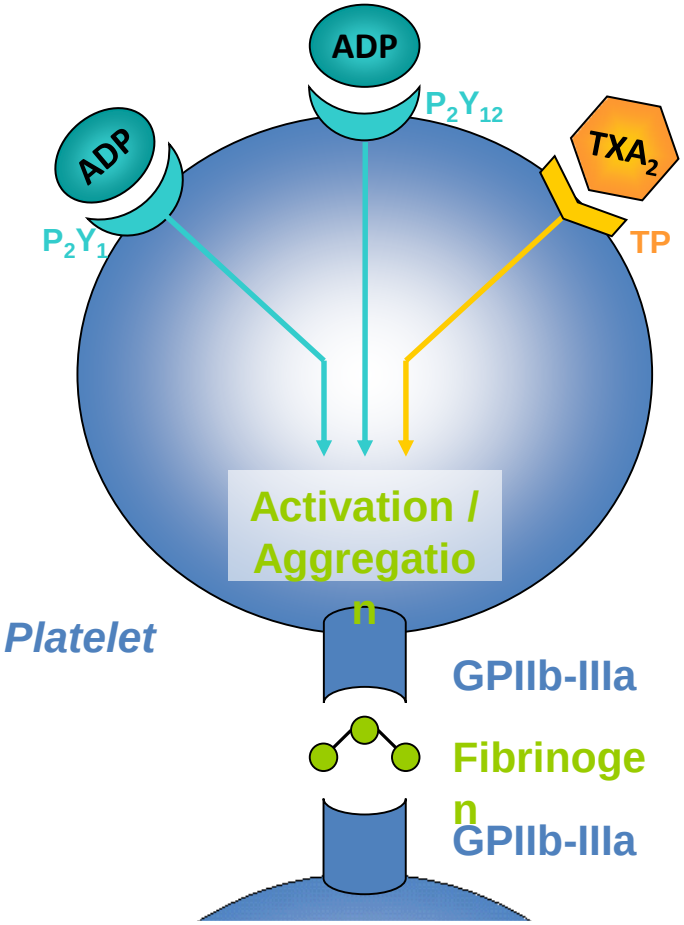
(ADP receptor / P2Y12 inhibitors)

- Ticlid® *(ticlopidine)*
- Plavix® *(clopidogrel)*
- Efient/Effient® *(prasugrel)*
- Brilique® *(ticagrelor)*
- Cangrelor *(in dev.)*
- MDCO-157 *(in dev.)*

** **MACE** = Acute myocardial infarction, ischemic stroke, coronary arterial occlusion or death*

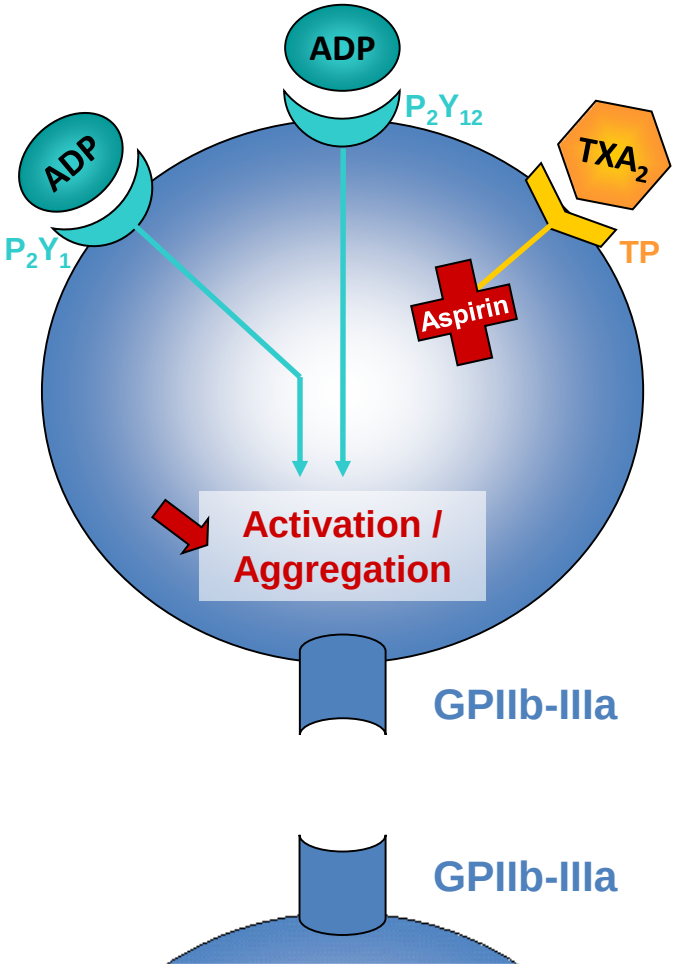
Antiplatelet Therapy

Aspirin



Normal physiology

During primary haemostasis step, ADP and TXA_2 facilitate platelet activation and aggregation

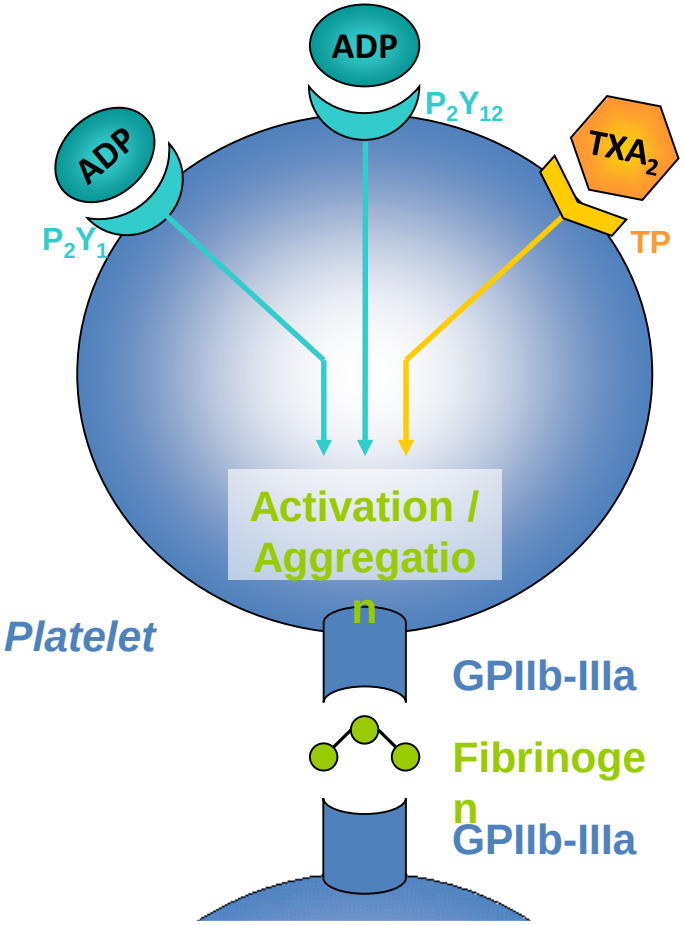


Inhibited State / Aspirin

Aspirin blocks the formation of thromboxane A_2 leading to decreases in the level of platelet activation and aggregation

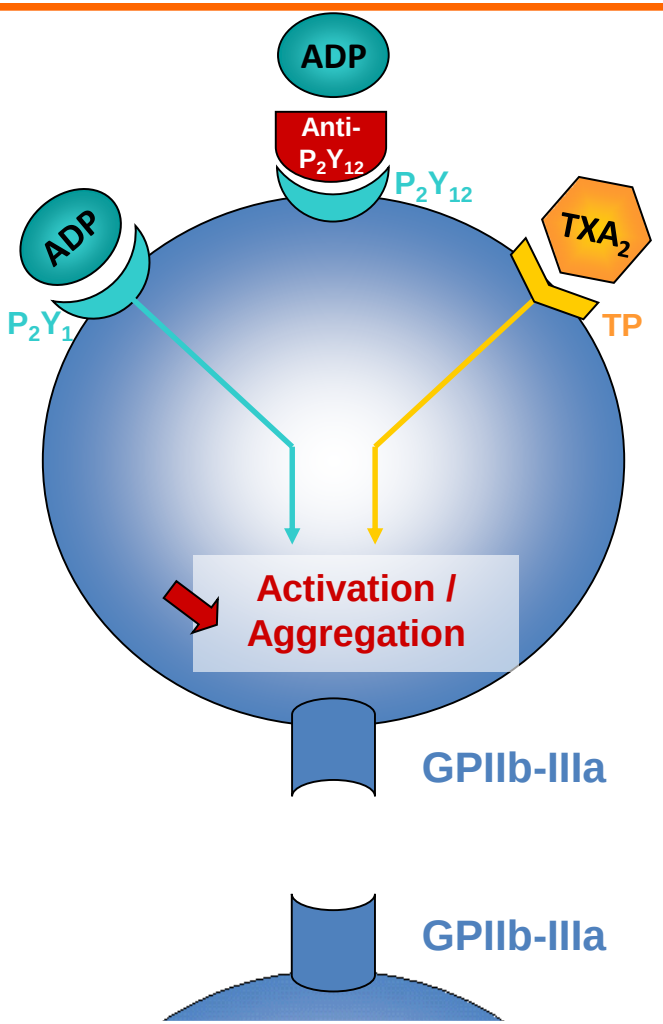
Antiplatelet Therapy

Anti-P_2Y_{12}



Normal physiology

During primary haemostasis step, ADP and TXA_2 facilitate platelet activation and aggregation

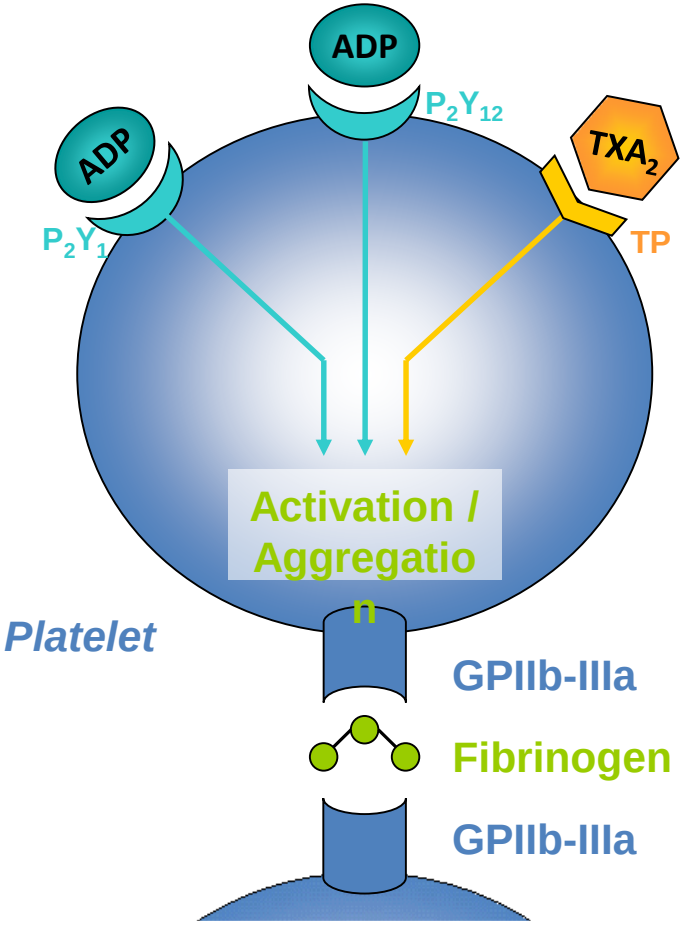


Inhibited State / Anti-P_2Y_{12}

Anti-P2Y12 drugs block the ADP receptor P_2Y_{12} leading to decreases in the level of platelet activation and aggregation

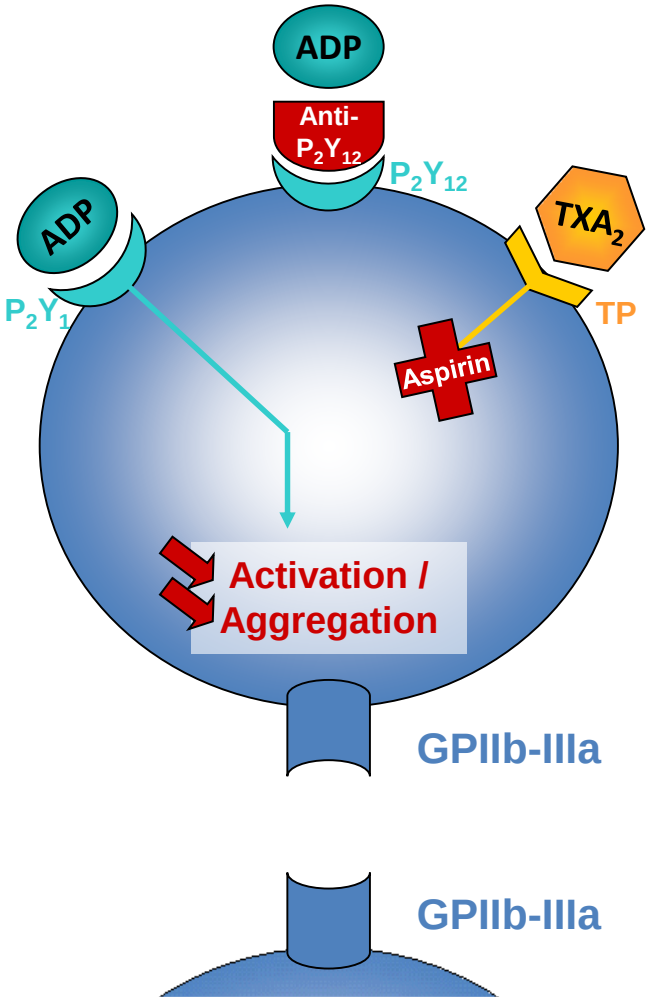
Antiplatelet Therapy

Aspirin + Anti-P_2Y_{12}



Normal physiology

During primary haemostasis step, ADP and TXA_2 facilitate platelet activation and aggregation



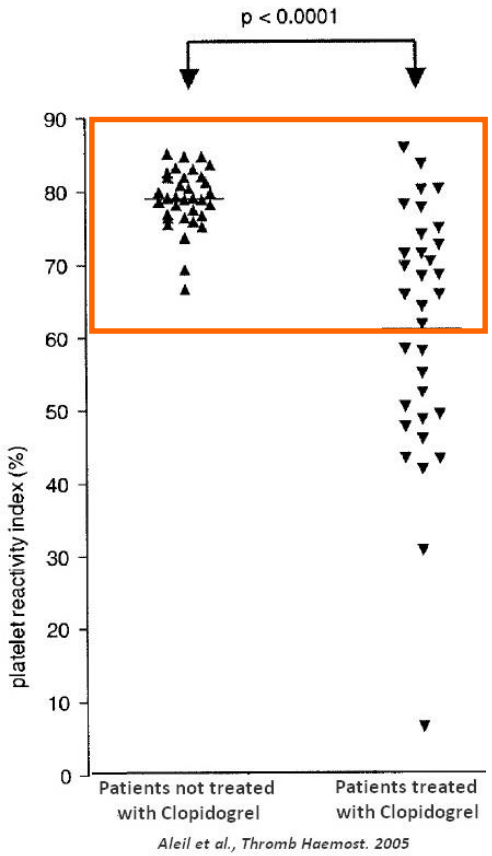
Inhibited State/Aspirin + Anti-P_2Y_{12}

Both pathways are blocked, leading to strong decreases in the level of platelet activation and aggregation

Laboratory Monitoring

Why monitoring?

Plavix® (clopidogrel) has an high inter-individual response variability.



2 resistance definitions:

- **Biological resistance:**

  15 to 30% of treated patients have a low level of platelet inhibition when monitored[1].
  This resistance does not automatically lead to thrombosis recurrence but may facilitate it[2]

- **Clinical resistance:**

  up to 10% of treated patients experience acute or subacute thrombosis recurrence after a coronary event or stenting[3]

Primary causes of resistances are:

- Lack of compliance
- Intestinal absorption variability
- Pro-drug hepatic metabolism variability due to CYP_{450} polymorphism
- Drug-Drug interactions

Bibliography

1 GURBEL *et al*. Randomized double-blind assessment of the ONSET and OFFSET, Circulation, 2009

2 BONELLO *et al*. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate, J Am Coll Cardiol, 2010

3 ALEIL *et al*. Flow cytometric analysis of intraplatelet VASP phosphorylation, Thromb Haemost. 2005

Laboratory Monitoring

When to monitor?

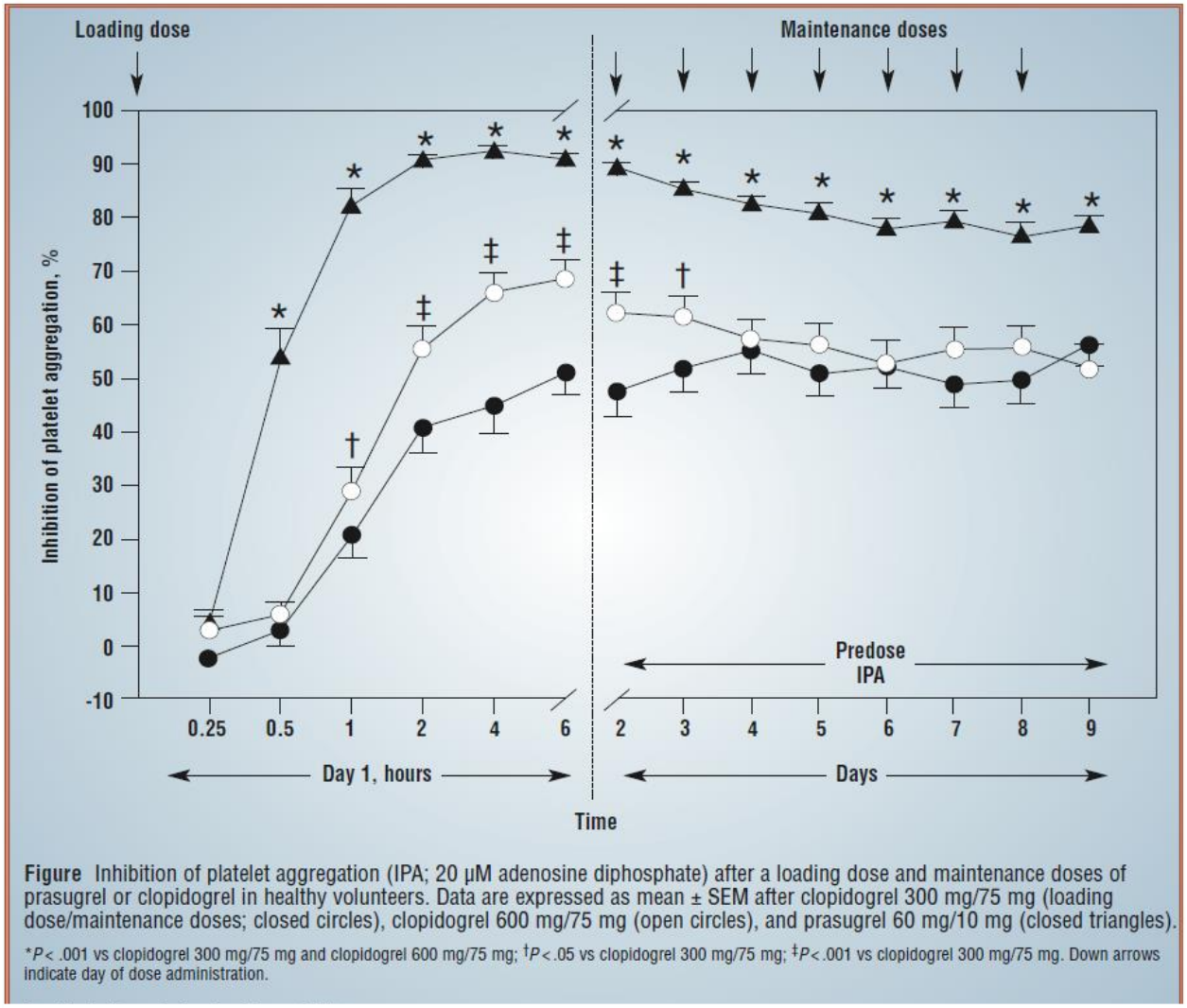


Figure Inhibition of platelet aggregation (IPA; 20 μM adenosine diphosphate) after a loading dose and maintenance doses of prasugrel or clopidogrel in healthy volunteers. Data are expressed as mean ± SEM after clopidogrel 300 mg/75 mg (loading dose/maintenance doses; closed circles), clopidogrel 600 mg/75 mg (open circles), and prasugrel 60 mg/10 mg (closed triangles).

*$P < .001$ vs clopidogrel 300 mg/75 mg and clopidogrel 600 mg/75 mg; †$P < .05$ vs clopidogrel 300 mg/75 mg; ‡$P < .001$ vs clopidogrel 300 mg/75 mg. Down arrows indicate day of dose administration.

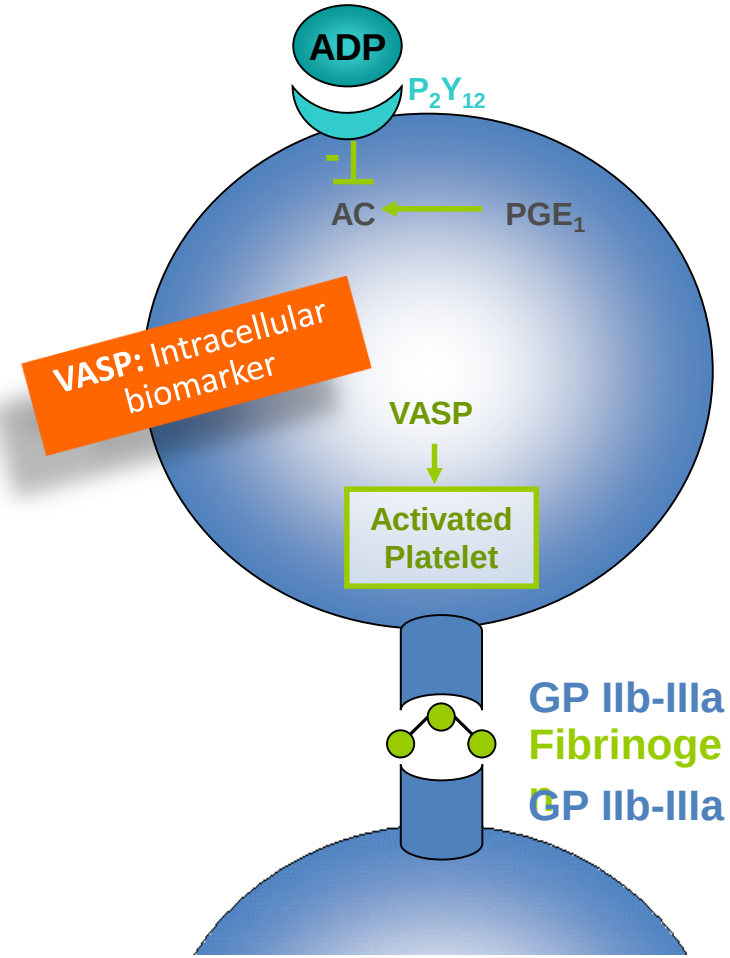
- ● clopidogrel 300mg/75mg
- ○ clopidogrel 600mg/75mg
- ▲ prasugrel 60mg/10mg

Ideal test timing will depend on:

- Drug type
- Dose
- Time to reach steady-state

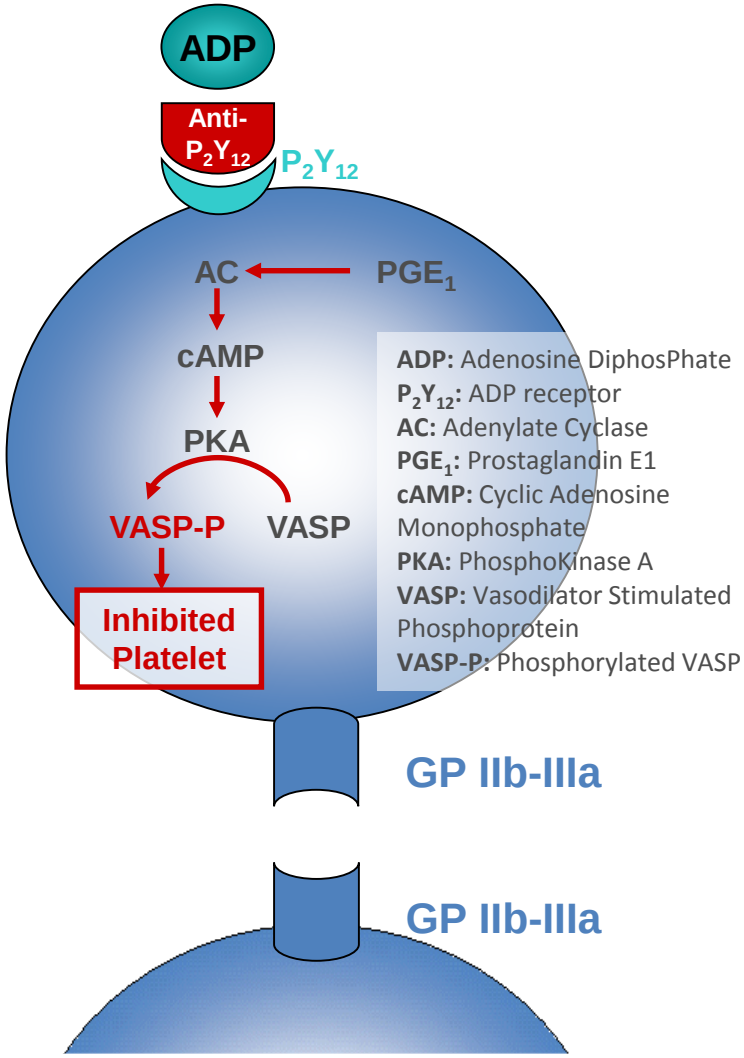
Payne *et al*. Increased active metabolite formation explains the greater platelet inhibition with prasugrel compared to high-dose clopidogrel.
J Cardiovasc Pharmacol. 2007

Regulation of VASP phosphorylation



Activated Platelet

When ADP binds to P_2Y_{12} receptor, VASP remains in its basal state, **unphosphorylated.** Platelet is activated and GPIIb-IIIa receptor binds fibrinogen, allowing platelet aggregation.

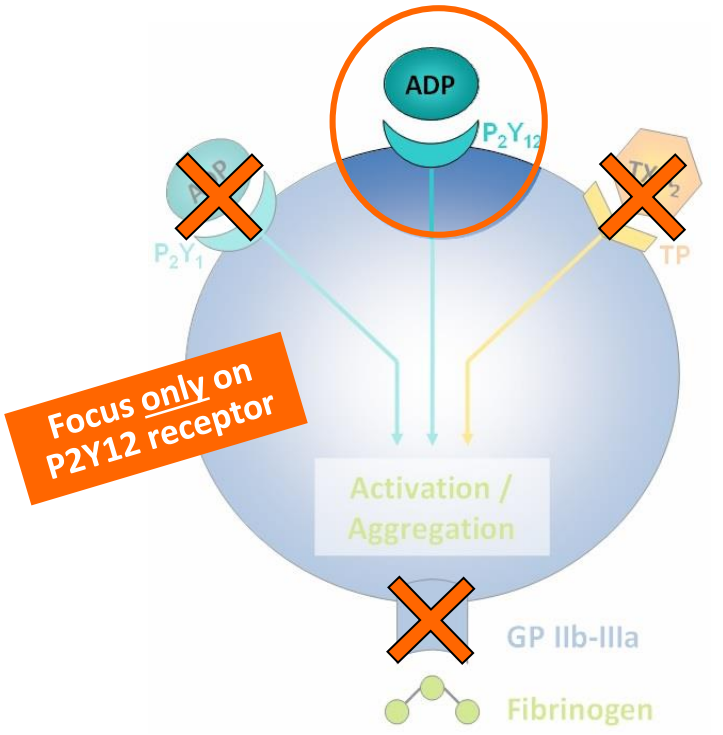


Inhibited Platelet

When P_2Y_{12} receptor is inhibited, VASP is **phosphorylated** under PGE_1 stimulation. GPIIb-IIIa receptor cannot bind fibrinogen anymore, preventing platelet aggregation.

VASP biomarker

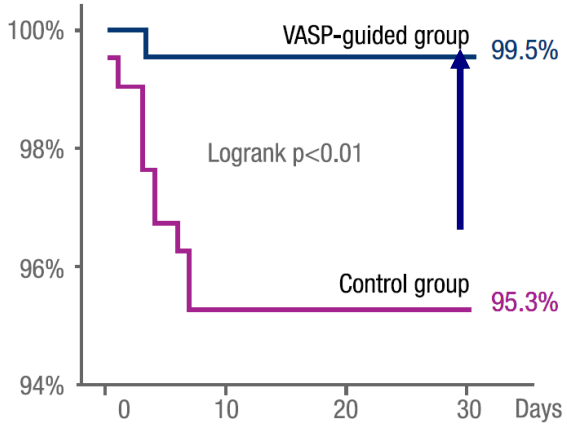
The most specific for P_2Y_{12}



- No interference from other ADP receptors such as P_2Y_1 (≠ all aggregation based assays)
- Insensitive to aspirin and anti-GPIIb/IIIa drugs (≠ all other assays)
- Insensitive to PLT count (≠ all other assays)
- Insensitive to VWF level (≠ PFA assay)

VASP biomarker

The most correlated with clinical outcome



Kaplan-Meier curve of freedom of definite stent thrombosis survival according to groups
BONELLO L. et al. Am J. Cardiol. 2009

When using VASP as biomarker, rate of major adverse cardiovascular events is significantly lower than the control group without monitoring.

In a 2009 study (Bonello *et al.*), the VASP guided group, clopidogrel Loading Dose (LD) was adjusted depending PRI result (from 600mg to 2,400mg).

The rate of early stent thrombosis after PCI was:

- 4,7% in the control group
- *vs* 0,5% in the VASP guided group (p<0,01)

Bibliography

BONELLO L. et al.: Am J Cardiol. 2009; 103:5-10

"A tailored clopidogrel loading dose according to platelet reactivity monitoring decreases the rate of early stent thrombosis after PCI without increasing bleeding"