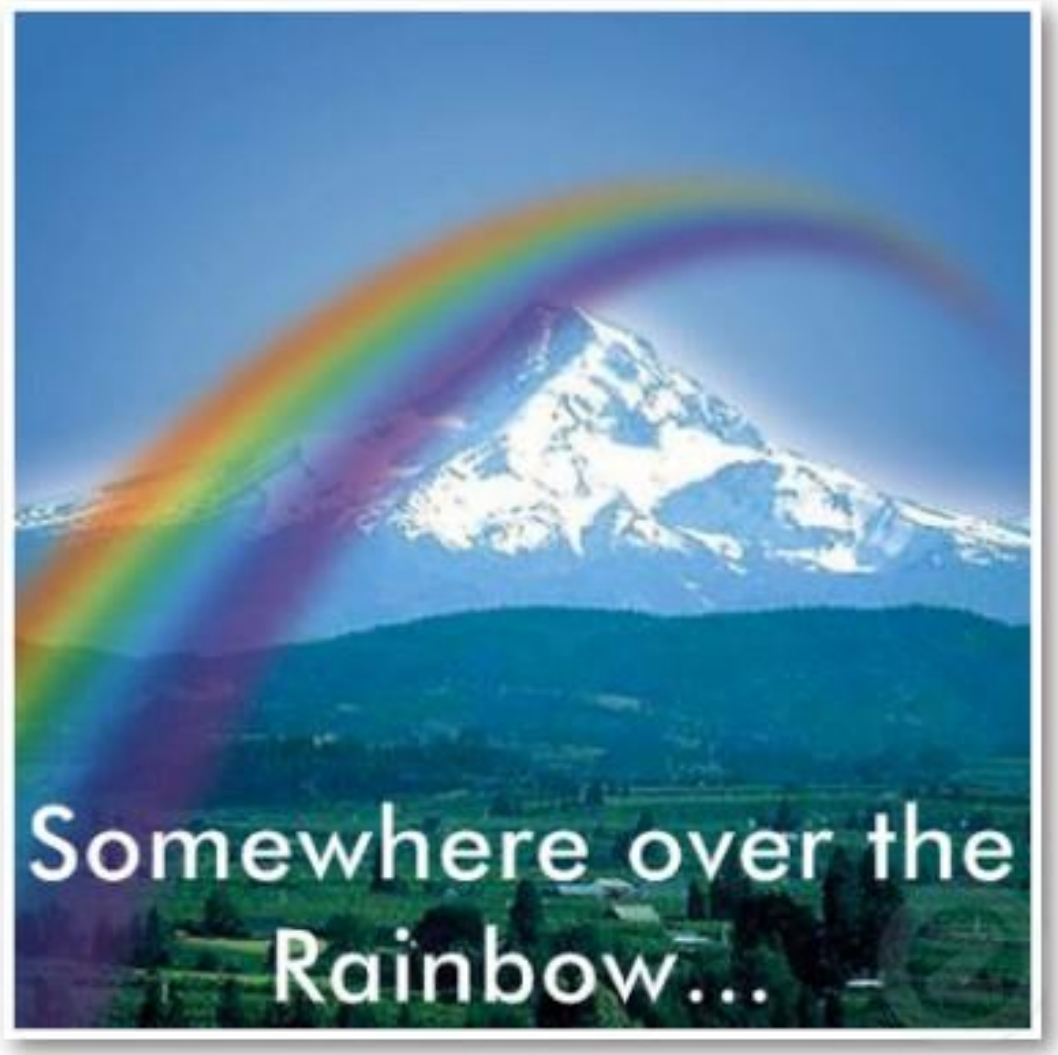
Platelet Function Beyond Hemostasis



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Disclosures

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- Astrazeneca
- Otsuka
- Accumetrics
- Haemonetics
- Han-Mi Pharmaceutical
- KSIC
- GNUH

Honoraria/Consulting

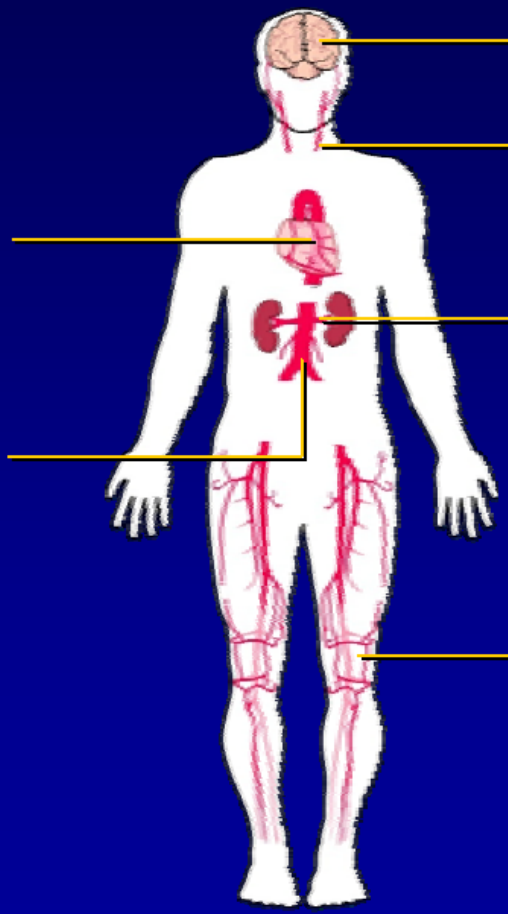
- Astrazeneca
- Daiichi Sankyo Inc
- Sanofi-Aventis
- Otsuka
- Haemonetics
- Dong-A Pharmaceutical

Atherothrombosis: Clinical Manifestations

Acute coronary syndromes
- STEMI
- NSTEMI
- Unstable angina

Stable CAD
Atrial Fibrillation
Angioplasty
Bare metal stent
Drug eluting stent
CABG

Abdominal aortic aneurysm (AAA)



Stroke
TIA
Intracranial stenosis

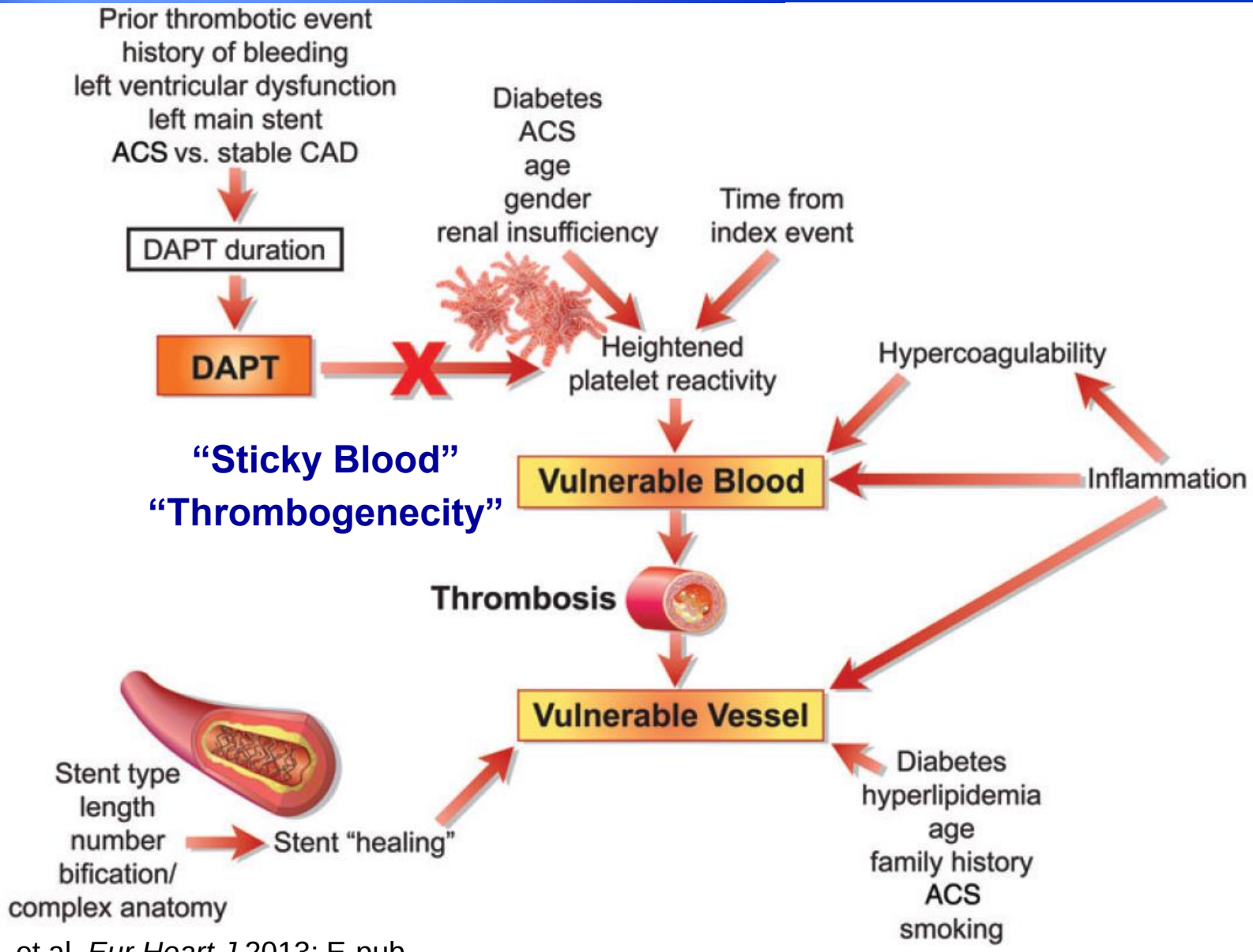
Carotid artery stenosis
CEA
Carotid stenting

Renal artery stenosis
Renal artery stenting

Peripheral arterial disease
Acute limb ischemia
Claudication
Amputation
Endovascular stenting
Peripheral bypass
Abnormal ABI

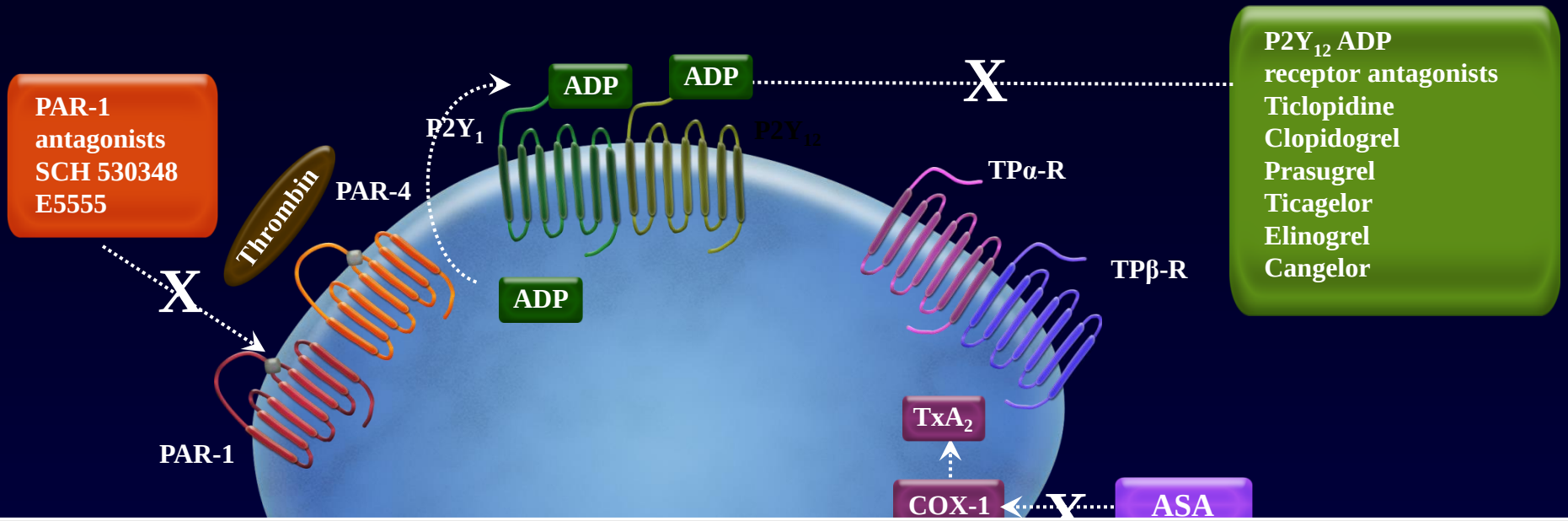
Meadows TA, Bhatt DL. *Circ Res.* 2007;100:1261-1275.

Pathogenesis of Atherothrombosis:
Interplay Between Vulnerable Vessel and Blood



Gurbel P, et al. *Eur Heart J* 2013; E-pub.

Platelet Agonists and Antiplatelet Agents



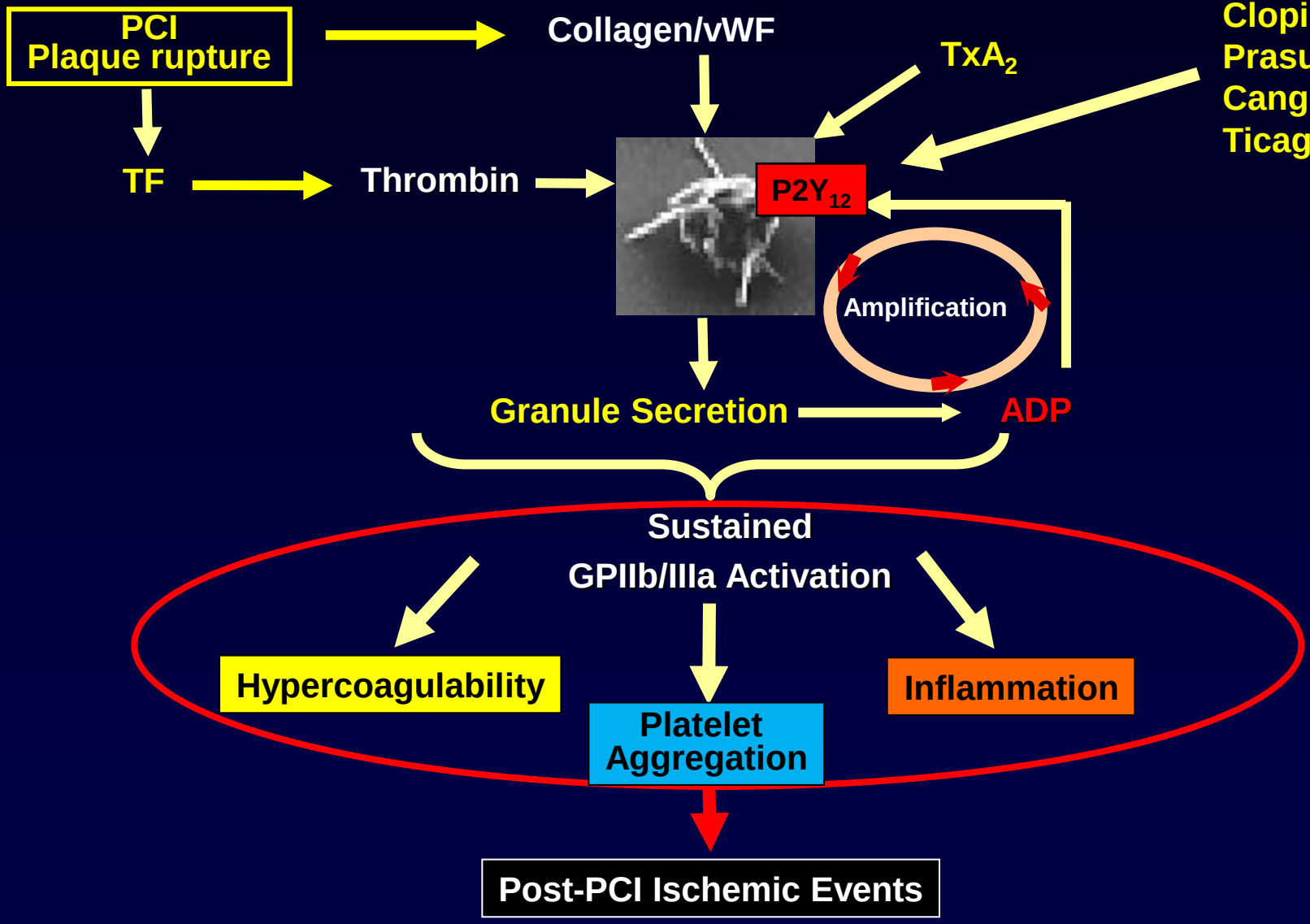
What is "ideal antiplatelet agent"?

Anti-thrombotic effect

+

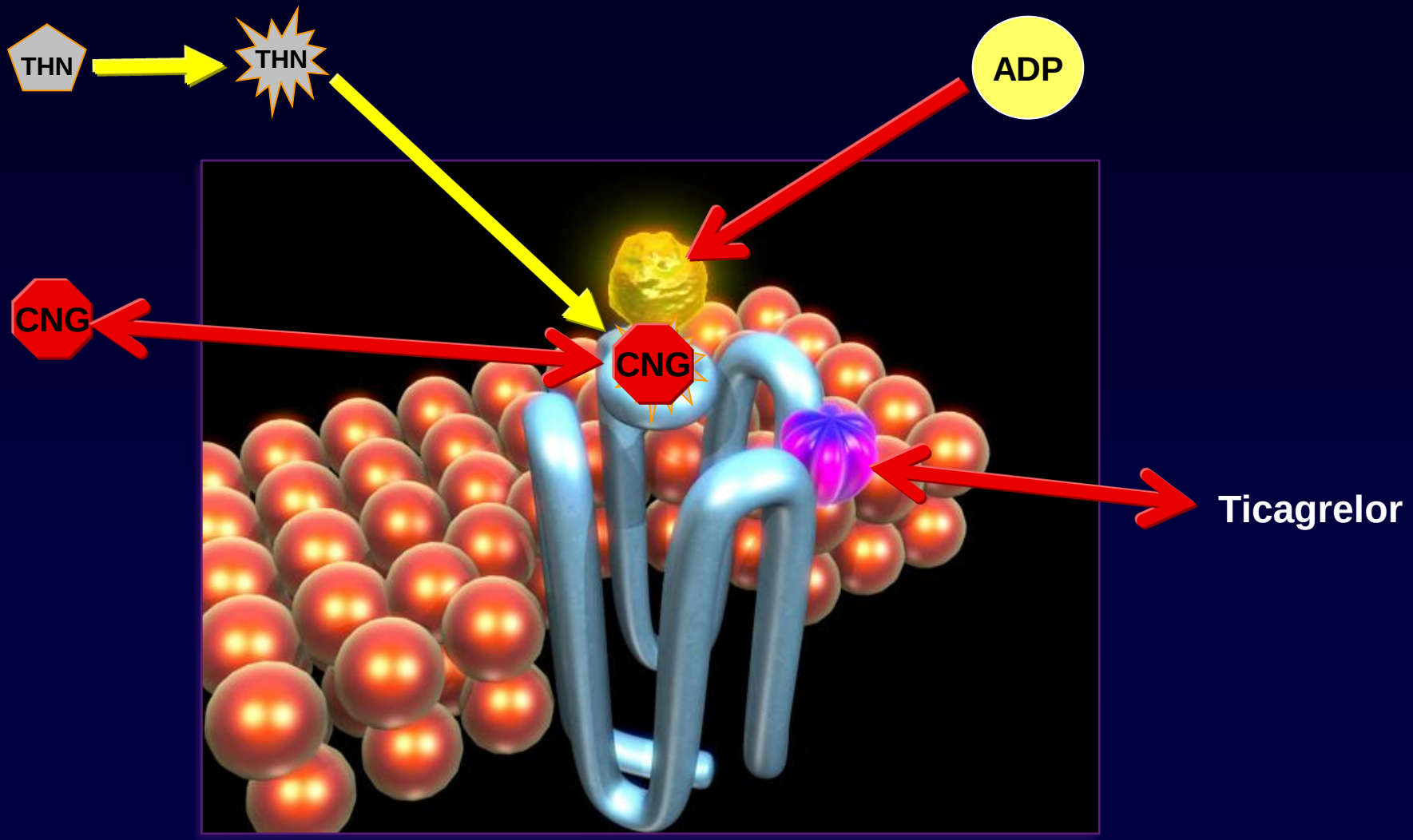
Anti-atherogenic effect

ADP-Platelet $P2Y_{12}$ Receptor Interaction: Central Role in Thrombosis Progression



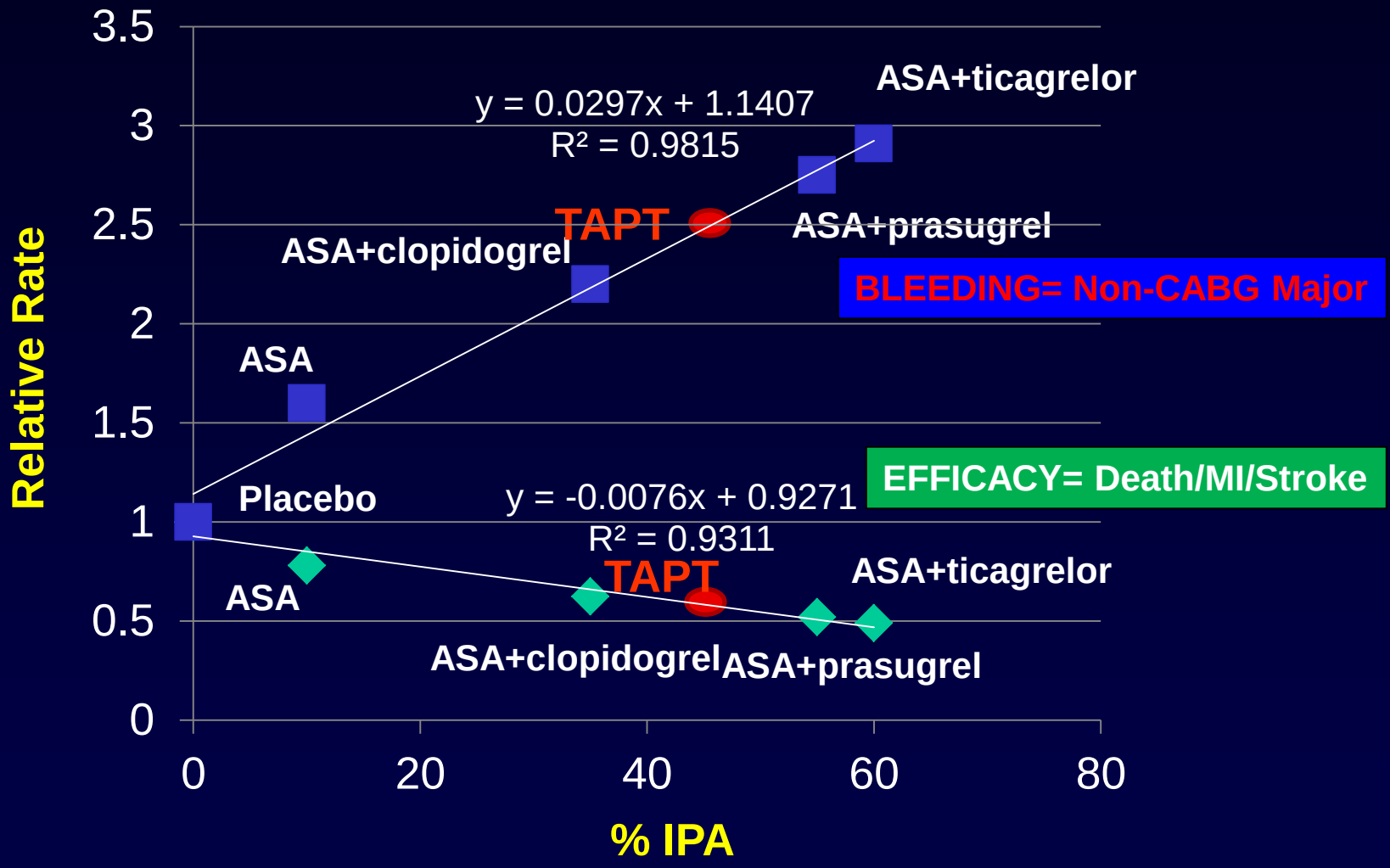
Gurbel PA et al. *Rev Cardiovasc Med*. 2006; 7: S20-S28.

Mechanism of ADP $P2Y_{12}$ Inhibitors



van Giezen JJ et al. *Thromb Res*. 2009;124:565-71

Efficacy and Safety Correlated with IPA

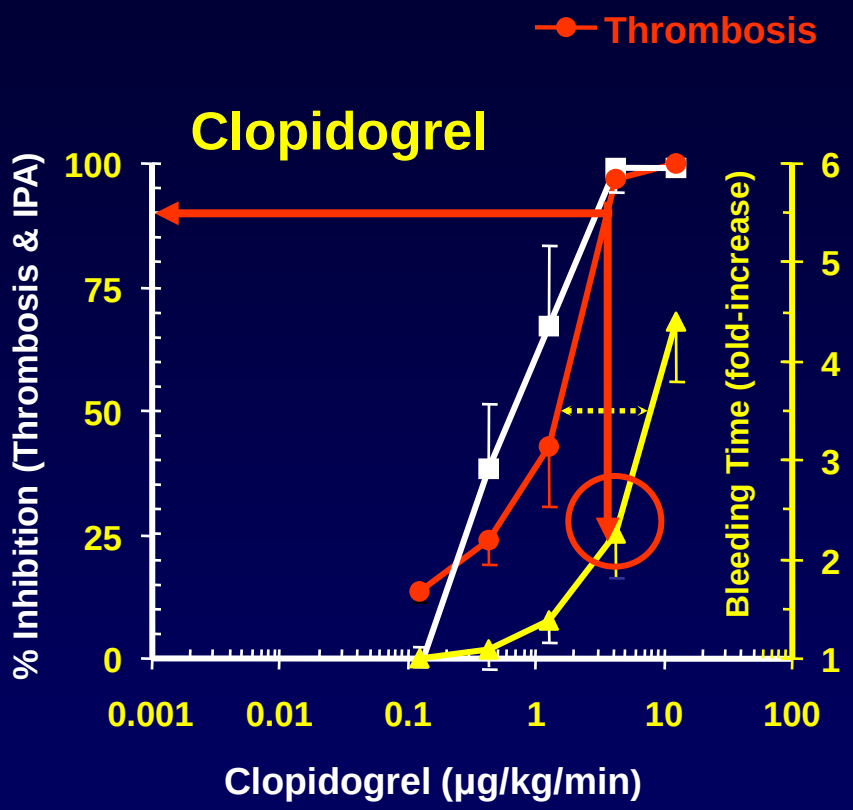


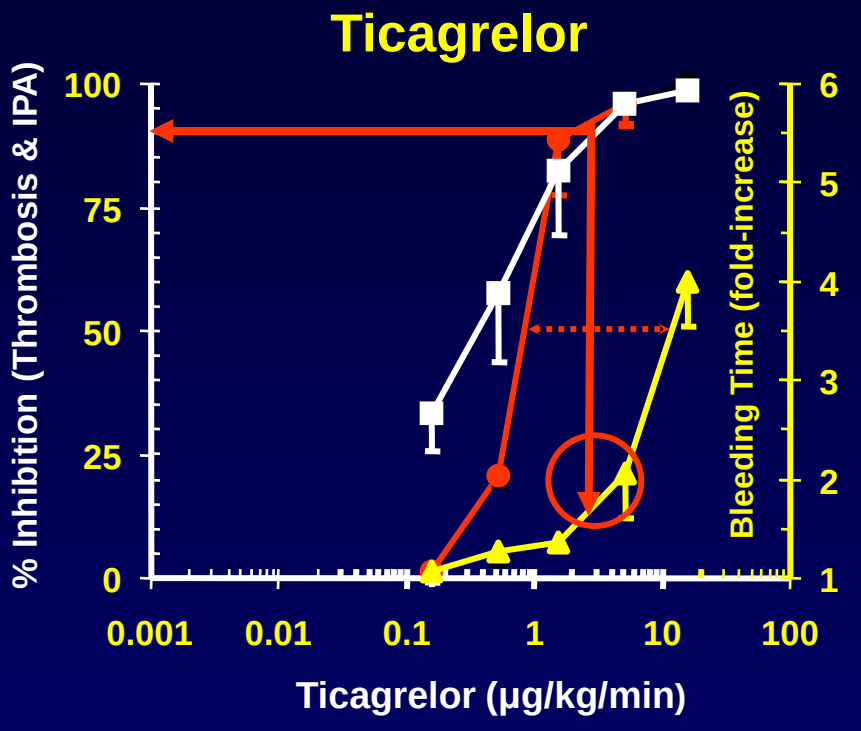
Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71
Yusuf et al. *N Engl J Med*. 2001;345:494
Wiviott et al. *N Engl J Med* 2007;357:2001-2015
Wallentin et al. N Engl J Med 2009;361:1-13

*IPA = inhibition of platelet aggregation

Preclinical Data for Clopidogrel and Ticagrelor:

Wider Therapeutic Window with a Reversible $P2Y_{12}$ Inhibitor



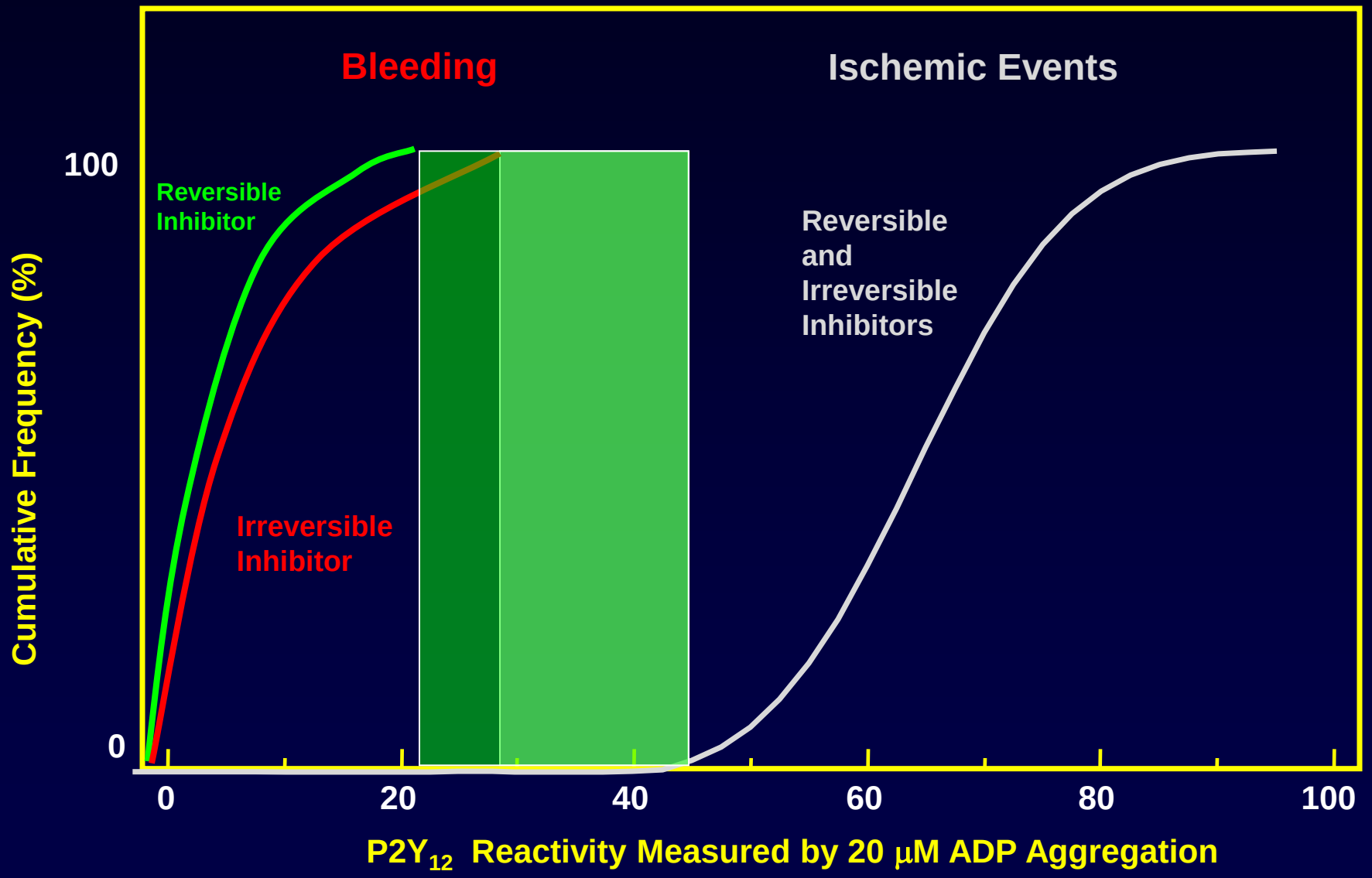


At 90% inhibition of the thrombotic response, clopidogrel induces a 120% increase in bleeding time

At 90% inhibition of the thrombotic response, ticagrelor induces a 40% increase in bleeding time

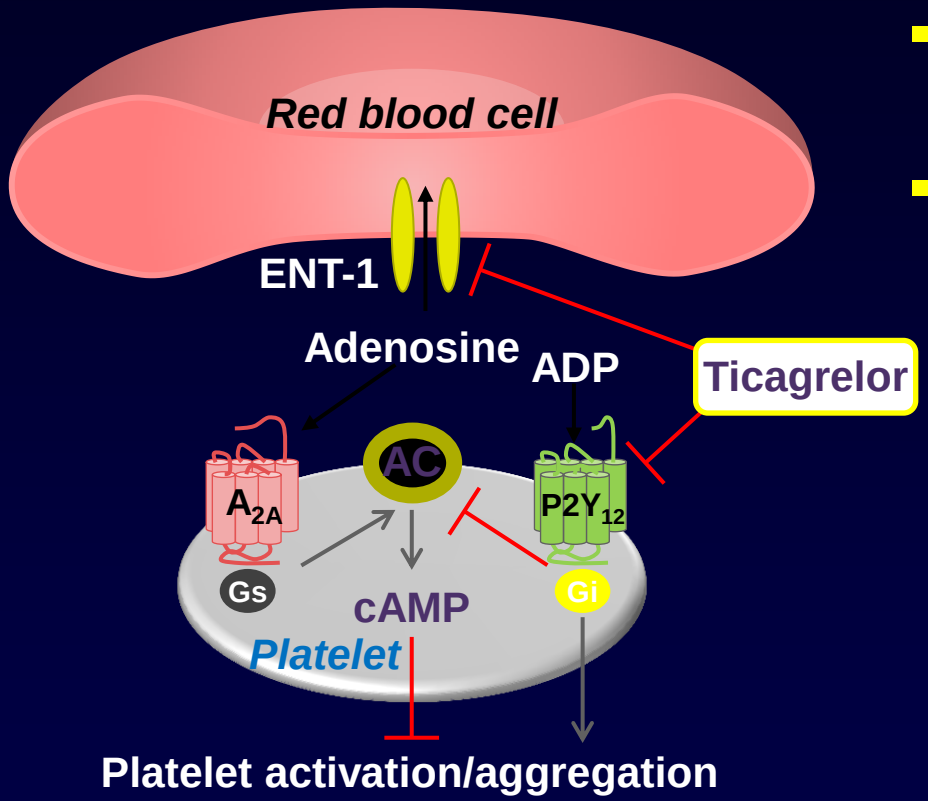
van Giezen JJ, Humphries RG. *Semin Thromb Hemost.* 2005;31:195-204.

Theoretical $P2Y_{12}$ Reactivity Therapeutic Window



Adapted from Gurbel PA et al. *J Am Coll Cardiol*. 2008;51:B86

Ticagrelor Works via a Dual Pathway: Antiplatelet Effect and ↑Adenosine Level



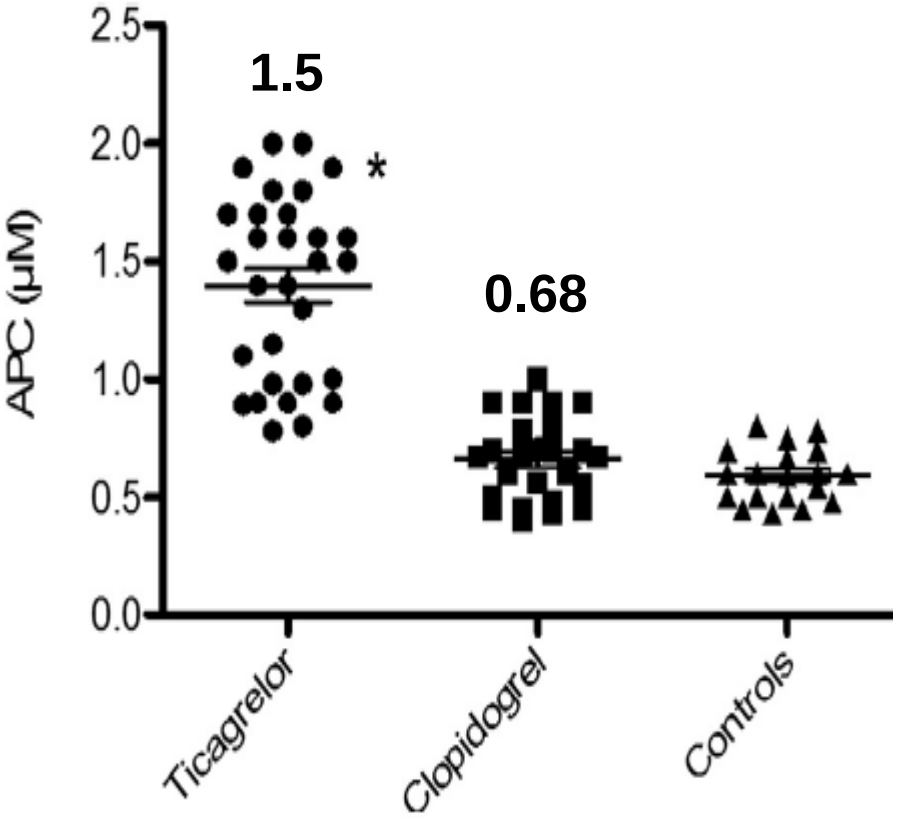
- Inhibition of $P2Y_{12}$ receptor[1,2]
  - Anti-platelet effect
- Inhibition of ENT-1 transporter[3,4,5]
  - Enhanced local adenosine response may result in:*
    - Additional inhibition of platelet aggregation/activation†[3]
    - Cardioprotection[6]
    - Vasodilation[5,7,8]
    - Modulation of inflammation
    - Dyspnoea[7]

 # PDE inhibitors (Dipyridamole/Cilostazol) & Ticagrelor:
↑ adenosine level in the blood by ENT-1 channel blockade

Figure adapted from Nylander S, et al. JTH 2013.
AC, adenylyl cyclase; ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate; ENT, equilibrative nucleoside transporter.

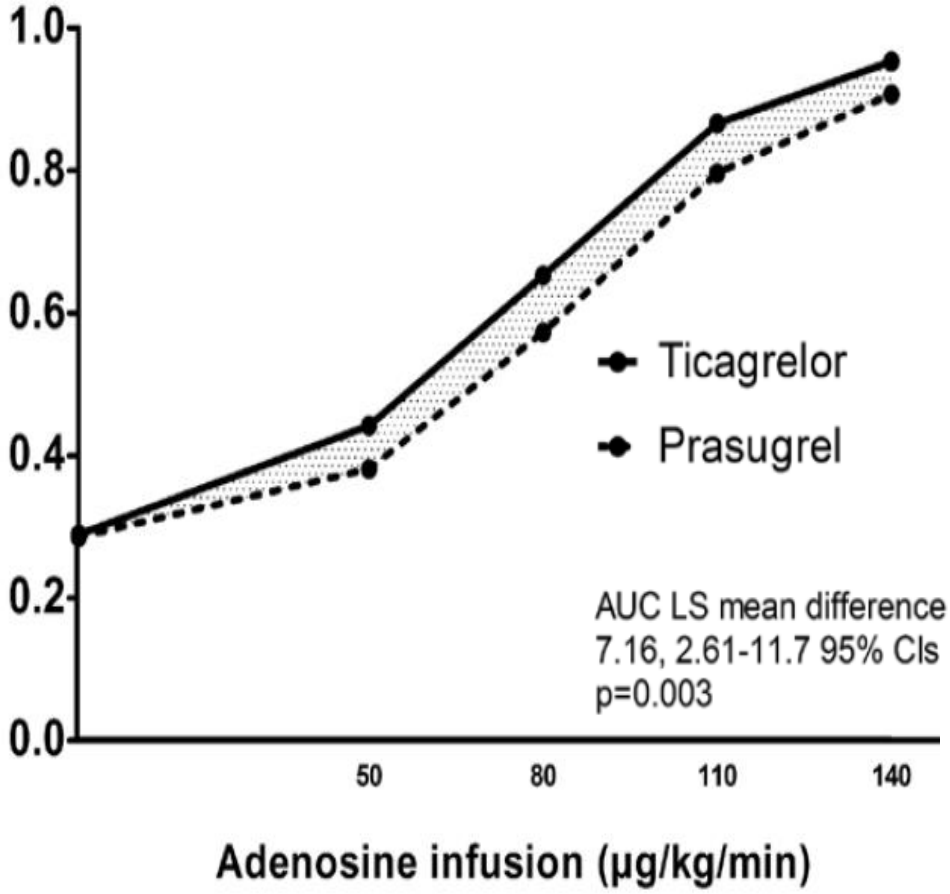
Effect of Ticagrelor in ACS Patients

Adenosine level after LD Tx



Bonello L et al. *JACC* 2014;63:872-7.

LAD maxCBFV during ADO infusion



Alexopoulos D et al. *Circ CV Interv* 2013;6:277-83.

Platelet Function Beyond Hemostasis

Diverse roles

- *Promoting inflammatory and immune response*
- *Maintaining vascular integrity*
- *Contributing wound healing*

Underlying mechanisms

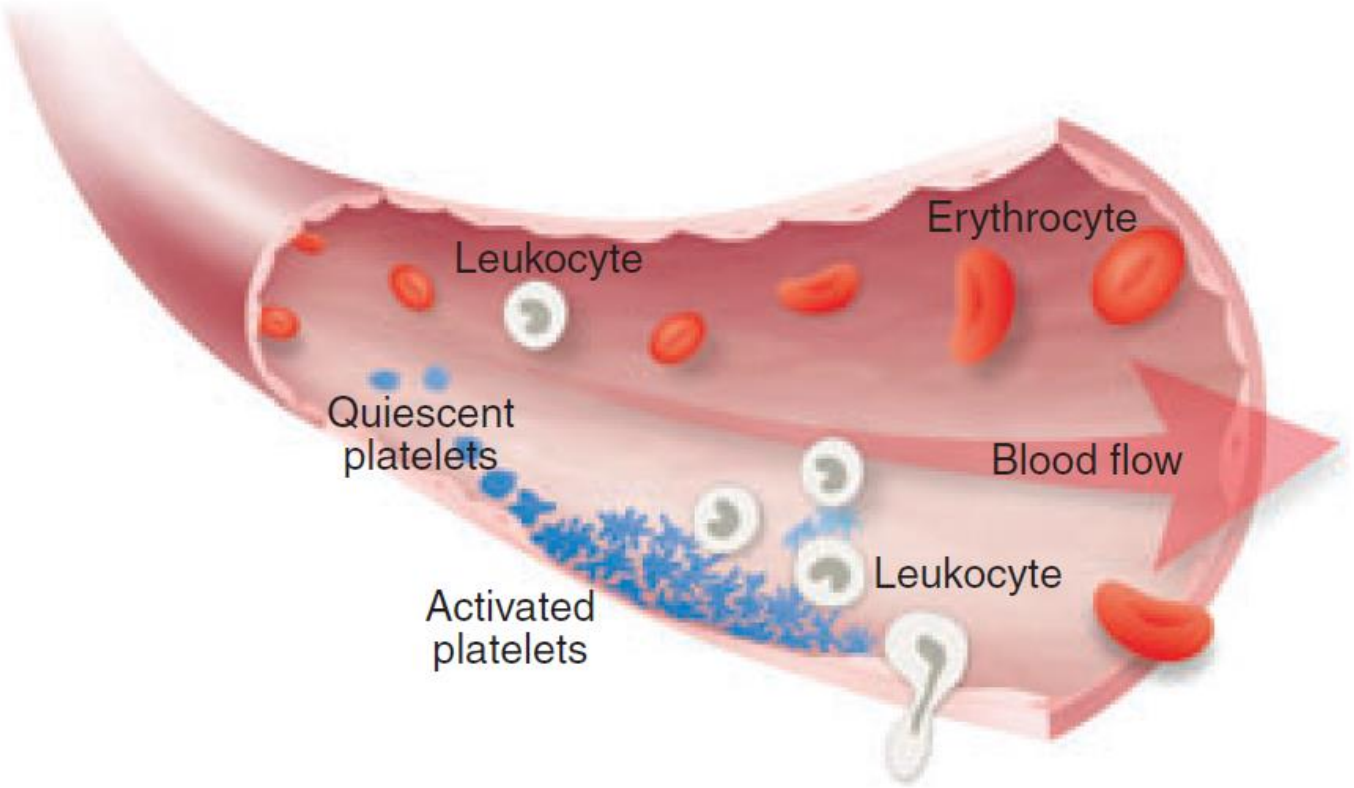
- *Recruit leukocytes / progenitor cells to sites of vascular injury / thrombosis*
- *Store, produce and release pro-inflammatory, anti-inflammatory and angiogenic factors and microparticles into the circulation*
- *Spur thrombin generation*

Diseases mediated with platelets

***Endothelial dysfunction, atherosclerosis*, restenosis, LV remodeling, cancer, IBD, RA, SLE, psoriasis, sepsis, acute lung injury, transplantation rejection…**

Smyth SS et al. *J Thromb Haemost* 2009;7:1759-66

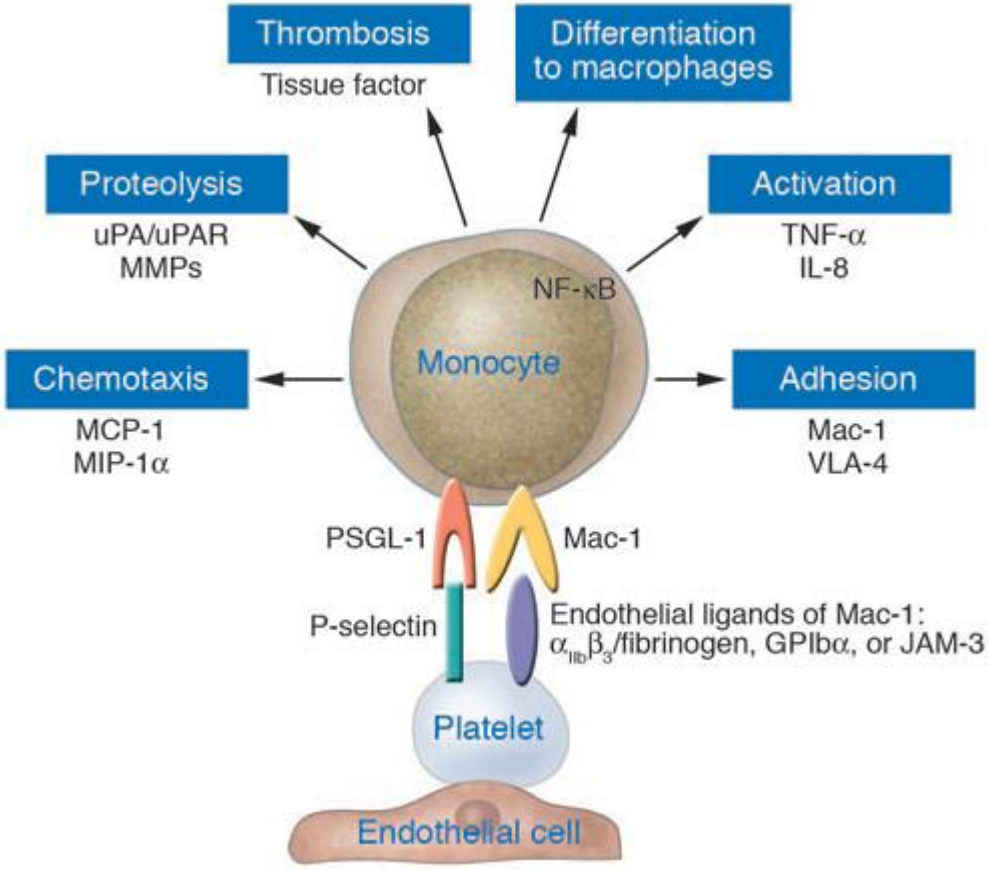
Endothelium-Platelet-Leukocyte Cross-talk

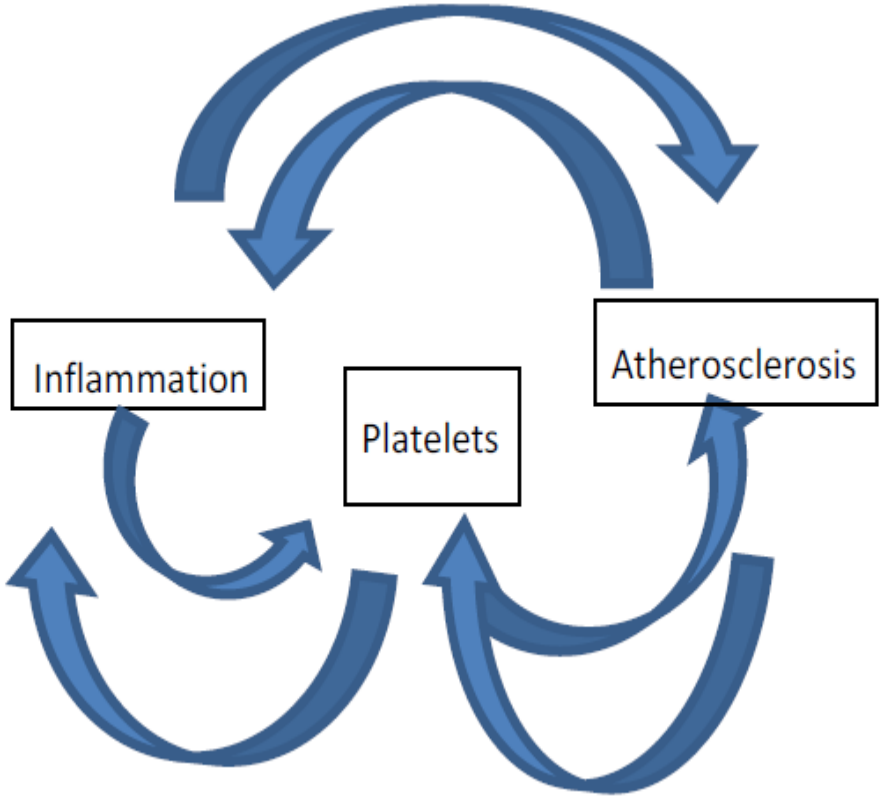


	Initial capture	*Released mediators*	*Firm adhesion*				
Leukocyte	PSGL-1		αMβ2 (Mac-1)	αMβ2 or αVβ3	CD36 (GP IV)	αLβ2	αMβ2 CD40
Blood		RANTES/CCL5, PAF, ENA-78, Groα, IL-1β	Fibrinogen (fibrin) thrombospondin				
platelet	P-selectin		GP Ibα	αIIbβ3	CD36 (GP IV)	ICAM-2	JAM3 CD40L

Smyth SS et al. *J Thromb Haemost* 2009;7:1759-66.

Central Role of Platelets in Atherosclerosis





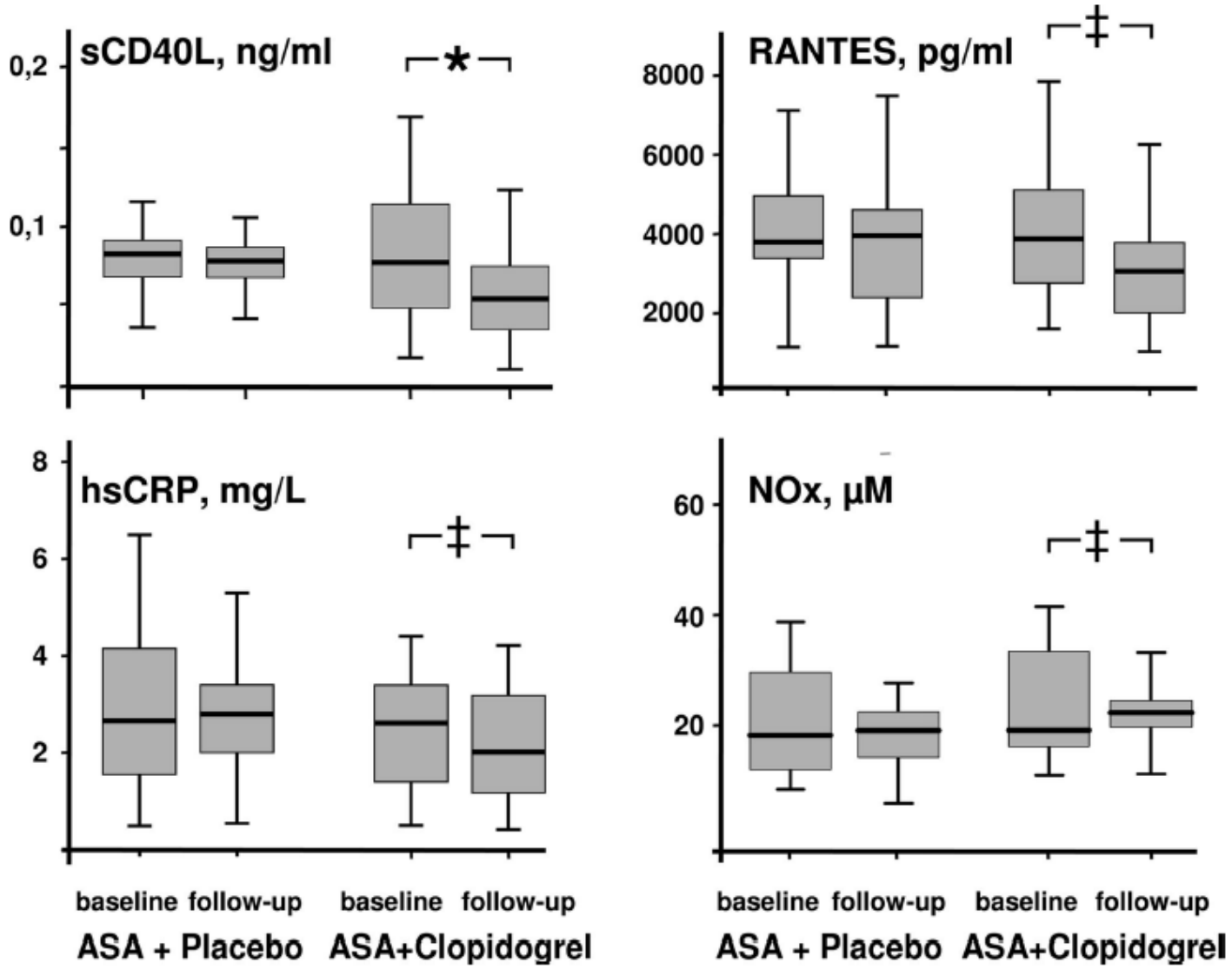
Clin Invest J. 2005;115:3378-84.

1. Platelet Function:

Inflammation and Coagulation

Clopidogrel on PLT Activation and Inflammation

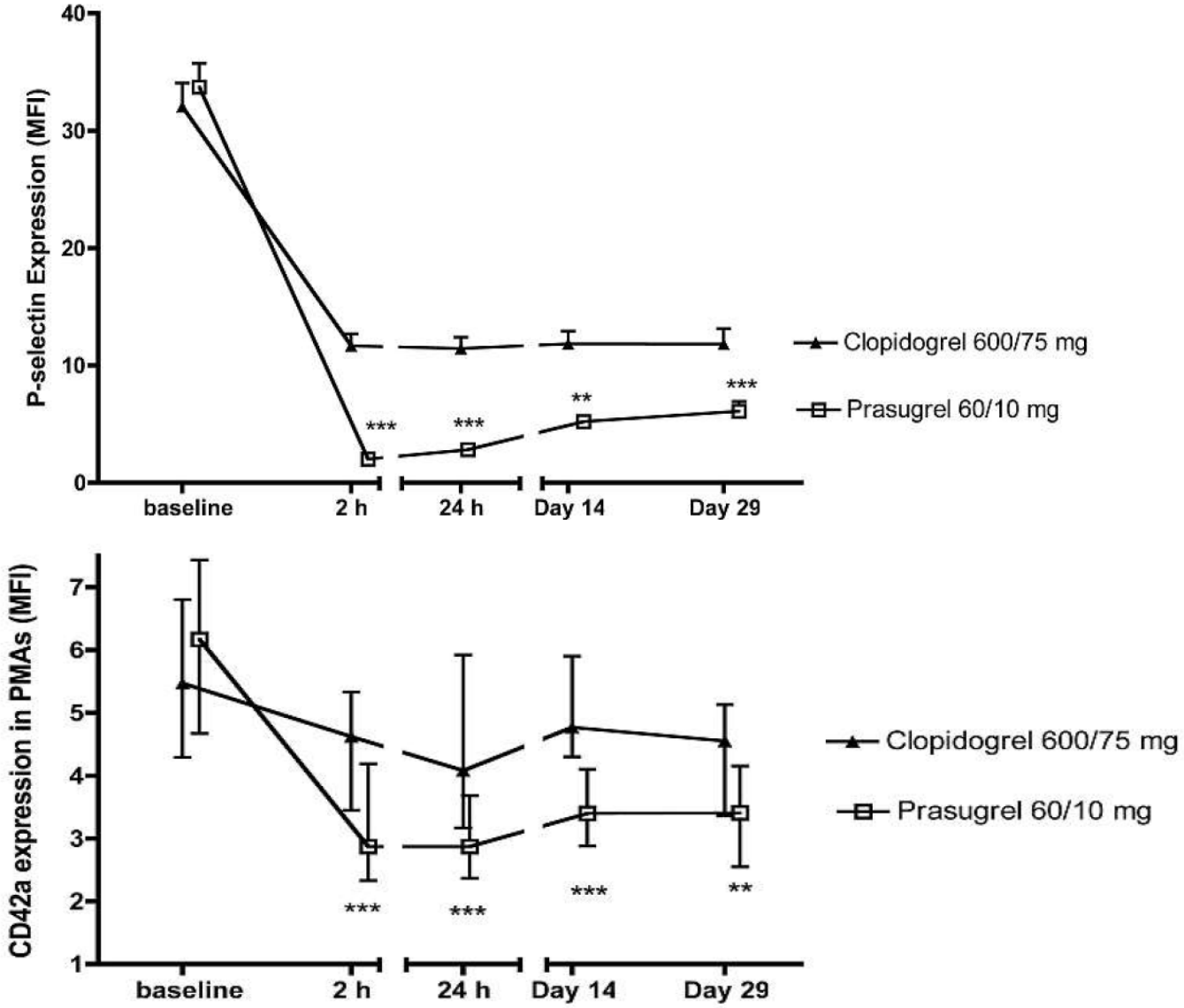
Symptomatic CAD on Aspirin: 5-week Clopidogrel (n = 77) vs. Placebo (n = 26)



Heitzer T et al. *ATVB* 2006;26:1648-52.

Prasugrel vs. Clopidogrel on Platelet Activation

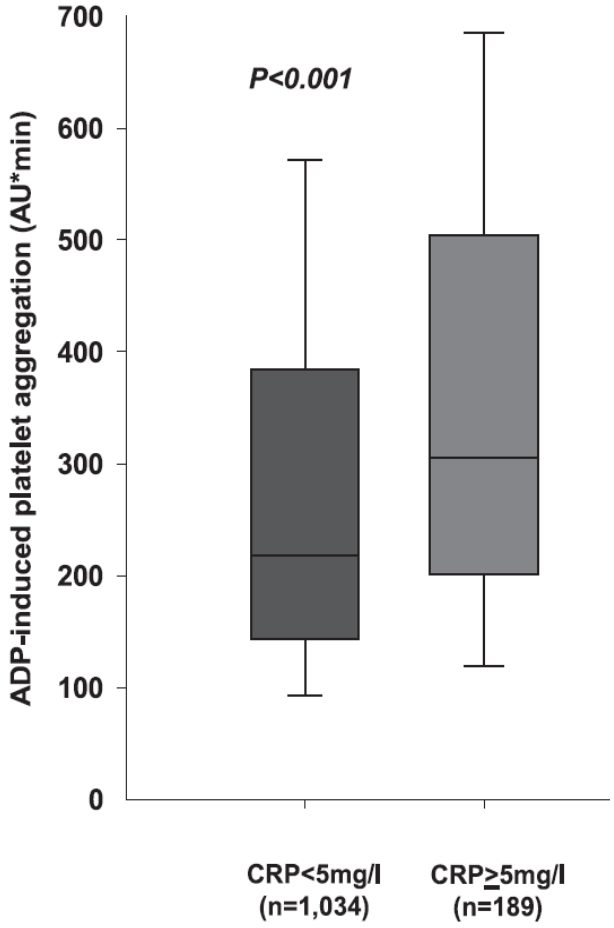
Stable CAD on Aspirin: 4-week Prasugrel (n = 55) vs. Clopidogrel (n = 55)

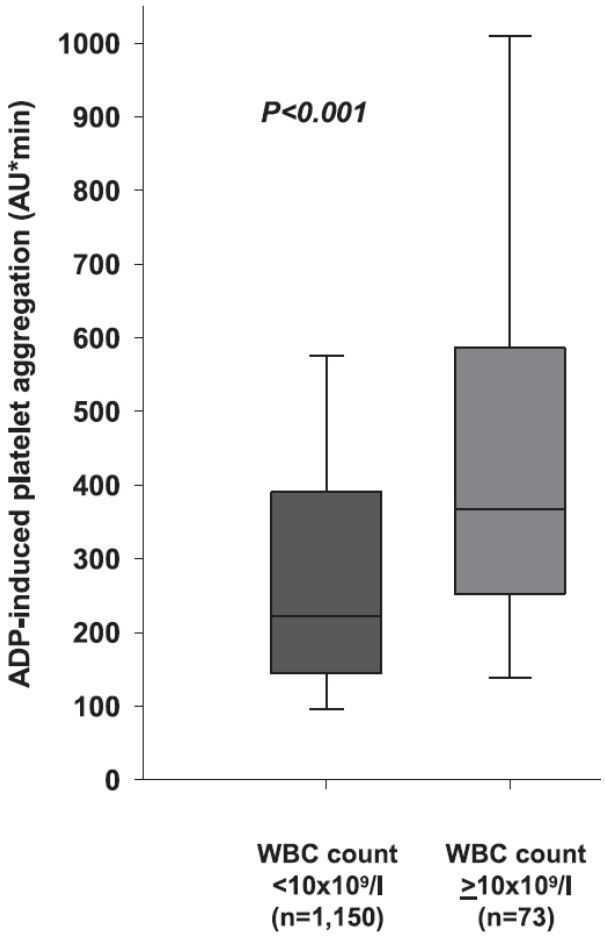


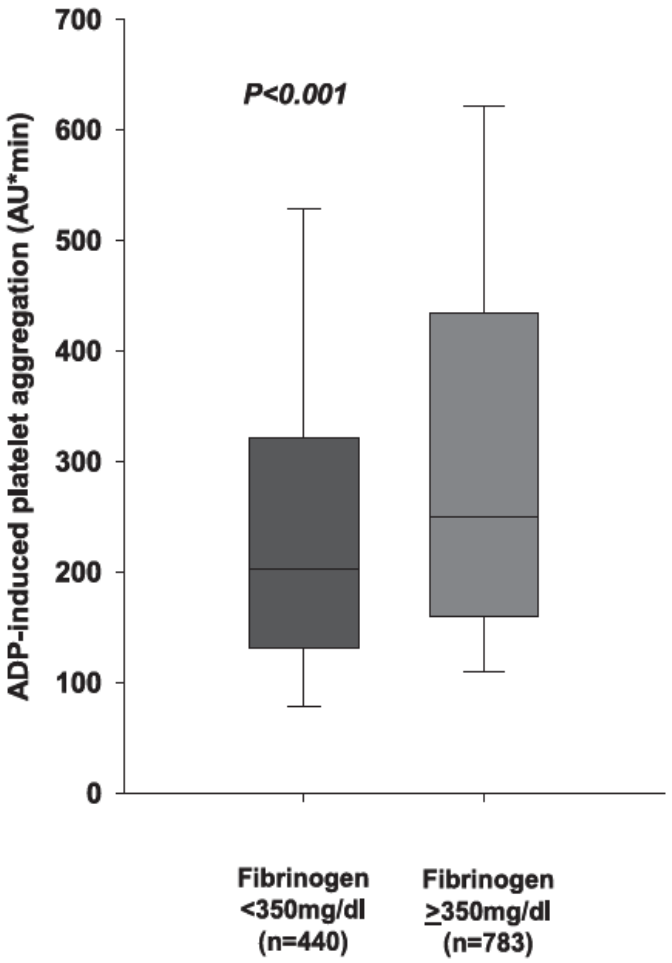
Braun OO et al. *Thromb Hemost* 2008;100:626-33.

Relationship Between Platelet Function and Inflammation/Coagulation in CAD Patients

Stable CAD on Chronic DAPT (n = 1,223)



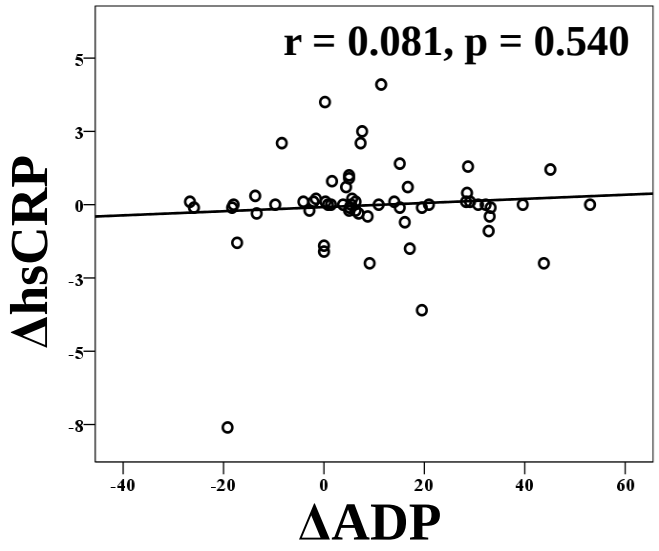


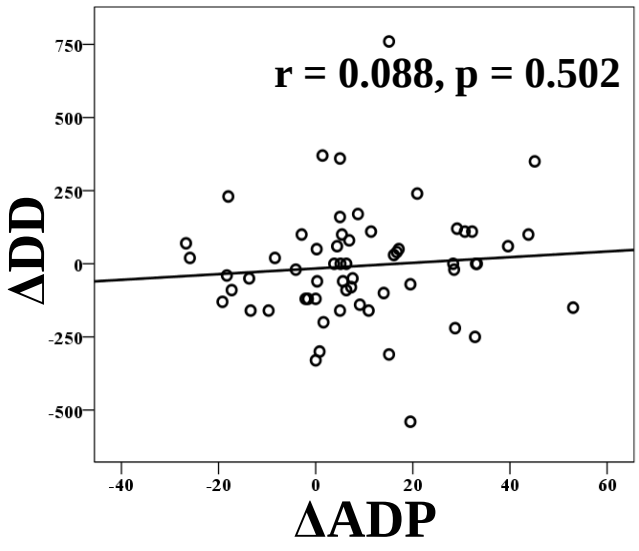


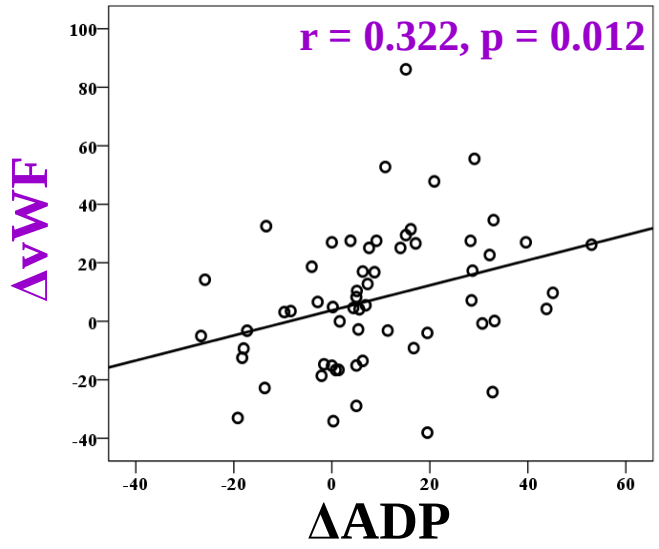
Bernlochner I et al. *Thromb Hemost* 2010;104:626-33.

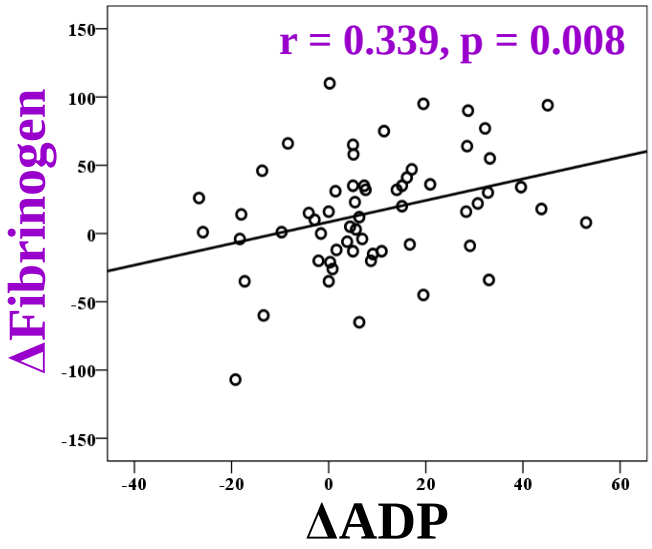
Relationship Between Platelet Function and Thrombogenic Markers in AF Patients on ASA

30-day Clopidogrel (n = 20) vs. Cilostazol (n = 20) vs. PUFA (n = 20)









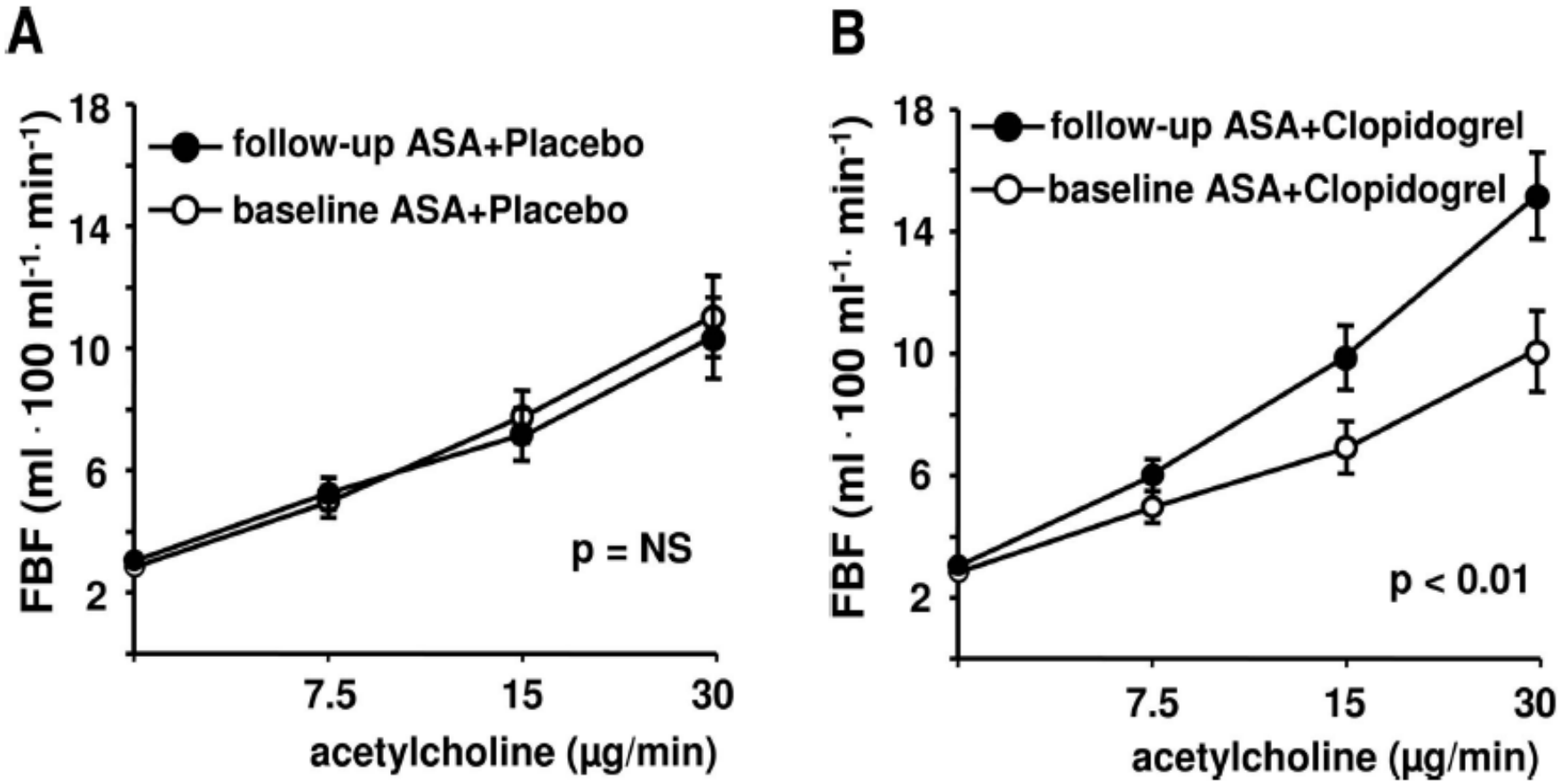
Park Y, Jeong YH, et al. *Unpublished*.

2. Platelet Function:

Endothelial Dysfunction and Atherosclerosis

Clopidogrel on Endothelial NO Bioavailability

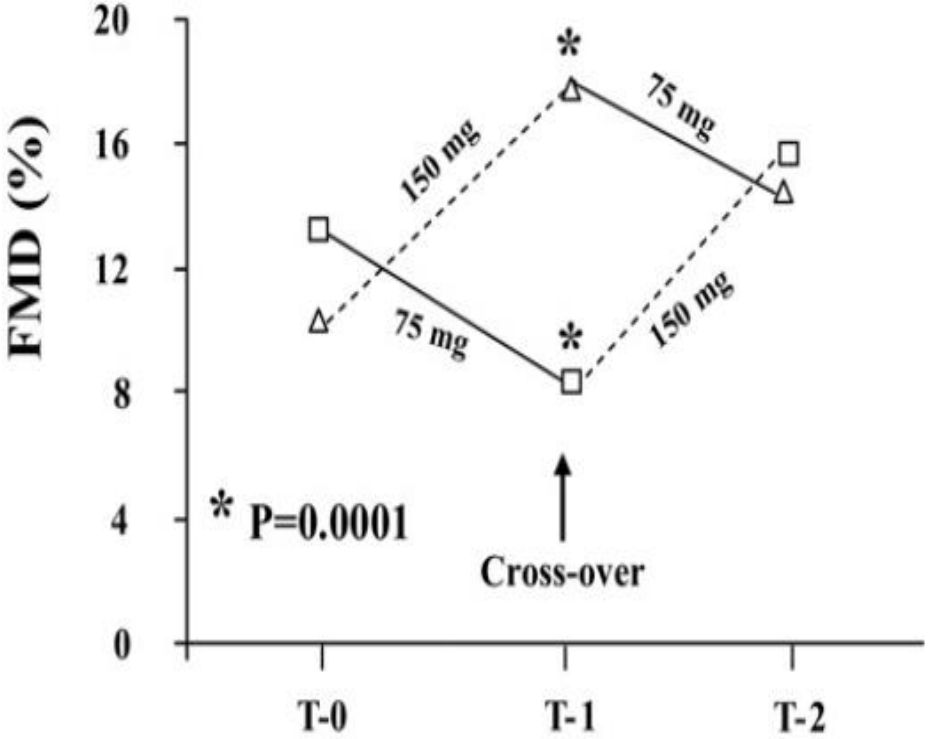
Symptomatic CAD on Aspirin: 5-week Clopidogrel (n = 77) vs. Placebo (n = 26)

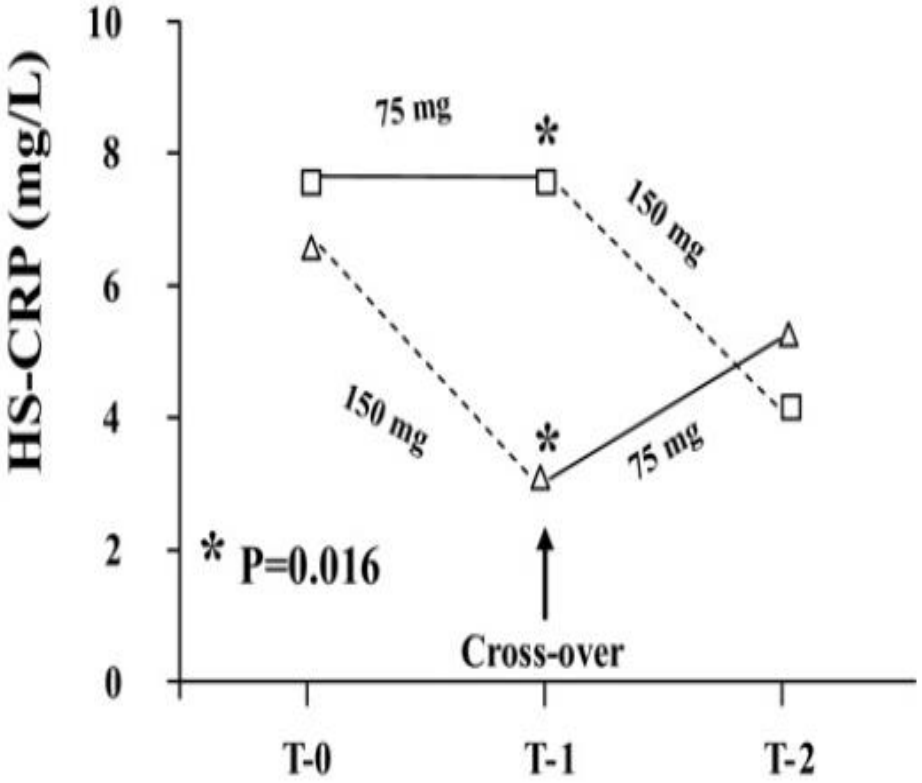


Heitzer T et al. *ATVB* 2006;26:1648-52.

HD Clopidogrel on Endothelial NO Bioavailability

PCI-treated Patients: 75 mg vs. 150 mg Clopidogrel (n = 50, 30-day cross-over)





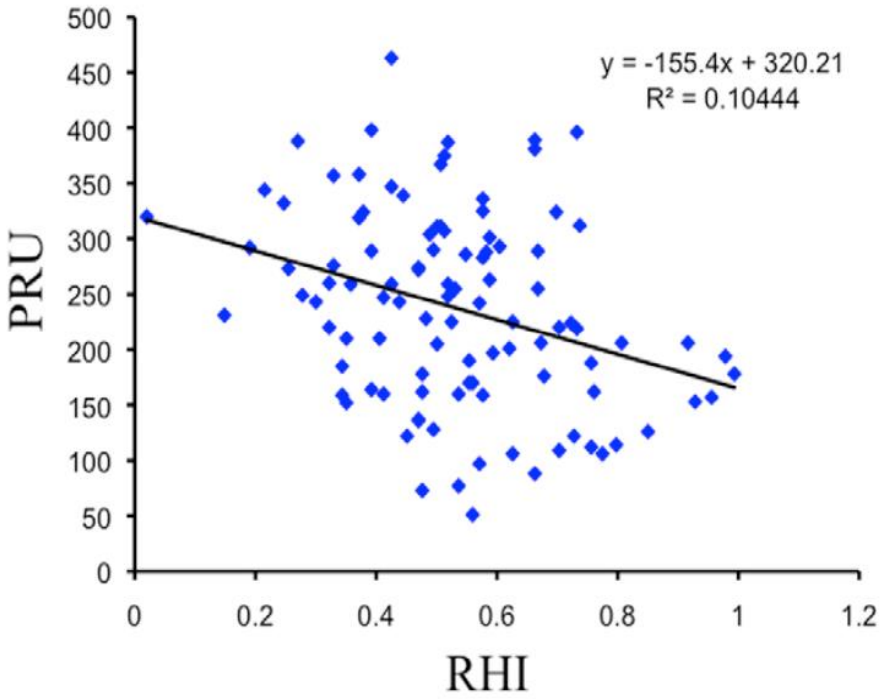
ARMYDA-150 mg. Patti G et al. *JACC* 2011;57:771-8.

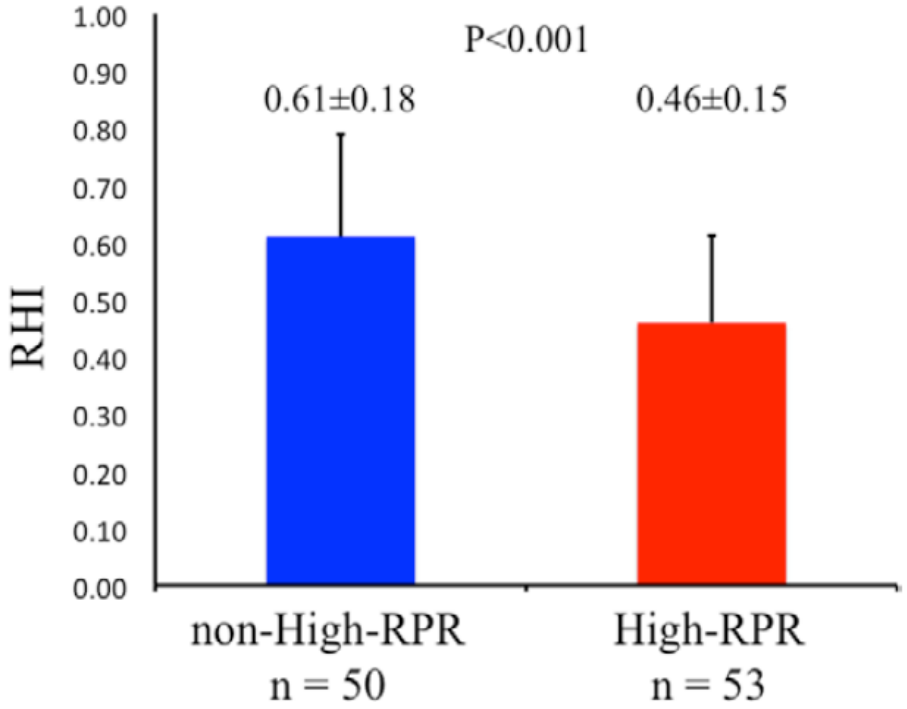
Relationship Btw Peripheral ED and HPR

PCI-treated Patients on Chronic DAPT (n = 103): HPR ≥ 230 PRU

RHI (Reactive Hyperemia Index):
Peripheral Endothelial Dysfunction

RHI=Ln{[RH-PAT ratio]*[0.226*Ln(baseline) – 0.2]}

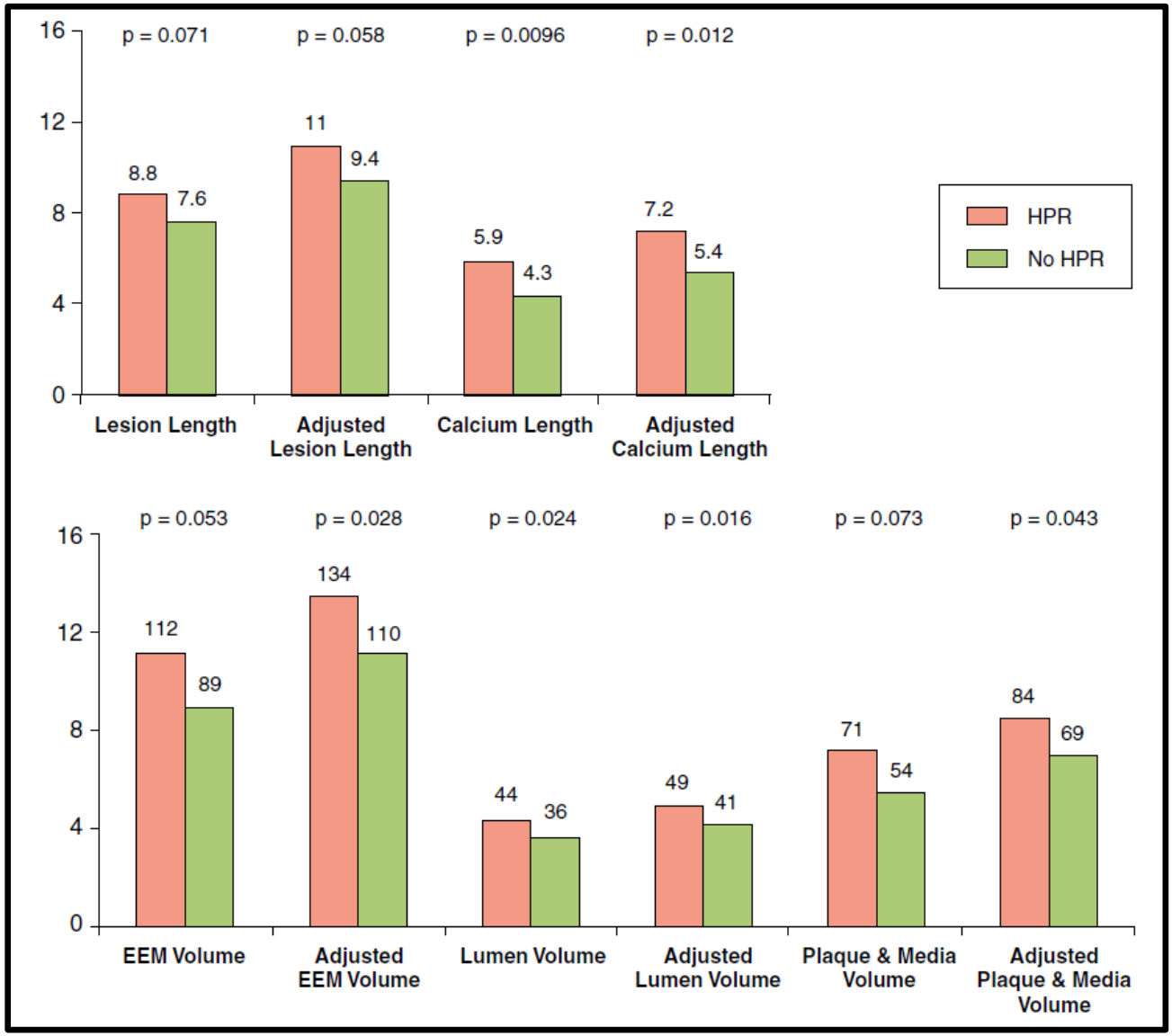




Fujisue K et al. *Circ CV Interv* 2013;6:452-9.

Relationship Between Atheroma Burden and HPR

IVUS imaging in PCI-treated Patients (n = 335): PRU > 230 (32.5%)



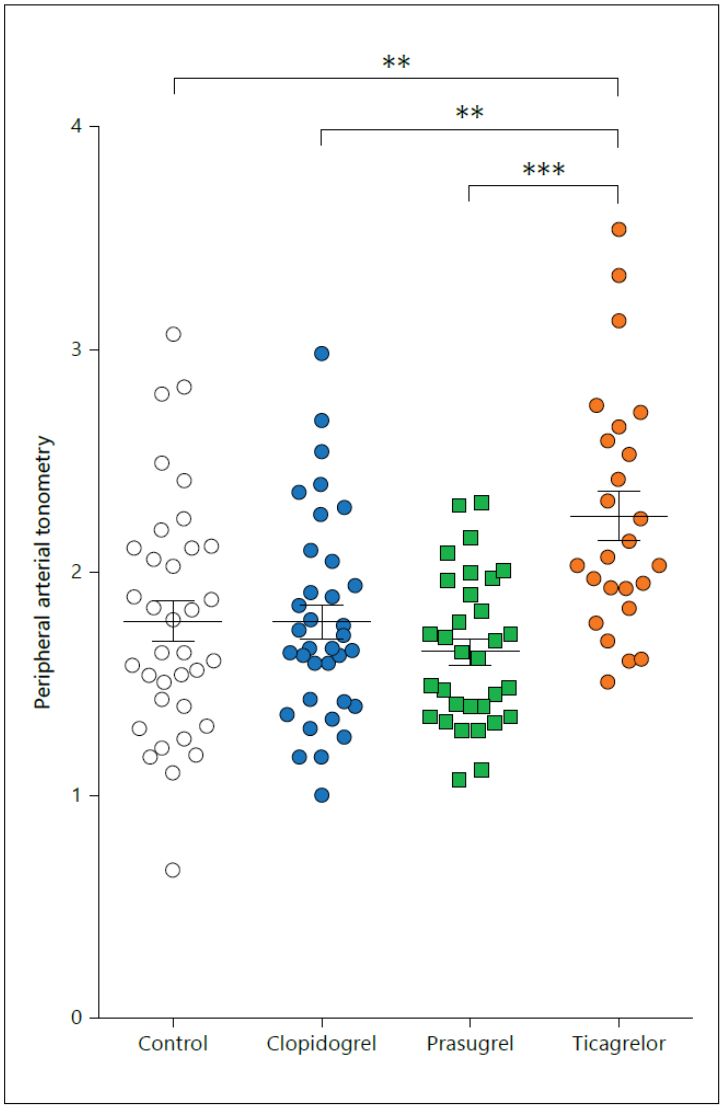
*** Adjustments for age, sex, DM, and CRF**

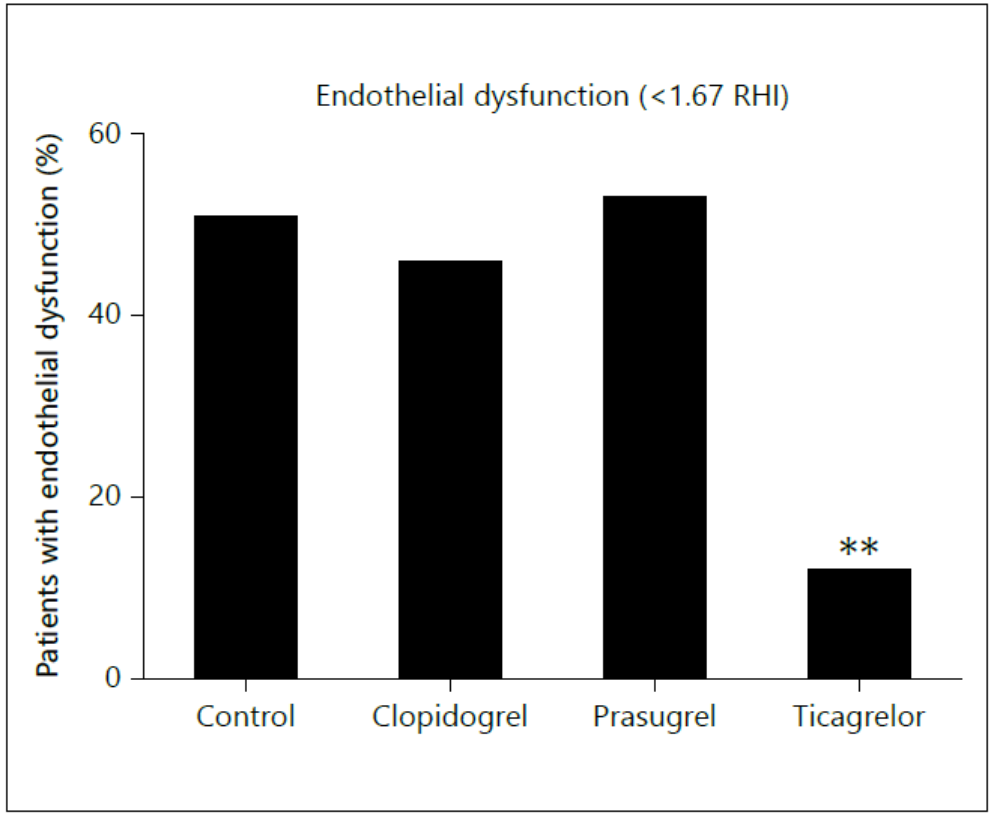
Chirumamilla AP, et al. *JACC CV Imaging* 2012;5:540-9.

Impact of APT on Peripheral ED in ACS Patients

ACS Pts on Chronic Aspirin 75 mg/d:

Control vs. CLPD 75 mg/d vs. PRAS 10 mg/d vs. TICA 90 mg bid (3-12 Mos.)

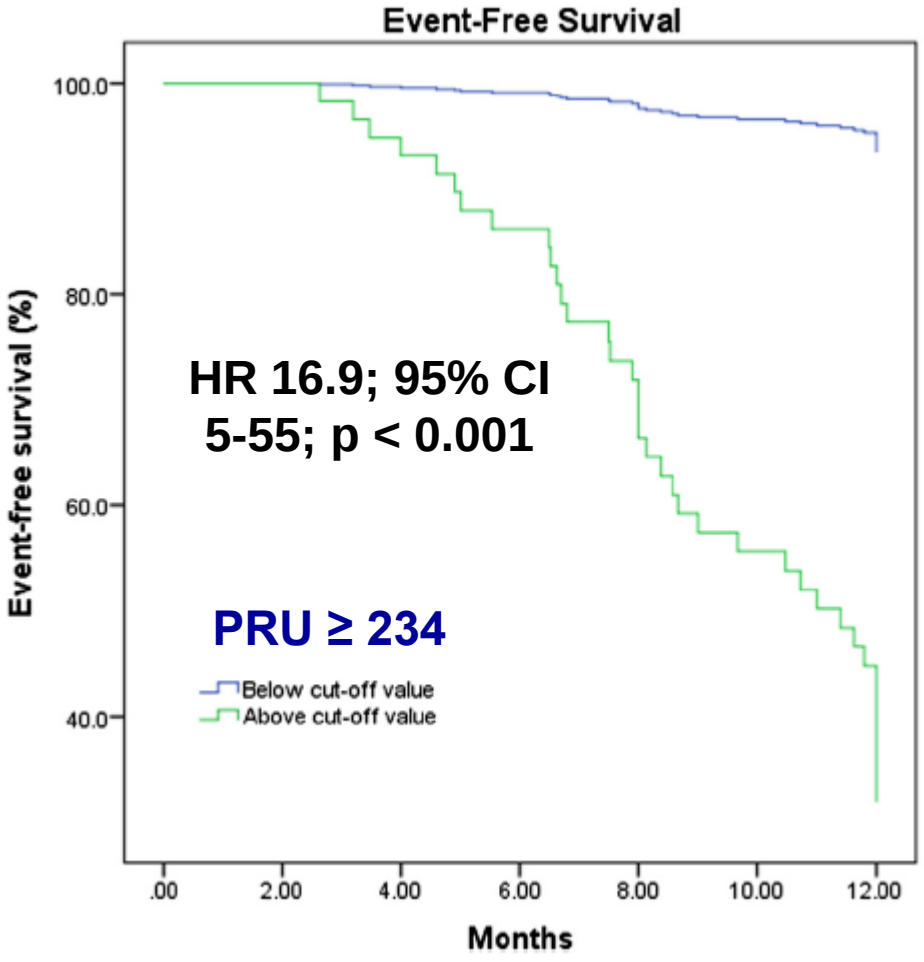




Torngren K, et al. *Cardiology* 2013;124:252-8.

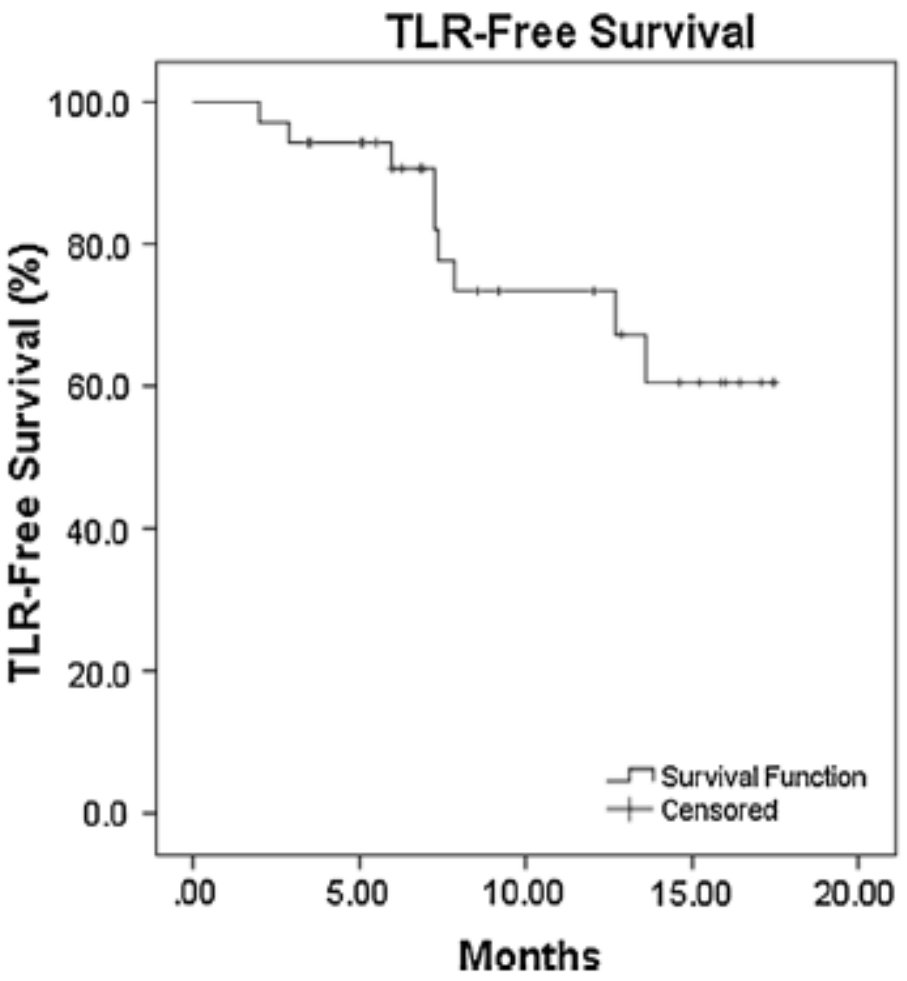
Impact of Ticagrelor on PEP-treated PAD

Clopidogrel-treated Pts (n = 100)



PRECLOP. Spiliopoulos S et al. *JACC* 2013;61:2428-34.

Ticagrelor-treated HPR Pts (n = 37)

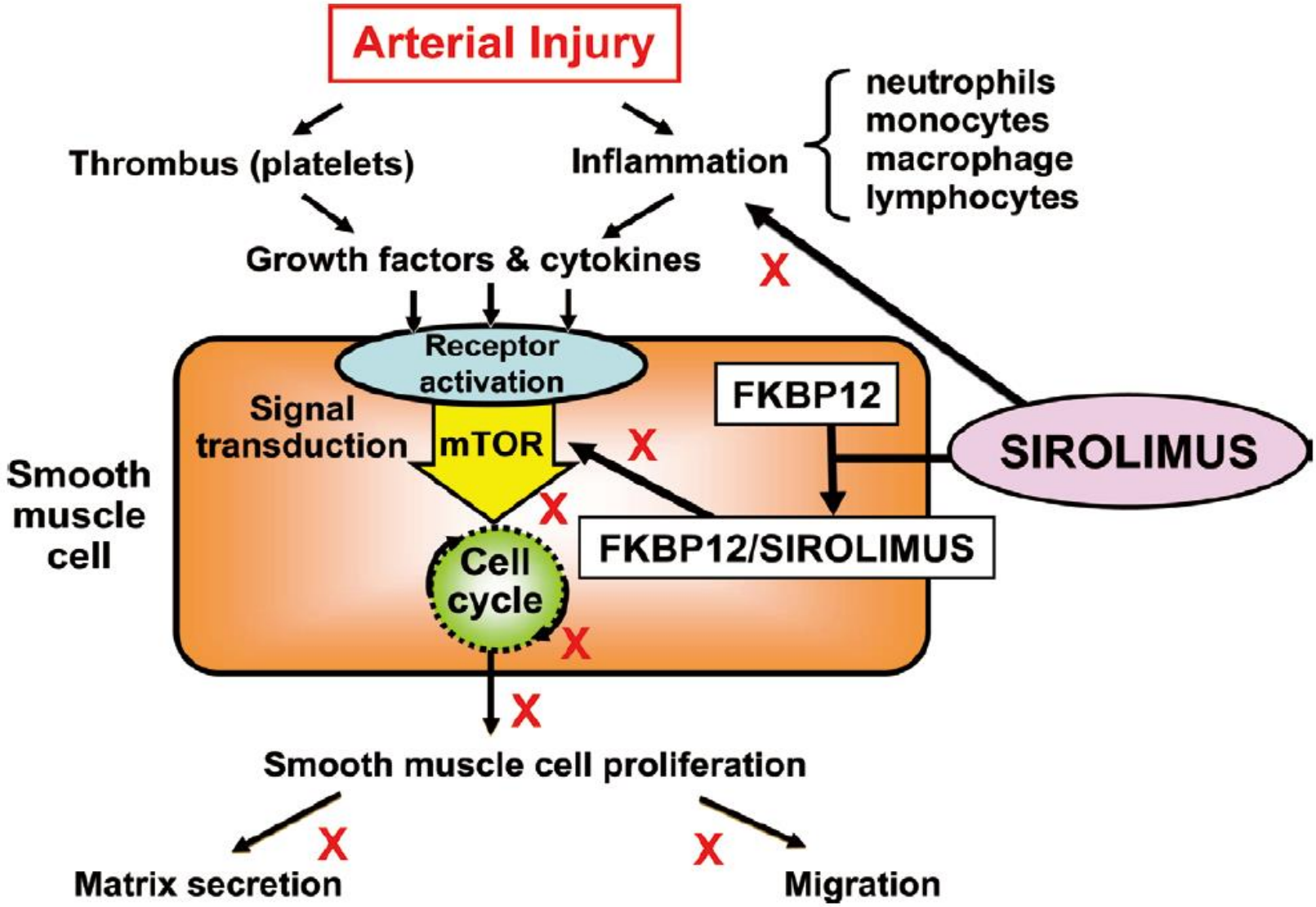


Spiliopoulos S et al. *CV Interv Radiol* 2014.

3. Platelet Function:

Post-stent Neointimal Hyperplasia

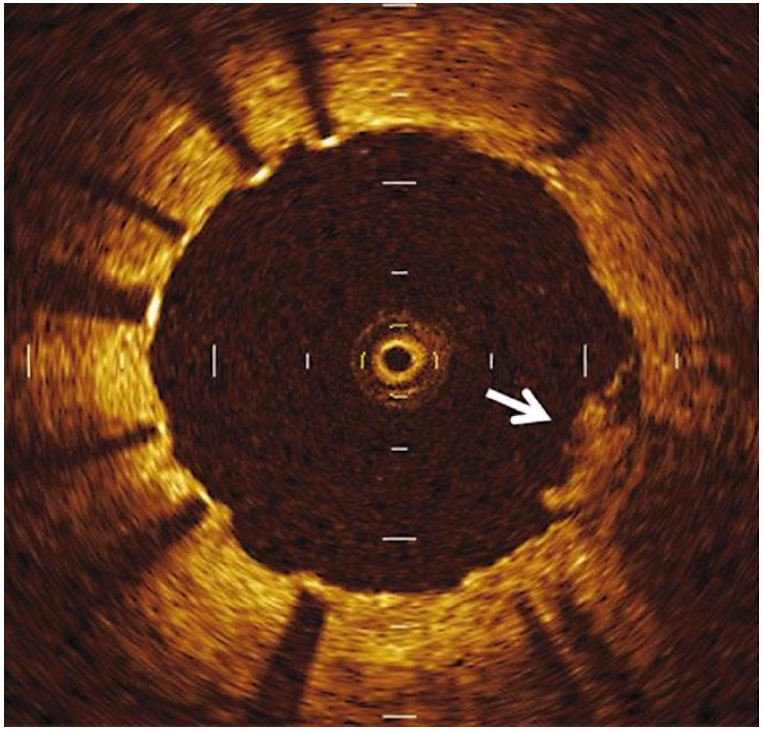
Leukocyte Migration Interacting With PLT-Fibrinogen Clot After Stenting

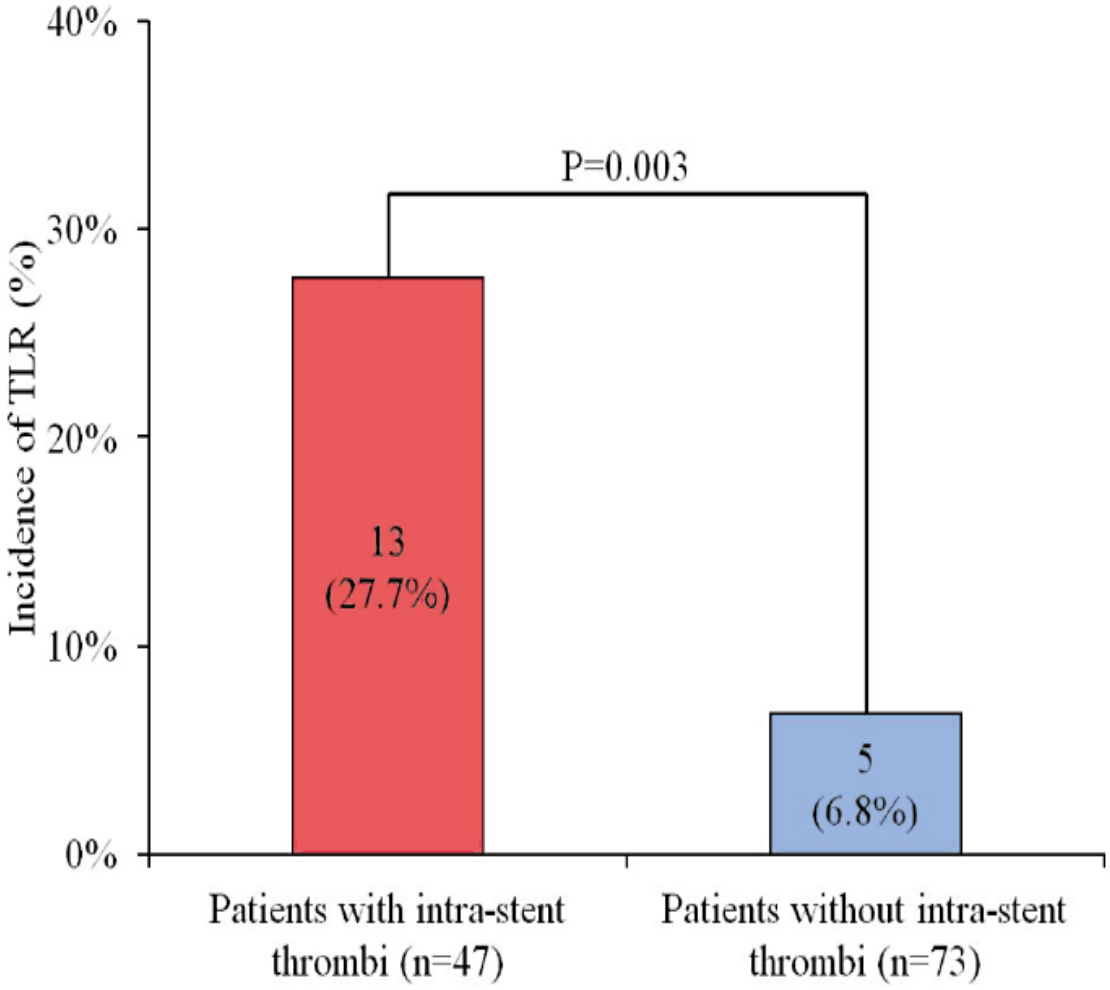


Inoue T et al. *JACC CV Interv* 2011;4:1057-66.

CYP2C19 SNP on Intra-stent Thrombi and TLR

Follow-up OCT imaging in DES-treated Patients on DAPT (n = 125)

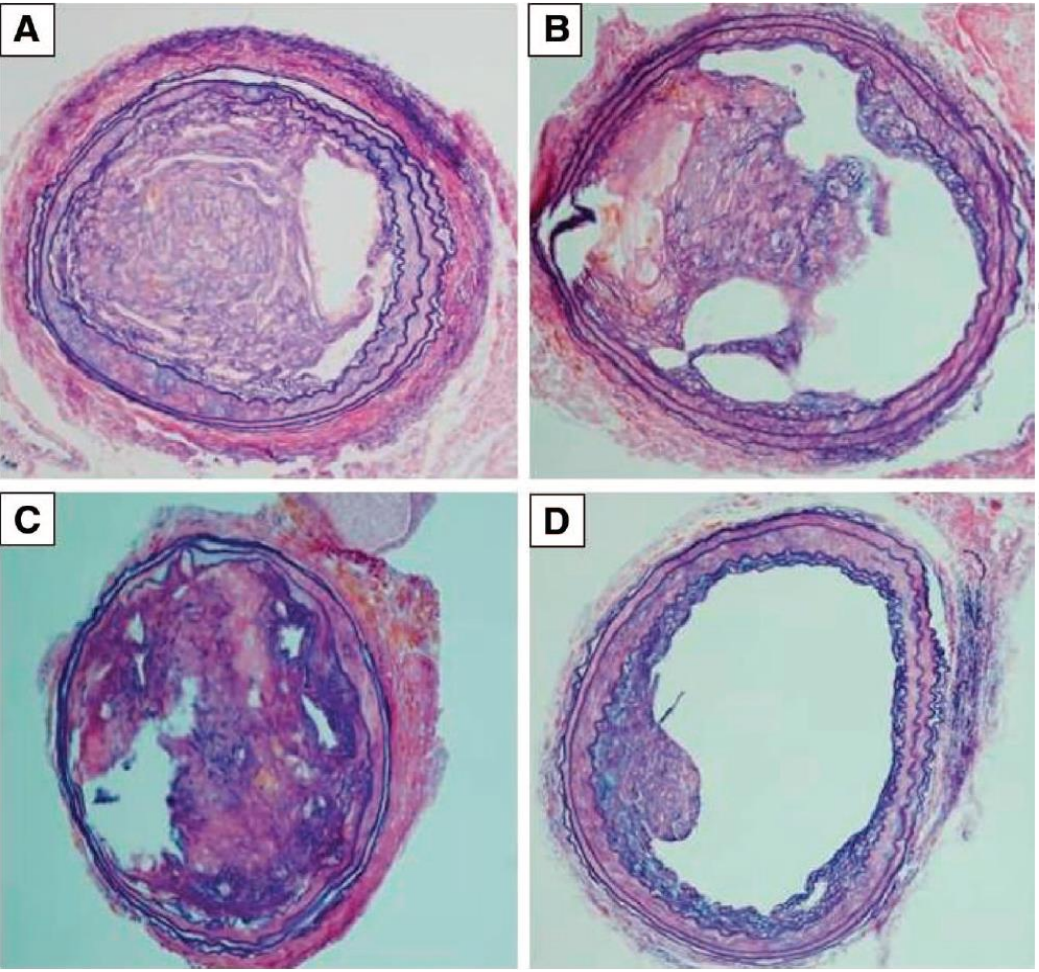


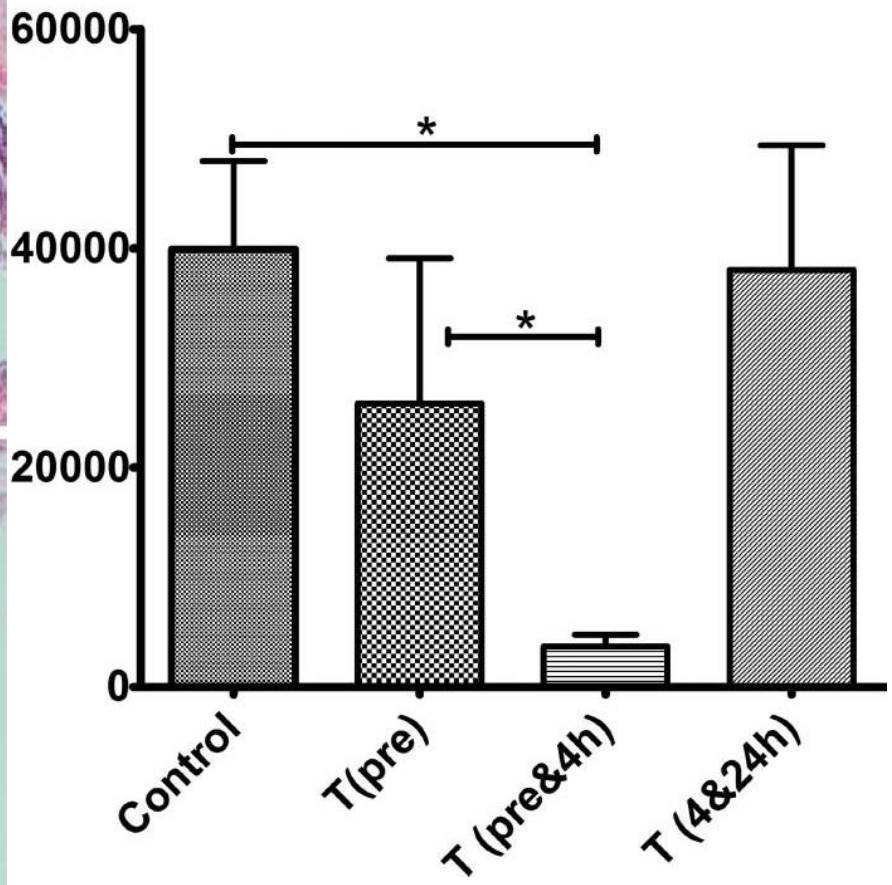


Nishio R et al. *Circ J* 2012;76:2348-55.

Sustained $P2Y_{12}$ Inhibition by Ticagrelor to Prevent Subsequent Neointima

3-week Neointima formation in $FeCl_3$-injured carotid artery (C57BL/6 mice)





Patil SB, et al. *ATVB* 2010;30:2385-91.

4. Platelet Function:

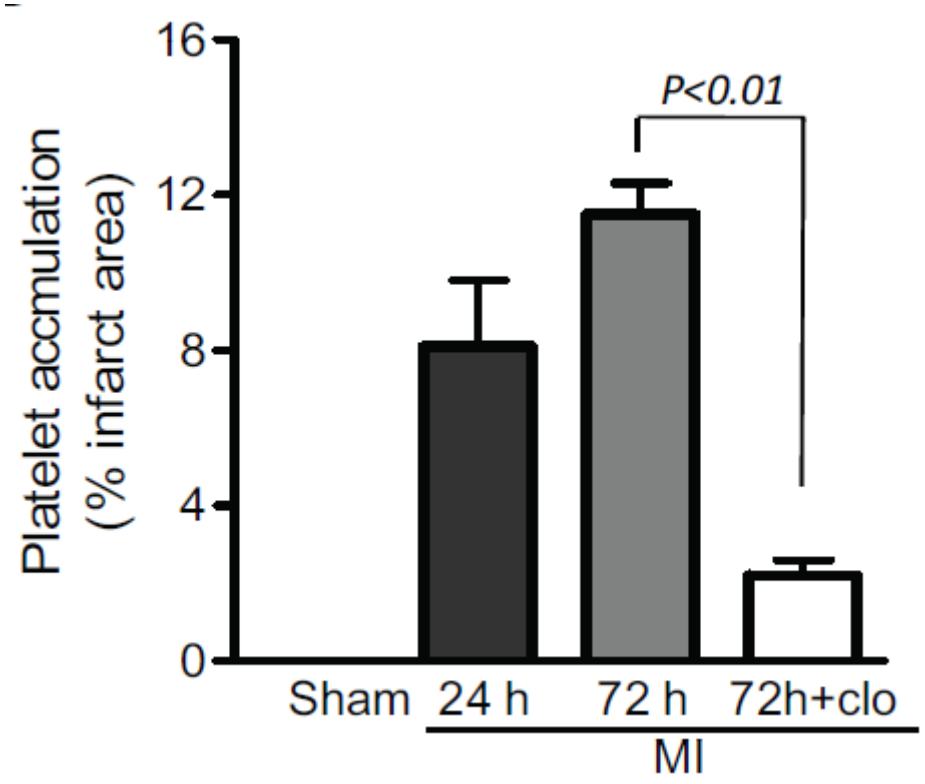
Post-MI Left Ventricular Remodeling

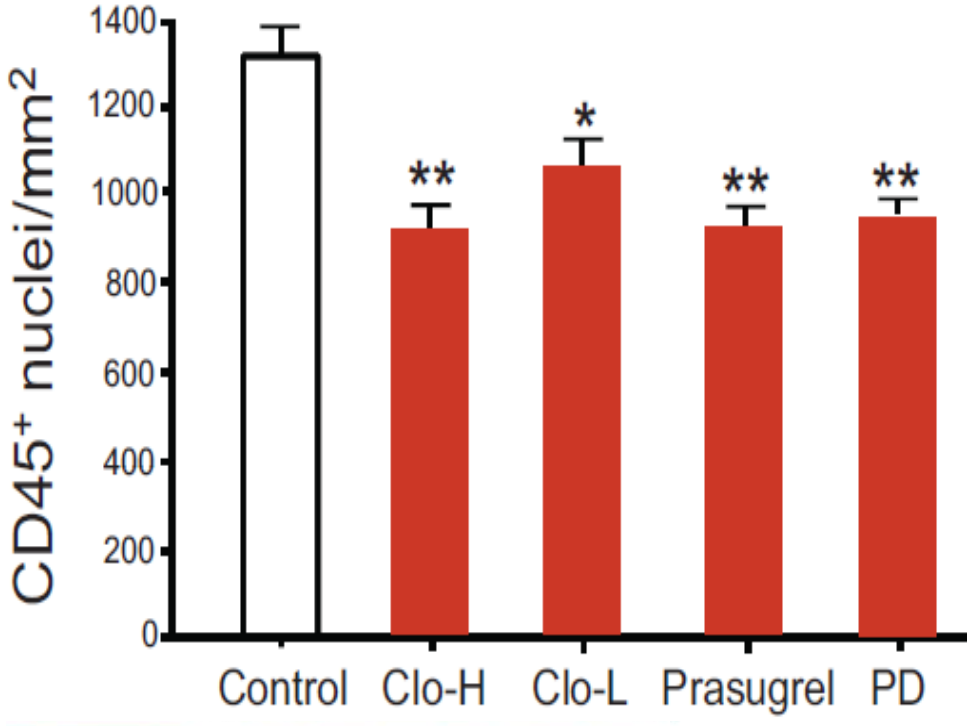
Role of Platelets in Mediating Inflammatory Responses for Post-MI LV Remodeling

Platelet-Leukocyte Accumulation in Infarcted Myocardium (C57BL/6 mice)

Randomized treatment started 2 hrs after MI and lasted for 3 days

Low-dose clopidogrel (15/5/5 mg/kg) vs. High-dose clopidogrel (50/15/15 mg/kg) vs. Prasugrel (5/5/5 mg/kg) vs. PD (platelet depletion) by CD41 antibody



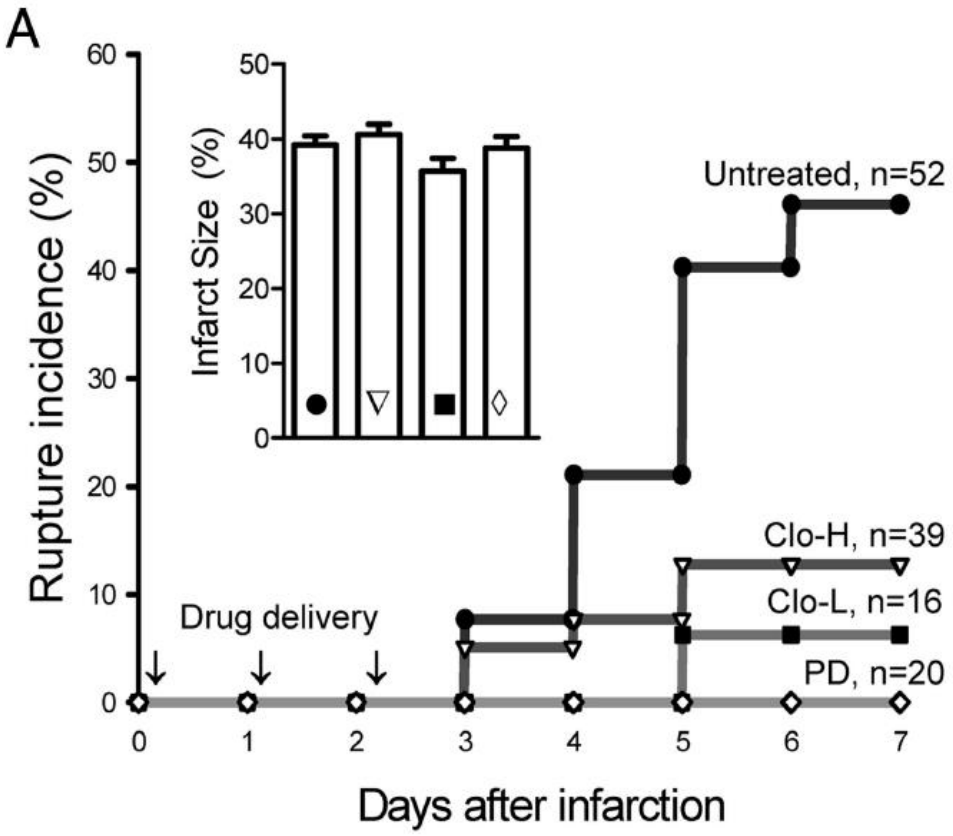


Liu Y, et al. *ATVB* 2011;31:834-41.

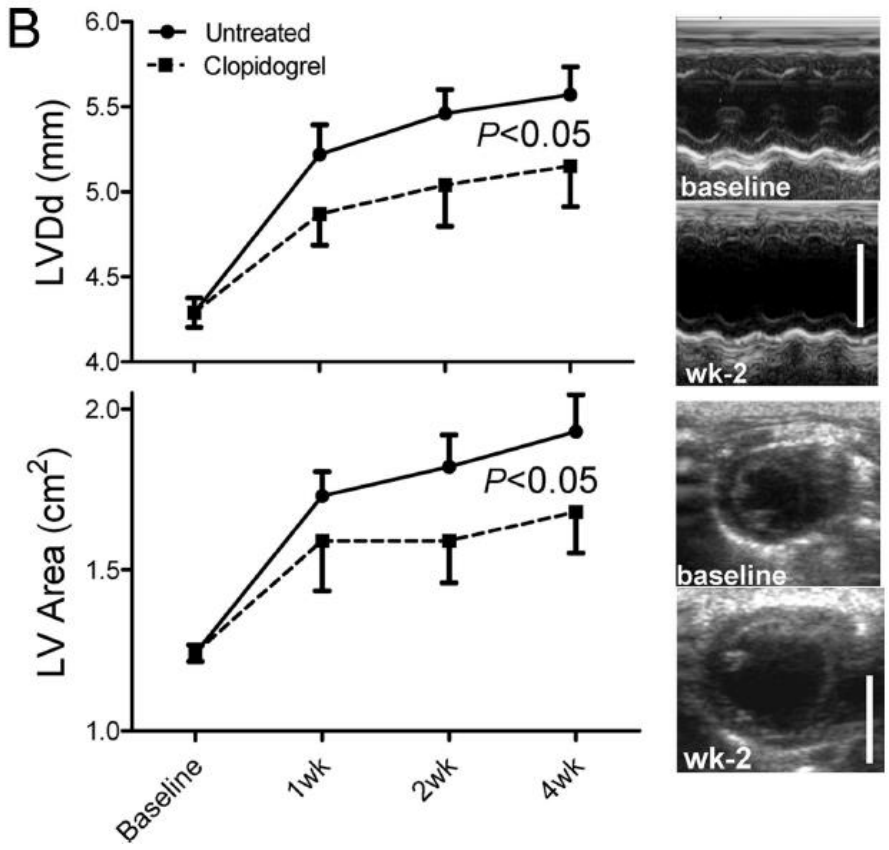
Role of Platelets in Mediating Inflammatory Responses for Post-MI LV Remodeling

Platelet-Leukocyte Accumulation in Infarcted Myocardium (C57BL/6 mice)

Acute phase: LV rupture



Chronic phase: LV remodeling



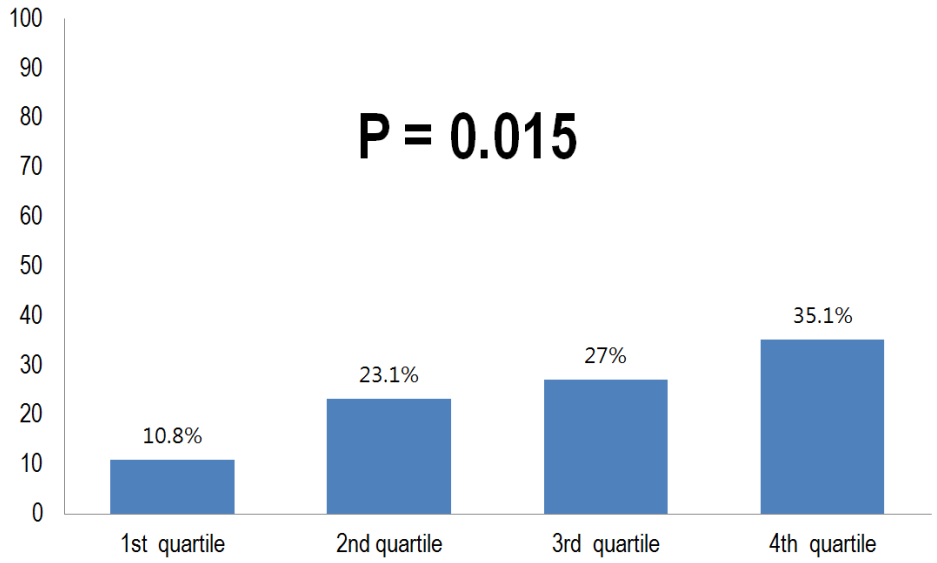
Liu Y, et al. *ATVB* 2011;31:834-41.

Novel Role of Platelet Reactivity and Inflammation in LV Remodeling Following STEMI

REMODELING Study: PPCI-treated STEMI Patients on ASP+CLPD (n = 150)

LV Remodeling: a relative *>20% increase in LV EDV between baseline and 1-month F/U*

LVR by PRU quartile



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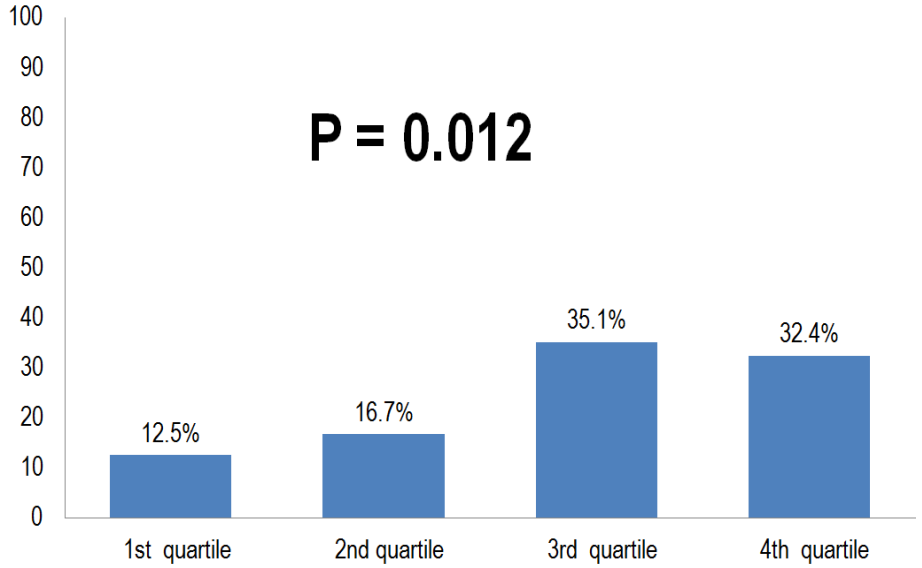
PRAS

LVR by hs-CRP quartile

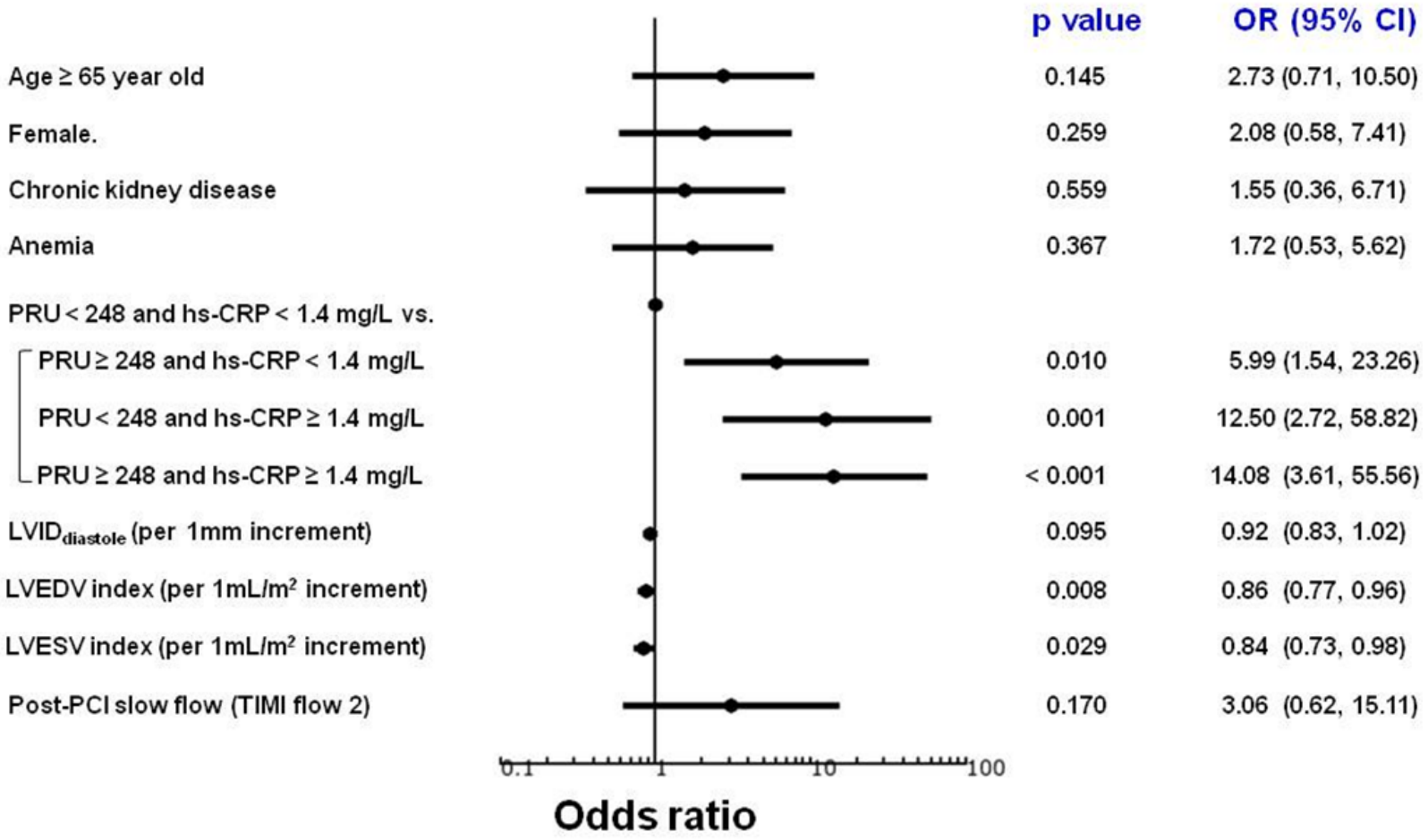


Park Y, Jeong YH, et al. *Unpublished*.

Cross-talk btw Platelet Reactivity and Inflammation in LV Remodeling Following STEMI

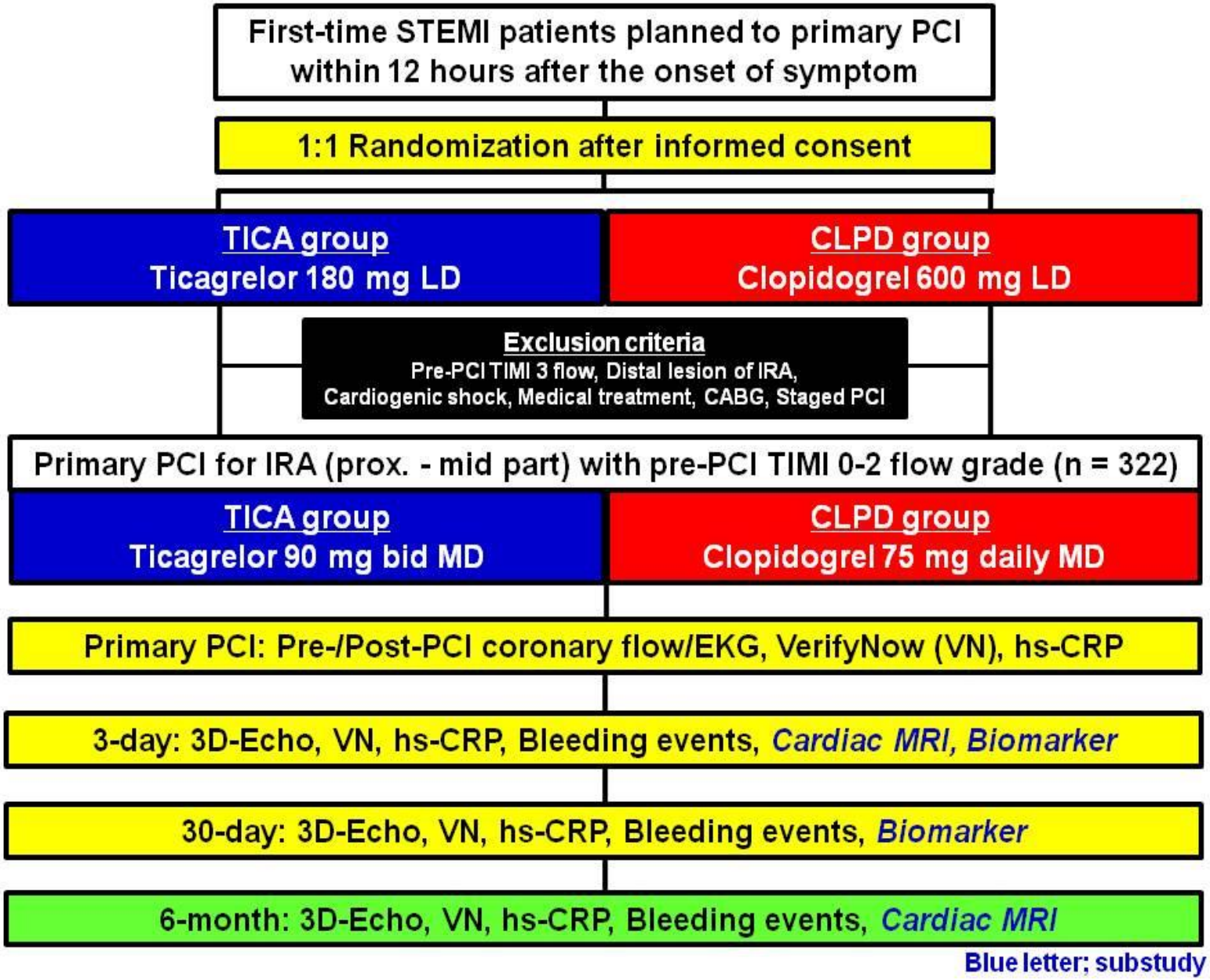
REMODELING Study: PPCI-treated STEMI Patients on DAPT (n = 150)

Predictors of LV Remodeling



Park Y, Jeong YH, et al. *Unpublished*.

The HEALING-AMI Trial

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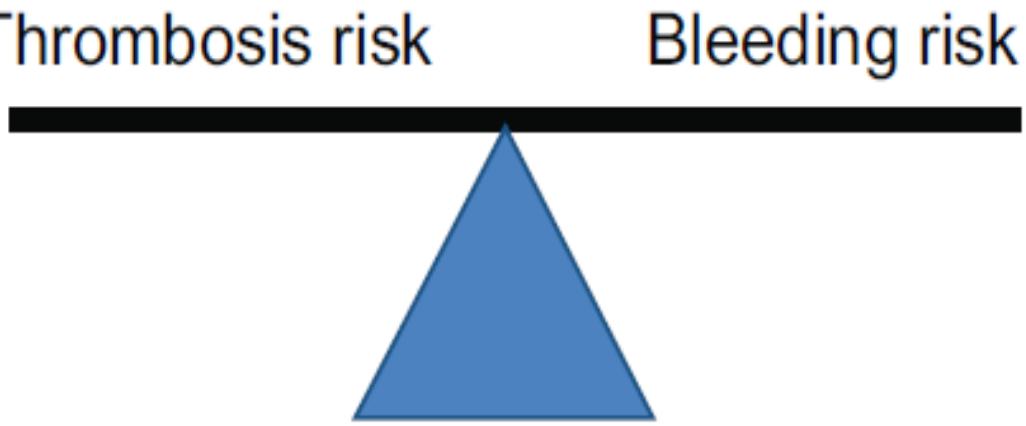
Risk-Benefit Balance in Antiplatelet Therapy

"Classic Concept"



"New Concept"