

# **Platelet Function Beyond Hemostasis**

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# Disclosures

## Research Grants/Support

*Otsuka*

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*Dong-A Pharmaceutical*

*Han-Mi Pharmaceutical*

## Honoraria/Consulting

*Otsuka*

*Sanofi-Aventis*

*Daiichi Sankyo Inc*

*Astrazeneca*

*Nanosphere*

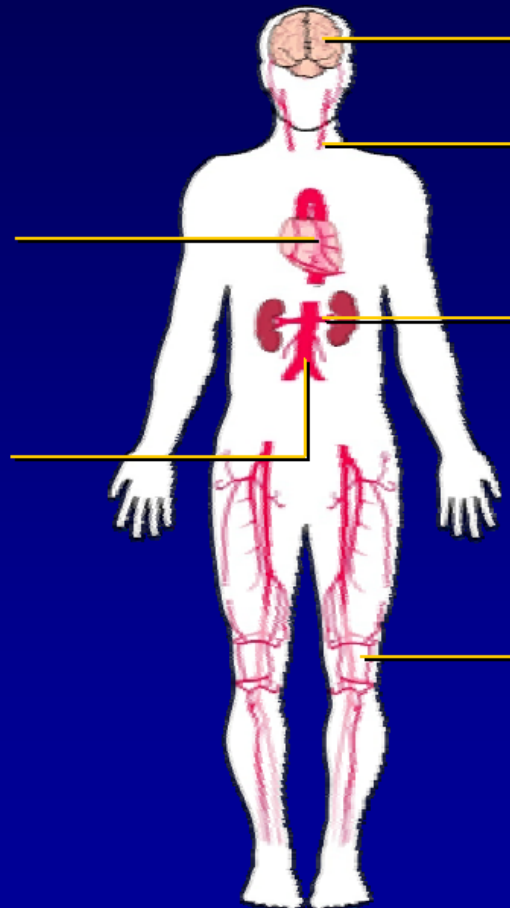
*Haemonetics*

*Han-Dok 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)

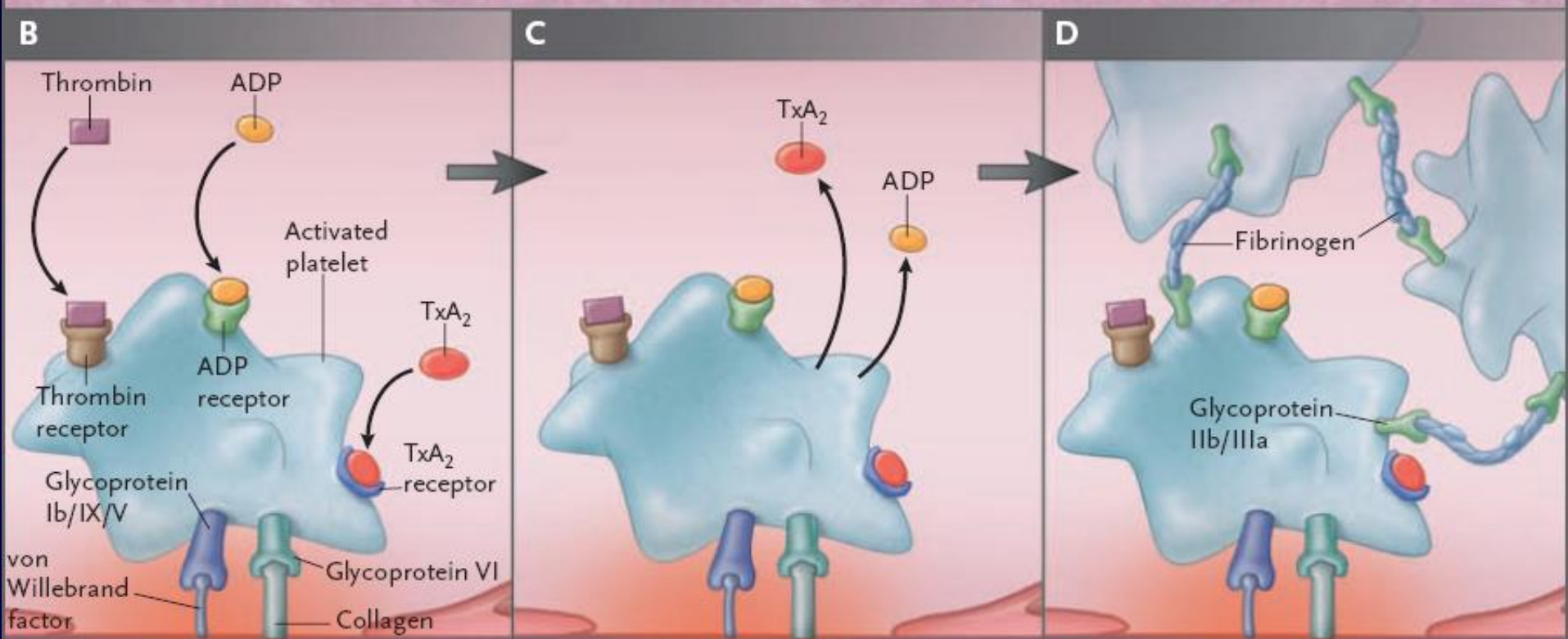
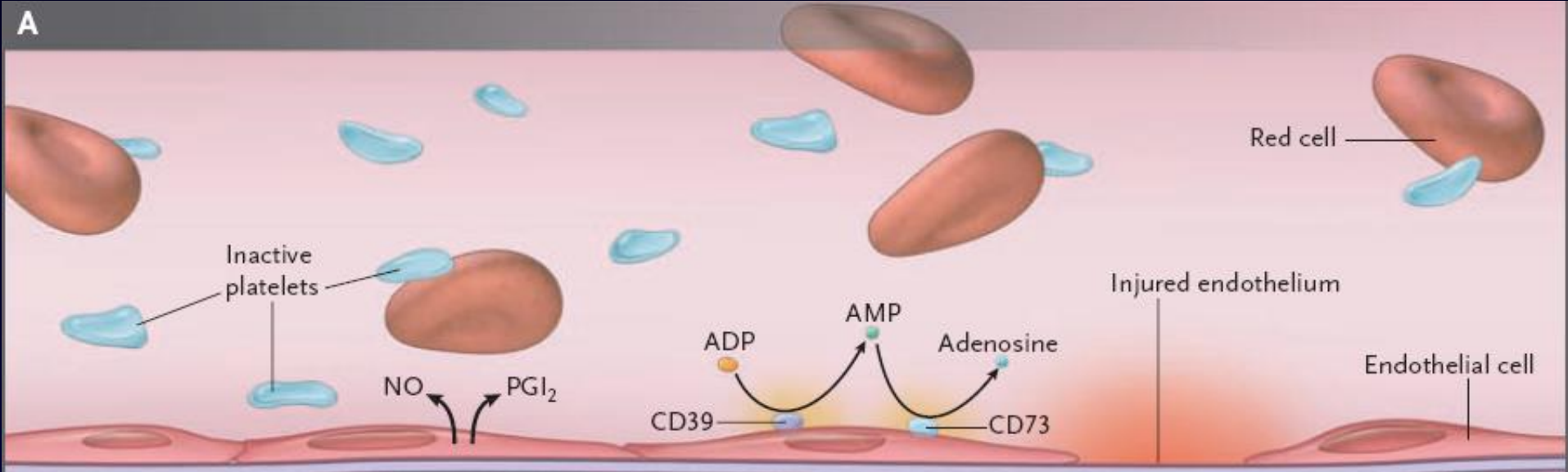


Stroke  
TIA  
Intracranial stenosis

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



# Platelet Function Beyond Hemostasis

## Diverse roles

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

## Underlying mechanisms

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

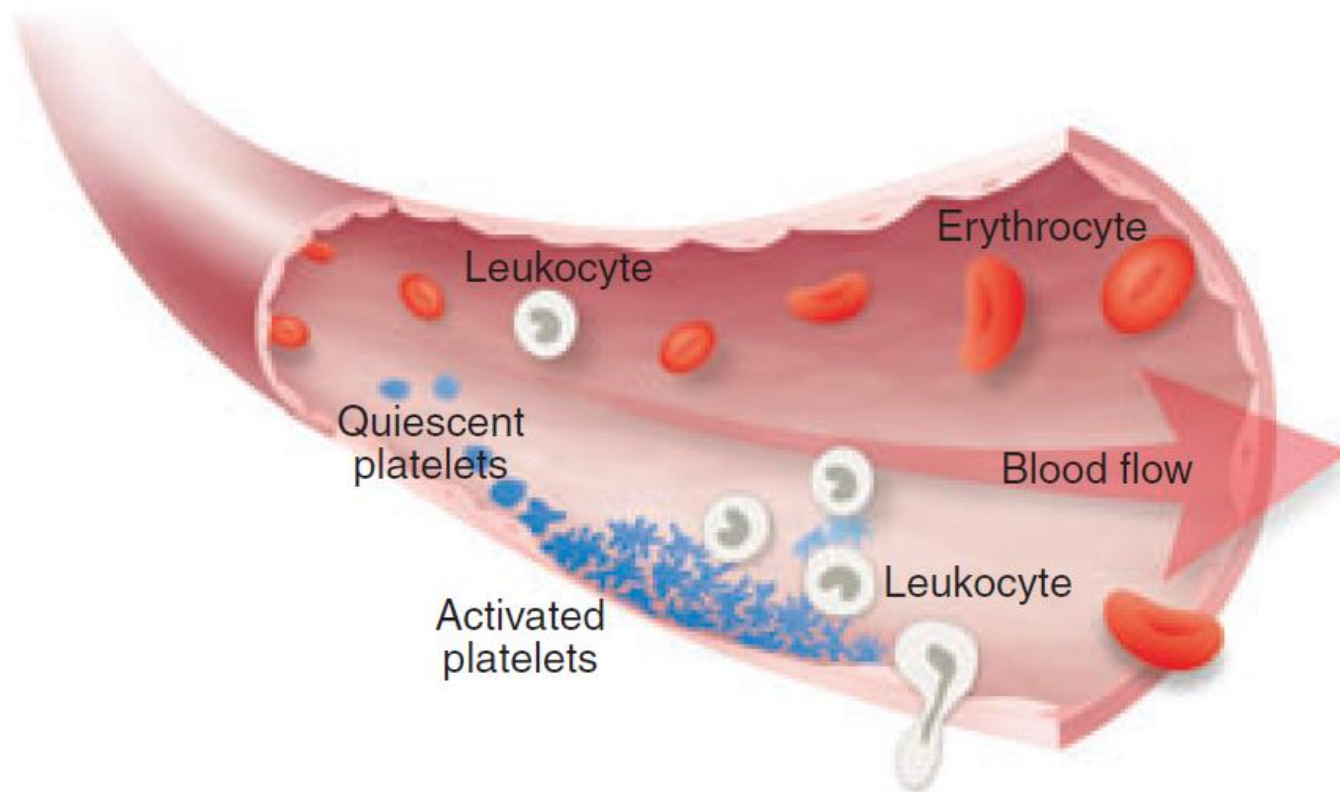
## ***Disease entities related with platelets***

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

# Platelet Granular and Secreted Molecules

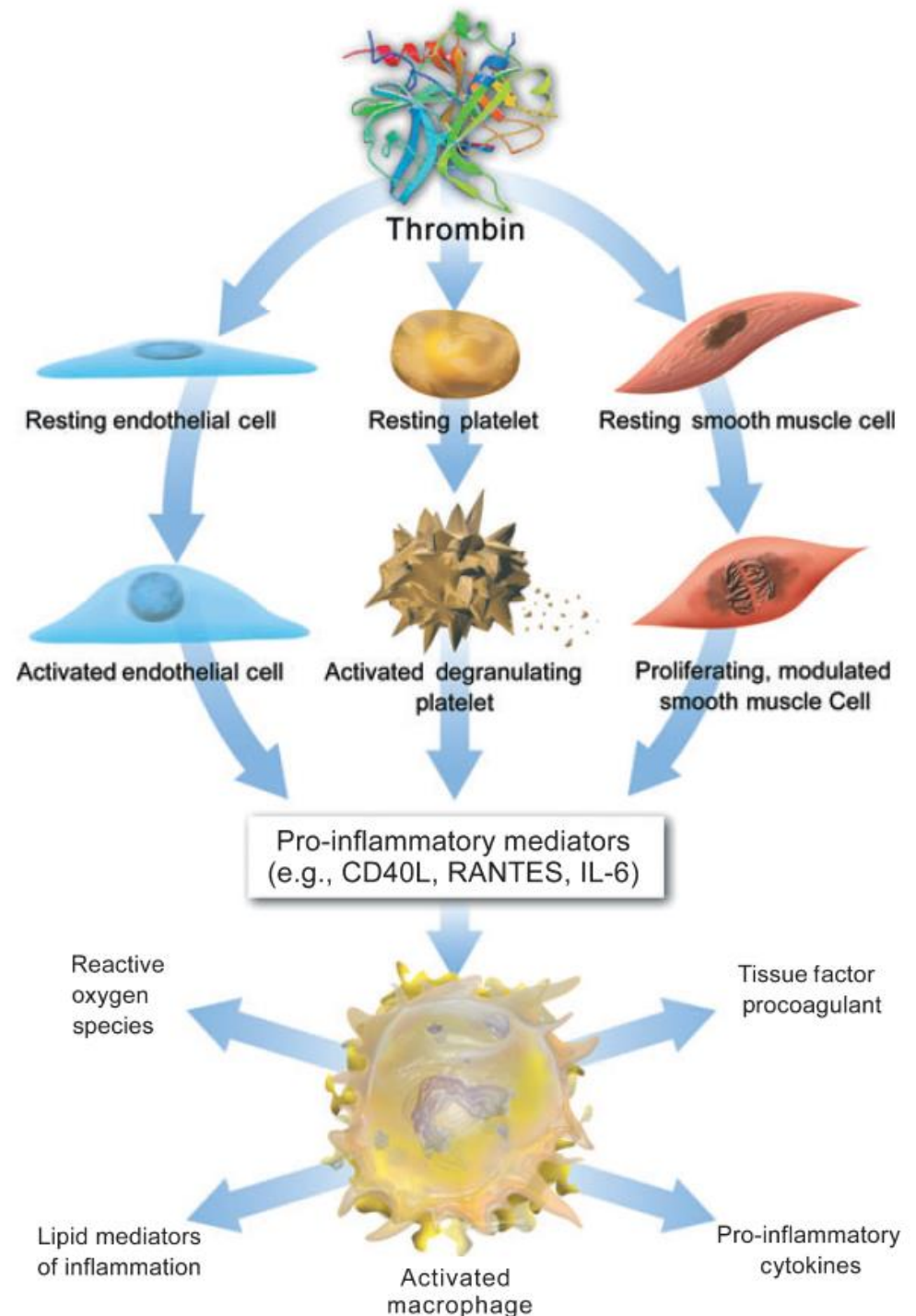
$\alpha$ -Granules	Dense bodies
Platelet-specific proteins	ADP
Platelet factor 4	ATP
$\beta$ -Thromboglobulin family*	Calcium
Multimerin	Serotonin
Adhesive glycoproteins	Pyrophosphate
Fibrinogen	GDP
von Willebrand factor	Magnesium
von Willebrand factor propeptide	Other secreted or released proteins
Fibronectin	Protease nexin I
Thrombospondin-1	Gas6
Vitronectin	Amyloid $\beta$ -protein precursor (protease nexin II)
Coagulation factors	Tissue factor pathway inhibitor
Factor V	Factor XIII
Protein S	$\alpha_1$ -Protease inhibitor
Factor XI	Complement I inhibitor
Mitogenic factors	High molecular weight kininogen
Platelet-derived growth factor	$\alpha_2$ -Macroglobulin
Transforming growth factor- $\beta$	Vascular permeability factor
Endothelial cell growth factor	Interleukin-1 $\beta$
Epidermal growth factor	Histidine-rich glycoprotein
Insulin-like growth factor I	Chemokines
Angiogenic factors	MIP-1 $\alpha$ (CCL3)
Vascular endothelial growth factor	RANTES (CCL5)
Platelet factor 4 (inhibitor)	MCP-3 (CCL7)
Fibrinolytic inhibitors	Gro- $\alpha$ (CXCL1)
$\alpha_2$ -Plasmin inhibitor	Platelet factor 4 (CXCL4)
Plasminogen activator inhibitor-1	ENA-78 (CXCL5)
Albumin	NAP-2 (CXCL7)
Immunoglobulins	Interleukin-8 (CXCL8)
Granule membrane-specific proteins	TARC (CCL17)
P-selectin (CD62P)	
CD63 (LAMP-3)	
GMP 33	

# Endothelium-Platelet-Leukocyte Interaction



	<i>Initial capture</i>	<i>Released mediators</i>	<i>Firm adhesion</i>				
<i>Leukocyte</i>	<u>PSGL-1</u>		<u>(Mac-1)</u> <u><math>\alpha</math>M<math>\beta</math>2</u>	$\alpha$ M $\beta$ 2 or $\alpha$ V $\beta$ 3	CD36 (GP IV) $\alpha$ L $\beta$ 2	$\alpha$ M $\beta$ 2	<u>CD40</u>
<i>Blood</i>		RANTES/CCL5, PAF, ENA-78, Gro $\alpha$ , IL-1 $\beta$		Fibrinogen (fibrin) thrombospondin			
<i>platelet</i>	<u>P-selectin</u>		<u>GP I<math>\alpha</math></u> $\alpha$ IIb $\beta$ 3		CD36 (GP IV) ICAM-2 JAM3		<u>CD40L</u>

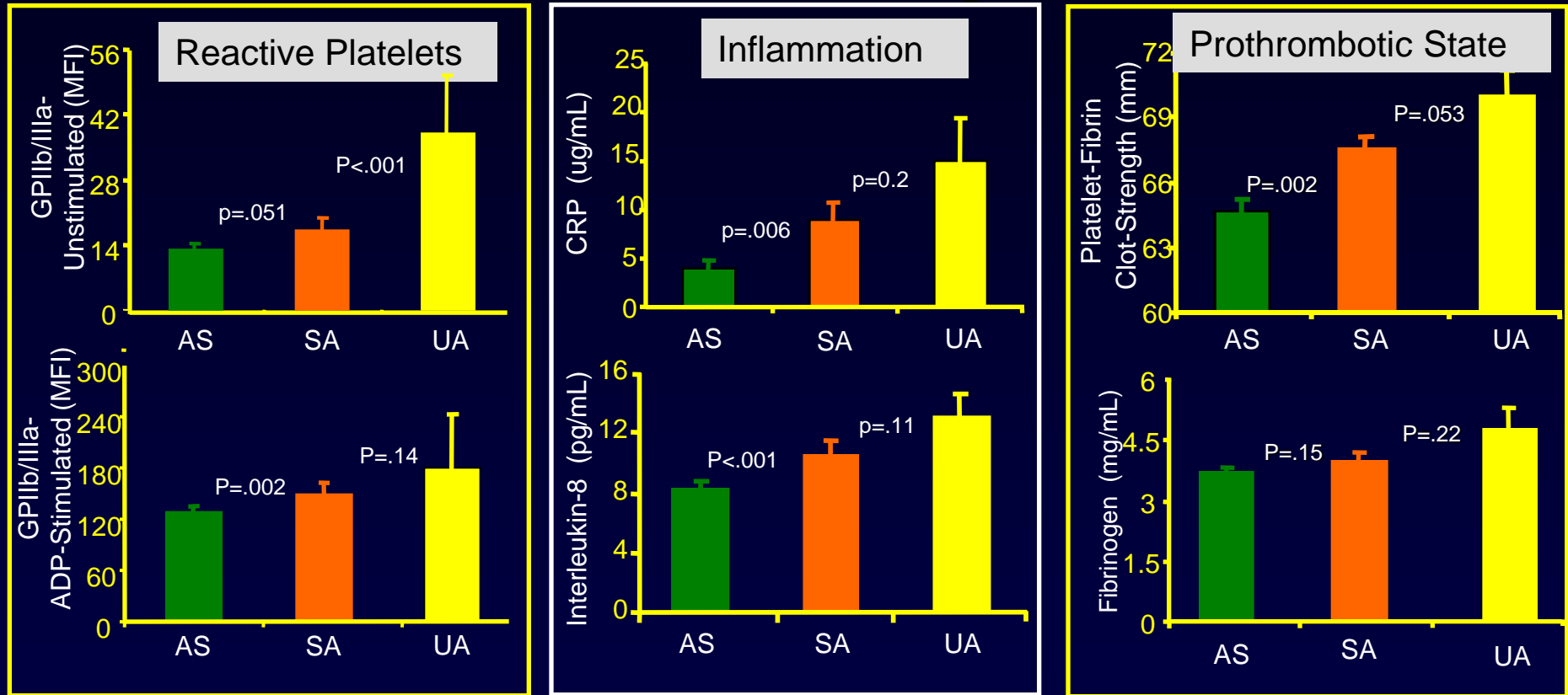
# Relationship Between Thrombosis & Inflammation



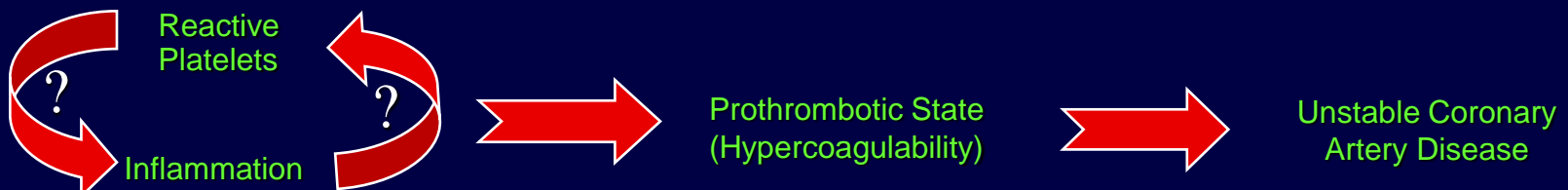


# Relation: Platelet Physiology, Inflammation and Disease Activity

AS = Asymptomatic Patients, SA= Stable Angina, UA= Unstable Angina



A distinct pathophysiological state of heightened platelet reactivity to ADP, platelet activation, inflammation and hypercoagulability, marks the development of symptomatic CV disease from chronic stable disease.



# Anti-inflammatory & Vasoprotective Effects of P2Y<sub>12</sub> Receptor Inhibitors

↑ *Nitric Oxide*

↑ *Prostaglandin I<sub>2</sub>*

↓ *Platelet-leukocyte aggregates*

↓ *P-selectin*

↓ *RANTES*

↓ *CD40 ligand*

↓ *CRP*

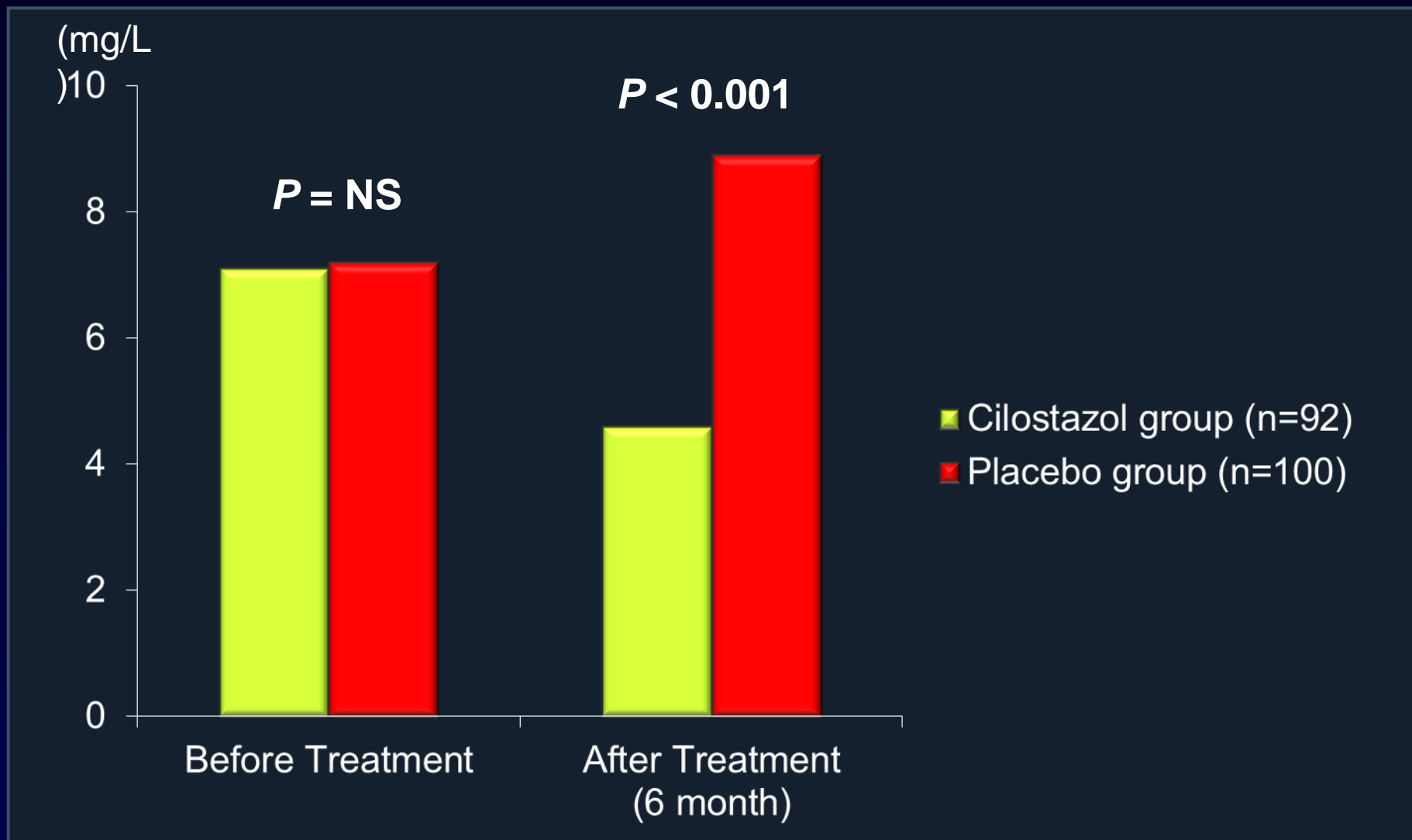
↓ *Tissue factor expression*

# **Platelet Function:**

**Platelet-Leukocyte Aggregates and Inflammation**

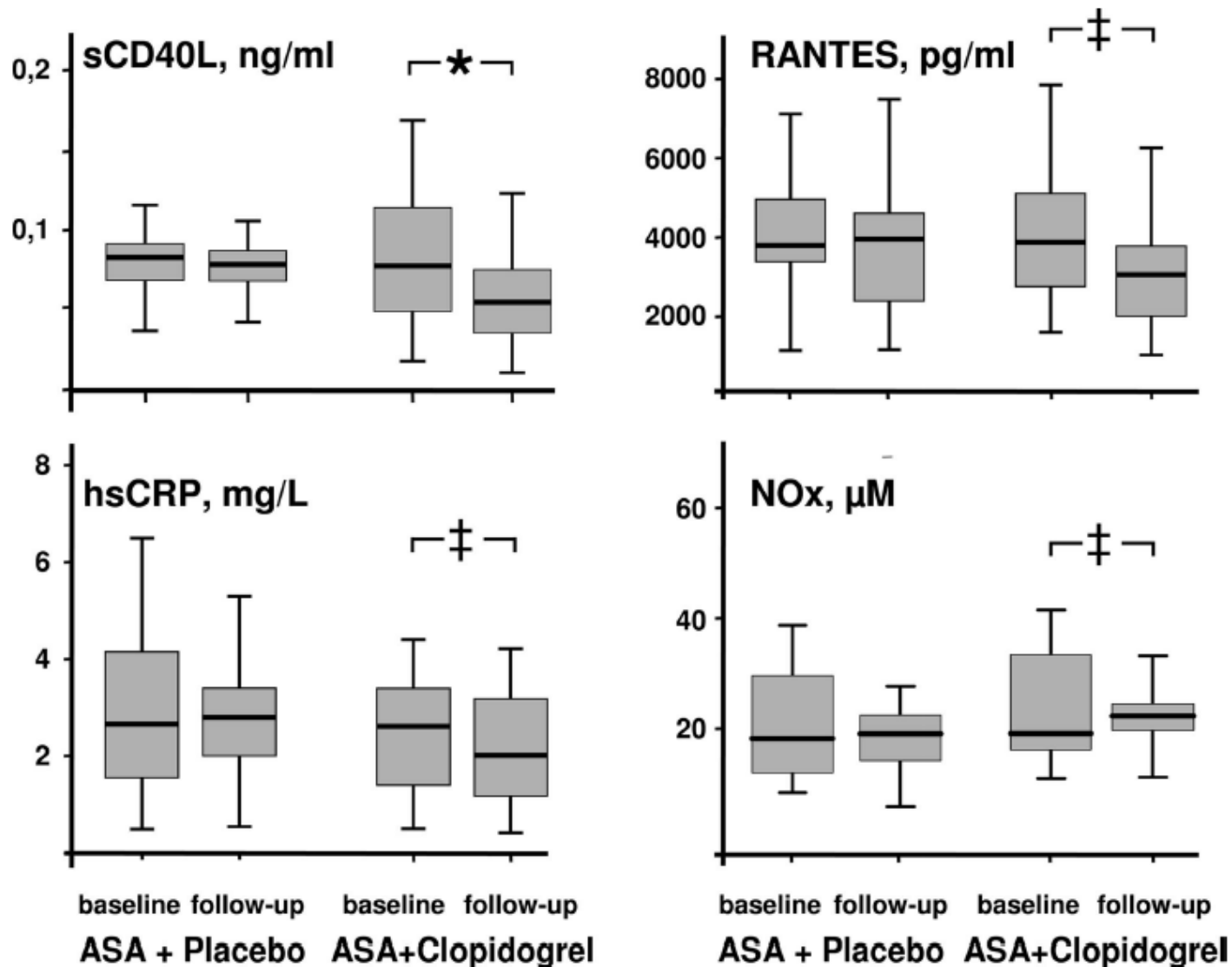
# Effect of Cilostazol on HS-CRP

Type 2 DM patients with PAOD (n = 192)



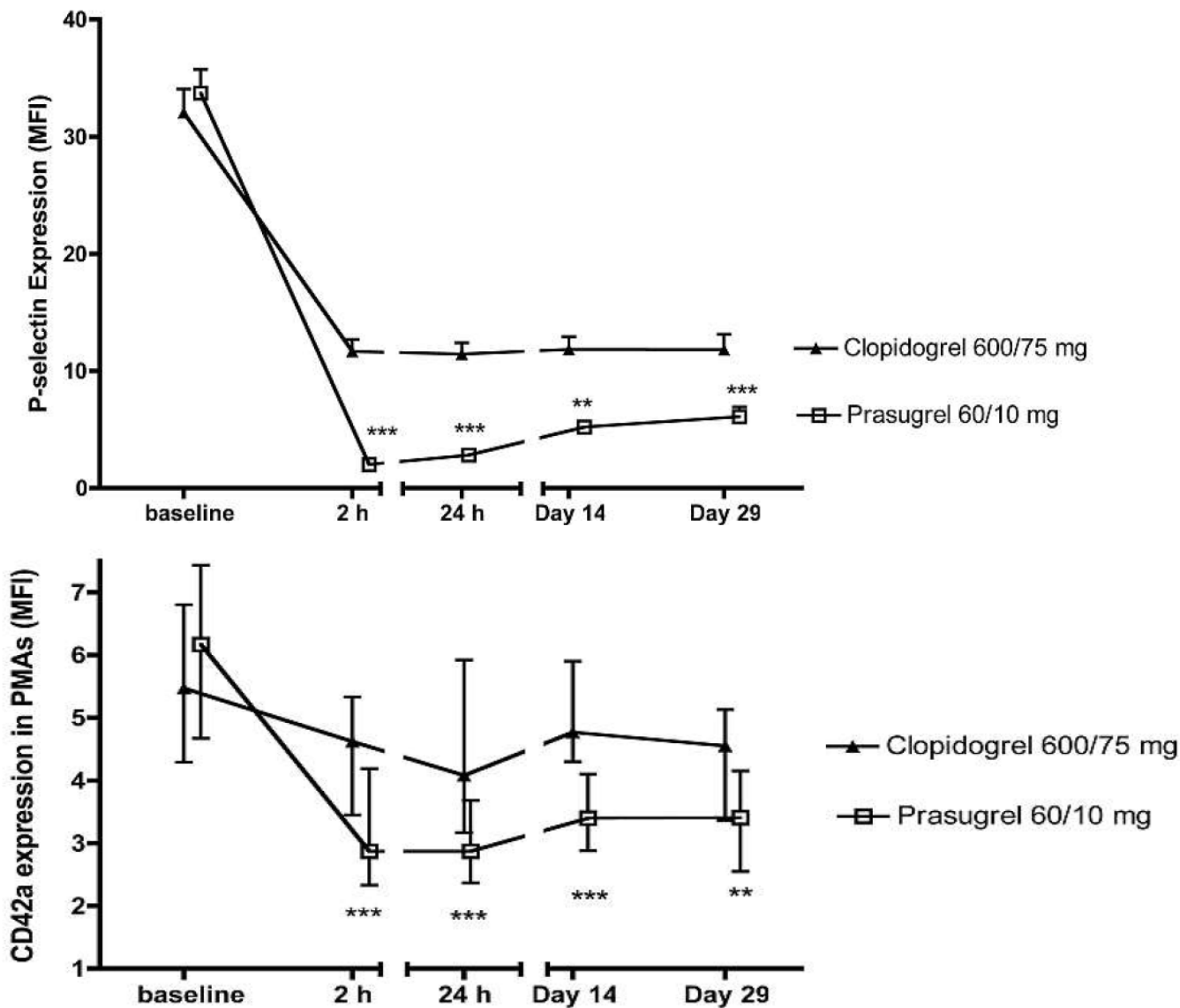
# Clopidogrel on PLT Activation and Inflammation

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



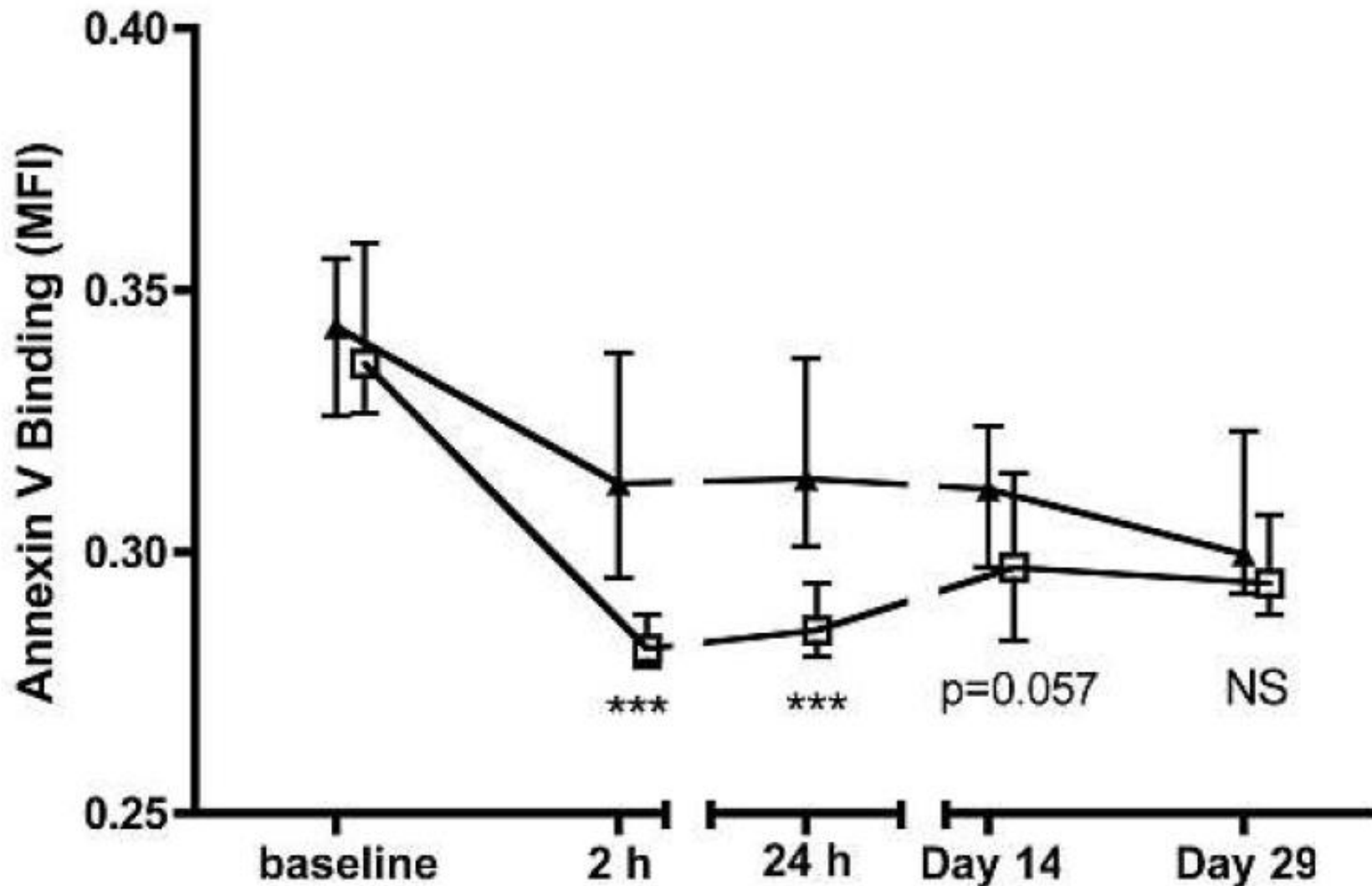
# Prasugrel vs. Clopidogrel on Platelet Activation

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



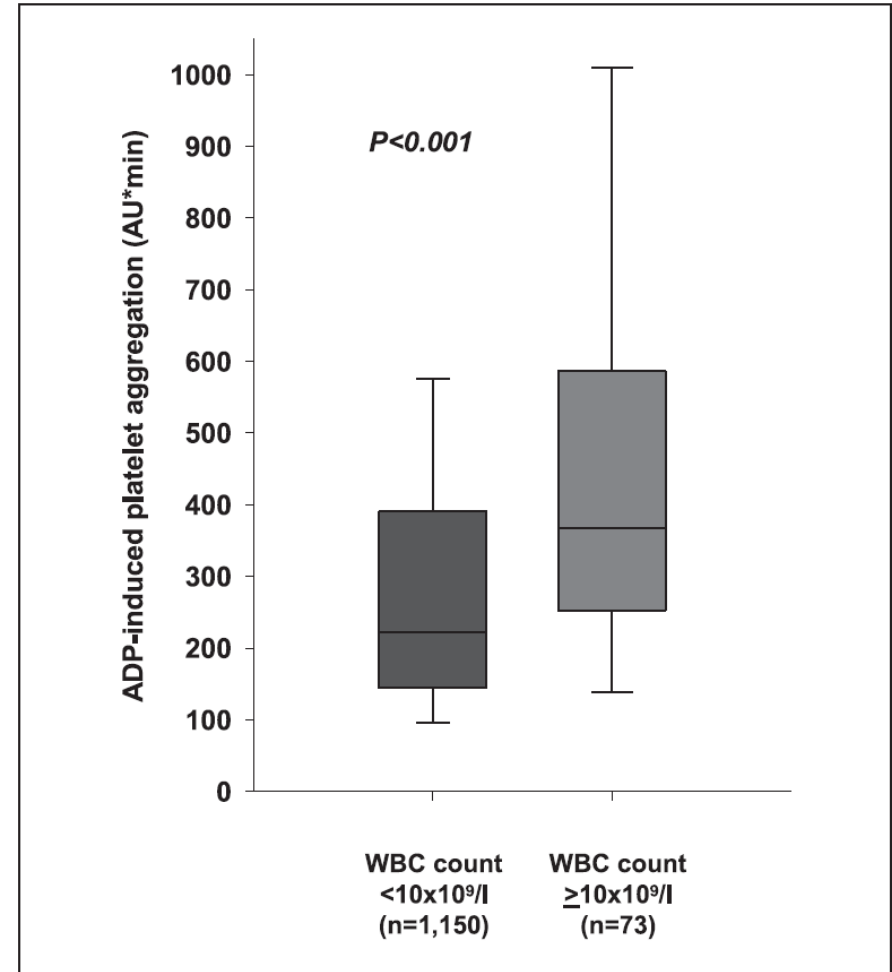
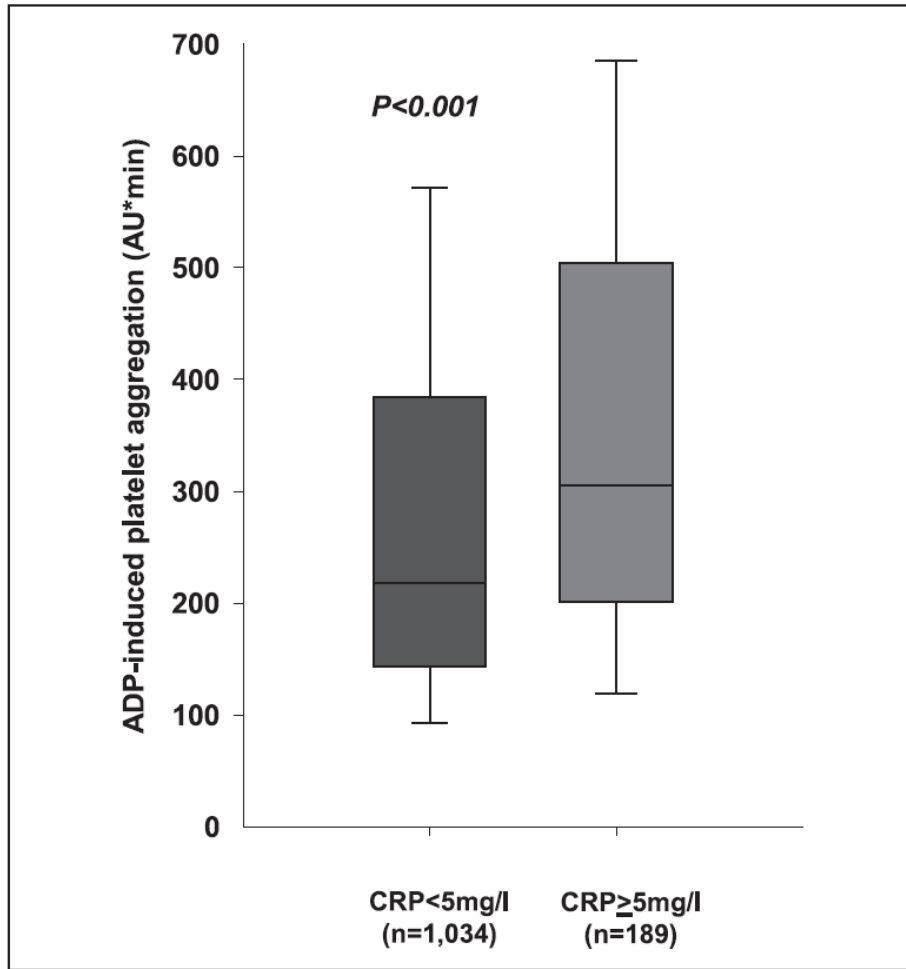
# Prasugrel vs. Clopidogrel on Coagulation Activation

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



# Relationship Between Inflammation and PFT

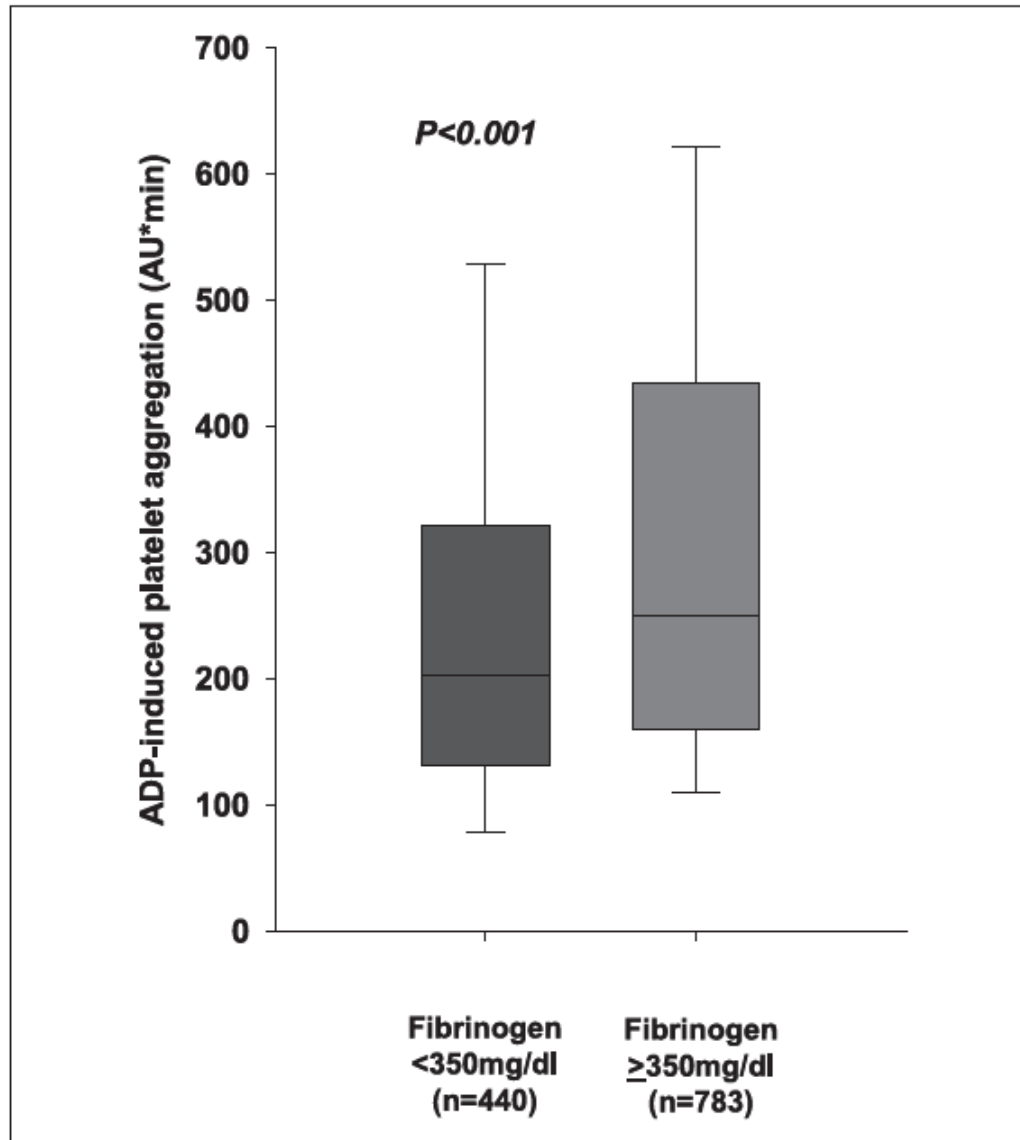
Stable CAD on Chronic DAPT (n = 1,223)





# Relationship Between Fibrinogen and PFT

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

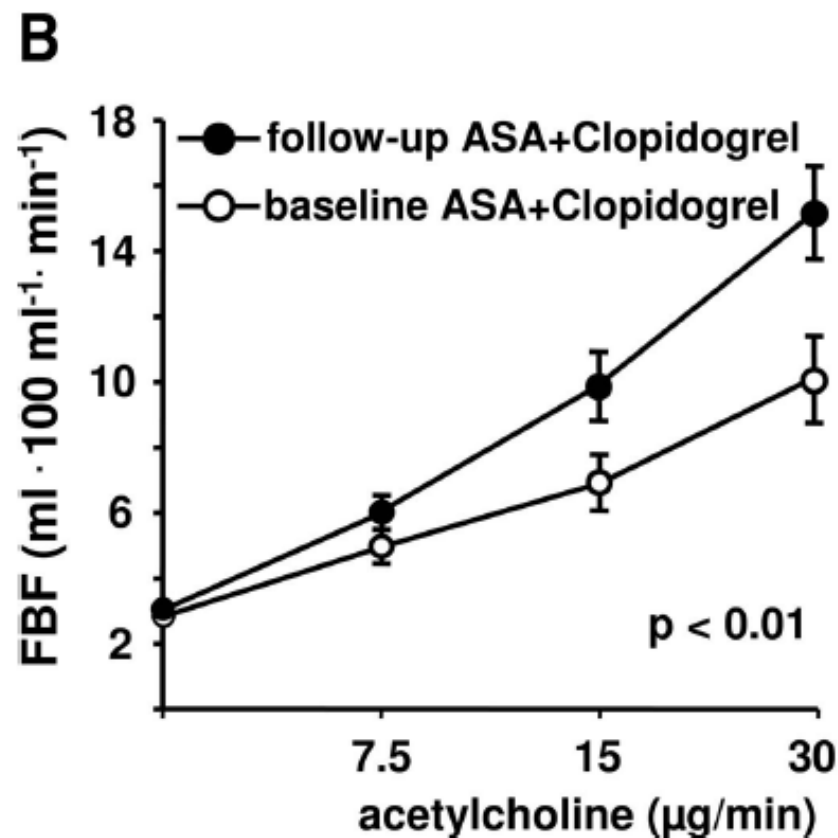
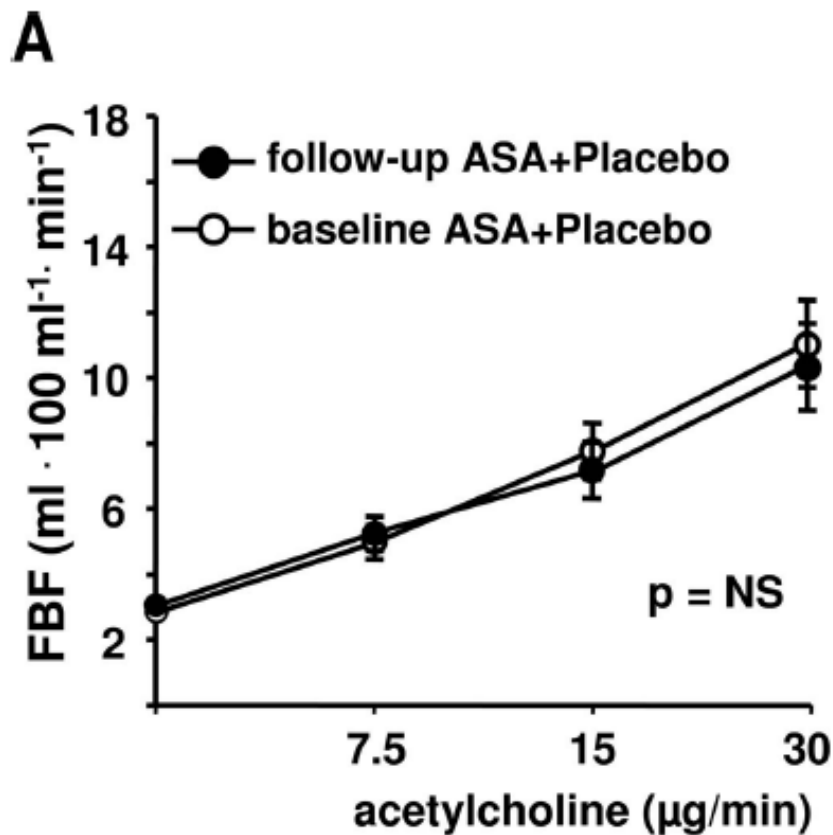


# **Platelet Function:**

**Endothelial Dysfunction and Atherosclerosis**

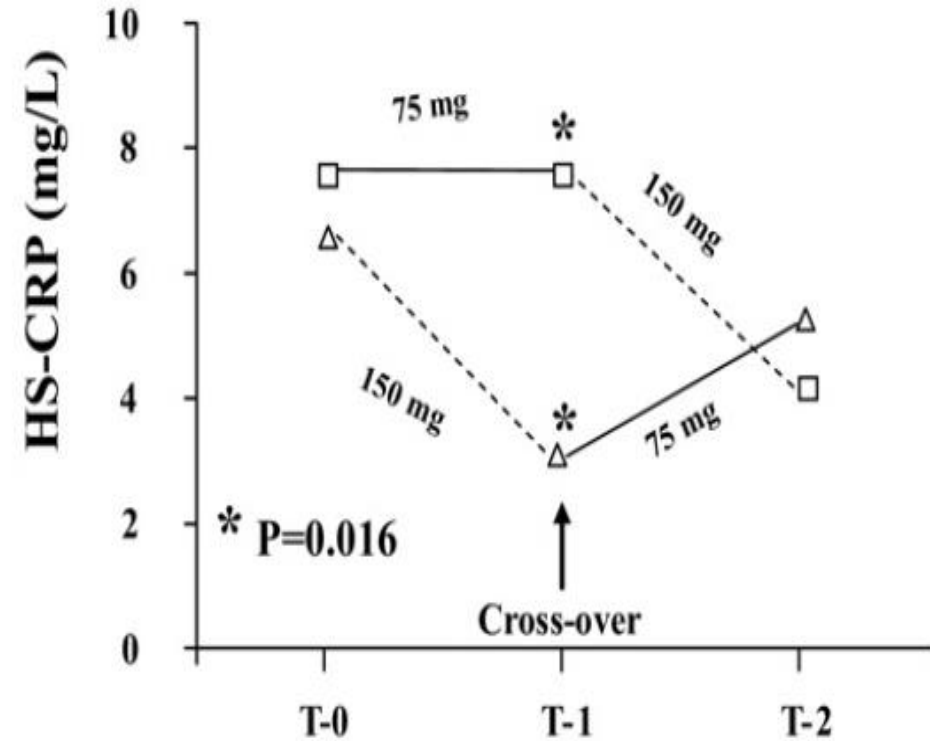
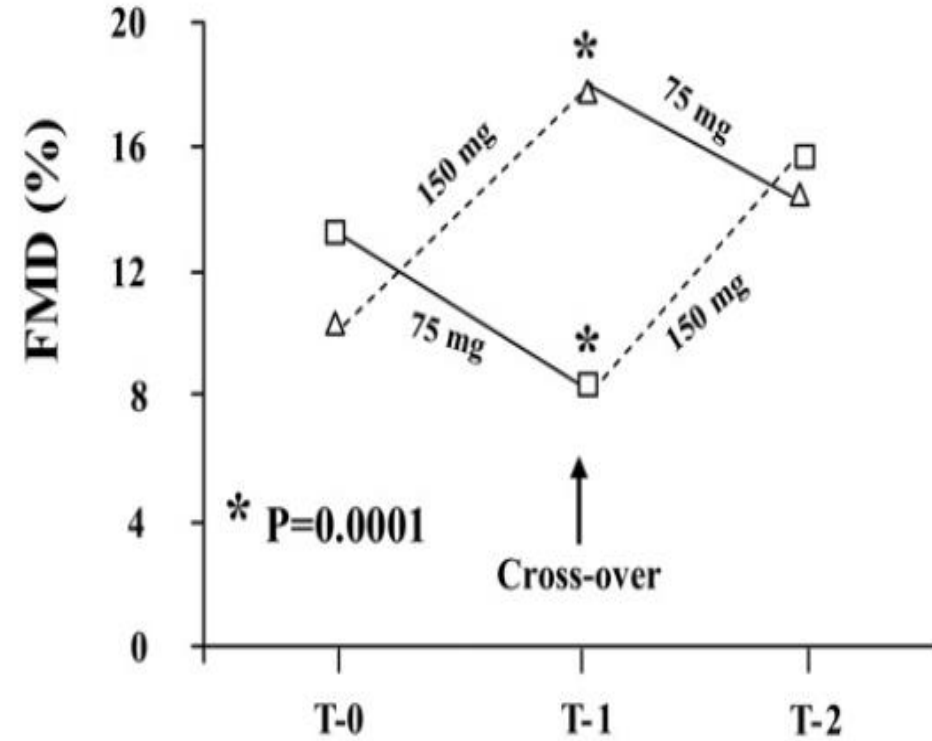
# Clopidogrel on Endothelial NO Bioavailability

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



# HD Clopidogrel on Endothelial NO Bioavailability

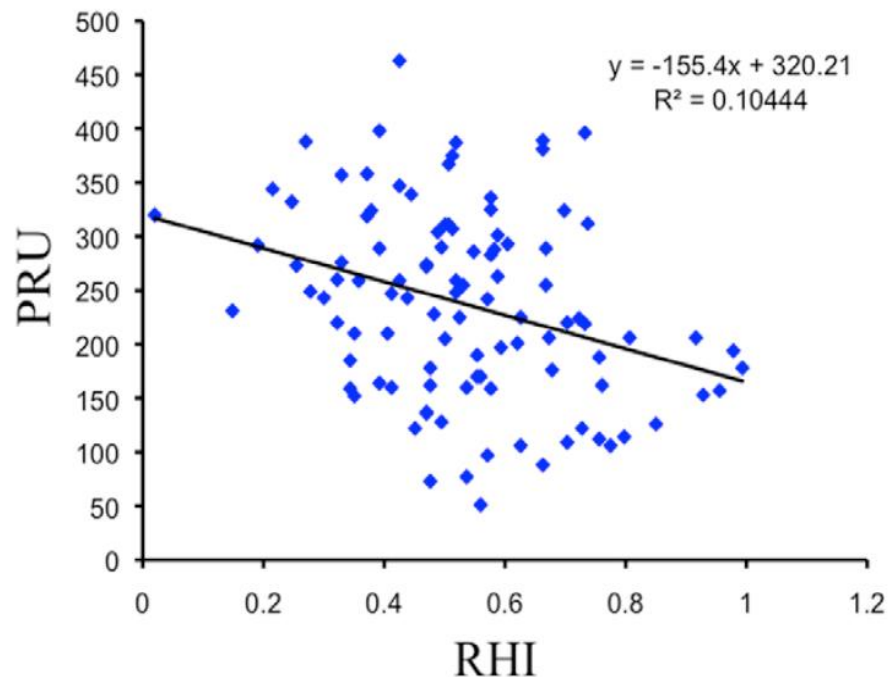
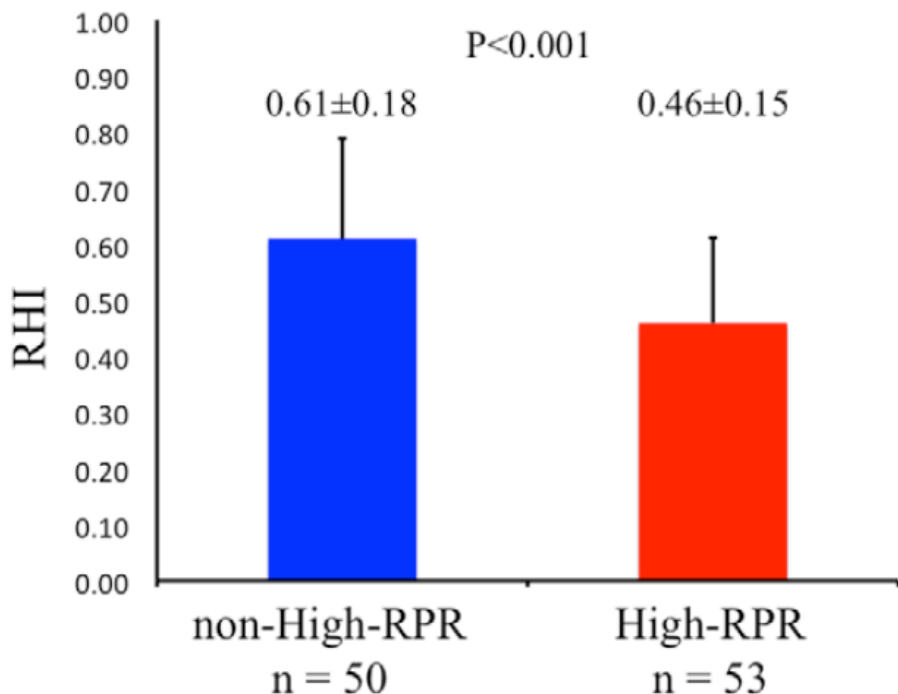
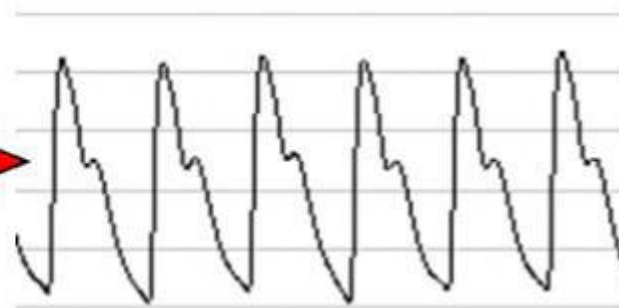
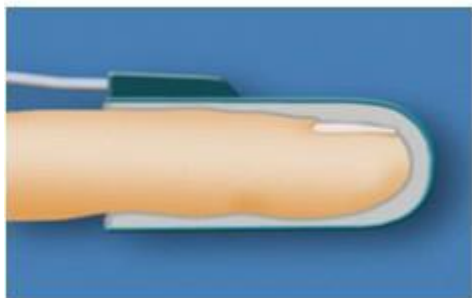
PCI-treated Patients: 75 mg vs. 150 mg Clopidogrel (n = 50, 30-day cross-over)



# Relationship btw Endothelial Dysfunction and HPR

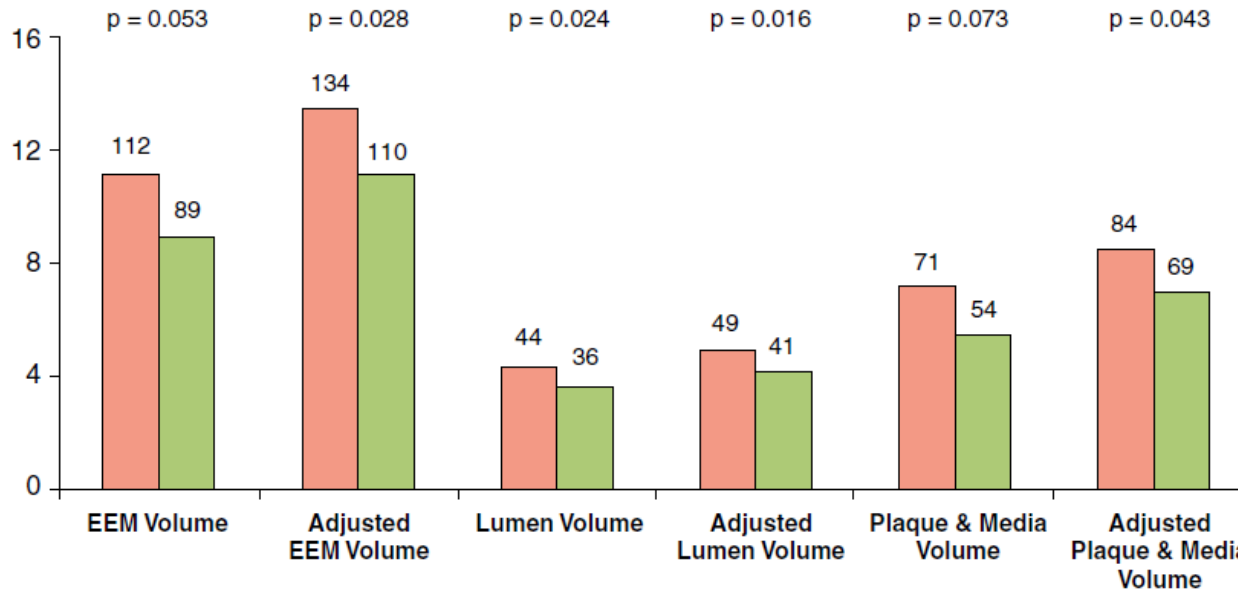
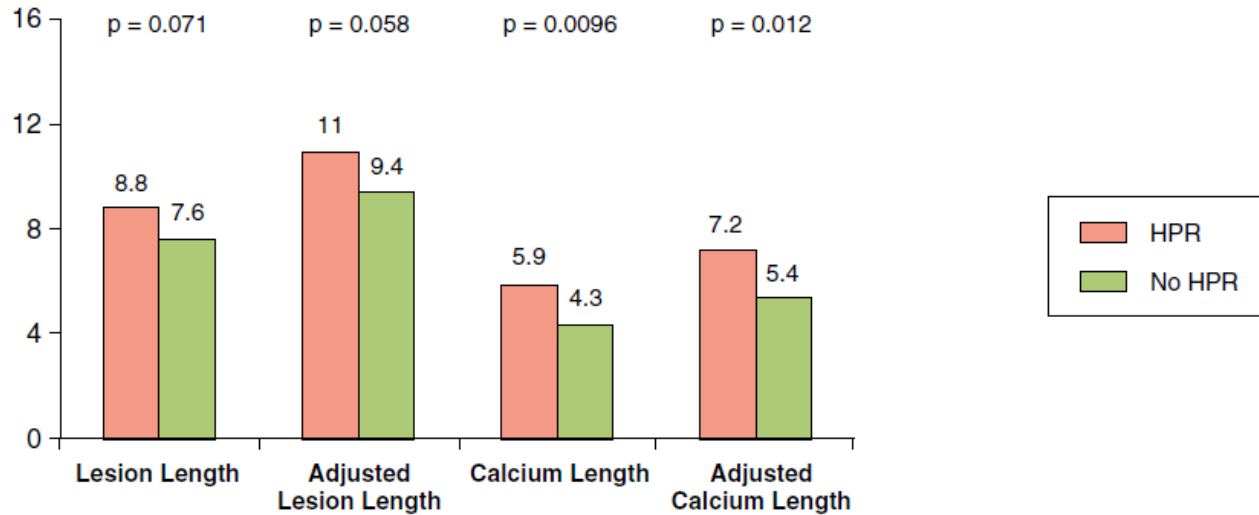
PCI-treated Patients on Chronic DAPT (n = 103): HPR  $\geq$  230 PRU

RHI (Reactive Hyperemia Index):  
peripheral ED



# Relationship Between Atheroma Burden and HPR

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



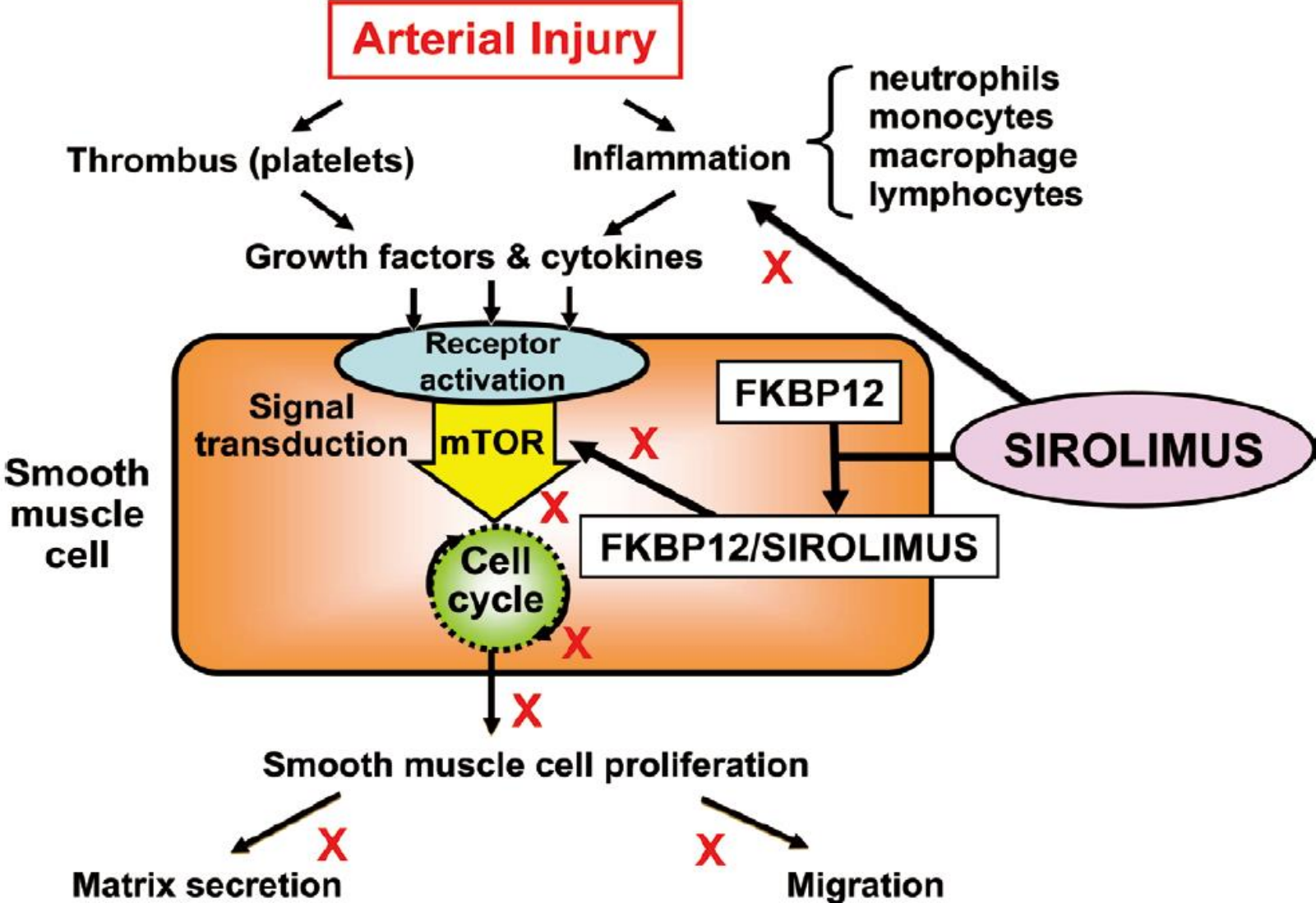
\* Adjustments for age, sex, DM, and CRF

Chirumamilla APet al. *JACC CV Imaging* 2012;5:540-9.

# **Platelet Function:**

**Post-injury or Post-stent Neointimal Hyperplasia**

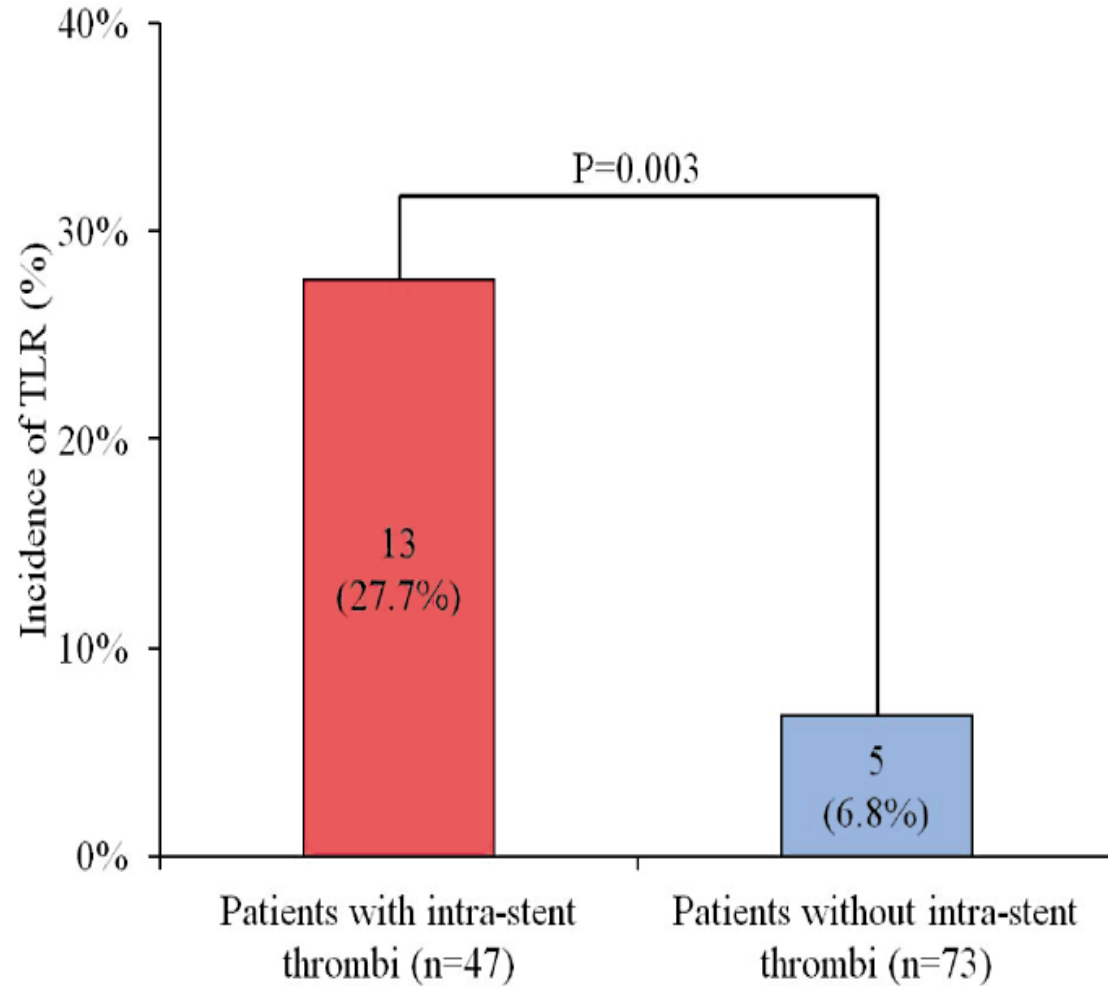
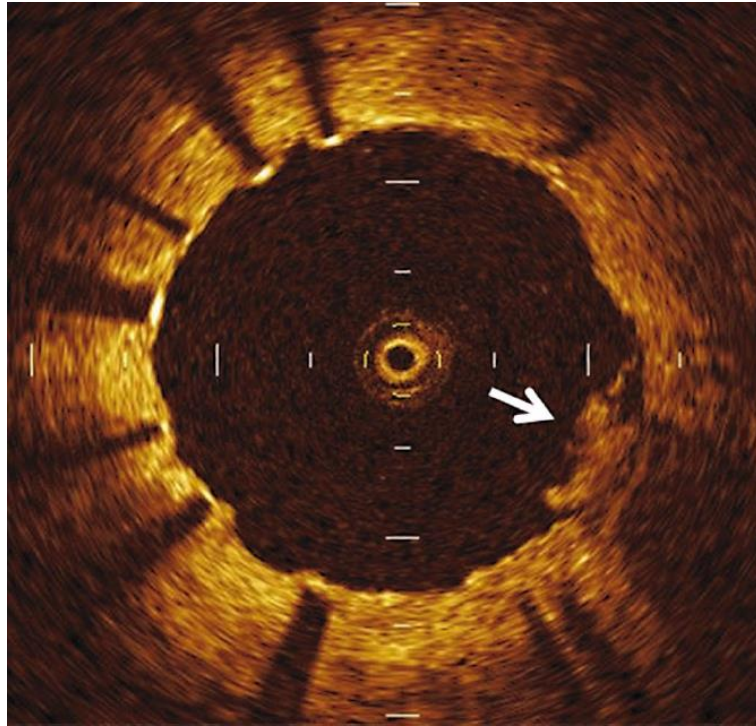
# Leukocyte Migration Interacting With PLT-Fibrinogen Clot After Stenting





# CYP2C19 SNP on Intra-stent Thrombi and TLR

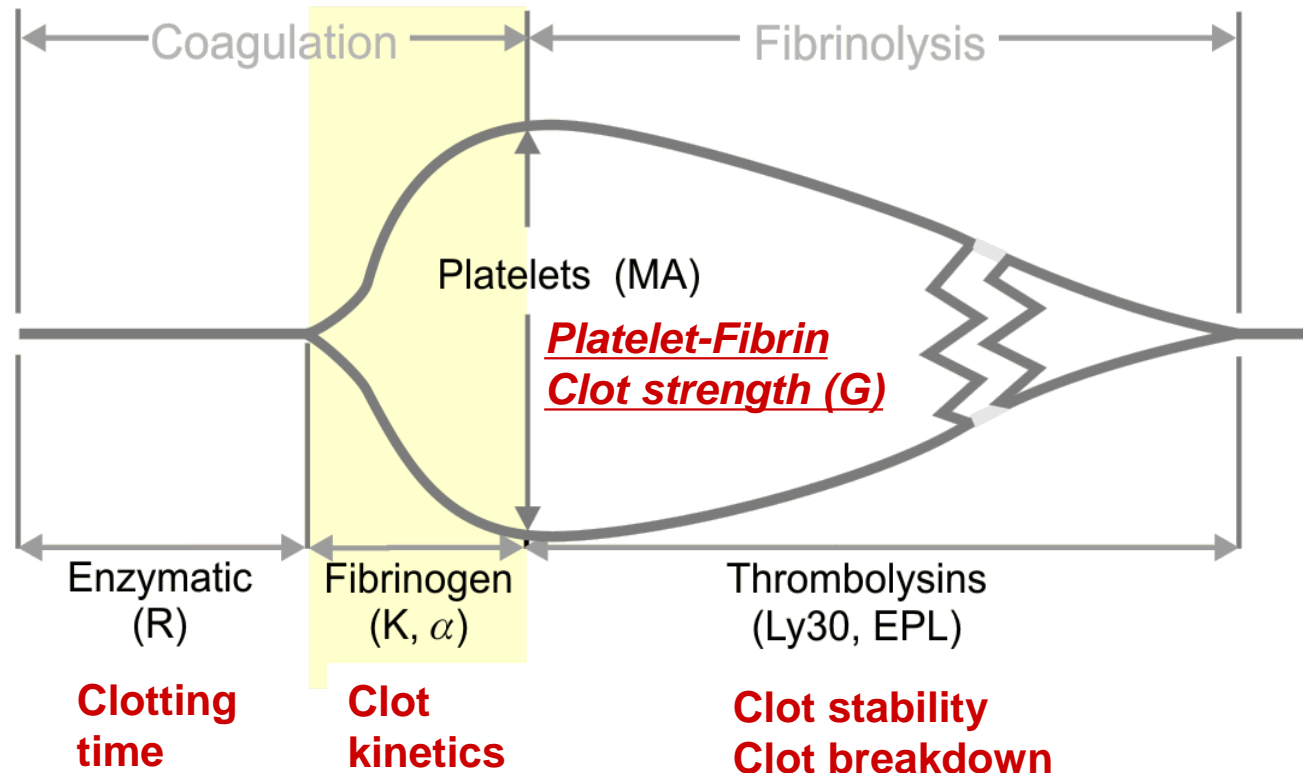
Follow-up OCT imaging in DES-treated Patients on DAPT (n = 125)



# Thrombelastography (TEG<sup>®</sup>) Hemostasis System



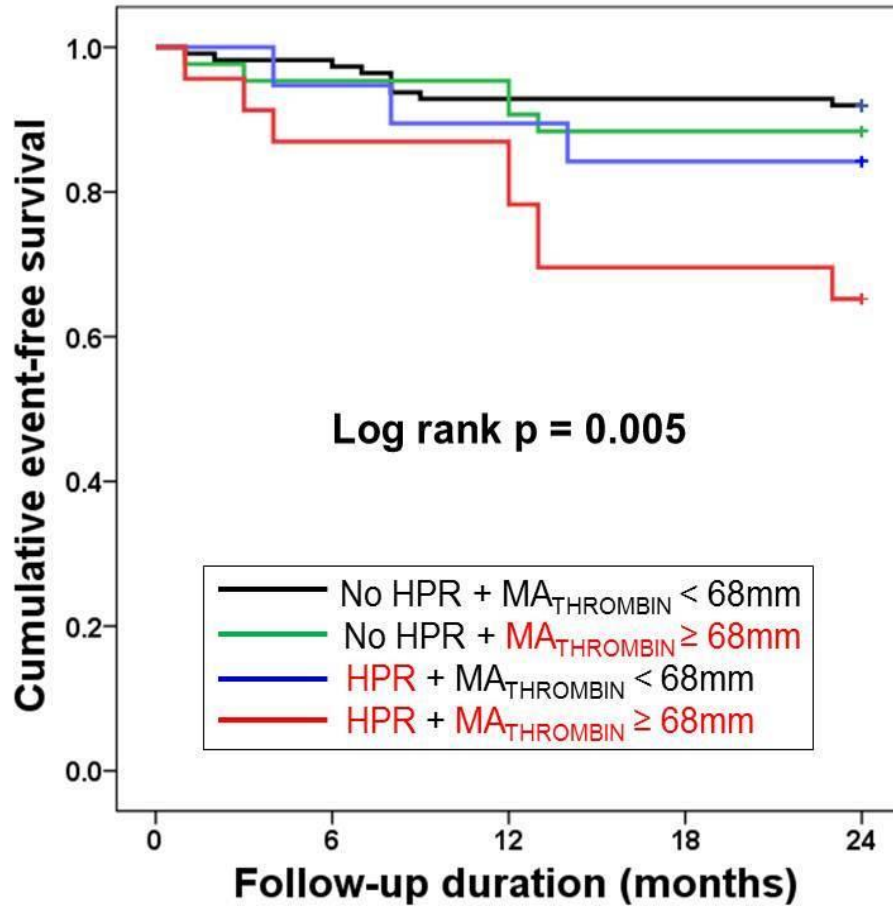
- Whole blood test
- Measures global hemostasis
  - From clot initiation to clot lysis
  - Net effect of components



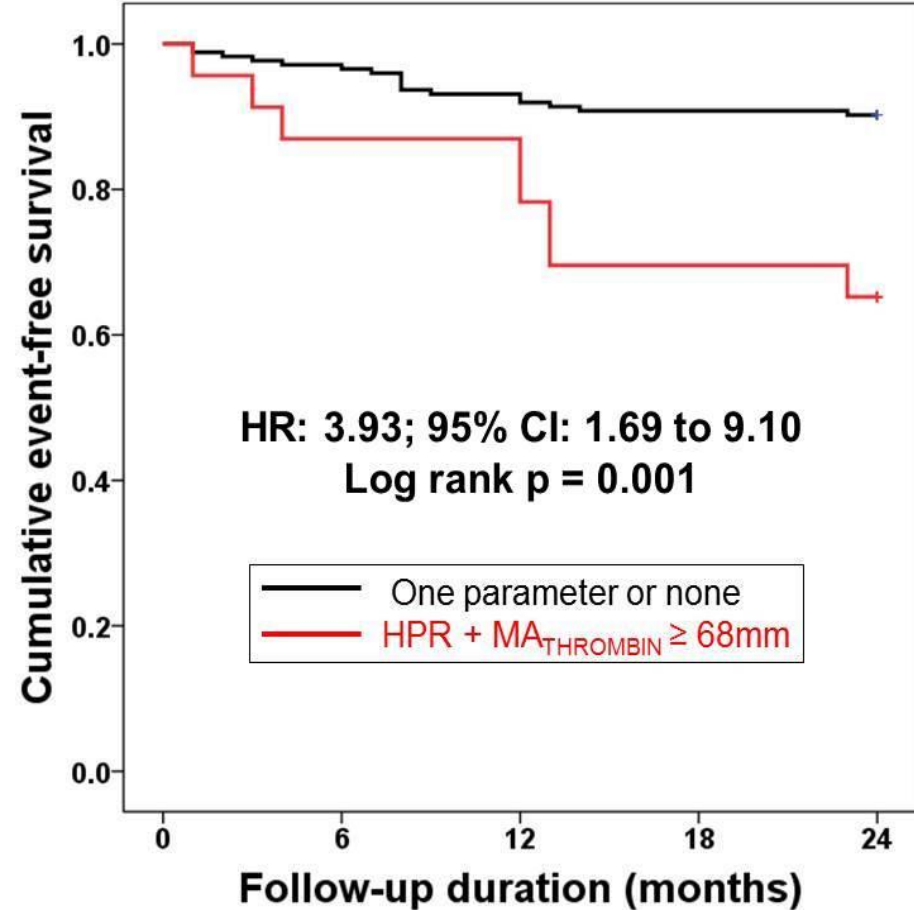
# Influence of HPR (LTA) and MA<sub>KH</sub> (TEG) on MACE

PCI-treated Patients on DAPT (n = 197): 2-year F/U (MACE, 12.7%)

A



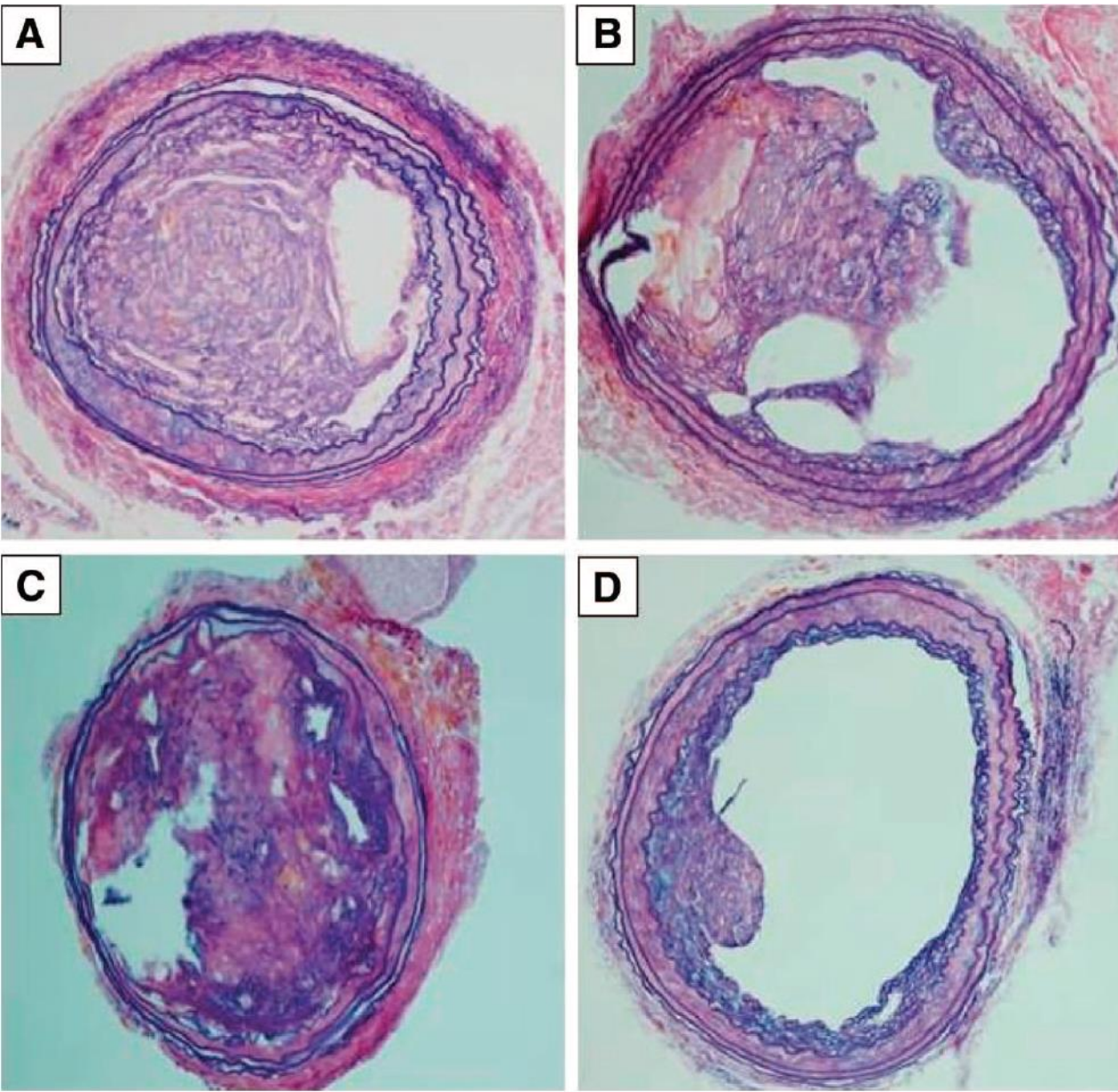
B



**Ischemia-driven TVR: 76% of MACE**

***“Platelet function or Clot strength” is associated with post-injury neointimal hyperplasia***

# Sustained P2Y<sub>12</sub> Inhibition by Ticagrelor to Prevent Subsequent Neointima



**Figure 6.** Representative carotid artery neointima sections in C57BL/6 mice treated with vehicle alone (A), ticagrelor before injury only (B), ticagrelor post-injury only at 4 and 24 hours (C), and ticagrelor before injury and 4 hours postinjury (D).

# **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)

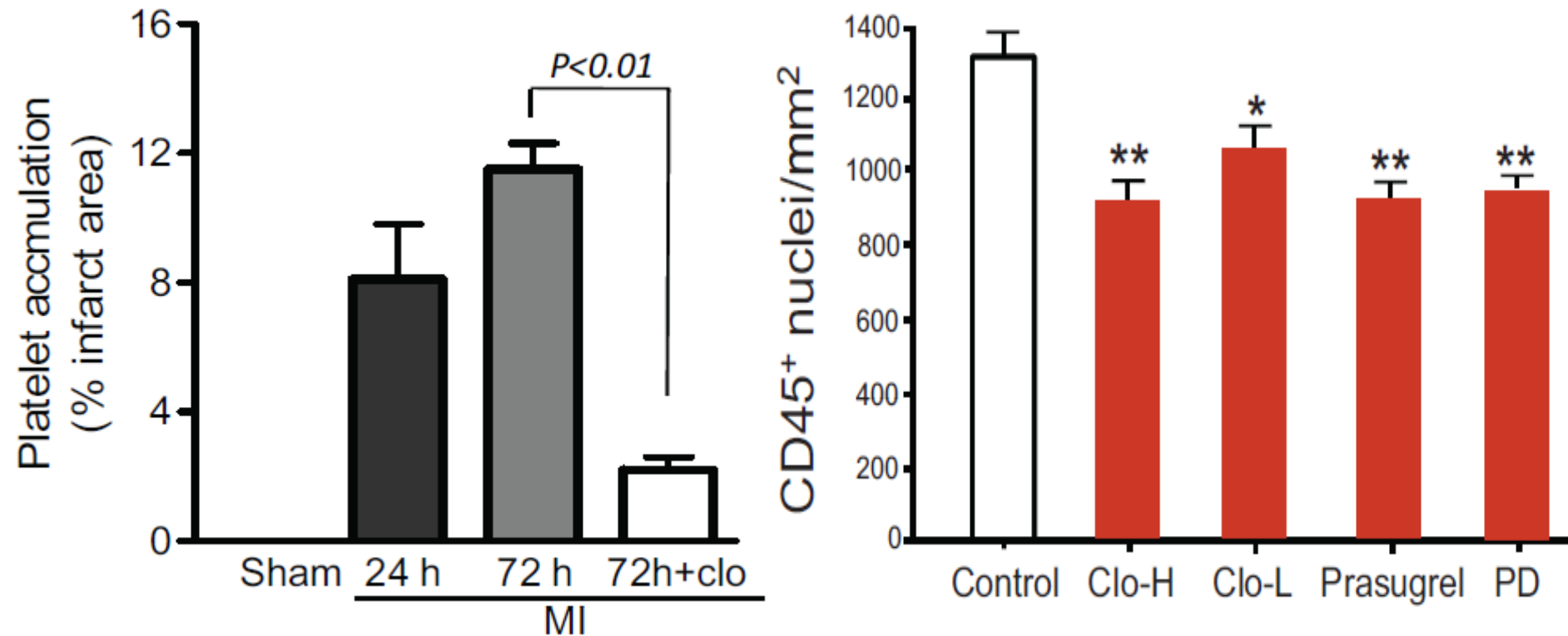
Randomized treatment started 2 hrs after MI and lasted for 3 days

*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*

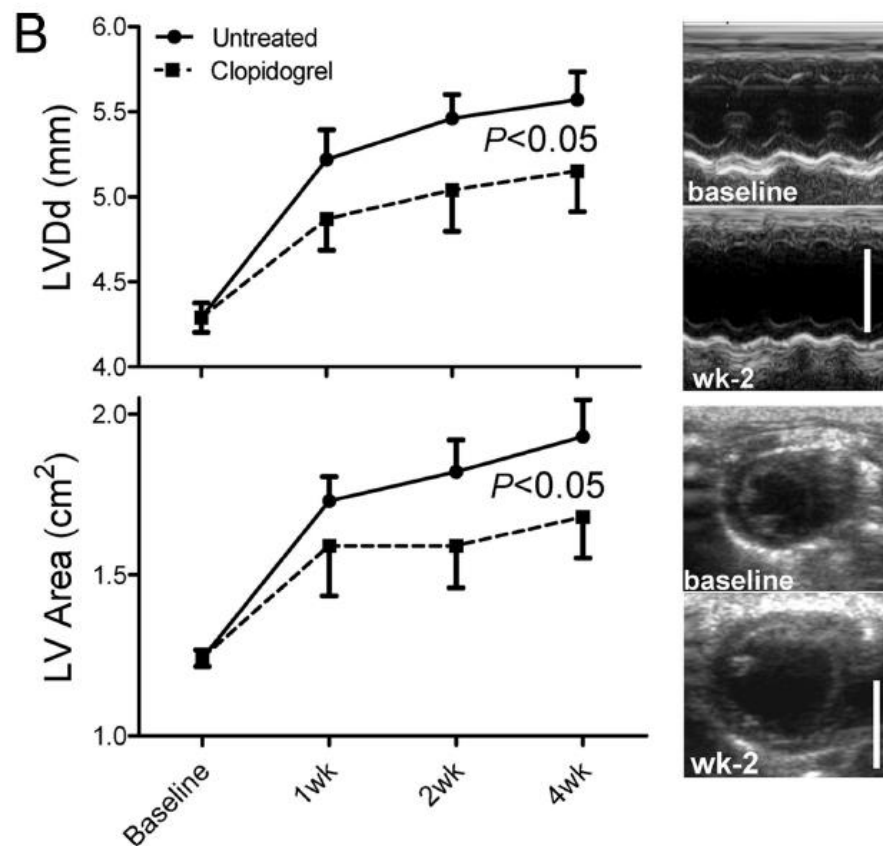
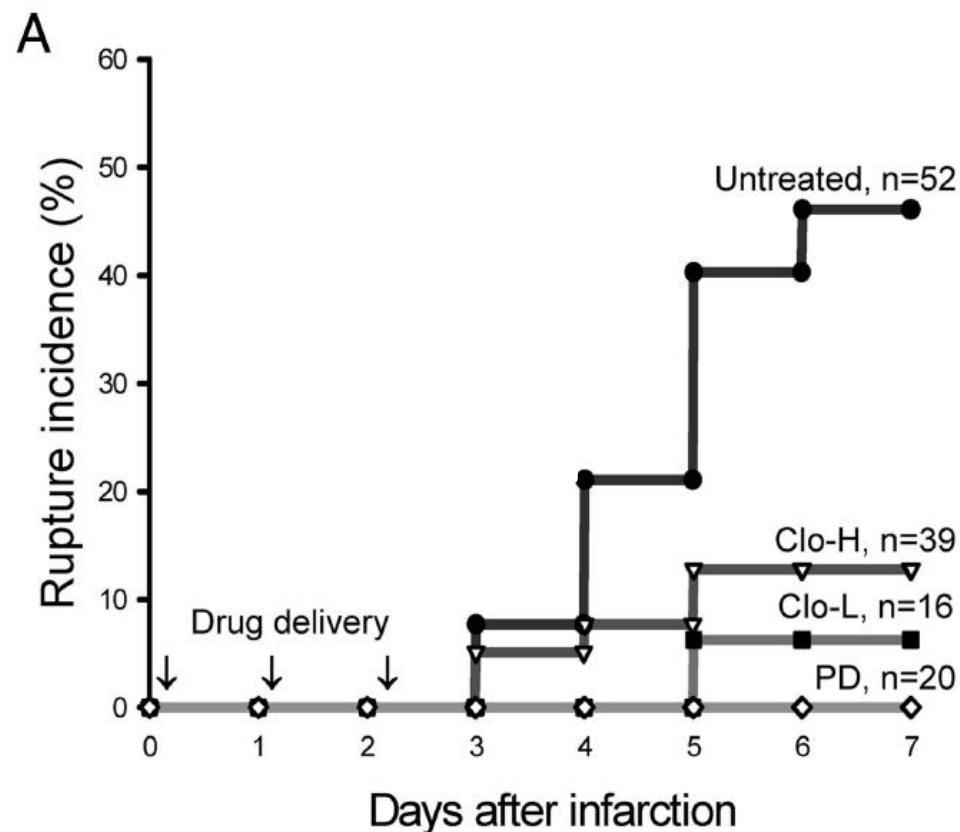


# Role of Platelets in Mediating Inflammatory Responses for Post-MI LV Remodeling

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

## Acute phase: LV rupture

## Chronic phase: LV remodeling

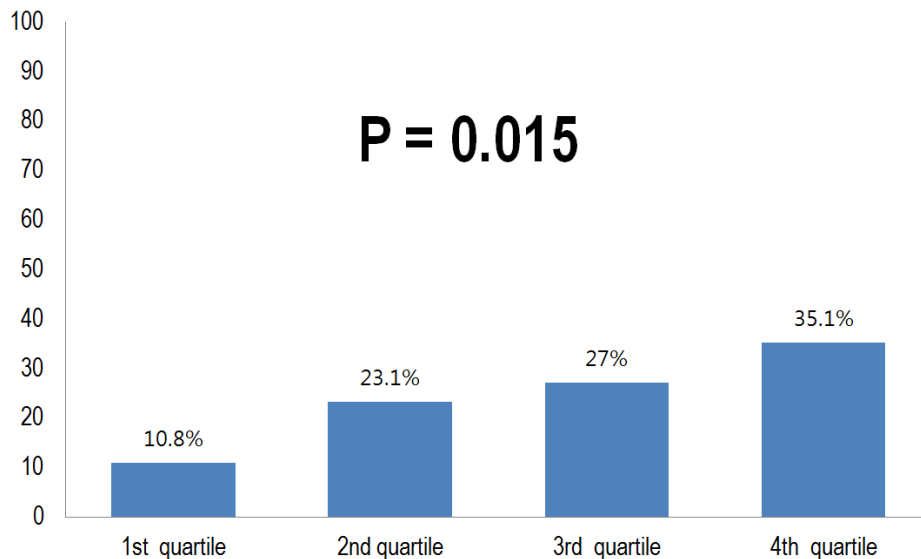


# Novel Role of Platelet Reactivity and Inflammation in LV Remodeling Following STEMI

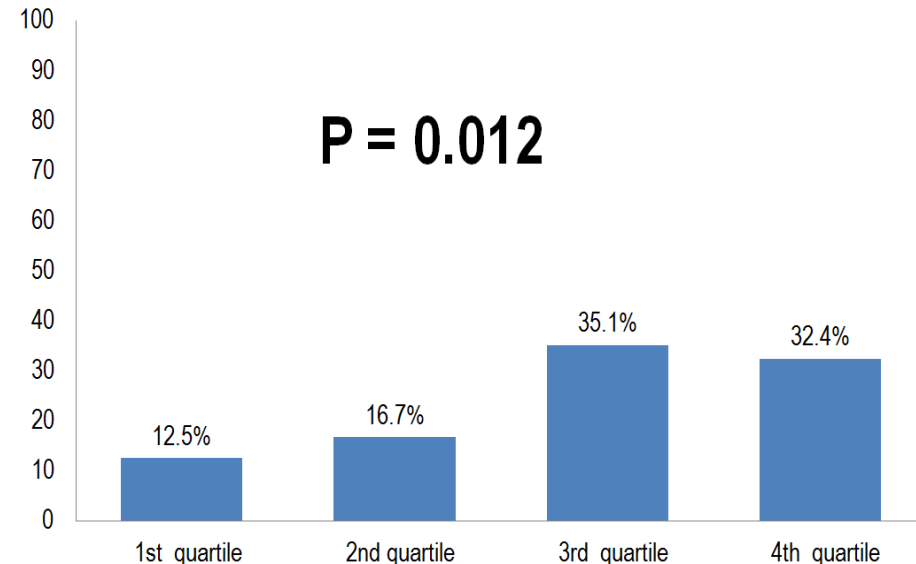
REMODELING Study: PPCI-treated STEMI Patients on DAPT (n = 150)

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

LVR by PRU quartile



LVR by hs-CRP quartile

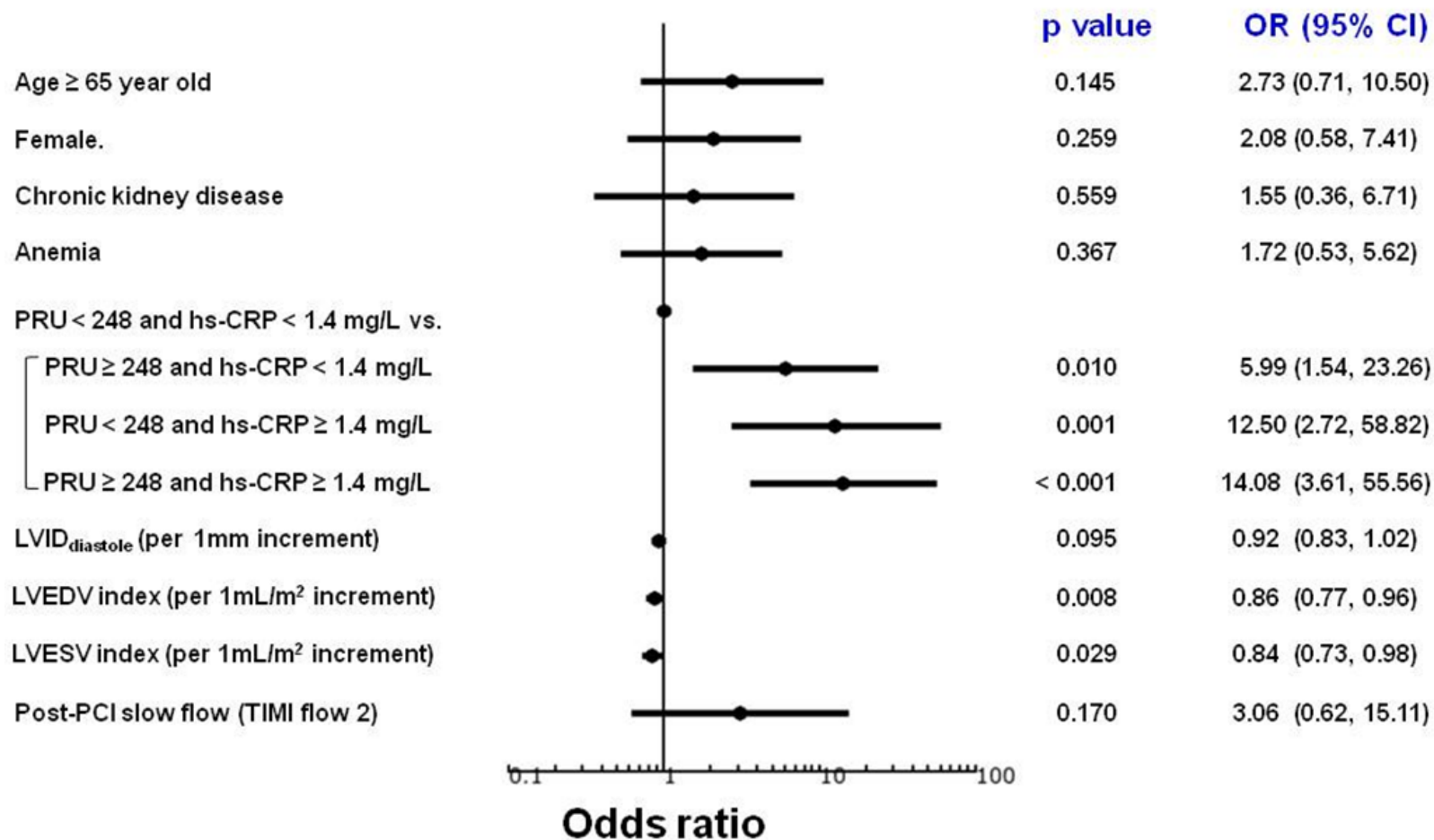




# Cross-talk btw Platelet Reactivity and Inflammation in LV Remodeling Following STEMI

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

## Predictors of LV Remodeling



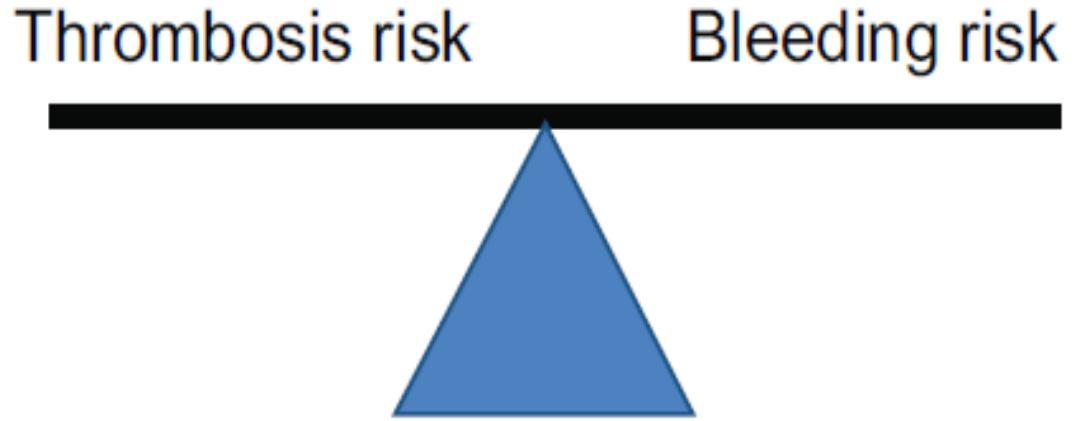
# Platelet Function in CV Disorder

## Key roles in “Atherothrombosis”

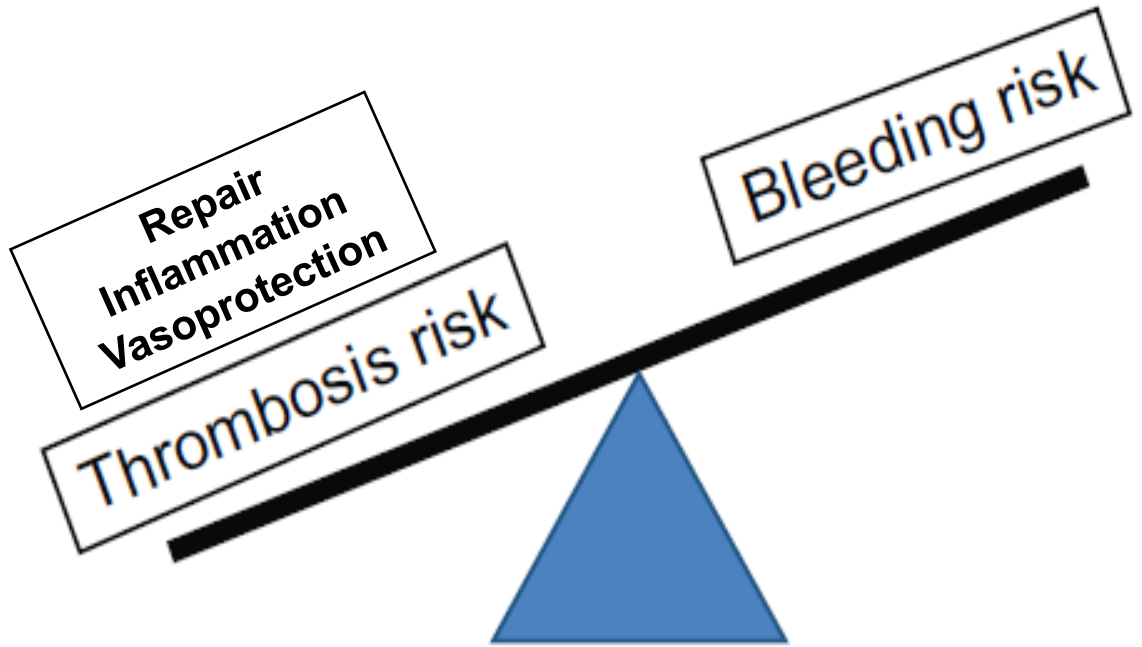
- **“Platelet activation & aggregation”** are related w/ **hemostasis and thrombosis**  
**endothelial dysfunction and atherosclerosis**  
**inflammatory cascade**  
**vascular, post-stent and myocardial repair...**
- **“Antiplatelet therapy”** has potentials to prevent and control **athero-thrombosis** through **multidisciplinary pathways.**

# Risk-Benefit Balance in Antiplatelet Therapy

“Classic Concept”



“New Concept”



**Thanks for  
your attention**

