I Prefer *Ticagrelor* in AMI Patients

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GNUH
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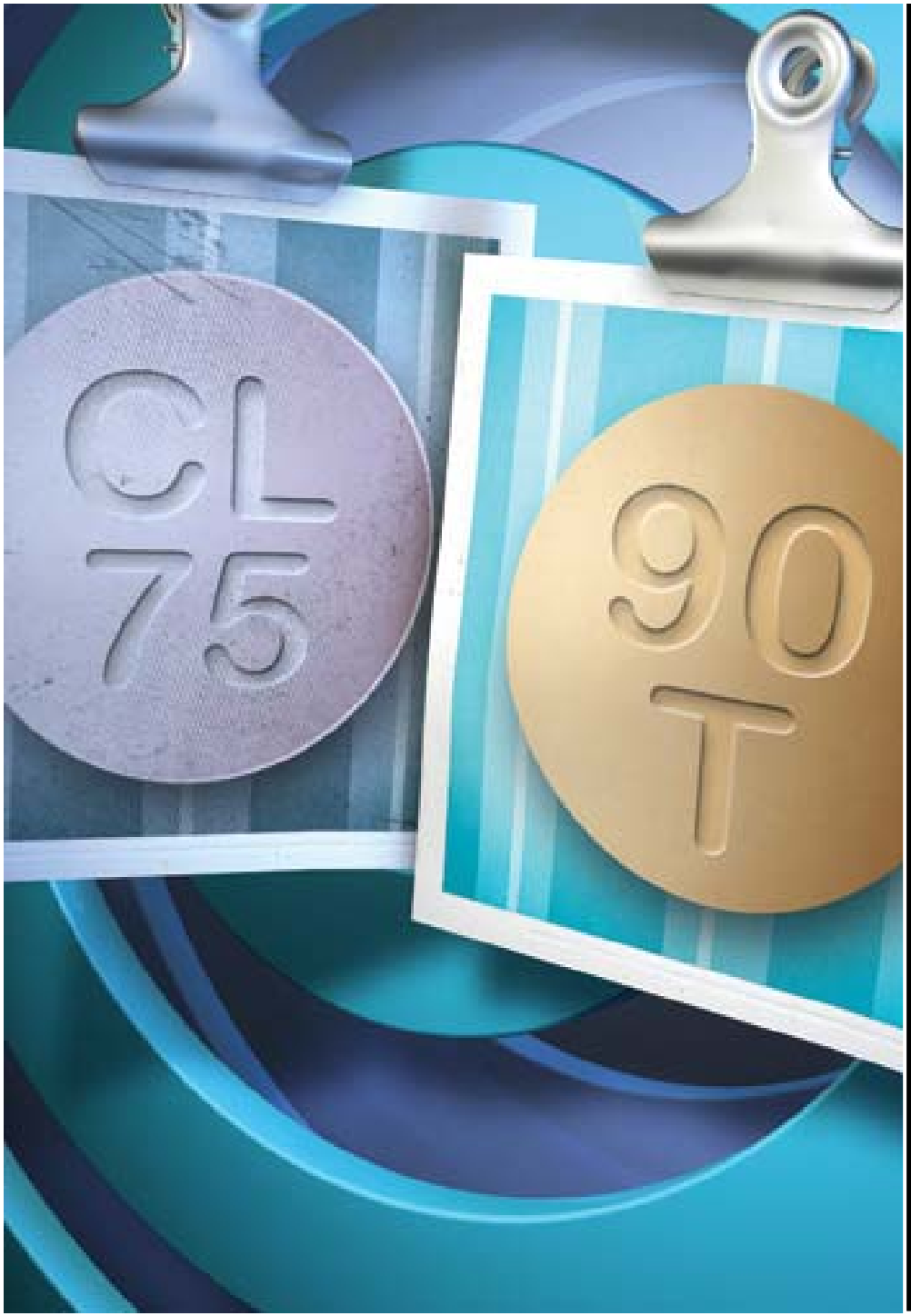
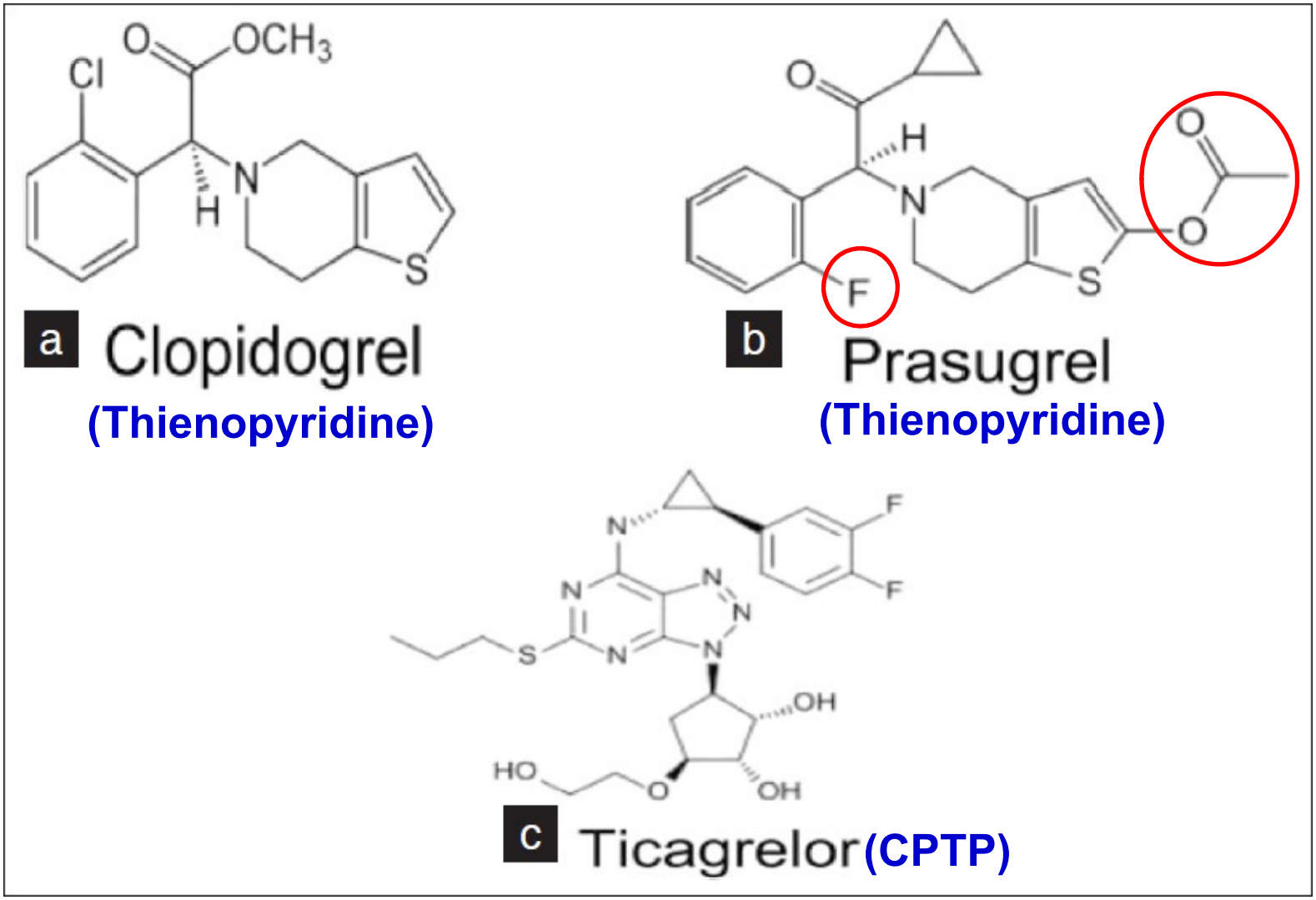


Dr Paul Gurbel:

There have been no drugs like this. Ticagrelor is "a magic bullet"

Structure of $P2Y_{12}$ Inhibitor



Levine GN, Jeong YH, et al. Nat Rev Cardiol 2014;11:597-606.

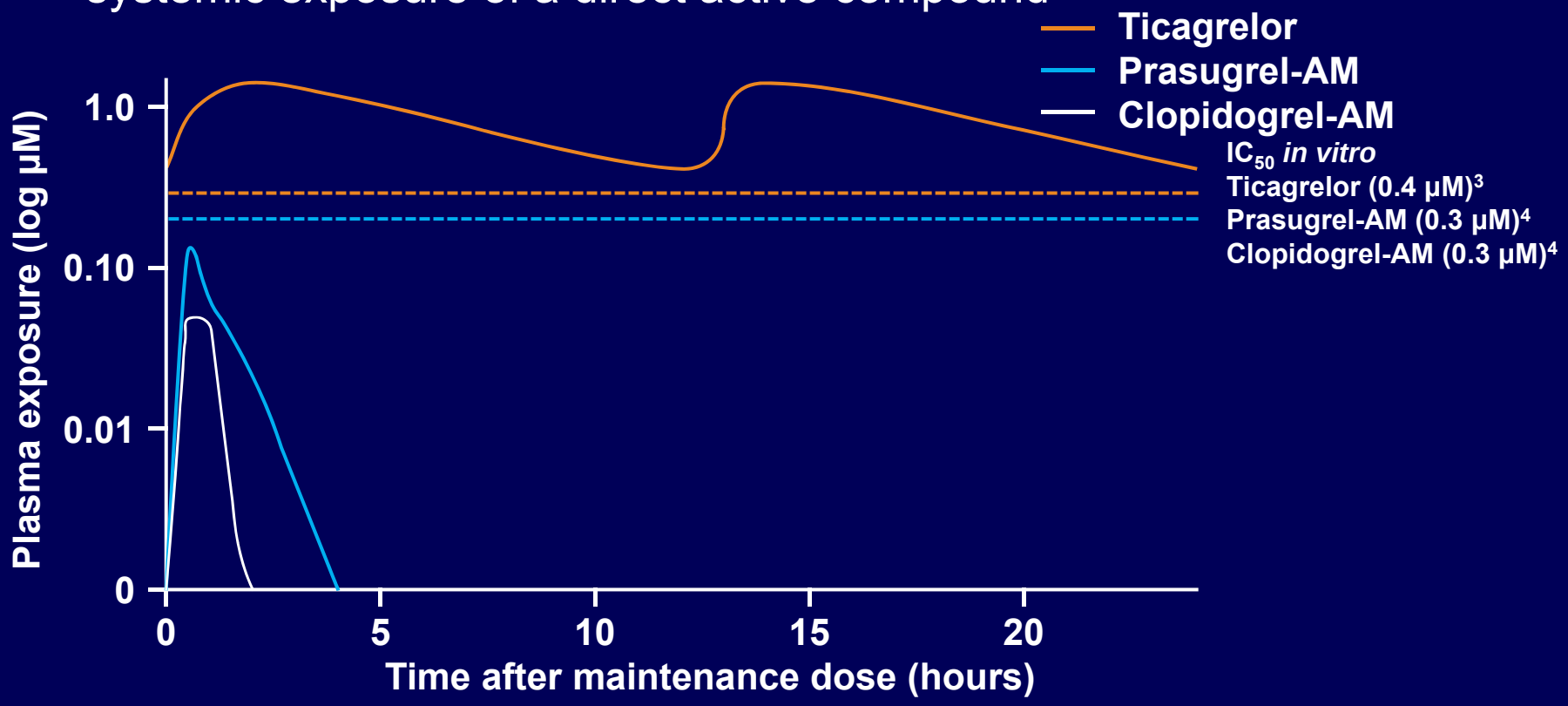
Mechanism of Action: Comparison

Ticagrelor	Clopidogrel/Prasugrel
CPTP	Thienopyridines
Direct acting	Prodrugs
24 hours PK & systemic profile	Intermittent PK & no systemic exposure
Reversible	Irreversible
Inhibition of ENT-1-mediated adenosine uptake (dual pathway)	**No additional Mechanism of Action**

Maintaining Drug Concentration

24-hour systemic potential versus minimal systemic potential

- Compared with the short plasma exposure of prasugrel and clopidogrel active metabolites, ticagrelor has significant 24-hour systemic exposure of a direct active compound[1,2]

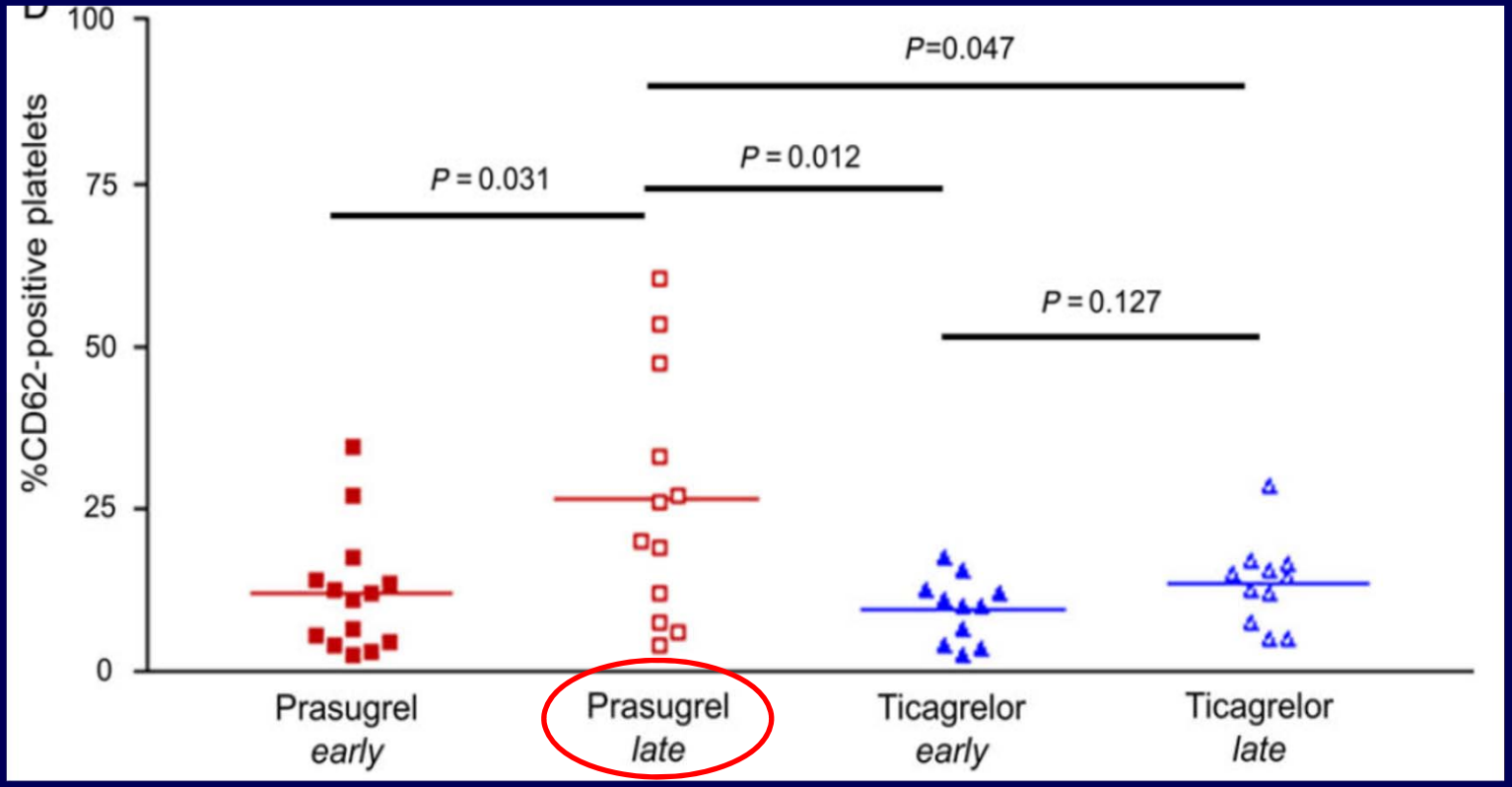


AM, active metabolite; IC, inhibitory concentration.

1. Wallentin L, et al. *Eur Heart J* 2008;29:21–30.
2. Storey RF, et al. *J Am Coll Cardiol* 2007;50:1852–1856.
3. Sugidachi A, et al. *J Thromb Haemost* 2007;5:1545–1551.

Ticagrelor vs. Prasugrel on Immature Platelets

- 100 billion new platelets are produced daily from megakaryocytes to sustain a sufficient platelet count.
- An accelerated platelet turnover during ACS results in a greater amount of immature platelets (reticulated PLTs) circulating in the blood stream with non-inhibited P2Y12 receptors on their surface.



Bernlochner I, et al. *Eur Heart J* 2015;36:3202-10.

Clinical Benefit of Ticagrelor in AMI Patients

Reversible Binding & Maintaining Concentration

Confirmative evidences from Large-scale RCTs

Adenosine-related Effect

Potential Pleiotrophic Effect

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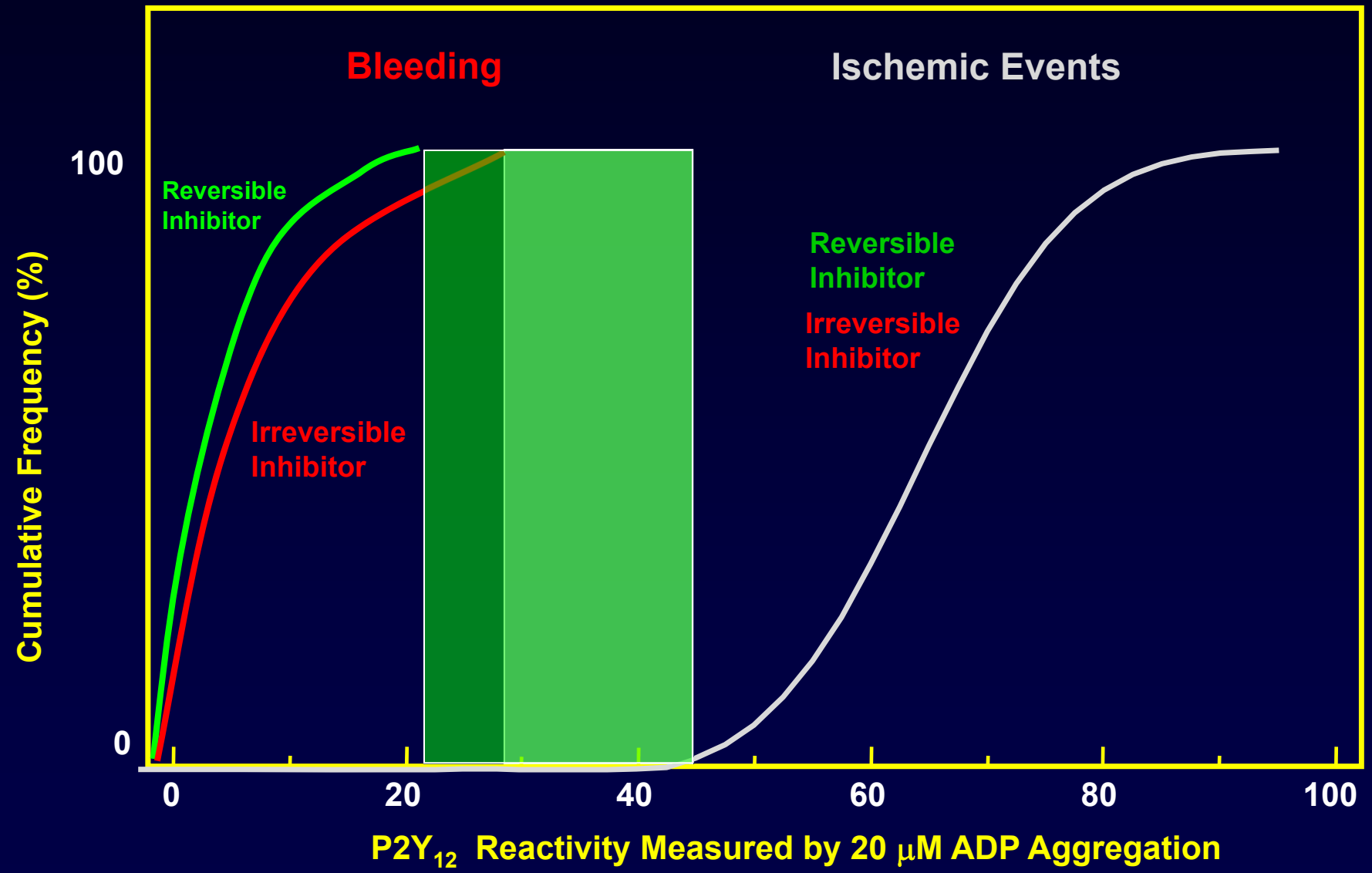
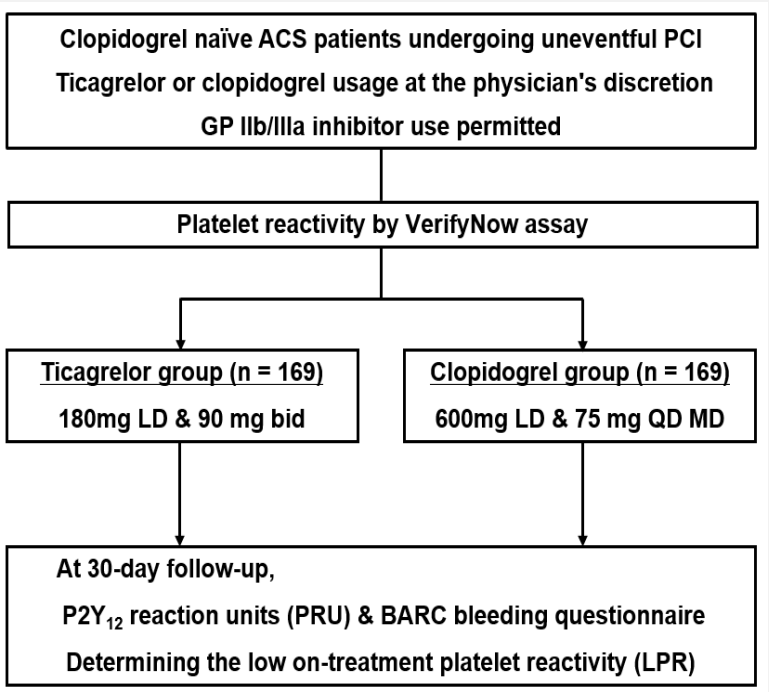
Ticagrelor: Wider Therapeutic Window



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

GNUH experience: Relationship between Platelet Reactivity and BARC Bleeding Episodes During Ticagrelor versus Clopidogrel Treatment

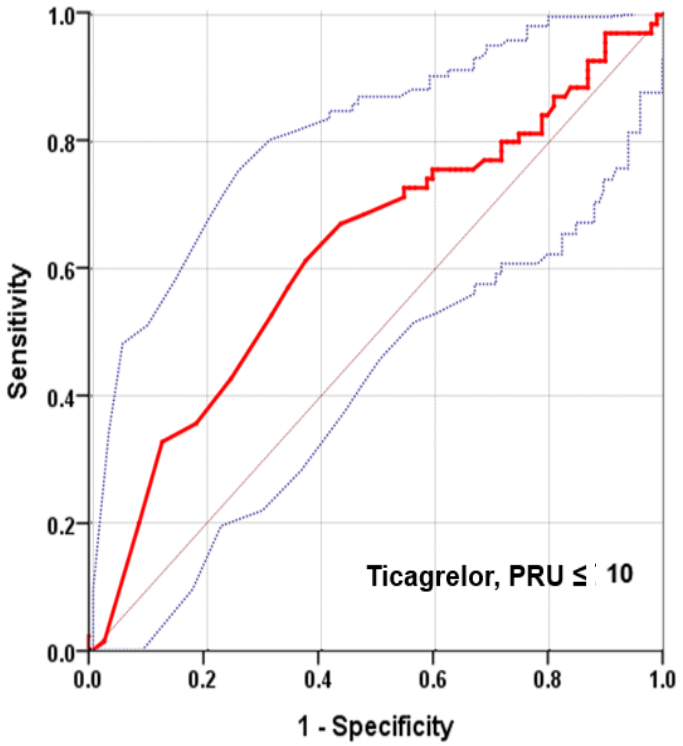


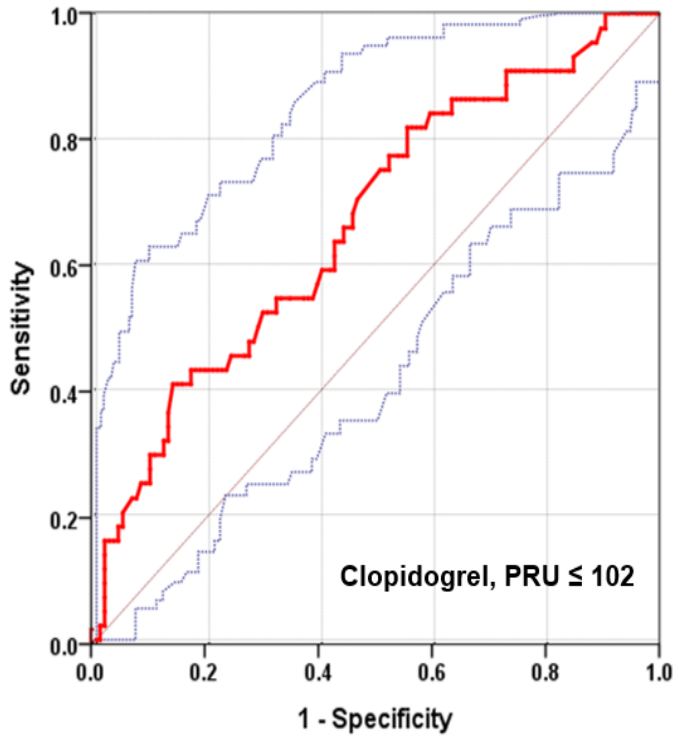
Variables	Ticagrelor	Clopidogrel	P value
$P2Y_{12}$ reaction unit, PRU			
Post-loading	178.7 ± 106.0	220.0 ± 81.3	<0.001
Pre-discharge	66.1 ± 71.7	203.2 ± 78.1	<0.001
30-day follow-up	30.4 ± 44.1	160.9 ± 67.2	<0.001
BARC bleeding during 30 days			
BARC 1	69 (40.8)	44 (26.0)	0.004
BARC 2	3 (1.8)	2 (1.2)	0.652
BARC 1 or 2	70 (41.4)	44 (26.0)	0.003

Kang MG, et al. ESC 2017.

GNUH experience: Relationship between Platelet Reactivity and BARC Bleeding Episodes During Ticagrelor versus Clopidogrel Treatment

PRU Cutoffs for Bleeding (LPR)

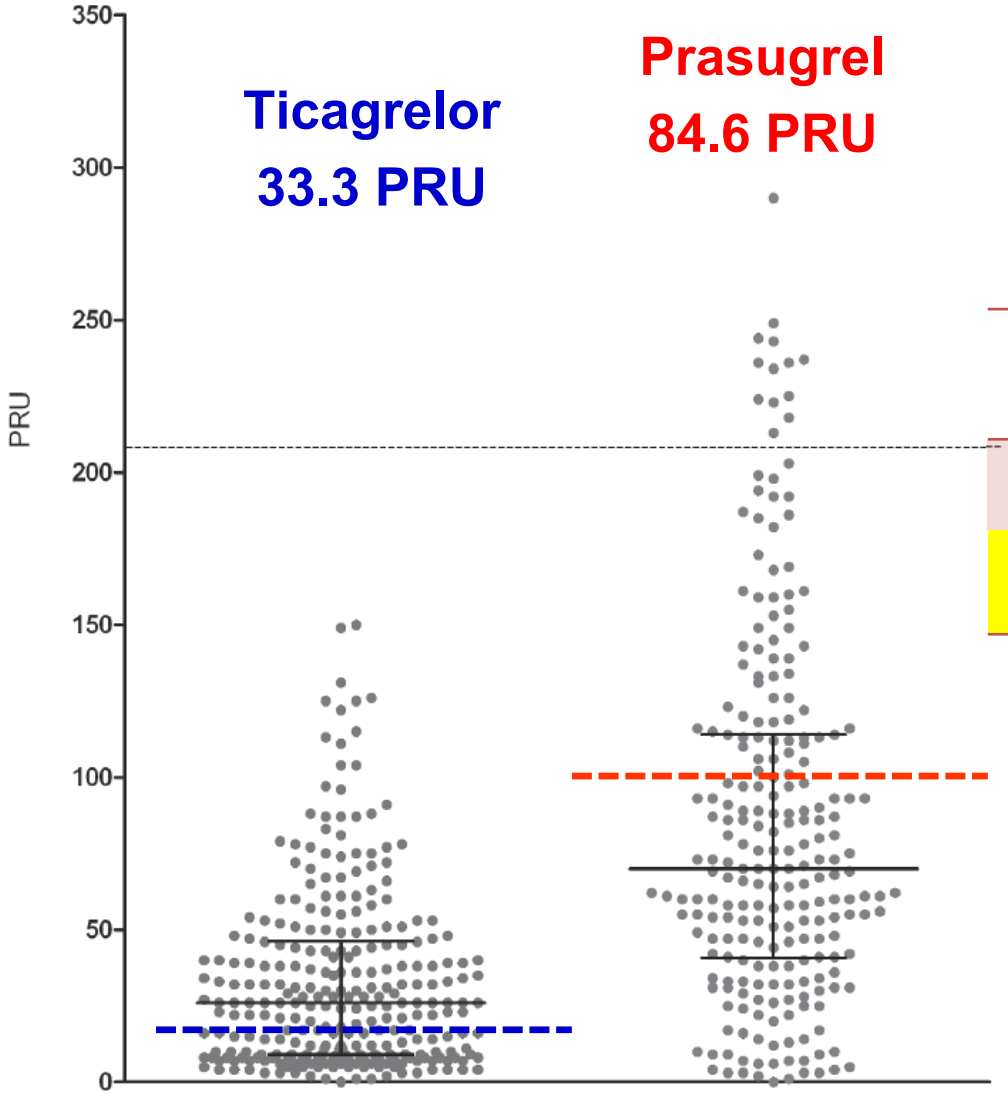




LPR cutoff for BARC bleeding	Sensitivity	Specificity	AUC	95% CI	P value
Ticagrelor, PRU ≤ 10	61.4%	62.3%	0.630	0.543 – 0.717	0.004
Clopidogrel, PRU ≤ 102	40.9%	86.4%	0.671	0.578 – 0.764	0.001

Kang MG, et al. ESC 2017.

Ticagrelor vs. Prasugrel: 1-mo Maintenance

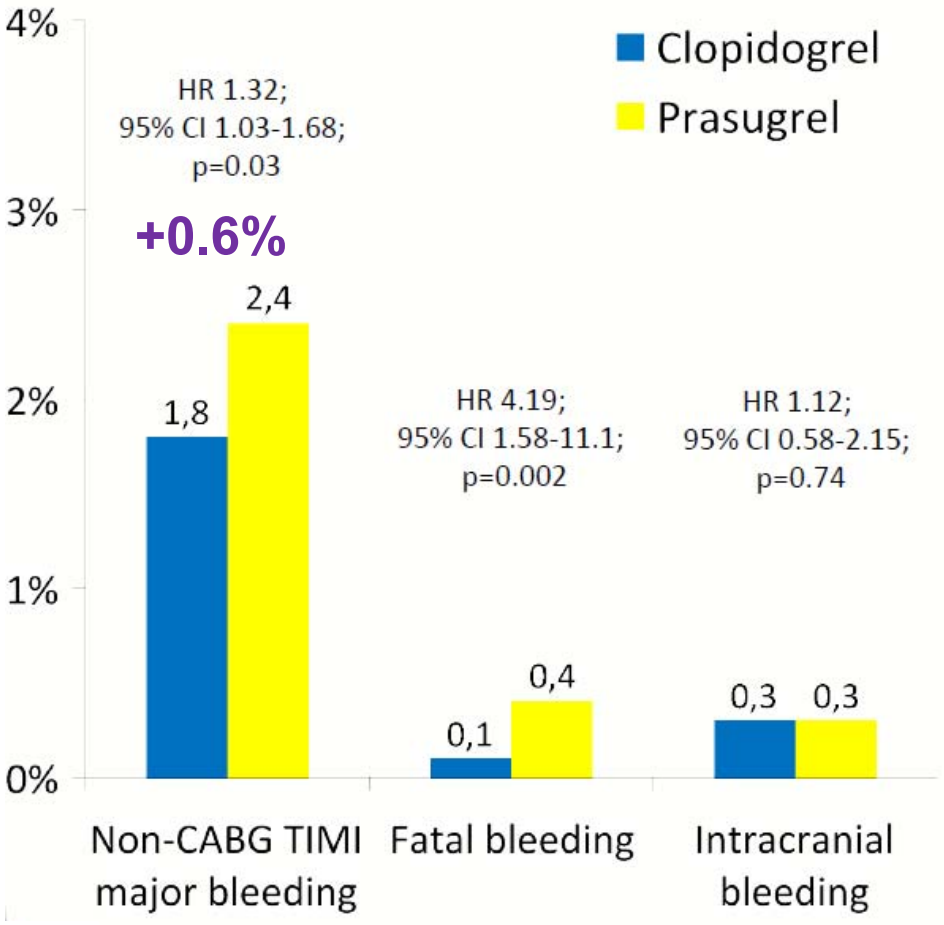


	TICA	PRAS	p
BARC 1	36.7%	28.2%	0.047
BARC 2	**2.1%**	**2.9%**	**0.8**

Alexopoulos D, et al. Thromb Haemost 2014;12.

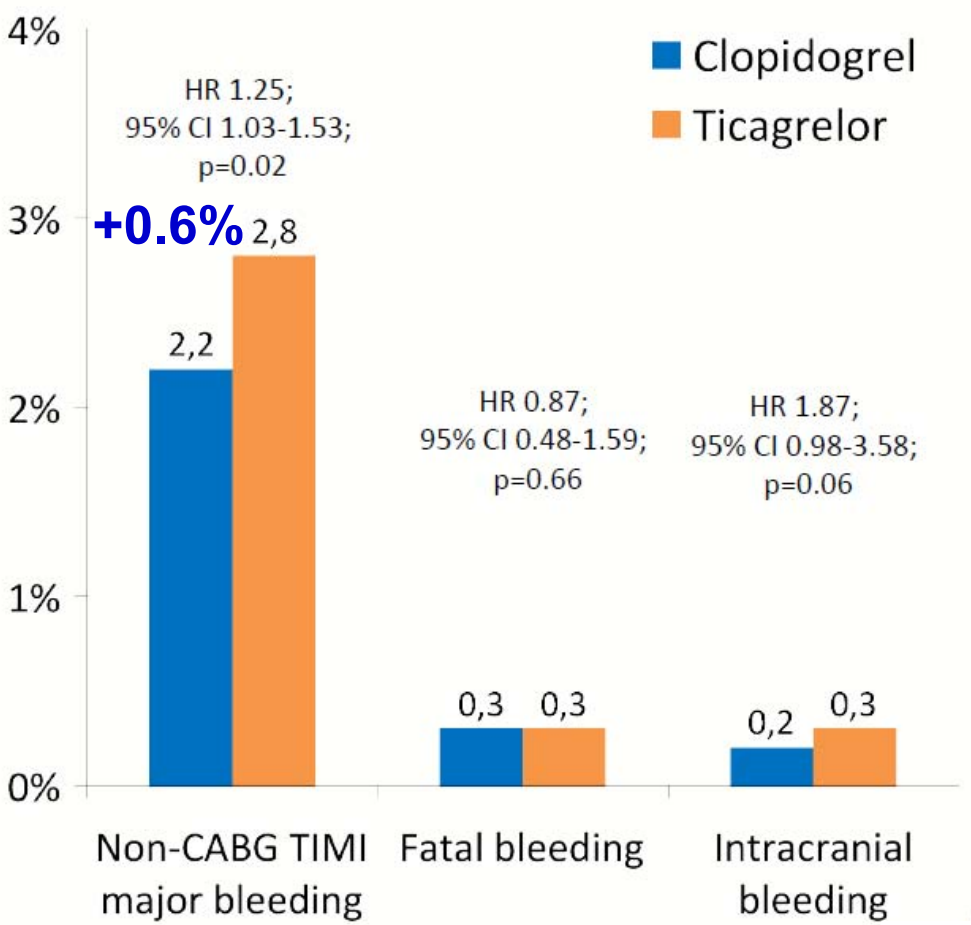
Bleeding on Ticagrelor vs. Prasugrel in ACS Pts

TRITON-TIMI 38



Wiviott et al. NEJM 2007;357:2001-15.

PLATO



Wallentin et al. NEJM 2009;361:1045-57.

Ticagrelor: Wider Therapeutic Window

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Mortality Outcomes with Prasugrel

Prasugrel/TRITON-TIMI 38 – mortality and safety outcomes (15 months)

Endpoint	Prasugrel, n (%) (N=6813)	Clopidogrel, n (%) (N=6795)	*HR (95% CI)	*P* value
Primary endpoint (CV death, MI or stroke)	643 (9.9%)	781 (12.1%)	0.81 (0.73–0.90)	<0.001
CV death	133 (2.1%)	150 (2.4%)	0.89 (0.70–1.12)	0.31
MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
All-cause death	188 (3.0%)	197 (3.2%)	0.95 (0.78–1.16)	0.64
Key safety endpoint (major bleeding)	146 (2.4%)	111 (1.8%)	1.32 (1.03–1.68)	0.03

*HR <1 favours prasugrel

Wiviott SD et al. N Engl J Med 2007;357:2001–2015

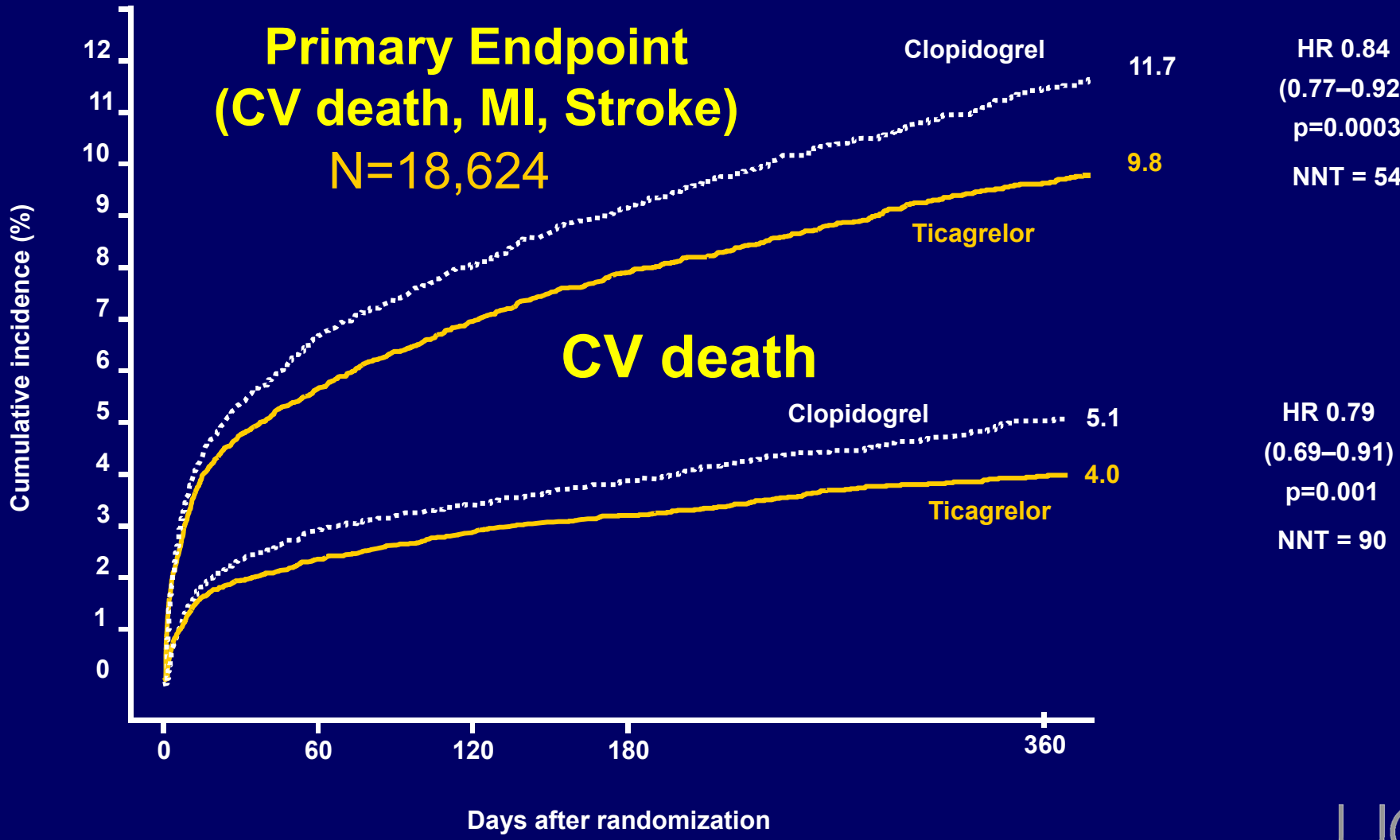
PLATO Analysis: Major Efficacy Outcomes

	Ticagrelor (n=9333)	Clopidogrel (n=9291)	HR* (95% CI)	*P* value
Primary endpoint, n (%)				
CV death + MI + stroke	864 (9.8)	1014 (11.7)	0.84 (0.77–0.92)	**<0.001**
Secondary endpoints, n (%)				
Total death + MI + stroke	901 (10.2)	1065 (12.3)	0.84 (0.77–0.92)	**<0.001**
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1290 (14.6)	1456 (16.7)	0.88 (0.81–0.95)	**<0.001**
MI	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	**0.005**
CV death	**353 (4.0)**	**442 (5.1)**	**0.79 (0.69–0.91)**	**0.001**
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	**0.22**
All-cause death	**399 (4.5)**	**506 (5.9)**	**0.78 (0.69–0.89)**	**<0.001**

*HR <1 favours ticagrelor
CI, confidence interval; HR, hazard ratio
Wallentin L et al. N Engl J Med 2009;361:1045–1057

Ticagrelor: The First and Only Oral Antiplatelet to Demonstrate Superior Reductions in CV Death vs Clopidogrel

PLATO



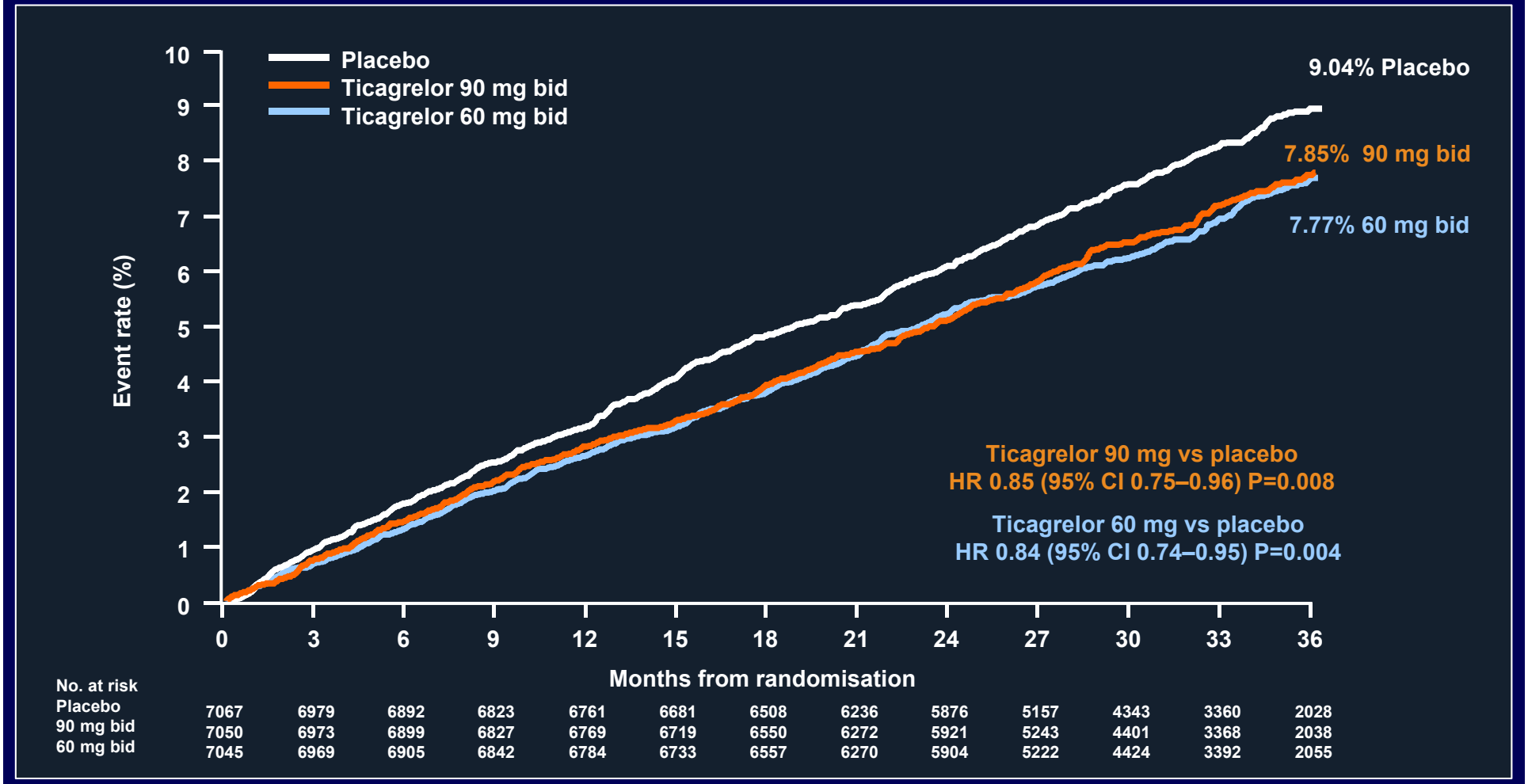
Duke Clinical Research Institute

Wallentin L, et al. *N Engl J Med.* 2009;361:1045-57.

UCR
UPPSALA CLINICAL RESEARCH CENTER

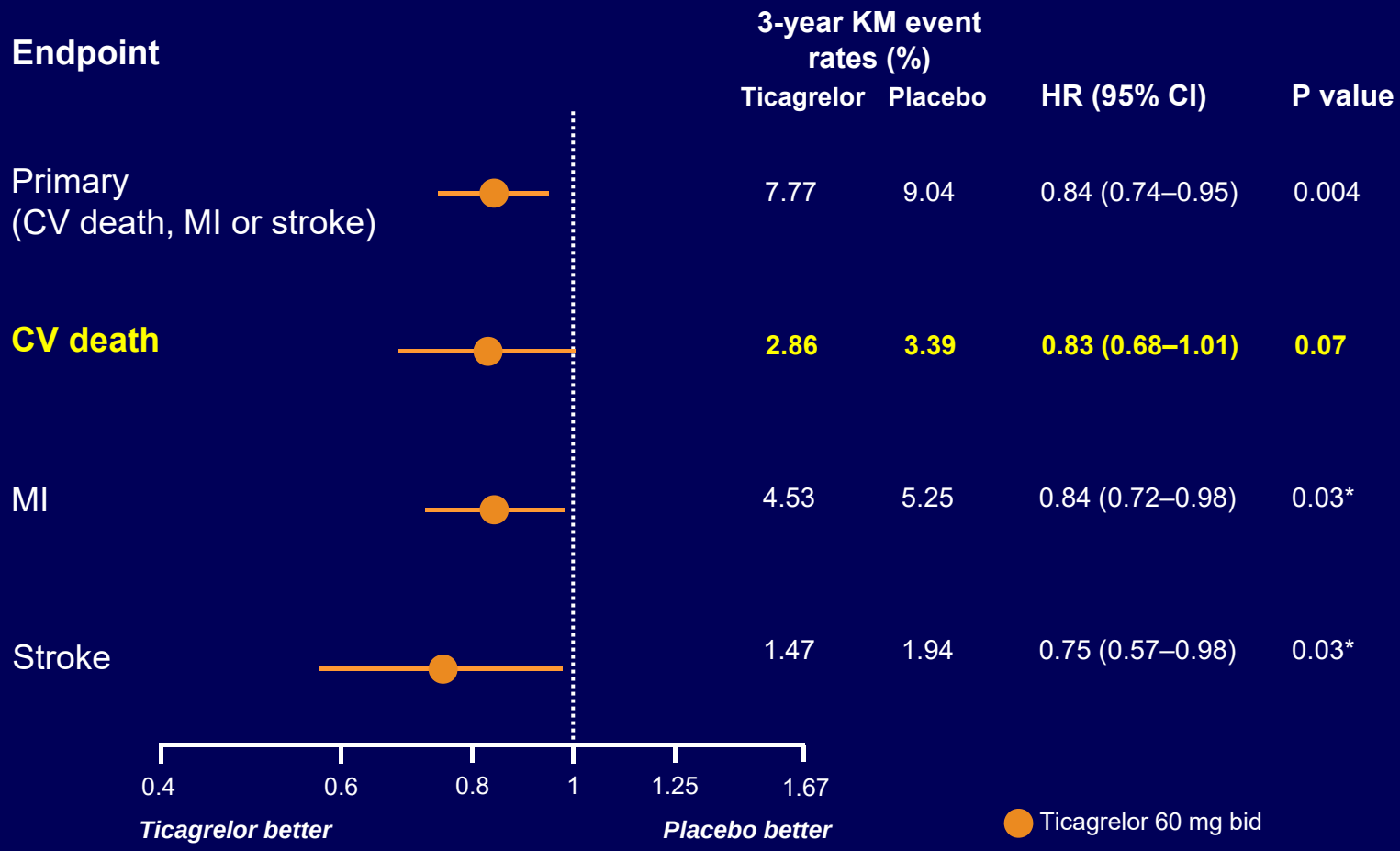
Long-term Secondary Prevention with Ticagrelor

- **PEGASUS**: 21,162 patients with prior MI randomized to ticagrelor 90 mg bid, ticagrelor 60 mg bid, or placebo



Bonaca MP, et al. N Engl J Med 2015;372:1791-800.

Ticagrelor 60mg vs ASA alone:
The only P2Y12 inhibitor proven to reduce CV events over 3years in high-risk post-MI patients
PEGASUS-TIMI 54: Efficacy Endpoints



*Indicates nominal P value; P<0.026 indicates statistical significance

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

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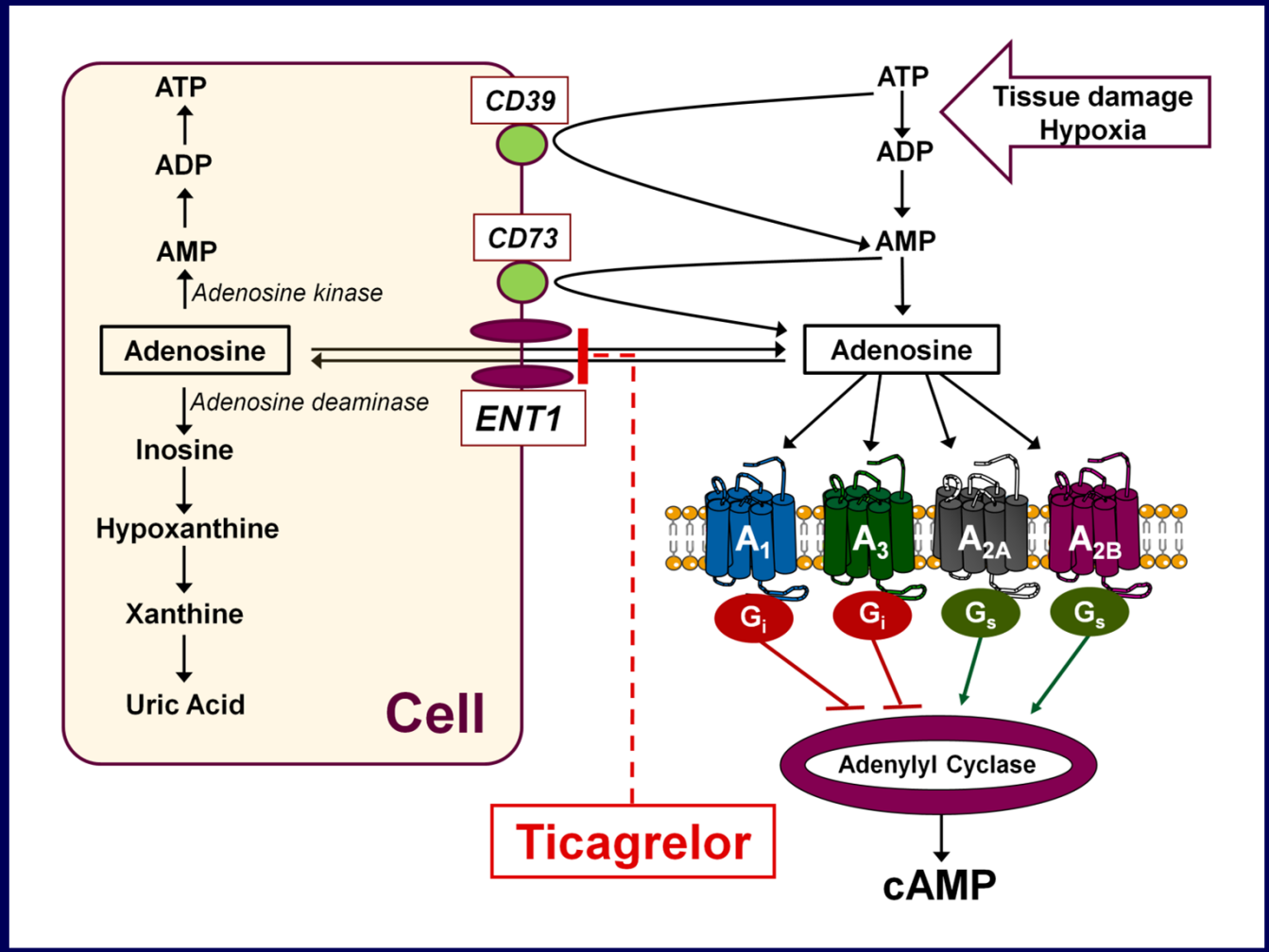
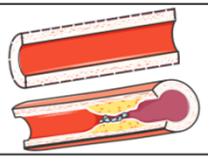
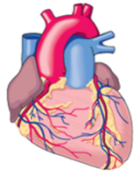
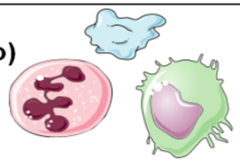
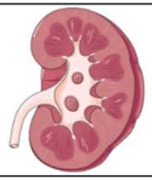
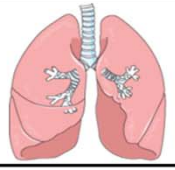
Adenosine Formation, Intracellular Uptake and Metabolism

ENT1 inhibition by ticagrelor results in enhanced response to adenosine, mediated by interaction with adenosine receptors



Overview of Adenosine-related Effects Mediated by Ticagrelor

Ticagrelor has shown adenosine-related attributes *in vitro* and in preclinical models: however, these effects have <u>not been proven</u> to correlate to a clinical effect/benefit

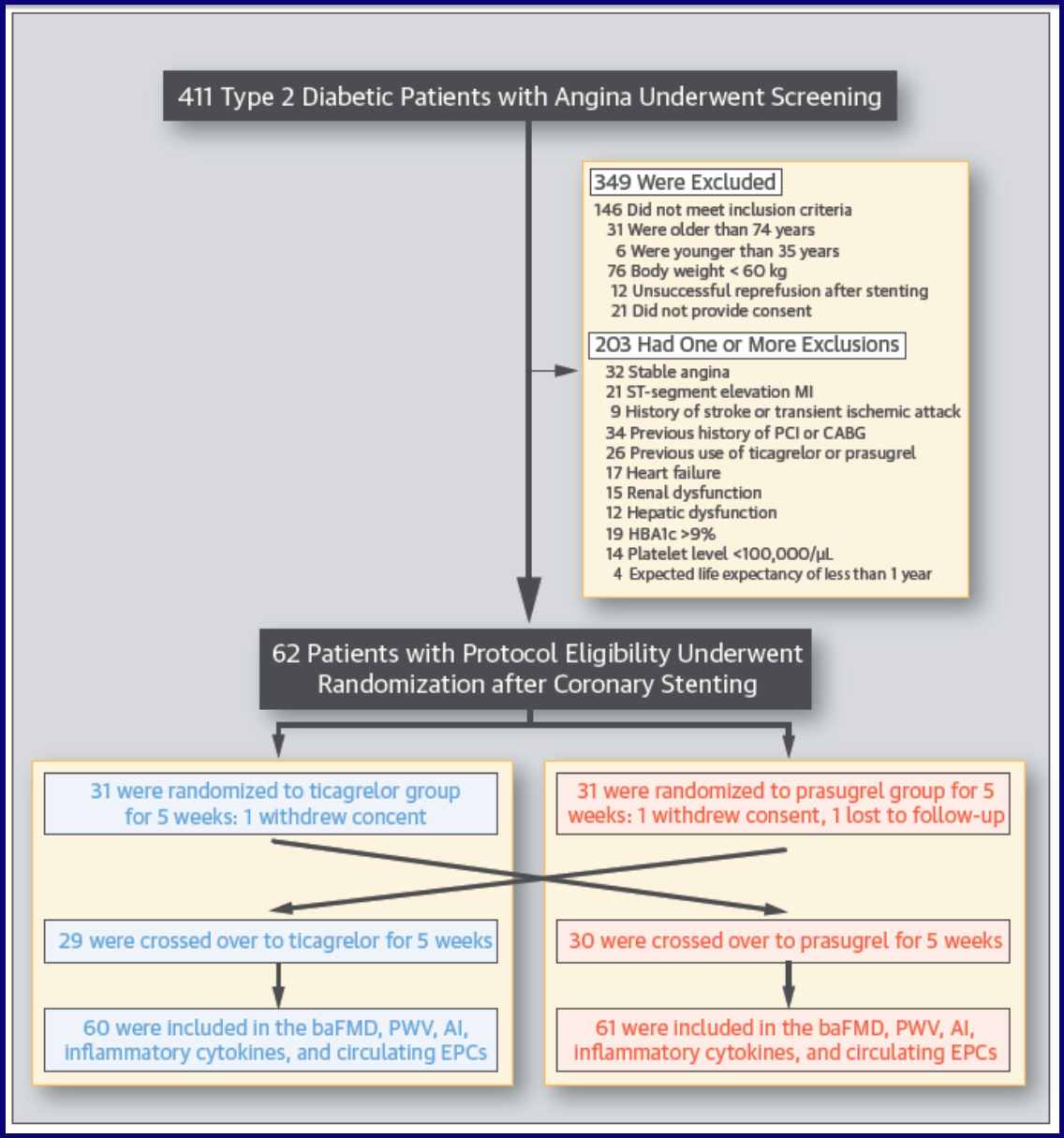
Ticagrelor		Adenosine
↑ Adenosine-induced increases in coronary blood flow (dogs and humans) ↑ Endothelial function (ACS patients)		↑ Vasodilation ↑ Endothelial progenitor cell migration
↓ Incidence of MACE (ACS patients) ↓ CV and all cause mortality (ACS patients) ↑ Incidence of ventricular pauses (ACS patients) ↓ Infarct size (animal models)		↓ Ischemia/reperfusion injury Induces pharmacological preconditioning ↓ Electrical conduction
↑ Adenosine-induced platelet inhibition (in vitro) ↓ Mortality (ACS patients with pulmonary infection)		↑ Platelet inhibition Modulates inflammation
↑ Creatinine levels (ACS patients)		↓ Glomerular filtration
↑ Incidence of dyspnea (ACS patients) ↑ Adenosine-induced dyspnea (healthy subjects)		↑ Incidence of dyspnea

Key studies describing the adenosine-mediated biological effects of ticagrelor

Adenosine-related Effect

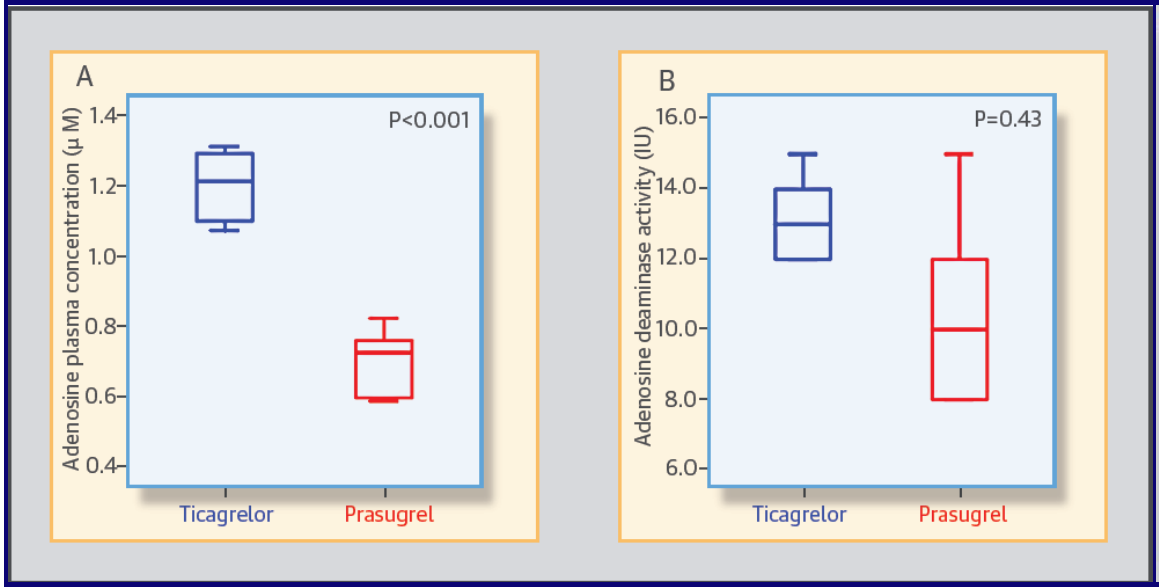
Reference	Main finding	Subjects	Conclusions
Impact of ticagrelor on the biological effects of exogenous adenosine			
van Giezen JJ et al. J Cardiovasc Pharmacol Ther 2012;17:164–172	Ticagrelor dose-dependently increased local blood flow by up to 150% in the coronary artery following infusion of adenosine	Dogs	Ticagrelor increases the effects of exogenous adenosine on blood vessels in dogs
Wittfeldt A et al. J Am Coll Cardiol 2013;61: 723–727	Ticagrelor significantly increased adenosine-induced coronary blood flow velocity (CBFV) versus placebo (P=0.008), and significantly enhanced the sensation of dyspnoea during adenosine infusion (P<0.05)	Healthy volunteers	Ticagrelor increases the effects of exogenous adenosine on blood vessels and the sensation of dyspnoea in humans
Alexopoulos D et al. Circ Cardiovasc Interv 2013;6:277–283	CBFV induced by adenosine infusion was significantly enhanced with ticagrelor compared with prasugrel (P=0.003)	NSTEMI patients undergoing PCI	Ticagrelor increases the effects of exogenous adenosine on blood vessels in ACS patients
Nylander S et al. J Thromb Haemost 2013;11:1867–1876	Platelet aggregation in whole blood was inhibited with adenosine + ticagrelor, and this effect was significantly greater than that of adenosine + prasugrel active metabolite (P<0.01)	Healthy volunteers	Ticagrelor increases the inhibitory effect of exogenous adenosine on platelet aggregation
Impact of ticagrelor on plasma levels of endogenous adenosine and on its biological effects			
Wang K et al. Thromb Haemost 2010;104: 609–617	Ticagrelor reduced infarct size by ~60% compared with clopidogrel	Canine model	Ticagrelor has a $P2Y_{12}$-independent cardioprotective effect
Birnbaum Y et al. J Am Coll Cardiol 2014;63(12 S):A22	Ticagrelor reduced infarct size and this effect was completely reversed by an adenosine receptor antagonist	Rat	$P2Y_{12}$-independent cardioprotective effect of ticagrelor is mediated via adenosine
Bonello L et al. J Am Coll Cardiol 2014;63:872–877	Adenosine plasma concentrations were significantly higher in blood samples taken 6 h after administration of ticagrelor 180 mg compared with clopidogrel 600 mg. *In vitro* uptake of exogenous adenosine by erythrocytes was inhibited by serum from ticagrelor-treated patients but not clopidogrel-treated patients	ACS patients	Concentration of ticagrelor *in vivo* after oral administration is sufficient to inhibit cellular uptake of adenosine

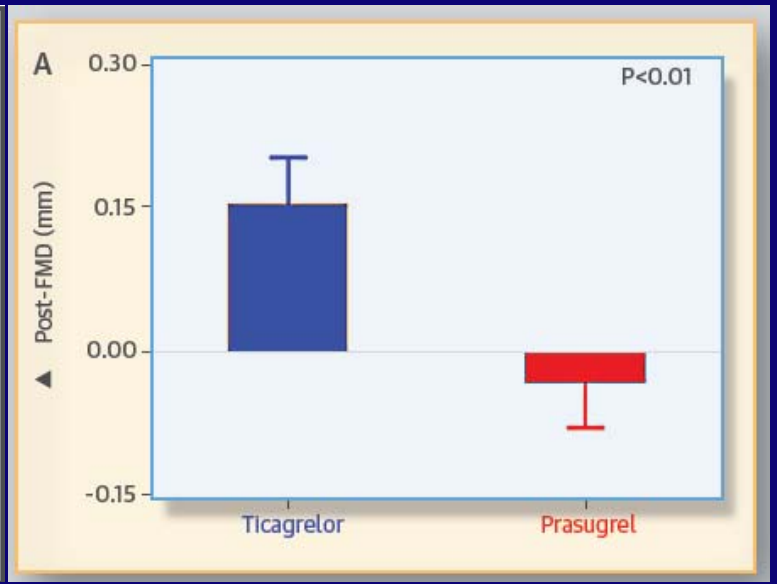
TICA vs. PRAS in Diabetic Patients

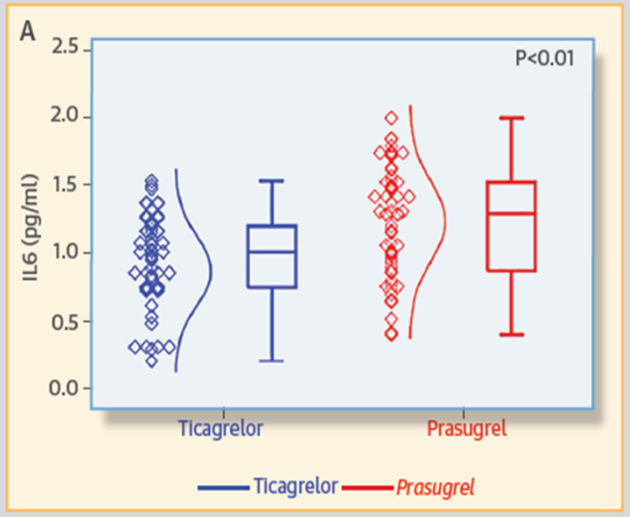


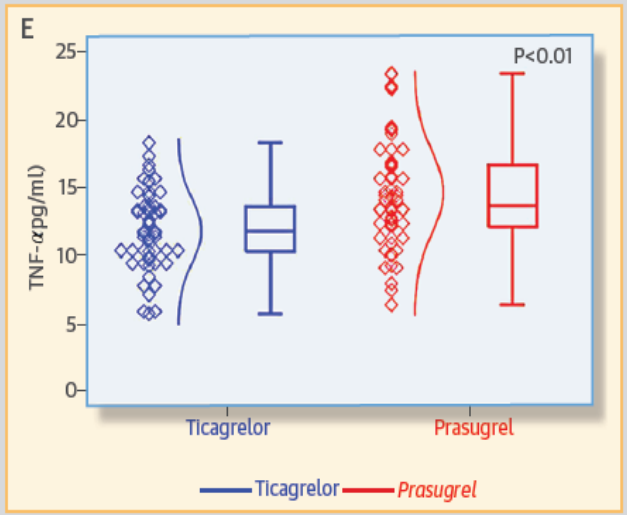
Jeong HS, et al. JACC CV Interv 2017;10:1646-58.

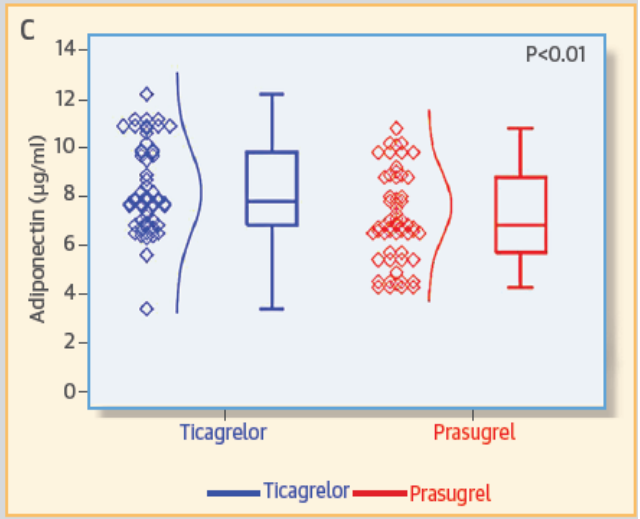
TICA vs. PRAS in Biomarkers





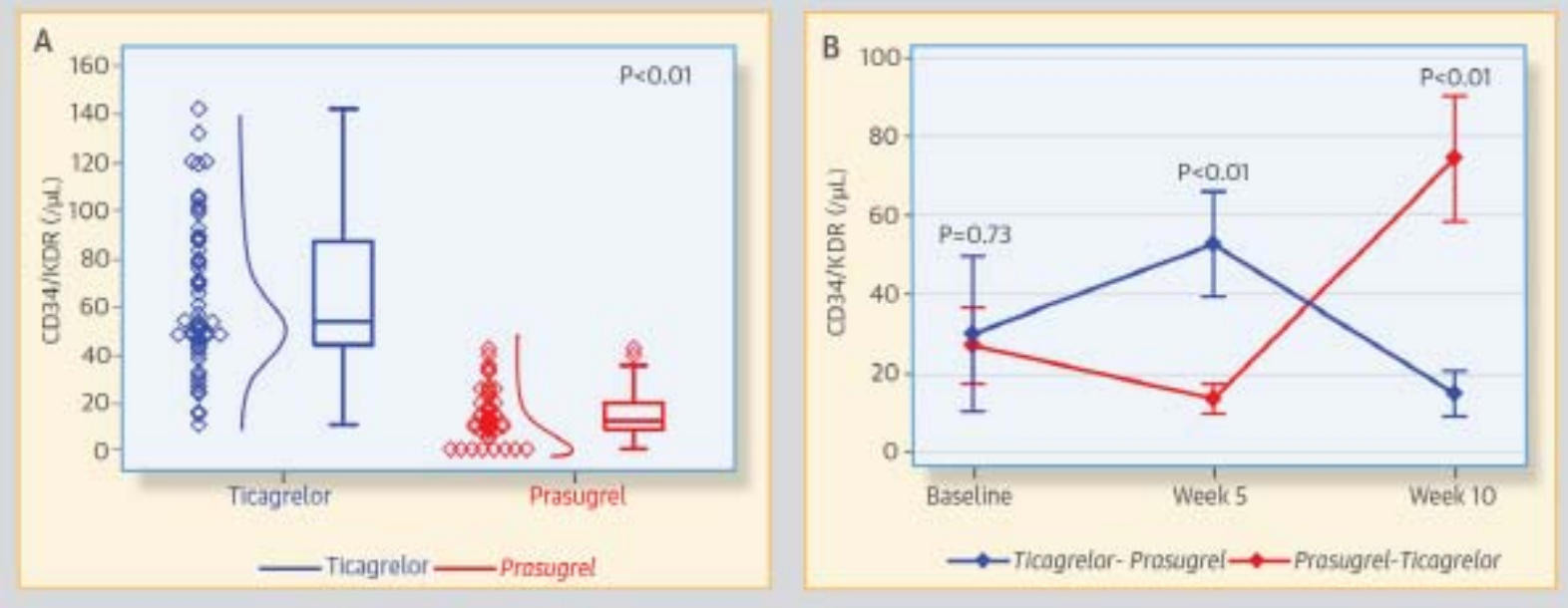


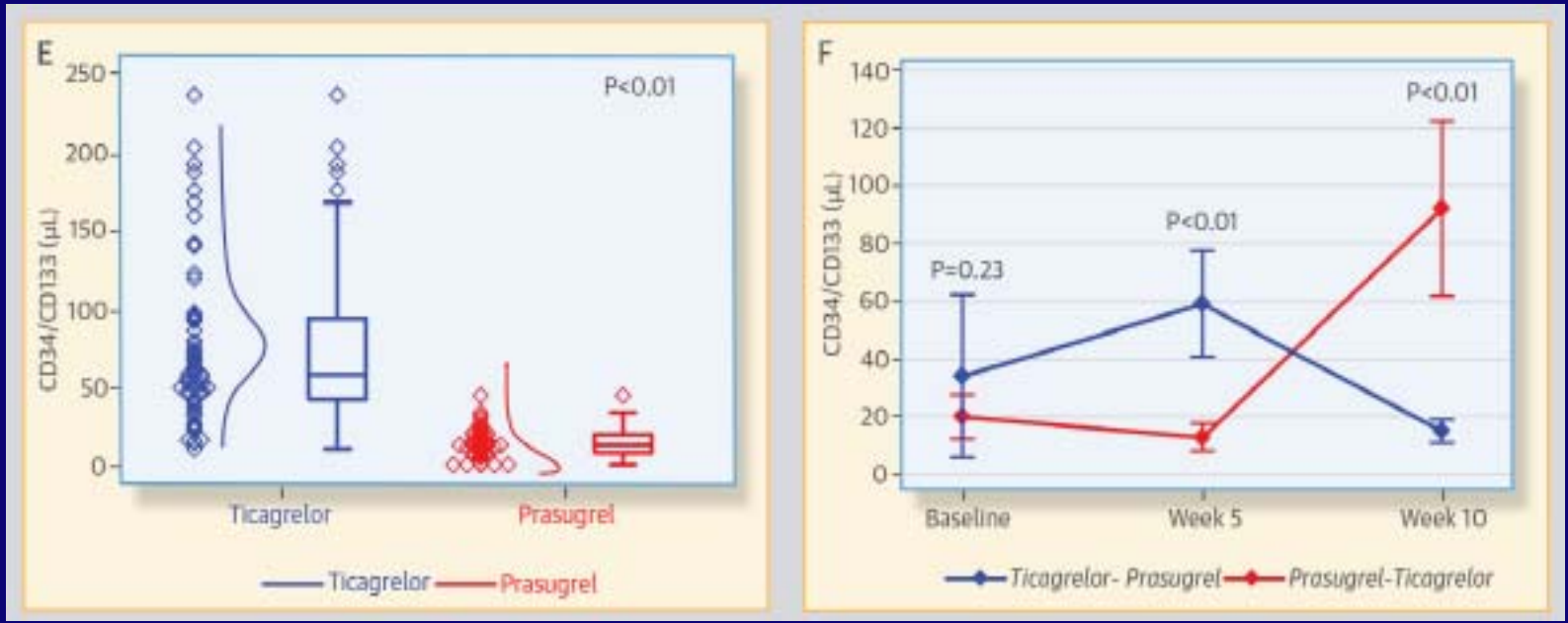




Jeong HS, et al. JACC CV Interv 2017;10:1646-58.

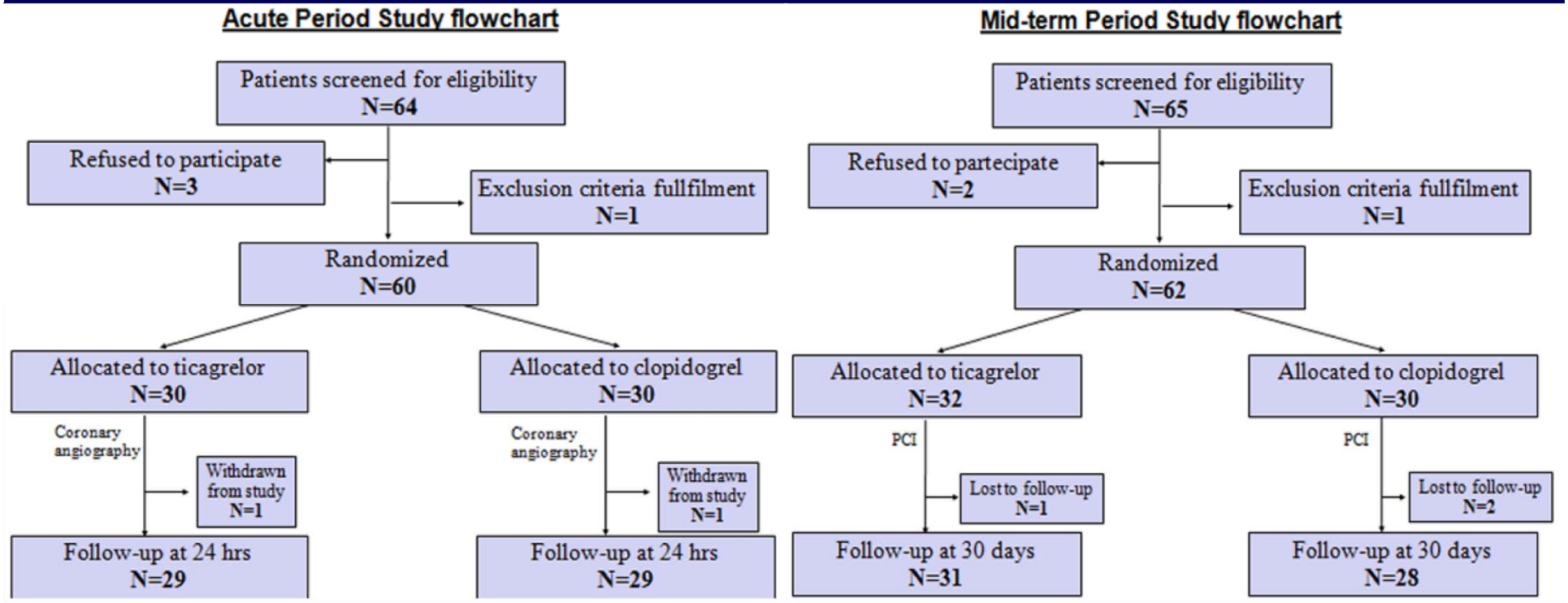
TICA vs. PRAS in Circulating EPCs





TICA vs. CLPD on Aortic Stiffness in CAD Pts

A randomized, assessor-blinded, parallel-group trial (n = 117)



Vlachopoulos C, et al. JAHA 2019;8:e012521.

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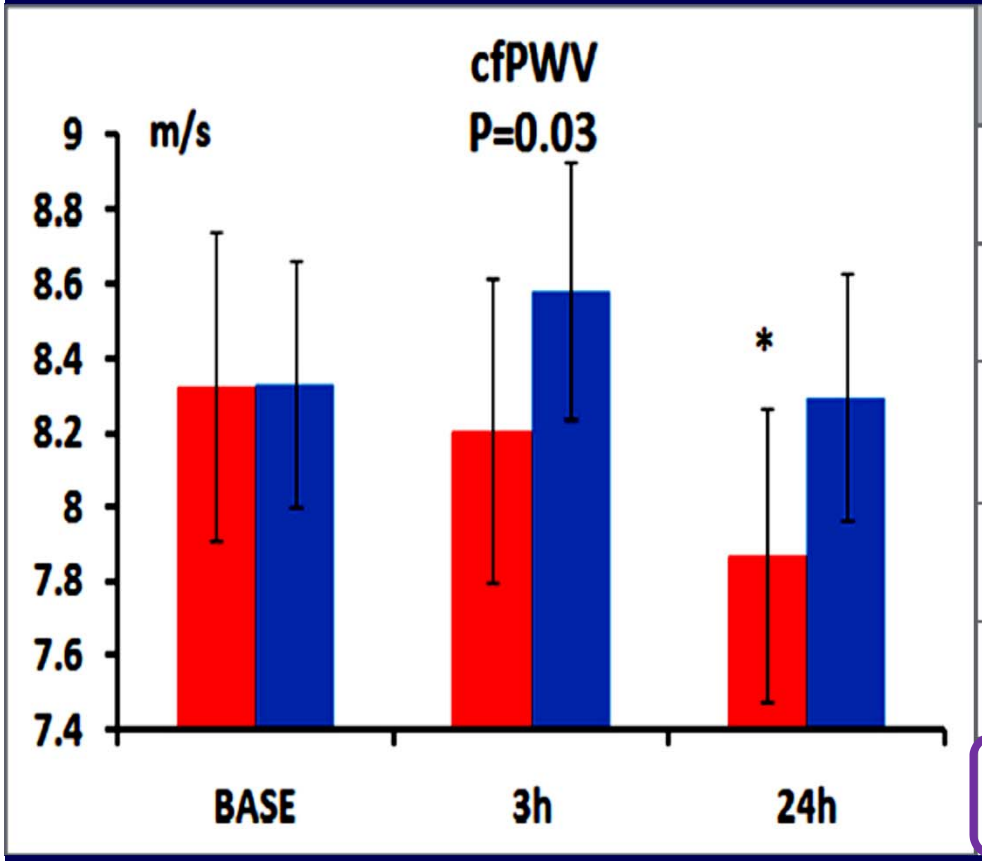


	Ticagrelor		Clopidogrel		
	Base	30 Days	Base	30 Days	*P* Value*
Systolic BP, mm Hg	133±15	132±11	129±12	133±8	
	−0.8±14		3.5±10		0.30
Diastolic BP, mm Hg	77±10	77±9	76±9	79±8	
	−0.4±9		2.3±10		0.37
Pulse pressure, mm Hg	55±11	55±9	52±9	54±5	
	−0.3±9		1.2±9		0.64
Mean BP, mm Hg	96±11	95±9	93±9	95±12	
	−0.7±11		2.6±11		0.49
Heart rate, bpm	68±11	71±6	65±8	71±6	
	3±9		6±8†		0.28
cfPWV, m/s	9.6±1.6	9.1±1.3	9.1±1.3	9.1±1.4	
	0.43±0.57‡		0.12±0.14		<0.001

Vlachopoulos C, et al. JAHA 2019;8:e012521.

Ticagrelor Reduces Cardiac Damage to a Larger Extent Than Clopidogrel: CMR Analysis

Analyses of Cardiac Damage and Function in Pig Model: 3T-CMR Analyses and Troponin-I Levels 24 Hours After MI Induction

		Placebo-Control	Clopidogrel	Ticagrelor	Ticagrelor+8SPT
CMR analyses of cardiac anatomic parameters	LV mass, g	70.0 (64.1–73.7)	72.2 (69.3–74.7)	70.6 (67.9–74.4)	66.5 (65.0–70.2)
	Edema, g LV	23.4 (20.9–31.1)	21.6 (19.5–25.2)	16.3 (14.2–19.9)*‡	24.6 (22.8–25.3)
	Edema, % LV	36.2 (33.9–43.2)	30.1 (26.6–34.5)	23.1 (20.2–24.4)†§	36.8 (33.6–39.4)
	Infarct mass, g LV	22.8 (17.3–25.8)	15.7 (14.2–16.2)*	12.0 (10.6–12.9)†§	14.9 (14.6–16.1)*
	Necrosis, % LV	31.1 (25.9–39.1)	20.9 (19.3–22.8)†	16.4 (15.5–17.9)†§	22.4 (21.8–23.9)*
	No reflow, g LV	4.6 (2.1–6.0)	2.0 (1.5–2.8)*	2.1 (1.8–3.0)*	2.2 (2.0–2.6)*
CMR analyses of cardiac functional parameters	LVEF, %	43.0 (42.0–43.6)	47.2 (45.4–48.2)†	47.2 (45.4–51.0)*	48.7 (46.6–51.0)*
	LVEDV, mL	93.0 (87.6–98.1)	73.7 (68.9–81.3)†	77.4 (71.8–89.2)*	84.4 (76.9–86.8)*
	LVESV, mL	54.0 (49.2–55.6)	39.5 (36.3–41.9)†	39.2 (37.3–46.0)*	44.2 (40.4–45.7)*
Serum troponin levels	Troponin, ng/mL	19 (16.5–21.7)	13.4 (13.0–14.0)†	10.9 (9.3–11.4)†§	14.2 (12.2–16.1)*

Placebo-control animals n=7; clopidogrel-treated animals n=8; ticagrelor-treated animals n=8; ticagrelor+8SPT administered animals n=7. CMR indicates cardiac MRI; LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; and 8SPT, 8-(*p*-sulfophenyl)theophylline. *$P<0.05$ versus placebo-control animals; †$P<0.005$ versus placebo-control animals; ‡ $P<0.05$ versus clopidogrel-treated animals; § $P<0.005$ versus clopidogrel-treated animals.

Vilahur et al. *Circulation. 2016;134:1708–1719.*

Effect of TICA vs. CLPD in Infarct Size (SMC. N=110 STEMI)

CMR at 7days	Ticagrelor (n = 45)	Clopidogrel (n = 50)	p Value
LV end diastolic volume (ml)	138.1±31.9	140.7±28.2	0.68
LV end systolic volume (ml)	63.2±24.8	67.2±22.2	0.42
LV ejection fraction (%)	55.2±9.5	52.8±8.7	0.21
LV mass (ml)	105.7±23.5	110.7±27.3	0.34
Infarct size (%LV)	21.5±10.9	26.5±11.3	0.03
Area at risk (%LV)	30.6±13.3	36.2±13.0	0.04
Myocardial salvage index (%)	41.9±10.8	38.3±8.7	0.08
Extent of MVO (%LV)	3.9±4.1	6.4±6.3	0.02
Mean transmurality score	1.9±0.5	2.1±0.4	0.06
Number of segment with transmural infarction ≥75%	2.0 (1.5-5.0)	4.0 (2.0-6.0)	0.074

Kim EK, Hahn JY, et al. JACC 2017;69:2098.

Clinical Benefit of Ticagrelor in AMI Patients

Reversible Binding & Maintaining Concentration

Confirmative evidences from Large-scale RCTs

Adenosine-related Effect

Potential Pleiotrophic Effect

PLATO: Causes of Death

Death caused by or related to infection or bleeding

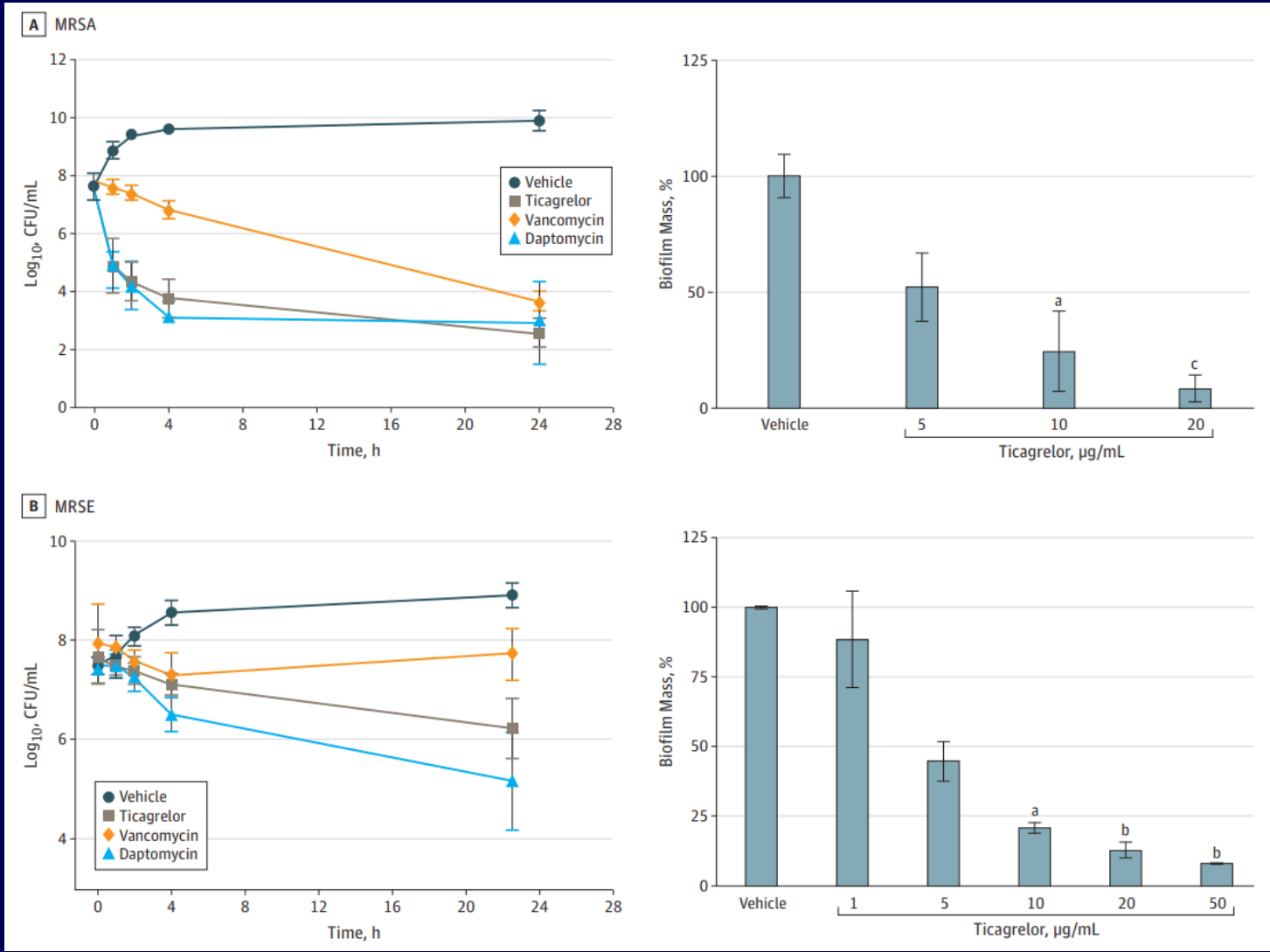
	Ticagrelor, n/N (%)	Clopidogrel, n/N (%)	HR* (95% CI)
Infection	51/9235 (0.5)	76/9186 (0.8)	0.67 (0.47–0.95) ***P*=0.03**
Bleeding	42/9333 (0.5)	42/9291 (0.5)	0.99 (0.65–1.53) ***P*=1.00**

- Significantly fewer cases of infection as either the direct or contributing cause of death with ticagrelor versus clopidogrel
- No significant difference in deaths due to bleeding

Varenhorst C et al. Eur Heart J 2013;34(Suppl 1):827 (data presented at ESC, 2013)

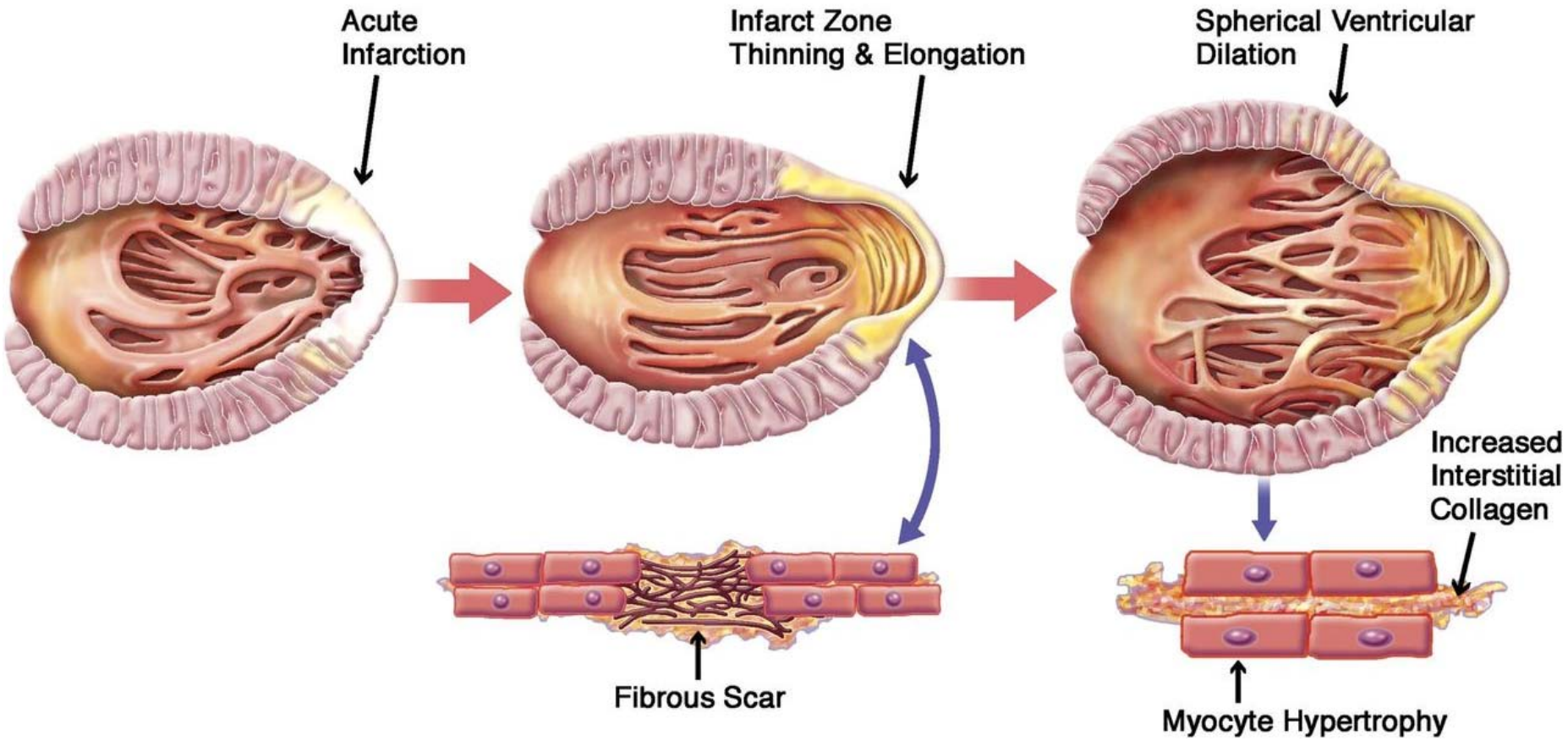
Effect of *Ticagrelor* in Conventional Antiplatelet Dosages Against Antibiotic-Resistant Gram-Positive Bacteria

Time-kill assays & Biofilm formation test



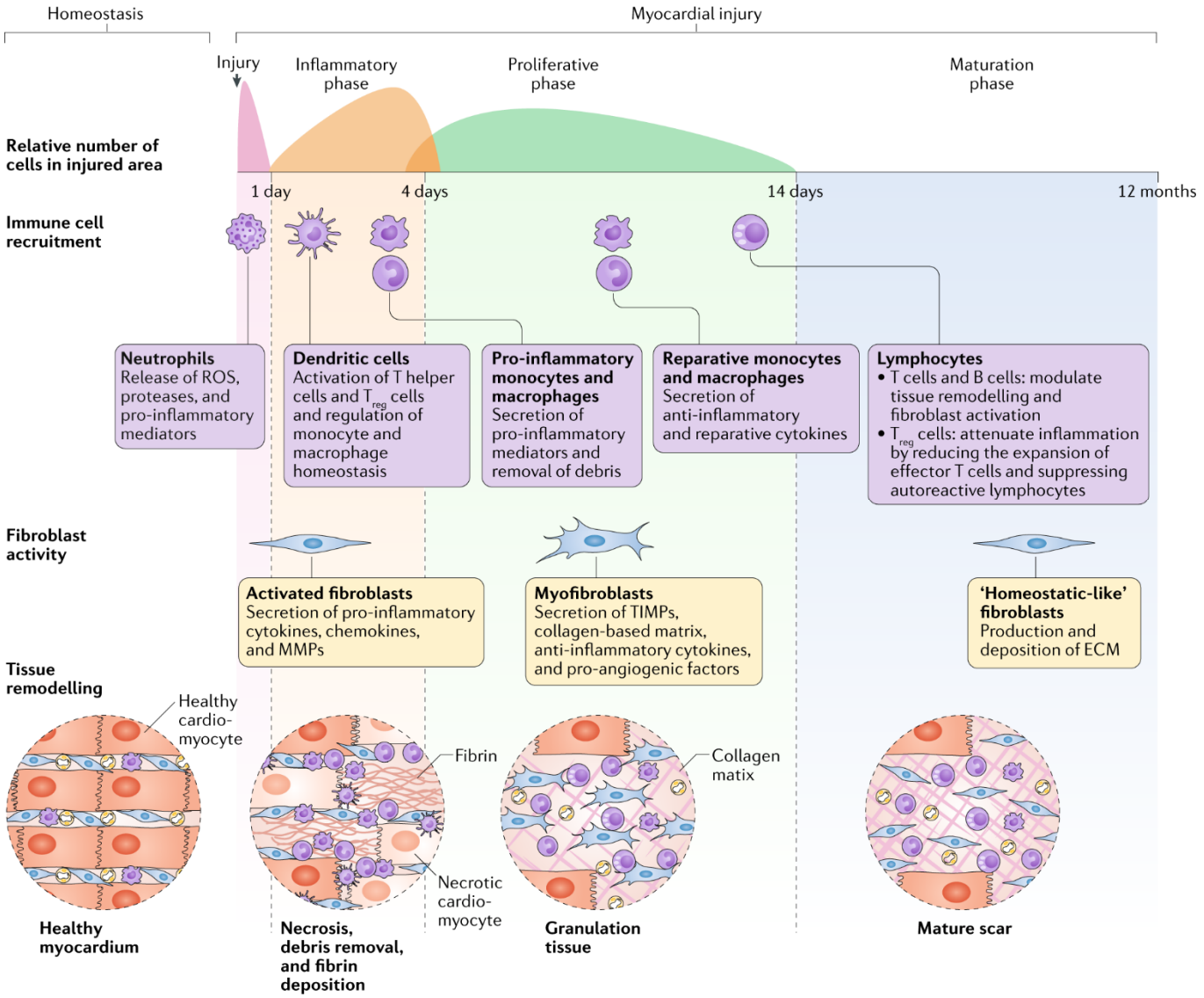
Lancellotti P, et al. JAMA Cardiology 2019.

Sequalae of MI: LV Remodeling in HF



Konstam MA, et al. JACC CV Imag 2011;4:98-108.

Cardiac Repair after Myocardiac Injury



Forte E, et al. Nat Rev Cardiol. 2018;15:601-16.

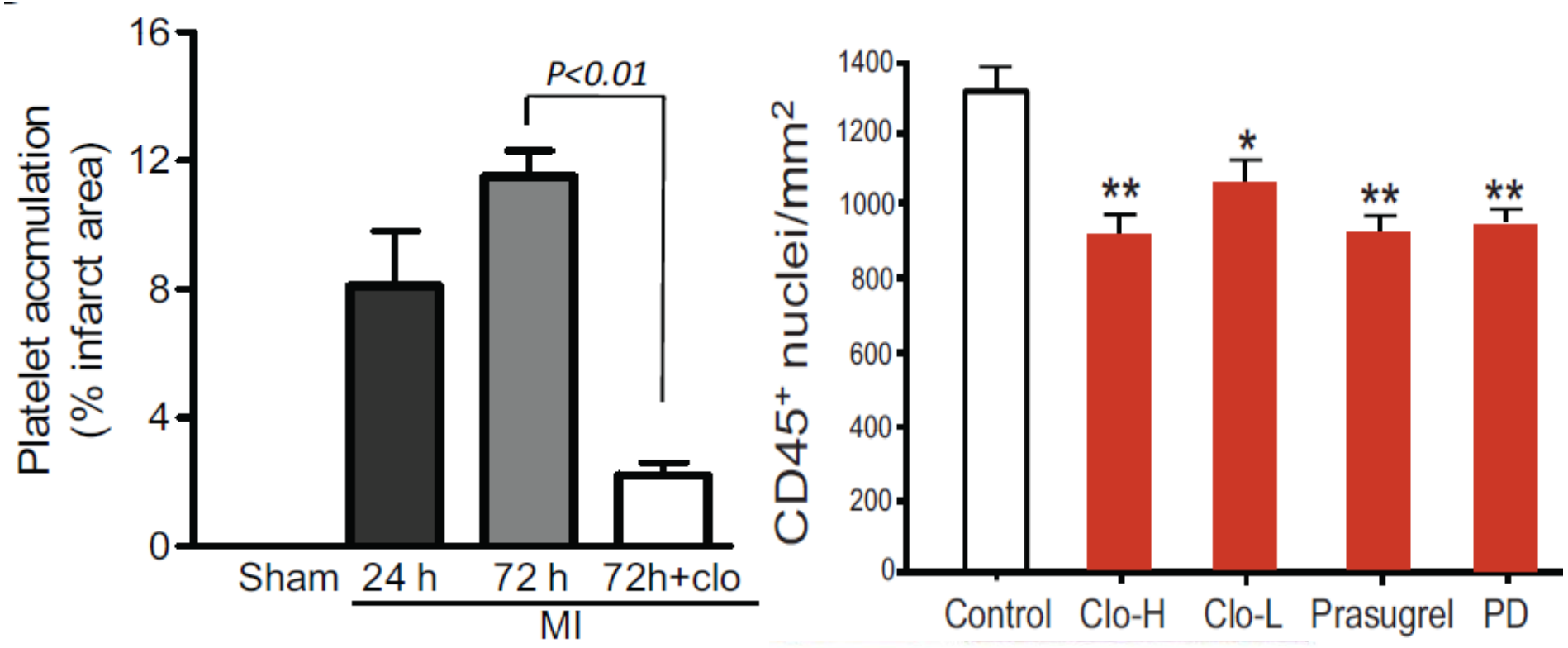
Platelet-Leukocyte Linkage in Infarcted Myocardium

MI model (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

Infarcted myocardium



Gyeongsang National University Hospital

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

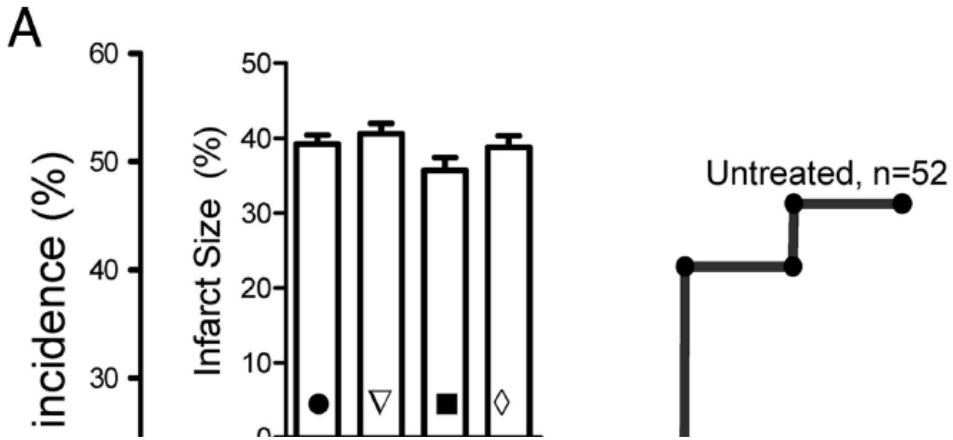
Role of Platelets for Post-MI LV Remodeling

MI model (C57BL/6 mice)

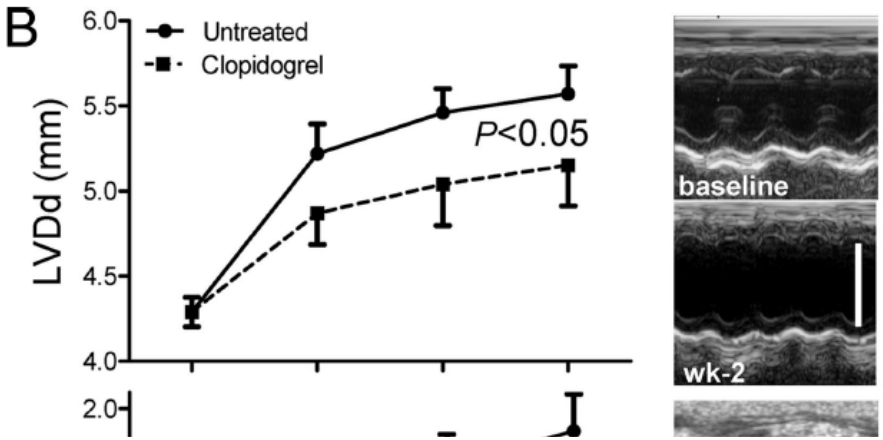
Randomized treatment started 2 hrs after MI and lasted for 3 days

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

Acute phase: LV rupture



Chronic phase: LV remodeling



- Role of platelets in post-MI LV remodeling: Important triggers for the first wave of inflammatory cells accumulating within the infarcted myocardium

HEALING-AMI: High platElet inhibition with ticAgrelor to improve LV remodeLING in patients with ST-segment elevAtion Myocardial Infarction:

A randomized, open-label, multi-center trial

Young-Hoon Jeong, MD and Yongwhi Park, MD
on behalf of the HEALING-AMI trial investigators

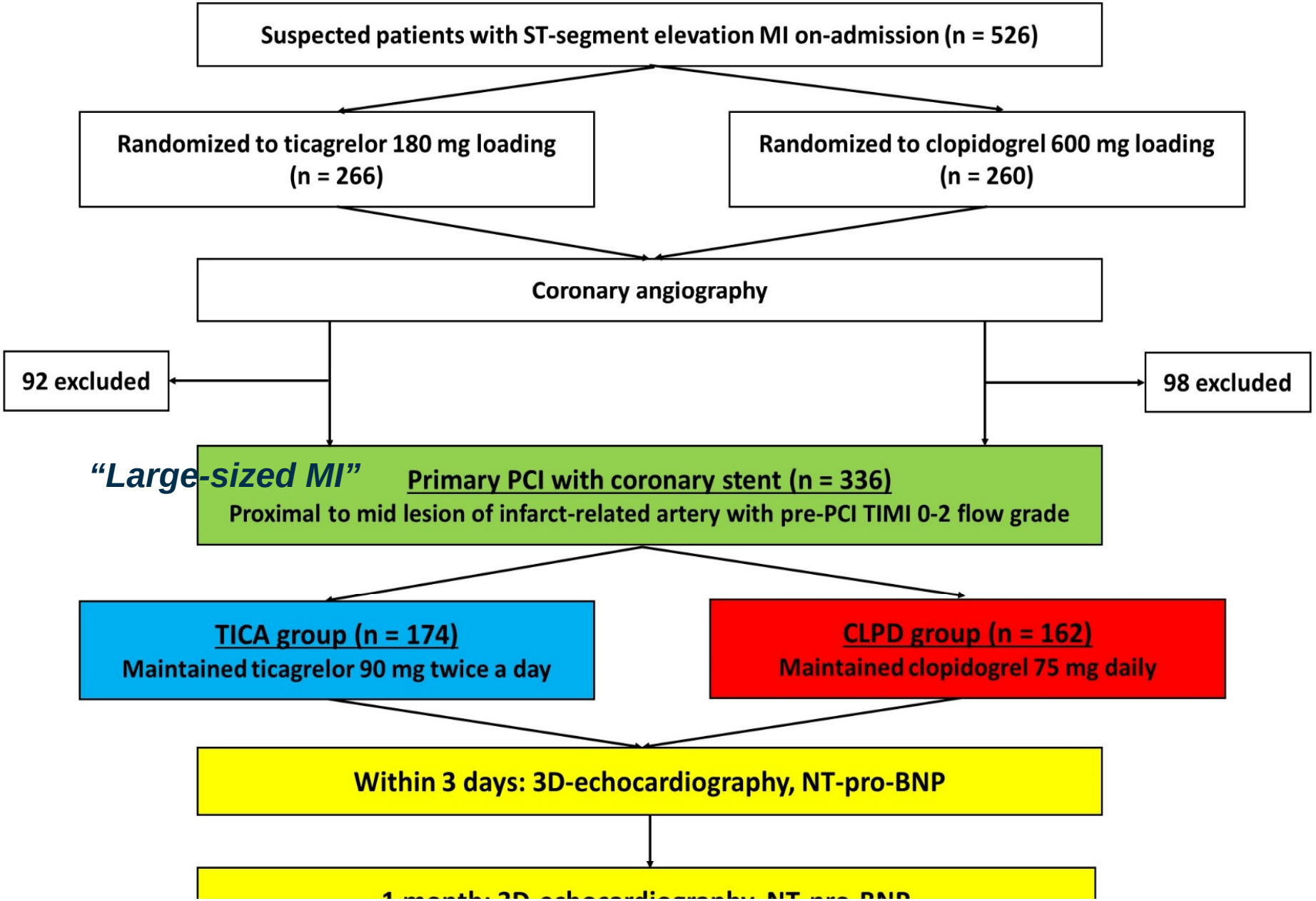
Gyeongsang National University Changwon Hospital

Study Endpoints

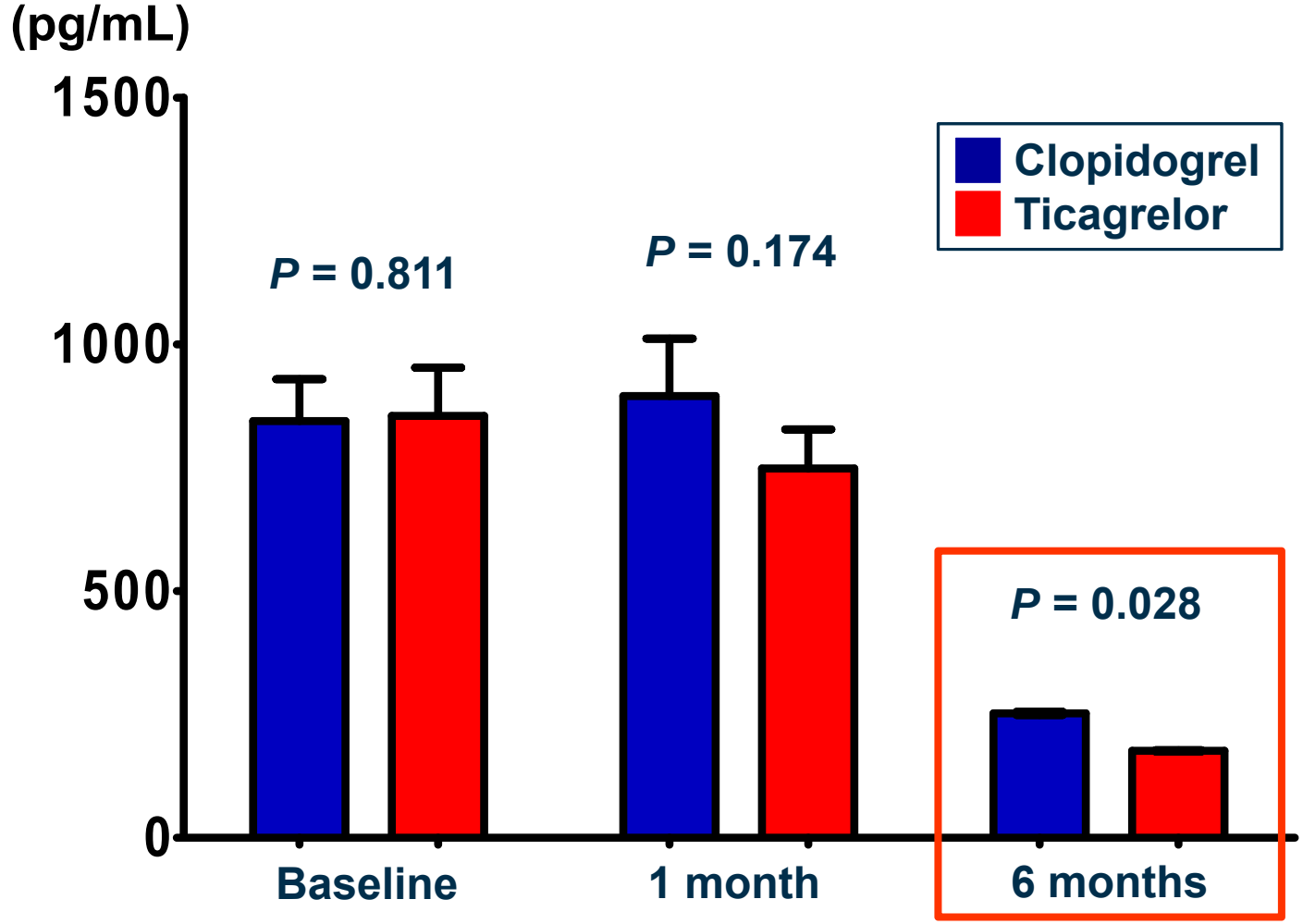
- **Co-primary endpoints**
  - LV remodeling index
  - NT-pro-BNP at 6-month
- **Secondary endpoints**
  - Changes between baseline and 6-month follow-up
    - LV end-systolic/end-diastolic volume indices (mL/m^2)
    - LV ejection fraction (%)
  - Prevalence of positive LV remodeling (LVRI > 20%)

$$\text{LV remodeling index} = \frac{\text{LVEDV}_{\text{follow-up}} - \text{LVEDV}_{\text{baseline}}}{\text{LVEDV}_{\text{baseline}}} \text{ X } 100\ (\%)$$

Study Flow


Suspected patients with ST-segment elevation MI on-admission (n = 526)
Randomized to ticagrelor 180 mg loading (n = 266)
Randomized to clopidogrel 600 mg loading (n = 260)
Coronary angiography
92 excluded
98 excluded
"Large-sized MI"
Primary PCI with coronary stent (n = 336)
Proximal to mid lesion of infarct-related artery with pre-PCI TIMI 0-2 flow grade
TICA group (n = 174)
Maintained ticagrelor 90 mg twice a day
CLPD group (n = 162)
Maintained clopidogrel 75 mg daily
Within 3 days: 3D-echocardiography, NT-pro-BNP

Co-primary Endpoints:
NT-pro-BNP at 6-month F/U



Prevalence of Positive LV Remodeling (LVRI >20%) and "High NT-pro-BNP" at 6 mo. (≥ 800 pg/mL)*

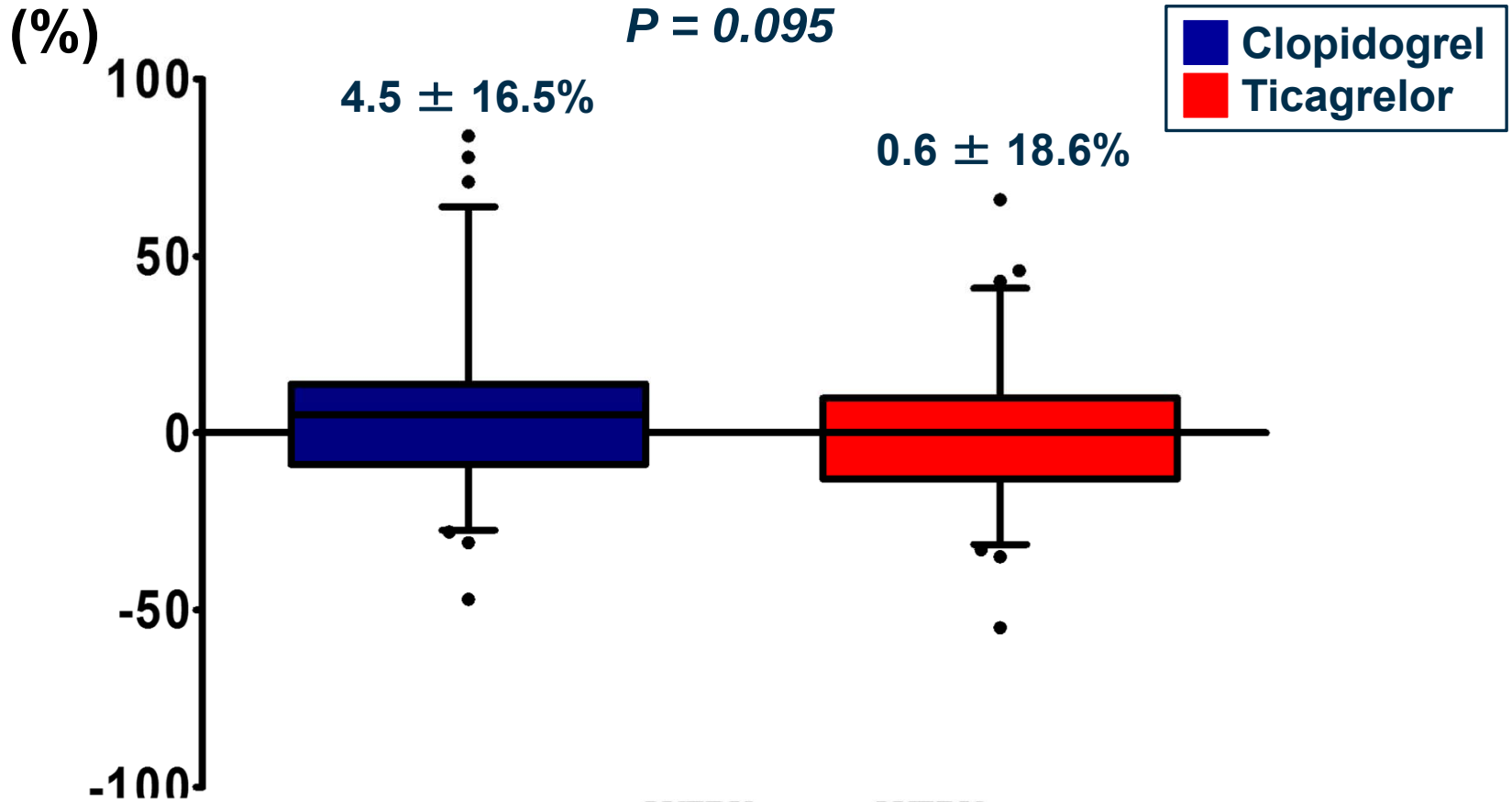
	LVRI ≤ 20%	LVRI > 20%	*P* Value
CLPD, n (%)	115 (82.7)	24 (17.3)	0.622
TICA, n (%)	119 (85.6)	20 (14.4)	

	NT-pro-BNP < 800	NT-pro-BNP ≥ 800	*P* Value
CLPD, n (%)	123 (93.2)	9 (6.8)	0.002
TICA, n (%)	131 (100)	0 (0)	

LVRI = left ventricular remodeling index; CLPD = clopidogrel; TICA = ticagrelor.

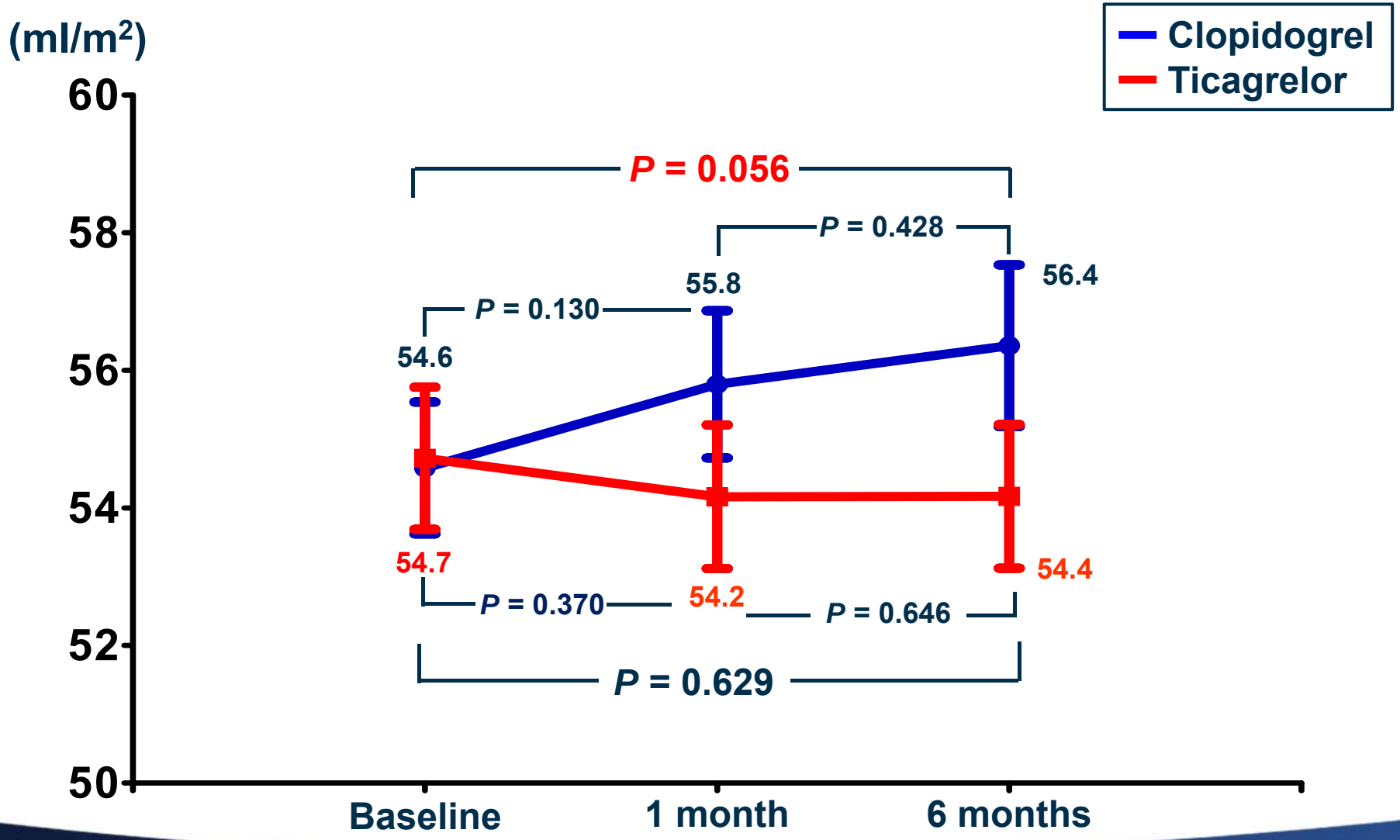
*COMMANDER HF. Zannad F, et al. N Engl J Med. 2018.

Co-primary Endpoints:
LV Remodeling Index



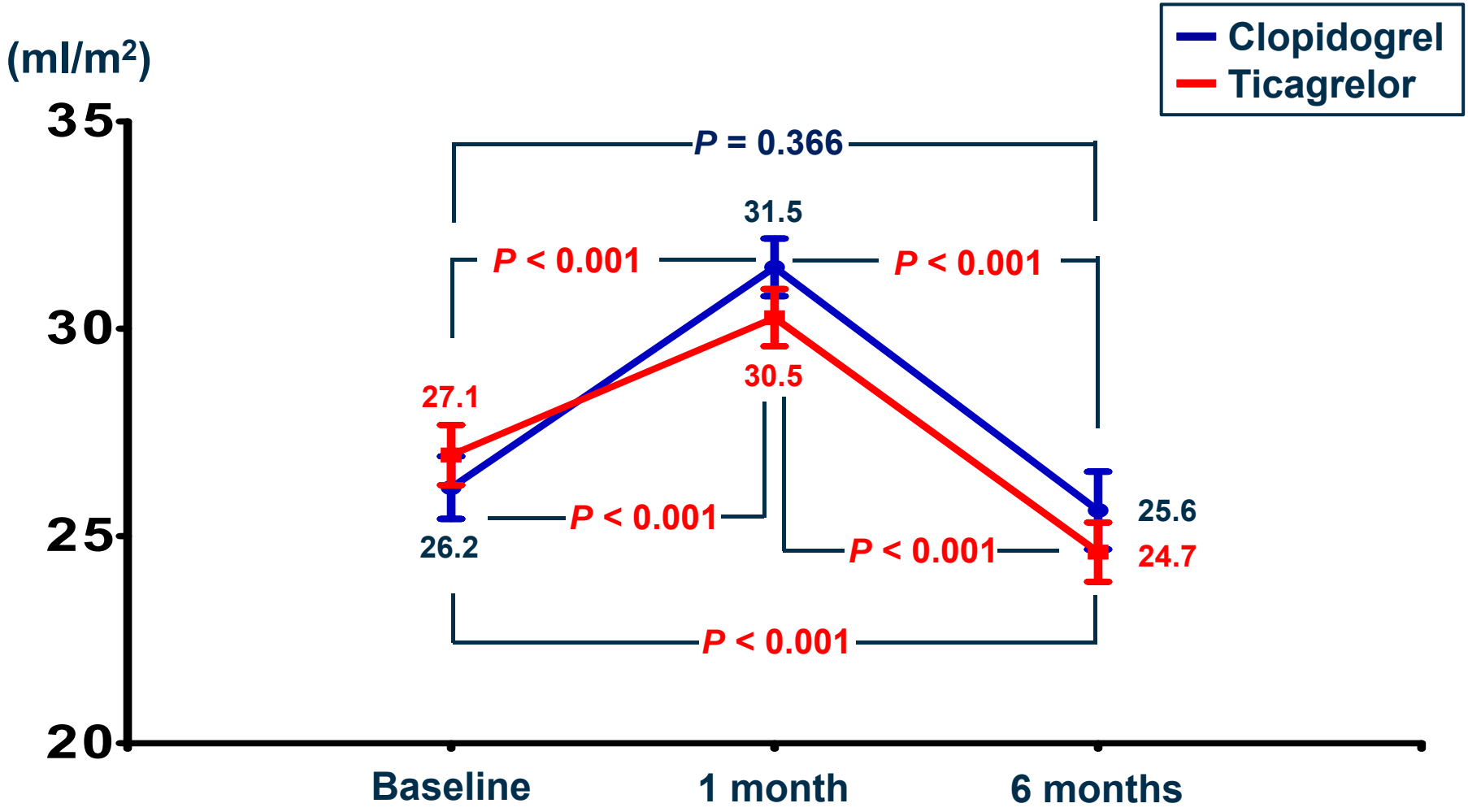
$$\text{LV remodeling index} = \frac{\text{LVEDV}_{\text{follow-up}} - \text{LVEDV}_{\text{baseline}}}{\text{LVEDV}_{\text{baseline}}} \text{ X } 100\ (\%)$$

LVEDV Index Profile



LVEDV index = LV end-diastolic volume index / body surface area

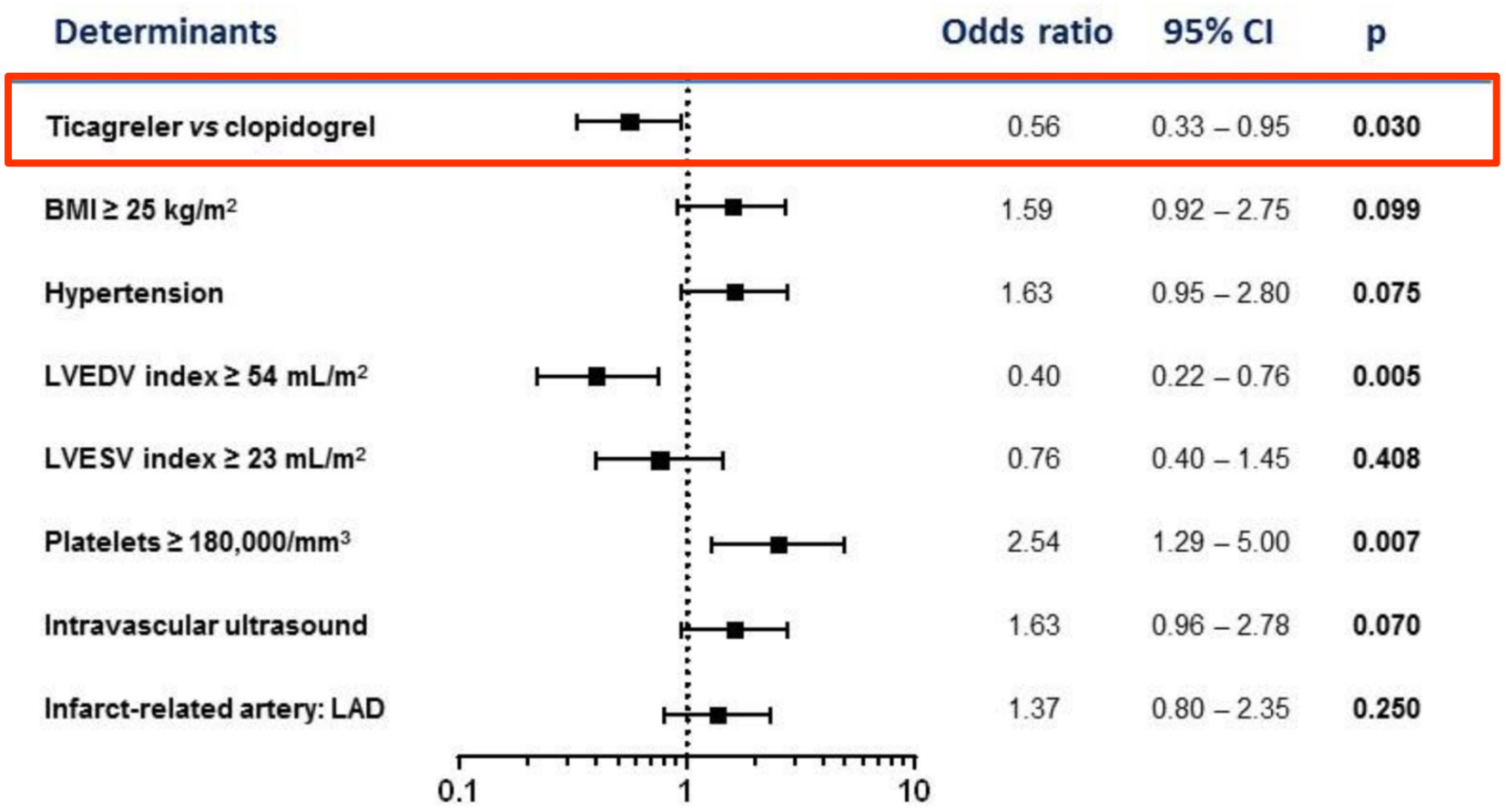
LVESV Index Profile



LVESV index = LV end-systolic volume / body surface area

Predictors of Positive LV Remodeling (LVRI > 0%)

Multivariate analysis including variables w/ P < 0.1 in univariate analysis



BRILINTA overcome some of the limitations of other antiplatelet agents

- **Rapid** onset of action[3]
- **Potent and highly effect** antiplatelet agent[3]
- **Consistent** antiplatelet effects[4]
- **Direct acting**, active post-absorption[5]
- **Reversible binding**[6]
- Inhibits newly formed platelets[7]
- Twice-daily dosing[8]
- **Pleiotropic effects (eg ENT-1)**[9,10]
- **PLATO** and **PEGASUS** data

ENT-1, equilibrative nucleoside transporter-1

1. Feher G *et al. World J Cardiol* 2010;2:171–86; 2. Matetzky S *et al. Circulation* 2004;109:3171–5; 3. Gurbel PA *et al. Circulation* 2009;120:2577–85; 4. Storey RF *et al. J Am Coll Cardiol* 2010;56:1456–62; 5. Schömig A. *N Engl J Med* 2009;361:1108–11; 6. Husted S, van Giezen JJ. *Cardiovasc Ther* 2009;27:259–74; 7. Storey RF *et al. J Am Coll Cardiol* 2007;50:1852–56; 8. Nylander S, Schulz R. *Br J Pharmacol* 2016;173:1163–78; 9. Armstrong D *et al. J Cardiovasc Pharmacol Ther* 2014;19:209–19; 10. Reiner MF *et al. Cardiovasc Res* 2017;113:61–9; 11. James S *et al. Eur Heart J* 2010;31:3006–16; 12. Bhatt D *et al J Am Coll Cardiol.* 2016;67;2732–40