Cilostazol: Triple Benefits – More is Better!

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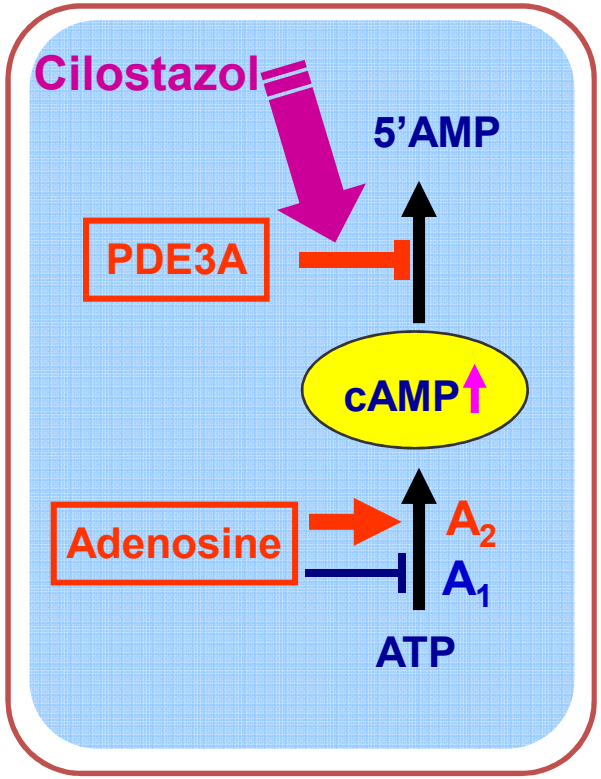
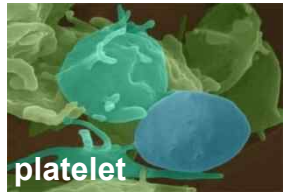
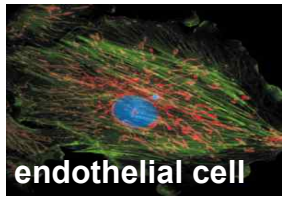
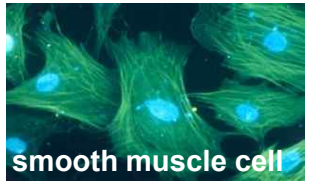
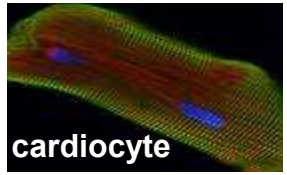
Mechanism of Cilostazol:
Inhibition of Phosphodiesterase III → Pleiotropic Effects



Elevation of cAMP and inhibition of adenosine uptake

Targets	cAMP actions (selected)
 platelet	• Inhibition of aggregation • Inhibition of expression of adhesion molecules
 endothelial cell	• Inhibition of expression of adhesion molecules • Angiogenesis
 smooth muscle cell	• Vasodilatory action • Inhibition of proliferation, migration and matrix synthesis • Headache
 cardiocyte	• Palpitation • Tachycardia

Impact of Cilostazol on Late Loss and TLR

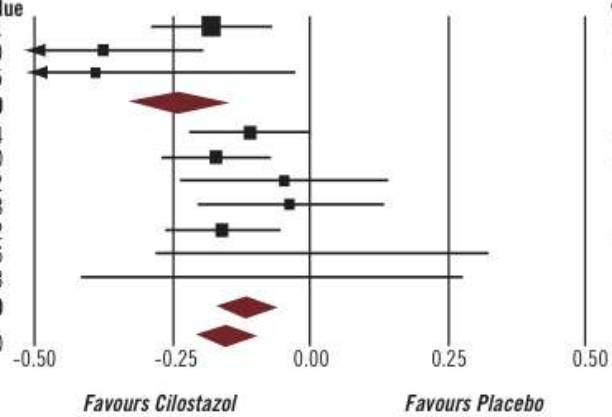
Meta-analysis of 10 randomized trials (2,809 patients)

Mean difference of late loss

Study name	Stent type	Year	Difference in means	Standard error	Number of Patients Cilostazol	Number of Patients Control	Lower limit	Upper limit	p-Value	Relative weight
CREST	BMS	2005	-0.180	0.055	259	267	-0.288	-0.072	0.001	69.04
CHEN YD et al	BMS	2006	-0.370	0.092	52	54	-0.550	-0.190	0.000	24.83
Min PK et al	BMS	2007	-0.390	0.185	35	30	-0.752	0.028	0.035	6.13
Late loss reduction in BMS subgroup			**-0.240**	**0.046**			**-0.330**	**-0.150**	**0.000**	
DECLARE-DIABETES	DES	2008	-0.110	0.054	163	167	-0.217	-0.003	0.044	23.19
DECLARE–Long	DES	2007	-0.170	0.048	210	205	-0.264	-0.076	0.000	29.76
Kim DH et al	DES	2008	-0.050	0.096	55	54	-0.238	0.138	0.602	7.49
CIDES	DES	2008	-0.040	0.085	113	124	-0.207	0.127	0.638	9.51
Lond-DES II	DES	2008	-0.160	0.053	168	164	-0.263	-0.057	0.002	24.81
Hong SJ et al	DES	2008	0.020	0.152	39	41	-0.278	0.318	0.896	2.97
Jeong JW et al	DES	2008	-0.070	0.175	23	30	-0.412	0.272	0.688	2.26
Late loss reduction in DES subgroup			**-0.124**	**0.026**			**-0.176**	**-0.073**	**0.000**	
Overall late loss reduction			-0.153	0.023			-0.198	-0.108	0.000	

Statistics for each study

Difference in means and 95% CI

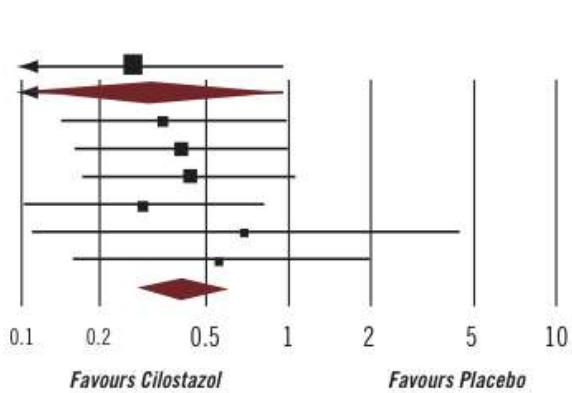


Target lesion revascularization

Study name	Stent type	Year	Odds ratio	Lower limit	Upper limit	p-Value	TLR / Total Cilostazol	TLR / Total Control	Relative weight
CHEN YD et al	BMS	2006	0.263	0.069	1.010	0.052	3 / 60	10 / 60	100.00
			0.263	0.069	1.010	0.052			
DECLARE-DIABETES	DES	2008	0.341	0.120	0.964	0.043	5 / 200	14 / 200	17.78
DECLARE–Long	DES	2007	0.395	0.161	0.970	0.043	7 / 250	17 / 250	23.86
CIDES	DES	2008	0.432	0.170	1.094	0.077	7 / 141	15 / 139	22.28
Lond-DES II	DES	2008	0.286	0.103	0.796	0.017	7 / 206	16 / 200	18.37
Hong SJ et al	DES	2008	0.677	0.109	4.194	0.675	2 / 64	3 / 66	5.79
Jeong JW et al	DES	2008	0.548	0.154	1.952	0.353	4 / 46	8 / 54	11.92
			0.397	0.256	0.615	0.000			

Statistics for each study

Odds ratio and 95% CI



Tamhane U et al. Eurointervention 2009; 5: 384-393

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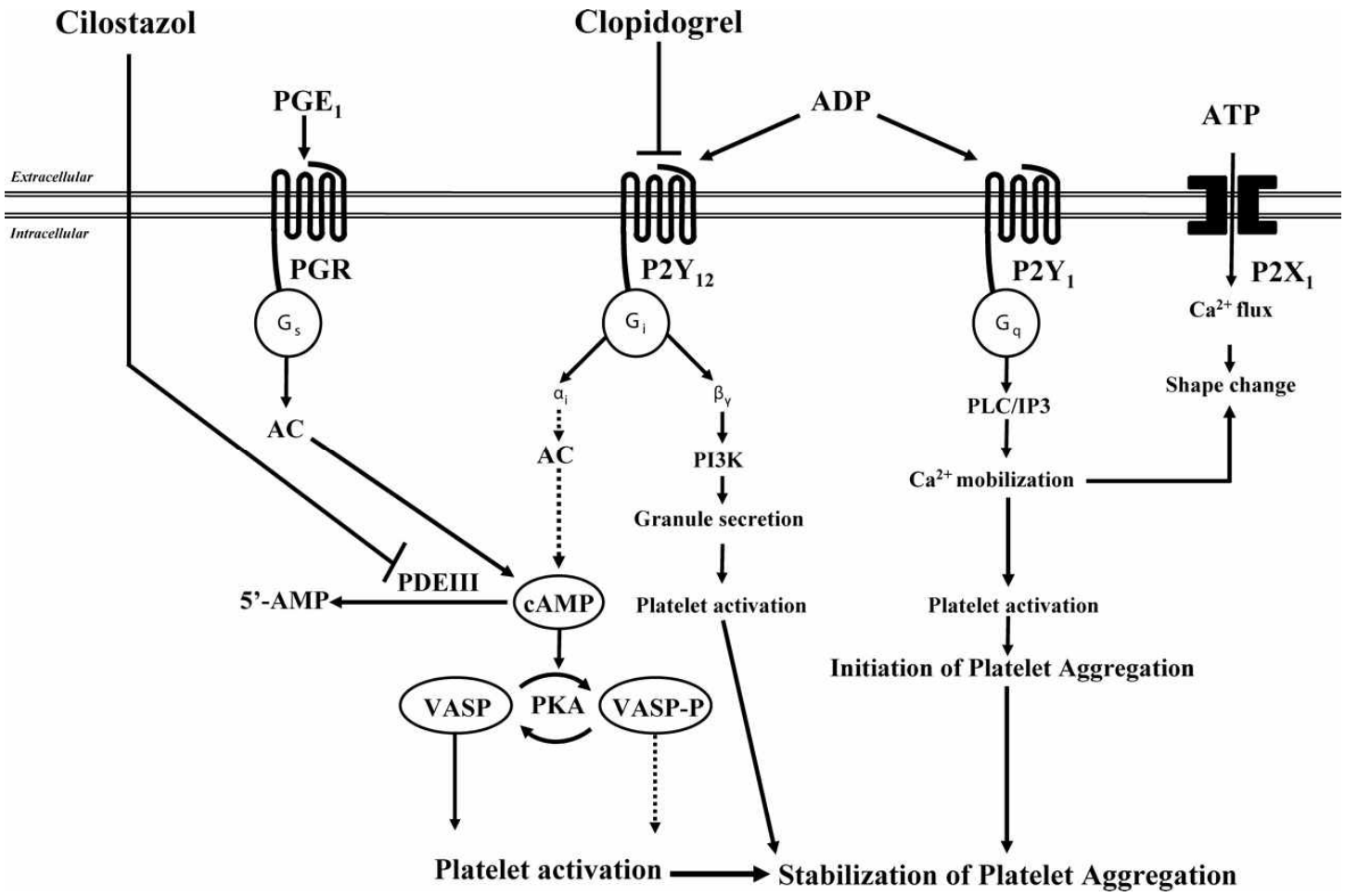
Impact of Cilostazol on the Downstream Effect of P2Y12-Receptor Activation

Potential Synergies with Clopidogrel

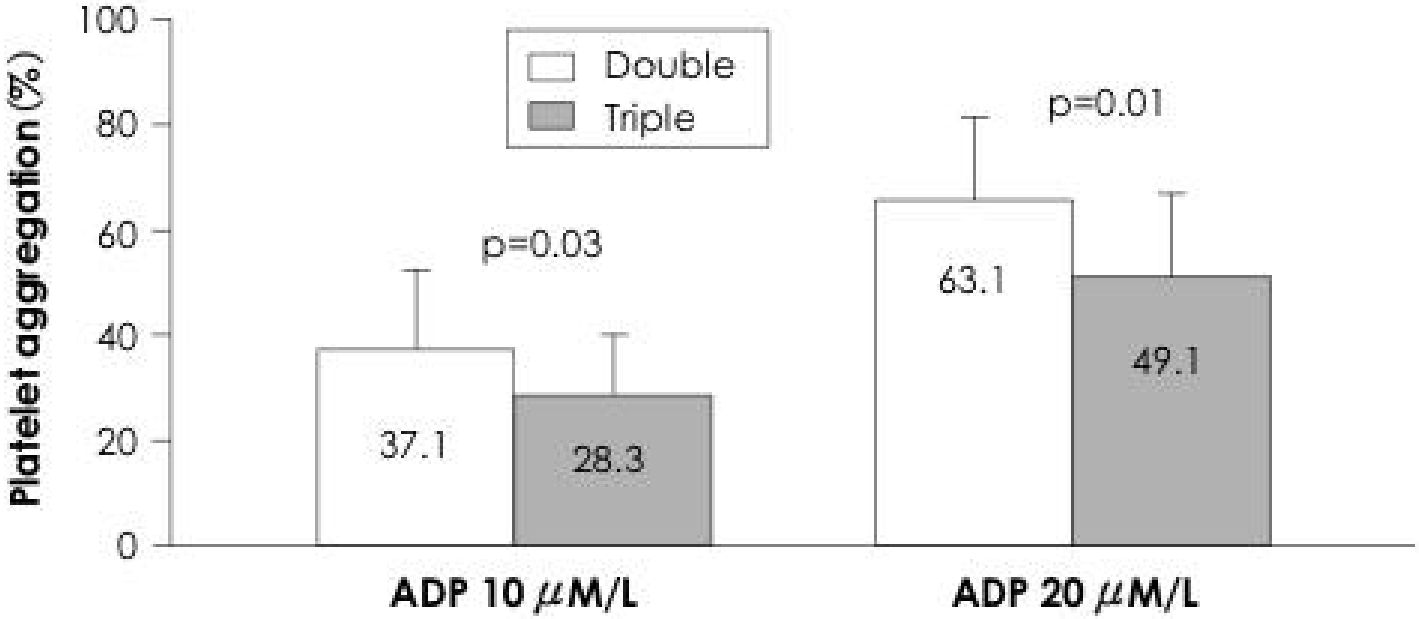


Angiolillo D et al, Eur Heart J 2008; 29:2202-2211

SCRIPPS CLINIC

TAT Enhances Inhibition of ADP-Induced Platelet Reactivity in Diabetics Compared with DAT

N=55

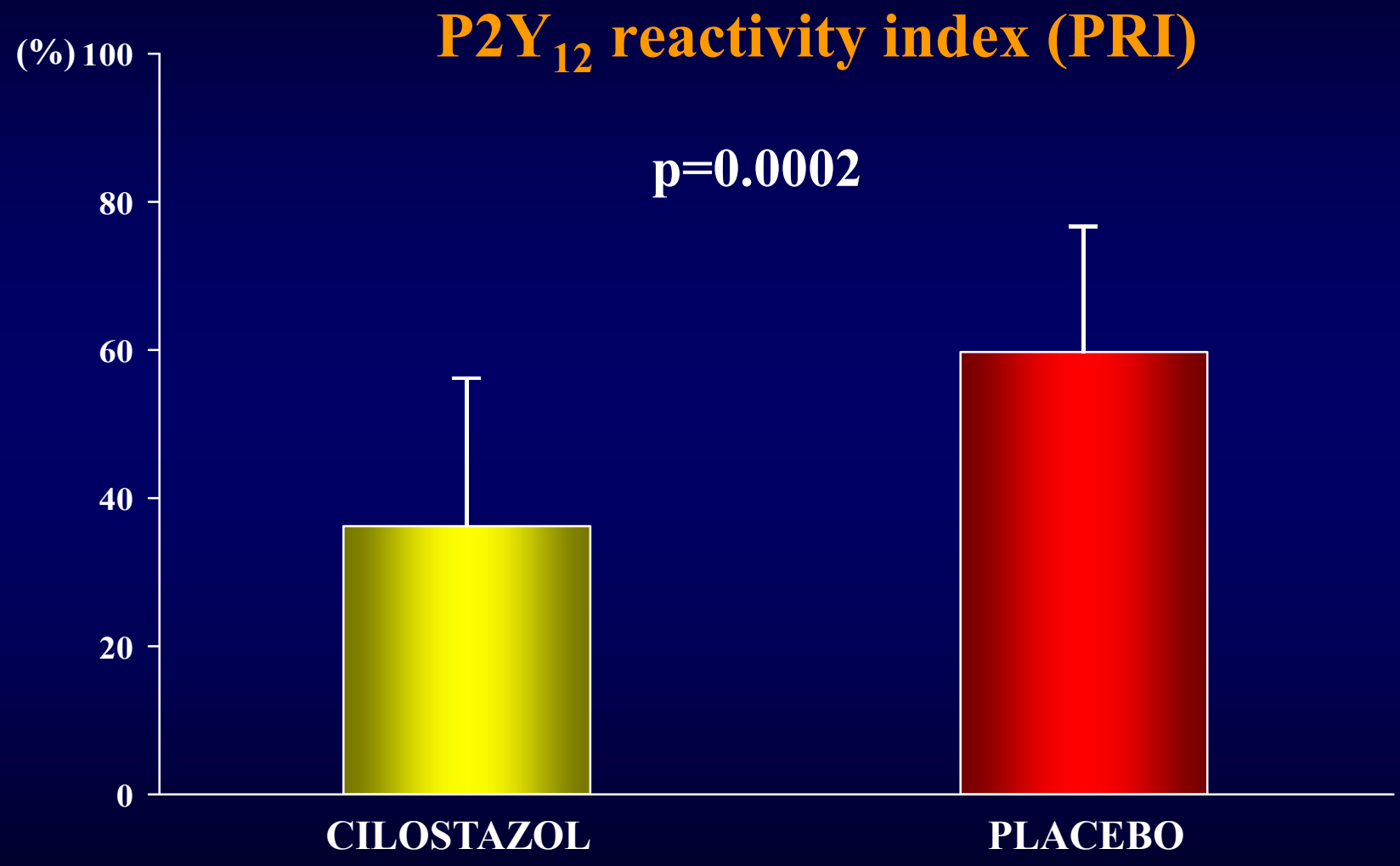


Yang TH et al, Korean Circ J 2009; 462-366

SCRIPPS CLINIC

OPTIMUS-2: Randomized Trial of Cilostazol 100mg bid versus Placebo in DM Patients on DAPT

Primary Endpoint



Angiolillo D et al, Eur Heart J 2008; 29:2202-2211

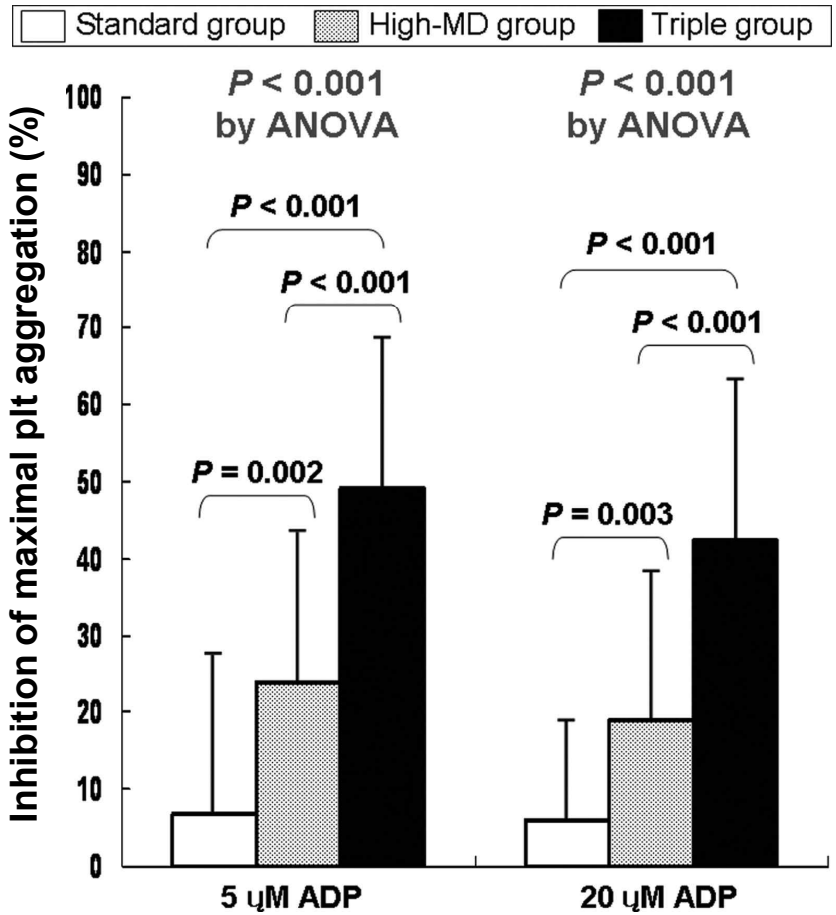
CURRENT

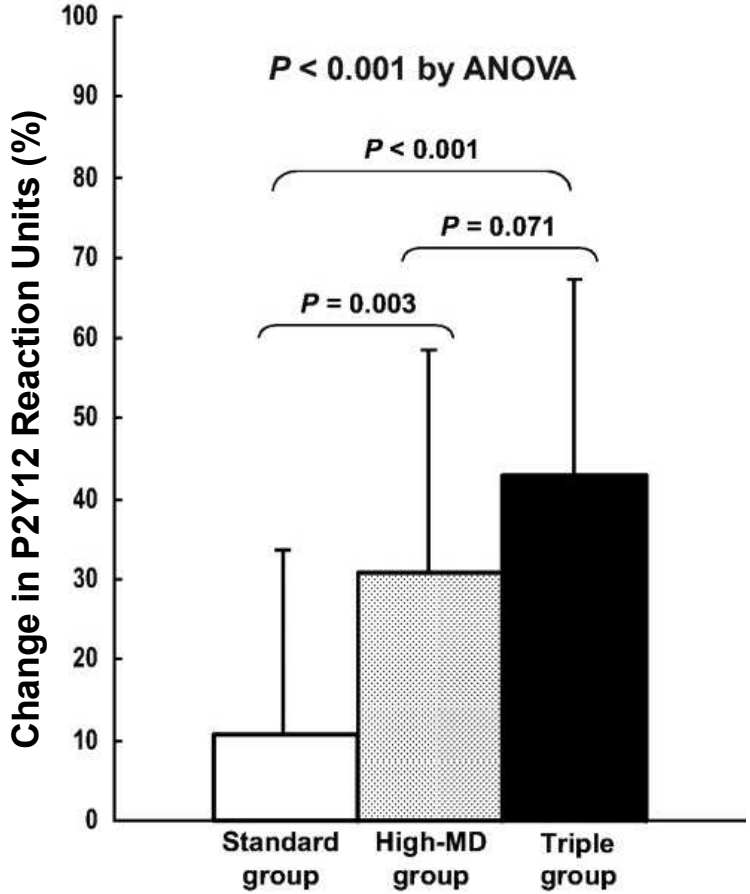
Clopidogrel: Double vs Standard Dose Primary Outcome and Components

	Standard	Double	HR	95% CI	P	Intn P
CV Death/MI/Stroke						
PCI (2N=17,232)	4.5	3.9	0.85	0.74-0.99	0.036	0.016
No PCI (2N=7855)	4.2	4.9	1.17	0.95-1.44	0.14	
Overall (2N=25,087)	4.4	4.2	0.95	0.84-1.07	0.370	
MI						
PCI (2N=17,232)	2.6	2.0	0.78	0.64-0.95	0.012	0.025
No PCI (2N=7855)	1.4	1.7	1.25	0.87-1.79	0.23	
Overall (2N=25,087)	2.2	1.9	0.86	0.73-1.03	0.097	
CV Death						
PCI (2N=17,232)	1.9	1.9	0.96	0.77-1.19	0.68	1.0
No PCI (2N=7855)	2.8	2.7	0.96	0.74-1.26	0.77	
Overall (2N=25,087)	2.2	2.1	0.96	0.81-1.14	0.628	
Stroke						
PCI (2N=17,232)	0.4	0.4	0.88	0.55-1.41	0.59	0.50
No PCI (2N=7855)	0.8	0.9	1.11	0.68-1.82	0.67	
Overall (2N=25,087)	0.5	0.5	0.99	0.70-1.39	0.950	

Adjunctive Cilostazol Provides More Inhibition of ADP-Induced Aggregation after Primary PCI for STEMI compared with High MD Clopidogrel: *ACCEL-AMI*

N=90





Jeong YH et al, Circ Cardiovasc Interv 2010;3:17-26

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DECREASE Registry (Lee SW, et al. Am Heart J 2010; 159: 284-291. e1)

Twelve-month risk of Events after DES Implantation of Triple versus Dual antiplatelet therapy

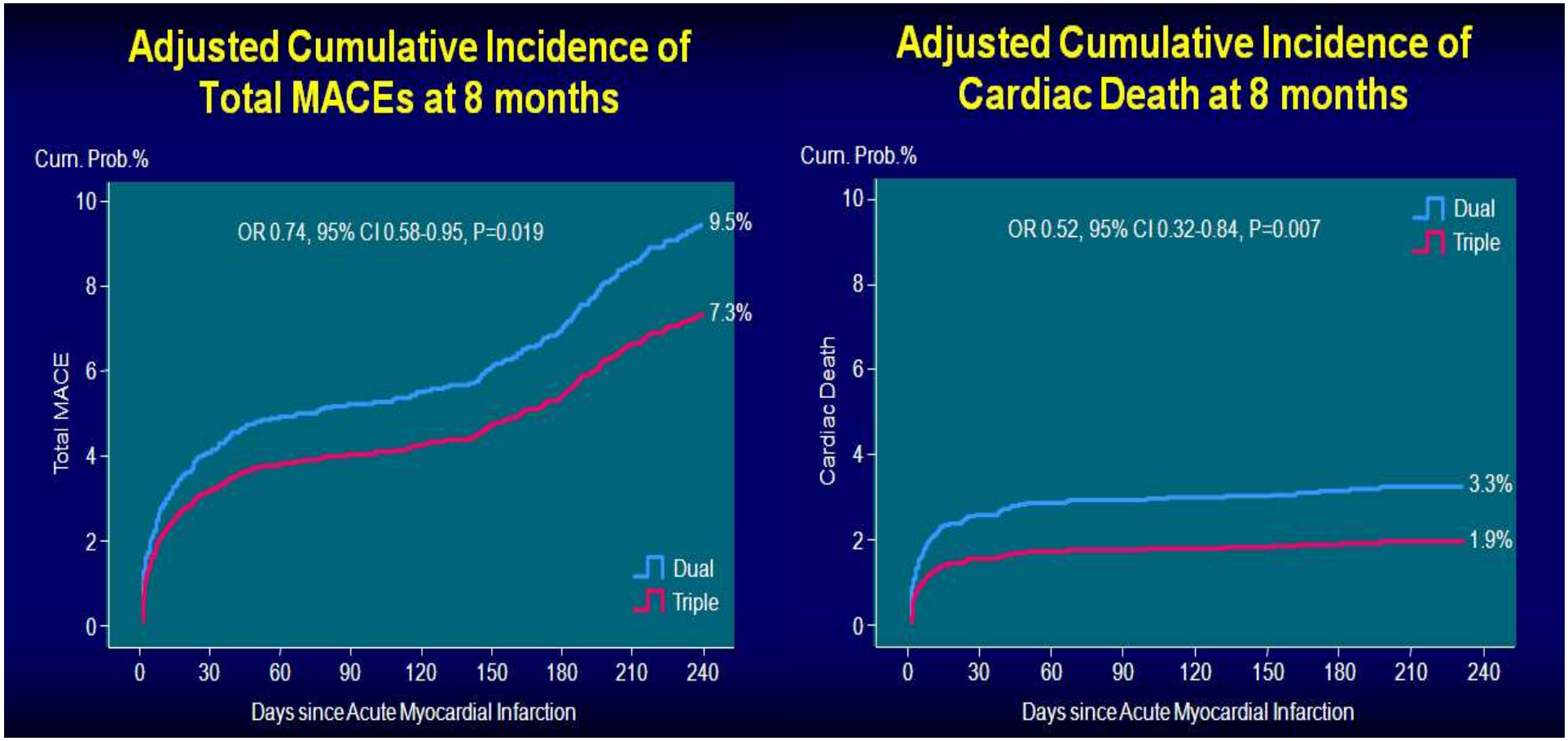
Variables	Crude		Inverse-probability-of-treatment weighted		Propensity-matched (965 pairs)	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Cardiac events						
Death	0.925 (0.521 -1.644)	0.7907	0.762 (0.401-1.448)	0.4062	0.644(0.300-1.381)	0.2584
MI	0.381 (0.138-1.048)	0.0617	0.233 (0.077-0.703)	0.0097	0.298 (0.082-1.086)	0.0665
Stent thrombosis	0.286 (0.081-1.013)	0.0524	0.136 (0.035-0.521)	0.0036	0.124 (0.016-0.996)	0.0496
Death/MI	0.761 (0.464-1.251)	0.2817	0.591 (0.3364-1.037)	0.0665	0.556 (0.287-1.075)	0.0811
Bleeding						
Major bleeding	0.850 (0.477-1.516)	0.5830	0.969 (0.443-2.119)	0.9372	0.683 (0.343-1.360)	0.2781
Minor bleeding	1.039 (0.757-1.426)	0.8125	1.062 (0.734-1.537)	0.7504	1.045 (0.703-1.555)	0.8267

Hazard ratios are for the triple group, as compared with the dual group.

KAMIR Registry: TAPT vs DAPT in STEMI

Observational, retrospective analysis

TAPT (n=1634) vs DAPT (n=2569)



Chen KY et al. Circulation 2009:119:3207-14.

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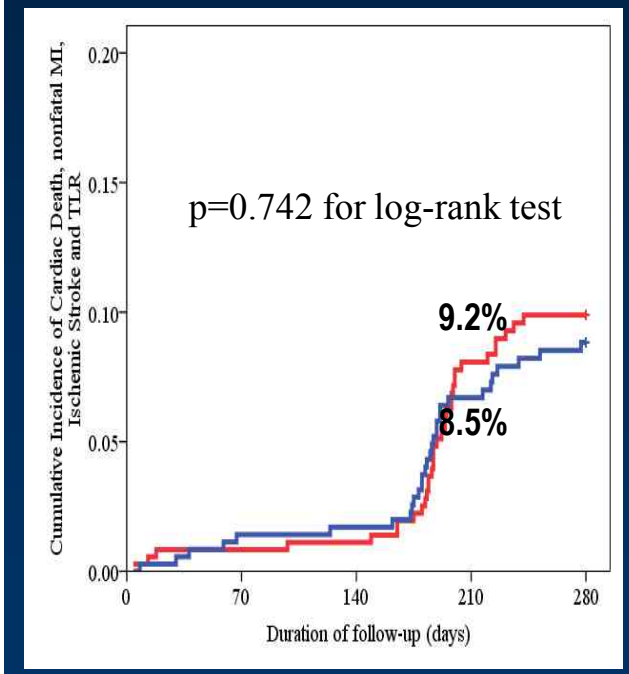
CILON-T: Randomized Multicenter Trial of TAT vs DAT after PCI
Clinical outcomes depending on anti-platelet regimen

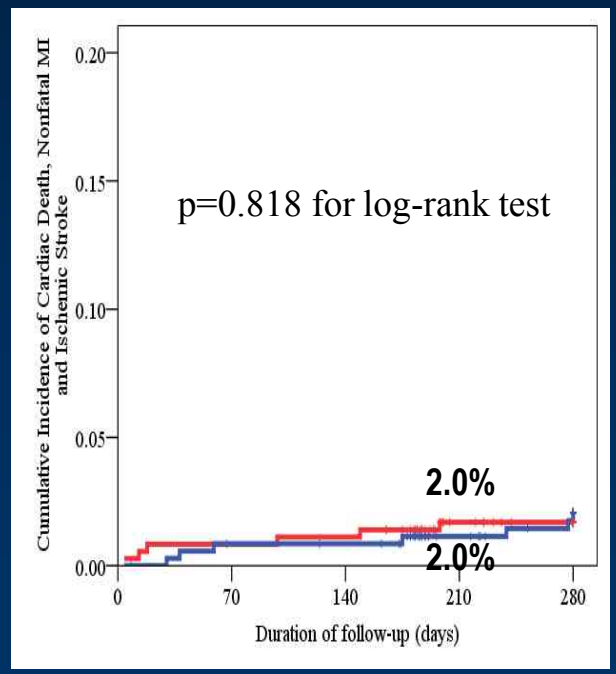
Double anti-PLT regimen — Triple anti-PLT regimen

Composite of CD, nonfatal MI, ischemic stroke & TLR



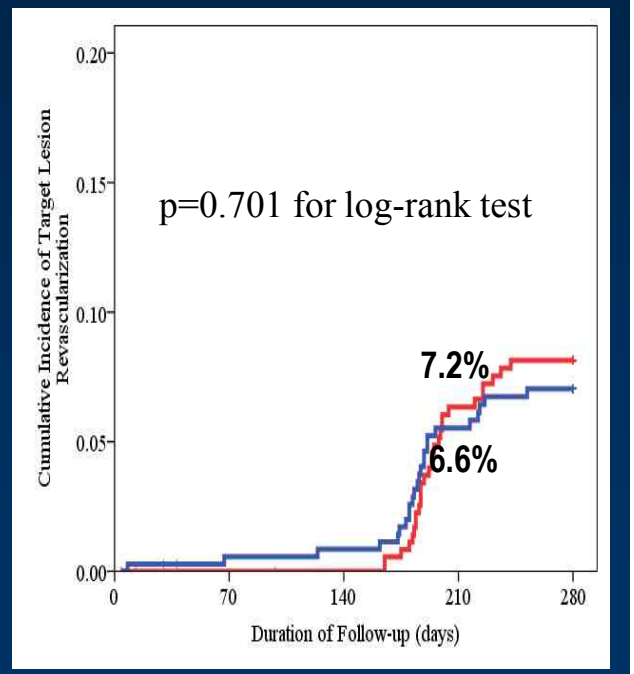
DAT	458	452	450	425	416
TAT	457	450	449	428	418

Composite of CD, nonfatal MI & ischemic stroke



DAT	458	452	451	449	447
TAT	457	452	452	451	448

TLR

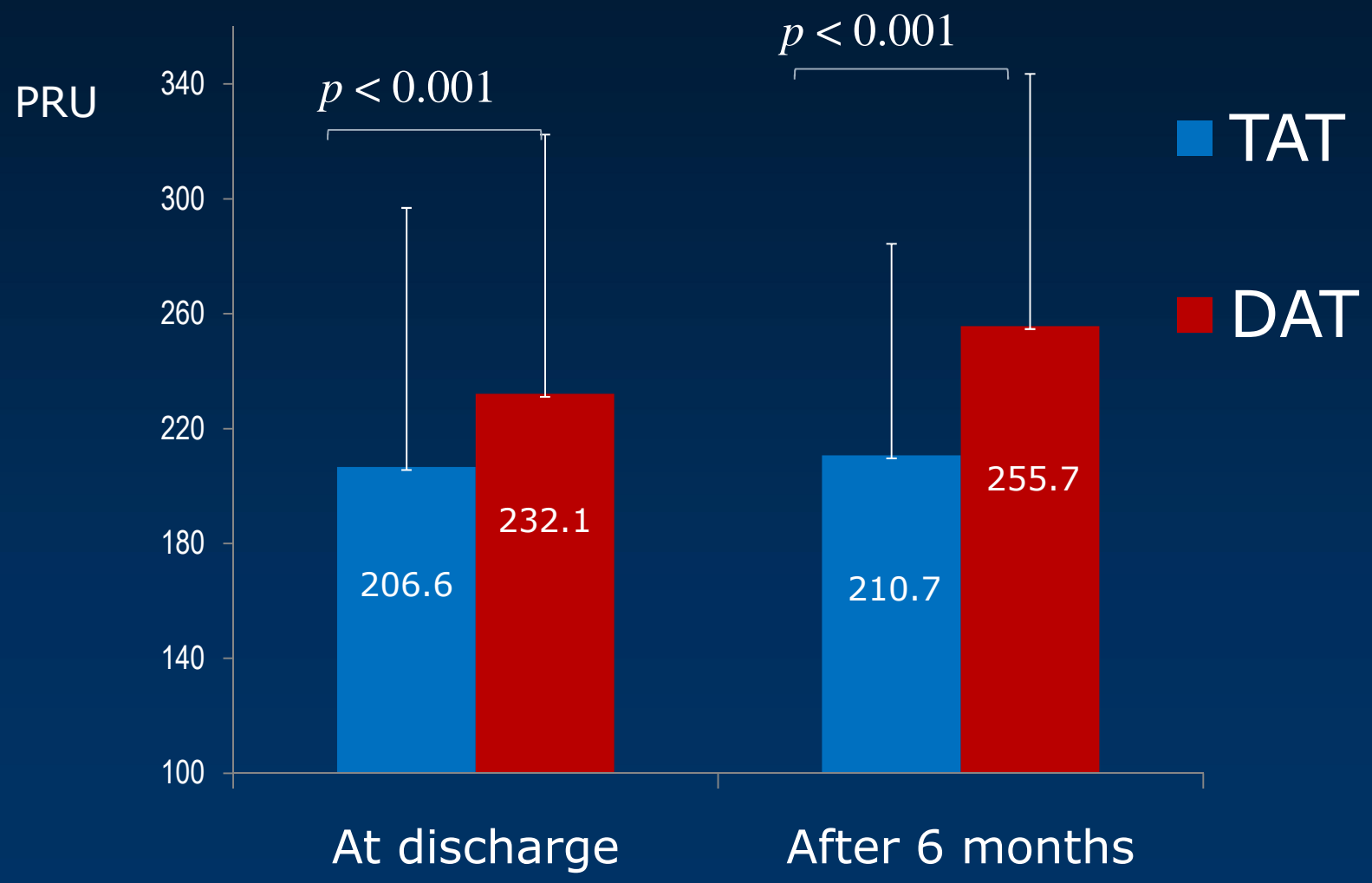


DAT	458	458	449	426	418
TAT	457	450	449	429	421

Kim HS, ACC 2010

Seoul National University Hospital

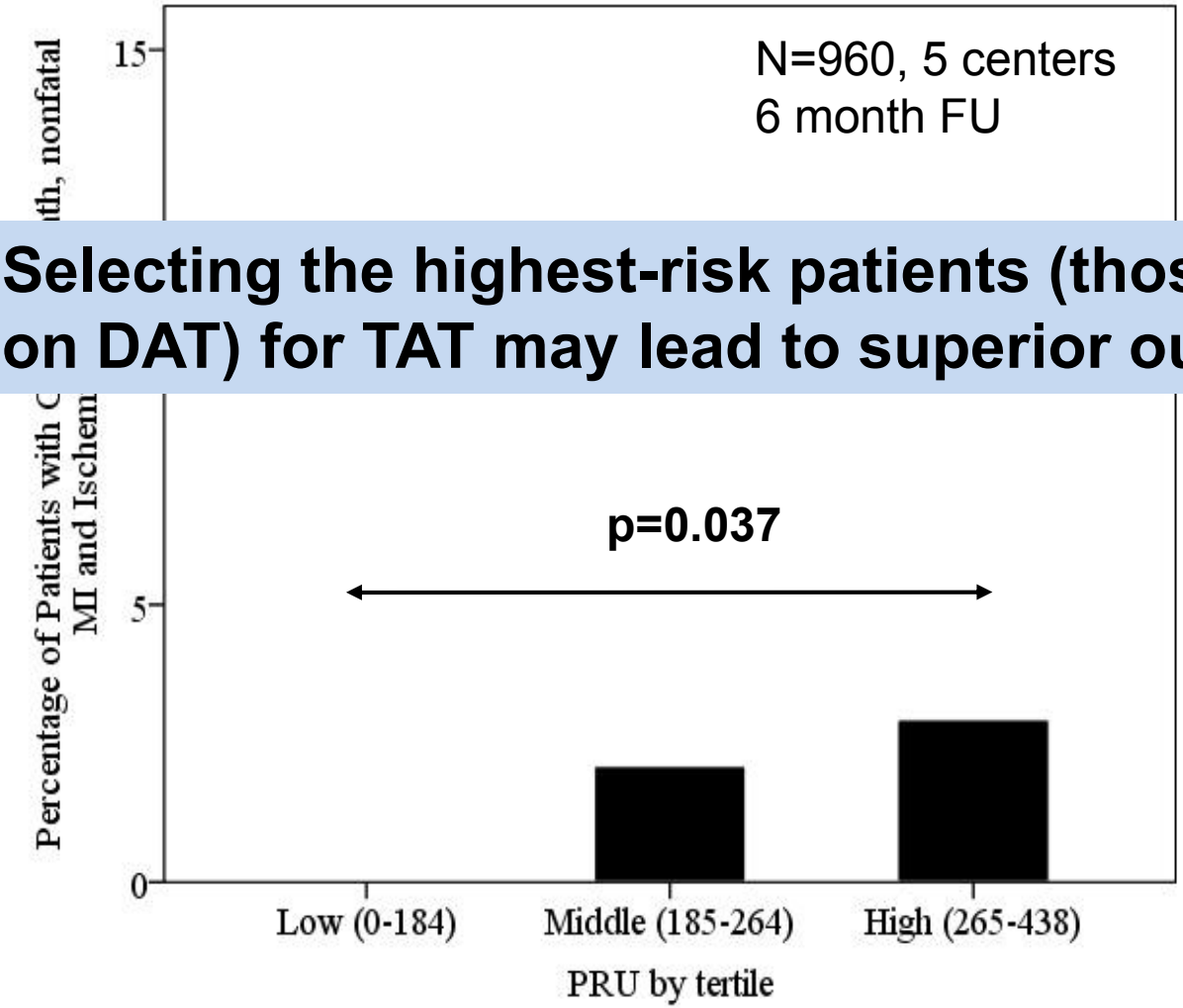
Cilon-T Results: P2Y12 reaction unit (PRU): TAT vs DAT



Kim HS, ACC 2010

CILON-T: Clinical Outcomes Stratified by Point-of-Care Platelet Function

Increasing PRU is an Independent Predictor of Ischemic Events



Selecting the highest-risk patients (those with high PRU on DAT) for TAT may lead to superior outcomes?

PRU (every ⇧in tertile):
Adj HR = 1.63 (1.12~2.37)

Insights into OPTIMUS 1 and 2 studies

Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Diabetic Patients With Clopidogrel Resistance

VASP – PRI (%) values before and after treatment

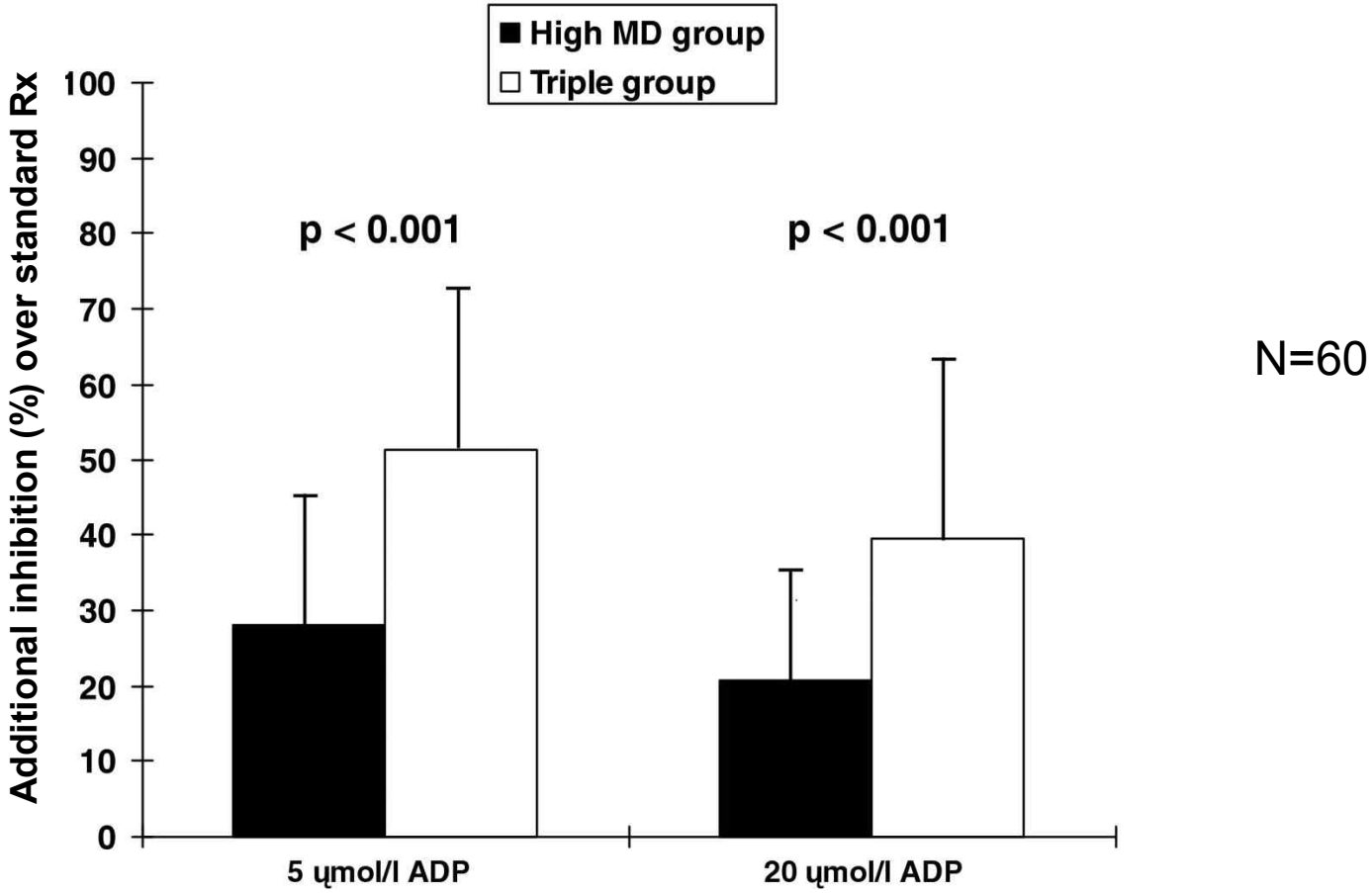
	High dose clopidogrel (150mg daily)	Triple therapy (cilostazol 100mg bid)	p
PRI before	70.7 ± 14.6	67.5 ± 8.5	0.477
PRI after	57.5 ± 14.7	45.1 ± 16.2	0.038
Δ PRI	13.2 ± 11.8	22.4 ± 12.2	0.045

Both strategies significantly reduced PRI levels (p<0.001 for both)

Ferreiro & Angiolillo. ACC 2010

Potential Management Strategies for Patients With High Platelet Reactivity on Standard Clopidogrel Therapy: *ACCEL-RESISTANCE*

Clopidogrel 150-mg day (**High MD**) vs. *Clopidogrel* + *Cilostazol* (**Triple Group***)* in non-responders to standard dosing



N=60

NR defined as > 50% Agg (max) with 5uml of ADP at least 12hrs after clop 300-mg

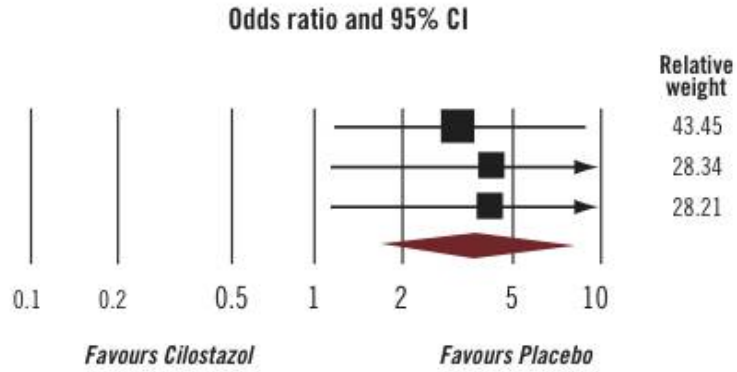
Jeong YH et al, J Am Coll Cardiol, 2009; 53:1101-110

SCRIPPS CLINIC

No Free Lunch: Cilostazol Is Not Tolerated In Many Patients….

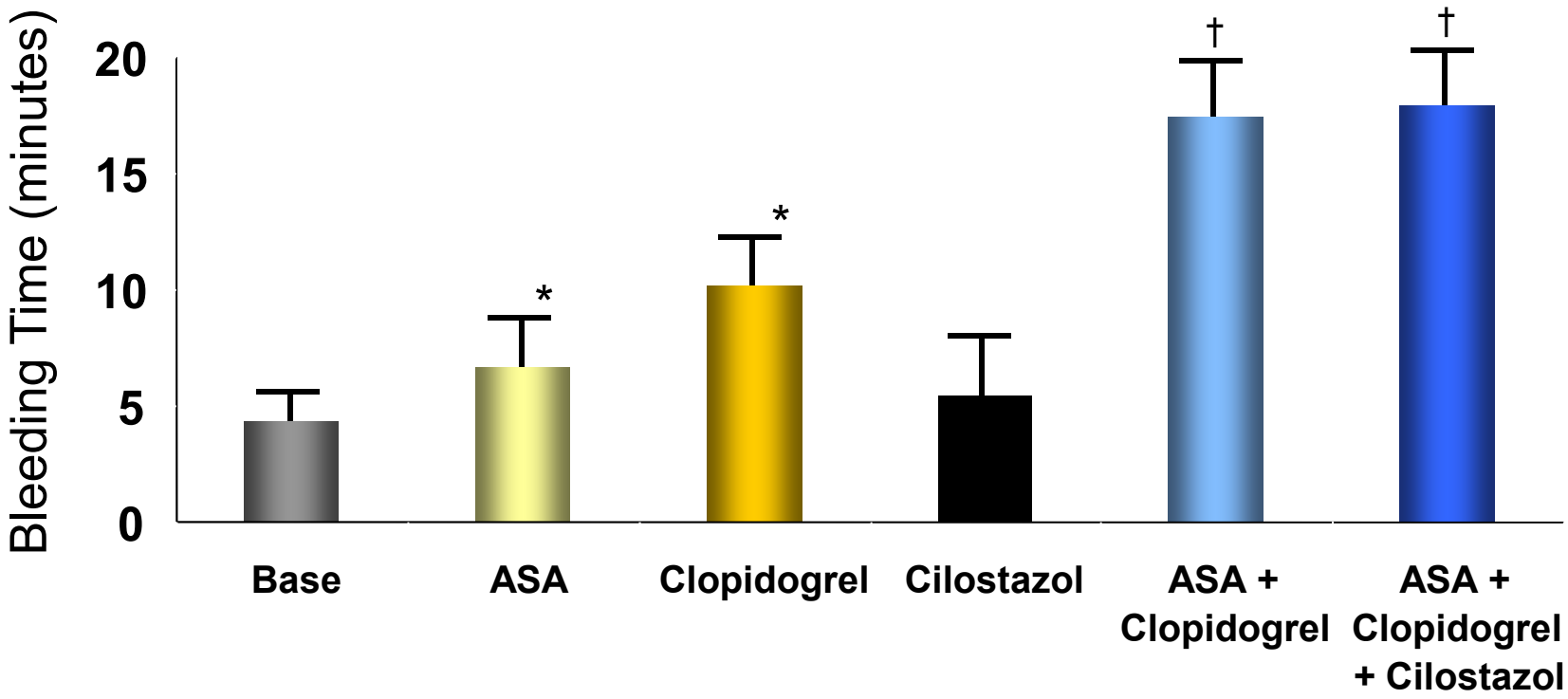
Incidence of Skin Rash

Study name	Stent type	Year	Statistics for each study				Skin rash / Total		Relative weight
			Odds ratio	Lower limit	Upper limit	p-Value	Cilostazol	Control	
DECLARE-DIABETES	DES	2008	3.162	1.127	8.874	0.029	15 / 200	5 / 200	43.45
DECLARE–Long	DES	2007	4.151	1.157	14.895	0.029	12 / 250	3 / 250	28.34
Lond-DES II	DES	2008	4.062	1.129	14.618	0.032	12 / 206	3 / 200	28.21
			3.666	1.857	7.237	0.000			



Tamhane U et al. Eurointervention 2009; 5: 384-393

…But Potentially, Cilostazol Does Not Result in A Substantial Incremental Risk For Bleeding



ASA, aspirin 325 mg QD. Clopidogrel 75 mg QD. Cilostazol 100 mg BID.
*$P \leq 0.05$ versus baseline.
†$P \leq 0.05$ versus all single agents and versus ASA + cilostazol and clopidogrel + cilostazol.

Adapted from Wilhite DB et al. J Vasc Surg. 2003;38:710-713.

CILON-T Results: Safety outcomes TAT vs DAT

Variable	TAT (n=457)	DAT (n=458)	P
Bleeding complications			0.511
Major	2 (0.4%)	1 (0.2%)	
Minor	1 (0.2%)	0 (0%)	
Drug discontinuation	30 (6.6%)	3 (0.7%)	<0.001
Heart rate, /min			
Baseline	69.7±11.9	69.2±12.7	0.62
6 months	73.3±12.0	68.4±13.7,	<0.001

Kim HS, ACC 2010

Summary:
Where Does Cilostazol Fit in a "Post CILON-T" World?

- In Cilon-T, routine TAT did not appear effective in reducing ischemic events after PCI.
- Larger studies with greater power than CILON-T are required to definitively answer whether routine TAT provides clinical benefit (less ischemic events without increased bleeding).
- However, TAT with cilostazol remains an attractive choice to *optimize* therapy in high-risk patients (e.g., STEMI) and those with high residual reactivity on clopidogrel, in particular:
  - *CYP2C19 poor metabolizers*
  - *Patients at high bleeding risk*
  - *Patients with high risk of restenosis*
- **So more is better – in many, many patients!**


Thank you for your attention!