Is the 3rd agent a solution for the resistance against anti-platelet agents?

CILostazol **O**n **N**eointimal growth and **T**hrombotic events in drug-eluting stents (CILON-T) trial

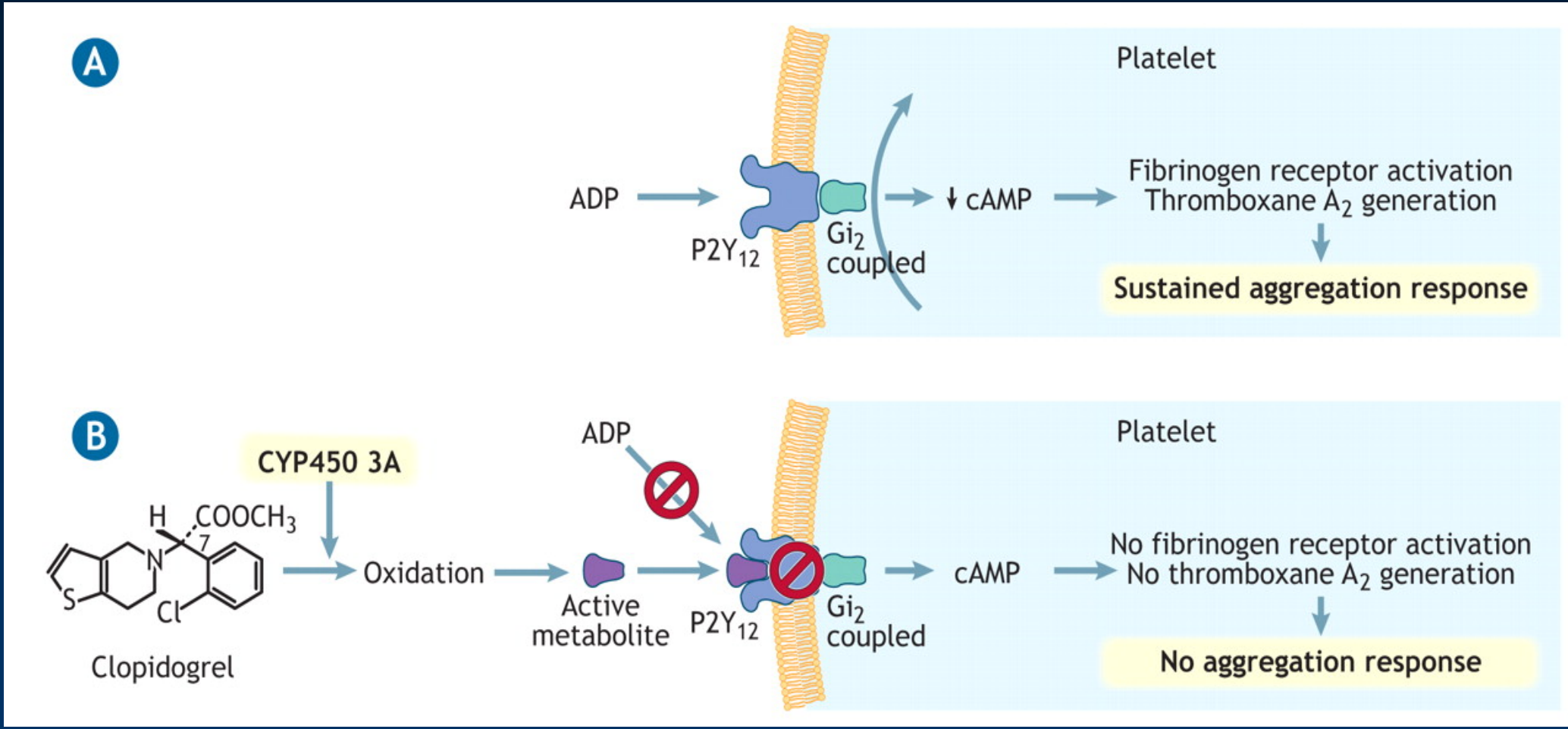
Jung-Won Suh , Hyo-Soo Kim MD, PhD

Seoul National University College of Medicine

SNUH Cardiovascular Center

Bundang SNUH Cardiovascular Center

Clopidogrel : mechanism



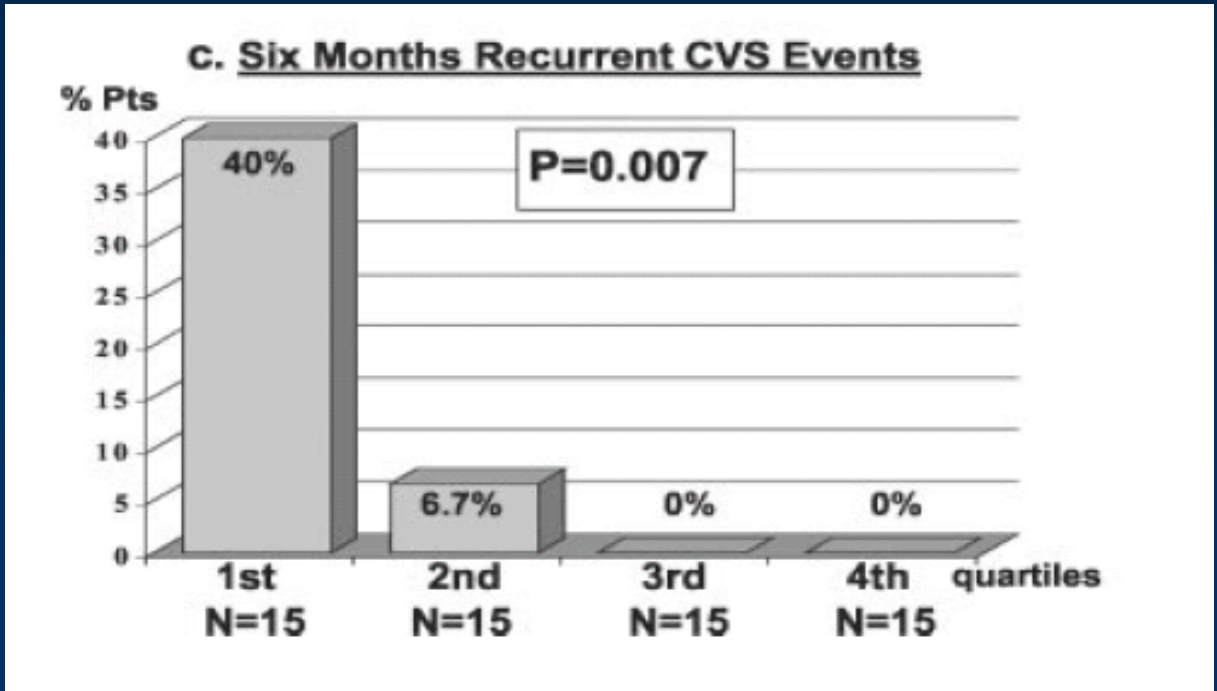
Causes of Clopidogrel Resistance

- Absorption
- P2Y12 Rc polymorphism
  - Controversial
  - Pro ; Cerebrovascular ds (Ziegler S, Stroke 2005), PAD (Fontana P, Circulation 2003)
  - Cons ; CAD (Smith SM, Platelets 2006/ Angiolillo DJ, Thromb Res 2005)
- Metabolism, Drug interaction
  - CYP3A4 activity (Lau WC, et al. Circulation 2004)
  - CYP3A5 polymorphism (Suh JW, et al. CMAJ 2006)
  - CYP2C19 polymorphism (Hulot JS, et al. Blood 2006)

Implication of Clopidogrel Resistance

Clopidogrel Resistance Is Associated With Increased Risk of Recurrent Atherothrombotic Events in Patients With Acute Myocardial Infarction

Shlomi Matetzky, MD; Boris Shenkman, MD, PhD; Victor Guetta, MD; Michael Shechter, MD; Roy Bienart, MD; Ilan Goldenberg, MD; Ilya Novikov, PhD; Hanna Pres, MSc; Naphtali Savion, PhD; David Varon, MD; Hanoch Hod, MD



Implication of Clopidogrel Resistance

Clopidogrel Effect on Platelet REactivity in Patients With Stent Thrombosis

Results of the CREST Study

Paul A. Gurbel, MD, FACC, Kevin P. Bliden, BS, Waiel Samara, MD Jason A. Yoho, MD, Kevin Hayes, MD, Mulugeta Z. Fissha, MD, Udaya S. Tantry, PHD

Baltimore, Maryland

	SAT (n = 20)	No SAT (n = 100)	p Value
LTA (5 μmol/l ADP) (%)	49 ± 4	33 ± 2	<0.001
LTA (20 μmol/l ADP) (%)	65 ± 3	51 ± 2	<0.001
LTA (1 mmol/l arachidonic acid)	1 non-responder	0 non-responders	
$P2Y_{12}$ reactivity ratio (%)	69 ± 5	46 ± 9	0.03
GP IIb/IIIa (MFI)			
Unstimulated	9 ± 1	15 ± 3	NS
Stimulated	138 ± 19	42 ± 4	<0.001

What can we do for ‘resistant’ patients?

Dose up

- Aspirin ; controversial
  - BRAVO-2, CURE ; Major bleeding risk ↑
- Clopidogrel
  - Increase of loading dose : 600mg >300mg
    - ARMYDA-2, ALBION, ISAR-CHOICE
  - Double maintenance dose in high risk patients :150mg >75mg
    - Type 2 DM in OPTIMUS

Compliance

- Schwartz KA et al. *(AJC 2005)*
  - Usual dose of daily aspirin (9%)
  - 2hrs after direct observed therapy of aspirin 325mg (<1%)

- Premature discontinuation of clopidogrel
  - Most important risk factor of stent thrombosis
  - HR 89.78 (C.I 29.9-269.60, p<0.001, *JAMA 2006*)

Control of Comorbidities

- Hyperglycemia
- HyperTG
- Active inflammation
- Congestive heart failure
- Catecholamine surge

Drug interaction

- Aspirin
  - Omeprazole
  - NSAIDs ; Ibuprofen, Indomethacin

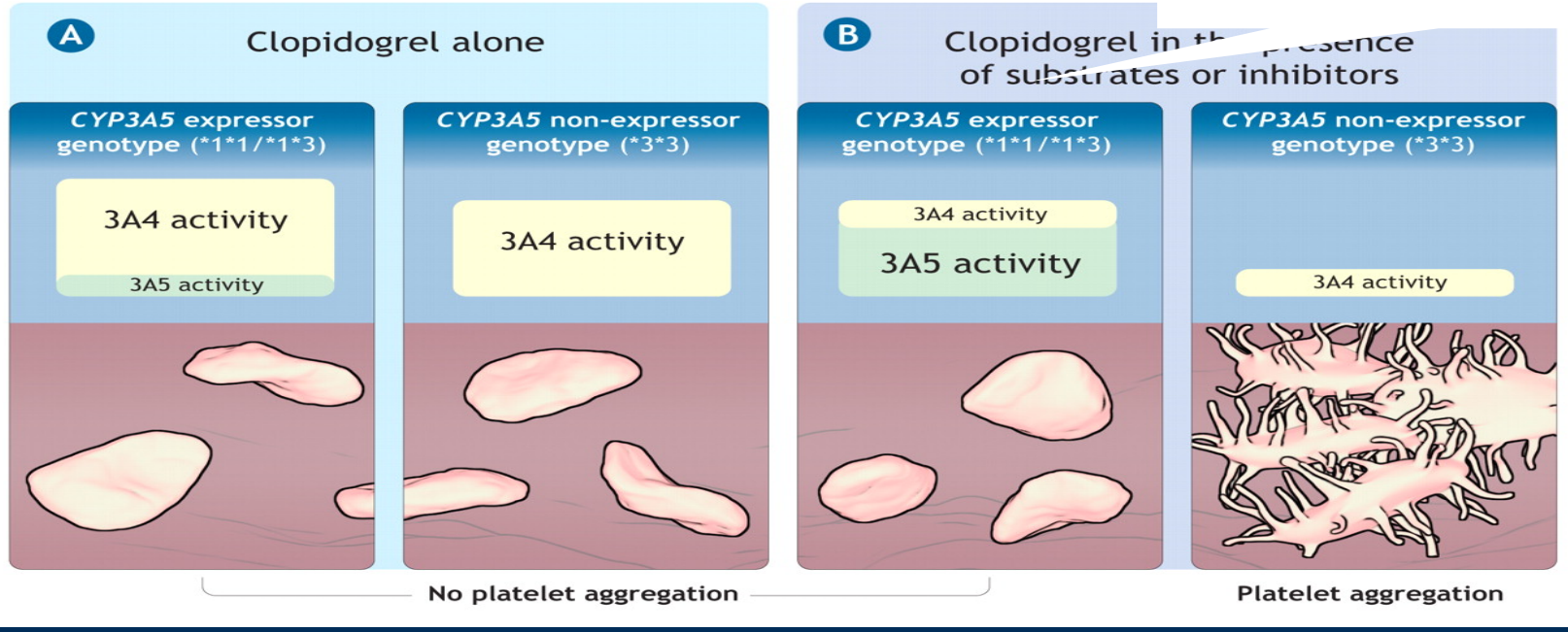
- Clopidogrel ; *via CYP3A*

Substrates	Diltiazem ,Verapamil, Nifedipine, Losartan, Atorvastatin, metoprolol, Benzodiazepine, Cyclosporine
Inducers	Rifampin, Alcohol, Phenobarbital, Phenytoin sodium Carbamazepine
Inhibitors	Ketoconazole, Itraconazole, Grapefruit juice Clarithromycin, Erythromycin, Cimetidine, Nefazodone Protease inhibitors, Verapamil

CYP3A5 SNP & Clopidogrel Drug Interacti

(Suh JW, et al. CMAJ 2006)

Lipophilic statin, metoprolol, diltiazem, nifedipine, losartan, cimetidine



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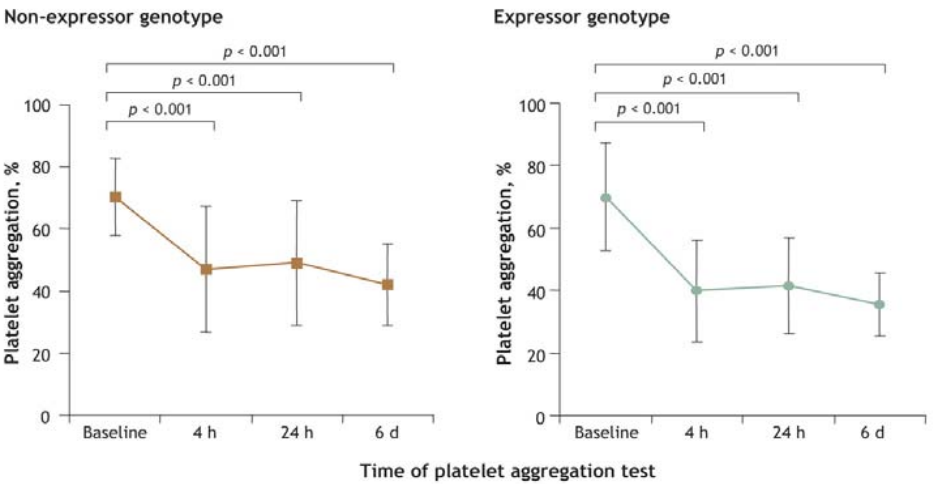
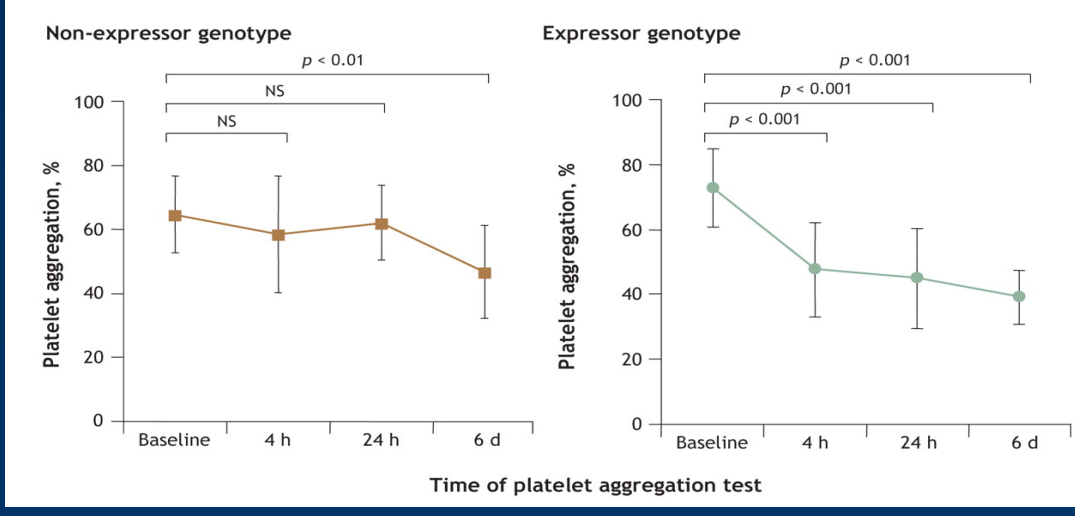




B

CYP3A5 SNP & Clopidogrel Drug Interaction

(Suh JW, et al. CMAJ 2006)

Table 3: Clinical outcomes after coronary angioplasty and bare-metal stent implantation, by *CYP3A5* genotype

Outcome after stent implantation	*CYP3A5* genotype; no. of patients: Non-expressor *n* = 193	Expressor *n* = 155	*p* value
At 1 mo			
Sudden death			
MI (subacute th			
Nonhemorrhagi			
Total			
1-6 mo			
Sudden death	0	0	—
MI	4	0	
Nonhemorrhagic stroke	0	0	
Total	4	0	0.10
6-mo cumulative	14	3	0.023

Note: MI = myocardial infarction.

Table 4: Risk factors for atherothrombotic events after coronary angioplasty and bare-metal stent implantation among patients taking clopidogrel

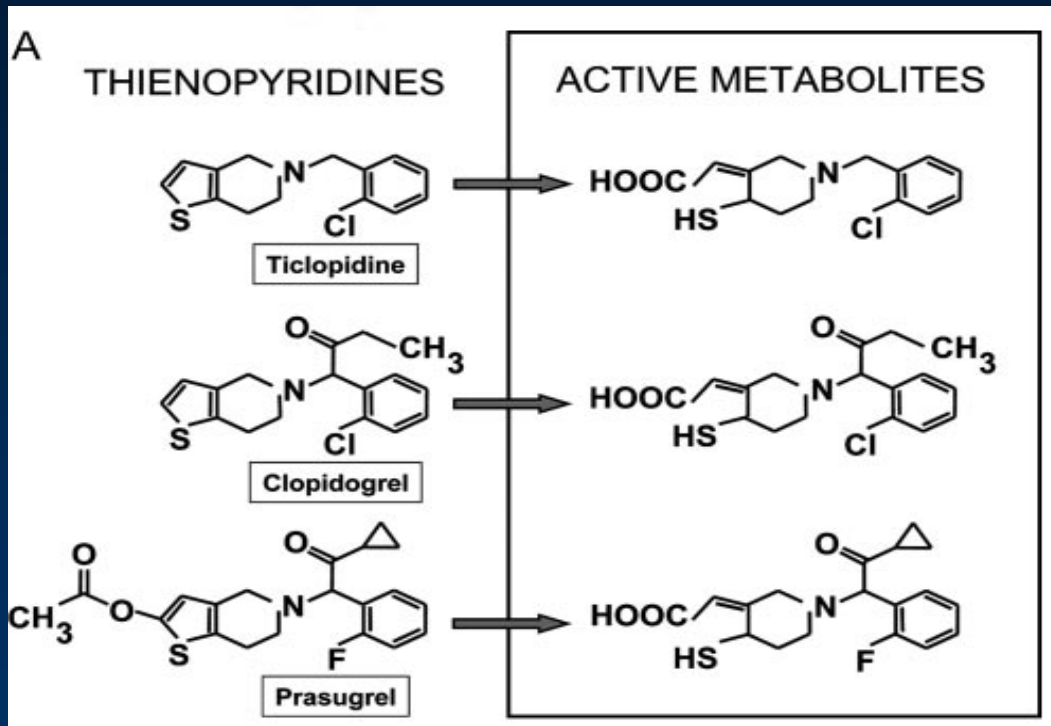
Risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
CYP3A5 non-expression (v. expression)	3.96 (1.12-14.0)	4.89 (1.28-18.7)
Co-administered CYP3A metabolizers† (every increase in no.)	2.15 (1.15-4.03)	2.22 (1.10-4.47)
Age ≥ 65 yr (v. < 65 yr)	0.98 (0.94-1.03)	0.98 (0.93-1.03)
Male sex (v. female)	1.74 (0.64-4.70)	2.08 (0.65-6.61)
Previous MI (v. no previous MI)	0.80 (0.22-2.86)	0.72 (0.17-3.10)
Diabetes mellitus (v. no diabetes)	1.52 (0.57-4.05)	1.15 (0.39-3.40)
LV systolic ejection fraction < 45% (v. > 45%)	1.12 (0.25-5.07)	1.13 (0.20-6.34)
Stent diameter ≥ 2.75 mm (v. < 2.75 mm)	0.89 (0.36-2.23)	0.66 (0.24-1.85)
Stent length ≥ 20 mm (v. < 20 mm)	0.99 (0.92-1.06)	0.98 (0.91-1.06)

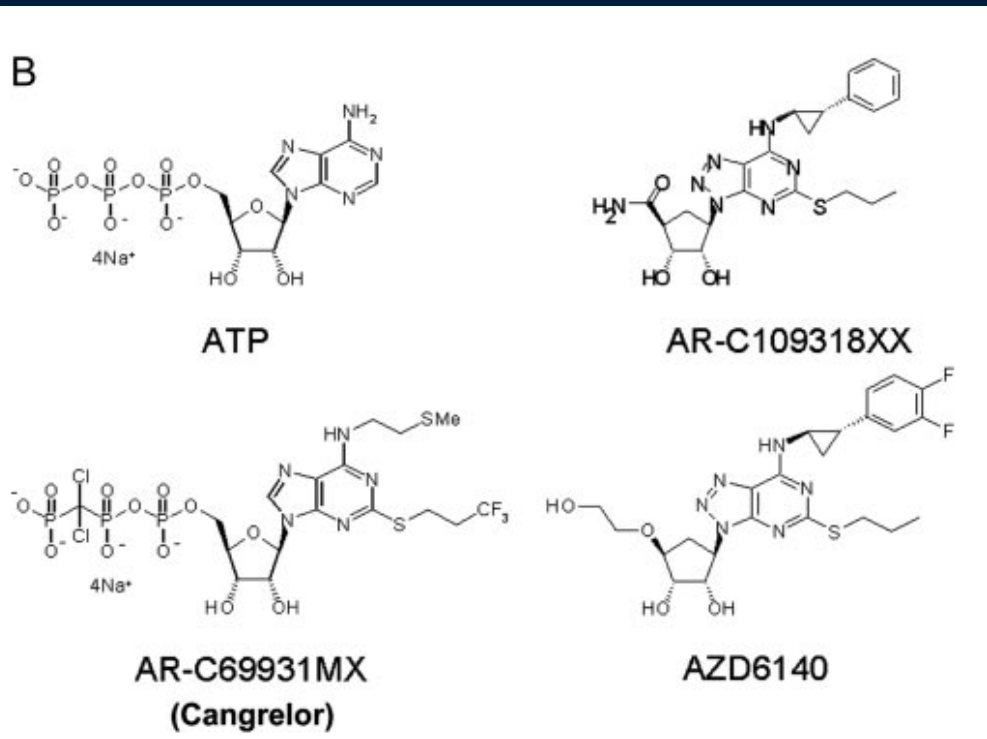
Clopidogrel Alternatives : P2Y12 Rc antagonists

Drug	Structure	Direct or Indirect	Reversible	Route	Frequency	Phase
Ticlopidine	Thienopyridine	I	No	PO	Twice/day	Approved
Clopidogrel	Thienopyridine	I	No	PO	Daily	Approved
Prasugrel	Thienopyridine	I	No	PO	Daily	3
AZD6140	ATP analog	D	Yes	PO	Twice/day	3
Cangrelor	ATP analog	D	Yes	IV	…	3
PRT60128	…	D	Yes	PO, IV	…	1

Michelson AD, Arterioscler Thromb Vasc Biol 2008

Clopidogrel Alternatives : Structures





Thienopyridine

ATP analogs

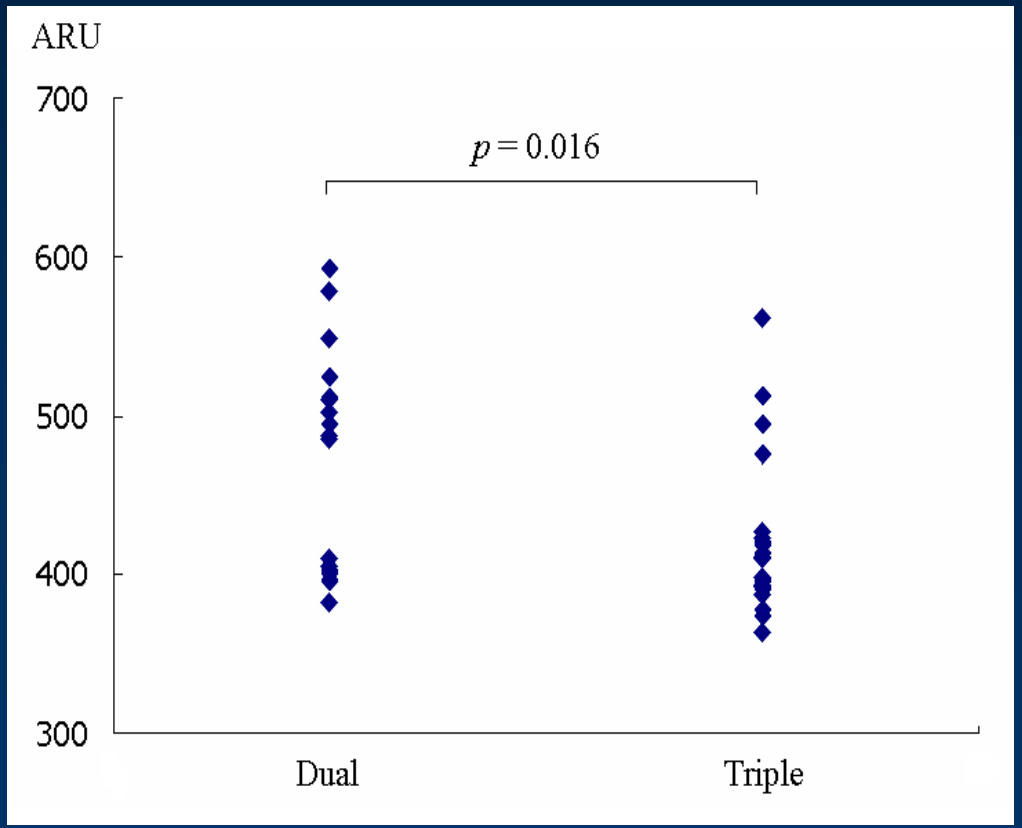
Michelson AD, Arterioscler Thromb Vasc Biol 2008

Clopidogrel Alternative ; under investigation

- Prasugrel
  - Oral thienopyridine
  - TRITON-TIMI 38
  - More rapid & potent, but high bleeding risk
- Cangrelor
  - IV form, direct antagonist of P2Y12 Rc
  - No liver metabolism, potent, short action, facilitated PCI
  - CHMPION-PCI, CHAMPION-PLATFORM : ongoing
- AZD6140
  - Oral ADP antagonist
  - Potency, no liver metabolism
  - PLATO : ongoing

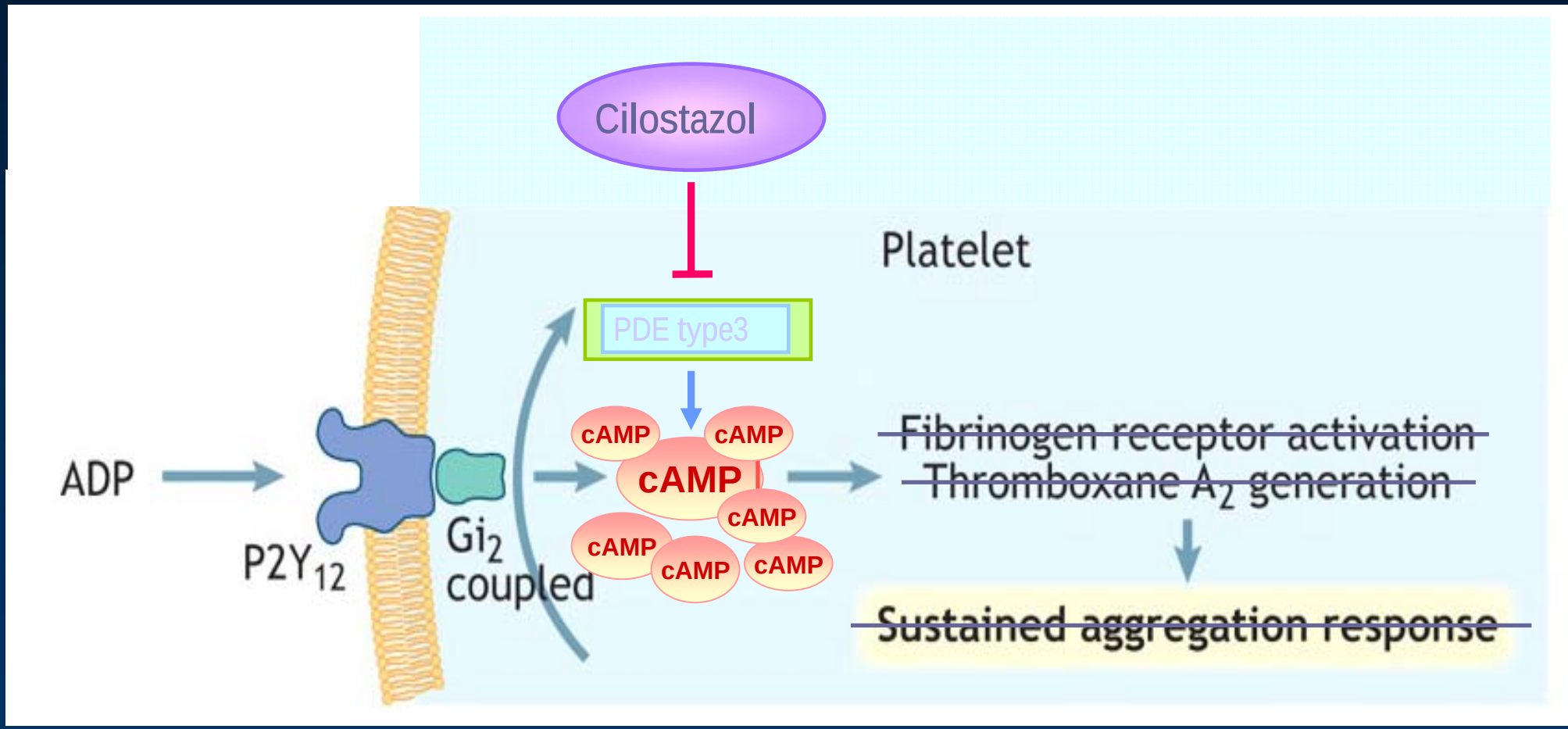
Another antiplatelet agent on top of dual agents

- Triflusal
  - COX-1 / COX-2 inhibition
  - NO production



Suh JW, et al. unpublished

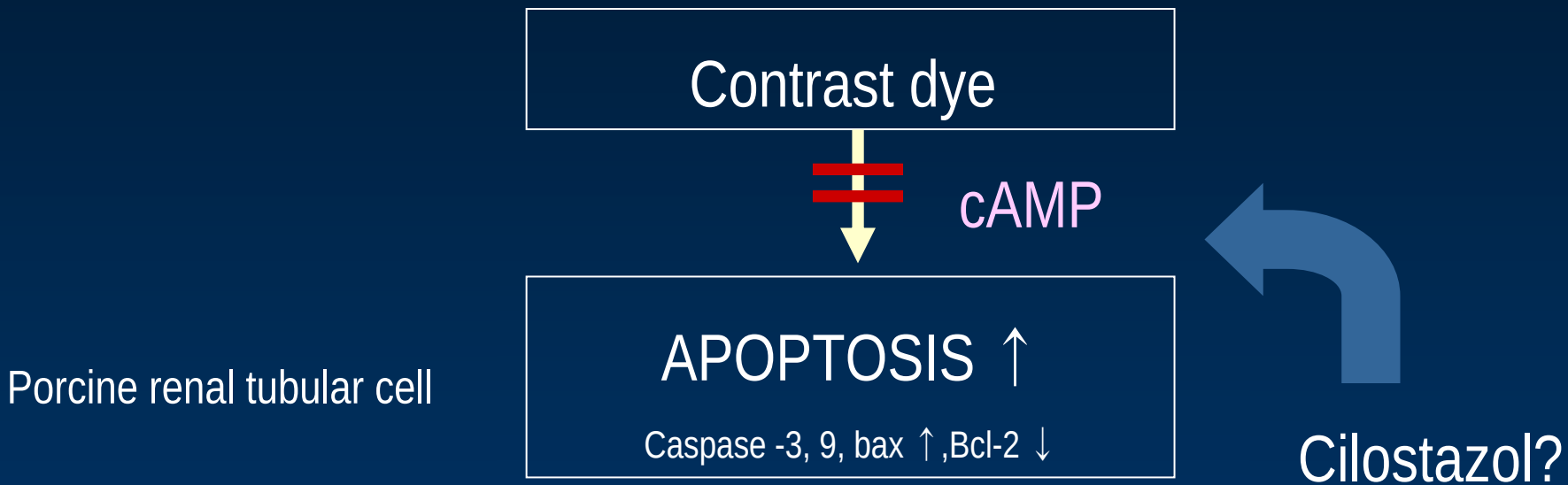
Cilostazol ; anti-platelet effect



Cilostazol ; Other actions → restenosis or CIN ?

- Vasodilation via VSMC
  - Cerebral
  - Low extremities
- Scavenging ROS
- Prevention of cell apoptosis
  - Endothelial cell
  - Brain white matter
  - Renal tubular cell

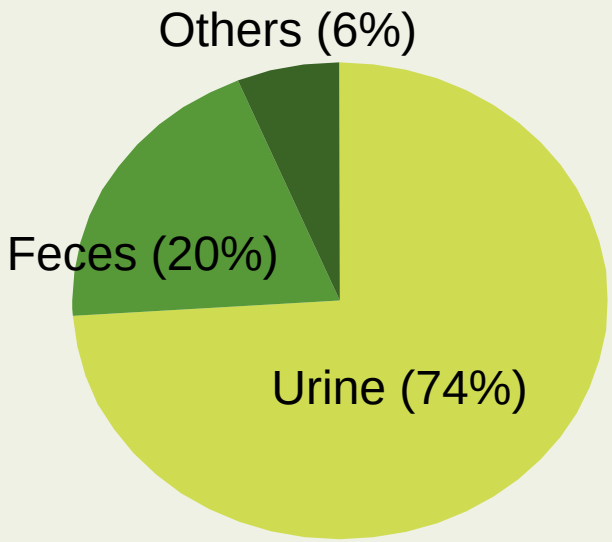
The role of cAMP in RTC



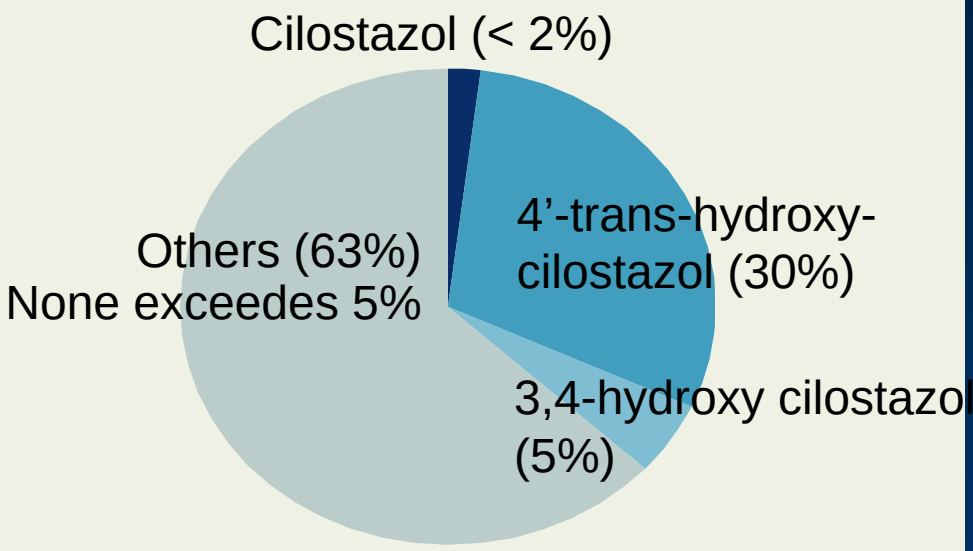
Itoh Y et al, Kidney Int 2006

PK of cilostazol

Excretion route (%)



Excretion forms (%)



CIN ; mechanism

Ischemia d/t vasoconstriction	⟷	Dopamine, Fenoldopam
Apoptosis by direct toxicity	⟷	Theophylline
Apoptosis by oxidative stress	⟷	NAC, Vit C

Cilostazol ; Potential candidate of CIN prophylaxis?

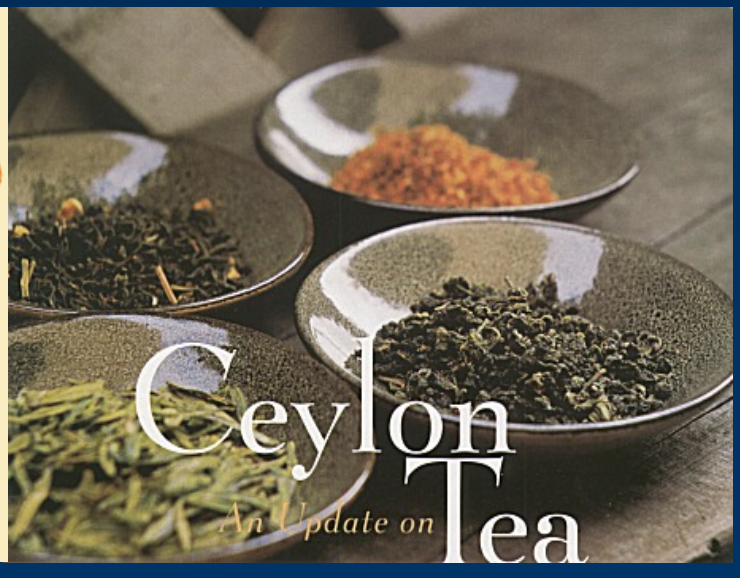
CILON-T trial

- **CIL**ostazol **O**n **N**eointimal growth and **T**hrombotic events in drug-eluting stents
- *Seoul National University Hospital (SNUH)

  *Bundang SNUH *Konyang University Hospital

  *Korea University Guro Hospital *Gwangju Veterans Hospital

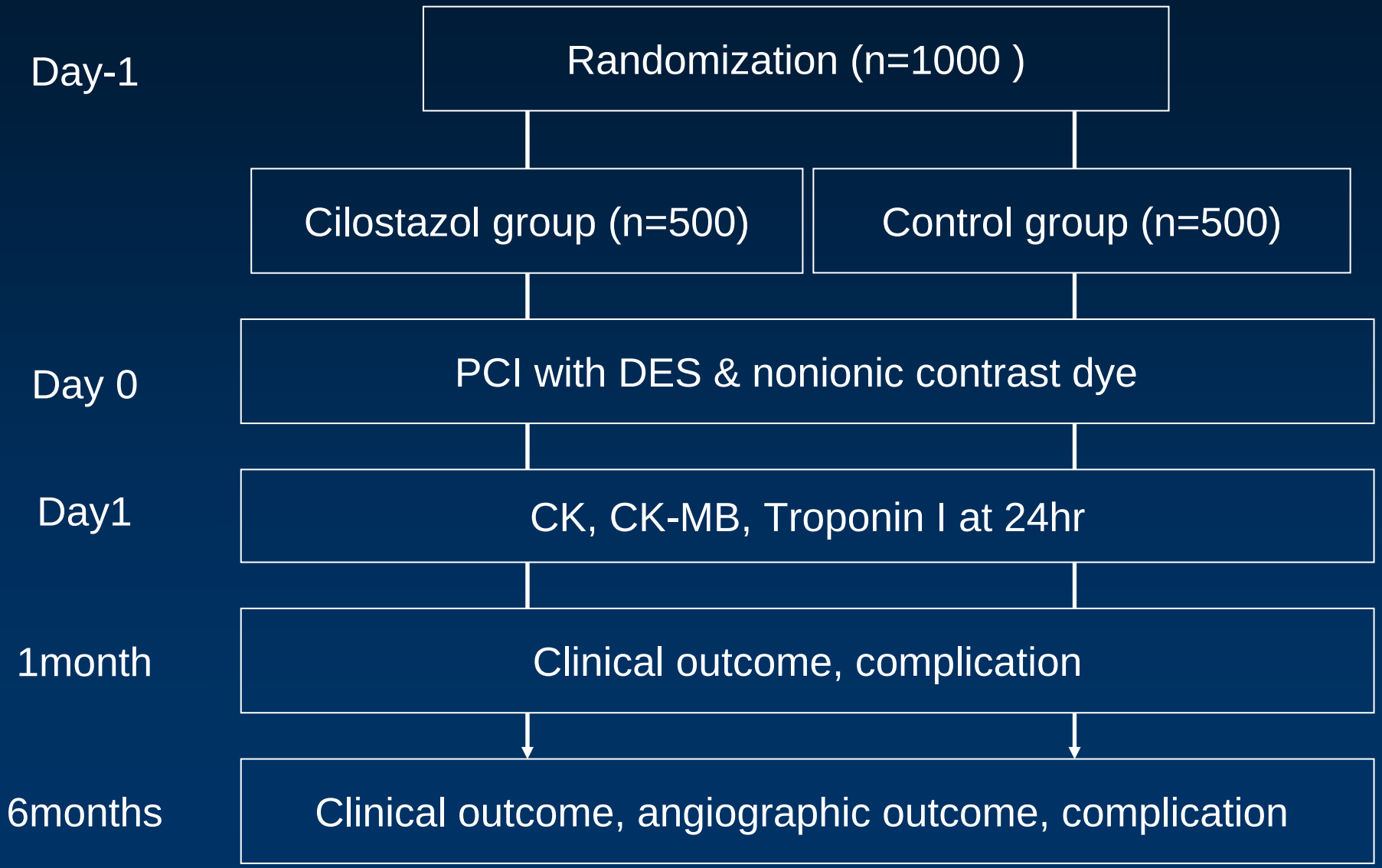
  *Chungbuk National University Hospital



Issues to be answered : background for CILON-T trial

- Statin type & drug interaction with clopidogrel
  - The role of CYP3A system in clopidogrel resistance
  - Head to head comparison of atorvastatin vs. rosuvastatin
- Clopidogrel resistance and genetics
- Cilostazol use in DES era ; thrombotic aspect
- Angiographic outcome according to stent type ; late loss
- Nephro-protective effect of cilostazol

Protocol of CILONT



Medication

- Cilostazol
  - D-1 or D0 ; 200mg qd
  - D1~D180 ; 100mg bid
- Antiplatelet agent ; ASA (100mg)+ Clopidogrel (75mg)
- CYP3A4 inhibitor / substrate
  - Avoid diltiazem, felodipine, nifedipine, cimetidine, erythromycin if possible
- Hydration
  - 0.9% saline for 48hrs
  - Avoid the use of NAC, ascorbic acid

Stratification by statin

	Atorvastatin 20mg/day	Rosuvastatin 10mg/day
ASA+PLAVIX	250	250
ASA+PLAVIX+CILO	250	250

Endpoints

- Primary Endpoint
  - MACE within 6 months (cardiac death, MI, stroke, TLR)
- Secondary Endpoint
  - Scr, Random urine ACR: baseline /6mo
  - Angiographic outcome (late loss, binary restenosis)
  - Bleeding Cx (cerebral, intraocular, Tf $\geq$2units)
  - Platelet function test
    - VerifyNow P2Y12
    - Platelet volume indices (MPV, PDW)
    - Platelet aggregometry
  - Genetic analysis

Current Status (Mar 2008)

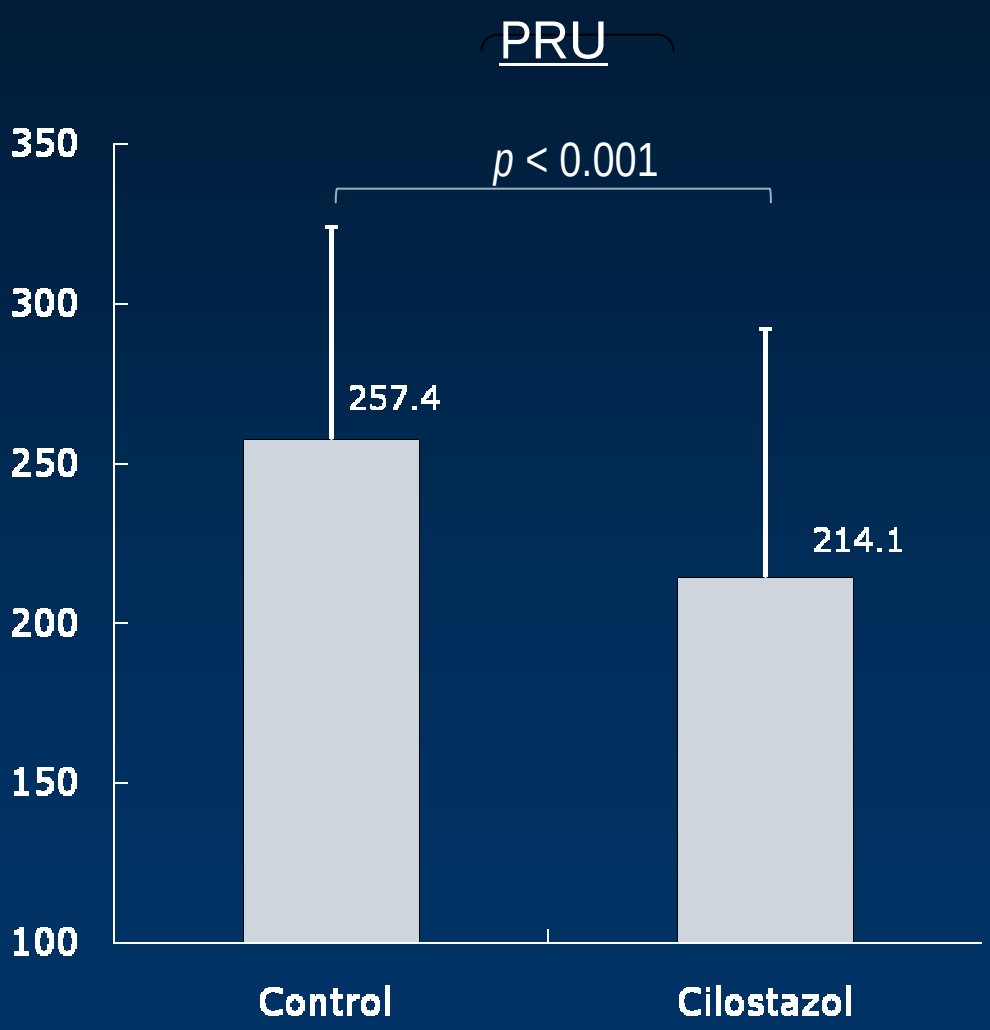
- Total enrollment (n=441, dual 233, triple 208)
- 6 Mo Interim analysis
  - Clinical F/U (n=278)
  - Noncardiac death 1 (suicide)
  - Cardiac death 1
  - MI d/t stent thrombosis 1
  - TLR (n=19), TVR (n=11)

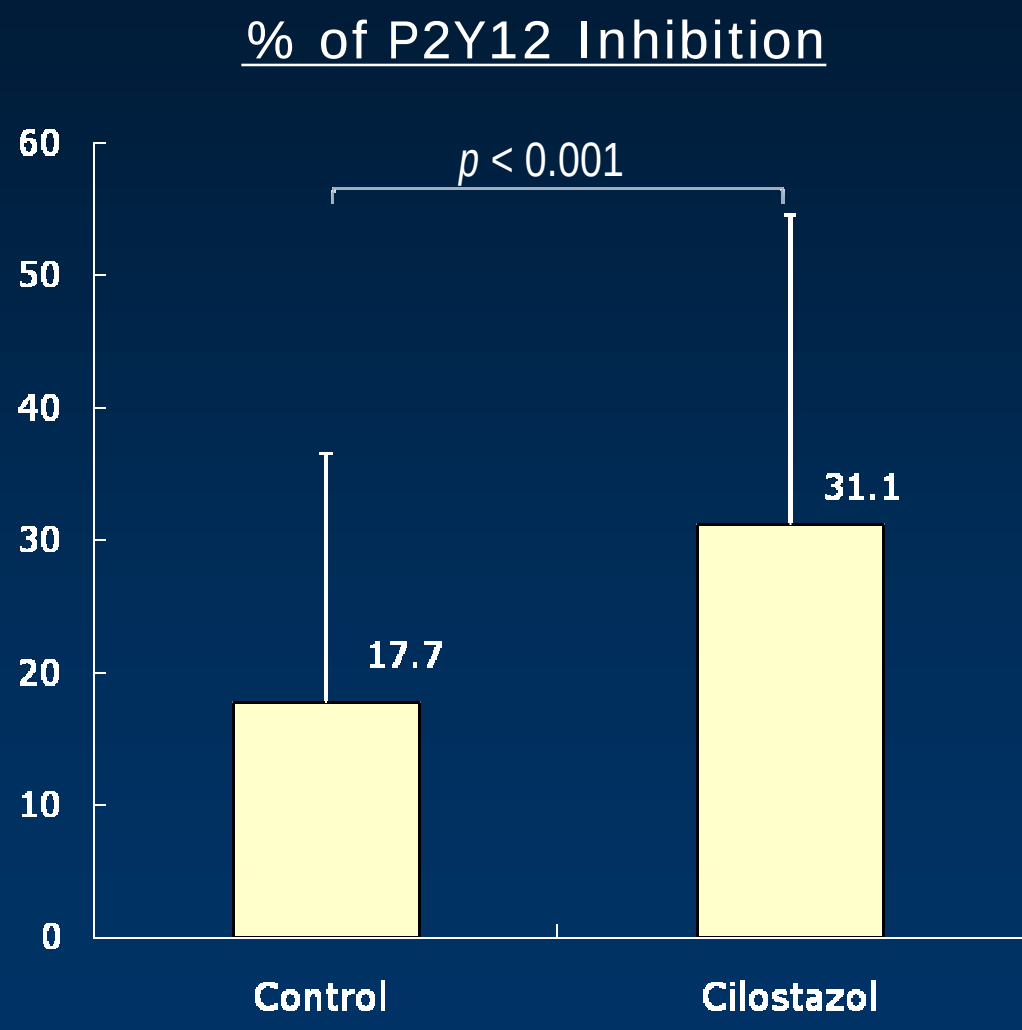
MACE (ITT)

	Dual (n=138)	Triple (n=140)	
Cardiac death	1	0	
MI	1	0	
Ischemic stroke	0	0	
TLR	12	7	
Composites	14	7	P=0.12

*A case of pulmonary embolism in the dual group

Platelet inhibition by cilostazol (6Mo F/U)





Control (n=109), Cilostazol (n=112)

Breakthrough of Clopidogrel Resistance?

	Dual (n=109)	Triple (n=112)
Resistance (+)	34 (31.2%)	22 (19.6%)
Resistance (-)	75 (68.8%)	90 (80.4%)

*p = 0.06

** Resistance : Highest Quartile of PRU (>286 unit)

Breakthrough of Clopidogrel Resistance?

	Dual (n=109)	Triple (n=112)
Resistance (+)	50 (45.9%)	29 (25.9%)
Resistance (-)	59 (54.1%)	83 (74.1%)

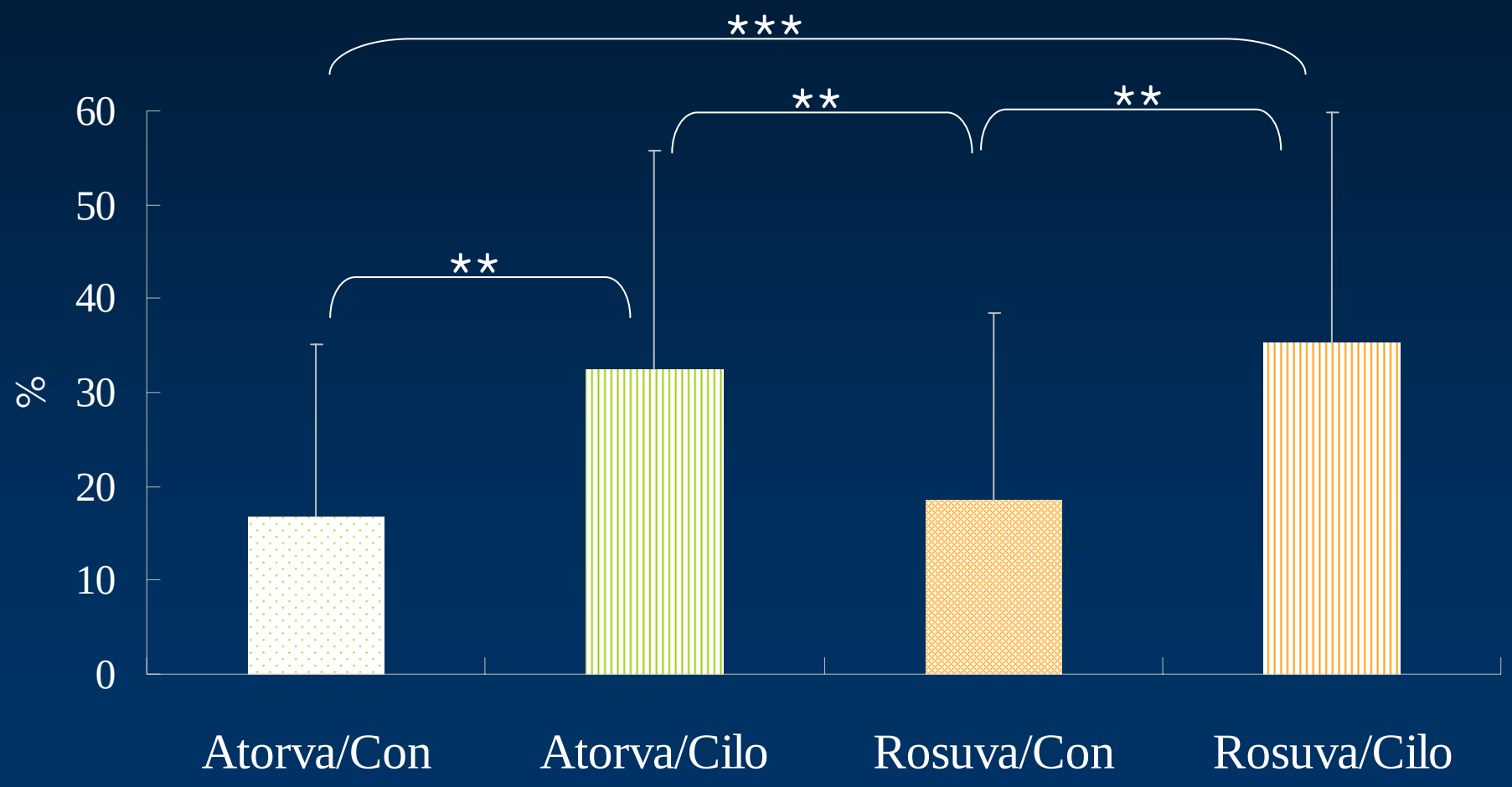
*p = 0.002

** Resistance : P2Y12 inhibition <10%

Platelet inhibition by cilostazol & statin type

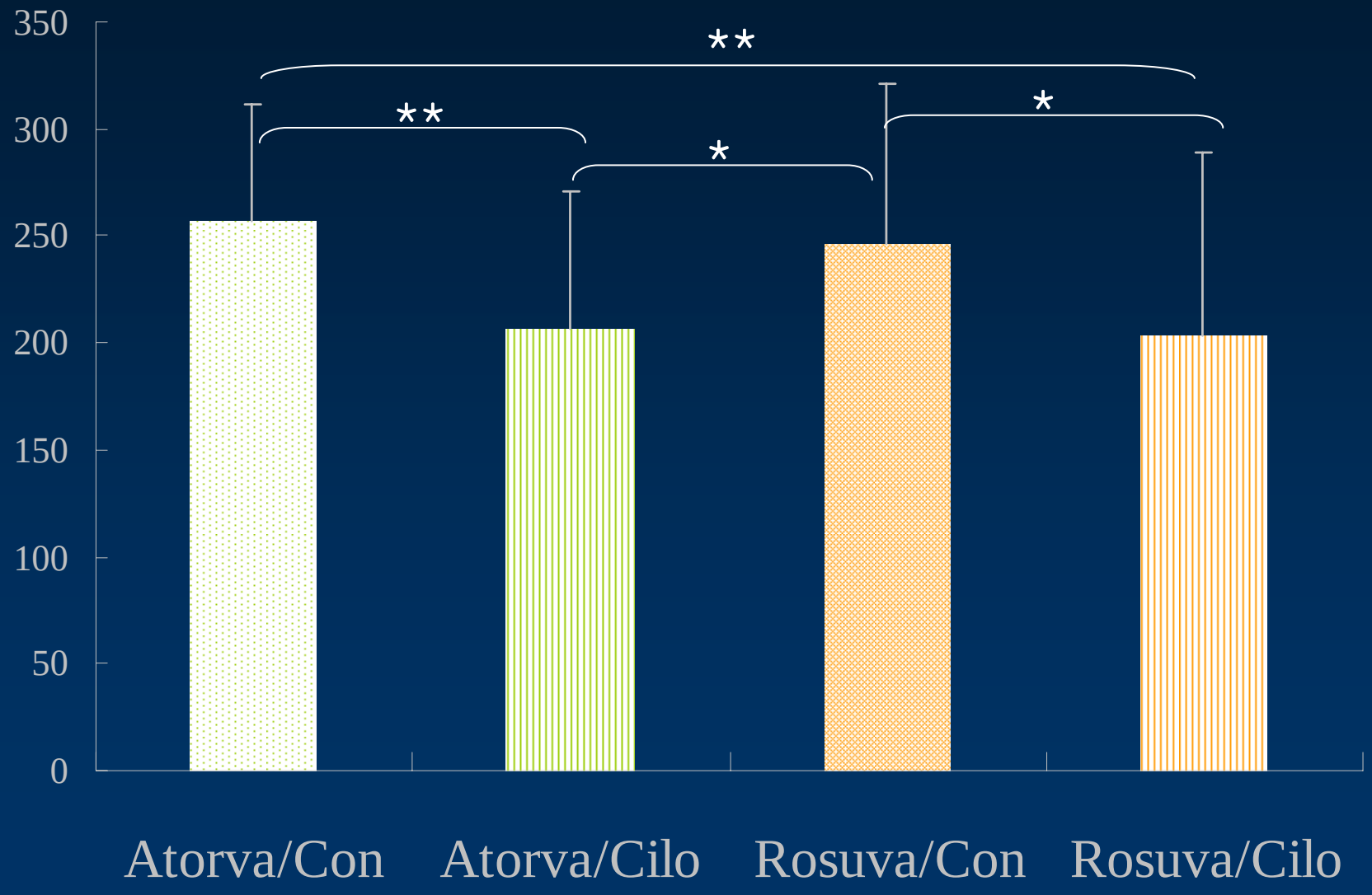
6 Mo	Atorva / Con (n=50)	Atorva / Cilo (n=51)	Rosuva / Con (n=50)	Rosuva / Cilo (n=46)	*p*
P2Y12 inhibition (%)	16.8±18.4	32.4±23.4	18.6±19.9	35.3±24.5	<0.001
Absolute PRU (unit)	256.7±59.2	206.9±74.9	246.4±73.9	203.2±81.9	<0.001

P2Y12 inhibition at 6 Mo



*** <0.001 ** <0.01 * <0.05

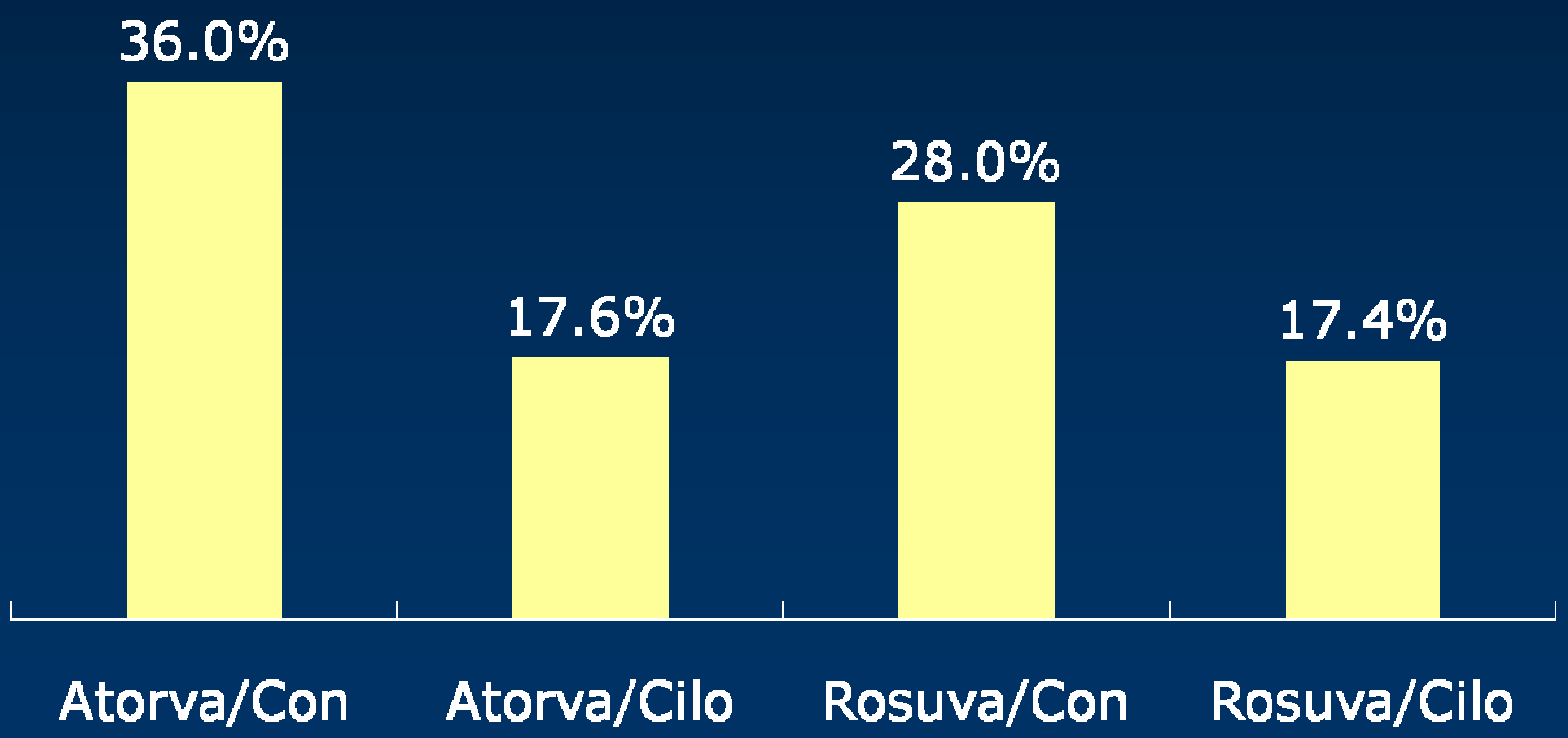
Absolute PRU level at 6 Mo



*** <0.001 ** <0.01 * <0.05

Pts with clopidogrel resistance : Interaction with statin ?

- Pts with highest quartile PRU (PRU>283)



Summary

- Clopidogrel resistance is clinically important.
- The interaction of statin type with clopidogrel resistance is not conclusive yet, but should be examined with follow up data of CILON-T trial.
- Cilostazol can be a good candidate of breakthrough of clopidogel resistance.
- Drug interaction & CYP 3A5 genotype ; pending
- Nephro-protective effect of cilostazol ; pending

Conclusion

Is the 3rd agent a solution

for the resistance against dual anti-platelet agents?

Yes, it can be.