Translational Cardiology: Where are we now?

One example of research ‘from bench to bedside’

(from Akt/COX2 to Mini-COREA clinical trial)

Hyo-Soo Kim, MD/PhD

Cardiovascular Center / Cardiovascular Research Laboratory

Seoul National University Hospital, Seoul, Korea

Modern Medicine is the Result of Translational Research

1. New Drugs

: RAAS biology → ACEI, ARB, RI

: Cholesterol metabolism → Statin, Ezetimibe

: Cell Signalling pathway → Monoclonal Ab to cancer

1. New Devices

: Taxol, limus → inhibitor of cell proliferation → DES

1. New Therapeutic Modality

: Stem cell biology → Cell therapy clinical trial

Focus of Translational Research
CV Laboratory in SNUH

#1 program

Search for Adjunctive Drugs

To Solve Restenosis after Coronary Stenting

#2 program

Search for Optimal Cell Therapy Protocol

To Solve Heart Failure after Myocardial Infarction

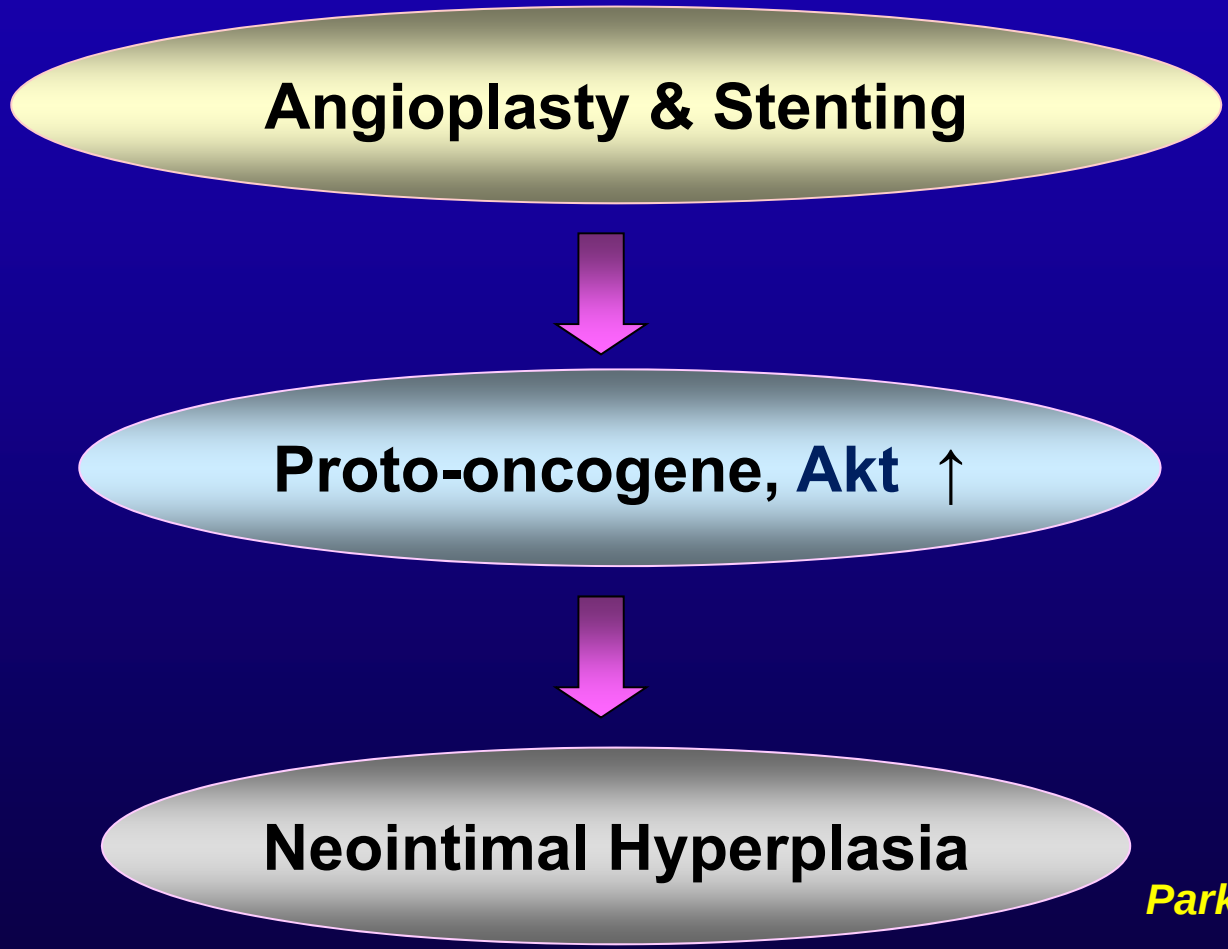
History of SNUH Akt/COX2 inhibitor Program
Communication between bench and bed side

1. Initiation point of Akt & Celecoxib at bench
2. Cautious Consideration between bench & bed-side
3. First clinical trial (COREA-TAXUS): bench to bed-side
4. Return to bench : further complicated story

   : Taxol → COX2 → MDR-1 → Neointima
5. Feasibility confirmation between bench & bed-side

   : genotype of MDR-1 in patients with DES
6. Second clinical trial (mini-COREA) : bench to bed-side

Molecular Mechanism for Neointimal Hyperplasia after Angioplasty



Park KW et al. ATVB 2003

Zhou RH et al. ATVB 2003

Shigematsu K et al. ATVB 2000

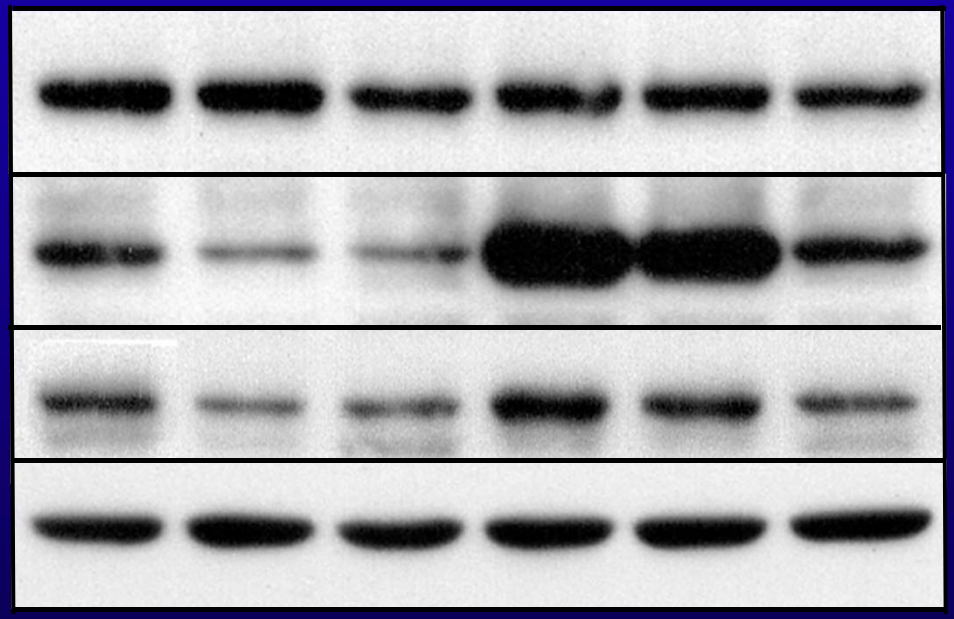
Celecoxib

- Selective COX-2 inhibiting anti-inflammatory agent
- Other pleiotropic effect of Celecoxib
  - Anti-proliferative effect
  - Pro-apoptotic effect
  - Anti-tumor effect
- Efficacy to prevent colorectal polyps

→ tested in 2 large randomized controlled trials

- *APC* (Adenoma Prevention with Celecoxib) Trial
- *PreSAP* (Prevention of Colorectal Sporadic Adenomatous Polyps) Trial

Celecoxib Inhibits Activation of Akt pathway in VSMC



Seoul National University Hospital, Seoul, Korea

Yang HM et al. Circulation 2004

Initiatioin point at bench: Akt/COX2 program

Celecoxib, a Cyclooxygenase-2 Inhibitor, Reduces Neointimal Hyperplasia Through Inhibition of Akt Signaling

Han-Mo Yang, MD; Hyo-Soo Kim, MD; Kyung-Woo Park, MD; Hyun-Jeong You, BA; Soo-In Jeon, BA; Seock-Won Youn, MS; Sung-Hwan Kim, MD; Byung-Hee Oh, MD; Myoung-Mook Lee, MD; Young-Bae Park, MD; Kenneth Walsh, PhD

Background—Celecoxib has been shown to have antitumor effects that may be mediated through the cyclooxygenase-independent inhibition of Akt signaling. Here, we examined the effects of celecoxib on neointimal formation after balloon injury and its mechanism of action.

Methods and Results—In vitro experiments were performed to evaluate the effects of celecoxib on the Akt/GSK signaling axis and the viability of rat vascular smooth muscle cells (VSMCs). In vivo experiments examined the effects of celecoxib, aspirin, and vehicle on neointimal growth after denudation injury to rat carotid arteries. In vitro, celecoxib suppressed the phosphorylation of Akt and GSK in cultured VSMCs, leading to a reduction in viable cell number, which was reversed by transduction of constitutively active Akt. Such a reduction in cell number was mediated by inhibition of proliferation and induction of apoptosis. In vivo, celecoxib reduced injury-induced phosphorylation of Akt and GSK, reduced VSMC proliferation, and increased caspase-3 activation and VSMC apoptosis at 3 days after injury, whereas aspirin had no effect. At 2 weeks after injury, celecoxib reduced intima-to-media ratio, whereas aspirin had no effect. Adenovirus-mediated delivery of dominant negative Akt was as effective as celecoxib at inhibiting neointimal formation. Conversely, gene delivery of constitutively active Akt significantly reversed the inhibition of intimal hyperplasia by celecoxib, providing causal evidence that the modulation of Akt signaling by celecoxib is a physiologically relevant mechanism.

Conclusions—Celecoxib is a potential inhibitor of neointimal formation by blocking injury-induced Akt activation. These findings suggest a potential use for celecoxib in the prevention of restenosis after angioplasty. (***Circulation***. **2004;110: 301-308.)**

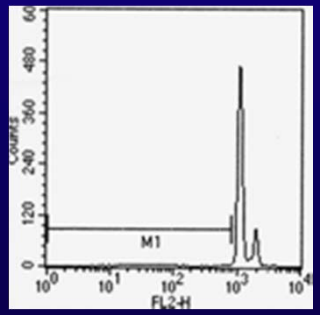
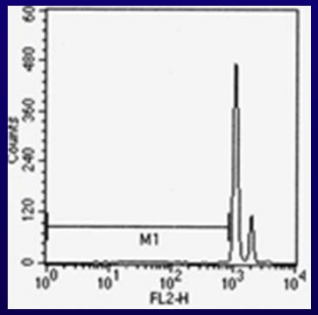
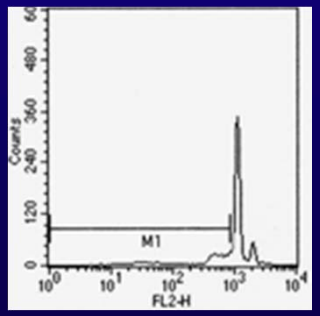
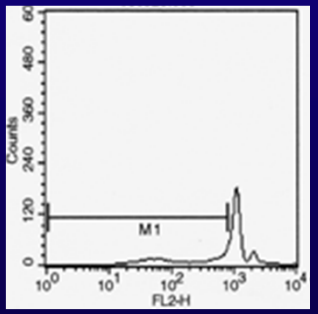
Key Words: Akt ■ cyclooxygenase inhibitors ■ restenosis ■ apoptosis ■ muscle, smooth

Seoul National University Hospital, Seoul, Korea

Yang HM, Kim HS, et al. Circulation 2004

Celecoxib Inhibits Proliferation & Induces Apoptosis of VSMCs

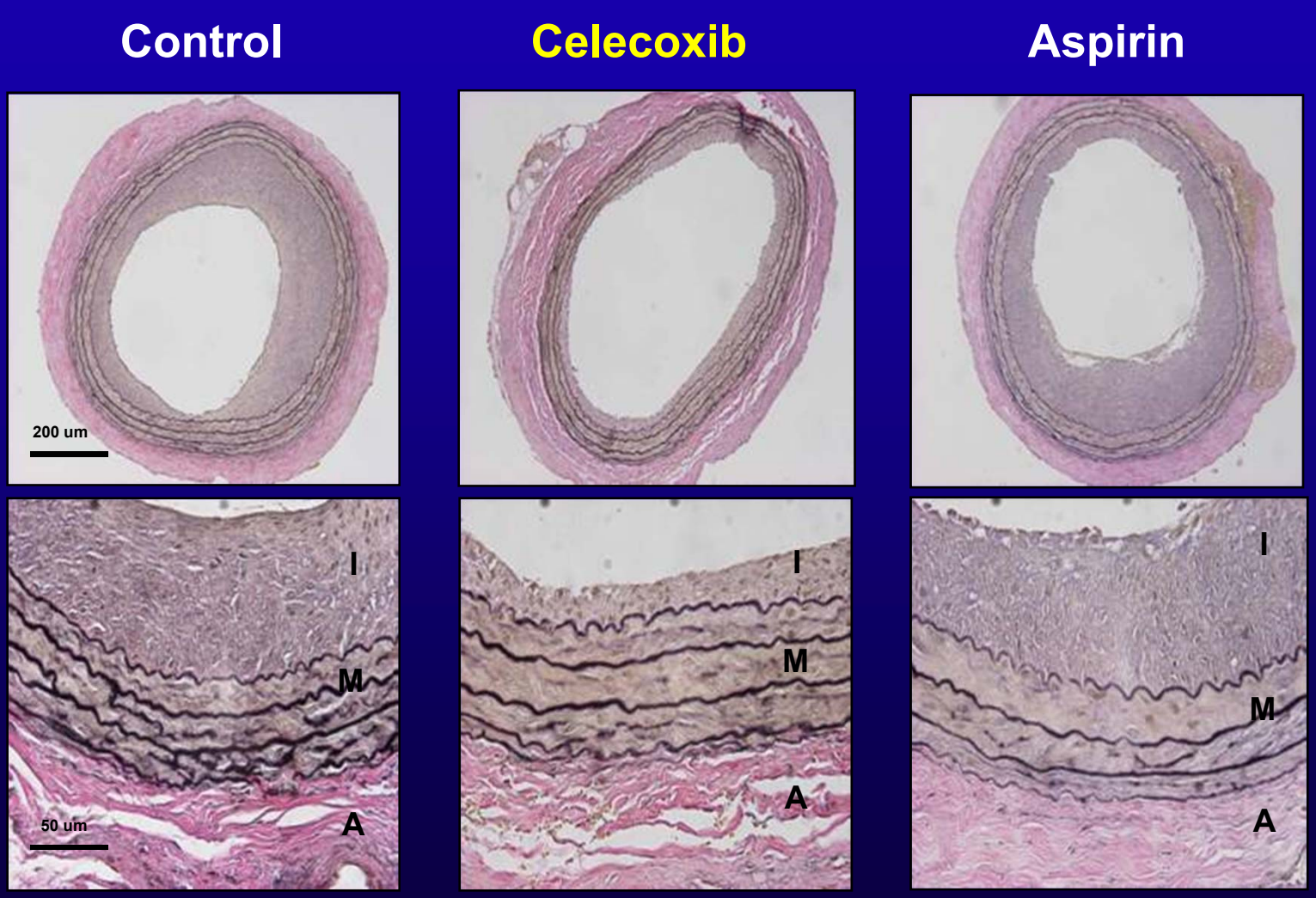
Cell Cycle Percent of Cells				
G1	85.8±2.2	81.2±1.1	87.3±1.3 *	92.7±2.1 *
S	6.8±1.4	10.3±1.2	5.3±1.4 *	3.1±1.0 *
G2-M	7.5±0.9	8.5±0.2	7.5±1.2	4.2±1.4 *

	Vehicle	+PDGF	CXB 5uM+PDGF	CXB 10uM+PDGF
Apoptosis				
Percent of Cells	4.4±0.5%	4.0±0.5%	16.6±1.4% *	24.7±2.5% *

Seoul National University Hospital, Seoul, Korea

Yang HM, Kim HS, et al. Circulation 2004

Celecoxib Inhibits Neointimal Hyperplasia in vivo



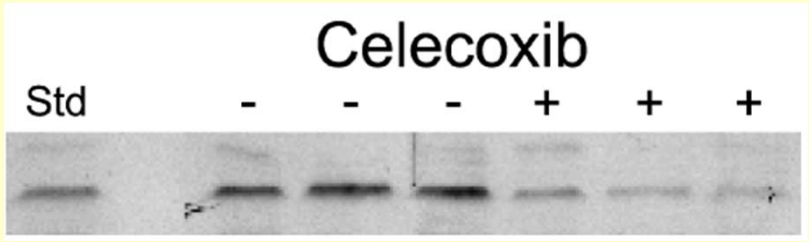
Seoul National University Hospital, Seoul, Korea

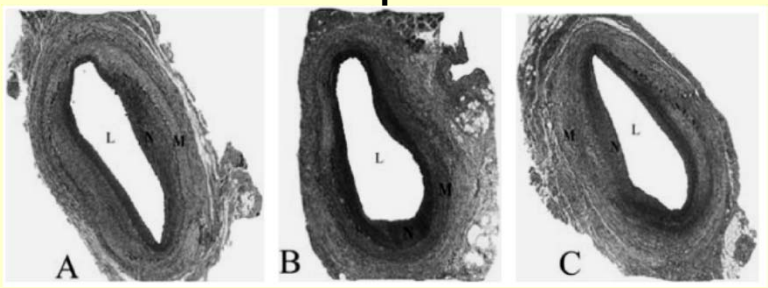
Yang HM et al. Circulation 2004

Beneficial Effect of Celecoxib in CV Disease

Experimental Data
Celecoxib Inhibits NIH
by suppressing MCP-1 Expression & MMP-2 Activity

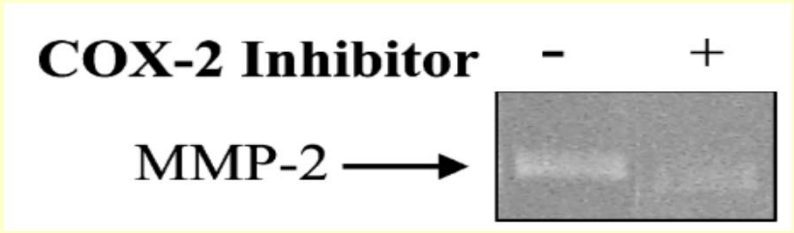
Decrease MCP-1 Expression

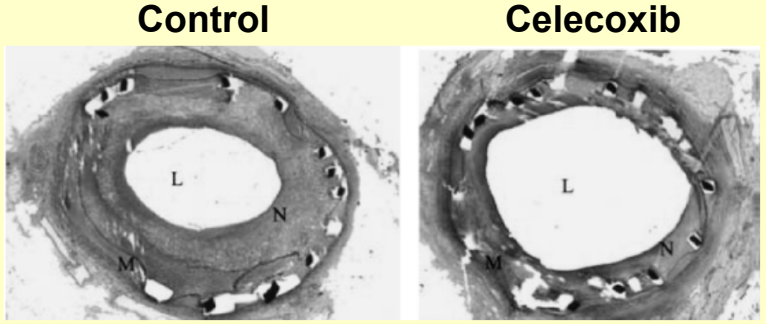




Celecoxib inhibits NIH after balloon injury

Inhibit MMP-2 Activity





Celecoxib inhibits NIH after stenting

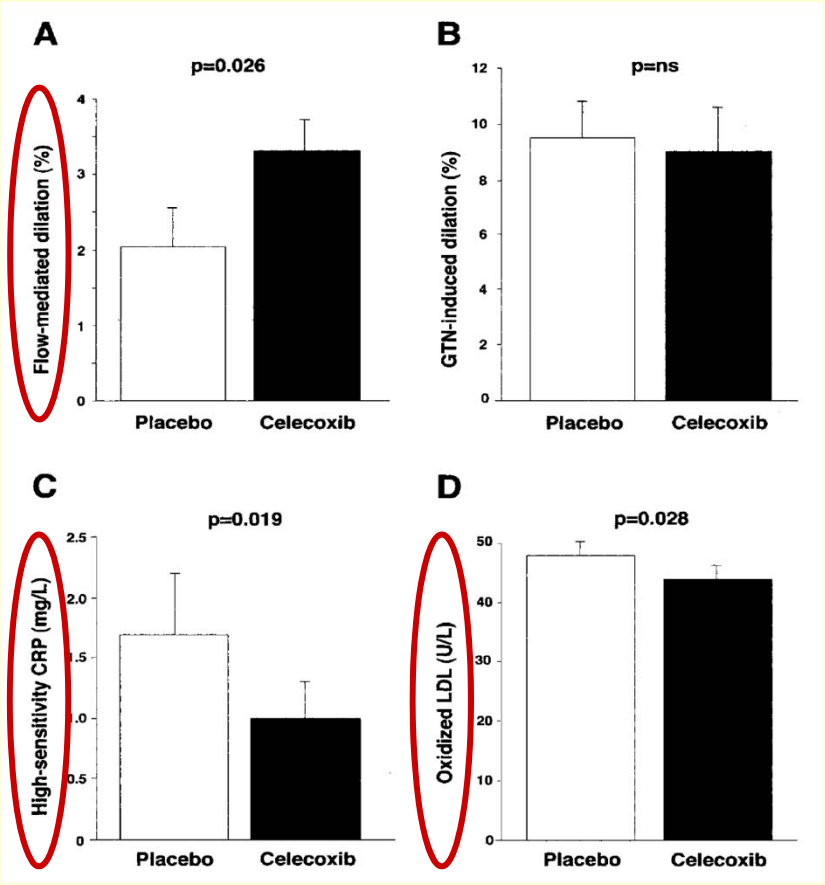
Seoul National University Hospital, Seoul, Korea

Wang K et al. J Cardiovasc Pharmacol 2005

Beneficial Effect of Celecoxib in CV Disease

Clinical Data

Celecoxib improves endothelial function in pts with CAD



Celecoxib

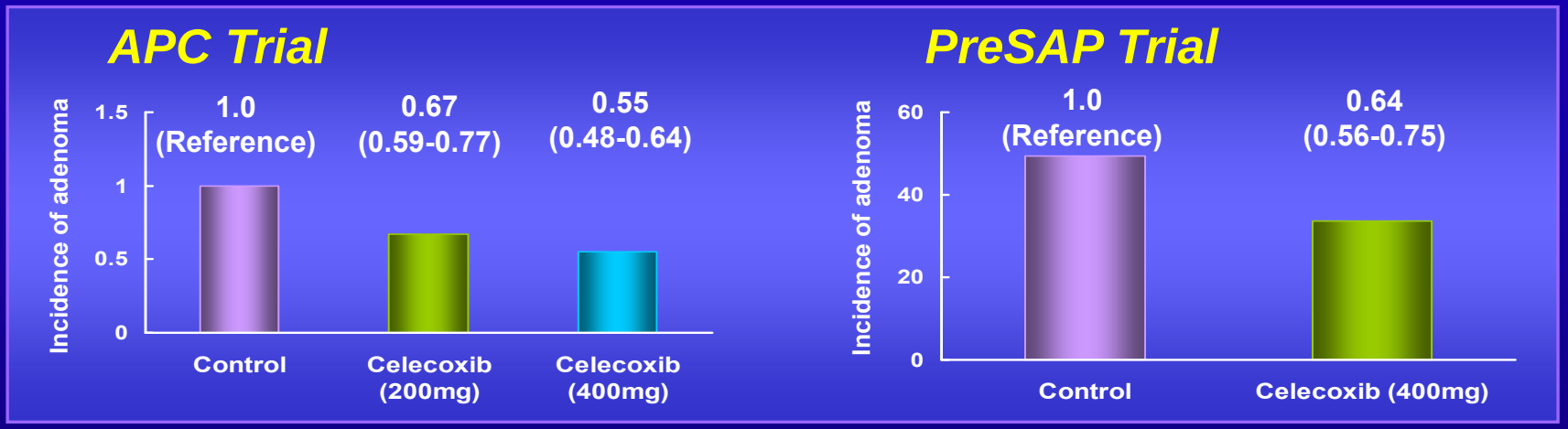
- **Improves endothelial function**
- **Reduces chronic inflammation**
- **Reduces oxidative stress**

in patients with CAD

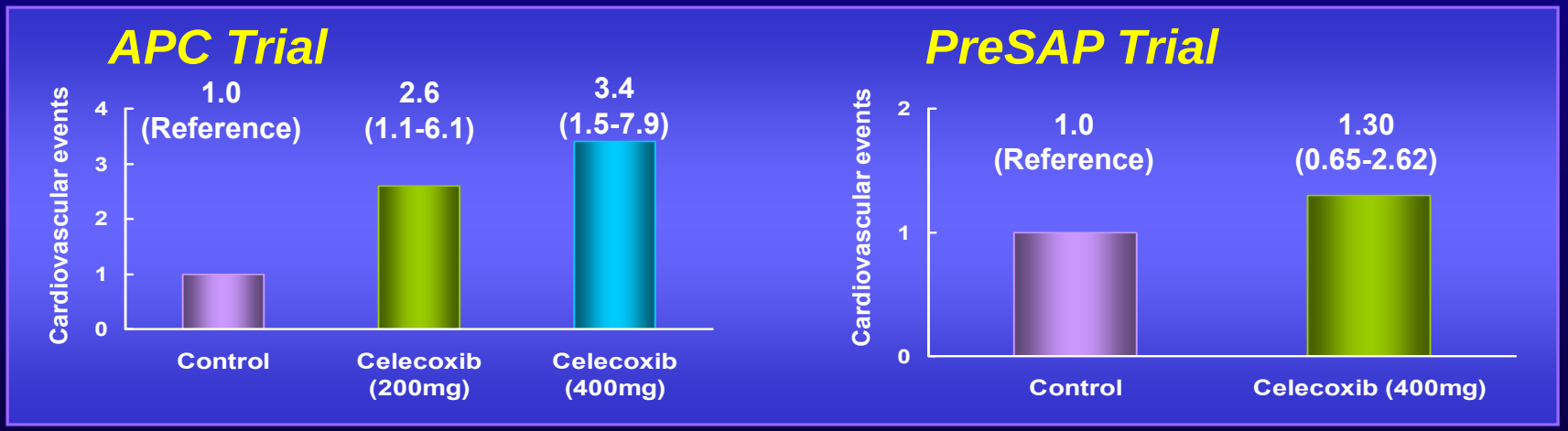
Chenevard R et al. Circulation 2003

APC & PreSAP Trial : RCT of Celecoxib for Adenoma

- **Effective in prevention of colorectal adenoma**



- **May increase risk of cardiovascular events**



Bertagnolli MM et al. NEJM 2006, Arber N et al. NEJM 2006

History of SNUH Akt/COX2 inhibitor Program

Communication between bench and bed side

1. Initiation point of Akt & Celecoxib at bench

2. Cautious Consideration between bench & bed-side

3. First clinical trial (COREA-TAXUS): bench to bed-side

4. Return to bench : further complicated story

   : Taxol → COX2 → MDR-1 → Neointima

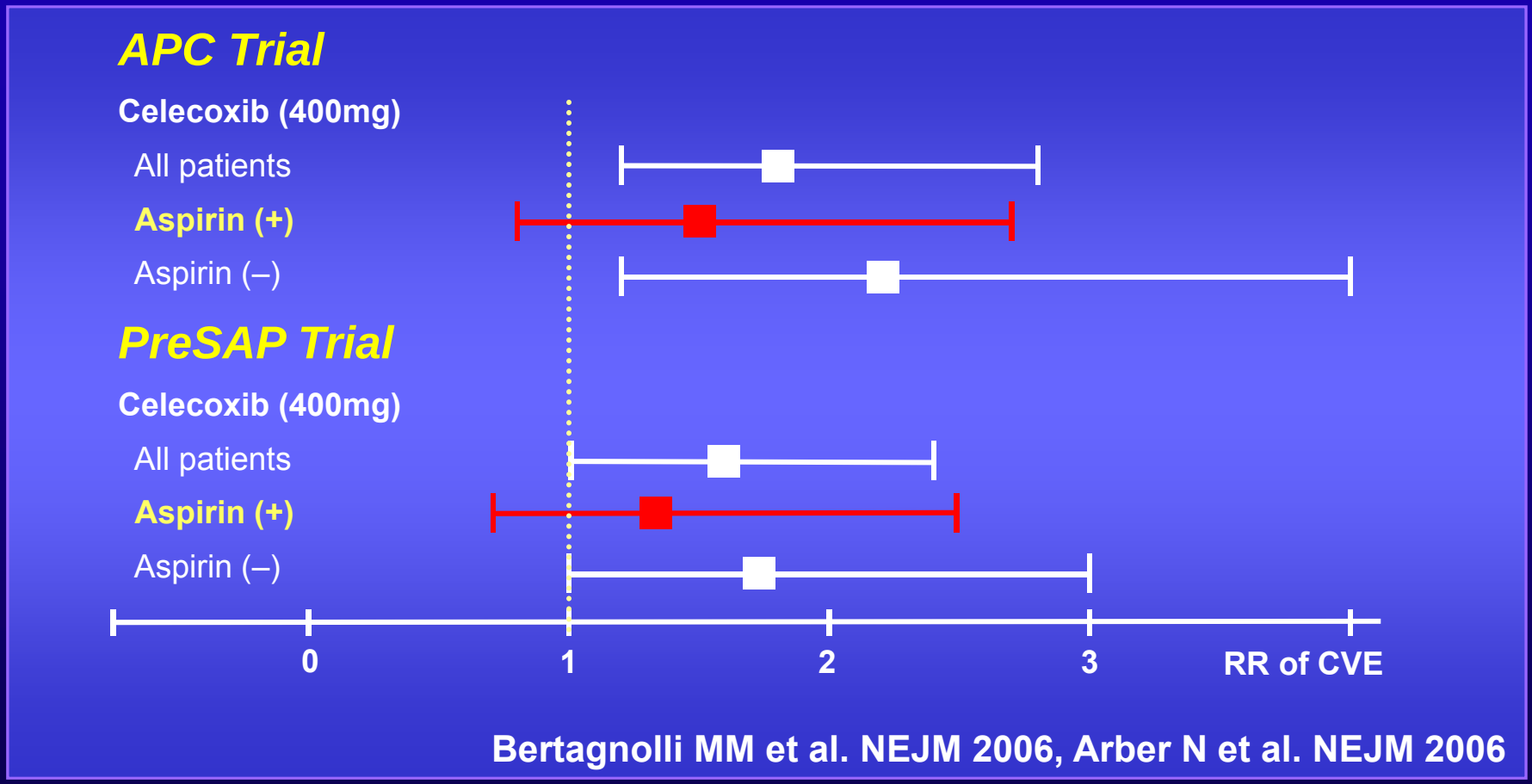
5. Feasibility confirmation between bench & bed-side

   : genotype of MDR-1 in patients with DES

6. Second clinical trial (mini-COREA) : bench to bed-side

APC & PreSAP Trial ; Combination of ASA & Celecoxib

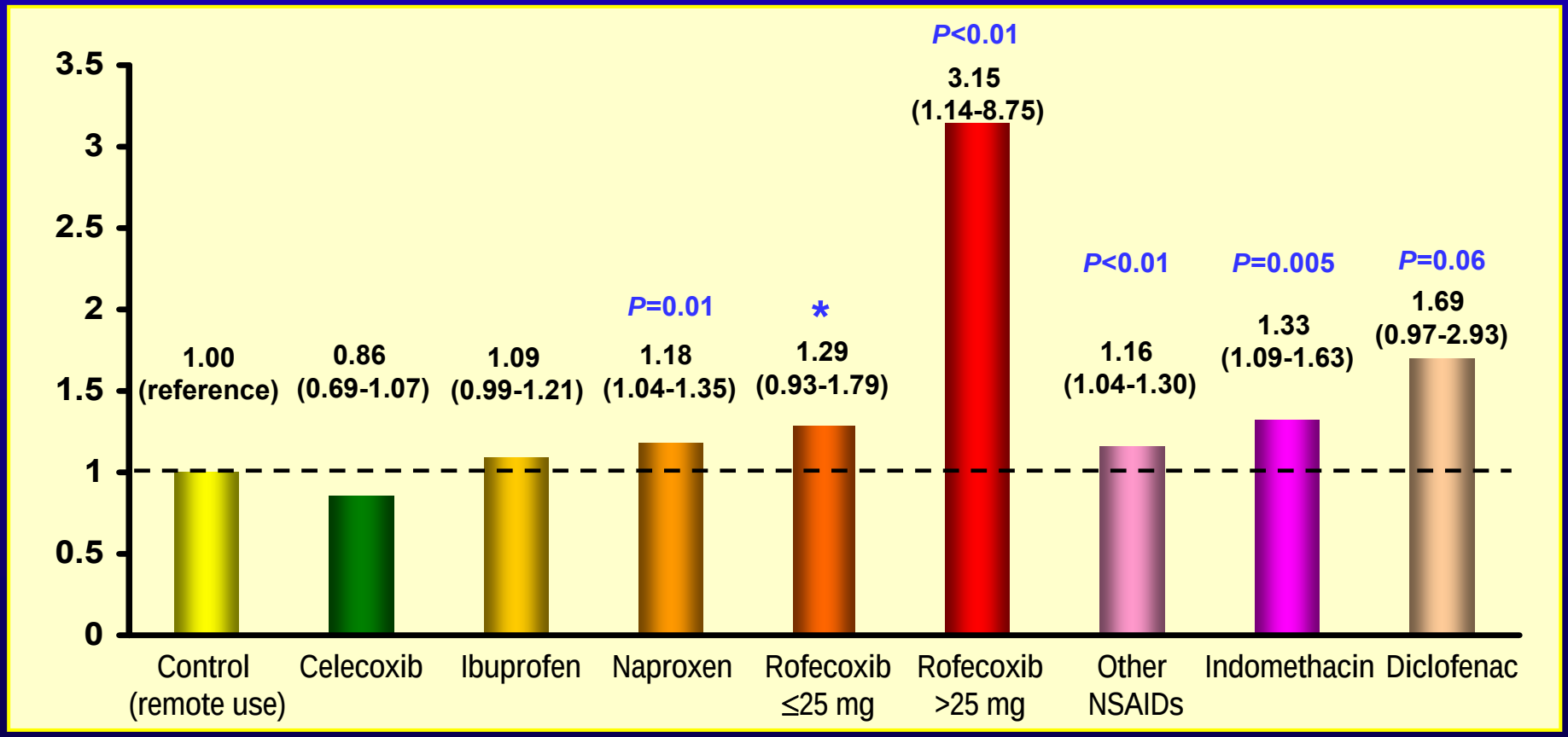
- **Combination with low-dose Aspirin may negate risk.**



Bertagnolli MM et al. NEJM 2006, Arber N et al. NEJM 2006

- **Duration of Celecoxib treatment : over 1 year.**
- **The severity & extent of CAD : not evaluated.**

Risk of AMI & SCD with Current Use of NSAIDs
: Meta-analysis of Case-Control Observational DB



The study cohort was derived from the 6 million Kaiser-Permanente members in California

AMI=acute myocardial infarction; SCD=sudden cardiac death. **P*=0.04 compared with celecoxib.
†Adjusted for age, gender, health plan region, medical history, smoking, and medication use.

Graham DJ et al. Lancet 2005

Meta-analysis of observational studies ; NSAID & CV Risk (N > 1.6 million)

Cyclooxygenase-1 & 2 Inhibitor

	RR	95% CI
Diclofenac	1.40	(1.16-1.70)
Indomethacin	1.30	(1.07-1.60)
Ibuprofen	1.07	(0.97-1.18)
Piroxicam	1.06	(0.70-1.59)
Naproxen	0.97	(0.87-1.07)

Cyclooxygenase-2 selective inhibitor

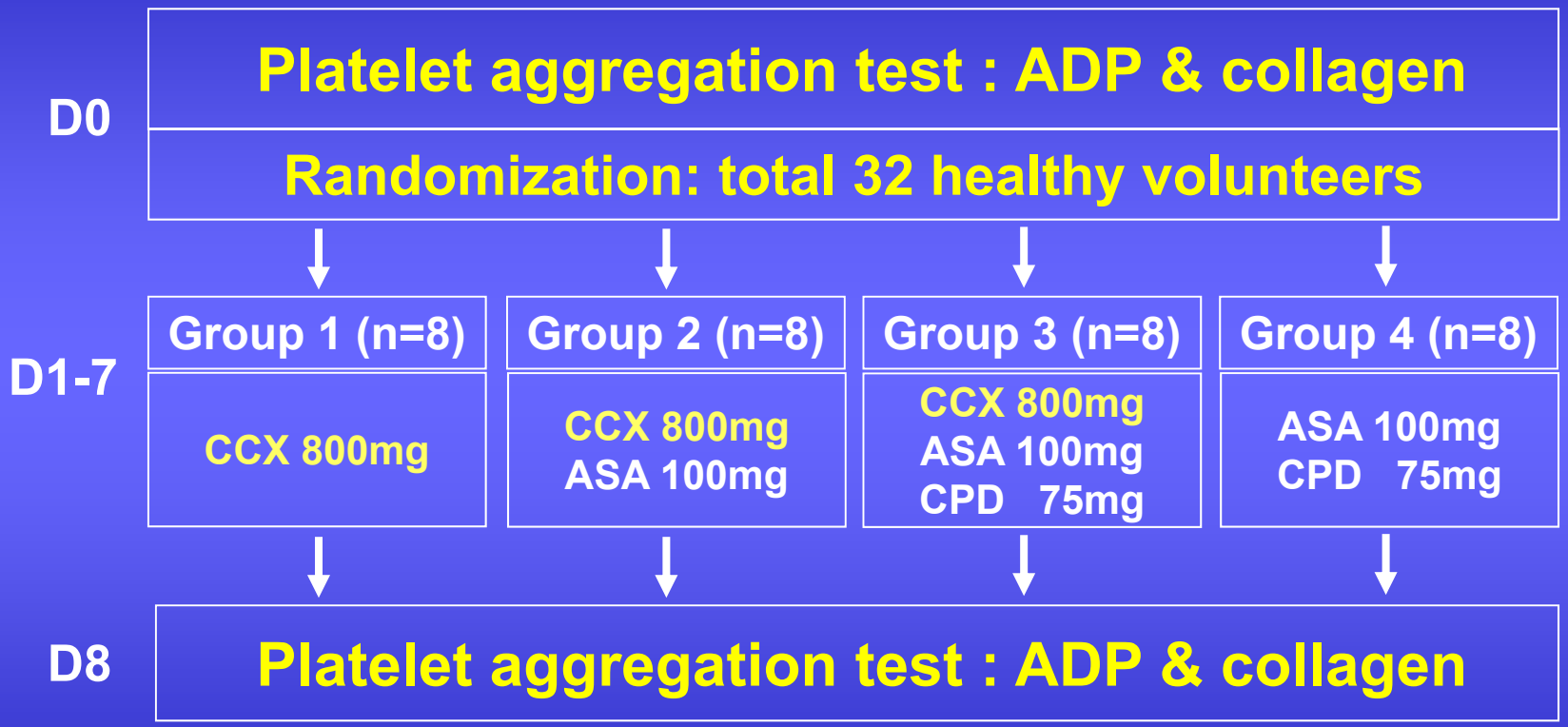
	RR	95% CI
Rofecoxib	1.35	(1.15-1.59)
Meloxicam	1.25	(1.00-1.55)
Celecoxib	1.06	(0.91-1.23)

Patricia McGettigan & David Henry. *JAMA. 2006;296:1633-1644*

Effect of Celecoxib on Anti-platelet therapy

Anti-platelet effects with co-administration of Celecoxib in healthy volunteers

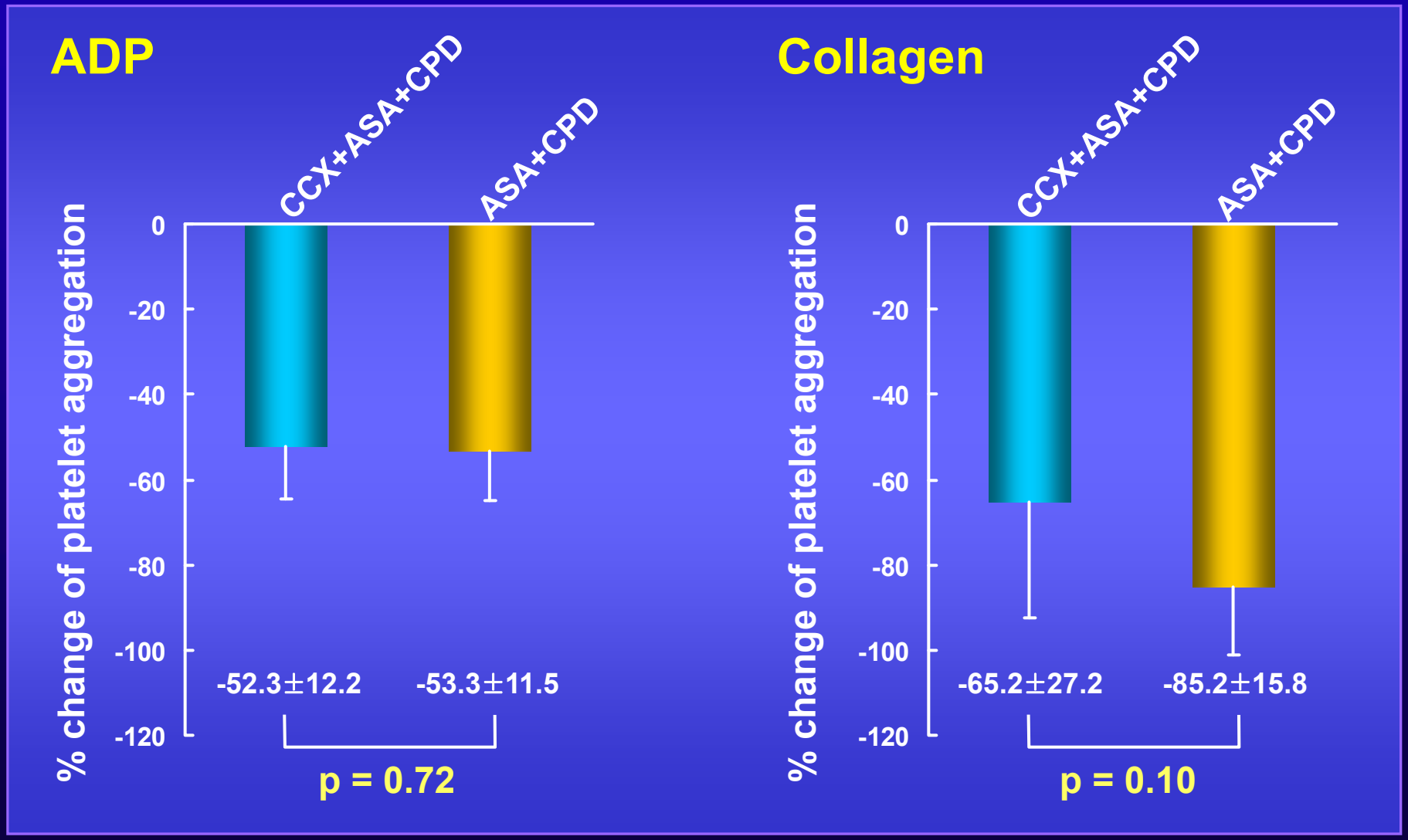
Study Protocol



CCX = Celecoxib; ASA = Aspirin; CPD = Clopidogrel

Effect of Celecoxib on Anti-platelet therapy

% Change of Platelet Aggregation Test

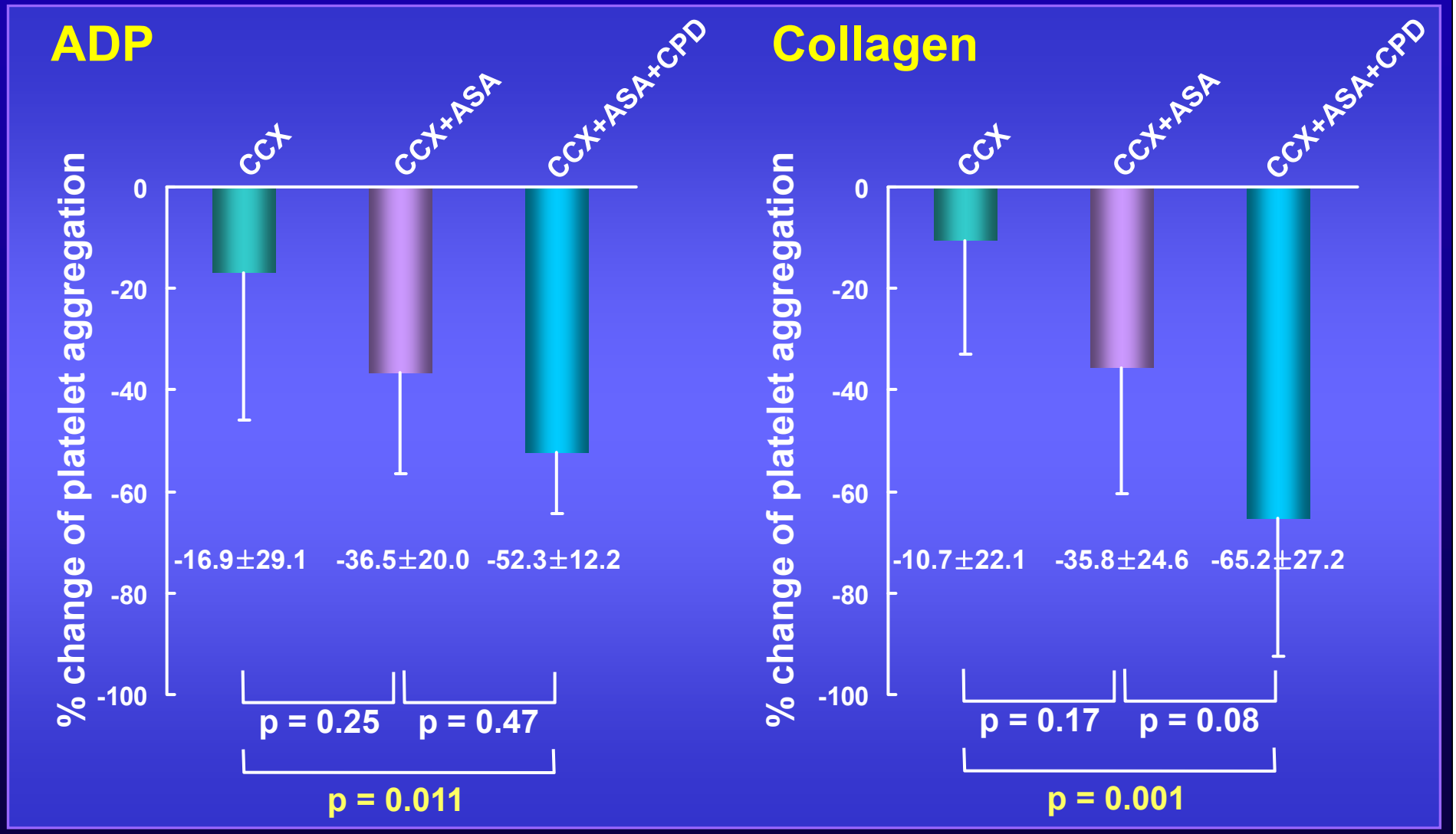


Seoul National University Hospital, Seoul, Korea

순환기 학회지 **2009**

Effect of Celecoxib on Anti-platelet therapy

% Change of Platelet Aggregation Test



Seoul National University Hospital, Seoul, Korea

순환기 학회지 **2009**

History of SNUH Akt/COX2 inhibitor Program

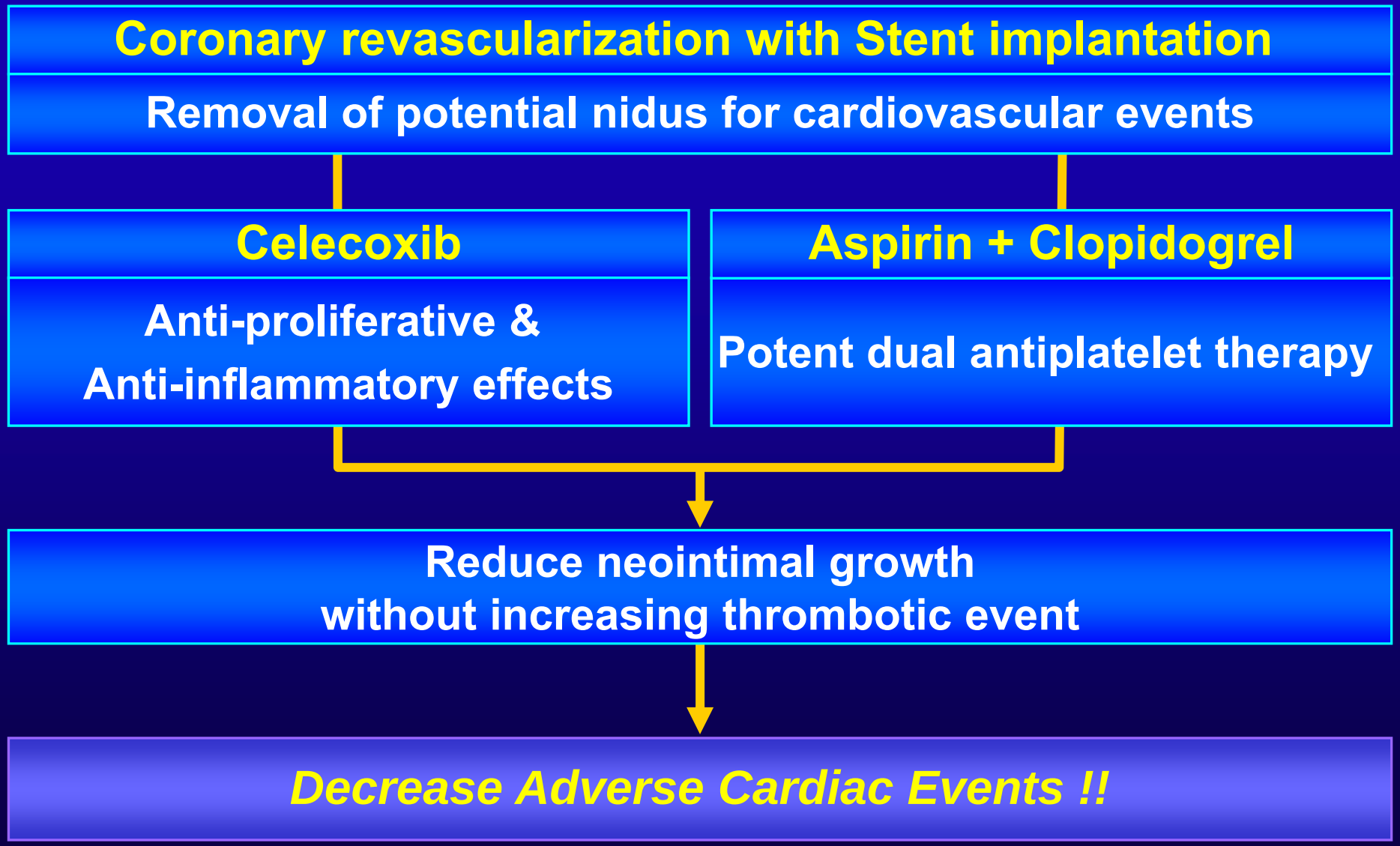
Communication between bench and bed side

1. Initiation point of Akt & Celecoxib at bench
2. Cautious Consideration between bench & bed-side
3. First clinical trial (COREA-TAXUS): bench to bed-side
4. Return to bench : further complicated story

   : Taxol → COX2 → MDR-1 → Neointima
5. Feasibility confirmation between bench & bed-side

   : genotype of MDR-1 in patients with DES
6. Second clinical trial (mini-COREA) : bench to bed-side

Hypothesis



Seoul National University Hospital, Seoul, Korea

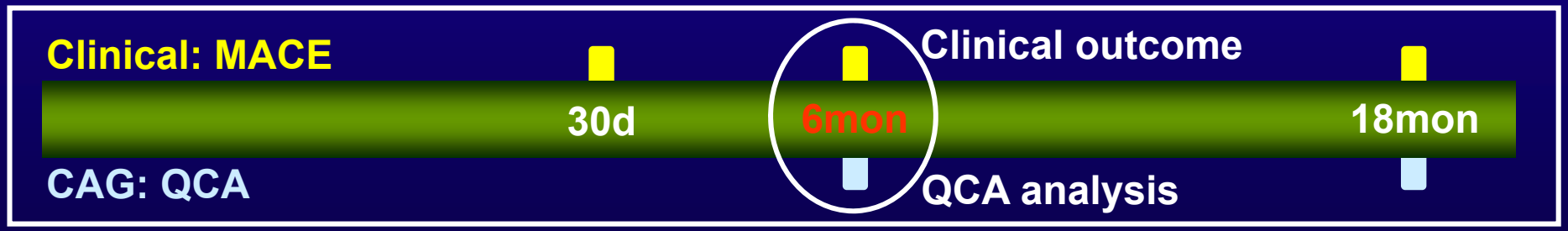
COREA-TAXUS Trial

A Prospective, Randomized, 2 Center (SNUH, SNUBH) trial

1:1 Randomization

Patients planned to deploy with Paclitaxel-Eluting Stents (PES)

Control Group	N = 274 patients	Celecoxib Group
Antiplatelet Therapy - Aspirin (ASA) - Clopidogrel (CPD)		**Celecoxib** - 400mg loading before PCI - Maintenance : 200mg bid for 6M Antiplatelet Therapy (ASA+CPD)



Primary Endpoint :	**In-stent late luminal loss by QCA at 6 months**
Secondary Endpoint :	**Target Lesion Revascularization (TLR) at 6 months**
	Cardiac death / Myocardial infarction at 6 months

Seoul National University Hospital, Seoul, Korea

COREA-TAXUS Trial

Exclusion Criteria

- Acute ST-elevation MI
- Left main coronary artery disease
- Hepatic dysfunction
  - AST/ALT ≥ 120 IU/L
- Renal dysfunction
  - creatinine ≥ 2.0 mg/dL
- Severe CHF (NYHA class ≥3)
- Hemodynamically unstable condition
- History of allergy to celecoxib
- Expected survival < 2yr

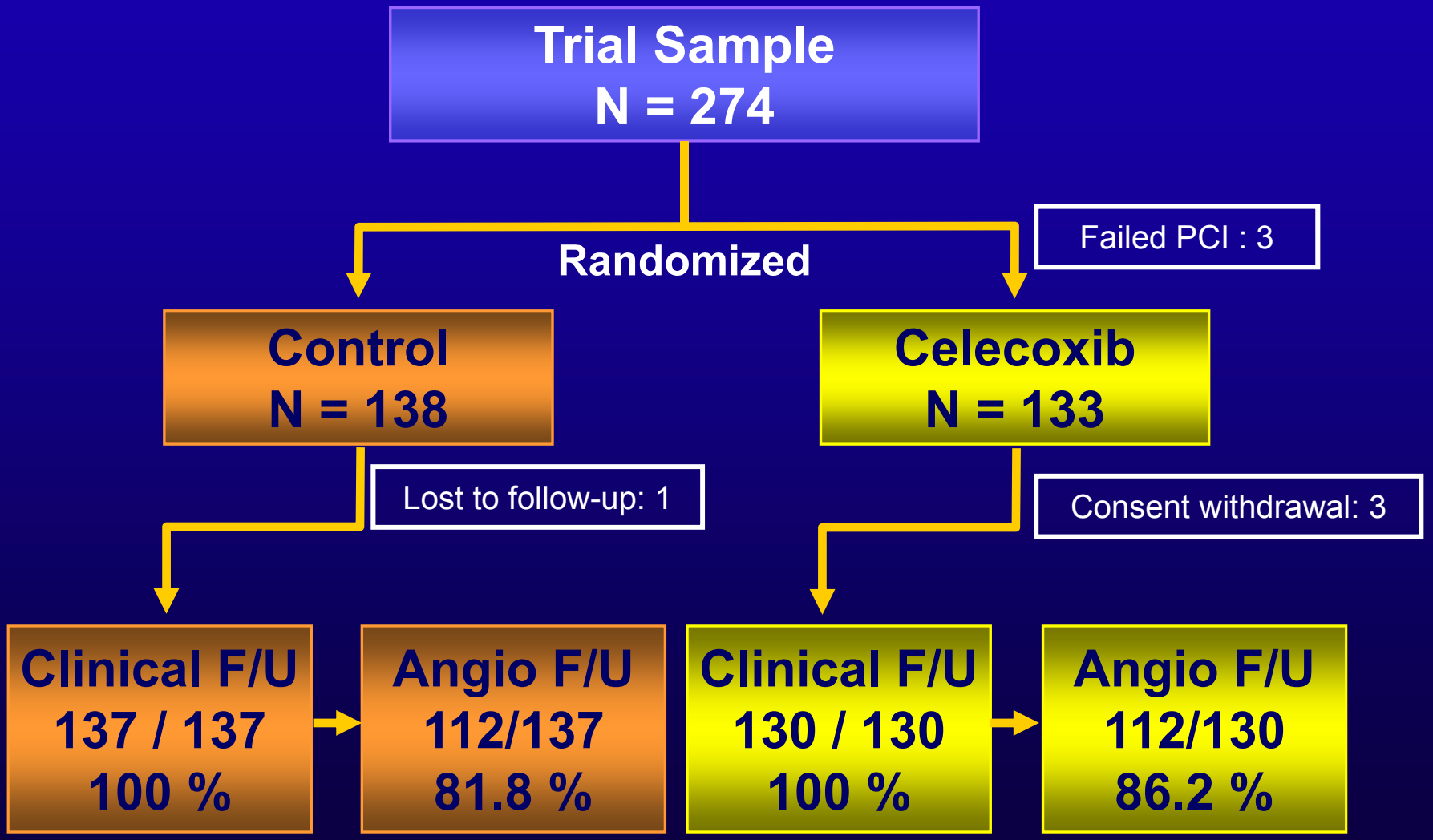
COREA-TAXUS Trial

Calculation of Sample Size

- Reduction of late loss was 0.18 mm
- Power of the study was 80%
- Alpha error was 5%
- Calculated sample size was 208 patients
- Sample increased to 270 patients in order to account for patients lost to follow-up

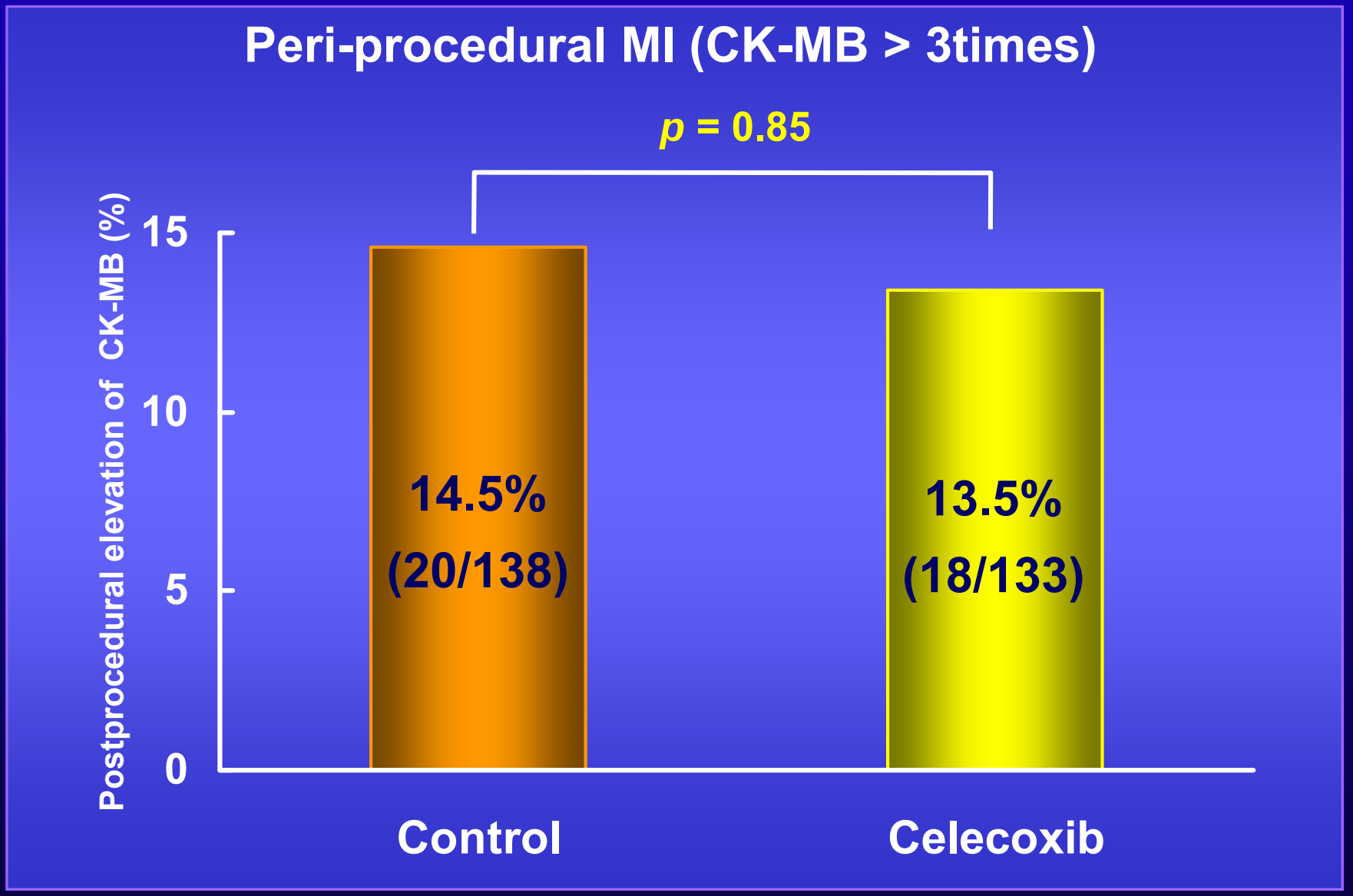
COREA-TAXUS Trial

Patient Flowchart



Seoul National University Hospital, Seoul, Korea

Peri-procedural Clinical Results



No significant difference between control and celecoxib group

Seoul National University Hospital, Seoul, Korea

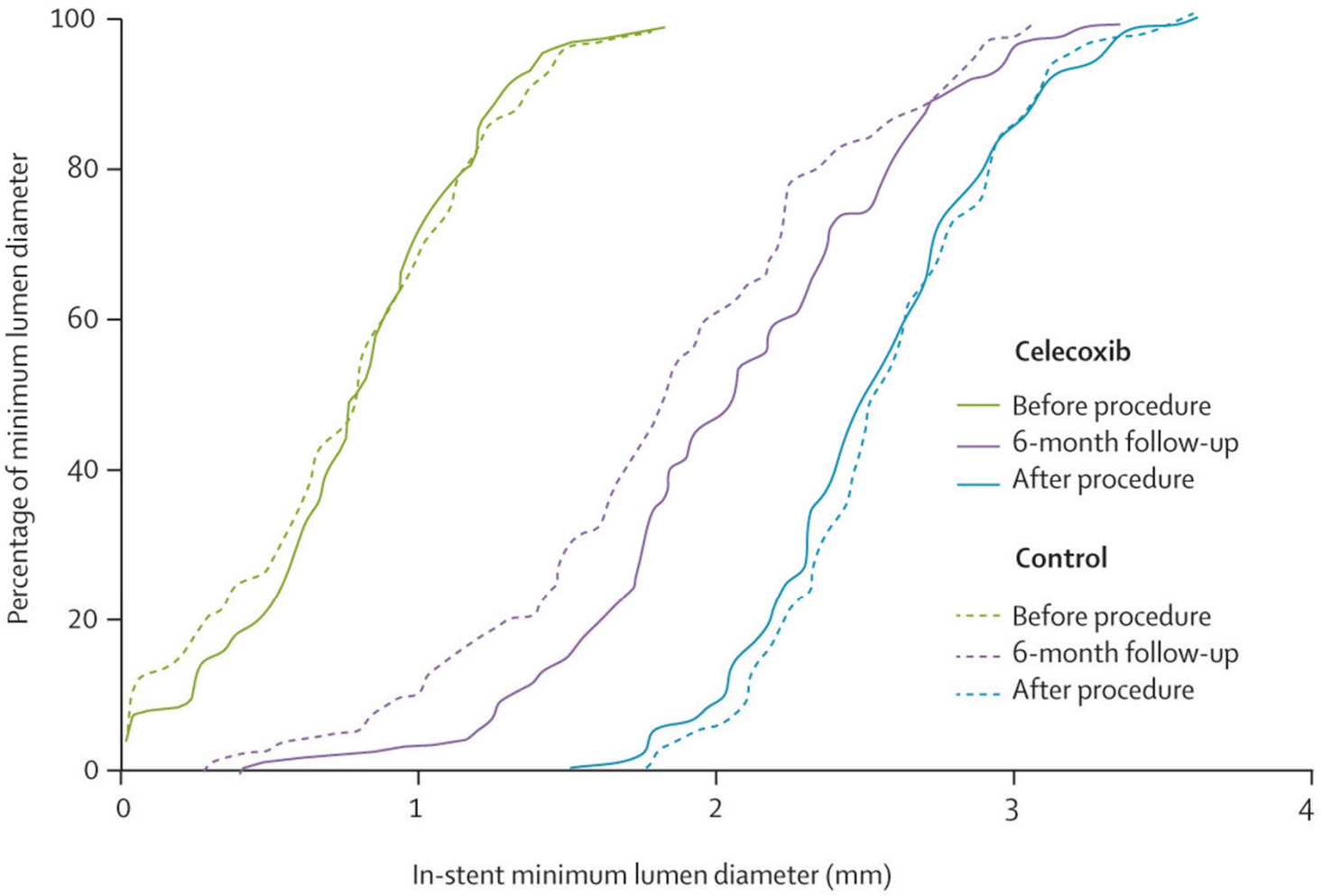
Quantitative Coronary Analysis for 6 months interval

	Control (n=112)	Celecoxib (n=112)	*p value*
Diameter stenosis in segment, %			
Before procedure	74.2 ± 15.8	73.6 ± 13.8	0.77
After procedure	24.3 ± 12.2	25.7 ± 12.3	0.40
At 6-month follow-up	40.1 ± 18.8	34.0 ± 15.4	0.008
Diameter stenosis in stent, %			
After procedure	14.2 ± 8.0	15.2 ± 9.3	0.42
At 6-month follow-up	36.6 ± 20.1	28.9 ± 16.6	0.002
Binary restenosis at 6-month follow-up			
In-stent	27 ± 24	12 ± 11	0.007
In-segment	34 ± 30	14 ± 13	0.001
Late loss, mm			
In-stent	0.75 ± 0.60	0.49 ± 0.47	<0.0001
In-segment	0.56 ± 0.57	0.33 ± 0.43	0.001

Seoul National University Hospital, Seoul, Korea

COREA-TAXUS Trial. Lancet 2007

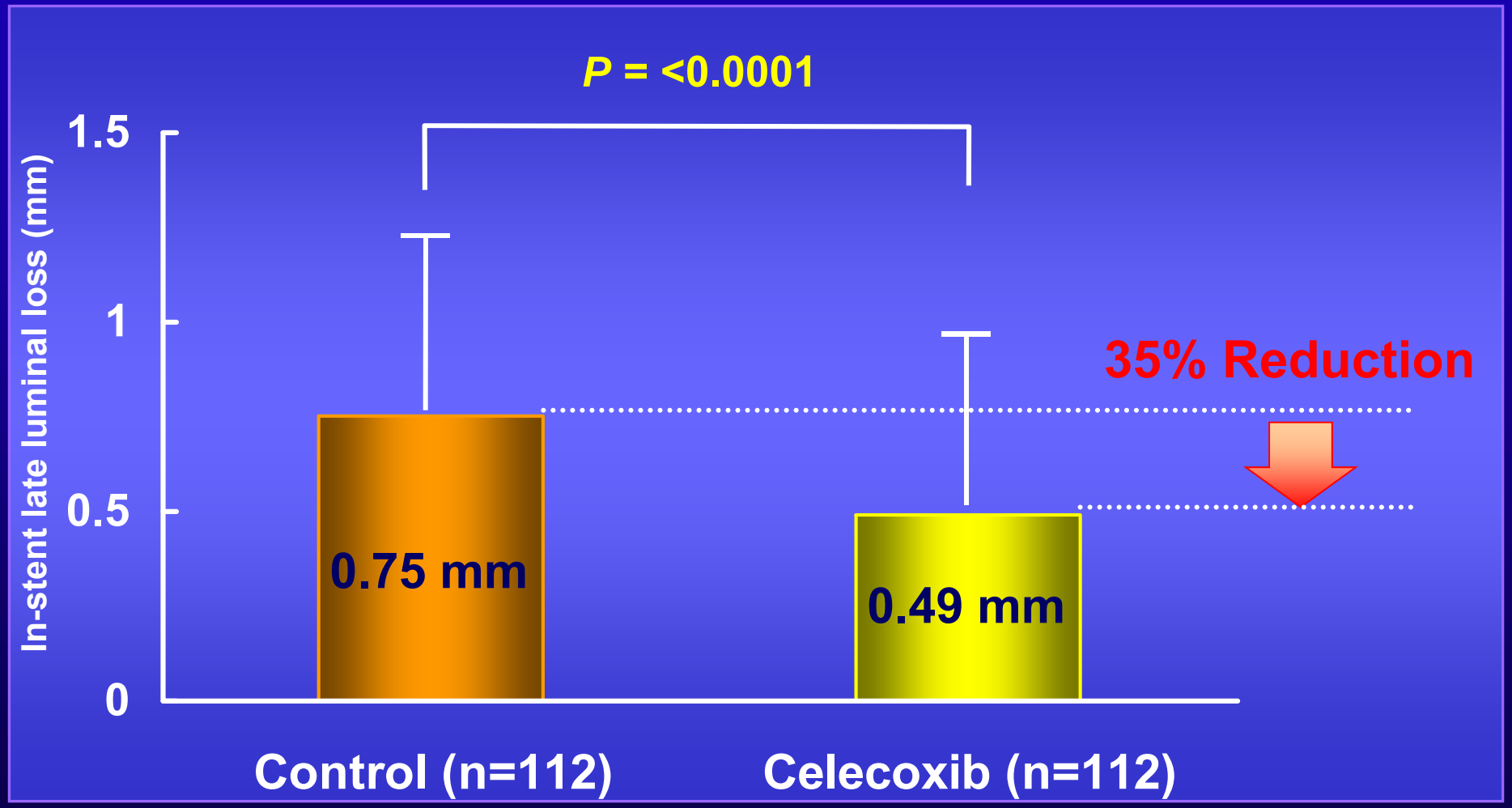
Minimum Lumen Diameter: In-stent



Seoul National University Hospital, Seoul, Korea

COREA-TAXUS Trial. Lancet 2007

Primary Endpoint : In-stent Late Loss of index lesion

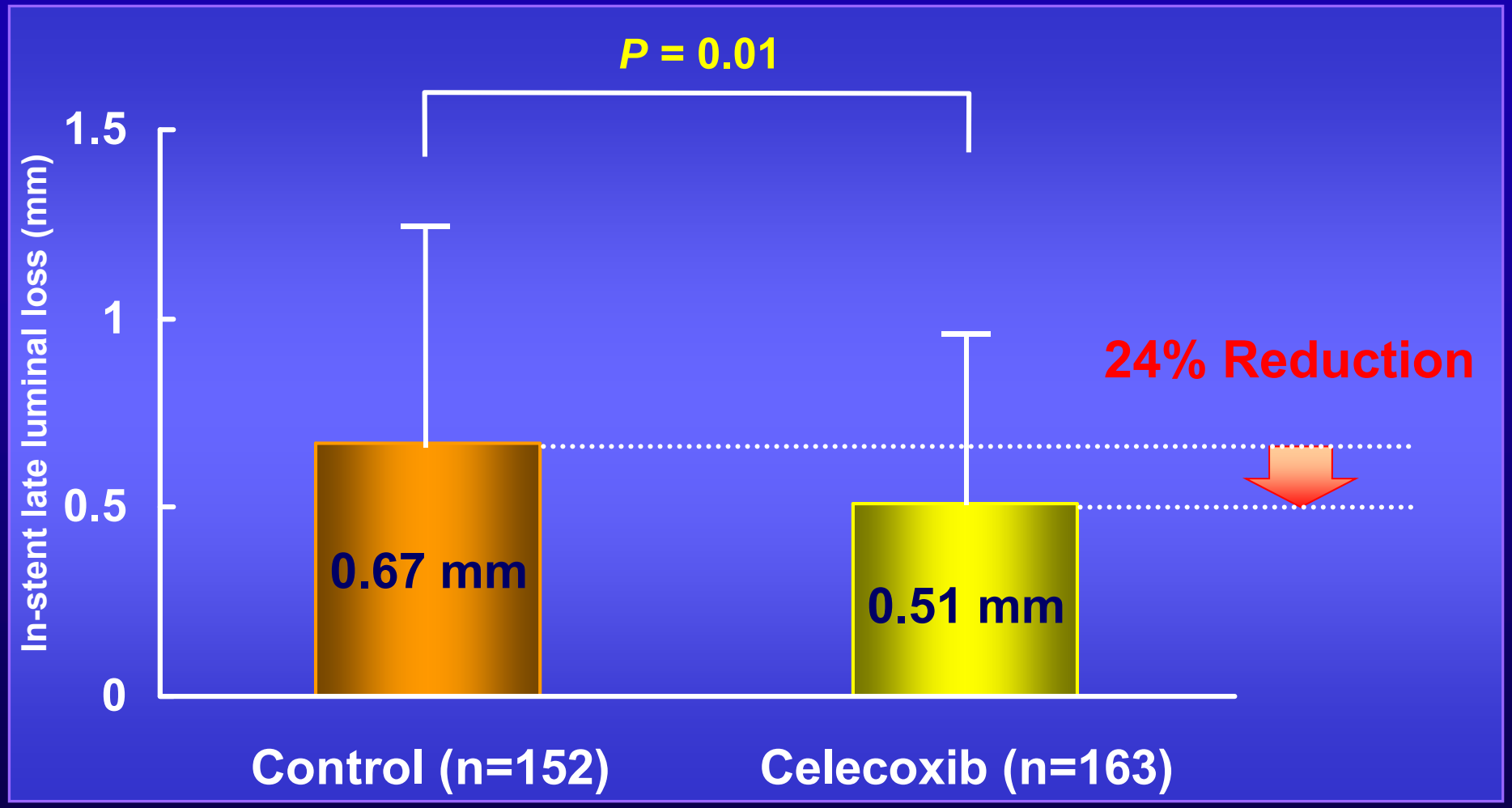


Celecoxib significantly reduced in-stent late luminal loss !!

Seoul National University Hospital, Seoul, Korea

COREA-TAXUS Trial. Lancet 2007

Primary Endpoint : In-stent Late Loss of all lesions



Celecoxib significantly reduced in-stent late luminal loss !!

Seoul National University Hospital, Seoul, Korea

COREA-TAXUS Trial. Lancet 2007

TAXUS V - *De Novo*

US Randomized *de novo* Lesion Pivotal

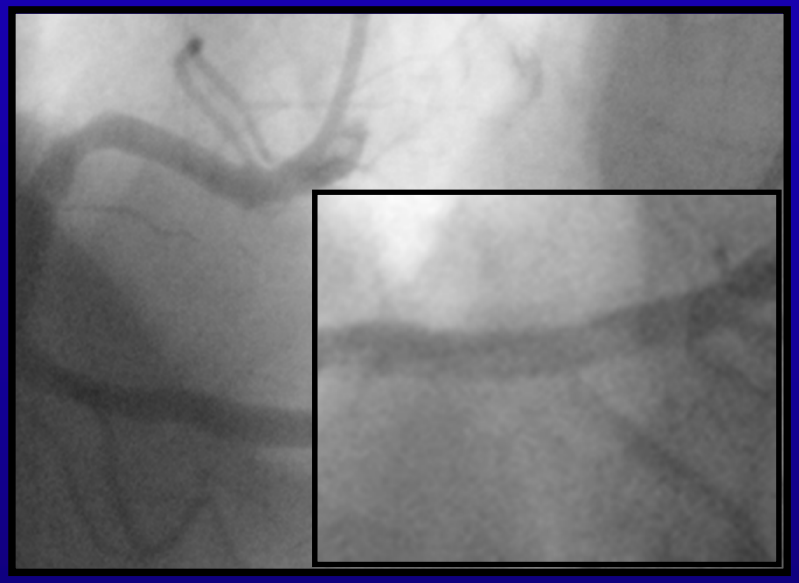
9-Month Subgroup Analysis** Patients Receiving Overlapping Stents, planned	*TAXUS Express²* *Paclitaxel-Eluting Stent (n=195)*
MACE	20.4% (39/191)
TVR, Overall	16.2% (31/191)
TLR, Overall	12.6% (24/191)
Stent Thrombosis	1.1% (2/190)
Late Loss (mm)	
Analysis Segment	0.45 ± 0.61 (173)
In-Stent	0.60 ± 0.67 (173)
Restenosis	
Analysis Segment	27.2% (47/173)
In-Stent	17.9% (31/173)
Lesion Length (mm)	25.03 ± 9.57 (192)
Baseline RVD (mm)	2.65 ± 0.55 (194)
Total Study Stent Length Implanted (mm)	43.61 ± 10.51 (195)

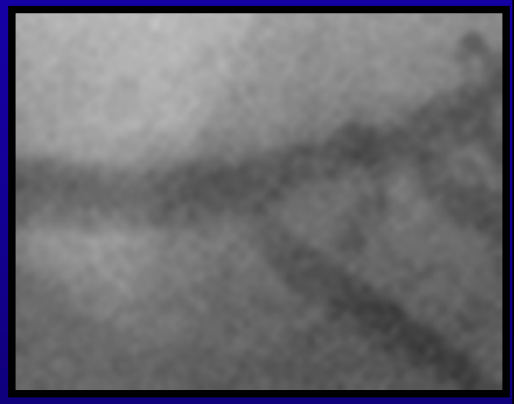
Exemplary Cases

Initial **6M F/U**

Celecoxib Case

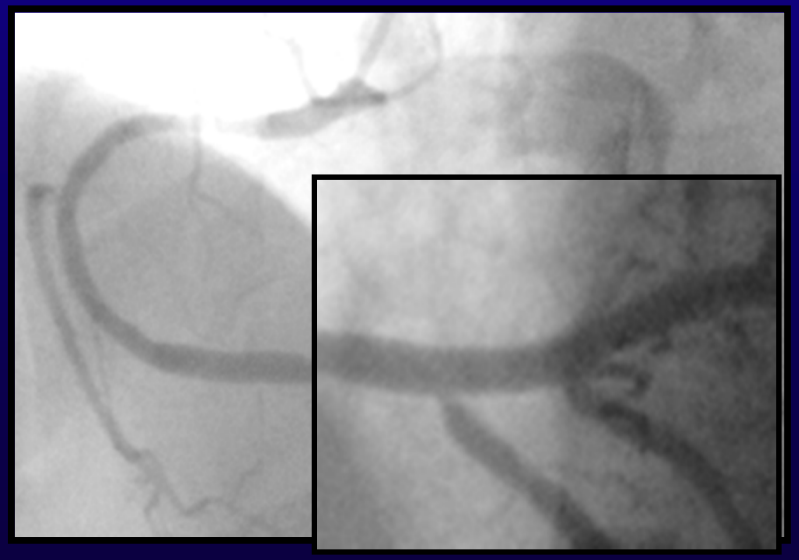
TAXUS 3.5x24mm

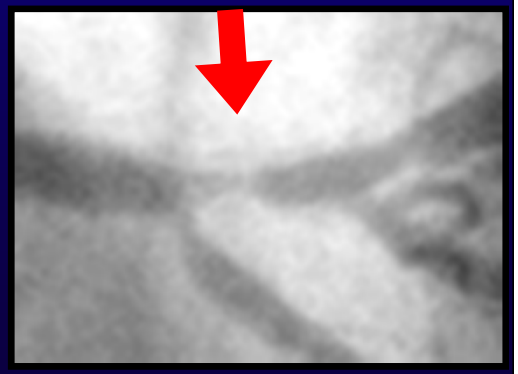




Control Case

TAXUS 3.5x24mm





Seoul National University Hospital, Seoul, Korea

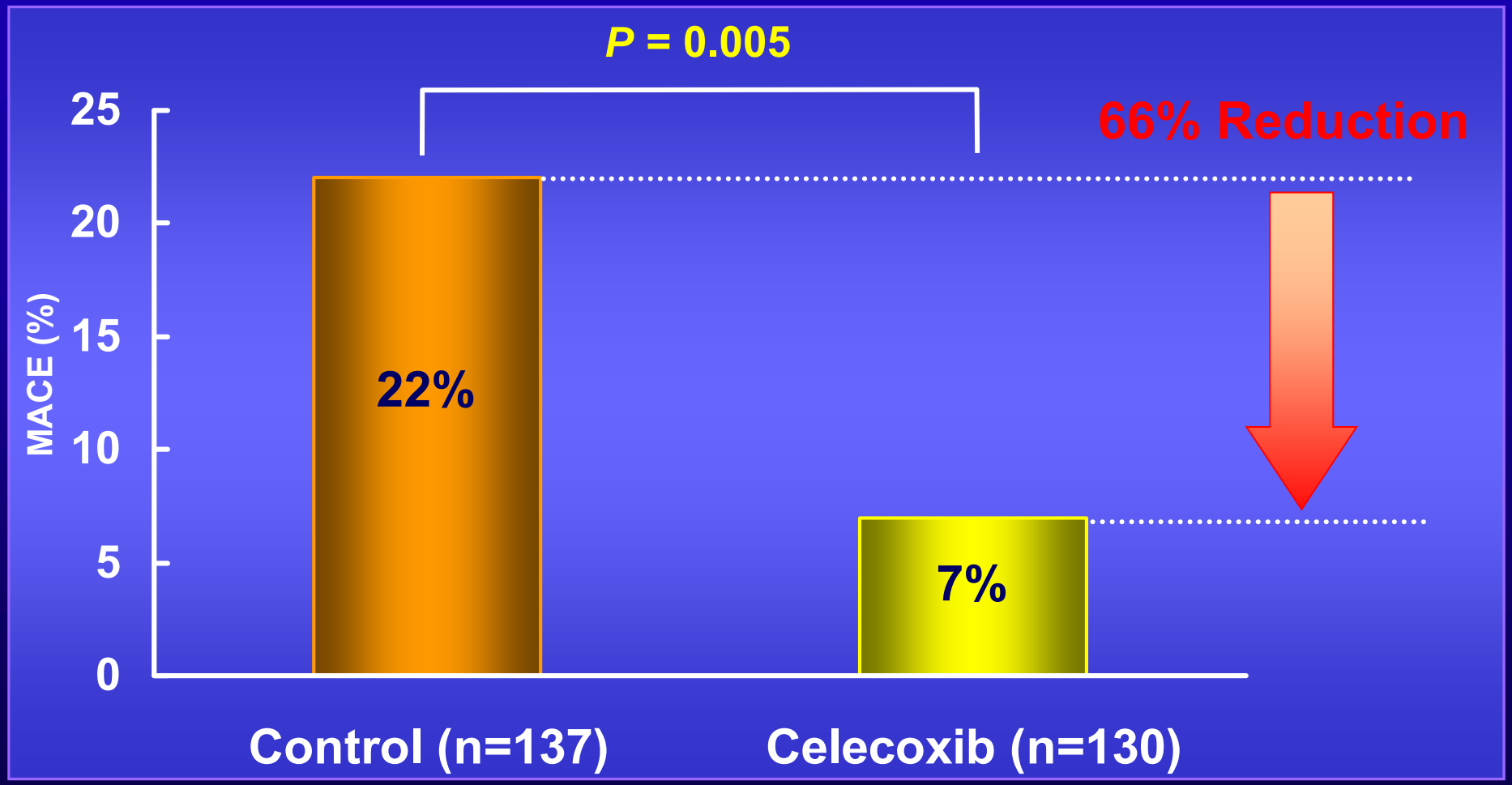
Major Adverse Cardiac Event at 6 month

	Control (n=137)	Celecoxib (n=130)	Relative Risk (95% CI)	p
TLR, %	21 ± 15	7 ± 5	0.35 (0.15-0.80)	0.008
Clinically driven TLR, %	16 ± 12	6 ± 5	0.40 (0.16-0.98)	0.036
Non-fatal MI, %	0 ± 0	1 ± 1		0.49
Cardiac death, %	1 ± 1	0 ± 0		1
Total, %	22 ± 16	7 ± 5	0.34 (0.15-0.76)	0.005

Celecoxib did not increase thrombotic complication !!

Seoul National University Hospital, Seoul, Korea

Major Adverse Cardiac Events within 6 month



Celecoxib reduced all MACE by 66% !!

Seoul National University Hospital, Seoul, Korea

COREA-TAXUS Trial

Conclusion

Coronary revascularization with PES implantation

Celecoxib
Anti-proliferative &
Anti-inflammatory effects

Aspirin + Clopidogrel
Dual antiplatelet therapy

Reduce neointimal growth
without increasing the risk of thrombotic events

Effective in Reducing Adverse Cardiac Events

Seoul National University Hospital, Seoul, Korea

Lessons of COREA-TAXUS Trial

Celecoxib	*Celecoxib*
for general population	*for CAD patients with PCI*
to prevent adenoma or arthritis	*To prevent restenosis after PCI*
CV thrombotic complication ?	*CV thrombotic complication resolved by dual anti-platelet tx.*

A given drug may have different value in different situations.

Seoul National University Hospital, Seoul, Korea

COREA-TAXUS Trial in Lancet 2007

Effect of celecoxib on restenosis after coronary angioplasty with a Taxus stent (COREA-TAXUS trial): an open-label randomised controlled study

Bon-Kwon Koo, Yong-Seok Kim, Kyung-Woo Park, Han-Mo Yang, Dong-A Kwon, Jin-Wook Chung, Joo-Yong Hahn, Hae-Young Lee, Jin-Shik Park, Hyun-Jae Kang, Young-Seok Cho, Tae-Jin Youn, Woo-Young Chung, In-Ho Chae, Dong-Ju Choi, Byung-Hee Oh, Young-Bae Park, Hyo-Soo Kim

Summary

Background In-vitro and animal experiments have shown that the cyclo-oxygenase 2 inhibitor celecoxib can reduce formation of neointima within stents. We aimed to test whether celecoxib has similar effects in a clinical setting.

Methods In a randomised two-centre trial, we enrolled 274 patients who had angina pectoris or a positive stress test and who had native coronary artery lesions for which implantation of paclitaxel-eluting stents was feasible. All patients were given aspirin (100 mg daily) and clopidogrel (75 mg daily). 136 patients were randomly assigned to receive celecoxib (400 mg before the intervention, and 200 mg twice daily for 6 months after the procedure). The primary endpoint was late luminal loss on quantitative coronary angiography at 6 months after the intervention. Secondary endpoints were cardiac death, non-fatal myocardial infarction, and revascularisation of the target lesion. Analysis was done on a modified intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT00292721.

Findings At 6 months, mean in-stent late luminal loss was lower in the celecoxib group (0·49 mm, SD 0·47) than in the control group (0·75 mm, 0·60) (absolute difference 0·26 mm; 95% CI 0·12–0·40). Frequency of secondary outcomes at 6 months was also lower in the celecoxib group, mainly because of a reduced need for revascularisation of the target lesion.

Interpretation These data suggest that the adjunctive use of celecoxib for 6 months after stent implantation in patients with coronary artery disease is safe and can reduce the need for revascularisation of the target lesion.

Lancet 2007; 370: 567–74

See Comment page 541

Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, Cardiovascular Center and Cardiovascular Research Institute, Seoul National University Hospital, Seoul, South Korea (B-K Koo MD, Y-S Kim MD, K-W Park MD, H-M Yang MD, D-A Kwon MD, J-W Chung MD, J-Y Hahn MD, H-Y Lee MD, J-S Park MD, H-J Kang MD, B-H Oh MD, Y-B Park MD, H-S Kim MD); **and Cardiovascular Center, Seoul National University Bundang Hospital, Gyeonggi-do, South Korea** (Y-S Cho MD, T-J Youn MD, W-Y Chung MD, I-H Chae MD,

Seoul National University Hospital, Seoul, Korea

History of SNUH Akt/COX2 inhibitor Program

Communication between bench and bed side

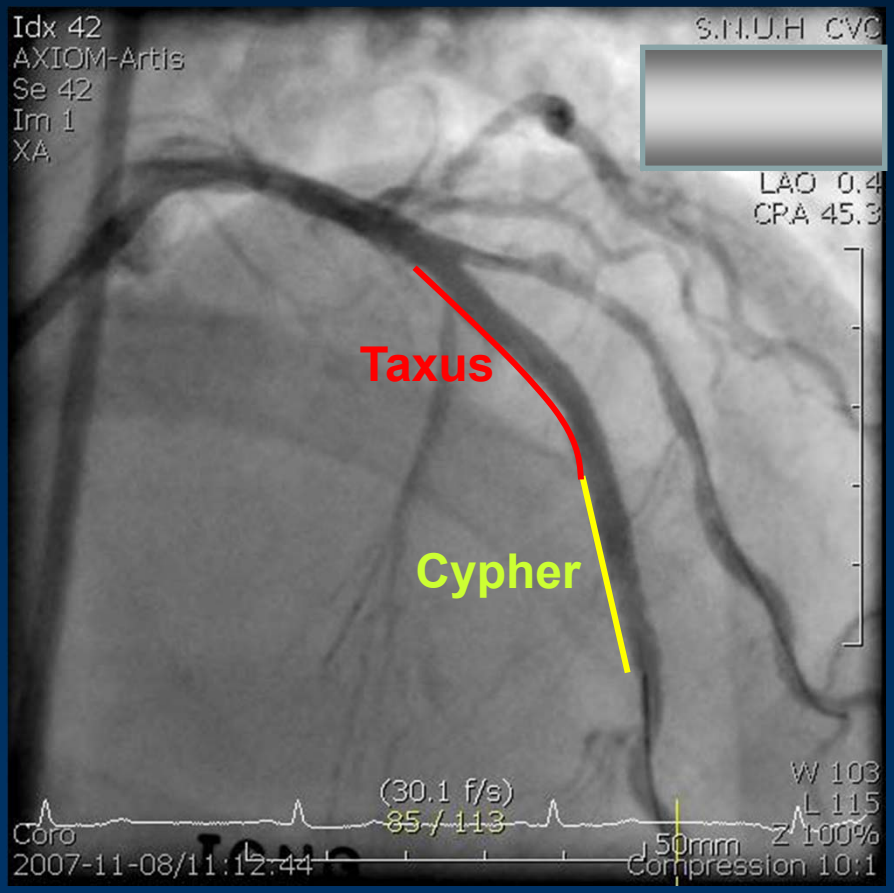
1. Initiation point of Akt & Celecoxib at bench
2. Cautious Consideration between bench & bed-side
3. First clinical trial (COREA-TAXUS): bench to bed-side
4. Return to bench : further complicated story

   : Taxol → COX2 → MDR-1 → Neointima
5. Feasibility confirmation between bench & bed-side

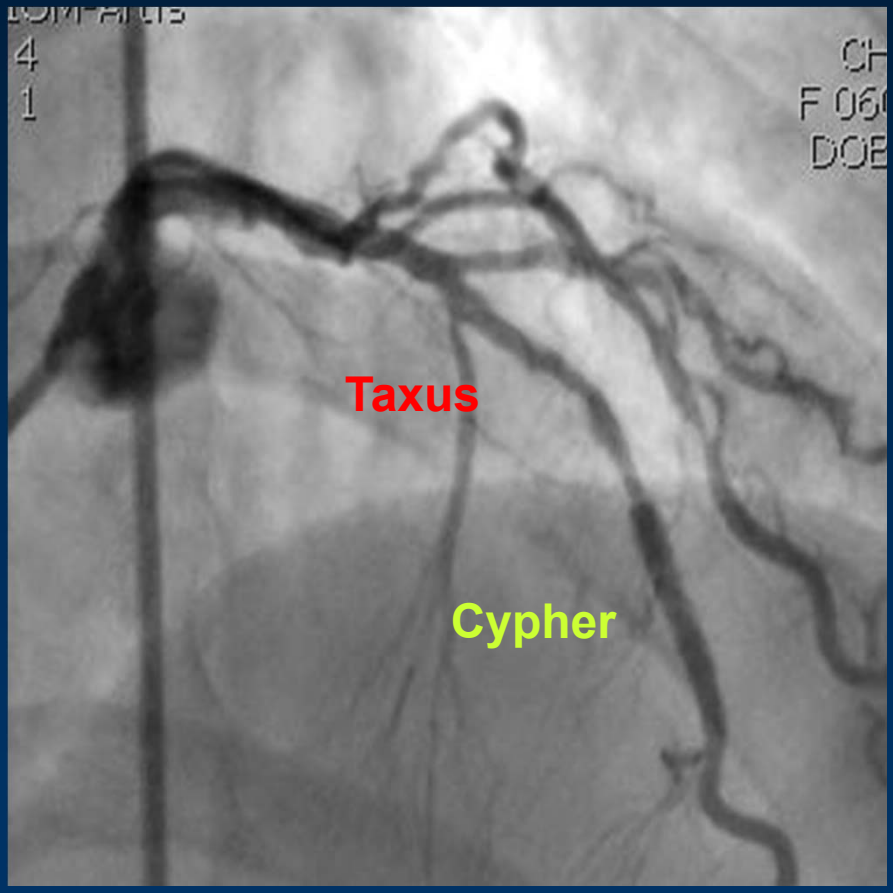
   : genotype of MDR-1 in patients with DES
6. Second clinical trial (mini-COREA) : bench to bed-side

Taxus vs Cypher (Case F/66)

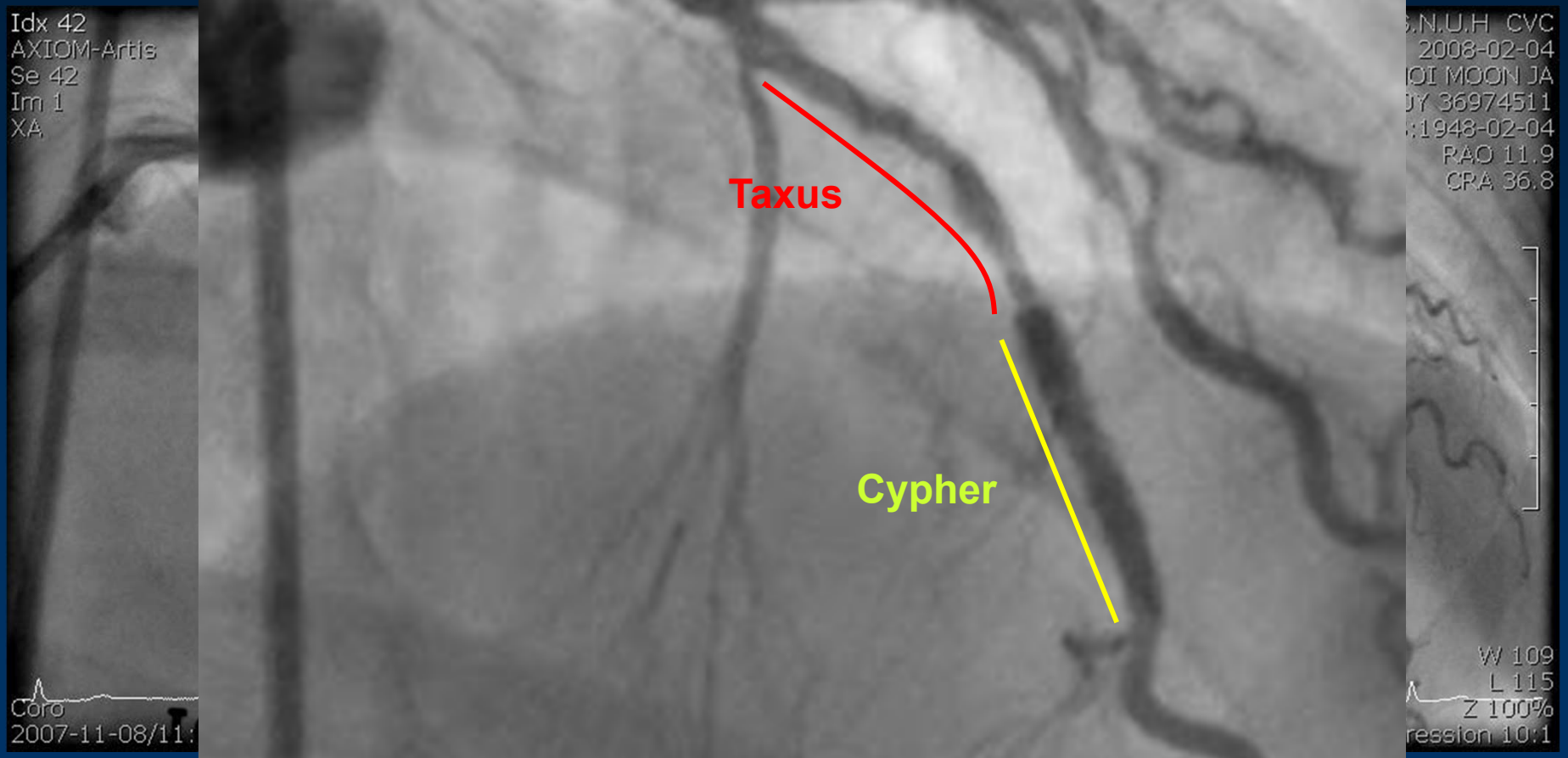
Baseline



6 Mo F/U

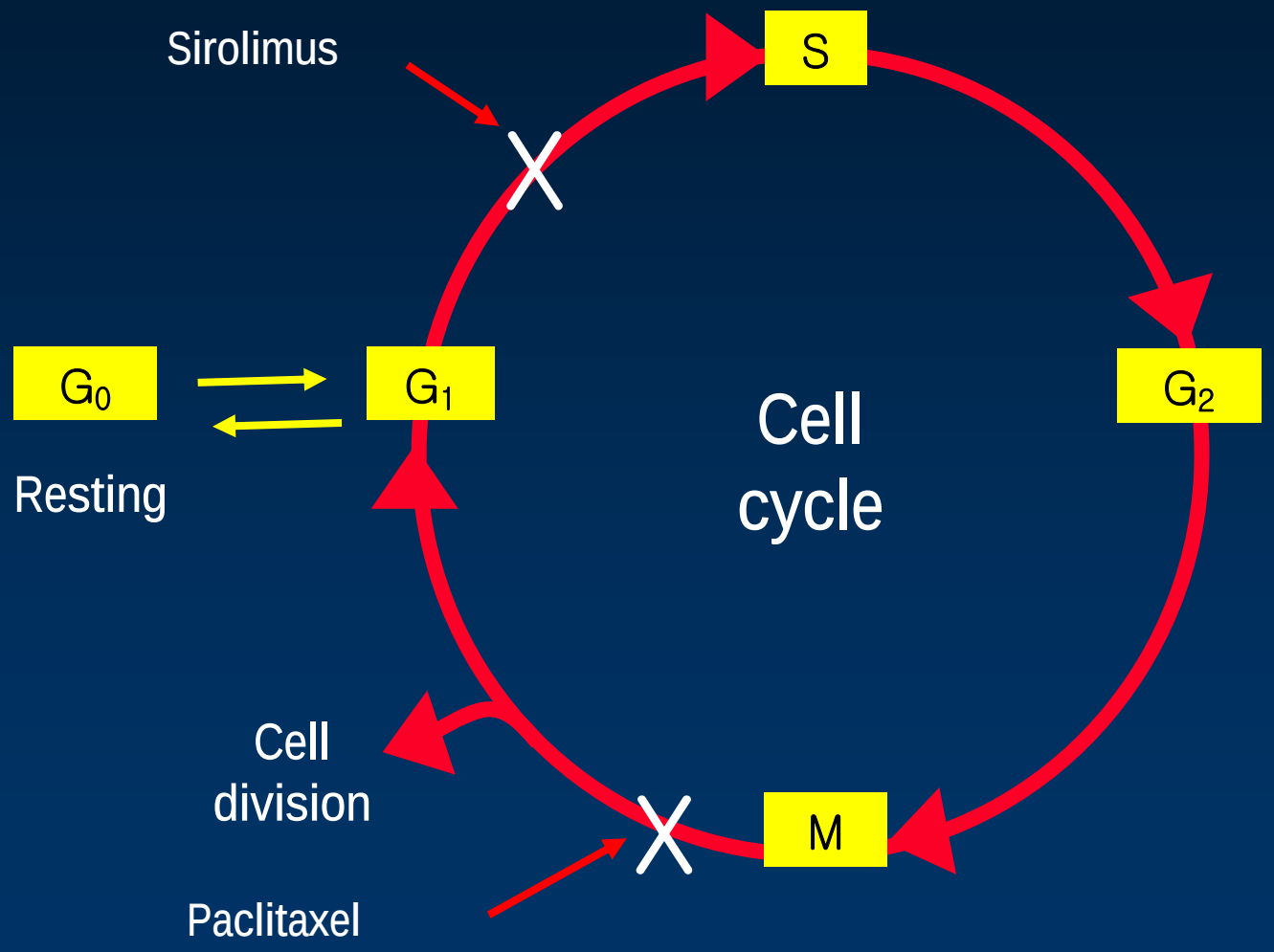


Taxu


Idx 42
AXIOM-Artis
Se 42
Im 1
XA
Coro
2007-11-08/11:
.N.U.H CVC
2008-02-04
OI MOON JA
Y 36974511
:1948-02-04
RAO 11.9
CRA 36.8
W 109
L 115
Z 100%
ression 10:1

Taxus
Cypher

Mechanisms of Sirolimus and Paclitaxel



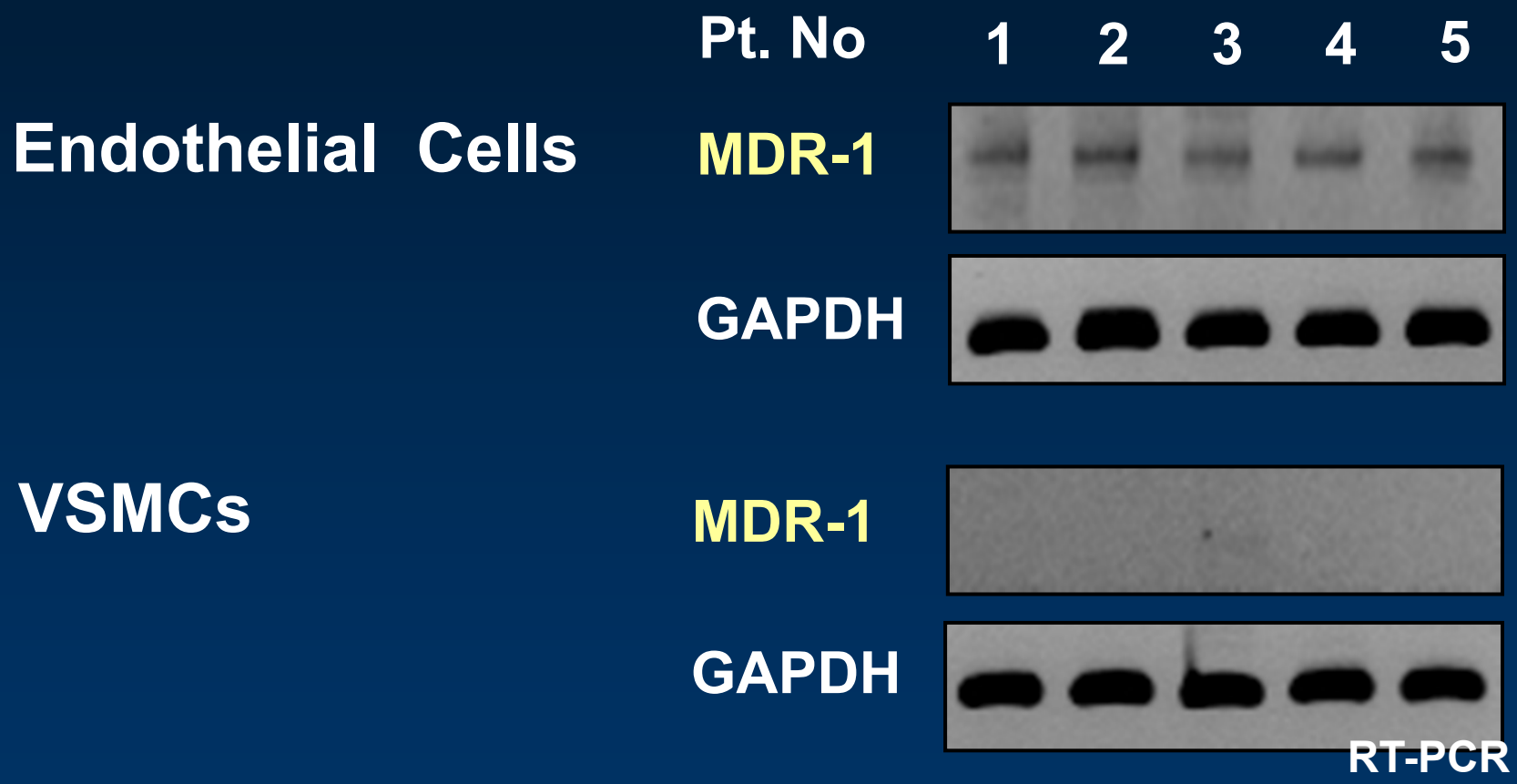
Why is Paclitaxel less effective in Reducing Restenosis?

1. **Difference in Previously Known Mechanisms**

2. **Difference in Concentration or Potency *in vitro* and *in vivo***

3. **Another Mechanism?**

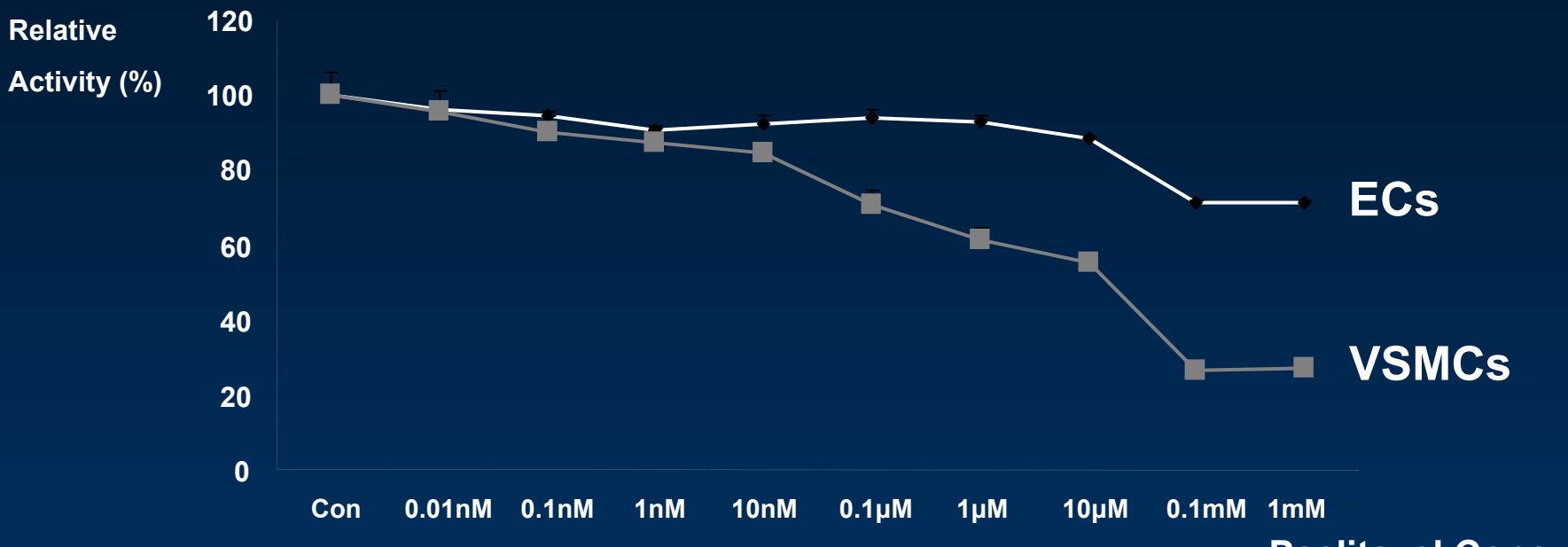
MDR-1 expression in human EC but not in VSMC

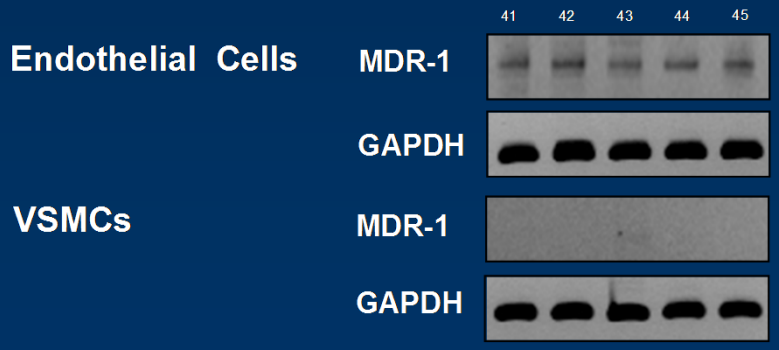


MDR-1 : Multidrug resistance-1

ECs & VSMCs from human GEA

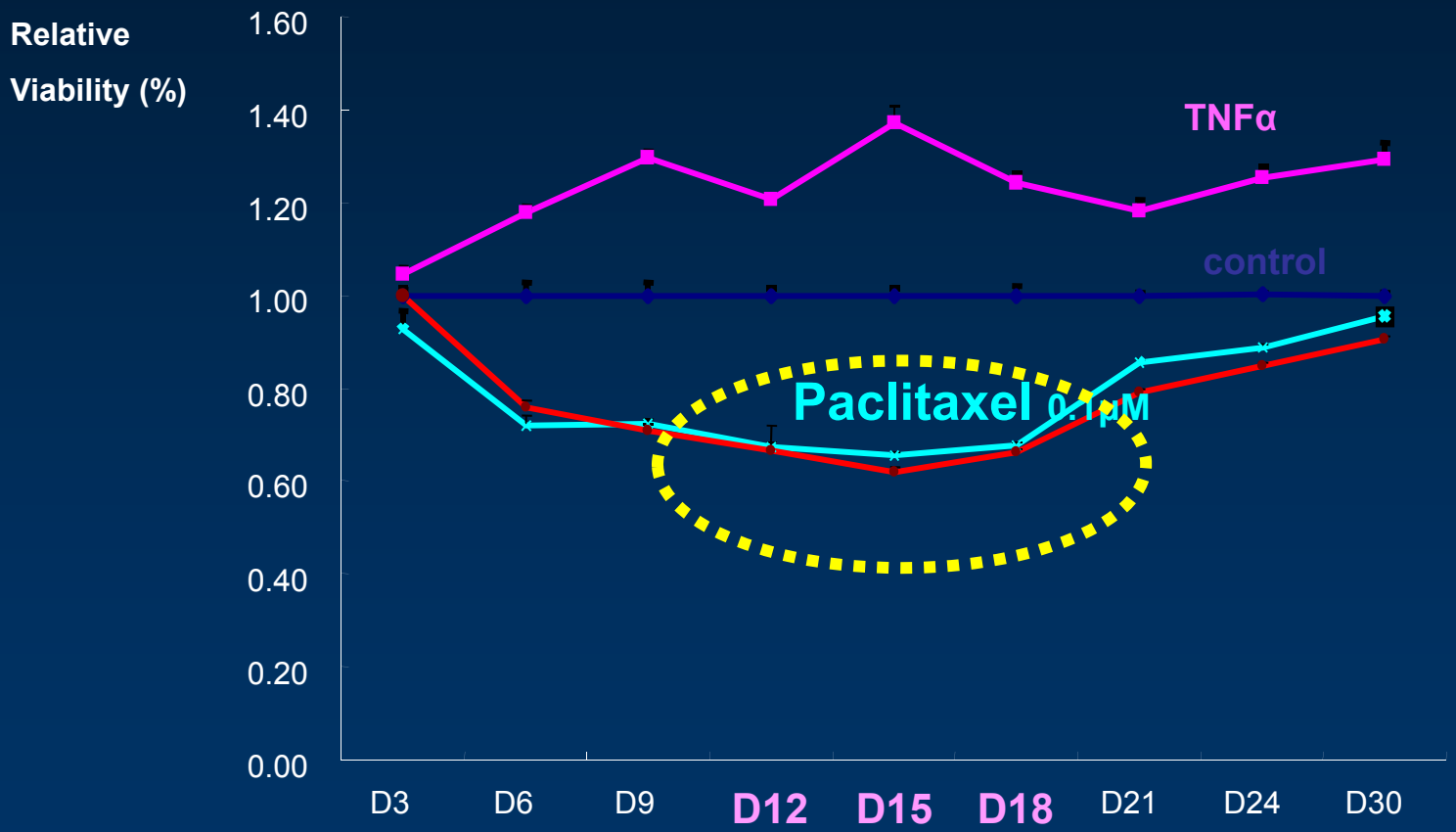
Effect of Paclitaxel on Cell Viability in EC & VSMC



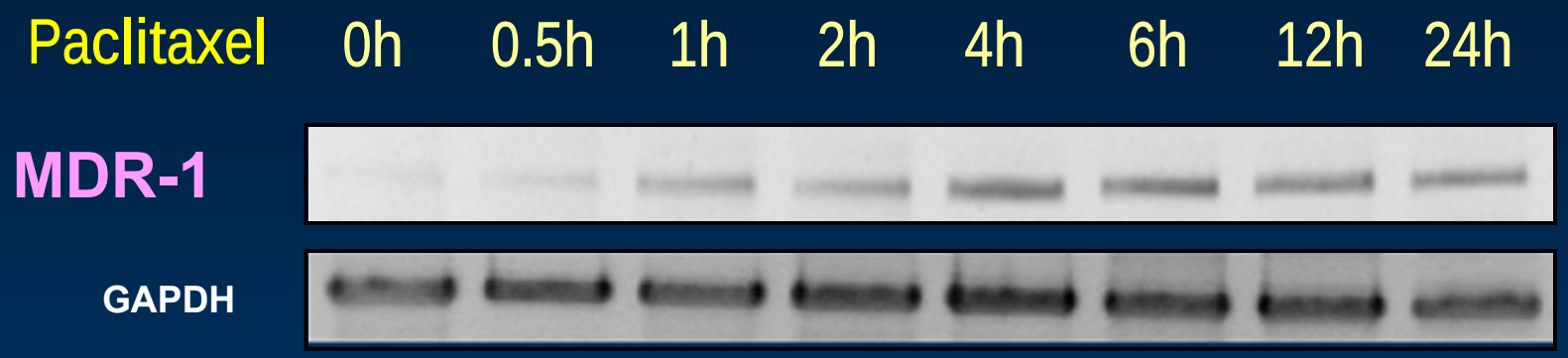


BrdU assay after 72hr treatment

Change of VSMC Viability after Paclitaxel Treatment



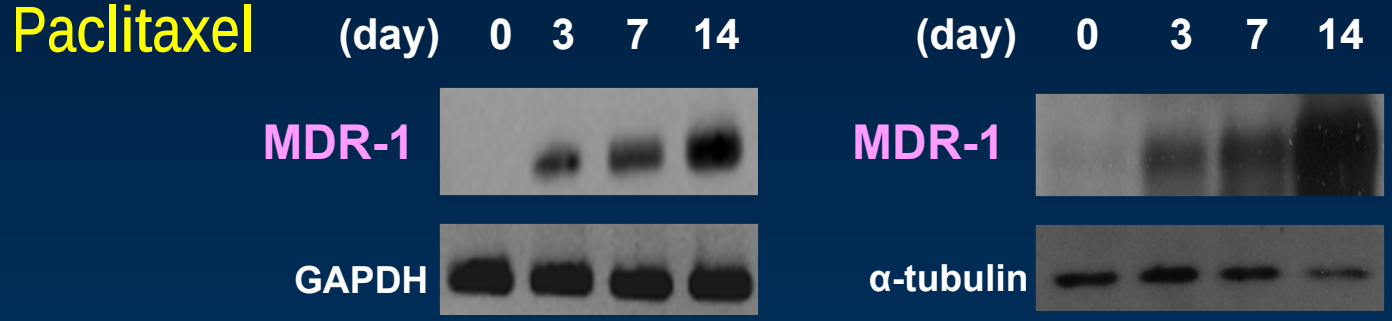
Paclitaxel Induces MDR-1 in human VSMCs



RT-PCR

Long-term Tx of Paclitaxel Induces MDR-1

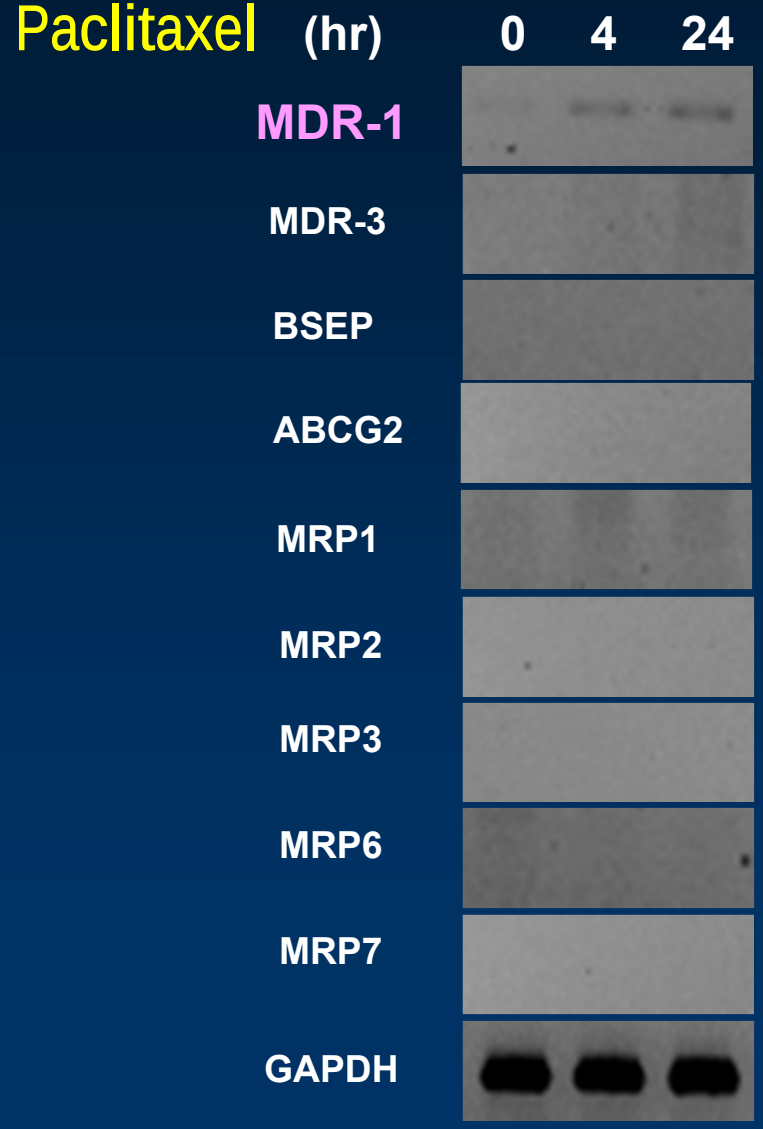
VSMCs from human Gastro Epiploic Artery



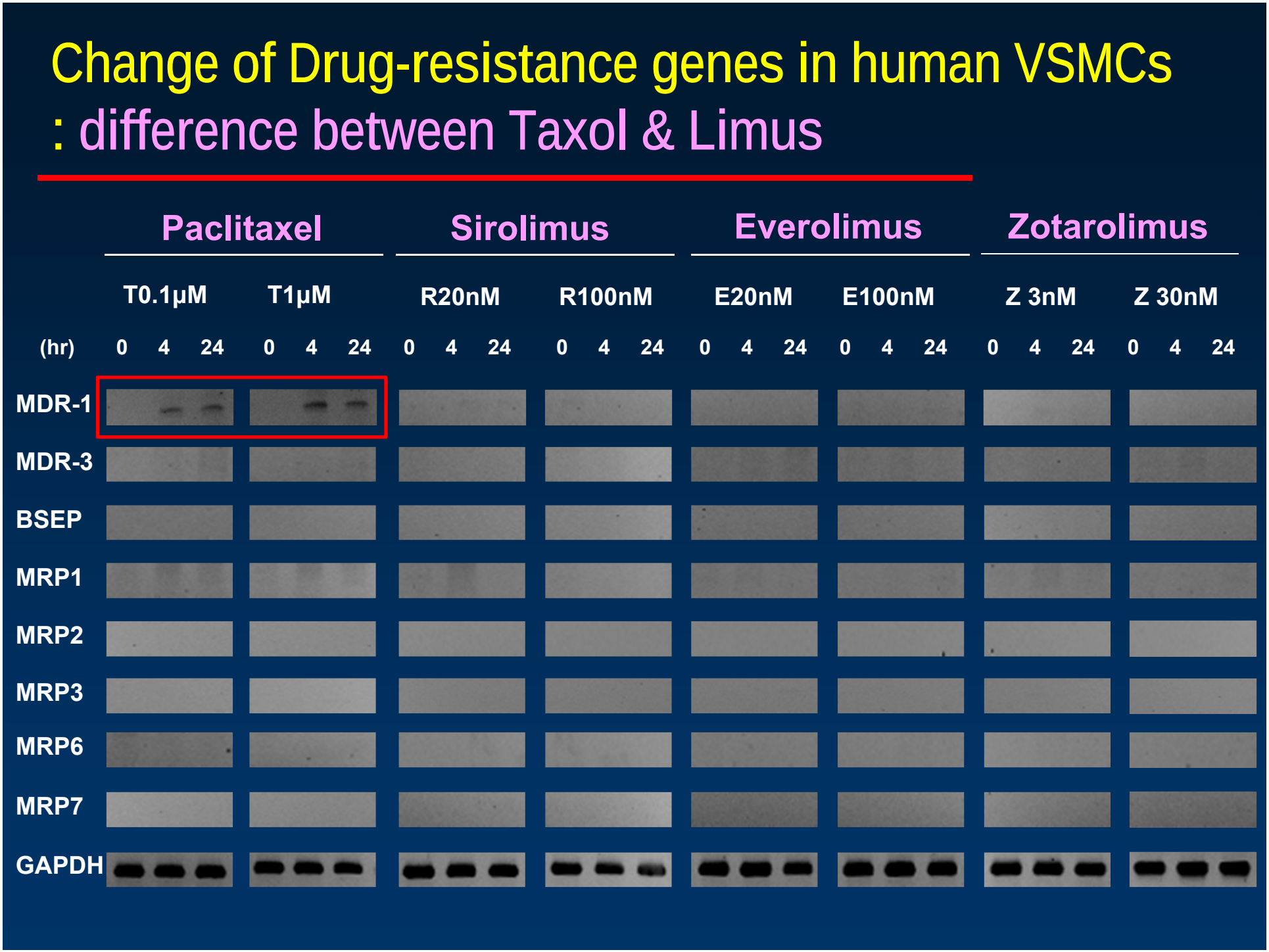
RT-PCR

Western Blot

Change of Drug-resistance genes after Paclitaxel Tx

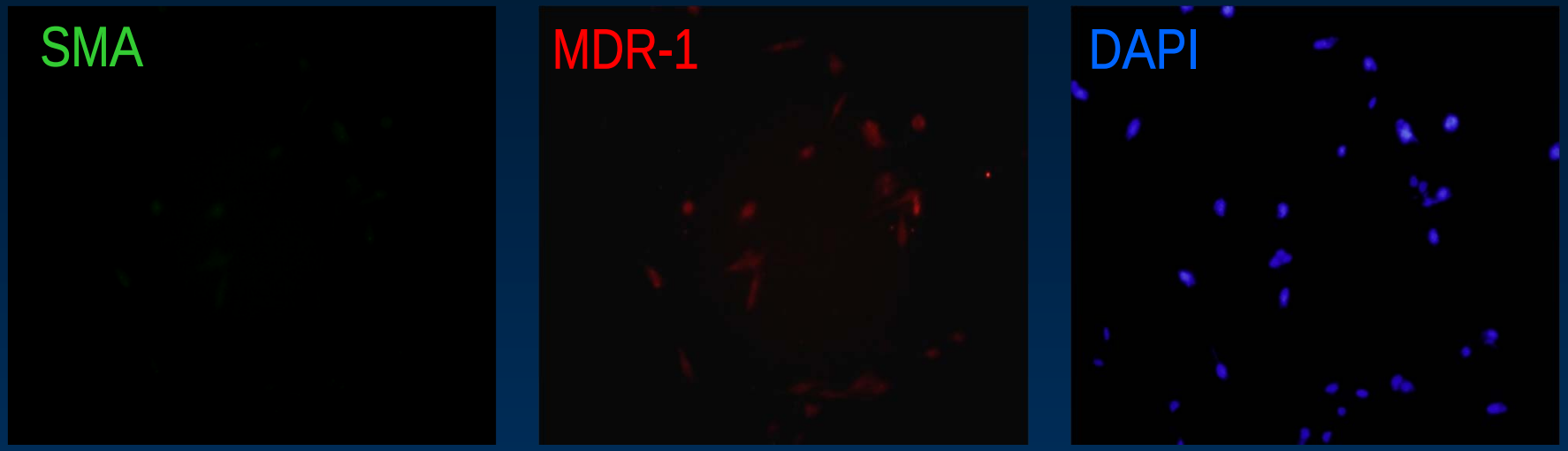


Change of Drug-resistance genes in human VSMCs : difference between Taxol & Limus



MDR 1 Expression with Long-term Paclitaxel Tx

Positive Control : Breast MDA Cells

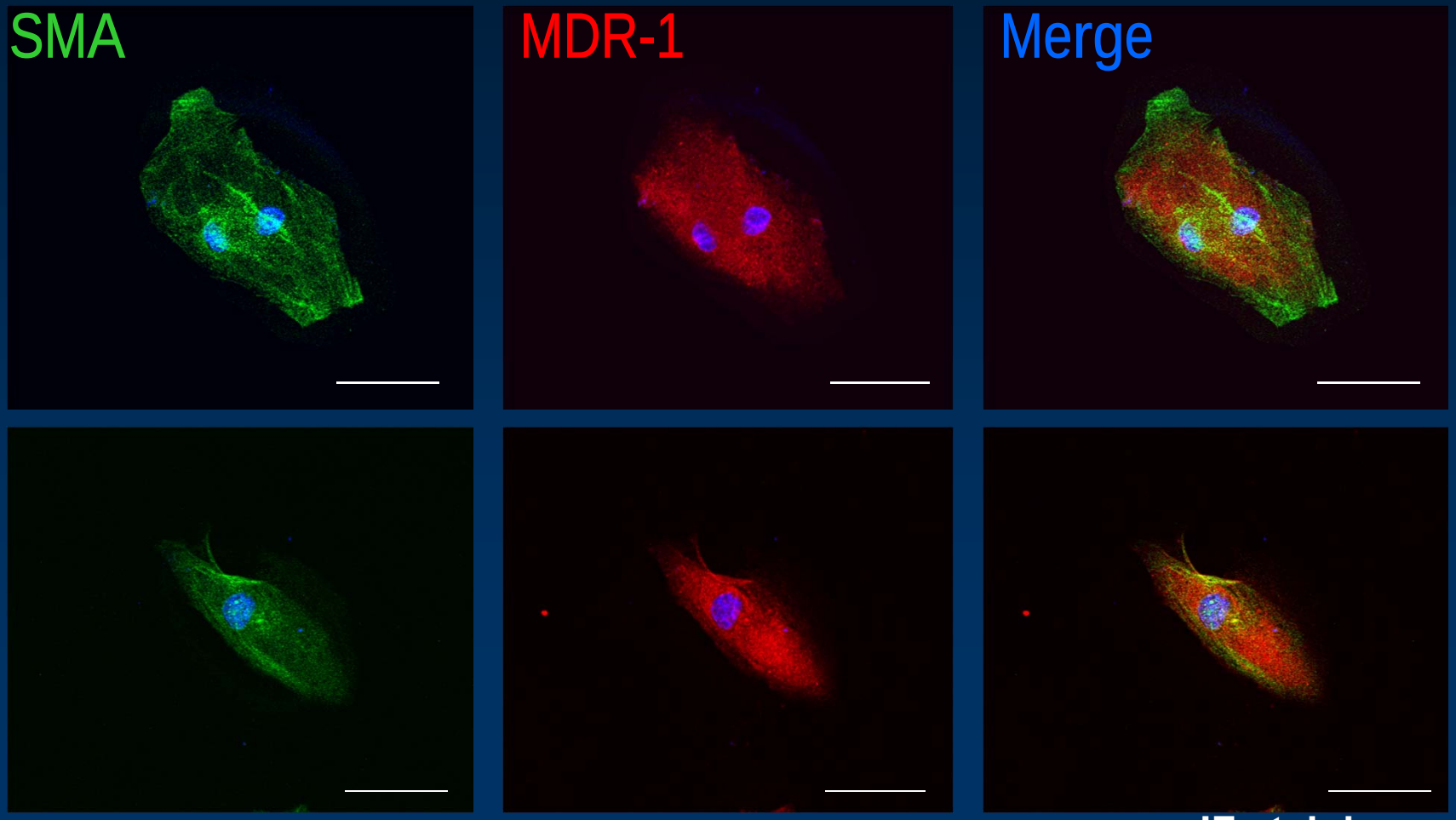


Vehicle Treatment for 3wk: VSMCs

IF staining

Long-term Tx of Paclitaxel Induces MDR-1

Paclitaxel for 3 weeks in human VSMC

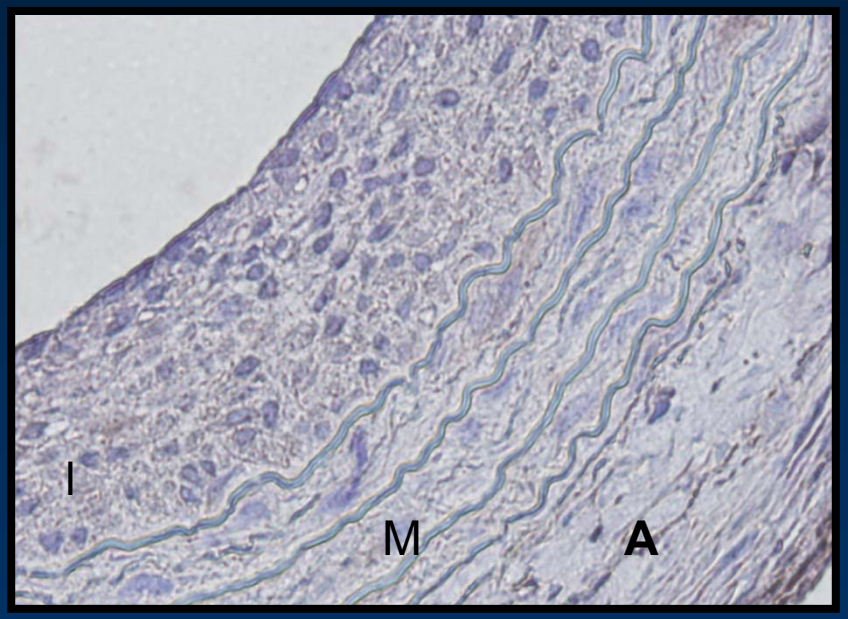


IF staining

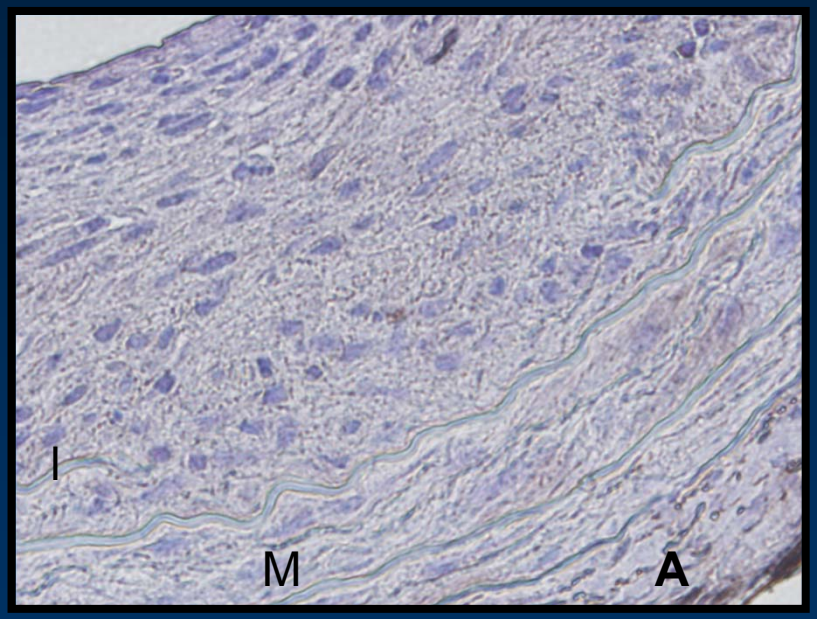
MDR-1 expression after Vascular Injury

Vehicle-treated Group

IHC for MDR-1



7 days after Injury



14 days after Injury

Rat carotid Injury Model

Animal Experiment :

Continuous systemic infusion of paclitaxel

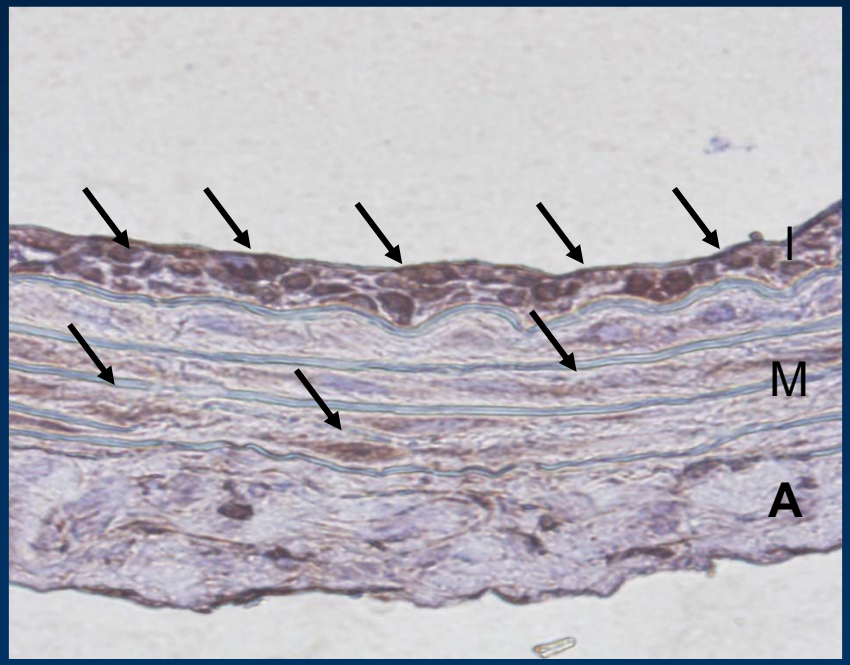
Rat Jugular Catheter

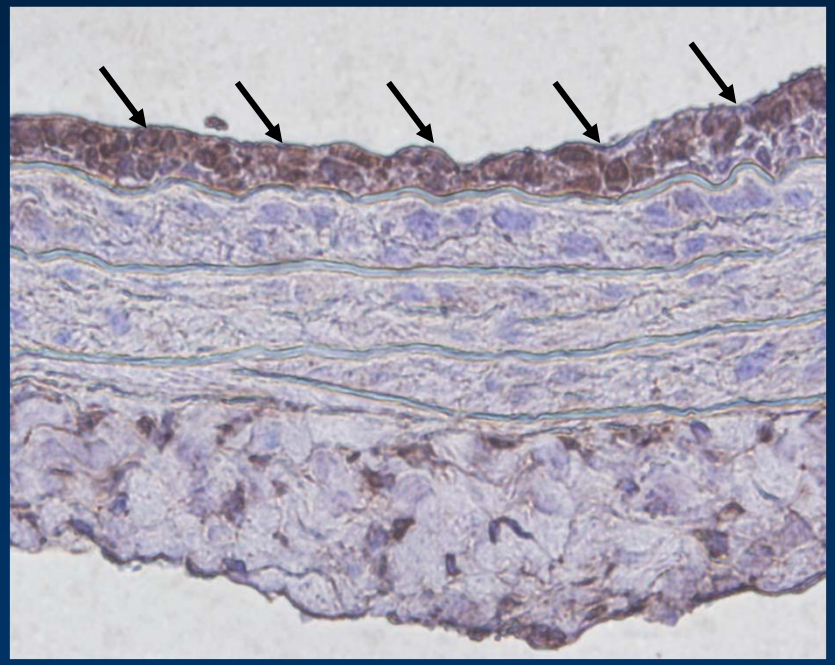
Via Alzet® osmotic pump and rat jugular vein catheter

MDR-1 expression after Vascular Injury

Paclitaxel-treated Group

IHC for MDR-1



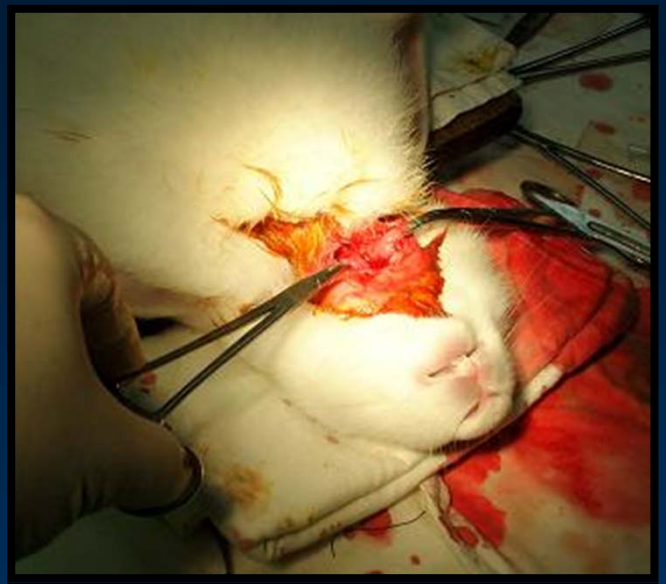


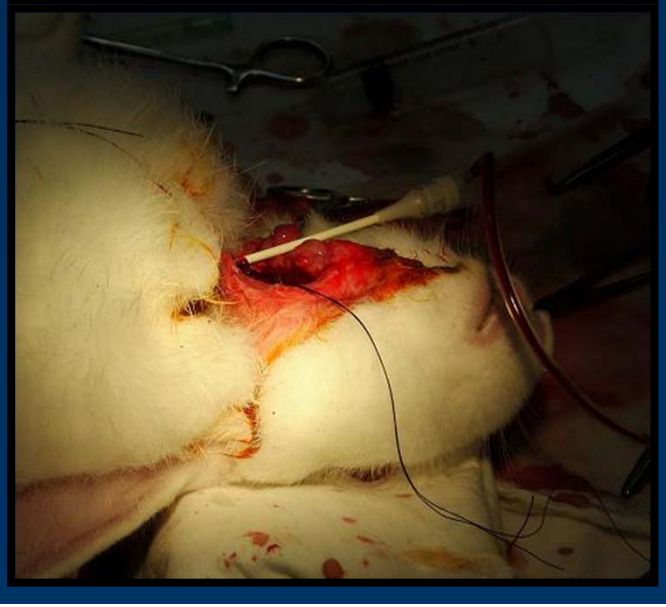
5 days after Injury

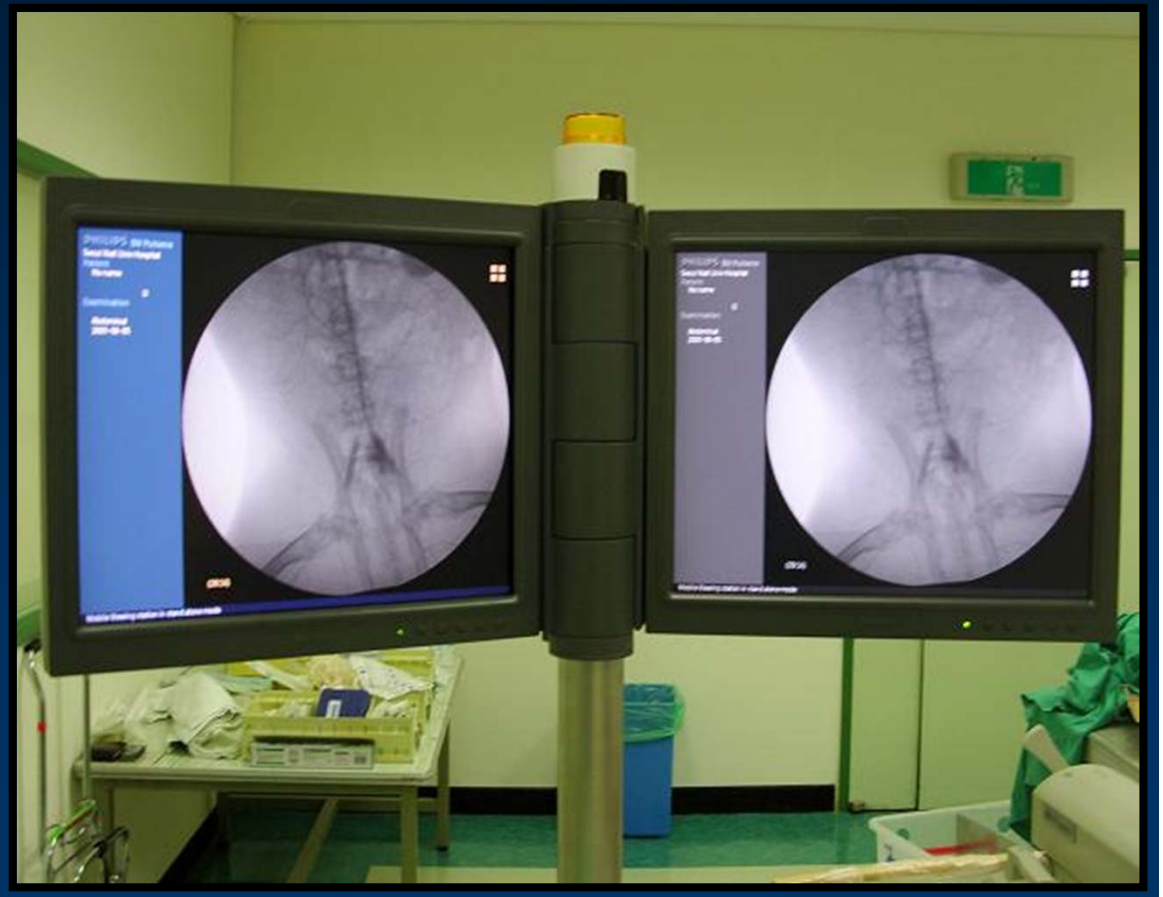
Rat carotid Injury Model

Rabbit Iliac Artery Stent Implantation Model

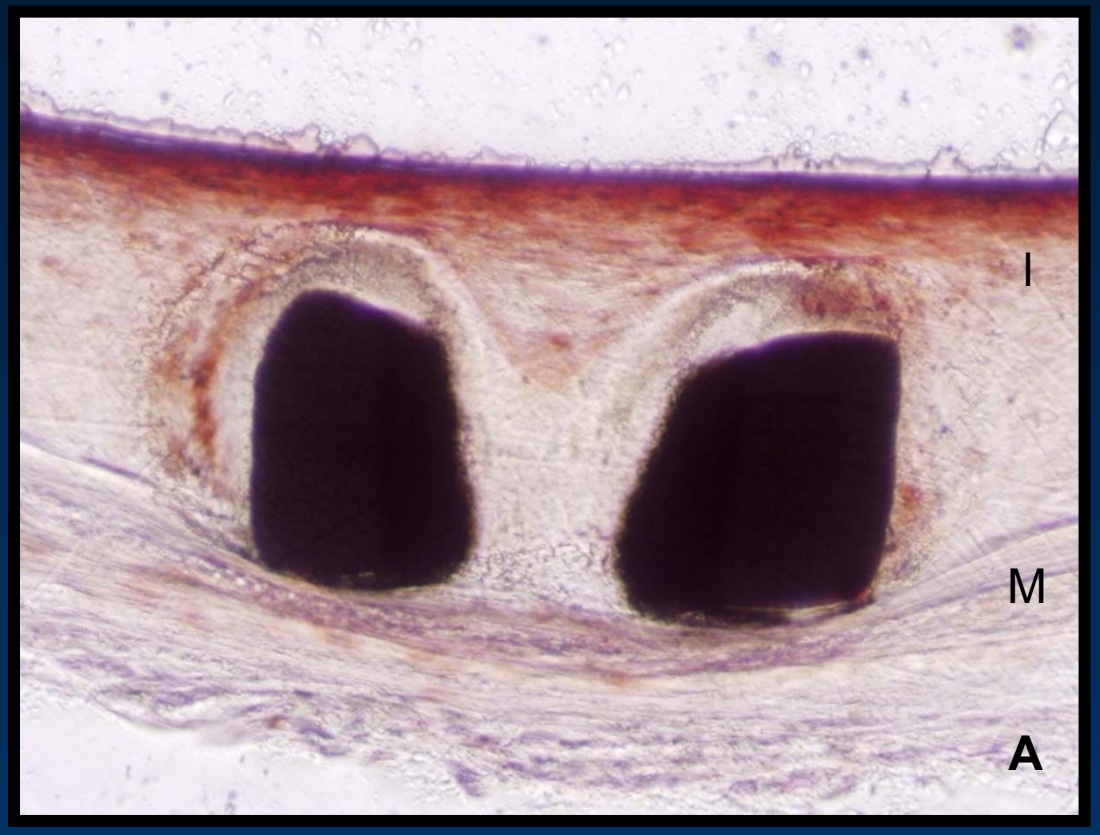
NZW Rabbits





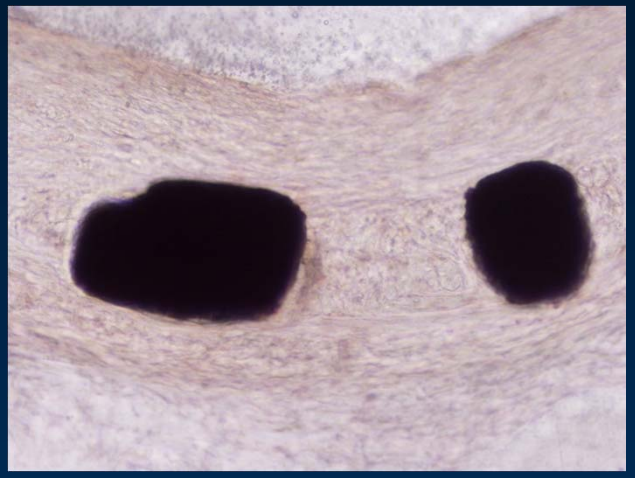


MDR-1 expression after PES implantation

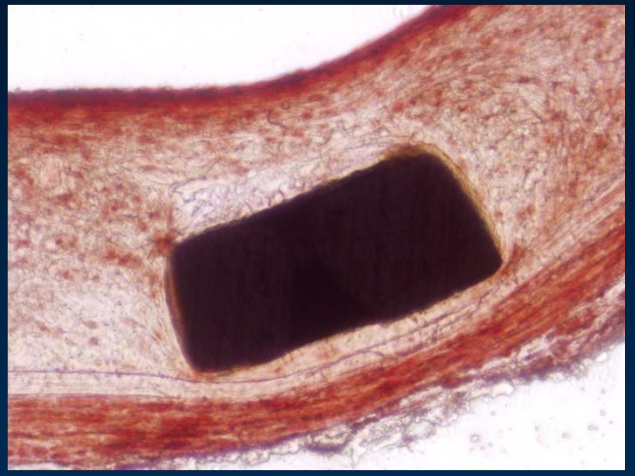


IHC for MDR-1 (Brown)
in the TAXUS-stented Rabbit Iliac Artery

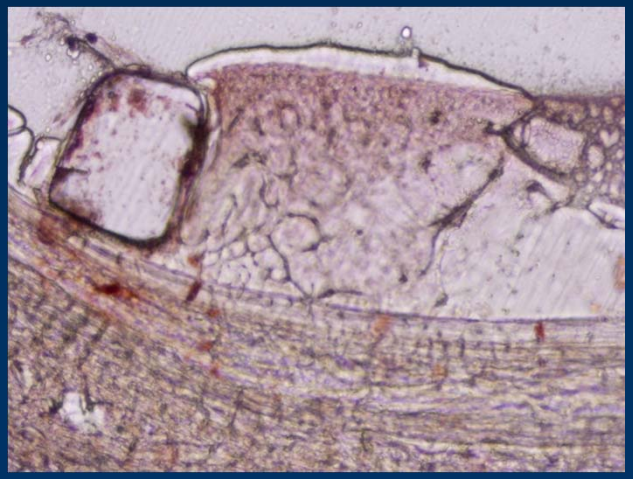
MDR-1 expression after DES Implantation



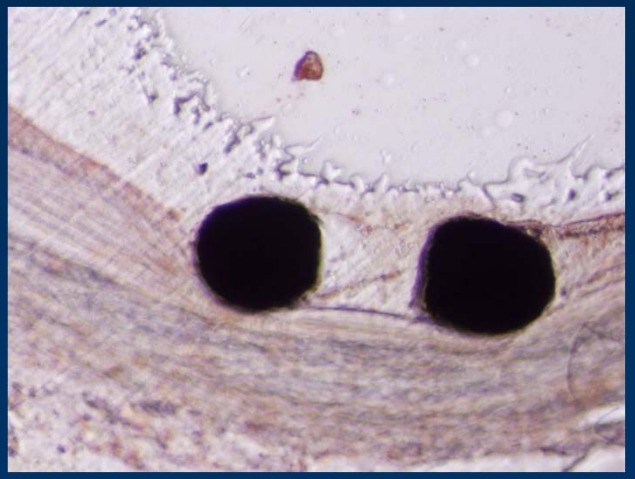
Bare-Metal Stents



Coroflex® Please (Paclitaxel)



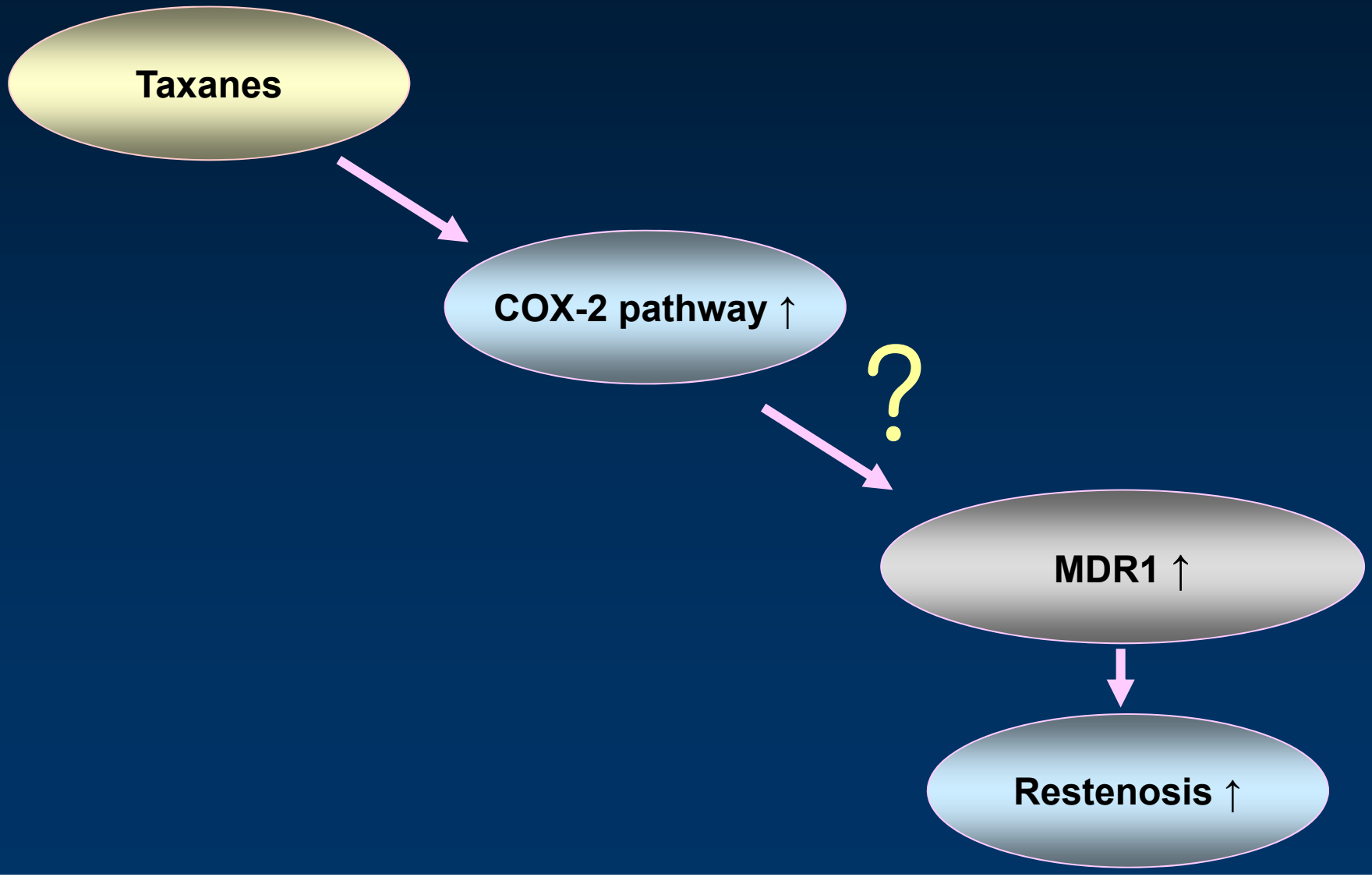
Cypher™ (Sirolimus)



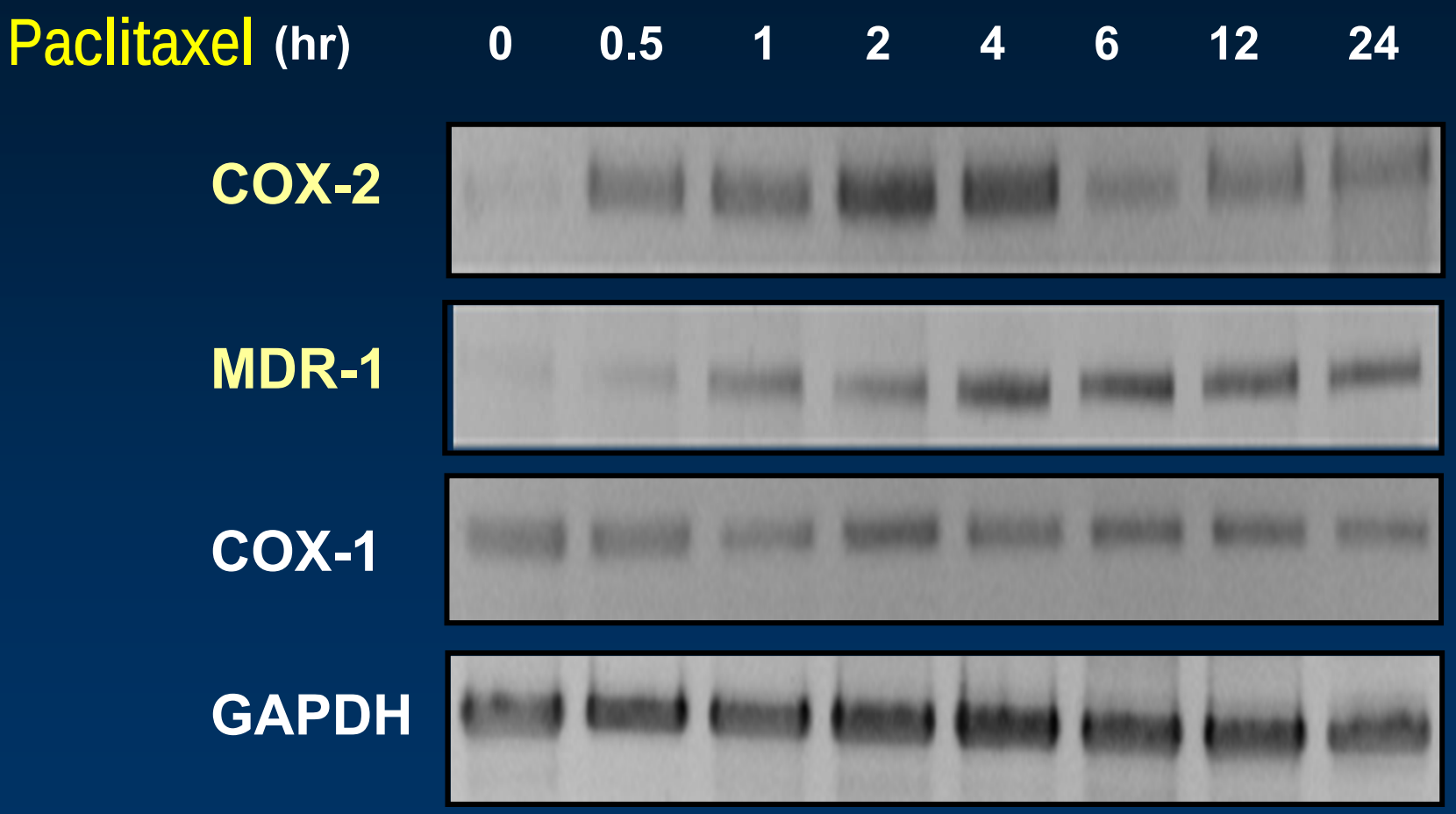
Endeavor® (Zotarolimus)

What Mechanism induces this self-resistance?

Paclitaxel Induces MDR-1 via COX-2 Pathway ??

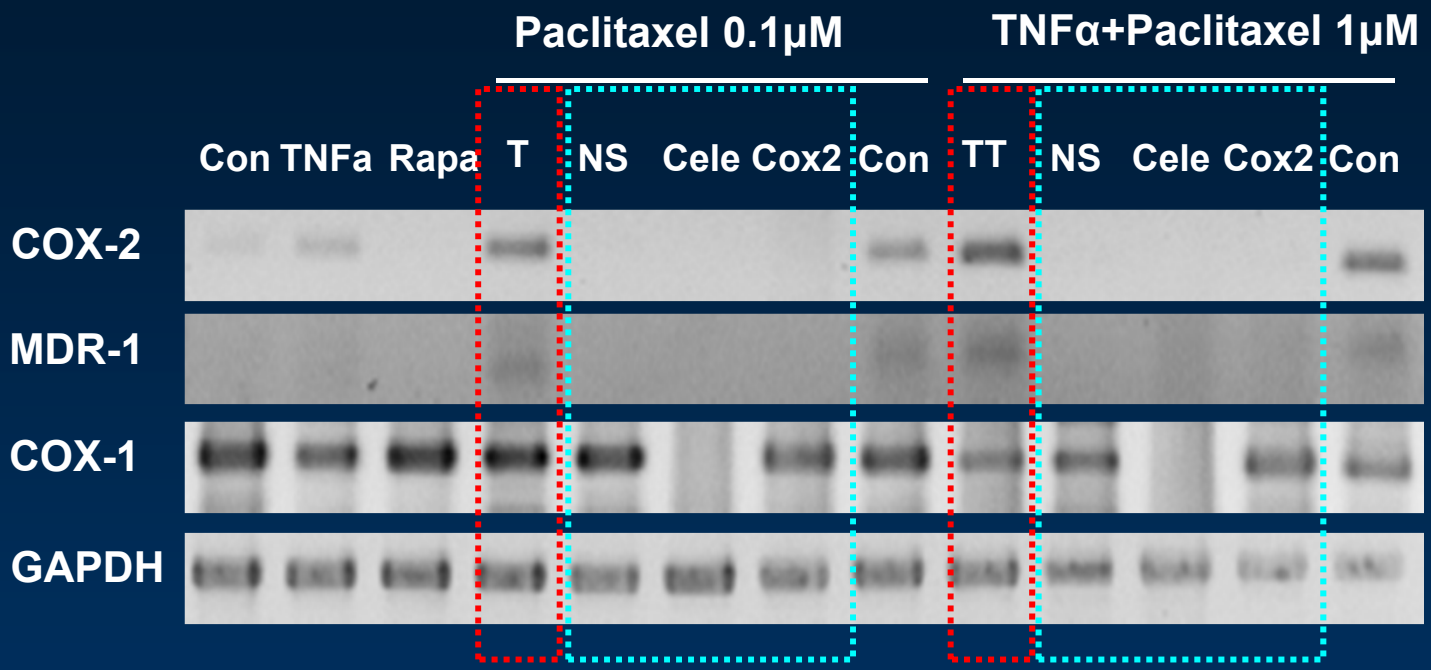


Paclitaxel Induces MDR-1 via COX-2 Pathway



RT-PCR / human VSMC

COX2 blockers inhibits Paclitaxel-induced MDR-1



NS: NS-398, COX-2 selective inhibitor

Cele: Celecoxib, COX-2 selective inhibitor

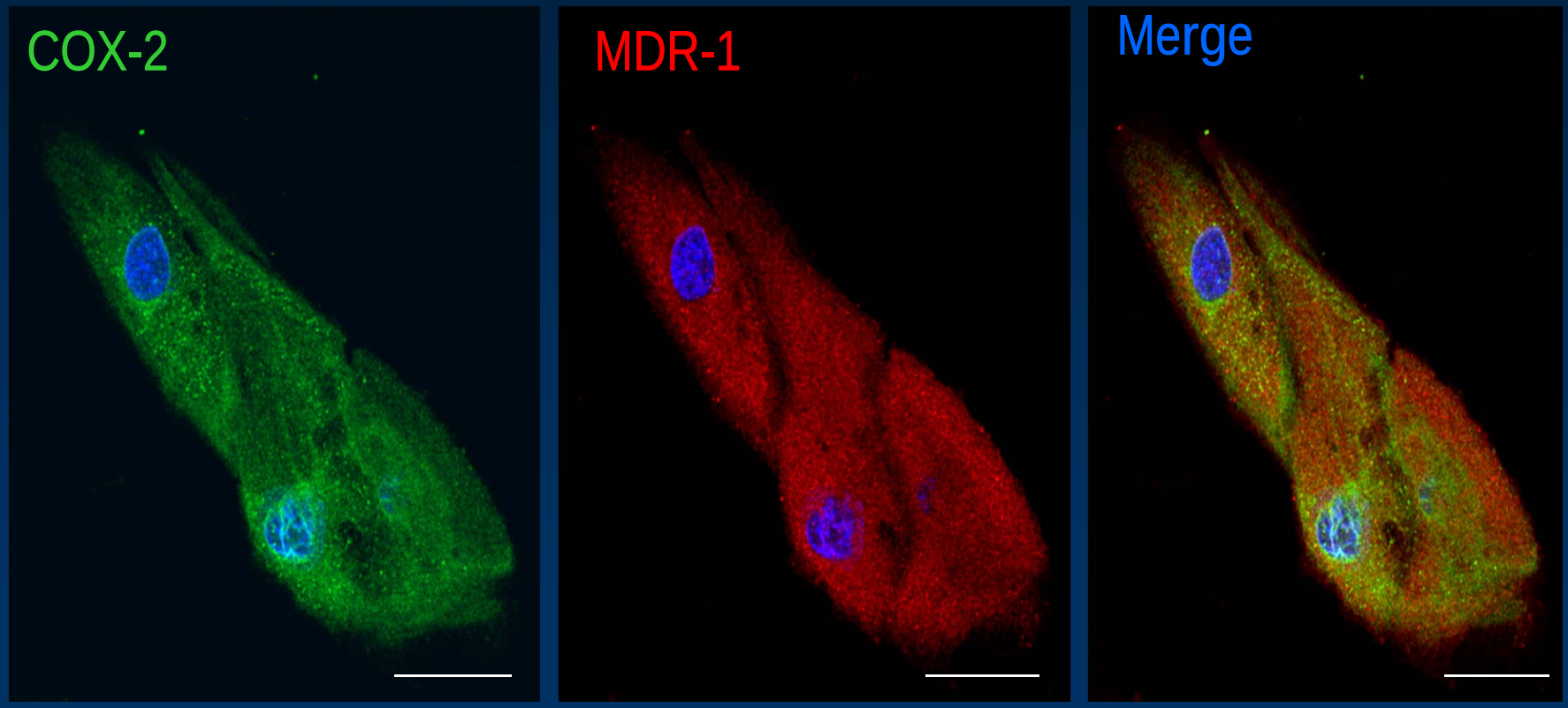
COX2: COX2 Si RNA

Con: Control Si RNA

RT-PCR / human VSMC

Paclitaxel Induces MDR-1 via COX-2 Pathway

Paclitaxel exposure to In vitro human VSMC

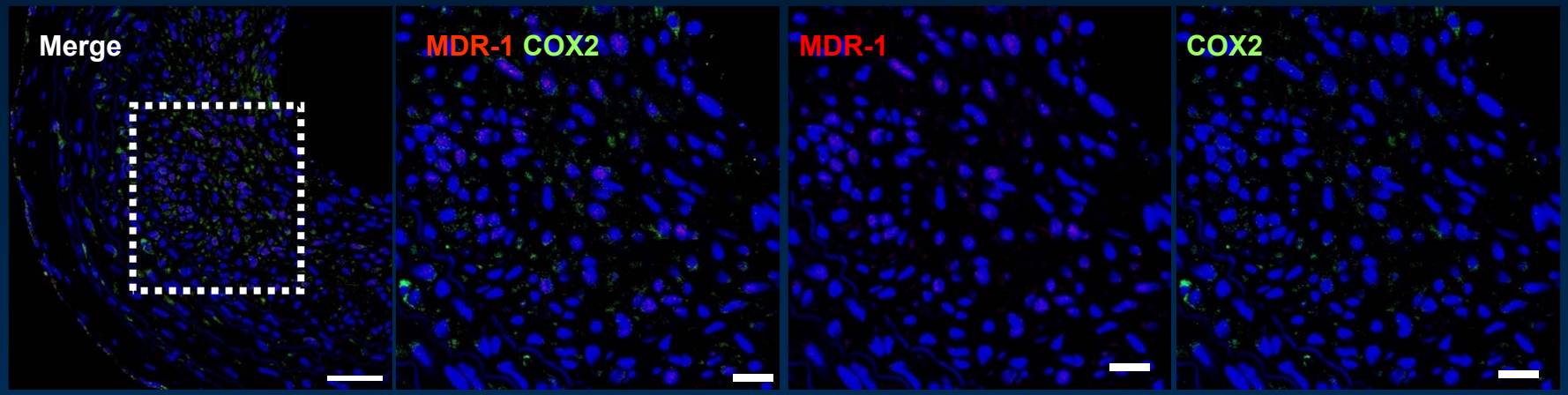


IF staining

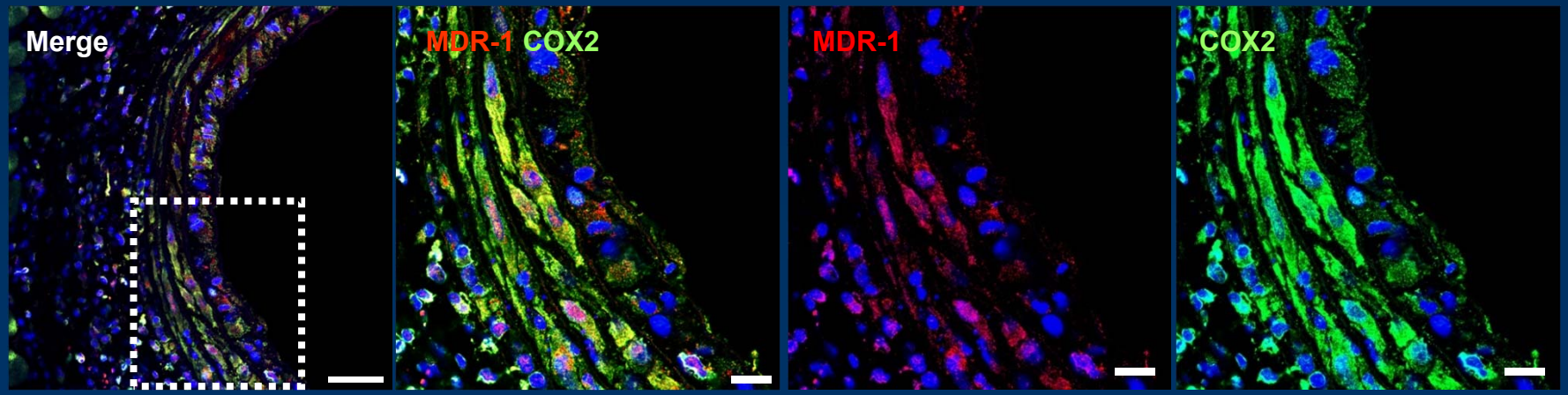
Systemic Paclitaxel Induces MDR-1 via COX-2 Pathway

Rat Carotid Artery Injury Model

Vehicle-Treated Artery after Injury



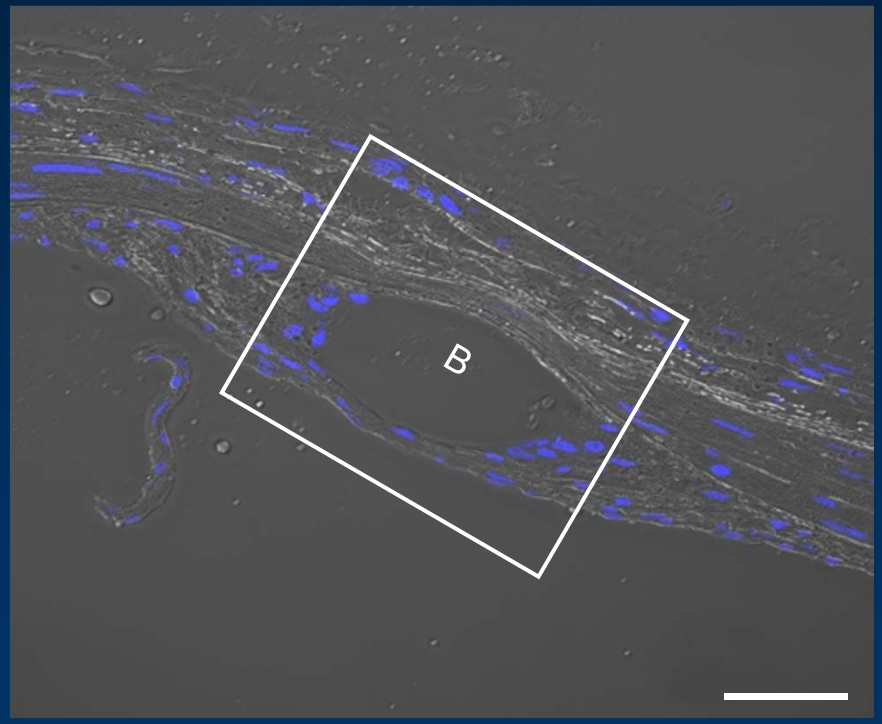
Paclitaxel-Treated Artery after Injury



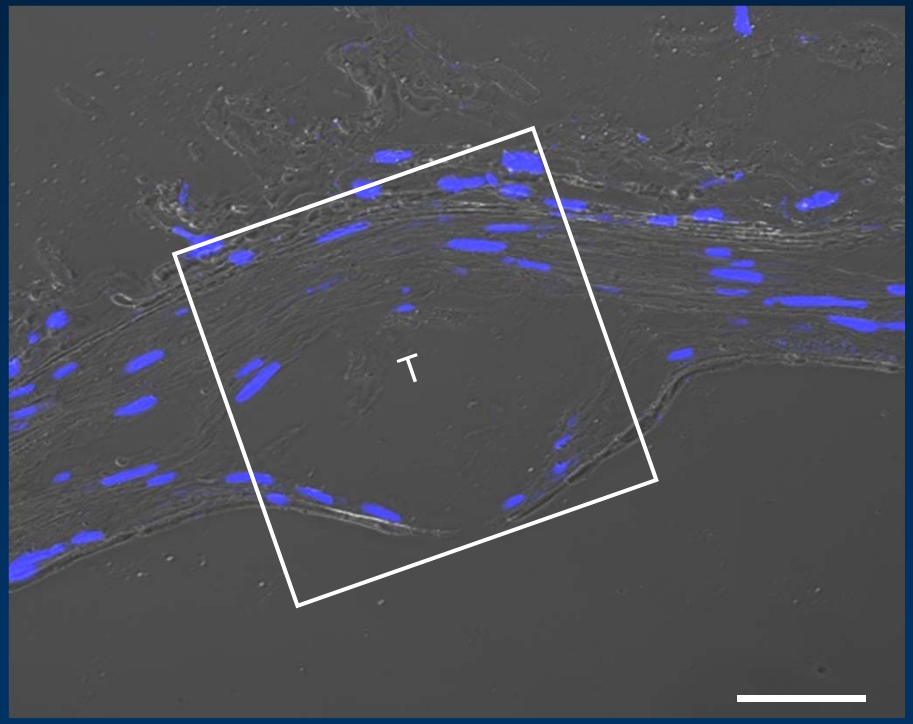
TAXOL-eluting stent Induces MDR-1 via COX-2 Pathway

Rabbit Iliac Artery Stenting Model

Bare-metal stent Implantation



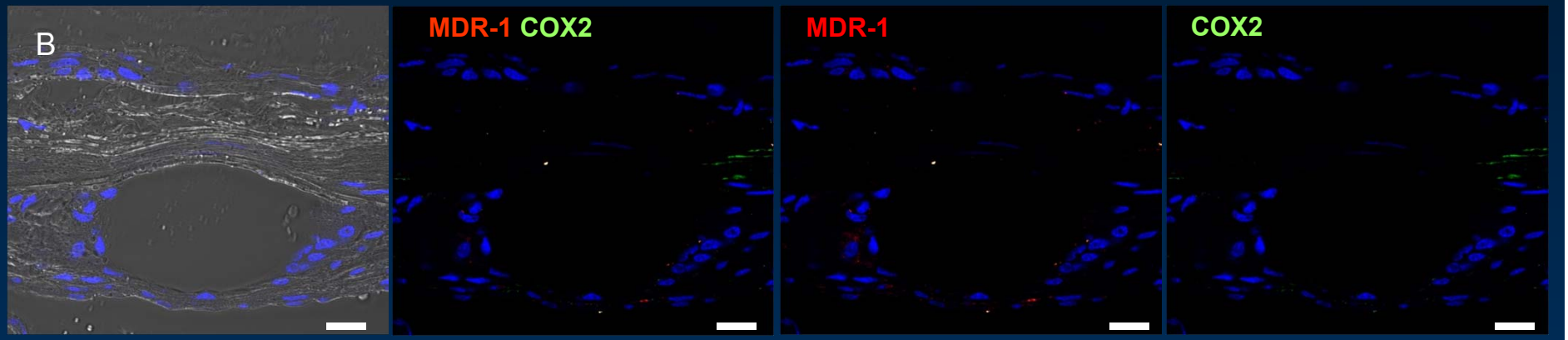
TAXOL-eluting stent Implantation



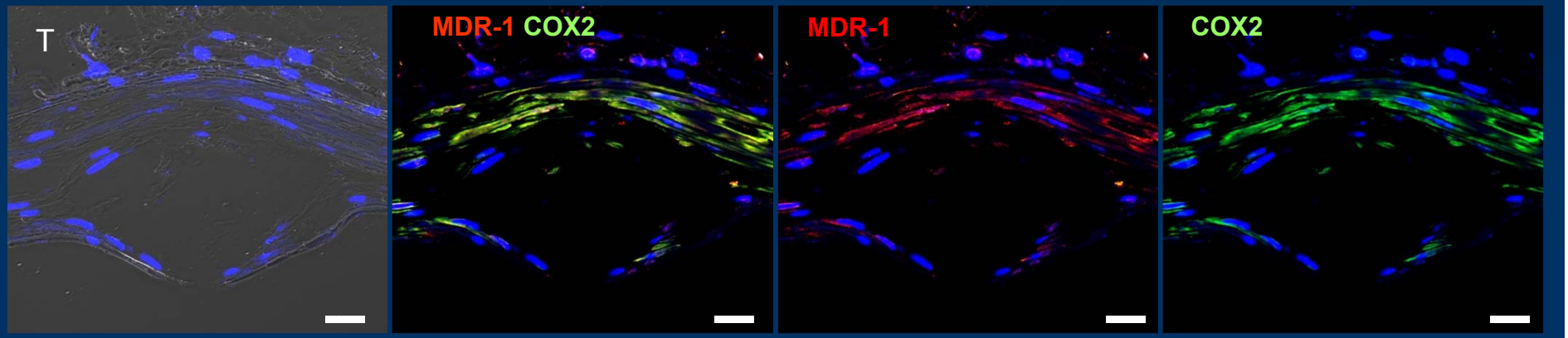
TAXOL-eluting stent Induces MDR-1 via COX-2 Pathway

Rabbit Iliac Artery Stenting Model

BMS stent Implantation



Paclitaxel-eluting stent Implantation

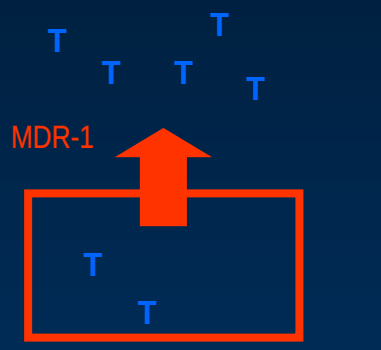


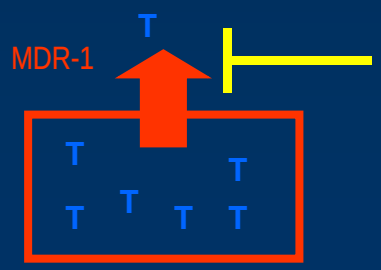
Paclitaxel-Induced MDR-1 is Functional?

and Enhances Cell Viability?

Paclitaxel-induced MDR-1 is Functional

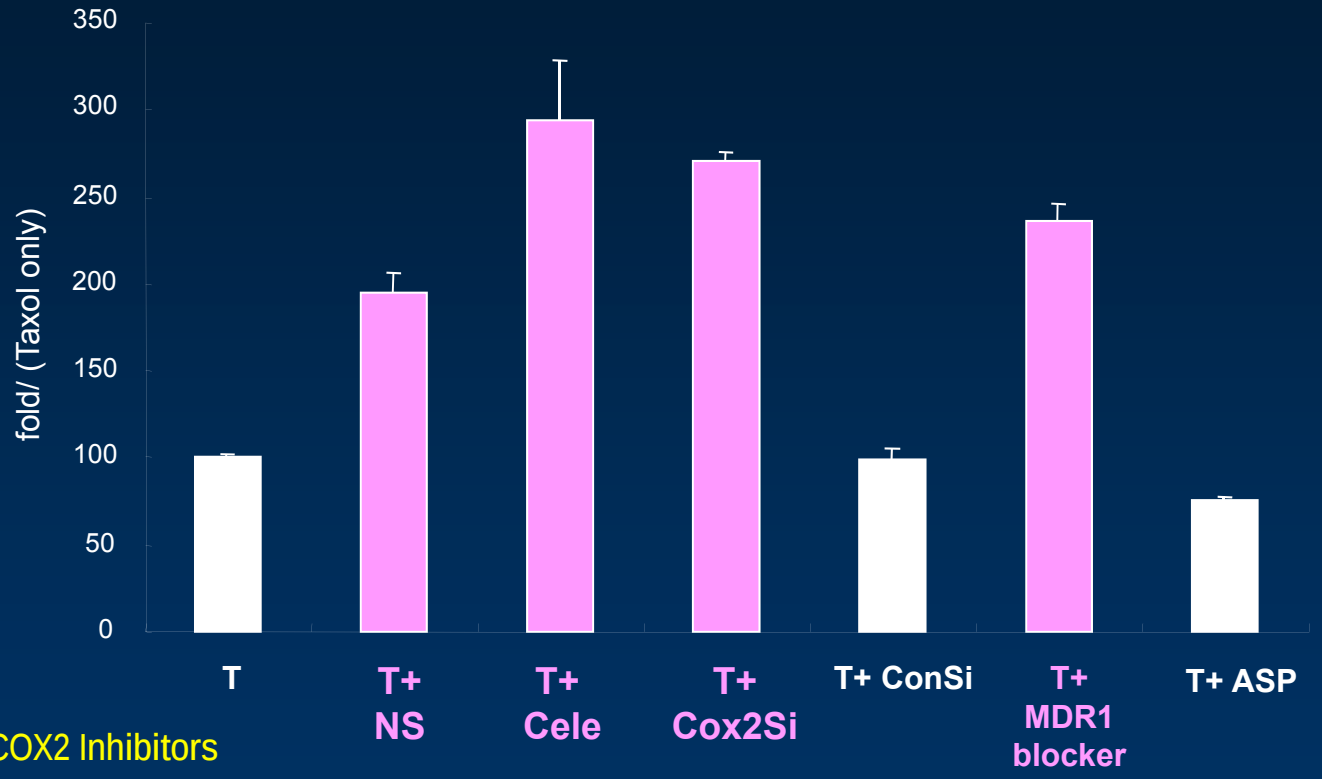
Intracellular Concentration of Radioisotope(C14)-tagged Paclitaxel





COX2 Inhibitors

MDR1 Blockers



NS: NS-398, COX-2 selective inhibitor

Cele: Celecoxib, COX-2 selective inhibitor

Cox2Si: COX2 Si RNA

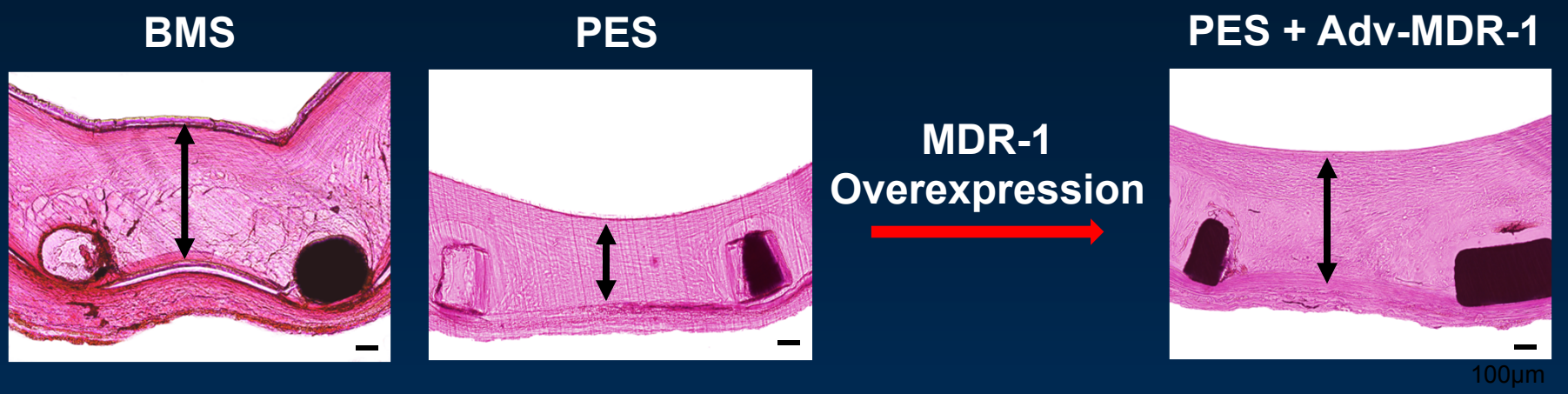
Con: Control Si RNA

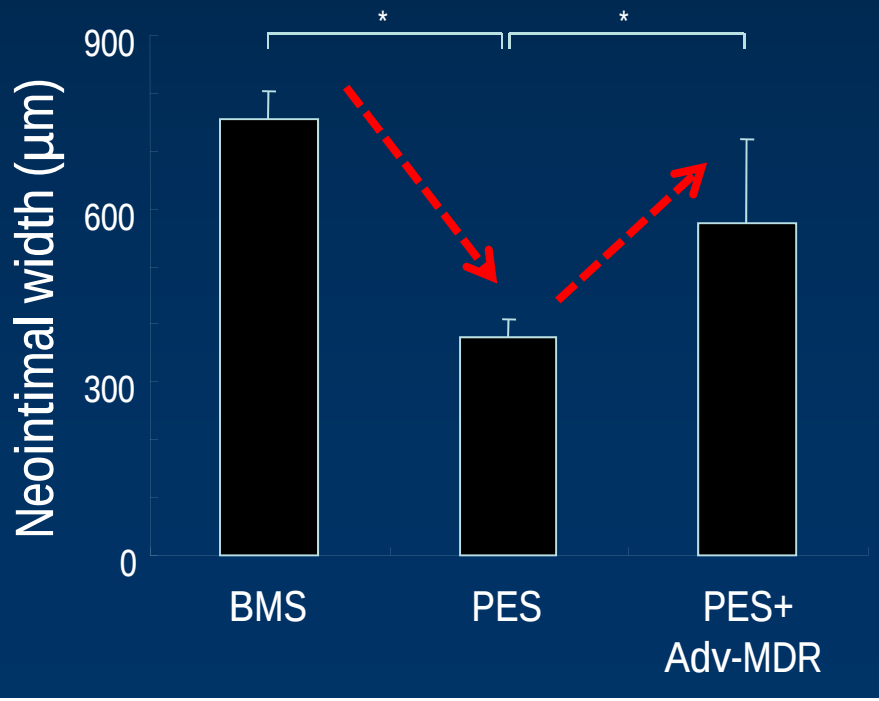
ASP: Aspirin

Does Paclitaxel-Induced MDR-1

Affects Restenosis *In Vivo*?

MDR-1 Overexpression = Resistance against Paclitaxel

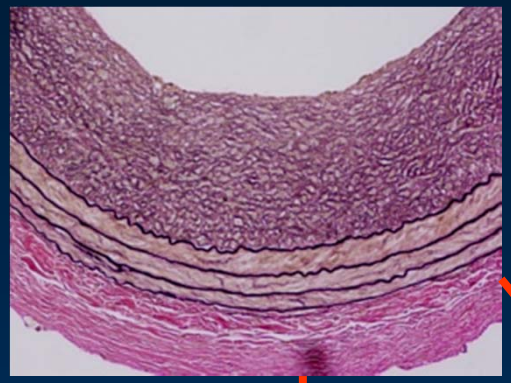




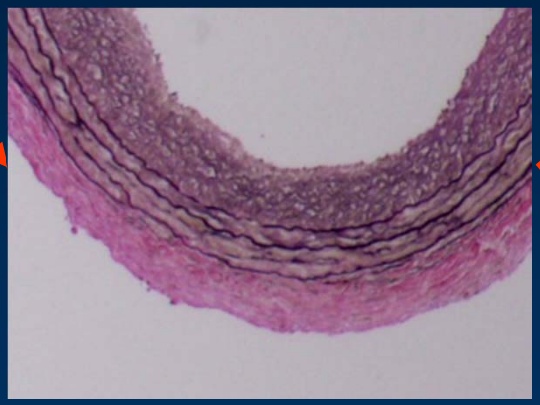
Paclitaxel-COX2-MDR-1 axis for Restenosis

Rat Carotid Artery Injury Model

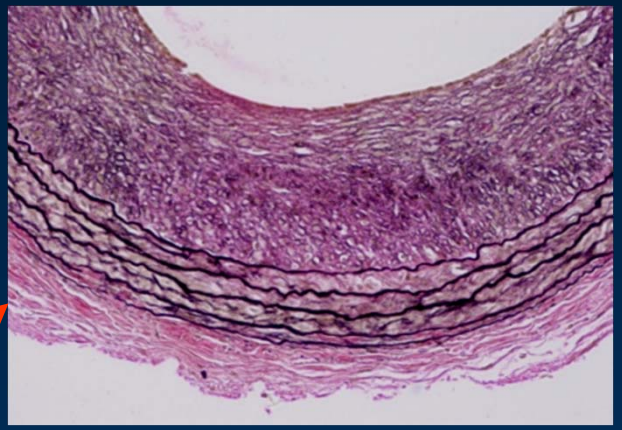
control

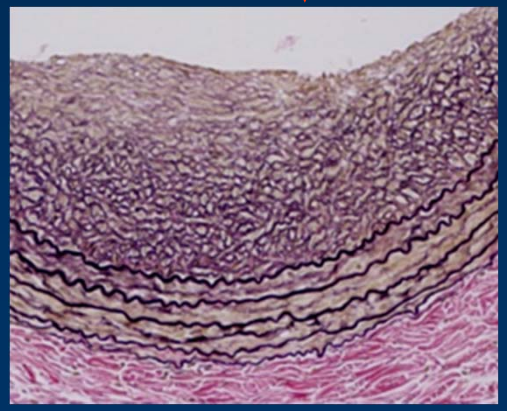


Paclitaxel

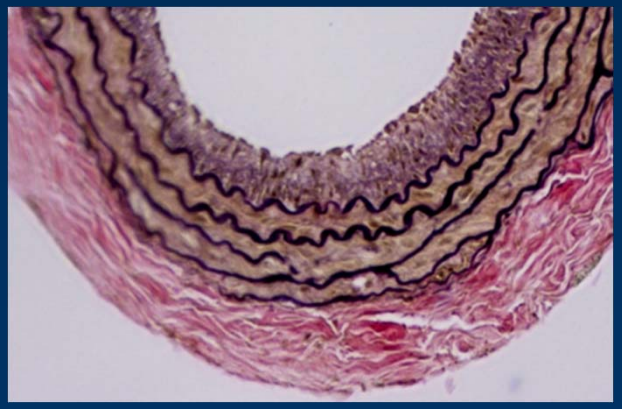


Paclitaxel + MDR





MDR Over-Exp.



Paclitaxel + COX-2 Inhibitor

History of SNUH Akt/COX2 inhibitor Program

Communication between bench and bed side

1. Initiation point of Akt & Celecoxib at bench
2. Cautious Consideration between bench & bed-side
3. First clinical trial (COREA-TAXUS): bench to bed-side
4. Return to bench : further complicated story

    : Taxol → COX2 → MDR-1 → Neointima

5. Feasibility confirmation between bench & bed-side

    : genotype of MDR-1 in patients with DES

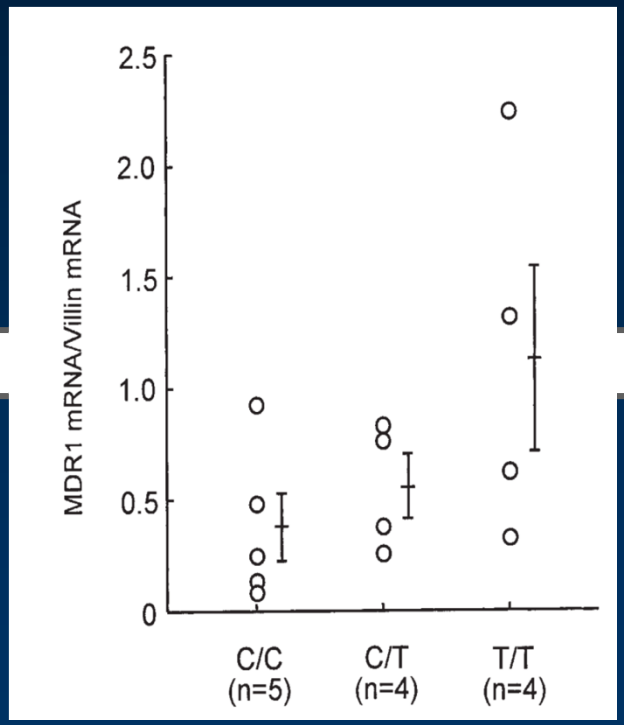
6. Second clinical trial (mini-COREA) : bench to bed-side

MDR1 gene TT genotype

Known to be associated with higher mRNA expression of MDR1

Effect of the mutation (C3435T) at exon 26 of the *MDR1* gene on expression level of MDR1 messenger ribonucleic acid in duodenal enterocytes of healthy Japanese subjects

Tsutomu Nakamura, PhD, Toshiyuki Sakaeda, PhD, Masanori Horinouchi, MSc, Takao Tamura, MD, PhD, Nobuo Aoyama, MD, PhD, Toshiro Shirakawa, MD, PhD, Masafumi Matsuo, MD, PhD, Masato Kasuga, MD, PhD, and Katsuhiko Okumura, PhD *Kobe, Japan*

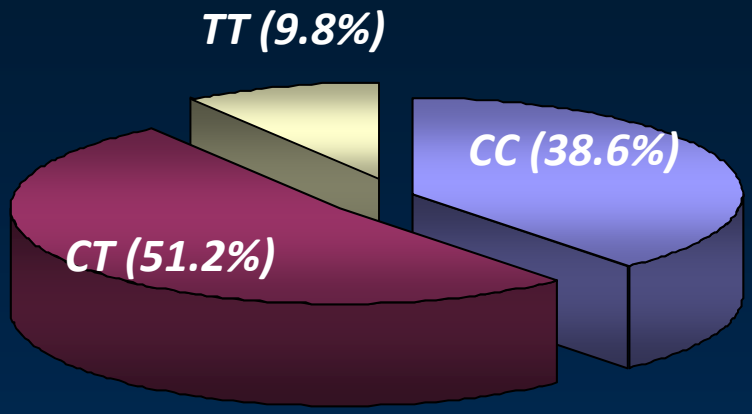


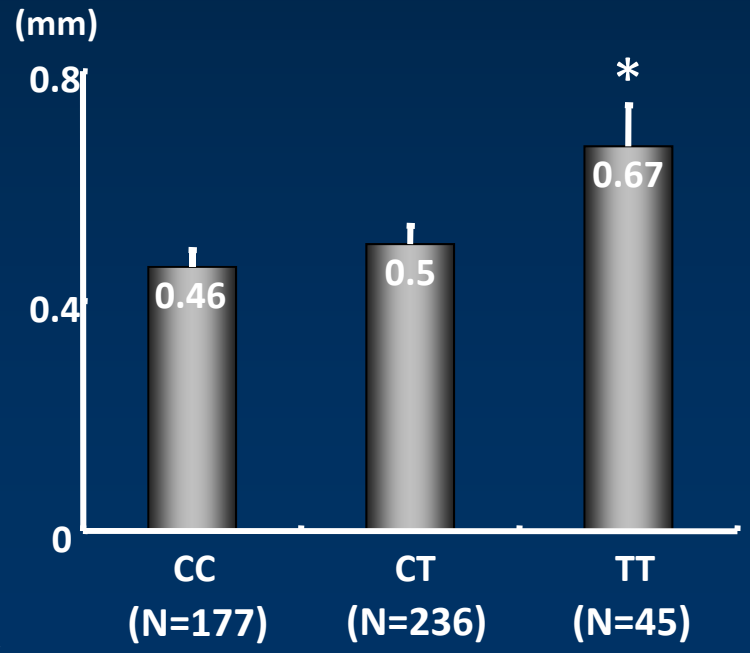
Nakamura T et al. Clin Pharmacol Ther 2002

MDR1 gene & PES:

MDR1 C3435T genotype and late loss after PES

Demographics	*n=458*
Age (yrs)	63.3 ± 8.9
Male	64.8% (297)
Risk Factors	
Diabetes	29.5% (135)
HTN	65.5% (300)
Dyslipidemia	63.3% (290)
Current smoker	22.3% (102)
Diagnosis	
Stable Angina	48.0% (220)
Acute coronary syndrome	49.3% (226)





History of SNUH Akt/COX2 inhibitor Program

Communication between bench and bed side

1. Initiation point of Akt & Celecoxib at bench
2. Cautious Consideration between bench & bed-side
3. First clinical trial (COREA-TAXUS): bench to bed-side
4. Return to bench : further complicated story

   : Taxol → COX2 → MDR-1 → Neointima
5. Feasibility confirmation between bench & bed-side

   : genotype of MDR-1 in patients with DES
6. Second clinical trial (mini-COREA) : bench to bed-side

Effects of Celecoxib On Restenosis after Coronary Intervention and Evolution of Atherosclerosis

: 6 month follow up results of Mini-COREA multicenter trial

강현재[1], 오일영[1] ,서정원[2] , 박경우[1] ,이해영[1] , 조영석[2] , 연태진[2] , 구본권[1] , 강원유[3], 김원[3], 나승운[4] ,배장호[5] ,채인호[2] ,최동주[2] ,김효수[1]

서울대학교병원 순환기내과[1]

분당서울대학교병원 순환기내과[2]

광주보훈병원 심장내과[3]

고려대학교 구로병원 순환기내과[4]

건양대학교병원 심장내과[5]

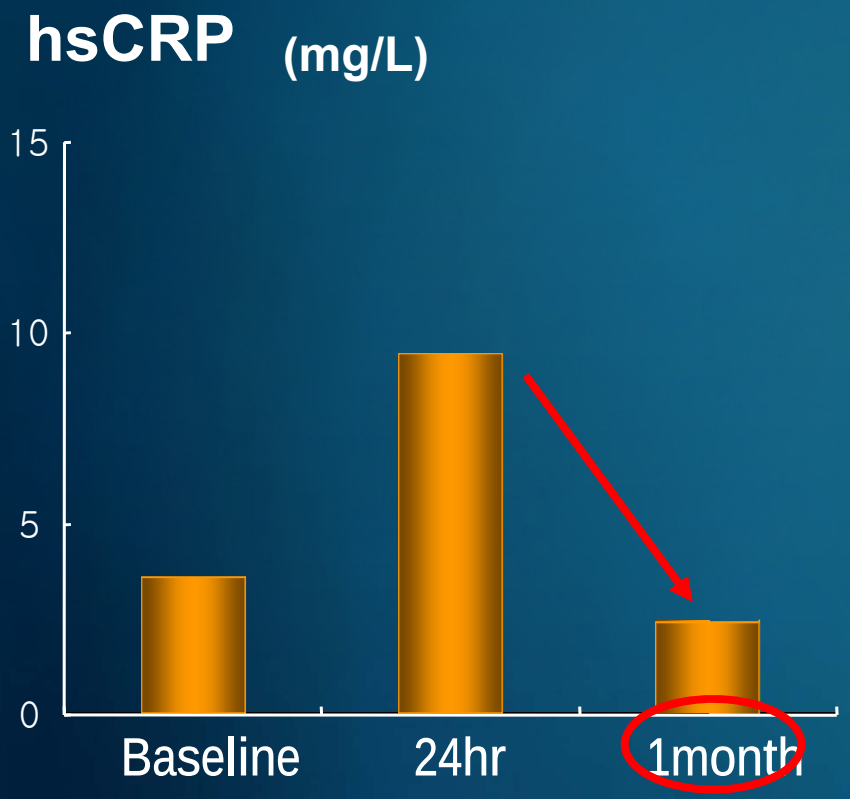
COREA-TAXUS: 2 years' Results

(Circulation Cardiovascular Intervention. 2010;3:243-248)

	1 year			2 year		
	Control	Celecoxib	p-value	Control	Celecoxib	p-value
Total MACE	18.2%	5.4%	0.001	19.7%	6.9%	0.002
TLR	17.5%	5.4%	0.002	18.2%	6.2%	0.003
Nonfatal MI	0	0.8%	0.49	0.7%	1.5%	0.61
Cardiac death	0.7%	0	>0.99	0.7%	0	>0.99
Stent thrombosis	0.7%	0.8%	>0.99	0.7%	0.8%	>0.99

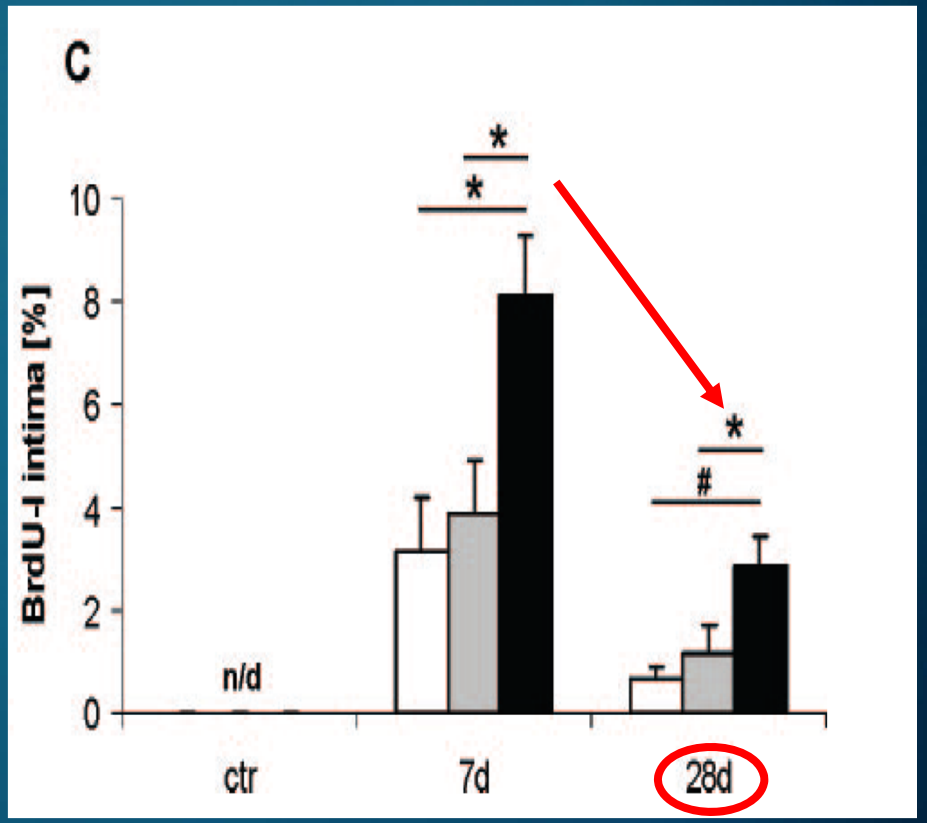
Celecoxib for 6 month seems to be sufficient, but necessary?

Inflammation



COREA-TAXUS trial

Proliferation



Matter et al. 2006 Stoke

mini-COREA-TAXUS trial

Effect of *C*elecoxib for *3 months* *O*n *RE*stenosis after coronary Intervention and Evolution of *A*therosclerosis:

A multicenter open-label randomized controlled study

- To evaluate effect of 3months celecoxib treatment on
  - Neointimal growth and plaque progression
  - Clinical outcomes

Mini COREA Trial

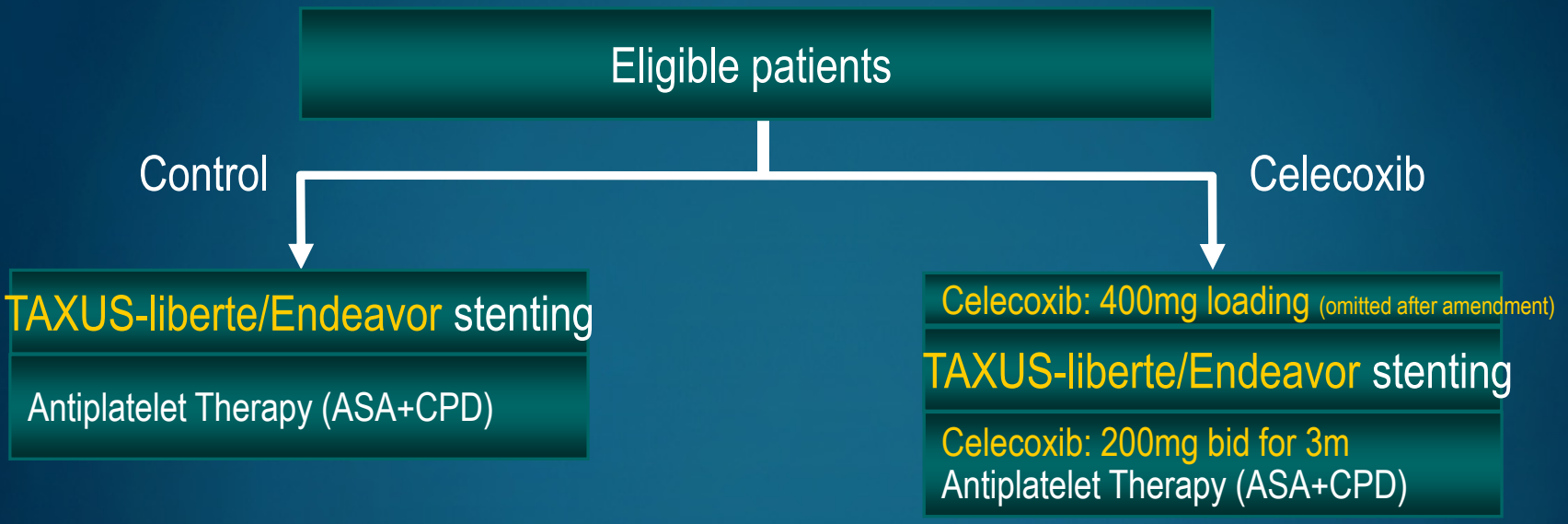
- Inclusion criteria
  - Aged > 30 years
  - Angina pectoris or a positive stress test
  - Significant native coronary artery stenosis feasible for TAXUS/Endeavor stenting
- Exclusion criteria
  - Acute ST-elevation MI
  - Definite intracoronary thrombus
  - Left main coronary artery disease
  - Chronic total occlusion
  - Severe CHF (NYHA class >3)
  - Uncorrected severe hematologic disorders
  - Hepatic dysfunction: serum AST/ALT ≥ 120 IU/L
  - Renal dysfunction: serum creatinine ≥ 2.0 mg/dL
  - ContraIx or Hx of allergy to ASA, clopidogrel, or celecoxib
  - On warfarin or fluconazole use
  - Expected survival < 1y

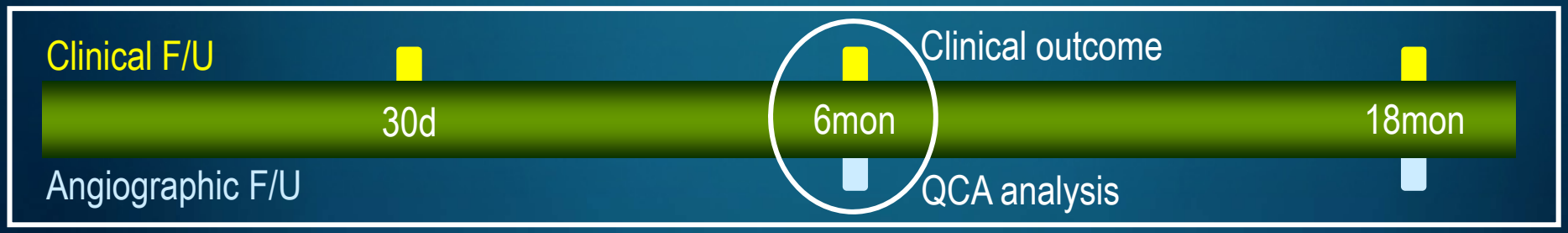
Mini COREA Trial

Calculation of Sample Size

- Estimated reduction of late loss by celecoxib was 25%
- Power of the study was 80%
- Alpha error was 5%
- Predicted follow-up loss: 15%
- Calculated sample size was
  - Taxus – 270 vs. 270
  - Endeavor – 180 vs. 180

mini-COREA-TAXUS Trial





Primary Endpoint : In-stent late luminal loss

Secondary Endpoint : Target lesion revascularization (TLR), Non-fatal MI, Cardiac death

Total pts: QCA at 6Month Follow-up

	Control	Celecoxib	*p* value
Follow-up	400	390	
Mean reference diameter, mm	2.76 ± 0.48	2.80 ± 0.49	0.24
Minimal luminal diameter, mm			
In-stent	1.94 ± 0.63	2.02± 0.63	0.07
In-segment	1.82 ± 0.58	1.90 ± 0.60	0.10
Diameter stenosis, %			
In-stent	29.4 ± 19.3	27.4 ± 19.6	0.17
In-segment	31.4 ± 19.5	29.9 ± 18.3	0.28
Late luminal loss, mm			
In-stent	0.64 ± 0.54	0.55 ± 0.47	0.02
In-segment	0.39 ± 0.51	0.38 ± 0.47	0.58
Binary restenosis, n (%)			
In-stent	57 (14.3)	48 (12.3)	0.42
In-segment	64 (16.0)	51 (13.1)	0.24

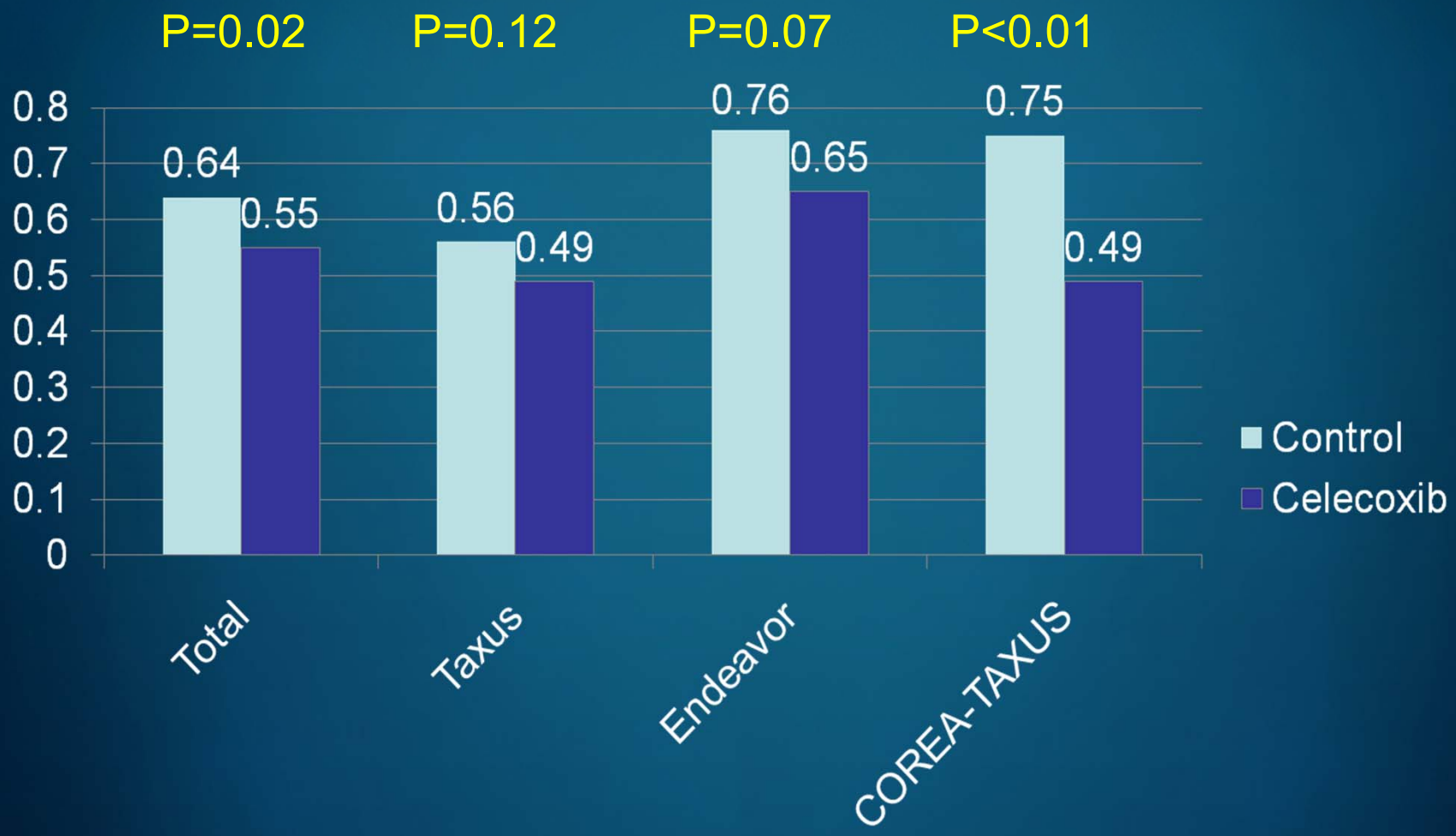
Taxus - QCA at 6Month Follow-up

	Control	Celecoxib	*p* value
Follow-up	237	231	
Mean reference diameter, mm	2.73 ± 0.49	2.76 ± 0.48	0.58
Minimal luminal diameter, mm			
In-stent	1.99 ± 0.62	2.05 ± 0.62	0.33
In-segment	1.86 ± 0.57	1.90 ± 0.59	0.46
Diameter stenosis, %			
In-stent	26.9 ± 19.3	25.2 ± 19.6	0.36
In-segment	29.4 ± 18.7	28.2 ± 18.3	0.50
Late luminal loss, mm			
In-stent	0.56 ± 0.50	0.49 ± 0.45	0.12
In-segment	0.32 ± 0.44	0.35 ± 0.45	0.57
Binary restenosis, n (%)			
In-stent	26 (11.0)	27 (11.2)	0.81
In-segment	30 (12.7)	29 (12.6)	0.97

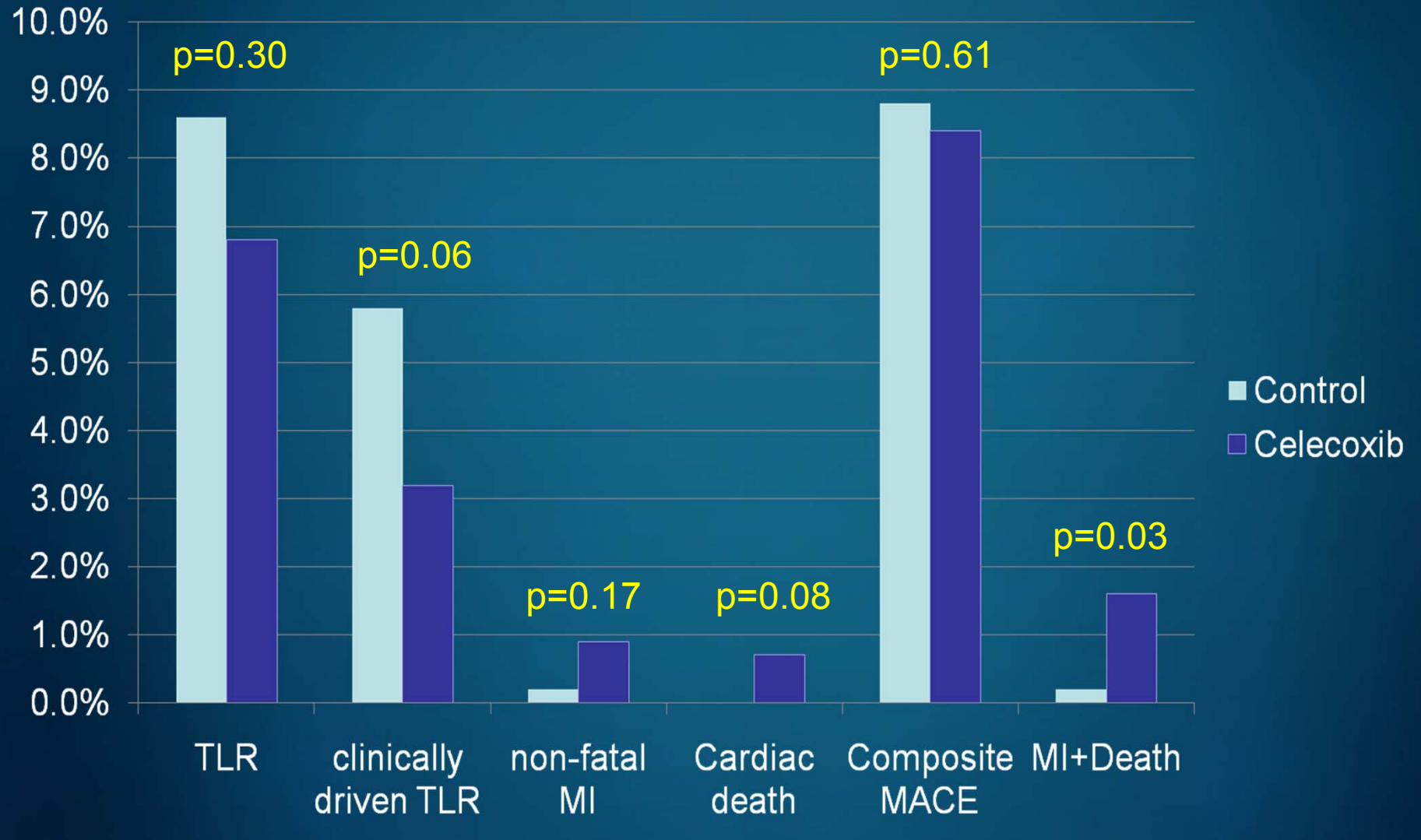
Endeavor - QCA at 6Month Follow-up

	Control	Celecoxib	*p* value
Follow-up	163	159	
Mean reference diameter, mm	2.80 ± 0.47	2.86 ± 0.50	0.24
Minimal luminal diameter, mm			
In-stent	1.86 ± 0.64	1.98 ± 0.64	0.09
In-segment	1.78 ± 0.59	1.89 ± 0.62	0.69
Diameter stenosis, %			
In-stent	32.9 ± 21.2	30.5 ± 19.1	0.28
In-segment	34.3 ± 20.4	32.4 ± 18.1	0.38
Late luminal loss, mm			
In-stent	0.76 ± 0.58	0.65 ± 0.50	0.07
In-segment	0.50 ± 0.55	0.42 ± 0.49	0.15
Binary restenosis, n (%)			
In-stent	31 (19.2)	21 (13.2)	0.16
In-segment	34 (20.9)	22 (13.8)	0.10

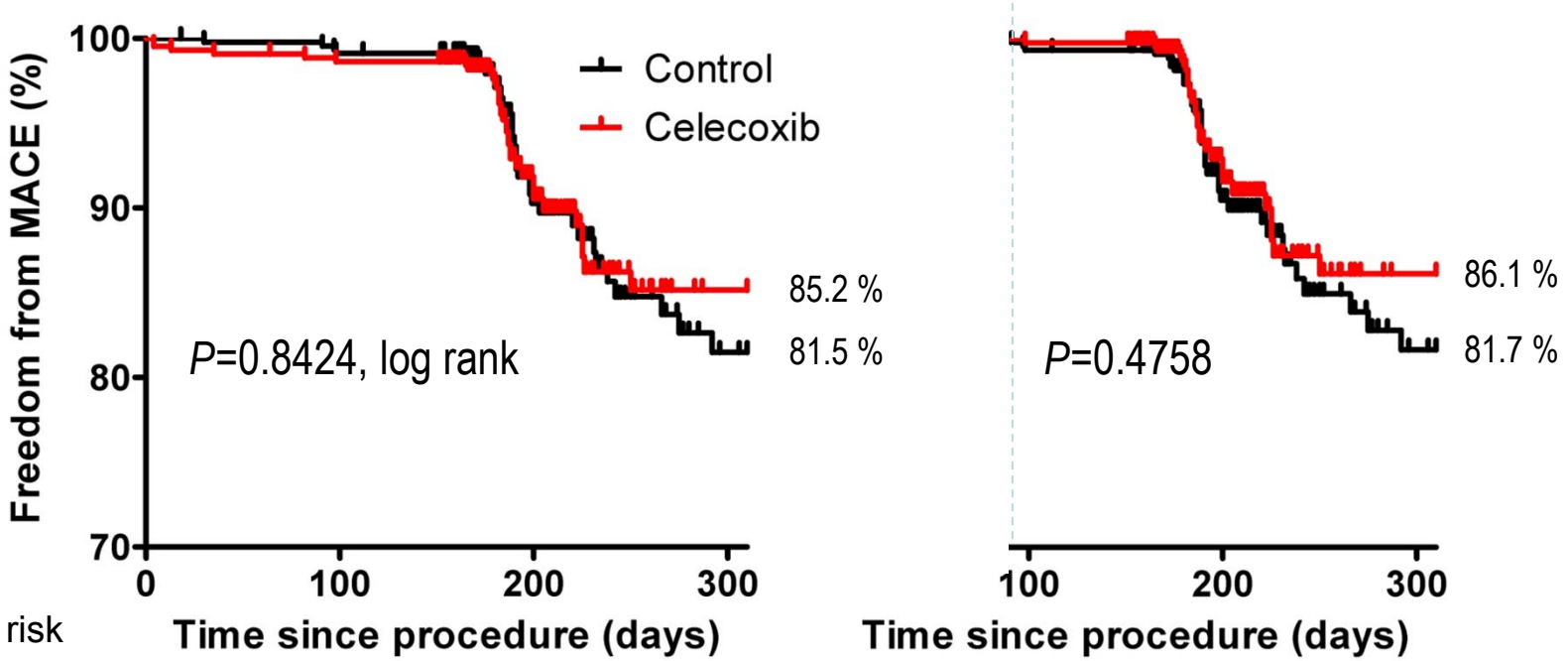
Primary endpoint: In-stent late luminal loss at 6 month



Clinical outcomes at 6 months follow-up



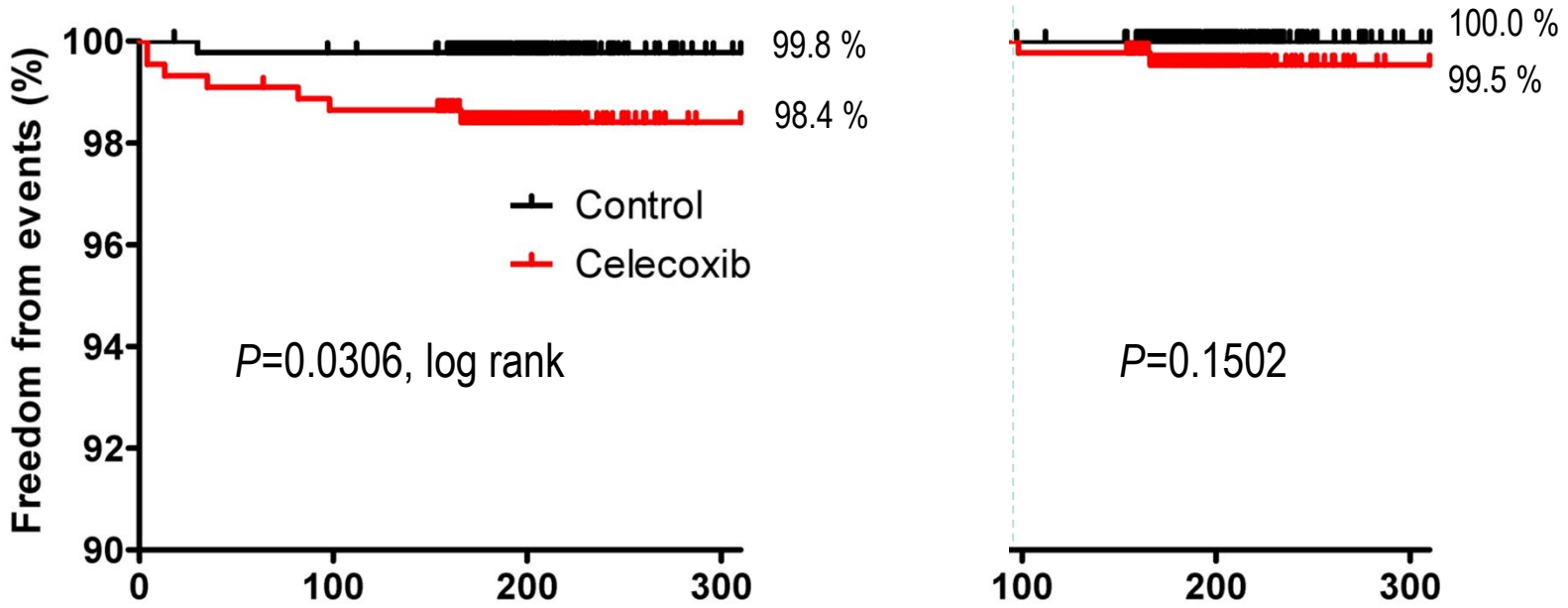
Freedom from MACE: Landmark analysis



Number at risk				
Celecoxib	442	435	141	69
Control	454	449	167	70

435	141	69
449	167	70

Freedom from hard end points : Land mark analysis



Number at risk				
Celecoxib	442	435	138	72
Control	454	451	170	73

435	138	72
451	170	73

Cilostazol's effect on hard end points

Dual antiplatelet therapy

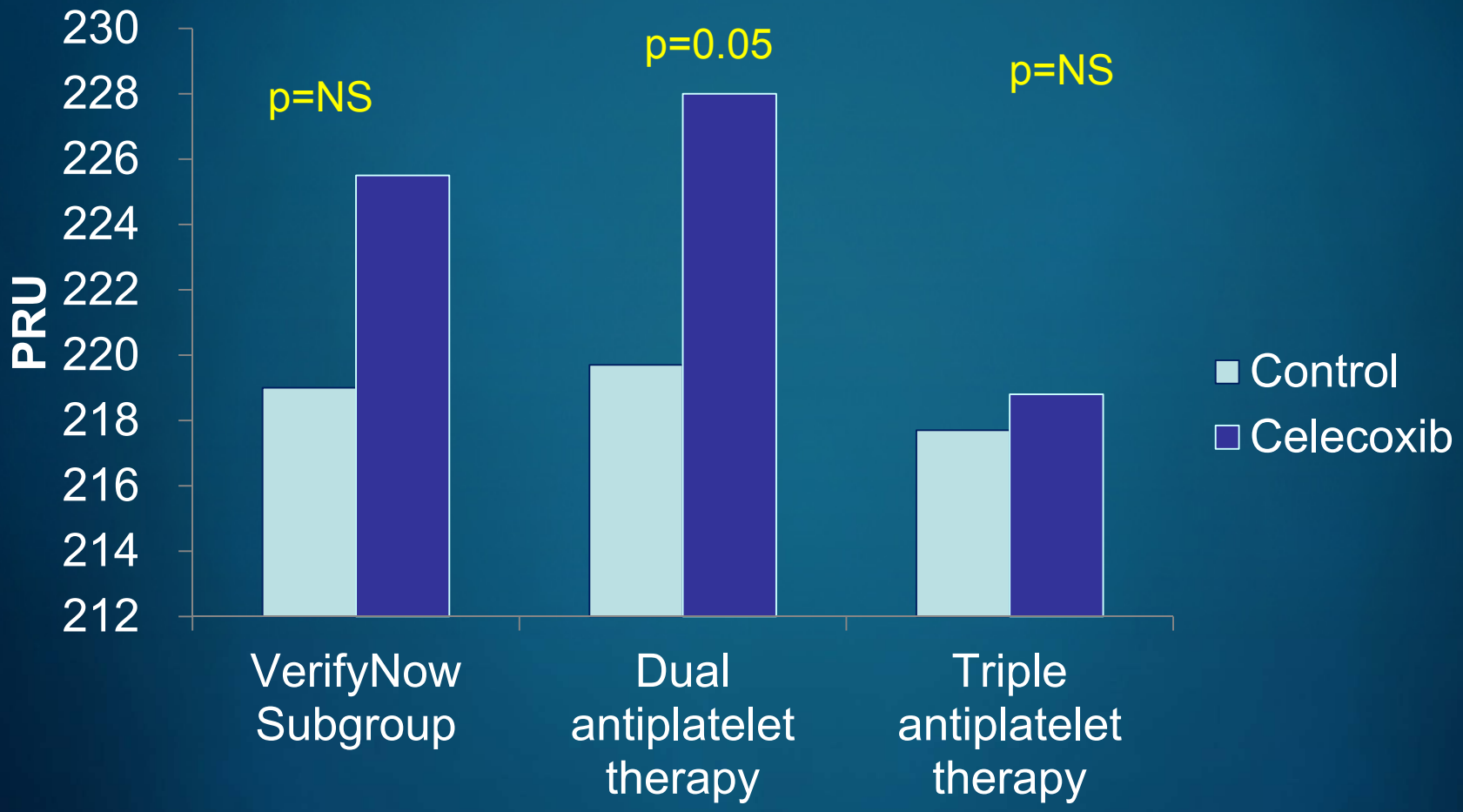
	Control (N=318)	Celecoxib (N=318)	p-value
Late loss (mm) N=281/286	**0.65 (0.54)**	**0.58 (0.49)**	**0.079**
TLR (%)	28 (8.8)	21 (6.6)	0.298
Clinically driven TLR (%)	20 (6.3)	12 (3.8)	0.147
Non-fatal MI (%)	0 (0.0)	3 (0.9)	0.083
Cardiac death (%)	0 (0)	3 (0.9)	0.083
Total (%)	28 (8.8)	25 (7.9)	0.667
Composite of CD, MI	**0 (0.0)**	**6 (1.9)**	**0.014**

Triple antiplatelet therapy

	Control (N=134)	Celecoxib (N=123)	p-value
Late loss (mm) N=119/104	**0.60 (0.56)**	**0.49 (0.42)**	**0.086**
TLR (%)	11 (8.2)	9 (7.3)	0.789
Clinically driven TLR (%)	6 (4.5)	2 (1.6)	0.189
Non-fatal MI (%)	1 (0.8)	1 (0.8)	0.952
Cardiac death (%)	0 (0.0)	0 (0.0)	-
Total (%)	11 (8.2)	9 (7.3)	0.789
Composite of CD, MI	**1 (0.8)**	**1 (0.8)**	**0.951**

VerifyNow Subgroup

587 among 996 patients were analyzed with VerifyNow.



mini-COREA-TAXUS trial

Message

- Adjunctive use of Akt/COX2 inhibitor (celecoxib)

– Positive aspect

: reduced late loss & TLR after DES

– Negative aspect

: increased thrombotic events d/t inhibition of DAT

: can be overcome by TAT

History of SNUH Akt/COX2 inhibitor Program
Communication between bench and bed side

1. Initiation point of Akt & Celecoxib at bench
2. Cautious Consideration between bench & bed-side
3. First clinical trial (COREA-TAXUS): bench to bed-side
4. Return to bench : further complicated story

   : Taxol → COX2 → MDR-1 → Neointima
5. Feasibility confirmation between bench & bed-side

   : genotype of MDR-1 in patients with DES
6. Second clinical trial (mini-COREA) : bench to bed-side

‘Misfortune’ in Translational Cardiology from Akt/COX2 to mini-COREA RCT

- Good luck is as important as good result.
- Impact of innovative results from translational research may be determined by the advance of the associated field.
- (Excellent new generation DESs nullify the necessity of new drug development.)

‘Hope’ in Translational Cardiology from Akt/COX2 to mini-COREA RCT

- New drugs with combined effects of (celecoxib + cilostazol) may be helpful for a specific subgroup having great late loss even after newest DES.

- For highest risk subpopulation : Multiple bifurcation stenting in patients with DM / CRF / Strong genetic background of atherosclerosis

Translational Cardiology: Where are we now?

One example of research ‘from bench to bedside’

(from Akt to Mini-COREA clinical trial)

Hyo-Soo Kim, MD/PhD

Cardiovascular Center / Cardiovascular Research Laboratory

Seoul National University Hospital, Seoul, Korea