Class of Drug Stents

연세의대 심장내과 고영국, 장 양 수

Commercially Available DES

- **Sirolimus-eluting stent (Cypher)**

  => RAVEL, SIRIUS, C- & E-SIRIUS, DIRECT, SVELTE, REALITY

- **Paclitaxel-eluting stent (TAXUS)**

  => TAXUS I, II, III, IV, V, VI

DES under Clinical Investigation

1. **Sirolimus and Analogues:**
   - Everolimus-Eluting Stent (Biosensors/Guidant) : *FUTURE I, II*
   - ABT-578 PC Stent (Abbott/Medtronic) : *ENDEAVOR I, II, III*
2. **Paclitaxel and Analogues:**
   - Taxane Quanam Stent (Boston Scientific) => Stopped
   - Non-polymer Paclitaxel-Eluting Stent (Cook/Guidant) : *ASPECT (effective), ELUTES (not effective)*
   - Paclitaxel-Eluting Stent (Conor) : *EUROSTAR*
   - Paclitaxel-Eluting Stent (Infinnium) : *SIMPLE I, II*

DES under Clinical Investigation

3. Pro-Healing Concepts :

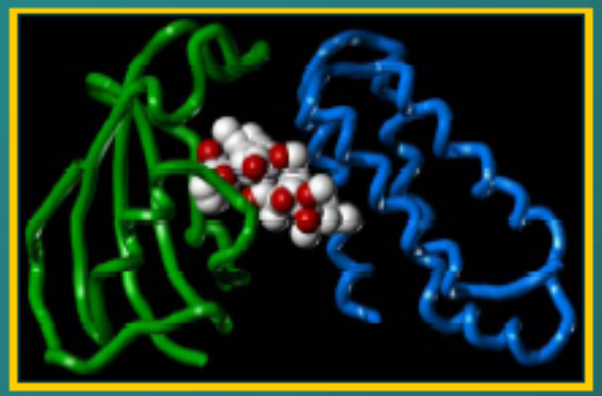
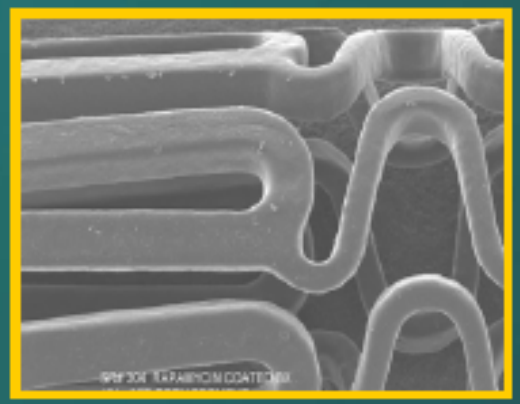
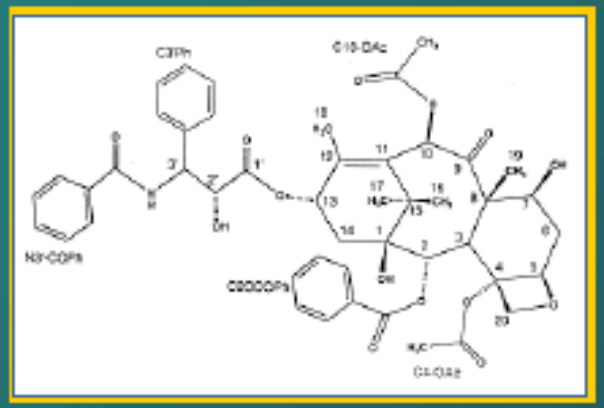
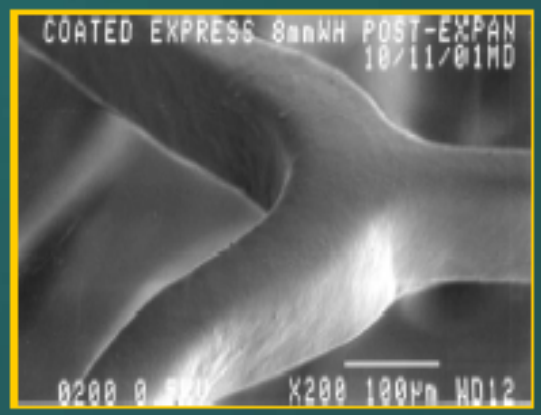
- 17- β Estradiol-Eluting Stent : *EASTER*
- Bisphosphonates (Biorest) – Targeting at macrophage
- Endothelial Progenitor Cells (Orbus)
- ReoPro Coating Stent (Humed)
- NO Donor-Eluting Stent (Blue Medical)

DES under Clinical Investigation

4. Other DESs :

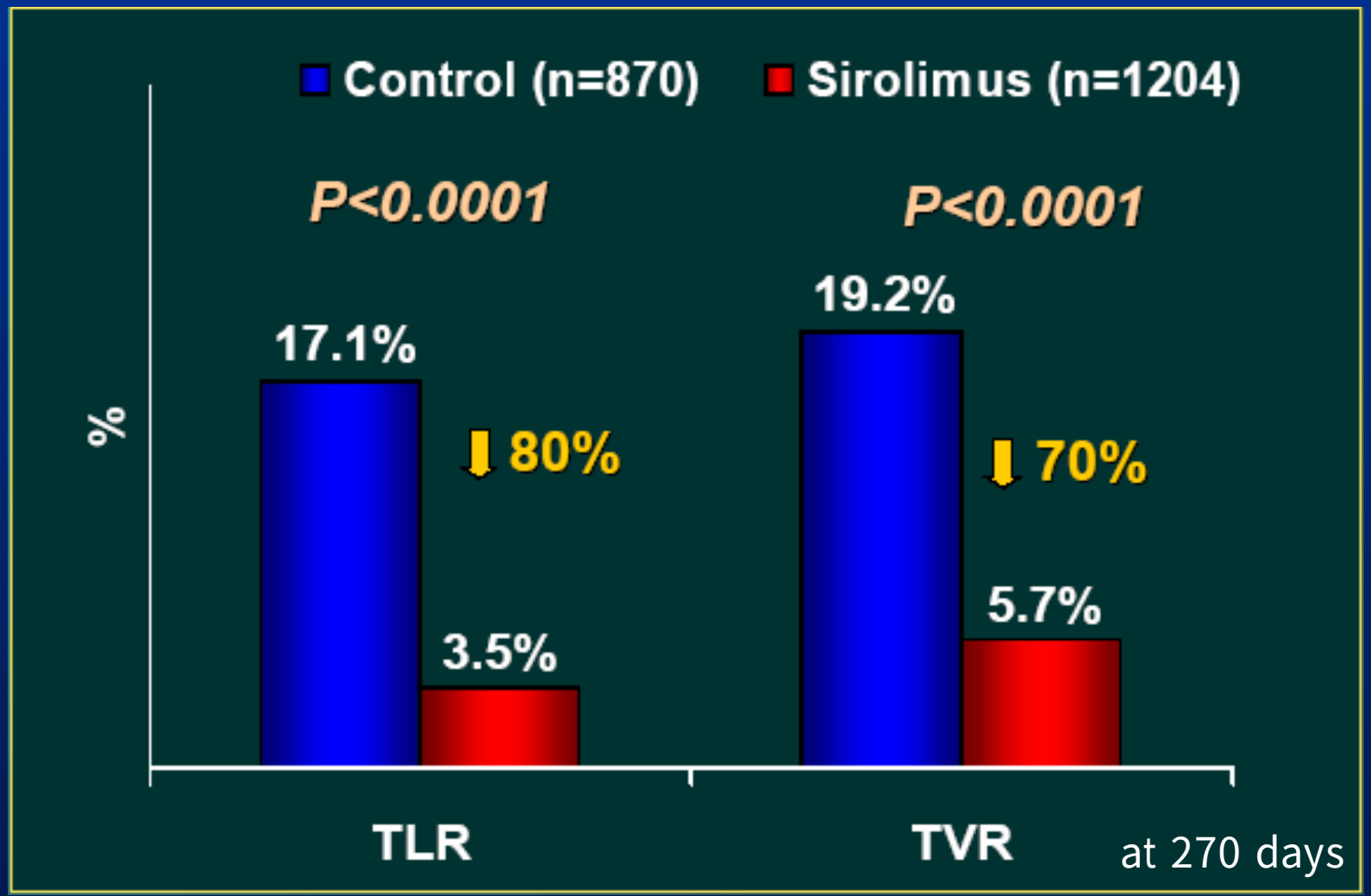
- Dexamethasone PC Stent (Abbott) => not effective
- Batimastat PC Stent (Abbott) => not effective
- Actinomycin-Eluting Stent (Guidant) => Stopped
- Mycophenolic Acid-Eluting Stent (Avantec)
- Ceramic Tacrolimus- Eluting Stent (Jomed) => not effective
- C-myc Antisense-Eluting Stent (Medtronic) => not effective

Cypher & TAXUS Stents

	Drug	Polymer	Stent
Cypher			
	Sirolimus	PEVA + PBMA blend	BX Velocity
TAXUS			
	Paclitaxel	Polyolefin derivative	Express^2

Cypher : Meta-analysis

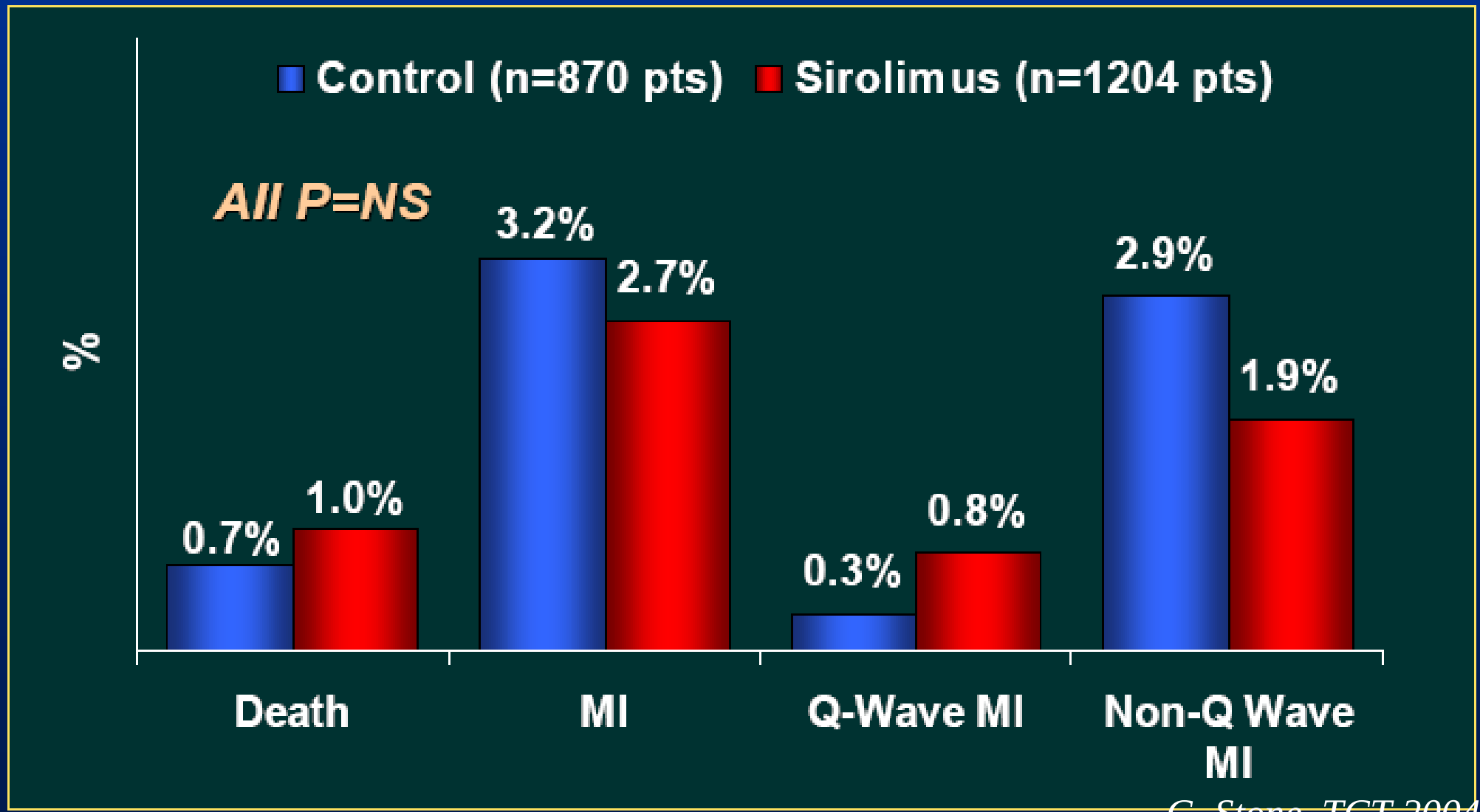
RAVEL, SIRIUS, C- & E-SIRIUS, SVELTE, DIRECT



G. Stone, TCT 2004

Cypher : Meta-analysis

RAVEL, SIRIUS, C- & E-SIRIUS, SVELTE, DIRECT



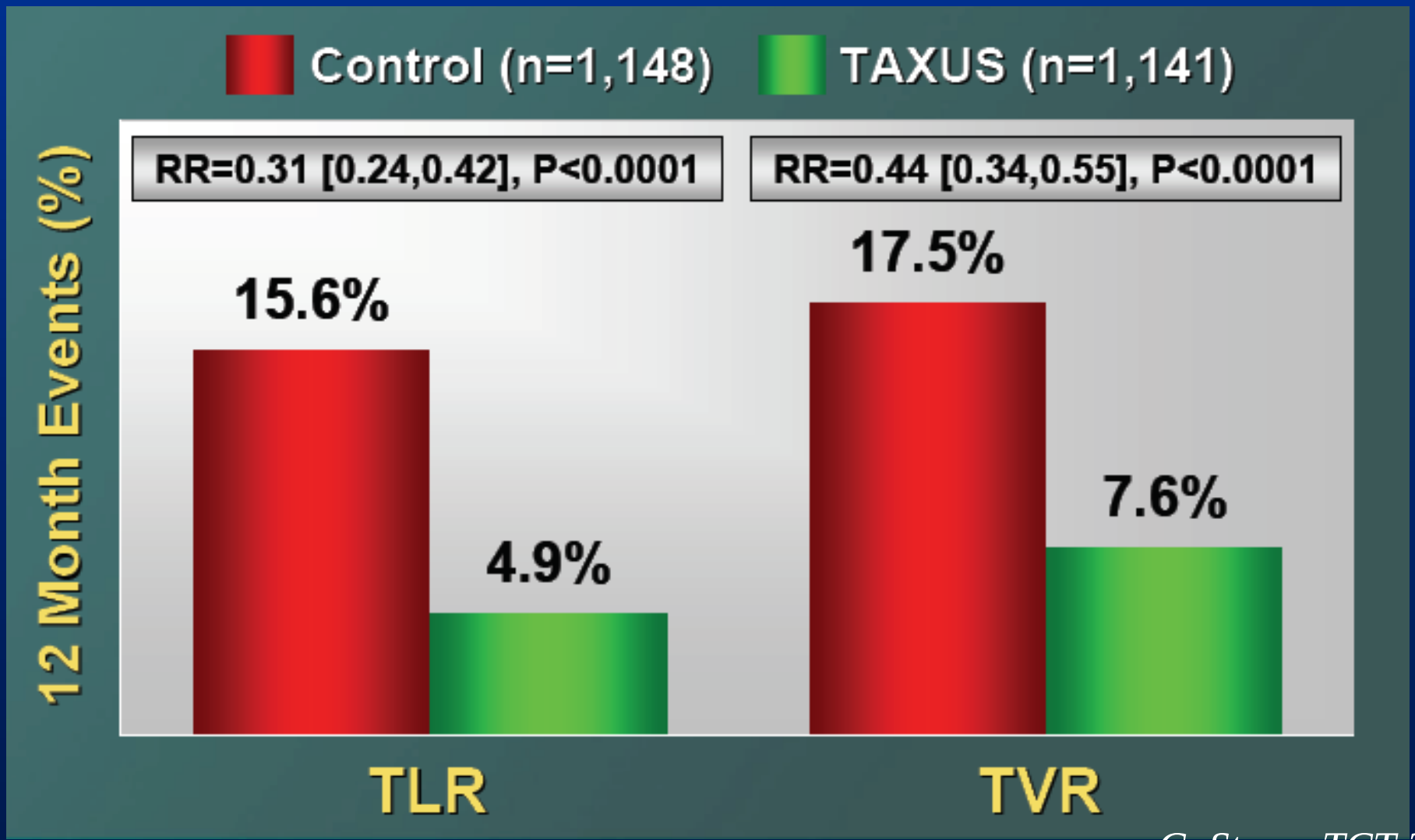
G. Stone, TCT 2004

Cypher Trials : In-segment Restenosis

G. Stone, TCT 2004

TAXUS II, IV & VI

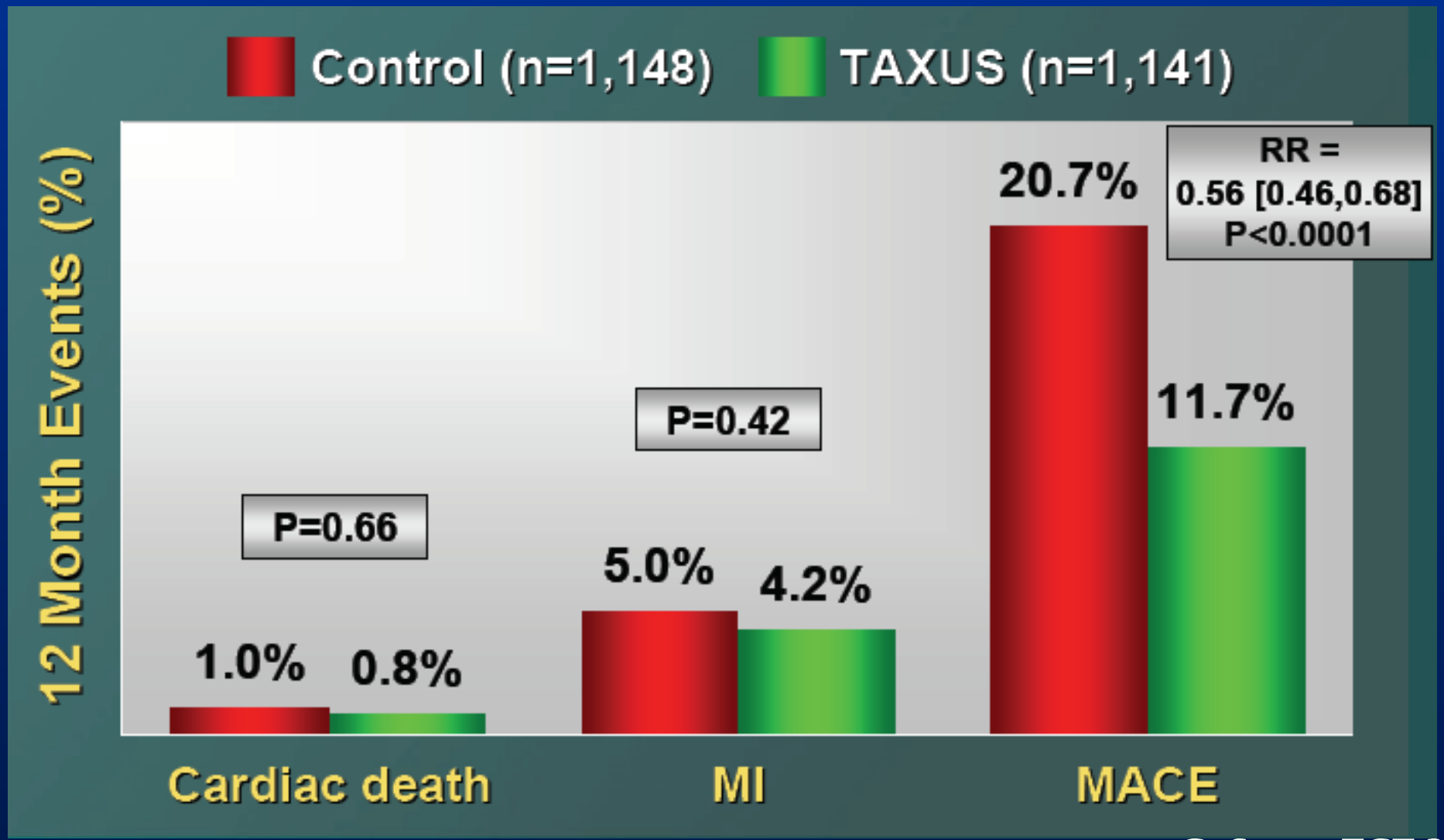
- TLR & TVR at 12 months -



G. Stone, TCT 2004

TAXUS II, IV & VI

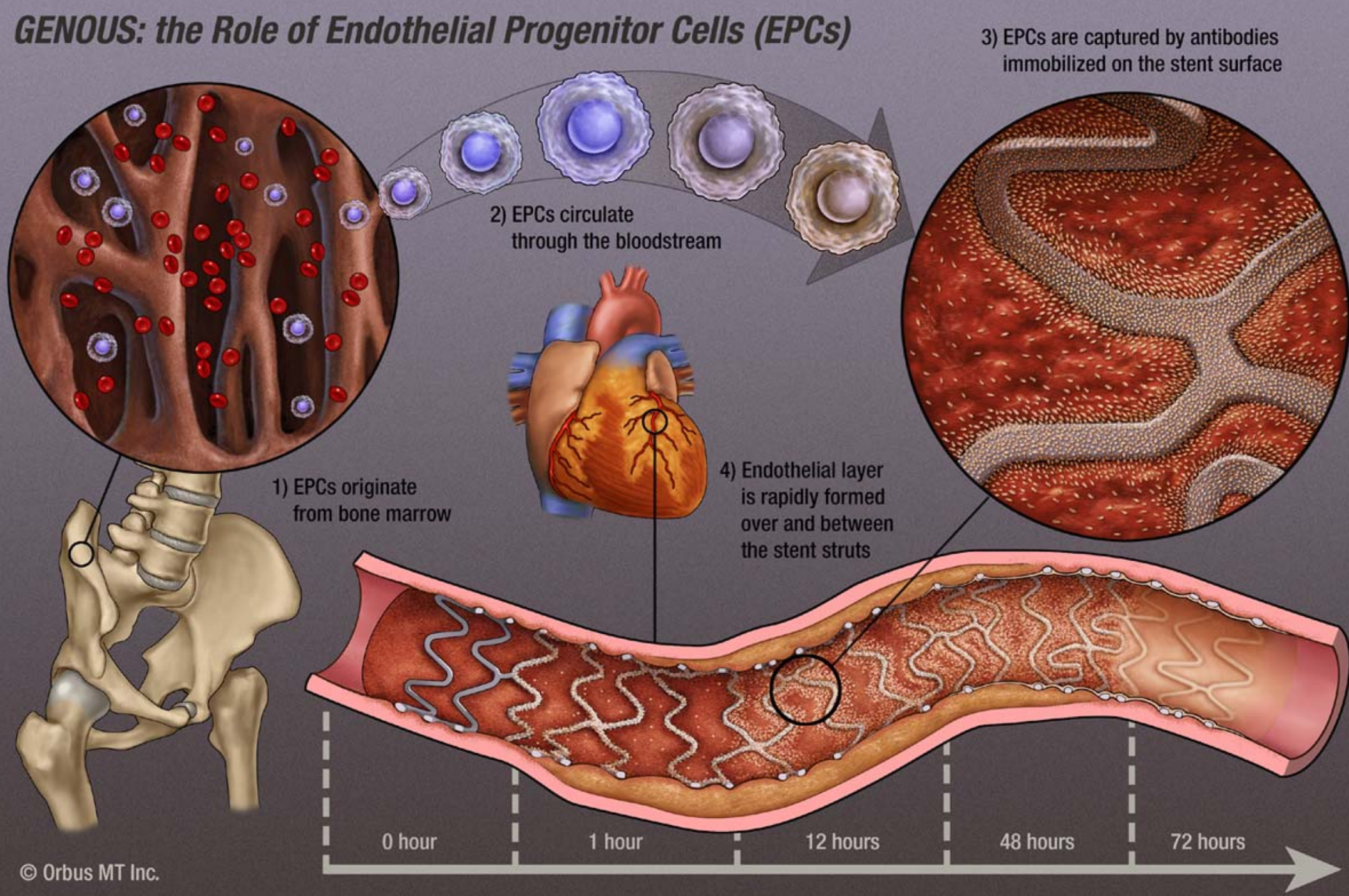
- MACE at 12 months -



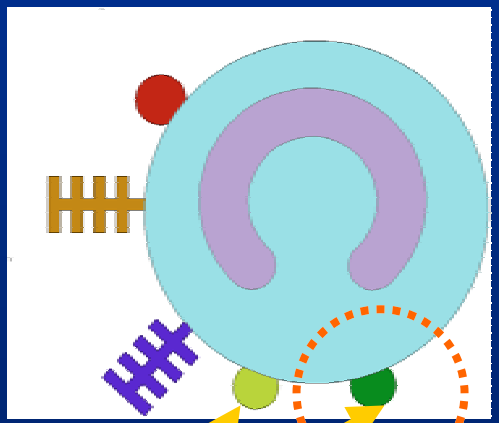
G. Stone, TCT 2004

DES using Antibodies

- Anti-CD34 antibody-coated stent
- Abxicimab-coated stent


GENOUS: the Role of Endothelial Progenitor Cells (EPCs)
3) EPCs are captured by antibodies immobilized on the stent surface
2) EPCs circulate through the bloodstream
1) EPCs originate from bone marrow
4) Endothelial layer is rapidly formed over and between the stent struts
0 hour
1 hour
12 hours
48 hours
72 hours
© Orbus MT Inc.

EPC Capture Coating



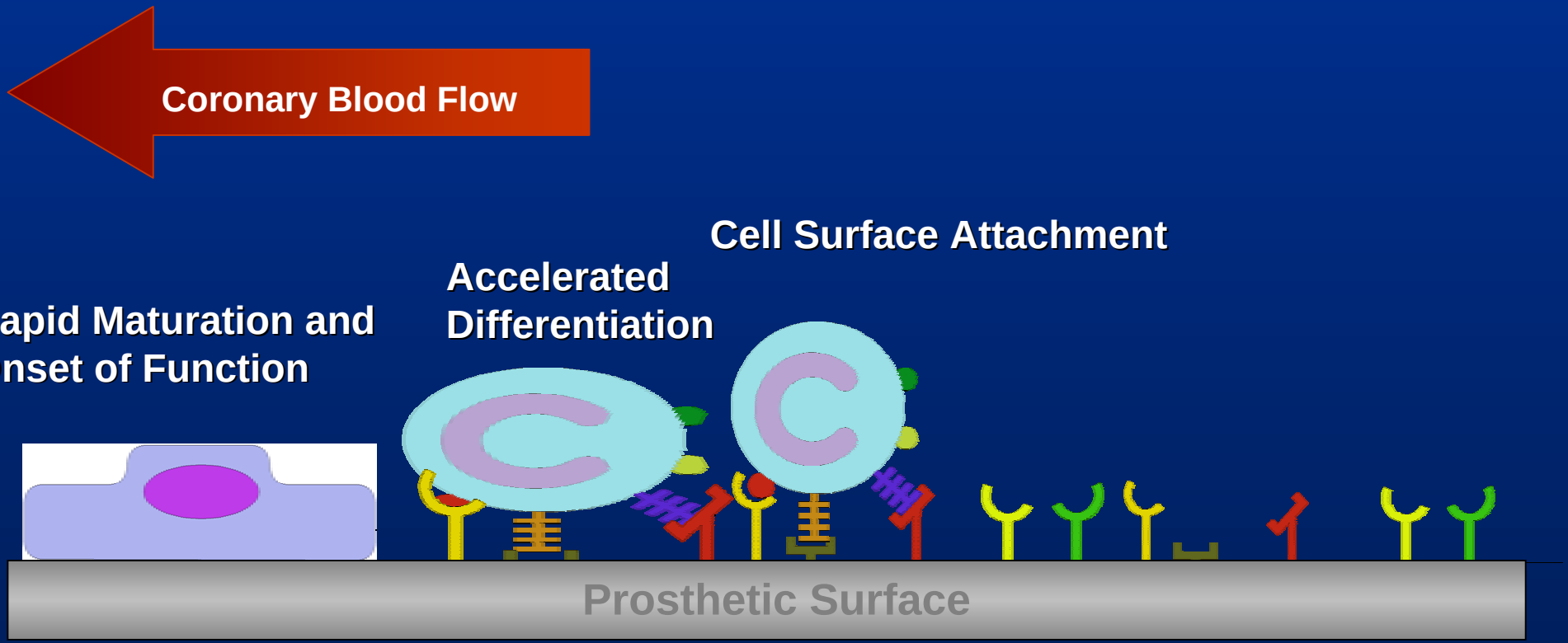
Endothelial Progenitor Cell (EPC)

CD34 Cell Surface Antigen

Anti-CD34 Antibody

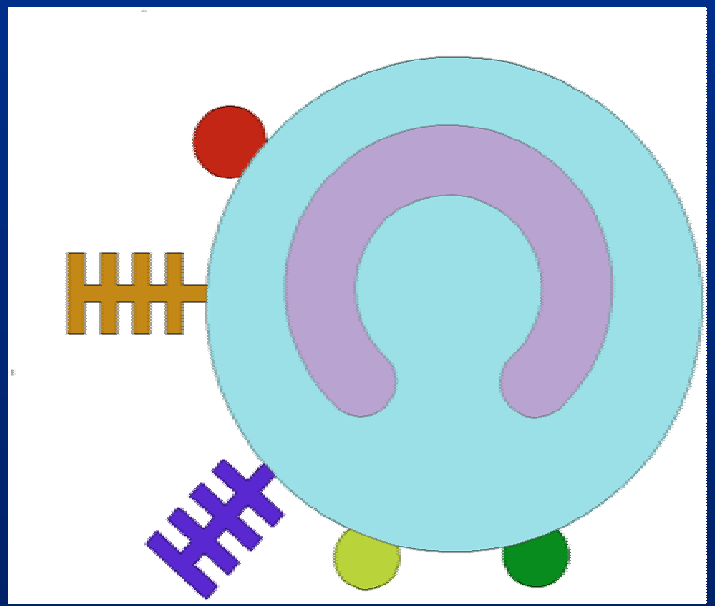
Prosthetic Surface

EPC Capture Coating



EPC Capture and Differentiation

EPC Capture Coating

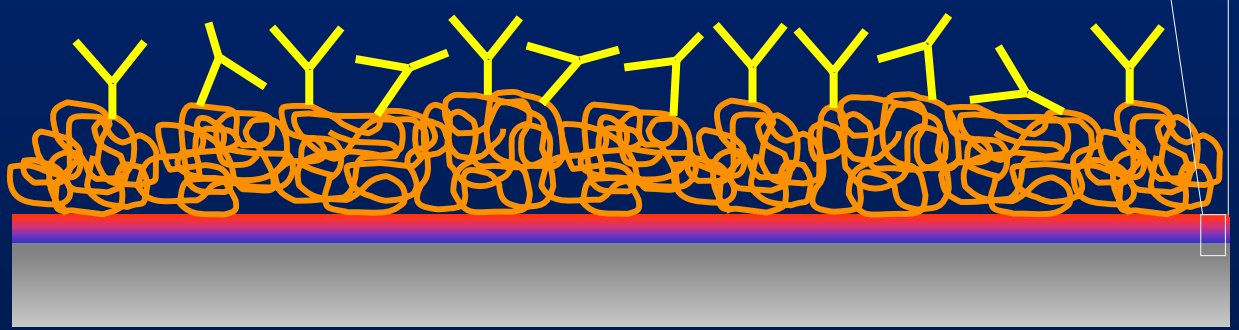


CD34 Antibody

Intermediate Layer

Plasma Deposition Layer

Stent Surface



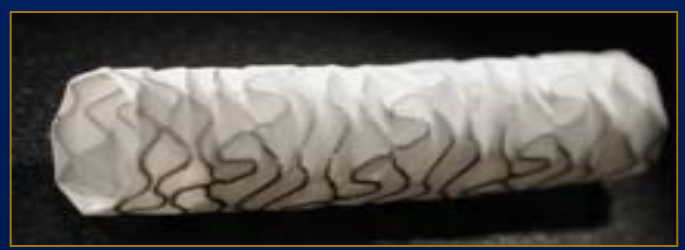
Chemical Functional Top-Layer

Stent Adhering Bottom Layer

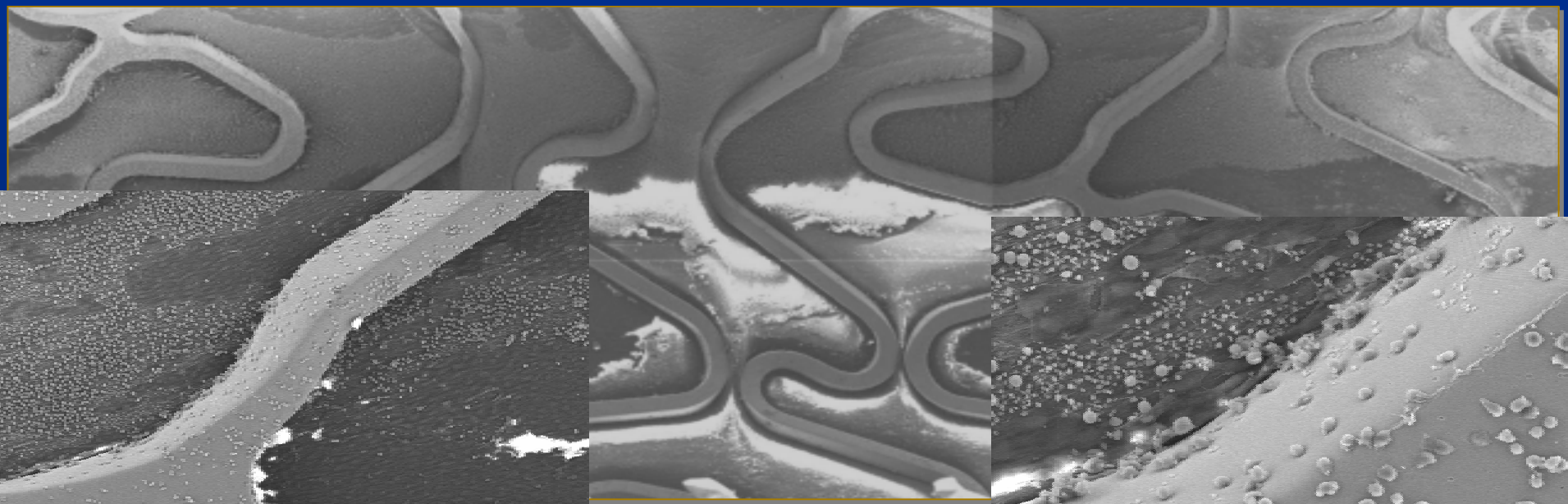
Stent Surface

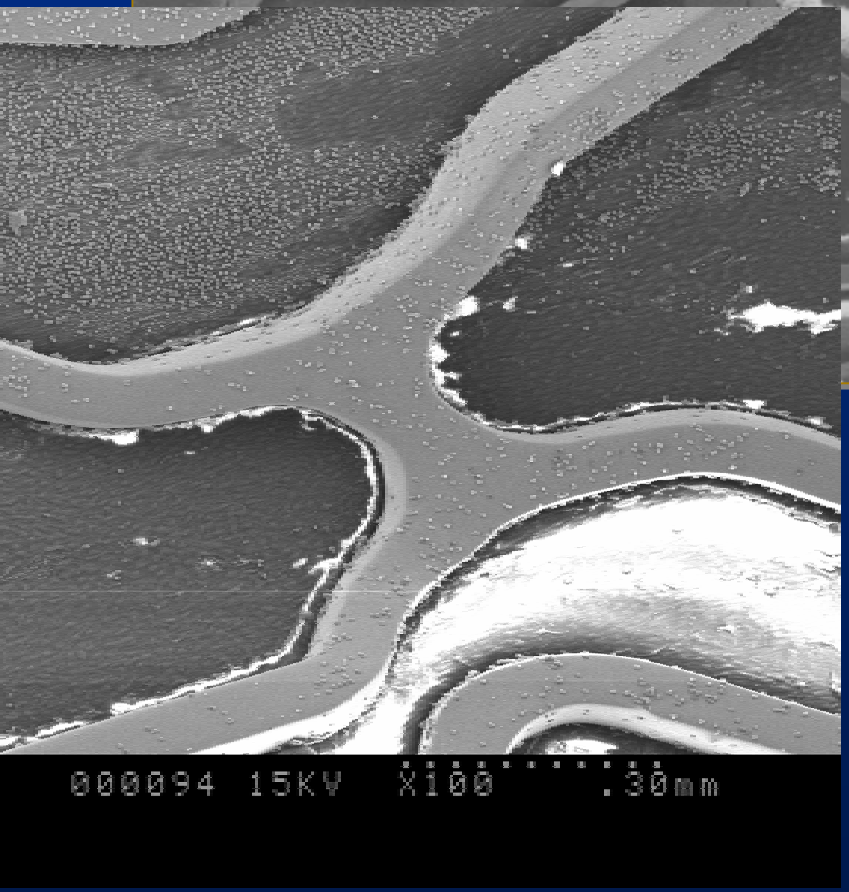
EPC Capture Coating

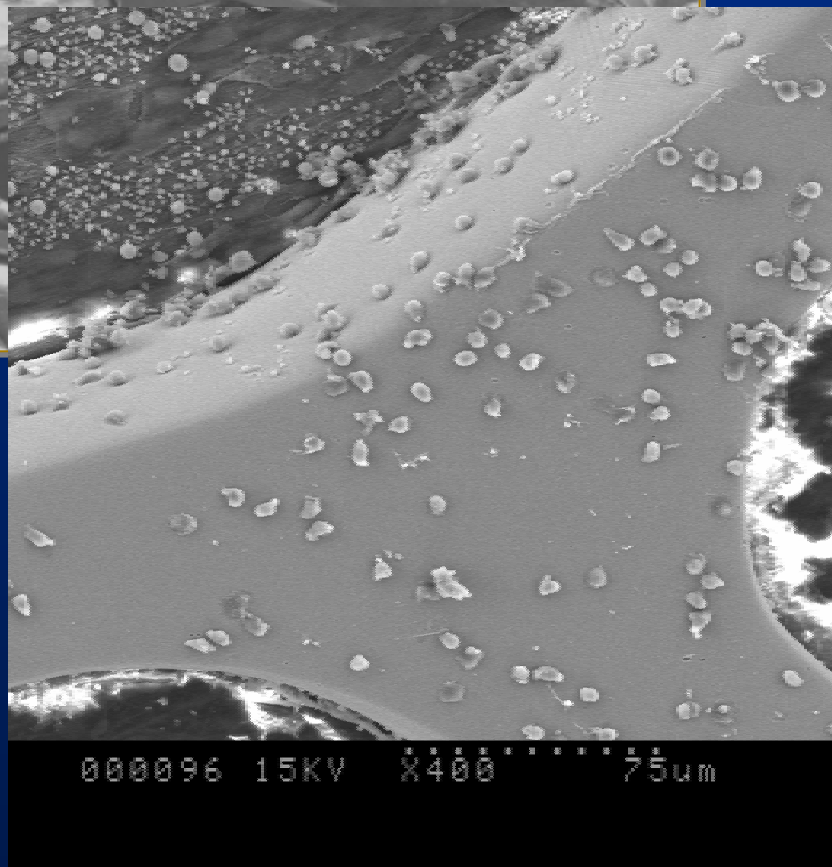
- Substrates
  - 316 L Stainless Steel
    - **Dextran Plasma Deposition**
    - Fullerene (C60) Coating
  - Expanded poly(tetrafluoroethylene) [ePTFE]
    - **Dextran Plasma Deposition**
    - Fullerene (C60) Coating
- EPC Cell Marker Targets
  - CD34
  - AC133/CD133



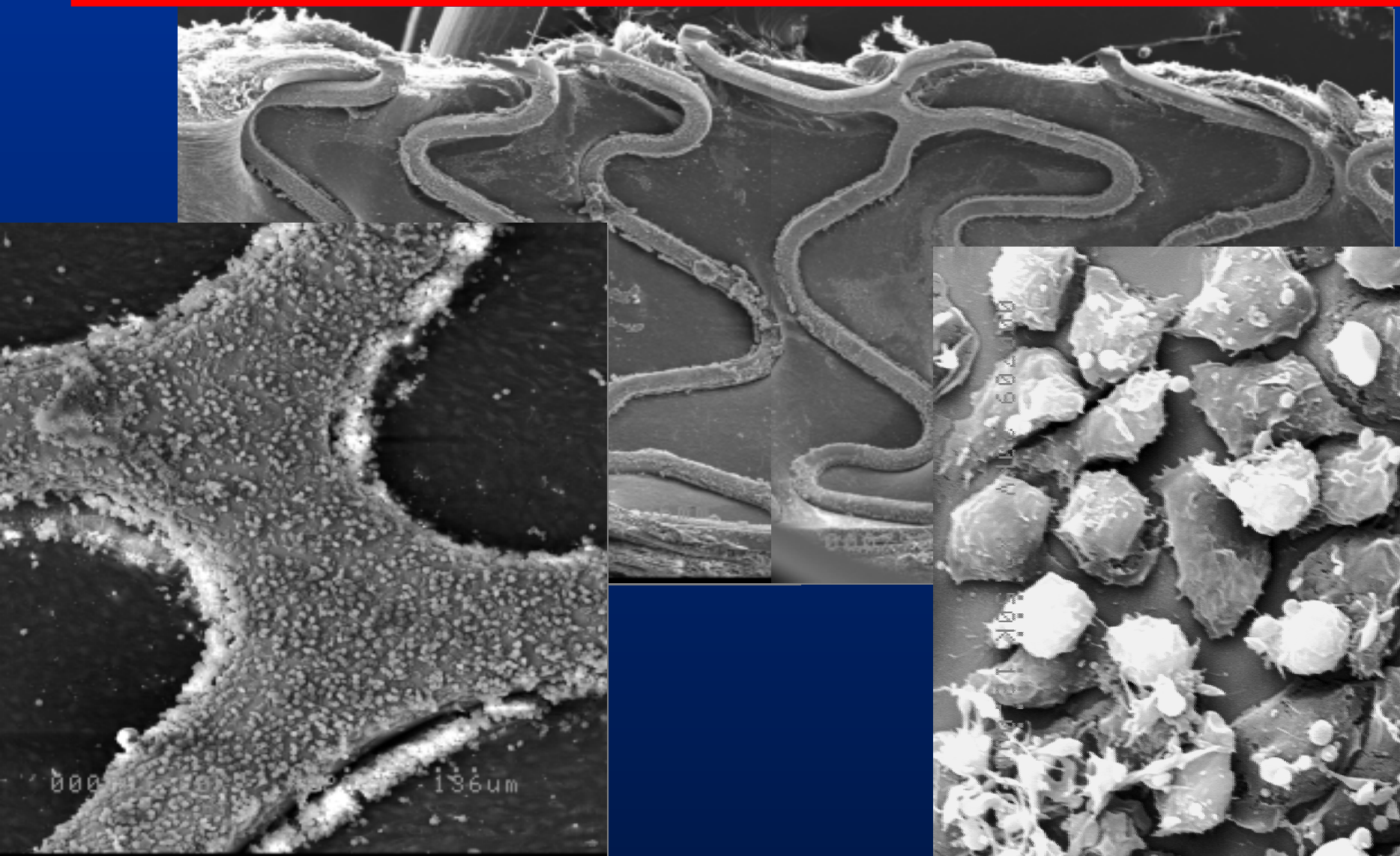
1h explant – Bare R-Stent





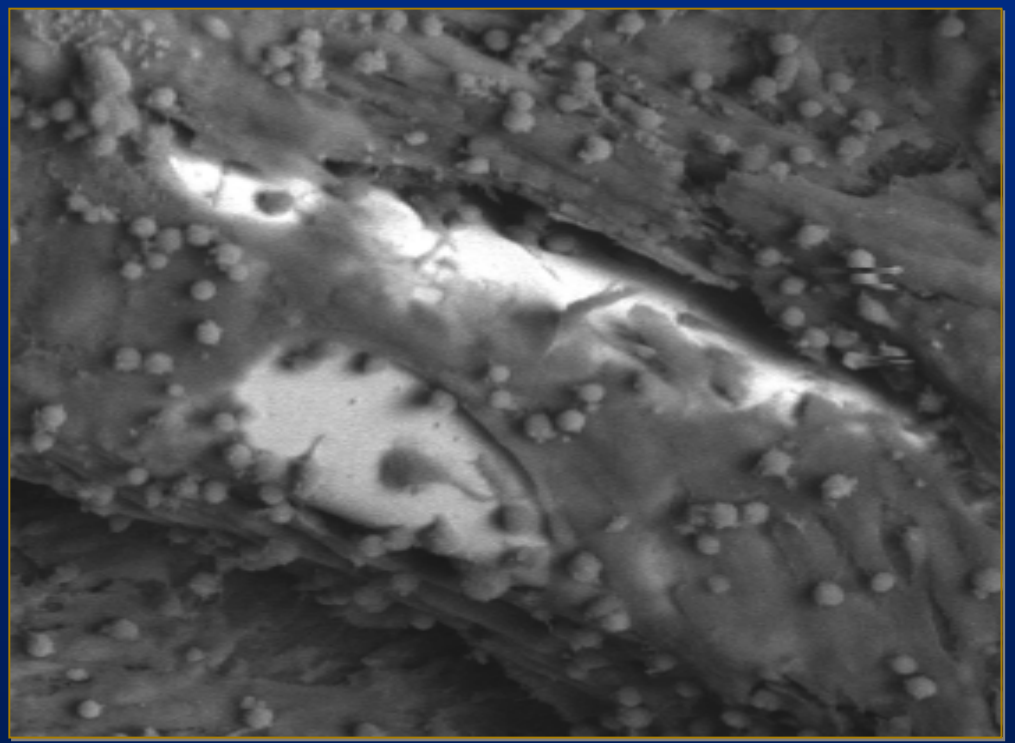


1h explant – Antibody Coated R-Stent

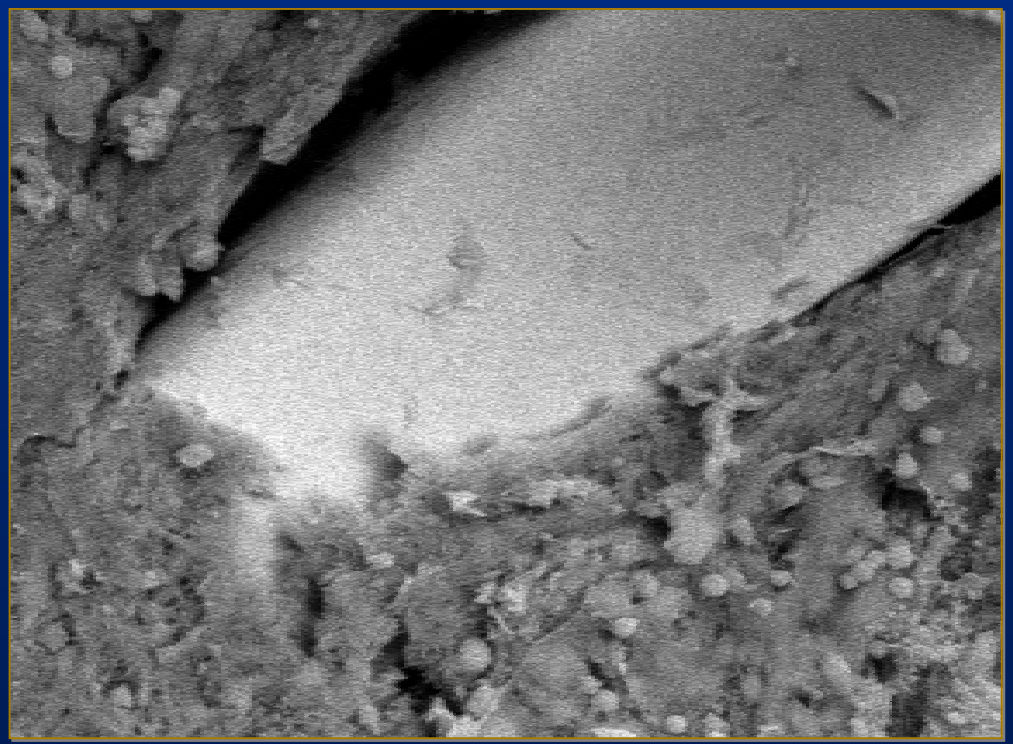


48h explant – Bare R-Stent

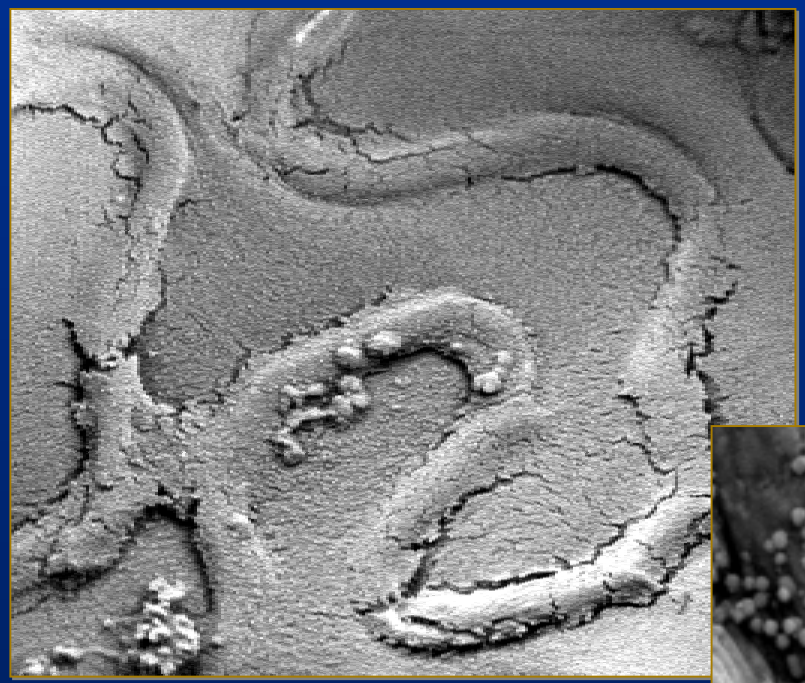
Ab coated - SST

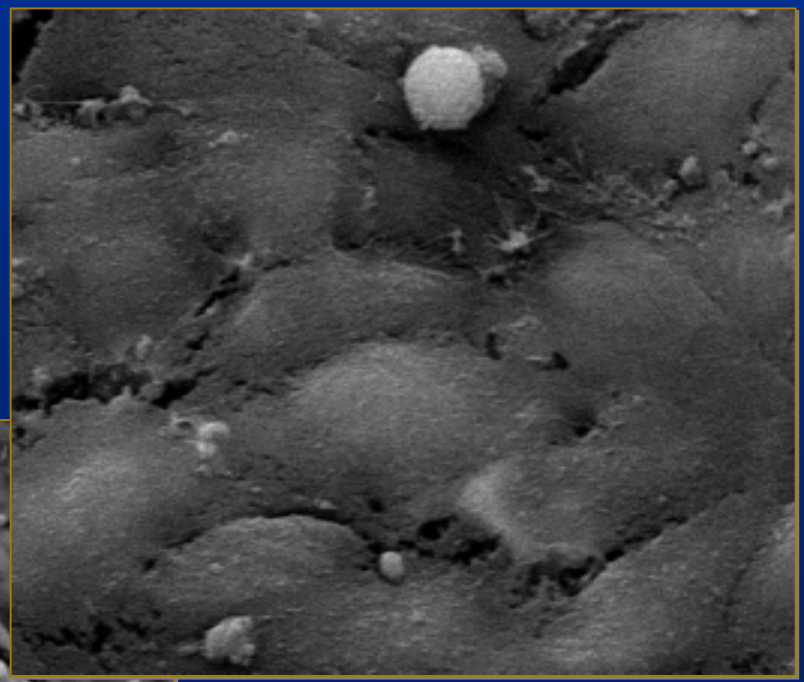


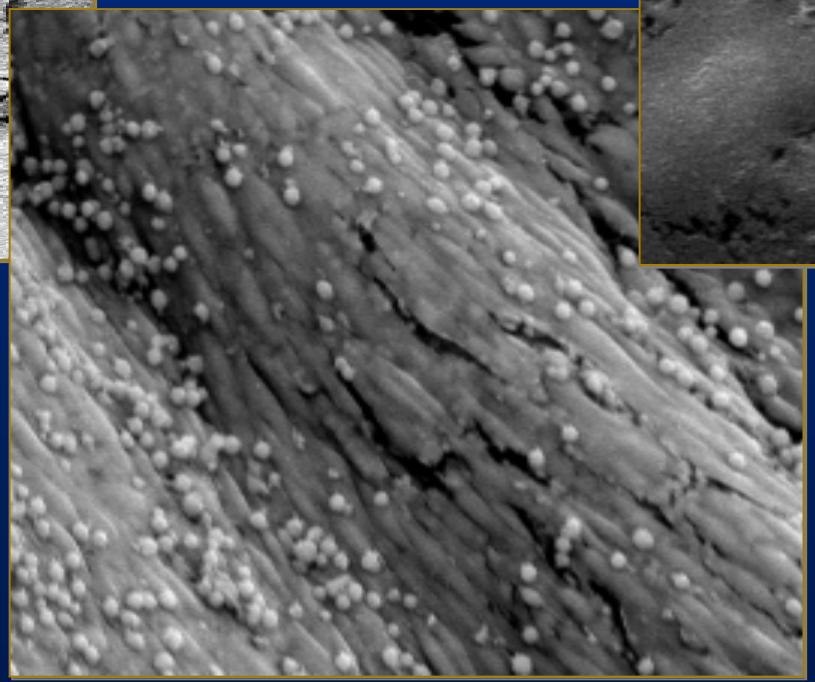
Control - SST



48h explant : Antibody Coated R-Stent



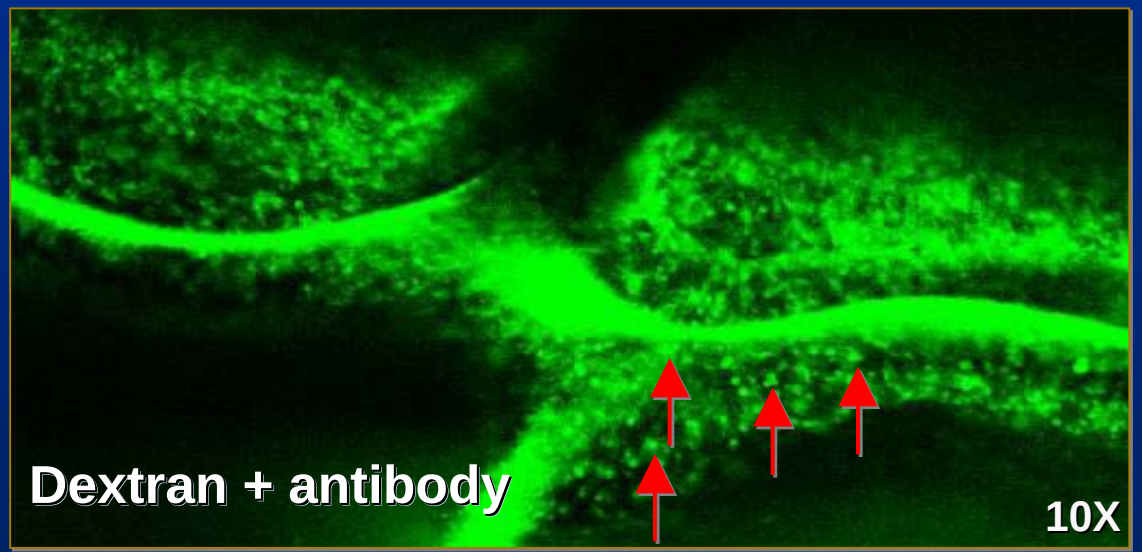




In Vivo EPC Capture : 48 hours

A

B



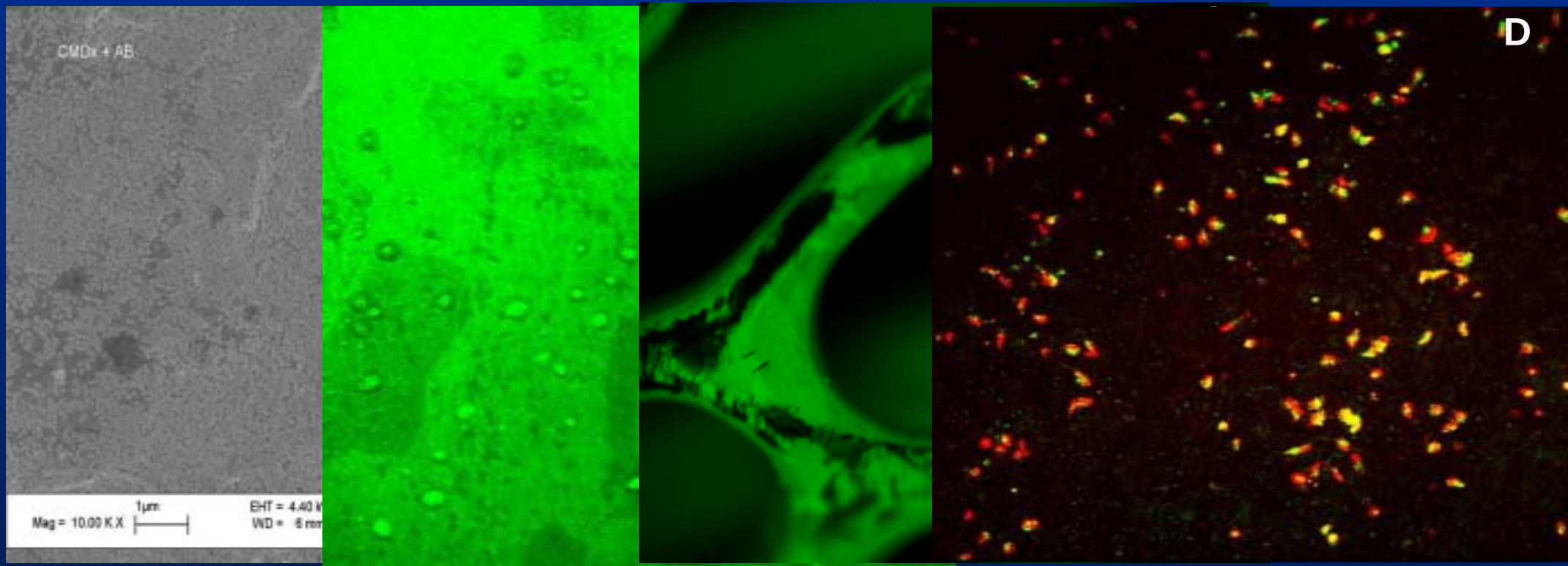
3.0 mm R stents with Antibody

48 hours post implant

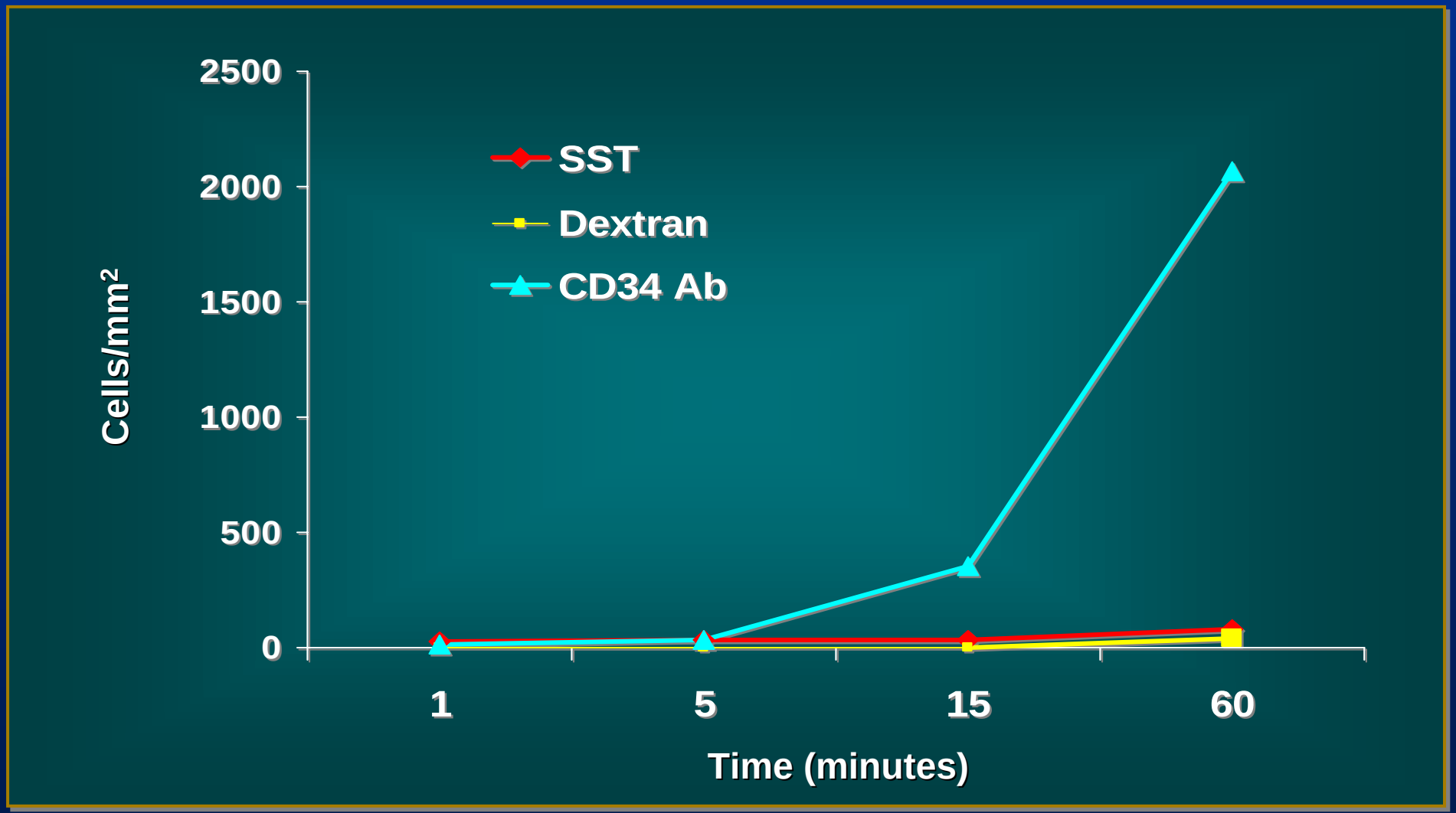
Stained with anti VEGFR-2

Dextran / Anti-CD34 Coated Stent

Dextran+Ab

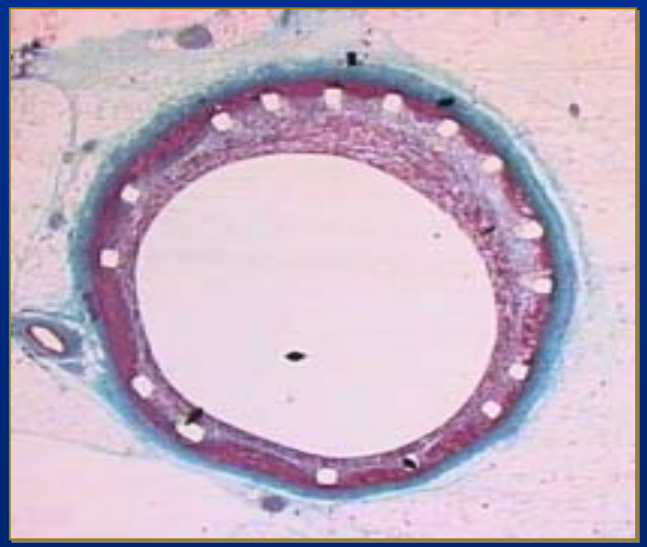


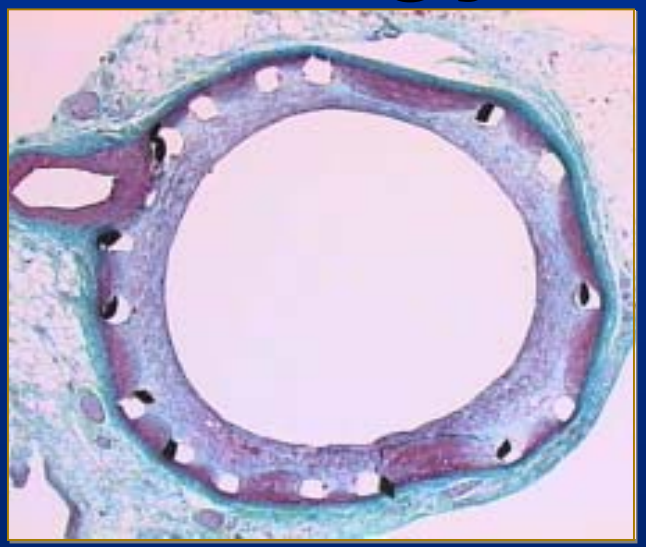
In vitro EPC Capture



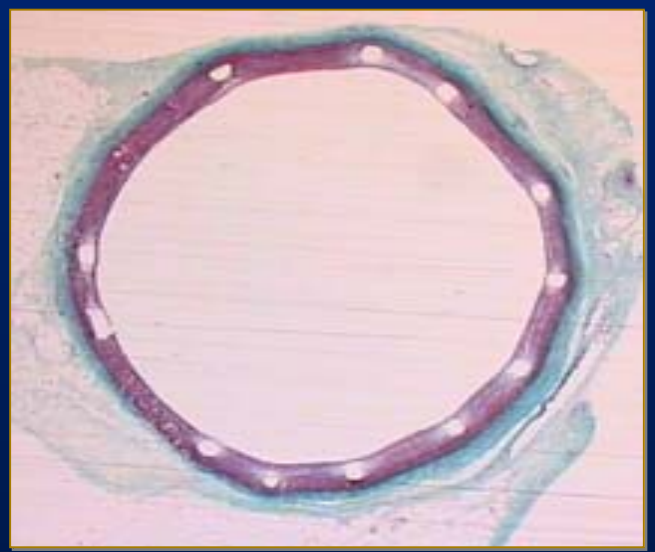
Kutryk et al. 2003

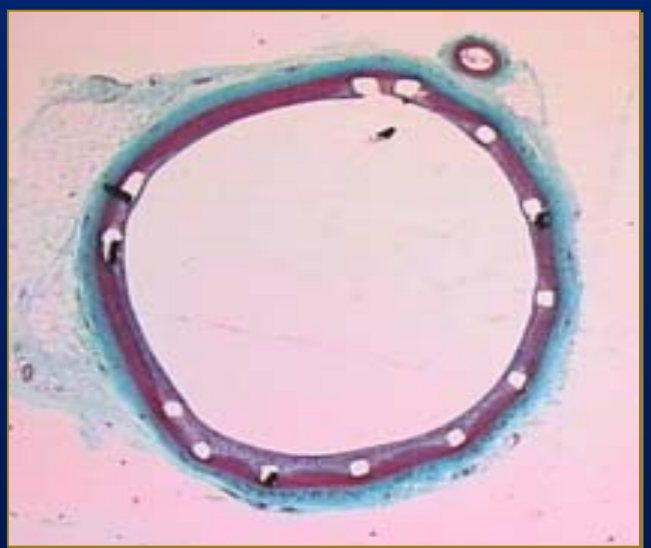
In Vivo EPC Capture – 28 Day Histology





Bare Stainless Steel





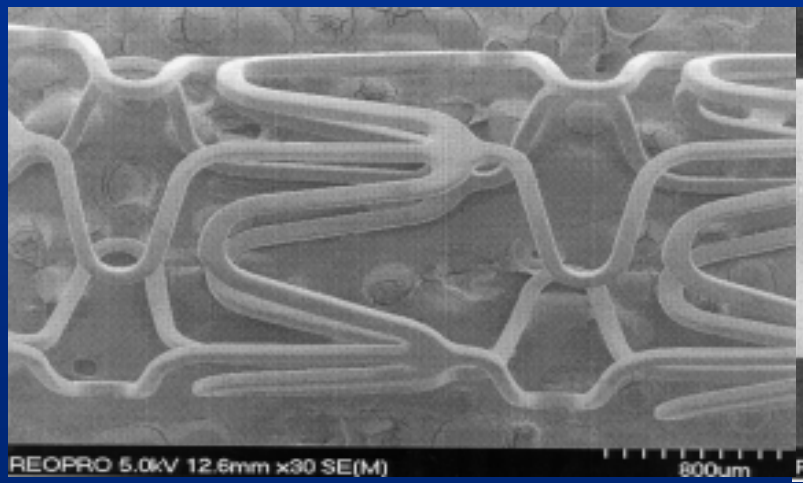
EPC Capturing

ReoPro® (Abciximab)

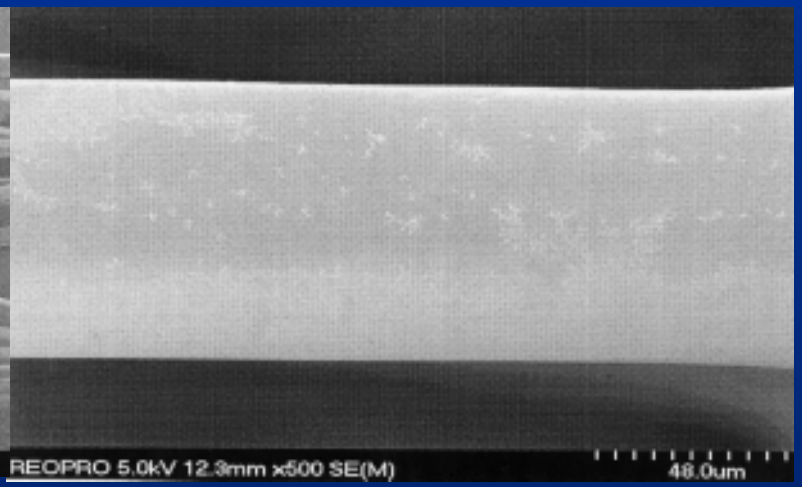
- **Proven Anti-platelet Activity through GP Iib/IIIa.**
- **Alpha V / Beta 3 antibody activity, which may capture EPC cells.**
- **Anti-inflammatory activity on neutrophil and monocyte by white-cell adhesion, white-cell-platelet interactions, and the inflammatory response to vessel injury through macrophage-1 receptor.**

This Presentation has conflict of interest with Humed ltd

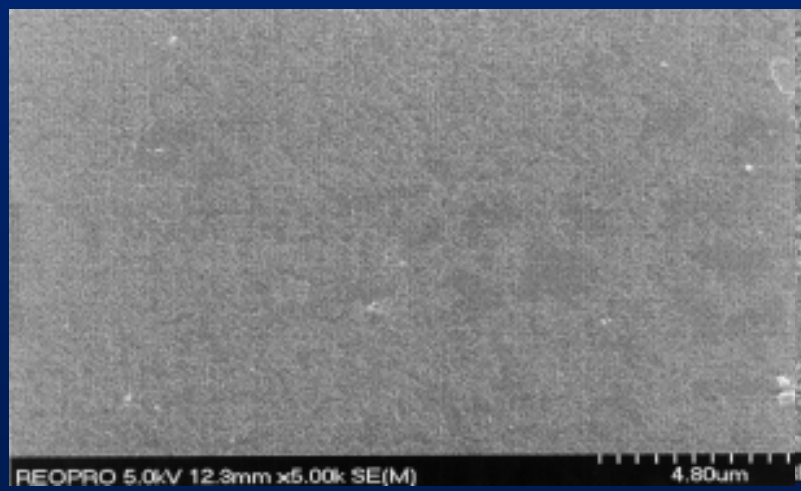
SEM Findings of ReoPro®-Coated Stent



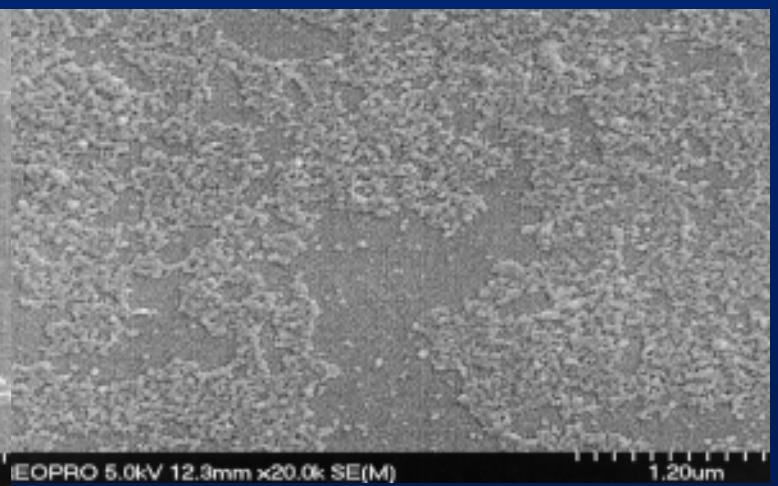
1 X 30



1 X 500

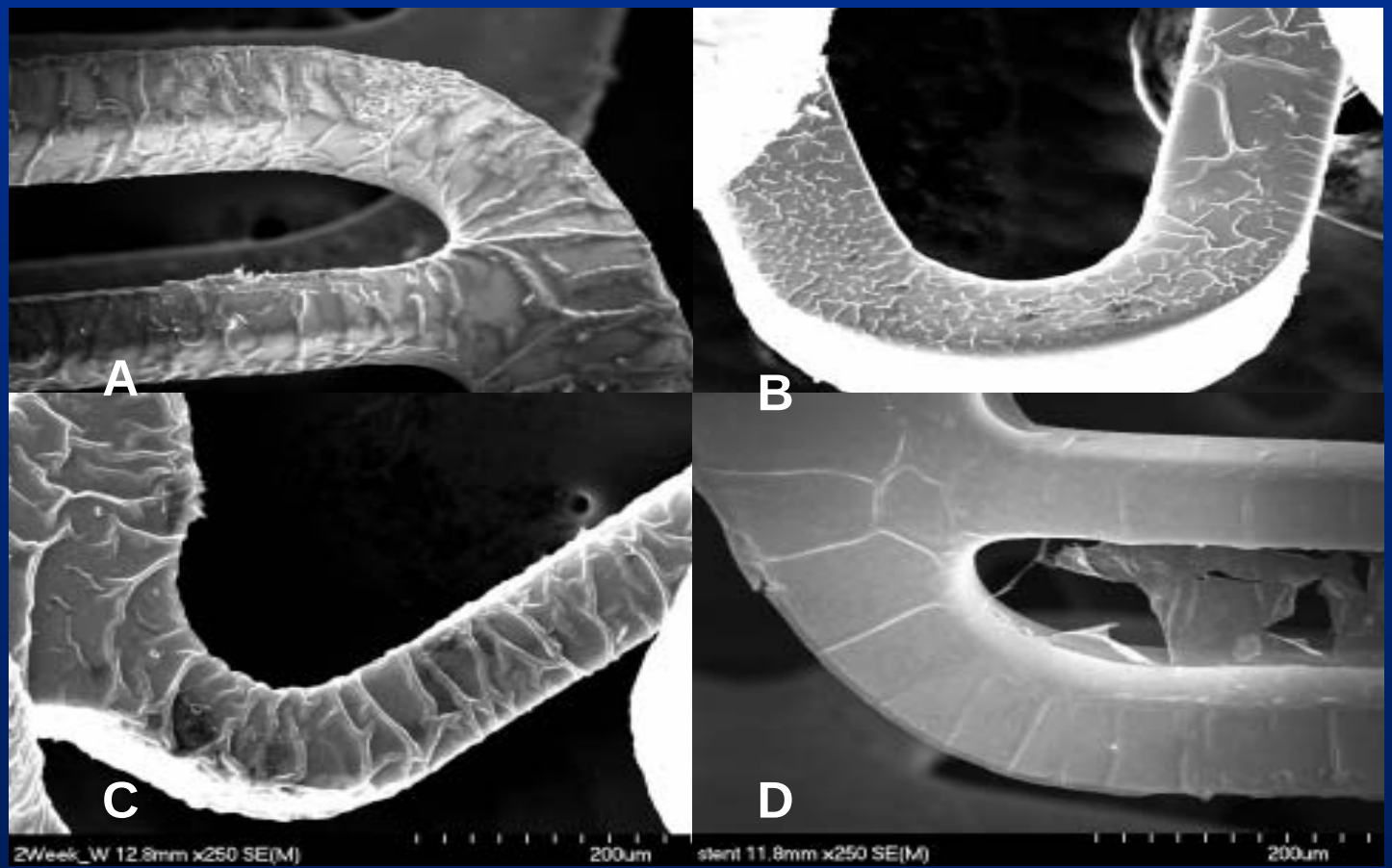


1 X 5,000



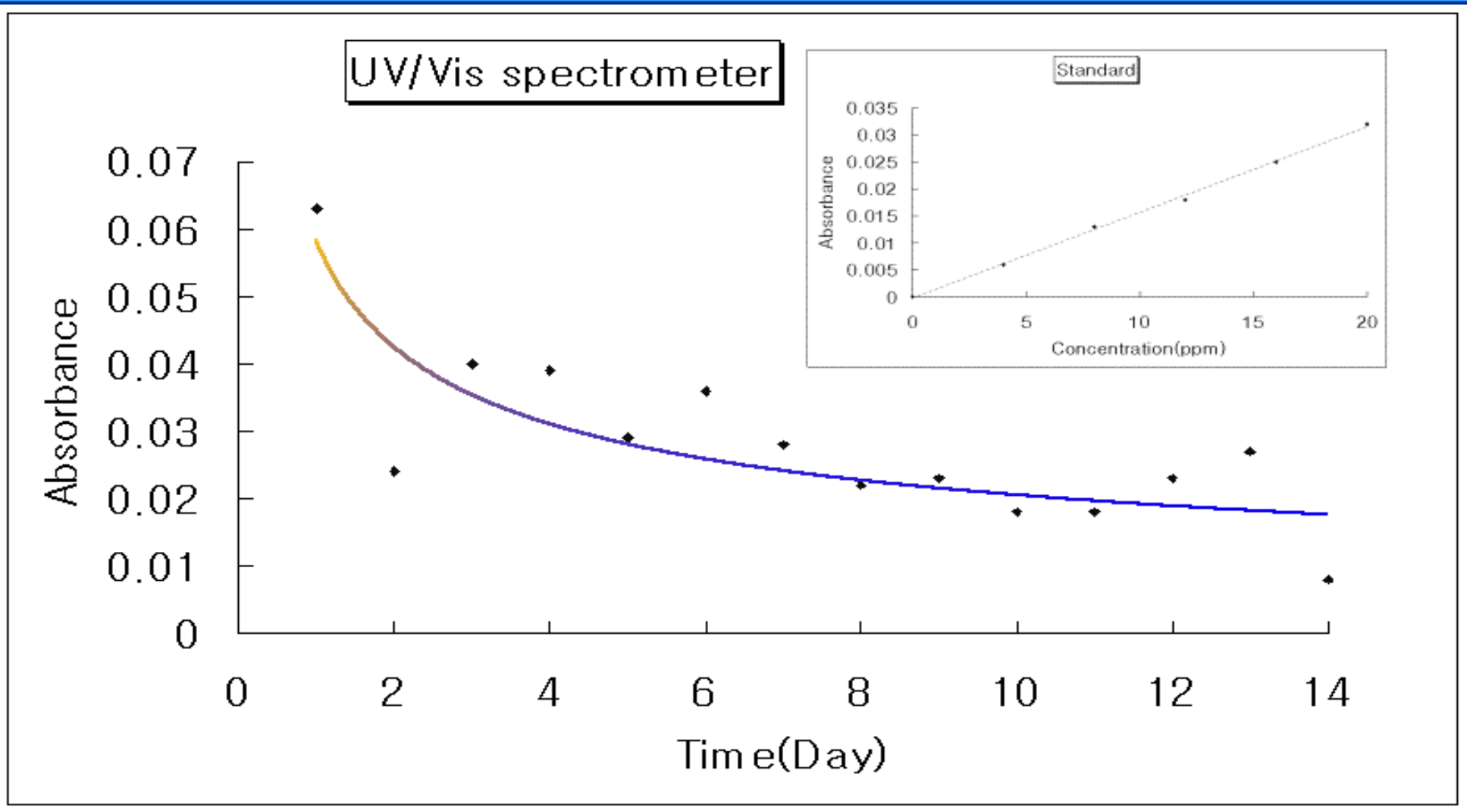
1 X 20,000

SEM of ReoPro® Grafting after Washing Test



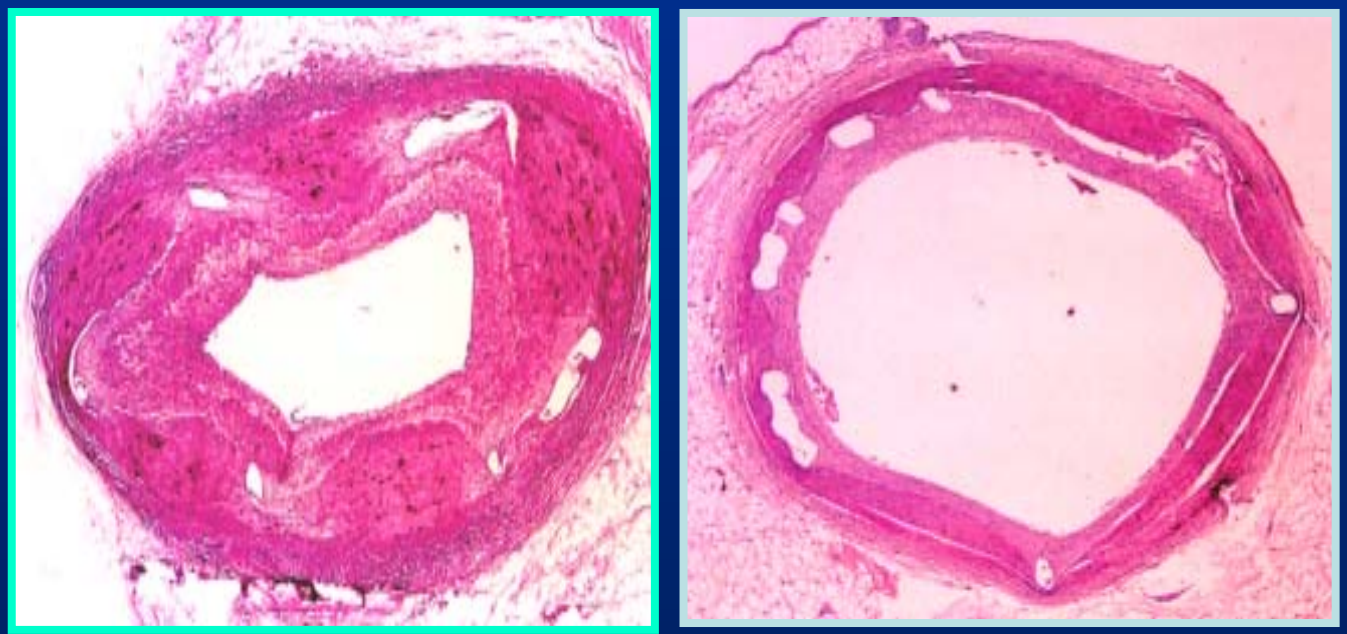
Stent surface of ReoPro® grafting; immediately (A), 5 hours (B), 2 weeks (C), 4 weeks (D) after washing test. Magnification 250X

In vitro Screening of ReoPro® Release from Stent



Right upper panel revealed absorbance in concentration of control drug

Platelet GP IIb/IIIa Receptor Blocker (ReoPro®)-Coated Stent in A Porcine Model



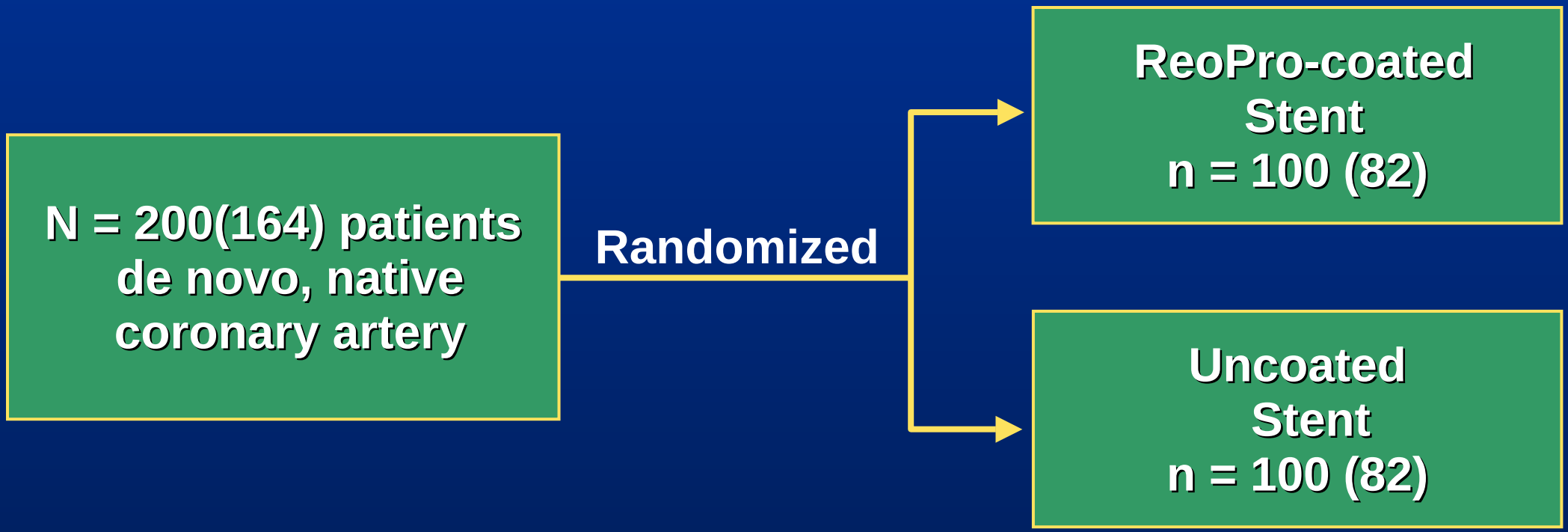
Control stent **ReoPro-coated stent**

↓

Anti-thrombotic, anti-proliferative and anti-inflammatory stent

CNUH data. 2001 ACC and AHA

First Clinical Experience of ReoPro®-Coated Stent



Primary Endpoint

late loss and area stenosis measured by QCA

Cross sectional area by IVUS at 6 months

MACE at 6 months

Baseline Clinical Characteristics

	ReoPro(n=82)	Control(n=82)	*P*
Age(YO)	56.1±10.0	57.3±10.5	0.463
Male(%)	66(80.5)	57(69.5)	0.149
Smoking(%)	45(54.9)	45(54.9)	1.00
HTN(%)	41(50.0)	41(50.0)	1.00
Hypercholesterolemia(%)	29(35.4)	26(31.7)	0.741
Diabetes mellitus(%)	19(23.2)	12(14.6)	0.231
Clinical Diagnosis(%)			0.938
Stable angina	9(11.0)	7(8.5)	
Unstable angina	42(51.2)	43(52.4)	
Non-ST elevation MI	9(11.0)	7(8.5)	
ST elevation MI	20(24.4)	22(26.8)	
Old myocardial infarction	2(2.4)	3(3.7)	
LV Ejection fraction(%)	63.0±10.1	63.0±11.8	0.975

ACS 85%

Angiographic Characteristics (I)

	ReoPro(n=82)	Control(n=82)	*P*
Diseased vessels(%)			0.852
Right coronary artery	21(25.6)	18(22.0)	
Left anterior descending artery	49(59.8)	52(63.4)	
Left circumflex artery	12(14.6)	12(14.6)	
ACC/AHA classification(%)			0.140
Type B1	73(89.0)	62(75.6)	
Type B2	8(9.8)	17(20.7)	
Type C	1(1.2)	2(2.4)	
TIMI flow(%)			0.722
TIMI flow 0	2(2.4)	4(4.9)	
TIMI flow 1	1(1.2)	1(1.2)	
TIMI flow 2	21(25.6)	17(20.7)	
TIMI flow 3	53(70.7)	60(73.2)	

30%

Angiographic Characteristics(II)

	ReoPro(n=82)	Control(n=82)	*P*
Pre-dilation ballooning			
Balloon length	**20.0±0.8**	**20.2±1.5**	**0.157**
Balloon size	**3.31±0.33**	**3.27±0.43**	**0.547**
Stent indication(%)			**0.377**
Elective and suboptimal	**72(87.8)**	**74(90.2)**	
Acute closure	**10(12.2)**	**8(9.8)**	
Stent size	**3.31±0.34**	**3.29±0.43**	**0.690**
Stent length(mm)	**17.1±1.1**	**17.4±4.3**	**0.428**

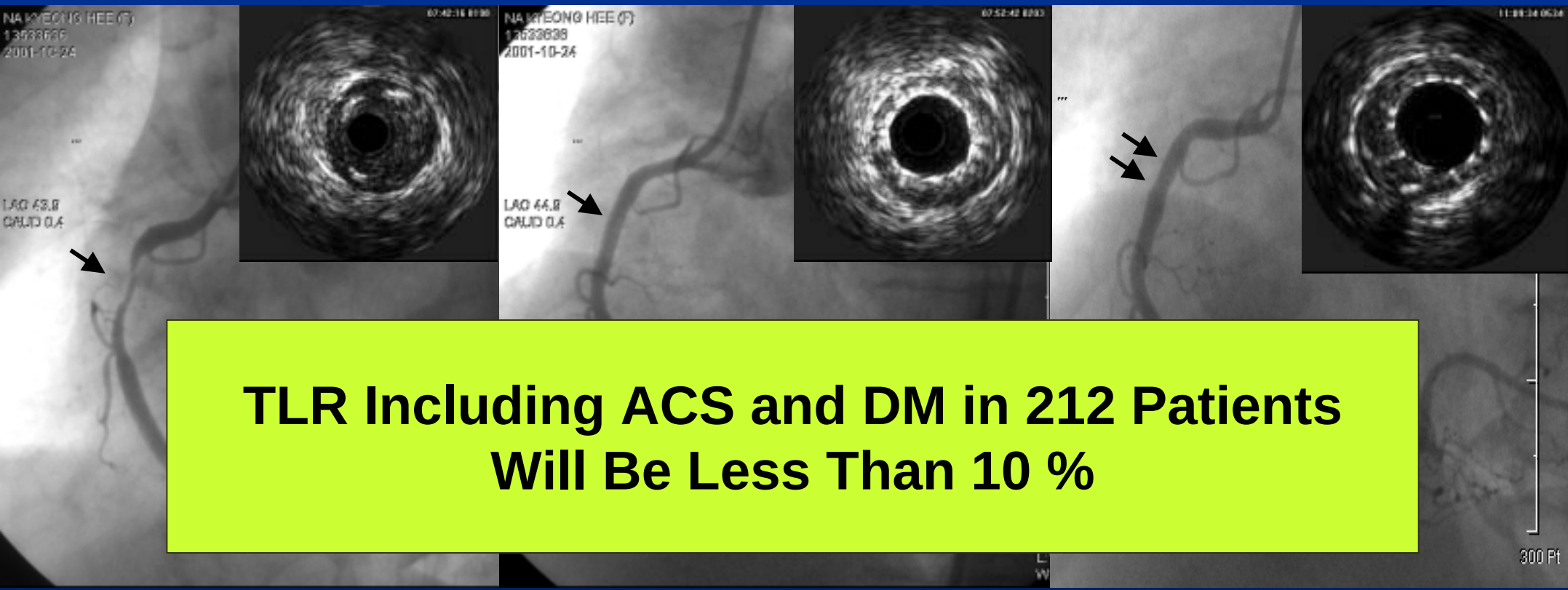
Quantitative Coronary Angiographic Results

	ReoPro (n=82)	Control (n=82)	*P*
Follow-up CAG (%)	58(70.7)	51(64.6)	0.504
Follow-up duration(days)	198.6±56.4	212.7±63.1	
Restenosis rate (%)	9/58(15.5)	17/54(31.5)	0.046
F/U Diameter stenosis (%)	16.7±5.5	34.4±6.1	0.011
Reference diameter (mm)	2.91±0.37	2.97±0.29	0.624
Lesion length (mm)	15.0±1.8	13.9±1.9	0.711
Late loss (mm)	0.35±0.30	0.89±0.41	0.004

Long-term Clinical Results

	ReoPro	Control	*P*
Clinical follow-up number(%)	79(96.3)	79(96.3)	1.00
Total follow-up MACE			
Cardiac death	0(0.0)	0(0.0)	1.00
Acute myocardial infarction	0(0.0)	2(2.4)	0.497
TLR	9(11.0)	13(15.9)	0.493
Non-TLR	3(3.7)	5(6.2)	0.720
CABG	0(0.0)	0(0.0)	1.00

53 YO Female, A Inf STEMI



TLR Including ACS and DM in 212 Patients Will Be Less Than 10 %

PCI with ReoPro®-coated Stent

F/U CAG & IVUS at 6 ms after PCI

CNUH data. ESC 2004 and AHA 2004, Am J Cardiol 2004 (in press)

ReoPro® (Abciximab)

- **Inhibitory platelet activity by platelet glycoprotein IIb/IIIa receptor blocking and possibly capture EPC on the internal stent surface.**
- **Anti-proliferative activity on smooth muscle cells by inhibition of smooth muscle cell migration and proliferation through vitronectin receptor on the outside of the stent surface.**
- **Anti-inflammatory activity on neutrophil and monocyte by white-cell adhesion, white-cell-platelet interactions, and the inflammatory response to vessel injury through CD 11b/18 or macrophage-1 receptor on the both side of the stent.**

Development of DES containing Abxicimab

- **Plasma Polymerization process :**

  => Introduction of amine group on stent surface from EDA(ethylenediamine) & DACH (diaminocyclo-hexane) using plasma polymerization.

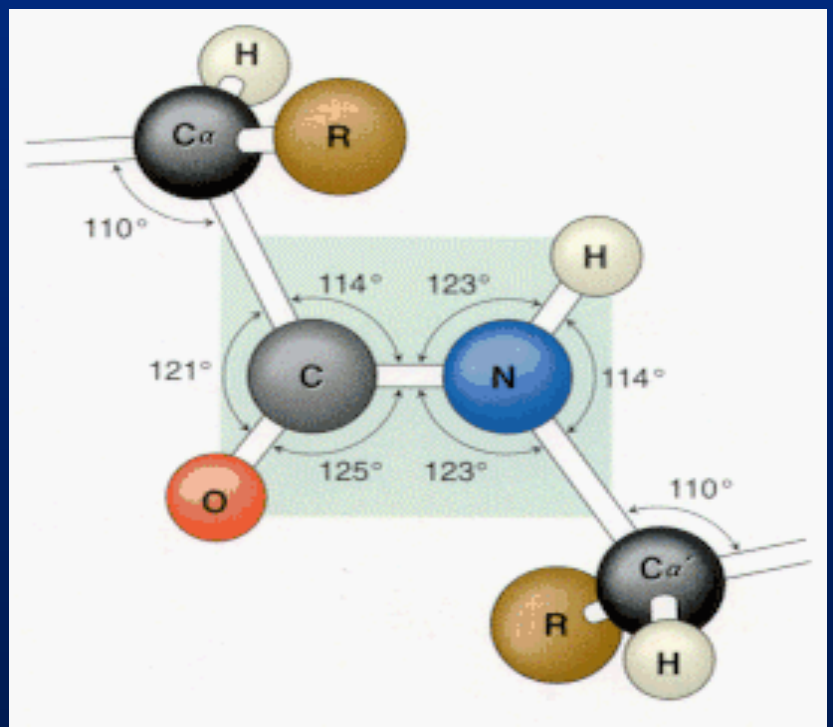
- **Grafting ReoProTM process :**

  => pH 5 sodium citrate solution (20ml) + carboXXXX + ReoProTM (5ml)

  => Activation for 8H in ice bath

Analysis through XPS

Peptide bond between end of ReoPro™ with Carboxyl (-COOH) group and Amine ($-NH_2$) group of EDA(Ethylenediamine) & DACH (Diaminocyclohexane)



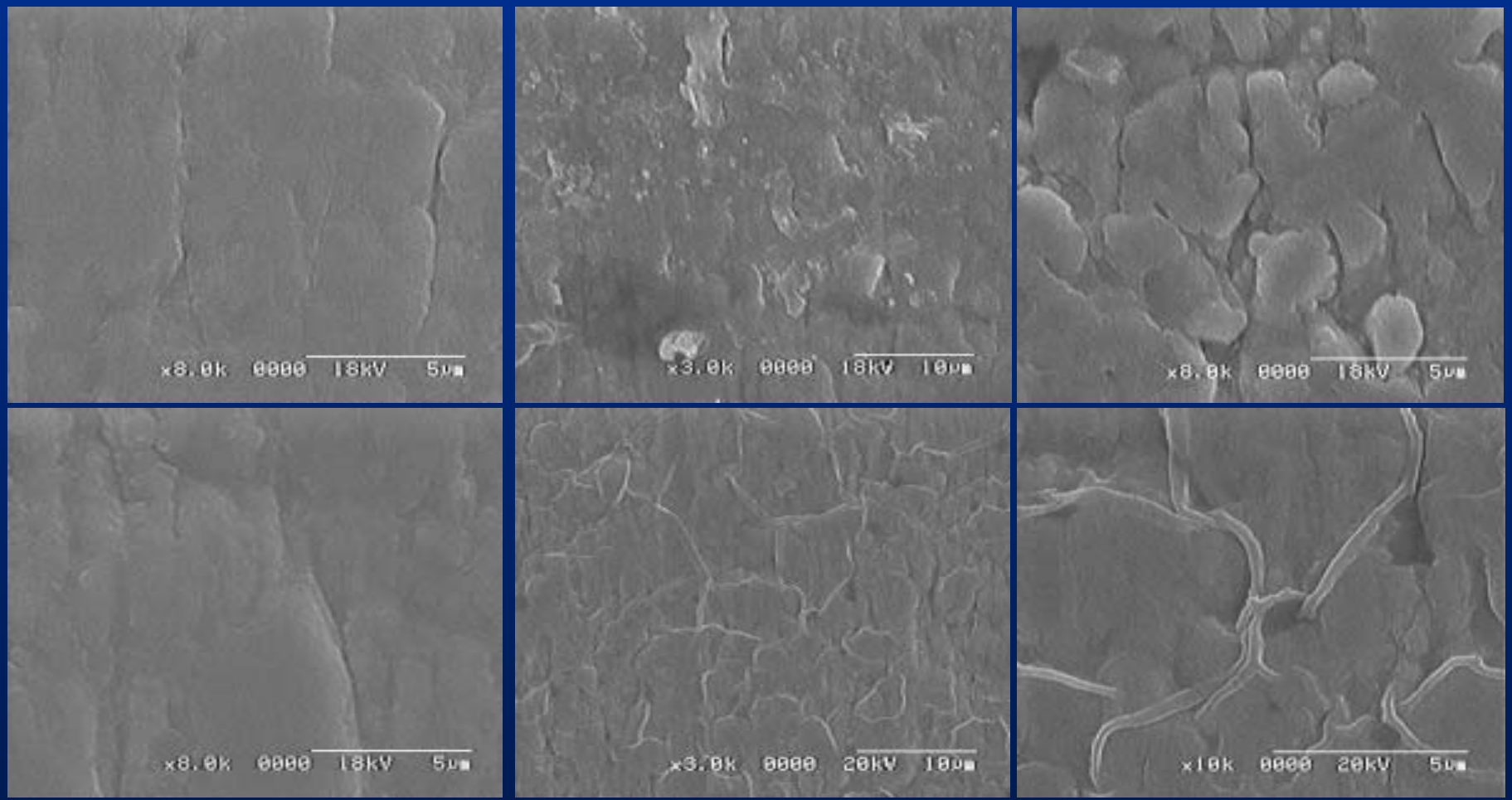
According to creating Peptide bond , in XPS 's data, analytic factor of C1s, N1s, O1s in fitting

C1s	**Ketone (C=O): ~288.0 eV** ⬆
N1s	**Amine ($-NH_2$): ~399.0 eV** ⬇ **C-N : 400.0 eV** ⬆
O1s	**=O : ~531.5 eV** ⬆

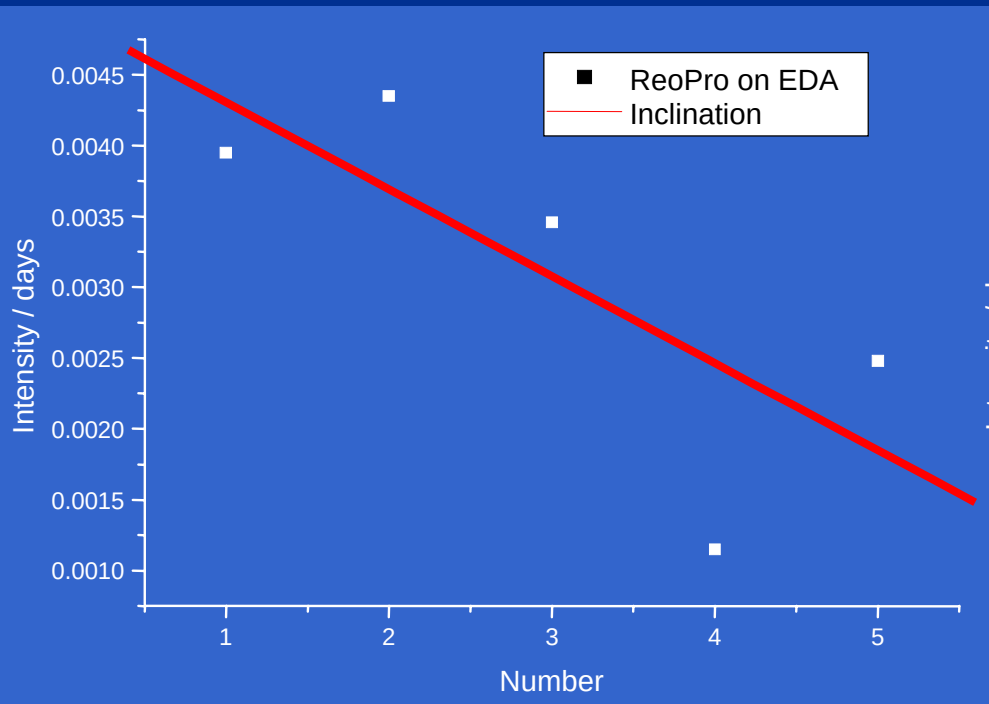
Observation through SEM

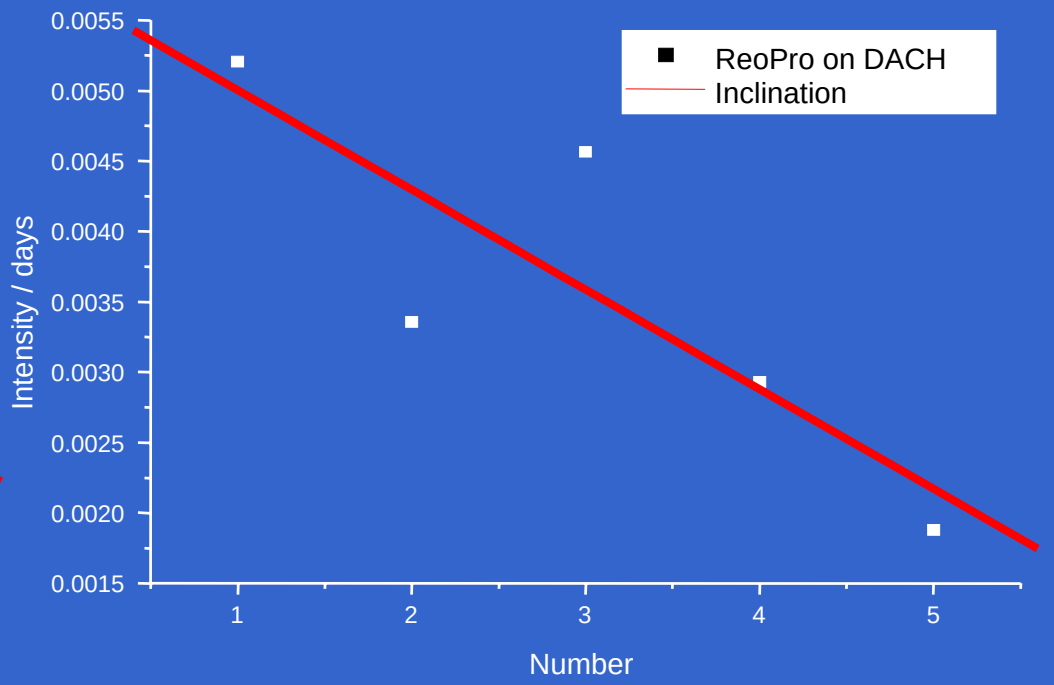
DACH

EDA



Release Behavior





Tine	Intensity	Intensity / days	Avg.Amount of release (µg)
1 (2days)	0.0079	0.00395	25.22
2(2days)	0.0087	0.00435	27.82
3(3days)	0.0104	0.0035	21.71
4(3days)	0.00345	0.00115	7.36
5(5days)	0.0124	0.0025	15.86

Time	Intensity	Intensity / days	Avg.Amount of release (µg)
1 (2days)	0.01041	0.00521	33.27
2(2days)	0.00674	0.00337	21.41
3(3days)	0.01369	0.00456	29.17
4(3days)	0.00881	0.00294	18.78
5(5days)	0.00942	0.00228	12.05

Stability of Dried ReoPro

Conc. (nM)	Platelet aggregation Inhibition (%)		
	Fresh-ReoPro	Dry-ReoPro (1 Day)	Dry-ReoPro (21 days)
Saline control	0	0	0
21 nM (1 ug/ml)	9.1	7	6
42 nM (2 ug/ml)	50	49	39.3
84 nM (4 ug/ml)	100	99	98

DES using Antibodies

1) Antibody coated stent will be a another spectrum of DES

2) DES with ReoPro will be a potential next generation of drug coating stent which do not need long duration of Plavix.

Thanks

1) 휴메드: 류용선 박사

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