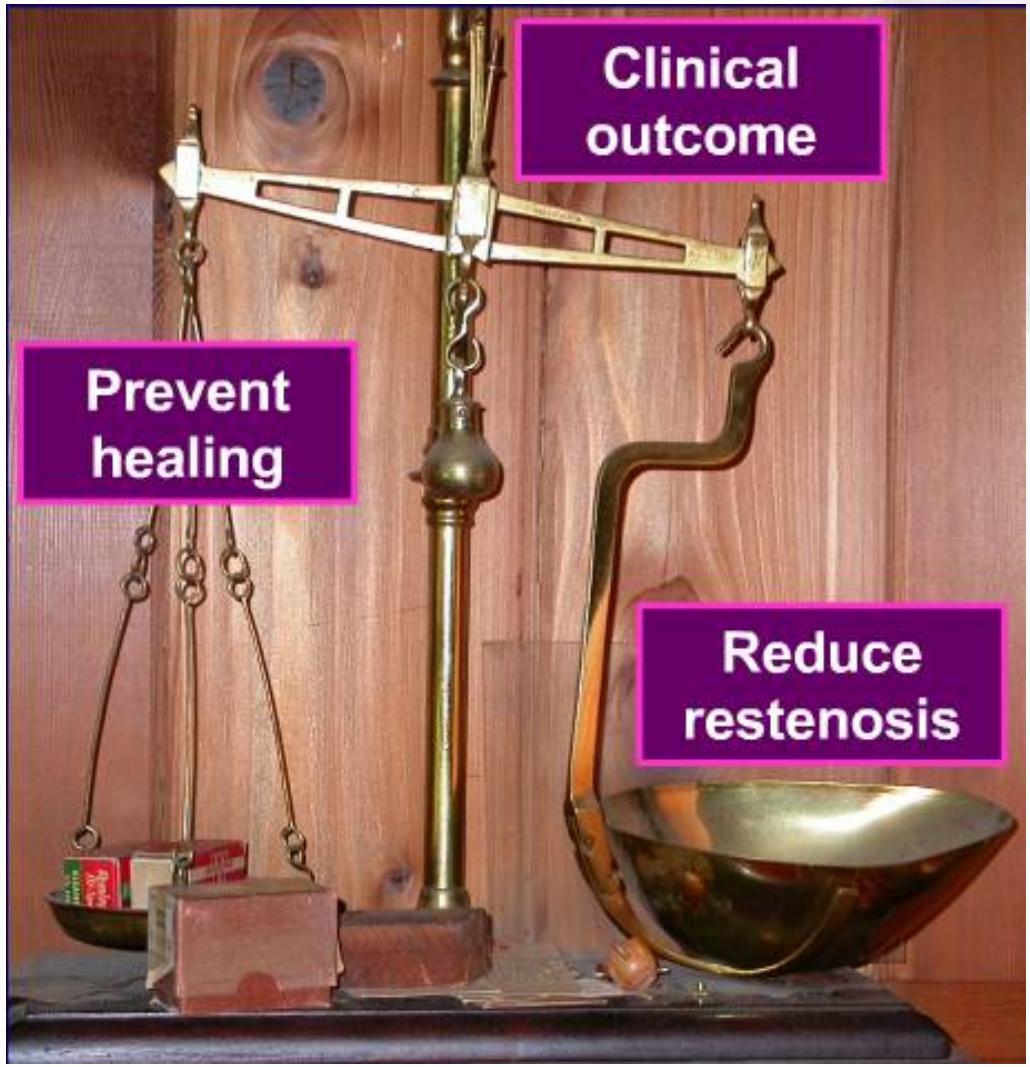
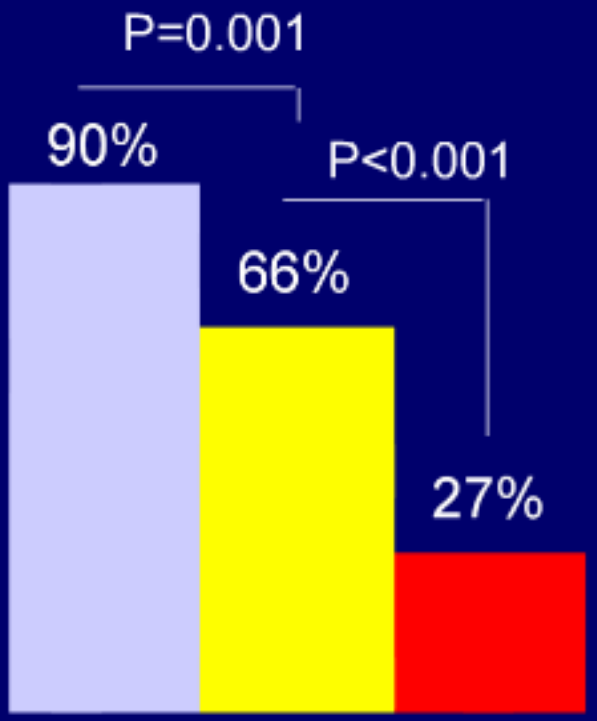
EPC Capture Technology and the Real World Experience

Michael JB Kutryk
Angioplasty Summit - TCT Asia Pacific
April 26, 2007
Seoul, South Korea

The DES scale

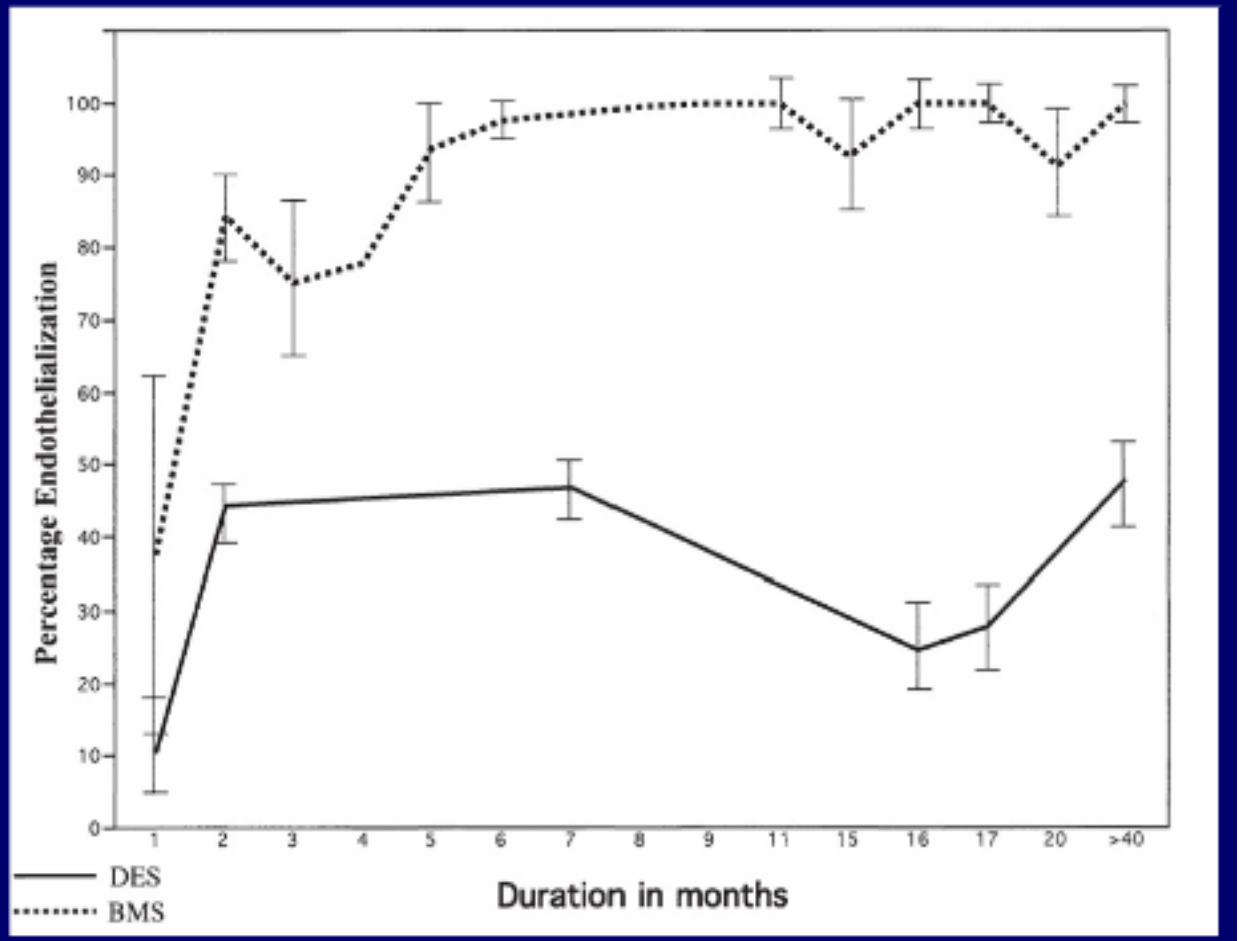


Healing after stent implantation in DES and BMS



Endothelialization

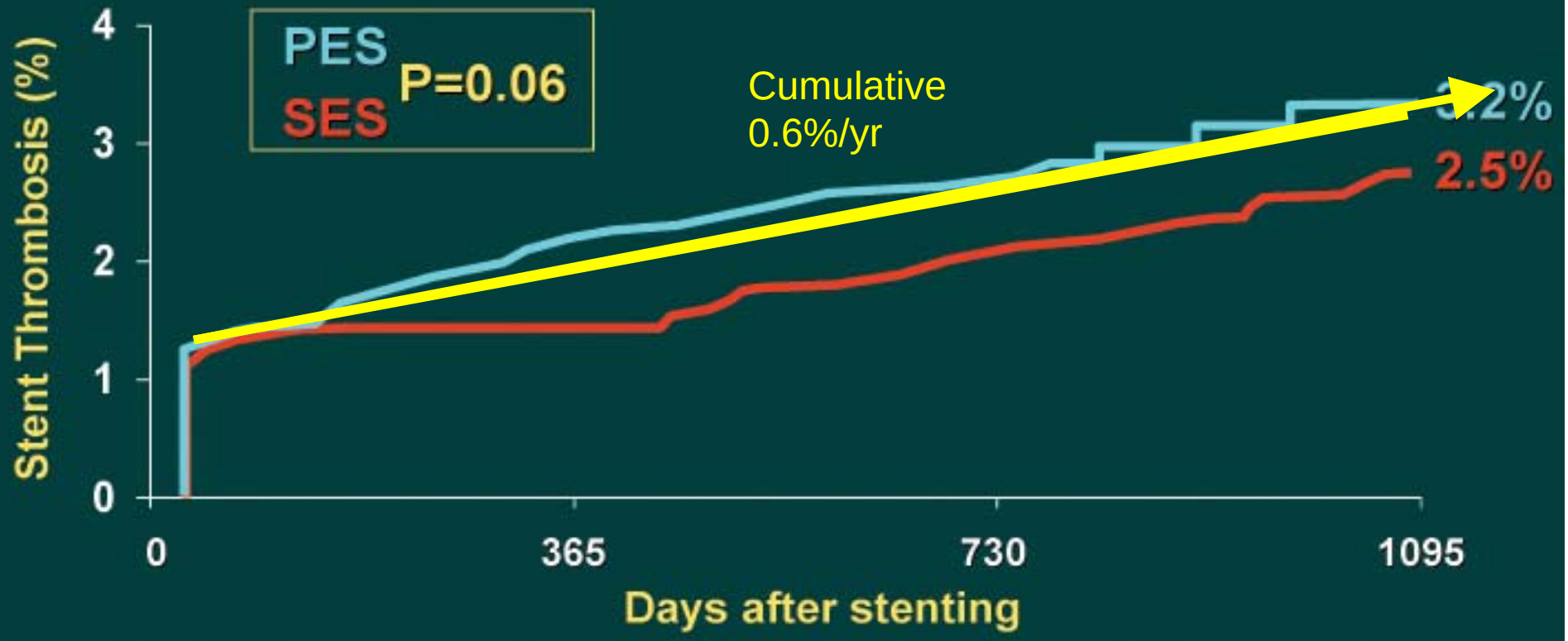
- BMS
- Patent DES
- Thrombosed DES



Joner, et al JACC 2006

create

Bern – Rotterdam cohort study
Angiographic DES Stent Thrombosis



Days after PCI	9	30	365	730	1095
Incidence SES (%)	1.0	1.1	1.3	1.9	2.5
Incidence PES (%)	1.2	1.3	2.0	2.7	3.2
Pts at risk	8146	7162	7002	2841	971

Daemen J et al. Lancet 2007

create

BASKET LATE Trial: Study Design

GenOus

743 patients randomized in the BASKET trial and WITHOUT AN EVENT DURING THE 6-MONTH CLOPIDOGREL PHASE

Drug-eluting stents (DES) (pooled paclitaxel and sirolimus DES groups) n=499	Bare metal VISION stents (BMS) n=244

Followed for 1 year off clopidogrel

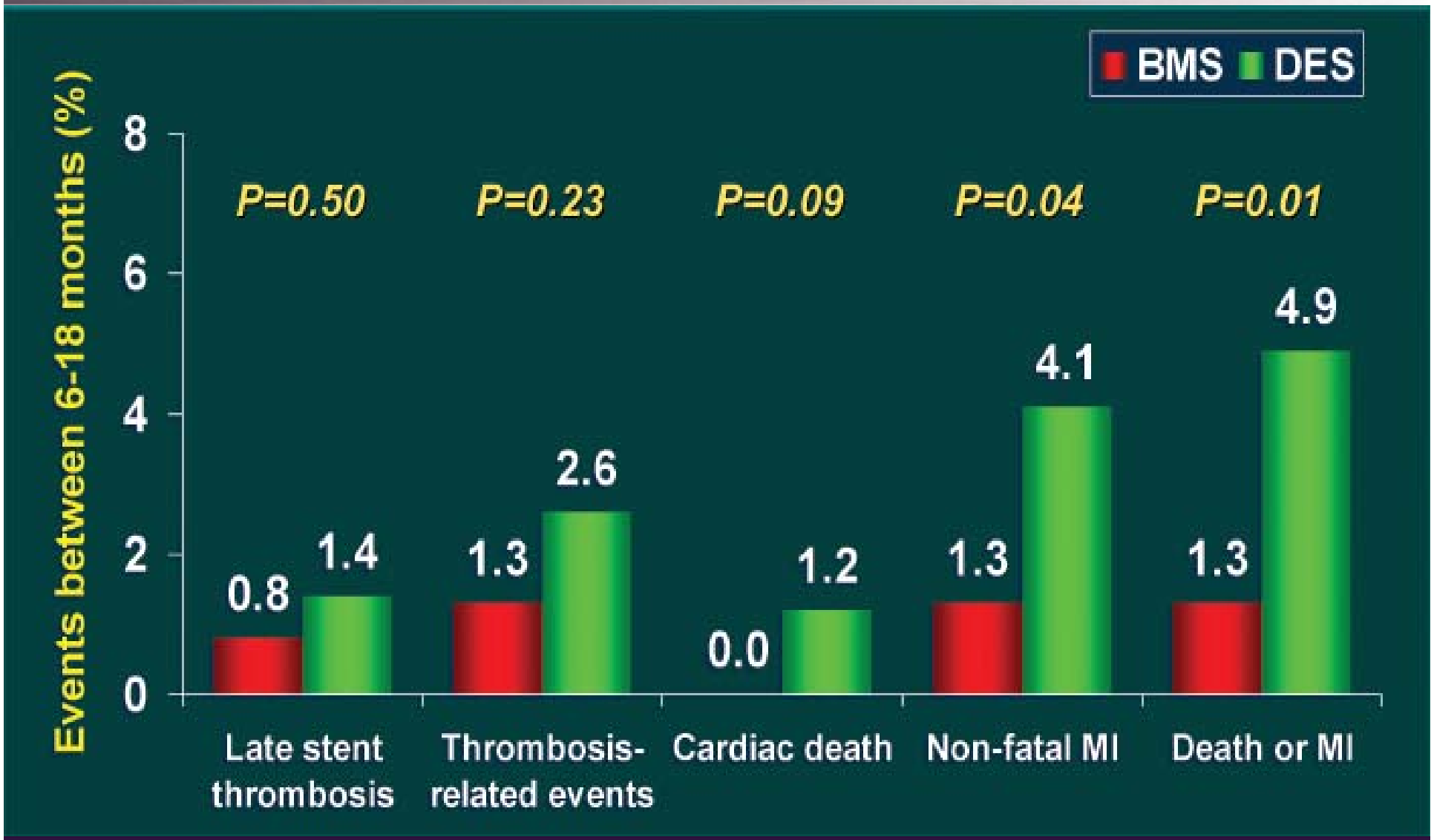
- Primary Endpoint: Composite cardiac death or nonfatal MI.
- Other Endpoints: "Thrombosis-related events"

Pfisterer M et al. JACC

create

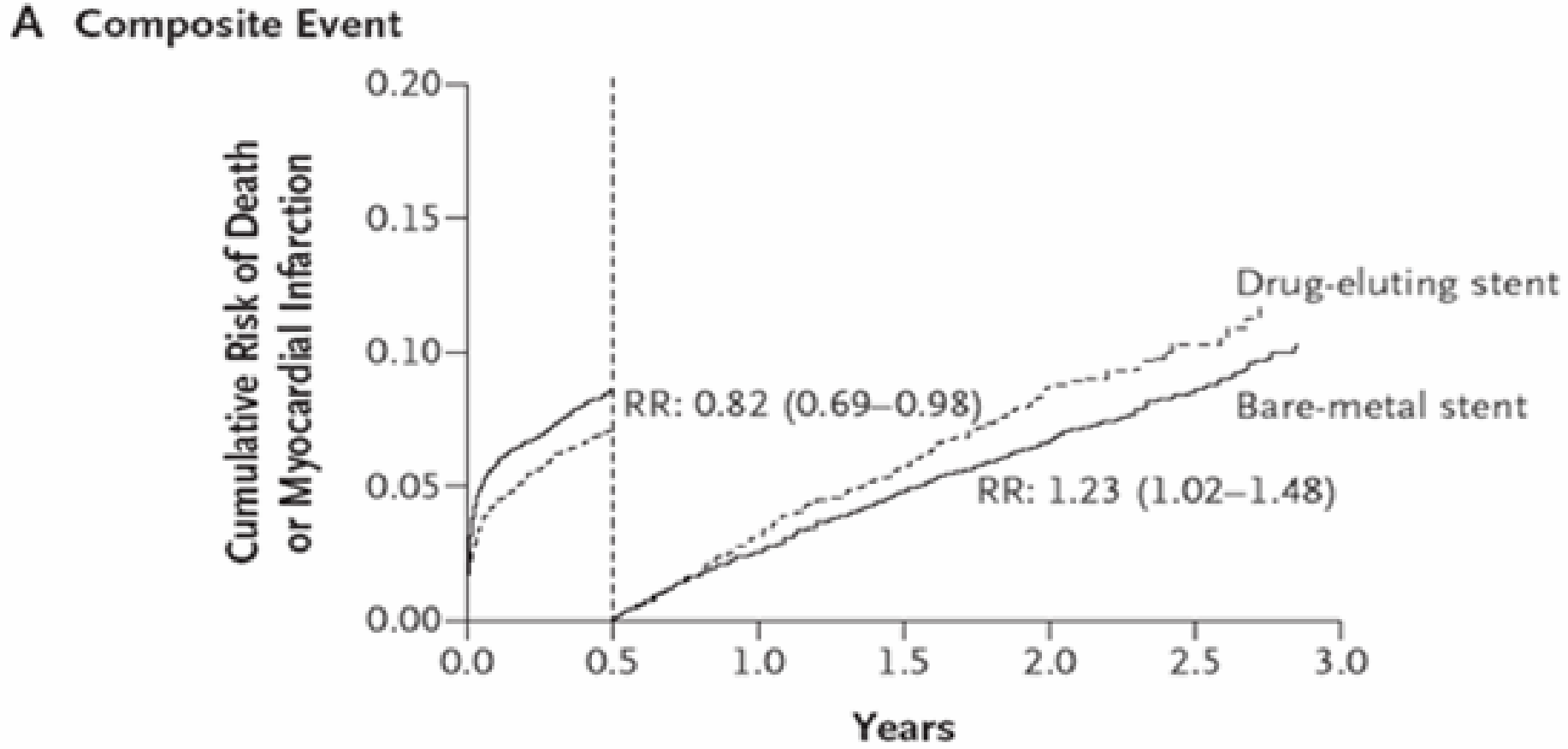
BASKET LATE Trial: 6-18 Month MACE

N=743 (pts with early events excluded)



Pfisterer M et al. J Am Coll Cardiol 2006;48:2584-91

Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden



No. at Risk

Bare-metal stent	9556	9292	9053	6827	4360	2328	7
Drug-eluting stent	3432	3341	3238	1981	982	369	0

Lagerquist B et al., NEJM 2007

Conclusions of 2 Day FDA Hearings

- Late stent thrombosis is a rare event
- Off-label DES use associated with LST
- There may be an increase in Death/MI
- DES recipients on ASA/plavix lifelong?

Unanswered Questions — Drug-Eluting Stents and the Risk of Late Thrombosis

GenOus

We Need Better Technologies

Maisel W et al., NEJM 2007

Farb A, Boam A, NEJM 2007

Genous Stent

Genous Healing Approach

The capture of circulating EPCs promotes the establishment of a functional endothelium, providing a physically passive and metabolically active surface essential for rapid and effective healing.

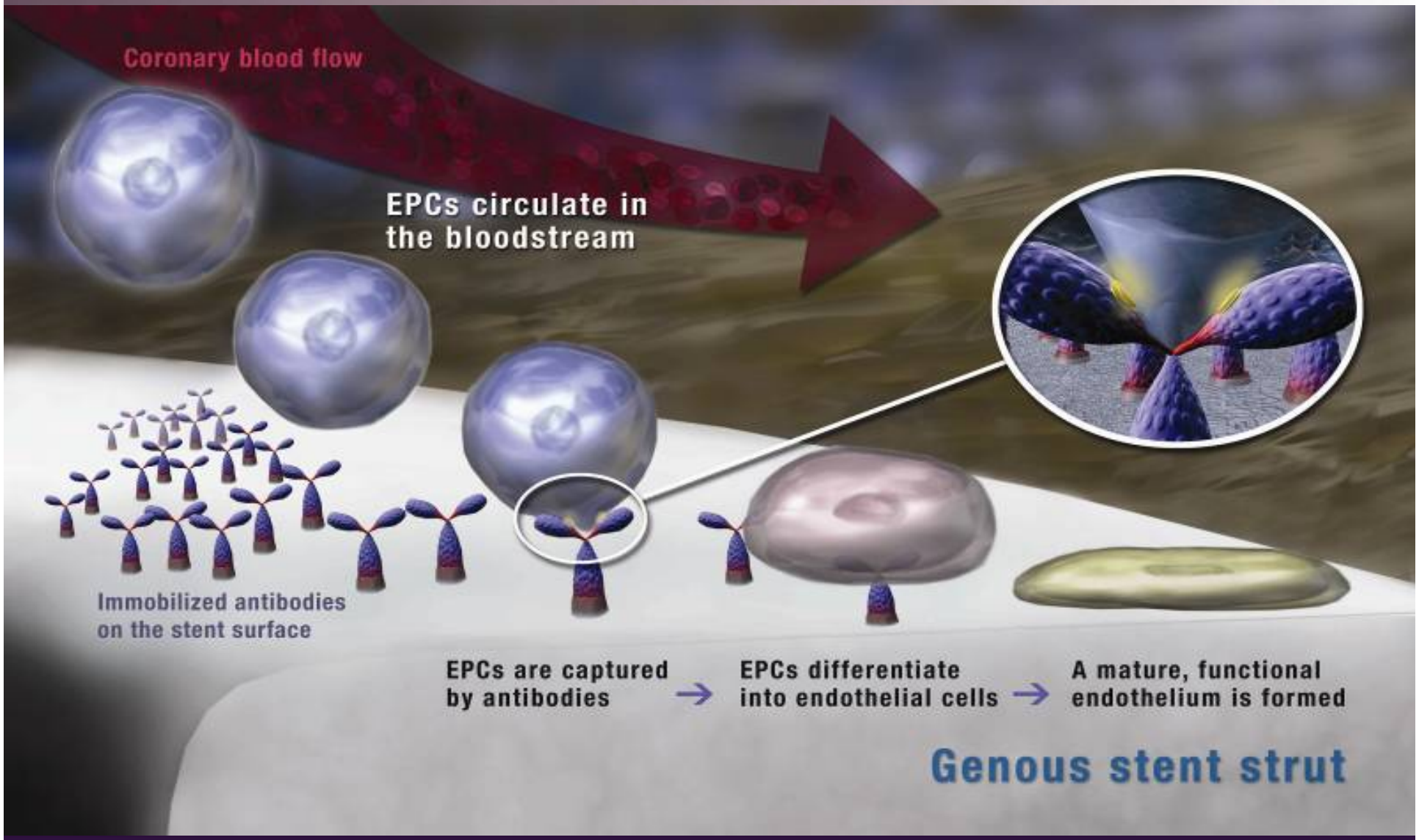
Genous Protects Against Thrombus Formation

The rapid establishment of a functional confluent endothelium effectively covers the stent struts and intra-strut spaces, thereby reducing the risk of thrombus formation. Long term antiplatelet therapy is not required.

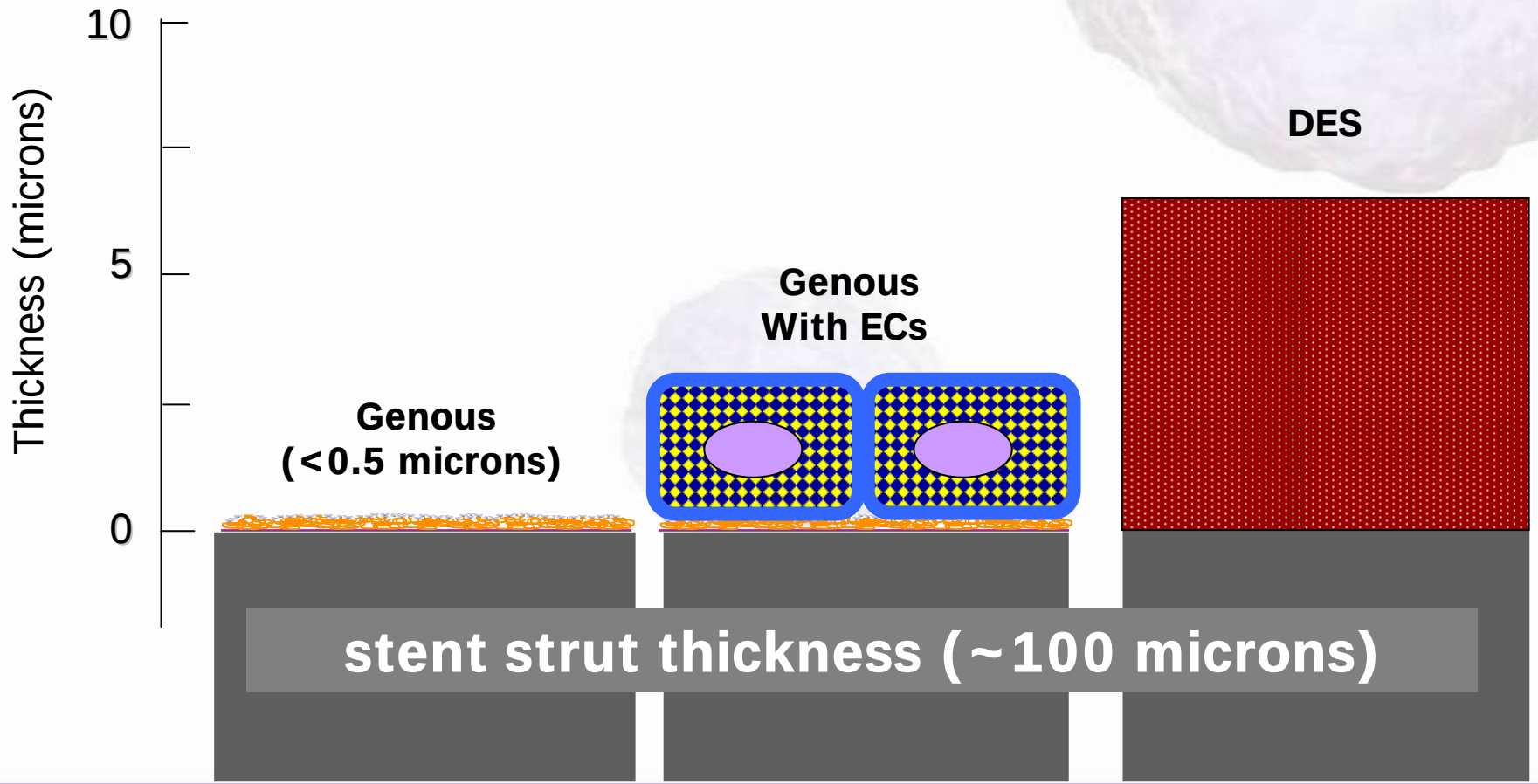
Genous Minimizes Restenosis

The establishment of a healthy endothelium modulates the healing response and inhibits excessive neointimal proliferation.

EPC Capture Technology



Genous Surface Thickness Compared with Drug Eluting Stents



Preclinical Proof of EPC Capture Concept

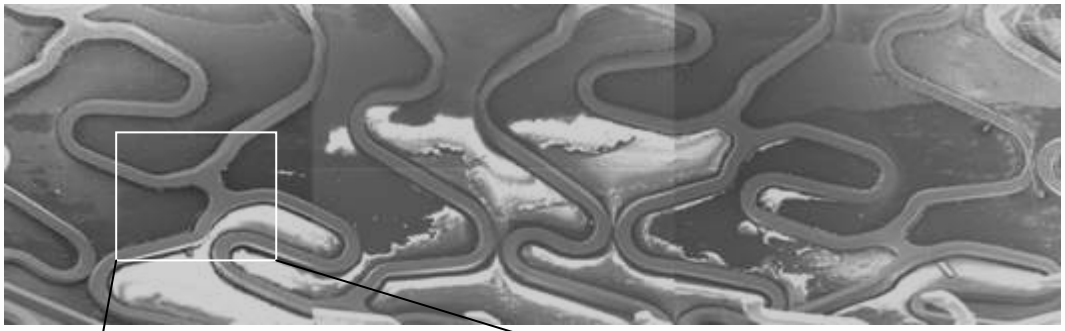
Comparison of bare metal stents with EPC capture coated Genous stents in:

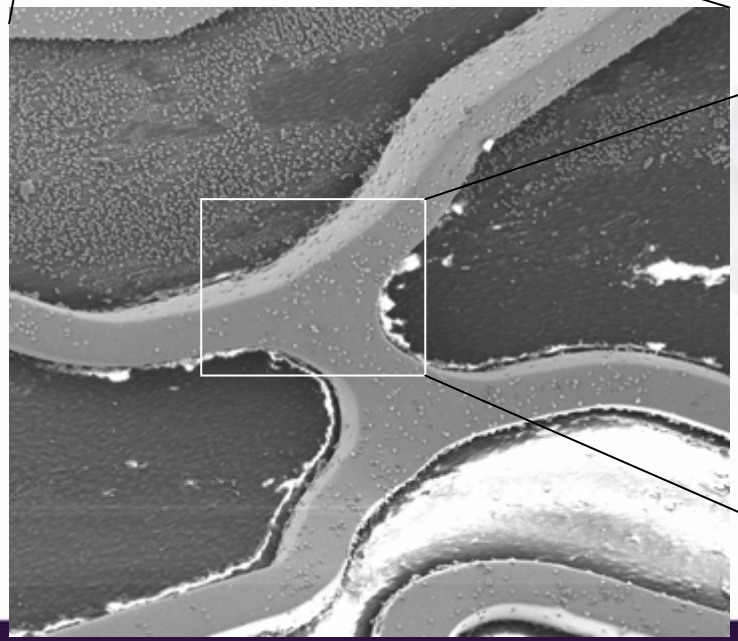
- Stented pig arterial segments explanted at 1 hour and 48 hours (M. Kutryk)
- Stented pig arterial segments explanted at 14 days (R. Virmani, M. Leon)
- Baboon Ex Vivo Shunt SEMs (S. Hanson, R. Virmani)

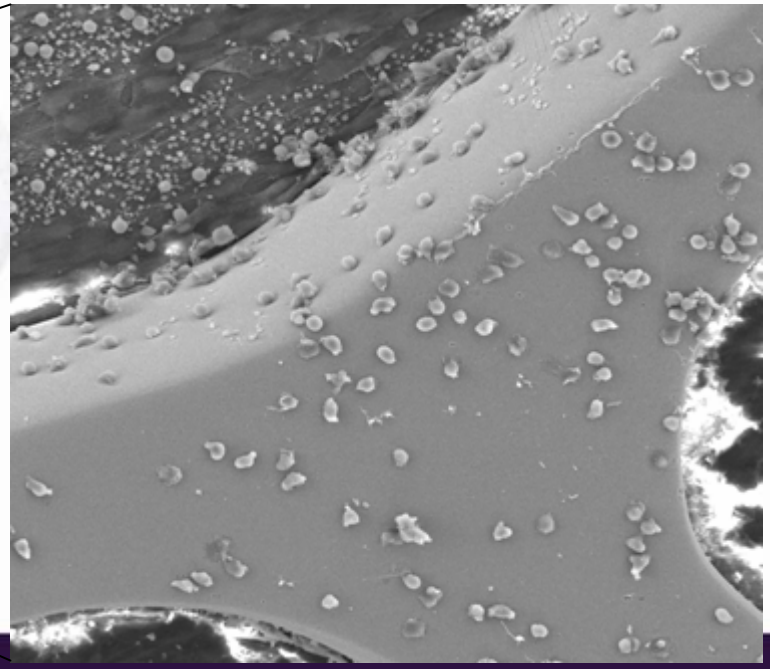
Comparison of DES with EPC capture coated DES in:

- Stented pig arterial segments explanted at 14 days (R. Virmani, M. Leon)

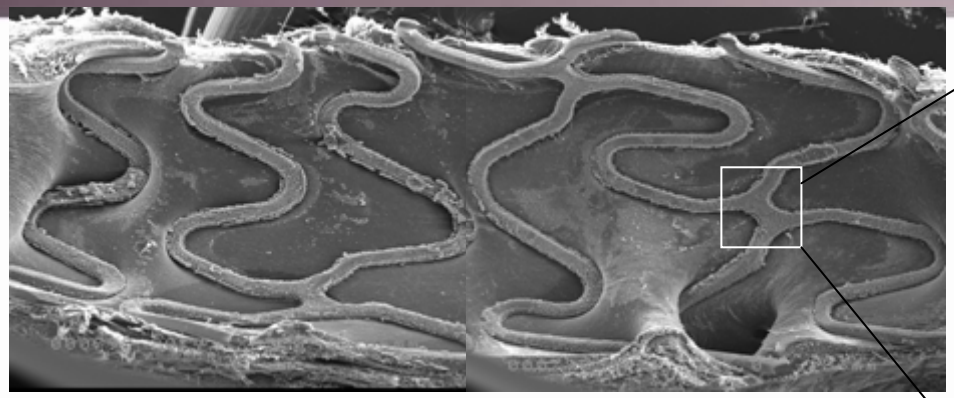
1 Hour Explants - Control Stent

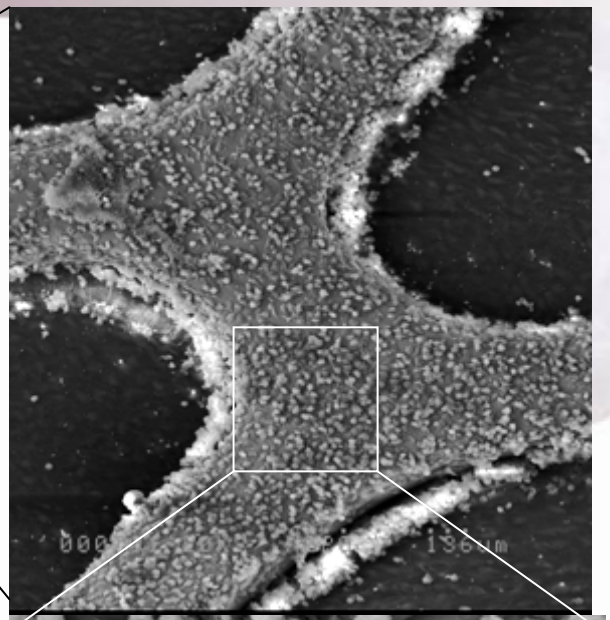


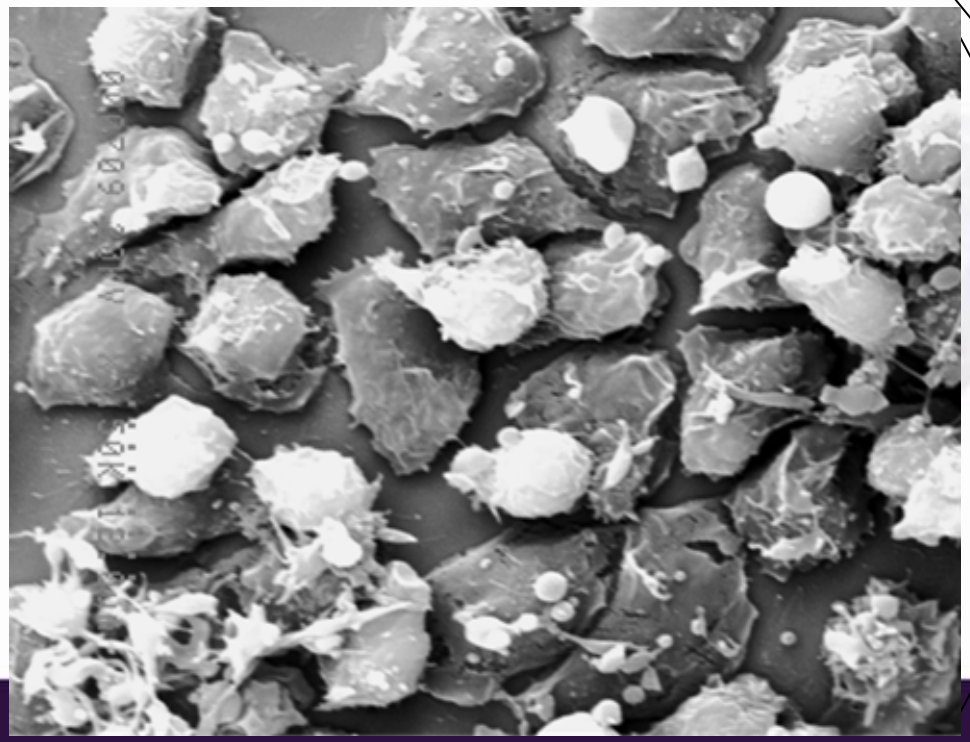


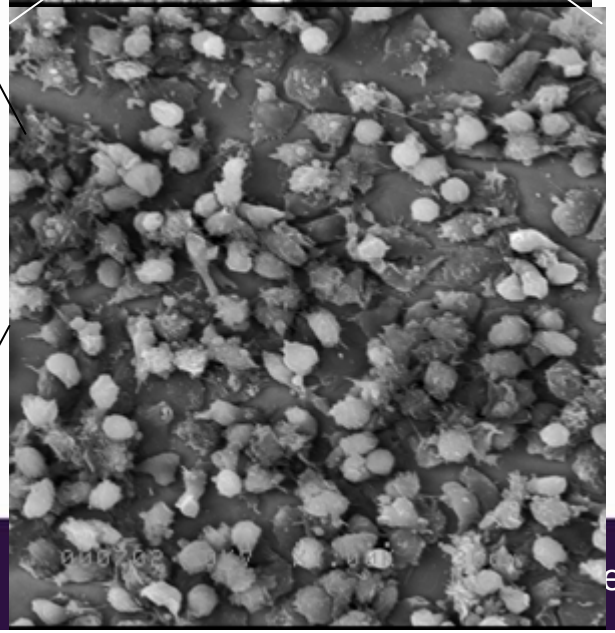


1 Hour Explants - Genous Stent



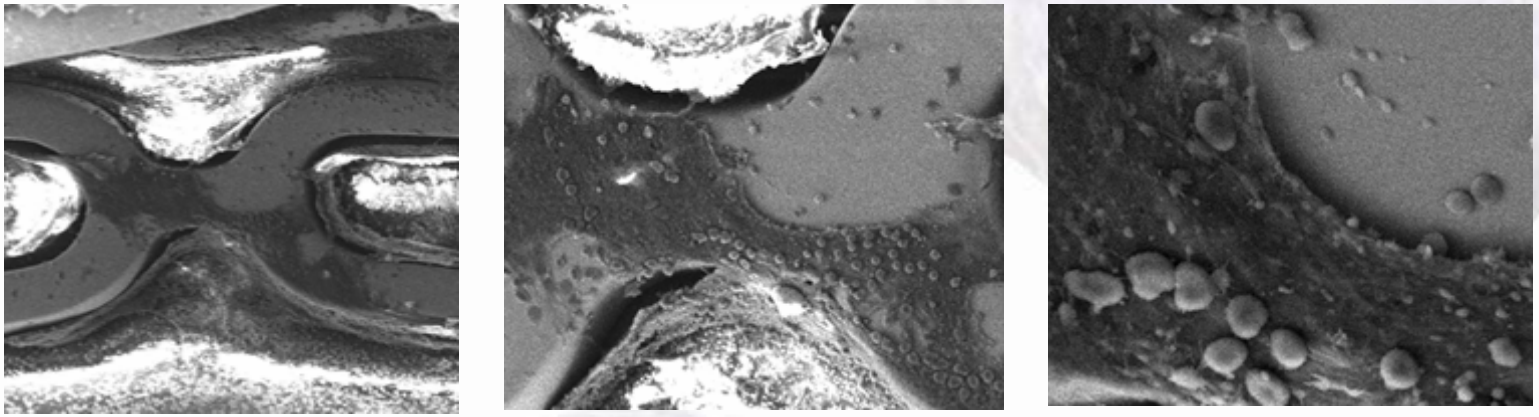




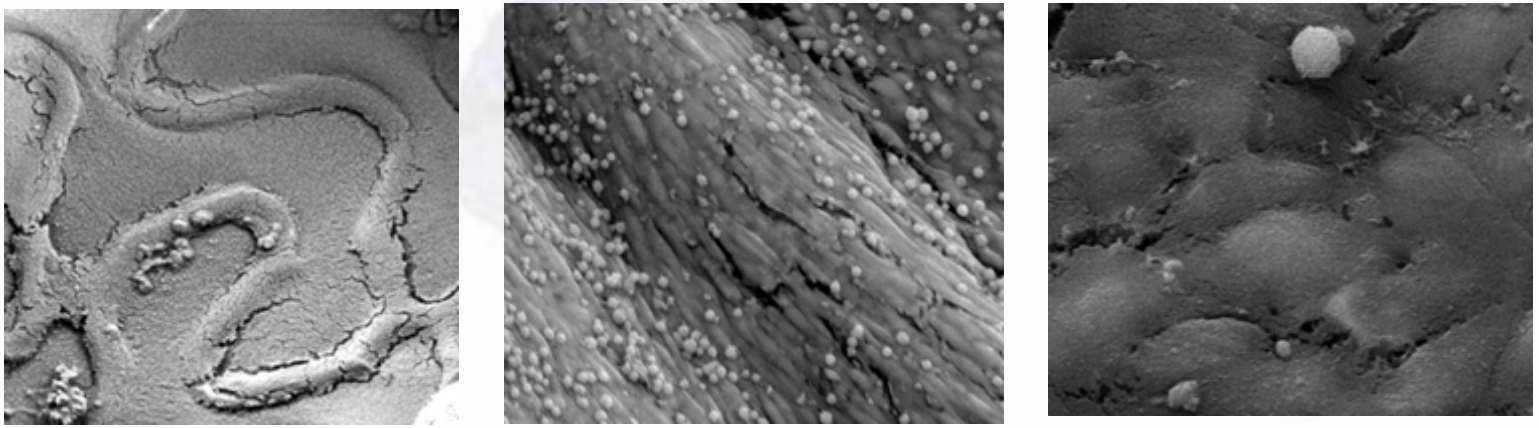


48 Hour Explants

Bare Metal Stent



Genous

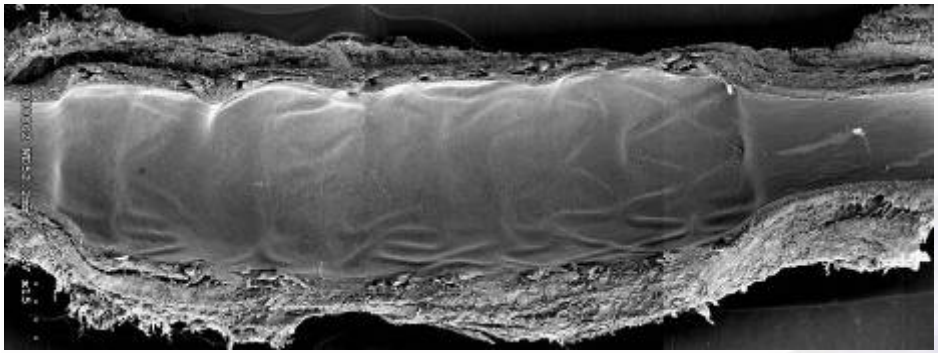


M. Kutryk; porcine coronary implants, unpublished data

14 Day Porcine Explants

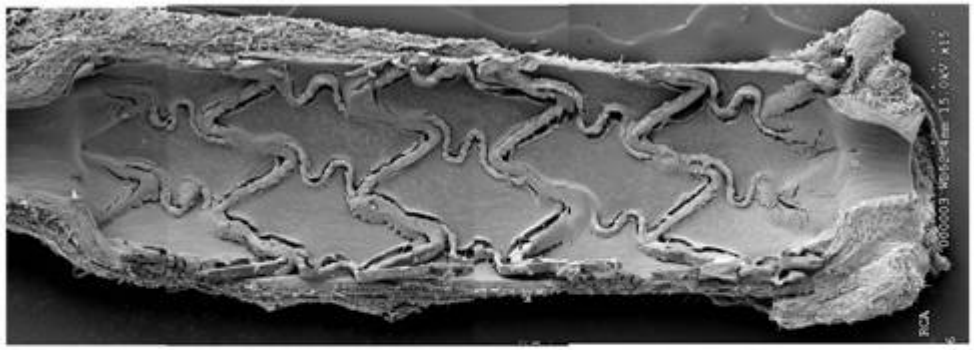
Genous Stent

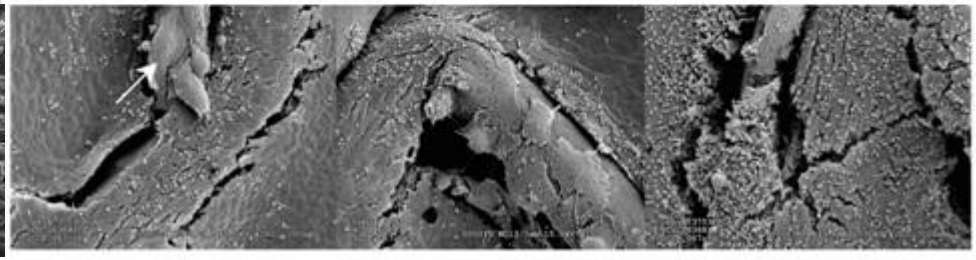
14 DAY – CV16376, 3550 RCA (AB)



Cypher Select

14 DAY - CV16369, 3755 RCA (SIR)



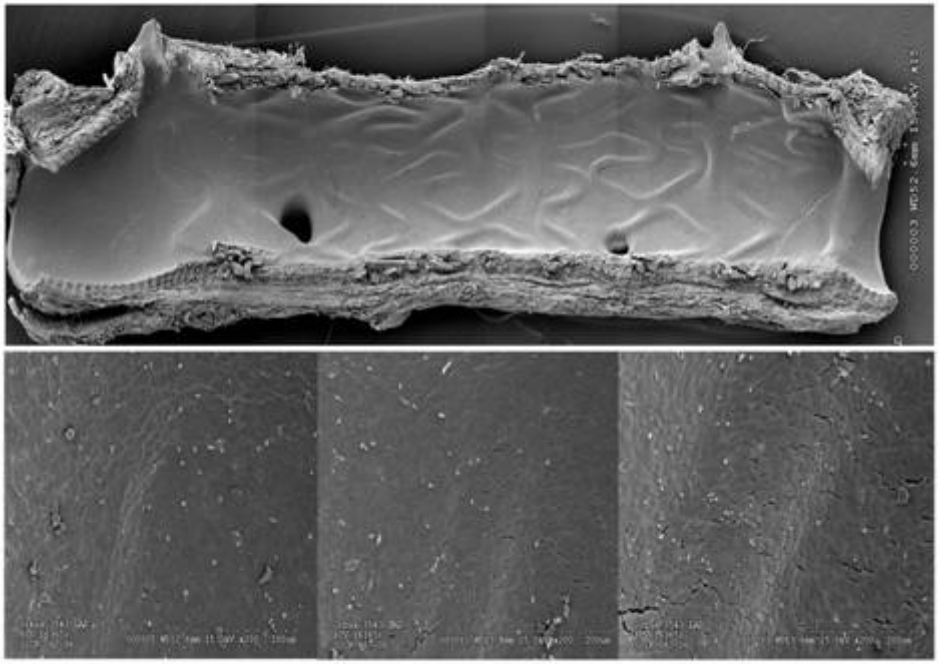


Virmani/Leon unpublished data 2006

14 Day Porcine Explants

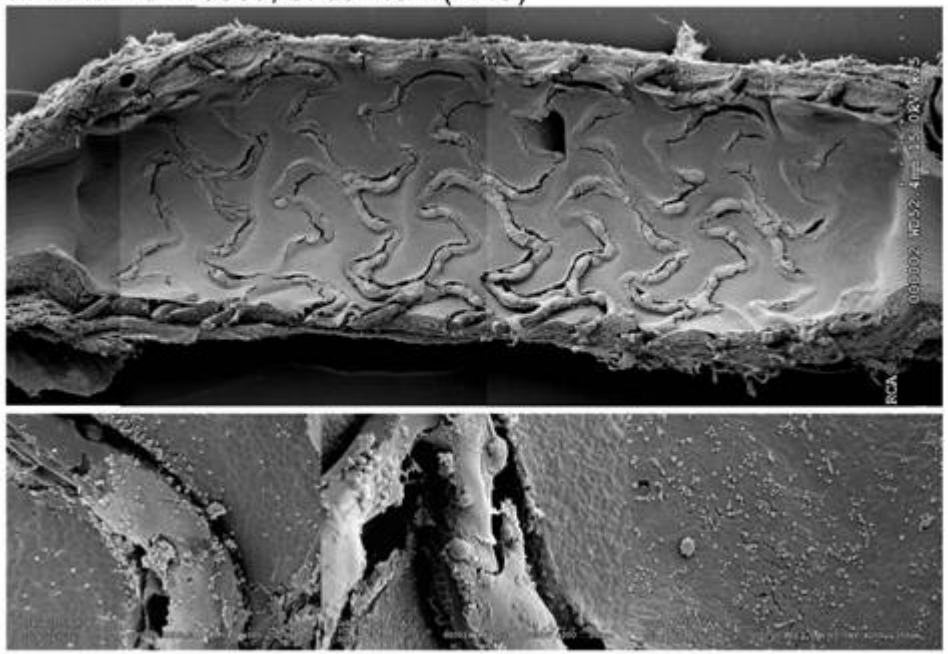
Genous Stent

14 DAY - CV16365, 3543 LAD (AB)



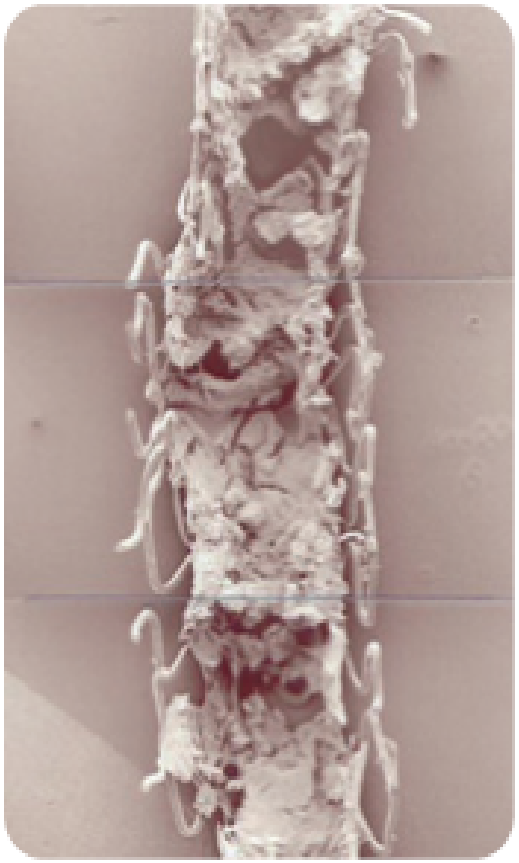
Taxus Liberte’

14 DAY - CV16369, 3755 RCA (PAC)

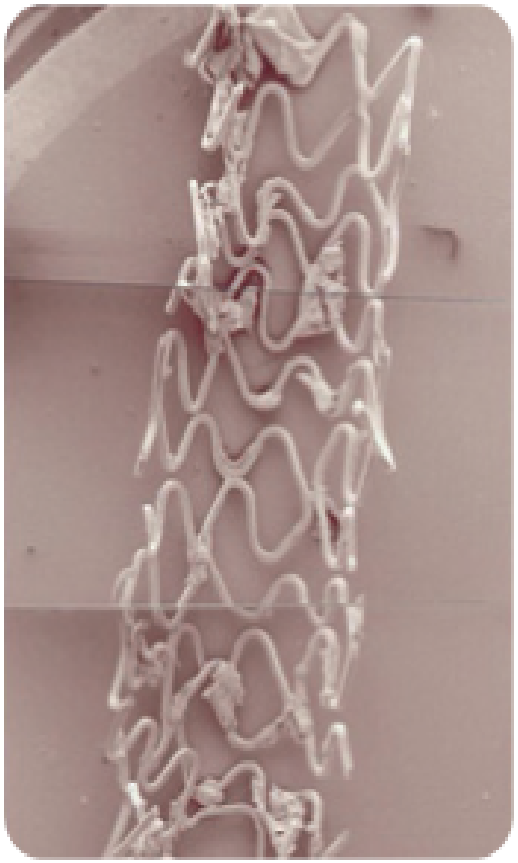


Virmani/Leon unpublished data 2006

AV Shunt Study



Bare Metal Stent
at 65 minutes



Genous at two hours

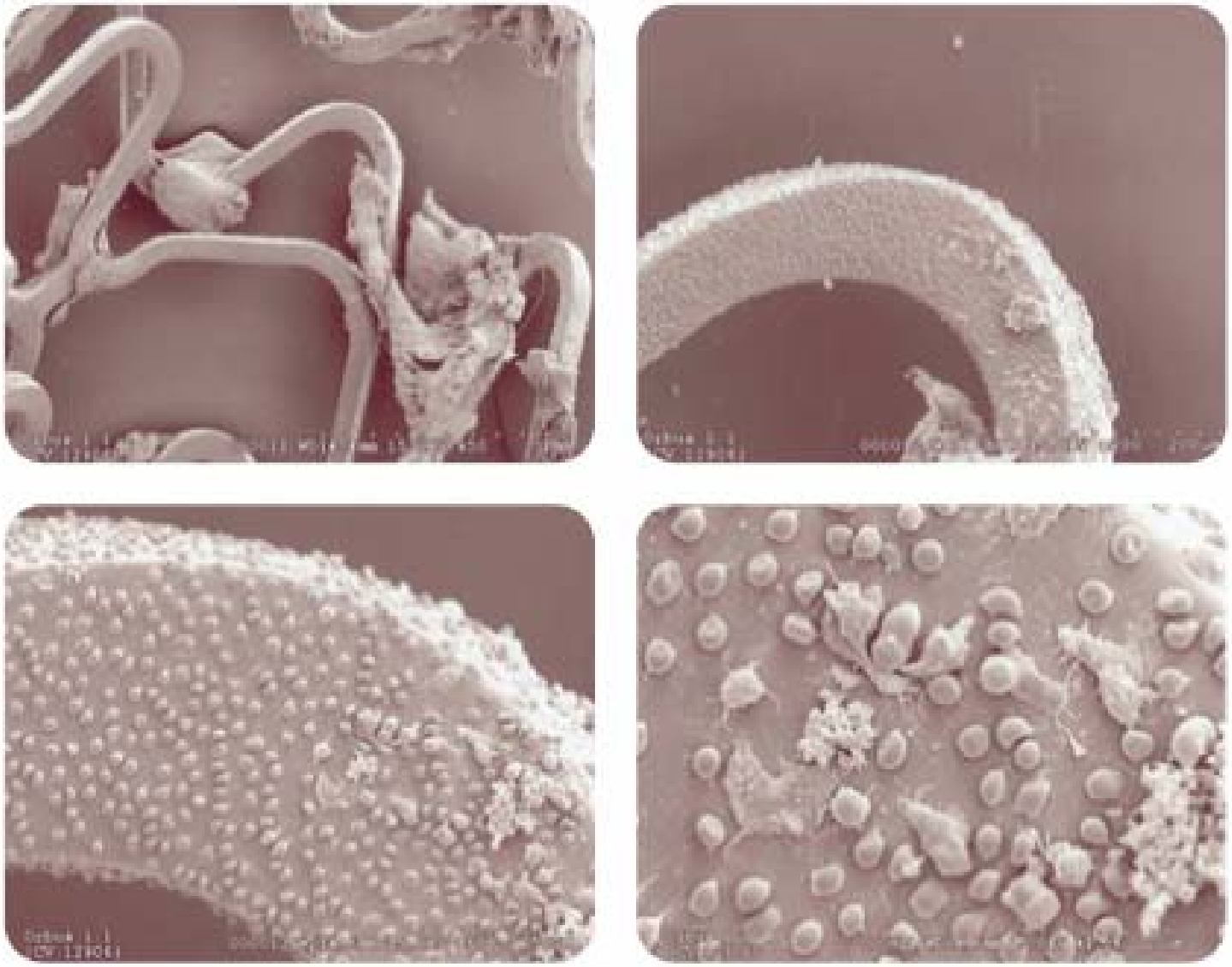
- Bare Metal Stent with flow occluding thrombus
- Genous widely patent at two hours

Ex Vivo Baboon AV Shunt Model

S. Hanson; unpublished data

create

Genous SEMs after Two Hours – AV Shunt Study

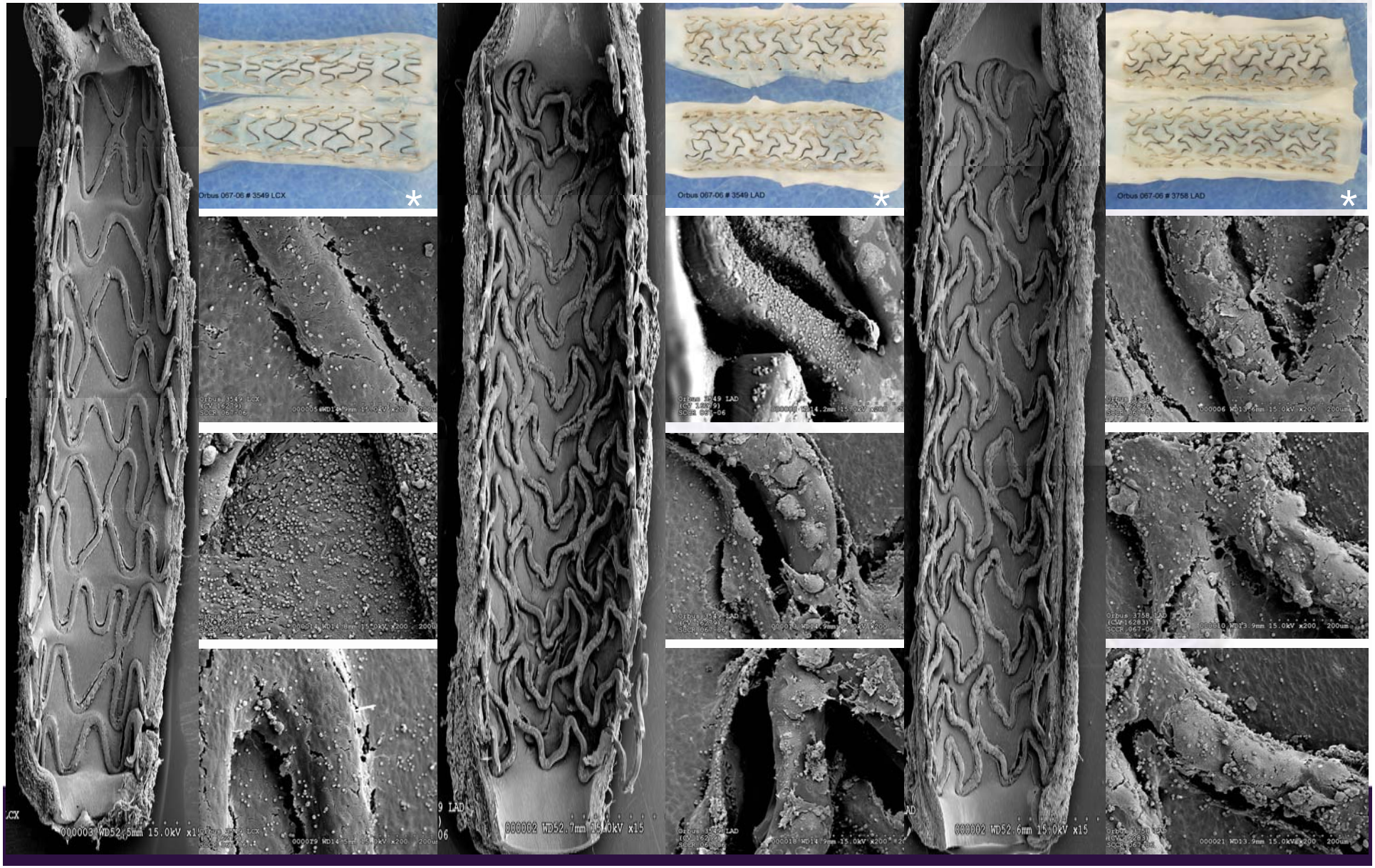


Surface Images of 3 day Genous, and Paclitaxel ± Anti-hCD34 Stented Arterial Explants

Genous

Paclitaxel

Paclitaxel + Anti-hCD34

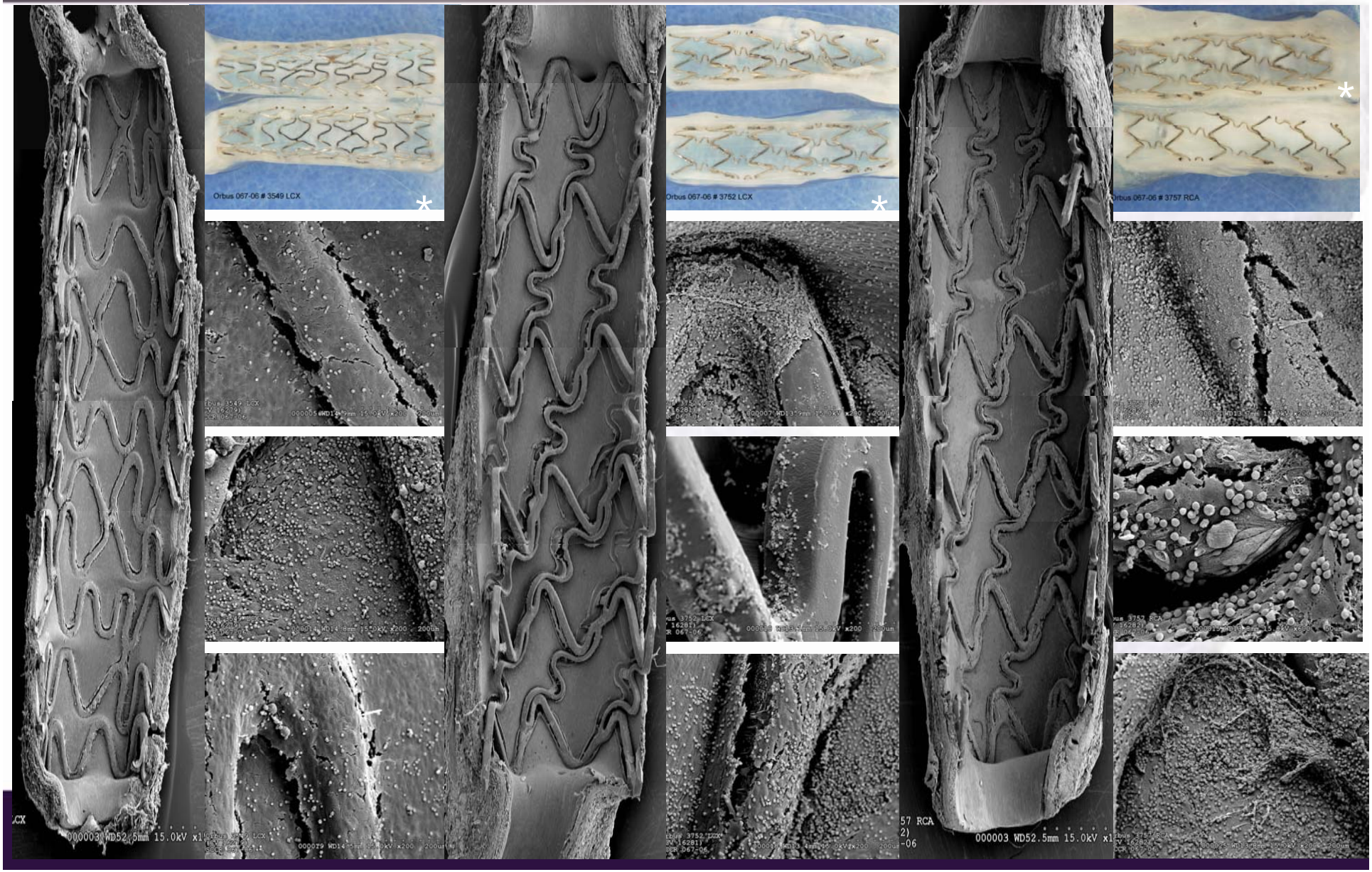


Surface Images of 3 day Genous, and Sirolimus ± Anti-hCD34 Stented Arterial Explants

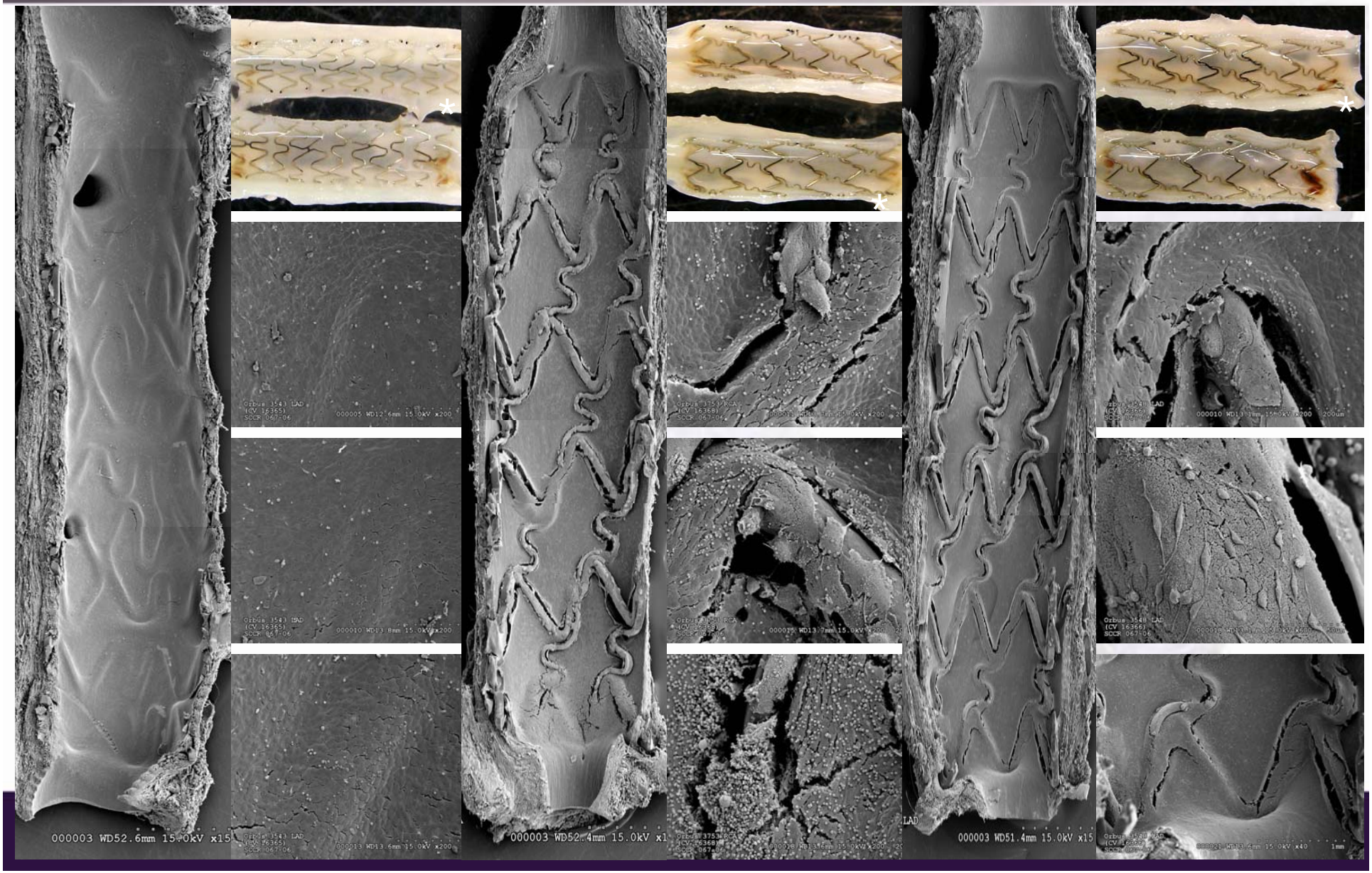
Genous

Sirolimus

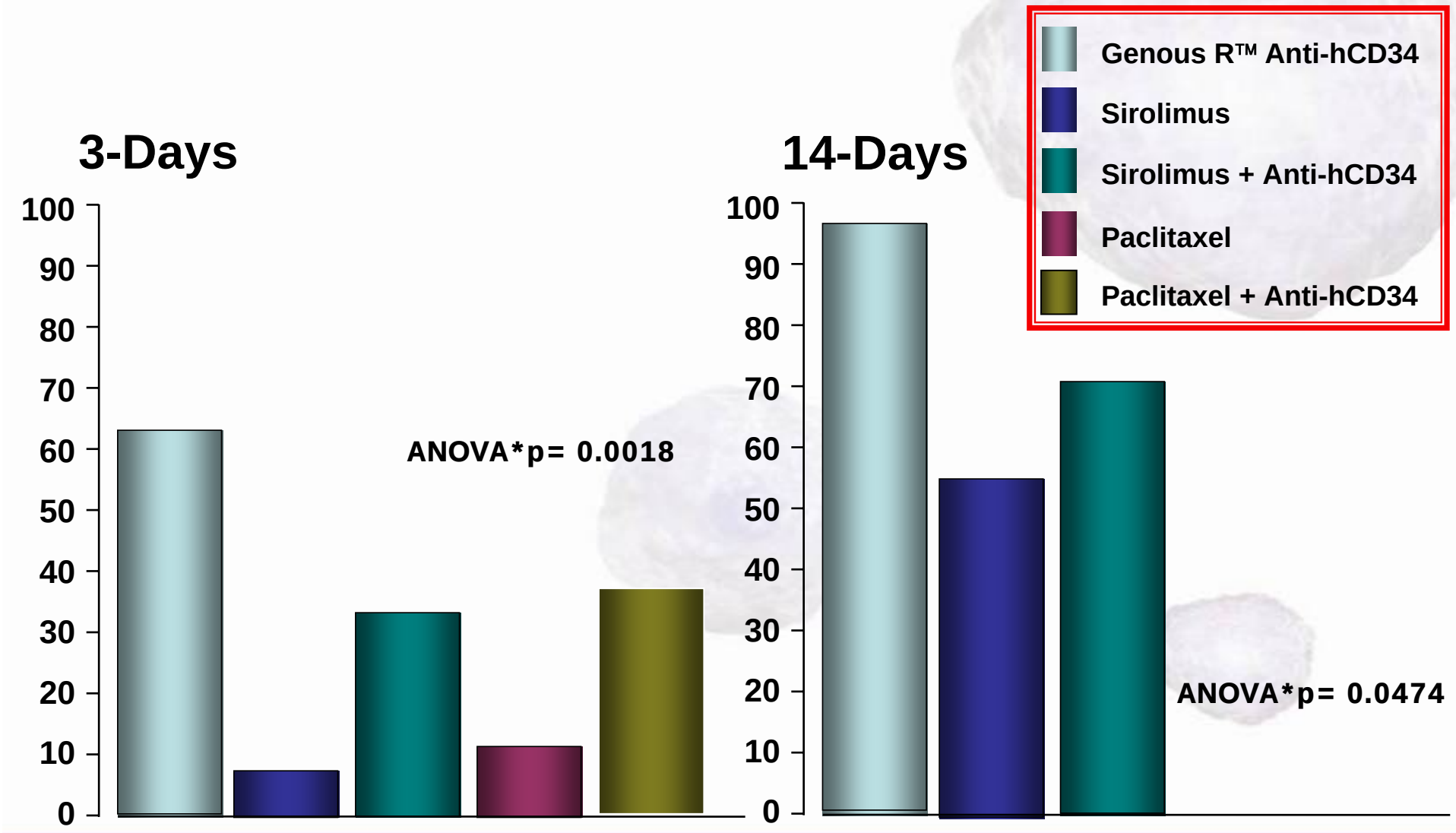
Sirolimus + Anti-hCD34



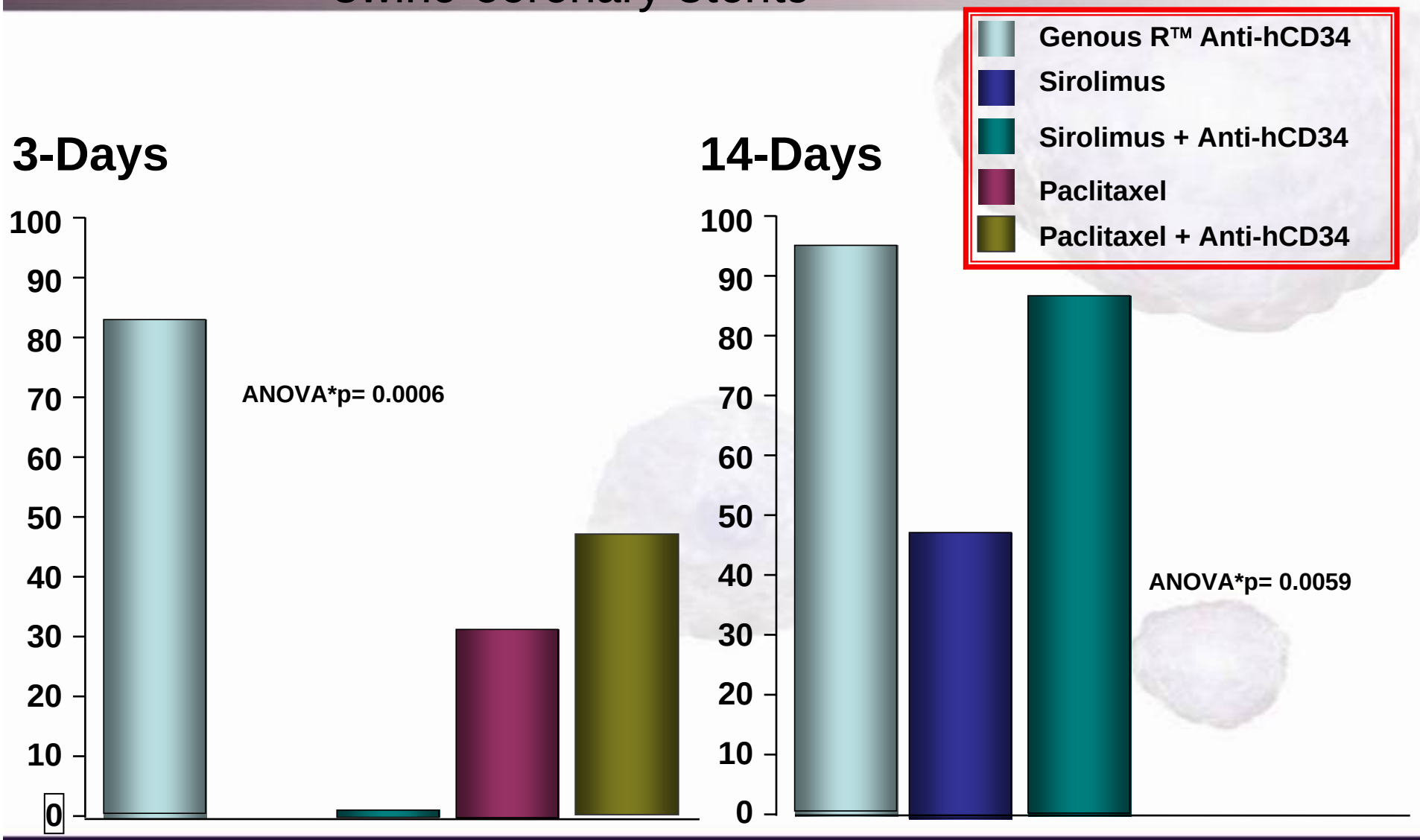
Surface Images of 14 day Genous, and Sirolimus ± Anti-hCD34 Stented Arterial Explants



Luminal Re-Endothelialization (%) Over Struts in Various 3- and 14-Day Swine Coronary Stents



Luminal Re-Endothelialization (%) by PECAM Expression Over Struts in Various 3- and 14-Day Swine Coronary Stents



HEALING II
clinical registry

HEALING II – Trial Design

HEALING II study design:

- Multi-centered, prospective, non-randomized trial
- 63 patients; 10 invited centers (NL, B, G)

- Objective:
  - Demonstrate the safety and efficacy of a stent designed for EPC capture
- Indication:
  - De novo & non-stented restenotic lesions in native coronary arteries with reference vessels 2.5-3.5 mm

- Device:
  - EPC coated R stent™ (OrbusNeich) pre mounted on E2 SDS
- Follow-up:
  - Quantitative coronary angiography and IVUS analysis at 6 (and 18) months
  - Clinical follow-up 6, 9 and 18 months

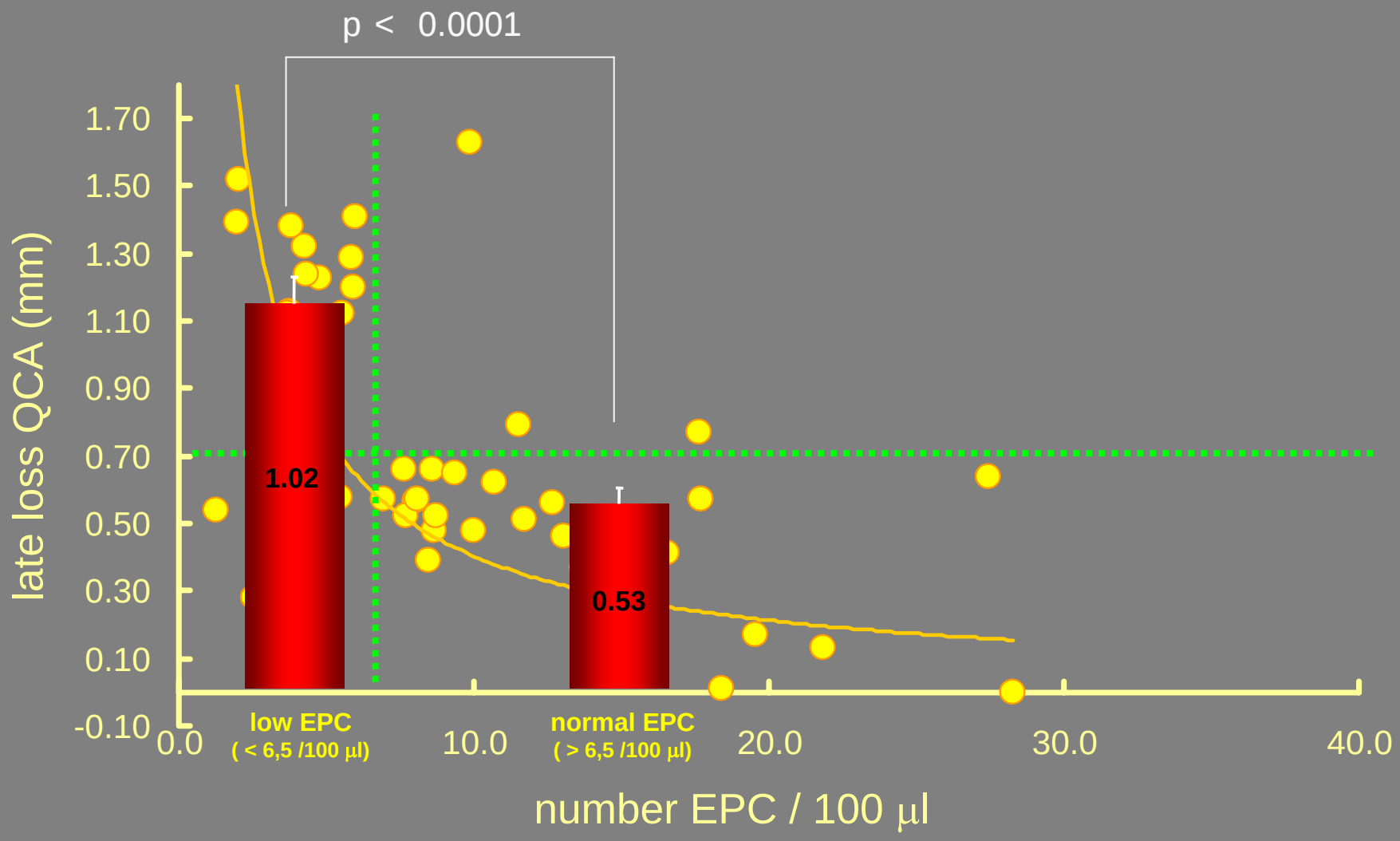
HEALING II - Late Luminal Loss

H2 Overall (n=58)	Avg	0.78
	Std Dev	0.39
Low EPC (n=25)	Avg	1.02
	Std Dev	0.30
Normal EPC (n=27)	Avg	0.53
	Std Dev	0.21

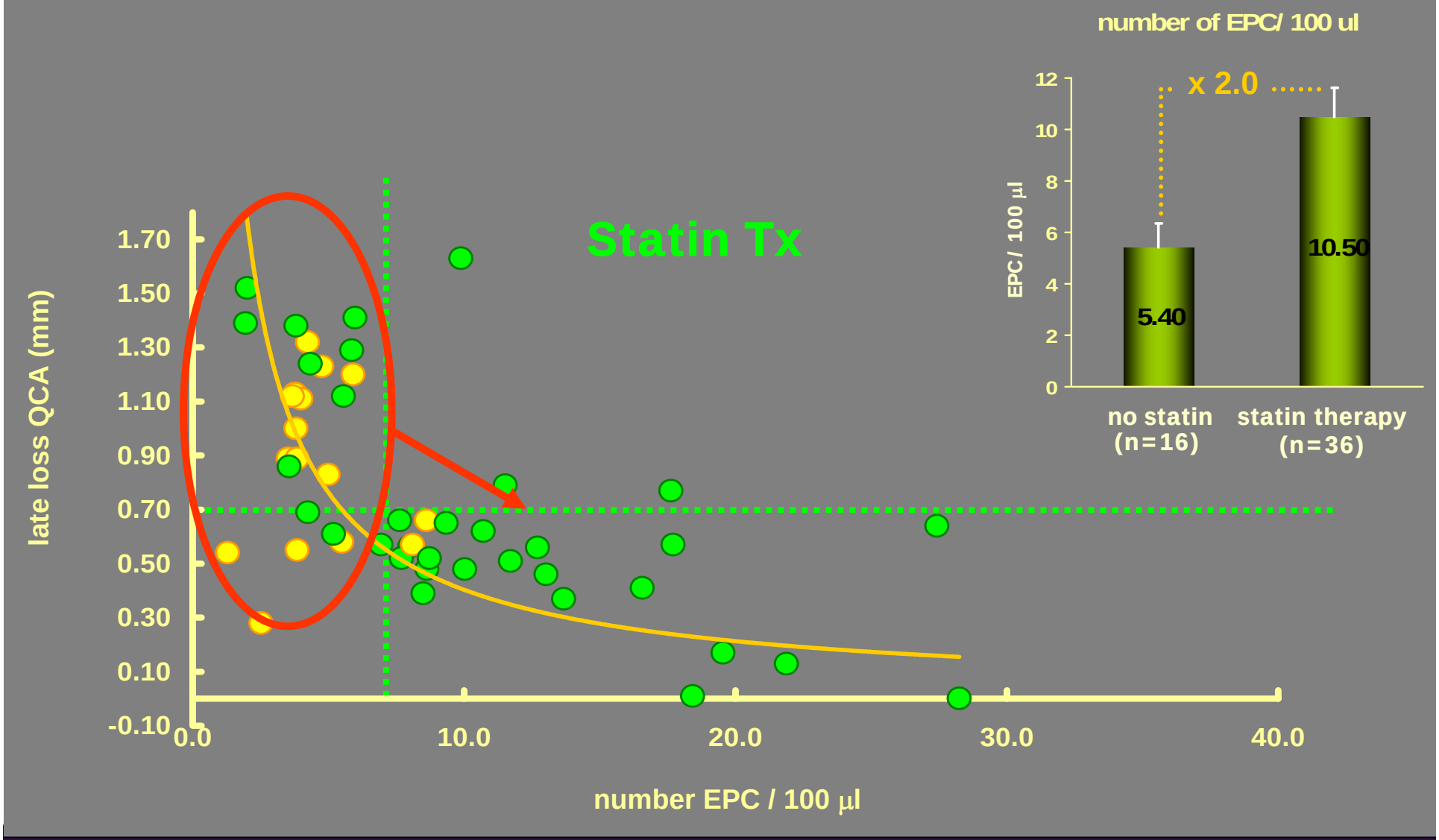
$p < 0.001$

* 2-tailed *t*-test

Correlation Late Luminal Loss and Circulating EPC Titer at 6 Months FU



Correlation Between Late Luminal Loss and Circulating EPC Titer at 6 Months FU



HEALING II Clinical Events and EPCs

GenOus

Major Adverse Cardiac Events
9 months*

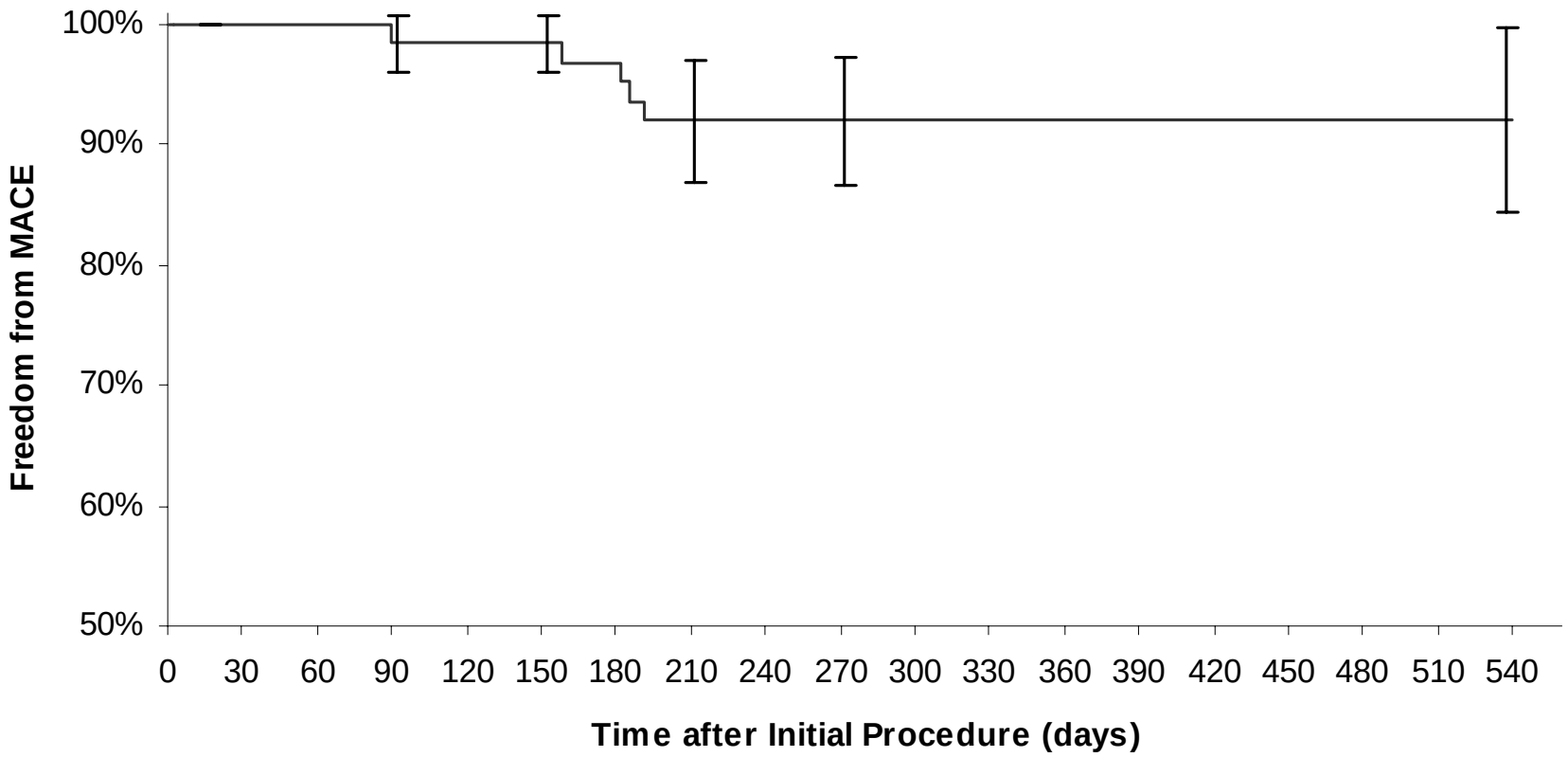
	H2 overall (n=63)	Low EPC (n=25)	Normal EPC (n=27)
Cardiac Death	1.6 %	0.0 %	0.0 %
MI	0.0 %	0.0 %	0.0 %
CABG	0.0 %	0.0 %	0.0 %
TLR (Clinically Driven)	6.3 %	8.0 %	0.0 %
MACE	7.9 %	8.0 %	0.0 %

Primary Endpoint: MACE at 30 days – 0%
Stent Thrombosis – 0%

*** 9 month window: +/- 1 month, no additional events reported from 6 month follow up**

MACE free to 18 months FU

Figure 14. Survival Free from Major Adverse Cardiac Event



No myocardial infarction or stent thrombosis reported out to 18 months.
No additional MACE between 6 and 18 months

MACE=cardiac death, MI, CABG, and clinically driven TLR

18 Month Angiographic Results In Stent Serial Analysis

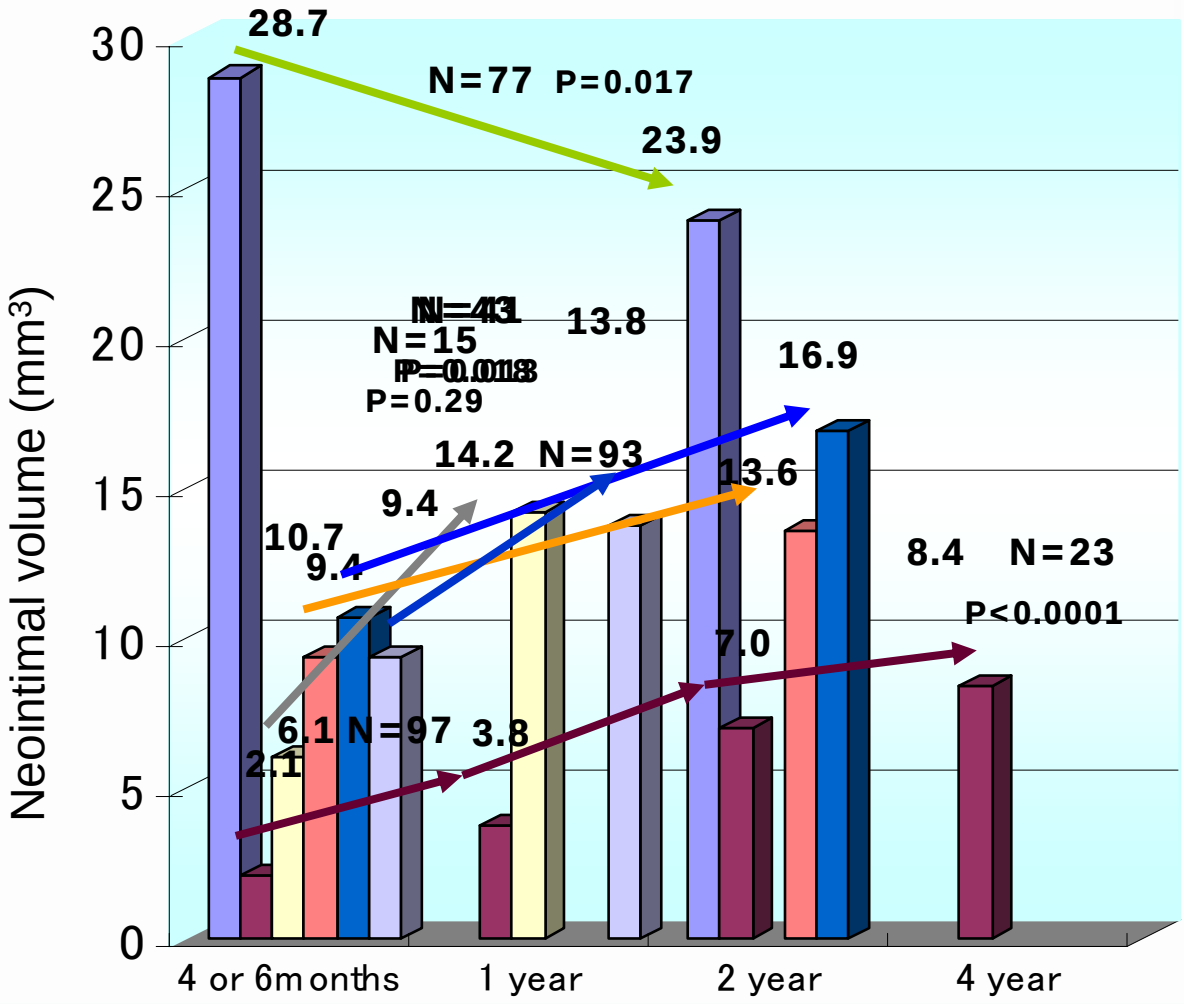
GenOus™

	Pre (n=30) mean ± SD	Post (n=29*) mean ± SD	6 month (n=30) mean ± SD	18 month (n=30) mean ± SD
RVD (mm)	2.62 ± 0.44	2.74 ± 0.38	2.50 ± 0.58	2.59 ± 0.50
MLD (mm)	1.00 ± 0.24	2.40 ± 0.32	1.69 ± 0.44	1.81 ± 0.41
DS (%)	61.3 ± 10.1	12.1 ± 5.9	31.5 ± 12.0	29.2 ± 11.7
Late Loss (mm)			0.71 ± 0.35	0.58 ± 0.31

* One post-procedure film not available

No additional MACE reported at 18 months.

Neointimal volume (mm^3) in DES clinical trials



Bare metal stent (from TAXUS II)*1

Sirolimus (FIM)*2

ABT-578 (ENDEAVOR)*3

TAXUS SR (TAXUS II)*1

TAXUS MR (TAXUS II)*1

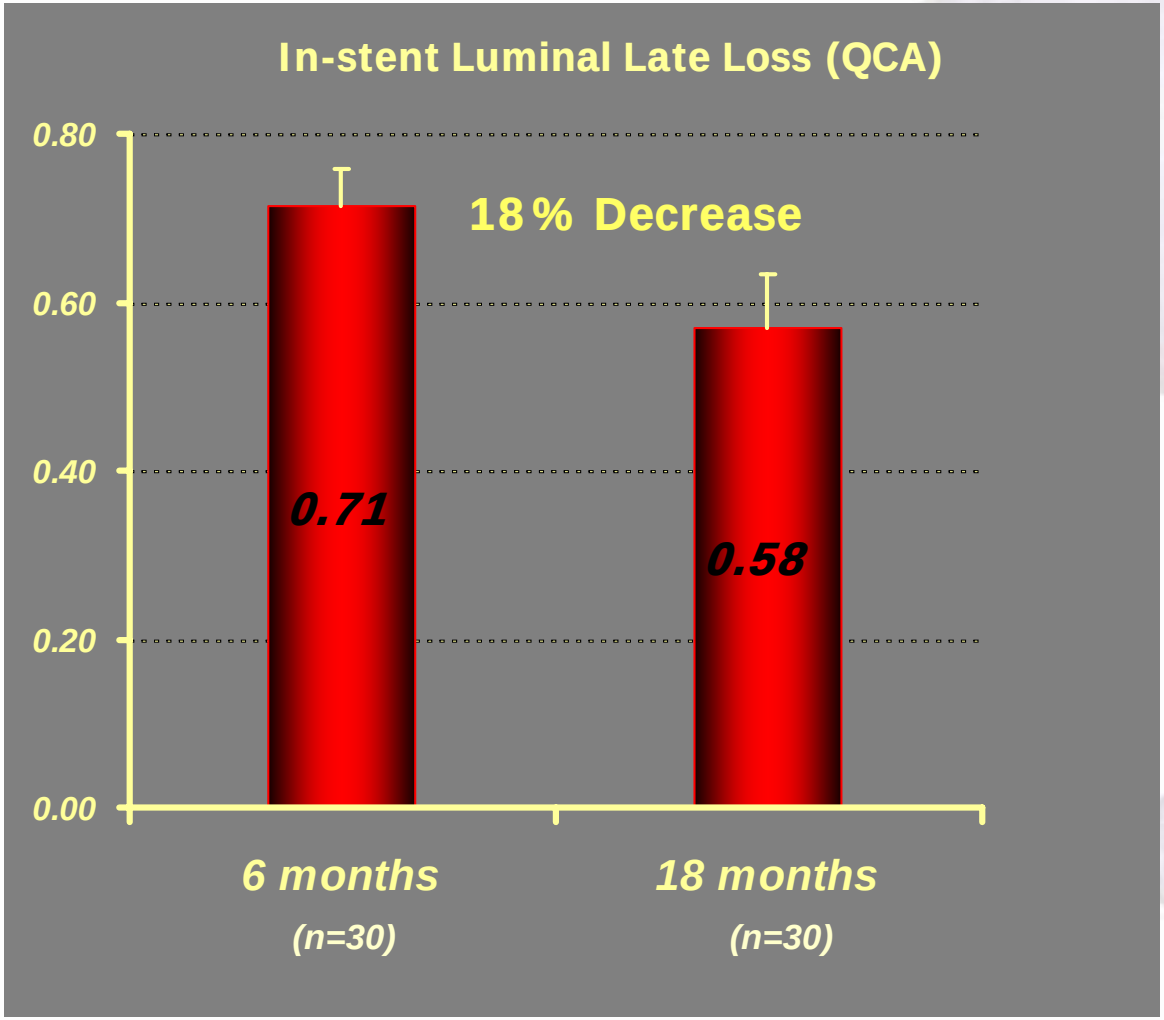
Conor (30day/30ug) (PISCES)*6

*1 Aoki, Serruys et al, Eurointerv 2005:1,253-255. *2 Aoki, Serruys et al, JACC 2005: 46(9):1670-6

*3 Meredith et al, EuroIntery 2005:1:157-164. *6 Aoki et al, EuroIntery 2005: 1:165-172

create

QCA Outcome of HEALING II
Serial Analysis of 6 & 18 Months FU



Interim 18 month data of patients which completed 6 & 18 month angiographic follow

e-HEALING Interim Analysis

Post Marketing Surveillance Registry of the
Genous Bio-engineered R stent

Interim Analysis

TCT 2006

e-HEALING Clinical Registry

Overview

- Principal Investigators: Prof. Silber and Dr. de Winter
- Multi-center (100-120 sites), worldwide, prospective registry of patients treated with a Genous Bio-engineered R stent in accordance with the Instructions for Use
- Recommendation of at least two weeks statin treatment prior to the procedure and one month clopidogrel post-procedure
- Follow-up: 1, 6, and 12 month clinical follow-up
- Primary outcome: Target Vessel Failure at 12 months

Status - 3354 patients entered to April 18th 2007

e-HEALING Clinical Registry Patient Demographics

Age	63.2 years
Males	77.9%
Diabetics	28.1%
Hypertension	64.4%
Hypercholesterolemia	76.1%
Current Smokers	23.8%
Family History	28.2%

Previous MI	38.4%
Previous PCI	21.7%
Previous CABG	6.7%
Previous Stroke	5.5%

n=1906; patients treated before October 20, 2006

e-HEALING Clinical Registry Lesion Characteristics

De novo	97.4%
Restenotic	2.6%

Lesion Classification	
Type A	19.1%
Type B1	36.2%
Type B2	26.9%
Type C	17.8%

Lesion Length (mm)	
Mean ± Std Dev	16.5 ± 8.6

Reference Vessel (mm)	
Mean ± Std Dev	3.0 ± 0.4

Number of stents/patient	1.5
Number of lesions/patient	1.4

n=1906; patients treated before October 20, 2006

e-HEALING Clinical Registry Clinical Events at 30 Days

	n=1286
Cardiac Death	**0.47 %**
MI	**1.01 %**
Q-wave	0.15 %
Non Q-wave	0.86 %
TLR (Clinically Driven)	**0.07 %**
PCI	0.07 %
CABG	0 %
MACE	**1.56 %**

Acute stent thrombosis	**0.15 %**
Sub acute thrombosis	**0.39 %**

patients treated before June 27, 2006; 96.2% compliance

all events adjudicated by CEC and worst case scenario assumed / final adjudication of events ongoing

MACE=cardiac death, MI, CABG, and clinically driven TLR

e-HEALING Clinical Registry

Registry	Product	30 Days	
		MACE	SAT
e- HEALING *	Genous	1.6%	0.4%
e-CYPHER[1]	CYPHER	1.4%	0.6%
ARRIVE 1[2]	Taxus	2.7%	1.3%

* Interim results of 1286 patients treated before June 27, 2006; 96.2% compliance; all events adjudicated by CEC and worst case scenario assumed / final adjudication of events ongoing

[1] N= 15,157 / Urban, et al, Safety of Coronary Sirolimus-Eluting Stents in Daily Clinical Practice, Circulation, 2006; 113:1434-1441.

[2] N= 2,586 / http://www.bostonscientific.com (unpublished data)

e-HEALING Clinical Registry
Clinical Events 30 Days - AMI sub-group

	n=69
Cardiac Death	**1.45 %**
MI	**0 %**
Q-wave	0 %
Non Q-wave	0 %
TLR (Clinically Driven)	**0 %**
PCI	0 %
CABG	0 %
MACE	**1.45 %**
Acute stent thrombosis	**0 %**
Sub-acute thrombosis	**1.45 %**

patients treated before June 27, 2006
all events adjudicated by CEC and worst case scenario assumed / final adjudication of events ongoing
MACE=cardiac death, MI, CABG, and clinically driven TLR

e-HEALING Clinical Registry

Clinical Events in patients with 6 month follow-up

	30 days	6 months
Cardiac Death	**0.28 %**	**1.11 %**
MI	**1.67 %**	**2.78 %**
Q-wave	0.28 %	0.56 %
Non Q-wave	1.39 %	2.22 %
TLR (Clinically Driven)	**0 %**	**2.78 %**
PCI	0 %	2.50 %
CABG	0 %	0.28 %
MACE	**1.94 %**	**6.67 %**

Acute stent thrombosis	**0 %**	
Sub-acute stent thrombosis	**0.56 %**	
Late stent thrombosis		**0 %**

Interim results as of September 27, 2006, Hierarchical, n=360

patients treated before January 24, 2006; 87.5% compliance
all events adjudicated by CEC
MACE=cardiac death, MI, CABG, and clinically driven TLR

e-HEALING Clinical Registry

Registry	Product	6 Months	
		MACE	Stent Thrombosis
e-HEALING *	Genous	6.7%	0.6%
e-CYPHER[1]	CYPHER	3.4%	0.9%
ARRIVE 1	Taxus	4.3%[2]	1.6%[3]

*Interim results of 360 patients treated before January 24, 2006; 87.5% compliance

all events adjudicated by CEC and worst case scenario assumed / final adjudication of these events ongoing

[1] N=14,190 / Urban, et al, Safety of Coronary Sirolimus-Eluting Stents in Daily Clinical Practice, *Circulation*, 2006; 113:1434-1441.

[2] N=2,532 / Lasala, Snapshot of DES Use and Outcomes in the US: ARRIVE Program, presented March 11, 2006 at ACC, Atlanta, GA, USA (unpublished data)

[3] N=2,522 & 2,511 / Boston Scientific brochure titled "Taxus™ Stent Clinical Trial and Registry Summary July 2006". 34 of 2,522 (1.3%) patients reported for Stent Thrombosis 0- 30 days and 7 of 2,511 (0.3%) patients reported for Stent Thrombosis 31-180 Days. (unpublished data)

e-HEALING Clinical Registry

Clinical Events in Diabetes Mellitus patients with 6 month F/U

	30 days	6 months
Cardiac Death	**0.94 %**	**1.89 %**
MI	**0.94 %**	**2.83 %**
Q-wave	0.94 %	0.94 %
Non Q-wave	0 %	1.89 %
TLR (Clinically Driven)	**0 %**	**0.94 %**
PCI	0 %	0.94 %
CABG	0 %	0 %
MACE	**1.89 %**	**5.66 %**

Acute stent thrombosis	**0 %**
Sub-acute stent thrombosis	**0.94 %**
Late stent thrombosis	**0 %**

patients treated before January 24, 2006; 87.5% compliance
all events adjudicated by CEC
MACE=cardiac death, MI, CABG, and clinically driven TLR

e-HEALING Clinical Registry

Clinical Events in TIMI 0/1 patients with 6 month F/U

	30 days	6 months
Cardiac Death	**1.30 %**	**2.60 %**
MI	**0 %**	**0 %**
Q-wave	0 %	0 %
Non Q-wave	0 %	0 %
TLR (Clinically Driven)	**0 %**	**2.60 %**
PCI	0 %	2.60 %
CABG	0 %	0 %
MACE	**1.30 %**	**5.19 %**

Acute stent thrombosis	**0 %**
Sub-acute stent thrombosis	**1.30 %**
Late stent thrombosis	**0 %**

patients treated before January 24, 2006; 87.5% compliance
all events adjudicated by CEC
MACE=cardiac death, MI, CABG, and clinically driven TLR

Conclusions

- The interim data from the e-HEALING Registry demonstrate that the Genous Bio-engineered R stent is safe and effective
- The 1.6% MACE and 0.4% SAT rates at 30 days in 1,286 patients are low
- Six month F/U data show favorable MACE rates with no late thrombosis
- Interim data from the AMI sub-group suggests Genous is safe in this high risk patient population
- Interim data from TIMI 0/1 subgroup show excellent long term TVR rates
- Further analyses with a larger cohort of patients with longer term follow-up is ongoing

HEALING
Clinical Development Program

Statin Dosing and EPC Level Study

- Multi-center study designed to evaluate the relationship of statins and EPC levels. Statin-naive CAD patients will receive different doses of atorvastatin followed by serial measurements of EPCs

HEALING IIB

- Multi-center, prospective trial designed to assess the safety and effectiveness of the Genous Stent, in conjunction with optimal statin therapy, in patients with *de novo* native coronary artery lesions

HEALING
Clinical Development Program

HEALING AMI

- Multi-center, prospective feasibility study designed to assess the safety and effectiveness of the Genous Stent patients with acute ST elevation myocardial infarctions

TRIAS

- Multi-center (30-40 sites) randomized trial comparing Genous with DES (high risk for restenosis) and Genous with BMS (low risk for restenosis)

Single Center Experience

Presented on Behalf of e-HEALING
principal investigator Robbert de Winter
as presented on March 25th at ACC

The HEALING program

Robbert J de Winter

Academic Medical Center
University of Amsterdam
The Netherlands

AMC single center experience

- Genous stents sept ’05 – feb ’07
- 251 patients
  - bifurcated lesions 27%
  - Long lesions, small vessels, ISR after DES, LM
  - Contra indications Clopidogrel (surgery, allergy)
  - Most pts on statin therapy ≥ 1 week prior to procedure
- One month dual anti-platelet therapy

AMC single center experience

Baseline characteristics	N = 251
Age	64 ± 11
Male	75 %
Hypertension	43 %
Hypercholesterolemia	50 %
Smoking	20 %
Diabetes mellitus	16 %
Previous MI	37 %
Previous PCI	29 %
Previous CABG	5 %
Stable angina	90 %
Unstable angina	6 %
MI	4 %

AMC single center experience

Lesion characteristics	N = 335
Lesion type	
A	19 %
B1	22 %
B2	34 %
C	25 %
RCA	21 %
LAD	48 %
RCX	26 %
LM	5 %
Stent diameter (mm)	3.2 ± 0.4
Stent length (mm)	24 ± 10

AMC single center experience

Six months clinical follow up	n = 152	
	N	%
Mortality		
cardiac	1	0.7
non-cardiac	1	0.7
MI		
peri-procedural	3	2
6 months	1	0.7
TVR		
PCI	4	2.6
CABG	1	0.7
MACE	6	3.9
Cardiac death, MI, TVR		

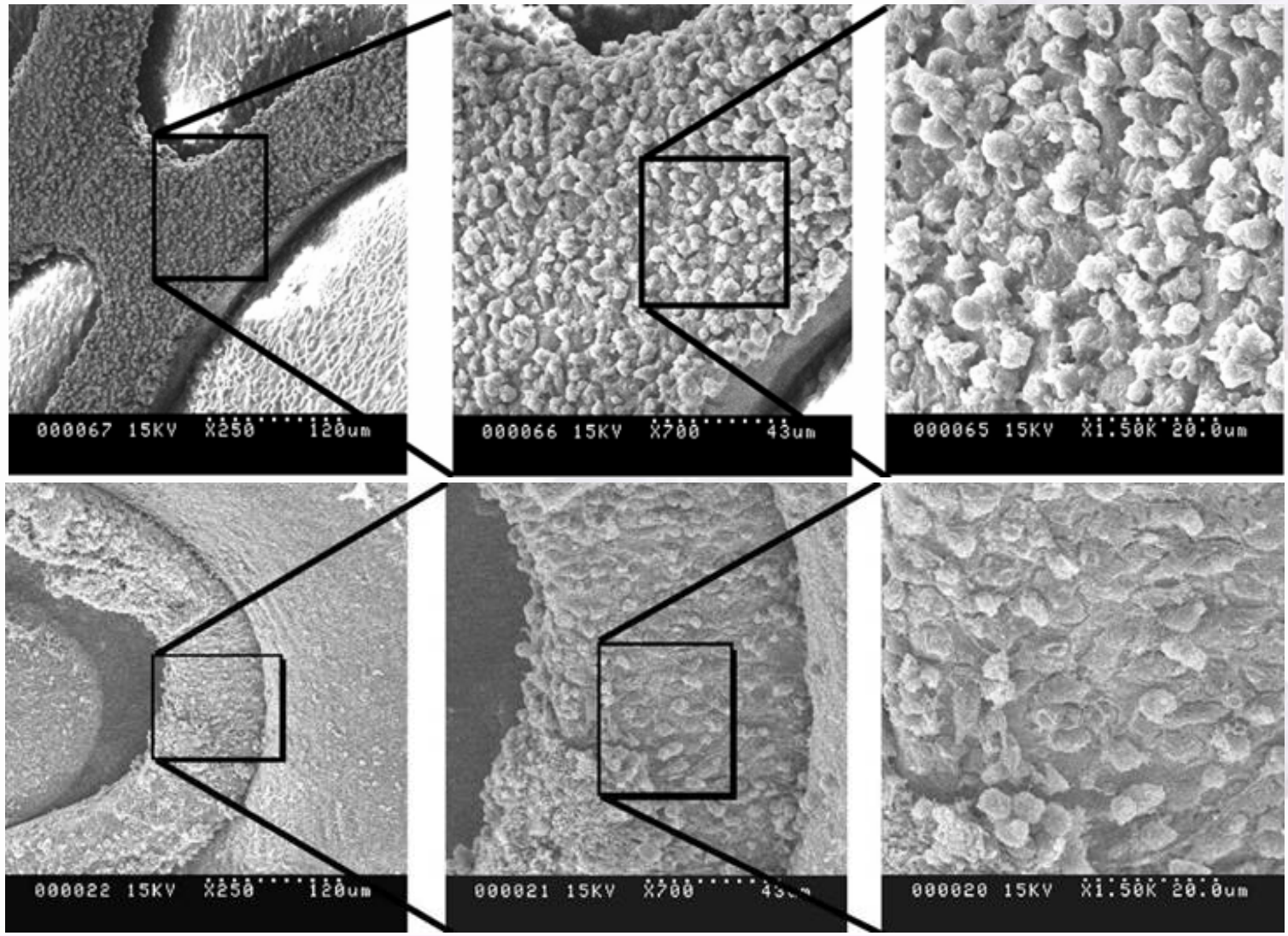
AMC single center experience

- High procedural success
- No late stent thrombosis
- All lesion types
- All patient subsets
- Repeat revascularization is low

EPC Capture
Advanced R&D Projects

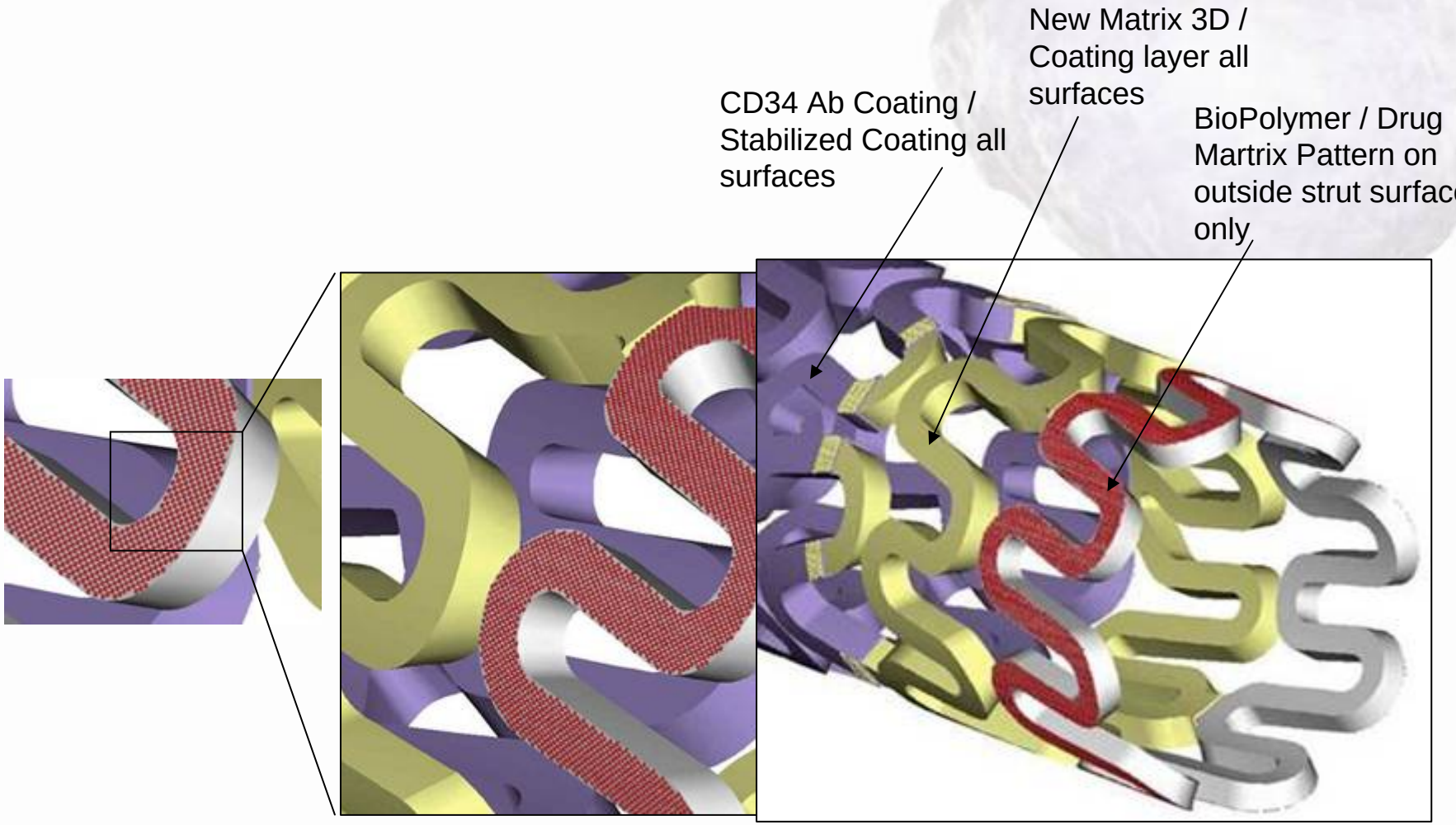
Cobalt Chromium Genous

1 Hour Pig Coronary Artery Explant – GENOUS on L605 CoCr



L605 Cobalt Chromium R stent Combination GENOUS/DES

DES/EPC Coronary R stent

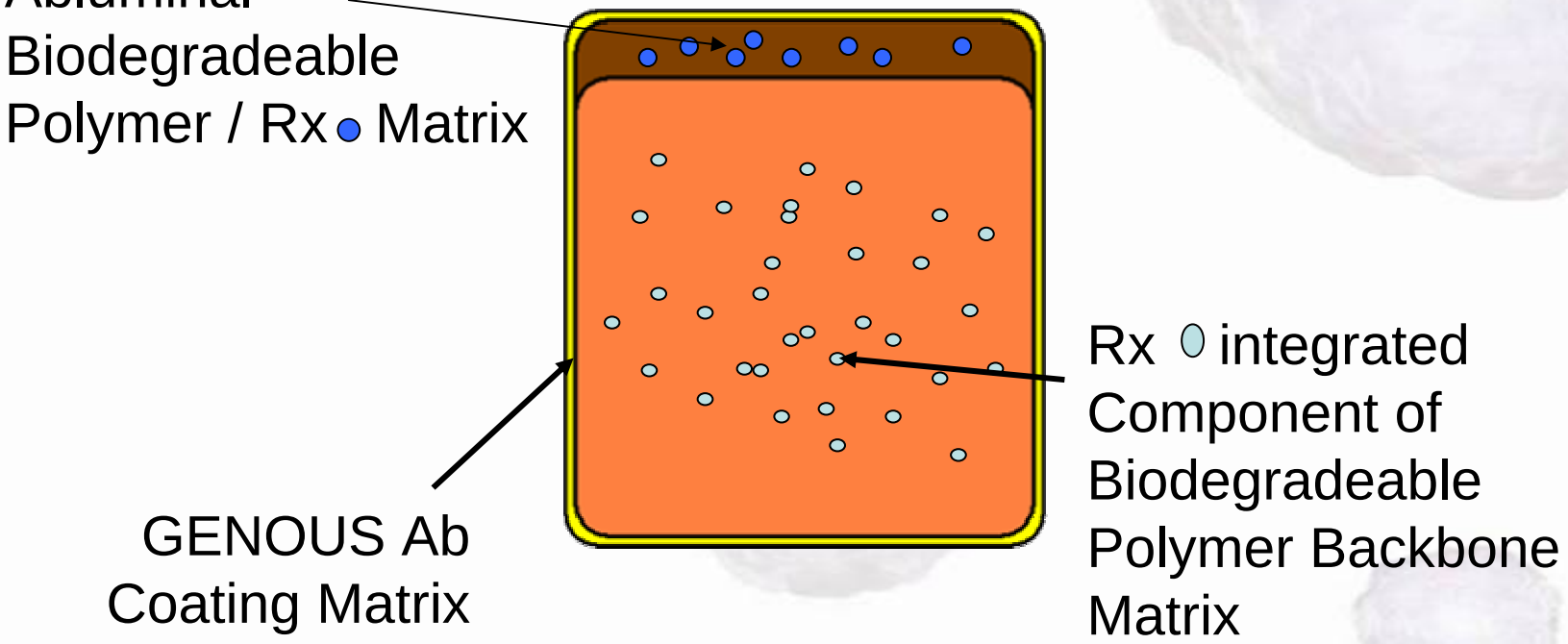


Fully Absorbable Combination Drug Eluting and EPC Capturing Coronary R stent

The Ultimate Dream

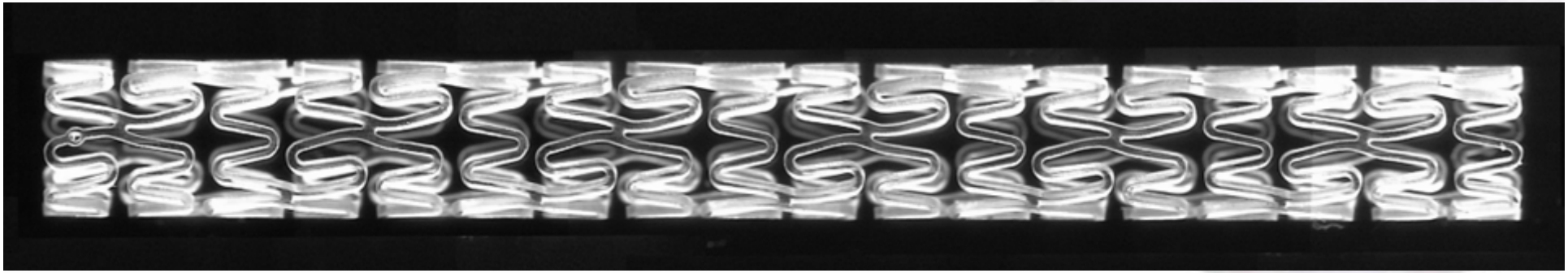
Develop a biodegradable, drug eluting, endothelial cell capturing platform, which performs mechanically equivalent to the current DES field... and then disappears.

Bioabsorbable R stent

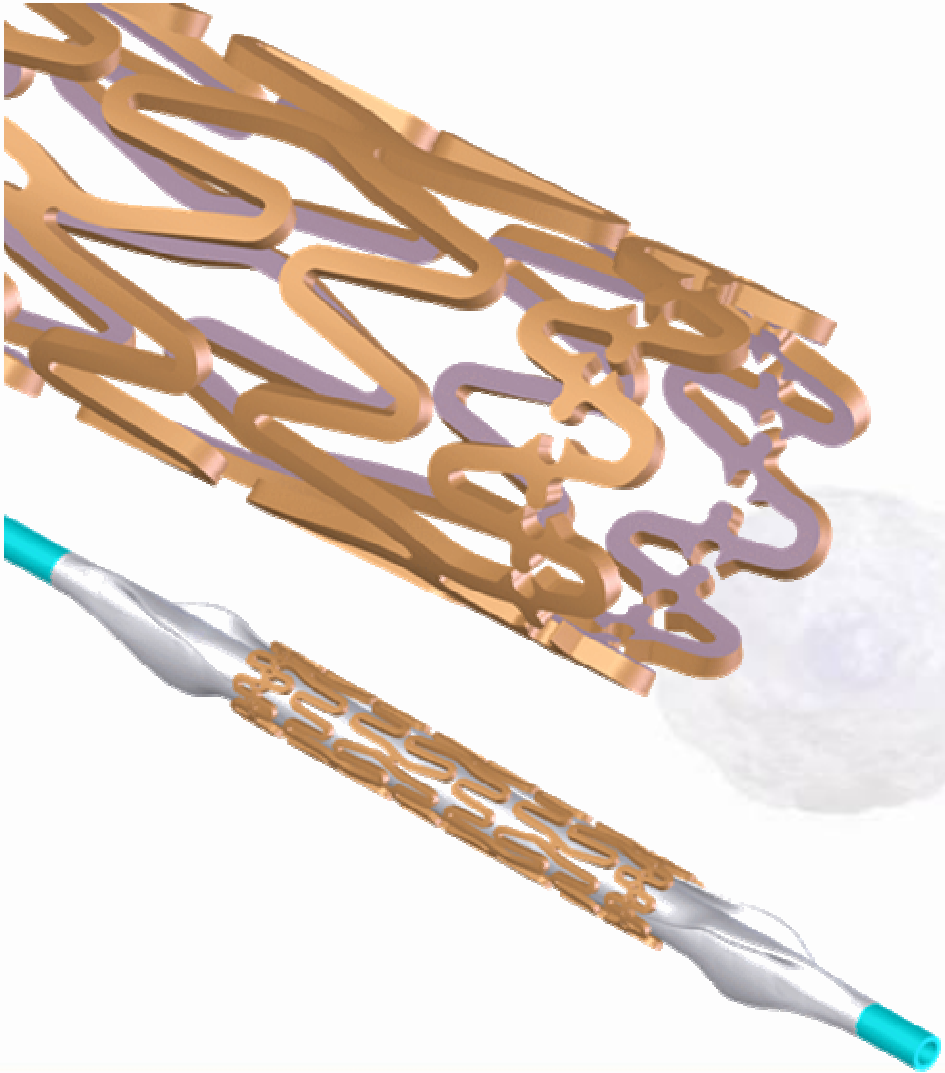


Design Iteration

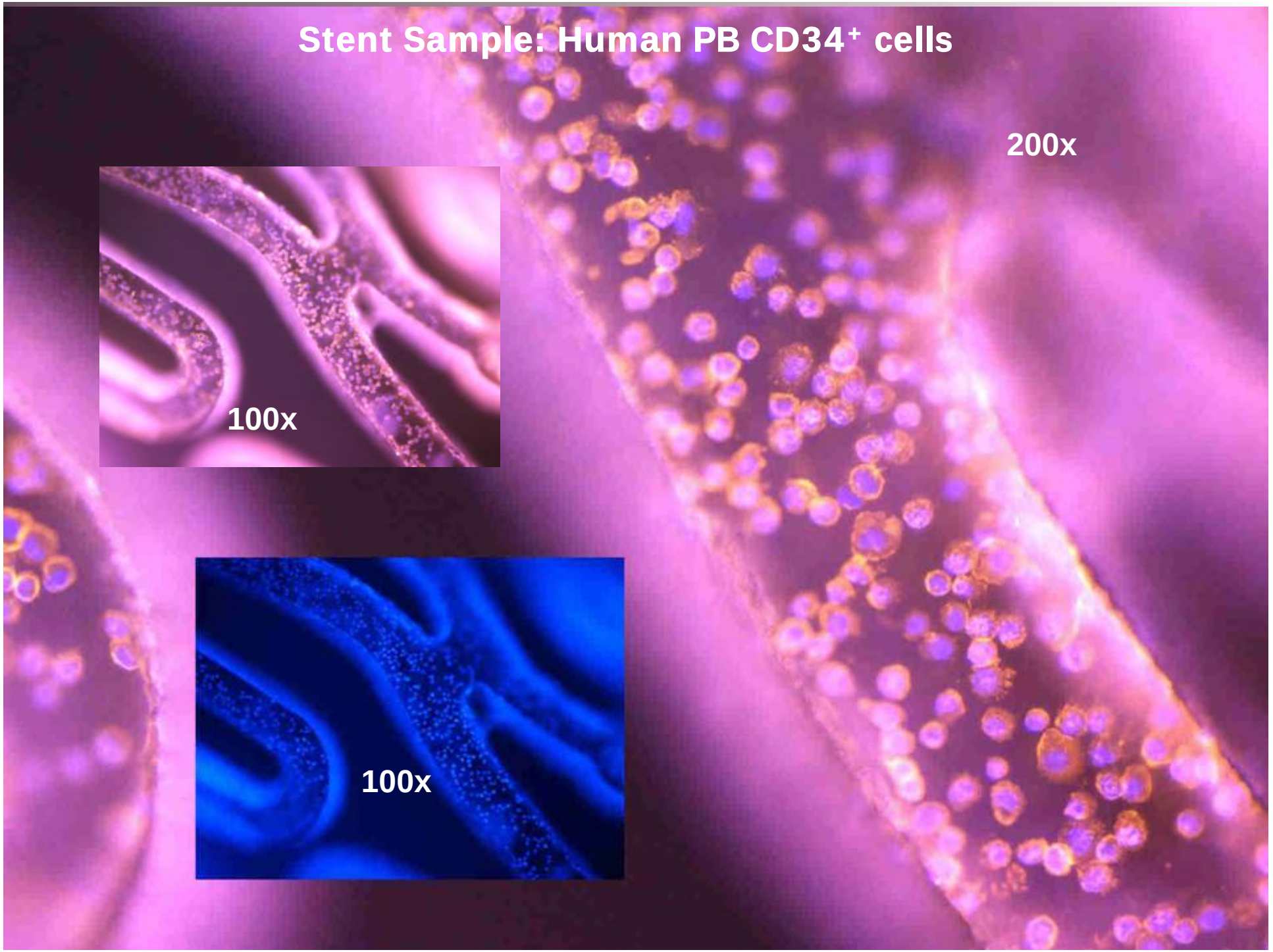
GenOus™



Stent Retention Features



- Snap-fit features to lock stent in crimped position
- Provide adequate stent retention force


Stent Sample: Human PB CD34+ cells
200x
100x
100x