Genous Endothelial Progenitor Capture Technology

Michael JB Kutryk
Angioplasty Summit - TCT Asia Pacific
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DES Rollercoaster

"Despite the implantation of millions of drug-eluting stents, uncertainty remains uncertain about their long-term safety."

We Need Better Technologies!

Maisel W et al., NEJM 2007

create

Genous Stent

Genous Healing Approach

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

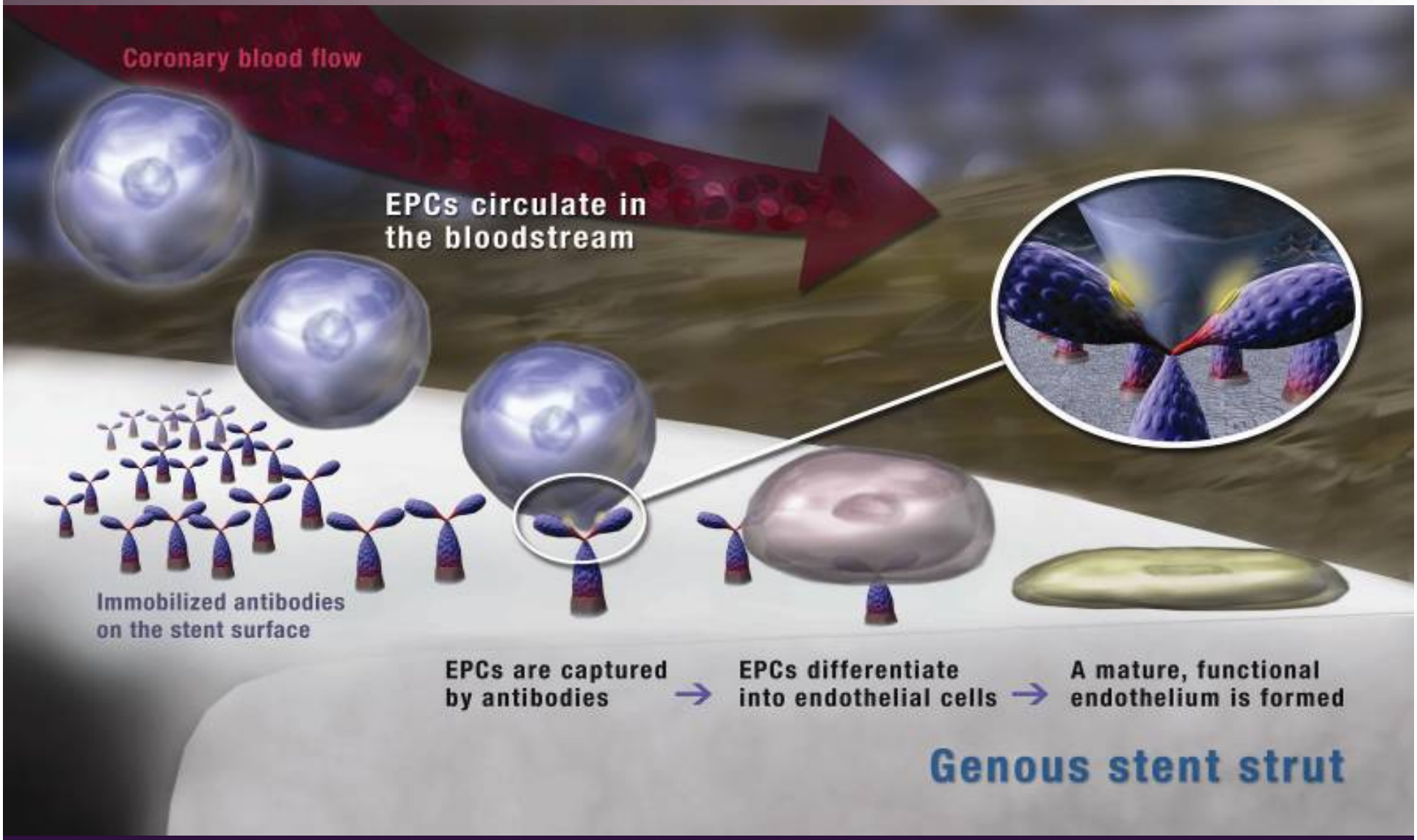
- **Genous Protects Against Thrombus Formation**

  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.

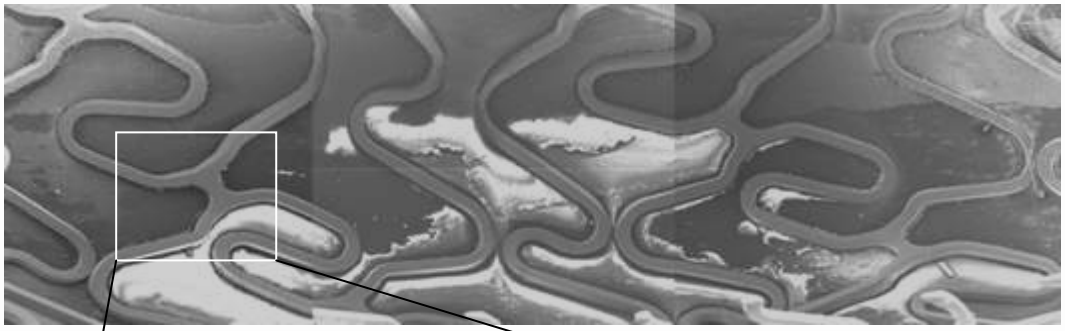
- **Genous Minimizes Restenosis**

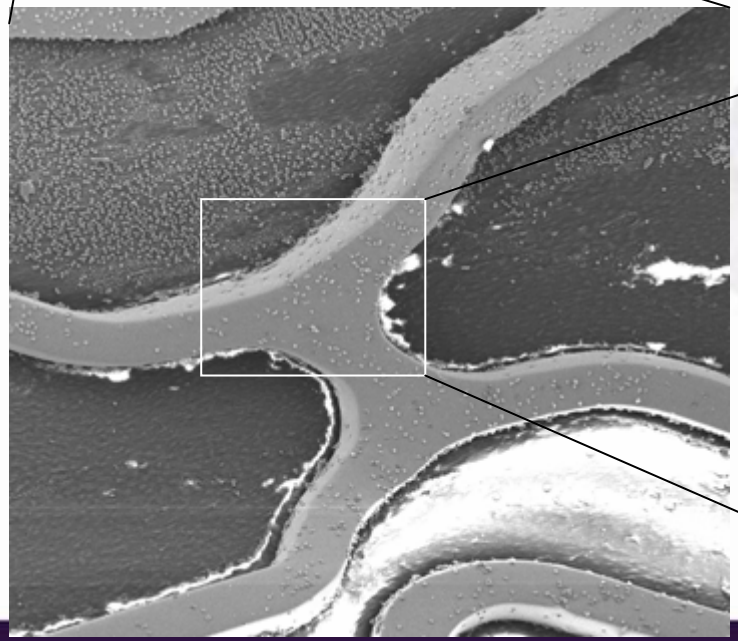
  The establishment of a healthy endothelium modulates the healing response and inhibits excessive neointimal proliferation.

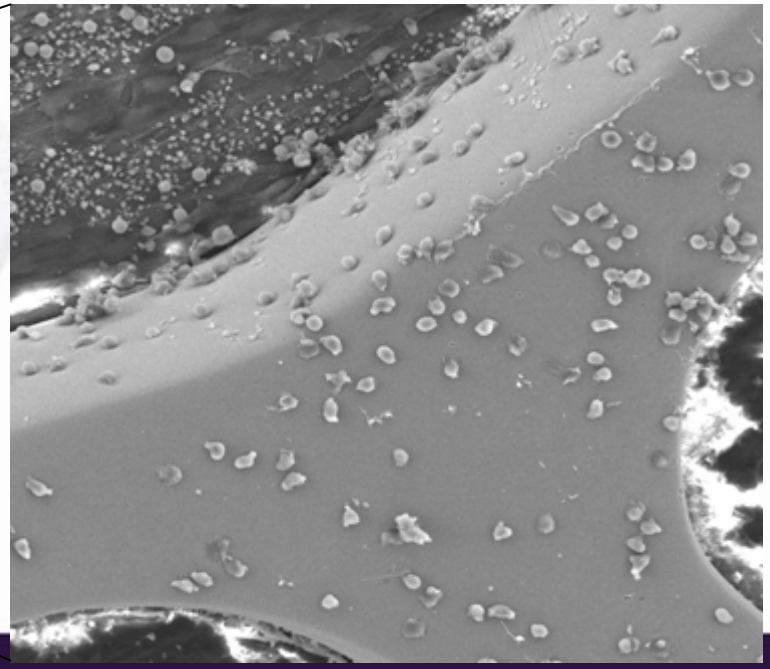
EPC Capture Technology



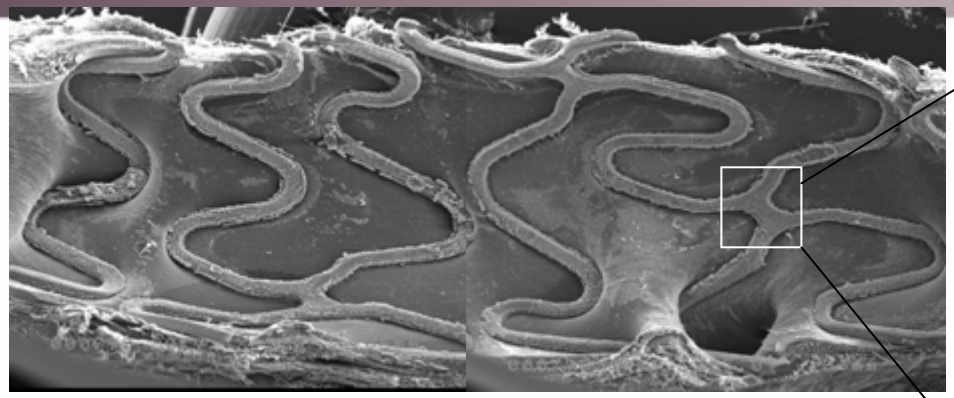
1 Hour Explants - Control Stent

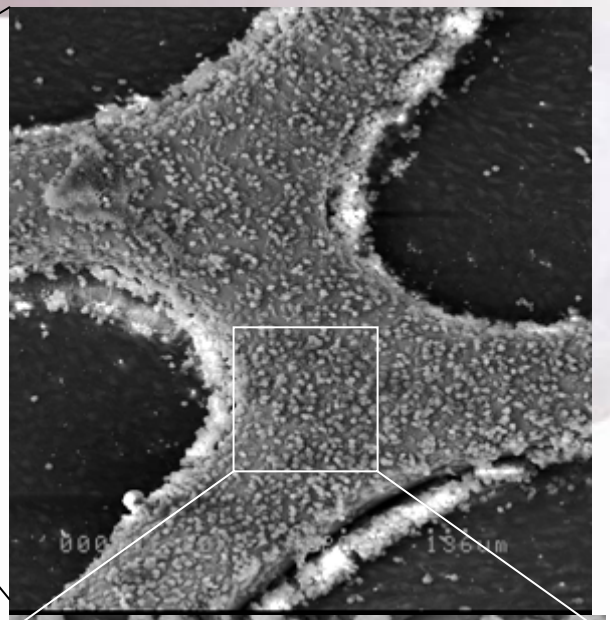


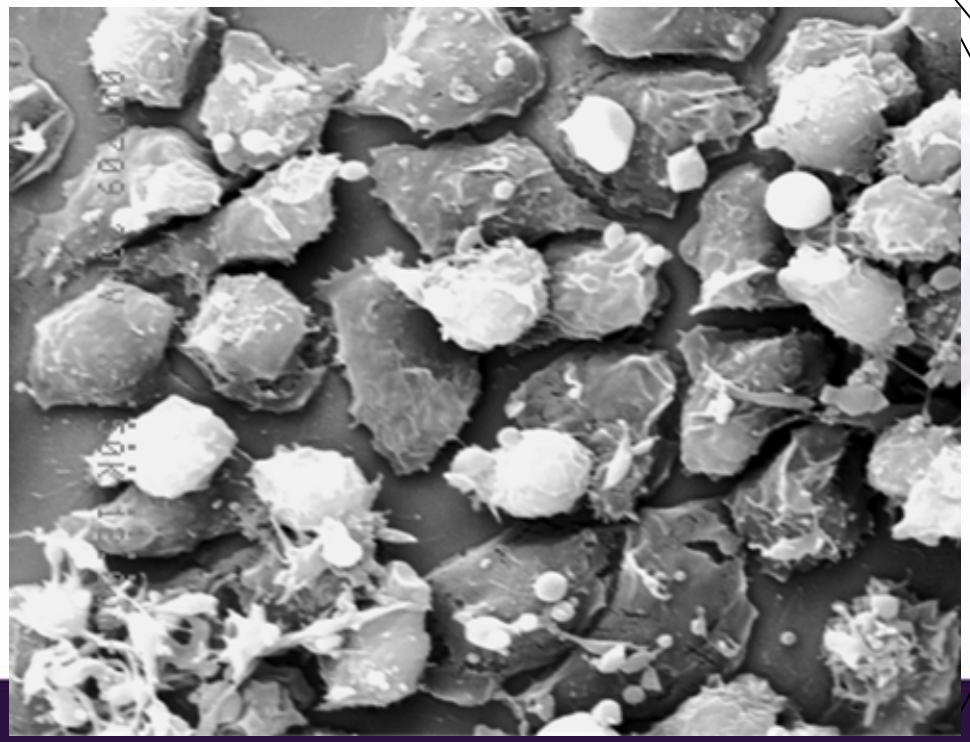


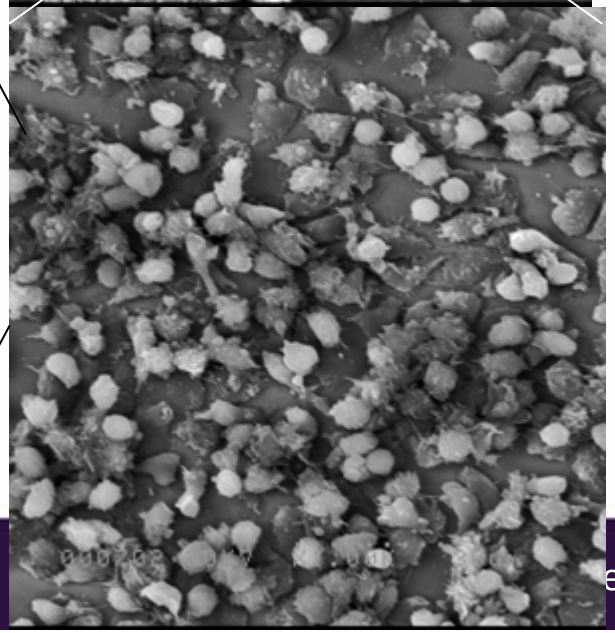


1 Hour Explants - Genous Stent

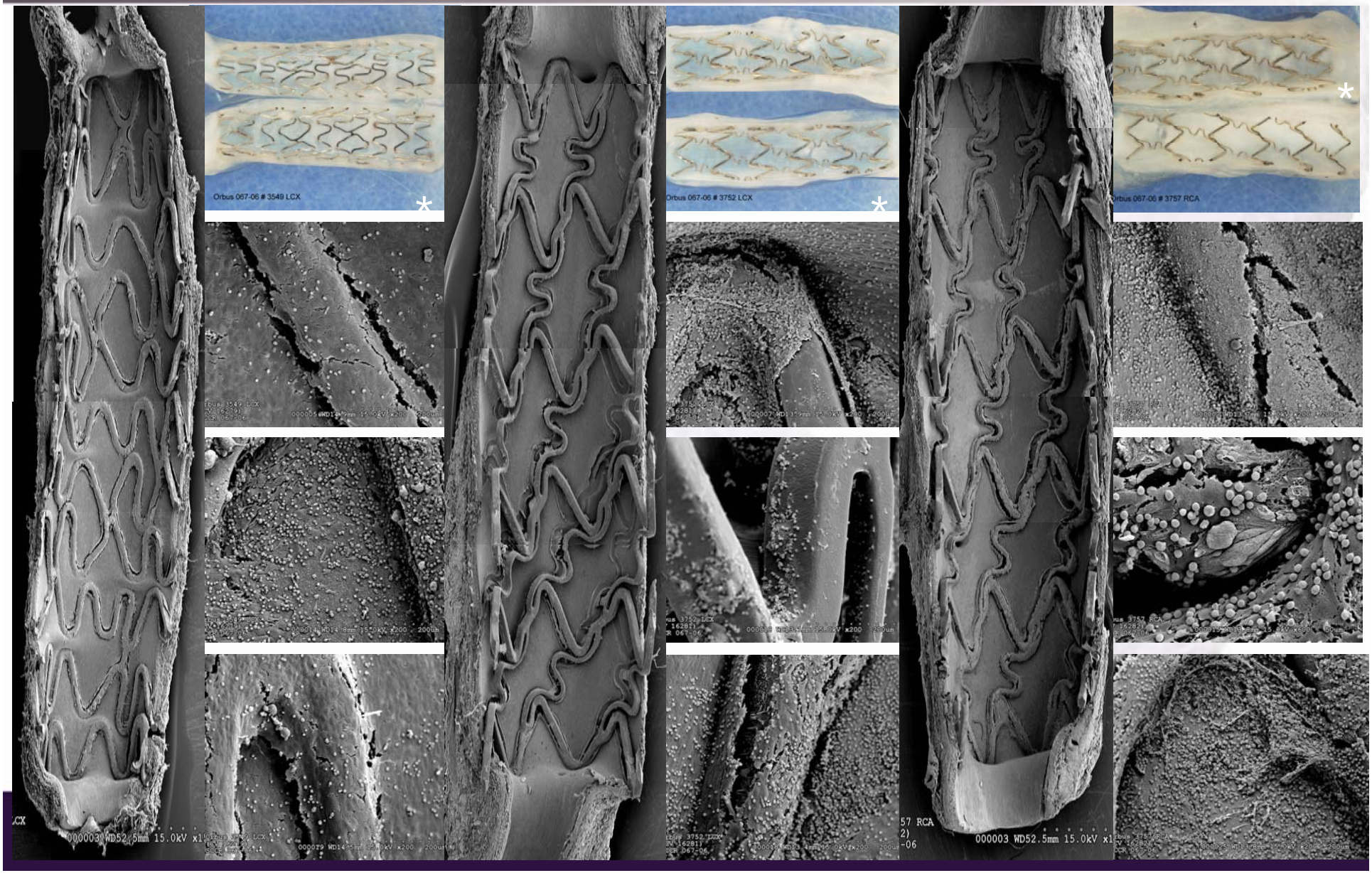




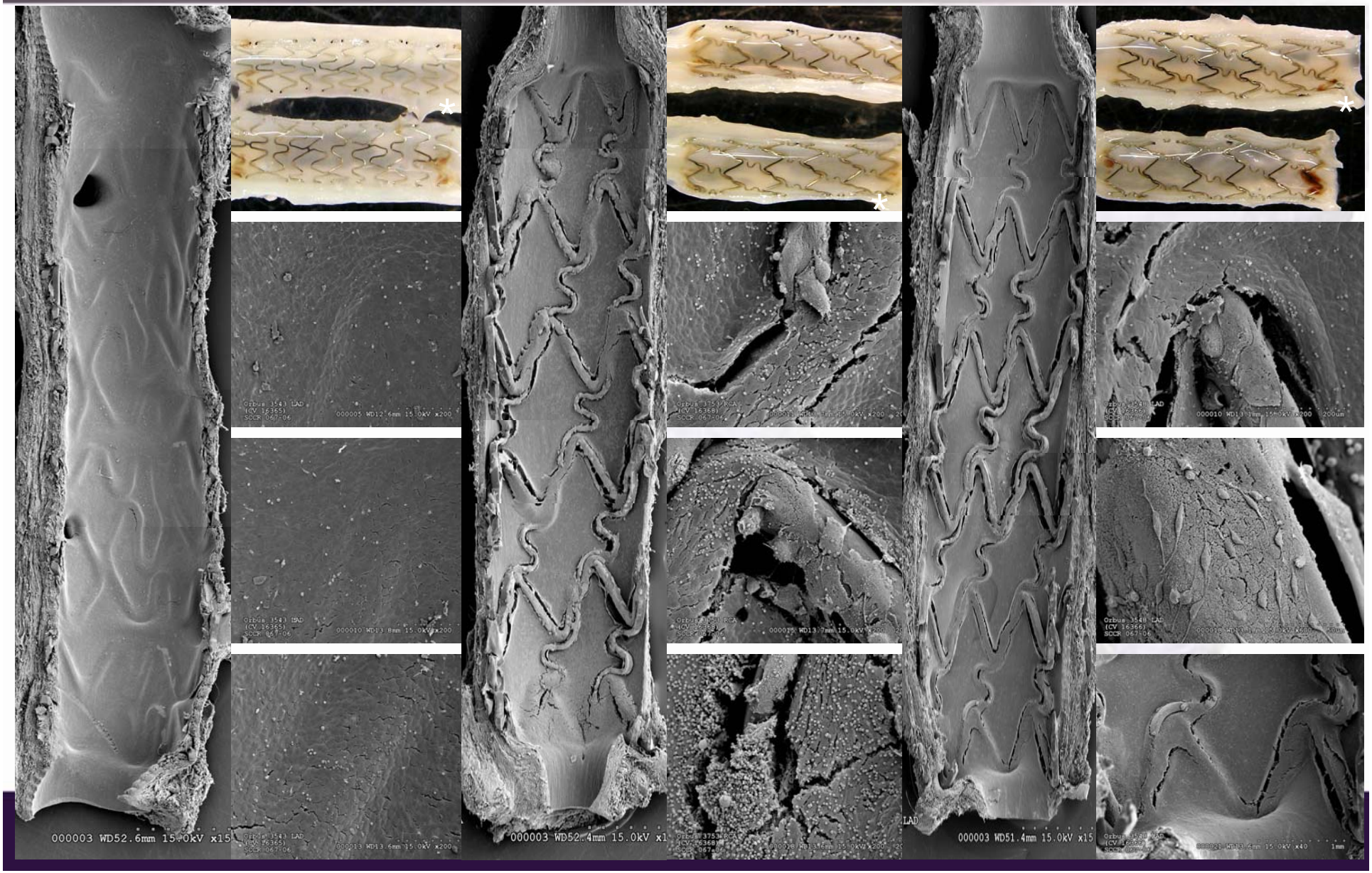




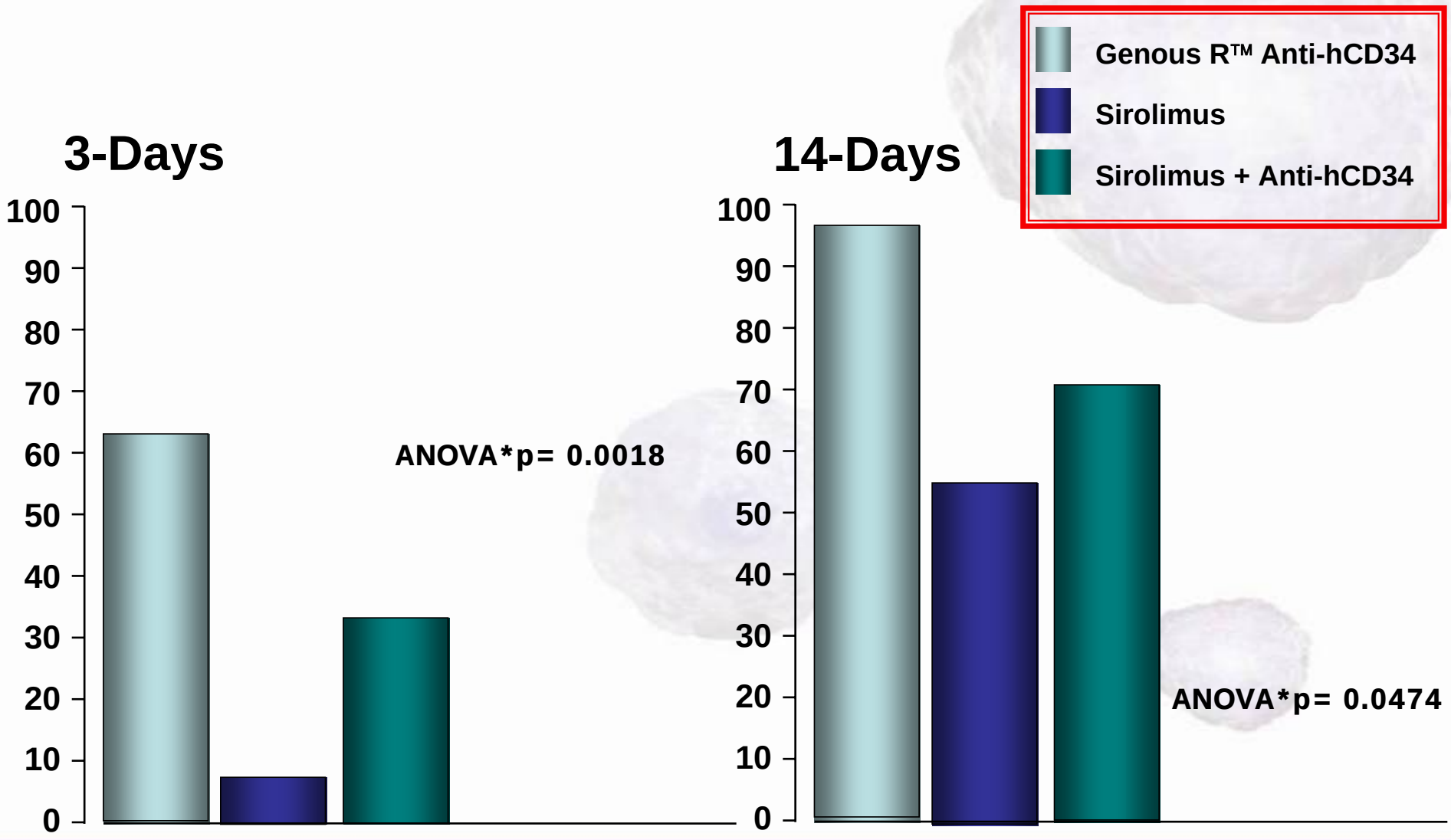
Surface Images of 3 day Genous, and Sirolimus ± Anti-hCD34 Stented Arterial Explants



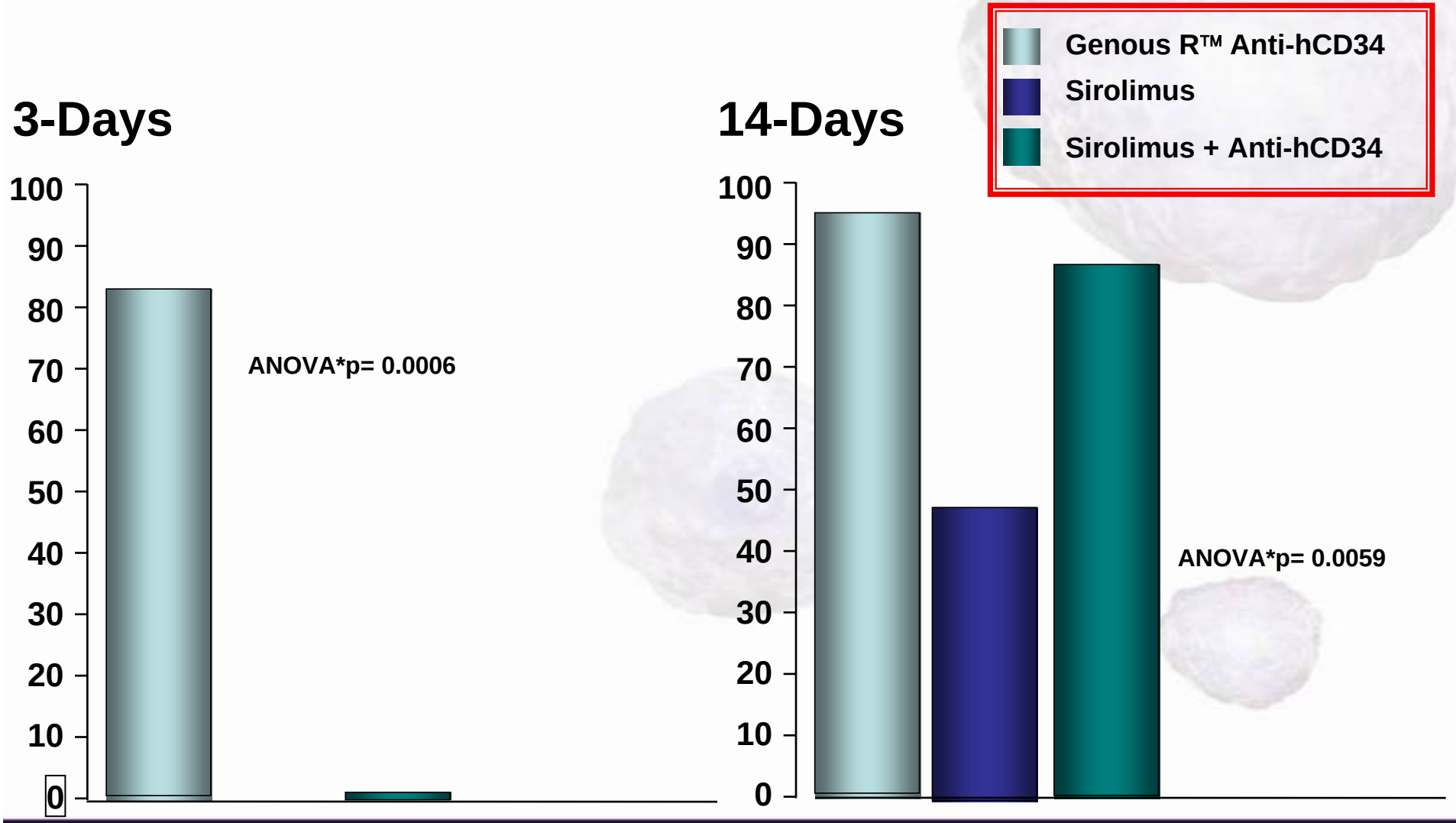
Surface Images of 14 day Genous, and Sirolimus ± Anti-hCD34 Stented Arterial Explants



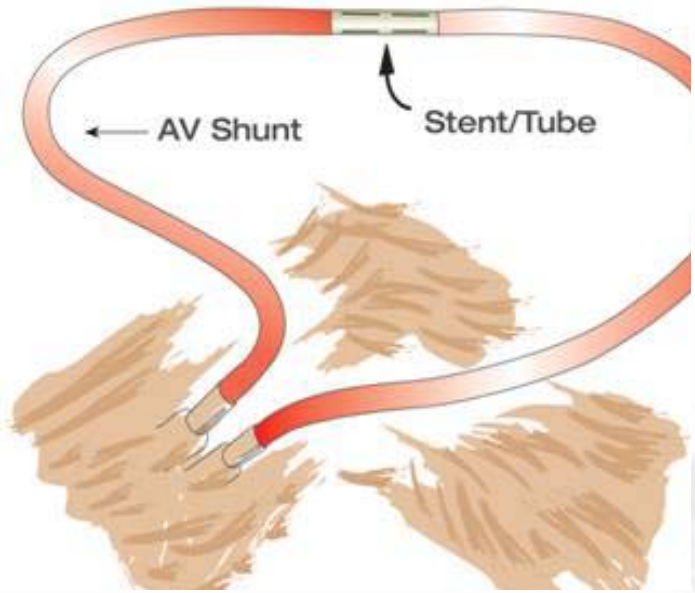
Luminal Re-Endothelialization (%) Over Struts in 3- and 14-Day Swine Coronary Stents



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



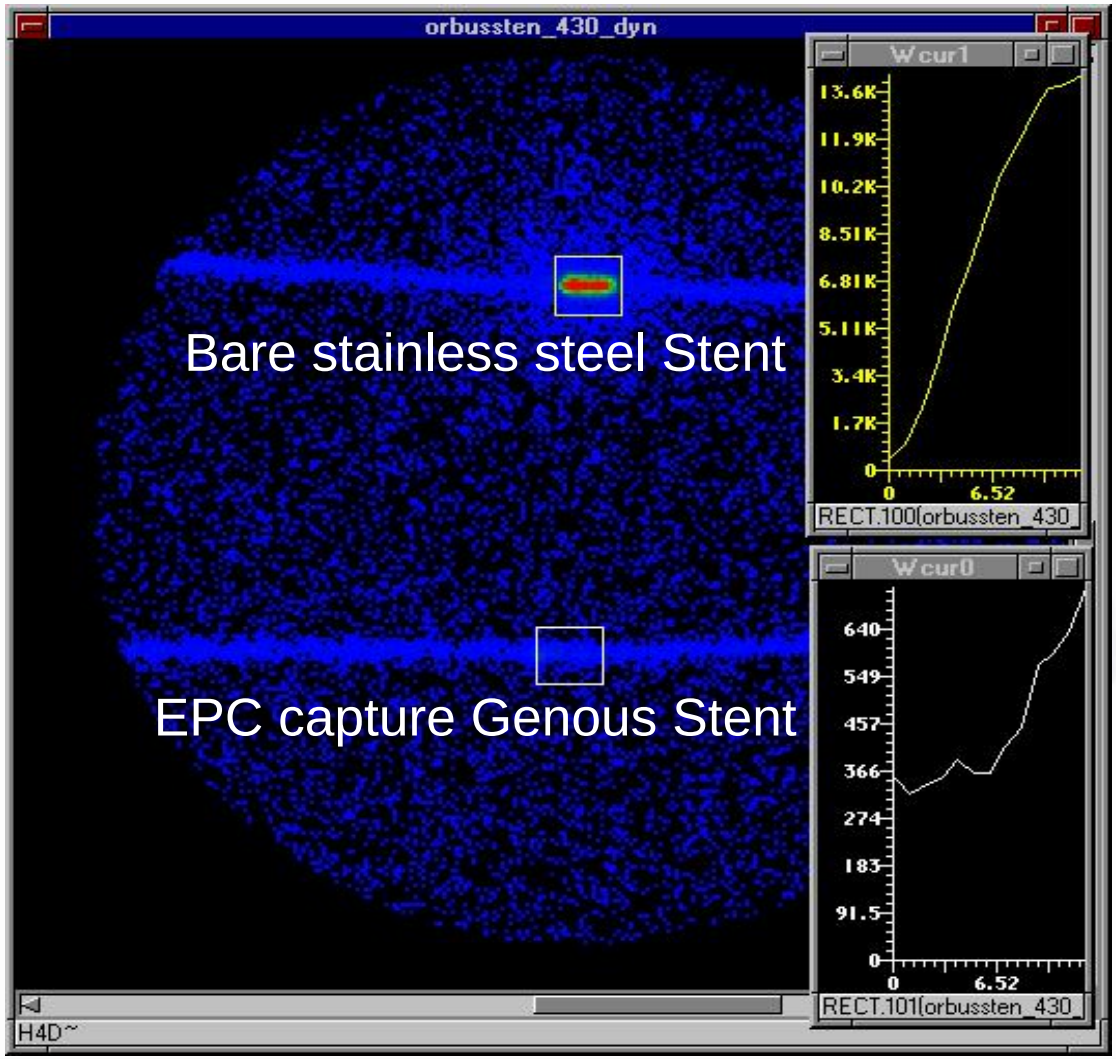
Ex vivo baboon AV shunt model
Genous and bare metal stent



Study Design

- Baboon chronic ex vivo AV shunt
- Platelets labeled with ^{111}In
- Gamma camera count recorded every 5 min
- Flow regulated at 100cc/min through shunt
- SEM observation
- No anticoagulation or antiplatelet therapy

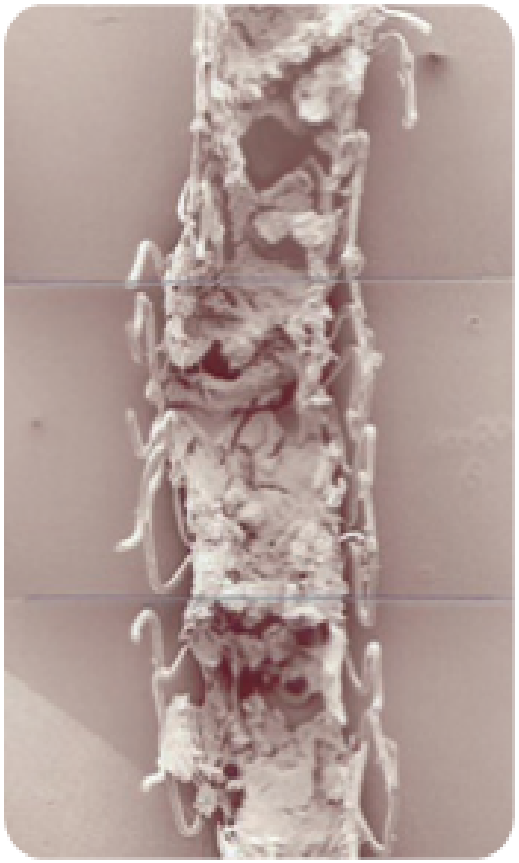
Baboon AV shunt
^{111}In labeled platelet deposition



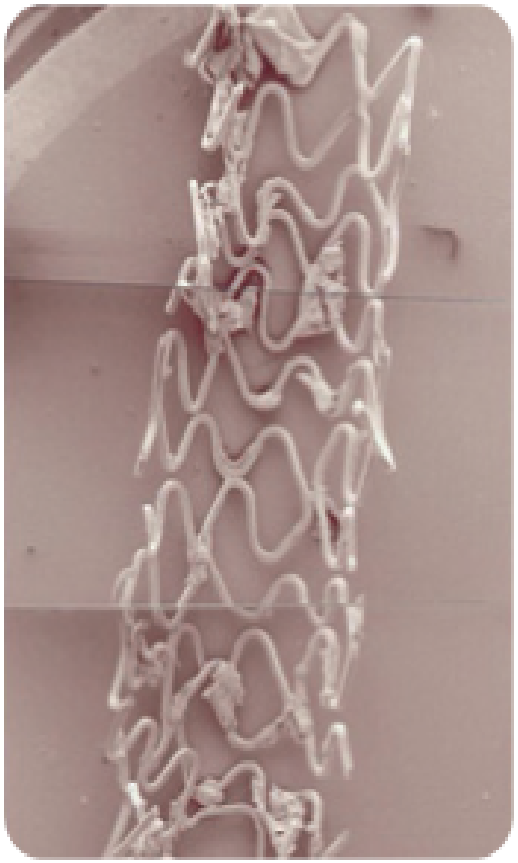
Terminated at 65 min
due to BMS obstruction

97% reduction at 65 min

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

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:
  - De novo native coronary lesions in vessels with reference vessels 2.5-3.5 mm
- Device:
  - Genous™ R stent (Orbus Nich) with anti-CD34 antibody for EPC capture
- Indication:
  - Demonstrate the safety and efficacy of a stent designed for EPC capture
- Follow-up:
  - Quantitative coronary angiography and IVUS analysis at 6 (and 18) months
  - Clinical follow-up 6, 9 and 18 months

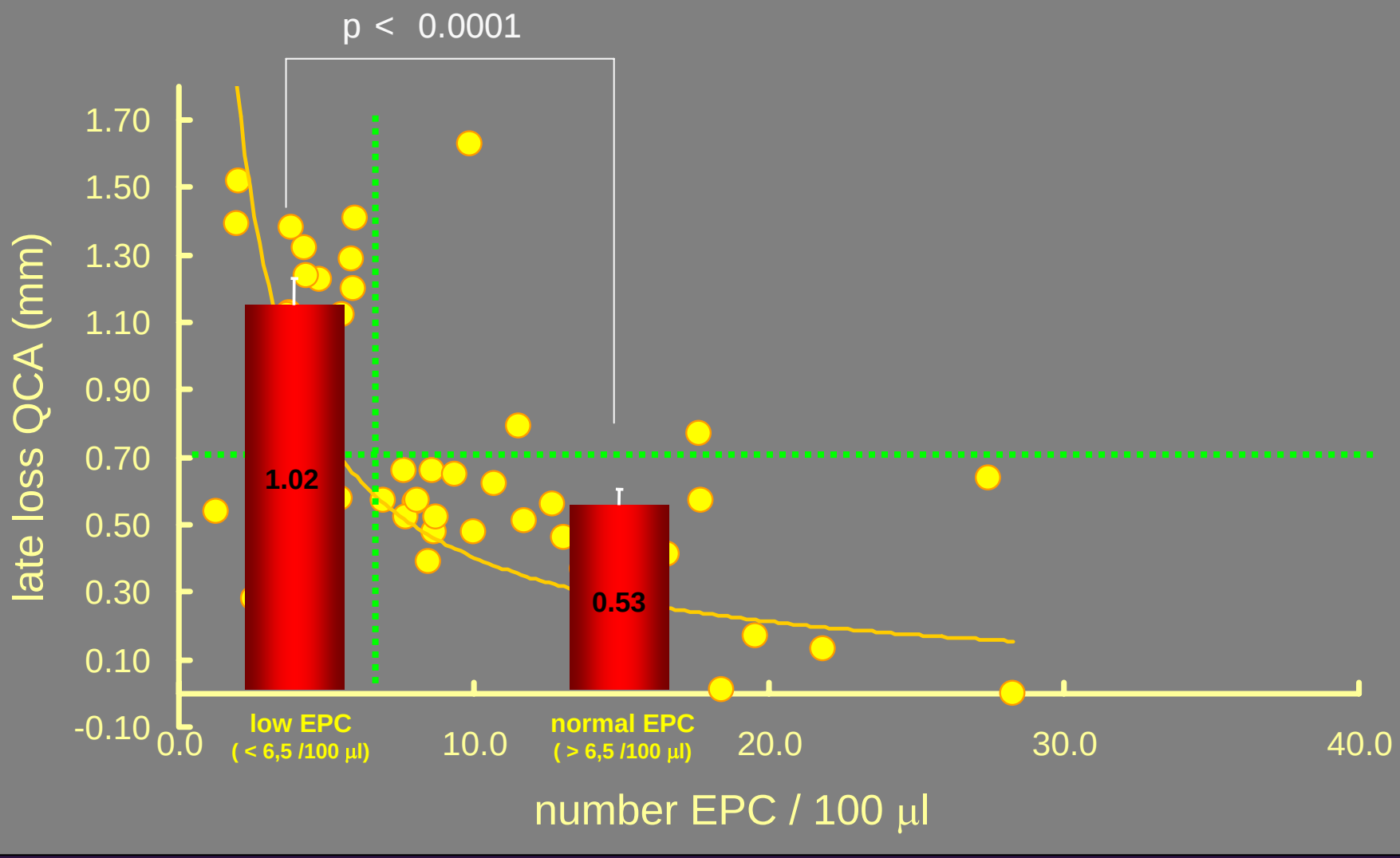
HEALING II - Late Luminal Loss

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

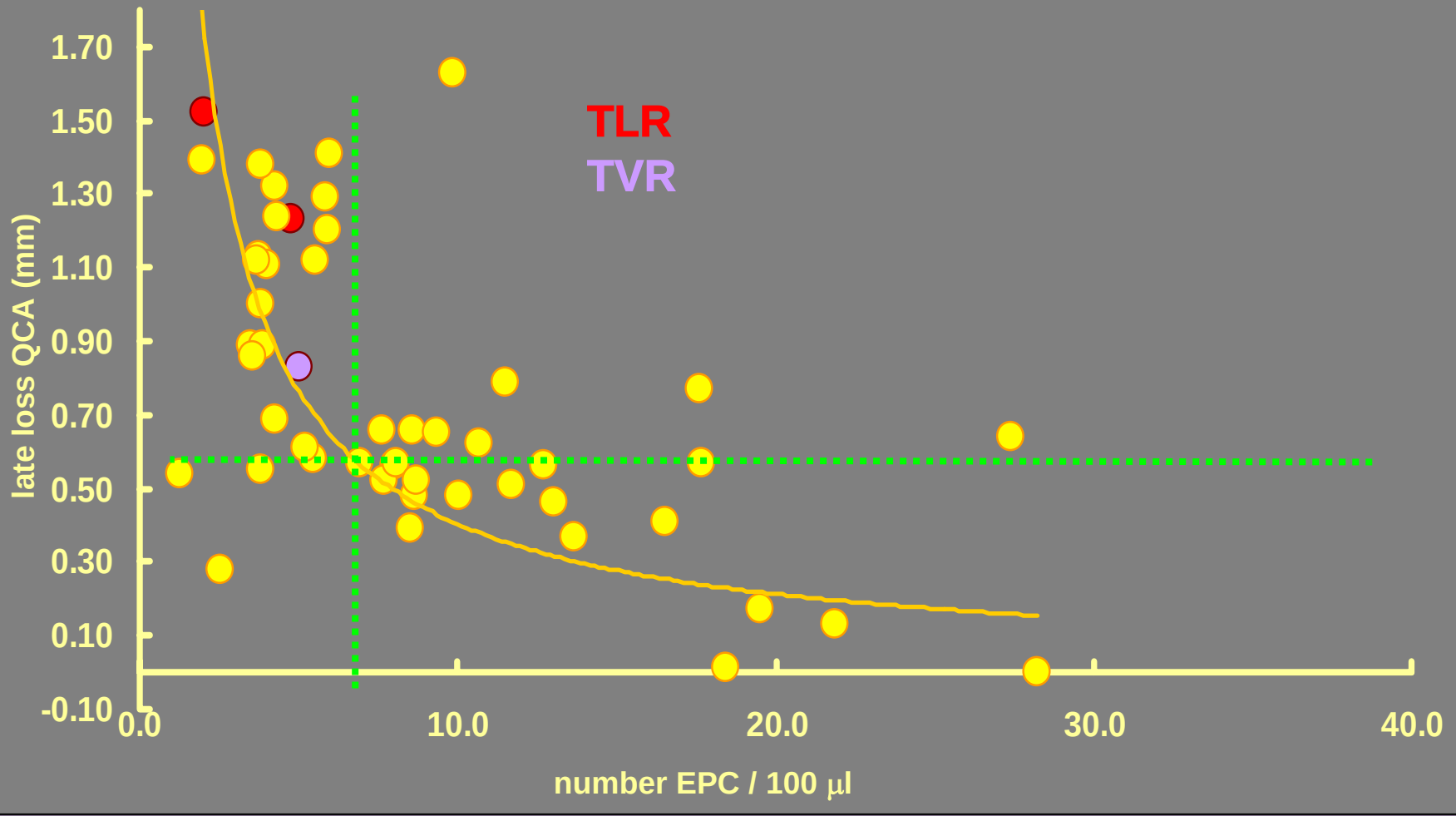
$p < 0.001$

* 2-tailed *t*-test

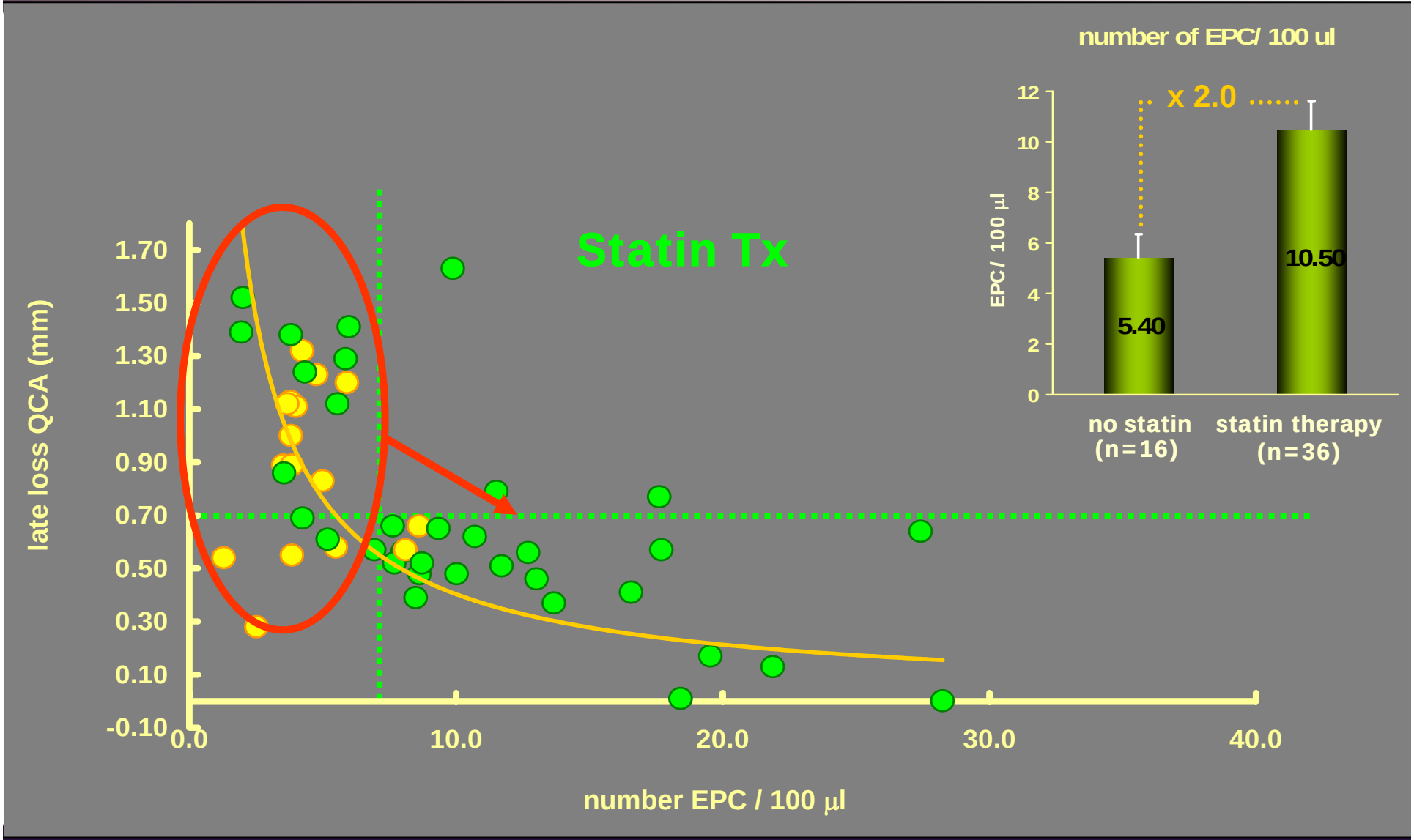
Correlation Late Luminal Loss and Circulating EPC Titer at 6 Months FU



Correlation 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

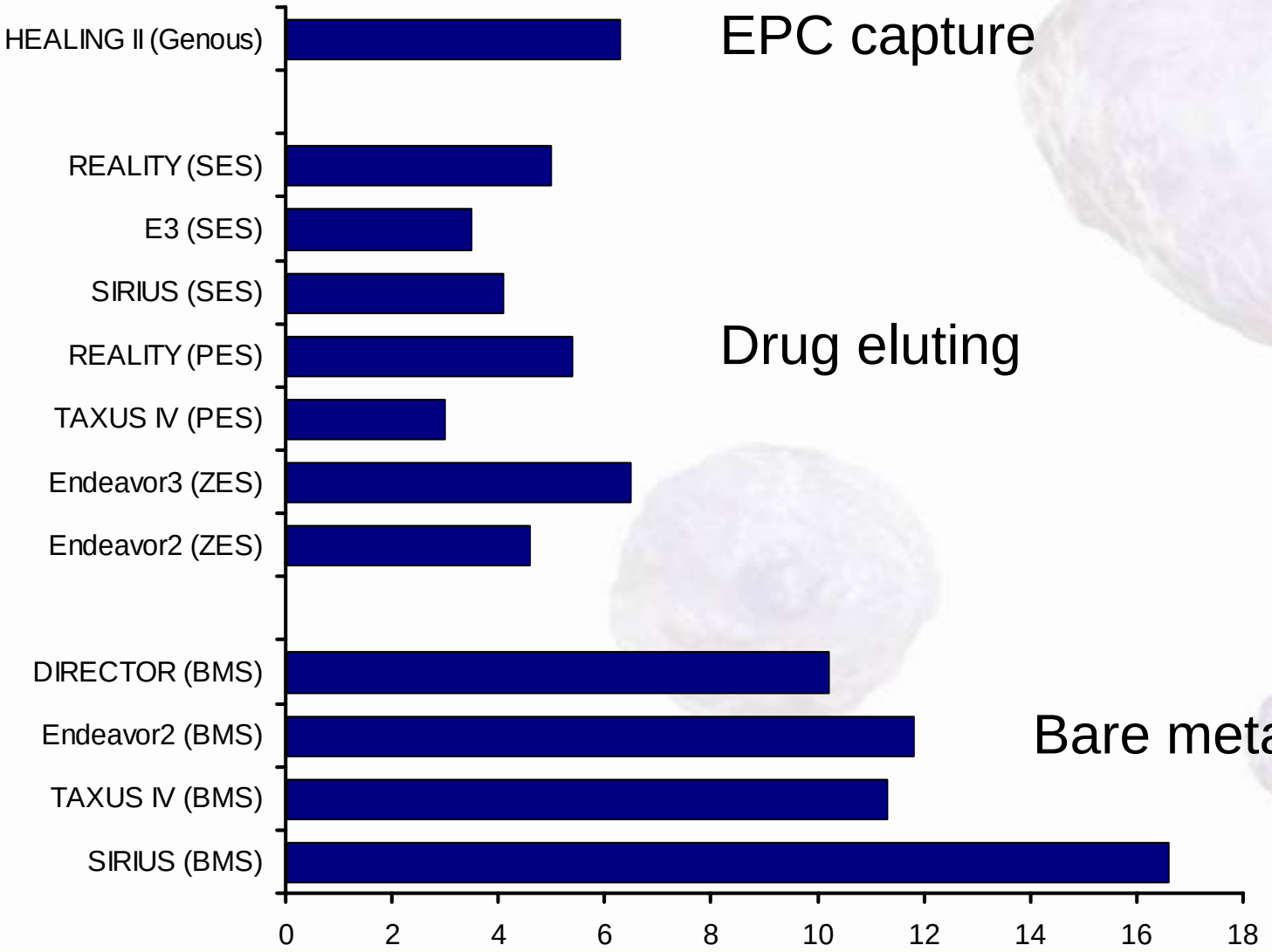
Major Adverse Cardiac Events
9 months*

	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 %

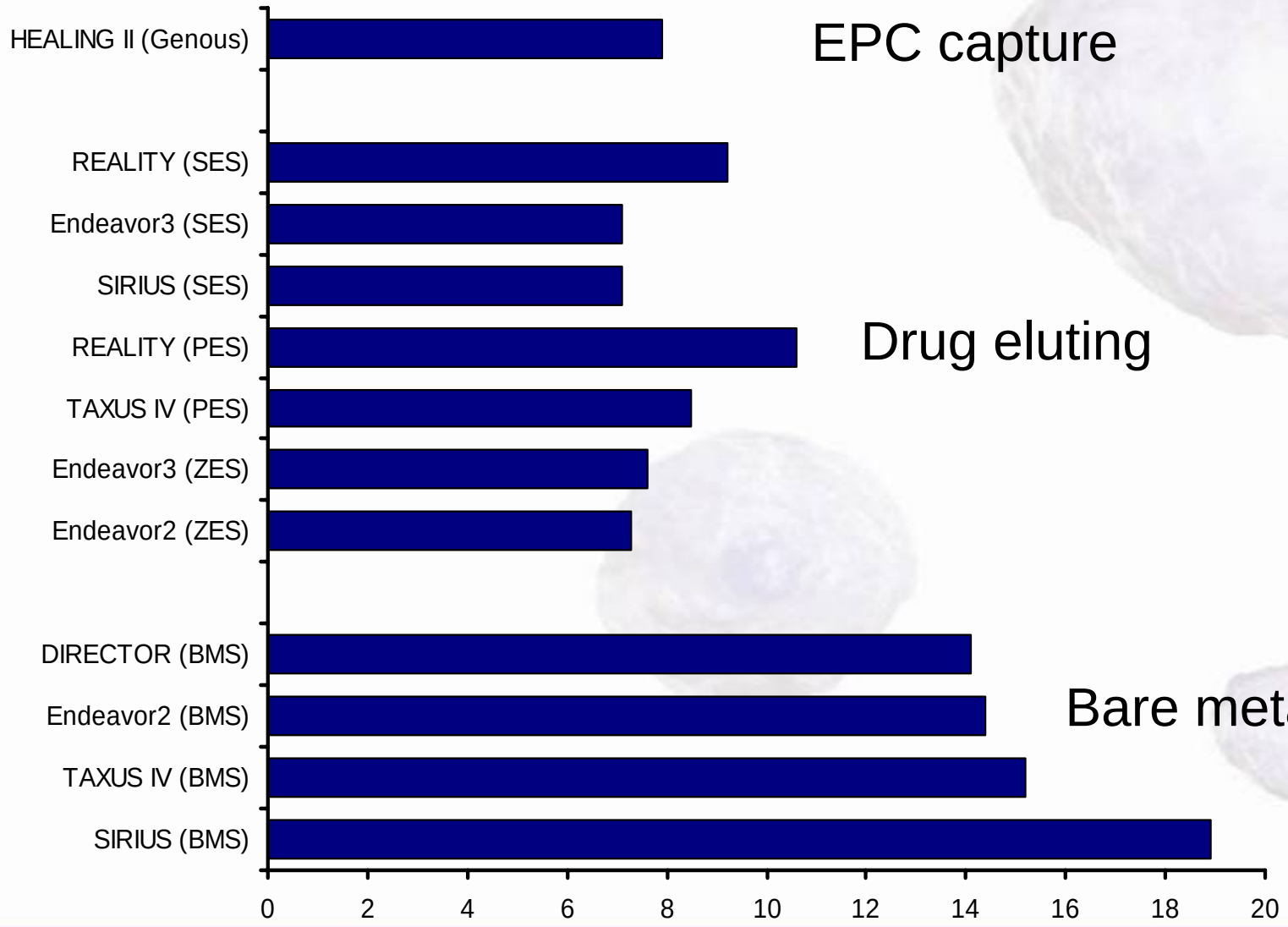
Primary Endpoint: MACE at 30 days – 0%
Stent Thrombosis – 0%

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

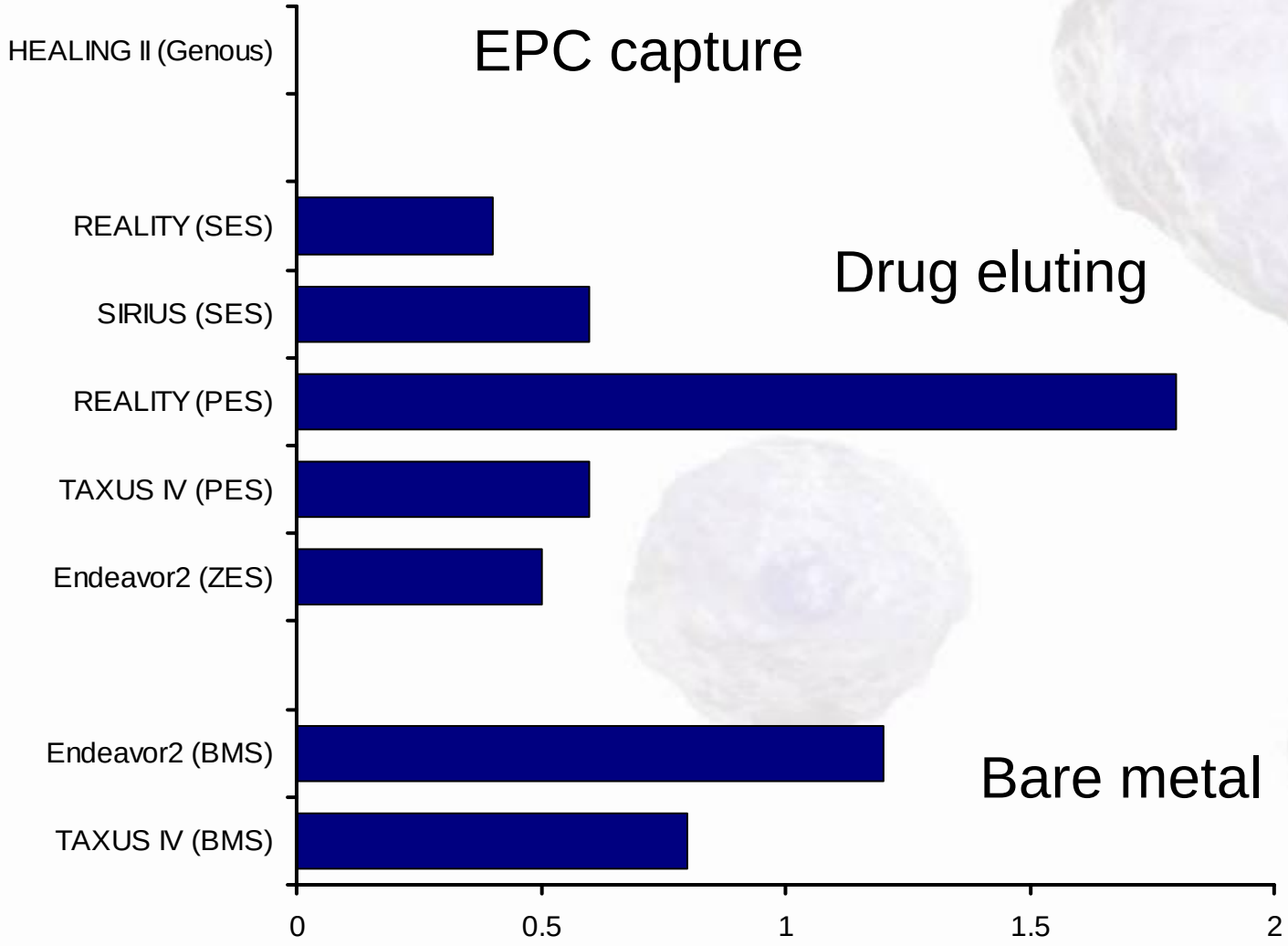
Target Lesion Revascularization (TLR) 8/9 months



Major Adverse Cardiac Events (MACE) 8/9 months

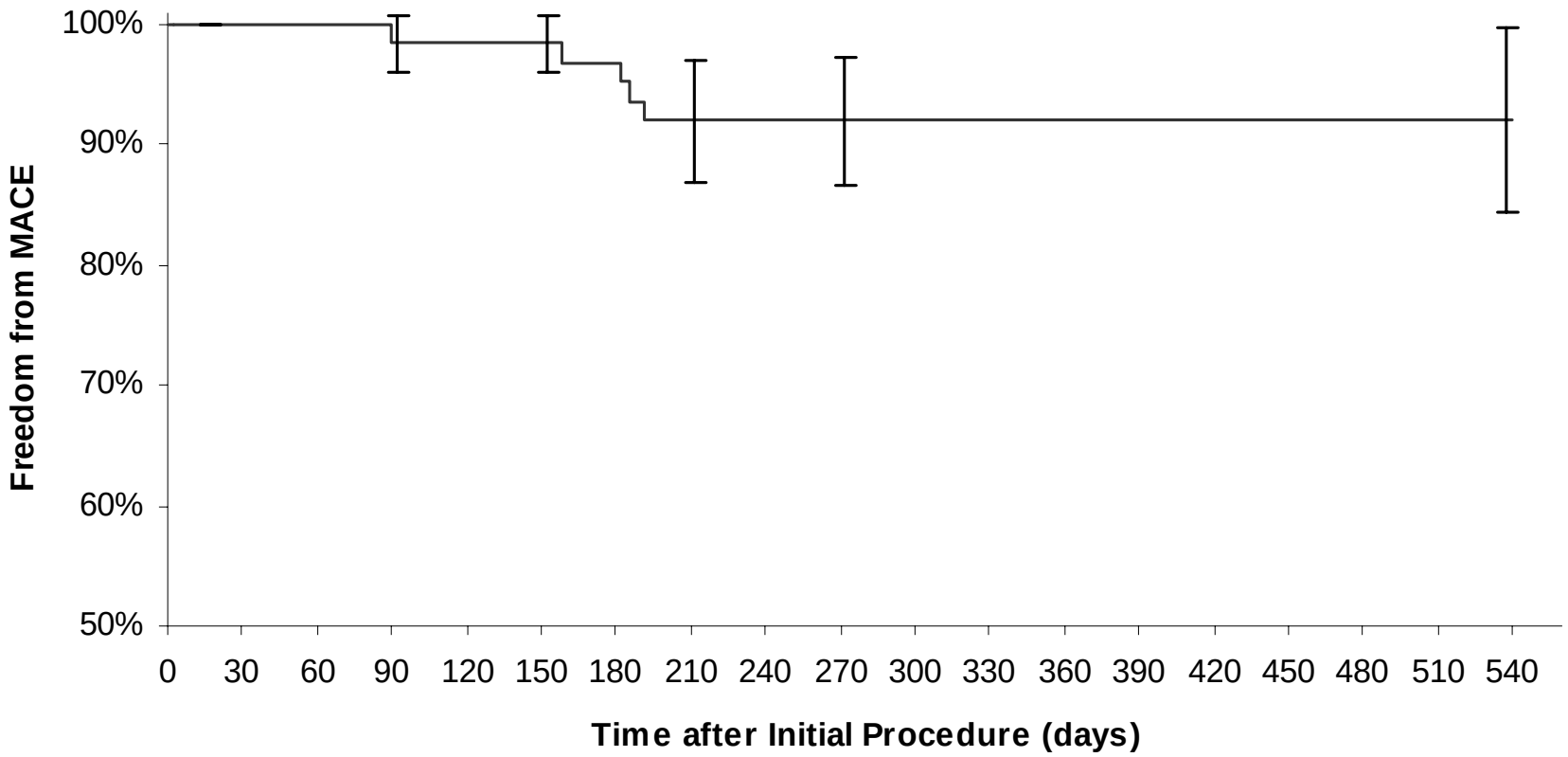


Stent Thrombosis 8/9 months



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

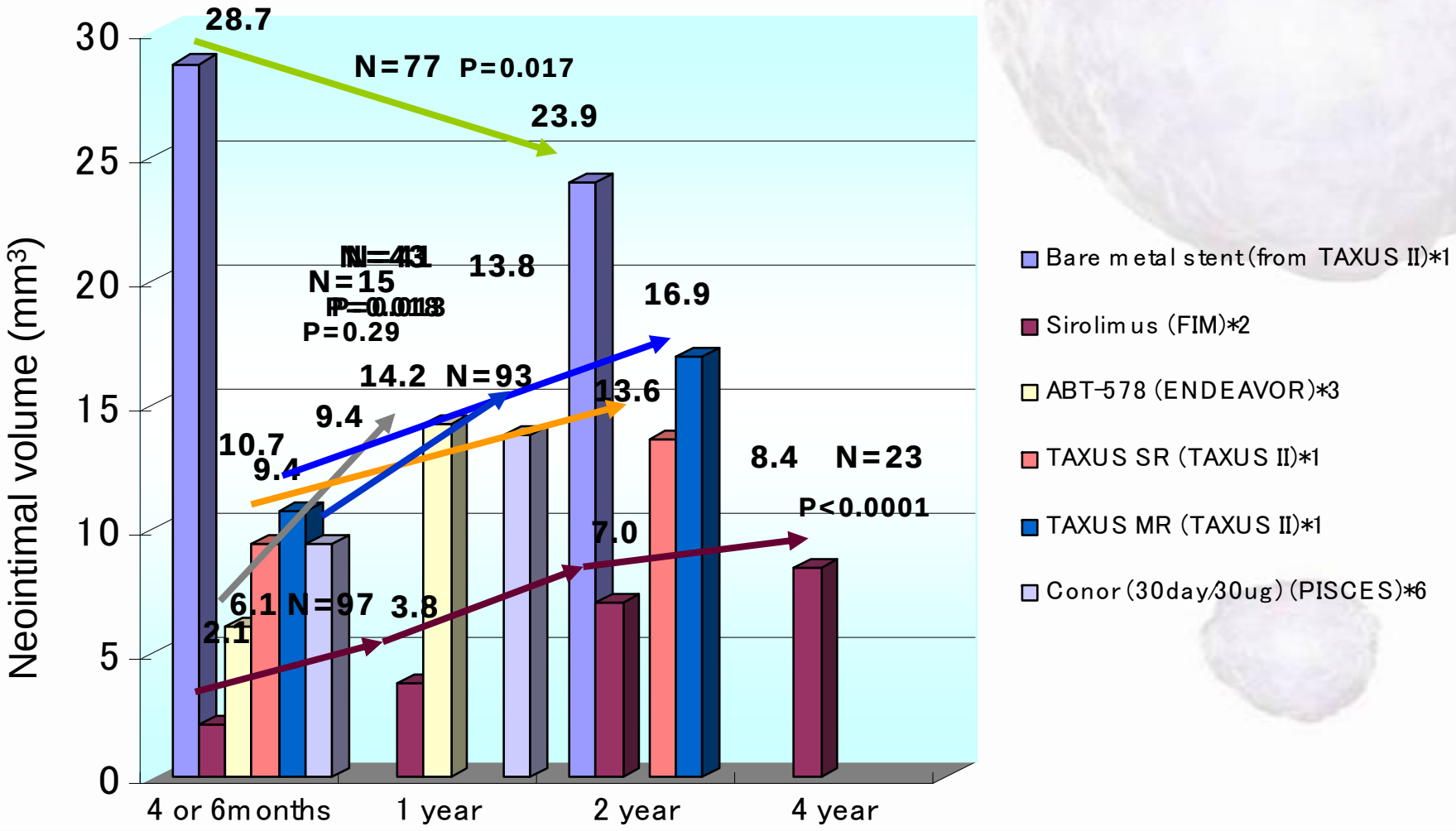
18 Month Angiographic Results In Stent Serial Analysis

	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

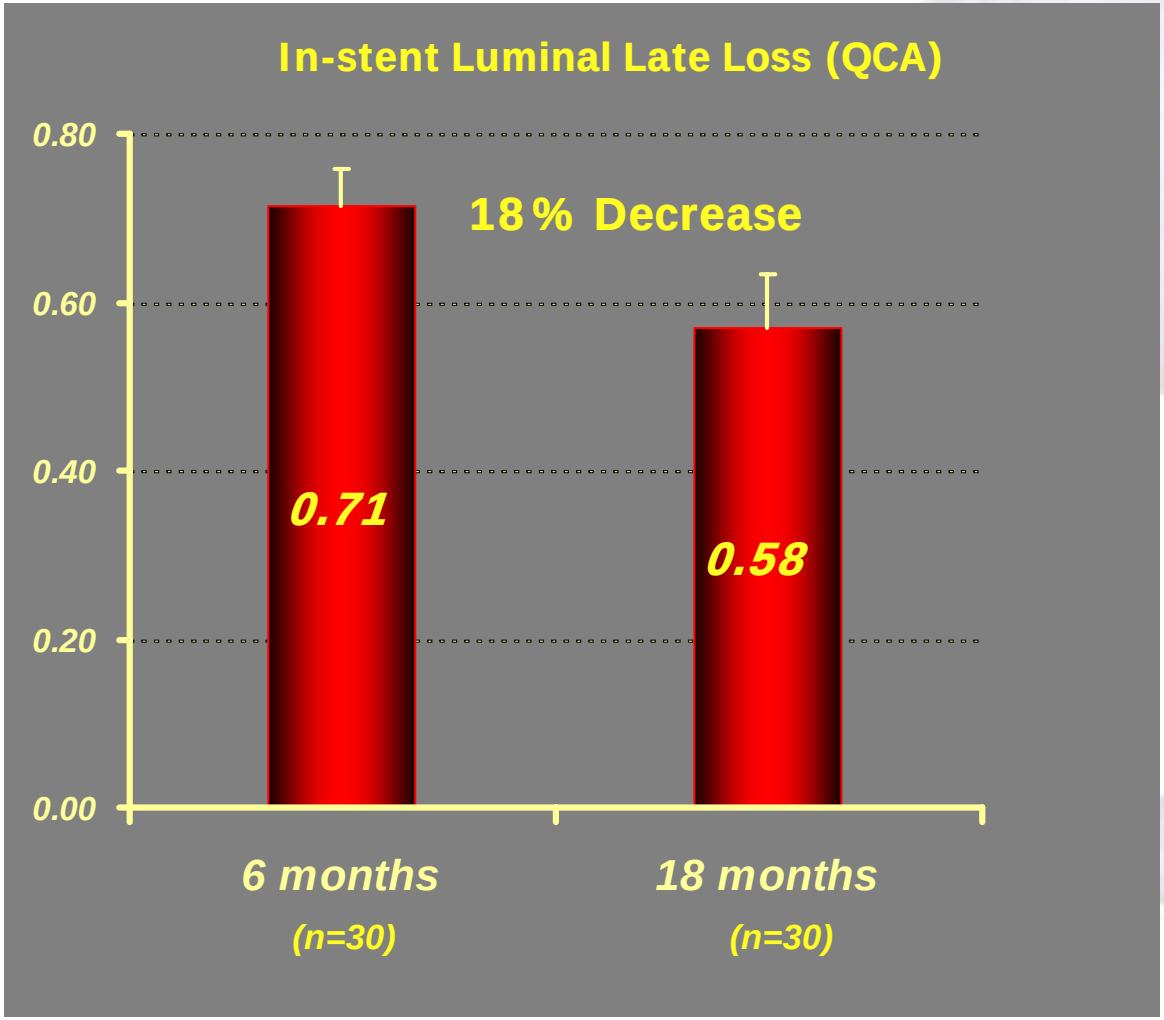


*1 Aoki, Serruys et al, Eurointerv 2005:1,253-255. *2 Aoki, Serruys et al, JACC 2005: 46(9):1670-6

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

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

GenOus

	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

GenOus

	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