Second Generation Drug Eluting Stents:
From Inhibition to Healing

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Professor of Medicine / Cardiology

Duke University Medical Center

Director, Cardiovascular Devices Unit

Duke Clinical Research Institute

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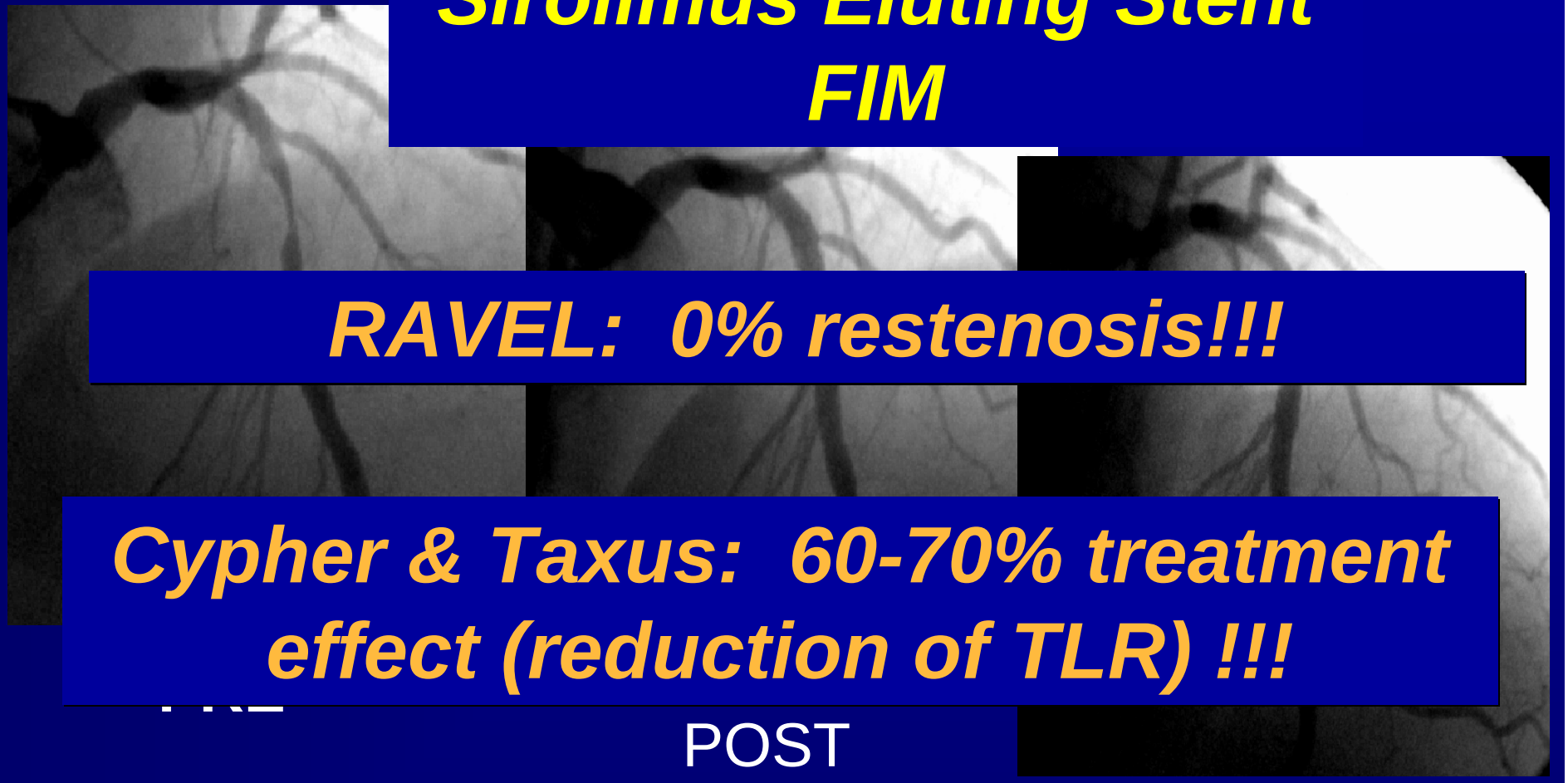
Sirolimus Eluting Stent FIM



RAVEL: 0% restenosis!!!

Cypher & Taxus: 60-70% treatment effect (reduction of TLR) !!!

POST

12-MONTH FU

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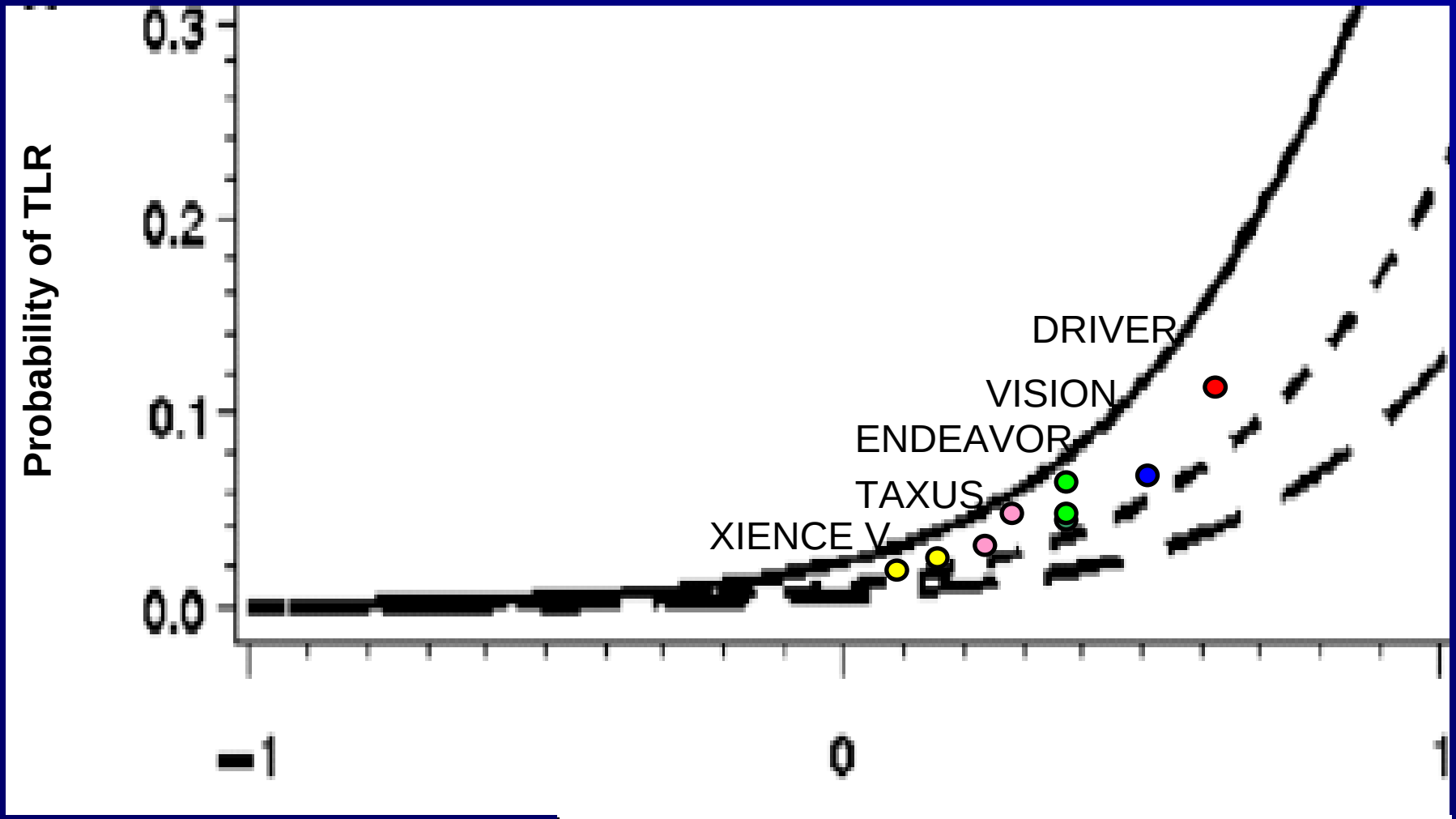
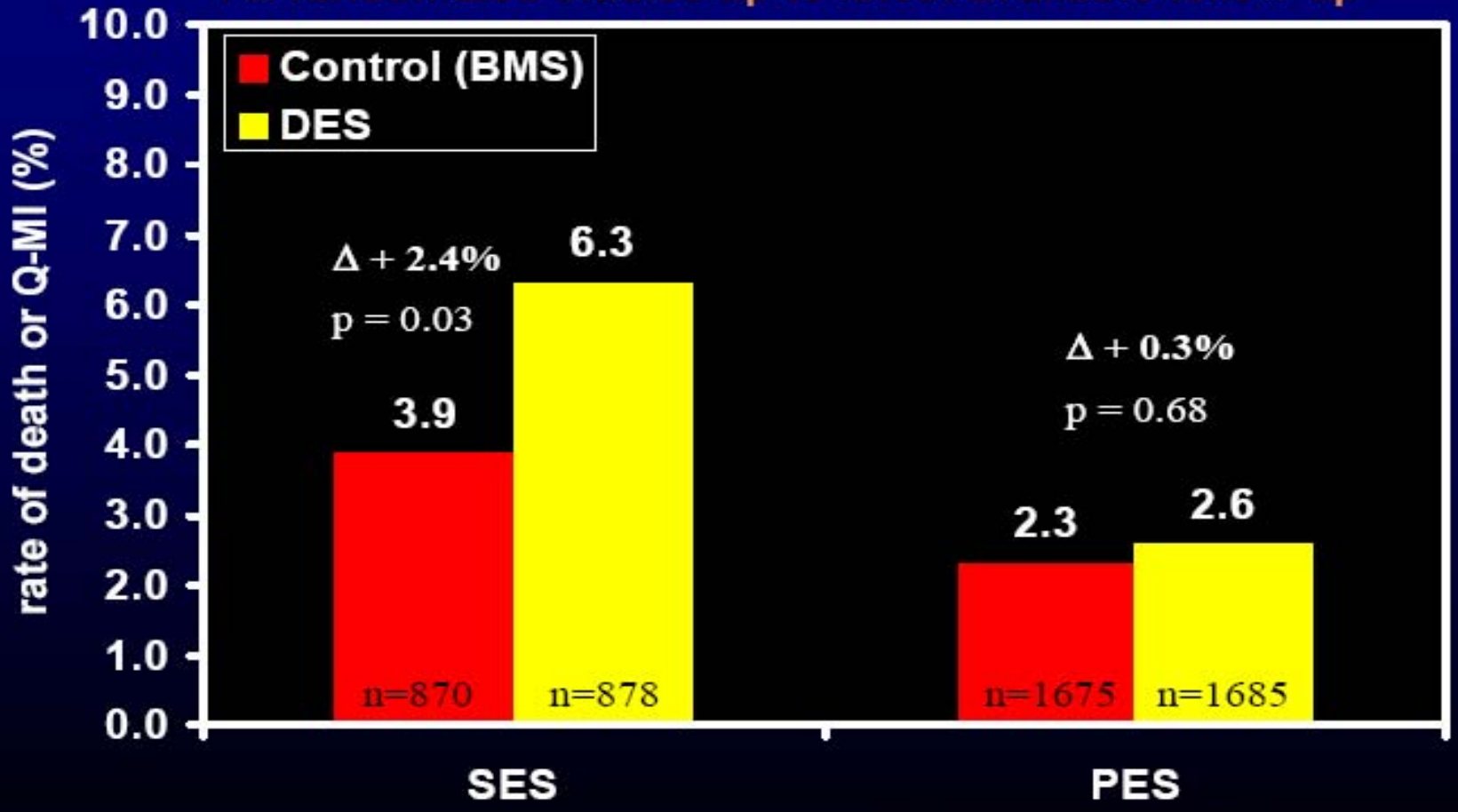
Bigger Is Better: Late Loss vs. Risk of TLR



Pocock et al, JACC in press

Incidence of Serious Adverse Events (Death or MI)

All randomized studies up to latest available follow-up



Camenzind E, ESC 2006, Oral Presentation #992

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TUESDAY

ESC Congress News

EUROPEAN SOCIETY OF CARDIOLOGY®

WORLD HEART FEDERATION®

World Congress of Cardiology 2006

The unique meeting of the European Society of Cardiology Congress 2006 and the World Heart Federation's XVth World Congress of Cardiology

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the

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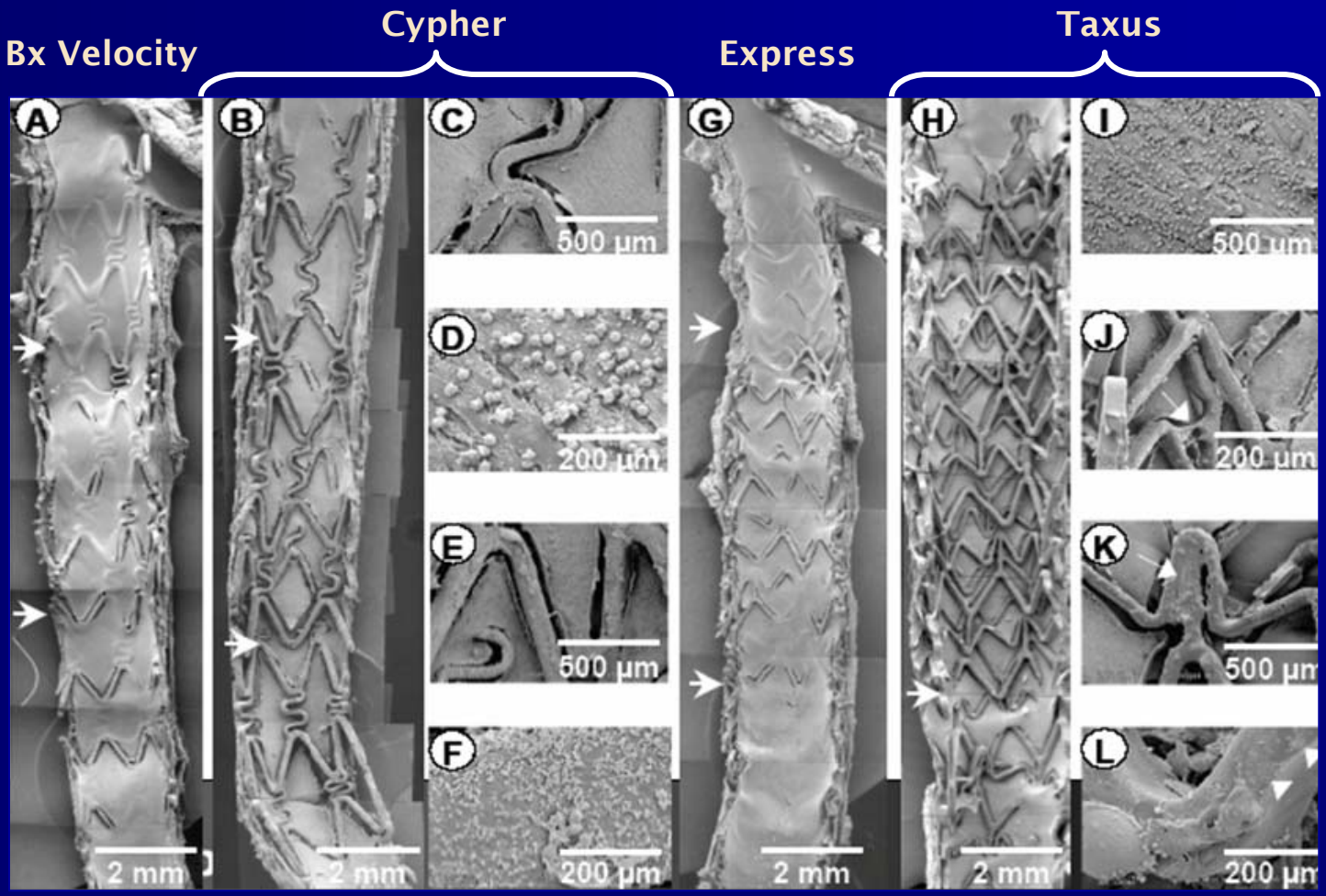
Animal Data on Delayed Healing



A. Finn, Renu Virmanin, SOLACI 2006

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
Learn and Live℠

Special Report

Drug-Eluting Stents "Deliver Heartburn"

How Do We Spell Relief Going Forward?

Mitchell W. Krucoff, MD; Ashley Boam, MSBE; Daniel G. Schultz, MD

"B…llab-
when …iased
outpa… …veral
high- …on to
attention to such issues, ultimately it is careful scientific … articles on DES outcomes were included in the March 8…

Addressing Healing as well as Restenosis:

Second Generation DES

Krucoff et al, *Circulation*. 2007.

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Second Generation DES: *What questions have we learned to ask from Cypher & Taxus?*

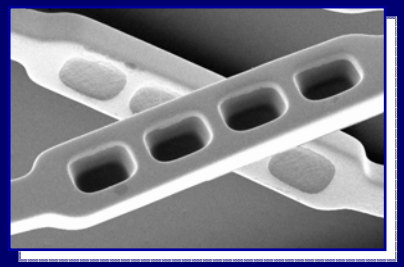
- Is local drug delivery sufficient to inhibit hyperplasia also toxic to vessels or to endothelial healing?
- Does local inflammatory response to polymer prevent endothelial healing?
- Are other aspects of device deployment or adjunctive therapy related to long term safety?

DRUG ELUTING STENTS:

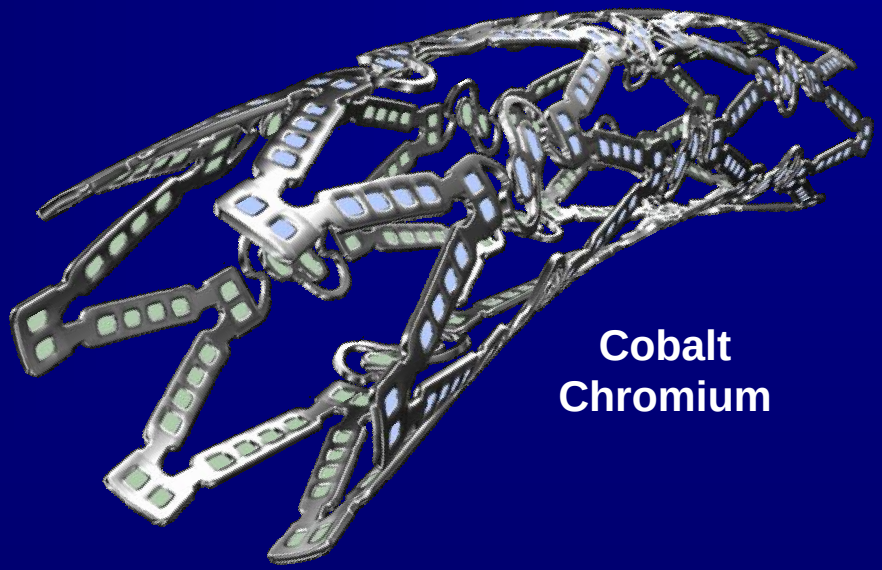
What if the polymer is minimal and goes away?

CoStar® Paclitaxel-Eluting Coronary Stent System

A Stent Specifically Designed for Controlled Drug Delivery from a Bioresorbable Polymer

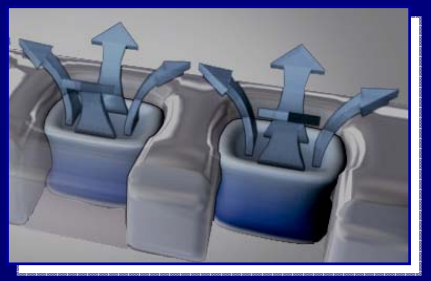


Reservoir Technology



Cobalt Chromium

Bioresorbable Polymer



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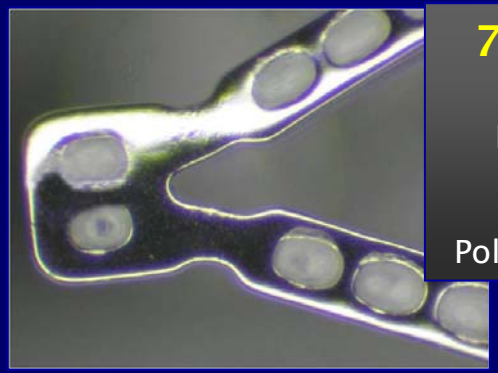
CoStar® Bioresorbable Polymer

- PLGA (Polylactide-co-glycolide)
- Widely used bioresorbable surgical suture material
- Mechanism of bio-degradation well characterized
- Degrades by random hydrolytic scission into Lactate & Glycolate



7 Day Porcine Explant
Following Tissue Removal
Showing Signs of Polymer Bioresorption

180 Day Porcine Explant
Following Tissue Removal
Showing No Residual Polymer

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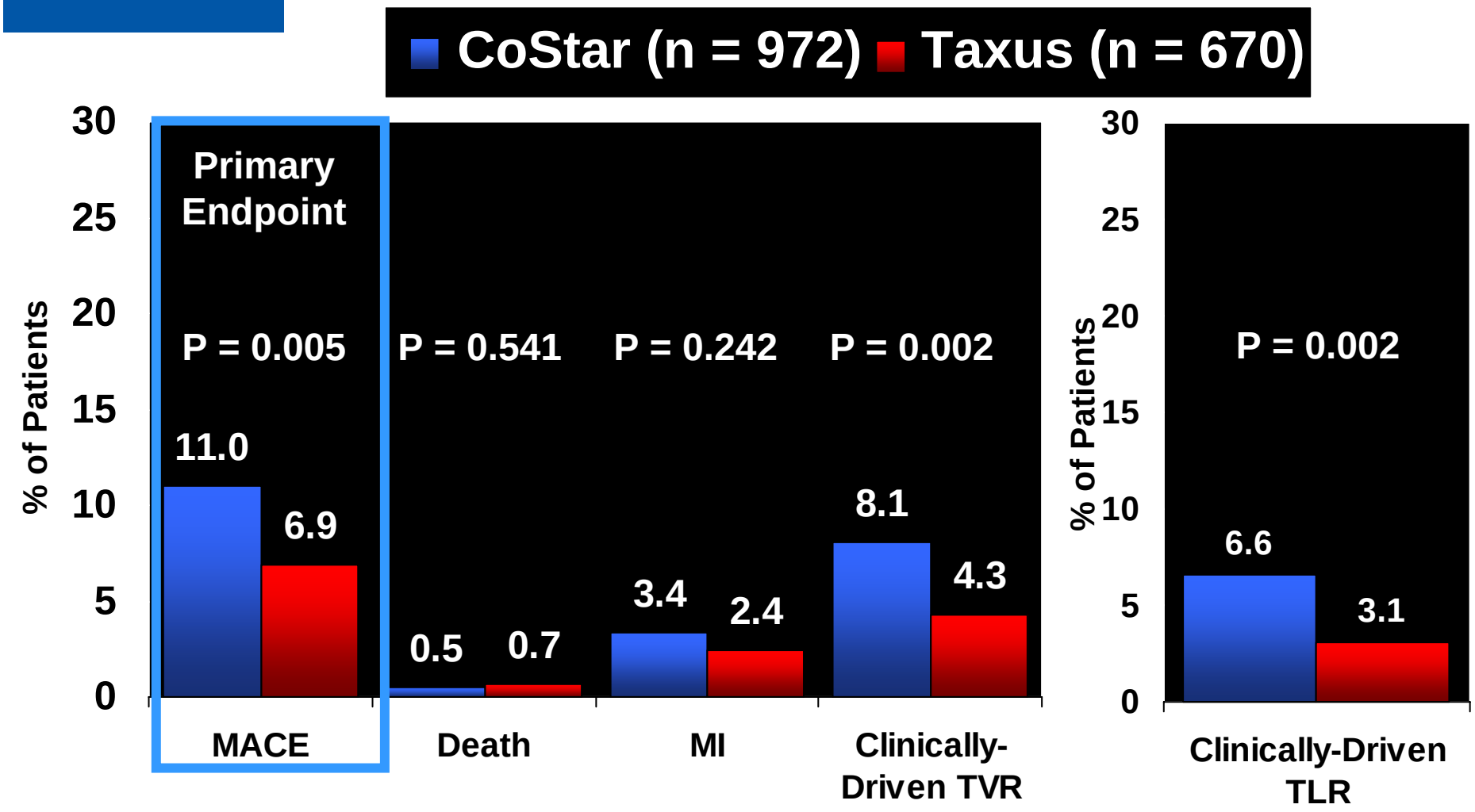
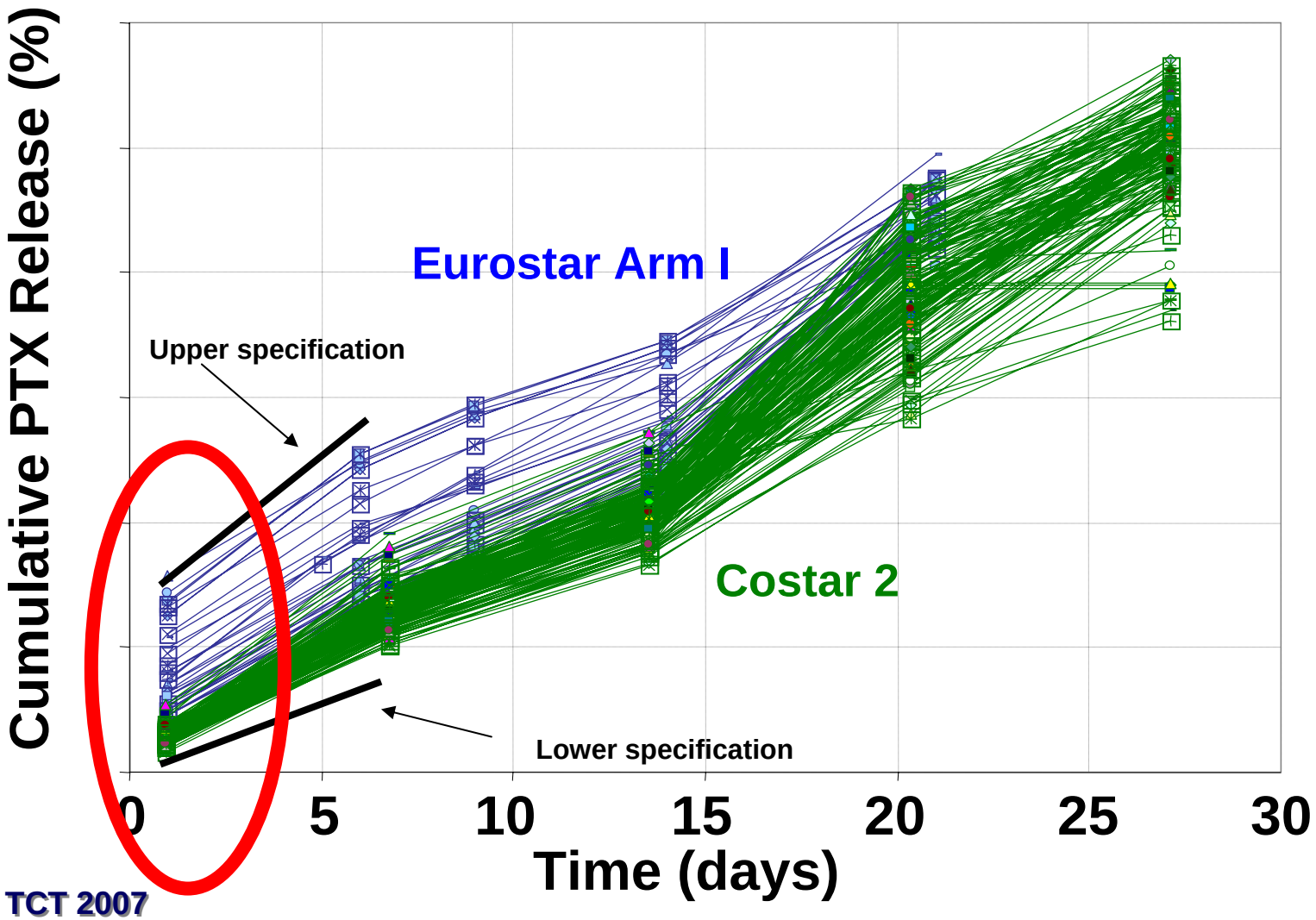
8-Month Non-hierarchical MACE and Clinically-Driven TLR



MACE: A composite of adjudicated death, MI, and and clinically driven TVR

Root Cause Analysis:
In-vitro Release of CoStar Paclitaxel



Krucoff, TCT 2007

J&J pulls plug on stent

Johnson & Johnson says experimental stent fails to meet primary goal, pulls from markets where use already approved.

May 7 2007: 8:17 AM EDT

CHICAGO (Reuters) -- Johnson & Johnson Monday said its experimental drug-coated stent failed to meet its primary study goal, leading it to drop development of the heart device.

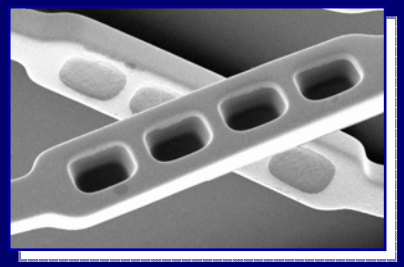
J&J (Charts, Fortune 500) unit Conor Medical Systems also said it will discontinue sales of the so-called CoStar stent in certain countries in Europe, Asia and Latin America - where it is already approved.

A pivotal study compared J&J's investigational device with one already sold by Boston Scientific (Charts, Fortune 500). Drug-coated stents are tiny wire mesh tubes used to prop open recently unclogged heart arteries and have until recently been reliable cash cows for device makers.

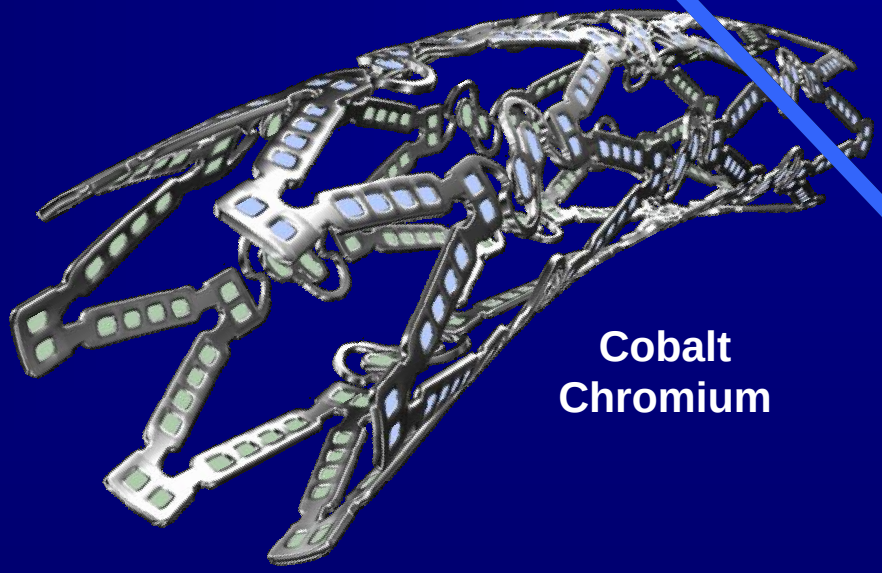
J&J said it saw no signs of safety troubles with the CoStar stent, but it failed to prove "non-inferiority" against Boston Scientific's Taxus stent. Other major competitors in the field include Medtronic (Charts, Fortune 500).

Cordis Conor-S Coronary Stent System

SIROLIMOUS

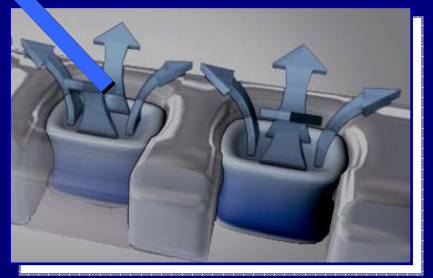


Reservoir Technology



Cobalt Chromium

Bioresorbable Polymer



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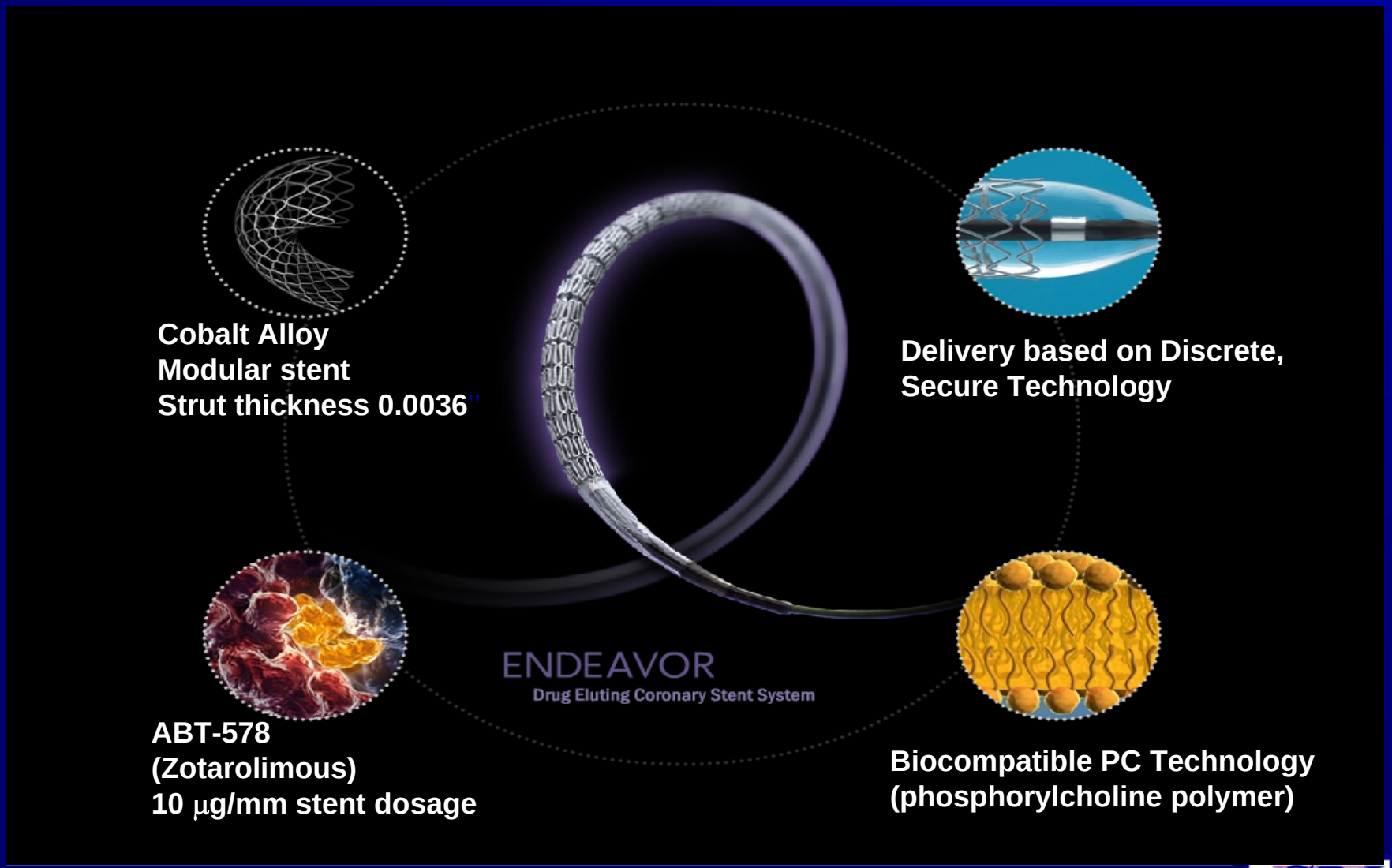
What if the drug inhibition was less?

Components of the Endeavor Stent



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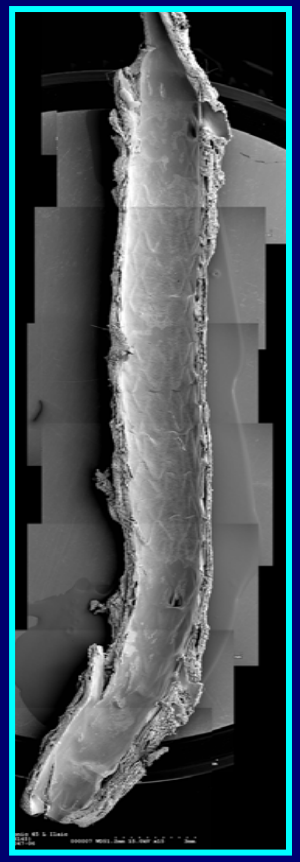
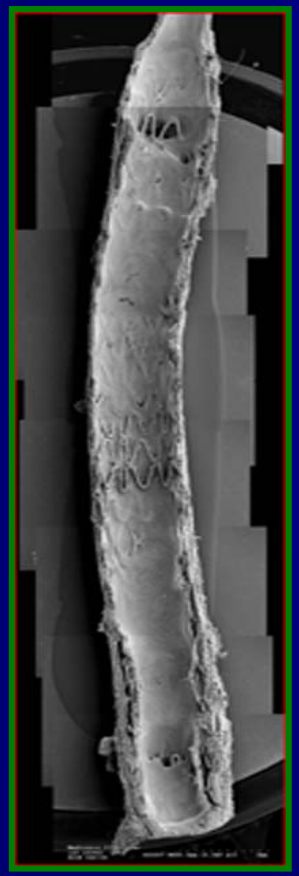
Strut Coverage and Endothelization

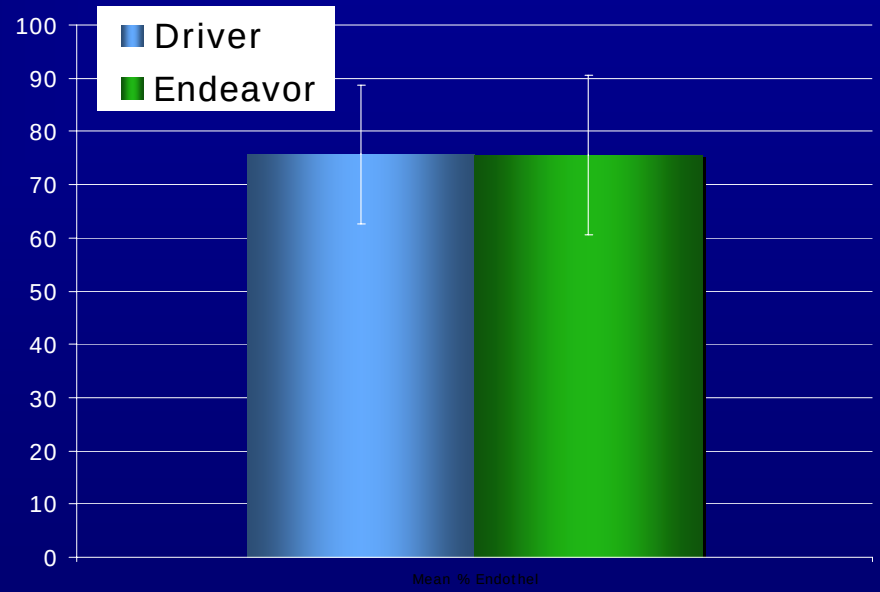
Driver



Endeavor



% of Struts Endothelialized



Virmani et. al; *PCR 2006*

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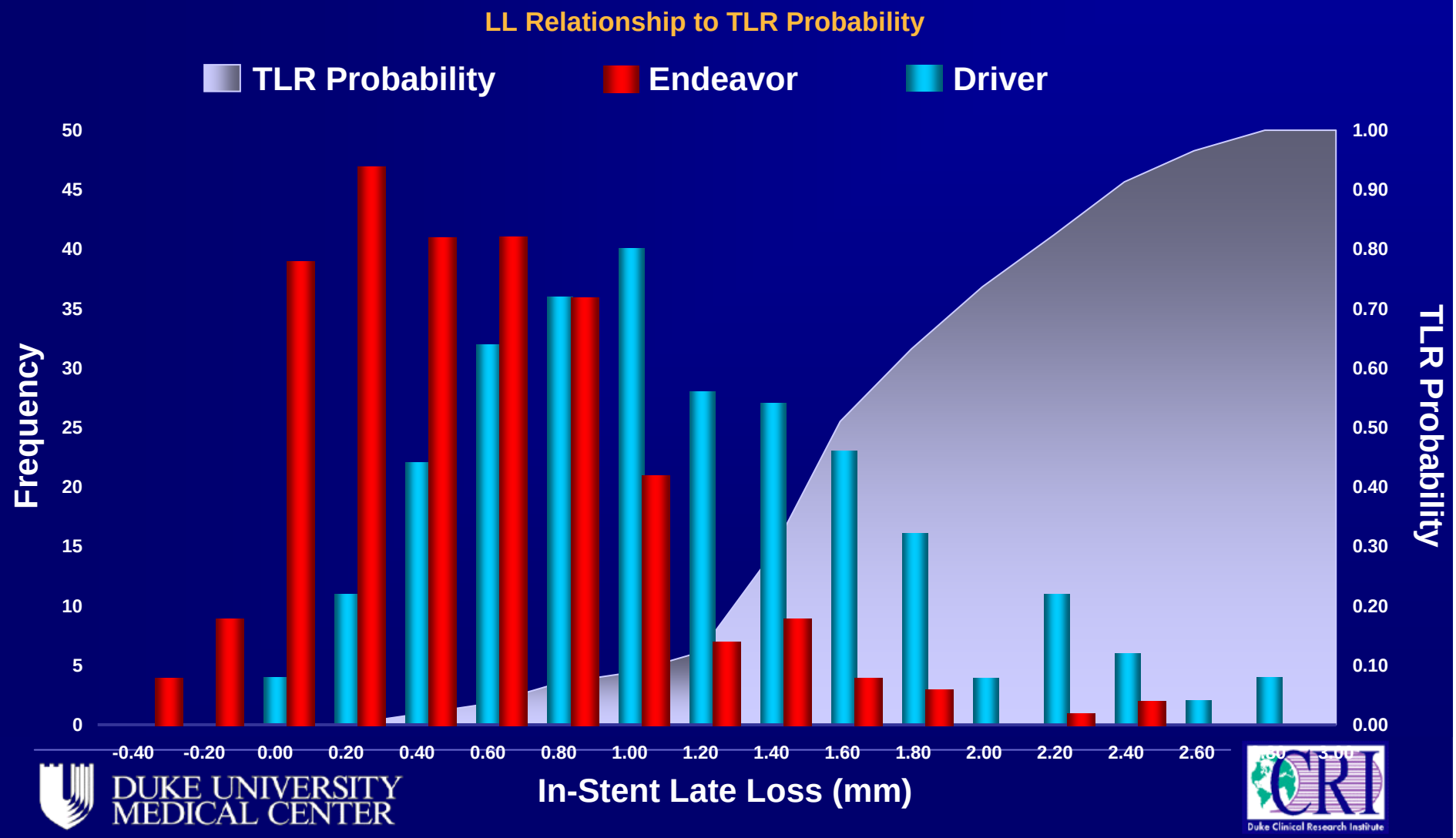
ENDEAVOR II

In-Stent Late Loss Distribution



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ENDEAVOR III: *Angiographic and IVUS Results at 8 Months*

		Endeavor n=282	Cypher n=94	*p*-value
Angiographic f/u % (N)		87.3 (323)	83.2 (113)	0.27
RVD (mm)		2.74	2.84	0.07
MLD (mm)	In-Stent	2.08	2.52	<0.001
	In-Segment	1.92	2.16	<0.001
DS (%)	In-Stent	24.3	11.0	<0.001
	In-Segment	29.9	23.9	<0.001
BAR (%)	In-Stent	9.2	2.1	0.02
	In-Segment	11.7	4.3	0.04
Late Loss (mm)	In-Stent	0.60	0.15	<0.001
	In-Segment	0.34	0.13	<0.001

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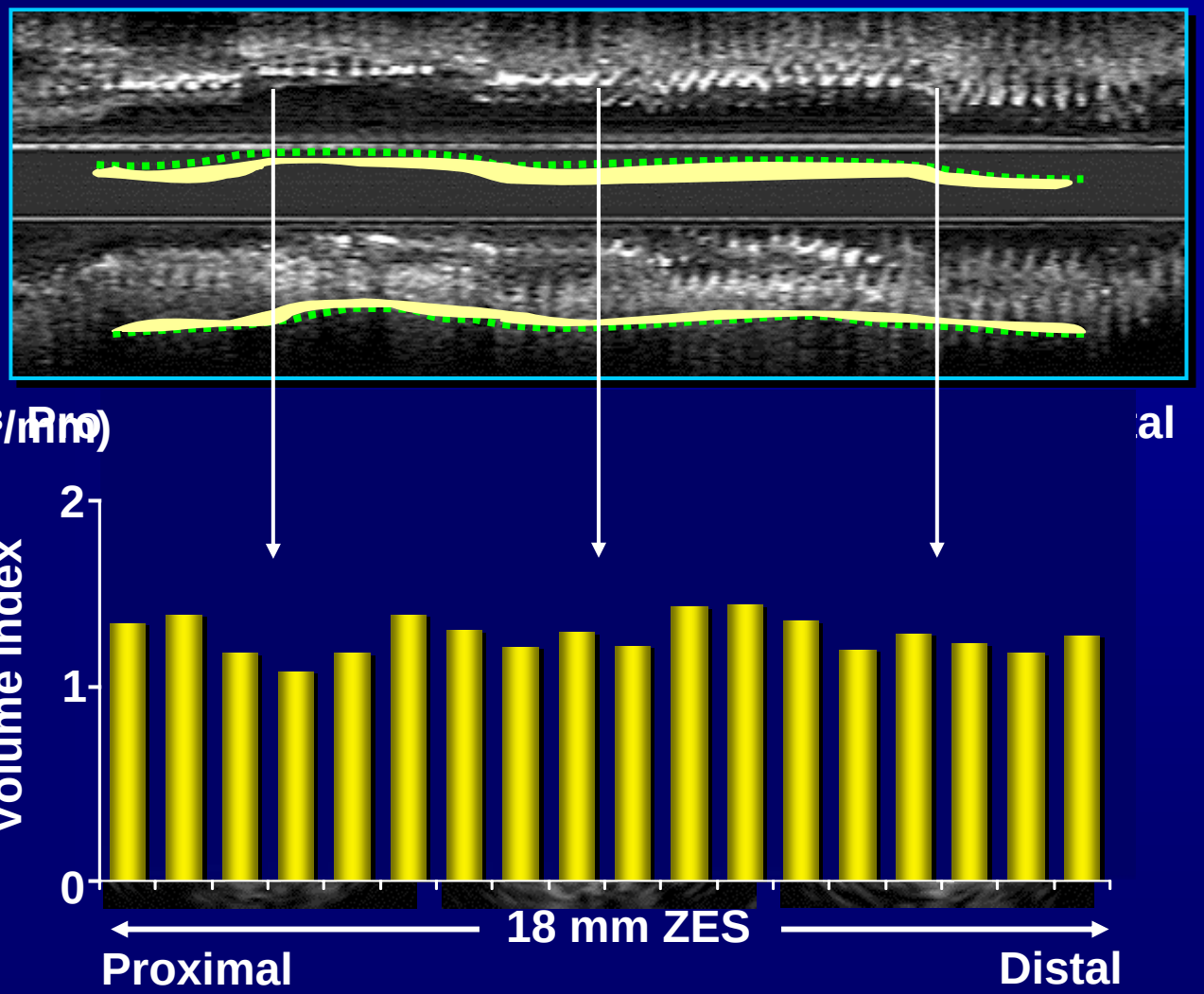
Endeavor: “Complete” NIH

Smooth Lumen, Even Neointimal Distribution



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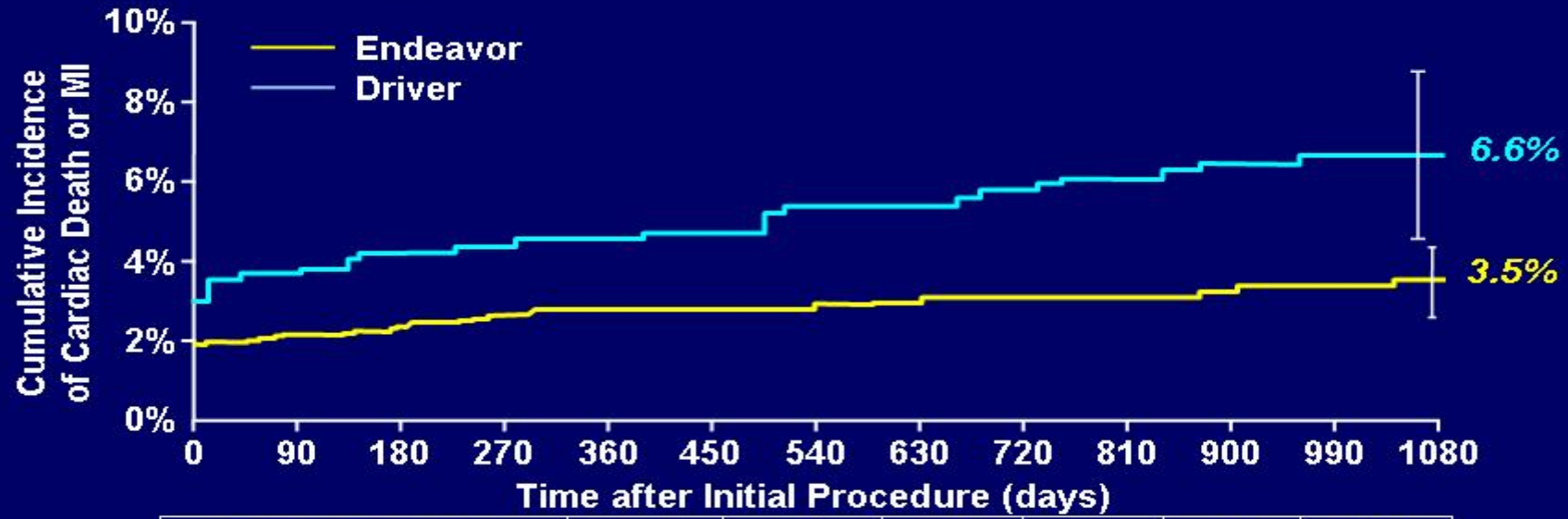
Endeavor Safety Analysis

Cumulative Incidence of Cardiac Death and MI to 1080 Days



Cardiac Death or MI	0	30	270	360	720	1080
Endeavor	**2132**	**2083**	**2052**	**2029**	**1222**	**1184**
# Events	30	12	14	4	3	5
% CI	1.4%	2.0%	2.6%	2.8%	3.1%	3.5%
Driver	**596**	**573**	**566**	**560**	**545**	**528**
# Events	15	6	5	1	7	5
% CI	2.5%	3.5%	4.4%	4.5%	5.8%	6.6%

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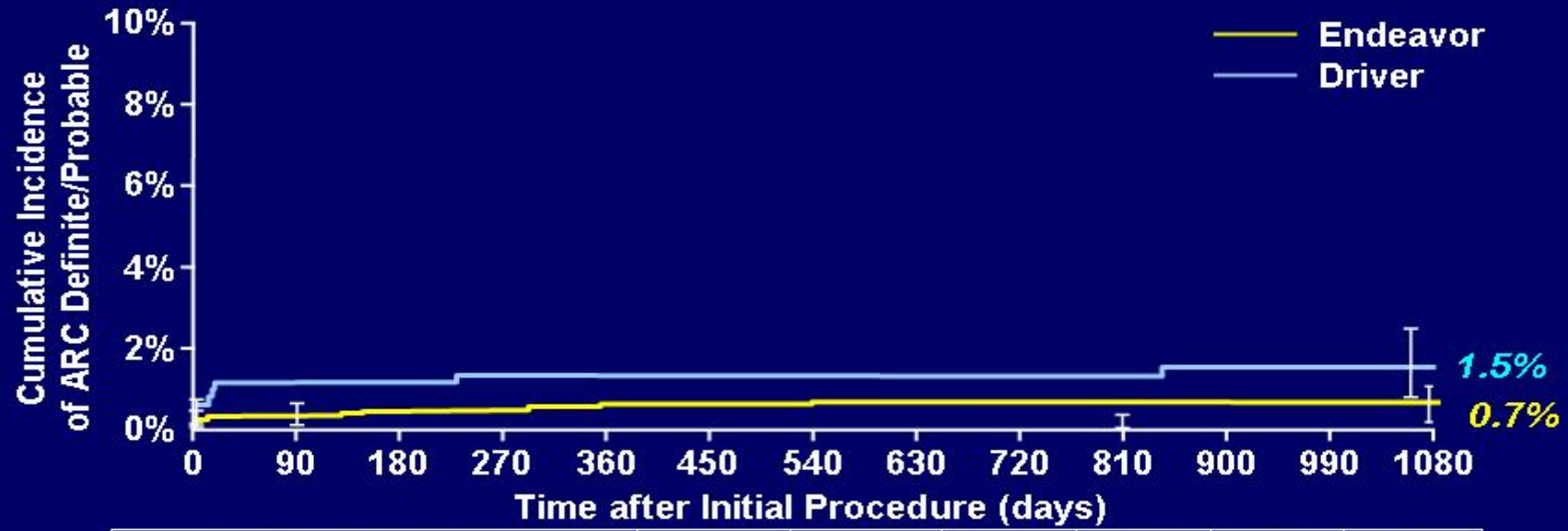
Endeavor Safety Analysis

Cumulative Incidence of ARC Definite/Probable ST to 1080 Days



Def/Prob Thrombosis	0	30	270	360	720	1080
Endeavor	**2132**	**2117**	**2085**	**2049**	**1251**	**1214**
# Events	1	6	4	2	1	0
% CI	0.0%	0.3%	0.5%	0.6%	0.7%	0.7%
Driver	**596**	**585**	**581**	**575**	**560**	**542**
# Events	1	6	1	0	0	1
% CI	0.2%	1.2%	1.3%	1.3%	1.3%	1.5%

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Circulatory Devices Advisory Panel Vote: *10-0 Approval w/Conditions*

Medtronic Receives FDA Approval for Endeavor® Zotarolimus-Eluting Coronary Stent System

New Drug-Coated Stent Offers Excellent Combination of Safety, Effectiveness and Deliverability

MINNEAPOLIS – Feb. 1, 2008 –Marking a major development in the field of interventional cardiology, Medtronic, Inc. (NYSE: MDT), announced today that it has received approval from the U.S. Food and Drug Administration (FDA) for the Endeavor® Zotarolimus-Eluting Coronary Stent System to be used in the treatment of coronary artery disease, which affects an estimated 13 million people in the United States and is the country's leading cause of death.

DRUG ELUTING STENTS:
Are Big Lumens Bad?

What if total design was better?

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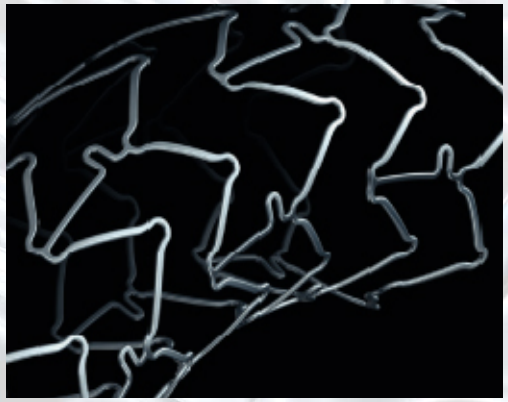
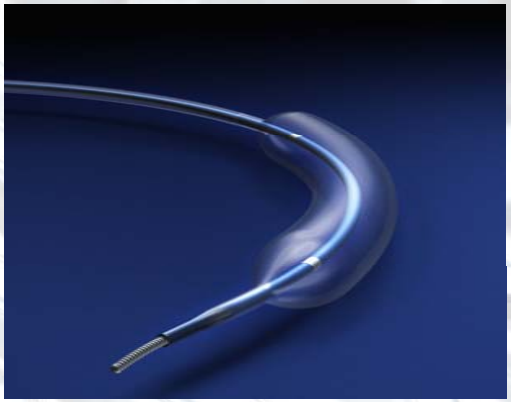
XIENCE™ V Everolimus Eluting CSS Components

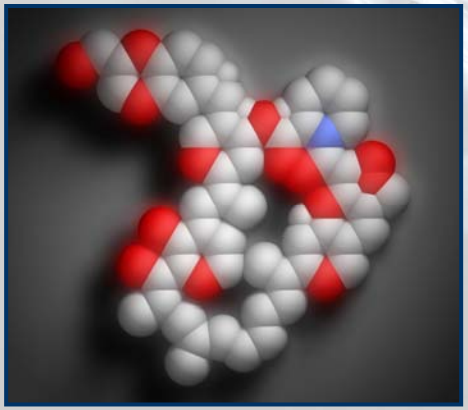
MULTI-LINK VISION® Stent



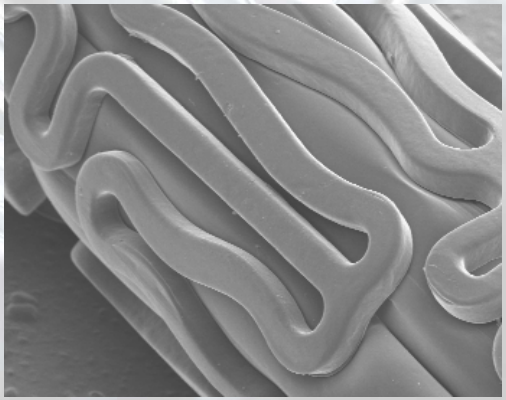
MULTI-LINK VISION® Stent Delivery System



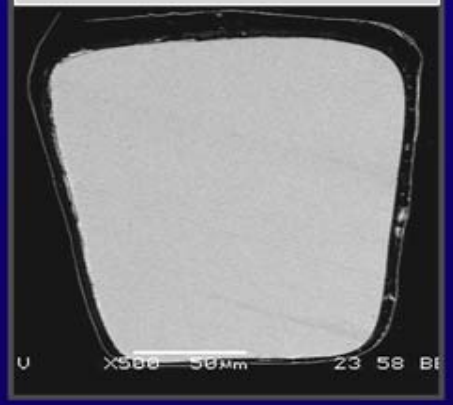
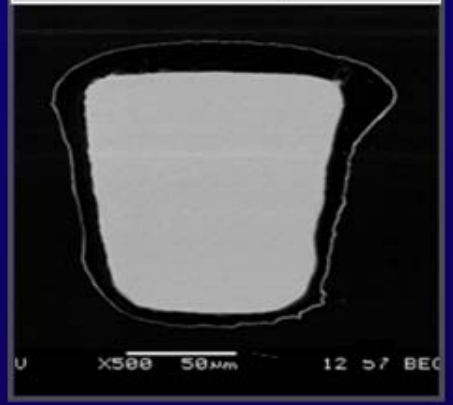
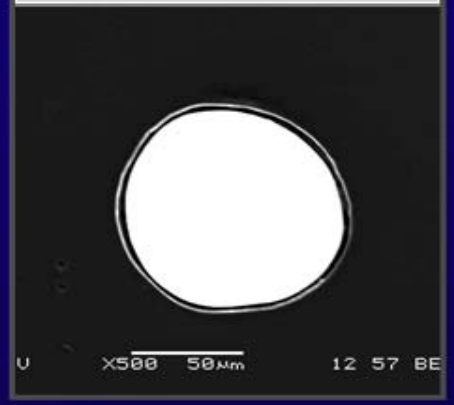
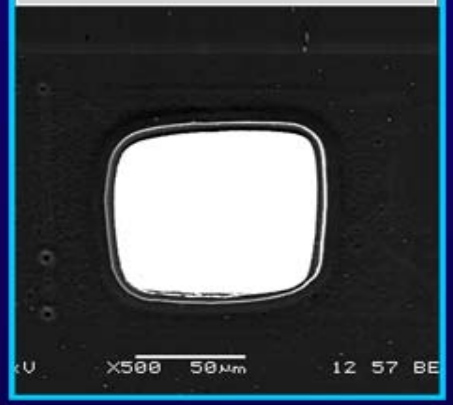
Everolimus



Fluoropolymer



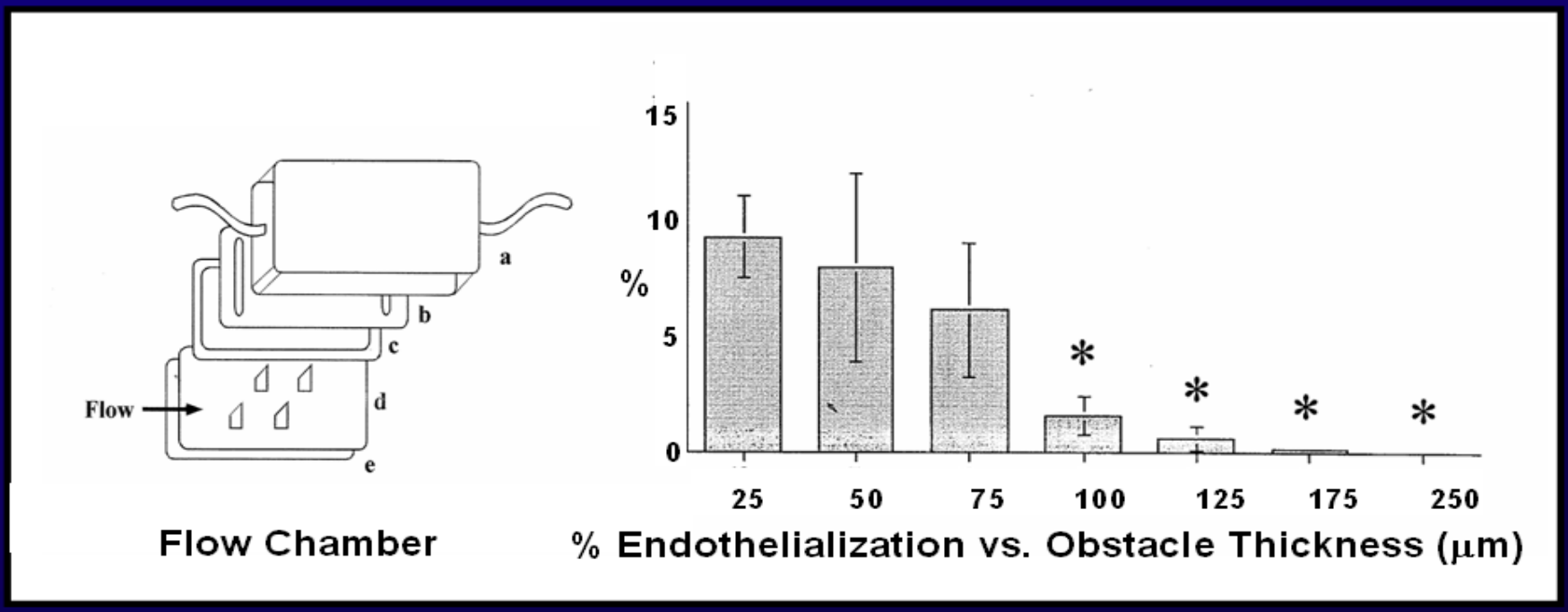
XIENCE V
Progression Towards Thinner Struts

CYPHER	TAXUS Express	ENDEAVOR™	XIENCE V
			
Strut Thickness: **140 µm**	Strut Thickness: **132 µm**	Strut Thickness: **91 µm**	Strut Thickness: **81 µm**
Coating Thickness: **12.6 µm**	Coating Thickness: **19.6 µm**	Coating Thickness: **4.8 µm**	Coating Thickness: **7.8 µm**

Abluminal coating thickness represented

Data on file at Abbott Vascular

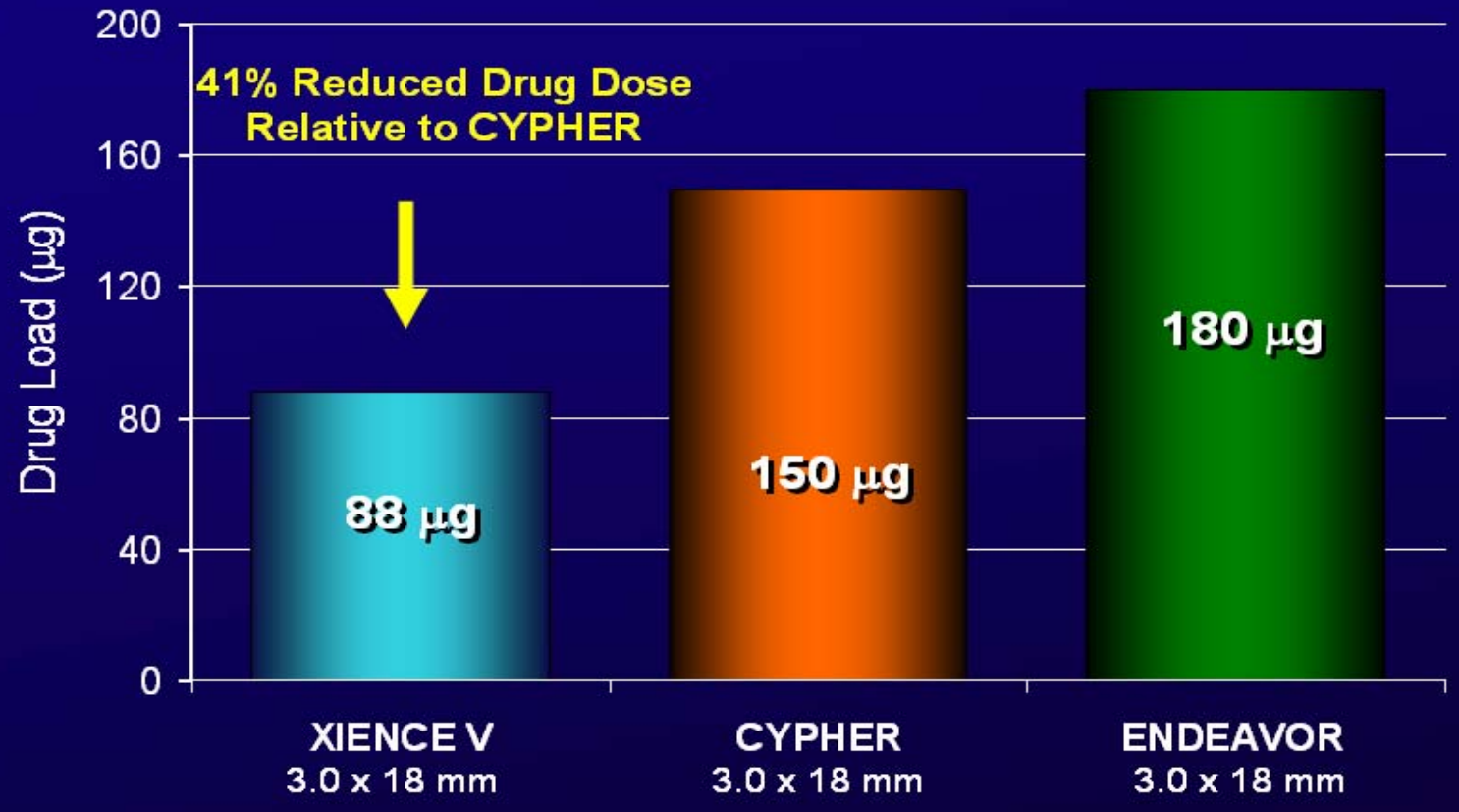
XIENCE V
Endothelialization and strut thickness



Endothelial coverage may be impaired for thicker stent struts

C. Simon, J. Palmaz, E. Sprague, J. Long-Term Effects Medical Implants, 10(1): 143-151 (2000).

XIENCE V
Reduced Drug Dose



Achieved effectiveness with reduced drug loading

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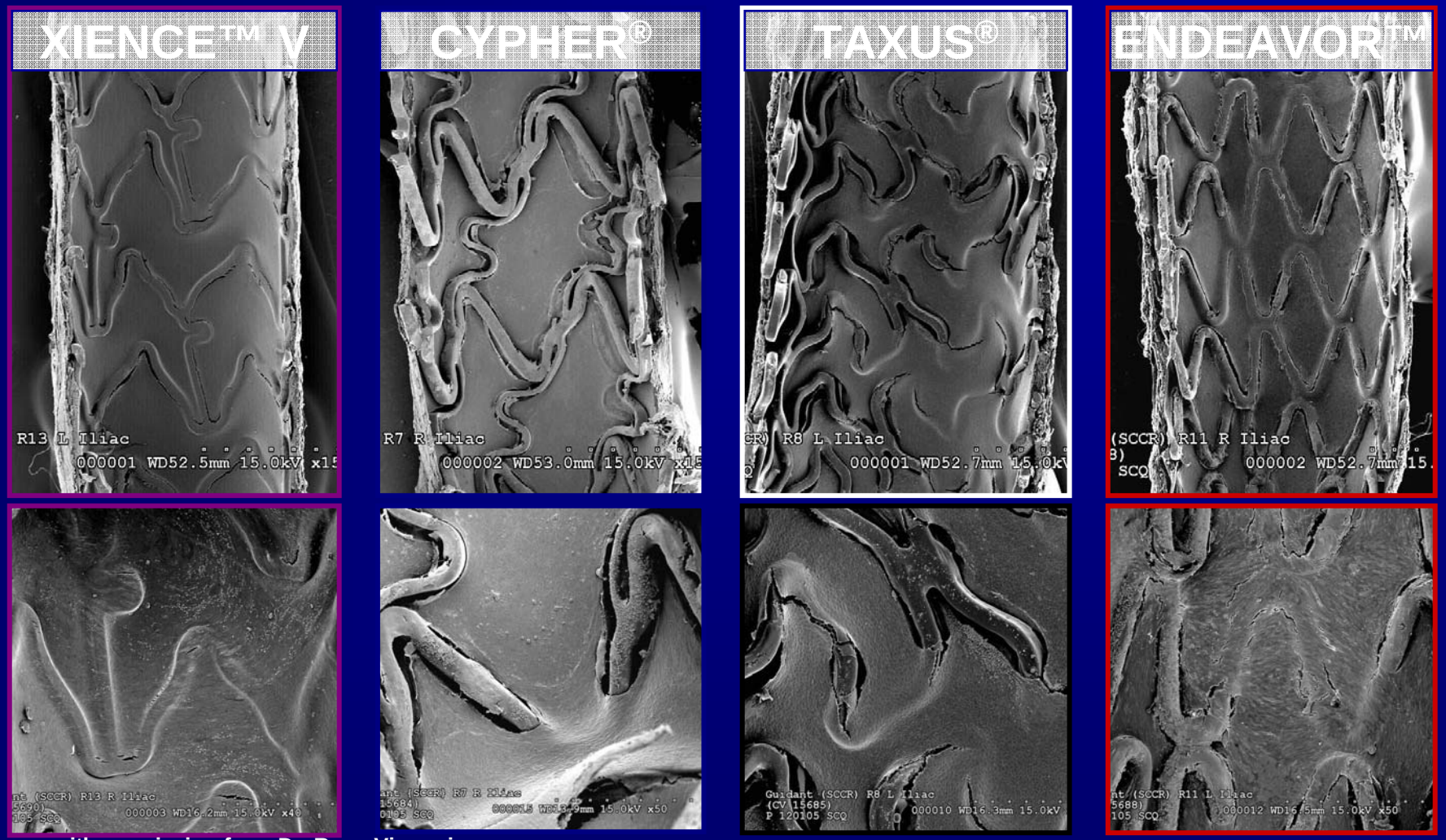
14-Day Rabbit Iliac Re-endothelialization Study:
Representative Photomicrographs of Competitive Stents



Shown with permission from Dr. Renu Virmani

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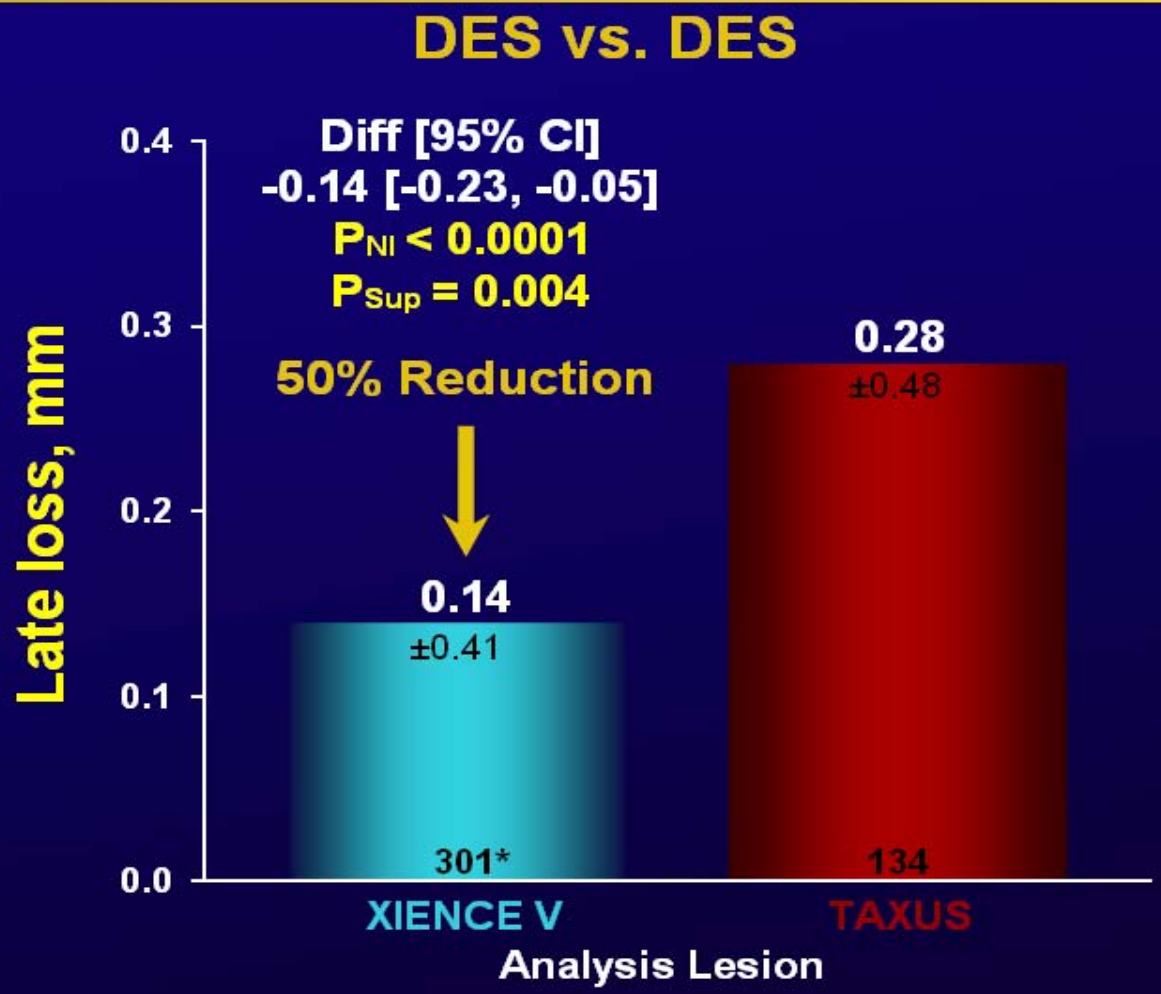
SPIRIT III: Primary Endpoint In-segment LL at 8 Months



* 1 additional patient had angiographic follow-up but baseline angiography was not available

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SPIRIT II & SPIRIT III: Summary of 1 year pooled analysis

		In-seg LL	In-stent LL	TLR @ 1 yr	In-seg ABR	In-stent ABR	TVF @ 1yr	MACE @ 1y
SPIRIT II	XIENCE V vs. TAXUS	↓ 54%	↓ 67%	↓ 72%	↓ 41%	↓ 63%	↓ 51%	↓ 70%
SPIRIT III	XIENCE V vs. TAXUS	↓ 50%	↓ 48%	↓ 48%	↓ 47%	↓ 60%	↓ 24%	↓ 43%
SPIRIT II & III pooled	XIENCE V vs. TAXUS	↓ 50%	↓ 58%	↓ 47%	↓ 47%	↓ 61%	↓ 29%	↓ 55%

XIENCE V Circulatory Advisory Panel
Washington D.C.
November 29, 2008

Vote: 9-1 Approval w/Conditions

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DRUG ELUTING STENTS:
Are Big Lumens Bad?

Maybe not!

Can Lumens Be Healed?
EPC Capture

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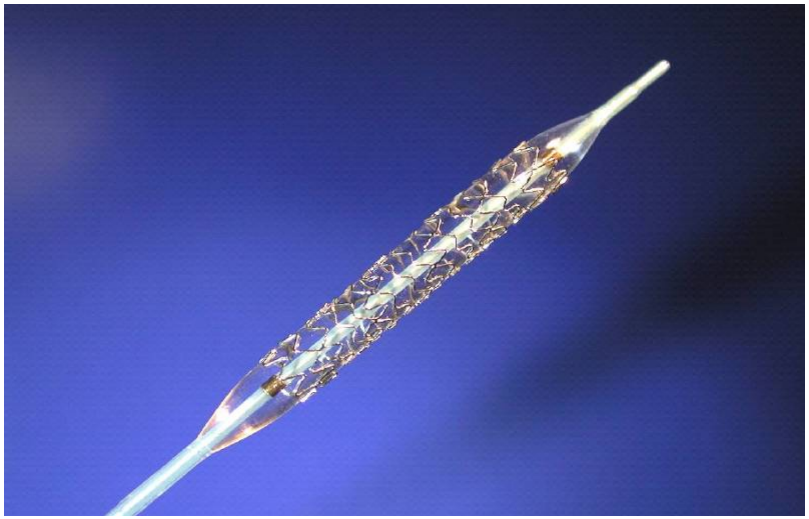
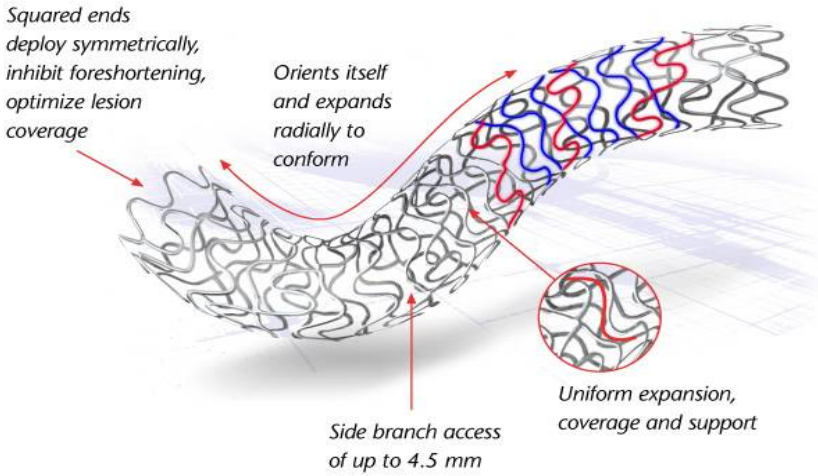
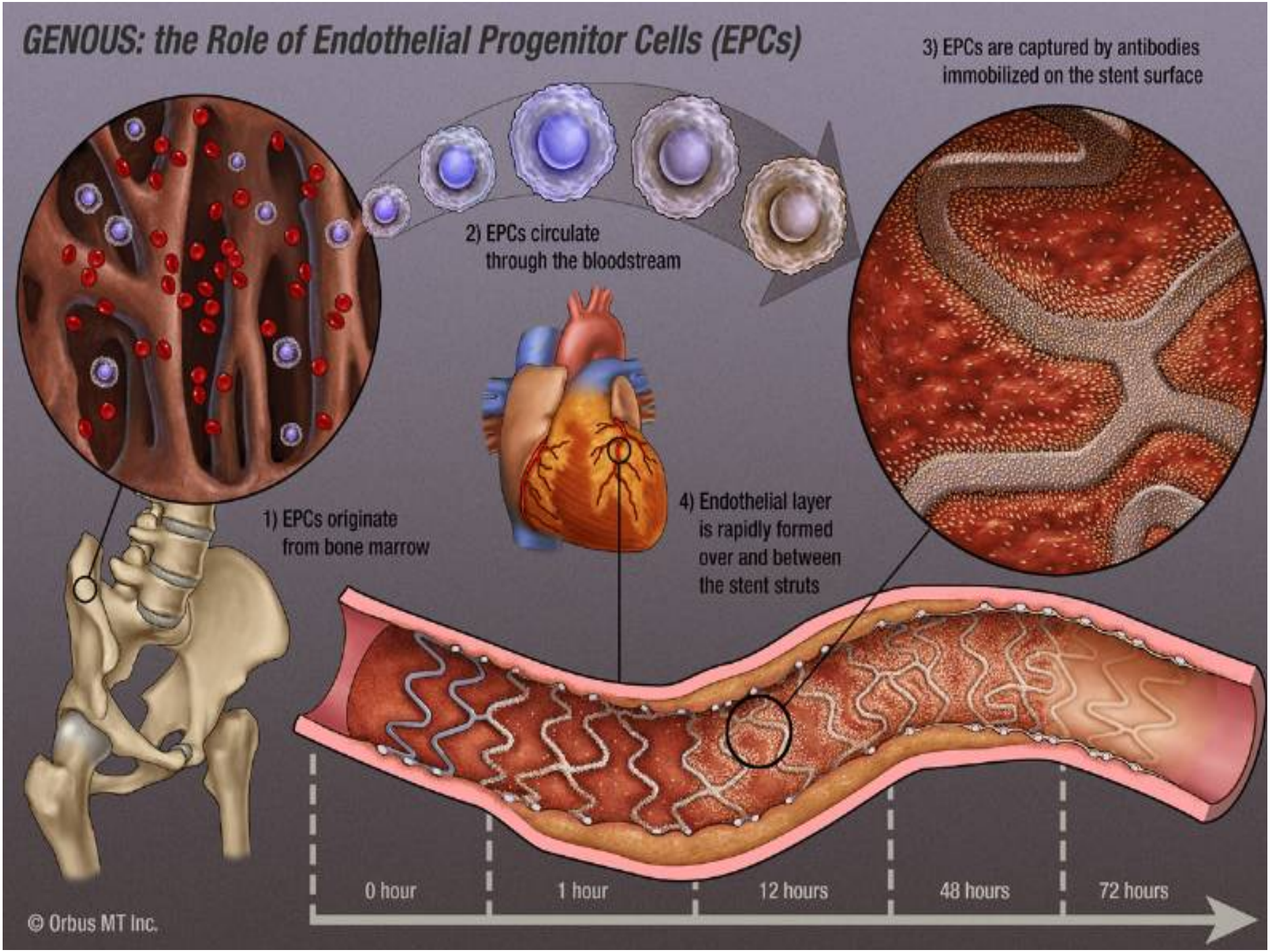
Genous Product Platform

- **R Stent**
- **Evolution 2 SDS**
- **Genous Bio-engineered surface**
  - **Anti-*h*CD34 Antibody**
- **Moisture-proof barrier packaging**
- **Sterile (gamma)**

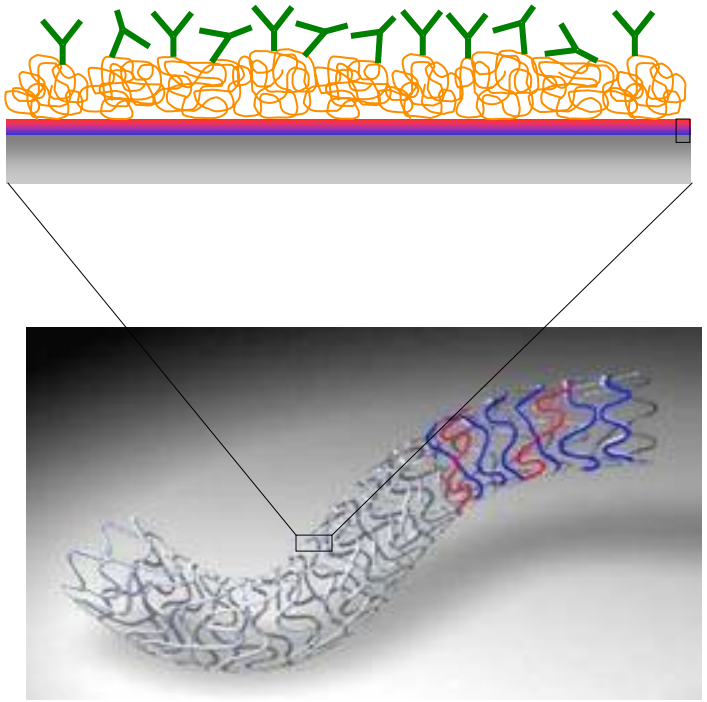




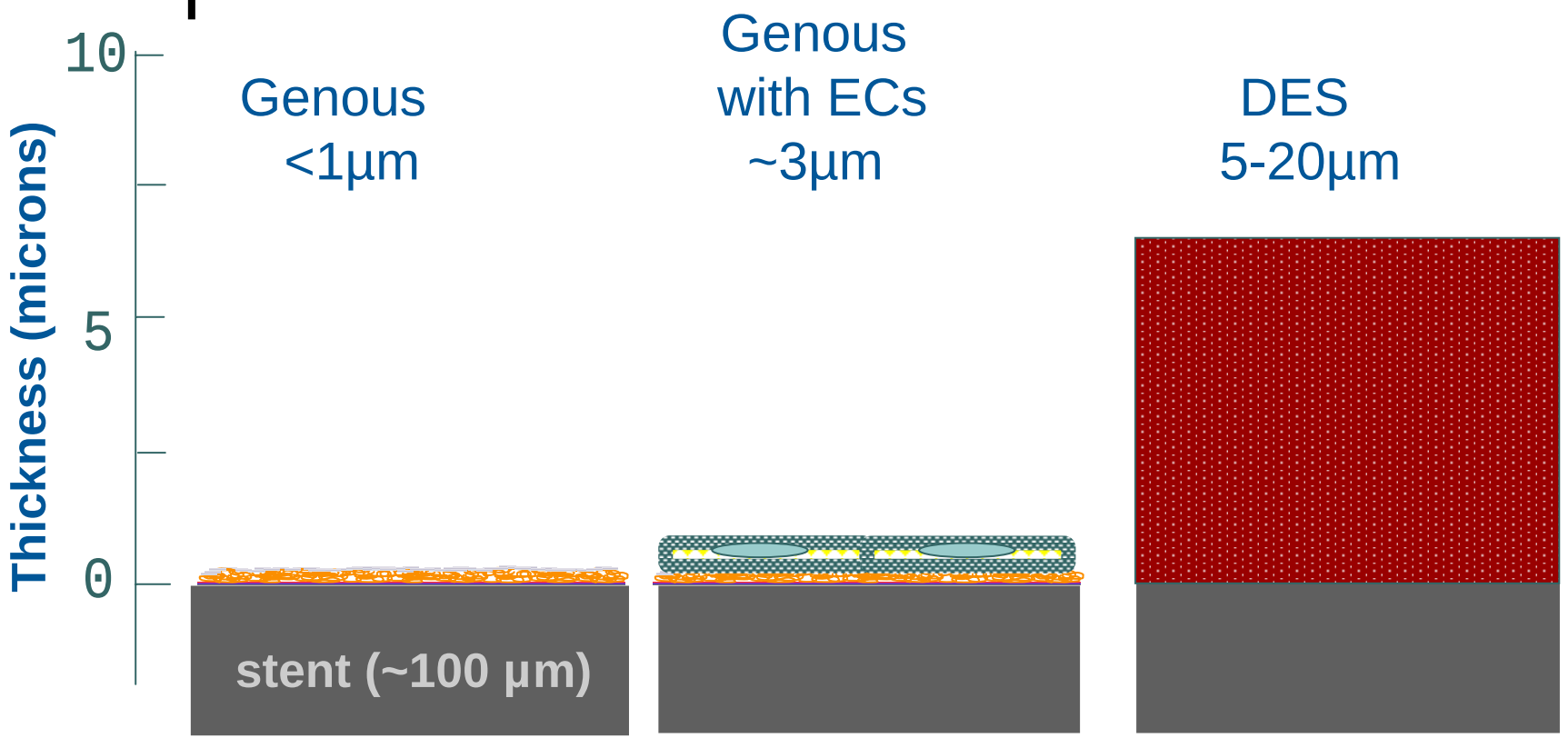

GENOUS: the Role of Endothelial Progenitor Cells (EPCs)
3) EPCs are captured by antibodies immobilized on the stent surface
2) EPCs circulate through the bloodstream
1) EPCs originate from bone marrow
4) Endothelial layer is rapidly formed over and between the stent struts
0 hour
1 hour
12 hours
48 hours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

Stent Surface Modification Procedure

CD34 antibody
base matrix layer
functionalization
stent surface

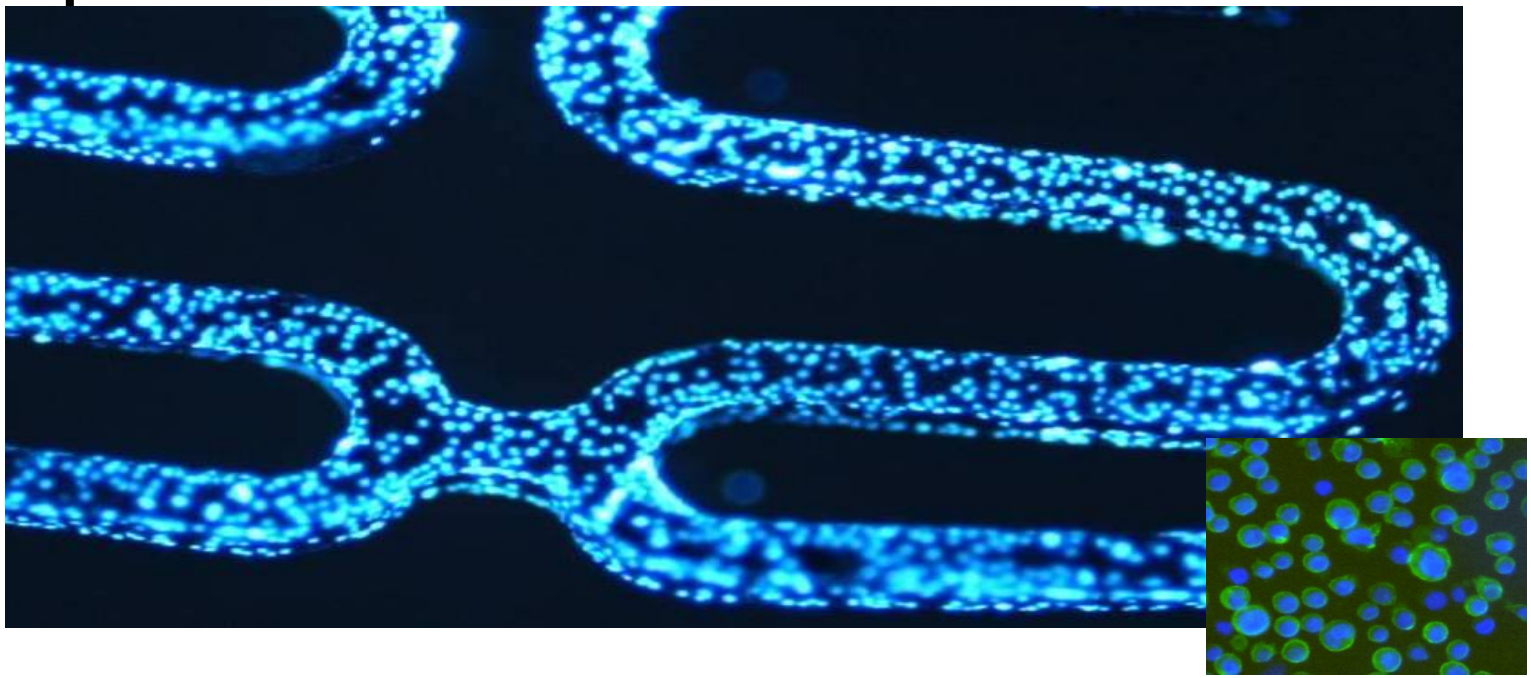


Genous Surface Thickness Compared to Drug-eluting Stent



Process parameters for controlling thickness:
MW, concentration, time, rinses

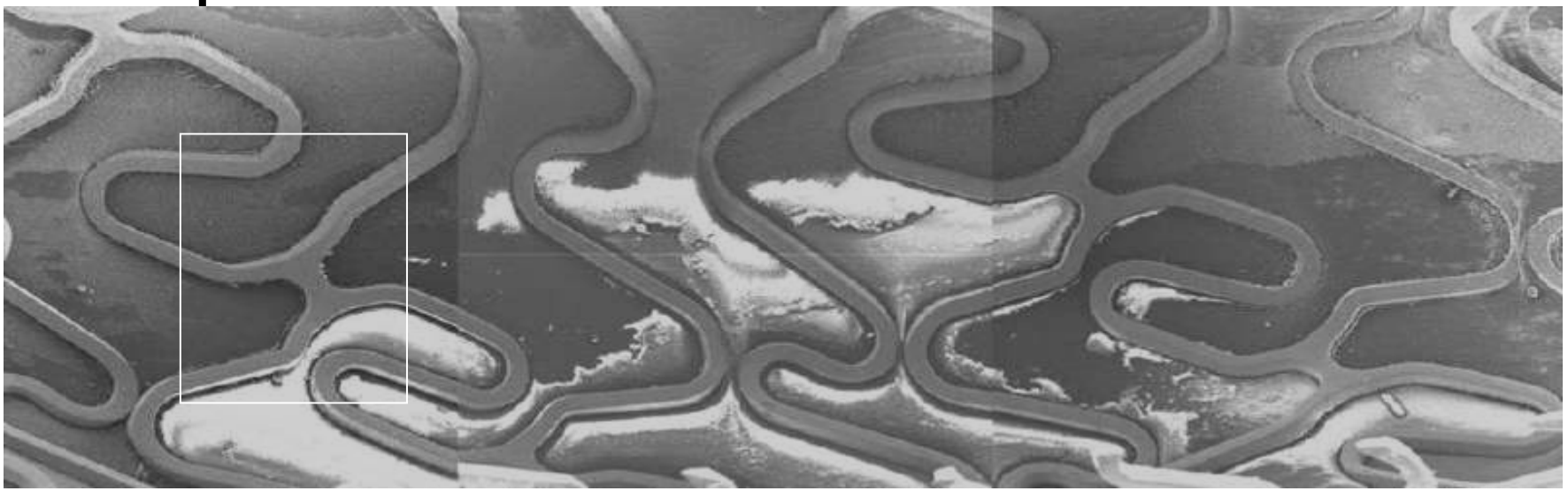
CD34+ Cell Binding

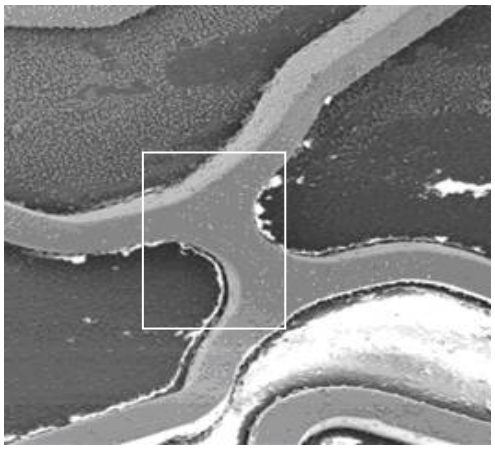


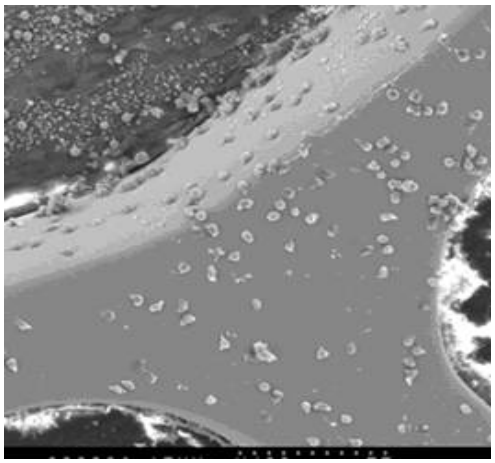
Anti-CD34 Stent with KG1a cells bound (stained with DAPI)
Insert: KG1a cells bound to an anti-CD34 antibody coverslip and dual-stained with DAPI and FITC-anti-CD34 antibody

Accelerated Endothelialization

Porcine Coronary 60 minute, Bare R stent



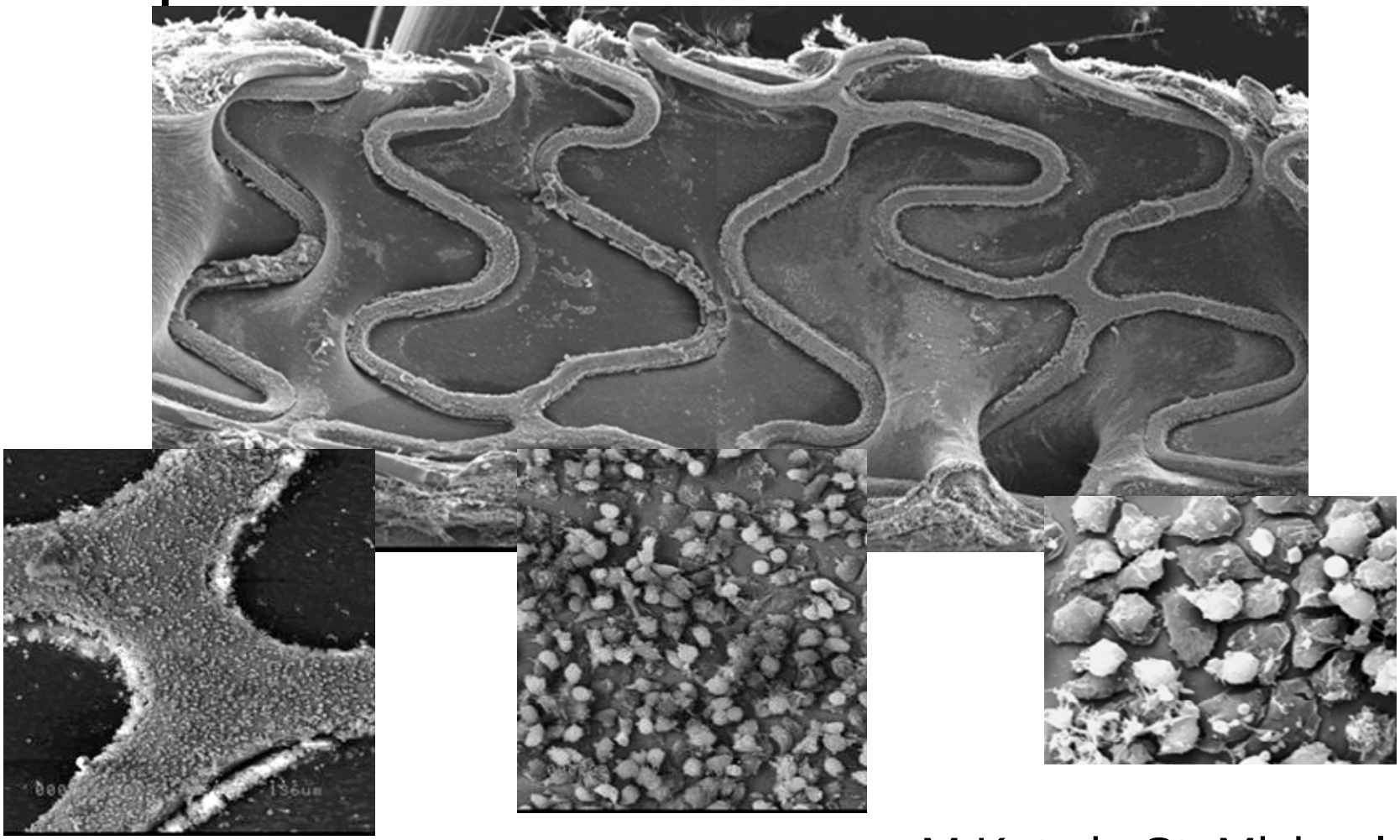




M Kutryk, St. Michaels

Accelerated Endothelialization

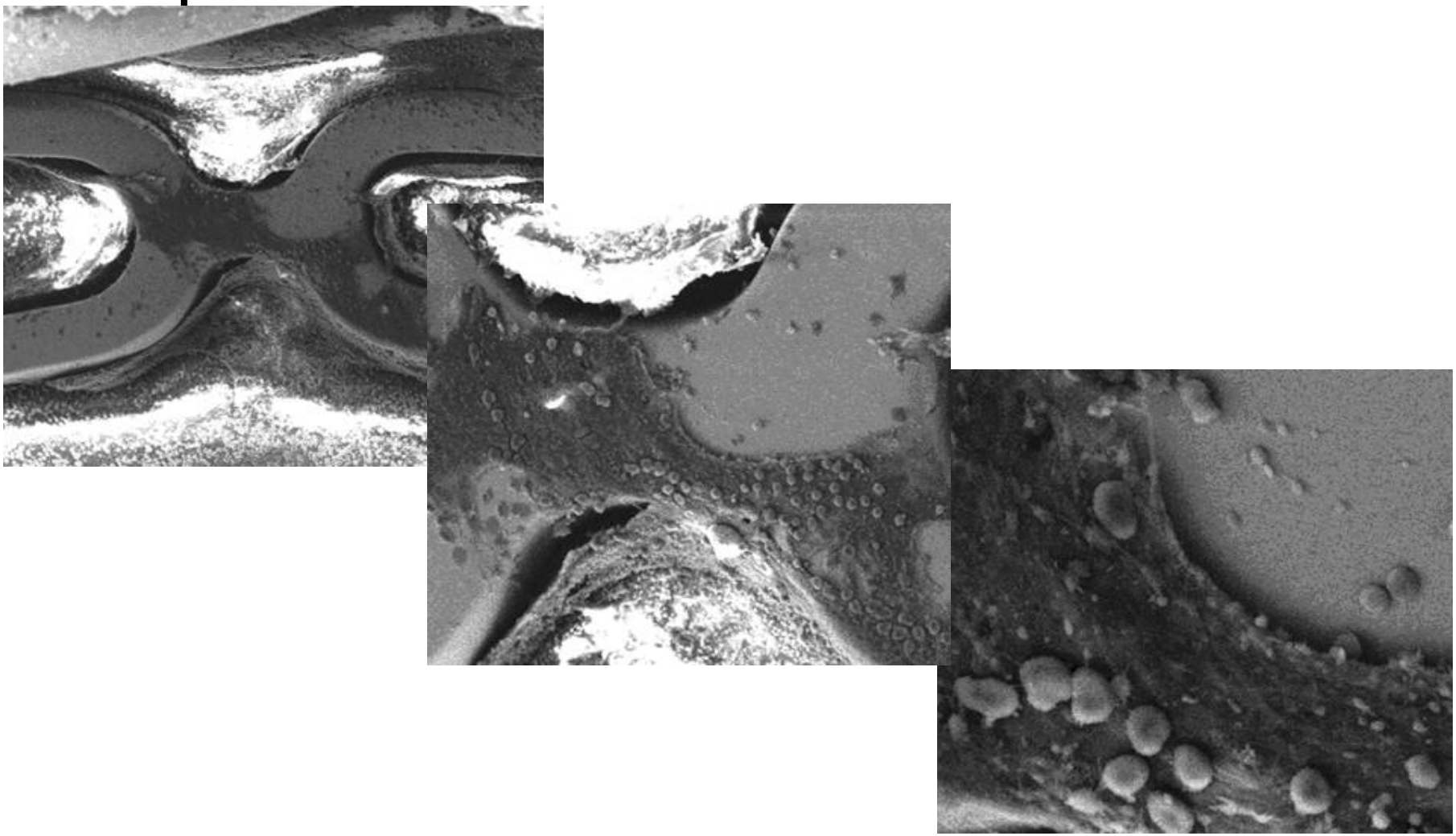
60 minute, EPC Capture stent



M Kutryk, St. Michaels

Accelerated Endothelialization

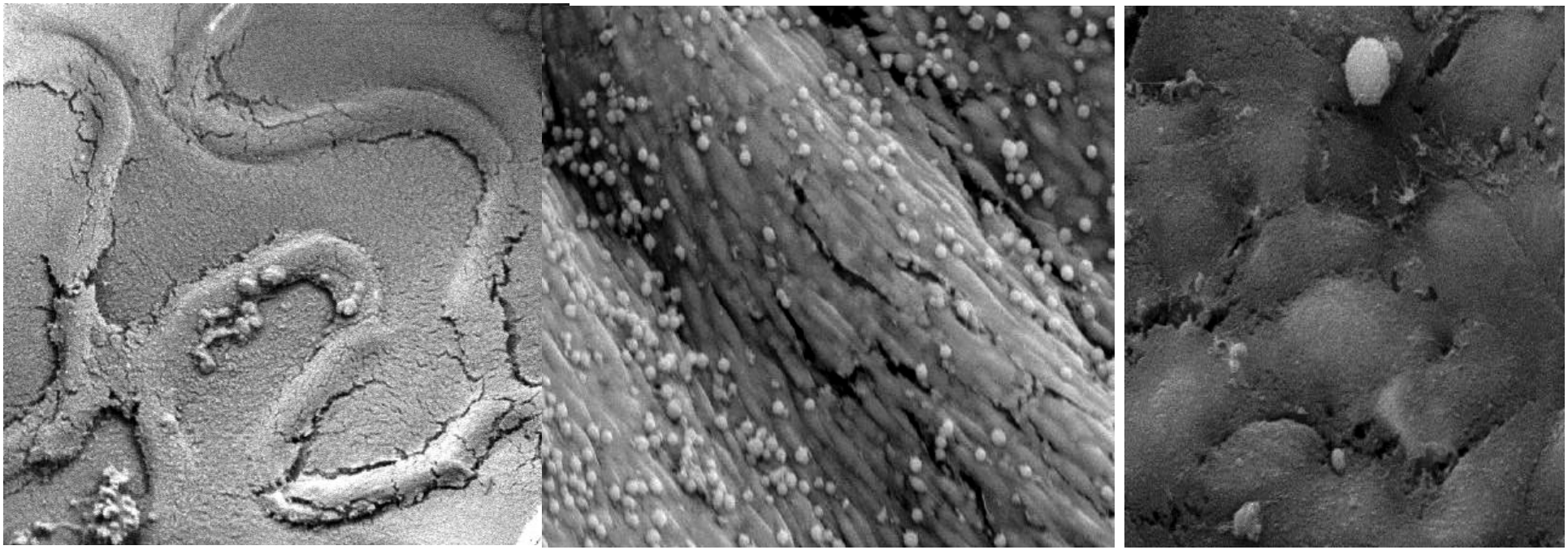
48 hour, Bare R stent



M Kutryk, St. Michaels

Accelerated Endothelialization

48 hour, EPC Capture stent



M Kutryk, St. Michaels

HEALING I: 6-month Angiographic Results - In-stent Analysis

	Pre (n=16) mean ± SD	**Post (n=16)** mean ± SD	**Follow-up (n=15*)** mean ± SD
RVD (mm)	2.63 ± 0.30	2.71 ± 0.31	2.69 ± 0.32
MLD (mm)	0.95 ± 0.33	2.47 ± 0.29	1.84 ± 0.56
DS (%)	63.7 ± 11.9	8.9 ± 3.4	32.1 ± 16.7
Late Loss (mm)			0.63 ± 0.52
Binary Restenosis (%)			13.3 % (2)

* 6 month angiogram not available for 1 patient (refused; asymptomatic)

HEALING II: In-stent Analysis 6-month Angiographic Results

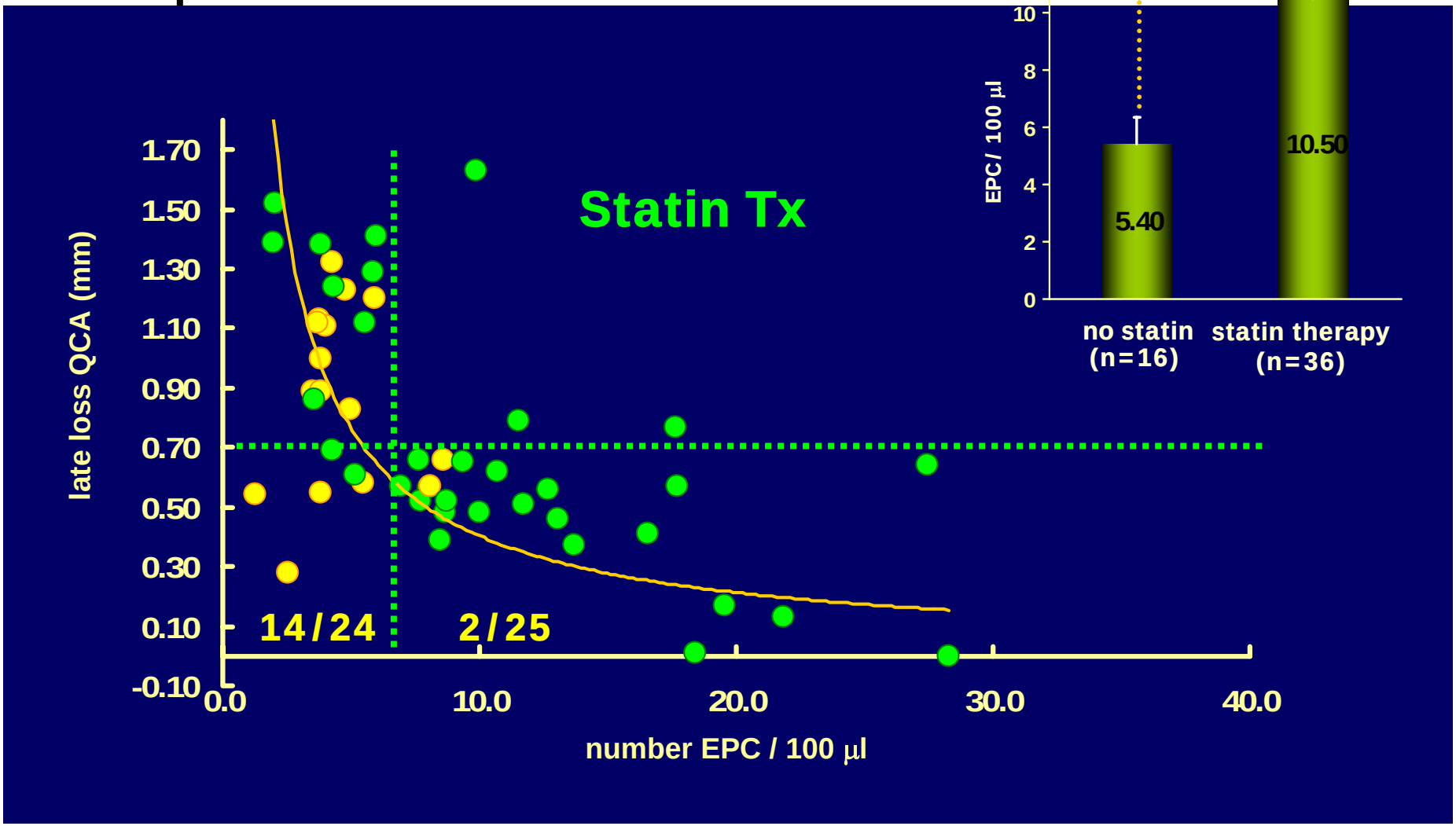
	Pre (n=63) mean ± SD	**Post** (n=62*) mean ± SD	**Follow-up** (n=58**) mean ± SD
RVD (mm)	2.63 ± 0.43	2.78 ± 0.40	2.56 ± 0.53
MLD (mm)	0.98 ± 0.24	2.45 ± 0.35	1.67 ± 0.51
DS (%)	62.0 ± 9.2	11.5 ± 5.4	34.9 ± 13.6
Late Loss (mm)			0.78 ± 0.39
Binary Restenosis (%)			17.2 % (10)

* One post-procedure film not available

** 6 month angiograms not available for 5 patients (2 patients died, 3 patients refused)

HEALING II

Correlation late luminal loss and circulating EPC titer at 6 months FU



Can Lumens Be Healed?
EPC Capture

A nice idea!

Healing & Second Generation DES

- **Improving each/all platform components of DES has potential to improve healing:**
  - Struts
  - Polymer
  - Drug
- **Shift from abluminal to luminal biotech based “DES” technologies such as EPC has a lot of promise, and a long way to go!**