Future DES Evaluation: Will We Know Whether "Different" is Really "Better"?

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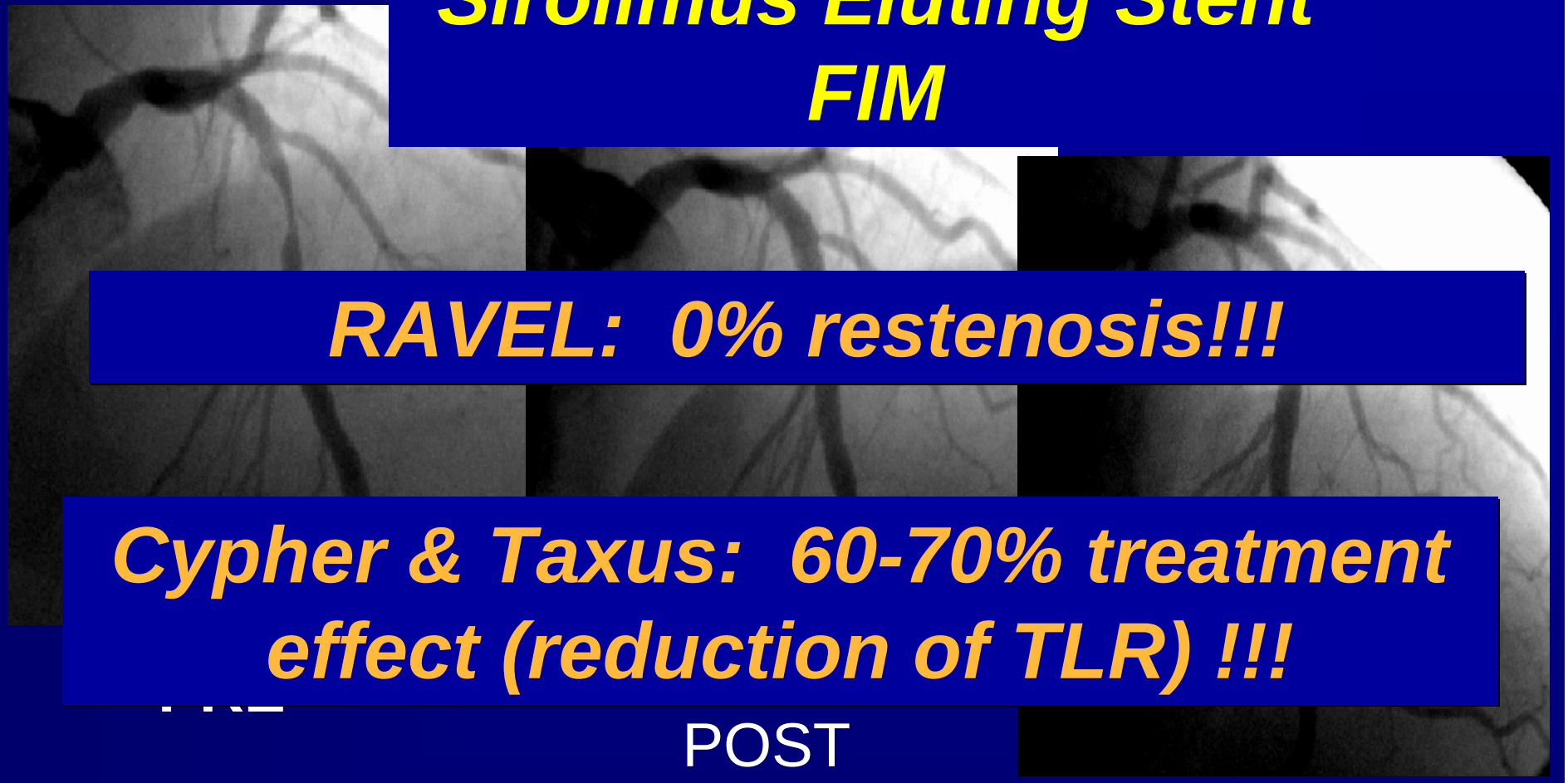
Sirolimus Eluting Stent FIM



RAVEL: 0% restenosis!!!

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

POST

12-MONTH FU

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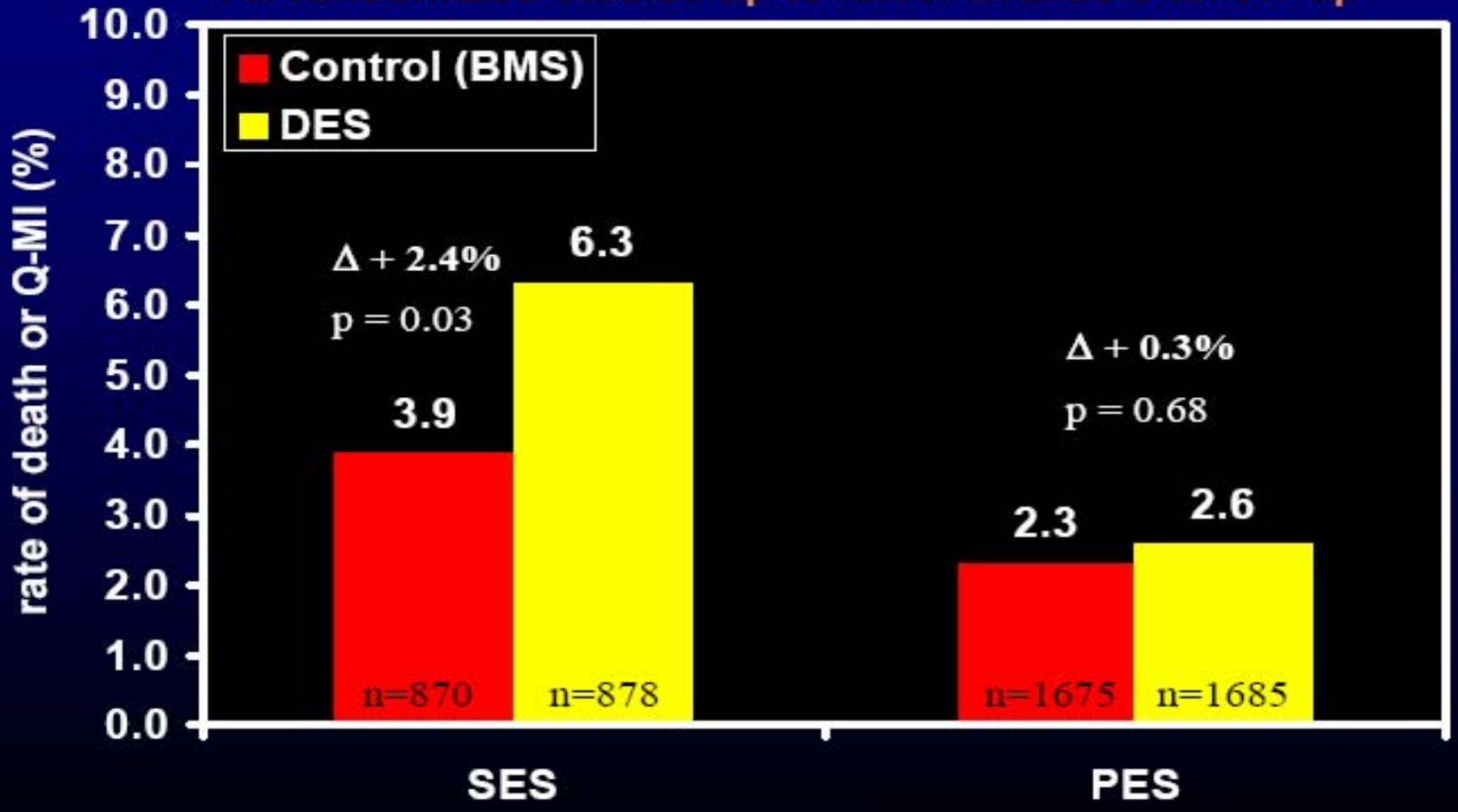
Incidence of Serious Adverse Events (Death or MI)

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

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

- Does local inflammatory response to polymer prevent endothelial healing?
- Is local drug delivery sufficient to inhibit hyperplasia also toxic to vessels or to endothelial healing?
- Can we stimluate endothelial recovery?
- What is “optimal” adjunctive anti-platelet therapy?

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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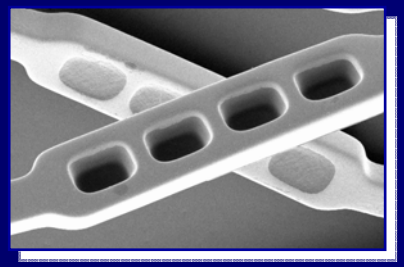
DRUG ELUTING STENTS:

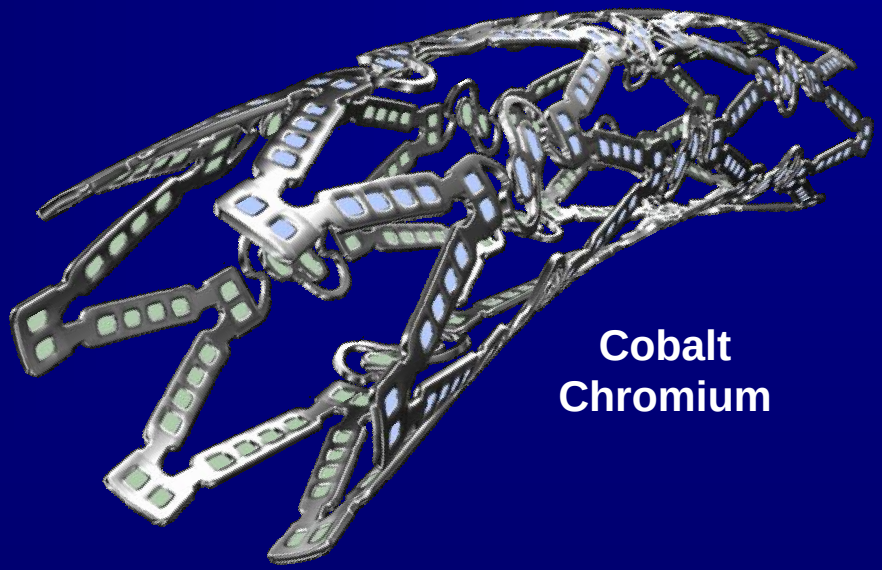
What if the polymer is minimal and goes away?

CoStar® Paclitaxel-Eluting Coronary Stent System

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

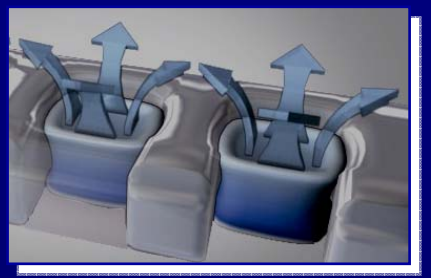


Reservoir Technology



Cobalt Chromium

Bioresorbable Polymer



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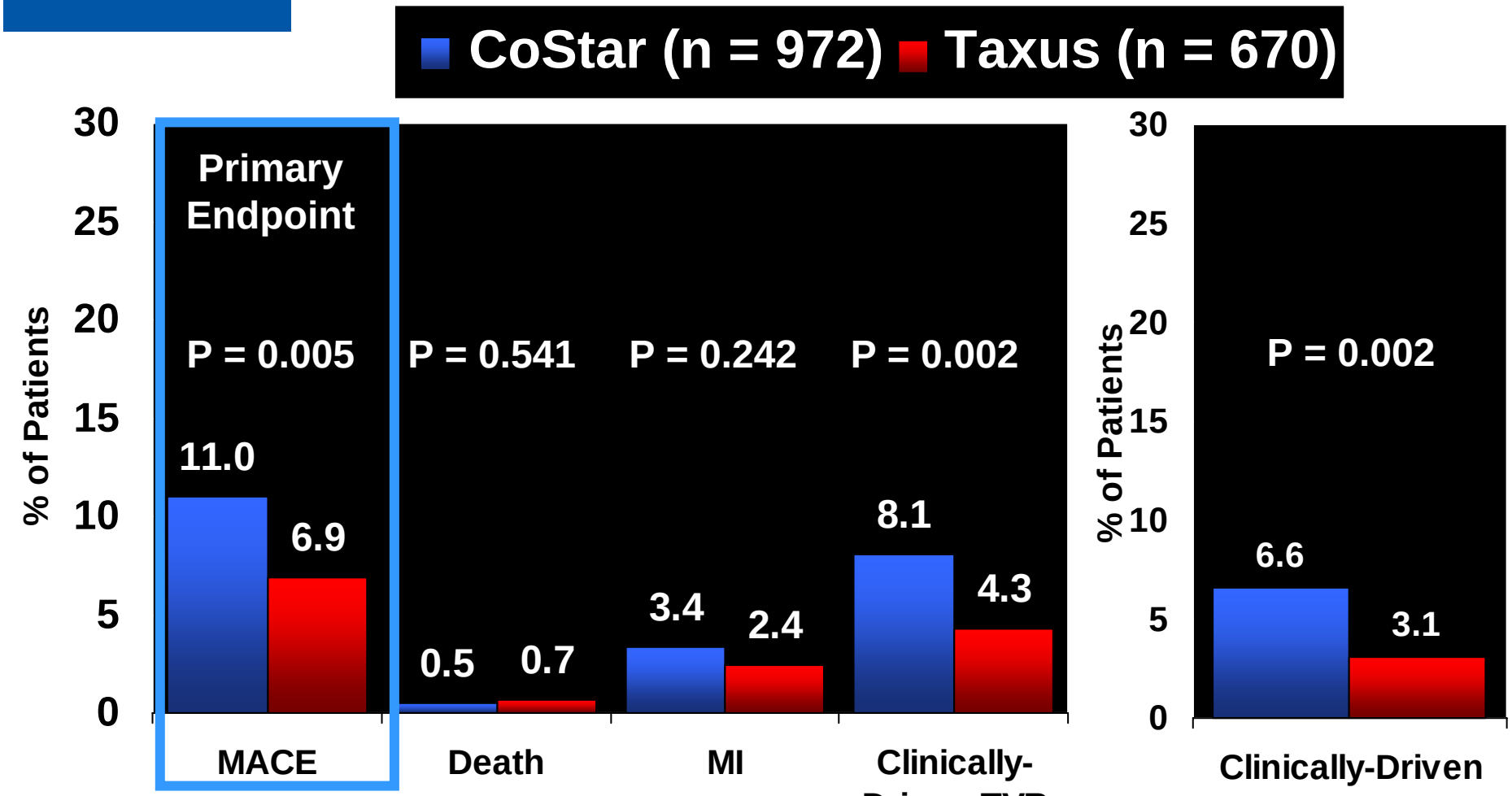
8-Month Non-hierarchical MACE and Clinically-Driven TLR



Krucoff MW et al, JACC in press

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

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.

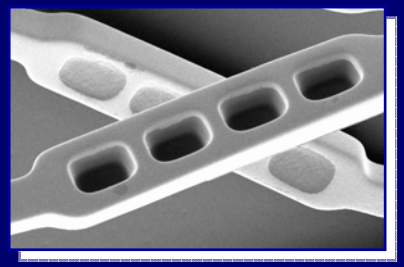
A pivotal study compared J&J's investigational device with one already sold by Boston Scientific (Charts, Fortune 500). Drug-coated stents are tiny wire mesh tubes used to prop open recently unclogged heart arteries and have until recently been reliable cash cows for device makers.

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).

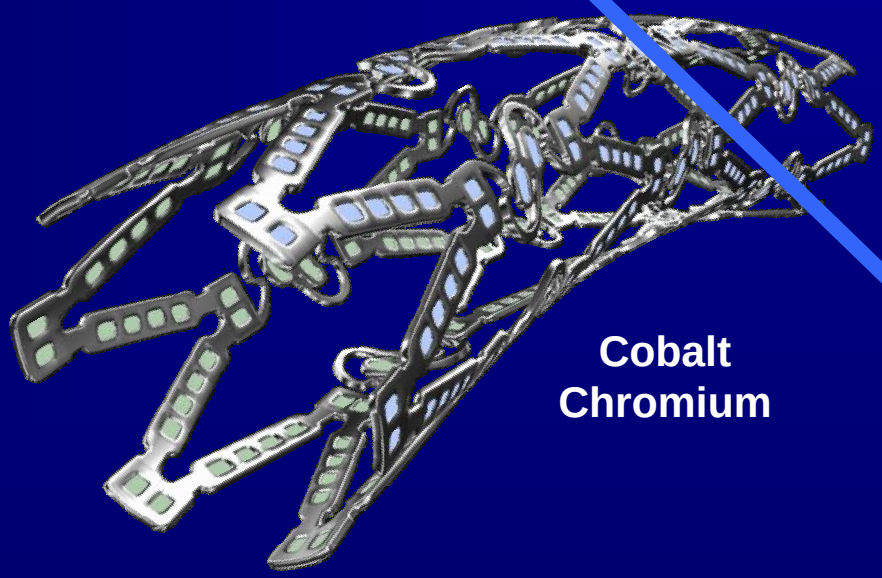
Cordis/Conor Coronary Stent

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

SIROLIMOUS

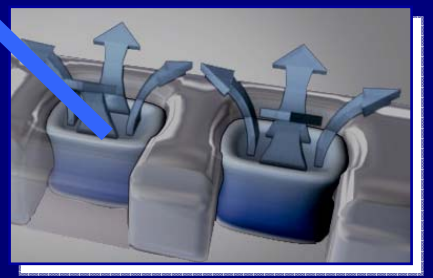


Reservoir Technology



Cobalt Chromium

Bioresorbable Polymer



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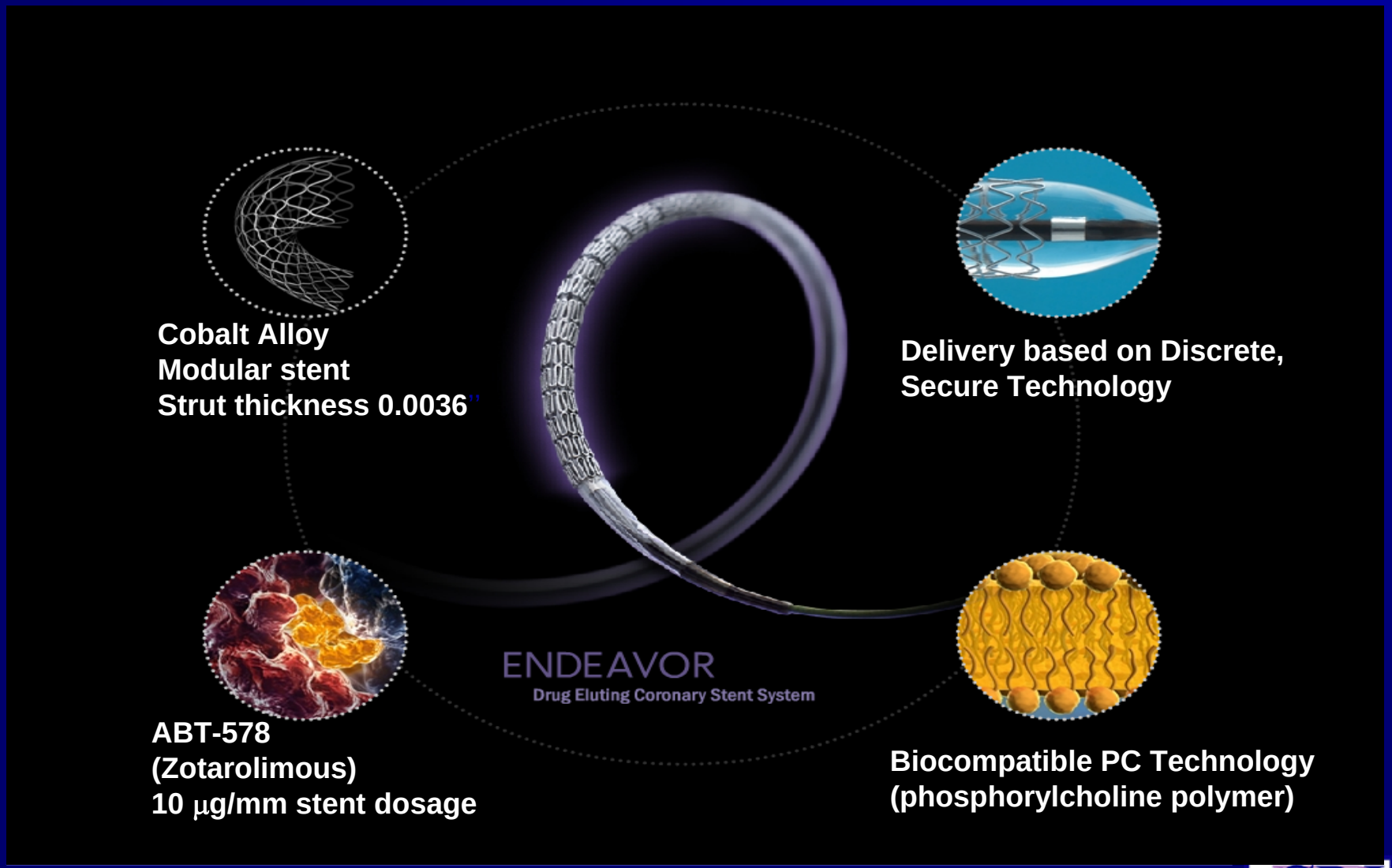
DRUG ELUTING STENTS:
Are Big Lumens Bad?

Components of the Endeavor Stent



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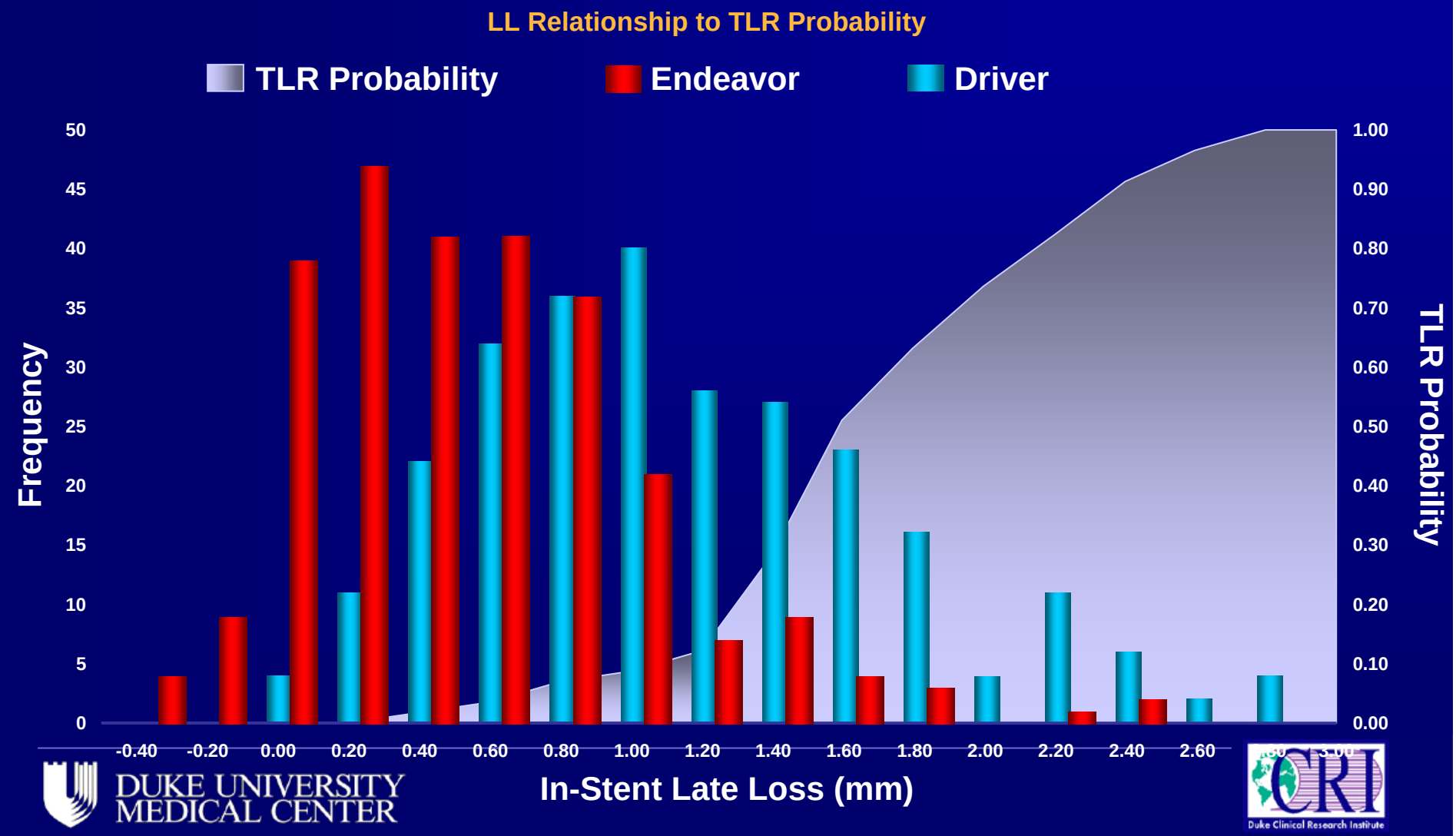
ENDEAVOR II: DES vs. BMS

In-Stent Late Loss Distribution



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ENDEAVOR III: DES vs DES

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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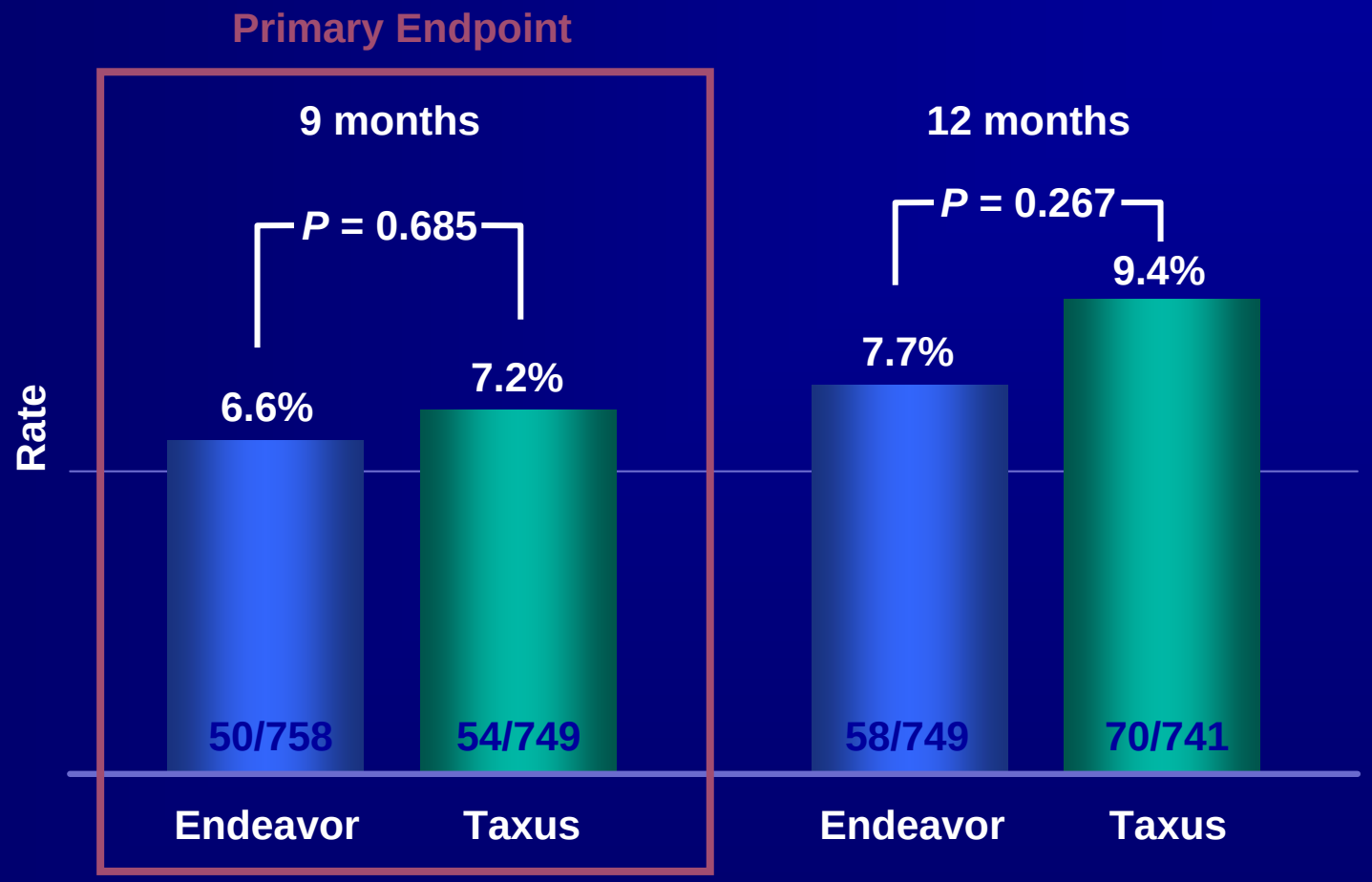
ENDEAVOR IV

Target Vessel Failure at 9 and 12 months



ENDEAVOR IV: Leon, TCT 2007 (trial analysis done using revised 9- and 12-month data set).

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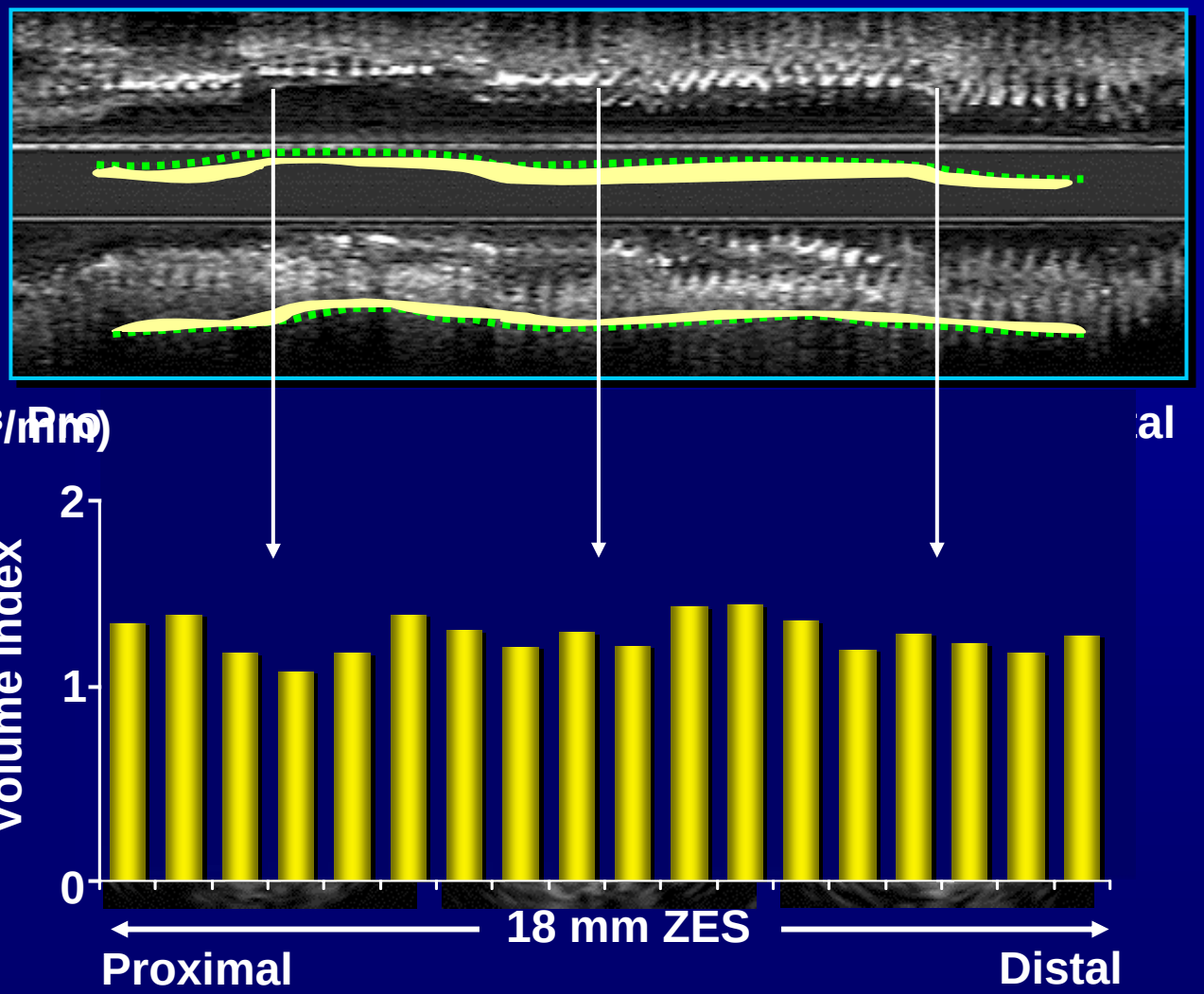
Endeavor: “Complete” NIH

Smooth Lumen, Even Neointimal Distribution



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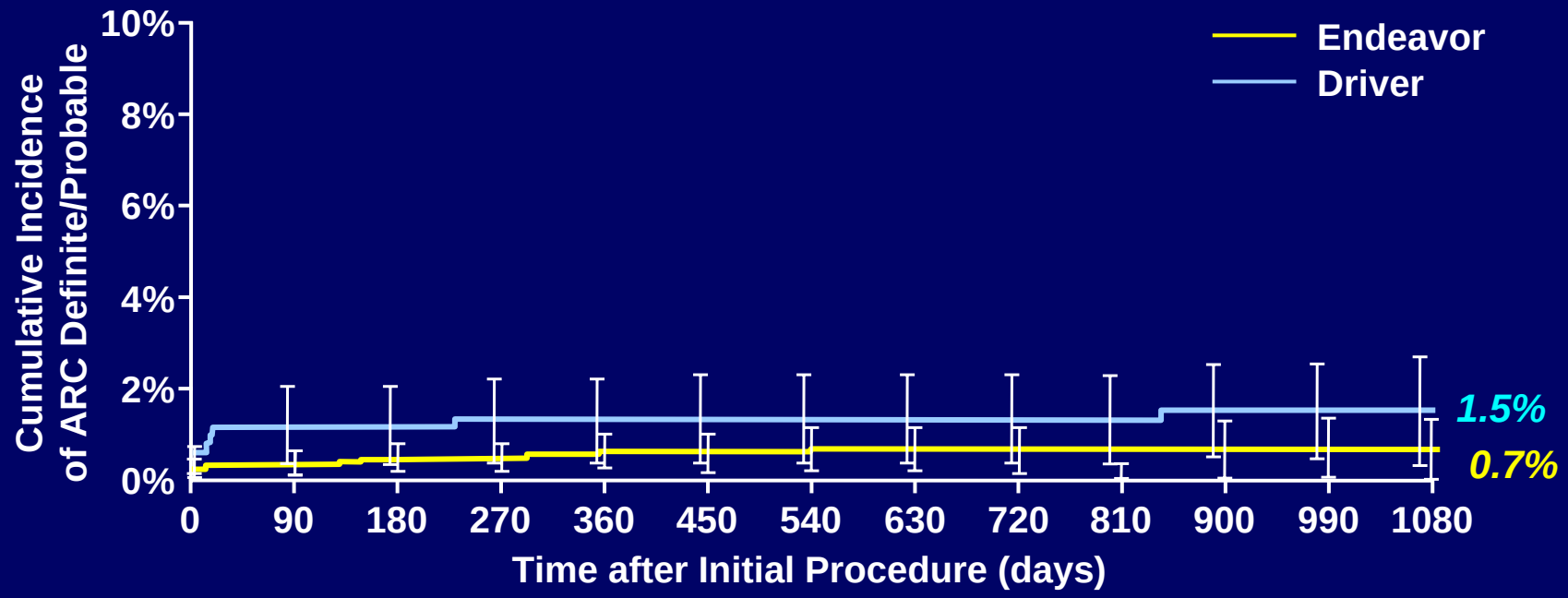
Endeavor Safety Analysis

Cumulative Incidence of ARC Definite/Probable ST to 1080 Days



Def/Prob Thrombosis	0	30	270	360	720	1080
Endeavor	**2132**	**2117**	**2085**	**2049**	**1247**	**648**
# Events	1	10	11	2	1	0
% CI	0.0%	0.5%	0.5%	0.6%	0.7%	0.7%
Driver	**596**	**585**	**581**	**575**	**560**	**542**
# Events	1	6	6	0	0	1
% CI	0.2%	1.2%	1.3%	1.3%	1.3%	1.5%

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?*

Maybe…

- ***in some patients***
- ***with some DES platforms***

DRUG ELUTING STENTS: *Are Big Lumens Necessarily Bad?*

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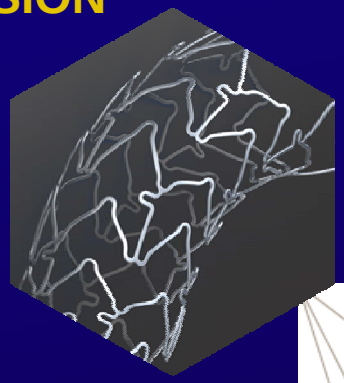
XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS)

PMA # P070015

U.S. FDA Circulatory Devices Panel
November 29, 2007
Washington, D.C.

XIENCE V
Scientific Design & Integration

MULTI-LINK VISION Stent



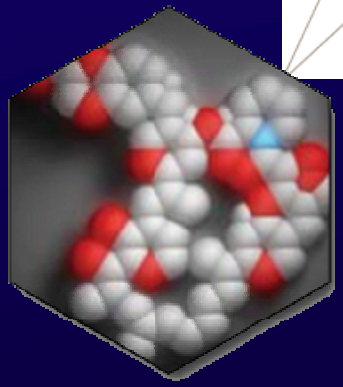
MULTI-LINK VISION Stent Delivery System

Deliverability

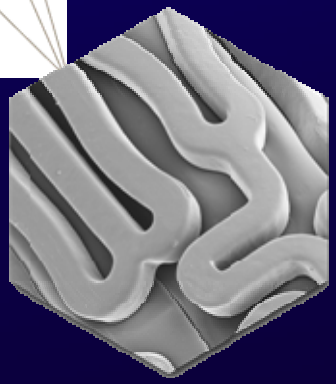
Efficacy

Safety

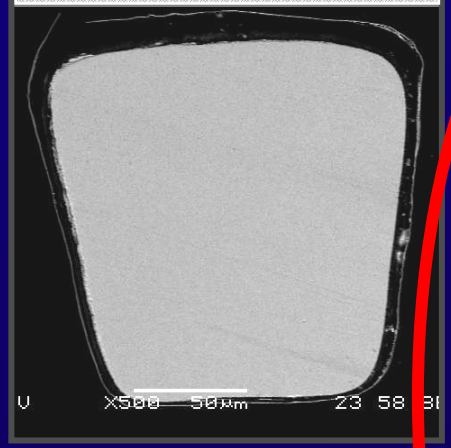
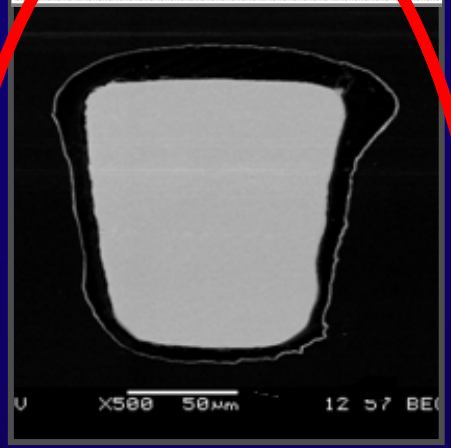
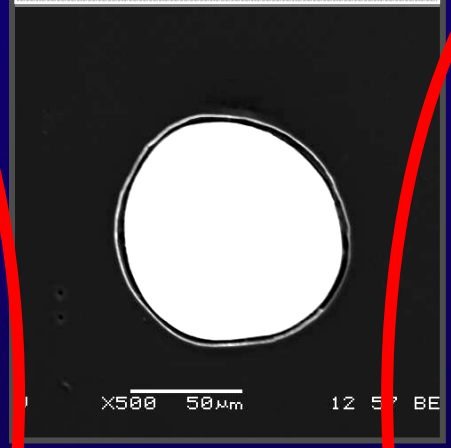
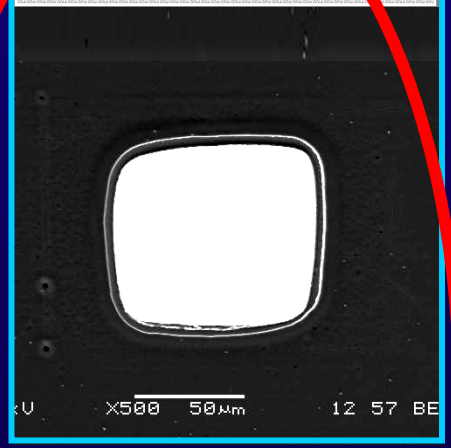
Everolimus



Fluorinated Copolymer



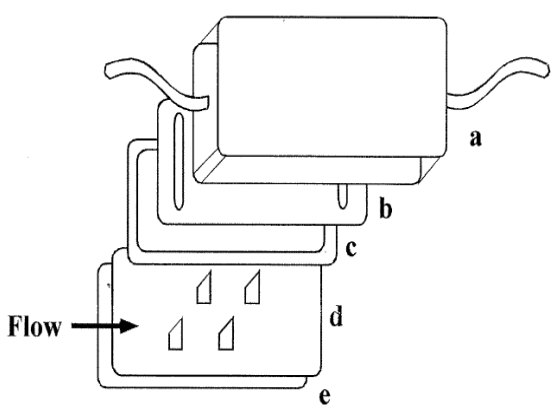
XIENCE V
Progression Towards Thinner Struts

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**

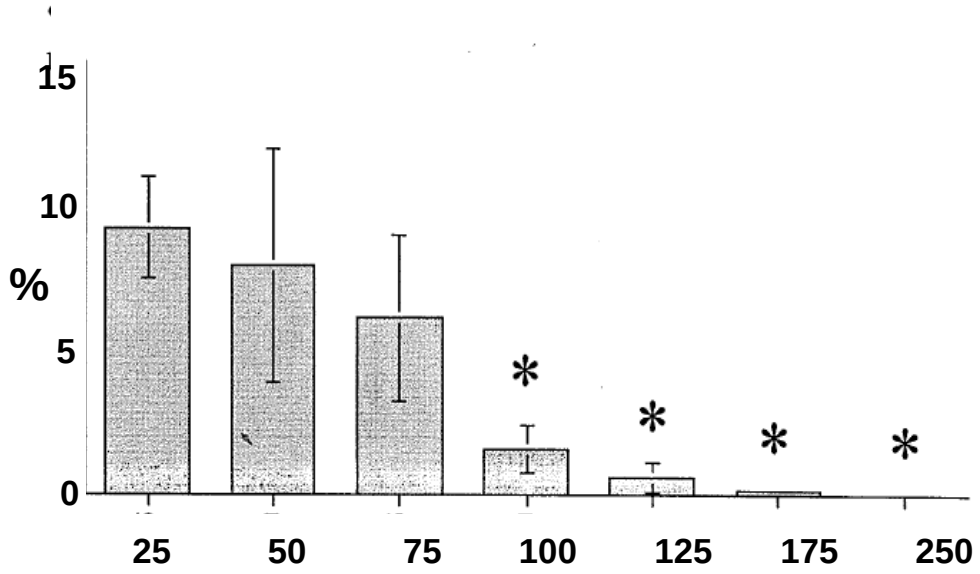
Abluminal coating thickness represented

Data on file at Abbott Vascular

XIENCE V
Endothelialization and strut thickness



Flow Chamber

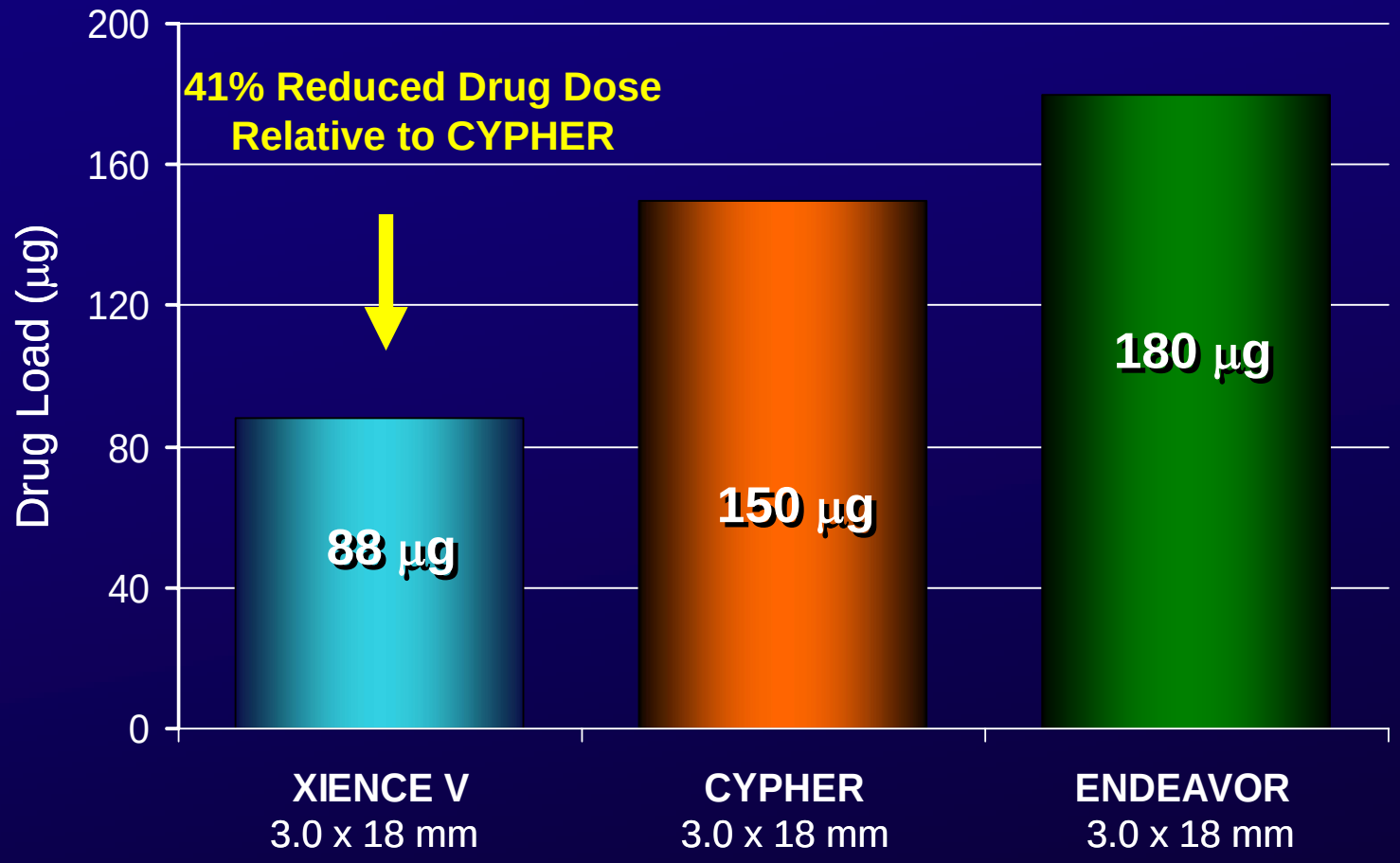


% Endothelialization vs. Obstacle Thickness (μm)

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

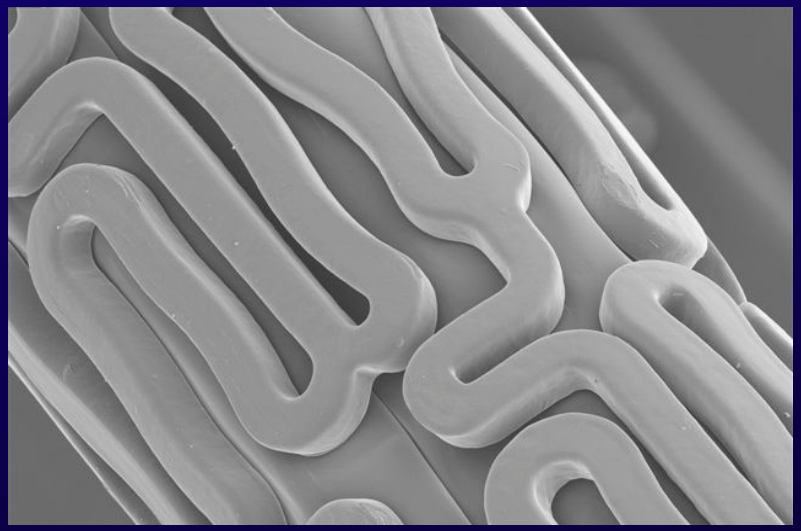


Achieved effectiveness with reduced drug loading

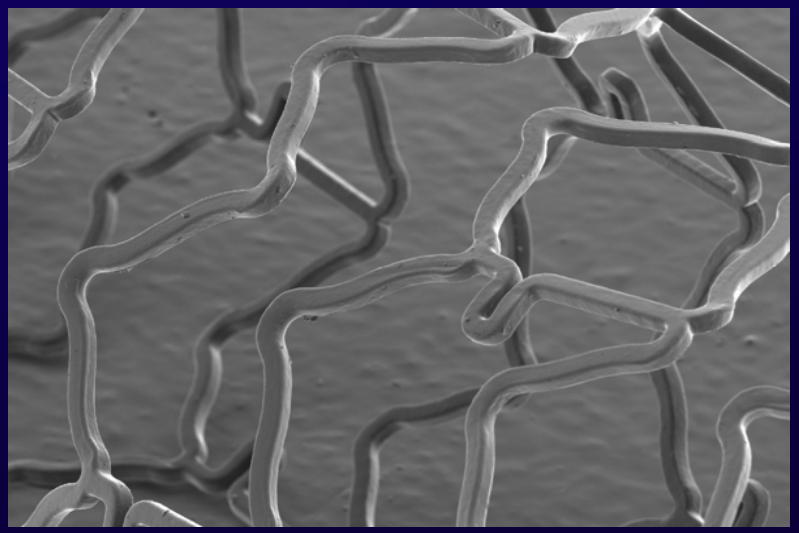
XIENCE V
Coating Integrity

- Coating designed to minimize webbing, bridging, and strut-strut contact in crimped state
- Coating integrity maintained after simulated use, stent expansion and fatigue testing

Crimped

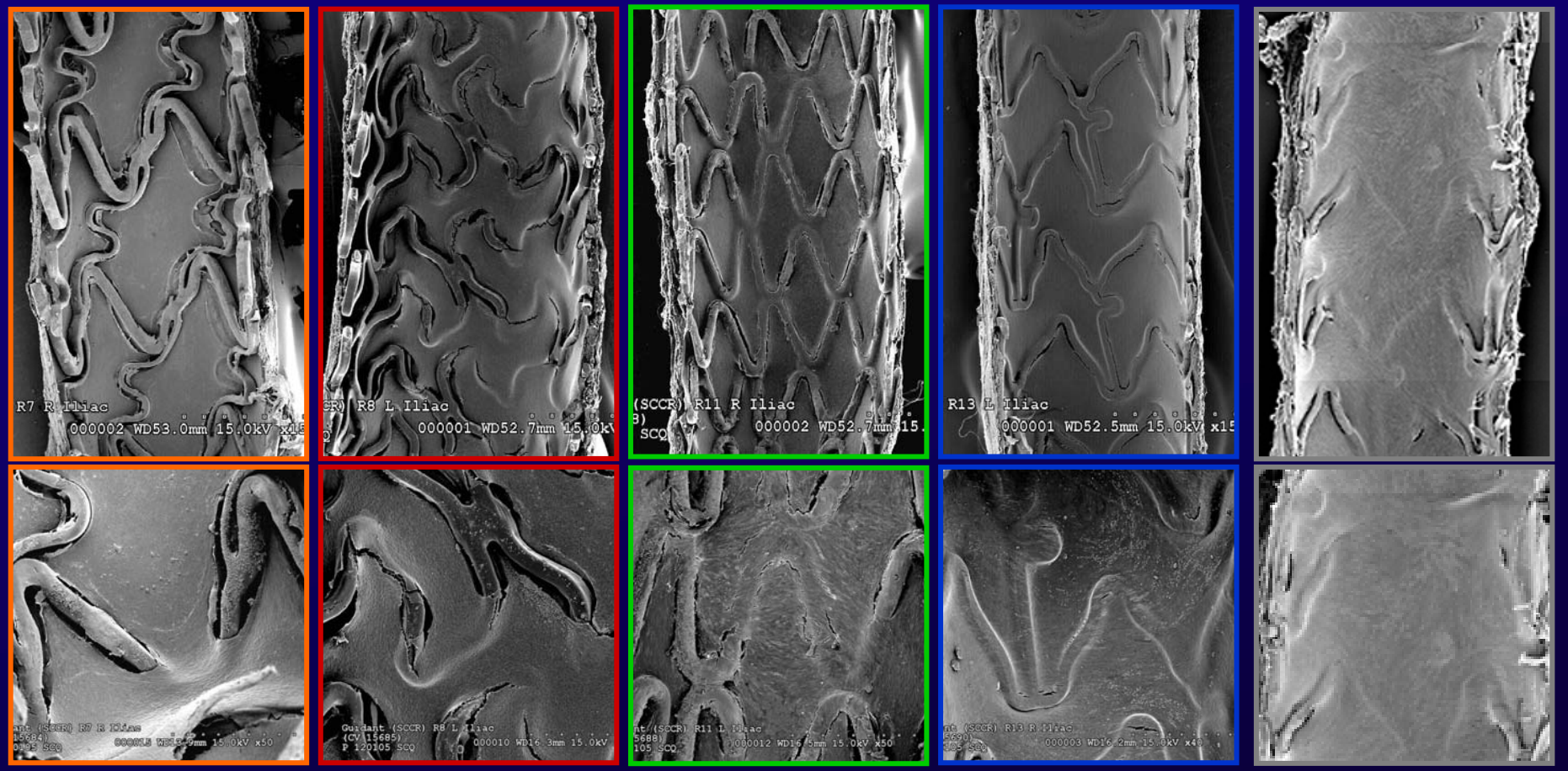


Post-expansion



Photos taken by and on file at Abbott Vascular

Qualitative Assessment of Endothelial Cell Coverage: 14-day Rabbit Iliac



CYPHER TAXUS ENDEAVOR XIENCE V VISION

Integrated Pre-Approval and Post-Approval Clinical Program (N > 16,000)

Pre-approval Clinical Data

SPIRIT First

SPIRIT II

SPIRIT III

SPIRIT III 4.0

SPIRIT III Jap

SPIRIT IV

SPIRIT V

XIENCE V
SPIRIT Women

XIENCE V USA

XIENCE India

DES vs DES

Consistency Across The Spectrum of Prospective Safety & Effectiveness

XIENCE V vs. TAXUS

Study	In-stent LL	In-seg LL	In-stent ABR	In-seg ABR	TLR @ 1 yr	MACE @ 1 yr	TVF @ 1 yr
SPIRIT II	↓ 69%	↓ 53%	↓ 63%	↓ 41%	↓ 73%	↓ 71%	↓ 51%
SPIRIT III	↓ 47%	↓ 50%	↓ 60%	↓ 47%	↓ 39%	↓ 42%	↓ 24%
SPIRIT II and III Pooled	↓ 58%	↓ 50%	↓ 61%	↓ 47%	↓ 47%	↓ 48%	↓ 29%

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

Vote: 9-1 Approval w/Conditions

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Duke Clinical Research Institute

DRUG ELUTING STENTS: *Are Big Lumens Necessarily Bad?*

Maybe not!

DRUG ELUTING STENTS:
Can big lumens be protected with DAP?

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Continuation Of Dual Antiplatelet Therapy in DES CODA-DES

An Expedited Cardiac Safety Critical Path Clinical Trial

http://www.fda.gov/oc/initiatives/criticalpath

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

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FDA News

FOR IMMEDIATE RELEASE
P06-147
September 27, 2006

Media Inquiries:
Press Office: 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA and Duke Clinical Research Institute Form Partnership to Collaborate on Cardiac Safety Virtual

FDA
U.S. Department of Health and Human Services
Food and Drug Administration
March 2004

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Duke Clinical Research Institute

DES & Extended Dual Antiplatelet Therapy: *What It Would Take: Collaboration*

Regulatory

- FDA:
  - CDER
  - CDRH
  - Off Comm
- E.U.
  - Austria
  - U.K.
  - Sweden
- MHLW/PMDA

Academia

- Duke
- Harvard
- Cleveland Clinic
- Columbia
- U of NM
- Wash Hrt Ctr
- London School of Hyg & Trop Med
- CVPath

Industry

- BSCI
- Medtronic
- Abbott
- Cordis/J&J
- Eli Lilly (Daichi)
- Sanofi
- BMS

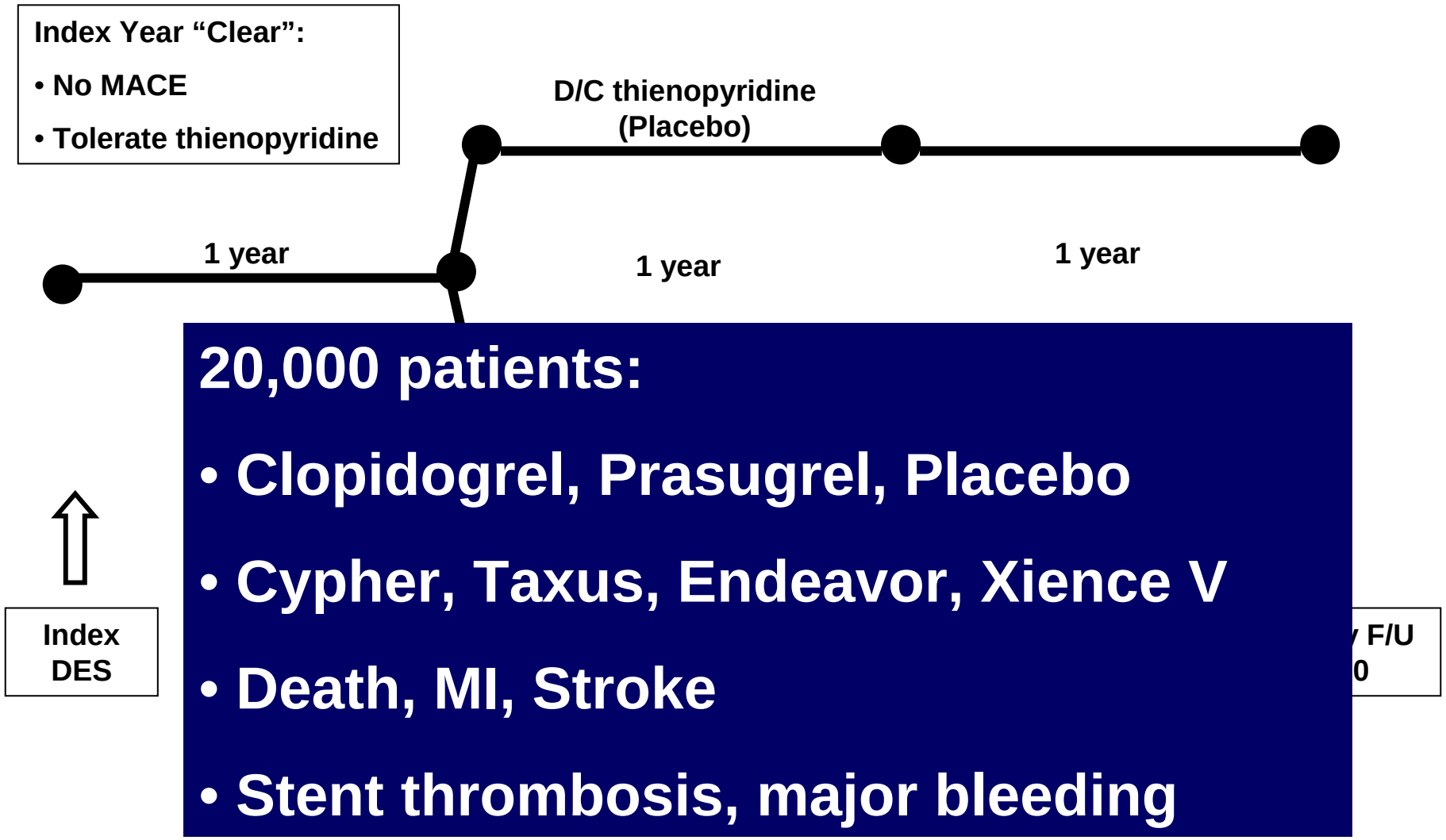
Societies

- ACC
- SCAI
- ESC

Federal

- NIH
- AHRQ

Figure 1: CODA-DES Study Design



Circulation

American Heart Association®

CONCLUSIONS

Understanding "Different" vs. "Better" DES:

- Novel polymer/drug delivery systems
- Better pre-clinical animal models
- Biological/mechanistic insights in vivo:
  - Role of QCA, IVUS and OCT
- Primary clinical endpoints, longer follow up
- Better understanding of adjunctive meds
- Global collaboration to work together!!!

Krucoff et al, *Circulation*. 2007.