ENDEAVOR 2008

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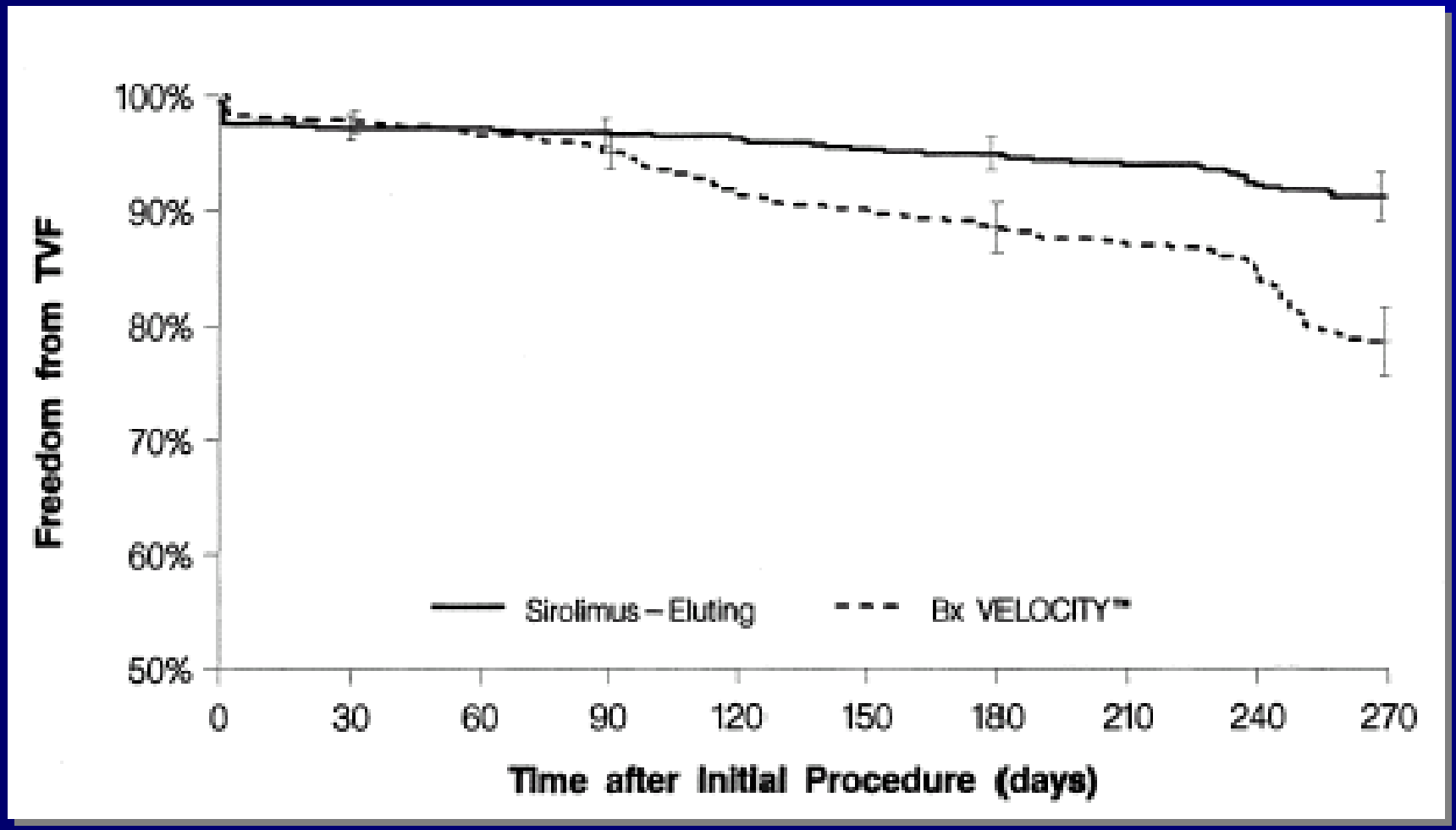
Slide Acknowledgments

- FDA Panel Presentations 2001-2007
- Marty Leon & Laura Mauri: Endeavor
- Renu Virmani
- Medtronic

SIRIUS: 59% Reduction in TVF



FDA Circulatory Devices Advisory Panel October 2001

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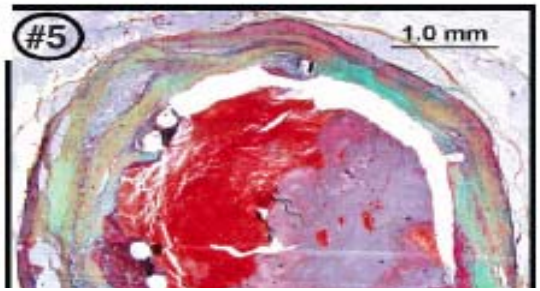
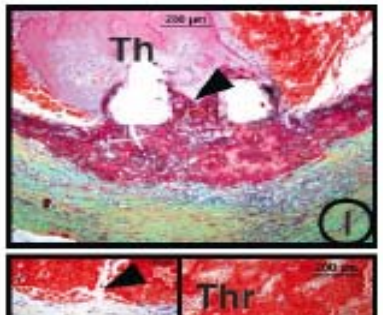
DRUG ELUTING STENTS:
More, Bigger Lumens

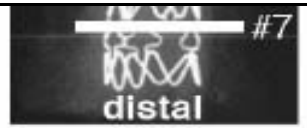
Lack of re-endothelialization at sites of thrombosis in DES

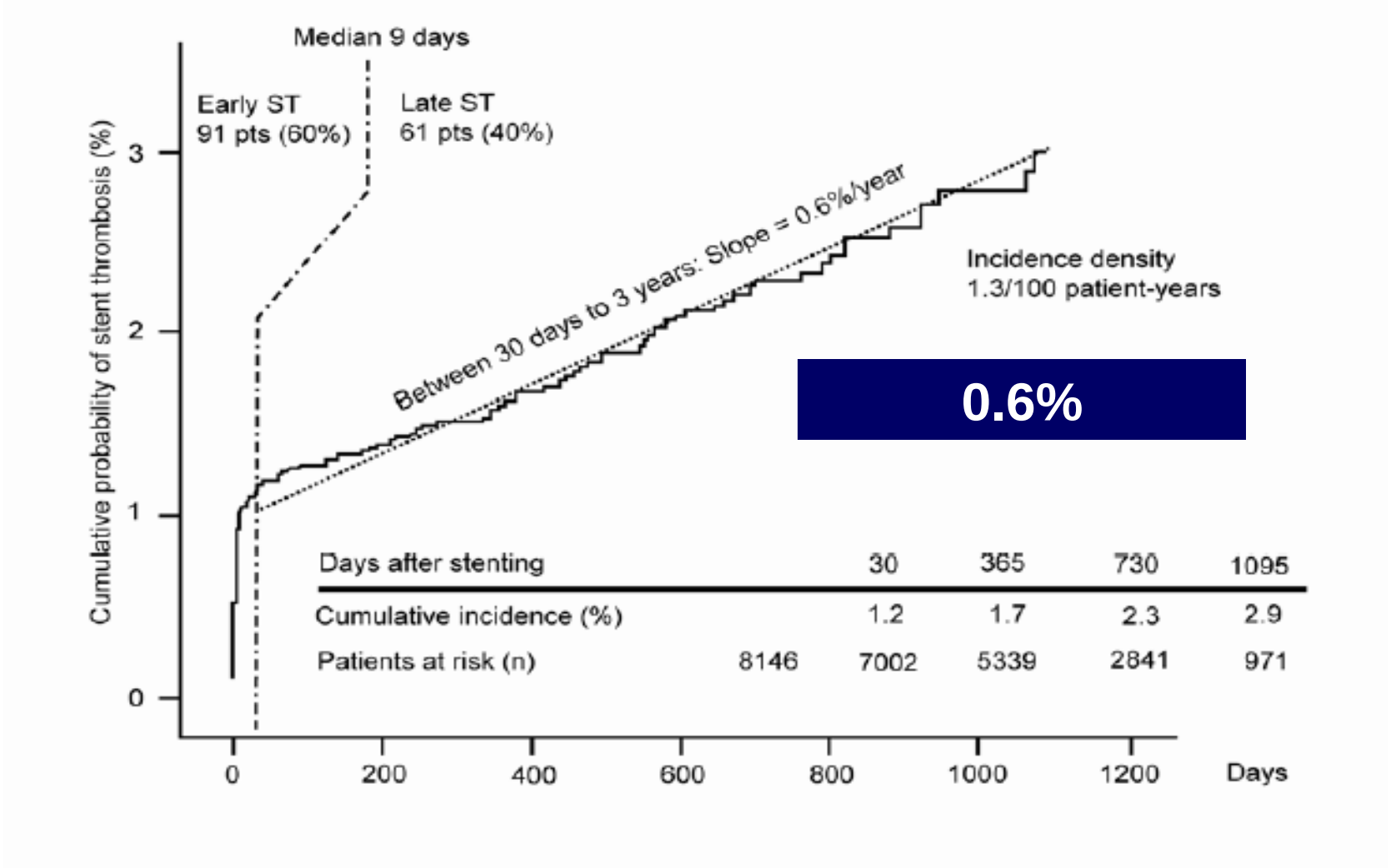




"A medical device is the replacement of one disease with another, hopefully a less severe one…."

William C. Roberts, MD ca. 1977





DES = drug eluting stent; N = number; pts = patients; ST = stent thrombosis. Adapted from (67)

Popma et al, FDA Advisory Panel Summary

DRUG ELUTING STENTS:
Are Big Lumens Bad?

Circulation

American Heart Association®
Learn and Live℠

Second Generation DES:

- **Combination Products: *Platform, Polymer, Drug***
- **Addressing healing/safety as well as restenosis**

Drug-Eluting Stents "Deliver Heartburn"

How Do We Spell Relief Going Forward?

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

"Breakthrough" technologies may produce rare or unexpected performance issues in postmarket use, especially when rapid market penetration into large patient populations outpaces the development of clinical knowledge. Although high-profile meetings or news media coverage may help draw attention to such issues, ultimately it is careful scientific

organizations, and academics are to be applauded for collaborative efforts to continue to collect and provide unbiased access to new and extended patient-level data, and several leading peer-reviewed journals have expedited publication to facilitate dissemination of these findings. For example, 7 articles on DES outcomes were included in the March 8

Krucoff et al, *Circulation*. 2007.

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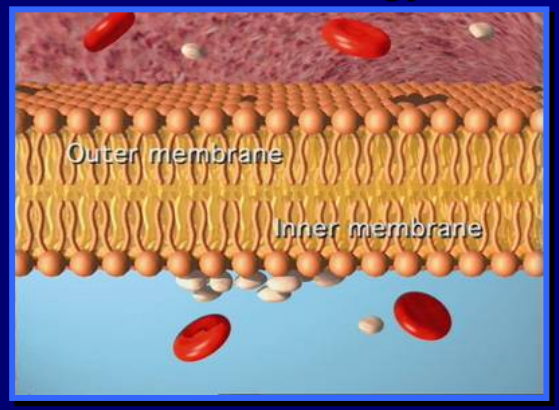
Endeavor: DES System Components

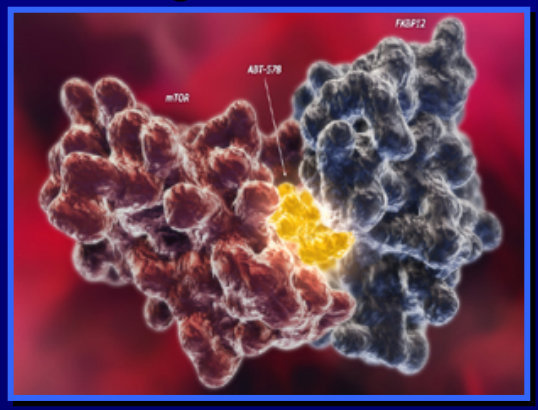
Driver® Cobalt Alloy Stent

Stent Delivery System

PC Technology



Drug: Zotarolimus



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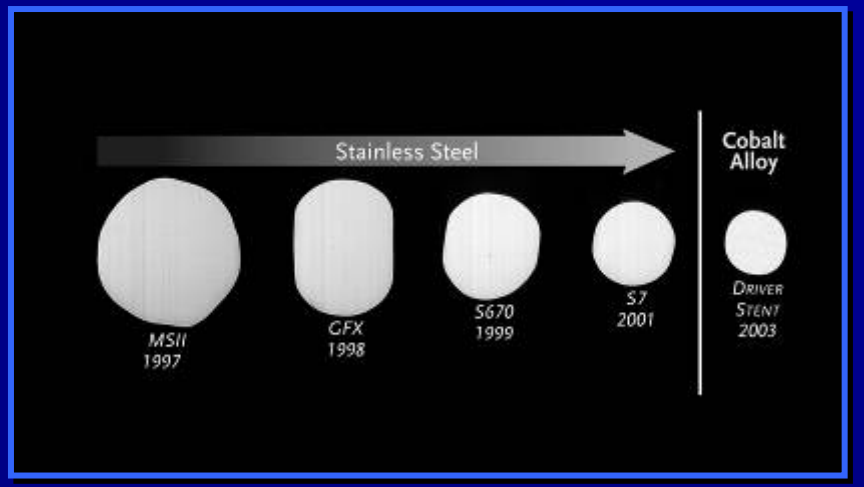
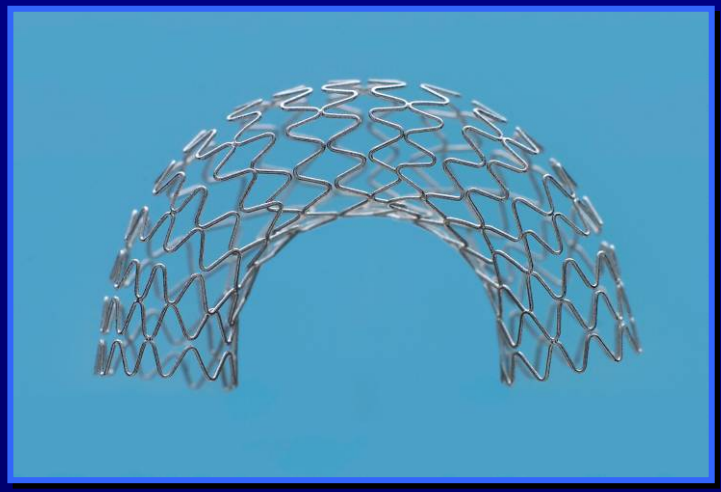
Endeavor: Driver Platform

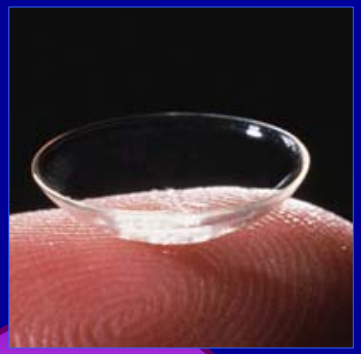
- **Atraumatic delivery**
  - Edgeless design
  - Thin struts, 0.0036 in.
- **Strength and visibility**
  - Cobalt alloy
  - Open-cell design
- **Vessel conformability**
  - 1-mm elements
  - Modular design

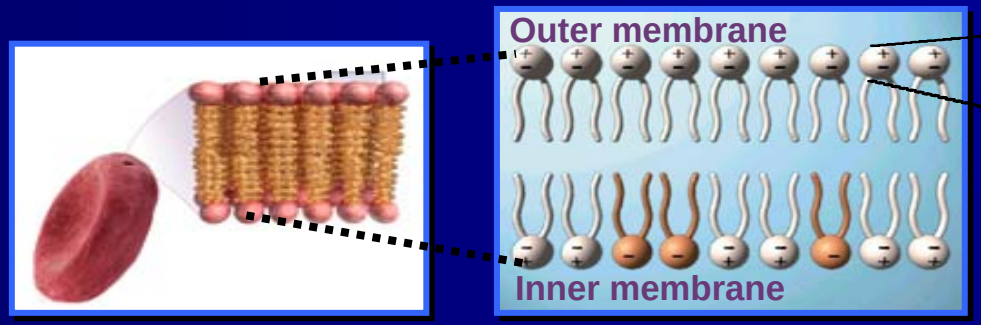


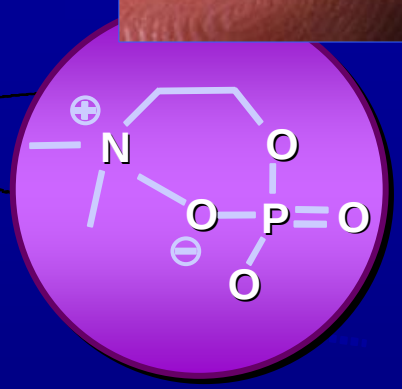


Endeavor: PC Technology Polymer

- The PC Technology polymer mimics the outside surface of a red blood cell

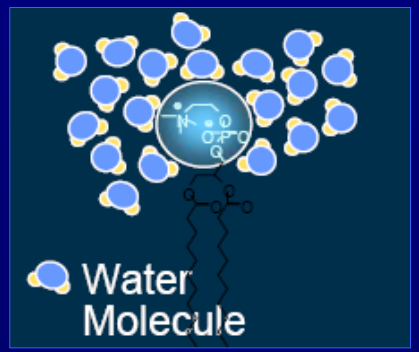






The Phosphorylcholine (PC) headgroup

- The PC Technology polymer has a high water affinity (hydrophilic)
- Water acts as a permanent barrier to protein adhesion



Hayward JA et al., *Biomaterials*. 1984;5:135–142.

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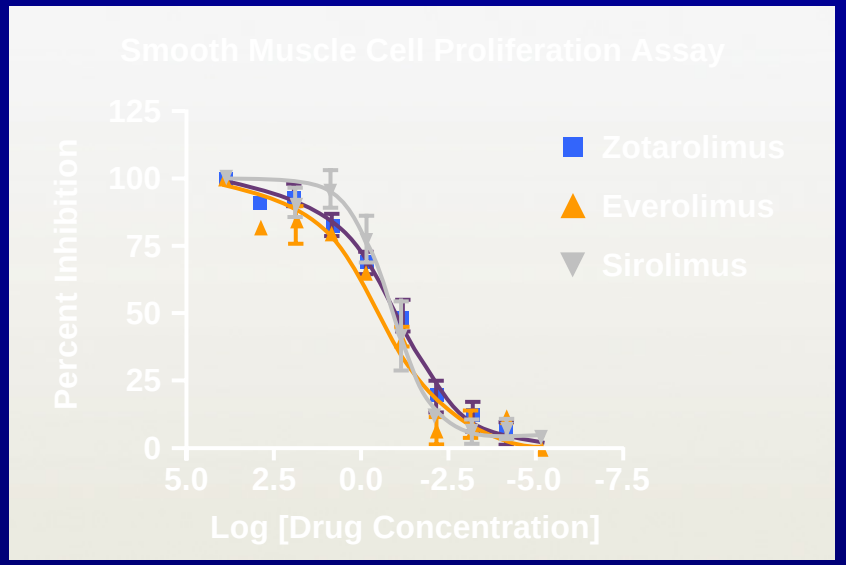
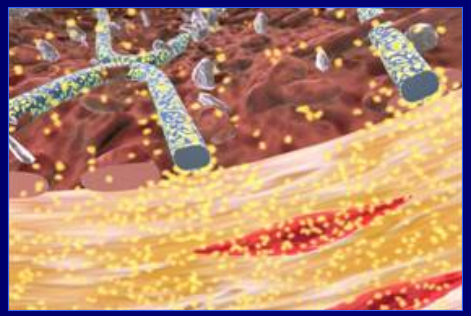
Endeavor: Zotarolimous Antiproliferative Drug

Non-cytotoxic
Blocks entry into S phase

Highly potent
Effective antiproliferative limus analog





Highly lipophilic
Enables rapid arterial tissue loading and drug retention

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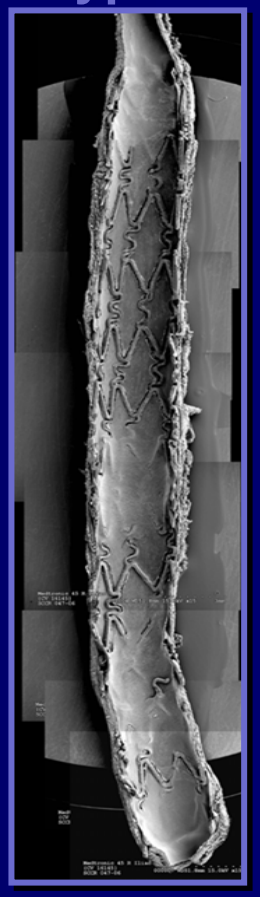
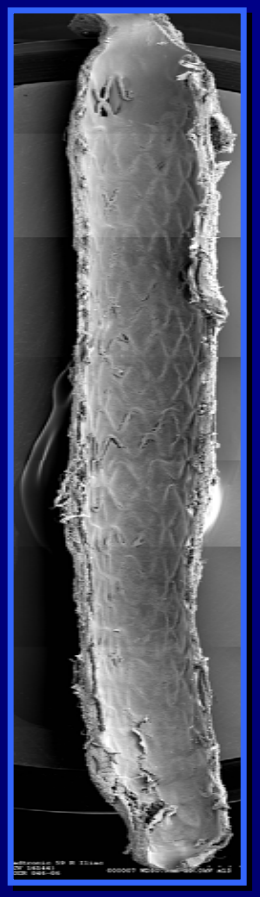
Endeavor Preclinical: 21 Day Endothelialization

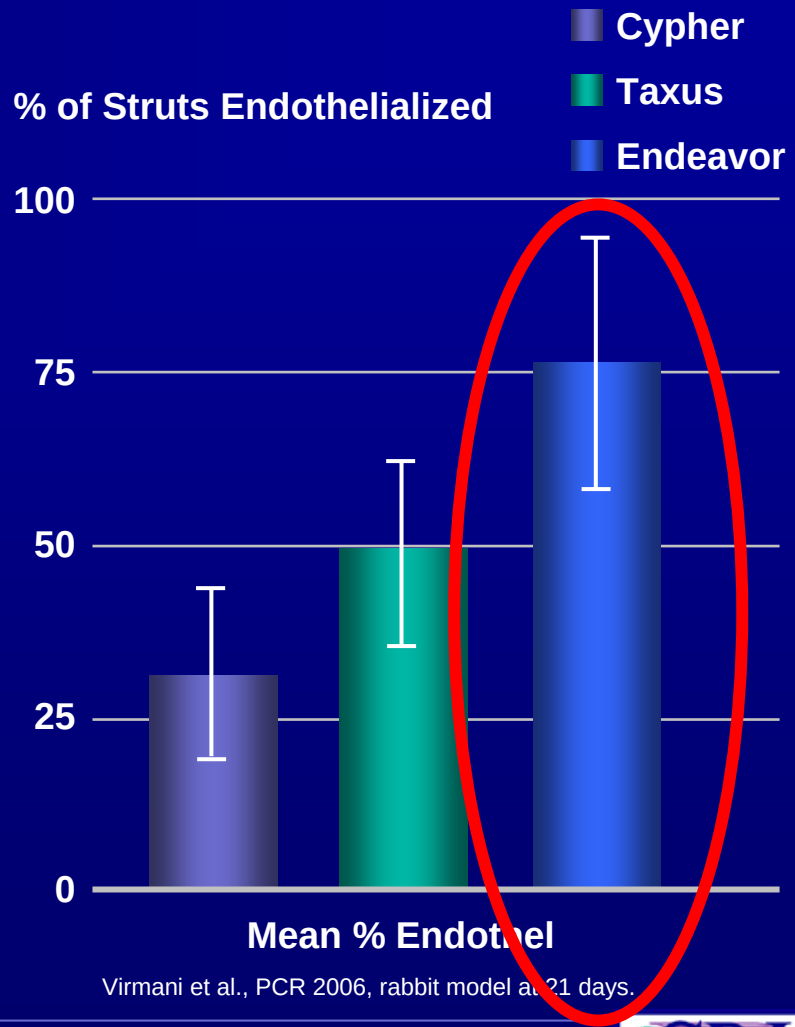
Cypher



Taxus

Endeavor





Virmani et al., PCR 2006, rabbit model at 21 days.

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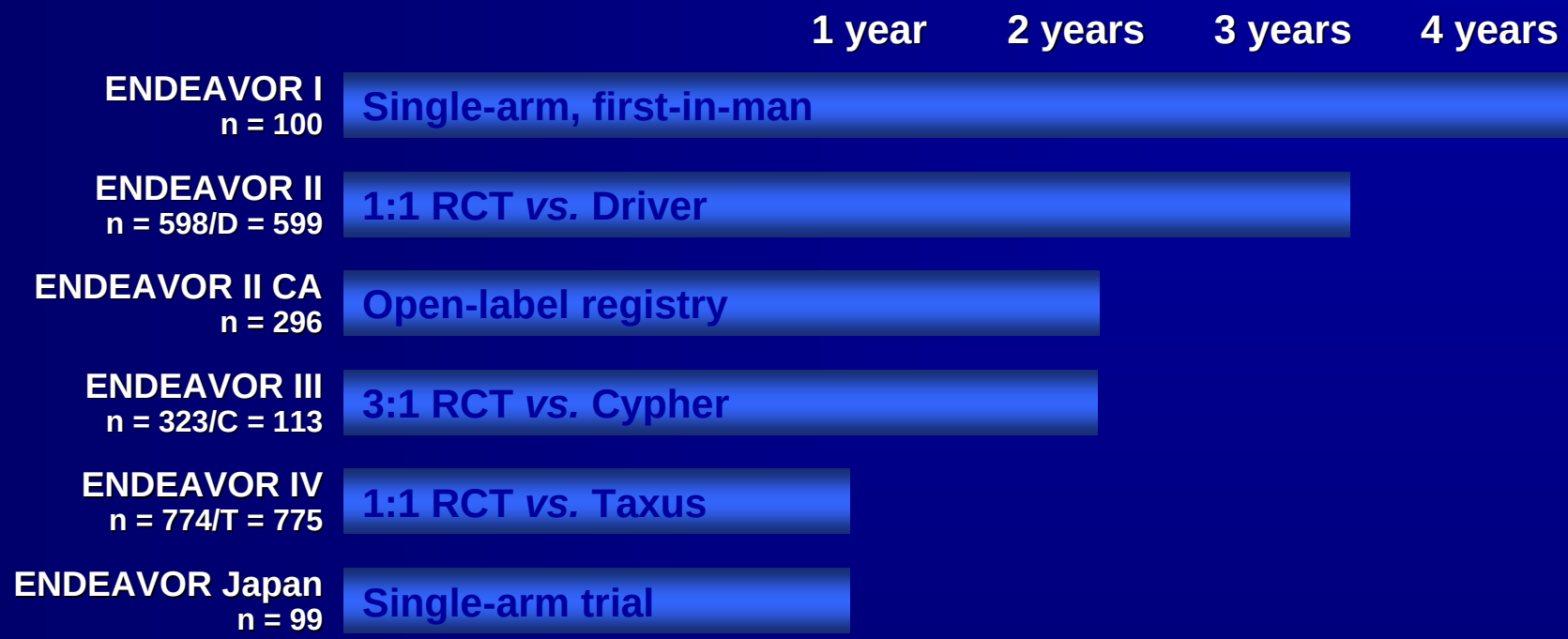
ENDEAVOR Clinical Program



2154 patients followed to 12 months

1287 patients followed to 2 years

675 patients followed to 3 years

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ENDEAVOR Clinical Program

	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Control	Driver BMS	Cypher	Taxus
N	E = 598 D = 599	E = 323 C = 113	E = 774 T = 775
Primary Endpoint	TVF (cardiac death, MI, TVR) at 9 months	In-segment late lumen loss by QCA at 8 months	TVF at 9 months
QCA, IVUS Subset	QCA = 600 (44.7%); IVUS = 300	QCA, IVUS = All	QCA, IVUS = 328 (21.2%)
DAPT	≥ 3 months	≥ 3 months	≥ 6 months[1]
Inclusion criteria	Single De Novo Native Coronary Artery Lesions Pre-dilatation required		
	Diameters: 2.25–3.5 mm Lesion Length: 14–27 mm	Stent Diameters: 2.5–3.5 mm Lesion Length: 14–27 mm	
Key Exclusion Criteria	Left ventricular ejection fraction <30%. Acute MI within 72 hours. Creatinine >2.0 mg/dl. Left main, ostial lesion, or bifurcation lesion		

[1] ≥6 month DAPT regimen in EIV due to 1:1 randomization vs. Taxus.

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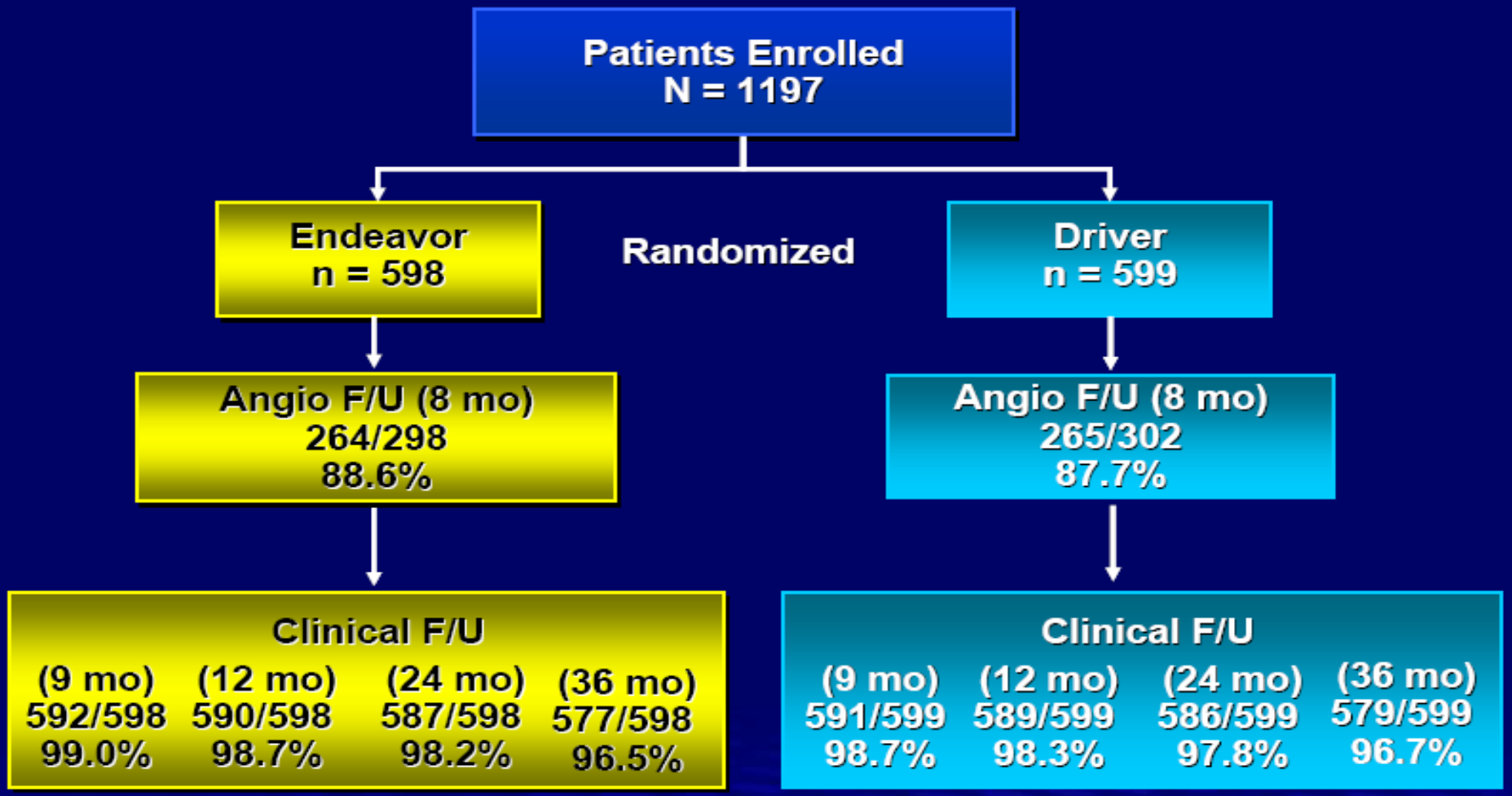
What the Endeavor Program Tells Us

- DES vs. BMS
- New DES vs. Approved DES

What the Endeavor Program Tells Us

- ***DES vs. BMS***
- **New DES vs. Approved DES**

ENDEAVOR II
Patient Flowchart



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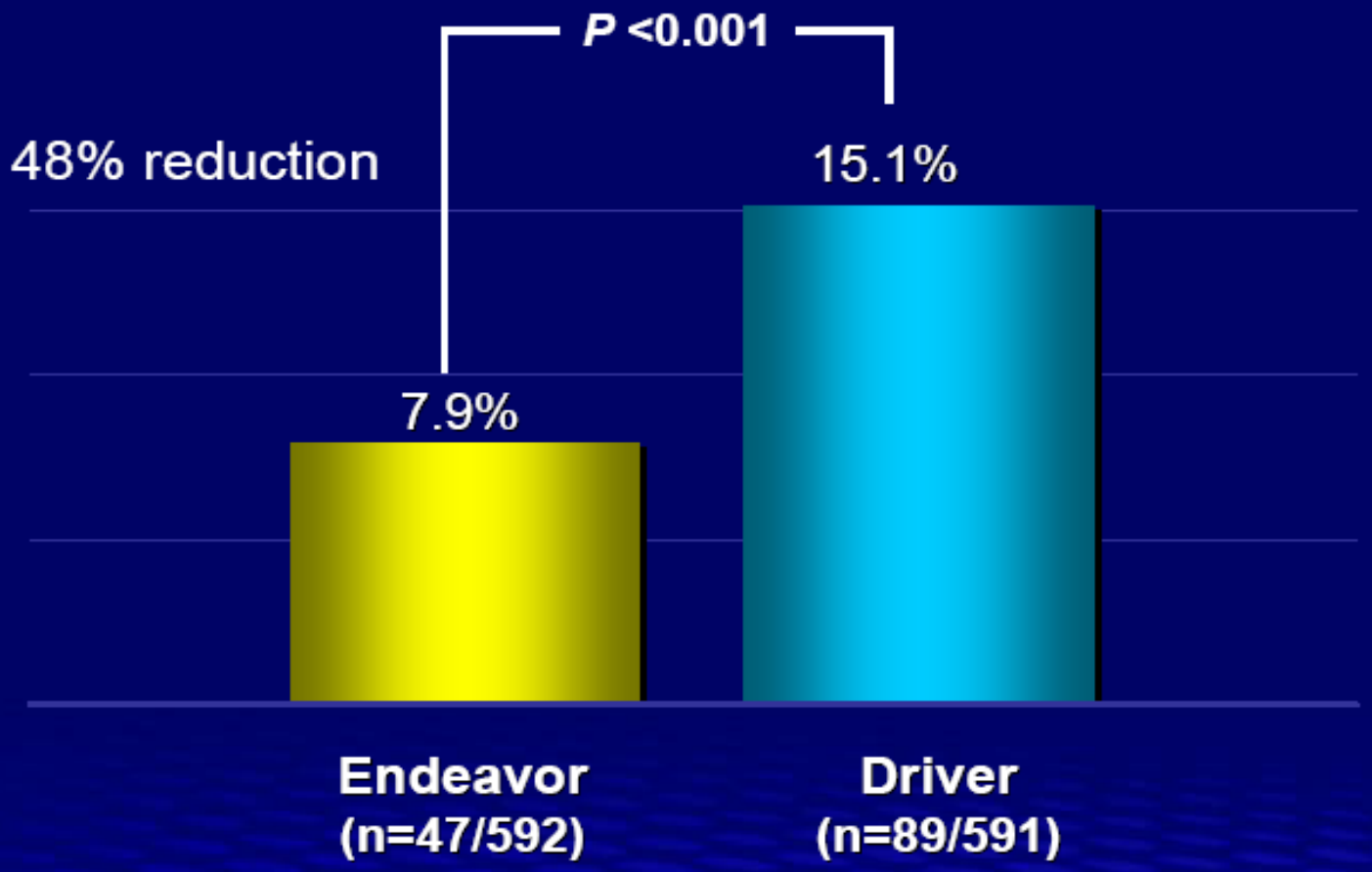
ENDEAVOR II

Primary Endpoint Result at 9 months

Target Vessel Failure



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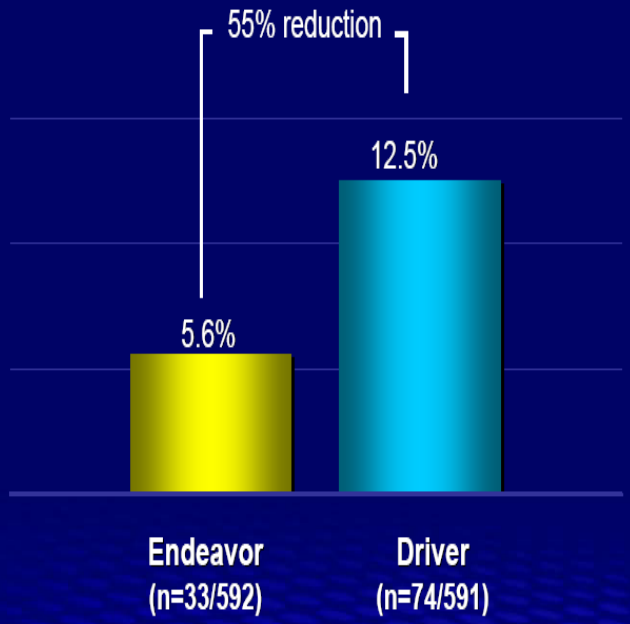
ENDEAVOR II

Efficacy at 9 months

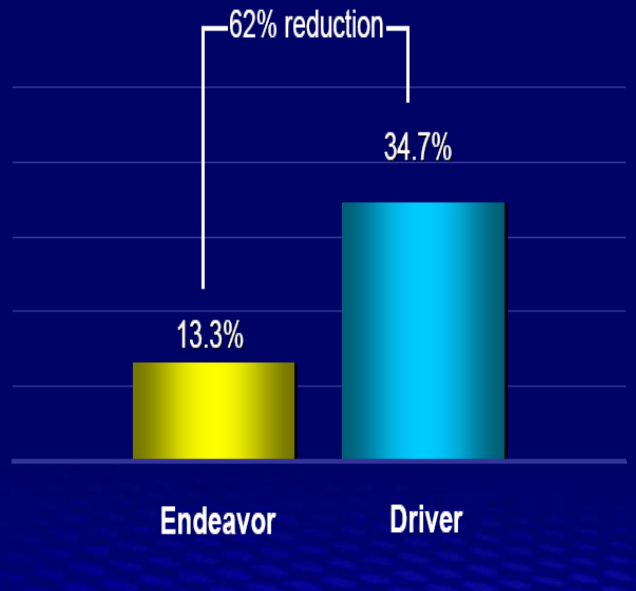
Target Vessel Revascularization



ENDEAVOR II

Angiographic Outcomes at 8 Months

In-Segment Angiographic Binary Restenosis



Endeavor DES vs. BMS: Safety

Endeavor Clinical Program
Baseline Characteristics

	EI n=100	EII n=598	EII CA n=296	EIII n=323	EIV n=773	EPK n=43	E2 Driver N=599
Diabetes (%)	16.0	18.2	25.8	29.7	31.2	41.9	22.2
RVD (mm)	2.96	2.73	2.63	2.75	2.73	2.54	2.76
Lesion Length (mm)	10.94	14.04	16.49	14.96	13.41	15.02	14.38
Recommended clopidogrel duration	≥3m	≥3m	≥3m	≥3m	≥6m	≥3m	≥3m
Clincal F/U							
12 m (%)	99	98.7	98.6	99.1	95.7*	97.7*	98.3
2y (%)	99	98.2	97.3	96.9			97.8
3y (%)	98	96.5					96.7

*9months

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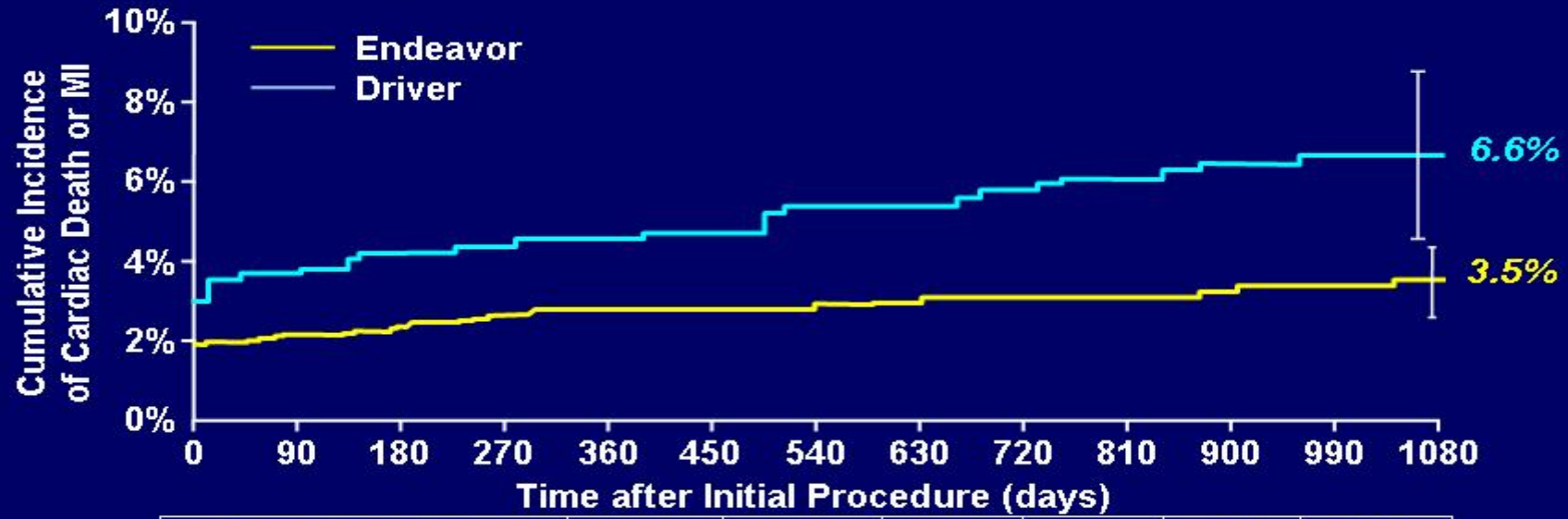
Endeavor Safety Analysis

Patient Characteristics

	Endeavor (n = 2132)	Driver (n = 596)	p value
RVD (mm)	2.73	2.76	0.128
Lesion length (mm)	14.16	14.38	0.446
Diabetes Mellitus (%)	26.1	22.2	0.054
Insulin Dependent Diabetes	8.3	7.4	0.49
Age – yrs	62.5±10.7	61.9±10.5	0.23
Male (%)	71.5	75.3	0.06
History of Smoking (%)	49.2	35.2	<0.001
Prior PCI (%)	26.0	18.0	<0.001
Hyperlipidemia (%)	81.2	76.9	0.02
Hypertension (%)	73.0	68.2	0.02

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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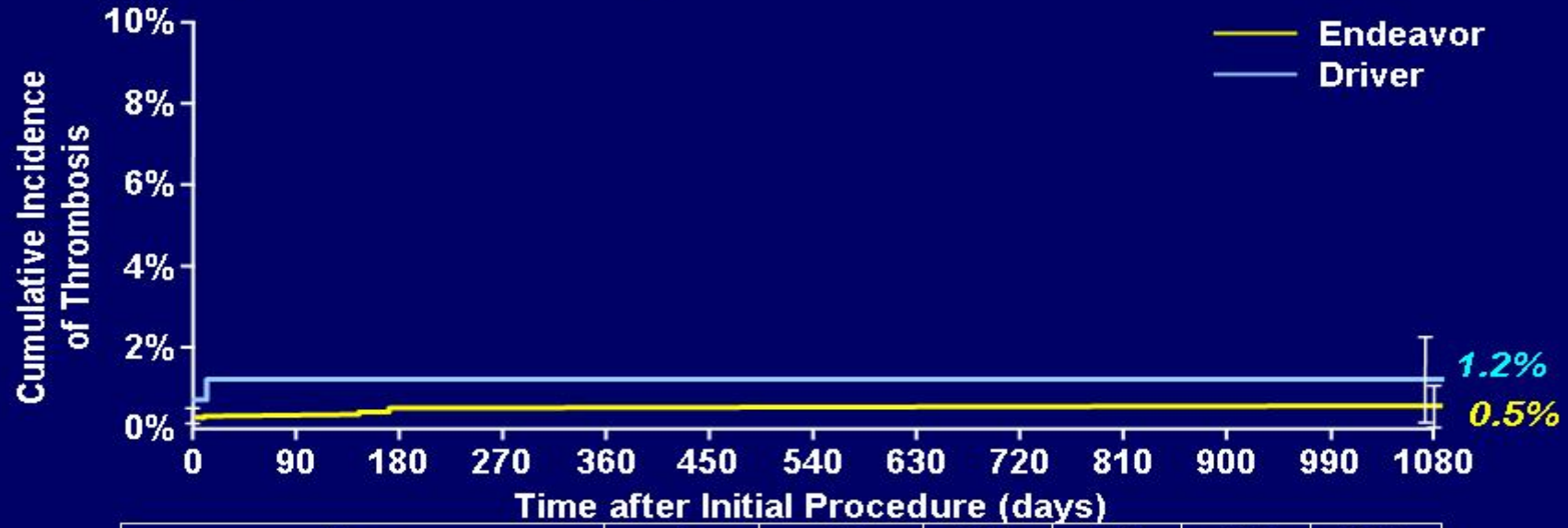
Endeavor Safety Analysis

Cumulative Incidence of Stent Thrombosis (Protocol) to 1080 Days



Days	0	30	270	360	720	1080
Endeavor	**2132**	**2117**	**2086**	**2065**	**1252**	**1214**
# Events	1	6	3	0	0	0
% CI	0.0%	0.3%	0.5%	0.5%	0.5%	0.5%
Driver	**596**	**587**	**581**	**576**	**561**	**544**
# Events	1	6	0	0	0	0
% CI	0.2%	1.2%	1.2%	1.2%	1.2%	1.2%

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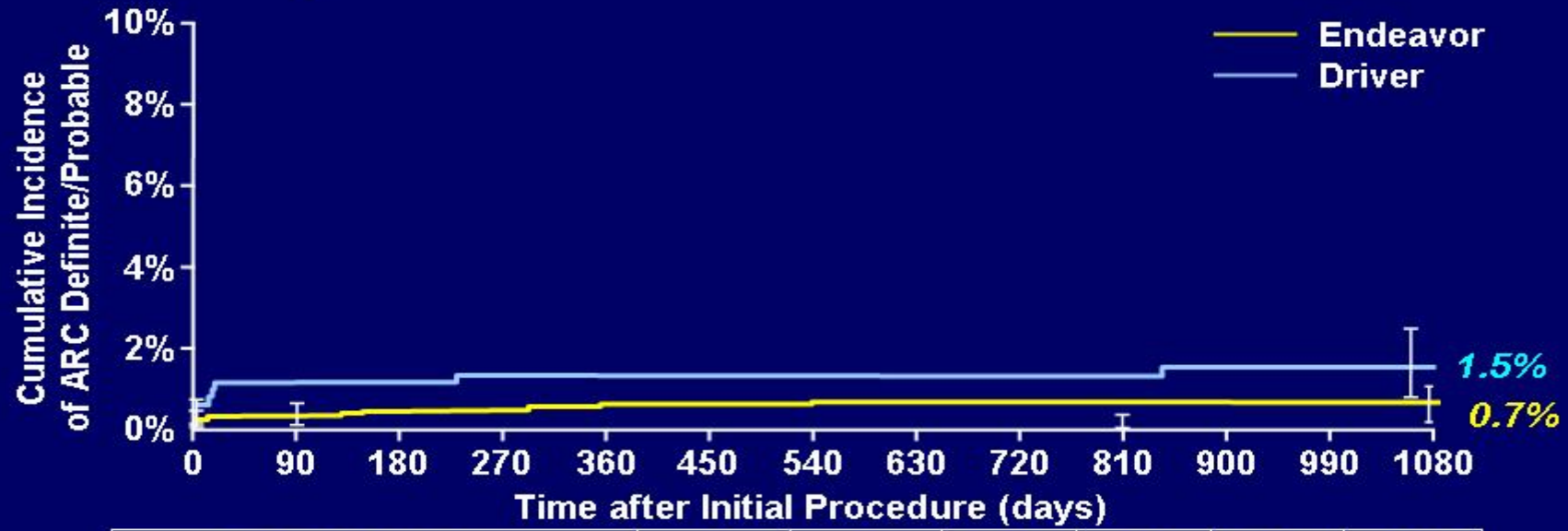
Endeavor Safety Analysis

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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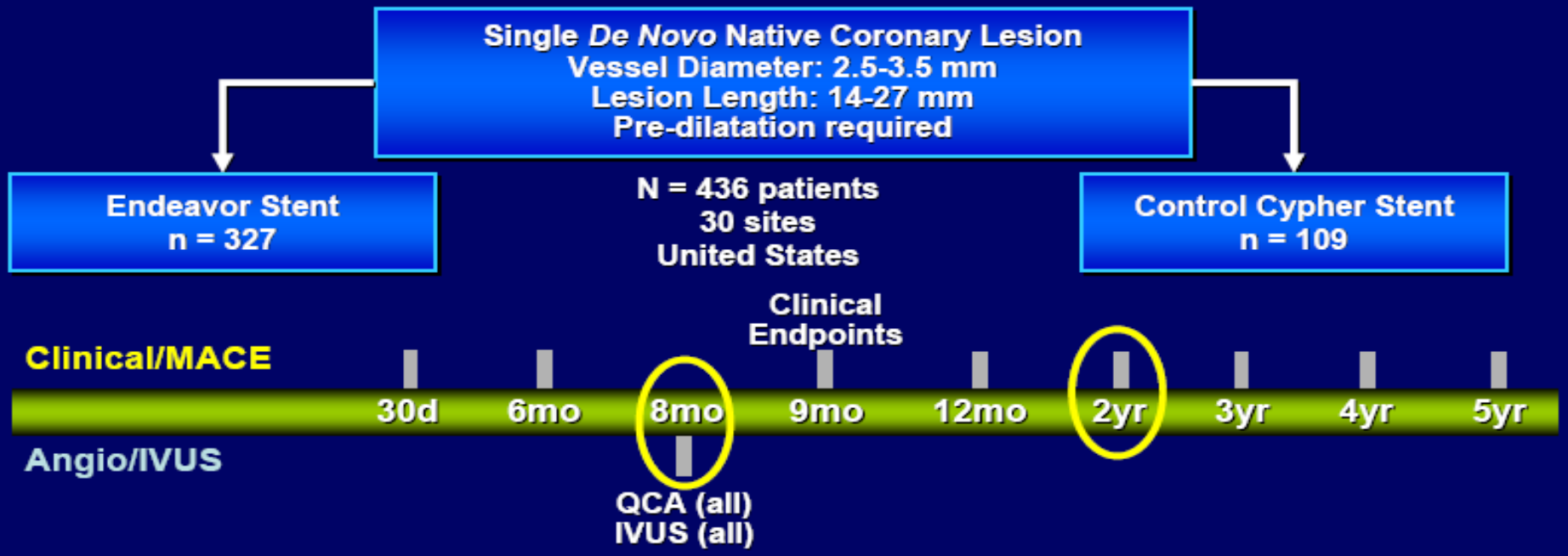
What the Endeavor Program Tells Us

- DES vs. BMS
- ***New DES vs. Approved DES***

ENDEAVOR III

3:1 RCT vs Cypher

PI: Martin B. Leon and David Kandzari



Primary Endpoint: In-segment late lumen loss by QCA at 8 months
Secondary Endpoints: TLR, TVR, TVF at 9 months and ABR at 8 months
Drug Therapy: ASA and Clopidogrel/Ticlid ≥3 months
Zotarolimus Dose: 10 μg per mm stent length

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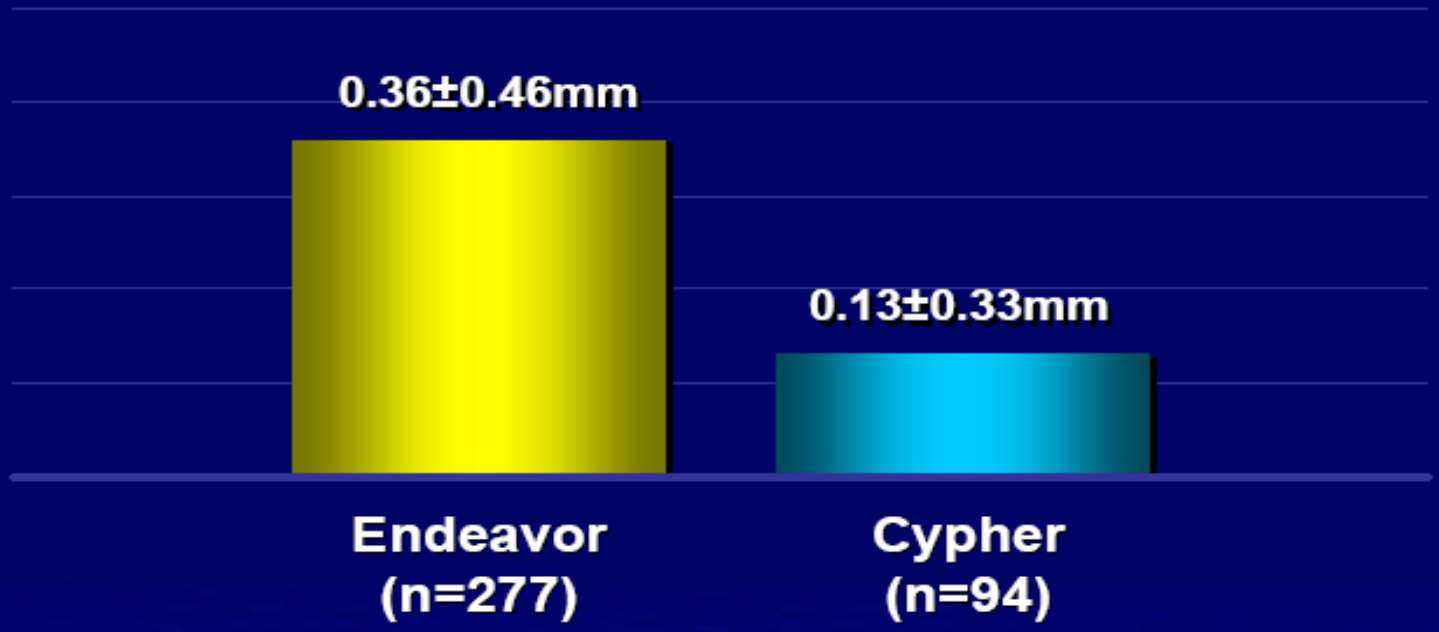
ENDEAVOR III

Primary Endpoint Result at 8 months

In-segment Late Loss

P for Non-Inferiority 0.791



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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 III
Clinical Events to 24 months

	Endeavor n=313	Cypher n=112	*Difference [95% CI]*
Death (all) - % (#)	1.6 (5)	4.5 (5)	-2.9%[-6.9%,1.2%]
Cardiac	0	0.9 (1)	-0.9%[-2.6%,0.8%]
MI (all) - % (#)	0.6 (2)	3.6 (4)	-2.9%[-6.5%,0.6%]
Q Wave	0	0	--
Non Q wave	0.6 (2)	3.6 (4)	-2.9%[-6.5%,0.6%]
Death (cardiac) + MI (all) - % (#)	0.6 (2)	3.6 (4)	-2.9%[-6.5%,0.6%]
Stent Thrombosis (all) - % (#)	0	0	--
0-30 days	0	0	--
31-720 days	0	0	--
TLR - % (#)	7.0 (22)	4.5 (5)	2.6%[-2.2%,7.3%]
TVR (non-TL) - % (#)	8.3 (26)	6.3 (7)	2.1%[-3.4%,7.5%]
TVR - % (#)	13.7 (43)	9.8 (11)	3.9%[-2.8%,10.6%]
MACE - % (#)	9.3 (29)	11.6 (13)	-2.3%[-9.1%,4.4%]
TVF - % (#)	14.4 (45)	13.4 (15)	1.0%[-6.4%,8.4%]

ENDEAVOR IV

1:1 RCT vs Taxus

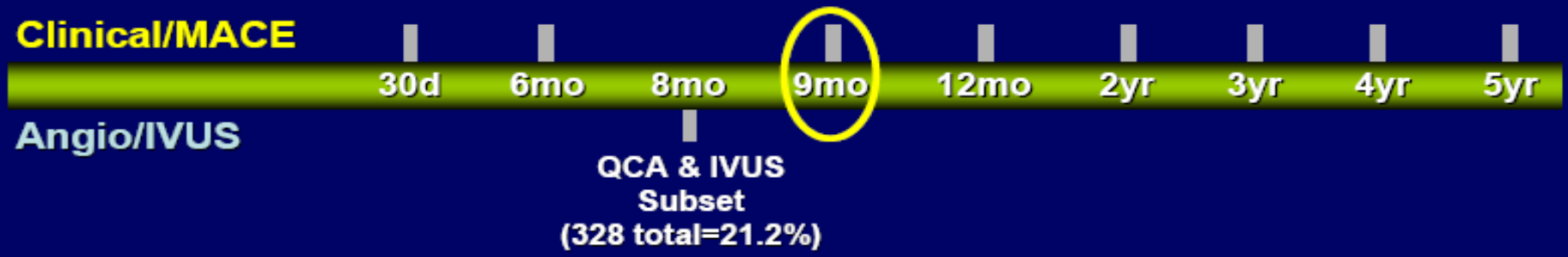
PI: Martin B. Leon

Single *De Novo* Native Coronary Lesion
Vessel Diameter: 2.5-3.5 mm
Lesion Length: ≤ 27 mm
Pre-dilatation required

1:1 randomization
N = 1,548 patients
80 sites
US

Endeavor Stent
n = 774

Taxus Stent
n = 774



Primary Endpoint: TVF at 9 months
Secondary Endpoints: In-segment % DS at 8 months; TLR and TVR at 9 months
Drug Therapy: ASA and Clopidogrel/Ticlid ≥6 months
Zotarolimus Dose: 10 μg per mm stent length

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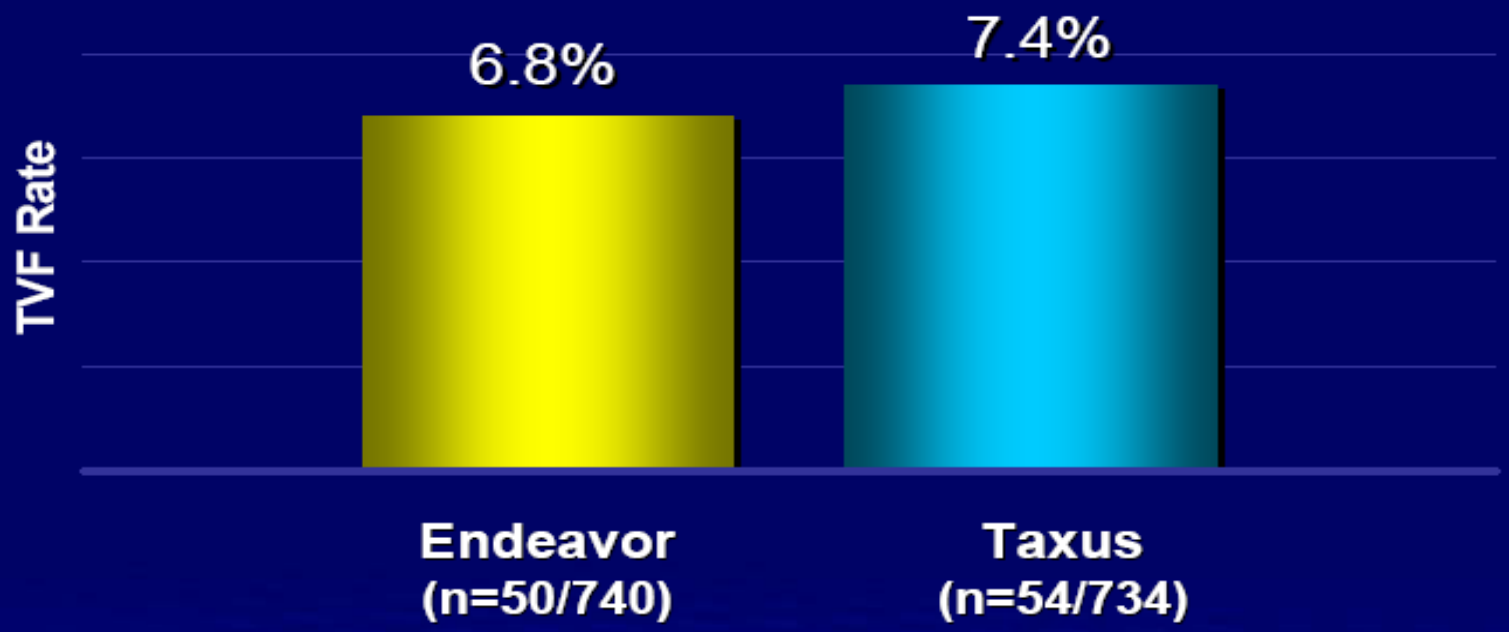
ENDEAVOR IV

Primary Endpoint Result at 9 months

Target Vessel Failure

P for Non-Inferiority < 0.001
Δ =3.8%



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ENDEAVOR IV

Angiographic and IVUS Results at 8 months

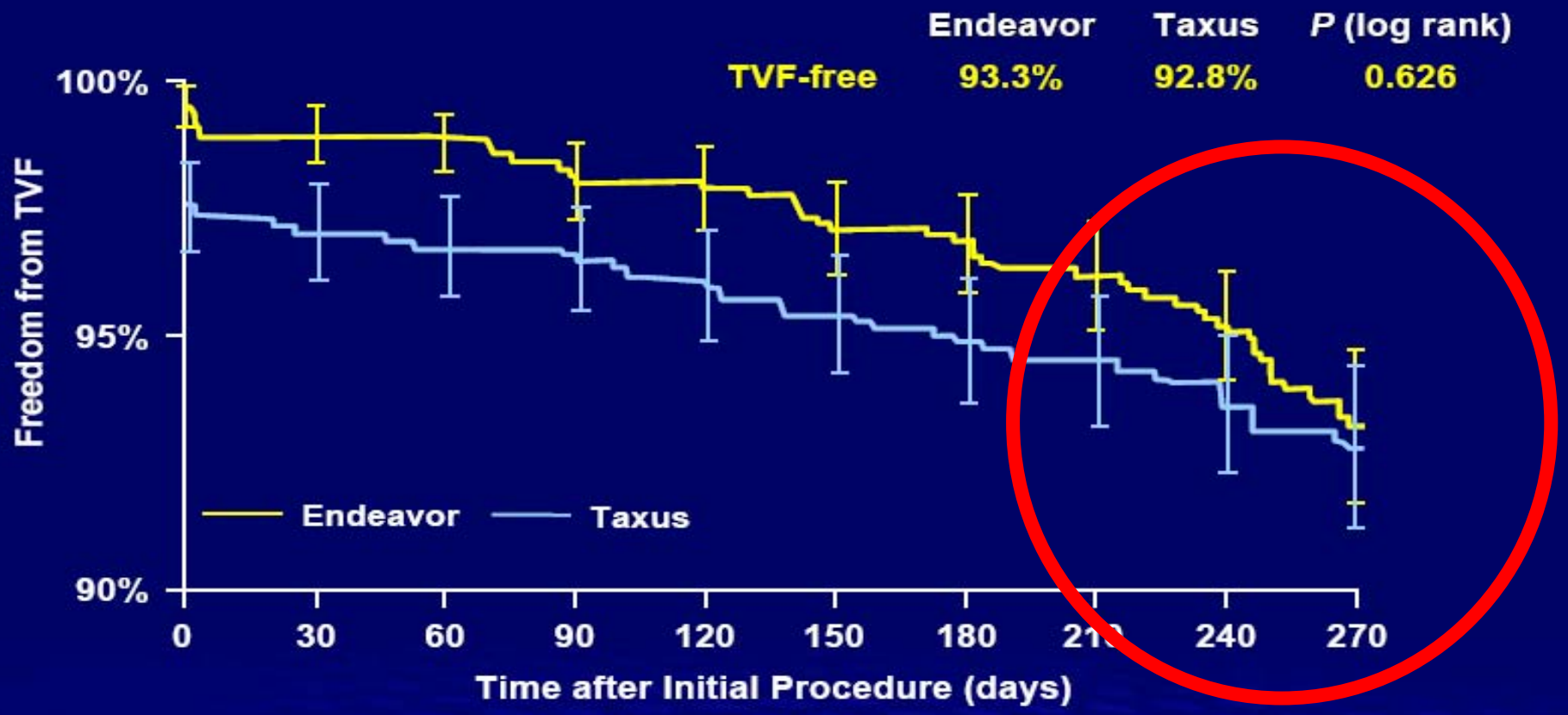
	Endeavor n = 144	Taxus n = 135	*Difference* [95% CI]
RVD – mm	2.65	2.68	-0.03 [-0.14, 0.08]
In-stent			
DS - %	26.41	16.09	[illegible]
LL - mm	0.67	0.42	0.25 [0.13, 0.37]
ABR - %	[illegible]	[illegible]	[illegible]% [-0.4%, 13.6%]
In-segment			
DS - %	32.28	26.61	5.68 [1.83, 9.52]
LL - mm	0.36	0.23	0.13 [0.02, 0.23]
ABR - %	15.3	10.4	4.9% [-2.9%, 12.7%]
IVUS			
Neointimal Volume - mm^3 (n)	24.14 (74)	14.88 (77)	9.26 [3.46, 15.06]
Vol Obstruction - % (n)	15.72 (74)	9.88 (77)	5.84 [2.68, 9.00]
Late Incomplete Apposition - % (#/n)	0.9 (1/106)	3.2 (3/95)	-2.2% [-6.2%, 1.8%]

ENDEAVOR IV
Clinical Events at 30 days

	Endeavor n=770	Taxus n=771	*Difference [95% CI]*
Death (all) - % (#)	0.3 (2)	0	0.3%[-0.1%,0.6%]
Cardiac	0.1 (1)	0	0.1%[-0.1%,0.4%]
MI (all) - % (#)	0.8 (6)	2.3 (18)	-1.6%[-2.8%,-0.3%]
Q Wave	0.3 (2)	0.1 (1)	0.1%[-0.3%,0.6%]
Non Q wave	0.5 (4)	2.2 (17)	-1.7%[-2.8%,-0.5%]
Death (cardiac) + MI (all) - % (#)	0.9 (7)	2.3 (18)	-1.4%[-2.7%,-0.2%]
Stent Thrombosis (all) - % (#)	0.4 (3)	0.1 (1)	0.3%[-0.2%,0.8%]
TLR - % (#)	0.4 (3)	0.8 (6)	-0.4%[-1.1%,0.4%]
TVR (non-TL) - % (#)	0	0.3 (2)	-0.3%[-0.6%,0.1%]
TVR - % (#)	0.4 (3)	0.9 (7)	-0.5%[-1.3%,0.3%]
MACE - % (#)	1.2 (9)	3.0 (23)	-1.8%[-3.2%,-0.4%]
TVF - % (#)	1.0 (8)	3.0 (23)	-1.9%[-3.3%,-0.5%]

ENDEAVOR IV

TVF Event Free Survival to 270 Days



Error bars represent ±1.5SE estimated by Peto formula

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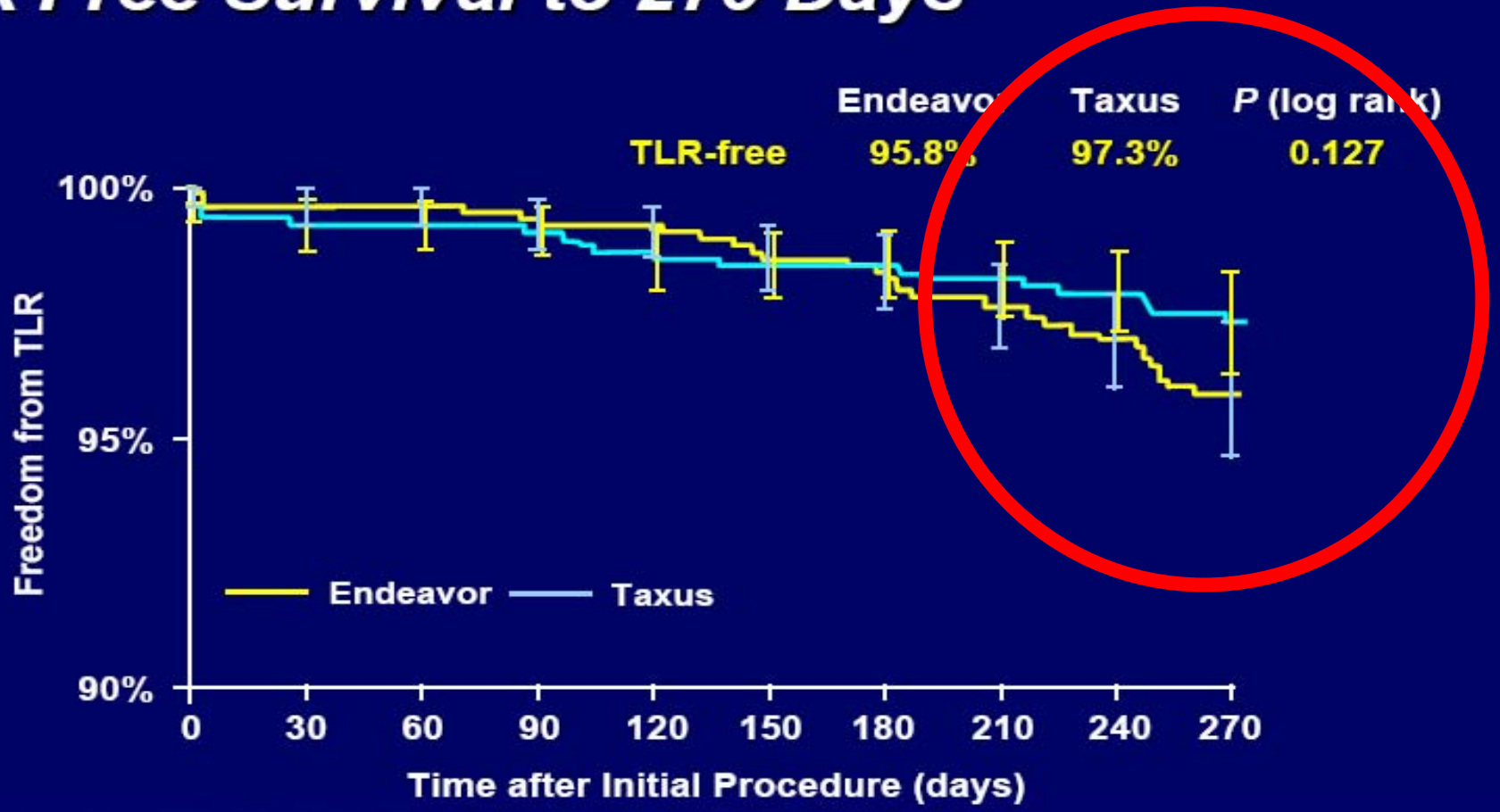
ENDEAVOR IV

TLR Free Survival to 270 Days



Error bars represent ±1.5SE estimated by Peto formula

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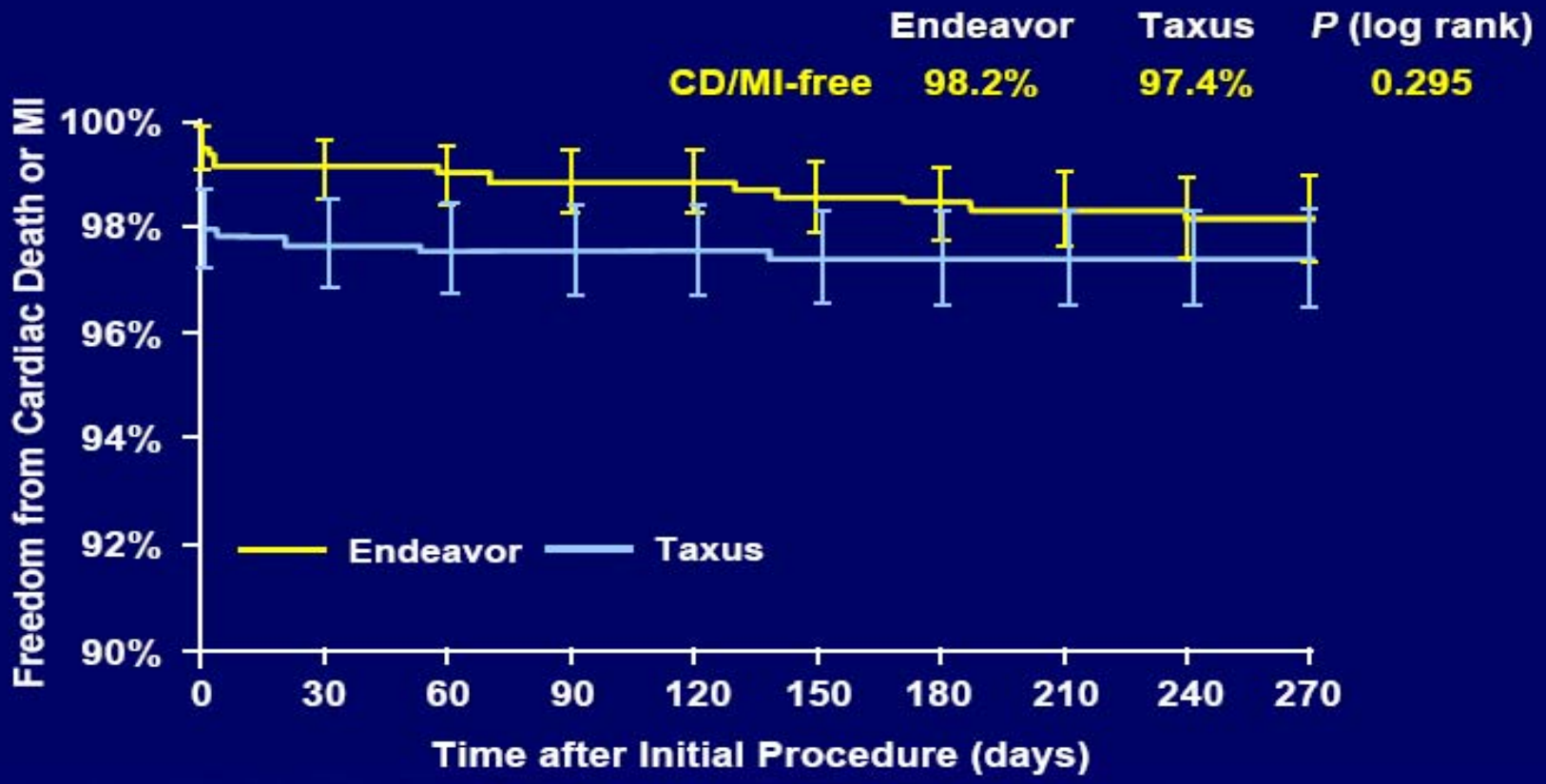
ENDEAVOR IV

Cardiac Death/MI Free Survival to 270 Days



Error bars represent ±1.5SE estimated by Peto formula

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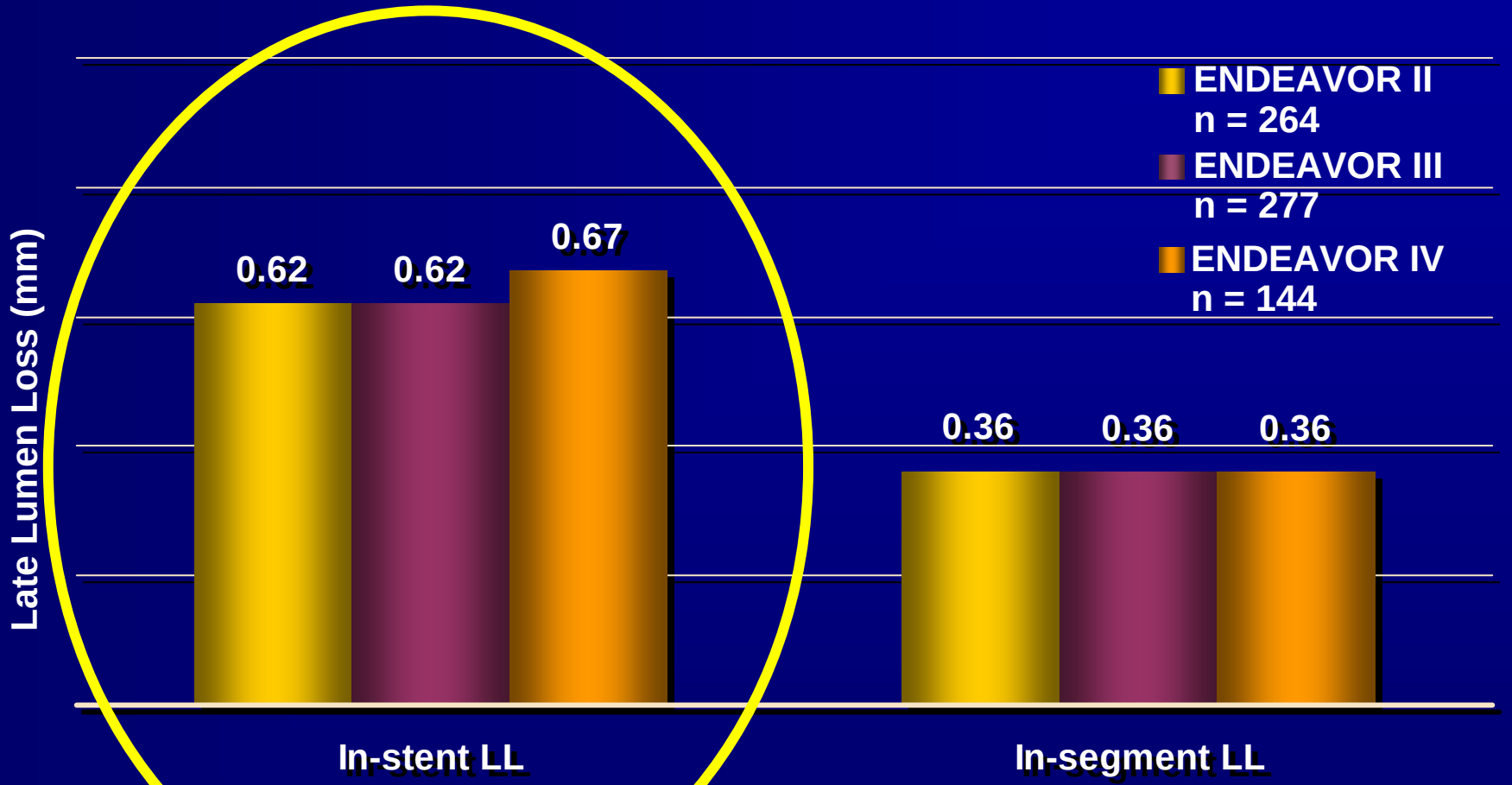
ENDEAVOR II-IV: Late Loss at 8 Months



ENDEAVOR II: Fajadet, et al., *Circulation*. 2006;114:798–806. ENDEAVOR III: Leon, M., ACC 2007.
ENDEAVOR IV: Leon, TCT 2007 (trial analysis done using revised 9-month data set).

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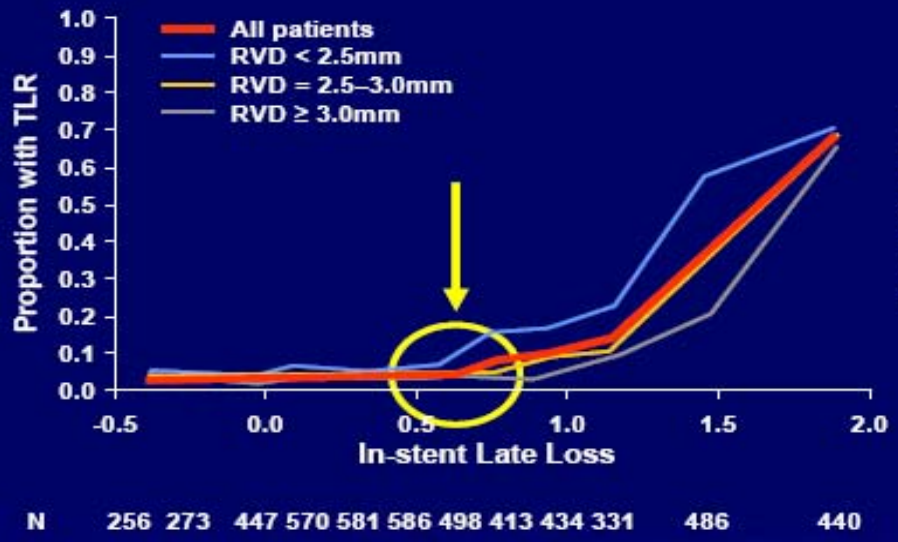
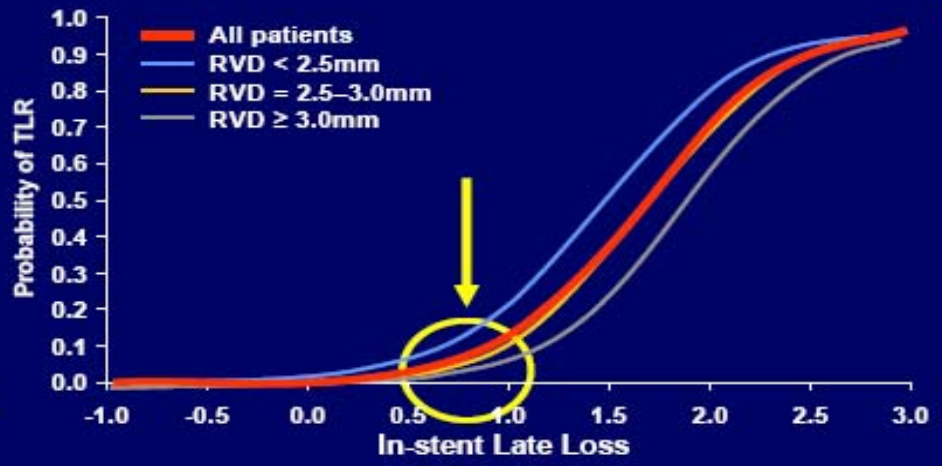
11 RCTs with Cypher, Taxus, Endeavor, and BMS (5381 pts)

Surrogate Angiographic Endpoints for Clinical Outcomes

LL vs. TLR - A monotonic but curvilinear relationship





Pocock et al., JACC, Vol. 51, No. 1, 2008

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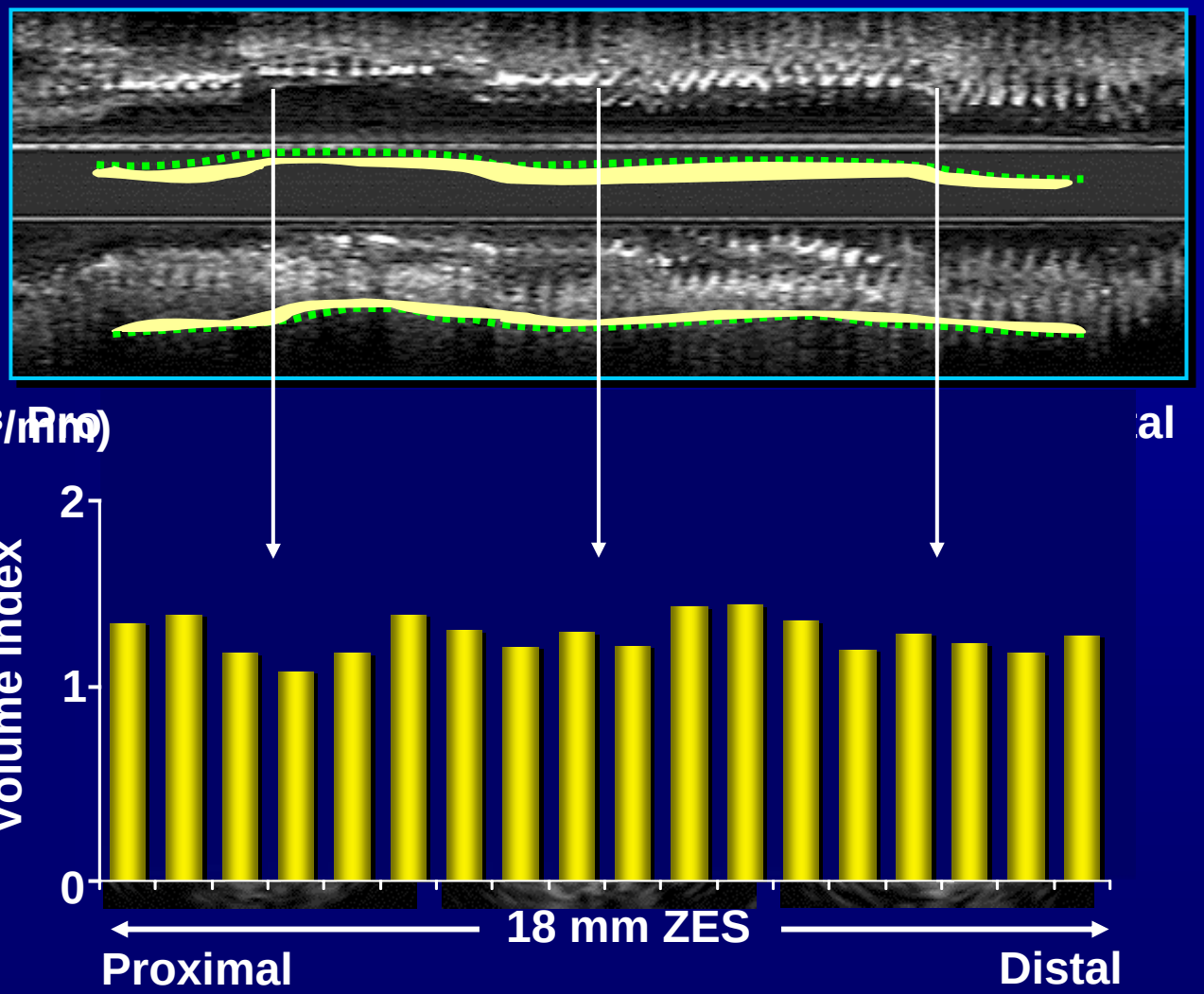
Endeavor: “Complete” NIH

Smooth Lumen, Even Neointimal Distribution



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ENDEAVOR Clinical Program Overview

Study	Comparator	Angio	Clinical	Safety
E-II	BMS	+++	++	=
E-III	DES	---	=	??
E-IV	DES	---	=	??

Are smaller lumens safer DES vs. DES?

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Endeavor 2008: Conclusions

- ***Second Generation Design:***
  - Cobalt chromium platform
  - Biocompatible polymer
  - New molecular entity
- ***Consistent results:***
  - Highly deliverable
  - High rate of procedural success
  - Late loss > 0.6 mm

Endeavor 2008: Conclusions

- ***vs. BMS:***
  - Superior efficacy
  - Equivalent safety
- ***vs. CYPHER:***
  - Not non-inferior late loss
  - Safety: ??
- ***vs. TAXUS:***
  - Non-inferior TVF
  - Safety: ??

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.

ENDEAVOR 2008

Mitchell W. Krucoff MD, FACC

Professor of Medicine / Cardiology

Duke University Medical Center

Director, Cardiovascular Devices Unit

Duke Clinical Research Institute

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