Endeavor™ Zotarolimus-Eluting Coronary Stent System

Medtronic Vascular Presentation

Sean M. Salmon
Vice President and General Manager,
Coronary and Peripheral, Medtronic Vascular

Endeavor Program Overview

- **Project Overview and Product Description**
  - Sean M. Salmon - VP and GM, Medtronic Vascular
- **Drug Substance and Pre-clinical Characterization**
  - LeRoy LeNarz, MD - Chief Medical Officer, Medtronic Vascular
- **Clinical Trial Results**
  - Martin B. Leon, MD - PI, Columbia University Medical Center
- **Clinical Trial Program – Safety Overview**
  - Laura Mauri, MD, MSc – Chief Scientific Officer, Harvard Clinical Research Institute
- **Post-Market Plan and Conclusions**
  - Richard E. Kuntz, MD, MSc – Sr. VP, Medtronic, Inc

Expert Consultants

- **Jeffrey Popma, MD**
  - Brigham and Women's Hospital Angiographic Core Lab
- **Peter Fitzgerald, MD, PhD**
  - Stanford IVUS Core Lab
- **Richard P. Chiacchierini, PhD**
  - R.P. Chiacchierini & Associates, LLC
- **Sean Willis, PhD**
  - Biocompatibles, Ltd.
- **Stephen Jones, PhD**
  - Biocompatibles, Ltd.

Purpose

- Provide an overview of the pre-clinical and clinical data that provide assurance based on valid scientific evidence of the safety and effectiveness of the Endeavor Zotarolimus-Eluting Coronary Stent System

Endeavor: Proposed Indications for Use

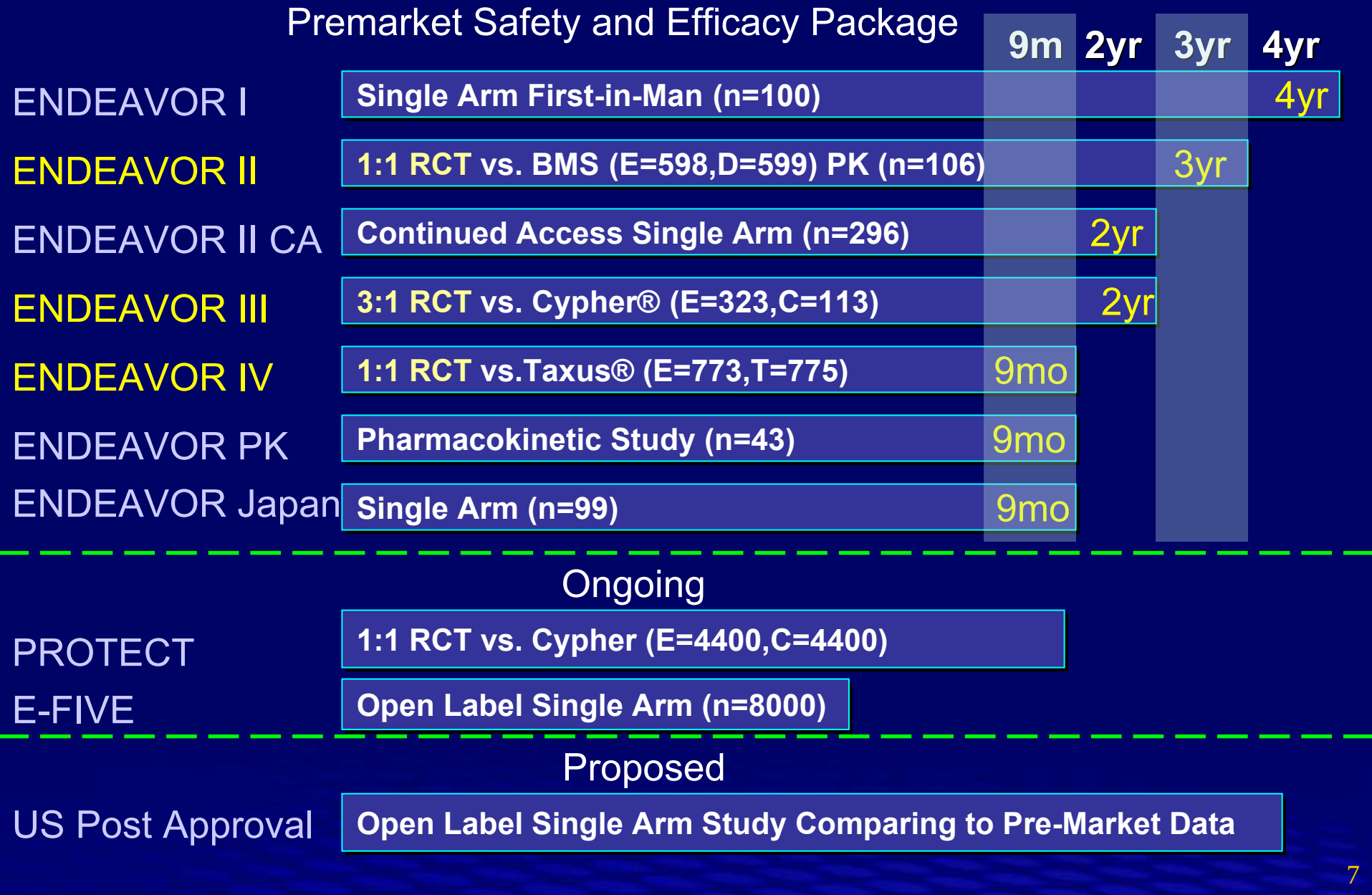
The Endeavor™ Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5mm to ≤ 3.5mm.

Stent Size Matrix

Diameter (mm)	Stent Length (mm)							
	8	9	12	14	15	18	24	30
2.5	✓	N/A	✓	✓	N/A	✓	✓	✓
3.0	N/A	✓	✓	N/A	✓	✓	✓	✓
3.5	N/A	✓	✓	N/A	✓	✓	✓	✓

Consistent dose of 10µg/mm stent length across sizes

Endeavor Program Overview



Endeavor Clinical Program Summary

- **Substantial Density of Safety and Efficacy Data**
  - *7 Clinical Trials: 3 Randomized, 4 Single Arm*
  - 2232 Endeavor patients enrolled
  - 1287 Endeavor patients with 2 or more years of follow-up
  - 675 Endeavor patients with 3 years of follow-up
  - 3980 Endeavor patient-years of follow-up
- **Clinical and angiographic superiority to BMS**
  - Treatment effect sustained through 3year follow-up
- **Clinical non-inferiority to an approved DES**
- **Consistent clinical and angiographic outcomes**
  - Across different geographies and studies
- **No observed safety signals before or after 1 year**
  - Low rates of ST, death, cardiac death, and MI

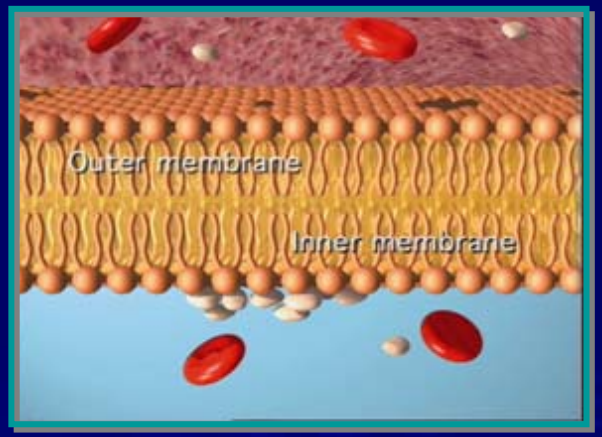
Endeavor: Product Description

Endeavor DES System

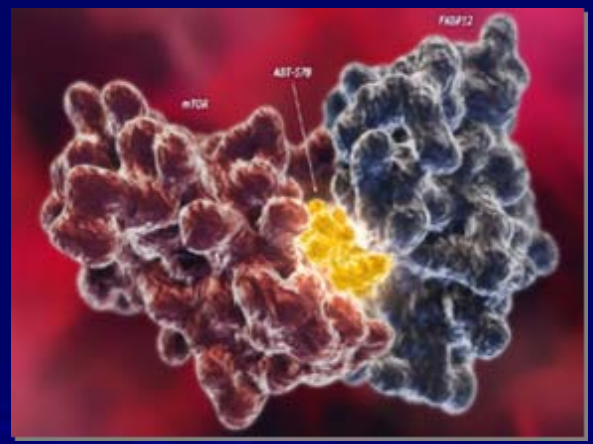
Driver Cobalt Alloy Stent

Stent Delivery System

PC Technology



Drug: Zotarolimus

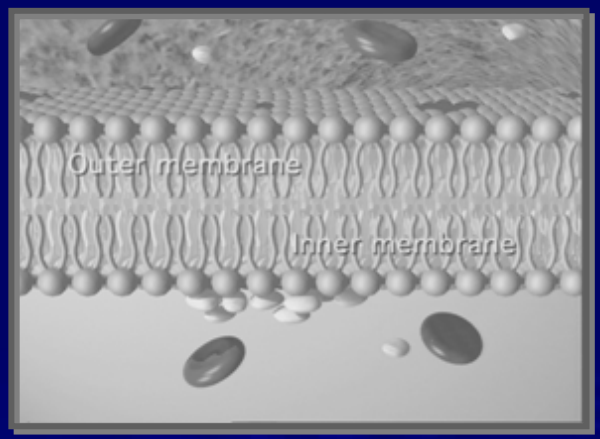


Endeavor DES System

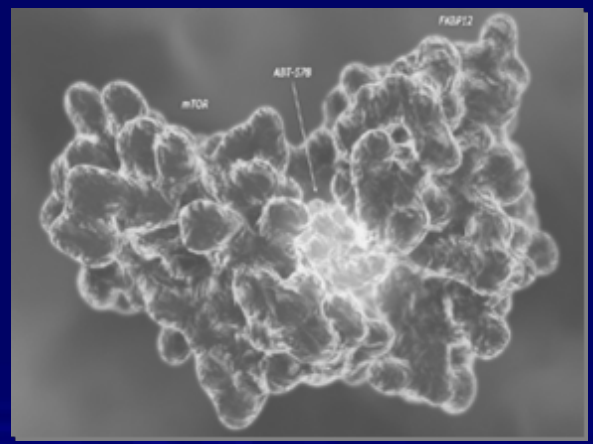
Driver Cobalt Alloy Stent

Stent Delivery System

PC Technology



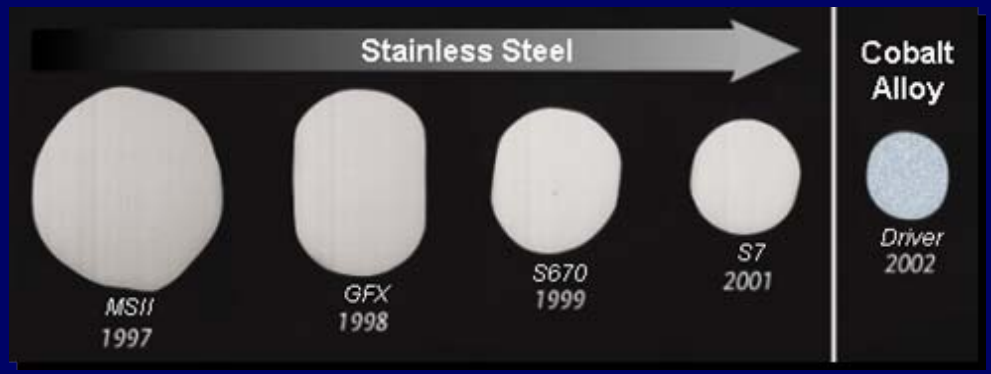
Drug: Zotarolimus



Endeavor Stent and Delivery System

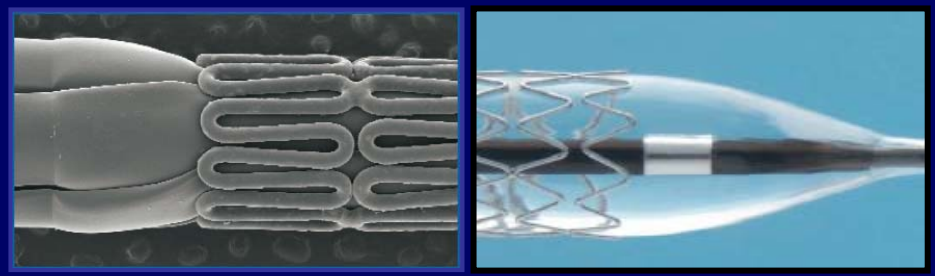
- Driver (3.0mm and 3.5mm) and Micro-Driver (2.5mm) stent systems (P030009)
  - Driver platform, approved October 1, 2003
  - Micro-Driver platform, approved April 21, 2006
- Rapid Exchange (RX), Over-The-Wire (OTW), and Multi Exchange II (MX^2) Delivery Systems
- Product matrix corresponds to the proposed indications:
  - ≥ 2.5mm to ≤ 3.5mm vessel diameter
    - 2.5 - 3.5 mm stent diameters
  - ≤ 27 mm lesion length
    - 8-30 mm stent lengths

Endeavor Stent Platform



- Cobalt alloy
- Thin struts – 0.0036”
- Strength & visibility

- Edgeless design
- Modular structure
- 1 mm elements
- Flexibility
- Scaffolding
- Conformability



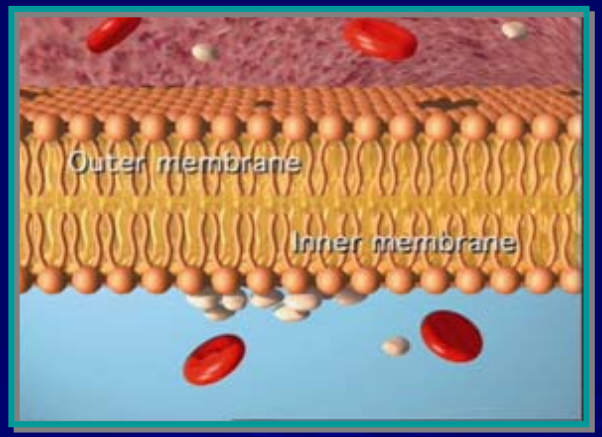
- Flexible and low profile balloon
- Pillows securement
- Minimal balloon overhang
- Nominal 9 atm
- RBP 16 atm

Endeavor DES System

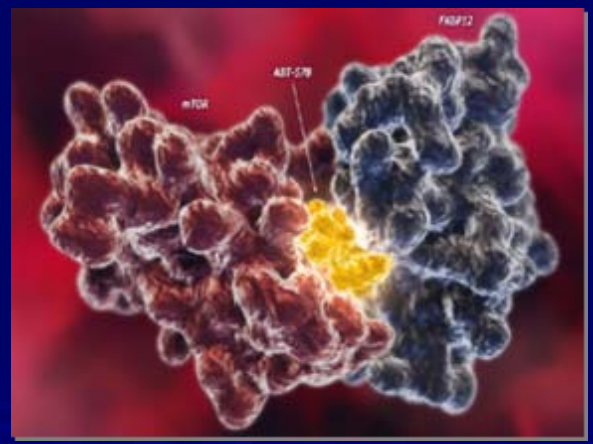
Driver Cobalt Alloy Stent

Stent Delivery System

PC Technology

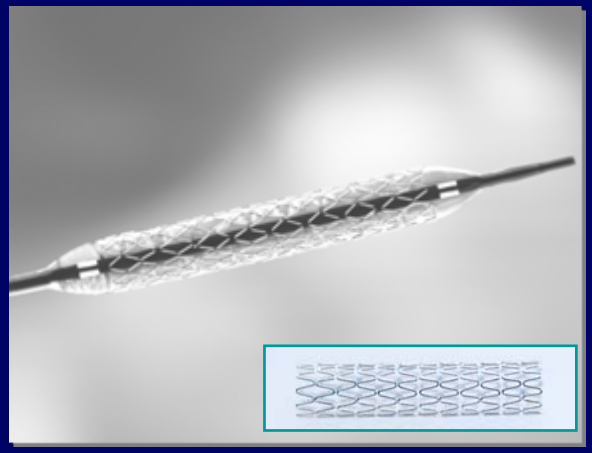


Drug: Zotarolimus



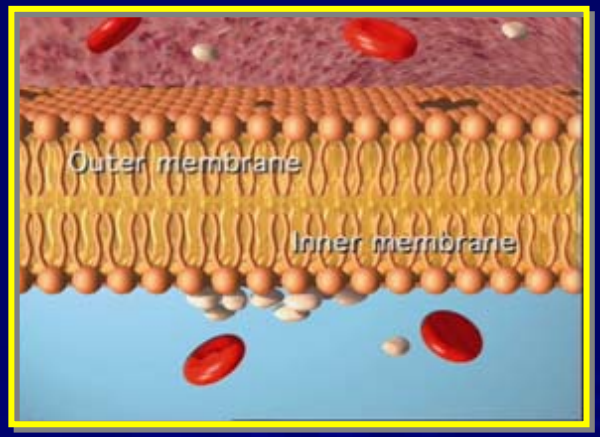
Endeavor DES System

Driver Cobalt Alloy Stent

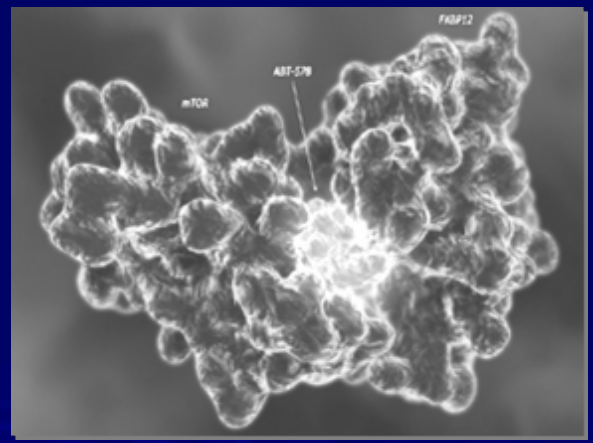


Stent Delivery System

PC Technology

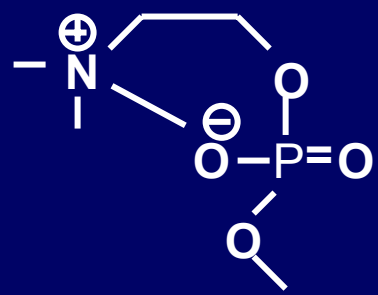


Drug: Zotarolimus



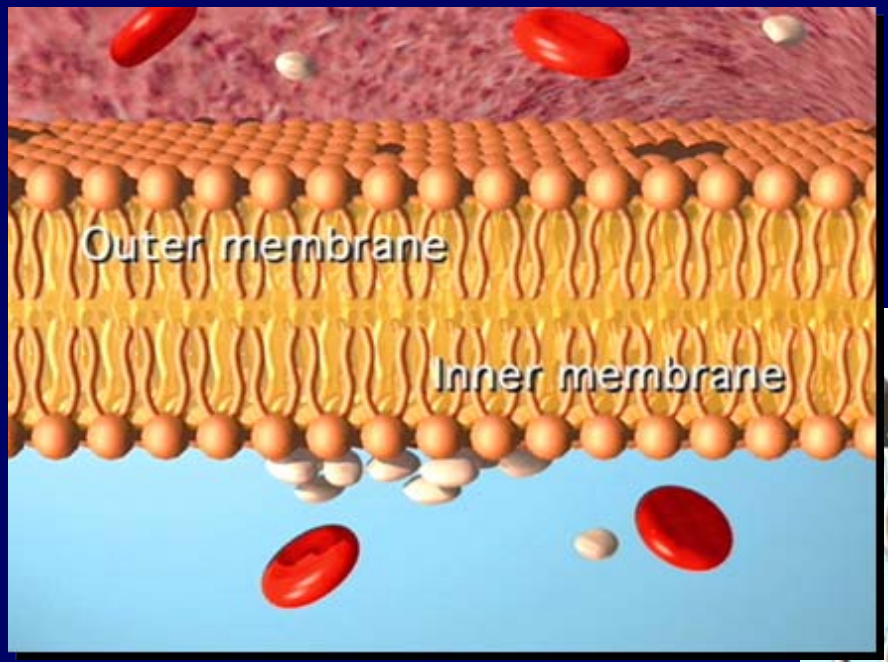
PC Technology ™

- **Phosphorylcholine (PC) Polymer**
  - Broad history of use in medical devices including coronary stents
    - BiodivYsio AS PC Coated Stent (P000011, approved September 29, 2000)
    - >150,000 stent implants world wide at the time of Endeavor development
- **Blended composite polymer primarily comprised of hydrophilic monomers**
- **PC mimics the chemical structure of phospholipid headgroups**

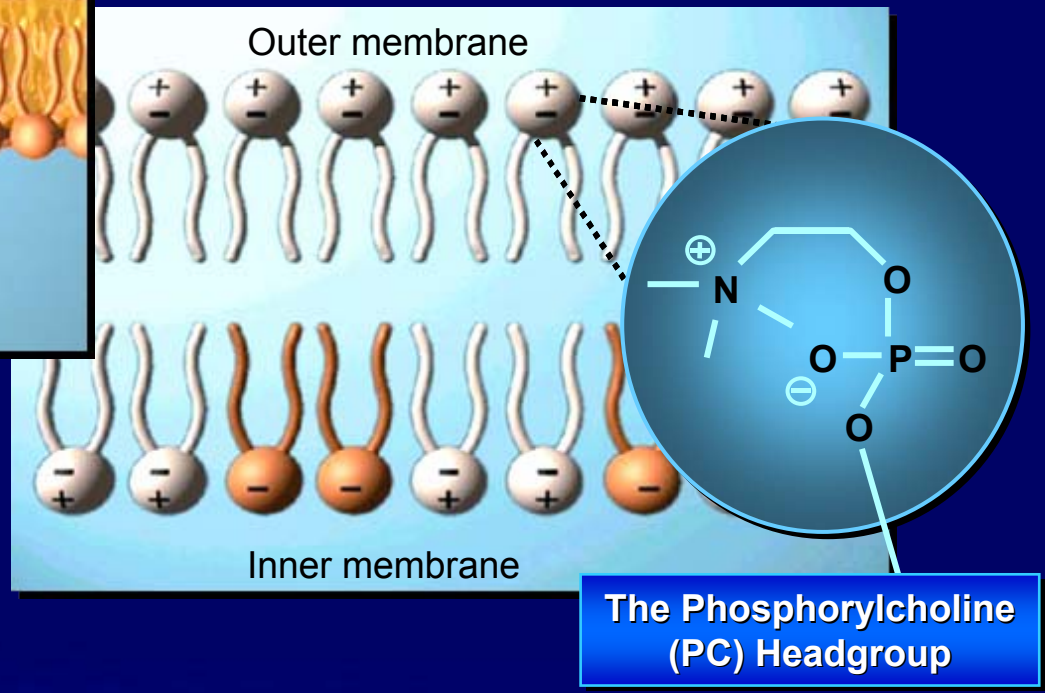


Hydrophilic PC Headgroup

PC Technology



90% of phospholipids in the outer membrane of a red blood cell contain the Phosphorylcholine (PC) headgroup

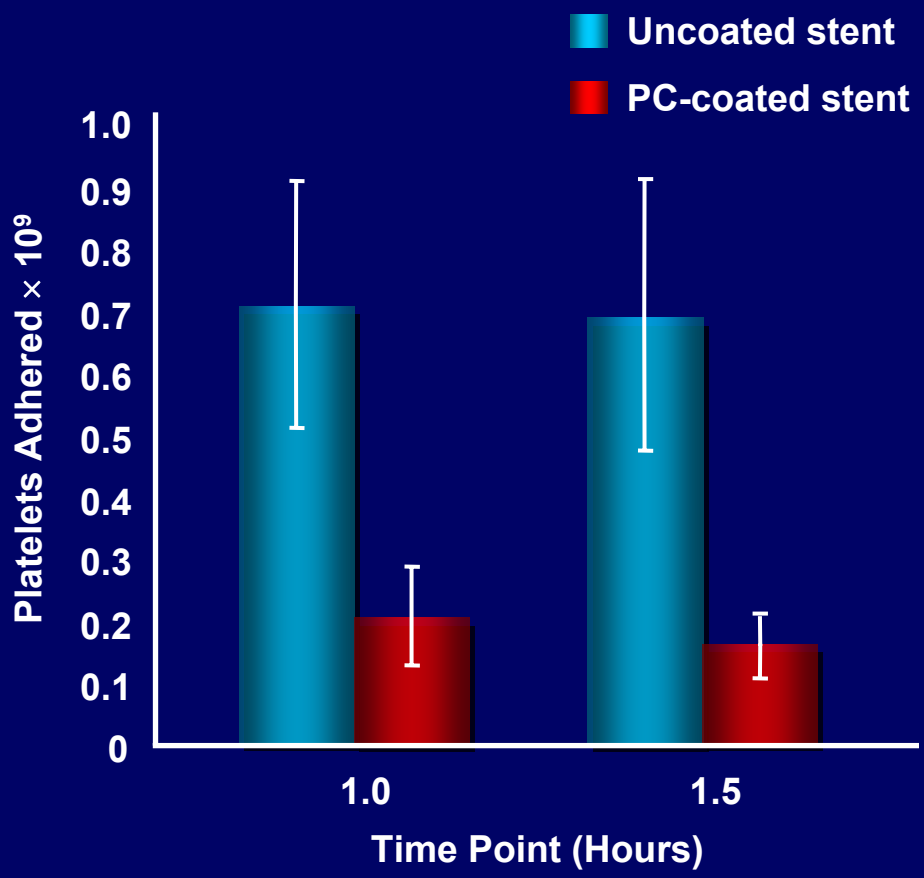


PC[1] mimics the chemical structure of the phospholipid headgroup

[1] Hayward JA & Chapman D; Biomaterials 5, 135, 1984.

PhosphoCoat™ – Thrombo-Resistant

- Non-thrombogenic (hemocompatible)
  - Non-inflammatory
  - Hydrophilic: Inhibits monocyte adhesion
- PC coated stents showed less platelet adhesion compared to uncoated stents in a baboon-shunt flow model*



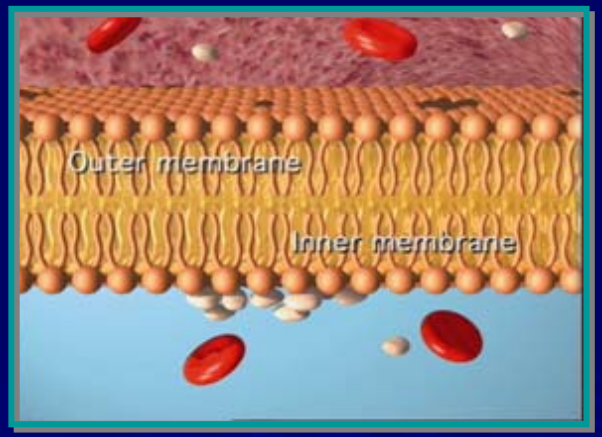
*Lewis AL, Coll Surf B; Biointerfaces, 2000, 18, 261

Endeavor DES System

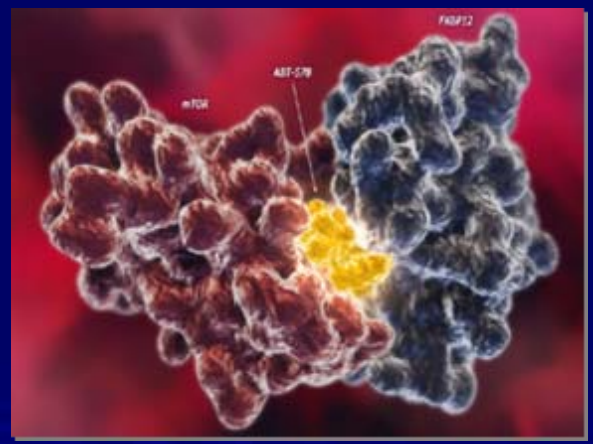
Driver Cobalt Alloy Stent

Stent Delivery System

PC Technology

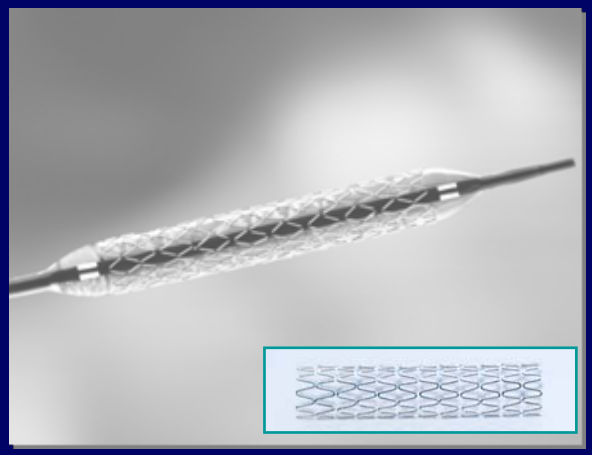


Drug: Zotarolimus



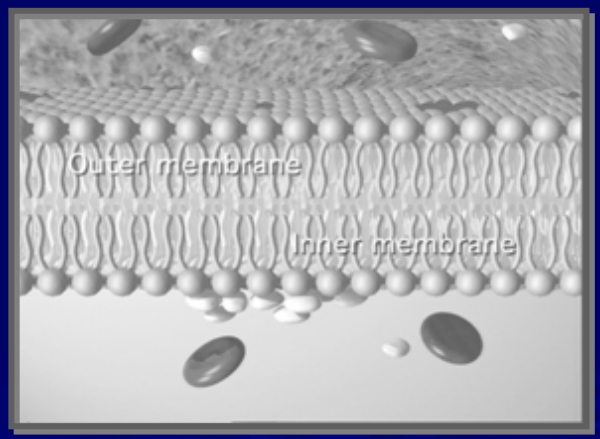
Endeavor DES System

Driver Cobalt Alloy Stent

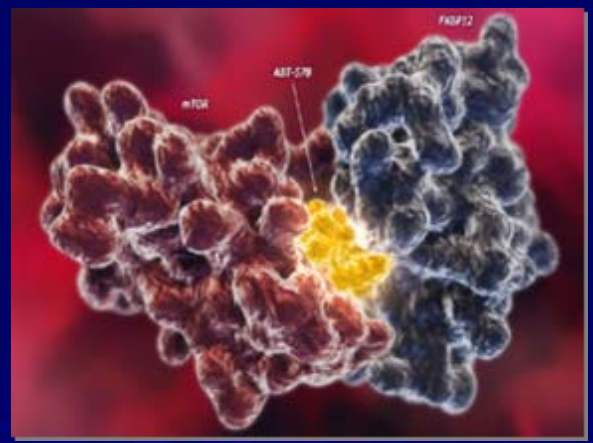


Stent Delivery System

PC Technology

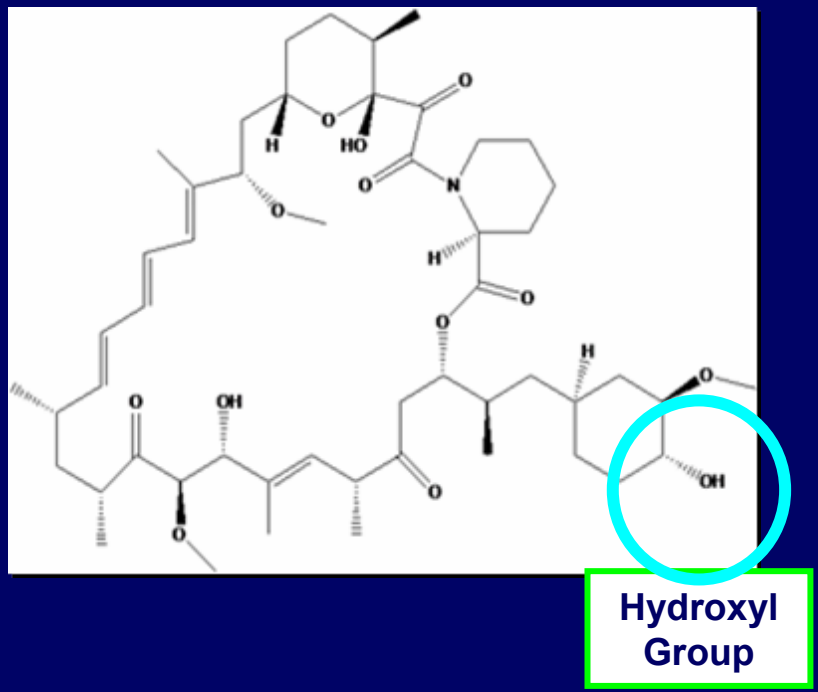


Drug: Zotarolimus

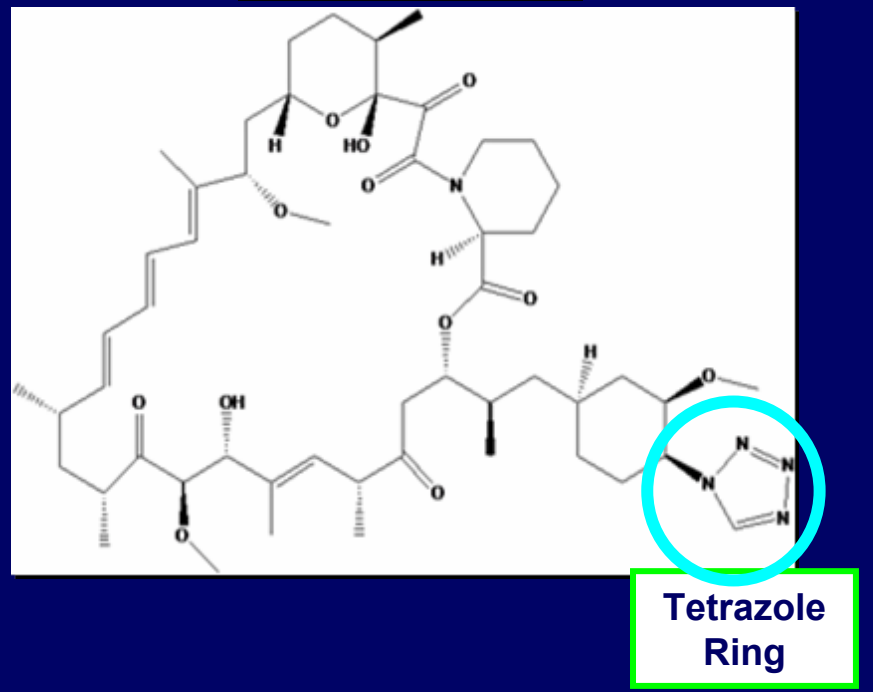


Zotarolimus: Structure and Properties

Sirolimus

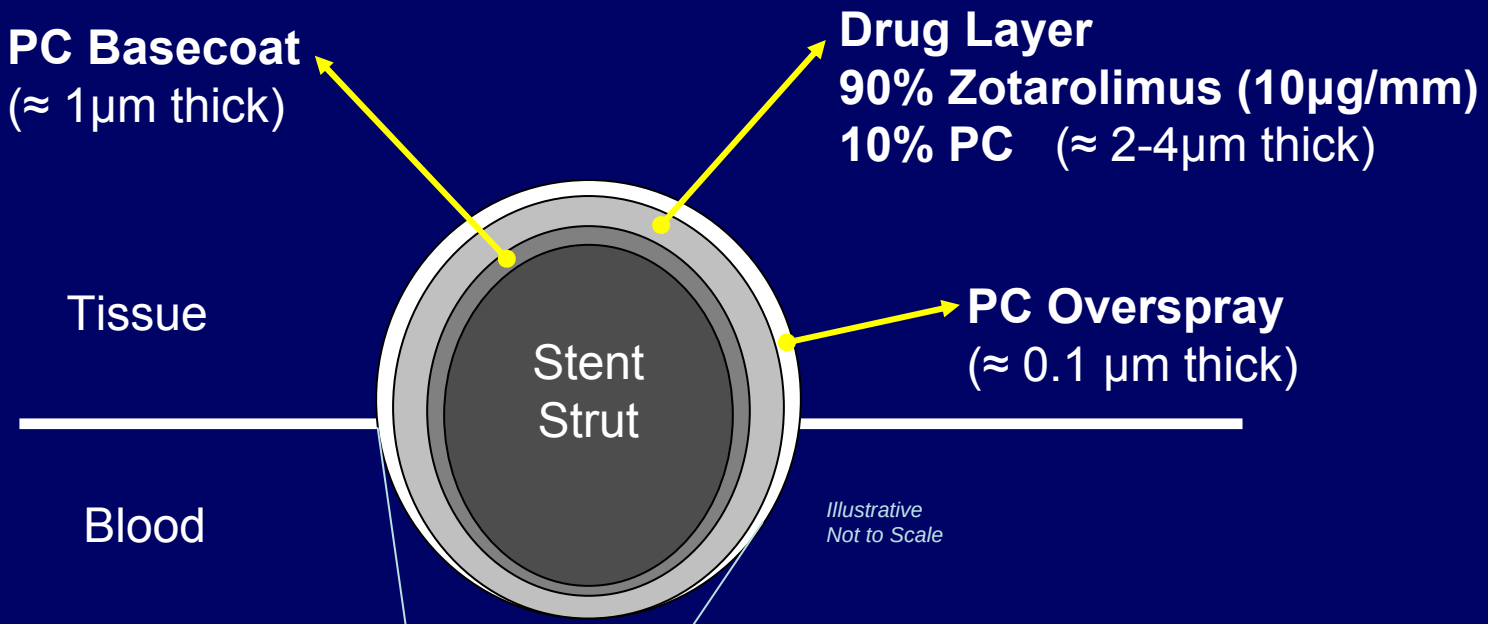


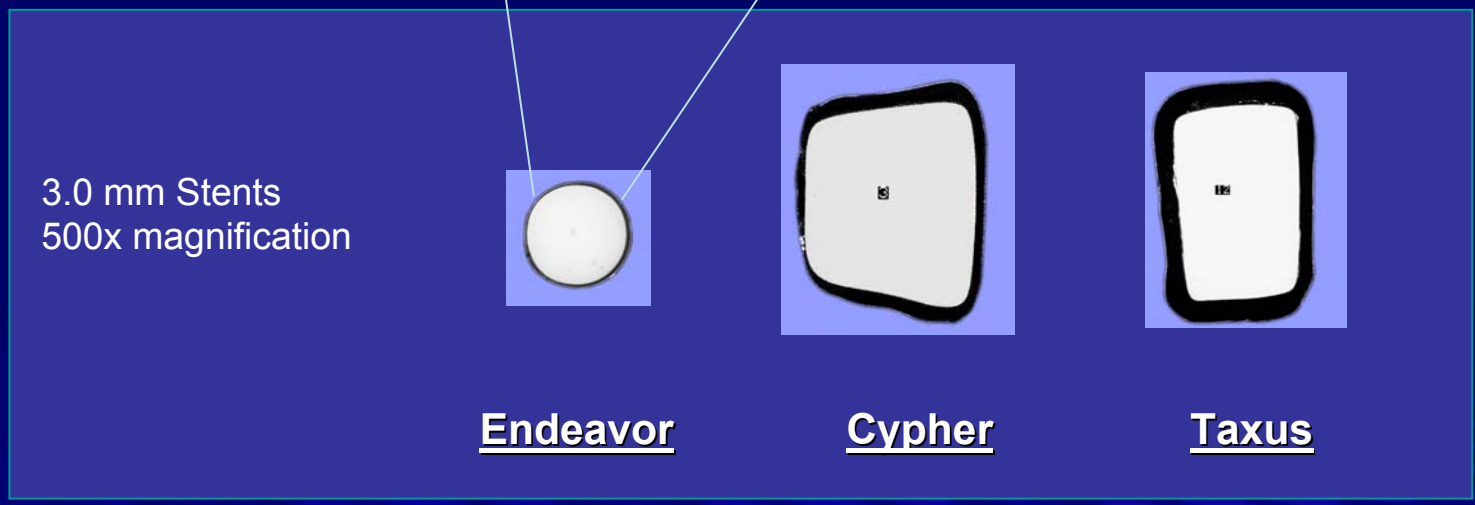
Zotarolimus



	Sirolimus	Zotarolimus
Lipophilicity	logD 3.6	logD >4.5
Potency	IC_{50} 0.4nM	IC_{50} 0.3nM

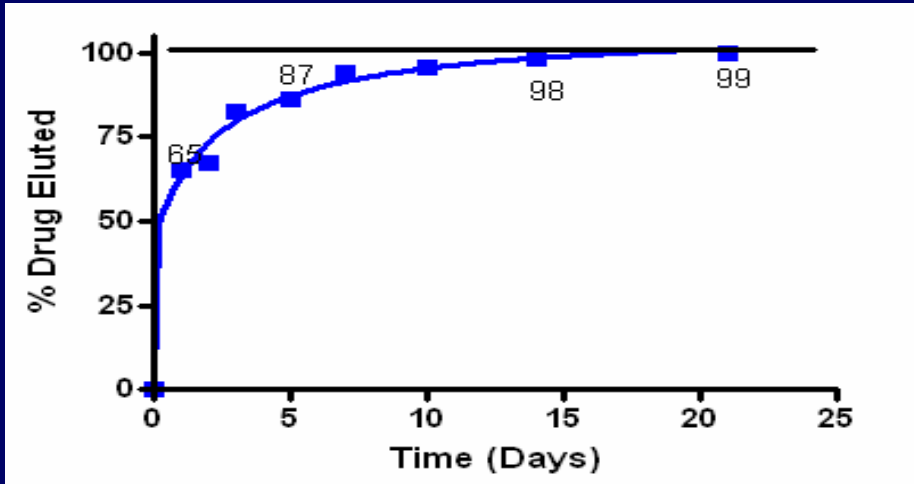
Polymer and Drug Matrix





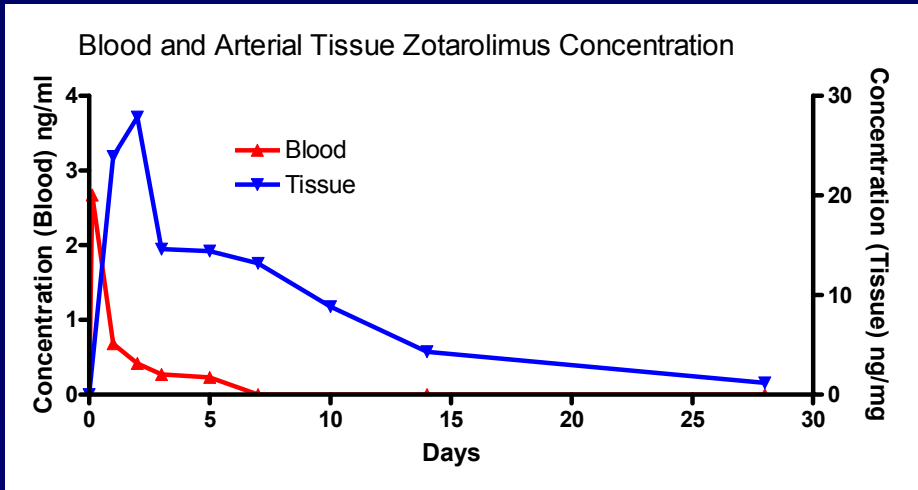
Porcine Drug Elution Kinetics and PK

Drug Elution by Recovered Drug from Stent



- Zotarolimus is hydrophobic and rapidly elutes from the hydrophilic PC polymer matrix within 14 days

Blood and Arterial Tissue Zotarolimus Concentration



- Zotarolimus is highly lipophilic enabling rapid arterial tissue loading and drug retention which is sustained for ~28 days

Drug Substance and Pre-clinical Characterization

LeRoy LeNarz, MD
Chief Medical Officer
Global VP, Medical Affairs
Medtronic Vascular

Zotarolimus Development

- **Full standard drug characterization**
- **Combination product with joint review by CDRH and CDER**
  - ICH guidelines and FDA guidance observed
  - Includes relevant pharmacology, ADME, toxicology, and other studies needed to characterize zotarolimus as a new chemical entity

Demonstrated Drug Safety

- **Standard safety pharmacology studies**

Examples:

- No respiratory toxicity in standard rat model at 50 ng/ml
- Non-antigenic in guinea pigs: did not induce systemic anaphylactic or passive cutaneous anaphylactic reactions
- No skin sensitization by lymph node assay
- No effect on platelet aggregation at 200 ng/ml or 50x highest anticipated C_{max} for 48 mm stent length

Demonstrated Cardiovascular Safety

- **Comprehensive cardiovascular evaluation**
  - hERG: no reduction in vitro current at highest achievable concentration (181ng/ml)
  - No significant prolongation in action potential duration In vitro canine cardiac Purkinje fibers
  - Both conscious and anesthetized dog (up to 232ng/ml) models, lack of effect on heart rate, Blood Pressure, Systemic Vascular Resistance, Pulmonary Vascular Resistance, and QTc
  - No significant hemodynamic findings in conscious primates with exposure up to 1357 ng/ml

ADME Studies

- **Standard Absorption, Distribution, Metabolism and Excretion (ADME) Testing**
- **High protein binding in all species, 99%**
- **Distributed on RBC and plasma at 20:1 ratio**
- **Radiolabel studies define feces as predominant path of excretion and little renal clearance (less than 6%)**
- **Metabolism mainly via CYP 3A4 pathways**
  - Non inhibitor at relevant concentrations
  - Minimal amplification by ketoconazole interaction studies in dog and man (less than 2x)

Toxicology Studies

- Genotoxicology studies negative
- Reproductive toxicity characterized
- Single and repeat dose 28 day studies in rat and monkey provide safety margin for anticipated use
- 90 day repeat dose studies in monkey define chronic safety

Endeavor: Human PK

Overview of Pharmacokinetics

Zotarolimus Pharmacokinetics

- **Phase-1 Single Dose I.V. Study (n=60)**
  - Drug concentrations in blood were demonstrated to be linear and dose proportional across the dose range from 100-900 micrograms

- **Phase-1 Multi Dose I.V. Study (n=72)**
  - Administered intravenously for 14 consecutive days in repeat doses of 200, 400 and 800 µg
  - Linear/dose proportional confirmed with steady state reached at day 10
  - No treatment emergent adverse effect

- **No deaths, SAEs reported in either Phase I PK study**

Pharmacokinetics

Comparison of Zotarolimus Pharmacokinetics between Endeavor US PK Study and Endeavor II (PK subset)

PK Parameters (unit)	Endeavor US PK Study			Endeavor-II PK Subset		
	180 µg (N = 24)	240 µg (N = 6)	300 µg (N = 7)	180 µg (N = 10)	240 µg (N = 22)	300 µg (N = 15)
C_{max} (ng/mL)	**1.51 ± 0.62**	**1.83 ± 0.21**	**2.66 ± 0.99**	**1.64 ± 0.57**	**1.84 ± 0.41**	**2.45 ± 0.40**
T_{max} (h)	**1.20 ± 0.60**	**1.40 ± 1.30**	**1.48 ± 1.29**	**1.18 ± 0.48**	**1.03 ± 0.54**	**0.90 ± 0.52**
AUC_{0-24} (ng•h/mL)	**20.0 ± 6.5**	**23.7 ± 3.6**	**31. 5 ± 9.2**	**25.1 ± 7.4**	**24.6 ± 6.8**	**31.7 ± 6.0**

The pharmacokinetics of zotarolimus from US PK study are consistent to those observed from the Endeavor II PK subset

Zotarolimus Exposure

- **Clinical studies establish wide safety margins of exposure for use based on 48 mm stent (ENDEAVOR US PK Study)**

	Cum. Dosage (µg/kg)	C_{max} (ng/ml)	Cum. AUC (ng•hr /ml)	Exposure margin		
				Dosage	C_{max}	AUC
Extrapolated Clinical	6.9	4.0	162	NA	NA	NA
90-d Monkey Cumulative 10 µg/kg/d (daily IV)	900	14.8	9661	130	4	60
Human Single Dose IV 900 µg	12.9	111	254	2	28	2
Human Multiple Dose IV 800 µg/d	160	38.9	2395	23	10	15

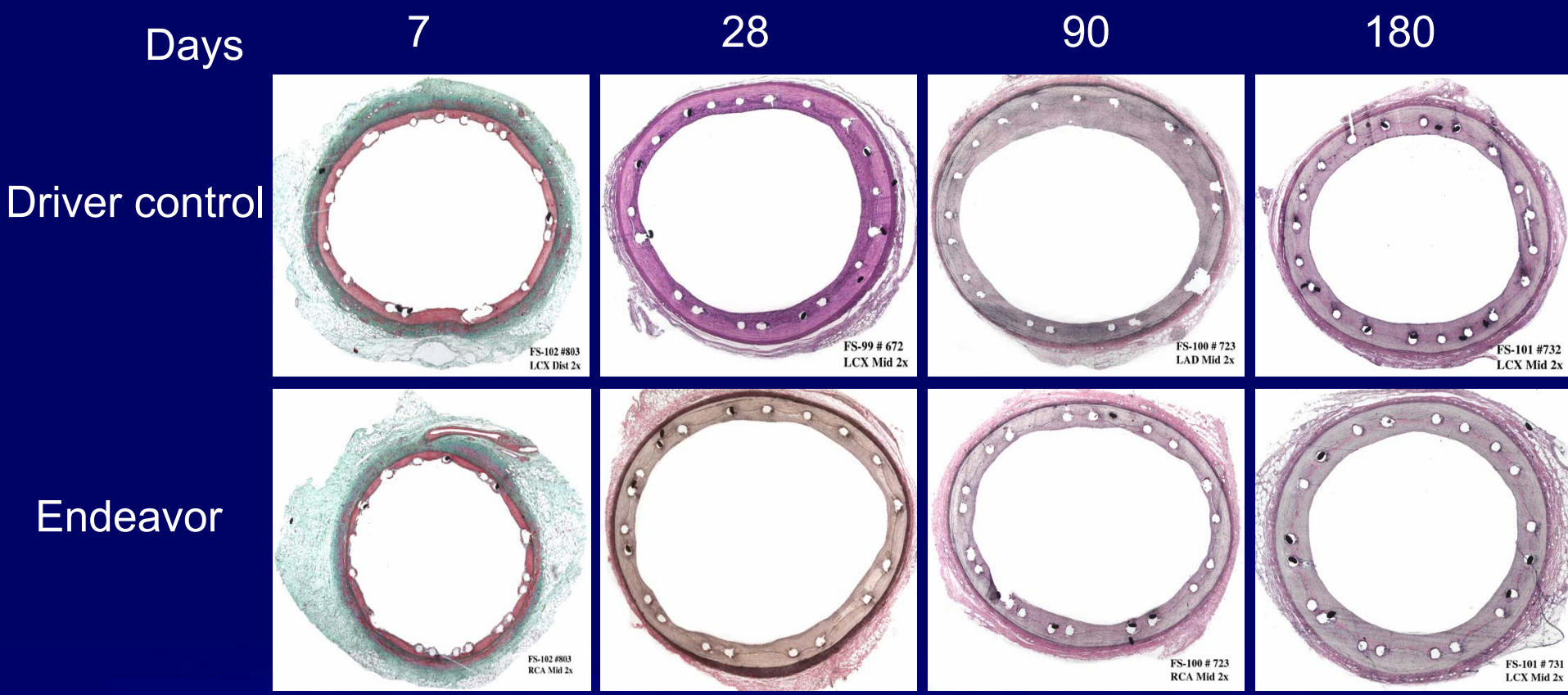
Endeavor Biocompatibility

Summary of Key Pre-Clinical Findings:

- Histopathology
- Inflammation
- Endothelialization *(coverage and function)*

Histopathology of Artery

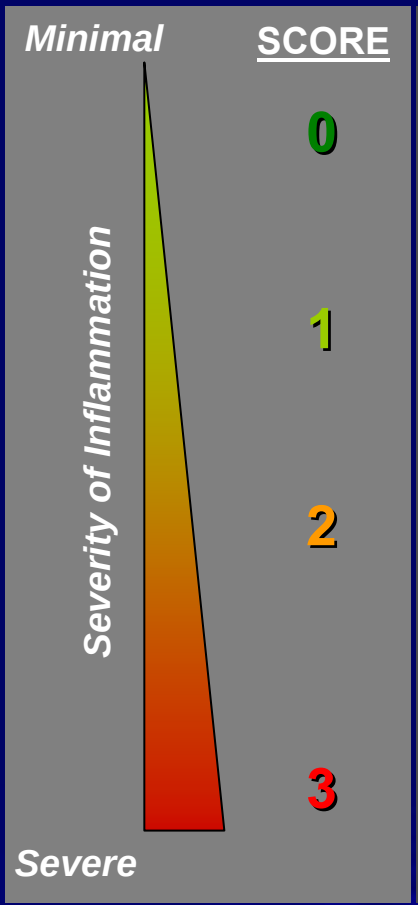
- **No indication of thrombosis or necrosis at 7 to 180 days in porcine studies involving 127 animals***



*CVPath, Dr Renu Virmani

Inflammation

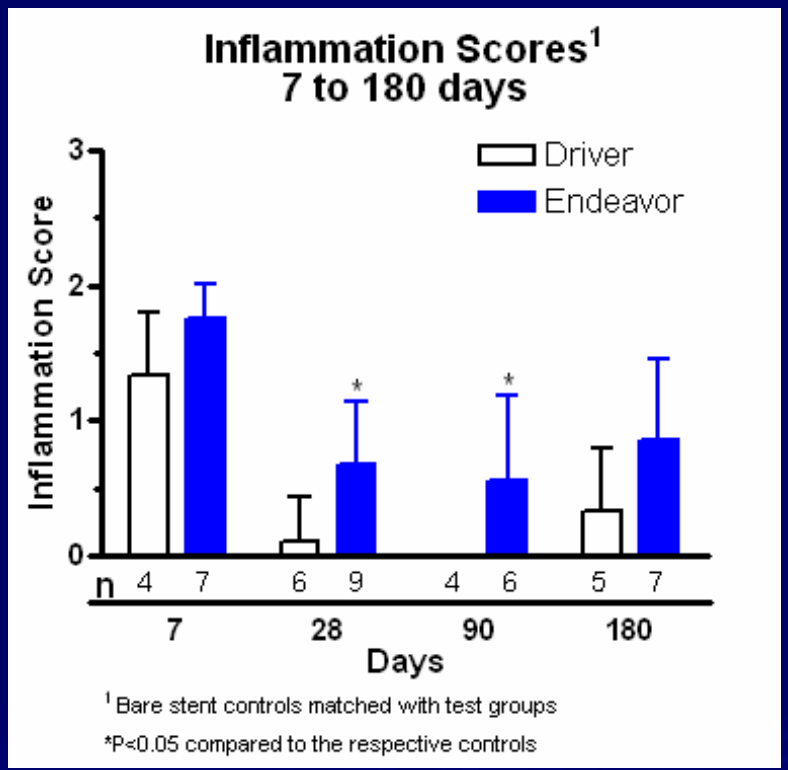
- Endeavor demonstrates consistently low inflammation based on a 0-3 scoring system
- A Score of 1 implies lack of organized inflammation

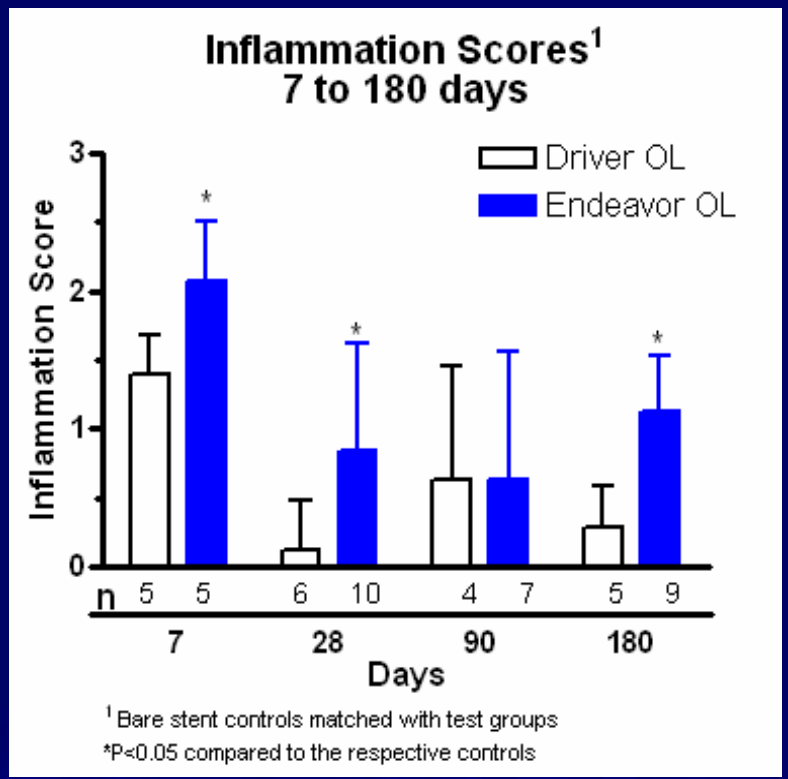


SCORE	
0	3 or fewer struts with 10 or fewer inflammatory cells surrounding the struts
1	3 to 6 struts with 10 or fewer inflammatory cells surrounding the struts
2	Greater than 6 but less than 50% of the struts with 10 or fewer inflammatory cells surrounding the struts
3	Greater than 10 inflammatory cells surrounding 50% or more struts

Biocompatibility (Inflammation Scores)

Porcine inflammation scores show mild response at all chronic time points up to 180 days with single and overlapped 10µg/mm stents*.

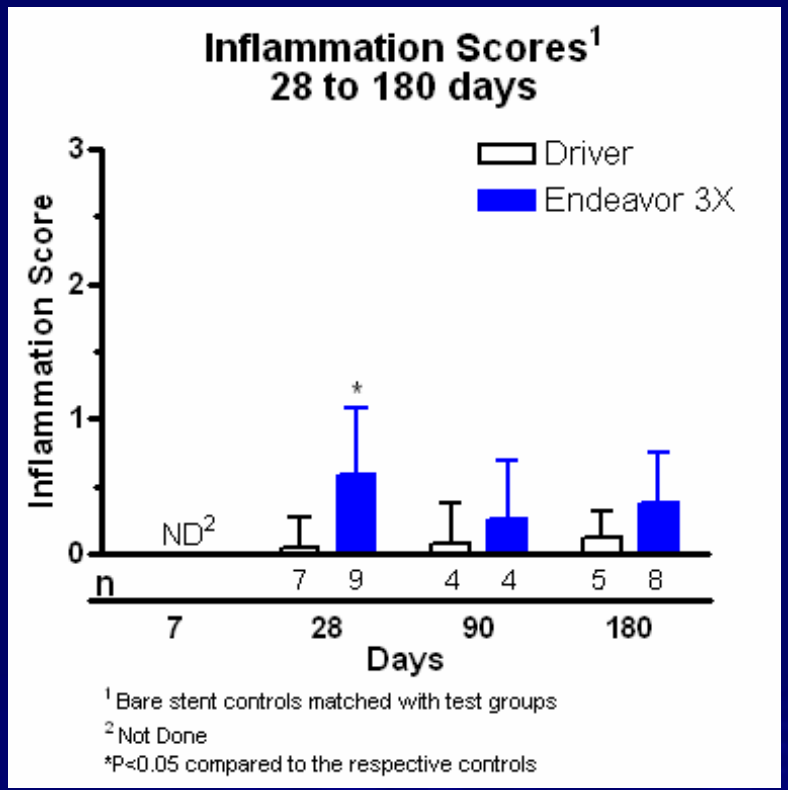


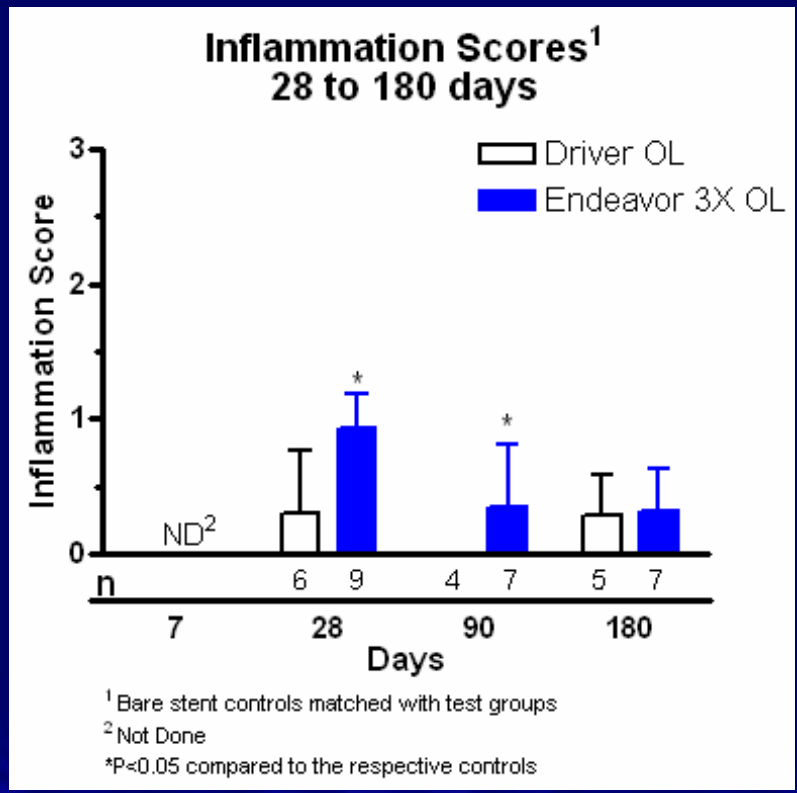


*CVPath, Dr Renu Virmani

Biocompatibility (Inflammation Scores)

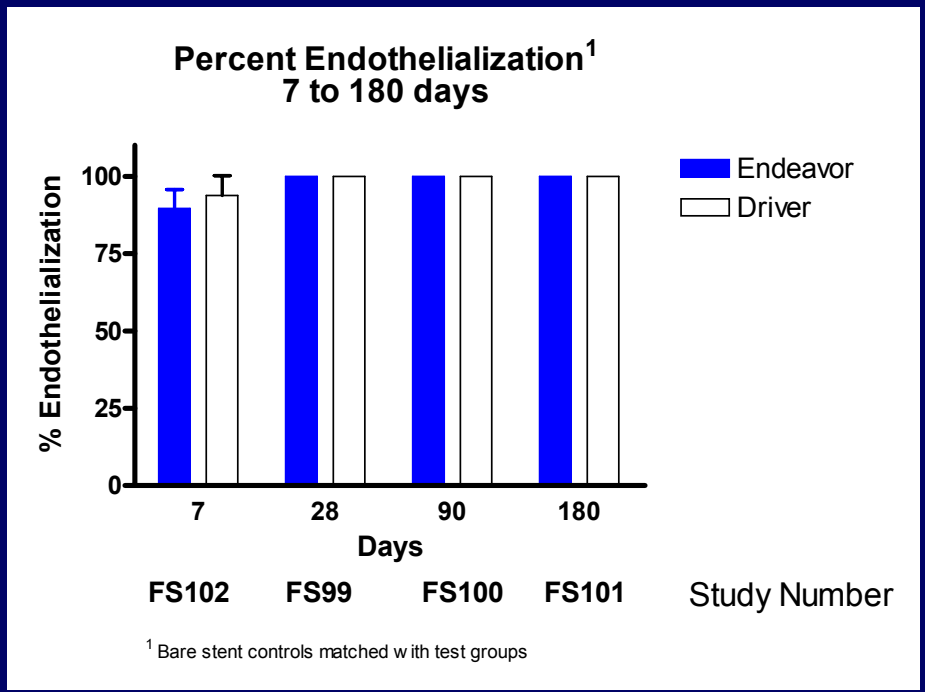
Porcine inflammation scores show mild response to a 3X overdose (30µg/mm) and 6X overdose (overlapping 30µg/mm) at all chronic time points up to 180 days with single and overlapped stents.



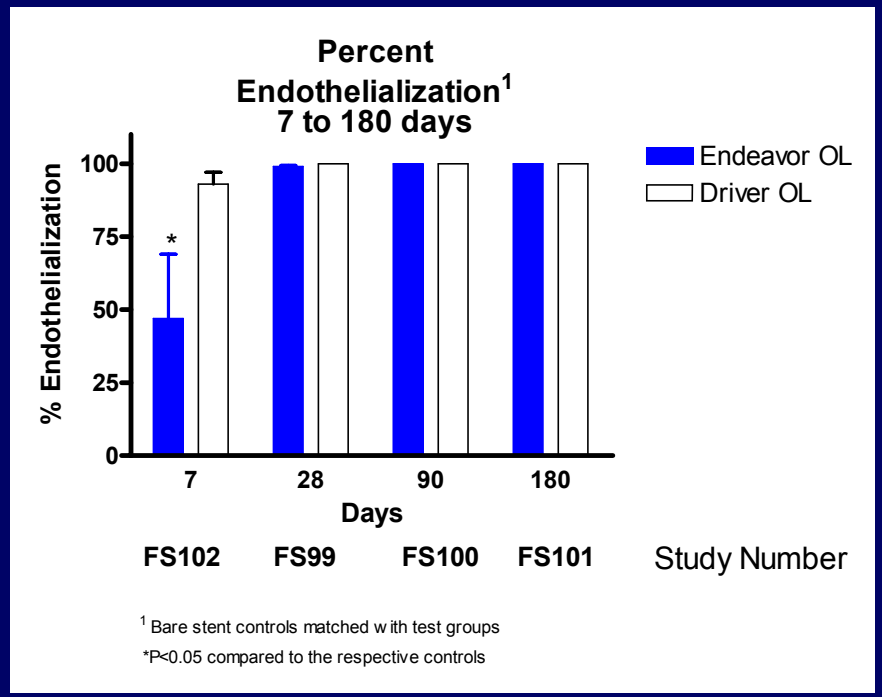


Endothelial Coverage

Porcine histology and SEM show rapid endothelial replacement with both single and overlapping (OL) stents*.



Single Stents

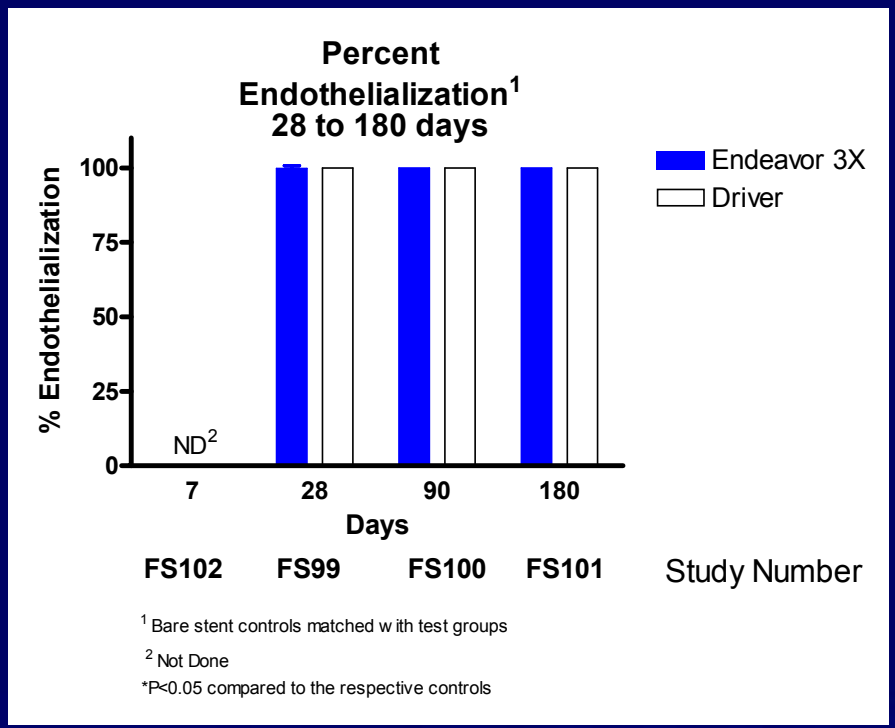


Overlapping (OL) Stents

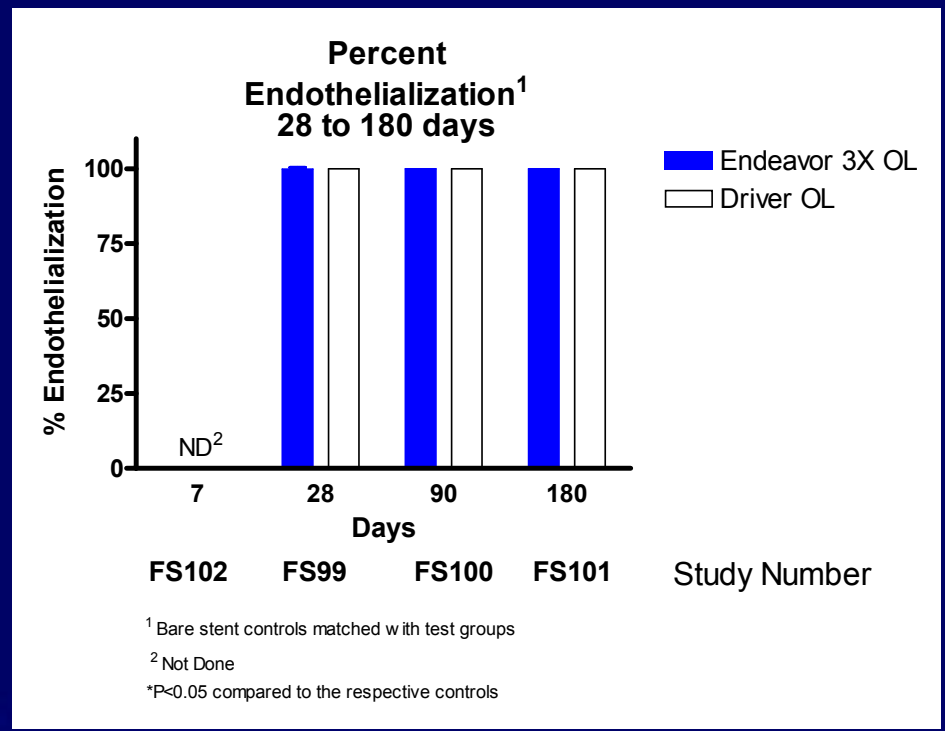
*CVPath, Dr Renu Virmani

Endothelial Coverage (Overdose)

Porcine histology and SEM show rapid endothelial replacement with Endeavor 3X overdose (30µg/mm) and 6X overdose (overlapping 30µg/mm) using both single and overlapped (OL) stents.



Single Stents

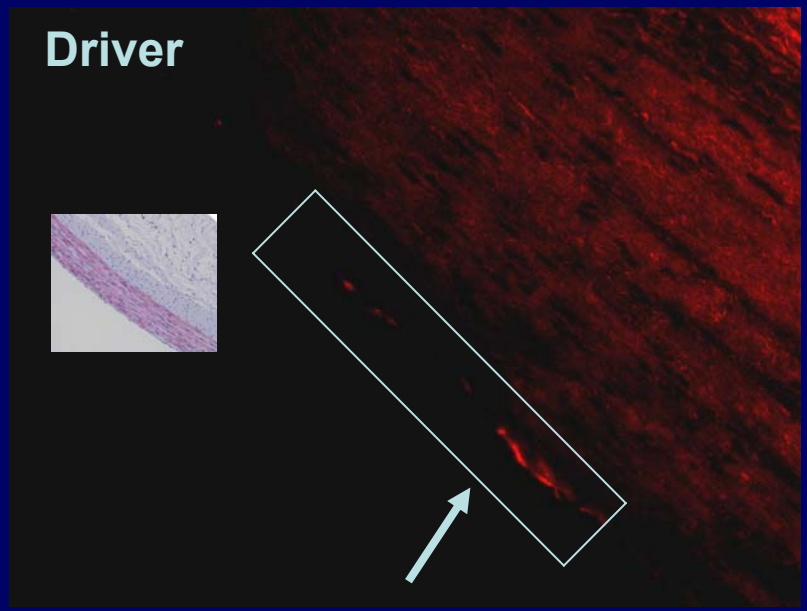


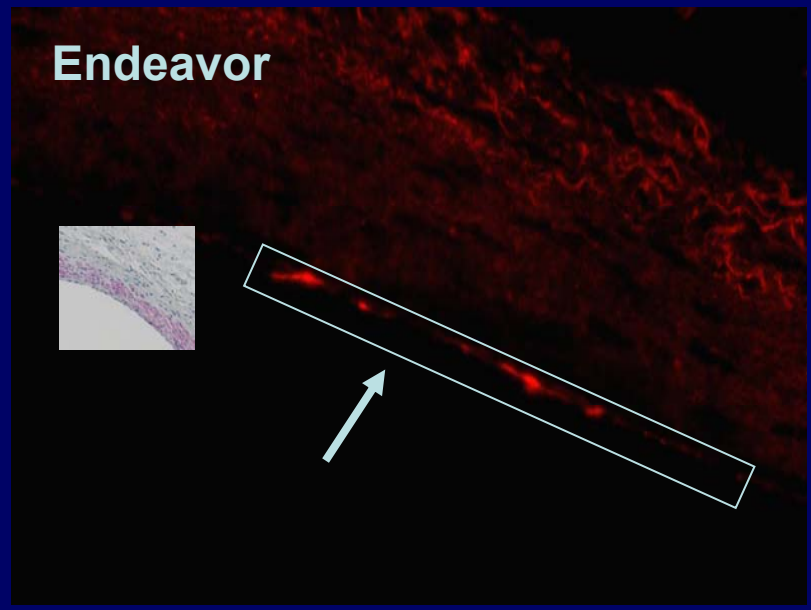
Overlapped (OL) Stents

Preserved Endothelial Function

In Vivo Assessment of Endothelial Function in Porcine Models: eNOS Staining

Immunohistochemistry Staining for Presence of eNOS

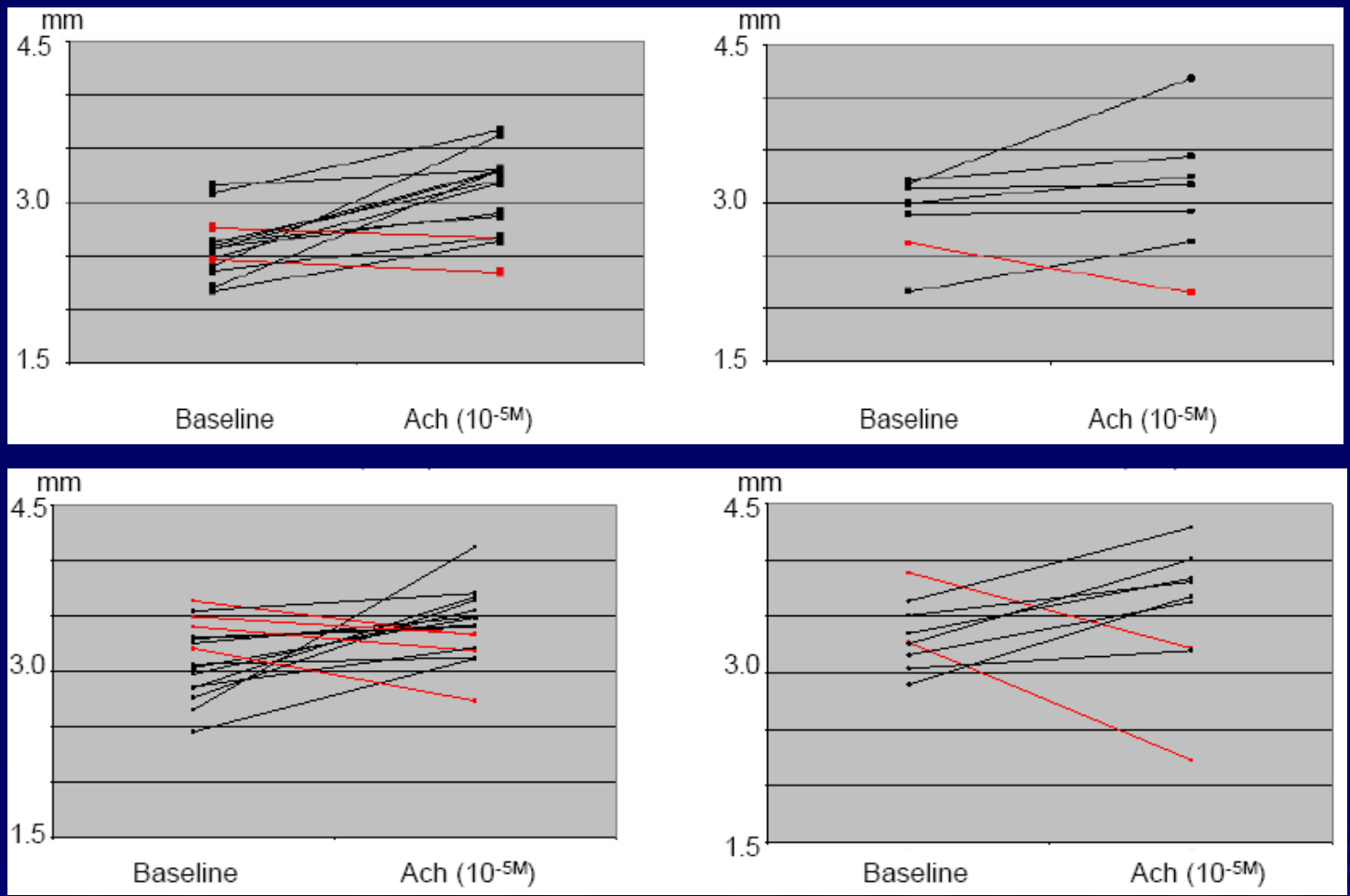




Preserved Endothelial Function

In Vivo Assessment of Endothelial Function in Porcine Models: Active Vasoreactivity

Distal Vessel Vasoreactivity Following Acetylcholine (Ach) Challenge



Pre-clinical Summary

Extensive pre-clinical evaluation at 10 μg/mm and overdose drug levels has demonstrated:

- No medial necrosis or aneurysms
- Low levels of drug/polymer induced inflammation
- Rapid, complete and functional endothelialization

Endeavor Clinical Drug Safety

Overview from Randomized Trials

Endeavor Drug Safety by Body System

Body System	ENDEAVOR II To 30 days		ENDEAVOR III To 30 days		ENDEAVOR IV To 30 days	
	Endeavor Stent (N= 598)	Driver Stent (N=599)	Endeavor Stent (N=323)	Cypher Stent (N=113)	Endeavor Stent (N=773)	Taxus Stent (N=775)
Hepatobiliary Disorders	7(1.2%)	4(0.7%)	2(0.6%)	0(0.0%)	2(0.3%)	1(0.1%)
Immune System Disorders	5(0.8%)	7(1.2%)	1(0.3%)	0(0.0%)	3(0.4%)	3(0.4%)
Renal and Urinary Disorders	10(1.7%)	16(2.7%)	8(2.5%)	7(6.2%)	17(2.2%)	15(1.9%)
Vascular Disorders	70(11.7%)	74(12.4%)	43(13.3%)	18(15.9%)	48(6.2%)	59(7.6%)

No significant body system treatment emergent events

Pre-clinical / Clinical Conclusions

- **Porcine studies demonstrated**
  - Drug/polymer coating is safe with respect to biocompatability
  - Normal endothelial coverage and function
- **Zotarolimus demonstrated**
  - Favorable safety margins
  - No anticipated drug-drug interaction
  - No treatment emergent events as a combination product

Endeavor
Clinical Trial Program

Martin B. Leon, MD

Disclosures:

- *Member of Medtronic's Coronary Advisory Board*
- *Principal Investigator of ENDEAVOR III and ENDEAVOR IV*

DES Use Considerations

Areas for improvement

Attribute	Bare Metal Stents	Current Generation DES
Safety	+++	++
Efficacy	++	++++
Deliverability	++++	++

Preserve efficacy advantage of DES, while improving safety and deliverability

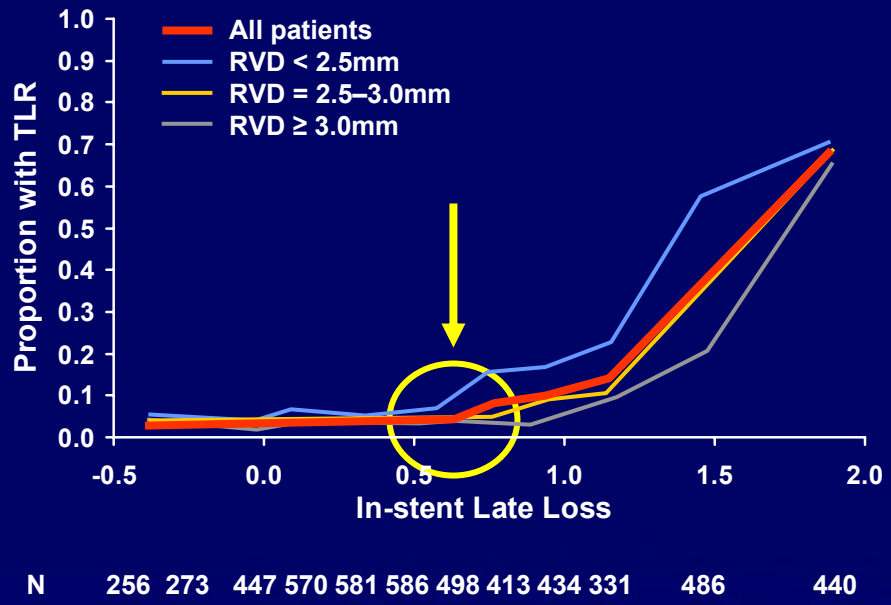
Early DES Assumptions (2002-06)

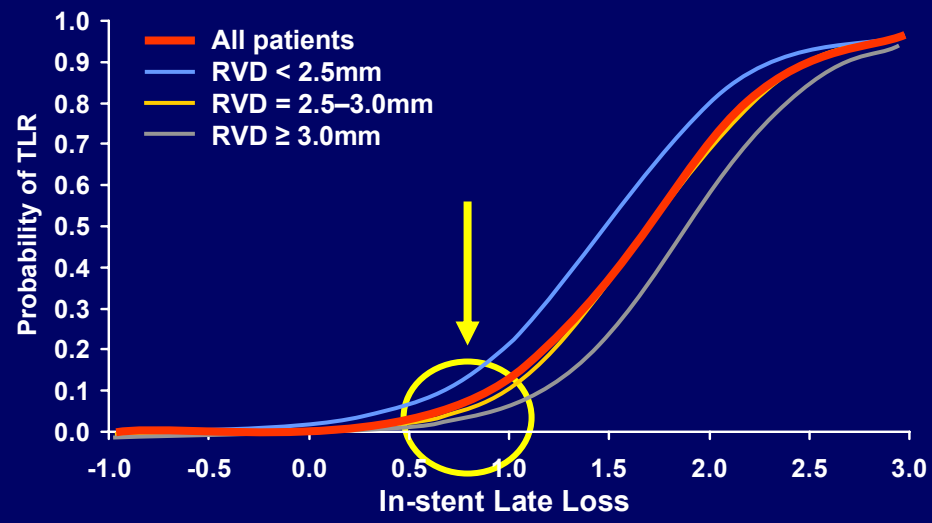
- ***Efficacy measures***
  - Angiographic late loss (LL) and binary restenosis were *robust* surrogates for target lesion revascularization (TLR)
- ***Safety considerations***
  - Safety (e.g. stent thrombosis) could be determined in the first year after DES implantation
- ***Clinical trial design***
  - Blinded superiority RCTs in low-medium complexity patients vs. BMS were sufficient to demonstrate DES safety and efficacy

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

Surrogate Angiographic Endpoints for Clinical Outcomes

LL vs. TLR - A monotonic but curvilinear relationship



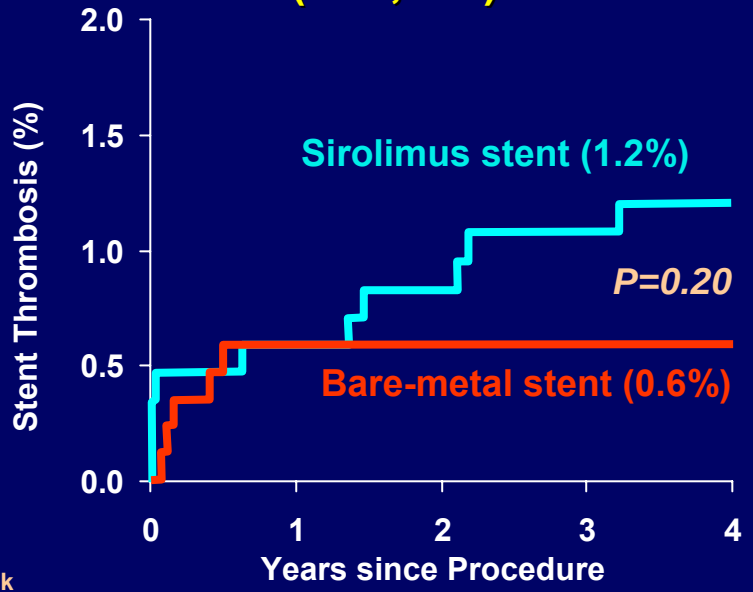


Pocock S. et al., JACC, in press

9 Prospective, Double-Blind, Randomized Trials

Freedom From (Protocol) Stent Thrombosis (4yr FU)

RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS (n=1,748)

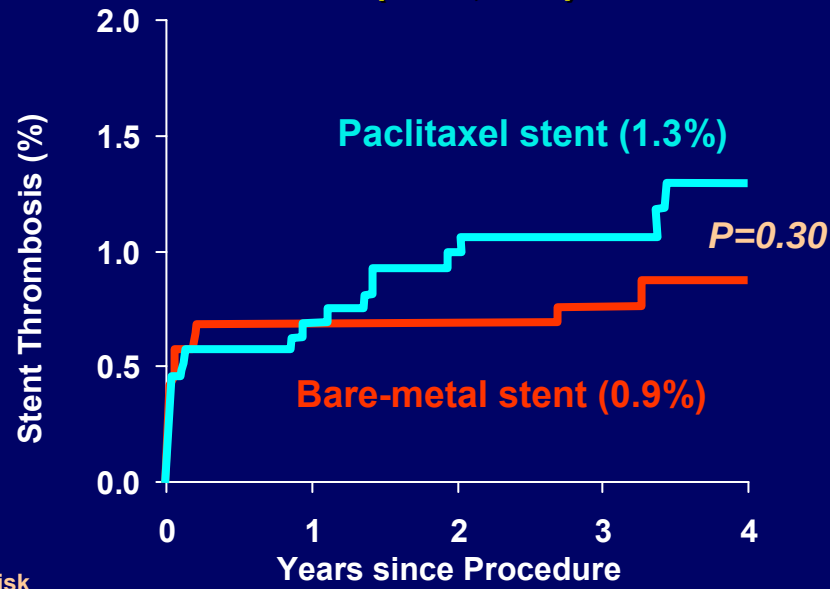


No. at Risk					
Bare-metal stent	870	852	833	806	742
Sirolimus stent	878	854	826	795	732

After 1 year

5 vs. 0, P=0.025

TAXUS I, II, IV, V, VI (n=3,506)



No. at Risk					
Bare-metal stent	1756	1692	1579	1126	319
Paclitaxel stent	1753	1687	1561	1106	279

After 1 year

9 vs. 2, P=0.028

Stone G. et al., *NEJM* 2007; 356: 998-1008

Consensus Observations on DES Safety from the Dec. 2006 FDA Panel

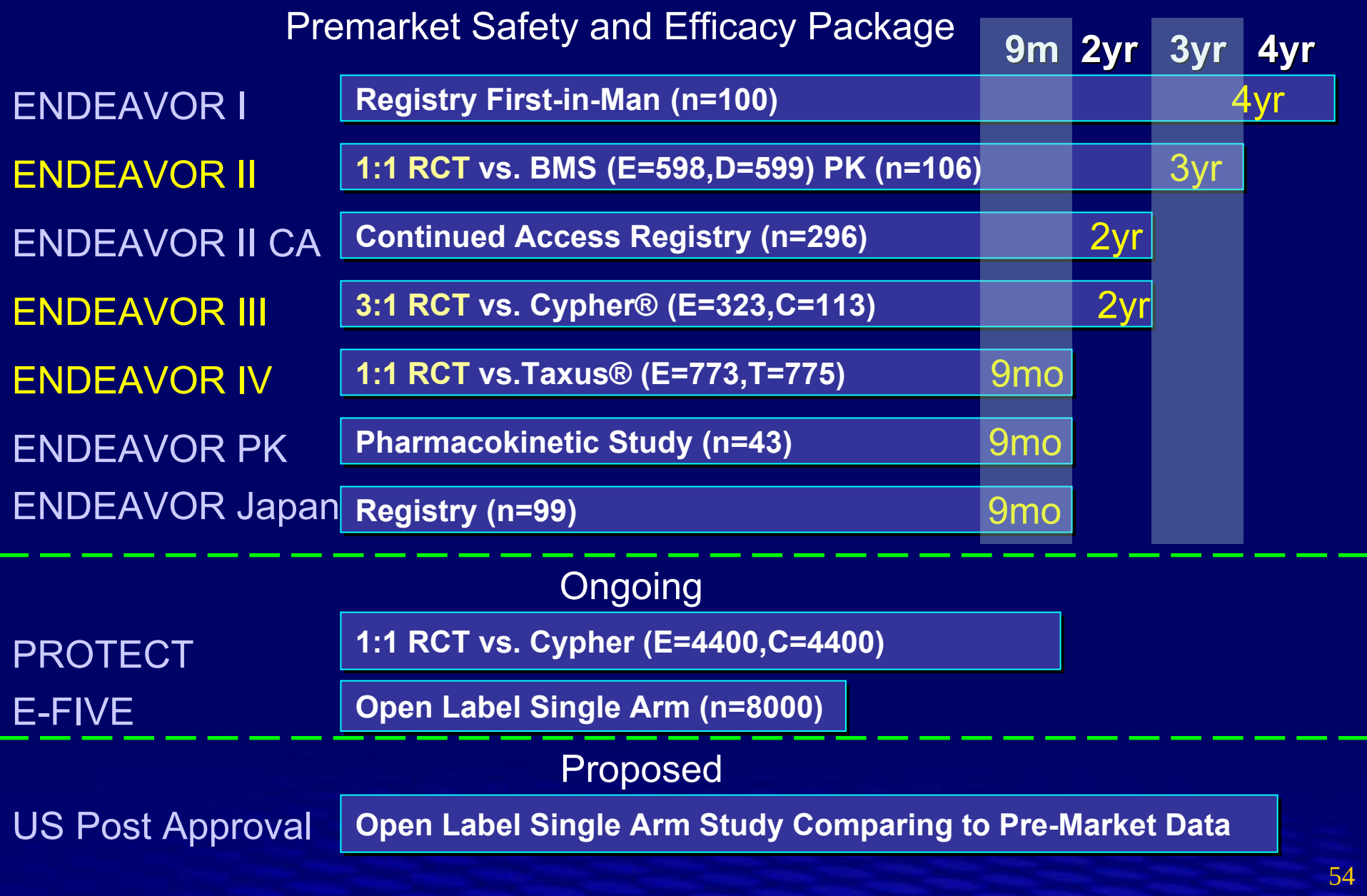
Approved DES…

- Very late stent thrombosis occurs after 1 year (0.2-0.6% per year) and may represent a constant hazard
- Little is known about DES safety for "off label" use indications, but preliminary data suggest a higher frequency of very late stent thrombosis vs. "on label" use
- Dual anti-platelet therapy should be extended in some DES patients, but duration of therapy, associated risks, and impact on very late stent thrombosis is controversial

Current DES Insights

- ***Efficacy measures***
  - The relationship between LL and TLR is non-linear and moderate LL may still result in low TLR
  - Angiographic follow up has a profound impact on TLR
- ***Safety considerations***
  - DES safety evaluations can no longer be confined to 1 year, as very late stent thrombosis is increased compared with BMS
- ***Clinical trial design***
  - Larger non-inferiority RCTs vs. approved DES and even larger "real world" studies (both with longer follow-up) are now required to discern clinical safety and efficacy

Endeavor Program Overview



Endeavor Studies Summary

- ***Submitted to FDA Panel:***
  - 3 Randomized Trials (3,181 pts)
    1,694 Endeavor pts
  - 4 Registries (538 pts)
    538 Endeavor pts
  - Patient years of follow-up
    Overall - 6,492
    Endeavor - 3,980

Endeavor Clinical Program
Goals

- Demonstrate superior reduction in restenosis compared with a BMS (both angiographic and clinical endpoints)
- Demonstrate a “BMS-like” early and late safety profile (death, MI, and stent thrombosis)
- Demonstrate comparable (non-inferior) outcomes vs. approved DES
- Show consistency of angiographic and clinical outcomes across all RCTs

Endeavor Randomized Trials

- Randomized Trials (total n=3181 pts)

Study (n=)	*Design*	*Control Arm*	*Primary EP*	*Duration of F/U*
EII (n=1197)	1:1 double blind superiority, pK	Driver & Micro Driver BMS	9 month TVF	3 years
EIII (n=436)	3:1 single blind non-inferiority	Cypher DES	8 month In-segment LL	2 years
EIV (n=1548)	1:1 single blind non-inferiority	Taxus DES	9 month TVF	9 months

Endeavor Clinical Program

Consistent data analysis and endpoint definitions (all RCTs)

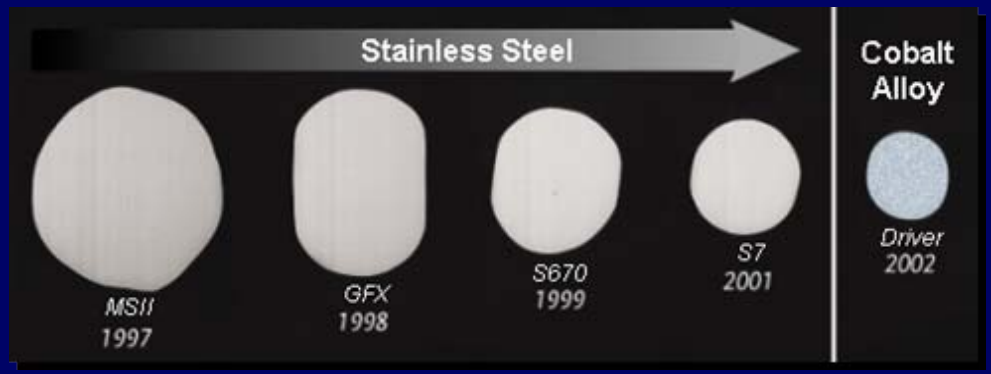
- QCA Core Lab
  - Brigham and Women's Hospital, Boston, MA, USA
  - Jeffrey J. Popma, MD
- IVUS Core Lab
  - Cardiovascular Core Analysis Lab
  - Stanford Interventional Cardiology, CA, USA
  - Peter Fitzgerald, MD
- ECG Core Lab
  - Harvard Clinical Research Institute, Boston, MA, USA
  - Peter Zimetbaum, MD
- Data Coordinating Center
  - Harvard Clinical Research Institute, Boston, MA, USA
  - Laura Mauri, MD
- Clinical Events Committee/DSMB
  - Harvard Clinical Research Institute, Boston, MA, USA
  - Donald Cutlip, MD

Endeavor Clinical Program

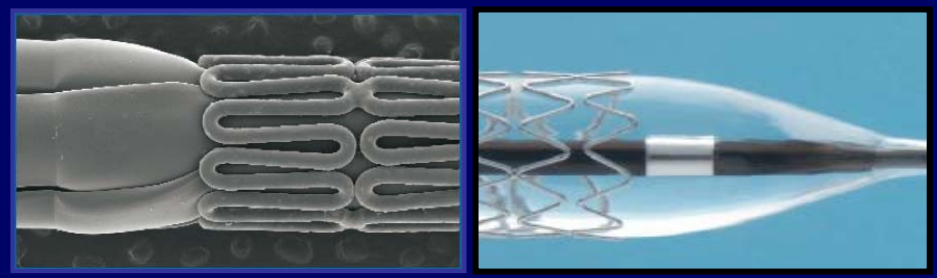
Key Baseline Variables across RCTs

	EII n=598	EIII n=323	EIV n=773
Diabetics - %	18.2	29.7	31.2
Unstable Angina - %	33.2	51.1	51.6
RVD - mm	2.73	2.75	2.73
Lesion length - mm	14.04	14.96	13.41
B2/C lesions - %	78.4	67.2	69.6
Angiographic F/U - % (eligible)	88.6	85.8	87.8
% (total)	44.1	85.8	18.6
n	264	277	144

Endeavor Stent Platform



- Cobalt alloy
- Thin struts – 0.0036”
- Strength & visibility
- Edgeless design (deliverable)
- Flexible, low profile
- Good scaffolding

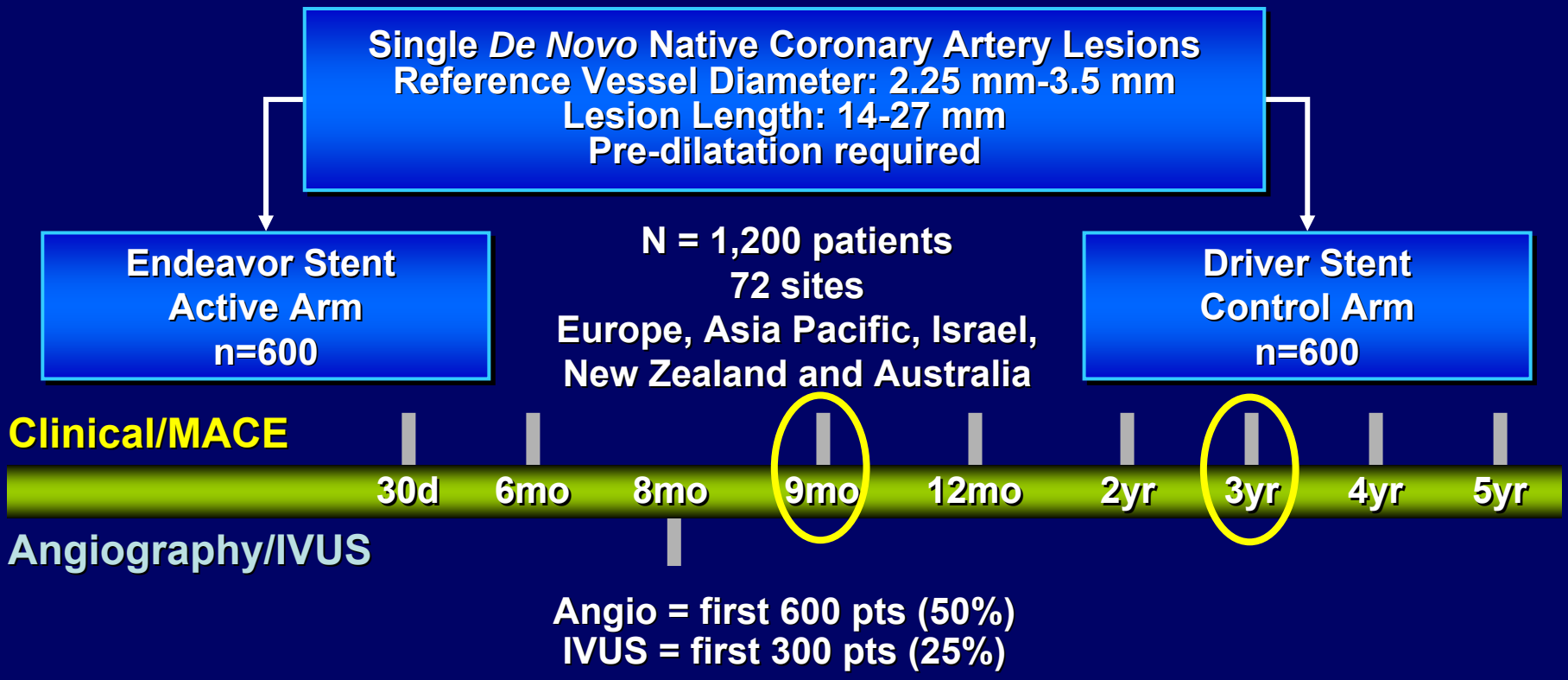


	EII	EIII	EIV
Endeavor Device Success (%)	98.8	98.8	97.3

ENDEAVOR II

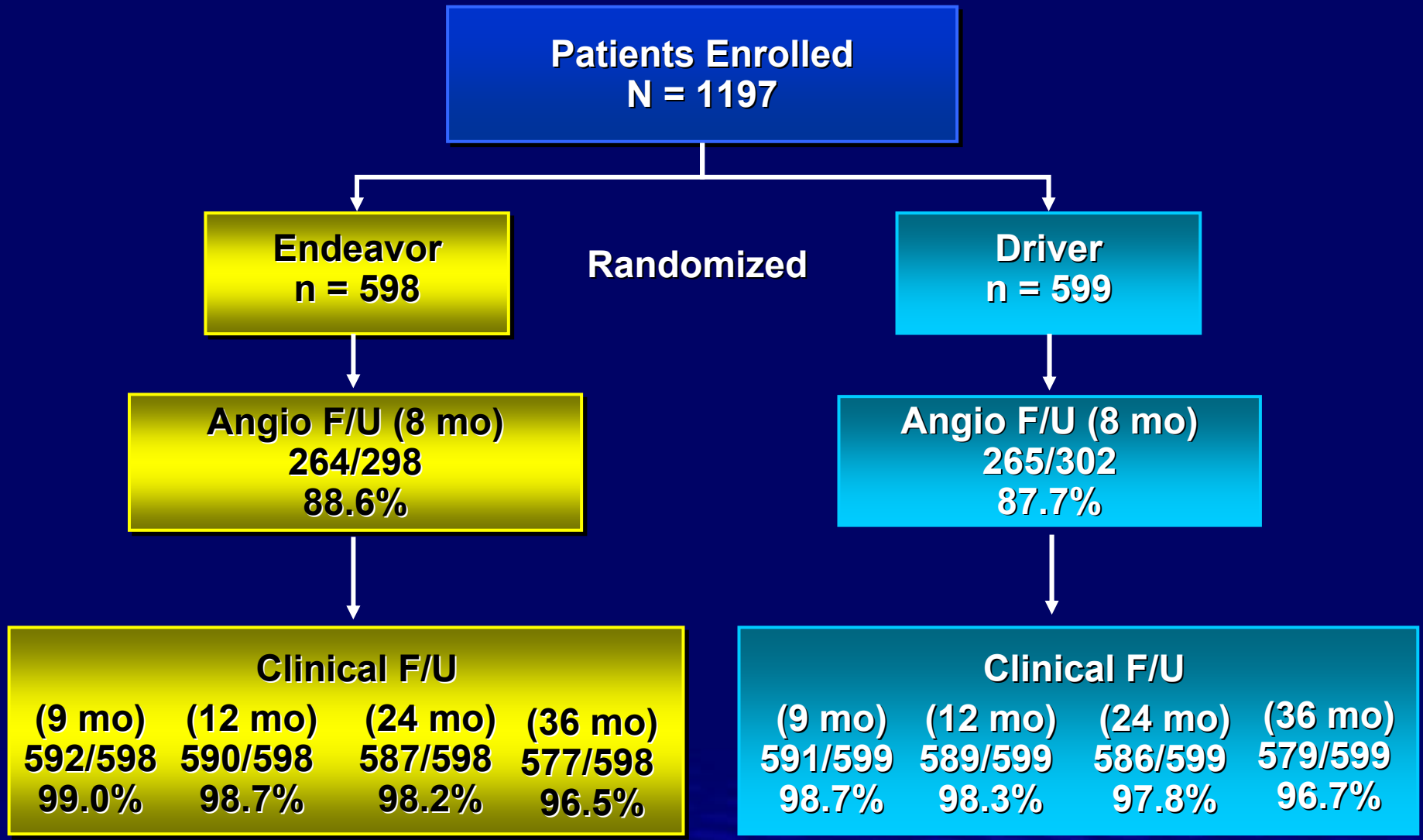
Double Blind RCT vs Driver

PI: Jean Fajadet, Richard Kuntz and William Wijns



Primary Endpoint: TVF at 9 months
Secondary Endopoints: MACE at 30 days and 9 months, ABR at 8 months
Drug Therapy: ASA and Clopidogrel/Ticlid ≥3 months
Zotarolimus Dose: 10 μg per mm stent length

ENDEAVOR II
Patient Flowchart



ENDEAVOR II
Baseline Characteristics

	Endeavor n=598	Driver n=599	*P value*
Males (%)	77.2	75.3	NS
Diabetics (%)	18.2	22.2	NS
Unstable Angina (%)	33.2	33.3	NS
RVD (mm)	2.73	2.76	NS
Lesion length (mm)	14.04	14.38	NS
B2/C lesions (%)	78.4	79.1	NS

ENDEAVOR II

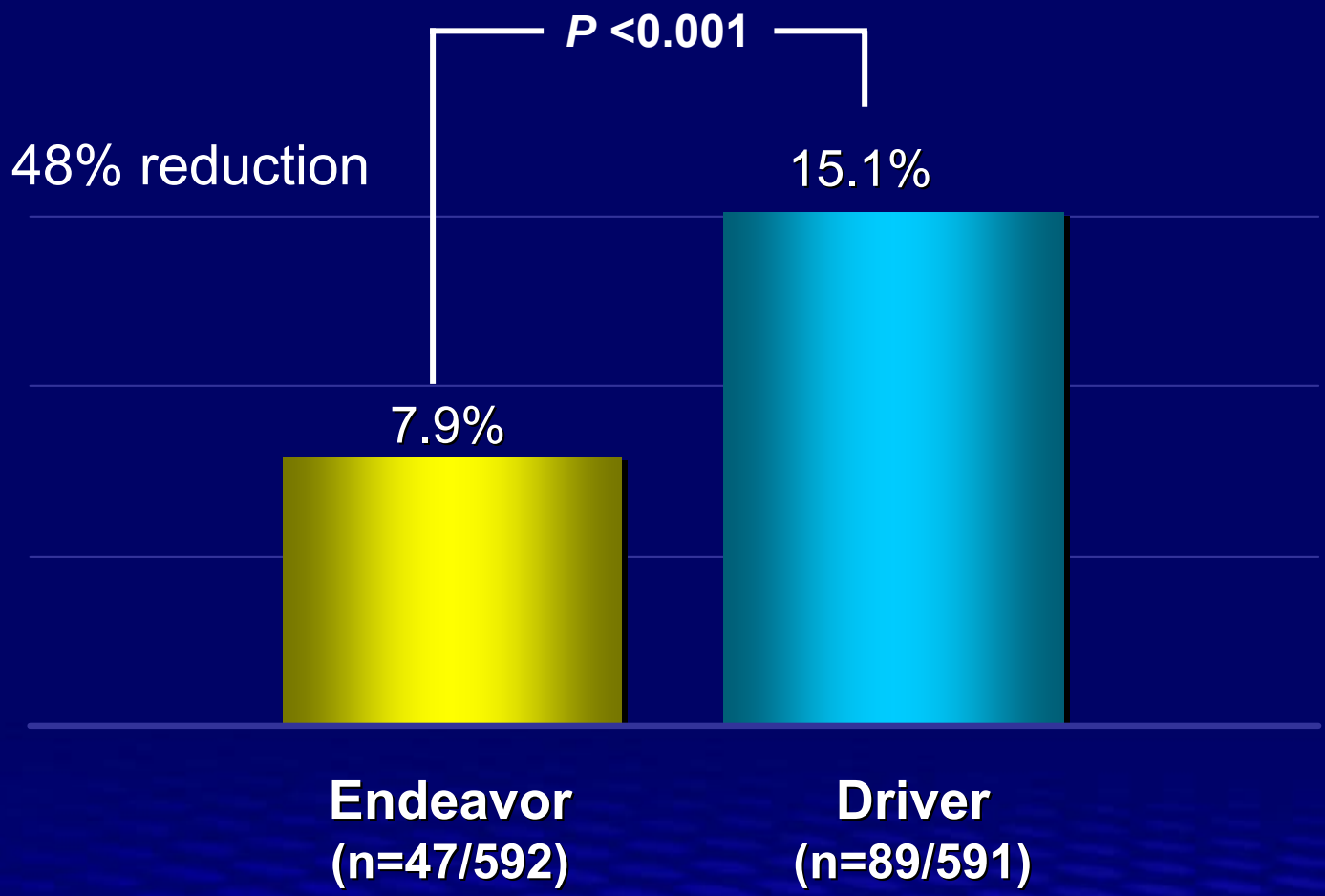
Clinical Events at 30 days

	Endeavor n=596	Driver n=594	*Difference [95% CI]*
Death (all) - % (#)	0.2 (1)	0	0.2%[-0.2%,0.5%]
Cardiac	0.2 (1)	0	0.2%[-0.2%,0.5%]
MI (all) - % (#)	2.7 (16)	3.5 (21)	-0.9%[-2.8%,1.1%]
Q Wave	0.3 (2)	0.8 (5)	-0.5%[-1.4%,0.4%]
Non Q wave	2.3 (14)	2.7 (16)	-0.3%[-2.1%,1.4%]
Death (cardiac) + MI (all) - % (#)	2.7 (16)	3.5 (21)	-0.9%[-2.8%,1.1%]
Stent Thrombosis (all) - % (#)	0.5 (3)	1.2 (7)	-0.7%[-1.7%,0.4%]
TLR - % (#)	0.8 (5)	1.2 (7)	-0.3%[-1.5%,0.8%]
TVR (non-TL) - % (#)	0.3 (2)	0	0.3%[-0.1%,0.8%]
TVR - % (#)	1.2 (7)	1.2 (7)	-0.0%[-1.2%,1.2%]
MACE - % (#)	2.9 (17)	3.7 (22)	-0.9%[-2.9%,1.2%]
TVF - % (#)	3.2 (19)	3.7 (22)	-0.5%[-2.6%,1.6%]

ENDEAVOR II

Primary Endpoint Result at 9 months

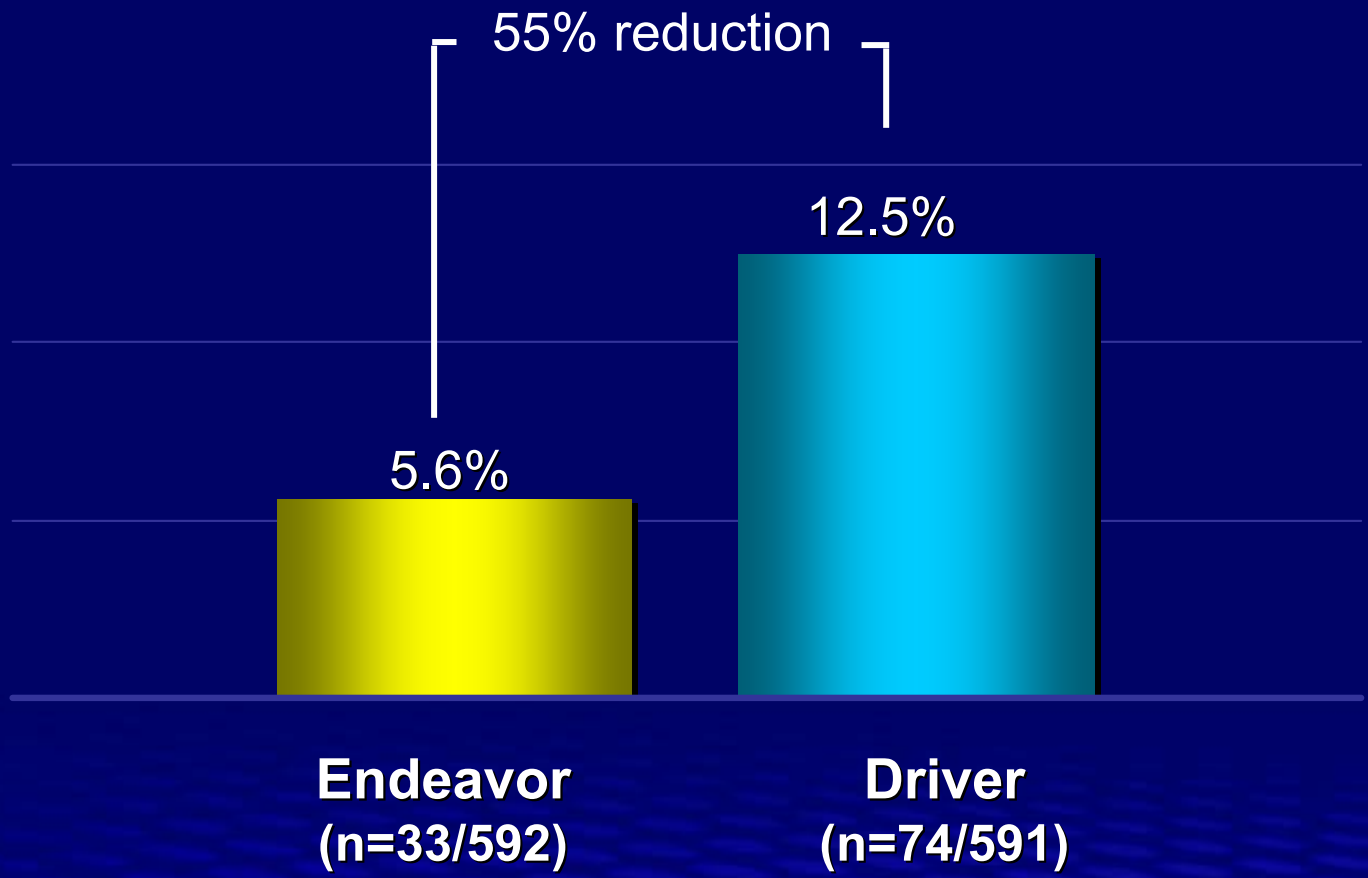
Target Vessel Failure



ENDEAVOR II

Efficacy at 9 months

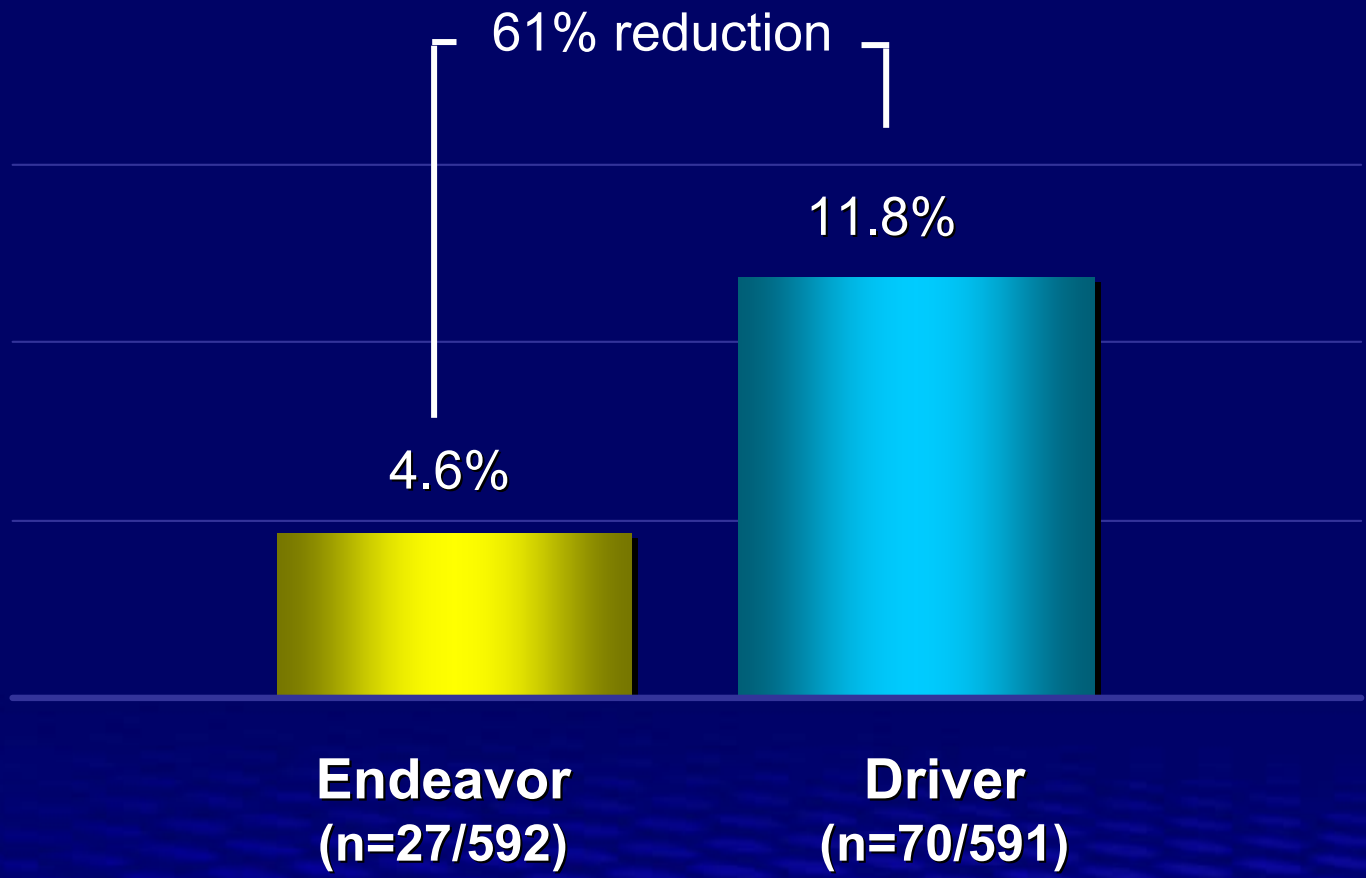
Target Vessel Revascularization



ENDEAVOR II

Efficacy at 9 months

Target Lesion Revascularization



ENDEAVOR II
Clinical Events to 9 months

	Endeavor n=592	Driver n=591	*Difference [95% CI]*
Death (all) - % (#)	1.2 (7)	0.5 (3)	0.7%[-0.4%,1.7%]
Cardiac	0.8 (5)	0.5 (3)	0.3%[-0.6%,1.3%]
MI (all) - % (#)	2.7 (16)	3.9 (23)	-1.2%[-3.2%,0.8%]
Q Wave	0.3 (2)	0.8 (5)	-0.5%[-1.4%,0.4%]
Non Q wave	2.4 (14)	3.0 (18)	-0.7%[-2.5%,1.2%]
Death (cardiac) + MI (all) - % (#)	3.4 (20)	4.4 (26)	-1.0%[-3.2%,1.2%]
Stent Thrombosis (all) - % (#)	0.5 (3)	1.2 (7)	-0.7%[-1.7%,0.4%]
0-30 days	0.5 (3)	1.2 (7)	-0.7%[-1.7%,0.4%]
31-270days	0	0	--
TLR - % (#)	4.6 (27)	11.8 (70)	-7.3%[-10.4%,-4.2%]
TVR (non-TL) - % (#)	1.5 (9)	2.2 (13)	-0.7%[-2.2%,0.9%]
TVR - % (#)	5.6 (33)	12.5 (74)	-6.9%[-10.2%,-3.7%]
MACE - % (#)	7.3 (43)	14.4 (85)	-7.1%[-10.6%,-3.6%]
TVF - % (#)	7.9 (47)	15.1 (89)	-7.1%[-10.7%,-3.5%]

ENDEAVOR II
Clinical Events to 9 months

	Endeavor n=592	Driver n=591	*Difference [95% CI]*
Death (all) - % (#)	1.2 (7)	0.5 (3)	0.7%[-0.4%,1.7%]
Cardiac	0.8 (5)	0.5 (3)	0.3%[-0.6%,1.3%]
MI (all) - % (#)	2.7 (16)	3.9 (23)	-1.2%[-3.2%,0.8%]
Q Wave	0.3 (2)	0.8 (5)	-0.5%[-1.4%,0.4%]
Non Q wave	2.4 (14)	3.0 (18)	-0.7%[-2.5%,1.2%]
Death (cardiac) + MI (all) - % (#)	3.4 (20)	4.4 (26)	-1.0%[-3.2%,1.2%]
Stent Thrombosis (all) - % (#)	0.5 (3)	1.2 (7)	-0.7%[-1.7%,0.4%]
0-30 days	0.5 (3)	1.2 (7)	-0.7%[-1.7%,0.4%]
31-270days	0	0	--
TLR - % (#)	4.6 (27)	11.8 (70)	-7.3%[-10.4%,-4.2%]
TVR (non-TL) - % (#)	1.5 (9)	2.2 (13)	-0.7%[-2.2%,0.9%]
TVR - % (#)	5.6 (33)	12.5 (74)	-6.9%[-10.2%,-3.7%]
MACE - % (#)	7.3 (43)	14.4 (85)	-7.1%[-10.6%,-3.6%]
TVF - % (#)	7.9 (47)	15.1 (89)	-7.1%[-10.7%,-3.5%]

ENDEAVOR II

Angiographic and IVUS Results to 8 months

	Endeavor n = 264	Driver n = 265	*Difference [95% CI]*
RVD - mm	2.75	2.78	-0.03 [-0.11,0.05]
In-stent			
DS - %	27.9	42.2	-14.33 [-17.68,-10.97]
LL - mm	0.62	1.03	-0.41 [-0.50,-0.32]
ABR - %	9.5	33.2	-23.7% [-30.4%,-17.1%]
In-segment			
DS - %	32.7	44.3	-11.66 [-14.82,-8.50]
LL - mm	0.36	0.72	-0.36 [-0.45,-0.27]
ABR - %	13.3	34.7	-21.5% [-28.5%,-14.4%]
IVUS			
Neointimal Volume - mm^3 (n)	30.15 (90)	53.51 (81)	-23.36 [-32.91,-13.81]
Vol Obstruction - % (n)	17.34 (90)	29.55 (81)	-12.22 [-16.51,-7.92]
Late Incomplete Apposition - % (#/n)	0 (0/114)	0 (0/104)	--

ENDEAVOR II

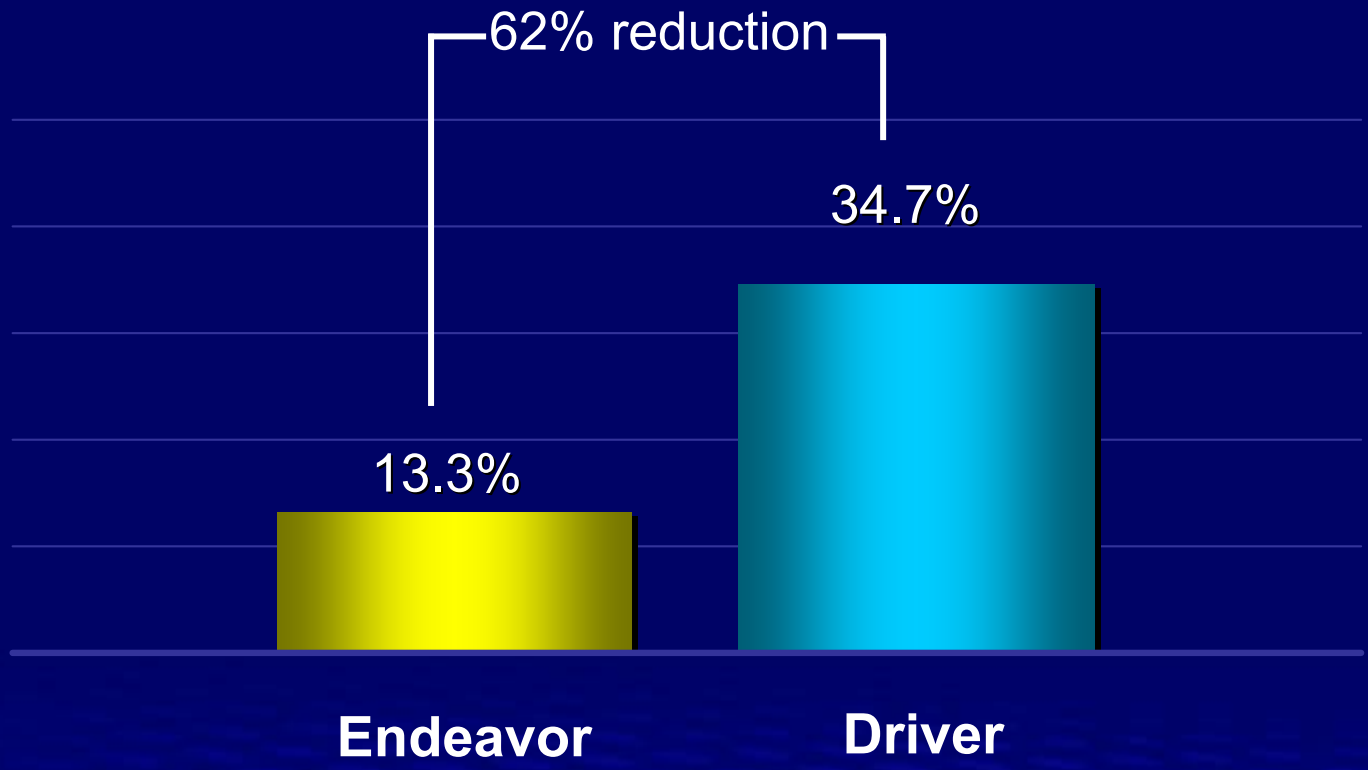
Angiographic and IVUS Results to 8 months

	Endeavor n = 264	Driver n = 265	*Difference [95% CI]*
RVD - mm	2.75	2.78	-0.03 [-0.11,0.05]
In-stent			
DS - %	27.9	42.2	-14.33 [-17.68,-10.97]
LL - mm	0.62	1.03	-0.41 [-0.50,-0.32]
ABR - %	9.5	33.2	-23.7% [-30.4%,-17.1%]
In-segment			
DS - %	32.7	44.3	-11.66 [-14.82,-8.50]
LL - mm	0.36	0.72	-0.36 [-0.45,-0.27]
ABR - %	13.3	34.7	-21.5% [-28.5%,-14.4%]
IVUS			
Neointimal Volume - mm^3 (n)	30.15 (90)	53.51 (81)	-23.36 [-32.91,-13.81]
Vol Obstruction - % (n)	17.34 (90)	29.55 (81)	-12.22 [-16.51,-7.92]
Late Incomplete Apposition - % (#/n)	0 (0/114)	0 (0/104)	--

ENDEAVOR II

Angiographic Outcomes at 8 Months

In-Segment Angiographic Binary Restenosis



ENDEAVOR II
Clinical Events to 36 months

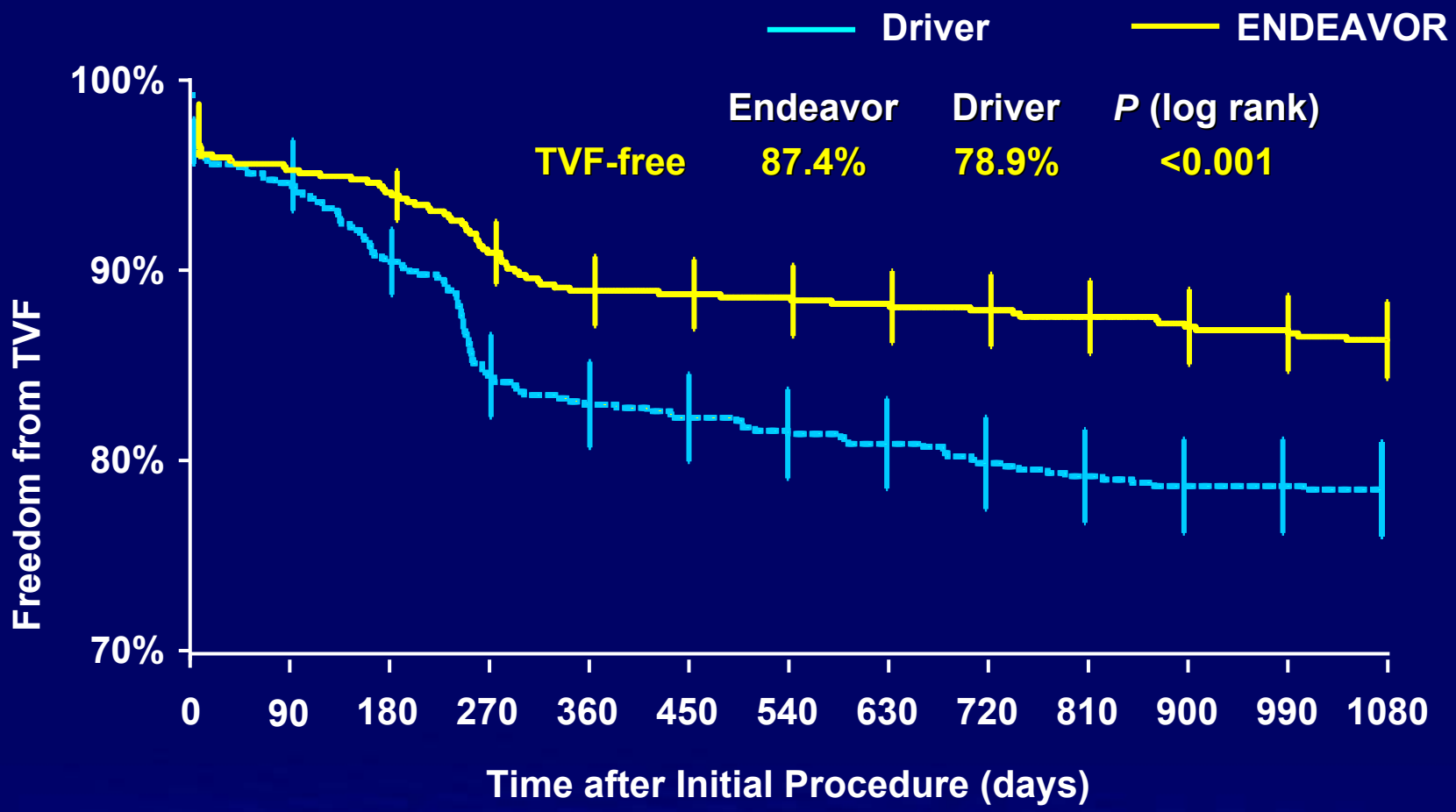
	Endeavor n=577	Driver n=579	*Difference [95% CI]*
Death (all) - % (#)	3.3 (19)	4.5 (26)	-1.2%[-3.4%,1.0%]
Cardiac	1.6 (9)	2.4 (14)	-0.9%[-2.5%,0.8%]
MI (all) - % (#)	3.3 (19)	4.3 (25)	-1.0%[-3.2%,1.2%]
Q Wave	0.3 (2)	1.0 (6)	-0.7%[-1.6%,0.3%]
Non Q wave	2.9 (17)	3.3 (19)	-0.3%[-2.3%,1.7%]
Death (cardiac) + MI (all) - % (#)	4.5 (26)	6.7 (39)	-2.2%[-4.9%,0.4%]
Stent Thrombosis (all) - % (#)	0.5 (3)	1.2 (7)	-0.7%[-1.8%,0.4%]
0-30 days	0.5 (3)	1.2 (7)	-0.7%[-1.7%,0.4%]
31-1080 days	0	0	--
TLR - % (#)	7.3 (42)	14.7 (85)	-7.4%[-11.0%,-3.8%]
TVR (non-TL) - % (#)	2.9 (17)	4.8 (28)	-1.9%[-4.1%,0.3%]
TVR - % (#)	9.5 (55)	17.6 (102)	-8.1%[-12.0%,-4.2%]
MACE - % (#)	12.0 (69)	20.7 (120)	-8.8%[-13.0%,-4.5%]
TVF - % (#)	12.8 (74)	21.4 (124)	-8.6%[-12.9%,-4.3%]

ENDEAVOR II
Clinical Events to 36 months

	Endeavor n=577	Driver n=579	*Difference [95% CI]*
Death (all) - % (#)	3.3 (19)	4.5 (26)	-1.2%[-3.4%,1.0%]
Cardiac	1.6 (9)	2.4 (14)	-0.9%[-2.5%,0.8%]
MI (all) - % (#)	3.3 (19)	4.3 (25)	-1.0%[-3.2%,1.2%]
Q Wave	0.3 (2)	1.0 (6)	-0.7%[-1.6%,0.3%]
Non Q wave	2.9 (17)	3.3 (19)	-0.3%[-2.3%,1.7%]
Death (cardiac) + MI (all) - % (#)	4.5 (26)	6.7 (39)	-2.2%[-4.9%,0.4%]
Stent Thrombosis (all) - % (#)	0.5 (3)	1.2 (7)	-0.7%[-1.8%,0.4%]
0-30 days	0.5 (3)	1.2 (7)	-0.7%[-1.7%,0.4%]
31-1080 days	0	0	--
TLR - % (#)	7.3 (42)	14.7%(85)	-7.4%[-11.0%,-3.8%]
TVR (non-TL) - % (#)	2.9 (17)	4.8 (28)	-1.9%[-4.1%,0.3%]
TVR - % (#)	9.5 (55)	17.6 (102)	-8.1%[-12.0%,-4.2%]
MACE - % (#)	12.0 (69)	20.7 (120)	-8.8%[-13.0%,-4.5%]
TVF - % (#)	12.8 (74)	21.4 (124)	-8.6%[-12.9%,-4.3%]

ENDEAVOR II

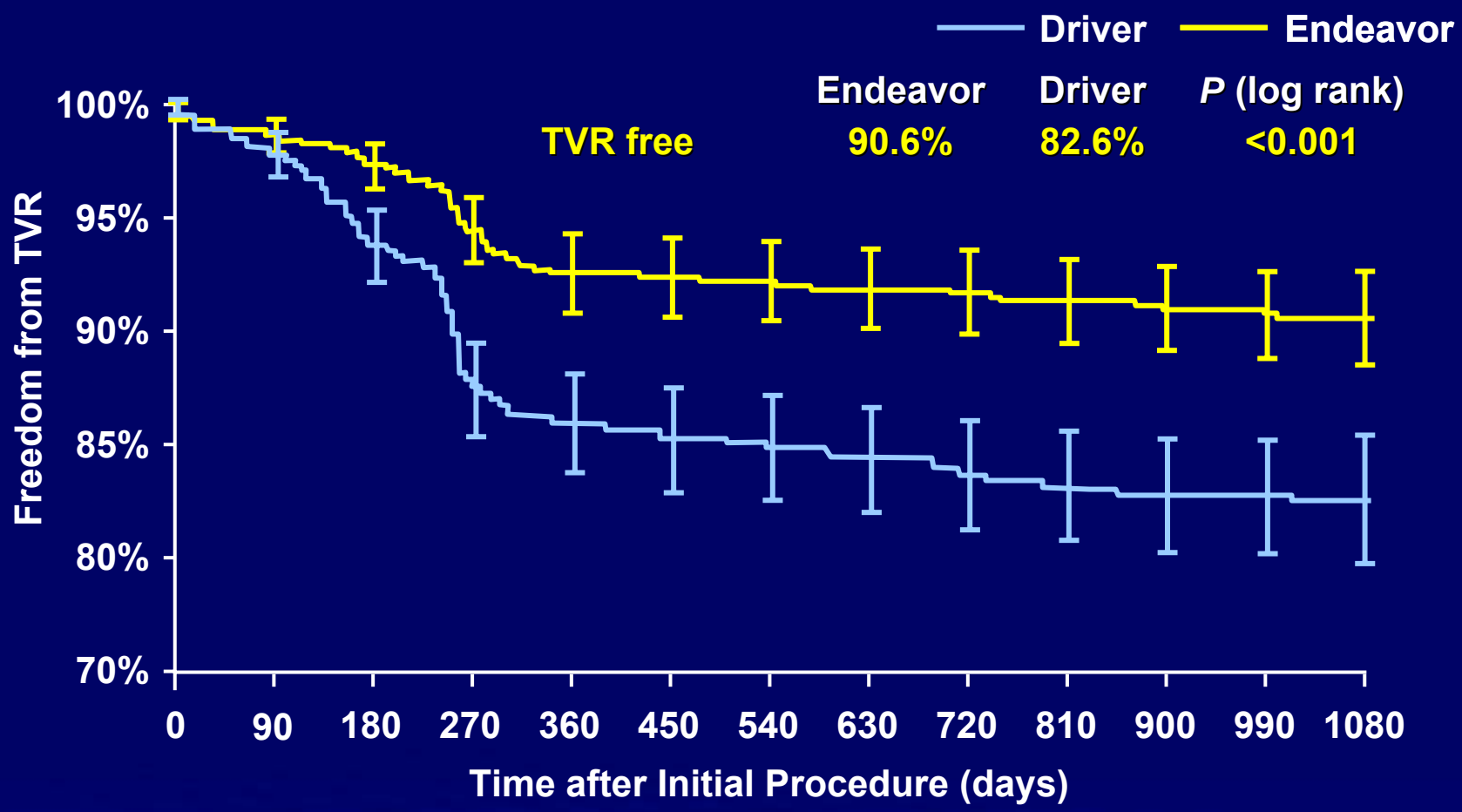
TVF Free Survival to 1080 days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR II

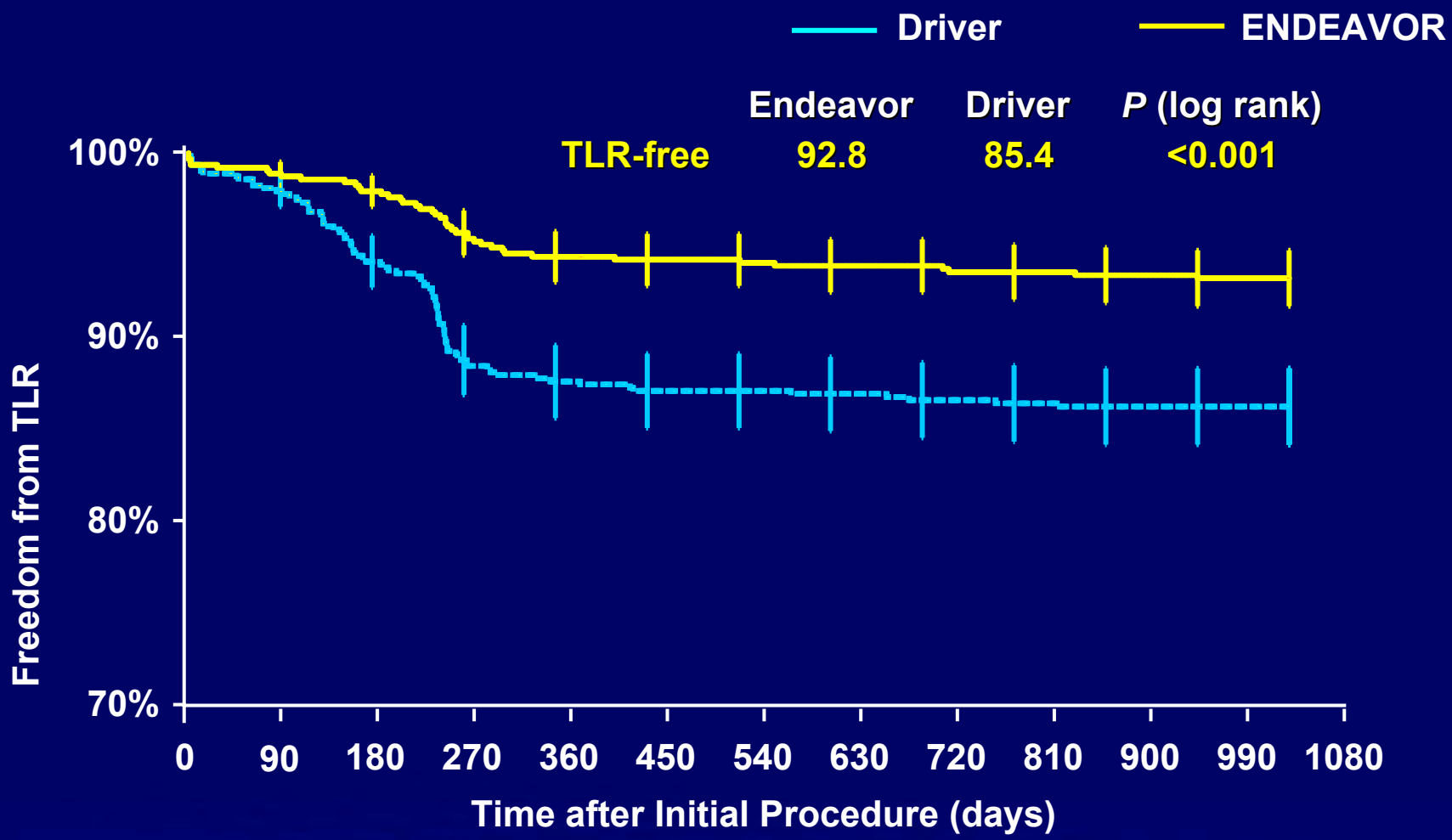
TVR Free Survival to 1080 days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR II

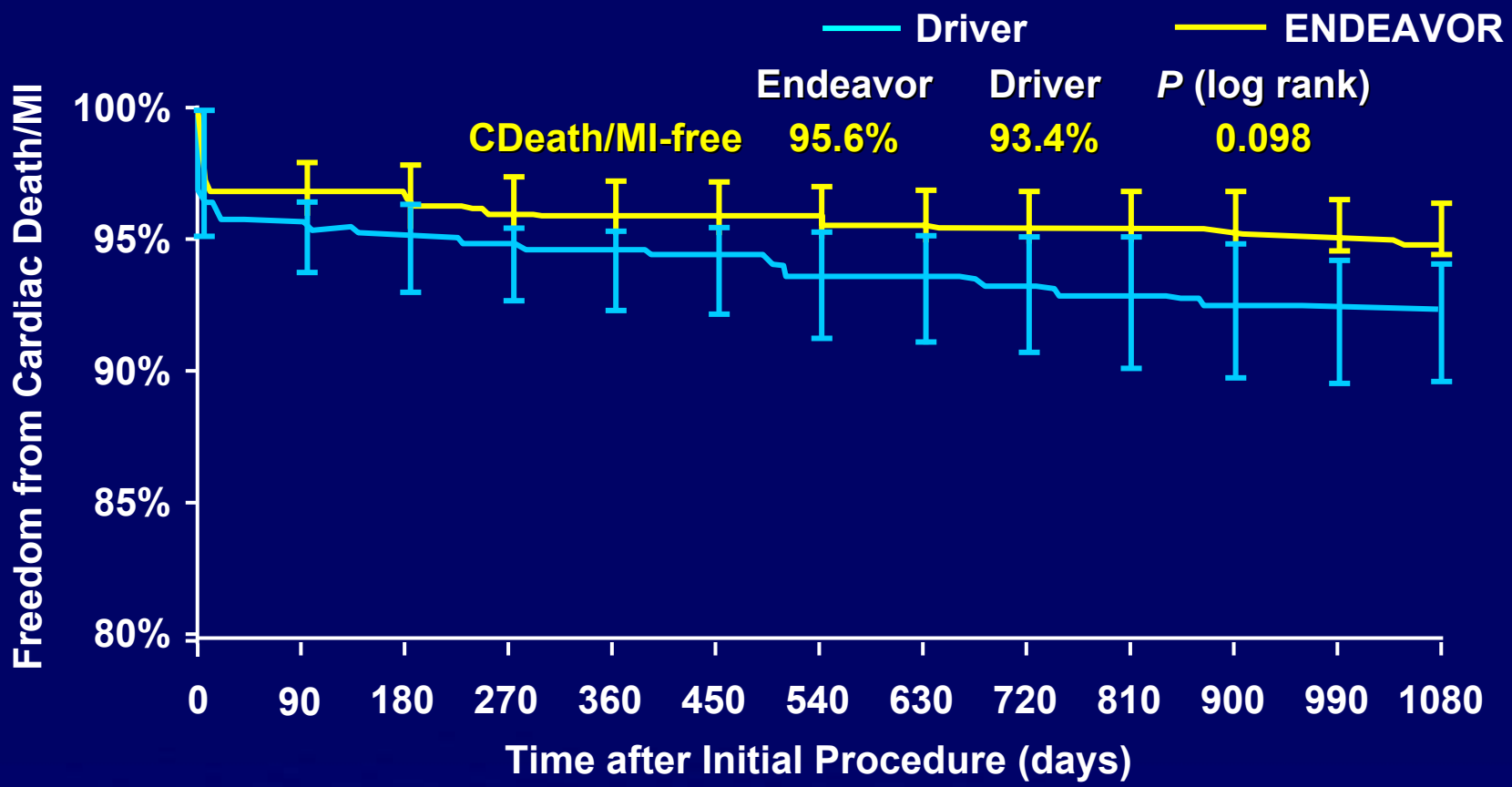
TLR Free Survival to 1080 days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR II

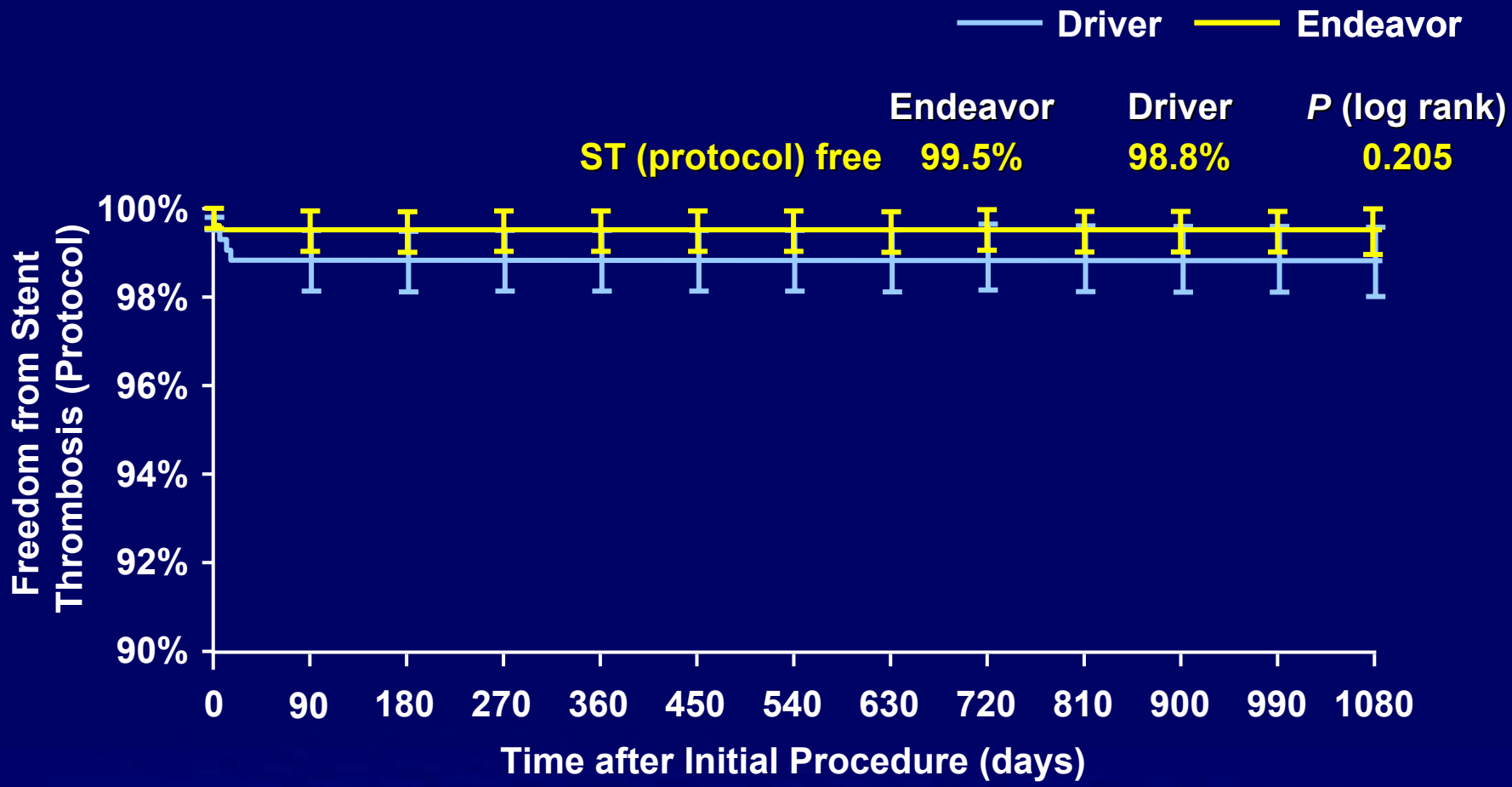
Cardiac Death/MI Free Survival to 1080 days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR II

Stent Thrombosis (Protocol) Free Survival to 1080 days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR II
Summary

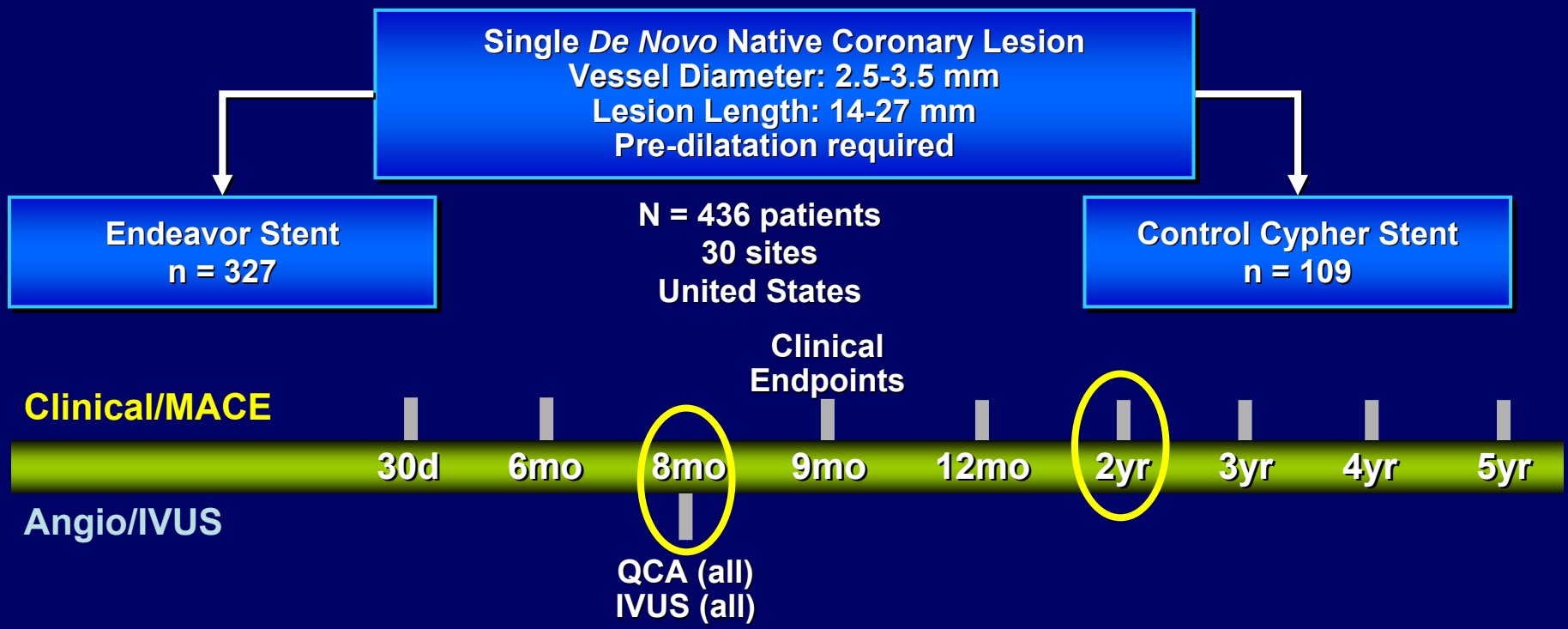
Compared with the bare metal Driver stent, the Endeavor DES demonstrated…

- **A similar safety profile (death, MI, and stent thrombosis) through 3 years of follow up**
- **Improved angiographic results at 8 months follow up (late loss and binary restenosis)**
- **Superior TVF rate (by 48%), due largely to a diminished TVR requirement (by 55%), which persisted through 3 years follow up**

ENDEAVOR III

3:1 RCT vs Cypher

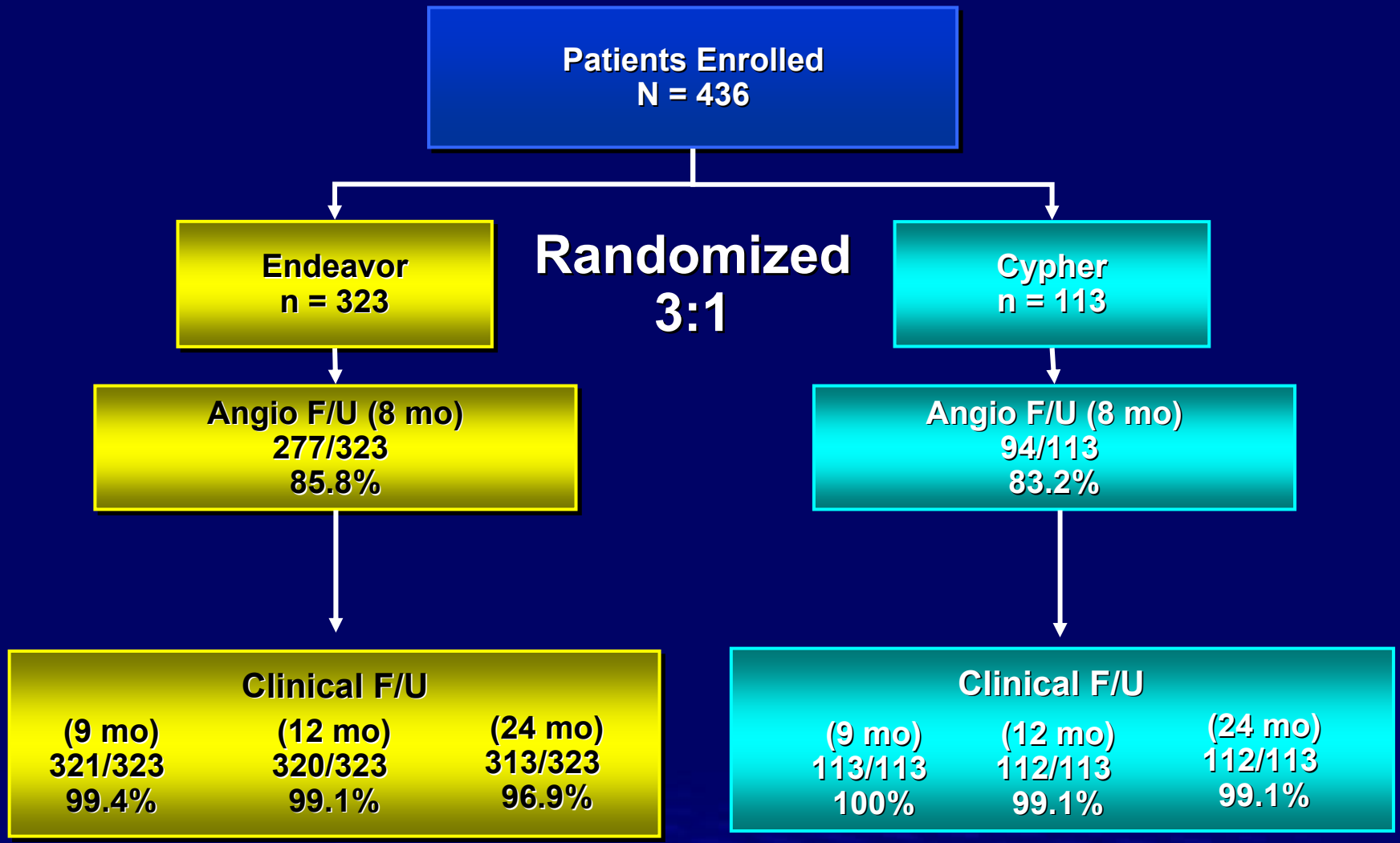
PI: Martin B. Leon and David Kandzari



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

ENDEAVOR III

Patient Flowchart



ENDEAVOR III

Baseline Characteristics

	Endeavor n=323	Cypher n=113	*P value*
Male (%)	65.3	81.4	0.001
Diabetics (%)	29.7	28.3	NS
Unstable Angina (%)	51.1	55.7	NS
RVD (mm)	2.75	2.79	NS
Lesion length (mm)	14.98	14.95	NS
B2/C lesions (%)	67.2	56.6	NS

ENDEAVOR III
Clinical Events at 30 days

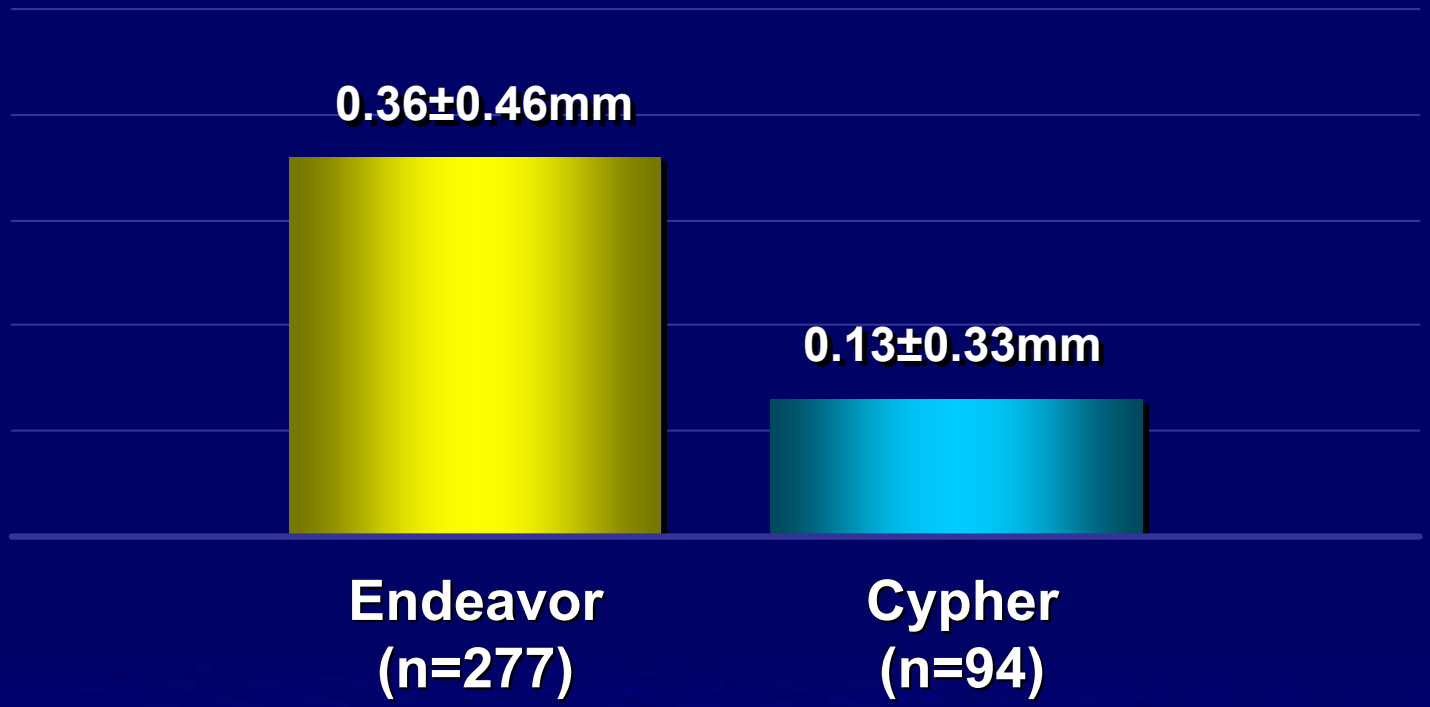
	Endeavor n=323	Cypher n=113	*Difference [95% CI]*
Death (all) - % (#)	0	0	--
Cardiac	0	0	--
MI (all) - % (#)	0.6 (2)	3.5 (4)	-2.9%[-6.4%,0.6%]
Q Wave	0	0	--
Non Q wave	0.6 (2)	3.5 (4)	-2.9%[-6.4%,0.6%]
Death (cardiac) + MI (all) - % (#)	0.6 (2)	3.5 (4)	-2.9%[-6.4%,0.6%]
Stent Thrombosis (all) - % (#)	0	0	--
TLR - % (#)	0	0	--
TVR (non-TL) - % (#)	0	0.9 (1)	-0.9%[-2.6%,0.8%]
TVR - % (#)	0	0.9 (1)	-0.9%[-2.6%,0.8%]
MACE - % (#)	0.6 (2)	3.5 (4)	-2.9%[-6.4%,0.6%]
TVF - % (#)	0.6 (2)	4.4 (5)	-3.8%[-7.7%,0.1%]

ENDEAVOR III

Primary Endpoint Result at 8 months

In-segment Late Loss

P for Non-Inferiority 0.791



ENDEAVOR III

Angiographic and IVUS Results at 8 Months

	Endeavor n = 277	Cypher n = 94	*Difference [95% CI]*
QCA			
In-stent			
DS - %	24.9	11.0	13.89 [9.88,17.90]
LL - mm	0.62	0.15	0.47 [0.36,0.58]
ABR - %	9.7	2.1	7.6% [3.1%,12.2%]
In-segment			
DS - %	30.4	23.9	6.56 [3.01,10.12]
LL - mm	0.36	0.13	0.24 [0.13,0.34]
ABR - %	12.3	4.3	8.0% [2.4%,13.6%]
IVUS			
Neointimal Volume -mm^3 (n)	24.09 (209)	3.74 (67)	20.36 [15.21,25.50]
Vol Obstruction - % (n)	15.9 (187)	2.7 (61)	13.27 [10.48,16.07]
Late Incomplete Apposition - % (#/n)	0.5 (1/189)	5.9 (4/68)	-5.4% [-11.0%,0.3%]

ENDEAVOR III

Angiographic and IVUS Results at 8 Months

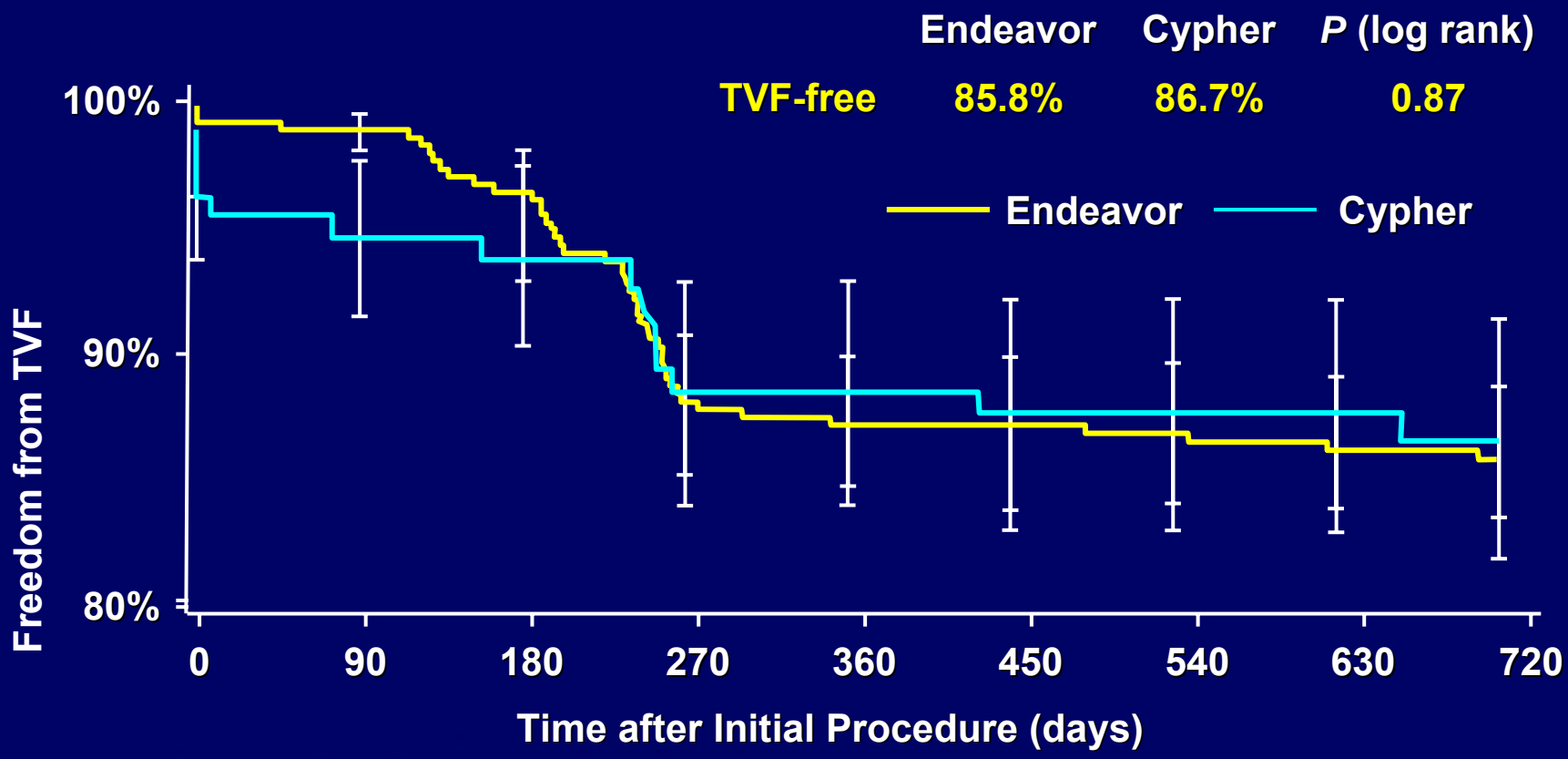
	Endeavor n = 277	Cypher n = 94	*Difference [95% CI]*
QCA			
In-stent			
DS - %	24.9	11.0	13.89 [9.88,17.90]
LL - mm	0.62	0.15	0.47 [0.36,0.58]
ABR - %	9.7	2.1	7.6% [3.1%,12.2%]
In-segment			
DS - %	30.4	23.9	6.56 [3.01,10.12]
LL - mm	0.36	0.13	0.24 [0.13,0.34]
ABR - %	12.3	4.3	8.0% [2.4%,13.6%]
IVUS			
Neointimal Volume -mm^3 (n)	24.09 (209)	3.74 (67)	20.36 [15.21,25.50]
Vol Obstruction - % (n)	15.9 (187)	2.7 (61)	13.27 [10.48,16.07]
Late Incomplete Apposition - % (#/n)	0.5 (1/189)	5.9 (4/68)	-5.4% [-11.0%,0.3%]

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 III

TVF Event Free Survival to 720 days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR III
Summary

Compared with the Cypher DES, the Endeavor DES demonstrated…

- Higher angiographic late loss at 8 months follow up
- Reduced peri-procedural non-Q MIs, and low rates of death, Q-MI, and stent thrombosis through 2 years of follow up
- Similar TVF through 2 years of follow up

ENDEAVOR IV

1:1 RCT vs Taxus

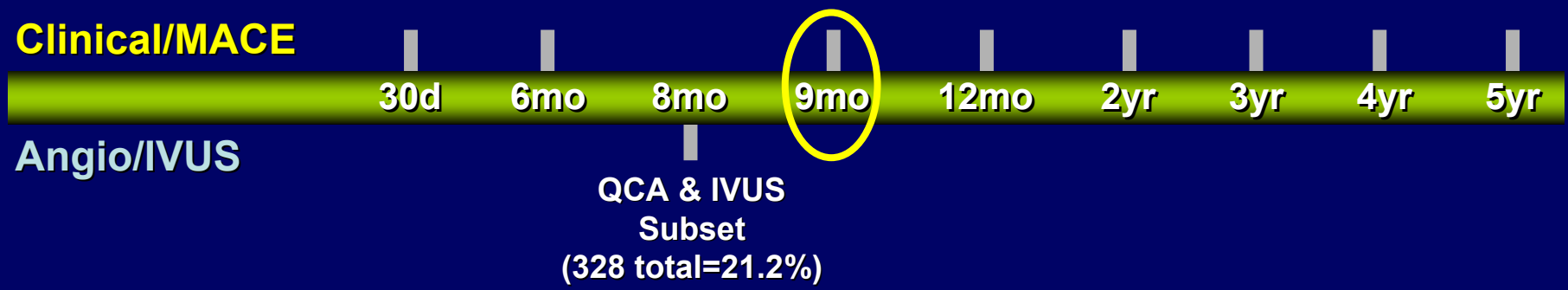
PI: Martin B. Leon

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

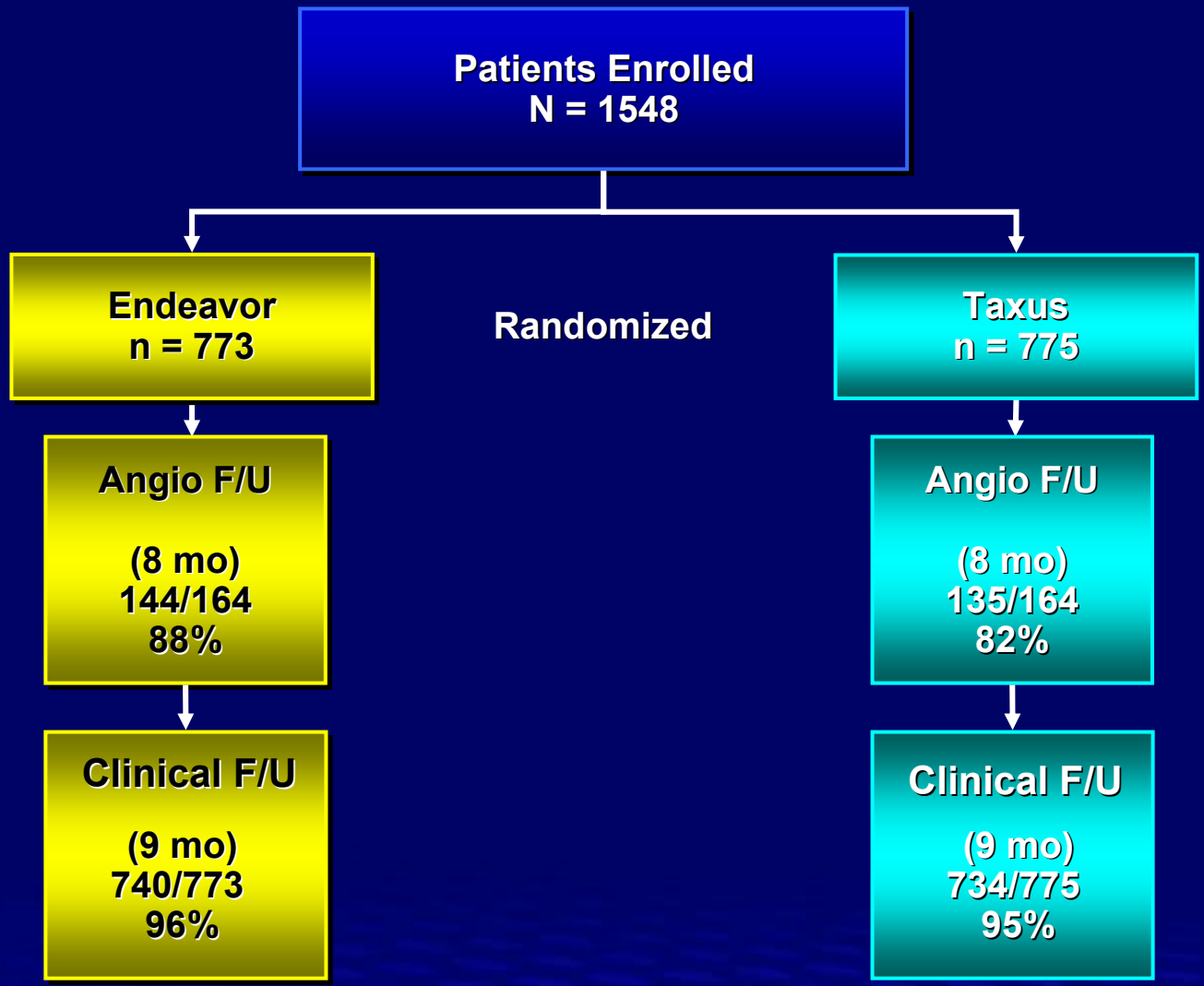
Endeavor Stent
n = 774

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

ENDEAVOR IV
Patient Flowchart



ENDEAVOR IV

Baseline Characteristics

	Endeavor n=773	Taxus n=775	*P value*
Male (%)	66.9	68.5	NS
Diabetics (%)	31.2	30.5	NS
Unstable Angina (%)	51.6	49.9	NS
RVD (mm)	2.73	2.70	NS
Lesion length (mm)	13.41	13.80	NS
B2/C lesions (%)	69.6	70.9	NS

ENDEAVOR IV

Clinical Events at 30 days

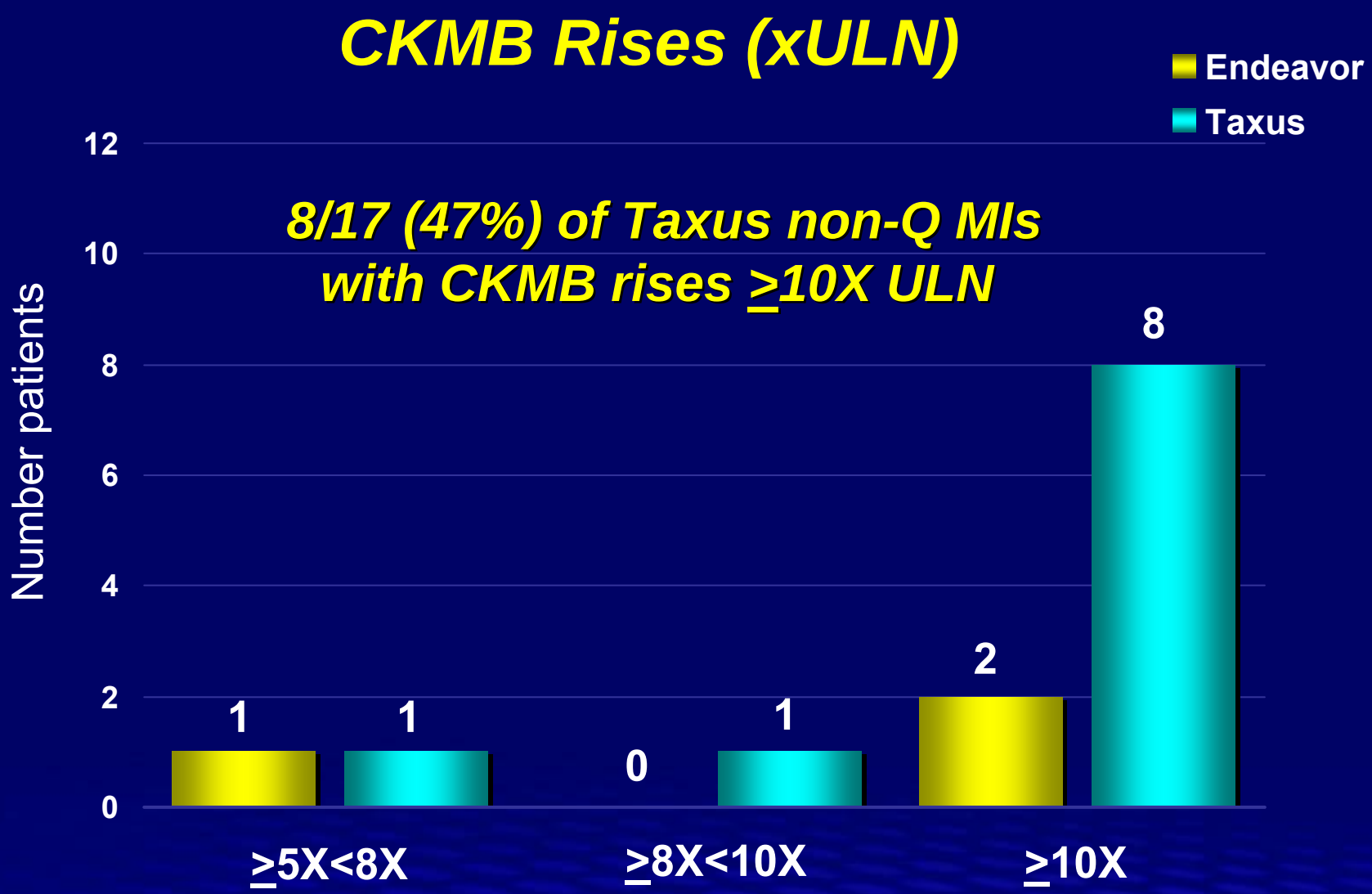
	Endeavor n=770	Taxus n=771	*Difference [95% CI]*
Death (all) - % (#)	0.3 (2)	0	0.3%[-0.1%,0.6%]
Cardiac	0.1 (1)	0	0.1%[-0.1%,0.4%]
MI (all) - % (#)	0.8 (6)	2.3 (18)	-1.6%[-2.8%,-0.3%]
Q Wave	0.3 (2)	0.1 (1)	0.1%[-0.3%,0.6%]
Non Q wave	0.5 (4)	2.2 (17)	-1.7%[-2.8%,-0.5%]
Death (cardiac) + MI (all) - % (#)	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
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

Peri-procedural MIs (CKMB rises)

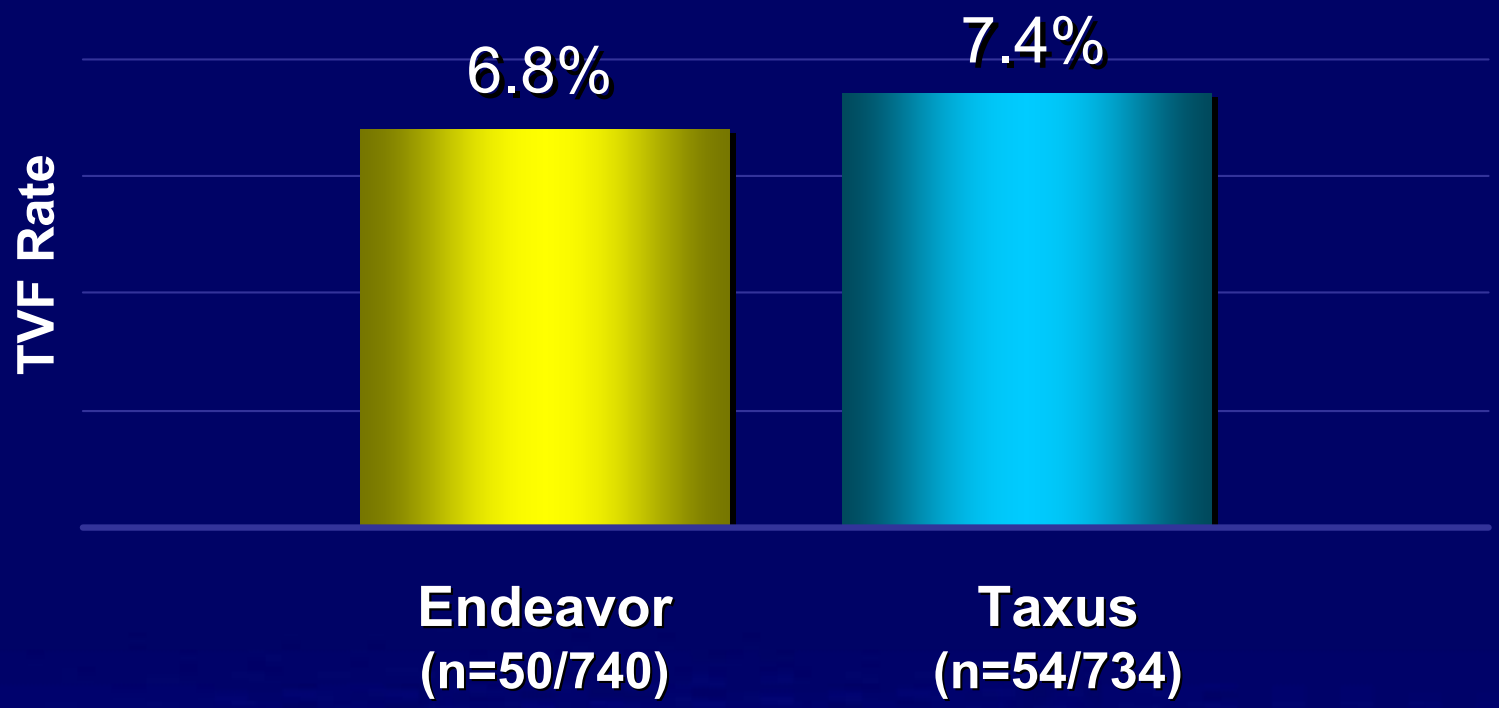


ENDEAVOR IV

Primary Endpoint Result at 9 months

Target Vessel Failure

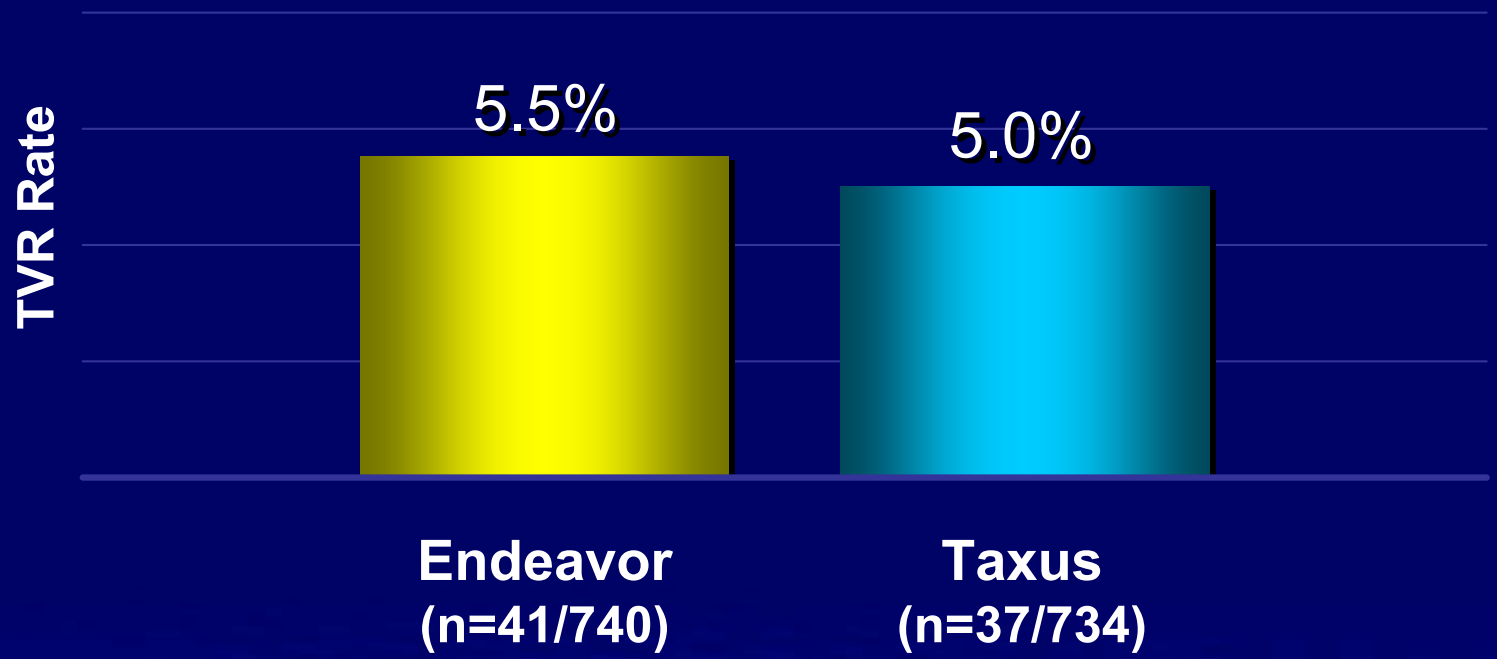
P for Non-Inferiority < 0.001
Δ=3.8%



ENDEAVOR IV

TVR at 9 months

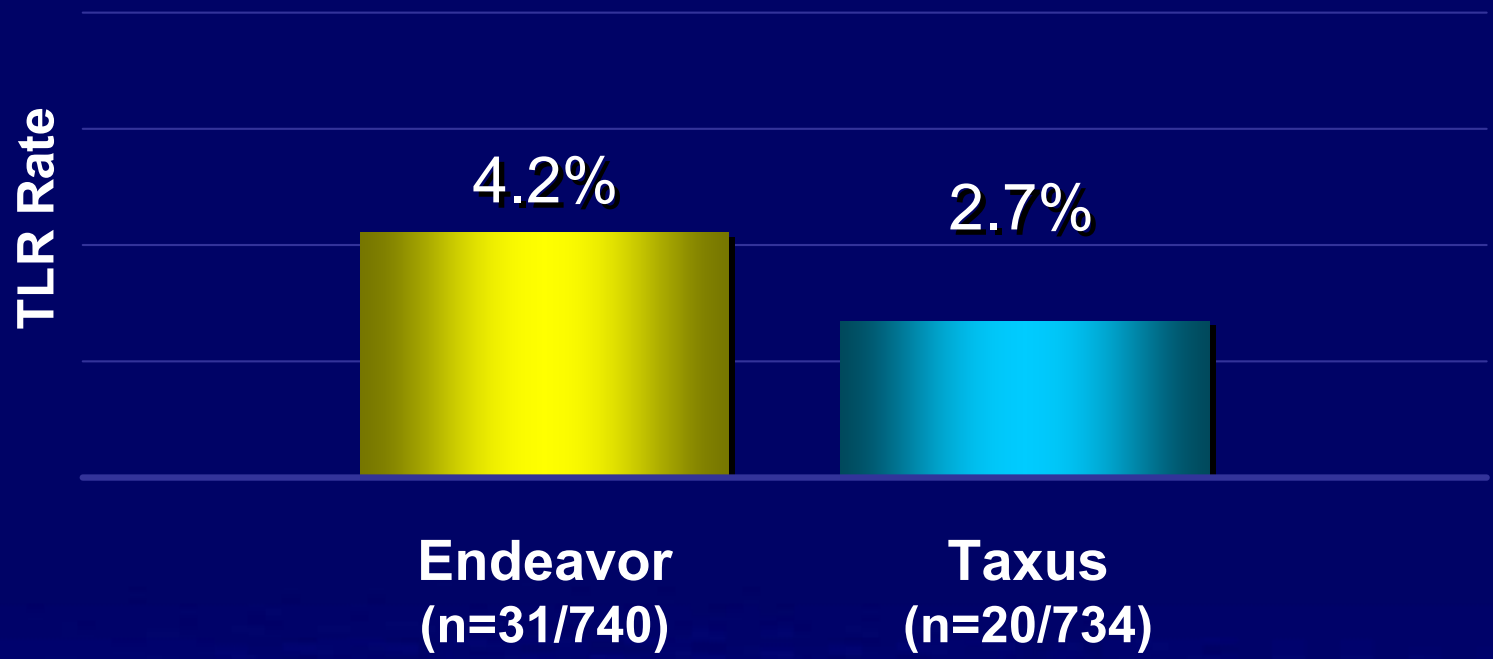
Target Vessel Revascularization



ENDEAVOR IV

TLR at 9 months

Target Lesion Revascularization



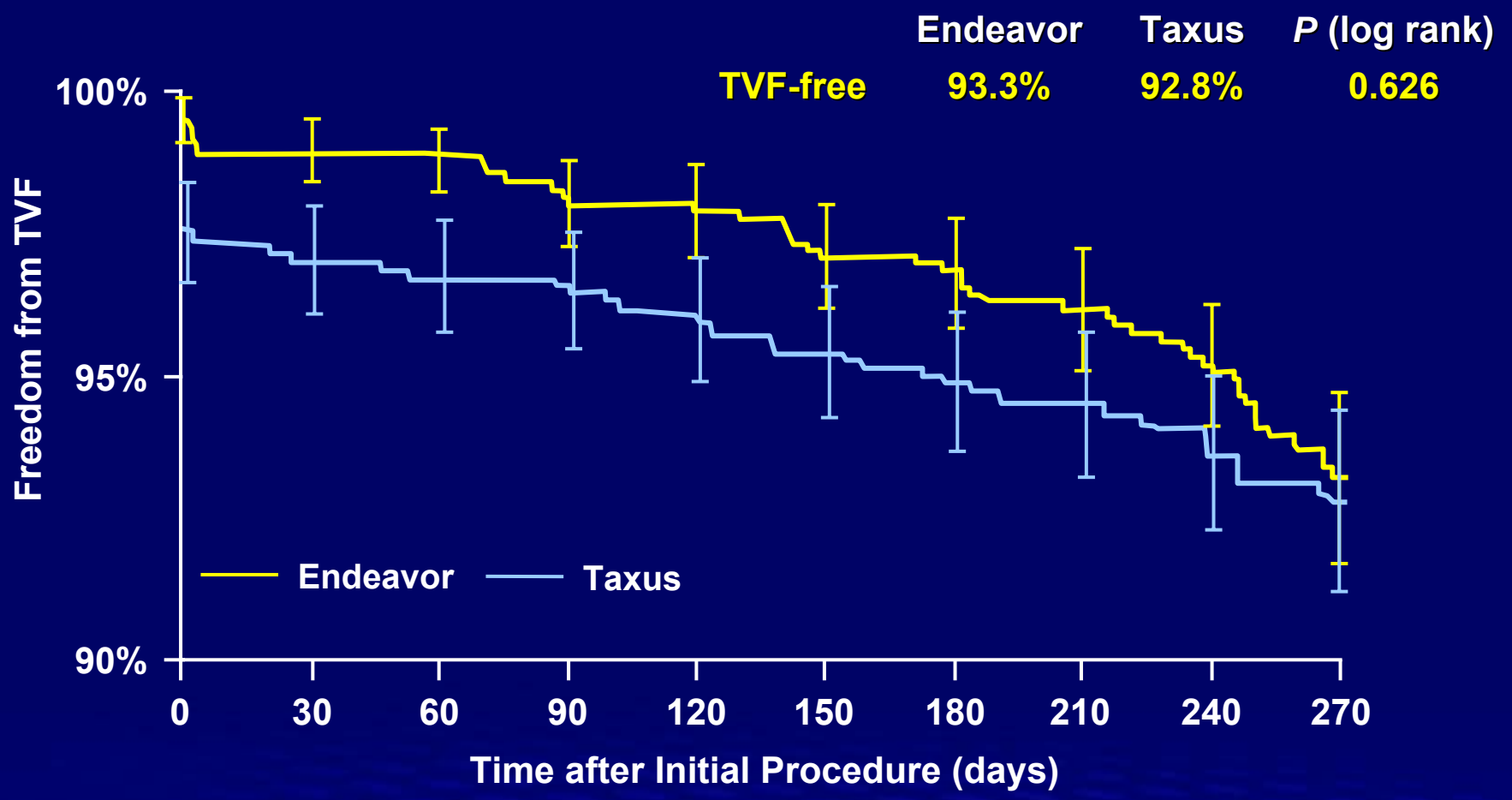
ENDEAVOR IV
Clinical Events to 9 months

	Endeavor n=740	Taxus n=734	*Difference [95% CI]*
Death (all) - % (#)	0.7 (5)	0.8 (6)	-0.1%[-1.0%,0.7%]
Cardiac	0.4 (3)	0.3 (2)	0.1%[-0.5%,0.7%]
MI (all) - % (#)	1.5 (11)	2.5 (18)	-1.0%[-2.4%,0.5%]
Q Wave	0.3 (2)	0.1 (1)	0.1%[-0.3%,0.6%]
Non Q wave	1.2 (9)	2.3 (17)	-1.1%[-2.4%,0.2%]
Death (cardiac) + MI (all) - % (#)	1.9 (14)	2.7 (20)	-0.8%[-2.4%,0.7%]
Stent Thrombosis (all) - % (#)	0.8 (6)	0.1 (1)	0.7%[-0.0%,1.4%]
0-30 days	0.4 (3)	0.1 (1)	0.3%[-0.2%,0.8%]
31-270days	0.4* (3)	0	0.4%[-0.1%,0.9%]
TLR - % (#)	4.2 (31)	2.7 (20)	1.5%[-0.4%,3.3%]
TVR (non-TL) - % (#)	2.0 (15)	2.9 (21)	-0.8%[-2.4%,0.7%]
TVR - % (#)	5.5 (41)	5.0 (37)	0.5%[-1.8%,2.8%]
MACE - % (#)	5.7 (42)	5.7 (42)	-0.0%[-2.4%,2.3%]
TVF - % (#)	6.8 (50)	7.4 (54)	-0.6%[-3.2%,2.0%]

*Day 83, 145, 171 (ST with MI on Day 171)

ENDEAVOR IV

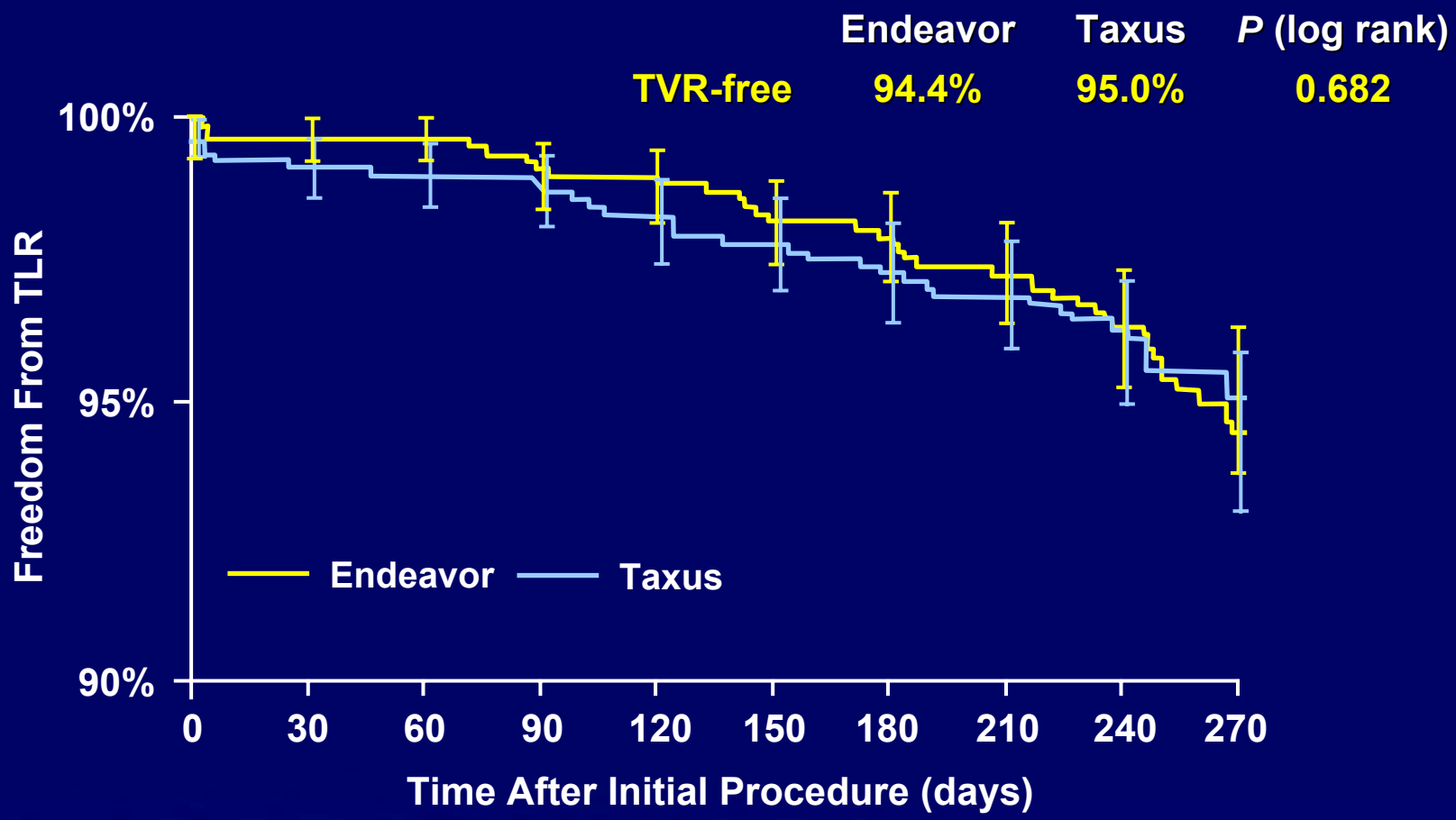
TVF Event Free Survival to 270 Days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR IV

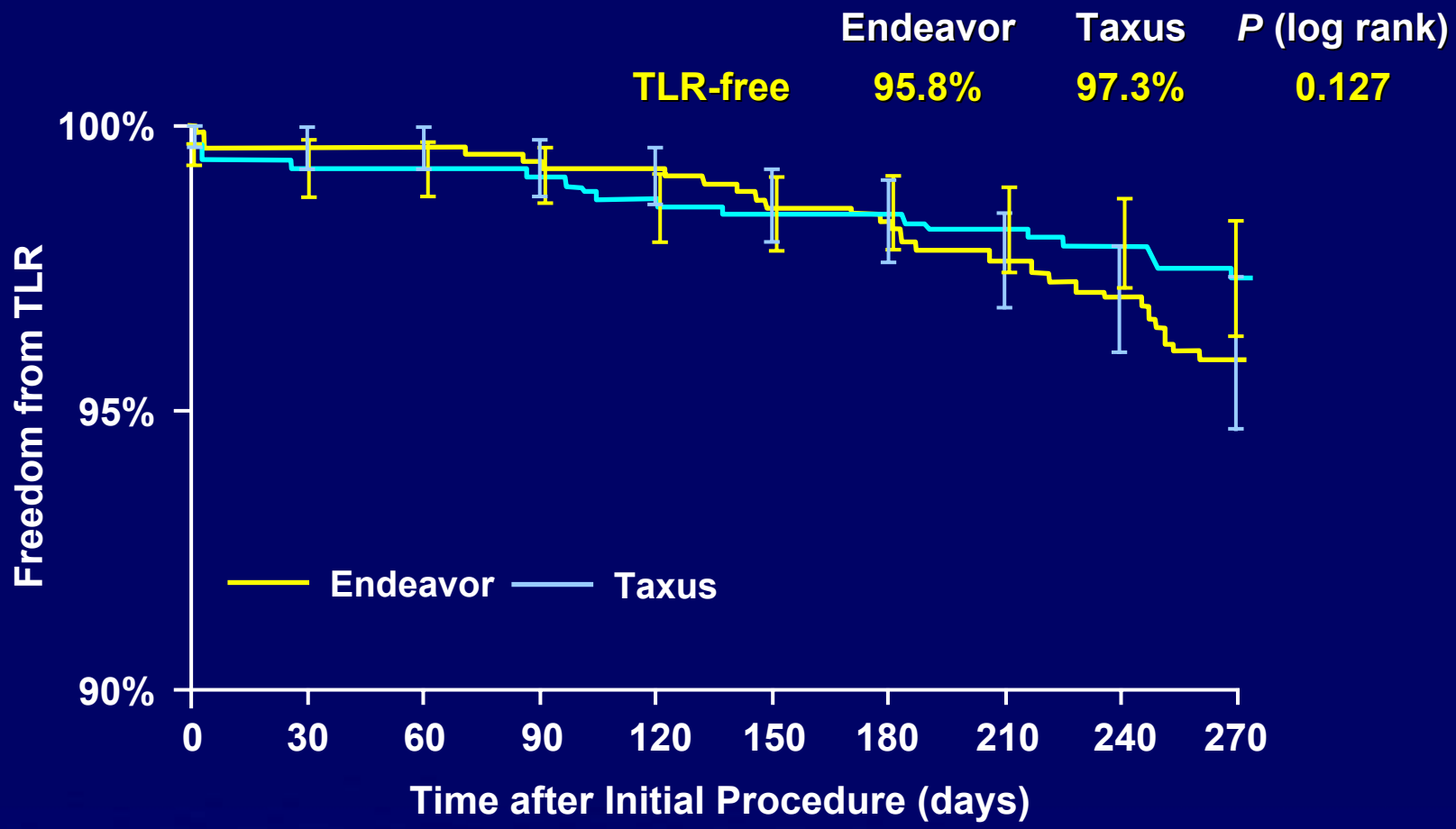
TVR Free Survival to 270 Days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR IV

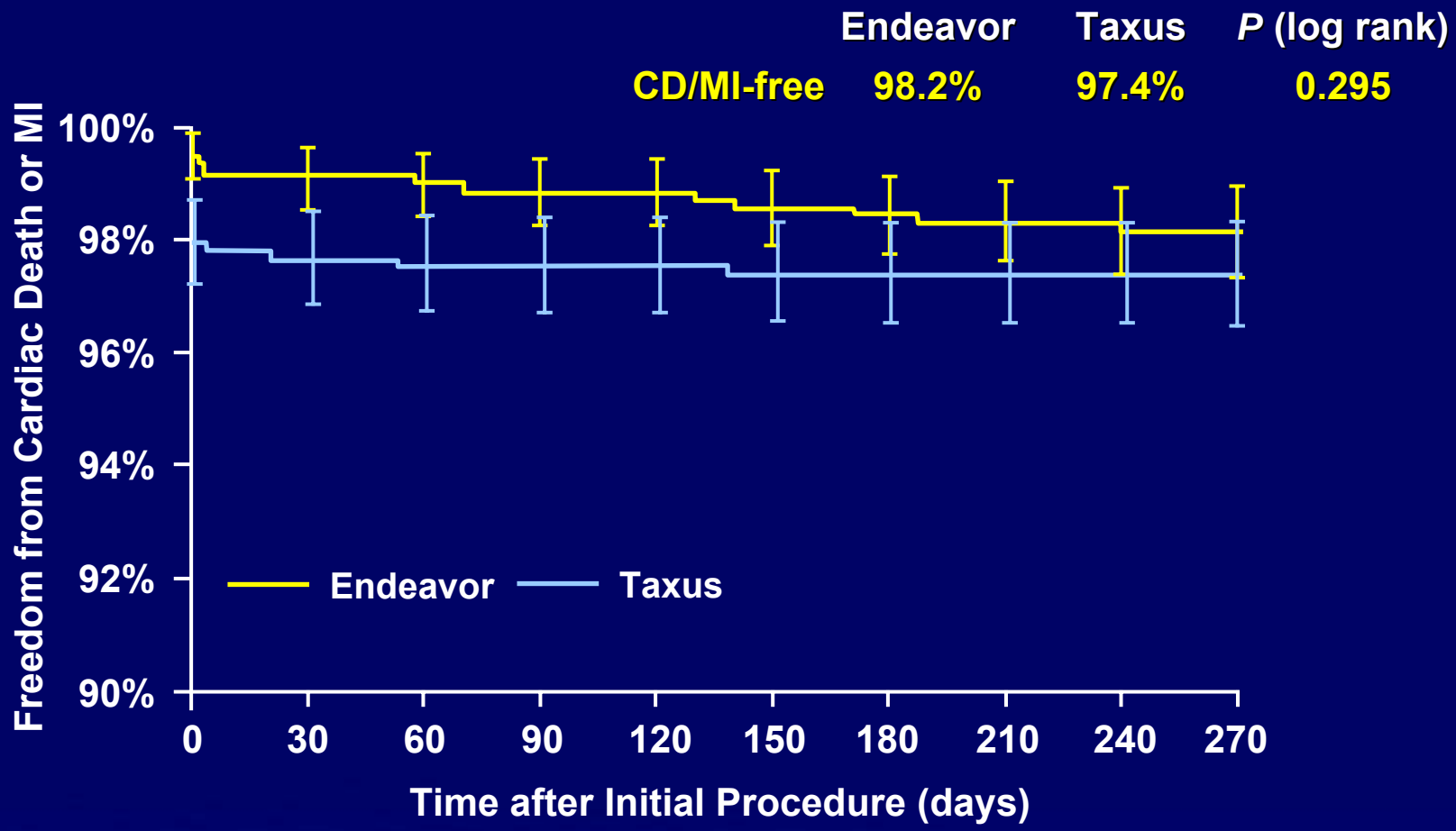
TLR Free Survival to 270 Days



Error bars represent ±1.5SE estimated by Peto formula

ENDEAVOR IV

Cardiac Death/MI Free Survival to 270 Days



Error bars represent ±1.5SE estimated by Peto formula

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	10.32 [5.85, 14.79]
LL - mm	0.67	0.42	0.25 [0.13, 0.37]
ABR - %	13.3	6.7	6.6% [-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%]

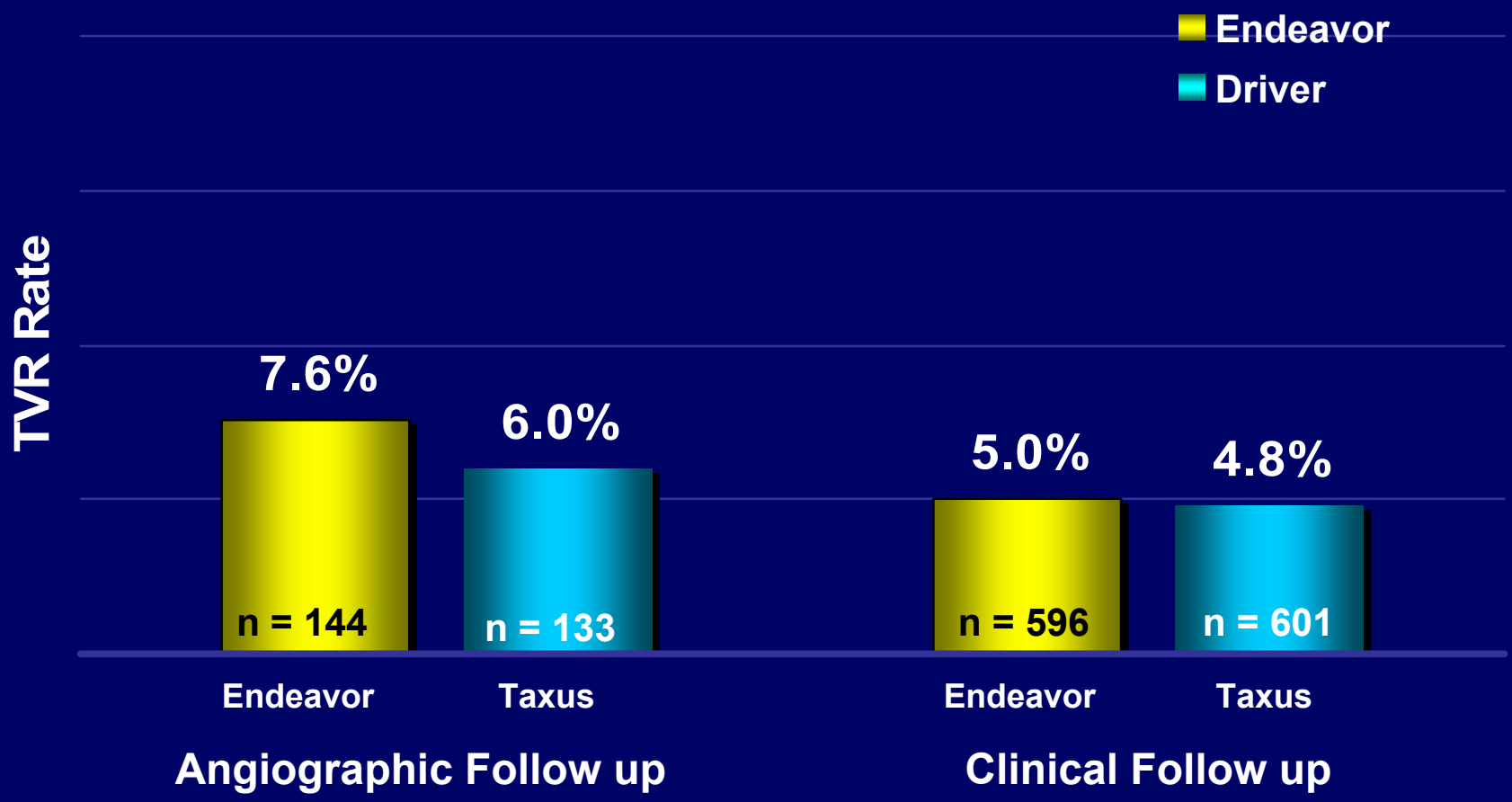
ENDEAVOR IV

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	10.32 [5.85, 14.79]
LL - mm	0.67	0.42	0.25 [0.13, 0.37]
ABR - %	13.3	6.7	6.6% [-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%]

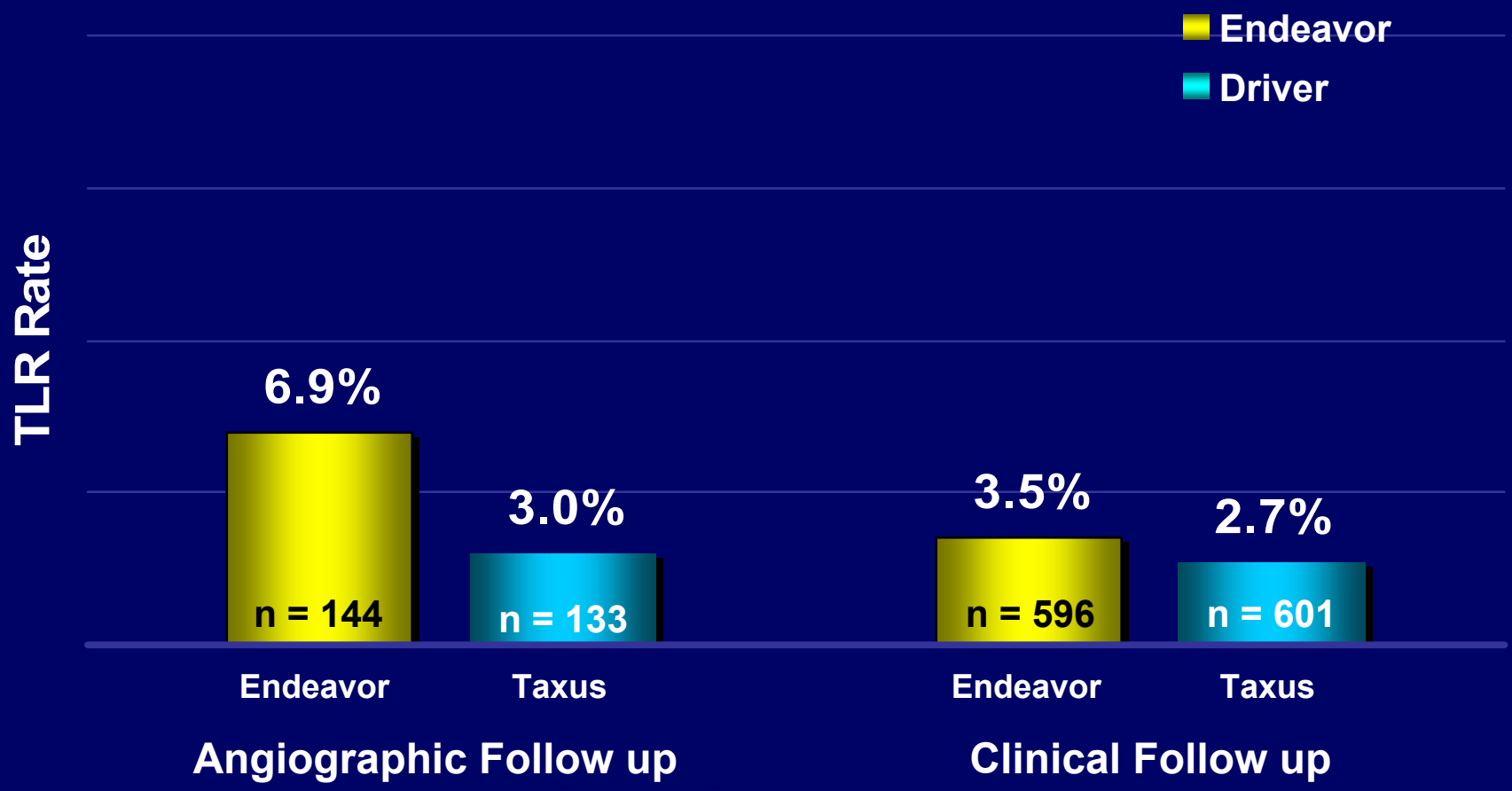
ENDEAVOR IV

TVR by Angiographic Follow-up at 9 months



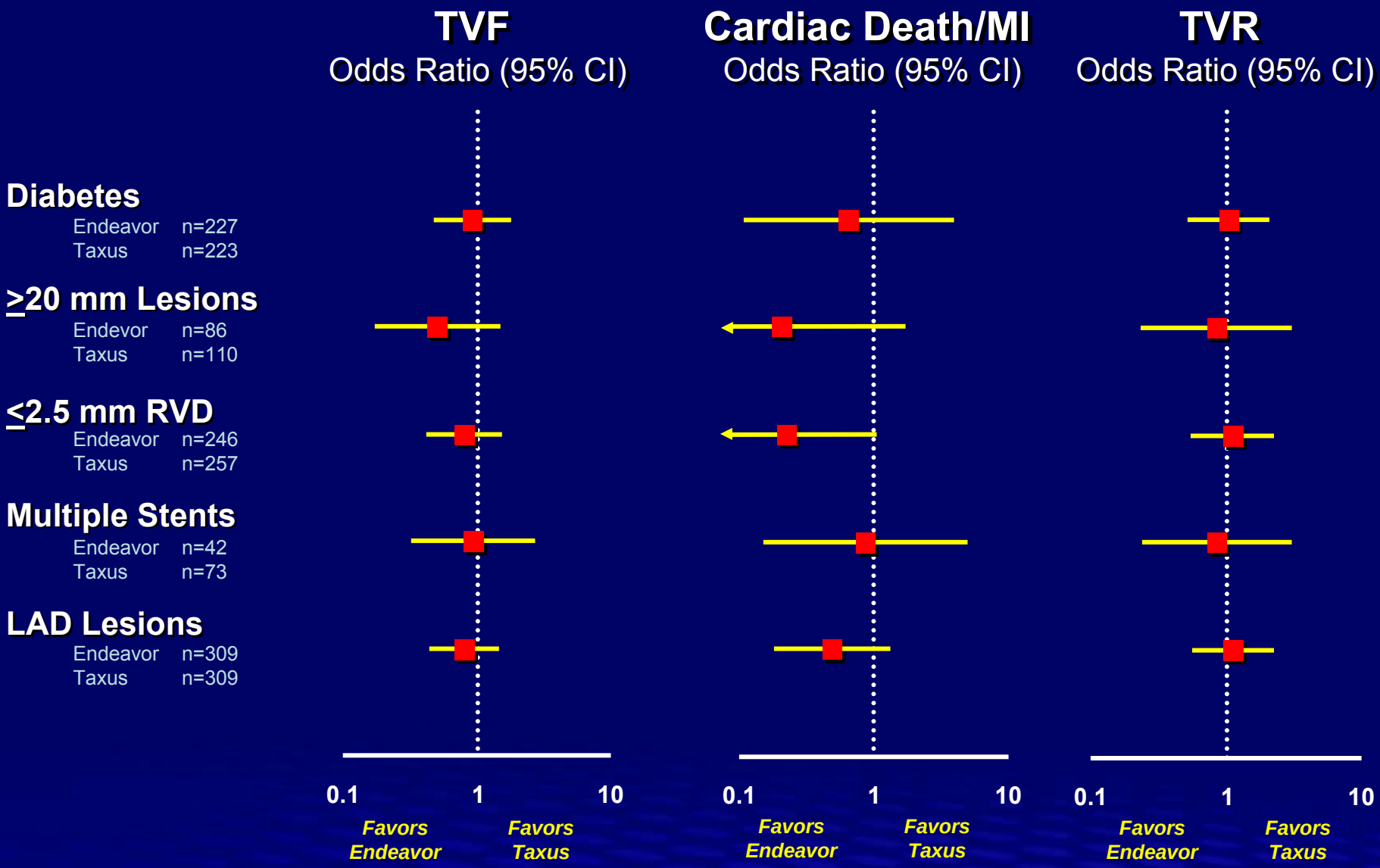
ENDEAVOR IV

TLR by Angiographic Follow-up at 9 months



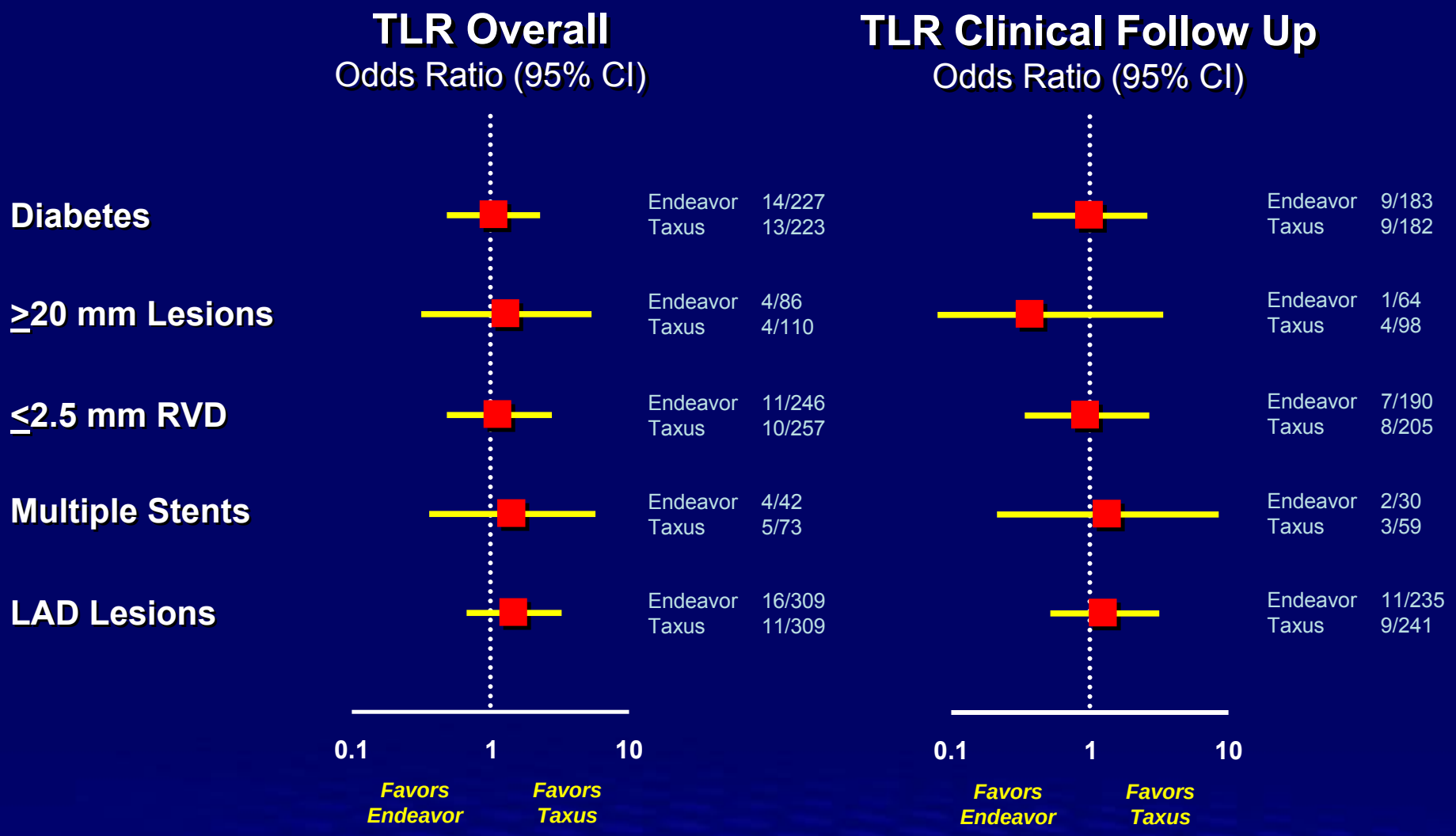
ENDEAVOR IV Post Hoc Subgroup Analysis

Endeavor vs. Taxus Odds Ratio [95% CI]



ENDEAVOR IV Post Hoc Subgroup Analysis

Endeavor vs. Taxus Odds Ratio [95% CI]



ENDEAVOR IV
Summary

Compared with the Taxus DES, the Endeavor DES demonstrated…

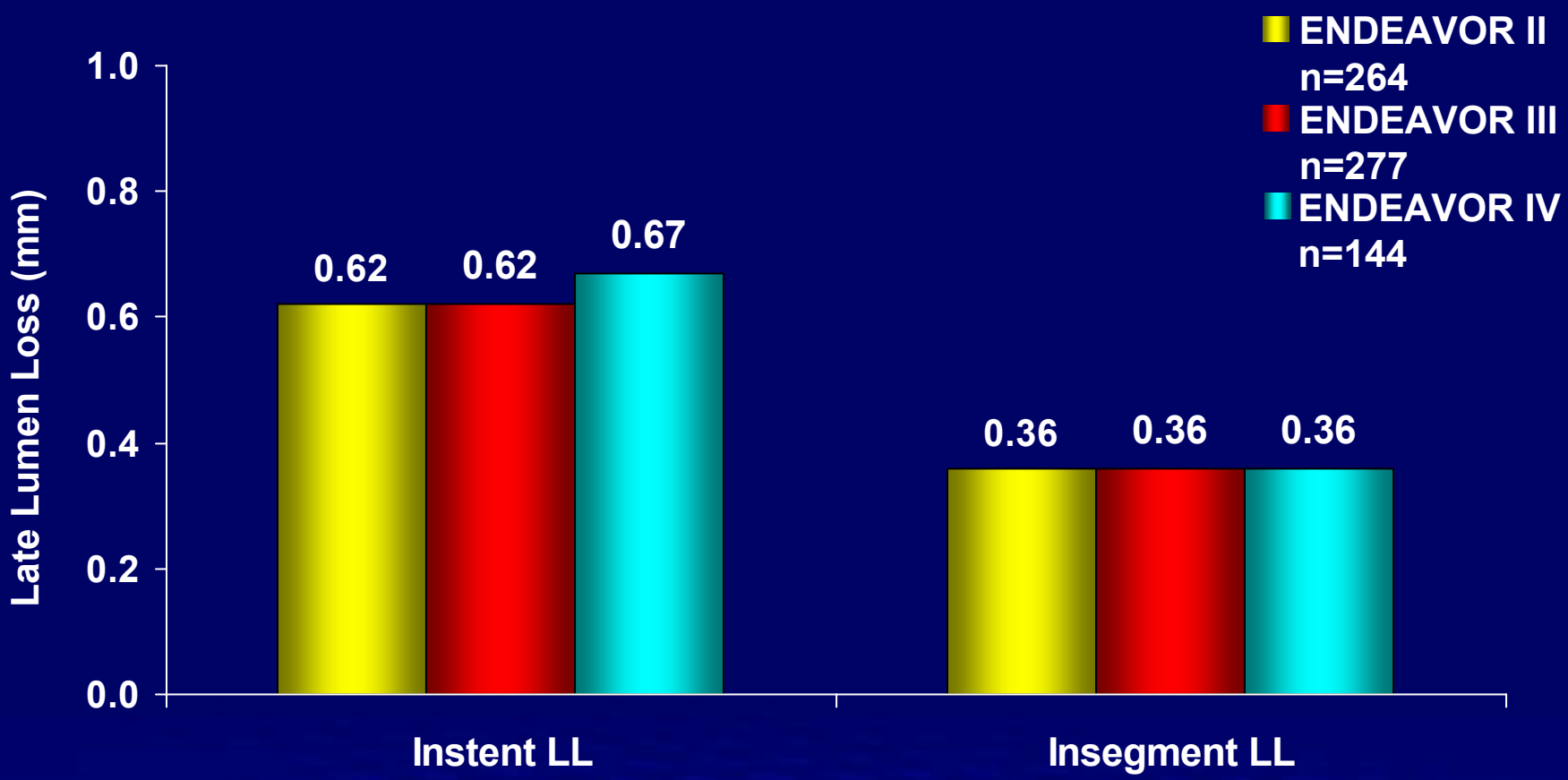
- **Reduced peri-procedural non-Q MIs, and a similar safety profile (death, Q-MI, and stent thrombosis) through 9 months follow up**
- **Met TVF primary endpoint**
- **Similar TVR/TLR in subsets of interest through 9 months follow up**
- **Higher angiographic late loss at 8 months follow up**

Endeavor Clinical Program

ENDEAVOR II, III and IV

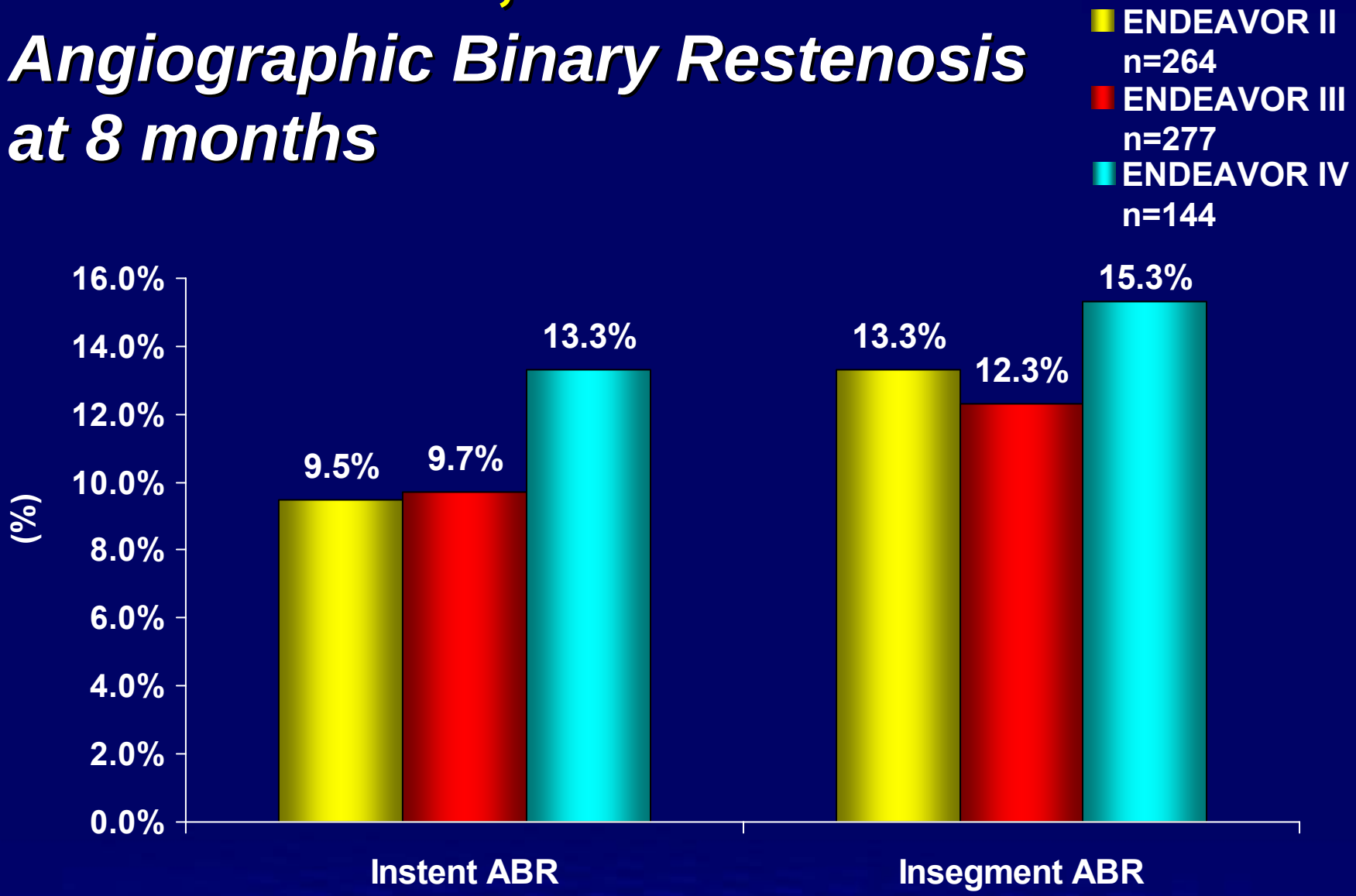
Late Lumen Loss at 8 months

(Endeavor patients)



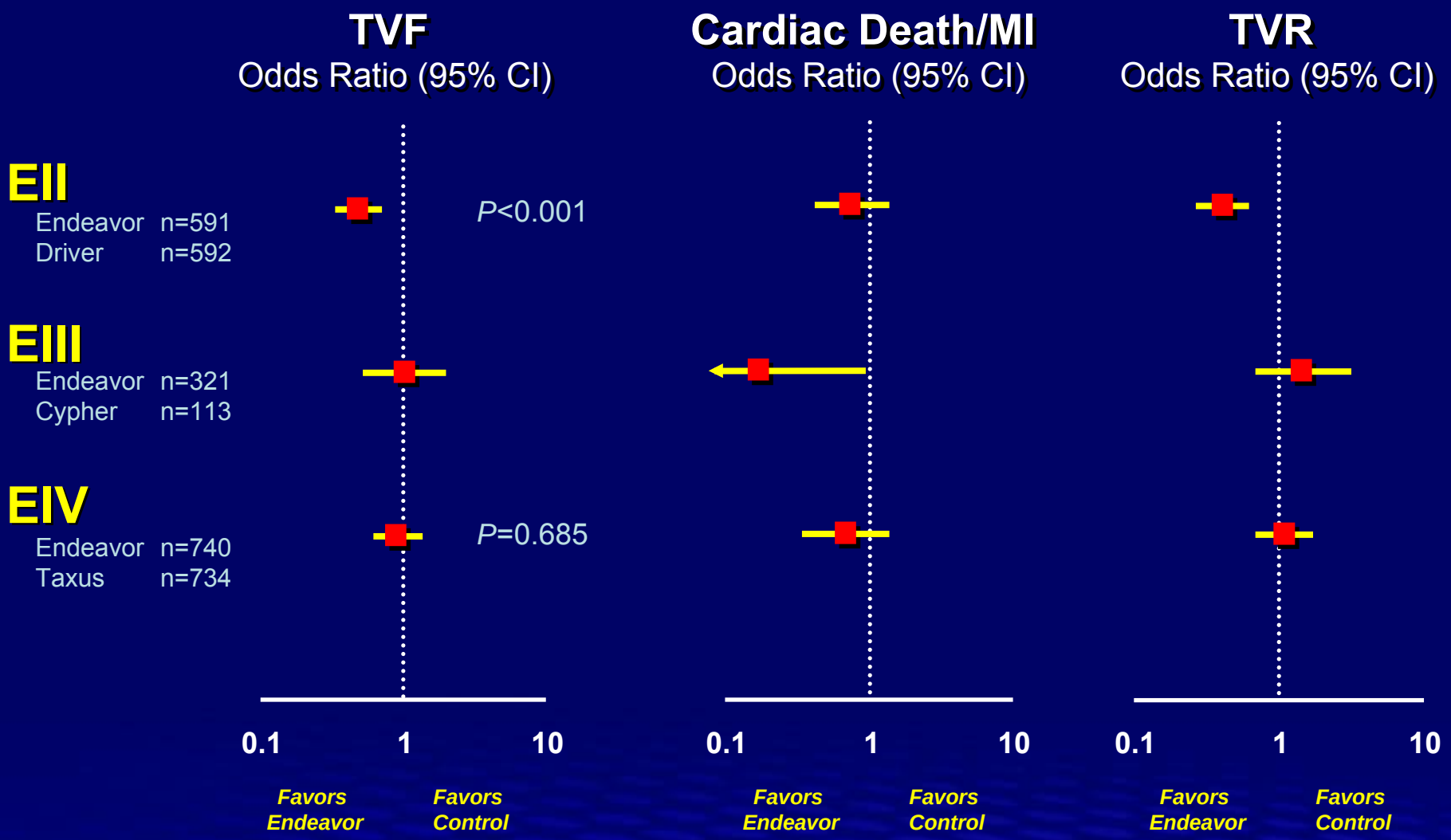
ENDEAVOR II, III and IV

Angiographic Binary Restenosis at 8 months



Target Vessel Failure to 9 Months in RCTs

Odds Ratio with 95% Confidence Intervals



Endeavor Clinical Program
Summary

In 3 randomized trials (3,181 pts), the Endeavor DES has demonstrated…

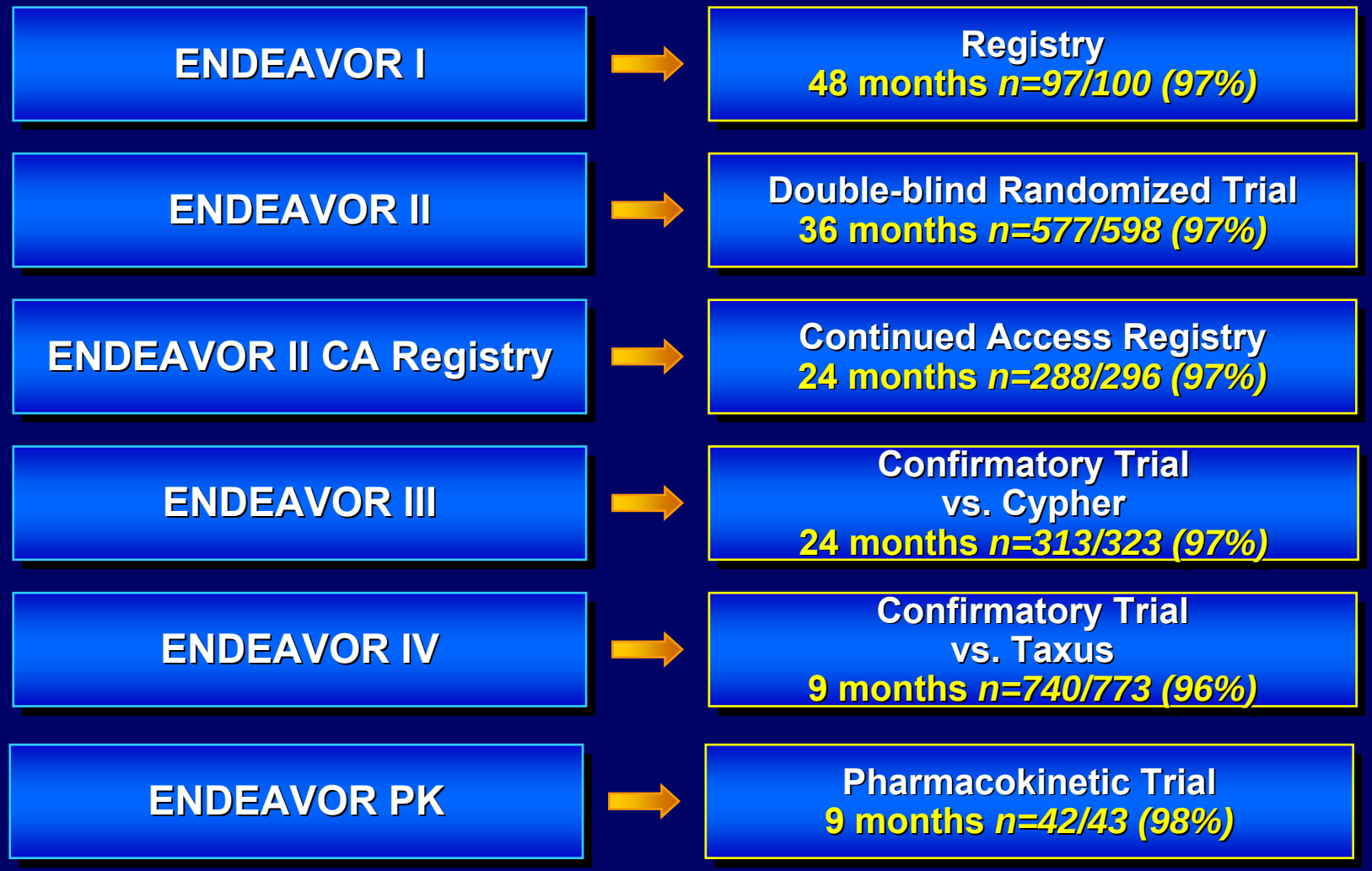
- **A safety profile similar to the Driver BMS (death, MI, and stent thrombosis)**
- **Superior reduction in restenosis (both angiographic and clinical endpoints) vs. a BMS (Driver)**
- **Comparable clinical outcomes as measured by TVF (TVR and cardiac death/MI) vs. an approved DES (Taxus)**
- **Durable clinical outcomes during long-term follow up (to 3 years)**
- **Consistent angiographic and clinical outcomes across all RCTs**

Endeavor Clinical Trial Program: Post Hoc Safety Overview

Laura Mauri, MD, MSc

Disclosures:

Member of Medtronic Advisory Board
Co-investigator for ENDEAVOR III
Chief Scientific Officer, Harvard Clinical Research Institute



270day follow up	n=2088
720day follow up	n=1287
1080day follow up	n=675

Endeavor Clinical Program
Safety Overview

- Objective:
  - to evaluate whether the Endeavor stent is associated with increased rates of death, MI, or stent thrombosis compared with Driver BMS
- Method:
  - Pooled individual patient level analysis
  - 6 Endeavor stent arms, 1 Driver BMS arm
  - Cumulative incidence at 360 and 1080 days
  - Strengths: Consistent definitions, density and duration of follow up
  - Limitations: Does not preserve randomization (only E2 trial randomized to Driver BMS)

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

Endeavor Clinical Program
Baseline Characteristics

	Endeavor n=2133	Driver n=599	*P Value*
Diabetes (%)	26.1	22.2	0.055
RVD (mm)	2.73	2.76	0.128
Lesion length (mm)	14.16	14.38	0.446

Endeavor Clinical Program

Dual Antiplatelet Therapy (DAPT) Usage

Percent of Patients on DAPT at:	1 Year	2 Years
Endeavor (EI, EII, EIICA)	29.1% (279/958)	11.2% (106/943)
Driver (EII)	29.0% (166/572)	13.5% (76/562)

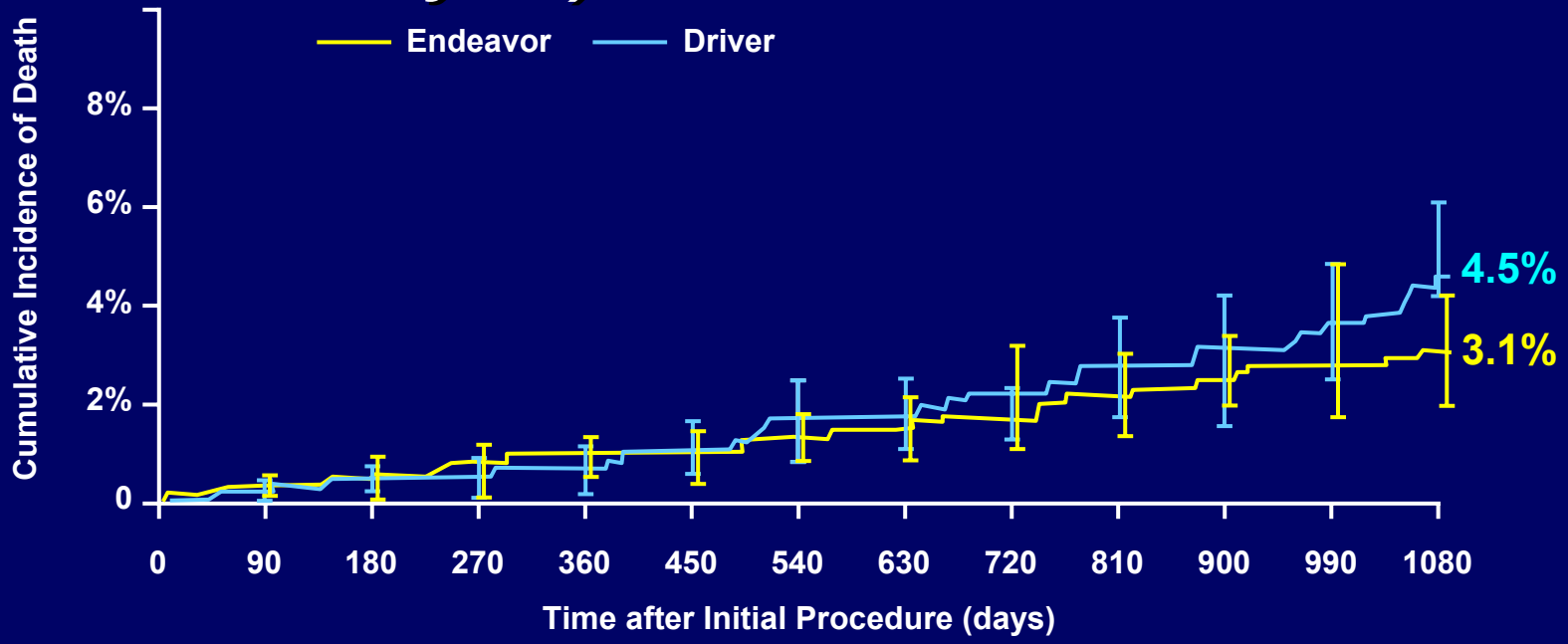
Endeavor Clinical Program - Safety
Overview

Cumulative incidence will be presented according to Kaplan Meier graphs, with interval rates presented to 1080 days (3 years)

- **Summary of results:**
  - **no evidence of increase in adverse events for Endeavor vs Driver when comparing death, cardiac death, myocardial infarction, or stent thrombosis**

Endeavor Clinical Program

Cumulative Incidence of Death to 1080 Days (post hoc analysis)

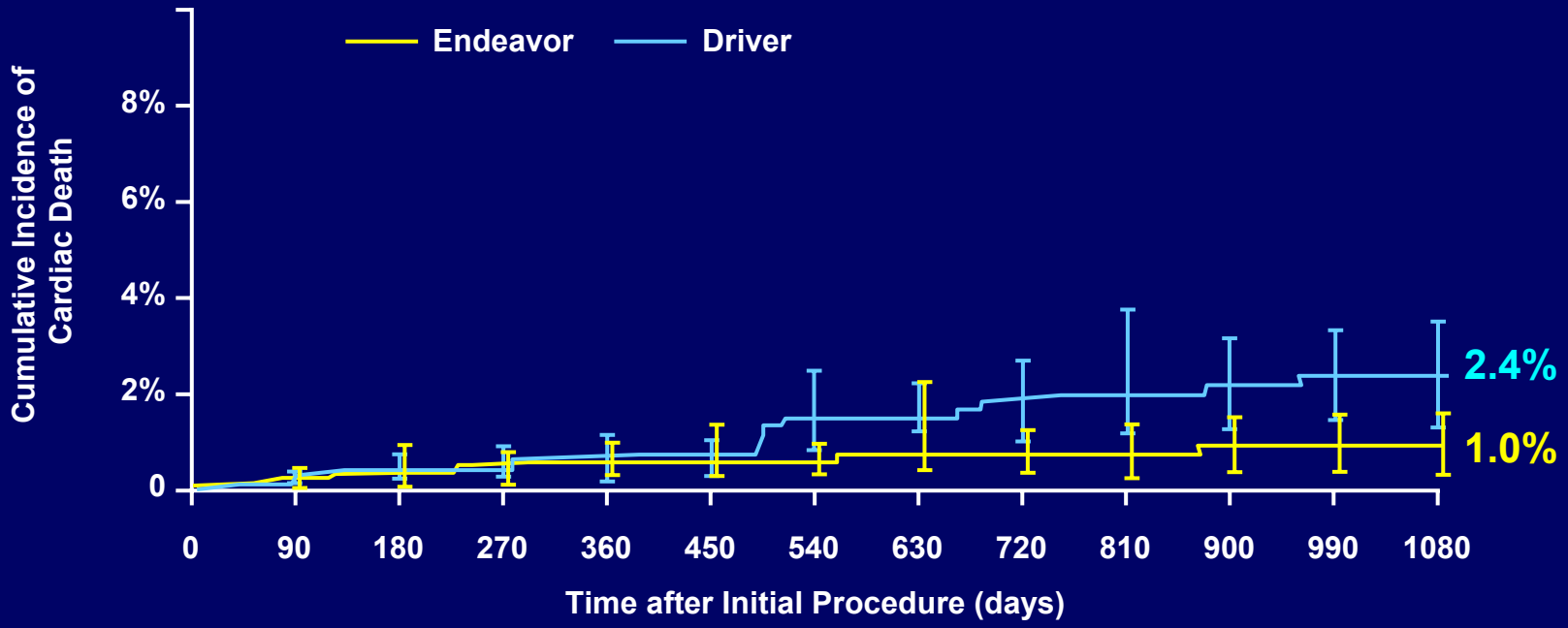


Days	0	30	360	720	1080
Endeavor n at risk	2132	2122	1926	1251	651
Cumulative incidence	0.0%	0.2%	0.9%	1.7%	3.1%
Interval change	0.0%	0.2%	0.7%	0.8%	1.4%
Driver n at risk	596	594	583	568	551
Cumulative incidence	0.0%	0.0%	0.7%	2.2%	4.5%
Interval change	0.0%	0.0%	0.7%	1.5%	2.3%

Error bars represent ±1.5SE estimated by Peto formula

Endeavor Clinical Program

Cumulative Incidence of Cardiac Death to 1080 Days (post hoc analysis)

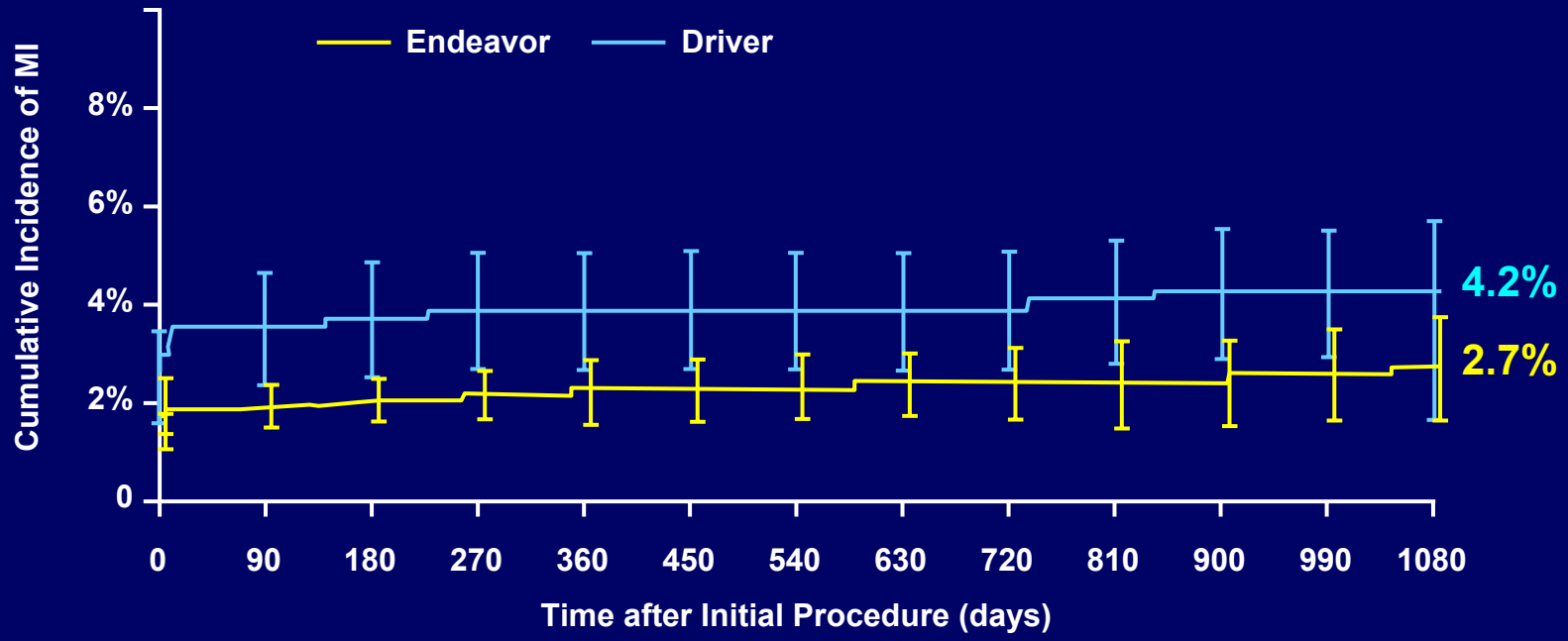


Days	0	30	360	720	1080
Endeavor n at risk	2132	2122	1926	1251	651
Cumulative incidence	0.0%	0.1%	0.6%	0.8%	1.0%
Interval change	0.0%	0.1%	0.5%	0.2%	0.2%
Driver n at risk	596	594	583	568	551
Cumulative incidence	0.0%	0.0%	0.7%	1.9%	2.4%
Interval change	0.0%	0.0%	0.7%	1.2%	0.5%

Error bars represent ±1.5SE estimated by Peto formula

Endeavor Clinical Program

Cumulative Incidence of MI prior to 1080 Days (post hoc analysis)

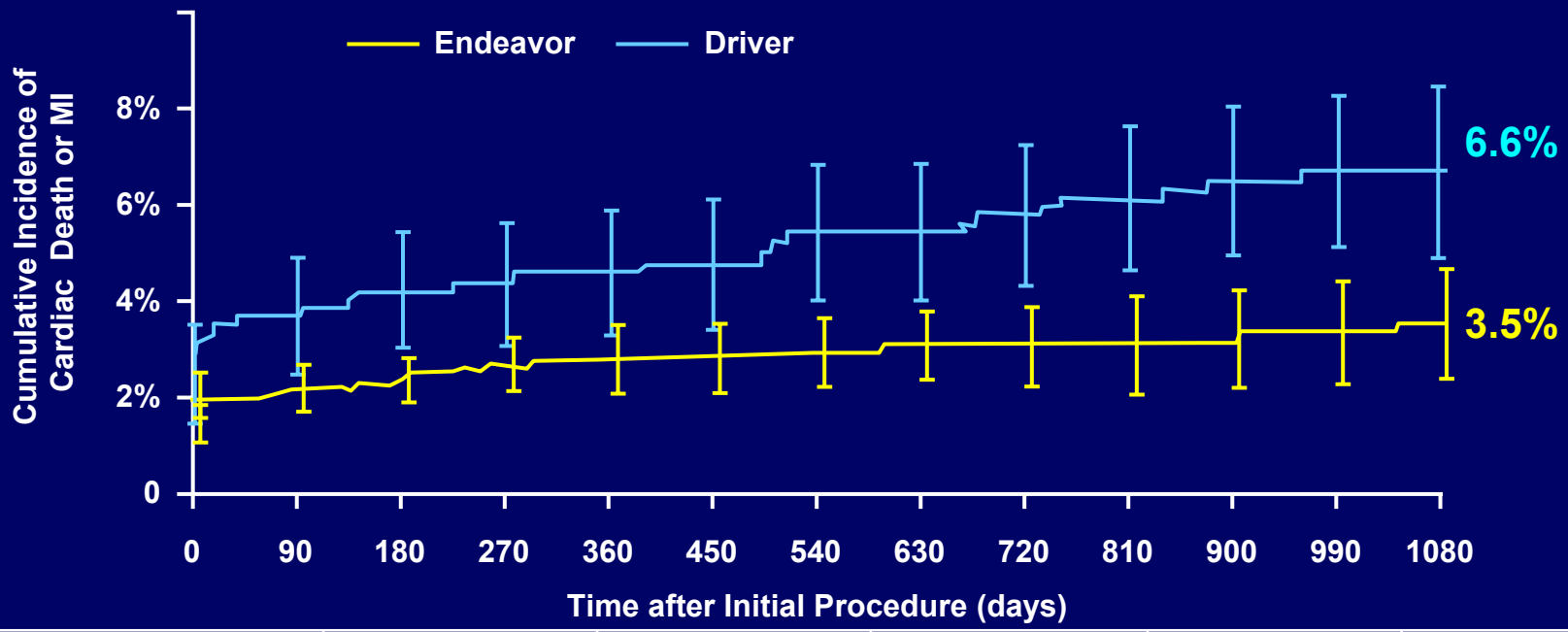


Days	0	30	360	720	1080
Endeavor n at risk	2132	2083	1883	1219	634
Cumulative incidence	1.4%	1.9%	2.2%	2.4%	2.7%
Interval Change	1.4%	0.5%	0.3%	0.2%	0.3%
Driver n at risk	596	573	560	545	528
Cumulative incidence	2.5%	3.5%	3.9%	3.9%	4.2%
Interval Change	2.5%	1.0%	0.4%	0.0%	0.3%

Error bars represent ±1.5SE estimated by Peto formula

Endeavor Clinical Program

Cumulative Incidence of Cardiac Death and MI prior to 1080 Days (post hoc analysis)



Days	0	30	360	720	1080
Endeavor n at risk	2132	2083	1883	1219	634
Cumulative incidence	1.4%	2.0%	2.8%	3.0%	3.5%
Interval Change	1.4%	0.6%	0.8%	0.2%	0.5%
Driver n at risk	596	573	560	545	528
Cumulative incidence	2.5%	3.5%	4.5%	5.8%	6.6%
Interval Change	2.5%	1.0%	1.0%	1.3%	0.8%

Error bars represent ±1.5SE estimated by Peto formula

Stent Thrombosis
Protocol Definition

- Coronary symptoms AND
- [Angiographic confirmation of thrombus or occlusion OR
- Pathologic confirmation of acute thrombosis]
- Unexplained death within 30 days
- Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion within 30 days
- Patients with intervening TLR were excluded

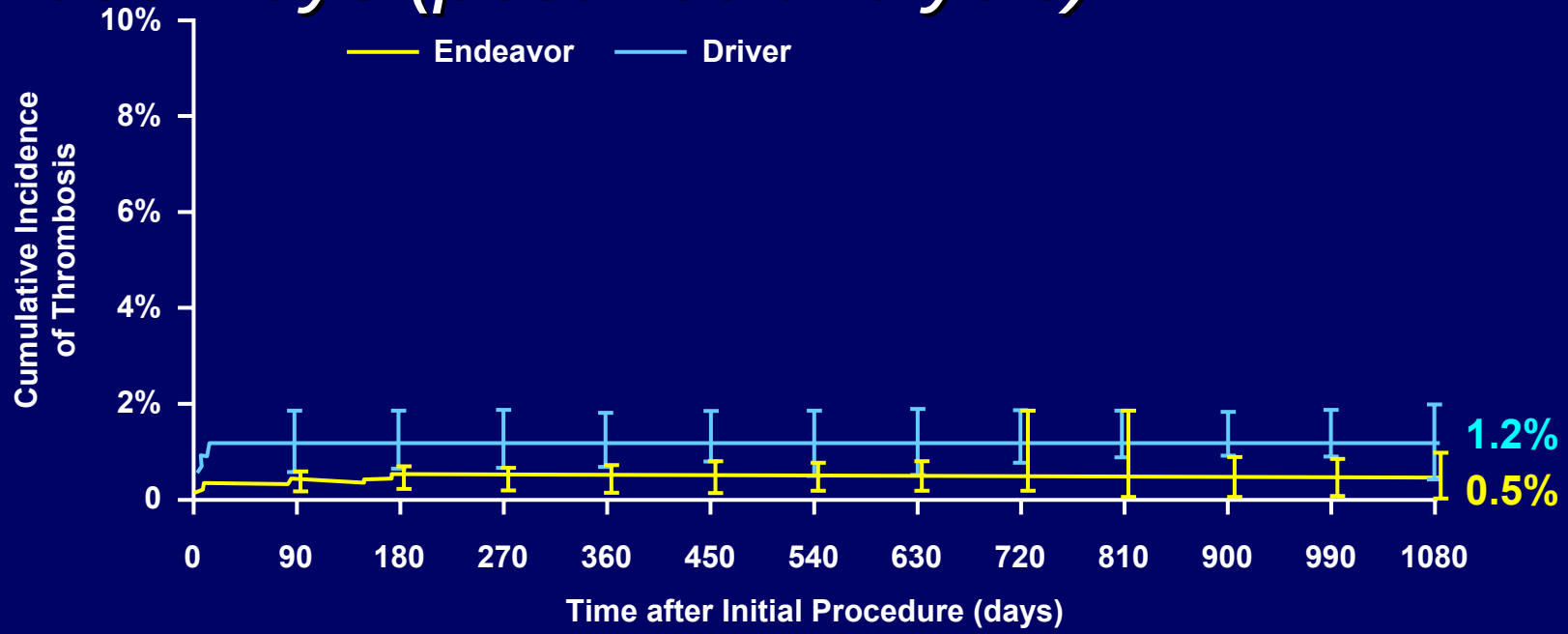
- Timing
  - Acute (within 24 hours)
  - Sub-Acute (1 day to 30 days)
  - Late (after 30 days)

Stent Thrombosis
Academic Research Consortium (ARC)

- Definite/Confirmed
  - Coronary symptoms AND
  - [Angiographic confirmation of thrombus or occlusion OR
  - Pathologic confirmation of acute thrombosis]
- Probable
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
- Possible
  - Unexplained death after 30 days
- Timing
  - Early (within 30 days)
  - Late (30 days to 1 year)
  - Very Late (past 1 year)

Endeavor Clinical Program

Cumulative Incidence of Thrombosis (Protocol) to 1080 Days (post hoc analysis)

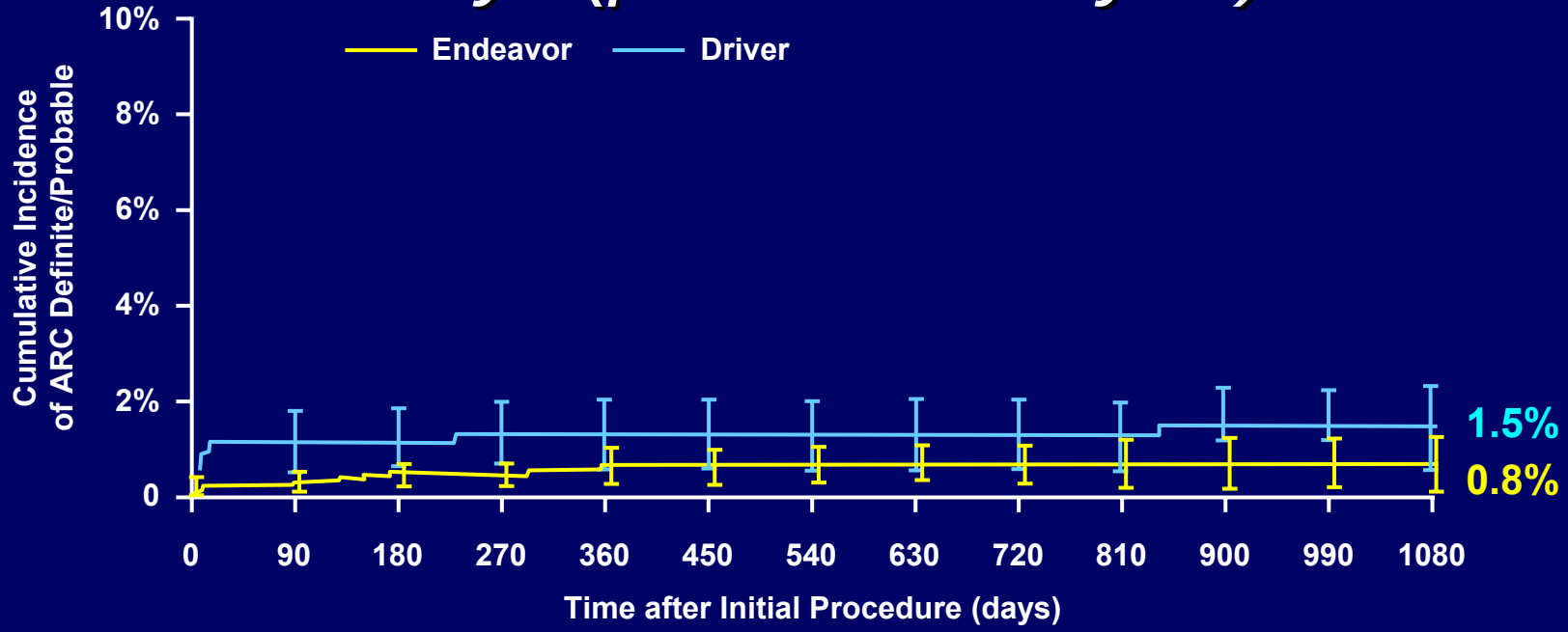


Days	0	30	360	720	1080
Endeavor n at risk	2132	2117	1918	1248	648
Cumulative incidence	0.0%	0.3%	0.5%	0.5%	0.5%
Interval Change	0.0%	0.3%	0.2%	0.0%	0.0%
Driver n at risk	596	587	576	561	544
Cumulative incidence	0.2%	1.2%	1.2%	1.2%	1.2%
Interval Change	0.2%	1.0%	0.0%	0.0%	0.0%

Error bars represent ±1.5SE estimated by Peto formula

Endeavor Clinical Program

Cumulative Incidence of ARC Definite/Probable prior to 1080 Days (post hoc analysis)



Days	0	30	360	720	1080
Endeavor n at risk	2132	2117	1917	1247	648
Cumulative incidence	0.0%	0.3%	0.7%	0.8%	0.8%
Interval Change	0.0%	0.3%	0.4%	0.1%	0.0%
Driver n at risk	596	587	575	560	542
Cumulative incidence	0.2%	1.2%	1.3%	1.3%	1.5%
Interval Change	0.2%	1.0%	0.1%	0.0%	0.2%

Error bars represent ± 1.5SE estimated by Peto formula

Endeavor Clinical Program

Cumulative Incidence of Stent Thrombosis by Time Interval (ARC definite and probable)

	Cumulative Incidence -%			
	Endeavor n=2132	*[95% CI]*	Driver n=596	*[95% CI]*
Early (0-30d)	0.3%	[0.09,0.57]	1.2%	[0.03,2.04]
Late (31-360d)	0.4%	[0.02,0.67]	0.2%	[0.00,0.51]
Very Late (361d-3y)	0.1%	[0.00,0.32]	0.2%	[0.00,0.59]
Cumulative (to 3y)	0.8%	[0.02,1.49]	1.5%	[0.35,2.71]

Standard error was estimated by Peto formula

Endeavor Clinical Program

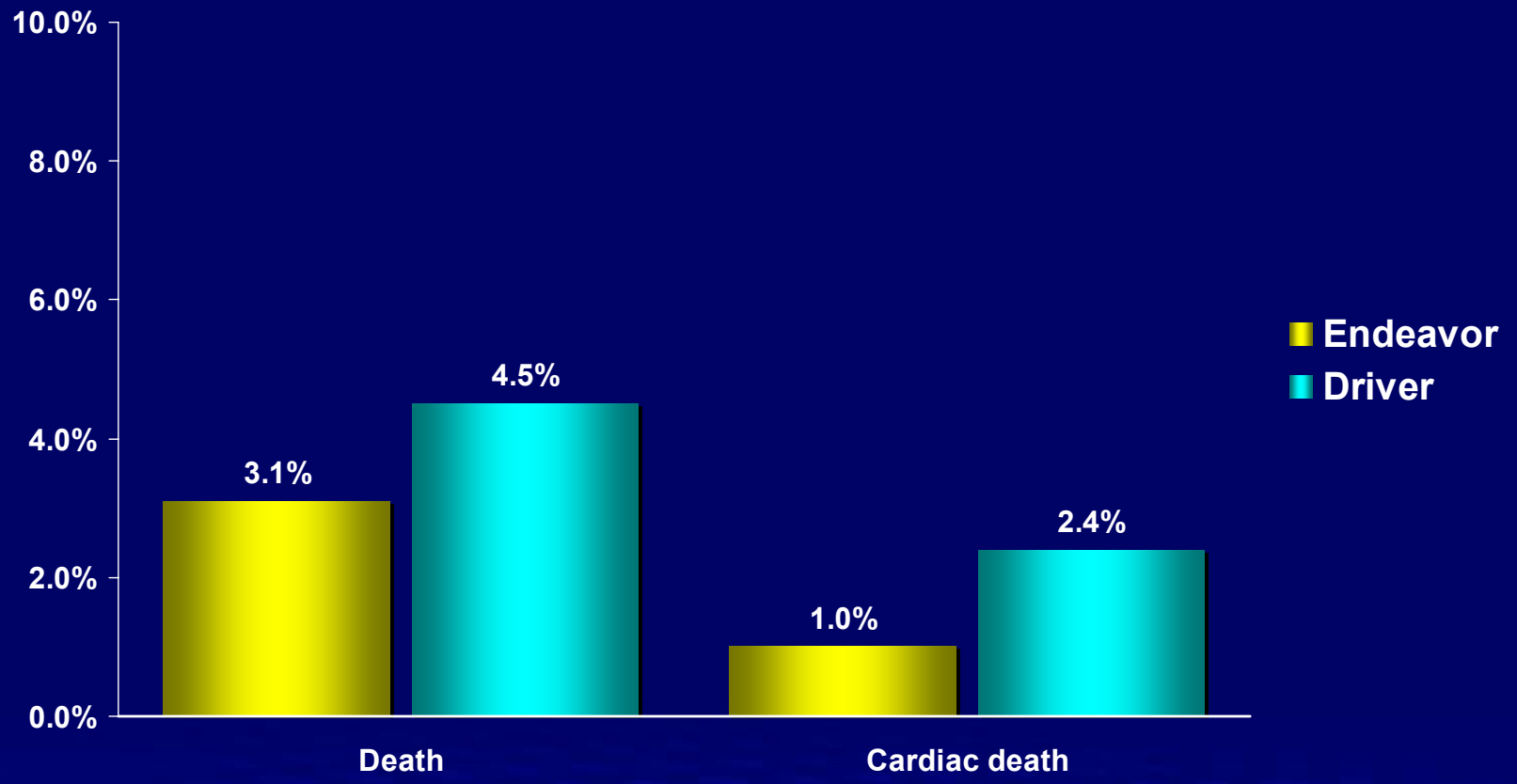
Cumulative Incidence of Safety Endpoints to 1080 days (post hoc analysis)

	Cumulative Incidence -%			
	Endeavor n=2132	*[95% CI]*	Driver n=596	*[95% CI]*
Death	3.1	[1.62,4.51]	4.5	[2.59,6.49]
Cardiac Death	1.0	[0.13,1.78]	2.4	[0.96,3.88]
MI	2.7	[1.33,4.09]	4.2	[2.30,6.15]
Cardiac Death/MI	3.5	[1.94,5.04]	6.6	[4.28,8.99]
Thrombosis (protocol)	0.5	[0.00, 1.06]	1.2	[0.14,2.21]
Thrombosis (Def/Prob)	0.8	[0.02,1.49]	1.5	[0.35,2.71]

Standard error was estimated by Peto formula

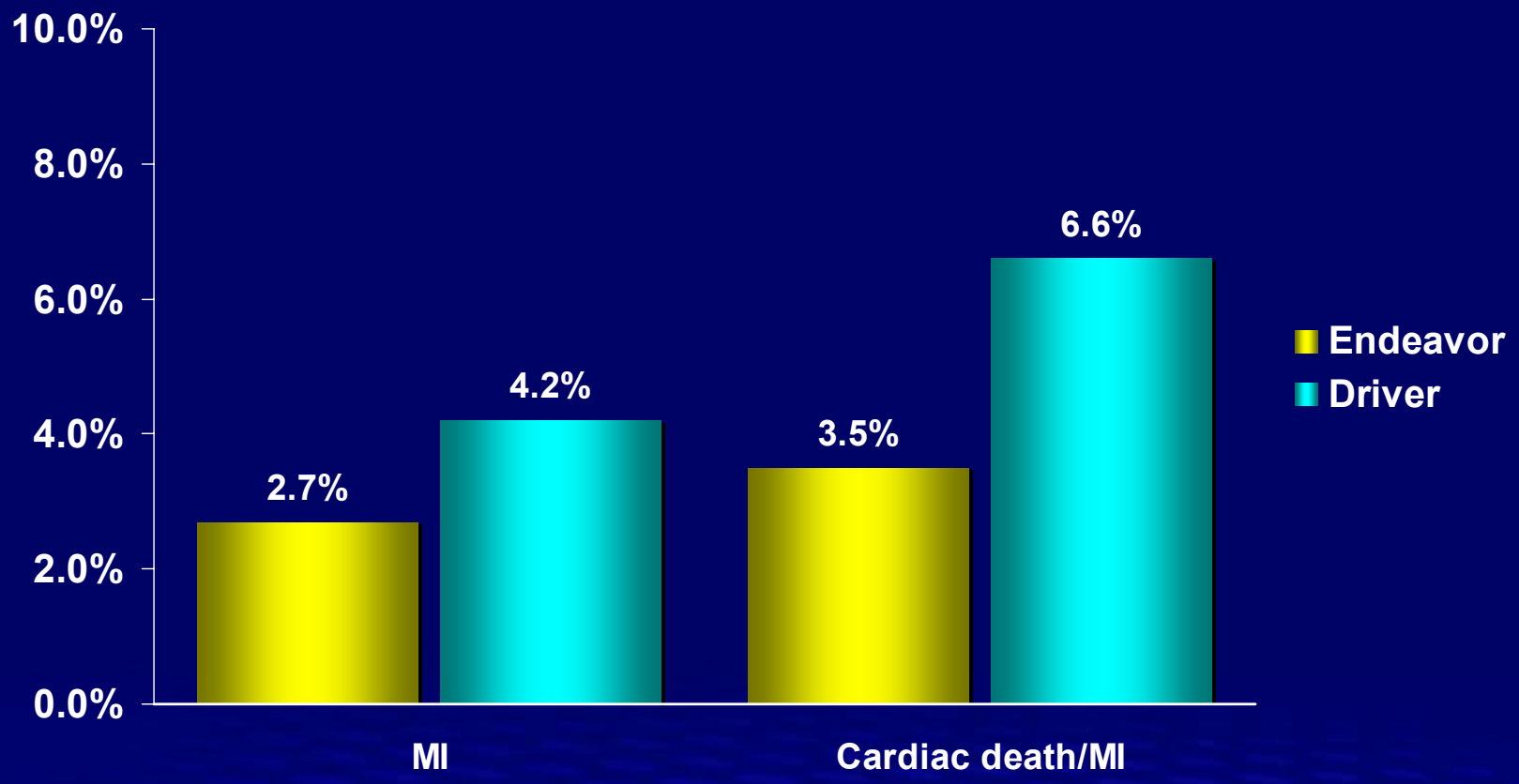
Endeavor Clinical Program

Cumulative Incidence of Death and Cardiac Death to 1080 days (post hoc analysis)



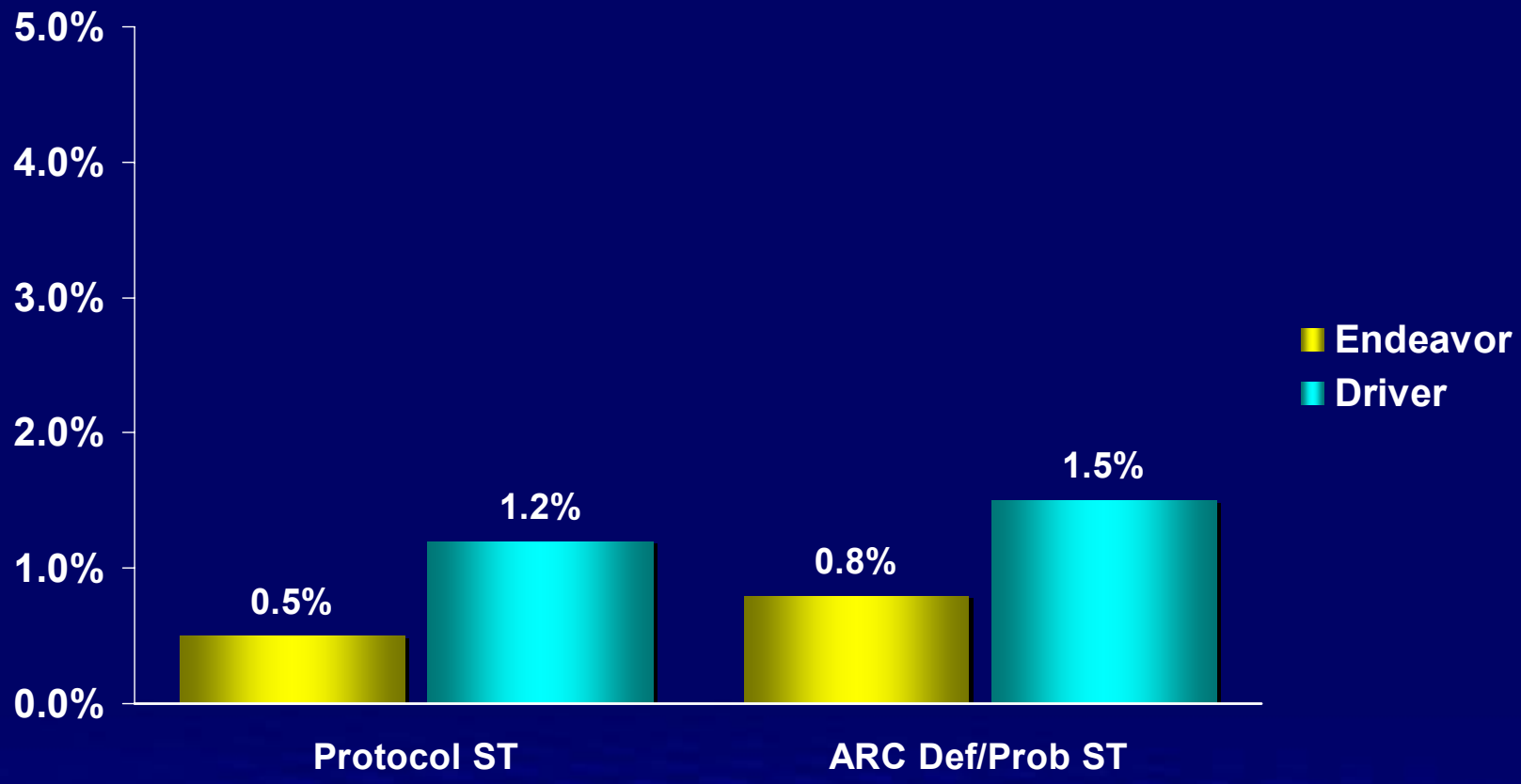
Endeavor Clinical Program

Cumulative Incidence of MI and Cardiac Death/MI to 1080 days (post hoc analysis)



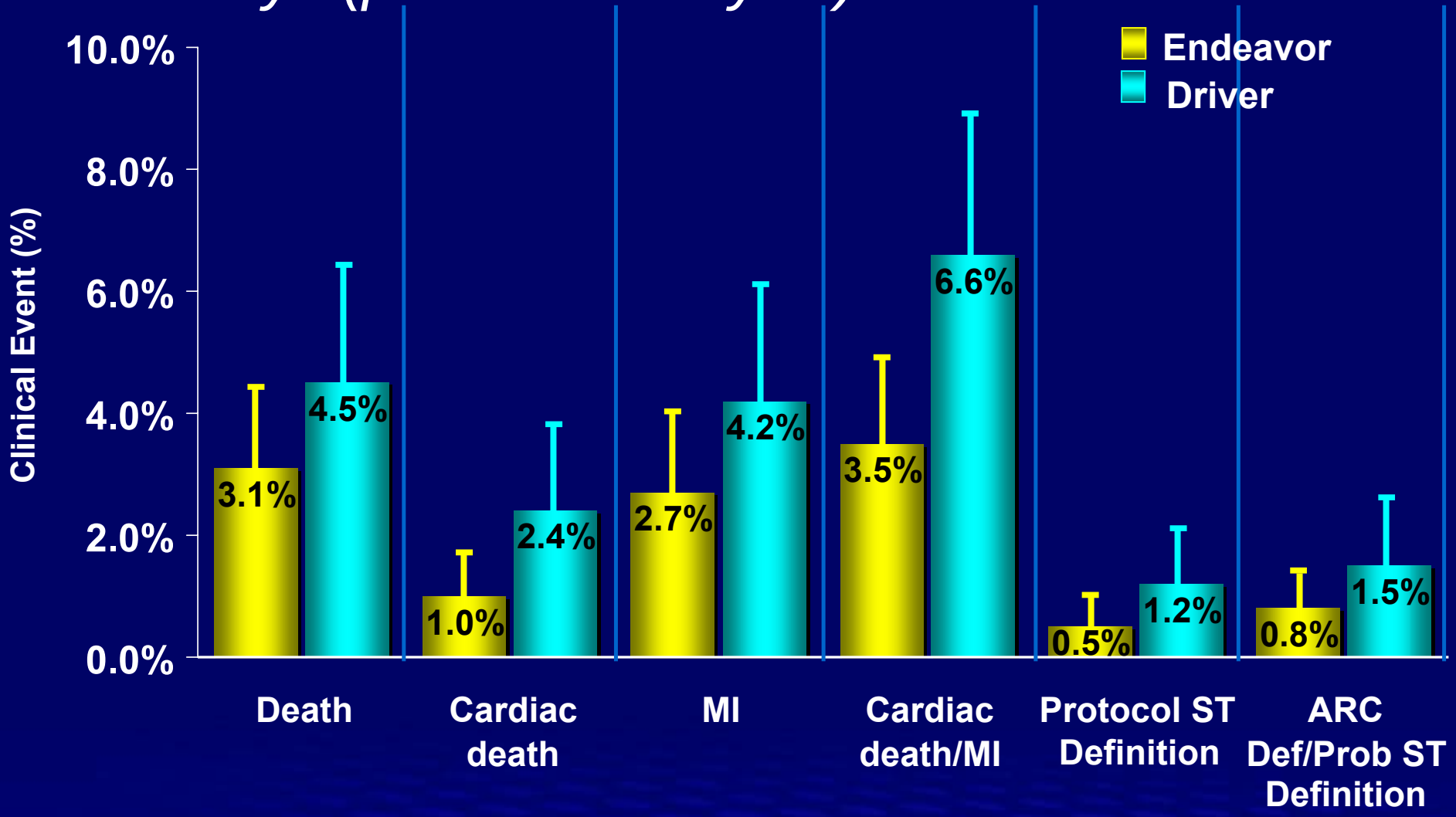
Endeavor Clinical Program

Cumulative Incidence of Stent Thrombosis to 1080 days (post hoc analysis)



Endeavor Clinical Program

Cumulative Incidence of Safety Endpoints to 1080 days (post hoc analysis)



Error bars represent 95% confidence intervals

Endeavor Clinical Program - Safety
Summary 1

From the Endeavor clinical program dataset of 2132 patients treated with Endeavor and 596 patients treated with Driver:

- There was no evidence of increased rates of death, cardiac death, or myocardial infarction in patients treated with the Endeavor stent compared with Driver BMS to 3 years follow up

- There was no evidence of increased stent thrombosis risk within 1 year (0.7% vs 1.3% ARC definite/probable)
  or in years 1-3 (0.1 vs 0.2%) in patients treated with the Endeavor stent compared with those treated with the Driver BMS

Endeavor Clinical Program - Safety

Summary 2

The observed safety profile should be considered in the context of the density of clinical follow up and concomitant antiplatelet therapy:

- **1287 Endeavor stent patients have been followed to 2 years, and 675 patients to 3 years**
- **71% of Endeavor stent patients were off dual antiplatelet therapy at 1 year and 89% were off dual antiplatelet therapy at 2 years**

ENDEAVOR
Conclusion and Post Approval Strategy

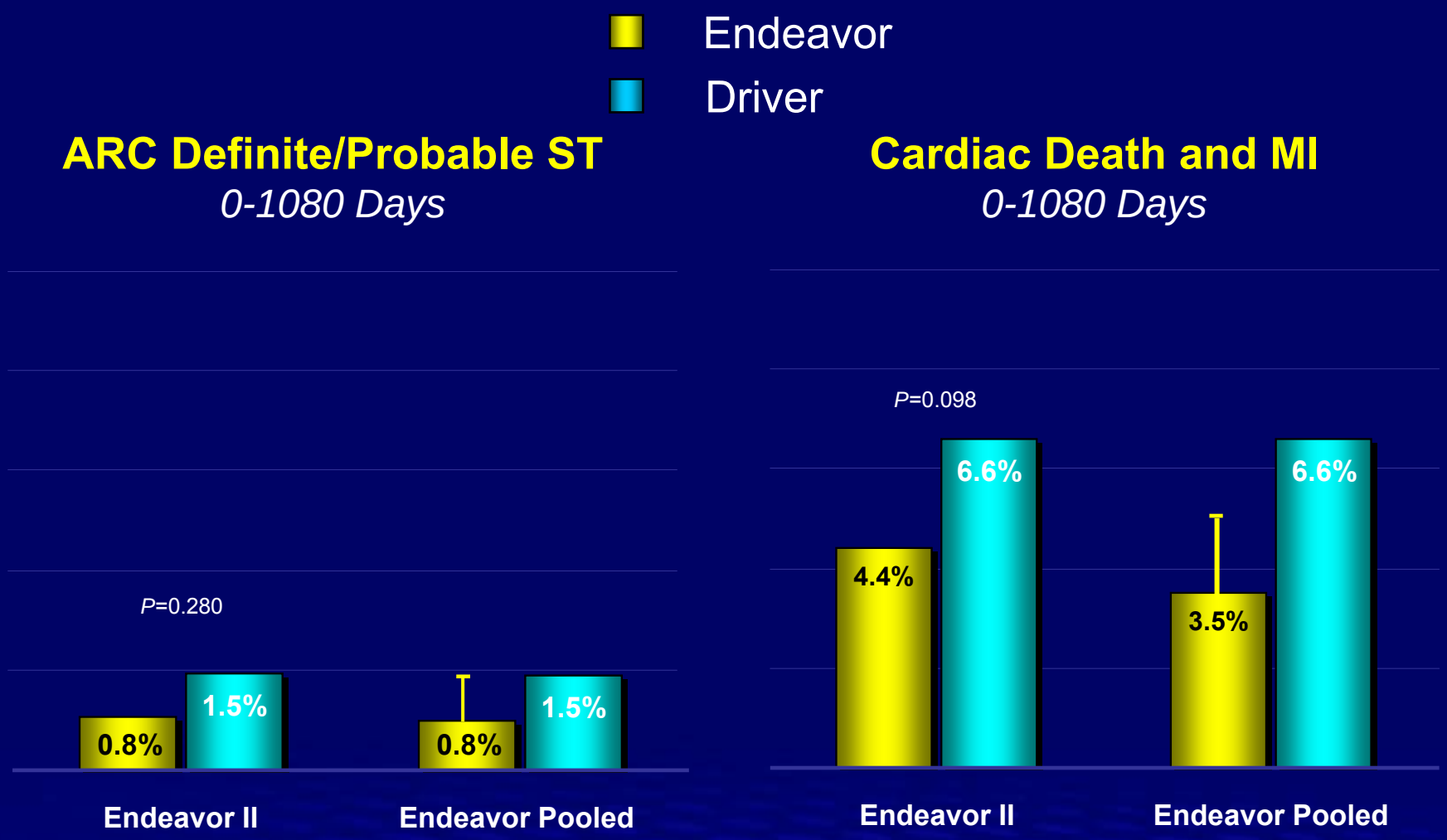
Rick Kuntz, MD, MSc
Sr. Vice President, Medtronic, Inc.

Summary

- **Safety Overview**
  - **No signal of adverse safety events prior to 1 year or in years 1 to 3**
- **Endeavor RCT Experience**
  - **Clinical and angiographic superiority in a double blinded 1:1 RCT**
  - **Clinical non-inferiority in a single blind 1:1 RCT despite modest increases in in-segment late lumen loss**
- **Preclinical and Drug Substance**
  - **Well characterized drug safety profile**
  - **Biomimetic polymer and non-cytotoxic drug preserves endothelial function with low inflammation**
  - **Proven cobalt alloy modular stent technology enhances deliverability**

Endeavor Safety Summary

Randomized Trial and Pooled Data to 3 years



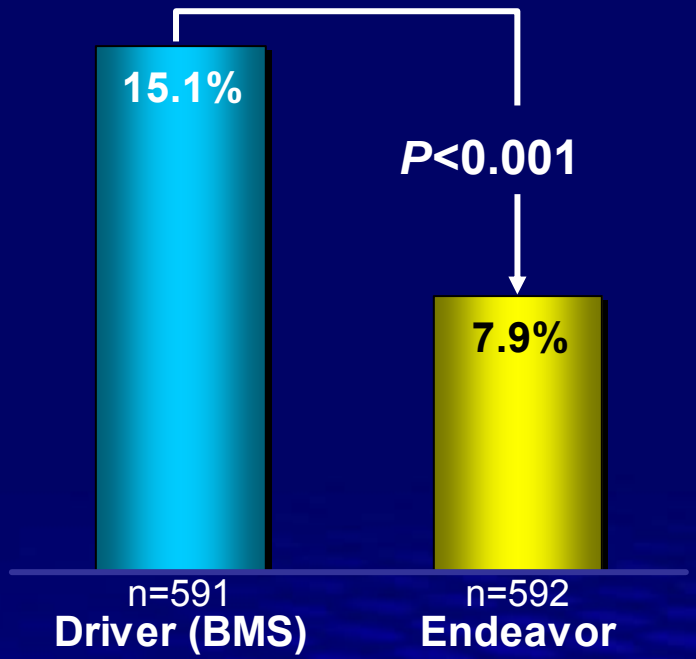
Summary

- Safety Overview
  - No signal of adverse safety events prior to 1 year or in years 1 to 3
- **Endeavor RCT Experience**
  - **Clinical and angiographic superiority in a double blinded 1:1 RCT**
  - **Clinical non-inferiority in a single blind 1:1 RCT despite modest increases in in-segment late lumen loss**
- Preclinical and Drug Substance
  - Well characterized drug safety profile
  - Biomimetic polymer and non-cytotoxic drug preserves endothelial function with low inflammation
  - Proven cobalt alloy modular stent technology enhances deliverability

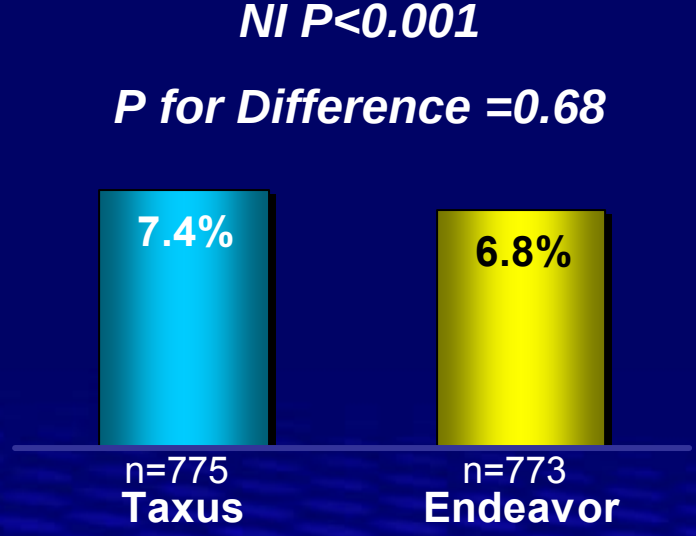
Endeavor Efficacy Summary

9 Month Primary Endpoint of TVF

Superior TVF at 9 Months Compared to BMS in a Double Blinded, Multi-center RCT



Non-Inferior TVF at 9 Months Compared to Taxus in a Single Blinded, Multi-center RCT

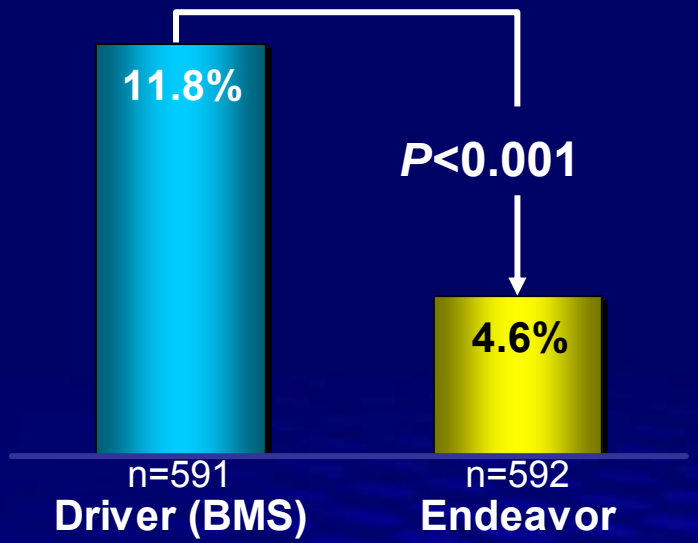


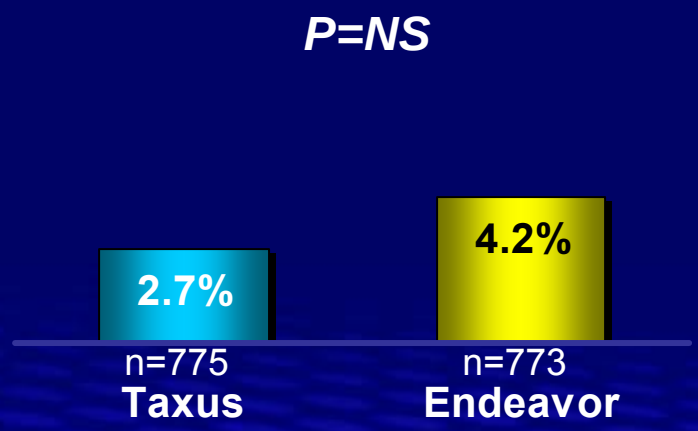
Endeavor Efficacy Summary

Target Lesion Revascularization to 9 Months

Superior TLR at 9 Months Compared to BMS in a Double Blinded, Multi-center RCT

No Difference in TLR to 9 Months Compared to Taxus in a Single Blinded, Multi-center RCT





Summary

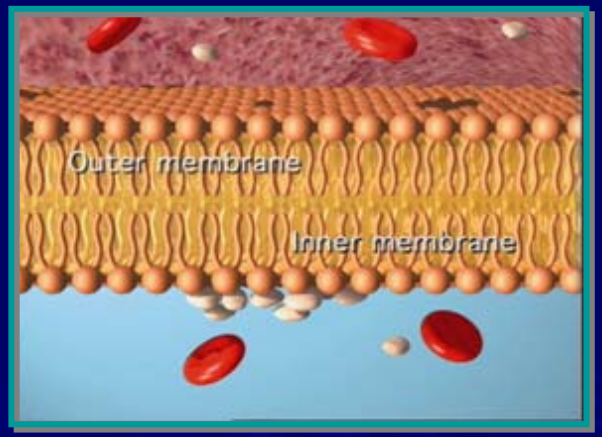
- Safety Overview
  - No signal of adverse safety events prior to 1 year or in years 1 to 3
- Endeavor RCT Experience
  - Clinical and angiographic superiority in a double blinded 1:1 RCT
  - Clinical non-inferiority in a single blind 1:1 RCT despite modest increases in in-segment late lumen loss
- **Preclinical and Drug Substance**
  - **Well characterized drug safety profile**
  - **Biomimetic polymer and non-cytotoxic drug preserves endothelial function with low inflammation**
  - **Proven cobalt alloy modular stent technology enhances deliverability**

Endeavor DES System

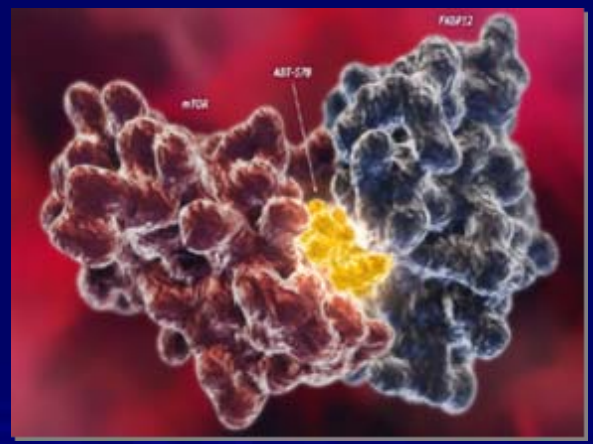
Driver Cobalt Alloy Stent

Stent Delivery System

PC Technology



Drug: Zotarolimus



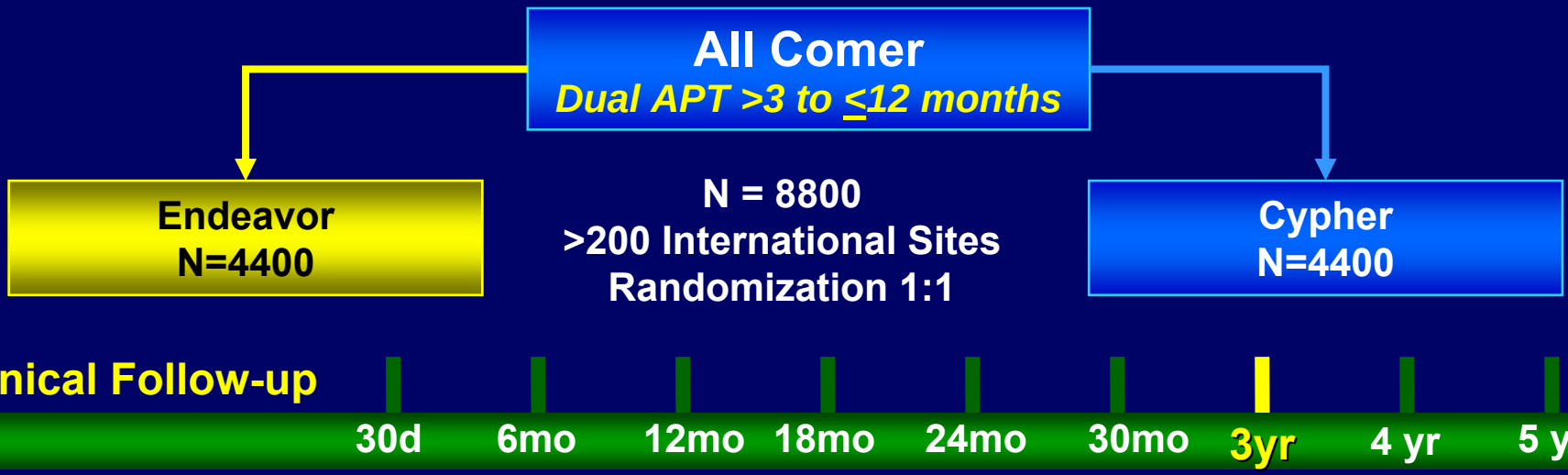
Summary

Dec FDA Panel Observations	Endeavor Program
An increased ST rate beyond 1 year rate was seen for DES compared with BMS	No increased ST rate was seen before or after 1 year regardless of definition
No increased risk of death or MI due to: 1. Revascularization or 2. Insufficient discriminating data	Lower TLR rates without increase in VLST rates, and numerically lower rates of death and MI at 3 years
Recommendations: Larger and longer ***pre-market*** clinical analysis	3 or more years of data sufficiently powered to show durable lower TLR rates, and safe VLST rates with measurable confidence boundaries

Ref: Adapted From http://www.fda.gov/cdrh/news/010407.html Updated January 4 2007

PROTECT

International RCT Designed to Estimate VLST (>1 year)



Primary Endpoint: ARC Definite or Probable Stent Thrombosis at 3 years

Principle Secondary Endpoints: Death/Non-Fatal MI, Cardiac death/Non-Fatal MI

Additional Endpoints: MACCE, TLR, TVR, Procedural Success

Clinical Follow up and Dual Antiplatelet Monitoring:

At 30 days, and every 6 months until 3 years, than each year until 5 years

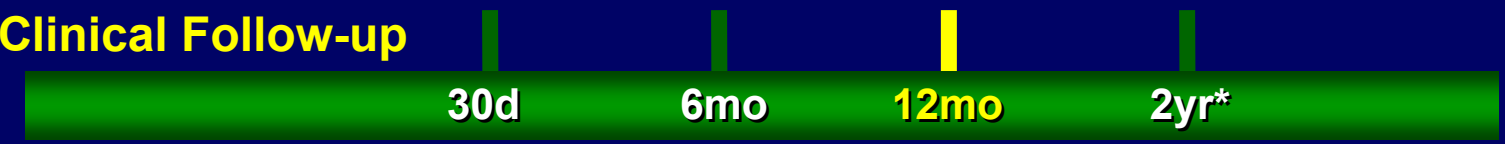
Enrollment Ongoing

E-Five Single Arm Registry

International Post-market, All comers

Single and Multiple Coronary Artery Lesions
Stent Diameters: 2.25-4.0 mm
Stent Length: 8/9-30 mm

N = 8000
Single Arm Registry
200 International Sites



Primary Endpoint:

MACE at 12 months

Secondary Endpoints:

MACE at 30 days and 6 mo, stent thrombosis, procedure success rate; device success rate; lesion success rate

Enrollment Complete

*Limited number of centers and specific patient subset.

US Post-Approval Single Arm Registry

Required US Post Market Study

Single and Multiple Coronary Artery Lesions
Stent Diameters: 2.5-3.5 mm
Stent Length: 8/9-30 mm

N = ~5300
(2000 US, ~3300 pooled from OUS PROTECT)
100 US Sites

Clinical Follow-up

Co-Primary Endpoints:

80% powered at each time-point with a one-sided alpha error of 5%

-ARC definite and probable stent thrombosis annually for 5 years

<1% rate at each yearly time interval for the on-label population

- Cardiac Death/MI annually for 5 years

Primary analysis of non-inferiority of Endeavor on-label patients with Driver (EII control) cardiac death/MI incidence yearly through 3 years

Endpoints assessed in per-label patients (n=2120) and all patients (n=5300)

Summary

Dec FDA Panel Observations	Endeavor Program
An increased ST rate beyond 1 year rate was seen for DES compared with BMS	No increased ST rate was seen before or after 1 year regardless of definition
No increased risk of death or MI due to: 1. Revascularization or 2. Insufficient discriminating data	Lower TLR rates without increase in VLST rates, and numerically lower rates of death and MI at 3 years
Recommendations: Larger and longer ***pre-market*** clinical analysis	3 or more years of data sufficiently powered to show durable lower TLR rates, and safe VLST rates with measurable confidence boundaries
Recommendations: Larger and longer ***post-approval*** studies 1. Uniform ST definitions 2. Monitoring of Antiplatelet Therapy	Large Post-market RCT (8800 pts) to test for lower VLST

Ref: Adapted From http://www.fda.gov/cdrh/news/010407.html Updated January 4 2007

In Closing….

- **Substantial Density of Safety and Efficacy Data**
  - *7 Clinical Trials: 3 Randomized, 4 Single Arm*
  - 2232 Endeavor patients enrolled
  - 1287 Endeavor patients with 2 or more years of follow-up
  - 675 Endeavor patients with 3 years of follow-up
  - 3980 Endeavor patient-years of follow-up
- **Clinical and angiographic superiority to BMS**
  - Treatment effect sustained through 3years follow-up
- **Clinical non-inferiority to an approved DES**
- **Consistent clinical and angiographic outcomes**
  - Across different geographies and studies
- **No observed safety signals before or after 1 year**
  - Low rates of ST, death, cardiac death, and MI

Thank you