

# **Endeavor Zotarolimus- Eluting Coronary Stent System**

## **FDA Review of P060033**

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Office of Device Evaluation  
October 10, 2007

# Device Description

- Combination Product
- Stent Platform: Driver balloon-expandable cobalt alloy (MP35N) stent
  - 2.5 to 3.5mm Ø and 8 to 30mm in length
  - approved October 1, 2003
- Polymer: phosphorylcholine (PC)
- Drug: zotarolimus (ABT-578)
- Catheter delivery systems
  - Over-The-Wire (OTW)
  - Rapid Exchange (RX)
  - Multi Exchange (MX2)

# 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  $\leq 27$  mm in native coronary arteries with reference vessel diameters of  $\geq 2.5$ mm to  $\leq 3.5$ mm.

# FDA Review Team

- Center for Drug Evaluation & Research (CDER)
  - Office of Clinical Pharmacology (OCP)
  - Office of New Drug Evaluation I (ODEI)
  - Office of New Drug Quality Assessment (ONDQA)
- Center for Devices & Radiological Health (CDRH)
  - Office of Device Evaluation (ODE)
  - Office of Surveillance & Biometrics (OSB)
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# Review of Drug Substance Safety Data

- Safety Pharmacology
- Toxicology
- Absorption, Distribution, Metabolism, and Excretion (ADME) Studies
- Human IV Dosing

# Pre-Clinical Review of the Finished Product

- Stent Functional Testing
- Stent Coating Testing
- Stent Delivery System Testing
- Animal Studies
- Chemistry, Manufacturing, and Controls (CMC)
- Sterilization
- Biocompatibility
- Manufacturing (QS/GMP)

# Clinical Studies

	US	Enrollment	Primary Endpoints	dAPT:	Available Follow-up
<b>ENDEAVOR I</b>		Endeavor: 100	30d MACE 4m Late Loss	ASA indefinitely + Plavix/Ticlid $\geq 3m$	48m
<b>ENDEAVOR II</b>		Endeavor: 598 Driver: 599	9m TVF 8m Late Loss*	ASA indefinitely + Plavix/Ticlid $\geq 3m$	36m
<b>ENDEAVOR II CA</b>		Endeavor: 296	30d MACE	ASA indefinitely + Plavix/Ticlid $\geq 3m$	24m
<b>ENDEAVOR III</b>	X	Endeavor: 323 Cypher: 113	8m Late Loss	ASA indefinitely + Plavix/Ticlid $\geq 3m$	24m
<b>ENDEAVOR IV</b>	X	Endeavor: 773 Taxus: 775	9m TVF 8m Late Loss*	ASA indefinitely + Plavix/Ticlid $\geq 6m$	9m
<b>ENDEAVOR PK</b>	X	Endeavor: 43	30d PK parameters	ASA indefinitely + Plavix/Ticlid $\geq 3m$	9m
<b>ENDEAVOR Japan</b>		Endeavor: 99	9m TVF	ASA indefinitely + Plavix/Ticlid $\geq 3m$	9m

\* Powered secondary endpoints

# FDA Presentation

- Clinical Review – Andrew Farb, MD
- Statistical Review – Yonghong Gao, PhD
- Summary – Andrew Farb, MD
- Epidemiology Review – Heshu Duggirala, PhD

# **FDA Clinical Review**

## **Endeavor Zotarolimus-Eluting Coronary Stent**

Andrew Farb, M.D.

Division of Cardiovascular Devices

Office of Device Evaluation

October 10, 2007

# Outline

- Relevant Study Outcome Definitions
- Key Inclusion and Exclusion Criteria
- Randomized Clinical Trials
- Non-Randomized Studies
- Pooled Data from the Endeavor Program
  - All Patients
  - Diabetics
  - Stent Thrombosis and Dual Antiplatelet Therapy Use
- Summary
  - Clinical and Angiographic Stent effectiveness Issues in DES Trials

# Relevant Study Definitions

## ■ Procedural Outcomes

- Device Success: Attainment of  $<50\%$  in-stent residual stenosis of the target lesion using only the assigned device
- Device-Specific Procedure Success: Device success and no in-hospital MACE

## ■ Angiographic Outcomes

- Late Lumen Loss: Difference between the post-procedure MLD and MLD at follow-up angiography
- Binary Restenosis: Angiographic follow-up % diameter stenosis of  $\geq 50\%$

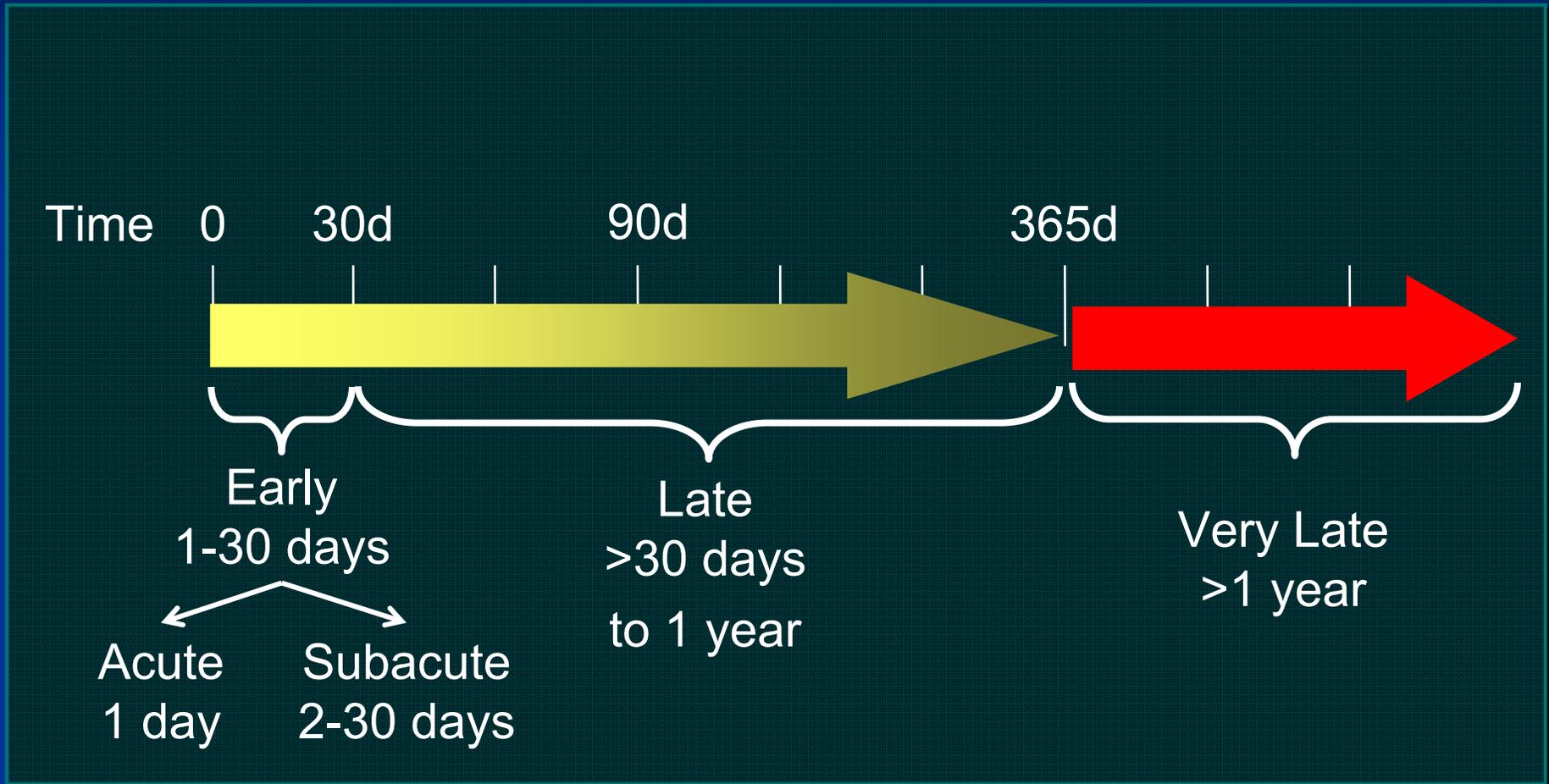
## Relevant Study Definitions

- TVR: Clinically driven repeat intervention (PCI or CABG) of the target vessel
- TLR: Clinically-driven repeat intervention of the target lesion of the target vessel
- TVF: Composite of TVR, cardiac death, or MI that could not be clearly attributed to a vessel other than the target vessel
- MACE: Composite of death, MI, emergent bypass surgery, or TLR

# Stent Thrombosis Per Protocol

- Any death not attributed to a non-cardiac cause within the first 30 days
- Late Stent Thrombosis
  - MI >30 days after index and attributable to the target vessel
  - Angiographic documentation
  - Freedom from interim revascularization of the target vessel

# ARC Stent Thrombosis Time Frame Classification



# ARC Stent Thrombosis

## Levels of Evidence

### ■ Definite/Confirmed

- Acute coronary syndrome 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

# Endeavor Program

## Key Inclusion/Exclusion Criteria

### ■ Key Inclusion Criteria:

- Stable or unstable angina, silent ischemia, or a positive functional study
- The target lesion was a *single de novo* lesion in a native coronary artery with a stenosis of  $\geq 50\%$  and  $< 100\%$ .
- The target lesion length:
  - $\leq 27$  mm (ENDEAVOR II, IICA, III, IV and PK)
  - $\leq 15$  mm (ENDEAVOR I only)
- Target vessel reference diameter
  - $\geq 2.25$  mm (ENDEAVOR II and II CA) and  $\leq 3.5$  mm
  - $\geq 2.5$  mm (ENDEAVOR III, IV, and PK) and  $\leq 3.5$  mm
  - $\geq 3.0$  mm (ENDEAVOR I) and  $\leq 3.5$  mm

# Endeavor Program

## Key Inclusion/Exclusion Criteria

- **Key Exclusion Criteria:**
  - Acute MI within 72 hours
  - Left ventricular ejection fraction <30%
  - Serum creatinine >2.0 mg/dl
  - Left main, ostial lesion, or bifurcation lesion
  - Thrombus within the target vessel

# Randomized Trials

- ENDEAVOR II
- ENDEAVOR III
- ENDEAVOR IV

# ENDEAVOR II

- Randomized double-blind **superiority** trial
- **Objective:** To demonstrate the safety and efficacy of the Endeavor stent vs. the uncoated Driver Stent for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter
- **Primary endpoint**
  - TVF at 9 months
- **Important secondary endpoints**
  - Device specific procedure success
  - Total MACE and rates of death, MI, revascularization, and stent thrombosis at 30 days and 6, 9, and 12-months and annually to 5 years
  - Angiographic in-segment late lumen loss at 8 months (powered secondary superiority endpoint)
    - Angiographic and IVUS follow-up in first 600 and 300 patients, respectively

# ENDEAVOR II

- **Conducted OUS**
  - Europe
  - Asia Pacific
  - Israel
  - Australia
  - New Zealand

# ENDEAVOR II

## Baseline Demographic and Clinical Characteristics

	Endeavor (N=598)		Driver (N=599)	
	N	%	N	%
Male	461	77.2%	449	75.3%
Diabetes mellitus	108/595	18.2%	132/595	22.2%
Insulin Dependent Diabetes*	27/594	4.5%	44/595	7.4%
Single Vessel Disease	387	64.8%	375	62.9%
Double Vessel Disease	140	23.5%	157	26.3%
Stable Angina	268/545	49.2%	276/543	50.8%
Unstable Angina	181/545	33.2%	181/543	33.3%
IIb/IIIa inhibitors	79/597	13.2%	62/594	10.4%

\*higher rate of Insulin Dependent Diabetes in Driver group (p=0.05)

# ENDEAVOR II

## Lesion and Vessel Characteristics

	Endeavor	Driver
Reference vessel diameter, mm*	2.73±0.48	2.76±0.49
Lesion length, mm*	14.04±5.56	14.38±5.73
Pre-procedure % Stenosis*	69.74±10.89	69.58±11.00
<b>Vessel Location</b>		
LAD	43.2%	47.5%
LCX	22.4%	21.2%
RCA	34.4%	31.3%
LMCA	0.0%	0.0%
<b>Post-procedure % Stenosis*</b>		
In-Stent	6.04±10.43	6.23±10.03
In-Segment	20.39±10.26	20.11±9.38

\*Mean±SD

# ENDEAVOR II

## Procedural Success and 30 Day MACE

- Device-specific procedure success in Endeavor-stented patients: 96.5%
- 30 Day MACE

ENDEAVOR II 30 Day MACE			
	Endeavor	Driver	Difference [95% CI]
MACE	2.9%	3.7%	-0.9% (-2.9%, 1.2%)
Q-wave MI	0.3%	0.8%	
Non Q-wave MI	2.3%	2.7%	

# ENDEAVOR II

## Primary Endpoint Results

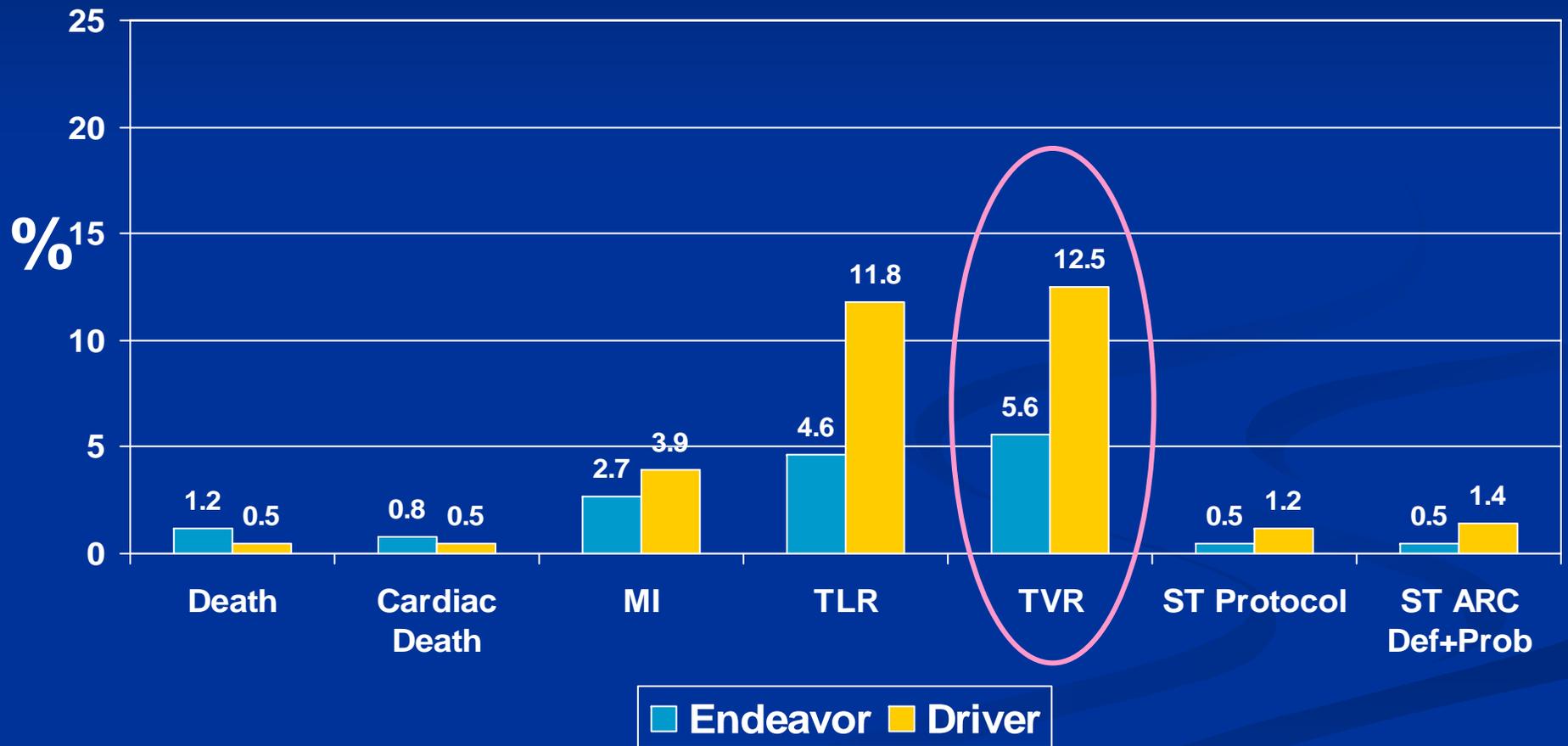
	Endeavor	Driver Control	Difference [95% CI]	P value
TVF Rate at 9 months	7.9% (47/592)	15.1% (89/591)	-7.1% [-10.7%, -3.5%]	<0.001

48% relative reduction in TVF

**Primary endpoint met**

# ENDEAVOR II

## Major Clinical Endpoint Results at 9 months



# ENDEAVOR II

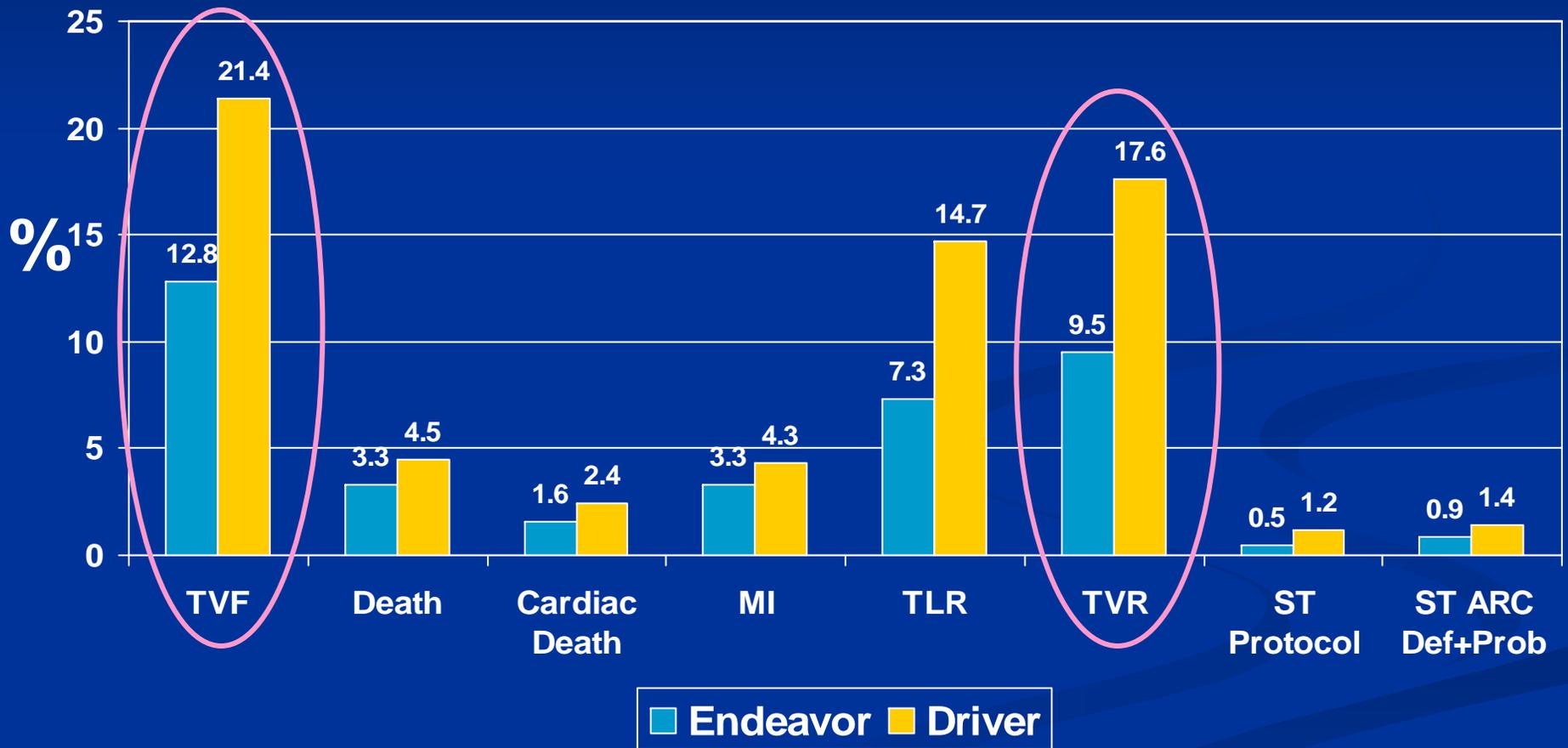
## Angiographic Results at 8 months

	Endeavor	Driver Control	Difference [95% CI]	P value
<b>In-segment late loss, mm (n)</b>	0.36±0.46 (264)	0.72±0.61 (263)	-0.36 [-0.45,-0.27]	<0.001
<b>% diameter stenosis, (n)</b>	32.67±16.27 (264)	44.33±20.45 (265)	-11.66 [-14.82,-8.50]	-
<b>Binary in-segment restenosis, %(n)</b>	13.3 (35/264)	34.7 (92/265)	-21.5 [-28.5%,-14.4%]	-
<b>IVUS Volume Obstruction, % (n)</b>	17.34±10.27 (90)	29.55±17.58 (81)	-12.22 [-16.51,-7.92]	-

**Secondary angiographic endpoint met**

# ENDEAVOR II

## Major Clinical Endpoint Results at Latest Available Follow-Up (36 months)



# ENDEAVOR III

- Randomized single-blind **non-inferiority** trial
  - Randomized 3:1 Endeavor:Cypher
- **Objective:** To demonstrate the equivalency in in-segment late loss at 8 months between the Endeavor Stent and the Cypher Stent for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter
- **Primary endpoint:** Angiographic in-segment Late Lumen Loss at 8 months
  - Equivalency margin ( $\delta$ ) = 0.20 mm
  - H0: Endeavor stent would have a mean late loss equal to or exceeding that of the Cypher stent by 0.2 mm or more
  - HA: Endeavor would have a mean in-segment late lumen loss less than the control Cypher stent plus 0.2 mm
- **Important secondary endpoints**
  - Device specific procedure success
  - Clinically-driven TLR, TVR, and TVF at 9 months
  - Total MACE and rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually to 5 years

# ENDEAVOR III

## Baseline Demographic and Clinical Characteristics

	Endeavor (N=323)		Cypher (N=113)	
	N	%	N	%
Male*	211	65.3%	92	81.4%
Diabetes mellitus	96/323	29.7%	32/113	28.3%
Insulin Dependent Diabetes	21/322	6.5%	10/113	8.8%
Single Vessel Disease	201	62.2%	66	58.4%
Double Vessel Disease	94	29.1%	34	30.1%
Stable Angina	118/274	43.1%	39/97	40.2%
Unstable Angina	140/274	51.1%	54/97	55.7%
IIb/IIIa inhibitors	142/323	44.0%	50/112	44.6%

\*higher percentage of women in Endeavor group (p=0.001)

# ENDEAVOR III

## Baseline Lesion and Vessel Characteristics

	Endeavor	Cypher
Reference vessel diameter, mm*	2.75 ± 0.46	2.79 ± 0.46
Lesion length, mm*	14.96±6.20	14.95±7.28
Pre-procedure % Stenosis*	66.81±12.40	67.91±12.42
Vessel Location		
LAD	41.2%	39.8%
LCX	23.2%	28.3%
RCA	35.6%	31.9%
LMCA	0.0%	0.0%
Post-procedure % Stenosis*		
In-Stent	4.33±9.77	5.92±9.07
In-Segment	19.38±9.25	20.17±11.74

\*Mean±SD

# ENDEAVOR III

## Procedural Success and 30 Day MACE

- Device-specific procedure success in Endeavor-stented patients: 98.1%
- 30 Day MACE

ENDEAVOR III 30 Day MACE			
	Endeavor	Cypher	Difference [95% CI]
MACE	0.6%	3.5%	-2.9% (-6.4%, 0.6%)
Q-wave MI	0	0	
Non Q-wave MI	0.6%	3.5%	

# ENDEAVOR III

## Primary Endpoint Results

	Endeavor n=323	Cypher n=113	Difference [One-sided 95% CI]	P value*
In-segment late loss at 8 months, mm (n)	0.36 ±0.46 (277)	0.13 ±0.33 (94)	0.24 [-∞, 0.32] (Prespecified non-inferiority margin 0.20)	0.791

\*test for non-inferiority

**Primary endpoint not met**

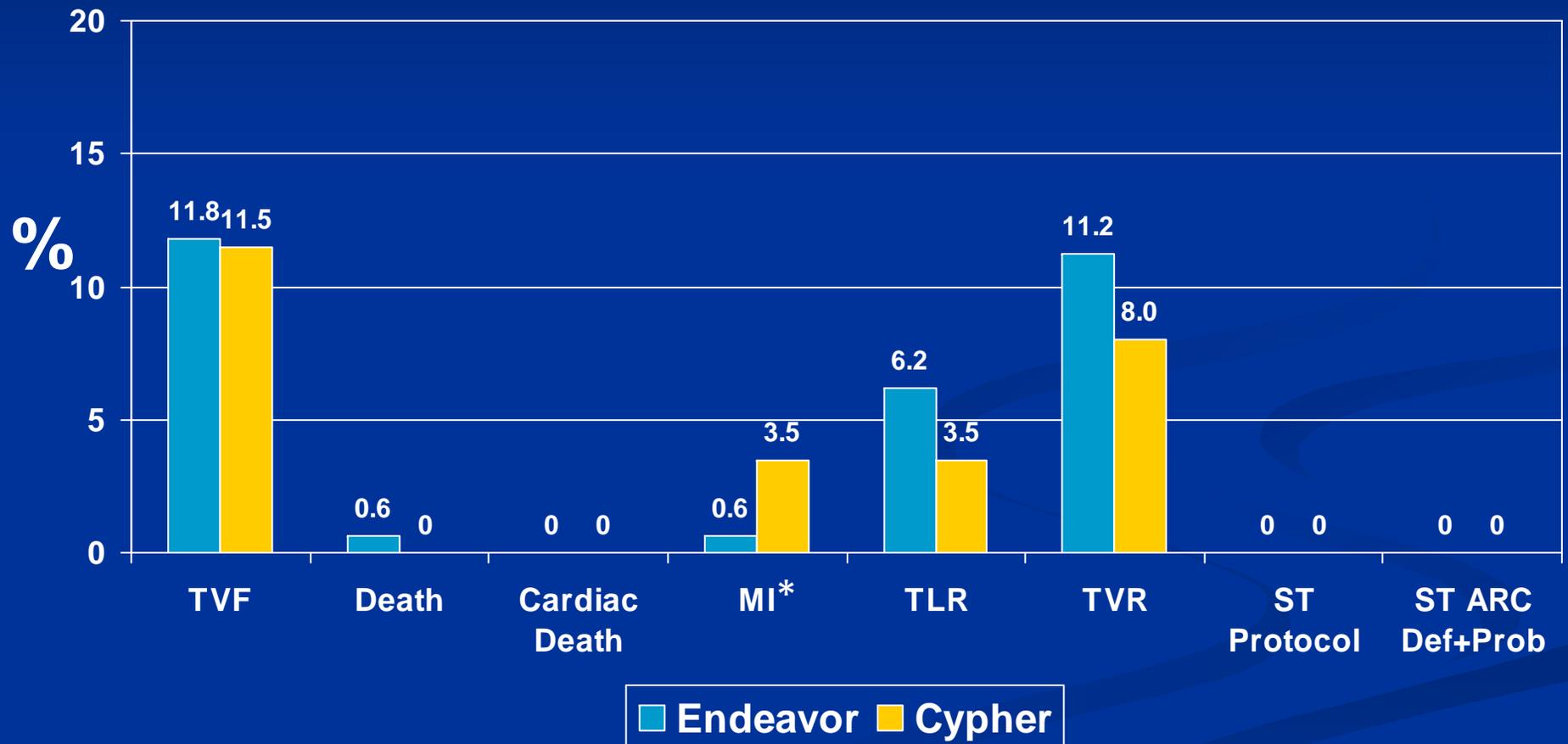
# ENDEAVOR III

## Other Angiographic and IVUS Results at 8 Months

	Endeavor	Cypher	Difference [95% CI]
% diameter stenosis (n)	30.42±15.57 (277)	23.86±13.87 (94)	6.56 [3.01,10.12]
Binary in-segment restenosis, % (n)	12.3 (34/277)	4.3 (4/94)	8.0 [2.4%,13.6%]
IVUS Volume Obstruction, % (n)	15.94±10.94 (187)	2.66±3.11 (61)	13.27 [10.48,16.07]

# ENDEAVOR III

## Major Clinical Outcomes at 9 Months

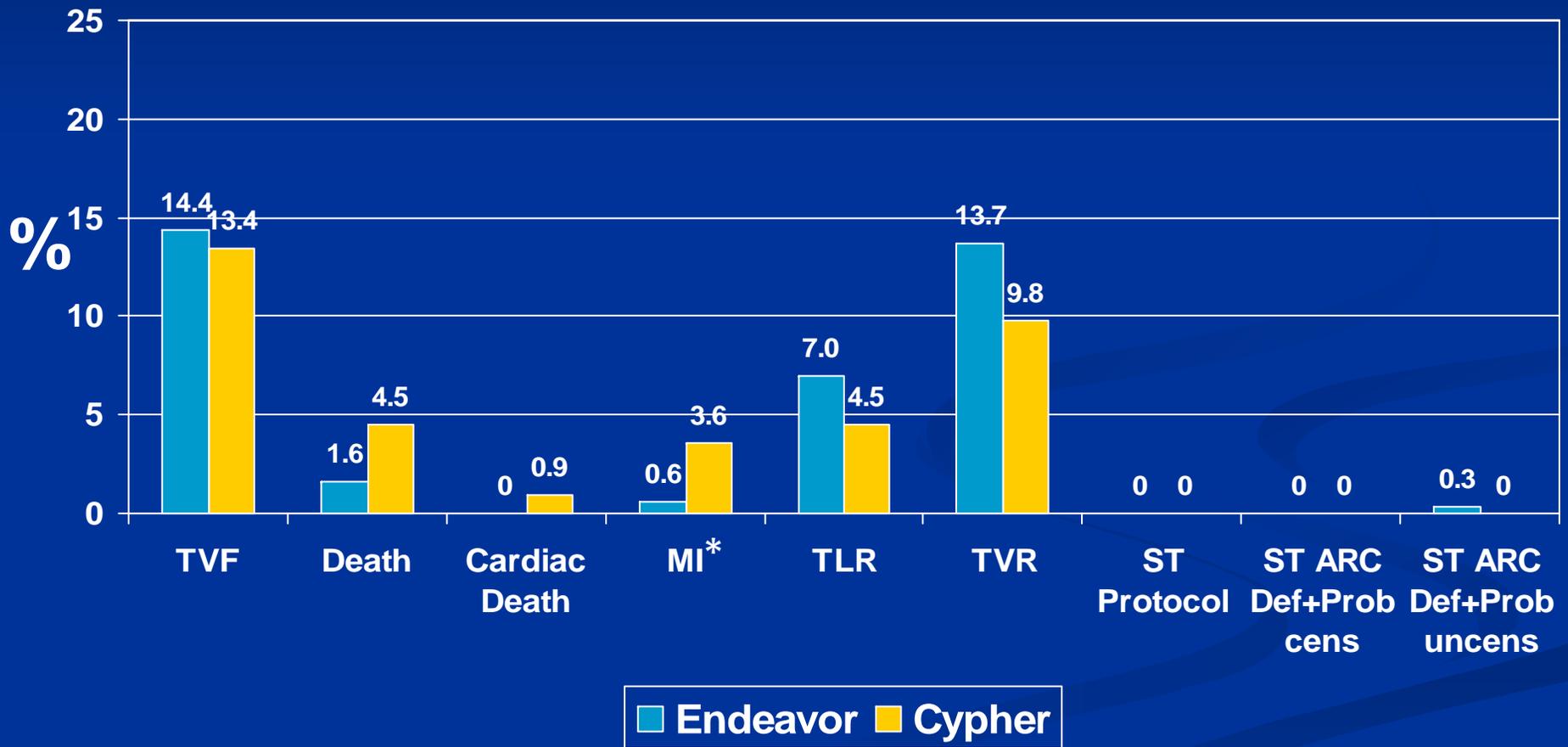


\*Non-Q MI



# ENDEAVOR III

## Major Clinical Endpoint Results at Latest Available Follow-Up (24 months)



\*Non-Q MI



# ENDEAVOR IV

- **Randomized single-blind non-inferiority trial**
- **Objective:** To assess the equivalence in safety and efficacy of the Endeavor stent compared to the Taxus stent for the treatment of single *de novo* lesions in native coronary arteries with a RVD of 2.5-3.5 mm
- **Primary endpoint:** TVF at 9 months
  - Assumed TVF rate for Endeavor and Taxus = 7.6%
  - Equivalency margin ( $\delta$ ) = 3.8%
  - H0: Endeavor stent would have a TVF rate equal to or exceeding that of the Taxus stent by 3.8% or more
  - HA: Endeavor would have a TVF rate less than the Taxus stent plus 3.8%

# ENDEAVOR IV

## Important secondary endpoints

- Device specific procedure success
- Total MACE and rates of death, MI, revascularization, and stent thrombosis at 30 days and 6, 9, and 12-months and annually to 5 years
- Angiographic in-segment late lumen loss at 8 months (powered secondary non-inferiority endpoint)
  - Angiographic and IVUS follow-up in first 328 patients
  - Equivalency margin ( $\delta$ ) = 0.20 mm
  - H0: Endeavor stent would have a mean late loss equal to or exceeding that of the Taxus stent by 0.2 mm or more
  - HA: Endeavor would have a mean in-segment late lumen loss less than the Taxus stent plus 0.2 mm

# ENDEAVOR IV

## Baseline Demographic and Clinical Characteristics

	Endeavor (N=773)		Taxus (N=775)	
	N	%	N	%
Male	517	66.9%	531	68.5%
Diabetes mellitus	241/773	31.2%	236/775	30.5%
Insulin Dependent DM	80/773	10.3%	64/775	8.3%
Single Vessel Disease	424	54.9%	443	57.2%
Double Vessel Disease	221	28.6%	202	26.1%
Stable Angina	281/616	45.6%	292/609	47.9%
Unstable Angina	318/616	51.6%	304/609	49.9%
IIb/IIIa inhibitors				
Pre-Procedure	50/209	23.9%	45/209	21.5%
During Procedure	195/209	93.3%	194/209	92.8%
Post-Procedure	154/209	73.7%	159/209	76.1%

# ENDEAVOR IV

## Baseline Lesion and Vessel Characteristics

	Endeavor	Taxus
Reference vessel diameter, mm*	2.73±0.47	2.70±0.46
Lesion length, mm*	13.41±5.67	13.80±6.09
Pre-procedure % Stenosis*	64.83±13.29	65.68±13.10
Vessel Location		
LAD	42.2%	41.5%
LCX	26.9%	26.1%
RCA	30.8%	32.4%
LMCA	0.0%	0.0%
Post-procedure % Stenosis*		
In-Stent	5.50±9.61	5.01±10.49
In-Segment	20.47±9.54	20.97±11.12

\*Mean±SD

# ENDEAVOR IV

## Procedural Success and 30 Day MACE

- Device-specific procedure success in Endeavor-stented patients: 96.5%
- 30 Day MACE

ENDEAVOR IV 30 Day MACE			
	Endeavor	Taxus	Difference [95% CI]
MACE	1.2%	3.0%	-1.8% (-3.2%, -0.4%)
Q-wave MI	0.3%	0.1%	
Non Q-wave MI	0.5%	2.2%	

# ENDEAVOR IV

## Primary Endpoint Results

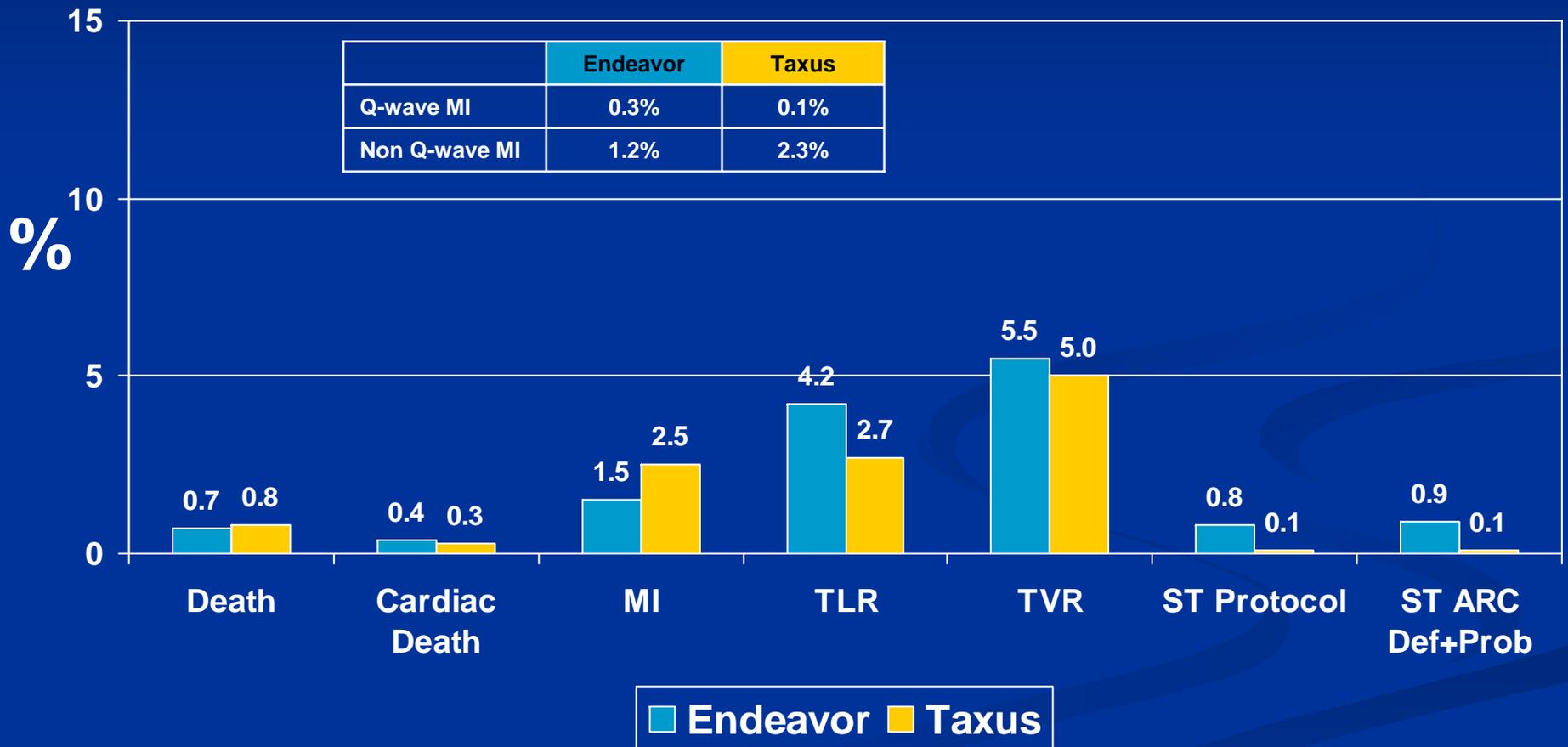
	Endeavor	Taxus	Difference [One-sided 95%CI]	P value*
<b>TVF at 9 Months</b>	6.8% (50/740)	7.4% (54/734)	-0.6% [-100%, 1.6%] (Prespecified non- inferiority margin 3.8%)	<0.001

\*test for non-inferiority

**Primary endpoint met**

# ENDEAVOR IV

## Major Clinical Outcomes at 9 Months



# ENDEAVOR IV

## Powered Secondary Endpoint Results

	Endeavor N=164	Taxus n=164	Difference [One-sided 95% CI]	P value*
In-segment late loss at 8 months, mm (n)	0.36±0.47 (143)	0.23±0.45 (135)	0.13 [-∞, 0.22] (Prespecified non- inferiority margin 0.20)	0.089

\*test for non-inferiority

**Secondary angiographic endpoint not met**

# ENDEAVOR IV

## Other Angiographic and IVUS Results at 8 Months

	Endeavor	Taxus	Difference [95% CI]
% diameter stenosis (n)	32.28±17.02 (144)	26.61±15.52 (135)	5.68 [1.83, 9.52]
Binary in-segment restenosis, % (n)	15.3 (22/144)	10.4 (14/135)	4.9 [-2.9, 12.7]
IVUS Volume Obstruction, % (n)	15.72±10.40 (74)	9.88±9.24 (77)	5.84 [2.68, 9.00]

# Non Randomized Studies

- ENDEAVOR I
- ENDEAVOR II Continued Access
- ENDEAVOR PK

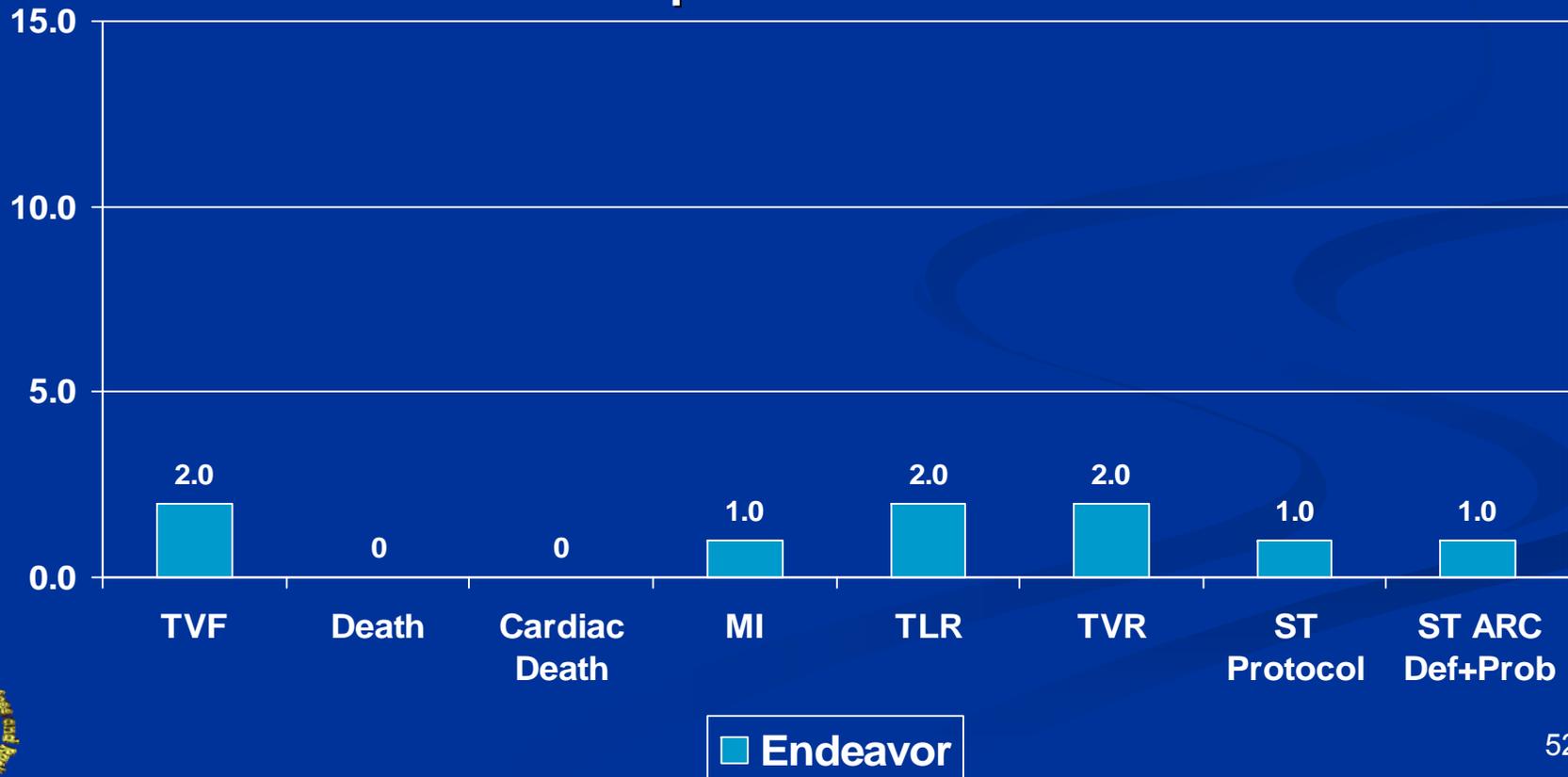
# ENDEAVOR I

- Non-randomized single arm feasibility trial
- **Objective:** To demonstrate the feasibility of the Endeavor stent for the treatment of single native coronary *de novo* lesions in
- **Primary endpoint**
  - MACE at 30 days
- **Important secondary endpoints**
  - TVF at 9 months
  - Clinically-driven TLR at 9 months

# ENDEAVOR I Clinical Results

Primary Endpoint	Endeavor (n=100)
MACE at 30 days	1.0% (1/100)

## Clinical Endpoint Results at 9 months

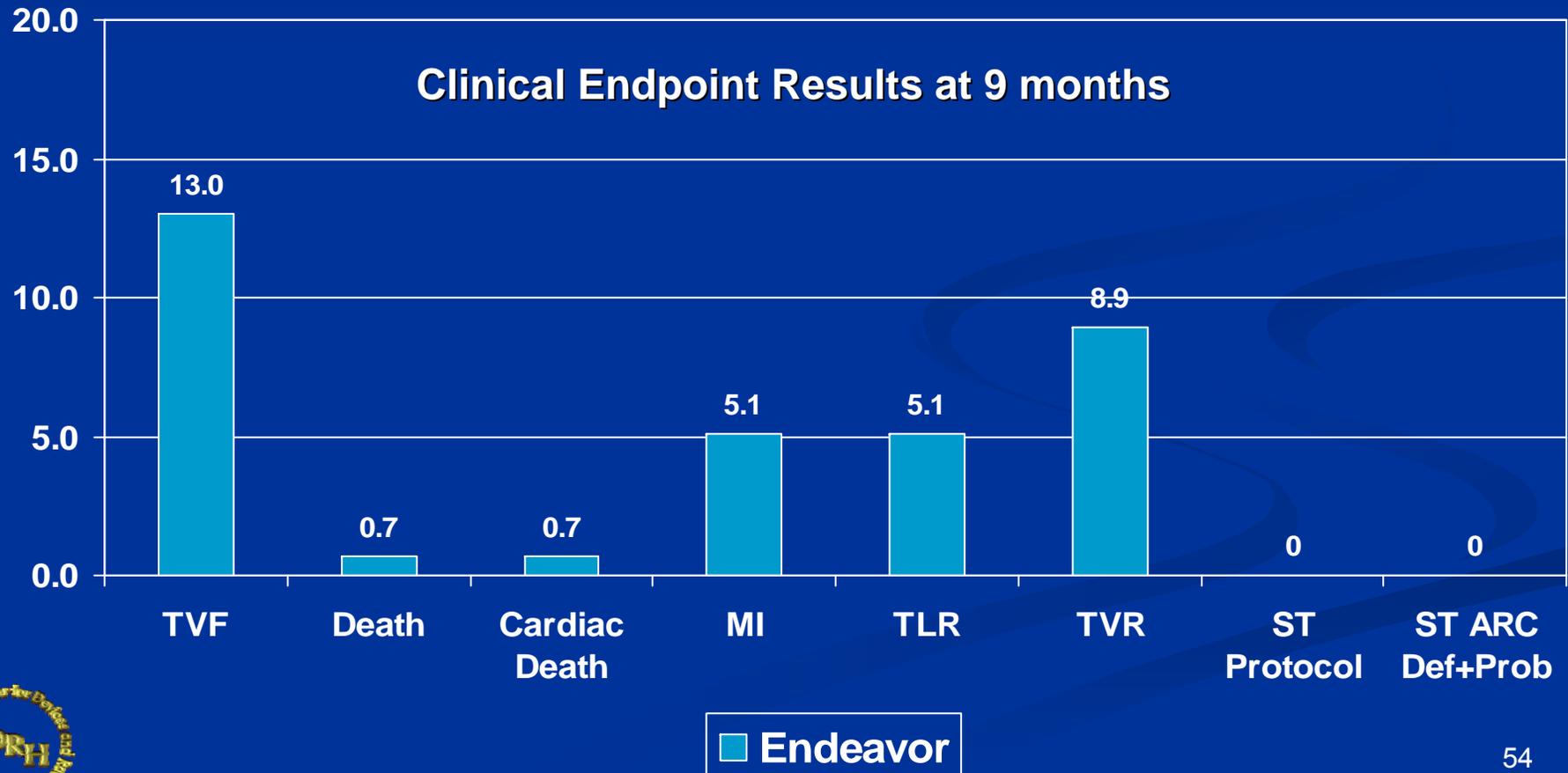


# ENDEAVOR II Continued Access (CA)

- Non-randomized single arm registry
- **Objective:** To expand the acute safety information and performance data of the Endeavor stent for the treatment of single *de novo* lesions in native coronary arteries
- **Primary endpoint:** MACE at 30 days
- **Important secondary endpoints**
  - Device specific procedure success
  - Total MACE and rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually out to five years
  - TLR, TVR, and TVF at 9 months

# ENDEAVOR II CA Clinical Results

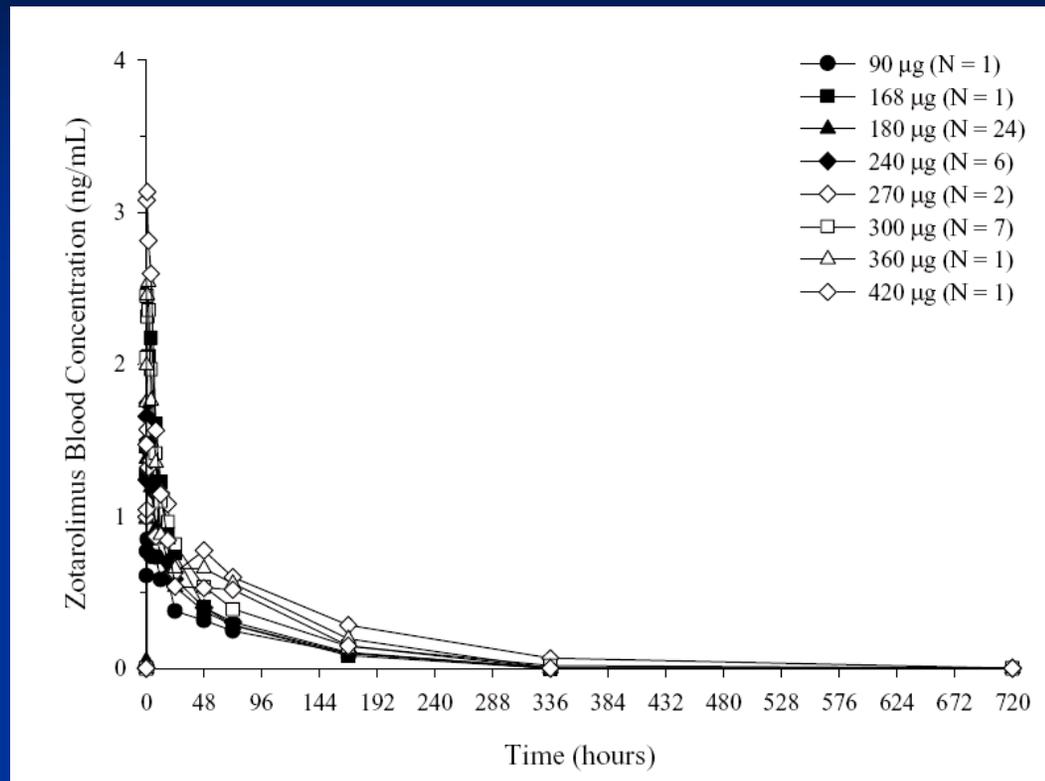
Primary Endpoint	<b>Endeavor (n=296)</b>
<b>MACE at 30 days</b>	<b>5.4% (16/296)</b>



# ENDEAVOR PK

- Non-randomized single arm trial
- **Objective:** To assess the acute pharmacokinetics and safety of zotarolimus from the Endeavor stent used to treat single *de novo* lesions in native coronary arteries
- **Primary endpoint:** Pharmacokinetic parameters
- **Important secondary endpoints**
  - Device specific procedure success
  - Total MACE and individual rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually out to 5 years
  - Clinically-driven TLR, clinically-driven TVR, and TVF at 9 months
- Patients enrolled: n=43

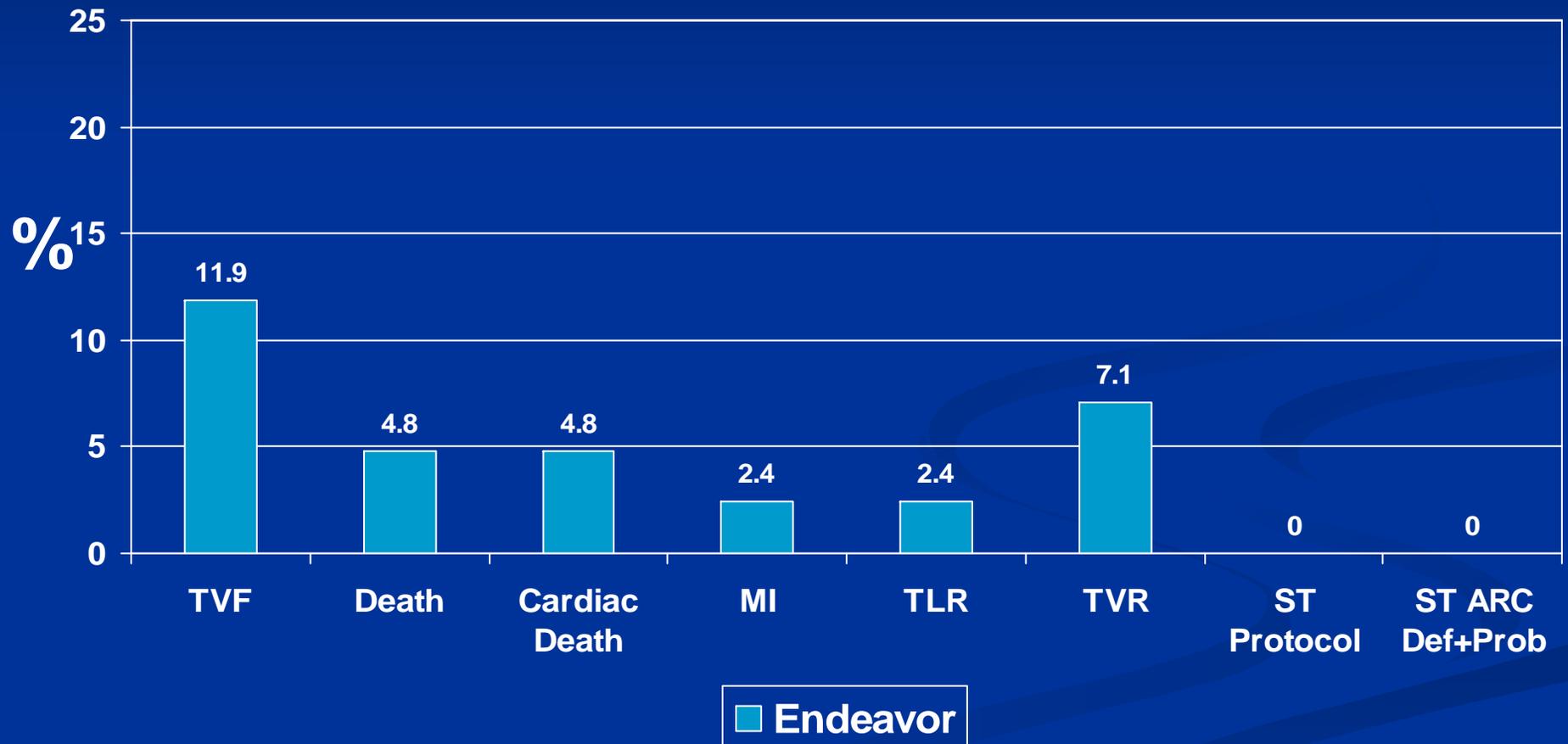
# Endeavor Stent PK Profile



**Mean Zotarolimus Blood Concentration Over Time Post-Endeavor Stent Implantation**

# ENDEAVOR PK

## Major Clinical Outcomes at 9 months



# Non Randomized Studies

- ENDEAVOR I
- ENDEAVOR II Continued Access
- ENDEAVOR PK

**Clinical results from single arm registries were qualitatively in-line with the RCT results with no apparent new safety concerns**

# Pooled Analysis

- FDA requested post-hoc analyses of clinical outcomes for patients treated with Endeavor stents pooled from the available clinical trials (ENDEAVOR I, II, II CA, III, IV, and PK)
  - All patients
  - Diabetic Patients
  - Stent thrombosis
- Follow-up through 3 years
- Patients treated with Driver stents in ENDEAVOR II are shown for comparison
  - Number at risk at 3 years = 579
- Results unadjusted for baseline covariates and multiple comparisons

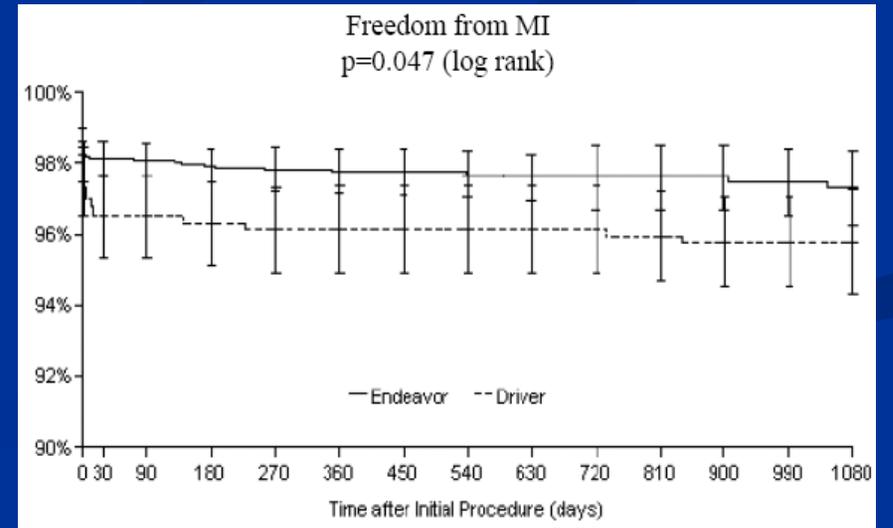
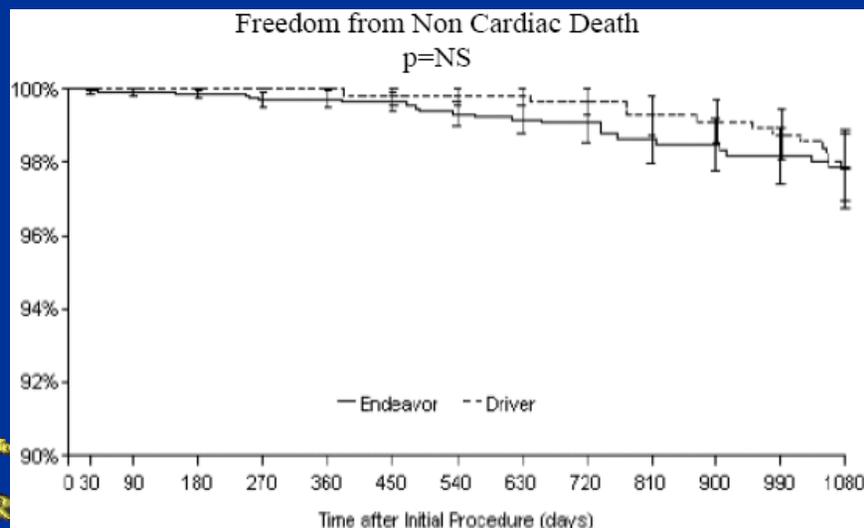
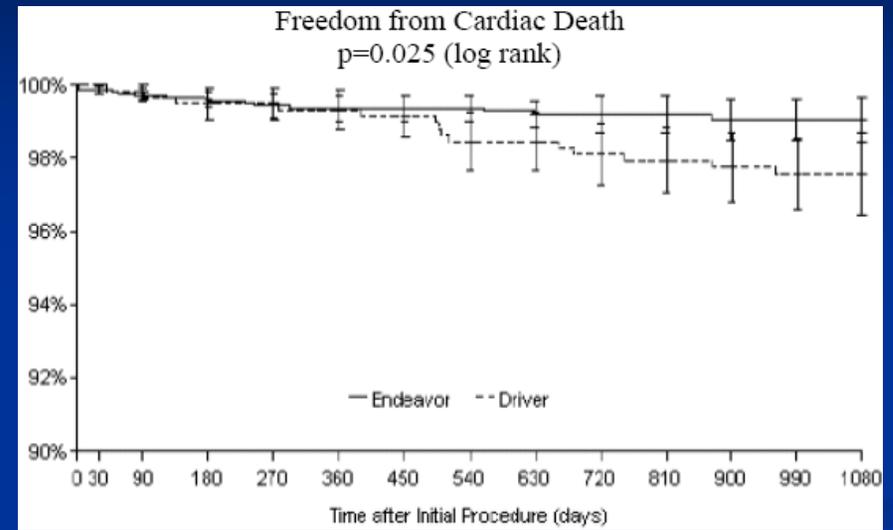
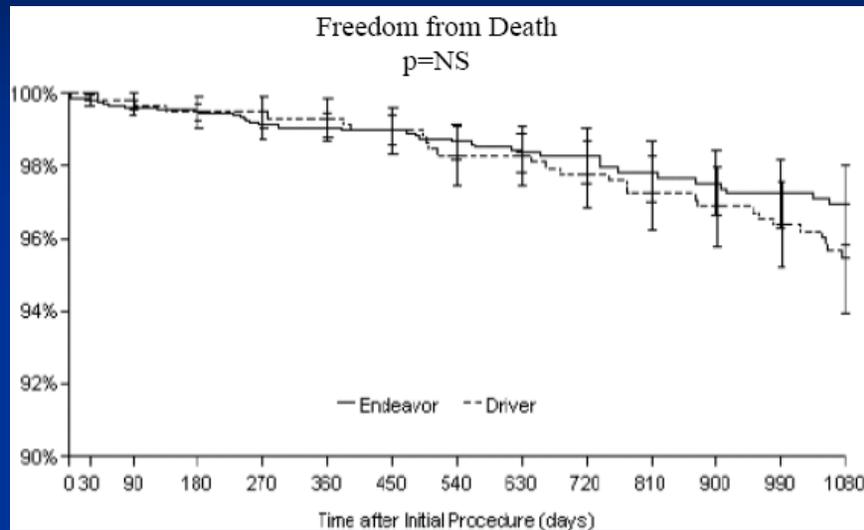
# Pooled Analysis: All Patients

- For NMEs such as zotarolimus, FDA requests a minimum 2,000 patient exposure for demonstration of drug safety
- Across the ENDEAVOR program, 2,123 patients have received the Endeavor stent, of which 1279 have been followed through 2 years

Latest Available Follow-Up: Endeavor Patients							
	30d	6m	9m	12m	2y	3y	4y
ENDEAVOR I	100	100	100	99	99	98	97
ENDEAVOR II	596	593	592	590	587	577	-
ENDEAVOR II CA	296	295	293	292	288	-	-
ENDEAVOR III	323	321	321	320	313	-	-
ENDEAVOR IV	770	766	740	-	-	-	-
ENDEAVOR PK	43	43	42	-	-	-	-
<b>Total</b>	<b>2128</b>	<b>2118</b>	<b>2088</b>	<b>1301</b>	<b>1287</b>	<b>675</b>	<b>97</b>

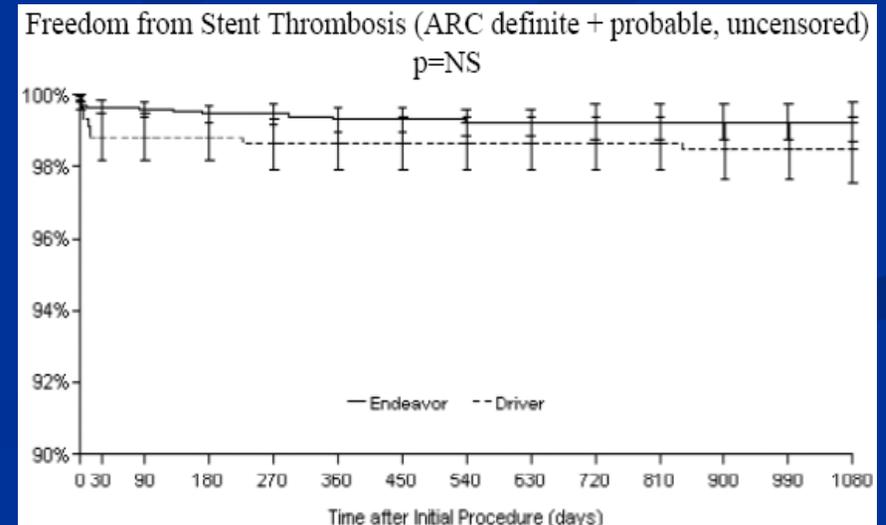
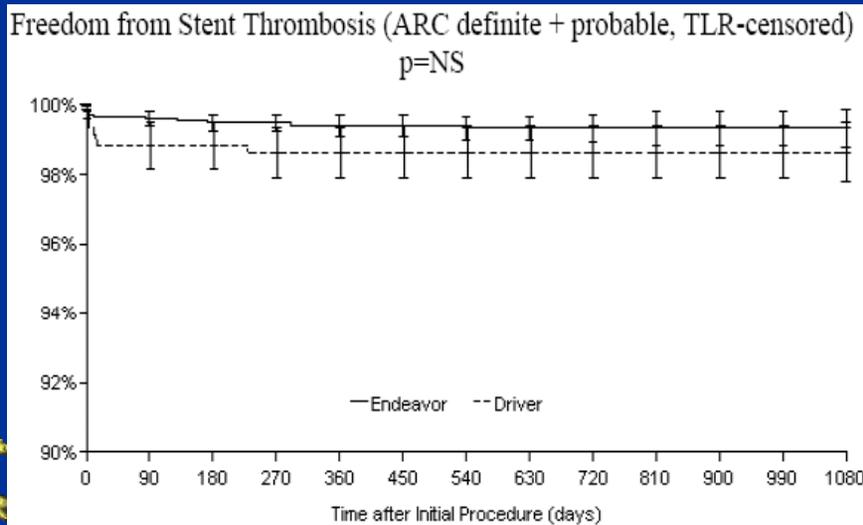
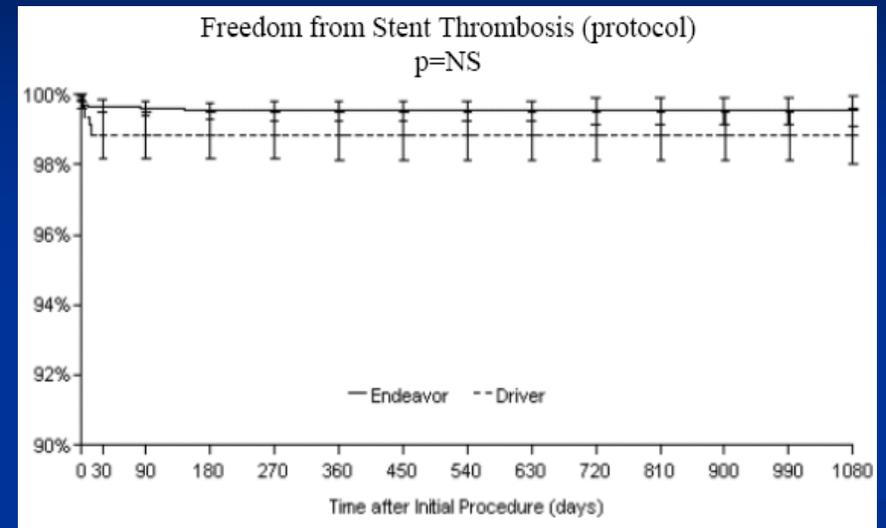
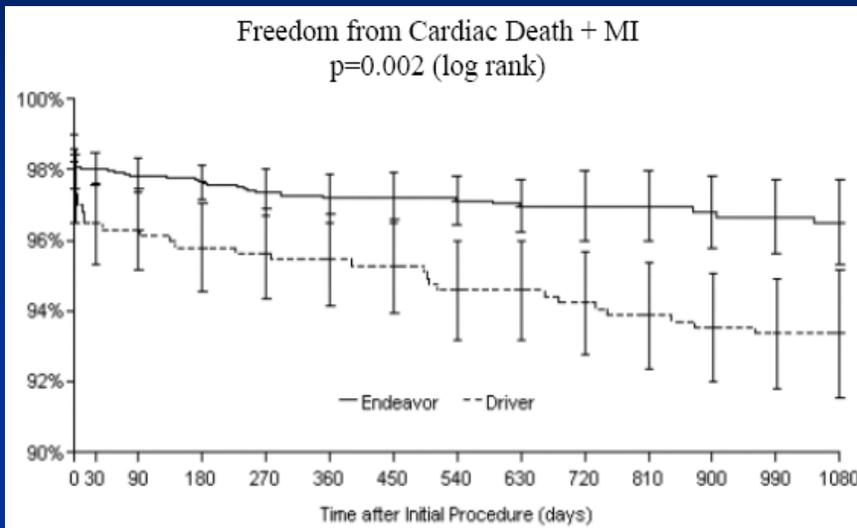
# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

## Freedom From Death, Cardiac Death, Non-Cardiac Death, MI



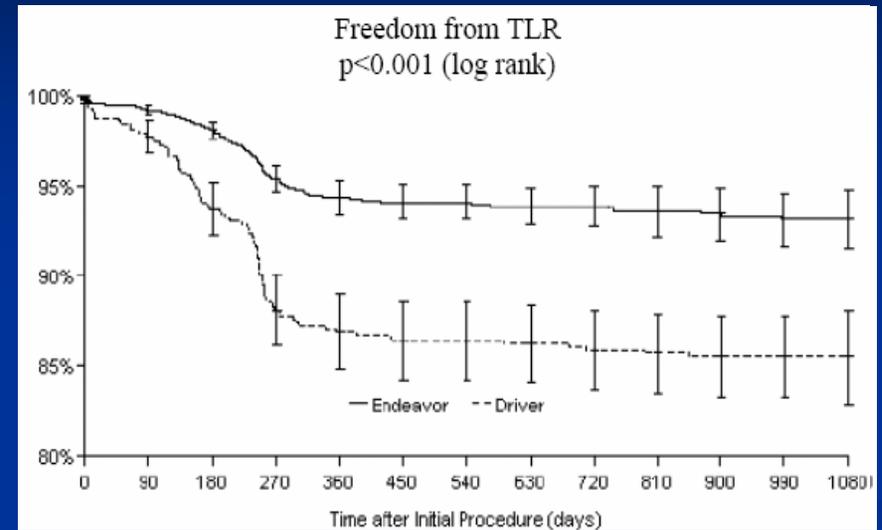
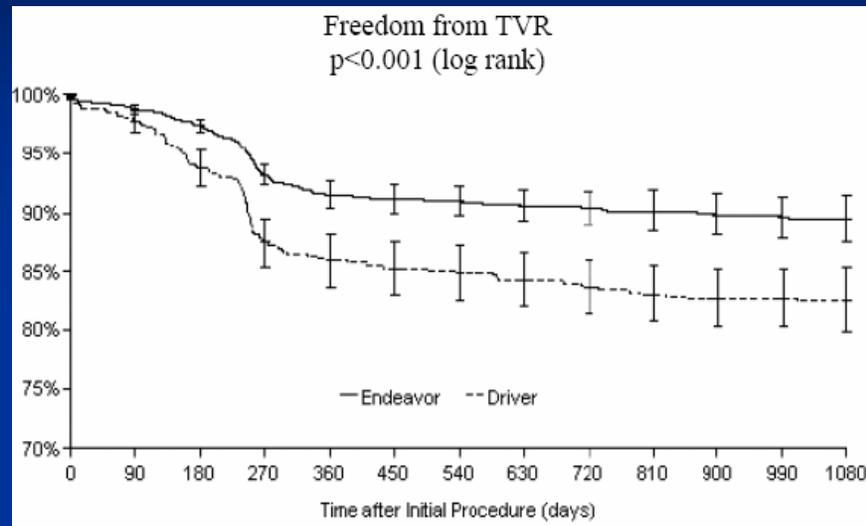
# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

## Freedom From Cardiac Death or MI, Stent Thrombosis



# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

## Freedom From TVR and TLR



# Diabetic Patients

- Diabetics comprise an important patient subgroup at increased risk for cardiovascular morbidity and mortality.
- Like previous DES applications diabetic patients were included in the Endeavor clinical trials.
- Although there were no pre-specified hypotheses or trial design features to warrant a specific labeled indication for the use of the Endeavor stent in diabetics, FDA believes that clinical outcomes in diabetics should be considered in the review of the Endeavor stent program.

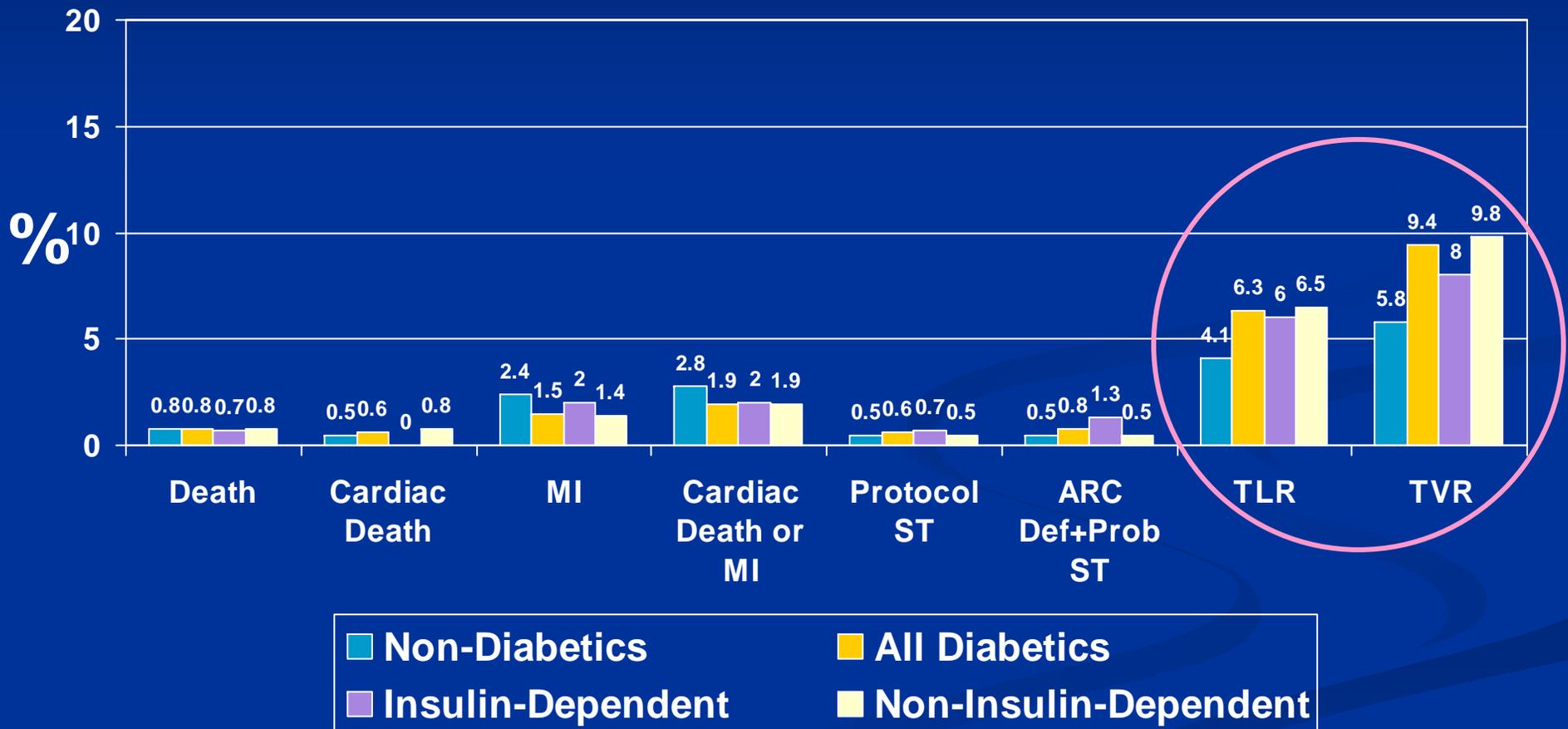
	Patients Analyzed With 270 days Follow-Up			
	Non-Diabetics	All Diabetics	Insulin-Dependent Diabetics	Non Insulin-Dependent Diabetics
<b>Pooled Endeavor EI, II, II CA, III, IV, PK</b>	1549	537	154	381
<b>Driver ENDEAVOR II</b>	463	132	44	88

# Pooled Analysis: Diabetic Patients

- FDA requested post-hoc analyses of clinical outcomes for diabetic patients treated with Endeavor stents pooled from the available clinical trials (ENDEAVOR I, II, II CA, III, IV, and PK)
  - Endeavor diabetics patients vs. Endeavor non-diabetic patients
  - Endeavor diabetic patients vs. Driver diabetic patients (ENDEAVOR II)
  - Analysis for all diabetics and stratified by insulin and non-insulin-dependent
- Clinical outcomes assessed 270 days

# Pooled Endeavor Stent-Treated Patients

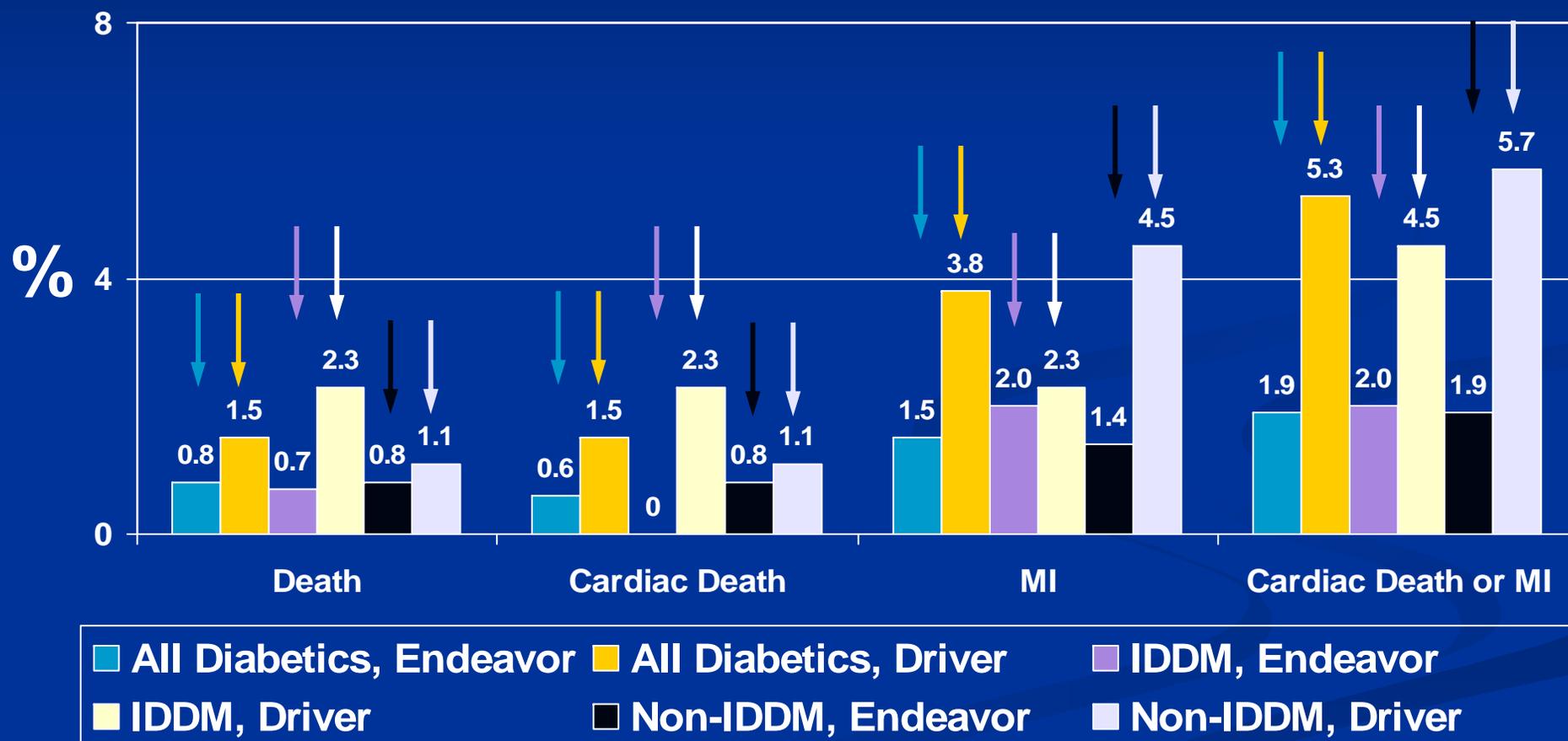
## Death, Cardiac Death, MI, Death or MI, Stent Thrombosis, TLR, TVR Diabetics vs. Non-Diabetics Through 270 Days



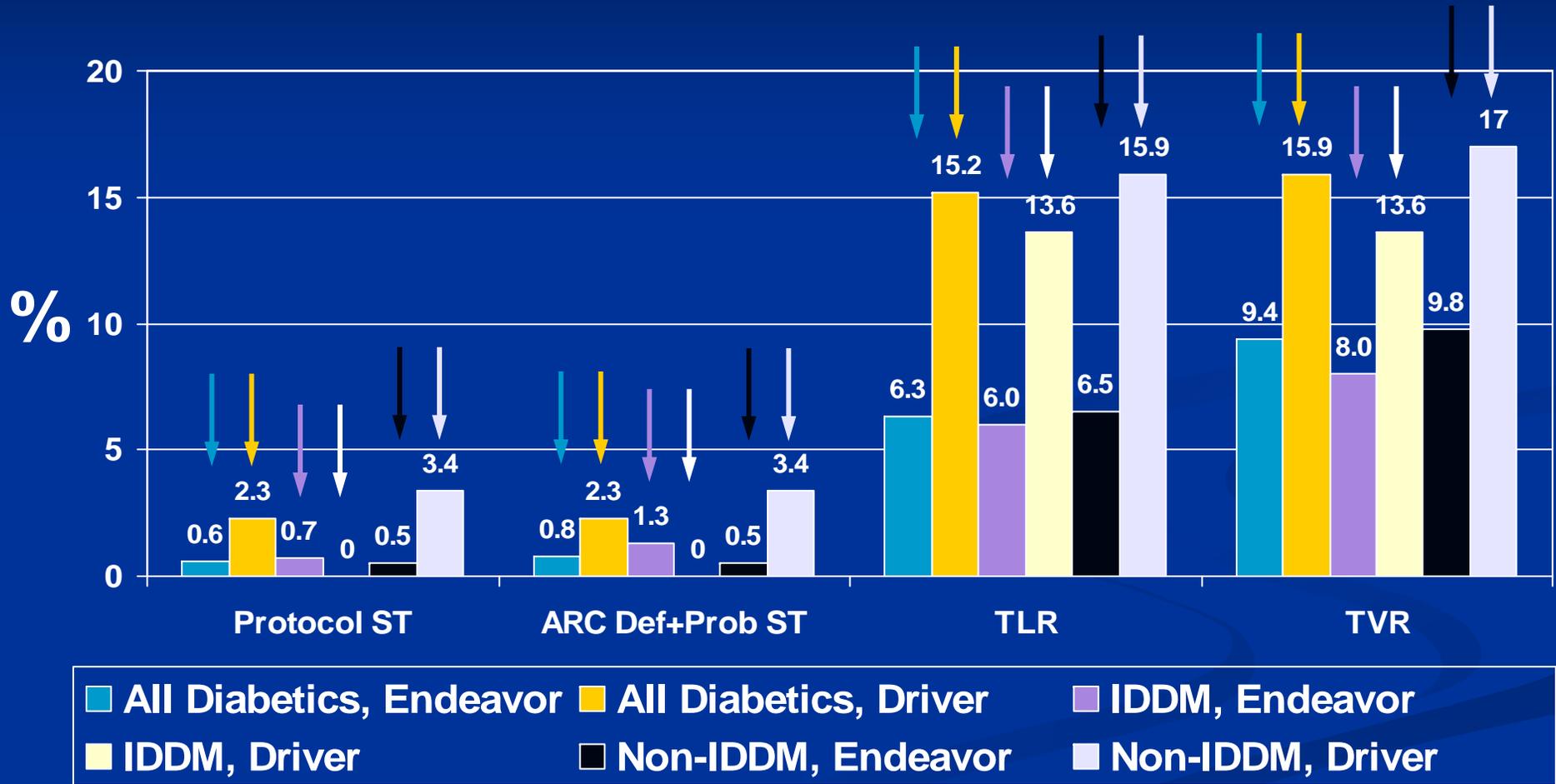
# Pooled Endeavor vs. Driver

## Death, Cardiac Death, MI, Death or MI Through 270 Days

### All Diabetics, IDDM, Non-IDDM



# Pooled Endeavor vs. Driver Stent Thrombosis, TLR, TVR Through 270 Days All Diabetics, IDDM, Non-IDDM

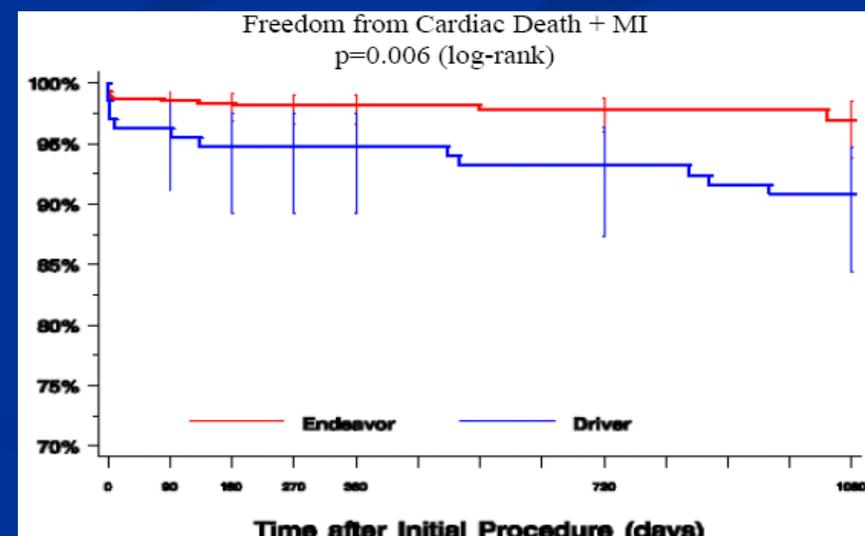
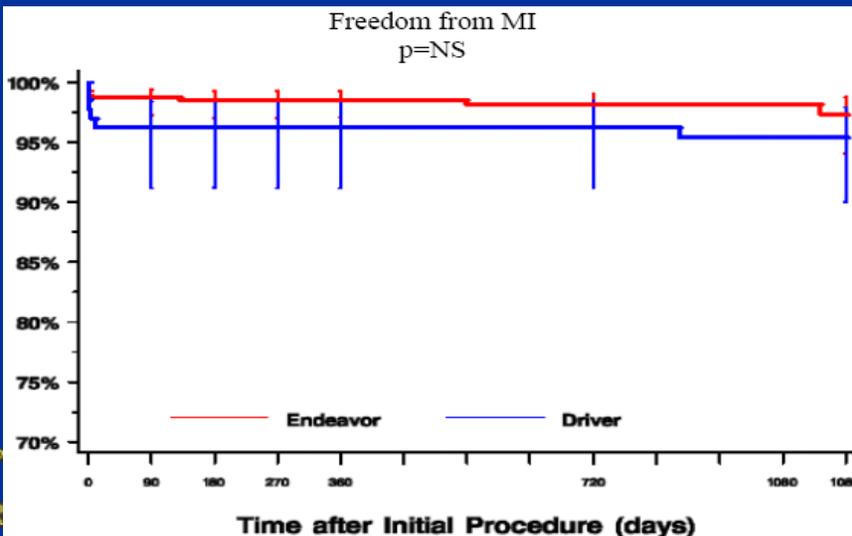
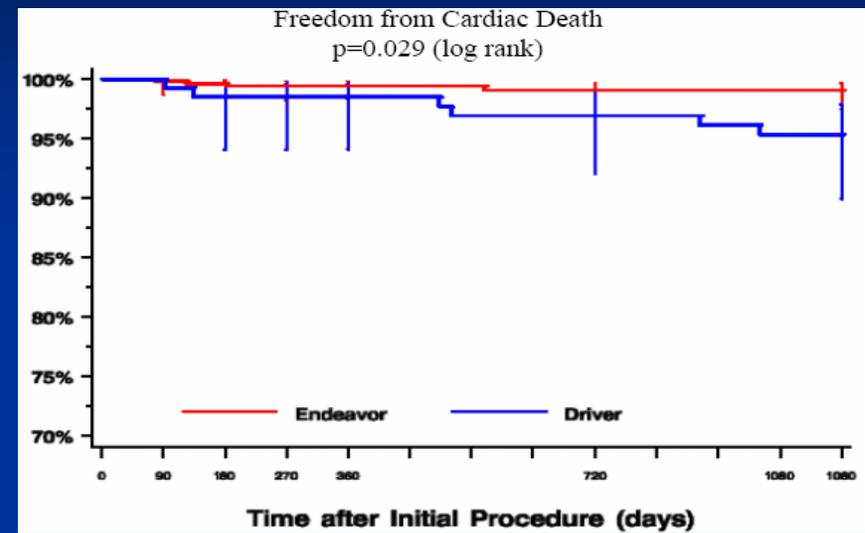
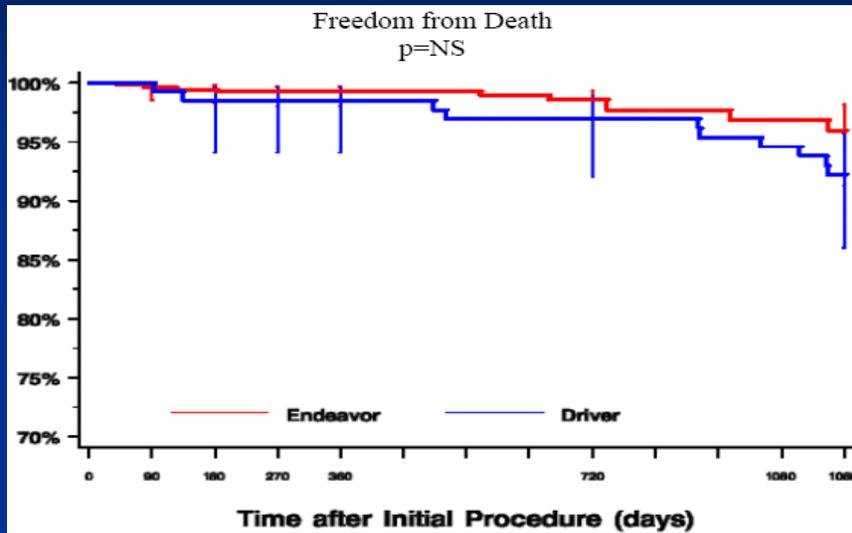


# Pooled Analysis: Diabetic Patients

- Endeavor stent treated diabetic patients pooled from ENDEAVOR I, II, II CA, III, IV, PK
- Survival analysis through 3 years
- Diabetic patients treated with Driver stents in ENDEAVOR II shown for comparison
- Results are post hoc and unadjusted for other baseline covariates and multiple comparisons

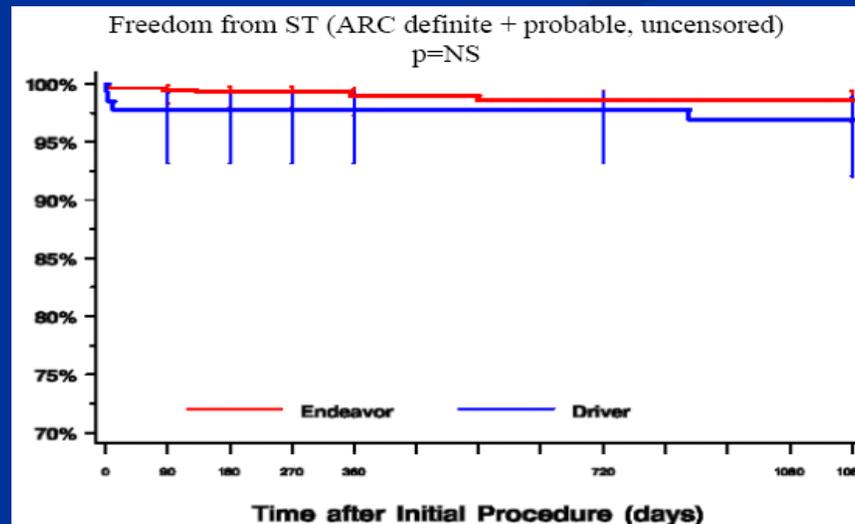
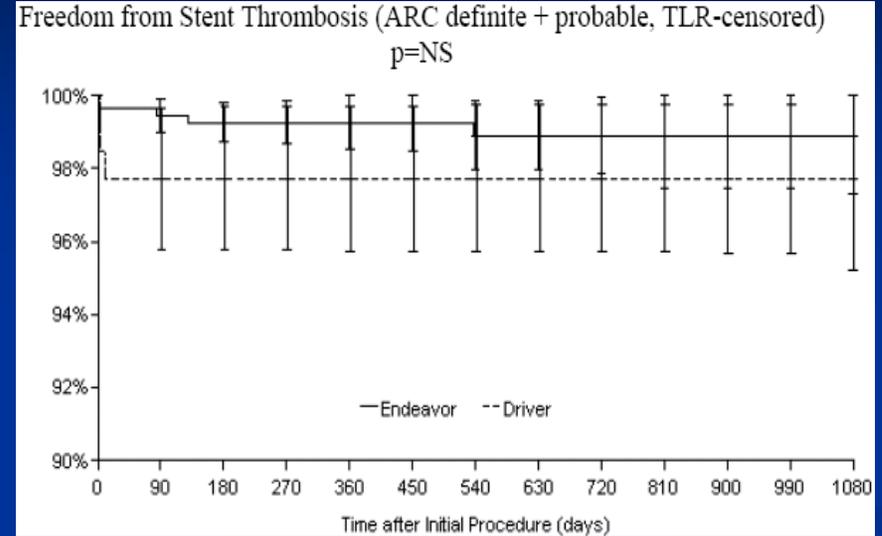
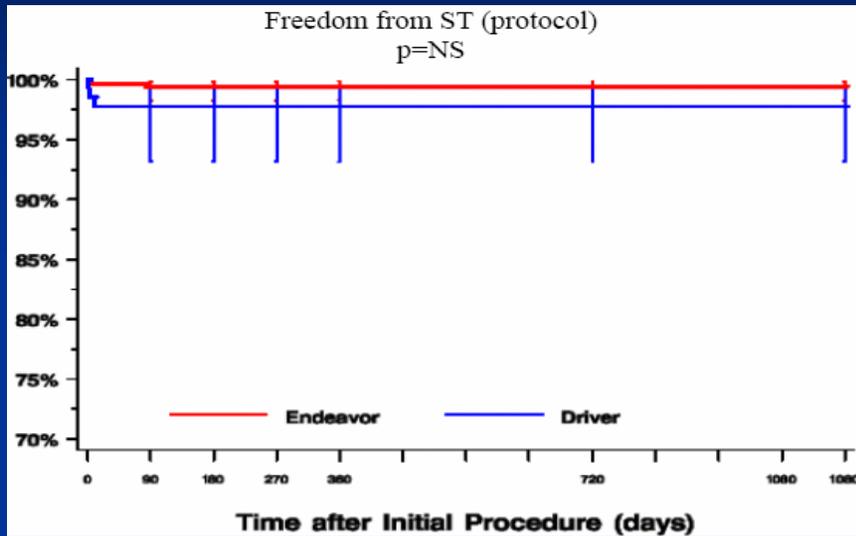
# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

## Death, Cardiac Death, MI, Cardiac Death or MI in Diabetics



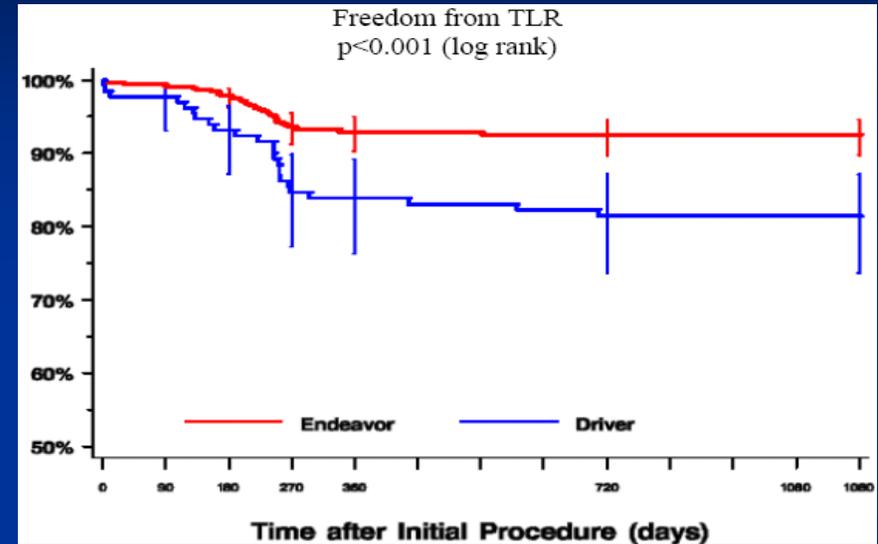
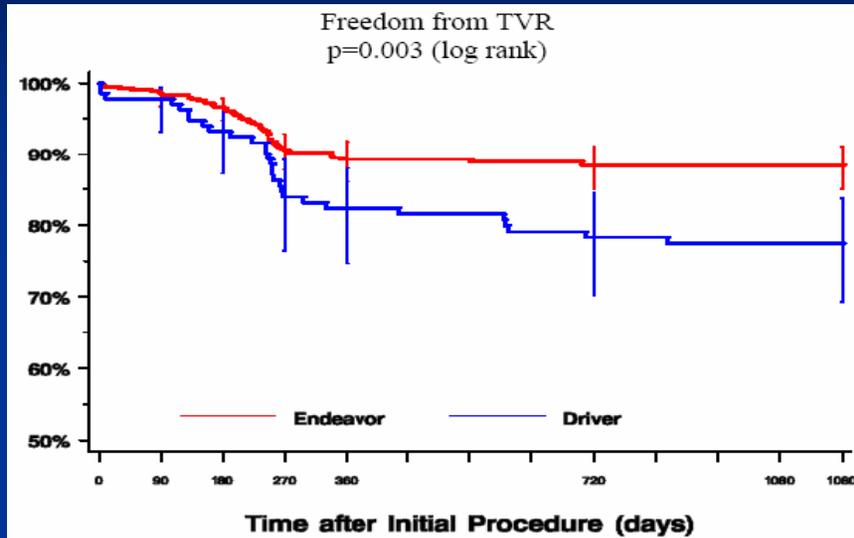
# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

## Freedom From Stent Thrombosis in Diabetics



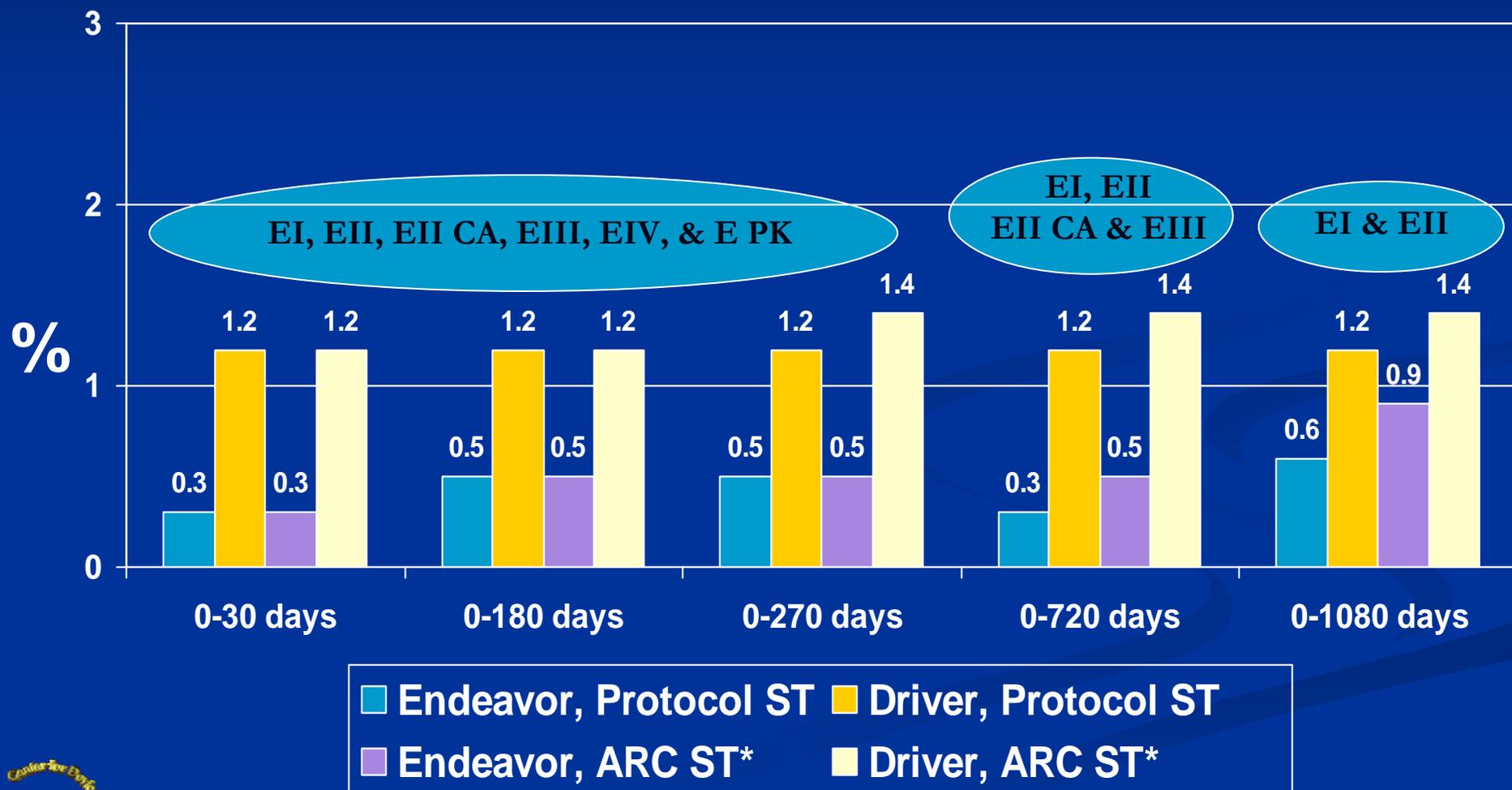
# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

## Freedom From Stent TVR and TLR in Diabetics



# Stent Thrombosis Rates

Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients



\*ARC ST reflects the definite + probable, TLR-censored definition



# Late Stent Thrombosis

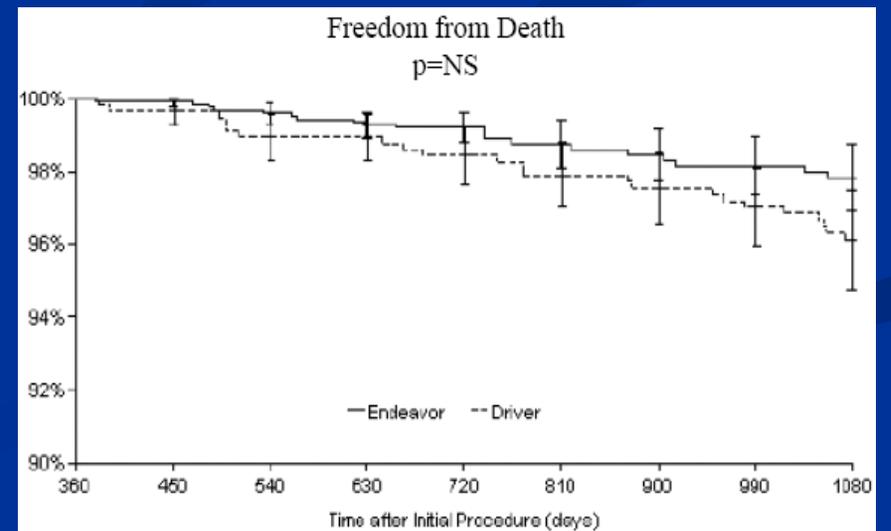
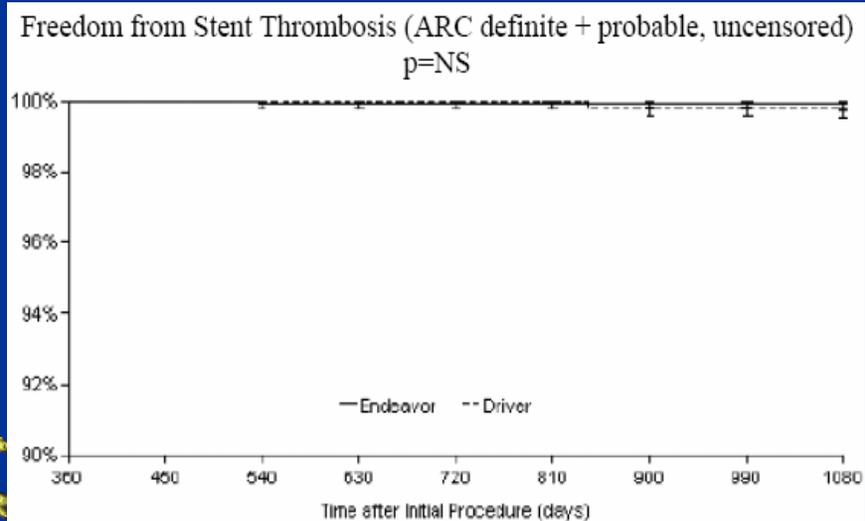
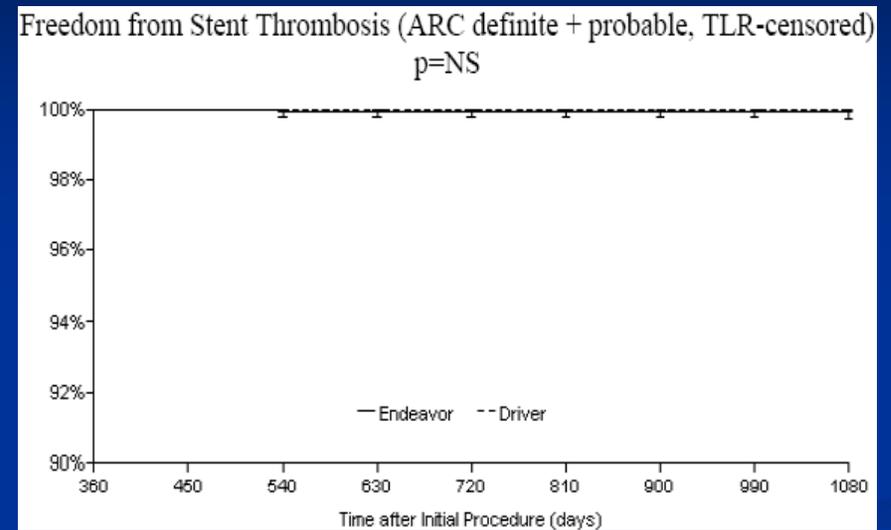
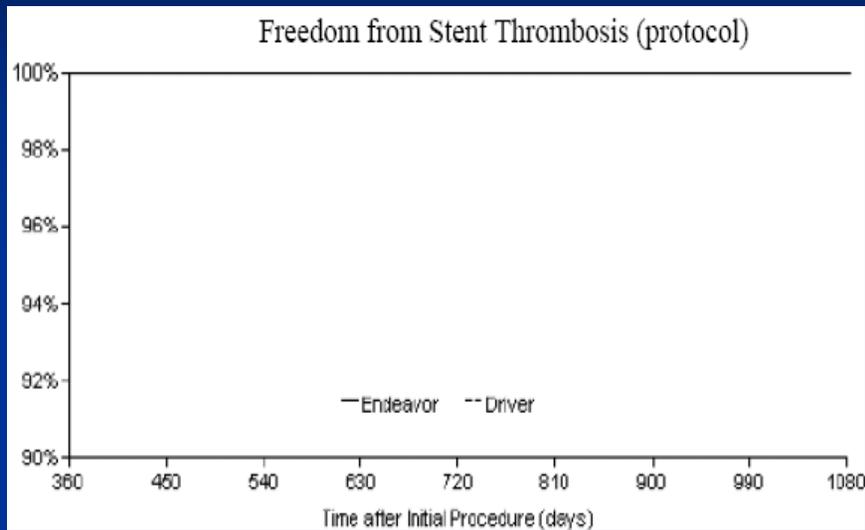
- DES that utilize drugs that interfere with the cell cycle (such as Sirolimus, Paclitaxel, and Zotarolimus) inhibit in-stent neointimal growth but also delay neointimal healing and endothelialization.
  - Prolongs the window of thrombotic risk vs. BMS
- Autopsy studies suggest that incomplete or delayed neointimal healing may be an important mechanism of late DES thrombosis.
- Although overall rates of stent thrombosis may be similar between DES and BMS, any observed increased rate of late stent thrombosis in DES patients is an important safety concern.

# Late Stent Thrombosis

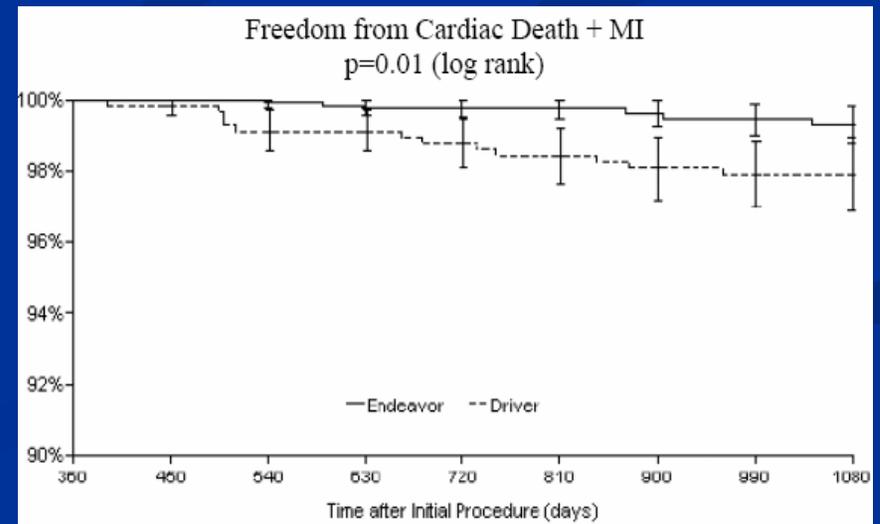
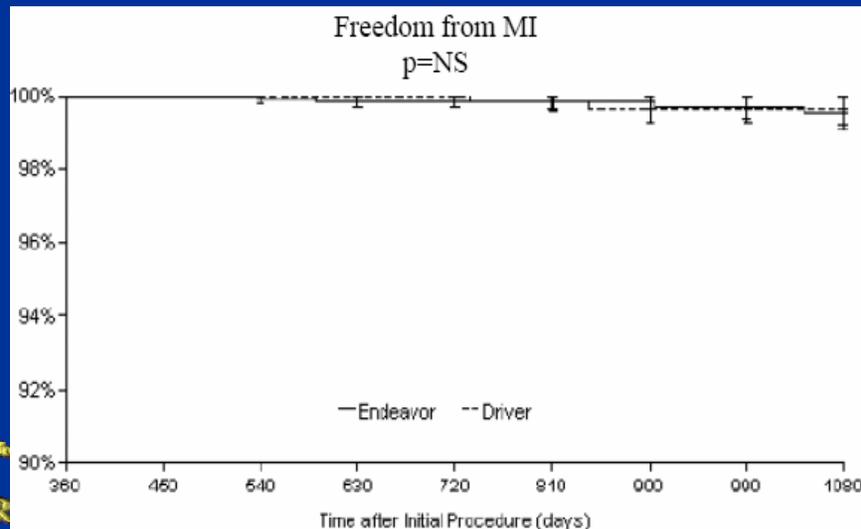
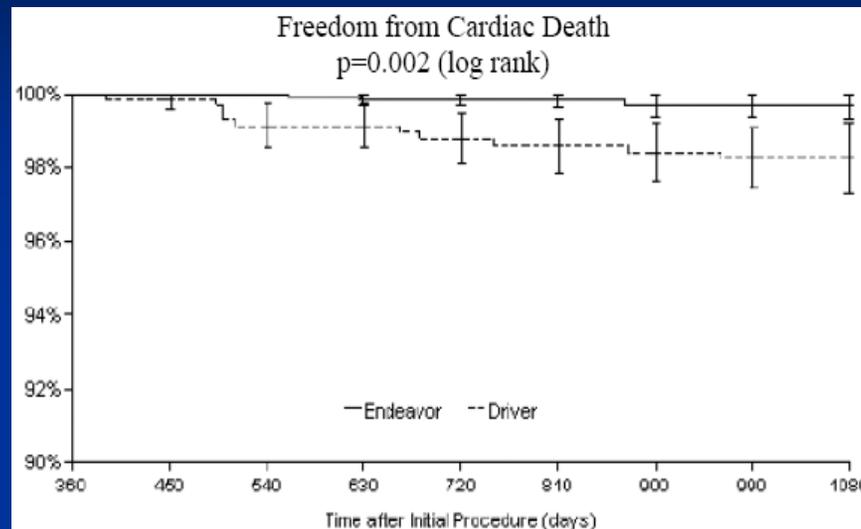
- FDA requested post-hoc analyses of data pooled from all Endeavor trials for potential signals of late cardiac death, MI, or stent thrombosis
- The following Kaplan-Meier curves depict late safety outcomes beyond the one year landmark in patients treated with Endeavor stents pooled from the Endeavor trials.
  - Patients treated with Driver stents in ENDEAVOR II are shown for comparison
  - Results are unadjusted for covariate imbalance and multiplicity

Number at Risk	1 year	2 years	3 years
Pooled Endeavor	1301	1287	675
Driver (ENDEAVOR II)	589	586	579

# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients Freedom From Stent Thrombosis, Death Beyond 1 Year



# Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients Cardiac Death, MI, Cardiac Death or MI Beyond 1 Year



# ENDEAVOR Patients Incomplete Stent Apposition

Difference	ENDEAVOR I*	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
ISA at Post-Procedure	12.6% (12/95)	24.8% (36/145)	12.4% (31/251)	12.5% (17/136)
ISA at 8 Month Follow-up	4.7% (4/86)	16.8% (21/125)	7.5% (17/226)	10.0% (12/120)
Resolved	8.1% (7/86)	7.0% (8/114)	5.8% (11/189)	3.8% (4/106)
Persistent	4.7% (4/86)	17.5% (20/114)	7.9% (15/189)	8.5% (9/106)
Late Acquired	0.0% (0/86)	0.0% (0/114)	0.5% (1/189)	0.9% (1/106)

\*ENDEAVOR I values are based on 12 month follow up

# Dual Antiplatelet Therapy Per Protocol

ENDEAVOR I, II, II CA, III, PK	ASA indefinitely + Clopidogrel or Ticlopidine for at least <b>3 months</b>
ENDEAVOR IV*	ASA indefinitely + Clopidogrel or Ticlopidine for at least <b>6 months</b>

\*At least 6 months of dual antiplatelet therapy used in ENDEAVOR IV to match the Taxus stent labeled recommendation

# ENDEAVOR Patients

## Dual Antiplatelet Therapy Use At 6 Months

	ENDEAVOR II (N=598)	ENDEAVOR II CA (N=296)	ENDEAVOR III (N= 323)	ENDEAVOR IV (N=773)
<b>Aspirin</b>	96.9% (561/579)	95.1% (272/286)	95.9% (303/316)	95.8% (713/744)
<b>Clopidogrel</b>	65.5% (377/576)	59.4% (170/286)	90.1% (264/293)	94.8% (697/735)
<b>Ticlopidine</b>	2.1% (12/569)	0% (0/287)	6.1% (2/33)	29.4% (5/17)
<b>Aspirin + Clopidogrel or Ticlopidine</b>	<b>64.8%</b> <b>(375/579)</b>	<b>55.9%</b> <b>(161/288)</b>	<b>81.6%</b> <b>(258/316)</b>	<b>92.3%</b> <b>(687/744)</b>

# Summary

## ■ Clinical endpoints

- Endeavor stent **met** its primary TVF superiority endpoint vs. the bare metal Driver stent (ENDEAVOR II)
- Endeavor stent **met** its primary TVF non-inferiority endpoint vs. the Taxus stent (ENDEAVOR IV)

## ■ Angiographic endpoints

- Endeavor stent **met** its late loss endpoint vs. the bare metal Driver stent (ENDEAVOR II)
- Endeavor stent **failed to meet** its non-inferiority late loss endpoint endpoints vs. the Cypher (ENDEAVOR III) and Taxus (ENDEAVOR IV) stents

# Safety

- The Endeavor clinical studies include a total of 2,133 patients assigned to receive Endeavor stents with 1,287 patients followed out to 24 months
- For the individual randomized trials (ENDEAVOR II, III, and IV), increased rates of death, cardiac death, MI, cardiac death or MI, or noncardiac death for the Endeavor stent vs. the control stents have not been observed
- Outcomes from an analysis of patients treated with Endeavor stents pooled from the submitted Endeavor clinical trials did not demonstrate unanticipated safety signals

# **FDA Statistical Review**

## **Endeavor Zotarolimus-Eluting Coronary Stent**

Yonghong Gao, PhD  
Gary Kamer, MS

Division of Biostatistics  
Office of Surveillance and Biometrics  
October 10, 2007

# Trial Overview

Six prospectively designed studies to evaluate the Endeavor Zotarolimus-Eluting Coronary Stent System

Trial	#Center	Endeavor Patients	Control Patients
EI	8	100	0
<b>EII</b>	<b>72</b>	<b>598</b>	<b>599 BMS</b>
EII CA	15	296	0
<b>EIII</b>	<b>29 (US)</b>	<b>323</b>	<b>113 Cypher</b>
<b>EIV</b>	<b>80 (US)</b>	<b>773</b>	<b>775 Taxus</b>
EPK	6 (US)	43	0

## Endeavor II

- Objective: superiority to Driver bare metal stent (BMS)
- Primary endpoint: TVF at 9-month
- Powered secondary endpoint: in-segment late loss at 8-month
- 1:1 randomization to DES or BMS:  
598 DES patients and 599 BMS patients, all **OUS**  
powered at 90% with 2-sided 5% type I error rate
- Angiographic subgroup: first 600 consecutively enrolled were evaluated for late loss

# Results of Endeavor II: TVF

- Primary endpoint: TVF at 9-month
- Superiority hypotheses:

$$H_0: P_e = P_c$$

$$H_a: P_e \neq P_c$$

	Enrolled	Available	TVF rate	DES - BMS 95% CI	p-value
DES	598	592	7.9%	-7.1% (-10.7%, -3.5%)	<0.001
BMS	599	591	15.1%		

- 14 pts (6 Endeavor vs. 8 Driver) were excluded from the analysis

# Missing Data: EII TVF

Sensitivity analysis:

TVF at 9-month	Endeavor DES (N=598)	Driver BMS (N=599)	Endeavor –Driver (95% CI)	p-value
<b>Multiple imputation</b>	<b>8.1%</b>	<b>15.4%</b>	<b>-7.3%</b> <b>(-9.0%, -5.5%)</b>	<b>&lt;0.001</b>
<b>Worst case</b>	<b>8.9%</b> <b>(53/598)</b>	<b>14.9%</b> <b>(89/599)</b>	<b>-6.0%</b> <b>(-9.6%, -2.3%)</b>	<b>0.002</b>
<b>Available case</b>	<b>7.9%</b> <b>(47/592)</b>	<b>15.1%</b> <b>(89/591)</b>	<b>-7.1%</b> <b>(-10.7%, -3.5%)</b>	<b>&lt;0.001</b>

- Same conclusion for all analyses: met the endpoint

## Results of Endeavor II: Late Loss

- Powered secondary endpoint: 8-month late loss in mm
- Superiority hypotheses:

$$H_0: \mu_e = \mu_c$$

$$H_a: \mu_e \neq \mu_c$$

	Available patients	mean	SD	Difference (DES - BMS) 95% CI	p-value
DES	262	0.36	0.46	-0.36, (-.452, -.267)	<0.001
BMS	263	0.72	0.61		

- 73 pts (34 DES vs. 39 BMS) were excluded from the analysis

# Missing Data: EI Late Loss

## Sensitivity analysis:

Late Loss	Endeavor (N=298) Mean $\pm$ SD	Driver (N=302) Mean $\pm$ SD	Endeavor – Driver, 2-sided 95%CI	p- value
Multiple imputation	0.35 $\pm$ 0.53	0.73 $\pm$ 0.63	-0.38, (-0.47,0.29)	<.001
Worst case	0.57 $\pm$ 0.74	0.57 $\pm$ 0.68	0.00, (-0.12, 0.11)	0.975
Available case	0.36 $\pm$ 0.46 (264)	0.72 $\pm$ 0.61 (263)	-0.36, (-0.45, -.27)	<0.001

- Multiple imputation and the available case analysis: met the endpoint
- Worst case analysis: failed to meet the criteria<sup>89</sup>

# Endeavor III

- Objective: non-inferior to Cypher in 8-month late loss

$$H_0: \mu_e \geq \mu_c + \delta$$

$$H_a: \mu_e < \mu_c + \delta$$

non-inferiority margin  $\delta=0.2\text{mm}$

- 3:1 randomization to Endeavor DES versus Cypher:  
323 Endeavor patients vs. 113 Cypher patients
- Powered at 90% with 1-sided alpha of 5%

# Non-inferiority Testing

- To demonstrate the test device is not worse than the control by more than the allowable margin
- Allowable margin is called non-inferiority margin (delta)
- Non-inferiority hypotheses
$$H_0: \mu_e \geq \mu_c + \delta$$
$$H_a: \mu_e < \mu_c + \delta$$
- Pre-specify the margin in the protocol
- One-tailed testing and one-sided confidence interval

## Results of Endeavor III: Late Loss

	Available (treated)	Mean (SD)	Endeavor - Cypher	Upper bound of 1-sided 95% CI	p- value*
EIII	277 (323)	0.36 (0.46)	0.23	0.32	0.791
Cypher	94 (113)	0.13 (0.33)			

- 14.6%=65/436 pts were excluded from the analysis  
46 Endeavor pts vs. 19 Cypher pts

# Missing Data: EIII Late Loss

## Sensitivity analysis

Late Loss	Endeavor (N=323) Mean±SD	Cypher (N=113) Mean±SD	Difference, Upper Bound of 1-sided 95% CI	p- value*
Multiple imputation	0.35± 0.50	0.17± 0.74	DIFF = 0.18 UB = 0.30	0.607
Worst case	0.63± 0.77	0.01± 0.40	DIFF = 0.62 UB = 0.74	0.995
Available case	0.36± 0.46 (277)	0.13± 0.33 (94)	DIFF = 0.24 UB = 0.32	0.791

- Same conclusion for all analyses: failed to show non-inferiority

# Baseline Covariates

- EII: statistically-significant covariate imbalance between the two arms was observed for gender:
  - 34.7% females for Endeavor vs. 18.6% for Cypher
- Propensity score analysis was performed, but the results of EII remained essentially unchanged

## Endeavor IV

- Objective: non-inferior to Taxus DES
- Primary endpoint: 9-month TVF
- Powered secondary endpoint: 8-month late loss
- 1:1 randomization to Endeavor DES or Taxus  
773 Endeavor patients vs. 775 Taxus patients  
powered at 84% with 1-sided 5% type I error rate
- First 328 consecutively enrolled pts (164 pts per arm) were evaluated for 8-month late loss  
powered at 80% with 1-sided 5% type I error rate

## Results of Endeavor IV: TVF

- Primary endpoint: TVF at 9-month
- Non-inferiority hypotheses:

$$H_0: P_e \geq P_c + \delta$$

$$H_a: P_e < P_c + \delta, \quad \text{non-inferiority margin } \delta = 3.8\%$$

	Available (enrolled)	TVF rate	Endeavor – Taxus	Upper bound of 1-sided 95% CI	p- value*
EIV	740 (773)	6.8% =50/740	-0.6%	1.6%	< 0.001
Taxus	734 (775)	7.4% =54/734			

- 74 pts excluded: 33 Endeavor vs. 41 Taxus

# Missing Data: EIV TVF

## Sensitivity analysis

TVF	Endeavor (N=773)	Taxus (N=775)	Difference Upper Bound of 1-sided 95% CI	p- value*
Multiple imputation	7.7%	8.0%	DIFF=-0.4% UB=1%	<0.001
Worst case	10.7% (83/773)	7.0% (54/775)	DIFF=3.8% UB=6.1%	0.492
Available case	6.8% (50/740)	7.4% (54/734)	DIFF=-0.6% UB=1.6%	<0.001

- Multiple imputation and available case analyses: supported non-inferiority
- Worst case analysis: failed to show non-inferiority
- Odds ratio in missing patients must be >8.1 to overturn non-inferiority

## Results of Endeavor IV: Late Loss

- Secondary endpoint: Late loss at 8-month
- Non-inferiority hypotheses:

$$H_0: \mu_e \geq \mu_e + \delta$$

$$H_a: \mu_e < \mu_e + \delta, \text{ non-inferiority margin } \delta = .2\text{mm}$$

	Available (planned)	Mean (SD)	Endeavor -Taxus	Upper bound of 1-sided 95% CI	p-value*
EIV	143 (164)	0.36 (0.47)	0.13	0.22	0.089
Taxus	135 (164)	0.23 (0.45)			

- 50 pts excluded: 21 Endeavor vs. 29 Taxus

# Missing Data: EIV Late Loss

## Sensitivity analysis

Late Loss	Endeavor (N=164) Mean±SD	Taxus (N=164) Mean±SD	Difference Upper Bound of 1-sided 95%CI	p- value*
Multiple imputation	0.35± 0.54	0.23± 0.49	DIFF=0.12 UB=0.20	0.057
Worst case	0.55± 0.68	0.05± 0.56	DIFF=0.50 UB=0.62	1
Available case	0.36± 0.47 (143)	0.23± 0.45 (135)	DIFF=0.13 UB=0.22	0.089

- Same conclusion for all analyses: failed to show non-inferiority

# Summary of Statistical Inference

- For 9-month TVF:
  - showed superiority to Driver (EII)
  - showed non-inferiority to Taxus (EIV)
- For 8-month in segment late loss:
  - showed superiority to Driver (EII)
  - failed to show non-inferiority to Cypher (EIII)
  - failed to show non-inferiority to Taxus (EIV)

# Summary

## ■ Clinical endpoints

- Endeavor stent **met** its primary TVF superiority endpoint vs. the bare metal Driver stent (ENDEAVOR II)
- Endeavor stent **met** its primary TVF non-inferiority endpoint vs. the Taxus stent (ENDEAVOR IV)

## ■ Angiographic endpoints

- Endeavor stent **met** its late loss endpoint vs. the bare metal Driver stent (ENDEAVOR II)
- Endeavor stent **failed to meet** its non-inferiority late loss endpoint endpoints vs. the Cypher (ENDEAVOR III) and Taxus (ENDEAVOR IV) stents

# Putting Clinical and Angiographic Endpoints into Perspective

- Reconcile a less effective stent with respect to inhibition of in-segment neointimal growth compared to approved DES with...
- A stent that is non-inferior to approved DES with respect to TVF
  - A composite clinical endpoint that combines safety (cardiac death and MI) and effectiveness (TVR) elements

# Clinical Endpoints

## DES vs. BMS Superiority Trials

- Historically (for the currently approved DES) and the Endeavor stent
  - Randomized trials show a significant reduction in the TVF composite endpoint by DES vs. BMS
    - E.g., 48% reduction in TVF in Endeavor vs. Driver in ENDEAVOR II (7.9% vs. 15.1%)
  - Superiority of DES driven by reduction in repeat revascularization rates (TLR and TVR)
    - E.g., 61% reduction in TLR in Endeavor vs. Driver
  - No significant differences in low rates of cardiac death or MI

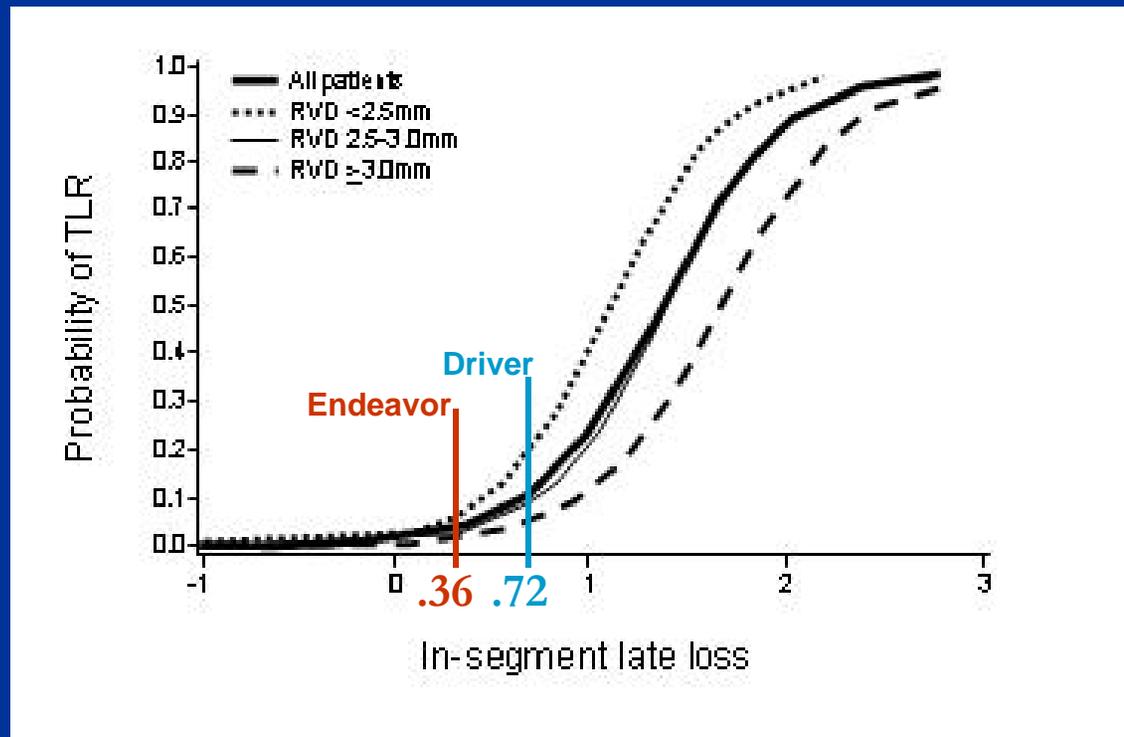
	Endeavor	Driver
Cardiac Death	0.8%	0.5%
MI	2.7%	3.9%

# Angiographic Endpoints DES vs. BMS Superiority Trials

- Angiography can directly assess the effect of a DES in preventing restenosis
- Historically (for the currently approved DES) and the Endeavor stent
  - Angiographic studies within randomized trials show that DES are significantly more effective in inhibiting neointimal growth
    - Reduced late lumen loss
    - Reduced percent stenosis
    - Reduced rates of binary restenosis
  - E.g., 50% reduction in late lumen loss in Endeavor stent vs. Driver stent in ENDEAVOR II

# Angiographic Surrogate Markers for Stent Effectiveness

- Serial angiographic studies from randomized trials of DES vs. BMS show that late loss and percent diameter stenosis are strong surrogate markers predictive of repeat revascularization



# Pivotal DES vs. DES Non-inferiority Trials

## Focus on Endeavor IV

- First head-to-head DES vs. DES trial powered for both clinical (TVF) and angiographic (late loss) endpoints
  - TVF endpoint for non-inferiority met

	Endeavor	Taxus	P value
TVF at 9 Months	6.8% (50/740)	7.4% (54/734)	<0.001

- Late loss endpoint for non inferiority not met

	Endeavor N=164	Taxus n=164	P value*
In-segment late loss at 8 months, mm	0.36±0.47	0.23±0.45	0.089

# Exploring Dichotomous Results in ENDEAVOR IV

- Rates of the components of TVF were low in both Endeavor and Taxus groups

Events at 270 Days	Endeavor	Taxus
Cardiac Death	0.4%	0.3%
MI	1.5%	2.5%
TVR	5.5%	5.0%

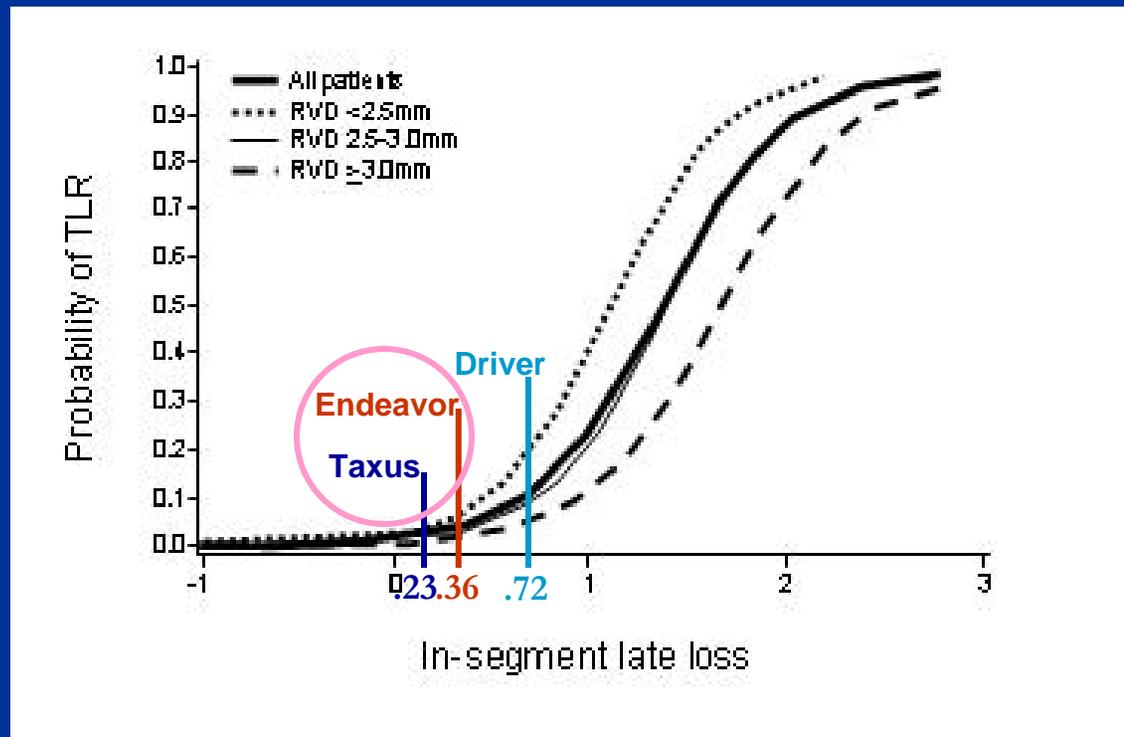
- TLR a superior clinical measure of stent effectiveness at the treated arterial segment compared with TVR
- Differences in rates of TLR were consistent with greater angio effectiveness of the TAXUS stent albeit with low rates of TLR in both groups

Events at 270 Days	Endeavor	Taxus.
Target Lesion Revascularization	4.2%	2.7%

- Since numerous factors that may affect whether a repeat revascularization is performed, the clinical impact of small differences in low rates of TVR or TLR is uncertain

# Angiographic Inferiority in ENDEAVOR IV

- The late loss/TLR graph is curvilinear
- Differences in late loss in Endeavor vs. Taxus stent located at the flat part of the curve associated with relatively small differences in revascularization rates compared to Endeavor vs. Driver stents



# Clinical Effectiveness

## DES vs. DES

- Based on the results of ENDEAVOR IV, it is uncertain whether the less effective angiographic results of the Endeavor stent will translate into a significantly greater frequency of repeat revascularization compared to the Taxus stent in a larger study population or with longer-term follow-up.
  - Follow-up for ENDEAVOR IV only available through 9 months
  - Longer-term follow-up of ENDEAVOR IV patients will provide important information on this issue.
- From a review of the Endeavor program, cases of TLR and TVR continue to accrue over time in all treatment groups (Endeavor, Driver, and Cypher) without a pattern of reduced clinical effectiveness of the Endeavor stent.

# Safety and Effectiveness

## Studies of DES vs. BMS or DES

- PMA approval is dependent on a reasonable expectation of safety and effectiveness
- What we have learned in the DES era:
  - In DES vs. BMS studies, any short or long-term risks of putting a drug on a stent need to be clearly outweighed by the clinical benefit of a drug-eluting device
  - Effectiveness over time should be evaluated in the context of long-term safety (death, MI, and stent thrombosis)

# **Post-Approval Considerations Endeavor Zotarolimus-Eluting Coronary Stent**

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October 10, 2007

# Outline

- General Principles
- Rationale/Postmarket Questions
- Proposed Post-Approval Study (PAS) Protocol
- Assessment of PAS Protocol
- PAS Issues for Panel Discussion

# Disclaimer

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

# General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

# General Objectives for Post-Approval Studies

- Gather postmarket information
  - Longer-term performance
  - Community performance
  - Effectiveness of training programs
  - Sub-group performance
  - Rare adverse events and real world experience
- Account for Panel recommendations

# Views on Post-Approval Studies for Drug Eluting Stents (DES)

- Not known if ST rate plateaus or continues to increase over time
- Study incidence rate of cardiac death and MI
- Study routine clinical use of DES

# Issues to be Considered in Endeavor PAS

- Stent thrombosis
  - Confirm incidence is  $<1\%$  for each 12 month period after 1 year
- 5-year patient informed consent
- Evaluate higher risk subgroups
  - Patient characteristics
  - Lesion characteristics

# Overview of Sponsor's Approach

- Endeavor US Postmarketing Registry (n=2000)
- OUS PROTECT - Patient Related Outcomes with Endeavor versus Cypher stenting Trial (n=4000)

# Overview of US Postmarketing Registry

Study Design	Non-randomized, prospective, multi-center, single-arm registry
Population	Consecutive patient who receive Endeavor stent and consent to participate
Sample Size	2000 patients
Follow-up	Up to 5 years
Primary Endpoint	Stent thrombosis rate up to 5-years
Co-Primary Endpoint	Rates of cardiac death and MI
Secondary Endpoints	Composite total death and non-fatal MI; composite cardiac death and non-fatal MI
Antiplatelet regimen	Per proposed labeling

# Overview of PROTECT Study

Study Design	Prospective, multi-center, randomized, two-arm trial
Randomization	1:1 Endeavor versus Cypher
Sample Size	8800 patients
Follow-up	Up to 5 years
Primary Endpoint	Overall stent thrombosis rate at 3 years
Secondary Endpoints	Composite total death and non-fatal MI; composite cardiac death and non-fatal MI
Antiplatelet regimen	Minimum 3 months

- A portion of PROTECT patients will be pooled with U.S. registry patients for an analysis of stent thrombosis rates.

# Proposed Statistical Analysis Plan

- Primary endpoint

Alternative hypothesis – the Endeavor Definite/Probable Stent Thrombosis rate per ARC definition during each yearly interval post-implant is less than 1.0% when used in accordance with the labeled indication.

- Co-primary endpoint

Alternative hypothesis - the incidence of cardiac death and MI in patients treated with the Endeavor DES will not exceed the endpoint incidence by 50% or more for patients treated with the Driver stent

- Pool U.S. Registry patients with portion of PROTECT patients

# PAS Issues for Panel Discussion

- The post-market study has been designed to:
  - Identify rates of stent thrombosis through five years.
  - Assess rates of cardiac death and MI to confirm long-term safety of the Endeavor stent when implanted in accordance with its labeled indications for use compared to the Driver bare metal stent.
  - Evaluate use of the Endeavor stent for potential safety signals associated with higher risk lesion and patient subsets, recognizing from published literature that such patients are likely to receive drug-eluting stents in clinical practice.

***Are the objectives identified above appropriate?  
Please discuss what additional objectives should be considered.***

# PAS Issues for Panel Discussion

- Not powered for sub-group analysis
- Unclear if 5-year follow-up is sufficient for long-term stent thrombosis evaluation
- Potential differences on anti-platelet therapy recommendations

***Please discuss if the study protocol should be revised to address these issues.***

**Questions?**