

# **Drug Eluting Stents**

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## **Post Market Surveillance**

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**Boston, MA**

# **OVERVIEW**

## **Post Market (PM) Surveillance**

- ❑ Background on PM Surveillance of Currently Approved DES**
- ❑ Strengths/Weaknesses of Approved DES PM Monitoring**
- ❑ Medtronic Endeavor PM Surveillance Issues**
- ❑ Specific Recommendations for PM Surveillance for Medtronic Endeavor**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

**Cordis' CYPHER 04/24/03**

**Boston Scientific's TAXUS 03/04/04**

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850



**APPROVED**

FDA Approval Letters  
Accessed at  
[www.fda.gov](http://www.fda.gov)



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- 2000 US patient registry to evaluate “for the potential for less frequent adverse events”



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- Long-term outcome (beyond 12 M) “unknown at this time”
- 5 year outcomes on original randomized pt cohorts
- 2000 US patient registry to evaluate “for the potential for less frequent adverse events”
- Reports 3M, 6M, 12M, 18M and annually thereafter



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# 6 CYPHER<sup>®</sup> Stent Registries



	<b>OUS e-CYPHER</b>	<b>US e-CYPHER*</b>	<b>D.E.S. COVER</b>	<b>S.T.L.L.R.</b>	<b>Japan- PMS</b>	<b>J-CYPHER</b>
<b>Study Type</b>	<b>Open Enrollment Registry</b>	<b>Open Enrollment Registry</b>	<b>Open Enrollment Registry</b>	<b>Angio eval: stent deployment on TVR</b>	<b>Open Enrollment Registry</b>	<b>Open Enrollment Registry</b>
<b>Enrollment</b>	<b>2002-2005</b>	<b>2003-2004</b>	<b>2004-2005</b>	<b>2004-2005</b>	<b>2004-2005</b>	<b>2004-2005</b>
<b># of Patients</b>	<b>15,157</b>	<b>2,067</b>	<b>4,235</b>	<b>1,554</b>	<b>2,032</b>	<b>14,087</b>
<b># of Sites</b>	<b>279</b>	<b>38</b>	<b>140</b>	<b>41</b>	<b>50</b>	<b>41</b>
<b>Location</b>	<b>41 Countries</b>	<b>United States</b>	<b>United States</b>	<b>United States</b>	<b>Japan</b>	<b>Japan</b>
<b>Independent CEC</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>Independent Data Mgmt</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>Monitoring</b>	<b>3%</b>	<b>100%</b>	<b>-</b>	<b>-</b>	<b>100%</b>	<b>3%</b>
<b>Anti-platelet Medications</b>	<b>ASA, Ticlopidine, Clopidogrel</b>				<b>ASA, Ticlopidine</b>	
<b>Clinical Follow-up</b>	<b>1, 6, and 12 months</b>					<b>Also yearly f/u to 5-years</b>

\* FDA mandated PMS

# 1 Year Registry F/U Published 3 Years Post Approval

## Interventional Cardiology

### Safety of Coronary Sirolimus-Eluting Stents in Daily Clinical Practice

#### One-Year Follow-Up of the e-Cypher Registry

Philip Urban, MD, FESC; Anthony H. Gershlick, MD; Giulio Guagliumi, MD, FESC;  
Philippe Guyon, MD; Chaim Lotan, MD; Joachim Schofer, MD; Ashok Seth, MD, MBBS, DSc;  
J. Eduardo Sousa, MD, PhD; William Wijns, MD, PhD, FESC; Claude Berge, MSc;  
Monika Deme, MD; Hans-Peter Stoll, MD; on behalf of the e-Cypher Investigators

**“This analysis of 1-year data...suggests a high degree of safety of SES, with a rate of ST similar to that observed in clinical trials”**

Circulation 2006; 113: 1434-41

# DES – Circa 2006

6 million implants - ? late stent thrombosis

**March 2006**

**BASKET-LATE  
ACC**

**September 2006**

**ESC Annual Meeting**

**Meta-analysis, DES RCT  
Death or Q wave MI**

	<b>BMS</b>	<b>DES</b>	<b>P</b>
<b>sirolimus</b>	<b>3.9%</b>	<b>6.3%</b>	<b>0.03</b>
<b>paclitaxel</b>	<b>2.6%</b>	<b>2.3%</b>	<b>0.68</b>

<b>Outcome</b>	<b>BMS (%)</b>	<b>DES (%)</b>	<b>p</b>
<b>CV death</b>	<b>0</b>	<b>1.2</b>	<b>0.09</b>
<b>Nonfatal MI</b>	<b>1.3</b>	<b>4.1</b>	<b>0.04</b>
<b>CV death/ nonfatal MI</b>	<b>1.3</b>	<b>4.9</b>	<b>0.01</b>
<b>Restenosis- related TVR</b>	<b>6.7</b>	<b>4.5</b>	<b>0.21</b>
<b>MACE</b>	<b>7.9</b>	<b>9.3</b>	<b>0.53</b>



Maisel NEJM 2007; 356: 981-984.

**Safety and Efficacy of Drug-Eluting Stents Reaffirmed in  
New England Journal of Medicine Articles and Editorial**

Boston Scientific Press Release September 13, 2006

**Two-year data suggest different rates of blood  
clots and heart attacks between the Cypher  
sirolimus-eluting coronary stent and the Taxus stent**

*Cordis Press Release  
September 4, 2006*

New York Times September 5, 2006

HEALTH AND MEDICINE

**Cardiologists question  
the risks in using  
drug-coated stents**

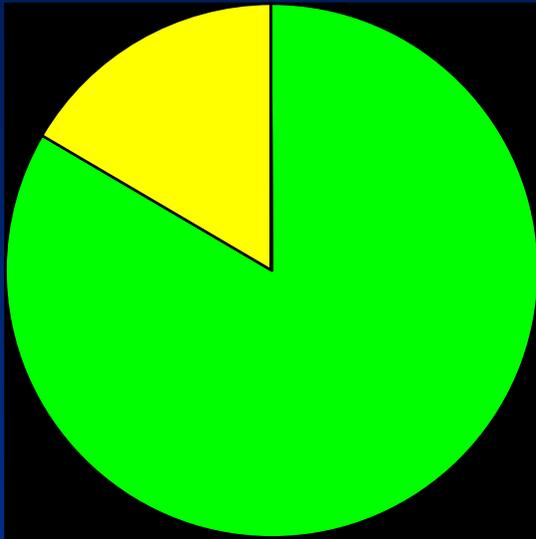
The data we currently  
have do not allow us to  
fully characterize the  
mechanism, risks, and  
incidence of DES  
thrombosis

FDA Statement  
September 14, 2006

# DES Information Management

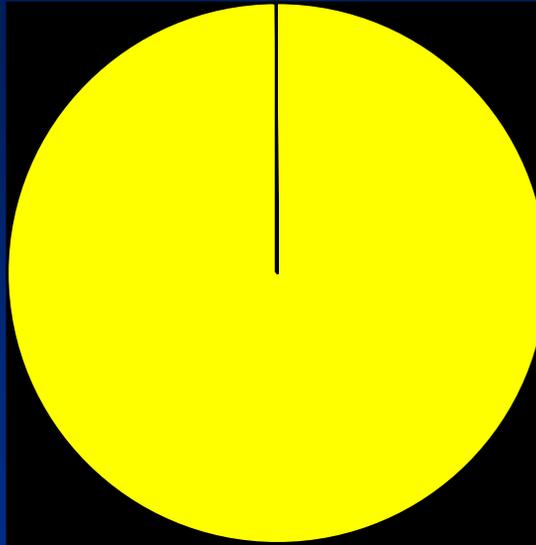
2006-2007

N=84



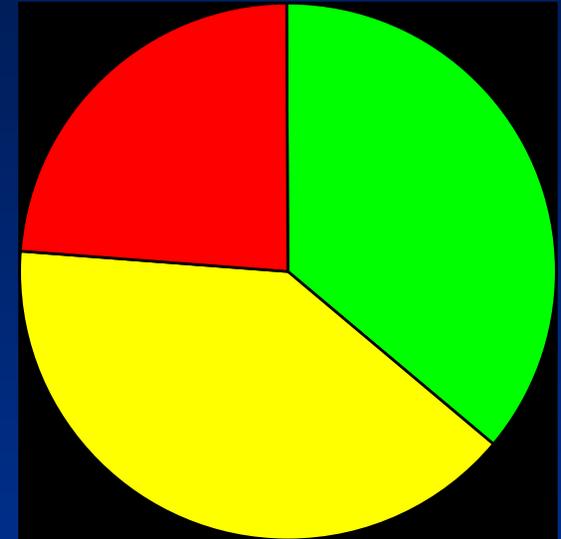
**Industry  
Press Releases**

N=3

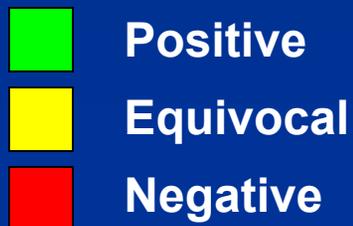


**FDA  
Press  
Releases/  
Patient  
Updates**

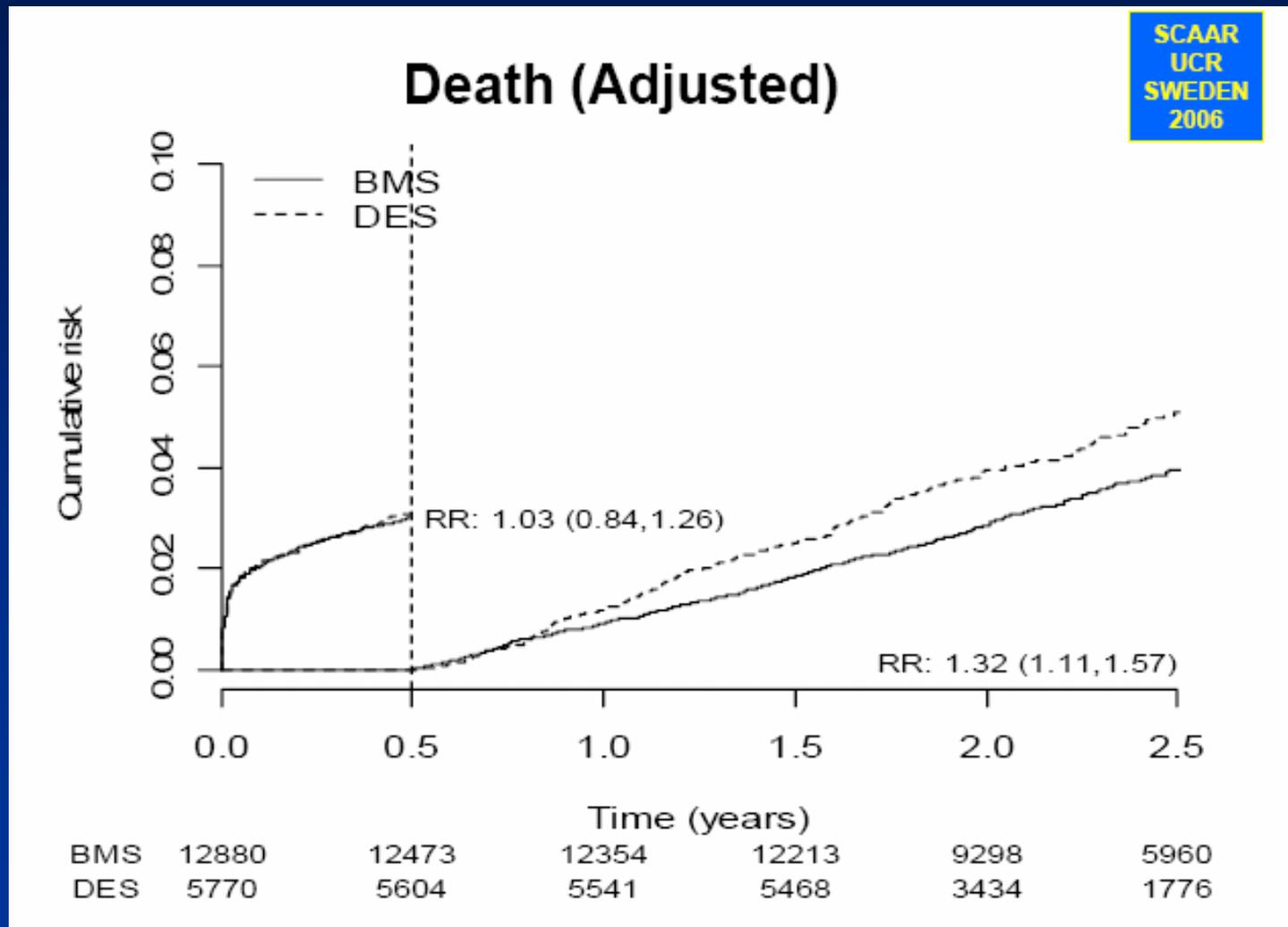
N=50



**Medical  
Journal  
Articles  
(JACC)**



# Swedish Coronary Angiography and Angioplasty Registry



Lagerqvist et al NEJM 2007; 356: 1009-19.

# Swedish Coronary Angiography and Angioplasty Registry

## DES Patients More Often Had:

Diabetes

HTN

Previous PCI

Previous CABG

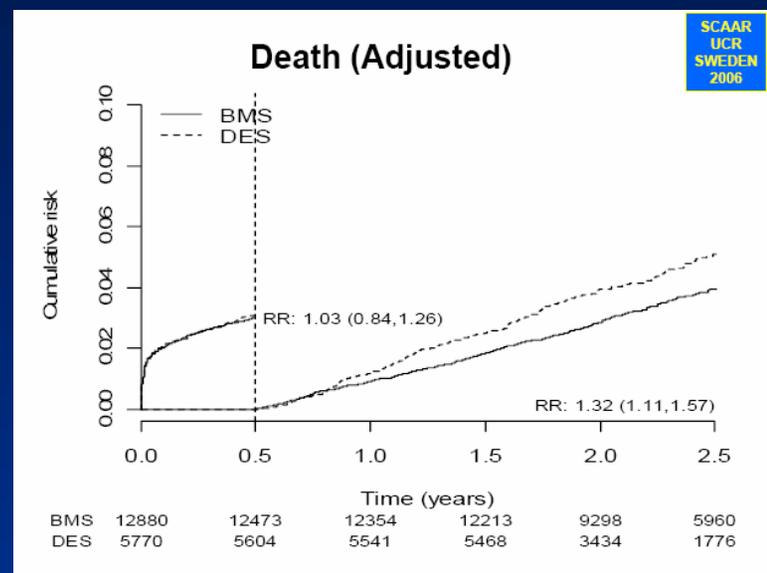
Previous MI

Previous HF

Previous Renal Failure

Multivessel Disease

Received Multiple Stents



**Not Randomized**

**Subject to Physician Bias**

# Swedish Coronary Angiography and Angioplasty Registry

**DES Patients More Often Had:**

Dialysis

HTN

Previous

Pr

Previous

Previous Renal Failure

Multivessel Disease

Received Multiple Stents

**New Swedish Registry Results Show No Overall Increased Deaths With DES**

**ESC Press Release  
September 2, 2007**

Death (Adjusted)

SCAAR  
UCR  
SWEDEN  
2006

BMS  
DES

RR: 1.32 (1.11,1.57)

2.0 2.5

541

5468

5960

1776

**Not Randomized**

**Subject to Physician Bias**

# What Has DES History Taught Us?

- Original PM surveillance plan for approved DES was reasonable but would have benefited from:
  - Longer Mandated F/U
  - Better Understanding of Physician Stent Choices
  - Better and More Timely Public Reporting

# Post-Approval Study Sponsor Proposal

## Medtronic Endeavor

- ❑ Prospective, Multi-center, Non-Randomized
- ❑ Single Arm, 5-year follow-up
- ❑ CEC
- ❑ ST = ARC Definite and Probable
- ❑ Proposed Sample Size 5300
  - 3300 OUS PROTECT; 2000 US Registry
  - Expected Yield 1941 On-Label Patients
  - Assumed ST rate 0.5% at 1 year

# Post-Approval Study Sponsor Proposal

## Medtronic Endeavor

### Choice of Control Group – US Study

Sponsor: Compare to Control Group (BMS) from RCT

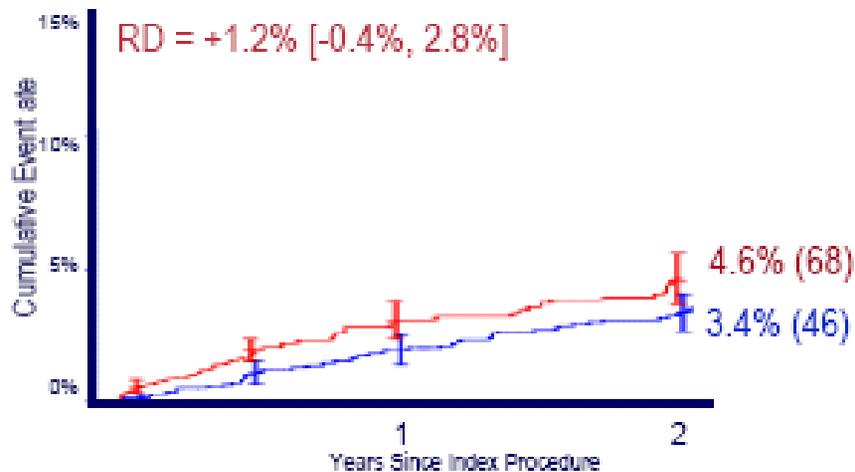


# ARRIVE Simple v. TAXUS Overall

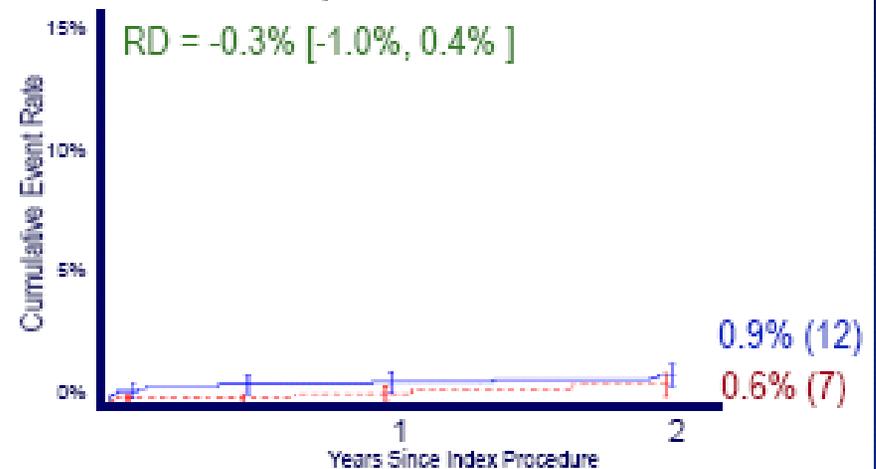
## N = 3,964

— TAXUS (N=1400)      — ARRIVE (N=2564)  
 RD = Rate Difference = ARRIVE — TAXUS  
No increase      Increase

### All Death



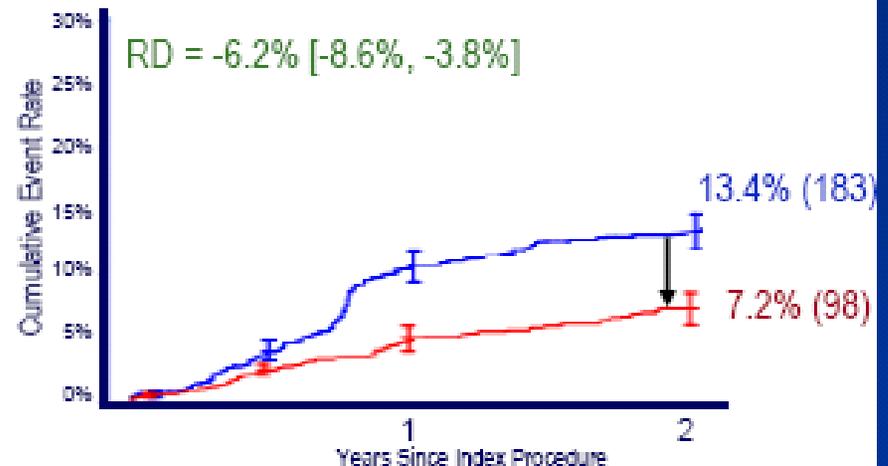
### Q Wave MI



### ARC Primary ST Definite/Probable



### TVR



# Post-Approval Study Sponsor Proposal

## Medtronic Endeavor

### Choice of Control Group – US Study

Sponsor: Compare to Control Group (BMS) from RCT

Better Control Would Be Concurrent Registry of Non-Endeavor Stent Patients

Must Ask About MD Reasons For Stent Selection



# Post-Approval Study Sponsor Proposal

## Medtronic Endeavor

### “Acceptable” Very Late ST Rates Too High

- Major Objective of Upper 95% CI for VLST < 1% for each 12 month period beginning at 12 M
- This would accept a 4% VLST rate at 5 years

# Implications of Small Increased Risk

**Assumes: 6 million Stent Implants**

**Excess 0.5% Risk in DES Group**

<b>Market Share</b>	<b>Number of Stents</b>	<b>Excess Stent Thrombosis</b>
<b>15%</b>	<b>900,000</b>	<b>4500</b>
<b>18%</b>	<b>1.08 million</b>	<b>5400</b>
<b>20%</b>	<b>1.2 million</b>	<b>6000</b>
<b>25%</b>	<b>1.5 million</b>	<b>7500</b>
<b>30%</b>	<b>1.8 million</b>	<b>9000</b>

# Power Calculation

## On-Label Comparison

$$\alpha=0.05 \quad \beta=0.80$$

Very Late Stent Thrombosis (%)					
BMS	0	0	0.1	0.1	0.2
DES	0.3	0.5	0.5	0.7	1.0
On-Label Sample Size	6488	3888	6830	4112	3404
Total Sample Size	16220	9720	17075	10280	8510

# Power Calculation

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**TAXUS Registries > 7000; Cordis Registries > 20,000**

# Post-Approval Study Sponsor Proposal

## Medtronic Endeavor

### Delay in Public Reporting of Study Findings

- “Blinding” results for 3 years is unnecessary and needlessly delays public access to data.
- Annual reports should be made public at time of submission to FDA.

# Recommendations

- Registry of ~10,000 PCI Patients (BMS and DES)**
- Reason for MD Stent Choice**
- Blinded Endpoint Adjudication**
- $\geq$  3 Year Follow-up**
- Public Release of Data Upon Submission to FDA**

# Conclusion

- Impossible to Identify All Safety Issues With a Device Prior to Device Approval
- We Can Do Better:
  - Larger Studies
  - Longer Studies
  - Better Understanding of Physician Choices
  - More Timely Public Reporting

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