

# FDA Summary

---

Takahiro Uchida, M.D.

Andrew Farb, M.D.

FDA/CDRH/ODE/DCD

Andrea Holton, Ph.D.

Hesha Duggirala, Ph.D.

FDA/CDRH/OSB

# Outline

- Regulatory history of DES
- Pathology and clinical overview of DES
  - Pathophysiology of restenosis prevention
  - Pivotal studies submitted to support PMA approval
  - Pathophysiology and clinical significance of stent thrombosis
  - Stent thrombosis in DES RCTs submitted to FDA
  - Recent meta-analyses of DES RCTs
  - New considerations in the definition stent thrombosis
  - Broad clinical use of DES and antiplatelet therapy issues
- FDA-Medical Device Report data
- Limitations of available study data
- Conclusions

# Regulatory history of DES as combination products

- DES regulated as combination products
  - CDRH primary review, with significant CDER consult
- Two DES approved in US
- Cordis Cypher Sirolimus-Eluting Coronary Stent, approved April 2003
  - 316L SS stent
  - PEVA/PBMA polymer
  - Sirolimus
- Boston Scientific Taxus Express<sup>2</sup> Paclitaxel-Eluting Coronary Stent, approved March 2004
  - 316L SS stent
  - SIBS polymer
  - Paclitaxel

# Data requirements for DES

- Complete safety information of drug substance
  - Generally available for approved drugs
- Complete characterization of finished stent
  - Bench testing
  - Animal studies
  - Chemistry and manufacturing
  - In vitro pharmacokinetics (PK)
- Comprehensive clinical evaluation
  - Pivotal plus supporting trials
  - In vivo PK evaluation
- Post-approval package
  - Continued follow-up of clinical trial patients
  - Enrollment of 2000 new patients following approval

# Clinical Trials for CYPHER

- First in Man (FIM)
  - Outside US (OUS) study
  - 30 pts, nonrandomized
  - Follow-up available through 4 years
- RAVEL
  - OUS study
  - 238 patients, randomized Cypher vs. BMS Bx Velocity
  - Follow-up available through 4 years
- SIRIUS
  - US pivotal study
  - 1058 patients, randomized Cypher vs. BMS Bx Velocity
  - Follow-up available through 4 years

# Clinical Trials for TAXUS

- TAXUS I
  - OUS study
  - 61 pts, randomized Taxus NIRx vs. BMS NIR
  - Follow-up available through 4 years
- TAXUS II-SR
  - OUS study
  - 267 pts, randomized Taxus NIRx vs. BMS NIR
  - Follow-up available through 3 years
- TAXUS IV
  - US pivotal study
  - 1413 pts, randomized Taxus Express vs. BMS Express
  - Follow-up available through 3 years

# DES Clinical Use

- Great clinical promise based on initial trials
- Rapid acceptance in clinical community
- Use quickly extended beyond the types of patients and lesions enrolled in the initial clinical trials
- FDA challenge is to monitor actual use of approved devices for safety signals

# “On-label” vs. “Broader Use”

- FDA approves each device with a specific “indication for use” that describes the condition in which the product should be used
- Device label includes summaries of the clinical trials and relevant inclusion/ exclusion criteria
- Physician may choose to treat an individual patient with a device even if not approved for that use (practice of medicine)
  - Sometimes called “off-label” or “extra label” use
- FDA does not regulate the practice of medicine
- FDA is responsible for any use of a device that raises a public health concern

# Pathology and Clinical Overview

Andrew Farb, M.D.

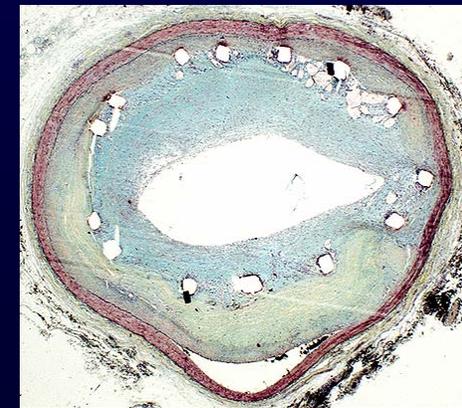
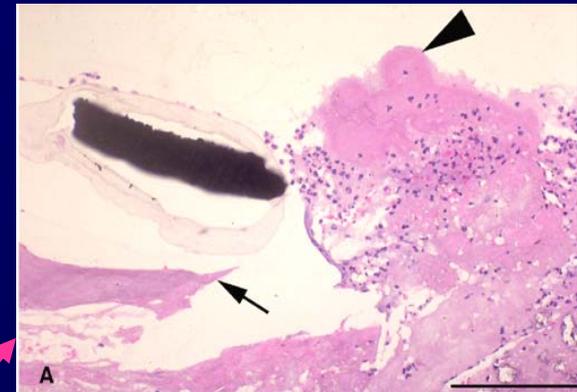
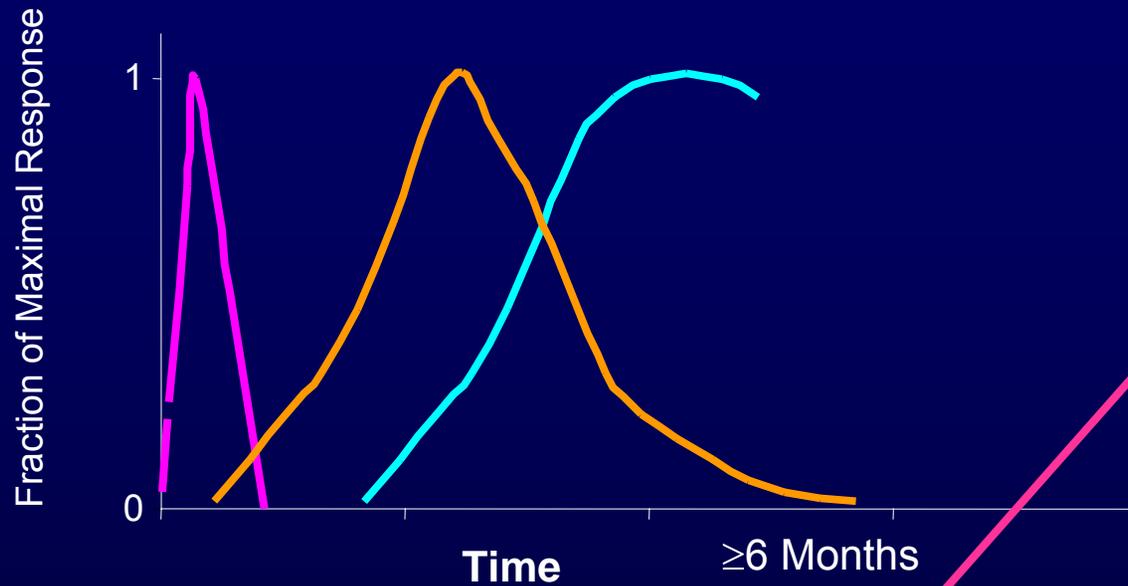
# Pathophysiologic Insights Into Restenosis Prevention With Drug-Eluting Stents

# Bare Metal Intracoronary Stents



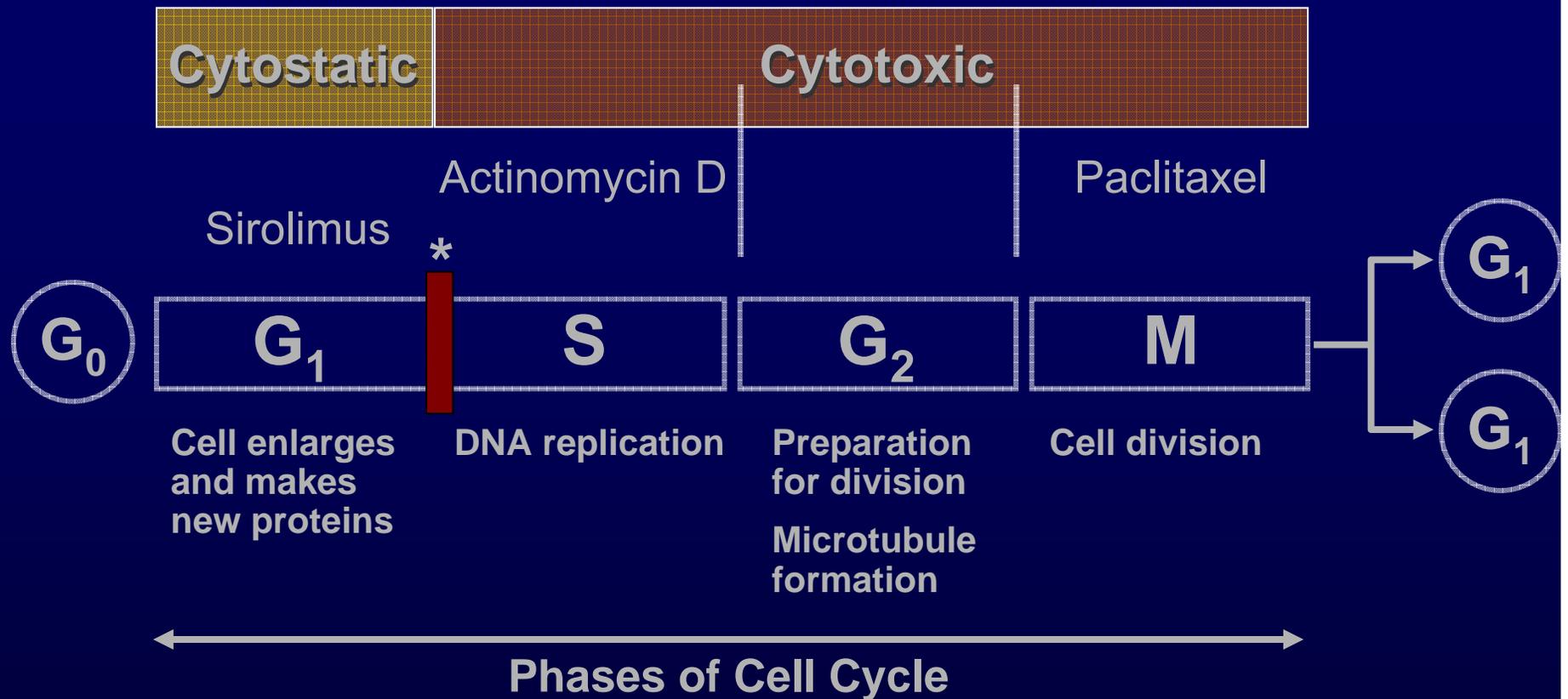
- Greater lumen dilatation vs. PTCA
- No recoil
- No negative remodeling (rigid metal scaffold)
- Mechanism of in-stent restenosis ( $\cong 30\%$  of cases): Intimal proliferation

# Cascade of Events Following Stent Placement



- **Platelet/Fibrin Deposition**
- **Smooth muscle cell proliferation**
- **Matrix deposition**
- Restenosis augmented by arterial injury and inflammatory responses

# Search for Candidates for DES

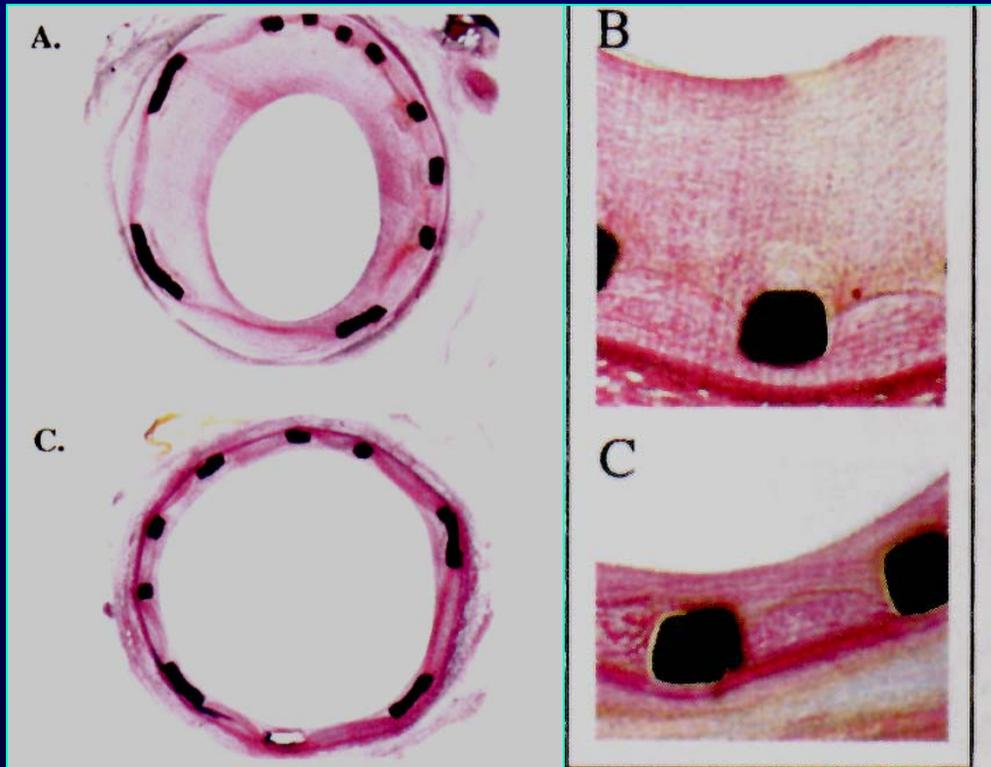


P. Serruys TCT 2002 (modified)

**-limus macrolide antibiotics** (Sirolimus, Everolimus, ABT-578): Cell cycle regulatory, antiproliferative, antimigratory, anti-inflammatory  
**Paclitaxel**: Stabilizes intracellular microtubules, antiproliferative

# Sirolimus-Eluting Stents in Swine Coronary Arteries Explanted at 28-Days

Control →



Sirolimus →

Suzuki et al., Circulation 2001;104:1188

# CYPHER Stent

## Pivotal study to support PMA approval

- SIRIUS
  - Key inclusion criteria
    - Stable or unstable angina and signs of myocardial ischemia
    - Single target lesion in a native coronary artery
    - 15 to 30 mm in length
    - $\geq 2.5$  mm and  $\leq 3.5$  mm reference vessel diameter
    - 51-99% stenosis
  - Key exclusion criteria
    - Myocardial infarction (within the previous 48 hours)
    - Ejection fraction  $< 25\%$
    - Target lesion in an ostium, a bifurcation, an unprotected left main coronary artery or in a vessel with thrombus or severe calcification

# CYPHER Stent: US Pivotal study

## SIRIUS Key Results

- **Primary Endpoint: Target Vessel Failure** (cardiac death, MI, or TVR) at 9 months  
*CYPHER 8.8% (47/533)*  
*Bx-Velocity 21.0% (110/525),  $p < 0.001$*
- No differences in rates of death or MI between CYPHER and BMS

	CYPHER (%)	Bx-Velocity (%)	p
Death	0.9	0.6	ns
MI	2.8	3.2	ns

# TAXUS Stent

## Pivotal study to support PMA approval

- TAXUS IV
  - Key inclusion criteria
    - Stable or unstable angina or provokable ischemia
    - Single, previously untreated lesion in a native coronary artery
      - 10-28 mm in length
      - Reference diameter 2.5-3.75 mm
      - Coverable by a single study stent
  - Key exclusion criteria
    - Serum creatinine >2.0 mg/dL
    - LVEF <25%
    - Recent MI
    - Complex morphologies including left main, ostial, or bifurcation lesions, total occlusions, and heavy calcified or thrombotic lesions

# TAXUS Stent: US Pivotal Study

## TAXUS IV Key Results

- **Primary Endpoint: Target Vessel Revascularization at 9 months:**  
*TAXUS 4.7% (31/ 655)*  
*Express 12.1% (78/ 645),  $p < 0.001$*
- No differences in rates of death or MI between TAXUS and Express

	TAXUS (%)	Express (%)	p
Cardiac Death	1.4	1.1	ns
MI	3.5	3.7	ns

# Current Indications for FDA-Approved DES

- The CYPHER Sirolimus-eluting Coronary Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions of length  $<30$  mm in native coronary arteries with reference vessel diameter of  $>2.5$  mm to  $<3.5$  mm.
- The TAXUS Express<sup>2</sup> Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions  $\leq 28$  mm in length in native coronary arteries  $\geq 2.5$  to  $\leq 3.75$  mm in diameter.

# Studies Required as Condition of Approval

## CYPHER Stent

- Report annually clinical outcomes through 5 years post-procedure on at least 80% of the patient enrolled from the SIRIUS, RAVEL, and FIM trials
- Conduct a 2000-U.S. patient post-marketing registry trial and report 3, 6, 12, and 18-month data following approval (regardless inside/outside of indication for use)

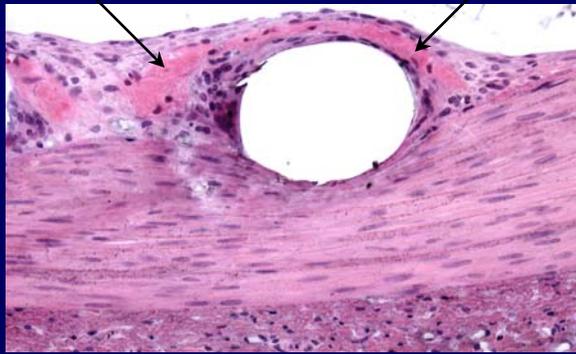
## TAXUS Stent

- Report annually clinical outcomes through 5 years post-procedure on at least 80% of the patient enrolled from the TAXUS I, II, and IV trials
- Conduct a 2000-U.S. patient post-marketing registry trial (500-750 patients during the continued access IDE, and at least 1,500 patients post market) and report 3, 6, 12, and 18-month data following approval (regardless inside/outside of indication for use)

# Pathophysiologic Insights Into Stent Thrombosis

- DES mechanism of action
  - Delayed healing
    - Longer window of thrombosis risk vs. BMS
    - Need for longer duration of antiplatelet therapy
- Lesion factors
  - Bifurcations
  - Highly necrotic plaques
  - Long lesions
  - Restenosis
- Hypersensitivity

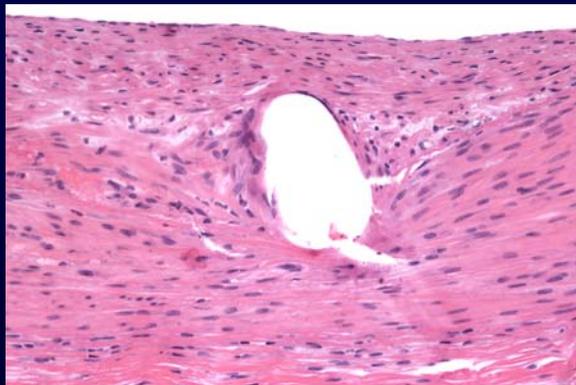
Fibrin



Bare metal  
stent at 7 days

## Drug Eluting Stents Delay Neointima Healing

Sirolimus-eluting  
stent at 28 days

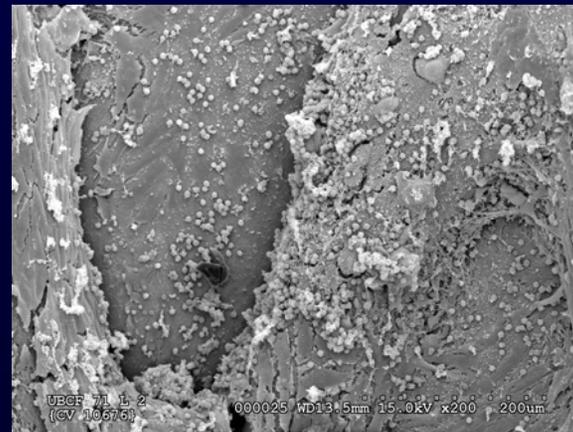
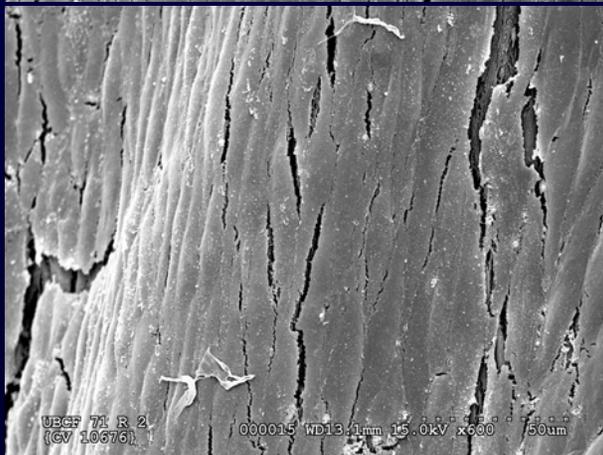
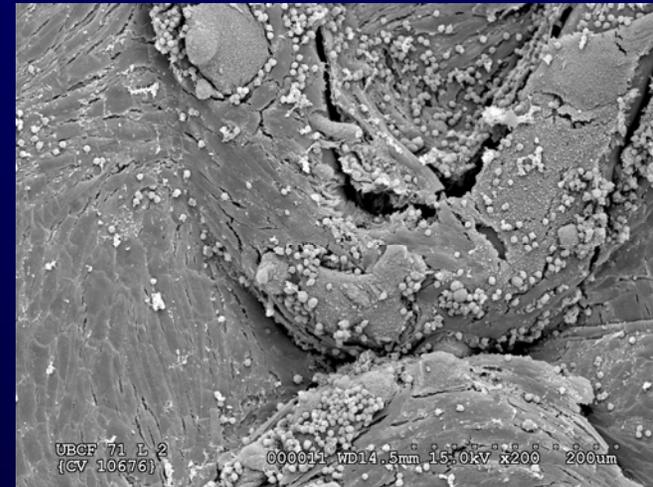
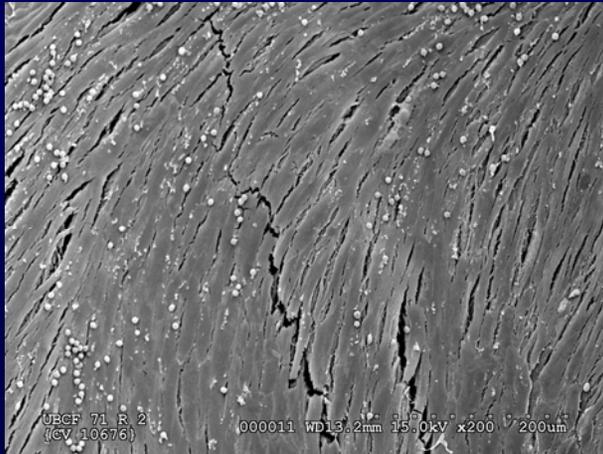
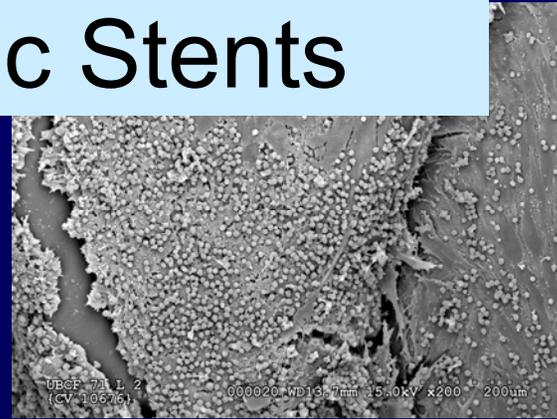
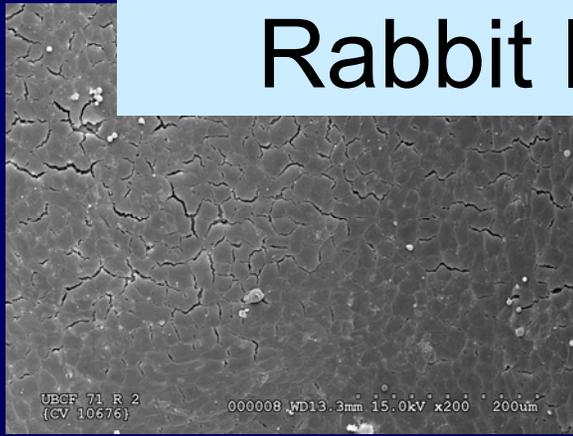


Bare metal  
stent at 28 days

# Rabbit Iliac Stents

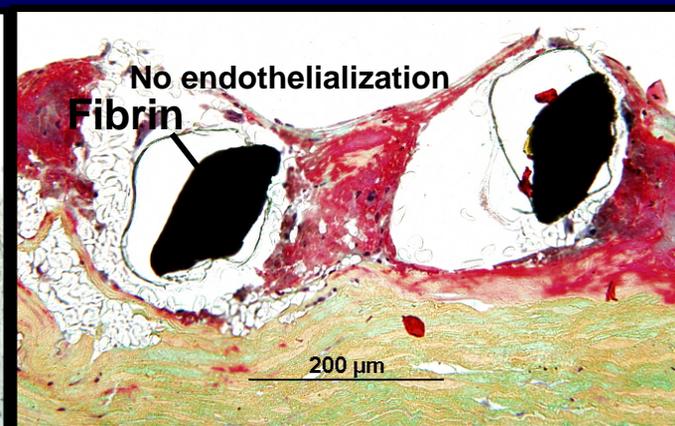
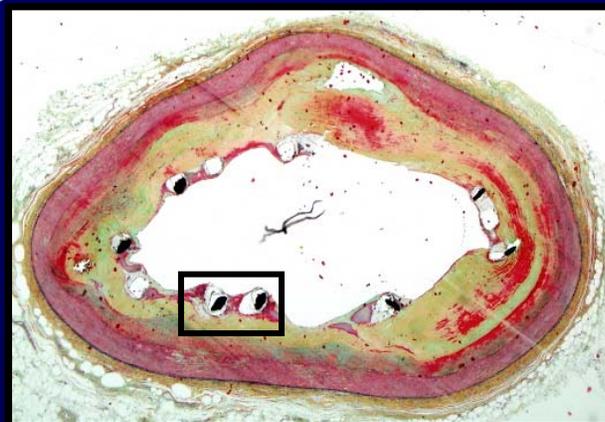
**DES @  
7 Days**

**BMS @  
7 Days**

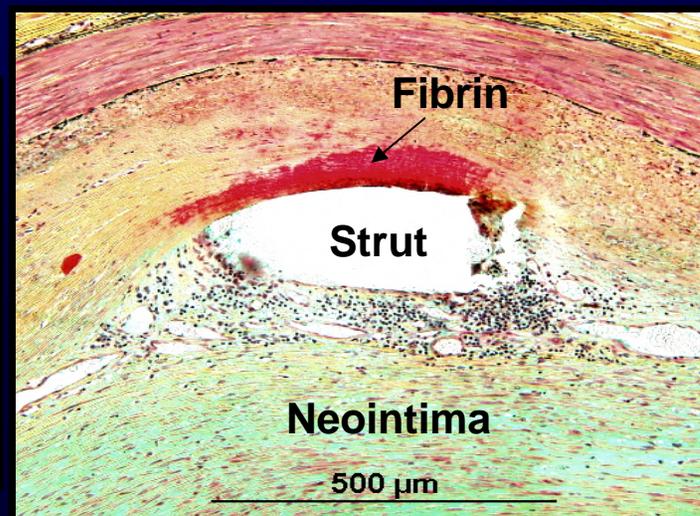
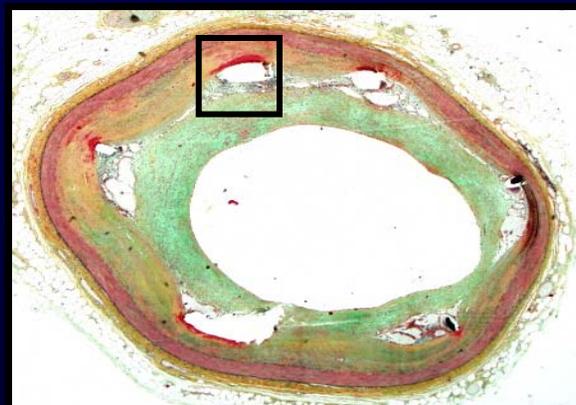


# Bare Metal Stent in Proximal RCA and SRL-Eluting Stent in Distal RCA 15 Months Antemortem (Non-Cardiac Death)

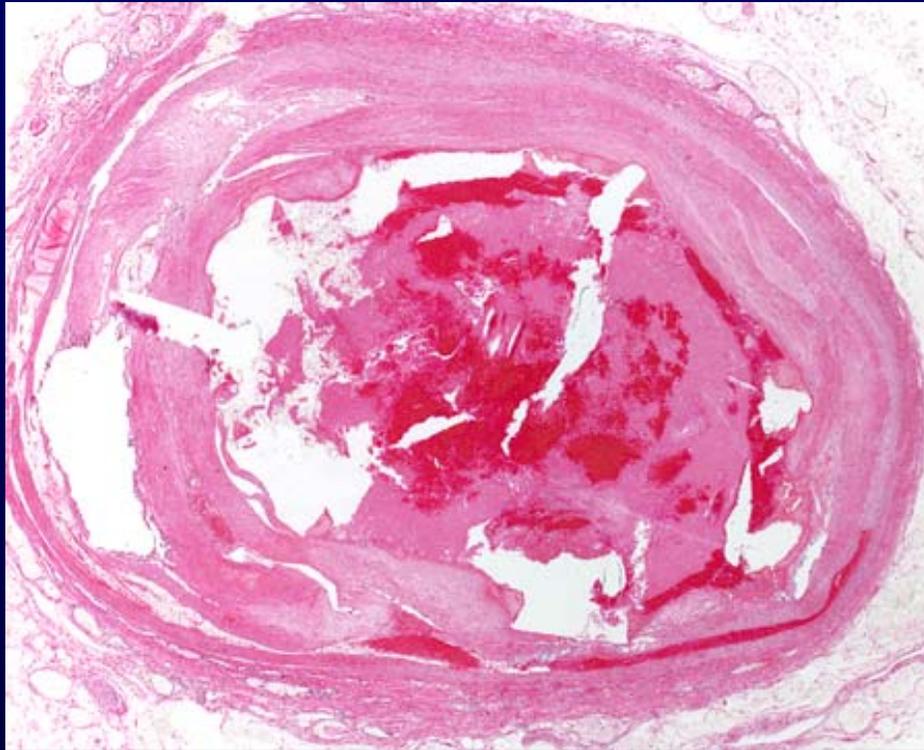
## SRL-Eluting



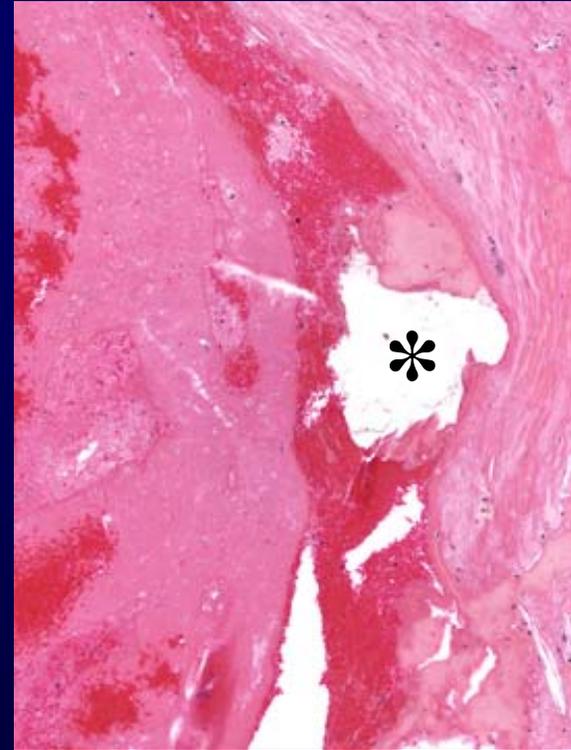
## Bare Metal Stent



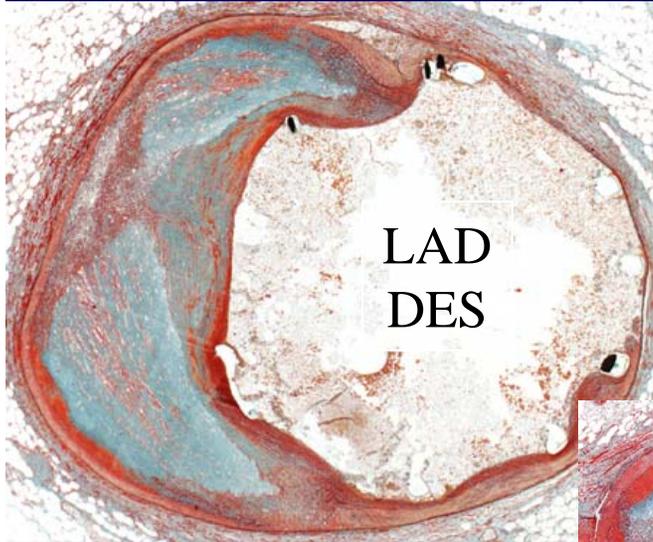
# Premature Discontinuation of Antiplatelet Therapy Late DES Thrombosis (38 days)



**Stent thrombosis**



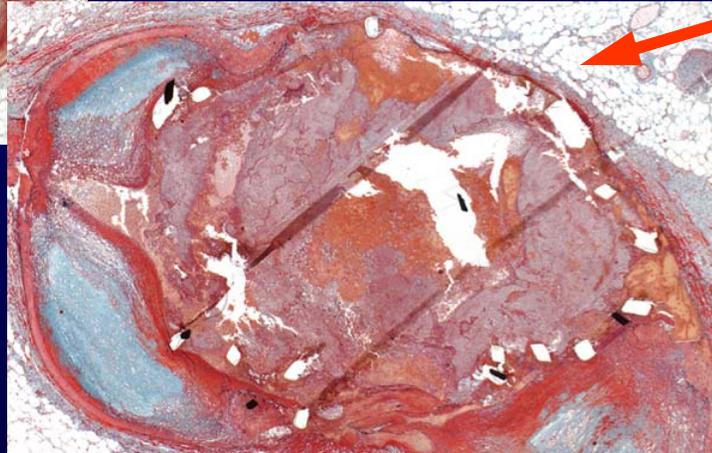
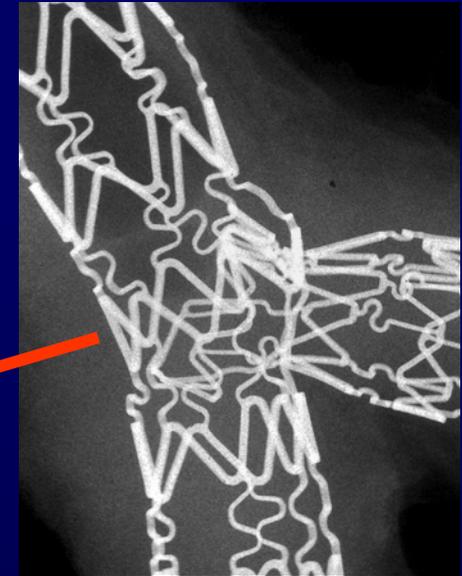
**Stent strut (\*) with  
overlying thrombus**  
•No neointima  
•No endothelium



LAD  
DES

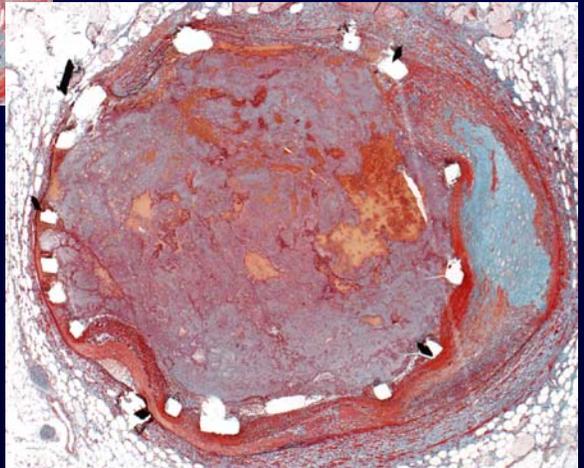
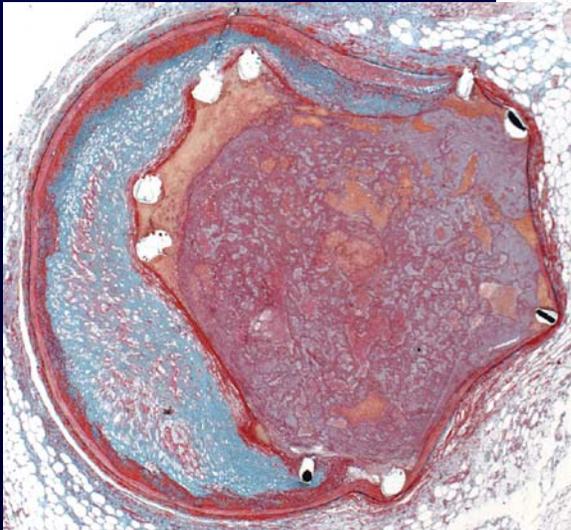
Acute Thrombosis of  
LAD DES and LD PC-  
Coated Stent

(Bifurcation Stenting)

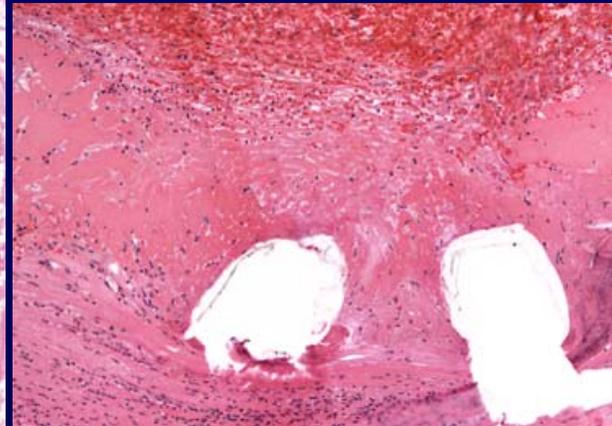
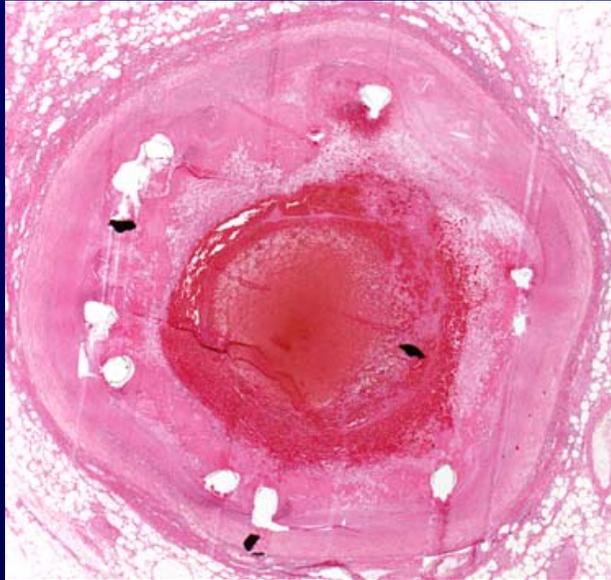


LAD DES

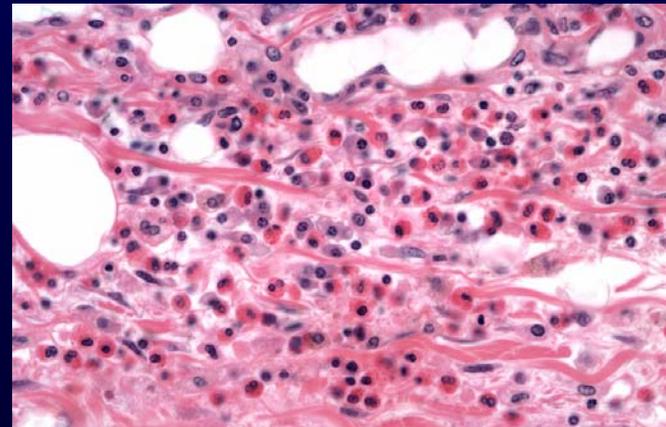
LD PC-coated BMS



# Late Stent Thrombosis 18 Months Post-CYPHER Stent



Impaired healing  
+  
Hypersensitivity  
(most likely  
to polymer)



Marked chronic inflamm + eos

**SRL-Stent  
Associated  
Hypersensitivity,  
Aneurysm  
Formation, &  
Thrombosis**

**CYPHER late stent thrombosis with aneurysm**

Virmani, Guagliumi, Farb, et al  
Circ 2004;109:701

DHHS/FDA

## Clinical importance of stent thrombosis: Death & MI

Author/yr	BMS/DES	ST Def	Death or MI	Death
Cutlip 2001	BMS	Angio or clinical	70%	21%
Heller 2001	BMS	Angio + AMI	100%	17%
Iakovou 2005	DES	Angio or clinical		45%
Ong 2005	DES	Angio & clinical	100%	25%
Kuchulakanti 2006	DES	Angio		31%

# Stent Thrombosis Rates in SIRIUS (CYPHER)

- Stent Thrombosis to 30 days
  - Definition : Subacute closure or unexplained death or Q-wave MI
  - Results: CYPHER 0.2% (1/533)  
Bx-Velocity 0.2% (1/525), p=NS
- Late Thrombosis to 360 days
  - Definition: MI occurring >30 days after the index procedure and attributable to the target vessel with angiographic documentation and freedom from an interim revascularization of the target vessel
  - Results: CYPHER 0.2% (1/533)  
Bx-Velocity 0.6% (3/525), p=NS

# Stent Thrombosis Rates in TAXUS IV (TAXUS)

- Definition of Stent Thrombosis
  - Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis
  - Acute MI in the distribution of the treated vessel
  - Death within first 30 days (without other obvious cause) if no angio performed
- Stent thrombosis through 12 months
  - Results: TAXUS 0.6%  
Express 0.8%, p=NS

# **Longer-term follow-up of on-label DES use (randomized clinical trials)**

# CYPHER: SIRIUS Study Through 1440 Days

Measure	CYPHER % (n)	Bx Velocity % (n)	p-value
Target vessel failure (CI)	19.6% (99/506)	33.5% (168/501)	<0.001
Major adverse cardiac events (CI)	17.2% (87/505)	31.9% (160/501)	<0.001
Target lesion revascularization (KM)	91.7%	75.4%	<0.001
Late thrombosis (incidence 31-1440 days)	0.8% (4/502)	0.6% (3/493)	1.00

994/1058 ITT (94.0%) patients had 4 year follow-up ( $\geq 1410$  days)

# TAXUS IV Pivotal Study Through 3 Years

Measure	TAXUS % (n)	Control % (n)	p-Value
<b>3-Year MACE</b>	18.9% (116/614)	29.0% (178/613)	<0.0001
Cardiac Death	2.6% (16/614)	2.6% (16/613)	1.0000
MI	5.9% (36/614)	6.5% (40/613)	0.6380
TVR, Overall	13.7% (84/614)	24.1% (148/613)	<0.0001
Stent Thrombosis	0.8% (5/594)	1.2% (7/595)	ns

Clinical follow-up available on >95% patients at 3 years

Of the Stent thromboses:

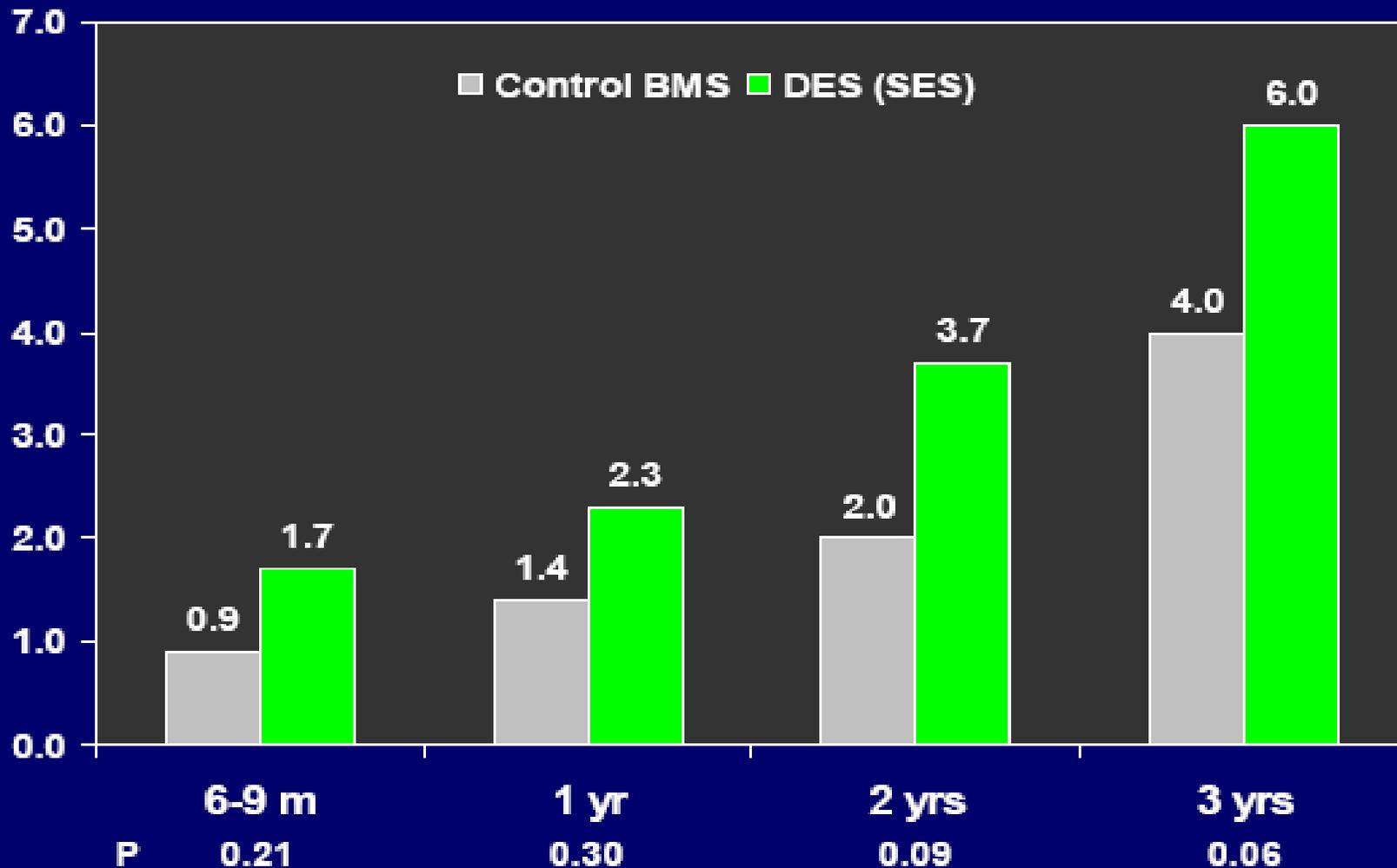
- 3 (0.5%, 3/641) occurred between 1 and 2 years for TAXUS and no additional stent thromboses beyond 2 years
- No additional stent thromboses after 6 months in the control group

**DES late thrombosis concerns:  
Recent meta-analyses of  
randomized clinical trials of DES**

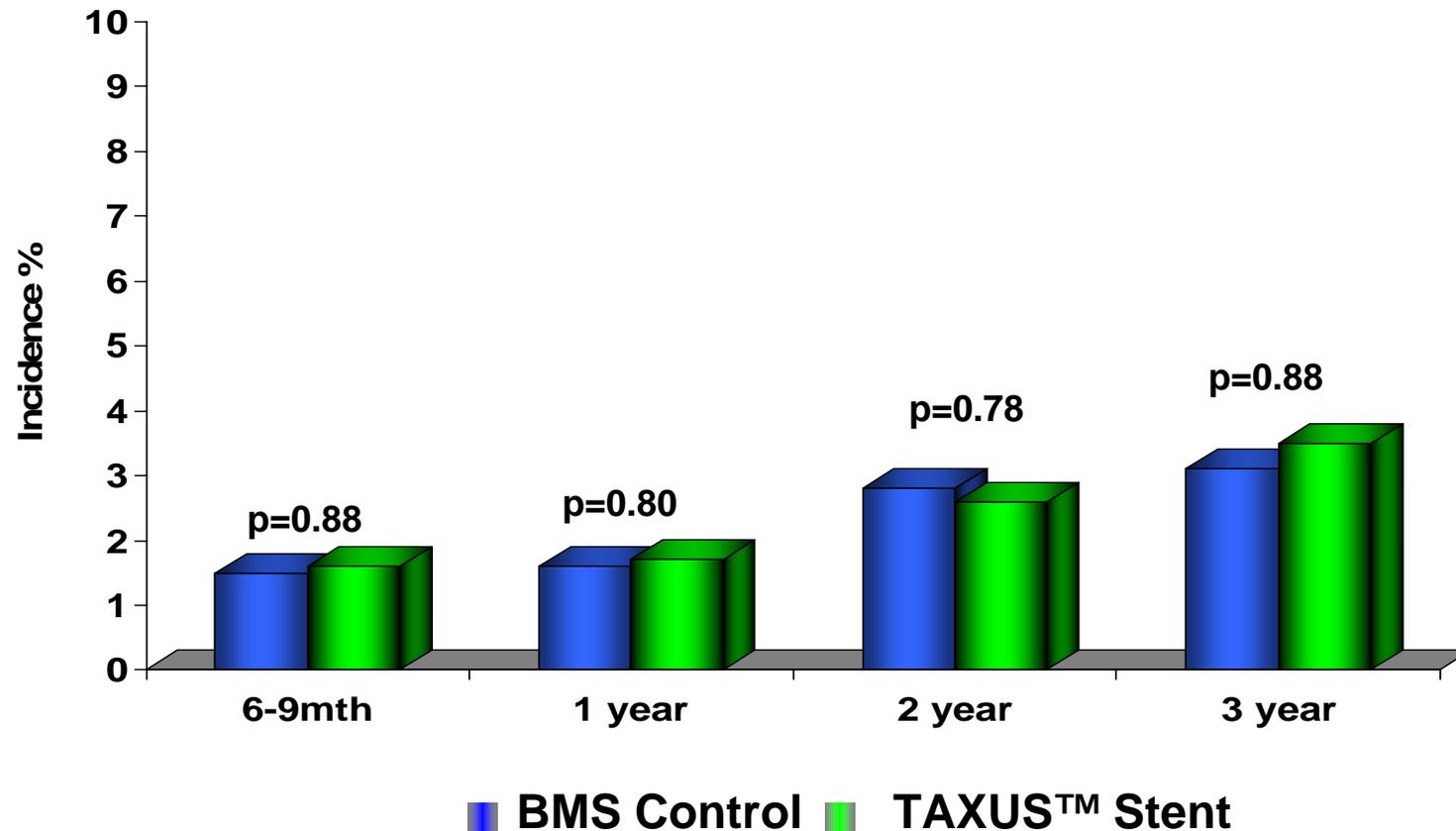
# Adverse Events (Death & Q-wave MI)

Meta-Analysis: RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

ESC/WCC 2006 Barcelona

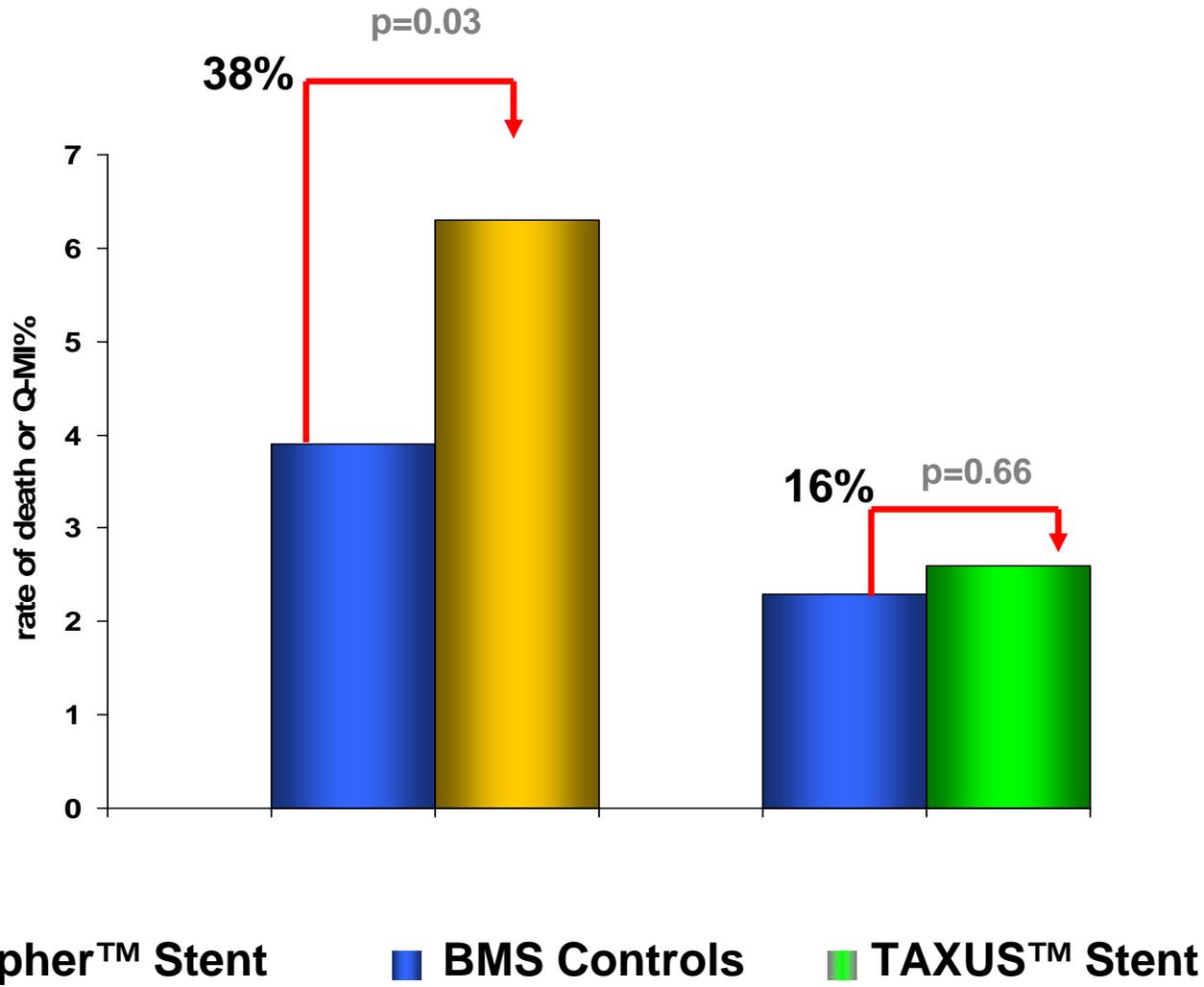


# Incidence of Death and Q-wave MI TAXUS I, II, IV, V, VI studies

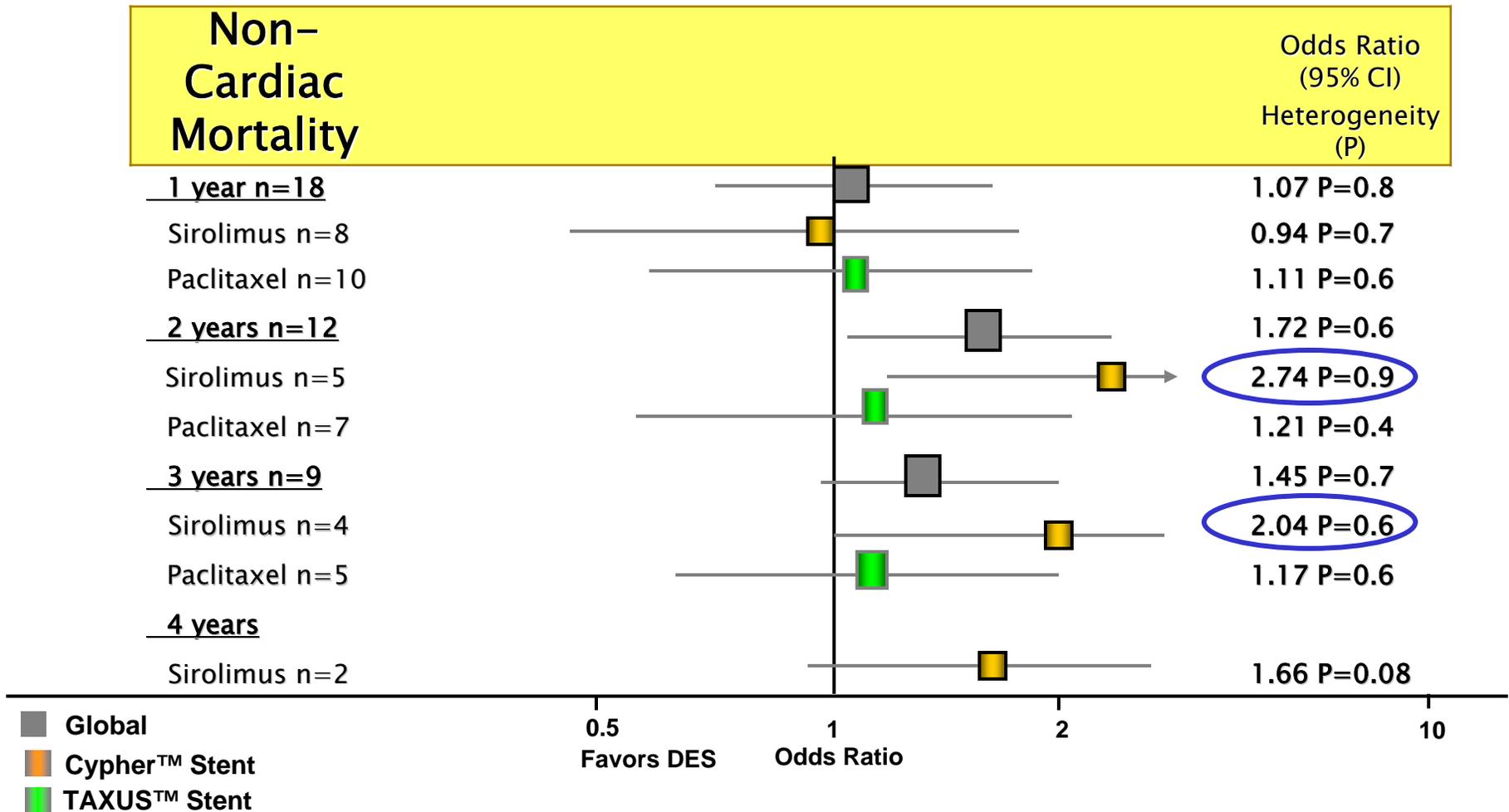


# Incidence of Death or Q-Wave MI

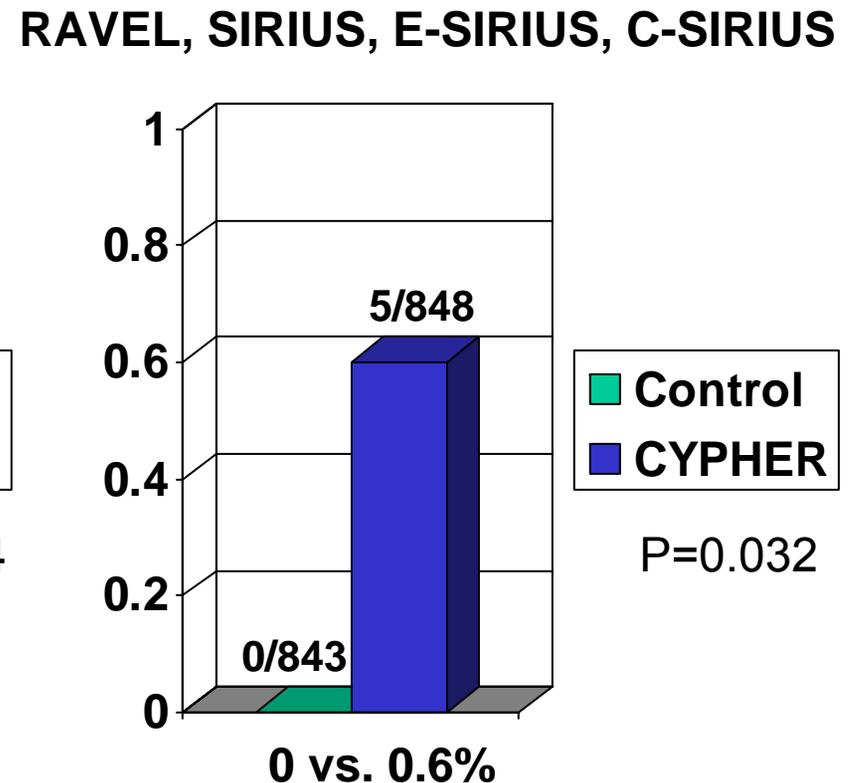
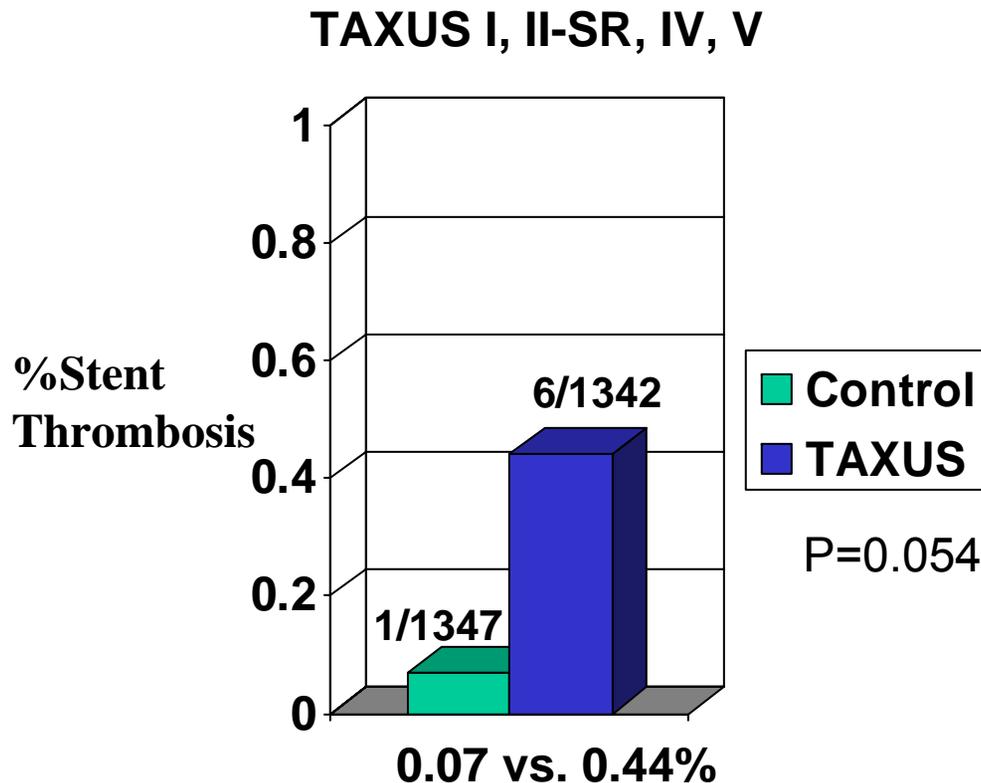
Randomised trials up to latest available follow up



# Meta-analysis of 17 randomized trials comparing CYPHER and TAXUS stents to bare metal stents



# Stent Thrombosis >1 Year Post-Implant Pooled RCT's Per Protocol Definitions



Both DES companies report independent analyses showing no overall differences in both TAXUS and CYPHER stents vs. BMS with respect to:

- Death (All & cardiac & non-cardiac)
- MI
- Death or MI

## Diabetic Subgroup Analyses: Pooled RCT's

	<b>CYPHER</b>	<b>BMS</b>	<b>P</b>	<b>TAXUS</b>	<b>BMS</b>	<b>P</b>
<b>Mortality (%)</b>	<b>11.8</b>	<b>4.3</b>	<b>0.006</b>	<b>9.2</b>	<b>10.7</b>	<b>NS</b>
<b>MI (%)</b>	<b>6.2</b>	<b>8.2</b>	<b>NS</b>	<b>7.2</b>	<b>7.4</b>	<b>NS</b>
<b>ARC Def/Prob ST (%)</b>	<b>1.0</b>	<b>2.1</b>	<b>NS</b>	<b>2.2</b>	<b>1.4</b>	<b>NS</b>

- Post-hoc analysis
- None of the RCT's prespecified hypotheses for patients with diabetes
  - No stratified randomization
- Studies not powered to detect differences in endpoints
- Neither DES specifically labeled for use in diabetics

# New Considerations in the Definition of Stent Thrombosis

- Definitions of stent thrombosis differed between the two approved DES and varies among published studies
- Identifying cases of DES thrombosis to determine the true frequency is problematic
- Stent thrombosis detected during coronary angiography or at autopsy is unequivocal evidence, but...
  - Many patients do not undergo follow-up angiography
  - Autopsy rates in the US are exceedingly low
  - Counting only cases of unequivocal stent thrombosis underestimates the true rate

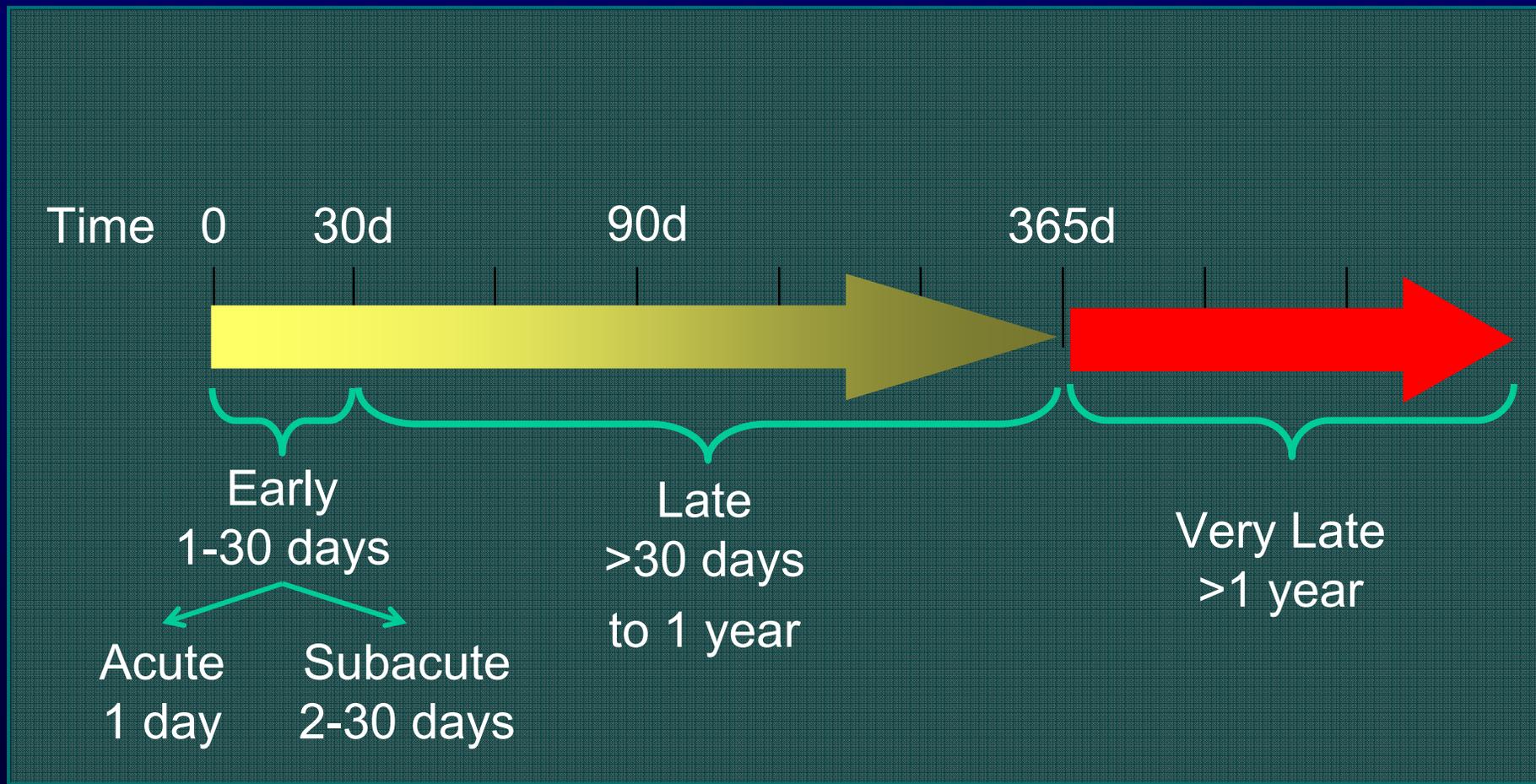
# New Considerations in the Definition of Stent Thrombosis

- Conversely, ascribing all new myocardial infarctions or sudden cardiac deaths to stent thrombosis inflates the rate of DES thrombosis
  - Coronary atherosclerosis is a multifocal, often progressive disease
  - Patients may have events secondary to rupture of a de novo plaque or die suddenly due to a lethal arrhythmia in the absence of stent thrombosis

# New Considerations in the Definition of Stent Thrombosis

- In recognition of the limitations inherent in establishing the precise incidence of stent thrombosis, FDA has participated in the Academic Research Consortium (ARC)
  - Roundtable of investigators, industry, and regulators to propose working definitions for DES adverse events, including stent thrombosis (based on available clinical evidence in each case) and the timing of the occurrence of the thrombotic event
- For the purposes of the discussion at the FDA Advisory Panel meeting
  - FDA finds the ARC definitions acceptable
  - Has requested Sponsors to apply them to their datasets when possible

# Stent Thrombosis Time Frame Classification



# Broader DES Use

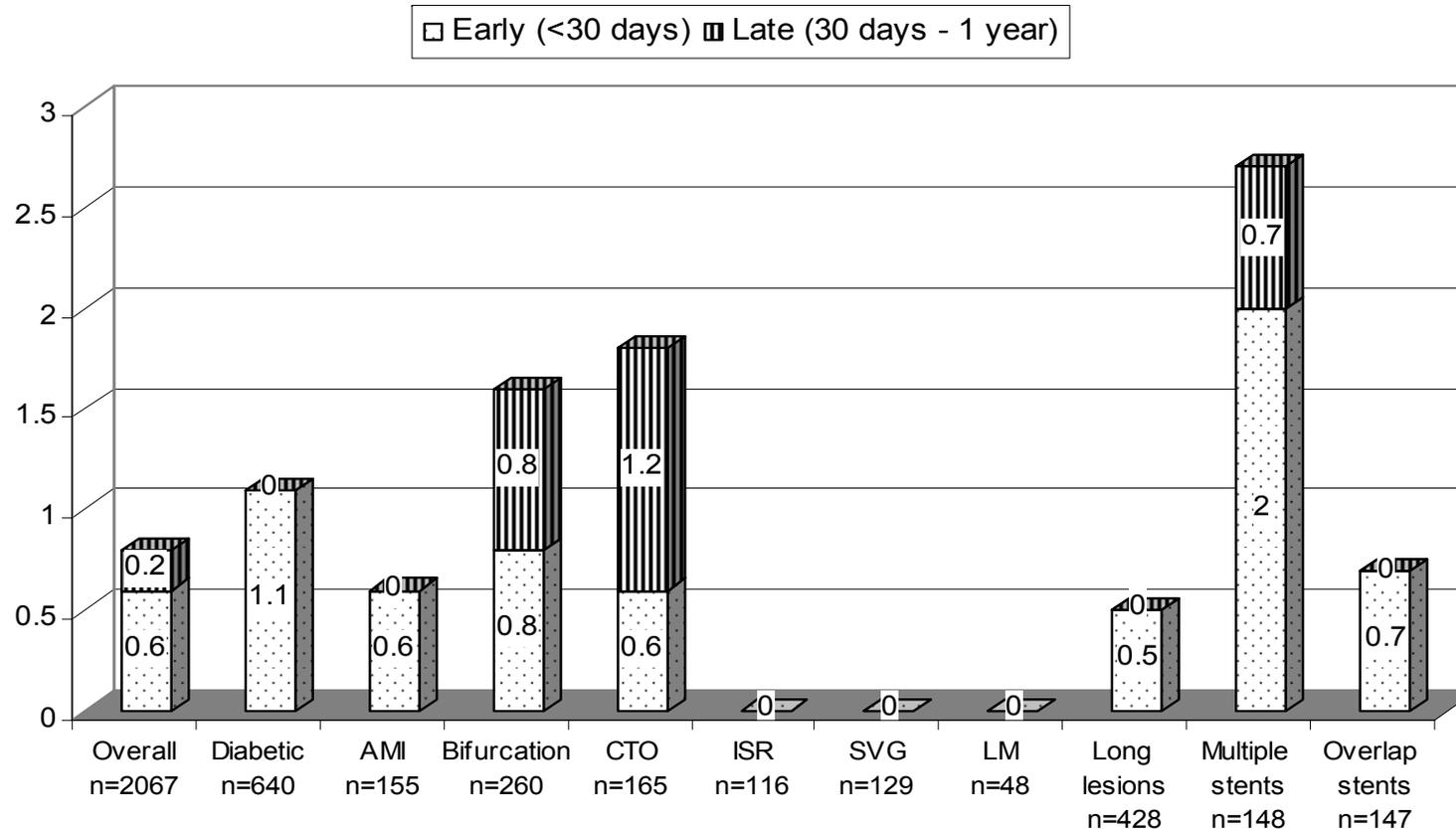
- Lesion subsets
  - Multivessel disease
  - Left

**At least 60% of current  
DES use is outside of the label**

- Small vessels
  - SVG's
- High risk patient subsets
  - Diabetics
  - Renal dysfunction

# e-Cypher US Post-Market Registry of 2067 Patients

## Stent Thrombosis rates (%) at 1 year: Subgroup analysis



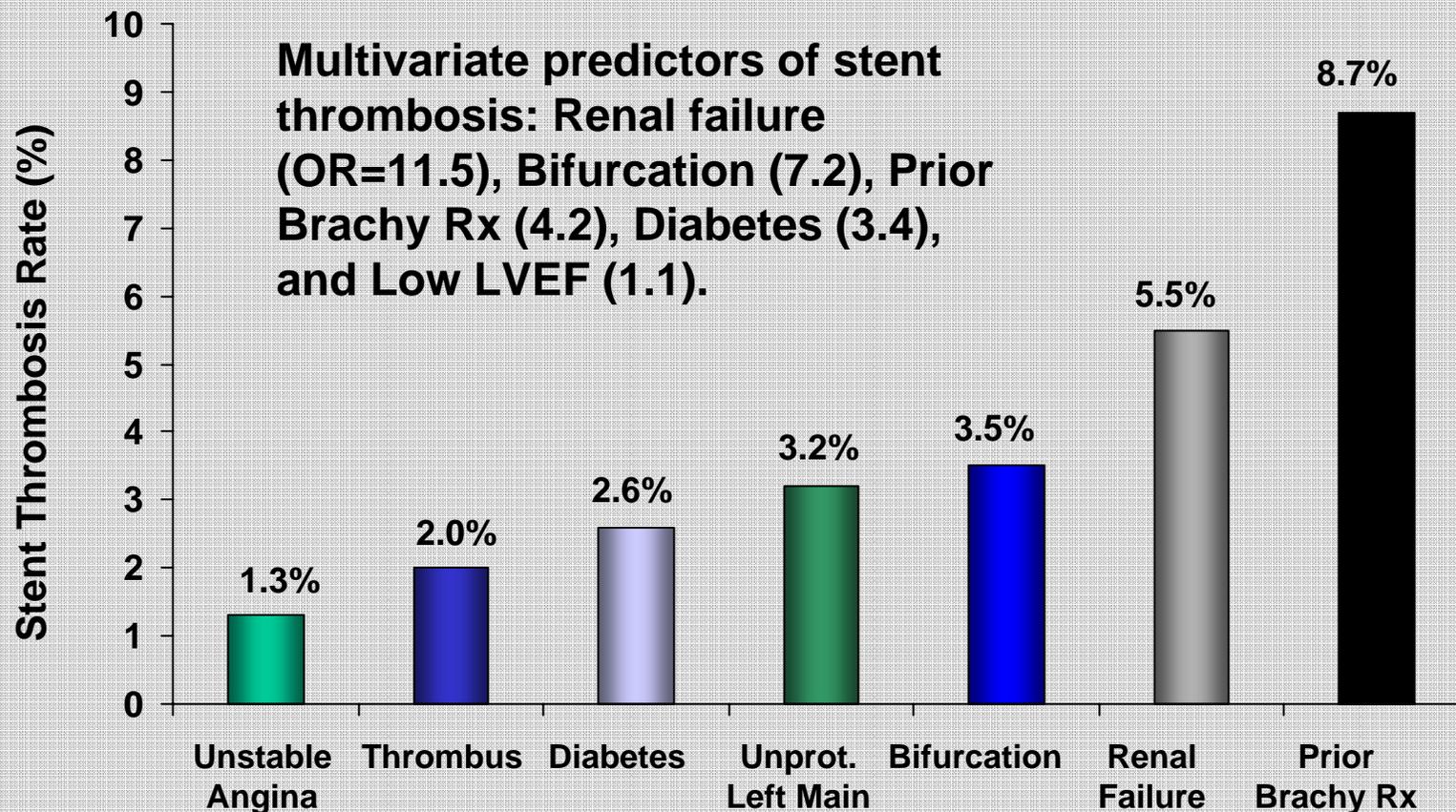
# The TAXUS ARRIVE 1 Peri-Approval Registry of 2585 Patients

Stent thrombosis rates through 12 months in selected complex patient/lesion subsets

	Long Lesions (> 20 mm)	Patients with Multiple TAXUS Stents	Lesions with Multiple TAXUS Stents	Multi-vessel Stenting	Bifurcations	Acute MI	Diabetic	Insulin-Requiring Diabetic
Stent Thrombosis	3.7% (23/624)	3.4% (34/1009)	4.1% (14/340)	3.8% (16/421)	3.5% (7/198)	2.9% (7/242)	3.1% (23/750)	6.3% (15/238)

# Incidence of Stent thrombosis after DES

2229 consecutive with successful DES implantation  
ASA indefinitely; Plavix or Ticlid  $\geq 3$  months (SRL) and  $\geq 6$  months (PXL)



Iakovou I et al. JAMA 2005;293:2126-2130

# Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluting Stents

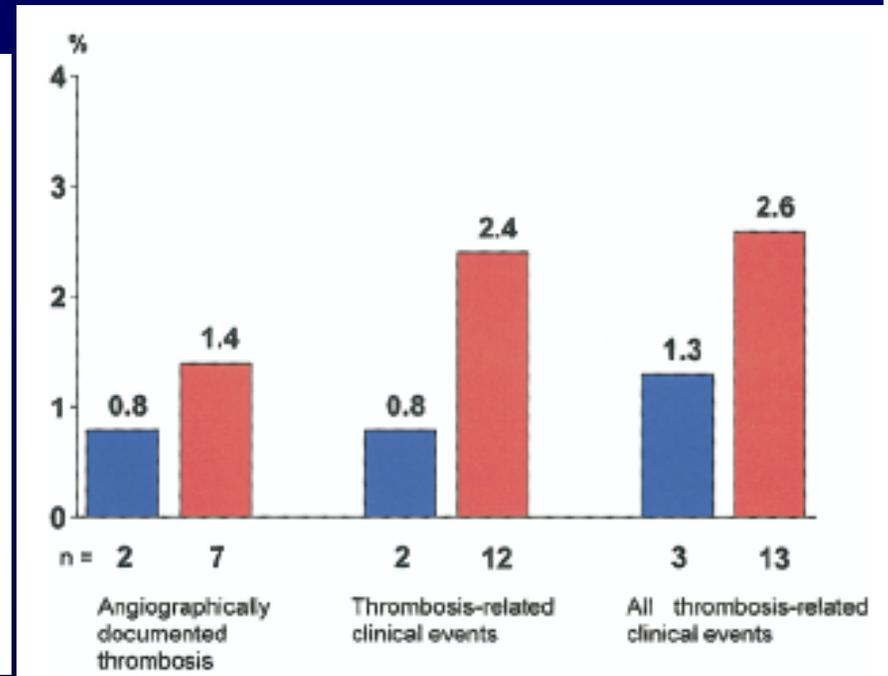
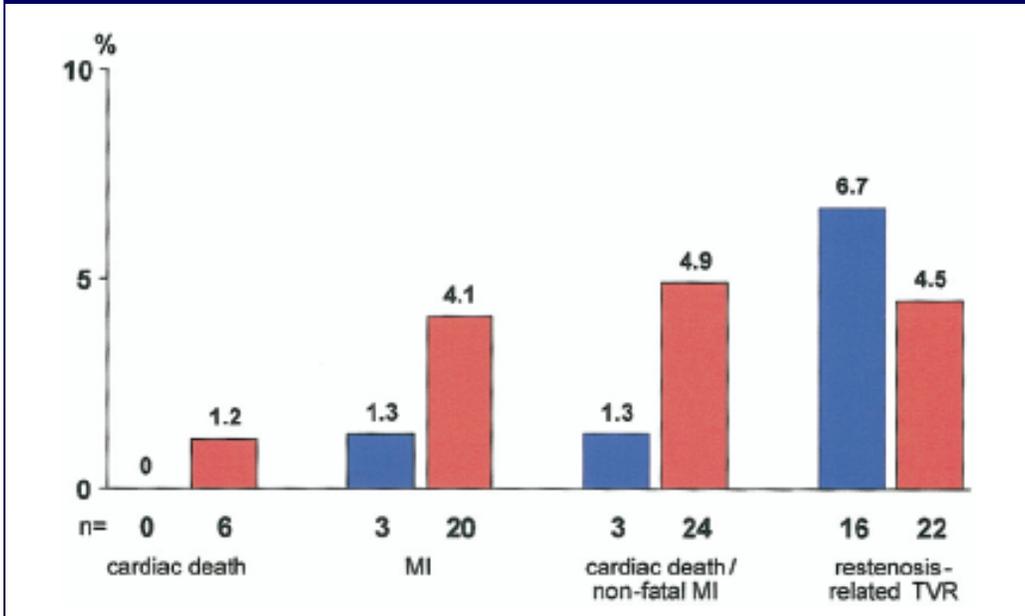
An Observational Study of Drug-Eluting Versus Bare-Metal Stents

Matthias Pfisterer, MD, FACC,\* Hans Peter Brunner-La Rocca, MD,\* Peter T. Buser, MD, FACC,\*

- The BASKET study: RCT - TAXUS or CYPHER vs. BMS
  - 21.0% with STEMI, 36.7% with UAP, 66.8% with multivessel disease
  - $1.9 \pm 1.0$  stents per patient,  $33 \pm 20$  mm total stent length per patient
- 746 patients who survived the first 6 months without nonfatal MI or repeat TVR enrolled in BASKET-LATE study and followed for additional 12 months
- Clopidogrel treatment stopped 6 months post-stenting
- Compared late events occurring between 7 and 18 months after stenting
  - Consisted of any cardiac death and documented nonfatal MI
  - All sudden cardiac deaths and all MI's attributable to the target vessel were considered to be "thrombosis-related"

*Pfisterer et al. J Am Coll Cardiol 2006; 48: in press*

# Basket-Late Results 7 – 18 Months Post-Stenting



Drug-Eluting Stent



Bare Metal Stent

*Pfisterer et al. J Am Coll Cardiol 2006; 48: in press*

# Full BASKET Cohort – 18 month results

- ESC Scientific Congress, September 2006
- Full 18-month results on all 826 patients in BASKET
- Rates of noninfarct-related target vessel revascularization lower in DES-treated patients
- No significant differences in rates of death/MI or overall MACE between treatment groups

## BASKET: 18-month outcomes

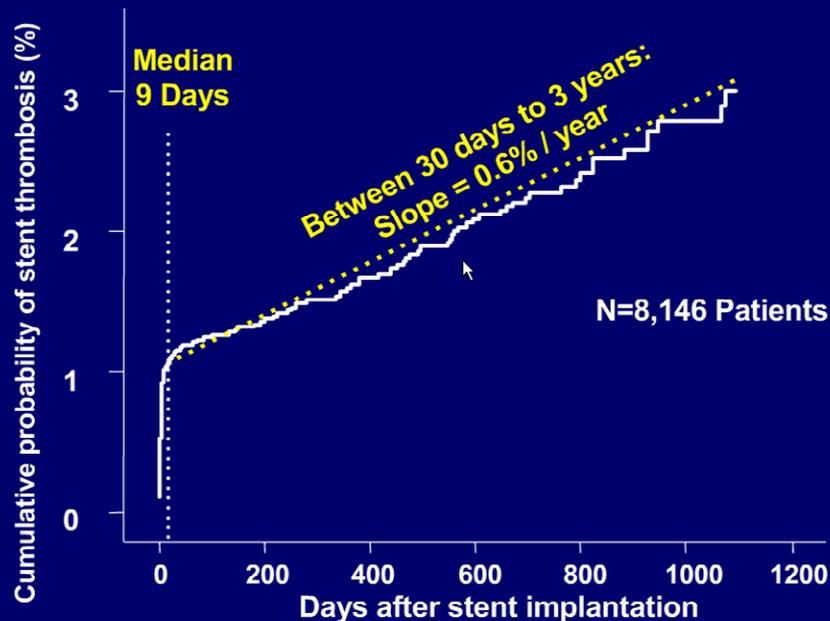
End point (%)	Bare-metal stent	DES	p
Death/MI	7.5	8.4	0.63
Noninfarct TVR	11.6	7.5	0.05
MACE	18.9	15.8	0.26

Kaiser C. World Congress of Cardiology 2006; September 2-6, 2006; Barcelona, Spain.

# SIRTAX, Post-SIRTAX, RESEARCH and T-SEARCH Registries

- 8,146 patients enrolled in the SIRTAX & Post-SIRTAX registries in Bern and the RESEARCH & T-SEARCH registries in Rotterdam
  - Only angiographically documented stent thromboses included
  - In Bern, dual antiplatelet therapy prescribed for 3-6 months
  - In Rotterdam, dual antiplatelet therapy prescribed for 3-12 months
- 
- 152 stent thromboses in 8146 patients (2.9%, 1.3 per 100 patient-years)
  - 1.2% at 30 days
  - 1.7% at one year
  - 2.3% at two years
  - 2.9% at three years,
  - Corresponds to a stent thrombosis rate of 0.6% / year between 30 days and 3 years

## Angiographic DES Stent Thrombosis Bern - Rotterdam Cohort Study



Courtesy dr S. Windecker

# Antiplatelet Therapy

- Pivotal RCT's
  - SIRIUS trial (CYPHER): ASA indefinitely and clopidogrel or ticlopidine for 3 months
  - TAXUS IV trial (TAXUS stent): ASA indefinitely and clopidogrel or ticlopidine 6 months
  - Current DES labeling reflects these antiplatelet regimens
- Multiple studies demonstrate increased rates of DES thrombosis, MI, or mortality associated with premature discontinuation of dual anti-platelet therapy
- Emerging issues associated with antiplatelet therapy use post-DES use:
  1. Patient non-compliance with or early discontinuation of recommended antiplatelet therapy
  2. Uncertainty regarding the optimal duration of dual antiplatelet therapy

# TAXUS ARRIVE 1 Peri-Approval Registry

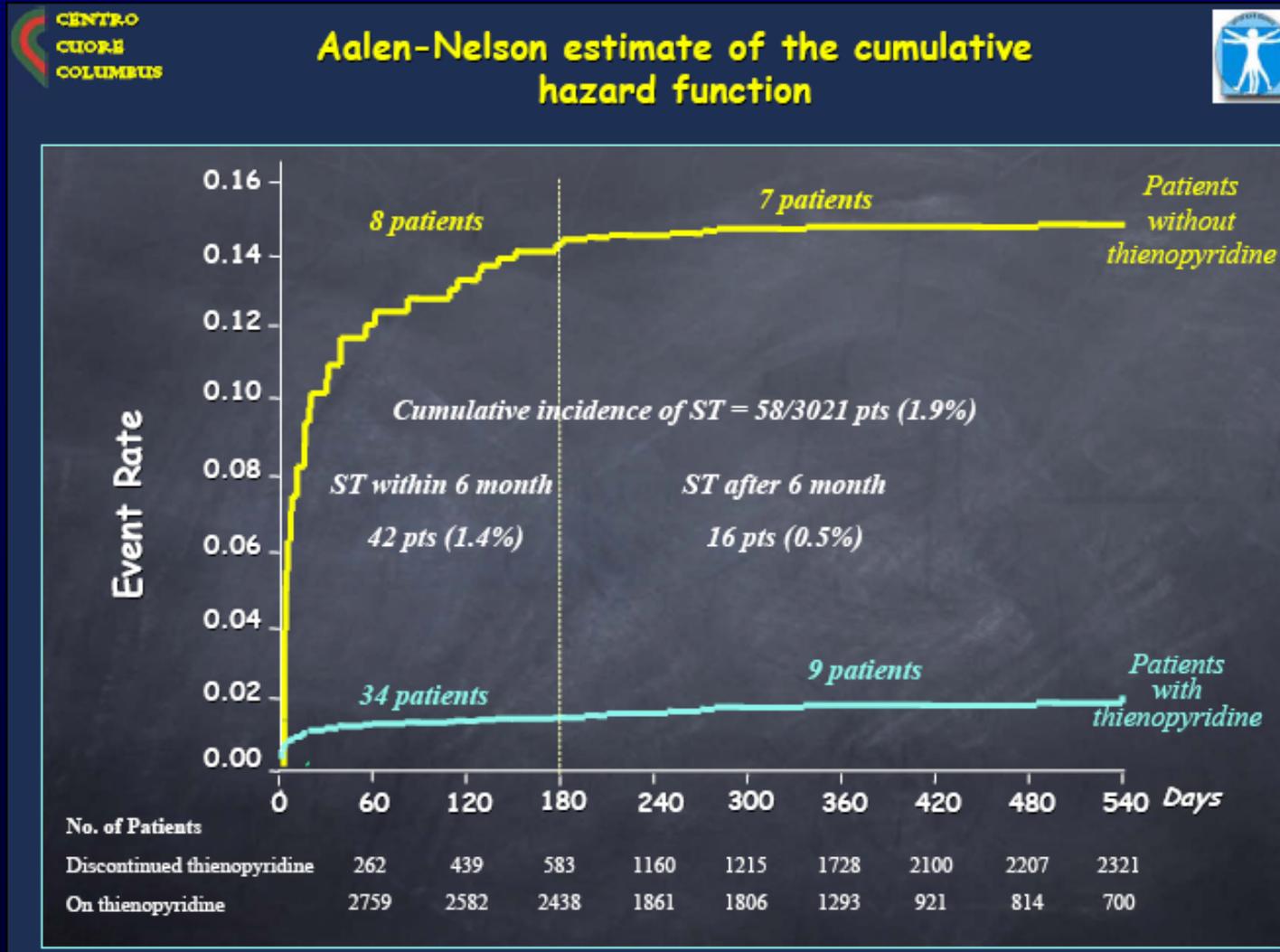
	Patients with ASA/Clopidogrel or ASA/Ticlopidine at:	Patients without ASA/Clopidogrel or ASA/Ticlopidine at:	
	<b>Discharge</b>	<b>Discharge</b>	<b>P-Value</b>
<b>1-Year Stent Thrombosis</b>			
Stent Thrombosis (by patient)	1.9% (44/2272)	3.8% (7/186)	0.1034
Stent Thrombosis (by vessel)	1.8% (49/2699)	5.2% (11/212)	0.0034
	<b>30-day</b>	<b>30-day</b>	<b>P</b>
<b>1-year Stent Thrombosis</b>			
Stent Thrombosis (by patient)	1.8% (42/2278)	5.0% (9/180)	0.0102
Stent Thrombosis (by vessel)	1.8% (48/2707)	5.9% (12/204)	0.0007
	<b>6-month</b>	<b>6-month</b>	<b>P-Value</b>
<b>1-Year Stent Thrombosis</b>			
Stent Thrombosis (by patient)	1.7% (37/2143)	4.4% (14/315)	0.0045
Stent Thrombosis (by vessel)	1.7% (43/2549)	4.7% (17/362)	0.0010

# Discontinuation of Antiplatelet Therapy & Stent Thrombosis

- *Iakovou et al., JAMA 2005*
  - An independent predictor of stent thrombosis was premature antiplatelet therapy discontinuation [rate 29% (5/17 patients), HR 89.78; 95% CI, 29.90-269.60;  $p < 0.001$ ].
- *Kuchulakanti et al. Circulation 2006*
  - The frequency of discontinuation of clopidogrel was significantly higher in patients with stent thrombosis compared to those without stent thrombosis (36.8% vs. 10.1%,  $p < 0.001$ )
  - Clopidogrel discontinuation was an independent predictor of stent thrombosis (OR 0.21, 95% CI 0.09-0.49,  $p = 0.0003$ ).

# Chieffo, TCT 2006

Discontinuation of Plavix beyond 6 months was not an independent predictor of thrombosis

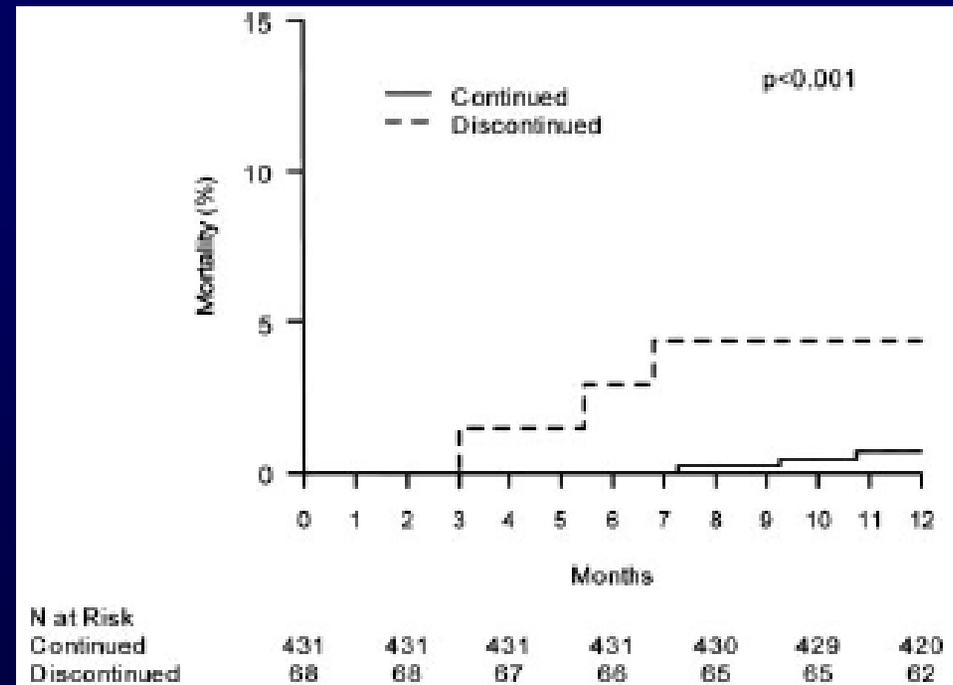


# PREMIER Registry

- 500 DES-treated acute MI patients discharged on clopidogrel therapy
- By 30 days, 68 patients (13.6%, 1 in 7) stopped therapy
- Patients who stopped clopidogrel therapy by 30 days were more likely to die during the next 11 months (7.5% versus 0.7%,  $P < 0.0001$ )

Those who stopped were:

- older
- less educated
- more likely to avoid health care because of cost
- less likely to have received discharge instructions about their medications
- less likely to receive a cardiac rehabilitation referral



Spertus et al. Circulation 2006; 113: 2803-2809

# Current Practice Guidelines

- ACC/AHA/SCAI PCI Practice Guidelines
  - Clopidogrel therapy for at least 3 months after CYPHER stent implantation, at least 6 months after TAXUS stent implantation
    - Reflects recommendations in the present label for the CYPHER and TAXUS stents, respectively
  - Ideally up to 12 months in patients who are not at high risk of bleeding (Class IB recommendation)
- The European Society of Cardiology
  - Clopidogrel administration for 6 to 12 months after DES implantation (Class IC recommendation)

# FDA Actions

- FDA recognized that patients may have their antiplatelet medications stopped inadvertently prior to elective procedures or need to have these agents stopped secondary to clinically significant bleeding
- Labeling changes: FDA worked collaboratively with DES manufacturers to inform cardiologists and patients of the need to continue anti-platelet therapy, without interruption, for its full recommended course.
  - Patients advised to consult their cardiologist before stopping antiplatelet therapy for any reason
- Requested review of emerging DES thrombosis data by 3 Advisory Panel members
- Meeting with DES manufacturers to review their data focused on stent thrombosis



[FDA](#) > [CDRH](#) > [News](#) > FDA Statement on Coronary Drug-Eluting Stents

*[Posted 9/14/06]*

## FDA Statement on Coronary Drug-Eluting Stents

- ❖ New data were released recently that suggest a small but significant increased risk of stent thrombosis in patients who have drug-eluting stents. The agency is keenly interested in this issue because of the potential for serious harm to patients—even though stent thrombosis occurs at low rates.
- ❖ While the new data are of interest to FDA and raise important questions, we do not have enough information yet to draw conclusions.
- ❖ FDA plans to convene a public panel meeting of outside scientific experts in the near future to assist us in a thorough review of *all* the data and make recommendations about what actions may be appropriate, such as possible labeling changes or additional studies.
- ❖ At this time, FDA believes that coronary drug-eluting stents remain safe and effective when used for the FDA-approved indications.

# Review of Adverse Event Reporting Data on DES

Andrea Holton, Ph.D.

# CDRH's Adverse Event Reporting System

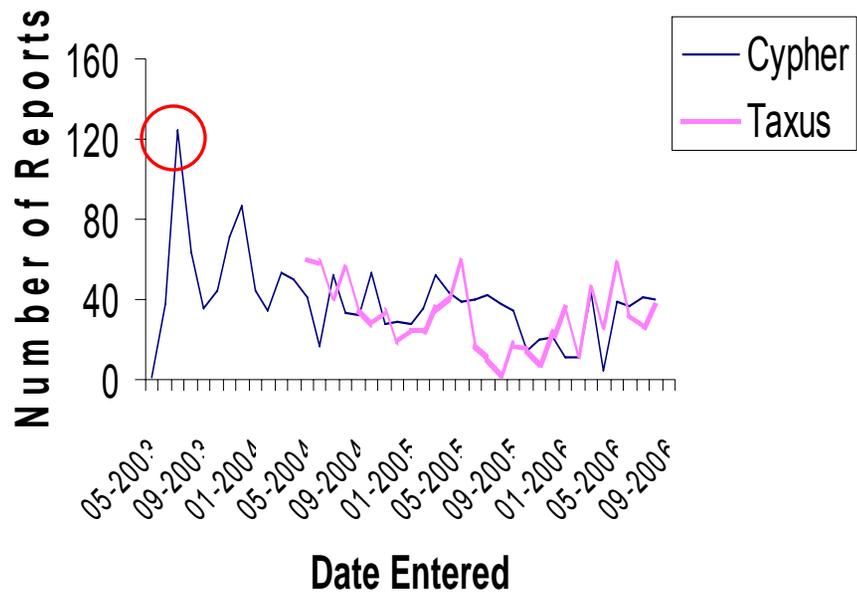
- Nationwide passive surveillance
- Mandatory and voluntary reporting
- Types of reports

# Methods

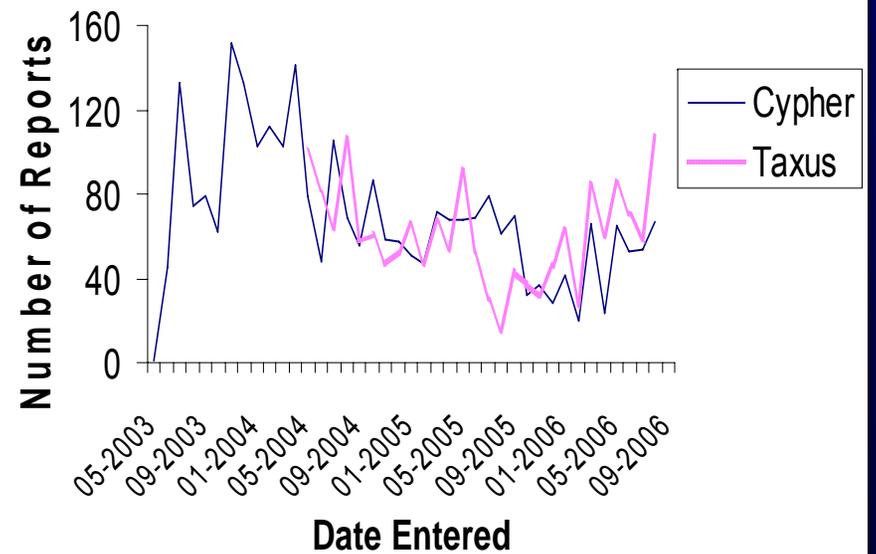
- Brand names: Cypher and Taxus
- Dates: April 2003 and March 2004 thru August 2006
- Patient problems: Thrombosis
- Patient problems: Thrombosis and/or patient signs/symptoms or cardiac events

# Results

## Thrombosis DES Reports



## Thrombosis + Associated Events DES Reports



# Limitations of MDR

- Underreporting/ no incidence data
- Inadequate/non-validated data
- Uncertain causality
- Biased reporting

# Considerations in Interpretation of Available Data

Hesha J. Duggirala, PhD, MPH

# Limitations of data – Post-approval registries

- These registries were meant to be descriptive (non-hypothesis driven) and non-comparative (i.e., without controls)
- Were only “powered” to confidently detect adverse events rates in the registry population on the order of one percent
- FDA seeks Panel input on whether currently mandated post-approval studies should be modified

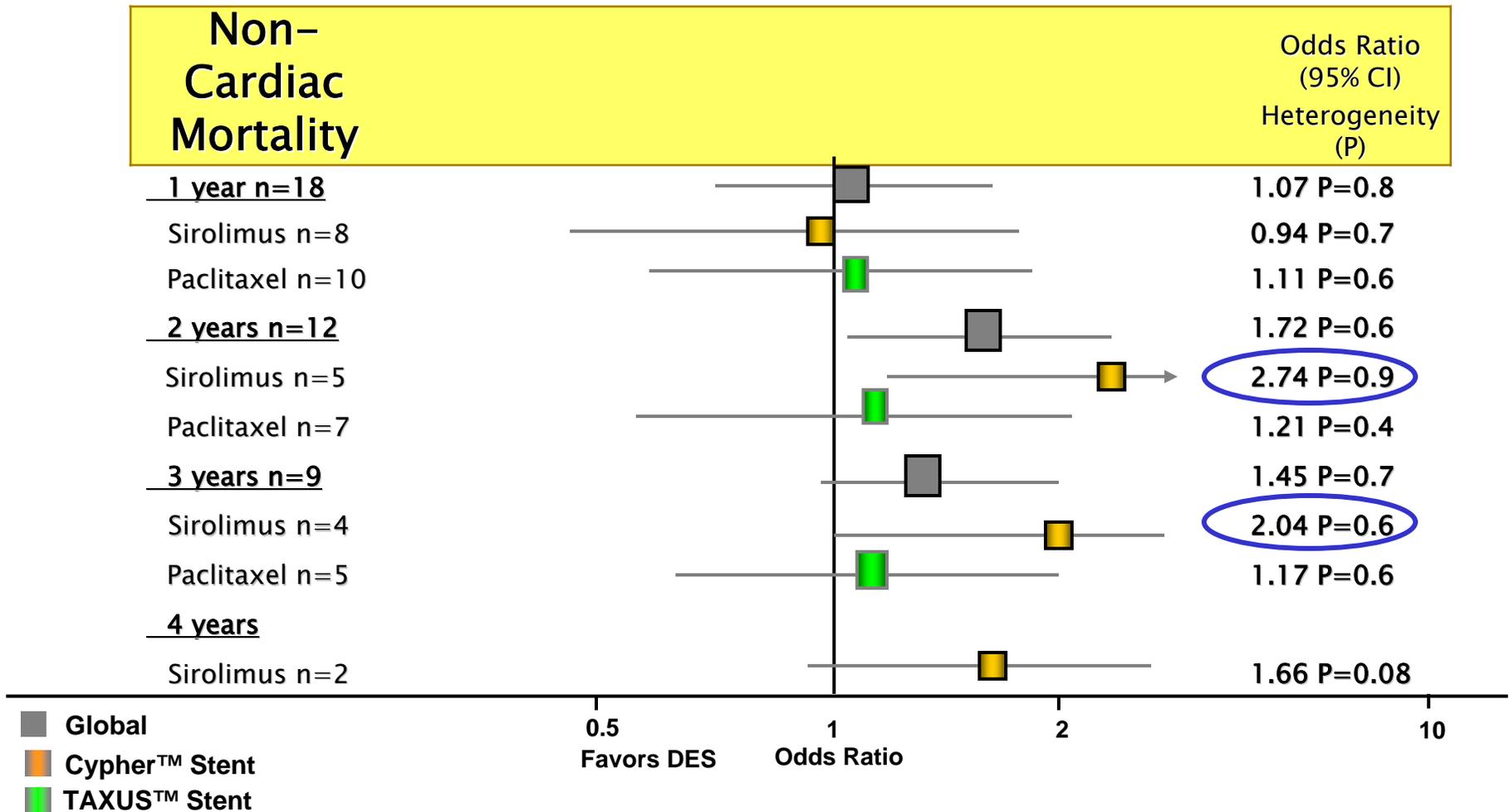
# Recent meta-analyses

- European Society of Cardiology (ESC), September 2006
  - Camenzind
  - Nordmann
- Transcatheter Cardiovascular Therapeutics (TCT), October 2006
  - Leon
  - Stone

# Types of meta-analyses

- Group-level analysis
  - Data available at level of published study
- Patient-level analysis
  - Data accessible at level of individual patient

# Meta-analysis of 17 randomized trials comparing CYPHER and TAXUS stents to bare metal stents



# Nordmann meta-analysis

- Key finding associated with non-cardiac mortality
- Publication bias cannot be ruled out
- Unclear if stent thrombosis was a pre-specified endpoint
- Differential loss to follow-up across studies
- No established mechanism to relate non-cardiac mortality to DES

# Preferred meta-analysis methods

- Prefer patient-level analysis
- Pre-specified study hypothesis and study protocol
- Complete data capture: published and unpublished trials
- Consistent data extraction methods
- Accurate definitions of outcomes
- Quantitative data synthesis
- Methods vetted in peer-review process

# Conclusions

# Conclusions

- Data available to FDA indicate that the currently approved DES (CYPHER and TAXUS), when implanted in accordance with their labeled intended use, are associated with:
  - Reduced rates of repeat procedures to treat restenosis compared to bare metal stents
  - A small but significant increased risk of late stent thrombosis (emerging 1-year post stent placement) compared to bare metal stents.
- It is not been established whether these thrombosis events translate into increased rates of death and MI.
- The total number of patients  $\geq 3$  years post-stenting remains relatively small, and it is uncertain whether cases of late stent thrombosis will continue to accrue with longer-term follow-up.

# Conclusions

- Studies indicate increased rates of DES thrombosis, MI, or mortality associated with premature discontinuation of dual anti-platelet therapy.
- The optimal duration of dual antiplatelet therapy, particularly in more complex patient and lesion subsets, is unknown
- It is not known whether an extended course of dual-antiplatelet therapy will prevent late thrombosis.
  - A recommendation for an increased duration of dual antiplatelet therapy must consider a potential benefit of a reduction in the incidence of stent thrombosis versus a potential increase in the risk of major bleeding

# Conclusions

- Since stent thrombosis is associated with high rates of death and myocardial infarction, continued efforts to clarify the mechanisms of stent thrombosis and interventions to reduce the risk of its occurrence will have public health benefits

Thank you



# BACK-UP SLIDES

## Bavry meta-analysis

- Found DES increase risk for late stent thrombosis
- Analytic methods not clear from publication
- Many studies included did not have follow-up > 1 year