

# ***Next Generation Drug-eluting Stent : Will It Solve the Problem?***

**Yangsoo Jang, M.D., Ph.D, FACC**

**Severance Cardiovascular Hospital**

**Yonsei University Healthcare System**

# Commercially Available DES

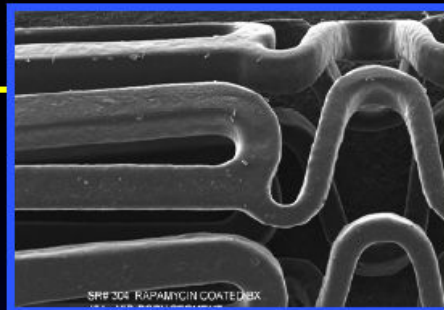
**Cypher**

**Drug**



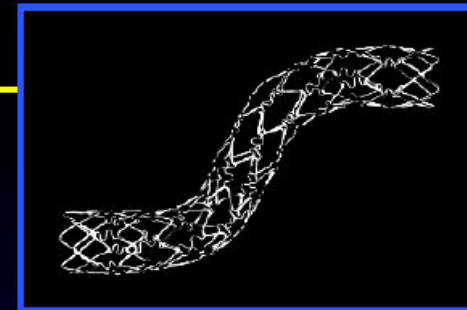
Sirolimus

**Polymer**



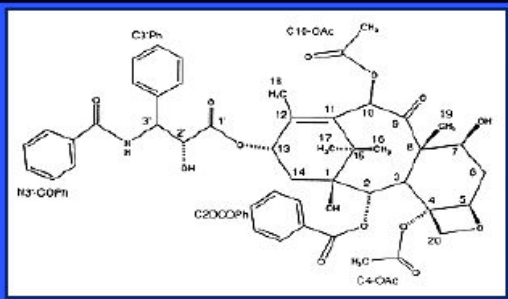
PEVA + PBMA blend

**Stent**

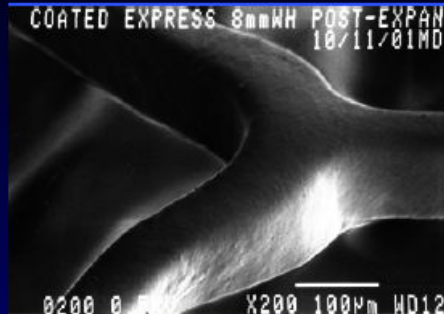


BX Velocity

**TAXUS**



Paclitaxel

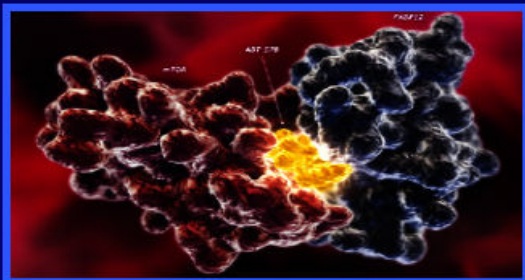


Polyolefin derivative

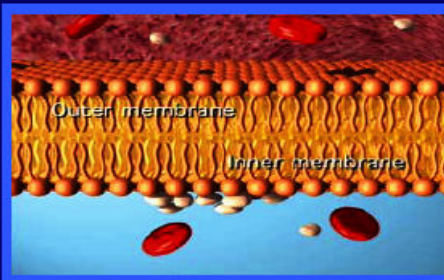


Express<sup>2</sup>

**Endeavor**



Zotarolimus



PC Coating



Driver Cobalt

# An Epidemic of Madness

## ESC Congress News



WORLD HEART  
FEDERATION\*

World Congress of Cardiology 2006

The unique meeting of the European Society of Cardiology Congress 2006  
and the World Heart Federation's XVth World Congress of Cardiology



## Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is 'unknown,'" said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more

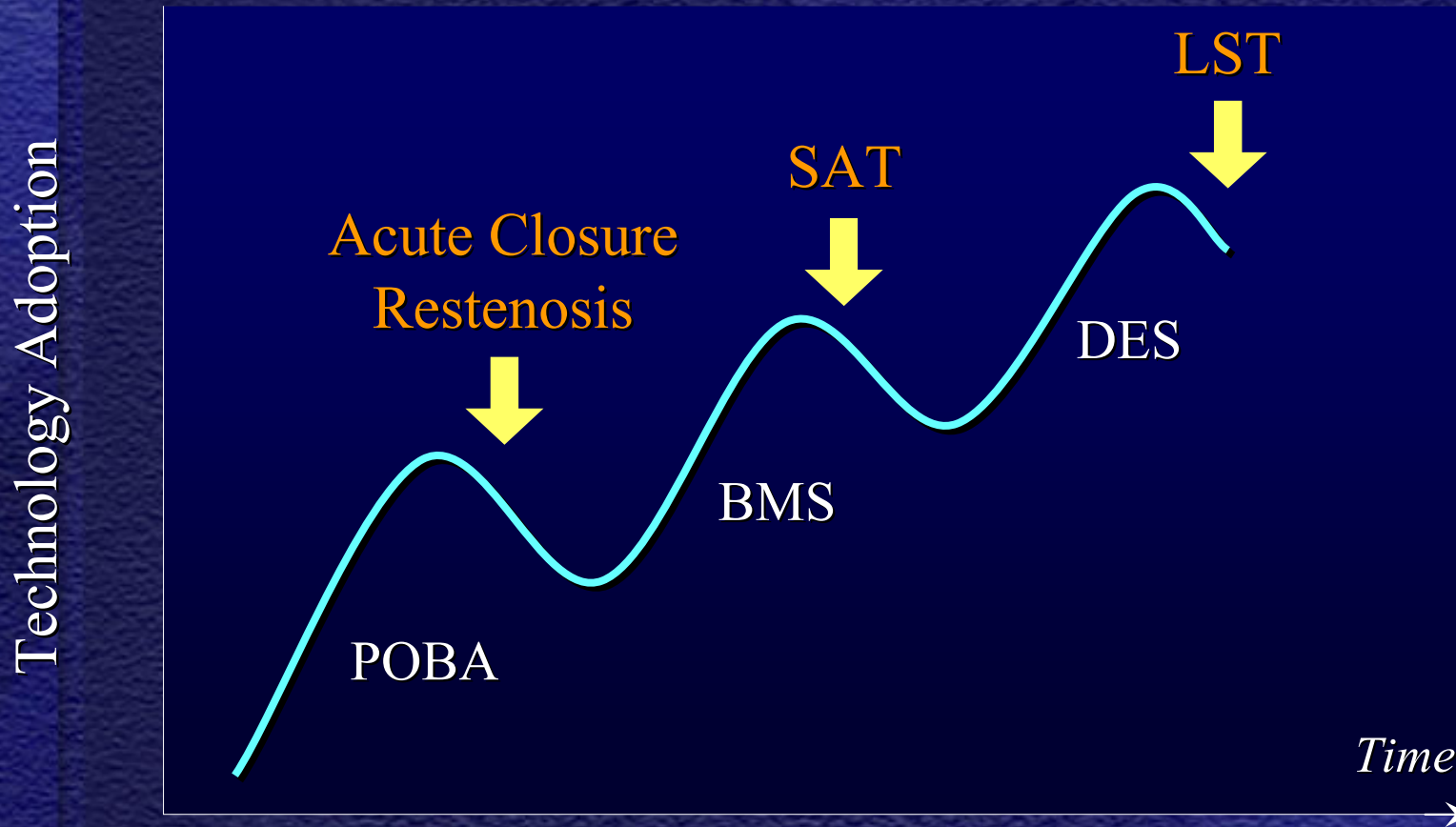


obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality - PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest

# Technology “in part” Solves Issues



- *Tsimikas, S. Drug-eluting stents and late adverse clinical outcomes: lessons learned, lessons awaited. JACC 2006*

# *The Changing balance between DES & BMS in USA:*



*91 % >>>> 71 %*

*65 % : 35 %*

*DES : BMS*

*June, 2007*

# Long-Term Outcomes with DES vs. BMS in Sweden



## CONCLUSIONS

Drug-eluting stents were associated with a higher rate of death, as compared with bare-metal stents. This difference was significant after 6 months, when the risk of death was 0.5 percentage point higher for drug-eluting stents and a composite of death or myocardial infarction

**Dangerous**

## No. at Risk

|                    |        |        |        |        |      |      |      |
|--------------------|--------|--------|--------|--------|------|------|------|
| Bare-metal stent   | 12,880 | 12,473 | 12,354 | 12,228 | 9298 | 5966 | 3199 |
| Drug-eluting stent | 5,770  | 5,605  | 5,541  | 5,471  | 3434 | 1777 | 626  |

# ***LaST: Is There A Problem?***

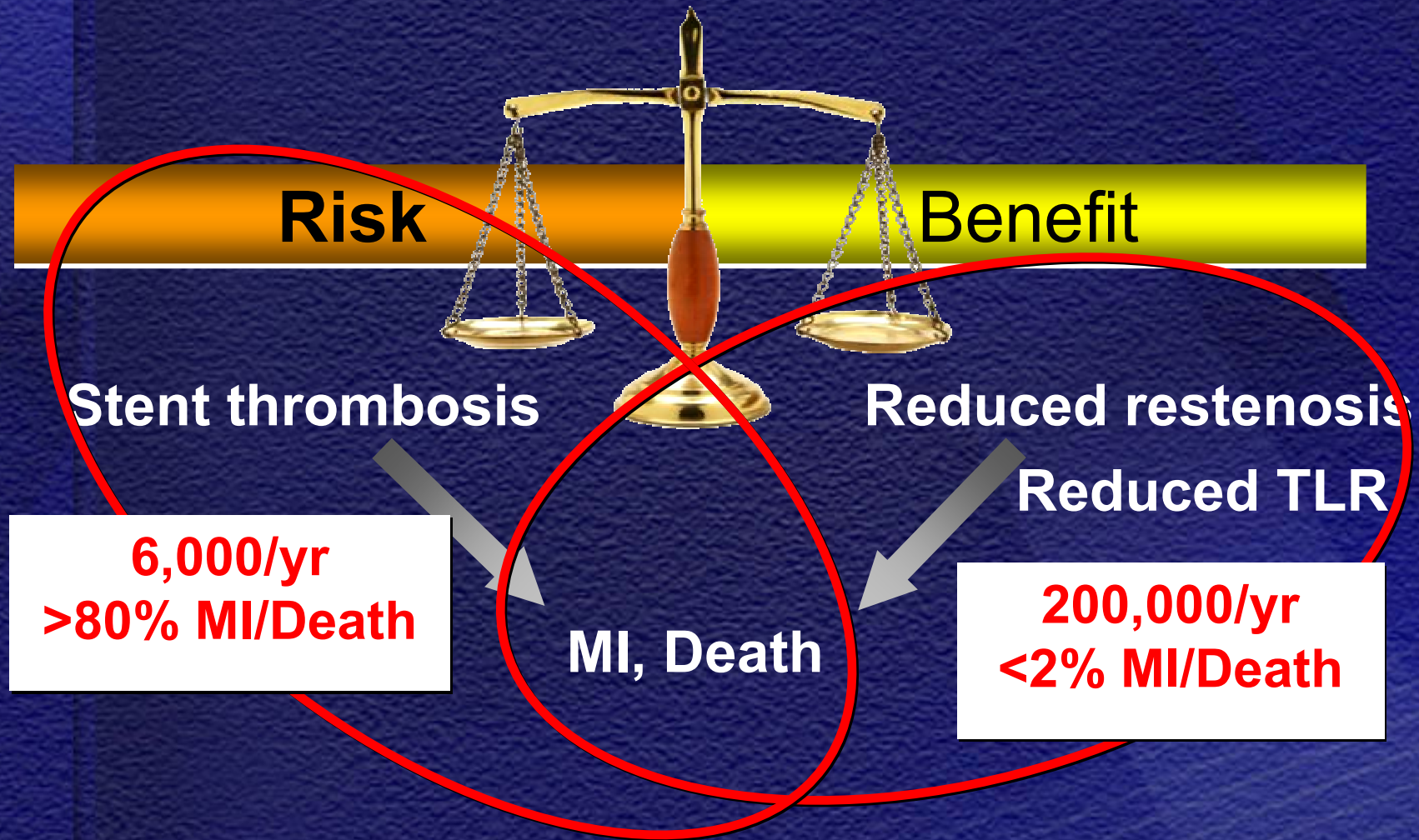
- ***7 million X 0.6%/year: 42,000 pts***
- ***1 million new DES/year: 6,000/yr***
- ***LaST: compared to what?***

***BMS?***

***DES?***

***Yes, there is a problem !!***

# *Benefit / Risk Profile of DES vs BMS*



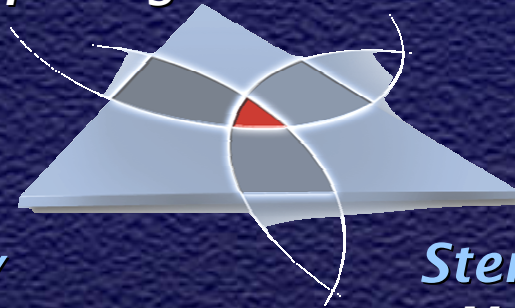


# Contributors to Stent Thrombosis

## *Compounding Factors Beyond the Stent*

### *Patient & Lesion Factors*

- *ACS, unstable angina*
- *Underlying coagulopathy, malignancy*
- *Diabetes, low ejection fraction or chronic renal failure*
- *Vessel size, lesion length, arterial structure*
- *Vulnerable plaque regions*



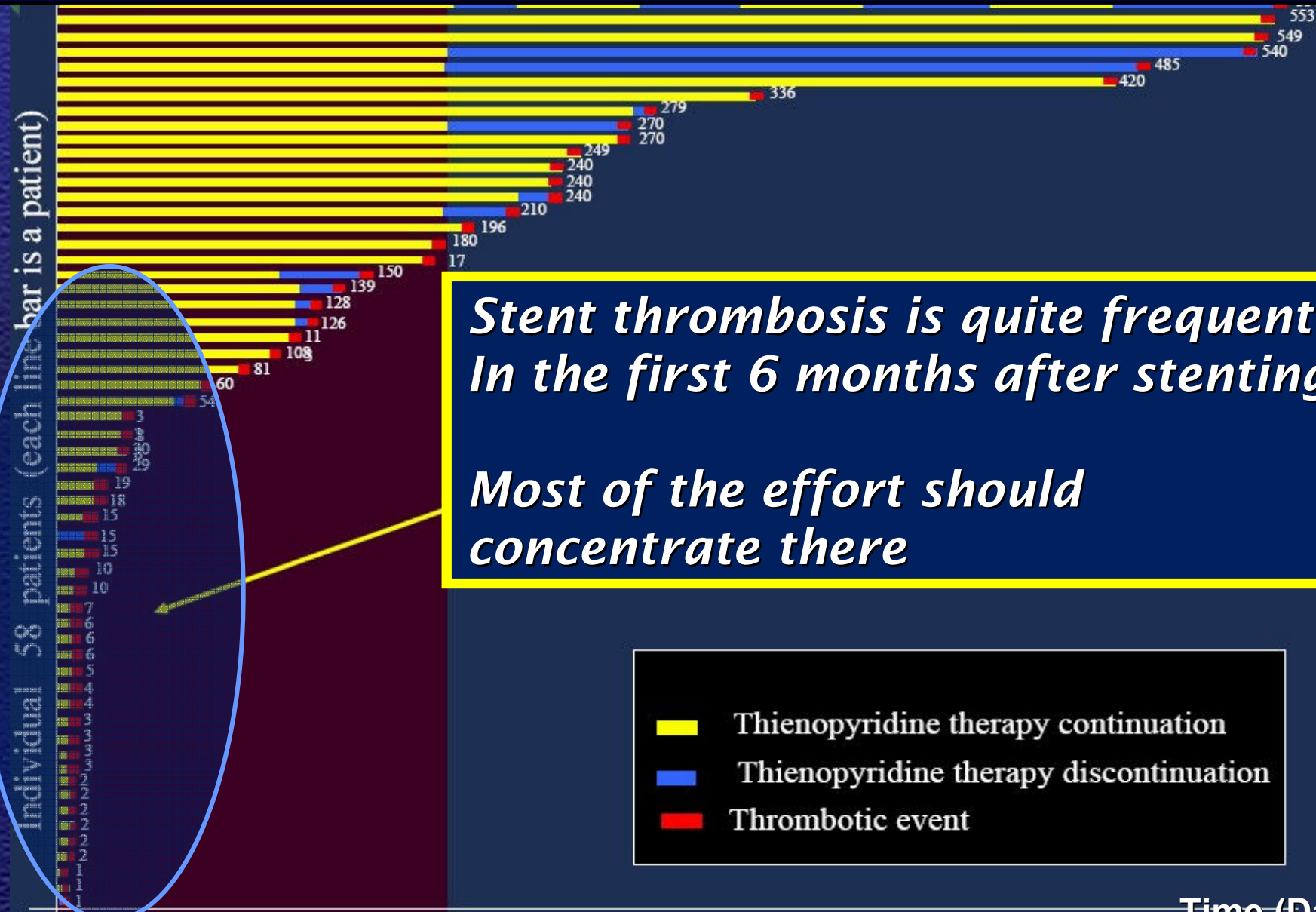
### *Procedural Complexity*

- *Morphometric (asymmetry, under-expansion, poor apposition)*
- *Morphologic (dissection, thrombus, protrusion)*
- *Mechanical vessel injury*
- *Anti-thrombotic therapy*

### *Stent Thrombogenicity*

- *Material*
- *Design*
- *Surface coating*
- *Local drug effect*
- *Incomplete endothelialization*

# Occurrence of Stent Thrombosis



*Stent thrombosis is quite frequent  
In the first 6 months after stenting*

*Most of the effort should  
concentrate there*

- Thienopyridine therapy continuation
- Thienopyridine therapy discontinuation
- Thrombotic event

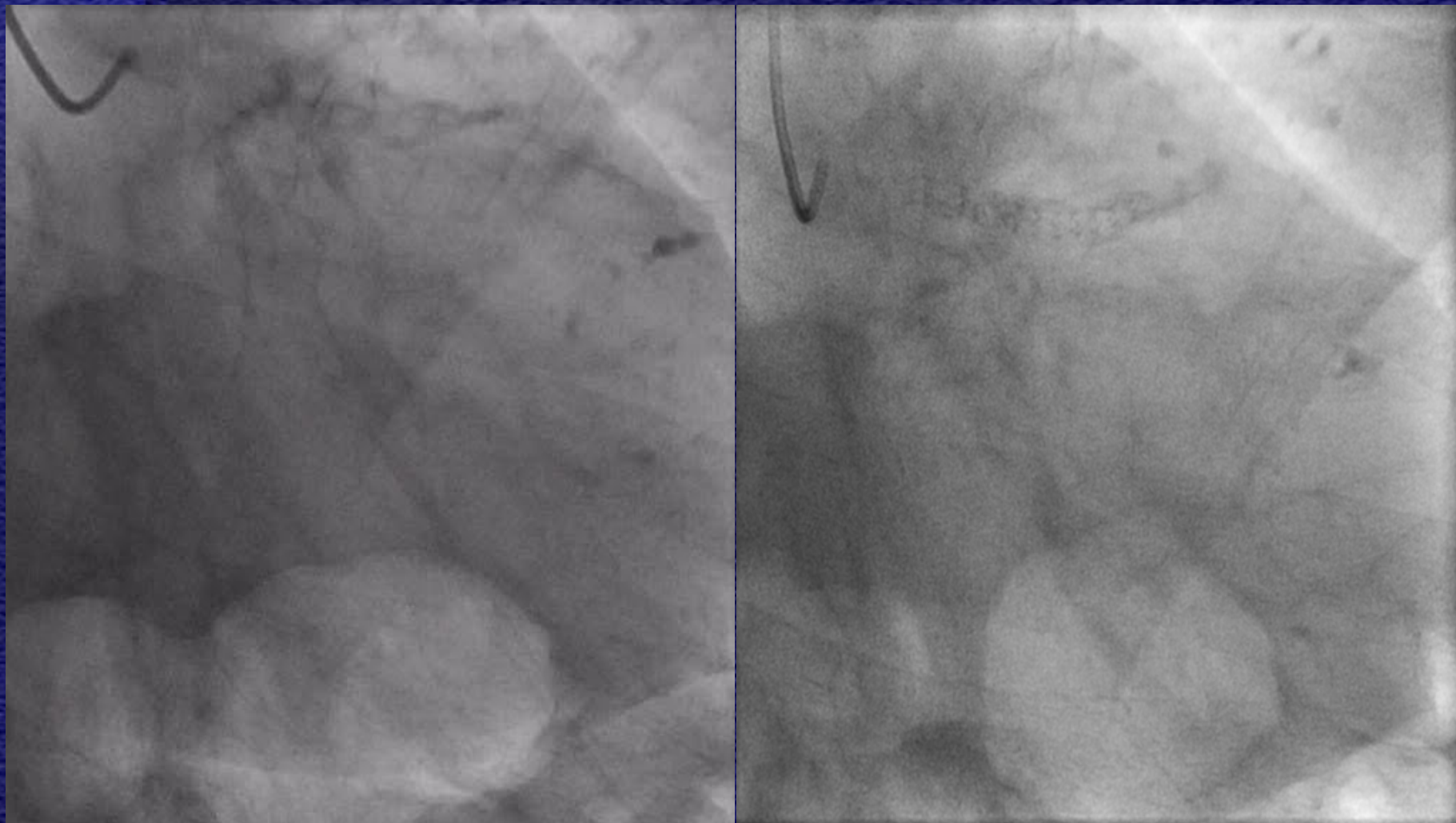
Time (Day)

## ***Procedural & In-Hospital Complication - Stent thrombosis vs No stent thrombosis***

| Events                      | ST<br>(n=38), n (%) | No ST<br>(n=2936), n (%) | P      |
|-----------------------------|---------------------|--------------------------|--------|
| Angiographic success        | 31 (79)             | 2718 (98)                | <0.001 |
| Abrupt closure              | 2 (6)               | 7 (0.3)                  | 0.006  |
| No reflow                   | 0                   | 9 (0.6)                  | ...    |
| Intra-arterial balloon pump | 3 (8)               | 80 (2.9)                 | 0.11   |
| Death                       | 0                   | 5 (0.2)                  | 1.0    |
| MI                          |                     |                          |        |
| Q wave                      | 4 (10)              | 11 (0.4)                 | <0.001 |
| Non-Q wave                  | 12 (32)             | 318 (12)                 | <0.001 |
| CABG                        | 1 (3)               | 3 (0.3)                  | 0.15   |
| Acute renal failure         | 3 (8)               | 24 (3)                   | 0.08   |
| Major bleeding              | 2 (5)               | 58 (2)                   | 0.21   |
| Vascular complications      | 2 (5)               | 85 (3)                   | 0.34   |

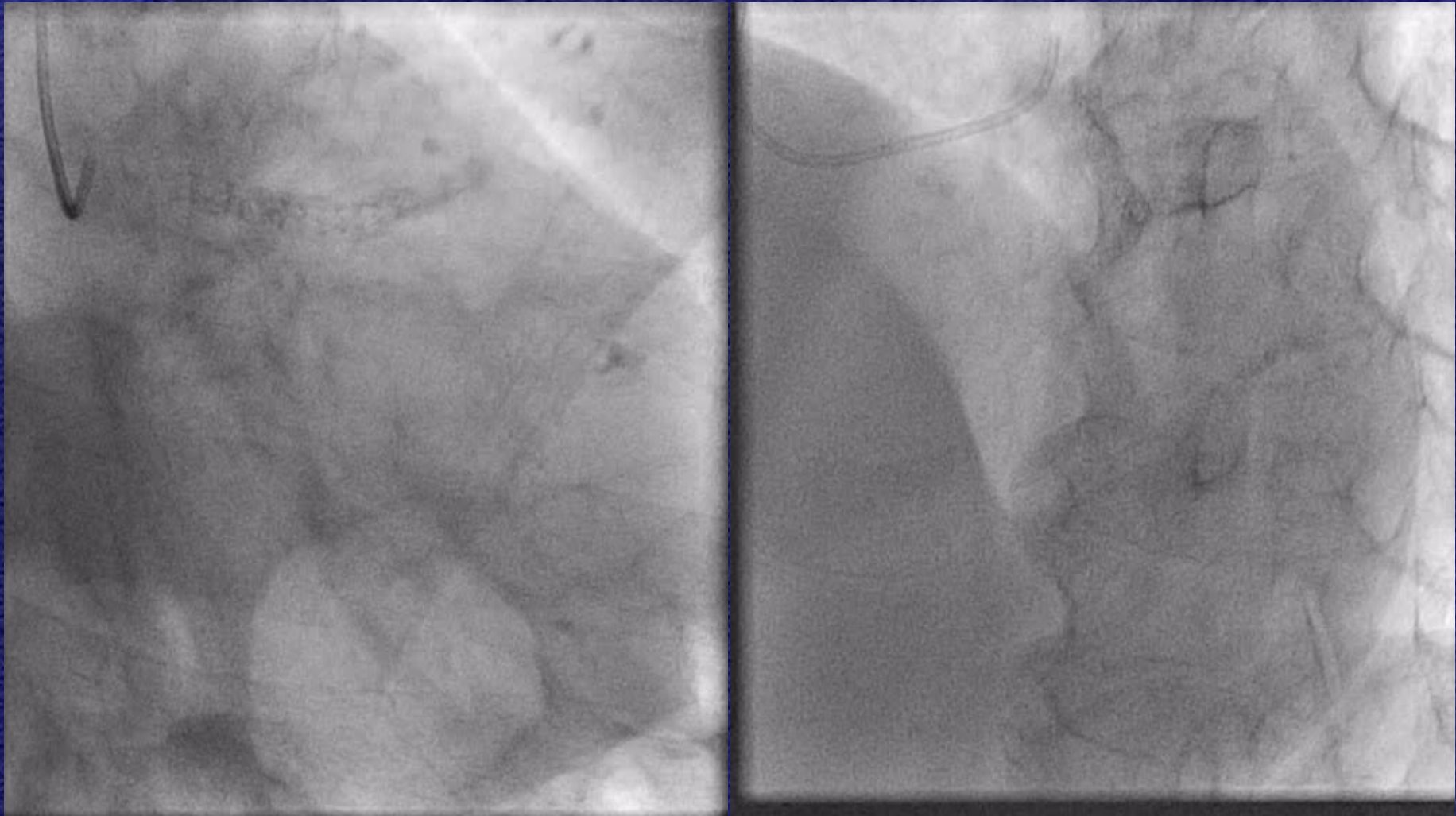
# M/70, Stable Angina

Cypher Stent at p-LAD on May 2006



# Follow-Up Angiography

March 2007 (9 mo. After Stenting)



# STEMI after Stopping Aspirin and Clopidogrel for 7 days

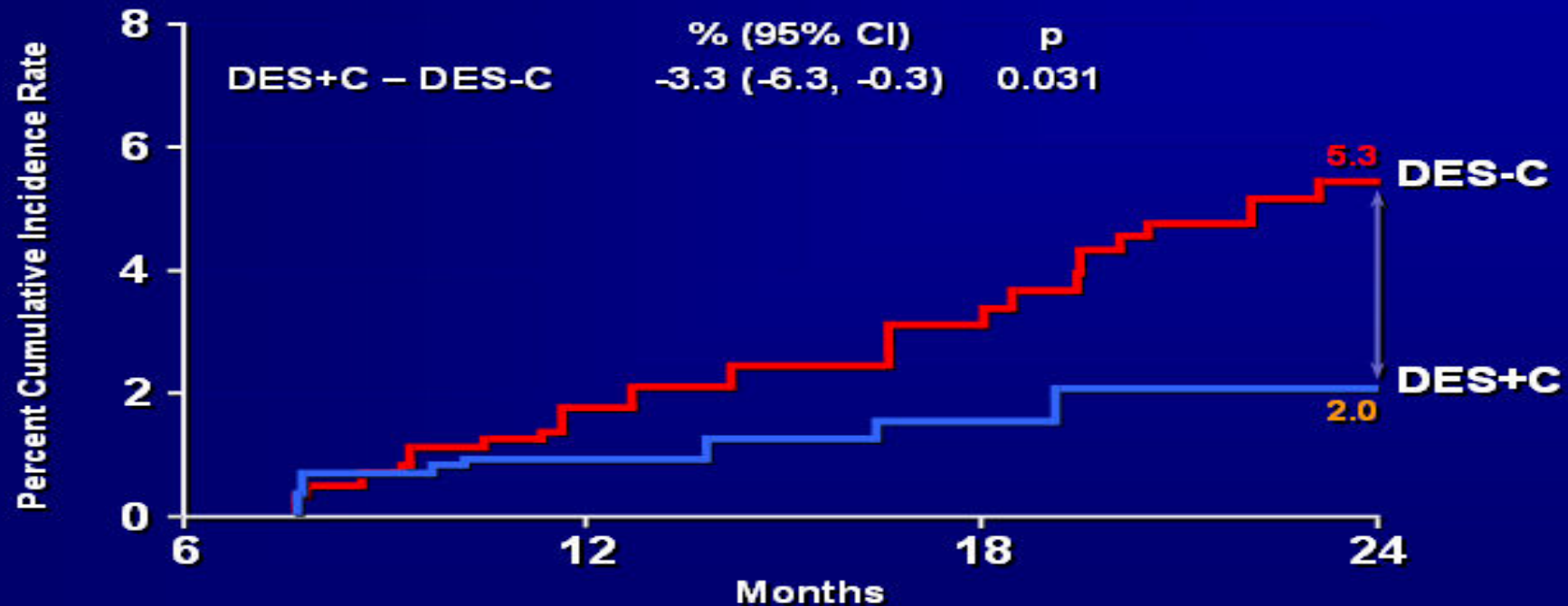
For EGD and Colonoscopy on September 2007



# Prolonged DAP: *Protecting the Patient vs. Protecting the Vessel*

- Does DAP prevent LaST?

## 6-Month Landmark Analysis *Adjusted Cumulative Mortality Rates*



Eisenstein et al. JAMA 2006

# ***DES thrombosis***

## ***Morphologic Predictors***

SAT 8/39, LST 11/39 : Autopsy study

### **Predictors**

1. Stent across ostia of major side branch
2. Strut penetration of necrotic core
3. Stent Malapposition
4. Increasing stent length
5. Delayed or absence of endothelialization
6. Hypersensitivity



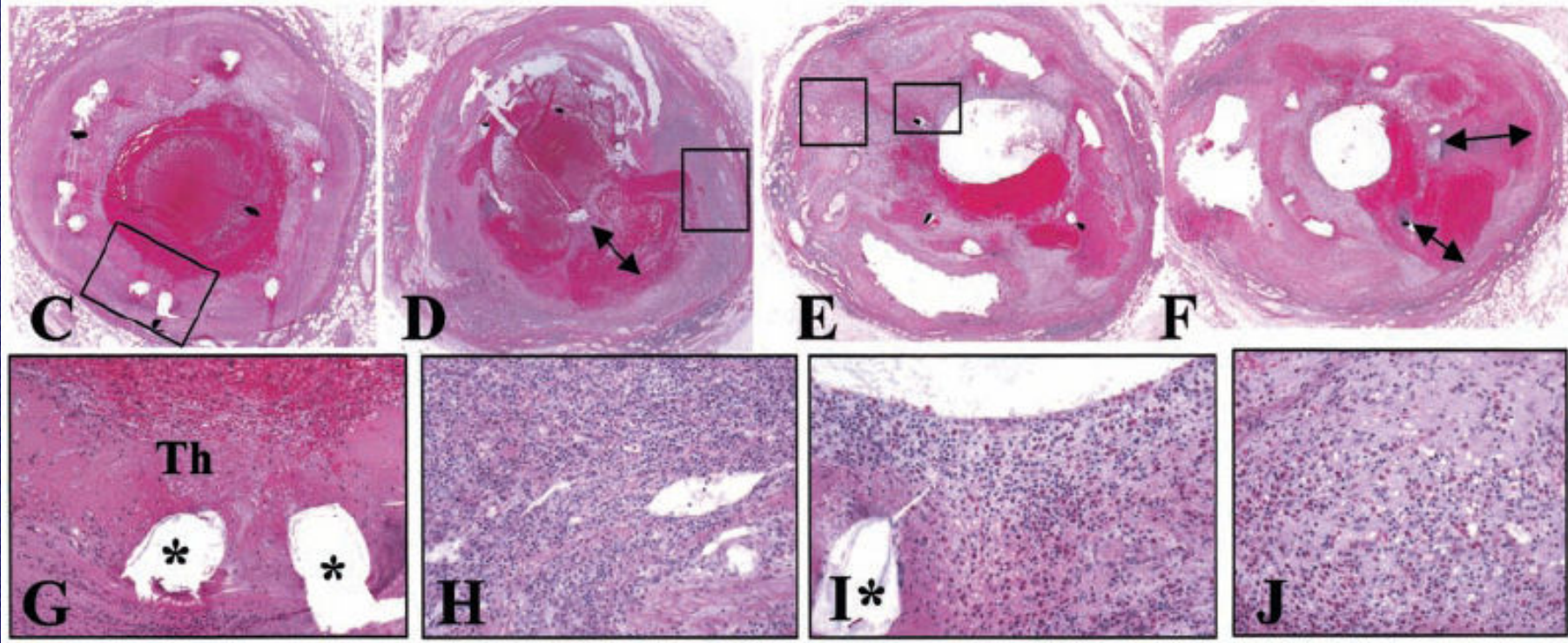
# Hypersensitivity - polymer/drug

## Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent

Should We Be Cautious?

Proximal Stent

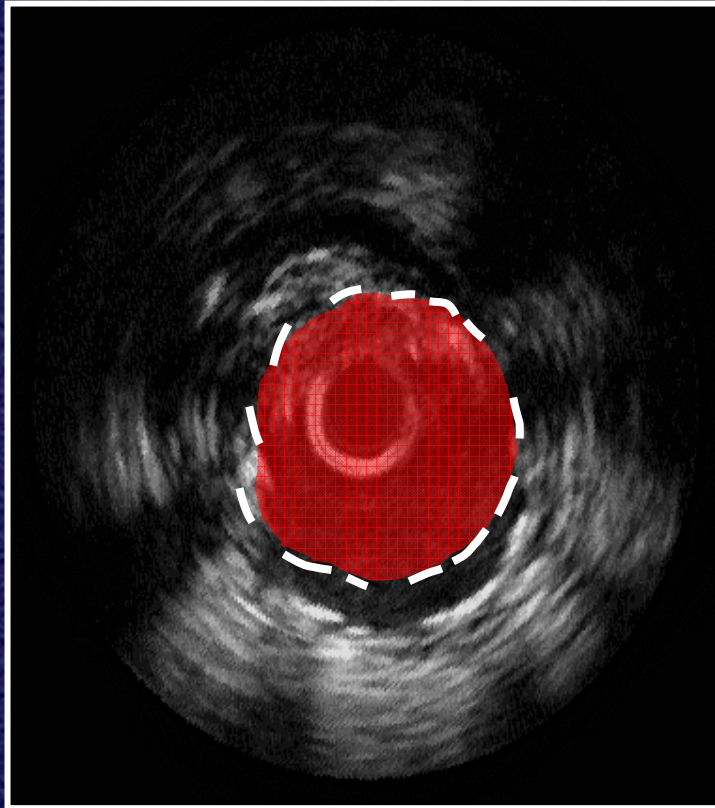
Distal Stent



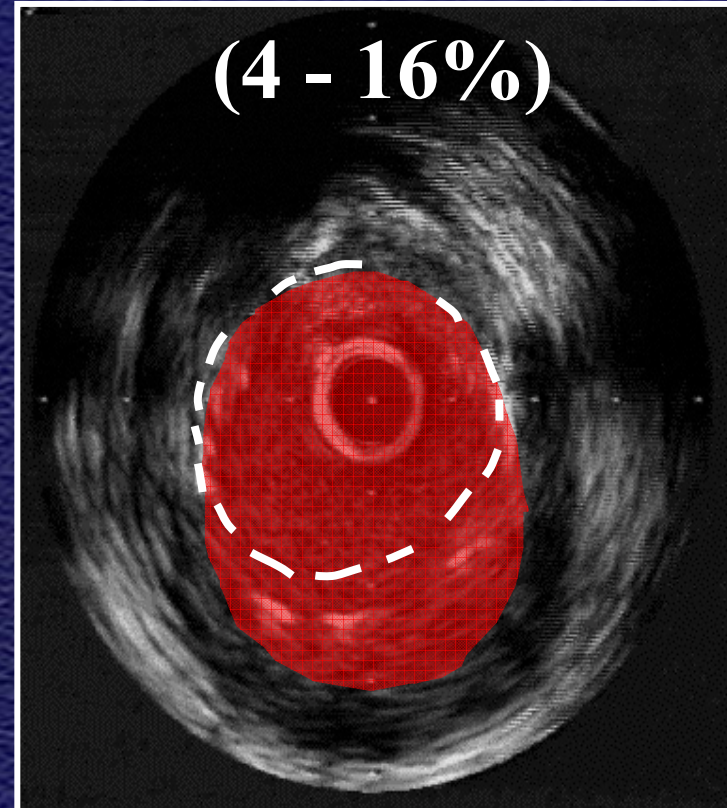
*Virmanii et al. Circulation 2004;109:701-5*

# *Late Stent Malapposition?*

*Drug-eluting stent group*



*Baseline*

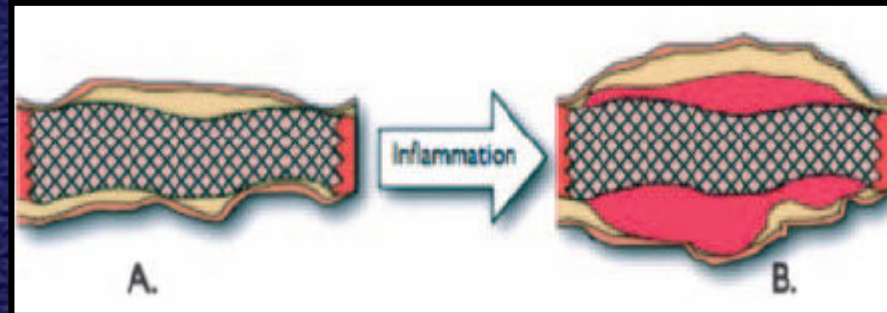


*Follow-up*

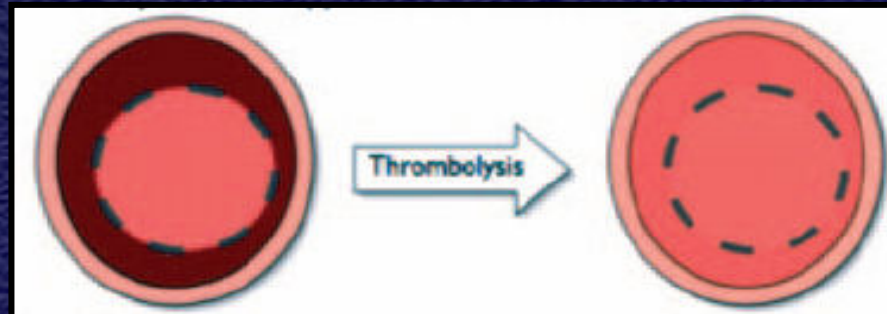
*Struts may be potentially vulnerable*

# Mechanisms Leading to DES Incomplete Stent Apposition

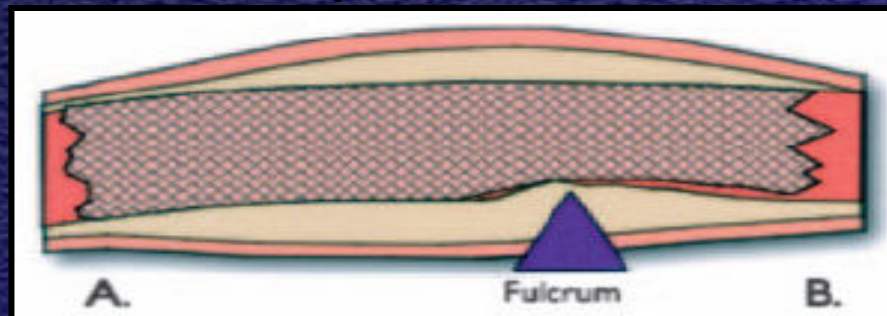
Positive Remodeling of an initially well apposed stent



A dissolution of jailed material in AMI due to thrombolysis



Localized initial underexpansion due to a site of calcification (fulcrum)



# *Malapposition ≠ Thrombosis ?*

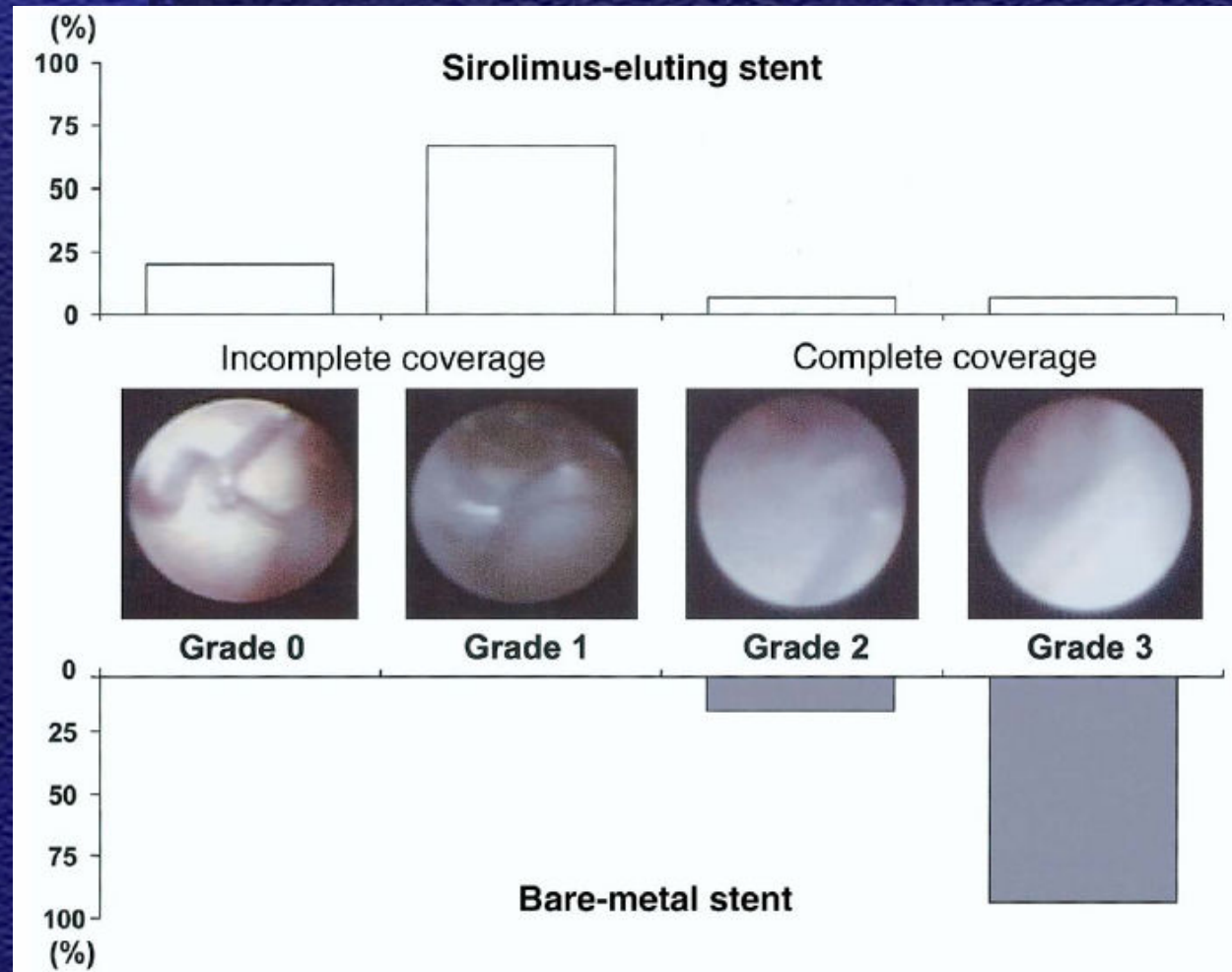
## **Late Stent Malapposition After Drug-Eluting Stent Implantation**

**An Intravascular Ultrasound Analysis With Long-Term Follow-Up**

- Late stent Malapposition in 12% after DES →  
*Predictors*
  1. Total stent length
  2. Primary stenting in AMI
  3. Chronic total occlusion
- Late stent thrombosis : none

# Incomplete Neointimal Coverage !

## Delayed endothelialization



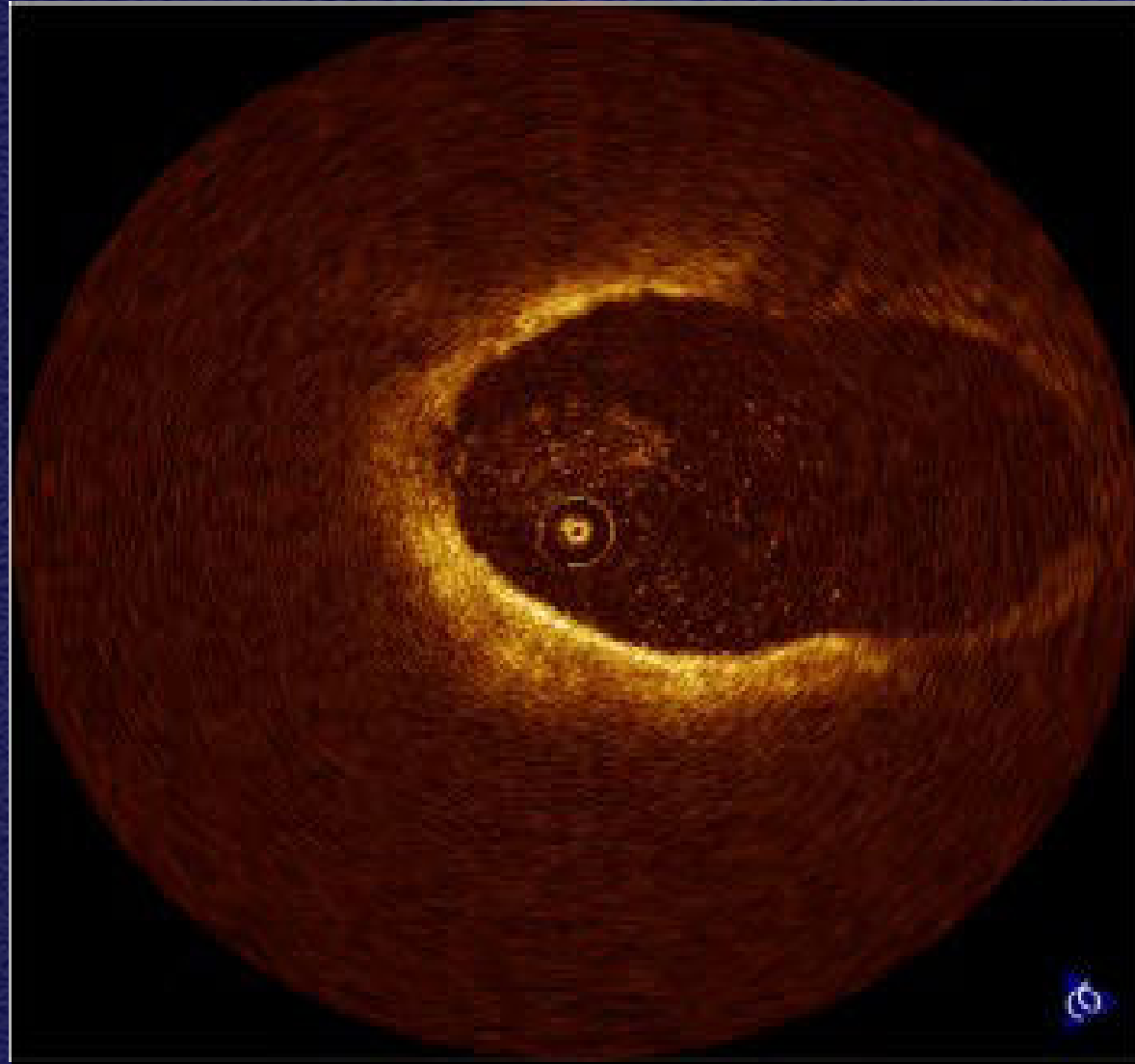
**Subclincial  
Thrombus**

**33 %**

**P = 0.14**

**14 %**

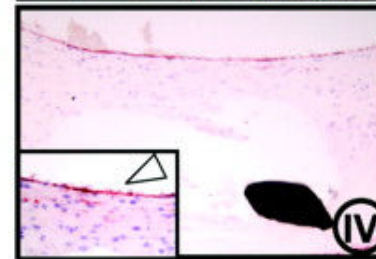
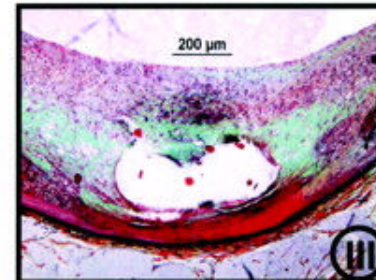
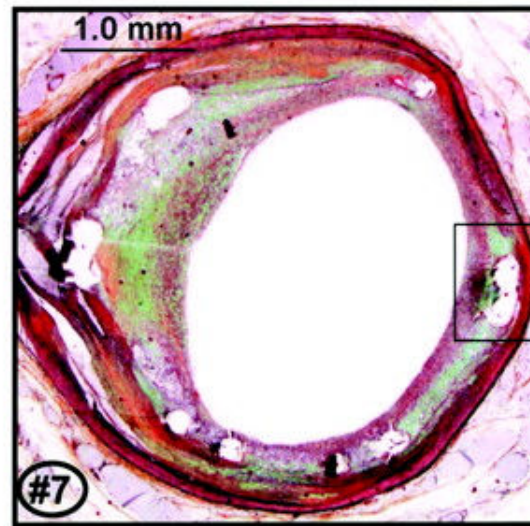
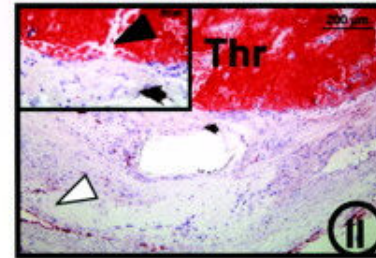
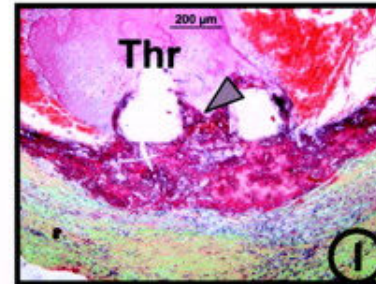
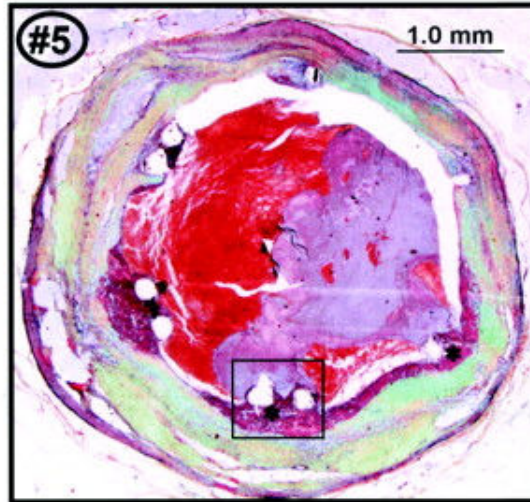
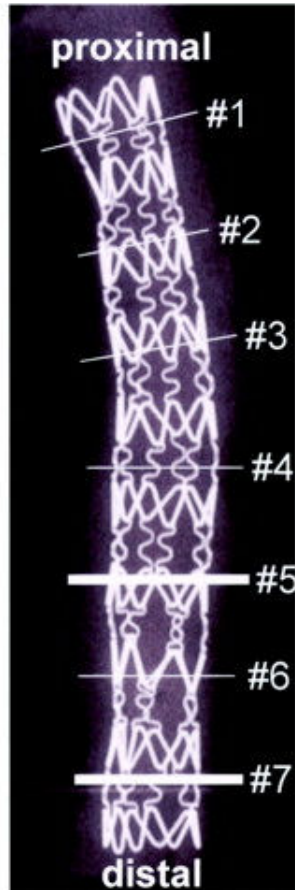
***Absence of Endothelialization – 9 months after cypher***



***Absence of Endothelialization may linked with malapposition***

# Heterogeneity of neointimal healing after DES

C



# Relationship Between VLST and ISA in DES Patients

*Very Late Stent Thrombosis (> 1 year) was more frequent in the presence of Incomplete Stent Apposition.*

ISA as evaluated by IVUS

|                                     | DES Patients with VLST<br>(n=13) | DES Control: Patients without VSLT<br>(n=175) | p-Value |
|-------------------------------------|----------------------------------|---|---------|
| # of Segments Evaluated             | 13                               | 175   |         |
| ISA (n, %)                          | 10/13 (77%)                      | 12/175 (12%)                                  | <0.001  |
| Maximal ISA Area (mm <sup>2</sup> ) | 8.3±7.5                          | 4.0±3.8                                       | 0.03    |

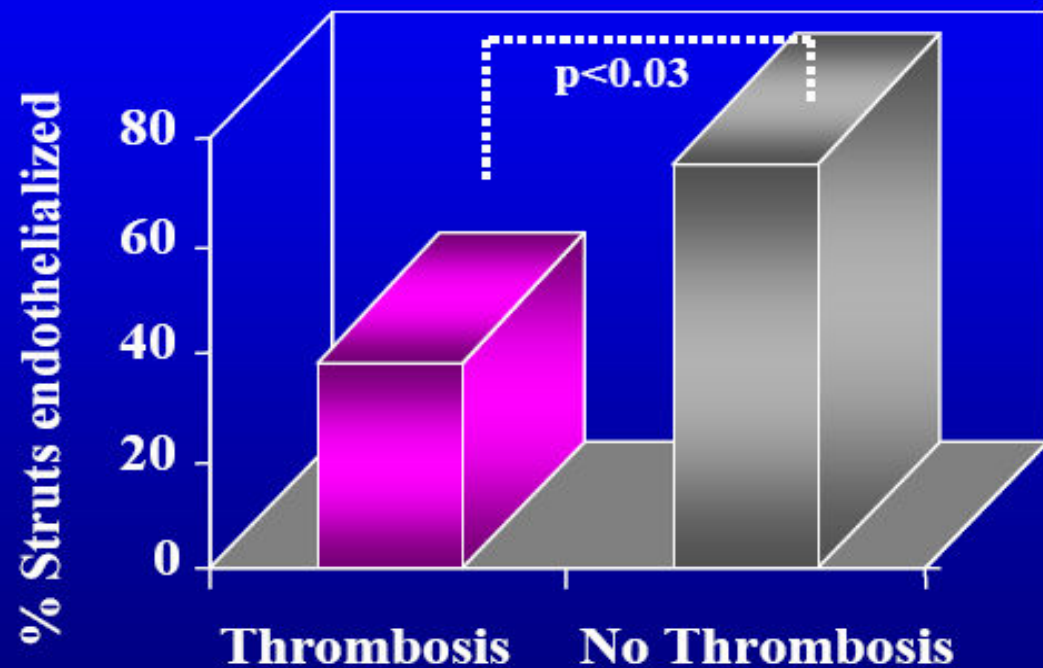
Cook S et al. Circulation.2007;115:2426-34

Incomplete Stent Apposition and Very Late Stent Thrombosis After Drug-Eluting Stent Implantation,



# *Human Post-Mortem: Fibrin & Endothelialization*

**Comparison of Endothelialization between  
DES with LST (>30 d) and Patent Stents**



# Endeavor (A1)

## Late Stent Thrombosis— Factors to Consider



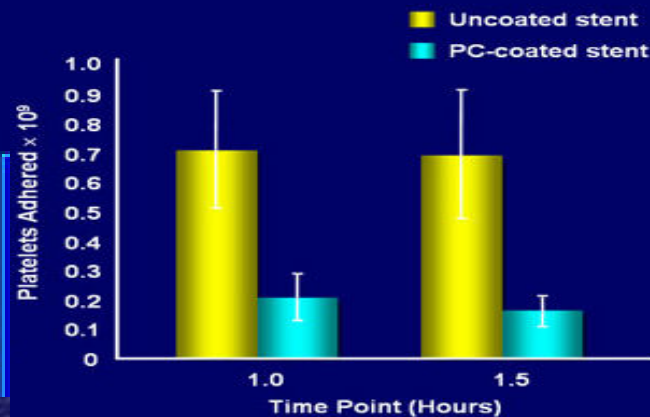
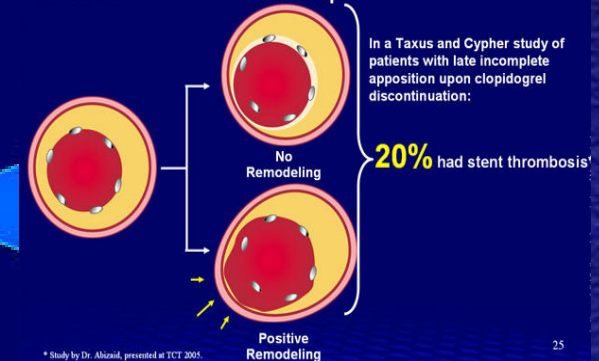
Discontinuation of  
Anti-Platelet Therapy

Nearly 100% of the drug  
elutes in the first 7 days  
and complete at 12 days

Late Stent  
Thrombosis

Baseline

Follow-up



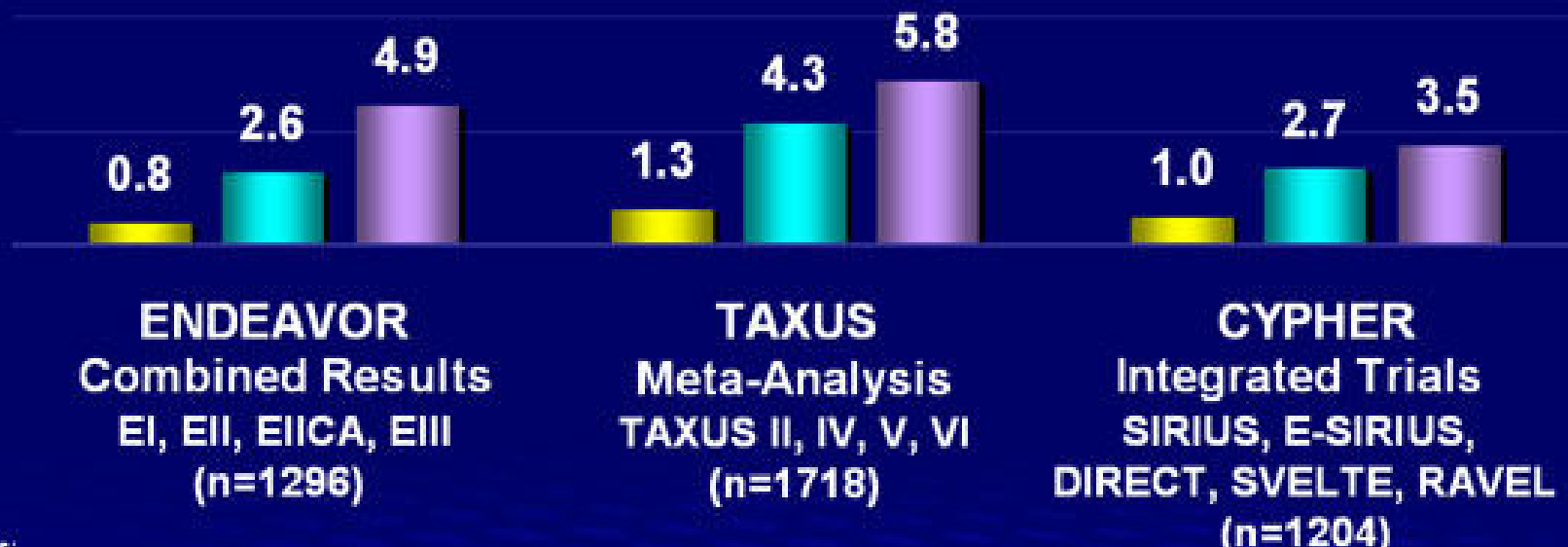
# Endeavor

## Clinical Events (%)

DES Arms from Combined Trials

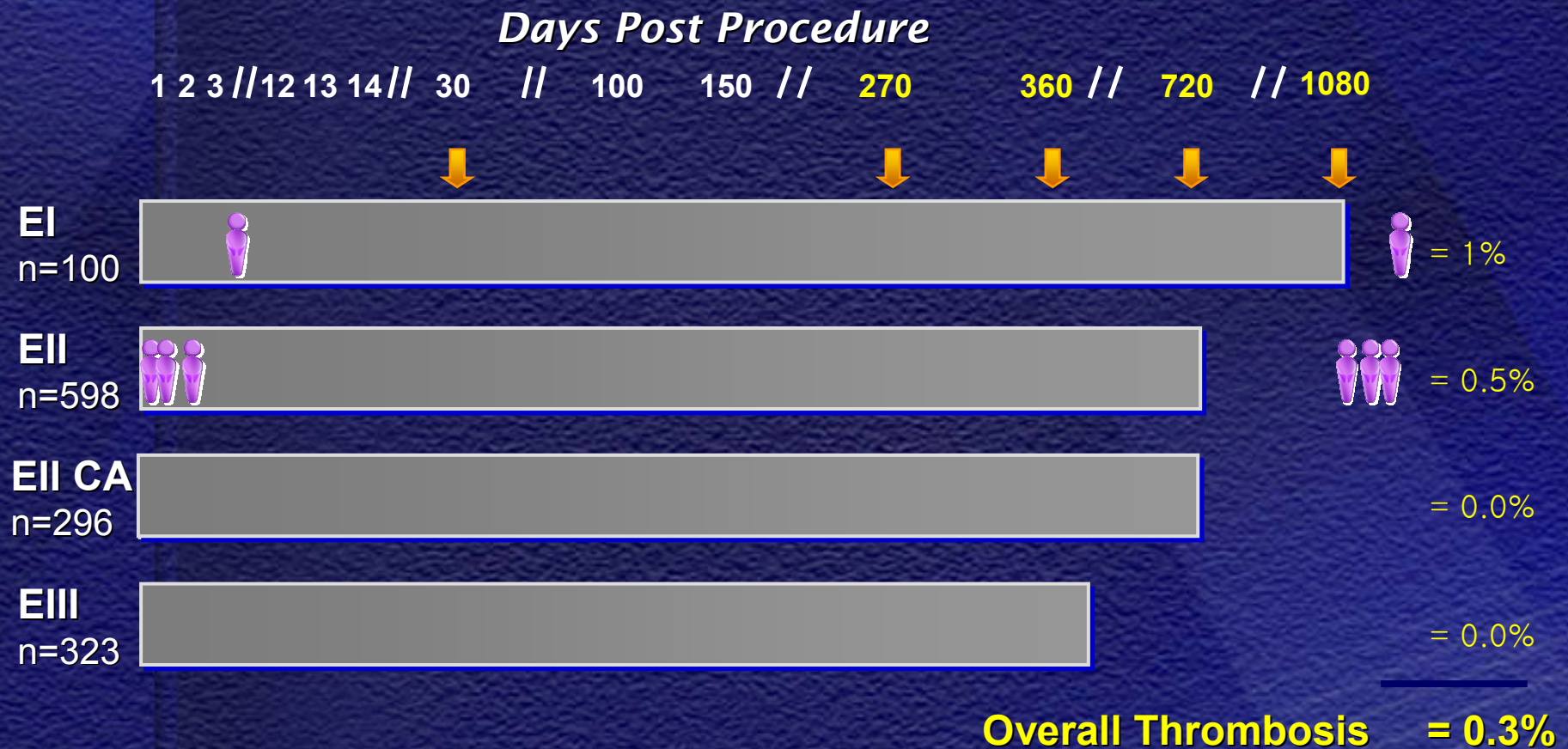
9-Month Follow-Up

■ DEATH  
■ MI  
■ TLR



# Endeavor

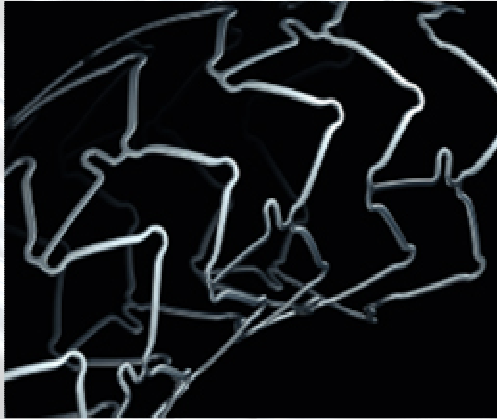
**No Late Stent Thrombosis in Over 1,300 Patients**  
**No Late Stent Thrombosis in 994 Patients > 2 yr f/u**



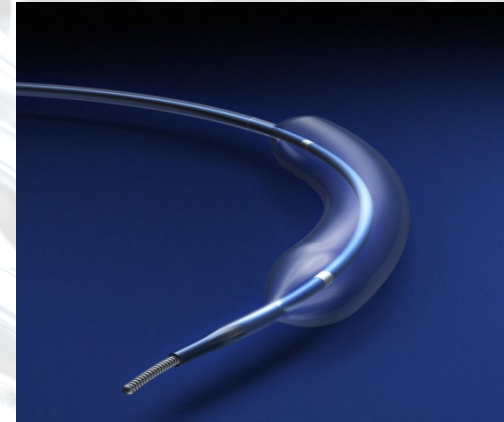
ENDEAVOR I-III Clopidogrel Therapy for  $\geq 3$  months

# ***XIENCE V (A2)***

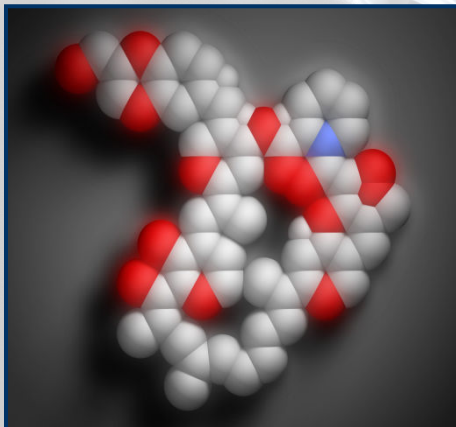
**MULTI-LINK VISION®  
Stent**



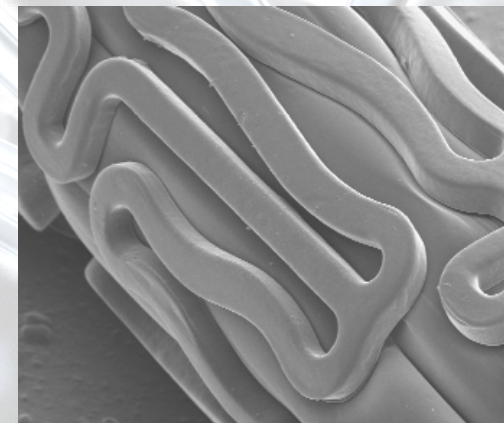
**MULTI-LINK VISION®  
Stent Delivery System**



**Everolimus**



**Fluoropolymer**



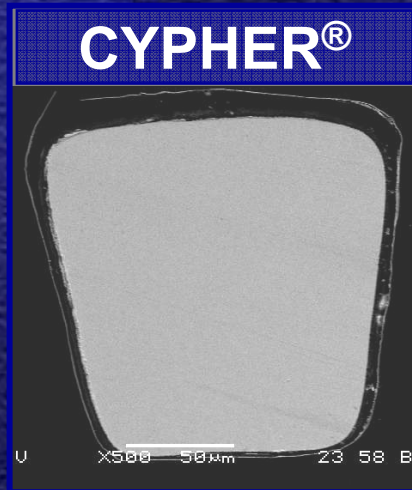
# Consistent Power in Late Loss

|  | <i>SPIRIT First<br/>30/30</i> | <i>SPIRIT II<br/>225/75</i>                                   | <i>Spirit III<br/>669/333</i> |
|--|-------------------------------|---|-------------------------------|
| <i>Late Loss<br/>in stent (mm)</i>     | <i>.10</i>                    | <i>.11/0.37*</i>  | <i>.16 / .31*</i>             |
| <i>Late Loss<br/>in segment (mm)</i>   | <i>.09</i>                    | <i>.07/0.15</i>   | <i>.14/.28*</i>               |
| <i>Binary ISR</i>                      | <i>0%</i>                     | <i>1.3%/3.5%</i>  | <i>2.3% /5.7%</i>             |
| <i>Binary Insegment<br/>restenosis</i> | <i>&lt;5%</i>                 | <i>3.4%/5.8%</i>  | <i>4.7%/8.9%</i>              |
| <i>MACE</i>                            | <i>7.7%</i>                   | <i>2.7%/ 6.5%</i><br><i>2.7%/ 9.2%*</i><br><i>12-month FU</i> | <i>4.6%/8.1%*</i>             |
| <i>Comparator</i>                      | <i>Xience V<br/>vs Vision</i> | <i>Xience V<br/>vs Taxus</i>                                  | <i>Xience V<br/>vs Taxus</i>  |

*\*Statistically Significant Difference p<0.05*

# **Minimal Injury**

## **Minimizing Strut and Polymer Thickness**



**Strut Thickness:**  
140 μm

**Polymer Thickness:**  
12.6 μm

**Total:**  
152.6 μm



**Strut Thickness:**  
132 μm

**Polymer Thickness:**  
16 μm

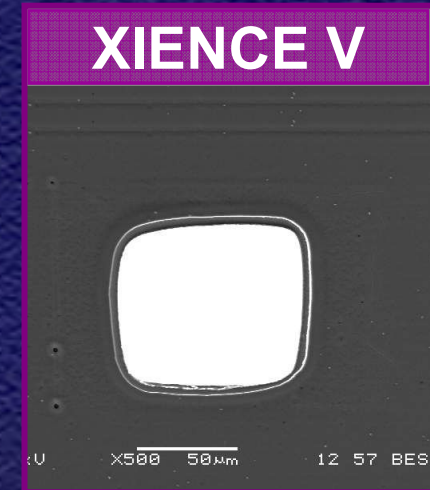
**Total:**  
148 μm



**Strut Thickness:**  
91 μm

**Polymer Thickness:**  
5.3 μm

**Total:**  
96.3 μm



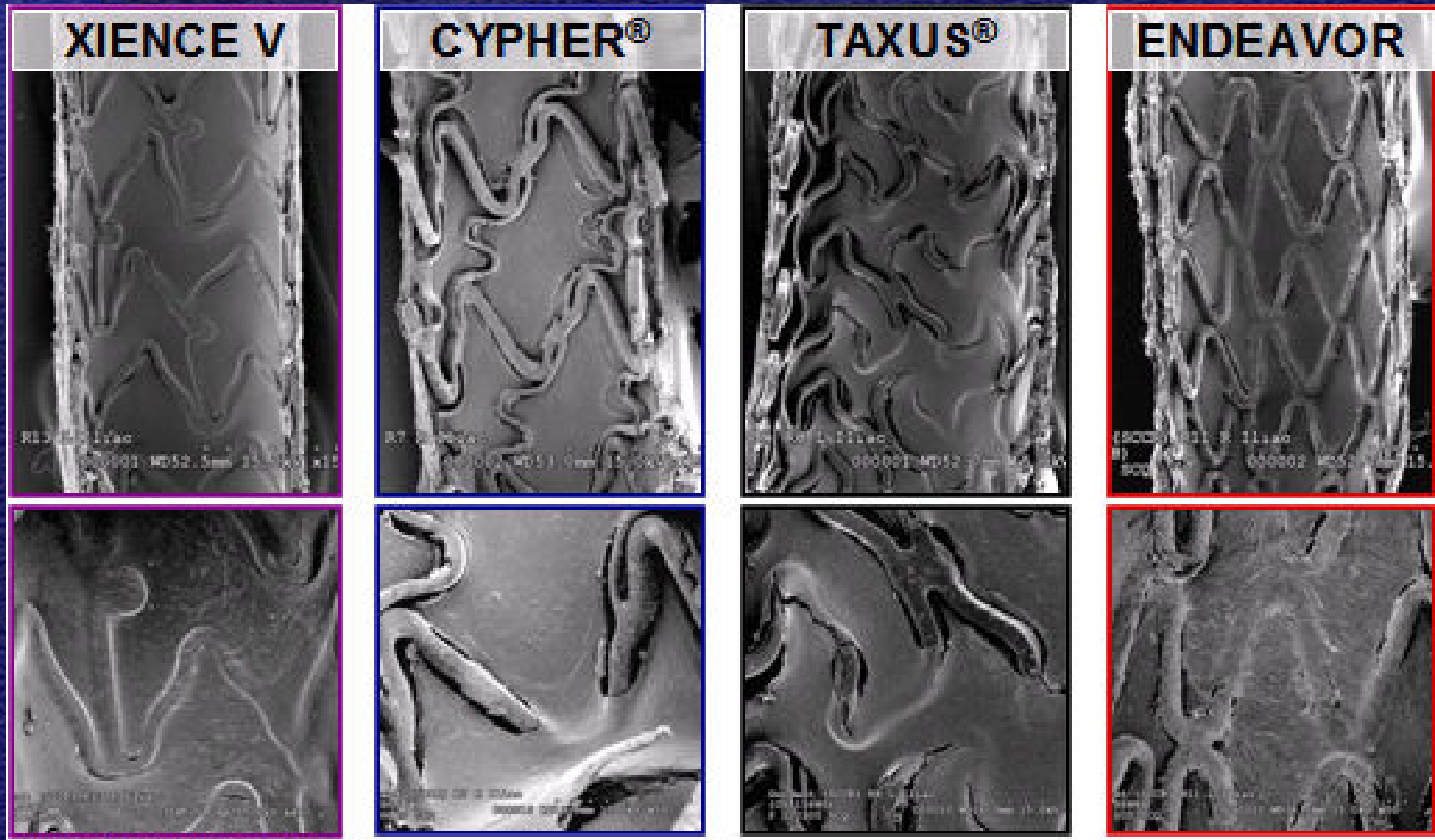
**Strut Thickness:**  
81 μm

**Polymer Thickness:**  
7.6 μm

**Total:**  
88.6 μm

**3.0 mm diameter stents, 500x magnification**

# *Rapid Re-endothelialization 14-Day Rabbit Iliac Study*



Courtesy of Dr. R Virmani



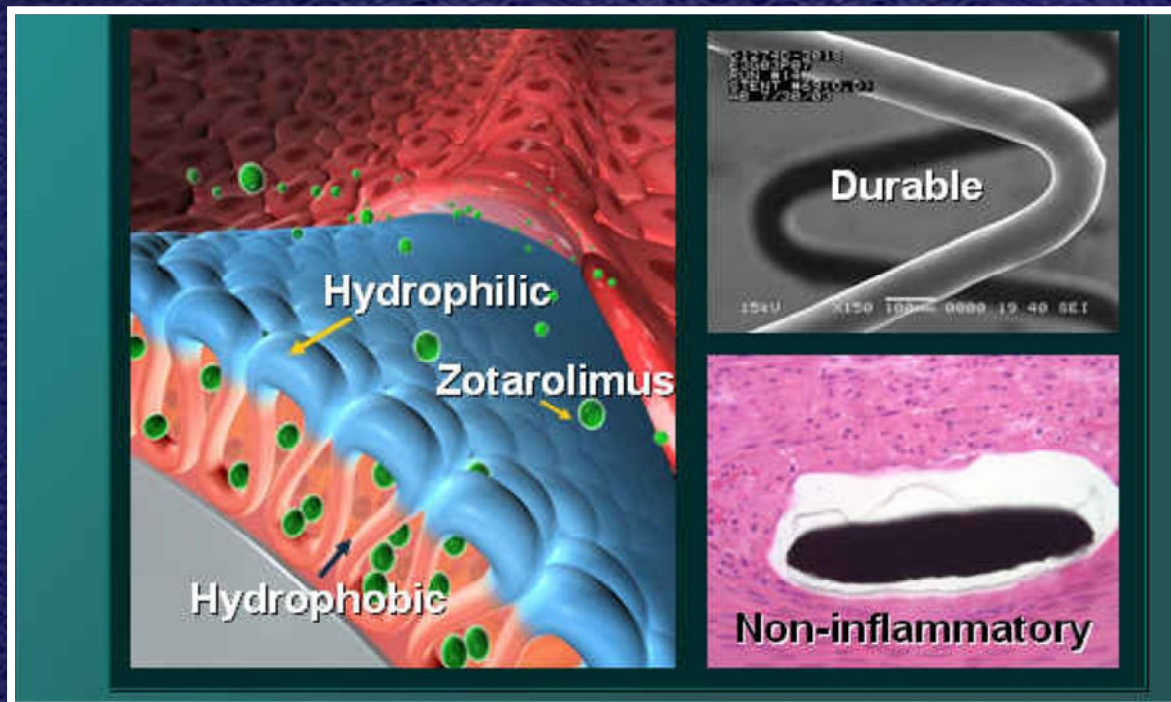
# ***New Polymer (A3)***

## ***BioLinx*** in “***Endeavor Resolute***”

*a C10 polymer ( lipophilic/hydrophilic, stimulate a controlled drug release )*

*a C19 polymer ( hydrophilic, more biocompatible, and helpful in drug elution)*

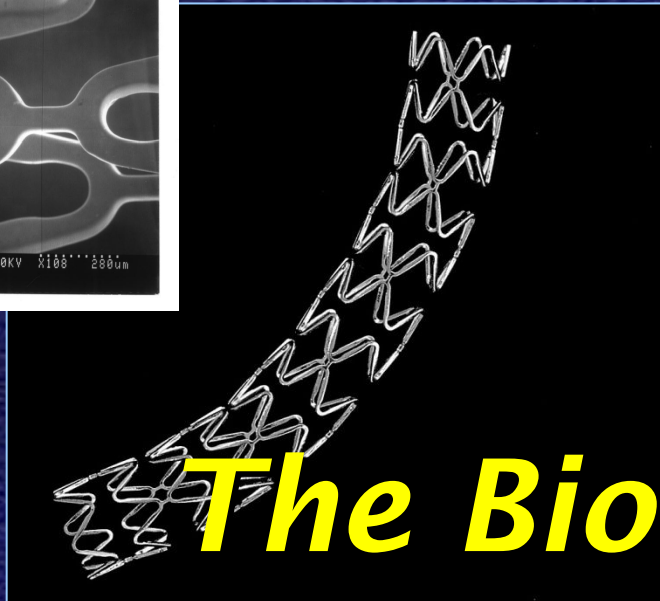
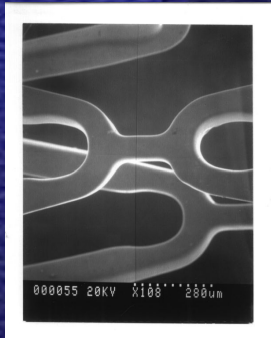
*a poly vinyl pyrrolidone (hydrophilic, initial drug burst)*



# Biodegradable Polymer (A4)

BIOMATRIX<sup>®</sup>

Biosensors  
International



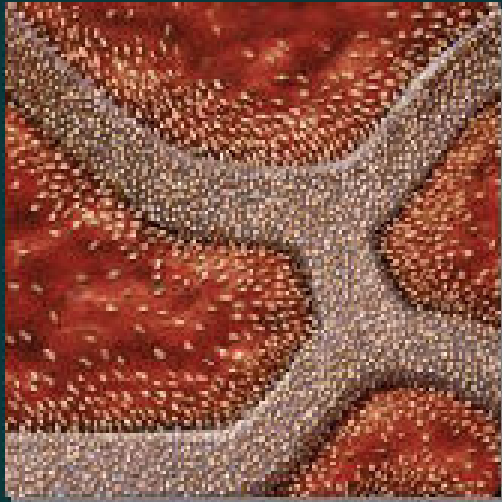
## The Biolimus A9 Stent

- **Stent:** S-Stent
- **Polymer:** Proprietary biodegradable PLA
- **Drug:** Biolimus A9<sup>®</sup>
- **Delivery System:** Tiger Rx balloon catheter
- **Sizes:**  
6-cell: 2.5-3.25mm / 8-28mm  
9-cell: 3.5-4.0mm / 8-28mm

# *Dual DES (A5)*

- *Zotarolimus+Dexamethasone*  
→ *Zodiac program*
- *Pimecrolimus/paclitaxel Vs Pimecorolimus*  
→ *GENESIS trial*
- *Sirolimus/Genistein*  
cf) *Genistein ....*  
*potential isoflavone, dose-dependent*  
*antiplatelet and antiproliferative properties*

# *Vasculoprotective DES (A6)*



**Endothelial Progenitor Cells  
Coating the Stent Surface**

**Vasculoprotective Effect of  
EPC Capture**

**Inhibits  
Inflammation**

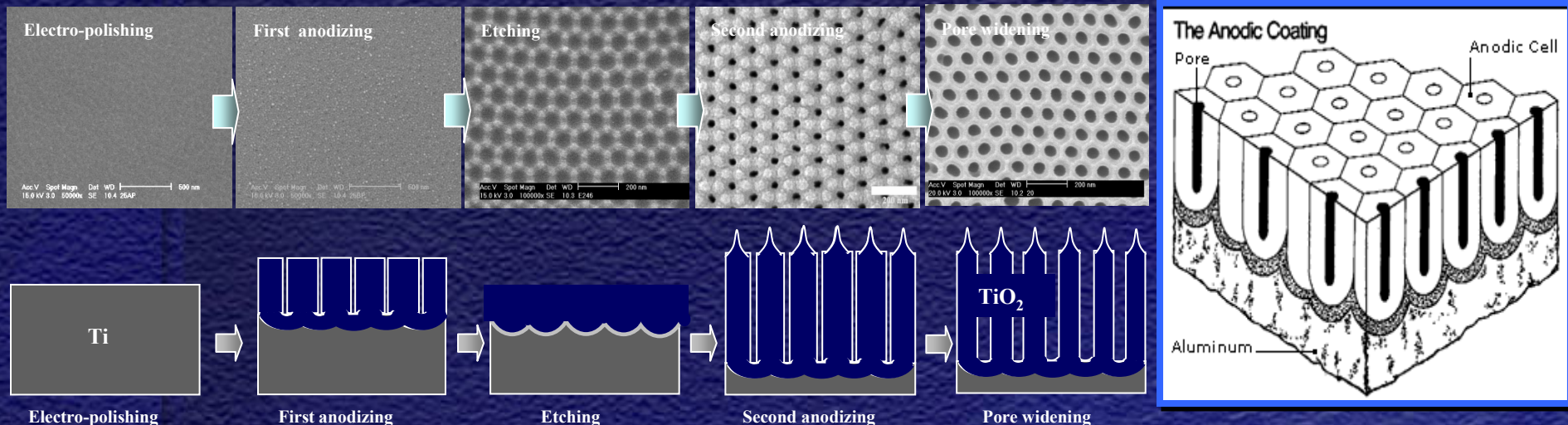
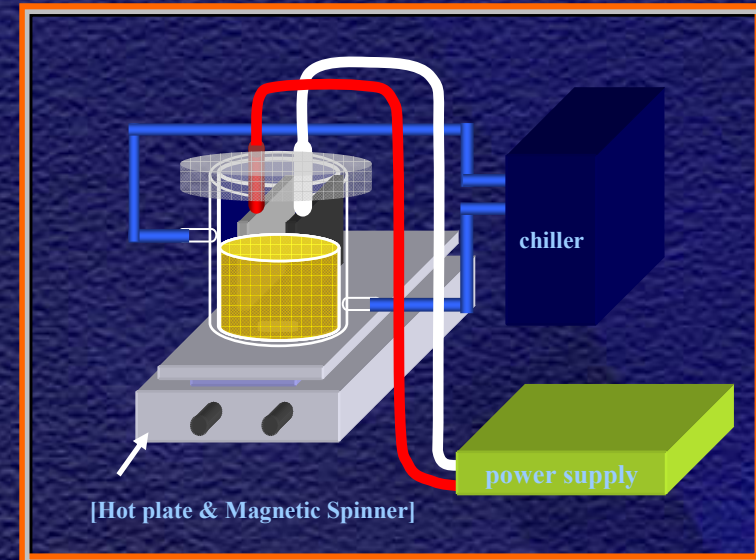
**Inhibits  
Proliferation**

**Inhibits  
Migration**

**Promote healing &  
re-endothelialization**

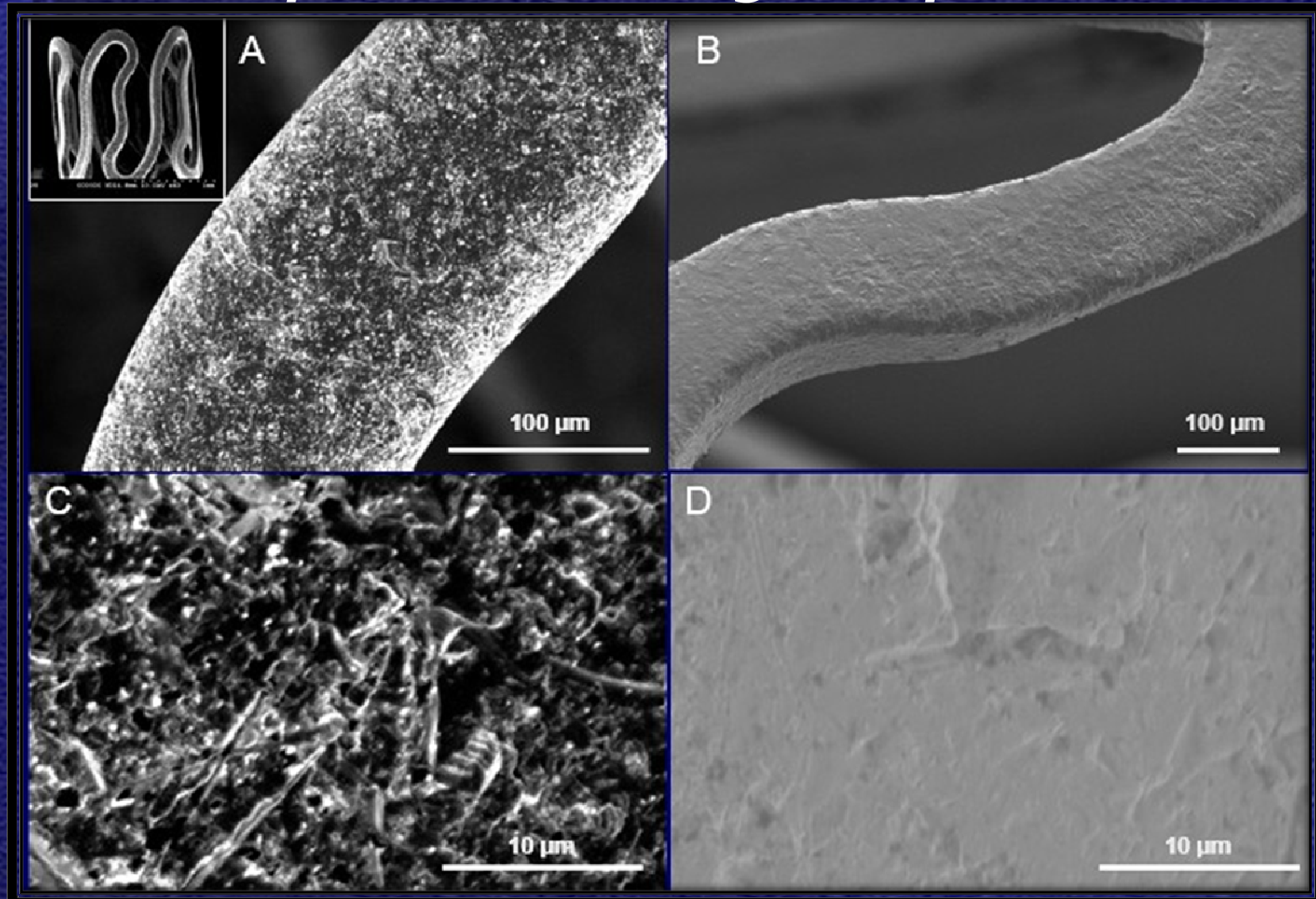
# Nano-porous $TiO_2$ coating (A7)

## Anodic Oxidation Process



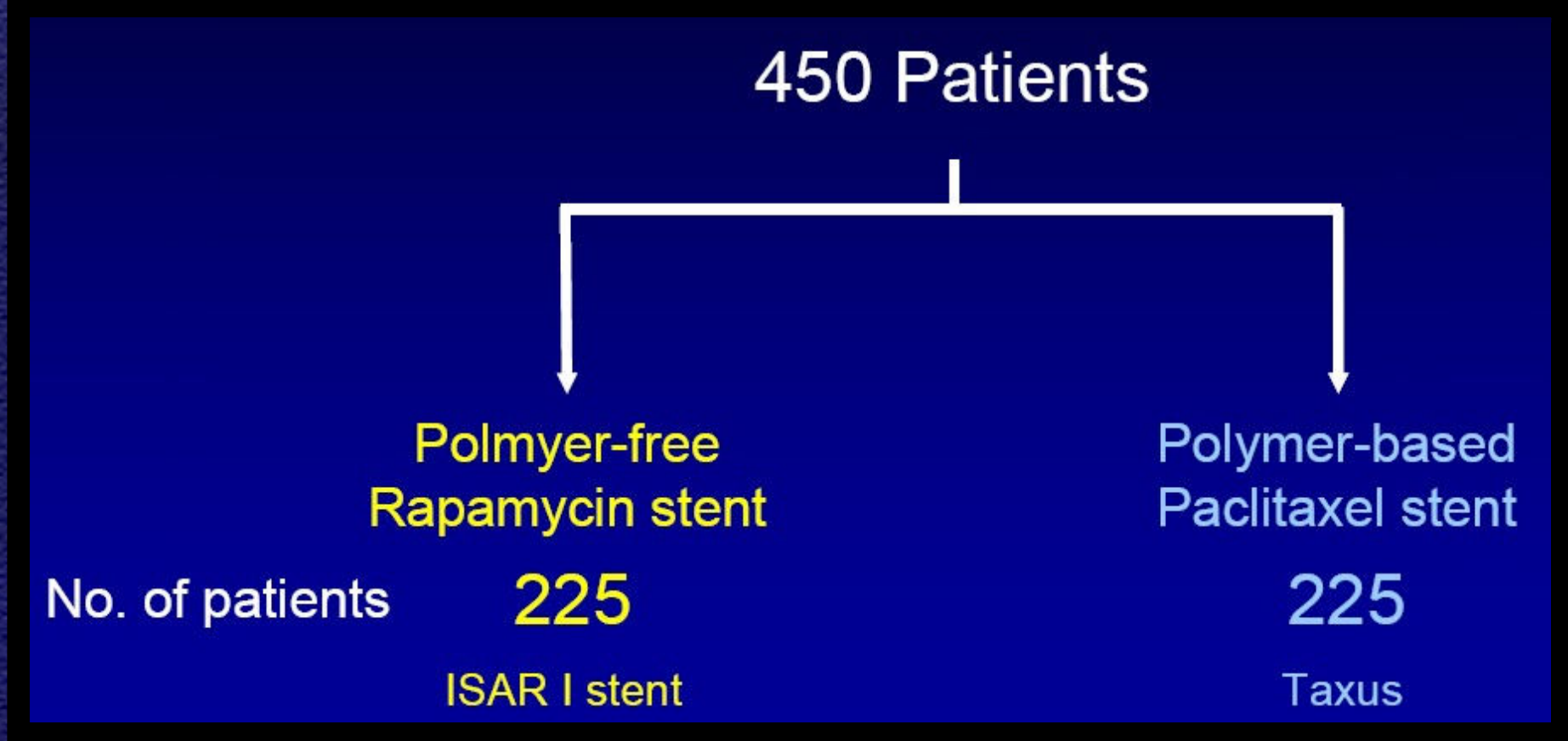
# Unique Microporous Stent Surface (On Site Coating)

Before Coating After

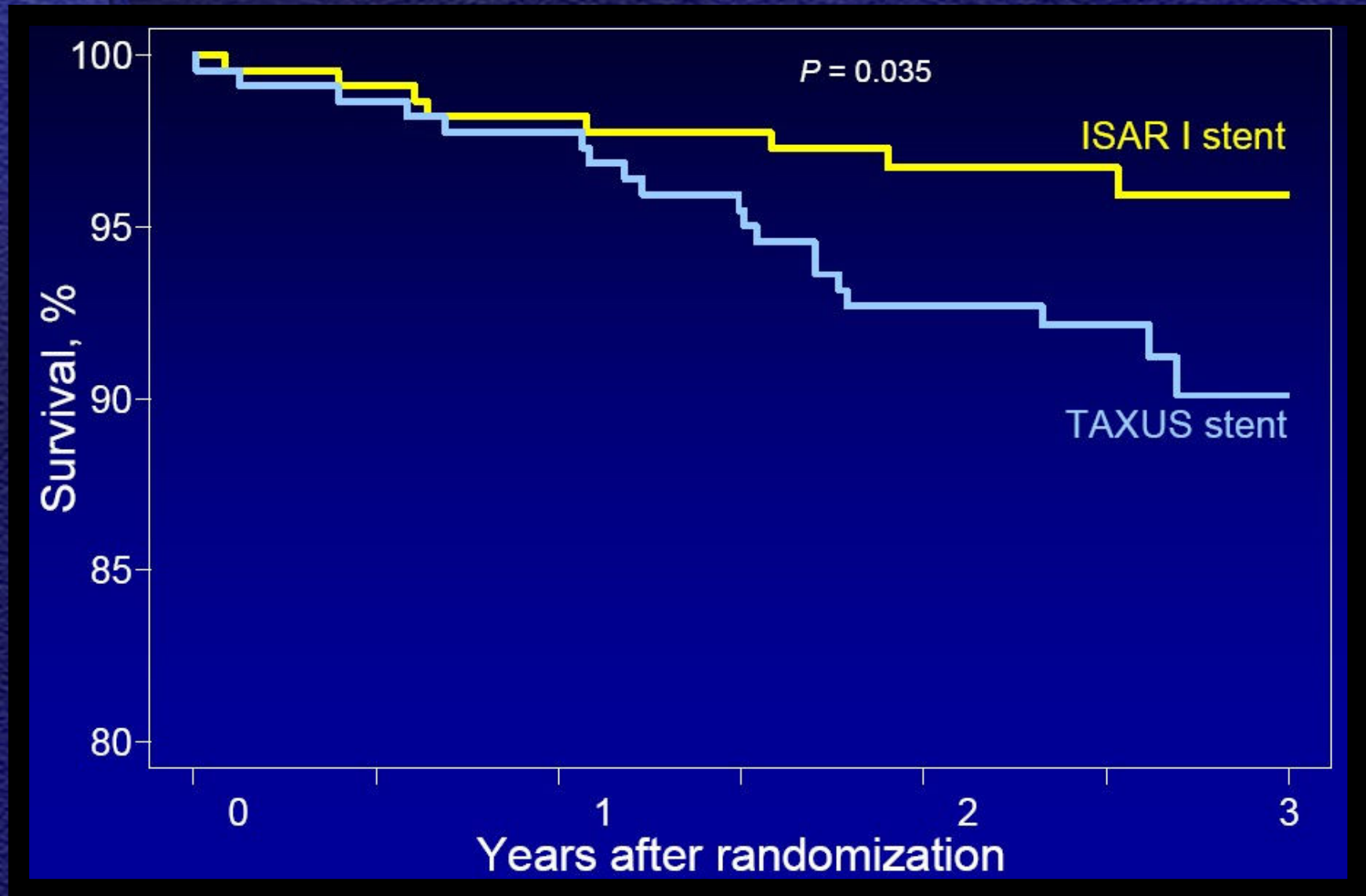


# ISAR-TEST

*Intracoronary Stenting and Angiographic Restenosis: Test Equivalence Between 2 Drug-Eluting Stents (Nanoporous Polymer Free coating)*



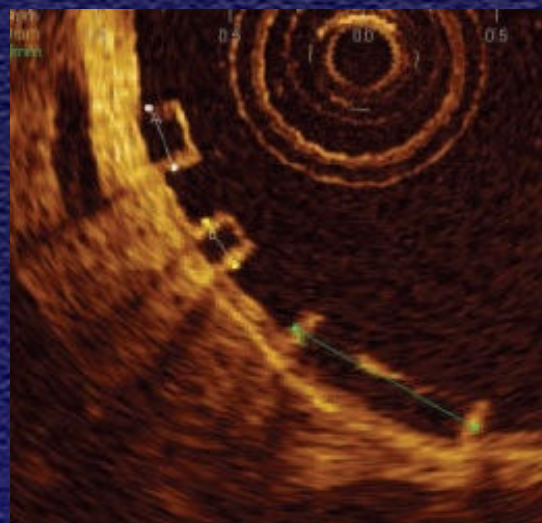
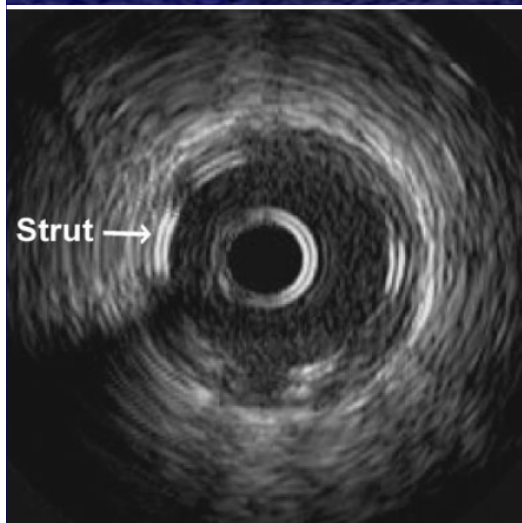
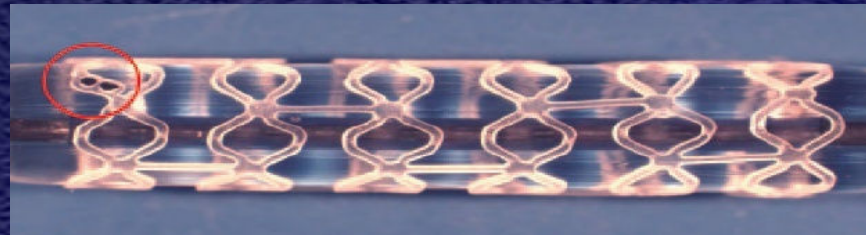
# Long-Term Survival



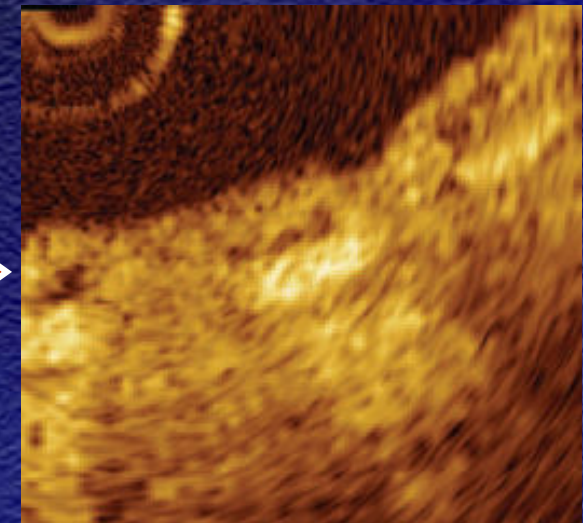


# ***BVS stent (A8)***

- *first fully absorbable DES, consist of*
  - Bioabsorbable polymer*
  - Everolimus*
  - Bioabsorbable BVS polylactic acid stent platform*

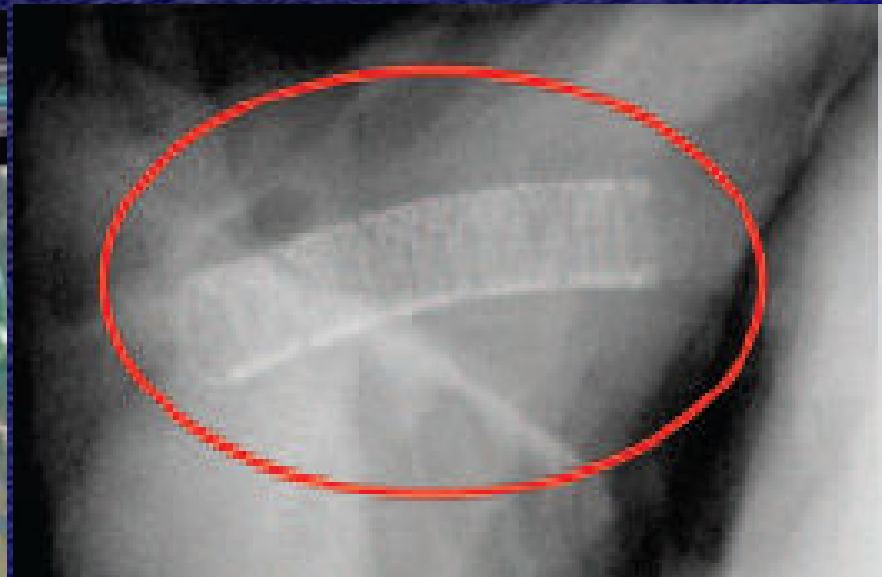
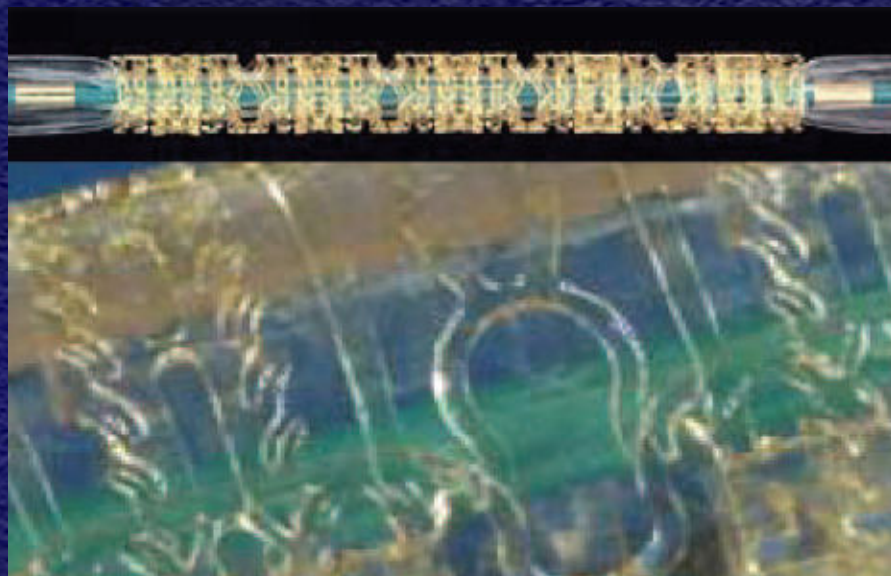


**6 M**



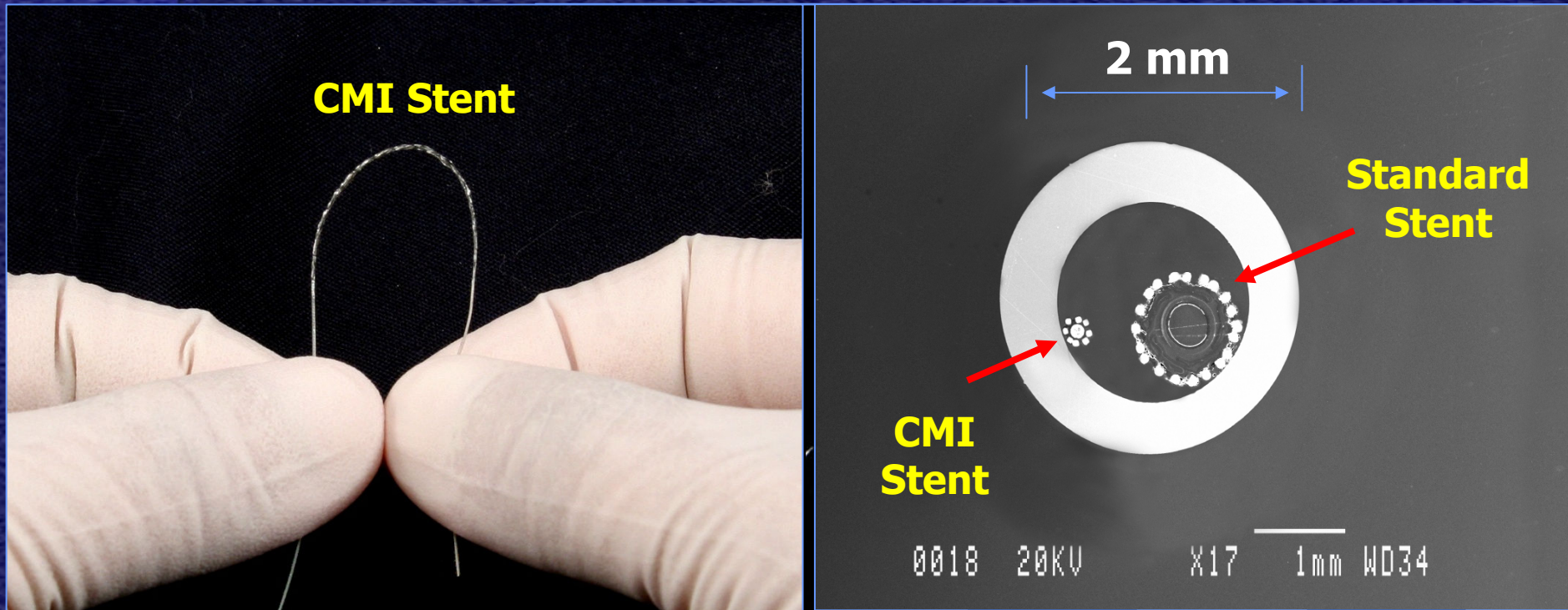
# ***REVA's "slide & lock" stent***

- *A fully absorbable polymer stent with a "slide & lock" design → negligible stent recoil*
- *Radiopaque tyrosine-derived polycarbonate backbone*
- *RESORB trials has been recently designed*



# The CardioMind™ .014" Wire Based Stent Delivery System

*(NoX instead of Rx)*



## Head to Toe Solution...

# *Conclusion*

- *Currently, various innovative DES are emerging with the intention to avoid the current pitfalls.*
- *Abolition of neointimal hyperplasia is no longer the ultimate goal and has been replaced by the development of **more thin, biocompatible and bioabsorbable stents that facilitate adequate endothelialization as well as normalization of arterial wall***

**Thank you for  
your attention !**