# Drug-Eluting Stent
## New Paradigm for PCI ?

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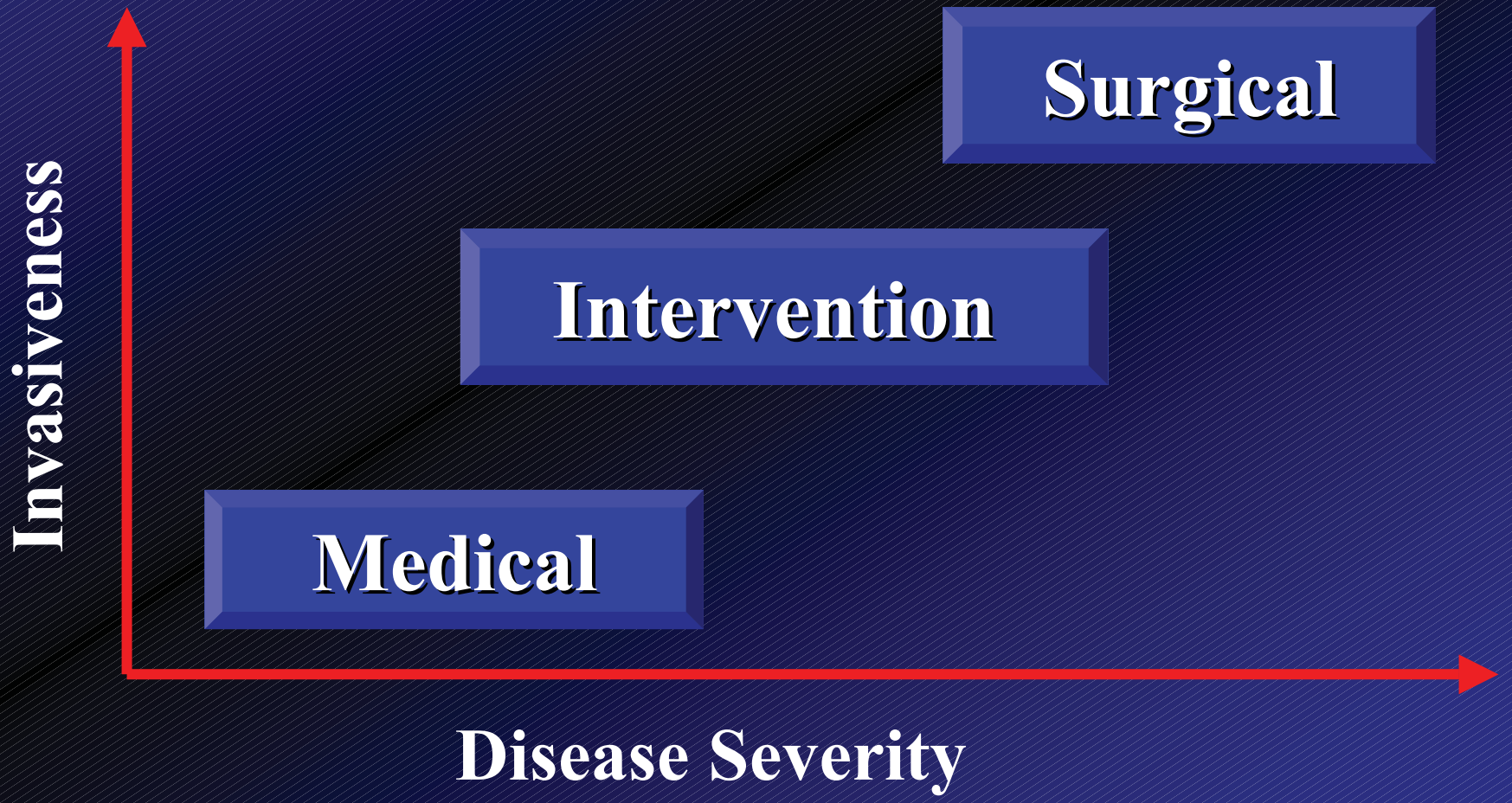
# Intervention 2003

## Treatment Alternatives for Coronary Heart Disease



# The History of Angioplasty is ...

the History of Response to Restenosis

# An Evolutionary Process
## in Interventional Cardiology

- 1977-1988 Balloon Angioplasty

# *Balloon Angioplasty …*

## Limitations

1. Abrupt closure (~5%),
   Suboptimal result (10-15%), and
   Restenosis (30-40%)
2. Relatively ineffective in “unfavorable” lesion morphology subgroups (e.g. SVG lesions, LMCA disease, ostial lesions,and heavy calcification)

# An Evolutionary Process
## in Interventional Cardiology

- 1977-1988 Balloon Angioplasty
- 1988-1993 New Device Angioplasty

**Athero-ablative devices**

DCA
Rotational atherectomy
Laser angioplasty

# *New Device Angioplasty …*

## Athero-ablative devices

In reality, incremental benefit was not well demonstrated comparable to PTCA, although it required greater operator expertise and more expense

# An Evolutionary Process
## in Interventional Cardiology

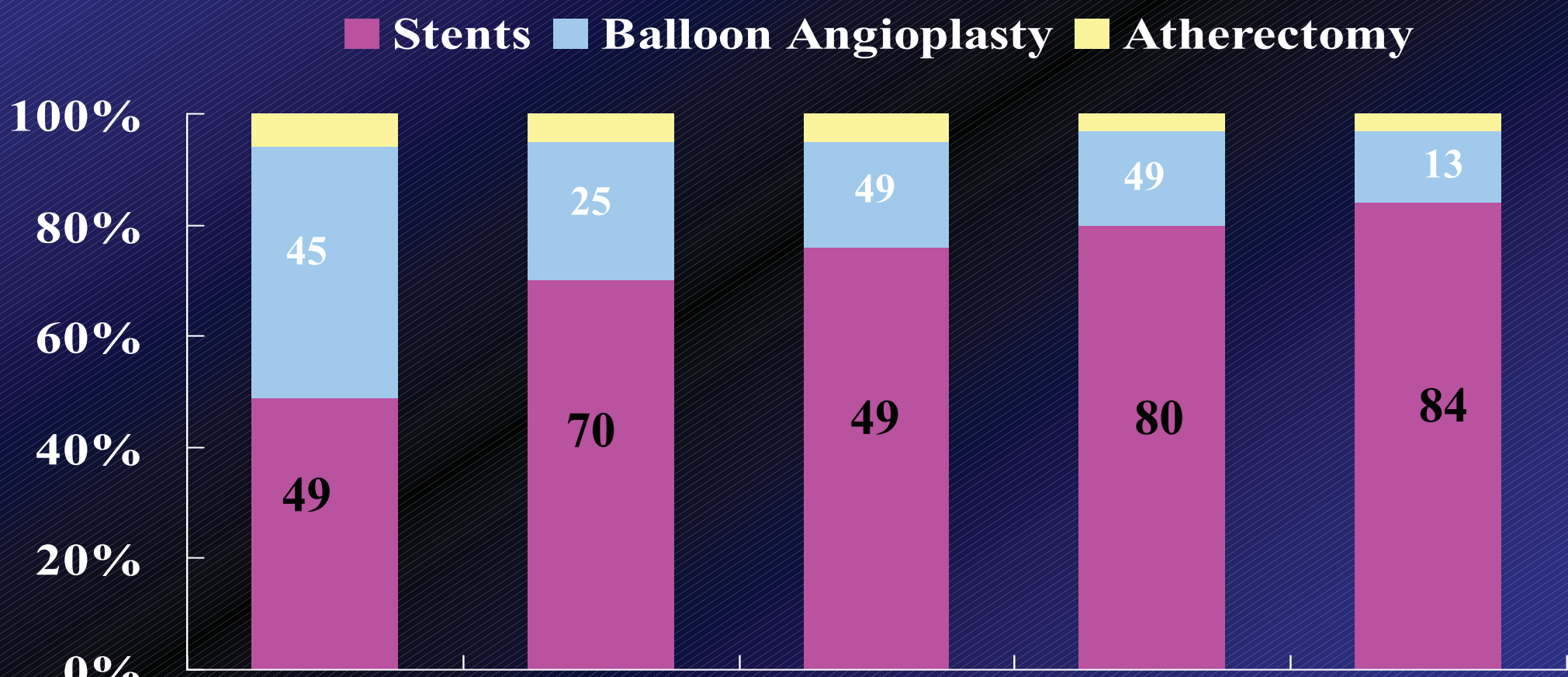
- 1977-1988 Balloon Angioplasty
- 1988-1993 New Device Angioplasty
- 1993-2000 Stent Frenzy

# *Stent Frenzy…*

1. Improved safety :
   Reversed abrupt/threatened closure
2. “First ever” anti-restenosis device therapy
   (Restenosis rate 20-25%)

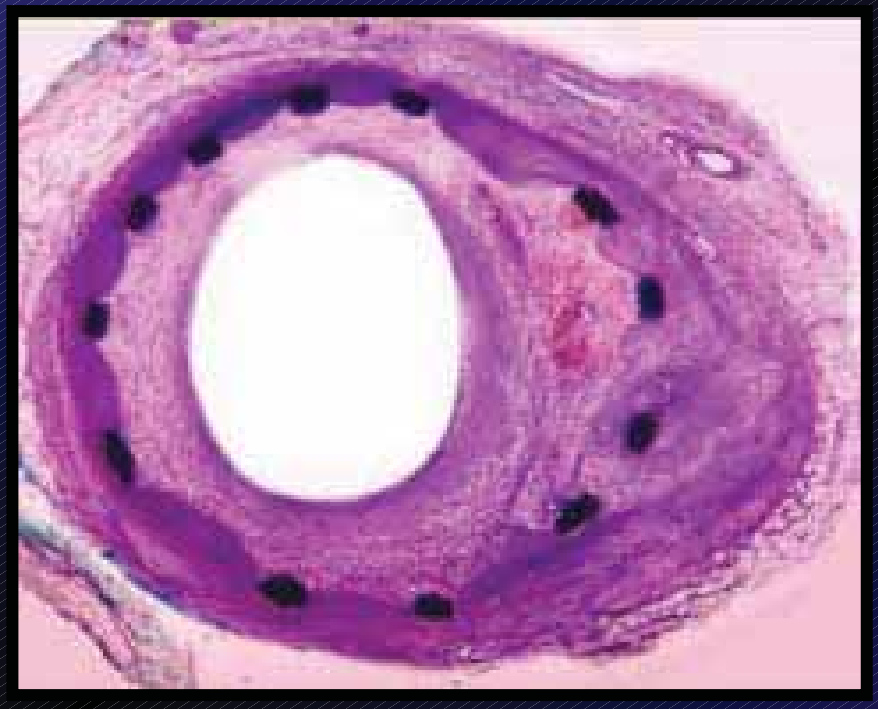
# Intervention 2002

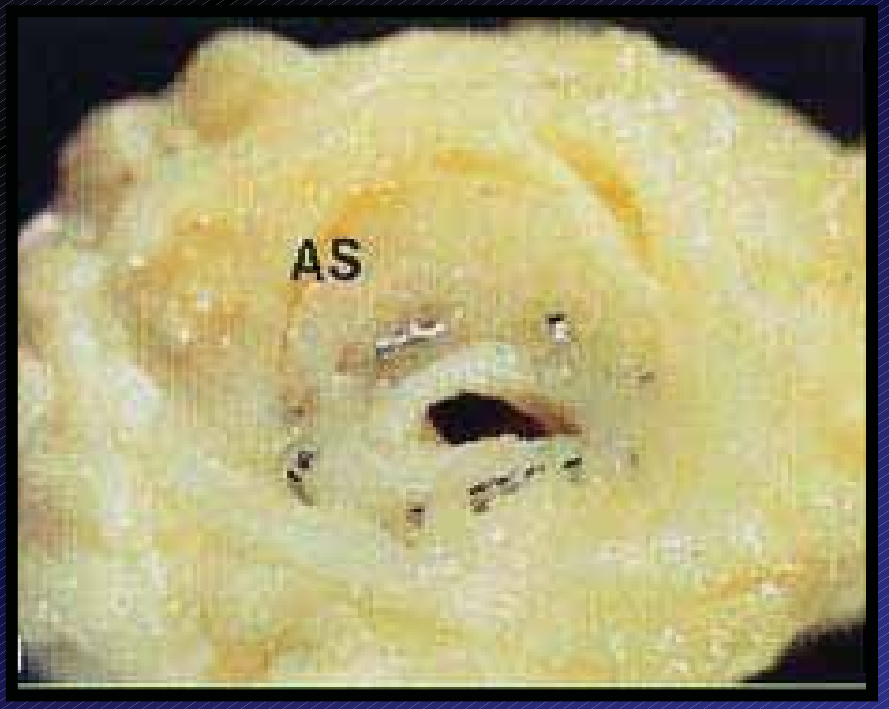
## Stents have become the "default" therapy …



# In-Stent Restenosis

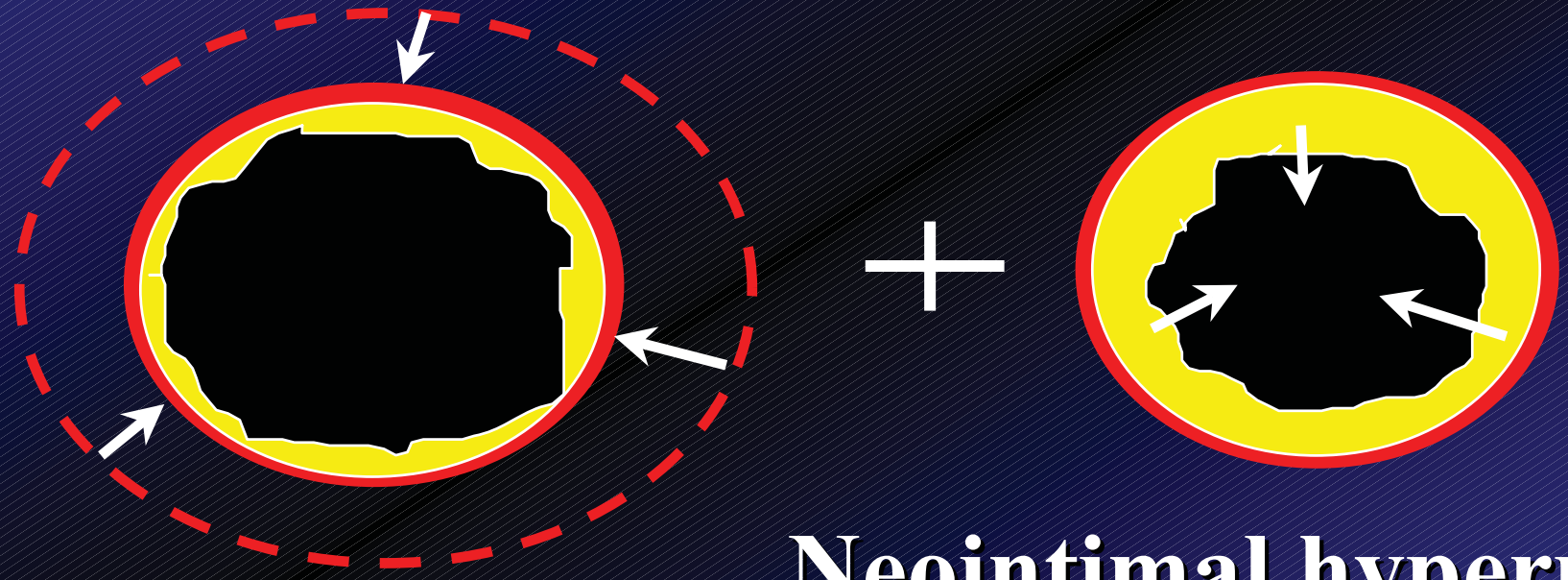
## *is the most serious problem (20-25%)*





# Restenosis

Recoil and remodeling



Neointimal hyperplasia

# Restenosis

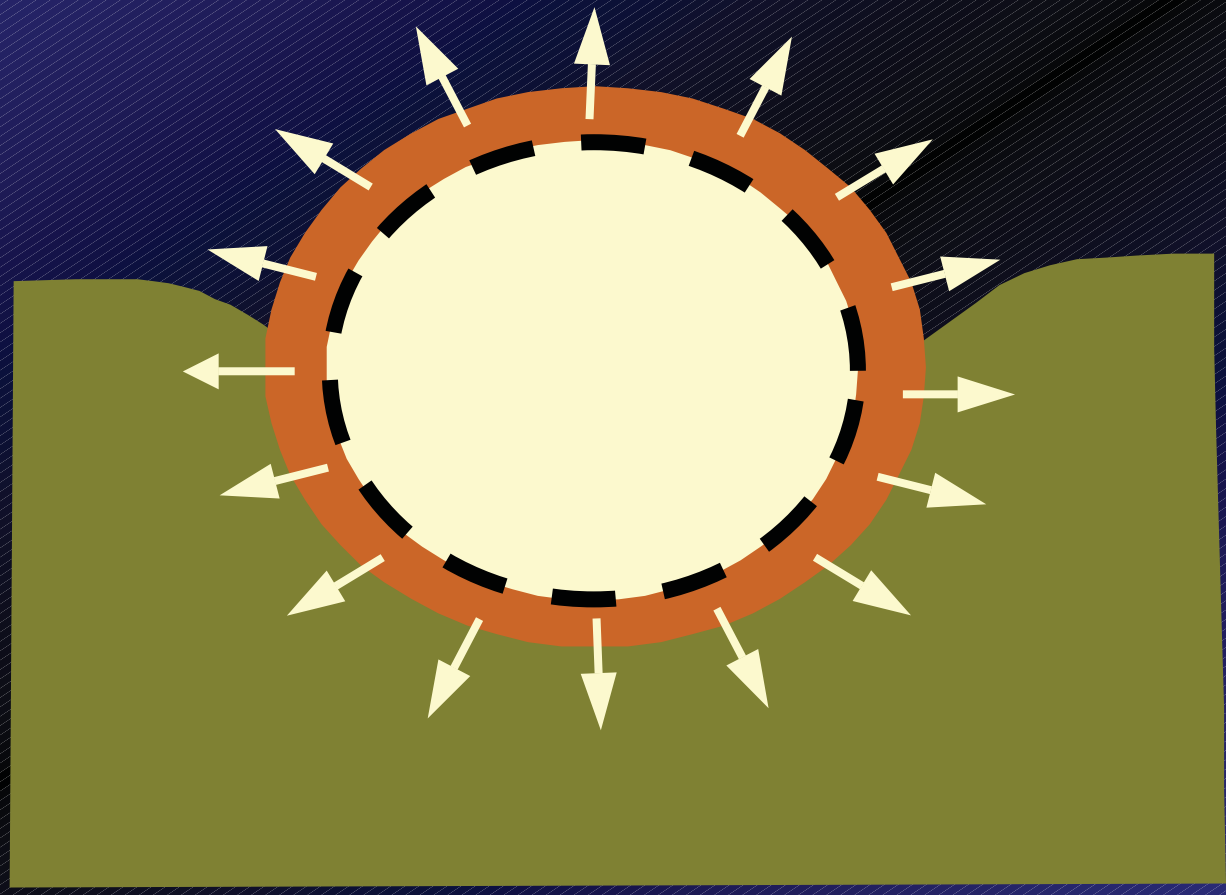
## Cause

Recoil and remodeling
Neointimal hyperplasia

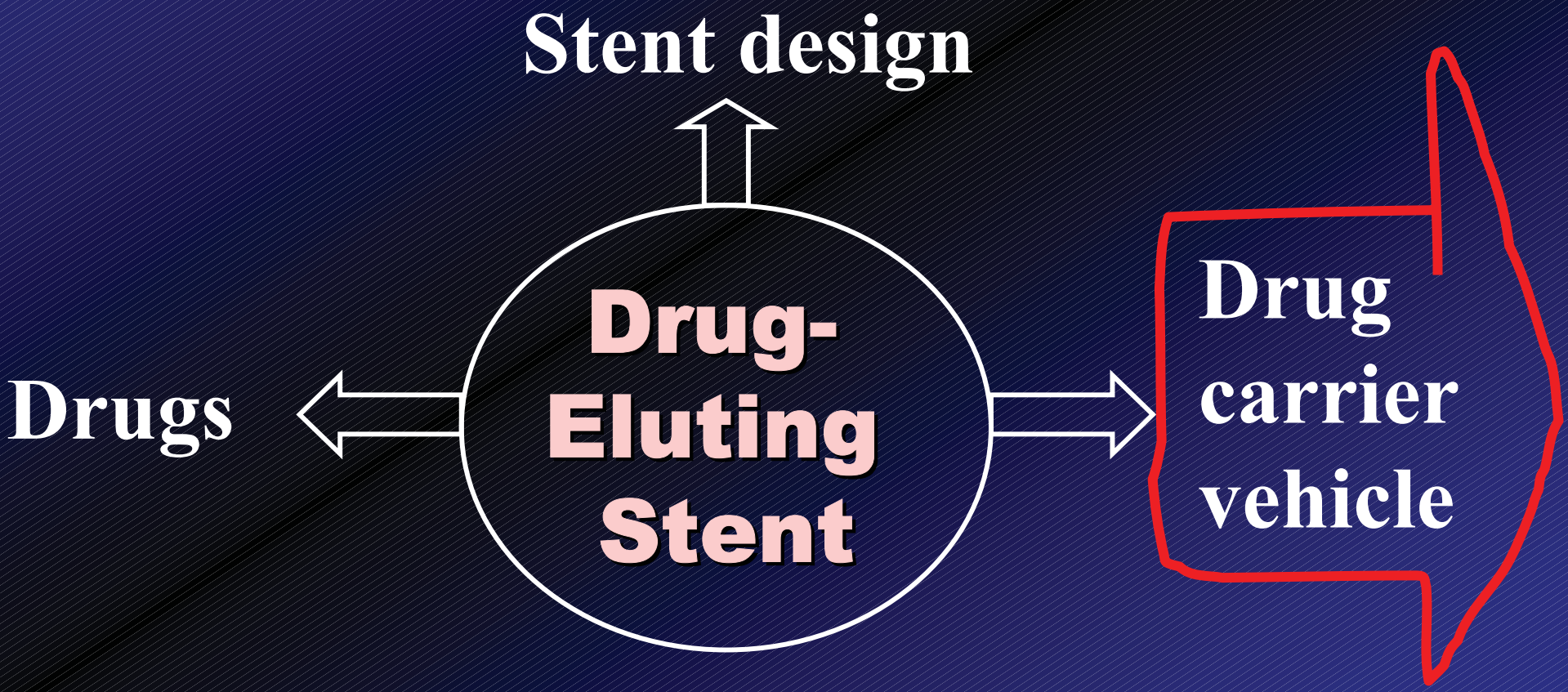
## Solution

- Stents will prevent vascular recoil and remodeling
- Active therapeutic agent is required to block neointimal hyperplasia

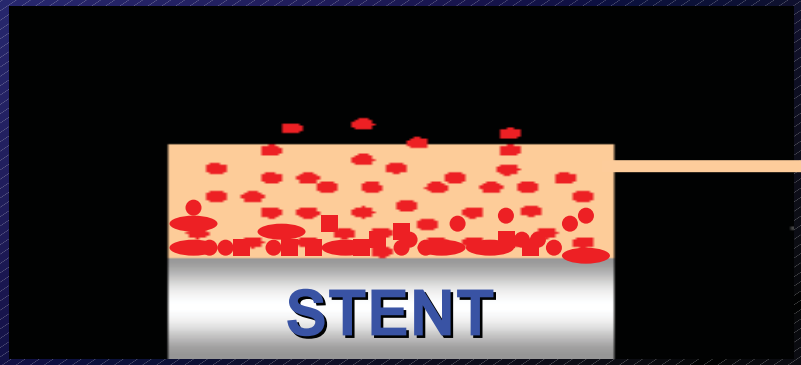
# Drug Eluting Stent



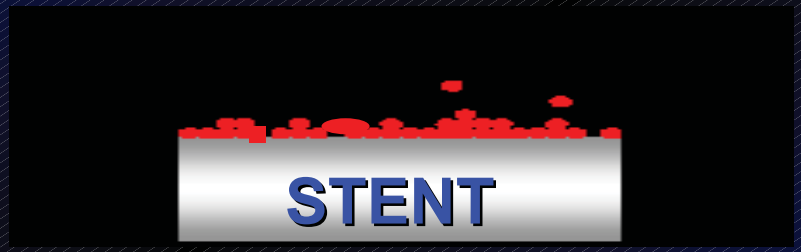
# Three Component System



# Methods of Stent-mediated Delivery




Polymer



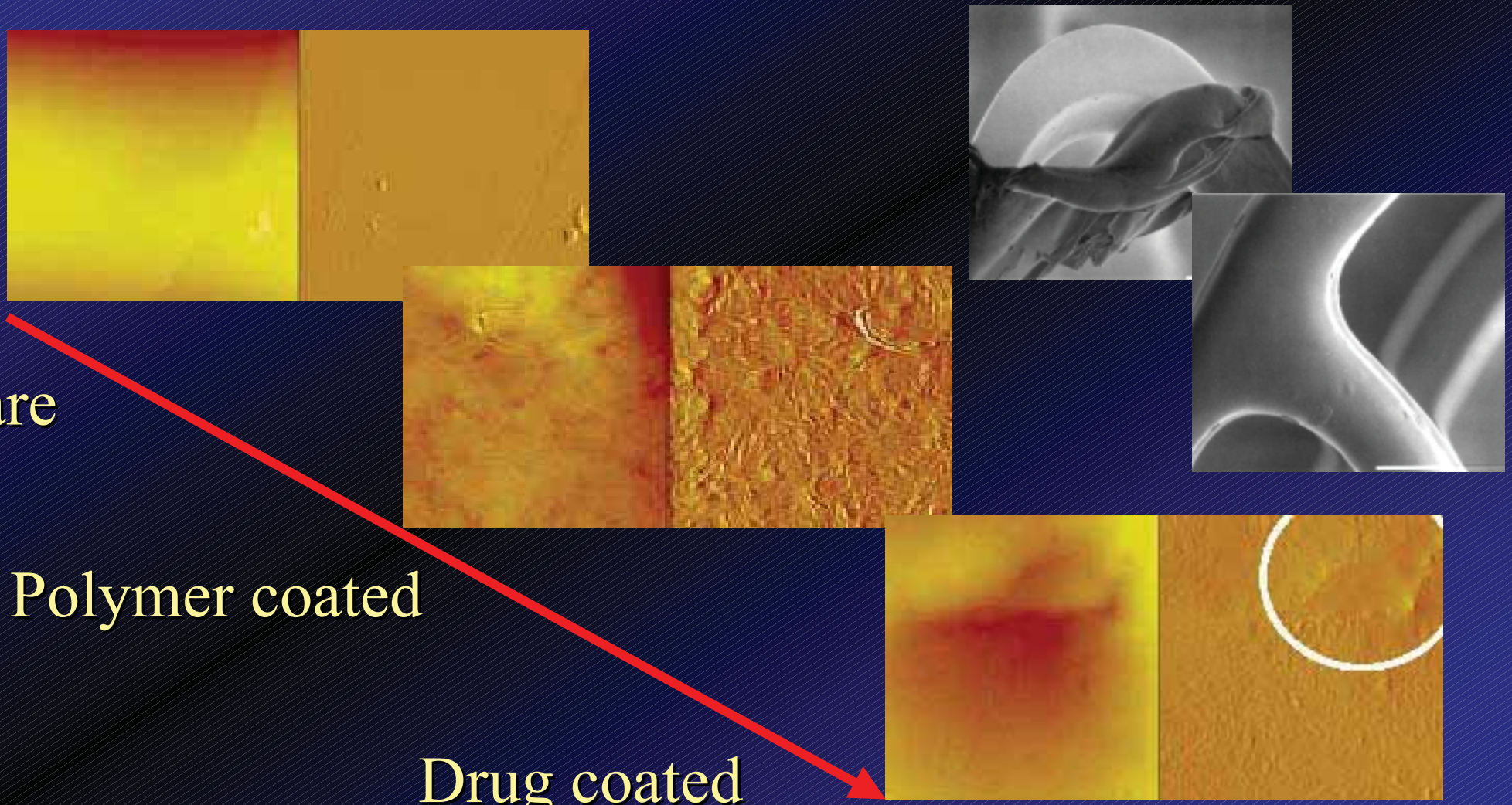

Non-polymer

# Drug Carrier Vehicle

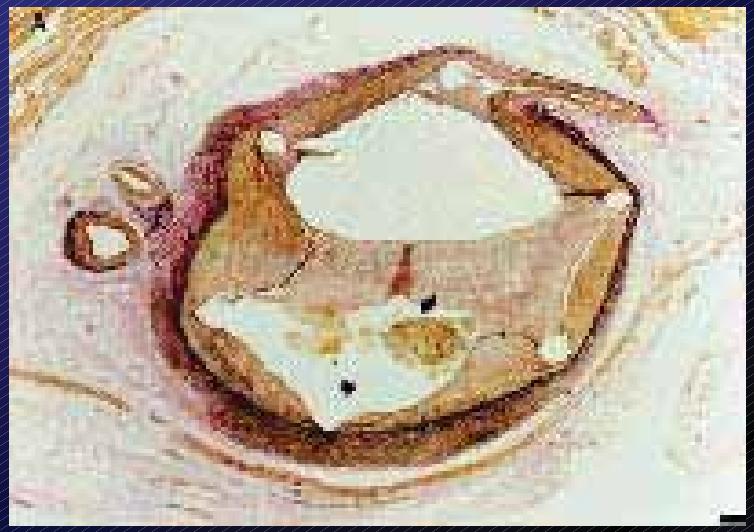
Polymer

# Drug Eluting Stent

*Microscopic technique - atomic force microscopy*



# Bad Polymer



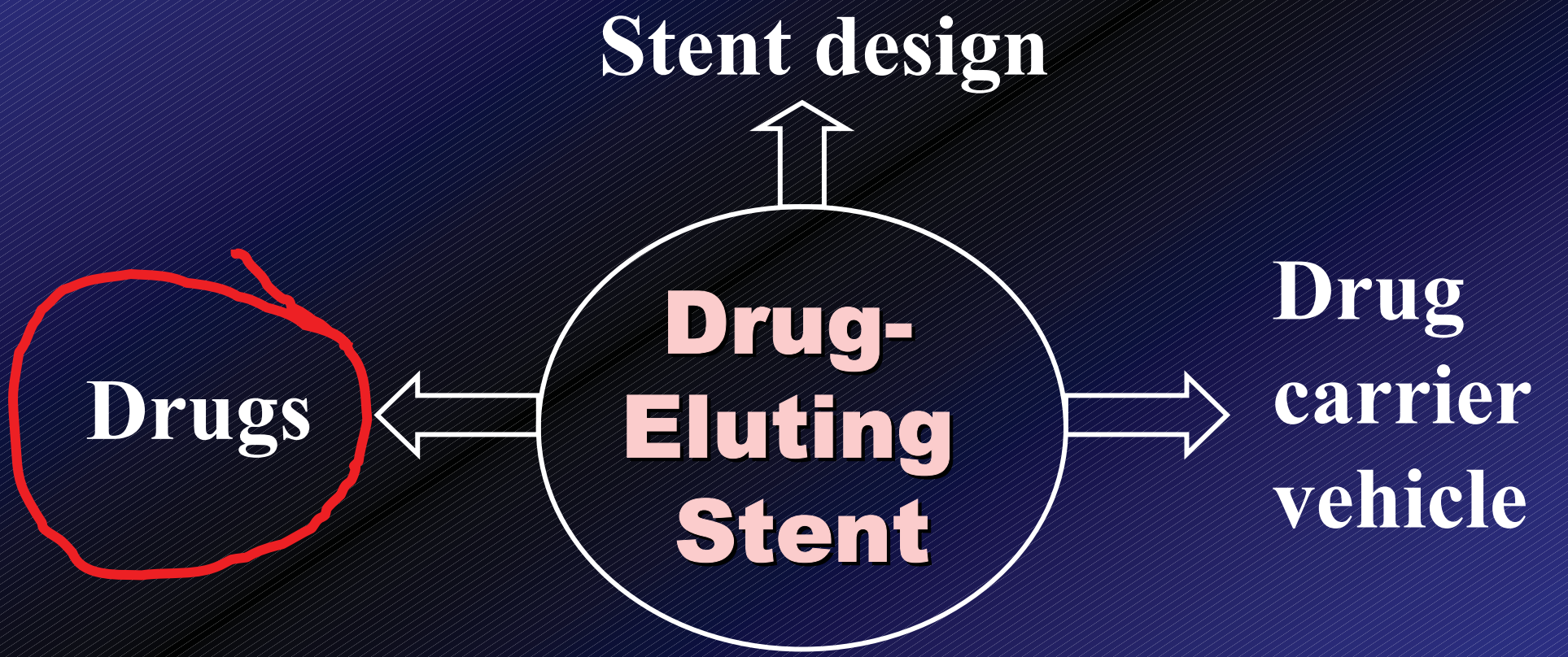
Potentially harmful due to marked inflammatory change…

# Drug Carrier Vehicle

## Polymer

- Phospholactic acid (PLA)
- Methylmethacrylate (MMA) / 2-hydroxyethyl methacrylate (HEMA)
- Phosphorylcholine
- Other new polymers

# Three Component System



# Drugs
## "Active" Anti-proliferative…

- Continuous biologic interactions with the vessel wall to reduce intimal proliferation
- Categories: drugs (anti-mitotics, anti-inflammatory agents, metallo-proteinase inhibitors, NO donors, estradiols, anti-sclerosiong agents), and "molecular" (genes, cells, anti-sense) approaches

# Drug

| | |
|---|---|
| **Antineoplastic** | Paclitaxel (Taxol™) |
| | Taxol derivative (QP-2) |
| | Actinomycin D |
| | Vincristine |
| **Antithrombins** | Hirudin and iloprost |
| | Heparin |
| **Immunosuppressants** | Sirolimus (Rapamycin ™) |
| | Tacrolimus (FK506) |
| | Tranilast |
| | Dexamethasone |
| **Collagen synthetase inhibitor** | Halofuginone |
| | Propyl hydroxylase |
| | C-proteinase inhibitor |
| **Angiopeptin, VEGF** | |

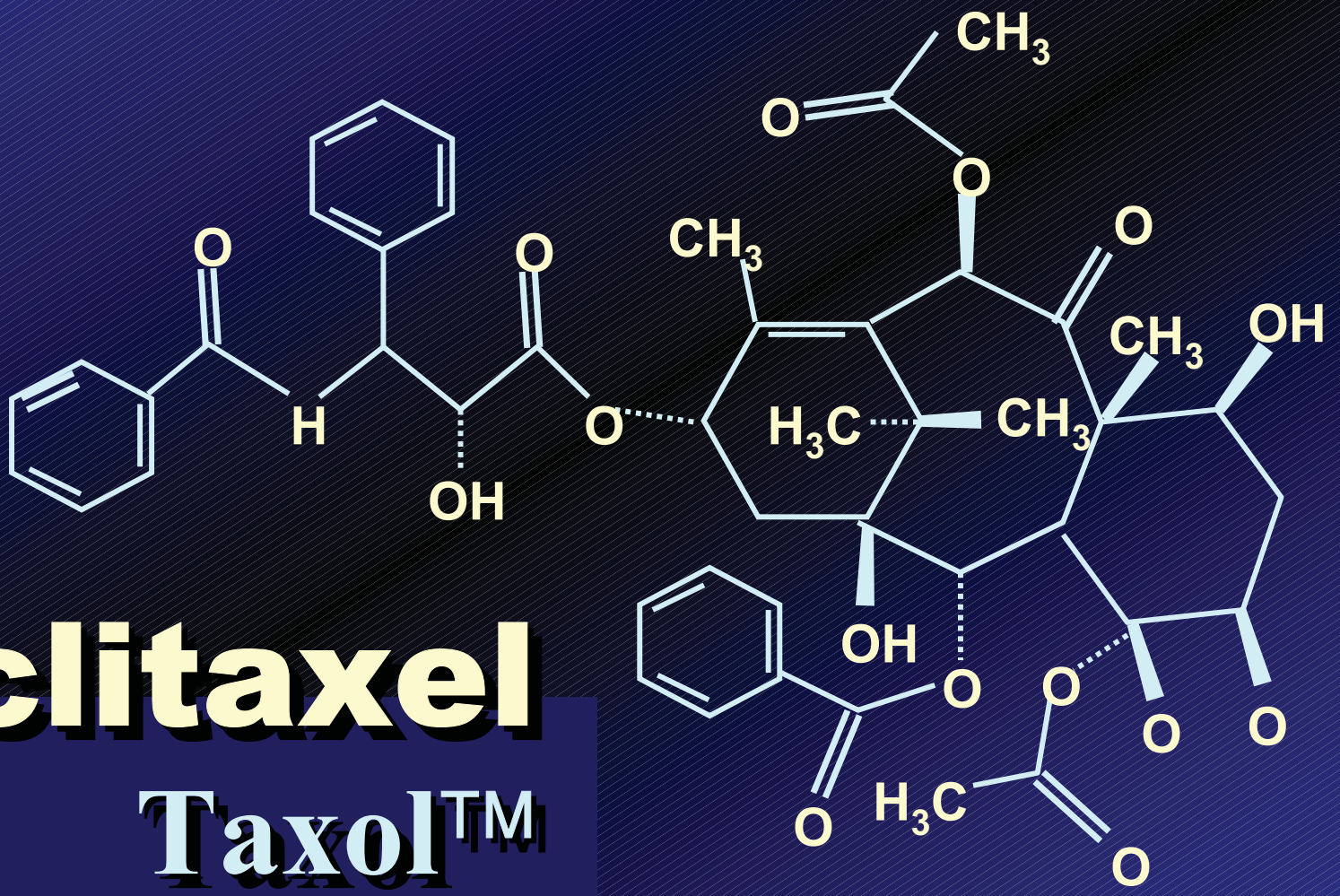
# Clinical Results of Various Drug Eluting Stents

# Drug Eluting Stent Trials

**Paclitaxel**

- Non-Polymer — **ASPECT, ELUTE**
- Polymer — **TAXUS I-VII**

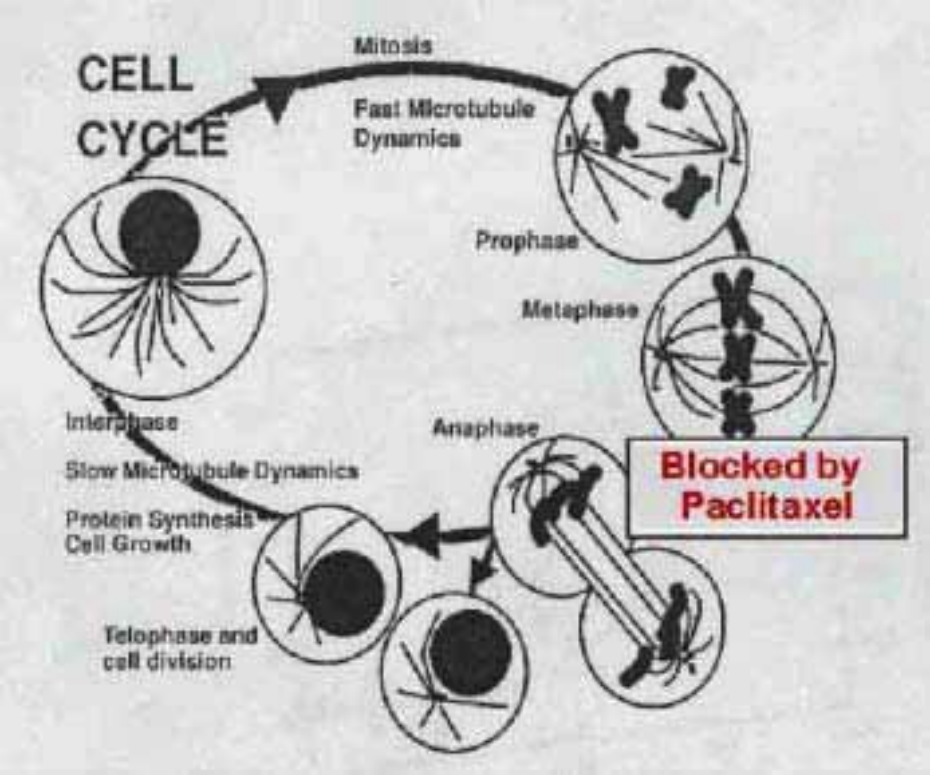
**Sirolimus** — **RAVEL, SIRIUS**




# Paclitaxel

## Taxol™

# Mechanism : Mitotic Arrest




Binds to microtubules

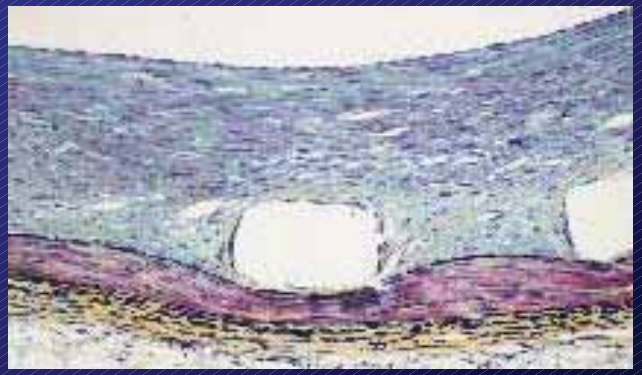
→Stabilizes microtubule structure

→Forms bundles and multiple asters

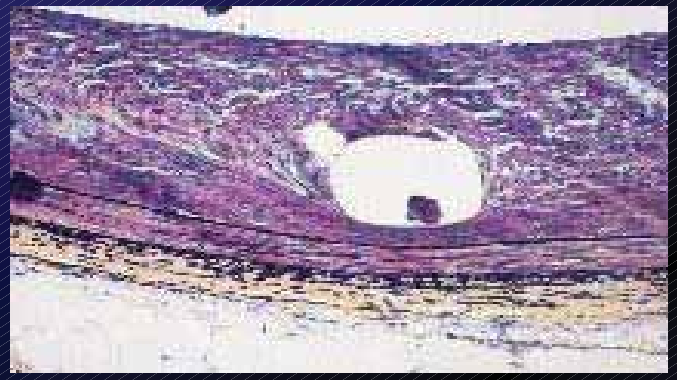
→Mitotic arrest

→Inhibits cell proliferation & migration

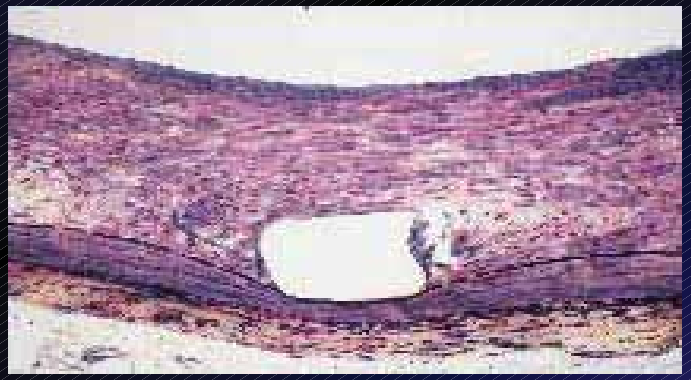
# Dose dependent pathology *Paclitaxel*



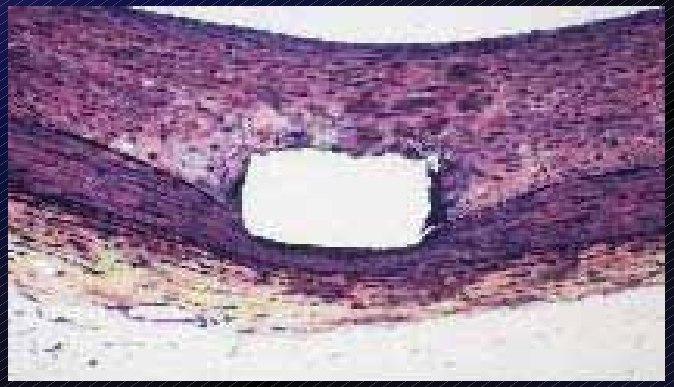
Uncoated



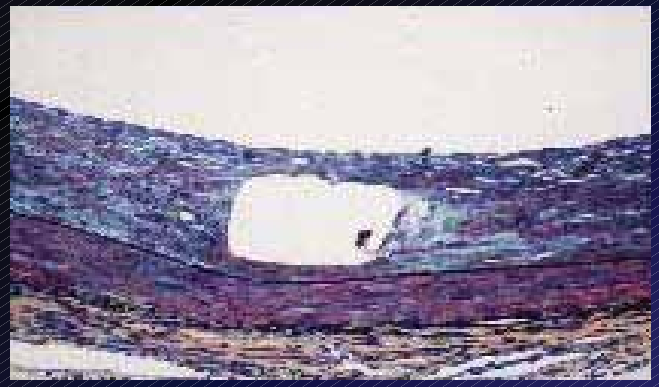
Chondroitin Sulfate
Gelatin Coated



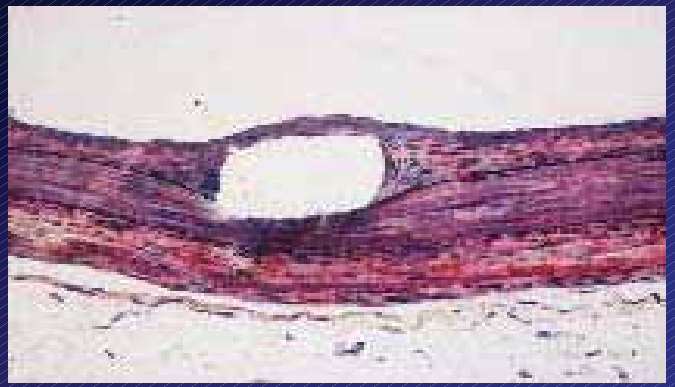
1.5 μg



8.6 μg



20.2 μg



42 μg

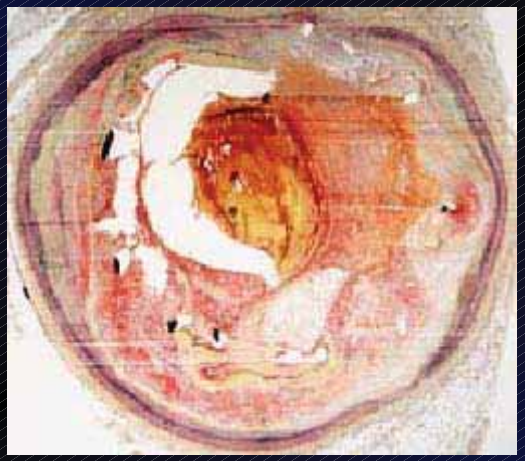
Farb A et al. Circ 2001;104:473

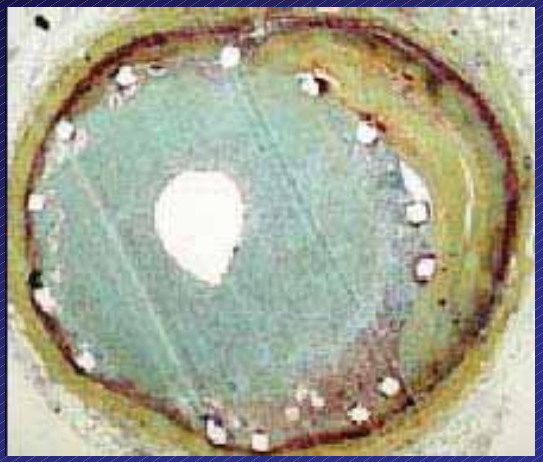
# Healing Response of DES

Late thrombosis with impaired healing

Patent and healed

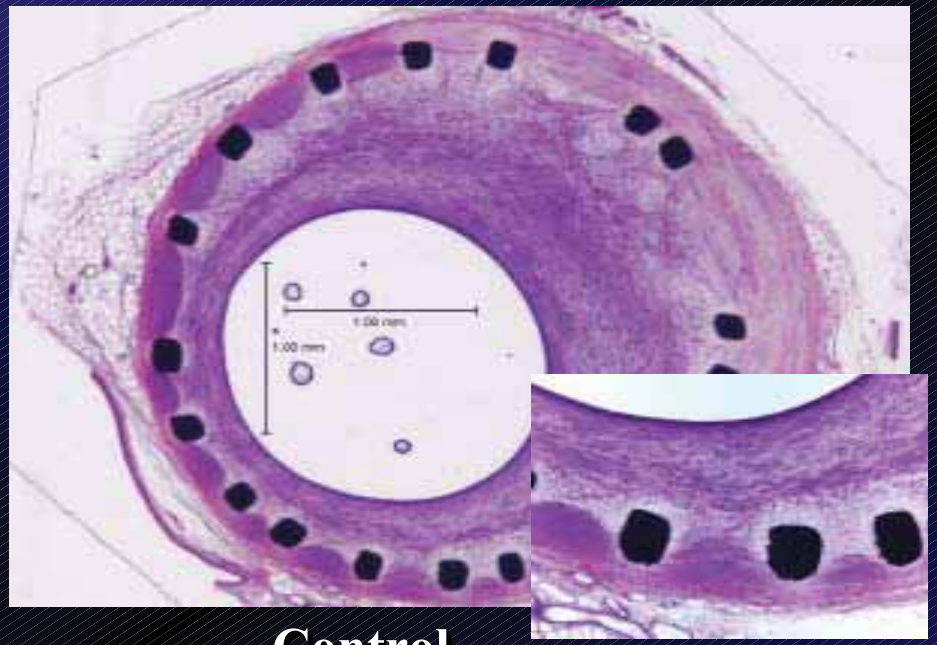
In-stent restenosis and late catch-up



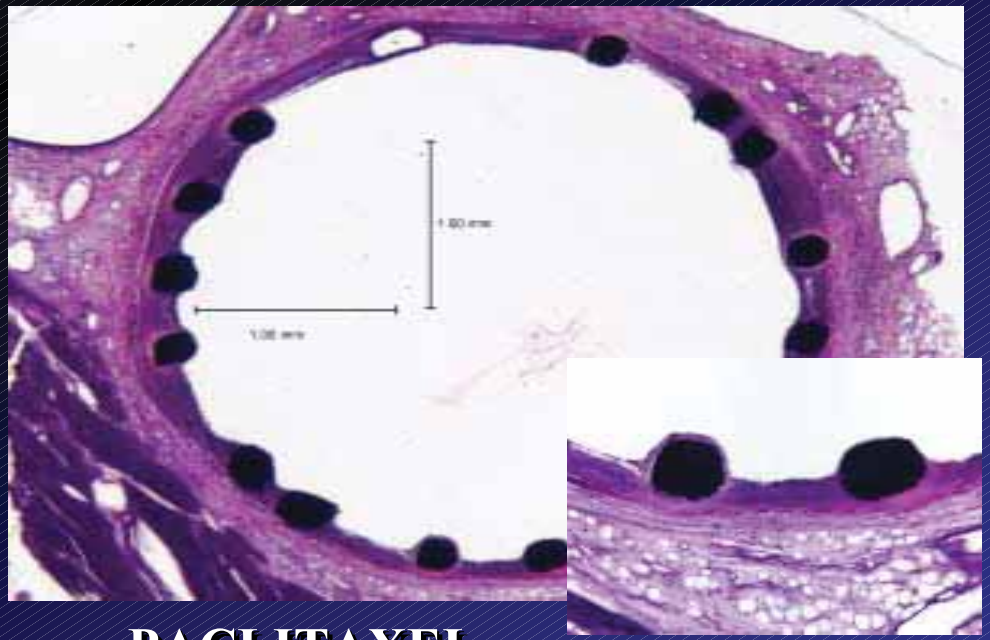


# Experimental data
## (One month Swine study)

Paclitaxel coated stents produce significant inhibition of neointimal hyperplasia



Control



PACLITAXEL

# ASPECT Clinical Study

# ASian Paclitaxel-Eluting Stent Clinical Trial

*Prospective, Randomized, Multicenter, Triple-blinded Study*

ASPECT
Clinical Study

# Device

STENT

Non-polymer

## Paclitaxel coated Supra G™ stent

- Stainless steel, slotted tube design
- Diameters:2.5, 3.0 or 3.5 mm, Length:15 mm

- Paclitaxel was adhered to the abluminal surface of stents using a proprietary process without the use of a polymer

# Inclusion Criteria

- De novo lesions in native artery
- Reference vessel diameter
  ≥ 2.25 mm, <3.5 mm
- Lesion length should be fully covered by one stent (15 mm)



# Study Design

Prospective, multicenter, randomized, triple-blind design with 3 treatment arms (Enrollment: 177 patients)

- **UNCOATED** control
- **LOW** dose density (1.3 mcg/mm$^2$)
- **HIGH** dose density (3.1 mcg/mm$^2$)

ASPECT
Clinical Study

# Patients Demographics

| | Paclitaxel Dose Density | | | |
|---|---|---|---|---|
| | 3.1 | 1.28 | 0.0 | Totals |
| **Age (yrs)** | 58 ± 9 | 60 ± 9 | 58 ± 11 | 60 ± 10 |
| **Males** | 80% | 72% | 76% | 76% |
| **Diabetics** | 18% | 24% | 17% | 20% |
| **Hypercholesterolemia** | 13% | 7% | 19% | 13% |
| **Hypertension** | 42% | 53% | 46% | 47% |

* No significant difference among treatment groups.

# Target Vessels (n = 177)

| | Paclitaxel Dose Density | | | |
|---|---|---|---|---|
| | 3.1 | 1.28 | 0.0 | Totals |
| LAD | 53% | 50% | 51% | 51% |
| RCA | 17% | 31% | 29% | 26% |
| LCx | 29% | 17% | 20% | 22% |
| Ramus | 2% | 2% | 0% | 1% |

* No significant difference among treatment groups.

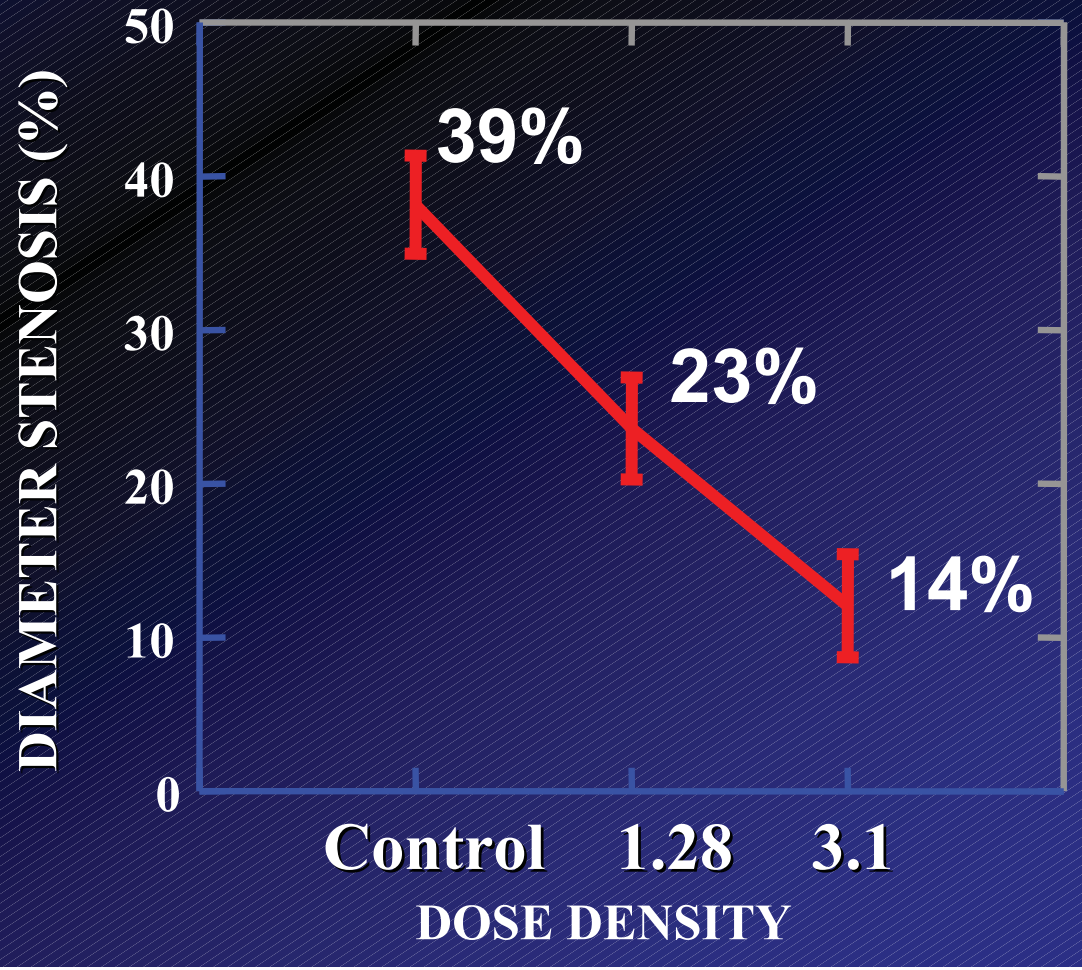
ASPECT
Clinical Study

# 6 month Follow-up
# % Diameter Stenosis

## QCA Results

| | |
|---|---|
| 3.1 vs Ctrl | p<0.001 |
| 1.28 vs Ctrl | p<0.003 |
| 3.1 vs 1.28 | p=N.S. |

By Analysis of Variance



ASPECT
Clinical Study

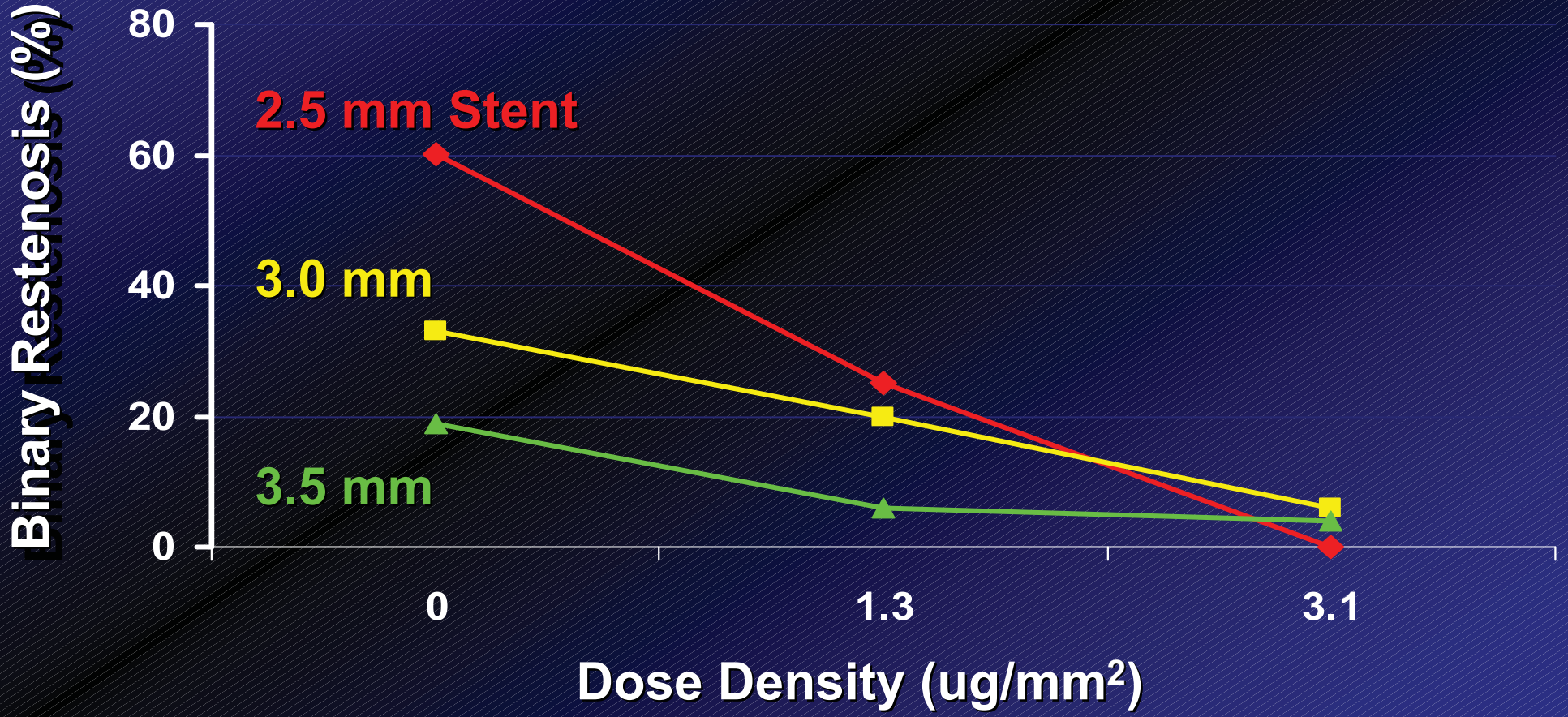
# 6 month follow-up
# Efficacy Data

| | High Dose Paclitaxel | Low Dose Paclitaxel | Control |
|---|---|---|---|
| **MLD pre** | 0.64 ± 0.29 | 0.57 ± 0.25 | 0.54 ± 0.33 |
| **MLD post (mm)** | 2.85 ± 0.34 | 2.84 ± 0.39 | 2.82 ± 0.42 |
| **MLD F/U (mm)** | 2.53 ± 0.72 | 2.28 ± 0.83 | 1.79 ± 0.86 |
| **Late Loss (mm)** | 0.29 ± 0.72 | 0.57 ± 0.71 | 1.04 ± 0.83 |
| **Average Loss/Gain** | 0.13 ± 0.33 | 0.26 ± 0.34 | 0.46 ± 0.37 |
| **DS (%)** | 14 ± 21 | 23 ± 25 | 39 ± 27 |
| IH Volume($mm^3$) | 12 | 18 | 31 |
| **Binary Restenosis** | **4%** | **12%** | **27%** |

Significant difference among treatment groups $p<0.0001$.

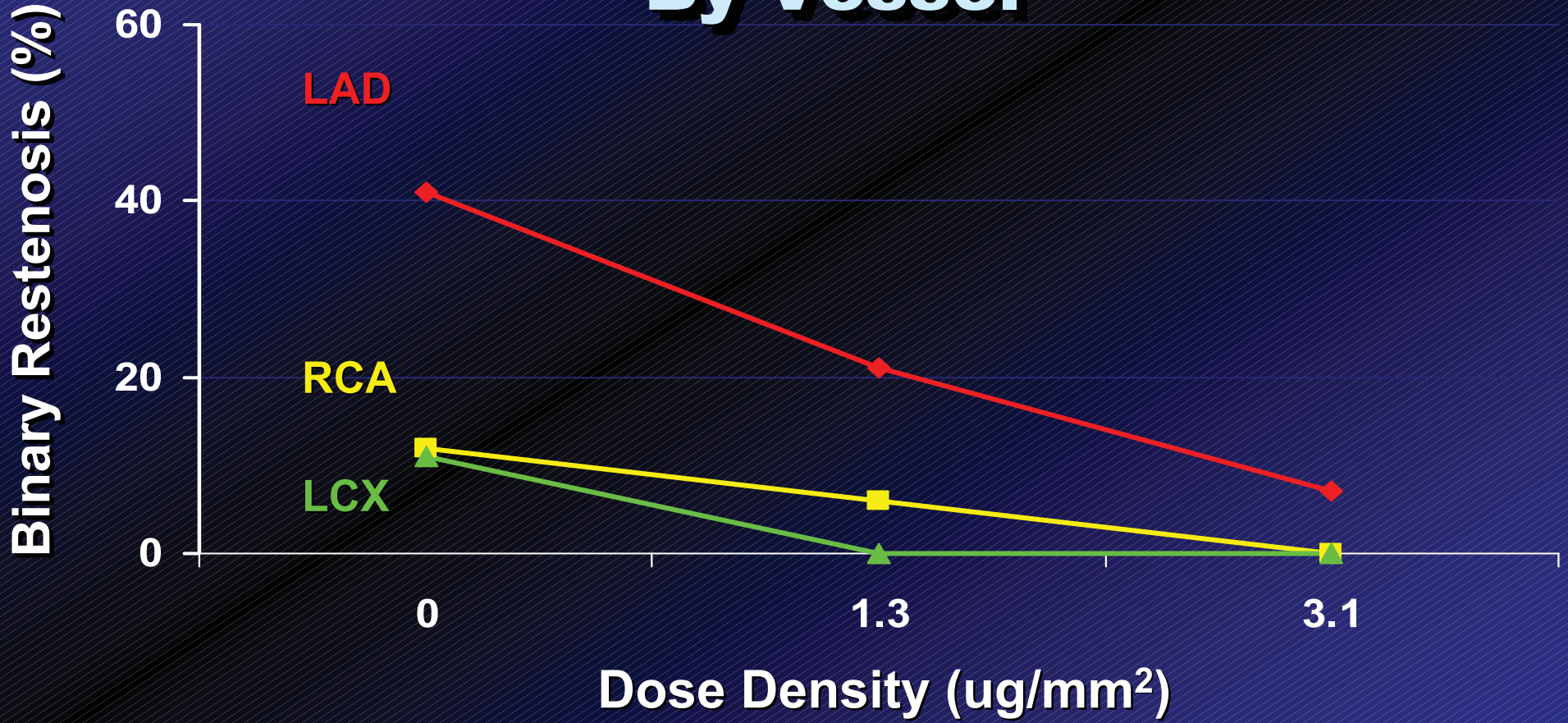
ASPECT
Clinical Study

# Binary Restenosis Rate
## By Stent Size



ASPECT
Clinical Study

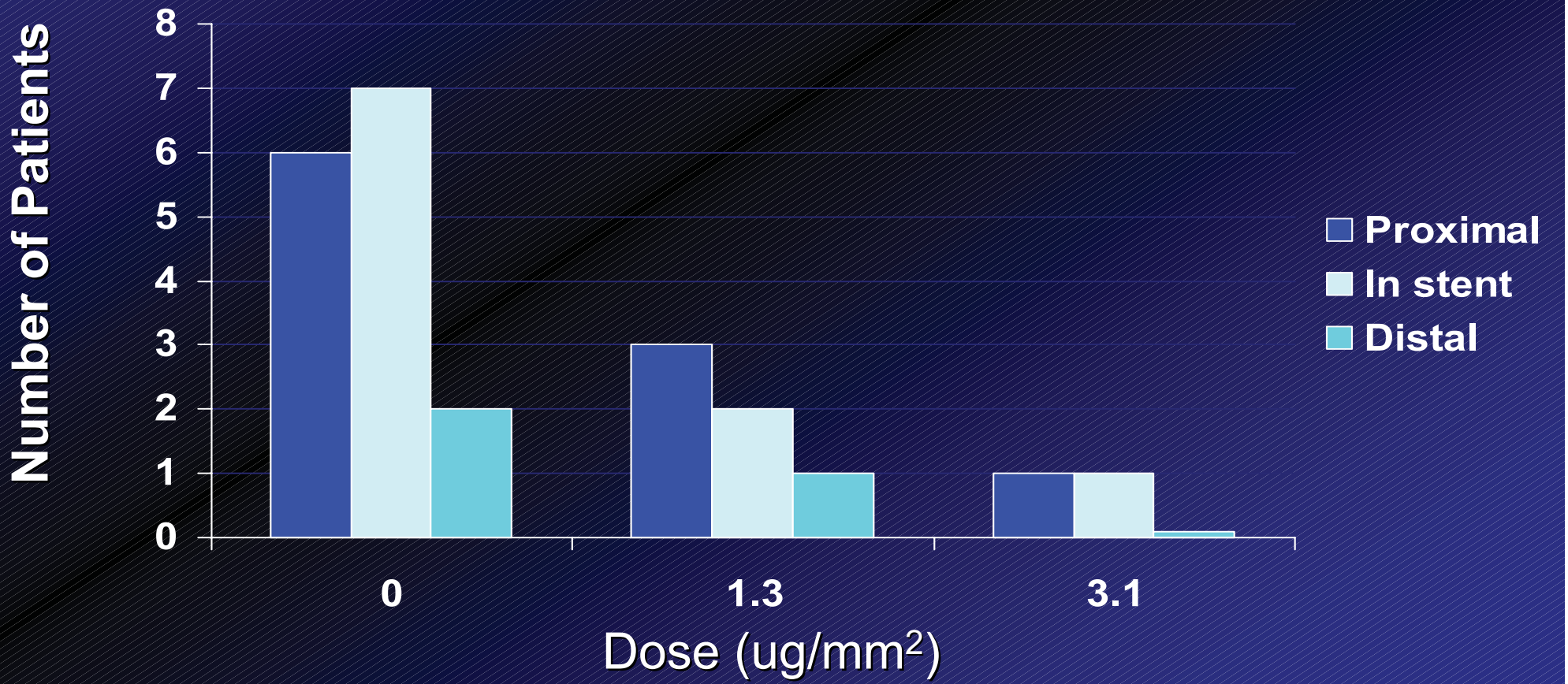
# Binary Restenosis Rate By Vessel



ASPECT
Clinical Study

# Location of the Restenosis

## Categorized as Proximal, Mid, Distal region



# 6-Month MACE Data

| Antiplatelet Tx: | ASA+Ticlid/Plavix | | | ASA+Cilostazol | | |
|---|---|---|---|---|---|---|
| Paclitaxel Dose: | High | Low | Control | High | Low | Control |
| n | 48 | 43 | 49 | 12 | 15 | 10 |
| **Death** | 0 | 0 | 0 | 0 | 1 | 0 |
| **Q-wave MI** | 0 | 0 | 0 | 0 | 0 | 0 |
| **CABG** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Non-Q-MI (<30d)** | 1 | 0 | 0 | 1 | 1 | 1 |
| **Non-Q-MI (>30d)** | 0 | 0 | 0 | 0 | 0 | 0 |
| **TLR (SAT)** | 0 | 0 | 0 | 3 | 1 | 0 |
| **TLR** | 1 | 2 | 2 | 1 | 0 | 0 |
| **Event-Free** | **96%** | **95%** | **96%** | **67%** | **87%** | **90%** |

Significant difference between the two groups $p<0.0001$.

# ELUTES

*E*uropean eva*L* *U*ation of pacli*T*axel *E*luting *S*tent

***ELUTES***

# Dose Finding Study

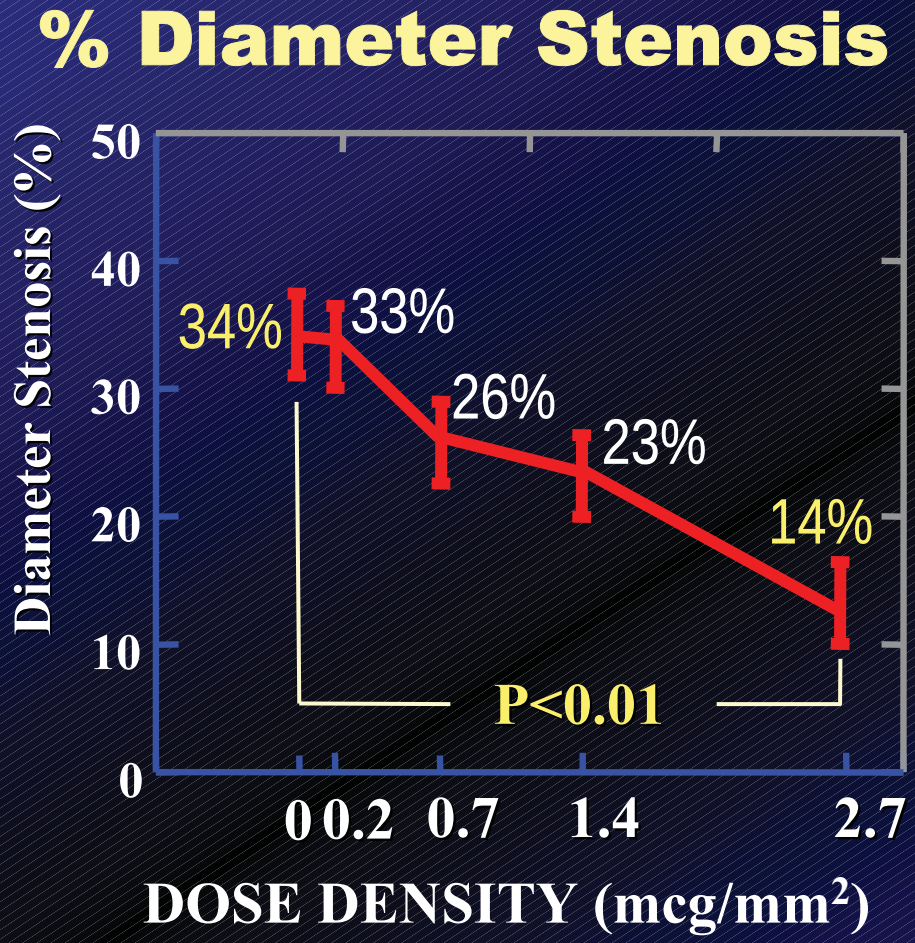
Prospective, multicenter, randomized, triple-blind design with 5 treatment arms (190 patients)

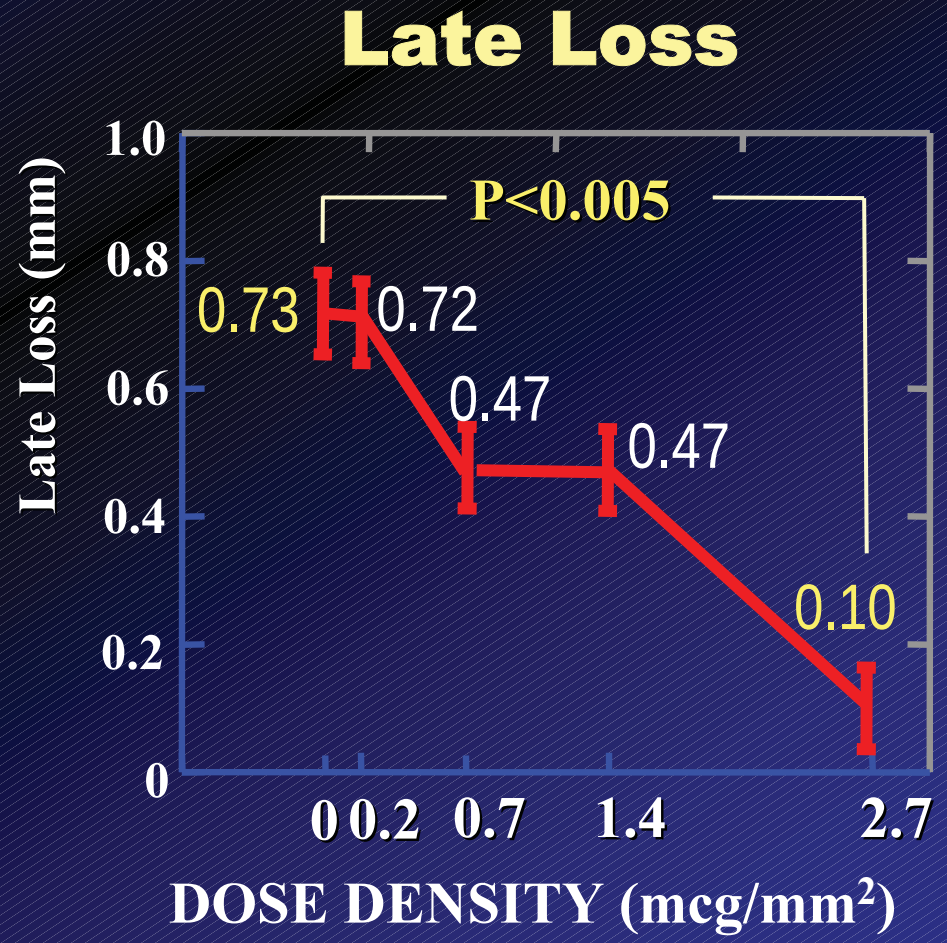
| Control | Dose 1 | Dose 2 | Dose 3 | Dose 4 |
|---|---|---|---|---|
| | 0.2 mcg/mm$^2$ | 0.7 mcg/mm2 | 1.4 mcg/mm2 | 2.7 mcg/mm2 |

To compare at 6-month follow-up
% DS, Late loss, TLR and MACE

# ELUTES

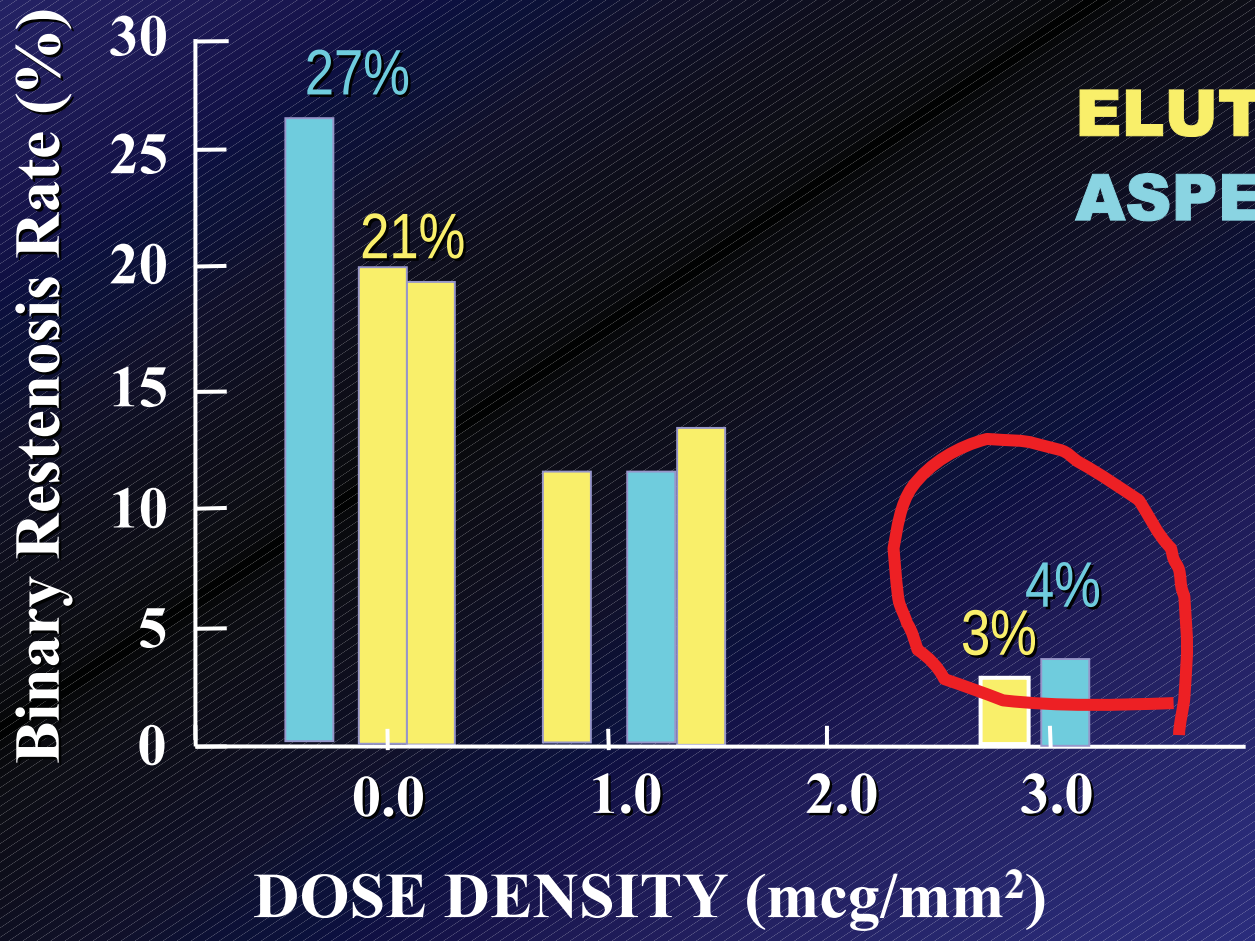
## 6 months QCA results



# ASPECT & ELUTES trials

# Binary Restenosis



# Drug Eluting Stent Trials

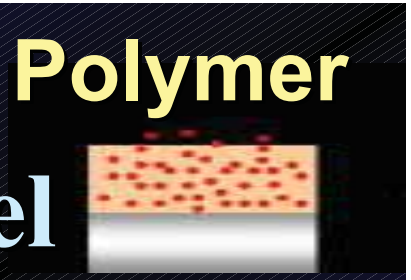
**Paclitaxel**

- Non-Polymer
- Polymer

**Sirolimus**

**ASPECT, ELUTE**
**TAXUS I-VII**
**RAVEL, SIRIUS**

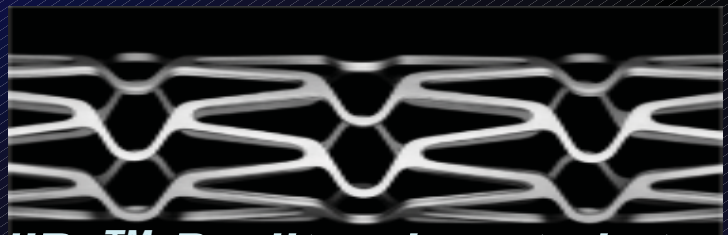
# TAXUS-I: Polymer with Paclitaxel




De novo, 3.0 and 3.5 mm
61 pts at 3 sites
1:1 Randomization (31 coated, 30 bare)

| | Coated | Bare |
|---|---|---|
| 30 day MACE | 0 % | 0 % |
| 6-month restenosis | 0 % | 10% |
| 6-month MACE | 0% | 7% |

# Ongoing TAXUS...



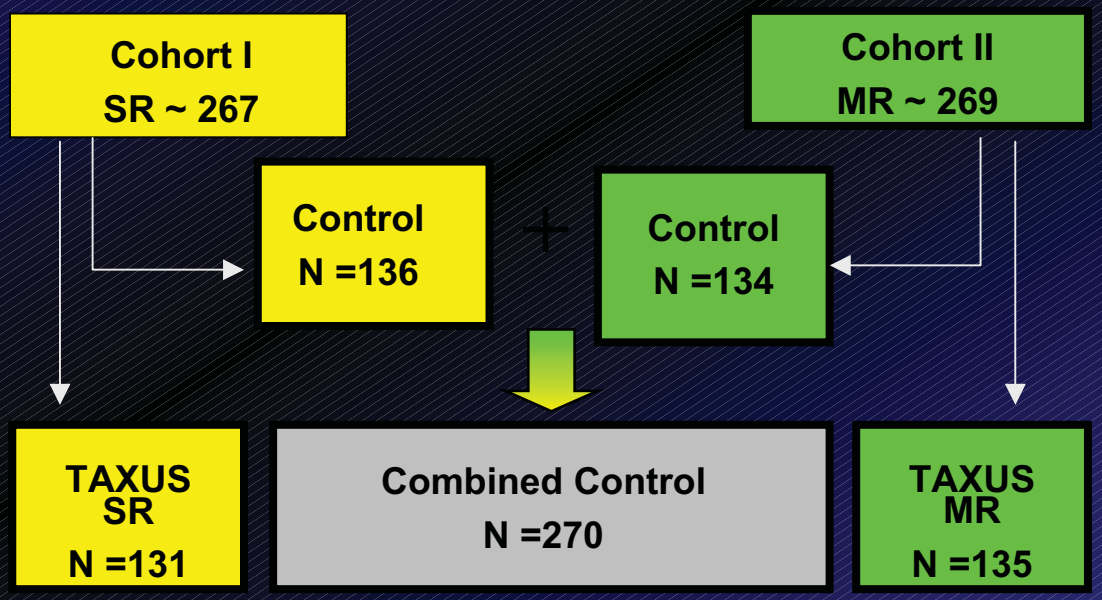
*NIRx™-Paclitaxel-coated stent*

| | |
|---|---|
| TAXUS-II | Denovo lesion (3.0 - 3.5 mm) |
| TAXUS-III | ISR |
| TAXUS-IV | Denovo lesion (2.5-3.5, <28 mm) |
| TAXUS-V | Denovo lesion (2.5-3.5, <48 mm) |
| TAXUS-VI | European study |
| TAXUS-VII | Long ISR (2.5-3.5, <40 mm) |

# Objective

Compare TAXUS Slow Release & Moderate Release groups with combined control groups (Cohort I + II) for

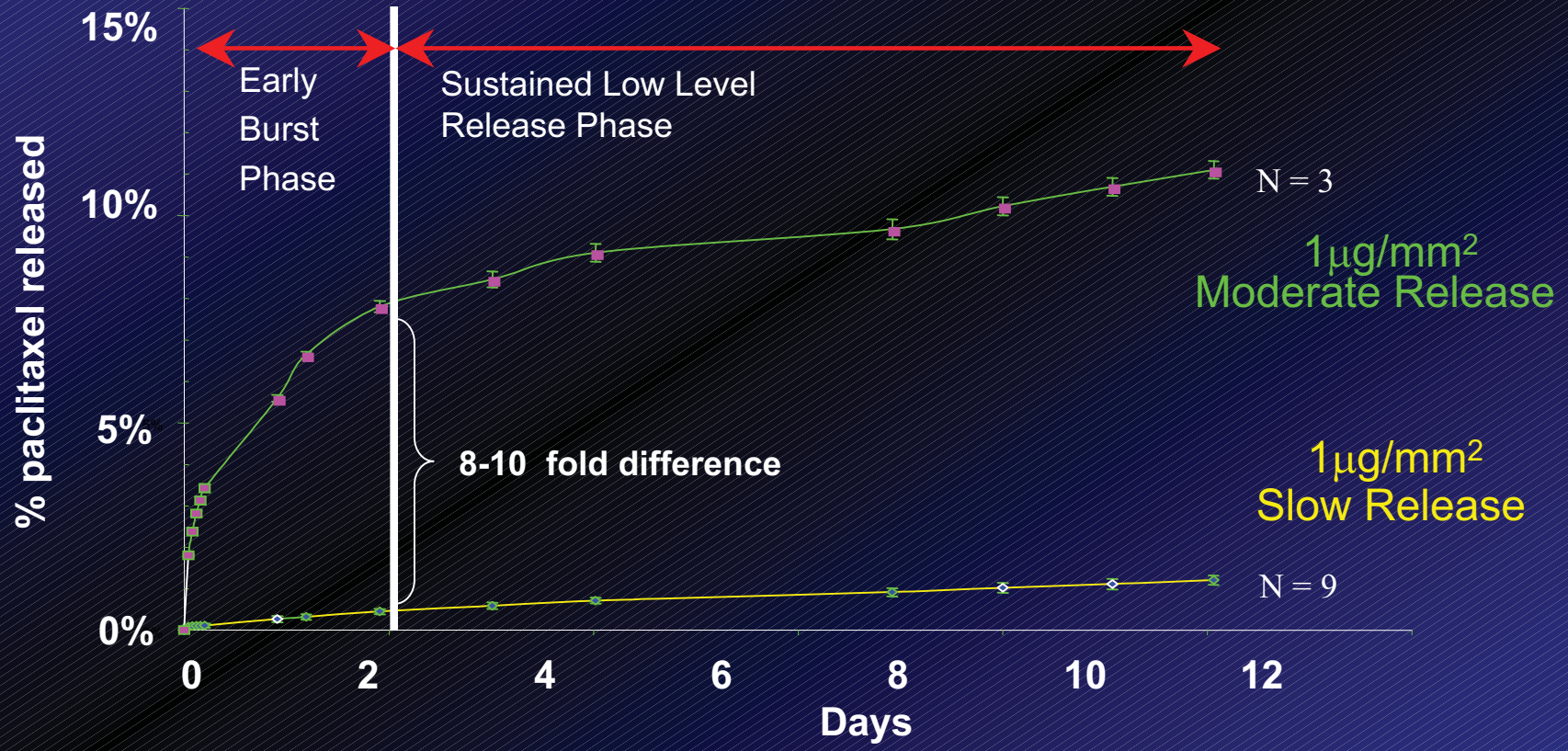
**Clinical measures the safety and efficacy**



TAXUS II

# In Vitro Release Kinetics

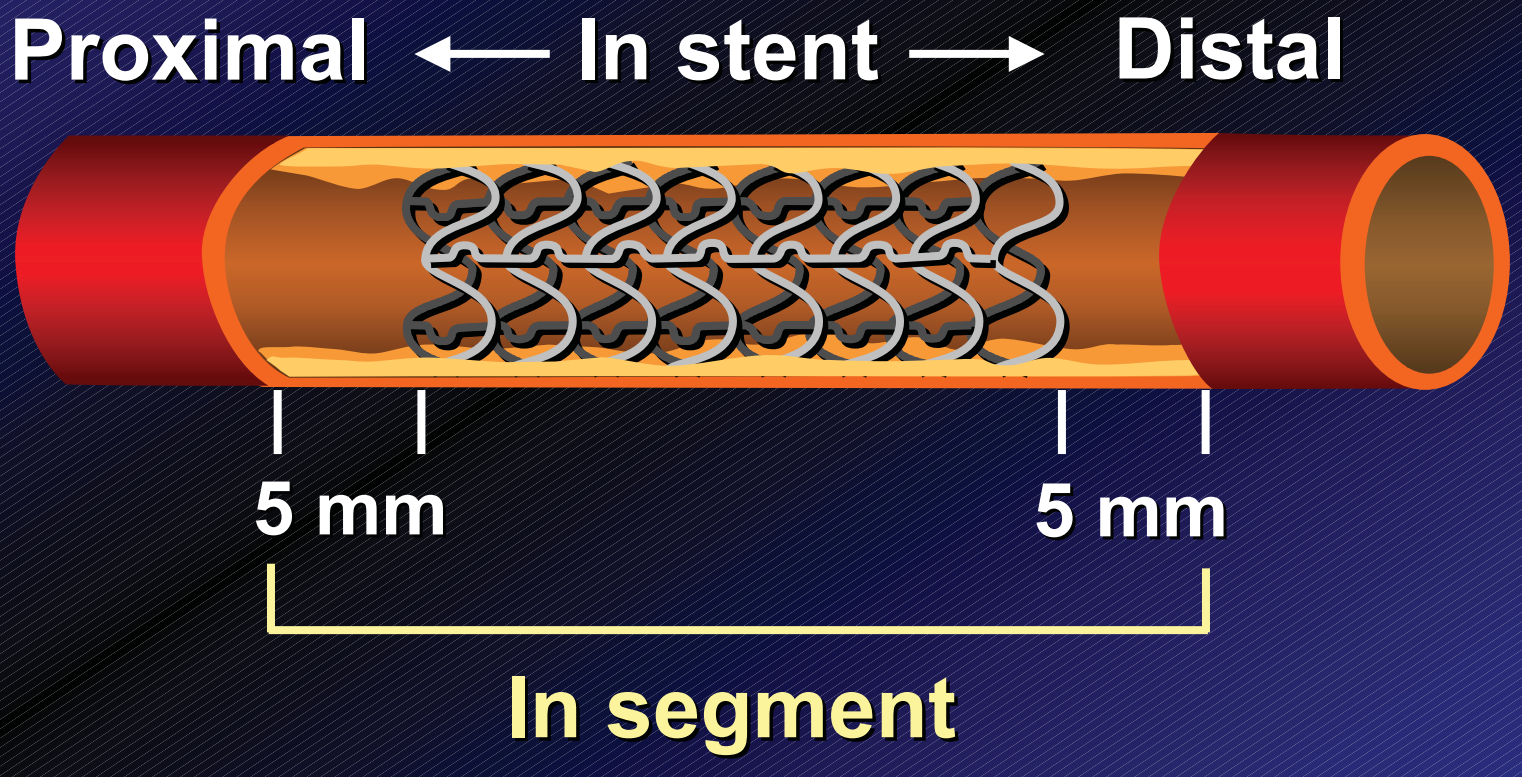
## Biphasic: 48 hr burst then slower 10 day low level phase




- Same total loaded dose -- different release rates
- Biphasic release -- early burst and sustained release phases
- 8 fold difference in release rate between SR and MR

# Definition of Restenosis

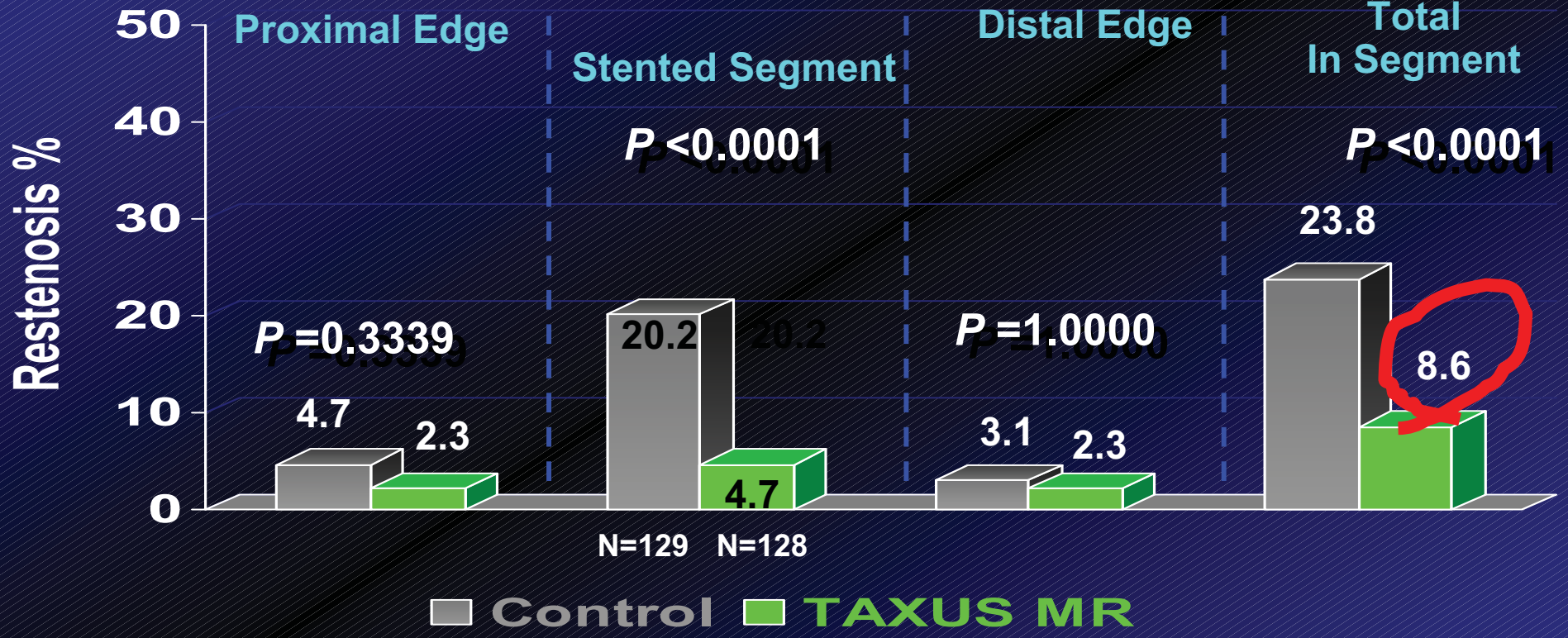
## Angiographic follow-up



TAXUS II

# Moderate release

## 6-month Binary Restenosis



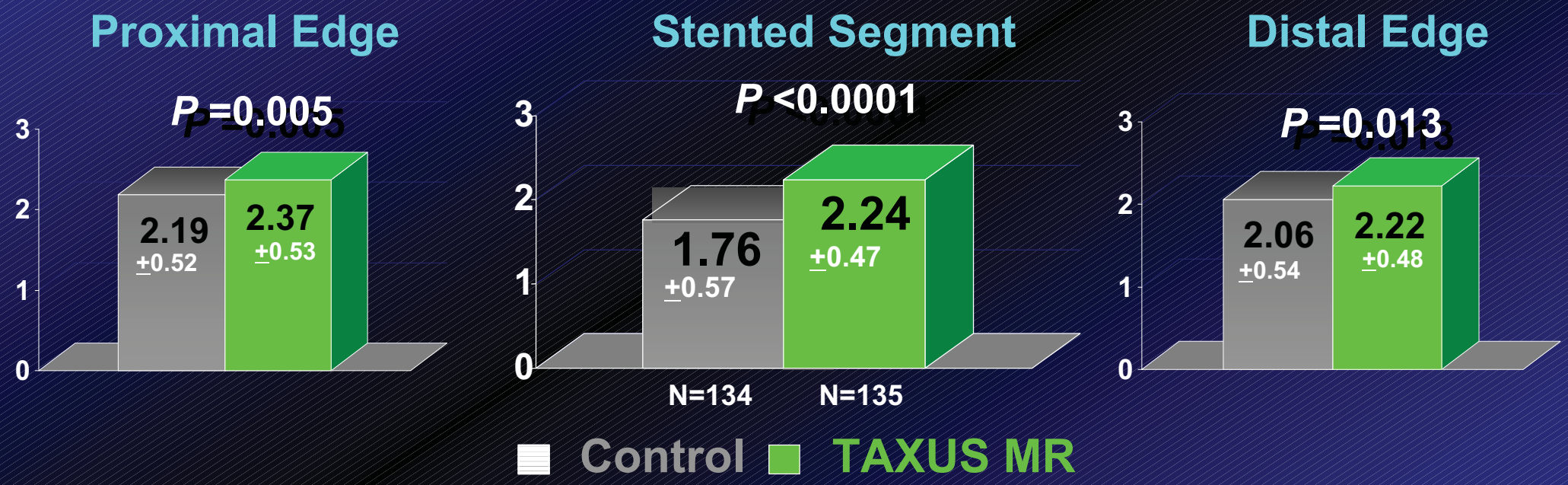

No difference at edges between TAXUS and control…

TCT, Oct 2002

TAXUS II

# Moderate release

## MLD at 6 month follow-up



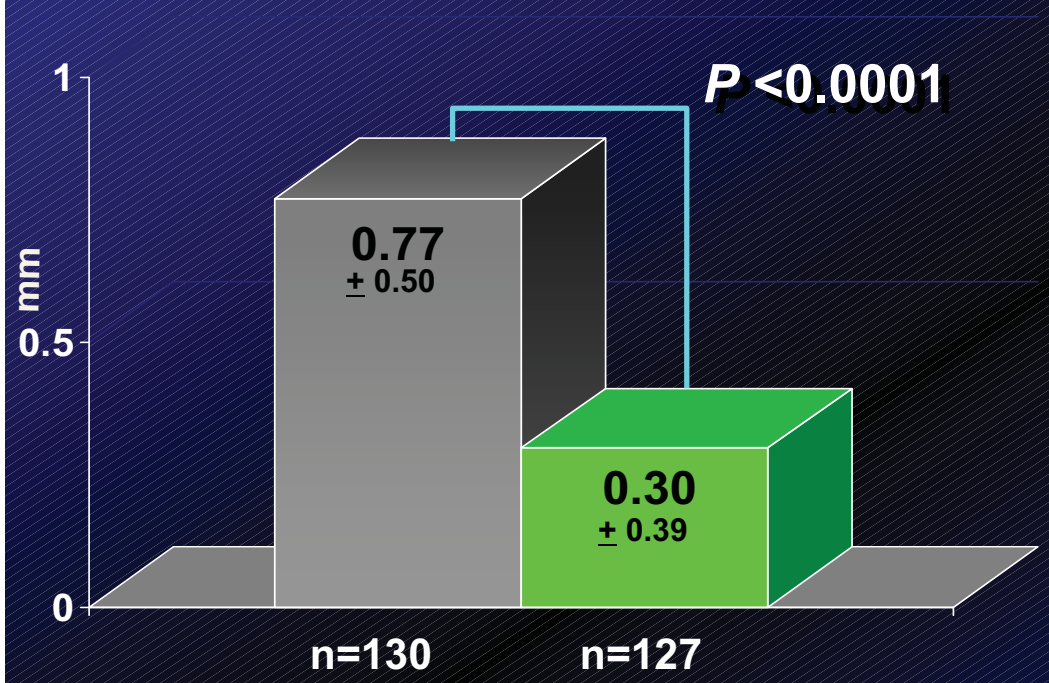

Small but significant improvement at both edges…

*TCT, Oct 2002*

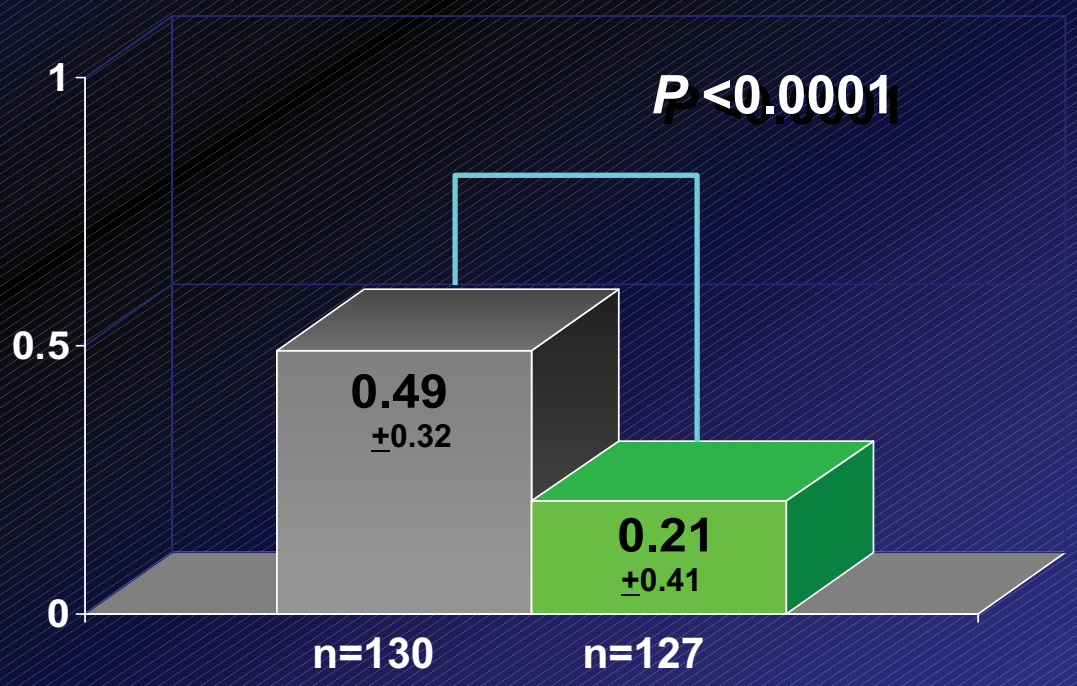
TAXUS II

# Moderate release

## Late Loss
(Stented Segment )




## Loss Index
(Stented Segment)




Control TAXUS MR

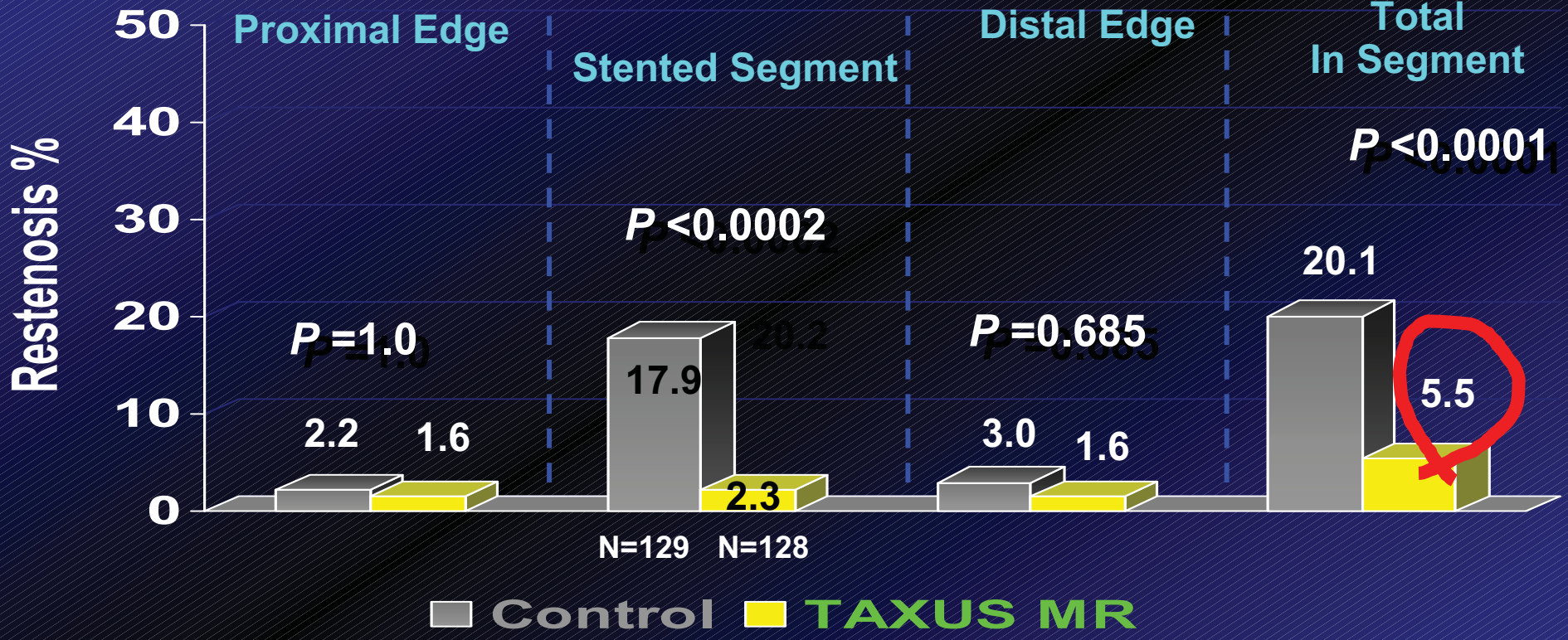
>60% Improvement…

TCT, Oct 2002

TAXUS II

# Slow release

## 6-month Binary Restenosis




No difference at edges between TAXUS and control…

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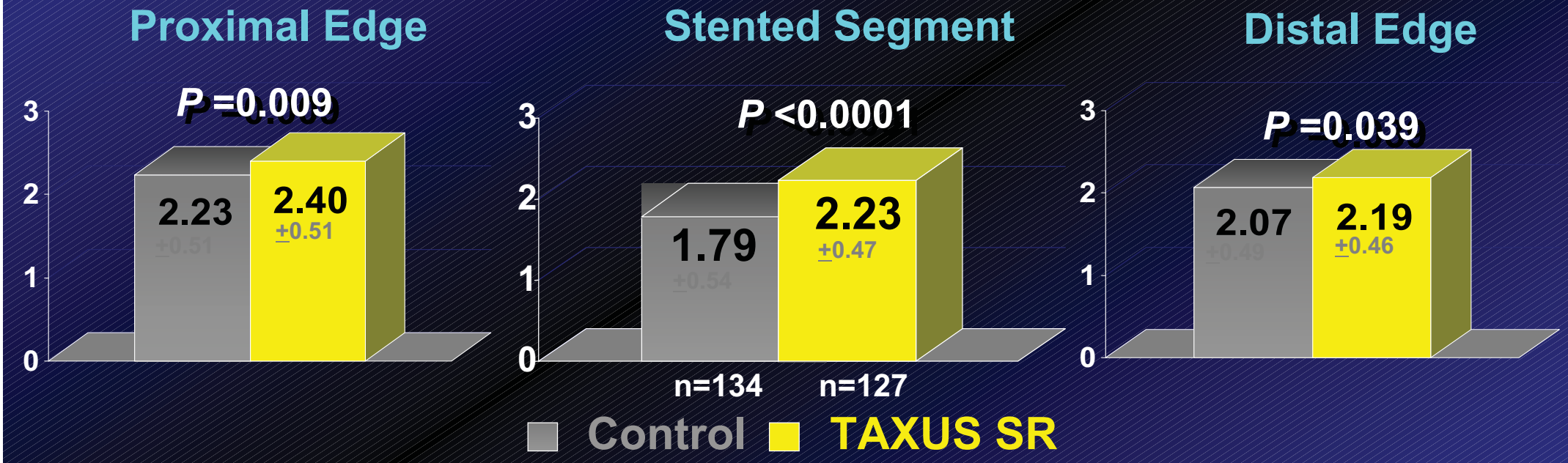
TAXUS II

# Slow release

## MLD at 6 month follow-up



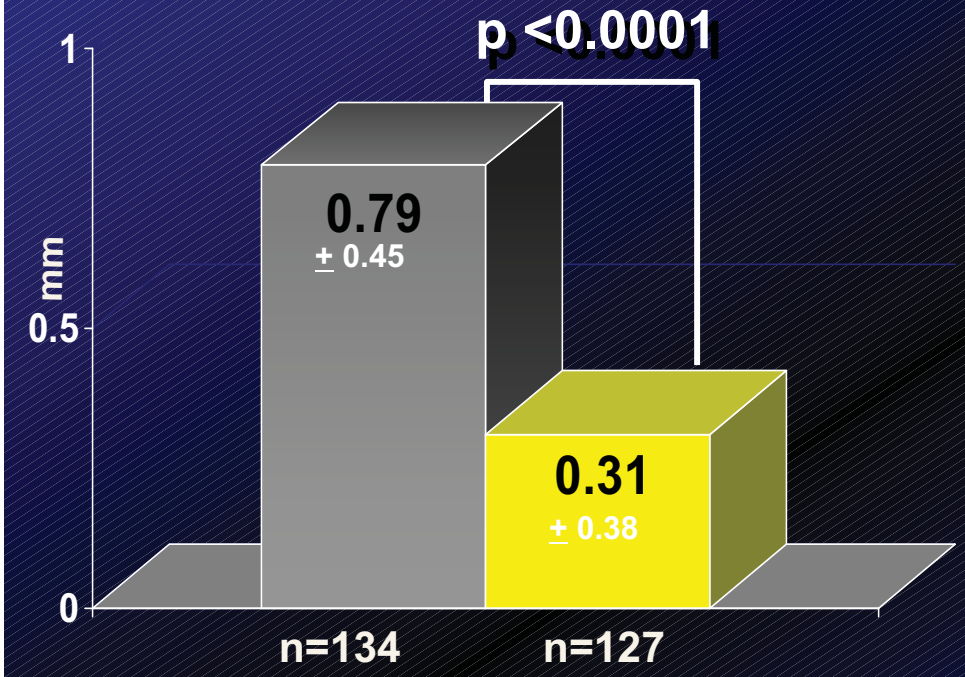

Small but significant improvement at both edges

TCT, Oct 2002

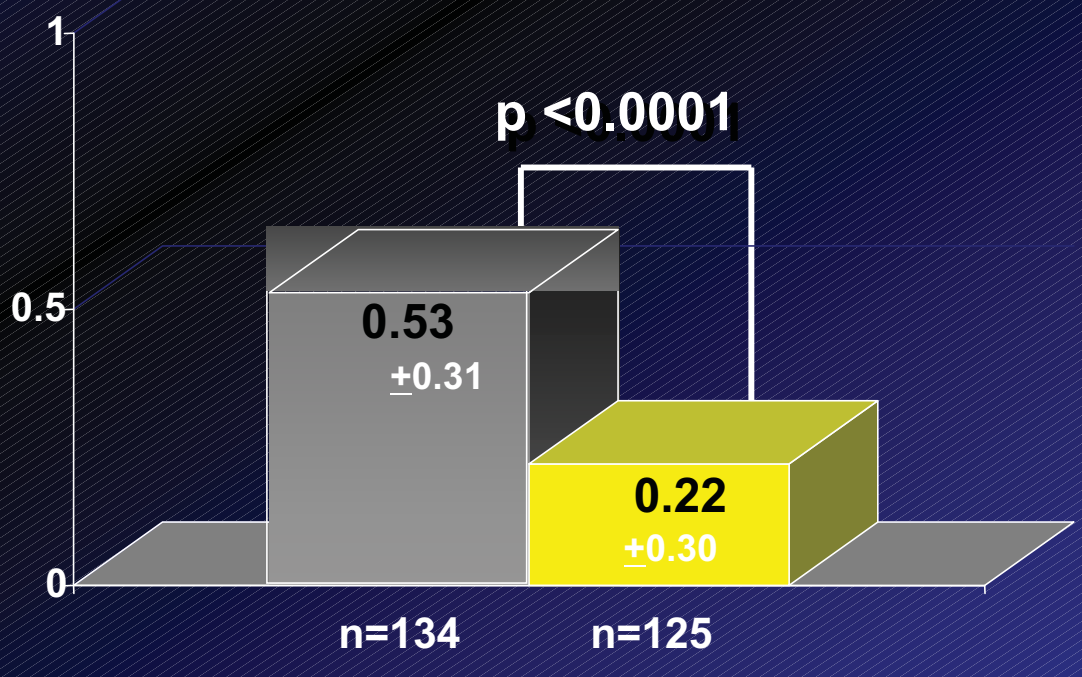
TAXUS II

# Slow release

## Late Loss
(Stented Segment )




## Loss Index
(Stented Segment)




Control  TAXUS SR

>60% Improvement…

TCT, Oct 2002

TAXUS II

# Moderate vs Slow release

## Early Clinical Events

| | Control (n=270) | TAXUS SR (n=131) | TAXUS MR (n=135) |
|---|---|---|---|
| **Stent Thrombosis** | | | |
| **< 1 day** | 0.0 % | 0.8 % (1) | 0.0 % |
| **1 – 30 days** | 0.0 % | 0.0 % | 0.0 % |
| **30-180 days** | 0.0 % | 0.0 % | 0.0 % |
| **30-day MACE** | 4.0 % | 2.0 % (3) | 2.0 % (3) |
| **Death (n)** | (1) | (0) | (0) |
| **MI** | (11) | (2) | (3) |

No differences in SR, MR or Controls…

*TCT, Oct 2002*

TAXUS II

# Moderate vs Slow release

## 6 month MACE

| % (n) | Control (n=270) | TAXUS SR (n=131) | TAXUS MR (n=135) | P-value SR vs Control | P-value MR vs Control | P-value SR vs MR |
|---|---|---|---|---|---|---|
| **6 month MACE** | 19.8 (52) | 8.5 (11) | 7.8 (10) | 0.004 | 0.002 | 1. |
| Death | 0.4 (1) | 0.0 | 0.0 | 1. | 1. | NA |
| Q-MI | 0.8 (2) | 0.0 | 0.0 | 1. | 1. | NA |
| Non-Q MI | 4.6 (12) | 1.5 (2) | 2.3 (3) | 0.156 | 0.403 | 0.684 |
| TVR-overall | 16.0 (42) | 7.7 (10) | 6.2 (8) | 0.026 | 0.006 | 0.808 |
| TLR | 13.3 (35) | 4.6 (6) | 3.1 (4) | 0.008 | 0.001 | 0.749 |
| TVR remote | 2.7 (7) | 3.1 (4) | 2.3 (3) | 0.757 | 1. | 1. |
| CABG | 0.8 (2) | 0.8 (1) | 1.0 (1) | 1. | 1. | 1. |

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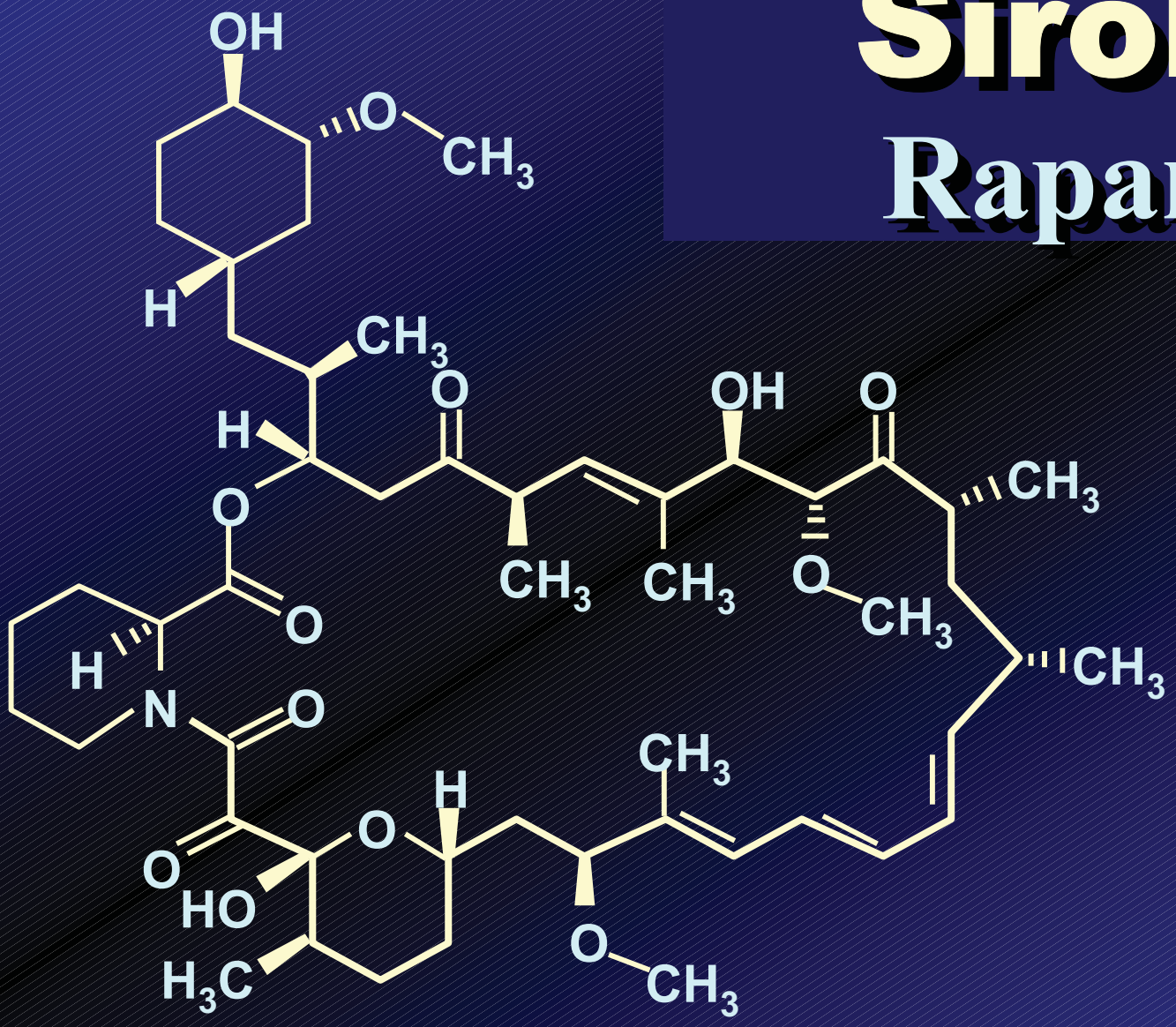
# Sirolimus

## Rapamycin™

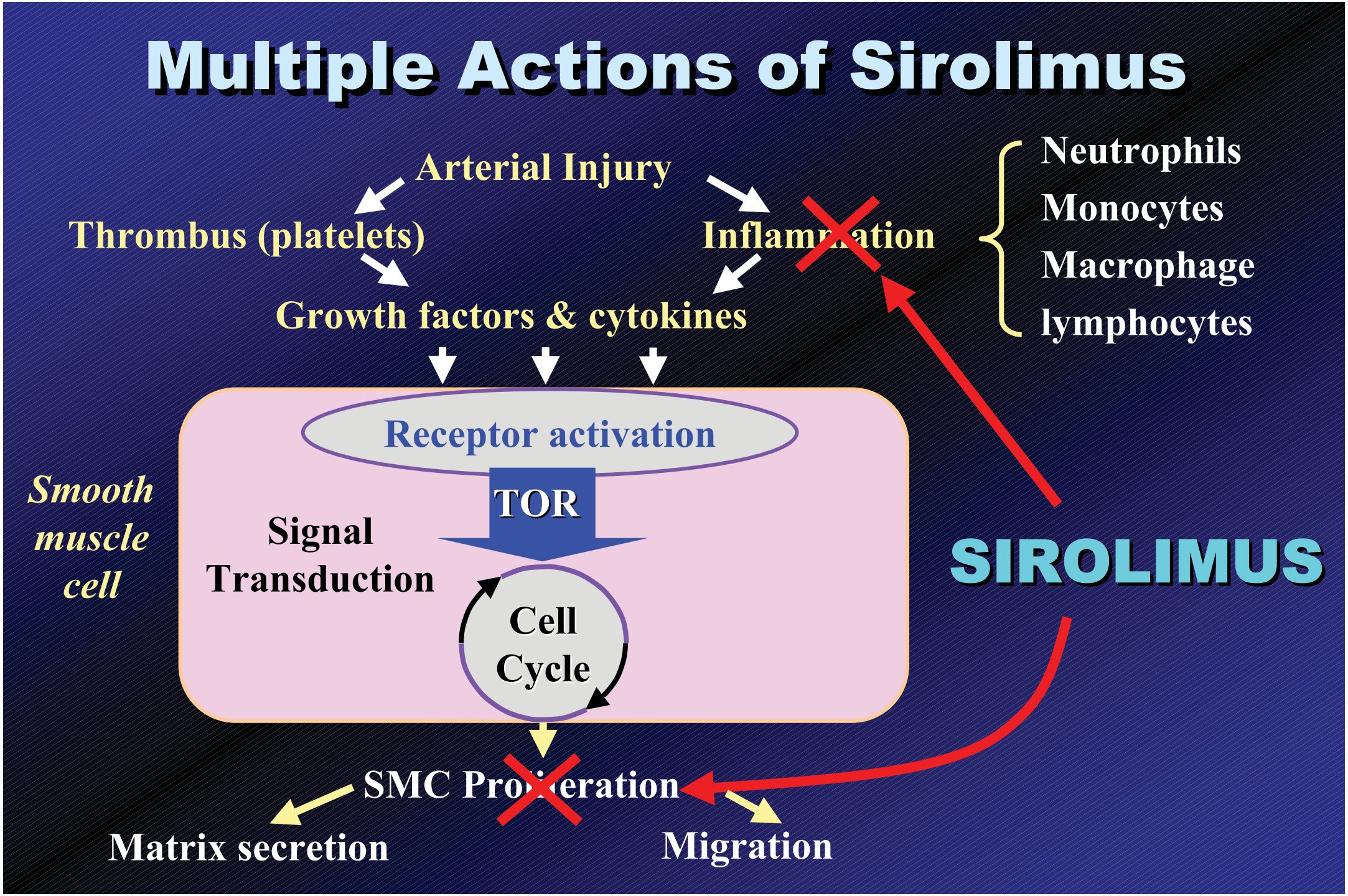


# Rapamycin™

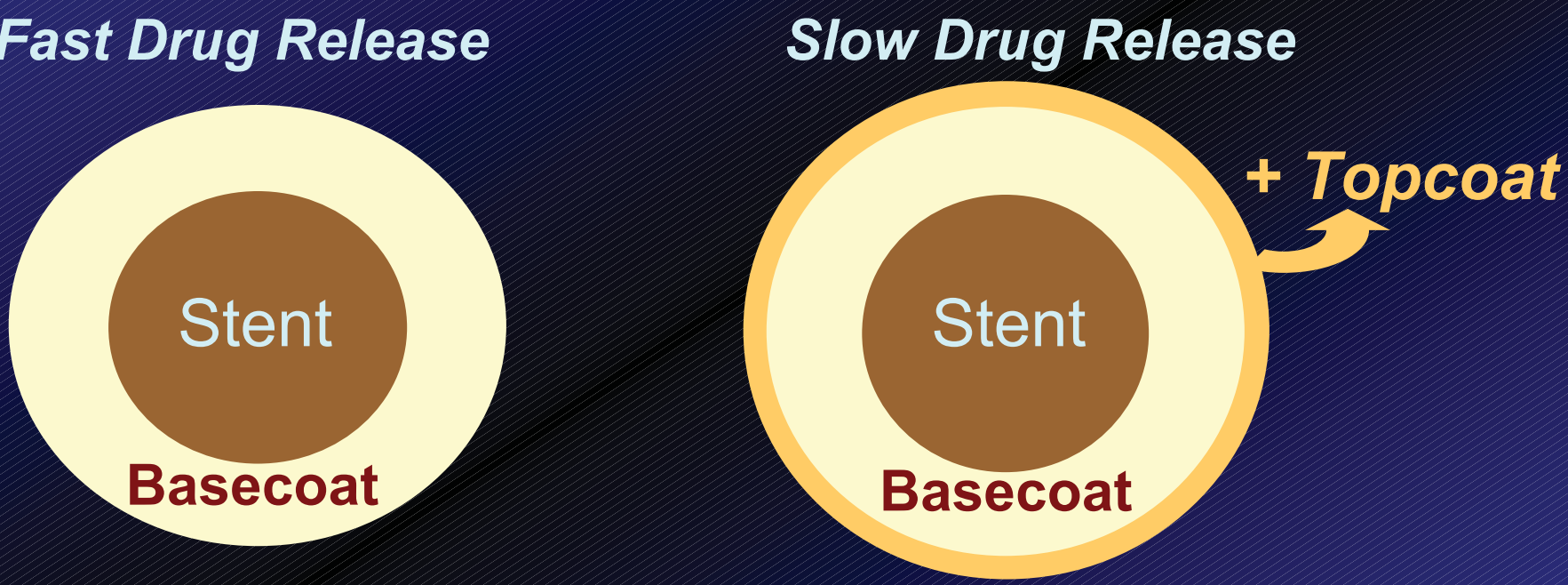
## Development

- Macrolide antibiotic
- Produced by *Streptomyces hygroscopicus*
- Collected from Easter Island (Rapa Nui)
- Initially, noted to have antifungal properties

→ Potent immunosuppressive properties (unsuitable for use as an antibiotic)


Multiple Actions of Sirolimus
Arterial Injury
Thrombus (platelets)
Inflammation
Neutrophils
Monocytes
Macrophage
lymphocytes
Growth factors & cytokines
Receptor activation
TOR
Signal Transduction
Cell Cycle
Smooth muscle cell
SIROLIMUS
SMC Proliferation
Matrix secretion
Migration

# Sirolimus-Coated Bx Velocity Stent




Stent: 316L SST, 2.5, 3.0, 3.5, 18mm

Polymer : Methacrylate

# RAVEL

**A *RA*ndomised (double blind) study with the sirolimus-coated BX *VE*locity balloon expandable stent in the treatment of patients with *de novo* native coronary artery *L*esions**

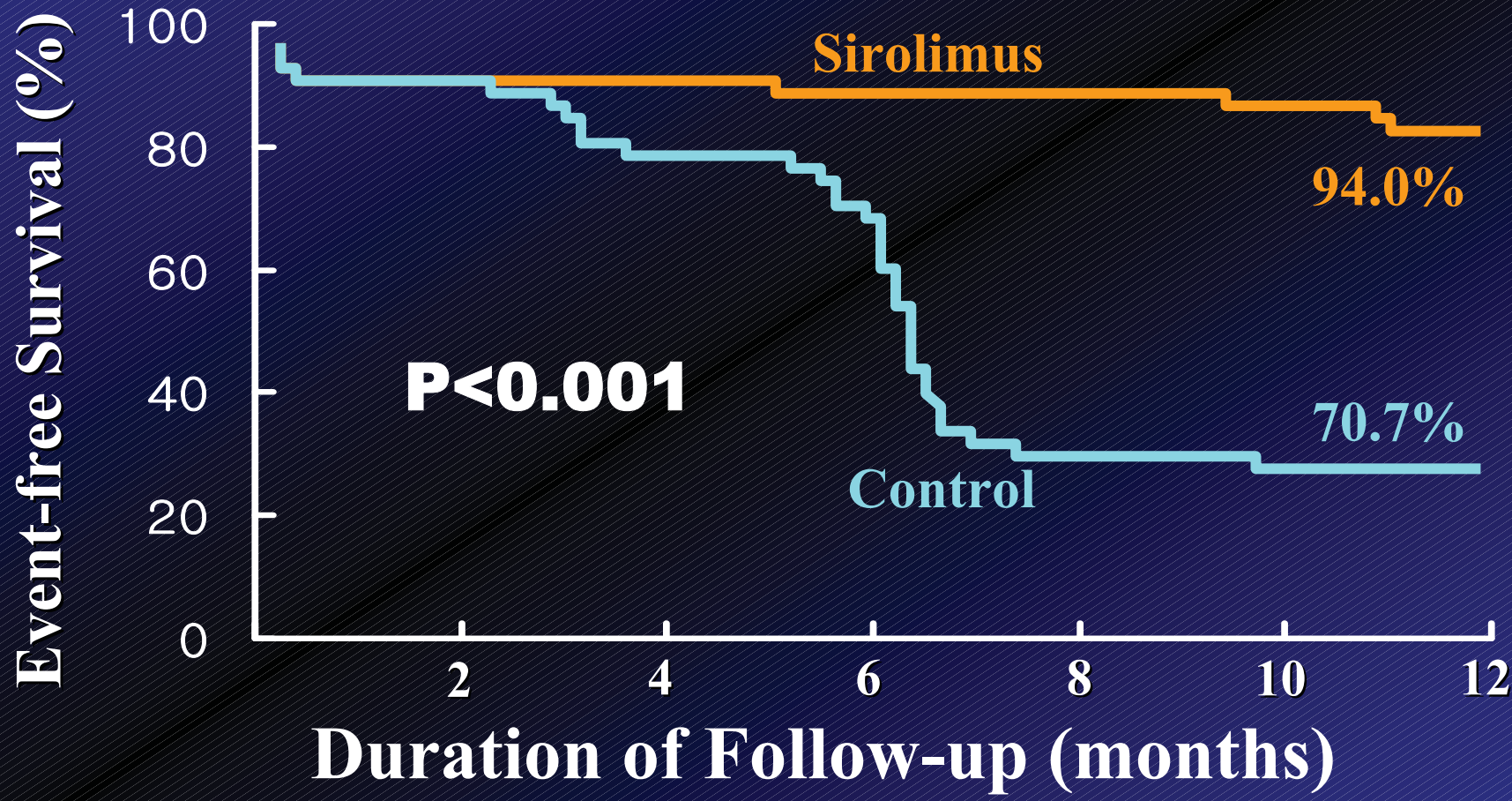
# RAVEL

## Sirolimus-Coated Bx Velocity (Cypher™)

| | Sirolimus-stent (N=118) | Bare-stent (N=120) | P value |
|---|---|---|---|
| Lesion Length, mm | 9.6 | 9.6 | NS |
| Pre-MLD, mm | 0.94 | 0.95 | NS |
| Post-MLD, mm | 2.43 | 2.41 | NS |
| Follow-up MLD, mm | 2.42 | 1.64 | < 0.001 |
| Late Loss, mm | -0.01±0.33 | 0.80±0.53 | < 0.001 |
| Angiographic Restenosis, % | 0 | 27 | < 0.001 |
| 1-Year TLR, % | 0 | 23 | < 0.001 |
| Death, % | 2 | 2 | NS |
| MACE- free survival, % | 97 | 73 | < 0.001 |

*Morice MC et al, NEJM 2002;346:1773*

# Event-free Survival:
## Death, MI, CABG, Re-PCI




*Morice MC et al, NEJM 2002;346:1773*

# RAVEL

- Restenosis = 0
- Late loss = 0
- TVR = 0
- Stent Thrombosis = 0

# SIRIUS

**A U.S. Multicenter, Randomized, Double-Blind Study of the *SIR*ol*I*m*US*-Eluting Stent in De Nove Coronary Lesions:**

*TCT, Oct 2002*

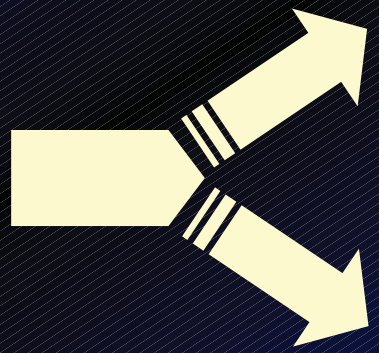
# SIRIUS :Study design

*Cypher™*

N=1101 patients

*De Novo* Coronary Lesions

2.5~3.5mm diameter
15~30mm length



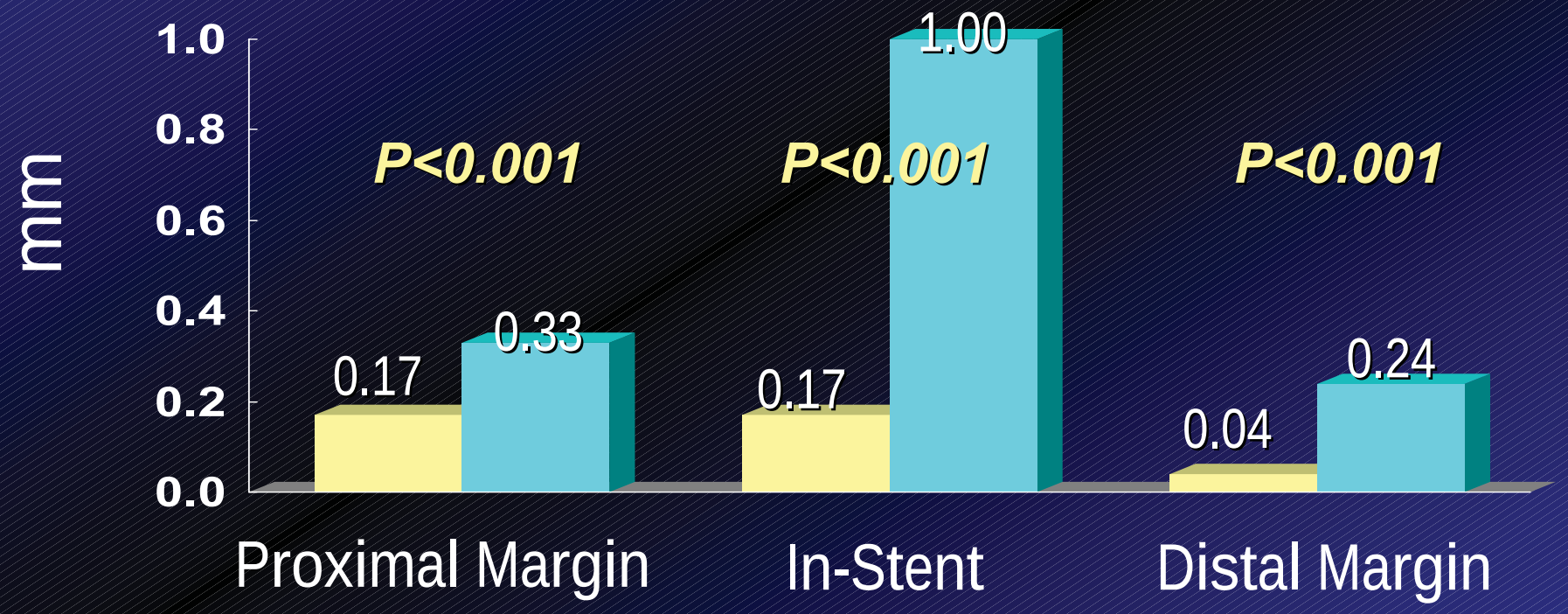
Uncoated
Bx Velocity
N=556

Sirolimus-coated
Bx Velocity
N=545

*TCT, Oct 2002*

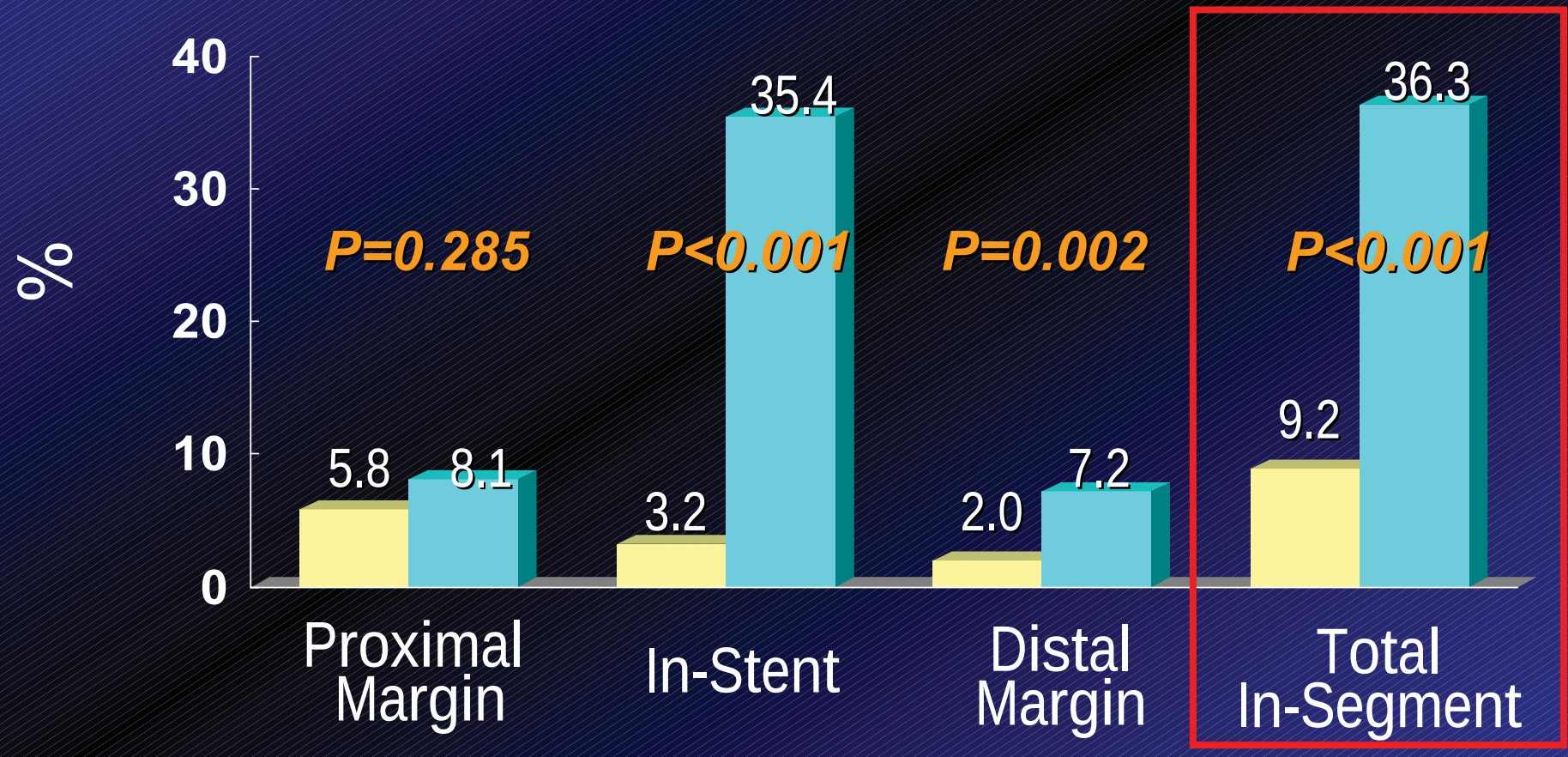
# SIRIUS: QCA analysis

## Late Loss (mm)




*TCT, Oct 2002*

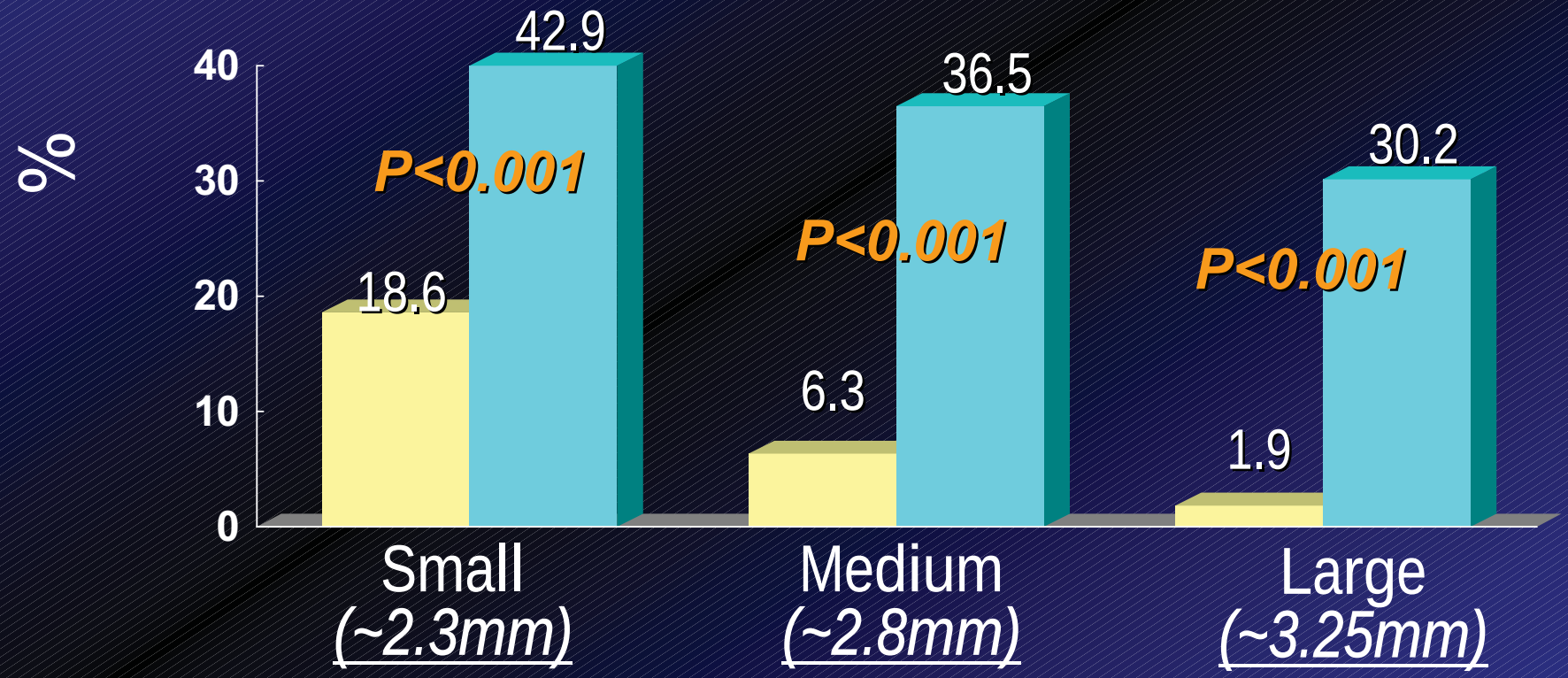
# SIRIUS: Restenosis Rate




*TCT, Oct 2002*

# SIRIUS: Vessel Size Subanalysis

## In-Segment Restenosis (%)

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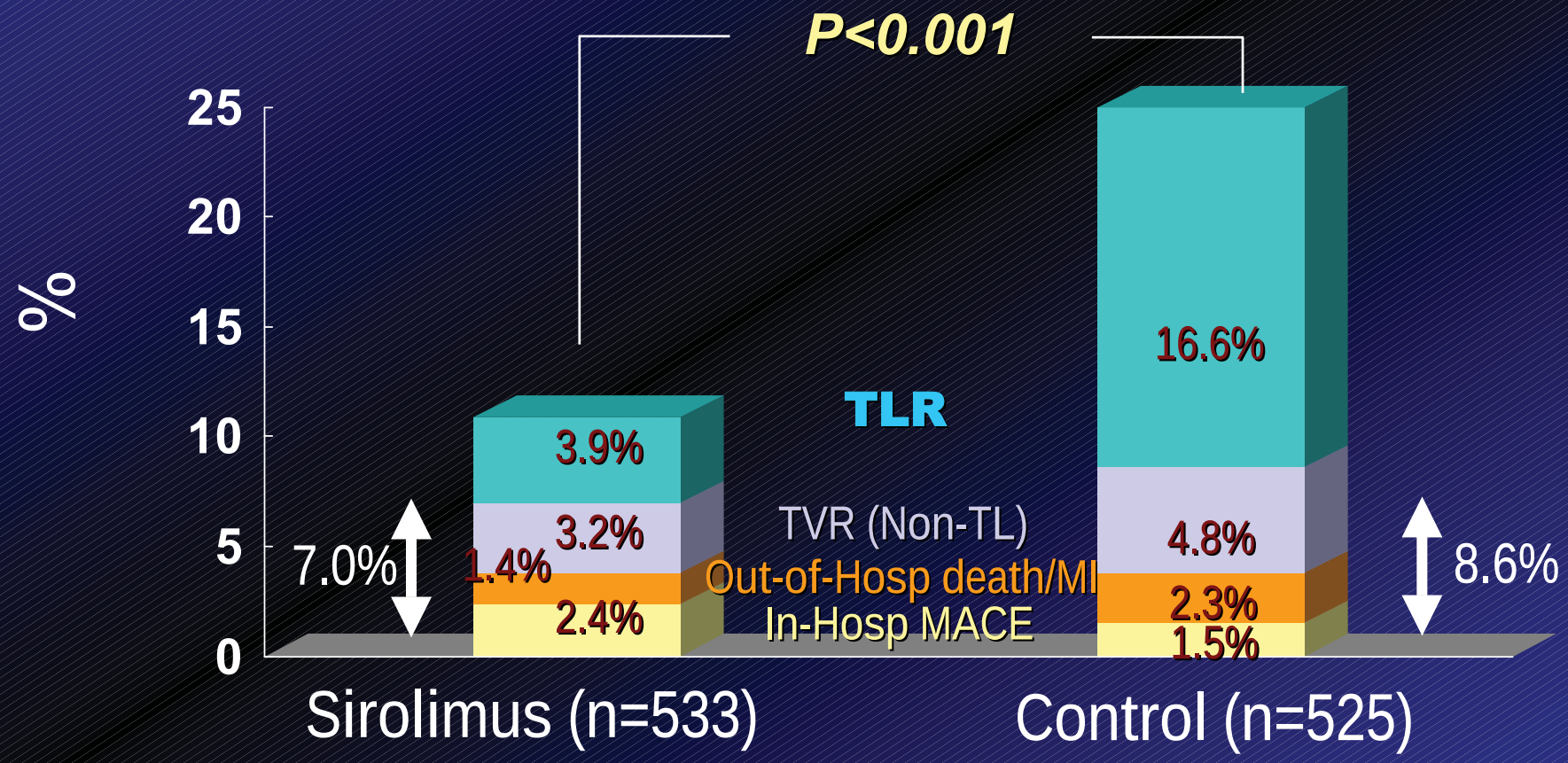
# SIRIUS: 9 mos Clinical Events




*TCT, Oct 2002*

# SIRIUS: Stent Thrombosis

| | Sirolimus (n=533) | Control (n=525) |
|---|---|---|
| Acute (<24hrs) | 0 | 0 |
| Subacute (1-30 days) | 1 (0.2%) | 1 (0.2%) |
| Late (1mo-9mo) | 1 (0.2%) | 3 (0.6%) |
| Total | 2 (0.4%) | 4 (0.8%) |

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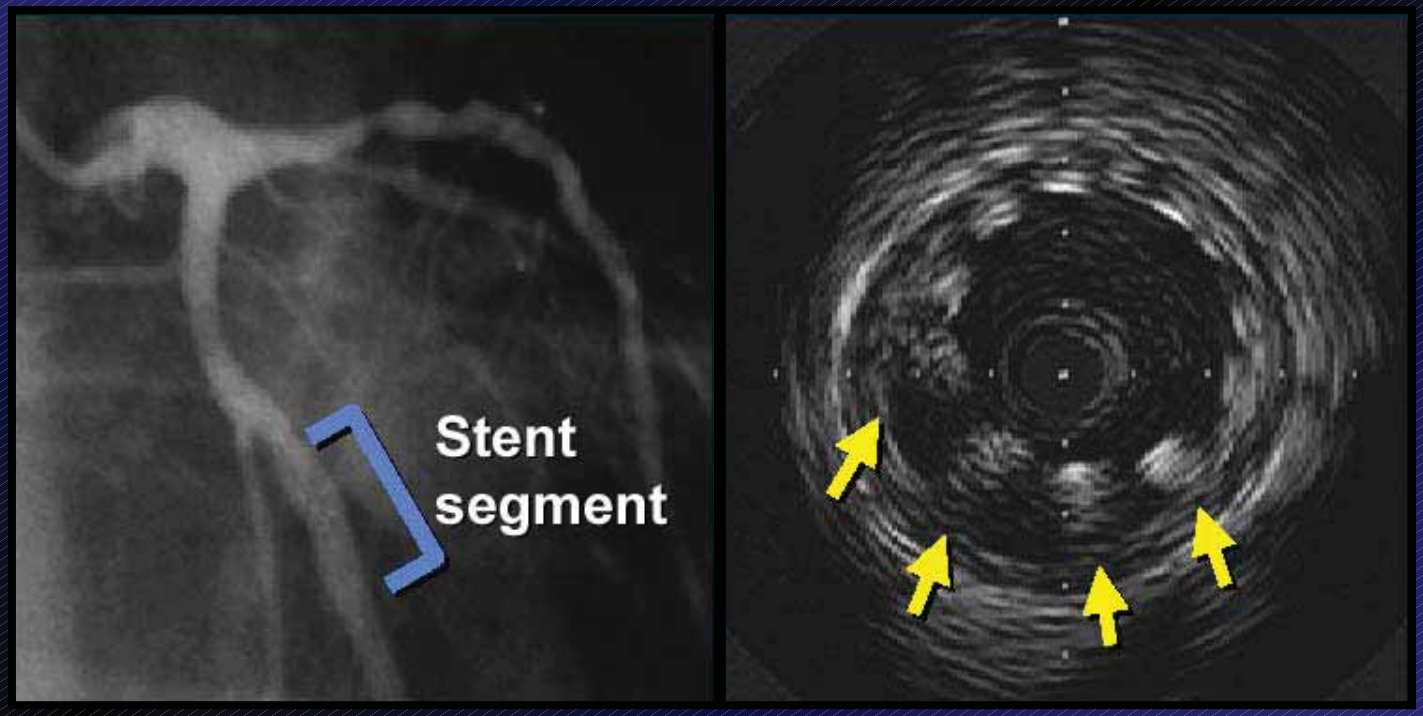
# Incomplete Apposition

## SIRIUS – IVUS analysis

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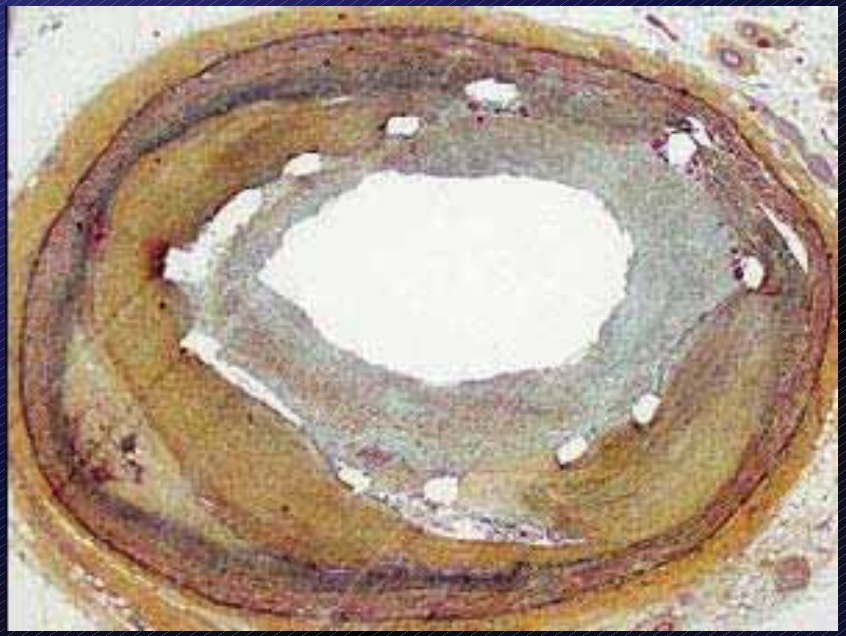
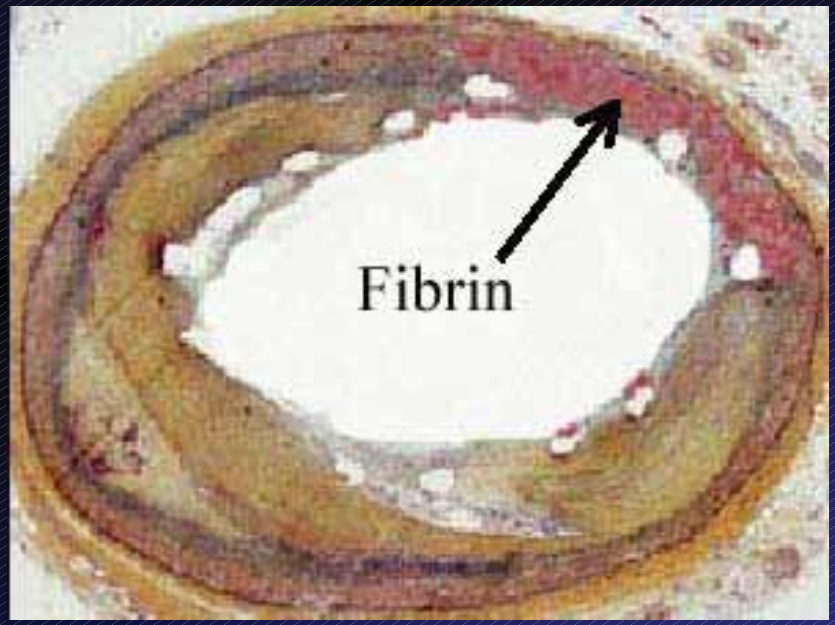
# Late Stent-Vessel Wall Incomplete Apposition



Control




42 μg paclitaxel eluting stent

# Incomplete Apposition (IA)

## SIRIUS – IVUS analysis

| | Control (n=61) | Sirolimus (n=80) | P value |
|---|---|---|---|
| Baseline IA | 9 (14.7%) | 13 (16.3%) | NS |
| Resolved IA | 3 (4.9%) | 7 (8.7%) | NS |
| Persistent IA | 6 (9.8%) | 6 (7.5%) | NS |
| Late IA | 0 (0%) | 7 (8.7%) * | < 0.05 |

* 3 of 7 patients (all sirolimus) with late IA had IVUS positive remodeling (>20% ↑EEM area) and 1 had an angiographic aneurysm

*TCT, Oct 2002*

# Incomplete Apposition
## SIRIUS – IVUS analysis

No associated clinical events in any patients with incomplete apposition at baseline or follow-up (death, MI, or stent thrombosis)…

*TCT, Oct 2002*

# SIRIUS – Overlapping stents

| | Sirolimus (n=176) | Control (n=168) | P value |
|---|---|---|---|
| **Late loss (mm)** | | | |
| In-stent | 0.23 | 1.14 | <0.001 |
| In-segment | 0.20 | 0.93 | <0.001 |
| **Restenosis (%)** | | | |
| In-stent | 7.1 | 42.7 | <0.001 |
| In-segment | 8.8 | 42.7 | <0.001 |

*TCT, Oct 2002*

# SIRIUS – Diabetic subgroup

| | Sirolimus (n=131) | Control (n=148) | P value |
|---|---|---|---|
| **Late loss (mm)** | | | |
| In-stent | 0.29 | 1.20 | <0.001 |
| In-segment | 0.40 | 1.00 | <0.001 |
| **Restenosis (%)** | | | |
| In-stent | 8.3 | 48.5 | <0.001 |
| In-segment | 17.6 | 50.5 | <0.001 |
| **TLR (%)** | 6.9 | 22.3 | <0.001 |
| **MACE (%)** | 9.2 | 25.0 | <0.001 |

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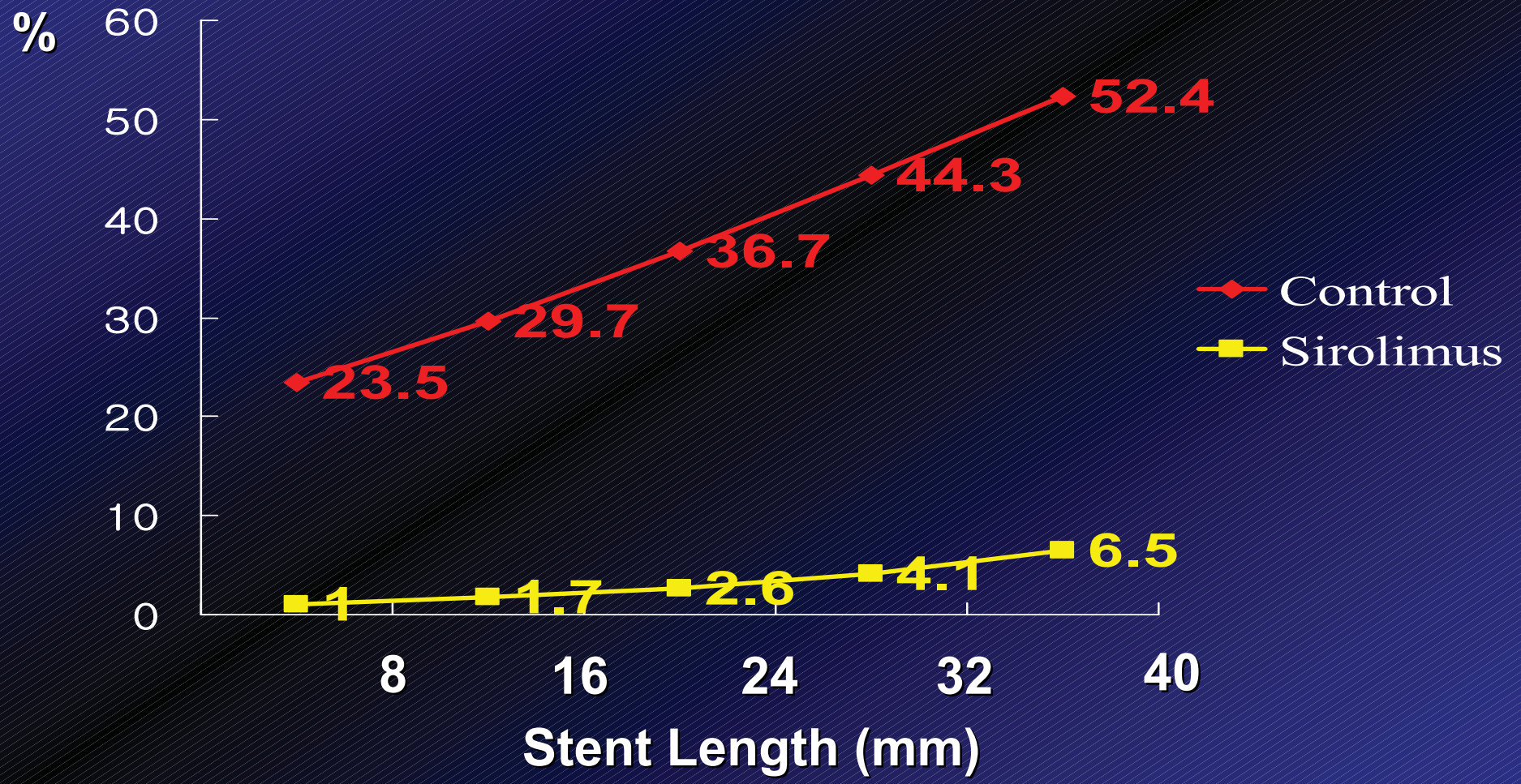
# SIRIUS – Restenosis vs Stent length




*TCT, Oct 2002*

# SIRIUS
## Relative reduction of In-Segment Restenosis

### Non-diabetic

| Ref Dia \ Lesion length | < 12mm | 12 – 15 mm | ≥ 15mm |
|---|---|---|---|
| > 3.0mm | 81.7 % | 81.2 % | 80.4 % |
| 2.5 – 3.0 mm | 79.8 % | 79.2 % | 77.9 % |
| < 2.5mm | 77.6 % | 76.6 % | 74.8 % |

### Diabetic

| Ref Dia \ Lesion length | < 12mm | 12 – 15 mm | ≥ 15mm |
|---|---|---|---|
| > 3.0mm | 78.0 % | 77.0 % | 75.3 % |
| 2.5 – 3.0 mm | 74.1 % | 72.7 % | 70.2 % |
| < 2.5mm | 69.6 % | 67.8 % | 64.5 % |

*TCT, Oct 2002*

# SIRIUS – LAD subgroup

| | Sirolimus (n=234) | Control (n=228) | P value |
|---|---|---|---|
| **Late loss (mm)** | | | |
| In-stent | 0.20 | 1.04 | <0.001 |
| In-segment | 0.26 | 0.81 | <0.001 |
| **Restenosis (%)** | | | |
| In-stent | 2.0 | 41.6 | <0.001 |
| In-segment | 10.1 | 41.6 | <0.001 |
| **TLR (%)** | 5.1 | 19.7 | <0.001 |
| **MACE (%)** | 8.5 | 22.4 | <0.001 |

*TCT, Oct 2002*

# Side by Side Comparison of Major Clinical Trials

# Different Study Design

| | ASPECT | ELUTE | TAXUS II SR | TAXUS II MR | RAVEL | SIRIUS |
|---|---|---|---|---|---|---|
| Sponsor | Cook | Cook | Boston | Boston | Cordis | Cordis |
| Drug | Paclitaxel | Paclitaxel | Paclitaxel | Paclitaxel | Sirolimus | Sirolimus |
| Dose | 3.1 ug/mm$^2$ | 2.7 ug/mm$^2$ | 1.0 ug/mm$^2$ | 1.0 ug/mm$^2$ | 185ug | 185ug |
| Polymer | No | No | Translute | Translute | 2 coat | 2 coat |
| Release | Fast | Fast | Slow | Moderate | Slow | Slow |
| Stent platform | Supra G | V-Flex PLUS | NIRx | NIRx | Bx Velocity | Bx Velocity |
| length (mm) | 15 | 16 | 15 | 15 | 18 | 18 |
| Dia (mm) | 2.5,3.0,3.5 | 3.0 & 3.5 | 3.0 & 3.5 | 3.0 & 3.5 | 2.5,3.0,3.5 | 2.5,3.0,3.5 |
| Lesion length | ≤ 15mm | ≤ 16mm | ≤ 12mm | ≤ 12mm | ≤ 18 | ✓ ≤ 30 |
| Dia. (mm) | ≥2.5, ≤3.5 | ≥2.5, ≤3.5 | ≥ 3.0, ≤3.5 | ≥3.0, ≤3.5 | ≥2.5, ≤3.5 | ≥2.5, ≤3.5 |

# Baseline characteristics

| % | ASPECT | ELUTE | TAXUS II SR | TAXUS II MR | RAVEL | SIRIUS |
|---|---|---|---|---|---|---|
| Number | 60 | 32 | 131 | 135 | 120 | 533 |
| Age (yr) | 58 | 60 | 61.5 | 59.3 | 60 | 62 |
| Male | 80 | 82 | 70 | 76 | 81 | 73 |
| Risk factors | | | | | | |
| Diabetes | 18 | 16 | 11 | 17 | 21 | 25 |
| Hypertension | 42 | 46 | 63 | 60 | 61 | 68 |
| PMI | | | 35 | 39 | 34 | 28 |
| Hyperchol | 13 | 50 | | | 43 | 73 |
| Smoking | 46 | 64 | 21 | 24 | 33 | 18 |
| Unstable Angina | | | 35 | 30 | 52 | |
| Multi-vessel | 34 | | | | 75 | 42 |
| IIb/IIIa use | | | | | 11 | 60 |

# Angiographic characteristics

| % | ASPECT | ELUTE | TAXUS II SR | TAXUS II MR | RAVEL | SIRIUS |
|---|---|---|---|---|---|---|
| Number | 60 | 32 | 131 | 135 | 120 | 533 |
| Location | | | | | | |
| LAD | 55 | 43 | 40 | 42 | 49 | 45 |
| LCX | 29 | 35 | 38 | 33 | 27 | 25 |
| RCA | 17 | 21 | 22 | 25 | 24 | 30 |
| Lesion charac | | | | | | |
| Type A | 92 | | | | 8 | 7 |
| Type B1 | | | | | 39 | 34 |
| Type B2 | 8 | | | | 54 | 33 |
| Type C | | | | | 0 | 26 |
| Multiple stent | No | No | 5 | 4 | 3 | 35 |

# QCA Findings

| mm | ASPECT | ELUTE | TAXUS II SR | TAXUS II MR | RAVEL | SIRIUS |
|---|---|---|---|---|---|---|
| Reference | 2.94 | 2.95 | 2.78 | 2.72 | 2.60 | 2.78 |
| Lesion length | 10.9 | 11.1 | 10.5 | 10.2 | 9.6 | 14.4 |
| MLD | | | | | | |
| Before | 0.64 | 0.56 | 1.02 | 0.95 | 0.94 | 0.98 |
| After | 2.85 | 2.66 | | | 2.43 | 2.38 |
| Follow up | 2.53 | 2.56 | 2.23 | 2.24 | 2.42 | 2.15 |
| Late loss | 0.29 | 0.10 | 0.31 | 0.30 | -0.01 | 0.24 |
| DS (%) | | | | | | |
| Before | 79.4 | 81.4 | 63.3 | 64.9 | 63.6 | 65.1 |
| After | 1.9 | 10.0 | | | 11.9 | 16.1 |
| Follow up | 14 | 14 | 19.5 | 18.2 | 14.7 | 23.6 |

# Restenosis Rate and Pattern

| | ASPECT | ELUTE | TAXUS II SR | TAXUS II MR | RAVEL | SIRIUS |
|---|---|---|---|---|---|---|
| Number | 60 | 32 | 131 | 135 | 120 | 533 |
| Restenosis (%) | 4 | 3.1 | 5.5 | 8.6 | 0 | 8.9 |
| Prox edge | | | 1.6 | 2.3 | | 5.8 |
| Stented seg | | 3.1 | 2.3 | 4.7 | | 3.2 |
| Dis edge | | | 1.6 | 2.3 | | 2.0 |
| Pattern of restenosis (n) | | | | | | |
| Diffuse | | | 0 | 0 | | 0 |
| Focal | | | 6 | 11 | | 27 |
| Total | | | 1 | 0 | | 2 |
| Diff prolifera | | | 0 | 1 | | 2 |

# 30 Day Clinical Follow-Up

| % | ASPECT | ELUTE | TAXUS II SR | TAXUS II MR | RAVEL | SIRIUS |
|---|---|---|---|---|---|---|
| Number | 60 | 32 | 131 | 135 | 120 | 533 |
| Pro. success | 99 | 99 | 95 | 96 | | |
| Stent throm. | 0 | 3.2 | 0.8 | 0 | | 0.2 |
| In-Hosp Cx. | | | | | | |
| Death | 0 | 3.2 | 0 | 0 | | 0.1 |
| Q MI | 0 | 0 | 0 | 0 | | 0.4 |
| NonQ MI | 2 | 3.2 | 2 | 2 | | 1.9 |
| Em CABG | 0 | 0 | 0 | 0 | | 0 |
| TLR | 0 | 0 | 0 | 0 | | 0.2 |
| TVR | 0 | 0 | | 0 | | 0 |
| MACE | 2 | 8 | 2 | 2 | | 2.4 |
| TVF | | | | | | 2.4 |

# Long-term Clinical Follow-Up

| % | ASPECT | ELUTE | TAXUS II SR | TAXUS II MR | RAVEL | SIRIUS |
|---|---|---|---|---|---|---|
| Number | 60 | 32 | 131 | 135 | 120 | 533 |
| Period (mon) | 6 | 6 | 6 | 6 | 7 | 9 |
| Stent thrombo | 0 | 1 | 0 | 0 | 0 | 0.4 |
| Long-term | | | | | | |
| Death | 0 | 3.2 | 0 | 0 | 0 | 0.9 |
| Q MI | 0 | 0 | 0 | 0 | 1.7 | 0.8 |
| NonQ MI | 2 | 3.2 | 1.5 | 2.3 | 0.8 | 2.1 |
| Em CABG | 0 | 0 | 0.8 | 0.8 | 0 | |
| TLR | 2 | 3.2 | 4.6 | 3.1 | 0 | 4.1 |
| TVR | | | 7.7 | 6.2 | 0.8 | 3.2 |
| MACE | 4 | 11 | 8.5 | 7.8 | 3.3 | 7.1 |
| TVF | | | | | | 8.6 |

# RAVEL,SIRIUS / TAXUS-II / ASPECT,ELUTE

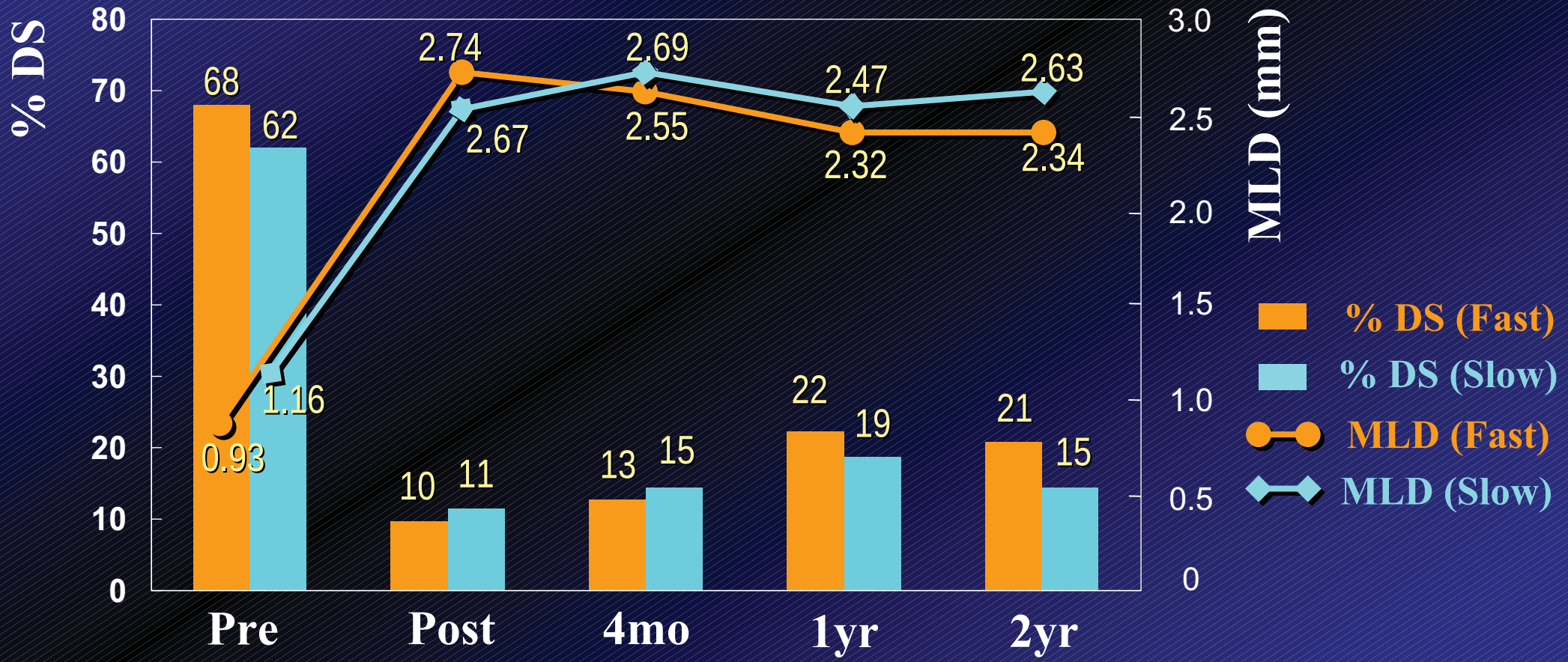
## The dream may come true…

| | |
|---|---|
| Restenosis Rate | 0 - 8.6 % |
| TLR | 4 - 8.5 % |

# What about long-term outcomes after DES ?

# First-In-Man Experience

## Changes in % DS and MLD: In-lesion (n=30)



# First-In-Man Experience

## MACE up to 2 Years (n=30)

- Death = 0
- Q-wave MI = 1* (3.3%)
- TLR (PCI) = 1 (3.3%)
- TVR (CABG) = 1* (3.3%)
- MACE-free survival = 27 (90.1%)

* No in-stent restenosis

# Dark Side of Drug Eluting Stent

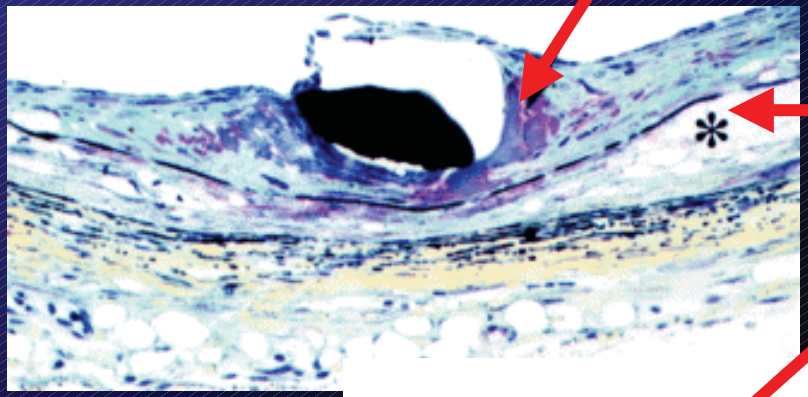
## Potentially Not Good or Bad…

- Late catch-up
- Early and Late Thrombus
- Edge Effect
- Stent Mal-apposition
- Aneurysmal Formation

# Toxicity

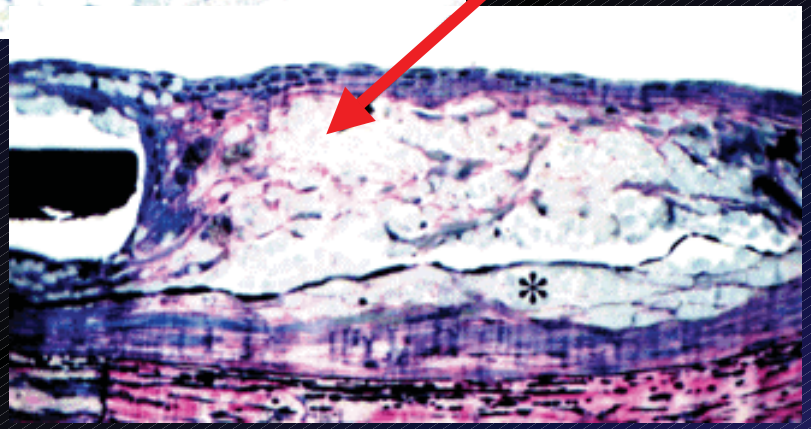
*by high drug concentration (42 ug/stent) of paclitaxel*

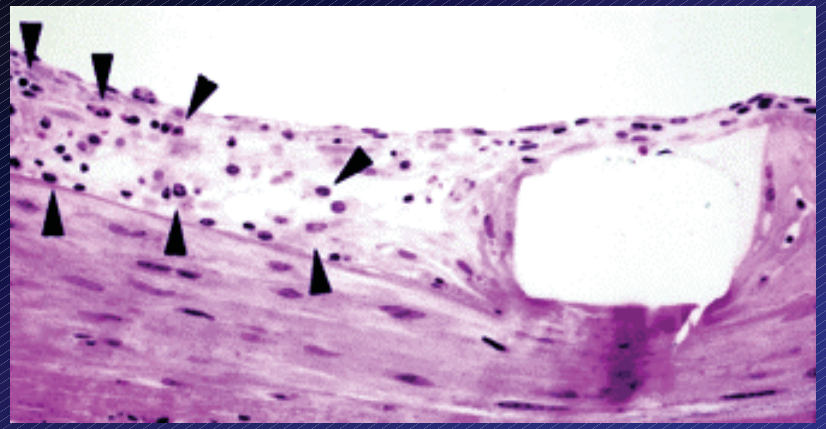
**Intimal fibrin deposition**



**Medial necrosis**

**Hemorrhage**





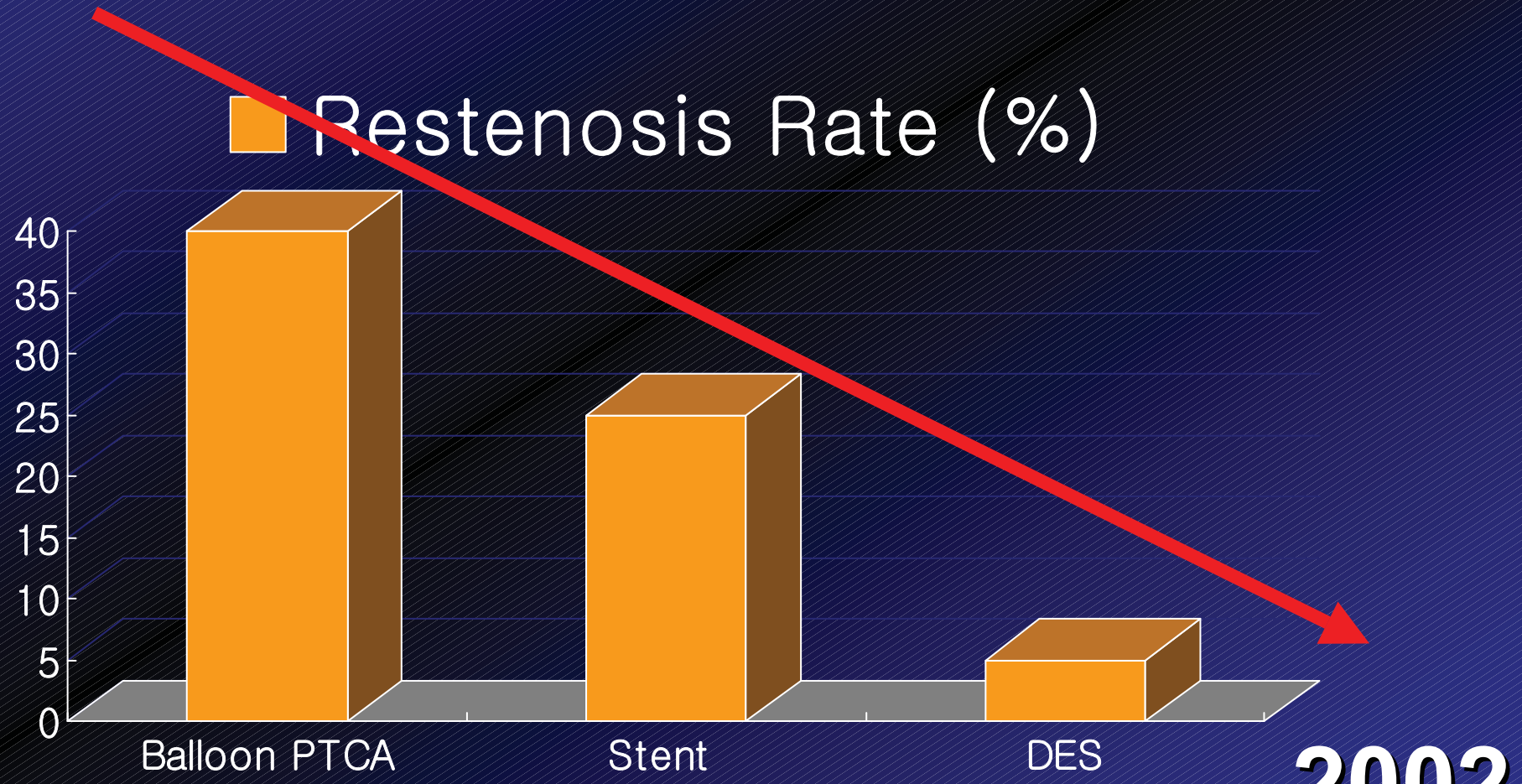
**Focal intimal acute and chronic inflammatory cell**

# Ideal Drug Eluting Stent

- Effective in
  - anti-thrombotic
  - anti-inflammatory
  - anti-proliferative
  - non-toxic
- Good endothelization
- No late catch up
- No late thrombosis

- Late catch up
- Delayed endothelization
- Late thrombosis
- Edge effect
- Aneurysm

# This stuff really works !




2002

# Drug-Eluting Stents

## *Direct Impact for clinical practice…*

1. Drug-eluting stents will become the "core technology" for interventional vascular therapy
2. All previous high-risk restenosis scenarios will be aggressively challenged (e.g. diabetics, long lesion, small vessel disease, Ostial lesion, LMCA disease, and Multi-vessel disease)
3. Economic factors will play an important role in strategic case-based decision-making

# Intervention 2003

## Treatment Alternatives for Coronary Heart Disease