Why Polymer Coated Paclitaxel Stents

Insight from Clinical Trials

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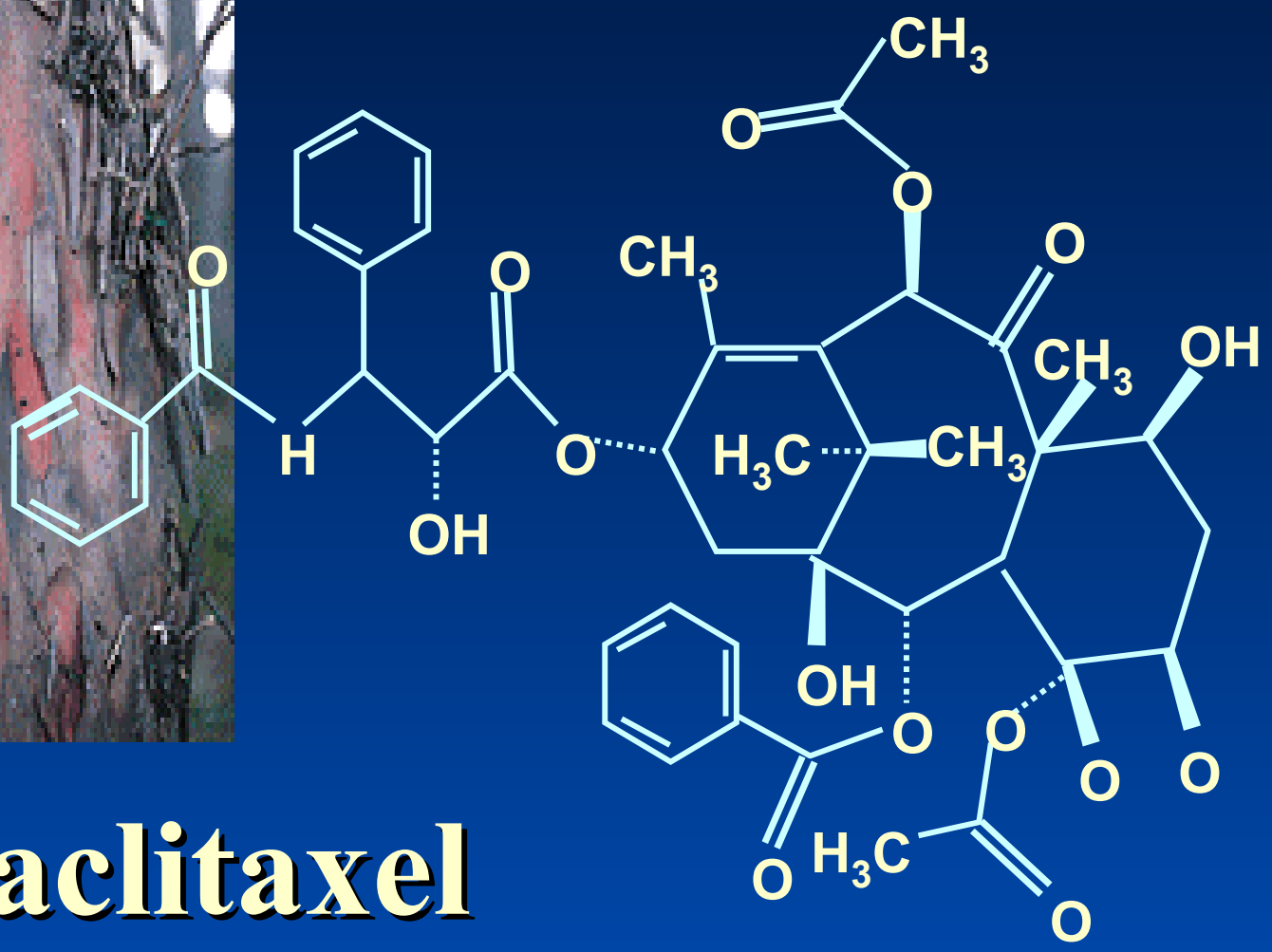
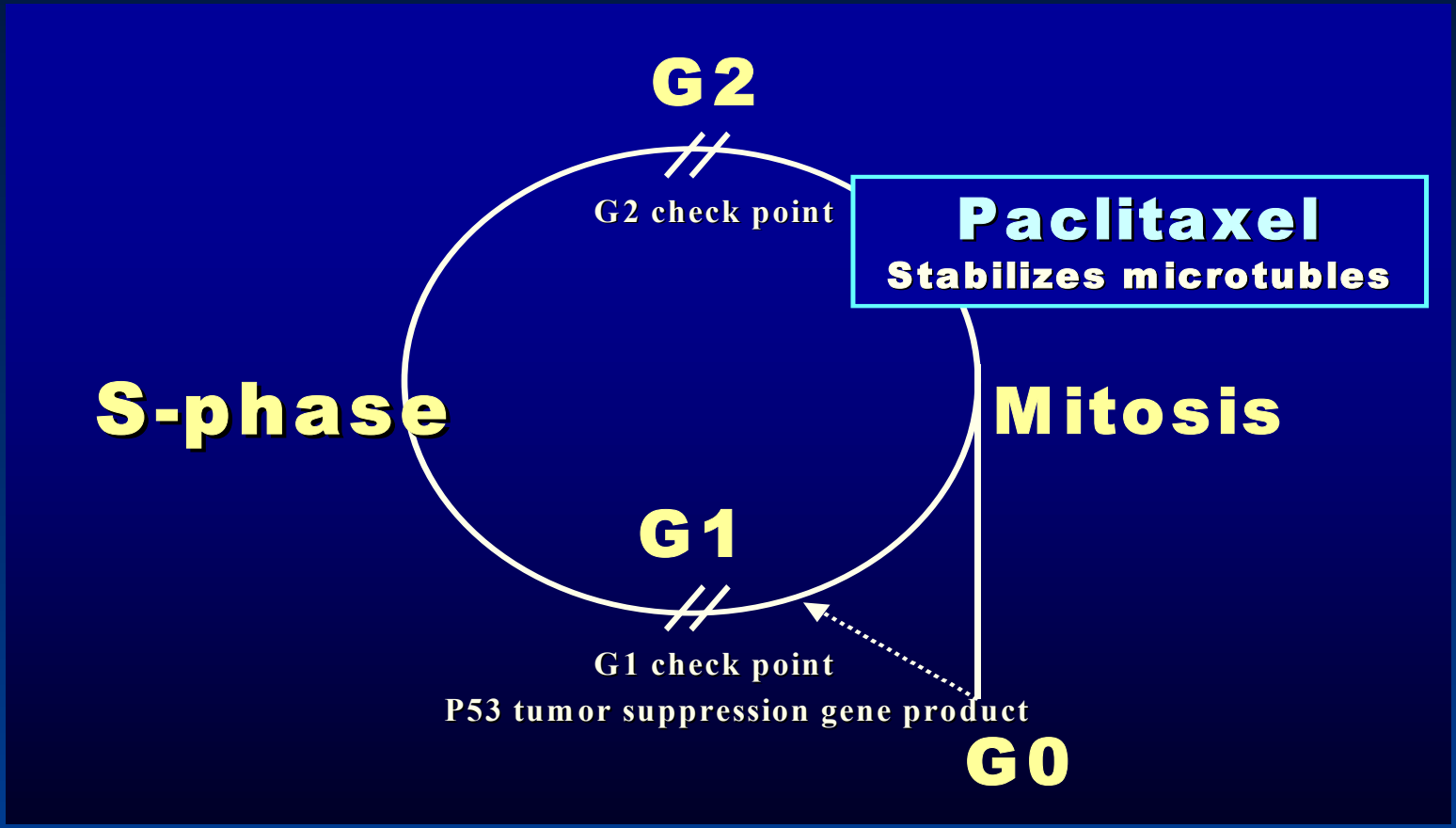
Why Paclitaxel ?

- Stable and potent at nanomolar concentrations
- Multifunctional
  (*Anti*-inflammatory, -proliferative, -migratory, - secretory,- extracellular matrix)
- Hydrophobic/liphophilic
- Large doses can be loaded in polymers
- Can be applied to metal as a durable simple coating, without need for a polymer
- Extensive human experiences



Paclitaxel

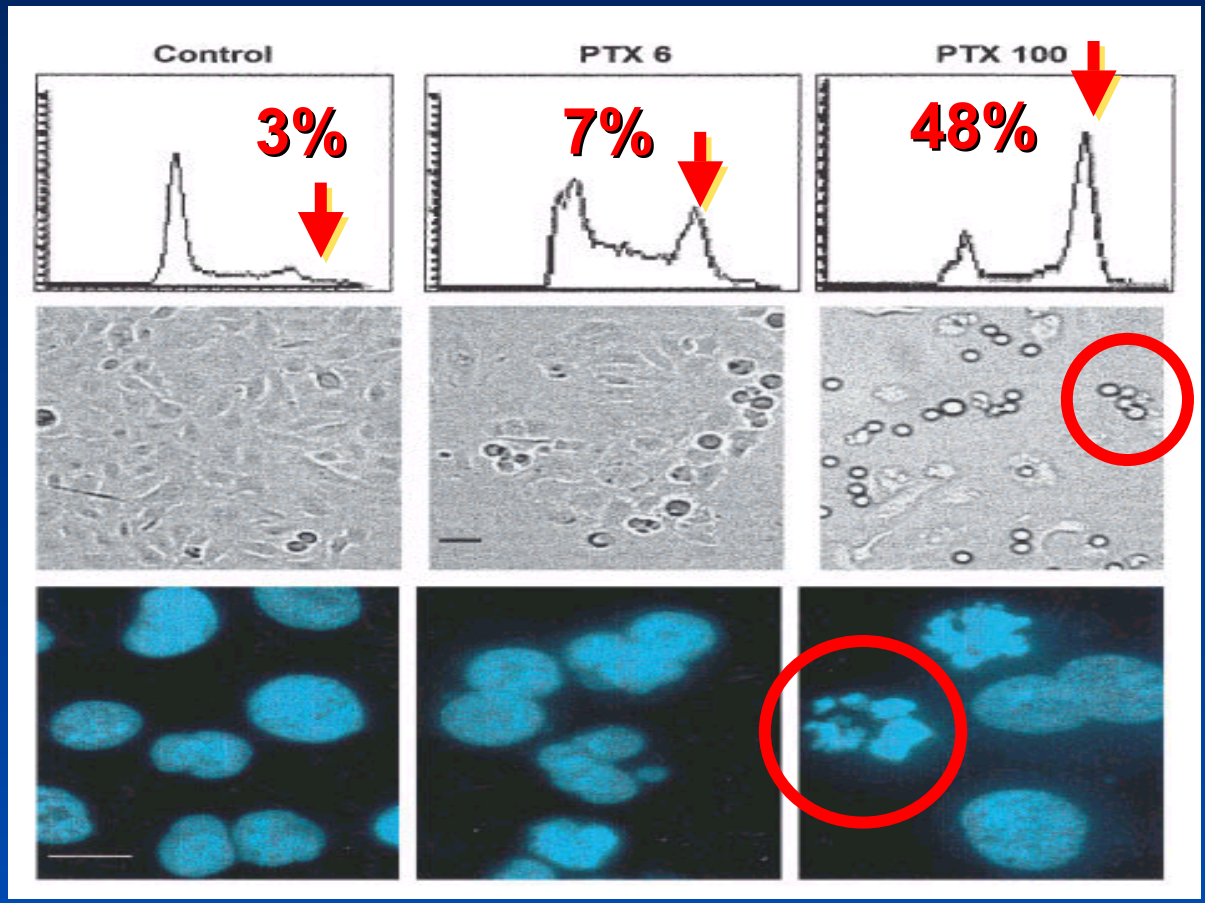
Taxol™



Paclitaxel inhibits cell processes dependent on microtubule turnover including mitosis, cell proliferation and cell migration while the cells remain viable (cytostatic).

Dose Dependent Mitotic Arrest

Control **6 nM** **100 nM Paclitaxel**



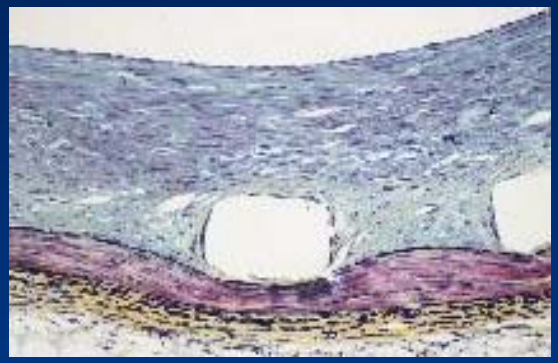
Flow cytometry
(mitotic index)

Microscopy
(round, detached cells)

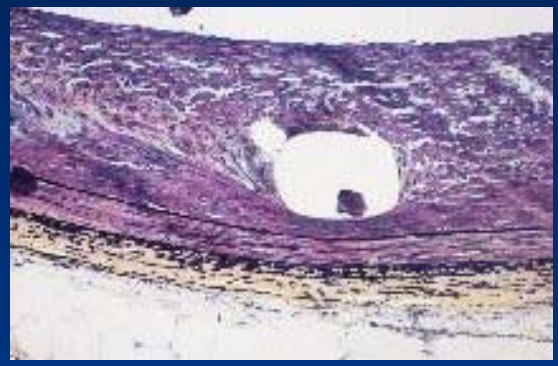
DAPI stain
(fragmented nuclei, mitotic arrest)

Giannakakou P et al. Oncogene 2001;20:3806-3813

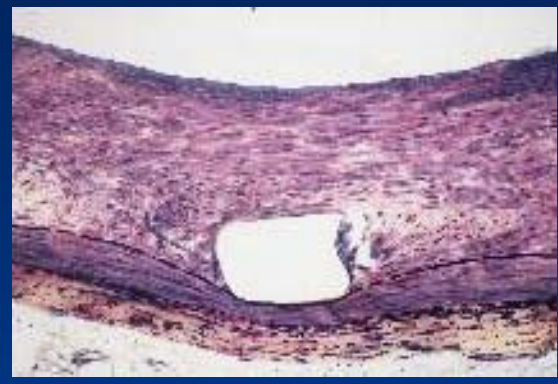
Dose Dependent Inhibition of Intimal Hyperplasia



Uncoated



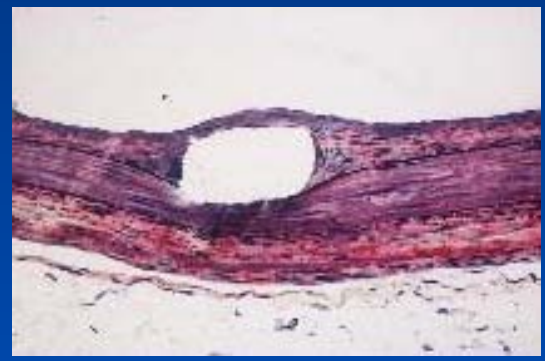
Chondroitin Sulfate Gelatin Coated



1.5 μg

8.6 μg

20.2 μg



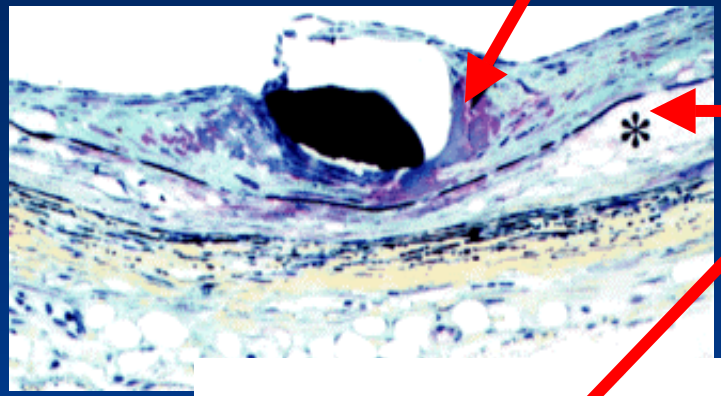
42 μg

Farb A et al. Circ 2001;104:473

Toxicity

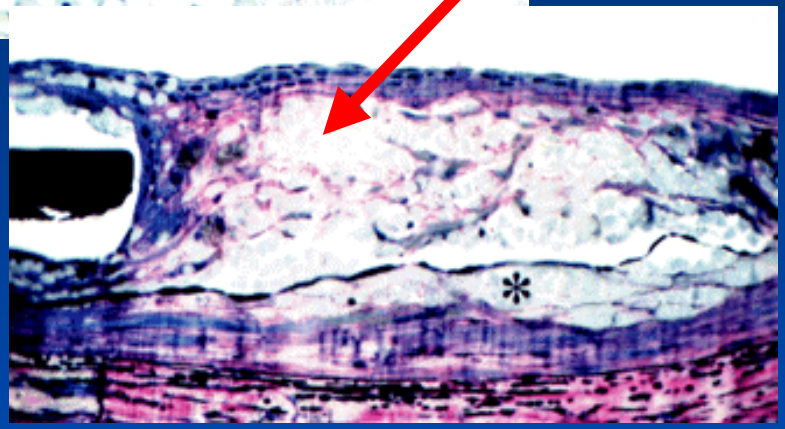
by high drug concentration (42 ug/stent) of paclitaxel

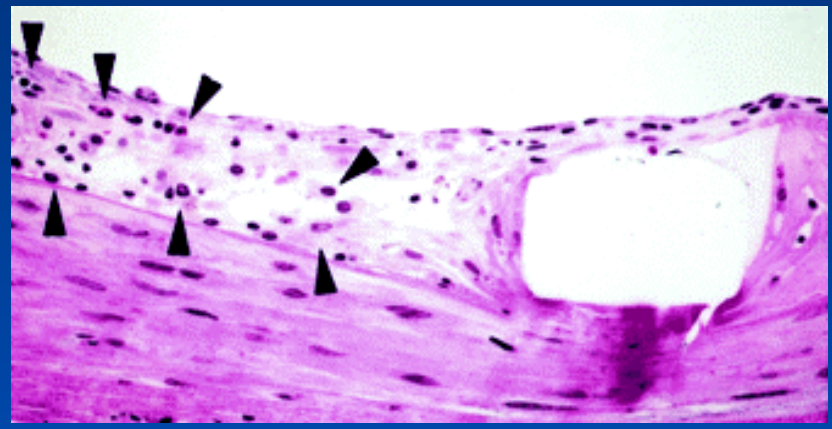
Intimal fibrin deposition



Medial necrosis

Hemorrhage



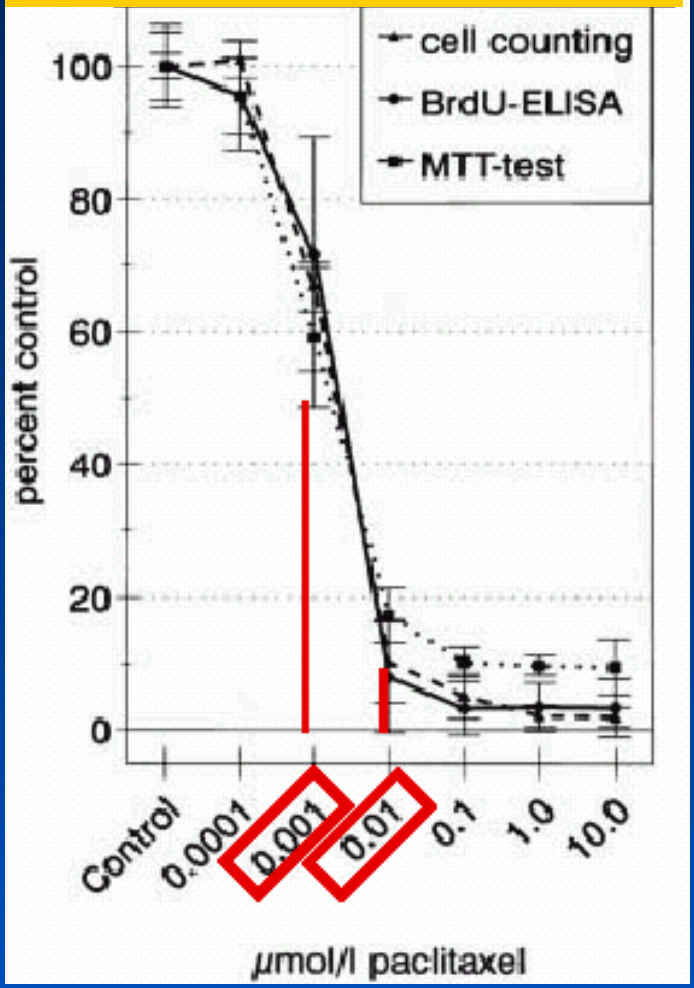


Focal intimal acute and chronic inflammatory cell

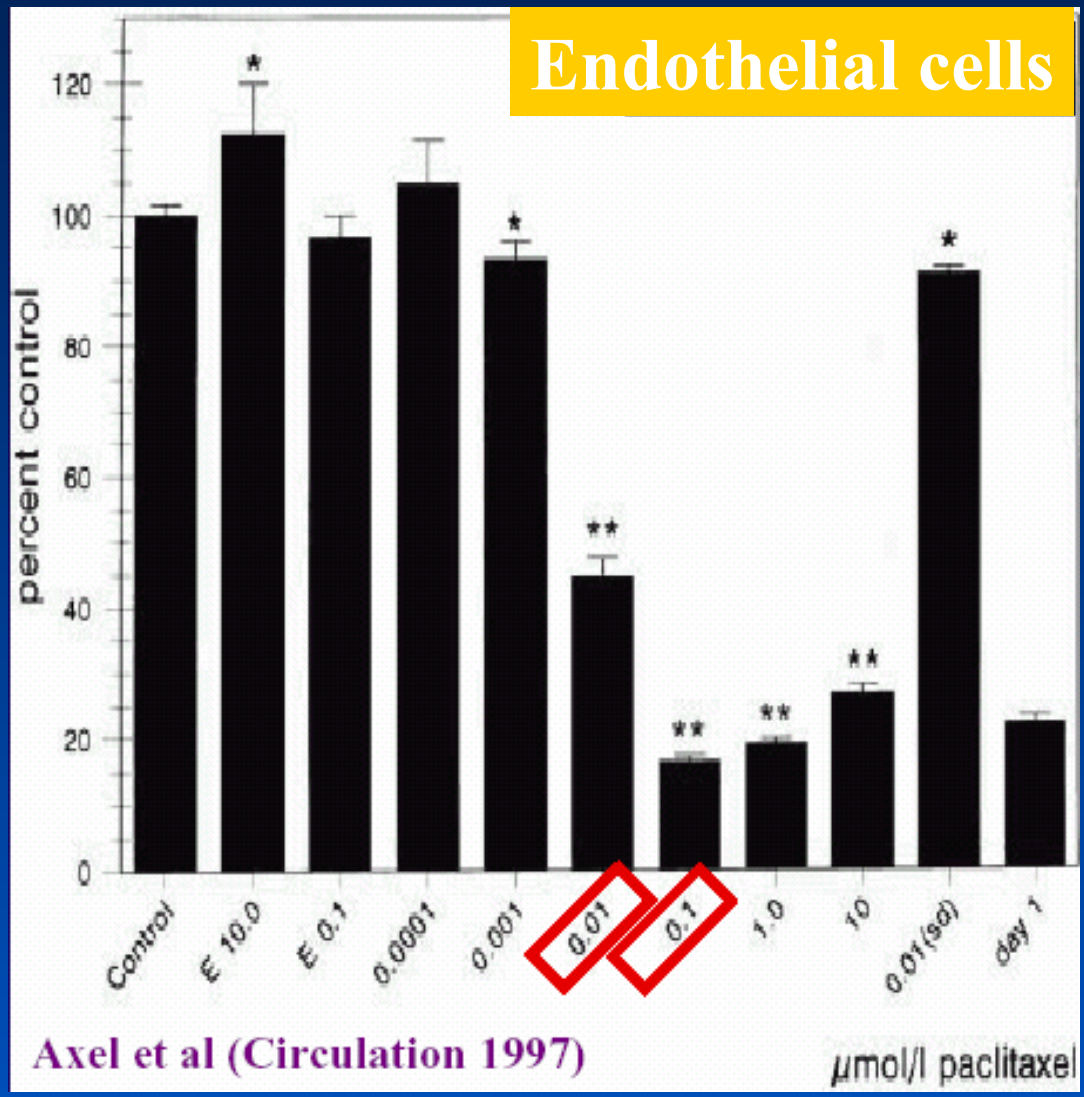
Farb A et al. Circ 2001;104:473

Dose Dependent Cellular Effect

Smooth muscle cells

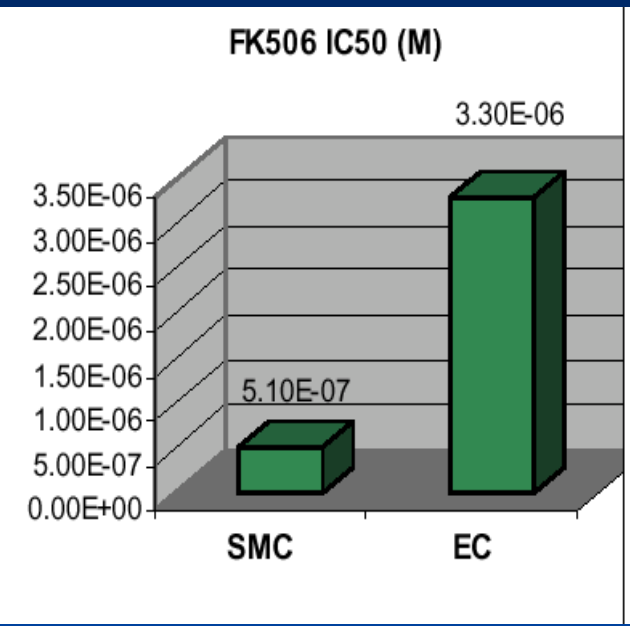


Endothelial cells



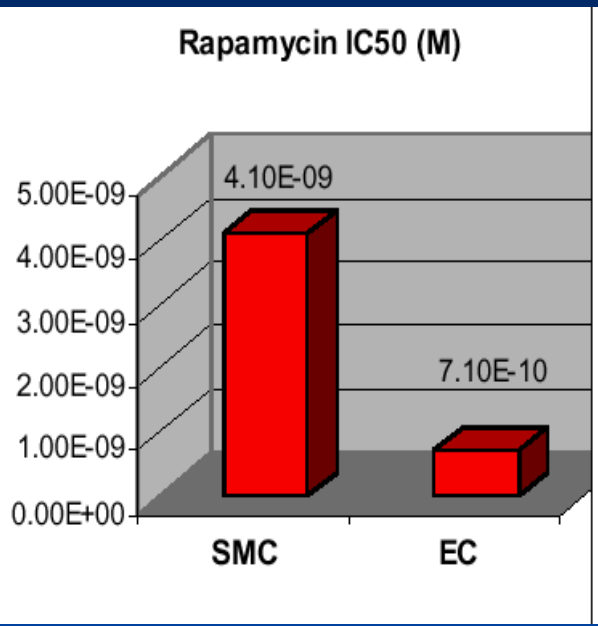
Impact of Anti-restenotic action

Tacrolimus



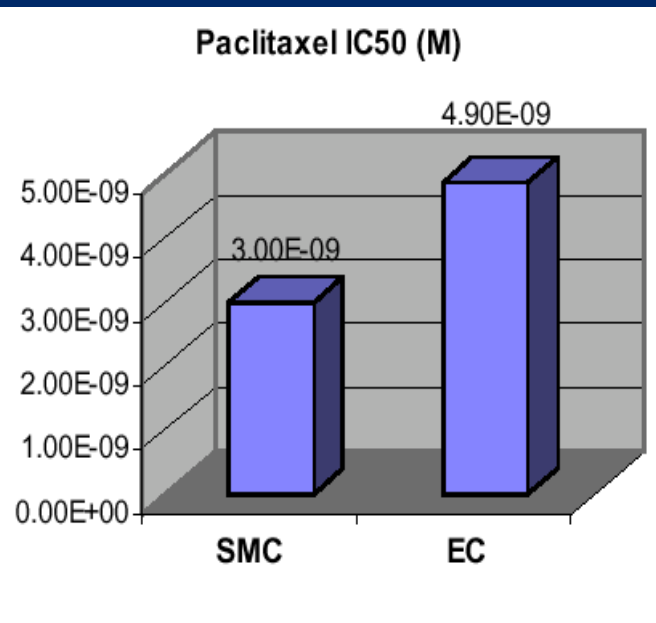
SMC : 5.7×10^{-7}
EC : 3.3×10^{-6}

Rapamycin



SMC : 4.1×10^{-9}
EC : 7.1×10^{-10}

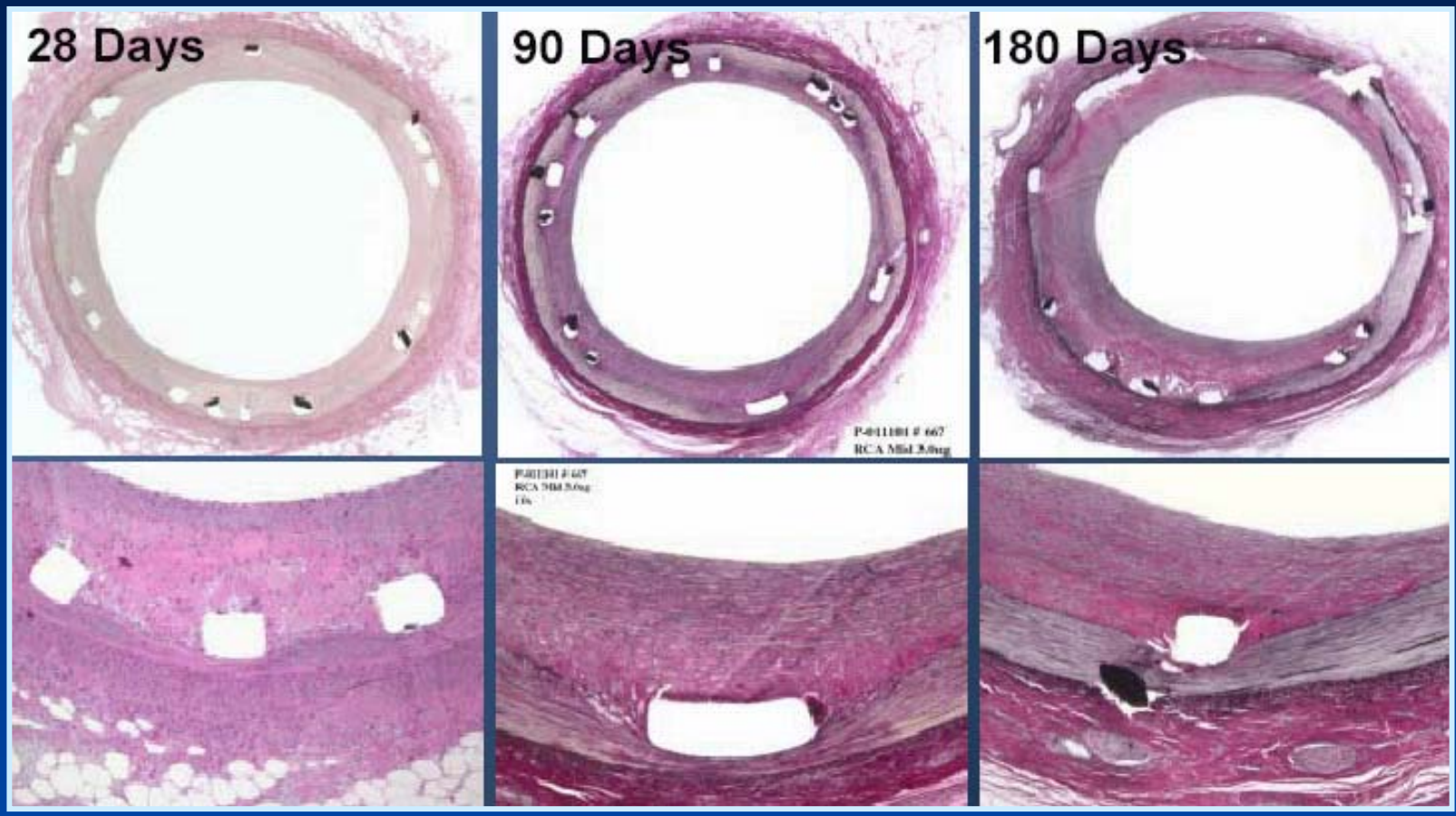
Paclitaxel



SMC : 3.0×10^{-9}
EC : 4.9×10^{-9}

IC50 : drug concentration to kill 50% in in-vitro cell culture

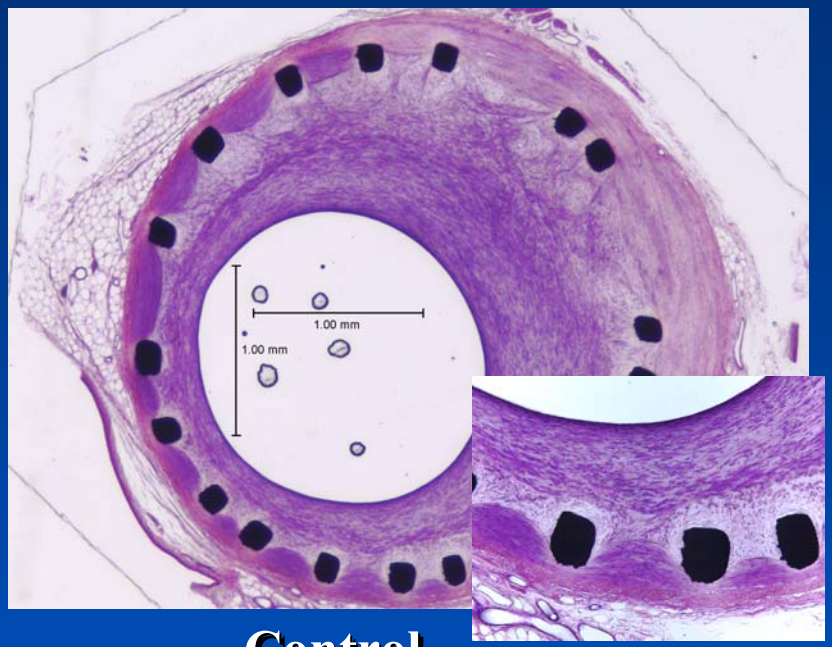
Paclitaxel has a good vascular compatibility



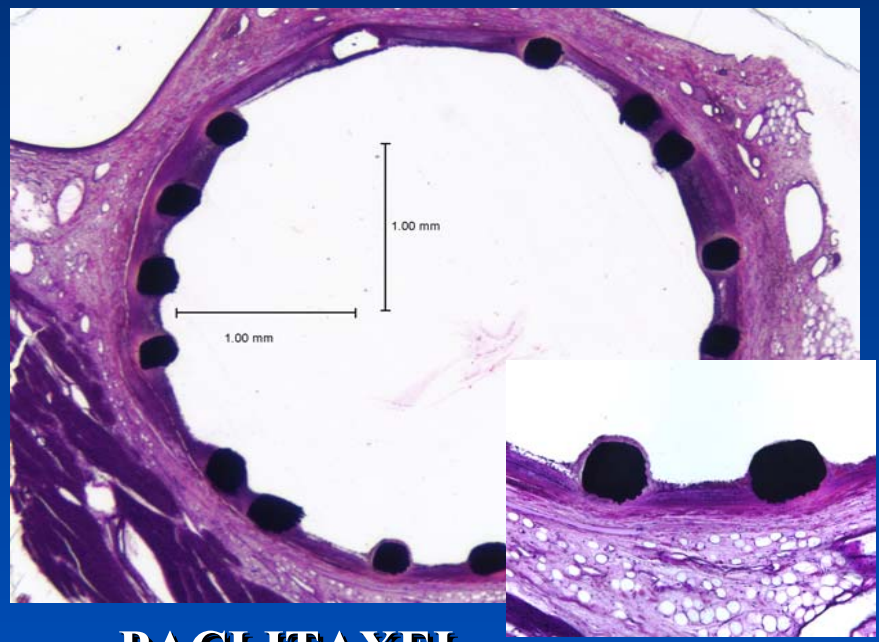
Complete healing, re-endothelization, minimal inflammation…

Experimental data
(One month Swine study)

Paclitaxel coated stents produce significant inhibition of neointimal hyperplasia



Control



PACLITAXEL

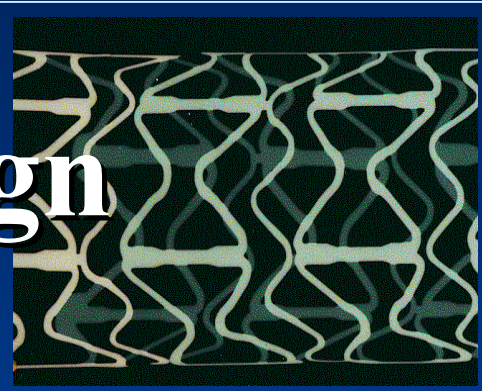
Non-Polymer Coating Stent

Dose Rating Clinical Studies

ASPECT / ELUTE

Supra-G stent
Three Component System

Stent design

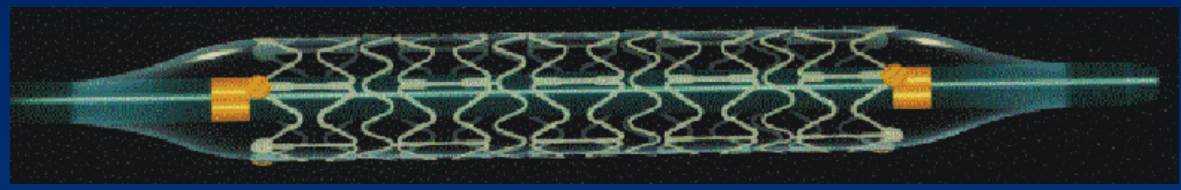


Drug Eluting Stent

Drugs
Paclitaxel

Non -Polymer

Device



Paclitaxel coated stent

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

Dose-Ranging Studies

ASPECT: (Asia) Randomized, Controlled, Triple-Blinded
Supra G™ 316L SS Coronary Stent

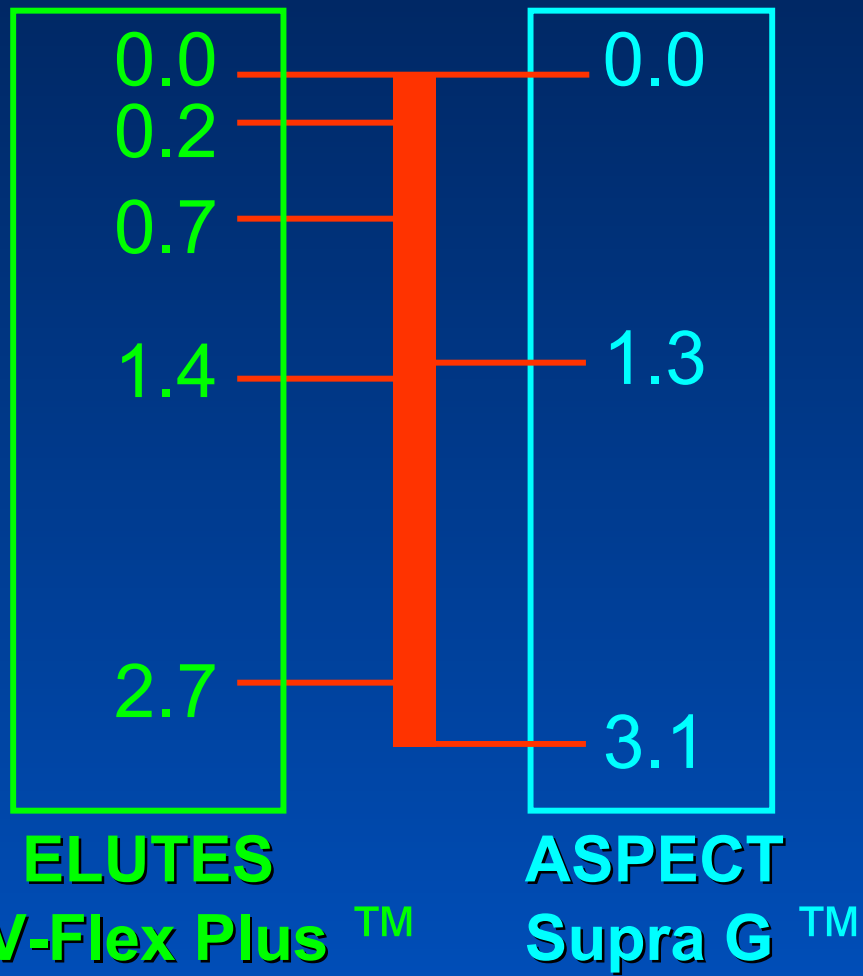
Diameter:	2.5, 3.0, 3.5 mm
Length:	15 mm
PTX Doses:	0.0/ 1.3/ 3.1 (μg/mm^2)

ELUTES: (Europe) Randomized, Controlled, Triple-Blinded
V-Flex Plus™ 316L SS Coronary Stent

Diameter:	3.0, 3.5 mm
Length:	16 mm
PTX Doses:	0.0/ 0.2/ 0.7/ 1.4/ 2.7 (μg/mm^2)

Comparison of Paclitaxel Dose

Paclitaxel Dose Density ($\mu g/mm^2$)



Dose-Ranging Studies

ASPECT: (Asia)
- 3 investigative sites / 177 pts enrolled
- Plavix for 1 month or 6 months
  - (37 pts cilostazol)
- Primary follow-up:
  - MACE at 1 & 6 months
  - Angiographic at 6 months
  - IVUS subset at 6 months
- Ongoing follow-up:
  - Clinical every year

ELUTES: (Europe)
- 9 investigative sites / 192 pts enrolled
- Plavix for 3 months
- Primary follow-up:
  - MACE at 1 & 6 months
  - Angiographic at 6 months
- Ongoing follow-up:
  - Clinical every year

Demographics

	ASPECT	ELUTES
Age (years)	60 ±10	60 ±11
Male	76%	82%
Diabetic	20%	16%
Hypercholesterolemia	13%	49%
Hypertension	47%	46%
Smokers	59%	64%
Multiple Vessel Disease	40%	43%

Lesion Characteristics

		ASPECT	ELUTES
Classification	*Type B1*	40%	64%
	Type B2	6%	8%
Tortuosity	*Mild*	37%	45%
	Moderate	3%	6%
Calcification	*Mild*	14%	38%
	Moderate	3%	5%
Eccentric		55%	51%
Angulation >45 degrees		1%	6%

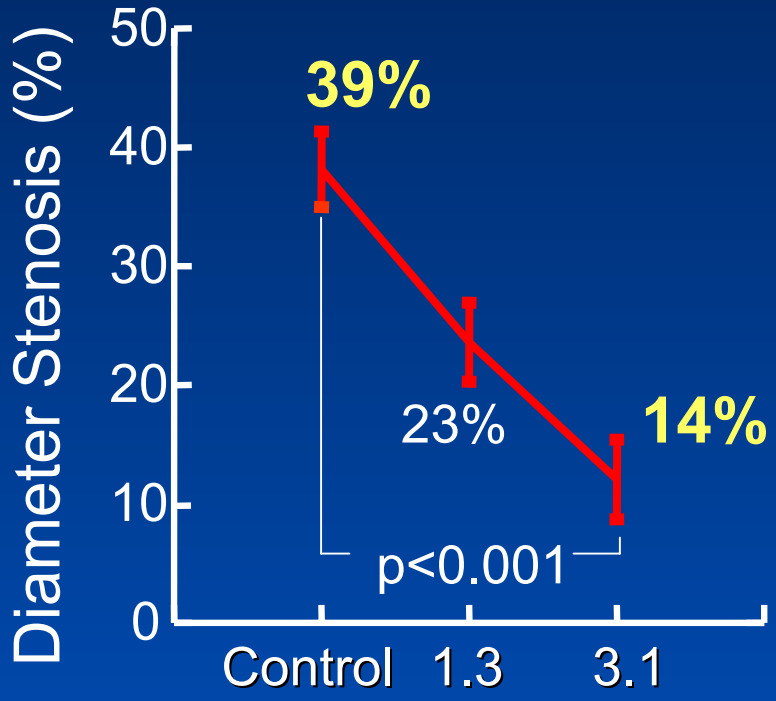
Baseline QCA

	ASPECT		ELUTES	
PTX Dose (μg/mm^2)	3.1	0.0	2.7	0.0
Lesion Length (mm)	10.9	10.5	11.1	10.9
RVD (mm)	2.94	2.88	2.95	2.99
MLD pre (mm)	0.64	0.54	0.56	0.53

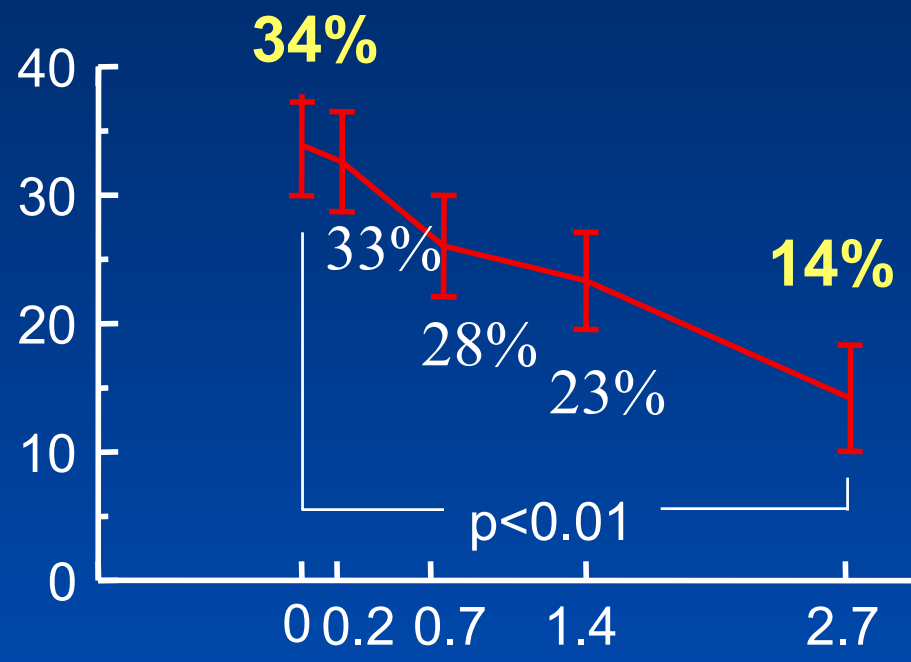
% Diameter Stenosis

6-Month QCA Results:

ASPECT

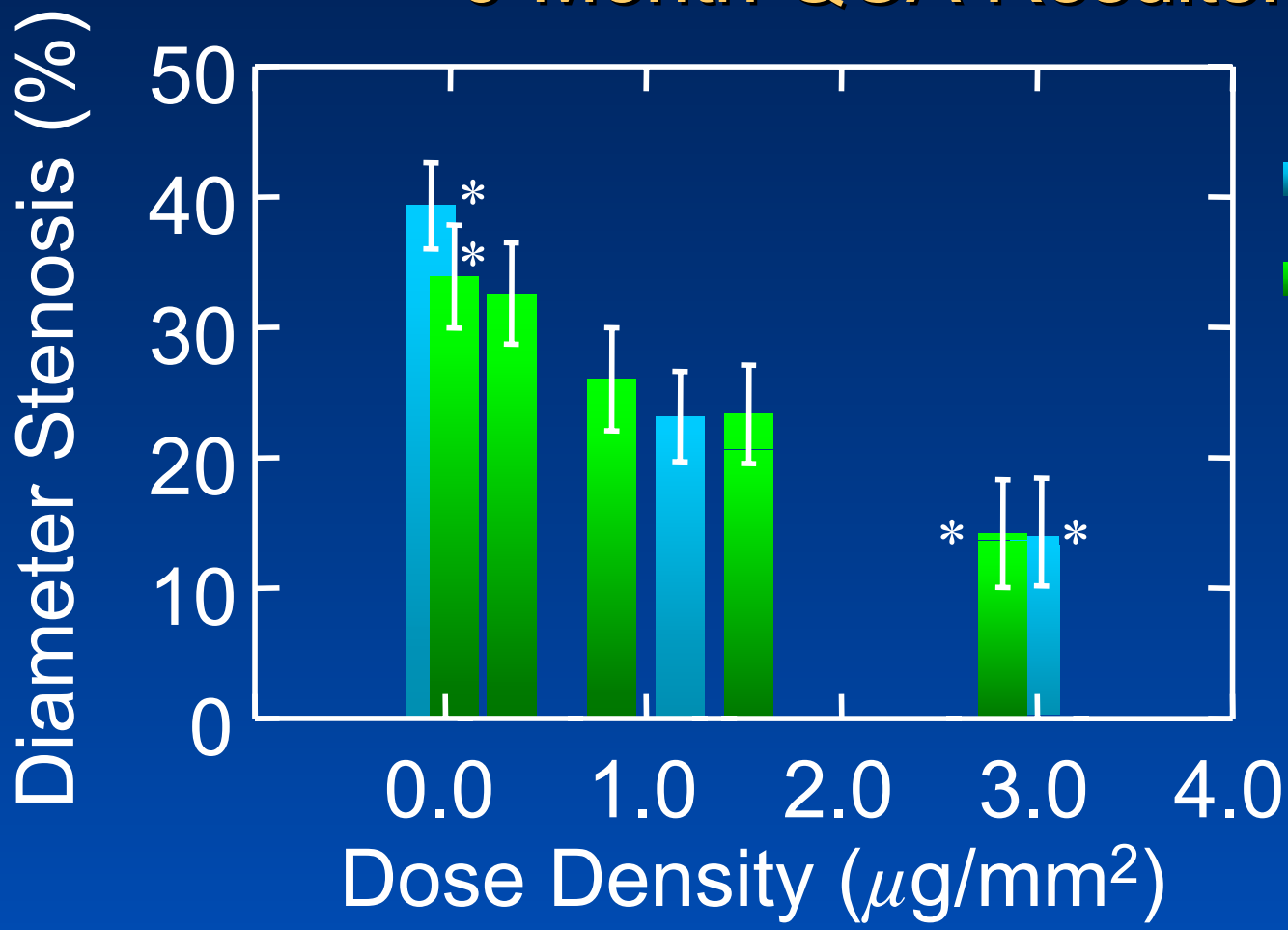


ELUTES



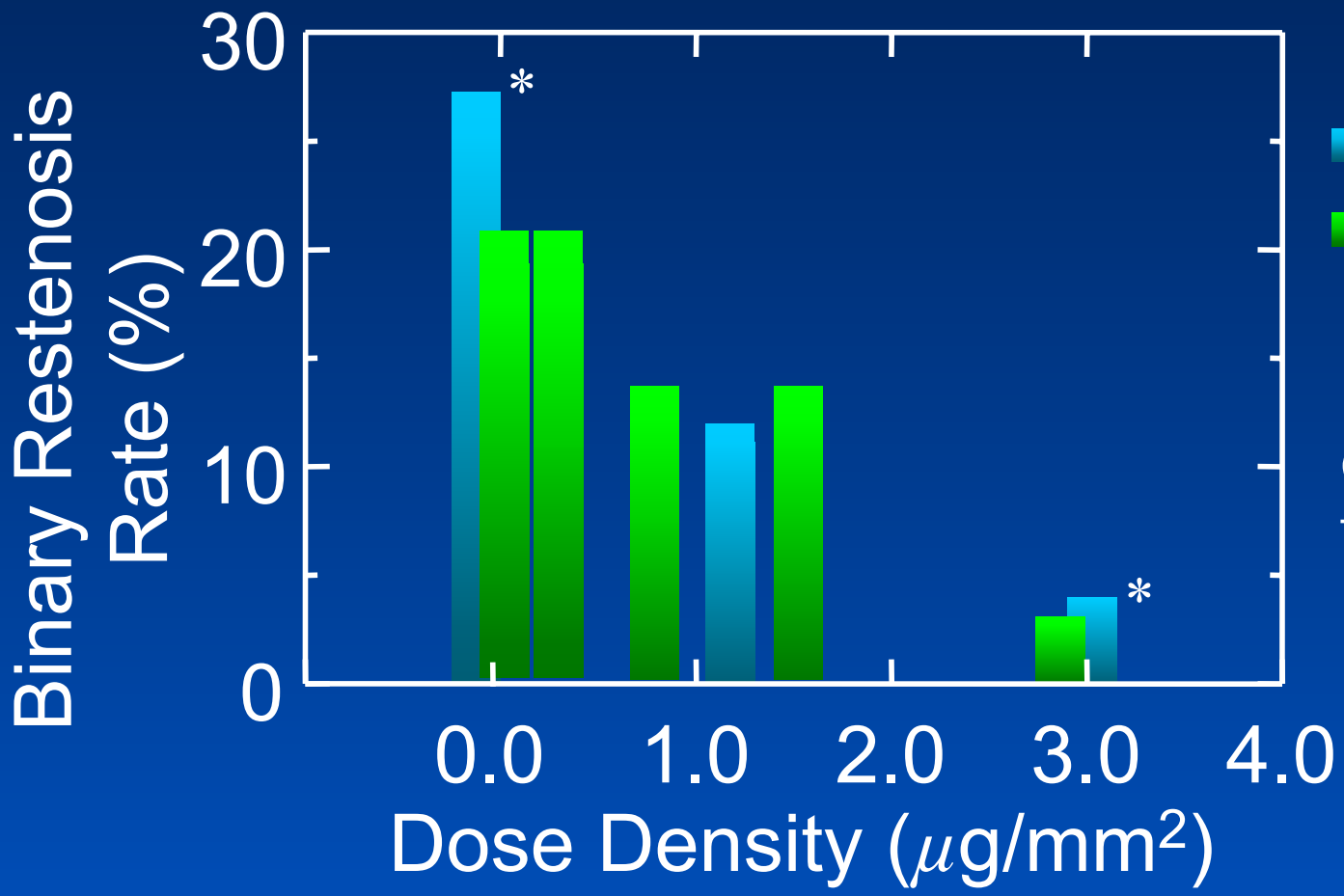
% Diameter Stenosis
-Dose response

6-Month QCA Results:



Binary Restenosis -Dose response

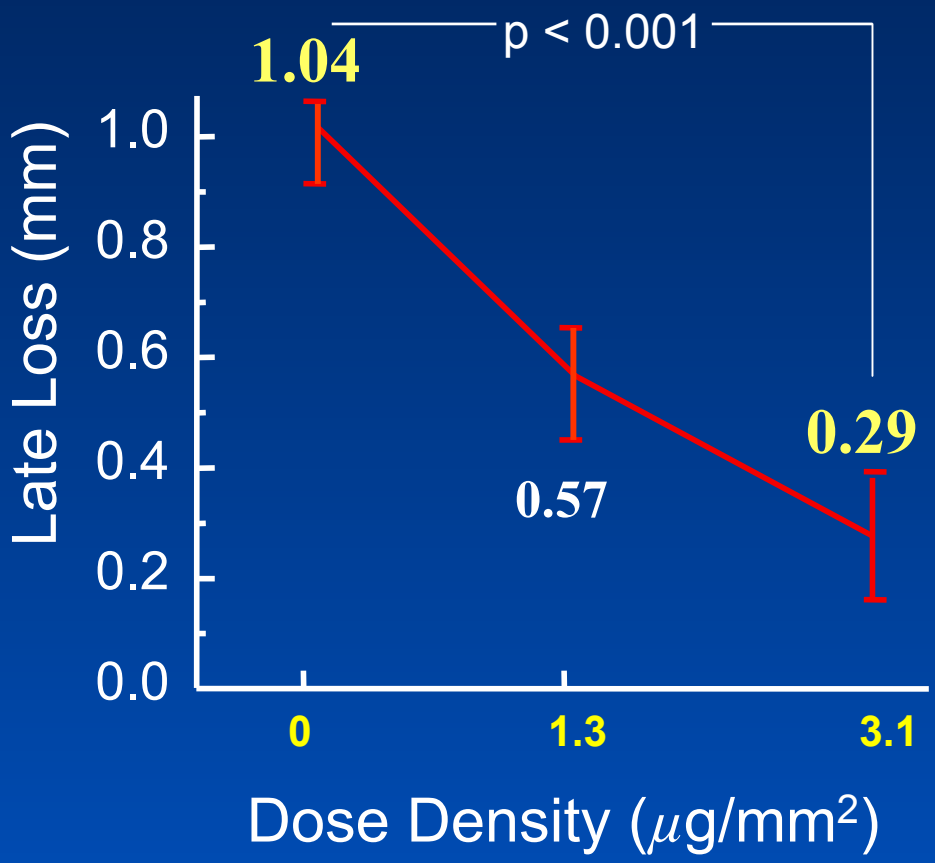
6-Month QCA Results:



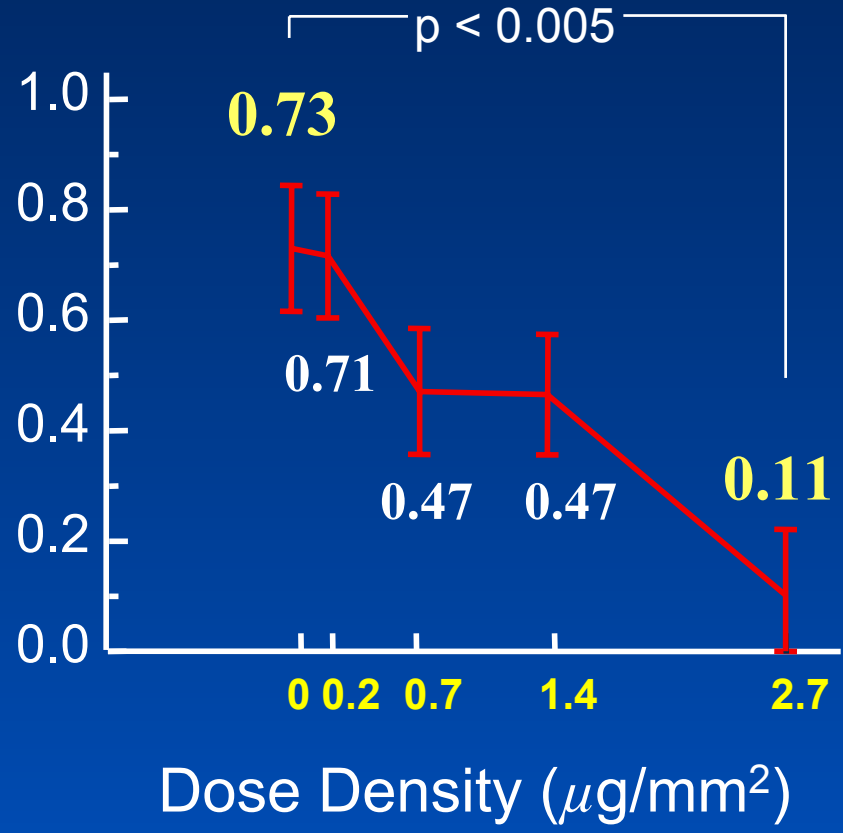
Late Loss

6-Month QCA Results:

ASPECT

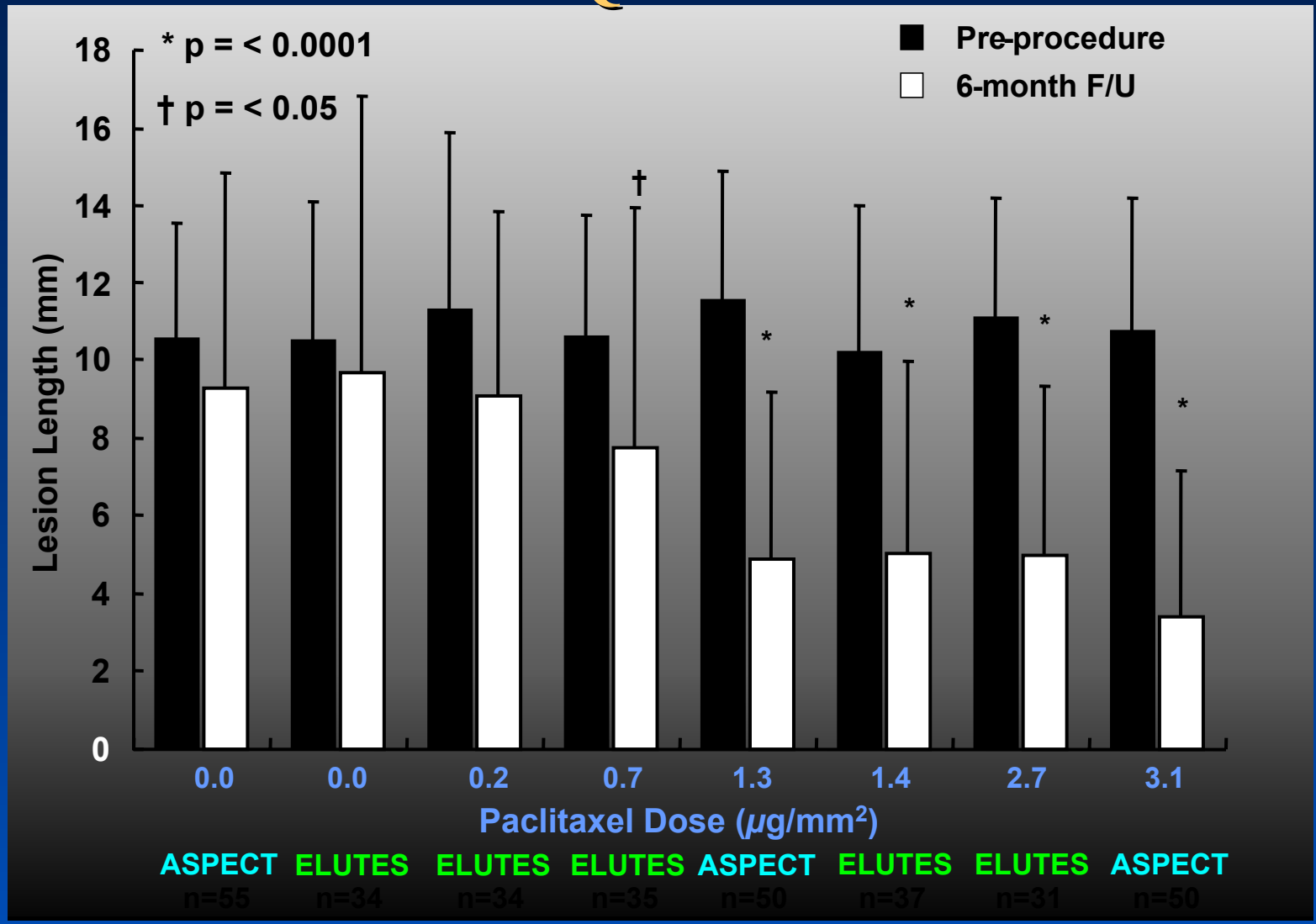


ELUTES



Lesion Length

6-Month QCA Results



Grzegorz Kaluza / Al Raizner QCA Core Lab

Safety: ELUTES Study

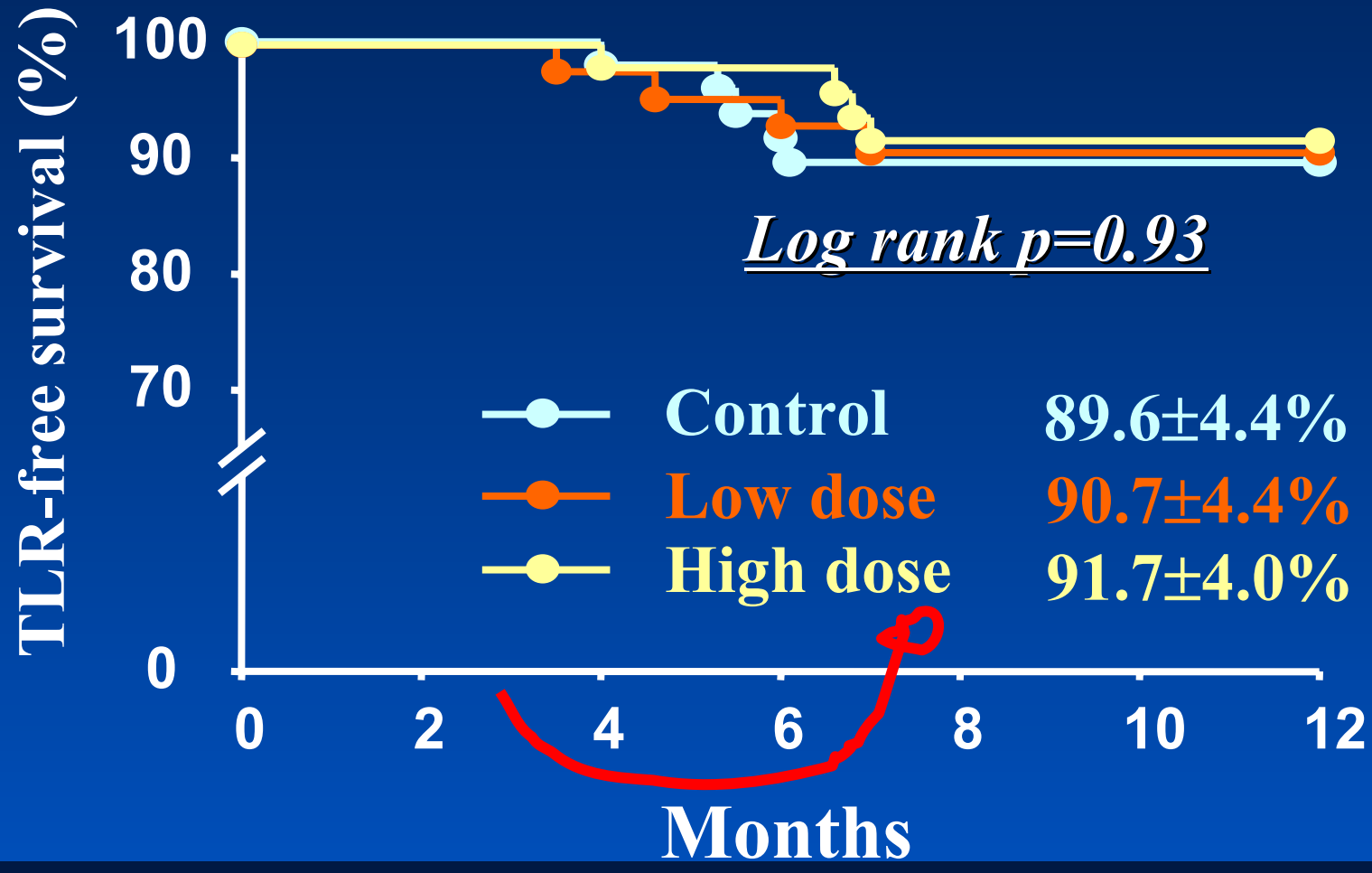
	1-Month		6-Month		12-Month	
PTX Dose:	2.7	0.0	2.7	0.0	2.7	0.0
n:	37	38	37	38	37	38
Death	1	0	1	0	1	0
QMI	0	0	0	0	0	0
CABG	0	0	0	0	0	1
SAT	1	1	1	1	1	1
Non-Q MI	1	0	1	0	1	0
PCI	0	0	1	4	2	5
SAE	3 (8%)	1 (3%)	4 (11%)	5 (13%)	5 (13%)	7 (18%)

Safety: ASPECT Study

	1-Month		6-Month		12-Month	
PTX Dose:	3.1	0.0	3.1	0.0	3.1	0.0
n:	48	49	48	49	48	49
Death	0	0	0	0	0	0
QMI	0	0	0	0	0	0
CABG	0	0	0	0	0	0
SAT	0	0	0	0	0	0
Non-Q MI	1	0	1	0	1	0
PCI	0	0	1	2	4	5
SAE	1 (2%)	0 (0%)	2 (4%)	2 (4%)	5 (10%)	5 (10%)

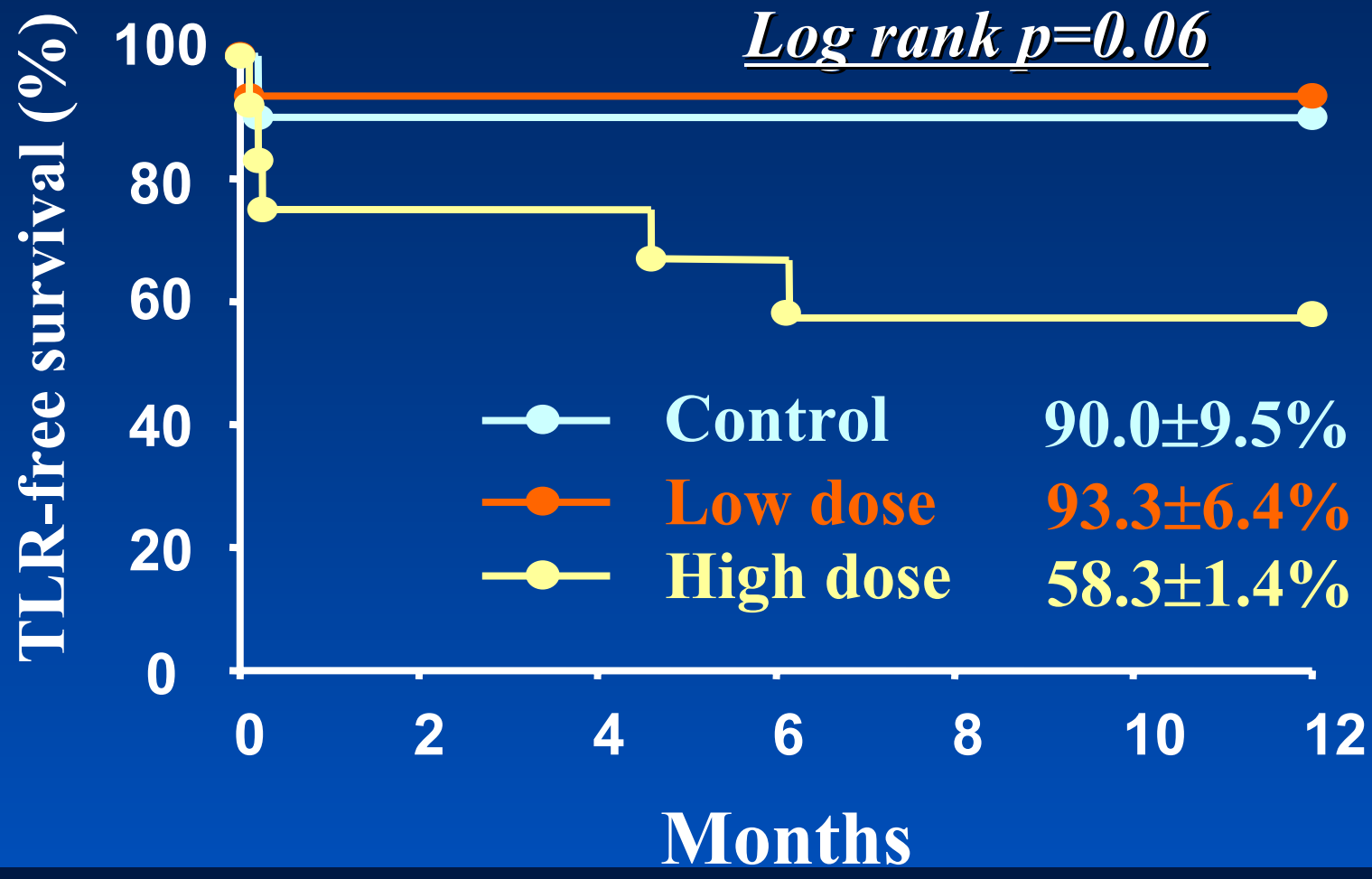
12-Month TLR-free Survival

ASA+Ticlid/Plavix



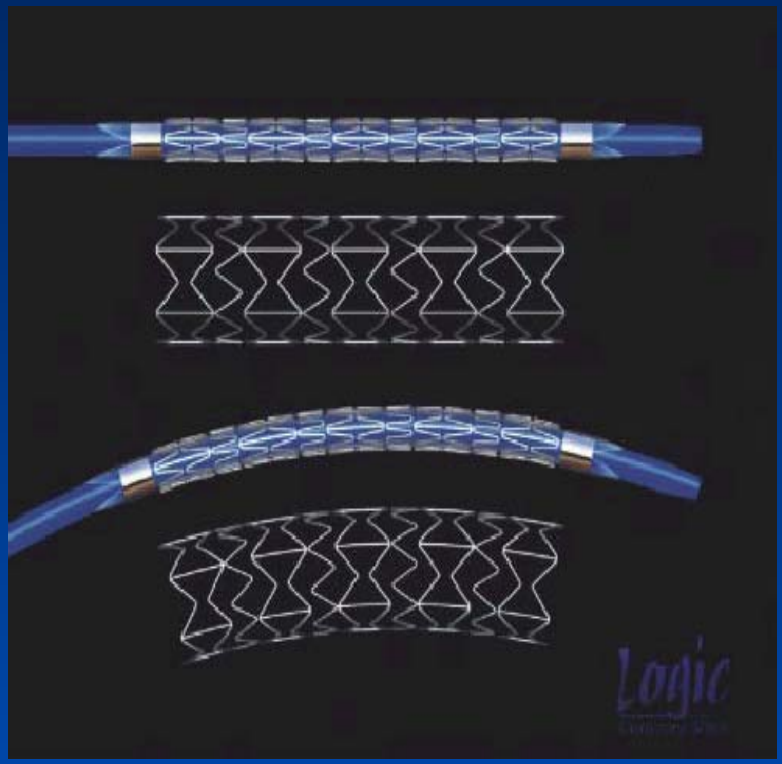
12-Month TLR-free Survival

ASA+Cilostazol



PATENCY

The Cook Logic PTX stent (n=50)



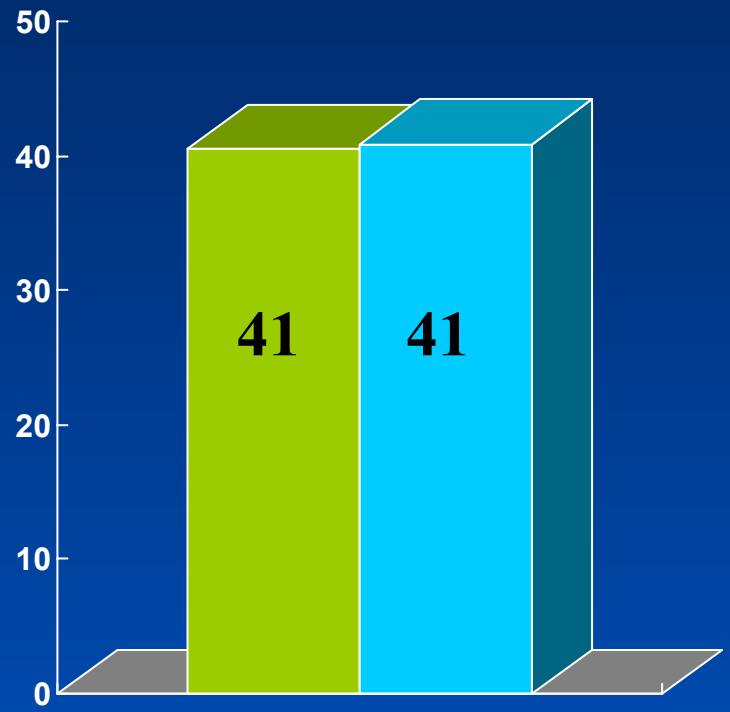
- Coating applied to abluminal surface using Cook's proprietary surface modification technology

- 2.0 ug/mm2 (nominal)

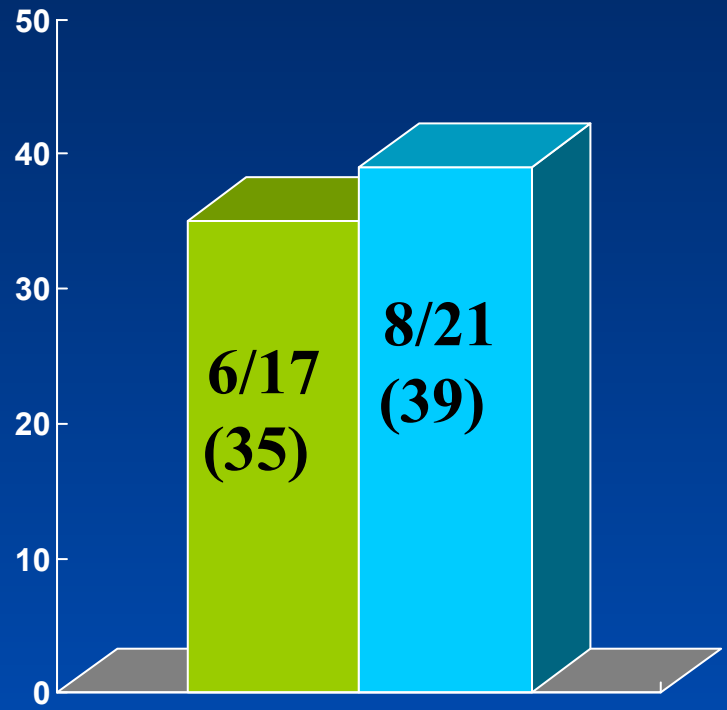
PATENCY

9-month Angiographic Data

Diameter Stenosis (%)



Binary Restenosis (%)



Control Logic PTX

Non-Polymer Coating Stent

Dose Rating Clinical Studies

ASPECT / ELUTE

Lessons from Experimental and Clinical studies

Nonpolymer Coating Paclitaxel Eluting Stent

- A paclitaxel eluting stent suppresses neointimal formation in a dose-dependent manner. However, a higher dose of paclitaxel is likely to be associated with delayed healing and local toxicity.

- The ASPECT, ELUTE, and PATENCY trials support the concept that an optimal dose density is essential for a sufficient restenosis-reducing effect.

Lessons from Experimental and Clinical studies

Nonpolymer Coating Paclitaxel Eluting Stent

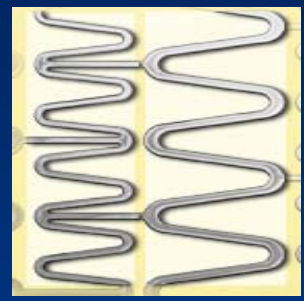
- The high dose density (3 mcg/mm^2) paclitaxel coating was the most effective in reducing restenosis.
- The paclitaxel effect is maintained at 12 months

Polymer Coating Stent

TAXUS Studies

TAXUS stent
Three Component System

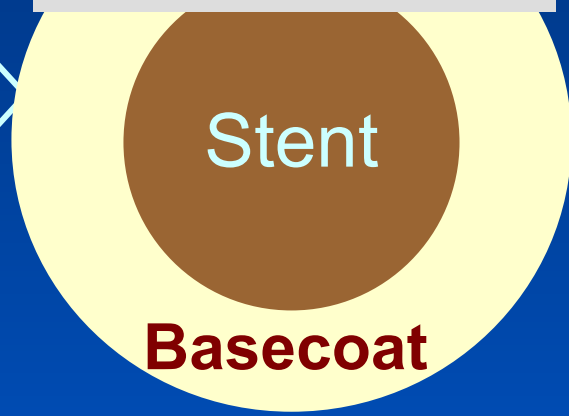
Stent design



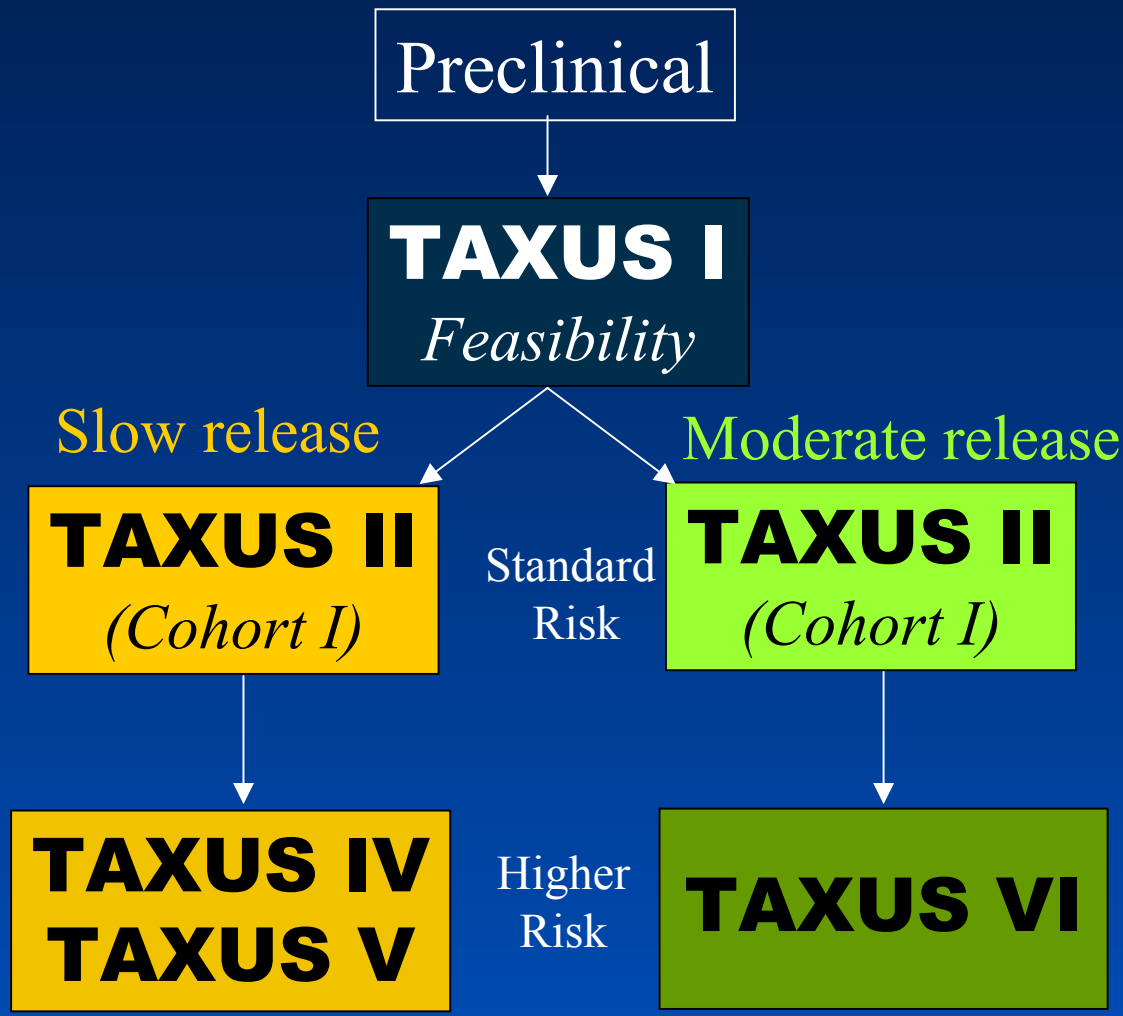
Drug Eluting Stent

Drugs
Paclitaxel

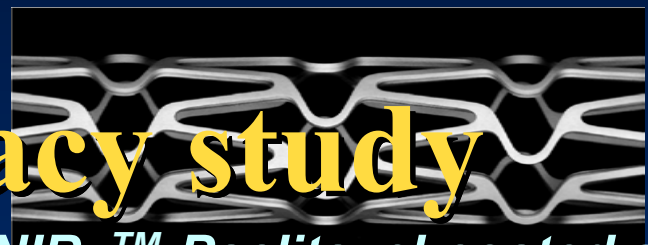
Translute



TAXUS Program



TAXUS-II: Efficacy study



NIRx™-Paclitaxel-coated stent

De novo, 3.0 and 3.5 mm, <12 mm
532 pts at 61 sites in 19 countries
1:1 Randomization
Enrollment completed, results at TCT 2002

TAXUS-III: Feasibility study

Coated stent for ISR lesions
30 pts at 2 sites

TAXUS-IV: Pivotal study I

De novo 10-28 mm lesions

1,172 pts at 80 U.S. sites

1:1 Randomization with single stent

2.5, 3.0, 3.5 mm Express (16, 24, 32 mm)

Enrollment to begin 1st quarter 2002

TAXUS-V: Pivotal study II

Express™-Paclitaxel-coated stent

De novo 10-48 mm lesions

1,110 pts at 80 sites

1:1 Randomization, multiple stents allowed

2.5, 3.0, 3.5 mm Express (8, 16, 24, 32 mm)

Enrollment anticipated 3rd quarter 2002

TAXUS-VI: *European arm*

TAXUS-VII: Pivotal study III

Express™-Paclitaxel-coated stent

ISR, 10-40 mm lesions

528 pts at up to 60 US sites

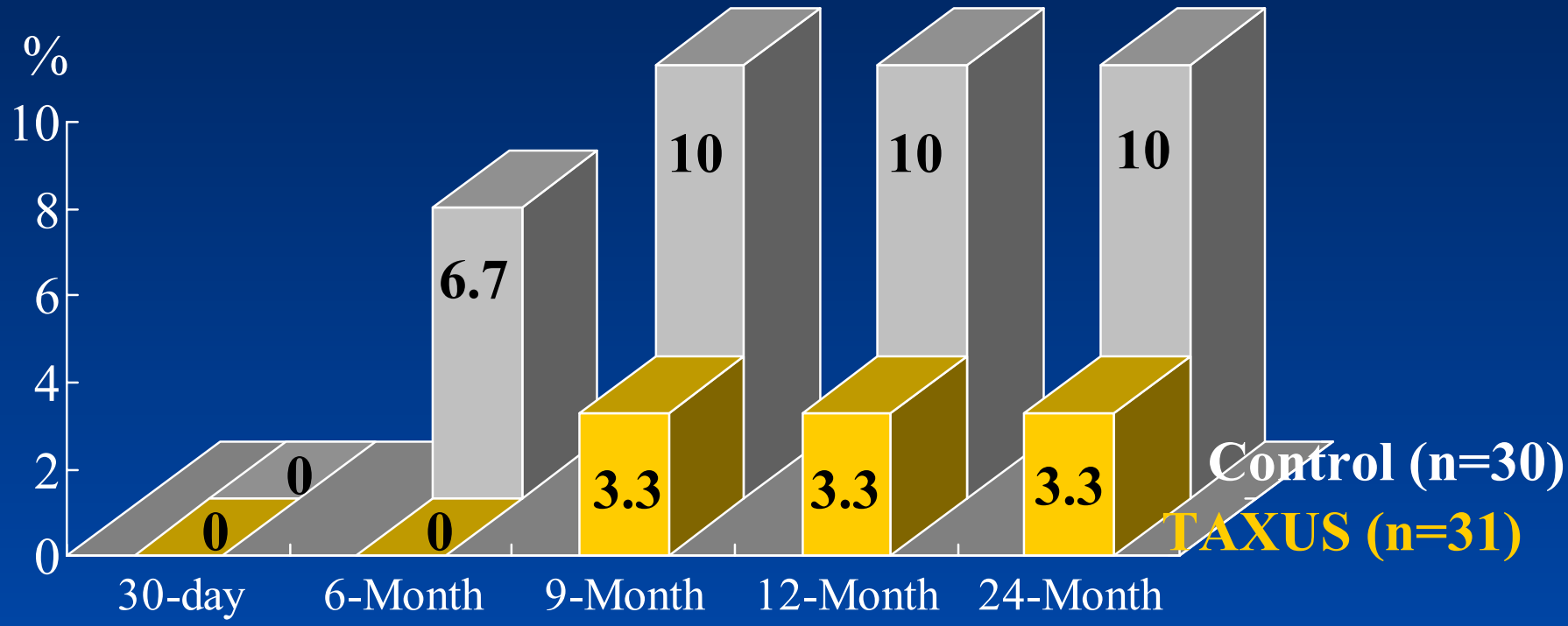
1:1 vs. brachytherapy

2.5, 3.0, 3.5 mm Express (8, 16, 24, 32 mm)

Enrollment anticipated 3rd quarter 2002

TAXUS I

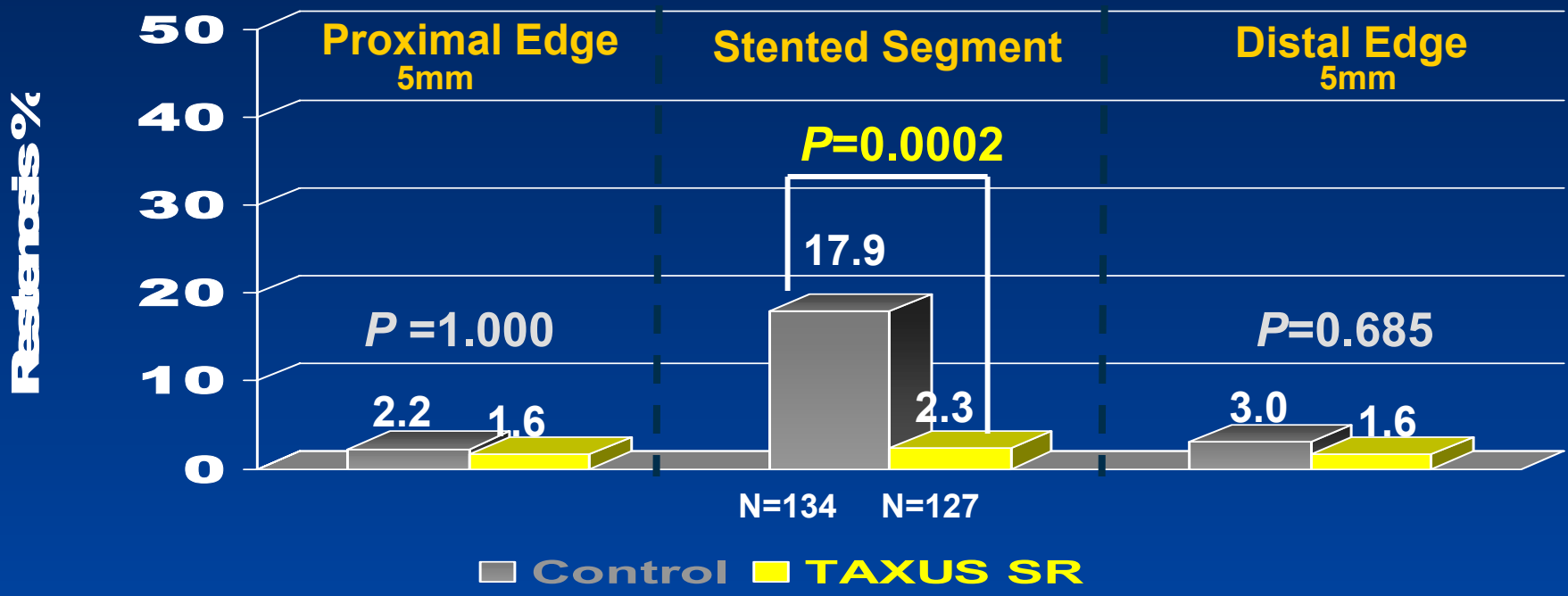
MACE over Time



Sustained benefit of TAXUS SR over 2 years

TAXUS II

Slow Release : 6-Month Restenosis

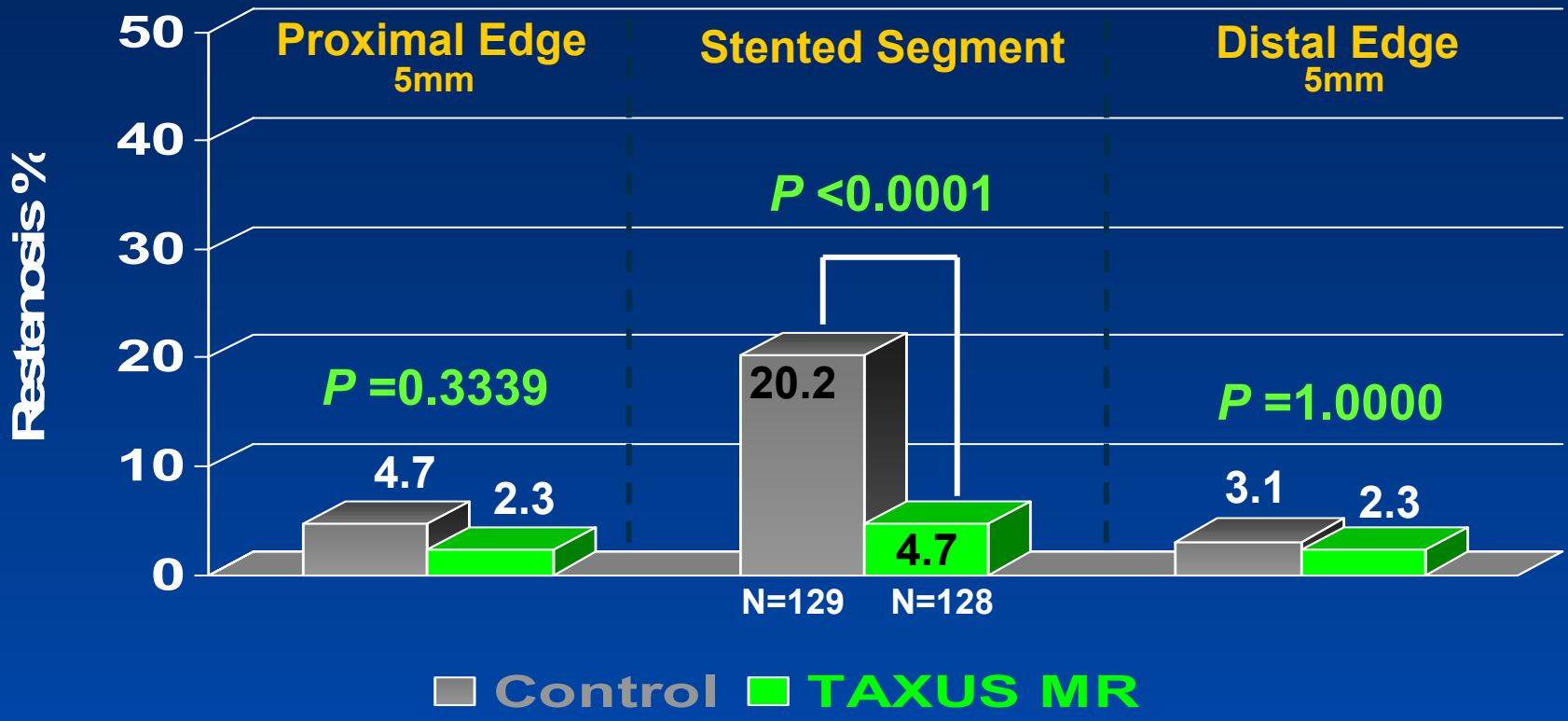


No difference at edges between TAXUS and control

TCT, Oct 2002

TAXUS II

Moderate Release : 6-Month Restenosis



No difference at edges between TAXUS and control

TCT, Oct 2002

TAXUS II

6-Month MACE

	Combined Control (n=270) Rate % / (n)	TAXUS^{NIRx} SR (n=131) Rate % / (n)	TAXUS^{NIRx} MR (n=135) Rate %/ (n)	P-value SR vs. Control	P-value MR vs. Control	P-value overall
Stent thrombosis	0	1	0	1.0000	1.0000	1.0000
6-Month MACE	19.8 (52)	8.5 (11)	7.8 (10)	0.0035	0.0019	0.0007
Death	0.4 (1)	0.0	0.0	1.0000	1.0000	1.000
Q-Wave MI	0.8 (2)	0.0	0.0	1.0000	1.0000	1.000
Non Q-Wave MI	4.6 (12)	1.5 (2)	2.3 (3)	0.1567	0.4029	0.2692
TVR - Overall	16.0 (42)	7.7 (10)	6.2 (8)	0.0262	0.0059	0.0053
TLR	13.3 (35)	4.6 (6)	3.1 (4)	0.0080	0.0010	0.0005
TVR Remote	2.7 (7)	3.1 (4)	2.3 (3)	0.7572	1.0000	0.9406
CABG	0.8 (2)	0.8 (1)	1.0 (1)	1.0000	1.0000	1.0000

TCT, Oct 2002

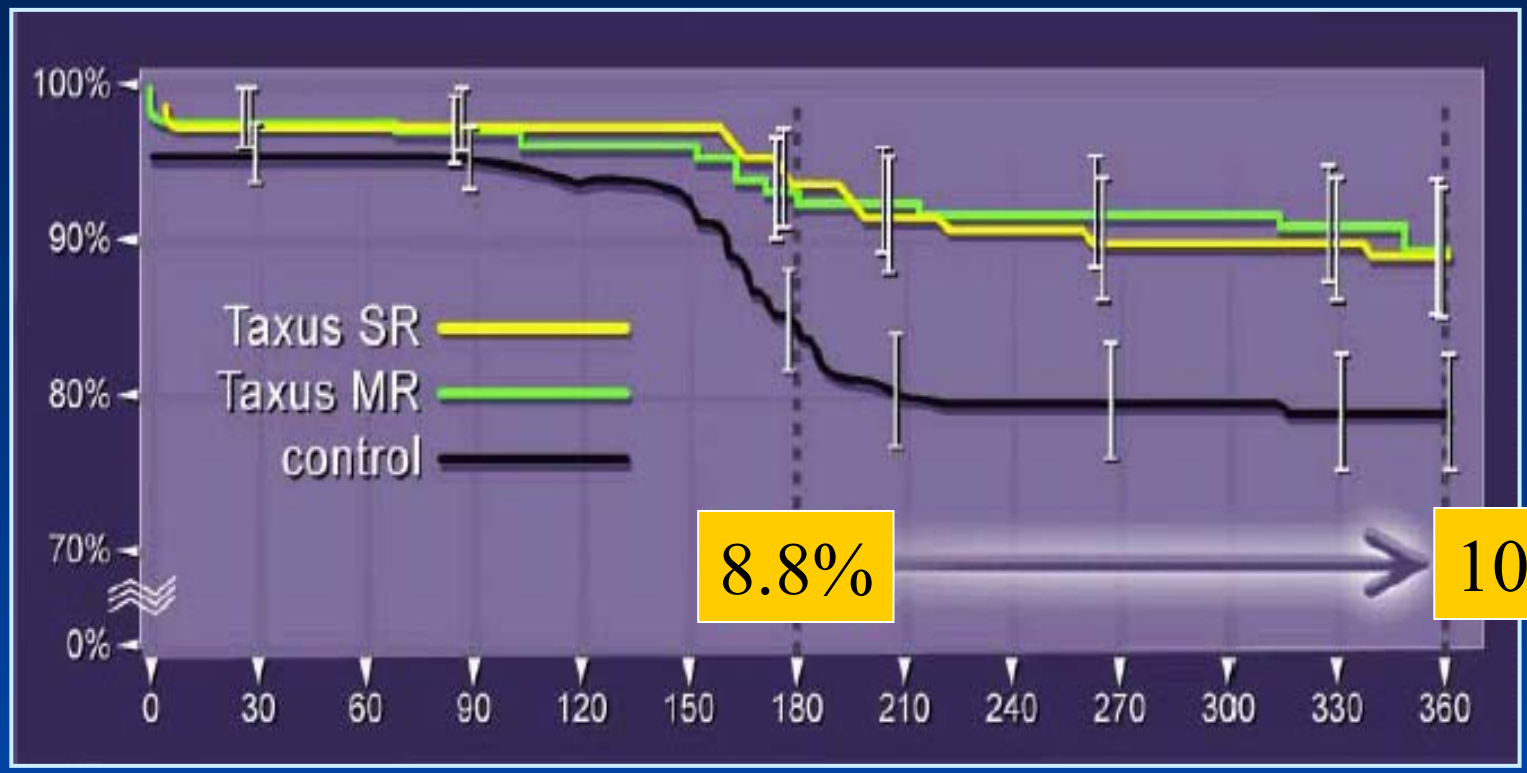
TAXUS II

12-Month MACE

	Combined Control (n=270) Rate % / (n)	TAXUS^{NIRx} SR (n=131) Rate % / (n)	TAXUS^{NIRx} MR (n=135) Rate %/ (n)	P-value SR vs. Control	P-value MR vs. Control	P-value overall
Stent thrombosis	0	1	1	0.3267	0.3333	0.2458
12-Month MACE	21.7 (57)	10.9 (14)	9.9 (13)	0.0082	0.0048	0.0023
Death	0.8 (2)	0.0	0.0	1.0000	1.0000	1.000
Q-Wave MI	1.1 (3)	0.8 (1)	1.5 (2)	1.0000	1.0000	1.000
Non Q-Wave MI	4.2 (11)	1.6 (2)	2.3 (3)	0.2354	0.4026	0.3552
TVR - Overall	17.5 (46)	10.1 (13)	6.9 (9)	0.0704	0.0034	0.0069
TLR	14.4 (38)	4.7 (6)	3.8 (5)	0.0035	0.0010	0.0003
TVR Remote	3.0 (8)	3.1 (4)	1.5 (2)	1.0000	0.5069	0.7279
CABG	1.1 (3)	3.1 (4)	1.5 (2)	0.2244	1.0000	0.3716

Euro PCR, 2003

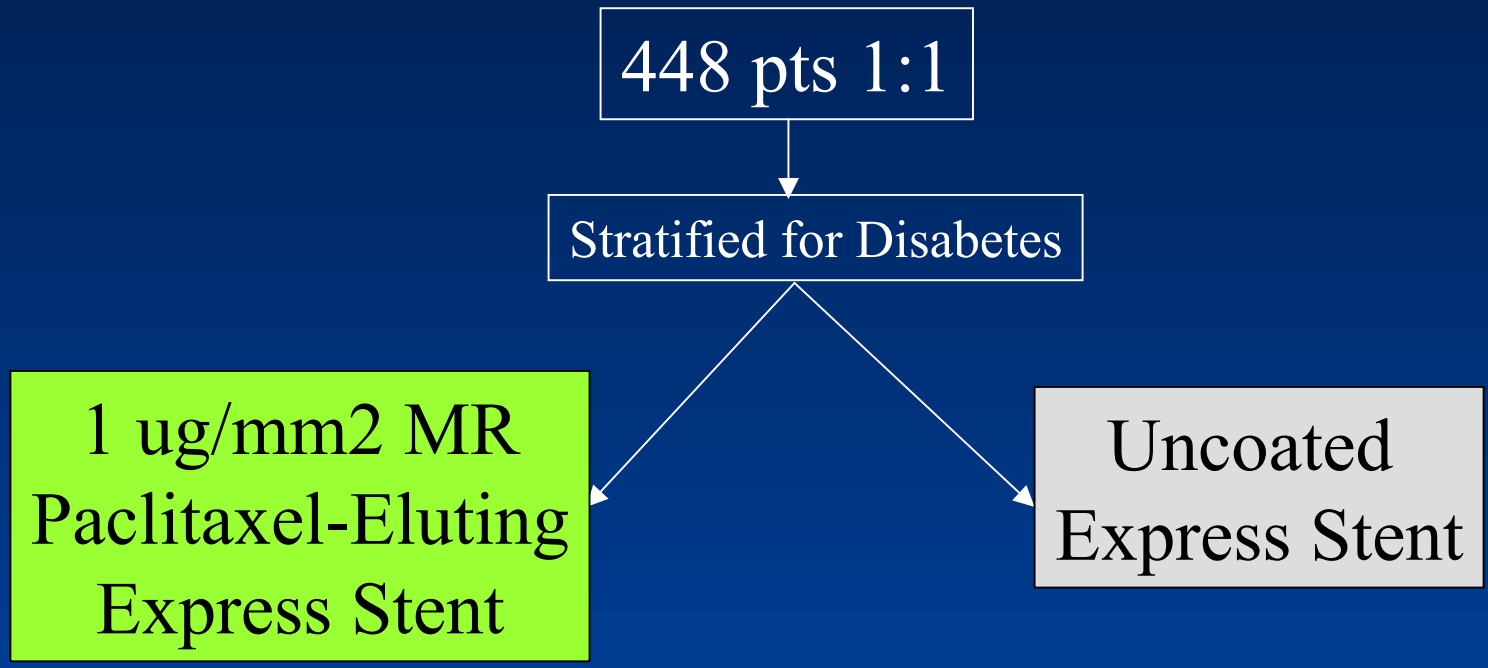
12-Month MACE Free Survival



Days after randomization

Sustained benefit of TAXUS stents from 6 to 12 months

TAXUS VI : Study Design



- Clopidogrel and aspirin for 6 months
- Clinical F/U at 1,3,6, and 9 months and annually
- Angiographic F/U (n=446) at 9 months
- IVUS substudy (n=171) F/U at 9 months

30-Day MACE

	MR TAXUS (n=350)	Control (n=309)	P
Stent thrombosis (%)	1 (0.4)	0 (0.0)	1.000
30-Day MACE	5.3	7.3	0.379
Cardiac death (%)	1 (0.4)	0 (0.0)	1.000
Overall MI (%)	9 (4.0)	16 (7.3)	0.125
Q-MI (%)	2 (0.9)	2 (0.9)	1.000
Non-Q MI (%)	7 (3.1)	14 (6,4)	0.099
TVR (%)	3 (1.3)	1 (0.5)	0.624

WISDOM Registry

Real world

9 countries, 26 sites

Real world safety data on the TAXUS EXPRESS Slow Release Stent System

529 patients from June 2002 to May 2003

- Diabetes mellitus :32%
- AMI : 10%
- Average lesion length : 15.0 ± 6.5 mm
- Average RVD : 2.9 ± 0.6 mm
- No of stents per pts : 1.23

Feasibility and Efficacy

Polymer Coating Paclitaxel Eluting Stent

- TAXUS I study demonstrated that polymer coated paclitaxel eluting stent is safe and feasible.
- TAXUS studies showed that polymer coated paclitaxel eluting stent has a dramatic effectiveness for inhibition of intimal hyperplasia compared to bare metal stent.
- Moreover its role was maintained for 2 years.

Safety and Efficacy by Experimental Studies

Paclitaxel should be OK !

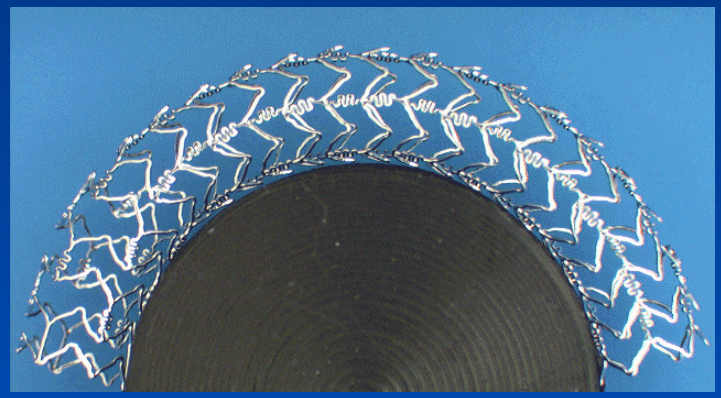
Drugs ⇦ DES

Why could not demonstrate the same efficacy of the Non-polymer Paclitaxel eluting stents in DELIVER ?

By chance or inevitable ?

DELIVER

The Guidant ACHIEVE stent

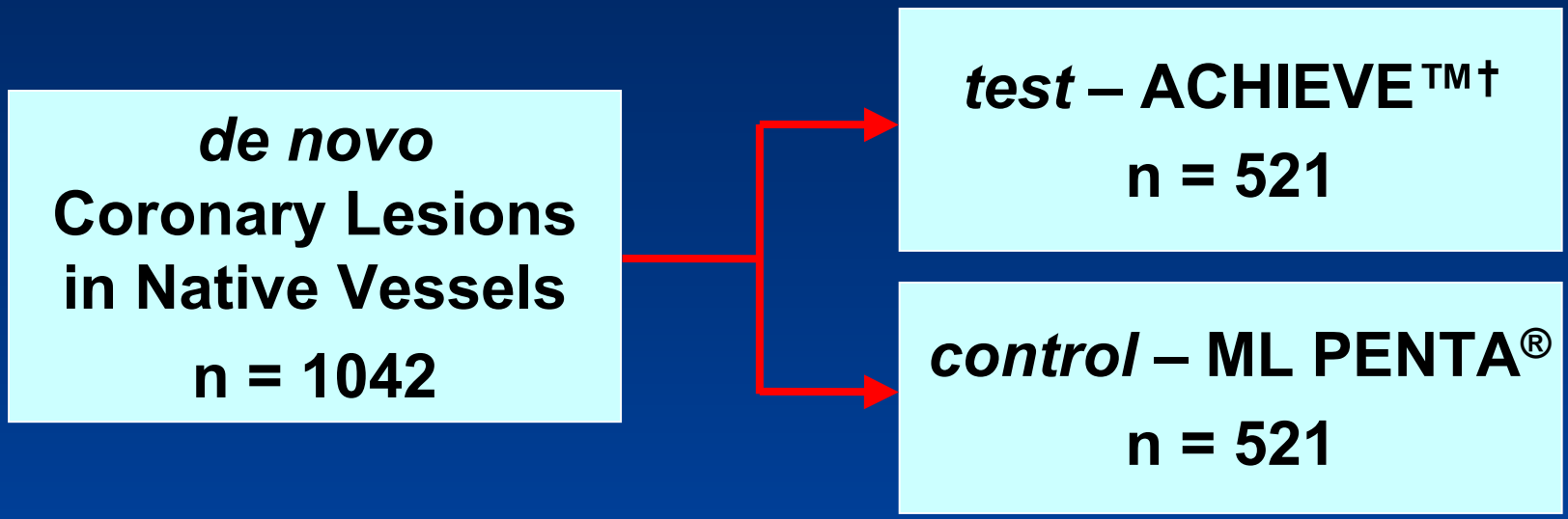


- Coating applied to abluminal surface using Cook's proprietary surface modification technology

- 3.0 ug/mm2 (nominal)

DELIVER

Study Design



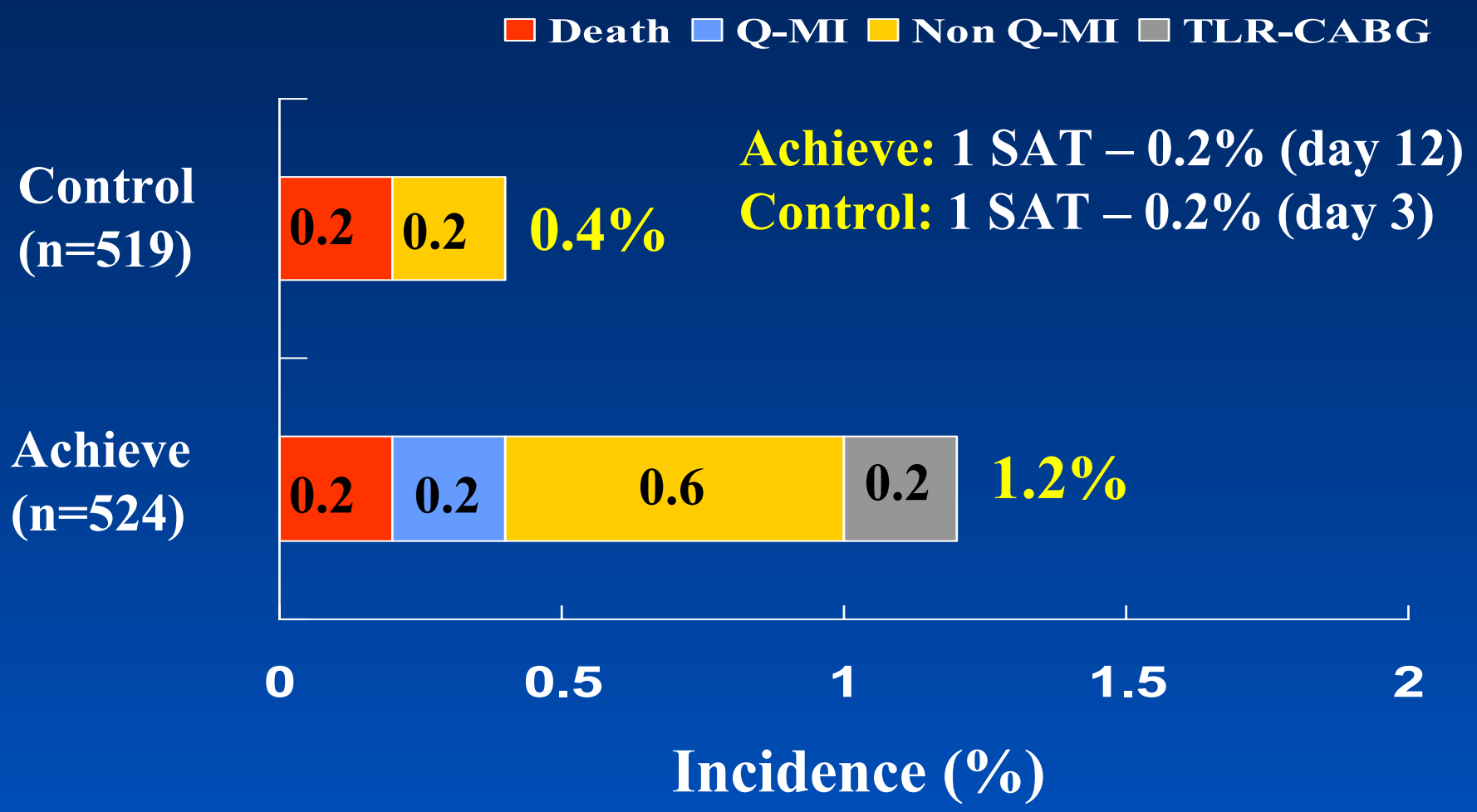
Prospective, randomized, single-blinded, parallel-group (two-arm), multi-center clinical trial

DELIVER

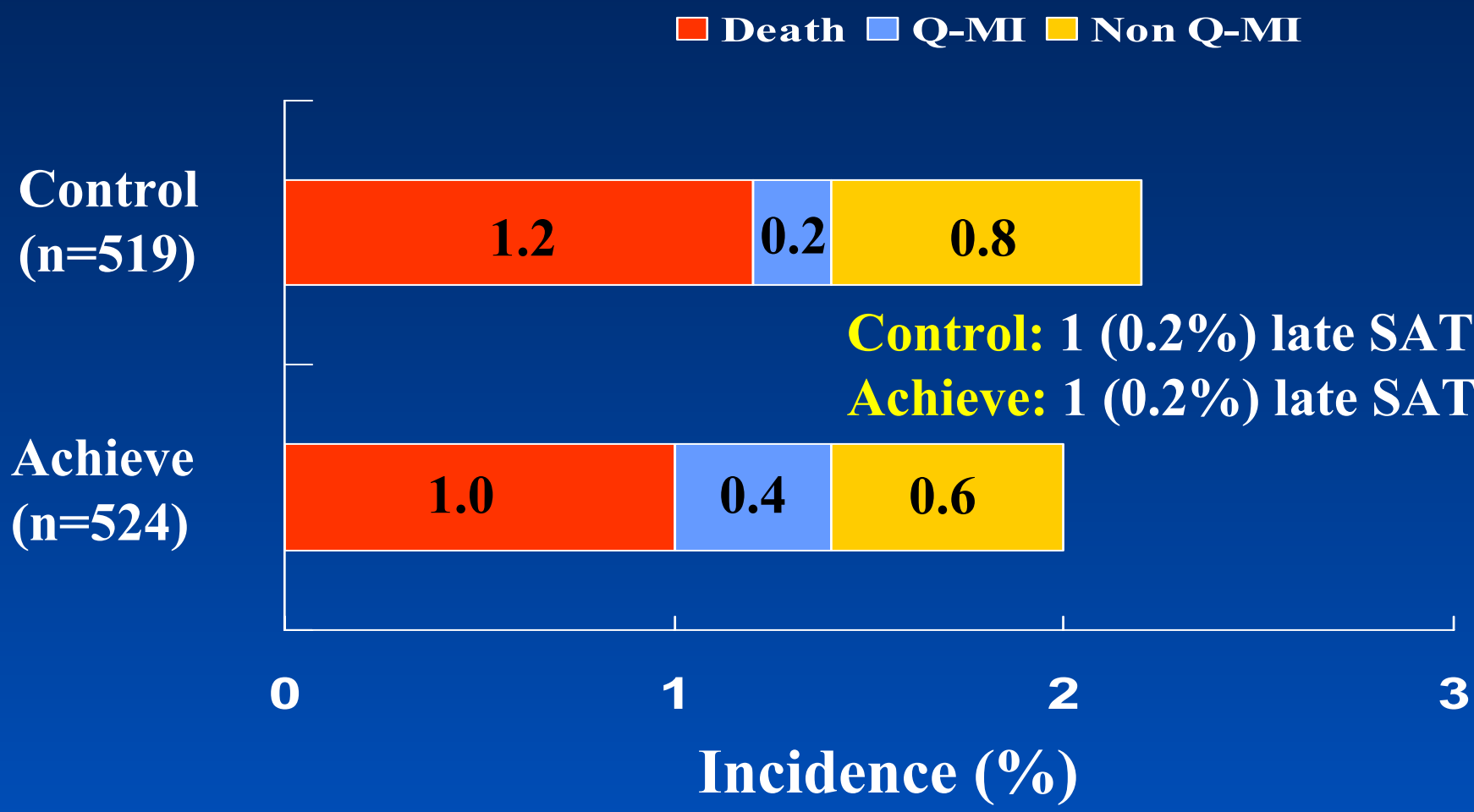
Inclusion Criteria

- Target vessel RVD 2.5 – 4.0 mm
- Target lesion length ≤25 mm visually estimated
- Up to two native vessels treated, one target and one non-target, with only one *de novo* lesion per vessel
- Target lesion %DS ≥50 and <100, and TIMI flow ≥1

DELIVER : 30-Day MACE



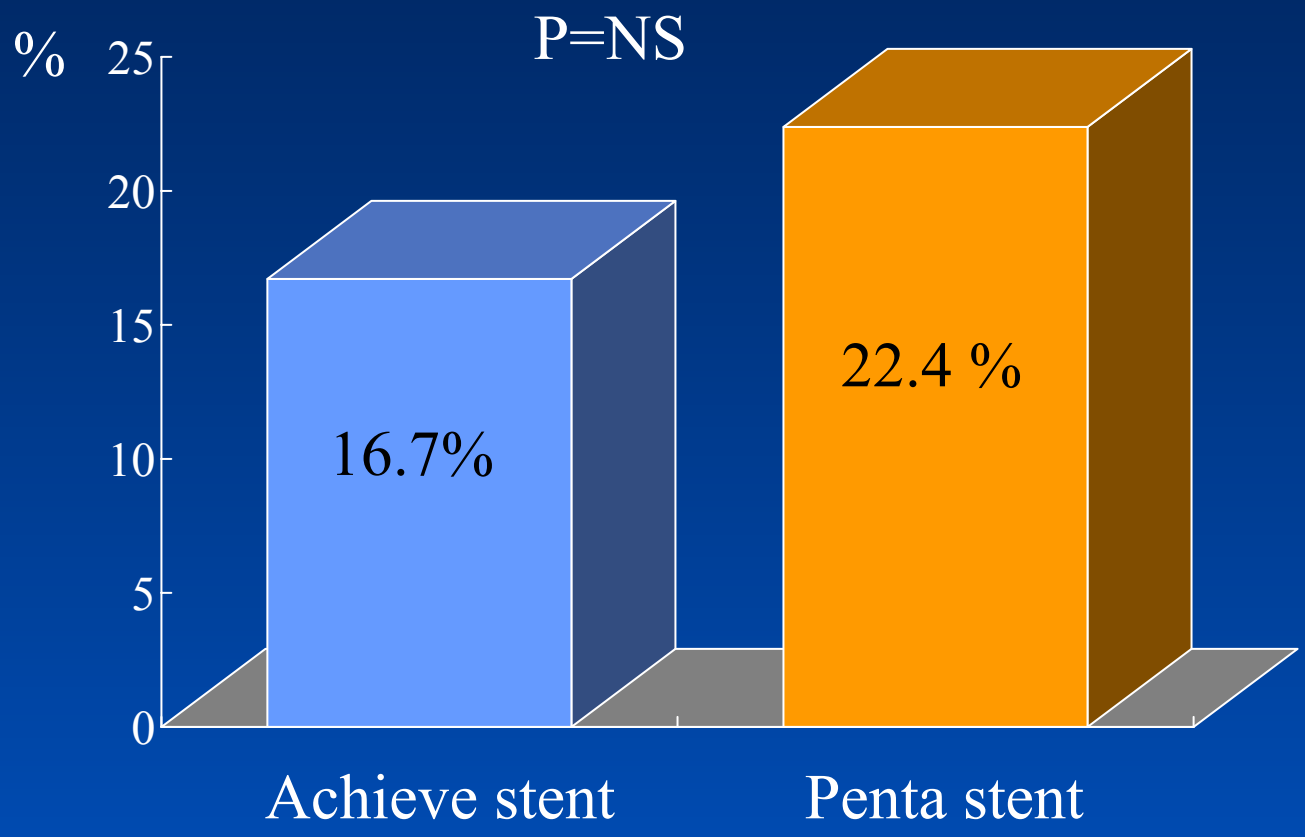
DELIVER : 9-Month Death, MI



Control: 1 (0.2%) late SAT

Achieve: 1 (0.2%) late SAT

DELIVER : Restenosis Rate



DELIVER

The complete data was not presented yet. However, It was reported that major clinical and angiographical end point were not met as powered.

We may speculate reasons why …

1. The drug paclitaxel and its concentration

We may speculate reasons why …

1. The drug paclitaxel and its concentration

It should be OK

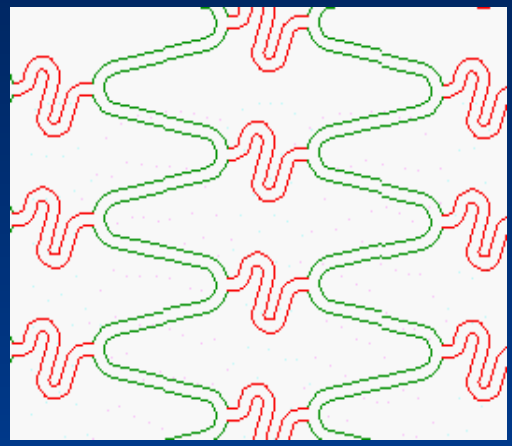
We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system

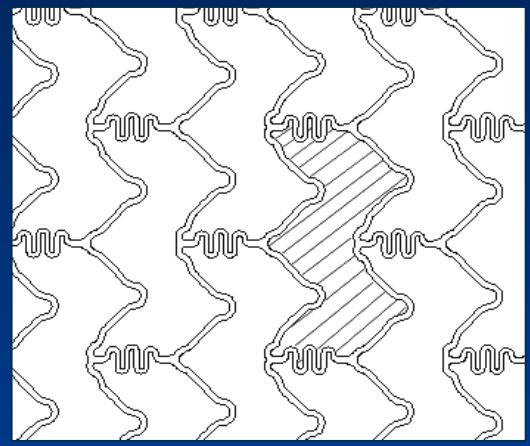
Optimal Stent Design

For Even Distribution of Drug

Open diamond design



Closed cell design



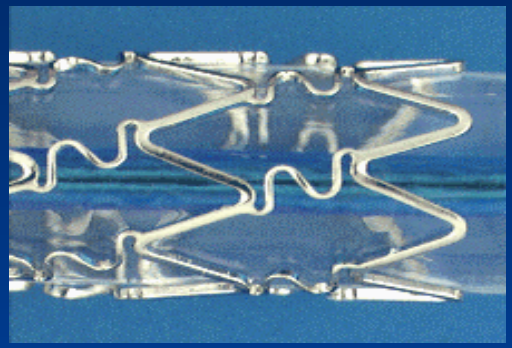
Corrugated ring cell design

Uneven distribution
With curved links

Even distribution
With curved links

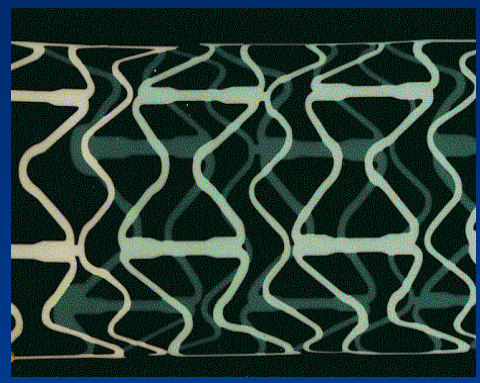
Comparison of Stents

Closed cell design

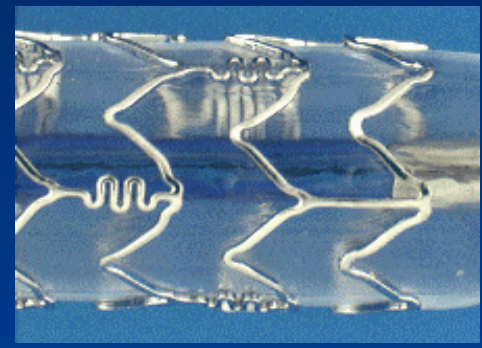


Bx Velocity
Sirolimus
Eluting stent

Corrugated ring cell design



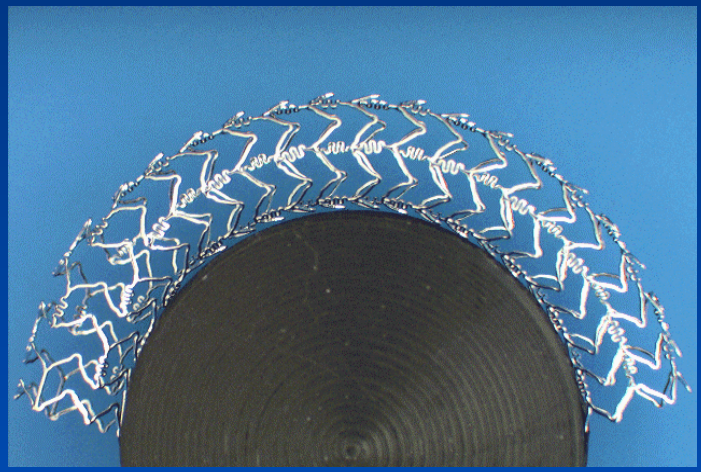
Supra G, V Flex
Non-polymer
Paclitaxel stent



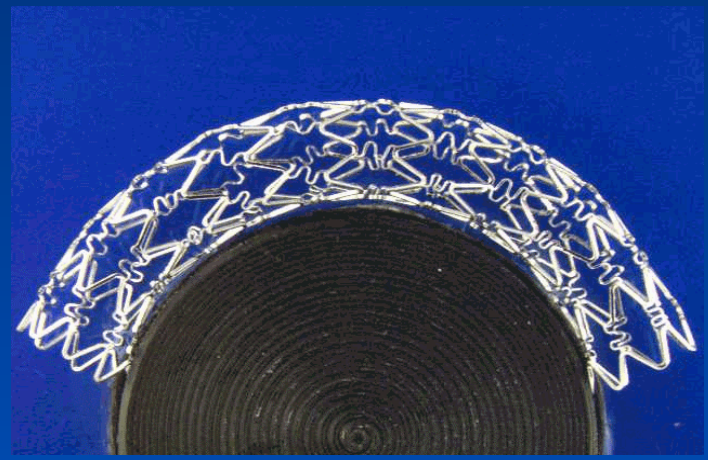
PENTA
Non-polymer
Paclitaxel stent

Comparison of Stents

	PENTA 3.0x18mm	BX Velocity 3.0x18mm
Unsupported Surface Area	3.85mm^2	3.29mm^2
Metal:Artery	14.16%	13.32%
Max. Circular USA	0.930mm^2	1.290mm^2



3.5x28mm PENTA



3.5x28mm BX Velocity

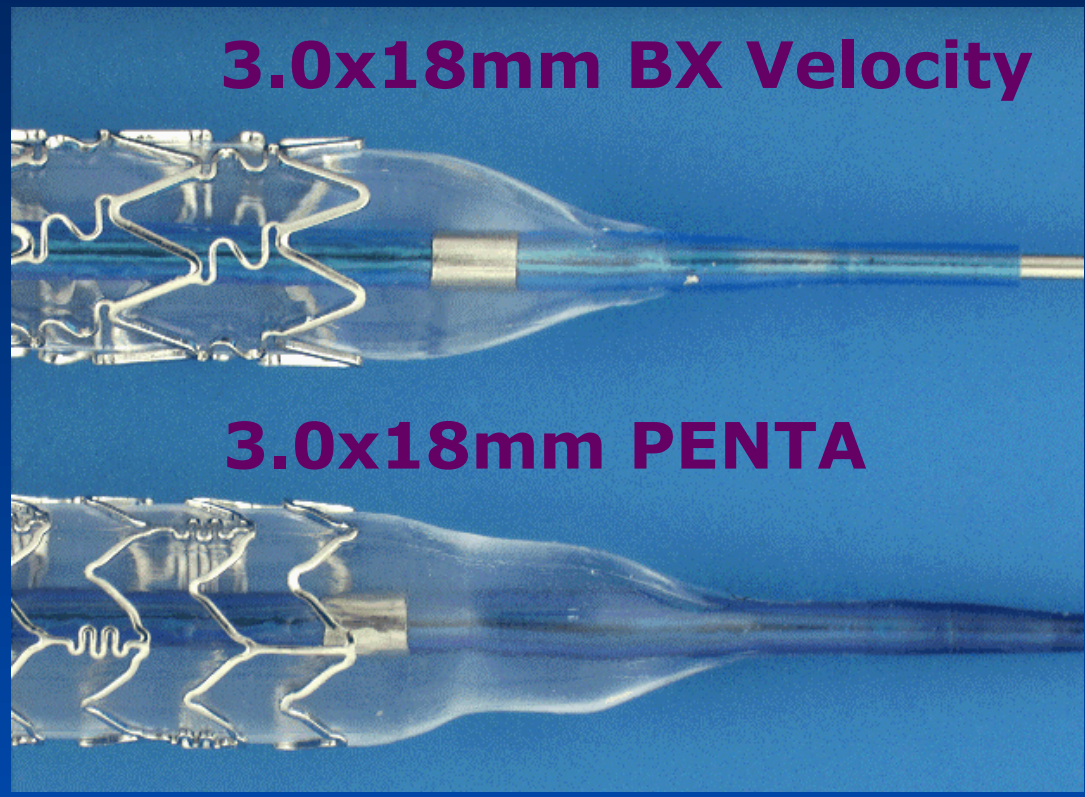
Diameter of Curvature: 15.33mm

Balloon Injury in Both Edges

Stent To Shoulder Distance

Mean Distal STS
= 1.333mm

Mean Distal STS
= 0.555mm



Less edge balloon injury…

We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system

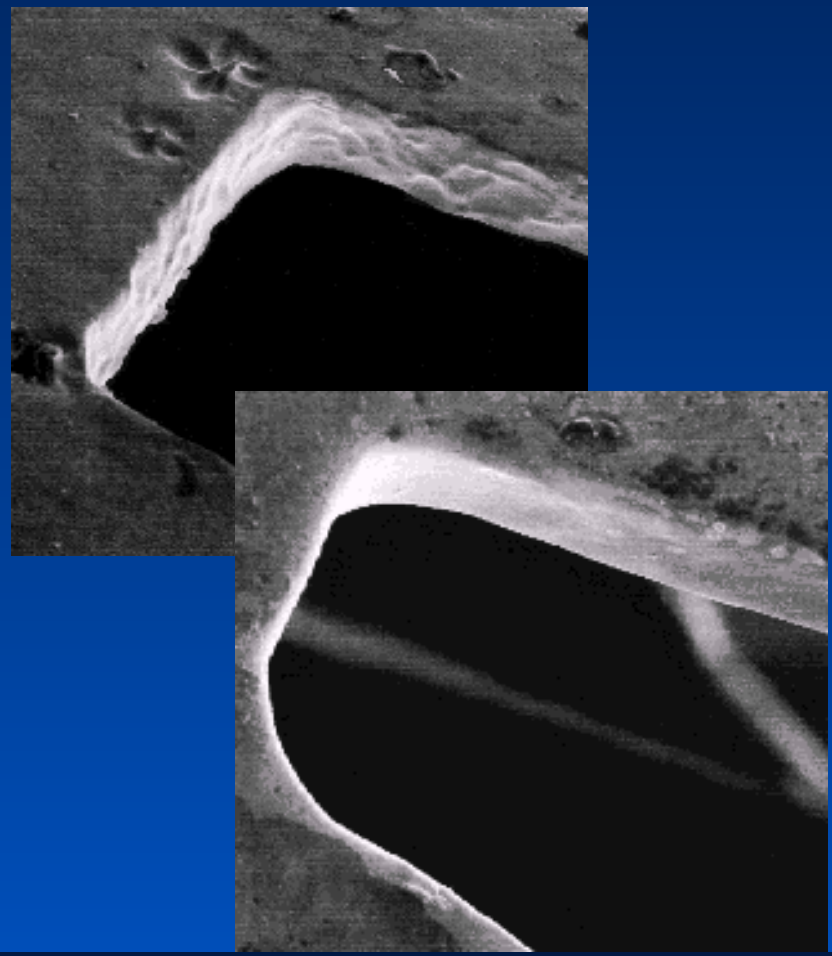
It should be OK

We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system
3. The manufacturing of drug coating and the release kinetics

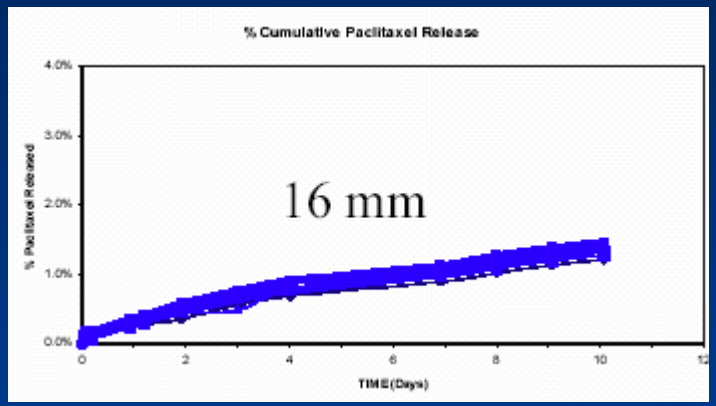
Why Polymer coating?

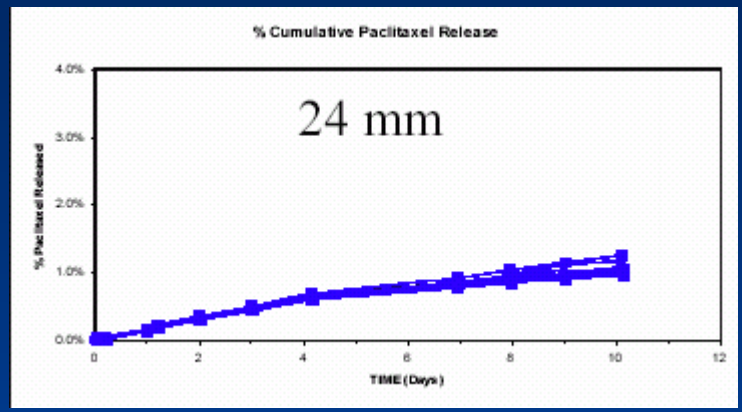
1. Consistent dosing
2. Controlled release kinetics
3. Structural integrity

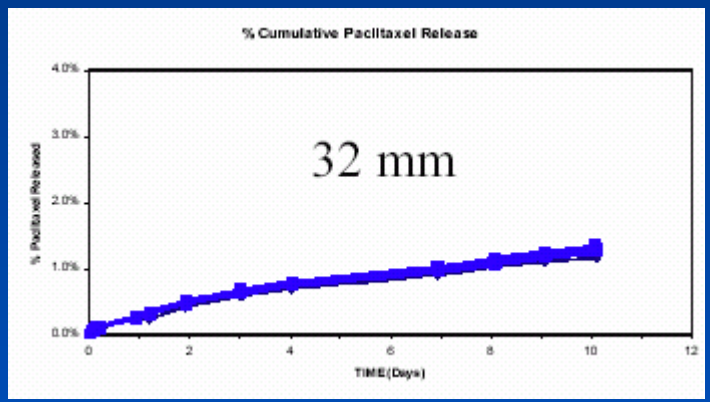


Why Polymer coating?

Reproducible release over time







From TAXUS trial

1.0 ug/mm^2, slow release
3 different lengths

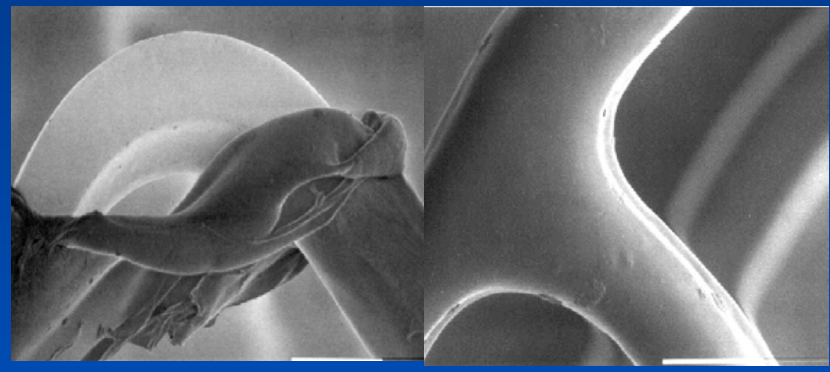
Why Non-Polymer Coating?

- **Less complex**
- **Less expensive**

Polymer coating leads to …

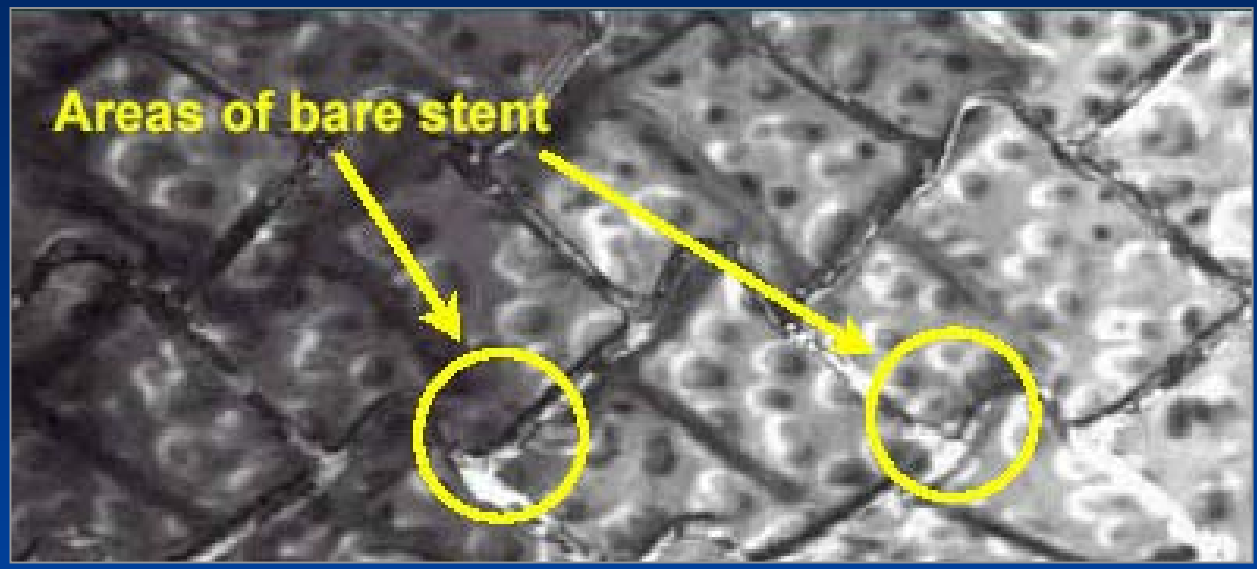
Initiation of tissue reaction

Cracking and Embolization



However,

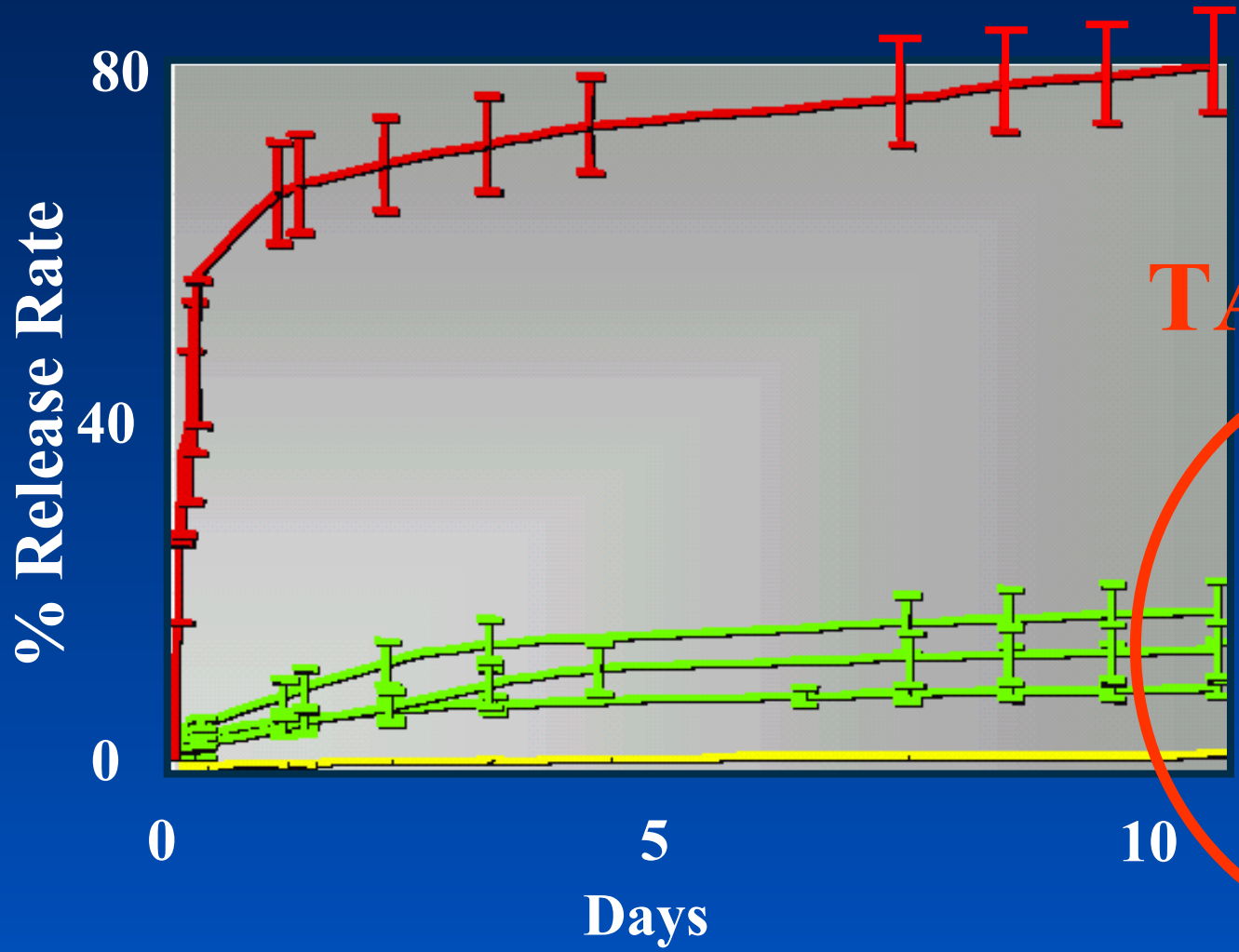
Non-polymer coating leads to ..



Up to 40% drug loss on expansion without a “carrier” in bench testing

Boston Scientific Polymer Coated stent

In vivo Paclitaxel Elution



Fast release

- 1 ug/mm² (108ug)

TAXUS trial

Moderate release

-4 ug/mm² (432ug)

-2 ug/mm² (216ug)

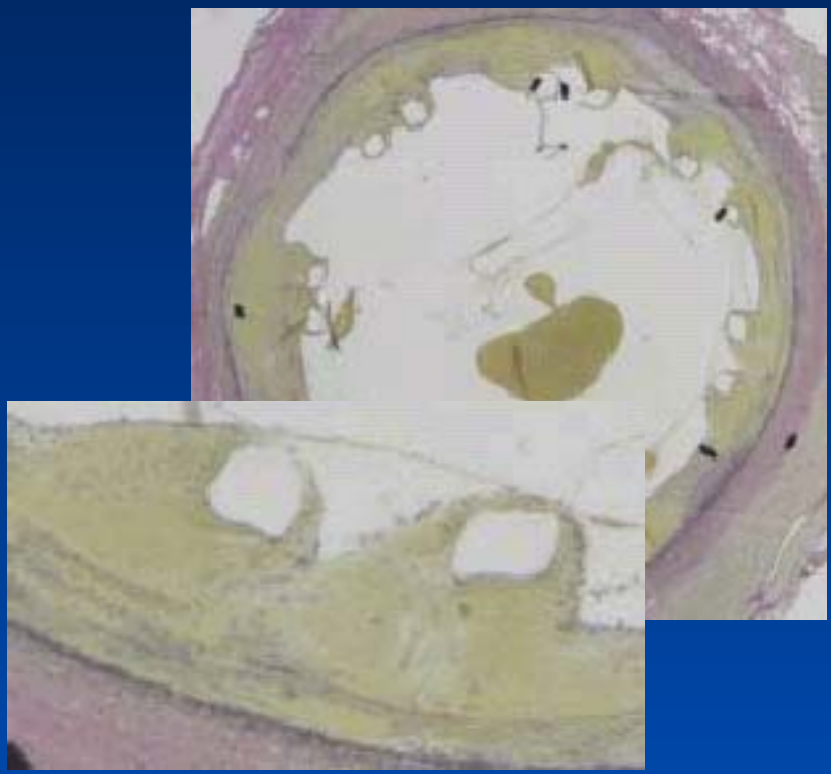
-1ug/mm² (108ug)

Slow release

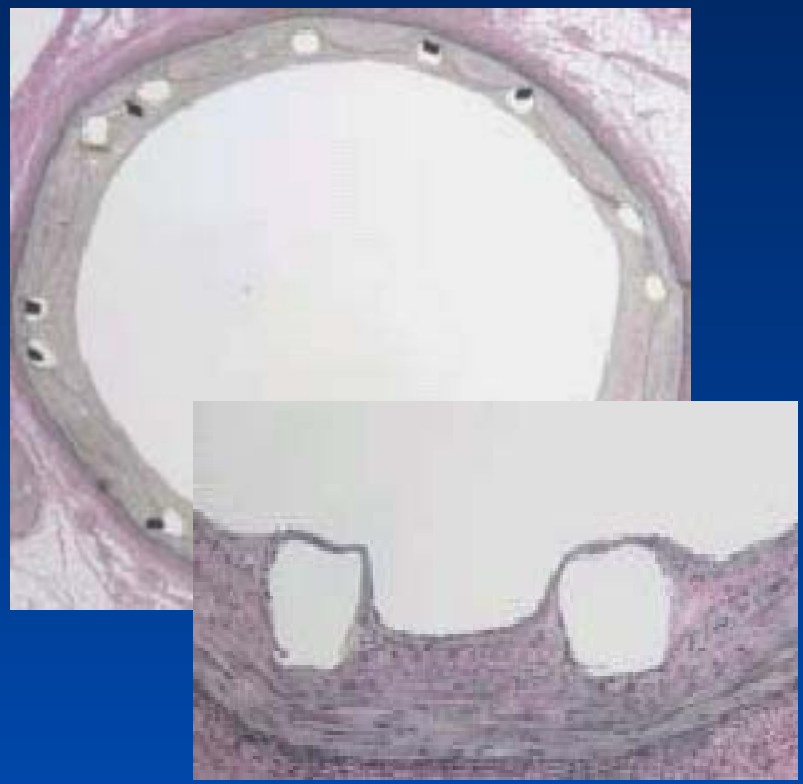
- 1 ug/mm² (108ug)

Vascular Inflammation

Fast release vs. Slow release



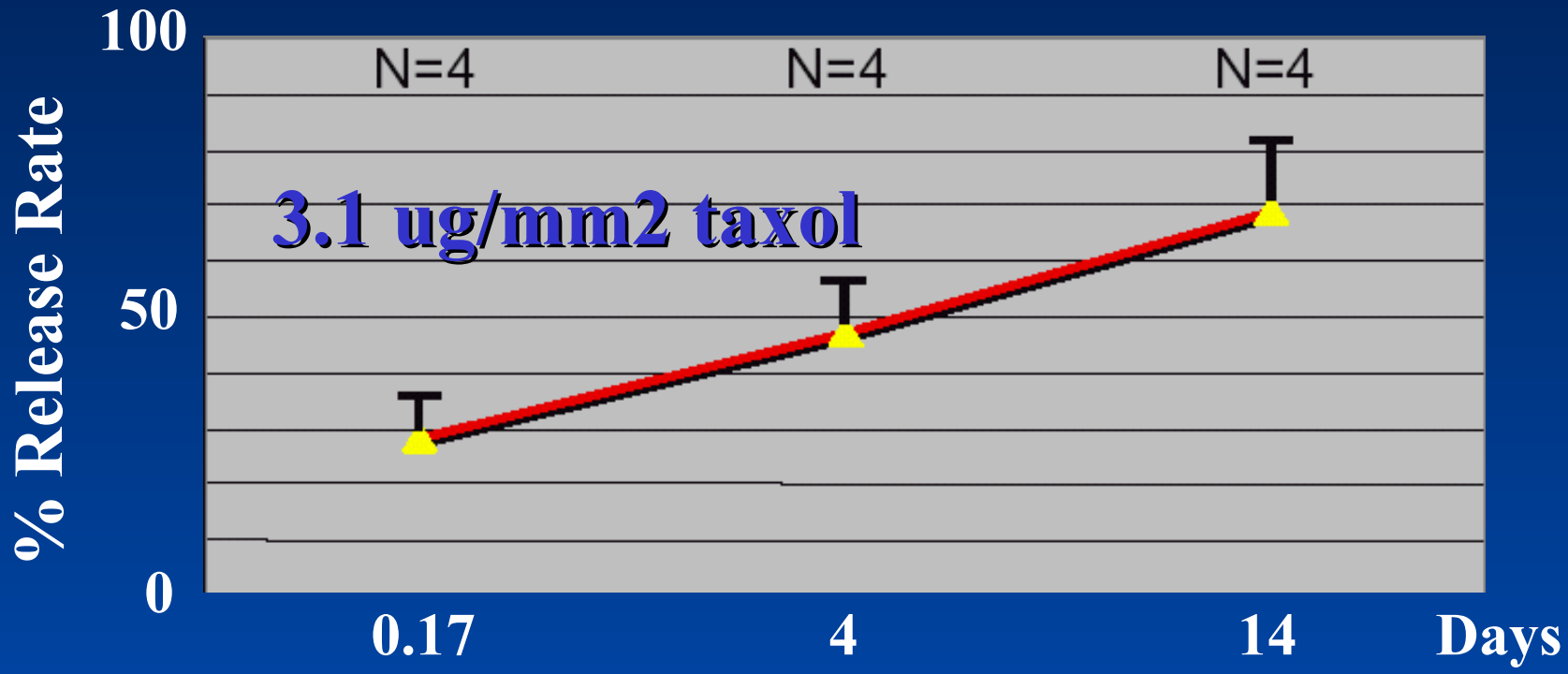
Fast release



Slow release

Non-Polymer SUPRA G stent (Cook)

In vivo Paclitaxel Elution



Faster Release ?

We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system
3. The manufacturing of drug coating and the release kinetics

Doubtful,

Doubtful…

1. Non-polymer surface modification technique simplifies the manufacturing of the drug coated stent, whereas it is difficult to guarantee the controlled release of paclitaxel.
2. Based on the *in vivo* release kinetics, the Cook non-polymer surface modification technique might release the paclitaxel faster than the polymer coated stents.

Doubtful…

3. Clinical studies about non-polymer paclitaxel eluting stent have a substantially different dose, delivery system and pharmacokinetic profiles. As a result, the diversity may lead to different outcomes.
4. Determinant of the right dose drug concentration for coating might be required for expected clinical outcomes.

Why Polymer ?

	Polymer coating	Surface modification
Potential Advantages	• Consistent dosing • Controlled release	• Less complex • Less expensive
Potential Disadvantages	• Difficulties with loading, sterilization, and expansion • Inflammatory responses	• Drug retention and uniformity • Consistent release kinetics

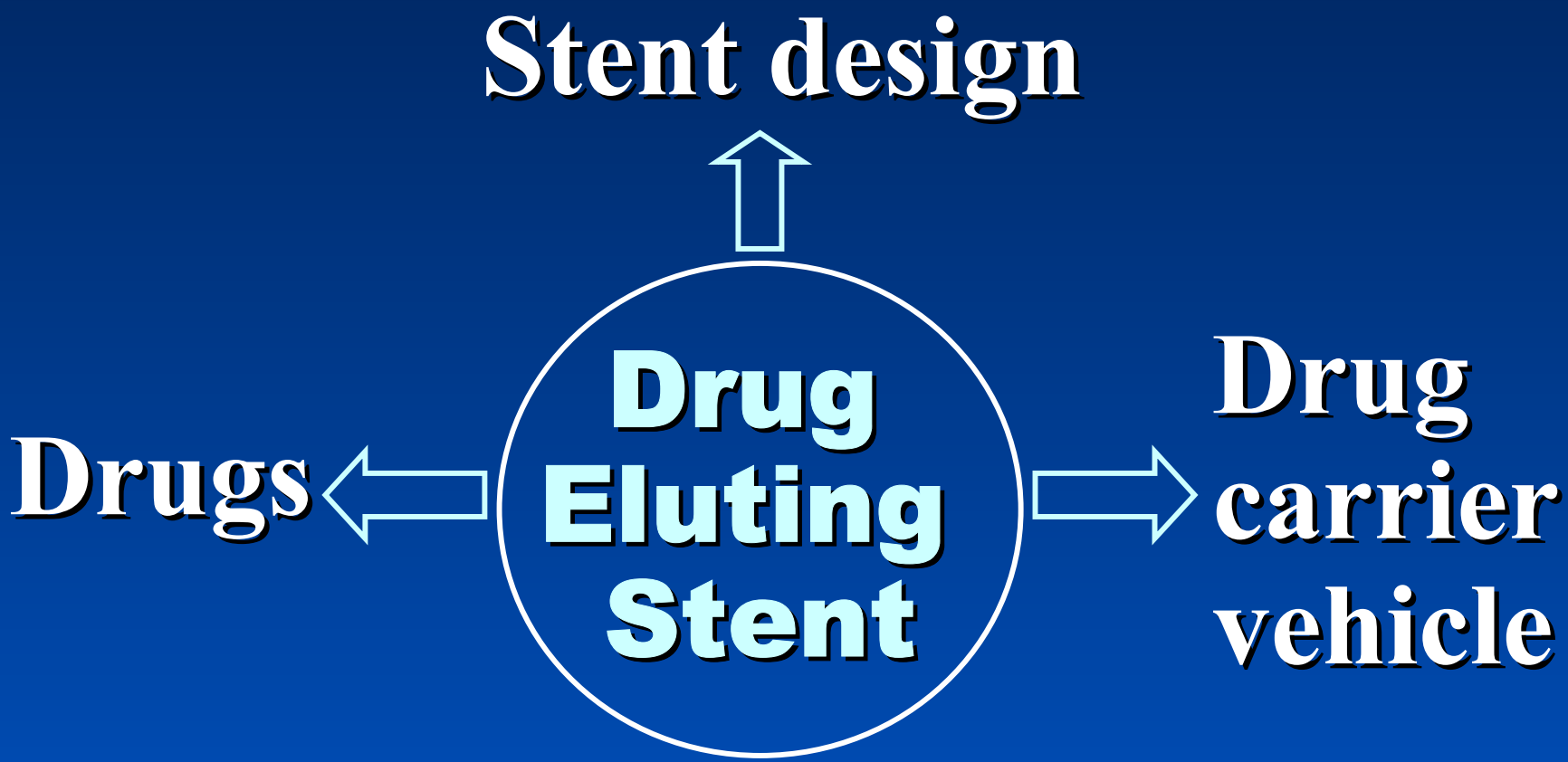
Efficacy of Paclitaxel Coated Stents

- Non-polymer coated stent …
  DELIVER trial give us doubt.

- Polymer coated stent….
  TAXUS trials give us trust.

Taxus vs. Cypher

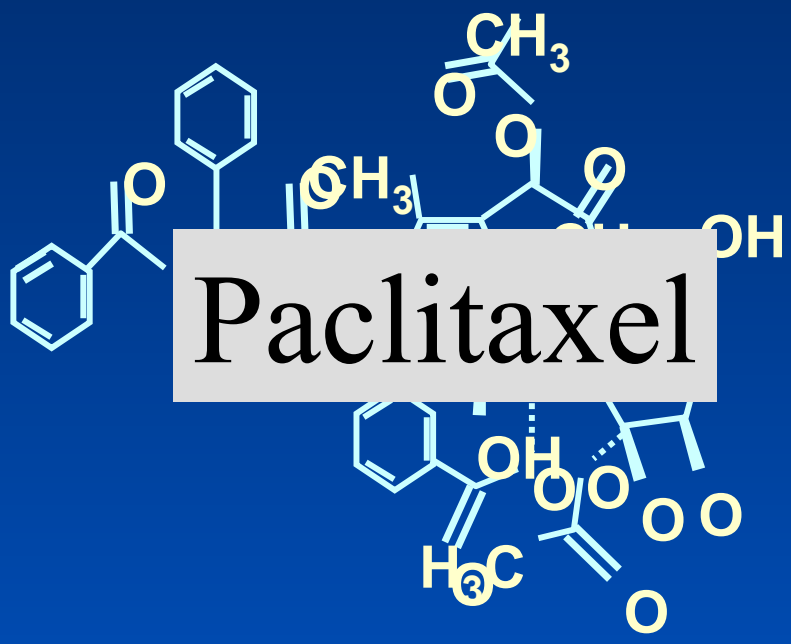
Which stent would be better ?



Taxus vs. Cypher

Which stent would be better ?

Drug

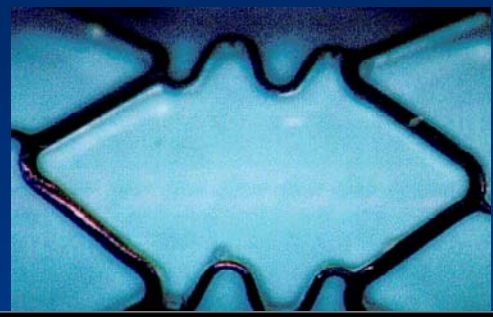


Taxus vs. Cypher

Which stent would be better ?

Stent

Express

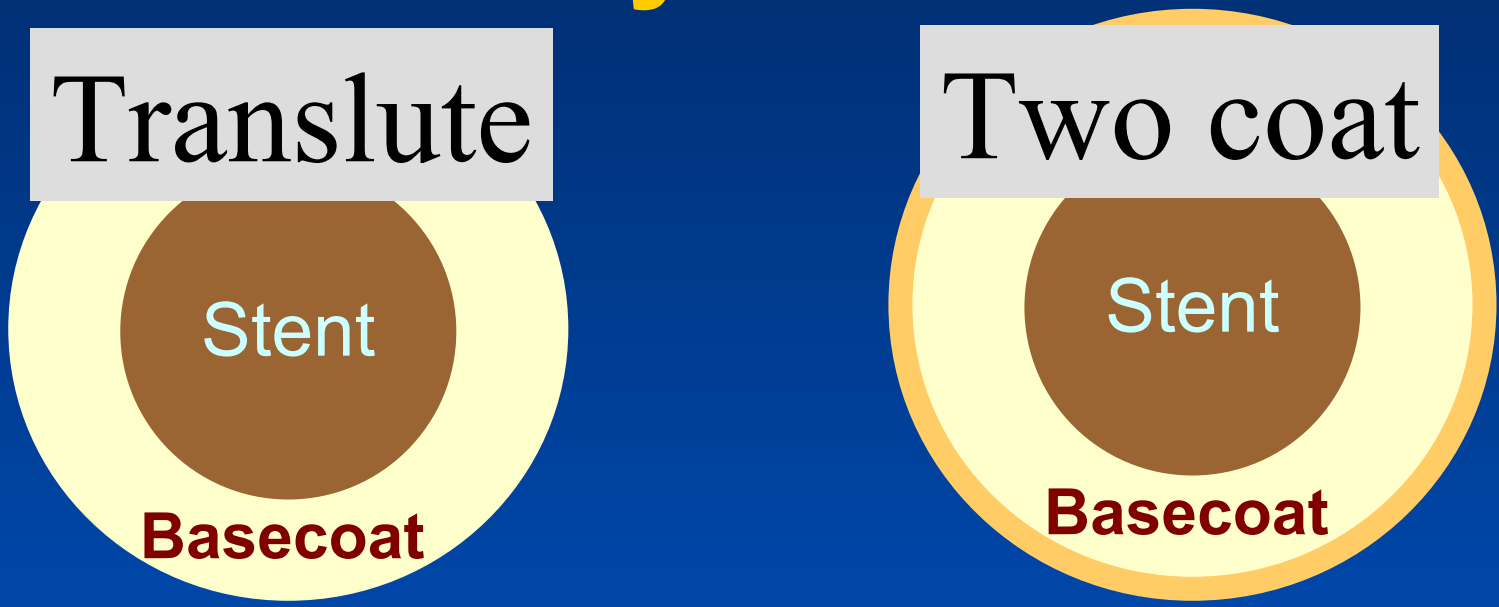


Bx velocity

Taxus vs. Cypher

Which stent would be better ?

Polymer



Taxus vs. Cypher

Which stent would be better ?

Based on Current data base

No clear Difference…

Taxus vs. Cypher

Then, Which will be the winner ?

- **Preoccupation of Cypher in the market,**
  depending on the management skill of BSC
- **Price,** *depending on* the policy of each company
- **Stent design,** *depending on* lesion characteristics
- **Doctor's preference,**
  depending on sponsorship…^-^