First Human Experience with a PC-coated Angiopeptin-eluting Stent

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Interventional Cardiologist VS Cardiac Surgeon Today

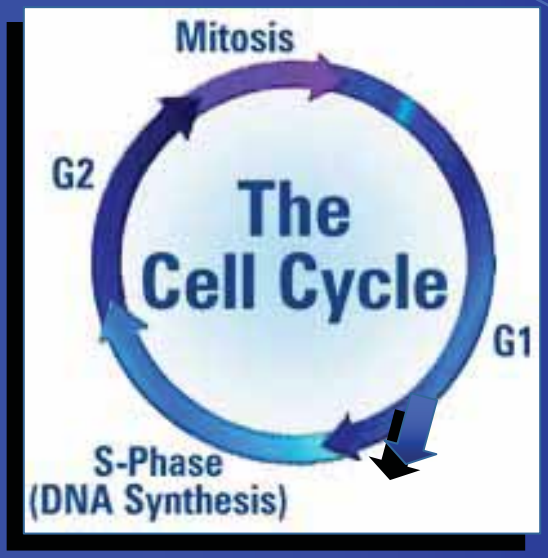
21% reduction in referrals for cardiac surgery

Ferreira AC et al. Ann Thorac Surg 2003; 75; 485-89

Targets for Restenosis Prevention after Coronary Stenting

PROLIFERATION

- Radiation
- Sirolimus
- Paclitaxel
- Angiopeptin
- Everolimus
- ABT-578
- Tacrolimus
- MPA/MMF
- Cyclosporin
- Resten NG
- c-myc Anti-sense
- Actinomycin D



MIGRATION

- MMPI (Batimastat)

PLATELET ACTIVATION

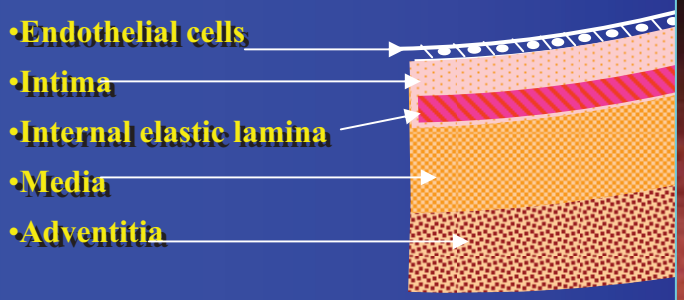
- αvβ3

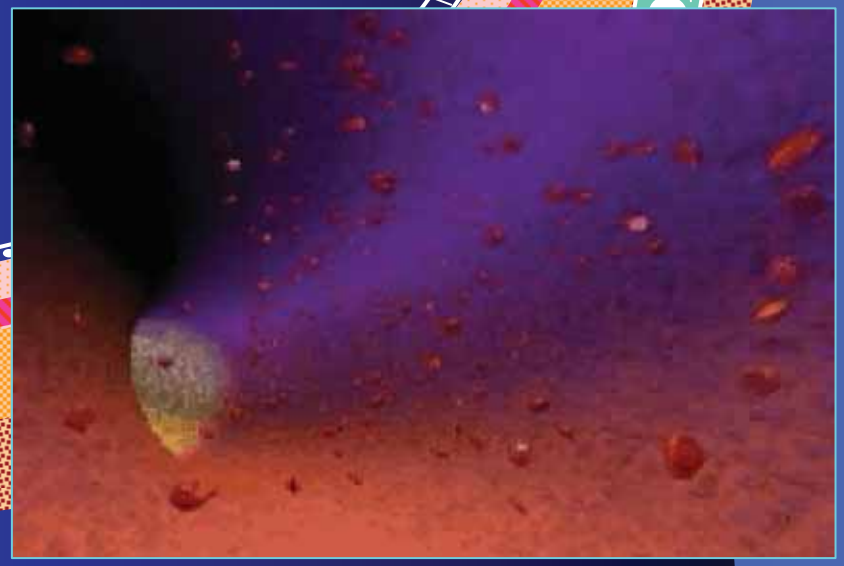
INFLAMMATION

- Dexamethasone
- Bisphosphonate

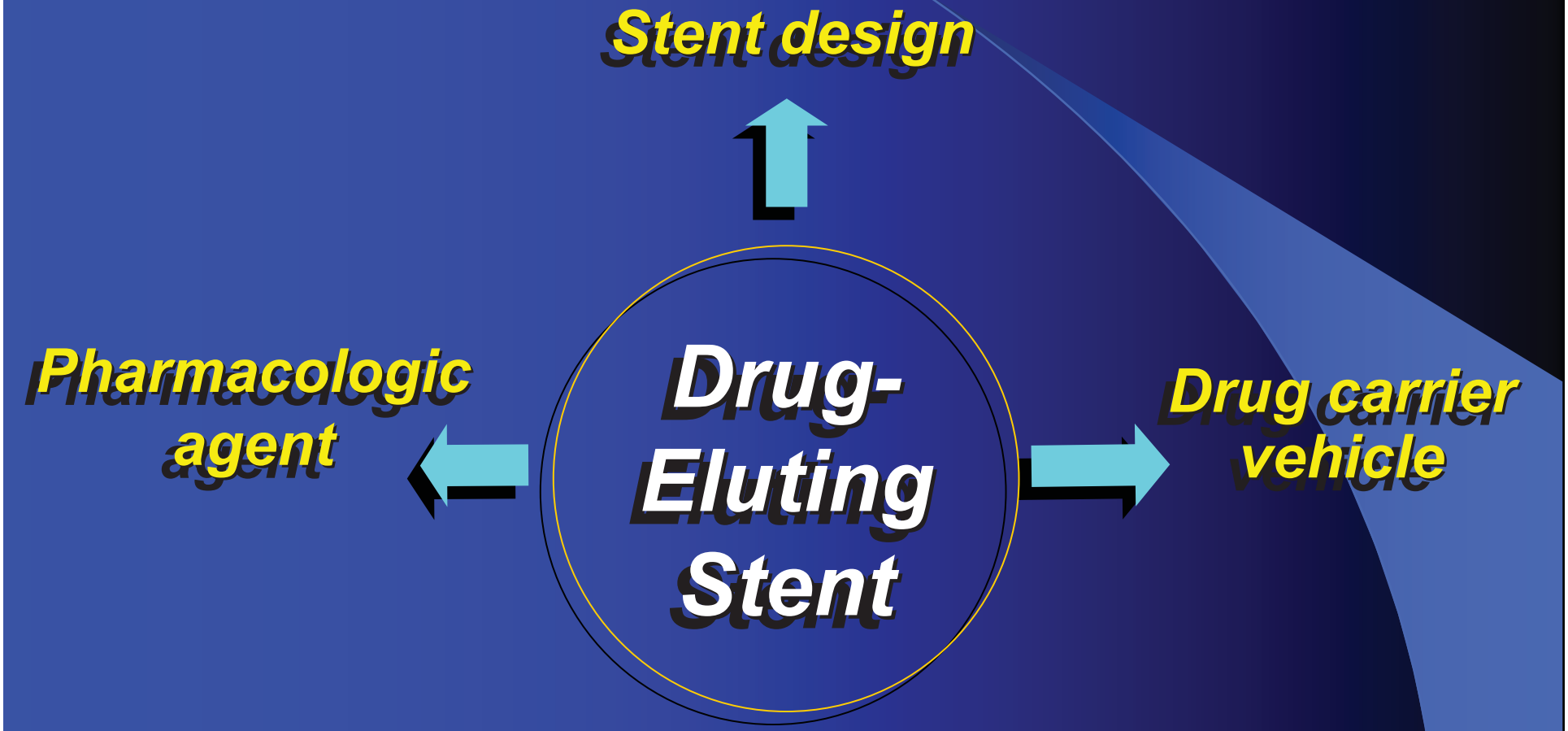
HEALING

- VEGF
- 17-β estradiol
- EPCs

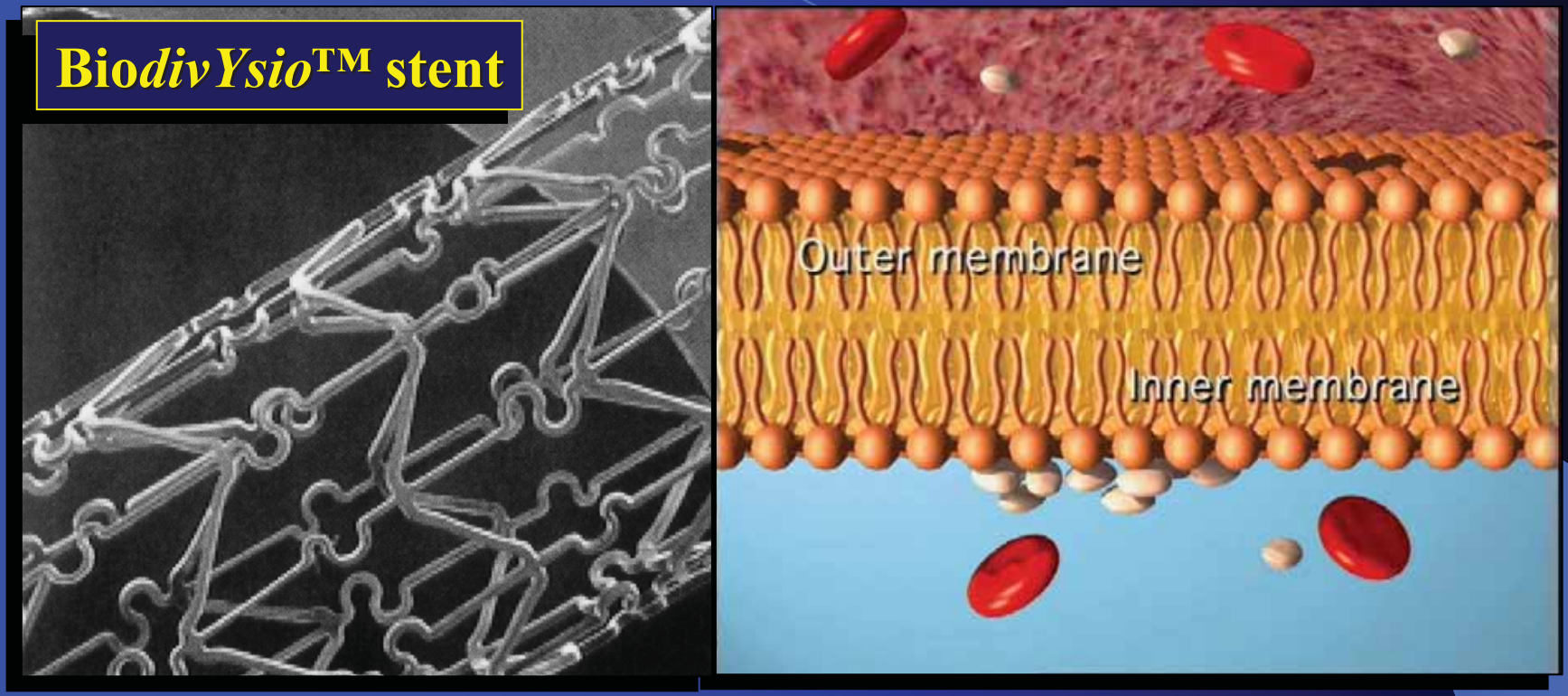




DES-Three Component System

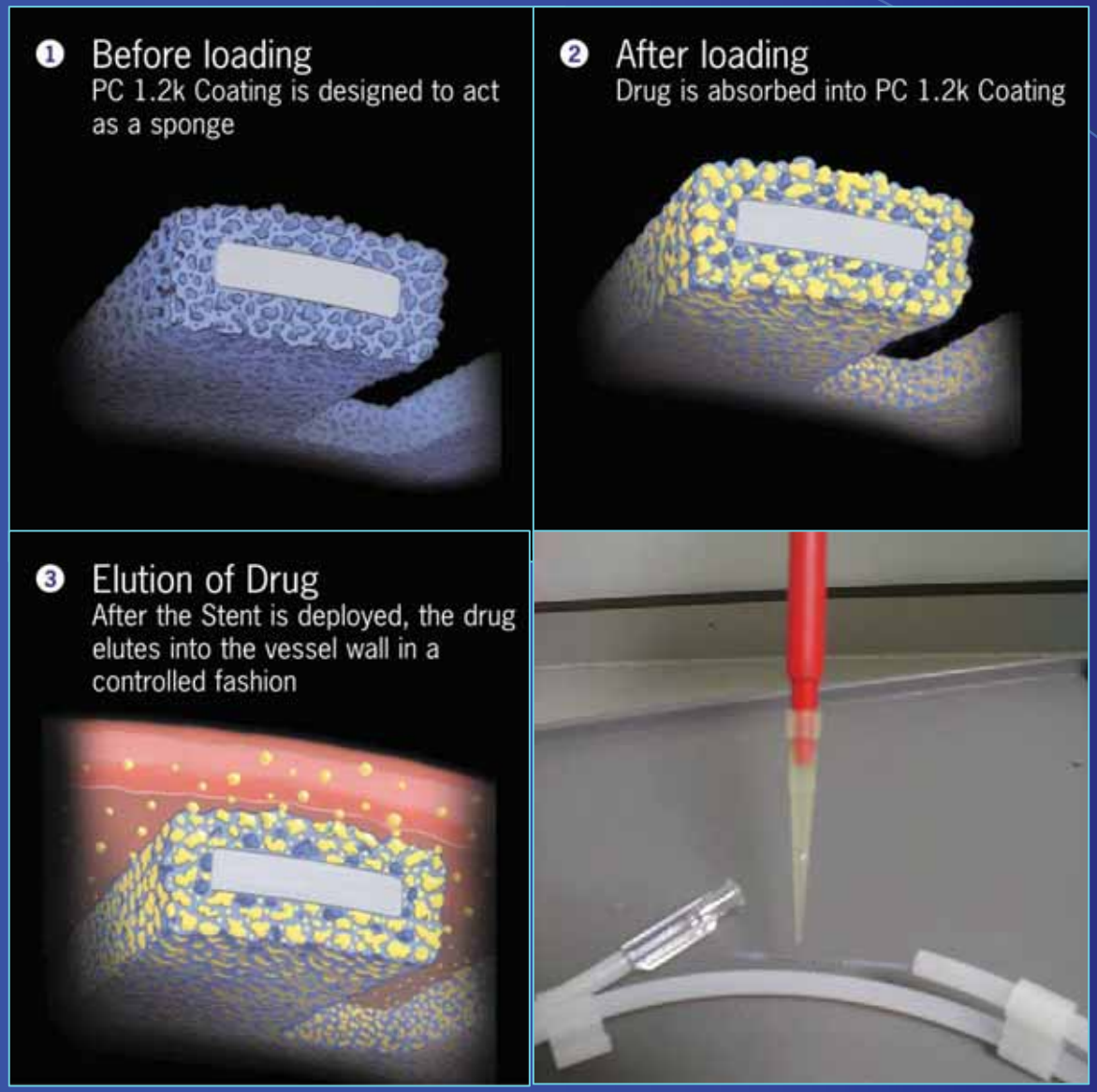


Phosphorylcholine (PC) Coating



- Phosphorylcholine is a synthetic copy of the outer membrane of a red blood cell.
- Over 90% of the phospholipid bilayer in the outer membrane contain the PC headgroup

Phosphorylcholine LDD "sponge" coating



Advantages of PC-Coating

- **Does not elicit an inflammatory response**
- **Acts as a reservoir for drug elution**
- **"On-site" loading of novel agents**
- **Elution duration over two weeks**

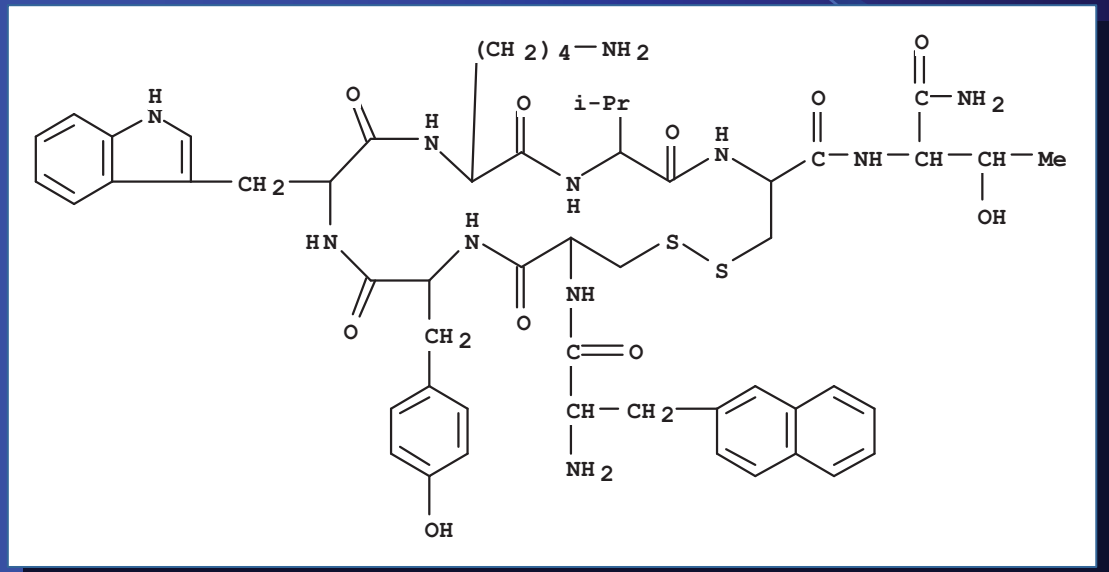
DES Trials Using the PC Platform

- Batimastat-Matrix Metalloproteinase Inhibitor (MMPI): BRILLANT & BATMAN Trials
- Dexamethasone: STRIDE study in Belgium
- Angiopeptin: Pilot Study in Hong Kong
- 17-Beta Estradiol: EASTER Trial
- ABT-578 (Medtronic AVE PC-coated Driver Stent): Endeavor Trial

Structure of Angiopeptin

Synthetic Cyclic Octapeptide Analogue of Somatostatin

D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2



- Plasma half-life = 90 minutes
- Molecular weight = 1096 daltons
- Both hydrophilic and lipophilic

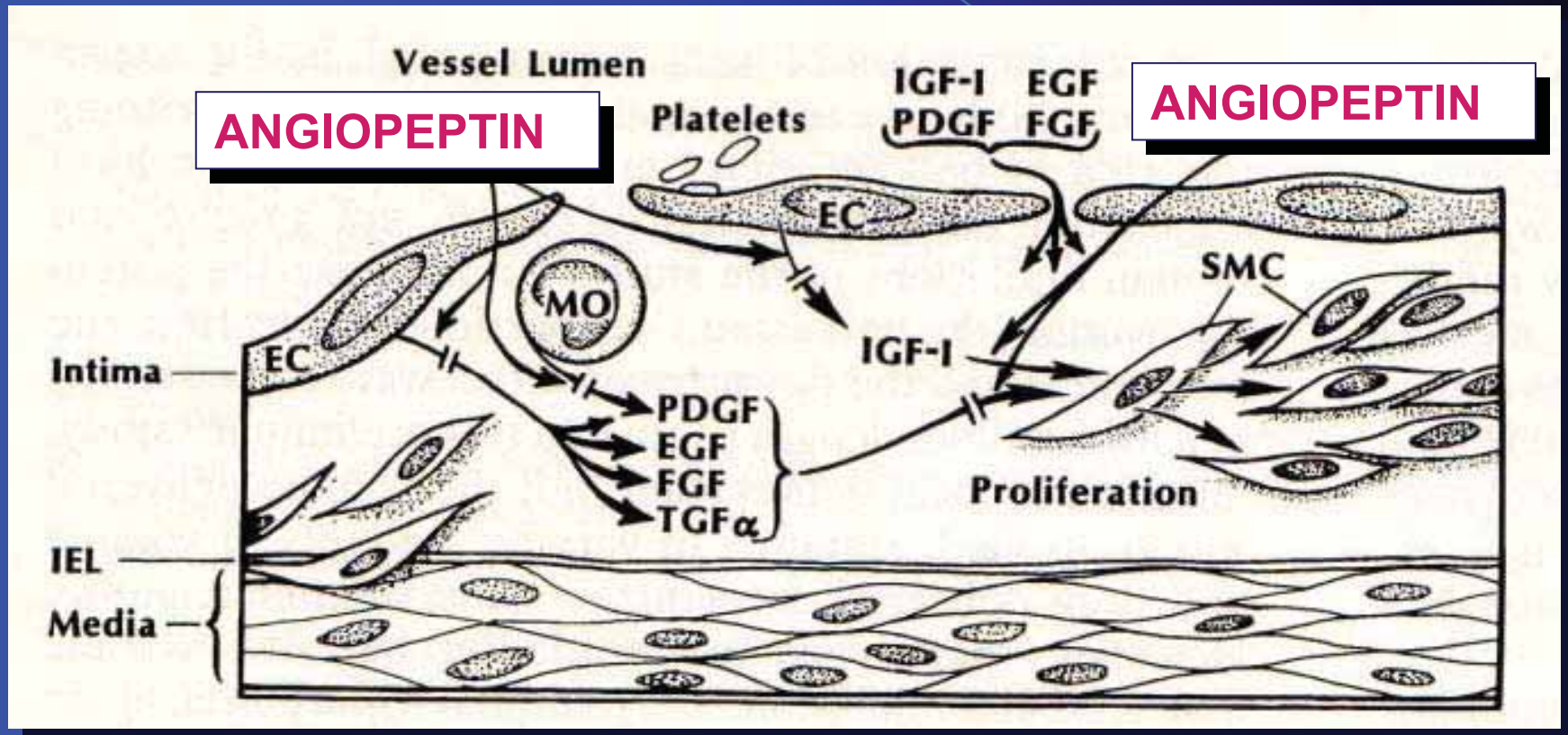
Generic:

Lanreotide (Beaufour Ipsen, UK)

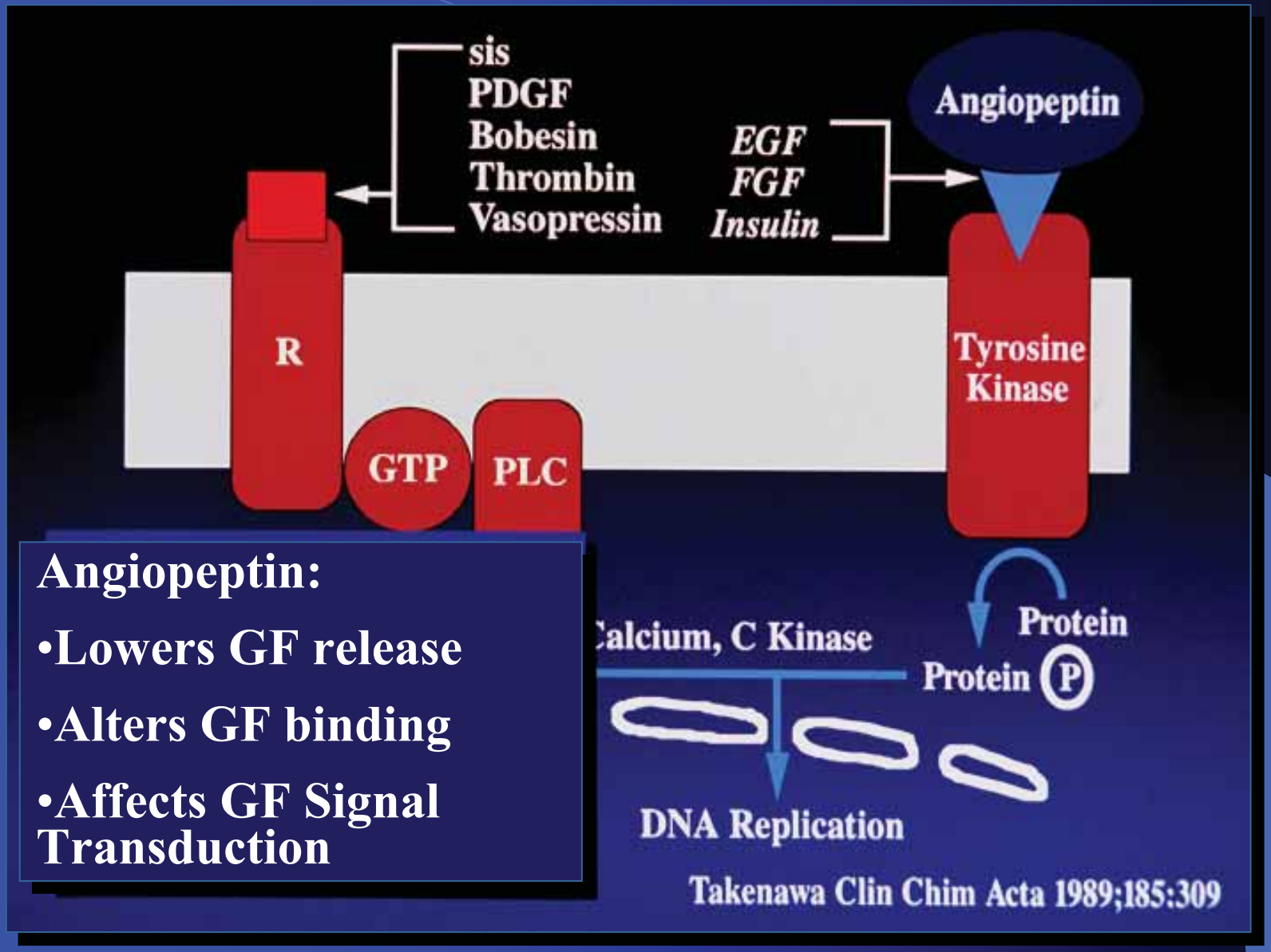
Mechanism(s) of Action

- Inhibits VSMC proliferation through altering the production and release of several growth factors including IGF, PDGF, b-FGF and EGF
- Activation of a membrane-bound phosphatase, which dephosphorylates tyrosine kinase
- Inhibits VSMC migration through G-protein mediated pathway
- Promotion of neo-endothelial function
- CYTOSTATIC-inhibits mitogen-induced cellular proliferation at G1 checkpoint
- Lack of local toxicity

Postulated Sites of Action by Angiopeptin



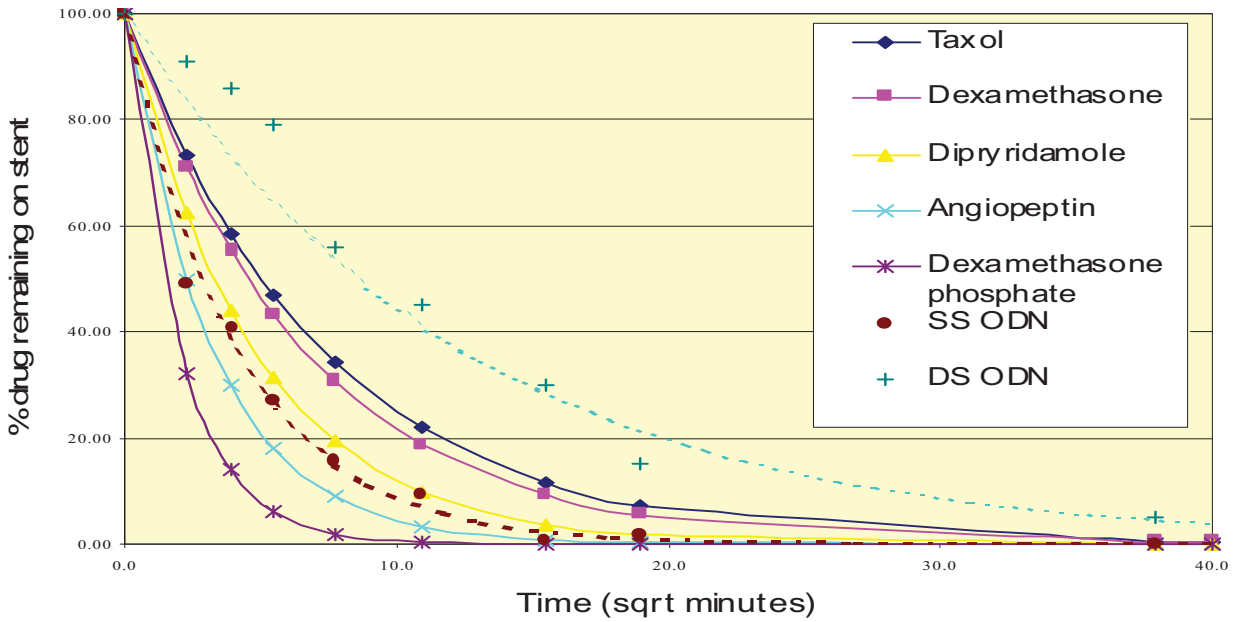
Hong et al. Circulation 1997; 95: 449-454



Angiopeptin:

- **Lowers GF release**
- **Alters GF binding**
- **Affects GF Signal Transduction**

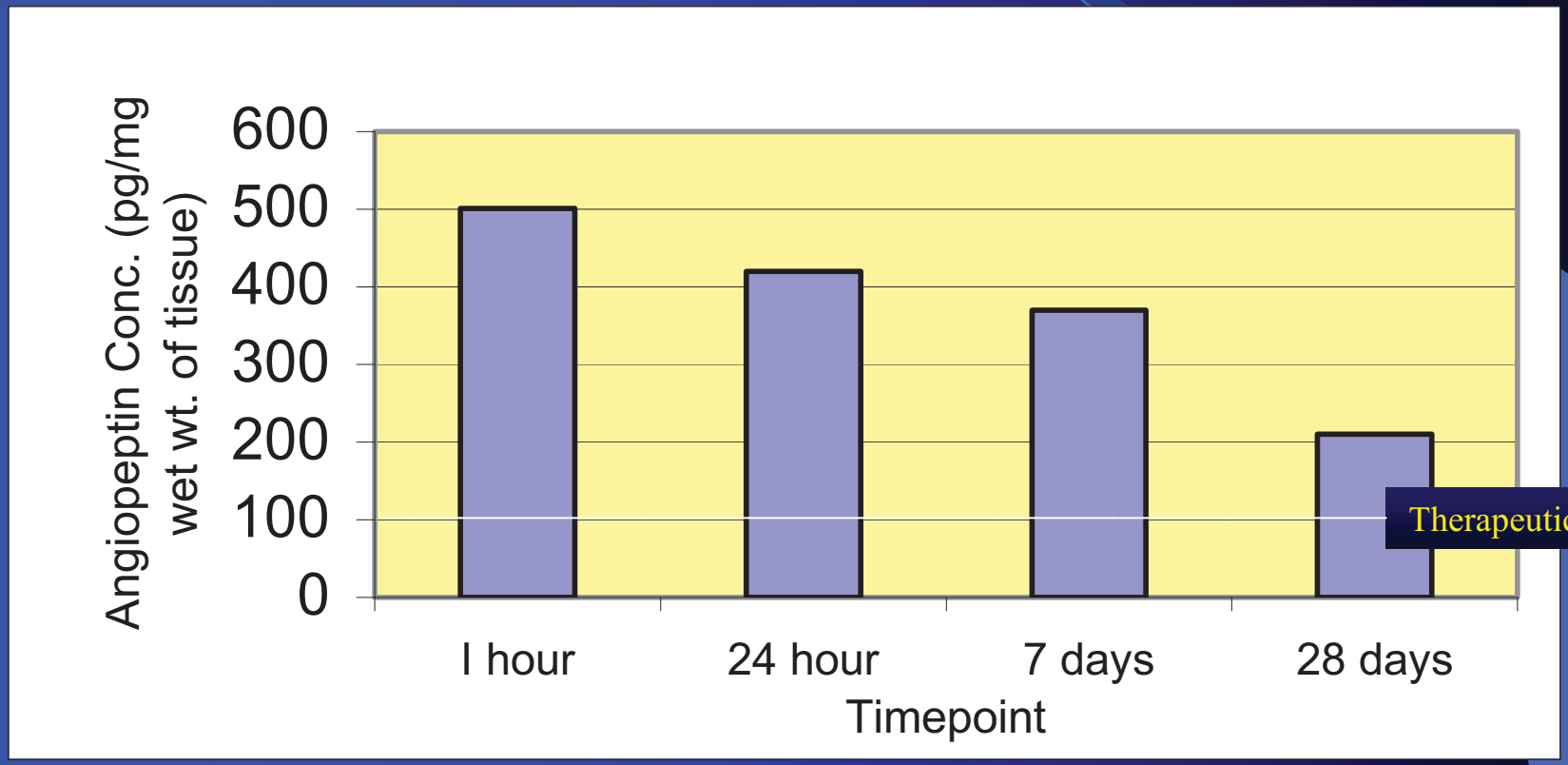
Comparative Release Studies (In-vitro)



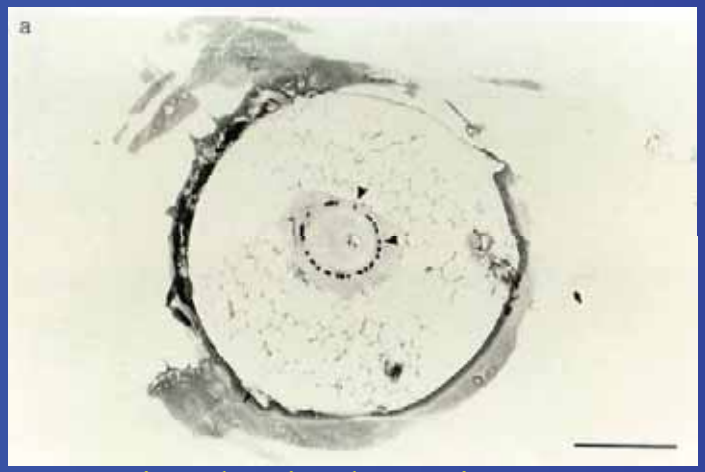
In-Vivo Delivery Efficacy of Angiopeptin from Bio*divYsio* DD PC Stent

- Radio-labelled Angiopeptin (I^{125})
- Loaded from 1mg/ml solution - 10µg/stent
- Porcine (LAD) coronary model (NGH Sheffield)
- 1 hour, 24 hours, 7days & 28 days, two animals per time point
- Angiopeptin (I^{125}) levels determined in blood, urine and tissue
- LAD sectioned for histology and auto-radiography

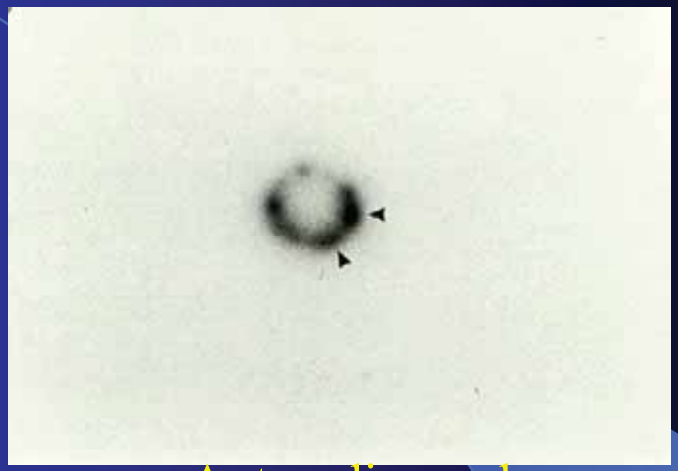
[^{125}I]-Angiopeptin Concentration within the Central Region of the Left Coronary Artery



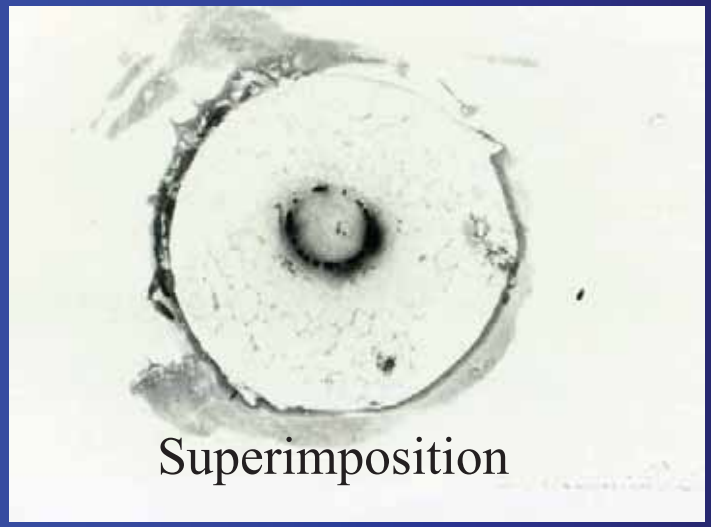
Histology and Autoradiography of Angiopeptin Loaded Bio*divYsio* DD PC Stent



Histological section



Autoradiograph



Superimposition

28 Days

Summary of In-vivo Findings

- Angiopeptin was locally delivered to the LAD in the porcine model at time-points *up to 28 days* from the Bio*divYsio* DD stent

- Angiopeptin was detected in blood at 1 and 24 hours, however, after 7 days none was detected

- Negligible amounts of angiopeptin were detected in tissues outside of the heart

Animal Studies (POSITIVE)

Animal model	Injury	Reference
Rat carotid	Balloon	Lundergan, et al. *Atherosclerosis* '89 :80:49-55
Rabbit iliac	Balloon	Foegh, et al. *J Vasc Surg* '94:19:1081-91
Rabbit aorta	Balloon/porous balloon	Hong, et al. *Circulation* '93:88:638-48

Animal Studies (POSITIVE)

Animal model	Injury	Reference
Porcine coronary	Balloon	Santoian, et al. *Circulation* ’93:88:11-14
Porcine coronary	Stent	Hong, et al. *Circulation* ’97:95:449-454 & *CAD* ’97:8:101-104
Porcine coronary	Stent (drug-coated stents)	De Scheerder, et al. *J Invas Cardiol* ’96:8:215-222

Reduction of In-Stent Restenosis

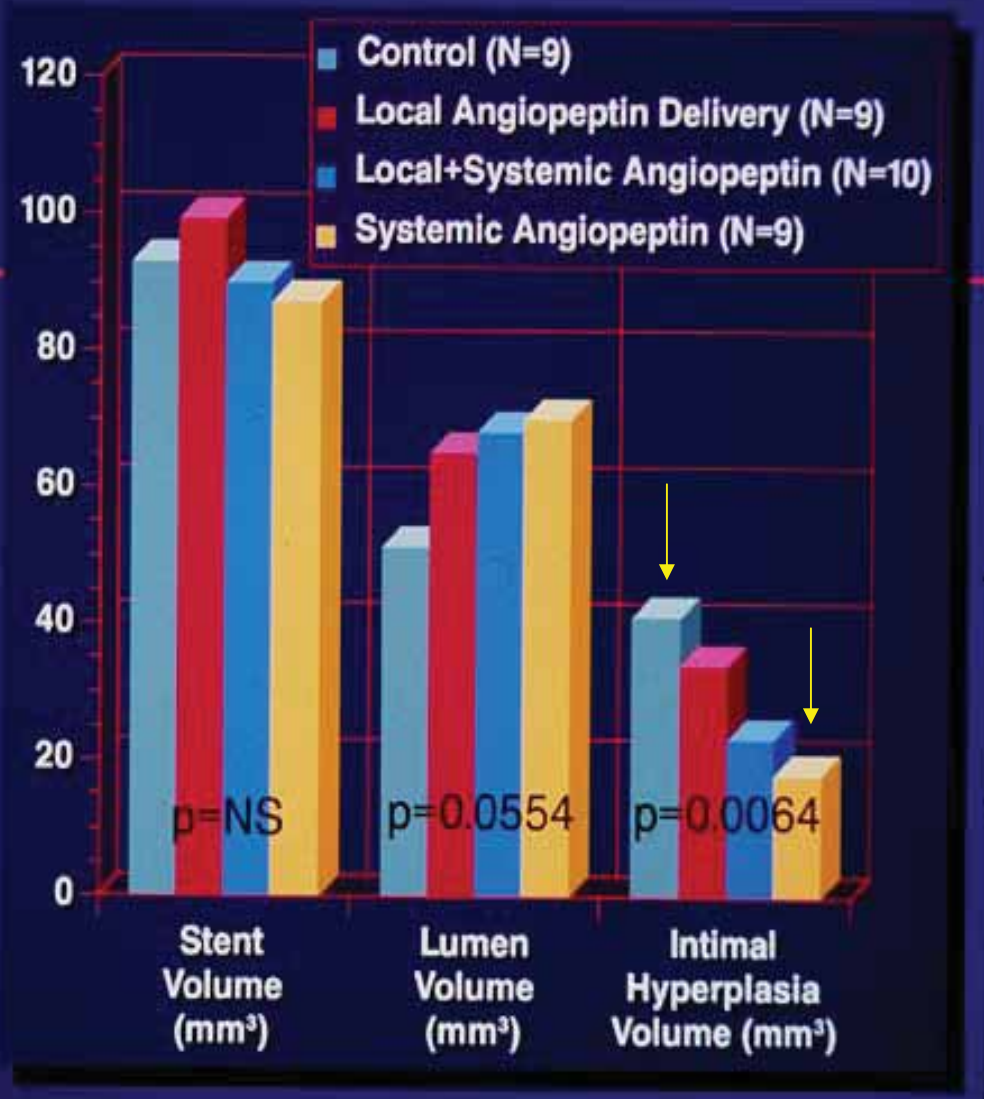
- Stent: Palmaz-Schatz
- Design: (1) Controls (no Angiopeptin Rx); (2) Local AP Rx (200ug) via Dispatch catheter, (3) Systemic AP Rx (200ug/kg via Alza minipump); (4) Combined local and systemic Rx
- Animal model: Porcine coronary overstretch in-stent restenosis model (N= 10/group)
- Results: Continuous systemic treatment significantly reduced in-stent neointima (~50%) compared with the controls

Hong et al. Circulation 1997:95:449-454

Hong et al. Circulation 1997; 95: 449-454

IVUS: Mechanisms of Restenosis

Systemic administration of angiopeptin is capable of reducing intimal hyperplasia volume within stents by >50%



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Reduction of In-Stent Restenosis

- Stent: Palmaz-Schatz
- Design: (1) Controls (no Angiopeptin Rx); (2) Slow-release systemic AP Rx (20mg IM) (3) Systemic AP Rx (200ug/kg SC via Alza minipump)
- Animal model: Porcine coronary overstretch in-stent restenosis model (N= 10/group)
- Results: Both treatment groups had significantly reduced in-stent neointima (~60%) compared with the controls

Hong et al. Coron Artery Dis 1997:8:101-104

Angiopeptin-Coated Stent

- Stent: Wiktor stent
- Polymer: Poly(organo)phosphazene
- Angiopeptin: 250 ug/stent
- Release kinetics: > 1-week
- Animal model: Overstretch in-stent restenosis in porcine coronary arteries
- Results: Significant reduction in neointima by Angiopeptin (2.2 ± 0.6 vs 1.6 ± 0.7 mm, $p<0.01$ and 1 ± 0.5 mm^2 vs 0.4 ± 0.3 mm^2, $p<0.01$)

De Scheerder et al. J Invas Cardiol 1996;8:215-222

Negative study

Angiopeptin-eluting stents: observations in human vessels and pig coronary arteries.

Armstrong J et al, J Invasive Cardiology 14(5): 230-238, 2002

- ***Delivery of angiopeptin from drug delivery PC-coated stents is safe, but does not lead to a significant reduction in neointimal growth at 28 days within the parameters of the study***

Limitations:

- Non-overstretched Porcine Coronary Model:

  -unable to bring out the difference of NIH between treatment and control groups
- ex-vivo human SVG: may not be a relevant surrogate

FIM study of Angiopeptin-eluting PC-coated stent

- 14 patients (16 lesions) underwent Angiopeptin-eluting stent implantation
- The mean age was 63.2±8.5 yrs (47-75 yrs)
- 50% of the patients were diabetic
- Clinical follow-up: 30 Days, 3, 6, 9, 12 and 24 months
- Angiographic & IVUS follow-up at 6 months

N.B. Physician-driven program

Stents With Angiopeptin Study

Primary (Clinical) Endpoint:

- 6 months Target Vessel Failure (TVF)

Secondary Endpoints:

- Angiographic:

  6 months binary restenosis, late lumen loss and late loss index

- Volumetric Intravascular Ultrasound (IVUS)

  6 months neointimal volume

- Safety Endpoints:

  6 –12 months MACE, up to 2 years

Major Inclusion Criteria

- Age > 30 and < 80 years of age
- Native de novo coronary artery lesion of ≥70% diameter stenosis by QCA.
- Target lesion must be located in a de novo native coronary artery between 3.0 and 4.0 mm in diameter and < 18 mm in length.
- The patient is hemodynamically stable before the treatment.
- The patient must agree to come for a 6-month angiographic follow-up and be available for clinical follow-up for at least 2 years.

Major Exclusion Criteria

- Imminent comorbid illness (i.e. life expectancy < 2 yrs)
- Acute coronary syndrome requiring emergent procedure.
- Acute myocardial infarction within 72 hours.
- Visualized thrombus by angiographic criteria.
- Left ventricular function < 20%.
- Unprotected left main disease
- Anticipated use of glycoprotein IIb/IIIa antagonist.
- Known allergy to aspirin, ticlid or plavix. OR unable to comply with prolonged combination anti-platelet treatment

Patients Demographics

• SEX	71.4%
• AGE	63.2±8.5 yrs
• DIABETES	50%
• Insulin-requiring	21.4%
• HYPERTENSION	71.4%
• HIGH CHOLESTEROL	50.0%
• HISTORY OF MI	14.3%
• Current smoker	14.3%

Protocol Flow chart

Informed consent obtained & patients deemed potentially eligible for procedure

↓

Predilation of the de novo target lesion with an under-sized balloon (preferably shorter than the anticipated stent length). Record the peak inflation pressure.

↓

Patient enrolled when all criteria, including angiographic, met

↓

Deploy Angiopeptin-coated stent. (Peak pressure recorded).

Perform Volumetric automatic pullback IVUS (Boston Scientific Atlantis 40MHz). If stent was not well apposed, further expand the stent with a non-compliant balloon, guided by IVUS

↓

1 month clinical follow-up

↓

6±1 months angiographic and volumetric IVUS follow-up

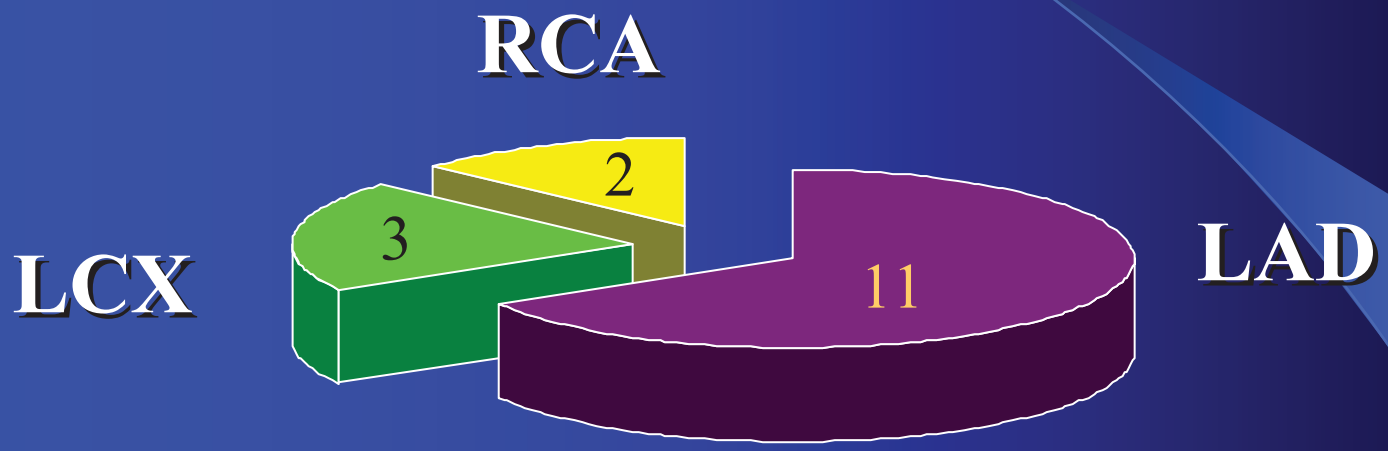
↓

1 and 2 year clinical follow-up

Adjunctive pharmacotherapy:

ALL patients receive Front-loaded Clopidogrel (Plavix®) 300mg p.o. at least 2 hours before the procedure followed by Clopidogrel 75mg QD for 90 days and Aspirin 100-325mg QD for life.

Lesion Location



AHA/ACC Lesion Morphology

Type B1	***56.2%***
Type B2	***43.8%***

Dosimetry

•Low dose:	22 µg/stent	13 lesions
•†High dose:	126 µg/stent	3 lesions

***†High dose:** Experimental data suggested that the local tissue concentration detected using the 126 µg angiopeptin-eluting PC-coated stent in a porcine coronary model was over **100-fold** that seen in the study performed by De Scheerder et al. in which significant reduction of neoinitma was observed*

In-Hospital Outcomes

Any MACE, %	0
Death, %	0
All MI, %	0
Q-wave	0
Non-Q-wave	0
Emergent CABG, %	0
TLR, %	0
Vascular Compl, %	0

Clinical Outcomes up to 1 year

Any MACE	0
Death	0
Q wave MI	0
TLR	0
TVF	0
SAT	0

Off-line Quantitative Coronary Angiographic Analysis (CAAS II QCA, Pie Medical, Netherlands)

Parameters *Pre-procedure*	*Low Dose (22μg) Angiopeptin-eluting stents N=13 lesions*	*High Dose (126μg) Angiopeptin-eluting stents N=3 lesions*
Reference vessel diameter	2.84±0.66mm	2.91±0.41mm
MLD	0.79±0.52mm	0.72±0.36mm
DS%	72.5±10.4%	76.2±8.6%
Lesion length	12.4±4.3mm	13.2±3.2mm

Off-line Quantitative Coronary Angiographic Analysis

(CAAS II QCA, Pie Medical, Netherlands)

Post-procedure	Low-Dose	High-Dose
Final MLD	2.88±0.52mm	2.97±0.33mm
Analysis segment	2.75±0.46mm	2.84±0.48mm
In-stent	2.82±0.49mm	2.89±0.36mm
Final DS%		
Analysis segment	4.0±8.2%	4.2±5.3%
In-stent	3.4±8.9%	3.2±7.7%
In-stent acute gain	1.97±0.52mm	1.99±0.47mm

Off-line Quantitative Coronary Angiographic Analysis

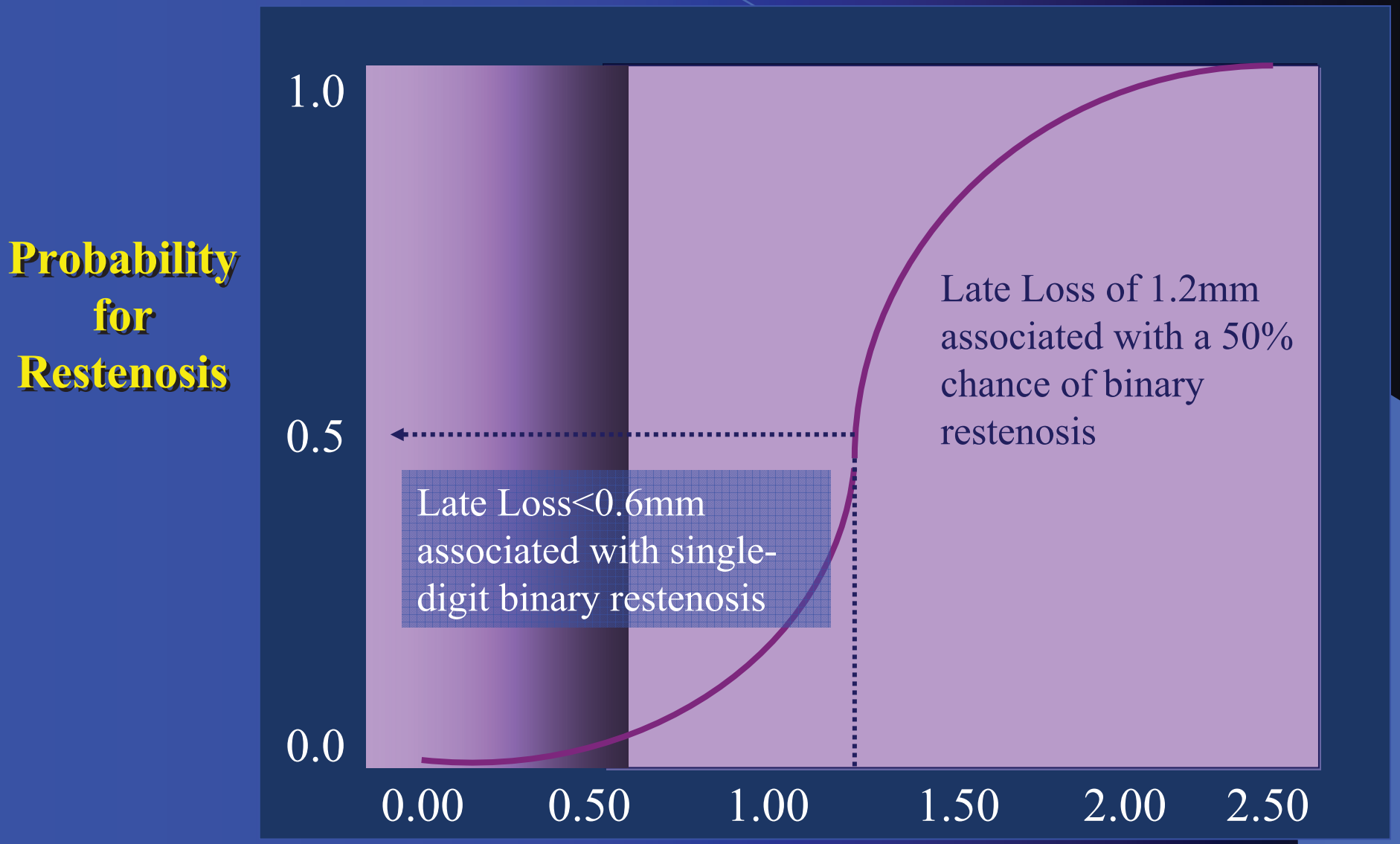
6 months follow-up	Low-Dose	High-Dose
Reference vessel diameter	2.83±0.45mm	2.89±0.42mm
MLD		
Analysis segment	2.36±0.67mm	2.59±0.46mm
In-stent	2.39±0.52mm	2.62±0.35mm
DS%		
Analysis segment	17.6±12.4%	10.2±5.8%
In-stent	15.6±12.0%	10.0±7.3%
Late loss		
Analysis segment	0.36±0.42mm	0.23±0.16mm
In-stent	**0.46±0.32mm**	**0.26±0.14mm**

In-stent late loss i

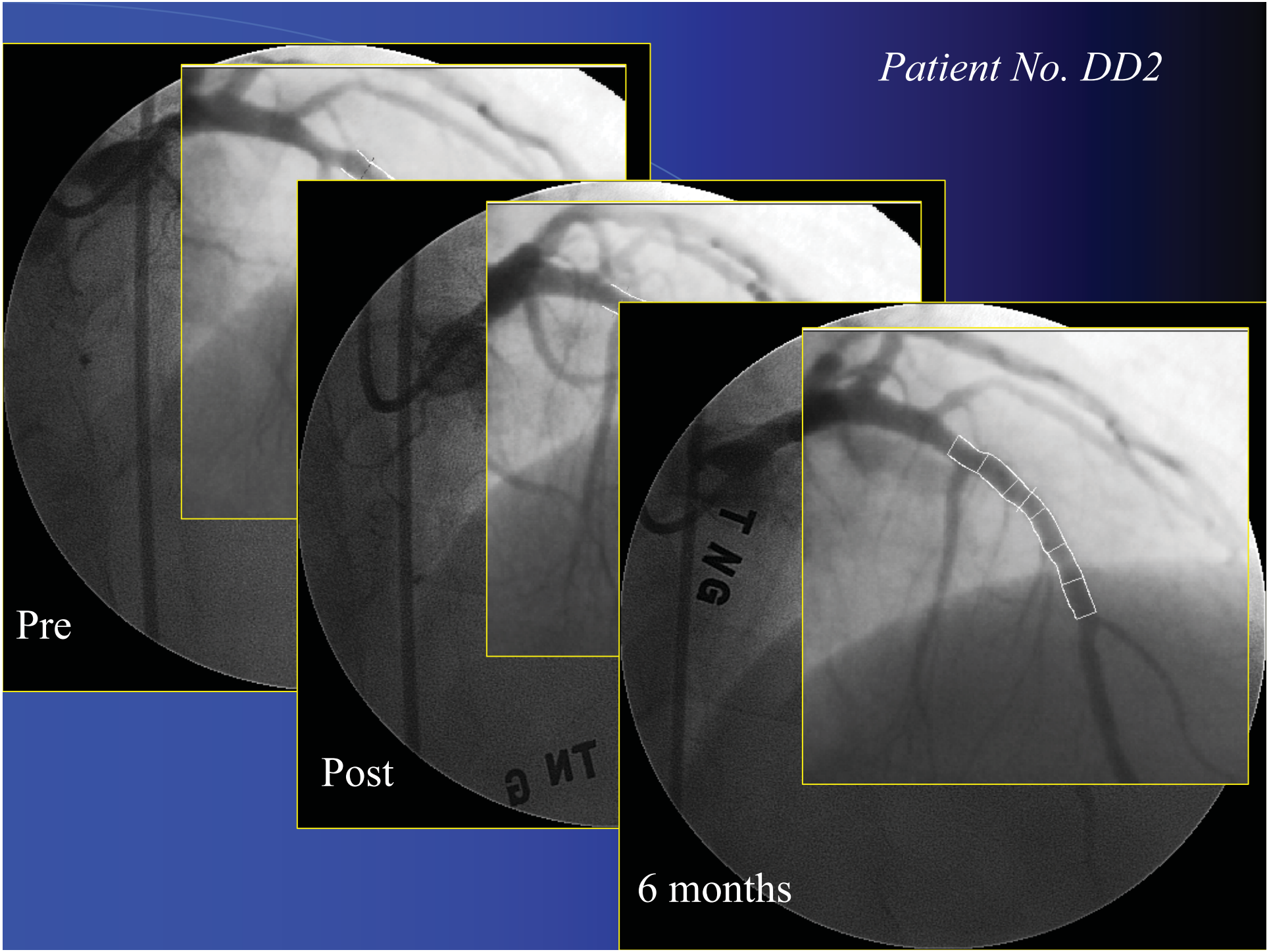
Late Loss in DISTINCT:	**0.94 ±0.61mm**
Late Loss in TAXUS IV:	**0.39 ±0.50mm**

Late Loss as A Predictor of Restenosis

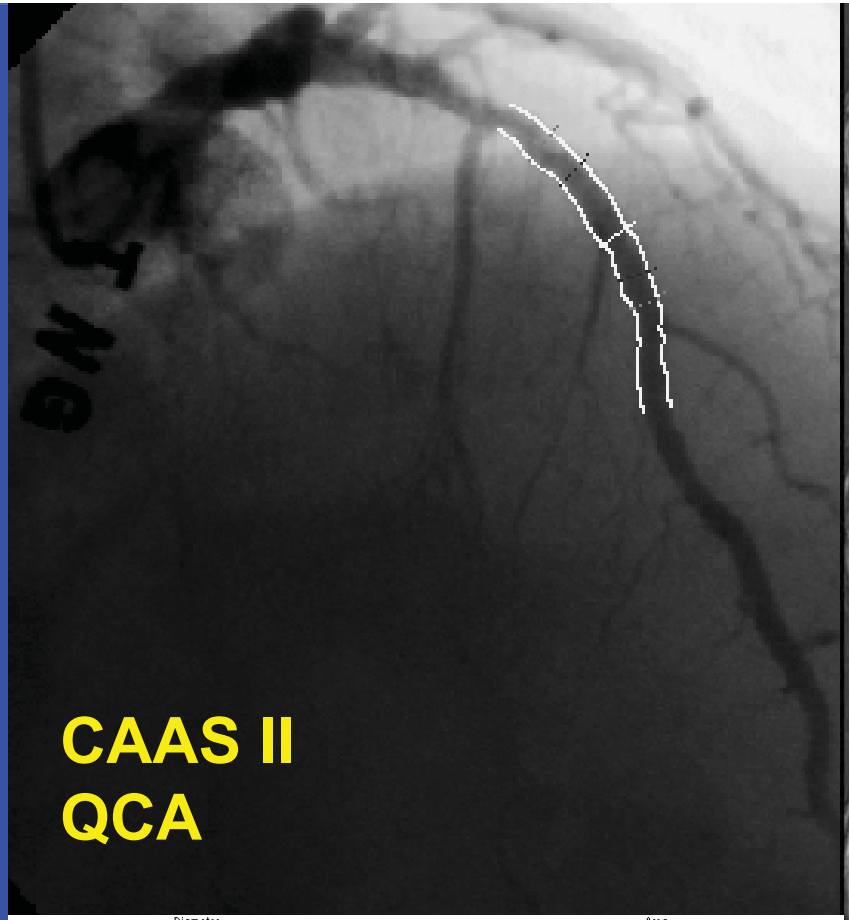
Logistic regression combining all patients



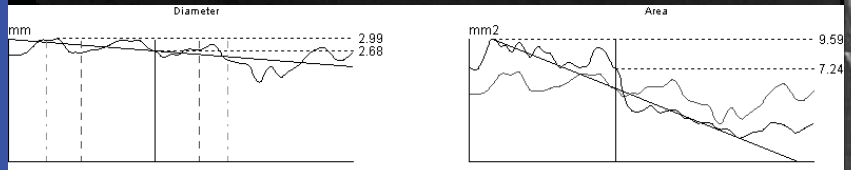
Patient No. DD2



Volumetric IVUS

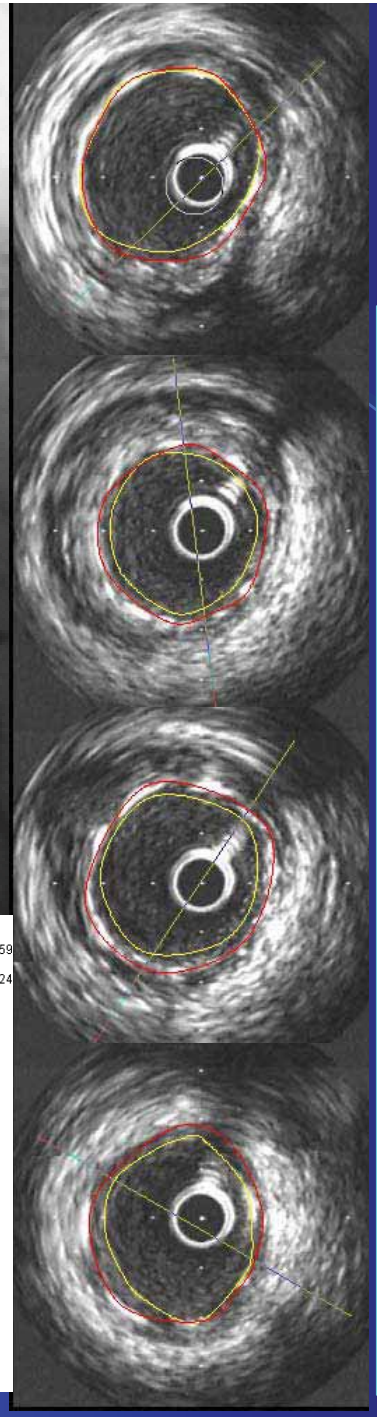


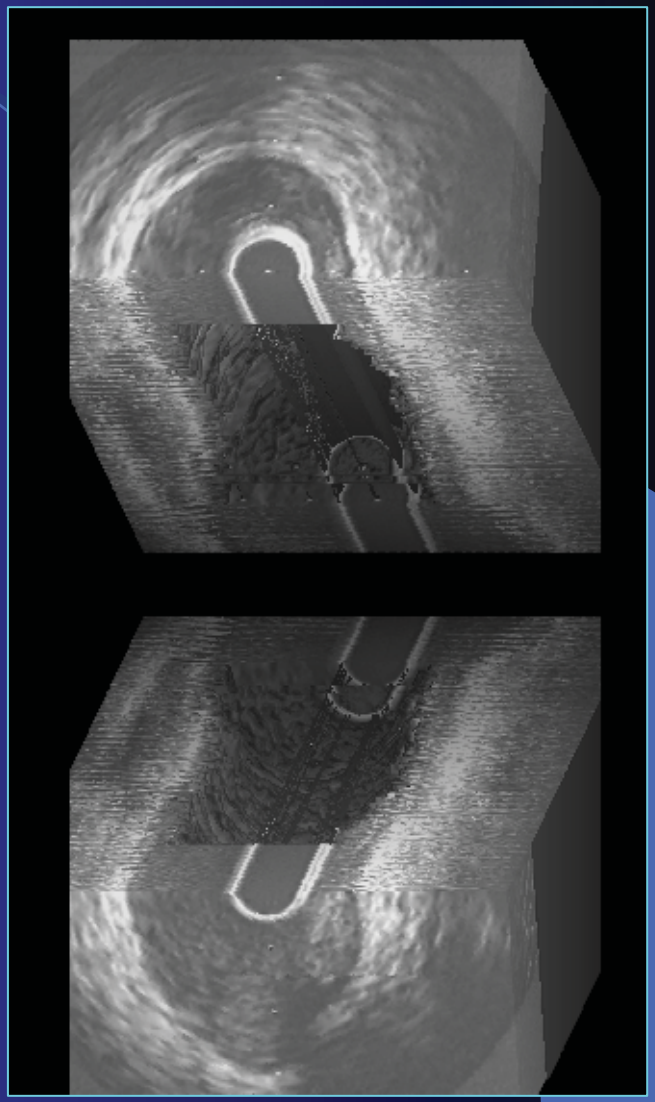
CAAS II QCA



Interpolated Reference Obstruction Analysis

MLD	:	**2.68**	mm
% diameter stenosis	:	**0**	%
Reference diameter	:	**2.69**	mm
Position reference diameter	:	3.91 21.06	mm
Length stenotic segment	:	**11.04**	mm
Position of proximal border	:	7.59	mm
Position of distal border	:	18.63	mm
Minimum area absolute	:	1.81	mm2
MLA densitometry	:	7.24	mm2
MLA circular	:	5.64	mm2
% area stenosis densitometry	:	**-27**	%
% area stenosis circular	:	**1**	%
Reference area	:	5.68	mm2





Echo Plaque Volumetric IVUS

3D-IVUS follow-up	Low-Dose	High-Dose
Stent volume	185.3±102.6mm³	188.4±64.6mm³
% neointimal hyperplasia volume	18.4±22.5%	10.2±5.8%

-No Late stent mal-apposition. No aneurysm.

N.B. In BMS, the % NIH is consistently around 30% by volumetric IVUS at 6-9 months

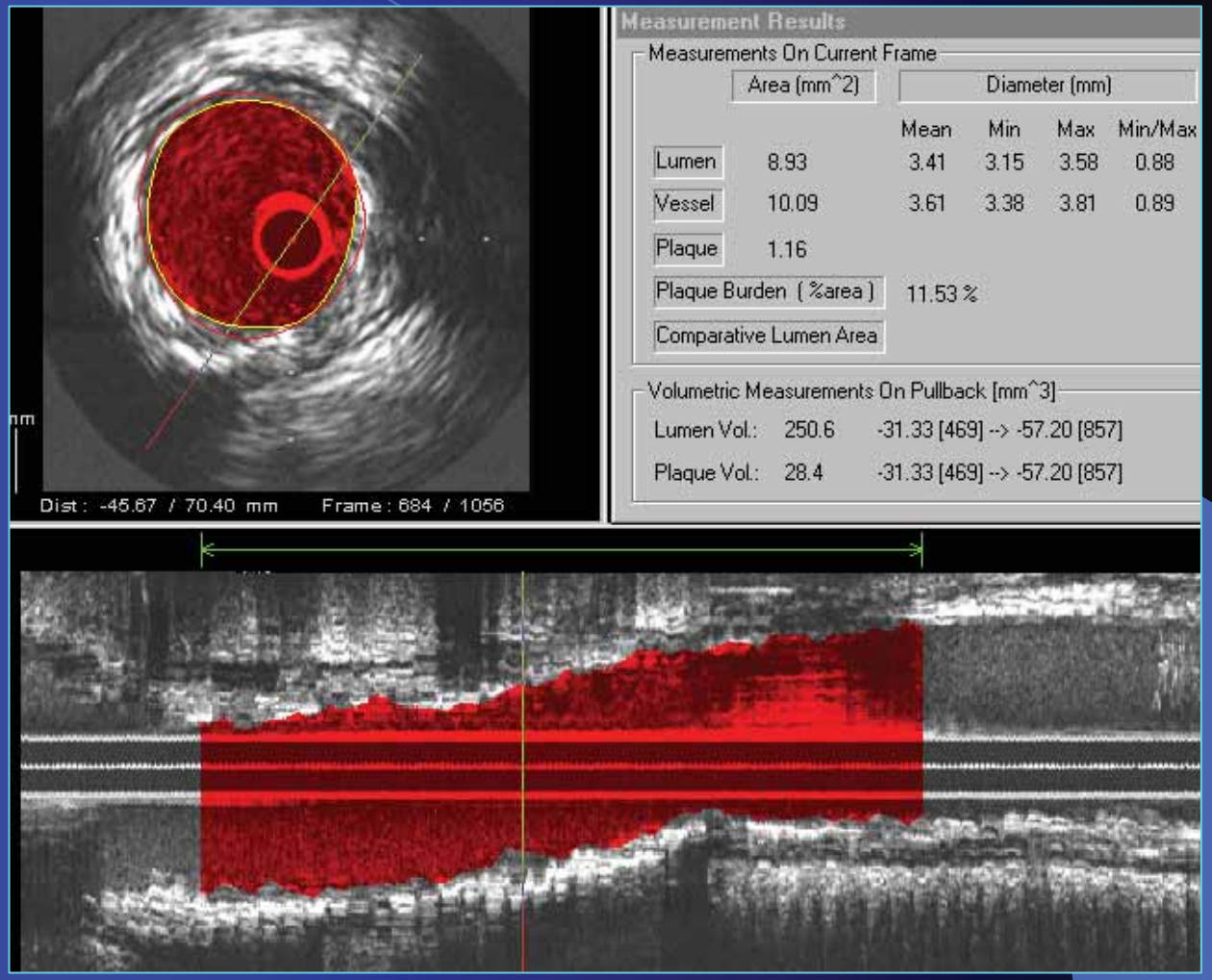
Echo Plaque Volumetric IVUS

F/52

- *Insulin-Dependent DM*
- *3.5x18mm Angiopeptin-eluting stent (126μg) in mid-LCx*

6-month FU

- *Late Lumen Loss=0.22mm (QCA)*
- *% Volume Obstruction=10.2% (3D-IVUS)*



Study Limitations and Future Directions

- *The sample size was too small to draw any conclusion on the efficacy of Angiopeptin-eluting stents in reducing restenosis*
- *By modifying the physical property of the PC polymer, the coating could be tailored to achieve better loading, release and less 'wash-out' of the drug. Pre-loading the drug with spray-loader by the industry would ensure more reliable and reproducible dosimetry*
- *There are at least 5 known Somatostatin receptor subtypes, SSTR1-SSTR5. Human blood vessels express high levels of SSTR-1 after injury. Research on SSTR-1 specific agonist is underway.*

Conclusions

- *Angiopeptin-eluting BiodivYsio™ DD PC stent appears feasible and safe in treating native de novo coronary lesions.*
- *Angiopeptin-eluting stents resulted in modest degree of neointimal hyperplasia and zero binary restenosis in this small cohort of patients (half DM). High-dose (126 μg) Angiopeptin-eluting stent appears more promising.*
- *The preliminary results warrant further confirmation by randomized, controlled trials.*

Acknowledgement

- On behalf of all the co-investigators, I would like to thank Dr. Mun K. Hong for his invaluable advice and pioneer work in the research.
- We would also like to thank Beaufour Ipsen, UK, for providing free samples of generic Lanreotide for our study