Angioplasty Summit 2004
Seoul, Korea

New Drug-Eluting Stents

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Sao Paulo, Brazil

New Drug-Eluting Stents

- 17- β Estradiol-Eluting Stent
- Avantec Mycophenolic Acid-Eluting Stent
- Conor Paclitaxel-Eluting Stents
- Biorest Bisphosphonates

New Drug-Eluting Stents

- **17-ß Estradiol PC Coated Stent**
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17β-Estradiol: Restenosis

"Vasculoprotective"

- ↓ "response to injury" / ↑ vascular healing
  - ↑ re-endothelialization
  - ↓ intimal proliferation and migration
  - ↓ adventitial fibroblast cell migration

Histomorphometric Analysis

Control	Low dose 17 β-estradiol	High dose 17 β-estradiol

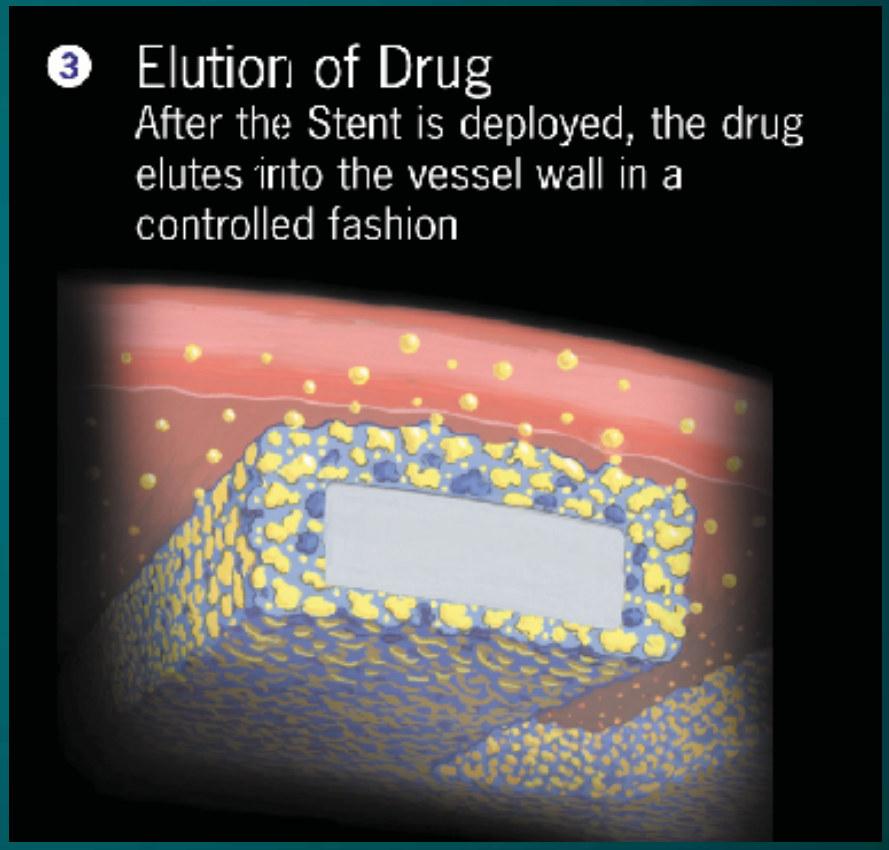
40% reduction in intimal area for high vs. control stents

New G. et al JACC in press

Stent-Based Drug Delivery

Bio*divYsio*® Matrix LO stent

- PC polymer
- Double thickness
- 2.54 μg/mm² of 17β-estradiol



EASTER – Study Design

- 1 Site: Brazil (PI: J. Eduardo Sousa)
- Registry (30 patients)
- Feasibility and safety study of 17β-Estradiol coated Bio*divYsio*™ Drug Delivery PC Stent System
- De novo lesions
  - (≤ 15mm length, 3.0 – 4.0mm diameter)
- Six-month angiographic and IVUS follow-up
- Primary Endpoint: safety and late loss @ 6-mos
- Secondary Endpoints: MACE, IVUS

EASTER

Demographics

	n = 30
Mean Age (yrs)	61 ± 12
Male	70%
Prior MI	38%
Diabetes Mellitus	10%
Hypertension requiring meds	49%
Hypercholesterolemia requiring meds	27%
Current Smoker	31%

EASTER – QCA Results

In-stent

n = 30

	Post Intervention	6-month Follow-up
Reference (mm)	2.76 ± 0.56	
MLD (mm)	2.44 ± 0.52	1.89 ± 0.57
Diameter stenosis %	13.6 ± 10.4	28.2 ± 14.8
Late loss (mm)		0.54 ± 0.44
Binary restenosis		(2) 6.6%

Lesion length = 9.1 ± 2.4

EASTER – QCA Results

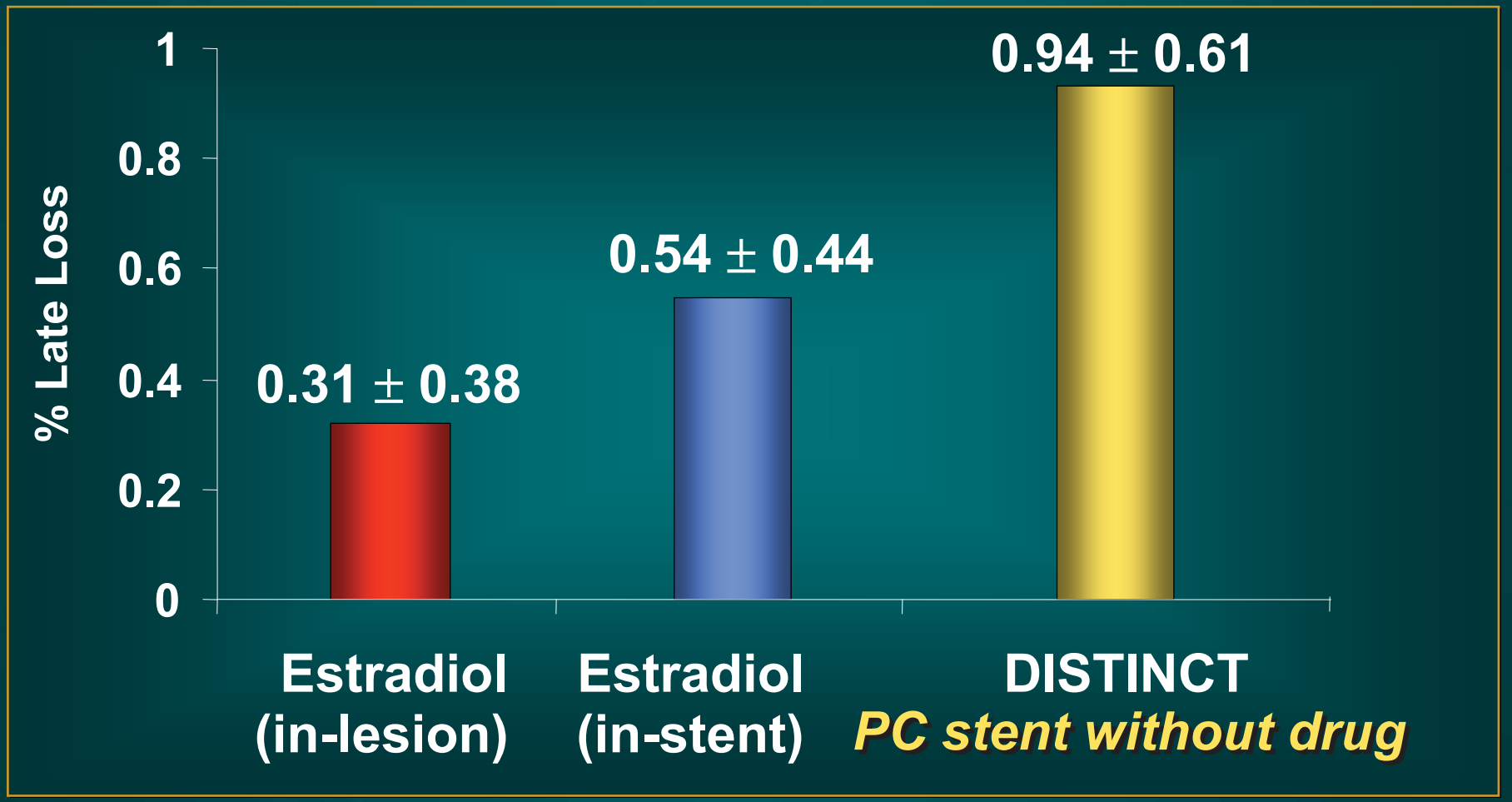
In-segment

n = 30

	Post Intervention	6-month Follow-up
MLD (mm)	2.04 ± 0.43	1.76 ± 0.56
Diameter stenosis %	23.4 ± 10.9	30.5 ± 14.9
Late loss (mm)		0.31 ± 0.38

BiodivYsio Trials

Late Loss Comparisons



EASTER – IVUS Results

In-stent

Vessel (mm^3)	268 ± 66
Stent (mm^3)	147 ± 43.6
Lumen (mm^3)	115 ± 41.9
Intimal hyperplasia (mm^3)	32.6 ± 14.7
% obstruction	23 ± 11%

EASTER – Clinical Follow-up (6 month)

	n = 30
Death	0%
Q wave MI	0%
TLR	3.3%
Non-TLR (other vessel)	3.3%
Event-free survival	93.4%

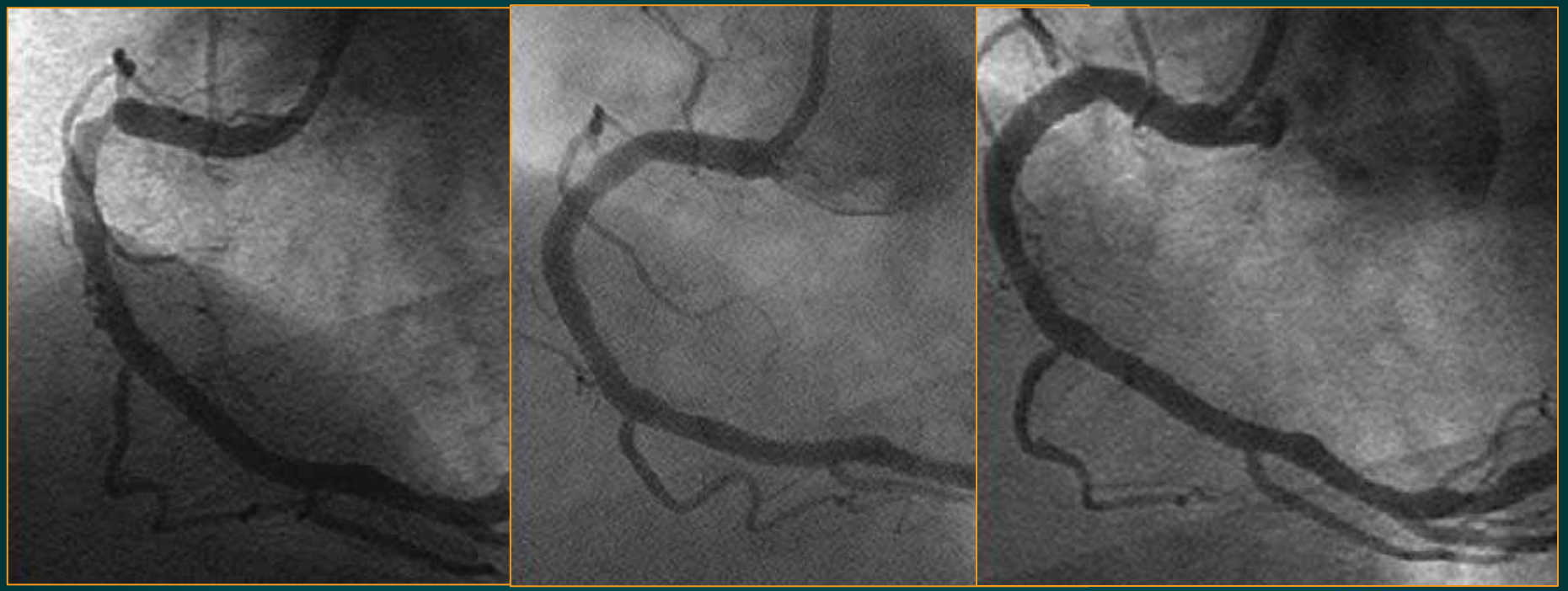
EASTER – Clinical Follow-up (24 month)

	n = 30
Death (non-cardiac)	3.3%
Q wave MI	0%
TLR	3.3%
Non-TLR (other vessel)	3.3%
Event-free survival	90.1%

EASTER

17ß-Estradiol-Eluting Bio*divYsio* Stent

Pt: MMSN



PRE | POST | FU 6 MONTHS

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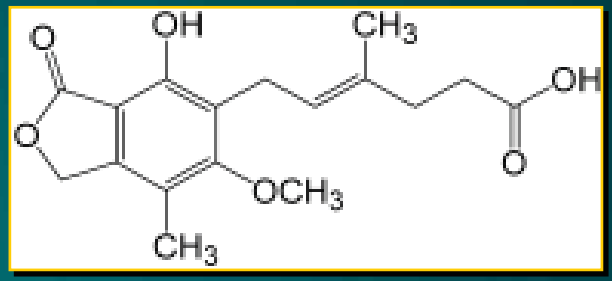
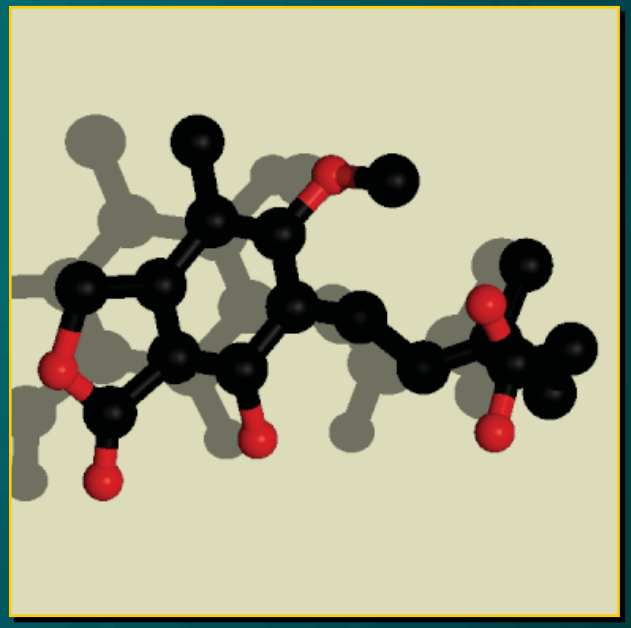
Mycophenolic Acid (MPA)

Stent Based Cytostatic Immunosuppressive Therapies

- Active metabolite of Mycophenolate mofetil (CellCept®), an approved drug in 70 countries, including USA, European Union countries and Japan

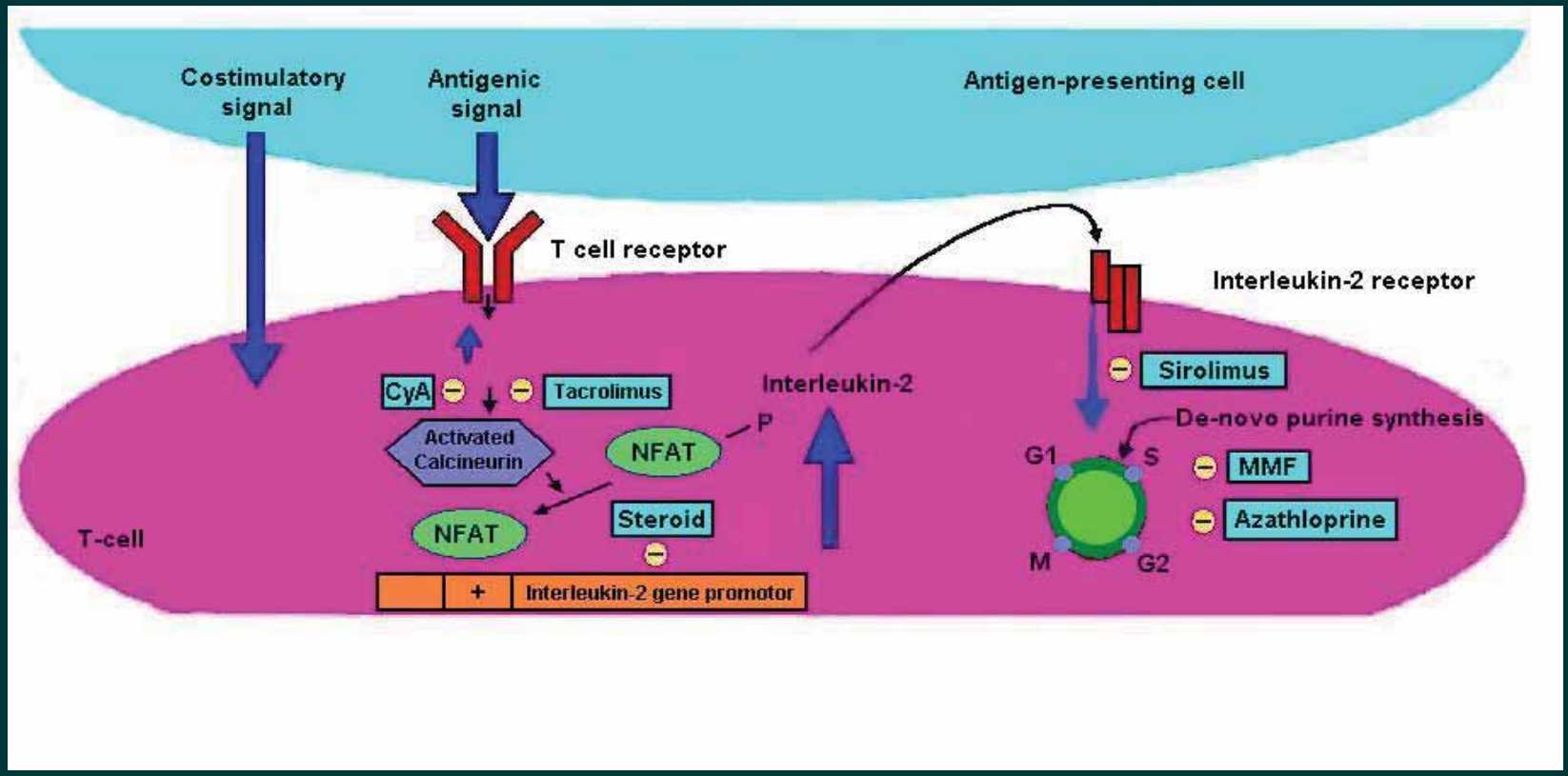
- Immunosuppression agent indicated for the prophylaxis of organ rejection in patients receiving allogenic renal, cardiac or hepatic transplants





Mechanism of Action of MPA

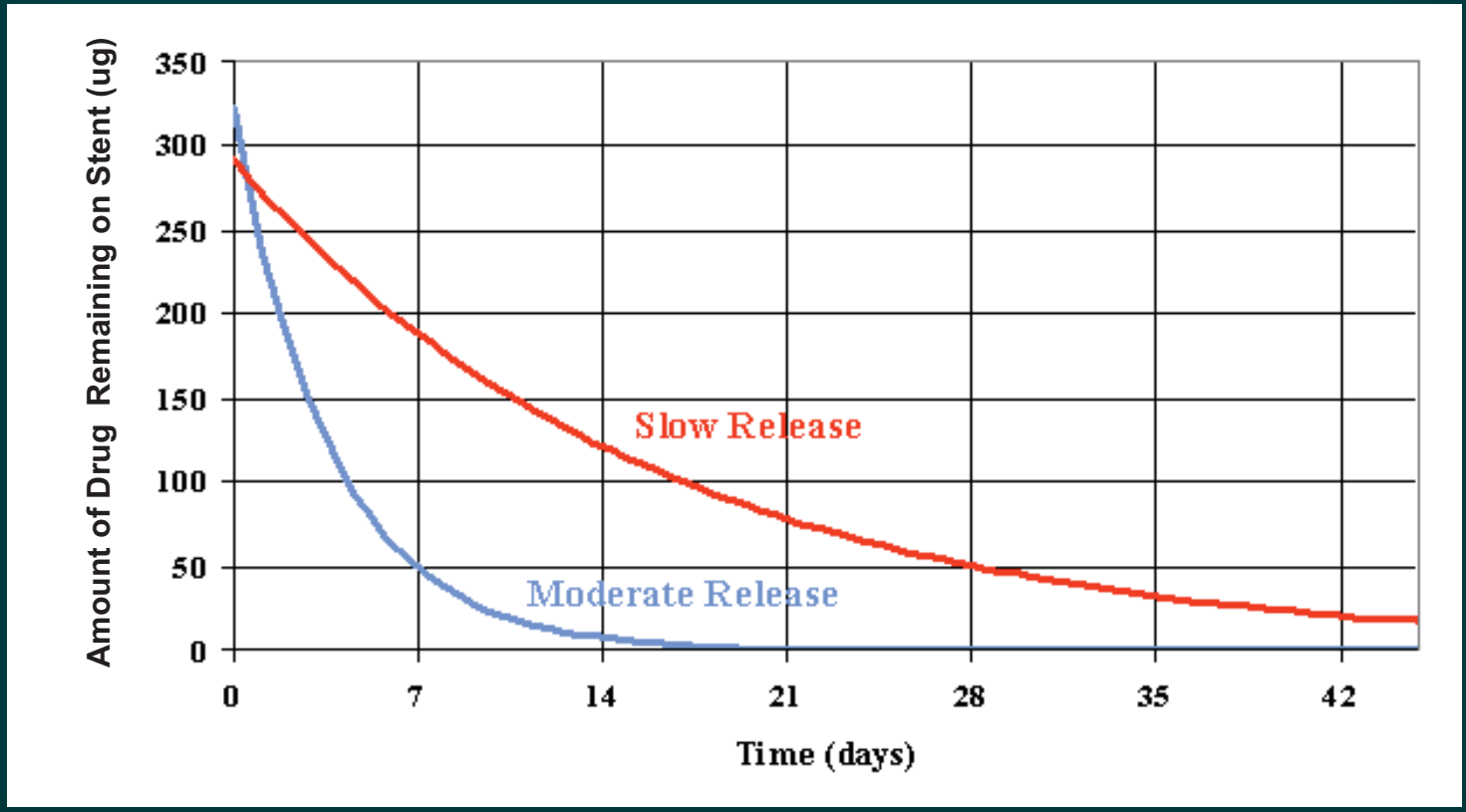
MPA is a cytostatic immunosuppressant which inhibits de novo purine synthesis



Reproduced from: Denton MD, et. al. *Immunosuppressive strategies in transplantation*. Lancet 1999, 353:1083-1091

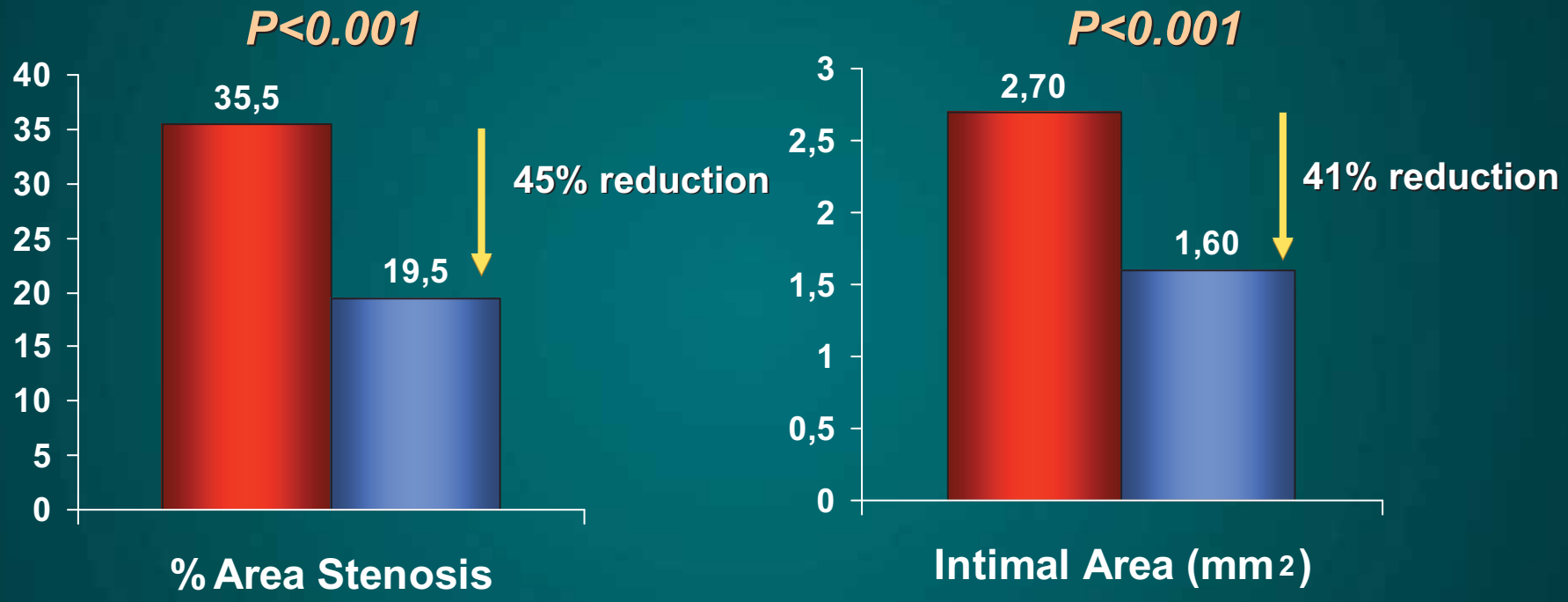
Controlled Release

In Vivo Pharmacokinetics (Porcine Coronary Model)



MPA Eluting Duraflex™ Stent

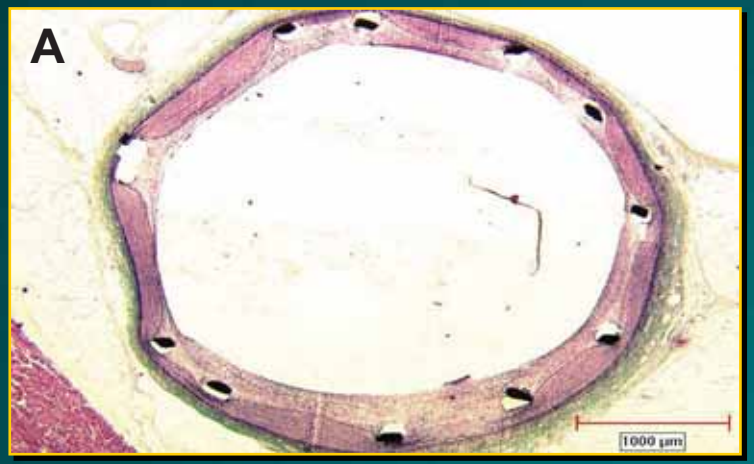
Safety & Efficacy Study (28d Porcine Coronary Model)



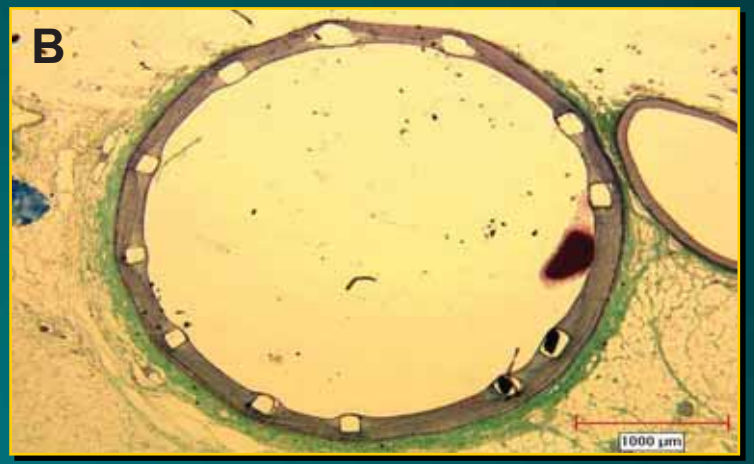
For comparison, Sirolimus decreased % area stenosis by 47%

Suzuki et al, *Circulation* 2001;104:1188-93.

Histology

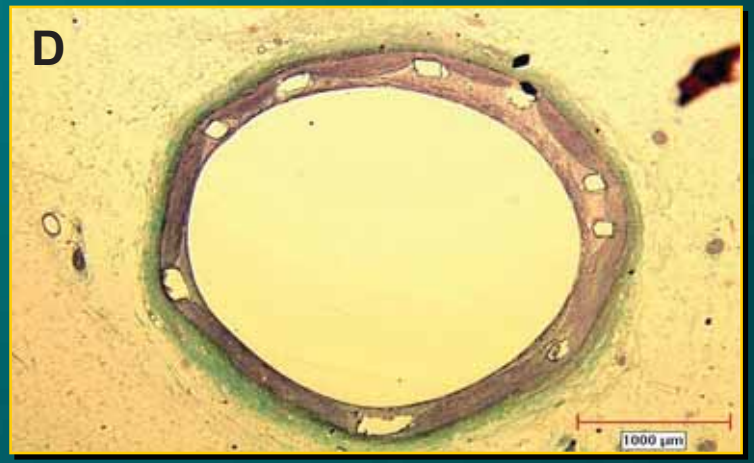


A. Bare metal Duraflex: Low Injury



B. MPA Eluting Duraflex : Low Injury

C. Bare metal Duraflex: High Injury



D. MPA Eluting Duraflex : High Injury

Guy Leclerc, MD University of Montreal, Montreal, Canada

IMPACT – Study Design

PI: J. Eduardo Sousa, MD
Co-PI: Alexandre Abizaid, MD

N= 150
De Novo Coronary Lesions
3.0 – 3.5mm diameter
≤ 14mm length

MPA-Eluting Duraflex
3.3μg/mm2
14 day release
n = 50

MPA-Eluting Duraflex
3.3μg/mm2
< 45 day release
n = 50

Bare Duraflex
n = 50

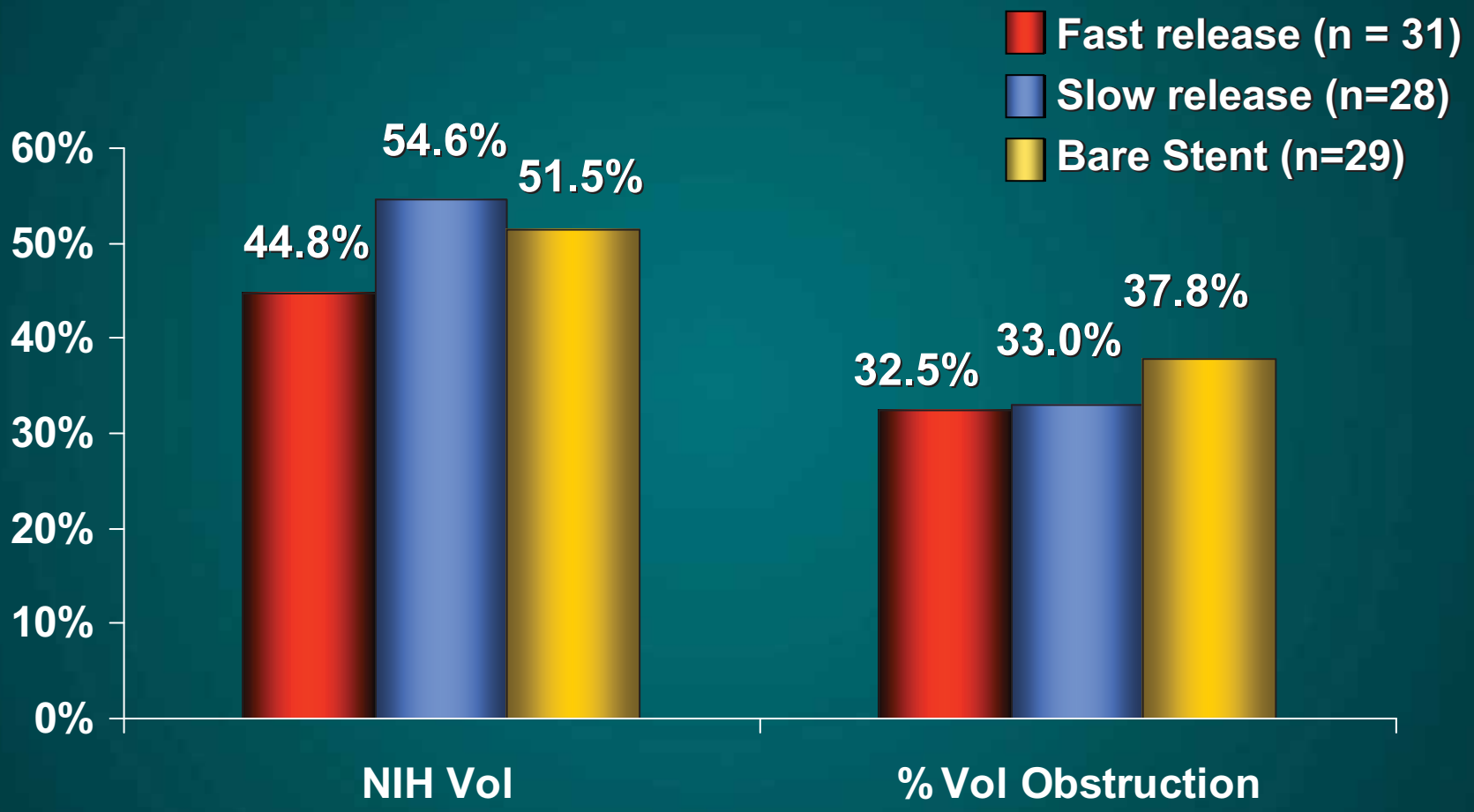
Primary Endpoint:
6-month late lumen loss as assessed by QCA

Clopidogrel for 3 months

QCA 6-month Follow-up

	Fast Release (14 Days) n=50	Slow Release (<45 Days) n=51	Bare Stent n=48	p-value
In-stent Restenosis(≥ 50%)	12%	12%	25%	ns
In-segment Restenosis	18%	16%	25%	ns
Late Loss (mm)	1.04 ±0.61	0.95 ±0.52	0.91 ±0.47	ns

IVUS Analysis at Follow-up



6-Month MACE

	Fast Release	Slow Release	Bare Stent
	n=50	n=56	n=50
Death	0	2 (3.6%)	0
Myocardial Infarction	2 (4%)	0	3 (6%)
QMI	0	0	0
Non-QMI	2* (4%)	0	3* (6%)
Revascularization	4 (8%)	7 (12.5%)	6 (12%)
CABG	0	3 (5.4%)	0
PTCI	4 (8%)	4 (7.1%)	6 (12%)
Total MACE	6 (12%)	9 (16.1%)	9 (18%)

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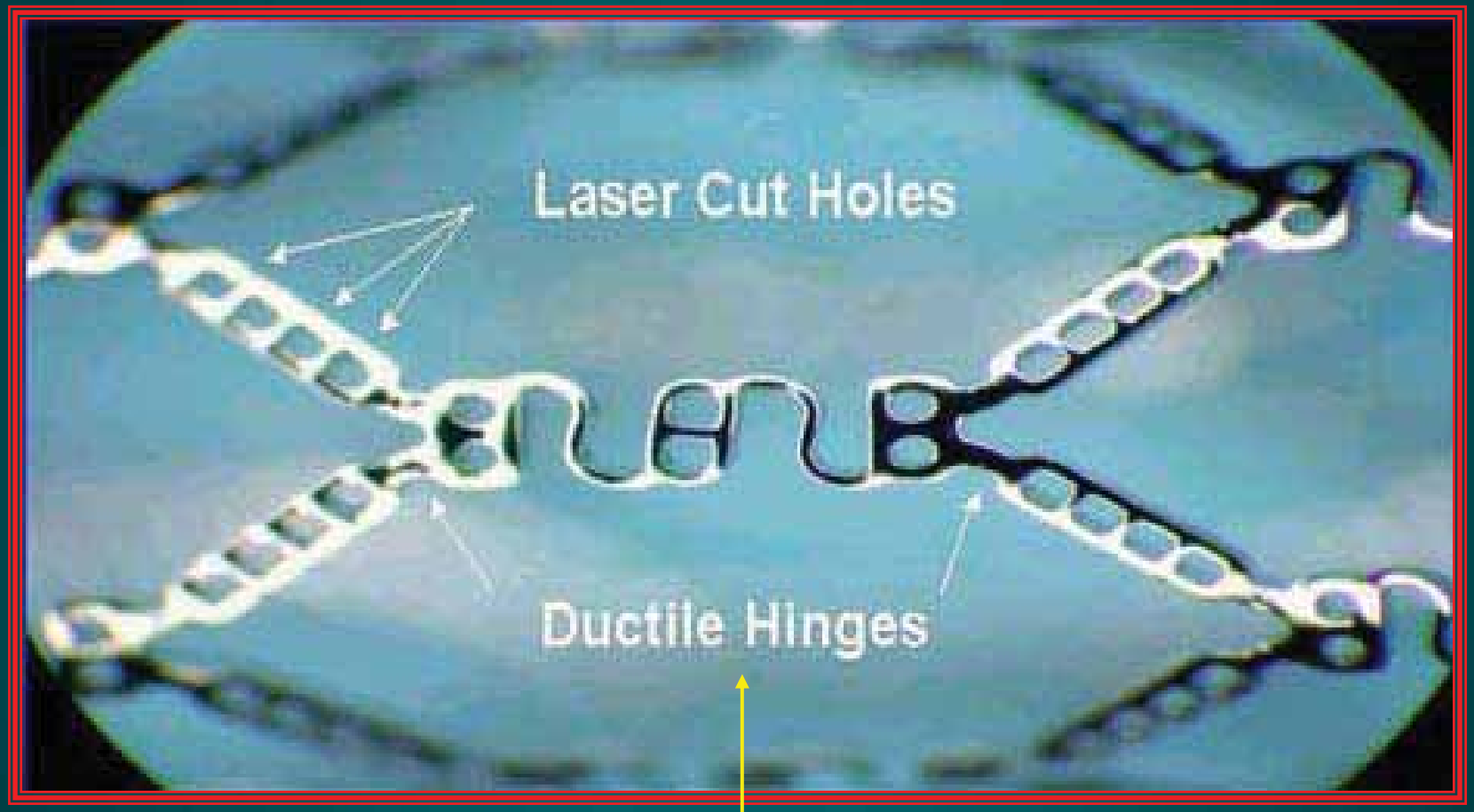
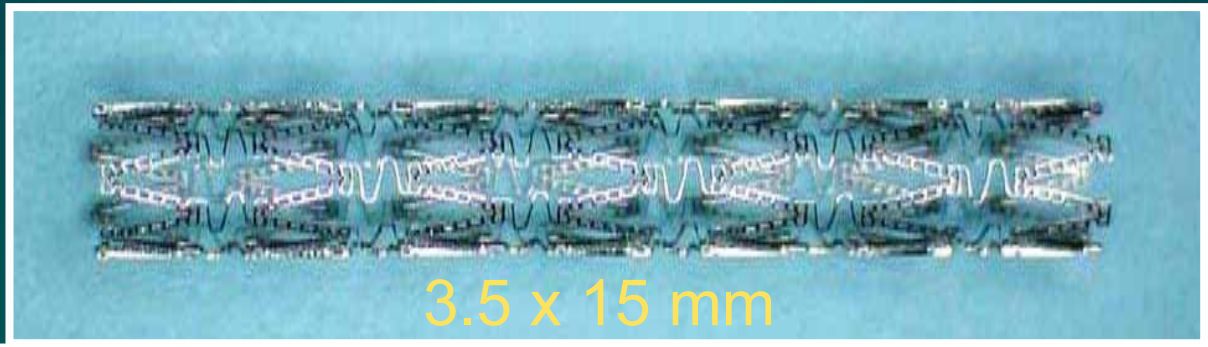
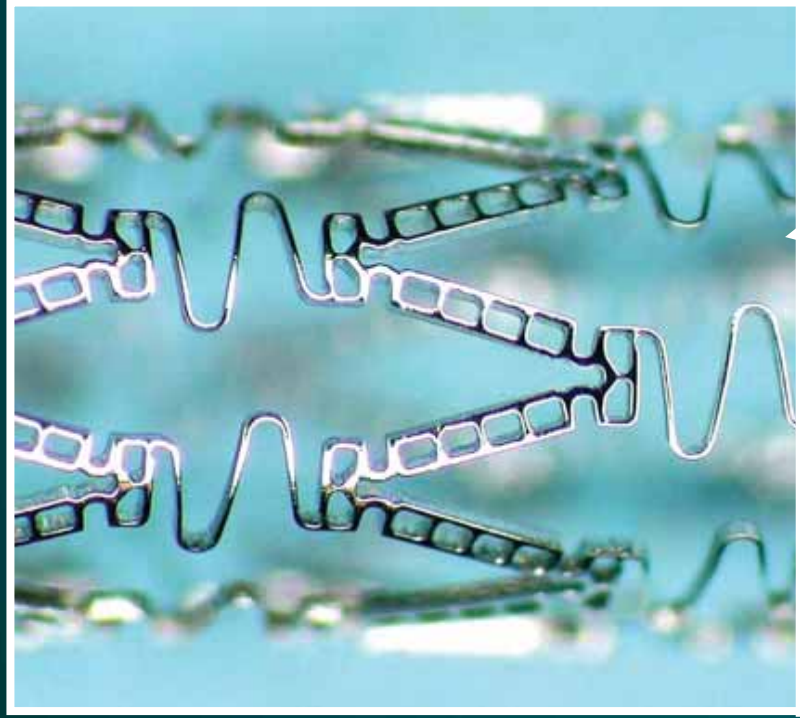
Technology : Conor Stent

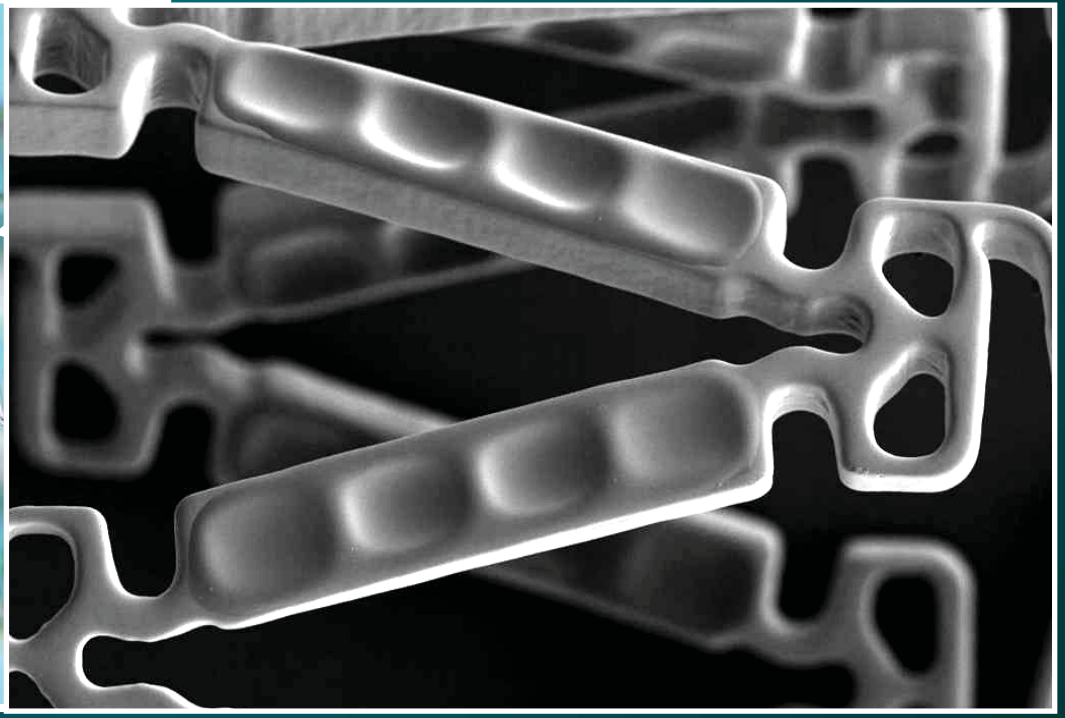


Ductile Hinges
allow struts to open
without deformation

The Conor Medsystems Stent:
A Stent Engineered for Drug Delivery

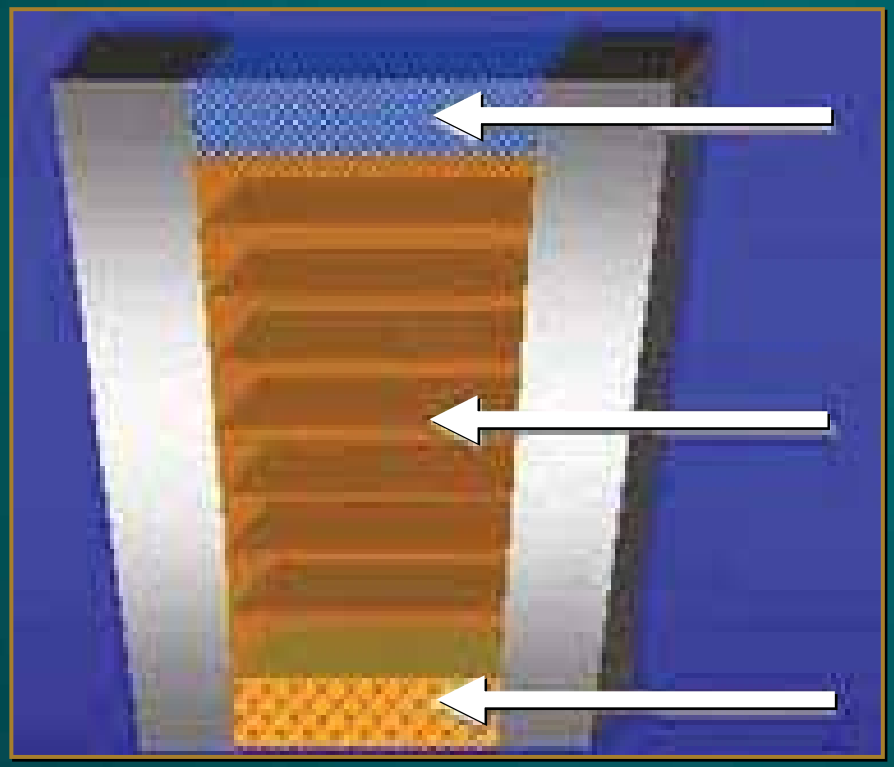




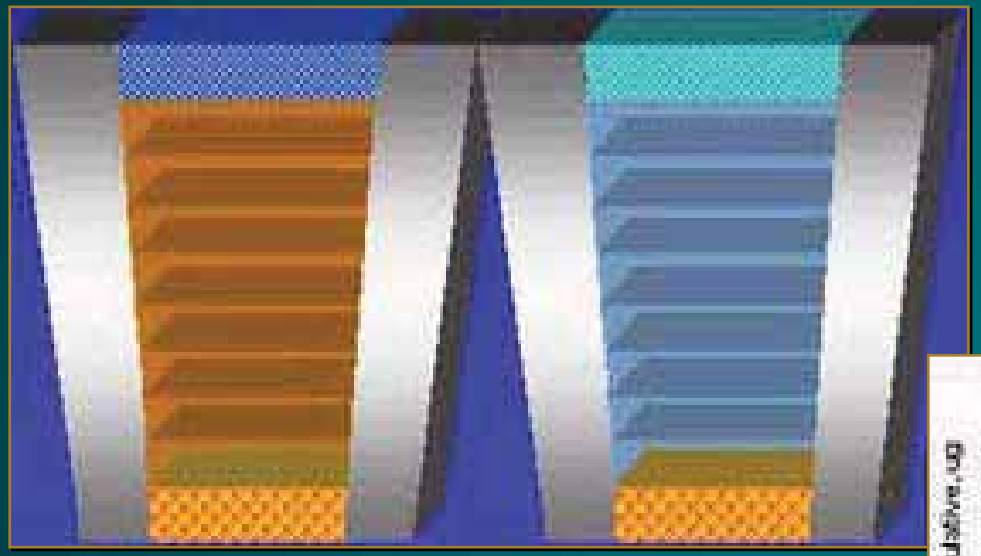


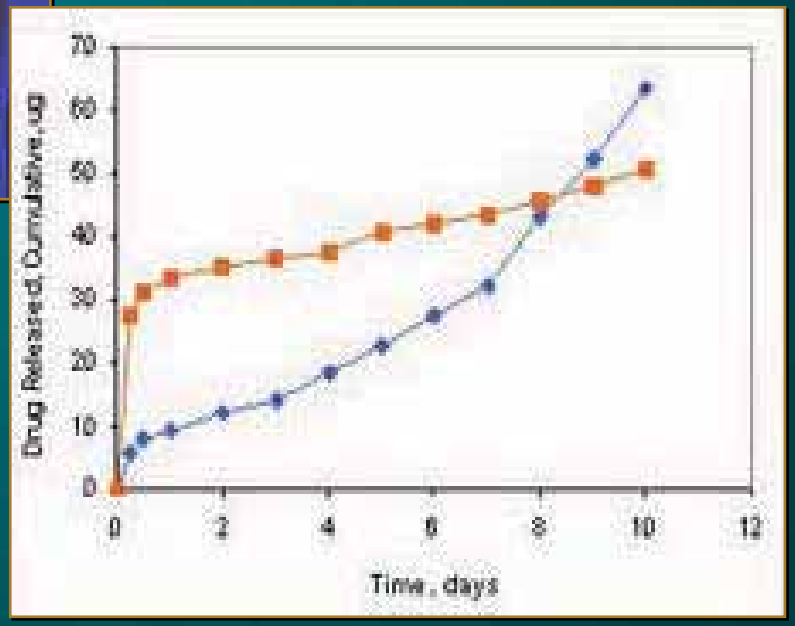
Drug Reservoir Microstructure

Bio-Resorbable Layered Polymers

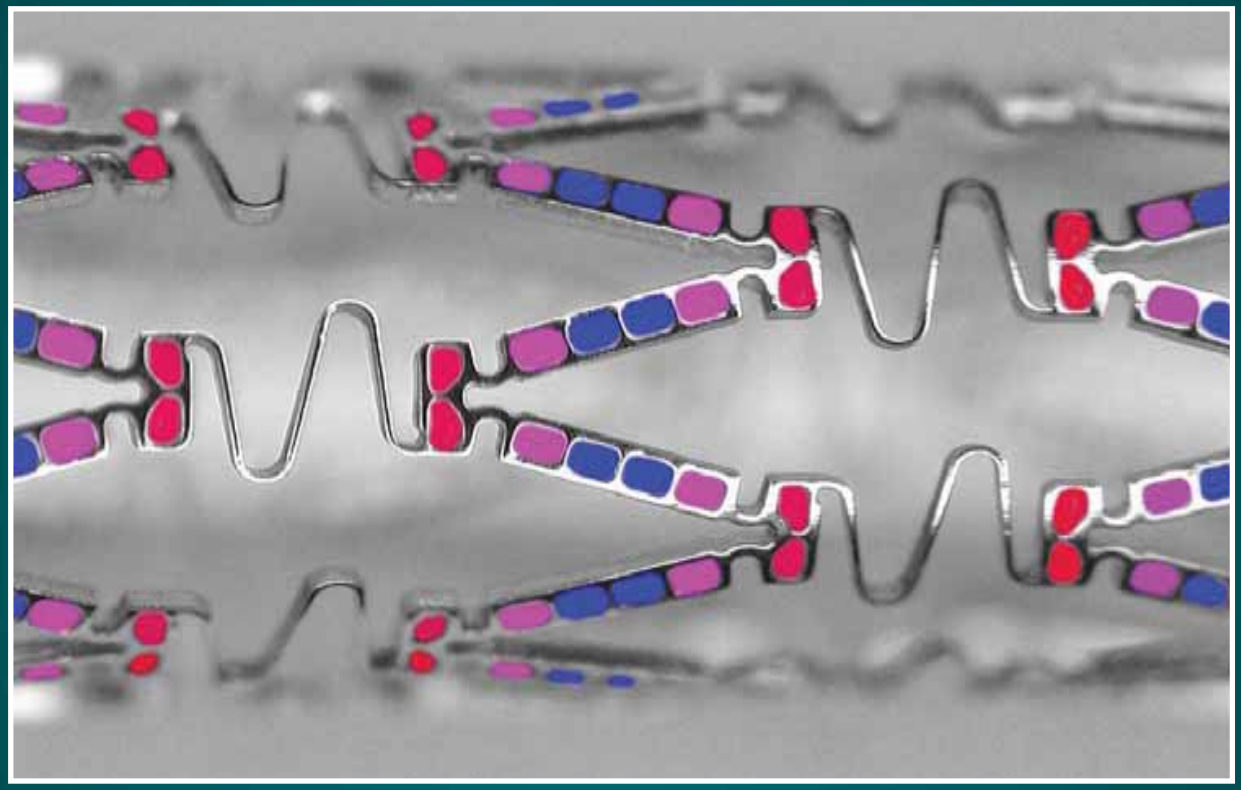


Different Drugs in Different Holes Independent Release Rates





How Can Adequate Drug Dose Reach All Locations of the Vessel Wall?



Polymer inlays are individually programmable for drug concentration enabling controlled spatial drug dose distribution.

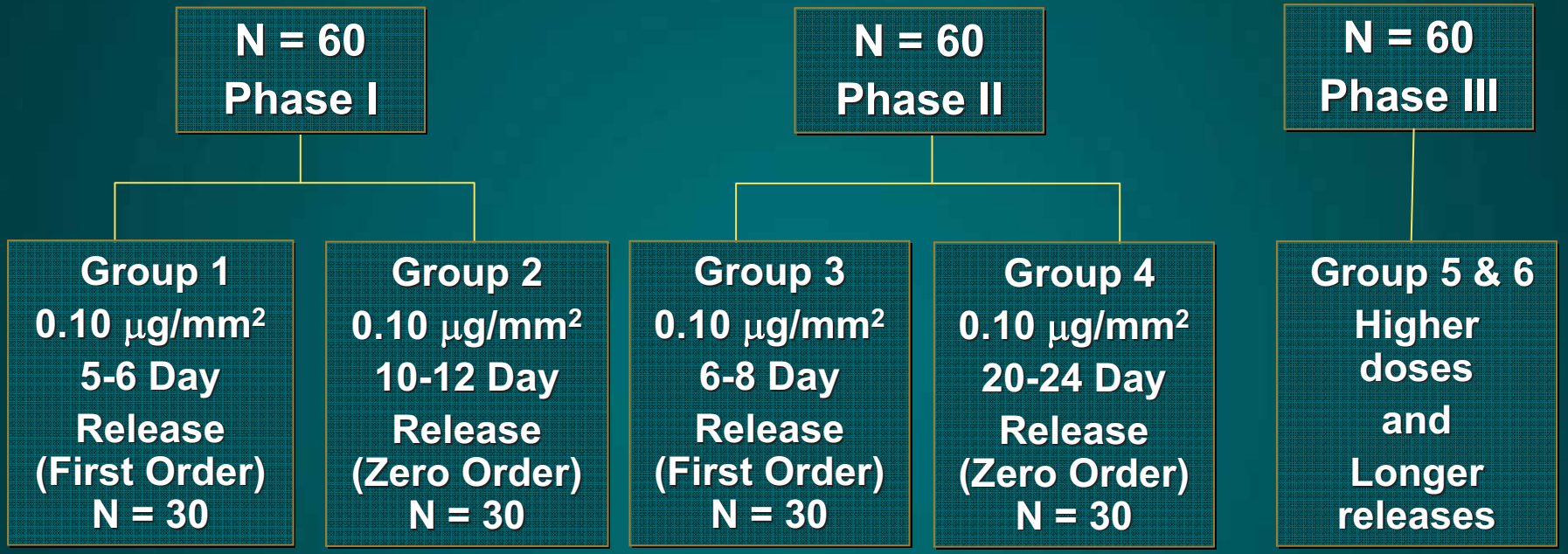
Conor Clinical Program

- DepoStent
- Stainless Steel Stent:
  - PISCES Trial
  - SCEPTER Trial
- Cobalt Chromium Stent:
  - COSTAR Trial
  - EuroSTAR Trial
  - U.S. Trial

PISCES Trial

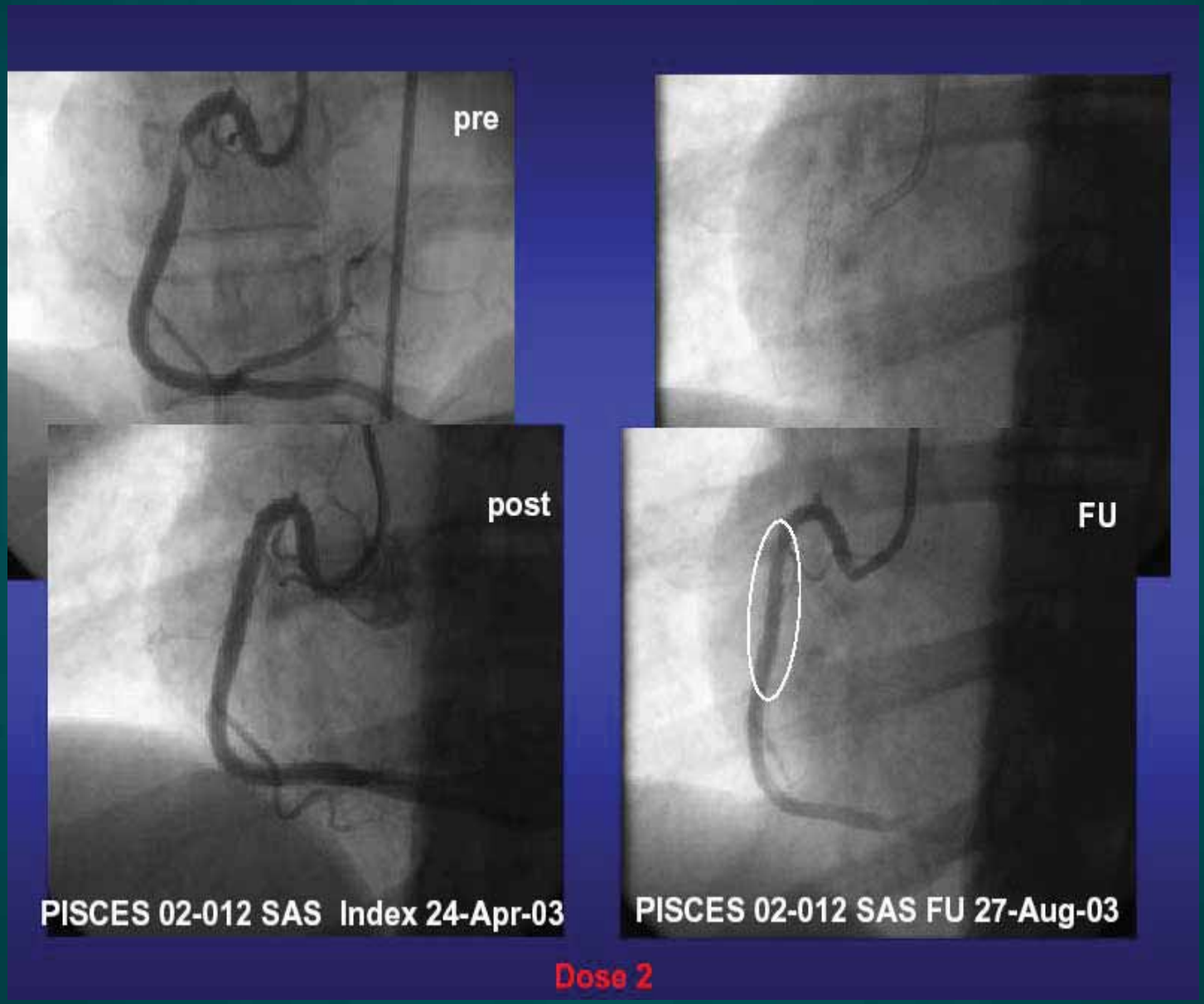
PI: P. Serruys

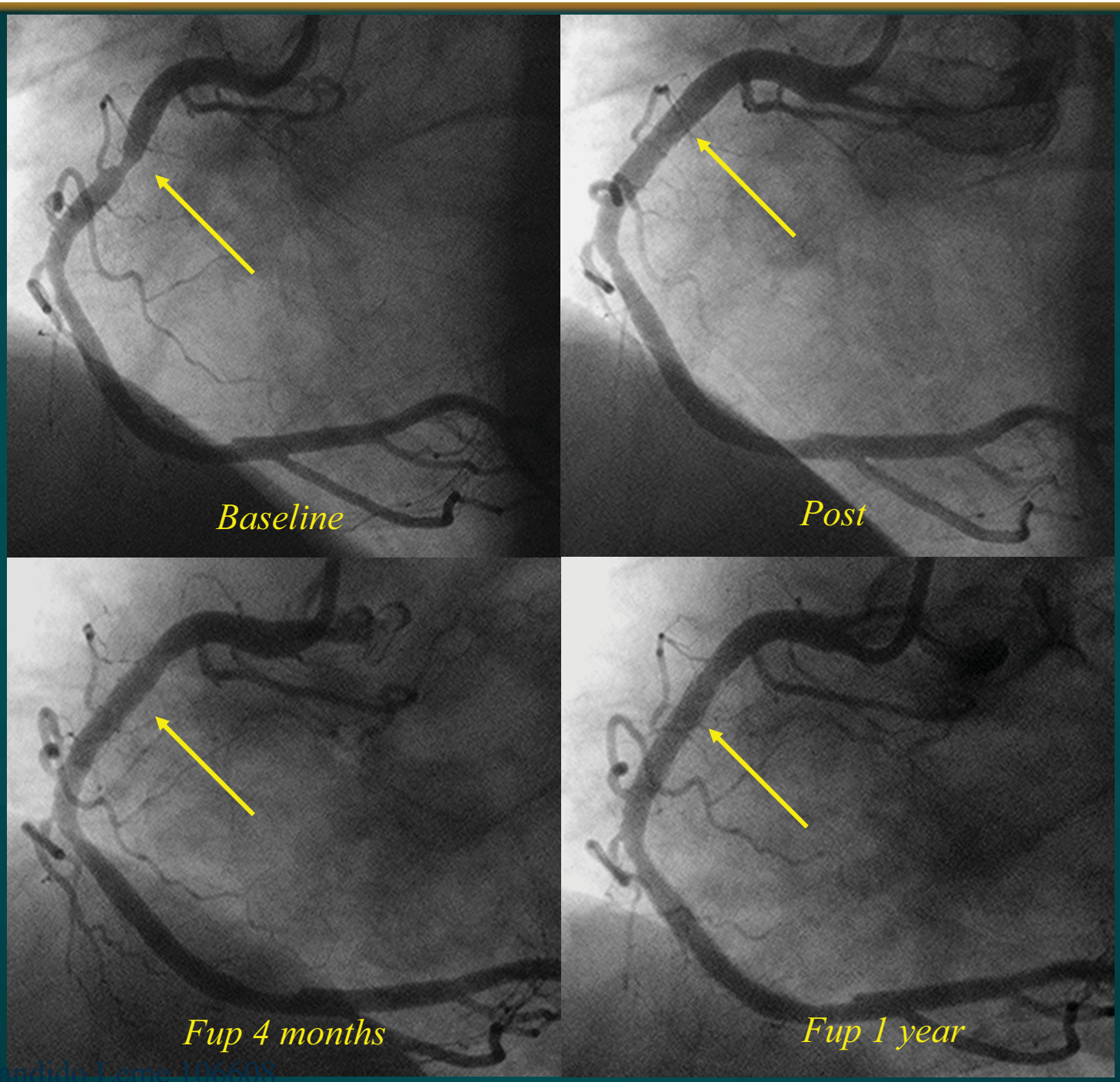
Paclitaxel In StentControlled Elution Study



4 & 12 Month Clinical and Angiographic Follow-up

PISCES Trial: 4-month angio follow-up



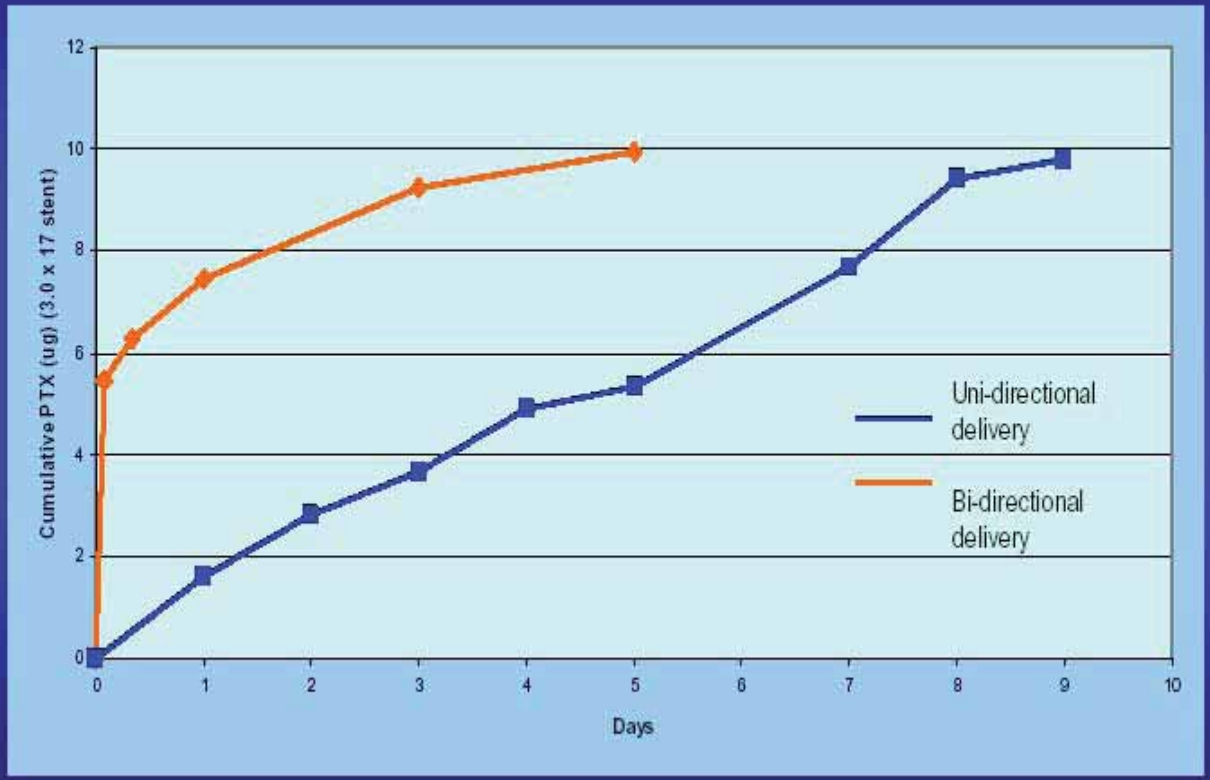


SCEPTER Trial

Study of Controlled Elution of Paclitaxel for
The Elimination of Restenosis

- CE Mark Approval Trial
- Safety and Performance
  - Late loss vs. bare stent at 6 months
  - Clinical safety MACE at 6 months
- N=260 pts; 2 formulations (slow and fast)
- 17 site in 6 countries
- Enrollment completed

SCEPTER Doses



SCEPTER Trial

Study of Controlled Elution of Paclitaxel for The Elimination of Restenosis

3-month results	Fast Release N= 138	Slow Release N= 133
Death	0	0
Mi Q-wave	2	2
MI non-Q	2	1
TVR / TLR	1	0
Any MACE	4 (2.9%)	3 (2.3%)

COSTAR Trial: Dose Optimization Study

Cobalt Chromium STent with
Antiproliferative for Restenosis

PI: Upendra Kaul (New Deli)

- Multicenter pilot registry: 40 pts, 67 stents
  - Complex pts inclusion (multivessel, DM, long lesions)
- Study Objectives
  - Evaluate new performance of cobalt-alloy stent
  - Confirm PISCES findings on new stent platform
- Efficacy endpoints: Late loss and IVUS % obstruction
- Status: enrollment completed

Euro STAR Trial

European Cobalt Chromium STent with
Antiprolidferative for Restenosis Trial

- Multicenter sequential Registry trial for 10µg (30-day) and 30µg (30-day release)
- N= 125 pts/arm, historical bare metal control
- Objective: to evaluate the safety and performance of the COSTAR cobalt alloy paclitaxel stent
- Primary Endpoint: Angiographic late loss
- PI's: Antonio Colombo and Keith Dawkins
- Status: First group (142 pts) enrolled, second dose to begin this spring

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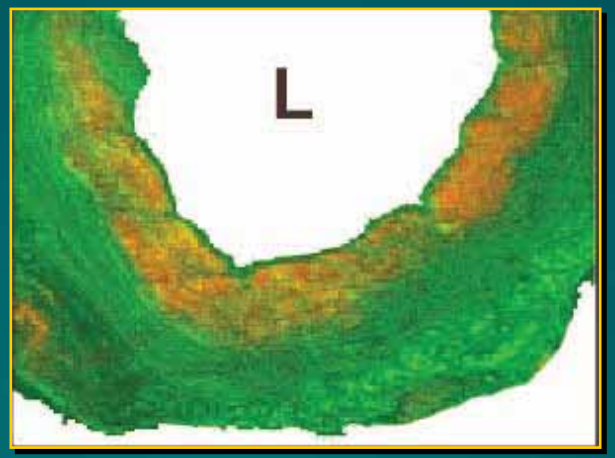
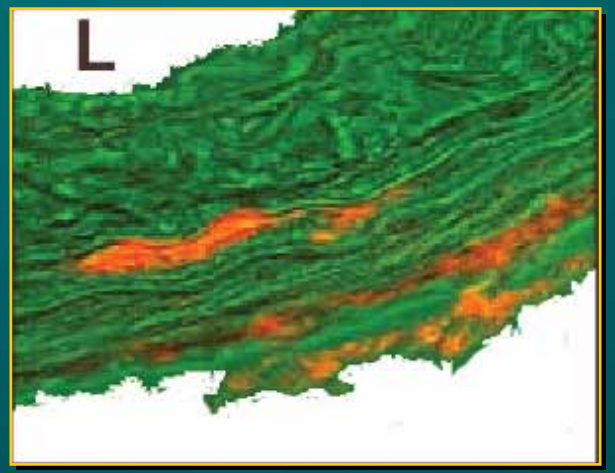
Inflammation Drives Vascular Injury

Non Injured

Injured





- Monocytes # is the most powerful predictor of final intimal area (Rogers et al., ATVB 16: 1312, 1996)
- Macrophages engulf fluorescent liposomes (orange): massive MΦ infiltration after injury mediates repair and adds to lesion bulk (Danenberg et al., Circulation 105:599, 2002)

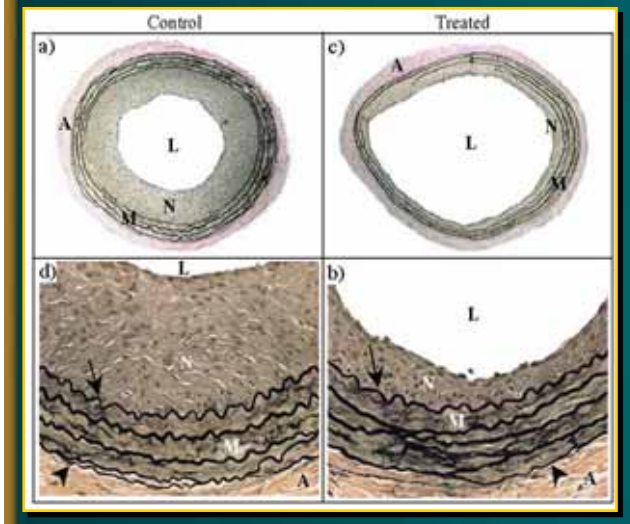
BIORest®

The BIOrest® Concept

- **Inflammation with macrophage recruitment** is the fundamental process precipitating restenosis after PCI-induced vascular injury
- **Biological targeting** of the PCI injury zone with non-toxic liposomal bisphosphonates (BPs) which inactivate macrophages and inhibit intimal hyperplasia is a more physiologic solution to restenosis
- **This approach allows more generalized anti-restenosis therapy (not restricted to stent-based drug delivery) and is independent of device use, treatment site(s), or degree of vascular injury**

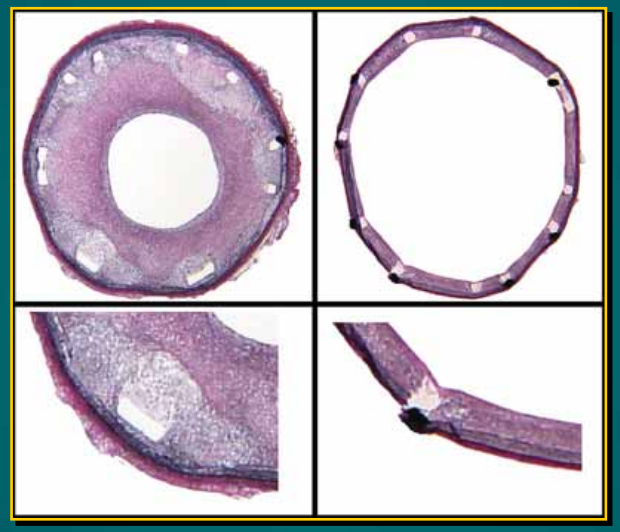
BIOrest® Aids Repair in Multiple Animal Models

Control Treated



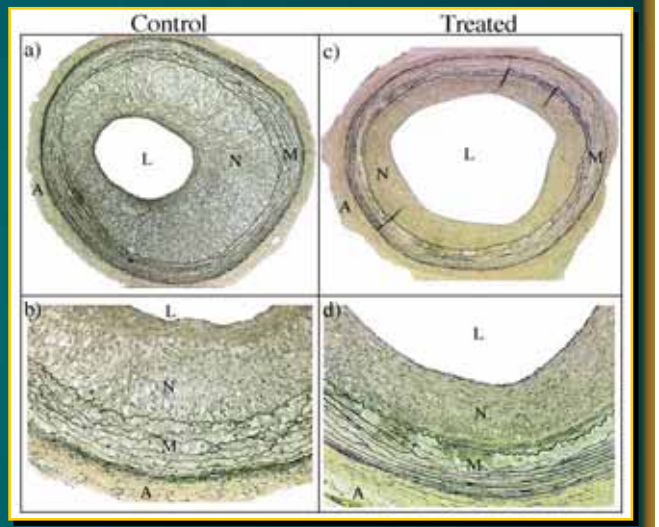
Rat
balloon injury
@ 14 days

Control Treated



Hypercholesterolemic
rabbit with stents
@ 28 days

Control Treated

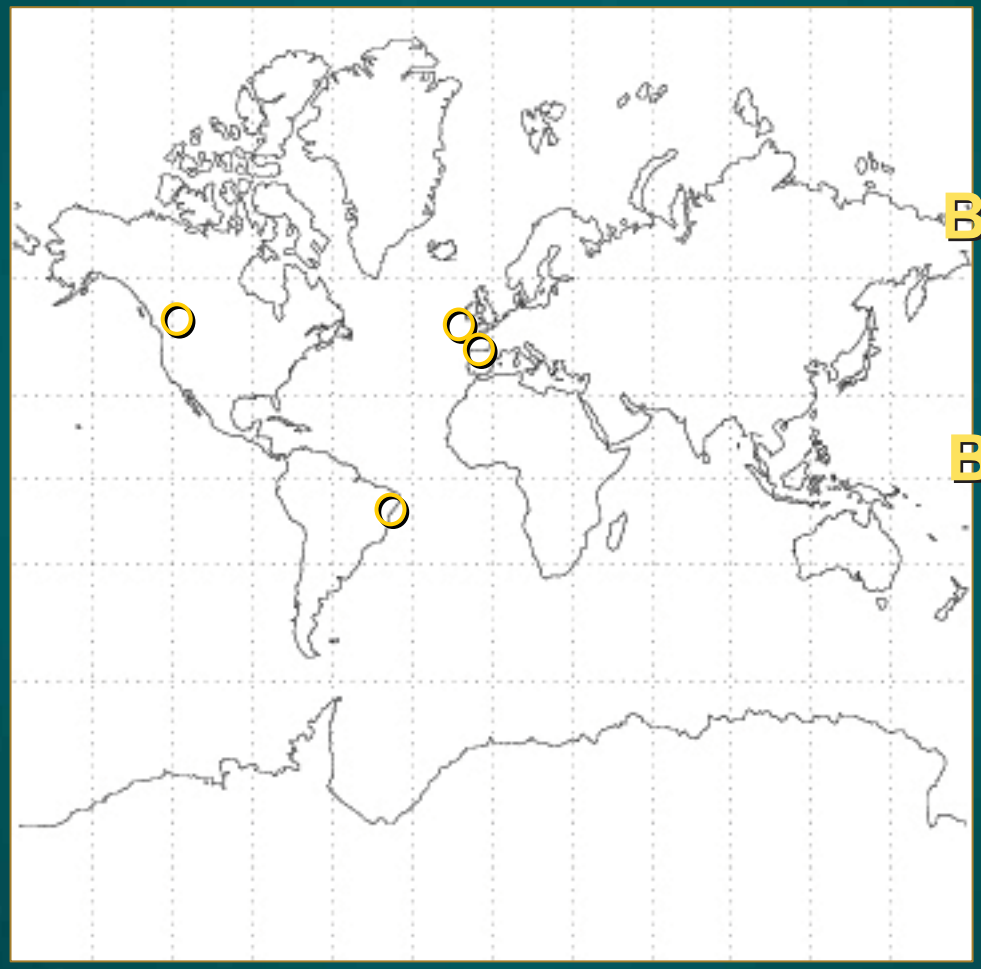


Hypercholesterolemic
rabbit balloon injury
@ 28 days

BIOrest Clinical Trial Strategy

BIO-Canada

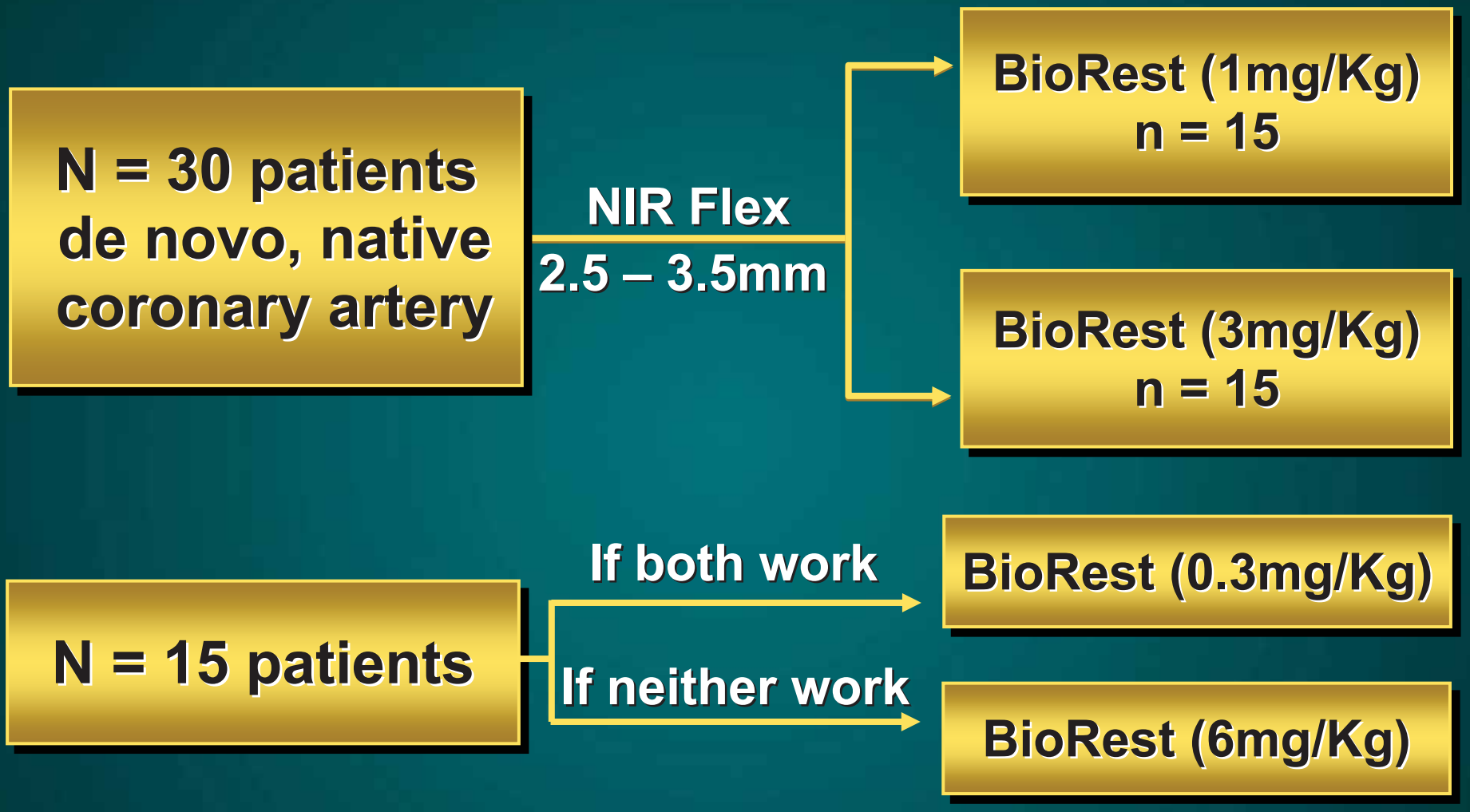
BIO-Brazil



BIO-Netherlands

BIO-Italy

Bio-Brazil – Study Design



Primary Endpoint

4-month Late loss and intimal hyperplasia by IVUS

BIOrest – Trials

- BIO-Italy (PI Antonio Colombo)
- BIO-Netherlands (PI Patrick Serruys)
- BIO-Canada (PI Japp Hamburger)

- Increasingly difficult patient population
  - Multi-vessel disease
  - Long lesions (> 30mm)
  - High percentage of diabetics
- Randomized comparison to DES (Cypher™)
- Endpoints:
  - Clinical: MACE
  - Angiographic: Late loss
  - IVUS: Intimal hyperplasia volume
  - Financial: Cost effectiveness

Restenosis has been the Achille's heel of angioplasty for the last 25 years

Restenosis has been put to rest

The New Achille's heel is cost