

The GENESIS Trial: 6-Month Results

**A Randomized, Multi-center Study of the
Pimecrolimus-Eluting and Paclitaxel-Eluting
Coronary Stent System in Patients with De Novo
Lesions of the Native Coronary Arteries**

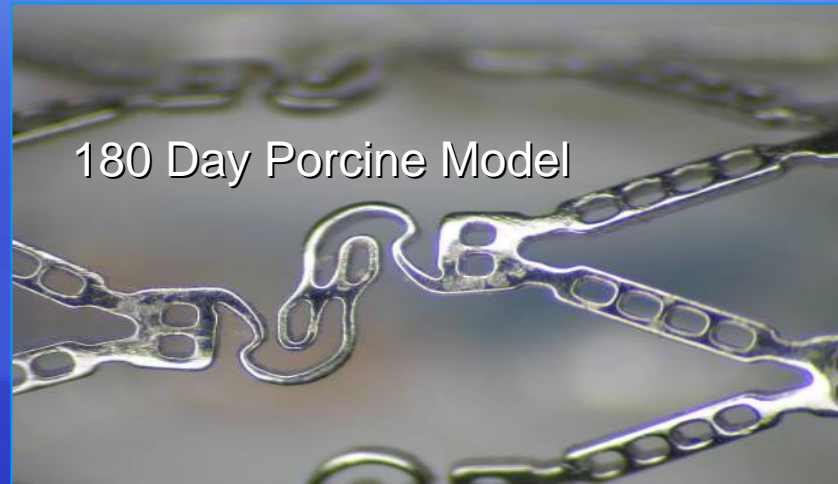
Stefan Verheye, MD, PhD
Antwerp Cardiovascular Institute
Middelheim, Antwerp, Belgium
SCAI / ACCi2 2008

Drug-Eluting Stents

Remaining Challenges

Challenge	Opportunity
Complex patient subsets still present a challenge	Optimized delivery of new or combination of active compounds
Acute and sub-acute stent thrombosis may be more frequent than with bare stents	New agents addressing different physiologic pathways
Delayed stent thrombosis, a previously unknown condition is a real and present danger	Different class of polymers Complete drug elution or less hypersensitivity inducing active agents
Coated Stents Have Inherent Limitations: <ul style="list-style-type: none"> - Poor control over release kinetics - Limited universe of deliverable drugs - Prone to peeling and sticking - Drug and polymer 'entombed' on stent 	'Broad Spectrum' delivery capability Different type of stents and polymers
Overlapping Stents: <ul style="list-style-type: none"> - Over dosing at overlap site - Dose dump at overlap site - Polymer contact erosion - Polymer flaking 	Different class of polymers or no polymers 'Gentler' class of active agents

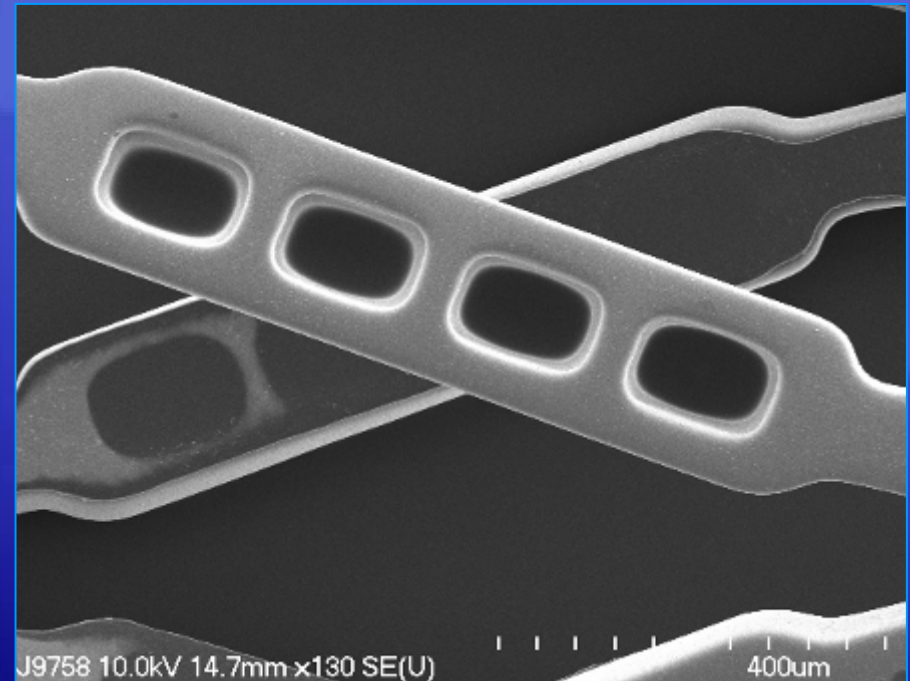
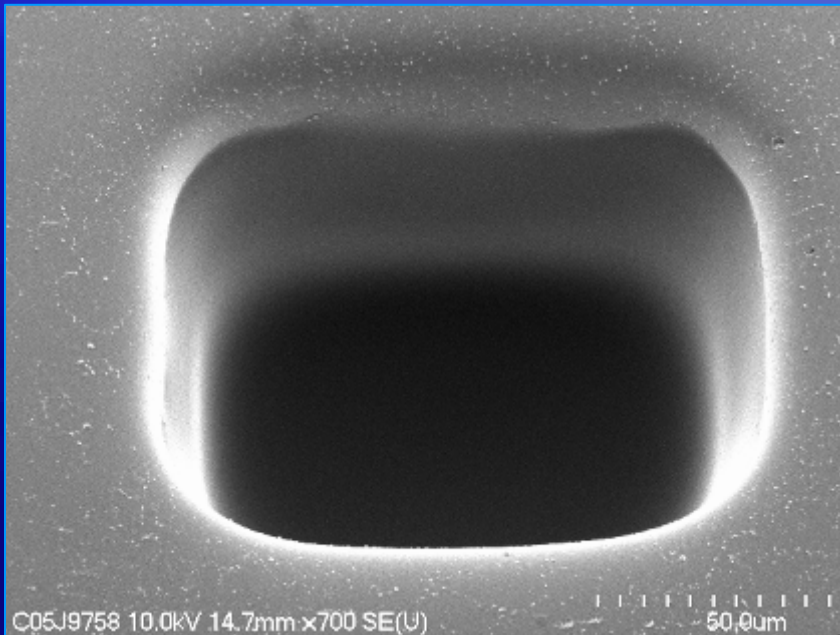
Conor CoStar™ Stent



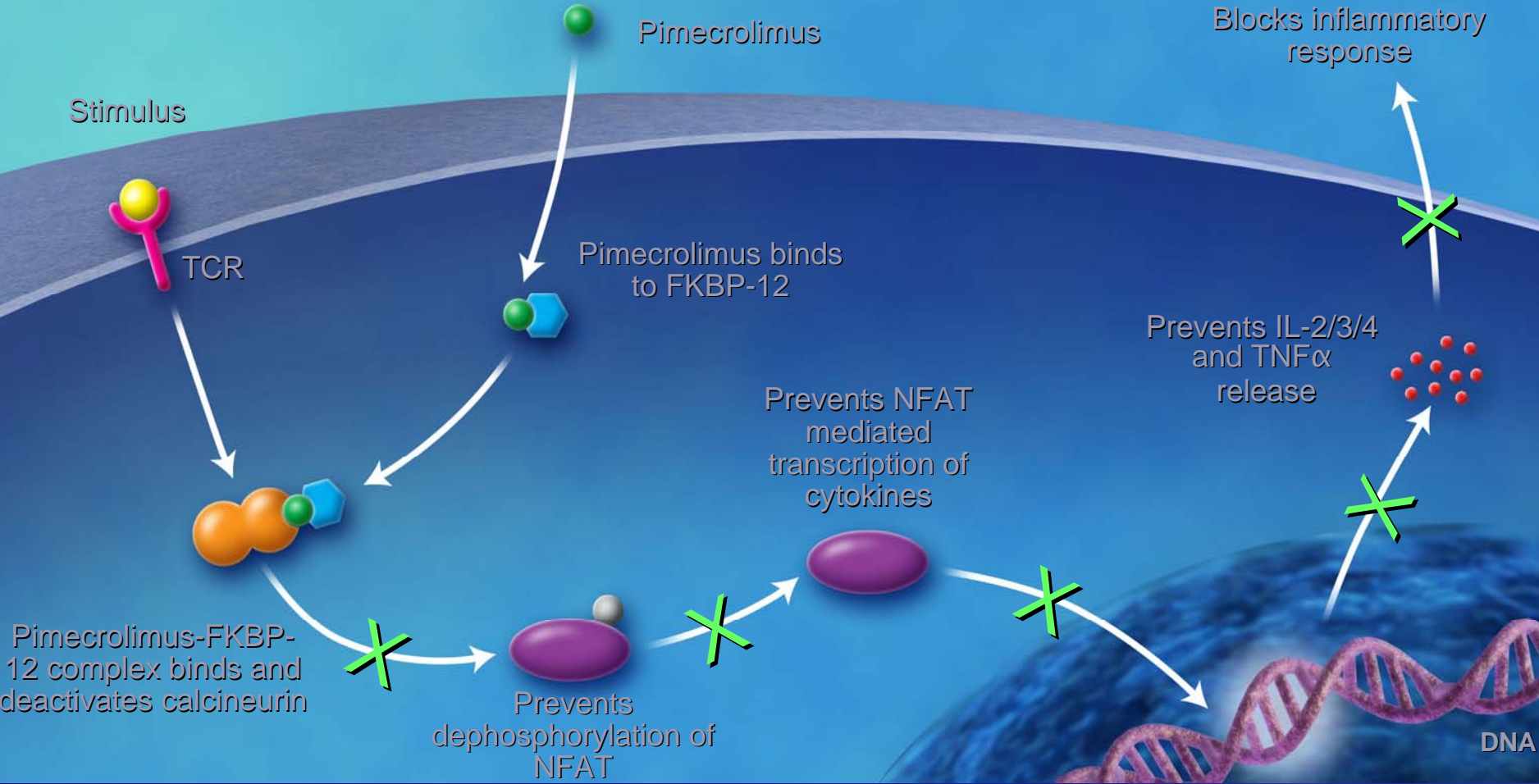
- A **second** generation polymer technology
 - Conor uses a bioresorbable polymer with minimal contact with the vessel wall, the result is reduced polymer tissue interaction and no long term residual drug or polymer

Conor Reservoir Technology

- A **unique** platform for drug delivery
 - The reservoir system in the Conor Stent design provides the ability to load drug and control the delivery time and rate

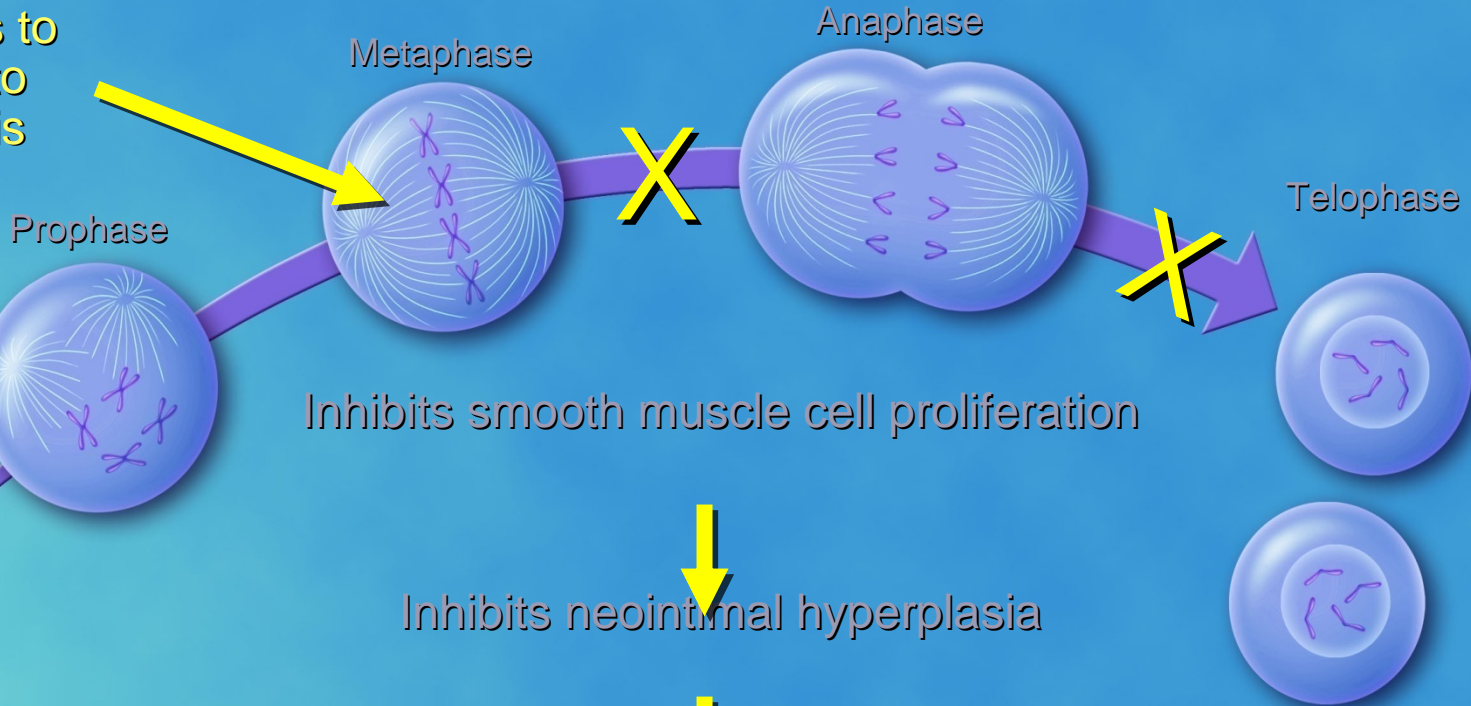


Pimecrolimus Inhibits the Inflammatory Response



Paclitaxel Inhibits Smooth Muscle Cell Proliferation

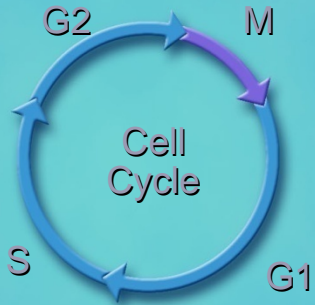
Paclitaxel binds to microtubules to prevent mitosis



Inhibits smooth muscle cell proliferation

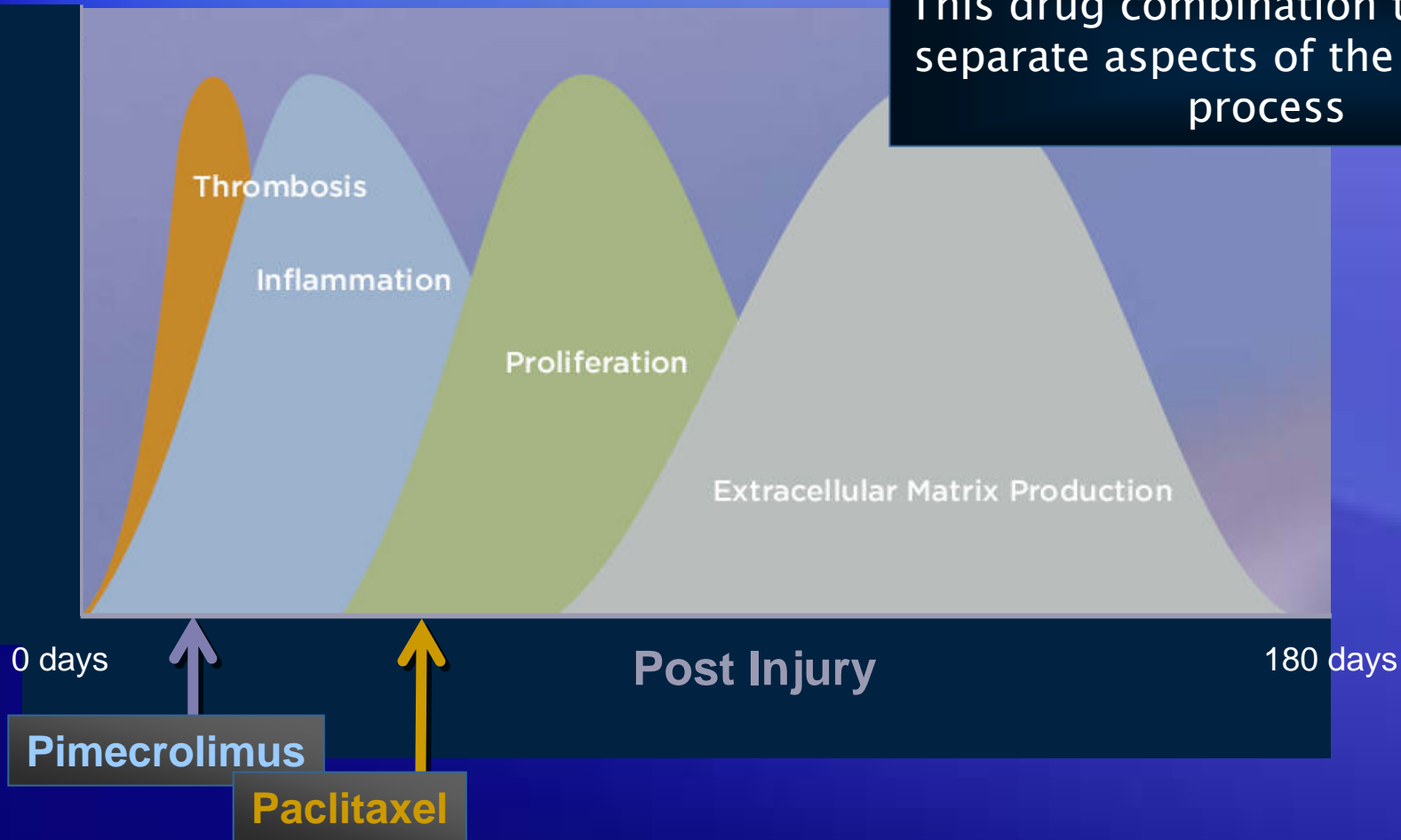
Inhibits neointimal hyperplasia

Prevents restenosis



Paclitaxel and Pimecrolimus Dual Drug Components

This drug combination targets two separate aspects of the restenosis process



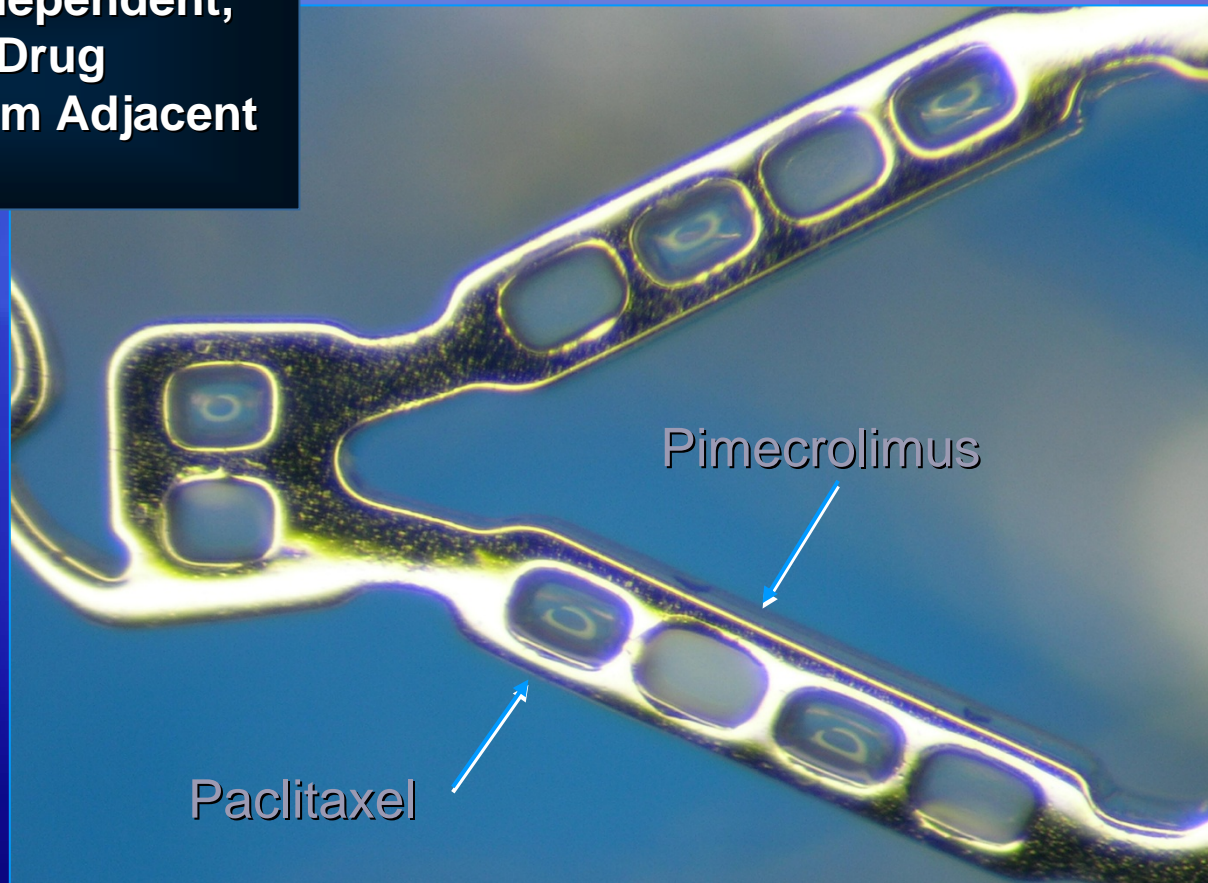
The Conor Drug Choice

Next generation 'gentler' drug

- Pimecrolimus is conducive to endothelial salvage
- Pimecrolimus has a broad therapeutic window
- Pimecrolimus' diffusion characteristics may better penetrate into the microvascular areas of atherosclerotic plaque
- Pimecrolimus potency may provide a more broad cytokine inhibition effect

Conor SymBio™ Dual Drug Stent

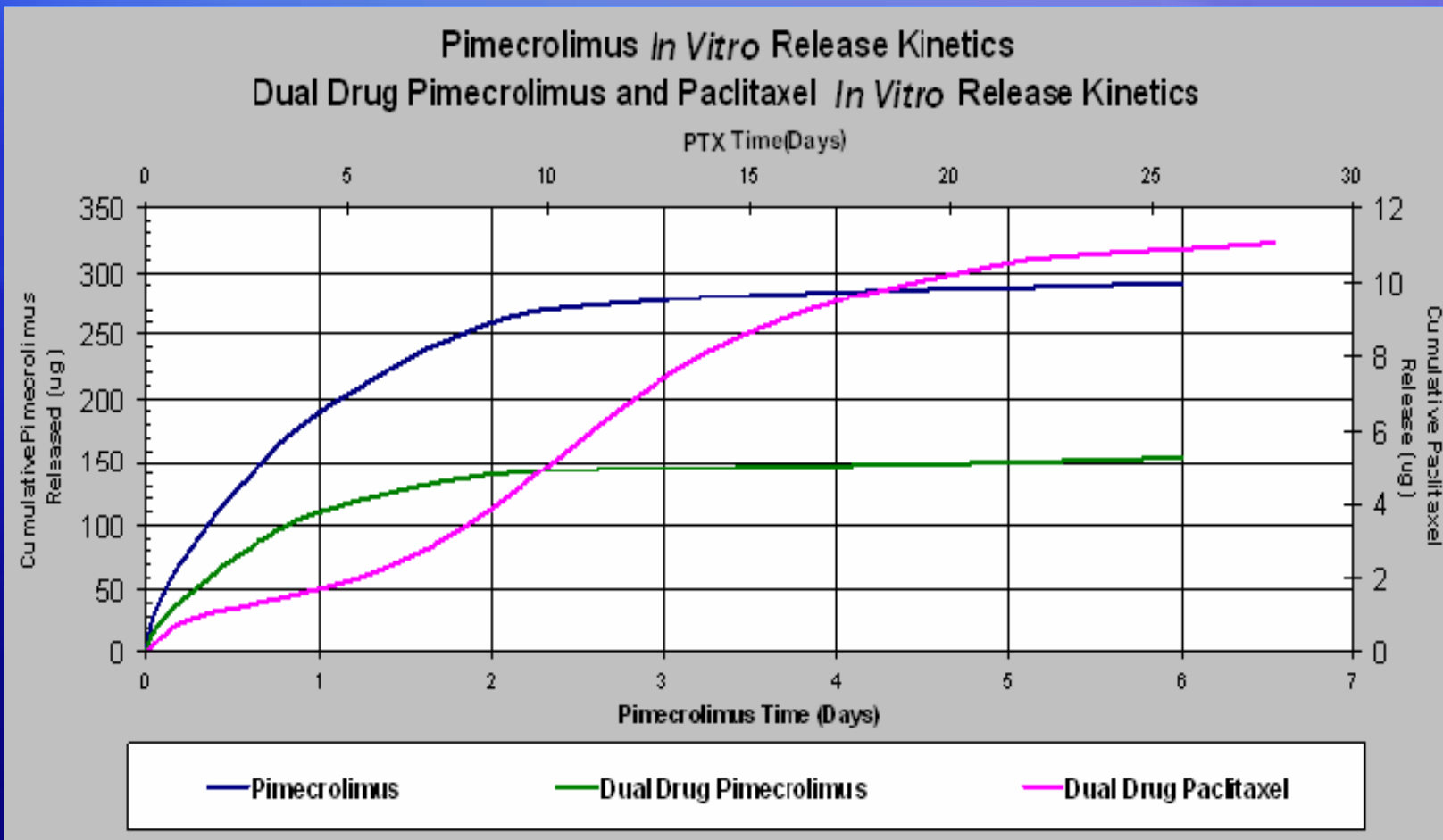
Multiple Independent,
Controlled Drug
Release from Adjacent
Reservoirs



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SymBio™

Pimecrolimus/Paclitaxel Dual-Drug
Coronary Stent System

In Vitro Release Kinetics for Pimecrolimus and Paclitaxel Studies



Potential Corio/SymBio Advantages

- **Pimecrolimus acts to prevent restenosis without delaying vessel healing**
- **Dual Drug Delivery is designed as a stronger solution to fight restenosis**
- **A Stent platform designed for better control of drug delivery with no residual drug and a reduced risk of long-term adverse events**

GENESIS Trial

Prospective, Three-arm, Asymmetric Randomization (1:2:2)

Single *De Novo* Native Coronary Artery Lesions
Reference Vessel Diameters: 2.5 - 3.5 mm
Lesion Length: <25 mm
Sites in UK, Belgium, France, Germany and Israel

CoStar[®]
Paclitaxel-Eluting
Stent (10 μ g)
N = 75 patients

SymBio[™]
Pimecrolimus/Paclitaxel-
Eluting Stent (162.5 μ g/10 μ g)
N = 150 patients

Corio[™]
Pimecrolimus-Eluting
Stent (325 μ g)
N = 150 patients

Primary Endpoint: 6-Month In-Stent Late Loss
Sub-Studies; 6-Month IVUS (first 30 pts. for each arm)
Dual antiplatelet therapy for 6 months

Clinical/MACE

30-Day

6-Mo.

1-Yr.

2-Yr.

3-Yr.

4-Yr.

5-Yr.

Angiographic/IVUS

Safety and Efficacy Endpoints

Primary Endpoint

- **Non-inferiority of in-stent late loss at six months**
 - Dual pimecrolimus/paclitaxel compared to CoStar®
 - Pimecrolimus compared to CoStar®

Secondary Endpoints

- **Device, lesion and procedural success**
- **Major Adverse Cardiac Event (MACE)**
 - 30 day, 6 month, 1 through 5 year follow-up
- **In-segment late loss**
- **In-stent and in-segment MLD and binary restenosis**
- **% Volume Obstruction**
- **Late acquired stent malapposition**

Trial Suspended

- Enrollment in the GENESIS Trial was suspended on April 28th, 2007, before full enrollment was completed
- This decision was made by the study PIs in consultation with Conor Medsystems
- The decision was made to analyze the data available on all enrolled patients at the time of trial suspension

Patient Demographics

	CoStar[®] (N = 49)	SymBio[™] (N = 97)	Corio[™] (N = 100)
Age	64.4 ± 9.6 (49)	59.9 ± 10.1 (97)	64.1 ± 10.0 (100)
Gender (% Male)	71.4% (35/49)	78.4% (76/97)	80.0% (80/100)
Prior MI	22.5% (11/49)	29.9% (29/97)	26.0% (26/100)
Prior PCI	26.5% (13/49)	28.9% (28/97)	33.0% (33/100)
Prior CABG	6.1% (3/49)	0.0% (0/97)	2.0% (2/100)
Diabetes Mellitus	36.7% (18/49)	17.5% (17/97)	32.0% (32/100)
Insulin Dependent	16.7% (3/18)	11.8% (2/17)	46.9% (15/32)
Unstable Angina	24.4% (10/41)	42.0% (34/81)	28.7% (25/87)
Ejection Fraction (%)	61.8 ± 8.9 (47)	63.7 ± 12.5 (87)	63.7 ± 12.1 (97)

Lesion Characteristics

	CoStar[®] (N = 49)	SymBio[™] (N = 101)	Corio[™] (N = 100)
Target Vessel			
LAD	40.8%	51.5%	49.0%
Circumflex	24.5%	17.8%	24.0%
RCA	34.7%	30.7%	27.0%
Lesion Length (mm)	14.42 ± 5.98	13.75 ± 5.42	14.93 ± 5.49
Eccentric	14.3%	33.7%	31.0%
Bifurcation Lesion	20.4%	27.7%	28.3%
Angulation > 45°	10.2%	7.9%	6.0%
Thrombus	0.0%	1.0%	0.0%
Calcification (mod/sev)	32.7%	20.8%	34.0%
TIMI 0 – 1 Flow	2.0%	0.0%	1.0%

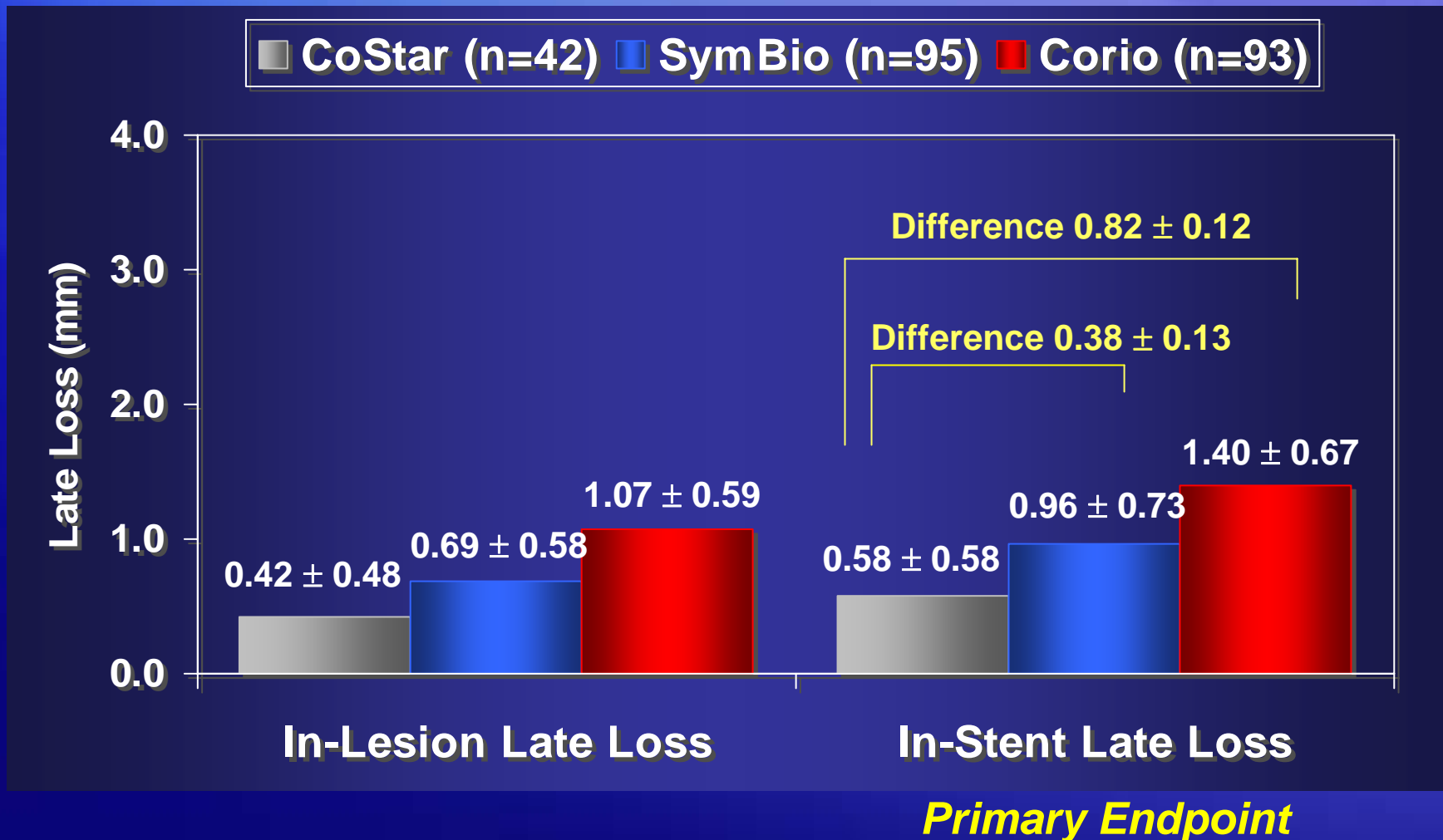
Procedural Success

	CoStar[®] (N = 49)	SymBio[™] (N = 97)	Corio[™] (N = 100)
Device Success	98.0%	97.9%	92.0%
Lesion Success	100.0%	100.0%	98.0%
Procedure Success	100.0%	100.0%	94.0%

QCA Analysis

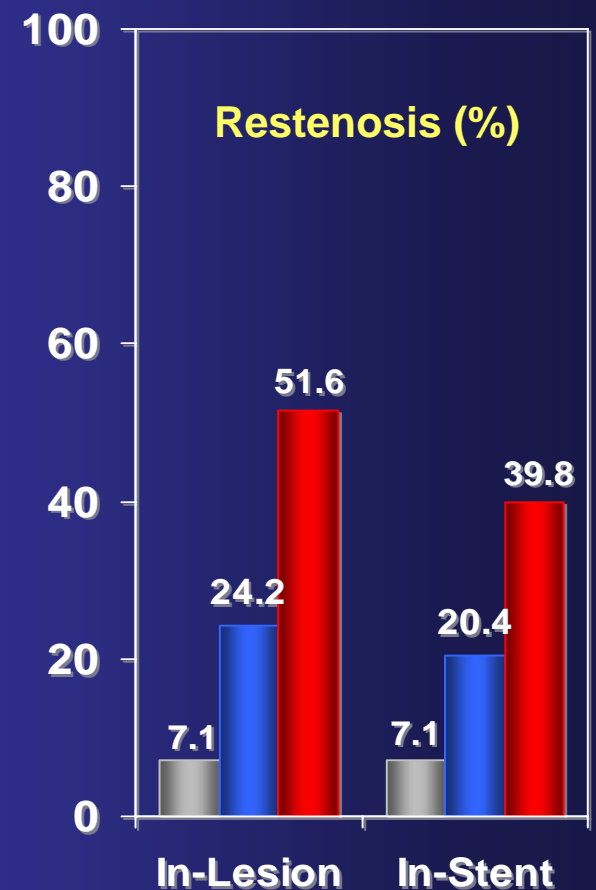
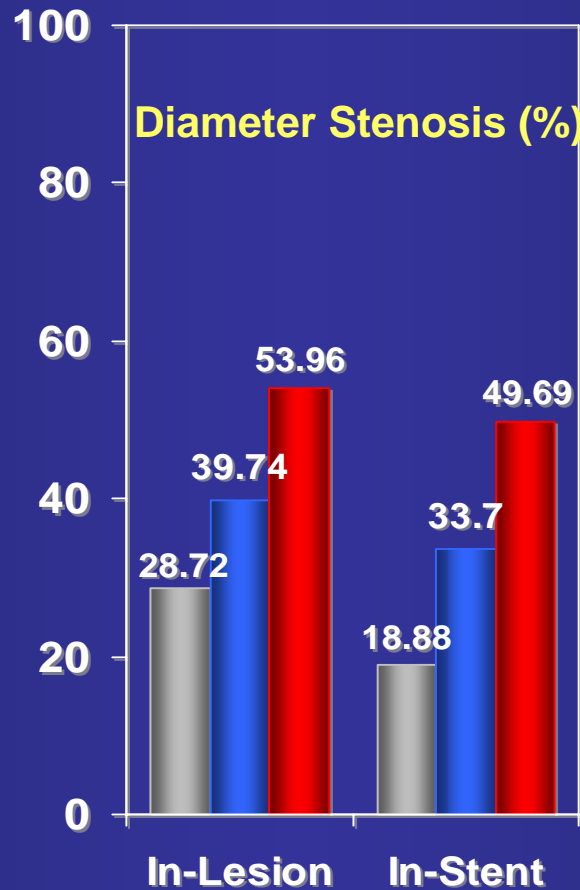
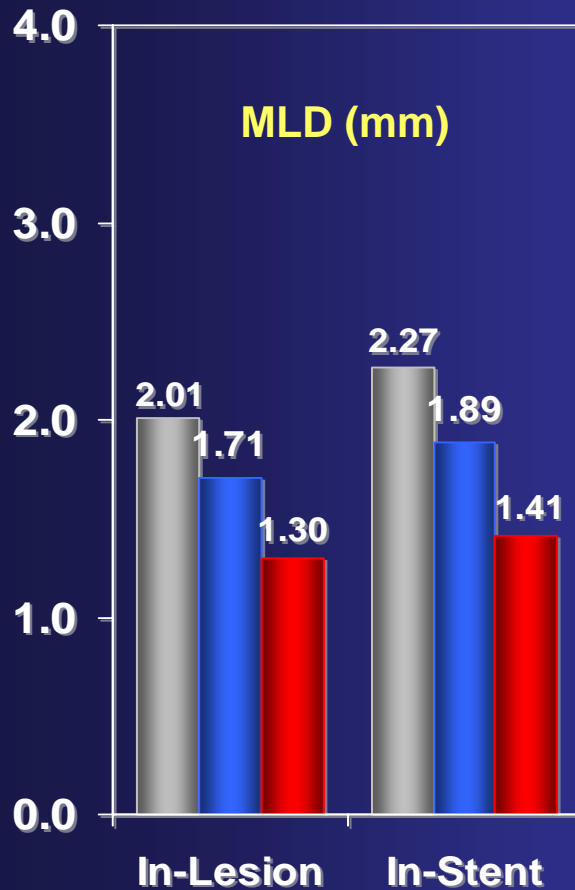
	CoStar[®] (N = 49)	Symbio[™] (N = 97)	Corio[™] (N = 100)
Pre-procedure QCA Measures			
RVD (mm)	2.81 ± 0.47 (49)	2.87 ± 0.50 (101)	2.79 ± 0.45 (99)
MLD (mm)	0.72 ± 0.31 (49)	0.78 ± 0.37 (101)	0.76 ± 0.38 (99)
% DS (%)	73.86 ± 10.78 (49)	72.41 ± 12.57 (101)	72.91 ± 12.09 (99)
Post-procedure QCA Measures			
RVD (mm)	2.84 ± 0.47 (49)	2.92 ± 0.51 (100)	2.82 ± 0.42 (100)
In-lesion MLD (mm)	2.41 ± 0.49 (49)	2.41 ± 0.45 (100)	2.33 ± 0.47 (100)
In-stent MLD (mm)	2.82 ± 0.42 (49)	2.83 ± 0.39 (98)	2.81 ± 0.38 (99)
In-lesion % DS (%)	15.50 ± 7.41 (49)	17.43 ± 7.98 (100)	17.67 ± 11.67 (100)
In-stent % DS (%)	5.41 ± 6.22 (49)	7.43 ± 5.74 (98)	6.15 ± 4.75 (99)
Acute Gain, In-lesion (mm)	1.69 ± 0.52 (49)	1.63 ± 0.52 (100)	1.57 ± 0.50 (99)
Acute Gain, In-stent (mm)	2.10 ± 0.49 (49)	2.05 ± 0.46 (98)	2.04 ± 0.43 (98)

Late Loss at 6 Months

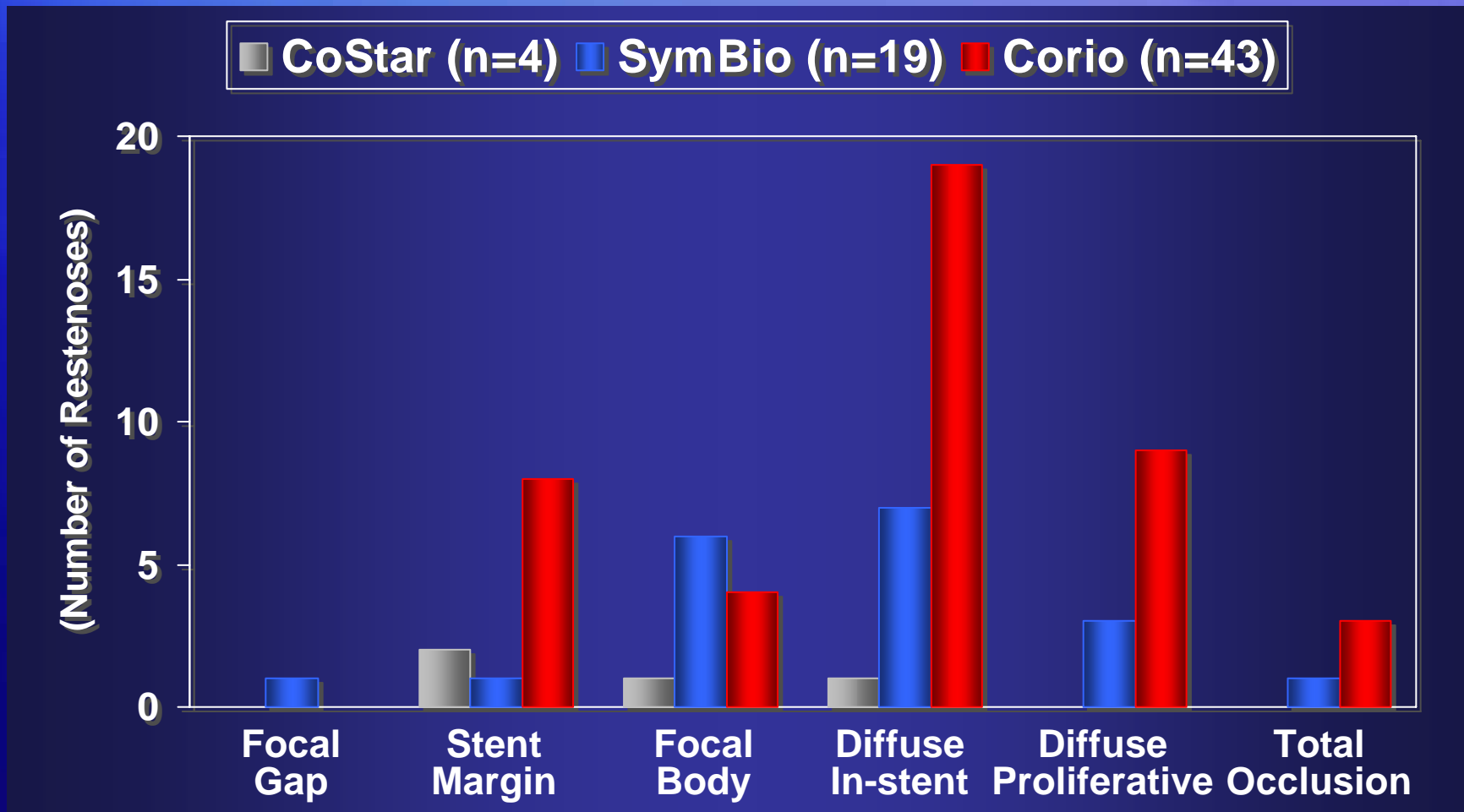


2° Angiographic Endpoints

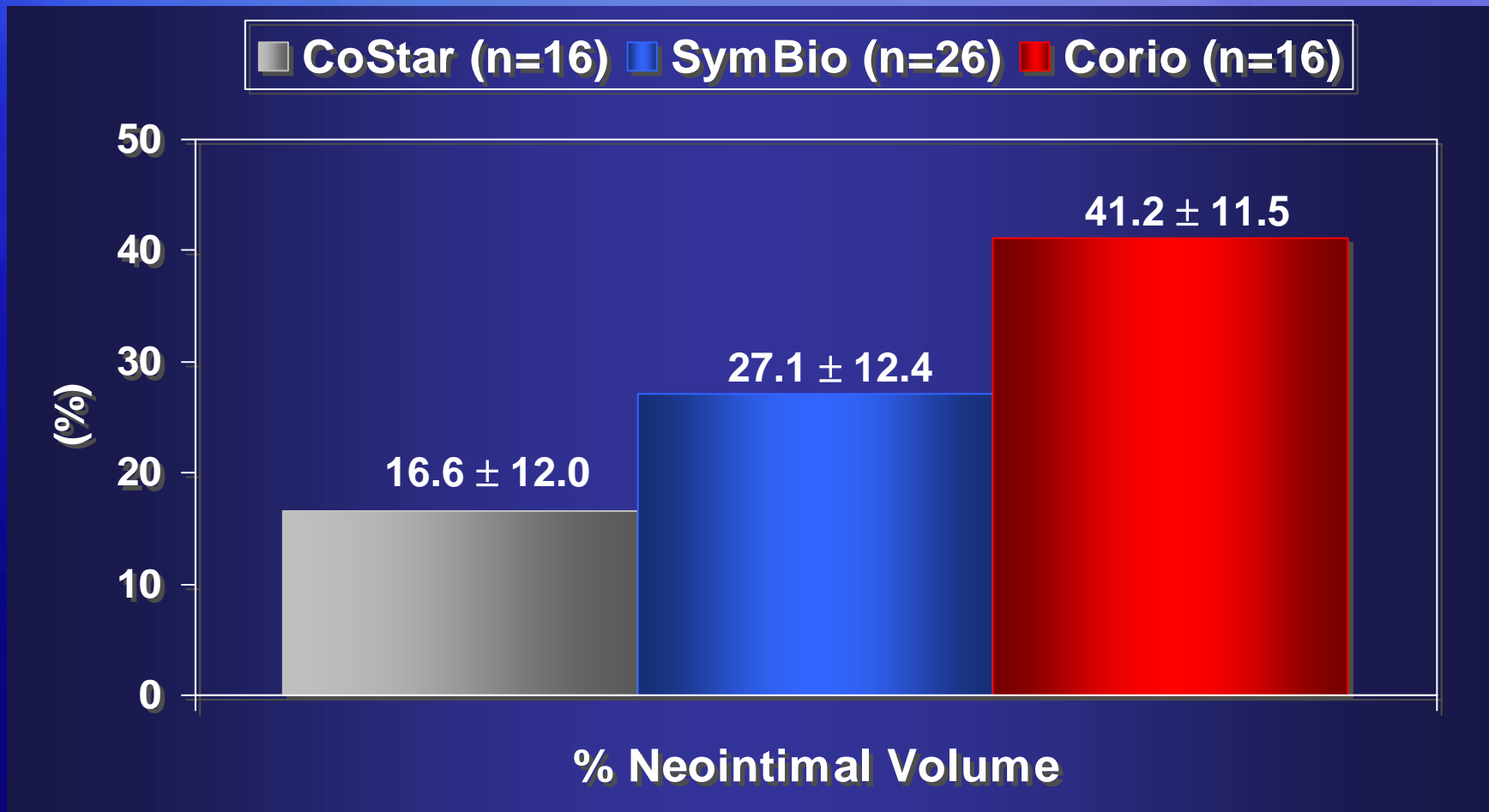
CoStar Symbio Corio



Pattern of Restenosis



IVUS Follow-up at 6 Months



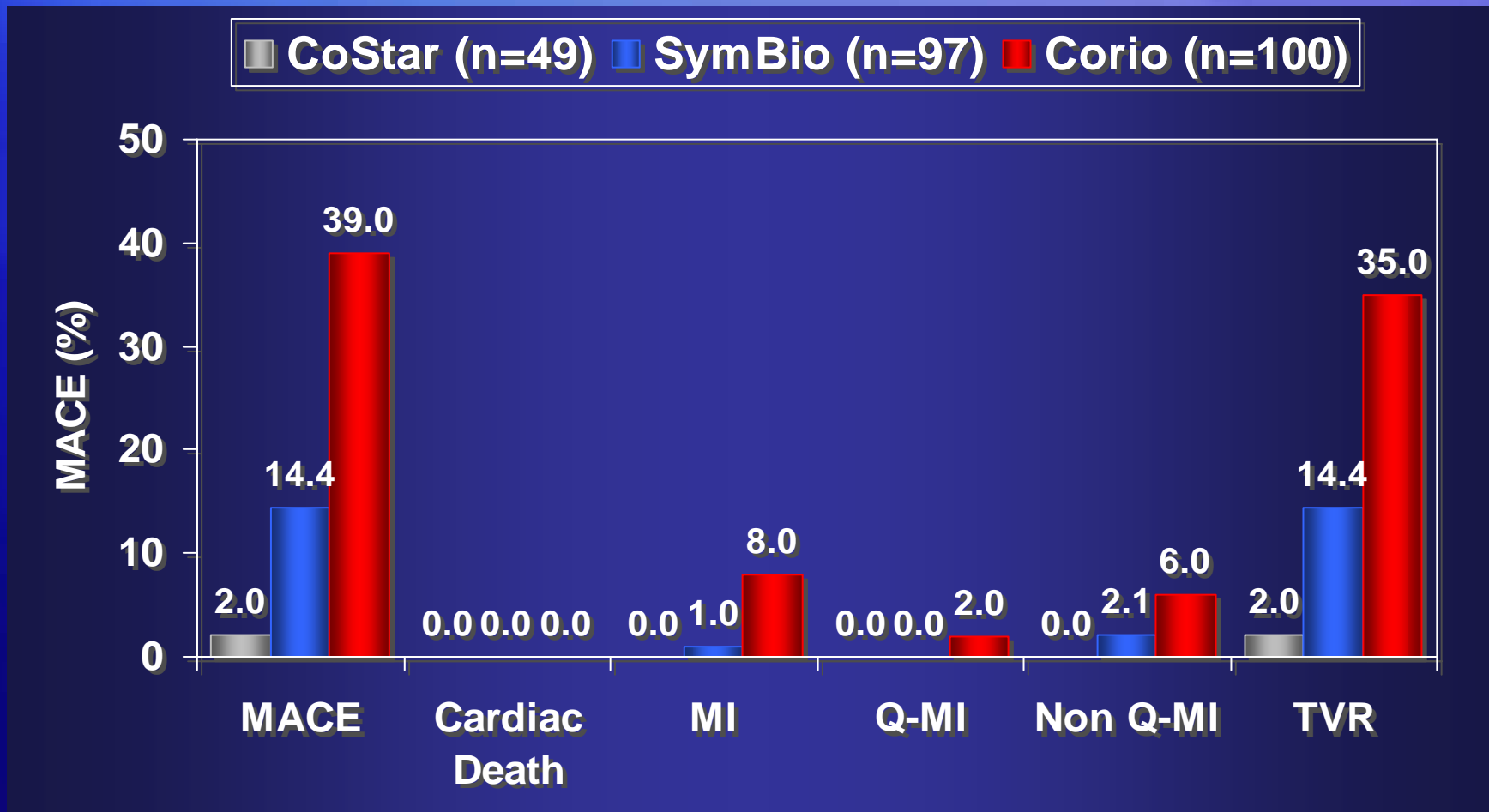
Stent Overlap Analysis

	CoStar®	SymBio™	Corio™
Post-procedure Stent Overlap QCA			
No. of Stent Overlap	2	8	8
Stent Overlap Length (mm)	4.06 ± 1.62	2.84 ± 1.34	3.05 ± 2.14
Overlap MLD (mm)	2.92 ± 0.29	2.88 ± 0.38	3.06 ± 0.30
Overlap % DS (%)	-3.98 ± 5.63	-0.54 ± 7.50	-1.06 ± 5.70
6-Month F/U Overlap QCA			
Overlap MLD (mm)	2.38 ± 0.29	2.33 ± 0.63	1.34 ± 0.96
Overlap % DS (%)	9.27 ± 14.22	10.71 ± 20.28	42.41 ± 39.56
Overlap Restenosis (%)	0.0%	0.0%	37.5%
Overlap Late Loss (mm)	0.54 ± 0.58	0.55 ± 0.63	1.72 ± 0.81

MACE at 30 Days

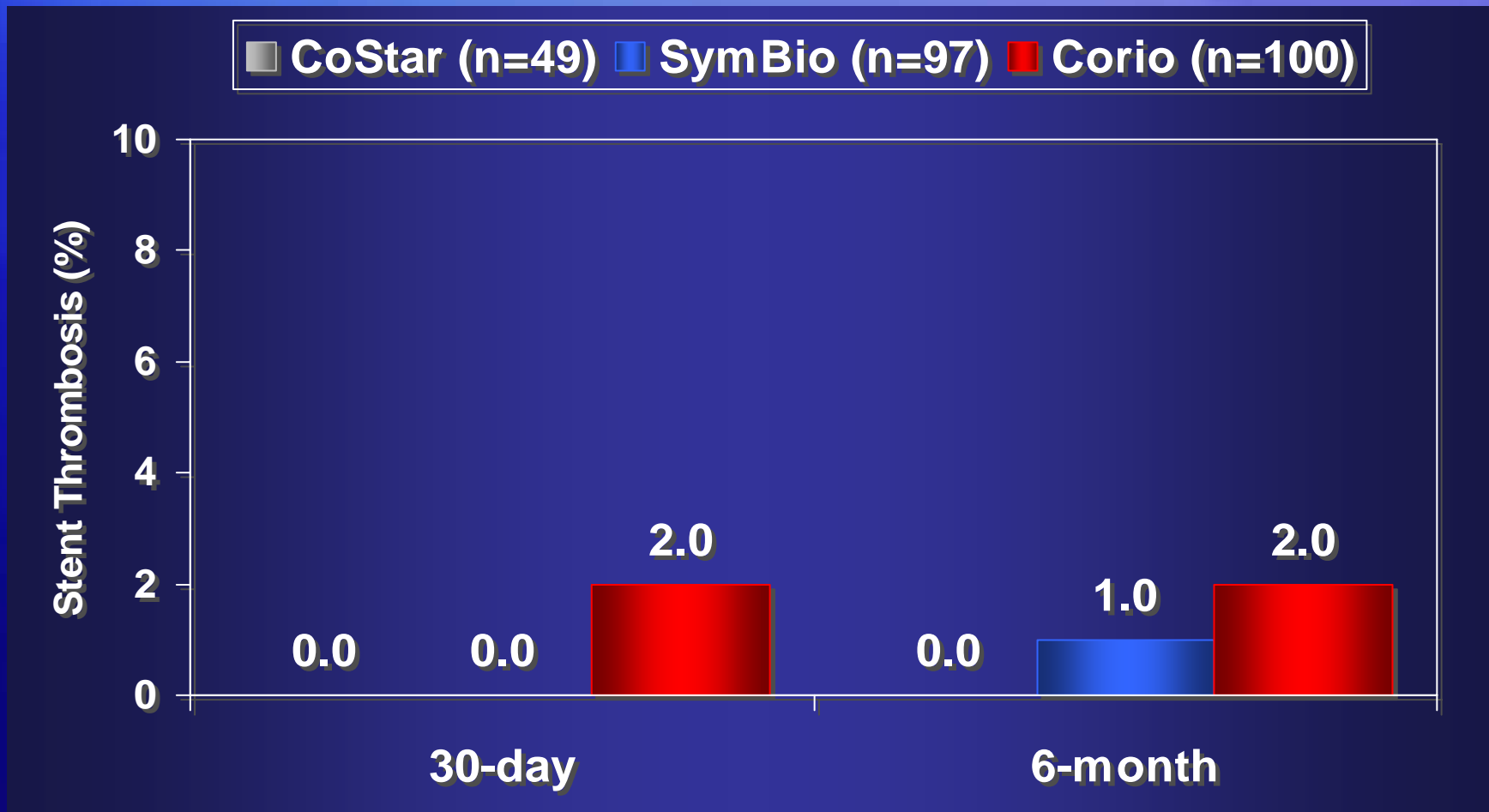
	CoStar[®] (N = 49)	SymBio[™] (N = 97)	Corio[™] (N = 100)
MACE	0.0%	0.0%	6.0%
Cardiac Death	0.0%	0.0%	0.0%
Myocardial Infarction	0.0%	0.0%	6.0%
Q-Wave MI	0.0%	0.0%	2.0%
Non Q-Wave MI	0.0%	0.0%	4.0%
TVR	0.0%	0.0%	1.0%

MACE at 6 Months



Overall MACE $p < 0.0001$
(Both Treatment Arms Compared with Control)

Stent Thrombosis



Conclusions

- Despite pre-clinical data suggesting marked efficacy of pimecrolimus in suppressing neointimal hyperplasia, the extent of tissue growth and resulting rates of TVR at 6 months were highest in patients treated with the Corio™ Pimecrolimus-Eluting Stent
- These rates were reduced by nearly 2/3 by co-elution of full-dose paclitaxel with 1/2 dose pimecrolimus in the SymBio™ Pimecrolimus/Paclitaxel Eluting Coronary Stent
- Suppression of neointimal hyperplasia was maximal with paclitaxel alone

Conclusions

- **The GENESIS trial is the first trial to use Conor reservoir technology to enable dual drug delivery for the treatment of *de novo* coronary lesions**
- **The trial demonstrates the ability to deliver two drugs independently with each drug having an affect on the tissue response to coronary intervention**