

# **Clinical Trials with the SMT Supralimus Sirolimus-Eluting Stent (Series I and PAINT)**

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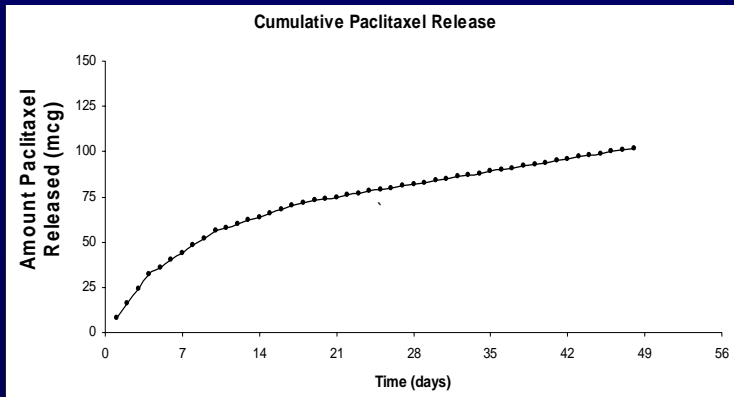
**São Paulo, Brazil**

**TCT 2007 – Breakfast Meet**

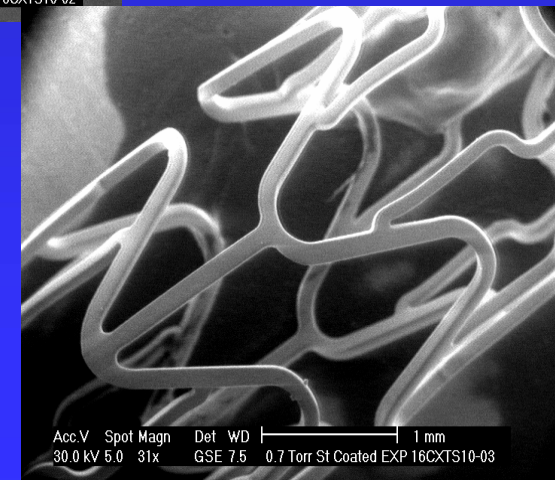
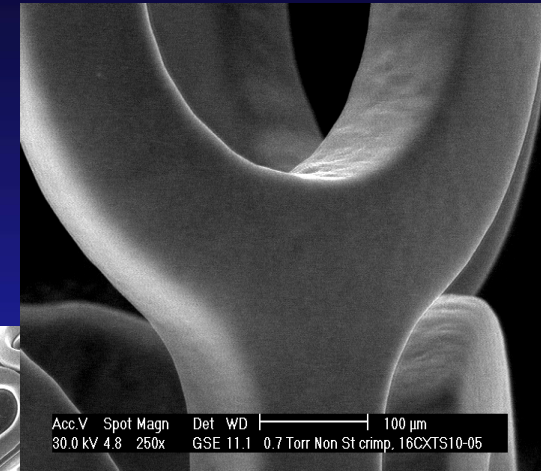
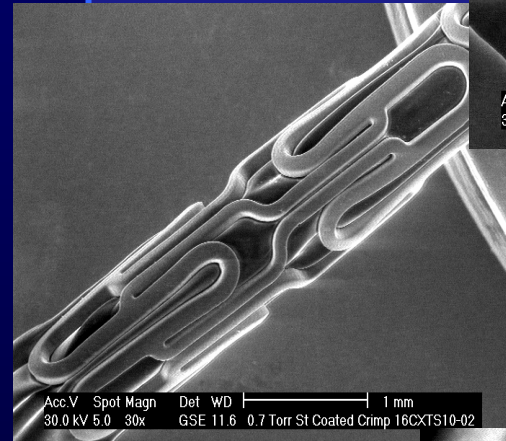
**SMTPL Advanced DES Systems**

**21st October - 07:00 – 08:00 (room 144C)**

# Supralimus – Sirolimus ES

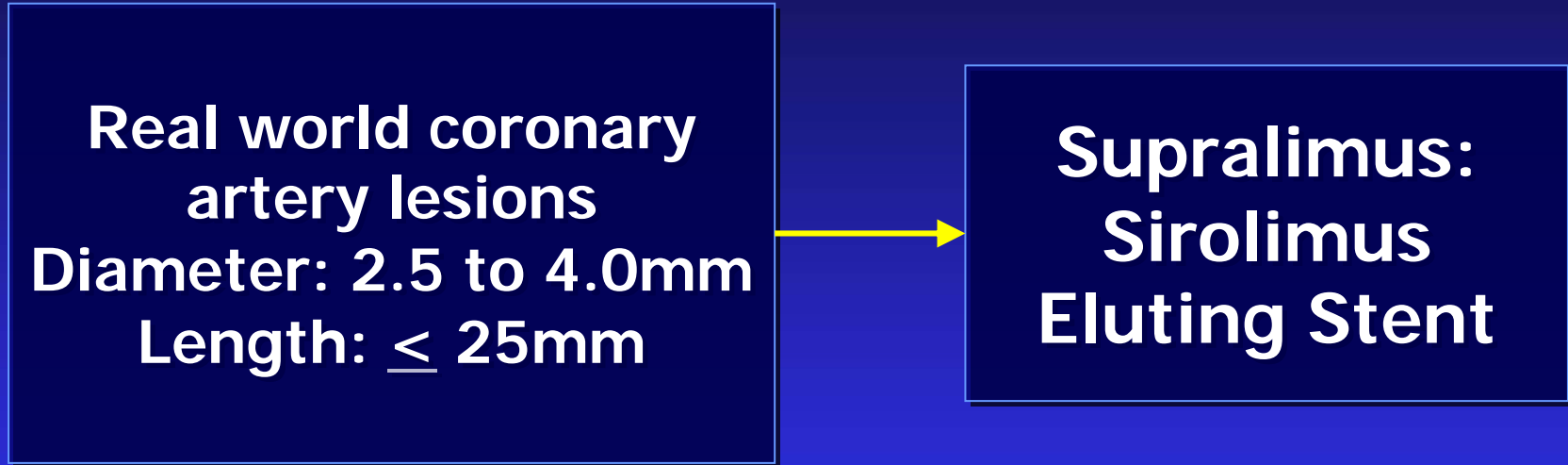


- **Slow Release profile**
  - 27% release within 1 week
  - 100% within 7 weeks.
- No residual drug-polymers
- Drug is released by diffusion
- Polymers breaks up by hydrolysis and enzymatic action into CO<sub>2</sub> and H<sub>2</sub>O.



# SERIES I: Study Design

N = 100 pts



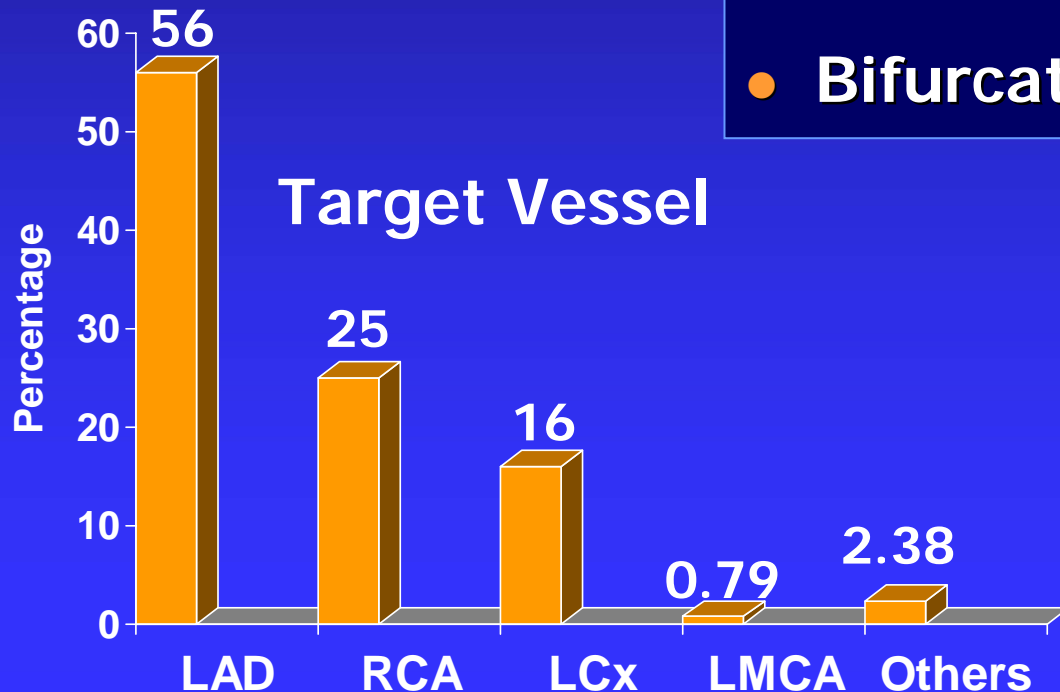
**Primary EP: 30-day MACE & 6-month in-stent restenosis**

**Secondary EP: Angiographic success & 9-month MACE**

# SERIES I: Patient & Lesion Characteristics

- Diabetes: 29%
- CHF: 7%
- MV disease: 27%

- CTO: 11.6%
- Thrombotic Lesions: 13.7%
- ISR Lesions: 0.7%
- Ostial Lesions: 5.5%
- Bifurcated Lesions: 3.4%



# SERIES I: 6-month QCA

Lesion Length  $10.50 \pm 4.30$  mm

Minimal luminal diameter

Pre  $0.73 \pm 0.61$  mm

Post  $2.53 \pm 0.43$  mm

FUP  $2.44 \pm 0.48$  mm

Diameter stenosis

Pre  $72.42 \pm 21.70$  mm

Post  $11.51 \pm 6.63$  mm

FUP  $14.20 \pm 9.50$  mm

**In-Stent Late Loss  $0.09 \pm 0.28$  mm**

**In Segment Late Loss  $0.02 \pm 0.37$  mm**

# SERIES I: 30-month Adverse Events

Clinical FUP	1 M	6 M	9 M	24 M	30 M
Death (%)	0 (0.0)	2 (2.0)	2 (2.0)	3 (3.1)	4 (4.1)
TLR (%)	0 (0.0)	2 (2.0)	4 (4.0)	4 (4.1)	4 (4.1)
Overall MACE (%)	0 (0.0)	4 (4.0)	6 (6.0)	7 (7.2)	8 (8.2)
Angiogr. Stent Thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

***Percutaneous INTervention with  
biodegradable-polymer based  
paclitaxel-eluting, sirolimus-eluting,  
or bare stents for the treatment of  
de novo coronary lesions***

**The PAINT trial**

# Centers



Fortaleza: A. A. Guimaraes

Natal: Itamar Oliveira

Vitória: Airton Arruda  
Vitoria: Bruno Machado

BH: Maurício Barbosa

RJ: Cesar Medeiros

SP1: Pedro Lemos  
SP2: Fabio Brito Jr  
SP3: Valter Lima  
SP3: Marco Perin

POA: Paulo Caramori

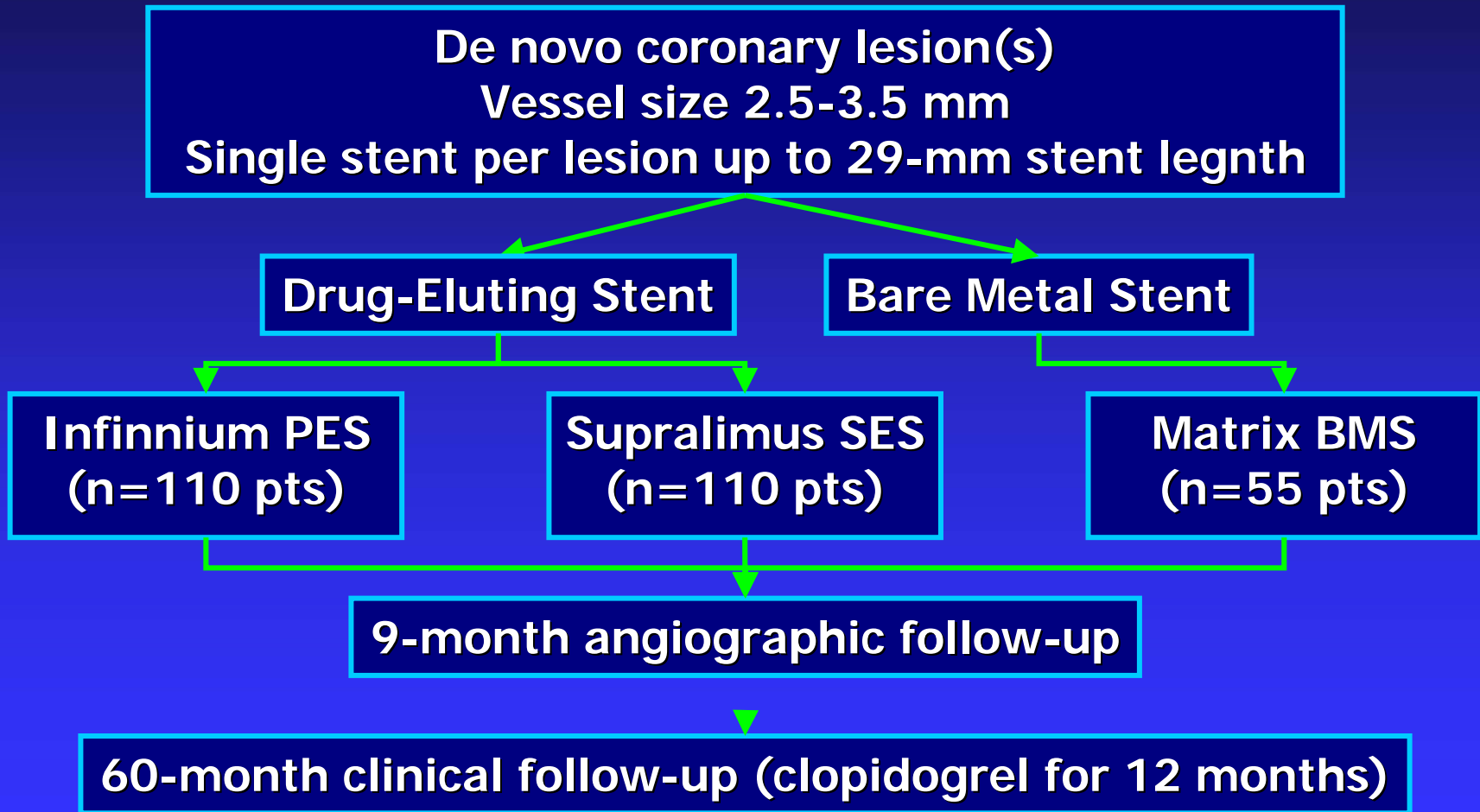
Chile: Francisco Ramirez

# Study Organization

- **Steering Committee**
  - Dr. Pedro A. Lemos
  - Dr. Eulógio E. Martinez
  - Dr. Expedito E. Ribeiro
  - Dr. Valter C. Lima
  - Dr. Bruno M. Machado
  - Dr. J. Airton Arruda
  - Dr. Itamar Ribeiro Oliveira
  - Dr. Maurício de Rezende Barbosa
  - Dr. Fábio S. de Brito Jr.
  - Dr. César R. Medeiros
  - Dr. Paulo Caramori
- **Data Safety and Adjudication Committee**
  - Dr. Antonio Carlos Carvalho (president)
  - Dr. Luciano Drager
  - Dr. Carlos Augusto Campos
- **Contract Research Organization**
  - CRO Fundação Zerbini, São Paulo, Brazil
- **Database management**
  - Coreware, São Paulo, Brazil
- **Angiographic core lab**
  - Cardialysis, Rotterdam, The Netherlands

# Study Design

- Multicenter, randomized (2:2:1), non-blinded



Primary EP: 9-month IS LL of DES vs. BMS

# PAINT 250

## Baseline Characteristics

	<b>Matrix</b> <i>(n=51 pts)</i>	<b>Infinnium</b> <i>(n=102 pts)</i>	<b>Supralimus</b> <i>(n=99 pts)</i>	<b>P</b>
<b>Age, y ± SD</b>	<b>58±10</b>	<b>60±10</b>	<b>59±10</b>	<b>0.5</b>
<b>Male, %</b>	<b>63</b>	<b>61</b>	<b>68</b>	<b>0.6</b>
<b>Hypertension, %</b>	<b>84</b>	<b>85</b>	<b>91</b>	<b>0.4</b>
<b>Diabetes, %</b>	<b>22</b>	<b>29</b>	<b>37</b>	<b>0.1</b>
<b>Previous MI, %</b>	<b>37</b>	<b>29</b>	<b>32</b>	<b>0.6</b>
<b>Previous PCI, %</b>	<b>18</b>	<b>16</b>	<b>14</b>	<b>0.9</b>
<b>Previous CABG, %</b>	<b>4</b>	<b>8</b>	<b>5</b>	<b>0.5</b>
<b>HF%</b>	<b>4</b>	<b>3</b>	<b>7</b>	<b>0.6</b>

# PAINT 250

## Stent Size

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	<b>Matrix</b> <i>(n=51 pts)</i>	<b>Infinnium</b> <i>(n=102 pts)</i>	<b>Supralimus</b> <i>(n=99 pts)</i>	<b>P</b>
<b>Diameter</b>				0.4
2.5 mm, %	20	20	16	
3.0 mm, %	40	50	57	
3.5 mm, %	40	30	26	
<b>Length</b>				0.2
19 mm, %	60	58	62	
23 mm, %	30	19	24	
29 mm, %	10	23	14	

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# PAINT 250

## Adverse Events at 30 days

	<b>Matrix</b> <i>(n=51pts)</i>	<b>Infinnium</b> <i>(n=102 pts)</i>	<b>Supralimus</b> <i>(n=99 pts)</i>	<b>P</b>
<b>Death, %</b>	0	1.0	1.0	0.8
<b>Myocardial infarction, %</b>	3.9	4.0	1.0	0.1
<b>Q-wave MI %</b>	0	1.0	0	0.9
<b>Re-intervention, %</b>	0	0	0	-
<b>CABG, %</b>	0	0	0	-
<b>Re-PCI, %</b>	0	0	0	-
<b>St thrombosis (any ARC), %</b>	0	0	0	-

# Conclusion

- Long-term 30-month results from the Series I trial suggest that the Supralimus SES has an excellent safety and efficacy profile.
- Preliminary and partial results from the randomized PAINT trial indicates that the BMS Matrix, the DES Infinnium (paclitaxel) and Supralimus (sirolimus) are safe at 30 days with low rates of major complications
- Final results of the PAINT trial will be presented at EuroPCR 2008



# Treated Vessels

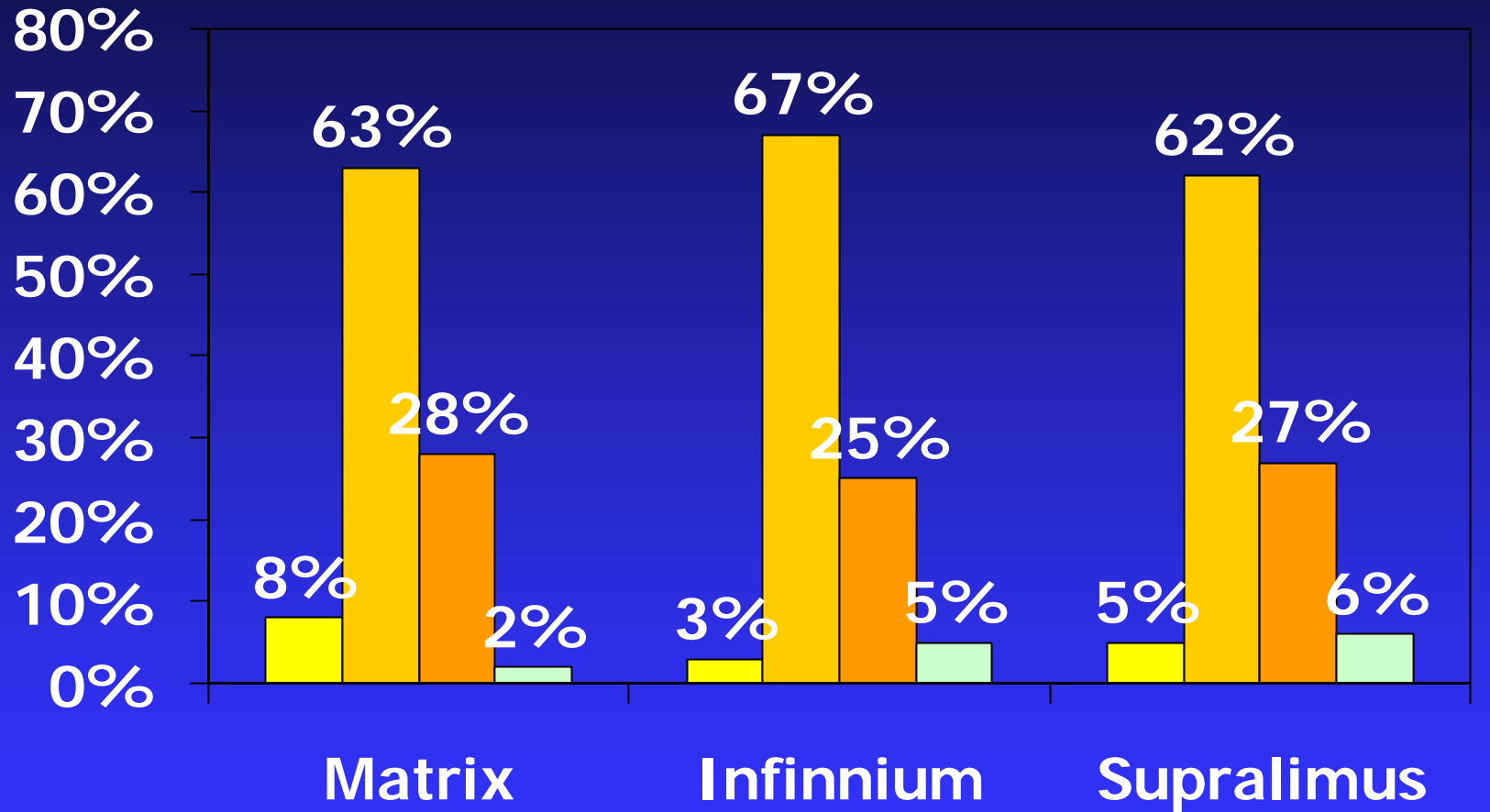
	<b>Matrix</b> <i>(n=51pts)</i>	<b>Infinnium</b> <i>(n=102 pts)</i>	<b>Supralimus</b> <i>(n=99 pts)</i>	<b>P</b>
<b>Vessel</b>				0.1
<b>RCA, %</b>	15	31	26	
<b>LAD, %</b>	56	44	56	
<b>LCx, %</b>	28	25	18	

# Secondary Objectives

- **Safety**

- To compare the incidence of Major Adverse Cardiac Events at 30 days, 9 months and 1 year among the paclitaxel, sirolimus, and control groups.
- To compare the incidence of Serious Adverse Events (SAE) up to 1 year among the paclitaxel, sirolimus, and control groups.
- To compare the incidence of stent thrombosis up to 1 year among the paclitaxel, sirolimus, and control groups.

# Clinical Presentation



■ SI ■ Stable angina ■ Unstable angina ■ Recent MI

# Secondary Objectives

- **Efficacy**

- To compare the rate of angiographic success among the paclitaxel, sirolimus, and control groups.
- To compare the rate of clinically driven target lesion revascularization at 9 months and 1 year among the paclitaxel, sirolimus, and control groups.
- To compare the rate of clinically driven target vessel revascularization at 9 months and 1 year among the paclitaxel, sirolimus, and control groups.
- To compare the cost-effectiveness profile at 1 year of the paclitaxel, sirolimus, and control groups.
- To compare the 9-month intra-stent luminal loss between the paclitaxel and the sirolimus groups.
- To compare the 9-month in-segment luminal loss among the paclitaxel, sirolimus, and the control groups.
- To compare the binary restenosis rate (in-stent and in-segment) among the paclitaxel, sirolimus, and the control groups

# CUMULATIVE DRUG ELUTION WITH TIME

Time	Cumulative % Elution
1 week	27
2 weeks	40
3 weeks	54
4 weeks	68
7 weeks	100

Drug Concentration =  $1.4 \mu\text{g} / \text{mm}^2$

# BACKGROUND

- There is a need for a safe, effective, indigenously developed drug eluting stent in India. (cost of a DES can be more than CABG in India)
- Use of a Biodegradable Polymer in a DES can have potential advantages.

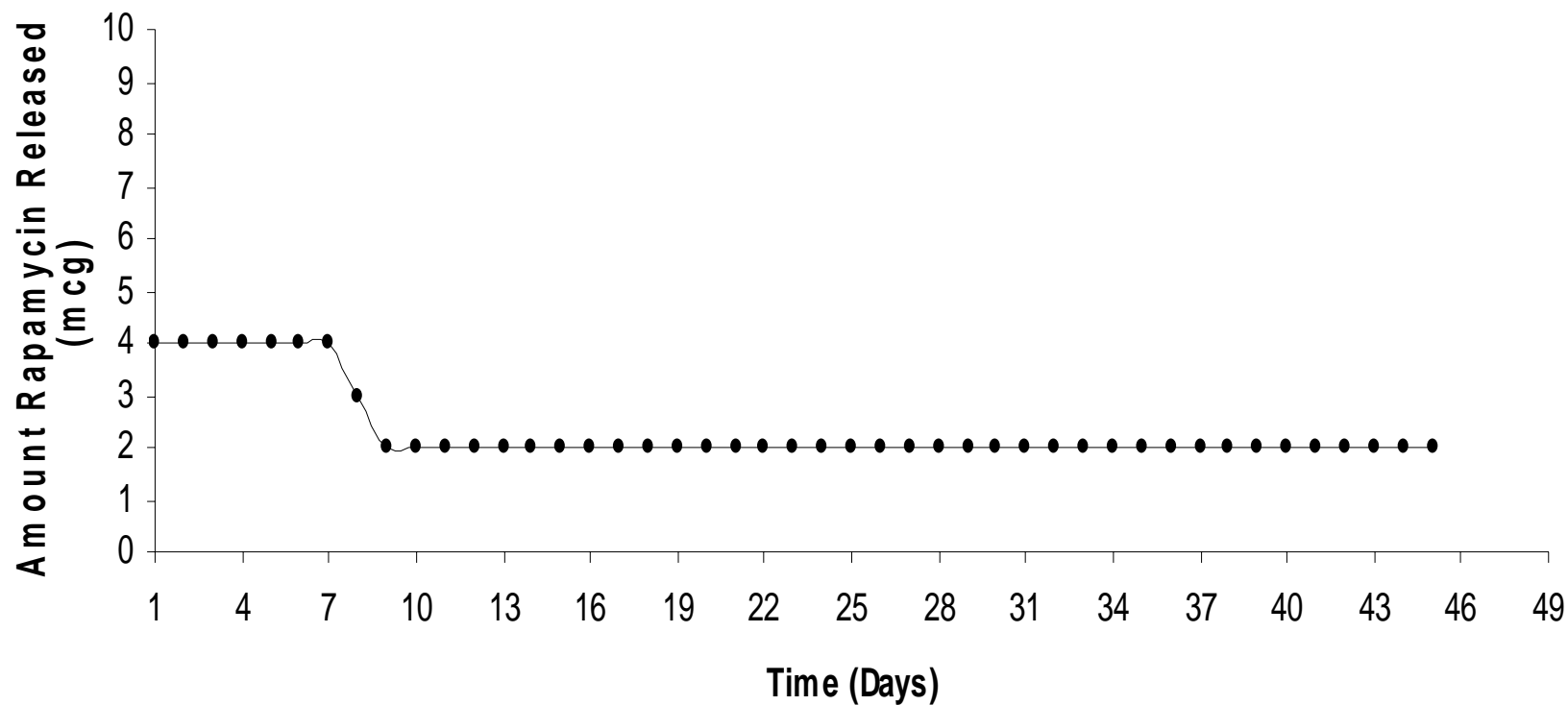
# SUPRALIMUS™ SIROLIMUS ELUTING CORONARY STENT SYSTEM

- Stent Platform → *Matrix™*  
stent  
design Millennium  
Slotted tube
- Drug → Sirolimus
- Drug Delivery Vehicle → Biodegradable  
Polymer
- Drug Release → Slow

# DRUG CONCENTRATION

Stent Length	Vessel Size	Drug Loading
11 mm	2.5 – 4.0 mm	72 µg
16 mm	2.5 – 4.0 mm	105 µg
19 mm	2.5 – 4.0 mm	125 µg
23 mm	2.5 – 4.0 mm	151 µg
29 mm	2.5 – 4.0 mm	190 µg
33 mm	2.5 – 4.0 mm	224 µg
39 mm	2.5 – 4.0 mm	258 µg

# SIROLIMUS ELUTION IN CONTROLLED MANNER FROM SUPRALIMUS™

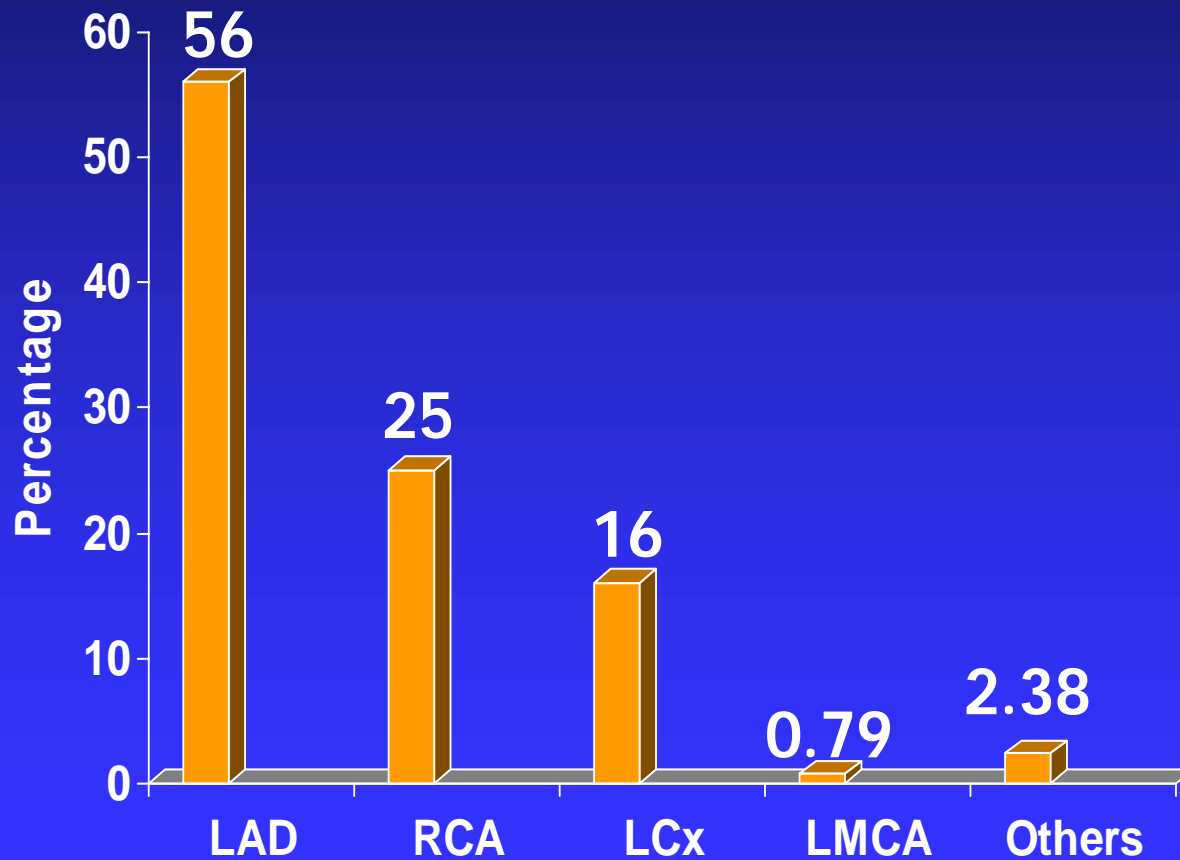


# AIMS AND OBJECTIVES

- To study the Feasibility, Safety and Efficacy of Supralimus (A new biodegradable polymer based Sirolimus Eluting Stent)
- To evaluate Immediate and intermediate results of Supralimus including ISR, ST and MACE rate.

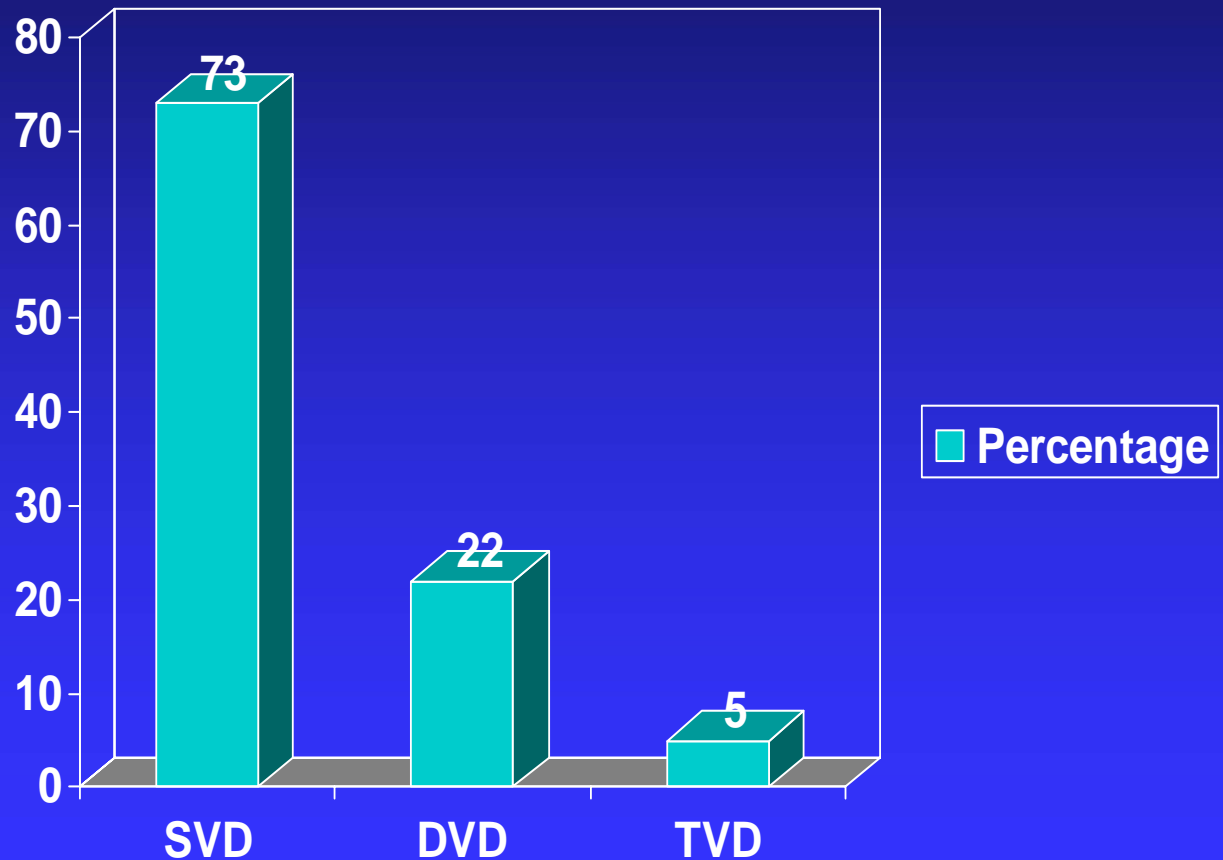
# CORONARY ARTERY PROFILE

## Target Vessel



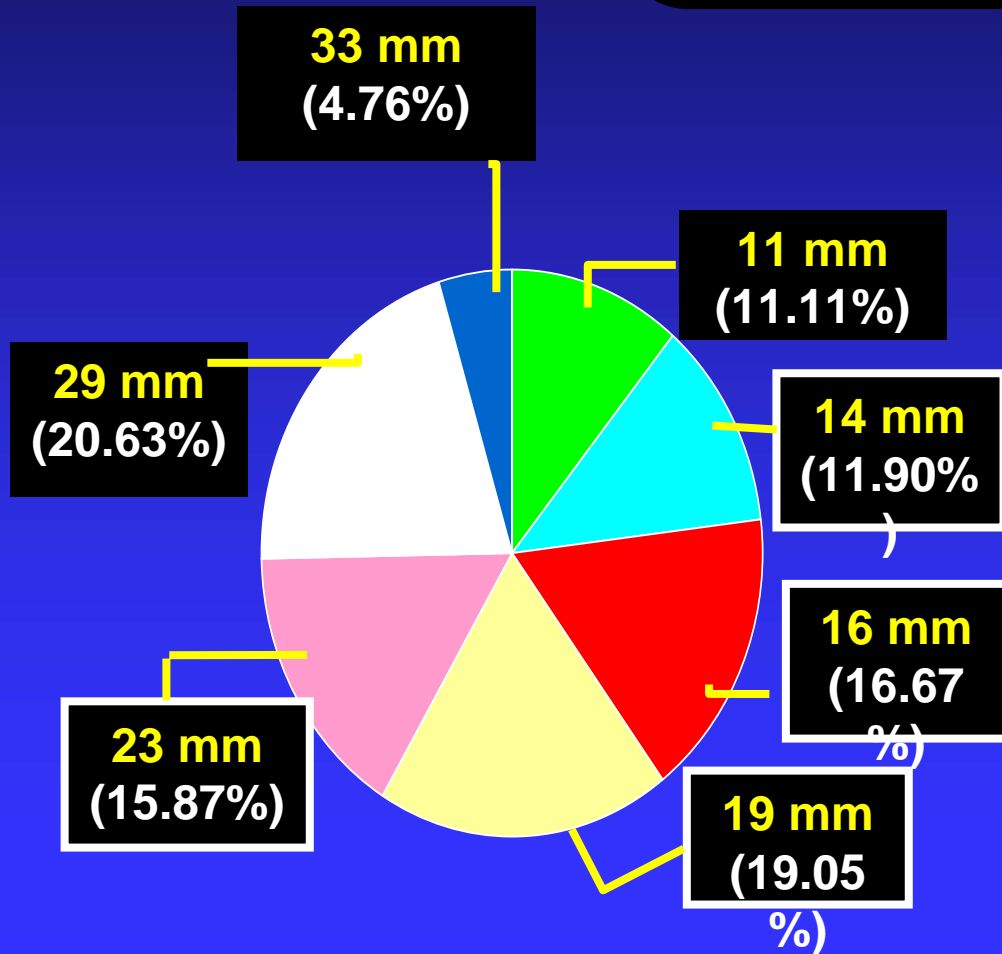
# CORONARY ARTERY PROFILE

## Number of Vessels Diseased



# SERIES I: Stent Characteristics (n=126)

## LENGTH

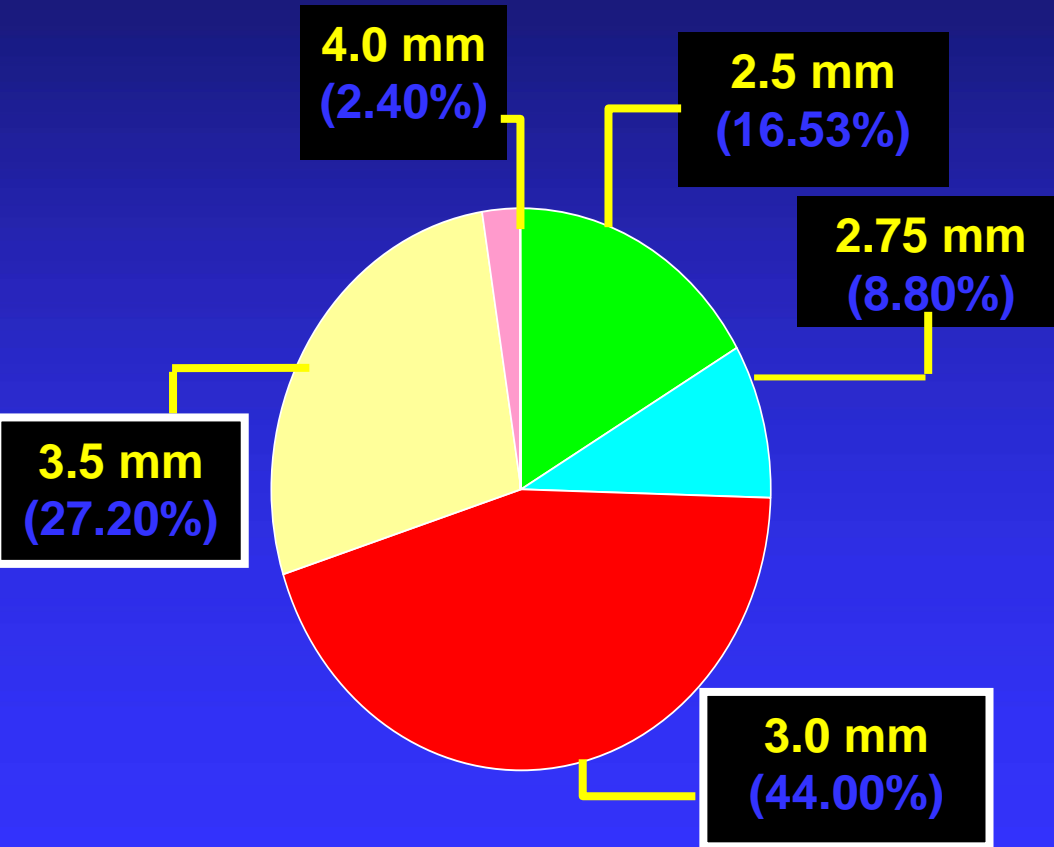


- **Average Stent Length :**  
 **$18.95 \pm 7.58$  mm**

- **Stent Length**
  - ◆ 11-14 mm = 21.70%
  - ◆ 16-19 mm = 37.21%
  - ◆  $\geq 23$ mm = 41.08%

# SUPRALIMUS STENTS (N = 126)

## Stent Size



- **Average Stent Diameter :**  
 **$2.95 \pm 0.44\text{mm}$**
- **Stent Diameter**
  - ◆ 2.5 mm = 13.18%
  - ◆ 2.75mm = 6.98%
  - ◆ 3.0 mm = 50.38%
  - ◆ 3.5 mm = 27.91%

# IMMEDIATE RESULTS

## I. IN-HOSPITAL COMPLICATIONS

- Reocclusion of Target Vs. : 0 (0%)
- Myocardial Infarction : 0 (0%)
- Death (Cardiac) : 0 (0%)
- Death (Non-Cardiac) : 0 (0%)
- PTCA : 0 (0%)
- OVERALL : 0 (0%)

## MACE AT ONE MONTH FU

● Subacute Thrombosis	:	0 (0%)
● PTCA	:	0 (0%)
● CABG	:	0 (0%)
● MI	:	0 (0%)
● Death (Cardiac) (0.0%)	:	0
Overall (0.0%)	:	0

## MACE AT 6 mo. FUP

- TLR : 2 (2%)
- MI : 0 (0%)
- Death : 2 (2%)\*
- MACE : 4 (4%)
- Event-Free Survival: 96%

\*Progressive Heart Failure

# Angiographic Outcome

6 mo Post Procedure

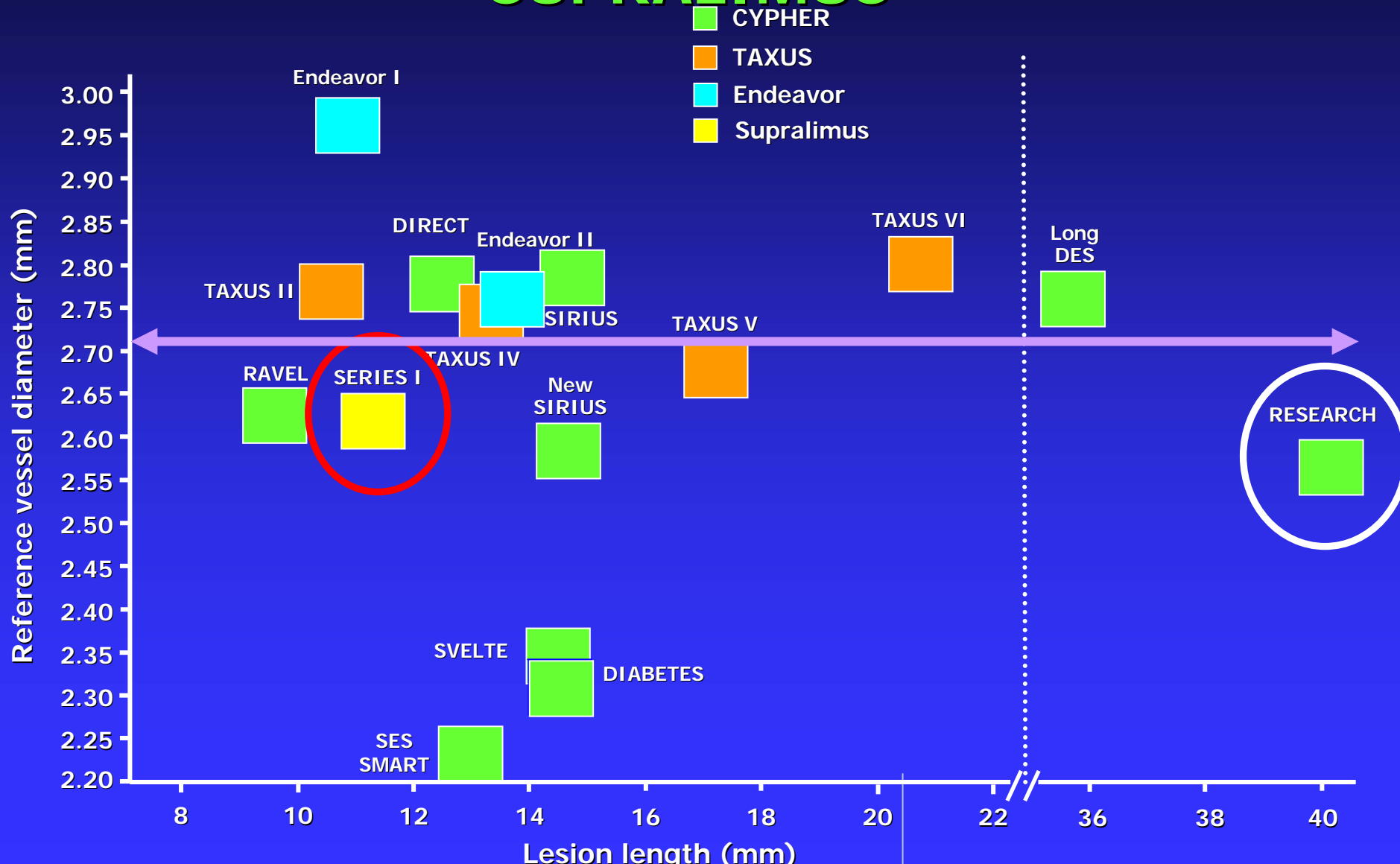
**In-Stent Late Loss (mm)** **0.09 ±**  
**0.28**

**In Segment Late Loss (mm)** **0.02 ±**  
**0.37**

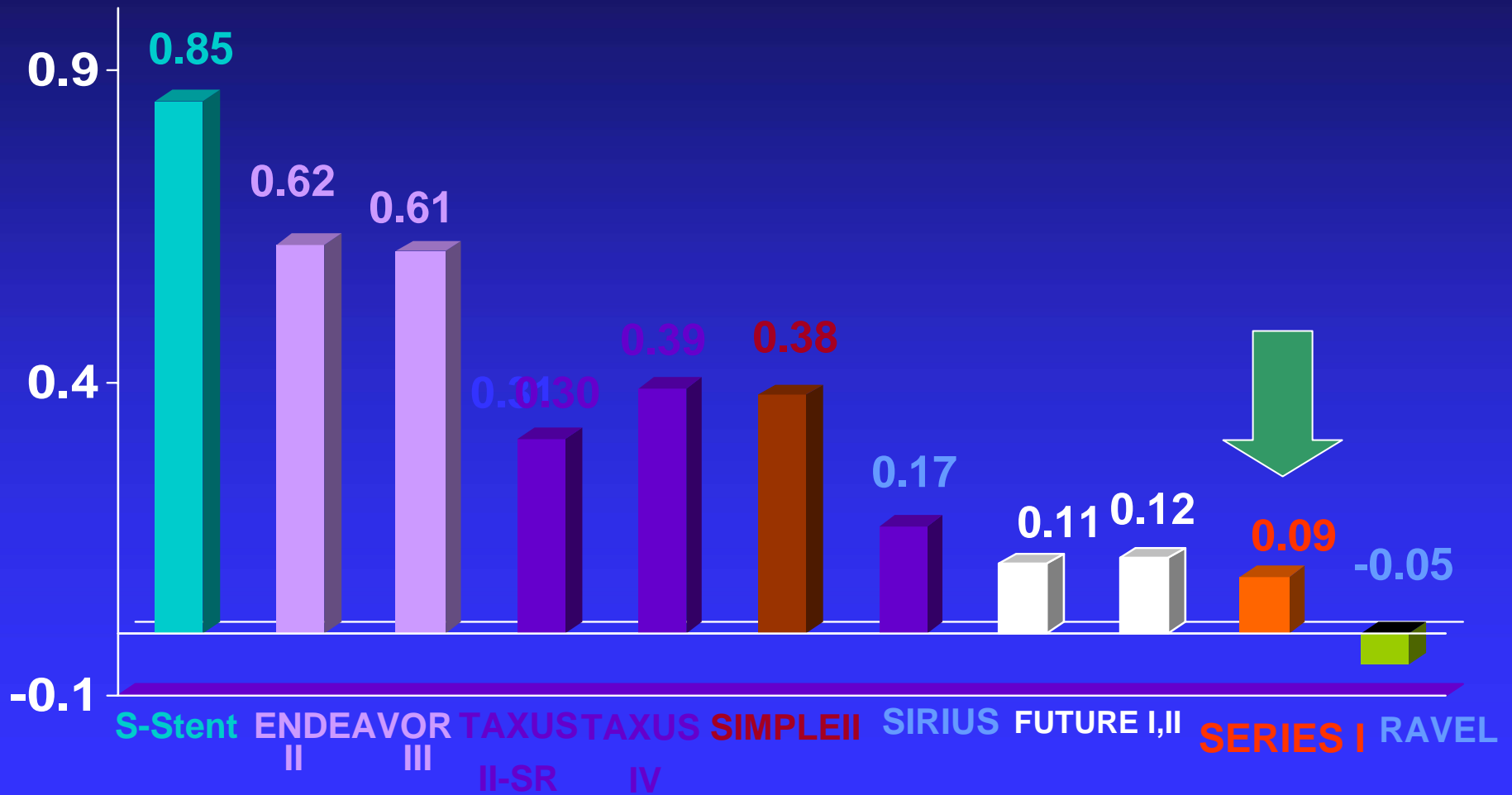
**In-Stent Net Gain** **1.80 ±**  
**0.71**

**In-Segment Net Gain** **1.41 ±**  
**0.70**

# Drug-eluting Stent Trials CYPHER, TAXUS, ENDEAVOR, SUPRALIMUS



# Comparison of In-Stent Late Loss



# QCA In-Stent Analysis

## SERIES I Vs RAVEL and C SIRIUS

		SERIES-I SUPRALIMUS	RAVEL CYPHER™	C SIRIUS CYPHER™
Lesion Length (mm)		10.50	9.56	14.5
Vessel Size (mm)		2.66	2.60	2.65
MLD	Pre	0.73	0.94	0.82
	Post	2.53	2.43	2.50
	FU	2.44	2.42	2.46
Late loss (mm)		0.09	- 0.01	0.09
Late loss index		0.05	- 0.02	N.D
Restenosis Rate		0	0	0
Diam Sten @ FU		14.20	15	N.D

# CONCLUSIONS

- Elution of Sirolimus using a Biodegradable polymer based stent(Supralimus) is feasible and therapeutically effective.
- 100% procedural success & the MACE free survival of 94% at 9 mo follow up is quite good and seems to be promisingly comparable to other DES available.

# CONCLUSIONS

- It seems that stent thrombosis is quite low with this stent, but the number of pts are less & aspirin-clopidogrel were prescribed indefinitely to these pts as is the current practice in this part of India
- Further clinical data is required to establish the long term safety and efficacy of Supralimus.

# Inclusion Criteria

- Age  $\geq$  18 years
- Symptomatic ischemic heart disease or objective evidence of myocardial ischemia
- Target lesion *de novo* coronary lesion (non-restenosis) with stenosis  $>$  50% (visual analysis)
- Target lesion in native vessel
- Target lesion in vessel 2.5 – 3.5mm (visual analysis)
- Target lesion can be treated with a single coronary stent up to 29-mm long
- Candidate for surgical coronary revascularization
- Signed written informed consent

# General Exclusion Criteria

- Q wave myocardial infarction < 48 hours
- Recent Q wave or non Q wave myocardial infarction still with elevated levels of cardiac markers at the time of index procedure
- Ejection fraction < 30%
- Serum creatinine > 2,0 mg/dl (177 µmol/l)
- Platelet count < 100,000 cels/mm<sup>3</sup> or 700,000 cels/mm<sup>3</sup>;
- Total white cells < 3,000 cels/mm<sup>3</sup>;
- Suspected or documented liver disease (included laboratorial evidence of hepatitis)
- Cardiac transplant recipient
- Known allergy to aspirin, clopidogrel, paclitaxel, sirolimus, heparin, or stainless steel
- Life expectancy < 12 months
- Concomitant enrollment in another clinical trial
- Coronary angioplasty > 6 months in a segment < 5 mm from the target lesion
- Coronary angioplasty < 6 months in any coronary segment
- Programmed coronary angioplasty within the next 12 months after the index procedure

# Angiographic Exclusion Criteria

- Target lesion in a previously dilated segment (restenosis)
- Need to treat more than one lesion in the same vessel
- Target vessel size  $< 2.5$  mm or  $> 3.5$  mm (visual analysis)
- Long lesion, not possibly treated with a single stent up to 29 mm in length
- Left main stenosis  $> 50\%$
- Target lesion in a surgical graft
- Target lesion in an occluded vessel (TIMI grade 0 or 1)
- Target lesion in ostial location
- Target lesion in a bifurcation site with lateral branch  $> 2.5$  mm or that could require stent placement
- Target lesion in severely calcified vessel
- Target lesion in severely tortuous vessel

# Randomization

## Non-blinded study

- **Before** randomization, the investigator **must** select:
  - Vessel to be treated
  - Stent length
  - Stent diameter
- After randomization, the investigator must maintain the primary strategy (vessel and stent size) selected before the randomization or objectively justify any deviation from the original plan.

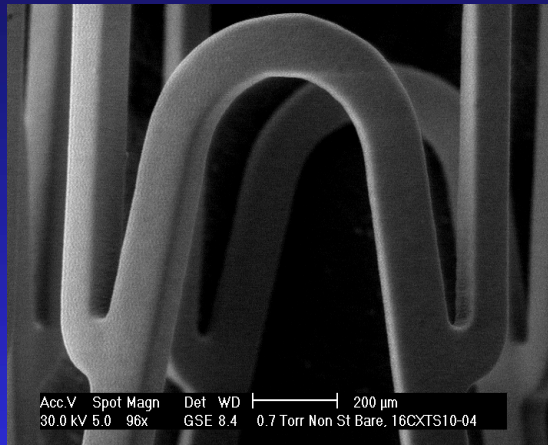
# Study Procedures

- **Available Stents:**
  - Diameter: 2.5, 3.0, and 3.5 mm
  - Length: 19, 23, and 29 mm
- **Stent Implantation**
  - Pre-dilatation recommended, but not obligatory
  - Stent should cover the entire lesion + pre-dilated segment + ~4 mm proximal and distal in the “normal” vessel
  - Post-dilatation should be performed within the stent limits, with a balloon shorter than the stent
- **Post-procedure medication**
  - Sirolimus and paclitaxel: clopidogrel or ticlopidina por 12 months
  - BMS: clopidogrel or ticlopidina for 1 month
- **Angiographic follow-up: 9 months after index procedure**
- **IVUS subestudy: 100 pts**

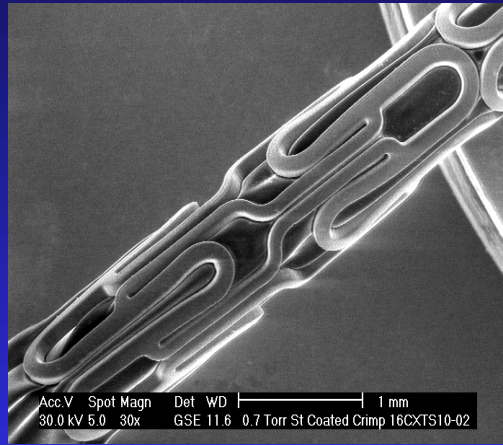
# Clinical Follow-up

- Patients will be follow-up for the occurrence of Major Adverse Cardiac Events, defined as:
  - Cardiac death
  - Myocardial infarction (with or without Q waves)
  - Clinically driven repeat intervention (surgical or percutaneous)
- Stent thrombosis
  - Defined as proposed by the Academic Research Consortium

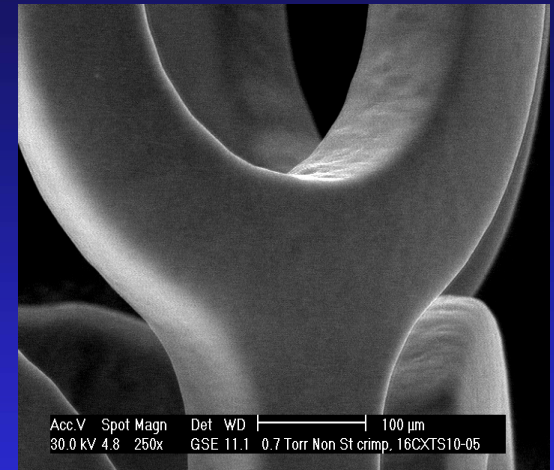
# SCANNING ELECTRON MICROSCOPIC IMAGES IN CRIMPED AND EXPANDED STATE SHOWING COATING WHICH IS UNIFORM AND SMOOTH



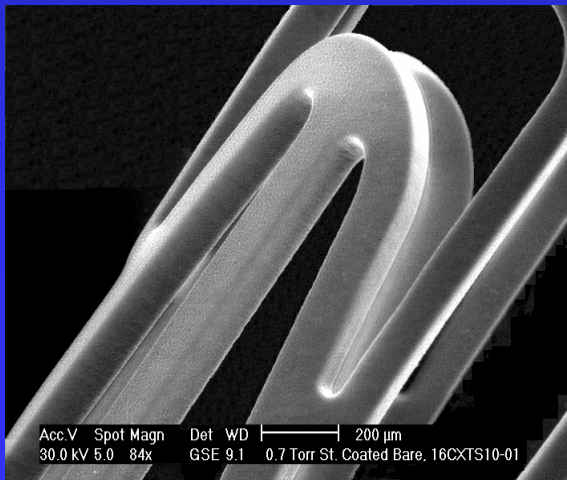
Non Sterile Bare Stent at 96x



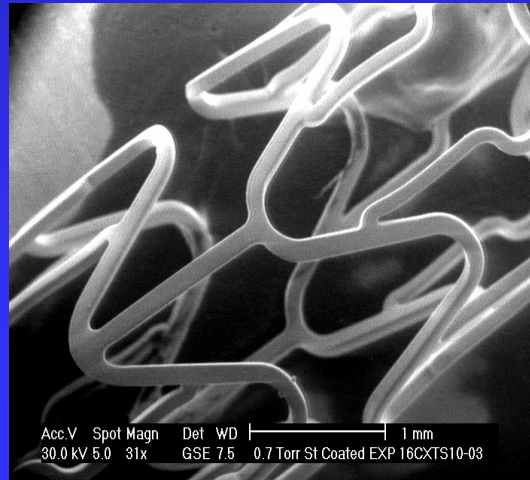
Sterile Drug Coated Crimped Stent at 30x



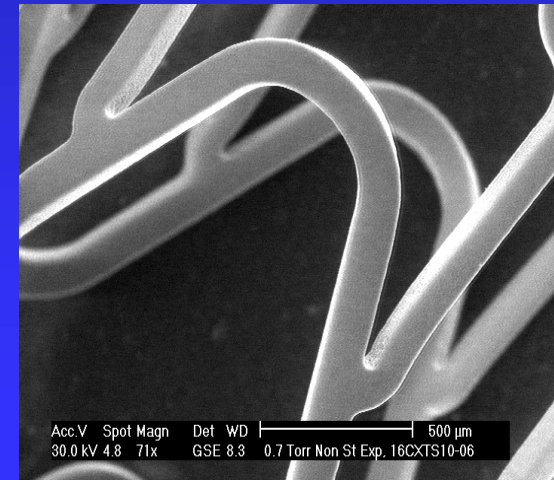
Non Sterile crimped at 250x



Sterile Bare Stent at 84x



Sterile Drug Coated expanded Stent at 31x



Non Sterile Expanded at 71x

# SERIES I: Stent Characteristics

- **Average Stent Length:  $18.95 \pm 7.58$  mm**

- **Stent Length**

- ◆ 11-14 mm = 21.70%
- ◆ 16-19 mm = 37.21%
- ◆  $\geq 23$ mm = 41.08%

- **Average Stent Diameter:  $2.95 \pm 0.44$ mm**

- **Stent Diameter**

- ◆ 2.5 mm = 13.18%
- ◆ 2.75mm = 6.98%
- ◆ 3.0 mm = 50.38%
- ◆ 3.5 mm = 27.91%
- ◆ 4.0 mm = 1.55%

# Sample size calculation

- 82% power to detect a difference of at least 0.25 using the Tukey-Kramer (Pairwise) multiple comparison at a 0.05 significance level (common SD 0.35); expected attrition rate of 15% of patients lost

# PAINT 250

• InCor – SP	.....	100 pts
• HUCAM – ES	.....	39 pts
• Sta Marcelina – SP	.....	32 pts
• Natal Hospital Center – RN	.....	17 pts
• UNIFESP – SP	.....	15 pts
• HU Walter Cantidio – CE	.....	15 pts
• Intercath Meridional – ES	.....	14 pts
• PUCRS – RS	.....	14 pts
• Rede D'Or – RJ	.....	7 pts
• Biocor – MG	.....	4 pts
• São Camilo – SP	.....	2 pts

# Primary Objective

- To compare the intra-stent 9-month luminal loss of drug-eluting stents (paclitaxel or sirolimus) with the control bare metal stent

# Baseline Characteristics II

	<b>Matrix</b> <i>(n=51 pts)</i>	<b>Infinium</b> <i>(n=102 pts)</i>	<b>Supralimus</b> <i>(n=99 pts)</i>	<b>P</b>
<b>Previous MI, %</b>	<b>37</b>	<b>29</b>	<b>32</b>	<b>0.6</b>
<b>Previous PCI, %</b>	<b>18</b>	<b>16</b>	<b>14</b>	<b>0.9</b>
<b>Previous CABG, %</b>	<b>4</b>	<b>8</b>	<b>5</b>	<b>0.5</b>
<b>HF%</b>	<b>4</b>	<b>3</b>	<b>7</b>	<b>0.6</b>
<b>PVD, %</b>	<b>2</b>	<b>5</b>	<b>2</b>	<b>0.4</b>
<b>Previous stroke, %</b>	<b>0</b>	<b>2</b>	<b>2</b>	<b>0.6</b>