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CYPHER™ Sirolimus-eluting Stent  
PMA # P020026

Cordis Presentation

Dennis Donohoe, MD

Vice President, Therapeutics and Clinical Research

# Agenda

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- Project Overview - D. Donohoe, MD
- Description of the Device
- Overview Clinical Trial Results
  - Phase I Studies
    - First in Man (FIM)
    - Pharmacokinetic Study (PK)
  - Phase II/III Studies
    - RAVEL
    - SIRIUS
- Sub-analyses of SIRIUS Data - R. Kuntz, MD

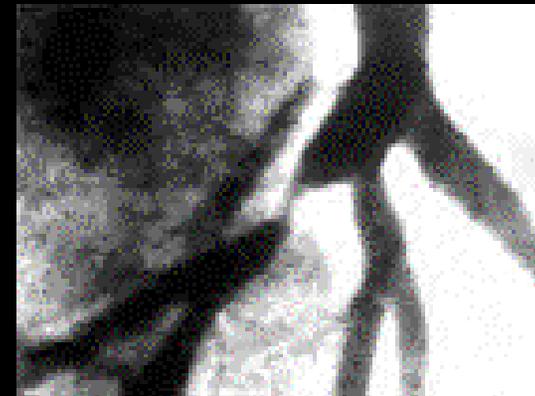
# Project Overview

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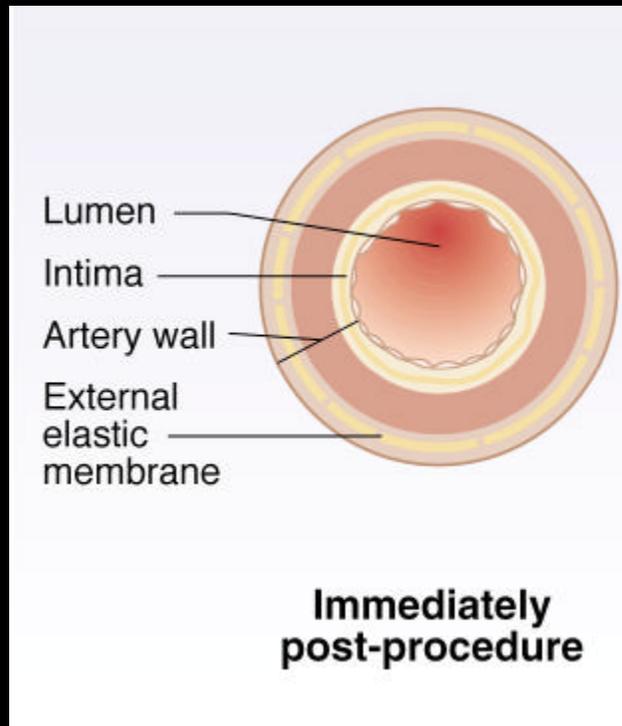
- Granted Expedited Review Status
  - Significant therapeutic advance
- CDRH Designated as Lead Center
  - Primary mode of action is a device function
  - Sirolimus to augment the performance of the stent
- Submitted PMA on June 28, 2002
  - Comparable safety profile to bare stents
  - Proven superior effectiveness to bare stents
  - Demonstrated durability of treatment

# The “Achilles Heel” of Interventional Cardiology

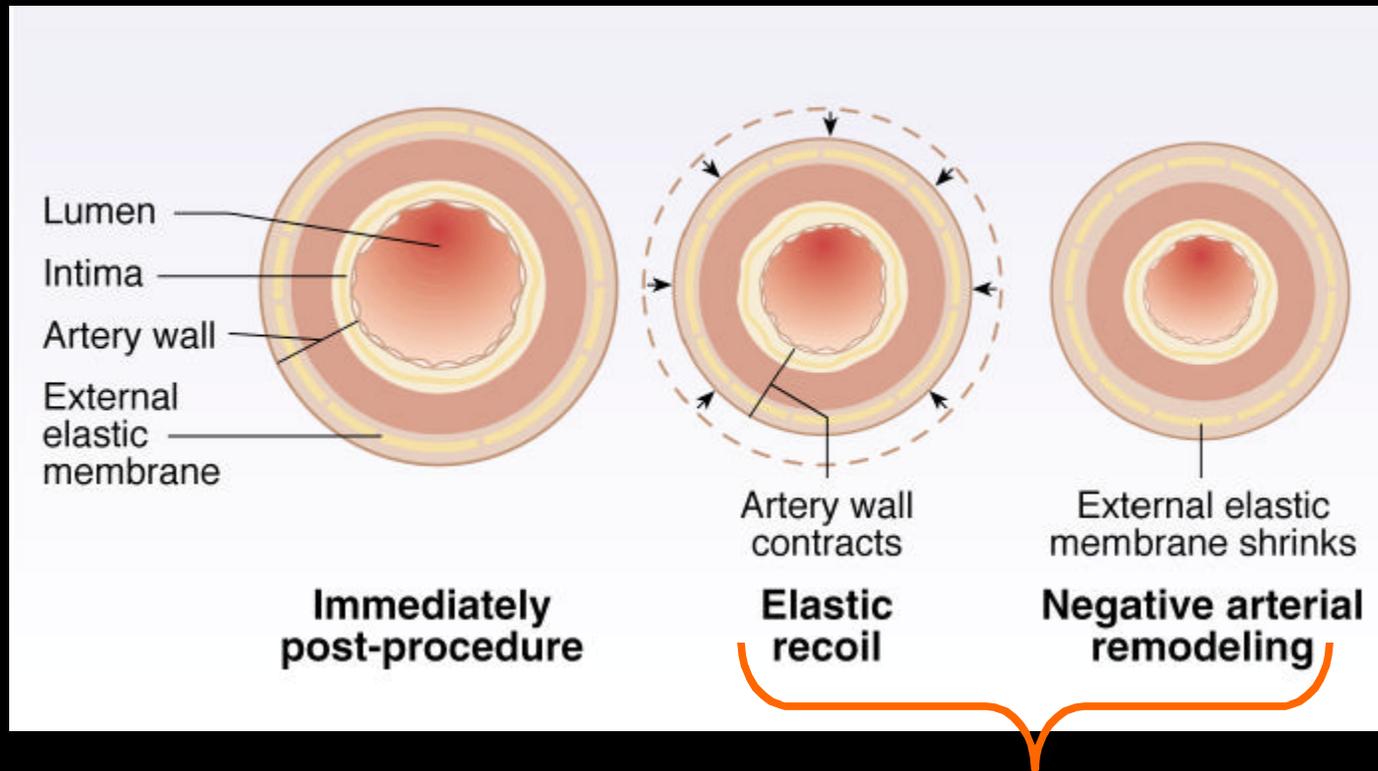
- Restenosis is a major limitation of percutaneous coronary intervention
  - 1 million performed per year
  - 80% receive a stent
- Angiographic restenosis rates
  - 30% to 50% after balloon angioplasty
  - 15% to 35% after stenting
- Treatment
  - Revascularization
  - CABG



# Processes Leading to Restenosis

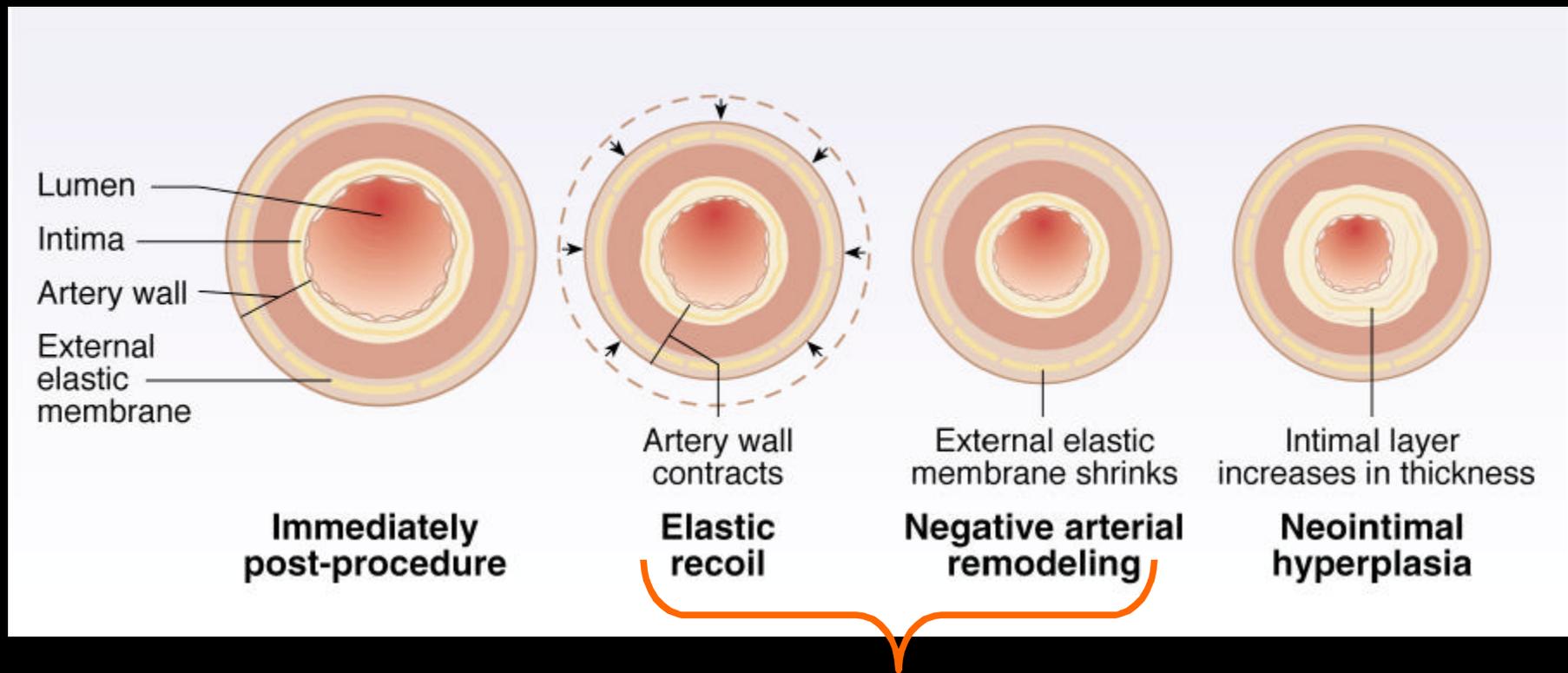


# Processes Leading to Restenosis (continued)



Large role in development of restenosis after plain old balloon angioplasty (POBA), but minimal role after stenting

# Processes Leading to Restenosis (continued)



Large role in development of restenosis after POBA, but minimal role after stenting

# Drug-eluting Stents

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- Stent and Stent Delivery System
  - Addresses remodeling and recoil
- Polymer
  - Provides base material to contain the drug
  - Provides consistent release of drug
- Drug
  - Addresses neointimal hyperplasia

# Bx VELOCITY<sup>®</sup> Stent

- Balloon-expandable stainless steel stent
- Approved in US
  - Threatened or abrupt closure: May 11, 2000
    - 2.25-4.0 mm diameters, 8-33 mm length
  - Elective: Feb. 2, 2001
    - 3.0-5.0 mm diameters and 8-33 mm length
- Data available from 6 well conducted clinical trials including over 1,100 patients
- Addresses *remodeling* and *recoil*



# Polymer

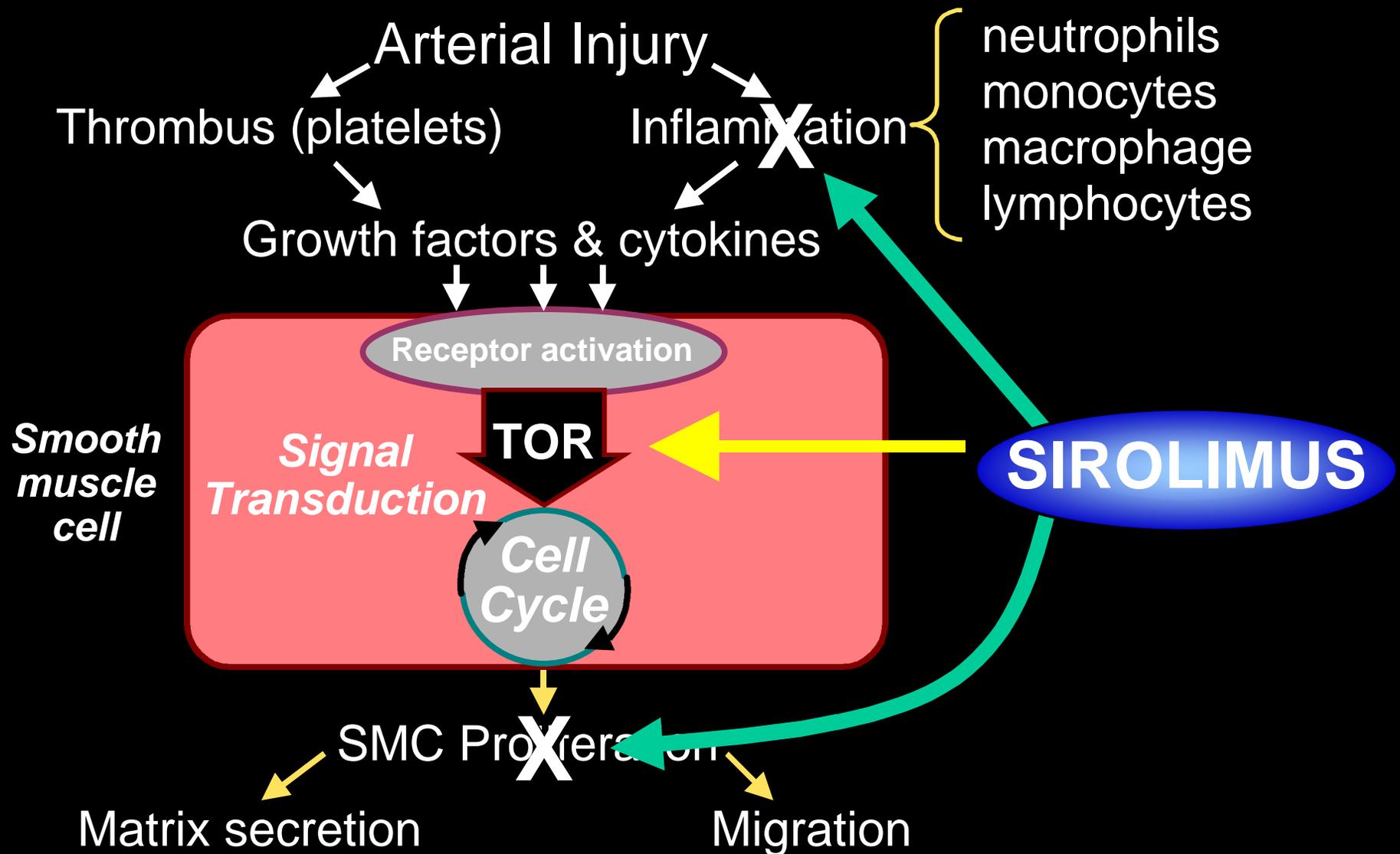
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- Polymer components are currently approved for use in medical devices (orthopedics)
- Provides consistent controlled release of sirolimus
- Biocompatible, non-erodable, non-thrombogenic, non-hemolytic, non-cytotoxic, non-irritating, non-sensitizing and non-mutagenic
- Polymer has elastomeric properties that accommodate stent expansion

# Sirolimus (Rapamune®)

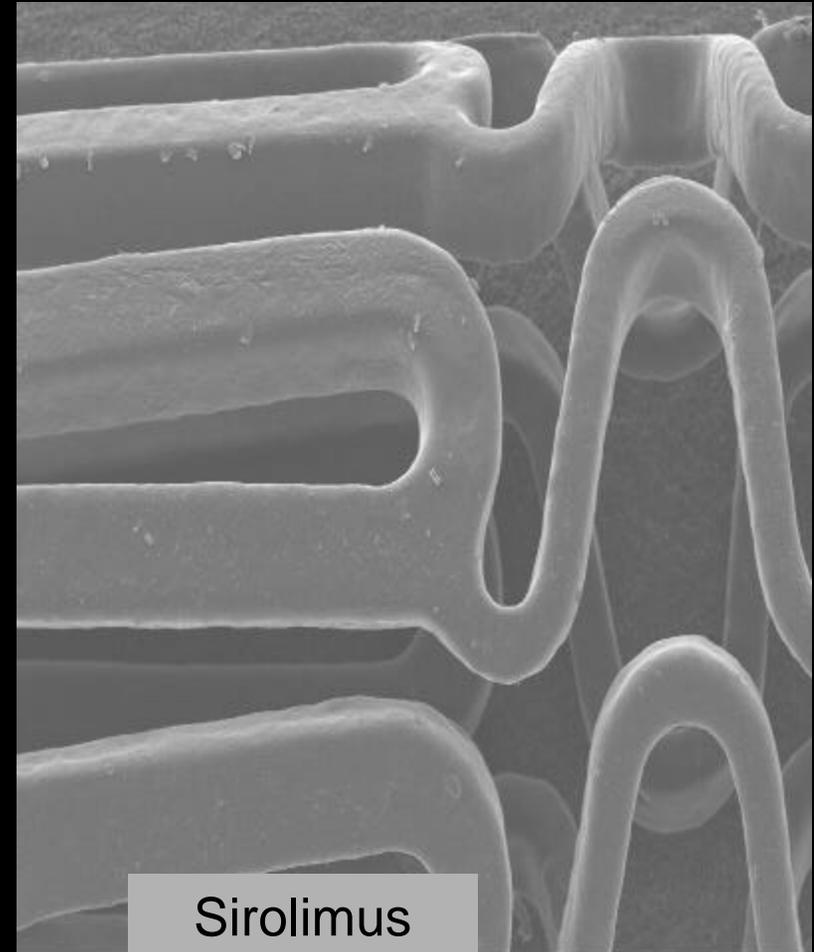
- Approved by FDA (Sept 1999) and EMEA (March 2001) for chronic systemic use as prophylaxis for renal transplant rejection (Wyeth)
- Safety and efficacy established in two randomized, multicenter trials involving 1295 patients
- Chronic administration of 2 mg/day or 5 mg/day produces mean steady-state whole blood trough levels of approximately 7.0 ng/mL and 14.0 ng/mL (chromatographic method), respectively
- Peak blood levels of >200 ng/ml following single dose intravenous administration have been found safe and well-tolerated in humans
- Wyeth is supplying sirolimus and has provided access to the NDA safety data

# Multiple Actions of Sirolimus



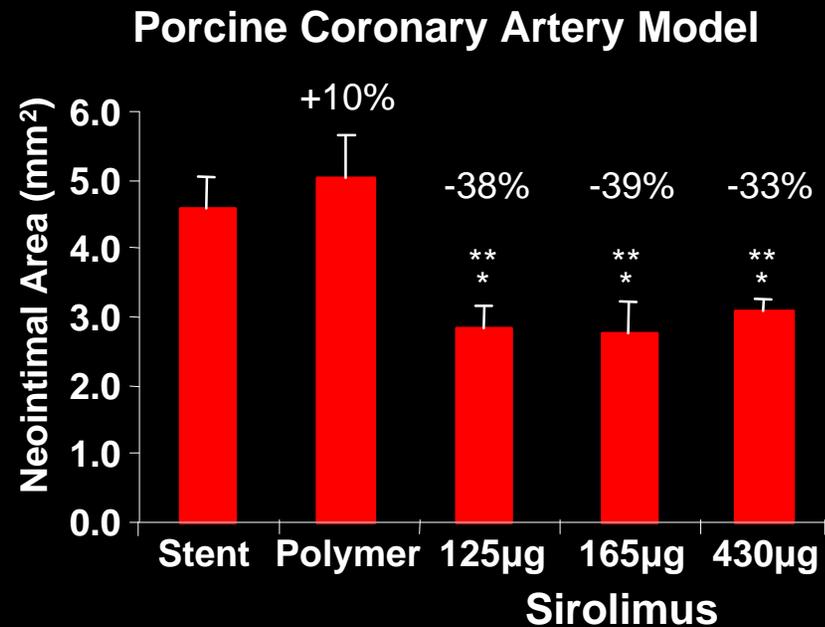
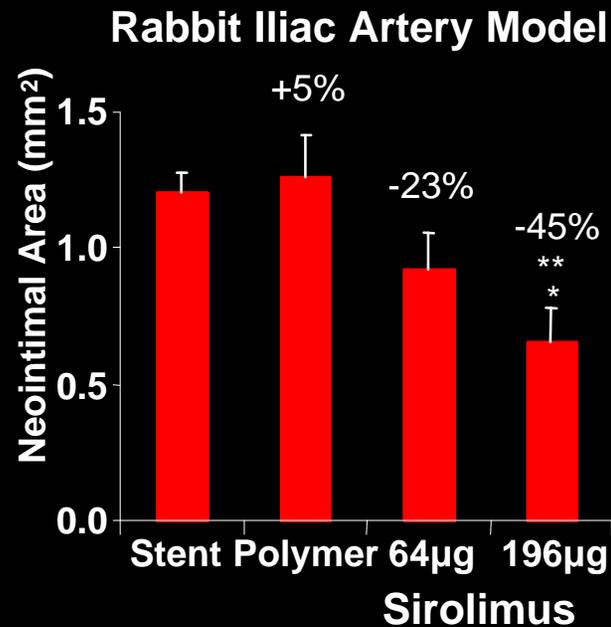
# Sirolimus-eluting Stent

- Thin uniform coating (5-10 $\mu$ m thick)
- Targeted drug delivery
  - maximizes drug effect where it is required
  - minimizes potential for systemic toxicity
  - controlled drug release



10kv 0.08kx 160X125.0P 003

# Sirolimus Dose Selection



*p* < 0.05 from Stent (\*) and Polymer (\*\*)

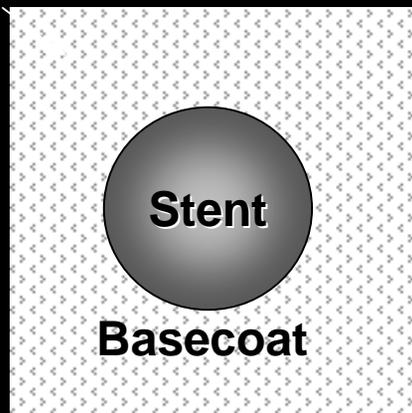
- 1) A dose-response to sirolimus is observed in the 28d rabbit iliac model between 64 - 196µg/stent. Most effective dose is 196µg/stent.
- 2) Doses from 125 - 430 µg/stent produce maximum response in pig coronary arteries at 28d. Most frequent dose studied is approximately 180µg/stent.

**Dose selected for clinical study: 180µg/3.5 x 18mm stent (140µg/cm<sup>2</sup>)**

# Controlled Elution from CYPHER™

*Sirolimus is released in a controlled manner from a polymer matrix bound to the stent*

Topcoat

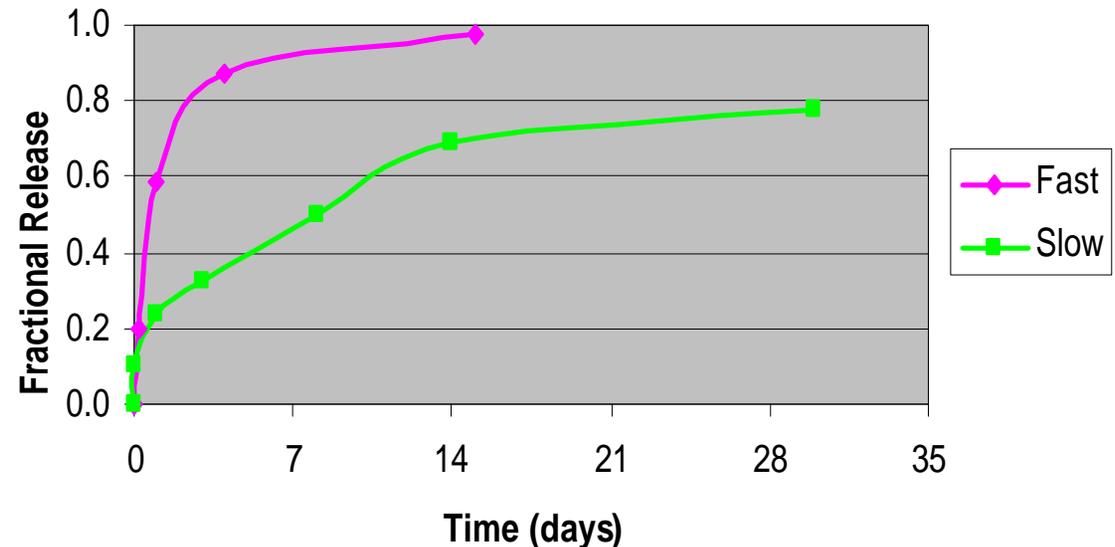


Basecoat = polymer/sirolimus

+

Topcoat = diffusion barrier

In Vivo Sirolimus Release in Pig Coronary Arteries



# Phase I Clinical Trials

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- **First in Man (FIM)**
  - 45 patients, 2 centers, two drug release formulations
- **Pharmacokinetic Study (PK)**
  - 19 patients, 2 centers, slow release formulation
    - 10 patients received one 18 mm stent
    - 9 patients received two 18 mm stents

# FIM: Study Flow

n=45

Native Coronary  
Artery Lesions  
Diameter: 3.0 - 3.5mm  
Length: <18mm  
2 months of antiplatelet therapy  
(Plavix/Ticlopidine)

## Sao Paulo

Sirolimus-eluting  
Bx VELOCITY<sup>®</sup>  
slow release n=15  
fast release n=15

## Rotterdam

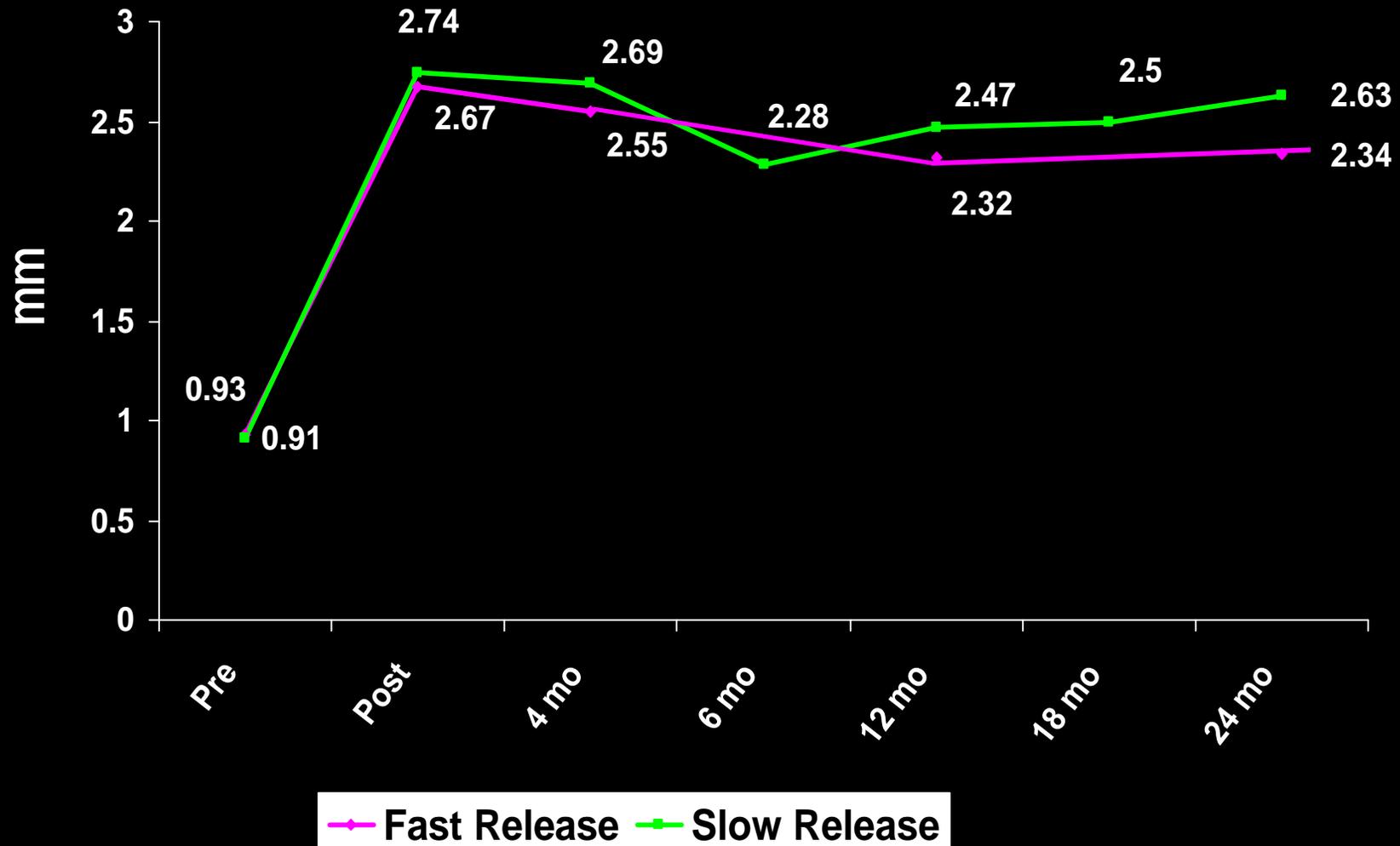
Sirolimus-eluting  
Bx VELOCITY<sup>®</sup>  
slow release n=15

*Angiographic, IVUS and Clinical F/U  
at 4, 12 and 24 months*

*Angiographic, IVUS and Clinical F/U at 6  
and 18 months, Clinical F/U at 24 months*

# FIM: Angiographic Results

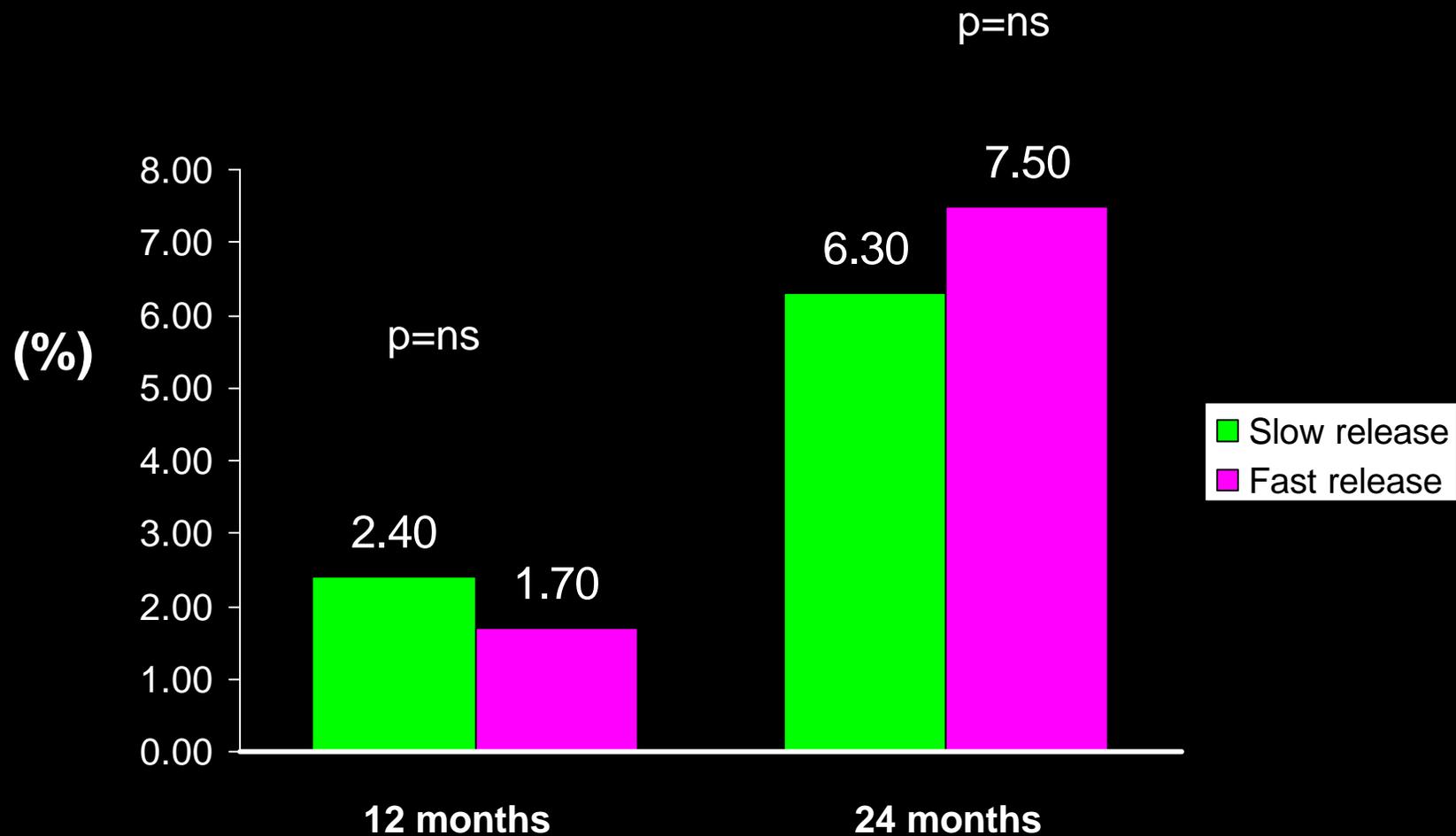
## *In-lesion Minimal Lumen Diameter (MLD)*



# FIM: IVUS Results

## Neointimal Hyperplasia at 12 and 24 Months

### *Volume obstruction*



# Definition Slide: Clinical Terms

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- TVF = Target Vessel Failure
  - Target Vessel Revascularization (TVR), infarction or cardiac death that could not be clearly attributed to a vessel other than the target vessel
- MI = Myocardial Infarction
  - Q-wave and Non-Q wave MI (WHO definition)
- MACE = Major Adverse Cardiovascular Events
  - Death, MI, emergent bypass surgery or repeat Target Lesion Revascularization (TLR)

# FIM: Clinical Events at 24 Months

Events	Sirolimus % (n= 45)
Death	2.2 (1)
MI	4.4 (2)
Q-wave	2.2 (1)
Non Q-wave	2.2 (1)*
TLR	6.7 (3)
PCI	6.7 (3)*
CABG	0
TVR (not involving TL)	6.7 (3)
All MACE	11.1(5)

\*Same patient

# FIM: Death

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- Death - 3 days post-procedure due to CVA at Day 1
  - 74 year-old female
  - Successful index procedure of lesion in proximal LAD
  - Patient became confused over the night, CT scan revealed large **intra cerebral bleed**
  - Patient expired 3 days post-procedure
  - Event considered unrelated to sirolimus-eluting stent

# PK: Study Design

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- Slow release formulation
- 2 sites, 19 patients
  - 10 patients received one sirolimus-eluting stent
  - 9 patients received two sirolimus-eluting stents
  - 2.5 to 3.5mm x 18mm stents used
    - 149.4  $\mu\text{g}$ , 150.1  $\mu\text{g}$ , and 177.7  $\mu\text{g}$  (mean)
- Blood Samples (Post-implantation)
  - 10 and 30 minutes, 1, 2, 4, 6, 12, 24, 72, and 168 hours

# Systemic Pharmacokinetics of CYPHER™ Slow Release

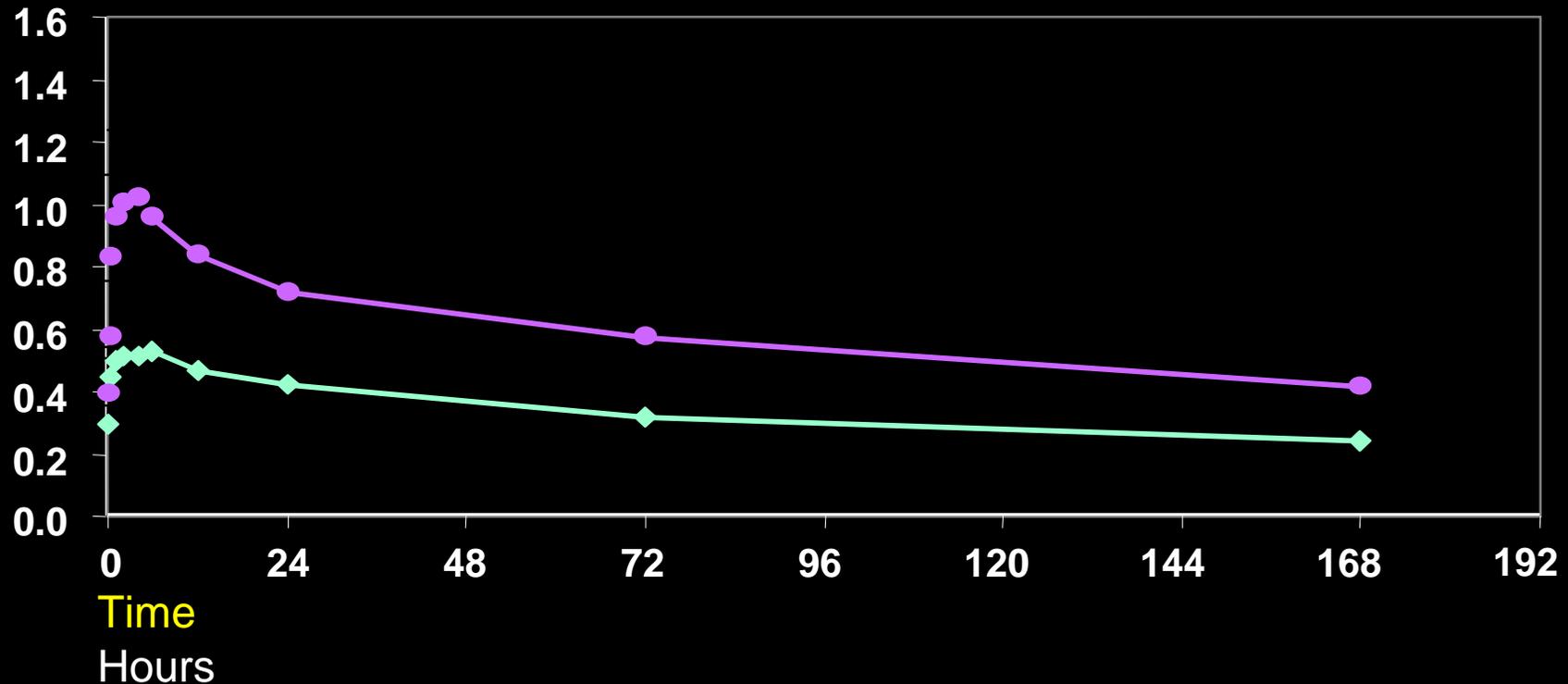
Human whole blood levels from prospective, non-randomized trial

Sirolimus

ng/ml

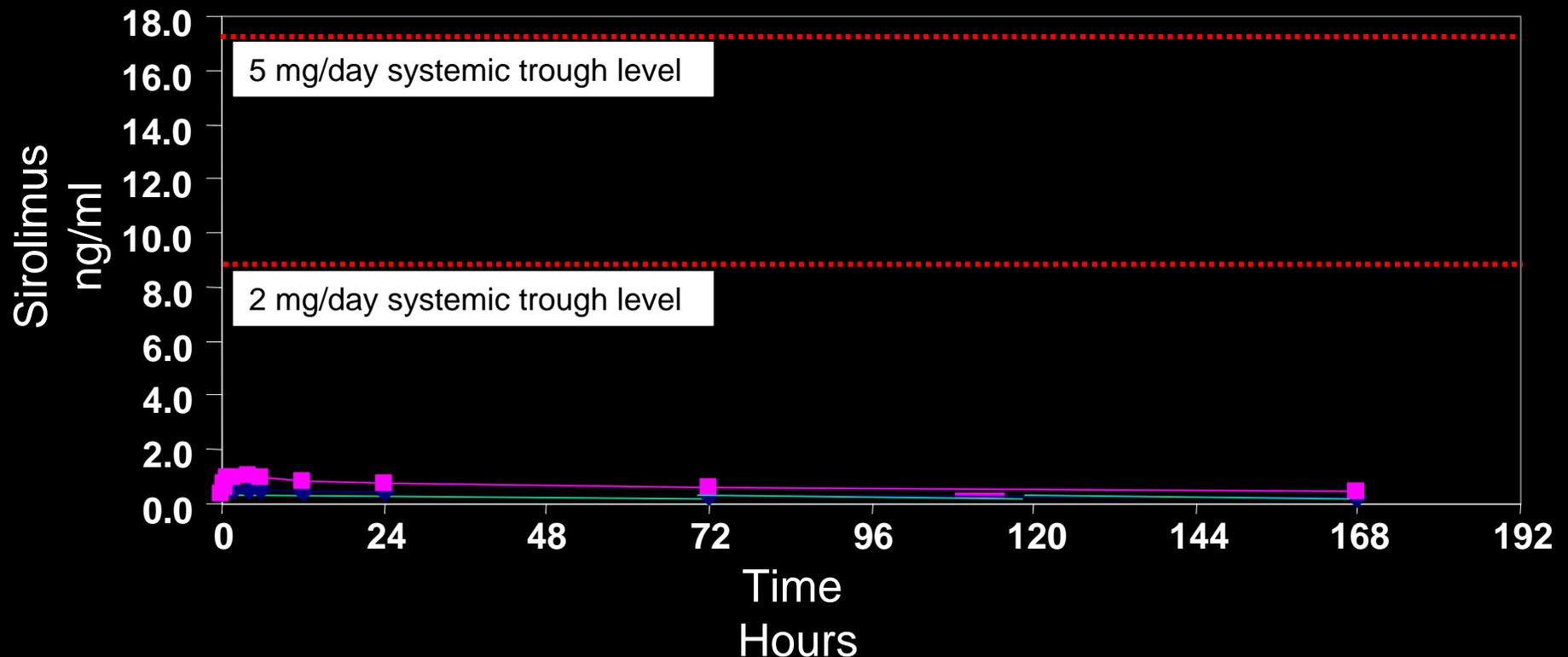
◆ 1 18 mm stent (10 patients)

● 2 18 mm stents (9 patients)



# Systemic Pharmacokinetics of CYPHER™ Slow Release

Human whole blood levels from prospective, non-randomized trial



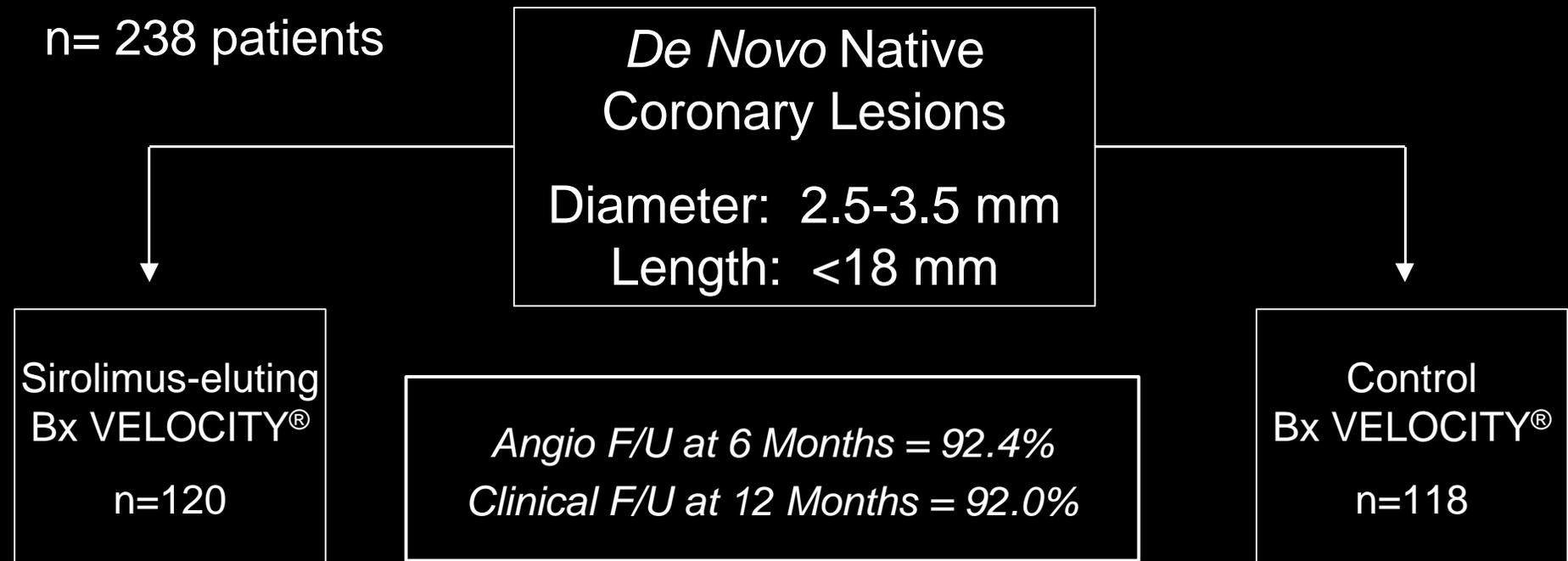
- Chronic blood levels of  $>8$  ng/ml are required for systemic immunosuppression
- Acute blood levels of 200 ng/ml are safely tolerated

# Phase II/III Clinical Trials

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- RAVEL
  - Double-blind, prospective, randomized, 19 centers, 238 patient trial
- SIRIUS
  - Double-blind, prospective, randomized, 53 centers, 1101 patient trial

# RAVEL: Randomized, Double-blind Trial



- Primary Endpoint: Angiographic late loss at 6 months
- Secondary Endpoints: IVUS at 6 mo. and clinical at 6 and 12 months and annually for 5 years
- Antiplatelet therapy for 60 days (clopidogrel/ticlopidine)

# RAVEL: Baseline Patient Demographics

	Sirolimus (%) n=120	Control (%) n=118
Mean Age (years)	61.8	59.7
Male	70.0	81.4
Prior MI	37.5	33.9
Prior Revascularization	20.9	18.6
Diabetes Mellitus	15.8	21.2
Hypercholesterolemia (treated)	37.5	42.7
Hypertension (treated)	61.7	61.0
Current Smoker	26.7	33.1

No statistically significant differences between groups

# RAVEL: Baseline Angiographic Results

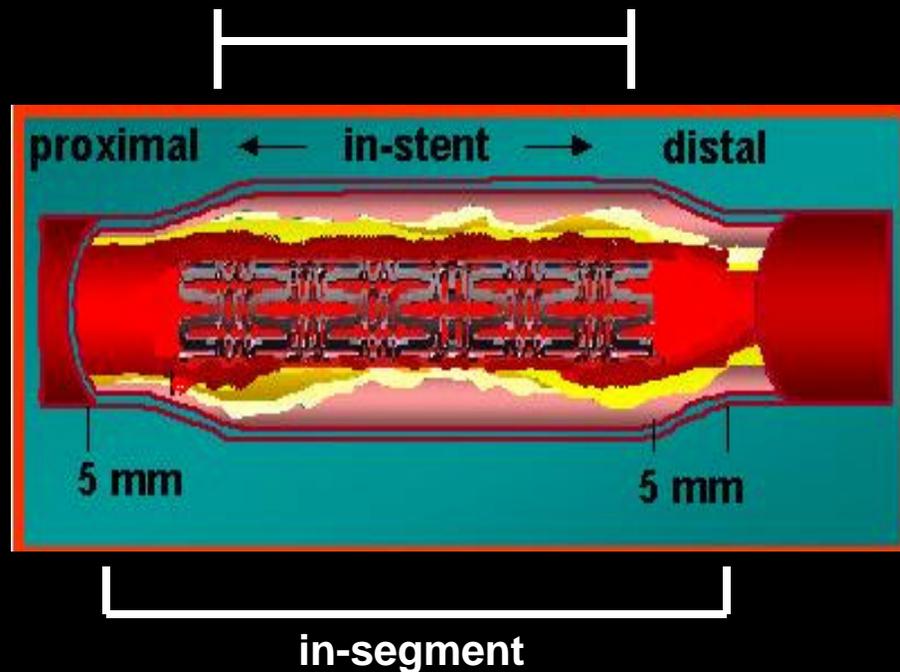
	Sirolimus (Mean) n=120	Control (Mean) n=118
RVD (mm)	2.60	2.64
MLD (mm)		
Pre	0.94	0.95
Post	2.43	2.41
DS (%)		
Pre	63.6	64.0
Post	11.9	14.0
Lesion length (mm)	9.6	9.6

No statistically significant differences between groups

# RAVEL: Success Measure

	Sirolimus (%) n=120	Control (%) n=118
Lesion Success	99.2	98.3
Device Success	99.2	95.7
Procedure Success	96.7	93.1

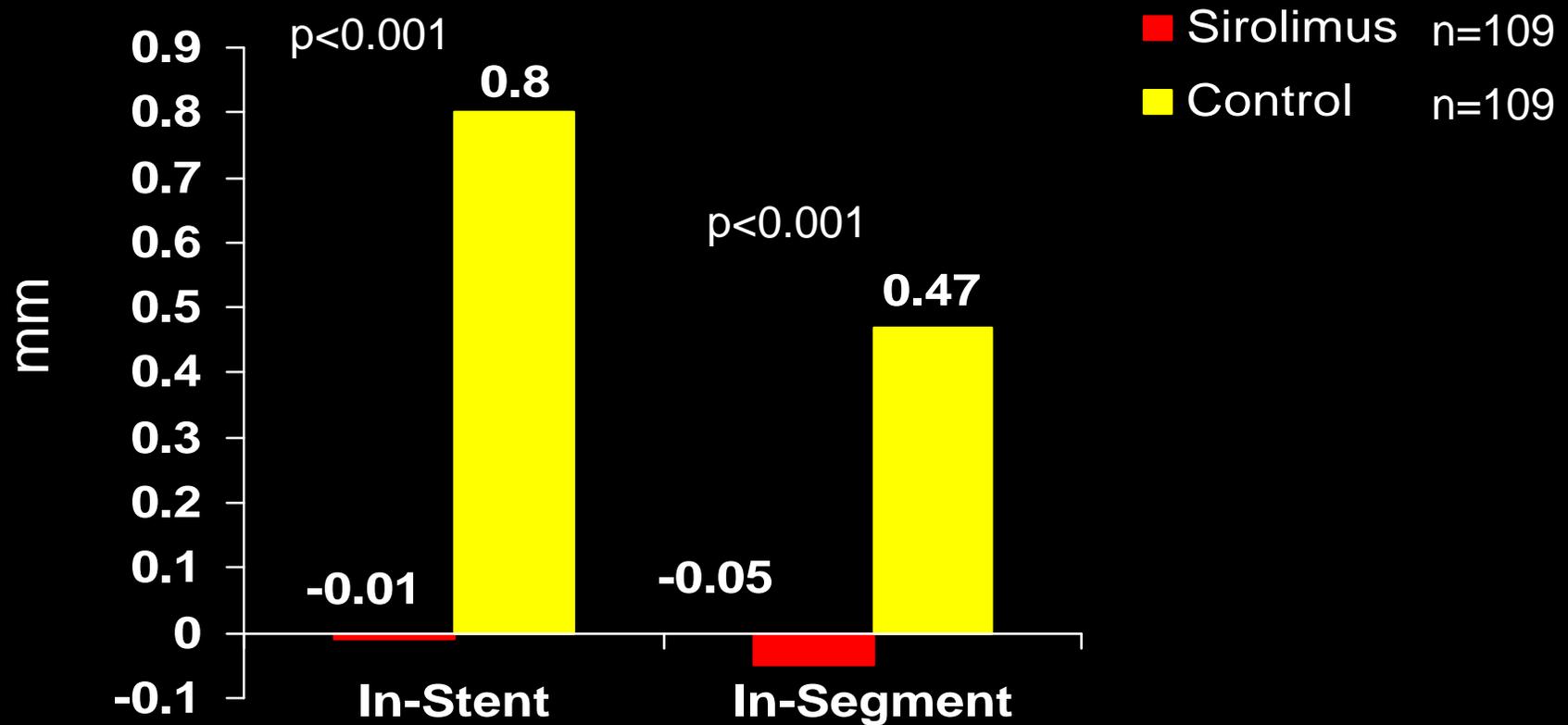
# Definition Slide: Angiographic Terms



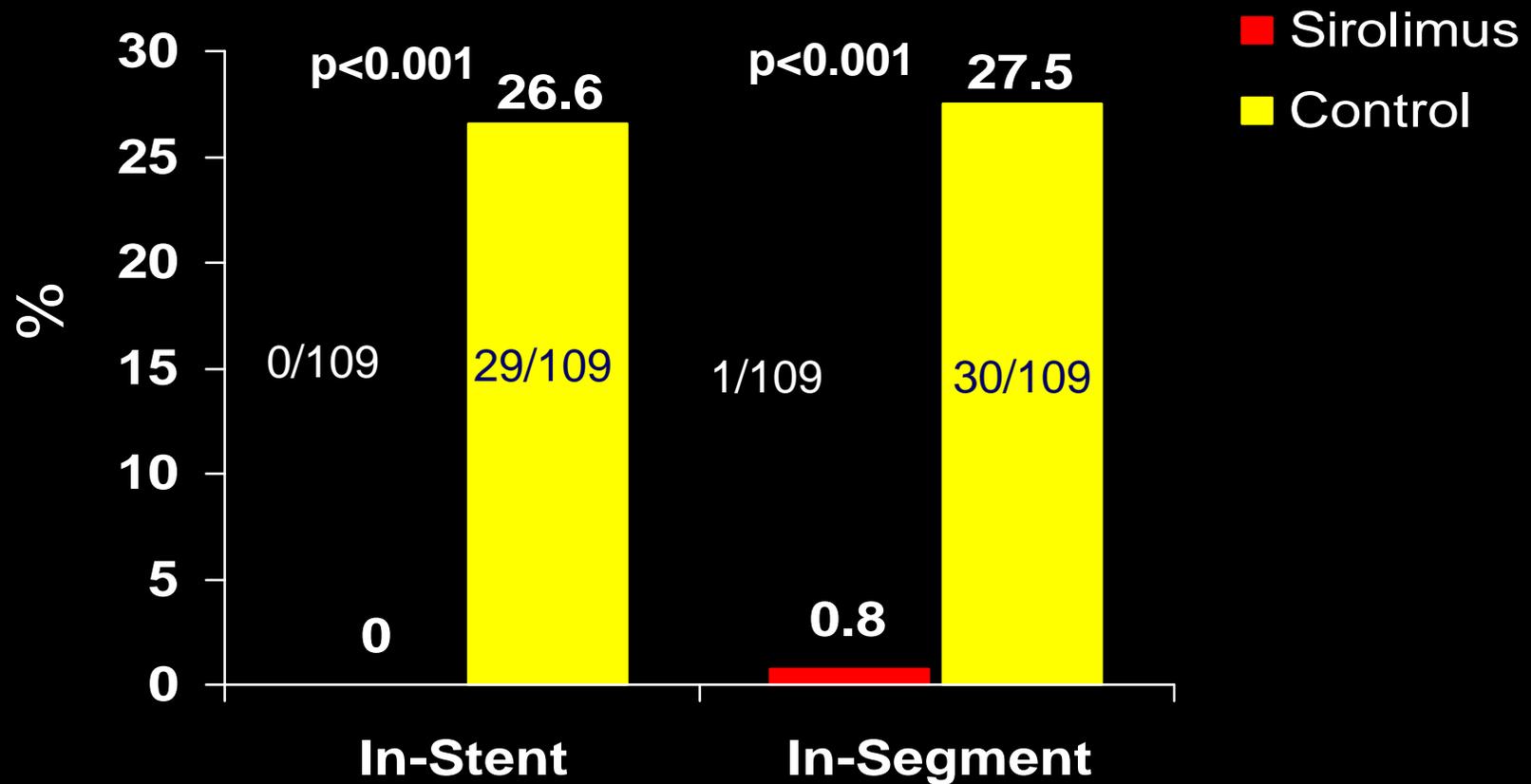
- In-stent = measurement within the stented area
- In-segment = measurements within the stented segment and within 5mm proximal and distal to the stent edges

# RAVEL: 6-Month QCA

## Late Loss



# RAVEL: 6-Month QCA Restenosis



# RAVEL: IVUS at 6 Months

	Sirolimus (Mean) n=69	Control (Mean) n=70	p-value
EEM volume (mm <sup>3</sup> )	280	290	---
Stent volume (mm <sup>3</sup> )	131	138	---
Neointimal volume (mm <sup>3</sup> )	2	34	<0.001
Lumen volume (mm <sup>3</sup> )	130	103	<0.001
% Volume obstruction	1.1	26.1	<0.001

# RAVEL: In-Hospital MACE Events

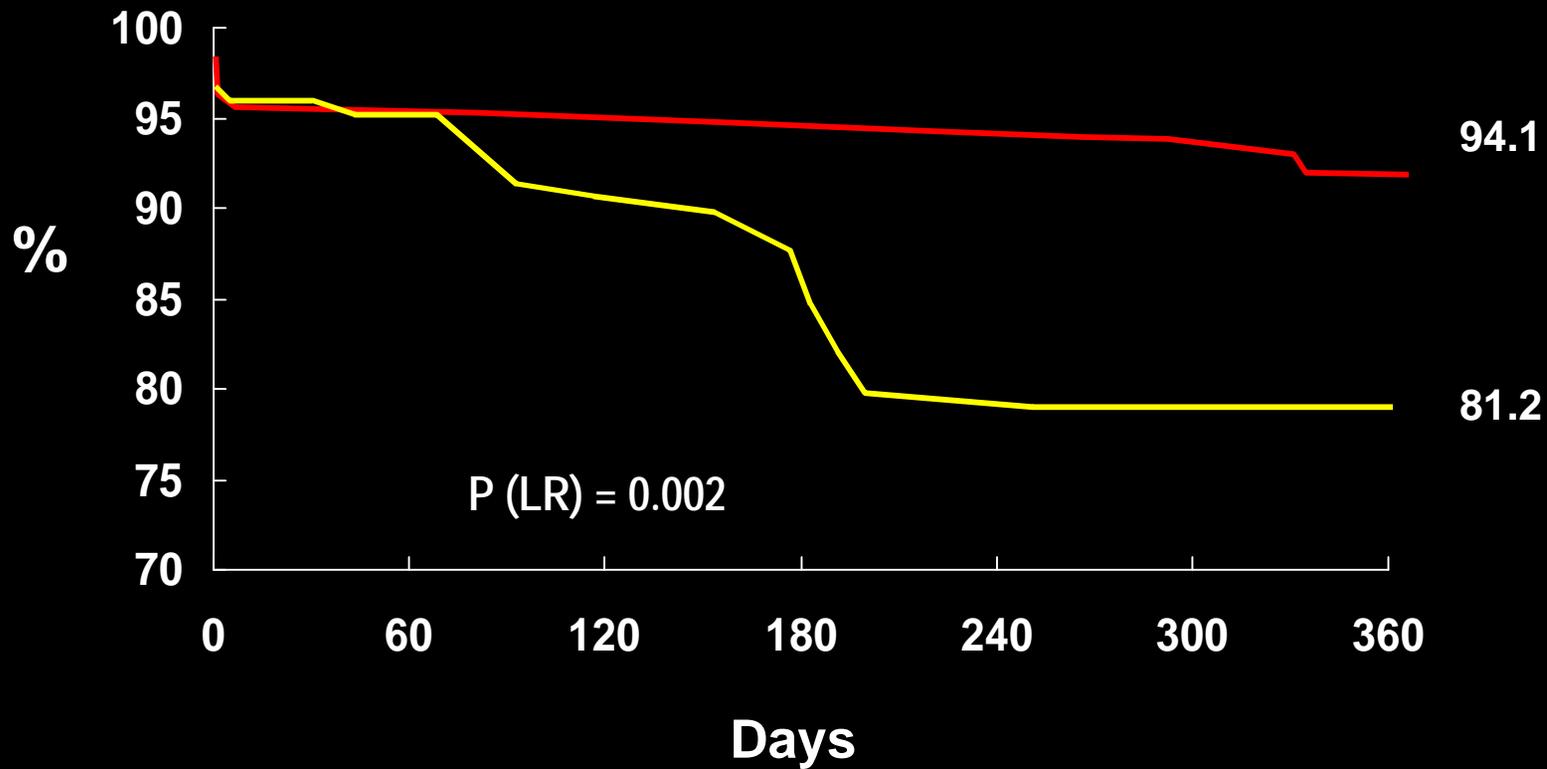
Events	Sirolimus % (n=120)	Control % (n=118)	p-value
Death	0.0(0)	0.0(0)	---
MI			
Q-wave	1.7(2)	0.8(1)	>0.999
Non Q-wave	0.8(1)	1.7(2)	0.62
TLR (clinically driven)			
PCI	0.0(0)	0.0(0)	---
CABG	0.0(0)	0.0(0)	---
TVF	2.5(3)	2.5(3)	>0.999
All MACE	2.5(3)	2.5(3)	>0.999

# RAVEL: Cumulative MACE Events to 365 Days

Events	Sirolimus % (n=120)	Control % (n=118)	p-value
Death	1.7(2)	1.7(2)	>0.999
MI			
Q-wave	1.7(2)	0.8(1)	>0.999
Non Q-wave	1.7(2)	4.2(5)	0.28
TLR (clinically driven)			
PCI	0.0(0)	13.6(16)	<0.001
CABG	0.8(1)	0.0(0)	>0.999
TVF	4.2(5)	19.5(23)	<0.001
All MACE	5.8(7)	18.6(22)	0.003

# RAVEL: Event Free Survival Death, MI, CABG, Re-PTCA

Patients without events  
Percent, P Log Rank 0.002



# RAVEL: Deaths to 365 Days in Sirolimus-eluting Stent Group

- **Patient number 1052**
  - 65 year old male
  - Successful index procedure of CFX
  - Patient expired 330 days post procedure of **gastro-intestinal cancer**
- **Patient number 1204**
  - 55 year old male
  - Index procedure of LAD. Stent placement successful. Type C-dissection at stented site, post pre-dilation.
  - Admitted 332 days post-procedure for sudden loss of consciousness with a Glasgow Classification of 4
  - CT showed subarachnoid hemorrhage due to rupture of cerebral artery aneurysm
  - Patient expired 333 days post procedure due to **subarachnoid hemorrhage**

# SIRIUS: Randomized, Double-blind Trial

n = 1101 patients

*De Novo* Native  
Coronary Lesions

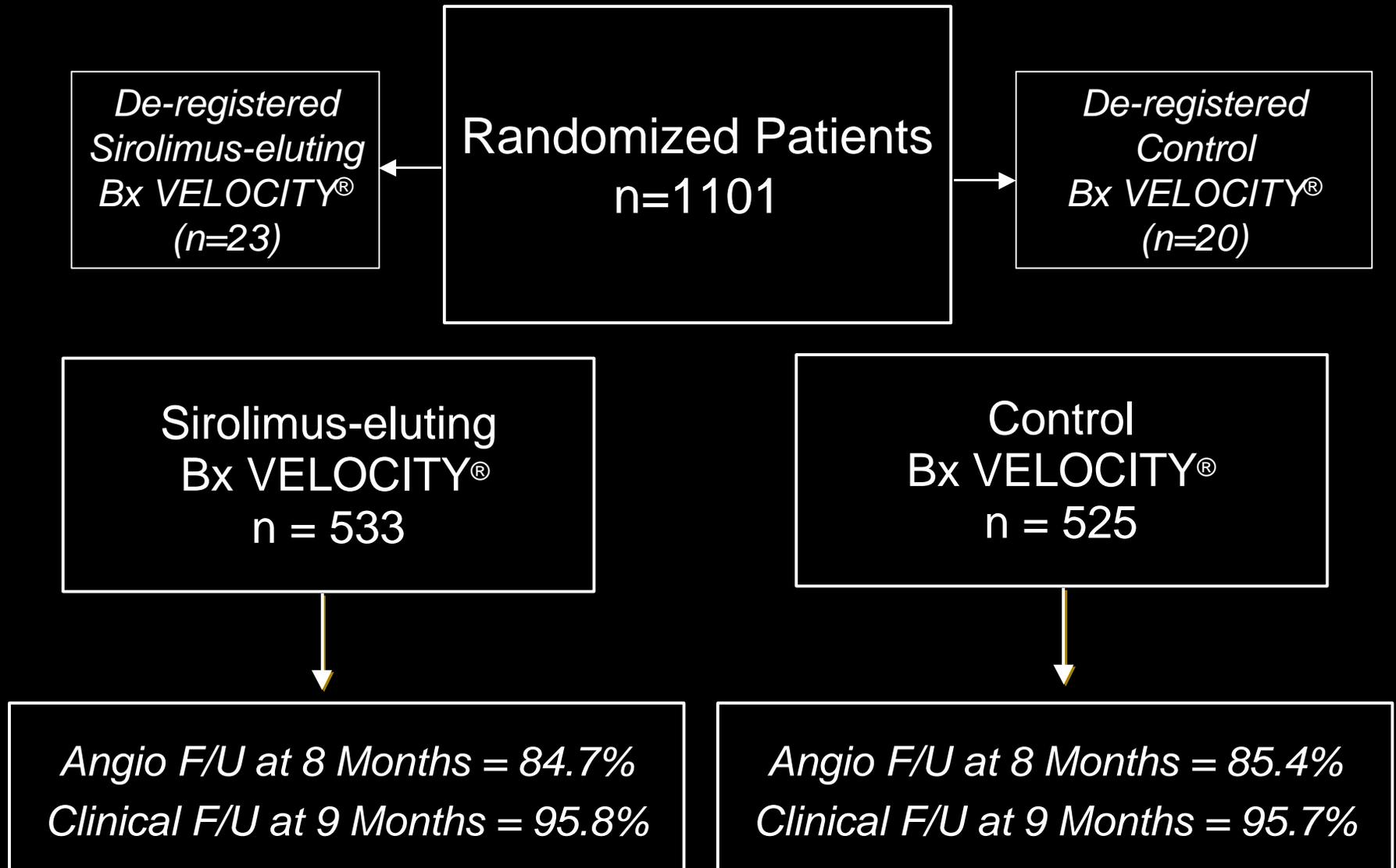
Diameter: 2.5-3.5 mm  
Length: 15-30 mm

Sirolimus-eluting  
Bx VELOCITY®  
n=556

Control  
Bx VELOCITY®  
n=545

- Primary Endpoint: target vessel failure (TVF) = cardiac death, MI or target vessel revascularization (TVR) (F/U at 9 months)
- Angiographic substudy: first 850 patients (F/U at 8 months)
- IVUS substudy: 250 patients at selected sites (F/U at 8 months)
- Antiplatelet therapy for 90 days (clopidogrel/ticlopidine)

# SIRIUS: Study Flow



# SIRIUS: De-registered Patients

	Sirolimus (n=23/556)	Control (n=20/545)
Device unavailable	2	2
Failed inclusion or exclusion criteria	21	17
Other	0	1
<i>Total</i>	<i>23</i>	<i>20</i>

# SIRIUS: Baseline Patient Demographics

	Sirolimus (%) n=533	Control (%) n=525
Age (years)	62.1	62.4
Male	72.6	69.7
Prior MI	28.2	32.9
Prior Revascularization	26.3	23.1
Diabetes Mellitus	24.6	28.2
Hypercholesterolemia	72.7	74.6
Hypertension	67.6	67.8
Current Smoker	17.7	22.4

No statistically significant differences between groups

# SIRIUS: Baseline Lesion Characteristics

	Sirolimus (%) n=533	Control (%) n=525
LAD	44.2	43.2
LCX	25.3	23.9
Class B1	34.0	38.1
Class B2	32.6	33.5
Class C	26.0	20.6
Overlapping Stents	28.5	26.9

No statistically significant differences between groups

# SIRIUS: Baseline Angiographic Results

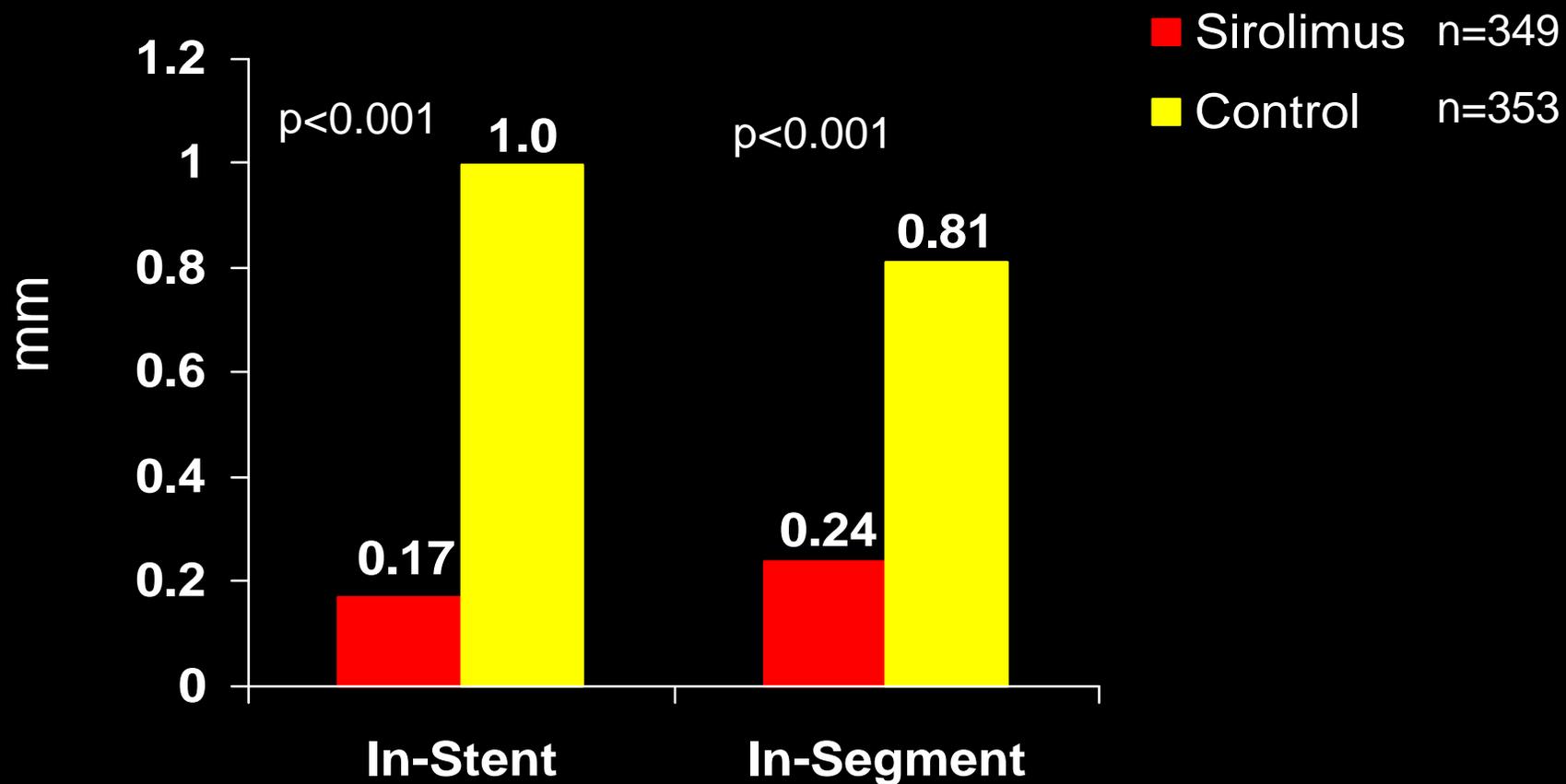
	Sirolimus (Mean) n=533	Control (Mean) n=525
RVD (mm)		
Pre	2.78	2.81
Post	2.84	2.86
MLD (mm)		
Pre	0.98	0.97
Post	2.67	2.68
DS (%)		
Pre	65.1	65.6
Post	5.4	6.0
Lesion length (mm)	14.4	14.4

No statistically significant differences between groups

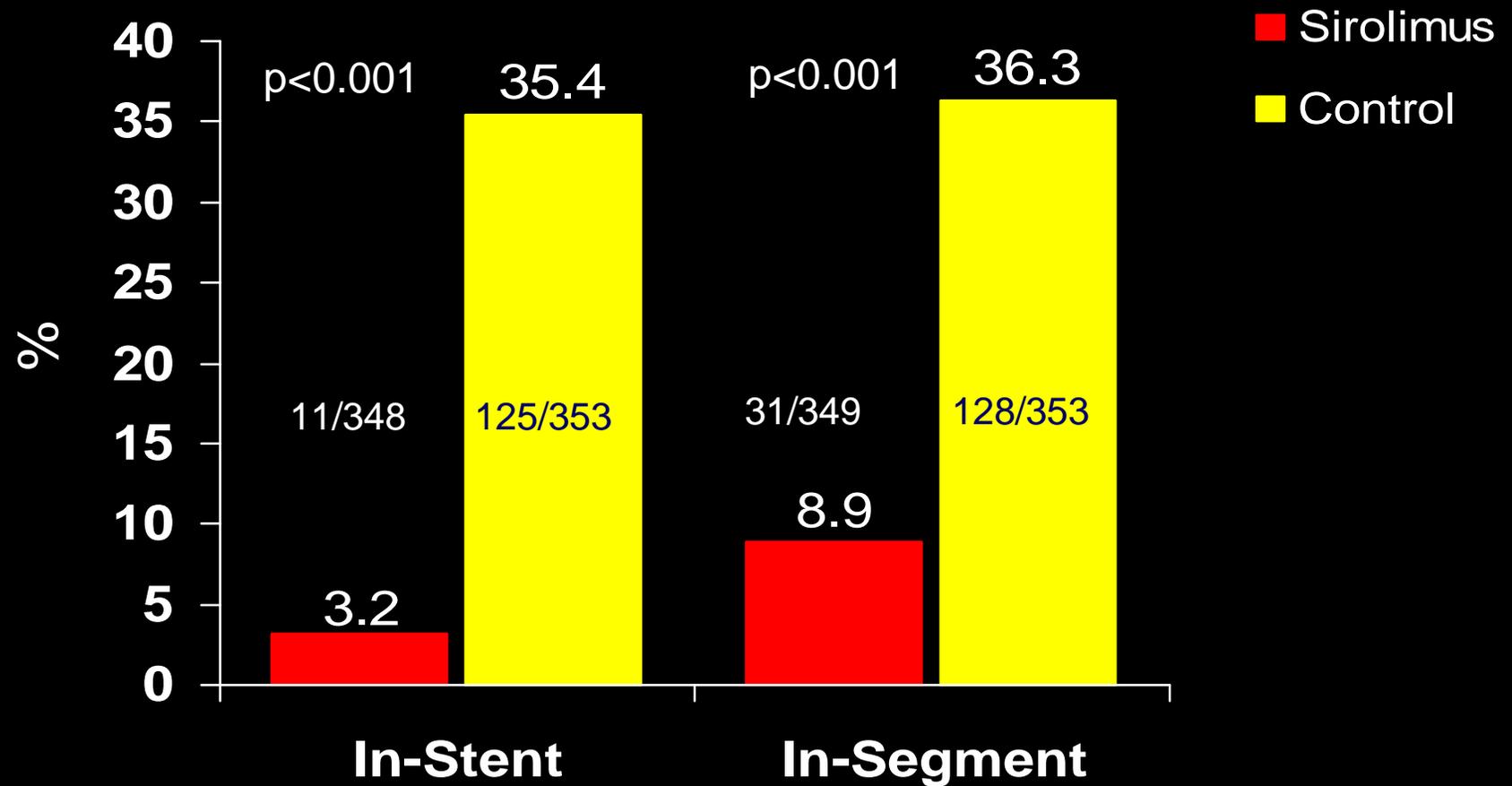
# SIRIUS: Success Measures

	Sirolimus (%) n=533	Control (%) n=525
Lesion Success	99.8	100
Device Success	97.9	98.7
Procedure Success	97.4	98.5

# SIRIUS: 8-Month QCA Late Loss



# SIRIUS: 8-Month QCA Restenosis



# SIRIUS: 8-Month IVUS Analysis

	Sirolimus (Mean) n=99	Control (Mean) n=76	p-value
EEM volume (mm <sup>3</sup> )	320.6 ± 130.6	333.5 ± 116.4	0.639
Mean lumen area (mm <sup>2</sup> )	6.7 ± 1.9	5.0 ± 1.9	<0.001
Mean NIH area (mm <sup>2</sup> )	0.6 ± 0.8	2.9 ± 1.5	<0.001
NIH volume (mm <sup>3</sup> )	4.1 ± 5.9	56.8 ± 31.7	<0.001
Volumetric plaque burden (%)	2.6 ± 4.1	34.2 ± 14.1	<0.001

# SIRIUS: Clinical Events

## All Events (In-Hospital)

Events	Sirolimus % n=533	Control% n=525	p-value
Death	0.2 (1)	0 (0)	0.999
MI (all)	2.3 (12)	1.5 (8)	0.500
Q-wave	0.4 (2)	0 (0)	0.500
Non Q-wave	1.9 (10)	1.5 (8)	0.813
TLR (clinically driven)	0.2 (1)	0 (0)	0.999
TVR (non-TL)	0 (0)	0 (0)	---
MACE	2.4 (13)	1.5 (8)	0.379
TVF (1 <sup>o</sup> endpoint)	2.4 (13)	1.5 (8)	0.379

# SIRIUS: Clinical Events

## All Events (Out-of-Hospital to 9 Months)

Events	Sirolimus % n=533	Control % n=525	p-value
Death	0.8 (4)	0.6 (3)	0.999
MI (all)	0.6 (3)	1.7 (9)	0.088
Q-wave	0.4 (2)	0.4 (2)	0.999
Non Q-wave	0.2 (1)	1.3 (7)	0.037
TLR (clinically driven)	3.9 (21)	16.6 (87)	<0.001
TVR (non-TL)	3.2 (17)	4.8 (25)	0.210
MACE	4.9 (26)	17.7 (93)	<0.001
TVF (1° endpoint)	6.4 (34)	19.6 (103)	<0.001