SYSTEMIC THERAPY AND ORAL RAPAMYCIN TO INHIBIT RESTENOSIS

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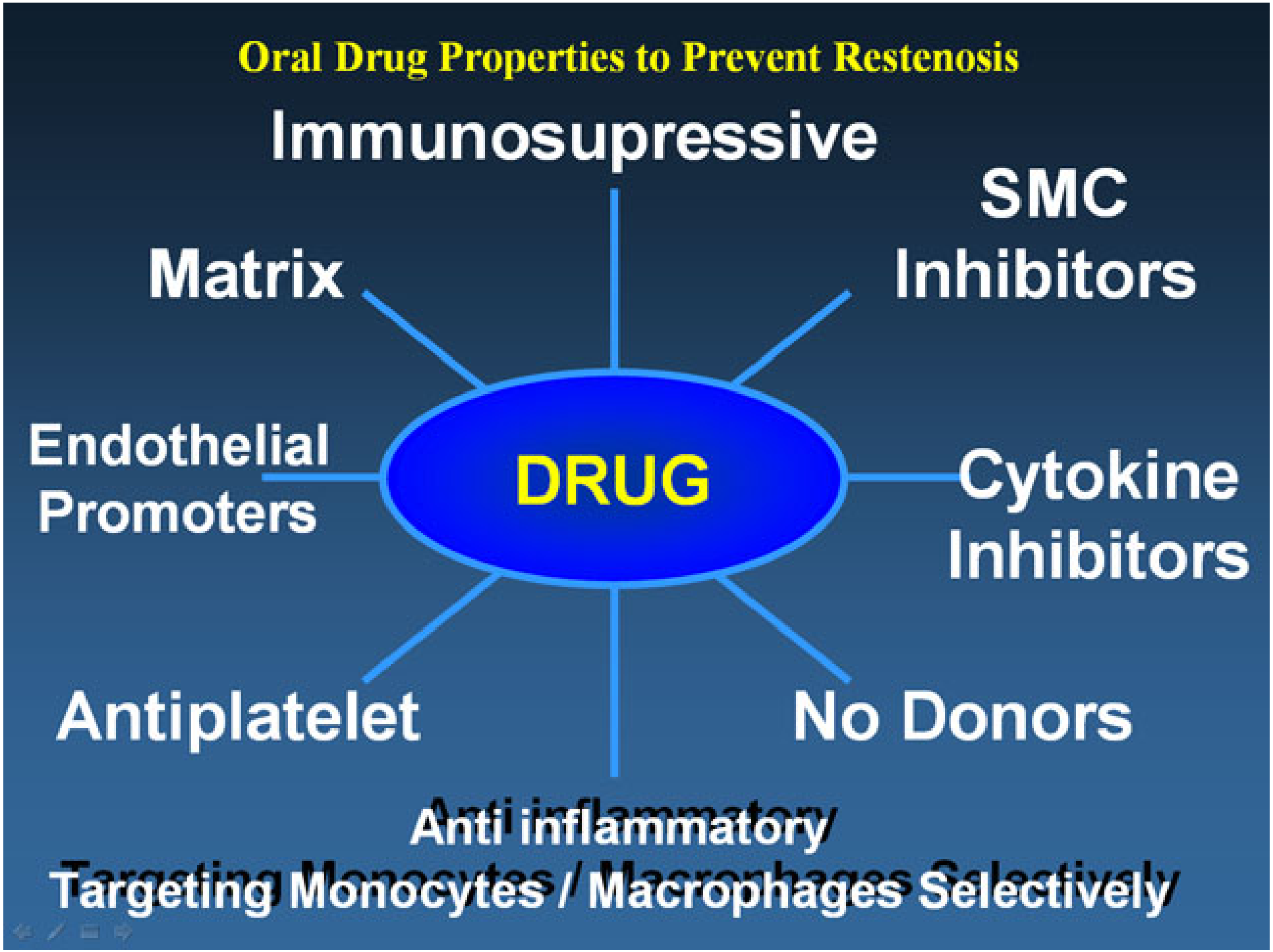
Washington Hospital Center

Rational for Alternative (non DES) Treatment to Restenosis

- DES continue to demonstrate restenosis in complex anatomy and selective subset population (diabetes)
- DES is limited to a stent platform
- DES technology may cause vessel toxicity: aneurysm, edge effect, thrombosis, malapposition.
- DES is expensive especially when multiple stents are needed for multivessel disease.

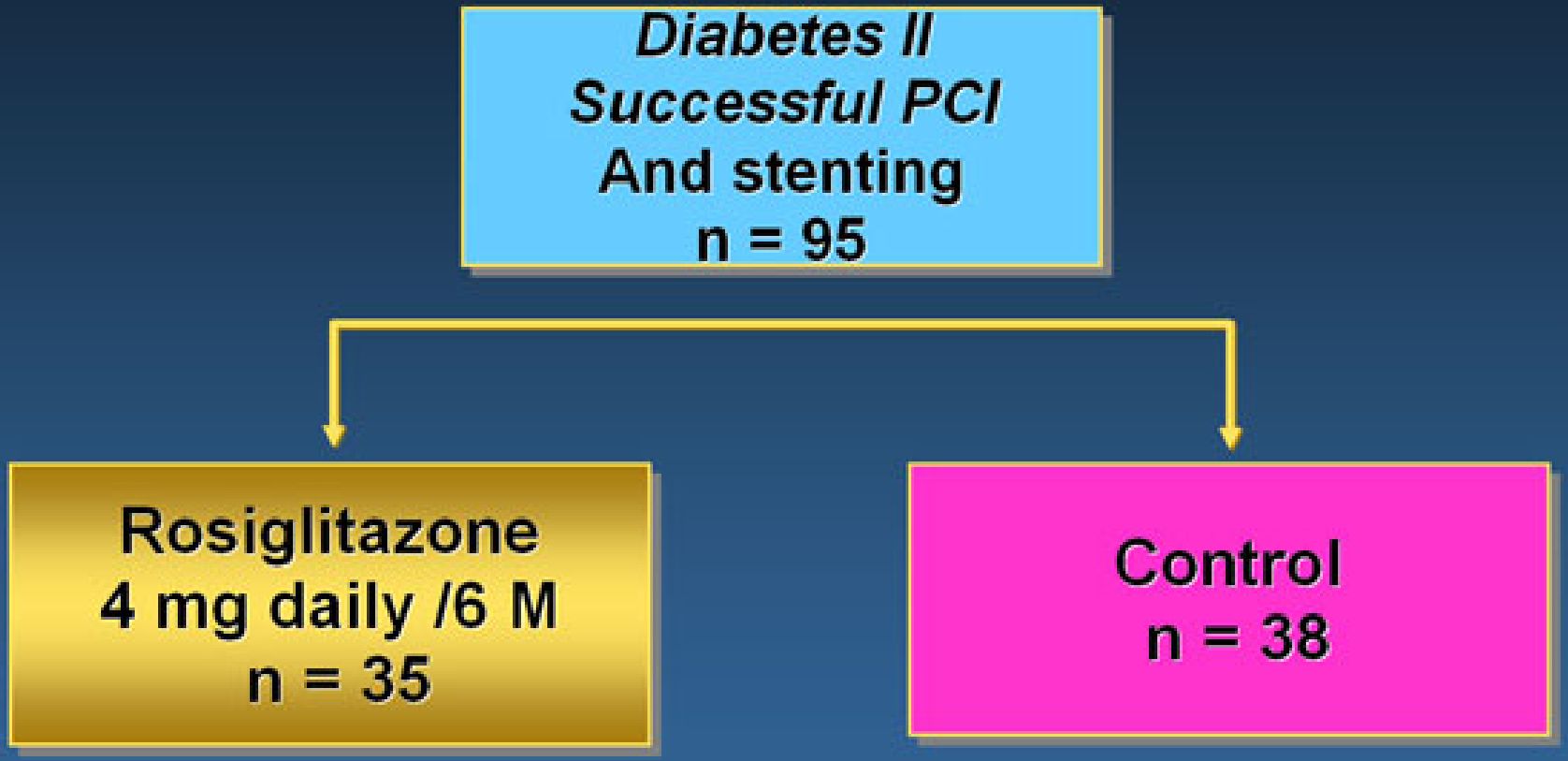

Oral Drug Properties to Prevent Restenosis
Immunosupressive
SMC Inhibitors
Matrix
Endothelial Promoters
DRUG
Cytokine Inhibitors
Antiplatelet
No Donors
Anti inflammatory
Targeting Monocytes / Macrophages Selectively

2000-2006

Medications for Restenosis Prevention

• Homocysteine lowering I	SWISS	Reduces restenosis
• Homocysteine lowering II	Bremen/Zwolle	Negative
• Antioxidant AGI	CART I	May be
• Rosiglithazone	KOREA	Positive
• Pioglithazone	Germany	Positive
• Corticosteroid	IMPRESS I&II	Positive
• Cilostazol	CREST	Positive
• Rapamune	ORBIT	Positive
• Rapamune	OSIRIS	Positive
• Verapamil	VESPA	Positive
• Rapamune	ORAR	Positive

Restenosis Drops in Diabetic Patients Given Rosiglitazone

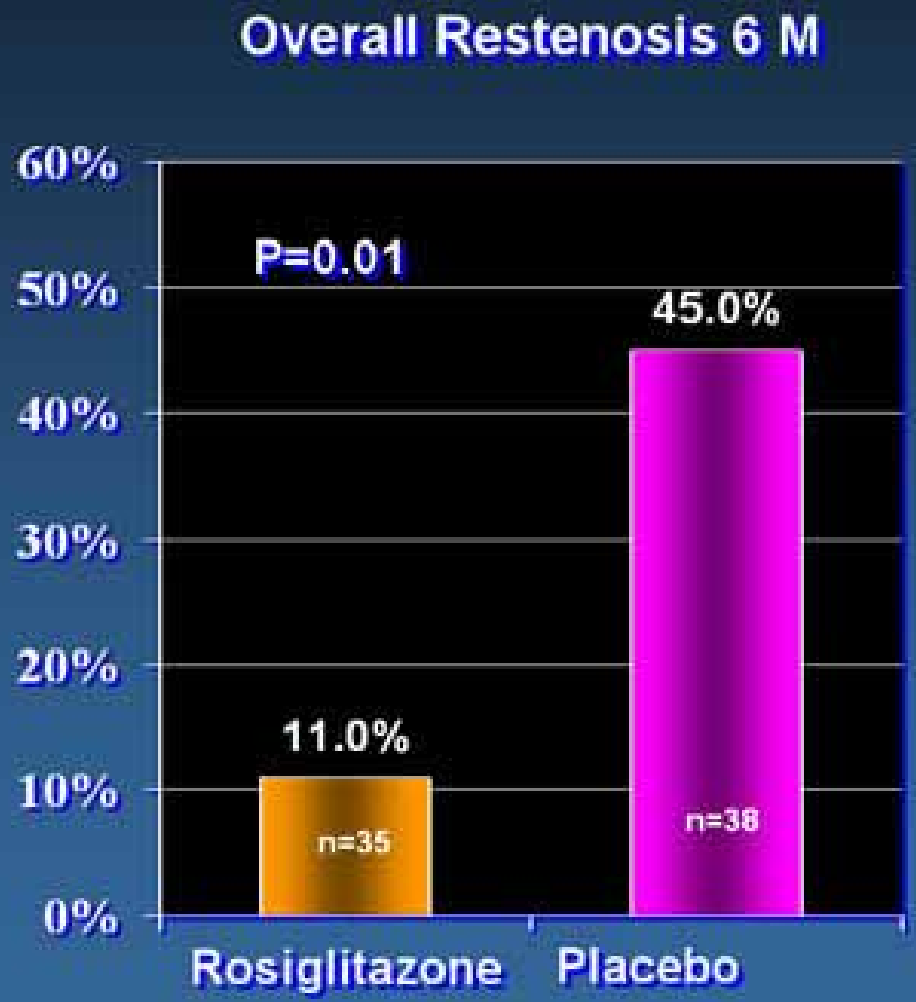


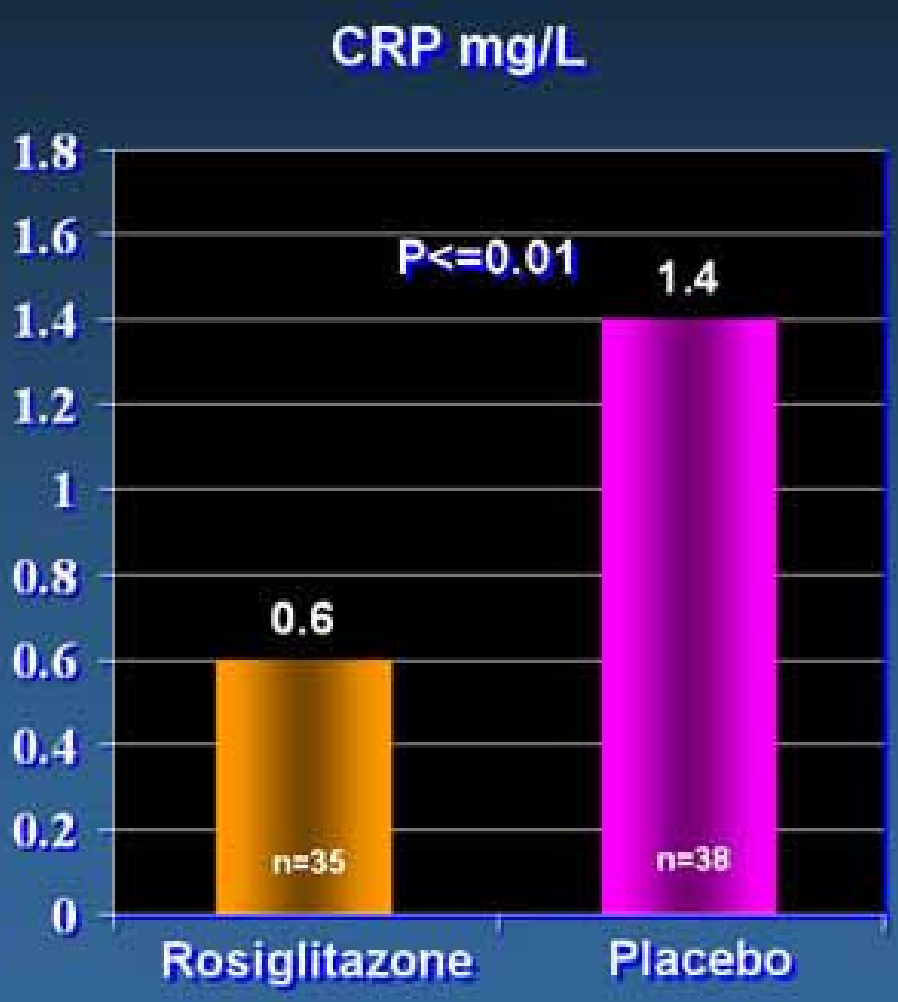
1° endpoint - Restenosis by QCA

Anti inflammatory action of Rosiglitazone

Choi et al, American Diabetes Associatian, New ORLEANS 2003

Rosiglitazone in Diabetes





Choi et al, American Diabetes Associatian, New ORLEANS 2003

Outcomes six months' post-PCI in rosiglitazone and placebo arms

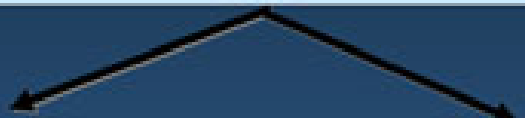
End point	Rosiglitazone	Placebo	p
Restenosis	12%	47%	<0.001
CRP (mg/L)	0.6±0.2	1.4±0.3	<0.01
Free fatty acids	672±70	819±60	<0.01
Triglycerides (mg/dL)	83±14	96±12	<0.01

Choi SH. American Diabetes Association 63rd Scientific Sessions; Jun 13-17, 2003; New Orleans

Pioglitazone Reduces Neointima Formation After Coronary Stent Implantation

50 non diabetic patients undergoing PCI in de novo lesions

Study arms had equivalent baseline fasting blood glucose, fasting insulin, HbA1c, and lipid levels



Pioglitazone

30 mg/OD
n=25

Placebo

- n=25

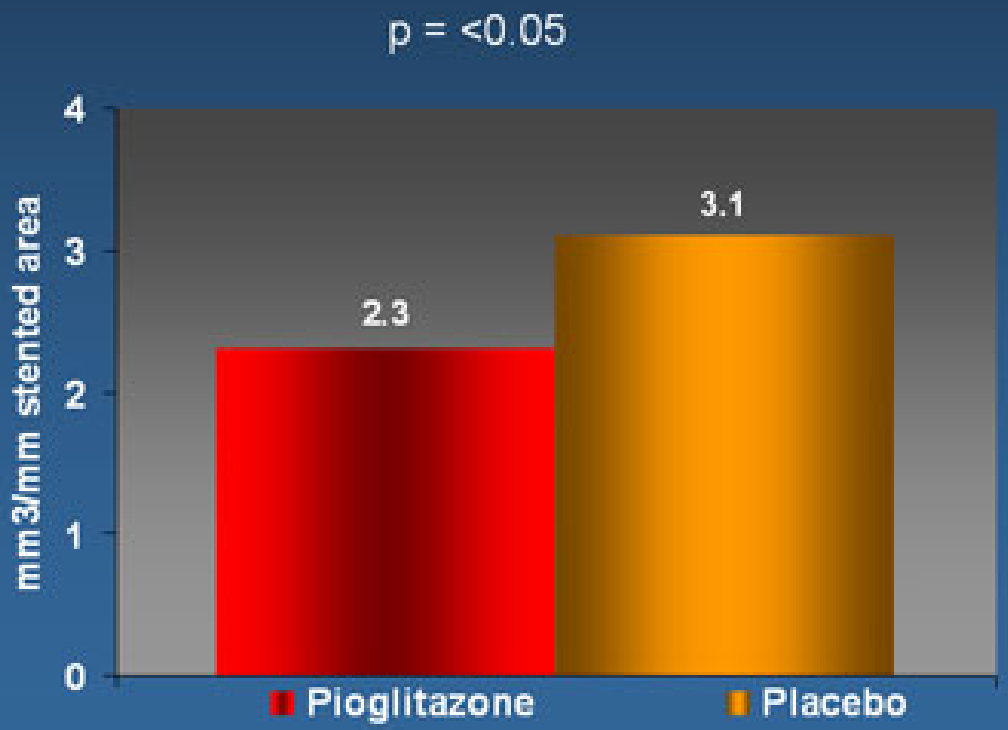
Endpoints:

- Primary – Neoinimal volume measured (measured with IVUS) within the stented segment at 6 months
- Secondary – Total plaque volume, minimum lumen diameter and percent stenosis at 6 months

Nikolaus Marx ACC 2005

Pioglitazone Trial: Primary endpoint

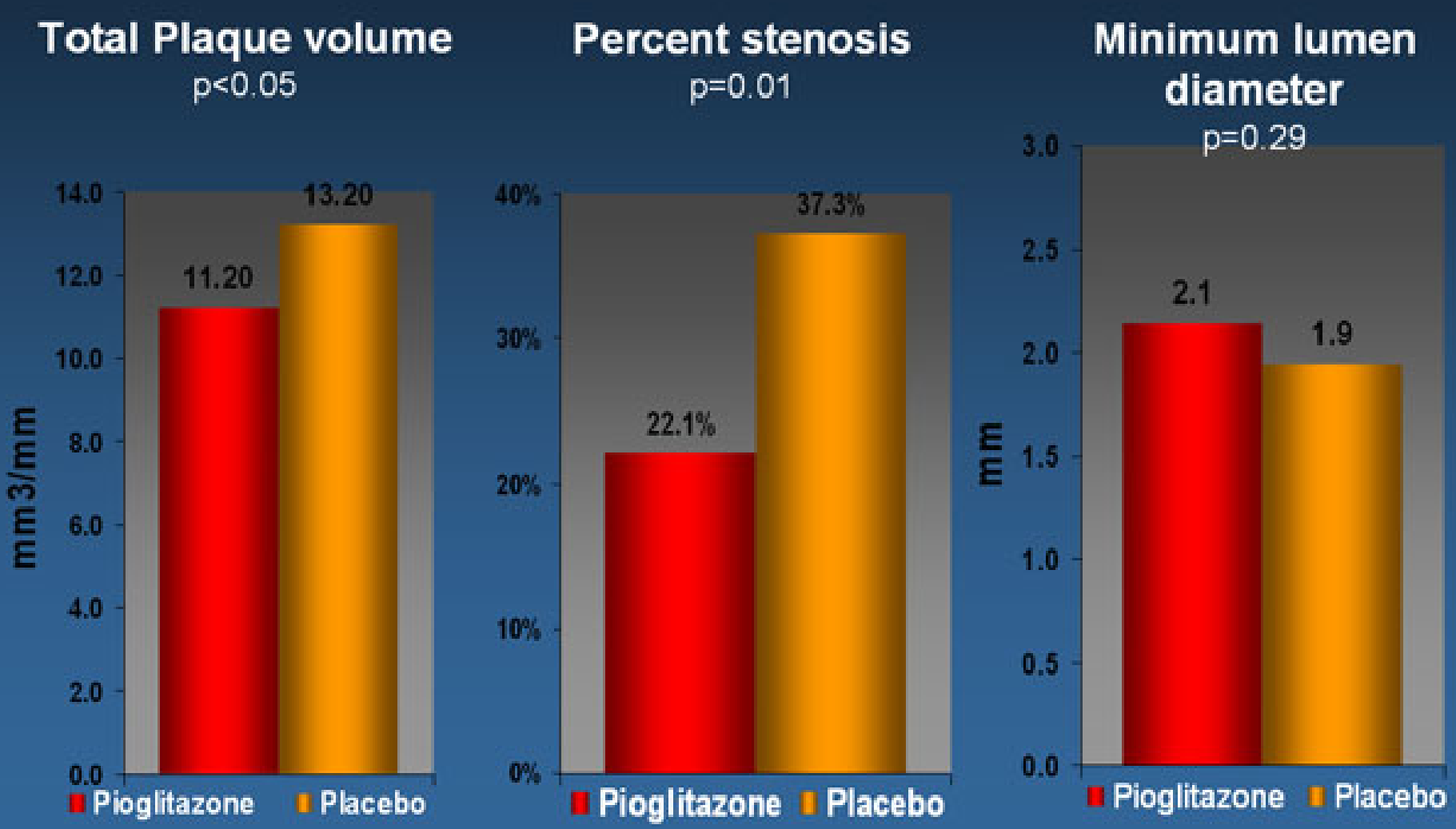
Neointima volume by intravascular untrasound at six months



- The primary endpoint of neointimal volume within the stented segment at 6 months was significantly lower in the pioglitazone group compared with placebo.

Nikolaus Marx ACC 2005

Pioglitazone Trial: Secondary Endpoint



ACC 2005

Pioglitazone Trial: Summary

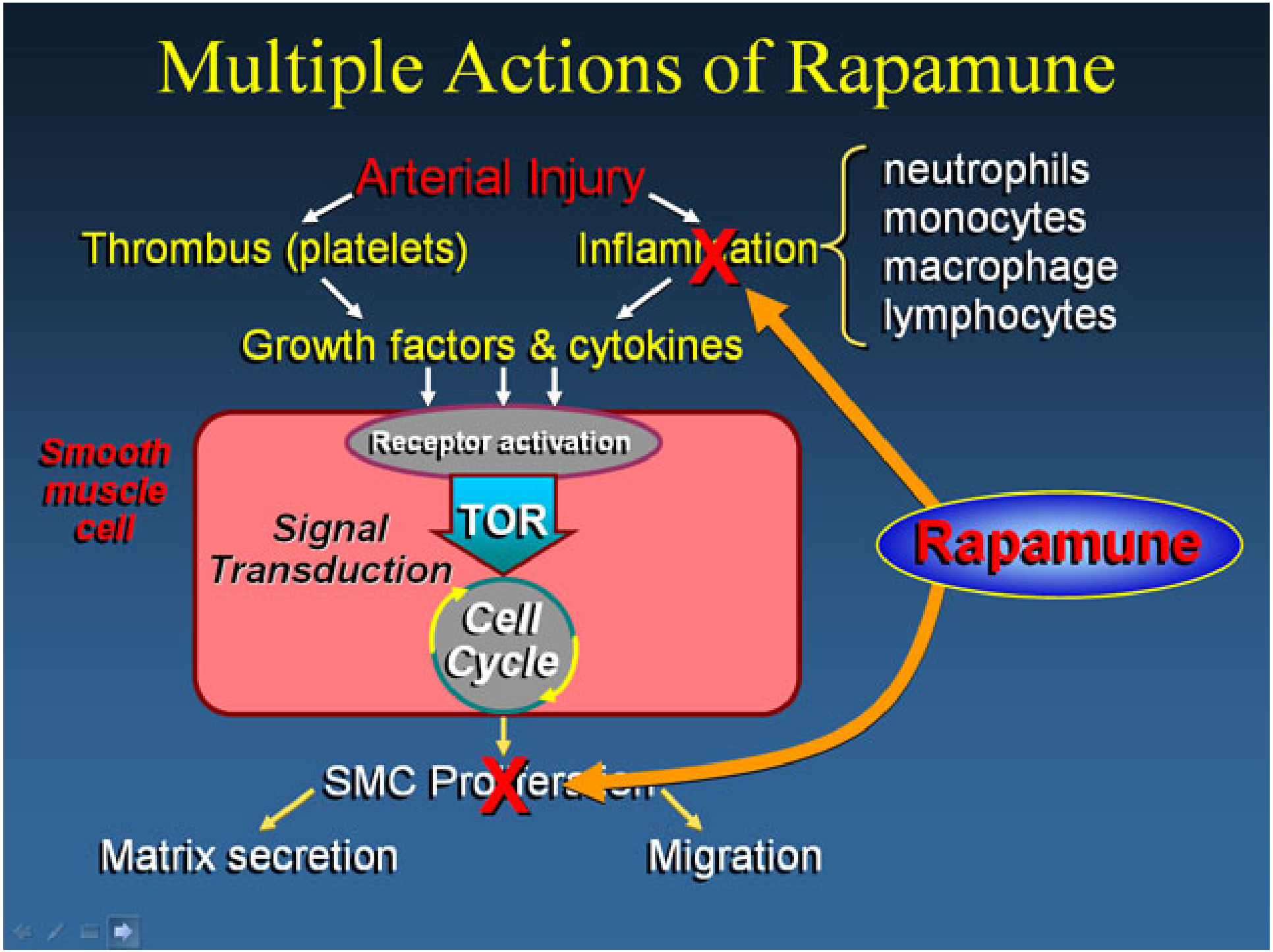
- Among nondiabetic patients undergoing coronary stent implantation for de novo lesions, treatment with pioglitazone was associated with a reduction in neointima formation compared with treatment with placebo at 6 month follow-up.
- The pioglitazone group also showed significant reductions in total plaque volume and stenosis at six months compared with the placebo group.

Immunosuppresive Therapy?

Corticosteroids

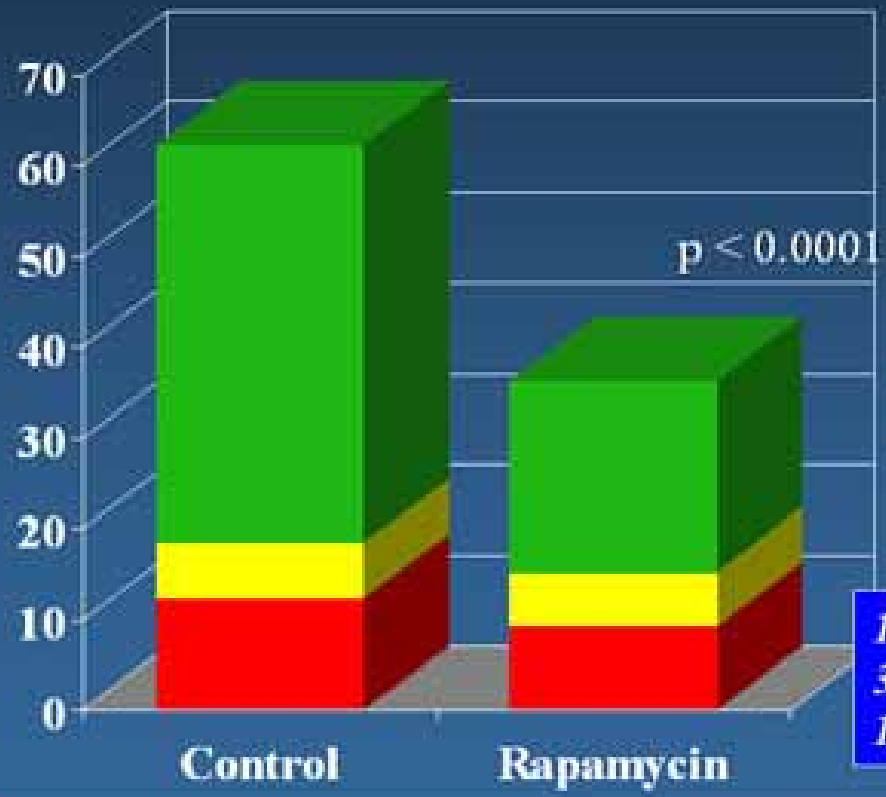
Rapamune & Analogues

Others

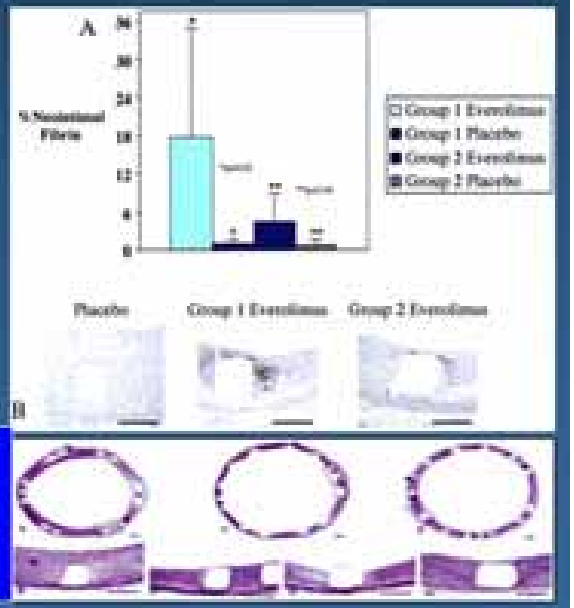

Multiple Actions of Rapamune
Arterial Injury
Thrombus (platelets)
Inflammation
neutrophils
monocytes
macrophage
lymphocytes
Growth factors & cytokines
Smooth muscle cell
Receptor activation
TOR
Signal Transduction
Cell Cycle
Rapamune
SMC Proliferation
Matrix secretion
Migration

Effect of Systemic Delivery Rapamycin or Everolimus in Animal Restenosis Models

- Rapamycin 3 d pre intervention
- IM 0.5 mg/kg load dose
- IM 0.25mg/kg 14 days
- Analysis at 4 weeks



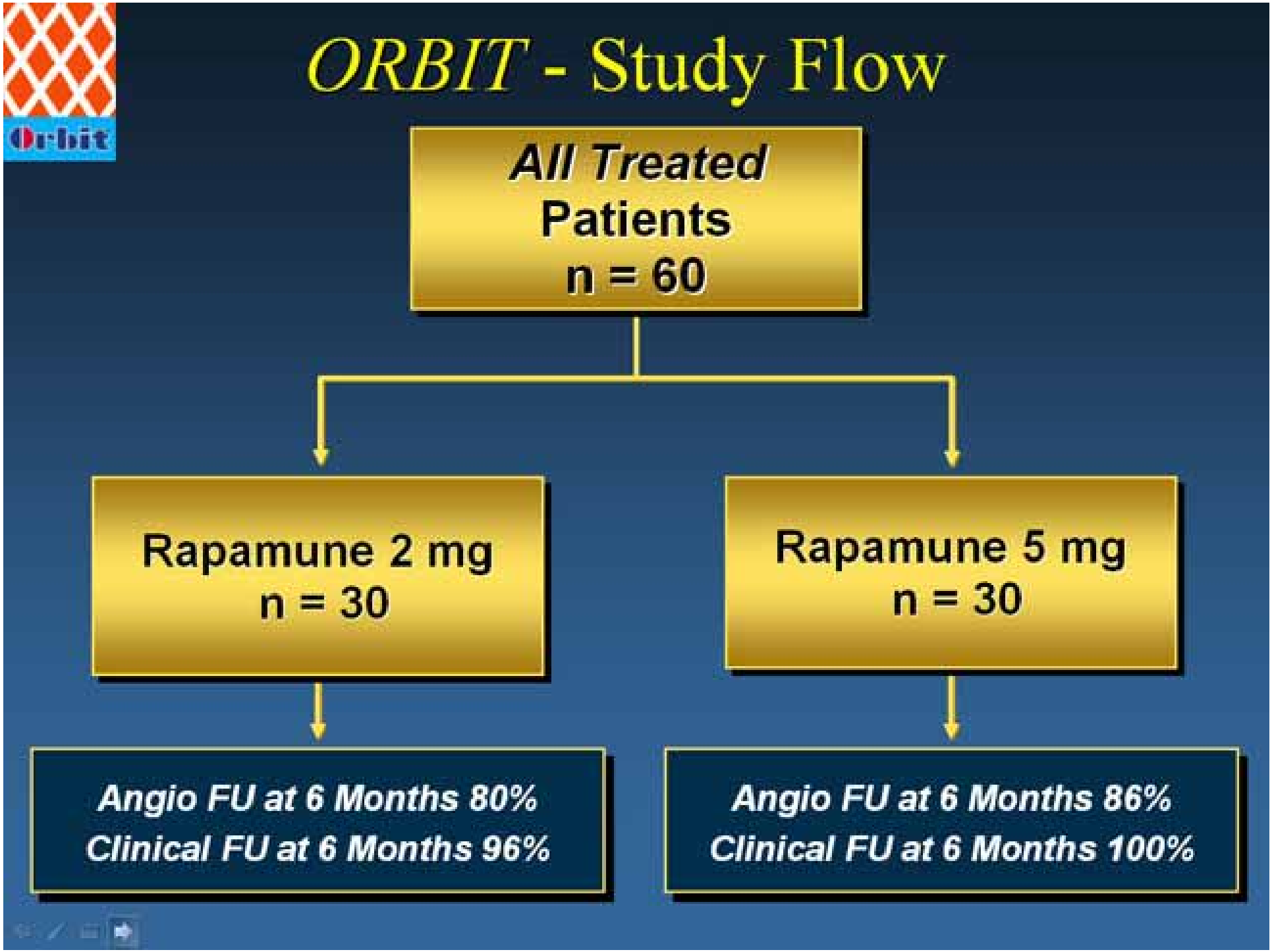
1-1.5 mg/kg everolimus
3 days prior to stenting
14-28 days



Gallo, et. al. - Circulation 1999; 99:2164-2170

Andrew Farb, **Oral Everolimus Inhibits In-Stent Neointimal Growth** Circulation, Oct 2002; 106: 2379 - 2384

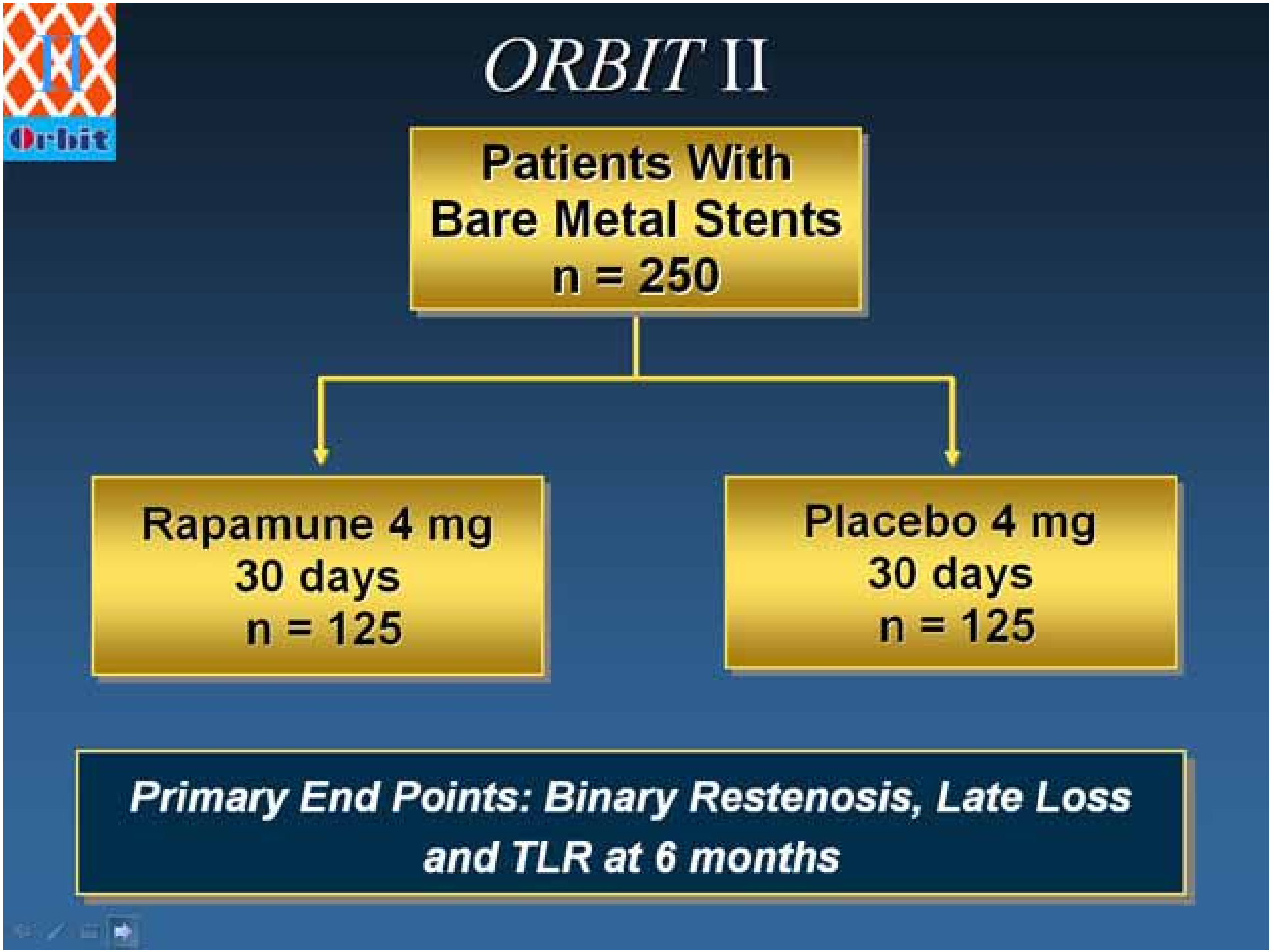
ORBIT - Study Flow



RESULTS

Side Effects of Systemic Rapamune

Drug Safety Profile 2 mg and Adverse Reactions	Drug Safety Profile 5 mg and Adverse Reactions
2 patients discontinue	2 patients discontinue
GI diarrhea 6 pts	GI diarrhea 5 pts
Oral Ulcers 2 pts	Oral Ulcers 6 pts
Skin Rash 2 pts	Skin Rash 5 pts
Mean duration of taking the Rapamune **26.7 ± 7.8 days**	Mean duration of taking the Rapamune **22.0 ± 11.7 days**


ORBIT II
Patients With
Bare Metal Stents
n = 250
Rapamune 4 mg
30 days
n = 125
Placebo 4 mg
30 days
n = 125
Primary End Points: Binary Restenosis, Late Loss
and TLR at 6 months

ORBIT II
Study Administration

Sponsor:	Medstar Research Institute
Data Center:	Medstar Research Institute
Principal Investigator:	Ron Waksman, MD
DSMC Chairman:	James Tcheng, MD
Research Pharmacist:	Claude Nogay, RPh
Study Coordinator:	Rebecca Torguson

Participating Centers

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Jerome Hines, MD	LaGrange Hospital, La Grange, IL
J. Eduardo Sousa, MD	Institute Dante Pazzanese of Cardiology, São Paulo, Brazil
Constantino Constantini, MD	Clinica Cardiológyca C. Constantini, Curitiba, Paraná, Brazil
Henry Meilman, MD	Union Memorial Hospital, Towson, MD
Michael Drossner, MD	Mid Atlantic Cardiovascular Associates, Towson, MD
Clifford Kavinsky, MD	Rush Heart Institute, Chicago, IL
David Eich, MD	Norfolk Sentera Hospital, Norfolk, VA

DEMOGRAPHICS

	Rapamune 4 mg n=21	Placebo n=22	p value
Age (years)	56.0 ± 19.14	56.7 ± 11.82	0.882
Male	18/21 (85.7)	16/22 (72.7)	0.457
Any Smoking History	13/21 (61.9)	12/22 (54.5)	0.625
History of Diabetes	6/21 (28.6)	5/22 (22.7)	0.213
Hypertension	13/21 (61.9)	16/21 (76.2)	0.317
Hyperlipidemia	16/20 (80.0)	14/20 (70.0)	0.465
History of Cancer (Any)	0/21 (0.0)	3/22 (13.6)	0.233
Prior Myocardial Infarction	7/18 (38.9)	1/21 (4.8)	0.015
Prior PCI	6/20 (30.0)	5/22 (22.7)	0.592
Prior CABG	1/21 (4.8)	3/22 (13.6)	0.607
Prior CVA	1/21 (4.8)	0/22 (0.0)	0.488
Left Ventricular Ejection Fraction	0.53 ± 0.10	0.57 ± 0.09	0.185

ANGIOGRAPHIC CHARACTERISTICS

	Rapamune 4 mg n=26	Placebo n=29	P value
Mean # lesions treated	1.2 ± 0.6	1.3 ± 0.6	0.662
Left Main, %	0/26 (0)	0/26 (0)	.
RCA, %	9/26 (34.6)	14/29 (48.3)	0.305
LAD, %	12/26 (46.2)	11/29 (37.9)	0.537
LCX, %	5/26 (19.2)	4/29 (13.8)	0.720
Lesion Length, mm	14.96 ± 6.89	14.06 ± 6.29	0.611
Reference vessel Diameter, mm	3.26 ± 0.42	3.21 ± 0.47	0.659
Pre Diameter Stenosis	0.81 ± 0.1	0.85 ± 0.09	0.161

Lesion Characteristics

	Rapamune 4 mg Lesion n=26	Placebo Lesion n=29	p value
Stents per Lesion	1.33 ± 0.66	1.27 ± 0.55	0.745
Average Stent Diameter (mm)	3.38 ± 0.69	3.33 ± 0.65	0.769
Average Stent Length (mm)	17.96 ± 6.94	16.15 ± 6.54	0.480
Devices Used			
Laser	0/26 (0)	0/29 (0)	.
Rota	0/26 (0)	1/29 (3.4)	1
Cutting Balloon	1/26 (3.8)	0/29 (0)	0.473
Pre-Dilatation with Balloon	7/16 (26.9)	8/29 (27.6)	0.956
Direct Stenting	19/26 (73.1)	20/29 (69.0)	0.737
Post-Dilatation with Balloon	14/26 (53.8)	11/29 (37.9)	0.237

Discharge Medications

All patients were discharge on clopidogrel and ASA for at least 6 months.

Study medication was prescribed for 30 days.

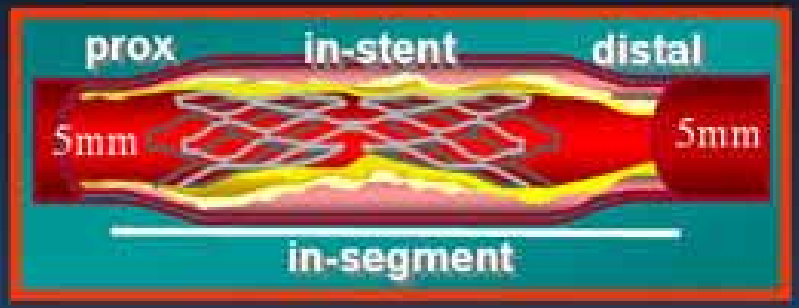
RESULTS

Adverse Reactions

n	Rapamune 4 mg Patient n=21	Placebo Patient n=22
Gastrointestinal Symptoms		
(Gas, Indigestion, Diarrhea, Nausea/ Vomiting, Gastritis)	13	3
Mucocutaneous Symptoms		
(Mouth Sores, Skin Dryness, Skin Rash, Sore Throat)	17	0
Other		
Fever	4	0
Infection	1	0
Joint Pain	0	1
Insomnia	1	1
Average Days on Study Drug	24.4 ± 9.5	28.6 ± 4.6*

*$p=0.09$

ANGIOGRAPHIC RESULTS



	4 mg	Placebo
	N=26 lesions	N=29 lesions
MLD PRE mm	1.27 ± 0.45	1.27 ± 0.55
MLD POST mm	2.34 ± 0.44	2.41 ± 0.45
FOLLOW-UP QCA	N=22 lesions	N=25 lesions
MLD at 6 Months (mm)	1.87 ± 0.55	1.85 ± 0.74
Binary Restenosis In-Stent	4/22 (18.2)	6/25 (24.0)
Binary Restenosis In-Segment	4/22 (18.2)	7/25 (28.0)
Late Loss (mm)	0.57 ± 0.51	0.59 ± 0.57

Results

MAJOR CLINICAL EVENTS AT 6 MONTHS

	Rapamune 4 mg Patient n=21 Lesion n=26	Placebo Patient n=21 Lesion n=28	p value
TVR MACE	3/21 (14.3)	4/21 (19.0)	1
Death	0/21 (0)	0/21 (0)	.
Myocardial Infarction			
Q Wave Myocardial Infarction	0/21 (0)	0/21 (0)	.
Non Q Wave Myocardial Infarction (CKMB 2x ULN)*	1/21 (4.8)	0/21 (0)	0.488
Target Lesion Revascularization	3/26 (11.5)	3/28 (10.7)	1
Target Vessel Revascularization	3/26 (11.5)	4/28 (14.3)	1
Late Thrombosis	0/26 (0)	0/28 (0)	.

* This patient experienced a Non Q wave MI in hospital

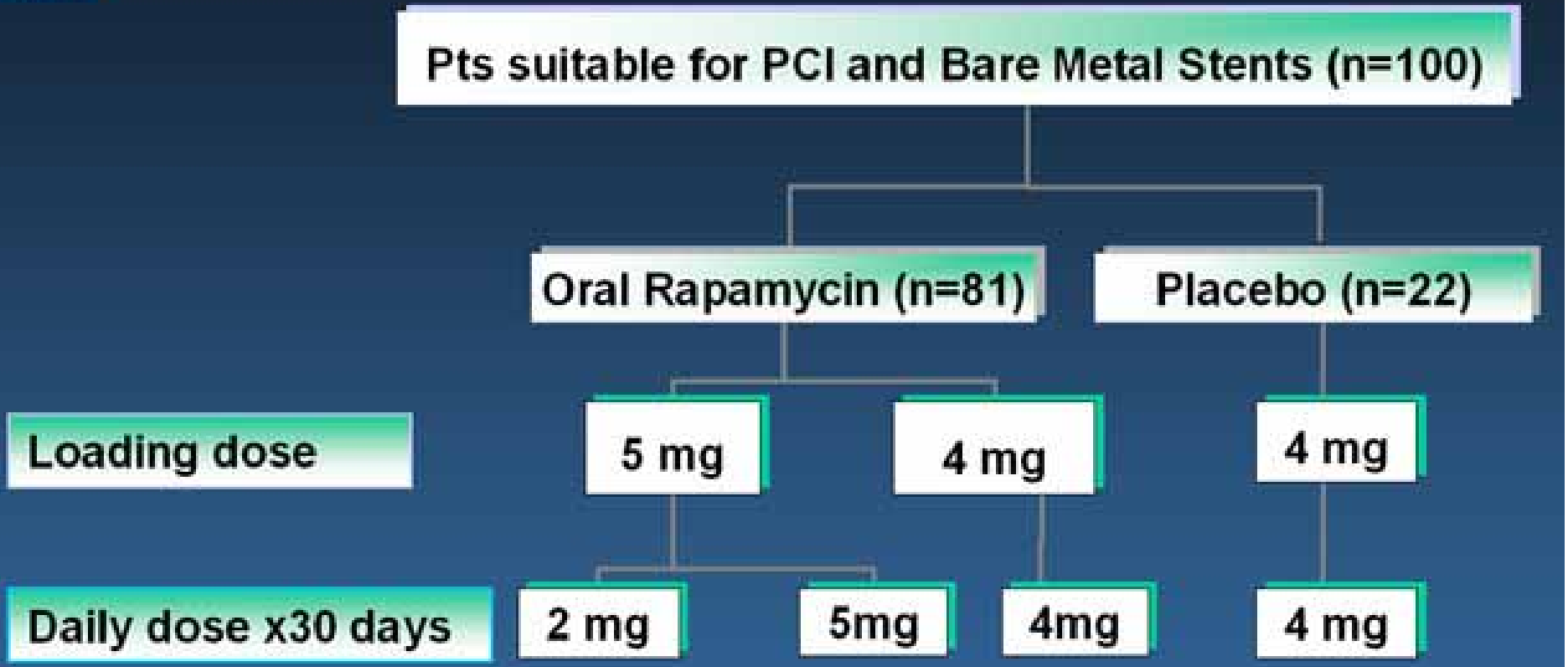
Results

MAJOR CLINICAL EVENTS AT 12 MONTHS

n, (%)	Rapamune 4 mg Patient n=20 Lesion n=25	Placebo Patient n=21 Lesion n=28	p value
TVR MACE	4/20 (25.0)	4/21 (19.0)	1
Death	0/20 (0)	0/21 (0)	.
Myocardial Infarction			
Q Wave Myocardial Infarction	0/20 (0)	0/21 (0)	.
Non Q Wave Myocardial Infarction (CKMB 2x ULN)*	1/20 (5.0)	0/21 (0)	0.488
Target Lesion Revascularization	4/25 (16.0)	4/28 (14.3)	1
Target Vessel Revascularization	4/25 (16.0)	6/28 (21.4)	0.736
Late Thrombosis	0/25 (0)	0/28 (0)	.

* This patient experienced a Non Q wave MI in hospital

ORBIT STUDIES



Clinical and Angiographic Follow up at 6 months

Side Effects

Their Severity Associated with the Study Medication

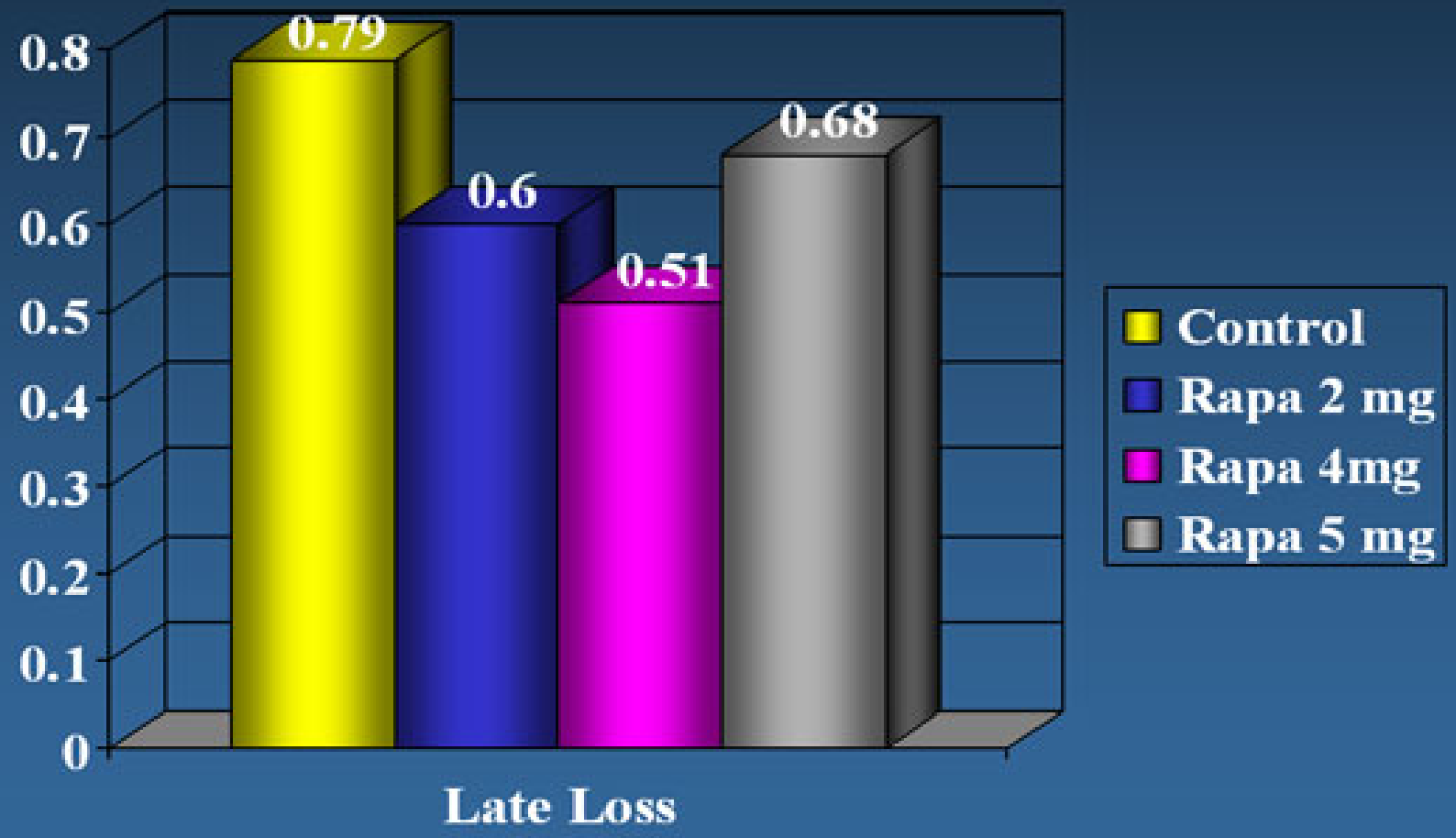
- Drug therapy was discontinued in 3 patients in 2 mg group, 6 patients in the 4 mg group, 9 patients in the 5 mg group and 1 patient in the placebo group due to rash, diarrhea, mouth ulcers, or fatigue (or a combination of these symptoms)
- There were no biochemical or hematological adverse effects.
- There was no evidence of dose effect on clinical outcomes

The ORBIT Studies

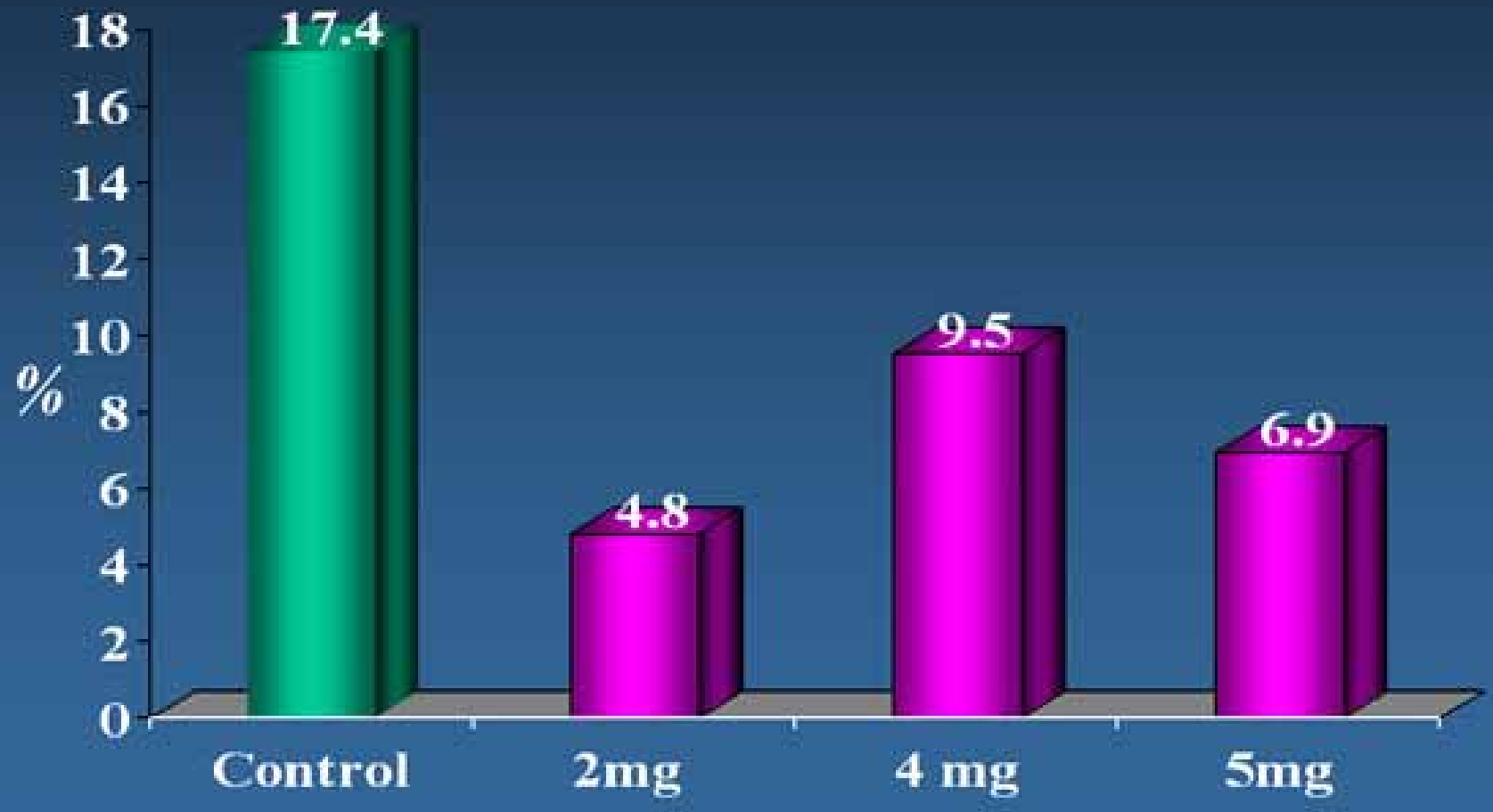
ANGIOGRAPHIC RESULTS

	Placebo	Rapamune 2 mg	Rapamune 4mg	Rapamune 5 mg
	N=29 lesions	N=49 lesions	N=26 lesions	N=37 lesions
MLD PRE mm	1.27 ± 0.55	1.08 ± 0.61	1.27 ± 0.45	1.36 ± 0.52
MLD POST mm	2.41 ± 0.45	2.88 ± 0.57	2.34 ± 0.44	2.95 ± 0.52
FOLLOW-UP QCA	N=25 lesions	N=42 lesions	N=22 lesions	N=29 lesions
MLD at 6 Months (mm)	1.85 ± 0.74	2.29 ± 0.61	1.87 ± 0.55	2.27 ±0.75
Binary Restenosis in Stent	24.0%	7.1%	18.2%	6.9%
Binary Restenosis in Segment	28.0%	4.8%	18.2%	6.9%
Late Loss (mm)	0.59 ± 0.57	0.60 ± 0.61	0.57 ± 0.51	0.68 ± 0.60

ORBIT II- Sneak Preview
Binary Late Loss



ORBIT II- Sneak Preview
Binary Restenosis in Stent Rates



Major Clinical Events at 6 Months

Drug and Dose Patient Lesions: FU*	R- 2 mg n=28 n=42	R-4mg n=21 n=26	R- 5 mg n=30 n=37	Placebo n=21 n=28
Cardiac death, n (%)	0/28 (0)	0/21 (0)	0/30 (0)	0/21 (0)
Non-cardiac death n (%)	0/28 (0)	0/21 (0)	0/30 (0)	0/21 (0)
Q-Wave MI, n (%)	0/28 (0)	0/21 (0)	0/30(0)	0/21 (0)
Non-Q-wave MI, n (%)	3/28 (10.7)	1/21 (4.8)	2/30 (6.7)	0/21 (0)
TVR, n (%)	7/42 (16.7)	3/26 (11.5)	6/37 (16.2)	4/28 (13.8)
TVR CABG, n (%)	4/42 (9.5)	1/26 (3.8)	5/37 (13.5)	2/28 (7.1)
TVR PCI, n (%)	3/42 (7.1)	2/26 (7.7)	1/37 (2.7)	2/28 (7.1)
TLR, n (%)	6/42 (14.3)	3/26 (11.5)	2/37 (5.4)	3/28 (10.7)
TLR CABG, n (%)	3/42 (7.1)	1/26 (3.8)	2/37 (5.4)	1/28 (3.6)
TLR PCI, n (%)	3/42 (7.1)	2/26 (7.7)	0/37 (0)	2/28 (7.1)
MACE. (%)	7/28 (25.0)	3/21 (14.3)	6/30 (20.0)	4/21 (19.1)

Randomization Protocol

In-Stent Restenosis

Patients with diagnosed in-stent restenosis

	Placebo	Usual Dose Sirolimus	High Dose Sirolimus
Day -2	Placebo	Placebo	12mg
Day -1	Placebo	6mg	8mg
PCI	Placebo	2mg	4mg
Day 1-7	Placebo	2mg	2mg
Patients	**102**	**99**	**99**

Patient Characteristics

In-Stent Restenosis

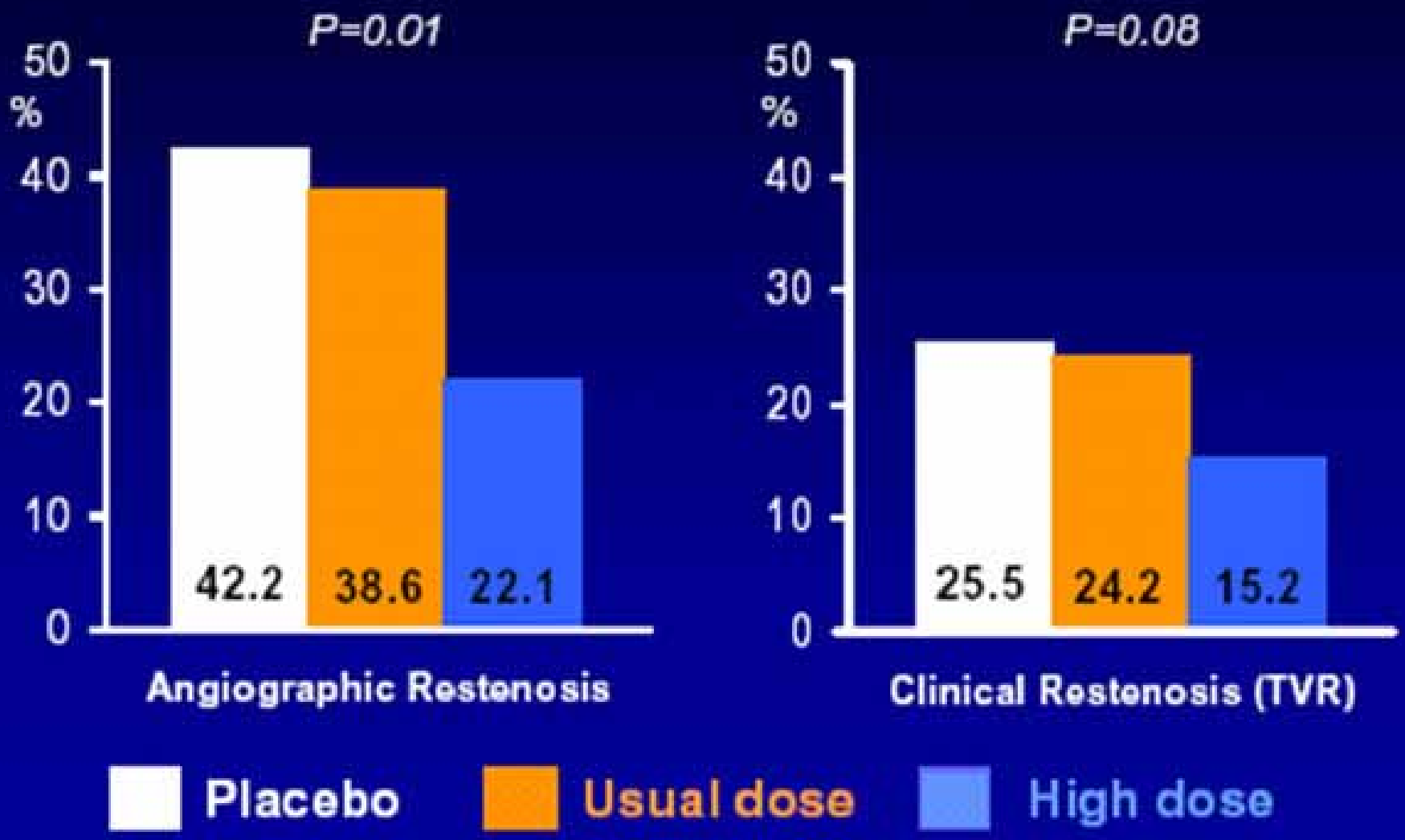
	Placebo	Usual dose	High dose	*P*
Age, years	65.4 ±10.4	65.3 ±9.4	65.3 ±9.3	*.99*
Female, %	25.5	25.3	16.2	*.18*
Diabetes, %	27.5	27.3	32.3	*.67*
Smoker, %	12.7	12.1	9.1	*.68*
Hypercholest., %	64.7	66.7	58.6	*.47*
Hypertension, %	56.9	60.6	65.7	*.63*
Prev. MI, %	40.2	53.5	46.5	*.17*
Prev. CABG, %	7.8	9.1	15.2	*.20*

Angiographic Characteristics

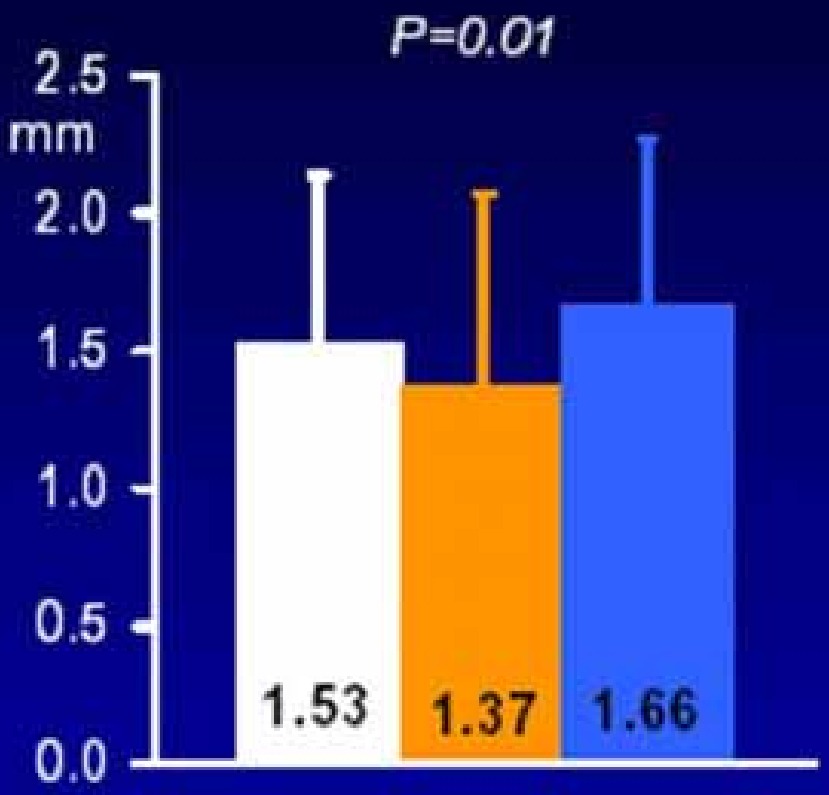
In-Stent Restenosis

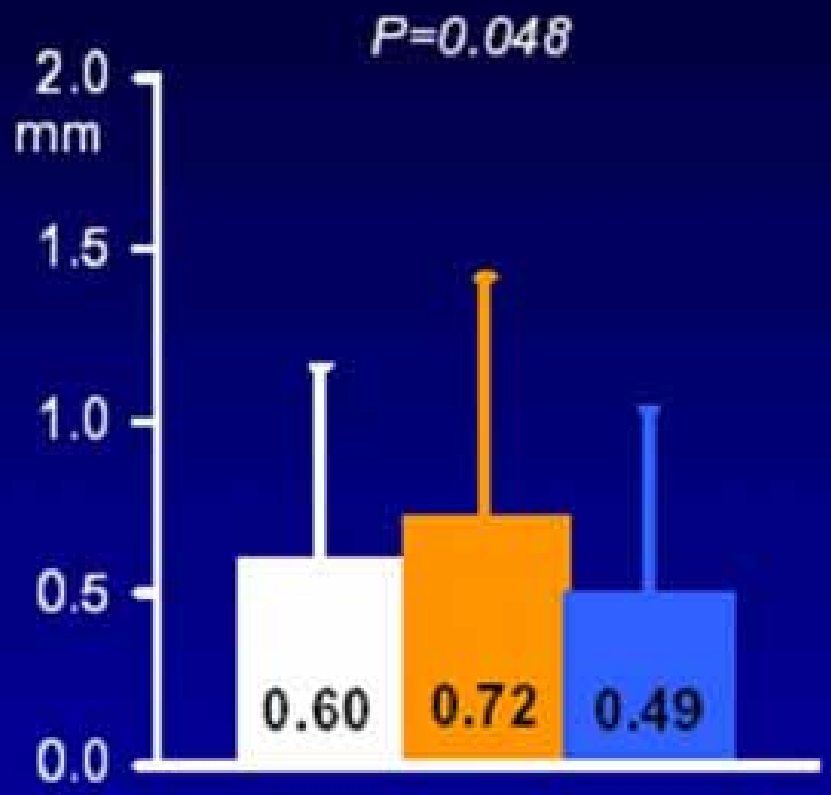
	Placebo	Usual dose	High dose	*P*
Ejection fract., %	55.7 ±12.1	55.4 ±12.8	55.2 ±14.0	*.96*
Diffuse ISR morphology, %	49.0	44.4	53.5	*.44*
ISR length, mm	15.5 ±7.2	15.9 ±7.2	13.9 ±7.8	*.13*
Vessel size, mm	2.61 ±0.53	2.60 ±0.48	2.57 ±0.53	*.79*
MLD, mm	0.85 ±0.37	0.88 ±0.41	0.91 ±0.45	*.60*
Stenosis grade, %	67.1 ±13.6	66.2 ±14.2	65.4 ±13.8	*.67*

In-Stent Restenosis



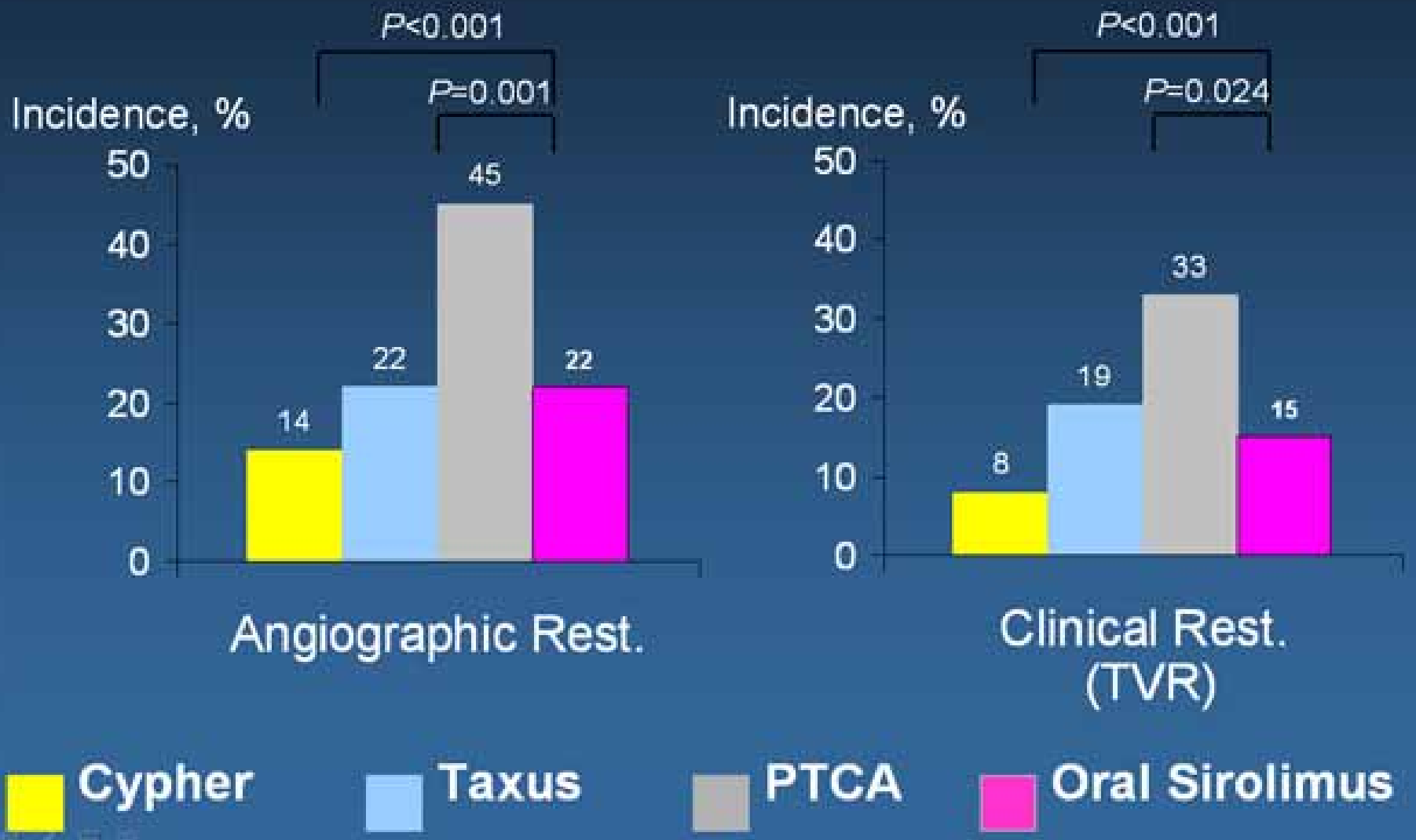
Angiographic Results





Placebo Usual dose High dose

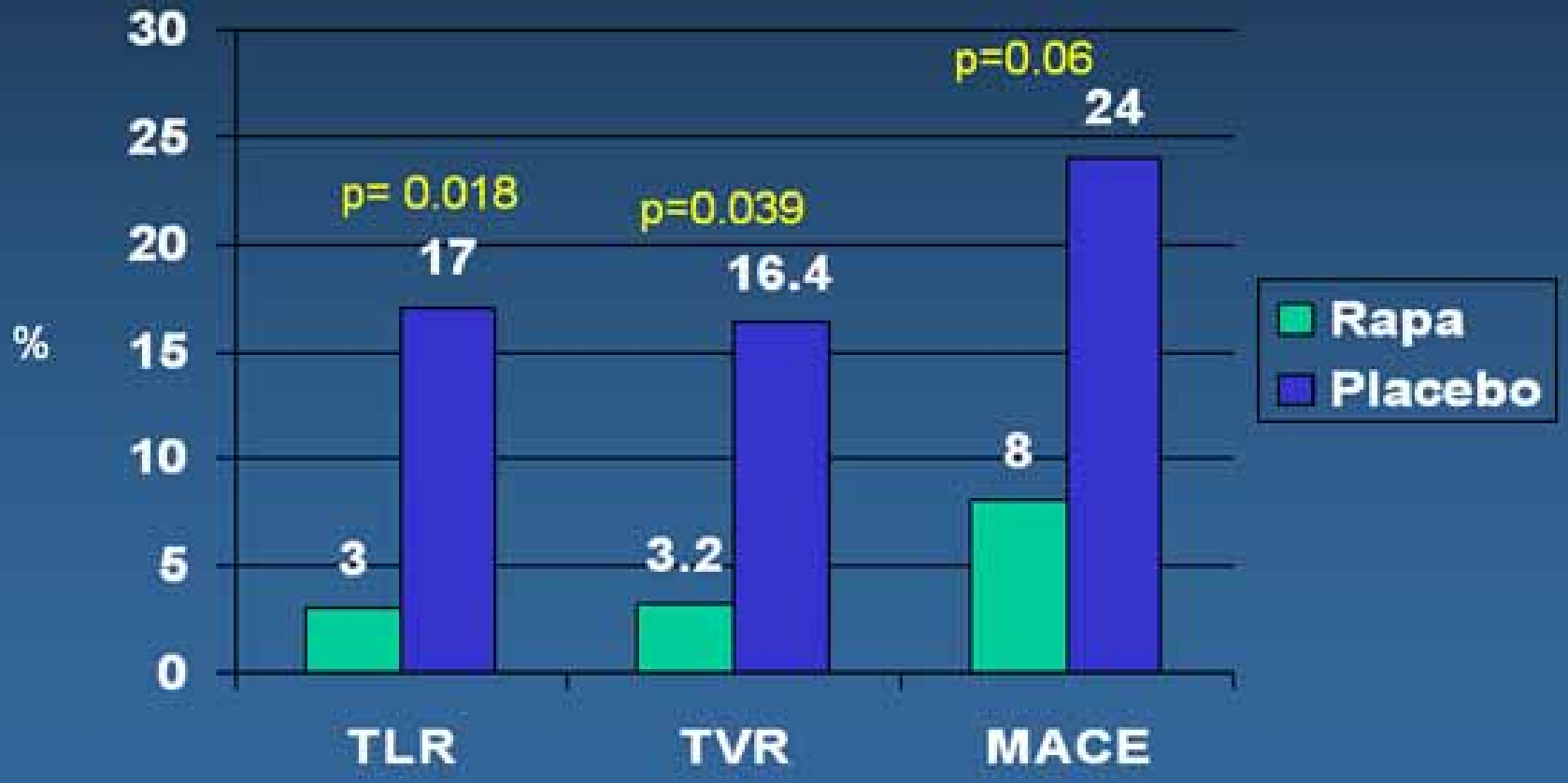
ISAR-DESIRE Versus OSIRIS



Oral Rapamycin after Stent. ORAR Trial.

A. Rodriguez et al. ACC 2005

100 patients randomized to Rapamune (6 mg pre + 3 mg daily for 2 weeks and Placebo).



Oral Rapamune for Restenosis Prevention

Conclusions in Progress

- Overall effective in reduction of angiographic and clinical restenosis compared to placebo but not as robust as DES
- Late Loss 0.45-0.65 mm across all trials
- Rapamune levels correlates with angiographic indices
- High loading dose 8-15 mg, 1-2 days prior to PCI
- Short term duration 7-15 days
- Side effects: mild to moderate sore throat, diarrhea, rash, no hematological or biochemical abnormalities
- Cost effective for the treatment of multivessel disease