PPAR-γ Agonist and In-Stent Restenosis

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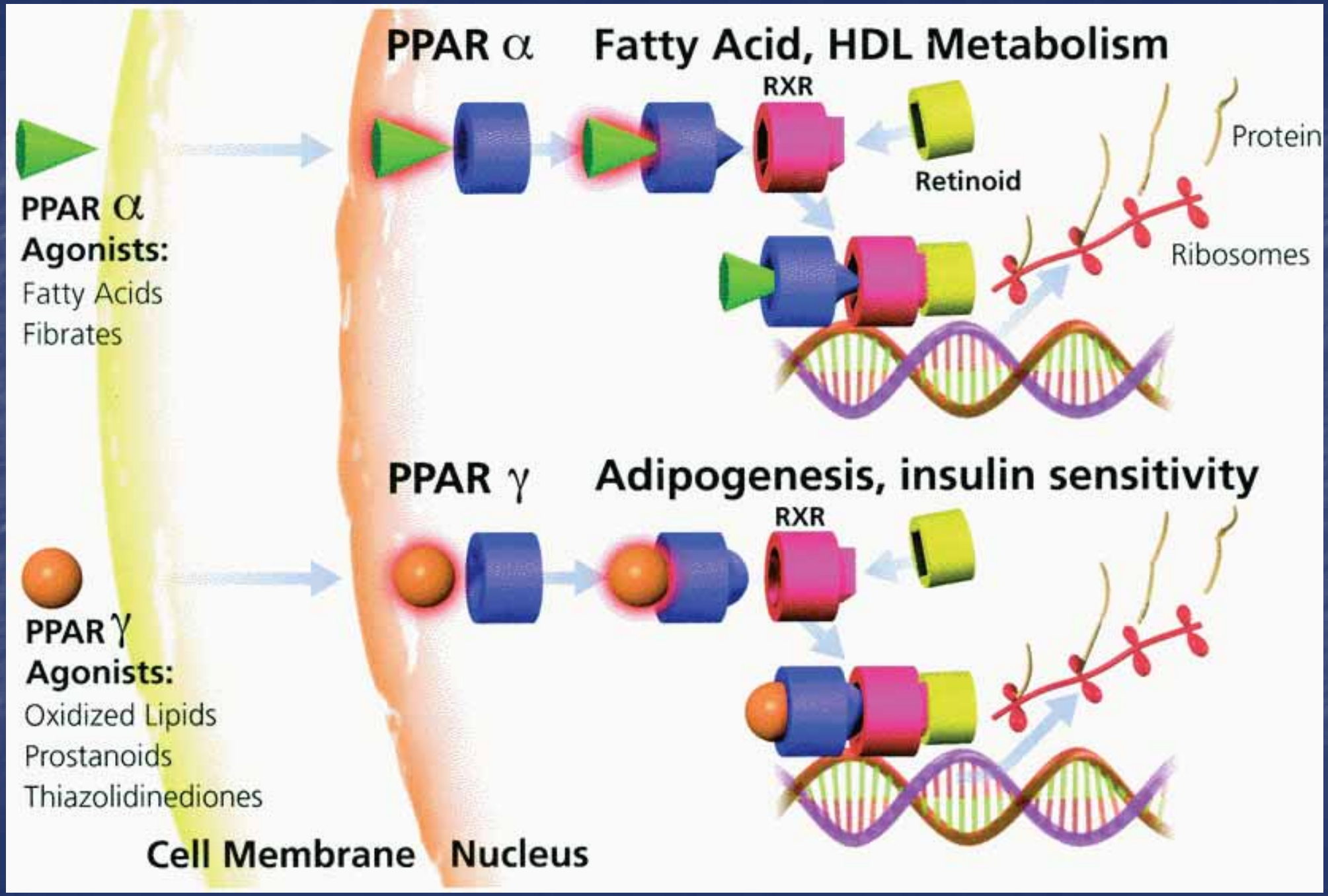
Peroxisome Proliferator-activated Receptors (PPAR)

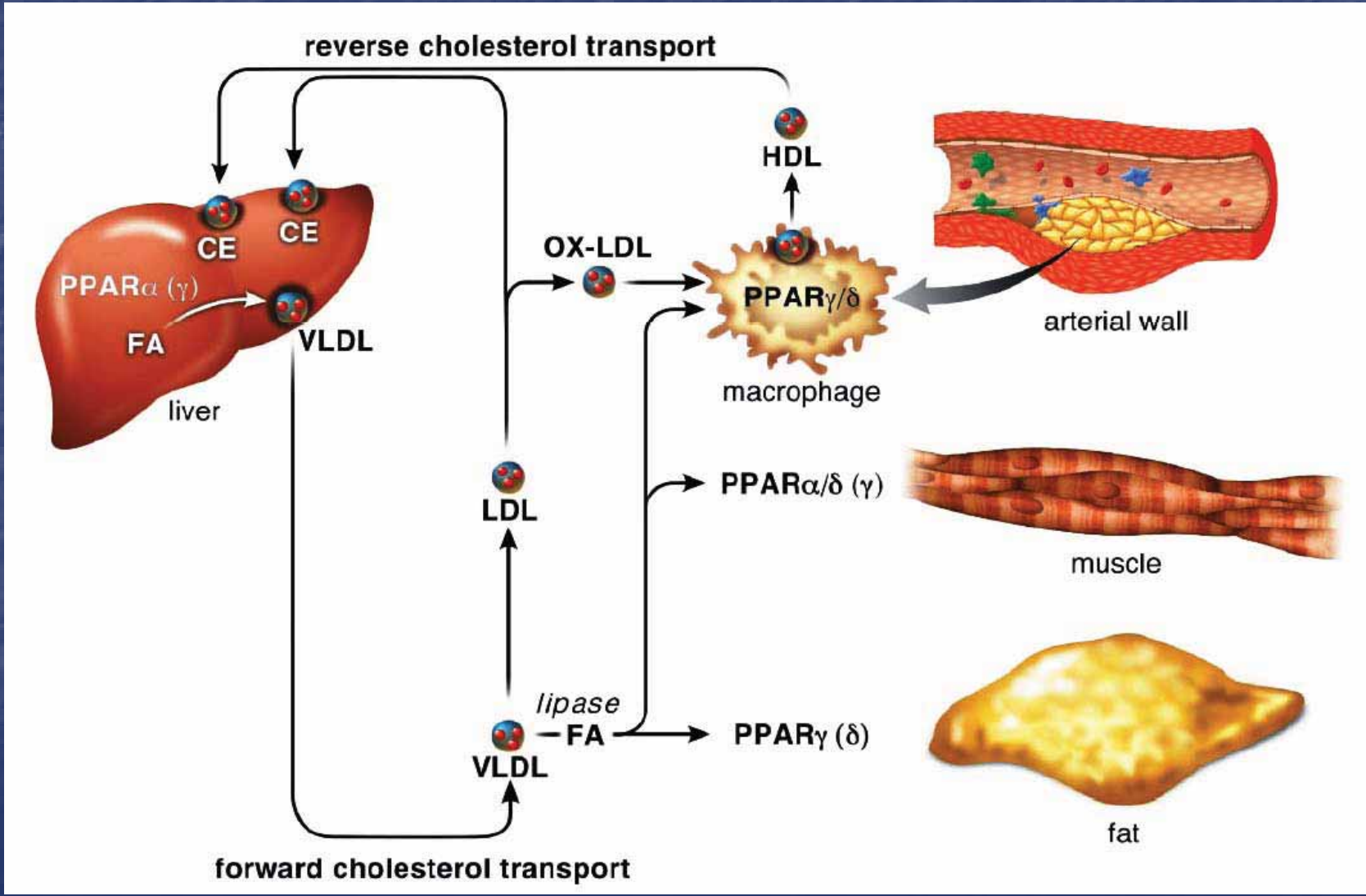
- Lipid-activated transcription factors :

  => regulating the expression of genes that control lipid & glucose homeostasis.

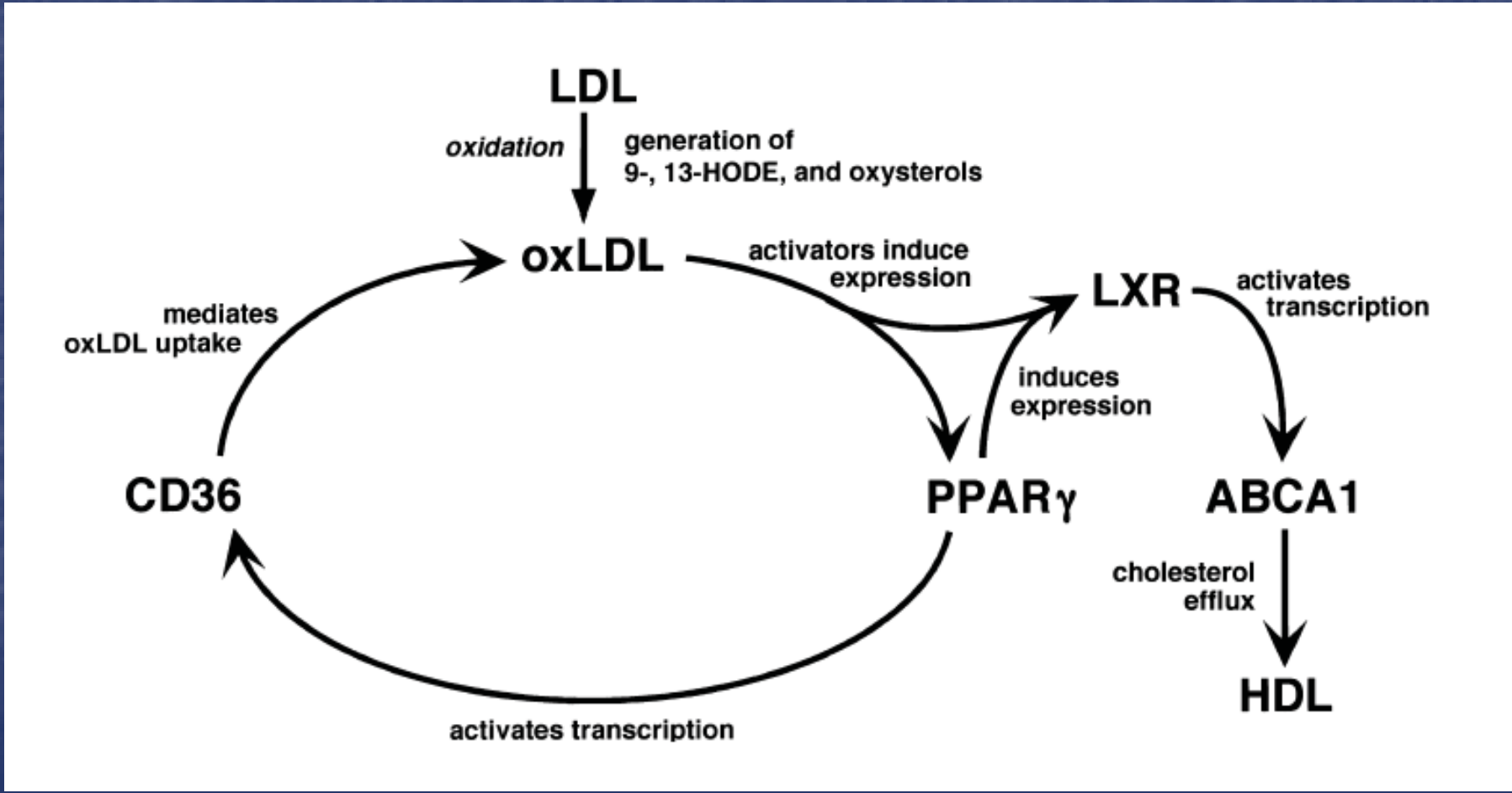
- Possibly modulates the onset and evolution of metabolic disorders


PPAR α
Fatty Acid, HDL Metabolism
RXR
Retinoid
Protein
Ribosomes
PPAR α
Agonists:
Fatty Acids
Fibrates
PPAR γ
Adipogenesis, insulin sensitivity
RXR
PPAR γ
Agonists:
Oxidized Lipids
Prostanoids
Thiazolidinediones
Cell Membrane
Nucleus

Role of PPAR in Lipid Regulation



Role of PPARγ in Atherosclerosis



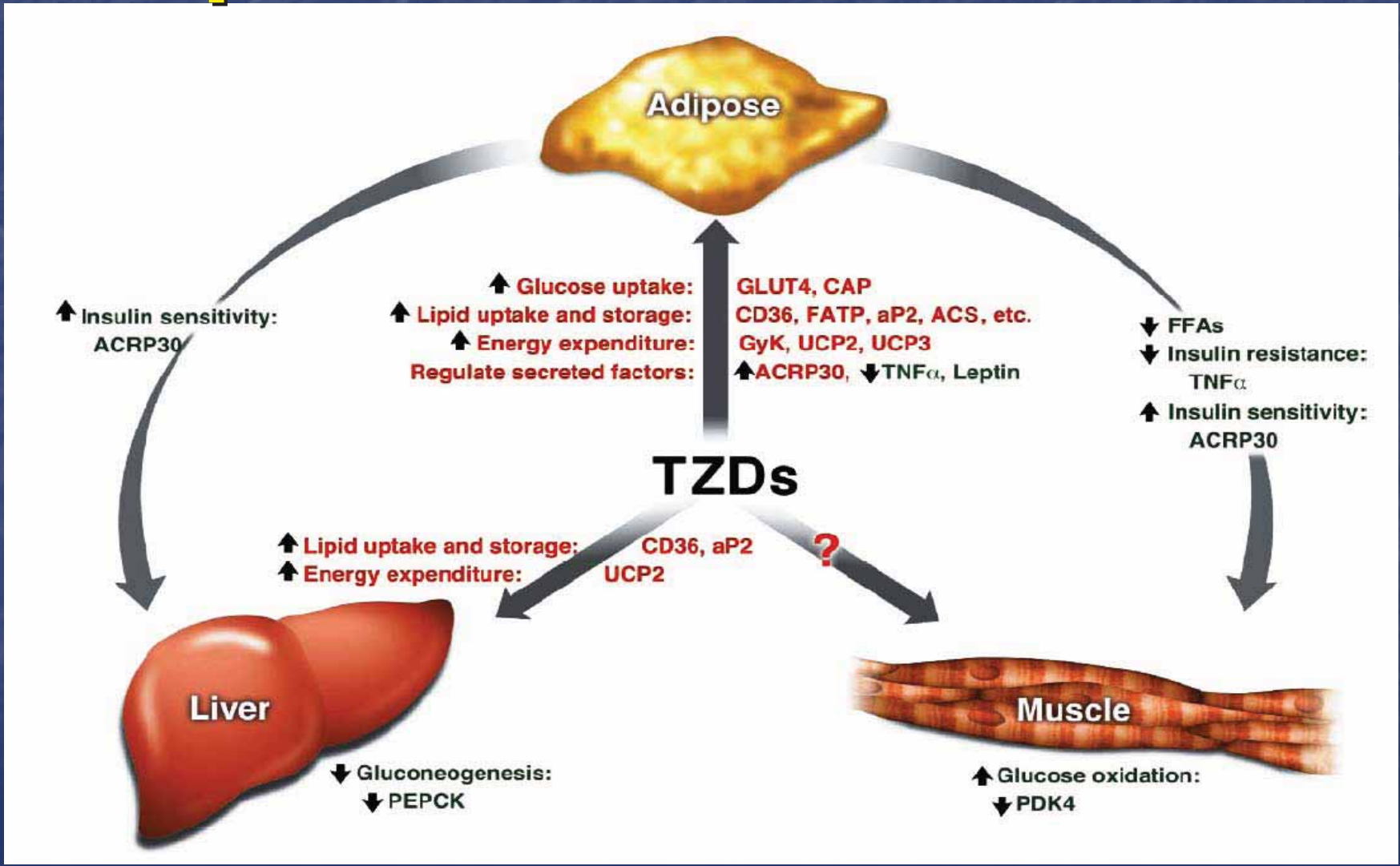
Chawla A. et al. Mol Cell 2001:7;161

Metabolic Effects of PPAR-γ

- ↑Reverse cholesterol transport

  => ↑ HDL, ↓TG, ↓ small dense LDL
- ↑Adiponectin
- ↑ Insulin sensitivity (fat, liver, skeletal muscle)
- ↓ Proinflammatory adipokines (fat)

Effects of TZDs in Lipid & Glucose Metabolism



Anti-atherogenic Effects of PPARγ in the Vasculature

PPARγ Ligands

Monocytes :

↓ Attachment to EC (↓ VCAM)

↓ Migration

↓ Inflammation

↑ Reverse Cholesterol Transport

VSMC :

↓ Growth

↓ Migration

↓ MMP production

↓ PAI-1

↓ Egr-1

Endothelial Cells :

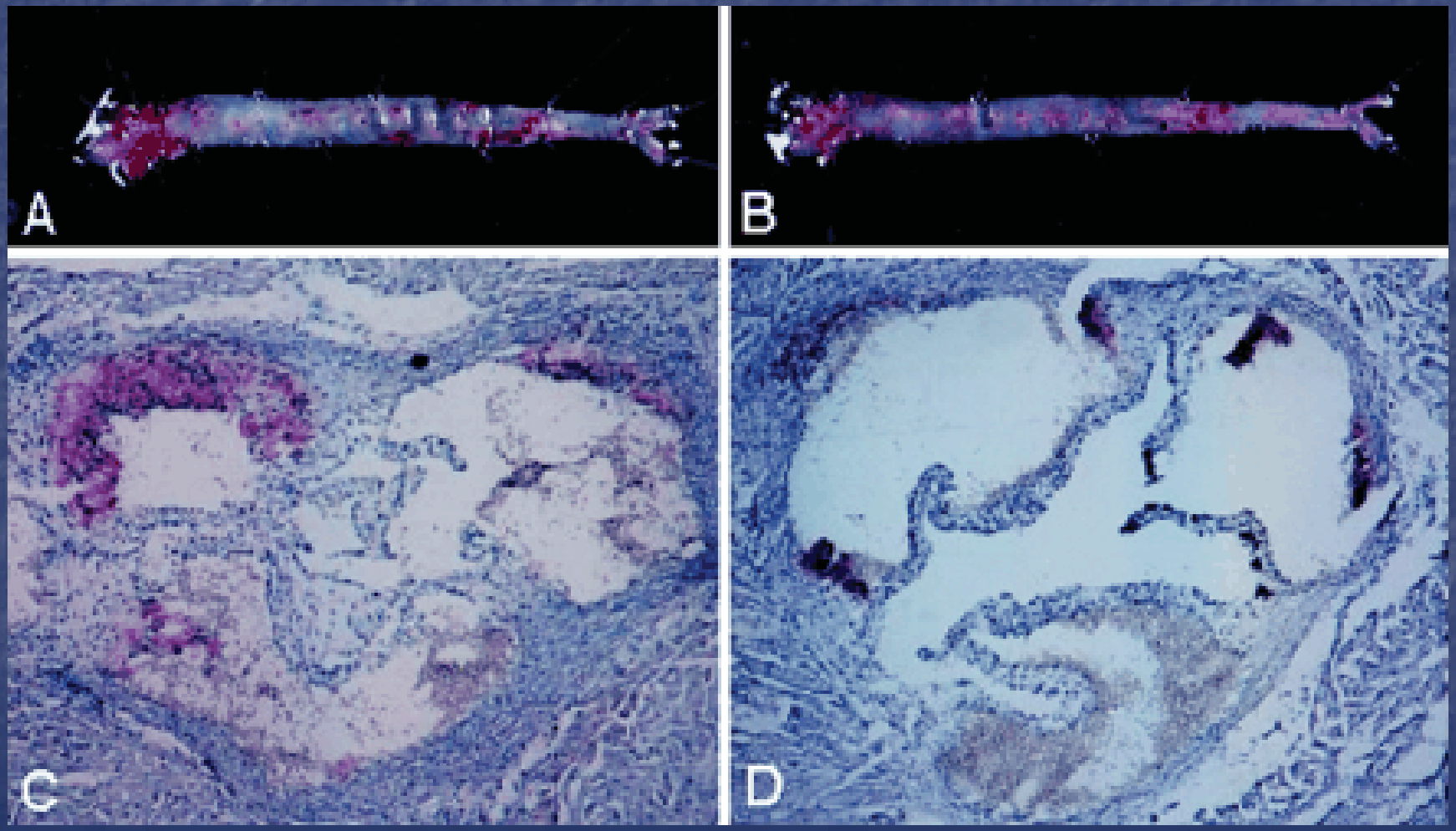
↓ Growth

↓ Migration

↓ Angiogenesis

↓ Atherosclerosis

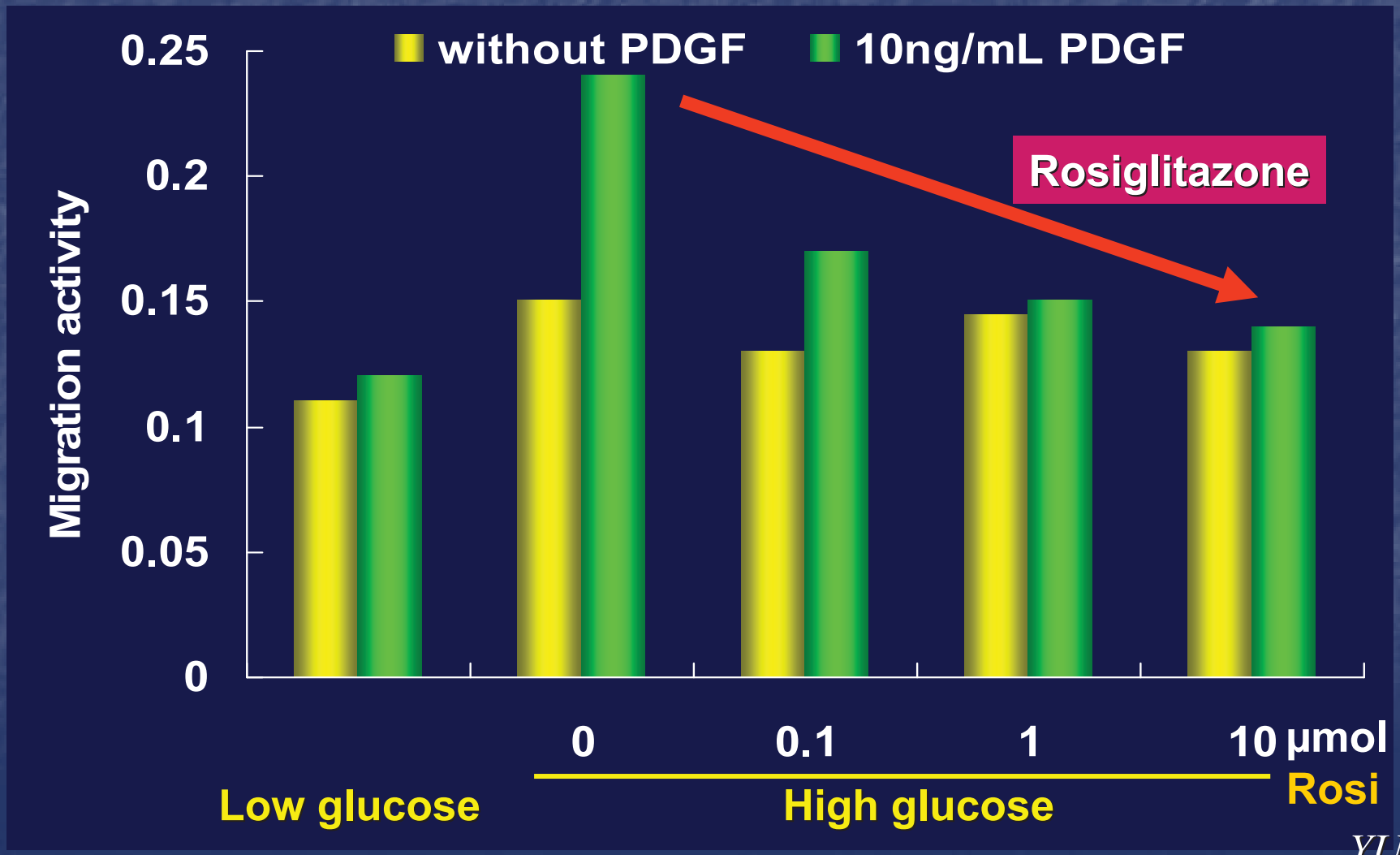
PPARγ Agonists Decrease Atherosclerosis in Mouse Model



Control

Troglitazone

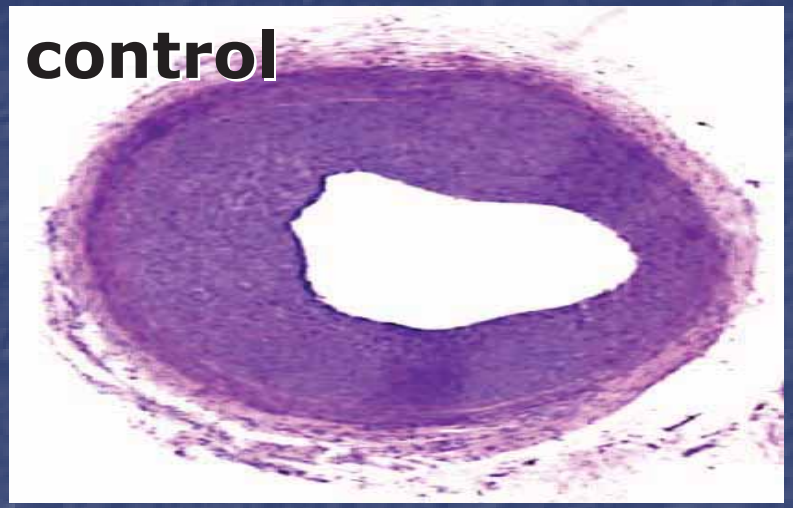
The Effects of Rosiglitazone on VSMC migration

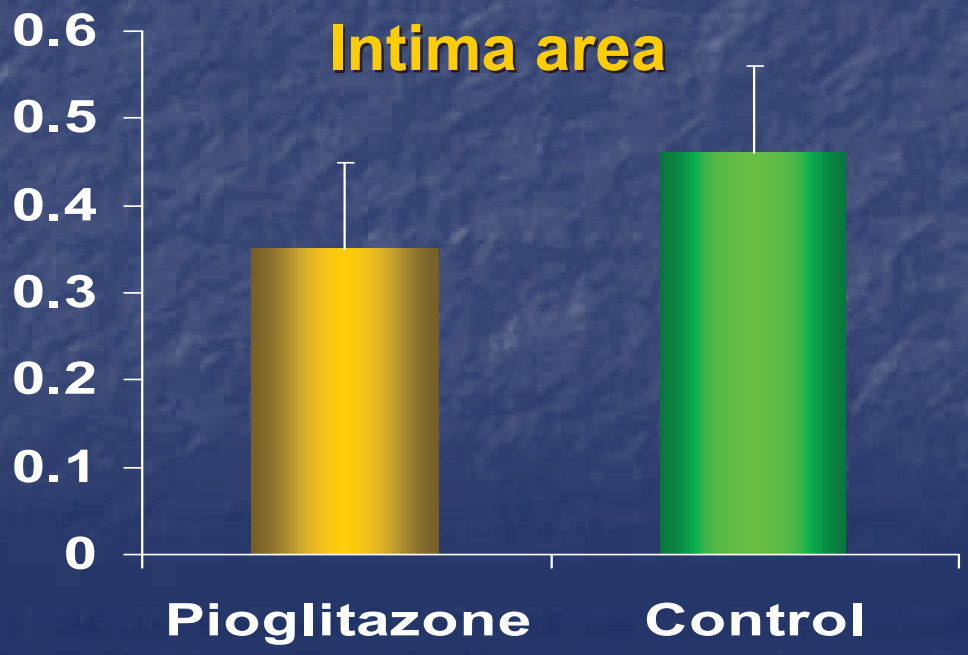


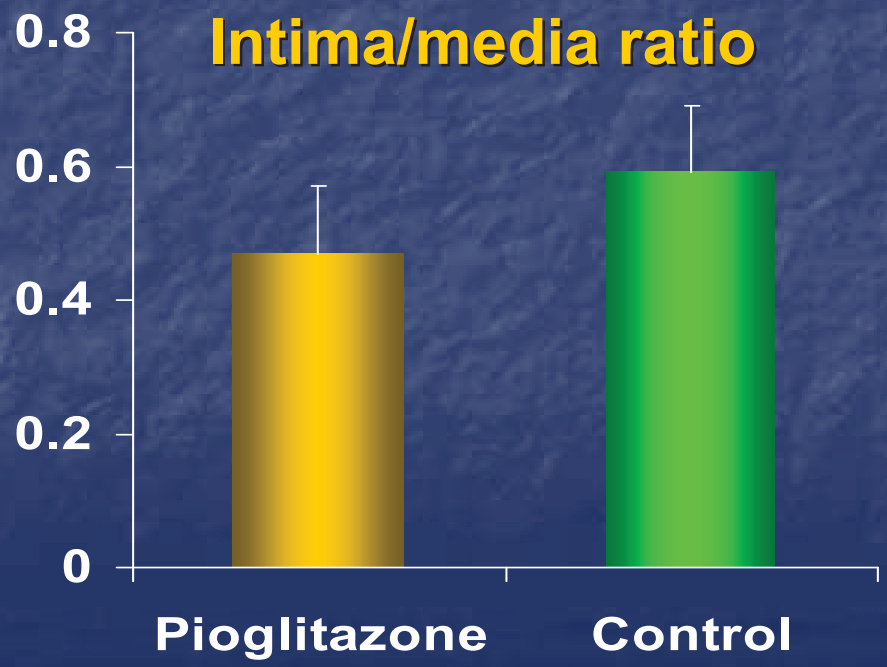
YUMC data

Carotid balloon injury model in OLETF Rat : Pioglitazone vs. Control

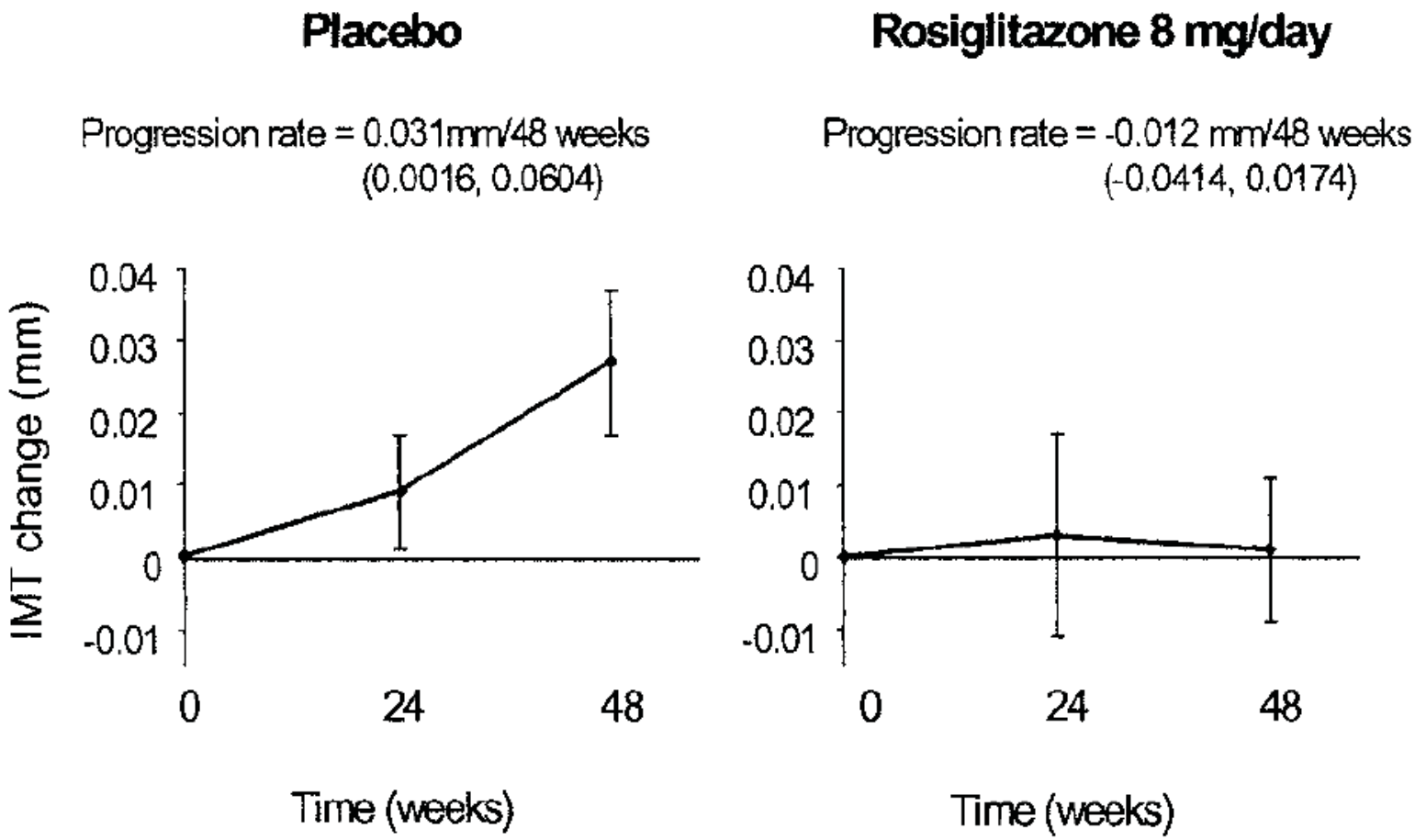
YUMC data





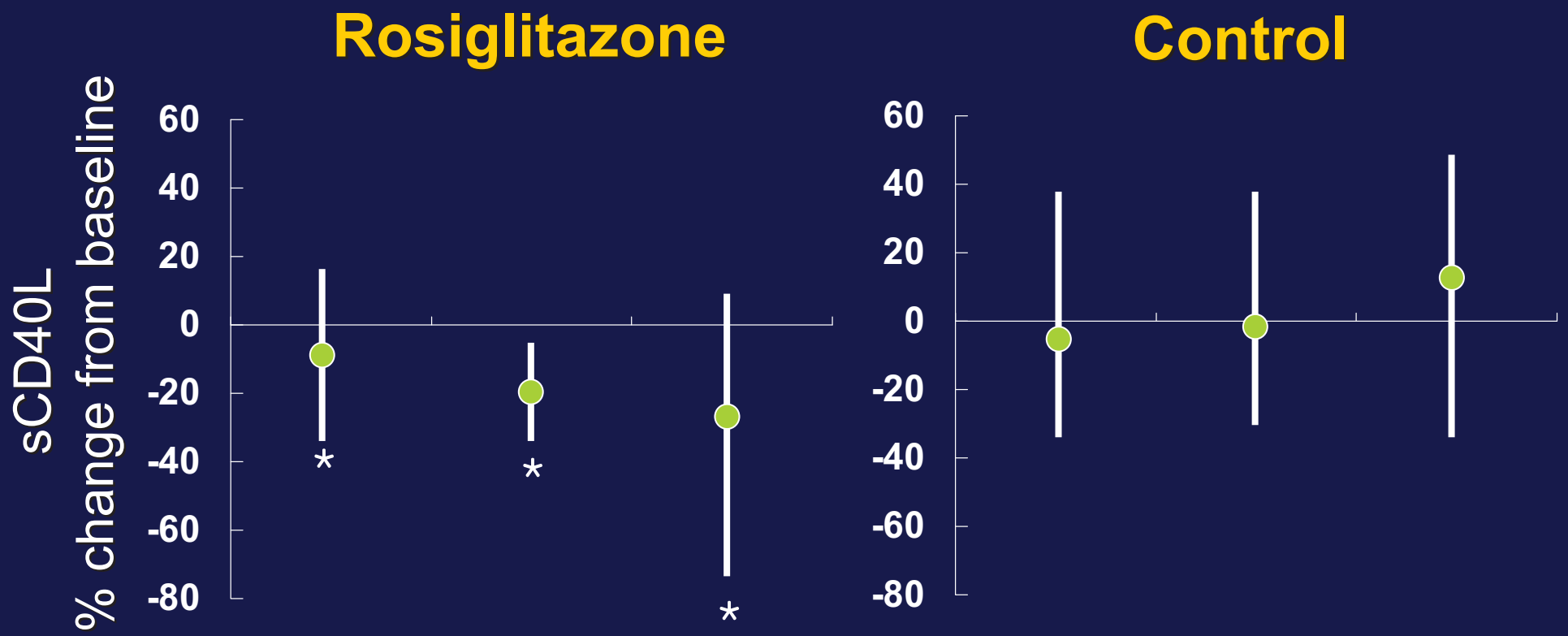


Rosiglitazone & Carotid IMT Progression in CAD Patients Without DM



Sidhu JS. Arterioscler Thromb Vasc Biol. 2004;24:1

Effect of Rosiglitazone on Soluble CD40L In Patients With Diabetes & CAD



* $p<0.05$

Marx N. Circulation. 2003;107:1954

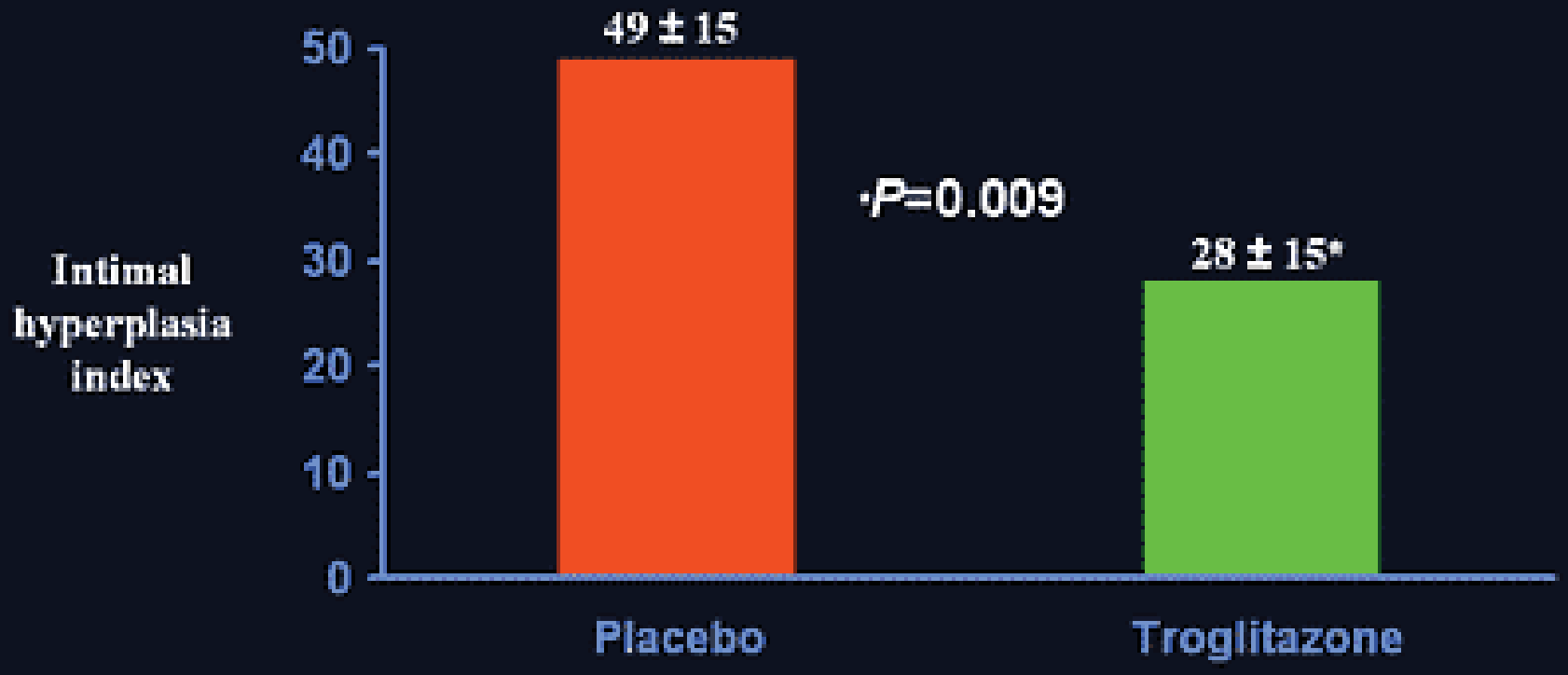
Effects of Rosiglitazone, on E-selectin, vWF, CRP, and Fibrinogen in Non-Diabetic CAD Patients

	Placebo (n = 44)	Rosiglitazone (n = 40)
E-selectin (ng/mL)		
Baseline	48.1 ± 21.2	48.9 ± 16.4
12 weeks	46.5 ± 24.1	43.4 ± 16.0*
vWF (IU/dL)		
Baseline	146 ± 54	138 ± 46
12 weeks	156 ± 49	131± 43*
Fibrinogen (g/L)		
Baseline	3.49 ± 0.68	3.81 ± 1.12
12 weeks	3.58 ± 0.75	3.38 ± 0.65 †
CRP (mg/L)		
Baseline	0.74 (0.41-1.39)	0.56 (0.34-1.02)
12 weeks	0.72 (0.36-1.30)	0.35 (0.26-0.50) †

** $p<0.05$, † $p<0.005$*

Sidhu JS. J Am Coll Cardiol 2003;42:1757

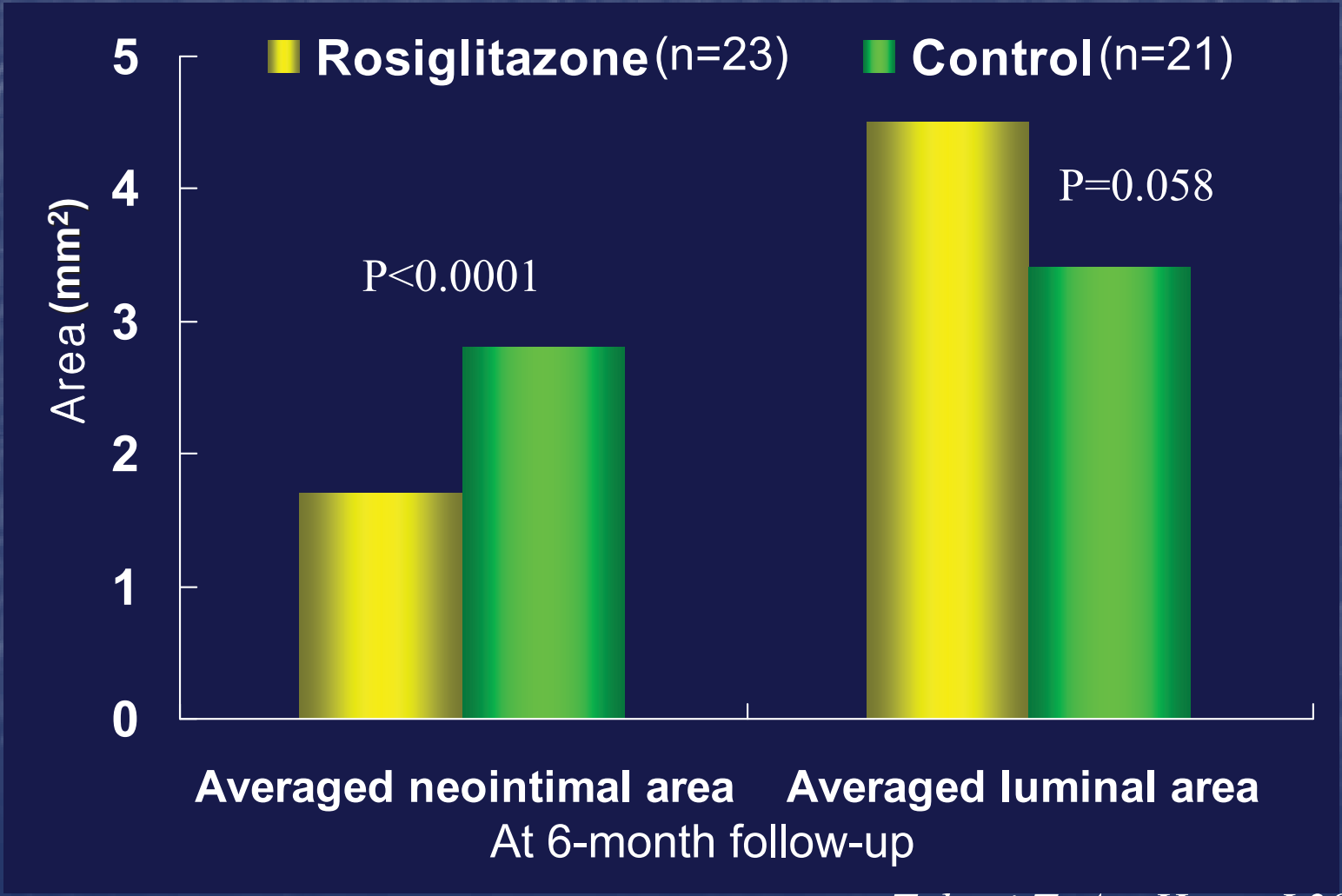
Effect of Troglitazone on Intimal Hyperplasia After Coronary Stenting



Takagi T et al. *J Am Coll Cardiol.* 1999;(suppl 1):Abstract 886-2.

Takagi T et al. J Am Coll Cardiol. 1999;(suppl1):886-2

Pioglitazone & In-stent Restenosis : IVUS study



Takagi T. Am Heart J 2003;146:e5

YUMC Rosiglitazone Study

A prospective single center control study

Type II DM patients

Rosiglitazone	Control
DM Group	DM Group
N=47	N=48

Coronary stenting

6 month clinical & c-angio follow-up

Study Objectives

- **Primary endpoint :**

  => Binary restenosis rate at 6 months

  angiographic follow-up

- **Secondary endpoint :**

  => Clinical outcome (MACE) at 6 months

Subjects (I)

- **Inclusion criteria :**

  - Type II DM patients undergoing coronary stenting at YUMC (April. 2001 ~ Feb. 2003)

- **Exclusion criteria :**

  - LVEF < 40% or evidence of CHF
  - GOT/GPT > 2 x upper limit of normal range
  - Cr > 2.0 mg/dL
  - Previous CABG
  - Primary PTCA

Subjects (II)

- Total : n=95 (122 lesions)

1) Rosiglitazone group : n = 47

=> angiographic follow-up : n = 38 (51 vessels)

2) Control group : n = 48

=> angiographic follow-up : n=42 (55 vessels)

Methods (I)

- **Rosiglitazone :**

  - 8 mg p.o. before coronary angio/PCI

  - 4 mg p.o. daily

- **Blood sugar control :**

  - continue individual conventional therapy to optimize blood sugar level.

- **Antiplatelet medication :**

  - aspirin 100 mg/d & ticlopidine 500 mg/d or clopidogrel 75 mg/d

Methods (II)

- **Stenting :**

  - predilation in all lesions

  - stent :

    Arthos™/Arthos™ Inert (AMG)

    BX Velocity™ (Cordis)

    Coroflex™ (B. Braun)

    Express™ (Boston Scientific)

    S7 ™ (Medtronic)

  => no significant difference in the choice of stents between Rosiglitazone and control group.

Baseline Characteristics

	Control	Rosiglitazone	P
n (male/female)	42 (31/11)	38 (24/18)	NS
Age (years)	59.9±9.3	60.9±9.3	NS
DM duration (years)	7.2±3.8	7.5±4.9	NS
BMI (kg/cm^2)	24.8±3.35	24.9±2.96	NS
LVEF (%)	55.1±11.4	54.3±10.1	NS
SBP (mmHg)	140.1±15.4	144.1±16. 2	NS
DBP (mmHg)	84.2±14.3	85.5±16.9	NS
AMI	14/42	10/38	NS
UA	12/42	14/38	NS

Biochemical Characteristics

	Control	Rosiglitazone	P
Fasting glucose (mg/dL)	150.3±28.4	160.3±34.4	NS
HbA1c (%)	7.72±1.13	7.79±1.30	NS
Fasting insulin (μU/mL)	4.97±2.51	5.60±2.70	NS
Total cholesterol (mg/dL)	191.1±48.9	190.5±37.6	NS
HDL-cholesterol (mg/dL)	41.1±10.9	38.9±11.0	NS
Triglyceride (mg/dL)	159.5±55.1	167.7±60.8	NS
Free fatty acid (μmol/L)	580.3±101.7	669.2±127.4	NS
hsCRP (mg/L)	2.01±1.33	2.92±1.98	NS

Medications

Medication	Control	Rosiglitazone	P
Statin	37 (88.1%)	31 (81.6%)	NS
ACE inhibitors	30 (71.4%)	28 (73.7%)	NS
Sulfonyl ureas	26 (61.9%)	25 (65.8%)	NS
Biguanides	22 (52.3%)	21 (55.3%)	NS
α-glucosidase inhibitor	15 (35.7%)	10 (26.3%)	NS

Baseline Angiographic Characteristics

	Control	Rosiglitazone	P
Multi vessel disease	23/42	27/38	NS
Stented lesions	55	51	NS
LAD	27 (49.1%)	26 (51.0%)	
LCX	11 (20.0%)	9 (17.6%)	
RCA	17 (30.9%)	14 (27.5%)	
Left main		2 (3.9%)	
Lesion type			NS
B1	5 (9.1%)	5 (12.5%)	
B2	27 (49.1%)	15 (37.5%)	
C	23 (41.8%)	25 (50.0%)	

Baseline Angiographic Characteristics

	Control	Rosiglitazone	P
RD (mm)	3.15±0.49	3.16±0.49	NS
MLD (mm)	0.65±0.41	0.83±0.57	NS
DS (%)	79.4±12.8	74.4±15.8	NS
Lesion length (mm)	16.48±5.16	19.02±6.09	<0.05

Post-stenting Angiographic Data

	Control	Rosiglitazone	P
No. of stents	1.22±0.47	1.32±0.53	NS
Stent diameter (mm)	3.24±0.42	3.29±0.41	NS
Stent length (mm)	18.40±4.75	20.28±5.73	NS
MLD (mm)	3.10±0.43	3.13±0.48	NS
Diameter stenosis (%)	2.49±4.26	2.25±4.44	NS
Acute gain (mm)	2.45±0.57	2.30±0.53	NS

Follow-Up Angiographic Data

	Control	Rosiglitazone	P
MLD (mm)	1.91 ± 1.05	2.49 ± 0.88	<0.001
Diameter Stenosis (%)	42.9 ± 32.2	24.2 ± 23.2	0.001
Lumen loss (mm)	1.17 ± 0.96	0.61 ± 0.71	0.003
Loss index	0.49 ± 0.41	0.27 ± 0.30	0.008
Restenosis rate (%)	**38.2**	**17.6**	**0.03**

Biochemical Characteristics at Baseline and Follow-up

	Control (n = 45)		Rosiglitazone (n = 38)	
	Baseline	Follow-up	Baseline	Follow-up
HbA1c (%)	7.72±1.13	7.23±0.93	7.79±1.30	7.17±0.98
Δ from baseline (%)	-0.75±1.07		-0.61±1.15	
Total cholesterol (mg/dL	191.1±48.9	171.7±34.0	190.5±37.9	167.7±32.4
Δ from baseline (mg/dL)	-19.4±36.5		-22.8±35.8	
HDL-cholesterol (mg/dL)	41.1±10.9	44.0±10.5	38.9±11.0	43.2±8.2
Δ from baseline (mg/dL)	2.9±8.5		4.3±8.1	
Triglyceride (mg/dL)	159.5±55.1	126.8±60.8	167.7±60.8	119.0±38.9
Δ from baseline (mg/dL)	-26.1±50.1		-48.7±50.0	

Clinical Outcome at 6 Months

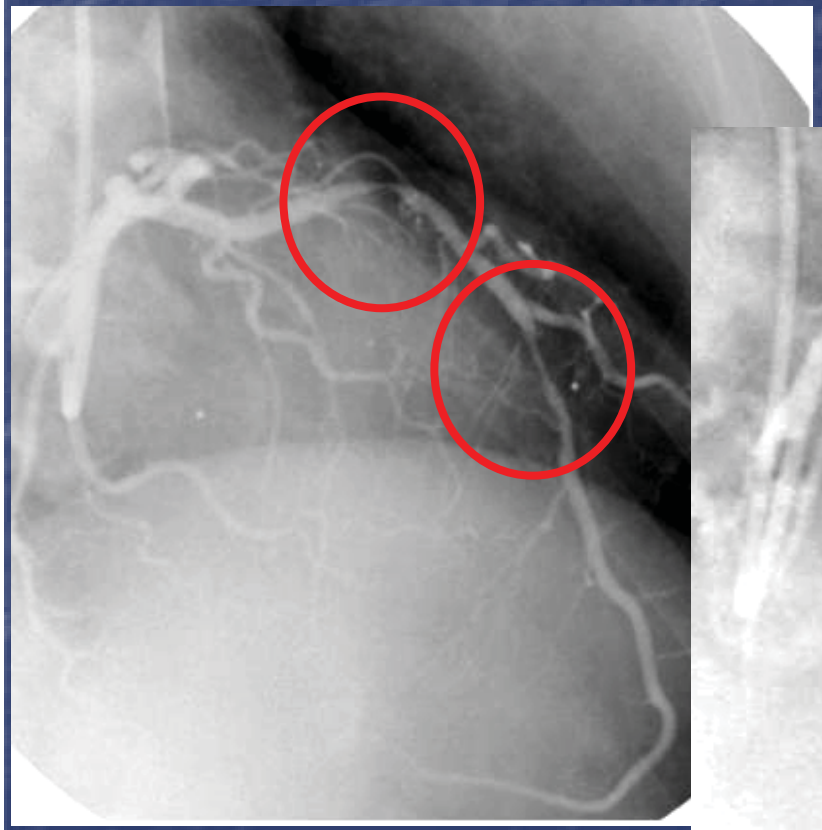
	Control	Rosi	p
Death	0	0	
MI	0	1*	
TLR	7	3	
MACE	7	3	0.25

** MI due to subacute thromosis*

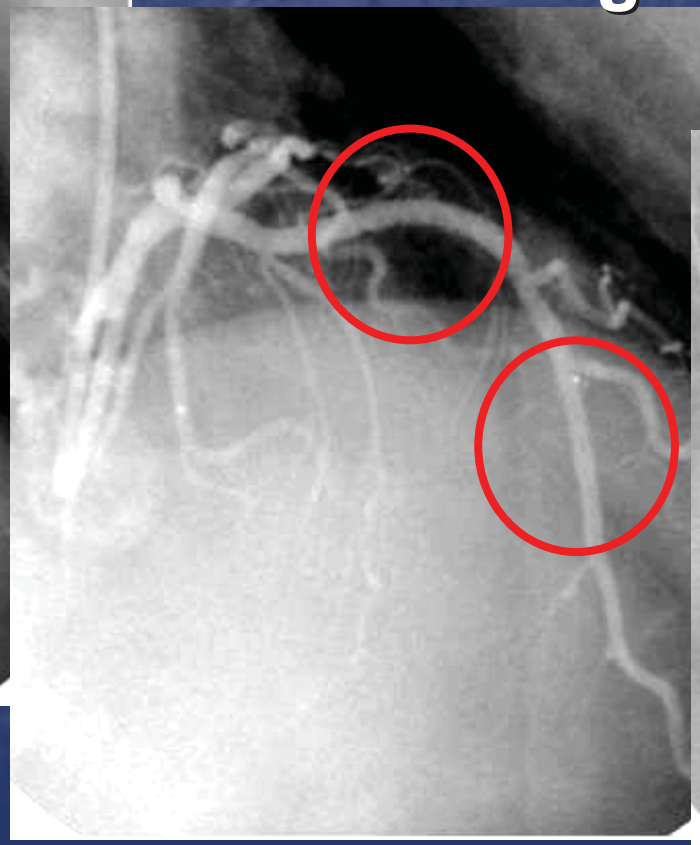
F/64 : S7 3.5 x 18 mm at m-LAD

Bx 3.0 x 23 mm at d-LAD

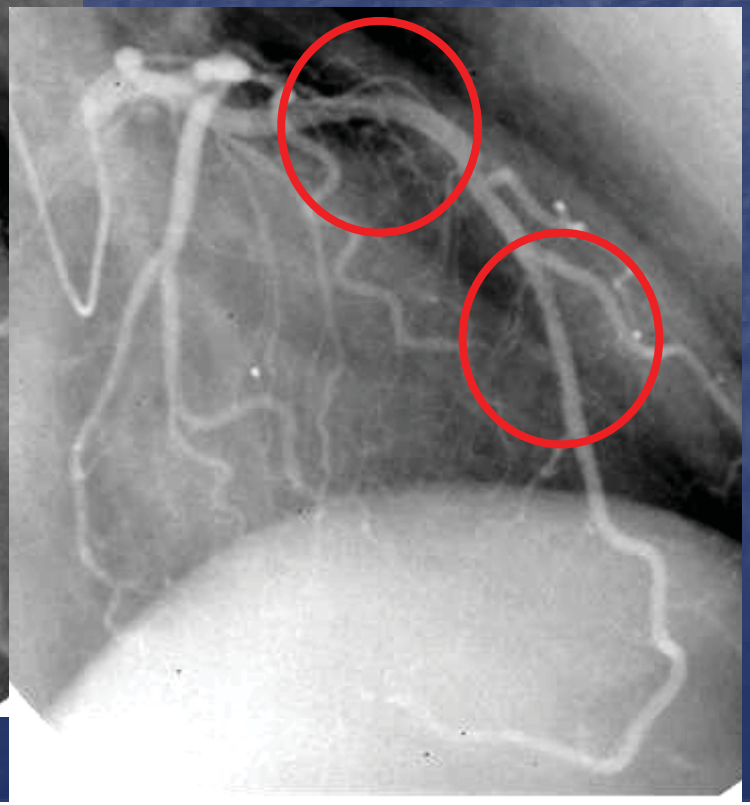
Initial



After stenting

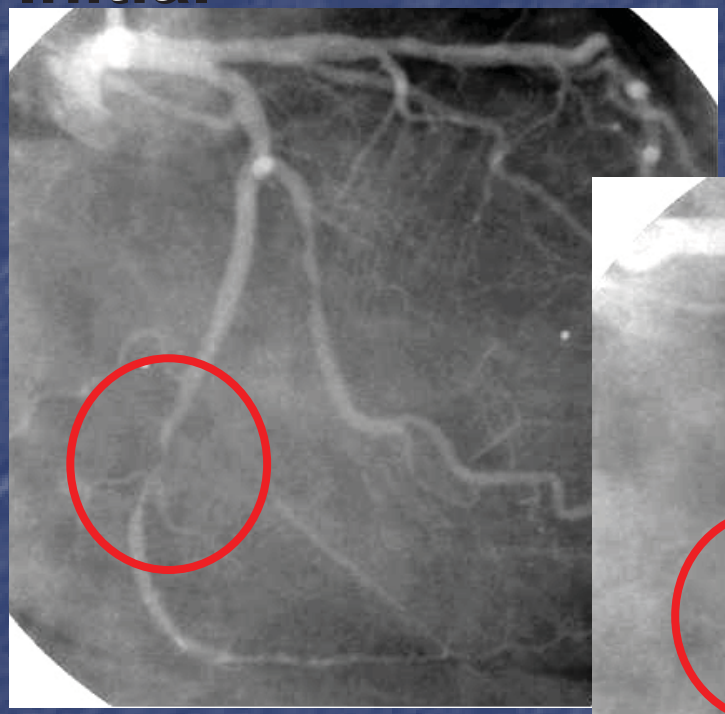


6-month f/u

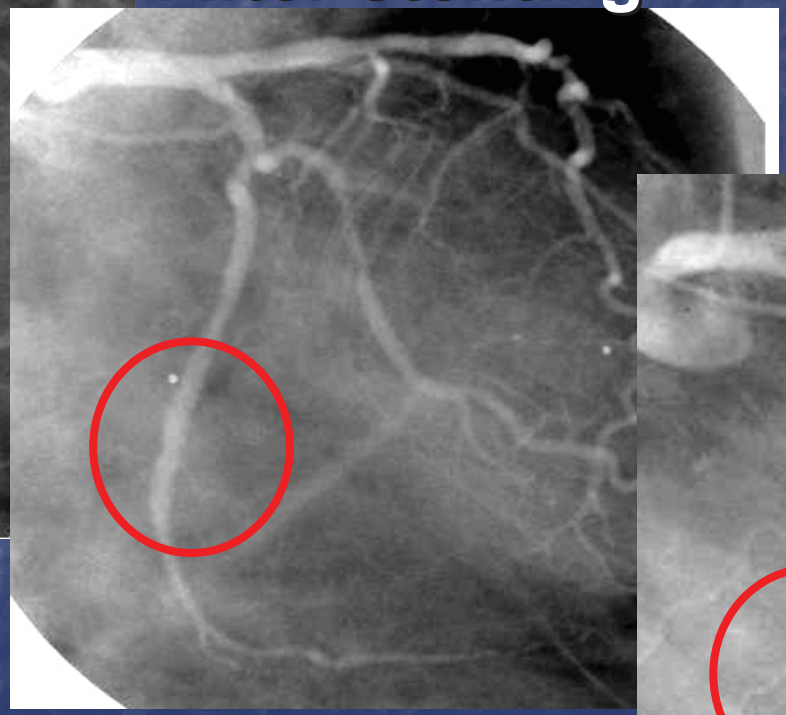


F/63 : Bx 2.75 x 18 mm at d-LCX

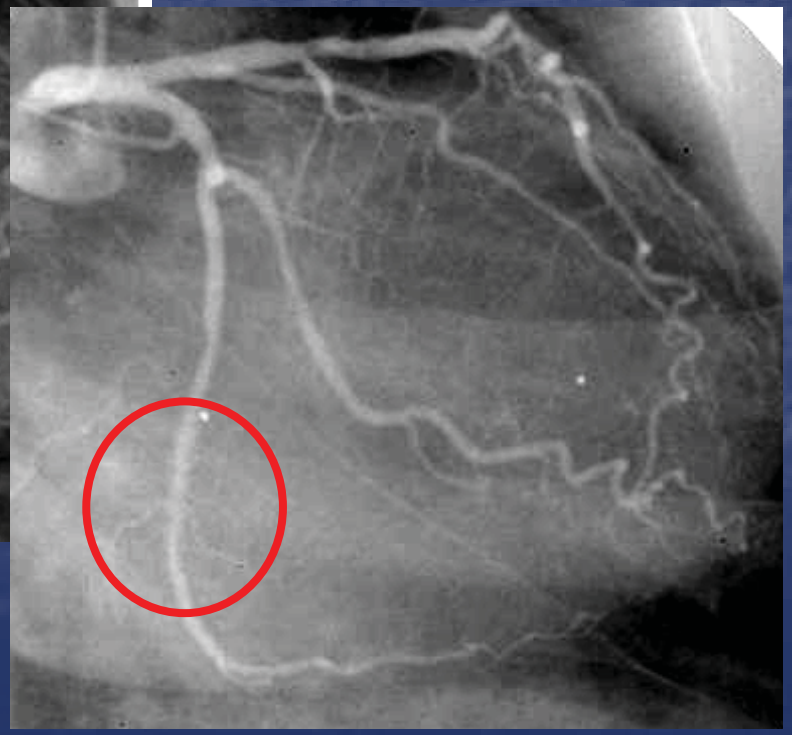
Initial



After stenting



6-month f/u



Conclusion

- Rosiglitazone reduced effectively the binary in-stent restenosis rate in type 2 diabetic patients.
- This outcome was independent of hypoglycemic effect of Rosiglitazone.
- A large randomized blinded study is needed to validate the results of this study.