Pioglitazone & Restenosis
- focus on cellular mechanism

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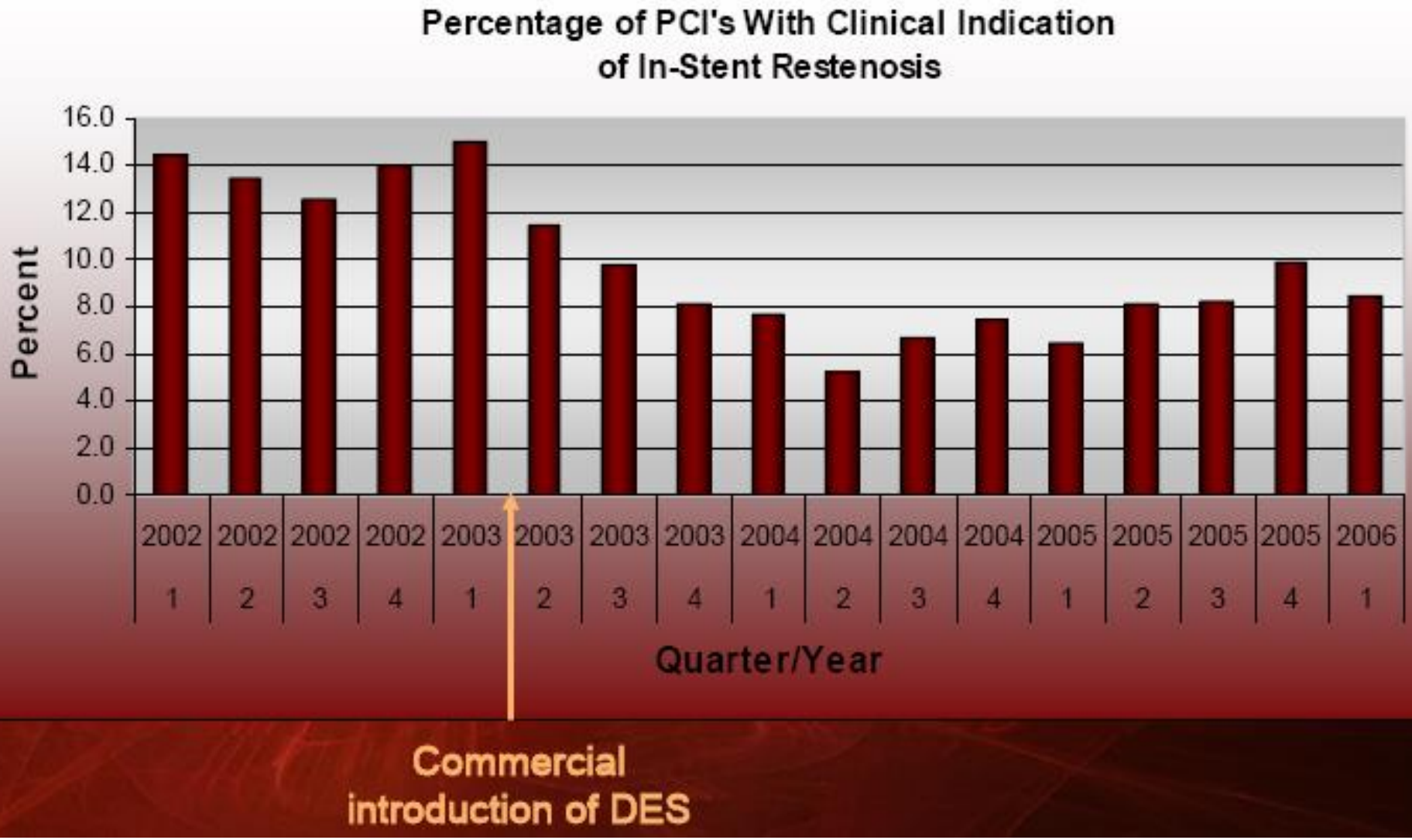
ISR: BMS vs. DES



Restenosis

ISR	**30~40%**	**15~30%**	**0~9%**

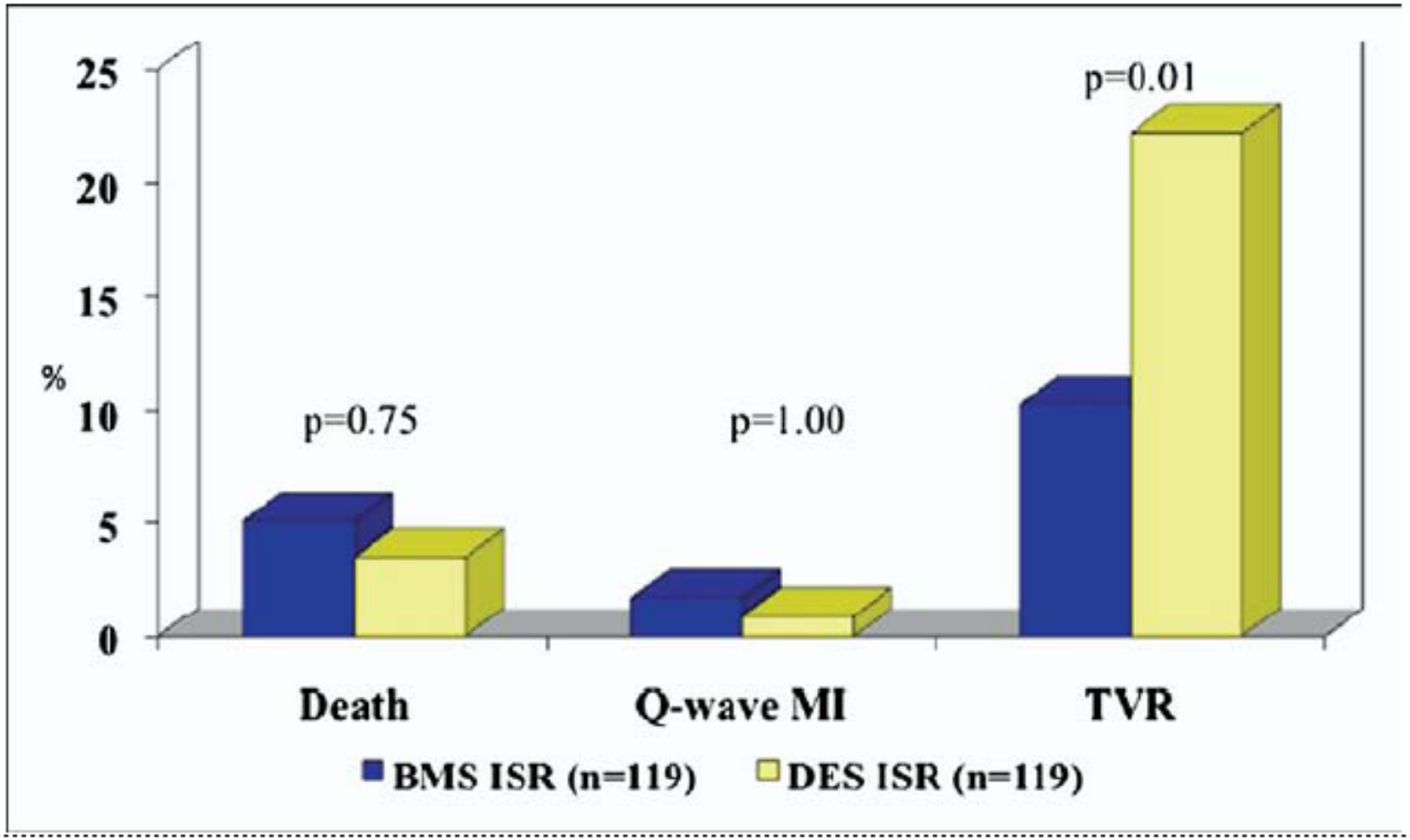
DES: Very promising, NOT perfect !

Reported TLR >10% of DES era

• Left Main	14.1% *
• Bifurcation	18.7-28% **
• SVG	>10% (SECURE)
• VBT Failure lesion	>47.8% (SECURE)
• Multivessel TAXUS	>12% (TAXUS V-TRUE)
• Multivessel Cypher	>11% (RECIPE Registry)
• >4 Cypher /pt	14% ***

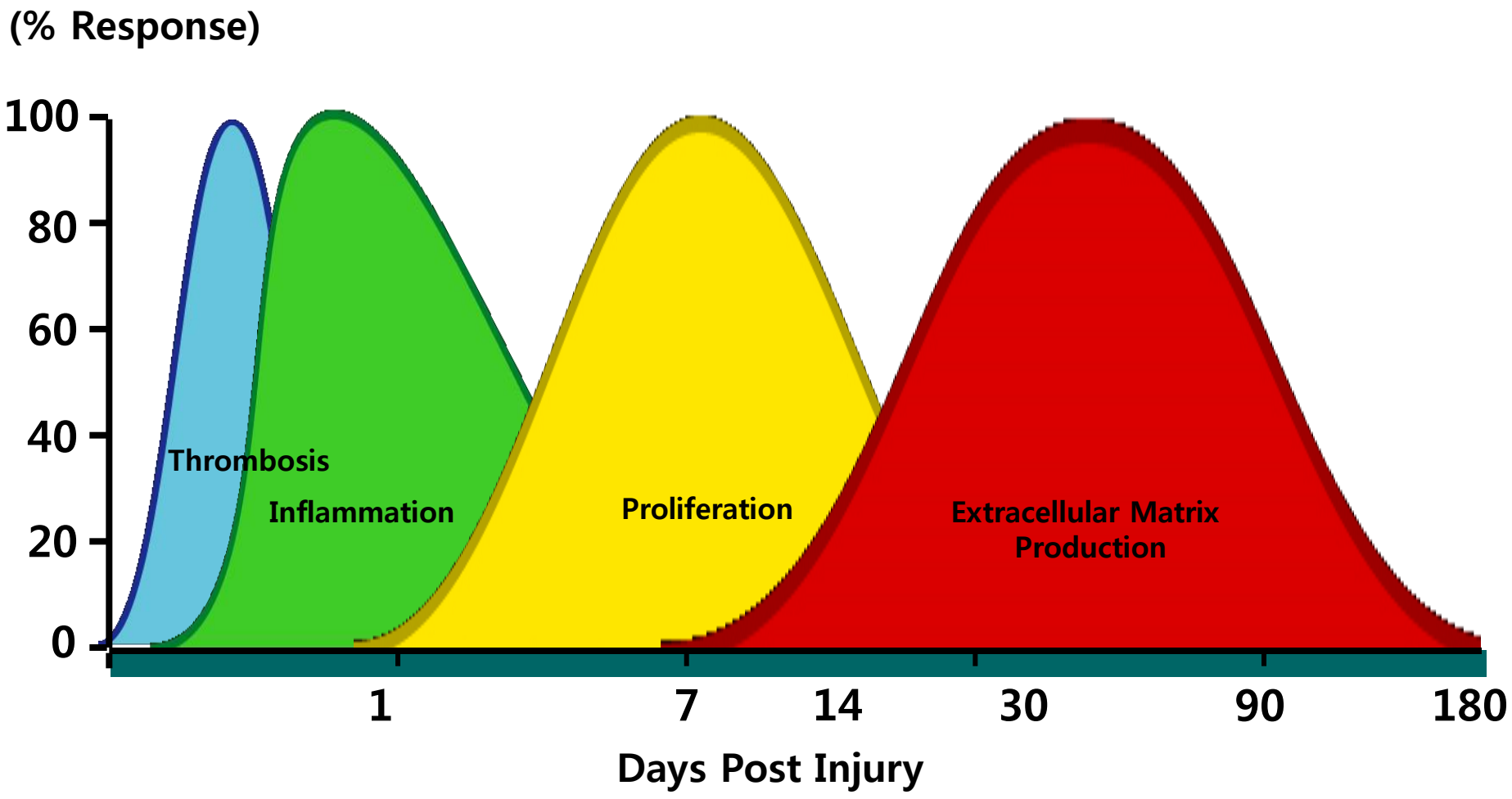
* Chieffo A, Circulation, 2005
** Colombo A, Circulation 2004
*** Iakovou I, et al CCI 2004

DES for DES-ISR vs. BMS-ISR



Am J Cardiol 2009;103:491– 495

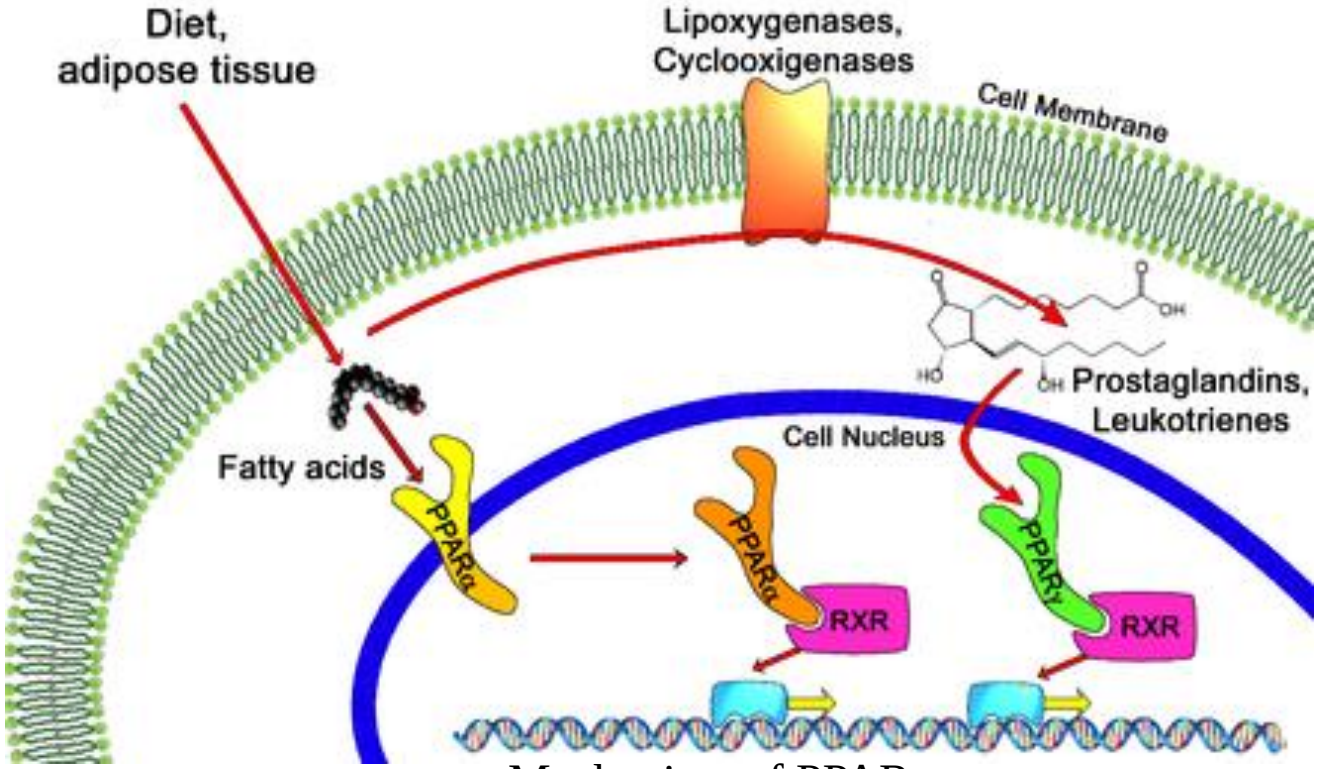
Restenosis: A Wound-Healing Response



Background – PPAR and PPAR agonist

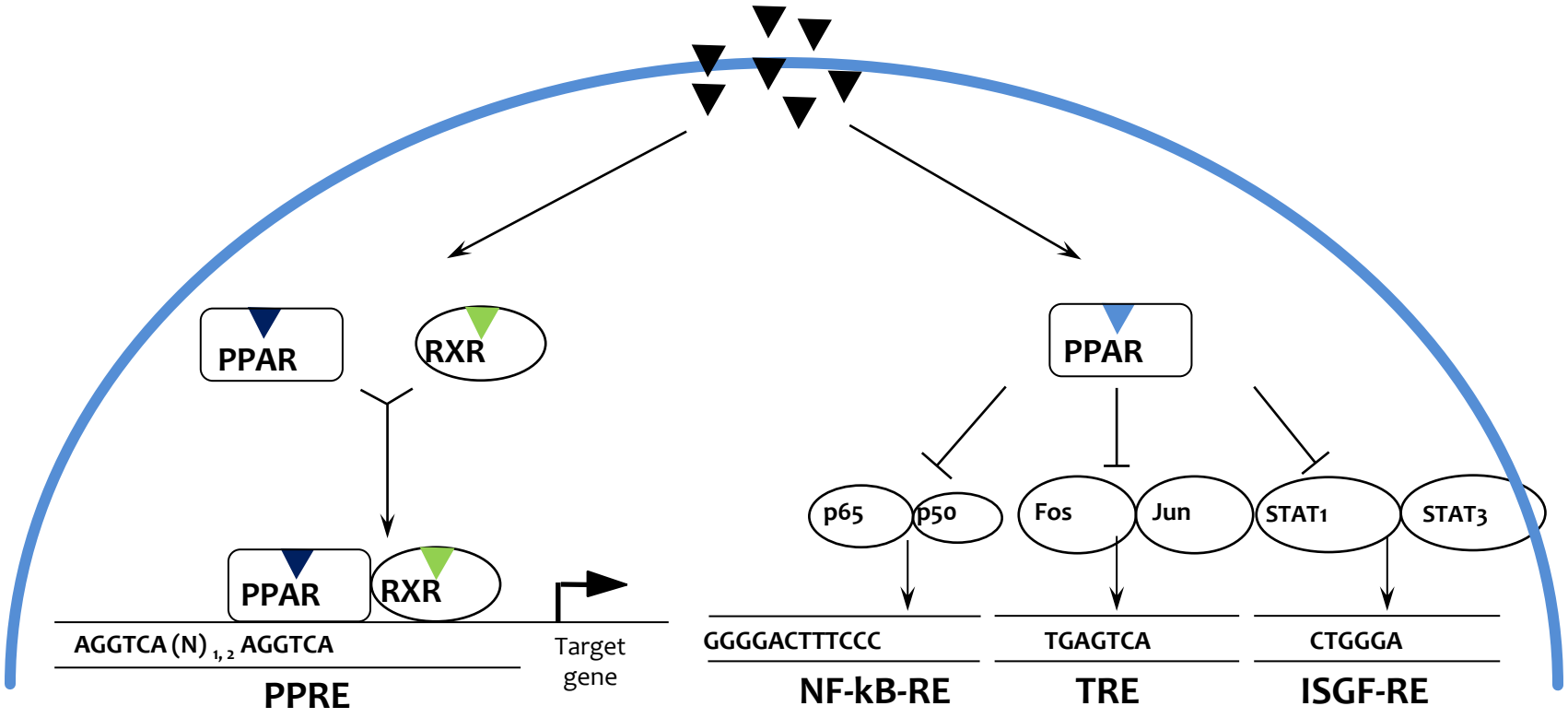
Peroxisome Proliferator Activated Receptor (PPAR)

- a group of nuclear receptor proteins that function as transcription factors
- play essential roles in the regulation of cellular differentiation, development, and metabolism.
- three types of PPARs have been identified, α, β, γ,
- PPAR γ is activated by PGJ2 (eg. prostaglandin)



Mechanism of PPAR

Molecular Mechanisms of Biologic Responses of PPAR Agonists



Trans- activation

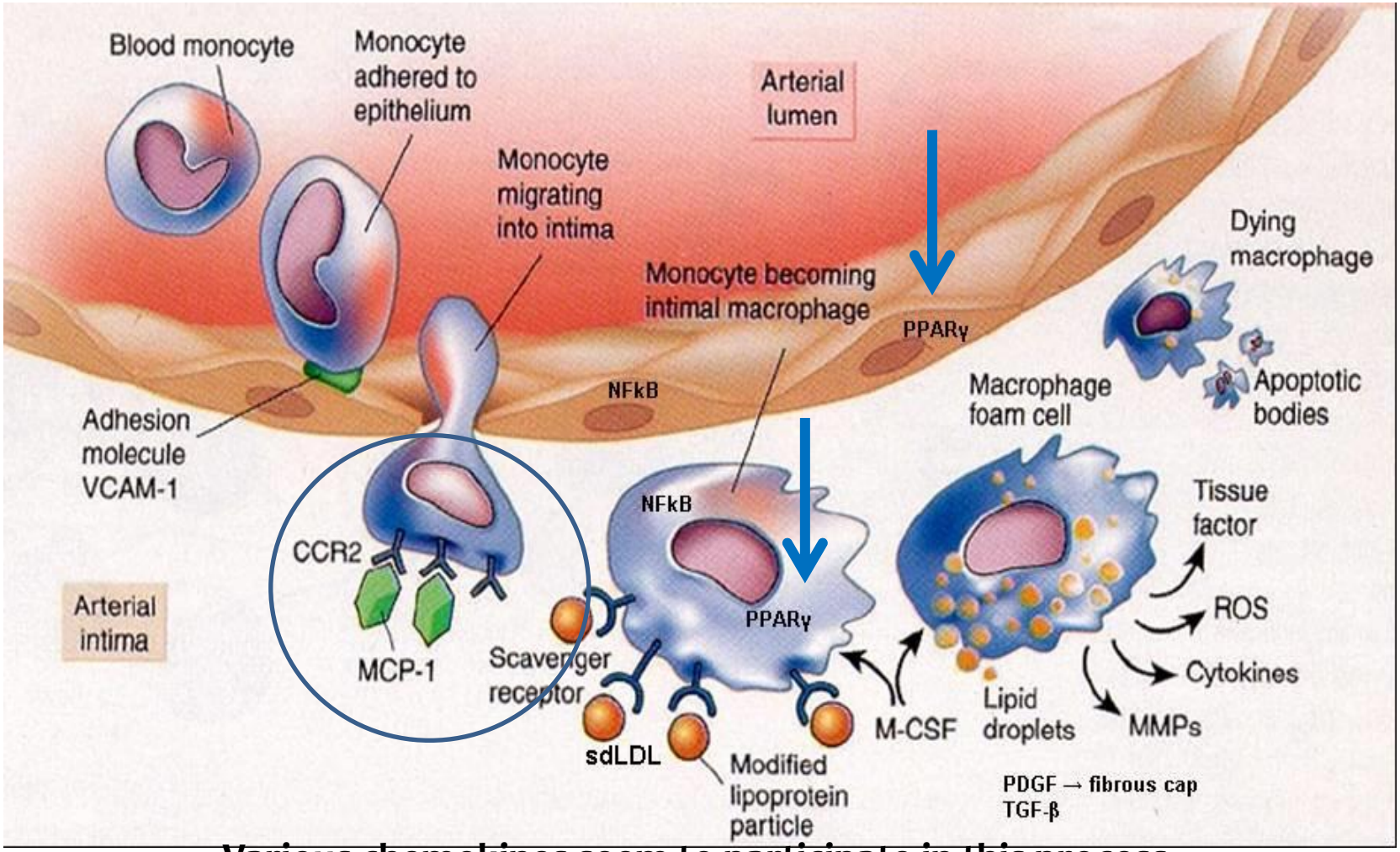
Lipid homeostasis

Glucose homeostasis

Trans-repression

Anti-inflammatory properties

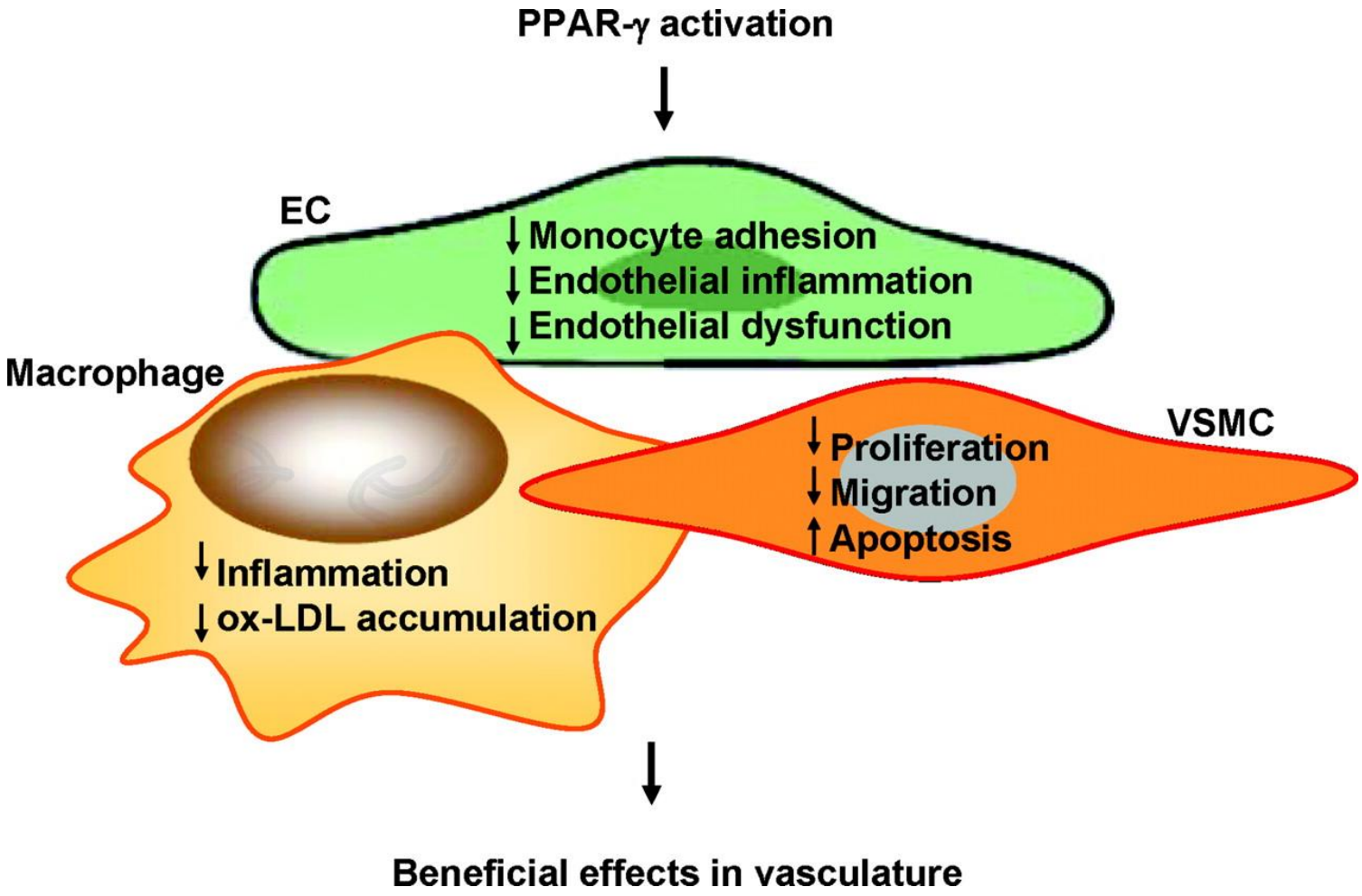
Atherosclerosis lesions and inflammation



Various chemokines seem to participate in this process, particularly interaction of MCP-1 with its receptor CCR2

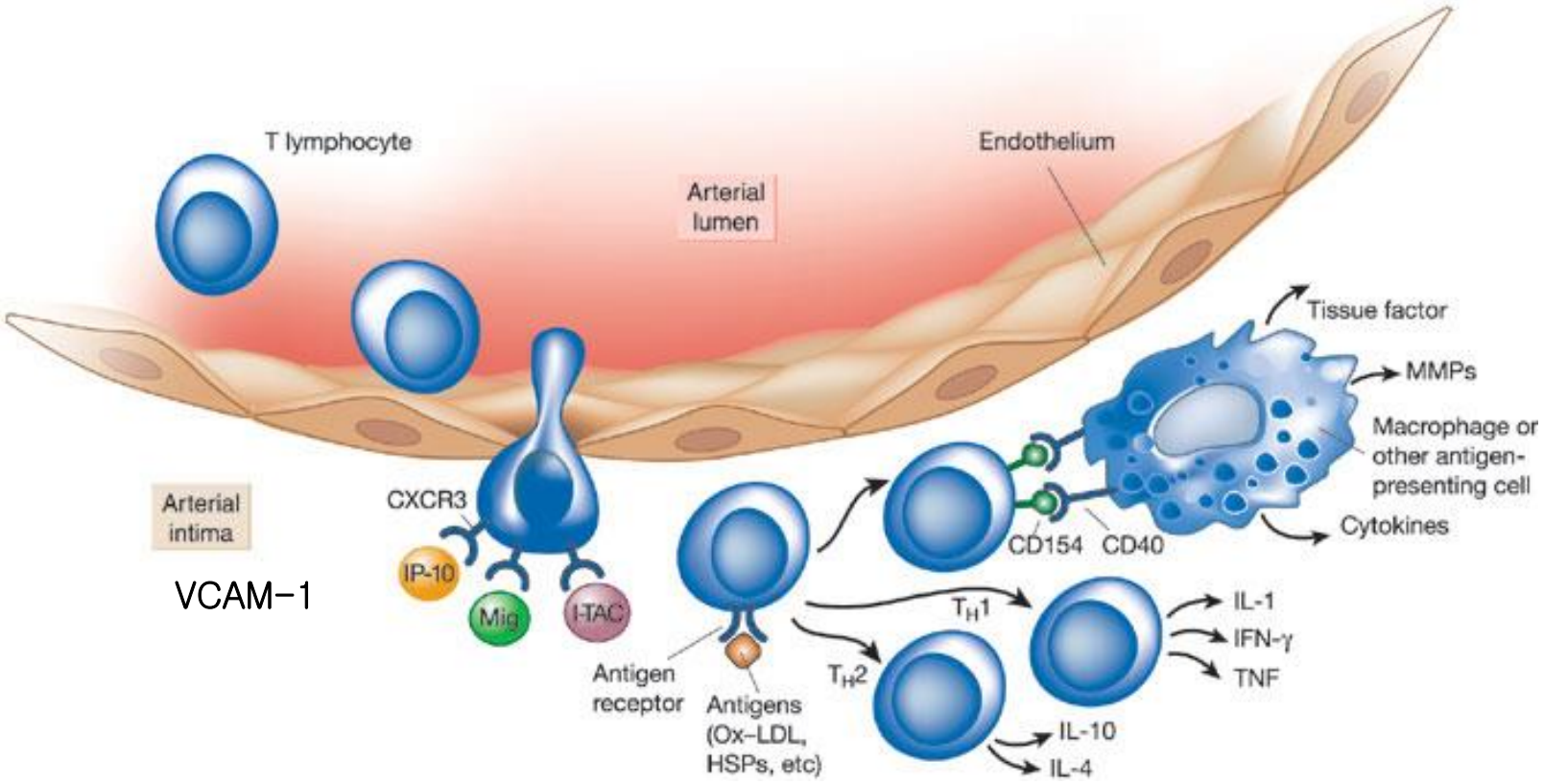
Libby P. Nature 2002; 420(19/26):869-74.

Beneficial Effect of PPAR-γ activation in Vasculature



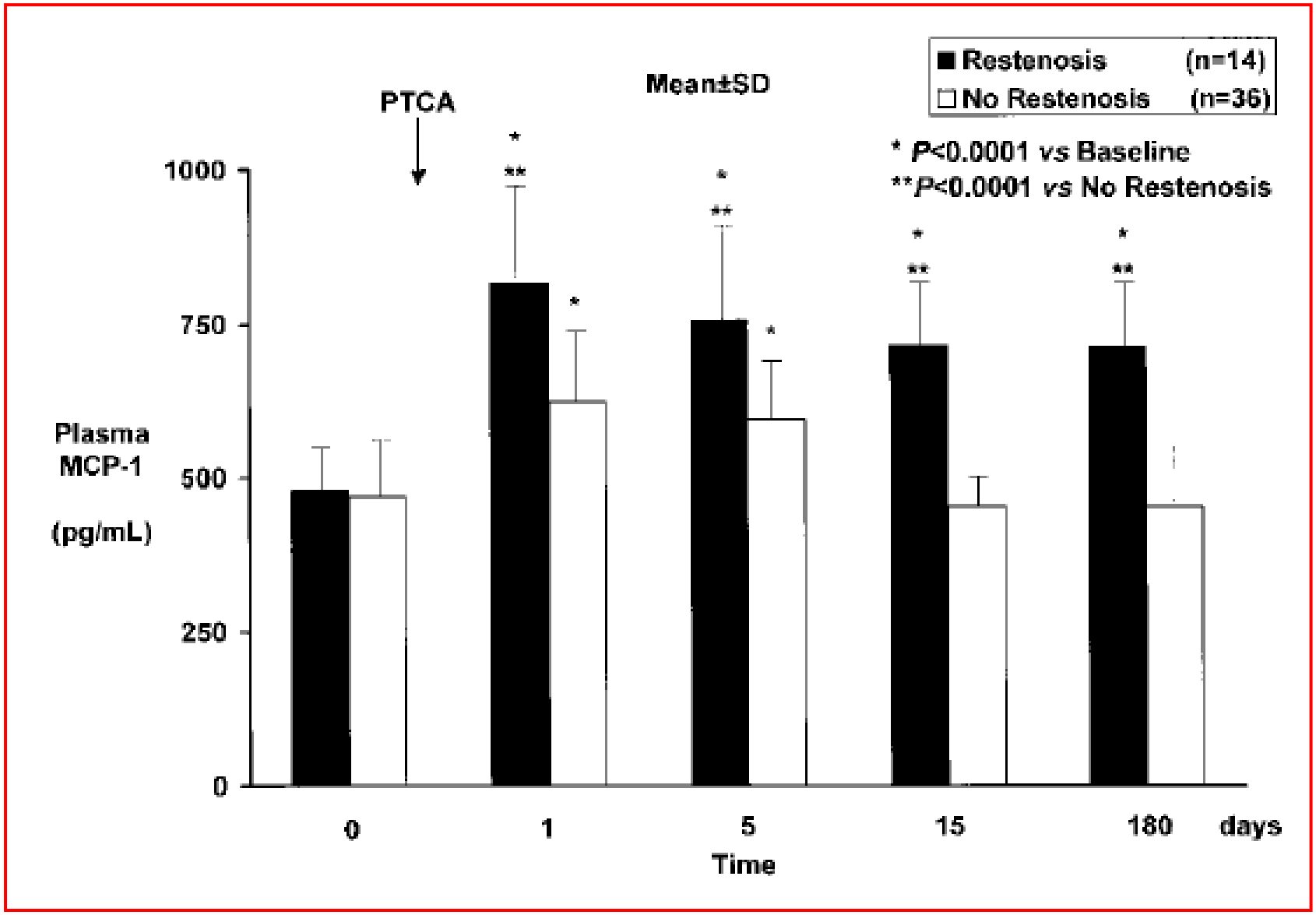
Duan, S. Z. et al. Circ Res 2008;102:283-294

The roles of T lymphocytes in atherogenesis.



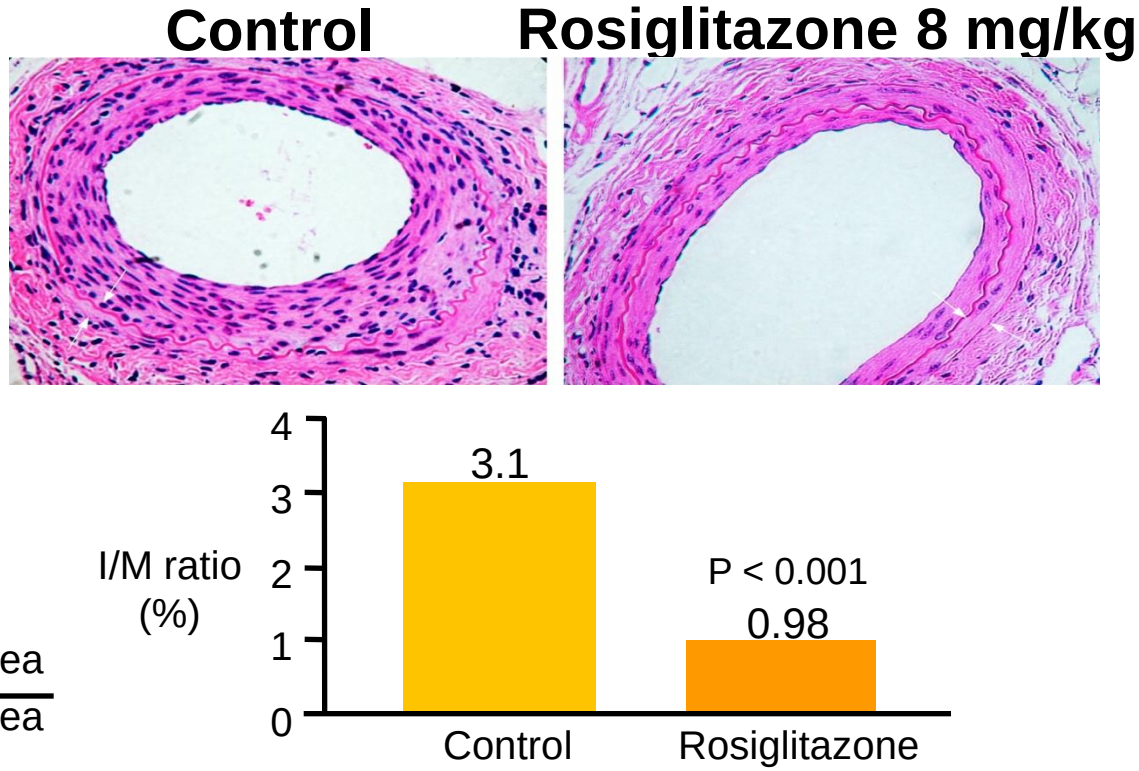
Chemoattractants bind to chemokine receptor CXCR3 expressed by T cells in the atherosclerotic lesion

Chemokines (MCP-1) & Restenosis : serial blood level analysis



PPARγ activation reduces intimal hyperplasia

Balloon injury in mouse model



$$\text{I/M ratio} = \frac{\text{Intimal area}}{\text{Medial area}}$$

There is a significant difference in the thickness of injured artery

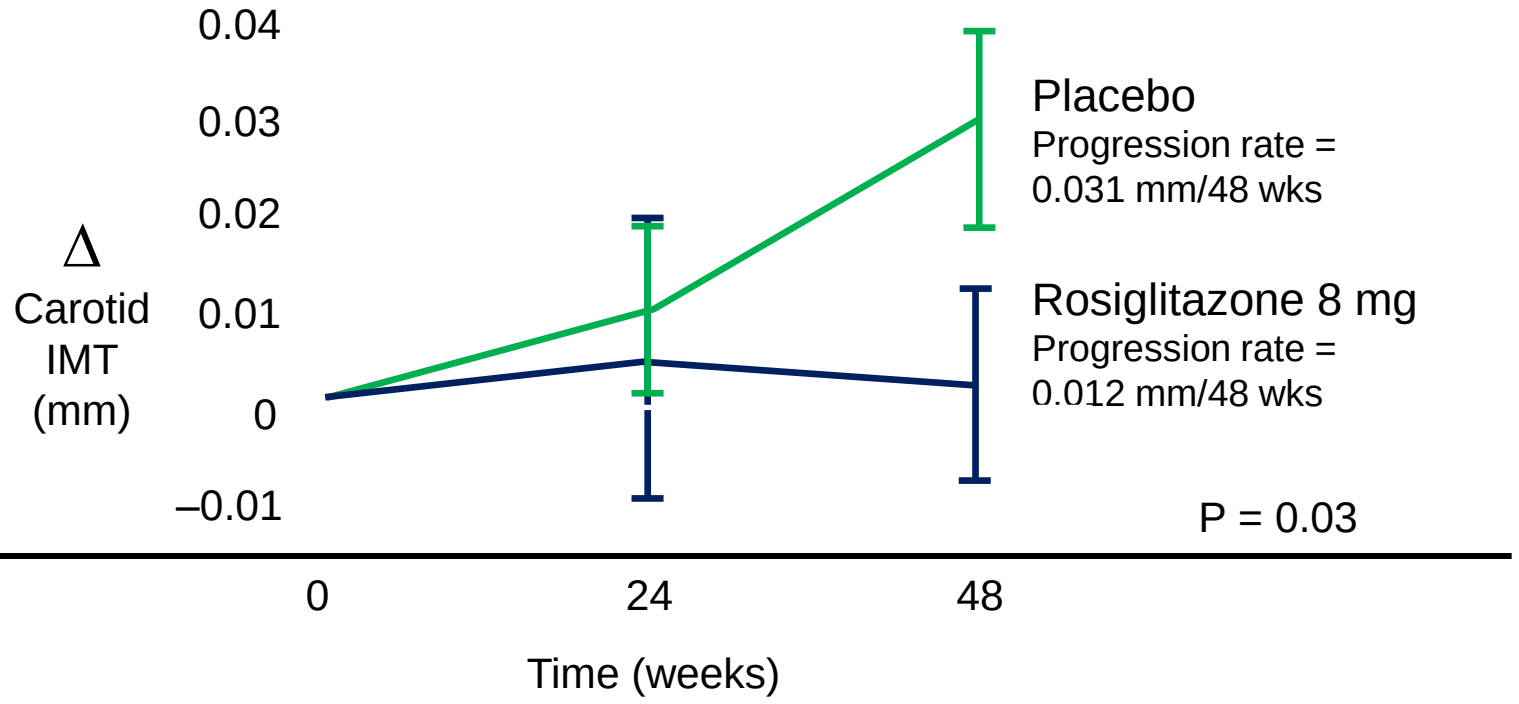
Wang C-H et al. *Circulation.* 2004;109:1392-400.

Vascular effects of thiazolidinediones

Effect of PPAR on vasculature in clinical studies

PPARγ activation blunts progression of carotid atherosclerosis in stable coronary artery disease

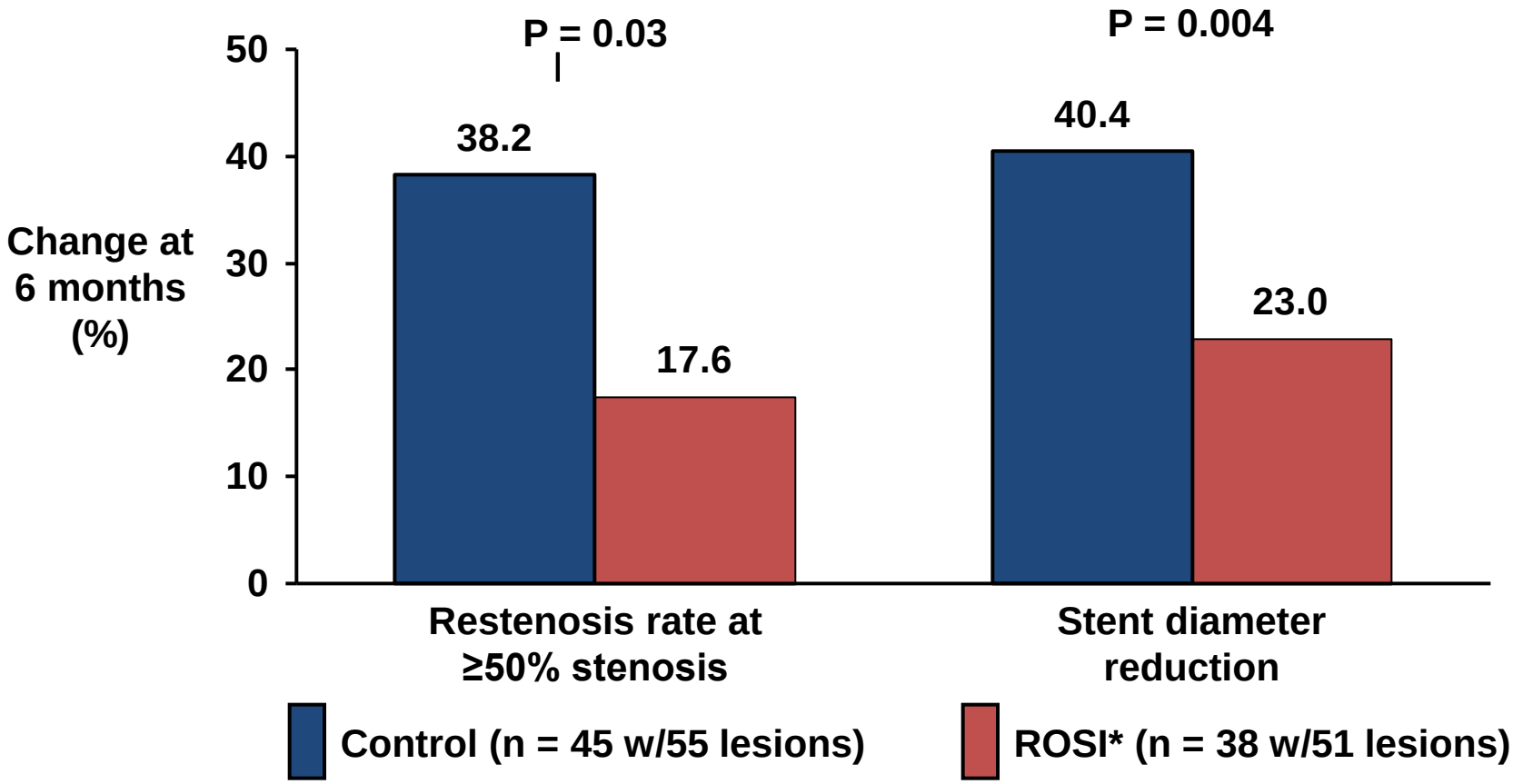
N = 92 without diabetes



Sidhu JS et al. *Arterioscler Thromb Vasc Biol*. 2004;24:930-4.

Thiazolidineones impact on restenosis in type 2 diabetes

N = 95 with T2DM and Coronary artery disease



Rosiglitazone (red bar) reduced restenosis as well as less reduction in stent diameter

Choi D et al. Diabetes Care. 2004;27:2654-60.

Study plan for PPAR-γ effect on coronary artery disease

- PPAR-γ activity affects neotimal growth after DES implantation in hypertensive, non-diabetic patients

- PPAR-γ activity reduces neintimal volume and pulse wave velocity after DES implantation in hypertensive, type 2 diabetic patients

- PPAR-γ agonist(Pioglitazone)affects atherosclerosis and neointimal growth in diabetic patients after DES implantation

- Cellular and molecular mechanism of PPAR-γ agonist(Pioglitazone) on inhibitory effects on neintimal growth in type 2 diabetic patients with coronary artery disease

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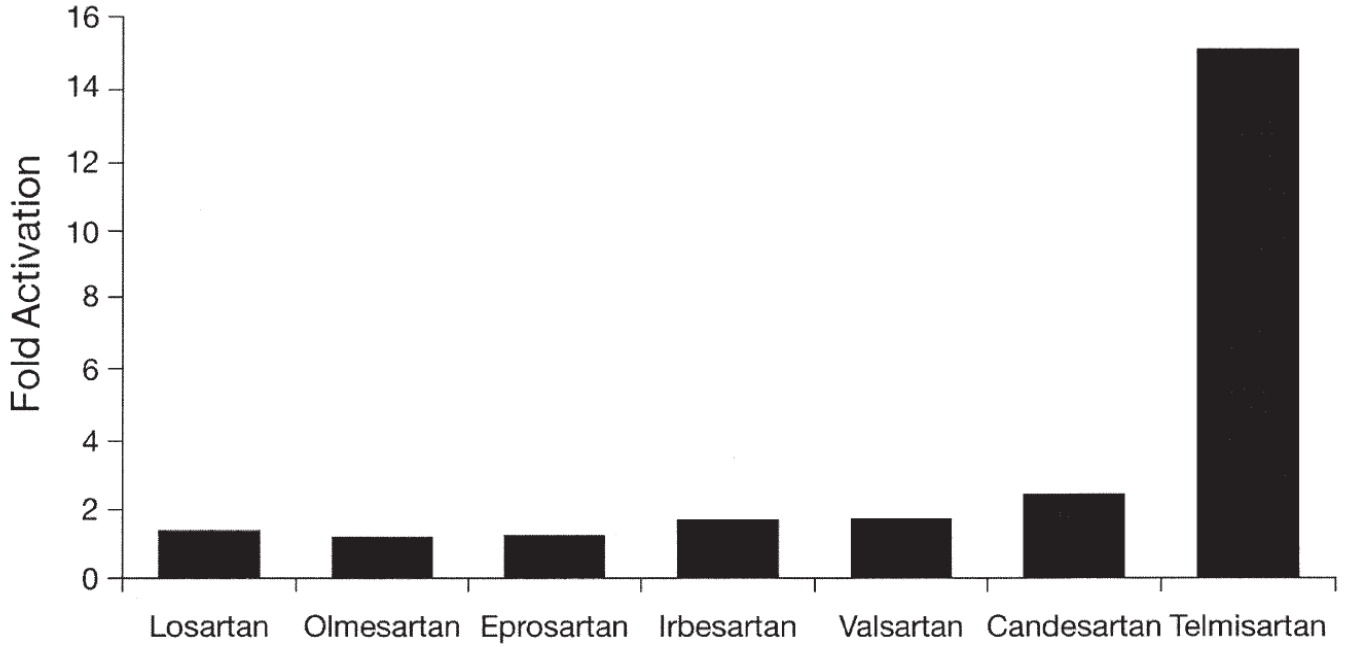
Telmisartan Reduces the Late Lumen Loss and Inflammatory Markers After Drug-Eluting Stent Implantation in Hypertensive Patients

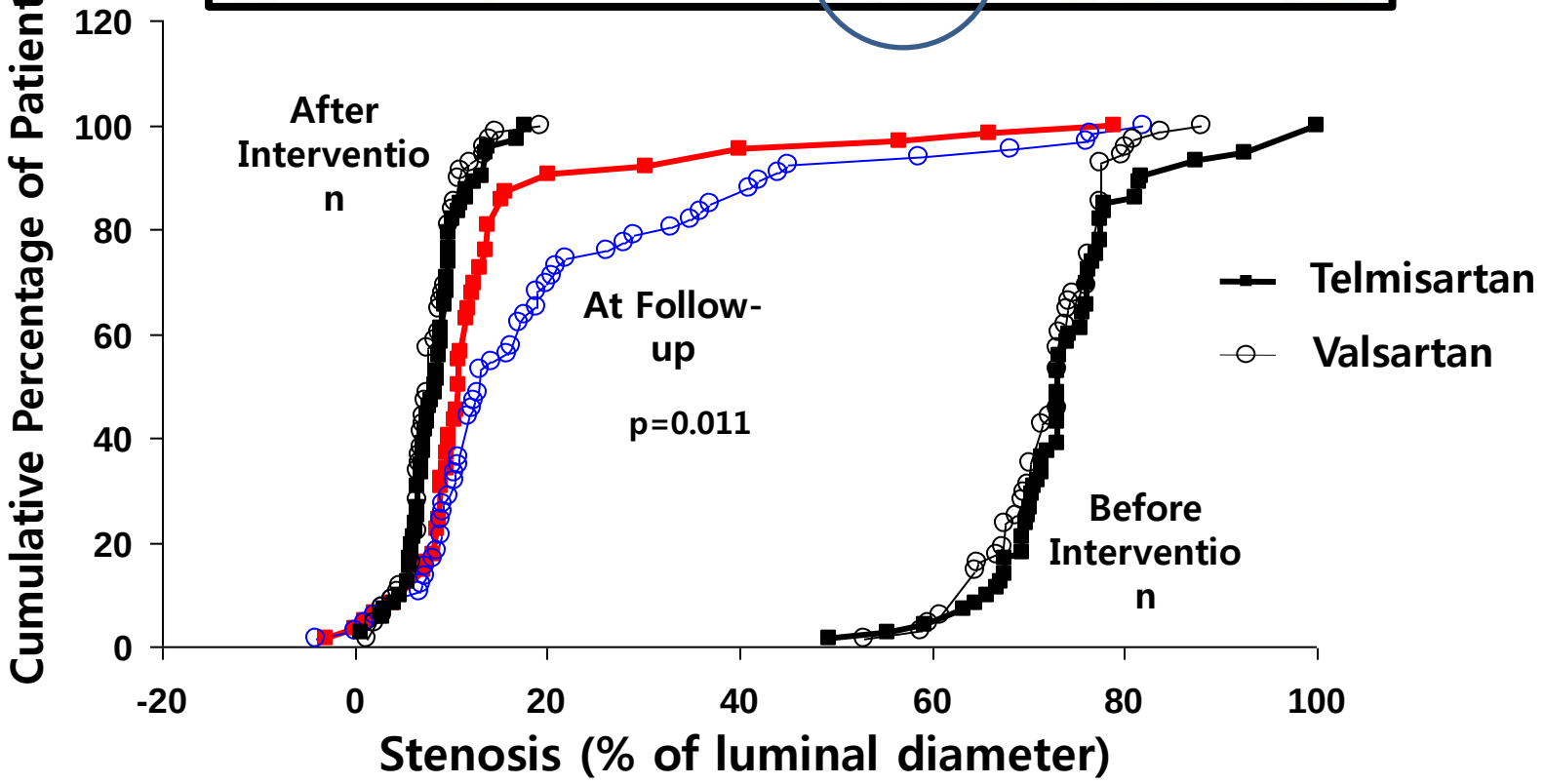
Activation of PPAR-gamma by ARBs in a cell-based transient transfection assay.



Telmisartan had about 15 fold increase in PPAR-gamma activity compared with other ARBs

Comparison of cumulative distribution curves for percent stenosis

Late lumen loss (mm)	0.1 ± 0.4	0.3 ± 0.5	0.001
Loss index	0.1 ± 0.2	0.2 ± 0.3	<0.001



Late loss & Percent stenosis was significantly lower in the telmisartan

Changes in inflammatory markers after Telmisartan

	Telmisartan Group (n=45)		Valsartan Group (n=46)	
	Baseline	8-month f/u	Baseline	8-month f/u
IL-6 (pg/ml)	1.41 ± 1.29	0.91 ± 0.55*†	1.35 ± 0.69	1.30 ± 0.94
Δ from baseline (pg/ml)	**-0.50 ± 1.04†**		**-0.05 ± 0.89**	
TNF-α (pg/ml)	13.2 ± 2.9	11.0 ± 1.9*†	13.0 ± 3.7	12.9 ± 3.5
Δ from baseline (pg/ml)	**-2.2 ± 2.3†**		**-0.2 ± 1.1**	
hsCRP (mg/L)	3.58 ± 2.15	1.73 ± 2.86*	2.56 ± 2.87	1.19 ± 1.33*
Δ from baseline (mg/L)	-1.85 ± 3.03		-1.37 ± 2.73	
Adiponectin (μg/ml)	5.53 ± 4.96	7.69 ± 3.76*	6.04 ± 2.71	6.50 ± 3.36
Δ from baseline (μg/ml)	**2.06 ± 2.73†**		**0.46 ± 2.08**	

* $p < 0.05$ compared with baseline. † $p < 0.05$ compared with valsartan group.

Telmisartan Reduces the Late Lumen Loss and Inflammatory Markers After Drug-Eluting Stent Implantation in Hypertensive Patients

- Hypertensive patients treated with telmisartan not only benefit from its antihypertensive effects but also from its anti-inflammatory and antiproliferative effects.

- PPAR-γ activation by telmisartan may provide new therapeutic options in the management of hypertensive patients with severe Coronary artery disease requiring stent implantation.

AJC 2007;100:1625-9.

Study plan for PPAR-γ effect on coronary artery disease

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Telmisartan Reduces Neointima Volume and Pulse Wave Velocity Eight Months after Zotarolimus-Eluting Stent Implantation in Hypertensive Type 2 Diabetic Patients

- **An antihypertensive medication** which could also modify carbohydrate and lipid abnormalities could be of significant clinical benefit to **hypertensive diabetic patients.**

Hypertension 2004;43:993-1002

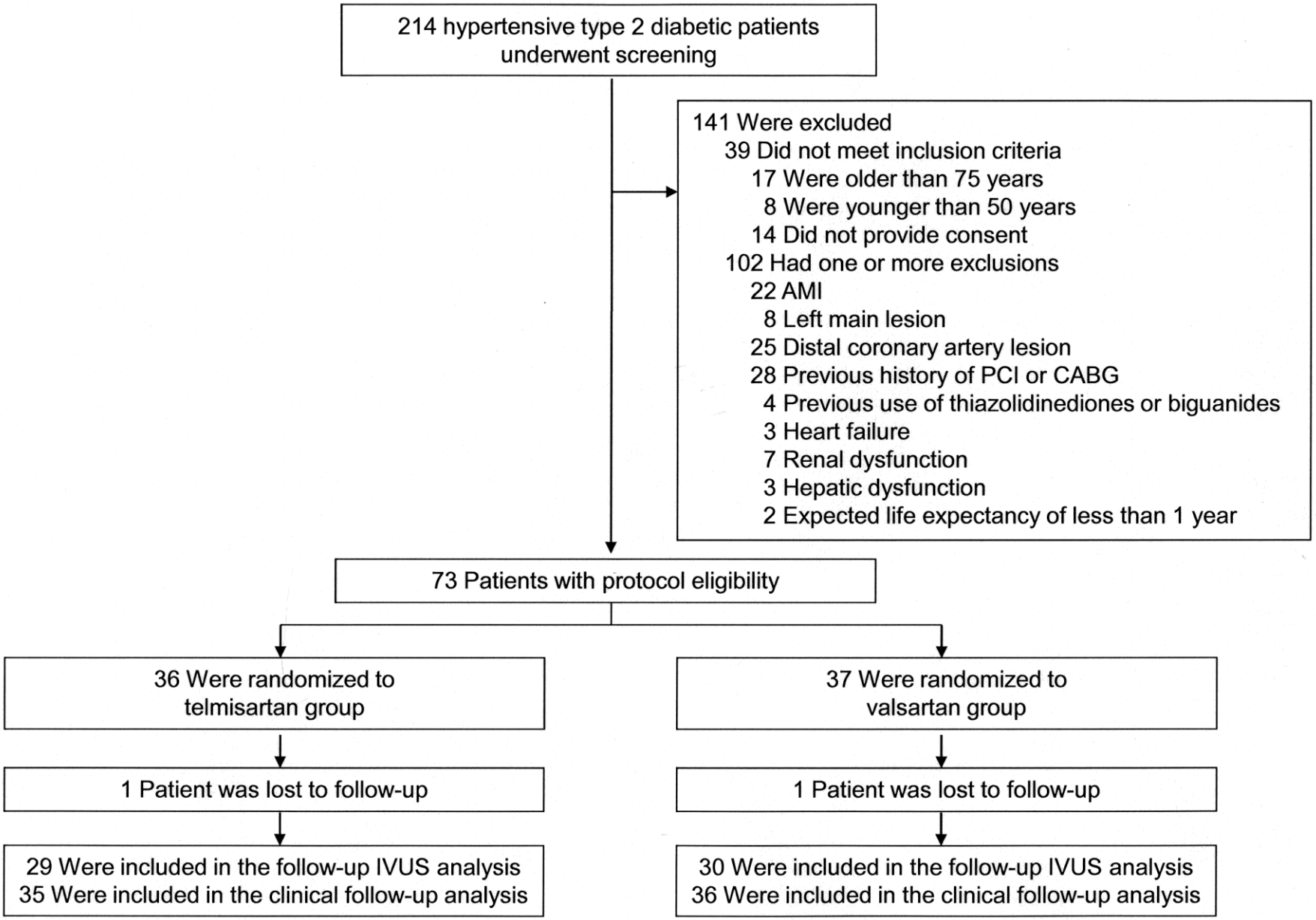
- **Telmisartan has been known to reduce late loss** in hypertensive patients with coronary artery disease requiring stent implantation.

AJC 2007;100:1625-9.

Objectives

- The purpose of this prospective, randomized, single-blinded, investigator-initiated 8 months follow-up study was to compare **the effects of telmisartan and valsartan** on *neointima volume, coronary atherosclerosis progression, and PWV* after ZES implantation in **hypertensive type 2 diabetic patients with significant coronary artery narrowing**.

Study Protocol



Methods

Primary end points

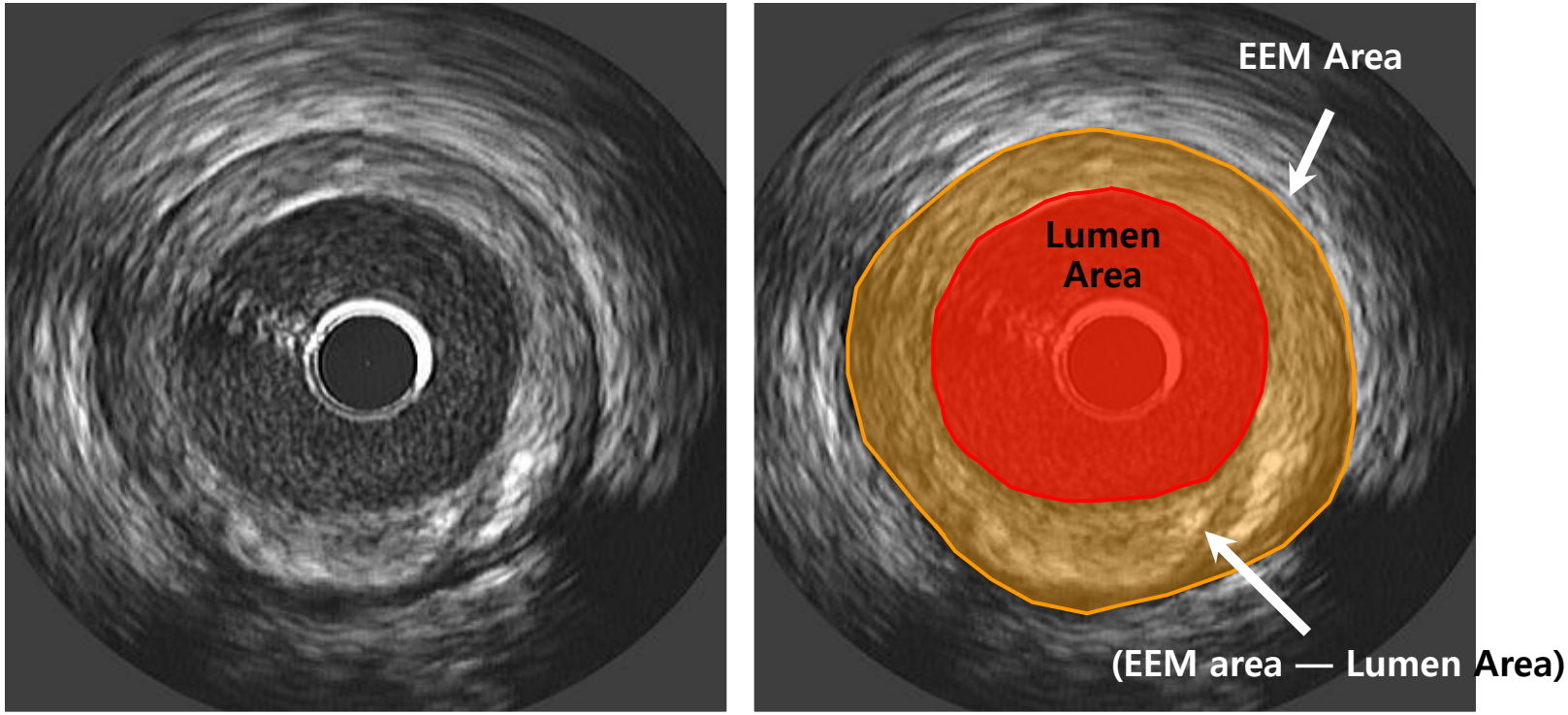
1. In-stent neointima volume on 8 months f/u,
2. Atherosclerosis progression at proximal and distal to the stent

Secondary end points

1. PWVs were compared between the 2 groups.
2. Inflammatory cytokines such as IL-6, TNF-α, and hsCRP, as well as the insulin resistance index such as HOMA index and RBP4 were compared between the 2 groups.

IVUS Determination of Atheroma Area

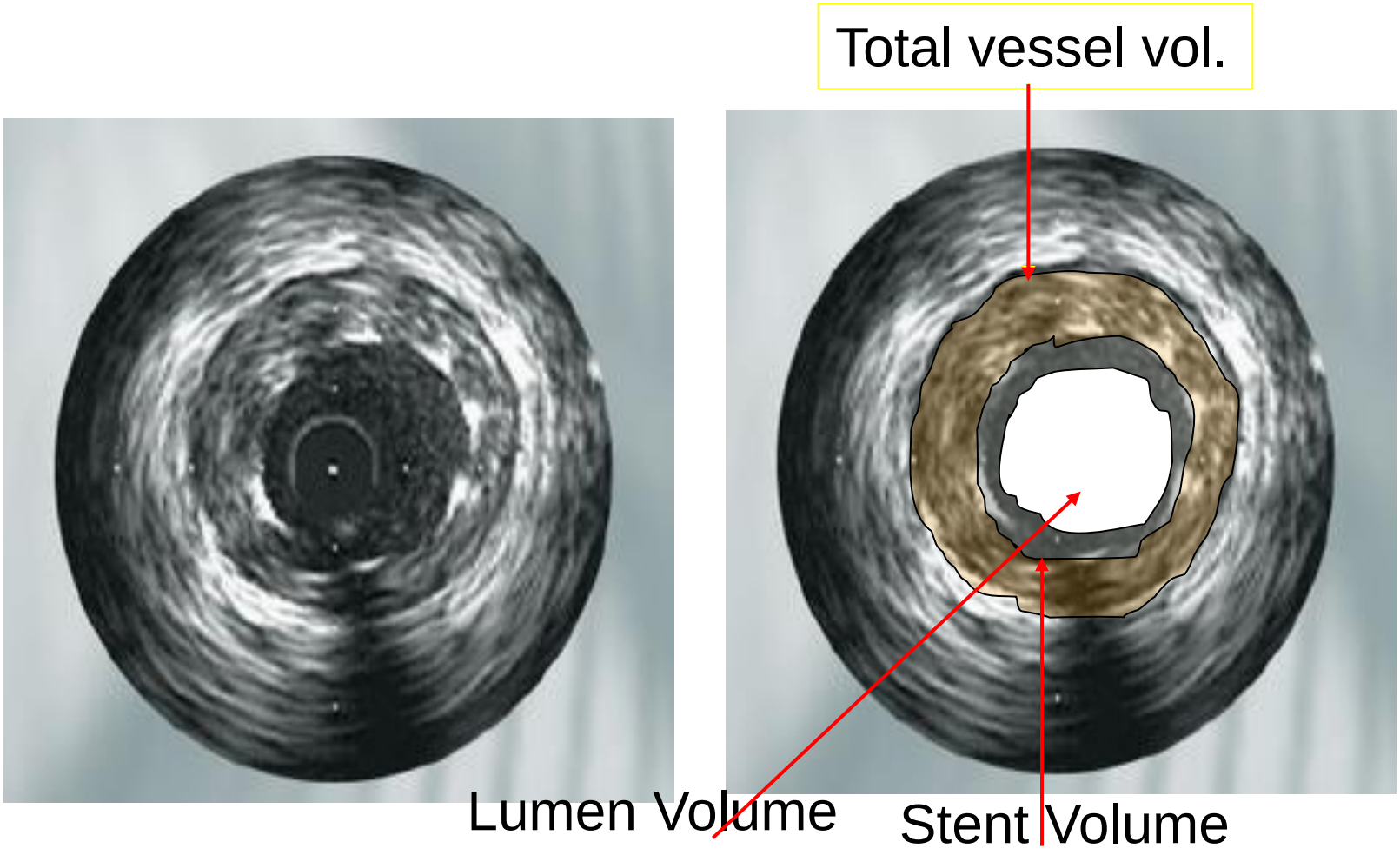
Precise Planimetry of EEM and Lumen Borders
allows calculation of Atheroma Cross-sectional Area



Elastic membrane area (EEM Area) and the Lumen area to be calculated.

Plaque vol. = EEM vol. – Lumen vol.

IVUS Determination of Neointima Volume after stent

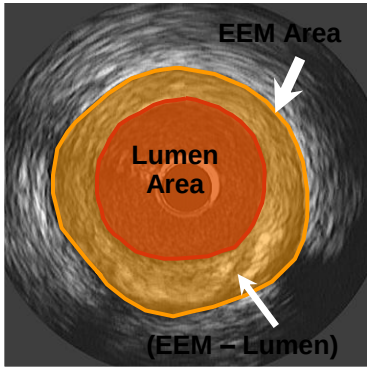


neointima volume was calculated by subtracting lumen volume from stent volume.

Neointima vol. = Stent vol. – Lumen vol.

IVUS Neointima Volume Analysis

The first primary endpoint was change from baseline in neointima volume in stent

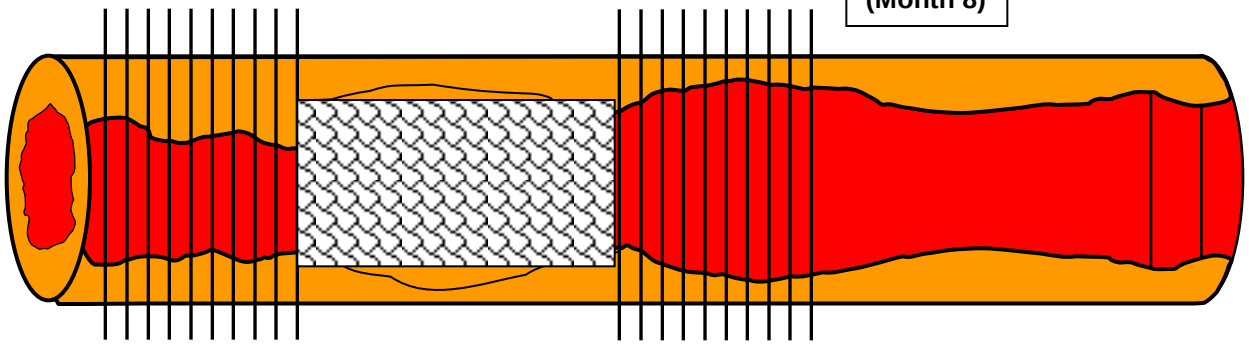


$$\text{Atheroma Volume } (mm^3/\text{-mm}) = \frac{\sum n(\text{Vessel vol.} - \text{Lumen vol.})_{CSA}}{\text{No. of CSA}}$$

(Month 8)

$$\text{Neointima Volume } (mm^3/\text{-mm}) = \frac{\sum n(\text{Stent vol.} - \text{Lumen vol.})_{CSA}}{\text{No. of CSA}}$$

(Month 8)



Calculated by subtracting the neointima volume at baseline from the neointima volume at 8 months

Baseline Patient Characteristics

Variable	Telmisartan (n=36)	Valsartan(n=37)	p Value
Age (years)	62.2 ± 7.5	62.8 ± 8.8	0.953
Men	26 (72.2 %)	29 (78.4 %)	0.542
Body mass index (kg/m^2)	23.9 ± 2.8	24.4 ± 4.1	0.534
Systolic blood pressure (mmHg)	140.7 ± 13.8	143.2 ± 12.6	0.415
Diastolic blood pressure (mmHg)	85.4 ± 6.9	87.3 ± 7.5	0.344
Heart rate (beats/minute)	70.5 ± 12.8	73.1 ± 10.4	0.664
Risk factors			
Hyperlipidemia	16 (44.4 %)	18 (48.6 %)	0.719
Current smoker	7 (19.4 %)	10 (27.0 %)	0.443
Family history of CAD	5 (13.9 %)	3 (8.1 %)	0.479
Left ventricular ejection fraction (%)	53.9 ± 7.4	55.3 ± 7.8	0.616
Unstable angina pectoris	10 (27.8 %)	8 (21.6 %)	0.542
Diabetes treatment before randomization			
Diet only	6 (16.7 %)	5 (13.5 %)	0.754
Oral glucose-lowering therapy	30 (83.3 %)	32 (86.5 %)	0.707
Insulin	3 (8.3 %)	3 (8.1 %)	1.000
Medication after randomization			
Biguanides	3 (8.3 %)	5 (13.5 %)	0.711
α-Glucosidase inhibitors	7 (19.4 %)	5 (13.5 %)	0.494
Sulfonylureas	26 (72.2 %)	29 (78.4 %)	0.542

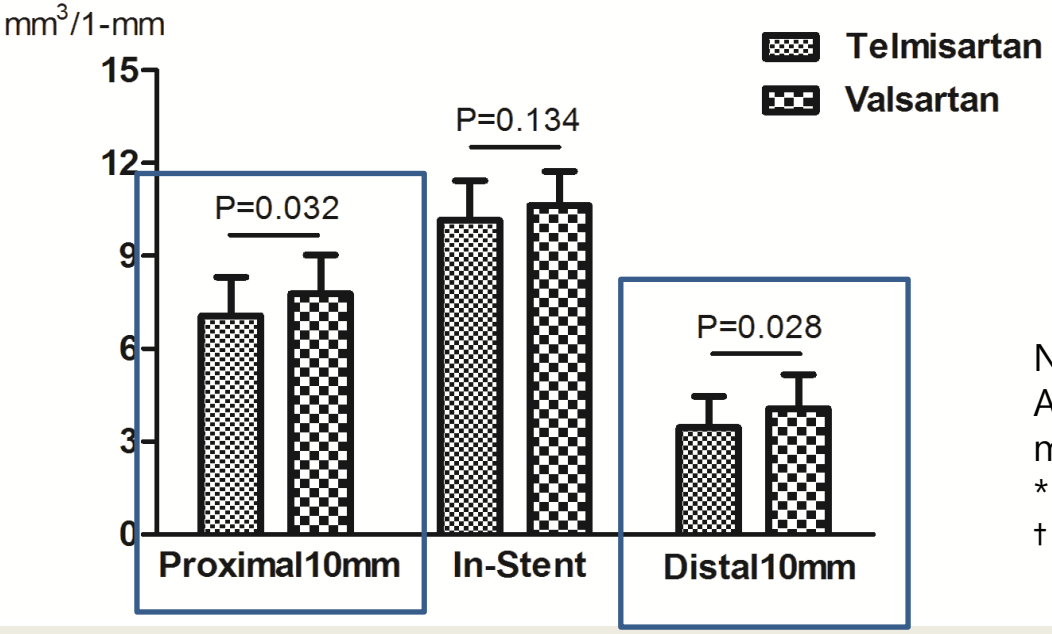
Baseline Angiographic Characteristics

Variable	Telmisartan (n=36)	Valsartan(n=37)	p Value
Number of lesions stented	55	59	
Target coronary artery			
Left anterior descending artery	20 (55.6 %)	19 (51.4 %)	0.719
Left circumflex artery	6 (16.7 %)	8 (21.6 %)	0.591
Right	10 (27.8 %)	10 (27.0 %)	0.943
Type of lesion (%)			
A	3 (8.3 %)	2 (5.4 %)	0.674
B_1	5 (13.9 %)	7 (18.9 %)	0.562
B_2	17 (47.2 %)	19 (51.4 %)	0.724
C	11 (30.6 %)	9 (24.3 %)	0.551
Baseline			
Reference diameter (mm)	2.83 ± 0.32	2.78 ± 0.38	0.767
Minimal lumen diameter (mm)	0.64 ± 0.36	0.75 ± 0.27	0.304
Percentage of stenosis	77.4 ± 9.3	73.0 ± 7.8	0.243
Mean lesion length (mm)	20.2 ± 12.2	18.9 ± 13.0	0.309
Postprocedure			
Reference diameter (mm)	2.93 ± 0.45	2.91 ± 0.37	0.662
Minimal lumen diameter (mm)	2.74 ± 0.41	2.72 ± 0.37	0.871
Percentage of stenosis	6.4 ± 3.9	6.5 ± 2.8	0.803
Acute gain (mm)	2.09 ± 0.37	1.98 ± 0.39	0.361
Number of stents, range	1.5 ± 1.1 (1-3)	1.6 ± 1.3 (1-3)	0.872
Mean stent length (mm)	24.8 ± 6.9	26.1 ± 6.1	0.669
Mean stent diameter (mm)	2.9 ± 0.4	2.8 ± 0.3	0.739

8-Month Angiographic Outcomes

Variable	Telmisartan Group (n=36)	Valsartan Group (n=37)	p Value
Number of patients with 8 months f/u	29 (80.6 %)	30 (81.1 %)	0.955
Eight-month follow-up			
Reference diameter (mm)	2.93 ± 0.37	2.92 ± 0.31	0.766
Minimal lumen diameter (mm)	2.23 ± 0.47	2.01 ± 0.44	0.026
Percentage of stenosis	23.8 ± 15.4	31.2 ± 16.7	0.031
Late lumen loss (mm)	0.51 ± 0.48	0.71 ± 0.49	0.042
Binary restenosis	3/29 (10.3 %)	4/30 (13.3 %)	1.000

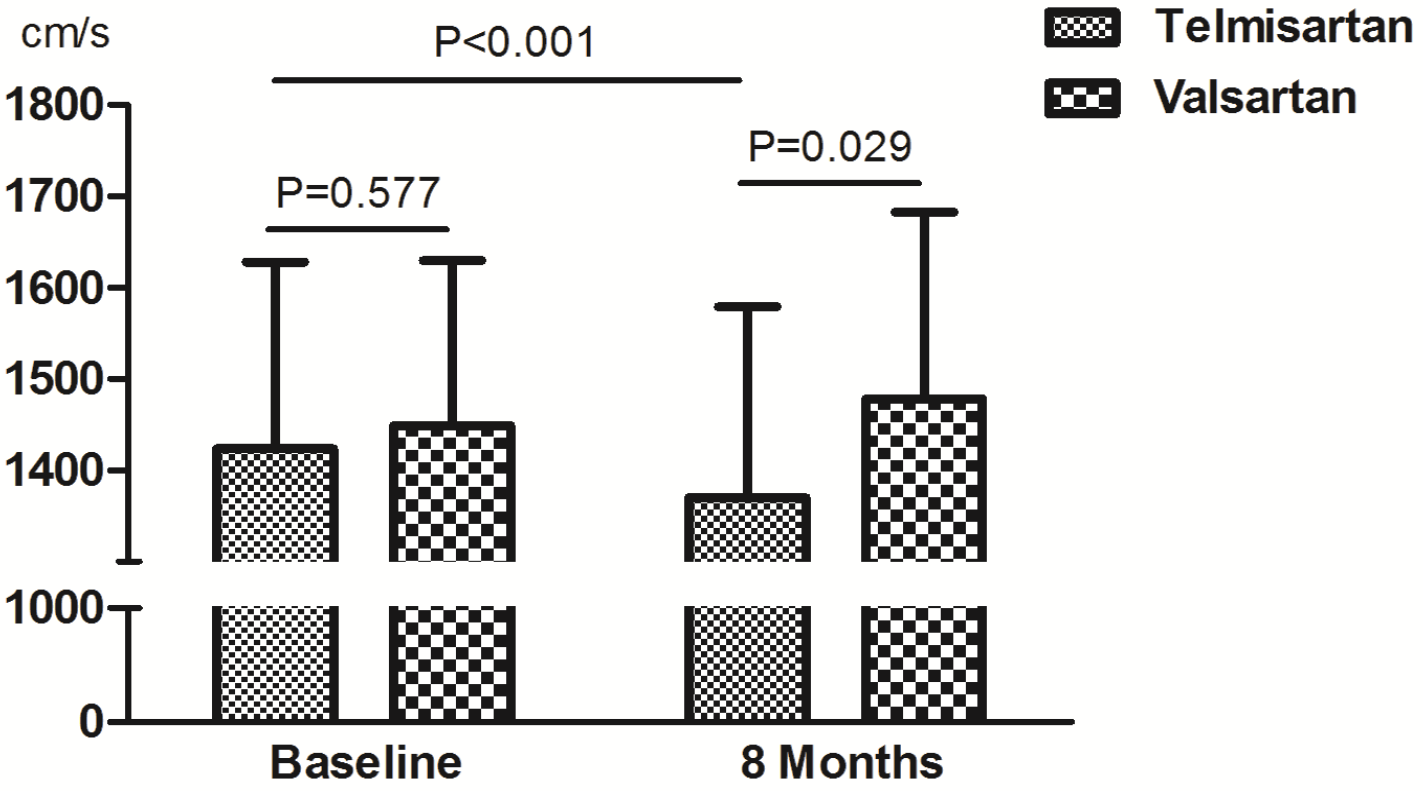
Eight-month follow-up IVUS outcomes



NA: not available.
All volumes are given in mm^3/1mm stented segment.
* $p < 0.05$ versus valsartan,
† $p < 0.05$ versus baseline.

Variable	Telmisartan Group (n=29)		Valsartan Group (n=30)	
	Baseline	8-month	Baseline	8-month
Total vessel volume	14.1 ± 4.2	14.2 ± 4.5	13.9 ± 4.5	14.0 ± 4.8
Total plaque volume	7.7 ± 2.7	10.2 ± 3.9†	7.8 ± 2.9	10.6 ± 3.6†
Stent volume	6.4 ± 1.6	6.3 ± 1.5	6.1 ± 1.9	6.0 ± 1.7
Lumen volume	6.4 ± 1.6	4.0 ± 1.5*†	6.1 ± 1.9	3.4 ± 1.8†
Neointima volume	NA	**1.9 ± 1.0***	NA	2.6 ± 1.4

The Mean PWVs between the 2 Groups



Changes in Blood Sugar

	Telmisartan Group (n=36)		Valsartan Group (n=37)	
	Baseline	**8-month f/u**	**Baseline**	**8-month f/u**
Fasting insulin (μU/mL)**	12.5 ± 4.5	9.4 ± 3.7*	13.3 ± 5.7	10.7 ± 6.1*
Changes from baseline (μU/mL)	-3.1 ± 3.9		-2.7 ± 3.1	
Fasting glucose (mg/dL)**	145.1 ± 49.7	115.7 ± 28.1*	139.0 ± 49.5	112.7 ± 28.9*
Changes from baseline (mg/dL)	-32.2 ± 46.6		-28.0 ± 66.1	
HOMA index**	4.5 ± 4.7	2.7 ± 2.7*	4.6 ± 4.6	2.9 ± 2.7*
Changes from baseline (%)	-1.8 ± 2.4		-1.7 ± 2.1	
HbA_{1c} (%)**	7.3 ± 1.4	6.8 ± 0.8*	7.2 ± 1.6	6.8 ± 0.9*
Changes from baseline (%)	-0.6 ± 1.0		-0.5 ± 0.6	

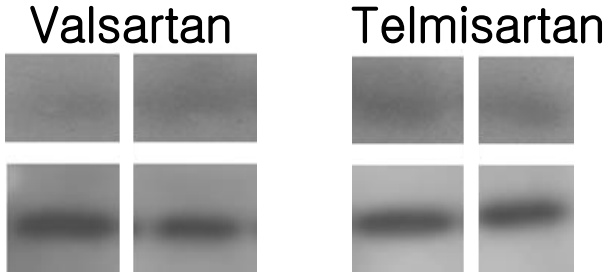
Changes in Lipid Profiles

	Telmisartan Group (n=36)		Valsartan Group (n=37)	
	Baseline	**8-month f/u**	**Baseline**	**8-month f/u**
Total cholesterol (mg/dL)	189.6 ± 67.1	135.5 ± 39.5*	185.9 ± 42.9	134.3 ± 55.3*
Changes from baseline (mg/dL)	-55.3 ± 35.5		-52.4 ± 47.3	
LDL-cholesterol (mg/dL)	122.3 ± 39.0	77.0 ± 44.5*	121.3 ± 50.5	81.9 ± 41.2*
Changes from baseline (mg/dL)	-45.4 ± 39.3		-42.5 ± 38.3	
HDL-cholesterol (mg/dL)	43.4 ± 10.3	44.6 ± 12.4	42.5 ± 8.5	43.9 ± 16.4
Changes from baseline (mg/dL)	2.3 ± 8.2		1.6 ± 12.2	
Triglyceride (mg/dL)**	138.5 ± 53.9	114.7 ± 44.5*	144.8 ± 67.0	122.0 ± 77.4
Changes from baseline (mg/dL)	-26.0 ± 64.0		-18.0 ± 65.0	

Changes in Inflammatory Markers

	Telmisartan Group (n=36)		Valsartan Group (n=37)	
	Baseline	**8-month f/u**	**Baseline**	**8-month f/u**
IL-6 (pg/ml)**	1.4 ± 1.1	1.0 ± 0.6*†	1.3 ± 0.7	1.4 ± 1.2
Changes from baseline (pg/ml)	-0.4 ± 1.0†		0.1 ± 0.9	
TNF-α (pg/ml)**	14.5 ± 3.4	11.2 ± 4.5*†	13.5 ± 4.5	13.1 ± 4.9
Changes from baseline (pg/ml)	-3.2 ± 4.3†		-0.4 ± 1.4	
hsCRP (mg/L)**	3.1 ± 2.8	1.6 ± 2.7*	2.9 ± 3.1	1.4 ± 1.7*
Changes from baseline (mg/L)	-1.6 ± 3.0		-1.5 ± 2.9	
Adiponectin (μg/ml)**	6.1 ± 6.6	7.9 ± 5.9*†	6.2 ± 4.7	6.5 ± 5.3
Changes from baseline (μg/ml)	1.8 ± 2.5†		0.3 ± 2.5	
RBP-4 (μg/ml)**	65.5 ± 19.7	52.7 ± 19.7*	63.8 ± 23.5	51.3 ± 18.4*
Changes from baseline (μg/ml)	-12.8 ± 5.0		-12.5 ± 5.8	

- **Western blot for PPAR-gamm activity- Monocytes**



Summary

- Telmisartan reduced the levels of inflammatory markers when compared to Valsartan.

- Telmisartan treatment reduced PWV, neointima volume, and atherosclerosis progression 10mm proximal and distal to the stented segment independent of blood pressure, glucose, and lipid control during the 8 months follow-up.

Conclusions

- **Hypertensive type 2 diabetic patients** treated with telmisartan not only benefit from its antihypertensive effects but also from its **anti-inflammatory and anti-atherogenic effects**.

- PPAR-γ activation by telmisartan may provide new therapeutic options in the management of hypertensive type 2 diabetic patients with severe coronary artery disease requiring stent implantation.

Study plan for PPAR-γ effect on coronary artery disease

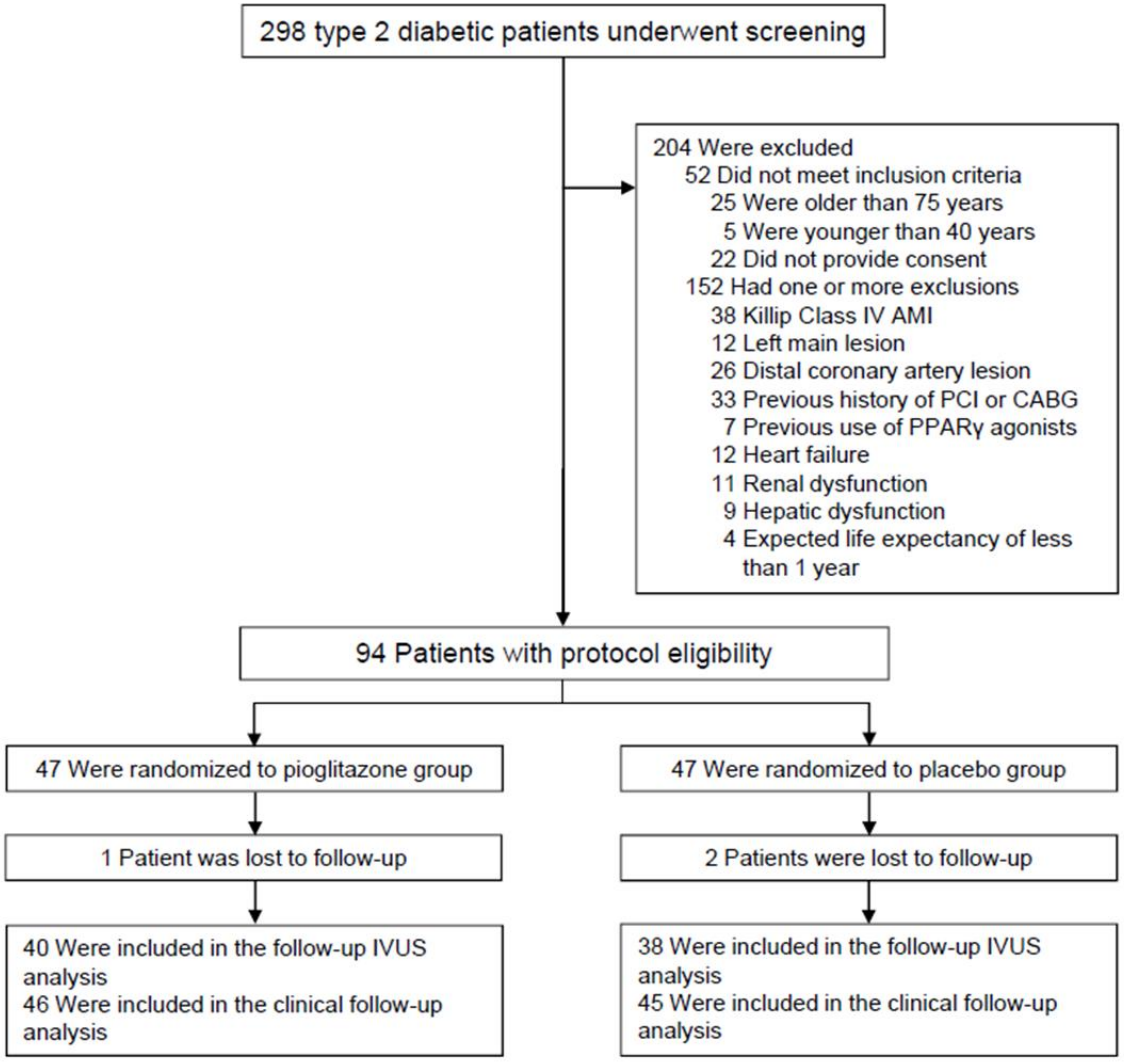
- PPAR-γ activity affects neotimal growth after DES implantation in hypertensive, non-diabetic patients

- PPAR-γ activity reduces neintimal volume and pulse wave velocity after DES implantation in hypertensive, type 2 diabetic patients

- PPAR-γ agonist(Pioglitazone)affects atherosclerosis and neointimal growth in diabetic patients after DES implantation

- Cellular and molecular mechanism of PPAR-γ agonist(Pioglitazone) on inhibitory effects on neintimal growth in type 2 diabetic patients with coronary artery disease

PPAR-γ agonist(Pioglitazone)affects atherosclerosis and neointimal growth in diabetic patients after DES implantation



Patient Characteristics

	Pioglitazone Group (n=47)	Placebo Group (n=47)	*p* value
Age (years)	63.5 ± 7.4	62.4 ± 8.3	0.761
Men	32 (68.1 %)	29 (61.7 %)	0.517
Body mass index (kg/m2)	23.4 ± 2.4	23.2 ± 4.3	0.939
Systolic blood pressure (mmHg)	140 ± 13	143 ± 12	0.415
Diastolic blood pressure (mmHg)	85 ± 6	87 ± 7	0.344
Risk factors			
Hypertension	24 (51.1 %)	21 (44.7 %)	0.536
Dyslipidemia	14 (29.8 %)	16 (34.0 %)	0.658
Current smoker	10 (21.3 %)	12 (25.5 %)	0.626
Left ventricular ejection fraction (%)	52 ± 7	54 ± 8	0.702
Unstable angina pectoris	12 (25.5 %)	15 (31.9 %)	0.494
Diabetes treatment			
Diet only	6 (12.8 %)	9 (19.1 %)	0.398
Oral glucose-lowering therapy	40 (85.1 %)	37 (78.8 %)	0.421
Insulin	3 (6.4 %)	2 (4.3 %)	1.000
Other diabetic medications after randomization			
Biguanides	8 (17.0 %)	11 (23.4 %)	0.441
α-Glucosidase inhibitors	10 (21.3 %)	12 (25.5 %)	0.626
Sulfonylureas	36 (76.7 %)	31 (66.0 %)	0.254

Patient Characteristics

	Pioglitazone Group (n=47)	Placebo Group (n=47)	*p* value
Other medications after stenting			
Aspirin	47 (100.0 %)	47 (100.0 %)	1.000
Clopidogrel	47 (100.0 %)	47 (100.0 %)	1.000
Atorvastatin	43 (91.5 %)	44 (93.6 %)	0.694
Angiotensin receptor blockers	16 (34.0 %)	14 (29.8 %)	0.658
Angiotensin converting enzyme inhibitors	8 (17.0 %)	11 (23.4 %)	0.441
Beta blockers	2 (4.3 %)	1 (2.1 %)	1.000
Calcium channel blockers	9 (19.1 %)	8 (17.0 %)	0.789
Diuretics	3 (6.4 %)	4 (8.5 %)	1.000

Angiographic Measurements

Variable	Pioglitazone Group (n=47)	Placebo Group (n=47)	p Value
Number of lesions stented	57	61	
Target coronary artery			
Left anterior descending artery	29 (61.7 %)	32 (68.1 %)	0.517
Left circumflex artery	10 (21.3 %)	8 (17.0 %)	0.600
Right	8 (17.0 %)	7 (14.9 %)	0.778
Type of lesion (%)			
A	3 (6.4 %)	2 (4.3 %)	1.000
B1	10 (21.3 %)	11 (23.4 %)	0.804
B2	22 (46.8 %)	25 (53.2 %)	0.536
C	12 (25.5 %)	9 (19.1 %)	0.458
Eccentric (%)	27 (57.4 %)	31 (66.0 %)	0.396
Baseline			
Reference diameter (mm)	2.71 ± 0.30	2.83 ± 0.33	0.767
Minimal lumen diameter (mm)	0.74 ± 0.22	0.62 ± 0.31	0.865
Percentage of stenosis	74 ± 7	79 ± 9	0.106
Postprocedure			
Reference diameter (mm)	2.91 ± 0.42	2.92 ± 0.31	0.320
Minimal lumen diameter (mm)	2.70 ± 0.43	2.73 ± 0.30	0.554
Percentage of stenosis	8 ± 3	8 ± 2	0.206
Acute gain (mm)	2.0 ± 0.3	2.1 ± 0.3	0.361
Number of stents, range	1.2 ± 0.4 (1-2)	1.3 ± 0.5 (1-2)	0.349

Angiographic Measurements

	Pioglitazone Group (n=47)	Placebo Group (n=47)	*p* value
Mean stent length (mm)	24.8 ± 6.9	26.1 ± 6.1	0.669
Mean stent diameter (mm)	2.90 ± 0.44	2.84 ± 0.31	0.158
Eight-month follow-up			
Reference diameter (mm)	2.91 ± 0.35	2.93 ± 0.32	0.766
Minimal lumen diameter (mm)	2.30 ± 0.41	2.09 ± 0.53	0.003
Percentage of stenosis	20 ± 14	28 ± 17	0.020
Late lumen loss (mm)	0.41 ± 0.40	0.65 ± 0.54	0.037
Binary restenosis	6 (15.0 %)	8 (21.1 %)	0.486

Eight-Month Follow-Up IVUS Outcomes for Stented Segment

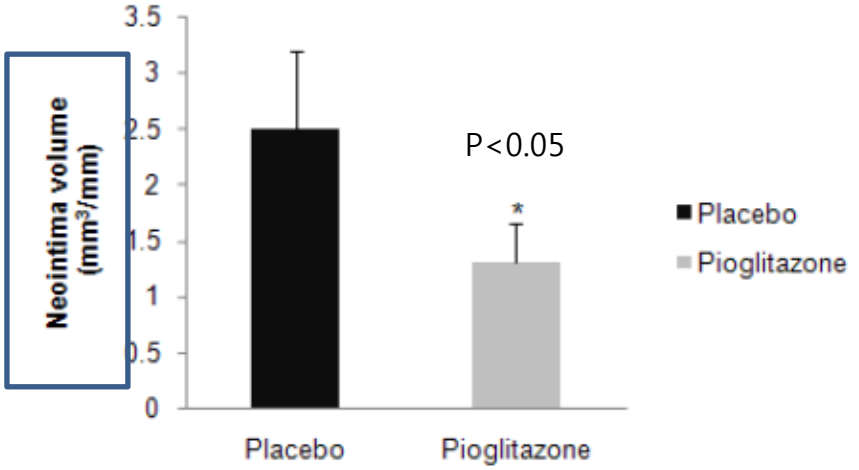
Variable	Pioglitazone Group (n=47)		Placebo Group (n=47)	
	Baseline	8-month	Baseline	8-month
Total vessel volume	14.5 ± 3.9*	14.3 ± 3.2*	15.5 ± 4.9	15.3 ± 3.9
Total plaque volume	7.9 ± 2.5	9.1 ± 2.8†*	8.3 ± 3.4	10.7 ± 2.6†
Stent volume	6.6 ± 1.8*	6.5 ± 1.5*	7.2 ± 2.3	7.1 ± 1.7
Lumen volume	6.6 ± 1.8*	5.3 ± 1.6†*	7.2 ± 2.3	4.6 ± 1.8†
Neointima volume	NA	1.3 ± 0.7*	NA	2.5 ± 1.4

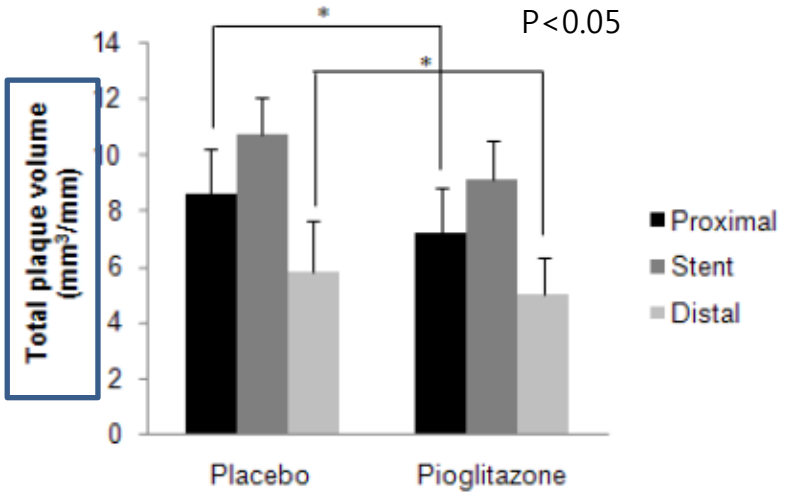
NA: not available

All volumes are given in $mm^3/1mm$ stented segment.

*p < 0.05 versus placebo, † p < 0.05 versus baseline

The Pioglitazone Group showed a significantly lower neointima volume when compared to the Placebo Group at 8 months





Levels of inflammation, insulin resistance, lipid profile

	Pioglitazone Group (n=47)		Placebo Group (n=47)	
	Baseline	8-month follow-up	Baseline	8-month follow-up
HOMA index	4.6 ± 2.4	2.4 ± 1.7*†	4.5 ± 2.6	2.9 ± 2.0*
Changes from baseline (%)	-2.2 ± 1.6†		-1.5 ± 1.1	
HbA1c (%)	7.3 ± 1.3	6.8 ± 0.8*	7.1 ± 1.6	6.7 ± 0.8*
Changes from baseline (%)	-0.6 ± 1.0		-0.5 ± 0.6	
Total cholesterol (mg/dL)	186.5 ± 37.1	152.3 ± 32.5*	185.8 ± 40.9	155.3 ± 27.3*
Changes from baseline (mg/dL)	-33.5 ± 37.2		-30.5 ± 40.1	
LDL-cholesterol (mg/dL)	120.1 ± 35.0	87.5 ± 24.3*	119.3 ± 30.4	87.9 ± 31.2*
Changes from baseline (mg/dL)	-32.5 ± 29.8		-31.5 ± 31.3	
HDL-cholesterol (mg/dL)	42.1 ± 10.3	43.4 ± 11.1	44.7 ± 9.2	45.2 ± 13.4
Changes from baseline (mg/dL)	2.3 ± 7.8		1.3 ± 12.2	
Triglyceride (mg/dL)	136.5 ± 50.9	112.7 ± 44.5	141.8 ± 62.0	121.0 ± 47.4
Changes from baseline (mg/dL)	-24.0 ± 44.9		-20.0 ± 68.0	

* $p < 0.05$ compared with baseline. † $p < 0.05$ compared with placebo group.

Study plan for PPAR-γ effect on coronary artery disease

- PPAR-γ activity affects neotimal growth after DES implantation in hypertensive, non-diabetic patients
- PPAR-γ activity reduces neintimal volume and pulse wave velocity after DES implantation in hypertensive, type 2 diabetic patients
- PPAR-γ agonist(Pioglitazone)affects atherosclerosis and neointimal growth in diabetic patients after DES implantation
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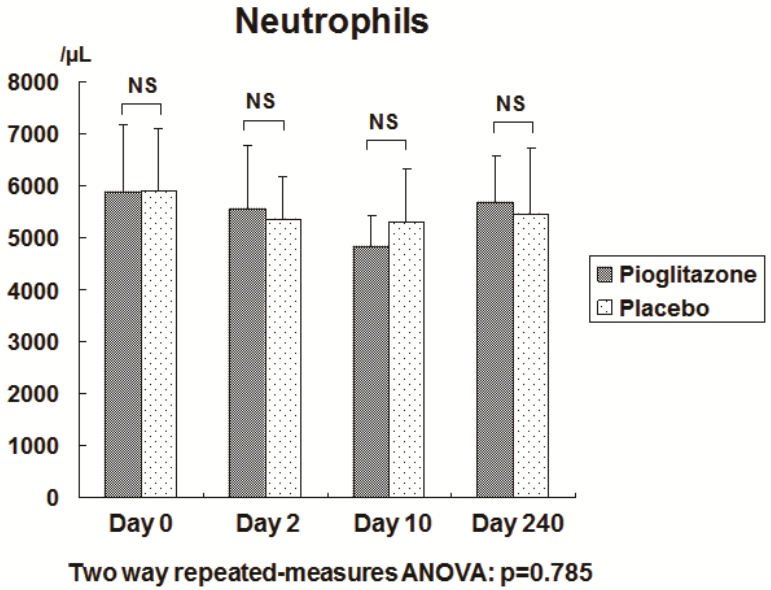
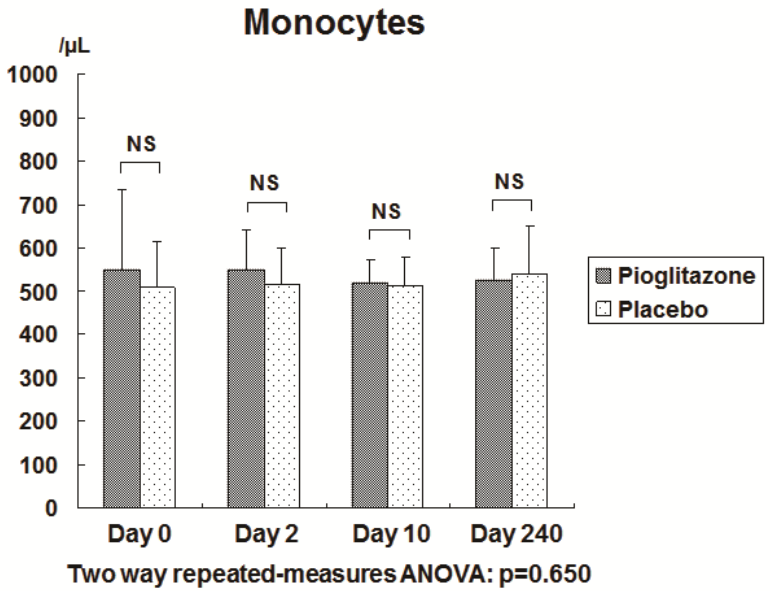
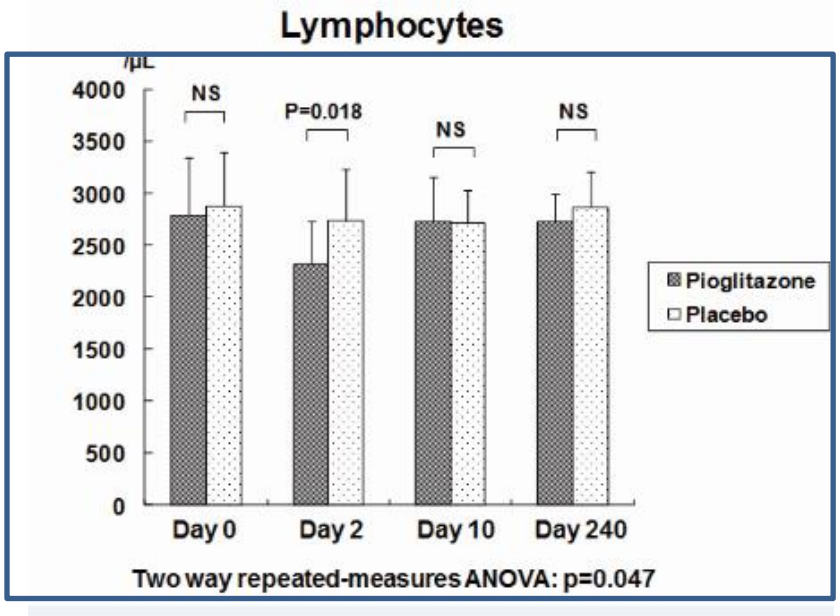
Peripheral Blood Mononuclear Cell





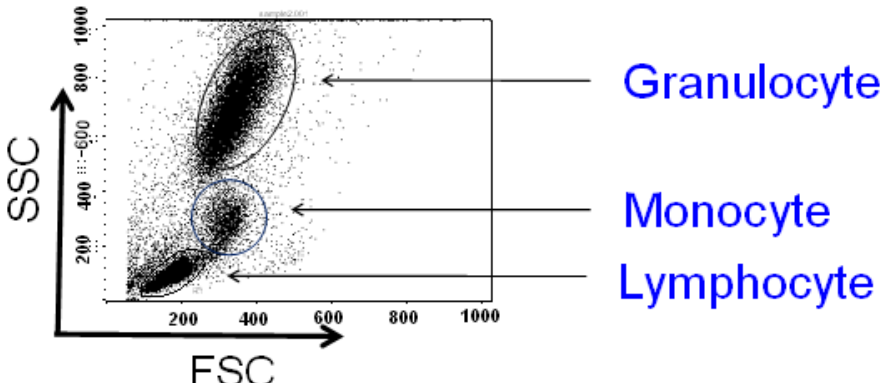


- Serial blood samples from patients
- Primary cell culture of smooth muscle cell

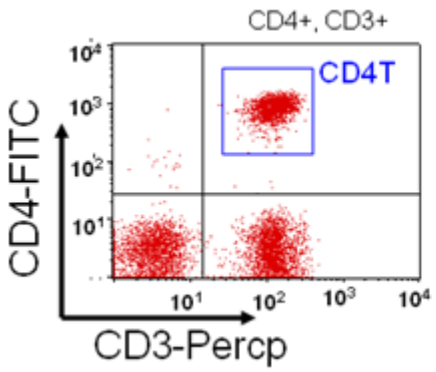
Absolute number of total lymphocytes showed significant decreases 2 days after stenting in the Pioglitazone Group

ATVB 2010

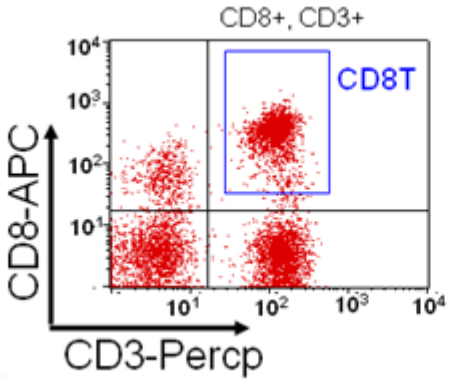
Lymphocyte subpopulation gating by flow cytometry



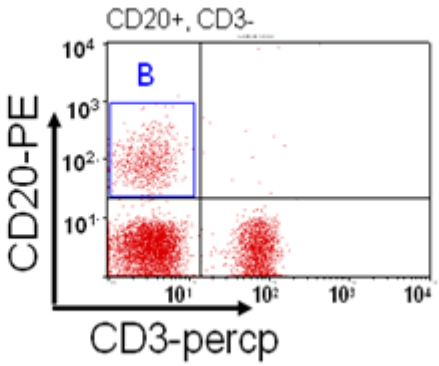
$CD3^+$ $CD4^+$ T cells



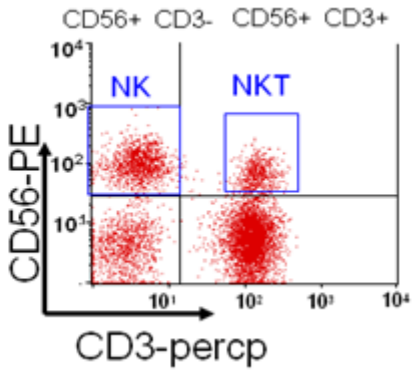
$CD3^+CD8^+$ T cells

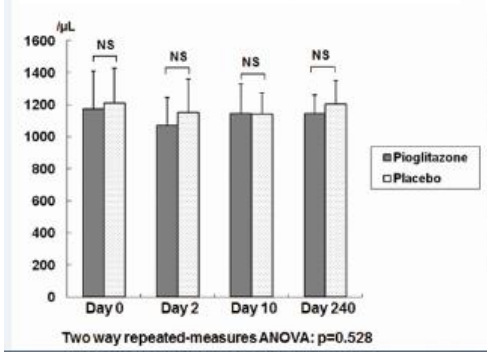


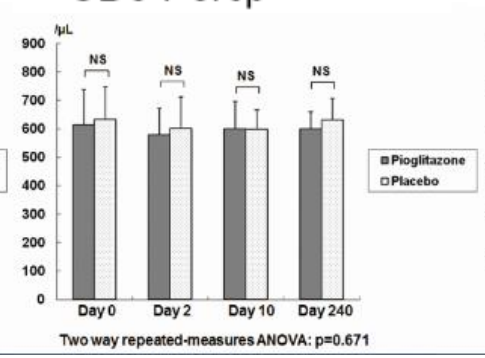
$CD3^-$ $CD20^+$ B cells

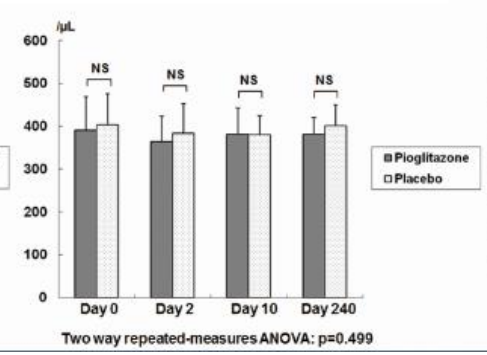


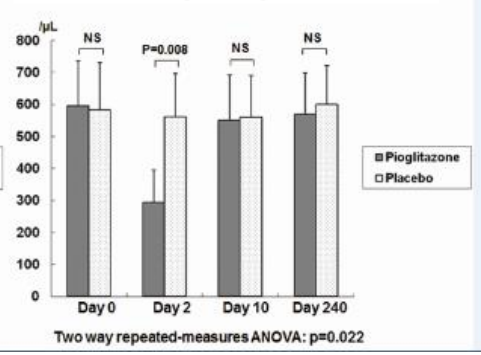
$CD3^-$ $CD56^+$ NK cells





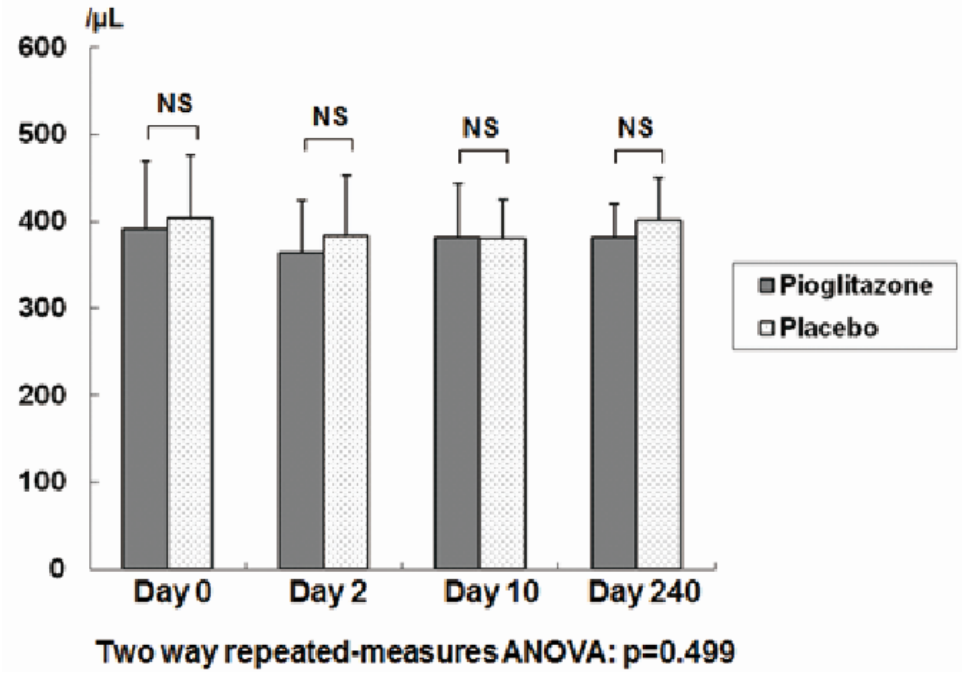






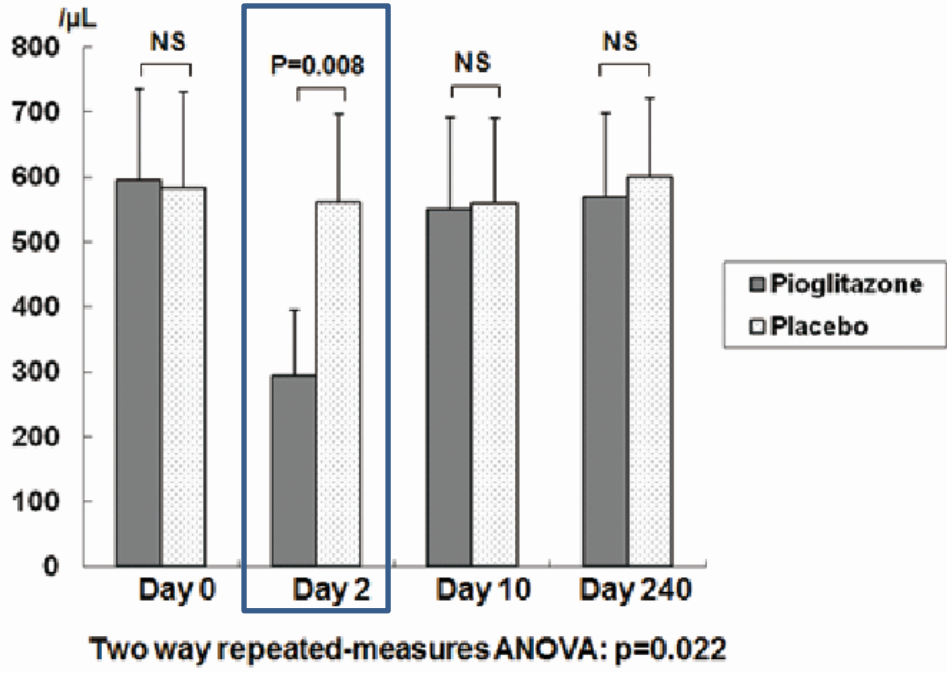
Level of lymphocyte population (B, NK cell)

B cells (CD20+.CD3-)



Two way repeated-measures ANOVA: p=0.499

NK cells (CD56+.CD3-)



Two way repeated-measures ANOVA: p=0.022

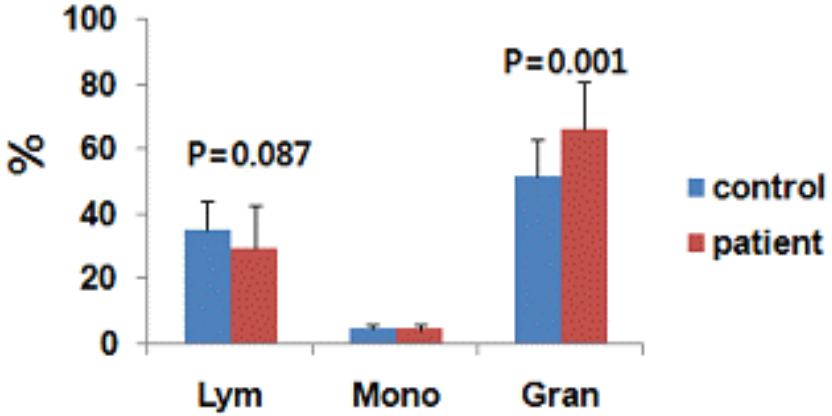
The decreased NK cells in peripheral blood is related to the decreased early stage immune responses

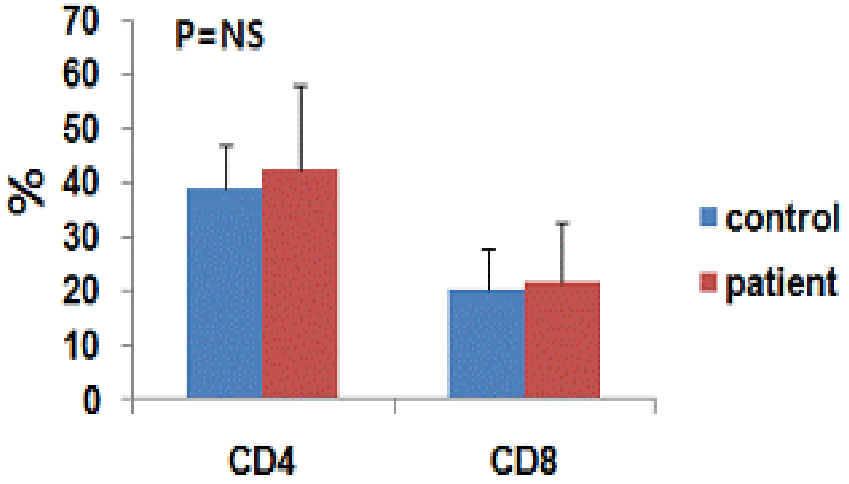
In vivo Expression of cellular immune reaction in progression of atherosclerotic change

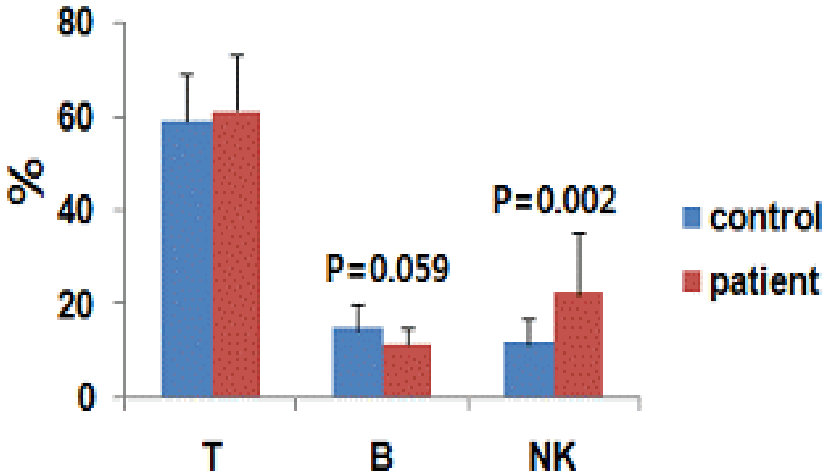
- Carotid endarterectomy (CEA) patients
  History of recent CVA or recurrent TIA
- Immune monitoring (phenotypes)
- Inflammatory marker

1. Control, N=25
2. CEA patients, N=24

Cellular composition of whole blood and immune cell







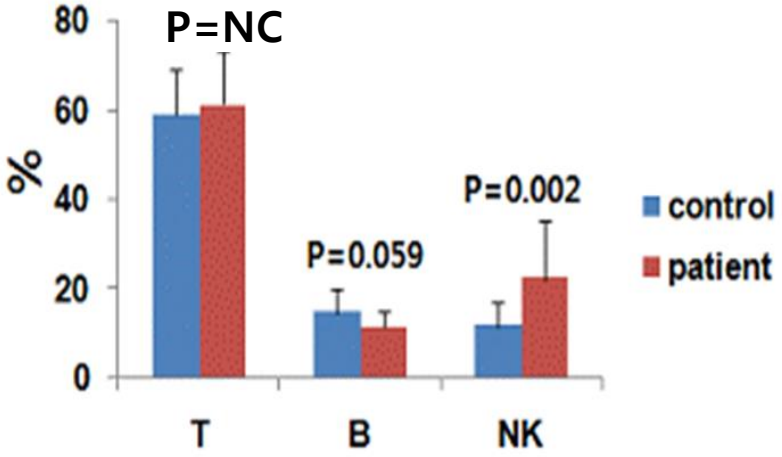
- Granulocyte(Neutrophil) was increased in patients with atherosclerosis
- Lymphocyte proportion was slightly decreased compared to control group

(*p<0.05, **p<0.001)

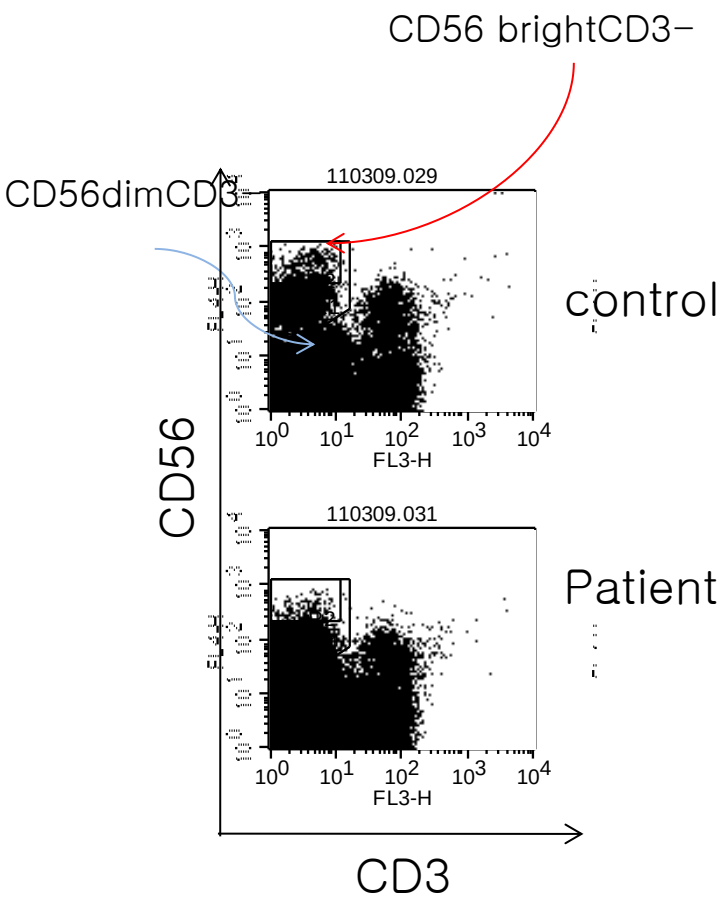
NK activity in atherosclerosis & inflammation

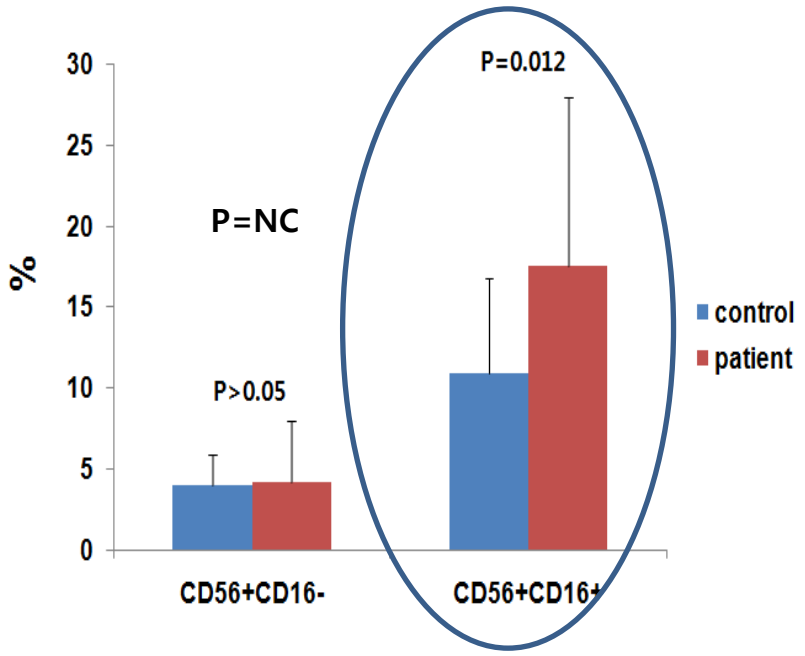
- Carotid endarterectomy patients
- Immune monitoring (phenotypes)

1. Control, N=25
2. CEA, N=24



NK subsets	Cytotoxicity	Perforin/ Granzyme	Cytokine production
$CD56^{bright}CD16-$	+	+	+++
$CD56^{dim}CD16+$	++	+++	+





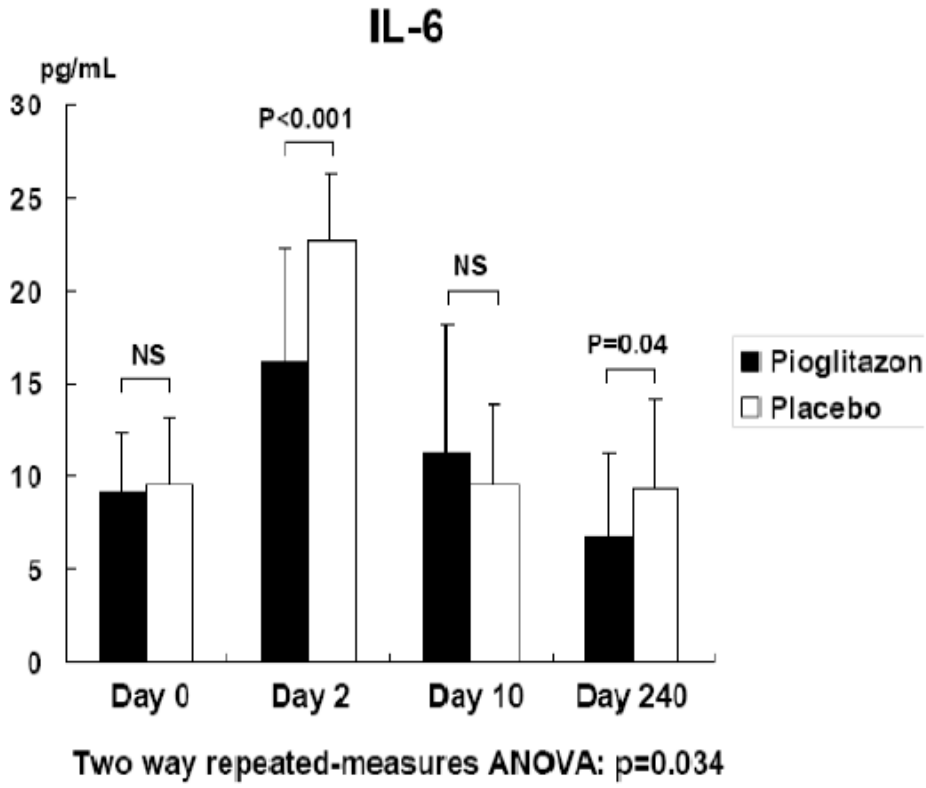
- NK fraction was increased in patients with atherosclerosis
- CD56dimCD16+subgroup was prevalent in CEA patients compared to control
- **Cytotoxic function rather than cytokine production in NK activity affects atherosclerotic progression**

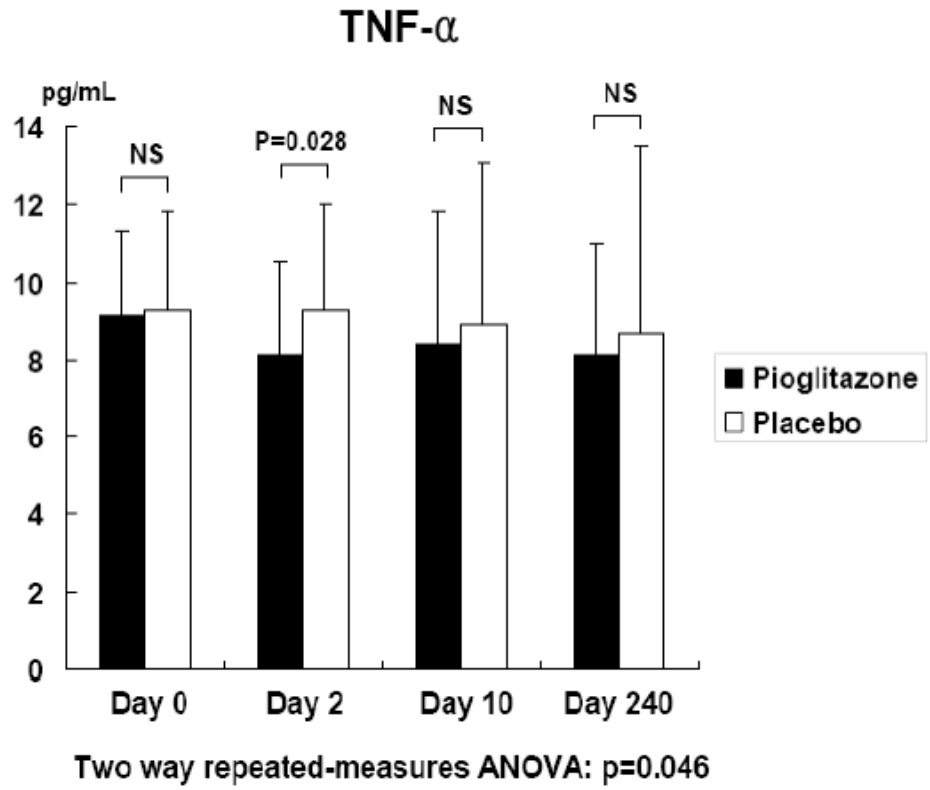
Levels of inflammation, insulin resistance, lipid profile

	Pioglitazone Group (n=47)		Placebo Group (n=47)	
	Baseline	8-month follow-up	Baseline	8-month follow-up
hsCRP (mg/L)	3.5 ± 2.2	1.8 ± 2.9*	2.8 ± 3.0	1.2 ± 1.4*
Changes from baseline (mg/L)	-1.8 ± 3.1		-1.5 ± 2.8	
Adiponectin (μg/ml)	5.7 ± 5.2	7.7 ± 3.9*†	6.0 ± 2.7	6.4 ± 3.3
Changes from baseline (μg/ml)	1.9 ± 2.7†		0.4 ± 2.0	
Fasting insulin (μU/mL)	12.8 ± 4.3	8.4 ± 1.7*†	13.4 ± 3.7	10.7 ± 3.1*
Changes from baseline (μU/mL)	-4.3 ± 2.2†		-2.8 ± 1.9	
Fasting glucose (mg/dL)	148.3 ± 46.7	113.8 ± 22.0*	135.0 ± 43.5	110.3 ± 25.9*
Changes from baseline (mg/dL)	-39.4 ± 56.5		-28.8 ± 46.1	

Adiponectin concentration increased significantly in the Pioglitazone

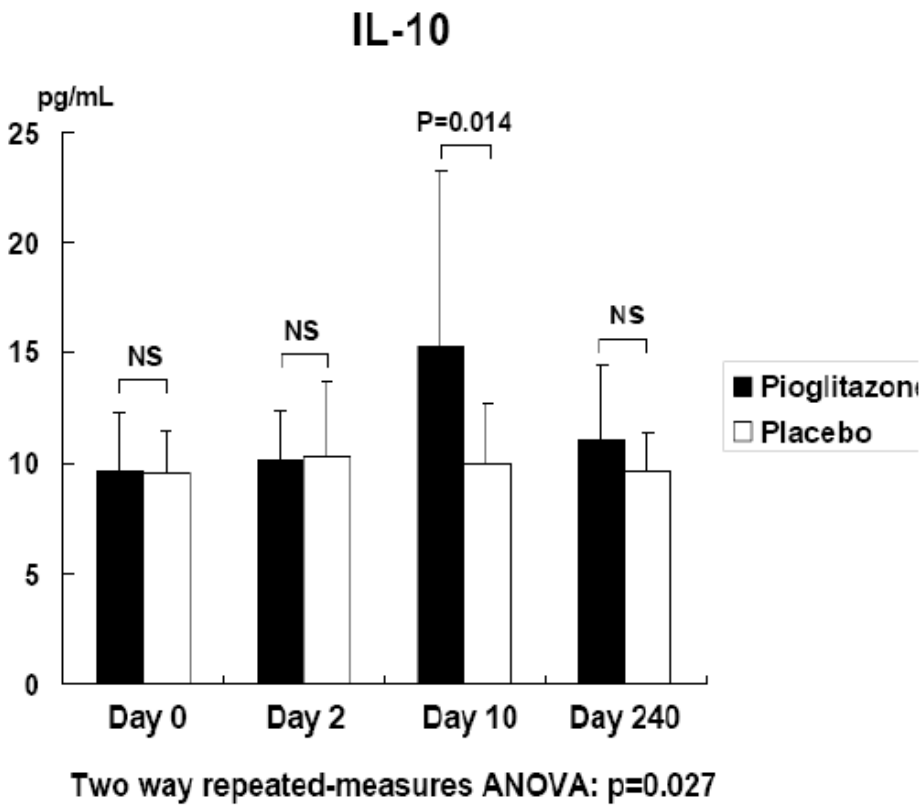
Level of inflammatory cytokines (IL-6, TNF-a)

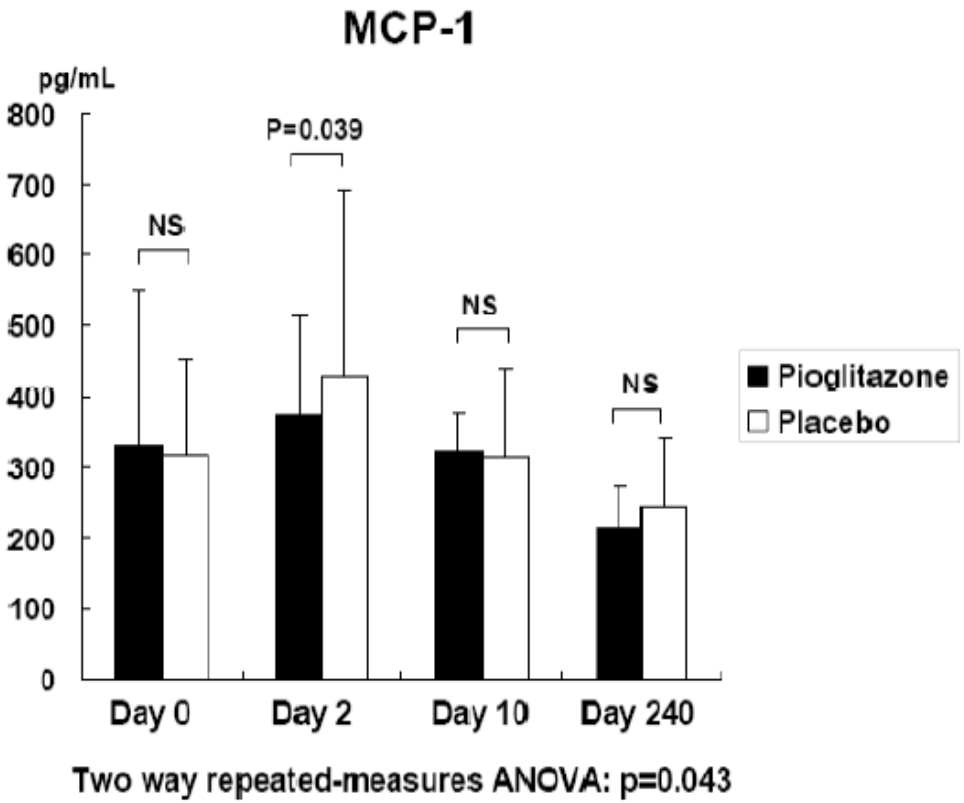




Decreased number of differentiated macrophages on the inflammatory site causes the reduction of IL-6, TNF-a secretion

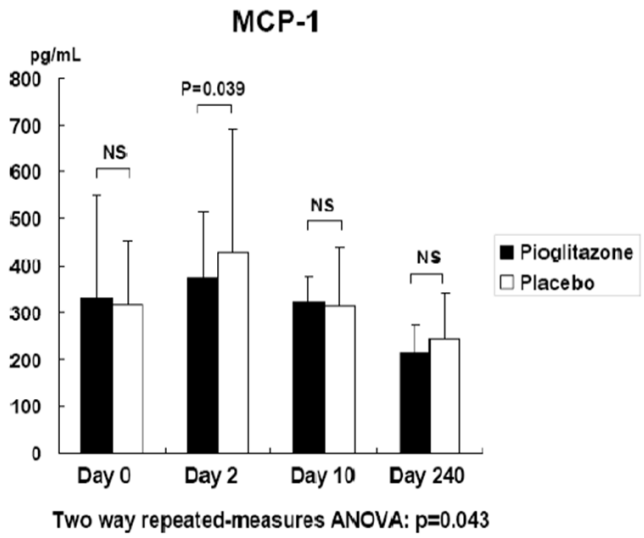
Level of inflammatory cytokines (IL-10, MCP-1)

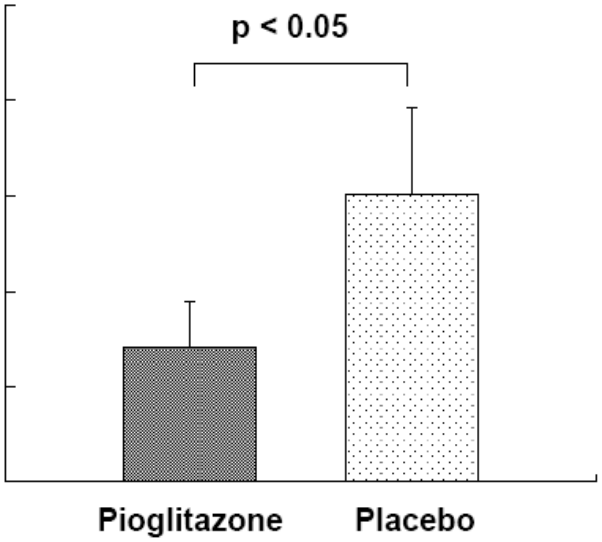


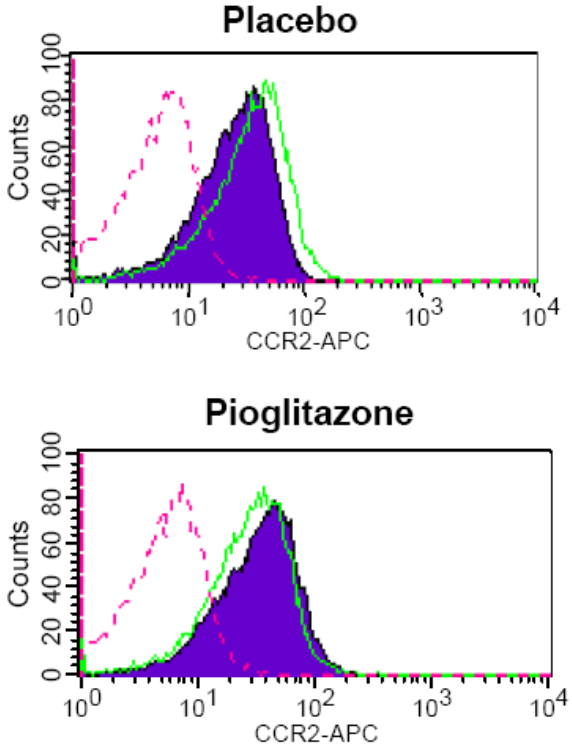


IL-10 showed a significant increase 10 days after stenting in the Pioglitazone Group

Level of CCR2 expression on CD14+ cells



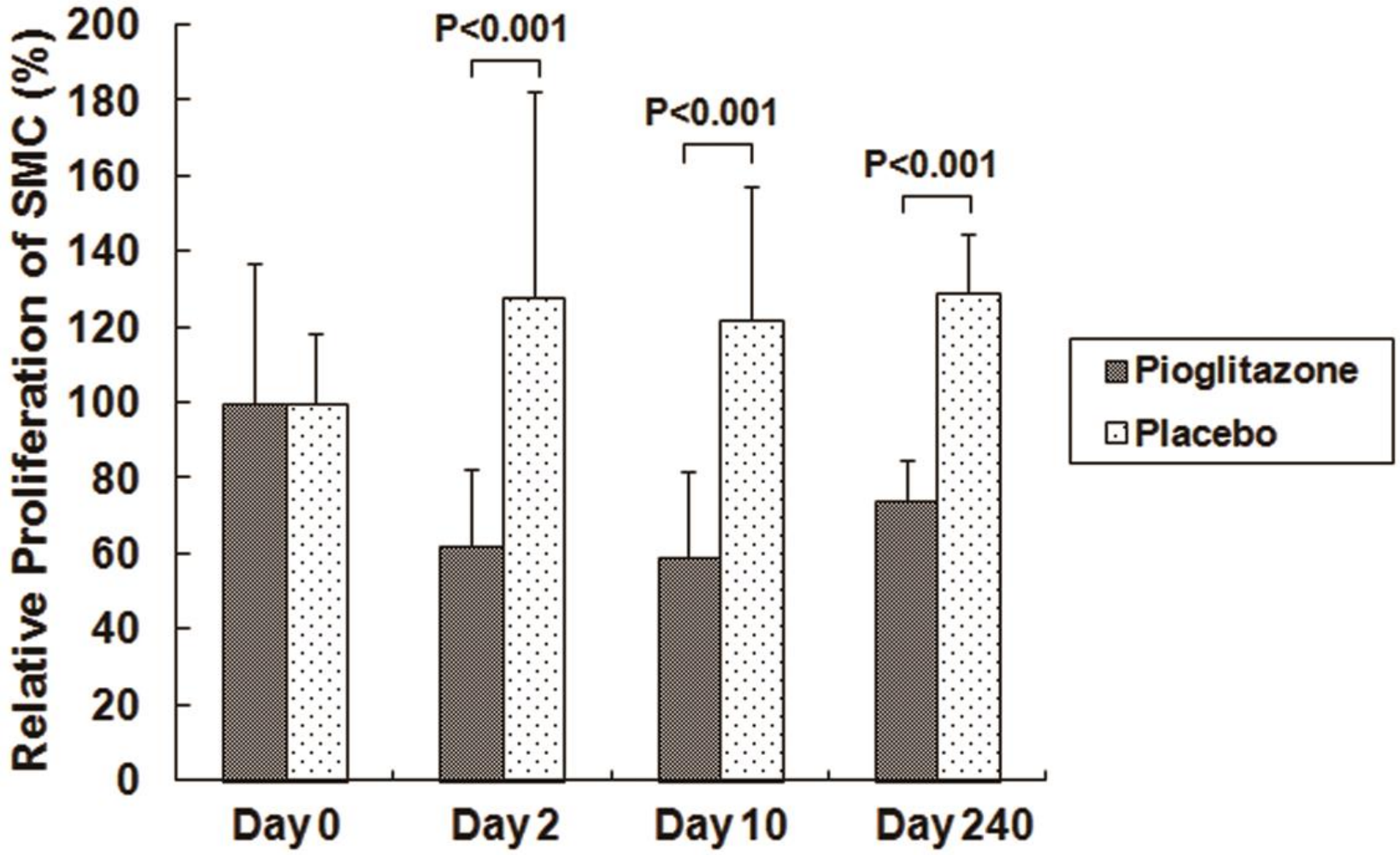




Decreased MCP-1 inhibits the monocyte infiltration from lumen into the stent lesion, that causes reduce the differentiation of monocytes into macrophages

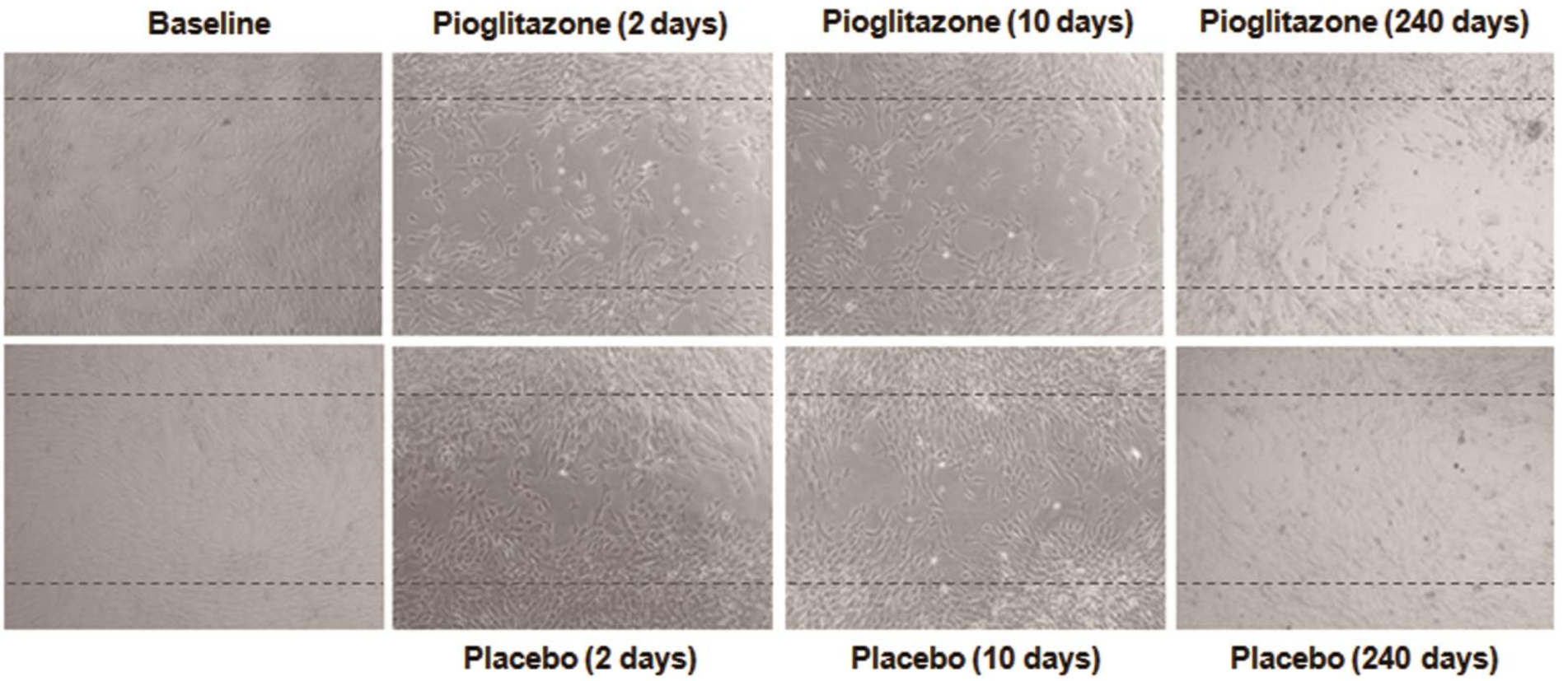
CCR2 expressions on CD14+ cells significantly reduced
2 days after stenting in the Pioglitazone Group

Inhibition of proliferation of smooth muscle cell (SMC)



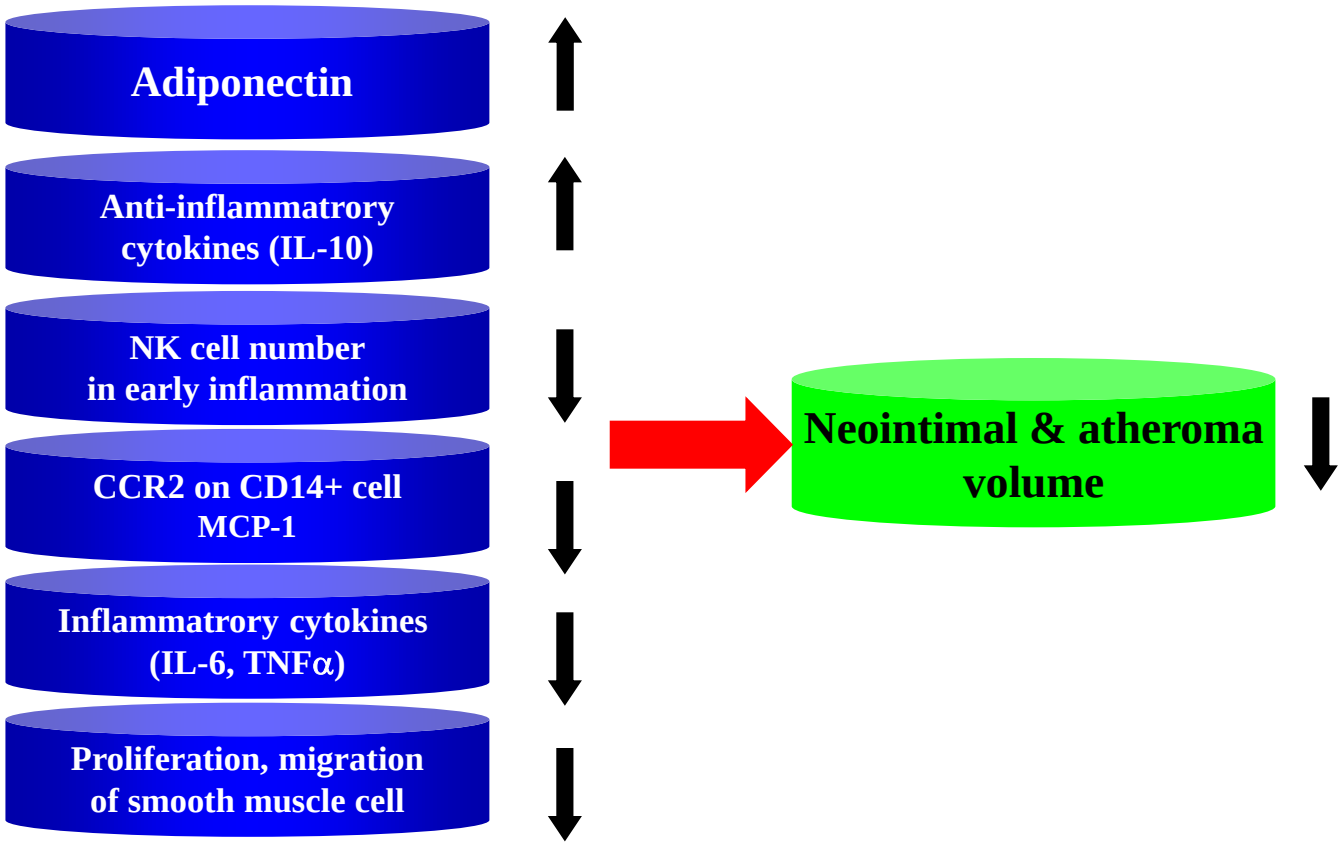
Plasma from Pioglitazone after 2, 10, 240 days inhibited human aortic SMC proliferation

Migration assay of smooth muscle cell



Plasma from Pio Group after 2 days and 10 days inhibited human aortic SMC migration, contributes to reducing neointimal growth after stenting

Summary



Pioglitazone-treated type2 DM patient with coronary atherosclerosis

Conclusion

- Pioglitazone treatment was associated with early decreases in NK cells, CCR2 expression on circulating CD14+ cells, and inflammatory cytokines and smooth muscle migration which contributed to the reduction in neointima volume and atherogenesis in type 2 diabetic patients with ZES implantation.

- PPAR-γ activation by pioglitazone may provide new therapeutic options in reducing not only neointima volume but also atheroma in type 2 diabetic patients with severe CAD requiring stent implantation.