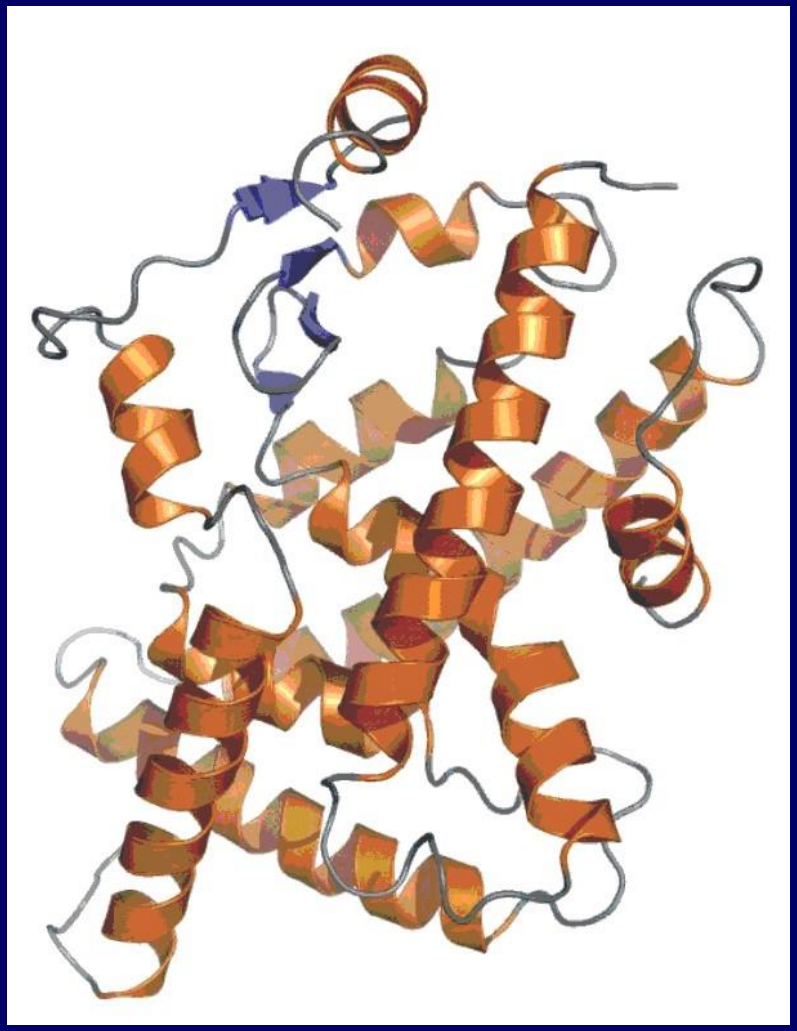
Effects of PPAR-γ Activators in Angiographic and Clinical Outcomes in Type 2 Diabetic Patients

Soon Jun Hong

Korea University Anam Hospital

Cardiovascular Center

Structure of PPAR-γ

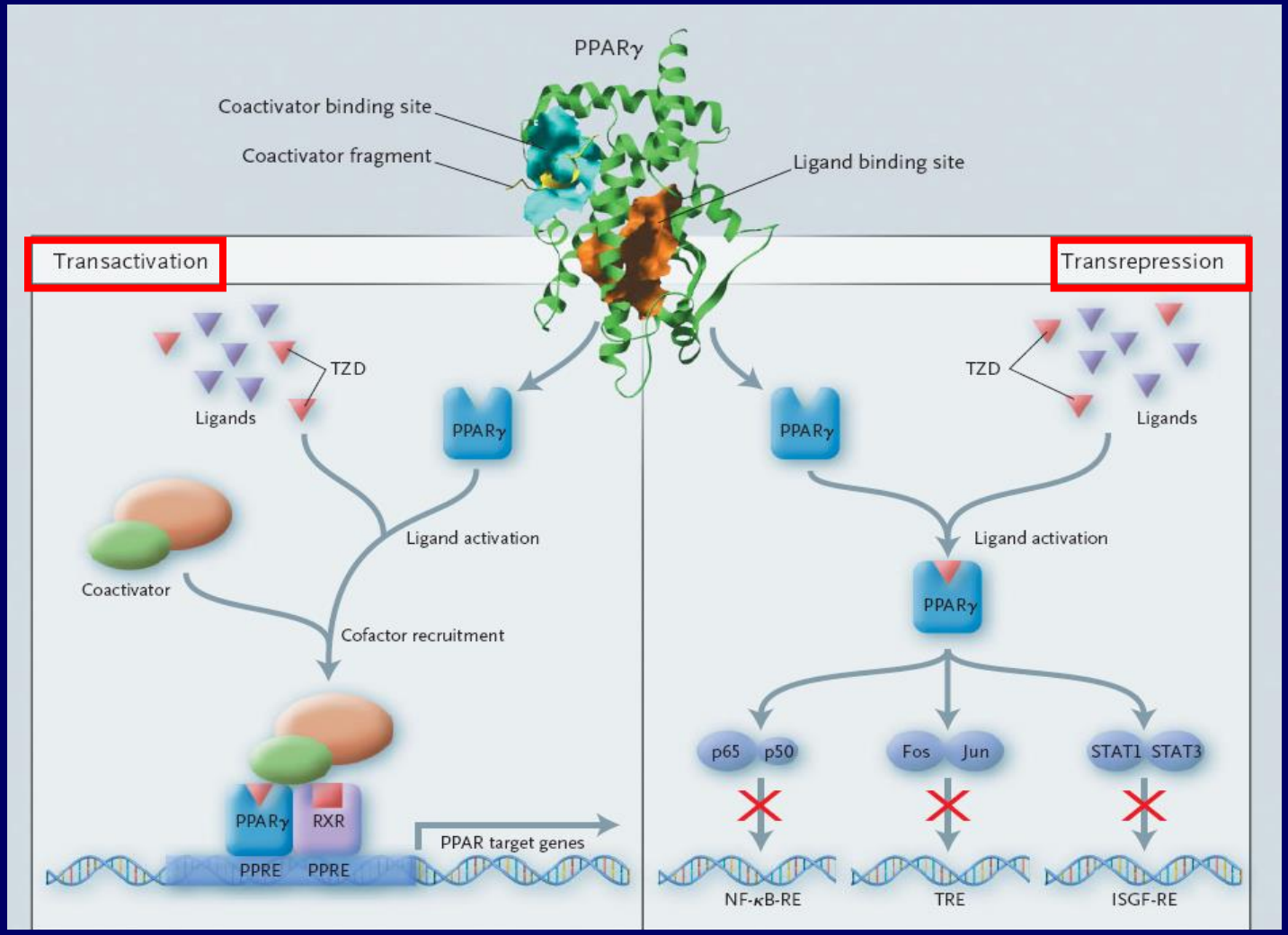


PPAR γ partial agonist:
Telmisartan

PPAR γ full agonist:
Rosiglitazone

PPAR γ and partial
PPAR α agonist:
Pioglitazone

PPAR-γ Regulate Gene Transcription



RXR: retinoid X receptor, PPRE: PPAR response elements
NF-kB RE: NF-kB response element, ISGF-RE: interferon-stimulated gene factor RE

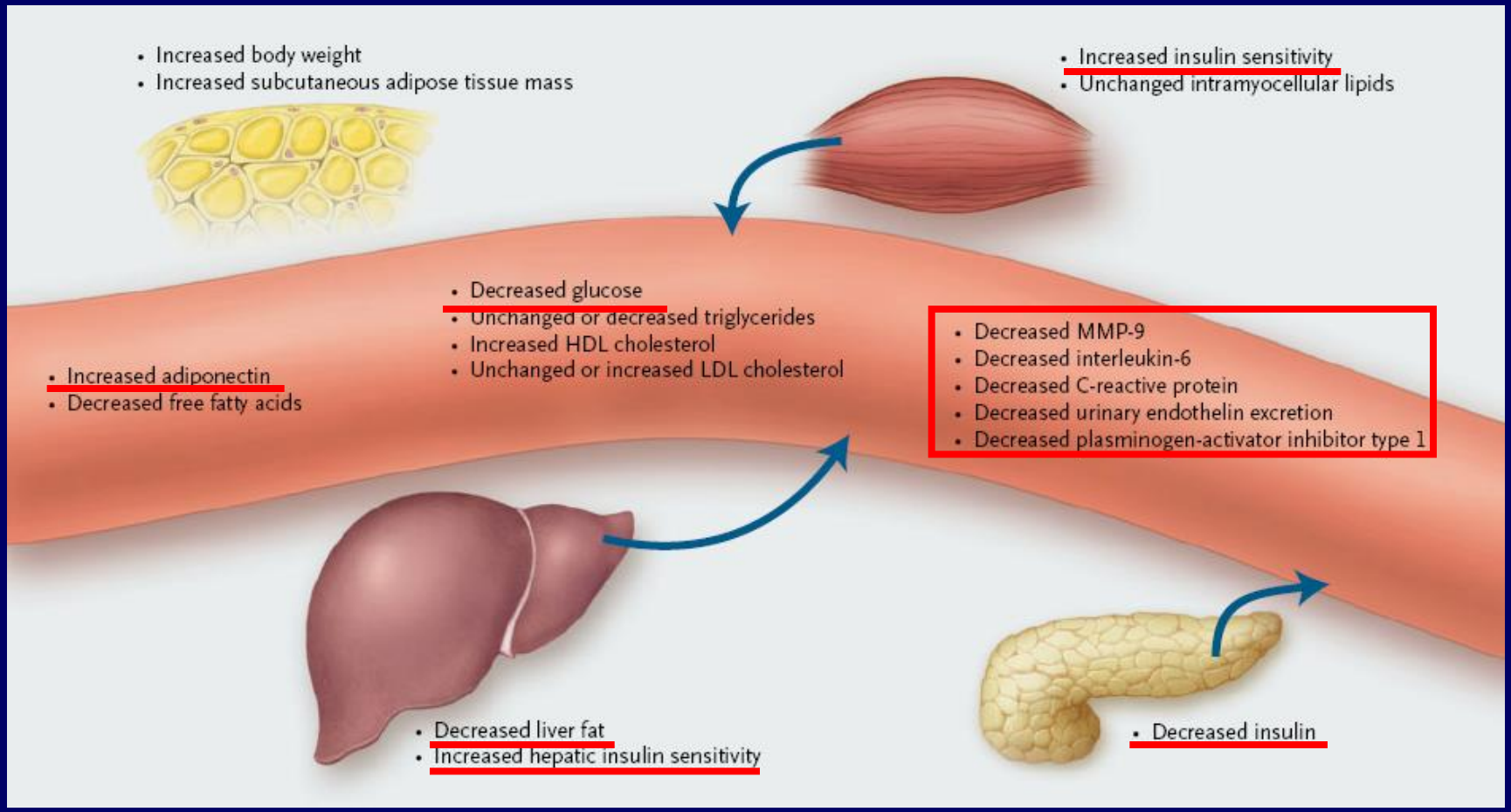
NEJM 2004;351:1106-18.

Effects of PPAR-γ on Markers of Cardiovascular Risk

- Body weight: 2~3 kg ↑ for every 1% ↓ in HbA1c
- Blood pressure: no effect on blood pressure
- Inflammatory markers: MMP-9 ↓, CRP ↓, IL-6 ↓
- Vascular function: improve FMD in type 2 DM, reduce carotid IMT

Circulation 2002;106:679-84.
ATBV 2003;23:283-8.

Mechanisms of Action of PPAR-γ Agonists



J Biol Chem 2002;277:48051-7.
NEJM 1999;341:410-8.

PPAR-γ

- Several different types of PPAR-γ agonists introduced in the market

  → Troglitazone (1997), Rosiglitazone (2000), Pioglitazone (2000)

- Troglitazone → withdrawn from the US market in 2000 due to its association with drug-induced hepatitis.
- What about Rosiglitazone ?

Annu Rev Biochem 2001;70:341-67.
Diabetologia 2000;43:1165-9.
Expert Opin Drug Saf 2008;7:367-76.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

Rates of MI and CV Death

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

43% ↑

64% ↑

NEJM 2007;356:2457-71.

Long-term Risk of Cardiovascular Events With Rosiglitazone

A Meta-analysis

Conclusion Among patients with impaired glucose tolerance or type 2 diabetes, rosiglitazone use for at least 12 months is associated with a significantly increased risk of myocardial infarction and heart failure, without a significantly increased risk of cardiovascular mortality.

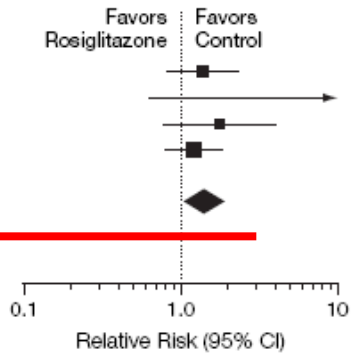
JAMA. 2007;298(10):1189-1195 September 12, 2007- www.jama.com

Sonal Singh et al. JAMA 2007;298:1189-95.

MI

Source	No. of Events/Total (%) Rosiglitazone	Control	Weight, %	Relative Risk (95% CI)
Kahn et al,[7] 2006	24/1456 (1.8)	34/2895 (1.2)	31.52	1.40 (0.84-2.36)
Dargie et al,[19] 2007	5/110 (4.5)	0/114 (0)	0.68	11.40 (0.64-203.69)
Gerstein et al,[5] 2006	16/2635 (0.6)	9/2634 (0.3)	12.47	1.78 (0.79-4.01)
Home et al,[12] 2007	49/2220 (2.2)	40/2227 (1.8)	55.33	1.23 (0.81-1.86)
Total (95% CI)	6421	7870	100.00	1.42 (1.06-1.91)

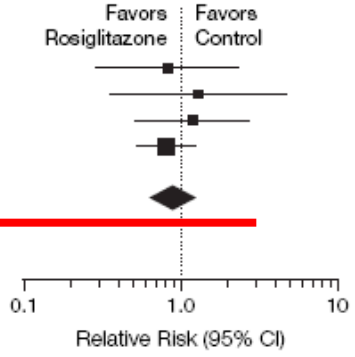
Total events: 94 (rosiglitazone), 83 (control)
Test for heterogeneity: $\chi^2_3 = 2.77$ ($P = .43$), $I^2 = 0\%$
Tests for overall effect: $Z = 2.33$ ($P = .02$)



CV Death

Source	No. of Events/Total (%) Rosiglitazone	Control	Weight, %	Relative Risk (95% CI)
Kahn et al,[7] 2006	5/1456 (0.3)	12/2895 (0.4)	11.83	0.83 (0.29-2.35)
Dargie et al,[19] 2007	5/110 (4.5)	4/114 (3.6)	5.79	1.30 (0.36-4.70)
Gerstein et al,[5] 2006	12/2635 (0.5)	10/2634 (0.4)	14.73	1.20 (0.52-2.77)
Home et al,[12] 2007	37/2220 (1.7)	46/2227 (2.1)	67.65	0.81 (0.53-1.24)
Total (95% CI)	6421	7870	100.00	0.90 (0.63-1.26)

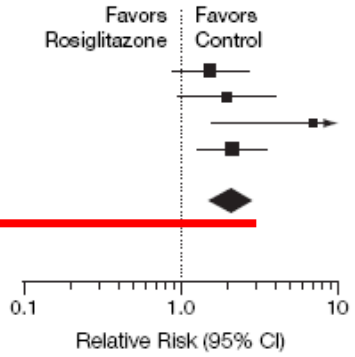
Total events: 59 (rosiglitazone), 72 (control)
Test for heterogeneity: $\chi^2_3 = 1.03$ ($P = .79$), $I^2 = 0\%$
Tests for overall effect: $Z = 0.63$ ($P = .53$)



CHF

Source	No. of Events/Total (%) Rosiglitazone	Control	Weight, %	Relative Risk (95% CI)
Kahn et al,[7] 2006	22/1456 (1.5)	28/2895 (1.0)	35.68	1.56 (0.90-2.72)
Dargie et al,[19] 2007	19/110 (17)	10/114 (8.8)	18.70	1.97 (0.96-4.04)
Gerstein et al,[5] 2006	14/2635 (0.5)	2/2634 (0.1)	3.81	7.00 (1.59-30.76)
Home et al,[12] 2007	47/2220 (2.1)	22/2227 (1.0)	41.82	2.14 (1.30-3.54)
Total (95% CI)	6421	7870	100.00	2.09 (1.52-2.88)

Total events: 102 (rosiglitazone), 62 (control)
Test for heterogeneity: $\chi^2_3 = 3.65$ ($P = .30$), $I^2 = 17.8\%$
Tests for overall effect: $Z = 4.51$ ($P = .00001$)



PPAR-γ

- Several different types of PPAR-γ agonists introduced in the market

  → Troglitazone (1997), Rosiglitazone (2000), Pioglitazone (2000)

- Troglitazone → withdrawn from the US market in 2000 due to its association with drug-induced hepatitis.
- Rosiglitazone → selling restriction in the US and withdrawn from the market in Europe due to its association with greater risk of myocardial infarction

Annu Rev Biochem 2001;70:341-67.
Diabetologia 2000;43:1165-9.
Expert Opin Drug Saf 2008;7:367-76.

PPAR-γ

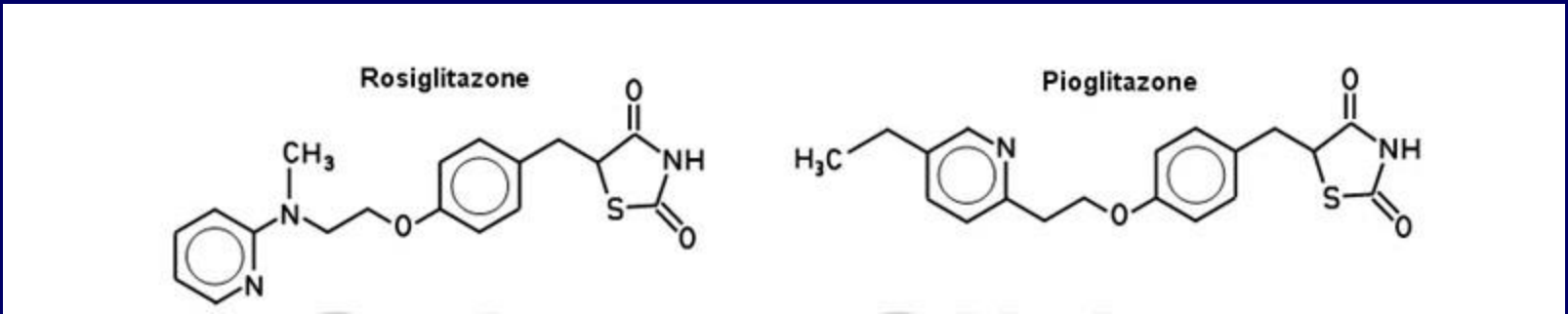
- Several different types of PPAR-γ agonists introduced in the market

  → Troglitazone (1997), Rosiglitazone (2000), Pioglitazone (2000)

- Troglitazone → withdrawn from the US market in 2000 due to its association with drug-induced hepatitis.
- Rosiglitazone → selling restriction in the US and withdrawn from the market in Europe due to its association with greater risk of myocardial infarction
- Pioglitazone → France and Germany have suspended the sale after its association with bladder cancer.

Annu Rev Biochem 2001;70:341-67.
Diabetologia 2000;43:1165-9.
Expert Opin Drug Saf 2008;7:367-76.

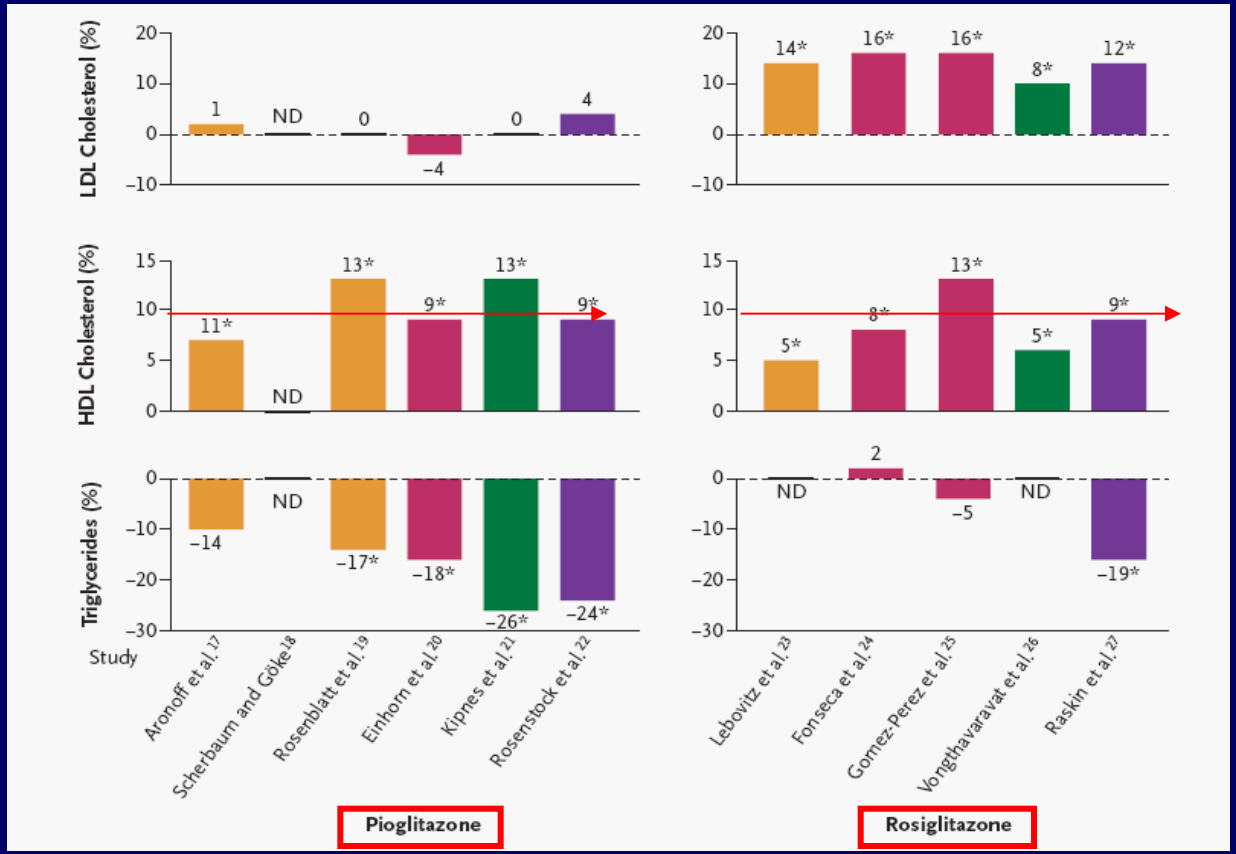
“Class Effect” of PPAR-γ?



Yes and No!

The patterns of gene activation or suppression differ substantially among various PPAR-γ agonists, even within closely related compounds!

Pioglitazone with More Favorable Effects On Lipids, Particularly Triglycerides



NEJM 2004;351:1106-18.
Diabetes Care 2001;24:710-9.
J Biol Chem 2002;277:48051-7.
NEJM 1999;341:410-8.

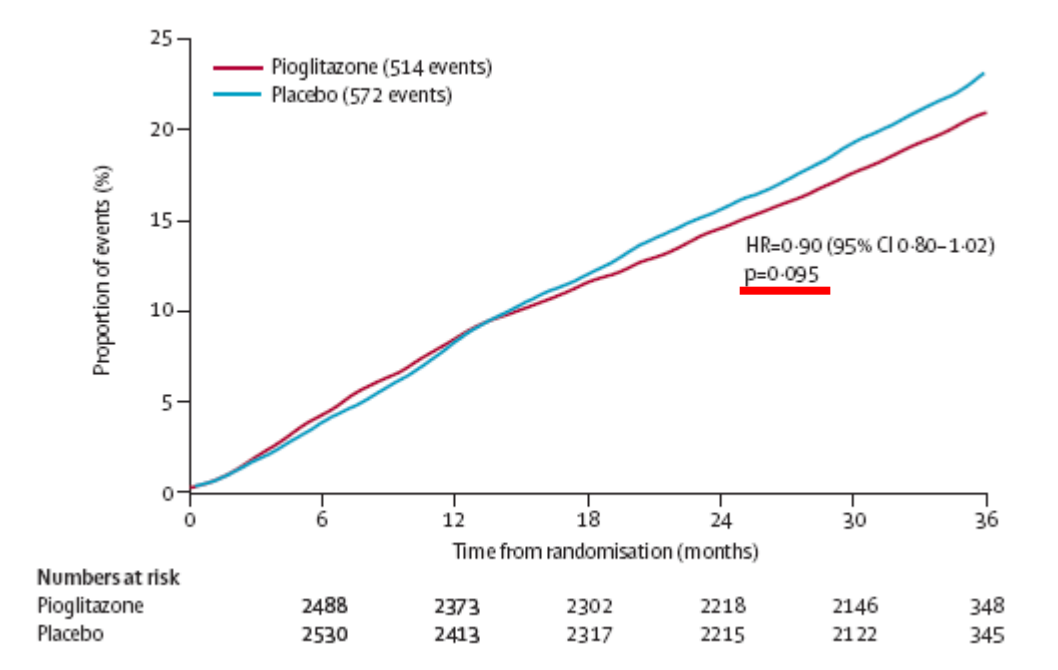
Is Pioglitazone Safe?

PROactive study

- Prospective pioglitazone clinical trial in macrovascular events (PROactive)
- 5,238 patients with type 2 DM & macrovascular disease.
- Pioglitazone (15~45mg) vs. Placebo
- Mean follow-up : 34.5 months
- Endpoint
  - Primary : all-cause mortality, non-fatal MI, stroke, ACS, endovascular or surgical intervention in coronary or leg arteries, amputation above the ankle.
  - Secondary : all-cause mortality, non-fatal MI and stroke

Dormandy JA et al. Lancet 2005;366:1279-89

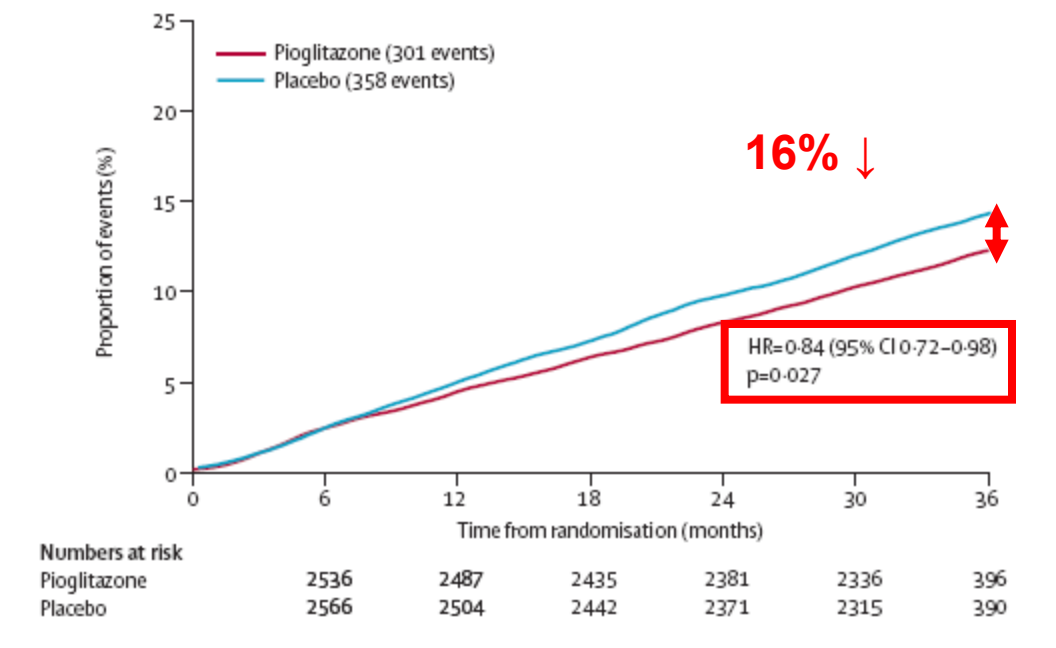
PROactive study
(primary endpoint)



Nonsignificant reduction in coronary and peripheral vascular events

Dormandy JA et al. Lancet 2005;366:1279-89

PROactive study
(main secondary endpoint)



Non-fatal **MI**, **Death** from any cause, or Stroke

Dormandy JA et al. Lancet 2005;366:1279-89

Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

A Meta-analysis of Randomized Trials

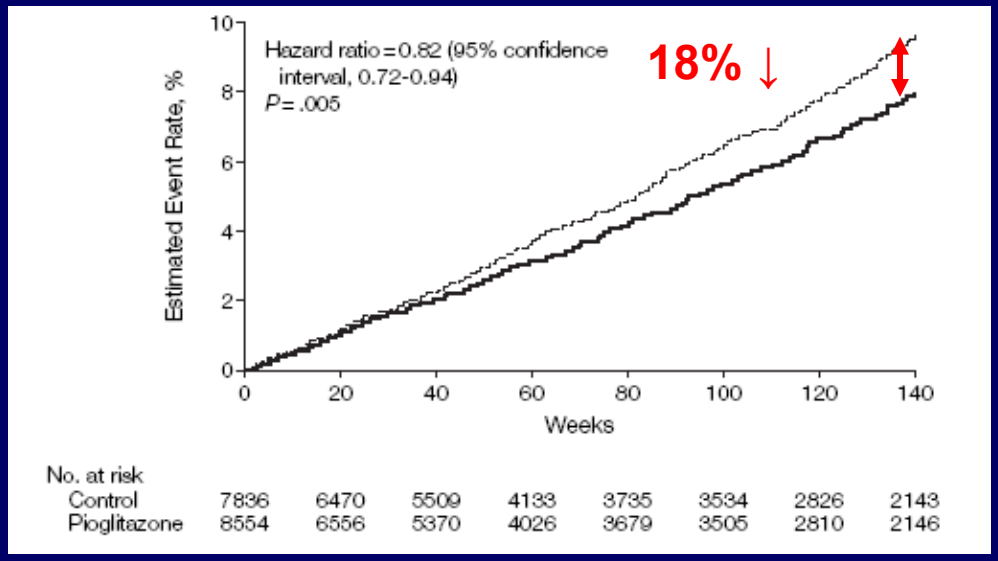
Conclusions Pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

JAMA. 2007;298(10):1180-1188 September 12, 2007 www.jama.com

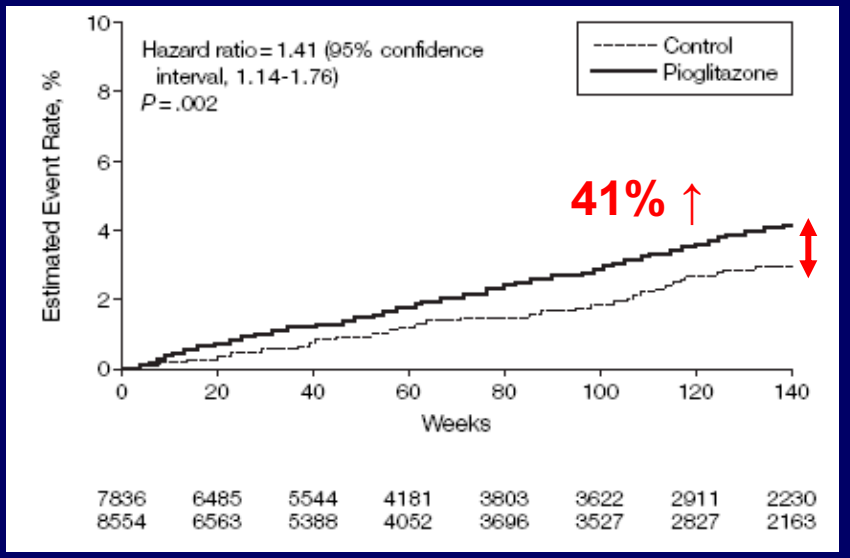
Lincoff AM, Nissen SE et al. JAMA 2007;298:1180-88.

Primary and Secondary Outcomes

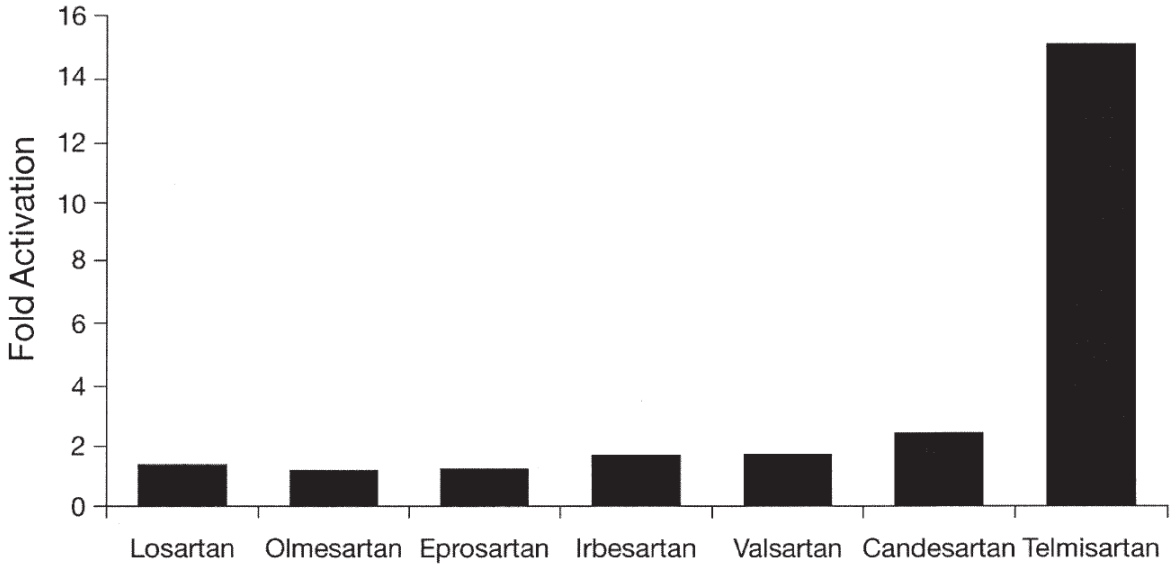
Death, MI, or Stroke



Serious Heart Failure



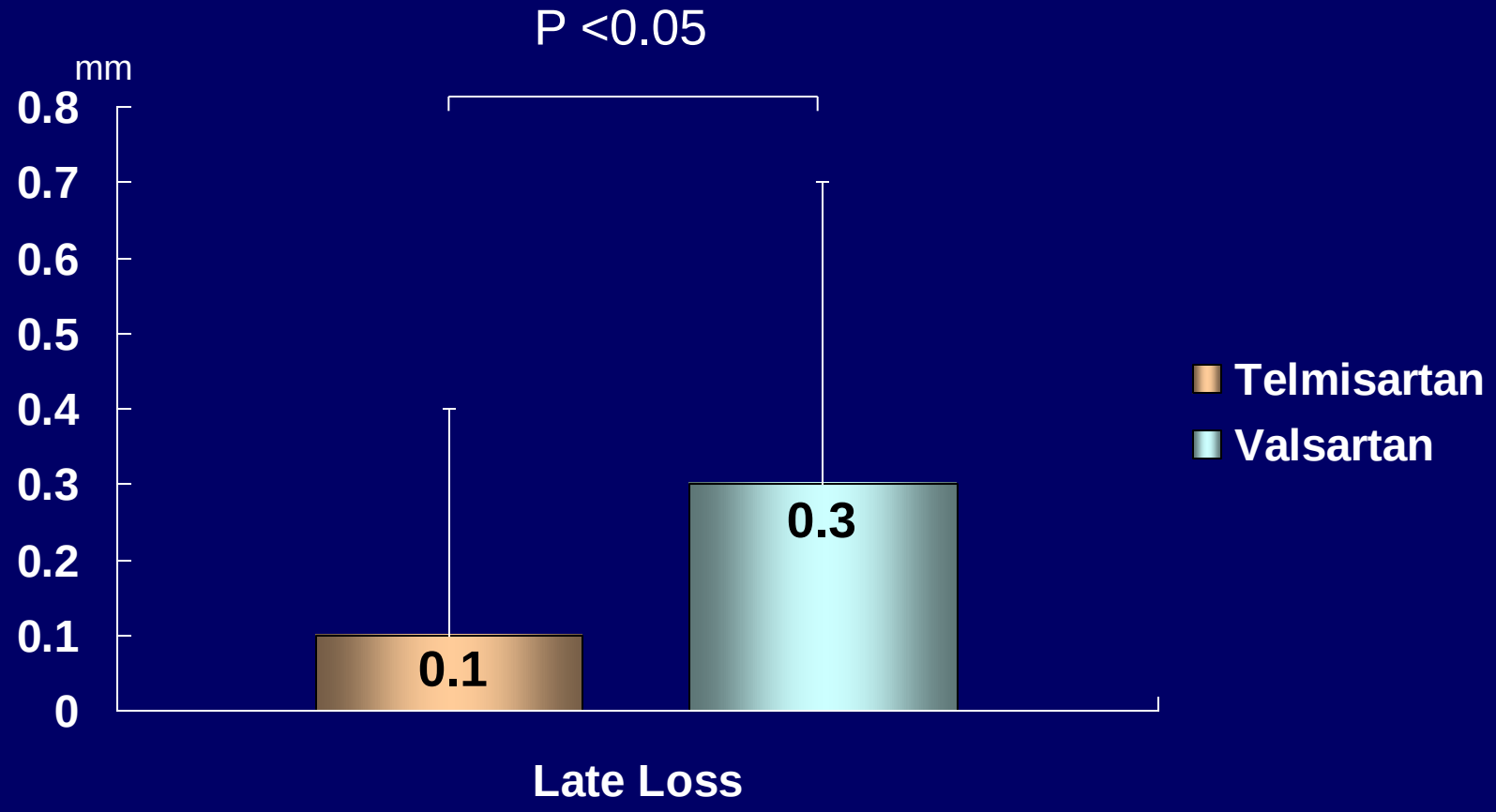
Lincoff AM, Nissen SE et al. JAMA 2007;298:1180-88.



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

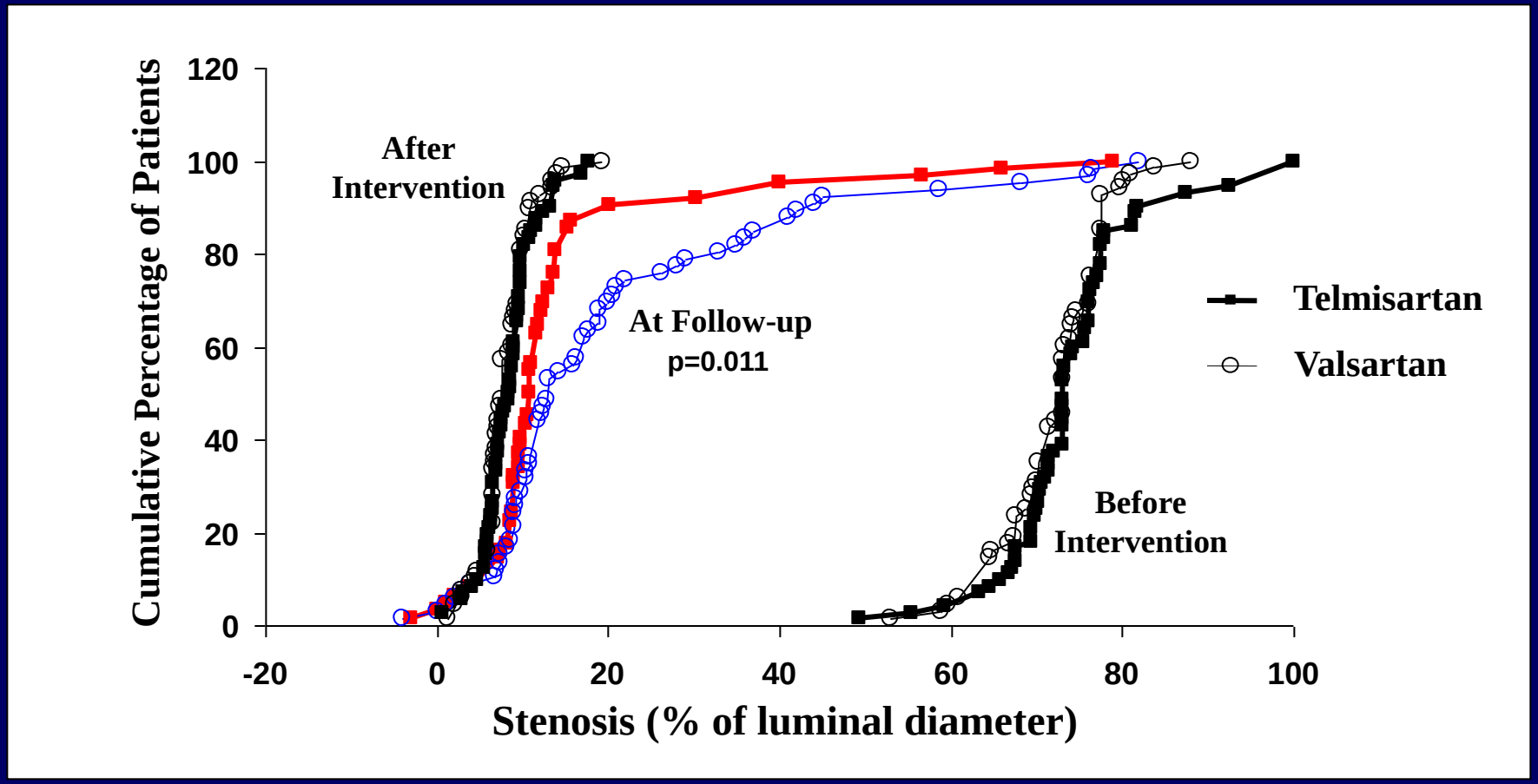
J Hypertens 2004,22:2253-2261

Telmisartan Reduced 8-Month F/U Late Lumen Loss in Hypertensive CAD Patients



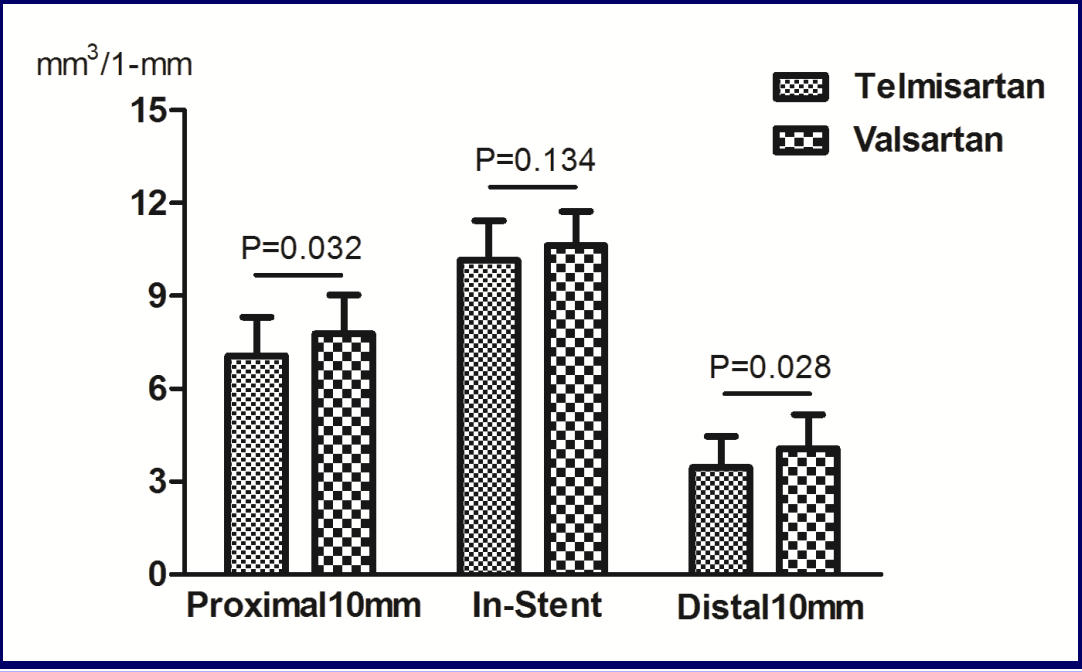
Hong SJ et al. AJC 2007;100:1625-9.

Comparison of Cumulative Distribution Curves for Percent Stenosis



Hong SJ et al. AJC 2007;100:1625-9.

Eight-Month F/U IVUS Outcomes

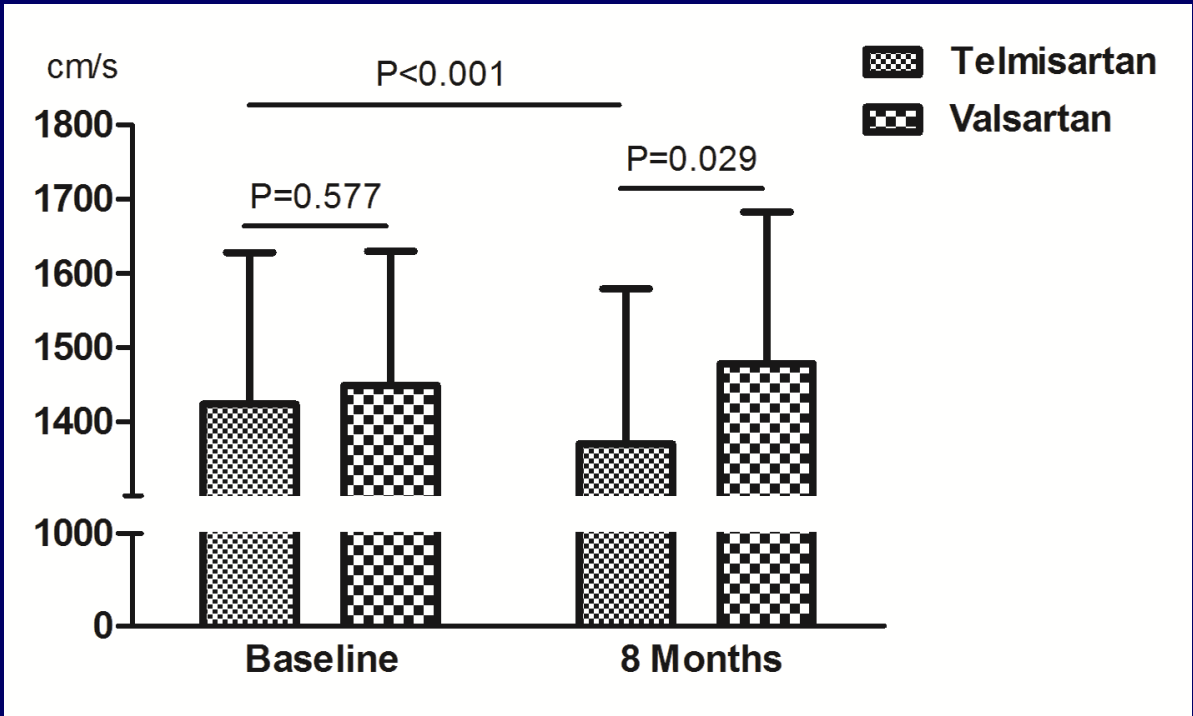


Variable	Telmisartan Group (n=29)		Valsartan Group (n=30)	
	Baseline	8-month	Baseline	8-month
Total vessel volume	14.1 ± 4.2	14.2 ± 4.5	13.9 ± 4.5	14.0 ± 4.8
Total plaque volume	7.7 ± 2.7	10.2 ± 3.9†	7.8 ± 2.9	10.6 ± 3.6†
Stent volume	6.4 ± 1.6	6.3 ± 1.5	6.1 ± 1.9	6.0 ± 1.7
Lumen volume	6.4 ± 1.6	4.0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

*$p < 0.05$ versus valsartan, † $p < 0.05$ versus baseline

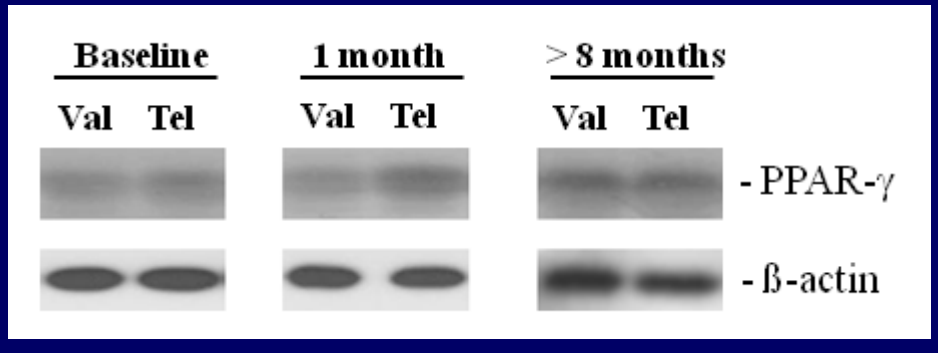
Hong SJ et al. Heart 2011;97:1425-32.

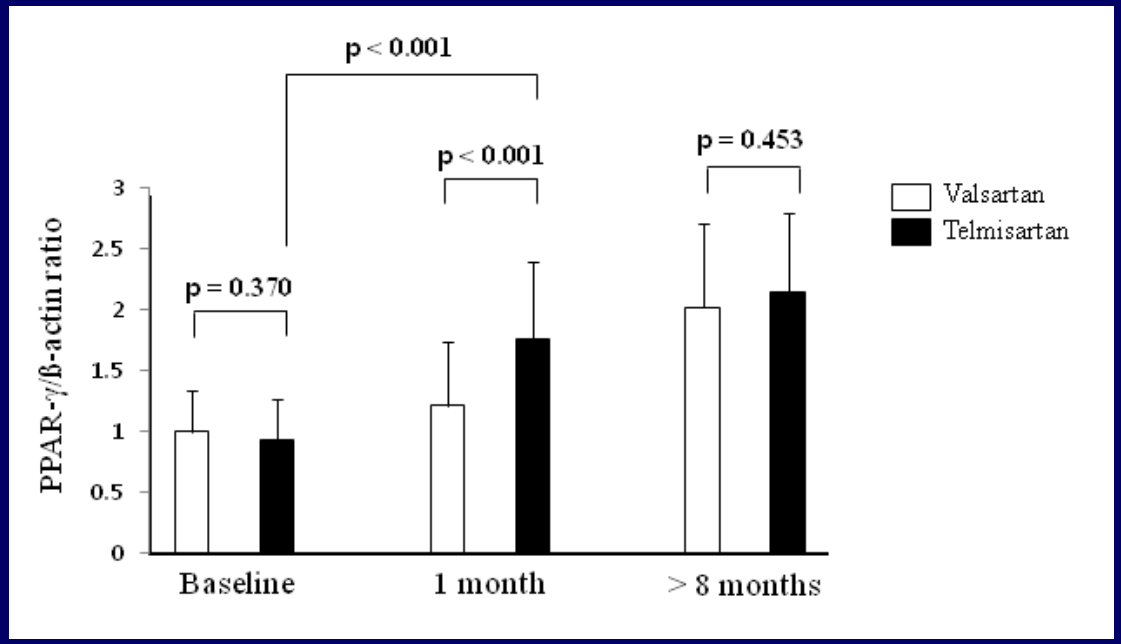
The Mean PWVs between the 2 Groups



Hong SJ et al. Heart 2011;97:1425-32.

Serial Changes in PPAR-γ Expressions in Monocytes





Hong SJ et al. Heart 2011;97:1425-32.

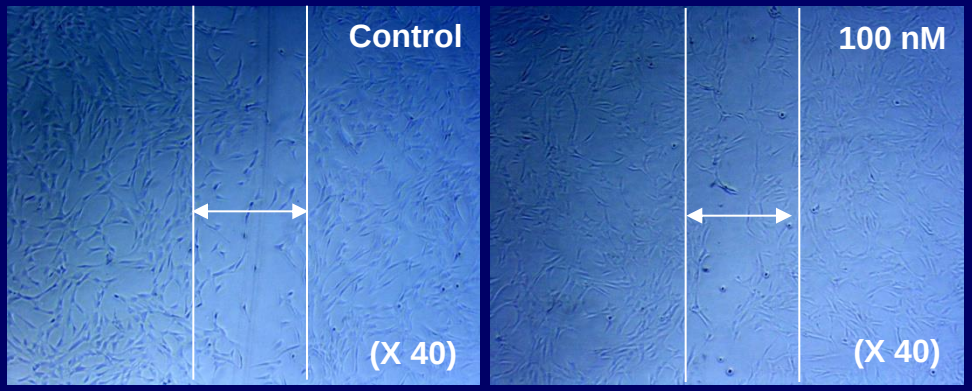
Pioglitazone and CV Events

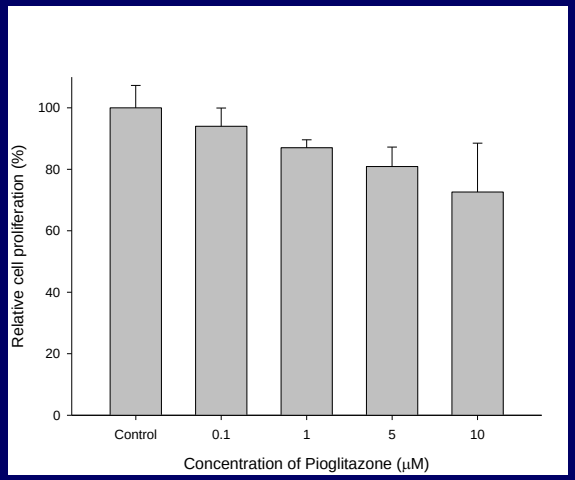
- Recent studies highlight the beneficial effect of pioglitazone in reducing in-stent restenosis in type 2 diabetic patients.
- However, the U.S. FDA has informed the public that use of the pioglitazone for more than 1 year may be associated with an increased risk of bladder cancer especially for men.
- A meta-analysis suggests that the pioglitazone confers excess risk for fractures especially for women.

Hong SJ et al. AJC 2007
Loke YK et al. CMAJ 2009;180:32.
Strom A et al. Circ Res. 2007;101(8):e83-89.
Finn AV et al. Circulation. 2005;112(2):270-278.

Effects of Pioglitazone on SMC Proliferation in Dose-Dependent Manner.

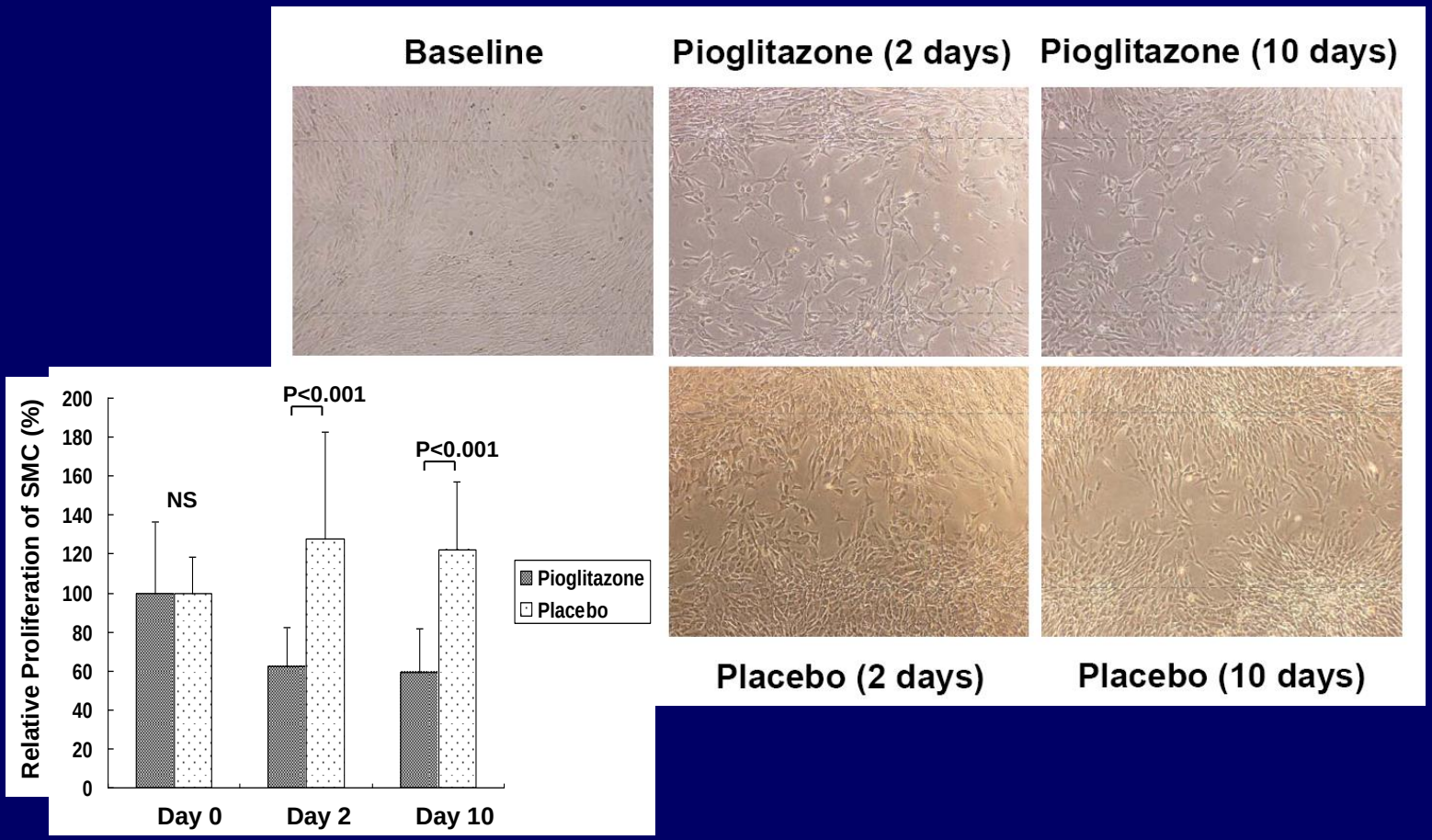
(MTT proliferation assay)





Hong SJ et al. ATVB. 2010;30:2655-65.

Inhibition of SMC Migration 10 hr after Treatment with Plasma



Hong SJ et al. ATVB. 2010;30:2655-65.

Three-Year Cardiovascular Event Rates Were Lower in Type 2 Diabetic Patients with Pioglitazone Treatment after Zotarolimus-Eluting Stent Implantation

(PRAISE Long-Term F/U)

- We prospectively investigated the effects of pioglitazone in reducing MACEs after zotarolimus-eluting stent (ZES) implantation in type 2 diabetic patients with significant coronary artery narrowing during the 3-year follow-up.

Methods

- A prospective, randomized single-blinded clinical trial.
- Either pioglitazone 15-30 mg/day or placebo in addition to standard diabetic management was administered during the 3-year follow-up.
- Baseline and 9-month coronary IVUS were compared for neointimal growth.

Methods

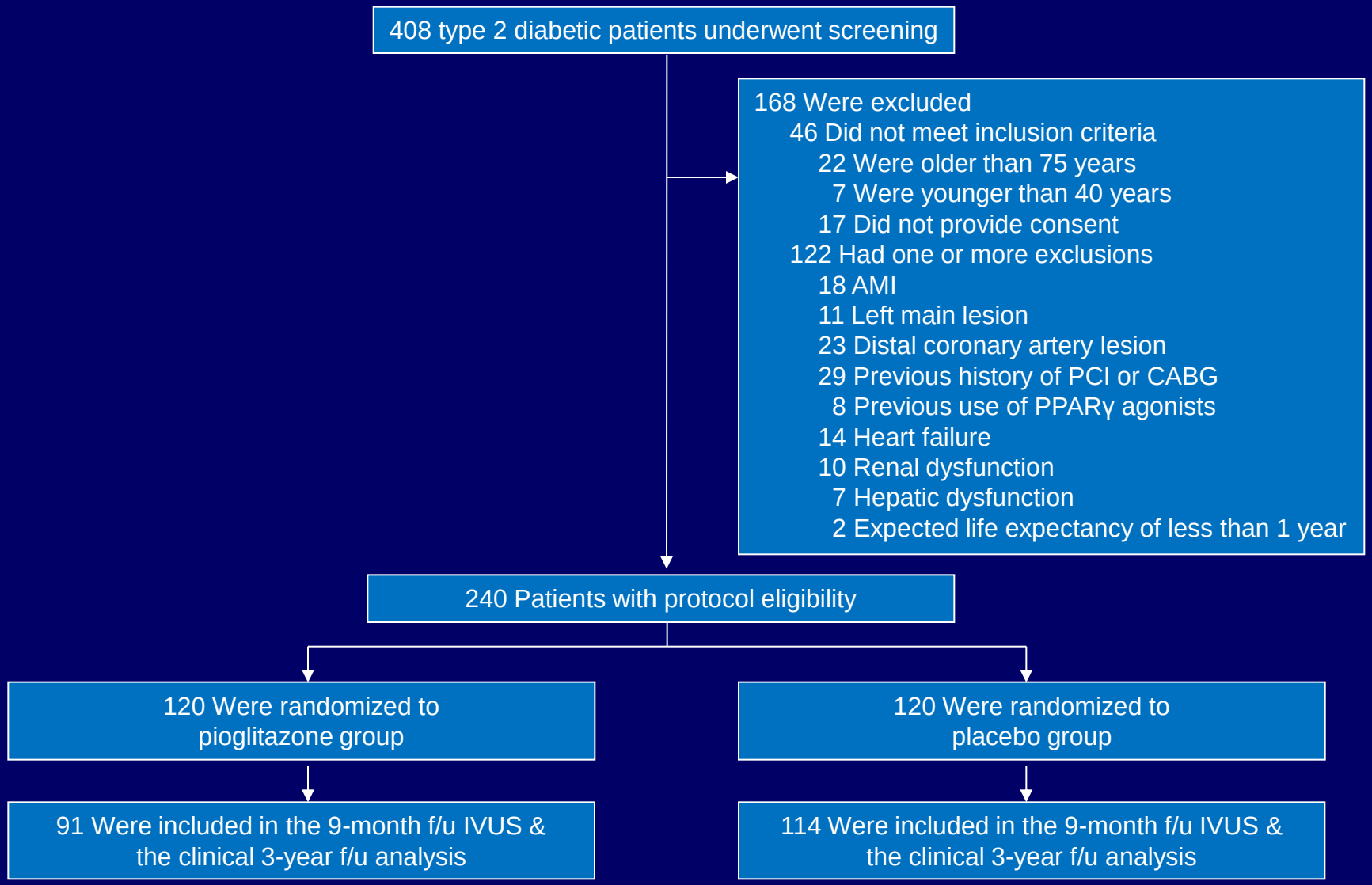
- **The inclusion criteria:**

  1) Patients with previously or newly diagnosed type 2 diabetes
  2) Aged 40 to 75 years
  3) Coronary artery disease requiring stent implantation

- **The exclusion criteria:**

  1) Left main CAD or distal CAD
  2) Previous history of PCI or CABG
  3) AMI
  4) EF < 40%
  4) Previous use of PPAR-gamma within 3 months
  5) Unsuccessful reperfusion after coronary stent implantation
  6) Liver or renal dysfunction

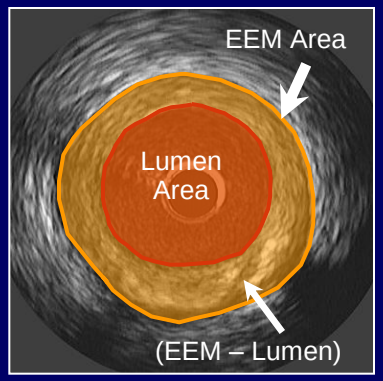
Study Protocol



- **Primary end point:**
  1. To compare major adverse cardiovascular events (MACEs defined as non-fatal MI, death, stroke, and TLR) during the 3-year f/u.

- **Secondary end point:**
  1. To compare rates of new-onset HF, fracture, and non-TLR TVR, and non-TVR during the 3-year f/u.
  2. To compare neointima volume and atherosclerosis progression at 9-month f/u IVUS
  3. To compare hsCRP, adiponectin, HOMA index, HbA1c, lipid profiles during the 9-month f/u .

IVUS Volume Analysis

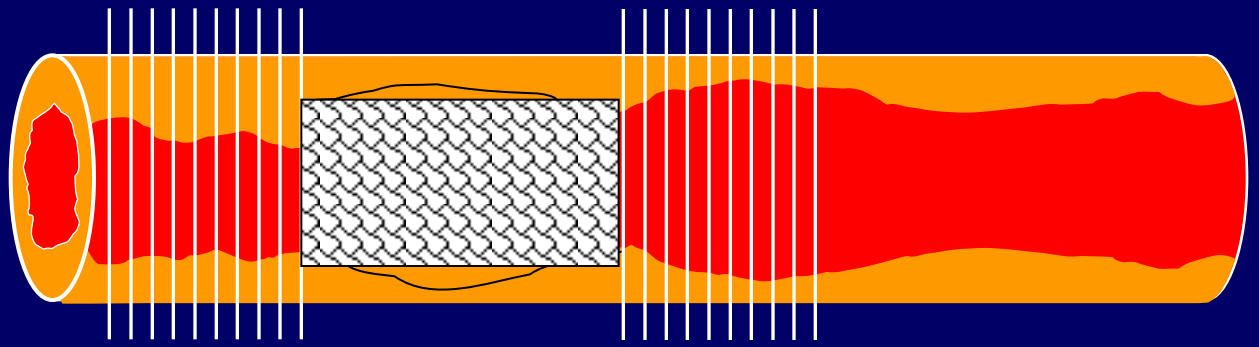


$$\text{Plaque Volume } (mm^3\text{/-mm}) = \frac{\sum n(\text{Vessel vol.} - \text{Lumen vol.})_{CSA}}{\text{No. of CSA}}$$

(Month 9)

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

(Month 9)



Results: Baseline Patient Characteristics

Variable	Pioglitazone Group (n=91)	Placebo Group (n=114)	p Value
Age (years)	61.3 ± 6.5	62.1 ± 7.5	0.672
Men	63 (69.2 %)	80 (70.2 %)	1.000
Body mass index (kg/m2)	25.1 ± 3.1	25.2 ± 3.0	0.876
Systolic blood pressure (mmHg)	138 ± 12	140 ± 11	0.576
Diastolic blood pressure (mmHg)	84 ± 5	86 ± 6	0.335
Risk factors			
Hypertension	73 (80.2%)	91 (79.8 %)	1.000
Hyperlipidemia	41 (45.1 %)	54 (47.4 %)	0.779
Current smoker	14 (15.4 %)	27 (23.7 %)	0.162
FHx of CAD	8 (7.0 %)	5 (5.5 %)	0.777
Left ventricular ejection fraction (%)	51 ± 6	53 ± 8	0.473
Diabetes treatment			
Diet only	12 (13.2 %)	7 (6.1 %)	0.095
Oral glucose-lowering therapy	72 (79.1 %)	98 (86.0 %)	0.262
Insulin	10 (11.0 %)	12 (10.5 %)	1.000
Medication after randomization			
Biguanides	57 (62.6 %)	65 (57.0 %)	0.475
α-Glucosidase inhibitors	10 (11.0 %)	12 (10.5 %)	0.626
Sulfonylureas	56 (61.5 %)	78 (68.4 %)	0.376

Other Medications During the 3-Year F/U

Variable	Pioglitazone Group (n=91)	Placebo Group (n=114)	p Value
Aspirin	91 (100 %)	114 (100 %)	1.000
Clopidogrel	69 (75.8 %)	79 (69.3 %)	0.348
Statins	80 (87.9 %)	96 (84.2 %)	0.547
ARBs	50 (54.9 %)	70 (61.4 %)	0.393
ACE inhibitors	13 (14.3 %)	17 (14.9 %)	1.000
Beta blocker	7 (7.7 %)	11 (9.6 %)	0.805
Calcium channel blockers	24 (26.4 %)	39 (34.2 %)	0.286
Diuretics	6 (6.6 %)	14 (12.3 %)	0.237

Target Lesion Characteristics

Variable	Pioglitazone Group (n=91)	Placebo Group (n=114)	p Value
Number of lesions stented	113	139	
Target coronary artery			
Left anterior descending artery	78 (69.0 %)	104 (74.8 %)	0.325
Left circumflex artery	18 (15.9 %)	22 (15.8 %)	1.000
Right	17 (15.0 %)	13 (9.4 %)	0.176
Type of lesion (%)			
A	4 (3.5 %)	5 (3.6 %)	1.000
B1	33 (29.2 %)	28 (20.1 %)	0.105
B2	42 (37.2 %)	56 (40.3 %)	0.697
C	34 (30.1 %)	50 (36.0 %)	0.349
Eccentric (%)	56 (49.6 %)	66 (47.5 %)	0.800
Overlapping stenting (%)	7 (6.2 %)	4 (2.9 %)	0.228

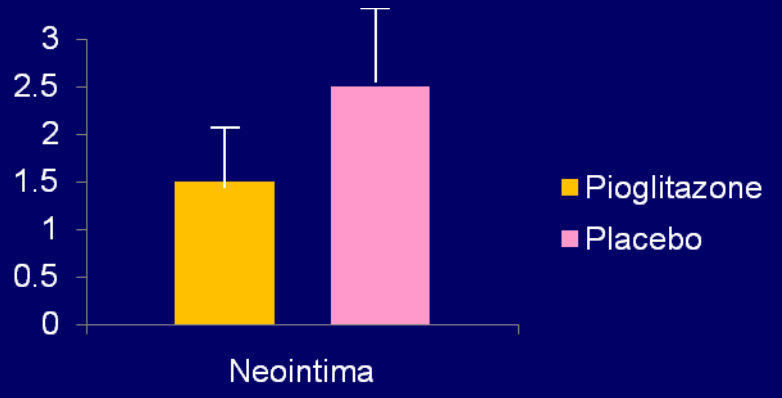
QCA Measurements

Variable	Pioglitazone Group (n=91)	Placebo Group (n=114)	p Value
Baseline			
RD (mm)	2.73 ± 0.32	2.85 ± 0.36	0.786
MLD (mm)	0.75 ± 0.24	0.65 ± 0.34	0.667
% stenosis	73 ± 7	77 ± 9	0.168
Mean lesion length (mm)	21.4 ± 14.0	20.9 ± 13.5	0.703
Postprocedure			
RD (mm)	2.90 ± 0.44	2.93 ± 0.38	0.624
MLD (mm)	2.73 ± 0.47	2.75 ± 0.35	0.710
% stenosis	6 ± 3	6 ± 2	0.866
Acute gain (mm)	2.0 ± 0.3	2.1 ± 0.3	0.767
Number of stents, range	1.2 ± 0.5 (1-3)	1.2 ± 0.5 (1-3)	0.743
Mean stent length (mm)	25.1 ± 7.7	26.0 ± 7.8	0.511
Mean stent diameter (mm)	2.90 ± 0.48	2.87 ± 0.39	0.757
9-month f/u			
RD (mm)	2.92 ± 0.39	2.94 ± 0.37	0.645
MLD (mm)	2.32 ± 0.30	2.13 ± 0.31	0.008
% stenosis	21 ± 13	28 ± 16	0.019
Late lumen loss (mm)	0.41 ± 0.37	0.62 ± 0.53	0.034
Binary restenosis	9 (9.9 %)	15 (13.2 %)	0.518

Nine-Month F/U IVUS Outcomes for Stented Segment

Variable	Pioglitazone Group (n=91)		Placebo Group (n=114)	
	Baseline	9-month	Baseline	9-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



Hong SJ et al. ATVB. 2010;30:2655-65

Nine-Month F/U IVUS for 10mm Proximal & Distal to the Stented Segment

Variable	Pioglitazone Group (n=91)				Placebo Group (n=114)			
	Proximal		Distal		Proximal		Distal	
	Baseline	9-month	Baseline	9-month	Baseline	9-month	Baseline	9-month
Total vessel volume	16.3 ± 5.2	16.9 ± 4.9	11.3 ± 3.8	11.6 ± 3.6*	16.5 ± 4.8	17.2 ± 4.9†	11.3 ± 5.0	12.7 ± 5.5†
Δ from baseline	0.5 ± 3.3		0.3 ± 3.3*		0.6 ± 3.3		1.3 ± 1.9	
Total plaque volume	7.6 ± 3.4	7.2 ± 3.2*	4.8 ± 2.4	5.0 ± 2.6*	7.5 ± 2.8	8.6 ± 3.2†	4.3 ± 2.4	5.8 ± 3.7†
Δ from baseline	**-0.3 ± 2.7***		**0.1 ± 1.6***		**1.0 ± 1.8**		**1.4 ± 2.5**	
Lumen volume	8.8 ± 4.0	9.7 ± 4.4*†	6.5 ± 2.7*	6.6 ± 2.8	9.0 ± 3.2	8.4 ± 3.2†	7.0 ± 3.6	6.9 ± 2.5
Δ from baseline	0.8 ± 2.3*		0.0 ± 1.4		-0.6 ± 2.5		-0.1 ± 2.4	

All volumes are given in mm^3/1mm proximal and distal vessel segment.
*p < 0.05 versus placebo, † p < 0.05 versus baseline

Hong SJ et al. ATVB. 2010;30:2655-65

Δ in Levels of Inflammation, Insulin Resistance During the 9-Month F/U

	Pioglitazone Group (n=91)		Placebo Group (n=114)	
	Baseline	9-month f/u	Baseline	9-month f/u
hsCRP (mg/L)	3.5 ± 2.2	1.8 ± 2.9*	2.8 ± 3.0	1.2 ± 1.4*
Δ 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
Δ 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*
Δ 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*
Δ from baseline (mg/dL)	-39.4 ± 56.5		-28.8 ± 46.1	
HOMA index	4.6 ± 2.4	2.4 ± 1.7*†	4.5 ± 2.6	2.9 ± 2.0*
Δ 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*
Δ from baseline (%)	-0.6 ± 1.0		-0.5 ± 0.6	

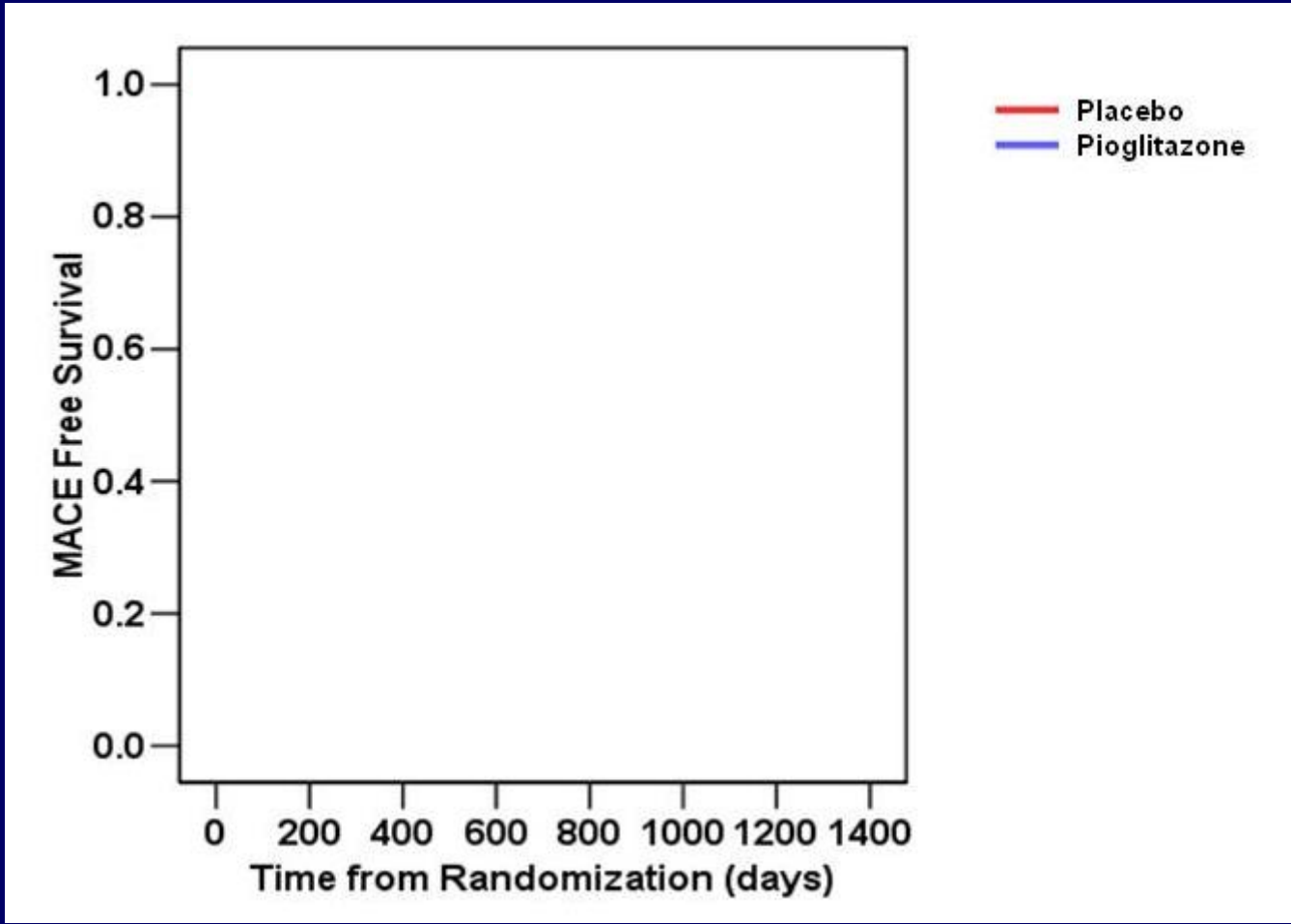
* $p < 0.05$ compared with baseline. † $p < 0.05$ compared with placebo group.

Changes in Levels of Lipid Profile During the 9-Month F/U

	Pioglitazone Group (n=91)		Placebo Group (n=114)	
	Baseline	9-month f/u	Baseline	9-month f/u
Total cholesterol (mg/dL)	186.5 ± 37.1	152.3 ± 32.5*	185.8 ± 40.9	155.3 ± 27.3*
Δ 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*
Δ 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
Δ 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
Δ 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.

MACE within 3 Years



MACE within 3 Years

	Placebo (n-114)	Pioglitazone (n=91)	Relative Risk (95% CI)	P Value
Non-fatal MI	0 (0.0%)	1 (1.1%)	1.011 (0.989-1.033)	0.444
Death	3 (2.6%)	0 (0.0%)	0.974 (0.945-1.004)	0.256
Stroke	1 (0.9%)	2 (2.2%)	2.539 (0.227-28.456)	0.586
TLR	**29 (25.4%)**	**9 (9.9%)**	**0.322 (0.144-0.721)**	**0.006**

Other Events within 3 Years

	Placebo (n-114)	Pioglitazone (n=91)	Relative Risk (95% CI)	P Value
Stomach ca	2 (1.8%)	2 (2.2%)	1.258 (0.174-9.111)	1.000
HCC	2 (1.8%)	1 (1.1%)	0.622 (0.056-6.973)	1.000
Lung cancer	1 (0.9%)	0 (0.0%)	0.991 (0.974-1.008)	1.000
Colon cancer	1 (0.9%)	0 (0.0%)	0.991 (0.974-1.008)	1.000
Breast cancer	1 (0.9%)	3 (3.3%)	3.852 (0.394-37.672)	0.325

Summary

- Pioglitazone decreases inflammation, SMC migration and proliferation.
- Pioglitazone was associated with significant decrease in neointimal hyperplasia and the coronary atherosclerosis progression.
- Follow-up fasting insulin and HOMA index were significantly lower in the pioglitazone group.
- Follow-up adiponectin concentration was significantly higher in the pioglitazone group.
- Significantly lower rate of MACE in the pioglitazone group.
- No differences in the incidence of fracture and cancer during the 3-year follow-up.

Positive Mechanisms of Pioglitazone Influencing CV Events

- Dyslipidemia
- Markers of inflammation
- Endothelial function
- Carotid IMT
- Progression of atherosclerosis on coronary IVUS

Inhibition of Atherosclerosis and Neointima Hyperplasia

Reducing CV Events

Take-Home Message

PPAR-γ activations by pioglitazone provide new therapeutic options in reducing neointima volume and the rates of MACEs in diabetic patients with coronary artery disease during the 3-year follow-up.

Thank You For Your Attention!