Thiazolidinediones 2021

Cardiovascular Disease
Cardiomyopathy

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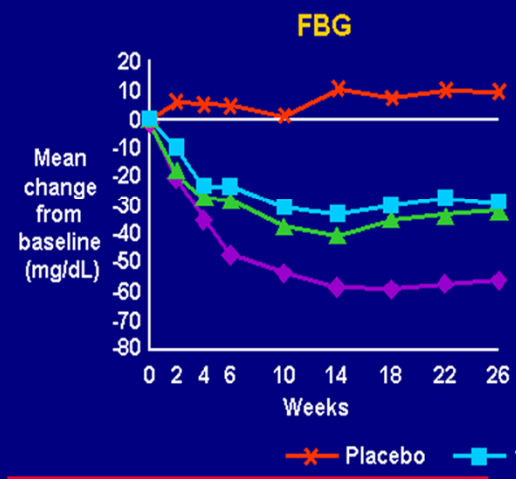
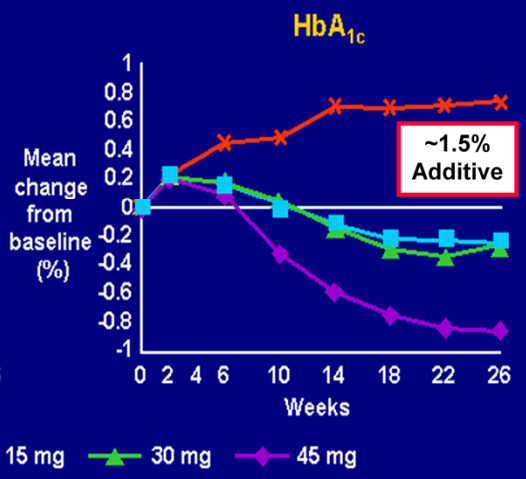
Effects of Pioglitazone Monotherapy on FBG and HbA_{1c}





Placebo — 15 mg — 30 mg — 45 mg

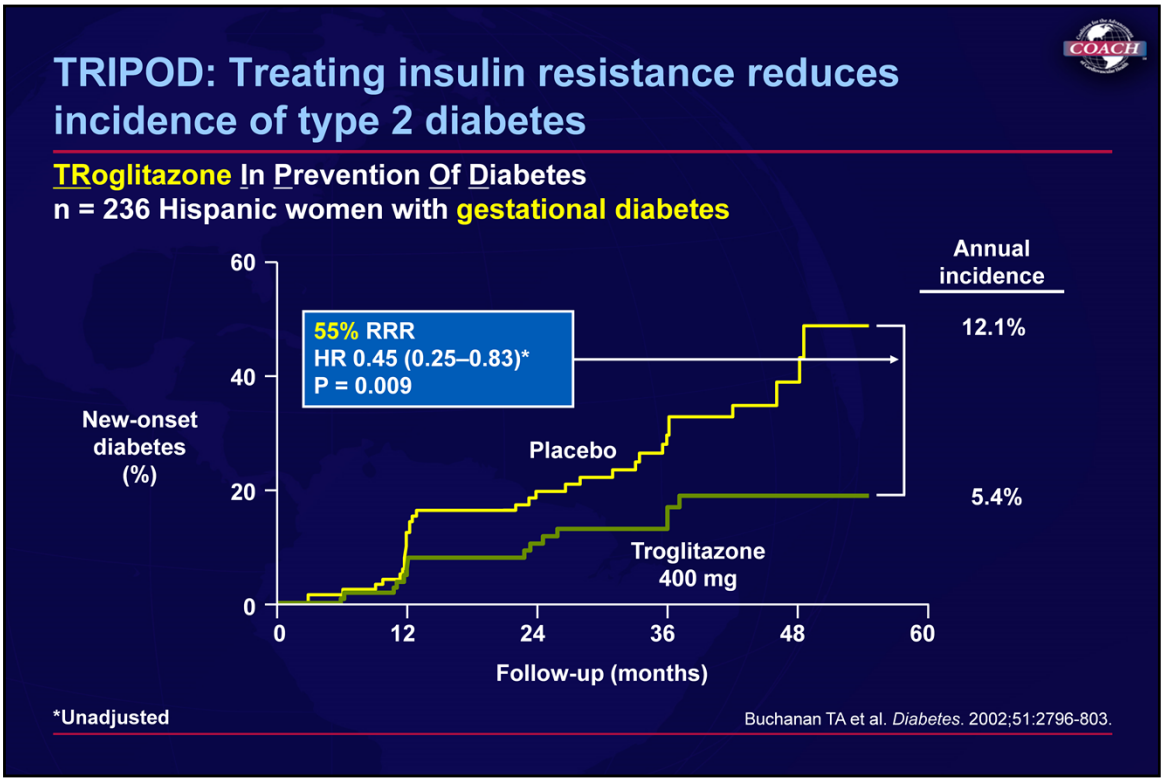
Pioglitazone

Pioglitazone 45 mg 90 tabs: Kroger - $20.73
GoodRx.com Walgreens - $274

Pioglitazone Package Insert.

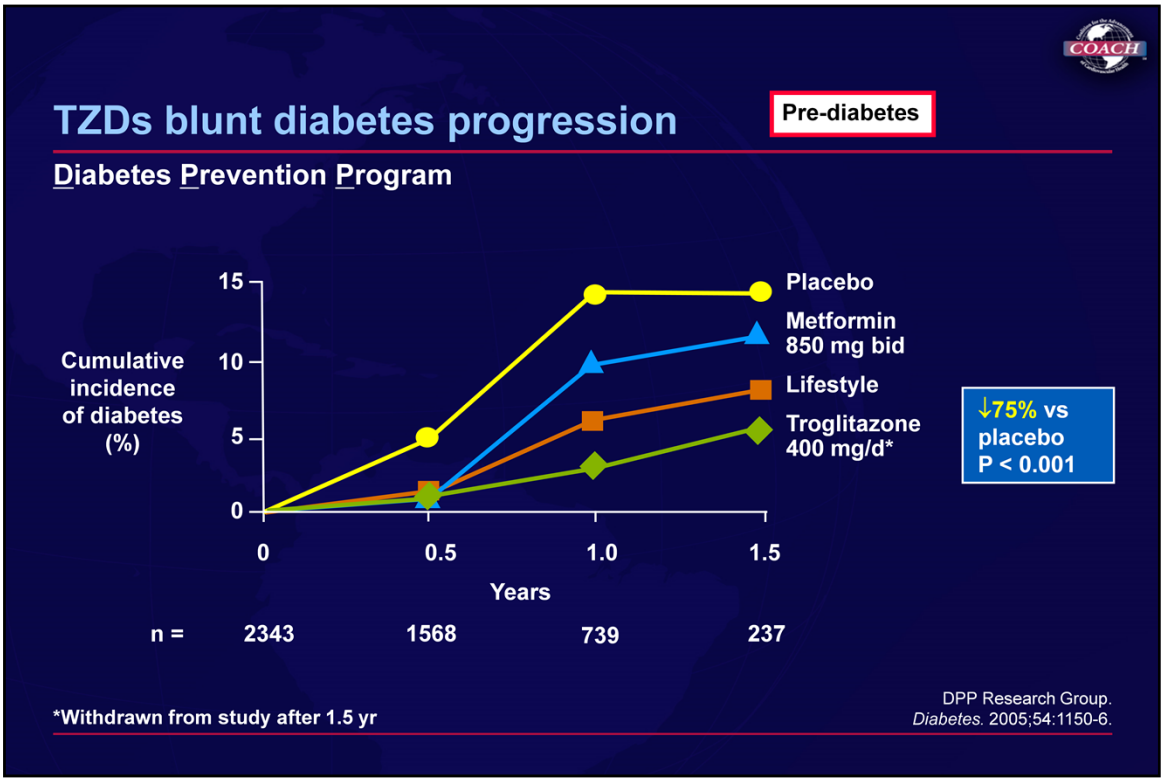
Schneider R et al. *Diabetes*. 1999;48(suppl 1):Abstract 0469.

IV.78



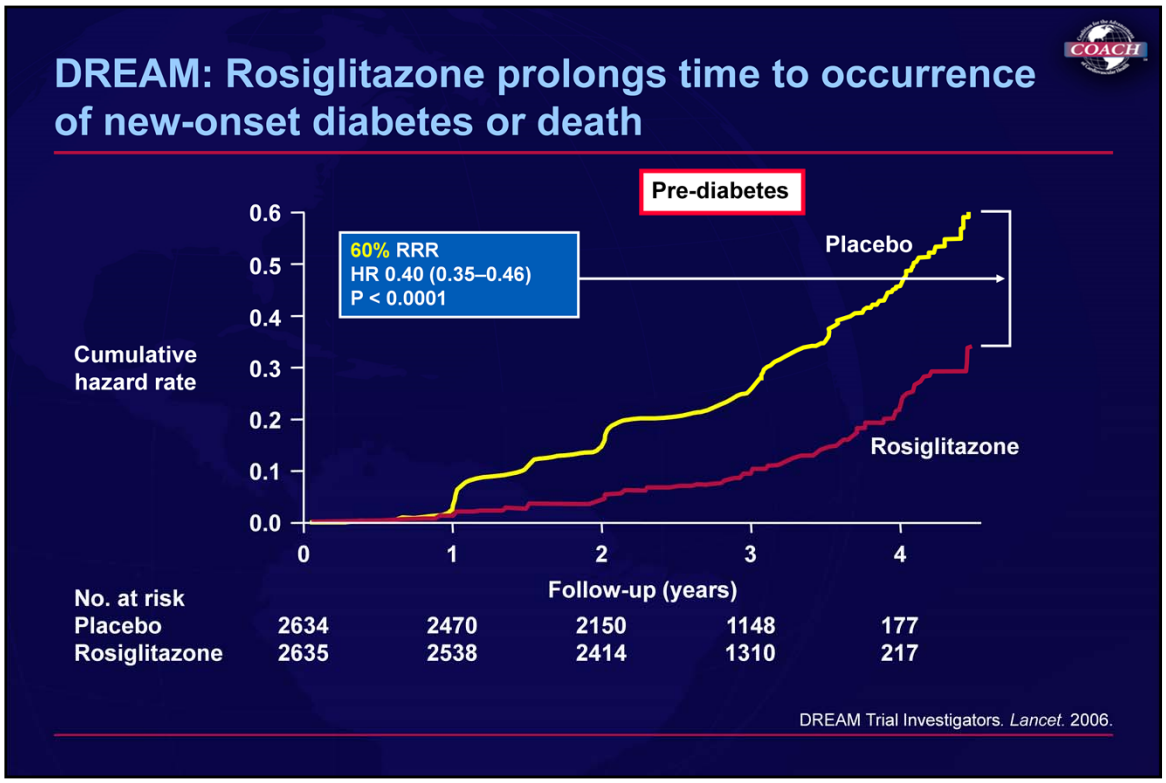
TRIPOD: Treating insulin resistance reduces incidence of type 2 diabetes

Abstract: Type 2 diabetes frequently results from progressive failure of pancreatic beta-cell function in the presence of chronic insulin resistance. We tested whether chronic amelioration of insulin resistance would preserve pancreatic beta-cell function and delay or prevent the onset of type 2 diabetes in high-risk Hispanic women. Women with previous gestational diabetes were randomized to placebo (n = 133) or the insulin-sensitizing drug troglitazone (400 mg/day; n = 133) administered in double-blind fashion. Fasting plasma glucose was measured every 3 months, and oral glucose tolerance tests (OGTTs) were performed annually to detect diabetes. Intravenous glucose tolerance tests (IVGTTs) were performed at baseline and 3 months later to identify early metabolic changes associated with any protection from diabetes. Women who did not develop diabetes during the trial returned for OGTTs and IVGTTs 8 months after study medications were stopped. During a median follow-up of 30 months on blinded medication, average annual diabetes incidence rates in the 236 women who returned for at least one follow-up visit were 12.1 and 5.4% in women assigned to placebo and troglitazone, respectively ($P < 0.01$). Protection from diabetes in the troglitazone group 1) was closely related to the degree of reduction in endogenous insulin requirements 3 months after randomization, 2) persisted 8 months after study medications were stopped, and 3) was associated with preservation of beta-cell compensation for insulin resistance. Treatment with troglitazone delayed or prevented the onset of type 2 diabetes in high-risk Hispanic women. The protective effect was associated with the preservation of pancreatic beta-cell function.



TZDs blunt diabetes progression

Abstract The Diabetes Prevention Program (DPP) was a randomized clinical trial of prevention of type 2 diabetes in high-risk people. Troglitazone, an insulin-sensitizing agent, was used initially but was discontinued during the trial. Troglitazone therapy was compared with other DPP interventions, considering both the short-term "in-trial" results and the longer-term results after troglitazone were discontinued. From 1996 to 1998, participants were randomly assigned to treatment with metformin (n = 587), troglitazone (n = 585), double placebo (n = 582), or intensive lifestyle intervention (ILS) (n = 589). Because of concern regarding its liver toxicity, the troglitazone arm was discontinued in June 1998, after which follow-up of all participants continued. During the mean 0.9 year (range 0.5-1.5 years) of troglitazone treatment, the diabetes incidence rate was 3.0 cases/100 person-years, compared with 12.0, 6.7, and 5.1 cases/100 person-years in the placebo, metformin, and ILS participants (P < 0.001, troglitazone vs. placebo; P = 0.02, troglitazone vs. metformin; P = 0.18, troglitazone vs. ILS). This effect of troglitazone was in part due to improved insulin sensitivity with maintenance of insulin secretion. During the 3 years after troglitazone withdrawal, the diabetes incidence rate was almost identical to that of the placebo group. Troglitazone, therefore, markedly reduced the incidence of diabetes during its limited period of use, but this action did not persist. Whether other thiazolidinedione drugs used for longer periods can safely prevent diabetes remains to be determined.



DREAM: Rosiglitazone prolongs time to occurrence of new-onset diabetes or death

Abstract

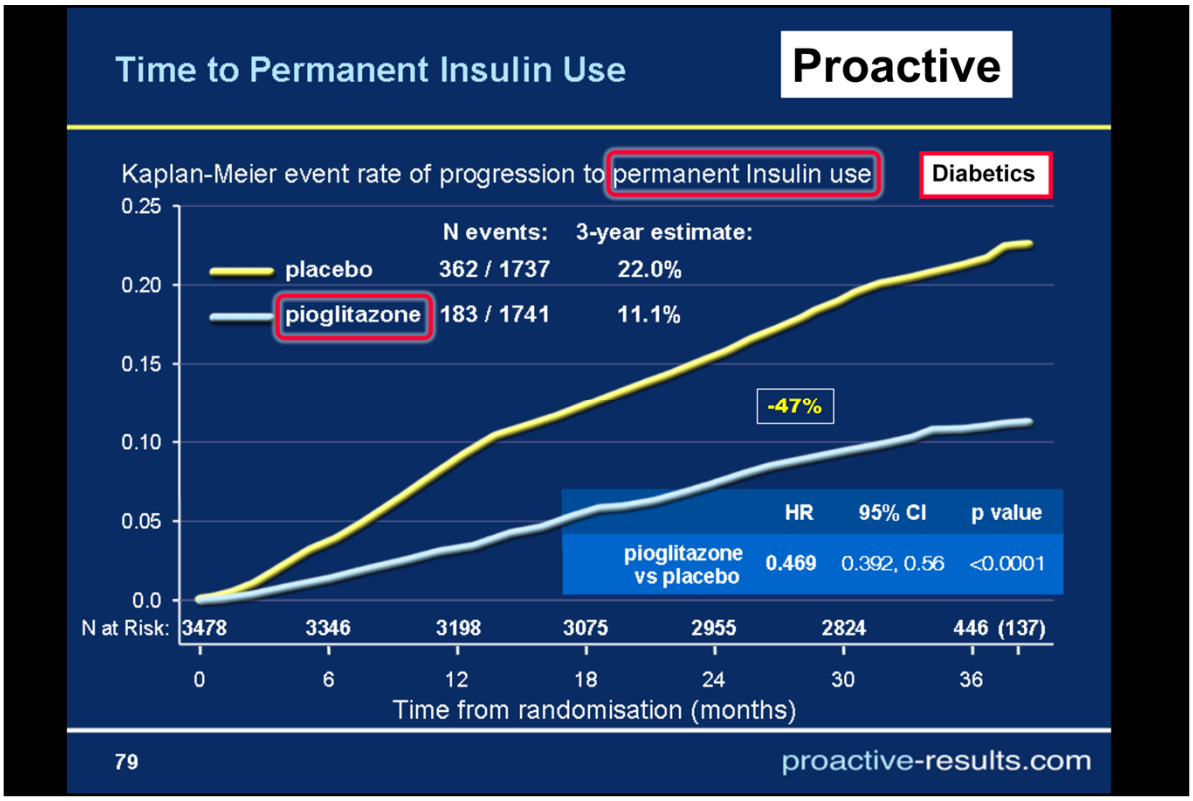
Background: Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.

Methods: 5269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2365) or placebo (2634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00095654.

Findings: At the end of study, 59 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 306 (11.6%) individuals given rosiglitazone and 686 (26.0%) given placebo developed the composite primary outcome (hazard ratio 0.40, 95% CI 0.35-0.46; p<0.0001); 1330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) in the placebo

group became normoglycaemic (1.71, 1.57-1.87; p<0.0001). Cardiovascular event rates were much the same in both groups, although 14 (0.5%) participants in the rosiglitazone group and two (0.1%) in the placebo group developed heart failure (p=0.01).

Interpretation: Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.



Abstract

Objectives: This analysis from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study assesses the effects of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes and a previous myocardial infarction (MI).

Background: People with type 2 diabetes have an increased incidence of MI compared with the general population. Those with diabetes and MI have a worse prognosis than nondiabetic patients with cardiovascular disease.

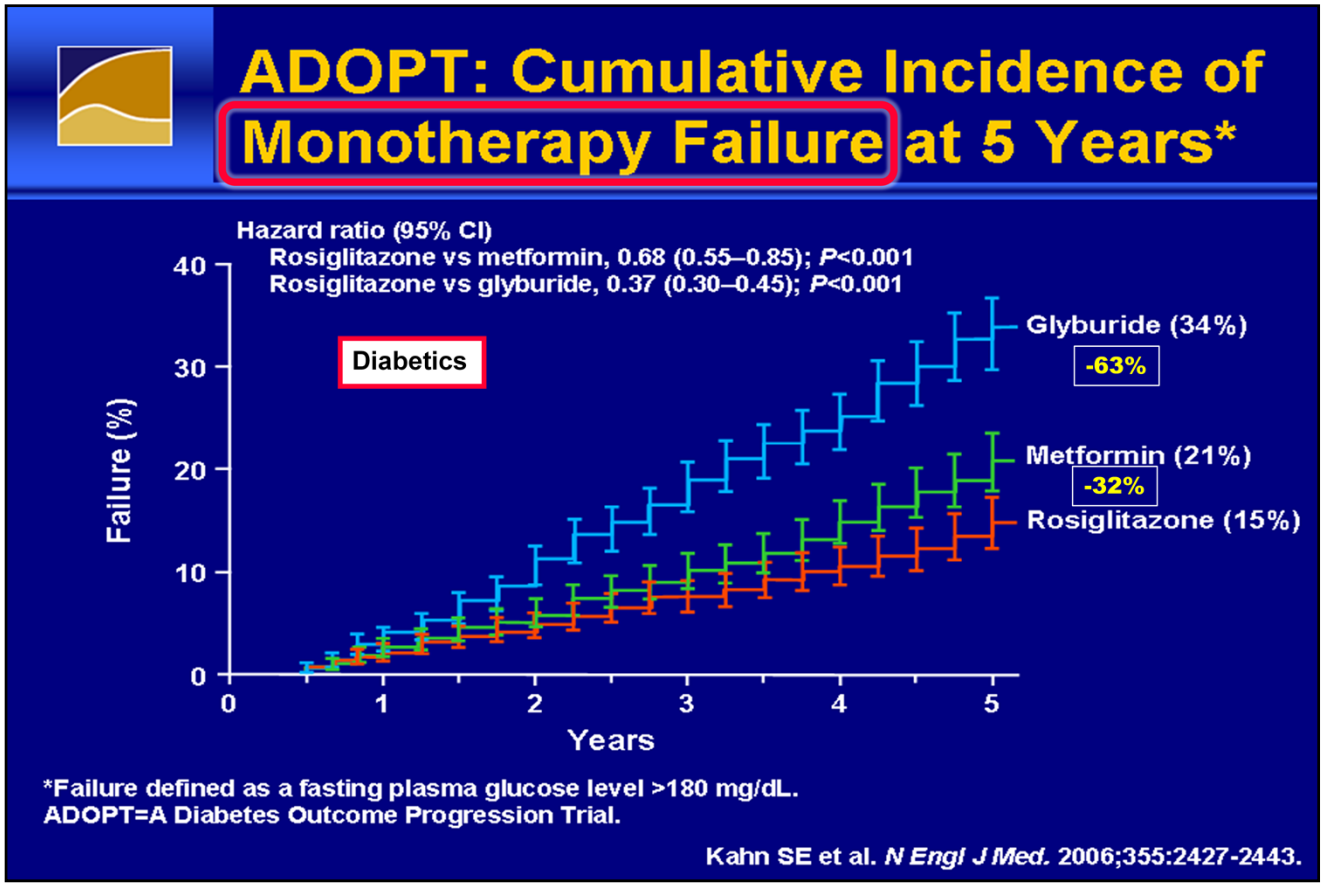
Methods: The PROactive study was a prospective, multicenter, double-blind, placebo-controlled trial of 5,238 patients with type 2 diabetes and macrovascular disease. Patients were randomized to either pioglitazone or placebo in addition to their other glucose-lowering and cardiovascular medication. Treatment of diabetes, dyslipidemia, and hypertension was encouraged according to the International Diabetes Federation guidelines. Patients were followed for a mean of 2.85 years. The primary end point was the time to first occurrence of macrovascular events or death. Of the total cohort, the subgroup of patients who had a previous MI (n = 2,445 [46.7%]; n = 1,230 in the pioglitazone group and n = 1,215 in the placebo group) was

evaluated using prespecified and post-hoc analyses.

Results: Pioglitazone had a statistically significant beneficial effect on the pre-specified end point of fatal and nonfatal MI (28% risk reduction [RR]; p = 0.045) and acute coronary syndrome (ACS) (37% RR; p = 0.035). There was a 19% RR in the cardiac composite end point of nonfatal MI (excluding silent MI), coronary revascularization, ACS, and cardiac death (p = 0.033). The difference in the primary end point defined in the main PROactive study did not reach significance in the MI population (12% RR; p = 0.135). The rates of heart failure requiring hospitalization were 7.5% (92 of 1,230) with pioglitazone and 5.2% (63 of 1,215) with placebo. Fatal heart failure rates were similar (1.4% [17 of the 92] with pioglitazone versus 0.9% [11 of the 63] with placebo).

Conclusions: In high-risk patients with type 2 diabetes and previous MI, pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS.

J Am Coll Cardiol: 49(17):1772-1780, 2007.



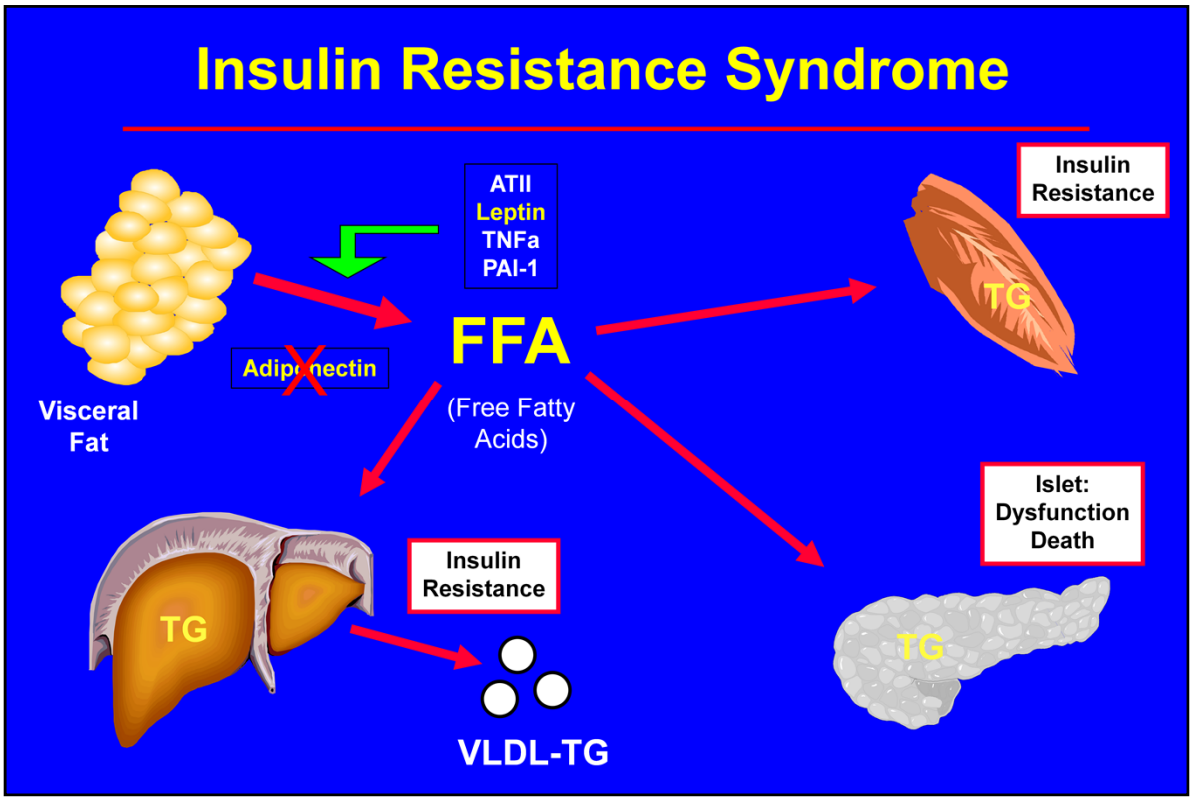
ADOPT: Cumulative Incidence of Monotherapy Failure at 5 Years

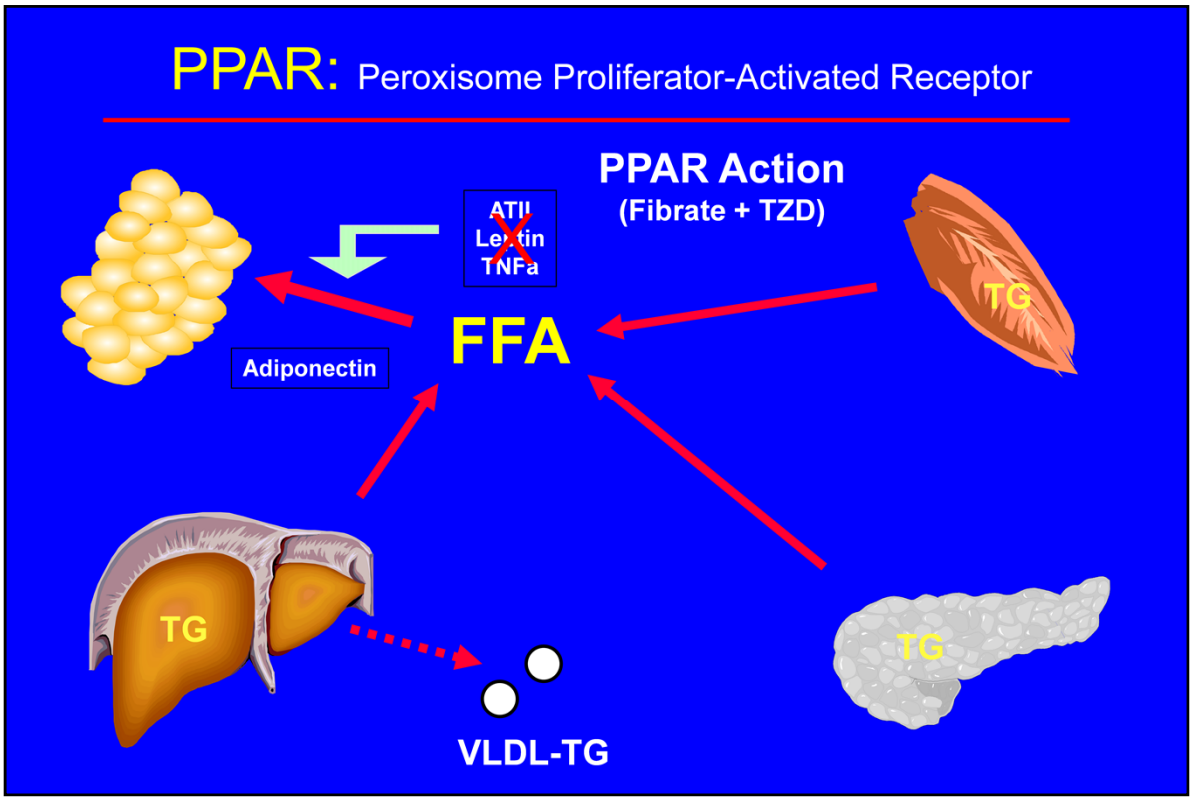
Using a double-blind, randomized, controlled clinical trial involving 4,360 patients, Kahn and colleagues evaluated rosiglitazone, metformin, and glyburide as initial treatment for recently diagnosed type 2 diabetes.

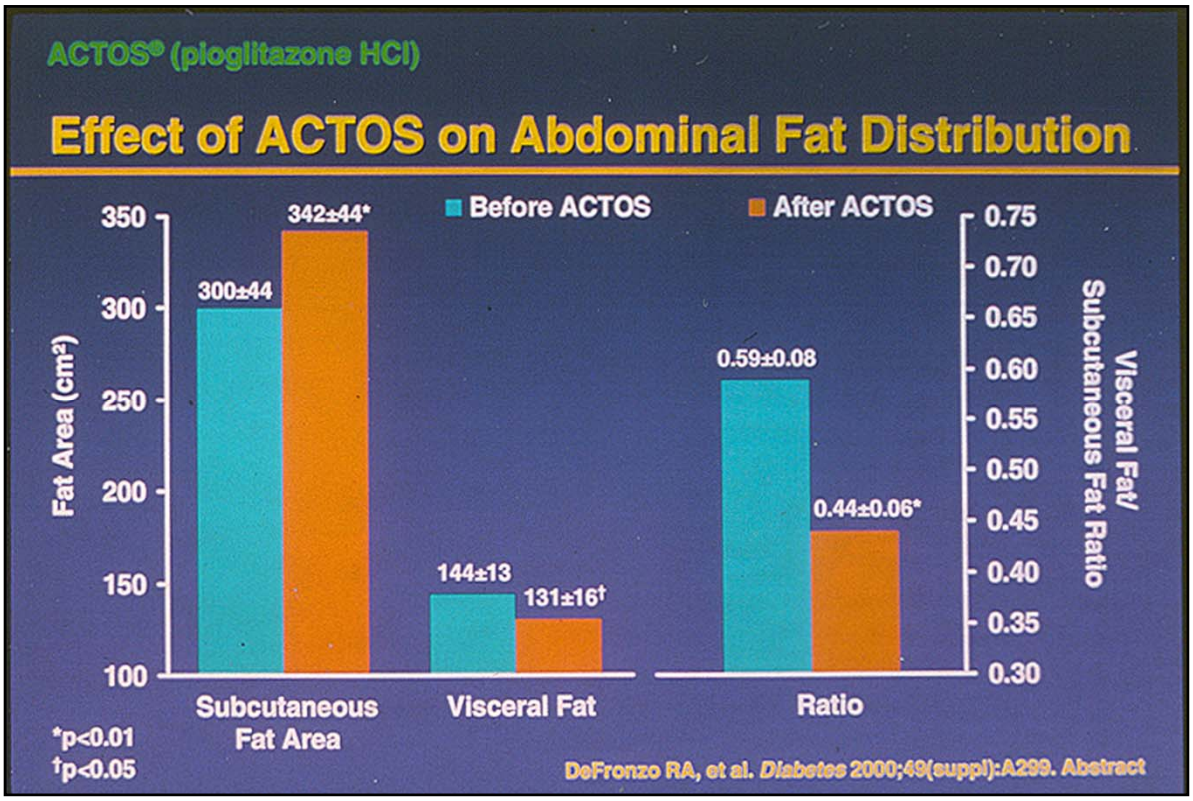
The patients were treated for a median of 4.0 years. The primary outcome was the time to monotherapy failure, defined as a confirmed level of fasting plasma glucose (FPG) of >180 mg/dL. Prespecified secondary outcomes were levels of FPG and A1C, insulin sensitivity, and beta-cell function.

Analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. This represents a risk reduction for rosiglitazone of 32% and 63% as compared with metformin and glyburide, respectively ($P<0.001$ for both comparisons).

Kahn SE et al. *N Engl J Med*. 2006;355:2427-2443.


Insulin Resistance Syndrome
ATII
Leptin
TNFa
PAI-1
Visceral Fat
Adiponectin
FFA
(Free Fatty Acids)
Insulin Resistance
TG
Islet: Dysfunction Death
TG
Insulin Resistance
TG
VLDL-TG


PPAR: Peroxisome Proliferator-Activated Receptor
PPAR Action
(Fibrate + TZD)
ATII
Lektin
TNFa
Adiponectin
FFA
TG
TG
TG
VLDL-TG

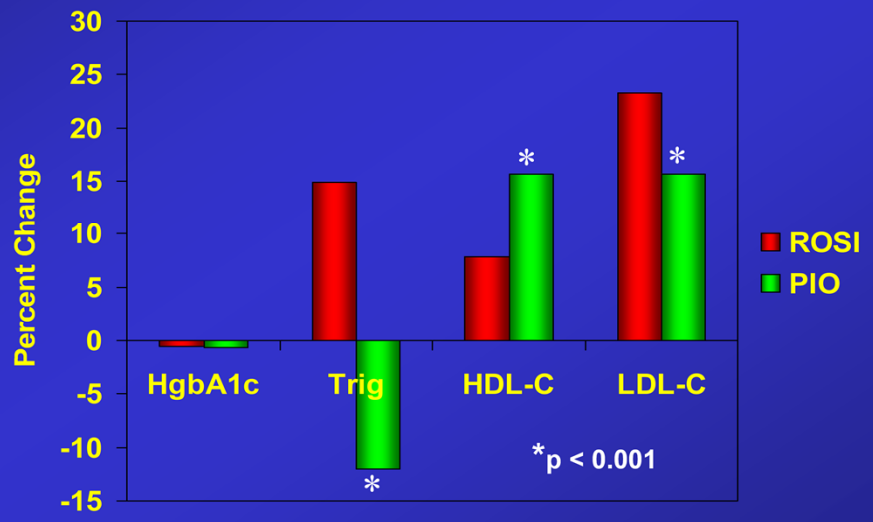

ACTOS® (pioglitazone HCl)
Effect of ACTOS on Abdominal Fat Distribution
Before ACTOS
After ACTOS
Fat Area (cm²)
350
300
250
200
150
100
300±44
342±44*
144±13
131±16†
0.59±0.08
0.44±0.06*
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
Visceral Fat/ Subcutaneous Fat Ratio
Subcutaneous Fat Area
Visceral Fat
Ratio
*p<0.01
†p<0.05
DeFronzo RA, et al. Diabetes 2000;49(suppl):A299. Abstract

Comparison of Lipid and Glycemic Effects of Glitazones: GLAI

Rosiglitazone
4 mg twice daily
Patients: 402

Pioglitazone
45 mg daily
Patients: 400

24 week study



Goldberg et al; AHA Annual Meeting, Nov, 2004

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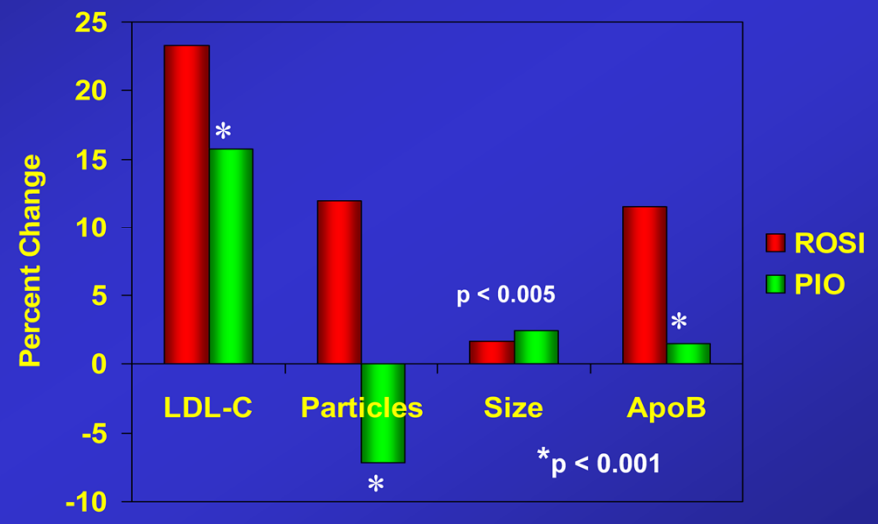

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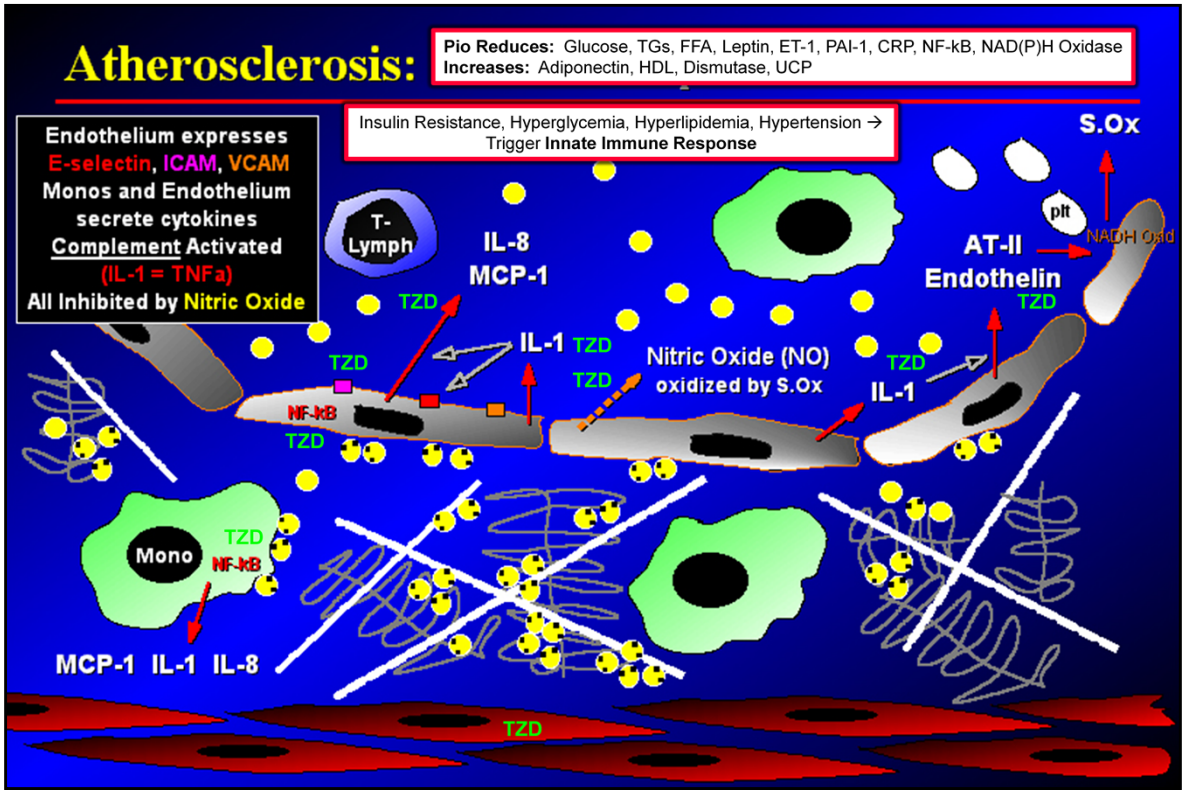
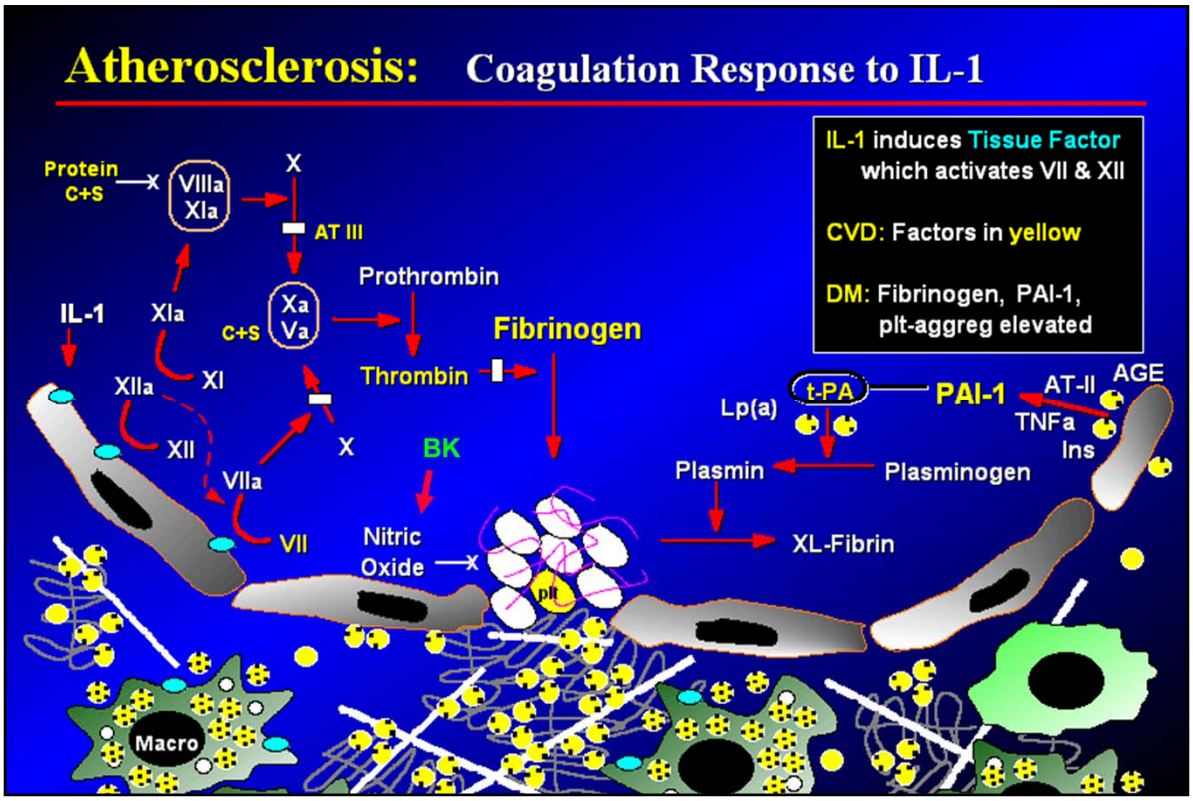
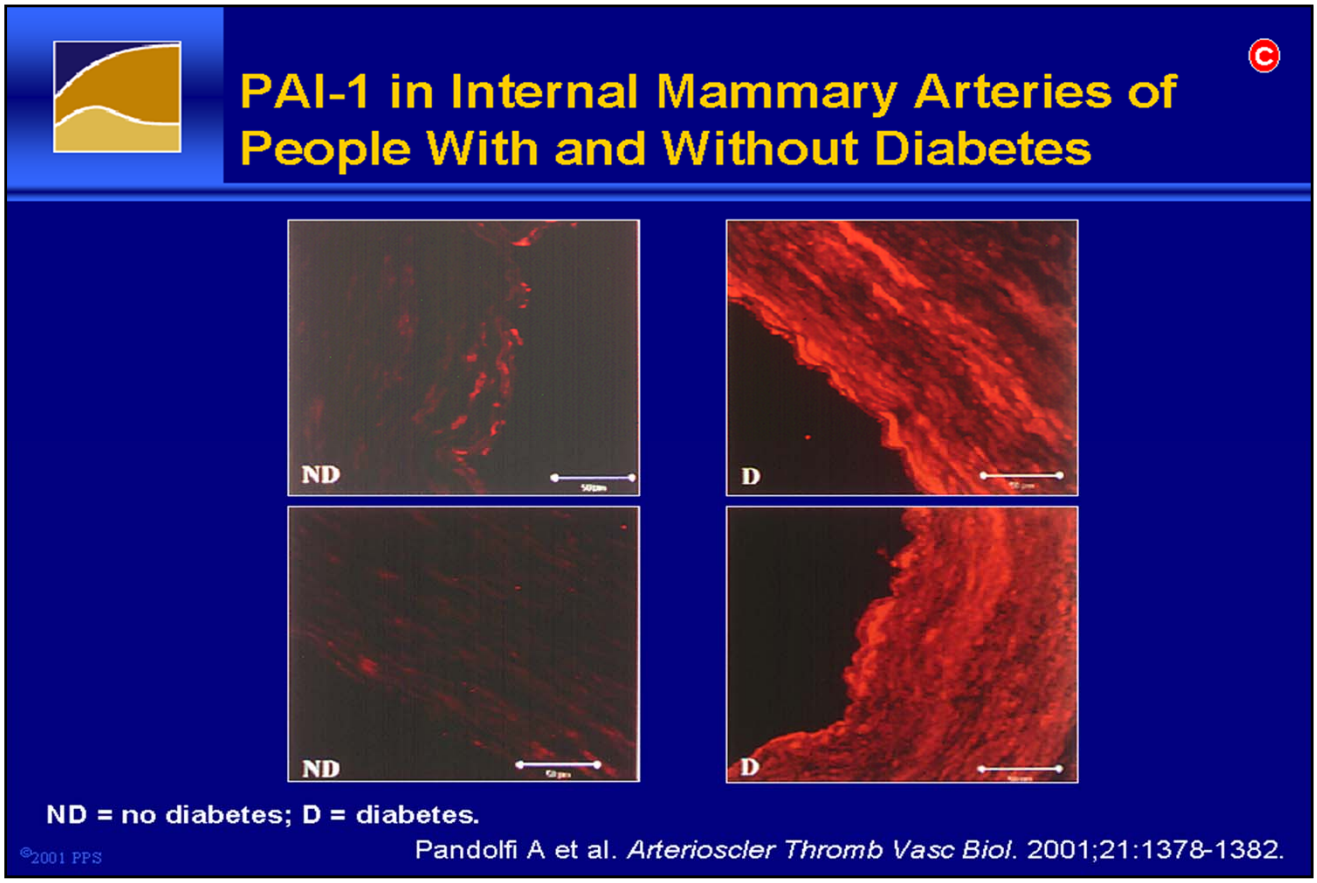

Atherosclerosis:
Pio Reduces: Glucose, TGs, FFA, Leptin, ET-1, PAI-1, CRP, NF-kB, NAD(P)H Oxidase
Increases: Adiponectin, HDL, Dismutase, UCP
Endothelium expresses
E-selectin, ICAM, VCAM
Monos and Endothelium
secrete cytokines
Complement Activated
(IL-1 = TNFa)
All Inhibited by Nitric Oxide
Insulin Resistance, Hyperglycemia, Hyperlipidemia, Hypertension →
Trigger Innate Immune Response
S.Ox
T-Lymph
IL-8
MCP-1
plt
NADH Oxid
AT-II
Endothelin
TZD
IL-1
NF-kB
Nitric Oxide (NO)
oxidized by S.Ox
Mono
MCP-1 IL-1 IL-8


Atherosclerosis: Coagulation Response to IL-1
IL-1 induces Tissue Factor which activates VII & XII
CVD: Factors in yellow
DM: Fibrinogen, PAI-1, plt-aggreg elevated
Protein C+S
VIIIa Xa
X
AT III
Prothrombin
IL-1
XIa
C+S
Xa Va
Fibrinogen
Thrombin
XIIa
XI
XII
X
BK
VIIa
VII
Nitric Oxide
plt
Lp(a)
t-PA
PAI-1
AT-II
AGE
TNFa
Ins
Plasmin
Plasminogen
XL-Fibrin
Macro



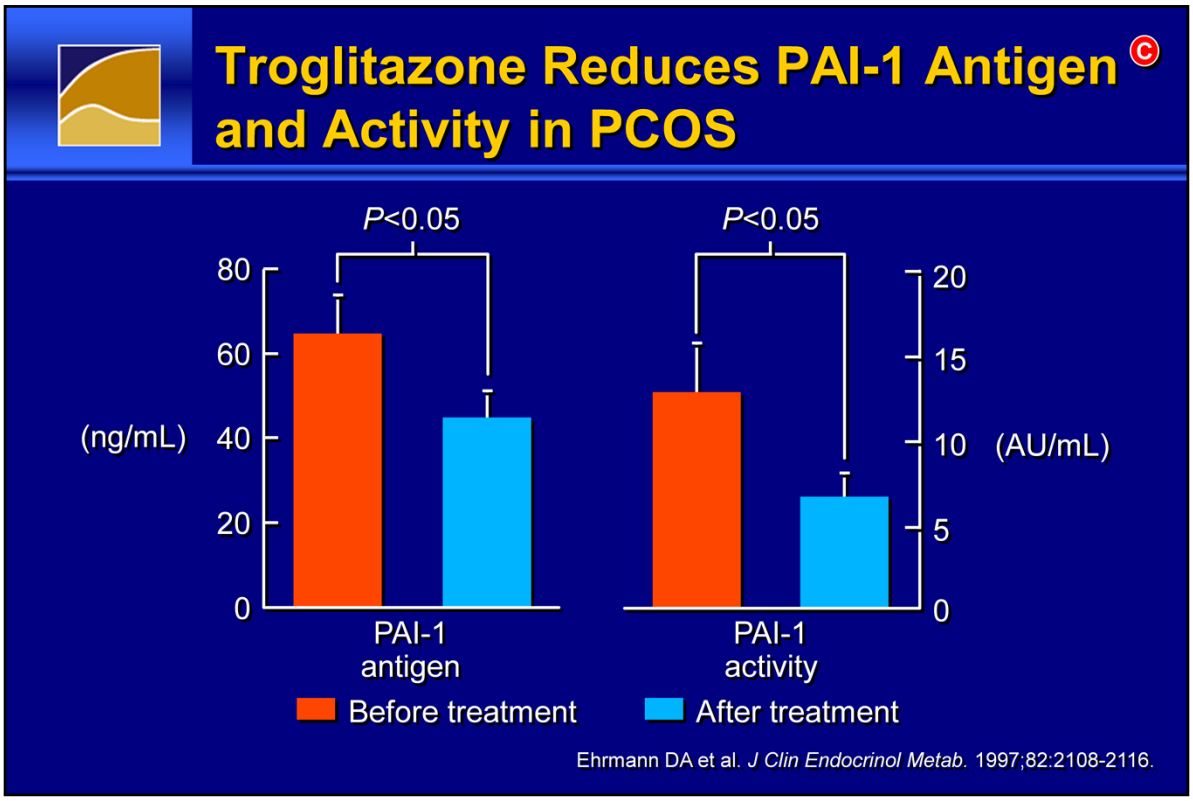
PAI-1 in Internal Mammary Arteries of People With and Without Diabetes

In this study, internal mammary arteries used for coronary artery bypass grafting were evaluated immunohistochemically for the presence of plasminogen activator inhibitor type 1 (PAI-1). Vessels were obtained from patients with type 2 diabetes and from those without diabetes. In both instances, the vessels appeared to be morphologically normal on the basis of a visible inspection before grafting.

In the left panels of the slide, PAI-1 immunostaining was barely visible in the vessel walls of arteries obtained from patients without diabetes. In contrast, PAI-1 immunostaining was clearly evident in the vessel walls of arteries obtained from the patients with diabetes.

These findings indicate that PAI-1 is overexpressed in vessels of patients with type 2 diabetes even before the vessels become morphologically abnormal. PAI-1 expression in the vessel wall is known to inhibit vascular smooth muscle cell migration from the media to the intima. Consequently, increased PAI-1 expression may be an etiologic factor in the evolution of vulnerable plaques typical of patients with type 2 diabetes.

Pandolfi A et al. *Arterioscler Thromb Vasc Biol*. 2001;21:1378-1382.
Sobel BE. *Proc Assoc Am Physicians*. 1999;111:313-318.



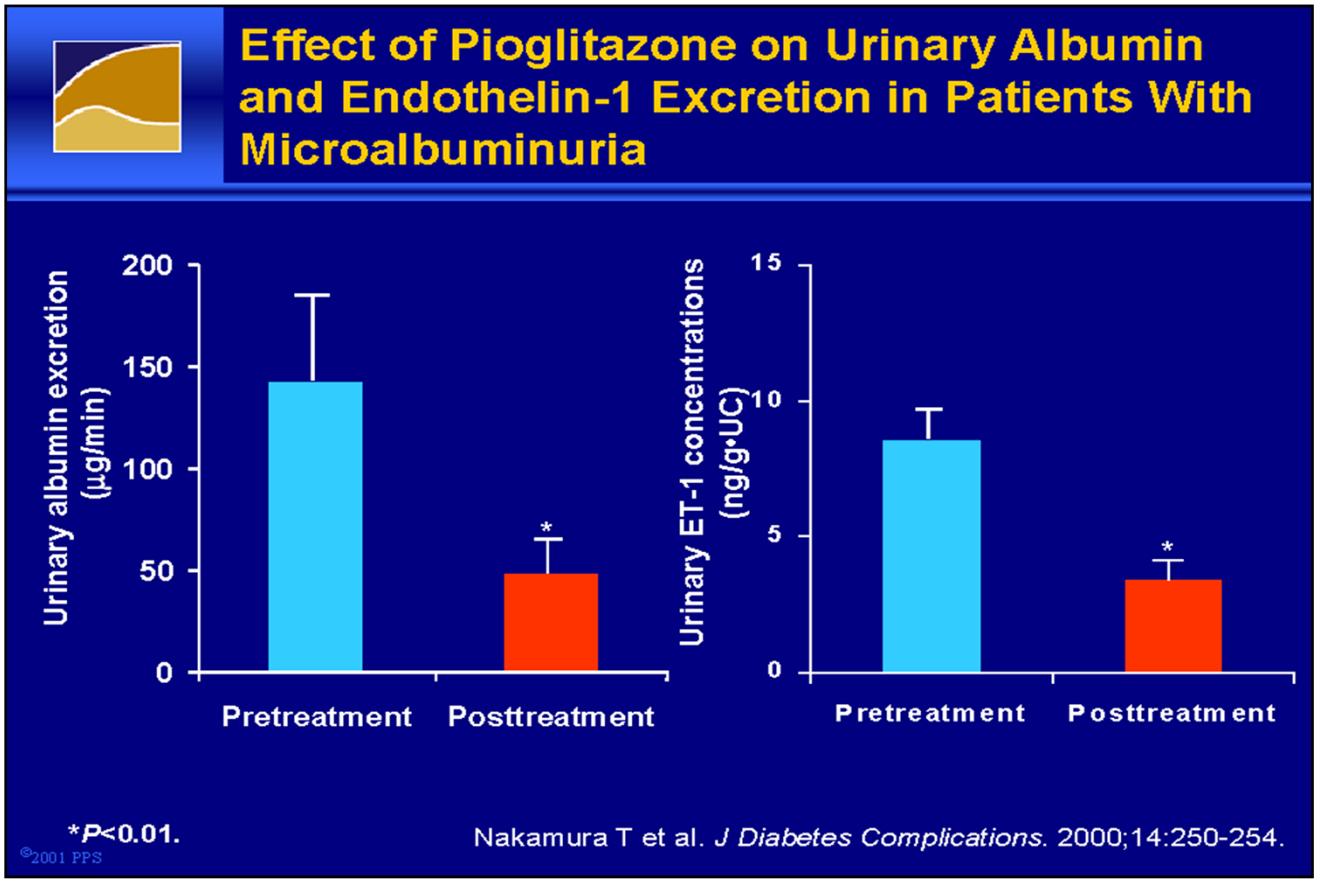
Abstract

Women with polycystic ovary syndrome (PCOS) are characterized by defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis. We administered the insulin-sensitizing agent troglitazone to 13 obese women with PCOS and impaired glucose tolerance to determine whether attenuation of hyperinsulinemia ameliorates these defects. All subjects had oligomenorrhea, hirsutism, polycystic ovaries, and hyperandrogenemia. Before and after treatment with troglitazone (400 mg daily for 12 weeks), all had 1) a GnRH agonist (leuprolide) test, 2) a 75-g oral glucose tolerance test, 3) a frequently sampled iv glucose tolerance test to determine the insulin sensitivity index and the acute insulin response to glucose, 4) an oscillatory glucose infusion to assess the ability of the beta-cell to entrain to glucose as quantitated by the normalized spectral power for the insulin secretion rate, and 5) measures of fibrinolytic capacity [plasminogen activator inhibitor type 1 (PAI-1) and tissue plasminogen activator].

There was no change in body mass index (39.9 +/- 1.4 vs. 40.2 +/- 1.4 kg/m2) or body fat distribution after treatment. Both the fasting (91 +/- 3 vs. 103 +/- 3 mg/dL; P < 0.001) and 2 h (146 +/- 8 vs. 171 +/- 6 mg/dL; P < 0.02) plasma glucose concentrations during the oral glucose tolerance test declined significantly. There was a concordant **reduction in glycosylated**

hemoglobin to 5.7 +/- 0.1 from a pretreatment level of 6.1 +/- 0.1% (P < 0.03). **Insulin sensitivity increased** from 0.58 +/- 0.14 to 0.95 +/- 0.26 10(-5) min-1/pmol.L (P < 0.01) after treatment as did the disposition index (745 +/- 135 vs. 381 +/- 96; P < 0.05). The ability of the beta-cell to appropriately detect and **respond to an oscillatory glucose infusion improved significantly** after troglitazone treatment; the normalized spectral power for the insulin secretion rate increased to 5.9 +/- 1.1 from 4.3 +/- 0.8 (P < 0.05). Basal levels of total testosterone (109.3 +/- 15.2 vs. 79.4 +/- 9.8 ng/dL; P < 0.05) and free testosterone (33.3 +/- 4.0 vs. 21.2 +/- 2.6 pg/mL; P < 0.01) declined significantly after troglitazone treatment. Leuprolide-stimulated levels of 17-hydroxyprogesterone, androstenedione, and total testosterone were significantly lower posttreatment compared to pretreatment. The reduction in androgen levels occurred independently of any changes in gonadotropin levels. **A decreased functional activity of PAI-1** in blood (from 12.7 +/- 2.8 to 6.3 +/- 1.4 AU/mL P < 0.05) was associated with a **decreased concentration of PAI-1 protein** (from 64.9 +/- 9.1 to 44.8 +/- 6.1 ng/mL; P < 0.05). No change in the functional activity of tissue plasminogen activator (from 5.3 +/- 0.4 to 5.1 +/- 0.5 IU/mL) was observed despite a decrease in its concentration (from 9.6 +/- 0.9 to 8.2 +/- 0.7 ng/mL; P < 0.05). The marked reduction in PAI-1 could be expected to improve the fibrinolytic response to thrombosis in these subjects.

We conclude that administration of troglitazone to women with PCOS and impaired glucose tolerance ameliorates the metabolic and hormonal derangements characteristic of the syndrome. Troglitazone holds potential as a useful primary or adjunctive treatment for women with PCOS.



Effect of Pioglitazone on Urinary Albumin and Endothelin-1 Excretion in Patients With Microalbuminuria

Urinary endothelin (ET)-1 is present in patients with type 2 diabetes and microalbuminuria, and an increase in circulating ET-1 level precedes the progression to diabetes-related microalbuminuria. Nakamura and colleagues studied the effects of pioglitazone, glibenclamide, and voglibose on urinary albumin excretion (UAE) and ET-1 in patients with type 2 diabetes and microalbuminuria. The study population included 30 healthy controls and 45 normotensive (BP<140/90 mm Hg) patients with type 2 diabetes and microalbuminuria.

On the basis of median UAE in at least three consecutive 4-hour urine collections, patients were classified as having normal (<20 µg/min) or increased UAE. The median UAE also established the baseline measurement for patients. UAEs in patients with type 2 diabetes (156.2 ± 42.8 µg/min) were significantly (P<0.001) higher than those in 30 healthy controls (8.2 ± 2.6 µg/min).

After establishing their baseline measurements of UAE and urine and plasma ET-1, patients were randomized to receive pioglitazone 30 mg/day (n=15), glibenclamide 5 mg/day (n=15), or voglibose 0.6 mg/day (n=15) for 3 months. As was done before treatment, median UAE and urinary ET-1 were measured in at least three consecutive 4-hour urine collections following the 3-month treatment period.

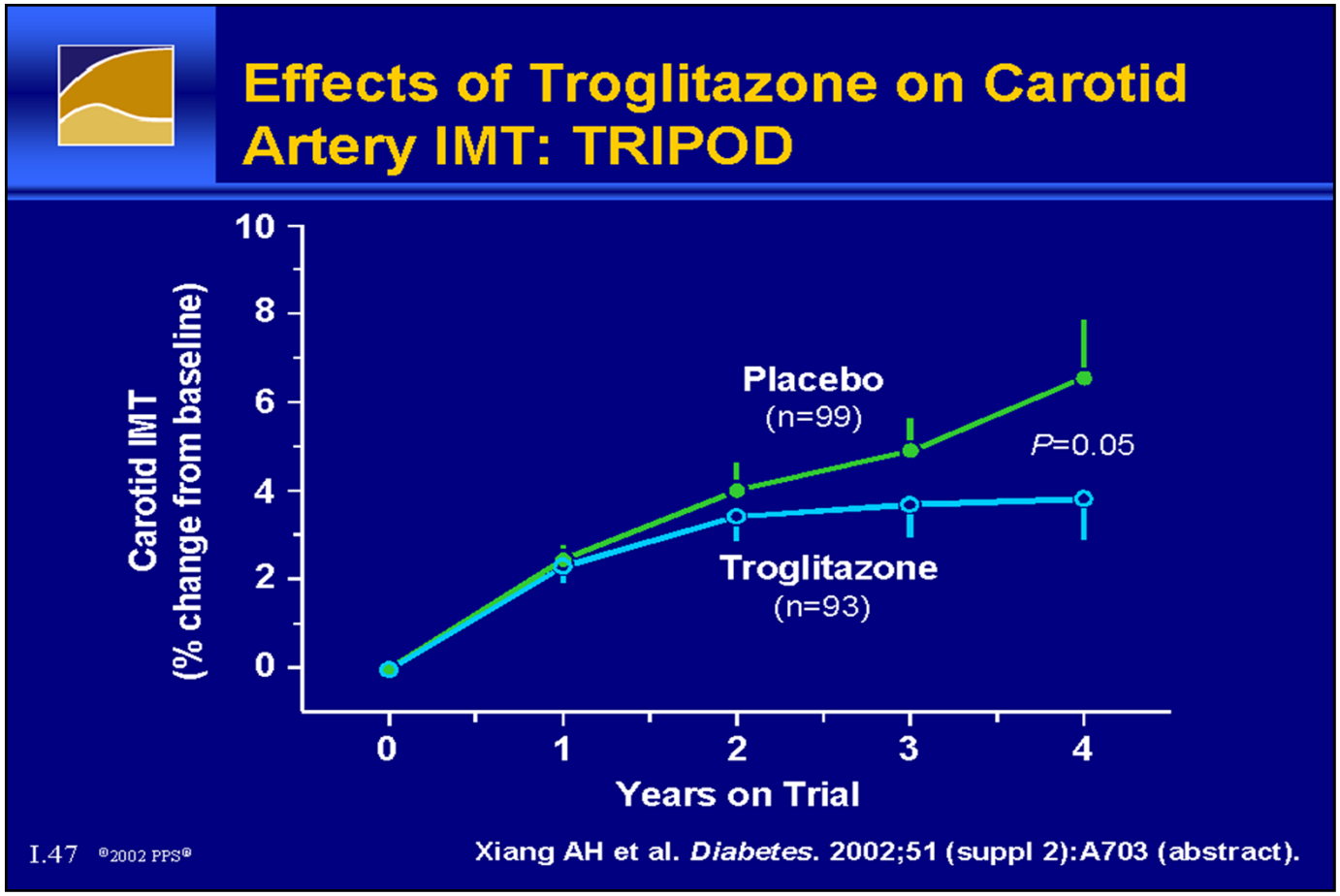
Before treatment, UAE and urine and plasma ET-1 concentrations differed very little among the three treatment groups. After treatment, UAE decreased significantly (P<0.01) from 142.8 ± 42.2 to 48.4 ± 18.2 µg/min in the pioglitazone group, but showed little change in the glibenclamide and voglibose groups (not shown).

Urinary ET-1 concentrations in the pioglitazone group decreased significantly (P<0.01) from 8.6 ± 1.3 to 3.4 ± 0.5 ng/g urinary creatinine, but showed little change after treatment in the glibenclamide and voglibose groups (not shown). In contrast, plasma ET-1 concentrations showed little change after treatment in all groups.

Nakamura T et al. *J Diabetes Complications*. 2000;14:250-254.

Cardiovascular Disease

Carotid Ultrasound
Intravascular Ultrasound → Coronaries
Cardiovascular Events



Effects of Troglitazone on Carotid Artery IMT: TRIPOD

Annual measurements of carotid intima media thickness were included in the Troglitazone in Prevention of Diabetes (TRIPOD) study. Patients were Hispanic women with a mean age of 35 years and a history of recent gestational diabetes. Treatments were troglitazone 400 mg/d or placebo.

At randomization, the two treatment groups had identical mean IMT values (not shown)

The graph shows rates of change in IMT, expressed as percent of the baseline measurement, during 4 years of follow-up. The rate was significantly lower in the women randomized to troglitazone

In an analysis to determine possible mechanisms for the IMT difference, adjustment for on-trial intergroup differences in annual measures of OGTT glucose area, OGTT insulin area, fasting lipids (LDL-C, HDL-C, and total cholesterol), blood pressure, and body weight had no impact on the intergroup IMT differences, indicating that glucose, insulin, lipids, blood pressure, and weight gain did not mediate the IMT differences.

In a separate analysis using measures of insulin resistance during the first 3 months on trial, it was observed that a reduction in the rate of IMT progression occurred only in women who increased their insulin sensitivity when placed on troglitazone.

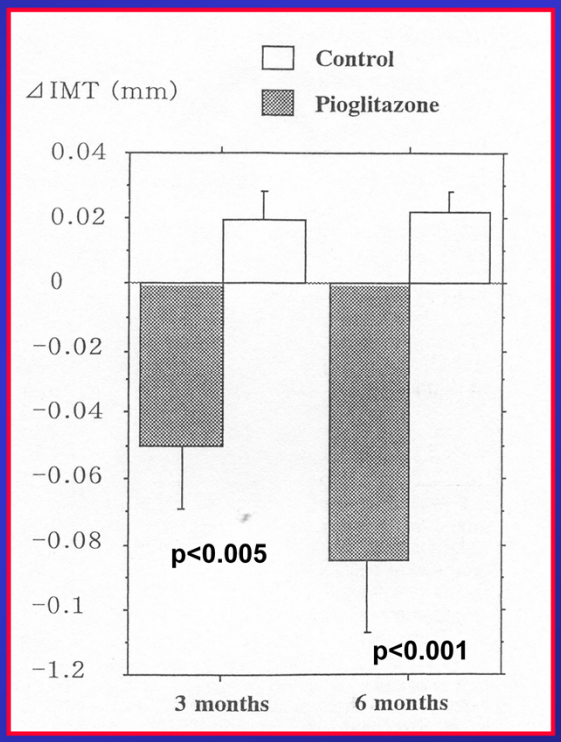
The authors suggest that the effect of troglitazone may be mediated by a direct effect of the drug on the arterial wall.

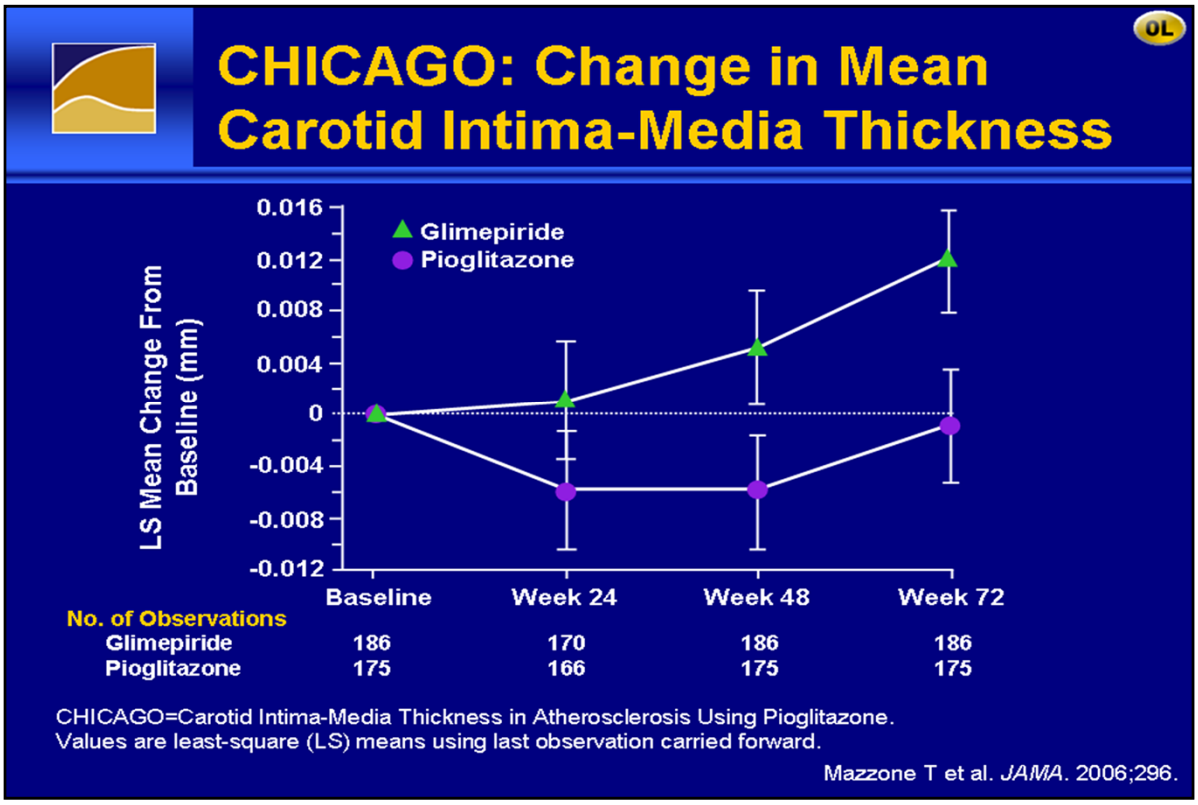
Xiang AH et al. *Diabetes*. 2002;51(suppl 2):A703 (abstract).

Pioglitazone
Carotid Ultrasound

106 Japanese with Type 2 DM
Randomized: Pio 30 mg or Placebo
Age: 62.2 ± 1.1 yrs ~ 55% male

Sulfonyureas: almost all
Statins: ~45% Aspirin: none
HgbA1c: 8.5 --> 7.5 --> 7.3% w/ Pio
No change: Chol, TG, HDL, BP





CHICAGO: Change in Mean Carotid Intima-Media Thickness

Carotid intima-media thickness (CIMT) is a noninvasive measure of carotid atherosclerosis that correlates with the risk of clinical cardiovascular events. Several previous studies have shown that thiazolidinediones can reduce CIMT levels and rates of progression in people with and without diabetes.

The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) study is another trial designed to examine the effects of thiazolidinediones, specifically pioglitazone, on rates of CIMT in 462 patients with type 2 diabetes but without symptomatic cardiovascular disease.

The study compared the effect of pioglitazone (15-45 mg/d) with that of glimepiride (1-4 mg/d) on progression of CIMT. Glimepiride was chosen as a comparator because it is a commonly used antidiabetic medication with a mechanism of action distinct from that of pioglitazone. (A placebo could not be expected to maintain adequate glycemic control.) CIMT was measured at baseline and at 24, 48, and 72 weeks. The primary endpoint was absolute change from baseline to final visit in mean posterior-wall CIMT in the right and left common carotid arteries.

The CIMT progression rate was relatively low in both treatment groups, but **significantly lower in the pioglitazone group at all time points evaluated**. At week 72, the primary endpoint of progression of mean CIMT was less with pioglitazone versus glimepiride with a difference of -0.013 mm, (95% confidence interval -0.024 to -0.002, *P*=0.02). Pioglitazone also slowed progression of maximum CIMT compared to glimepiride with a difference of -0.024 mm (95% confidence interval -0.042 to -0.006, *P*=0.008). The beneficial effect of pioglitazone on CIMT was similar among participants regardless of age, sex, systolic blood pressure, duration of diabetes, BMI, A1C level, and statin use.

The CHICAGO study confirms other trials that have shown significant reductions in CIMT or in CIMT progression rates with other thiazolidinediones, providing strong evidence for a class effect.

Mazzone T et al. *JAMA*. 2006;296:published online Nov. 13, 2006.

Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Type 2 DM

PERISCOPE Randomized Controlled Trial – *JAMA 299:1561-1573, 2008*

Table 1. Baseline Demographic Characteristics and Medications at the Time of Randomization

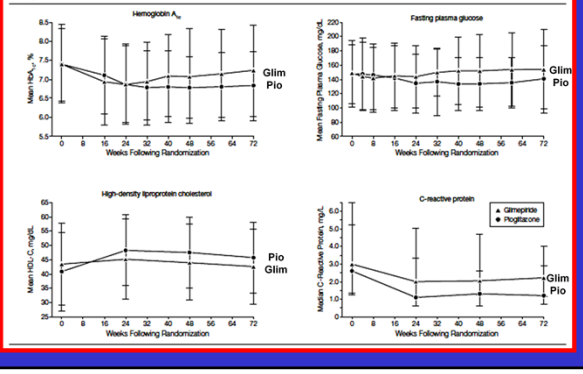
	Glimepiride (n = 273)	Pioglitazone (n = 270)	*P* Value[a]
Age, mean (SD), y	59.7 (9.1)	60.0 (9.4)	.64
Men, No. (%)	180 (65.9)	186 (68.9)	.39
Race, No. (%)[b]			
White	220 (80.6)	225 (83.3)	.17
Black	27 (9.9)	30 (11.1)	
Asian	16 (5.9)	12 (4.4)	
Native American	10 (3.7)	3 (1.1)	
Ethnicity, No. (%)			
Hispanic	71 (26)	63 (23.3)	.21
Weight, mean (SD), kg	92.8 (18.5)	94.2 (19.7)	.28
BMI, mean (SD)	32.0 (5.2)	32.1 (5.3)	.91
Smoking status, No. (%)			
Current	53 (19.4)	31 (11.5)	.01
Past	119 (43.6)	147 (54.4)	.44
Never	99 (36.4)	89 (33.0)	.42
Duration of disease, median (IQR), mo			
Diabetes, mo	71.0 (30.0-131.0)	70.0 (27.0-129.0)	.74
Coronary disease	8.0 (1.0-56.0)	9.0 (1.0-50.0)	.90
Hypertension, No. (%)	250 (91.6)	225 (83.3)	.002
Prior myocardial infarction, No. (%)	70 (25.6)	83 (30.7)	.08
Medication use, No. (%)			
Aspirin	251 (91.9)	242 (89.6)	.29
β-Blocker	211 (77.3)	205 (75.9)	.84
ACE inhibitor or ARB	229 (83.9)	217 (80.4)	.30
Statin	224 (82.0)	220 (81.5)	.87
Other lipid-lowering agent	17 (6.2)	13 (4.8)	.50
Metformin	174 (63.7)	176 (65.2)	.69
Insulin	63 (23.1)	49 (18.1)	.09

Mean Daily Dosages:
Glimepiride: 2.9 mg
Pioglitazone: 37.4 mg

All other DM medications were allowed

	Change From Baseline[e,f,g]	Pioglitazone	
HbA_{1c} level, LS mean (95% CI), %	−0.36 (−0.48 to −0.24)	−0.55 (−0.68 to −0.42)	.03
Fasting blood glucose, LS mean (95% CI), mg/dL	0.41 (−3.66 to 4.48)	−8.5 (−12.73 to −4.27)	.003
Fasting insulin levels, median (95% CI), μU/mL, [% change][d]	1.33 (−0.5 to 5.0) [8.5]	−5.0 (−7.0 to −4.0) [−28.3]	<.001
Cholesterol, LS mean (95% CI), mg/dL [% change]			
Total	1.16 (−2.9 to 5.3) [3.1]	2.5 (−3.3 to 8.3) [4.4]	.39
LDL	1.1 (−2.4 to 4.6) [6.9]	2.1 (−1.5 to 5.8) [6.6]	.69
HDL	0.9 (−0.3 to 2.1) [4.1]	5.7 (4.4 to 7.0) [16.0]	<.001
Fasting triglycerides, median (95% CI), mg/dL [% change]	3.3 (−10.7 to 11.7) [0.6]	−16.3 (−27.7 to −11.0) [−15.3]	<.001
C-reactive protein, median (95% CI), mg/L [% change][d]	−0.4 (−0.9 to −0.2) [−18.0]	−1.0 (−1.5 to −0.8) [−44.9]	<.001
Brain-type natriuretic peptide, median (95% CI), pg/mL	0.58 (−2.0 to 4.5)	8.0 (5.0 to 10.5)	.001
Blood pressure, median (95% CI), mm Hg			
Systolic	2.3 (0.9 to 3.7)	0.1 (−1.4 to 1.5)	.03
Diastolic	0.9 (0.1 to 1.7)	−0.9 (−1.7 to −0.01)	.003
Weight, median (95% CI), kg[d]	1.6 (0.8 to 2.4)	3.6 (2.8 to 4.4)	<.001

Figure 2. Changes in Mean Hemoglobin A_{1c}, Fasting Plasma Glucose Levels, High-Density Lipoprotein Cholesterol, and C-Reactive Protein During the Trial (n = 360)



Context No antidiabetic regimen has demonstrated the ability to reduce progression of coronary atherosclerosis. Commonly used oral glucose-lowering agents include sulfonylureas, which are insulin secretagogues, and thiazolidinediones, which are insulin sensitizers.

Objective To compare the effects of an insulin sensitizer, pioglitazone, with an insulin secretagogue, glimepiride, on the progression of coronary atherosclerosis in patients with type 2 diabetes

Design, Setting, and Participants Double-blind, randomized, multicenter trial at 97 academic and community hospitals in North and South America (enrollment August 2003-March 2006) in 543 patients with coronary disease and type 2 diabetes.

Interventions A total of 543 patients underwent coronary intravascular ultrasonography and were randomized to receive glimepiride, 1 to 4 mg, or pioglitazone, 15 to 45 mg, for 18 months with titration to maximum dosage, if tolerated. Atherosclerosis progression was measured by repeat intravascular ultrasonography examination in 360 patients at study completion.

Main Outcome Measure Change in percent atheroma volume (PAV) from baseline to study completion.

Results Least squares mean PAV increased 0.73% (95%CI, 0.33% to 1.12%) with glimepiride and decreased 0.16% (95% CI, −0.57% to 0.25%) with pioglitazone (*P*=.002). An alternative analysis imputing values for non-completers based on baseline characteristics showed an increase in PAV of 0.64% (95% CI, 0.23% to 1.05%) for glimepiride and a decrease of 0.06% (−0.47% to 0.35%) for pioglitazone (between-group *P*=.02). Mean (SD) baseline HbA1c levels were 7.4% (1.0%) in both groups and declined during treatment an average 0.55% (95% CI,−0.68% to −0.42%) with pioglitazone and 0.36% (95% CI,−0.48% to −0.24%) with glimepiride (between-group *P*=.03). In the pioglitazone group, compared with glimepiride, high-density lipoprotein levels increased 5.7 mg/dL (95% CI, 4.4 to 7.0 mg/dL; 16.0%) vs 0.9 mg/dL (95% CI, −0.3 to 2.1 mg/dL; 4.1%), and median triglyceride levels decreased 16.3 mg/dL (95% CI, −27.7 to −11.0 mg/dL; 15.3%) vs an increase of 3.3 mg/dL (95%CI,−10.7 to 11.7 mg/dL; 0.6%) (*P*<0.001 for both comparisons). Median fasting insulin levels decreased with pioglitazone and increased with glimepiride (*P*=.001). Hypoglycemia was more common in the glimepiride group and edema, fractures, and decreased hemoglobin levels occurred more frequently in the pioglitazone group.

Conclusion In patients with type 2 diabetes and coronary artery disease, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.

Trial Registration clinicaltrials.gov Identifier: NCT00225277 *JAMA. 2008;299(13):1561-1573*

Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Type 2 DM

PERISCOPE Randomized Controlled Trial – *JAMA 299:1561-1573, 2008*

Table 3. Baseline, Follow-up, and Change From Baseline in Intravascular Ultrasound End Points

	Glimepiride (n = 181)		Pioglitazone (n = 179)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	*P* Value[a]
Baseline Examination					
Percent atheroma volume, %[b]	40.3 (8.9)	40.3 (34.7 to 45.9)	40.6 (8.4)	40.3 (34.1 to 46.0)	.54
Maximum atheroma thickness, mm[c]	0.82 (0.26)	0.80 (0.64 to 0.98)	0.81 (0.25)	0.79 (0.61 to 1.00)	.94
Normalized total atheroma volume,[c] mm^3	219.8 (95.2)	197.8 (148.1 to 277.7)	207.5 (83.8)	190.9 (147.6 to 254.5)	.27
Atheroma volume in 10-mm most diseased segment,[c] mm^3	64.7 (31.5)	62.1 (40.9 to 86.6)	62.7 (28.1)	59.4 (43.6 to 78.7)	.59
Follow-up Examination					
Percent atheroma volume, %[b]	41.0 (9.0)	40.5 (35.2 to 46.9)	40.5 (8.5)	40.5 (33.6 to 46.3)	.73
Maximum atheroma thickness, mm[c]	0.83 (0.26)	0.81 (0.64 to 0.99)	0.80 (0.24)	0.76 (0.62 to 0.97)	.39
Normalized total atheroma volume,[c] mm^3	217.7 (95.3)	192.6 (150.9 to 278.3)	200.8 (81.6)	184.5 (144.6 to 248.4)	.13
Atheroma volume in 10-mm most diseased segment,[c] mm^3	62.4 (31.2)	57.8 (39.5 to 83.1)	60.0 (27.5)	57.9 (39.7 to 77.8)	.62
Nominal Change From Baseline					
	LS Mean (95% CI)	*P* Value Change From Baseline	LS Mean (95%CI)	*P* Value Change From Baseline	*P* Value[d]
Percent atheroma volume, %[b]	0.73 (0.33 to 1.12)	<.001	−0.16 (−0.57 to 0.25)	.44	.002
Maximum atheroma thickness, mm[c]	0.011 (−0.0002 to 0.022)	.054	−0.011 (−0.022 to 0.0004)	.06	.006
Normalized total atheroma volume,[c] mm^3	−1.5 (−4.50 to 1.54)	.34	−5.5 (−8.67 to −2.38)	<.001	.06
Atheroma volume in 10-mm most diseased segment,[c] mm^3	−2.1 (−3.33 to −0.84)	.001	−2.0 (−3.33 to −0.67)	.003	.93

Abbreviation: CI, confidence interval; IQR, interquartile range; LS, least squares.
[a] *P* values for baseline and average follow-up values were generated from a 2-way analysis of variance model with terms for treatment and pooled center.
[b] Primary efficacy parameter.
[c] Secondary efficacy parameter.
[d] *P* values from 2-way analysis of variance with terms for treatment and pooled center and baseline value as covariates.

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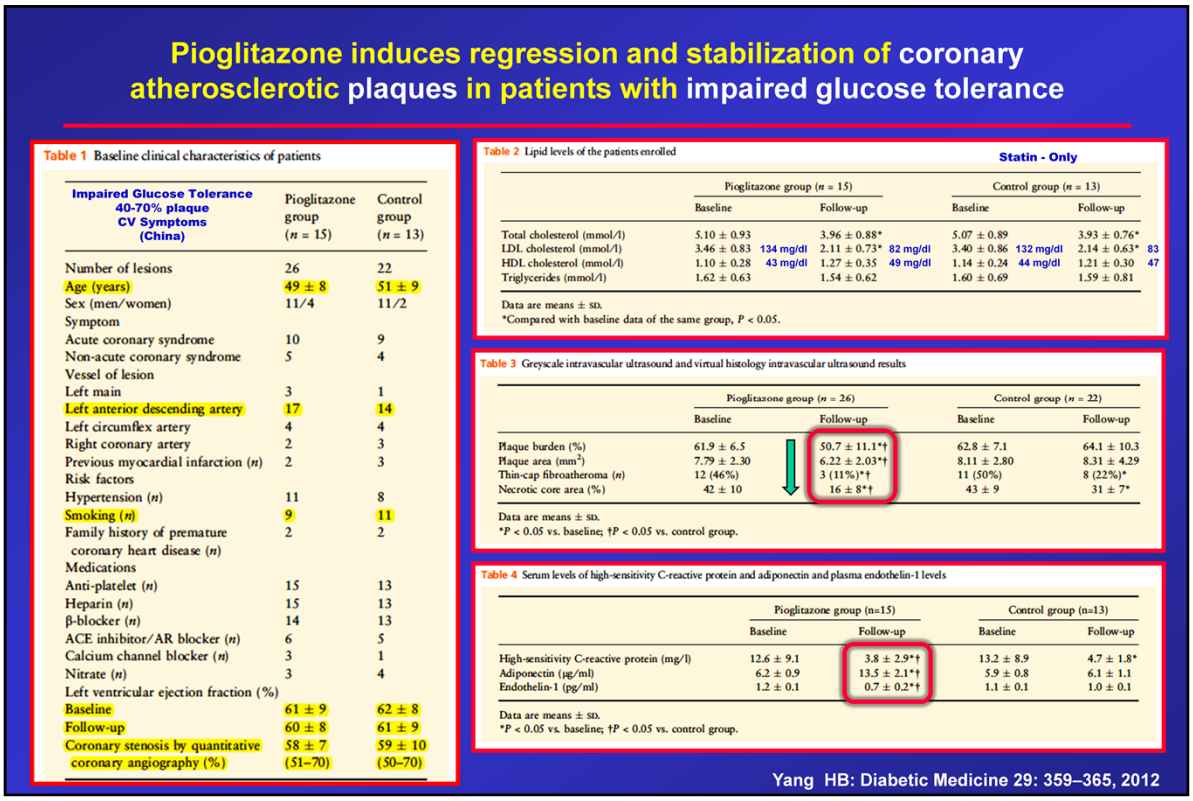


Aims To observe the effects of pioglitazone on coronary plaque area, plaque burden, serum high-sensitivity C-reactive protein, adiponectin and plasma endothelin-1 levels in patients with impaired glucose tolerance and coronary borderline lesions.

Methods Thirty patients were randomly divided into two groups: a pioglitazone group and a control group. The latter was administered placebo in addition to standard therapy; the former pioglitazone 15 mg/d in addition to standard therapy. Before treatment and 6 months later, left ventricular ejection fraction, serum lipid profile, high-sensitivity C-reactive protein, adiponectin and plasma endothelin-1 levels were detected. Coronary plaque area and plaque burden were examined using intravascular ultrasound.

Results No significant differences were found in left ventricular ejection fraction and serum lipid levels pre- and post-trial. Compared with the control group, 6 months' treatment with pioglitazone significantly decreased coronary plaque burden (50.7±11.1 vs. 64.1±10.3%, $P < 0.05$), plaque area (6.22±2.03 vs. 8.31±4.29, $P < 0.05$), thin-cap fibroatheroma prevalence (11 vs. 22%, $P < 0.05$) and percentage of necrotic core area (16±8 vs. 31±7%, $P < 0.05$). Compared with the control group, serum high-sensitivity C-reactive protein and plasma endothelin-1 levels were significantly lower and

adiponectin level significantly higher in patients in the pioglitazone group. Serum adiponectin level was negatively correlated with plasma endothelin-1 level and coronary plaque area ($r = 0.739$ and -0.431, respectively, both $P < 0.05$).

Conclusions Pioglitazone may induce regression and stabilization of coronary atherosclerotic plaques. The mechanisms might involve inhibition of inflammation, increase in adiponectin level and improvement in endothelial function.

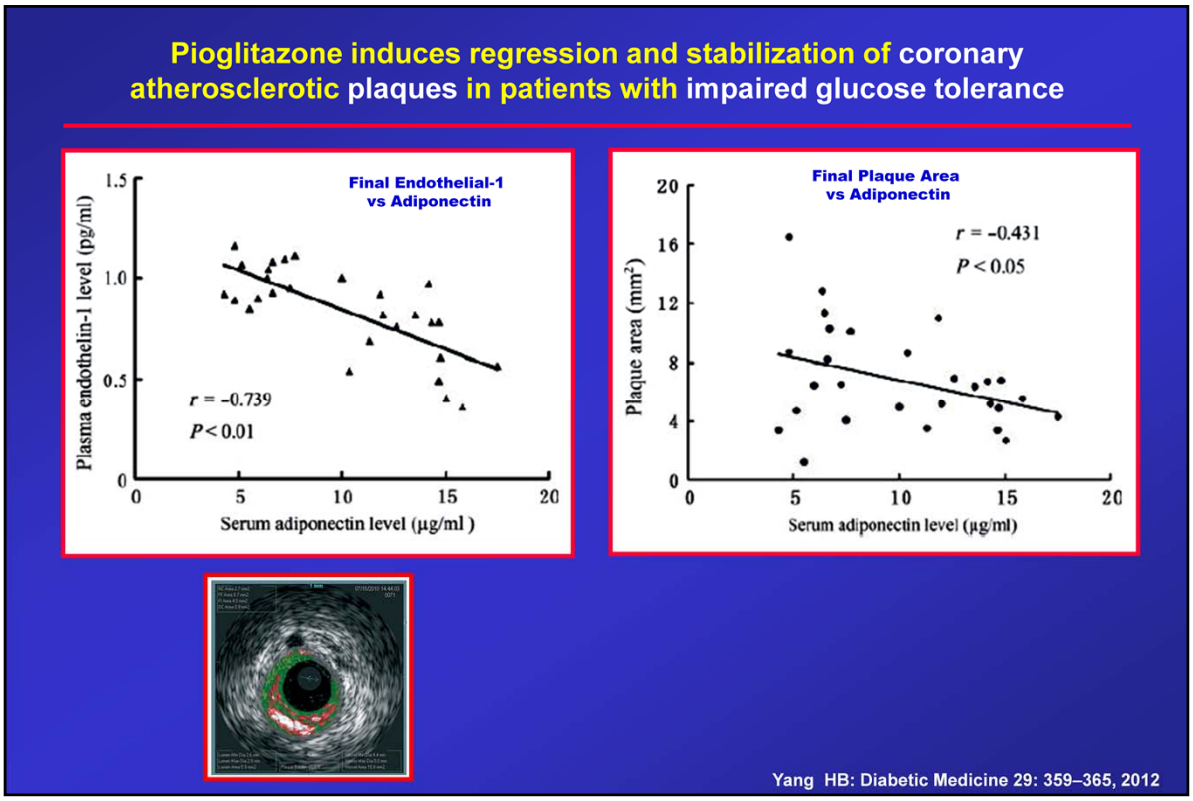


FIGURE 1 Representative image of virtual histology intravascular histology. The four virtual histology plaque components were color-coded as white (dense calcium), red (necrotic core), light green (fibro-fatty), and dark green (fibrotic tissue).

FIGURE 2 Correlation between serum level of adiponectin and plasma level of endothelin-1. Data of the follow-up of all patients in the two groups were analyzed.

FIGURE 3 Correlation between serum level of adiponectin and coronary plaque area. Data of the follow-up of all patients in the two groups were analyzed, and the most serious lesion analysed if two or more lesions were present in the same patient.

Cellular & Molecular Changes Associated With Inhibitory Effect of Pioglitazone on Neointimal Growth in Patients With Type 2 DM After Zotarolimus-Eluting Stent Implantation

94 Diabetic Patients

Randomized: Pioglit 30 mg or Placebo

Followed for 8 months

Both Groups:
A1c ~7.3 → 6.8% (p<0.05)
LDL ~120 → 88 mg/dl (p<0.05)
TGs ~138 → 116 (ns)

Pio Group Only:
Adiponectin 5.7 → 7.7 (p<0.05)

Hong SJ et al: Arterioscler Thromb Vasc Biol 30:2655-2665, 2010

Table 1. Baseline Characteristics of Patients*

Characteristic	Pioglitazone Group (n=47)	Placebo Group (n=47)	P Value
Age, yr†	63.5±7.4	62.4±8.3	0.76
Male sex	32 (68.1)	29 (61.7)	0.52
Body mass index†‡	23.4±2.4	23.2±4.3	0.94
Blood pressure, mm Hg†			
Systolic	140±13	143±12	0.42
Diastolic	85±6	87±7	0.34
Risk factors			
Hypertension	24 (51.1)	21 (44.7)	0.54
Dyslipidemia	14 (29.8)	16 (34.0)	0.66
Current smoker	10 (21.3)	12 (25.5)	0.63
Left ventricular ejection fraction, %†	52±7	54±8	0.70
Unstable angina pectoris	12 (25.5)	15 (31.9)	0.49
Diabetes treatment			
Diet only	6 (12.8)	9 (19.1)	0.40
Oral glucose-lowering therapy	40 (85.1)	37 (78.7)	0.42
Insulin	3 (6.4)	2 (4.3)	>0.99
Other diabetic medications after randomization			
Biguanides	8 (17.0)	11 (23.4)	0.44
α-Glucosidase inhibitors	10 (21.3)	12 (25.5)	0.63
Sulfonylureas	36 (76.6)	31 (66.0)	0.25
Other medications after stenting			
Aspirin	47 (100.0)	47 (100.0)	>0.99
Clopidogrel	47 (100.0)	47 (100.0)	>0.99
Atorvastatin	43 (91.5)	44 (93.6)	0.69
Angiotensin receptor blockers	16 (34.0)	14 (29.8)	0.66
Angiotensin converting enzyme inhibitors	8 (17.0)	11 (23.4)	0.44
β-blockers	2 (4.3)	1 (2.1)	>0.99
Calcium channel blockers	9 (19.1)	8 (17.0)	0.79
Diuretics	3 (6.4)	4 (8.5)	>0.99

Table 2. Results of Angiographic Measurements*

Variable	Pioglitazone Group (n=47)	Placebo Group (n=47)	P Value
No. of lesions stented	57	61	NA
Target coronary artery†			
Left anterior descending artery	29 (61.7)	32 (68.1)	0.52
Left circumflex artery	10 (21.3)	8 (17.0)	0.60
Right artery	8 (17.0)	7 (14.9)	0.78
Type of lesion, %†			
A	3 (6.4)	2 (4.3)	>0.99
B1	10 (21.3)	11 (23.4)	0.80
B2	22 (46.8)	25 (53.2)	0.54
C	12 (25.5)	9 (19.1)	0.46
Eccentric, %†	27 (57.4)	31 (66.0)	0.40
Baseline			
Reference diameter, mm	2.71±0.30	2.83±0.33	0.77
Minimal lumen diameter, mm	0.74±0.22	0.62±0.31	0.86
% of stenosis	74±7	79±9	0.11
Lesion length, mm	20.2±12.2	18.9±13.0	0.31
Postprocedure			
Reference diameter, mm	2.91±0.42	2.92±0.31	0.32
Minimal lumen diameter, mm	2.70±0.43	2.73±0.30	0.55
% of stenosis	8±3	8±2	0.21
Acute gain, mm	2.0±0.3	2.1±0.3	0.36
No. of stents‡	1.2±0.4 (1–2)	1.3±0.5 (1–2)	0.35
Stent length, mm	24.8±6.9	26.1±6.1	0.67
Stent diameter, mm	2.90±0.44	2.84±0.31	0.16
Follow-up at 8 mo			
Reference diameter, mm	2.91±0.35	2.93±0.32	0.77
Minimal lumen diameter, mm	2.30±0.41	2.09±0.53	0.003
% of stenosis	20±14	28±17	0.02
Late lumen loss, mm	0.41±0.40	0.65±0.54	0.04
Binary restenosis†	6 (15.0)	8 (21.1)	0.49

Objective: To investigate the mechanistic basis underlying antirestenosis and the antiatherogenic effect of pioglitazone in patients with type 2 diabetes mellitus who were undergoing zotarolimus-eluting stent implantation.

Methods and results: Recent studies highlight the beneficial effect of pioglitazone in attenuating neointimal growth after stent implantation. Patients with coronary artery diseases were randomly assigned to pioglitazone (n=47) or placebo (n=47) after stent implantation. Pioglitazone significantly reduced neointimal hyperplasia within the stented lesion and attenuated total plaque burden in the in-segment regions of the stent, as assessed by intravascular ultrasonography at the 8-month follow-up. These changes were preceded by reduced circulating natural killer (NK) cells, diminished interleukin 6 and monocyte chemoattractant protein-1 levels, and downregulation of chemokine receptor 2 at 2 days after stent implantation; and an elevated interleukin 10 level at 10 days after implantation. Furthermore, the proliferation and migration of vascular smooth muscle cells were inhibited in the presence of pioglitazone-treated patient serum, demonstrating that the antiproliferative effects of pioglitazone occurred concurrently with its anti-inflammatory action.

Conclusions: Our data present early cellular and immunologic changes by

pioglitazone that might have been associated with antirestenotic and antiatherogenic effects in diabetic patients. Inhibiting proinflammatory responses while promoting anti-inflammatory circuits, together with an antiproliferative action, may, in part, account for the antirestenotic effect of pioglitazone by altering vascular remodeling processes in the early phase.

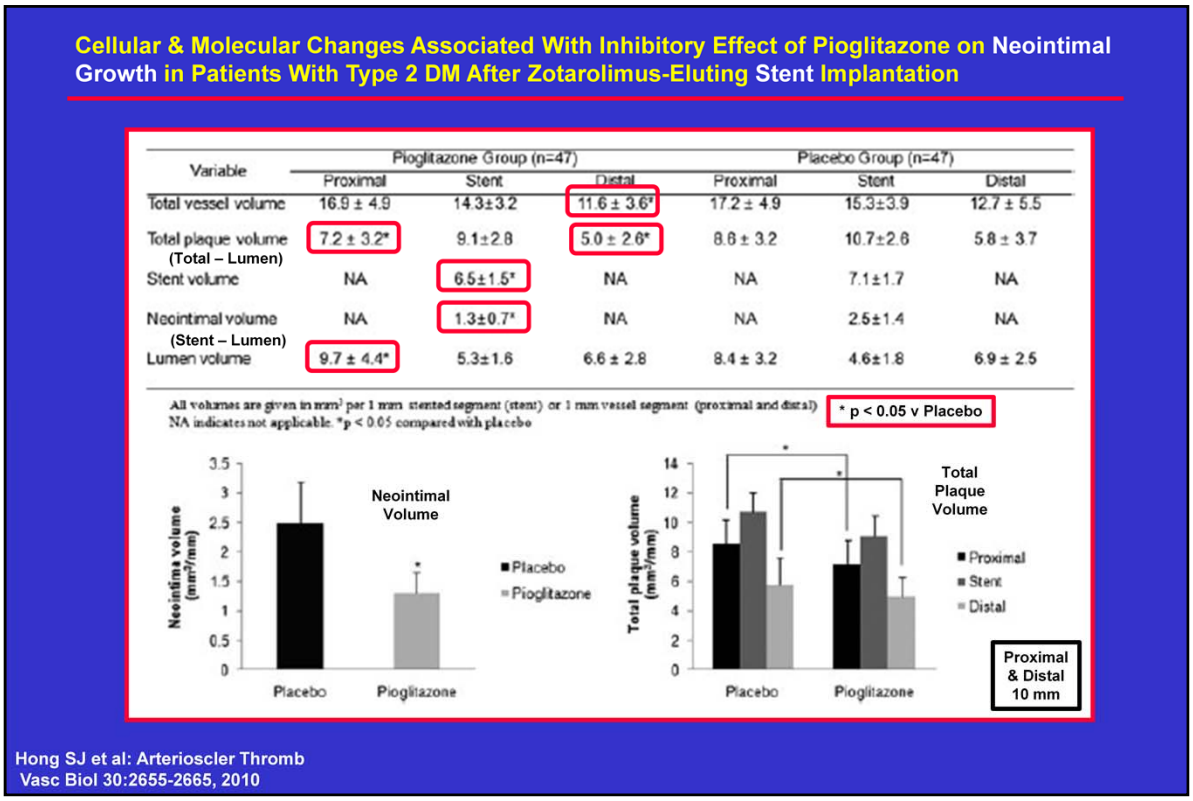


Figure 2. IVUS measurements at the 8-month follow-up. The IVUS measurements were performed as described in the "Methods" section. Pioglitazone reduced the neointima volume and the total plaque volume at the 8-month follow-up after ZES implantation in patients with type 2 diabetes, as assessed by IVUS. **P*<0.05 vs placebo.

A significantly lower neointima volume was detected within the stented segment compared with the placebo group at 8 months (1.3±0.7 versus 2.5±1.4 mm^3/mm, as measured by IVUS; *P*<0.001). Measurement of proximal and distal 10-mm segments of the stent revealed that patients receiving pioglitazone showed less plaque volume in the adjacent segments compared with that in the placebo group (7.2±3.2 versus 8.6±3.2 for the proximal segment, and 5.0±2.6 versus 5.8±3.7 for the distal segment). Probability values calculated from multivariate nonparametric methods for Mann-Whitney statistics demonstrated that none of the variables measured in the placebo and pioglitazone groups at baseline appeared to significantly modulate the anti-restenotic effect of pioglitazone: sex (*P*=0.24), age (*P*=0.87), total cholesterol (*P*=0.72), triglyceride (*P*=0.72), HDL (*P*=0.86), LDL (*P*=0.58), hsCRP (*P*=0.27), and number of white blood cells (*P*=0.94). Therefore, the anti-restenotic effect of pioglitazone appeared to be because of its intrinsic anti-atherogenic property, independent of other individual factors.

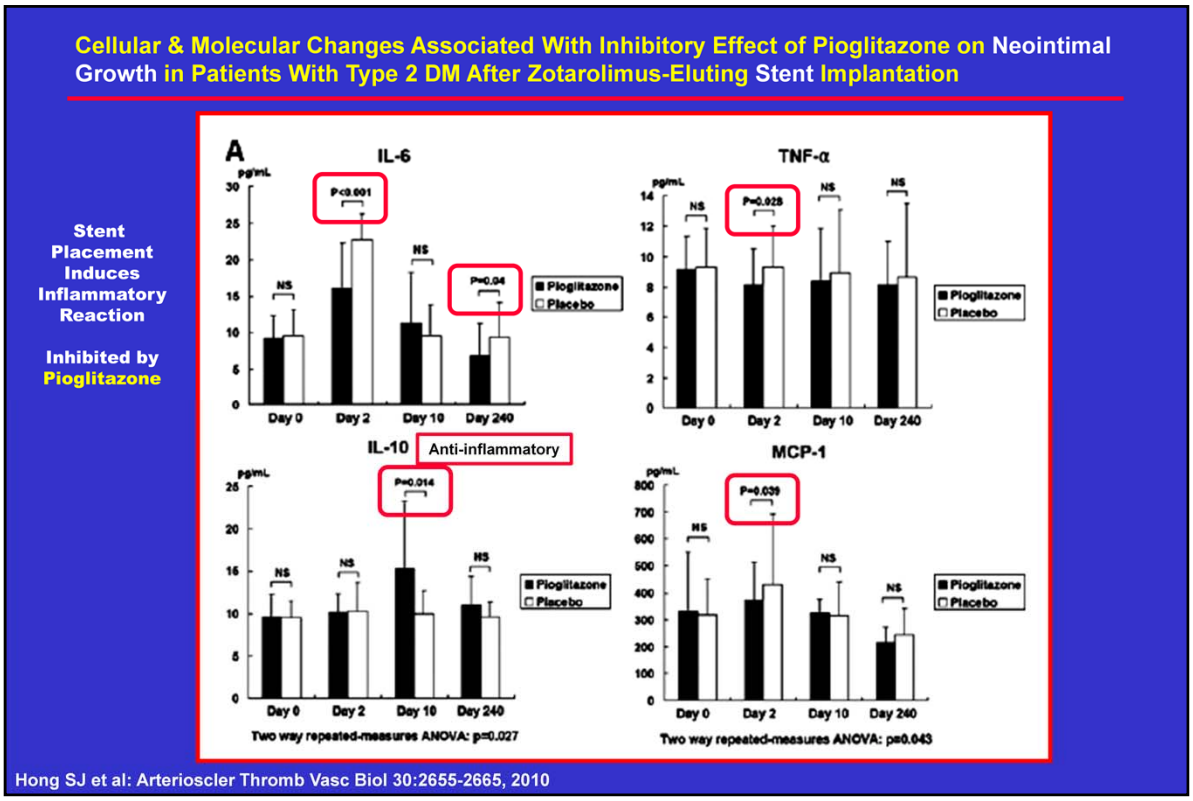


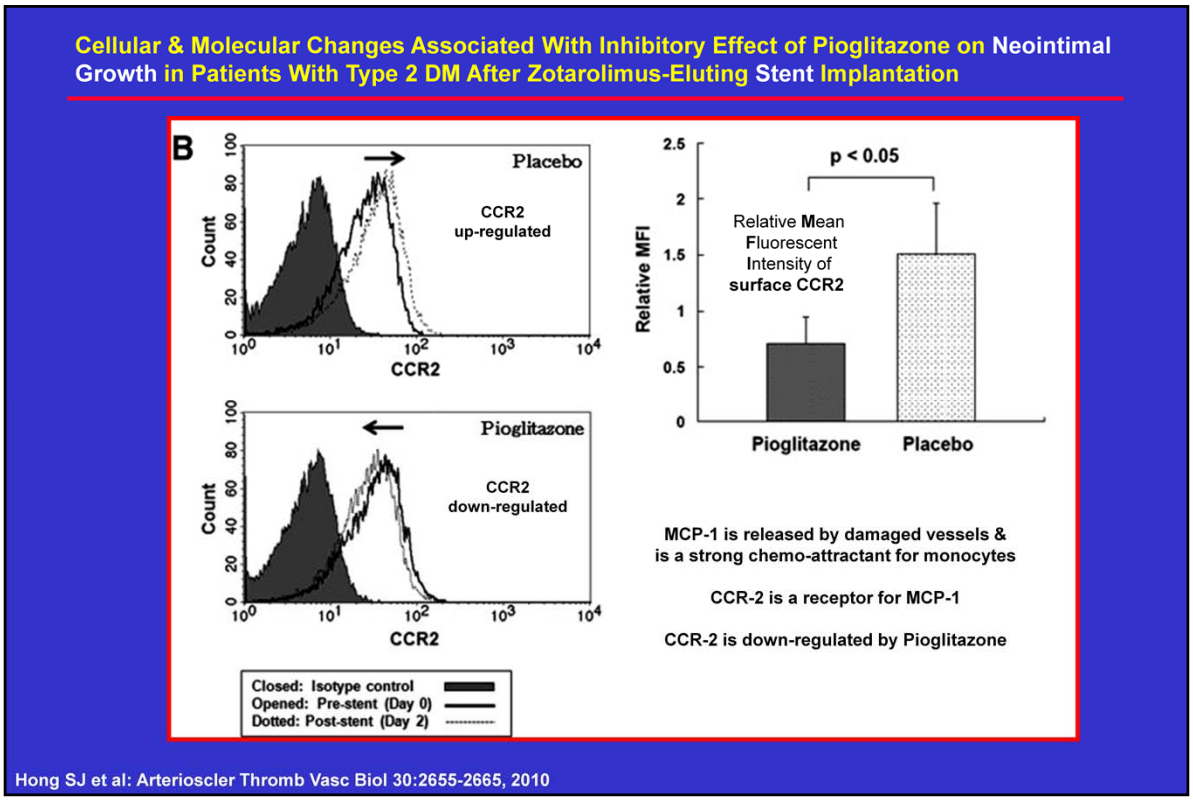
Figure 4. Analysis of inflammatory cytokines and chemokines.

A, Serum levels of IL-6, TNF-, IL-10, and MCP-1 were determined by CBA kits, as described in the "Methods" section.

Changes in Inflammatory Cytokines and Chemokines During the 8-Month Follow-Up

We further investigated if the reduction of NK cells in the peripheral blood was associated with changes in the inflammatory cytokines or chemokines. The Cytokine Bead Assay (CBA) was performed because it allowed the detection of multiple cytokines in one patient's PBMC sample. IL-6 and TNFa were chosen for their role in promoting inflammation in CAD while IL-10 was chosen for its anti-inflammatory role. MCP-1 is a chemoattractant for monocytes and has been shown to play an important role in initiating local inflammation at the damaged site. We found that the levels of IL-6 and MCP-1, but not TNFa, were increased within 48 hours of stent implantation and then returned to the basal level by day 10 in both the pioglitazone and placebo groups. The increase in IL-6 and MCP-1 at the 48-hour point was significantly attenuated by pioglitazone treatment compared with the placebo group (16.1±6.1 versus 22.6±3.7 pg/mL [P<0.001] for IL-6 and 374+140 versus 429+264 pg/mL [P=0.04] for MCP-1). Different from IL-6 and MCP-1, the serum level of TNFa was constant at baseline, after implantation, and at

the 8-month follow-up in both groups (Figure 4A). Nevertheless, pioglitazone induced a small but statistically significant decrease in the serum TNFa level (8.1±2.4 pg/mL in the pioglitazone group versus 9.3±2.7 pg/mL in the placebo group; *P*=0.03) at 2 days after stent implantation. On the contrary, we found that the serum level of the anti-inflammatory cytokine, IL-10, was significantly increased at 10 days after stent implantation only in the pioglitazone group (15.3±8.0 versus 10.0±2.7 pg/mL; *P*=0.01) (Figure 4A). These data demonstrate that pioglitazone-induced suppression of pro-inflammatory responses was followed by induction of anti-inflammatory IL-10 cytokines.



Because MCP-1 was released from damaged vessels and functions as a strong chemoattractant for blood monocytes, we investigated if administration of pioglitazone resulted in alterations of its counter-receptor, CCR2, on blood monocytes. To test this, we obtained PBMCs from the pioglitazone and placebo groups 48 hours after stent implantation, and the expression of CCR2 on purified CD14 monocytes was monitored using flow cytometry. As seen in Figure 4B, although CD14 monocytes from the patients receiving placebo showed slight upregulation of surface CCR2, those from the pioglitazone group resulted in down-regulation of CCR2 after stent implantation. When averaged, the difference in relative mean fluorescent intensity of surface CCR2 between the pioglitazone and placebo group was approximately 2-fold (Figure 4B, bar graph; $P<0.05$). Together, these data strongly demonstrate that pioglitazone caused attenuation of systemic inflammation and, thereby, inhibited recruitment of monocytes to the damaged stent sites within the coronary artery in the patients with type 2 diabetes.

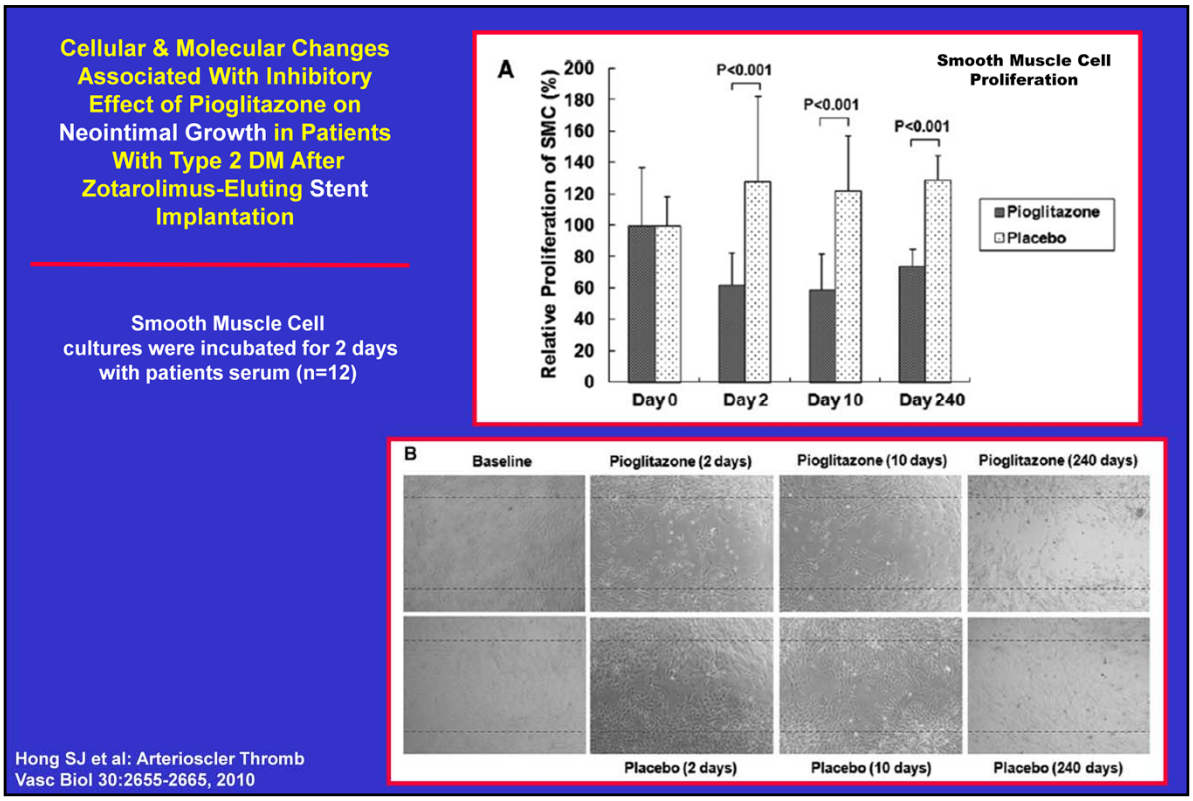
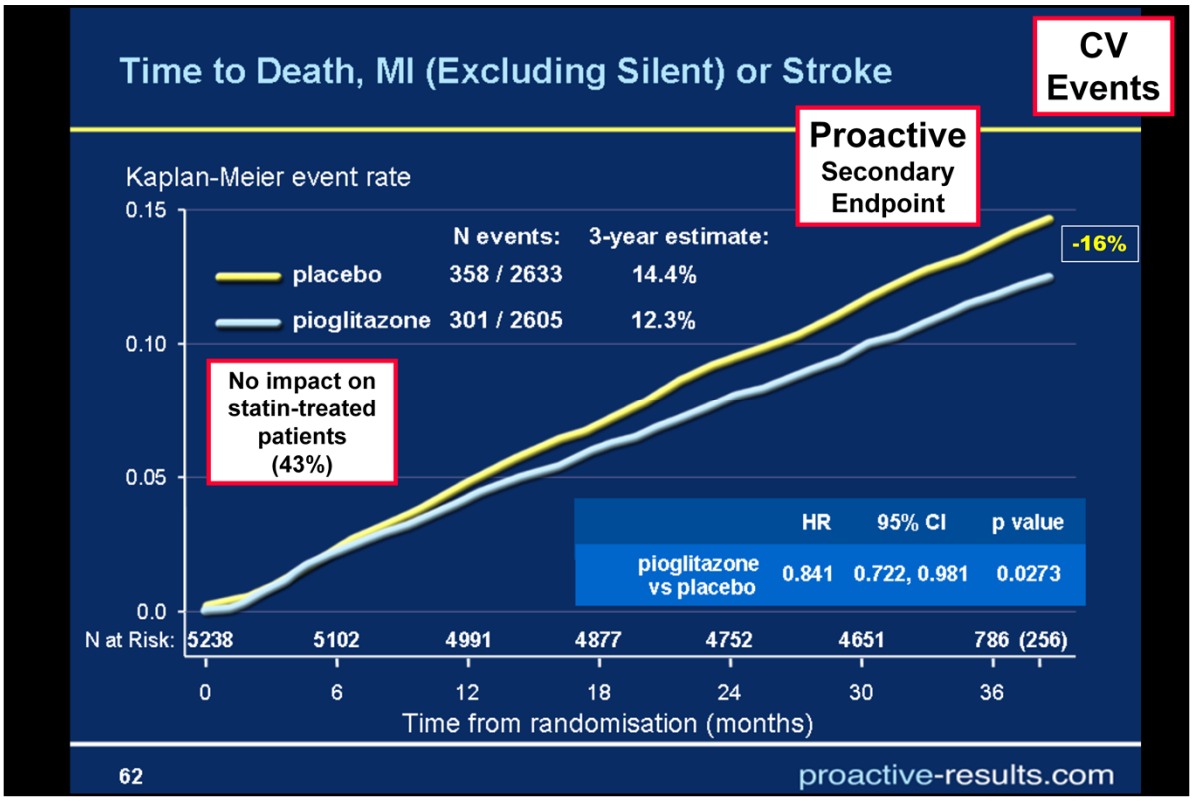


Figure 5. Effect of patients' serum on the proliferation and migration of SMCs. Cells were cultured as described in the "Methods" section.

A, Subconfluent SMC cultures were incubated for 2 days with patient serum samples (n12; supplemental material III) obtained from either the placebo or pioglitazone group at 2, 10, or 240 days after randomization. The relative proliferation of SMCs was calculated by dividing the intensity of SMCs cultured with patient serum for 2 days by that without patient serum.

B, Serum obtained from the pioglitazone group at 2, 10, or 240 days after randomization was added to the SMC cultures after making a linear line of scratch, and photographs were taken using an inverted microscope. The data shown are from 1 particular experiment representing 3 independent experiments.



Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

Lancet 366(9493): 1279-1289, 2005

Background: Patients with type 2 diabetes are at high risk of fatal and non-fatal myocardial infarction and stroke. There is indirect evidence that agonists of peroxisome proliferator-activated receptor 7 (PPAR 7) could reduce macrovascular complications. Our aim, therefore, was to ascertain whether pioglitazone reduces macrovascular morbidity and mortality in high-risk patients with type 2 diabetes.

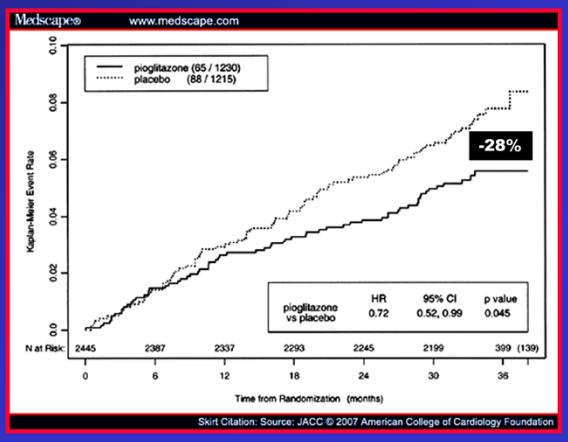
Methods: We did a prospective, randomised controlled trial in 5238 patients with type 2 diabetes who had evidence of macrovascular disease. We recruited patients from primary-care practices and hospitals. We assigned patients to oral pioglitazone titrated from 15 mg to 45 mg (n=2605) or matching placebo (n=2633), to be taken in addition to their glucose-lowering drugs and other medications. Our primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle.

Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN NCT00174993.

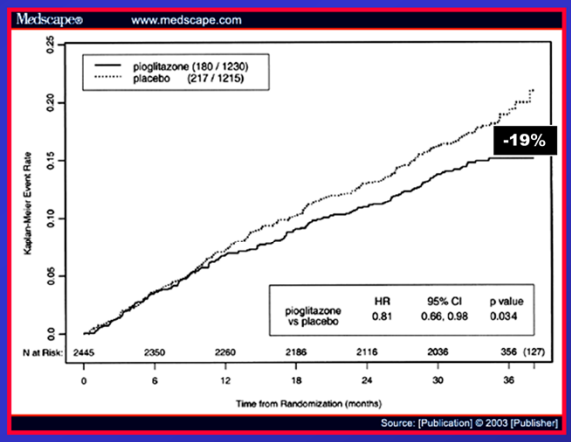
Findings: Two patients were lost to follow-up, but were included in analyses. The average time of observation was 34.5 months. 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0•90, 95% CI 0•80-1•02, p=0•095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint (0-84, 0-72-0-98, p=0-027). Overall safety and tolerability was good with no change in the safety profile of pioglitazone identified. 6% (149 of 2065) and 4% (108 of 2633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure; mortality rates from heart failure did not differ between groups.

Interpretation: Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events.

The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction. Results From PROactive (PROactive 05)



Kaplan-Meier curve of the time to fatal/nonfatal myocardial infarction



Time to Nonfatal MI (Excluding Silent MI), Coronary Revascularization, Acute Coronary Syndrome, or Cardiac Death

Original Primary Composite Cardiac End Point

Erdmann E et al: J Am Coll Cardiol 49(17):1772-1780, 2007

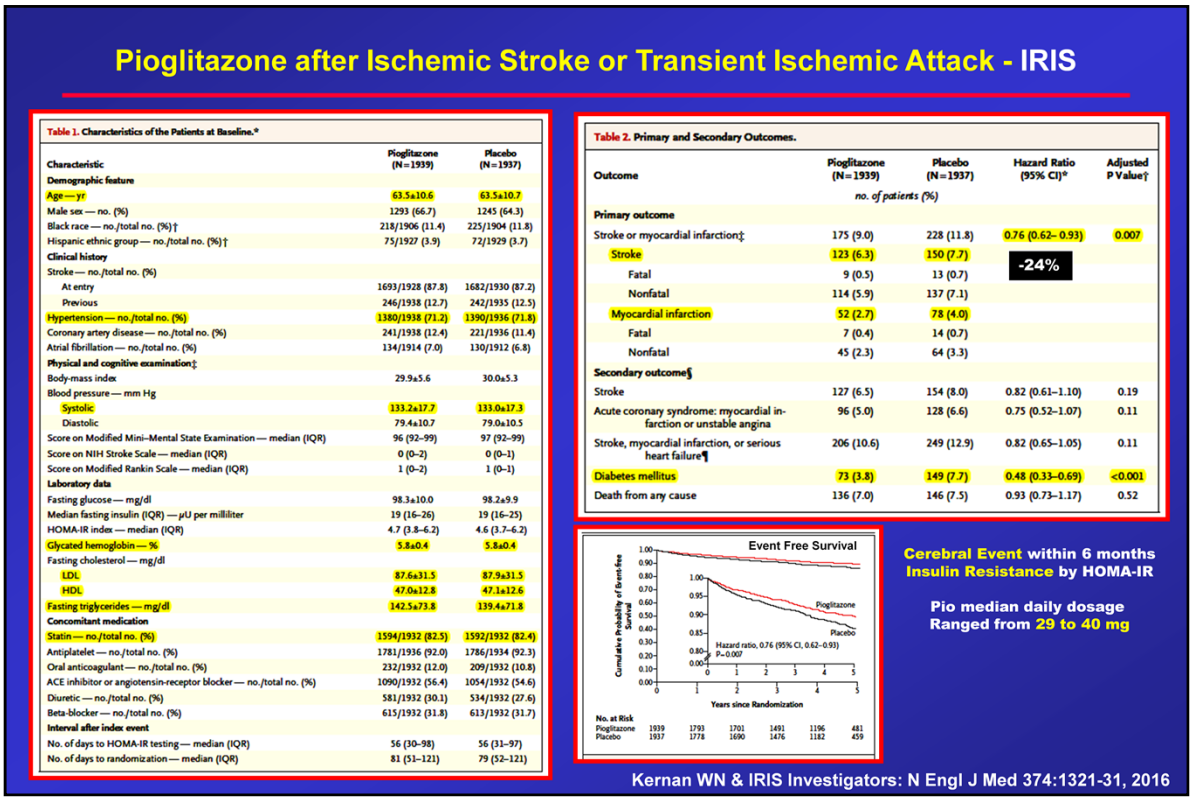
Objectives: This analysis from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study assesses the effects of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes and a previous myocardial infarction (MI).

Background: People with type 2 diabetes have an increased incidence of MI compared with the general population. Those with diabetes and MI have a worse prognosis than nondiabetic patients with cardiovascular disease.

Methods: The PROactive study was a prospective, multicenter, double-blind, placebo-controlled trial of 5,238 patients with type 2 diabetes and macrovascular disease. Patients were randomized to either pioglitazone or placebo in addition to their other glucose-lowering and cardiovascular medication. Treatment of diabetes, dyslipidemia, and hypertension was encouraged according to the International Diabetes Federation guidelines. Patients were followed for a mean of 2.85 years. The primary end point was the time to first occurrence of macrovascular events or death. Of the total cohort, the subgroup of patients who had a **previous MI** (n = 2,445 [46.7%]; n = 1,230 in the pioglitazone group and n = 1,215 in the placebo group) was evaluated using pre-specified and post-hoc analyses.

Results: Pioglitazone had a statistically significant beneficial effect on the pre-specified end point of fatal and nonfatal MI (28% risk reduction [RR]; p = 0.045) and acute coronary syndrome (ACS) (37% RR; p = 0.035). There was a 19% RR in the cardiac composite end point of nonfatal MI (excluding silent MI), coronary revascularization, ACS, and cardiac death (p = 0.033). The difference in the primary end point defined in the main PROactive study did not reach significance in the MI population (12% RR; p = 0.135). The rates of heart failure requiring hospitalization were 7.5% (92 of 1,230) with pioglitazone and 5.2% (63 of 1,215) with placebo. Fatal heart failure rates were similar (1.4% [17 of the 92] with pioglitazone versus 0.9% [11 of the 63] with placebo).

Conclusions: In high-risk patients with type 2 diabetes and previous MI, **pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS**.



BACKGROUND

Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.

METHODS

In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.

RESULTS

By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval

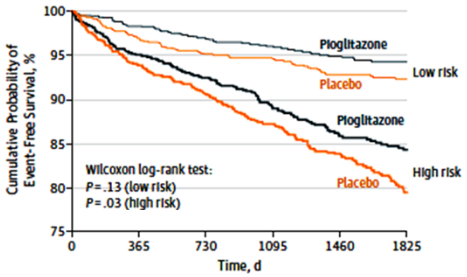
[CI], 0.62 to 0.93; P = 0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P = 0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P = 0.003).

CONCLUSIONS

In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture. (Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov number, NCT00091949.)

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack - IRIS

Figure. Time to First Stroke or Myocardial Infarction (MI) by Treatment Group and Baseline Risk Strata



No. at risk						
Low risk						
Pioglitazone	966	912	880	776	639	277
Placebo	960	896	861	765	630	264
No. at risk						
High risk						
Pioglitazone	963	875	815	708	555	244
Placebo	964	872	818	703	547	223

Time to first stroke or MI by treatment group and baseline risk strata as assigned using risk prediction model A. The thin lines (low-risk strata) indicate baseline predicted risk for stroke or MI below the median; the thick lines (high-risk strata) indicate baseline predicted risk for stroke or MI at or above the median. Risk strata were demarcated by the median value of linear predictor, which is 3.12.

JAMA Neurol. 2017;74(11):1319-1327

Table 3. Adverse Events, According to Severity.*

Event	Pioglitazone (N=1939)	Placebo (N=1937)	P Value
	no. of patients (%)		
Serious adverse event			
Hospitalization	908 (46.8)	946 (48.8)	0.21
Death	136 (7.0)	146 (7.5)	0.53
Incident cancer			
Any	133 (6.9)	150 (7.7)	0.29
Prostate	28 (1.4)	25 (1.3)	0.68
Breast	10 (0.5)	16 (0.8)	0.24
Lung	13 (0.7)	11 (0.6)	0.68
Bladder	12 (0.6)	8 (0.4)	0.37
Other	75 (3.9)	93 (4.8)	0.15
Bone fracture†	99 (5.1)	62 (3.2)	0.003
Heart failure‡	51 (2.6)	42 (2.2)	0.35
Other§	2 (0.1)	1 (0.1)	0.50
Other adverse event			
Bone fracture¶	133 (6.9)	94 (4.9)	0.008
Heart failure¶	29 (1.5)	32 (1.7)	0.70
Weight gain			
>4.5 kg	1013 (52.2)	653 (33.7)	<0.001
>13.6 kg	221 (11.4)	88 (4.5)	<0.001
Edema‖	691 (35.6)	483 (24.9)	<0.001
Shortness of breath	342 (17.6)	292 (15.1)	0.03
Alanine aminotransferase >ULN	26 (1.3)	59 (3.0)	<0.001
Macular edema	3 (0.2)	2 (0.1)	0.66

* ULN denotes the upper limit of the normal range.
† This category of adjudicated bone fracture refers to bone fracture that resulted in hospitalization, surgery, or a procedure.
‡ This category of adjudicated heart failure refers to heart failure that resulted in hospitalization or death.
§ Other serious events included sigmoid lipoma resulting in obstruction and sigmoid colectomy and hypoglycemia with unresponsiveness in the pioglitazone group and severe headache in the placebo group.
¶ Included in this category are adjudicated events that did not meet the criteria for serious events, as defined above.
‖ Edema was defined as self-reported new or worse swelling of the feet or lower legs.

Kernan WN & IRIS Investigators: N Engl J Med 374:1321-31, 2016

BACKGROUND Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.

METHODS In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.

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CONCLUSIONS In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture.

(Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov number, NCT00091949.)

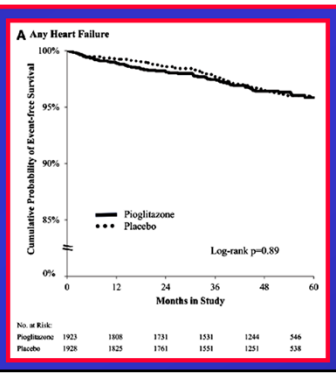
Cardiomyopathy

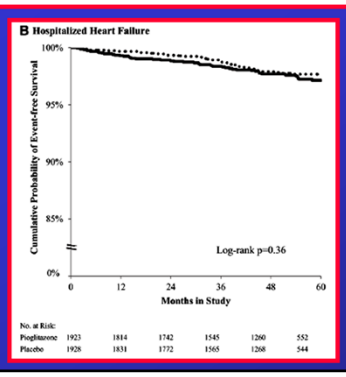
Congestive Heart Failure
Diastolic Dysfunction
Myocardial Glucose Uptake
Atrial Fibrillation

Heart Failure After Ischemic Stroke or Transient Ischemic Attack in Insulin-Resistant Patients Without Diabetes Mellitus Treated With Pioglitazone - IRIS

Table 1. HF During Follow-Up, Overall, and by Treatment Group

HF Type	All Participants (n=3851)			Pioglitazone (n=1923)			Placebo (n=1928)			Hazard Ratio (95% CI)	*P* Value
	No. of Events	No. of Patients	Risk (%)*	No. of Events	No. of Patients	Risk (%)*	No. of Events	No. of Patients	Risk (%)*		
Any	153	133	4.2	76	67	4.1	77	66	4.2	1.02 (0.73–1.44)	0.89
Hospitalized	97	82	2.6	51	45	2.9	46	37	2.3	1.23 (0.79–1.89)	0.36
Fatal	3	3	0.1	1	1	0.1	2	2	0.1	0.50 (0.05–5.53)	0.57
Hospitalized, nonfatal	94	80	2.5	50	44	2.8	44	36	2.3	1.23 (0.79–1.91)	0.35
Not hospitalized	56	55	1.7	25	25	1.5	31	30	1.9	0.84 (0.49–1.43)	0.51





Young LH & IRIS Investigators: Circulation 138:1210–1220, 2018

Background: The IRIS trial (Insulin Resistance Intervention After Stroke) demonstrated that **pioglitazone reduced the risk for both cardiovascular events and diabetes mellitus** in insulin-resistant patients. However, concern remains that pioglitazone may increase the risk for heart failure (HF) in susceptible individuals.

Methods: In IRIS, patients with insulin resistance but without diabetes mellitus were randomized to pioglitazone or placebo (1:1) within 180 days of an ischemic stroke or transient ischemic attack and followed for ≤5 years. To identify patients at higher HF risk with pioglitazone, we performed a secondary analysis of IRIS participants without HF history at entry. HF episodes were adjudicated by an external review, and treatment effects were analyzed using time-to-event methods. A baseline HF risk score was constructed from a Cox model estimated using stepwise selection. Baseline patient features (individually and summarized in risk score) and post-randomization events were examined as possible modifiers of the effect of pioglitazone. Net cardiovascular benefit was estimated for the composite of stroke, myocardial infarction, and hospitalized HF.

Results: Among 3851 patients, the mean age was 63 years, and 65% were male. The **5-year HF risk** did not differ by treatment (**4.1% pioglitazone, 4.2% placebo**). Risk for **hospitalized HF was low and not significantly greater** in pioglitazone compared with placebo groups (2.9% versus 2.3%, P=0.36). Older

age, atrial fibrillation, hypertension, obesity, edema, high C-reactive protein, and smoking were risk factors for HF. However, the effect of pioglitazone did not differ across levels of baseline HF risk (hazard ratio [95% CI] for pioglitazone versus placebo for patients at low, moderate, and high risk: 1.03 [0.61-1.73], 1.10 [0.56-2.15], and 1.08 [0.58-2.01]; interaction P value=0.98). HF risk was increased in patients with versus those without incident myocardial infarction in both groups (pioglitazone: 31.4% versus 2.7%; placebo: 25.7% versus 2.4%; P<0.0001). **Edema, dyspnea, and weight gain in the trial did not predict HF hospitalization** but led to more study drug **dose reduction** with a lower mean dose of pioglitazone versus placebo (**29**±17 mg versus **33**±15 mg, P<0.0001). Pioglitazone reduced the composite outcome of stroke, myocardial infarction, or hospitalized HF (hazard ratio, 0.78; P=0.007).

Conclusions: In IRIS, with surveillance and dose adjustments, pioglitazone did not increase the risk of HF and conferred net cardiovascular benefit in patients with insulin resistance and cerebrovascular disease. The risk of HF with pioglitazone was not modified by baseline HF risk. The IRIS experience may be instructive for maximizing the net benefit of this therapy.

Heart Failure After Ischemic Stroke or Transient Ischemic Attack in Insulin-Resistant Patients Without Diabetes Mellitus Treated With Pioglitazone - IRIS

Increased Risk:
- Age
- A-Fib
- CAD
- HBP
- Smoker
- Obesity
- Edema
- Elevated CRP

Young LH & IRIS Investigators: Circulation 138:1210–1220, 2018

Table 2. Baseline Patient Features and HF During Follow-Up (N=3851)

Feature	Feature Present		Feature Absent		Cox Hazards Models			
					Univariable†		Multivariable‡	
	No. of Patients	HF (%)*	No. of Patients	HF (%)*	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
Age <65, y (reference)	2221	(2.0)						
65–79			1375	(4.4)	2.19	<0.0001	2.26	0.0001
80+			255	(11.0)	5.98	<0.0001	5.93	<0.0001
Female sex	1328	(4.1)	2523	(3.1)	1.36	0.08		
Black race	440	(4.5)	3345	(3.4)	1.37	0.19		
Non-Hispanic ethnicity	3684	(3.5)	147	(1.4)	2.63	0.17		
Clinical history								
Stroke (versus transient ischemic attack)	3353	(3.5)	480	(3.3)	1.07	0.81		
Modified Rankin grade 3+	322	(3.1)	3528	(3.5)	0.91	0.79		
Atrial fibrillation	256	(10.9)	3593	(2.9)	4.11	<0.0001	2.79	<0.0001
Coronary artery disease	450	(6.2)	3398	(3.1)	2.05	0.0008		
Hypertension history	2749	(4.0)	1100	(2.0)	2.07	0.002	1.74	0.02
Health habits								
Current smoker	619	(3.6)	3229	(3.4)	1.09	0.72	1.65	0.04
Alcohol >2[m]/1[w] drinks/day	273	(4.4)	3528	(3.4)	1.31	0.38		
No aerobic exercise	1968	(3.7)	1857	(3.2)	1.15	0.42		
Physical examination								
Body mass index ≥30 kg/m²	1671	(4.1)	2168	(2.9)	1.40	0.05	1.47	0.04
Leg edema, grade 1 or 2	527	(6.6)	3323	(2.9)	2.31	<0.0001	1.66	0.01
Blood pressure ≥140/90 mm Hg	1349	(4.1)	2490	(3.1)	1.33	0.10		
Laboratory data								
A1c ≥5.7%	2495	(3.8)	1355	(2.8)	1.36	0.11		
Glucose ≥110 mg/dL	520	(4.0)	3331	(3.4)	1.24	0.37		
HOMA-IR >6.2 (upper quartile)	956	(3.2)	2895	(3.5)	0.95	0.82		
LDL >100 mg/dL	1110	(3.0)	2703	(3.7)	0.81	0.30		
HDL <40 [for males]/50 [for females] mg/dL	1706	(3.9)	2137	(3.1)	1.21	0.27		
CRP >3.0 mg/dL	1543	(4.5)	2279	(2.8)	1.63	0.005	1.52	0.023

TABLE 2 & Figure 2. In the aggregate cohort (ie, both treatment groups combined), older age, atrial fibrillation, hypertension history, obesity, preexisting leg edema, and elevated C-reactive protein at baseline were associated with an increased risk for HF during follow-up in univariable and multivariable analyses. Cigarette smoking was a risk factor after adjustment for age, accounting for the fact that smokers tended to be younger. These patient features were similarly associated with a greater risk for HF when either treatment group was considered separately (Table IV in the online-only Data Supplement). A neutral effect of pioglitazone on HF, including hospitalized HF, was observed consistently across groups defined by individual HF risk factors. When the 7 baseline features that independently predicted HF in the study cohort were combined into a risk score, the effect of treatment was not significant (*P*=0.93), and the hazard ratios for pioglitazone versus placebo were close to unity across the range of risk.

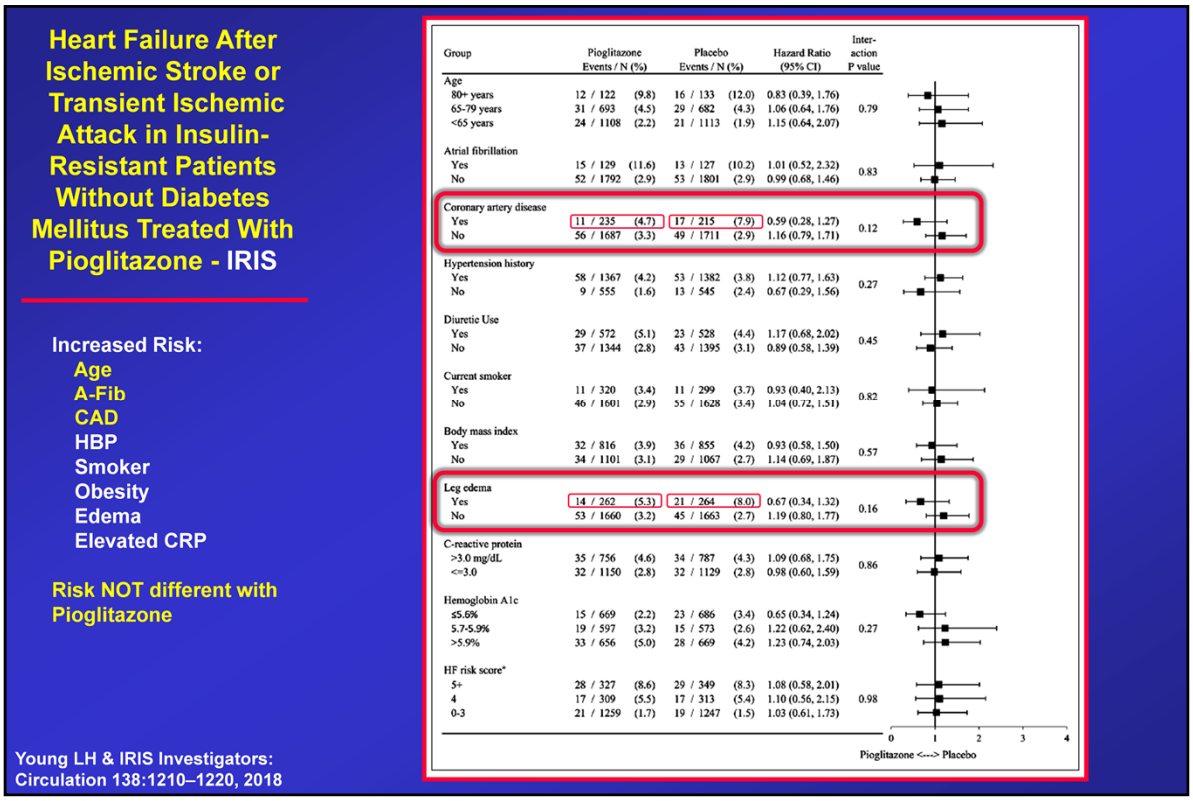


TABLE 2 & Figure 2. In the aggregate cohort (ie, both treatment groups combined), older age, atrial fibrillation, hypertension history, obesity, preexisting leg edema, and elevated C-reactive protein at baseline were associated with an increased risk for HF during follow-up in univariable and multivariable analyses. Cigarette smoking was a risk factor after adjustment for age, accounting for the fact that smokers tended to be younger. These patient features were similarly associated with a greater risk for HF when either treatment group was considered separately (Table IV in the online-only Data Supplement). A neutral effect of pioglitazone on HF, including hospitalized HF, was observed consistently across groups defined by individual HF risk factors. When the 7 baseline features that independently predicted HF in the study cohort were combined into a risk score, the effect of treatment was not significant (*P*=0.93), and the hazard ratios for pioglitazone versus placebo were close to unity across the range of risk.

Heart Failure After Ischemic Stroke or Transient Ischemic Attack in Insulin-Resistant Patients Without Diabetes Mellitus Treated With Pioglitazone - IRIS

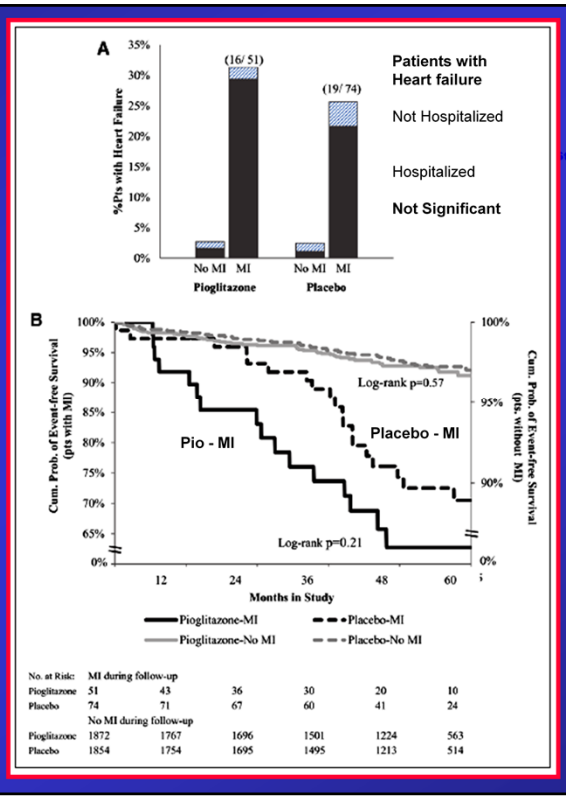


Figure 3. Association of incident MI with heart failure (HF)

HF occurring on or after date of MI for patients with MI or at any time during follow-up for patients without MI.

Young LH & IRIS Investigators: Circulation 138:1210–1220, 2018

Myocardial Infarction Pioglitazone was associated with a significantly lower risk for MI compared with placebo (hazard ratio, 0.69; 95% CI, 0.48–0.99; *P*=0.04). However, for patients who did have an MI during follow-up, concurrent or subsequent HF occurred much more frequently than for patients without MI in both treatment groups (16/51 [31.4%] versus 51/1872 [2.7%] in the pioglitazone group; 17/74 [25.7%] versus 45/1854 [2.4%] in the placebo group; *P*<0.0001 for both groups) (Figure 3A). HF and MI occurred on the same day for 22 patients (12 in the pioglitazone group and 10 in the placebo group). Among patients with MI, risk for HF (on or after MI) was numerically but not significantly higher in the pioglitazone group compared with the placebo group (Figure 3B).

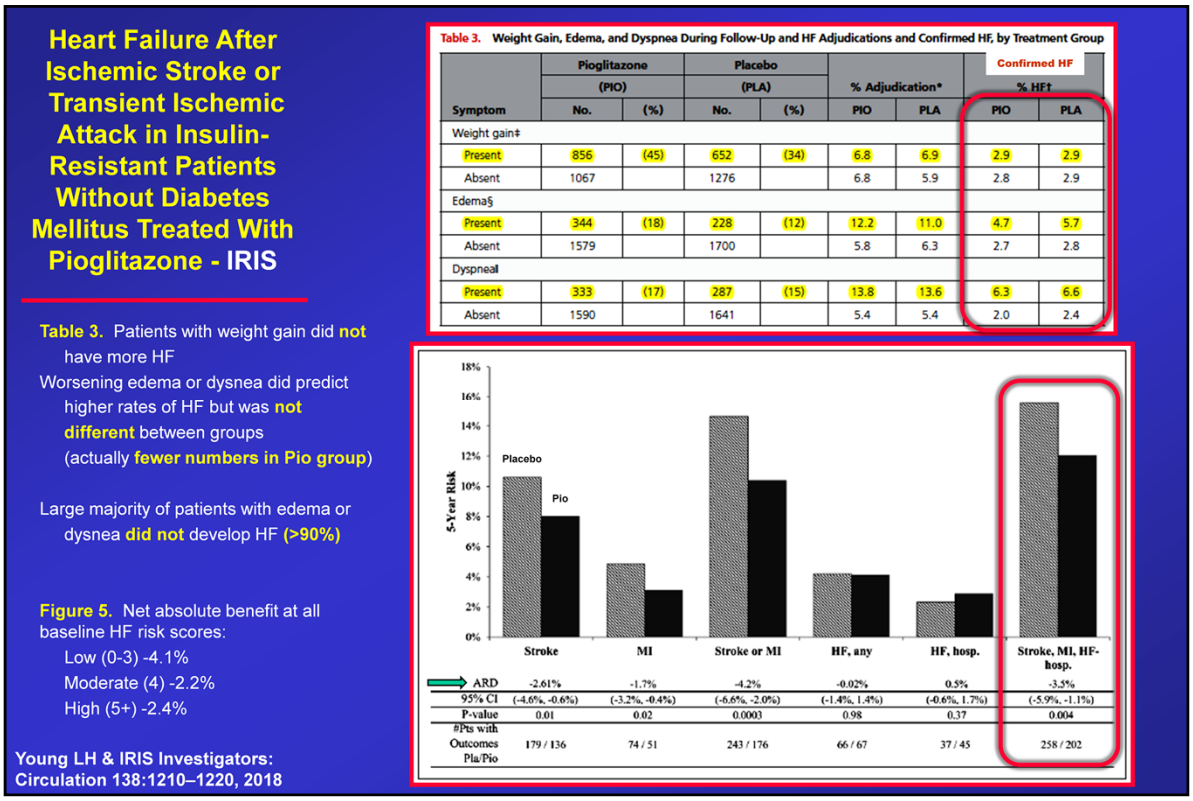


Table 3 Study Drug Side Effects In addition to any reported diagnosis of HF, patients were periodically and carefully assessed for weight gain, lower extremity edema, and shortness of breath during the trial. These complaints were observed in both the pioglitazone and placebo groups, but as previously reported, they were seen more often in those assigned to the active drug. Excessive weight gain was especially common in the pioglitazone group, but it was not related to subsequent development of HF. New or worsened significant lower extremity edema or dyspnea required clinical evaluation for HF by the local investigator or healthcare provider. Patients with these symptoms did have higher rates of confirmed HF in both treatment arms. However, the large majority of patients with edema or dyspnea did not develop HF during the trial.

Figure 5 At 5 years, the risk for composite outcome was 12.0% in the pioglitazone group and 15.6% in the placebo group (absolute risk difference, –3.5%; *P*=0.004; hazard ratio, 0.78; 95% CI, 0.65–0.93; *P*=0.007). **Net absolute benefit** was observed in patients stratified by baseline HF risk (–4.1%, –2.2%, and –2.4% in patients at low [score=0–3], moderate [score=4], and high [score=5+] HF risk, respectively).

Pioglitazone Improves Cardiac Function and Alters Myocardial Substrate Metabolism Without Affecting Cardiac Triglyceride Accumulation and High-Energy Phosphate Metabolism in Patients With Well-Controlled Type 2 Diabetes Mellitus

78 Well-Controlled DM
Short Duration
No CAD or CHF by
dobutamine stress
echocardiography

Pioglitazone 30 mg daily
or
Metformin 2,000 mg daily

Netherlands

Table 1. Patient Characteristics at Baseline*

	Pioglitazone (n=39)	Metformin (n=39)
Age, y	56.8±1.0	56.4±0.9
Time since diagnosis of diabetes, y	4 (3–6)	3 (1–5)
Current smoker, n (%)	10 (26)	7 (18)
Body mass index, kg/m^2	28.2±0.5	29.3±0.6
Waist circumference, cm	103.8±1.5	104.9±1.8
Concomitant medication, n (%)		
Statin	19 (48.7)	19 (48.7)
Any antihypertensive medication	19 (48.7)	15 (38.5)
β-Blocker	5 (12.8)	2 (5.1)
Diuretic	6 (15.4)	6 (15.4)
ACE inhibitor	9 (23.1)	9 (23.1)
ARB	6 (15.4)	3 (7.7)
Calcium antagonist	1 (2.6)	3 (7.7)

van der Meer RW et al: Circulation 119:2069-2077, 2009

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Table 2. Biochemical and Metabolic Characteristics and Whole-Body Insulin Sensitivity at Baseline and 24 Weeks

	Pioglitazone			Metformin			
	Baseline	24 Weeks	*P*	Baseline	24 Weeks	*P*	*P* (Between Groups)
Fasting							
HbA_{1c}, %	7.1±0.2	6.5±0.1	<0.001	7.0±0.1	6.3±0.1	<0.001	0.146
Plasma glucose, mmol/L	8.4 (7.2–10.3)	7.6 (6.7–9.4)	0.002	8.2 (6.8–9.1)	6.8 (5.8–7.4)	0.001	0.141
NEFA, mmol/L	0.45 (0.41–0.59)	0.46 (0.34–0.57)	0.369	0.53 (0.39–0.77)	0.49 (0.39–0.56)	0.136	0.933
Insulin, pmol/L	58 (38–83)	49 (34–70)	0.106	80 (31–99)	59 (32–98)	0.377	0.151
Lactate, mmol/L	1.2 (1.0–1.5)	1.0 (0.8–1.2)	0.001	1.1 (1.0–1.5)	1.5 (1.2–1.8)	0.012	0.001
Total cholesterol, mmol/L	4.5±0.1	4.6±0.2	0.374	4.9±0.2	4.5±0.2	0.001	0.042
LDL cholesterol, mmol/L	2.5±0.1	2.5±0.1	0.380	2.9±0.1	2.6±0.2	0.001	0.107
HDL cholesterol, mmol/L	1.07 (0.94–1.28)	1.23 (0.99–1.46)	0.003	1.13 (0.90–1.42)	1.02 (0.86–1.26)	0.133	0.009
Triglycerides, mmol/L	1.4 (1.0–2.2)	1.4 (0.9–2.3)	0.926	1.5 (0.9–2.1)	1.7 (0.9–2.3)	0.519	0.596
NT-proBNP, ng/L	24 (20–38)	26 (19–40)	0.731	32 (18–43)	33 (20–43)	0.134	0.505
During hyperinsulinemia							
NEFA, mmol/L	0.07 (0.05–0.13)	0.04 (0.02–0.05)	<0.001	0.09 (0.04–0.16)	0.06 (0.03–0.14)	0.006	0.036
Insulin, pmol/L	572 (503–620)	521 (447–590)	0.014	614 (540–710)	520 (472–601)	<0.001	0.292
Lactate, mmol/L	1.1 (1.0–1.3)	1.1 (1.0–1.2)	0.070	1.0 (0.9–1.3)	1.4 (1.2–1.7)	<0.001	0.001
M/I value, (mg/kg · min)/(pmol/L)	0.46 (0.28–0.73)	0.54 (0.43–0.97)	0.001	0.45 (0.19–0.80)	0.58 (0.35–1.00)	0.033	0.501

van der Meer RW et al: Circulation 119:2069-2077, 2009

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Table 3. Hemodynamic Parameters and Cardiac Dimensions and Function at Baseline and 24 Weeks

	Pioglitazone			Metformin			
	Baseline	24 Weeks	*P*	Baseline	24 Weeks	*P*	*P* (Between Groups)
Hemodynamics							
Systolic blood pressure, mm Hg	130±2	125±2	0.036	126±2	121±2	0.026	0.486
Diastolic blood pressure, mm Hg	77±1	74±1	0.064	74±1	73±1	0.118	0.971
Heart rate, beats/min	65±1	63±1	0.235	65±1	64±1	0.061	0.904
Rate pressure product, (beats/min) · mm Hg	8508±256	7853±195	0.040	8206±215	7744±193	0.009	0.771
Cardiac function and dimensions							
LV mass, g	108±2	105±3	0.171	107±3	103±3	0.066	0.542
LV end-systolic volume, mL	66±3	66±3	0.821	60±2	59±2	0.704	0.911
LV end-diastolic volume, mL	160±4	166±5	0.045	152±4	148±4	0.148	0.003
Stroke volume, mL	94±3	99±3	0.016	92±3	89±2	0.095	0.001
Ejection fraction, %	59±1	60±1	0.228	61±1	60±1	0.574	0.533
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.9±0.1	2.9±0.1	0.845	2.9±0.1	2.7±0.1	0.019	0.008
Cardiac work, mm Hg · $L^{-1} \cdot min^{-1}$	57±2	57±2	0.898	55±2	50±2	0.002	0.006
E peak filling rate, mL/s	422±15	440±14	0.067	409±14	407±13	0.890	0.047
$E\text{-}dec_{peak}$, $mL/s^2 \times 10^{-3}$	3.5±0.2	3.8±0.2	0.034	3.5±0.2	3.5±0.2	0.792	0.106
$E\text{-}dec_{mean}$, $mL/s^2 \times 10^{-3}$	2.3±0.1	2.4±0.1	0.080	2.3±0.1	2.2±0.1	0.498	0.064
E/A peak flow	1.07±0.05	1.09±0.05	0.583	1.01±0.04	1.01±0.03	0.939	0.348
E/Ea	9.2 (7.4–11.4)	9.1 (6.6–12.0)	0.695	9.3 (6.3–12.3)	10.3 (8.3–11.8)	0.203	0.254

Improved Compliance

van der Meer RW et al: Circulation 119:2069-2077, 2009

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Effect of pioglitazone on left ventricular diastolic function and fibrosis of type III collagen in type 2 diabetic patients

ON: 15 Patients DM2 treated with pioglitazone 15-30 mg for 6 months (Japan)
OFF: 24 Patients DM2 on pioglitazone for 16.9 months discontinued → reassessed in 6 months

Table 1 Baseline clinical characteristics.

	ON group ($n = 15$)	OFF group ($n = 24$)
Gender (M/F)	8/7	12/12
Age (years)	67.8 ± 12.9	67.2 ± 7.0
HT treatment	6 (40.0)	13 (54.2)
ACEI or ARB	3 (20.0)	7 (29.2)
DM treatment	14 (93.3)	21 (87.5)
SU	4 (26.7)	9 (37.5)
BG	10 (66.6)	15 (62.5)
αGI	4 (26.7)	4(16.7)
Insulin	3 (20.0)	5 (20.8)
Known DM duration (years)	9.5 ± 9.1	13.2 ± 6.6

Terui G et al: Journal of Cardiology 54:52-58, 2009

Background: Myocardial fibrosis is the major factor that regulates left ventricular (LV) diastolic function. Pioglitazone, an anti-diabetic drug, is reported to improve the LV diastolic function in diabetic patients, but its influence on myocardial fibrosis has not been clarified. We evaluated the effect of pioglitazone on LV diastolic function and myocardial fibrosis in type 2 diabetic (T2DM) patients.

Methods and results: Fifteen T2DM patients were enrolled in the ON group, and the parameters were examined before and after pioglitazone administration (15—30 mg/day) for 6 months. Twenty-four T2DM patients were assigned to the OFF group, and the parameters were examined before and 6 months after cessation of pioglitazone. We measured echocardiographic parameters such as early diastolic mitral annular velocity (*E*) and plasma concentration of aminoterminal propeptide of procollagen type III (PIIIP), a marker of myocardial fibrosis. In the ON group, pioglitazone significantly increased *E* (6.04±1.70 cm/s vs. 6.51±1.64 cm/s, $p < 0.01$) and decreased PIIIP (0.553±0.056 U/ml vs. 0.517±0.072 U/ml, $p < 0.05$). There was a significant negative correlation between the change in PIIIP and the change in *E* ($r = -0.424$, $p = 0.046$). On the other hand, *E* was significantly decreased (5.69±1.34 cm/s vs. 4.97±1.20 cm/s, $p < 0.01$) in the OFF group. PIIIP was not significantly changed in the OFF group, but there was a significant negative correlation between the change in PIIIP and the

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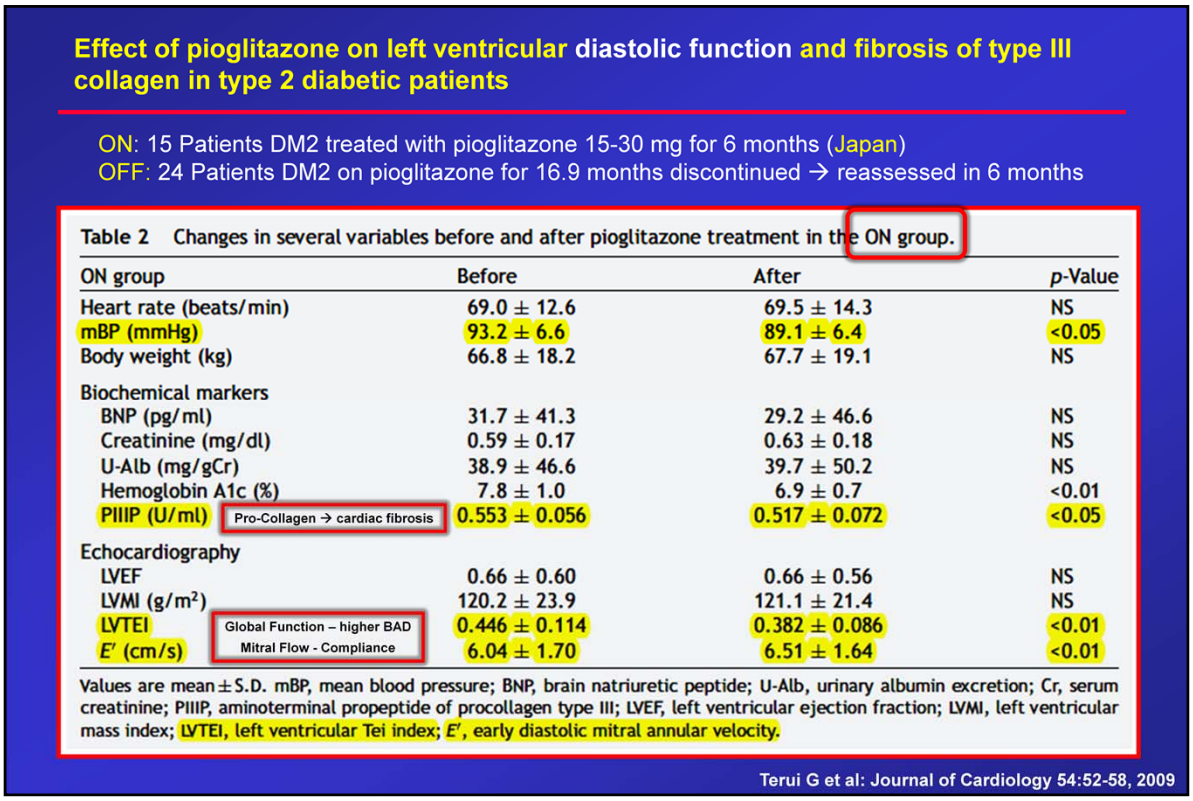
Conclusion: Six months of pioglitazone administration suppressed the synthesis of type III collagen, and this was associated with improved LV diastolic function in T2DM patients. Cessation of pioglitazone weakened the suppression of the synthesis of type III collagen, which in turn seemed to be associated with worse LV diastolic function.



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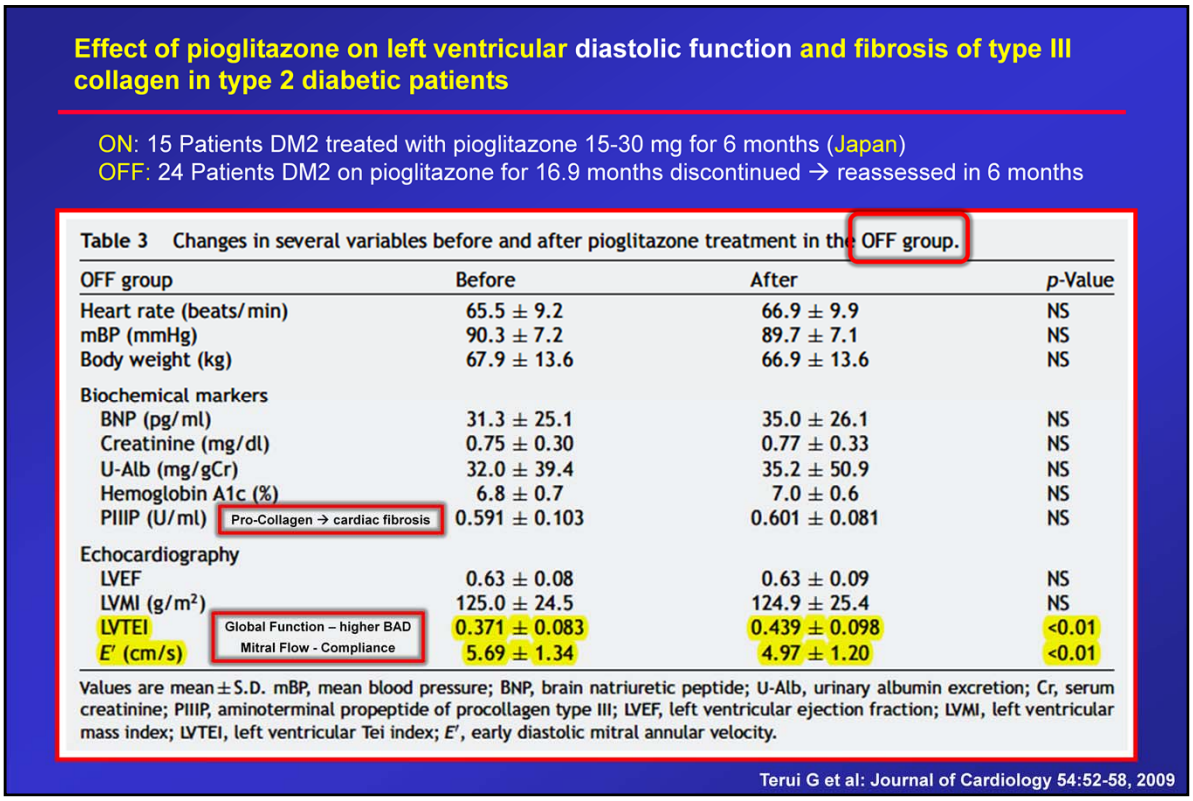

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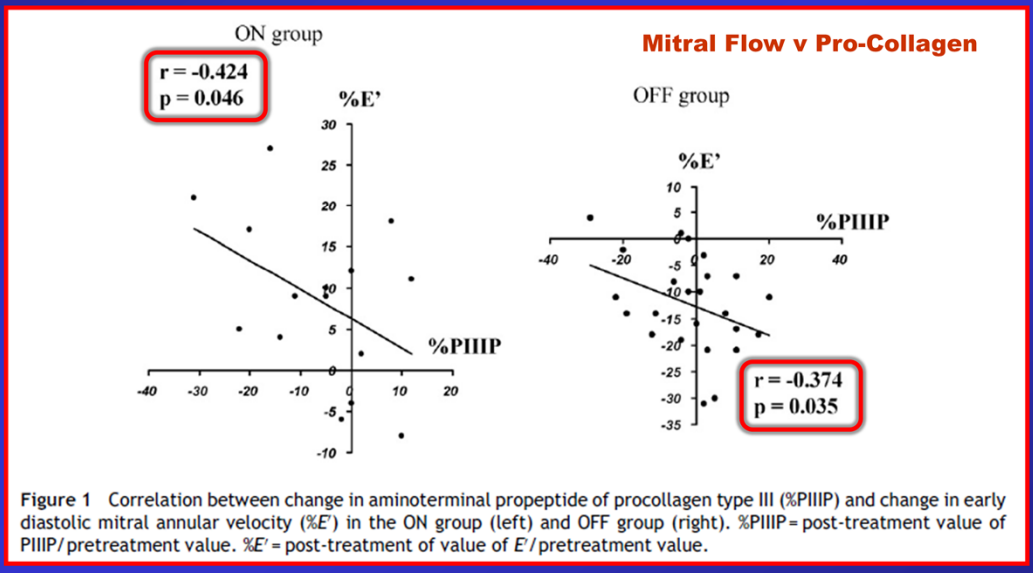

Figure 1 Correlation between change in aminoterminal propeptide of procollagen type III (%PIIIP) and change in early diastolic mitral annular velocity (%*E'*) in the ON group (left) and OFF group (right). %PIIIP = post-treatment value of PIIIP/pretreatment value. %*E'* = post-treatment of value of *E'*/pretreatment value.

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A randomized placebo controlled double blind crossover study of pioglitazone on left ventricular diastolic function in type 2 diabetes

24 Patients DM2 treated with pioglitazone 45 mg for 12 weeks (London) & crossed-over

Table 1
Baseline characteristics of participants.

Variable	Mean (SD) or *N* (%)
Age, years	59.5 (11.0)
Male sex, *n* (%)	17 (71)
Height, cm	169.9 (9.5)
Current smoker, *n* (%)	5 (21)
Antihypertensive treatment, *n* (%)	15 (63)
Sulphonylurea treatment, *n* (%)	17 (71)
Metformin treatment, *n* (%)	22 (92)

Table 2
Baseline measures and effect of pioglitazone.

Variable	Baseline	Change (Δ) due to pioglitazone	*p*
	Mean (SD or IQR)	Marginal mean (95% CI)	Value
Weight, kg	88.6 (15.5)	1.3 (0.6, 2.0)	<0.001
WHR	1.00 (0.07)	0.00 (−0.01, 0.01)	0.8
Glucose, mmol/l	9.1 (8.3, 12.0)	−0.69 (−0.78, −0.61)	<0.001
HbA1c, %	8.65 (8.1, 9.2)	−0.9 (−1.0, −0.9)	0.02
SBP, mm Hg	135 (14)	−2 (−7, 3)	0.4
DBP, mm Hg	80 (10)	−1 (−4, 1)	0.3
HR, bpm	79 (12)	0 (1, −4)	0.2

Hughes AD et al: International Journal of Cardiology 2012

Background/Objectives: Thiazolidinediones (TZDs), such as pioglitazone, are widely used to treat type 2 diabetes but there is evidence that their use is associated with an increased risk of heart failure. We compared the effect of pioglitazone vs. placebo on left ventricular (LV) diastolic and systolic function in people with type 2 diabetes.

Methods and results: 24 male or female patients with type 2 diabetes were randomized to pioglitazone (45 mg/day) or placebo in addition to current therapy for 12 weeks using a prospective double blind crossover protocol following a run-in period >1 week and a 2 week washout period at crossover. Tissue Doppler early peak velocity (e′), a measure of LV diastolic function, was the primary outcome. Pioglitazone significantly increased e′ by 0.7 (0.1, 1.3) cm/s (mean (95% confidence interval); p=0.02) compared with placebo. Pioglitazone also increased E/A and mitral deceleration index, ejection fraction, stroke volume and weight, whereas fasting glucose, HbA1c, total peripheral resistance and LV meridional end systolic stress were decreased.

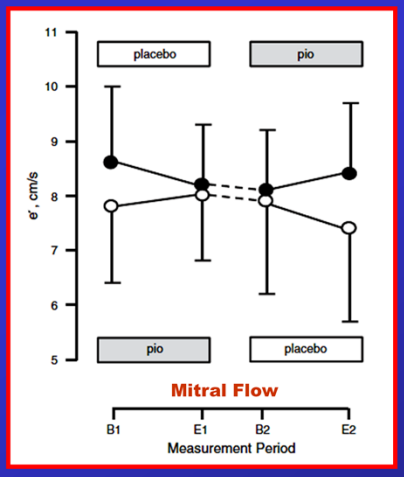
Conclusions: Treatment with pioglitazone for 12 weeks improves left ventricular diastolic and systolic function in people with type 2 diabetes.

A randomized placebo controlled double blind crossover study of pioglitazone on left ventricular diastolic function in type 2 diabetes

24 Patients DM2 treated with pioglitazone 45 mg for 12 weeks (London) & crossed-over

Table 3
Baseline echocardiographic measures and the effect of pioglitazone.

Variable	Baseline	Change (Δ) due to pioglitazone	p
	Mean (SD)	Marginal mean (95% CI)	Value
Primary outcome			
e′, cm/s (Mitral Flow - Compliance)	8.0 (1.7)	0.7 (0.1, 1.3)	0.02
Other measures			
E/A (E-wave (Passive filling) to Atrial Wave)	0.86 (0.19)	0.12 (0.05, 0.19)	0.001
E/e′	8.6 (2.0)	0.0 (−0.8, 0.8)	>0.9
Mitral deceleration index (MDI)	0.30 (0.08)	0.03 (0.00, 0.05)	0.04
s′, cm/s	8.6 (1.2)	−0.3 (−0.6, 0.1)	0.2
a′, cm/s	11.0 (1.6)	0.2 (−0.4, 0.8)	0.5
LVMI, g/m^2	91.7 (12.0)	3.3 (−1.6, 8.2)	0.2
LVEDD, cm	4.6 (0.3)	−0.0 (−0.1, 0.1)	0.8
Ejection fraction, %	63.7 (5.4)	3.7 (1.2, 6.3)	0.004
SV, ml (Stroke Volume)	56.2 (9.2)	3.5 (0.6, 6.4)	0.02
Cardiac output, l/min	4.4 (0.8)	0.3 (−0.0, 0.6)	0.06
TPR, mm Hg.min/l (Total Periph Resistance)	23.1 (5.4)	−1.8 (−3.4, −0.1	0.04
SV/PP, ml/mm Hg	1.1 (0.3)	0.1 (−0.1, 0.2)	0.3
Endocardial fractional shortening, %	39 (3.2)	2.3 (−0.7, 1.2)	0.6
Midwall fractional shortening, %	14.8 (1.7)	0.5 (−0.1, 1.1)	0.1
End systolic stress, kdyn/cm^2	62.7 (12.0)	−7.9 (−11.3, −4.5)	<0.001



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Conclusions: Treatment with pioglitazone for 12 weeks improves left ventricular diastolic and systolic function in people with type 2 diabetes.

Pioglitazone Improves Left Ventricular Diastolic Function in Subjects With Diabetes

12 Subjects with DM2 & 12 Controls (US)
DM2 treated with pioglitazone 45 mg for 24 weeks

MGU: Myocardial **Glucose** Uptake
EF: Ejection Fraction

Diastolic Function
Transmitral E/A Flow Ratio:
early diastolic relaxation to atrial contraction

pLVFR / BSA:
peak LV Filling Rate / Body Surface Area

Table 1—Metabolic and cardiac MRI values obtained in control subjects with NGT and subjects with T2D before and after pioglitazone treatment

	NGT control	T2D baseline	T2D after pioglitazone
Sex, *n*			
Male	9	10	10
Female	3	2	2
Age (years)	47.7 ± 10.5	50.7 ± 9.1	51.3 ± 9.1
BMI (kg/m^2)	28.4 ± 4.4	30.8 ± 4.3	31.3 ± 4.2
Body fat (%)	29.3 ± 8.6	31.9 ± 5.7	33.4 ± 6.1
HbA_{1c} (%)	5.5 ± 0.4	6.7 ± 1.3***	5.6 ± 0.8‡
Fasting plasma glucose (mg/dL)	93 ± 6	149 ± 48***	112 ± 23†
Fasting FFAs (mmol/L)	0.32 ± 0.1	0.52 ± 0.17***	0.30 ± 0.14‡
HDL cholesterol (mg/dL)	55.7 ± 9.8	38.8 ± 11.9***	41.5 ± 9.7†
Triacylglycerol (mg/dL)	128 ± 94	265 ± 155***	153 ± 74‡
Matsuda index of insulin sensitivity	8.7 ± 4.8	2.8 ± 1.9***	5.8 ± 3.4‡
Glucose infusion rate (mg/kg · min)	7.5 ± 2.8	3.4 ± 1.3***	5.8 ± 2.1‡
MGU (μmol/min · g)	0.38 ± 0.14	0.24 ± 0.14*	0.42 ± 0.13‡
Myocardial perfusion (mL/min · g)	0.83 ± 0.20	0.95 ± 0.16	1.10 ± 0.25†
Systolic function			
Resting heart rate (beats/min)	63.3 ± 6.8	78.1 ± 10.5**	71.3 ± 11.3
Cardiac index (L/min · m^2)	2.85 ± 0.32	2.90 ± 0.70	2.91 ± 0.74
EF (%)	64.2 ± 4.7	60.7 ± 6.3	65.6 ± 6.9†
Stroke volume/BSA (mL/m^2)	42.7 ± 5.0	37.7 ± 7.3*	41.7 ± 8.5†
Peak LV ejection rate/BSA (mL/s · m^2)	226 ± 36	224 ± 52	255 ± 54
Myocardial mass/BSA (g/m^2)	60.2 ± 9.4	64.1 ± 8.5	61.4 ± 8.6
Diastolic function			
Transmitral E/A flow ratio	1.48 ± 0.37	1.04 ± 0.28**	1.25 ± 0.38‡
ESV/BSA (mL/m^2)	26.4 ± 9.7	24.3 ± 5.4	21.2 ± 5.3
EDV/BSA (mL/m^2)	69.1 ± 10.3	61.9 ± 9.1*	62.9 ± 9.3
PLVFR/BSA (mL/s · m^2)	196 ± 33	171 ± 52*	212 ± 54‡

Data are mean ± SD. *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$ determined by unpaired *t* test for T2D baseline vs. NGT control. †$P < 0.05$ and ‡$P < 0.01$ for T2D baseline vs. T2D after pioglitazone (determined by paired *t* test).

Clark GD (DeFronzo) et al: Diabetes Care 40:1530–1536, 2017

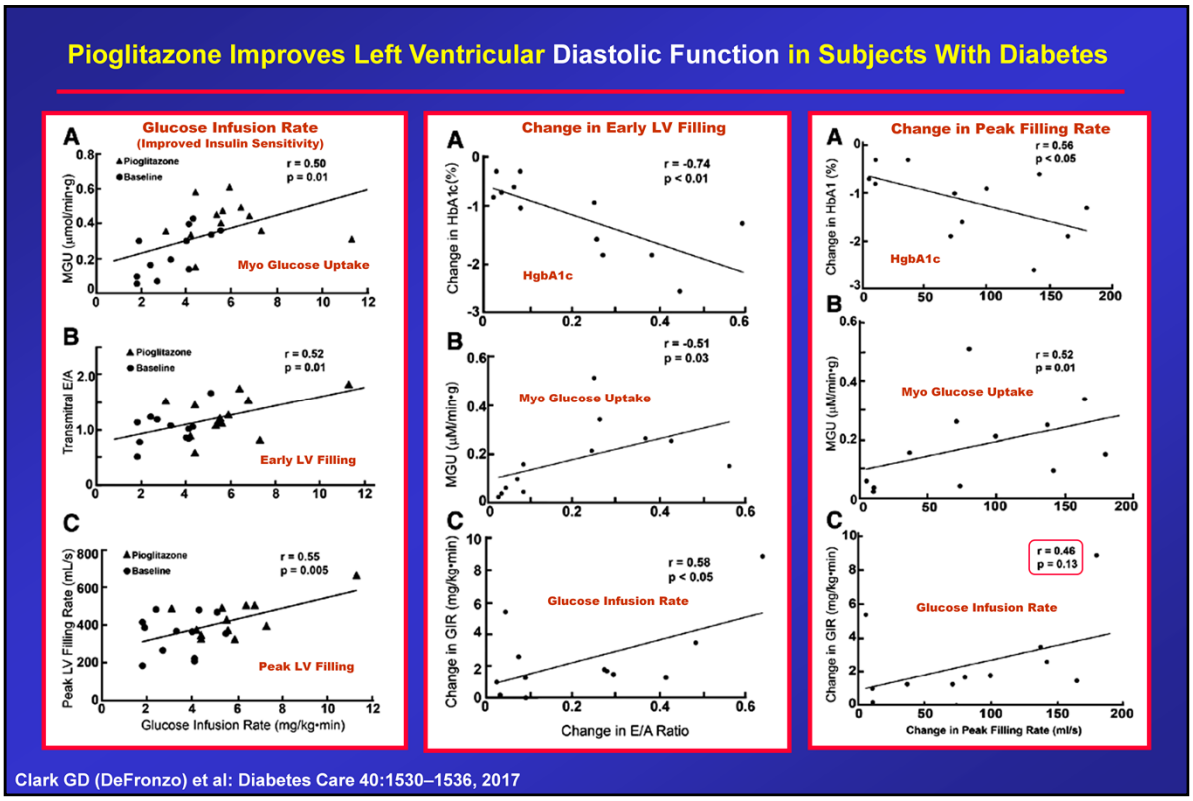
Objective: To examine the effect of pioglitazone on myocardial insulin sensitivity and left ventricular (LV) function in patients with type 2 diabetes (T2D).

Research design and methods: Twelve subjects with T2D and 12 with normal glucose tolerance received a euglycemic insulin clamp. Myocardial glucose uptake (MGU) and myocardial perfusion were measured with [^{18}F]fluoro-2-deoxy-d-glucose and [^{15}O]H_2O positron emission tomography before and after 24 weeks of pioglitazone treatment. Myocardial function and transmitral early diastolic relation/atrial contraction (E/A) flow ratio were measured with magnetic resonance imaging.

Results: Pioglitazone reduced HbA_{1c} by 0.9%; decreased **systolic and diastolic blood pressure** by 7 ± 2 and 7 ± 2 mmHg, respectively ($P < 0.05$); and increased whole-body insulin-stimulated glucose uptake by 71% (3.4 ± 1.3 to 5.8 ± 2.1 mg/kg · min; $P < 0.01$) in subjects with T2D. Pioglitazone enhanced **MGU** by 75% (0.24 ± 0.14 to 0.42 ± 0.13 μmol/min · g; $P < 0.01$) and **myocardial perfusion** by 16% (0.95 ± 0.16 to 1.10 ± 0.25 mL/min · g; $P < 0.05$). Measures of diastolic function, **E/A ratio** (1.04 ± 0.3 to 1.25 ± 0.4) and **peak LV filling rate** (349 ± 107 to 433 ± 99 mL/min), both increased ($P < 0.01$). End-systolic volume, end-diastolic volume, peak LV

ejection rate, and cardiac output trended to increase (*P* not significant), whereas the **ejection fraction** (61 ± 6 to 66 ± 7%) and **stroke volume** increased significantly (71 ± 20 to 80 ± 20 L/min; both $P < 0.05$).

Conclusions: Pioglitazone improves whole-body and myocardial insulin sensitivity, LV diastolic function, and systolic function in T2D. Improved myocardial insulin sensitivity and diastolic function are strongly correlated.



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Beneficial Effects of Pioglitazone on Retardation of Persistent Atrial Fibrillation Progression in Diabetes Mellitus Patients

DM Patients with 1st episode of AF for 7 days or requiring cardioversion, not on ACE-I or ARB
Randomized to Pioglitazone 30 mg or placebo → 14 months (China)

Table I. Clinical Characteristics

	Placebo ($n = 76$)	Pioglitazone ($n = 70$)	P
Male gender	50 (65.8%)	52 (74.3%)	0.284
Age (years)	62.25 ± 12.39	60.70 ± 12.25	0.449
Hypertension	23 (30.3%)	20 (28.6%)	0.859
Current smokers	42 (55.3%)	41 (58.6%)	0.739
Alcoholic history	16 (21.1%)	19 (27.1%)	0.441
CAD	23 (30.3%)	20 (28.6%)	0.857
VHD	7 (9.2%)	5 (7.1%)	0.767
CHOL (mmol/L)	5.44 ± 1.61	5.30 ± 0.97	0.541
TG (mmol/L)	2.24 ± 1.77	2.42 ± 1.65	0.615
LDL-C (mmol/L)	2.69 ± 0.73 ~105 mg/dl	2.72 ± 0.46	0.706
HDL-C (mmol/L)	1.08 ± 0.38	1.10 ± 0.24	0.732
Amiodarone	15 (19.7%)	13 (17.1%)	0.831
Beta-blockers	29 (38.2%)	29 (41.4%)	0.736
CCB	13 (17.1%)	14 (20%)	0.675
Propafenone	10 (13.2%)	6 (8.6%)	0.435
Statins	26 (34.2%)	22 (31.4%)	0.729
LVEF	0.57 ± 0.04	0.58 ± 0.04	0.494
HbA1c (%)	6.19 ± 1.45	6.41 ± 1.83	0.407
SBP	132 ± 19	131 ± 21	0.877
DBP	76 ± 10	77 ± 12	0.653

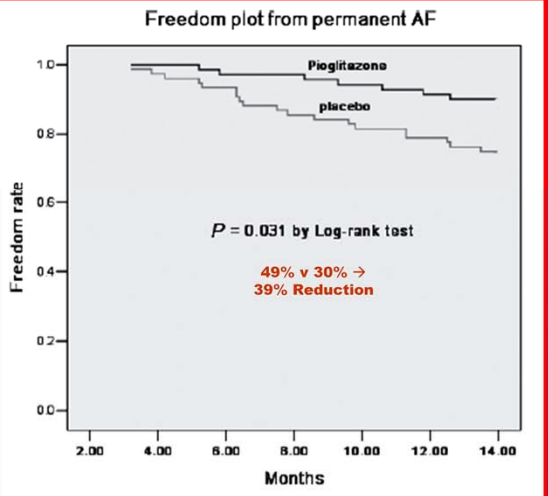


Figure 1. Kaplan-Meier permanent AF-free survival curve for pioglitazone and placebo groups. AF indicates atrial fibrillation.

Liu B, Wang G, Wang J: International Heart J 2014; 55: 499-505, 2014

This study aimed to explore the effects of pioglitazone treatment on progression from persistent atrial fibrillation (AF) to permanent atrial fibrillation in diabetes mellitus (DM) patients and to investigate the possible mechanisms involved in those effects. A total of 146 diabetes mellitus (DM) patients with first identified persistent AF were selected. Seventy patients were randomized into the pioglitazone (30 mg/day) group and 76 into the placebo group. Pro-collagen type I carboxyterminal peptide (PICP), advanced glycation end products (AGEs), and angiotensin II were assayed and left atrial diameter (LA diameter) was measured at the first presence of persistent AF, and at 6 and 14 months of follow-up. The time point of identification of permanent AF and the incidence of permanent AF in the patients were all recorded. Thirty-seven **(49%)** of the 76 patients in the placebo group and 21 **(30%)** of the 70 patients in the pioglitazone group progressed to permanent AF (P = 0.028). No significant differences existed in the follow-up time (20.5 ± 3.97 months for pioglitazone group versus 20.9 ± 4.14 months for placebo group) between the two groups (P = 0.535). In the pioglitazone group, no significant change was found in angiotensin II level. The PICP level did not change significantly at 6-months of follow-up, but decreased significantly at 14-months of follow-up (P = 0.032). The AGE (P = 0.037 at 6-month follow-up, P < 0.035 at 14-month follow-up) level was significantly lower at both 6 and 14-months of follow-up. By lowering the PICP level, pioglitazone treatment may decrease the incidence of permanent AF in DM patients with persistent AF.

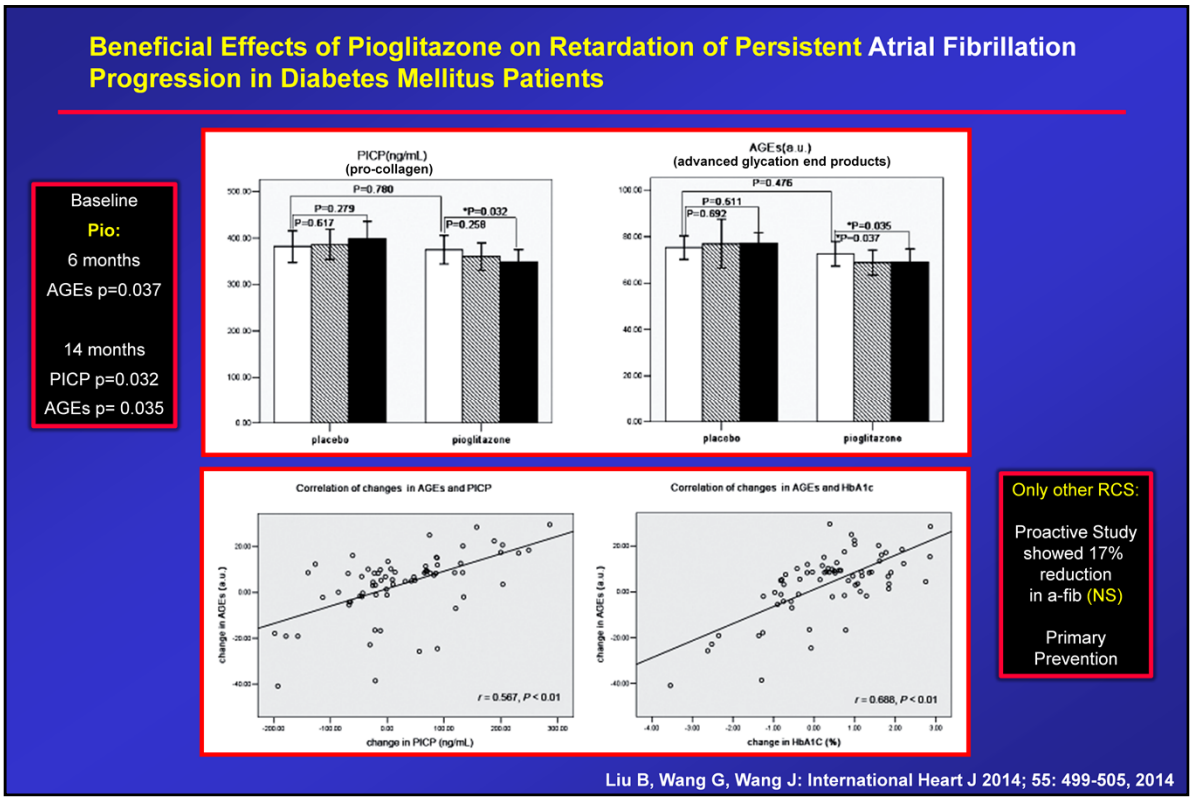


Figure 3. Baseline (white bars), 6 month (stripe bars), and 14 month (black bars) mean serum PICP levels, serum angiotensin II levels, LA diameters, and serum AGEs levels in patients randomized to the placebo-treatment group and in patients randomized to the pioglitazone-treatment group.

AF indicates atrial fibrillation; LA diameter, left atrial diameter; PICP, pro-collagen type I carboxy-terminal peptide; and AGEs, advanced glycation end products.

* Difference is significant.

Figure 4. Correlation of the change in AGEs with the changes in HbA1c and PICP after 14-months of follow-up. PICP indicates pro-collagen type I carboxy-terminal peptide; AGEs, advanced glycation end products; and HbA1c, Haemoglobin A1c.

Pioglitazone & Heart Disease

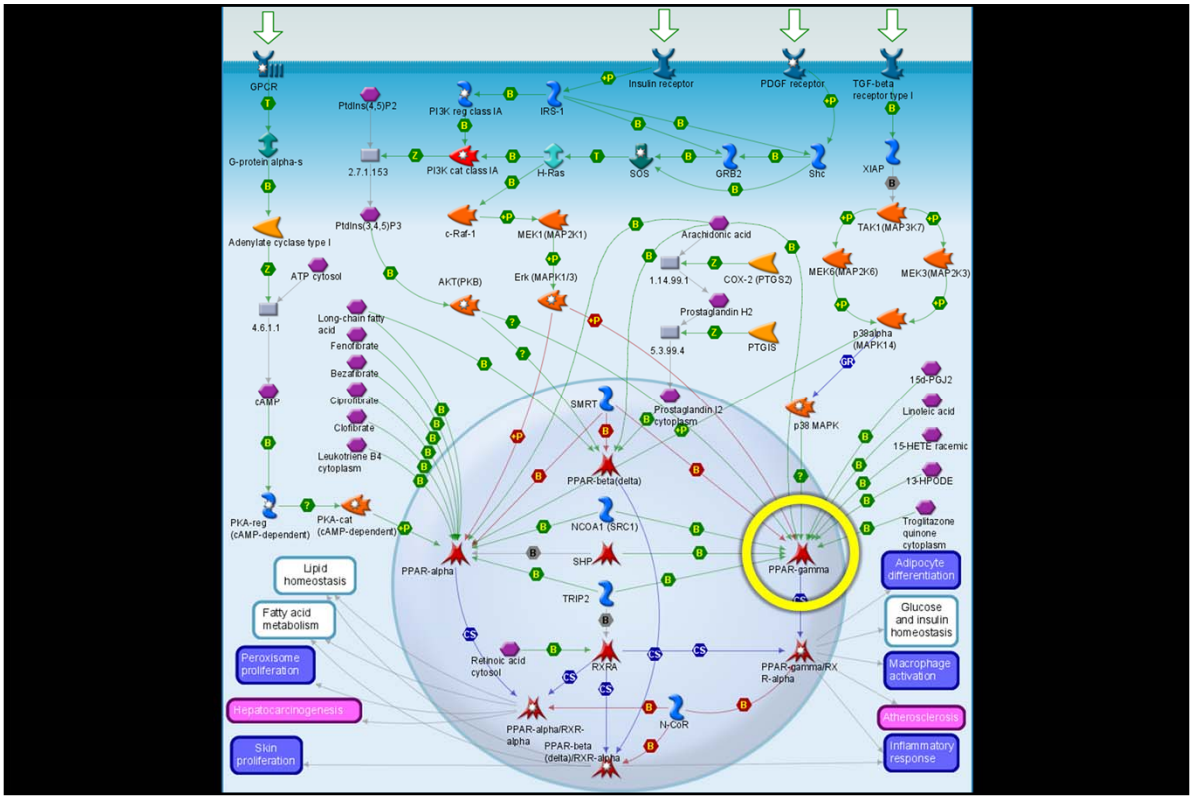
Systemic Benefits of Pioglitazone (cost ~$20):

- Lowers blood sugars and HgbA1c by improving insulin resistance
- Does not cause hypoglycemia
- Preserves beta-cells and normalizes insulin secretory patterns
- Reduces visceral fat mass
- Lowers Triglycerides
- Raises HDL & apoA-I by stimulating ABCA1 & LPL
- Reduces FFAs, Leptin, NF-kB, PAI-1, Endothelin-1, IL-1, TNFa, MCP-1, hsCRP →
  - Reduced SMC proliferation
- Increases Adiponectin
- Treats Steato-hepatitis
- Reduces micro-Albuminuria
- Possible benefits in CNS disorders, IBD, asthma, cystic fibrosis, & arthritis

Pioglitazone & Heart Disease

Cardiovascular Benefits of Pioglitazone:

- Shrinks arterial plaques in patients with Diabetes & Impaired Fasting Glucose
- Slows neo-intimal growth in stents by inhibiting IL-1, TNFa, & MCP-1 & down-regulating CCR2 (receptor for MCP-1) → inhibits SMC proliferation
- Prevents Myocardial Infarcts, especially second MI's
- Prevents MI + Stroke following a stroke in non-Diabetic patients with insulin resistant
- Hospitalization for CHF not statistically increased; most caused by A-Fib or MI
  - 4.2% reduction MI & Stroke vs 0.5% increase in CHF hospitalization
- Reduces sBP (maybe dBP); increases stroke volume & LV compliance
- Reduces pro-Collagen & improves LVTEI (global function); reversed when discontinued
- Reduces Total Peripheral Resistance (edema) & sometimes improves Ejection Fraction
- Improves Myocardial Glucose Uptake & Myocardial Perfusion


GPCR
Insulin receptor
PDGF receptor
TGF-beta receptor type I
G-protein alpha-s
Ptdins(4,5)P2
PI3K reg class IA
IRS-1
2.7.1.153
PI3K cat class IA
H-Ras
SOS
GRB2
Shc
XIAP
Adenylate cyclase type I
Ptdins(3,4,5)P3
c-Raf-1
MEK1(MAP2K1)
Arachidonic acid
TAK1(MAP3K7)
ATP cytosol
AKT(PKB)
Erk (MAPK1/3)
1.14.99.1
COX-2 (PTGS2)
MEK6(MAP2K6)
MEK3(MAP2K3)
4.6.1.1
Long-chain fatty acid
Fenofibrate
Bezafibrate
Ciprofibrate
Clofibrate
Leukotriene B4 cytoplasm
Prostaglandin H2
5.3.99.4
PTGIS
p38alpha (MAPK14)
cAMP
SMRT
Prostaglandin I2 cytoplasm
p38 MAPK
15d-PGJ2
Linoleic acid
15-HETE racemic
13-HPODE
PPAR-beta(delta)
Troglitazone quinone cytoplasm
PKA-reg (cAMP-dependent)
PKA-cat (cAMP-dependent)
NCOA1 (SRC1)
PPAR-alpha
SHP
PPAR-gamma
Adipocyte differentiation
Lipid homeostasis
TRIP2
Glucose and insulin homeostasis
Fatty acid metabolism
Retinoic acid cytosol
RXRA
PPAR-gamma/RXR-alpha
Peroxisome proliferation
Macrophage activation
Hepatocarcinogenesis
PPAR-alpha/RXR-alpha
N-CoR
Atherosclerosis
Skin proliferation
PPAR-beta (delta)/RXR-alpha
Inflammatory response