# TZD, beyond glycemic control

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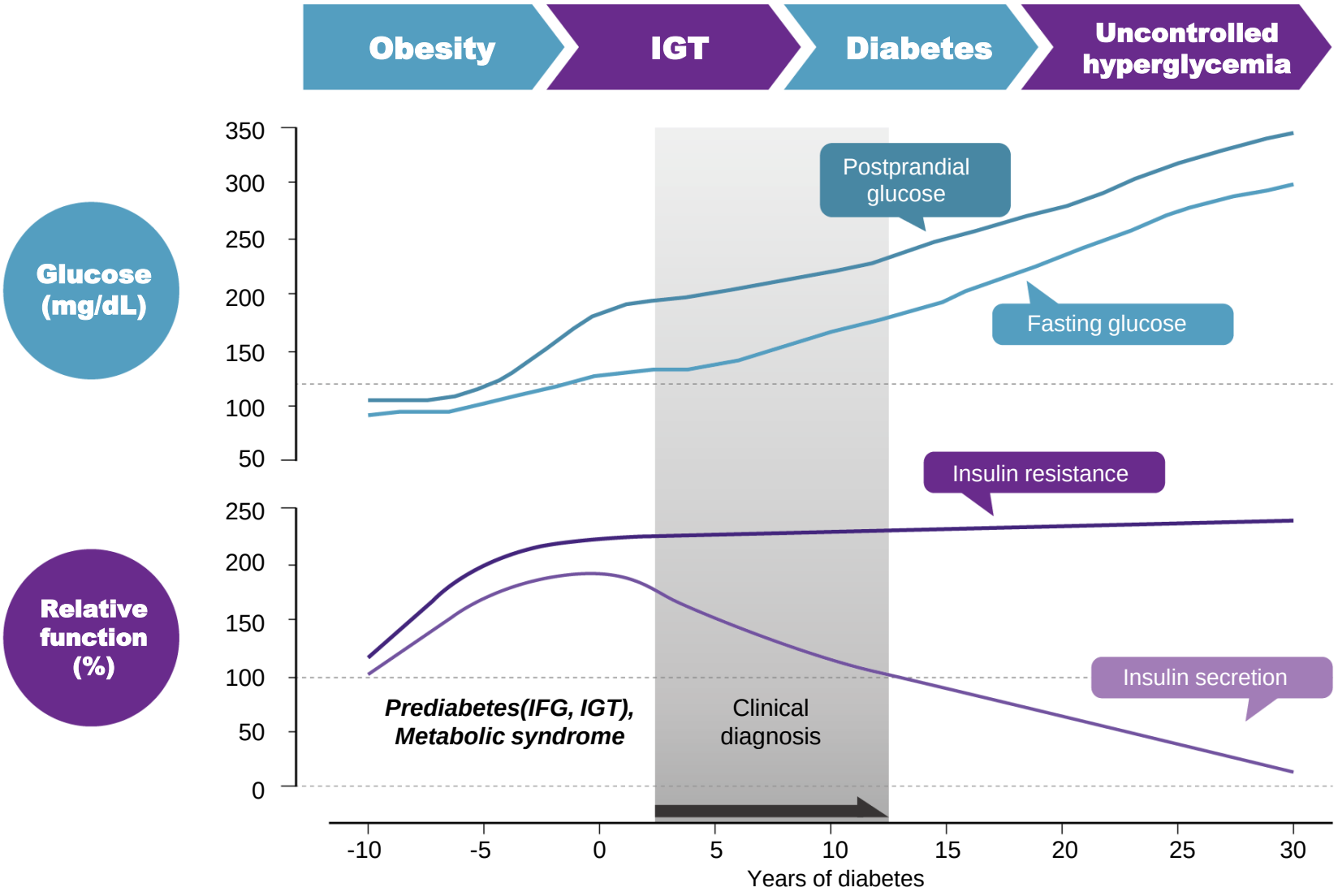
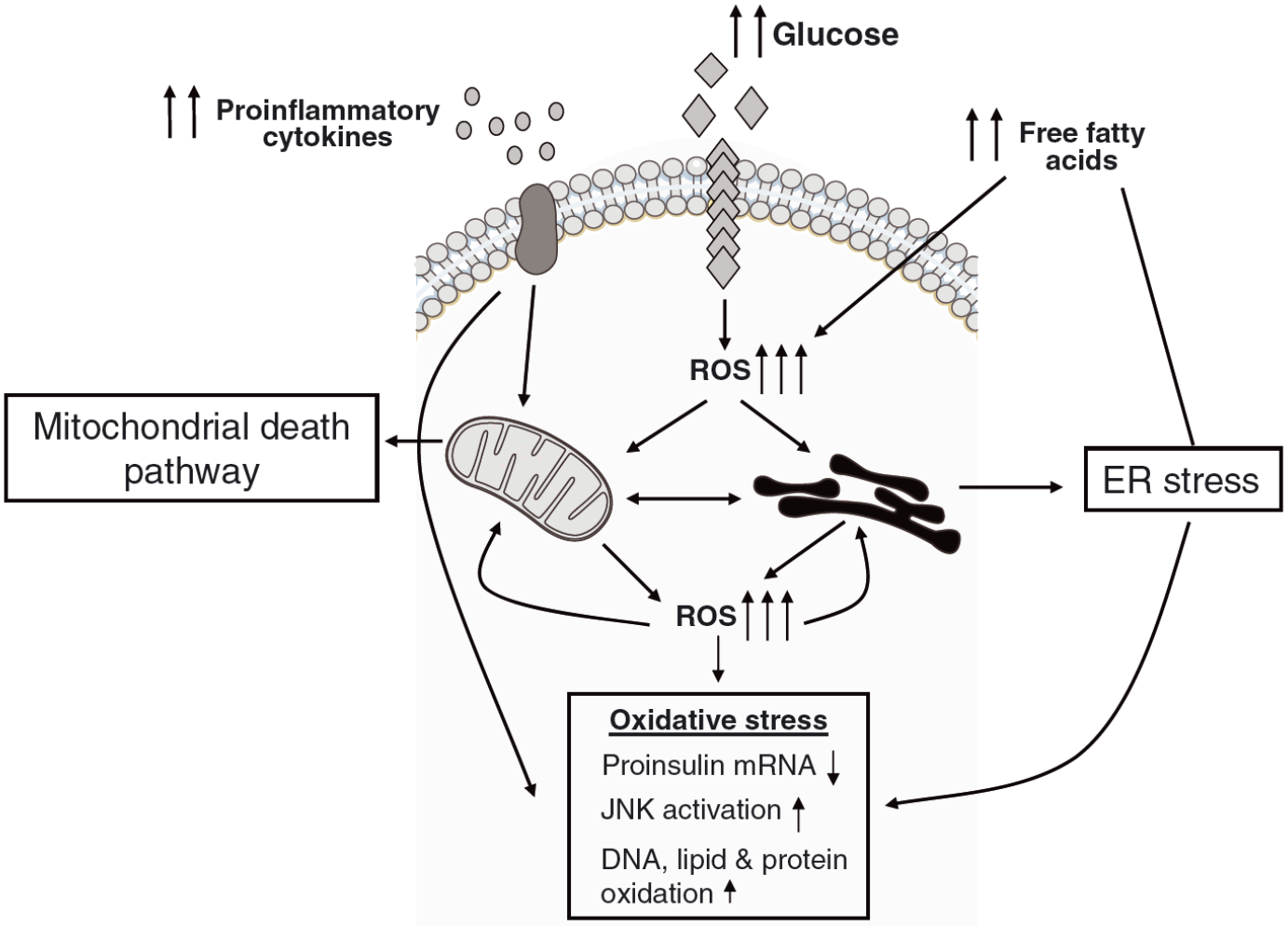
# Underlying Factors in Type 2 Diabetes: Insulin Resistance and β-Cell Dysfunction



# " Glucolipotoxicity" – the main mechanisms for islet dysfunction




High glucose and FFA results in excess generation of ROS from mitochondria and ER of β-cell.
ROS impair mitochondrial and ER function which induce transcription failure and cellular apoptosis.

Leibowitz G, Diabetes Obes Metab. 2010 Oct;12 Suppl 2:66-75.

# Contents

- Introduction of TZD – what do we know?
- What should we do?
  - TZD and weight gain
  - TZD and HF
  - TZD and bone
  - TZD and cancer
  - TZD and dementia
  - Effects of TZD on NAFLD

# Case: 56/M

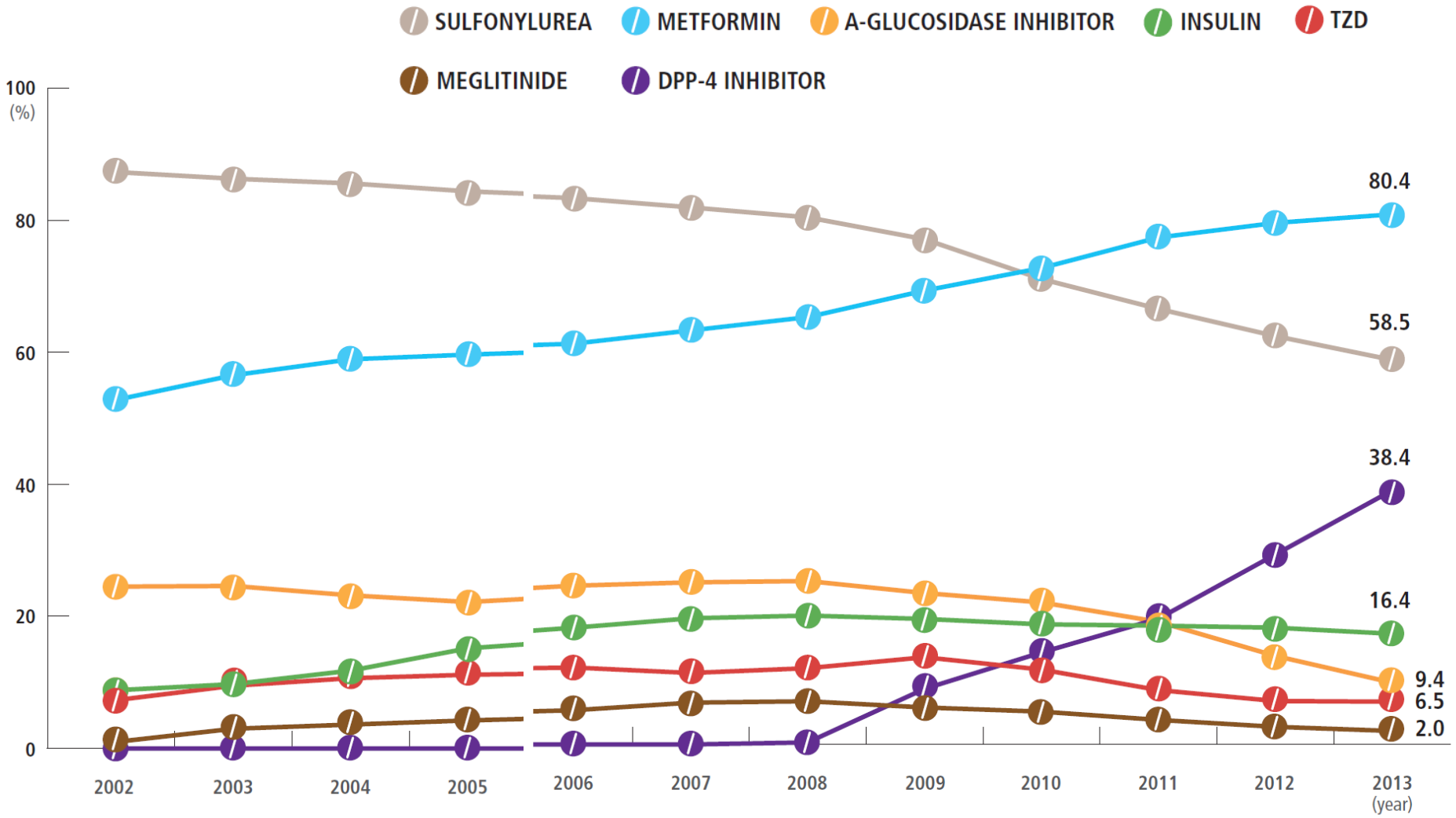
- Admitted to Endo in 2001.2
- Weight loss 5 kg/3 months
- Pp2hrs 242 mg/dL, HbA1c 6.7%
- BMI 27.8 kg/$m^2$

- MFMT 500 mg bid + TZD

# Case: 56/M

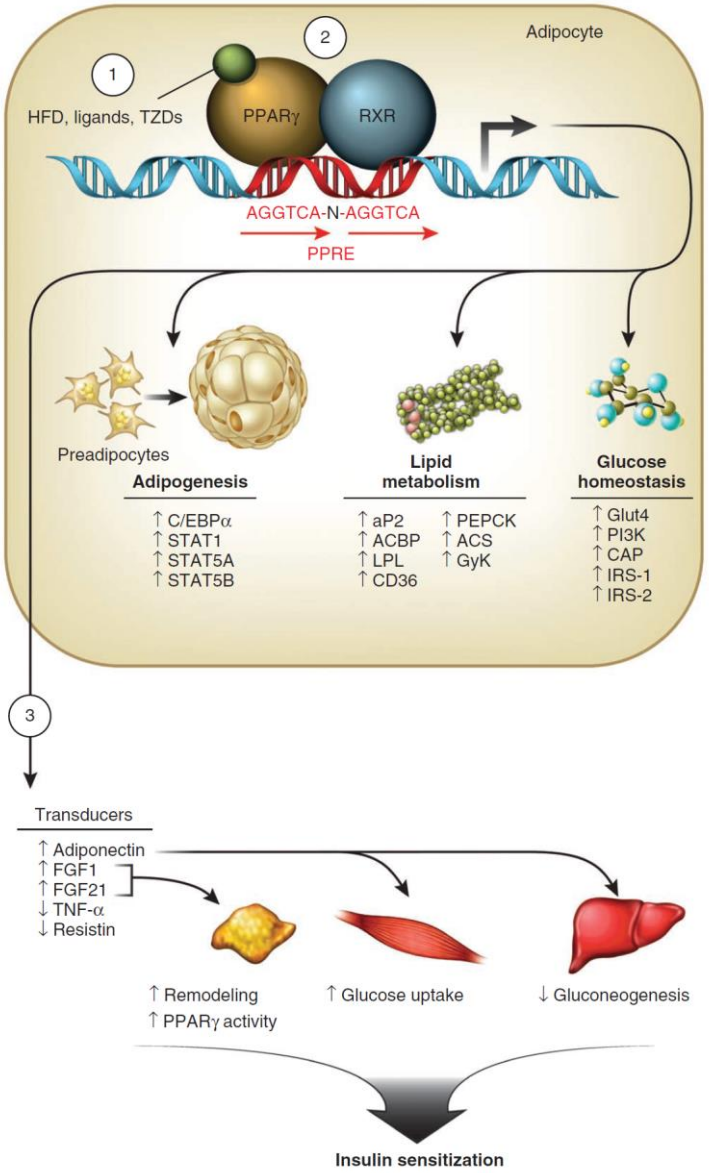
- 2015.8
- HbA1c 6.6%
- PIO 15 mg + MFMT 850 mg bid
- C-peptide level (fasting/pp) : 1.21 / 3.76 ng/mL

# TZD is a steady seller…




KDA Diabetes Fact Sheet, 2015

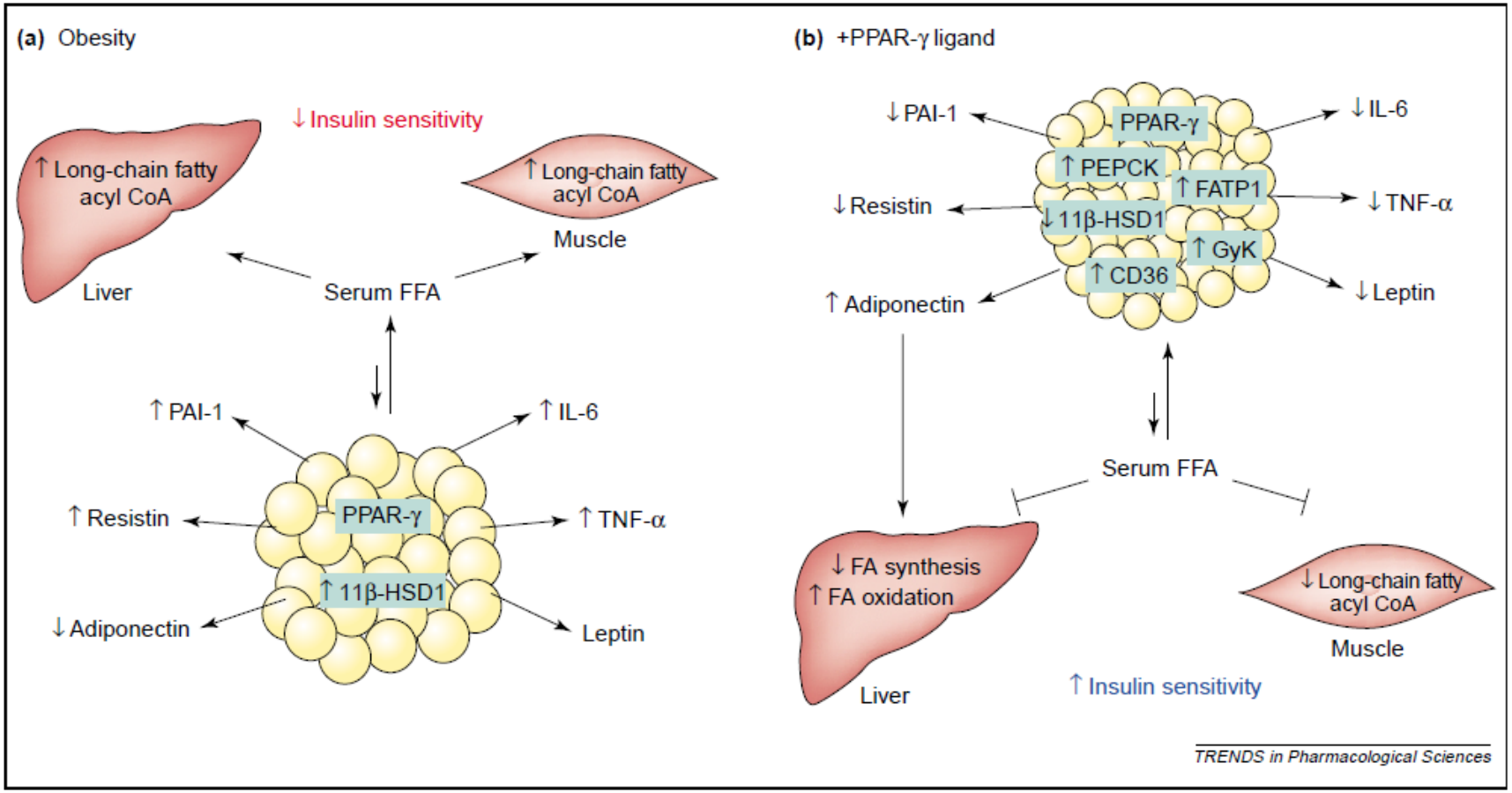
# PPAR gamma: Peroxisome proliferator-activated receptor-gamma




- Member of the peroxisome proliferator-activated receptor subfamily of nuclear receptors
- Regulates transcription of various genes associated with fatty acid storage and glucose metabolism, adipocyte differentiation

Ahmadin M et al. Nat Med, 2013

# ‘Lipid-steal’ theory of TZD

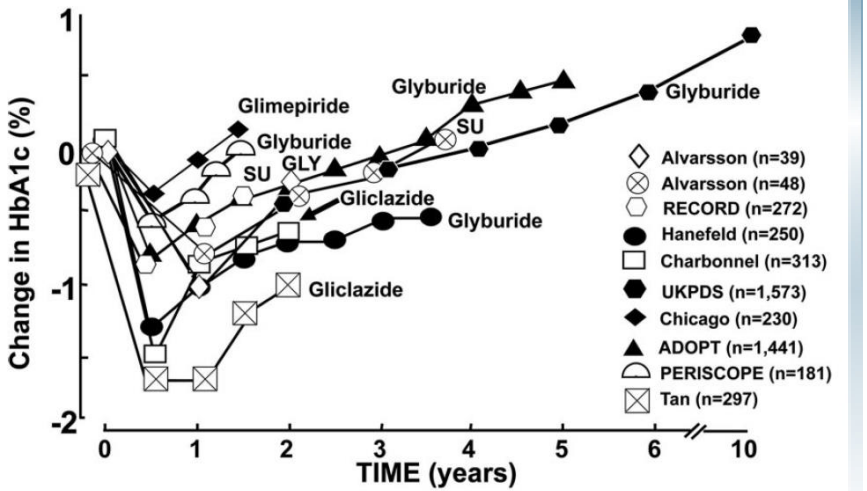



Rangwara SM et al. Trends Pharmacol Sci, 2004

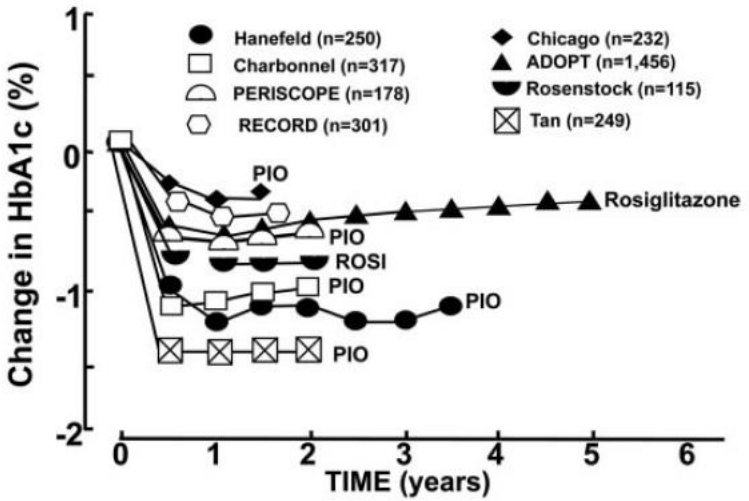
# Durability of TZDs

TZD produced sustained, long-term reductions in HbA1c in contrast to SU

## SU



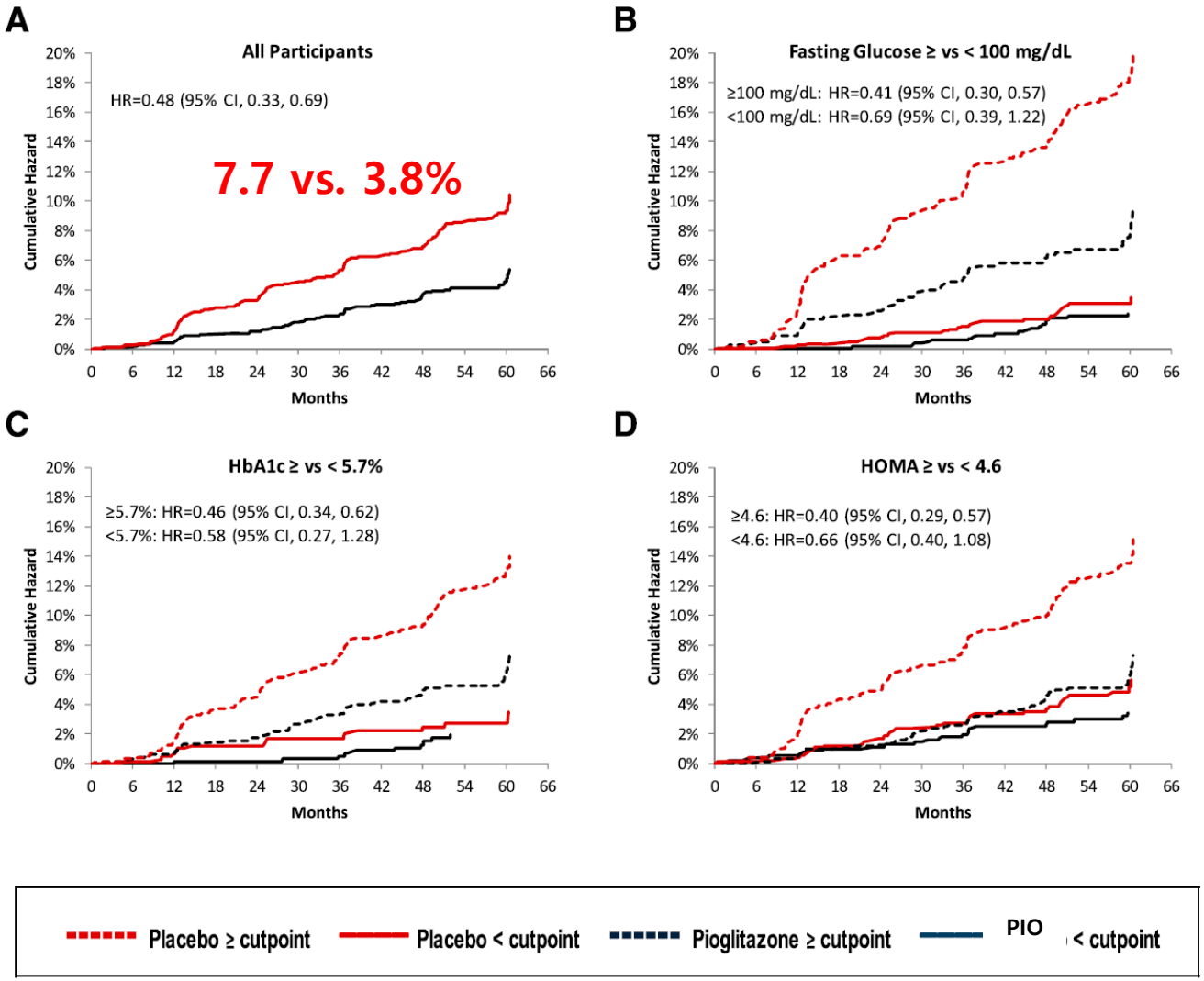

## TZDs




Diabetes 2009;58:773-795

# PIO prevents diabetes in insulin-resistant non-diabetic patients with cerebrovascular disease

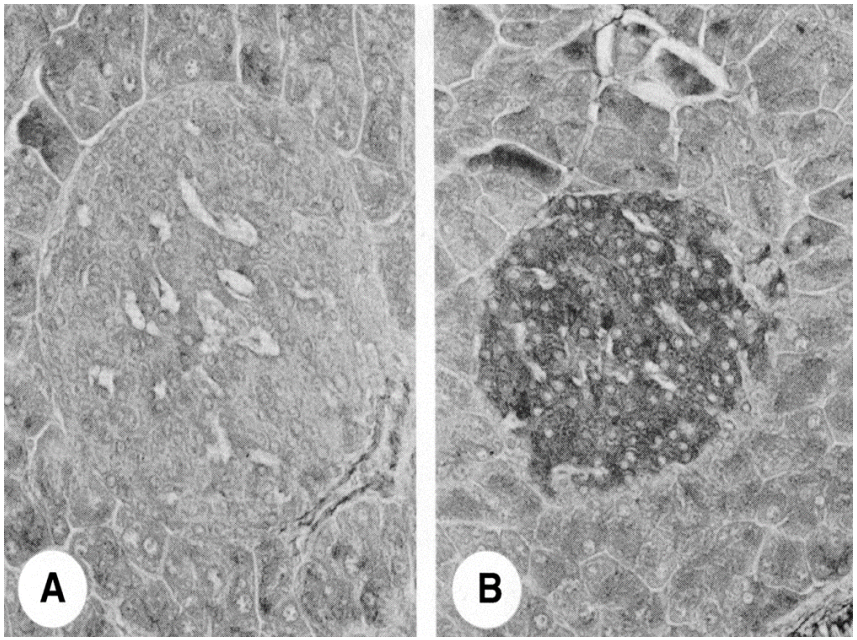
In 3,875 insulin resistant patients (HOMA-IR > 3.0) with TIA or ischemic stroke
Randomized to placebo or PIO for 4.8 years




Inzucchi SE et al. Diabetes Care, 2016

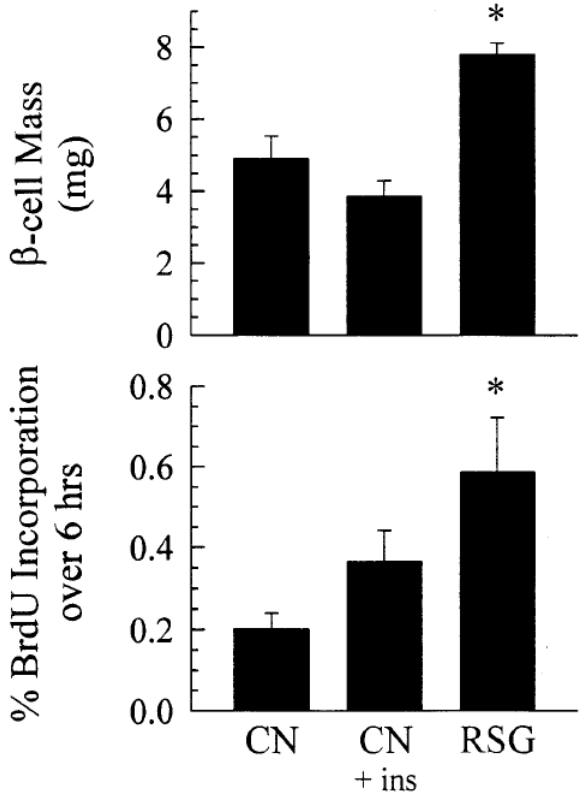
# Effects of TZD Tx on Pancreatic Beta cell mass

**Pioglitazone Tx in ob/ob mouse islet**



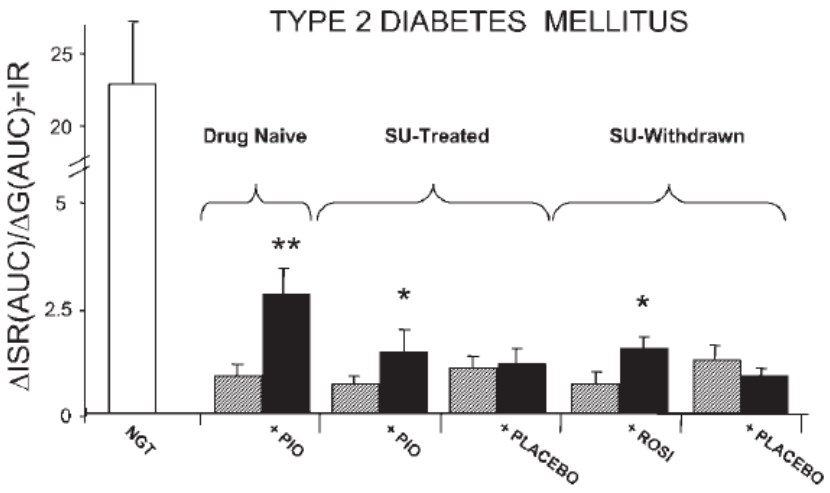

Control Pioglitazone

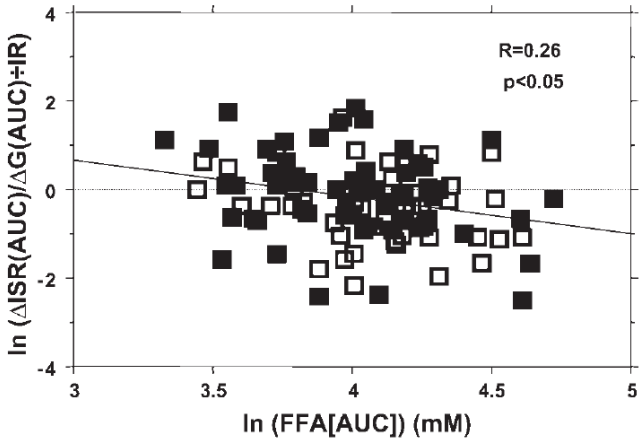
**Rosiglitazone Tx in Zucker Diabetic Fatty Rats**

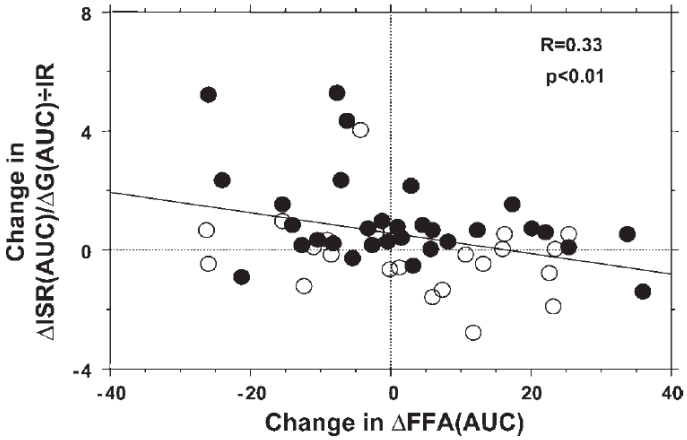



Diani et al, AJP 286: E116, 2004
Finegood DT et al. Diabetes, 2001

# TZD improves beta-cell function in T2DM through the attenuation of FFA levels



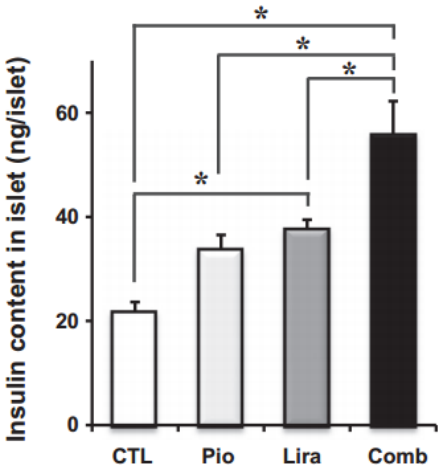



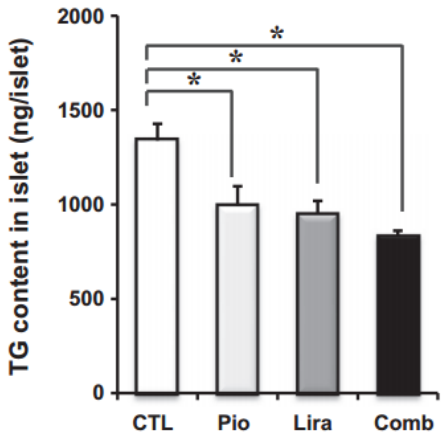

Gastaldelli A et al. AJPEM, 2007

# Effect in early and advanced stage (pioglitazone and/or liraglutide)

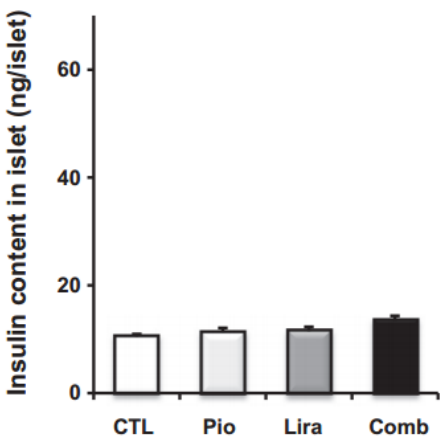
| | |
|---|---|
| **Animal** | 7-(early) or 16-week (advanced) old *db/db* mice |
| **Treatment** | Pioglitazone 25 mg/kg PO, liraglutide 0.4 mg/kg SC for 2 weeks |

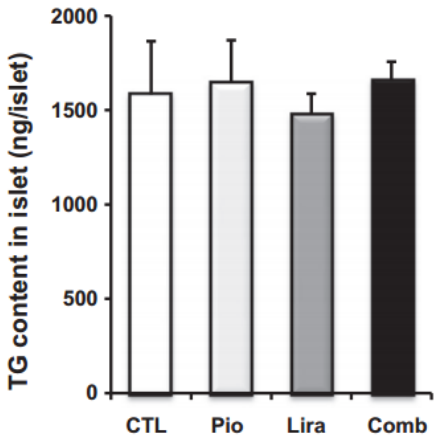
**Early stage**




**Advanced stage**




Kimura T, et al. Mol Cell Endocrinol 2015;400:78

The NEW ENGLAND JOURNAL of MEDICINE

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

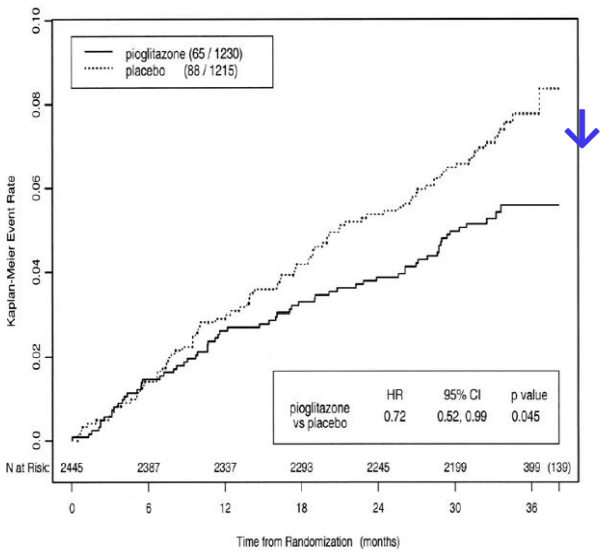
Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

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

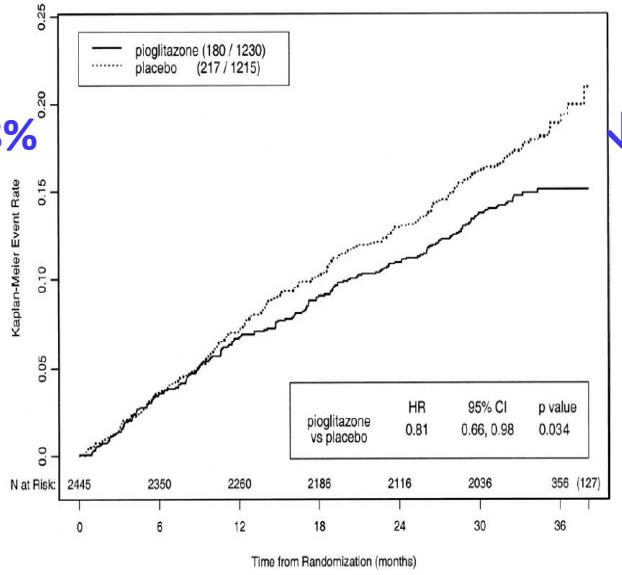
trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

# Effect of pioglitazone on recurrent MI in 2,445 patients with T2DM and previous MI: sub-analysis of PROactive study

In 2,445 patients with previous MI




↓28%




↓19%

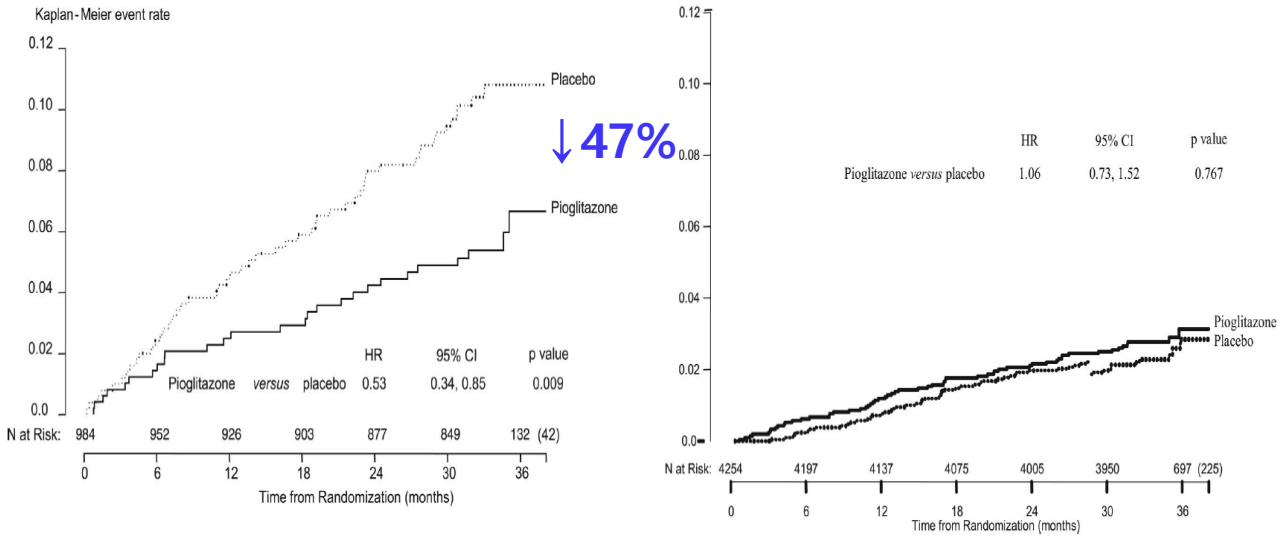
Time to fatal/nonfatal MI

Time to nonfatal, coronary revascularization, acute coronary SD or cardiac death

Erdmann E et al. JACC, 2007

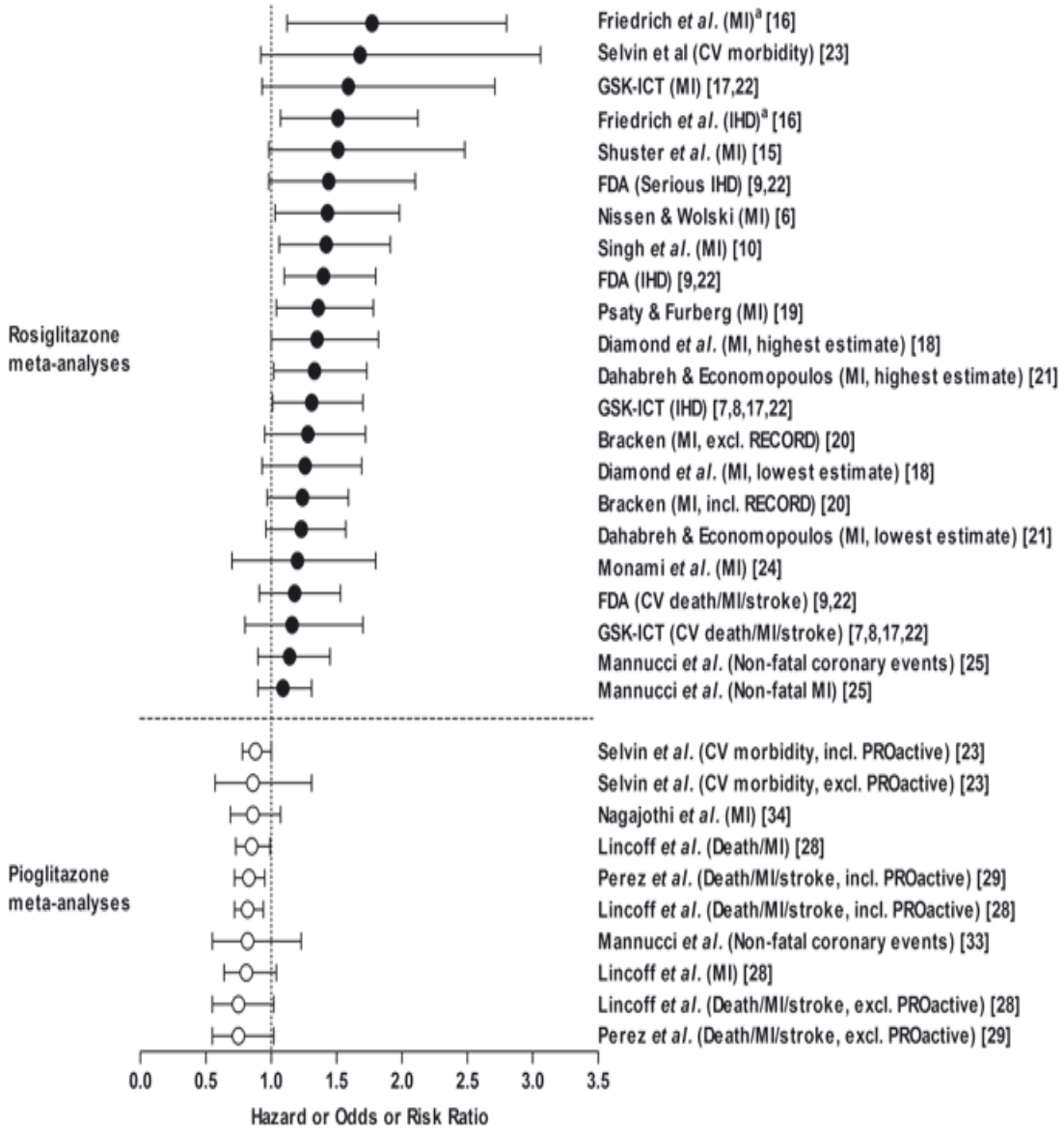
# Effect of pioglitazone in patients with T2DM with or without previous stroke: sub-analysis of PROactive study

In T2DM patients **with** (n=984) and **without** (n=4254) prior stroke




Wilcox R et al. Stroke, 2007

# TZD and CVD – meta-analyses




Schernthaner G et al. DOM, 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, L.M. Brass,* G.G. Schwartz, H.P. Adams, Jr., L. Berger, A. Carolei, W. Clark, B. Coull, G.A. Ford, D. Kleindorfer, J.R. O'Leary, M.W. Parsons, P. Ringleb, S. Sen, J.D. Spence, D. Tanne, D. Wang, and T.R. Winder, for the IRIS Trial Investigators†

## ABSTRACT

### 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

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kernan at 2 Church St. S., Suite 515, New Haven, CT 06519, or at walter.kernan@yale.edu.

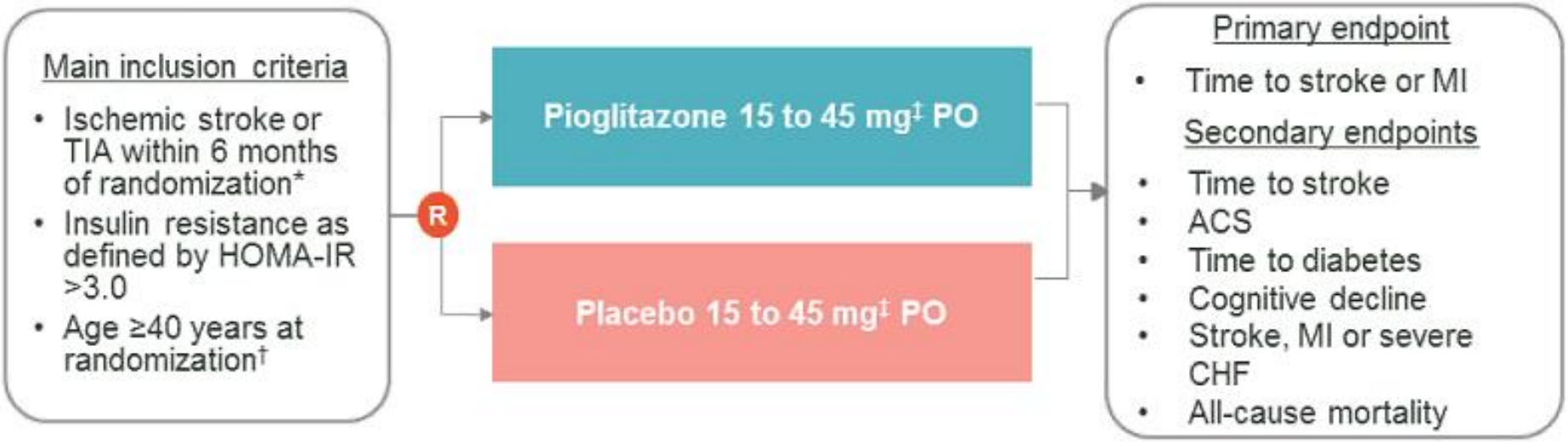
*Deceased.

†A complete list of the Insulin Resistance Intervention after Stroke (IRIS) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 17, 2016, at NEJM.org.

# IRIS: study design

**Multicenter, randomized, double-blind, placebo-controlled study in an insulin-resistant, non-diabetic patient population (N=3,876)[1]**




**Objectives :**
To test the effectiveness of pioglitazone and TZD class for reducing the incidence of stroke and MI among insulin resistant nondiabetic patients with a recent ischemic stroke or TIA.

*Patients without a prior or current diagnosis of diabetes were enrolled. A qualifying ischemic stroke was defined by focal neurologic symptoms or signs persisting for ≥24 hours and/or associated with a new area of infarction on brain imaging in an appropriate location

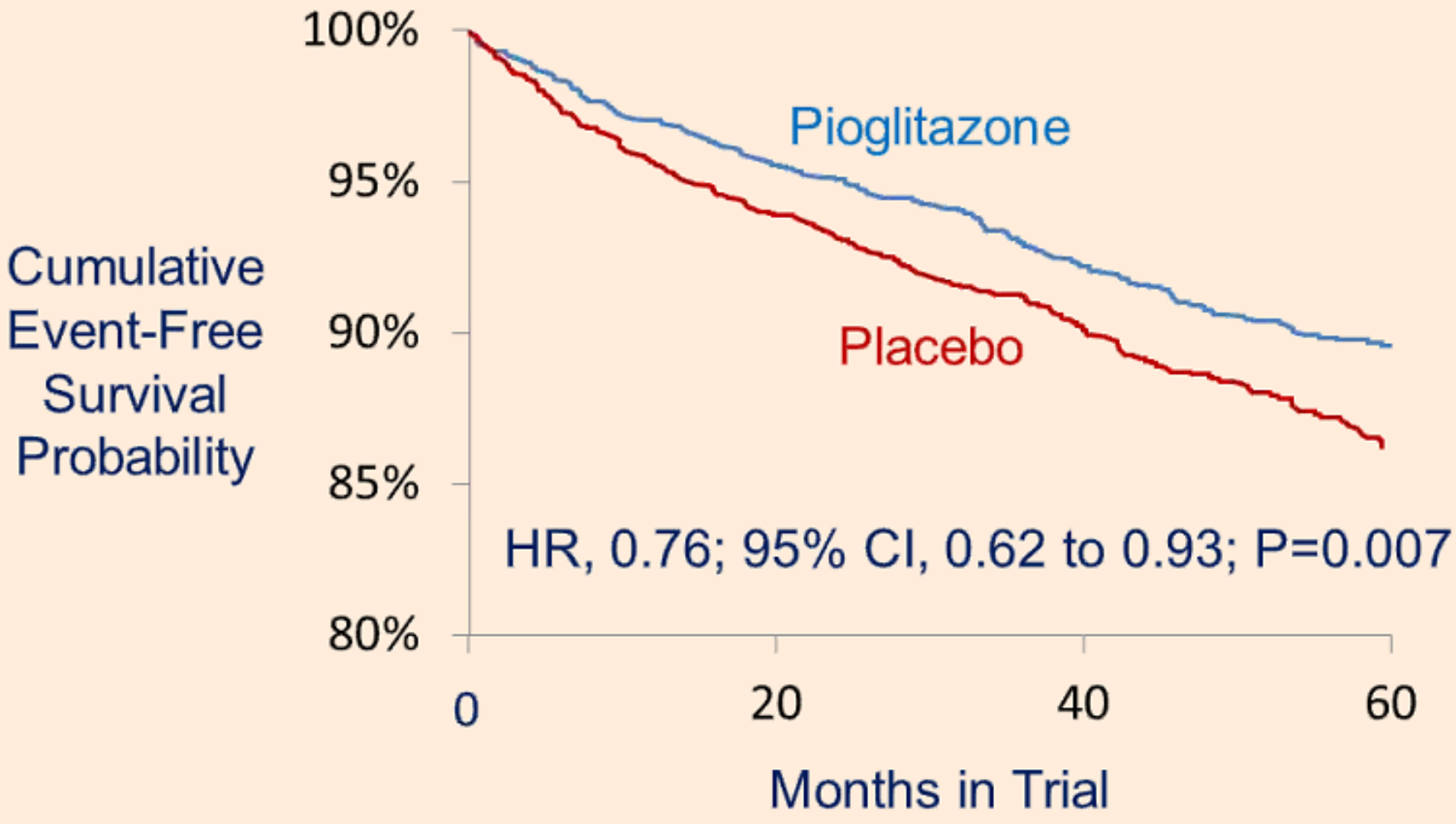
†Changed from 45 years in October 2007

‡Study medication (or placebo) was initiated at a dose of 15mg daily. Study medication was increased at four weeks to two tablets daily (30mg pioglitazone or matching placebo) and at eight weeks to three tablets daily. Participants at full protocol dose were supplied with pioglitazone 45mg or matching placebo tablets at 12 weeks

ACS=acute coronary syndrome; CHF=congestive heart failure; HOMA-IR=Homeostasis Model Assessment-Insulin Resistance; MI=myocardial infarction; PO=orally; R=randomization; TIA=transient ischemic attack; TZD=thiazolidinedione.

Viscoli CM, et al. *Am Heart J*. 2014;168.823–829.

# Primary Outcome



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- What should we do?
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  - TZD and HF
  - TZD and bone
  - TZD and cancer
  - TZD and dementia
  - Effects of TZD on NAFLD

# Impact of weight gain on all-cause mortality and CVD mortality in PROactive study

**Table 3**
Impact of weight gain and weight loss on all-cause mortality (A) and on cardiovascular mortality (B). Hazard ratios for 1% weight change.

| Outcome | Bivariable model[a] | | | Multivariable model[b] | | |
|---|---|---|---|---|---|---|
| (A) All cause mortality | HR | 95%CI | *P* | HR | 95%CI | *P* |
| All patients, adjusted for treatment | | | | | | |
| Weight gain (1%) | 0.97 | 0.94–1.01 | 0.14 | 0.97 | 0.94–1.01 | 0.14 |
| Weight loss (1%) | **1.13** | **1.11–1.16** | **<0.0001** | **1.13** | **1.10–1.15** | **<0.0001** |
| Placebo arm | | | | | | |
| Weight gain (1%) | 1.02 | 0.95–1.08 | 0.61 | 1.01 | 0.95–1.08 | 0.70 |
| Weight loss (1%) | **1.15** | **1.11–1.18** | **<0.0001** | **1.13** | **1.10–1.17** | **<0.0001** |
| Pioglitazone arm | | | | | | |
| Weight gain (1%) | **0.96** | **0.92–1.00** | **0.037** | **0.96** | **0.92–1.00** | **0.035** |
| Weight loss (1%) | **1.12** | **1.09–1.15** | **<0.0001** | **1.12** | **1.09–1.16** | **<0.0001** |
| (B) Cardiovascular mortality | HR | 95%CI | *P* | HR | 95%CI | *P* |
| All patients, adjusted for treatment | | | | | | |
| Weight gain (1%) | 0.97 | 0.93–1.01 | 0.15 | 0.97 | 0.93–1–01 | 0.11 |
| Weight loss (1%) | **1.08** | **1.04–1.11** | **<0.0001** | **1.07** | **1.03–1.10** | **0.0003** |
| Placebo arm | | | | | | |
| Weight gain (1%) | 1.00 | 0.93–1.08 | 0.89 | 1.00 | 0.93–1.08 | 0.94 |
| Weight loss (1%) | **1.08** | **1.04–1.13** | **0.0003** | **1.06** | **1.01–1.11** | **0.015** |
| Pioglitazone arm | | | | | | |
| Weight gain (1%) | 0.96 | 0.91–1.00 | 0.075 | **0.95** | **0.90–1.00** | **0.042** |
| Weight loss (1%) | **1.07** | **1.02–1.13** | **0.004** | **1.07** | **1.02–1.13** | **0.0008** |

Doehner W et al. IJC, 2012

# Subjects with high WHR responds better to TZD

In 125 T2DM patients, 12 wks of RSG Tx

Table 3
Comparison of baseline clinical and biochemical characteristics between rosiglitazone-responders and nonresponders

| | Rosiglitazone group ($n = 60$) | | Non-obese (BMI $<25\,kg/m^2$) ($n = 43$) | | Obese (BMI $\geq 25\,kg/m^2$) ($n = 17$) | |
|---|---|---|---|---|---|---|
| | Responder ($n = 45$) | Nonresponder ($n = 15$) | Responder ($n = 32$) | Nonresponder ($n = 11$) | Responder ($n = 13$) | Nonresponder ($n = 4$) |
| Sex (male:female) | 9:36‡ | 5:10 | 5:27* | 6:5 | 4:9* | 4:0 |
| Age (years) | 60.0 ± 7.9 | 56.7 ± 10.9 | 59.8 ± 8.4 | 58.6 ± 10.8 | 60.3 ± 6.8 | 51.8 ± 10.9 |
| DM duration (years) | 12.6 ± 6.4 | 11.3 ± 6.3 | 13.1 ± 6.8 | 12.1 ± 5.8 | 11.4 ± 5.5 | 9.3 ± 7.9 |
| M:M + S ($n$) | 21:24 | 8:7 | 14:18 | 6:5 | 7:6 | 2:2 |
| BMI ($kg/m^2$) | 24.2 ± 2.6 | 23.2 ± 2.2 | 22.8 ± 1.2 | 22.2 ± 1.3 | 27.5 ± 1.7 | 26.1 ± 0.7 |
| Waist–hip ratio | 0.96 ± 0.08† | 0.92 ± 0.03 | 0.94 ± 0.07 | 0.92 ± 0.03 | 1.02 ± 0.08* | 0.90 ± 0.02 |
| C-peptide (μg/l) | 1.89 ± 0.66 | 1.82 ± 0.97 | 1.89 ± 0.68 | 1.87 ± 1.09 | 1.91 ± 0.65 | 1.68 ± 0.65 |
| Fasting insulin (ρmol/l) | 60.6 ± 26.9† | 38.0 ± 20.3 | 59.3 ± 29.4* | 38.2 ± 20.2 | 64.0 ± 20.1* | 37.2 ± 24.0 |
| FPG (mmol/l) | 12.3 ± 2.4* | 10.7 ± 2.2 | 12.4 ± 2.4* | 10.8 ± 2.3 | 12.1 ± 2.6 | 10.4 ± 2.4 |
| $HbA_{1c}$ (%) | 10.1 ± 1.7† | 8.7 ± 1.4 | 10.4 ± 1.7* | 8.9 ± 1.3 | 9.3 ± 1.6 | 8.3 ± 1.7 |
| Total cholesterol (mmol/l) | 5.44 ± 0.99 | 5.12 ± 0.75 | 5.43 ± 1.01 | 5.05 ± 0.85 | 5.46 ± 0.96 | 5.31 ± 0.32 |
| HDL cholesterol (mmol/l) | 1.15 ± 0.23 | 1.15 ± 0.29 | 1.14 ± 0.22 | 1.12 ± 0.25 | 1.20 ± 0.25 | 1.21 ± 0.41 |
| LDL cholesterol (mmol/l) | 3.15 ± 1.13 | 2.98 ± 0.77 | 3.04 ± 1.23 | 2.83 ± 0.79 | 3.42 ± 0.83 | 3.39 ± 0.63 |
| Triglyceride (mmol/l) | 2.45 ± 1.83 | 2.17 ± 0.81 | 2.71 ± 2.10 | 2.39 ± 0.75 | 1.81 ± 0.56 | 1.54 ± 0.68 |
| Systolic BP (mmHg) | 142.8 ± 17.0† | 130.9 ± 17.0 | 143.4 ± 16.1 | 132.2 ± 18.5 | 141.2 ± 19.8 | 127.5 ± 13.2 |
| Diastolic BP (mmHg) | 84.5 ± 10.1 | 80.0 ± 11.2 | 84.7 ± 10.9 | 81.6 ± 10.9 | 84.2 ± 8.3 | 75.8 ± 12.6 |
| $HOMA_{IR}$ | 4.59 ± 2.01† | 2.57 ± 1.76 | 4.52 ± 2.17* | 2.66 ± 1.93 | 4.75 ± 1.61* | 2.34 ± 1.41 |
| $HOMA_{\beta\text{-cellfunction}}$ | 21.6 ± 16.0 | 15.8 ± 9.5 | 21.0 ± 17.7 | 15.6 ± 9.4 | 22.9 ± 11.6 | 16.4 ± 11.2 |
| QUICKI | 0.313 ± 0.026† | 0.342 ± 0.029 | 0.315 ± 0.029* | 0.341 ± 0.028 | 0.308 ± 0.016* | 0.347 ± 0.037 |

Kim YM et al. DRCP, 2005

# Weight gain-fluid? Fat?

Om 19 diabetic subjects before and after 45 mg of PIO for 12 weeks

| | Pioglitazone | | |
|---|---|---|---|
| | Before | After | Δ |
| Fasting plasma glucose (mmol/l) | 8.4 ± 0.7 | 8.8 ± 0.9 | +0.4 |
| A1C (%) | 6.9 ± 0.3 | 7.5 ± 0.8 | +0.6 |
| Weight (kg) | 92.1 ± 7 | 95.2 ± 9 | +3.1 |
| Body fat (kg) | 38.3 ± 5 | 39.2 ± 6 | +0.9 |
| Total abdominal fat ($cm^2$) | 500 ± 80 | 468 ± 67 | −32 |
| Visceral fat ($cm^2$) | 217 ± 48 | 201 ± 43 | −16 |
| Body water (l) | 47.6 ± 3.6 | 50 ± 3.3 | +2.4* |
| Body water/fat-free mass | 0.84 ± 0.02 | 0.88 ± 0.02 | +0.04* |
| VEGF (pmol/l) | 6.2 ± 1.3 | 7.0 ± 1.4 | +0.8 |
| Diastolic blood pressure (mmHg) | 84.2 ± 4 | 75.8 ± 4 | −8.4 |
| Mean blood pressure (mmHg) | 102 ± 5 | 92.5 ± 5 | −9.5 |
| Systemic vascular resistance (dynes/s per $m^2$) | 2,785 ± 336 | 2,227 ± 136 | −561* |
| Cardian output (l/min) | 6.2 ± 0.4 | 6.7 ± 0.4 | +0.5 |
| Cardiac index (l per $m^2$/min) | 2.8 ± 0.2 | 3.0 ± 0.2 | +0.2 |

2.4 kg increase (75%) of total weight gain (3.1kg) due to body water

50 patients with T2DM in placebo or PIO 45 mg for 16 weeks

**Table 2 Effect of treatment with PIO and placebo on body composition, parameters of glycemic control, blood counts, serum electrolytes, and blood pressure**

| | Placebo | Pioglitazone | *P* value# |
|---|---|---|---|
| ΔBMI ($kg/m^2$) | 0.1 ± 0.2 | 1.4 ± 0.2* | 0.0003 |
| Δtotal body weight (kg) | 0.1 ± 0.5 | 3.8 ± 0.7* | 0.0004 |
| Δfat-free mass (kg) | 0.1 ± 0.1 | 0.2 ± 0.1 | NS |
| Δfat weight (kg) | 0.1 ± 0.4 | 3.6 ± 0.6* | 0.0006 |
| Δtotal body water (L) | 0.02 ± 0.08 | 0.16 ± 0.06 | NS |
| ΔECW (L)[a] | 0.26 ± 0.46 | 0.21 ± 0.34 | NS |
| Δ$HbA_{1c}$ (%) | 0.8 ± 0.3 | −1.7 ± 0.3* | <0.0001 |
| Δfasting plasma glucose (mmol/L) | 1.8 ± 0.4* | −1.5 ± 0.4* | <0.0001 |
| Δfasting plasma insulin (pmol/L) | 2.3 ± 10.6 | −28.3 ± 6.6* | 0.016 |
| ΔAUC glucose (mol/L 120 min) | −0.23 ± 0.13 | −0.15 ± 0.08 | NS |
| ΔAUC insulin (nmol/L 120 min) | −5.66 ± 5.54 | −0.08 ± 1.3 | NS |
| Δhemoglobin (g/dL) | −0.3 ± 0.2 | −0.9 ± 0.2* | 0.03 |
| Δhematocrit (%) | −0.5 ± 0.5 | −2.4 ± 0.5* | 0.02 |
| ΔWBC count (× $10^3/mm^3$) | −0.2 ± 0.2 | −0.8 ± 0.1* | 0.014 |
| Δplatelet count (× $10^3/\mu l$) | 8.1 ± 14 | −15 ± 6* | NS |
| Δserum albumin (g/dL) | −0.13 ± 0.8 | −0.15 ± 0.07* | NS |
| Δserum creatinine (mg/dL) | −0.02 ± 0.04 | 0.08 ± 0.02* | 0.02 |
| Δcreatinine clearance (ml/min) | −24 ± 15 | −27 ± 10 | NS |
| Δserum urea nitrogen (mg/dL) | −1.1 ± 0.9 | 2.3 ± 0.7* | 0.013 |
| Δserum sodium (mmol/L) | −2.1 ± 0.6* | 0.2 ± 0.5 | 0.01 |
| Δserum osmolality | −4.1 ± 1.1* | 0.3 ± 1.2 | 0.028 |
| Δsystolic BP (mm Hg) | −5.1 ± 3.8 | −5.9 ± 2.9* | NS |
| Δdiastolic BP (mm Hg) | −2.6 ± 2.0 | −4.9 ± 1.6* | NS |

89% increment of body weight due to fat

Basu A et al. Diabetes Care, 2006
Berria R et al. Nat Med, 2007

# Subjects with high WHR responds better to TZD

In 125 T2DM patients, 12 wks of RSG Tx

Table 3
Comparison of baseline clinical and biochemical characteristics between rosiglitazone-responders and nonresponders

| | Rosiglitazone group ($n = 60$) | | Non-obese (BMI $<25\,kg/m^2$) ($n = 43$) | | Obese (BMI $\geq 25\,kg/m^2$) ($n = 17$) | |
|---|---|---|---|---|---|---|
| | Responder ($n = 45$) | Nonresponder ($n = 15$) | Responder ($n = 32$) | Nonresponder ($n = 11$) | Responder ($n = 13$) | Nonresponder ($n = 4$) |
| Sex (male:female) | 9:36‡ | 5:10 | 5:27* | 6:5 | 4:9* | 4:0 |
| Age (years) | 60.0 ± 7.9 | 56.7 ± 10.9 | 59.8 ± 8.4 | 58.6 ± 10.8 | 60.3 ± 6.8 | 51.8 ± 10.9 |
| DM duration (years) | 12.6 ± 6.4 | 11.3 ± 6.3 | 13.1 ± 6.8 | 12.1 ± 5.8 | 11.4 ± 5.5 | 9.3 ± 7.9 |
| M:M + S ($n$) | 21:24 | 8:7 | 14:18 | 6:5 | 7:6 | 2:2 |
| BMI ($kg/m^2$) | 24.2 ± 2.6 | 23.2 ± 2.2 | 22.8 ± 1.2 | 22.2 ± 1.3 | 27.5 ± 1.7 | 26.1 ± 0.7 |
| Waist–hip ratio | 0.96 ± 0.08† | 0.92 ± 0.03 | 0.94 ± 0.07 | 0.92 ± 0.03 | 1.02 ± 0.08* | 0.90 ± 0.02 |
| C-peptide (μg/l) | 1.89 ± 0.66 | 1.82 ± 0.97 | 1.89 ± 0.68 | 1.87 ± 1.09 | 1.91 ± 0.65 | 1.68 ± 0.65 |
| Fasting insulin (ρmol/l) | 60.6 ± 26.9† | 38.0 ± 20.3 | 59.3 ± 29.4* | 38.2 ± 20.2 | 64.0 ± 20.1* | 37.2 ± 24.0 |
| FPG (mmol/l) | 12.3 ± 2.4* | 10.7 ± 2.2 | 12.4 ± 2.4* | 10.8 ± 2.3 | 12.1 ± 2.6 | 10.4 ± 2.4 |
| $HbA_{1c}$ (%) | 10.1 ± 1.7† | 8.7 ± 1.4 | 10.4 ± 1.7* | 8.9 ± 1.3 | 9.3 ± 1.6 | 8.3 ± 1.7 |
| Total cholesterol (mmol/l) | 5.44 ± 0.99 | 5.12 ± 0.75 | 5.43 ± 1.01 | 5.05 ± 0.85 | 5.46 ± 0.96 | 5.31 ± 0.32 |
| HDL cholesterol (mmol/l) | 1.15 ± 0.23 | 1.15 ± 0.29 | 1.14 ± 0.22 | 1.12 ± 0.25 | 1.20 ± 0.25 | 1.21 ± 0.41 |
| LDL cholesterol (mmol/l) | 3.15 ± 1.13 | 2.98 ± 0.77 | 3.04 ± 1.23 | 2.83 ± 0.79 | 3.42 ± 0.83 | 3.39 ± 0.63 |
| Triglyceride (mmol/l) | 2.45 ± 1.83 | 2.17 ± 0.81 | 2.71 ± 2.10 | 2.39 ± 0.75 | 1.81 ± 0.56 | 1.54 ± 0.68 |
| Systolic BP (mmHg) | 142.8 ± 17.0† | 130.9 ± 17.0 | 143.4 ± 16.1 | 132.2 ± 18.5 | 141.2 ± 19.8 | 127.5 ± 13.2 |
| Diastolic BP (mmHg) | 84.5 ± 10.1 | 80.0 ± 11.2 | 84.7 ± 10.9 | 81.6 ± 10.9 | 84.2 ± 8.3 | 75.8 ± 12.6 |
| $HOMA_{IR}$ | 4.59 ± 2.01† | 2.57 ± 1.76 | 4.52 ± 2.17* | 2.66 ± 1.93 | 4.75 ± 1.61* | 2.34 ± 1.41 |
| $HOMA_{\beta\text{-cellfunction}}$ | 21.6 ± 16.0 | 15.8 ± 9.5 | 21.0 ± 17.7 | 15.6 ± 9.4 | 22.9 ± 11.6 | 16.4 ± 11.2 |
| QUICKI | 0.313 ± 0.026† | 0.342 ± 0.029 | 0.315 ± 0.029* | 0.341 ± 0.028 | 0.308 ± 0.016* | 0.347 ± 0.037 |

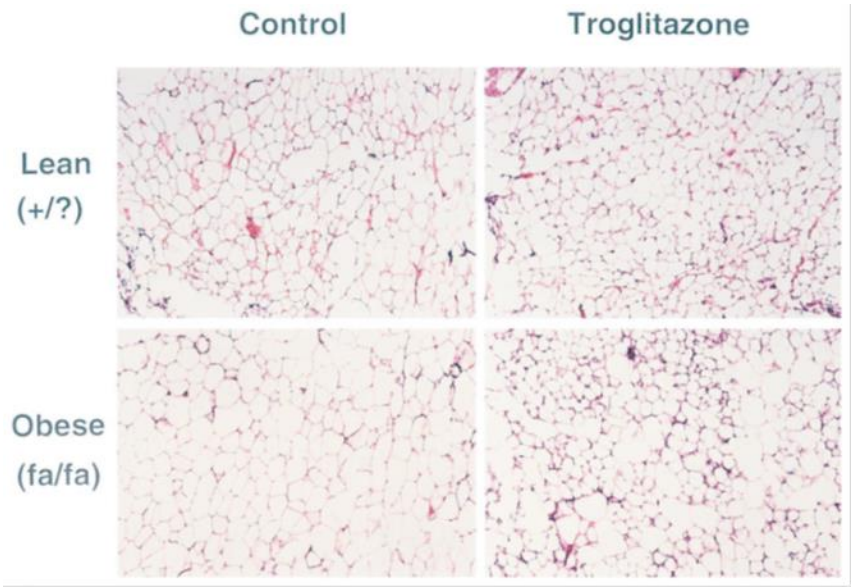
Kim YM et al. DRCP, 2005

# TZD increases the number of small adipocytes without the change of WAT mass in obese rats

Tro administered in obese Zucker rat for 15 days

*Table II. Morphometric Analysis of WATs*

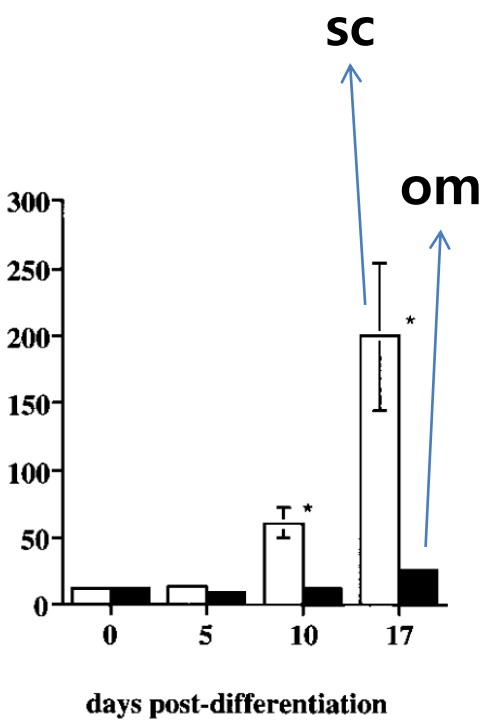
| Treatment | Number | Average size | Small adipocyte number (< 2,500 μm²) | Large adipocyte number (> 5,000 μm²) |
|---|---|---|---|---|
| Retroperitoneal WAT | | | | |
| Lean | | | | |
| control | 353 | 2608±106 | 194 | 43 |
| troglitazone | 411 | 2255±70 | 250 (×1.3) | 20 (×0.47) |
| Obese | | | | |
| control | 184 | 5031±242 | 45 | 81 |
| troglitazone | 328 | 2864±163 | 195 (×4.3) | 35 (×0.43) |
| Subcutaneous WAT | | | | |
| Lean | | | | |
| control | 371 | 2485±101 | 219 | 27 |
| troglitazone | 600 | 1492±40 | 542 (32.5) | 8 (×0.30) |
| Obese | | | | |
| control | 174 | 5501±285 | 39 | 85 |
| troglitazone | 294 | 3134±173 | 177 (×4.5) | 46 (×0.54) |

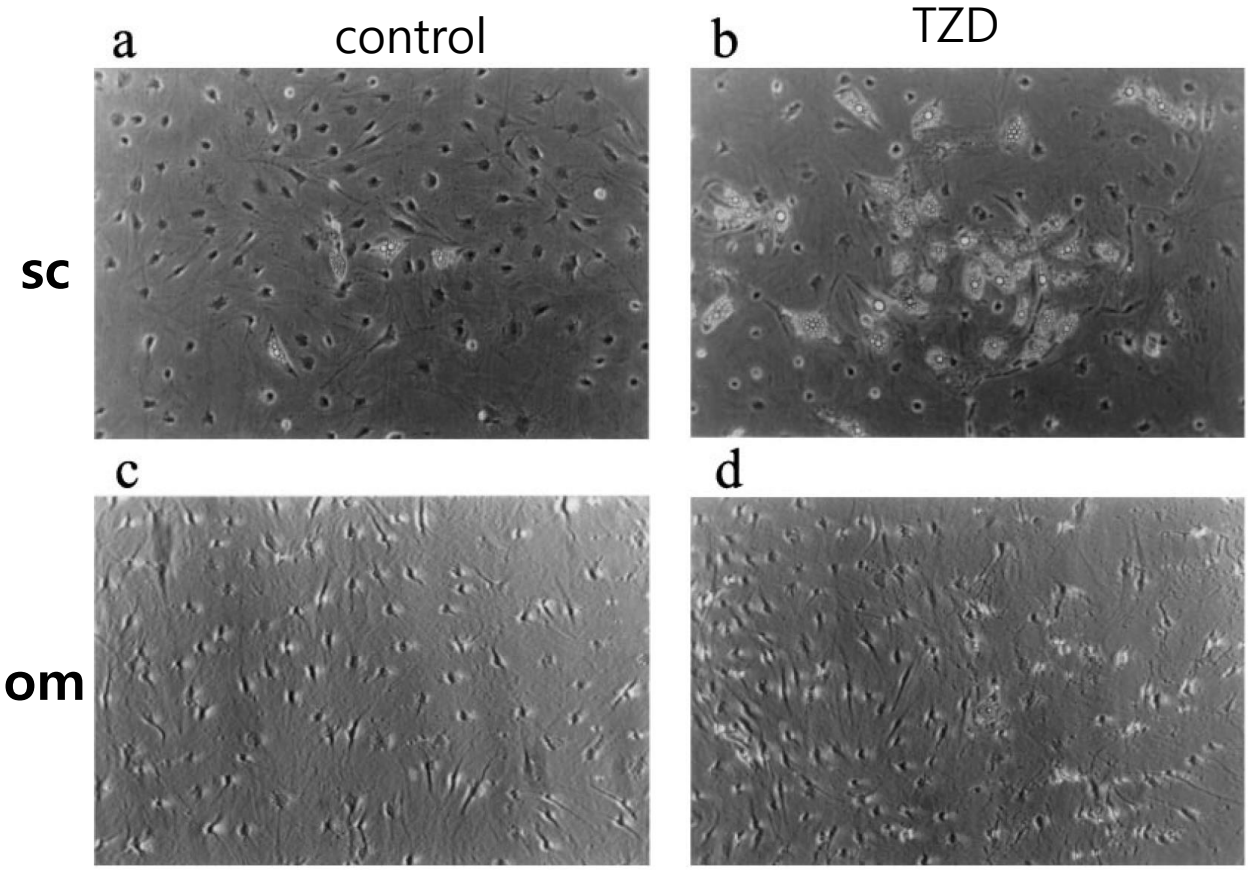



Tro did not change the total weight of WAT

Okuno A et al. JCI, 1998

# Depot specific effects of PPARγ activation on preadipocyte differentiation




Adams M et al. J Clin Invest, 1997

# Contents

- Introduction of TZD – what do we know?
- What should we do?
  - TZD and weight gain
  - TZD and HF
  - TZD and bone
  - TZD and cancer
  - TZD and dementia
  - Effects of TZD on NAFLD

# Increased risk of HF in DREAM trial

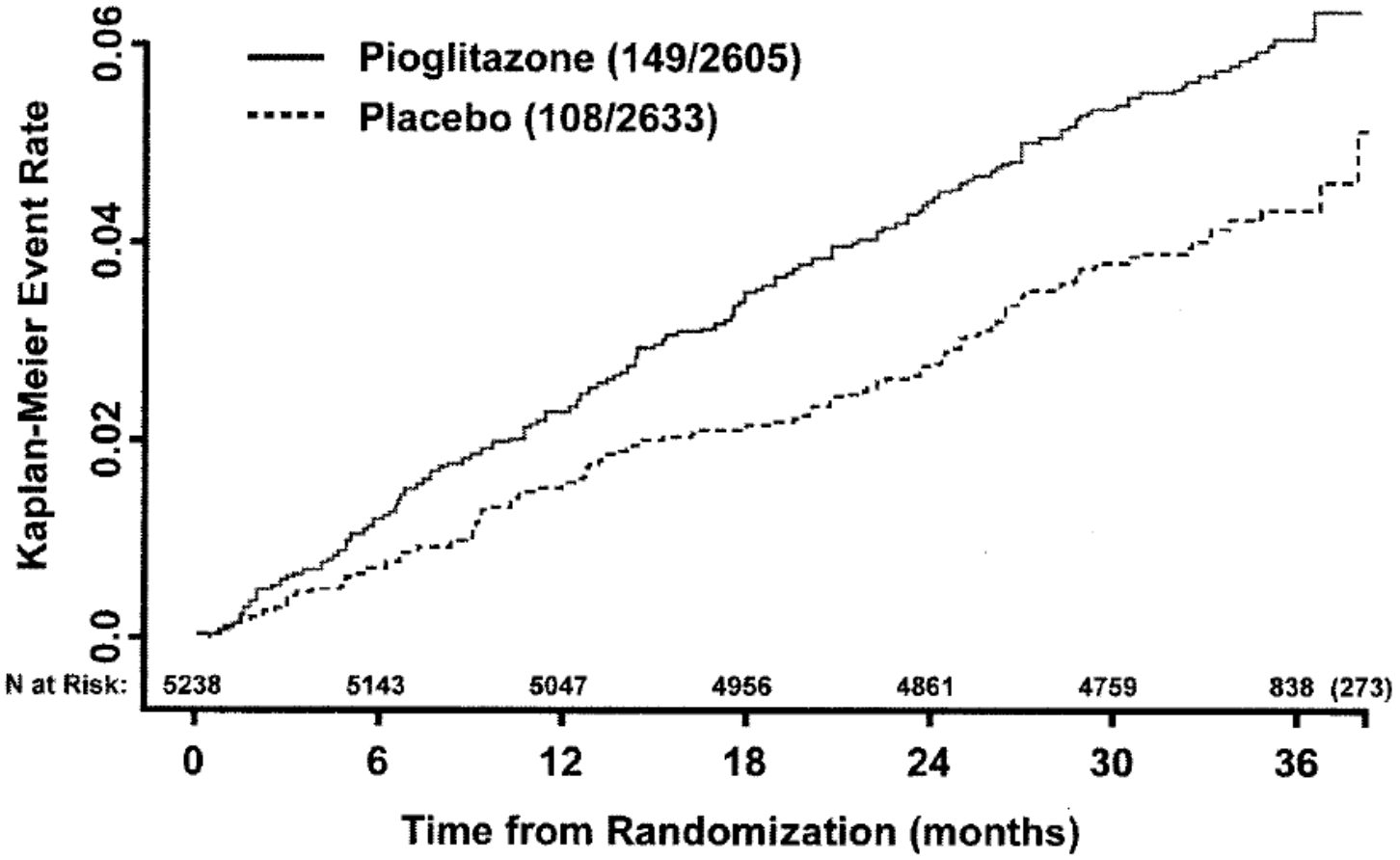
Table 2—*Cardiovascular component of the cardiorenal composite*

| Event | Ramipril | Placebo | HR (95% CI) | Rosiglitazone | Placebo | HR (95% CI) |
|---|---|---|---|---|---|---|
| Cardiovascular composite | 69 (2.6) | 64 (2.4) | 1.09 (0.78–1.53)* | 77 (2.9) | 56 (2.1) | 1.38 (0.98–1.95)† |
| Cardiovascular death | 12 (0.5) | 10 (0.4) | 1.21 (0.52–2.80) | 12 (0.5) | 10 (0.4) | 1.20 (0.52–2.77) |
| MI | 14 (0.5) | 11 (0.4) | 1.29 (0.59–2.84) | 16 (0.6) | 9 (0.3) | 1.78 (0.79–4.03) |
| Stroke | 4 (0.2) | 8 (0.3) | 0.50 (0.15–1.66) | 7 (0.3) | 5 (0.2) | 1.40 (0.44–4.40) |
| Congestive heart failure | 12 (0.5) | 4 (0.2) | 3.06 (0.99–9.48) | 14 (0.5) | 2 (0.1) | 7.04 (1.60–31.0) |
| Revascularization | 28 (1.1) | 38 (1.4) | 0.74 (0.46–1.21) | 37 (1.4) | 29 (1.1) | 1.27 (0.78–2.07) |
| New angina | 24 (0.9) | 20 (0.8) | 1.21 (0.67–2.19) | 24 (0.9) | 20 (0.8) | 1.20 (0.66–2.17) |
| Cardiovascular death, MI, or stroke | 27 (1.0) | 29 (1.1) | 0.94 (0.56–1.59)* | 33 (1.3) | 23 (0.9) | 1.43 (0.84–2.44)* |
| Total mortality | 31 (1.2) | 32 (1.2) | 0.98 (0.60–1.61)* | 30 (1.1) | 33 (1.3) | 0.91 (0.56–1.49)* |

Data are *n* (%) unless otherwise indicated. Revascularization = interventions on either coronary or peripheral arteries. The cardiovascular composite outcome represents the first occurrence of cardiovascular death, MI, or stroke. For the other individual events, all participants with an event are included in each row. *$P >$ 0.1; †$P = 0.067$

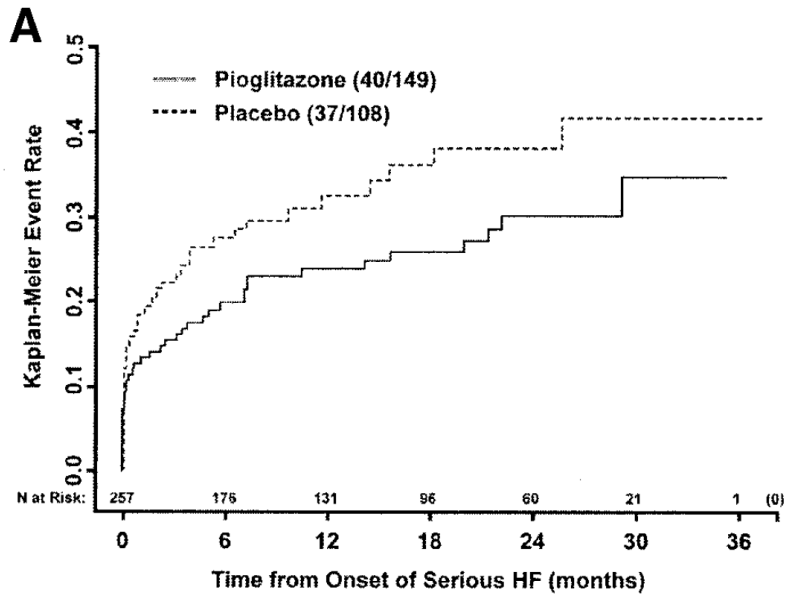
DREAM Trial Investigators. NEJM, 2008

# Increased risk of serious heart failure in PIO user – PROactive

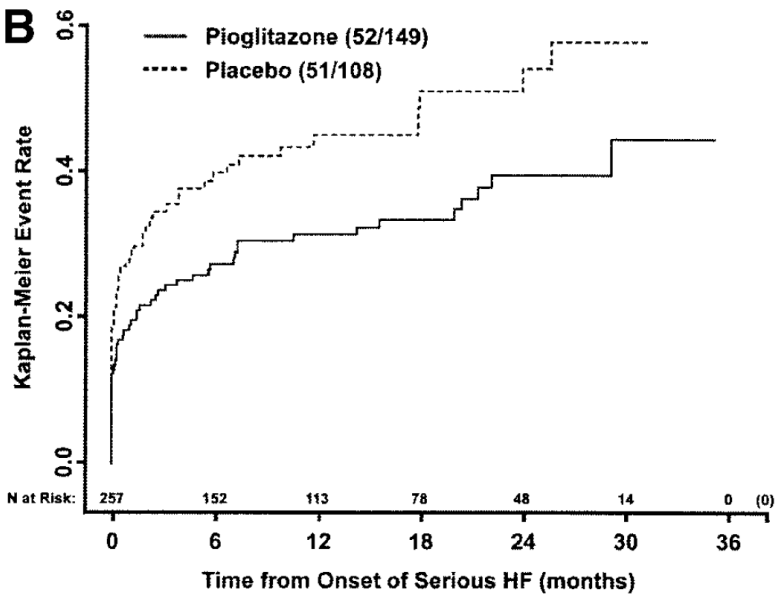



Erdmann E et al. Diabetes Care, 2007

# Mortality not increased in patients with serious heart failure




All-cause mortality




Composite end-point of all-cause mortality, nonfatal MI, stroke

Erdmann E et al. Diabetes Care, 2007

# Differences of the effects on HF according to drug

In 227,571 Medicare beneficiaries (>65 yrs)

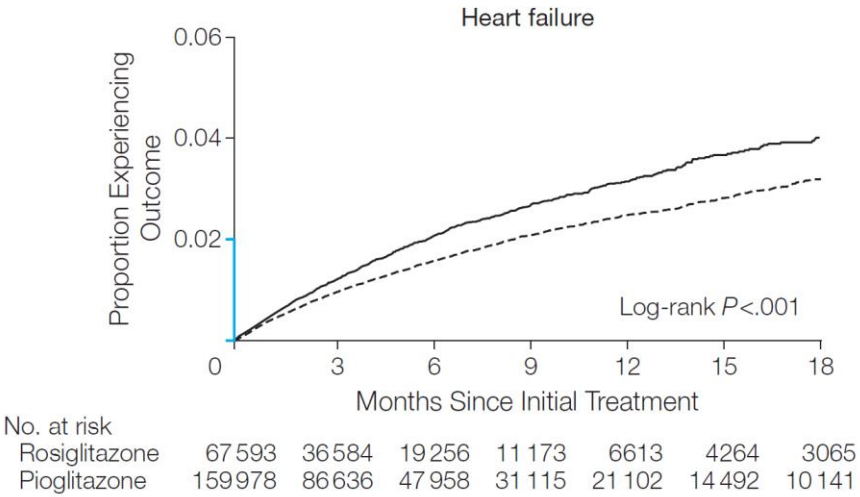



**Table 4.** Incidence Rates, Attributable Risks (Rate Differences), and Numbers Needed to Harm for AMI, Stroke, Heart Failure, All-Cause Mortality, and a Composite Individual End Point in Elderly Medicare Patients Treated With Rosiglitazone vs Pioglitazone

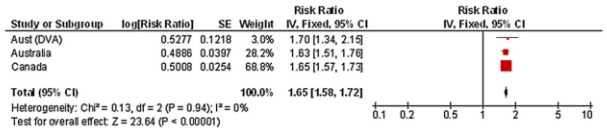
| End Point | Events, No. | | Incidence Rate per 100 Person-Years | | Attributable Risk (95% CI) per 100 Person-Years | No. Needed to Harm (95% CI), Person-Years | HR (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| | Rosiglitazone | Pioglitazone | Rosiglitazone | Pioglitazone | | | Unadjusted | Adjusted[a] |
| AMI | 523 | 1223 | 1.83 | 1.68 | 0.15 (–0.03 to 0.33) | NA[b] | 1.07 (0.97-1.19) | 1.06 (0.96-1.18) |
| Stroke | 363 | 689 | 1.27 | 0.95 | 0.32 (0.17-0.47) | 313 (213-588) | 1.31 (1.15-1.49) | 1.27 (1.12-1.45) |
| Heart failure | 1125 | 2182 | 3.94 | 3.00 | 0.94 (0.68-1.20) | 106 (83-147) | 1.27 (1.18-1.37) | 1.25 (1.16-1.34) |
| All-cause mortality | 814 | 1748 | 2.85 | 2.40 | 0.45 (0.22-0.67) | 222 (149-455) | 1.17 (1.07-1.27) | 1.14 (1.05-1.24)[c] |
| AMI, stroke, heart failure, or all-cause mortality | 2593 | 5386 | 9.10 | 7.42 | 1.68 (1.27-2.08) | 60 (48-79) | 1.20 (1.14-1.26) | 1.18 (1.12-1.23)[c] |

Graham DJ et al. JAMA, 2010

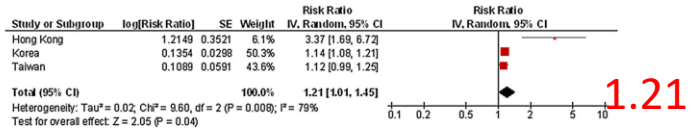
# Variation in association between TZD and heart failure across ethnic groups: Retrospective analysis of large healthcare claims databases in 6 countries

Asian PharmacoEpidemiology Network (AsPEN)

**Incident rosiglitazone and incident furosemide: Australian and Canadian populations**

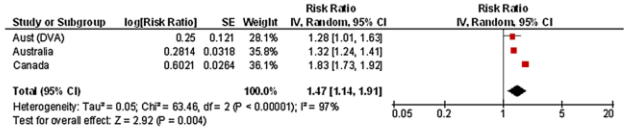



**Incident rosiglitazone and incident furosemide: Asian populations**

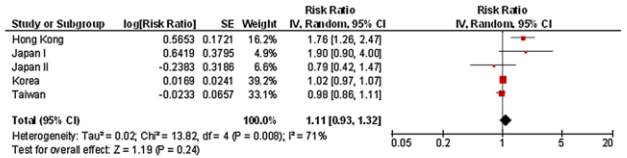



1.21

**Incident pioglitazone and incident furosemide: Australian and Canadian populations**




**Incident pioglitazone and incident furosemide: Asian populations**

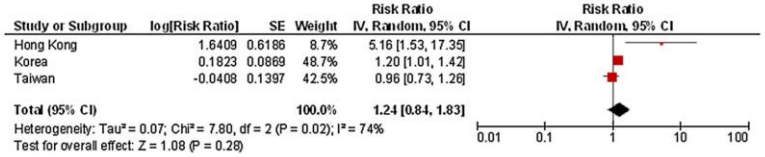



Furosemide dispensing

**Rosiglitazone and heart failure hospitalisation: Australia (Canadian data unavailable)**

Risk ratio, 95% CI
1.25; [0.76, 2.05}

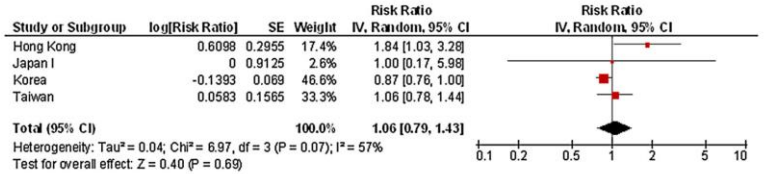
**Rosiglitazone and heart failure hospitalisation: Asian countries**




**Pioglitazone and heart failure hospitalisation: Australia (Canadian data unavailable)**

Risk ratio, 95% CI
1.88; [1.01, 3.5}

**Pioglitazone and heart failure hospitalisation: Asian countries**

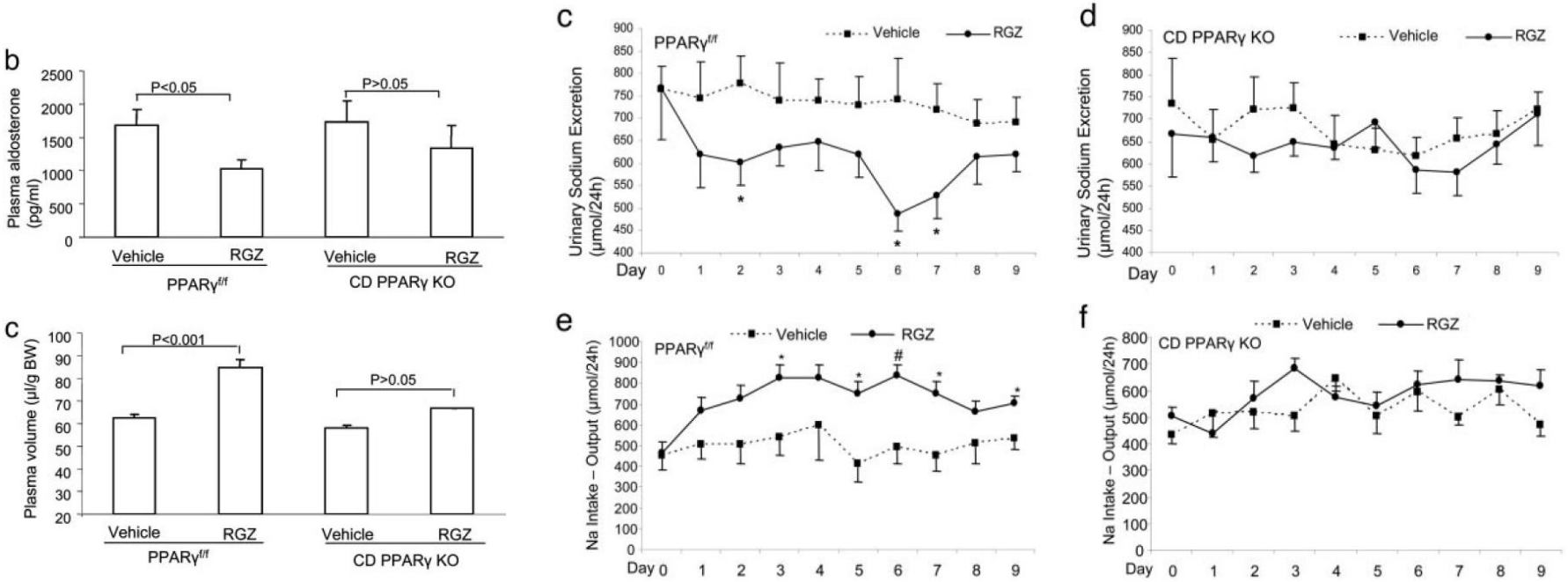



Hospitalization for HF

Roughead EF et al. Drug Saf, 2015

# CD-specific deletion of PPARγ blocks TZD-induced fluid retention

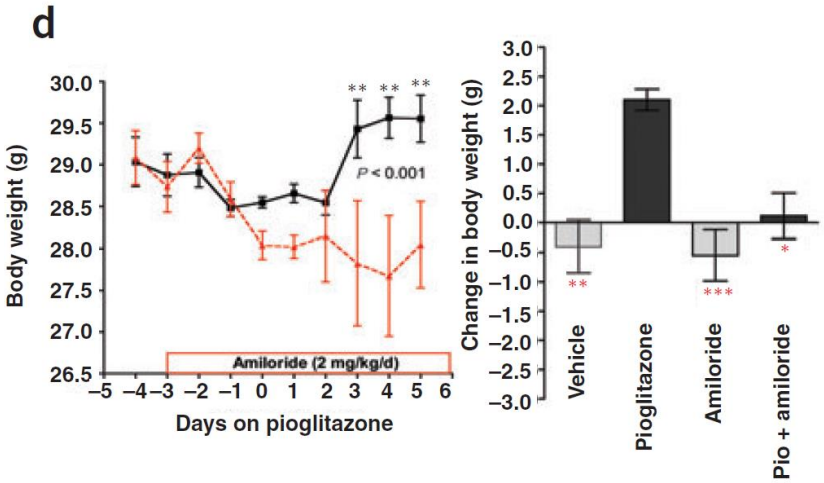
In collecting duct-specific deletion of PPARγ



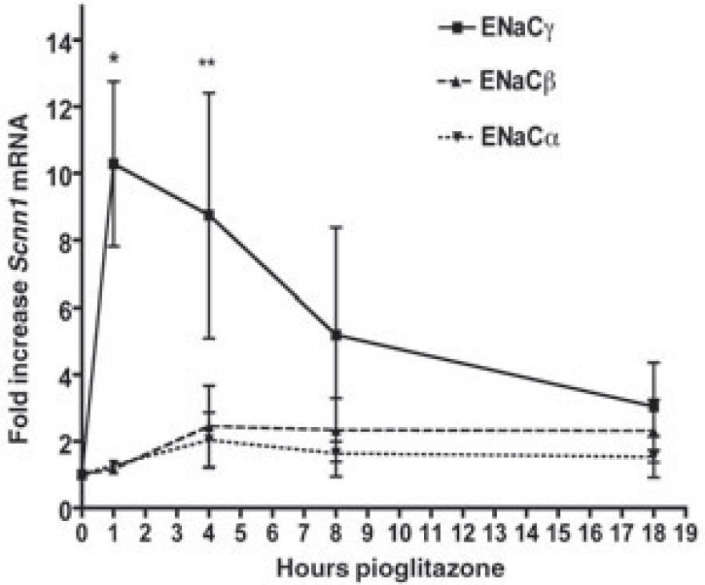

Zhang H et al. PNAS, 2005

# TZD expand body fluid volume through PPARγ stimulation of ENaC-mediated renal salt absorption

Amiloride blocked weight gain produced by PIO




PIO stimulates Scnn1 (ENaCγ) expression in mouse inner medullary collection duct




Guan YF et al. Nat Med, 2005

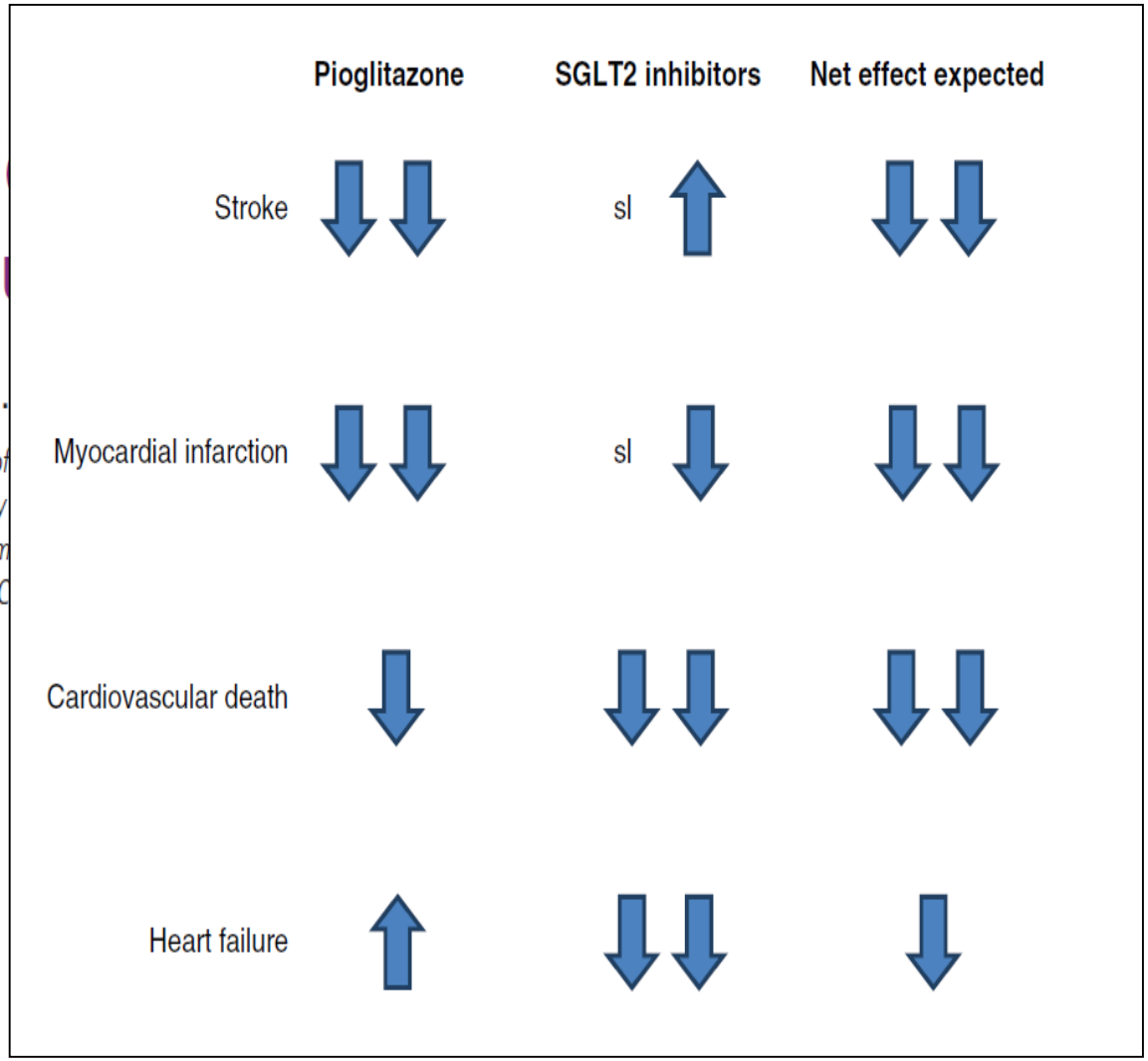
perspective

*Diabetes, Obesity and Metabolism* 18: 454–462, 2016.


# Revitalizati be combined with a sodi

R. A. DeFronzo[1], R.

[1] *Diabetes Division, University of*
[2] *Cardiology Division, University*
[3] *Diabetes Division and Departm*
[4] *Diabetes and Endocrine Unit, C*



# Recommendation

- Start from as low dose as possible
- Combine diuretics if edema feels intolerable to the patient
- Inform the patient about the mechanism of drug and side effect
- Consider anti-diabetic drug that is known to reduce weight
- Do not prescribe TZD in patients with NYHA III/IV

# Contents

- Introduction of TZD – what do we know?
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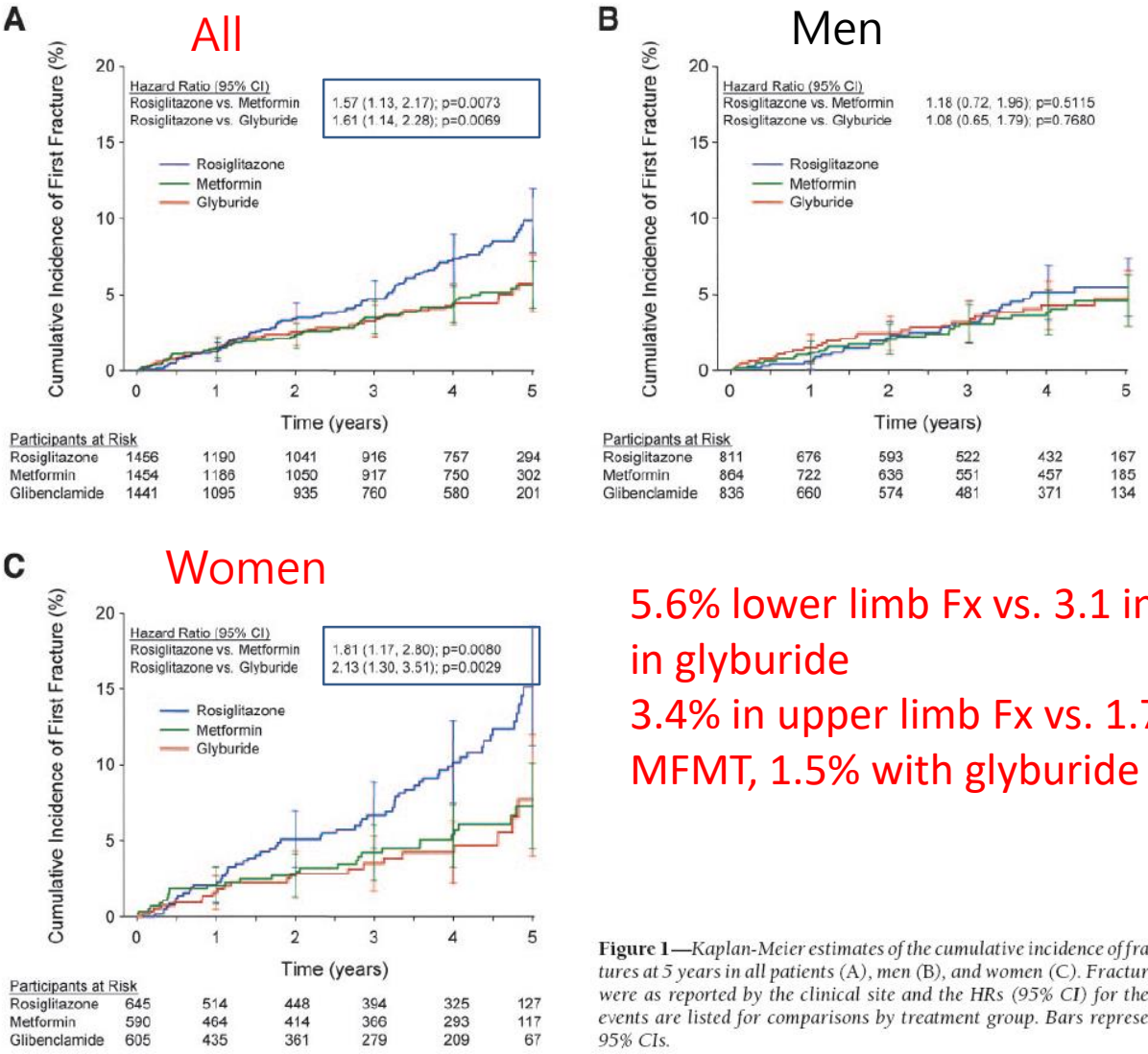
  - TZD and bone
  - TZD and cancer
  - TZD and dementia
  - Effects of TZD on NAFLD

# Rosiglitazone-associated fracture in type 2 diabetes – Analysis from ADOPT




5.6% lower limb Fx vs. 3.1 in MFMT, 1.3 in glyburide

3.4% in upper limb Fx vs. 1.7% with MFMT, 1.5% with glyburide

**Figure 1**—*Kaplan-Meier estimates of the cumulative incidence of fractures at 5 years in all patients (A), men (B), and women (C). Fractures were as reported by the clinical site and the HRs (95% CI) for these events are listed for comparisons by treatment group. Bars represent 95% CIs.*

Kahn SE et al., Diabetes Care 31:845-851, 2008

# TZD and bone loss in older diabetic adults

In 666 diabetic participants (70-79 yrs)

Additional annualized percent change in BMD per year of TZD use

| Model | WOMEN | | | MEN | | |
|---|---|---|---|---|---|---|
| | Estimate (% change) | (95% CI) | p-value | Estimate (% change) | (95% CI) | p-value |
| Whole Body | | | | | | |
| Adjusted for age, race | -0.67 | (-1.03, -0.30) | <0.001 | 0.00 | (-0.32, 0.31) | 0.987 |
| Multivariable[a] | -0.61 | (-1.02,-0.21) | 0.003 | 0.04 | (-0.30,0.39) | 0.810 |
| Lumbar Spine[b] | | | | | | |
| Adjusted for age, race | -1.14 | (-1.90,-0.37) | 0.004 | -0.19 | (-0.96,0.58) | 0.627 |
| Multivariable[a] | -1.23 | (-2.06,-0.40) | 0.004 | -0.25 | (-1.10,0.60) | 0.567 |
| Femoral Neck | | | | | | |
| Adjusted for age, race | -0.26 | (-0.86,0.34) | 0.391 | 0.09 | (-0.39, 0.56) | 0.713 |
| Multivariable[a] | -0.32 | (-0.94, 0.29) | 0.303 | -0.05 | (-0.54, 0.44) | 0.843 |
| Trochanter | | | | | | |
| Adjusted for age, race | -0.50 | (-1.02, 0.03) | 0.063 | -0.17 | (-0.57, 0.23) | 0.414 |
| Multivariable[a] | -0.65 | (-1.18, -0.12) | 0.016 | -0.32 | (-0.72, 0.09) | 0.124 |

[a] Age, race, baseline BMD, baseline weight, weight change, average A1C, insulin, metformin, sulfonylureas, other hypoglycemic medications, diabetes duration, GFR, vitamin D supplements, calcium supplements, oral steroids, osteoporosis drugs (bisphophonates, calcitonin, raloxifene), thiazide diuretics, statins and oral estrogen (women only).

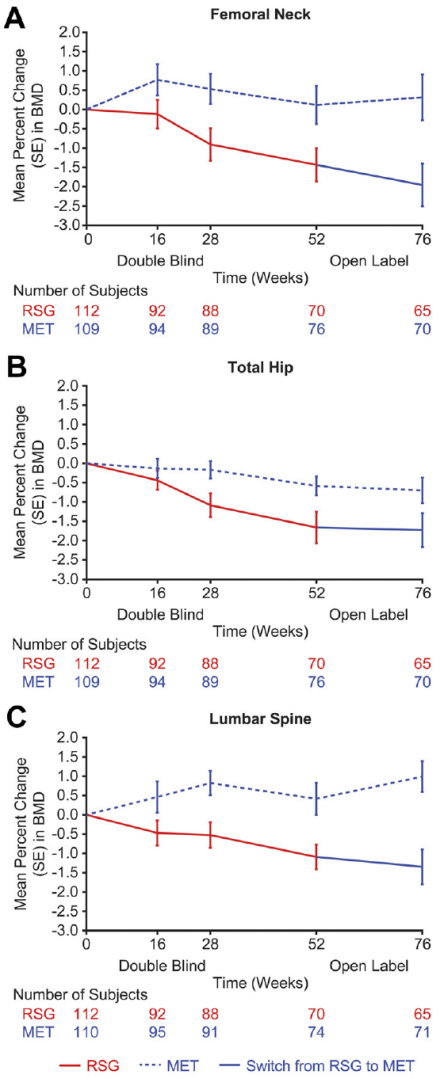
[b] Obtained from lumbar spine subregion of whole body DXA scans

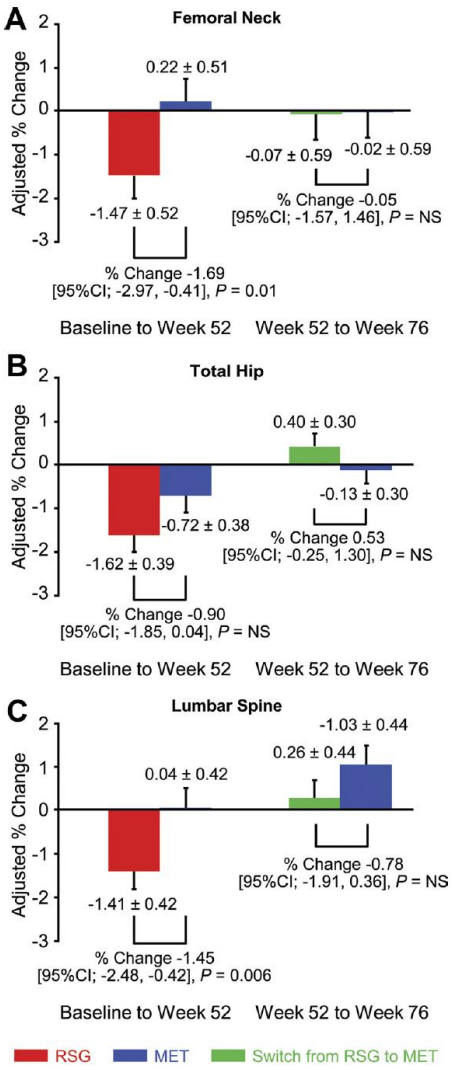
Whole body, L-spine, Trochanter BMD decreased in participants in Health, Aging, Body Composition study

Schwartz AV et al. JCEM, 2006

# Decreased BMD in RSG users – 1 yrs F/U

In 225 postmenopausal women with T2DM




Bilezikian JP et al. JCEM, 2013

# Effects of TZD on fracture-Meta-analysis

In 24,554 participants in 22 RCTs

**Table 2**
Subgroup analysis of odds ratio of fracture with TZD use.

| Study group | N | Sample size(events) | Heterogeneity | | Pooled results | | Test for interaction |
|---|---|---|---|---|---|---|---|
| | | | $P_h$ | $I^2$(%) | OR(95%CI) | $P$ | $P_i$ |
| Overall result | 22 | 24,544(896) | 0.32 | 10 | 1.41(1.23, 1.62) | <0.001 | |
| Gender | | | | | | | |
| Women | 13 | 8979(476) | 0.69 | 0 | 1.94(1.60, 2.35) | <0.001 | <0.001 |
| Men | 10 | 11,782(349) | 0.67 | 0 | 1.02(0.83, 1.27) | 0.83 | |
| Drug | | | | | | | |
| >24 months | 4 | 9450(295) | 0.53 | 0 | 1.08(0.85, 1.36) | 0.53 | |
| Age | | | | | | | |
| Women | | | | | | | |
| <60 years | 8 | 6088(349) | 0.66 | 0 | 1.89(1.51, 2.36) | <0.001 | 0.69 |
| ≥60 years | 5 | 2891(127) | 0.38 | 4 | 2.07(1.42, 3.01) | <0.001 | |
| Men | | | | | | | |
| <60 years | 6 | 6667(231) | 0.78 | 0 | 1.16(0.89, 1.51) | 0.27 | 0.12 |
| ≥60 years | 4 | 5115(118) | 0.65 | 0 | 0.81(0.56, 1.17) | 0.26 | |

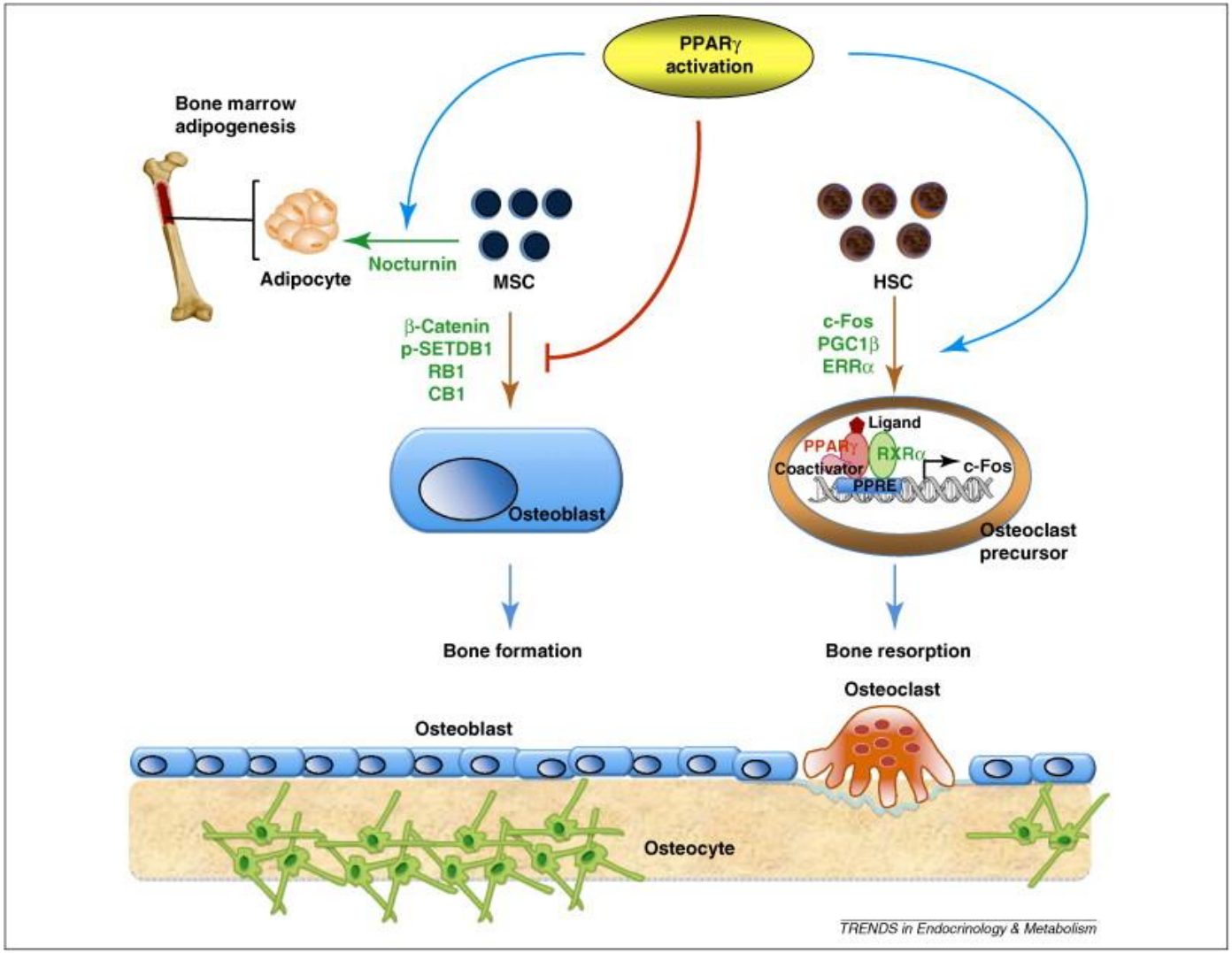
N: number of included studies, $P_h$: $P$ values for heterogeneity of Q test, $Pi$: $P$ values for interaction of Chi$^2$ test.

Women, Treated longer than 2 yrs, >60yrs,

Pio < Rosi

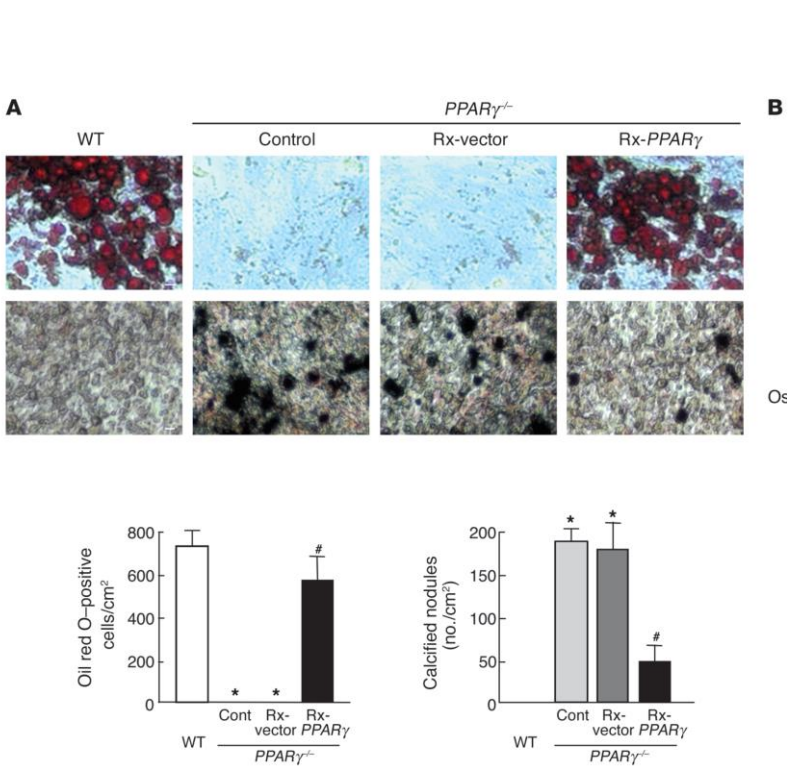
Zhu ZN et al. Bone, 2014

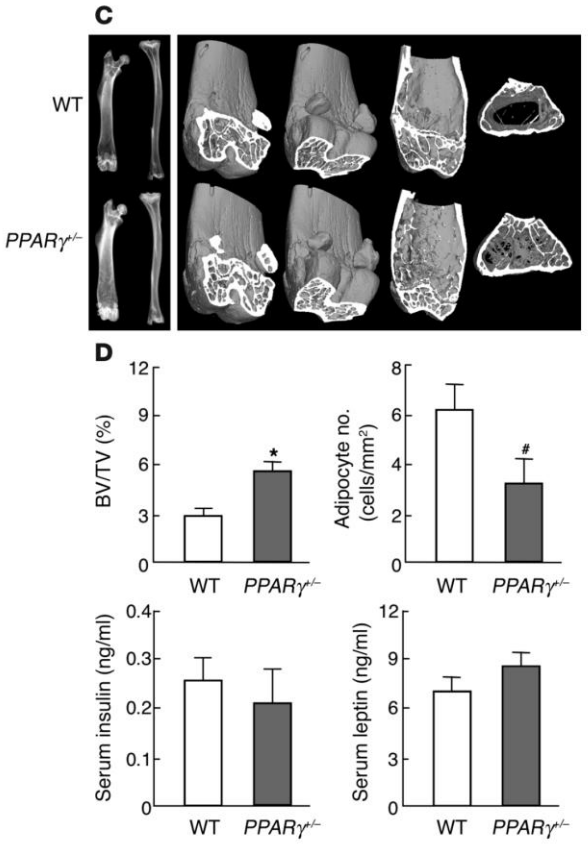
# PPARγ is a crucial cellular and metabolic switch




Wan Y. Trends Endocrinol Metab, 2010

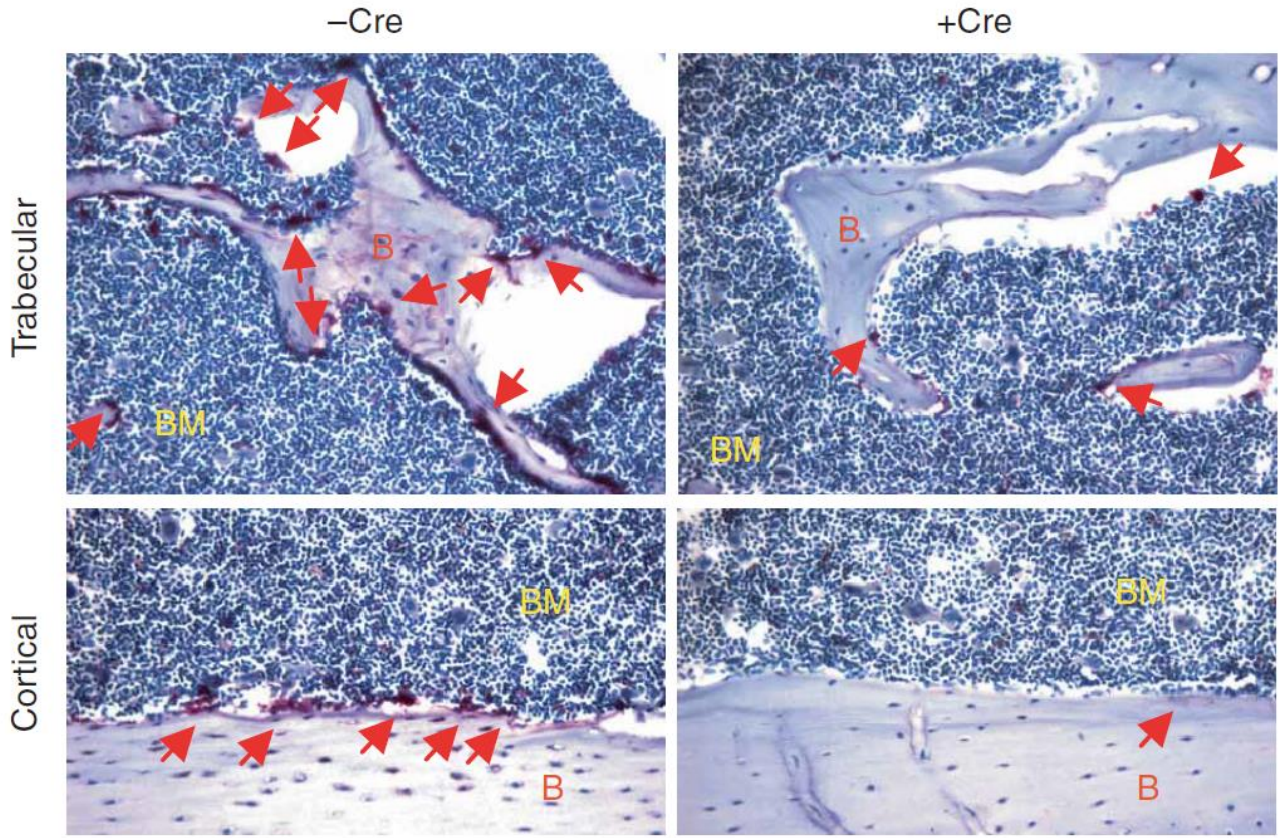
# PPARγ insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors



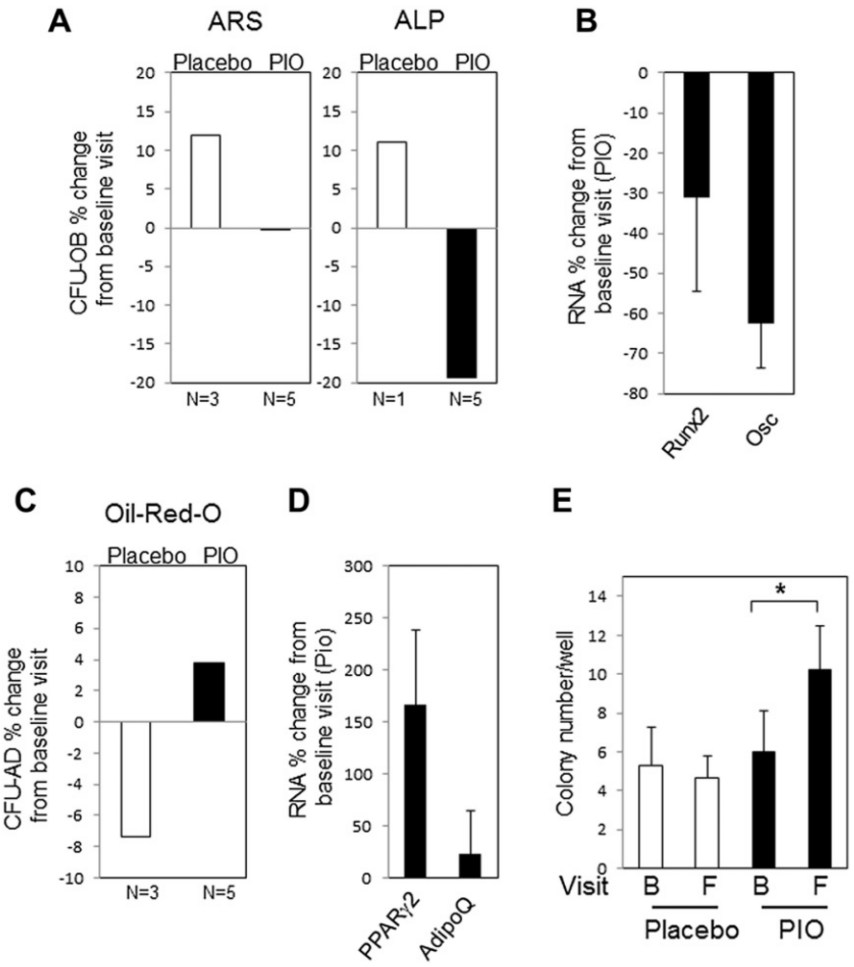

Akune T et al. JCI, 2004

# PPARγ regulates osteoclastogenesis in mice



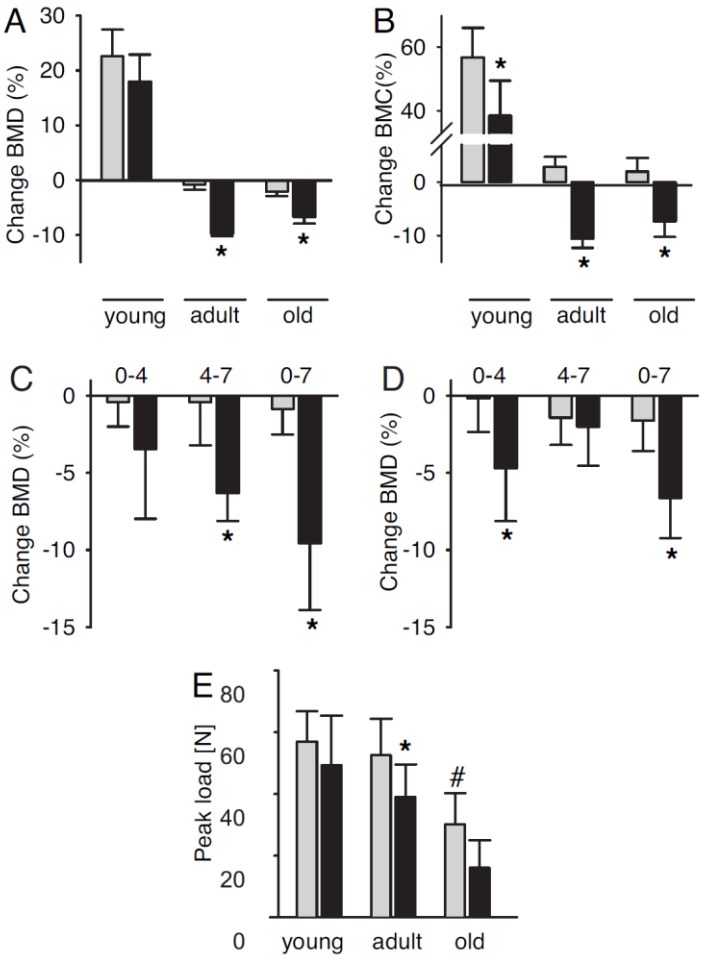

Wan Y et al. Nat Med, 2007

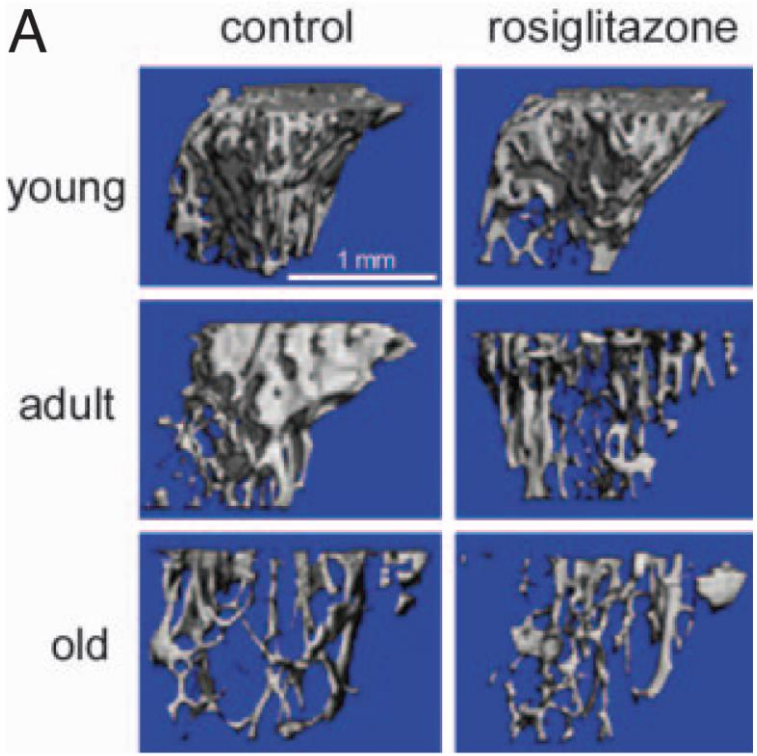
# TZD treatment on human BMC differentiation in vivo in T2DM patients




Beck GR et al. Transl Res, 2013

# The effect of TZD on bone resembles aged bone




Oxana P et al. Endocrinology, 2007

# Factors identifying people who should be assessed for osteoporosis before starting PIO Tx

| Major risk factors | Minor risk factors |
|---|---|
| Vertebral compression fracture | Rheumatoid arthritis |
| Fragility fracture after age 40 | Past history of clinical Hyperthyroidism |
| Family history of osteoporosis fracture (especially maternal hip fracture) | Long-term anticonvulsant therapy |
| Systemic glucocorticoid therapy of > 3 months' duration | Low dietary calcium intake |
| Malabsorption syndrome | Smoker |
| Primary hyperparathyroidism | Excessive alcohol intake |
| Propensity to fall | Excessive caffeine intake |
| Osteopenia apparent on X-ray film | Weight < 57 kg |
| Hypogonadism | Chronic heparin therapy |
| Early menopause (before age 45) | |

Consoli A et al. DOM, 2013

# Contents

- Introduction of TZD – what do we know?
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  - TZD and cancer
  - TZD and dementia
  - Effects of TZD on NAFLD

# Increased bladder cancer with PIO exposure

In 1,491,060 (155,535 PIO exposurer)

**Table 2** Risk of bladder cancer with pioglitazone exposure: French cohort of diabetic patients aged 40–79 years (followed between 2006 and 2009)

| Characteristic | Overall study population | | | Men | | | Women | | |
|---|---|---|---|---|---|---|---|---|---|
| | (*N*=1,491,060; 2,016 cases) | | | (*n*=796,586; 1,790 cases) | | | (*n*=694,474; 226 cases) | | |
| | HR[a] | (95% CI) | *p* value | HR[a] | (95% CI) | *p* value | HR[a] | (95% CI) | *p* value |
| Sex, reference women | | | | | | | | | |
| Men | 7.65 | (6.66, 8.79) | <0.01 | | N/A | | | N/A | |
| Age | | | | | | | | | |
| 45 | | | | | | | | | 32 |
| 50 | | | | | | | | | 32 |
| 55–59 | 7.89 | (2.93, 21.28) | <0.01 | 9.65 | (3.08, 30.25) | <0.01 | 2.30 | (0.29, 18.11) | 0.43 |
| 60–64 | 15.34 | (5.72, 41.13) | <0.01 | 18.82 | (6.04, 58.67) | <0.01 | 4.31 | (0.57, 32.37) | 0.16 |
| 65–69 | 20.61 | (7.70, 55.19) | <0.01 | 24.57 | (7.89, 76.50) | <0.01 | 8.69 | (1.19, 63.35) | 0.03 |
| 70–74 | 30.37 | (11.36, 81.17) | <0.01 | 35.54 | (11.43, 110.49) | <0.01 | 14.74 | (2.05, 105.93) | 0.01 |
| 75–79 | 35.08 | (13.12, 93.80) | <0.01 | 41.32 | (13.28, 128.53) | <0.01 | 16.02 | (2.23, 115.14) | 0.01 |
| Exposure to glucose-lowering drugs[b] | | | | | | | | | |
| Pioglitazone | 1.22 | (1.05, 1.43) | 0.01 | 1.28 | (1.09, 1.51) | <0.01 | 0.78 | (0.44, 1.37) | 0.39 |
| Rosiglitazone | 1.08 | (0.92, 1.26) | 0.35 | 1.10 | (0.93, 1.30) | 0.25 | 0.89 | (0.53, 1.49) | 0.66 |
| Metformin | 1.03 | (0.93, 1.13) | 0.60 | 1.03 | (0.93, 1.14) | 0.58 | 0.99 | (0.75, 1.31) | 0.96 |
| Sulfonylurea | 0.92 | (0.84, 1.01) | 0.08 | 0.91 | (0.83, 1.01) | 0.06 | 0.99 | (0.76, 1.30) | 0.95 |
| Other OHA | 1.00 | (0.90, 1.11) | 0.93 | 0.95 | (0.85, 1.07) | 0.40 | 1.36 | (1.02, 1.81) | 0.04 |
| Insulin | 1.08 | (0.97, 1.21) | 0.15 | 1.08 | (0.96, 1.21) | 0.20 | 1.10 | (0.81, 1.50) | 0.53 |

(adjusted HR 1.22 [95% CI 1.05, 1.43])

Neumann A et al. Diabetologia, 2012

Original Investigation

# Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes

*JAMA*. 2015;314(3):265-277.

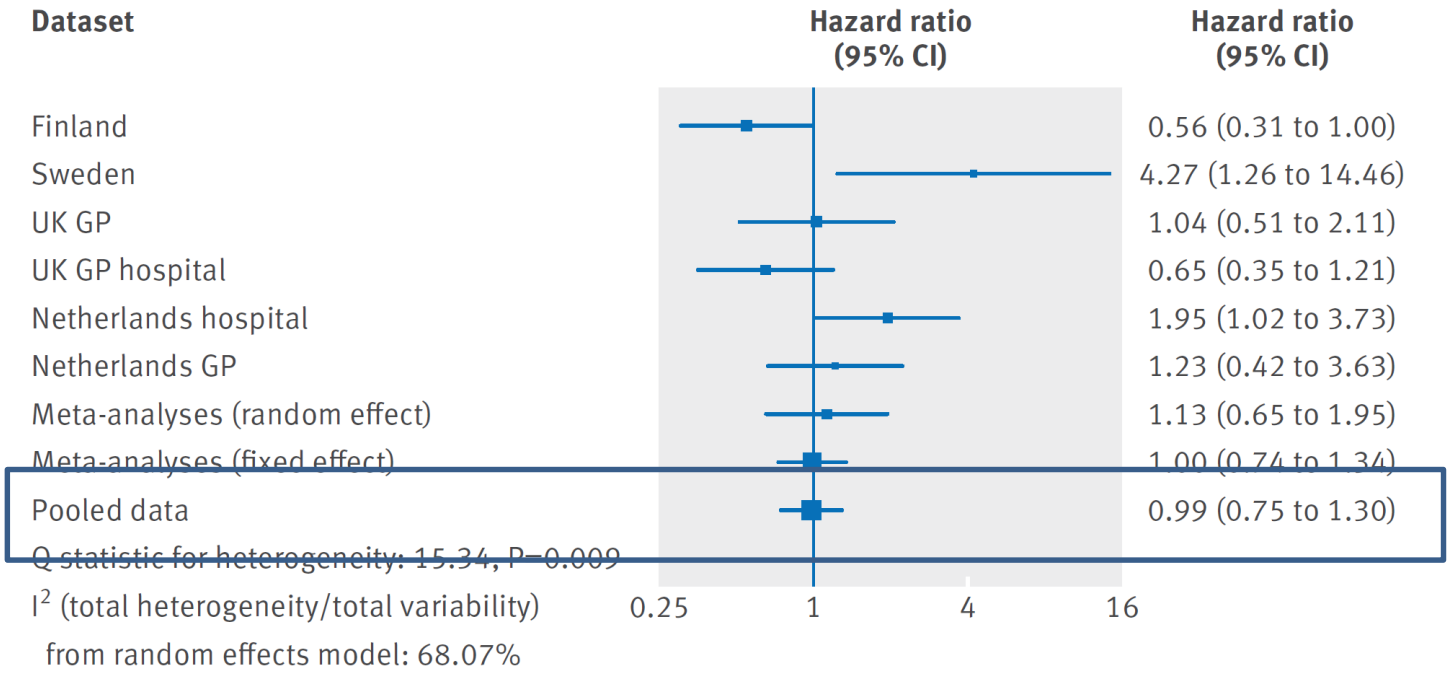
Table 4. Odds Ratios for the Association of Pioglitazone Treatment and Bladder Cancer in the Nested Case-Control Study (Kaiser Permanente Northern California Diabetes Registry)

| | Cases (n = 464) | Controls (n = 464) | Odds Ratio (95% CI) | |
|---|---|---|---|---|
| | | | Unadjusted | Adjusted[a] |
| Never use of pioglitazone | 373 | 383 | 1 [Reference] | 1 [Reference] |
| Ever exposed | 91 | 81 | 1.14 (0.79-1.65) | 1.18 (0.78-1.80) |
| Time since starting pioglitazone, y | | | | |
| <4.5 | 46 | 36 | 1.36 (0.84-2.21) | 1.42 (0.80-2.52) |
| 4.5-8.0 | 32 | 26 | 1.33 (0.75-2.36) | 1.20 (0.62-2.32) |
| >8.0 | 13 | 19 | 0.65 (0.29-1.43) | 0.70 (0.27-1.78) |
| Duration of therapy, y | | | | |
| <1.5 | 25 | 24 | 1.10 (0.62-1.96) | 1.16 (0.59-2.25) |
| 1.5-4.0 | 39 | 27 | 1.55 (0.90-2.67) | 1.78 (0.93-3.40) |
| >4.0 | 27 | 30 | 0.94 (0.54-1.64) | 0.81 (0.42-1.55) |
| Cumulative dose, mg | | | | |
| 1-14 000 | 31 | 27 | 1.19 (0.70-2.03) | 1.26 (0.69-2.33) |
| 14 001-40 000 | 33 | 27 | 1.27 (0.75-2.15) | 1.27 (0.68-2.36) |
| >40 000 | 27 | 27 | 1.06 (0.59-1.88) | 0.98 (0.50-1.93) |

[a] Adjusted for other diabetes medications, race, smoking history, high-risk occupations, urinary tract infections, and hemoglobin $A_{1c}$ concentration.

# Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries

In 56,337 patients with T2DM in Healthcare database from 4 european countries




Korhonen P et al. BMJ, 2016

# Pioglitazone and bladder cancer – Taiwan study

In 54,928 patients with T2DM

Table 1—*Incidences and HRs for bladder cancer associated with pioglitazone use*

| Pioglitazone use | Bladder cancer (*n*) | Incidence rate (95% CI) per 100,000 person-years | Age- and sex-adjusted HR (95% CI) | *P* | HR adjusted for previously identified risk factors (95% CI)* | *P* | Fully adjusted HR (95% CI)** | *P* |
|---|---|---|---|---|---|---|---|---|
| Never users | 155 | 78.93 (66.99–92.38) | | | | | | |
| Ever users | 10 | 104.47 (50.10–192.13) | 1.261 (0.665–2.392) | 0.4773 | 1.148 (0.601–2.192) | 0.6767 | 1.305 (0.661–2.576) | 0.4424 |
| Time since starting pioglitazone (months) | | | | | | | | |
| <18 vs. never users | 4 | 111.98 (30.51–286.71) | 1.388 (0.514–3.746) | 0.5179 | 1.251 (0.461–3.395) | 0.6603 | 1.375 (0.494–3.829) | 0.5425 |
| 18–36 vs. never users | 5 | 121.33 (39.40–283.15) | 1.443 (0.592–3.516) | 0.4202 | 1.319 (0.538–3.230) | 0.5453 | 1.538 (0.616–3.839) | 0.3560 |
| >36 vs. never users | 1 | 53.23 (1.35–296.56) | 0.633 (0.089–4.521) | 0.6482 | 0.579 (0.081–4.148) | 0.5861 | 0.653 (0.090–4.766) | 0.6747 |
| $P_{trend}$ | | | | 0.6811 | | 0.8781 | | 0.6352 |
| Duration of therapy (months) | | | | | | | | |
| <12 vs. never users | 8 | 124.05 (53.56–244.43) | 1.525 (0.749–3.106) | 0.2445 | 1.360 (0.664–2.785) | 0.4010 | 1.540 (0.727–3.262) | 0.2591 |
| >12 vs. never users | 2 | 64.05 (7.76–231.36) | 0.745 (0.185–3.006) | 0.6792 | 0.706 (0.174–2.860) | 0.6254 | 0.816 (0.199–3.347) | 0.7773 |
| $P_{trend}$ | | | | 0.7512 | | 0.9348 | | 0.6919 |
| Cumulative dose (mg) | | | | | | | | |
| 1–10,500 vs. never users | 8 | 116.82 (50.43–230.18) | 1.429 (0.702–2.910) | 0.3250 | 1.281 (0.625–2.623) | 0.4987 | 1.450 (0.686–3.064) | 0.3306 |
| >10,500 vs. never users | 2 | 73.44 (8.89–265.28) | 0.858 (0.213–3.462) | 0.8296 | 0.809 (0.200–3.281) | 0.7672 | 0.935 (0.227–3.844) | 0.9256 |
| $P_{trend}$ | | | | 0.7705 | | 0.9562 | | 0.7125 |

Tseng CH et al. Diabetes Care, 2012

# Risk of bladder cancer among patients with T2DM treated with 15 mg pioglitazone dose in Korea

In 101953 control patients and 11240 PIO-treated patients

**Table 2.** Incidence rates of bladder cancer according to pioglitazone treatment

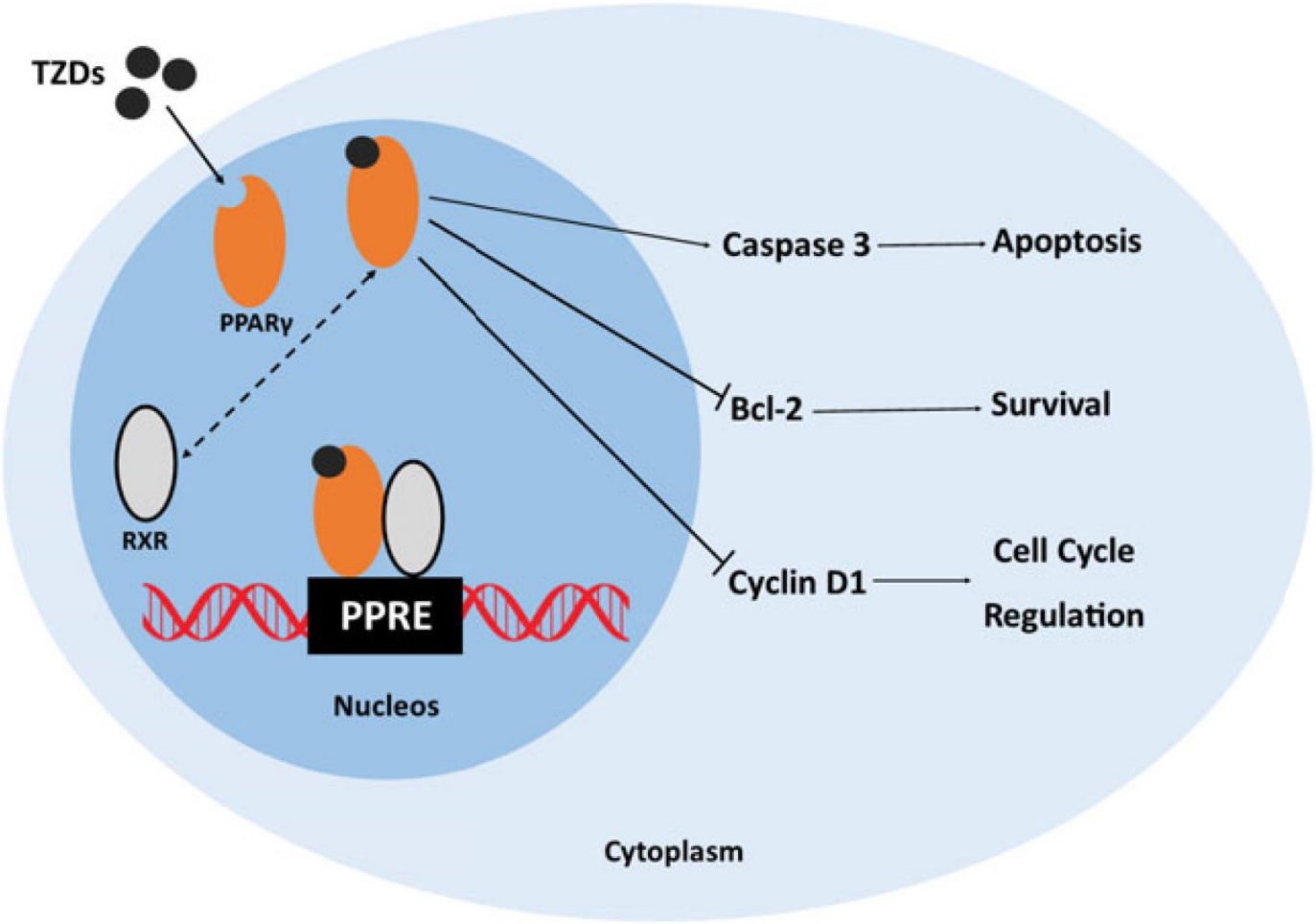
| Groups | Bladder cancer incidence rate (per 100,000 person-years) | HR (95% CI) adjusted for age and sex | |
|---|---|---|---|
| | | All study subjects (n = 113,193) | Subjects without congestive heart failure (n = 98,591) |
| Controls | 64.9 | Ref. | Ref. |
| Pioglitazone-treated | 54.9 | 1.135 (0.769-1.677) | 1.004 (0.654-1.542) |

**Table 4.** Pioglitazone use and the risk of bladder cancer among cases and matched controls

| | Controls (n = 620) | Bladder cancer (n = 208) | Crude risk ratio (95% confidence interval) | Adjusted risk ratio (95% confidence interval) |
|---|---|---|---|---|
| Never use of pioglitazone | 559 (83.4%) | 182 (87.5%) | 1 (reference) | 1 (reference) |
| Ever use of pioglitazone | 61 (9.8%) | 26 (12.5%) | 1.319 (0.800-2.175) | 1.353 (0.748-2.445) |
| Use of pioglitazone for > 6 months | 39 (6.5%) | 22 (10.8%) | 1.832 (1.033-3.248) | 1.969 (1.020-3.802) |

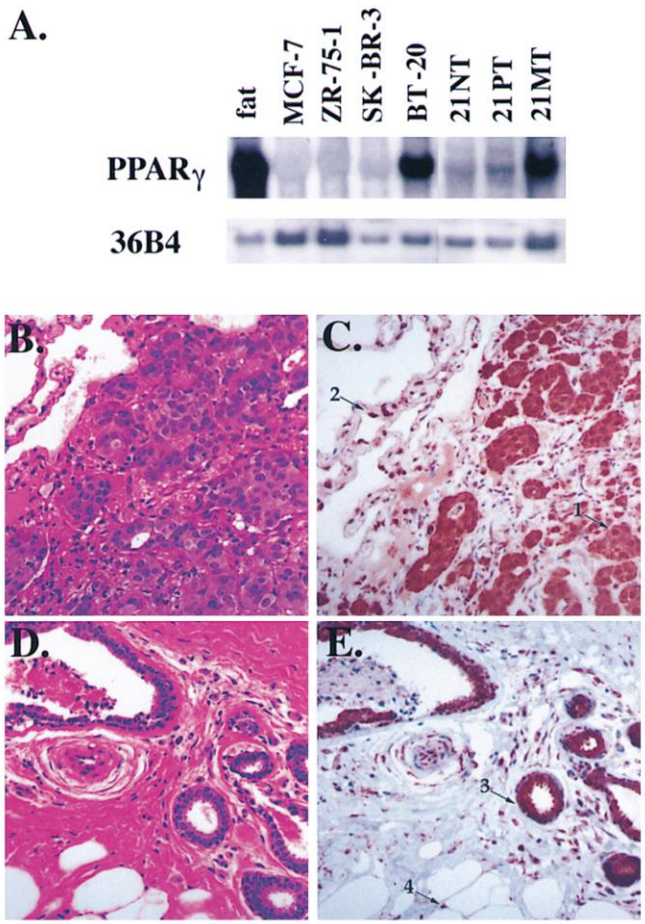
Jin SM et al. KJIM, 2014

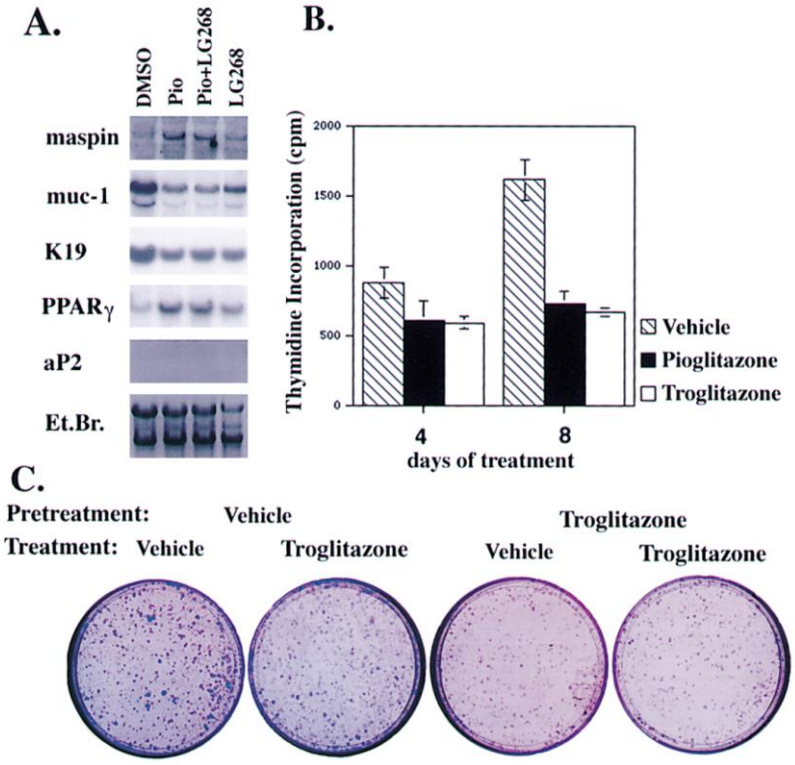
# Mechanism of anti-tumor effect of TZD




Shafiei-Irannejad et al.

# PPARγ expressed in human breast cancer cell lines and its activation decreases tumor growth




Mueller et al. Mol Cell, 1998

# Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies

M. Ferwana[1,2], B. Firwana[1,3,4], R. Hasan[1,3,4], M. H. Al-Mallah[1,5], S. Kim[4,6], V. M. Montori[4,7] and M. H. Murad[4,8]

[1]National and Gulf Center for Evidence Based Health Practice, King Saud bin Abdulaziz University for Health Sciences, [2]Family Medicine and Primary Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3]Department of Internal Medicine, University of Missouri, Columbia, MO, [4]Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, MN, USA, [5]King Abdul-Aziz Cardiac Center, Riyadh, Saudi Arabia, [6]Department of Urology, [7]Division of Diabetes and Endocrinology and [8]Division of Preventive Medicine, Mayo Clinic, Rochester, MN, USA

*Accepted 23 January 2013*

## Abstract

**Aims** Pioglitazone, a thiazolidinedione, was approved for treatment of Type 2 diabetes. However, several observational studies suggest an association of pioglitazone with an increased risk of bladder cancer in patients with diabetes. Therefore, we sought to perform a systematic review and meta-analysis to evaluate the magnitude of this association and the quality of the supporting evidence.

**Methods** Electronic databases were queried to identify controlled studies of pioglitazone that measured the risk of bladder cancer.

**Results** Six studies involving 2
44 months. The hazard of deve
ratio 1.23; 95% CI 1.09–1.39;
studies. Considering an incidence rate of 20.8 per 100 000 person years, the number needed to harm was five additional cases of bladder cancer per 100 000 person years.

**Number needed to harm =1/20,000**

**Conclusions** Patients treated with pioglitazone have a slight increased risk of bladder cancer compared to general population. Patient involvement and weighing treatment benefits versus risks should be discussed with patient toward shared decision. Patients with type 2 diabetes with risk factors, such as family history, smoking, or exposure to certain forms of chemotherapy may need to consider other anti-hyperglycemic agents. Also, pioglitazone should be discontinued in type 2 diabetes patients with newly diagnosed bladder cancer.

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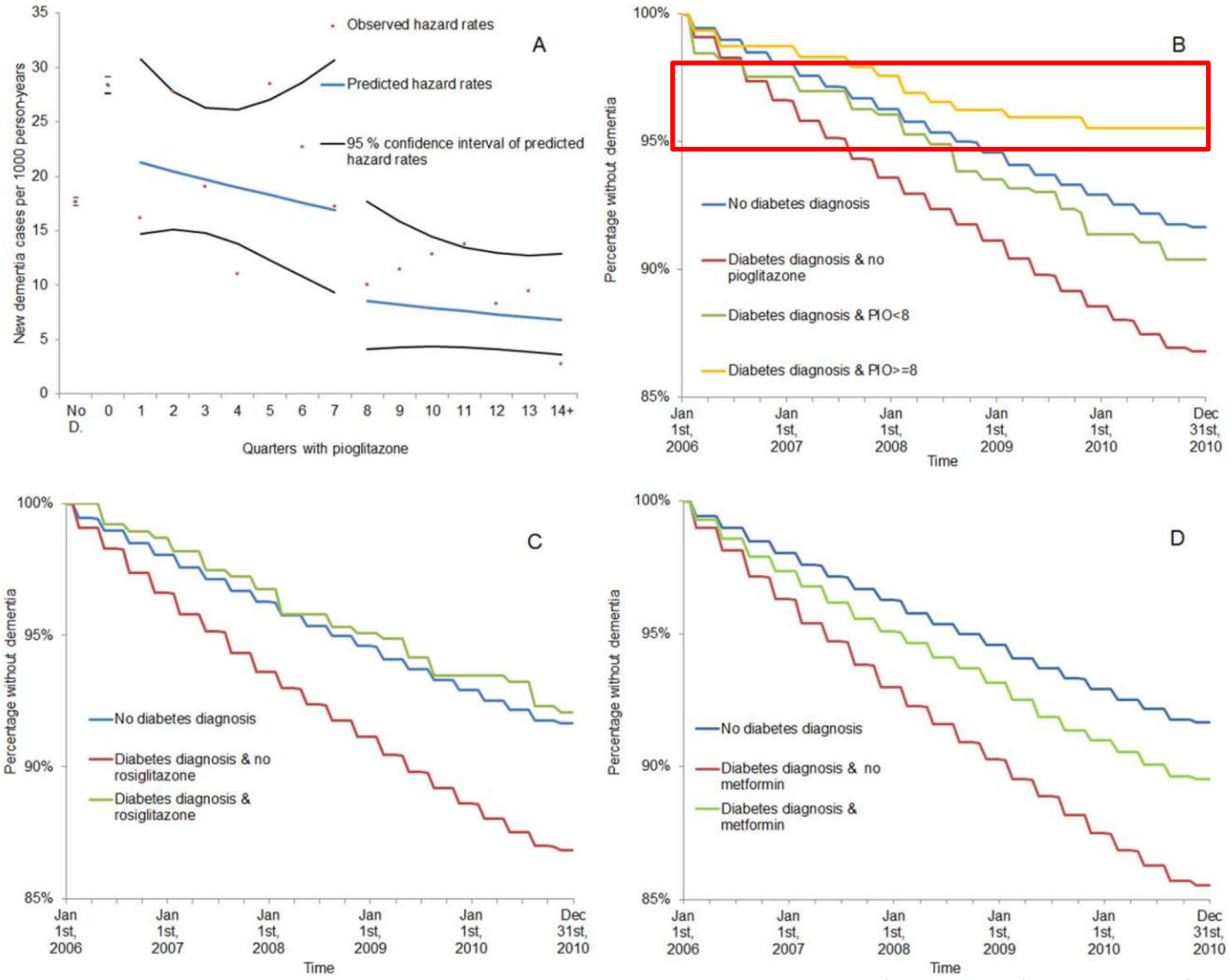
- Introduction of TZD – what do we know?
- What should we do?
  - TZD and weight gain
  - TZD and HF
  - TZD and bone
  - TZD and cancer
  - TZD and dementia
  - Effects of TZD on NAFLD

# Effect of PIO on the incidence of dementia

Observational data from 2004-2010 in 145,928 German subjects aged ≥60 years




Heneka MT et al. Ann Neurol, 2015

# Effects of TZD on mild cognitive dysfunction

Total of 9 studies comprising 1314 patients and 1311 controls

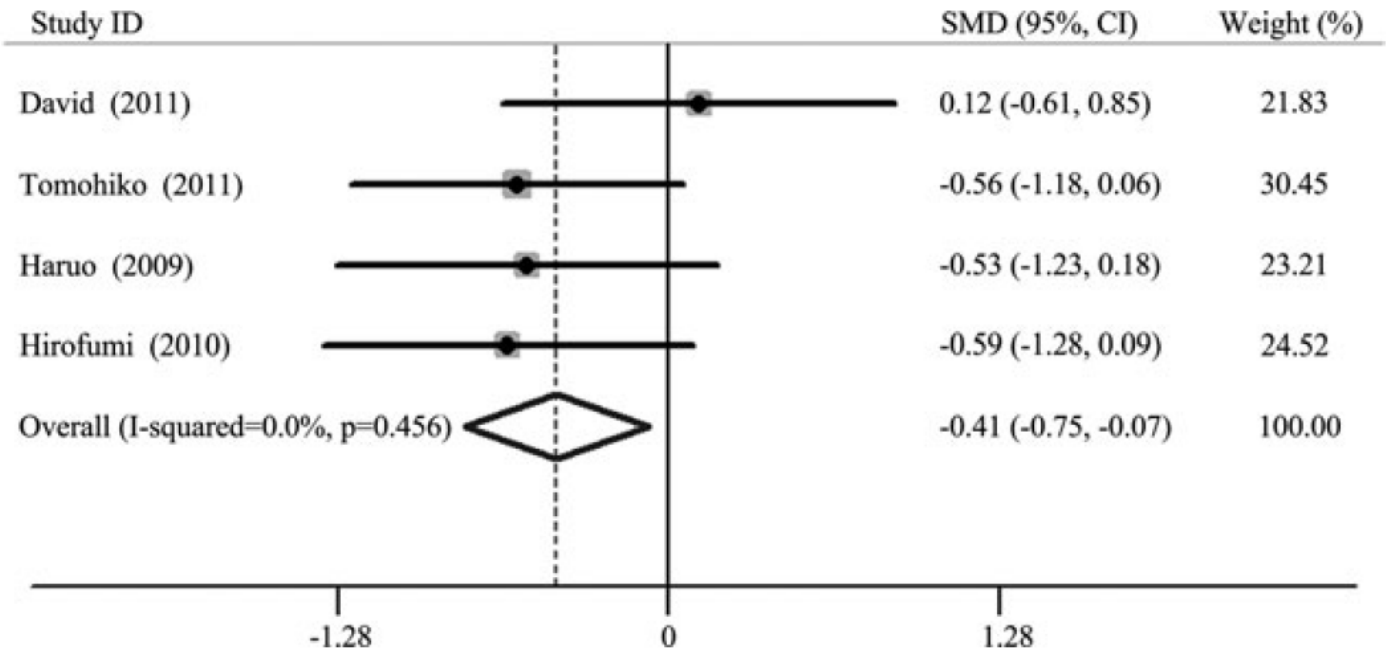
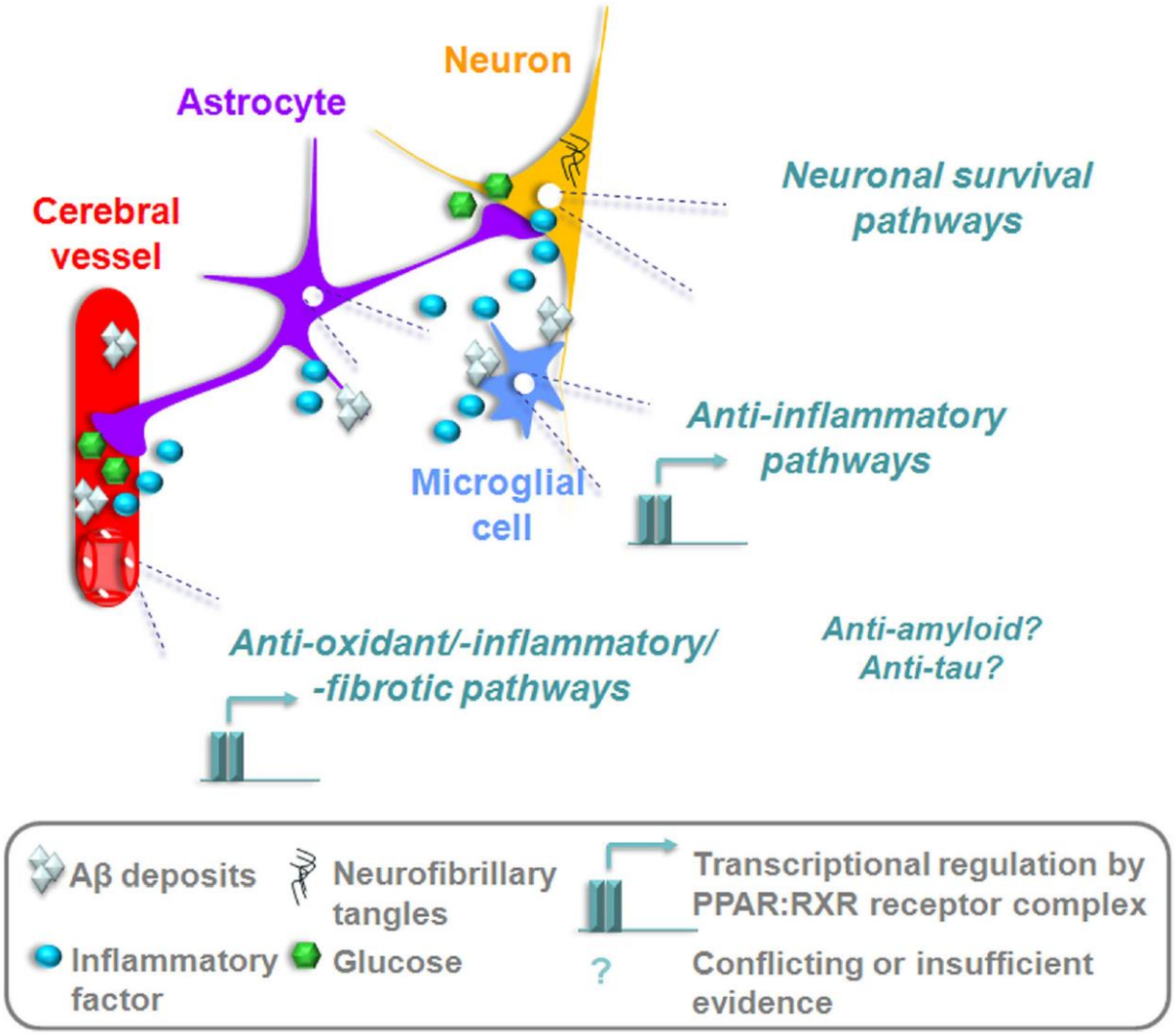



Figure 1. Forest plot for pioglitazone ADAS-cog scores.

Cheng H et al. Int J Neurosci, 2016

# PPARγ activation could rescue vascular, glial, and neuronal compartments in AD brain




Nicolakakis N et al. Front Aging Neurosci, 2010

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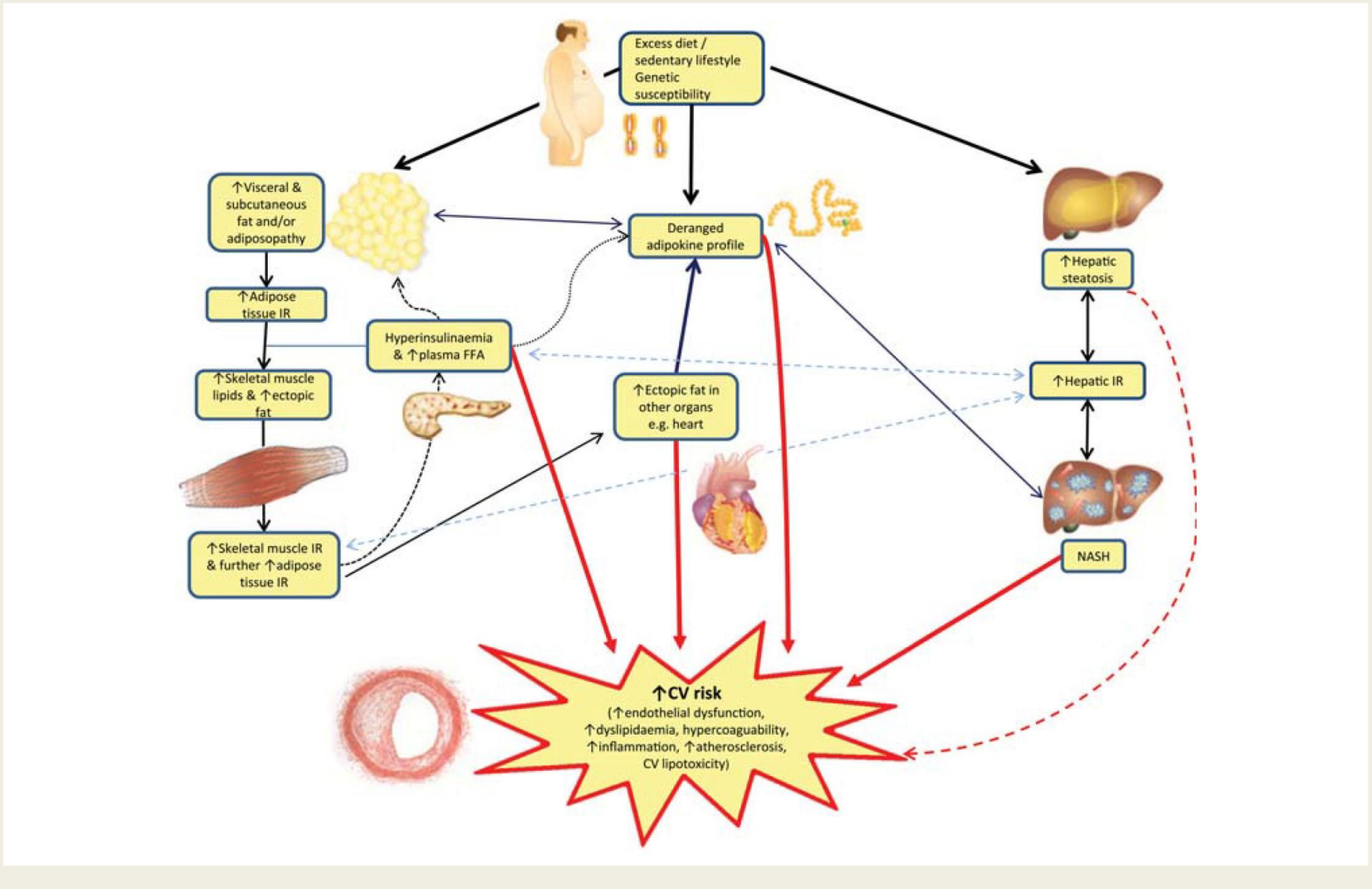
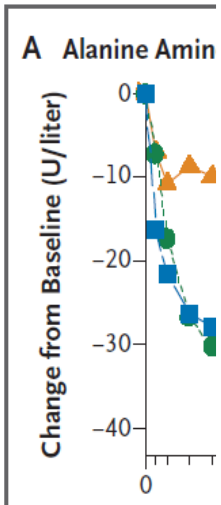
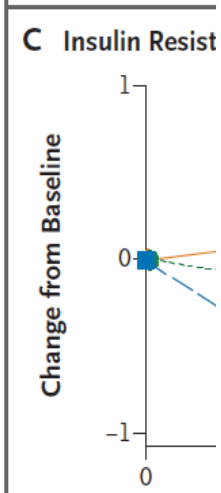
# Pathophysiological processes involved in NAFLD leading to CV risk

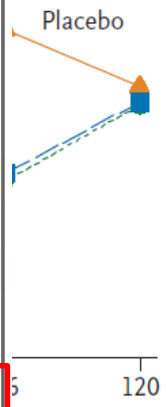



Bhatia LS et al. Eur Heart J, 2012

# Effects of Pioglitazone on NAFLD in subjects without diabetes: the PIVENS trial



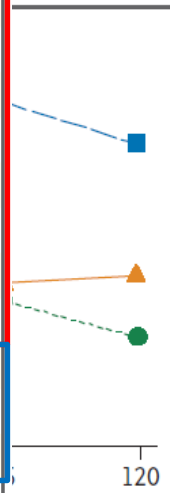




**Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.**

| Variable | Placebo | Vitamin E | Pioglitazone | P Value* | |
|---|---|---|---|---|---|
| | | | | Vitamin E vs. Placebo | Pioglitazone vs. Placebo |
| **Primary outcome†** | | | | | |
| No. of subjects randomly assigned | 83 | 84 | 80 | | |
| Subjects with improvement (%) | 19 | 43 | 34 | 0.001 | 0.04 |
| **Changes from baseline in histologic features** | | | | | |
| No. of subjects with biopsy specimens at baseline and 96 wk | 72 | 80 | 70 | | |
| Steatosis | | | | | |
| Subjects with improvement (%) | 31 | 54 | 69 | 0.005 | <0.001 |
| Mean change in score | −0.1 | −0.7 | −0.8 | <0.001 | <0.001 |
| Lobular inflammation | | | | | |
| Subjects with improvement (%) | 35 | 54 | 60 | 0.02 | 0.004 |
| Mean change in score | −0.2 | −0.6 | −0.7 | 0.008 | <0.001 |
| Hepatocellular ballooning | | | | | |
| Subjects with improvement (%) | 29 | 50 | 44 | 0.01 | 0.08 |
| Mean change in score | −0.2 | −0.5 | −0.4 | 0.03 | 0.01 |
| Total NAFLD activity score (mean change) | −0.5 | −1.9 | −1.9 | <0.001 | <0.001 |
| Fibrosis‡ | | | | | |
| Subjects with improvement (%) | 31 | 41 | 44 | 0.24 | 0.12 |
| Mean change in score | −0.1 | −0.3 | −0.4 | 0.19 | 0.10 |
| Resolution of definite nonalcoholic steatohepatitis (% of subjects) | 21 | 36 | 47 | 0.05 | 0.001 |

Sanyal AJ et al. NEJM, 2010

# Rosiglitazone for Nonalcoholic Steatohepatitis: One-Year Results of the Randomized Placebo-Controlled Fatty Liver Improvement With Rosiglitazone Therapy (FLIRT) Trial

Figure 1.

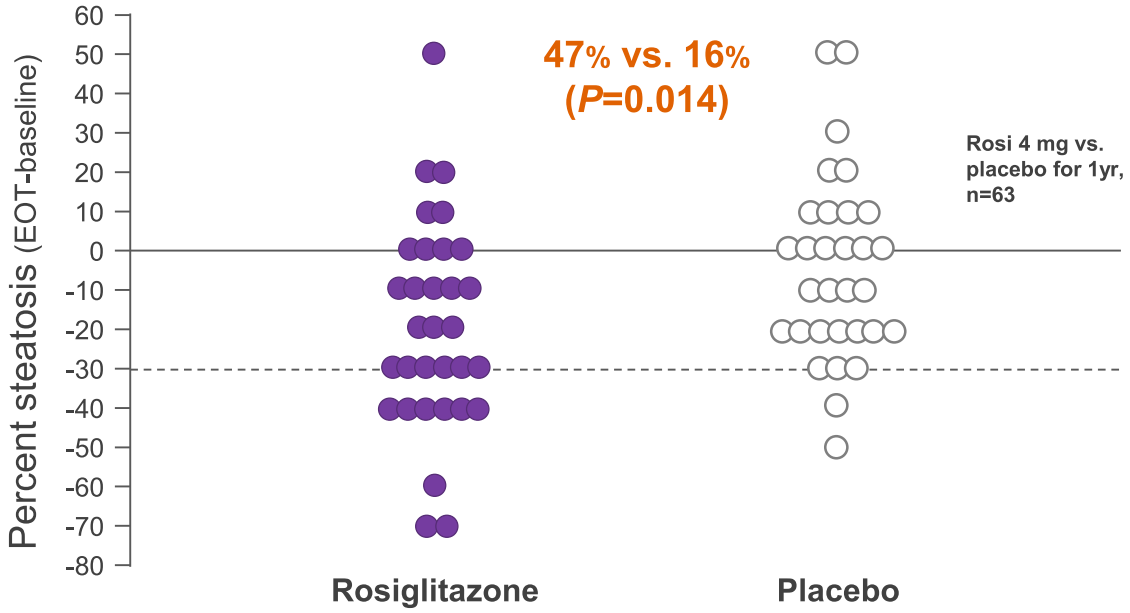



Figure 2.

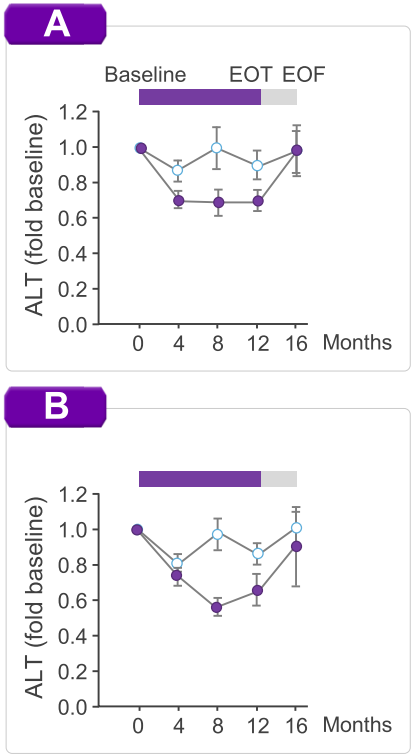



Figure 1. Difference in the histologic score for steatosis between EOT and baseline liver biopsy specimens in both rosiglitazone (*black circles*) and placebo (*white circles*). Steatosis is expressed as the percentage of hepatocytes containing fat droplets. Responders for steatosis (ie, patients having lost >30% during treatment) are those on or below the dashed line.

Figure 2. ALT course during therapy. Results are expressed as means(±SD) of fold elevation over baseline values at each time point during treatment and at EOT (month 12) and end of follow-up (month 16). (A) Rosiglitazone *(black circles)* and placebo (*white circles*); mean ALT values were significantly lower in the rosiglitazone group at months 4, 8, and 12. (B) Responders for steatosis (*black circles*) and nonresponders (*white circles*); mean ALT values were significantly lower in respondersat months 8 and 12.

Ratziu V et al, Gastroenterology 2008; 135:100-110

# Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or T2DM

*Table* Effect of 18 mo of Pioglitazone Treatment on Primary and Secondary Liver Histologic Outcomes*

| Outcome | Placebo ($n$ = 51) | Pioglitazone ($n$ = 50) | Treatment Difference (95% CI) | $P$ Value |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| ≥2-point reduction in NAS (in 2 categories) without worsening of fibrosis, *n (%)* | 9 (17) | 29 (58) | 41 (23 to 59) | <0.001 |
| **Secondary outcomes** | | | | |
| Resolution of NASH, *n (%)*† | 10 (19) | 26 (51) | 32 (13 to 51) | <0.001 |
| Steatosis | | | | |
| ≥1-point improvement, *n (%)* | 13 (26) | 35 (71) | 44 (25 to 63) | <0.001 |
| Mean change in score (SD) | −0.2 (0.8) | −1.1 (1.0) | −0.9 (−1.3 to −0.5) | <0.001 |
| Inflammation | | | | |
| ≥1-point improvement, *n (%)* | 11 (22) | 25 (49) | 27 (8 to 46) | 0.004 |
| Mean change in score (SD) | −0.1 (0.8) | −0.6 (0.9) | −0.6 (−0.9 to −0.2) | <0.001 |
| Ballooning | | | | |
| ≥1-point improvement, *n (%)* | 12 (24) | 25 (51) | 27 (7 to 47) | 0.004 |
| Mean change in score (SD) | −0.2 (0.7) | −0.6 (0.6) | −0.4 (−0.7 to −0.2) | 0.001 |
| Fibrosis | | | | |
| ≥1-point improvement, *n (%)* | 13 (25) | 20 (39) | 14 (−6 to 34) | 0.130 |
| Mean change in score (SD) | 0 (1.2) | −0.5 (1.0) | −0.5 (−0.9 to 0) | 0.039 |

NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis.
* Multiple imputation was used to impute missing histologic data for patients who did not complete 18 mo of therapy (**Appendix**). Numbers of patients may not always seem to match the proportion because they were estimated from the combination of 40 imputed data sets.
† Defined as absence of NASH after 18 mo of therapy in patients with definite NASH at baseline.

Cusi K et al. Ann Intern Med. 2016 Jun 21. doi: 10.7326/M15-1774

JAMA Internal Medicine | Original Investigation

# Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis
## A Meta-analysis

Giovanni Musso, MD; Maurizio Cassader, PhD; Elena Paschetta, MD; Roberto Gambino, PhD

**IMPORTANCE** Nonalcoholic steatohepatitis (NASH) is projected to be the leading cause of liver transplantation by 2020. Advanced fibrosis (stage F3-F4) on liver biopsy independently predicts all-cause and liver-related mortality in NASH. There are no known efficacious treatments for advanced fibrosis related to NASH. Thiazolidinedione therapy has been extensively evaluated in NASH, and new randomized clinical trials (RCTs) of its efficacy have been completed.

**OBJECTIVE** To synthesize the evidence about the association of thiazolidinedione therapy with advanced liver fibrosis in NASH.

**DATA SOURCES** MEDLINE, Ovid MEDLINE In-Process, Cochrane Library, EMBASE, clinicaltrials.gov, PubMed, and Scopus databases (without language restrictions), as well as other registries and scientific meeting presentations, from database inception through August 15, 2016.

**STUDY SELECTION** Randomized clinical trials evaluating the effect of thiazolidinedione therapy on histologic features of the liver in biopsy-proven NASH.

**DATA EXTRACTION AND SYNTHESIS** Two investigators extracted study data independently and in duplicate and rated the risk of bias using the Cochrane Risk of Bias Tool.

**MAIN OUTCOMES AND MEASURES** The primary outcome was a dichotomous improvement in advanced fibrosis on liver biopsy, defined as an improvement in fibrosis stage from F3-F4 to F0-F2. Secondary outcomes were at least a 1-point improvement in fibrosis of any stage and NASH resolution. This meta-analysis also evaluated adverse effects of thiazolidinedione therapy, including weight gain, lower limb edema, congestive heart failure, bone fractures, cancer, and anemia. With the use of random-effects models, dichotomous variables are presented as odds ratios (ORs) with 95% CIs, and continuous variables are presented as weighted mean differences with 95% CIs.

Invited Comm

Supplement

Figure 1. Evidence Acquisition Flow Diagram

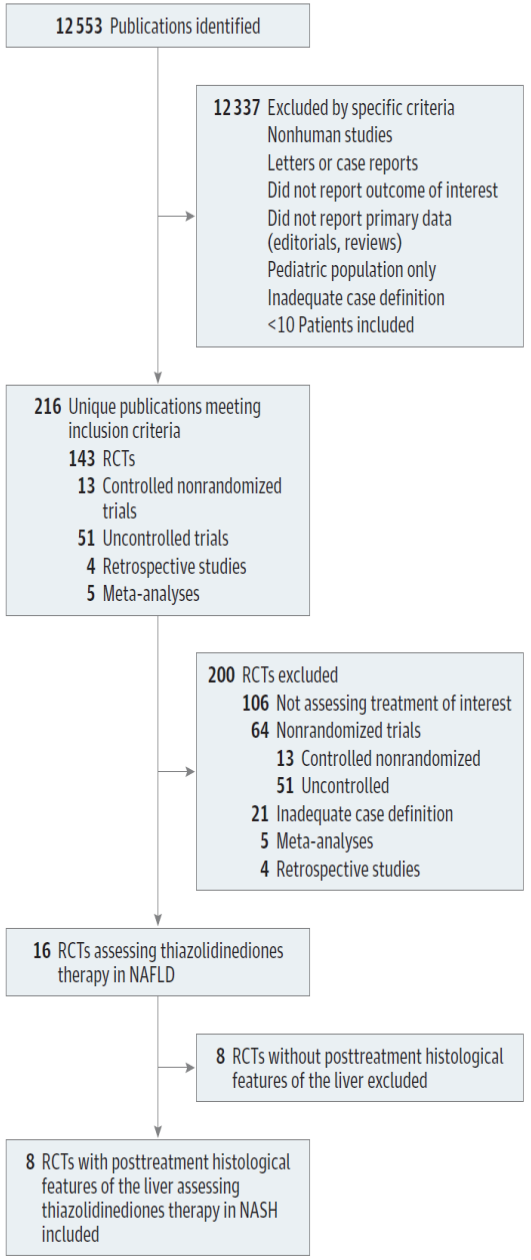
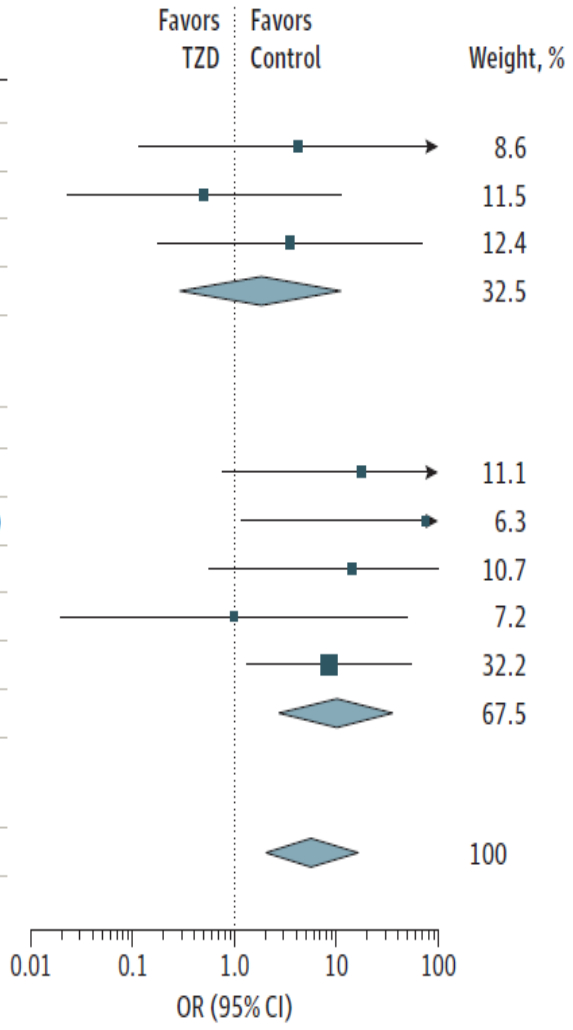


Figure 2. Thiazolidinedione Therapy (TZD) and Improvement in Advanced Fibrosis, Improved Fibrosis of Any Stage, and Nonalcoholic Steatohepatitis (NASH) Resolution

B Patients with NASH with advanced fibrosis at baseline

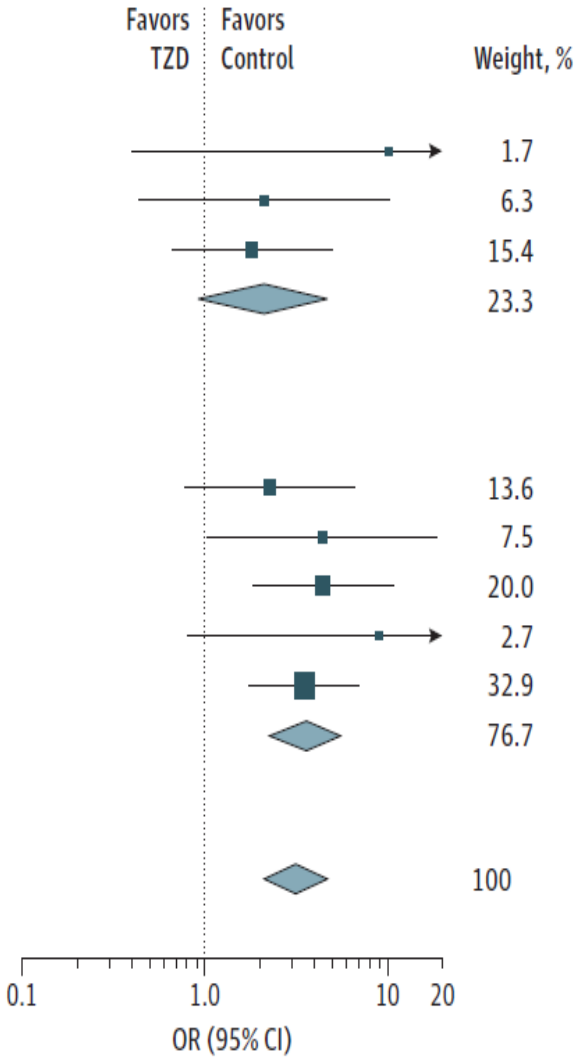
| Source | TZD No. of Events | TZD No. of Patients | Control No. of Events | Control No. of Patients | Odds Ratio (95% CI) | Weight, % |
|---|---|---|---|---|---|---|
| Rosiglitazone maleate | | | | | | |
| Idilman et al,[19] 2008 | 1 | 3 | 0 | 3 | 4.20 (0.12-151.97) | 8.6 |
| Omer et al,[21] 2010 | 1 | 7 | 1 | 4 | 0.50 (0.02-11.09) | 11.5 |
| Ratziu et al,[18] 2008 | 1 | 5 | 1 | 15 | 3.50 (0.18-69.34) | 12.4 |
| Total (95% CI) | 3 | 15 | 2 | 22 | 1.84 (0.29-11.66) | 32.5 |
| Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.06$; $P=.59$; $I^2=0\%$<br>Overall effect: $z=0.65$; $P=.52$ | | | | | | |
| Pioglitazone hydrochloride | | | | | | |
| Aithal et al,[17] 2008 | 3 | 7 | 0 | 11 | 17.89 (0.76-420.49) | 11.1 |
| Belfort et al,[16] 2006 | 7 | 7 | 0 | 2 | 75.00 (1.16-4868.64) | 6.3 |
| Cusi et al,[12] 2016 | 4 | 7 | 0 | 5 | 14.14 (0.57-352.00) | 10.7 |
| Sanyal et al,[15] 2004 | 1 | 2 | 1 | 2 | 1.00 (0.02-50.40) | 7.2 |
| Sanyal et al,[20] 2010 | 6 | 12 | 2 | 19 | 8.50 (1.33-54.13) | 32.2 |
| Total (95% CI) | 21 | 35 | 3 | 39 | 10.17 (2.83-36.54) | 67.5 |
| Heterogeneity: $\tau^2=0.00$; $\chi^2_2=2.43$; $P=.66$; $I^2=0\%$<br>Overall effect: $z=3.55$; $P<.001$ | | | | | | |
| Total (95% CI) | 24 | 50 | 5 | 61 | 5.84 (2.04-16.71) | 100 |
| Heterogeneity: $\tau^2=0.00$; $\chi^2_2=5.71$; $P=.57$; $I^2=0\%$<br>Overall effect: $z=3.29$; $P=.001$ | | | | | | |



## Figure 3. Improved Fibrosis of Any Stage and Nonalcoholic Steatohepatitis (NASH) Resolution

B Induction of NASH resolution

| Source | TZD No. of Events | TZD No. of Patients | Controls No. of Events | Controls No. of Patients | Odds Ratio (95% CI) | Weight, % |
|---|---|---|---|---|---|---|
| Rosiglitazone maleate | | | | | | |
| Idilman et al,[19] 2008 | 4 | 11 | 0 | 8 | 10.20 (0.47-222.45) | 1.7 |
| Omer et al,[21] 2010 | 5 | 20 | 3 | 22 | 2.11 (0.43-10.28) | 6.3 |
| Ratziu et al,[18] 2008 | 16 | 32 | 11 | 31 | 1.82 (0.66-5.00) | 15.4 |
| Total (95% CI) | 25 | 63 | 14 | 61 | 2.14 (0.94-4.86) | 23.3 |
| Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.11$; $P=.58$; $I^2=0\%$<br>Overall effect: $z=1.82$; $P=.07$ | | | | | | |
| Pioglitazone hydrochloride | | | | | | |
| Aithal et al,[17] 2008 | 14 | 31 | 8 | 30 | 2.26 (0.77-6.63) | 13.6 |
| Belfort et al,[16] 2006 | 11 | 26 | 3 | 21 | 4.40 (1.03-18.74) | 7.5 |
| Cusi et al,[12] 2016 | 26 | 50 | 10 | 51 | 4.44 (1.83-10.78) | 20.0 |
| Sanyal et al,[15] 2004 | 5 | 10 | 1 | 10 | 9.00 (0.81-100.14) | 2.7 |
| Sanyal et al,[20] 2010 | 38 | 80 | 17 | 83 | 3.51 (1.76-7.01) | 32.9 |
| Total (95% CI) | 94 | 197 | 39 | 195 | 3.65 (2.32-5.74) | 76.7 |
| Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.56$; $P=.82$; $I^2=0\%$<br>Overall effect: $z=5.61$; $P<.001$ | | | | | | |
| Total (95% CI) | 119 | 260 | 53 | 256 | 3.22 (2.17-4.79) | 100 |
| Heterogeneity: $\tau^2=0.00$; $\chi^2_2=3.90$; $P=.79$; $I^2=0\%$<br>Overall effect: $z=5.79$; $P<.001$ | | | | | | |



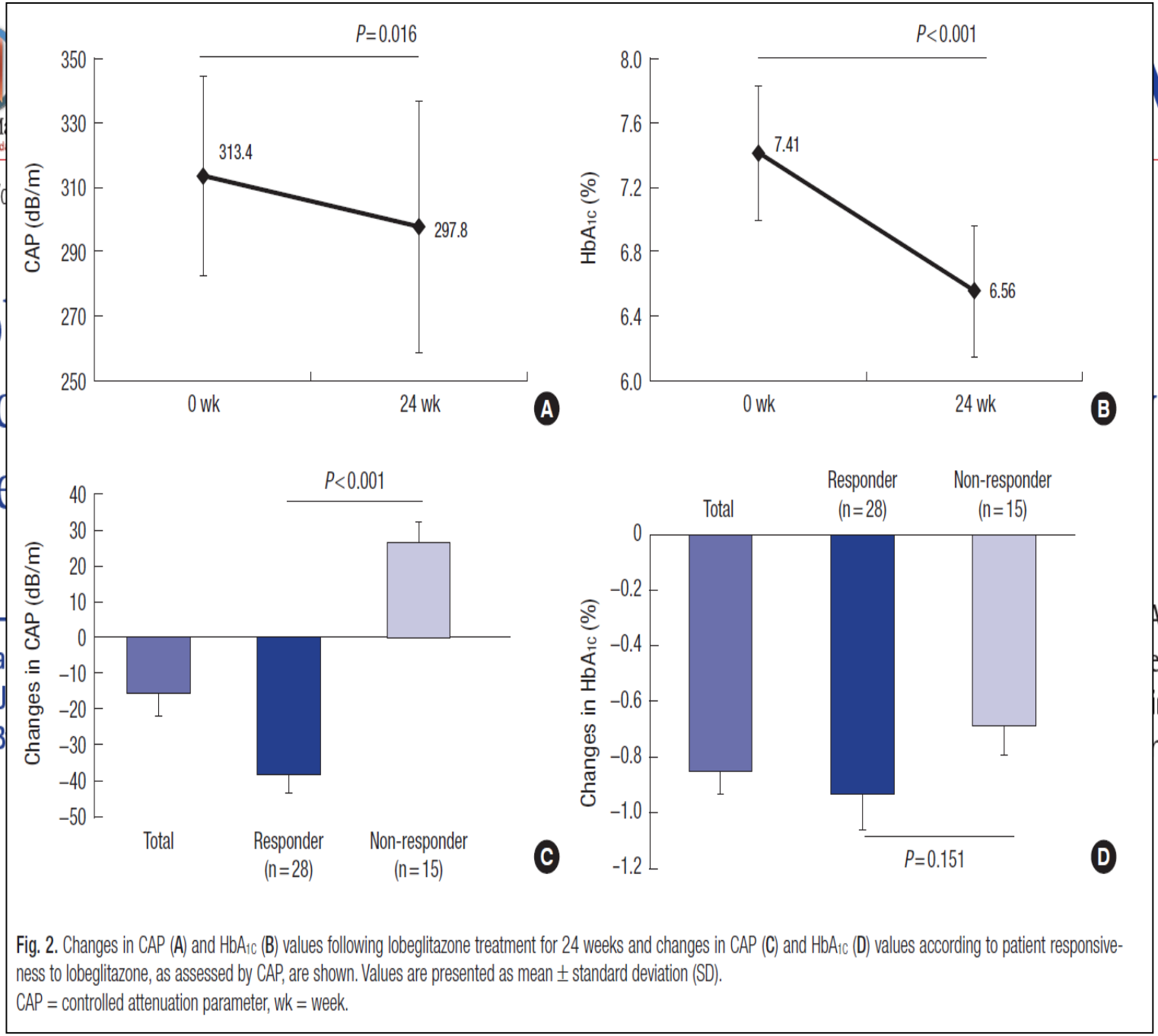



**Fig. 2.** Changes in CAP (**A**) and $HbA_{1C}$ (**B**) values following lobeglitazone treatment for 24 weeks and changes in CAP (**C**) and $HbA_{1C}$ (**D**) values according to patient responsiveness to lobeglitazone, as assessed by CAP, are shown. Values are presented as mean ± standard deviation (SD).
CAP = controlled attenuation parameter, wk = week.

# EASL-EASD-ESO Clinical Practice Guidelines for the management of NAFLD

**Recommendations**

- Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression (i.e. with diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates to prevent disease progression (**B1**)
- While no firm recommendations can be made, pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short term) or their combination could be used for NASH (**B2**)

Diabetologia, 2016

# EASL-EASD-ESO Clinical Practice Guidelines for the management of NAFLD

- The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy; in patients with normal ALT at baseline, no recommendations can be made (**C2**)
- Statins may be confidently used to reduce LDL-cholesterol and prevent cardiovascular risk, with no benefits or harm on liver disease. Similarly *n*-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH (**B1**)

Cell Metabolism
Review

# Thiazolidinediones and the Promise of Insulin Sensitization in Type 2 Diabetes

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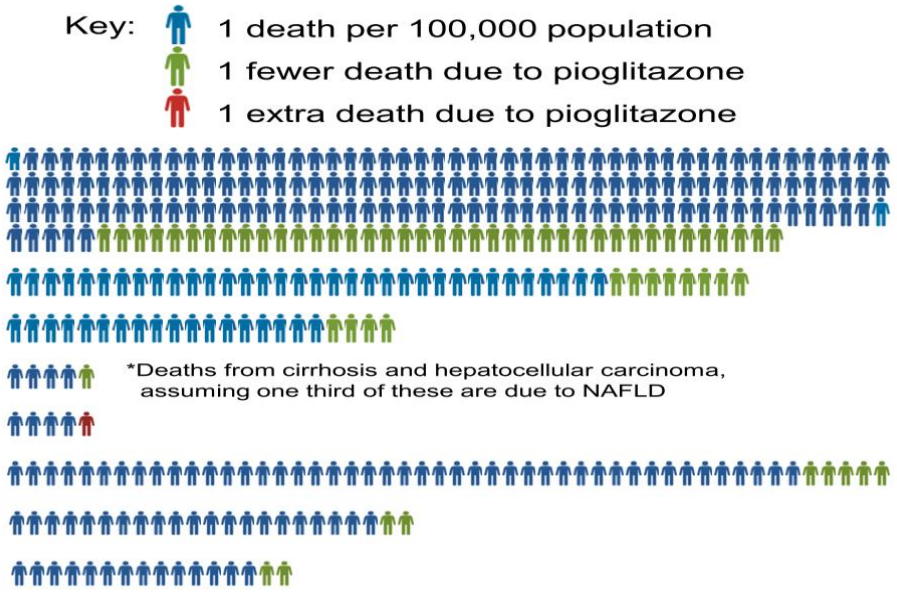
http://dx.doi.org/10.1016/j.cmet.2014.08.005

| Cause of death | Deaths per 100,000 | Potential effect of pioglitazone | |
|---|---|---|---|
| | | Risk | Deaths |
| Heart Disease | 194 | -20% | -39 |
| Stroke | 42 | -20% | -8 |
| Diabetes | 22 | -20% | -4 |
| NAFLD-related* | 5 | -20% | -1 |
| Bladder cancer | 4 | +20% | +1 |
| Lung cancer | 50 | -10% | -5 |
| Breast cancer | 23 | -10% | -2 |
| Colon cancer | 16 | -10% | -2 |




Soccio et al. Cell Metab 20:573, 2014