"Actos: 1-800-BAD DRUG"

The Clash of Science, Medicine, Media, & the Judiciary

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Pioglitazone & Bladder Cancer

Objectives:

1. To review the physiology of pioglitazone and it's impact on carcinogenesis
2. To review the available clinical trial data concerning pioglitazone and bladder cancer
3. To better understand the risk-benefit balance in the clinical use of pioglitazone

Disclosures: none

Pioglitazone & Bladder Cancer

77 yo white male with Type 2 Diabetes, hypertension, hyperlipidemia, gout, cardiomyopathy, and hypothyroidism presented with gross hematuria in May, 2012 (Intermittent proteinuria since 2000)

Medications: Piogliazone (2005 – 45 mg 3/wk), Metformin, Furosemide, Losartan, Amlodipine, Sotalol, Atorvastatin, L-T4, & Allopurinol

Social History: Smoker for 26 yrs (quit 1974); drinks 2-3 martinis daily

Family History: Maternal grandmother had bladder cancer

Work-up: Ultrasound → hydronephrosis of L kidney; no metastatic disease
Cytoscopy → bladder tumor at L ureteral orifice; stent placed w/ difficulty (June)
Pathology → high-grade TCC w/ extensive invasion of muscularis propria
Bone Scan → negative
Creat increased to 2.5 which delayed chemotherapy → returned to baseline in Aug (1.1)
He has now completed chemotherapy and surgery

Question: Did Pioglitazone:

A. Have no effect on this bladder cancer?
B. Cause the cancer?
C. Promote the growth or malignancy of the cancer?
D. Increase the early diagnosis of the cancer?

Pioglitazone & Bladder Cancer

Background:

Pioglitazone induced a low incidence of bladder tumors in a 2-year bioassay study in male rats (Physicians Desk Reference, 2008). They were not seen in female rats or other rodents.

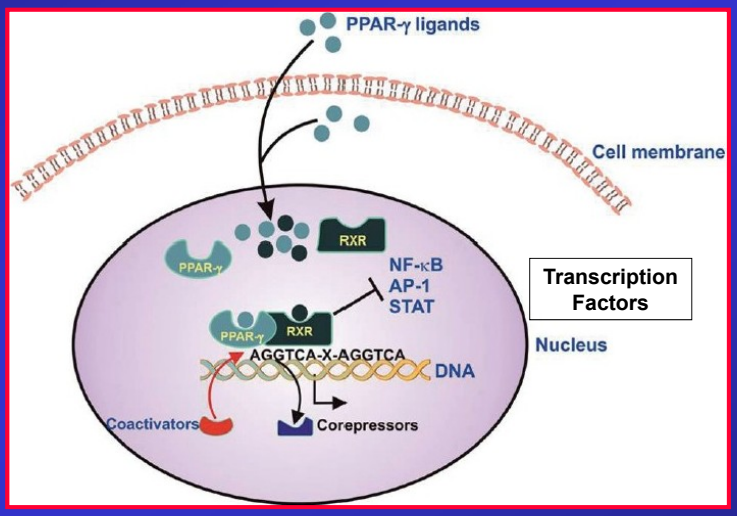
Suzuki et al fed male rats pioglitazone (16 mg/kg, 25x therapeutic dose) for 4 weeks:

1. Induced cytotoxicity & necrosis of the urothelial superficial layer, with increased cell proliferation and hyperplasia.
2. Produced calcium-containing crystals and calculi.
3. 'In vitro' PIO reduced urothelial cell proliferation and induced uroplakin synthesis, a specific differentiation marker in urothelial cells.
4. Their data support the hypothesis that bladder tumors produced in male rats by pioglitazone are related to the formation of urinary solids. This data strongly supports the previous conclusion in studies with muraglitazar that this is a rat-specific phenomenon and does not pose a urinary bladder cancer risk to humans.

(Toxicological Sciences 113(2), 349–357, 2010)

Pioglitazone & Bladder Cancer

PPAR-gamma Pathway



Pioglitazone & Bladder Cancer

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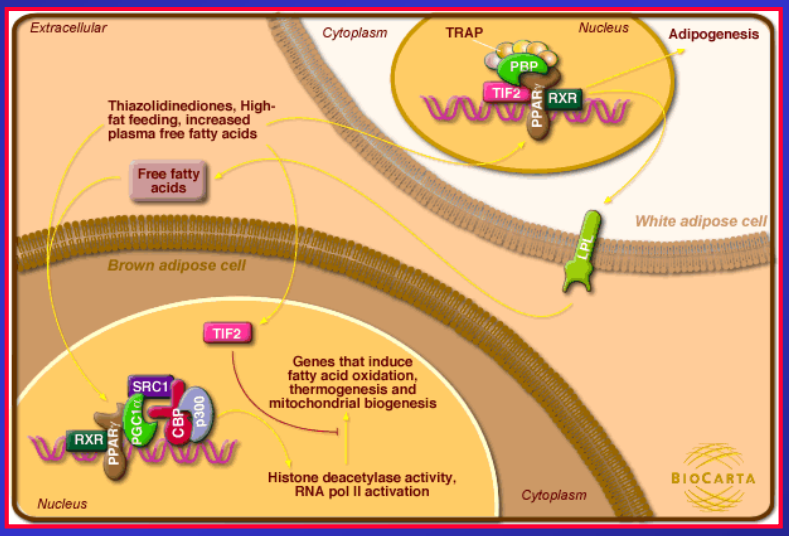
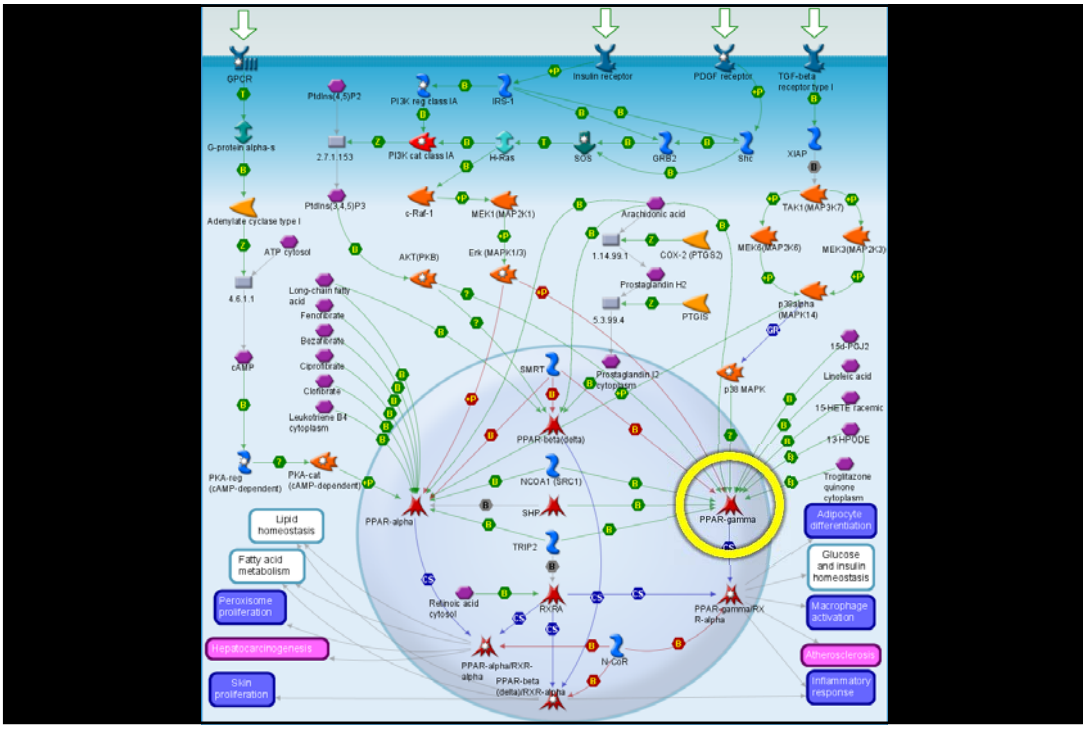
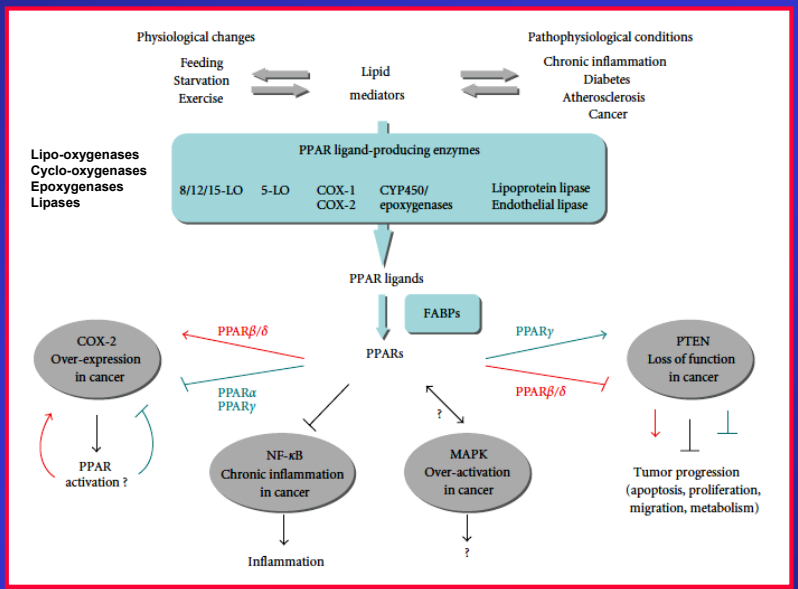




Pioglitazone & Bladder Cancer



Michalik & Wahli
PPAR Research
Article ID 134059
2008

Pioglitazone & Bladder Cancer

PPAR-gamma, Bioactive Lipids, and Cancer Progression (Robbins & Nie: Front Biosci 17:1816–34, 2012)

PPARg agonists (LOX, COX → PG) → cell differentiation, growth inhibition, apoptosis, anti-angiogenesis

PPARg mRNA & protein inversely correlates w/ tumor progression and prognosis in many carcinomas
May be an inducible tumor suppressor (colon, stomach, breast, prostate, lung)

Cancer → PPARg+RXR frequently inhibited by mutations, induction of co-repressors (SMRT), or MAPK Phosphorylation → uncontrolled growth

Mechanisms by which PPARg may inhibit cancer:

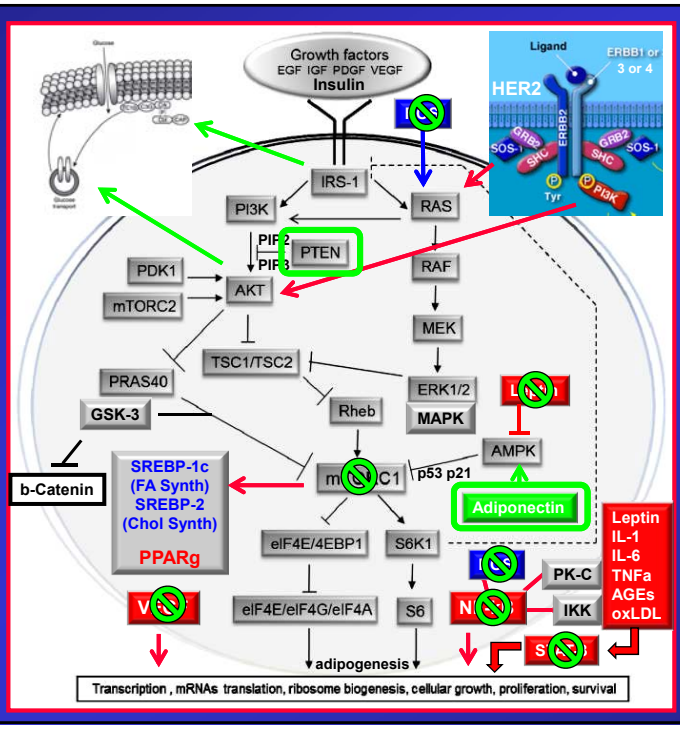
- Direct Inhibition of pathways that induce de-differentiation, growth, anti-apoptosis, &/or angiogenesis
  - PI3K/AKT/mTOR* (PTEN) – mTOR C1 increases while mTOR C2 down-regulates PPARg
  - IL-6 → STAT3 → NF-kB → Lin28 (active in half cancer cell lines) (blocks prot-binding to NF-kB)
- Inhibit Oncogenes
  - Active PPARg+RXR up-regulates E-Cadherin (membrane protein) which binds beta-Catenin (Wnt-activated oncogenic protein) & prevents its transfer to nucleus → stops activation of Cyclin D & c-Myc
  - E-Cadherin gene frequently hyper-methylated in bladder cancer cell lines
- Induce Tumor Suppressor Genes
  - PTEN (PPRE), p53 (apoptosis, cell cycle arrest, autophagocytosis); both lost in many cancers
- Bind Co-Repressors which may allow activation of tumor suppressor genes (may not need agonist)
  - SMRT, NCoR
- Bind Co-Activators which may down-regulate oncogenes (or vis versa)
  - Ligand-dependent: PGC-1a, CPB/p300, SRC-1; Ligand independent: ARA70, SHP

mTOR Signaling Pathway in Human Cancer

mTOR: central regulator of cell growth and proliferation in response to environmental & nutritional conditions.

mTOR signaling is regulated by growth factors, amino acids, ATP, and O_2 levels.

mTOR regulates:
cell-cycle progression
translation initiation
transcriptional stress responses
protein stability & survival of cells



HER2 Receptor Over-expressed in bladder Ca

Correlates w/ stage, grade, & survival

PPARg activates: PTEN, Adiponec, & p53

Inhibits: mTOR complex 1, ROS, NF-kB, STAT3, Leptin, VEGF, & iNOS

mTOR complex 2, MEK, ERK, JNK, Leptin, & MAPK inhibit PPARg

Populo et al
Int J Mol Sci:
13(2):1886–1918,
2012

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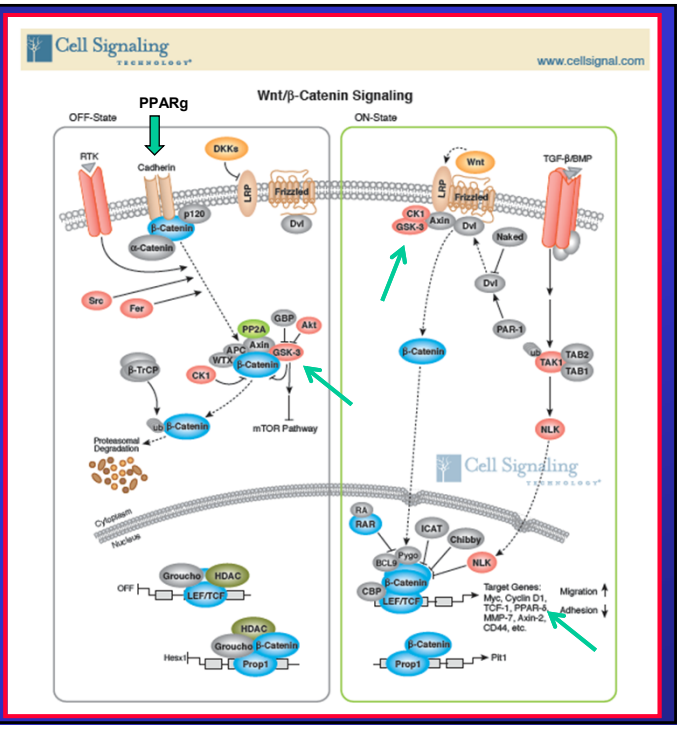
Pioglitazone & Bladder Cancer

Wnt Pathway
Present in slime molds
Controls cell-cell communication
Embryonic Development
Maintains Adult Cell Differentiation
Cell Polarity

Wnt controls beta-Catenin
Wnt5a → PL-C → IP3, DAG
(increased in prostate cancer)

APC defic or b-Catenin mutation → excess stem cell renewal & proliferation



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Pioglitazone & Bladder Cancer

Incidence Rates by Race

Race/Ethnicity	Male	Female
All Races	37.0 per 100,000 men	8.9 per 100,000 women
White	40.0 per 100,000 men	9.6 per 100,000 women
Black	21.2 per 100,000 men	7.1 per 100,000 women
Asian/Pacific Islander	16.2 per 100,000 men	4.0 per 100,000 women
American Indian/Alaska Native [a]	14.8 per 100,000 men	3.2 per 100,000 women
Hispanic [b]	19.6 per 100,000 men	5.3 per 100,000 women

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
In situ (only in the layer of cells in which it began)	51	96.4
Localized (confined to primary site)	35	70.2
Regional (spread to regional lymphnodes)	7	32.9
Distant (cancer has metastasized)	4	5.5
Unknown (unstaged)	3	48.8

Age at Diagnosis
Median: 73 years

Age	Percent:
<20	0.1%
20-34	0.4%
35-44	1.6%
45-54	7.4%
55-64	18.4%
65-74	27.4%
75-84	31.4%
85+	13.3%

1.15% of **Men** will develop bladder Ca between age 50-70
0.32% of **Women**

2009 **Alive w/ B-Ca**:
411,234 men
143,113 women

http://seer.cancer.gov/statfacts/html/urinb.html

Pioglitazone & Bladder Cancer

Table 1
Environmental factors and their association with bladder cancer

Causative	Indeterminate	No association
Cigarette smoking [14–16]	Second-hand smoke [23,26–28]	Aniline [40,43,46,52]
Cigar/pipe smoking [24,25]	Chlorinated water [137–140]	Artificial sweeteners [131,132]
1-Naphthylamine, 2-naphthylamine, benzidine, 4-aminobiphenyl, ortho-toluidine and chloroaniline [43–46]	Halogentated hydrocarbons [74,83,84]	Analgesics excluding phenacetin [122–124]
High arsenic levels (drinking water concentration > 0.2 mg/l) [64,70]	Low arsenic levels (drinking water concentration < 0.1 mg/l) [68,69,71]	
Polyaromatic hydrocarbons [75–77]	HPV [103,104]	
Ionizing radiation [85,87]	Pioglitazone [125,126]	
Schistosoma haematobium [92,95]	Nitrates and nitrites [134–136]	
Chronic inflammation [97,98]	Vitamin D deficiency [143–145]	
Immunosuppression [105,106,108]		
Oxazophosphorines [109,110,115]		
Phenacetin [117,120]		
Aristolochia fangchi [127,128]		

For all environmental risk factors, ability to cause bladder cancer is dependent on level and duration of exposure. Associations based on level of scientific evidence found on literature review, see select references.

Bladder Cancer incidence is 4 times higher in smokers than non-smokers
50% of all bladder cancers in men & 30% in women are due in part to cigarette smoking
Latency 20+ yrs Quit 1 yr → 30% reduction Takes 20 yrs to return to Baseline

Pioglitazone & Bladder Cancer

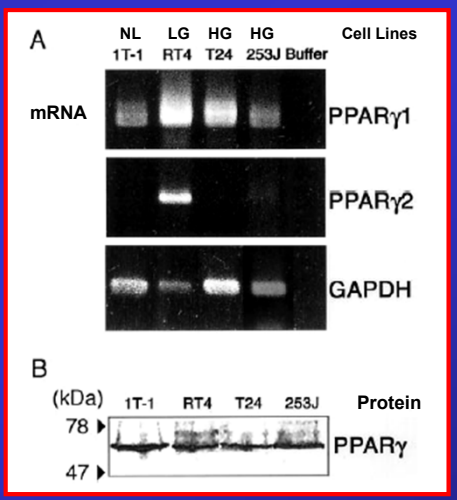
PPARg ligands inhibit the growth of breast, prostate, and colon cancer cells *in vitro* and *in vivo*

Normal bladder cells and low grade tumors or cell lines have a high level of PPARg expression but high grade tumors lose PPARg

Table 1. Immunohistochemical Expression of PPARγ in Bladder Carcinoma

Grade	*n*, Total	Cases expressing PPARγ, *n*		
		Diffuse*	Focal*	None
1	18	17	1	0
2	14	11	3	0
3	16	3	7	6†

*Diffuse staining: all tumor cell nuclei stained. Focal staining: 75% of tumor cell nuclei stained in grade 1 carcinomas whereas stained nuclei ranged from 30 to 90% in grade 2 carcinomas, and 10 to 95% in grade 3 carcinomas.



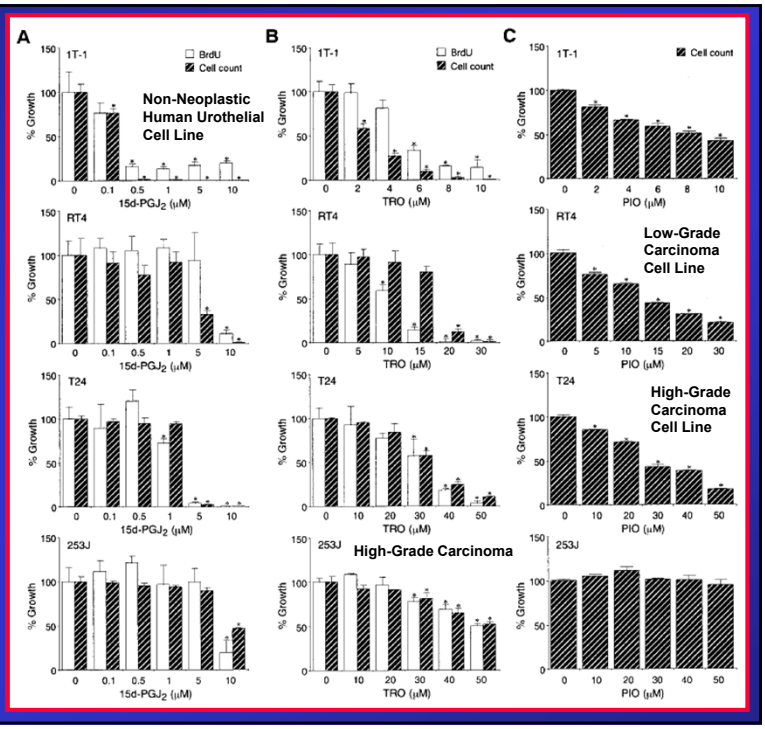
Nakashiro et al: *Amer J Path 159(2): 591-7; 2001*

Pioglitazone & Bladder Cancer

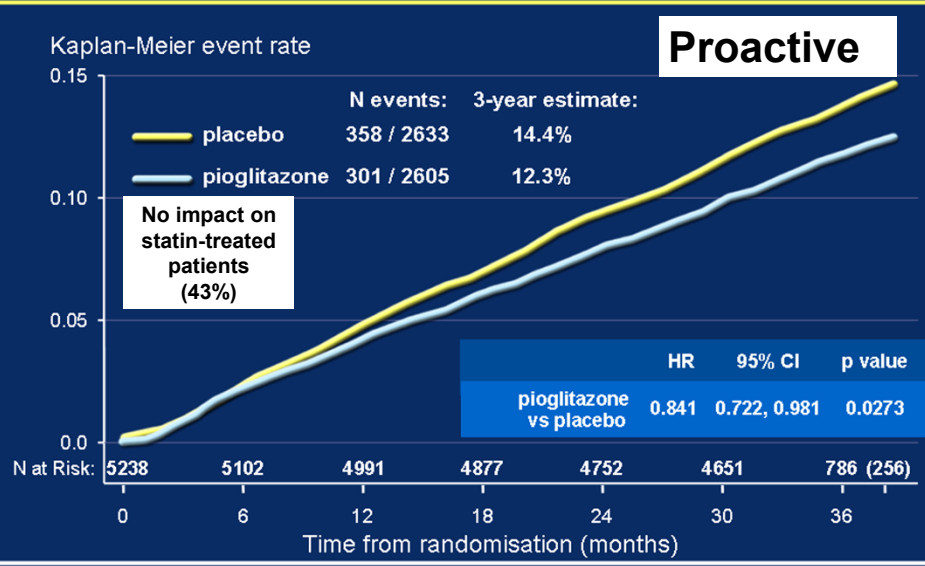
Nakashiro et al: *Amer J Path 159(2): 591-7; 2001*

PPARg agonists **inhibit** growth or have no effect

No Stimulatory Effect



Time to Death, MI (Excluding Silent) or Stroke



proactive-results.com

Pioglitazone & Bladder Cancer

Table VI. Incidence of malignant neoplasms

Event	Pioglitazone (n=2605) [no. (%)]	Placebo (n=2633) [no. (%)]
No. of patients with any malignant neoplasm	97 (3.7)	99 (3.8)
colorectal	16 (0.6)	15 (0.6)
lung	15 (0.6)	12 (0.5)
bladder	14 (0.5)	6 (0.2)
haematological	6 (0.2)	10 (0.4)
breast	3 (0.1)	11 (0.4)
prostate	9 (0.3)	5 (0.2)
pancreas	8 (0.3)	6 (0.2)
gastric	5 (0.2)	6 (0.2)
renal	3 (0.1)	7 (0.3)
skin	6 (0.2)	4 (0.2)
metastases	5 (0.2)	5 (0.2)
ovarian/uterine	4 (0.2)	5 (0.2)
other	7 (0.3)	10 (0.4)

Proactive

Average F/U: 34.5 mths

Review of Bladder Ca → 11 cases (8/3) from the 1st yr eliminated → 6/3
One Placebo case was benign → 6/2
Five had known risk factors: smoking (5), bladder irritation (2), exp carcinogen (1)
Leaving 3 cases (2/1)
Subsequent 4 years: no excess cancer

Dormandy et al: Drug Safety 32(3): 187-202, 2009

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)

Multi-center, randomized, open-label trial
5 Years

Rosi reduces Pancr Ca (85%) and Hyperglycemia (50%)
Doubles fractures (in women) & CHF

	Women		Men		All	
	Rosiglitazone (N=1078)	Active control (N=1075)	Rosiglitazone (N=1142)	Active control (N=1152)	Rosiglitazone (N=2220)	Active control (N=2227)
All	124 (154)	68 (78)	61 (71)	50 (54)	185 (225)	118 (132)
Upper limb	63 (78)	36 (39)	23 (23)	19 (19)	86 (101)	55 (58)
Distal lower limb	47 (49)	16 (17)	23 (24)	11 (11)	70 (73)	27 (28)
Femur/hip	7 (8)	7 (7)	3 (3)	1 (1)	10 (11)	8 (8)
Spine	8 (8)	4 (4)	6 (6)	5 (5)	14 (14)	9 (9)
Pelvis	0	1 (1)	0	3 (3)	0	4 (4)
Other	11 (11)	10 (10)	14 (15)	15 (15)	25 (26)	25 (25)

Numbers are participants (events). Some participants had more than one fracture and in different areas of the body.

Table 7: Bone fractures reported as serious and non-serious adverse events

	Rosiglitazone (N=2220)	Active control (N=2227)	p value
Infections	139 (6·3%)	157 (7·0%)	0·32
Pneumonia	41 (1·8%)	35 (1·6%)	0·56
Malignancies	126 (5·7%)	148 (6·6%)	0·20
Prostate cancer*	15 (1·3%)	21 (1·8%)	0·41
Breast cancer*	11 (1·0%)	17 (1·6%)	0·34
Colon cancer	10 (0·5%)	14 (0·6%)	0·54
Pancreatic cancer	2 (<0·1%)	13 (0·6%)	0·0074
Bladder cancer	6 (0·3%)	5 (0·2%)	0·99
Gastrointestinal disorders	133 (6·0%)	119 (5·3%)	0·39
Myocardial infarction	74 (3·3%)	67 (3·0%)	0·59
Myocardial ischaemia	14 (0·6%)	10 (0·4%)	0·54
Unstable angina	39 (1·8%)	38 (1·7%)	0·99
Angina pectoris	48 (2·2%)	37 (1·7%)	0·27
Coronary artery disease	24 (1·1%)	33 (1·5%)	0·29
Atrial fibrillation	33 (1·5%)	34 (1·5%)	1·00
Heart failure	82 (3·7%)	42 (1·9%)	0·0003
Cerebrovascular accident	43 (1·9%)	63 (2·8%)	0·064
Transient ischaemic attack	22 (1·0%)	25 (1·1%)	0·78
Hypertension	19 (0·9%)	21 (0·9%)	0·89
Pulmonary embolism	10 (0·5%)	13 (0·6%)	0·68
Bone fracture†	49 (2·2%)	36 (1·6%)	0·18
Osteoarthritis	29 (1·3%)	24 (1·1%)	0·58
Non-cardiac chest pain	21 (0·9%)	19 (0·9%)	0·89
Hyperglycaemia	27 (1·2%)	55 (2·5%)	0·0027
Hypoglycaemia‡	15 (0·7%)	6 (0·3%)	0·076
Macular oedema‡	0 (0·0%)	0 (0·0%)	..
Cataract	17 (0·8%)	13 (0·6%)	0·57
Anaemia	16 (0·7%)	10 (0·4%)	0·32

Data are number of patients (%). Data are for serious adverse events reported for more than 20 people or those predefined as being of particular interest in the context of thiazolidinedione therapy. *For prostate cancer, data are for men only, and for breast cancer data are for women only. †For non-serious adverse events and details, see table 7 and text. ‡For non-serious adverse events, see text.

Table 6: Patients with serious adverse events

Pioglitazone & Bladder Cancer

Assessing the Association of Pioglitazone Use and Bladder Cancer Through Drug Adverse Event Reporting Piccinni C et al: Diabetes Care 34:1369-71, 2011

Mean Age: 70 yrs (53-84)
Only Signif in >65 yrs
Men 23 Women 8
10 during Clinical Trails

<6 mths: 6
6-24 mths: 5
>24 mths: 4
Unknown: 16

One Pt on cytotoxic Rx
Smoking Hx Unknown

Notoriety Bias??

Table 1—*ROR of bladder cancer for antidiabetic drugs*

Active substance	Cases*	All ADR	ROR	95% CI	P†
Pioglitazone	31	37,841	4.30	2.82–6.52	<0.001
Insulin	29	124,873	1.01	0.06–1.55	0.961
Metformin	25	138,900	0.73	0.46–1.15	0.158
Glimepiride	13	35,388	1.66	0.89–3.01	0.080
Exenatide	8	100,946	0.30	0.14–0.64	0.001
Gliclazide	6	7,560	3.56	1.42–8.39	0.001
Glipizide	5	34,816	0.61	0.22–1.54	0.272
Sitagliptin	4	11,638	1.51	0.48–4.22	0.416
Acarbose	4	3,479	5.12	1.61–14.33	<0.001
Rosiglitazone	4	44,006	0.38	0.12–1.05	0.045
Glibenclamide	3	38,214	0.33	0.08–1.06	0.043
Nateglinide	2	4,994	1.75	N.A.	N.A.
Repaglinide	2	6,060	1.44	N.A.	N.A.
Phenformin	1	65	68.30	N.A.	N.A.
Voglibose	1	2,938	1.48	N.A.	N.A.
Other antidiabetic drugs	0	7,367	N.A.	N.A.	N.A.
Total	138	599,085			

ADR, adverse drug reaction; N.A., not available. *Cases of bladder cancer. †Mantel-Haenszel corrected.

Pioglitazone & Bladder Cancer

Risk of Bladder Cancer Among Diabetic Patients Treated with Pioglitazone
Lewis JD et al: Diabetes Care 34:916-922, 2011

Table 1—*Demographics of the study cohort according to ever use of pioglitazone: the KPNC diabetes registry, 1997–2008*

Kaiser-Perm	Ever use of pioglitazone*	Never use of pioglitazone*
N	30,173	162,926
Age (years)		
40–49	8,612 (28.5)	36,452 (22.4)
50–59	9,945 (33.0)	41,962 (25.8)
60–69	7,799 (25.8)	42,691 (26.2)
≥70	3,817 (12.7)	41,821 (25.7)
Sex (female)	14,157 (46.9)	75,686 (46.5)
Race/ethnicity		
White	14,768 (48.9)	80,777 (49.6)
Black	2,823 (9.4)	16,731 (10.3)
Asian	3,834 (12.7)	18,877 (11.6)
Hispanic	3,320 (11.0)	14,430 (8.9)
Other	1,691 (5.6)	8,876 (5.4)
Missing	3,737 (12.4)	23,235 (14.3)
Current smoker	6,052 (20.1)	28,023 (17.2)
Renal function		
Normal creatinine	23,174 (76.8)	125,879 (77.3)
Elevated creatinine†	1248 (4.1)	13,993 (8.6)
Missing	5,751 (19.1)	23,054 (14.2)
Bladder condition‡	3,686 (12.2)	25,581 (15.7)
Congestive heart failure	969 (3.2)	11,038 (6.8)
Income		
Low§	14,413 (47.8)	82,270 (50.5)
High	12,825 (42.5)	66,133 (40.6)
Missing	2,935 (9.7)	14,523 (8.9)
Baseline A1C (%)		
<7	4,873 (16.2)	46,407 (28.5)
7–7.9	5,455 (18.1)	31,517 (19.3)
8–8.9	3,921 (13.0)	17,060 (10.5)
9–9.9	2,979 (9.9)	11,524 (7.1)
≥10	7,330 (24.3)	28,017 (17.2)
Missing	5,615 (18.6)	28,401 (17.4)
Newly diagnosed with diabetes at the start of follow-up¶	14,687 (48.7)	94,739 (58.1)
Duration of diabetes (years)		
0–5	17,363 (57.5)	102,916 (63.2)
5–9	2,983 (9.9)	9,671 (5.9)
≥10	2,956 (9.8)	17,432 (10.7)
Missing	6,871 (22.8)	32,907 (20.2)
Other cancer prior to baseline	1,186 (3.9)	8,762 (5.4)
Other diabetes medications		
Other TZDs	2,754 (9.1)	2,470 (1.5)
Metformin	24,797 (82.2)	70,956 (43.6)
Sulfonylureas	26,311 (87.2)	95,429 (58.6)
Other oral hypoglycemic drugs	1,482 (4.9)	1,865 (1.1)
Insulin	13,123 (43.5)	41,337 (25.4)
Pioglitazone use during follow-up		
Time since starting pioglitazone (months)	39.5 (1–102)	N/A
<18	7,245 (24.0)	N/A
18–36	6,681 (22.1)	N/A
>36	16,247 (53.8)	N/A
Duration of therapy (months)	24.1 (1–102)	N/A
<12	7,332 (24.3)	N/A
12–24	7,677 (25.4)	N/A
>24	15,164 (50.3)	N/A

Pioglitazone & Bladder Cancer

Risk of Bladder Cancer Among Diabetic Patients Treated with Pioglitazone

Lewis JD et al: Diabetes Care 34:916-922, 2011

Table 2—*Incidence rate and HR of bladder cancer with pioglitazone use: the KPNC diabetes registry, 1997–2008*

	Median (range) bladder cancer incidence rate (per 100,000 person-years)	HR (95% CI) adjusted for age and sex	Fully adjusted HR (95% CI)*
Never use of pioglitazone	68.8 (64.1–73.6)	Ref.	Ref.
Ever use of pioglitazone†	81.5 (64.7–98.4)	1.2 (0.9–1.5)‡	1.2 (0.9–1.5)
Time since starting pioglitazone (months)†			
<18	67.1 (41.8–92.4)	1.1 (0.8–1.6)	1.2 (0.8–1.7)
18–36	85.2 (51.8–118.6)	1.3 (0.9–2.0)	1.4 (0.9–2.1)
>36	93.1 (63.5–122.7)	1.3 (0.9–1.8)	1.3 (0.9–1.8)
P_{trend}	—	0.04	0.07
Duration of therapy (months)†			
<12	48.4 (29.0–67.8)	0.8 (0.5–1.2)	0.8 (0.6–1.3)
12–24	86.7 (52.0–121.4)	1.3 (0.9–2.0)	1.4 (0.9–2.1)
>24	102.8 (71.7–133.8)	1.5 (1.1–2.0)	1.4 (1.03–2.0)
P_{trend}	—	0.02	0.03
Cumulative dose (mg)†			
1–10,500	59.7 (39.0–80.4)	1.0 (0.7–1.4)	1.0 (0.7–1.5)
10,501–28,000	76.8 (48.3–105.2)	1.1 (0.8–1.6)	1.2 (0.8–1.8)
>2,8000	105.9 (68.0–143.8)	1.5 (1.1–2.2)	1.4 (0.96–2.1)
P_{trend}	—	0.05	0.08

Actos Rx →
3% Regional or Advanced (3 of 90 pts Advanced)

non-Actos Rx →
9% Regional or Advanced

*Includes all potential confounders listed in Table 1 in the statistical model. †Never use of pioglitazone was the reference group for the calculation of the HR associated with ever use of pioglitazone and time, duration, and dose of pioglitazone use. ‡Also adjusted for use of other diabetes medications.

Pioglitazone & Bladder Cancer

Pioglitazone and Risk of Bladder Cancer among Diabetic Patients in France: a Population-Based Cohort Study

Neumann et al: Diabetologia 55:1953-62, 2012

Table 3 Risk of bladder cancer with increasing level of pioglitazone use during follow-up: French cohort of diabetic patients aged 40–79 years (followed between 2006 and 2009)

Age 40-79 followed 42 months – Excluded 1st 6 mths - NO SMOKING DATA OR HISTOLOGY

Actos: 155,535 – 175
DM2: 1,491,060 – 1,841

Exposure	Overall study population		Men		Women	
	HR[a] (95% CI)	*p* value	HR[a] (95% CI)	*p* value	HR[a] (95% CI)	*p* value
Cumulative dose (mg)[b]						
<10,500	1.12 (0.89, 1.40)	0.34	1.17 (0.92, 1.48)	0.21	0.77 (0.36, 1.65)	0.51
10,500–27,999	1.20 (0.93, 1.53)	0.16	1.24 (0.96, 1.60)	0.10	0.84 (0.35, 2.06)	0.71
≥28,000	1.75 (1.22, 2.50)	<0.01	1.88 (1.30, 2.71)	<0.01	0.57 (0.08, 4.11)	0.58
Duration of exposure (days)[b]						
<360	1.05 (0.82, 1.36)	0.68	1.10 (0.84, 1.43)	0.49	0.76 (0.34, 1.72)	0.51
360–719	1.34 (1.02, 1.75)	0.03	1.39 (1.06, 1.84)	0.02	0.87 (0.32, 2.35)	0.79
≥720	1.36 (1.04, 1.79)	0.02	1.44 (1.09, 1.91)	0.01	0.71 (0.22, 2.23)	0.56

Data are from SNIIRAM and PMSI databases

Reduced Head & Neck Cancer – HR 0.85 (CI 0.73-0.99; p=0.041)

[a] Adjusted HRs estimated from multivariate Cox model including age, sex (when applicable), level of pioglitazone use (i.e. cumulative dose and duration of exposure, respectively) and exposure to other glucose-lowering drugs

[b] Non-exposure was the reference group for calculating the HR associated with increasing level of pioglitazone use

Pioglitazone & Bladder Cancer

The Use of Pioglitazone and Risk of Bladder Cancer in People with Type 2 Diabetes: Nested Case-Control Study Azoulay et al: BMJ 344:e3645 (May 31, 2012)

Gen Practice Database: 600+ general practices in UK

Cohort: Type 2 Diabetics newly-treated w/ oral agents from 1988 to 2009 (included decade prior to Pio release)
Means: Age 64.1 yrs; F/U 4.6 yrs; HgbA1c 8.2%; 2.2 yrs use
Exposure → ever use of pioglitazone (**0.5%** of patients v **67%** started on Metformin → **579 pts on TZD!**)
All incident cases of bladder cancer → 470 in 115,727 → 89.4 per 10^6
General UK Population >65 yrs in 2008 → 73 per 10^6

Matched to ~20 controls → DOB, year of entry, gender, & F/U duration
Excluded those w/o 1 yr of data prior to entry → 376 cases & 6,699 controls → rate 1.83 (Pio v non-Pio)
>24 mths → rate 1.99 **(Unknown tumor grade or stage)**

Table 3| **Thiazolidinediones and risk of bladder cancer among cases of bladder cancer and matched controls***

Use of thiazolidinediones	No (%) of cases (n=376)	No (%) of controls (n=6699)	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)†
Never use of any thiazolidinedione	319 (84.8)	5856 (87.4)	1.00 (reference)	1.00 (Reference)
Exclusive ever use of pioglitazone	19 (5.1)	191 (2.9)	1.87 (1.13 to 3.09)	1.83 (1.10 to 3.05)
Exclusive ever use of rosiglitazone	36 (9.6)	596 (8.9)	1.16 (0.79 to 1.69)	1.14 (0.78 to 1.68)
Ever use of both pioglitazone and rosiglitazone	2 (0.5)	56 (0.8)	0.74 (0.18 to 3.08)	0.78 (0.18 to 3.29)

*Matched on year of birth, year of cohort entry, sex, and duration of follow-up.

Cancer Incidence >24 mths PIO Rx: 88 per 10^6

†Adjusted for excessive alcohol use, obesity, smoking status, HbA_{1c}, previous bladder conditions, previous cancer (other than non-melanoma skin cancer), Charlson comorbidity score, and ever use of other antidiabetic agents (metformin, sulfonylureas, insulin, and other oral hypoglycaemic agents).

Pioglitazone & Bladder Cancer

Association Between Longer Therapy With Thiazolidinediones and Risk of Bladder Cancer: A Cohort Study
Mamtani et al: J Natl Cancer Inst, 2012

Conclude: >5 yrs of TZDs may increase Ca; No Diff between TZDs

Used "New Use" Pts
UK Incidence: 73/100K

Age 60 v 65 (TZD v SU)
Male ~57%
Smokers ~66%
HgbA1c ~8.5%
DM Duration 3.8 v 2.3 y
Metformin 89% v 63%
Statins 74% v 59%

TZD: 37% previous SU

Cancer Stage Unknown

Table 2. Incidence rate and risk of bladder cancer in study (TZD) and comparator (SU) cohorts*

Exposure category	Incident cancers (PYS)	IR (95% CI), per 100 000 PYS	HR (95% CI), unadjusted	HR (95% CI), age- and sex-adjusted	HR (95% CI), fully adjusted†
New use of SU	137 (127 821)	107.2 (89.9 to 126.7)	1.00 (referent)	1.00 (referent)	1.00 (referent)
New use of TZD	60 (68 887)	87.1 (66.5 to 112.1)	0.81 (0.60 to 1.10)	1.03 (0.76 to 1.40)	0.93 (0.68 to 1.29)
	196,788				
TZD, duration of therapy, y					
<1	19 (18 239)	104.2 (62.7 to 162.7)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1 to <2	13 (16 629)	78.2 (41.6 to 133.7)	0.75 (0.37 to 1.53)	0.77 (0.38 to 1.56)	0.77 (0.38 to 1.57)
2 to <3	9 (10 790)	83.4 (38.1 to 158.3)	0.79 (0.36 to 1.76)	0.81 (0.37 to 1.81)	0.73 (0.32 to 1.67)
3 to <4	10 (7059)	141.7 (67.9 to 260.5)	1.36 (0.63 to 2.95)	1.38 (0.64 to 3.00)	1.24 (0.56 to 2.77)
4 to <5	3 (4004)	74.9 (15.5 to 218.9)	0.73 (0.21 to 2.48)	0.76 (0.22 to 2.58)	0.51 (0.12 to 2.19)
≥5	6 (3532)	169.9 (62.4 to 369.8)	1.67 (0.65 to 4.26)	1.83 (0.72 to 4.66)	1.87 (0.73 to 4.78)
P_{trend}‡	—	—	.35	.29	.47
SU, duration of therapy, y					
<1	56 (38 191)	146.6 (110.8 to 190.4)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1to <2	30 (29 464)	101.8 (68.7 to 145.4)	0.70 (0.44 to 1.09)	0.71 (0.45 to 1.11)	0.84 (0.52 to 1.34)
2 to <3	21 (18 126)	115.9 (71.7 to 177.1)	0.77 (0.46 to 1.29)	0.77 (0.46 to 1.29)	0.96 (0.56 to 1.63)
3 to <4	12 (12 282)	97.7 (50.5 to 170.7)	0.64 (0.34 to 1.21)	0.63 (0.33 to 1.19)	0.79 (0.41 to 1.50)
4 to <5	11 (8303)	132.5 (66.1 to 237.1)	0.92 (0.47 to 1.79)	0.90 (0.46 to 1.76)	0.94 (0.45 to 1.96)
≥5	7 (11 874)	59.0 (23.7 to 121.5)	0.42 (0.18 to 0.94)	0.41 (0.18 to 0.93)	0.55 (0.24 to 1.25)
P_{trend}‡	—	—	.07	.06	.25
	15,406 – 8%				
Duration of therapy, y					
<1	—	—	0.71 (0.42 to 1.19)	0.88 (0.52 to 1.50)	0.95 (0.55 to 1.63)
1 to <2	—	—	0.76 (0.40 to 1.46)	0.96 (0.50 to 1.84)	0.87 (0.45 to 1.69)
2 to <3	—	—	0.73 (0.33 to 1.59)	0.93 (0.43 to 2.04)	0.72 (0.32 to 1.63)
3 to <4	—	—	1.50 (0.65 to 3.47)	1.94 (0.83 to 4.50)	1.50 (0.63 to 3.58)
4 to <5	—	—	0.56 (0.15 to 2.00)	0.74 (0.21 to 2.66)	0.51 (0.11 to 2.38)
≥5	—	—	2.84 (0.95 to 8.44)	3.90 (1.31 to 11.6)	3.25 (1.08 to 9.71)
P_{trend}‡	—	—	.06	.04	.20

Pioglitazone & Bladder Cancer

Benefits of Pioglitazone:

- Lowers blood sugars and HgbA1c by improving insulin resistance
- Preserves beta-cells and normalizes insulin secretory patterns
- Does not cause hypoglycemia
- Reduces visceral fat mass
- Lowers Triglycerides
- Raises HDL & apoA-I (ABCA1, LPL)
- Shrinks arterial plaques
- Reduces cardiovascular events & improves LV compliance
- Reduces FFAs, PAI-1, Endothelin-1, hsCRP, & SMC proliferation
- Treats Steatohepatitis
- Reduces microAlbuminuria
- Poss benefits in CNS disorders, IBD, asthma, cystic fibrosis, & arthritis

Pioglitazone & Bladder Cancer

Adverse Effects of Pioglitazone:

- Fluid Retention (increases cardiac output; no effect on heart structure)
- Increases subcutaneous fat mass (removes TGs from organs & muscle)
- Increases appetite (by suppressing Leptin)
- Raises LDL (mild – probably by reducing portal insulin which down-regulates LDL-R)
- Reduces bone mass & increases peripheral fractures in post-menopausal women

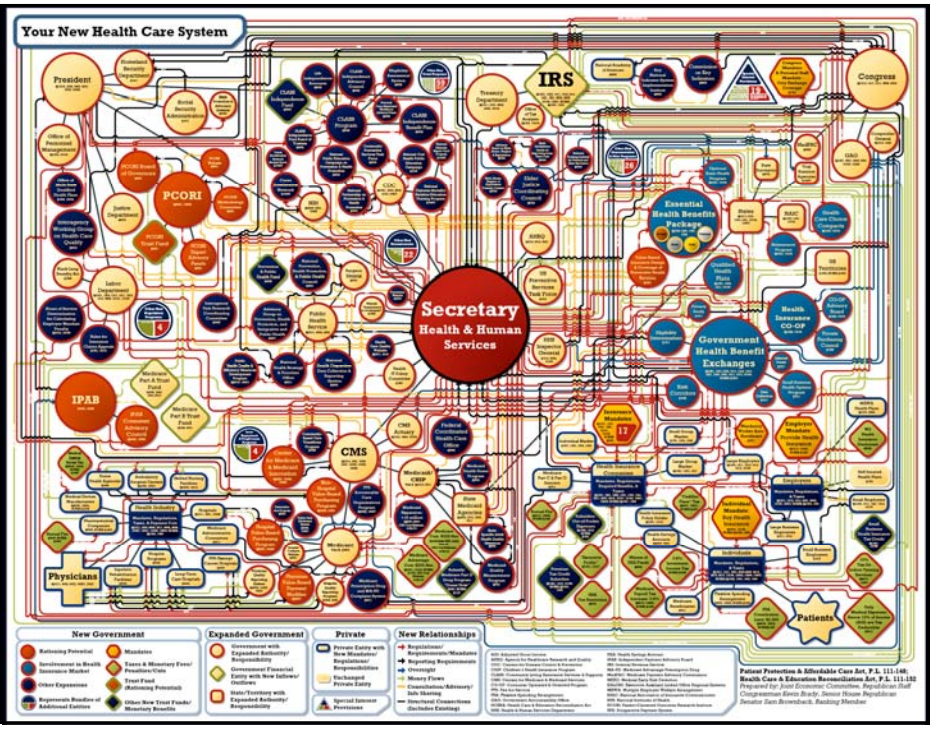
Pioglitazone & Bladder Cancer

Findings:

- PPARg receptors are found in normal bladder cells, low-grade tumors, & some high-grade tumors
- PPARg agonists inhibit growth “in vivo” in normal cells, low-grade tumors, & some high-grade tumors
- Pio RCT (1) → increased freq of Dx within 1st yr (8/3); most others had risk factors for B Cancer
- Rosi RCT (2) → no increase
- Cohort Studies → 20% to 80% increased diagnosis of Bladder Cancer
  - One study showed 3-fold increase in more advanced cancer in non-Pioglit group (9% v 3%)
  - Other studies did not report tumor grade or stage
- There is some suggestion of increased diagnoses with increasing treatment duration

- Questions:
  - Does Pioglitazone cause bladder cancer?
  - Does Pioglitazone promote the growth or malignancy of bladder cancer?
  - Does Pioglitazone increase the early diagnosis and, possibly, the cure rate of bladder cancer?
  - Does Pioglitazone prevent bladder and other cancers?

One-Third of the administrative structure of the new Health Care System

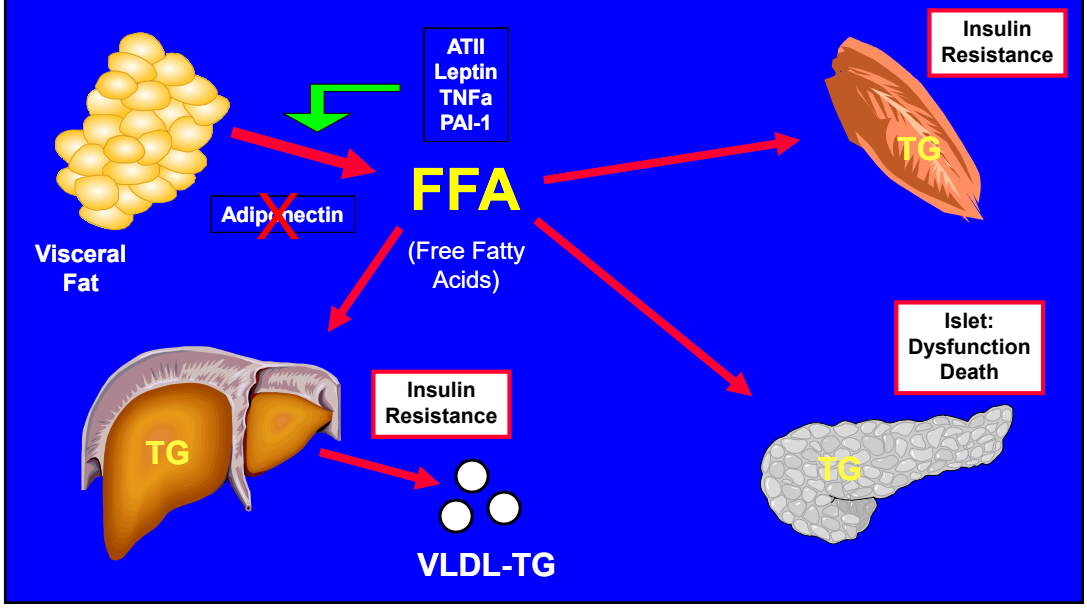


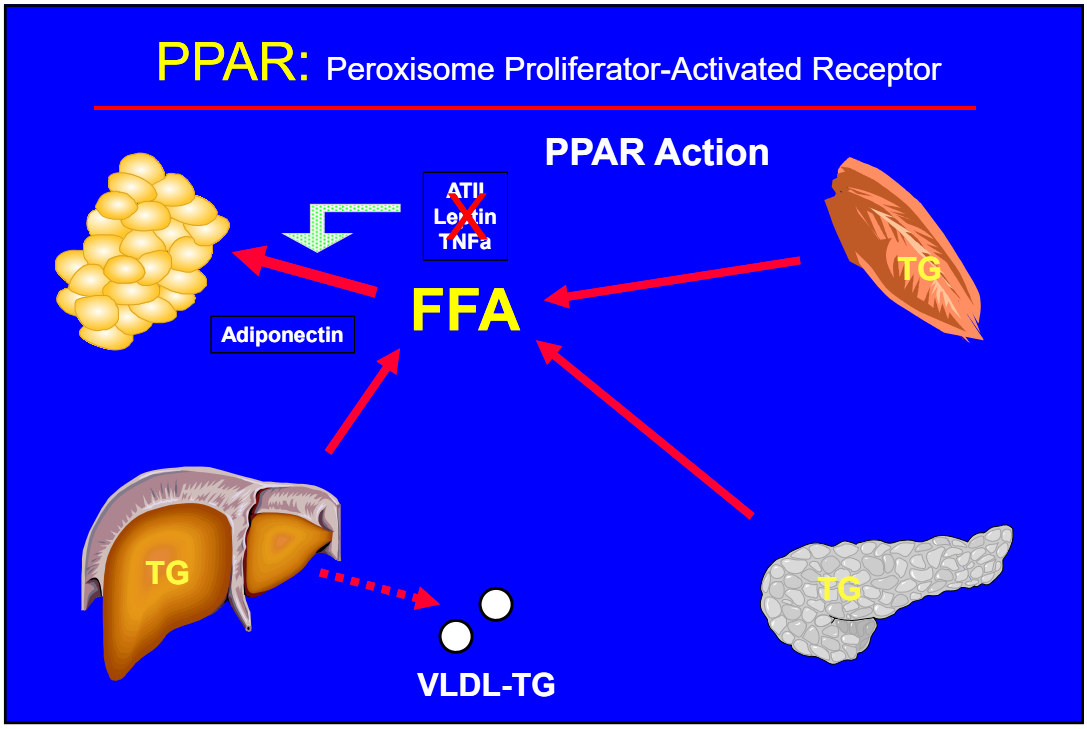
Thiazolidinediones 2010

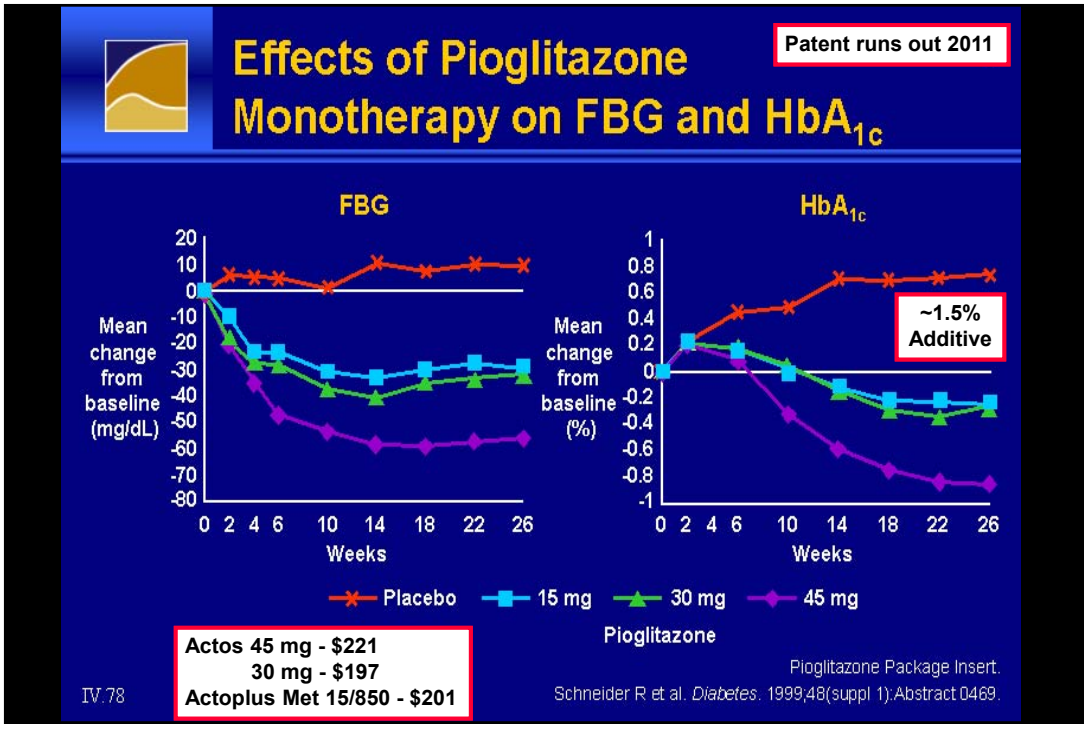
Should the FDA be Making Clinical Decisions?

Thomas A. Hughes, M.D.
Professor of Medicine
Division of Endocrinology, Metabolism, and Diabetes
University of Tennessee Health Science Center
www.uthsc.edu/endocrinology

Insulin Resistance Syndrome

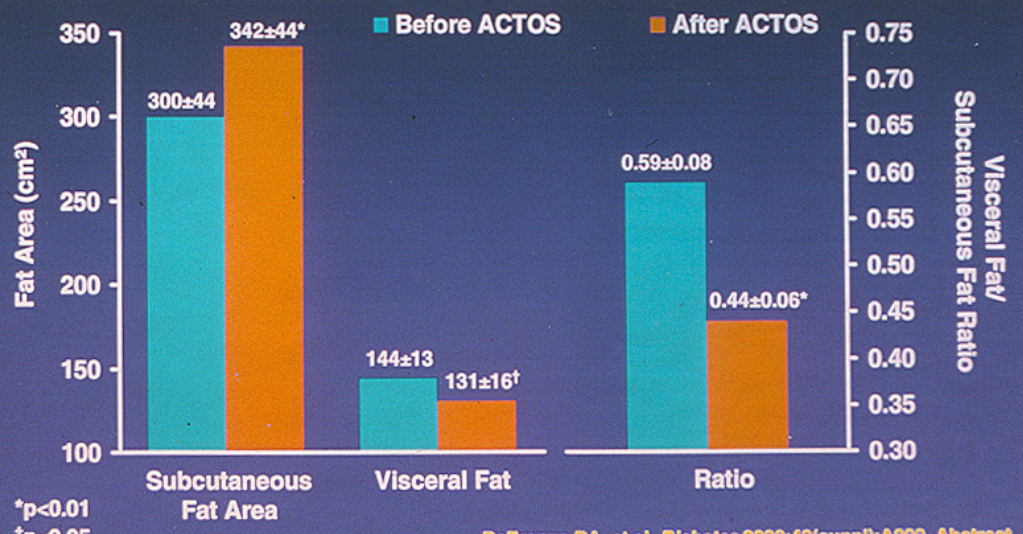



PPAR: Peroxisome Proliferator-Activated Receptor
PPAR Action
ATII
Leptin
TNFa
Adiponectin
FFA
TG
TG
TG
VLDL-TG


Effects of Pioglitazone Monotherapy on FBG and HbA1c
Patent runs out 2011
FBG
HbA1c
Mean change from baseline (mg/dL)
Mean change from baseline (%)
Weeks
Weeks
~1.5% Additive
Placebo
15 mg
30 mg
45 mg
Pioglitazone
Actos 45 mg - $221
30 mg - $197
Actoplus Met 15/850 - $201
IV.78
Pioglitazone Package Insert.
Schneider R et al. Diabetes. 1999;48(suppl 1):Abstract 0469.

ACTOS® (pioglitazone HCl)

Effect of ACTOS on Abdominal Fat Distribution

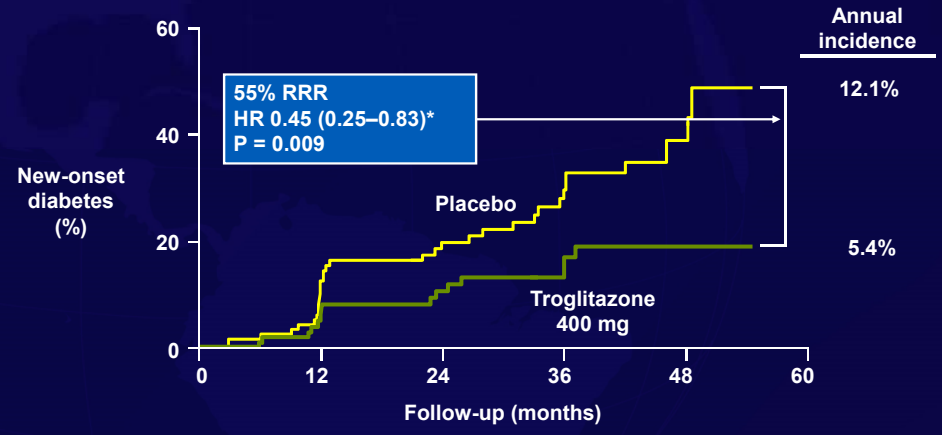


*p<0.01
†p<0.05

DeFronzo RA, et al. *Diabetes* 2000;49(suppl):A299. Abstract

TRIPOD: Treating insulin resistance reduces incidence of type 2 diabetes

TRoglitazone In Prevention Of Diabetes
n = 236 Hispanic women with gestational diabetes



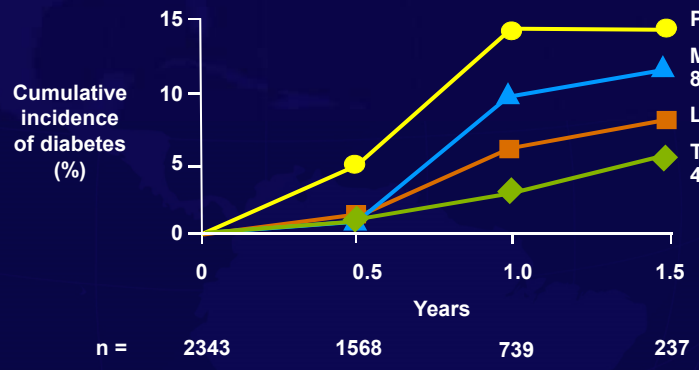
*Unadjusted

Buchanan TA et al. *Diabetes*. 2002;51:2796-803.

TZDs blunt diabetes progression

Pre-diabetes

Diabetes Prevention Program



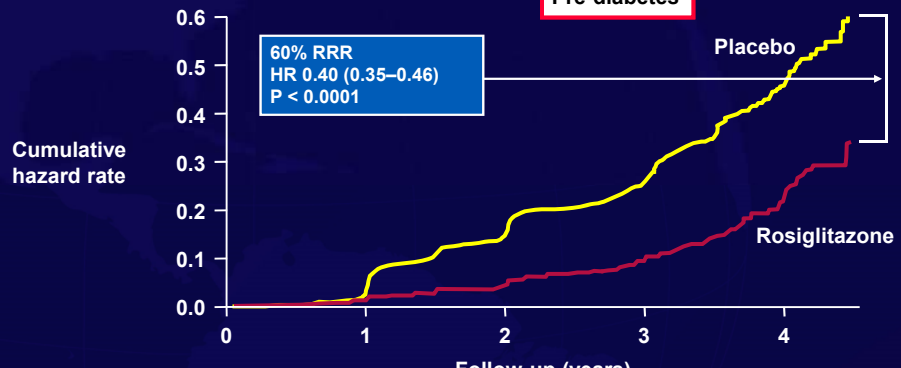
↓75% vs placebo
P < 0.001

*Withdrawn from study after 1.5 yr

DPP Research Group. *Diabetes*. 2005;54:1150-6.

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

Pre-diabetes



No. at risk					
Placebo	2634	2470	2150	1148	177
Rosiglitazone	2635	2538	2414	1310	217

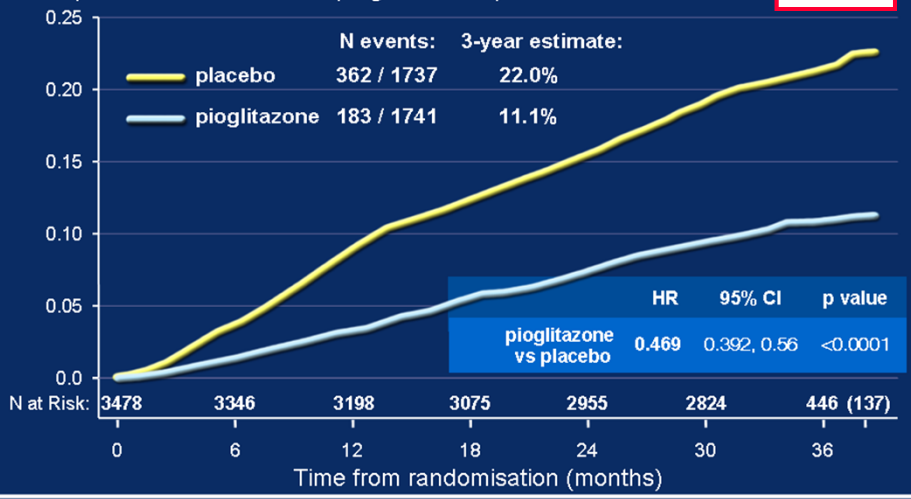
DREAM Trial Investigators. *Lancet*. 2006.

Time to Permanent Insulin Use

Proactive

Kaplan-Meier event rate of progression to permanent Insulin use

Diabetics

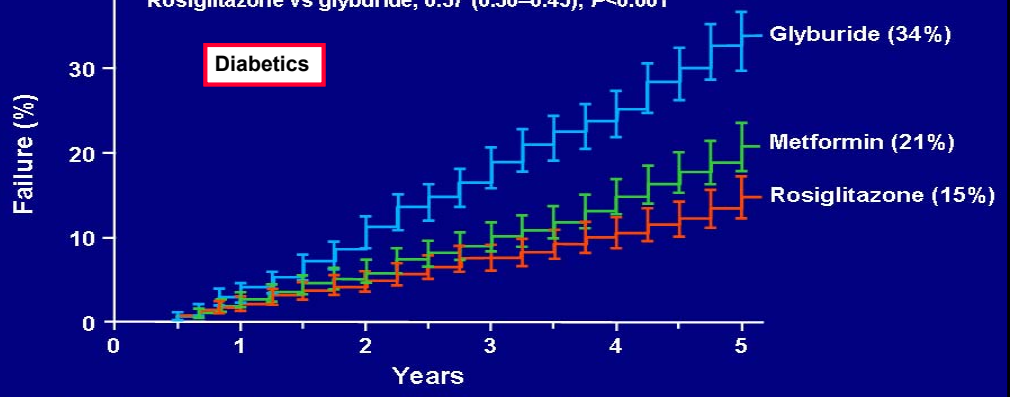


proactive-results.com

ADOPT: Cumulative Incidence of Monotherapy Failure at 5 Years*

Hazard ratio (95% CI)
Rosiglitazone vs metformin, 0.68 (0.55–0.85); *P*<0.001
Rosiglitazone vs glyburide, 0.37 (0.30–0.45); *P*<0.001

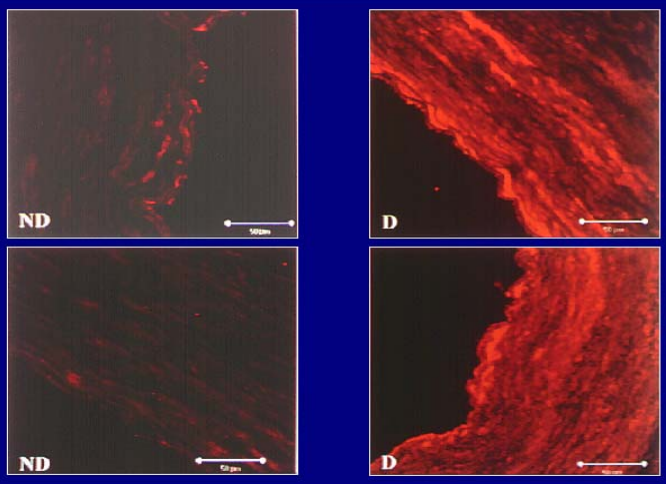
Diabetics



*Failure defined as a fasting plasma glucose level >180 mg/dL.
ADOPT=A Diabetes Outcome Progression Trial.

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

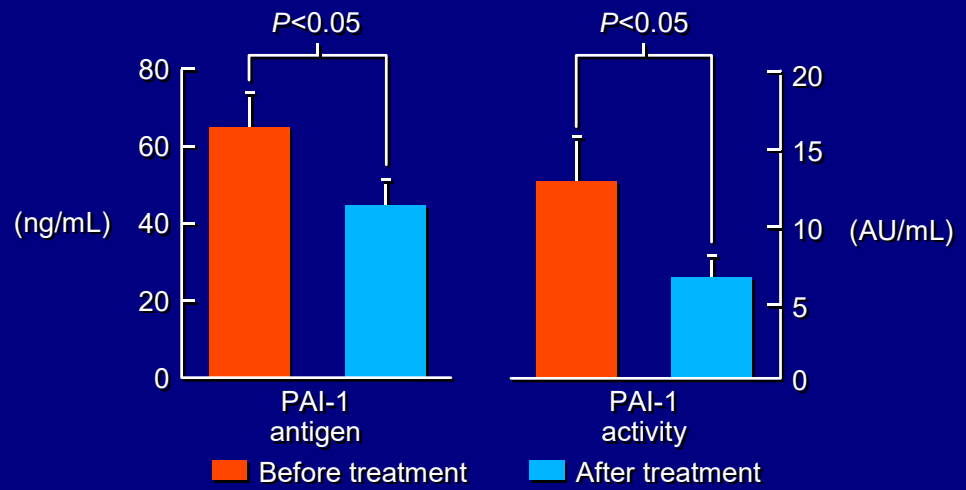
PAI-1 in Internal Mammary Arteries of People With and Without Diabetes



ND = no diabetes; D = diabetes.

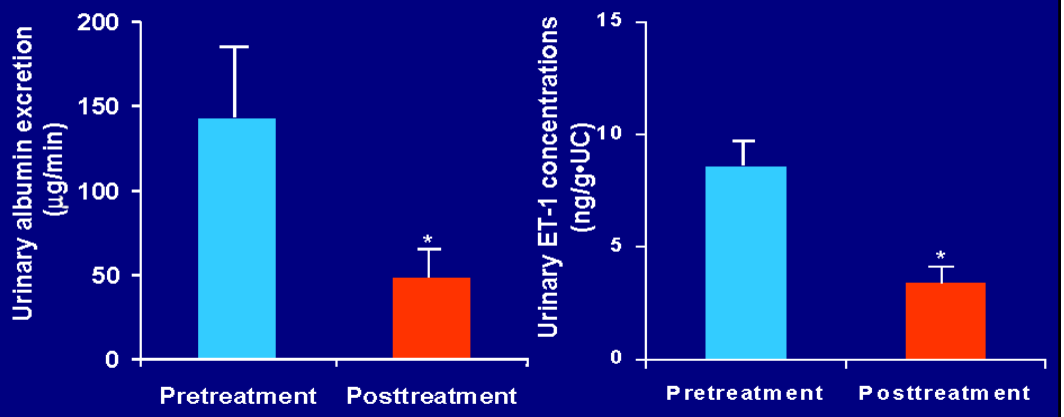
Pandolfi A et al. *Arterioscler Thromb Vasc Biol*. 2001;21:1378-1382.

Troglitazone Reduces PAI-1 Antigen and Activity in PCOS



Ehrmann DA et al. *J Clin Endocrinol Metab*. 1997;82:2108-2116.

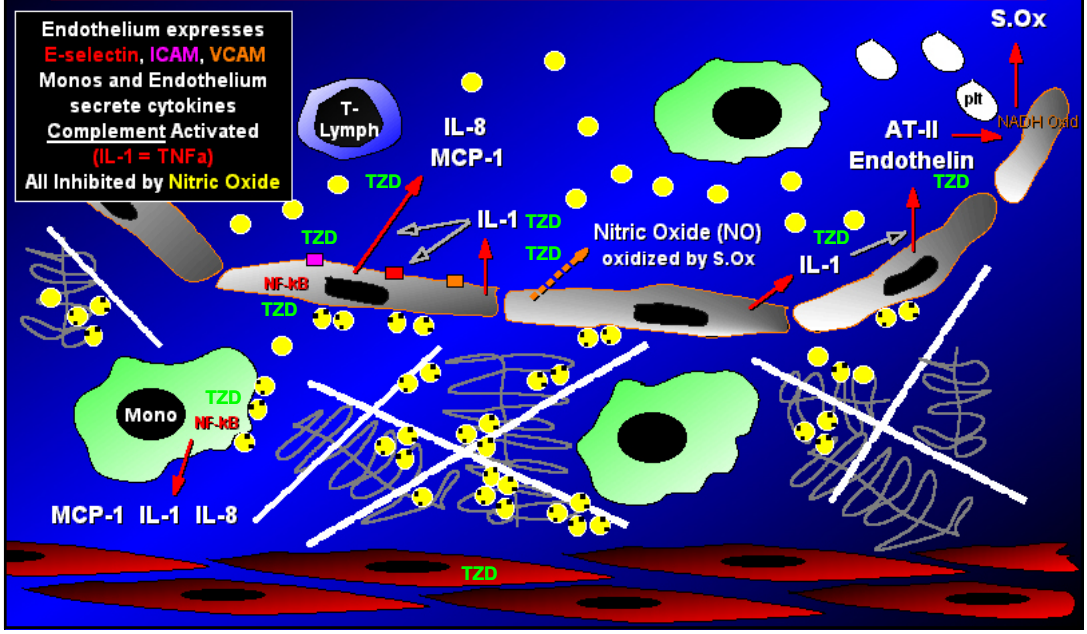
Effect of Pioglitazone on Urinary Albumin and Endothelin-1 Excretion in Patients With Microalbuminuria



*P<0.01.

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

Atherosclerosis: Cellular Response to oxLPs

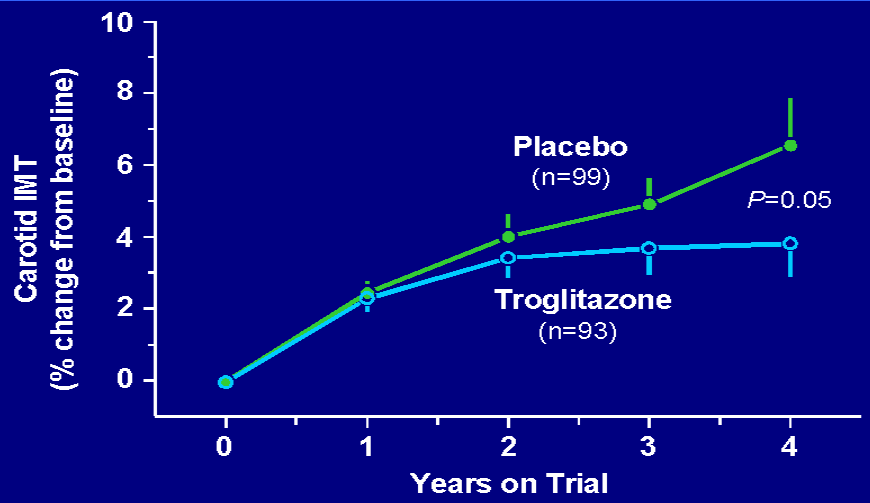


TZDs: Focus on PPARγ activation

- Reduces insulin resistance and HgbA1c
- Preserves pancreatic β-cell function
- Improves CV risk profile
  - Improves dyslipidemia (pioglitazone: ↑HDL, ↓LDL density, ↓ TG)
  - ↓ Renal microalbumin excretion
  - ↓ Blood pressure
  - ↓ VSMC proliferation/migration in arterial wall
  - ↓ PAI-1 levels
  - ↓ C-reactive protein levels
  - ↑ Adiponectin
  - ↓ Free fatty acids

Inzucchi SE. *JAMA*. 2002;287.360-72.

Effects of Troglitazone on Carotid Artery IMT: TRIPOD



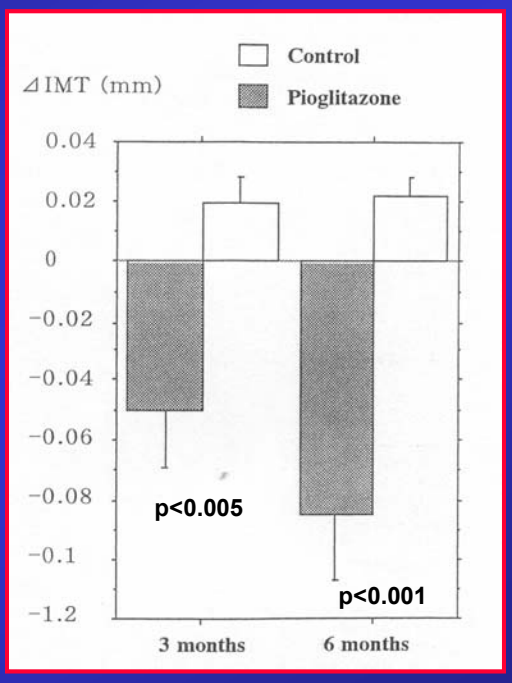
Xiang AH et al. *Diabetes*. 2002;51 (suppl 2):A703 (abstract).

Pioglitazone
Carotid Ultrasound

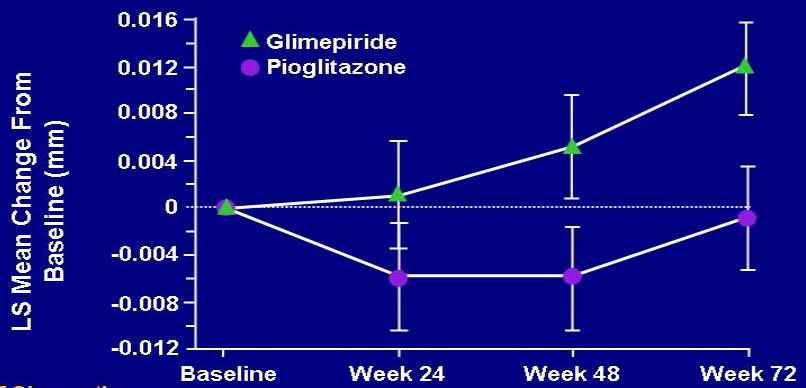
106 Japanese with Type 2 DM
Randomized: Pio 30 mg or Placebo
Age: 62.2 ± 1.1 yrs ~ 55% male

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

Several similar trials with Rosiglit have shown improvement or no change; none showed an increase



CHICAGO: Change in Mean Carotid Intima-Media Thickness



No. of Observations	Baseline	Week 24	Week 48	Week 72
Glimepiride	186	170	186	186
Pioglitazone	175	166	175	175

CHICAGO=Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone.
Values are least-square (LS) means using last observation carried forward.

Mazzone T et al. *JAMA*. 2006;296.

Effect of Rosiglitazone on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History Trial

Table 5. IVUS End Points

Mean Value of IVUS Measurement (SD)	Glipizide			Rosiglitazone			Treatment Difference (95% CI)
	Baseline	Follow-Up	Change* (95% CI)	Baseline	Follow-Up	Change* (95% CI)	
Mean (SD) PAV†	40.6 (11.0)	41.0 (11.2)	0.43 (−0.22, 1.08)	40.4 (11.8)	40.2 (11.4)	−0.21 (−0.86, 0.44)	−0.64 (−1.46, 0.17)§
Mean (SD) TAV_N, mm^3‡	232.8 (115.2)	233.2 (116.5)	1.2 (−2.68, 5.08)	226.1 (100.6)	221.6 (100.7)	−3.9 (−7.82, −0.02)‖	−5.12 (−9.98, −0.26)¶
Mean (SD) atheroma volume in the most diseased 10-mm segment, mm^3‡	75.6 (32.6)	72.2 (33.3)	−3.6 (−5.31, −1.80)#	71.0 (30.0)	66.0 (30.7)	−5.3 (−7.04, −3.51)#	−1.7 (−3.93, 0.49)
Mean (SD) total vessel volume, mm^3	609.4 (311.8)	603.1 (304.3)	−4.6 (−11.40, 2.27)	555.1 (298.0)	547.2 (298.2)	−8.1 (−14.9, −1.32)**	−3.6 (−12.15, 5.02)
Mean (SD) total lumen volume, mm^3	359.7 (195.7)	353.5 (192.2)	−4.9 (−11.88, 2.05)	332.7 (192.4)	328.7 (191.9)	−4.6 (−11.52, 2.34)	0.3 (−8.40, 9.05)

Primary - PAV: Percent Atheroma Volume – p=0.12 vs glip
Secondary - TAV: Total Atheroma Volume – p=0.04 vs glip

All changes in Rosiglit group were negative →
AV in most diseased vessel & total vessel volume were significantly reduced

Circulation 121:1176-1187, 2010

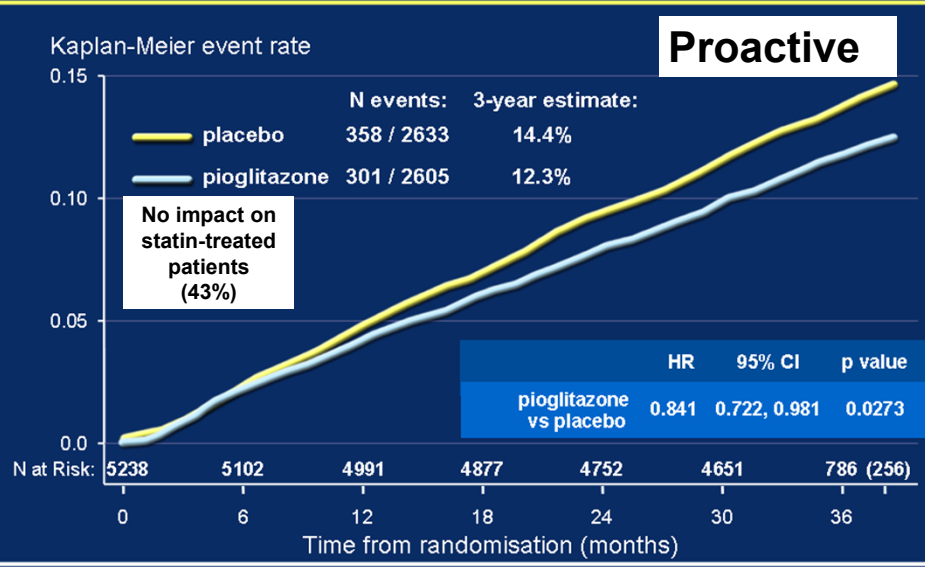
Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Type 2 DM

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)		*P* Value[a]
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
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

Time to Death, MI (Excluding Silent) or Stroke



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proactive-results.com

Adverse Events Associated With Thiazolidinedione Treatment

- Hypoglycemia
  - observed when used in combination with insulin and/or sulfonylurea
- Weight gain
  - averages 1-5 kg (2-11 lbs), correlated with improvement in A1C
  - greatest in combination with sulfonylurea and insulin
  - attenuates when A1C stabilizes
  - associated with redistribution of fat
  - can be limited by calorie restriction
- Fluid retention
  - most common when used in combination with insulin
  - rarely severe
  - evidence that fluid retention in thiazolidinedione-treated subjects with heart failure is more likely to be peripheral than pulmonary
  - likely PPAR effect on renal tubule ?

Asnani S et al. *Curr Med Res Opin.* 2003;19:609-613. Nesto RW et al. *Diabetes Care.* 2004;27:256-263.
Hussein Z et al. *Med J Aust.* 2004;181:536-539. Tang WHW et al. *J Am Coll Cardiol.* 2003;41:1394-1398.
Krentz AJ, Bailey CJ. *Drugs.* 2005;65:385-411. Zhang H et al. *PNAS.* 2005;102:9406-9411.

ACTOS™ (pioglitazone HCl) Summary of Adverse Events

Echocardiography Conclusions

- No difference between placebo and any treatment for:
  - Interventricular septal thickness
  - Left ventricular internal dimension
  - Left ventricular wall thickness
  - Left ventricular mass
  - Fractional shortening
- No difference within treatment groups between baseline and endpoints
- No evidence of echocardiographic changes in patients receiving ACTOS for up to 2 years

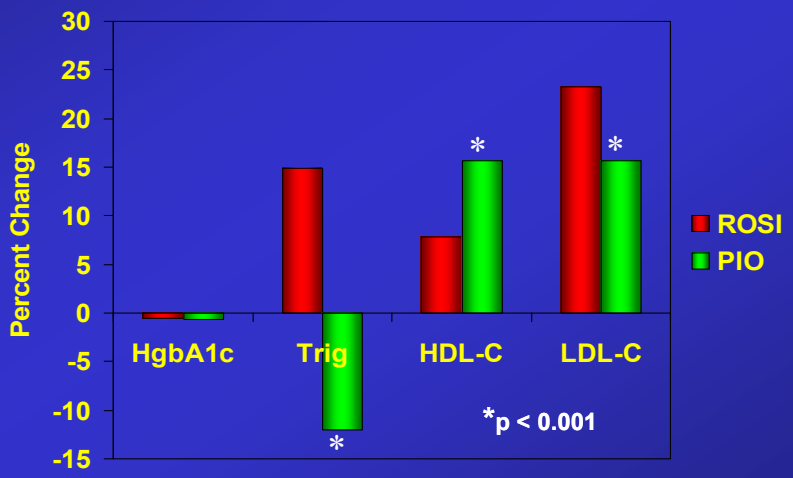
Takeda Pharmaceuticals America, Data on file 120 Day Safety Update

Comparison of Lipid and Glycemic Effects of Glitazones: GLAI

Rosiglitazone
4 mg BID
Patients: 402

Pioglitazone
45 mg qD
Patients: 400

24 wk study



Goldberg et al; AHA Annual Meeting, Nov, 2004

Comparison of Lipid and Glycemic Effects of Glitazones: GLAI

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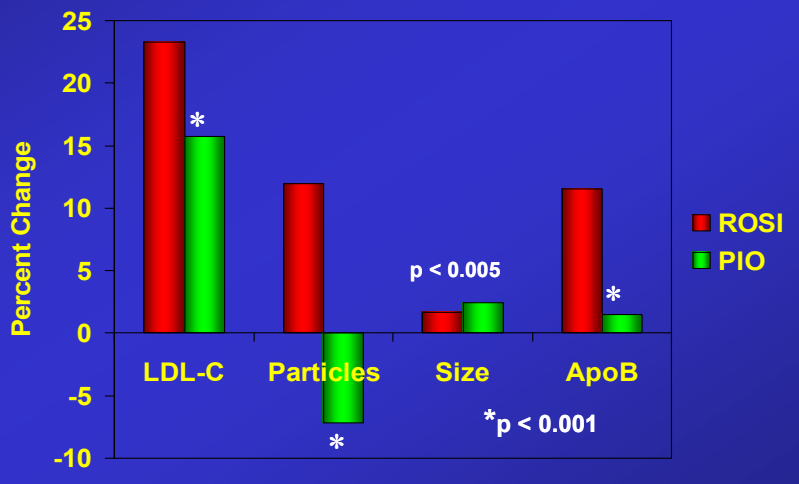


Goldberg et al; AHA Annual Meeting, Nov, 2004

VBWG

Meta-analysis: MI risk with rosiglitazone

n = 15,560 on rosiglitazone; n = 12,283 on comparator drug or placebo

Study	Rosiglitazone group No. of events/Total no. (%)	Control group No. of events/Total no. (%)	Odds ratio (95% CI)	P
Myocardial infarction				
Small trials combined	44/10,280 (0.43)	22/6105 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1456 (1.85)	41/2895 (1.44)	1.33 (0.80–2.21)	0.27
Overall	60 / 10,000	62 / 10,000	1.43 (1.03–1.98)	0.03

Is a p-value of 0.03 an adequate level of significance for this type of analysis?

Nissen SE, Wolski K. *N Engl J Med.* 2007;356.

VBWG

Meta-analysis: CV mortality risk w/ rosiglitazone

Study	Rosiglitazone group No. of events/Total no. (%)	Control group No. of events/Total no. (%)	Odds ratio (95% CI)	P
Cardiovascular death	38 / 10,000 (19)	19 / 10,000	(just small trials)	
Small trials combined	25/6557 (0.38)	7/3700 (0.19)	2.40 (1.17–4.91)	0.02
DREAM	12/2365 (0.51)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1456 (0.14)	5/2854 (0.18)	0.80 (0.17–3.86)	0.78
Overall	38 / 10,000 (14)	24 / 10,000	1.64 (0.98–2.74)	0.06
Include all patients:	39 / 14,371 (17) 27 / 10,000 (8)	22 / 11,634 19 / 10,000		

The real issue is that there is no indication that rosi will prevent CV events as pio does!
Meta-anal: Pio 4.4% vs Controls 5.7% (MI, CVA, & death); Hosp CHF 2.3% vs 1.8% (JAMA 2007)

Nissen SE, Wolski K. *N Engl J Med.* 2007;356.

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)
(Multi-center, randomized, open-label trial)

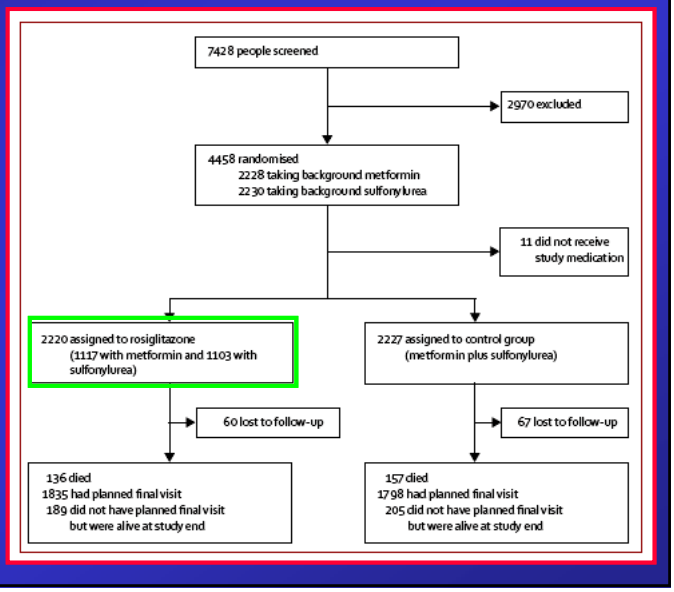
364 centers in 25 countries in Europe and Australia

Age: 40-75 years
BMI >25
HgbA1c: 7.0 – 9.0 on max MonoRx

Exclusion: CV event in 3 mths or CHF

Recruitment: Apr 2001 to Apr 2003
Final visits: Aug to Dec 2008
Interim analysis: 2006

Rescue Rx if HgbA1c >8.5% →
Rosi: Add Metf or Sulfon
Next: Change Rosi to Insulin
M+S: Change to Insulin



Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)

(Multi-center, randomized, open-label trial)

Similar Demographics

Except 'Stable Angina'

	Background metformin		Background sulfonylurea	
	Rosiglitazone (N=1117)	Sulfonylurea (N=1105)	Rosiglitazone (N=1103)	Metformin (N=1122)
Age (years)	57·0 (8·0)	57·2 (8·1)	59·8 (8·3)	59·7 (8·2)
Sex (male)	601 (53·8%)	584 (52·9%)	541 (49·0%)	568 (50·6%)
Ethnic origin (white)	1105 (98·9%)	1087 (98·4%)	1095 (99·3%)	1112 (99·1%)
Ischaemic heart disease	171 (15·3%)	164 (14·8%)	212 (19·2%)	225 (20·1%)
Stable angina	105 (9·4%)	86 (7·8%)	122 (11·1%)	144 (12·8%)
Myocardial infarction	50 (4·5%)	62 (5·6%)	54 (4·9%)	52 (4·6%)
Stroke	26 (2·3%)	20 (1·8%)	29 (2·6%)	33 (2·9%)
Transient ischaemic attack	27 (2·4%)	25 (2·3%)	24 (2·2%)	22 (2·0%)
Peripheral arterial disease	80 (7·2%)	96 (8·7%)	117 (10·6%)	117 (10·4%)
Heart failure	4 (0·4%)	4 (0·4%)	8 (0·7%)	5 (0·4%)
Retinopathy	73 (6·5%)	77 (7·0%)	141 (12·8%)	157 (14·0%)
Current smoker	199 (17·8%)	194 (17·6%)	164 (14·9%)	149 (13·3%)
Microalbuminuria or proteinuria*	225 (20·1%)	192 (17·4%)	215 (19·5%)	219 (19·5%)
Duration from diabetes diagnosis (years)	6·1 (4·2)	6·3 (4·4)	7·9 (5·5)	7·9 (5·2)
Weight (kg)	93·5 (16·5)	93·3 (16·3)	85·0 (14·5)	84·3 (14·4)
Body-mass index (kg/m²)	32·8 (5·0)	32·7 (5·2)	30·3 (4·1)	30·1 (4·3)
HbA_{1c} (%)	7·8 (0·7)	7·8 (0·7)	8·0 (0·7)	8·0 (0·7)
Fasting plasma glucose (mmol/L)	9·5 (2·1)	9·5 (2·1)	10·2 (2·6)	10·1 (2·3)
Systolic blood pressure (mm Hg)	140 (16)	139 (16)	138 (15)	138 (15)
Diastolic blood pressure (mm Hg)	84 (9)	83 (9)	82 (8)	82 (8)
Heart rate (beat/min)	74 (9)	74 (9)	73 (9)	74 (9)
LDL cholesterol (mmol/L)	3·2 (0·9)	3·2 (0·9)	3·4 (0·9)	3·4 (0·9)
HDL cholesterol (mmol/L)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)
Triglyceride (mmol/L)	2·3 (1·3)	2·4 (1·5)	2·3 (1·7)	2·2 (1·6)
Serum creatinine (μmol/L)	63·7 (16·1)	64·5 (21·1)	65·3 (16·3)	65·3 (16·5)

Data are number (%) or mean (SD). HbA_{1c}=haemoglobin A_{1c}. *Microalbuminuria is defined as albumin to creatinine ratio >2·5 mg/mmol (men) or >3·5 mg/mmol (women).

Table 1: **Baseline characteristics of the people with diabetes studied, divided by background treatment stratum and randomised therapy group**

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)

(Multi-center, randomized, open-label trial)

	Background metformin			Background sulfonylurea		
	Rosiglitazone	Sulfonylurea	p	Rosiglitazone	Metformin	p
HbA_{1c} (%)	−0·28 (0·03)	0·01 (0·04)	<0·0001	−0·44 (0·03)	−0·18 (0·04)	<0·0001
LDL cholesterol (mmol/L)†	−0·33 (0·04)	−0·50 (0·03)	0·0001	−0·22 (0·04)	−0·53 (0·03)	<0·0001
HDL cholesterol (mmol/L)†	0·12 (0·01)	0·04 (0·01)	<0·0001	0·11 (0·01)	0·07 (0·01)	0·002
Triglycerides (mmol/L)†	−0·14 (0·04)	−0·02 (0·05)	0·046	−0·13 (0·04)	−0·14 (0·04)	0·82
Weight (kg)	3·8 (0·24)	0·0 (0·2)	<0·0001	4·1 (0·2)	−1·5 (0·2)	<0·0001
Blood pressure (mm Hg)						
Systolic	−1·5 (0·5)	−2·2 (0·5)	0·31	−1·5 (0·5)	−0·9 (0·5)	0·34
Diastolic	−3·6 (0·3)	−3·4 (0·3)	0·72	−3·1 (0·3)	−2·4 (0·3)	0·060

Data are mean (SE). HbA_{1c}=haemoglobin A_{1c}. *Estimates of 5-year changes obtained with a baseline-adjusted repeated-measures model for all patient data (and p values for treatment difference). †Lipids were not measured after initiation of any insulin therapy.

Table 2: **Mean change in cardiovascular risk factors from baseline to 5-year follow-up***

Rosiglit: **Lower HgbA1c**
Less reduction in LDL (Despite more statin use: 55% vs 46%)
Better HDL
More Weight gain (Despite more loop diuretics: 13% vs 8%)

No effect on BP
Minimal diff in TGs

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)
(Multi-center, randomized, open-label trial)

	Rosiglitazone		Active control	
	Baseline (N=2220)	At 5 years (N=1918)	Baseline (N=2227)	At 5 years (N=1892)
Statins	400 (18·0%)	1059 (55·2%)	428 (19·2%)	871 (46·0%)
Fibrates	131 (5·9%)	211 (11·0%)	121 (5·4%)	203 (10·7%)
Thiazide diuretics	209 (9·4%)	411 (21·4%)	225 (10·1%)	368 (19·5%)
Loop diuretics	69 (3·1%)	250 (13·0%)	68 (3·1%)	153 (8·1%)
β-adrenergic blockers	501 (22·6%)	716 (37·3%)	465 (20·9%)	700 (37·0%)
ACE inhibitors/A2R blockers	957 (43·1%)	1196 (62·4%)	937 (42·1%)	1216 (64·3%)
Calcium channel blockers	424 (19·1%)	615 (32·1%)	481 (21·6%)	685 (36·2%)
Nitrates	132 (5·9%)	196 (10·2%)	140 (6·3%)	200 (10·6%)
Antiplatelet agents	445 (20·0%)	683 (35·6%)	422 (18·9%)	689 (36·4%)

Data are number (%). ACE=angiotensin-converting enzyme. A2R=angiotensin 2 receptor.

Table 3: **Concomitant cardiovascular medications at baseline and at 5 years**

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)
(Multi-center, randomized, open-label trial)

	Rosiglitazone (N=2220)	Active control (N=2227)	HR	Rate difference per 1000 person-years	p
CV death or CV hospitalisation	321	323	0·99 (0·85 to 1·16)	−0·2 (−4·5 to 4·1)	0·93
All-cause death	136	157	0·86 (0·68 to 1·08)	−1·7 (−4·3 to 0·9)	0·19
CV death	60	71	0·84 (0·59 to 1·18)	−0·9 (−2·7 to 0·9)	0·32
Myocardial infarction*	64	56	1·14 (0·80 to 1·63)	0·6 (−1·1 to 2·4)	0·47
Stroke*	46	63	0·72 (0·49 to 1·06)	−1·4 (−3·1 to 0·2)	0·10
CV death, MI, or stroke	154	165	0·93 (0·74 to 1·15)	−1·0 (−3·9 to 1·9)	0·50
Heart failure*	61	29	2·10 (1·35 to 3·27)	2·6 (1·1 to 4·1)	0·0010

Data are numbers, HR (95% CI), or rate differences (95% CI). CV=cardiovascular. MI=myocardial infarction. *Fatal and non-fatal.

Table 4: **Deaths and hospitalisations from cardiovascular causes**

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)
(Multi-center, randomized, open-label trial)

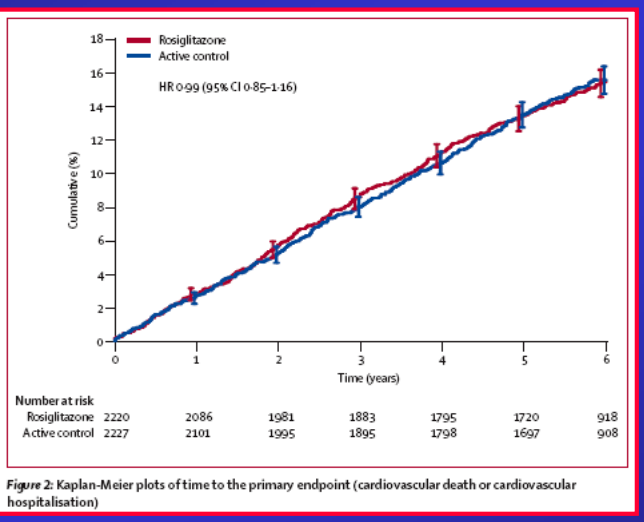
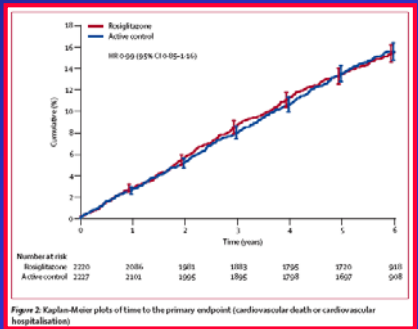
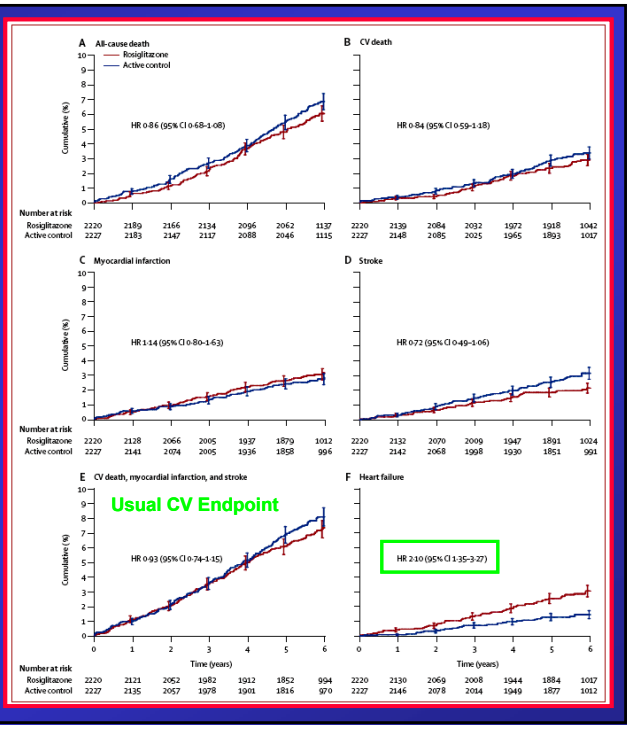


Figure 2: Kaplan-Meier plots of time to the primary endpoint (cardiovascular death or cardiovascular hospitalisation)

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)
(Multi-center, randomized, open-label trial)





Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)

(Multi-center, randomized, open-label trial)

Rosi Reduced:

- All Cause Deaths (-13%)
- CV Death (-15%)
- Sudden Death (-33%)
- MI Death (-30%)
- Stroke Death (-100%)
- Stroke Hosp (-27%)
- Amputations (-66%)
- Invasive Procedures (-15%)

Rosi Increased:

- CHF death (+500% - 8)
- CHF Hosp (+50%)
- MI Hosp (+15%)

No Difference: CV Hosp

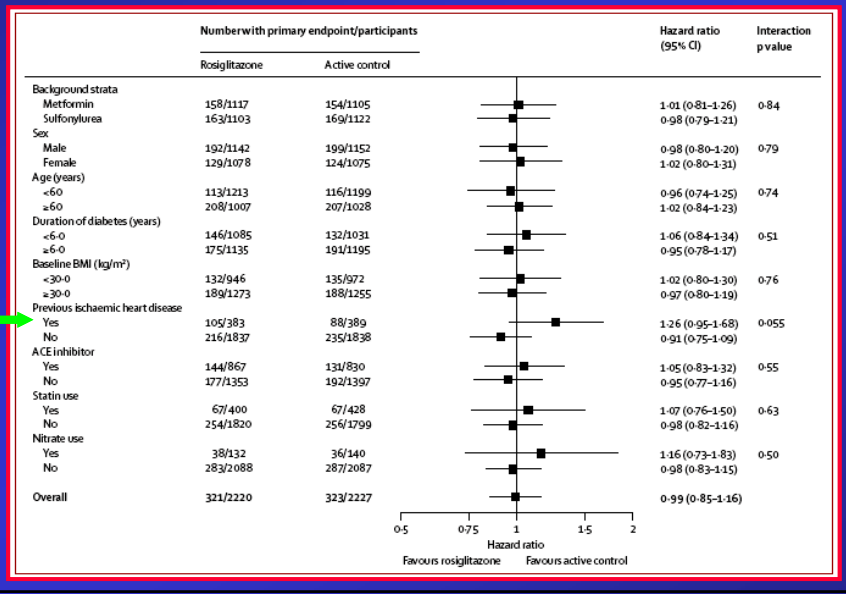
	Rosiglitazone (N=2220)	Active control (N=2227)
Deaths		
All cause	136	157
Cardiovascular death	60	71
Sudden death	8	12
Myocardial infarction	7	10
Heart failure	10	2
Stroke	0	5
Other acute vascular event	1	5
Other cardiovascular mortality	6	4
Unattributed cause*	28	33
Cardiovascular hospitalisation	288 (483)	284 (490)
Invasive cardiovascular procedures	85 (99)	100 (116)
Myocardial infarction	60 (66)	52 (57)
Stroke	46 (51)	63 (67)
Heart failure	57 (69)	29 (36)
Atrial fibrillation	35 (39)	36 (47)
Angina pectoris	25 (31)	26 (29)
Unstable angina pectoris	24 (28)	24 (28)
Transient ischaemic attack	10 (10)	10 (10)
Amputation of extremities	5 (6)	15 (23)
Other	71 (84)	66 (77)

Data are all events not just first events, and so may add up to higher numbers than those given in table 4. *Fatal events of unknown cause were regarded as being of cardiovascular origin, unless evidence existed to adjudicate them otherwise.

Table 5: Patients with events (numbers of events) for various cardiovascular hospitalisations or deaths

Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)

(Multi-center, randomized, open-label trial)



Rosiglitazone: CV Outcomes in combo therapy for DM#2 (RECORD)

(Multi-center, randomized, open-label trial)

Rosi reduces Pancr Ca (85%) and Hyperglycemia (50%)
Doubles fractures (in women) & CHF

	Women		Men		All	
	Rosiglitazone (N=1078)	Active control (N=1075)	Rosiglitazone (N=1142)	Active control (N=1152)	Rosiglitazone (N=2220)	Active control (N=2227)
All	124 (154)	68 (78)	61 (71)	50 (54)	185 (225)	118 (132)
Upper limb	63 (78)	36 (39)	23 (23)	19 (19)	86 (101)	55 (58)
Distal lower limb	47 (49)	16 (17)	23 (24)	11 (11)	70 (73)	27 (28)
Femur/hip	7 (8)	7 (7)	3 (3)	1 (1)	10 (11)	8 (8)
Spine	8 (8)	4 (4)	6 (6)	5 (5)	14 (14)	9 (9)
Pelvis	0	1 (1)	0	3 (3)	0	4 (4)
Other	11 (11)	10 (10)	14 (15)	15 (15)	25 (26)	25 (25)

Numbers are participants (events). Some participants had more than one fracture and in different areas of the body.

Table 7: **Bone fractures reported as serious and non-serious adverse events**

	Rosiglitazone (N=2220)	Active control (N=2227)	p value
Infections	139 (6·3%)	157 (7·0%)	0·32
Pneumonia	41 (1·8%)	35 (1·6%)	0·56
Malignancies	126 (5·7%)	148 (6·6%)	0·20
Prostate cancer*	15 (1·3%)	21 (1·8%)	0·41
Breast cancer*	11 (1·0%)	17 (1·6%)	0·34
Colon cancer	10 (0·5%)	14 (0·6%)	0·54
Pancreatic cancer	2 (<0·1%)	13 (0·6%)	0·0074
Bladder cancer	6 (0·3%)	5 (0·2%)	0·99
Gastrointestinal disorders	133 (6·0%)	119 (5·3%)	0·39
Myocardial infarction	74 (3·3%)	67 (3·0%)	0·59
Myocardial ischaemia	14 (0·6%)	10 (0·4%)	0·54
Unstable angina	39 (1·8%)	38 (1·7%)	0·99
Angina pectoris	48 (2·2%)	37 (1·7%)	0·27
Coronary artery disease	24 (1·1%)	33 (1·5%)	0·29
Atrial fibrillation	33 (1·5%)	34 (1·5%)	1·00
Heart failure	82 (3·7%)	42 (1·9%)	0·0003
Cerebrovascular accident	43 (1·9%)	63 (2·8%)	0·064
Transient ischaemic attack	22 (1·0%)	25 (1·1%)	0·78
Hypertension	19 (0·9%)	21 (0·9%)	0·89
Pulmonary embolism	10 (0·5%)	13 (0·6%)	0·68
Bone fracture†	49 (2·2%)	36 (1·6%)	0·18
Osteoarthritis	29 (1·3%)	24 (1·1%)	0·58
Non-cardiac chest pain	21 (0·9%)	19 (0·9%)	0·89
Hyperglycaemia	27 (1·2%)	55 (2·5%)	0·0027
Hypoglycaemia‡	15 (0·7%)	6 (0·3%)	0·076
Macular oedema‡	0 (0·0%)	0 (0·0%)	..
Cataract	17 (0·8%)	13 (0·6%)	0·57
Anaemia	16 (0·7%)	10 (0·4%)	0·32

Data are number of patients (%). Data are for serious adverse events reported for more than 20 people or those predefined as being of particular interest in the context of thiazolidinedione therapy. *For prostate cancer, data are for men only, and for breast cancer data are for women only. †For non-serious adverse events and details, see table 7 and text. ‡For non-serious adverse events, see text.

Table 6: **Patients with serious adverse events**

Setting the RECORD Straight: Steven E. Nissen, MD

JAMA 303(12), March 24/31, 2010

On May 1, 2007, Wolski and I submitted for publication a meta-analysis of 42 randomized rosiglitazone clinical trials, showing a hazard ratio (HR) for myocardial infarction (MI) of 1.43 (95% confidence interval, 1.03-1.98, *P*=.03)….

Faced with the potential loss of revenue for a drug that had reached more than $3 billion in annual sales, company officials, in internal e-mails, proposed a strategy to preserve the company's market share, GSK management decided to unblind and publish the ongoing RECORD trial, an extremely unusual procedure that would seriously undermine the statistical validity and credibility of the final trial results. In e-mails, the company officials extensively discussed unblinding the trial. One official wrote, "My personal view is that short pub of the planned safety interim is warranted (as is) followed in short order by what might be coined as an orderly close out of the main phase of the trial and that accompanying full publication (sic). But the company faced a dilemma. Although the RECORD study was an industry-controlled clinical trial, the company had appointed an academic steering committee to oversee the study. It is always expected that such oversight includes authority over critical decisions about trial conduct and reporting of results.

Setting the RECORD Straight: Steven E. Nissen, MD

JAMA 303(12), March 24/31, 2010

1. Event rate for MI was extremely low (~ 0.5%/per year), < 1/3 the rate in Pio study
   Suggests most MIs were not ascertained
   (So investigators doing a CV event trial cannot diagnosis an MI??)

2. Claimed that rosiglitazone was administered during 88% of potential person years
   In response to questions from journalists, the company acknowledged that 40% of patients were no longer taking the drug by the end of the study, indeed at the time of the interim analysis in 2007, the authors reported that 27% of patients in the rosiglitazone treatment group were no longer taking the assigned medication. Thus, the reported 88% overall adherence is mathematically implausible. This is a critical issue because, in a safety study, if patients are not actually taking the drug or cross over to the alternative treatment group, the HR converges on 1.0. (Lied??)

3. Another factor was a significant imbalance in statin administration (P=.01) favoring the rosiglitazone group. (LDL was worse w/ Rosi)

Each of these situations was controlled by the investigators, not the company

Rosiglitazone Revisited: *Updated Meta-analysis of Risk for MI & CV Mort*

Steven E. Nissen, MD; Kathy Wolski, MPH (Arch Int Med, June 28, 2010)

Table 4. Primary Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality

Method	No. of Studies	Rosiglitazone Group	Control Group	Peto OR (95% CI)	*P* Value
Risk for Myocardial Infarction[a]					
Including RECORD trial[4]	41	159/17 258	136/14 449	1.28 (1.02-1.63)	.04
Excluding RECORD trial	40	95/15 038	80/12 222	1.39 (1.02-1.89)	.04
Risk for Cardiovascular Mortality[b]					
Including RECORD trial	26	105/13 672	100/12 175	1.03 (0.78-1.36)	.86
Excluding RECORD trial	25	45/11 452	29/9949	1.46 (0.92-2.33)	.11

MI - Gross Calculation:

92 / 10,000	(-2)	94 / 10,000
63 / 10,000	(-2)	65 / 10,000

MI → Why are there not 19,509 & 16,022 patients included in analysis?

Why are there fewer total patients in the mortality analysis?

Thiazolidinediones - 2010

Should the FDA be Making Clinical Decisions?

Conclusions

1. Rosiglitazone and Pioglitazone have similar effects on serum glucose, insulin resistance, islet cell function/preservation, and inflammation
2. Side effects (edema, wt gain) are similar
3. Pioglitazone has more beneficial effects on lipids than Rosiglitazone
4. Rosiglit does not make atherosclerosis worse and probably reduces it (Multiple carotid studies and 1 IVUS trial → APPROACH)
5. There is no evidence that Rosiglitazone increases CV mortality
6. There is no proof that Rosiglitazone increases CV events

Thiazolidinediones - 2010

Should the FDA be Making Clinical Decisions?

Perspective

1. **Hypoglycemic agents are supposed to control glucose which prevents the triopathy**
2. **Rosiglitazone does improve glucose control**
3. **Does glucose control reduce CV events?**
4. **Hard to tell – hypoglycemia may counter benefits**
5. **Which hypoglycemic agents have been shown to reduce CV events?**
6. **Metformin & Pioglitazone (insulin? sulfonylureas?)**