The role of pioglitazone in the treatment of Type 2 Diabetes - Update 2016

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Optimal Treating of Type 2 Diabetes means treating Hyperglycaemia and the Dysmetabolic Syndrome

NEED TO TREAT

Good glycaemic control

Microvascular & Macrovascular Complications

Dysmetabolic syndrome
  Insulin resistance, obesity, hyperinsulinaemia, hypertension, dyslipidaemia, atherosclerosis, procoagulant state
PPARγ activation and atherosclerosis

Ligand: Endogenous or synthetic (TZDs) → Activated PPARγ

Direct
Vascular and inflammatory cells
- Cytokines
- Chemokines
- Cholesterol efflux
- Adhesion molecules

Indirect
Fat, liver, skeletal muscle cells
- FFA
- Glucose
- Insulin sensitivity
- Triglycerides
- HDL
- Atherogenic LDL

Reduces inflammation
Inhibits Atherosclerosis

Plutzky J. Science. 2003
Powerful HbA1c Lowering:
Similar as Metformin or Exenatide once a week
DURATION 4: Effects of Monotherapy of Pioglitazone, Metformin, Sitagliptin or Exenatide once weekly in early Type 2 Diabetes on HbA1c

<table>
<thead>
<tr>
<th>Changes in HbA1c (%)</th>
<th>n=597</th>
<th>n=597</th>
<th>n=163</th>
<th>n=246</th>
<th>n=248</th>
<th>n=163</th>
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<tbody>
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<tr>
<td></td>
<td>-1.4</td>
<td>-1.5</td>
<td>-1.6</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.2</td>
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</tbody>
</table>

- Pioglitazone
- Metformin
- Pioglitazone
- Metformin
- Exenatide once a week
- Sitagliptin

Number of Patients: 1194
Duration of Diabetes: 3 years
Duration of Treatment: 12 months

Number of Patients: 800
Duration of Diabetes: 2 years
Duration of Treatment: 6 months

Weight Change (kG)

+ 1.9
- 2.5
+ 1.8
- 2.2
- 2.3
- 0.8

Schernthaner G et al. JCEM 2004, 89:6068
Russel-Jones et al. Diab Care 2012; 35:252-258
Low Risk of Hypoglycemia
### Effects of oral antidiabetic Drugs on HbA1c, Hypoglycemic Events & Weight Gain in 4 randomised double blind large Studies (Quartet)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug组合</th>
<th>Number of Patients</th>
<th>HbA1c (%)</th>
<th>Hypoglycemia (%)</th>
<th>Weight Change (kg)</th>
<th>Weight Difference (kg)</th>
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<tr>
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<td>Metformin</td>
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<td>+1.9</td>
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<tr>
<td>2</td>
<td>SU</td>
<td>626</td>
<td>-1.35</td>
<td>10.1</td>
<td>+1.9</td>
<td>0.9</td>
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<tr>
<td>2</td>
<td>Pioglitazone</td>
<td>624</td>
<td>-1.43</td>
<td>3.5</td>
<td>+2.8</td>
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<tr>
<td>3</td>
<td>Metformin + Pioglitazone</td>
<td>317</td>
<td>-1.5</td>
<td>1.3</td>
<td>+1.5</td>
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<tr>
<td>3</td>
<td>Metformin + SU</td>
<td>317</td>
<td>-1.4</td>
<td>11.2</td>
<td>+1.4</td>
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<td>4</td>
<td>SU + Pioglitazone</td>
<td>319</td>
<td>-1.35</td>
<td>10.7</td>
<td>+2.8</td>
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<tr>
<td>4</td>
<td>SU + Metformin</td>
<td>320</td>
<td>-1.43</td>
<td>14.1</td>
<td>-1.0</td>
<td></td>
</tr>
</tbody>
</table>

SU = Sulfonylureas

1. Schernthaner et al; JCEM 2004; 89:6068
4. Hanefeld et al; Diab.Care 2004;27:141
Weight Gain, but significant lowering of Visceral Fat and Hepatic Fat
Waist is not a relevant marker of visceral fat on Pioglitazone due to the fat redistribution shown on Pioglitazone.

Case: Male/59 years old

Baseline

Pioglitazone for 16 weeks

Subcutaneous Fat Area: 144.3 cm²
Visceral Fat Area: 140.0 cm²
Body Weight: 67.4 kg
FPG: 184 mg/dl
HbA₁c: 7.3%

Subcutaneous Fat Area: 204.7 cm²
Visceral Fat Area: 105.1 cm²
Body Weight: 69.2 kg
FPG: 117 mg/dl
HbA₁c: 6.5%

+ 42%
Visceral fat actually decreases on Pioglitazone: the « abdominal obesity » parameter is improved.

Case: Male/59 years old

Baseline

- Subcutaneous Fat Area: 144.3 cm²
- Visceral Fat Area: 140.0 cm²
- Body Weight: 67.4 kg
- FPG: 184 mg/dl
- HbA₁c: 7.3 %

Pioglitazone for 16 weeks

- Subcutaneous Fat Area: 204.7 cm²
- Visceral Fat Area: 105.1 cm²
- Body Weight: 69.2 kg
- FPG: 117 mg/dl
- HbA₁c: 6.5 %

- 25 %
Progression of Diabetes: HbA$_{1C}$ - Increase per Year
(Two-Year Results from the QUARTET-Studies)

Superior to Metformin in Reducing Insulin Resistance
Treatment-induced changes in Insulin-mediated Glucose Uptake (M value) with Metformin and Thiazolidinediones.

Metformin

- Open: + 18%
- Double-blind/placebo-controlled: + 11%

Thiazolidinediones

- Open: + 36%
- Double-blind/placebo-controlled: + 34%

Natali A and Ferrannini E. Diabetologia 2006; 49:434-41
Potential anti-atherogenic Effects of Thiazolidinediones

Traditional Risk Factors
- Decrease of HbA1c, FPG, PRS
- Lowering of Systolic BP
- Increase of HDL-Cholesterol
- Decrease of Triglycerides
- Decrease of Lp (a)
- Decrease of small-dense LDL-Particles

Non-traditional Risk Factors
- Reduction of vascular Inflammation → Lowering of CRP, IL-6, NFkB, sICAM, sVCAM, MCP-1, MMP-9
- Antiplatelet Effects: sCD40L, P-Selectin
- Improvement of Fibrinolysis → lowering of PAI-1
- Improvement of Endothelial Dysfunction → lowering of ADMA
- Neovascularisation & Neoangiogenesis → Increase of endothelial progenitor cells (EPC)
Superior to Metformin in Reducing Microalbuminuria
Significant lowering of urinary albumin/creatinine ratio by treatment with **Pioglitazone** in type 2 diabetic patients.

- Schernthaner et al. JCEM 2004; 89:6086

**Change of urinary albumin/creatinine ratio after 52 weeks (%)**

- Pioglitazone (n=597): -19 (p<0.002)
- Metformin (n=597): -1 (p<0.002)
- PIO +SU (n=319): +2 (p<0.017)
- PIO +Metformin (n=317): +6 (p<0.027)
- SU +Metformin (n=313): +10
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of subjects</th>
<th>N</th>
<th>Daily doses of regimens compared</th>
<th>Duration</th>
<th>Mean effect on UAE versus baseline in TZD groups (%)</th>
<th>Mean effect on SBP/DBP versus baseline in TZD groups (mmHg)</th>
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<tbody>
<tr>
<td>Sironi et al.</td>
<td>DM2, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>200 mg Tro versus plb</td>
<td>8 weeks</td>
<td>+11%</td>
<td>-4/-3&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Imano et al.</td>
<td>DM2, mA, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30</td>
<td>400 mg Tro versus 500 mg Met</td>
<td>12 weeks</td>
<td>-39%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-3/0</td>
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<tr>
<td>Nakamura et al.</td>
<td>DM2, mA or MA</td>
<td>32</td>
<td>400 mg Tro versus 5 mg Gli</td>
<td>12 months</td>
<td>-67%&lt;sup&gt;c&lt;/sup&gt; in mA 0% in MA</td>
<td>-6&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Nakamura et al.</td>
<td>DM2, mA</td>
<td>45</td>
<td>30 mg Pio versus 5 mg Gli versus 0.6 mg Vog</td>
<td>3 months</td>
<td>-66%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-6/-4</td>
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<td>Nakamura et al.</td>
<td>DM2, mA</td>
<td>28</td>
<td>30 mg Pio versus plb</td>
<td>6 months</td>
<td>-59%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-4&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Aljabri et al.</td>
<td>DM2, (mA)&lt;sup&gt;e&lt;/sup&gt;, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62</td>
<td>30-45 mg Pio versus isophane insulin</td>
<td>16 weeks</td>
<td>-44%</td>
<td>-8/-5</td>
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<td>Yanagawa et al.</td>
<td>DM2, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>Pio versus Met or Gli</td>
<td>12 weeks</td>
<td>-45%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
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<tr>
<td>Hanefeld et al.</td>
<td>DM2, (mA)&lt;sup&gt;e&lt;/sup&gt;, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>639</td>
<td>15-45 mg Pio versus 850-2550 mg Met</td>
<td>12 months</td>
<td>-15%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Schernthaner et al.</td>
<td>DM2, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1199</td>
<td>15-45 mg Pio versus 850-2550 mg Met</td>
<td>12 months</td>
<td>-19%&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Matthews et al.</td>
<td>DM2, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>15-45 mg Pio versus 80-320 mg Gli</td>
<td>12 months</td>
<td>-10%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Agarwal R, et al.</td>
<td>DM2, MA (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44</td>
<td>Pio versus Glip</td>
<td>4 months</td>
<td>-7%</td>
<td>+3.7/+2.2&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Lebovitz et al.</td>
<td>DM2, (mA)&lt;sup&gt;e&lt;/sup&gt;, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>493</td>
<td>4 or 8 mg Rosi versus plb</td>
<td>26 weeks</td>
<td>4 mg group: -14%</td>
<td>NA</td>
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<tr>
<td>Bakris et al.</td>
<td>DM2, (mA)&lt;sup&gt;e&lt;/sup&gt;, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>129</td>
<td>8mg Rosi versus Gli</td>
<td>12 months</td>
<td>-30%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.1&lt;sup&gt;c&lt;/sup&gt;/-2.3&lt;sup&gt;bc&lt;/sup&gt;</td>
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<td>Sarafidis et al.</td>
<td>DM2, hyp, (mA)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>20</td>
<td>4mg Rosi, non-mA patients: Rosi versus Nat, mA patients: Rosi versus plb</td>
<td>6 months</td>
<td>-35%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-5.4&lt;sup&gt;c&lt;/sup&gt;/-4.1&lt;sup&gt;bc&lt;/sup&gt;</td>
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<tr>
<td>Pistroscch et al.</td>
<td>DM2, (mA)&lt;sup&gt;e&lt;/sup&gt;, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19</td>
<td>4mg Rosi, non-mA patients: Rosi versus Nat, mA patients: Rosi versus plb</td>
<td>12 weeks</td>
<td>+18%&lt;sup&gt;g&lt;/sup&gt;, mA patients: -66%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
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<tr>
<td>Bakris et al.</td>
<td>DM2, mA, (hyp)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>389</td>
<td>Rosi versus Gli</td>
<td>32 weeks</td>
<td>-23%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-1.3&lt;sup&gt;c&lt;/sup&gt;/-2.3&lt;sup&gt;bc&lt;/sup&gt;</td>
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</tbody>
</table>
Significant Increase of HDL-Cholesterol, which is a strong predictor of CV Mortality in Patients with Type 2 Diabetes
Benefits of **Pioglitazone: Lipid Metabolism**

- Pioglitazone improves **diabetic dyslipidaemia**
  - Decreases triglyceride levels
  - Increases high-density lipoprotein (HDL) cholesterol levels

Dormandy JA et al. Lancet 2005;366:1279-
Mazzone T et al., JAMA 2006; 296: 2572
Which Studies do we have indicating that Pioglitazone has antiatherogenic and cardioprotective effects?

- Four Randomized Controlled Trials
  PROactive
  CHICAGO
  PERISCOPE
  IRIS
- Several Metaanalyses
- Three Large Observational Studies from UK
Existing therapy

- Diet and Glucose-lowering agents
- Antihypertensives
- Lipid-altering agents
- Antithrombotic agents

Pioglitazone + existing therapy

Placebo + existing therapy

Forced titration up to 45 mg/day

Patient management throughout study to be according to the 1999 International Diabetes Federation (Europe) Guidelines
Overlap of Previous Macrovascular Events

Previous Macrovascular Disease
50% Myocardial Infarction
25% Stroke
25% Peripheral Vascular Disease

* - including 1043 with peripheral arterial obstructive disease
* Death from any cause, non-fatal myocardial infarction (including silent MI), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, bypass surgery/revascularisation of the leg
Significant Reduction of the combined Clinical Outcome of Death, Myocardial Infarction & Stroke

Placebo: Events 358 / 2633 (14.4%)

Pioglitazone: Events 301 / 2605 (12.3%)

Kaplan-Meier Event Rate

Time from Randomisation (months)

Pioglitazone vs Placebo

HR 95 % CI p value
0.841 0.722, 0.981 0.0237 *

- 16% at 3-year (p=0.0237)

Primary Composite Endpoint – CV Death, Myocardial Infarction and Stroke

- ACCORD
- ORIGIN
- SAVOR
- EXAMINE
- PROactive (secondary primary endpoint*)
- SAVOR, EXAMINE, TECOS
- EMPA REC OUTCOME
- LEADER, SUSTAIN-6

In March, 2005, the steering committee identified this endpoint as the intended main secondary endpoint. The final version was signed and released on May 13, 2005. A copy of the plan was registered as received by the US Food and Drug Administration on May 17, 2005. The study database was formally locked on May 25, 2005 and statistical analysis of unblinded data started only after that date. (Lancet March 25th, 2006)
Pioglitazone’s effect on recurrent stroke in patients with previous stroke

N at Risk:

Time from Randomisation (months)

Kaplan-Meier event rate

Placebo (51 / 498)

Pioglitazone (27 / 486)

HR  95% CI  p value
pioglitazone vs placebo  0.53  0.34, 0.85  0.008

Wilcox R et al. STROKE 2007; 38: 865-873
Pioglitazone’s effect on recurrent MI in patients with previous MI

Kaplan-Meier Event Rate

Pioglitazone vs Placebo

HR 95% CI p-Value

0.72 0.52, 0.99 0.045

N. at risk: 2455

Placebo (88 / 1215)

Pioglitazone (65 / 1230)

-28%

Erdmann E. et al. JACC 2007; 49: 1772-1780
Pioglitazone’s effect on Acute Coronary Syndrome in patients with previous MI

Erdmann E. et al. JACC 2007; 49: 1772-1780

Kaplan-Meier Event Rate

<table>
<thead>
<tr>
<th>Time from Randomisation (months)</th>
<th>Pioglitazone (35 / 1230)</th>
<th>Placebo (54 / 1215)</th>
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<tr>
<td>0</td>
<td>0.0</td>
<td>0.04</td>
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<td>0.04</td>
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<tr>
<td>36</td>
<td>0.08</td>
<td>0.04</td>
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</tbody>
</table>

Pioglitazone vs Placebo

HR: 0.63
95% CI: 0.41, 0.97
p-Value: 0.035

-37 %
**PROACTIVE: Time to Permanent Insulin Use**

- **Pioglitazone (183 / 1741)**
- **Placebo (362 / 1737)**

Kaplan-Meier Event Rate

<table>
<thead>
<tr>
<th>Time from Randomisation (months)</th>
<th>N at Risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3478</td>
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<td>30</td>
<td>2824</td>
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<tr>
<td>36</td>
<td>446 (137)</td>
</tr>
</tbody>
</table>

**HR vs Placebo:** 0.469, 95% CI: 0.392, 0.56, p value: 0 ***

Dormandy et al. (Lancet 2005; 366: 1279-1289)
Reduces CV Risk and Mortality in Patients with Type 2 Diabetes and Chronic Kidney Disease (CKD) or End-Stage Renal Disease
Effect of Pioglitazone Treatment on the combined Endpoint of all-cause Mortality, Myocardial Infarction and Stroke in Patients with and without CKD (PROactive)

Kaplan-Meier estimate of 3-year event rate

Event Rate

Placebo: Combined endpoint significantly higher (P <0.0001) in patients with CKD (GFR <60 ml/min/l) vs. those without CKD: 18.3% vs. 11.5%; HR=1.65

Pioglitazone: Significant benefit in patients with CKD: Reduction of combined Endpoint from 21.4% vs. 14.6% HR=0.66 (p<0.0001)

Chicago
Objectives: Demonstrate the impact of Pioglitazone vs Glimepiride on atherosclerosis as measured by CIMT and EBCT in 400 patients with type 2 diabetes mellitus (18 month treatment period)
CHICAGO TRIAL: A Study Evaluating Carotid Intima-Media Thickness in Atherosclerosis comparing Pioglitazone versus Glimepiride

Mean Change in Average CIMT

- Glimepiride
- Pioglitazone HCI

Baseline CIMT (mm) GLM (N=186) PIO (N=175)
LS mean (SE) 0.779 (0.008) 0.771 (0.008)

Treatment group difference, Final Visit
LS mean change from Baseline Posterior Wall CIMT (mm)
-0.013 (95% CI: -0.024, -0.002)
PERISCOPE
Intravascular Ultrasound (IVUS) can detect ‘Silent’ Atheroma

Angiogram

No evidence of disease

IVUS

Little evidence of disease

Atheroma

Determining the Atheroma Area


Precise planimetry of EEM and lumen borders allows calculation of atheroma cross-sectional area.

Images courtesy of Cleveland Clinic Intravascular Ultrasound Core Laboratory
Primary Endpoint:
Change in Percent Atheroma Volume (%)

Presented at: American College of Cardiology
March 29-April 1, 2008; Chicago, IL

Glimepiride (n=181)
Pioglitazone (n=179)

Nissen SE et al (JAMA 2008; 299:1561)
Pioglitazone after Ischemic Stroke or Transient Ischemic Attack (IRIS)

Multicenter, RCT of 3876 patients who had had a recent ischemic stroke or TIA who received either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance.

- The primary outcome (fatal or nonfatal stroke or myocardial infarction) after 4.8 year occurred in 175 of 1939 patients (9.0%) in the pioglitazone and in 228 of 1937 (11.8%) in the placebo group (HR 0.76; 95% [CI], 0.62 to 0.93; P=0.007). The secondary outcome of diabetes diagnosis was also reduced by 52 % (HR 0.48; 95% C, 0.33–0.69; P < 0.001.)

- Pioglitazone was associated with a greater weight gain (> 4.5 kg) than placebo (52% vs. 34%, P<0.001), edema (35% vs. 25%, P<0.001), and bone fractures (5.1% vs. 3.2%, P = 0.003).

- Rates of Heart failure and Cancer were not increased in the pioglitazone treated patients

IRIS: Insulin Resistance Intervention after Stroke

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

A Meta-analysis of Randomized Trials

Risk of death, MI or stroke with **Pioglitazone vs Control**

Lincoff AM et al JAMA 2007; 298; 1180-1188

Hazard Ratio = 0.82 (95% confidence interval, 0.72-0.94)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pioglitazone</th>
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<tr>
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<tr>
<td>140</td>
<td>2143</td>
<td>2146</td>
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</tbody>
</table>

P = 0.005
CARDIOVASCULAR OUTCOMES FROM PIOGLITAZONE
META-ANALYSIS OF CLINICAL TRIALS (excludes PROactive)

Kaplan-Meier Estimate of Event Rate for Death, MI, Stroke

Time (weeks)

Comparator

Pioglitazone

HR = 0.75

CI = 0.55-1.02

FDA and Center for Drug Evaluation & Research; July 30, 2007

Probability of Events

0.06

0.04

0.02

0

0

TIME (weeks)

0 40 80 120 160

Comp

5203 2978 1297 488 34

Pio

5949 2859 1247 459 40
Risk of MI, IHD or a composite of major Macrovascular Events from Meta-analyses of Trials with Rosiglitazone or Pioglitazone versus Comparators

**Rosiglitazone meta-analyses**
- Friedrich et al. (MI) [25]
- Selvin et al. (CV morbidity) [22]
- GSK-ICT (MI) [7,8,20,21]
- Friedrich et al. (IHD) [25]
- Schuster et al. (MI) [17]
- FDA (Serious IHD) [9,21]
- Nissen & Wolski (MI) [6]
- Sing et al. (MI) [10]
- FDA (IHD) [9,21]
- Psaty & Furberg (MI) [16]
- Diamond et al. (MI, highest estimate) [15]
- Dahbreh & Economopoulos (MI, lowest estimate) [19]
- GSK-ICT (IHD) [7,8,20,21]
- Bracken (MI, excl.RECORD) [18]
- Diamond et al. (MI, lowest estimate) [15]
- Bracken (MI, incl.RECORD) [18]
- Dahbreh & Economopoulos (MI, lowest estimate) [19]
- Monami et al. (MI) [23]
- FDA (CV death/MI/stroke) [7,8,20,21]
- GSK-ICT (CV death/MI/stroke) [7,8,20,21]
- Manucci et al (Non-fatal coronary events) [24]
- Manucci et al (Non-fatal MI) [24]

**Pioglitazone meta-analyses**
- Selvin et al (CV morbidity, incl.PROactive) [22]
- Selvin et al (CV morbidity, incl.PROactive) [22]
- Nagajothi et al (MI) [34]
- Lincoff et al (Death/MI) [28]
- Perez et al (Death/MI/stroke, incl.PROactive) [29]
- Lincoff et al (Death/MI/stroke, incl.PROactive) [28]
- Manucci et al (Non-fatal coronary events) [33]
- Lincoff et al (MI) [28]
- Lincoff et al (Death/MI/stroke, excl.PROactive) [28]
- Perez et al (Death/MI/stroke, excl.PROactive) [28]

Balance of Benefit / Risk of Pioglitazone in the Treatment of Type 2 Diabetes

**Benefit**
- Reduces insulin resistance
- Potent lowering of HbA1c (durable effect with low risk for hypoglycemia)
- Improves CV risk factors (HDL, Triglycerides, inflammation, microalbuminuria)
- Decreases cardiovascular risk (PROactive: secondary prevention of MI, stroke)
- Reduces risk in CKD & hemodialysis
- Improves liver damage in NASH
- Strongest effect in diabetes prevention (ACT NOW: associated with decrease in IMT)
- Protection of several common cancers (e.g. liver cancer)

**Adverse Events/Risks**
- Weight gain (water retention)
- Heart failure (no increase in mortality)
- Bone fractures (peripheral)
- Bladder cancer ??
Kaplan-Meier estimates of time to Serious Heart Failure

Erdmann et al (Diabetes Care; 2007; 30: 2773-2778)

**Kaplan-Meier Event Rate**

Time from Randomisation (months)

Number at Risk:

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Pioglitazone (149/2605)</th>
<th>Placebo (108/2633)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5238</td>
<td>5238</td>
</tr>
<tr>
<td>6</td>
<td>5143</td>
<td>5143</td>
</tr>
<tr>
<td>12</td>
<td>5047</td>
<td>5047</td>
</tr>
<tr>
<td>18</td>
<td>4956</td>
<td>4956</td>
</tr>
<tr>
<td>24</td>
<td>4861</td>
<td>4861</td>
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<tr>
<td>30</td>
<td>4759</td>
<td>4759</td>
</tr>
<tr>
<td>36</td>
<td>4759</td>
<td>4759</td>
</tr>
</tbody>
</table>

Erdmann et al (Diabetes Care; 2007; 30: 2773-2778)

HR 1.41

5.7%

4.1%

* p=0.007
Pioglitazone’s effect on the main Secondary Endpoint (All Cause Mortality, Non-fatal MI & Stroke) after a serious HF

Placebo (51/108)
Pioglitazone (52/149)

HR 0.64
47.2 %
34.9 %

* p=0.02

Kaplan-Meier Event Rate
Number at Risk: 257 152 113 78 0 0
Time from Onset of Serious Heart Failure (months)

Erdmann et al (Diabetes Care; 2007, 30: 2773-2778)
Three recent large studies do not show any evidence of an association between use of pioglitazone and risk of bladder cancer


**Pioglitazone use and risk of bladder cancer in type 2 diabetes:** Retrospective cohort study using datasets from four EU countries

Korhonen P. et al. BMJ 2016;354:i3903

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No of events</th>
<th>Incidence</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pioglitazone exposure</strong></td>
<td></td>
<td></td>
<td>Crude model</td>
</tr>
<tr>
<td>Never</td>
<td>153</td>
<td>9.62</td>
<td>0.83 (0.66 to 1.05)</td>
</tr>
<tr>
<td>Ever</td>
<td>130</td>
<td>7.97</td>
<td>0.93 (0.71 to 1.22)</td>
</tr>
<tr>
<td>Duration of pioglitazone exposure</td>
<td></td>
<td></td>
<td>Crude model</td>
</tr>
<tr>
<td>Never</td>
<td>153</td>
<td>9.62</td>
<td>0.69 (0.47 to 1.01)</td>
</tr>
<tr>
<td>&lt;18 months</td>
<td>83</td>
<td>8.12</td>
<td>0.76 (0.41 to 1.42)</td>
</tr>
<tr>
<td>18-&lt;48 months</td>
<td>35</td>
<td>7.29</td>
<td>0.86 (0.60 to 1.23)</td>
</tr>
<tr>
<td>&gt;48 months</td>
<td>12</td>
<td>9.37</td>
<td>0.56 (0.30 to 1.06)</td>
</tr>
<tr>
<td>Cumulative pioglitazone dose</td>
<td></td>
<td></td>
<td>Crude model</td>
</tr>
<tr>
<td>Never</td>
<td>153</td>
<td>9.62</td>
<td>0.88 (0.67 to 1.17)</td>
</tr>
<tr>
<td>1-14 000 mg</td>
<td>79</td>
<td>7.80</td>
<td>0.86 (0.60 to 1.23)</td>
</tr>
<tr>
<td>14 001-40 000 mg</td>
<td>40</td>
<td>8.72</td>
<td>0.56 (0.30 to 1.06)</td>
</tr>
<tr>
<td>&gt;40 000 mg</td>
<td>11</td>
<td>6.92</td>
<td>0.86 (0.60 to 1.23)</td>
</tr>
</tbody>
</table>

Patients with type 2 diabetes who initiated pioglitazone (n=56 337) matched with patients with type 2 diabetes in the same country exposed to diabetes drug treatments other than pioglitazone (n=317 109).

Korhonen P. et al. BMJ 2016;354:i3903
Pioglitazone use and risk of bladder cancer in type 2 diabetes: Retrospective cohort study using datasets from four EU countries

This study shows no evidence of an association between ever use of pioglitazone and risk of bladder cancer compared with never use, which is consistent with results from other recent studies that also included a long follow-up period.

Korhonen P. et al. BMJ 2016;354:i3903
Consider initial dual combination therapy if metformin is contraindicated.

Begin with these options if metformin is contraindicated.

Healthy eating, weight control, increased physical activity

- **Metformin**
  - high
  - low risk
  - neutral/loss
  - GI/lactic acidosis
  - low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

- **Metformin +**
  - Sulfonylurea
    - high
    - moderate risk
    - gain
  - Thiazolidinedione
    - high
    - low risk
    - gain
    - edema, HF, fx's
  - DPP-4 Inhibitor
    - intermediate
    - low risk
    - neutral
  - GLP-1 receptor agonist
    - high
    - low risk
    - loss
    - GI
  - Insulin (usually basal)
    - highest
    - high risk
    - gain
    - hypoglycemia
    - variable

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

- **Metformin +**
  - Sulfonylurea +
    - TZD
    - DPP-4-i
    - GLP-1-RA
    - Insulin
  - Thiazolidinedione +
    - SU
    - DPP-4-i
    - GLP-1-RA
    - Insulin
  - DPP-4 Inhibitor +
    - SU
    - TZD
  - GLP-1 receptor agonist +
    - SU
    - TZD
    - Insulin
  - Insulin (usually basal)
    - TZD
    - DPP-4-i
    - GLP-1-RA

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

- **Insulin**
  - (multiple daily doses)

*Diabetes Care* 2012;35:1364–1379
*Diabetologia* 2012;55:1577–1596
Risk of **All-cause Mortality** for Different Comparisons of Drug Groups: Follow up of 91,521 Patients for 7.1 Years

(UK GPRD)

- HR 1.43
- HR 1.40
- HR 1.37
- HR 1.40
- HR 0.80
- HR 0.60

*Any therapy (monotherapy and combinations).
**Other drugs and combinations of any oral antidiabetes drugs excluding rosiglitazone and pioglitazone.

Tzoulaki I, et al. BMJ. 2010
What should follow metformin in 2016

Many options

Add an oral agent

Add Sulfonylurea
Add DPP-4 Inhibitor
Add Pioglitazone
Add SLGT-2 Inhibitor

Add injections

Add insulin
Add GLP-1 agonist

Combination

HbA1c ≥7%

Good medicine is not "the same option for all"

Treatments must be personalised, according to each patient needs
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

**Healthy eating, weight control, increased physical activity, and diabetes education**

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>high</td>
<td>low risk</td>
<td>neutral / loss</td>
<td>GI / lactic acidosis</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>Hypo risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- **Metformin + Sulfonylurea**
  - Efficacy: high
  - Hypo risk: moderate risk
  - Weight: gain
  - Hypoglycemia: low
  - Costs?

- **Metformin + Thiazolidinedione**
  - Efficacy: high
  - Hypo risk: low risk
  - Weight: gain
  - Hypoglycemia: rare
  - Costs?

- **Metformin + DPP-4 inhibitor**
  - Efficacy: intermediate
  - Hypo risk: neutral
  - Weight: loss
  - Hypoglycemia: high
  - Costs?

- **Metformin + SGLT2 inhibitor**
  - Efficacy: intermediate
  - Hypo risk: neutral
  - Weight: loss
  - Hypoglycemia: high
  - Costs?

- **Metformin + GLP-1 receptor agonist**
  - Efficacy: high
  - Hypo risk: highest
  - Weight: gain
  - Hypoglycemia: variable
  - Costs?

- **Metformin + Insulin (basal)**
  - Efficacy: high
  - Hypo risk: high risk
  - Weight: gain
  - Hypoglycemia: variable
  - Costs?

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- **Metformin + Sulfonylurea + TZD**
  - Efficacy: high
  - Hypo risk: moderate risk
  - Weight: gain
  - Hypoglycemia: low
  - Costs?

- **Metformin + Sulfonylurea + DPP-4i**
  - Efficacy: high
  - Hypo risk: low risk
  - Weight: gain
  - Hypoglycemia: rare
  - Costs?

- **Metformin + Sulfonylurea + SGLT2i**
  - Efficacy: high
  - Hypo risk: moderate risk
  - Weight: gain
  - Hypoglycemia: rare
  - Costs?

- **Metformin + DPP-4 inhibitor + SGLT2 inhibitor**
  - Efficacy: intermediate
  - Hypo risk: neutral
  - Weight: loss
  - Hypoglycemia: high
  - Costs?

- **Metformin + DPP-4 inhibitor + GLP-1 receptor agonist**
  - Efficacy: high
  - Hypo risk: highest
  - Weight: gain
  - Hypoglycemia: variable
  - Costs?

- **Metformin + DPP-4i + Insulin (basal)**
  - Efficacy: high
  - Hypo risk: high risk
  - Weight: gain
  - Hypoglycemia: variable
  - Costs?

- **Metformin + DPP-4i + SGLT2i**
  - Efficacy: high
  - Hypo risk: moderate risk
  - Weight: gain
  - Hypoglycemia: rare
  - Costs?

- **Metformin + GLP-1 receptor agonist + Insulin (basal)**
  - Efficacy: high
  - Hypo risk: highest
  - Weight: gain
  - Hypoglycemia: variable
  - Costs?

- **Metformin + GLP-1 receptor agonist + SGLT2i**
  - Efficacy: high
  - Hypo risk: moderate risk
  - Weight: gain
  - Hypoglycemia: rare
  - Costs?

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

<table>
<thead>
<tr>
<th>Combination injectable therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Basal insulin + Mealtime insulin or GLP-1-RA</td>
</tr>
</tbody>
</table>

Inzucchi S et al. Diabetes Care 2015;38:140–149
2nd line Therapy (PIO, DPP4-Inh, RSG) after Metformin: Adjusted HRs versus Metformin plus Sulfonylureas

Morgan CL, Poole CD, Evans M, Barnett AH, Jenkins-Jones, S Currie CJ. JCEM 2013; 98:668-677
Kaplan–Meier survival plots and the number at risk for the composite CV endpoint among 10,118 patients treated with a DPP-4 inhibitor (red solid line) or TZD (green dashed line) compared with a sulphonylurea (SU; blue dotted line) when added to metformin monotherapy.

HR 0.68 (95% CI 0.54; 0.85; p=0.001) when adding a TZD to metformin.
HR 0.78 (95% CI 0.55; 1.11; p=0.17) when adding a DPP-4 inhibitor to metformin.

Zghebi et al. DOM 2016; 18; 916-924
Protection of multiple Organs by Pioglitazone

↓ 47% of Secondary Stroke in Patients with previous Stroke (PROactive)

↓ 28% of Re-Infarction in Patients with previous MI (PROactive)

↓ 37% of Acute Coronary Syndrome after previous MI (PROactive)

↓ 51% Mortality in Patients on Hemodialysis (USA)

Stop of Progression of Coronary Atherosclerosis (PERISCOPE)

Reduction of Inflammation & Necrosis in NASH (Nonalcoholic Steatohepatitis)

Reduction of CIMT (Carotid artery Intima-Media Thickness)

CHICAGO

Schernthaner G Diabetes Care 2013
Pioglitazone **Benefit - Risk Remains Positive**

- The combination of the mechanism of action, efficacy, and durability with low incidence of hypoglycemia distinguish **pioglitazone** from other currently available antidiabetic medications
- Is the only antidiabetic drug with cardiovascular safety documented by a prospective outcomes study
- Risks are well characterised in more than 20 million patient-years of experience in the past 10 years globally
- The very small risk of bladder cancer (?) should be balanced by the benefits of pioglitazone in the context of the overall morbidity of patients with T2DM
- Pioglitazone continues to be an important therapeutic option for the successful management of patients with T2DM
# Effect of Glucose Lowering Drugs on the Combined Endpoint of CV Mortality, Nonfatal Myocardial Infarction and Stroke

<table>
<thead>
<tr>
<th>Antidiabetic Drug</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROactive Pioglitazone</td>
<td>0.84 (CI 0.72 - 0.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>ORIGIN Insulin Glargine</td>
<td>1.02 (CI 0.94 -1.11)</td>
<td>NS</td>
</tr>
<tr>
<td>SAVOR Saxagliptin</td>
<td>1.00 (CI 0.89 -1.12)</td>
<td>NS</td>
</tr>
<tr>
<td>EXAMINE Alogliptin</td>
<td>0.96 (CI 0.80-1.15)</td>
<td>NS</td>
</tr>
<tr>
<td>ELIXA Lixisenatide</td>
<td>1.02 (CI 0.89, 1.17)</td>
<td>NS</td>
</tr>
<tr>
<td>TECOS Sitagliptin</td>
<td>0.98 (CI 0.89, 1.08)</td>
<td>NS</td>
</tr>
<tr>
<td>EMPA-REG Empagliflozin</td>
<td>0.86 (CI 0.74-0.99)</td>
<td>0.038</td>
</tr>
<tr>
<td>LEADER Liraglutide</td>
<td>0.87 (CI 0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>SUSTAIN-6 Semigludtide</td>
<td>0.78 (CI 0.66-0.93)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

## Proposal for Antidiabetic Combination Therapy in Patients presenting with established Cardiovascular Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metformin</th>
<th>Pioglitazone</th>
<th>Empagliflozin</th>
<th>Anticipated Effect ?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Death</td>
<td>↓</td>
<td>←</td>
<td>↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>All Cause Death</td>
<td>↓</td>
<td>←</td>
<td>↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td>Stroke</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td>Fluid Retention</td>
<td>←</td>
<td>↑</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>←</td>
<td>↑</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>Weight</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>←</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>HbA1c</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>↓</td>
<td>←</td>
<td>↑</td>
<td>←</td>
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<tr>
<td>HDL Cholesterol</td>
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<tr>
<td>Albuminuria</td>
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<td>↓</td>
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<td>↓</td>
</tr>
<tr>
<td>Insulin Sensitivity</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

↓, lowered; ↑, elevated; ←, unchanged.

Some positive or negative effects of the 3 individual drugs may be neutralized in combination, some positive effects could work synergistic.

Positioning of Pioglitazone: patients in whom the benefits are likely to exceed the risks

1 oral agent

- insulin-resistant patients with renal impairment *(metformin contra-indicated)*

2 oral agents

- On the top of *metformin*, in insulin-resistant patients, at high CV risk

- The following markers of insulin resistance will predict a good and sustained HbA1c reduction on Pioglitazone:
  - Abdominal obesity
  - Slightly increased liver enzymes
  - Low HDL-cholesterol

- Post-MI *(if no heart failure)*
- Post-stroke
- Chronic Kidney Disease

3 oral agents

- Triple oral therapy, when to avoid injections seems preferable

- On the top of *insulin*, when large doses of insulin fail, *due to insulin-resistance*

Schernthaner G et al (2013)