

Evidence Tables

Glit1: Is Pioglitazone effective in the control of blood glucose in people with type 2 diabetes either alone or in combination compared to other antidiabetic treatment regimens?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Sour of fundi
Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. 2006. Cochrane Database of Systematic Reviews. ID 3238	Cochrane systematic review 1++	Twenty-two trials which randomised approximately 6,200 people to pioglitazone treatment were identified. Studies included had a minimum follow-up of 24 weeks. (Last search August 2006) 16 of the 22 included publications investigated pioglitazone monotherapy versus another monotherapy, 6 publications evaluated the combination of pioglitazone with another glucose-lowering intervention versus a comparable combination.	The mean age of patients randomised to pioglitazone treatment encompassed 53 to 63 years. Diabetes duration ranged between 3 to 14 years. The main ethnic group participating in the trials consisted of white people, a few studies included a Hispanic population as well. Pharmac-naive patients usually constituted a minor part of the study participants.	Pioglitazone as monotherapy or in combination with other OAD or insulin	Placebo or any other active intervention	Most studies had a treatment duration of approximately six months, nine lasted 12 months and the longest trial had a mean duration of 34.5 months	Primary outcomes · mortality · morbidity · adverse events Secondary outcomes · health-related quality of life (using a validated instrument); · costs; · metabolic control as measured by glycosylated haemoglobin A1c (HbA1c).	Mortality and Morbidity With the exception of one study no trial explored mortality and morbidity as endpoints (Dormandy et al 2005). In this study, the primary composite endpoint (time from randomisation to all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group: The hazard ratio (HR) was 0.90 (95% CI 0.80 to 1.02, p=0.095). Of all secondary endpoints only the so-called "main" secondary endpoint (time to the first event of the composite endpoint of death from any cause, myocardial infarction (excluding silent myocardial infarction) and stroke) indicated a statistical significant difference between pioglitazone and placebo (HR 0.84 (95% CI 0.72 to 0.98, p=0.027). The individual components of	Comment [r1]: We have 2 MA in this topic ID 5051 (ref 117) and this one here which is ref 141 in the GL

		<p>Inclusion criteria Investigators specified various inclusion criteria, such as diet non-responders or certain glycosylated haemoglobin A1c (HbA1c) levels.</p> <p>Exclusion criteria Investigators specified various exclusion criteria. Eight of 22 included studies stipulated specific criteria for the severity of congestive heart failure (NYHA (New York Heart Association) classification): Five studies mentioned NYHA class III or IV as an exclusion criterion and one study NYHA II or above, I-IV or II-IV, respectively.</p>	<p>but 3 studies exclusively investigated this group. Most study participants with type 2 diabetes mellitus were also obese, the BMI in patients randomised to pioglitazone therapy ranged between 24.4 and 33.7 kg/m², two Japanese studies showed a mean BMI of 24.4 and 25.8. Metabolic control as measured by mean HbA1c varied in the pioglitazone arms between 7.4% and 10.3%, most participants ranged between 8% and 9%.</p>				<p>the primary composite endpoint did not disclose statistically significant differences between intervention and control groups.</p> <p>Metabolic control *HbA1c Active glucose-lowering compounds like metformin, glibenclamide, gliclazide or glimepiride resulted in similar reductions of HbA1c compared to pioglitazone treatment.</p> <p>Weight gain 15 studies evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment, 7 studies described a rise in body mass index up to 1.5 kg/m².</p> <p>Adverse events The percentage of overall and serious adverse events was comparable between intervention and control groups. The review noted a somewhat higher discontinuation rate following pioglitazone administration especially in comparison to monotherapy with other oral antidiabetic drugs. However, true numbers were difficult to evaluate due to study protocols defining withdrawals because of lack of efficacy as a serious adverse event.</p> <p>6 studies reported a more pronounced (sometimes dose-related) decrease of haemoglobin after pioglitazone intake in comparison to other active compounds or placebo. Haemoglobin reductions ranged between 0.5 and 0.75 g/dl</p>	
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								<p>Oedema The specific adverse event "oedema" was evaluated in 18 of 22 studies. Overall, 11,565 participants provided data on the occurrence of oedema. The total number of events was 842 in the pioglitazone and 430 in the control groups. Pooling of the 18 studies revealed a relative risk of 2.86 (95% confidence interval (CI) 2.14 to 3.18, $p < 0.00001$). The test for heterogeneity indicated an I²-value of 45.8%. The use of a fixed-effect model resulted in a risk ratio of 1.98 (95% CI 1.78 to 2.20). The robustness of this result was also tested by repeating the analysis using the odds ratio as a different measure of effect size, demonstrating an odds ratio of 3.15 (95% CI 2.34 to 4.23) and 2.22 (95% CI 1.96 to 2.52) for a random-effects and fixed-effect model, respectively.</p> <p>Hypoglycaemia Eleven of the 22 included studies showed data on hypoglycaemic episodes: Compared to active monotherapy control pioglitazone treatment resulted in somewhat lower rates of hypoglycaemia. If pioglitazone was combined with insulin more hypoglycaemic incidents happened. The biggest trial which compared pioglitazone versus placebo in combination with a variety of other glucose lowering drugs reported hypoglycaemia rates of 27.9% after pioglitazone and 20.1% after placebo combinations (Dormandy 2005). Severe</p>	
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Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Sour of fundi
A. M. Lincoff, Wolski.K., S. J. Nicholls, and S. E. Nissen. Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Trials. <i>JAMA : the journal of the American Medical Association</i> 298 (10):1180-1188, 2007. ID 5051	MA 1+	19 trials with 16,390 patients	General: adult patients with Type 2 diabetes mellitus and inadequate glycemic control and excluded patients with undue safety risks. Other criteria were variable between trials	Pioglitazone (monotherapy or combination)	Placebo or active comparator	Range: 16 to 104 weeks	Death, MI, Stroke, Serious heart failure	<p>hypoglycaemic events were rarely reported.</p> <p>Death/MI/Stroke: Odds/HR 0.82 (95% CI 0.72 to 0.94) p=0.005</p> <p>Death/MI: Odds/HR 0.85 (95% CI 0.73 to 0.99) p=0.04</p> <p>Serious heart failure: Odds/HR 1.41 (95% CI 1.14 to 1.76) p=0.002</p>	Take

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow- up	Outcome measures	Effect size	Source of funding
<p>Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, and Schernthaner G. 2005. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. Diabetes/Metabolism Research Reviews: 21: 167 - 174 REF ID: 127.</p> <p>*****</p> <p>Charbonnel B,</p>	<p>RCT. Multicentre double-blind</p> <p>1++</p>	<p>N= 630 randomized</p> <p>ITT=620 (10 patients were not eligible due to missing HbA1c data)</p> <p>Patients from 75 centers in nine European countries and Australia.</p>	<p>Male and female patients with T2D, inadequately managed with metformin alone (at ≥ 505 of the maximum recommended dose or at the maximum tolerated dose for ≥ 3 months) were screened.</p> <p>Inclusion criteria : age between 35 and 75 years, inclusive; HbA1c of $\geq 7.5\%$ or $\leq 11.0\%$; fasting C- peptide of $\geq 1.5\text{ng/ml}$ (0.5 nmol/l) and stable or worsening glycaemia control</p>	<p>N=317</p> <p>Pioglitazone 15mg o.d + Metformin at pre- study dose</p> <p>16-weeks forced dose titration²</p> <p>pioglitazone dose was titrated to 30mg and 45mg</p> <p><u>At the end of the 16-week, 70% of patients had been titrated to the maximum pioglitazone dose (45mg o.d.)³</u></p>	<p>N=313</p> <p>Gliclazide 80mg o.d + Metformin at pre- study dose</p> <p>16-weeks forced dose titration</p> <p>gliclazide dose was titrated to 160mg, 240mg (160mg + 80mg) and 320mg (160mg b.d.).</p> <p><u>At the end of the 16-week,</u> 33% of patients were receiving the maximum gliclazide dose of</p>	52 weeks	<p>Primary efficacy measure: Change in HbA1c from baseline to Week 52.</p> <p>Secondary endpoints: FPG Lipid profile Albumin/creatinine ratio Adverse events</p>	<p>*HbA1c 52 weeks No statistically significant between-group differences</p> <p><i>Two year follow-up</i> The differences in the changes from baseline among the ITT population were not statistically significant at week 104 (although there was a statistically significant between group difference in HbA1c reduction at week 104 in patients treated for a minimum of 18 months (per protocol population; 1.07% and 0.76% with pioglitazone and gliclazide respectively, $p=0.003$).</p> <p>*FPG 52 weeks No statistically significant between-group differences</p>	Takeda and Eli Lilly

¹ NB This is the 2 year follow-up for the Matthews study ID127 and the Hanefeld study (SEC 1 question) ID 396

² Cessation of titration or down-titration was permitted only on the basis of tolerability issues, including actual hypoglycaemia or increased risk of hypoglycaemia. Patient continued to the next dose level, unless the investigator considered that the increase could put them at risk or hypoglycaemia (increase postponed for one visit from week 4 or week 8 or week-8 dose maintained for rest of study), or the patient reported symptomatic hypoglycaemia (1-step reduction) or if the patient experienced adverse events that required dose reduction (1-step reduction at week 8, 12 or 16 with no further down titration)

³ The mean daily doses of study medication at Week 16 were 39-mg pioglitazone and 212-mg gliclazide

<p>Scherthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes¹. Diabetologia 2005; 48(6):1093-1104. Ref ID: 3137</p>			<p>for ≥ 3 months prior to screening.</p> <p>Previous treatment with insulin, gliclazide, pioglitazone or other sulphonylureas or glitazones was not permitted</p> <p>Females had to be postmenopausal, sterilized or using satisfactory contraception.</p> <p>The groups were well balanced with respect to demographic and metabolic characteristics.</p> <p><u>In the Met/Pio group</u> HbA1c 8.71\pm1.00, BMI 32.6\pm5.0, mean metformin dose 1726mg/day</p>	<p>36-week maintenance phase⁴</p> <p>The dose of pioglitazone achieved at week 16 was maintained for the remaining 36 weeks.</p>	<p>320mg/day</p> <p>36-week maintenance phase</p> <p>The dose of gliclazide achieved at week 16 was maintained for the remaining 36 weeks.</p>		<p><i>Two year follow-up</i></p> <p>There was a statistically significant difference in FPG between the pioglitazone add-on to metformin group and the gliclazide add-on to metformin group at week 104 (-1.8 vs -1.1 mmol/l, p<0.001).</p> <p>*Triglycerides – HDL <i>52 weeks</i> Treatment with Met/Pio resulted in a decrease from baseline triglyceride levels of 0.60 mmol/L and a mean increase in HDL of 0.18 mmol/L at Week 52. In the group Met/Gli there was a 0.22 mmol/L decrease in triglycerides and no change in HDL.</p> <p>The differences between groups were statistically significant favouring the Met/Pio treatment (p<0.001 log-transformed data). <i>(No other data was reported)</i></p> <p>*LDL <i>52 weeks</i> Met/Pio treatment was associated with a mean increase in LDL of 0.27 mmol/L compared</p>	
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⁴ no decrease in metformin dose from pre-study level was permitted

⁵ Two patients receiving Met/Gli were withdrawn following hypoglycaemic episodes

⁶ In the Met/Pio group, oedema led to one patient being withdrawn from the study and two patients had pulmonary, but no peripheral, oedema (one unrelated to the study drug; the other was a serious adverse events associated with myocardial infarction and judged to be related to the study drug by the reporting investigator).

			<p><u>In the Met/Gli group</u> HbA1c 8.53±0.89, BMI 32.6±5.8, mean metformin dose 1705mg/day</p>				<p>to a decrease of 0.11 mmol/L in LDL with Met/Gli treatment</p> <p>The differences between groups were statistically significant favouring the Met/Gli treatment (p<0.001 log-transformed data). <i>(No other data was reported)</i></p> <p><i>Lipids (two year follow-up)</i> There was a statistically significant percentage difference between the pioglitazone add-on to metformin group and the gliclazide add-on to metformin from baseline to last value for triglycerides (-23% vs -7%; p<0.001), HDL cholesterol 22% vs 7%; p<0.001) and LDL cholesterol (2 vs -6%; p<0.001).</p> <p><i>*Body weight</i> 52 weeks There were mean increases in body weight of 1.5 kg in the Met/Pio group and 1.4 kg in the Met/Gli group</p> <p><i>Two year follow-up</i> There was a mean increase from baseline of 2.5kg in the pioglitazone group and 1.2kg in the gliclazide group.</p> <p><i>*Adverse events</i> 52 weeks AE occurred in similar</p>	
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								<p>proportions of patients in both treatment groups:</p> <p><u>Met/Pio</u> 55.5% n=176; with a total of 533 events, of which 140 were study-related</p> <p><u>Met/Gli</u> 58.1% n=182; with a total of 628 events, of which 210 were study-related</p> <p>Hypoglycaemia was the most commonly reported event and occurred more frequently in the Met/Gli group⁵ (n=35; 11.2%) than in the Met/Pio group (n=4; 1.3%)</p> <p>In the Met/Pio group the most commonly occurring event was oedema, reported for 20 patients (6.3%)⁶ versus 7 patients (2.2%) in the Met/Gli group. The oedema was no associated with an increased incidence of heart failure.</p> <p>Discontinuation</p> <p><u>Met/Pio</u> Did not complete week 52 17.7% Adverse events 4.1%</p> <p><u>Met/Gli</u> Did not complete week 52 13.4% Adverse events 4.5%</p>	
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								<p><i>Two year follow-up</i></p> <p>A similar number of patients in each group discontinued the add-on therapy due to adverse events with 6.9% in the pioglitazone add on to metformin group vs 6.9% in the gliclazide add on to metformin group.</p> <p>There were more symptoms of hypoglycaemia (11.5% vs 2.2%) and GI disorders (5.1% vs 3.8%) in the gliclazide group but less aggravated congestive heart failure (0.6% vs 1.6%) and oedema (3.5% vs 7.6%) than in the pioglitazone group.</p>	
Davidson JA, Perez A, Zhang J. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: Results of a double-blind, multicentre, randomized study. Diabetes, Obesity &	RCT Double-blind 1+	N= 690	<u>Inclusion criteria:</u> adults ≥ 18 with T2D and poorly controlled glycaemia (A1C ≥8% at screening) despite therapy with a stable insulin regimen were selected. Eligible patients must have	Pioglitazone30mg + Insulin ^{7 8} N= 345	Pioglitazone45mg + Insulin N= 345	24 weeks	HbA1c FPG Lipid profile Adverse events	<p>HbA1c</p> <p>Statistically significant mean decreases from baseline A1c were observed in both treatment groups at each monthly, post-baseline evaluation (p≤ 0.05).</p> <p>Pioglitazone 45 vs. 30 mg was statistically significant from week 8 to week 24 (p≤ 0.05). From baseline to week 24 , LS mean A1C decreases were 1.2 from</p>	Takeda

Patients were required to discontinue taking any antidiabetic medication other than insulin 2 weeks before entering the 1-week single-blind lead-in period and were to avoid concurrent use of a corticosteroid for more than 2 weeks. During the double-blind, active treatment period, investigators were permitted to modify (i.e. change timing of doses or relative proportions of insulin products) or decrease (but not increase) their patient's insulin dosages, as necessary in response to hypoglycaemia (FPG <60 mg/dl on two occasions or symptoms of hypoglycaemia not explained by other conditions). Three of these patients had a history of CHF, hypertension and MI before enrolment in the study, and one patient had a history of confounding factors but no CV disease.

<p>Metabolism 2006; 8(2):164-174. Ref ID: 279</p>			<p>received 30 or more units per day of the same insulin type for at least 30 days immediately prior to screening. Patients were required to have a BMI between 25 and 45 kg/m² and have been willing to participate in dietary counselling, follow and ADA-recommended diet and measure blood glucose on a daily basis using a SM test.</p> <p><u>Exclusion criteria:</u> history of T1D, diabetic ketoacidosis, chronic alcoholism or drug abuse in the prior year, persistent microscopic or unexplained macroscopic haematuria, or cardia or cerebrovascular conditions (e.g. MI, coronary angiography or bypass graft</p>				<p>9.9% and 1.5 from 9.7% in the pioglitazone 30- and 45-mg groups, respectively (p<0.0001 for each relative to baseline; p=0.011, 30 vs. 45 mg)</p> <p><u>Subgroup analysis</u> Mean decreases from baseline in A1C were greater among patients with baseline A1C> 9.0% but were not affected by gender, age, race or baseline dose of insulin. In comparison with baseline, as significantly higher (p<0.001) proportion of patients in each treatment group had A1C< 7% at week 24 (13.1 and 22.3% of patients in the pioglitazone 30- and 45-mg groups, respectively, compared with 0.3% at baseline for both groups; p<0.001 for 30 vs. 45 mg at week 24)</p> <p>FPG From baseline to week 24, LS mean FPG decreases were 32mg/dl from a baseline of 202mg/dl and 46 mg/dl from 199mg/dl, respectively, relative to baseline values in the pioglitazone 30- and 45 groups (p<0.0001) for each relative to baseline; p=0.015, 30 vs 45mg)</p> <p>Lipid profile At 12 and 24 weeks, patients in the pioglitazone 45-mg group had significant reductions from baseline (p≤0.05) in free fatty</p>	
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			<p>surgery, unstable angina, transient ischaemic attacks or cerebrovascular accident) within 6 months before screening. Pregnant or lactating women and patients with significant CV disease (CHF class III or IV or with left ventricular ejection fraction <40%), active liver disease, hypothyroidism, abnormal laboratory data or unstable medical conditions were excluded.</p> <p>The two groups were well matched at baseline</p>				<p>acids, triglycerides and VLDL cholesterol and significant increases from baseline ($p \leq 0.05$) in HDL cholesterol. Patients in the pioglitazone 30-mg group had significant reduction from baseline ($p \leq 0.05$) in free fatty acids at 12 and 24 weeks and in triglycerides and VLDL cholesterol at 12 weeks.</p> <p>NS differences were identified between the two groups.</p> <p>Adverse events The overall incidence of drug-related adverse events with onset during the double-blind treatment period were 59% (202/345) in the 30-mg group and 68% (234/345) in the 45-mg group ($p=0.0072$). most AE were mild or moderate in intensity. The most commonly reported drug-related AE were hypoglycaemia (37 and 43% of patients respectively), followed by lower limb oedema (13 and 12%), weight gain (7 and 13%~) and aggravated oedema in patients with oedema at baseline (4 and 3%).</p> <p>At the last measurement , a mean increase in mean body weight was observed in both treatment groups: 2.94 and 3.38 kg in the 30- and 45-mg groups, respectively ($p < 0.001$ for both groups). Body weight increased</p>	
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							consistently over the course of the study. A statistically significant dose response for weight gain was observed at all time points. Frequency of CV adverse events related to study group was low and comparable between groups (1.2 and 0.6% for the 30- and 45-mg groups, respectively). Drug related CHF was reported for 3 patients receiving pioglitazone 30mg (one possibly related and two probably related) and one patient receiving 45mg (possibly related) ⁹ . * Drop outs Of the 690 patients who were randomly assigned and received study drug, 486 completed the assigned treatment, and 204 patients (29 and 30% of patients in the pioglitazone 30- and 45-mg groups, respectively)		
Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM. The effect of pioglitazone on	Post-hoc analysis of PROactiveRCT 1+	N= 2,445 ¹⁰	Inclusion criteria: patients with T2D who were aged 35–75 years if they had an HbA1c > 6.5% despite existing	Pioglitazone N= 1,230	Placebo N=1,215	T= 34.5 months	Primary end-point: all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, ACS, cardia	There was a significant beneficial effect of pioglitazone on the end points of fatal/nonfatal MI, excluding silent MI RR= 28%; P=0.045. Acute Coronary Syndrome	Takeda

The analysis presented here investigates the effects of treatment with pioglitazone versus placebo in patients who qualified for entry into the PROactive study (N= 5,238) on the basis of a previous MI 6 months or more before randomization

Objective evidence of coronary artery disease was defined as a positive exercise test, angiography showing at least one stenosis of more than 50%, or positive scintigraphy. Obstructive arterial disease of the leg was defined as a previous major amputation or intermittent claudication with an ankle or toe brachial pressure index of less than 0.9

<p>recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive 05 Study. J Am Coll Cardiol 2007; 49(17):1772-1780. Ref ID: 4935</p>			<p>treatment with diet alone or with oral glucose-lowering agents with or without insulin. Patients also had to have evidence of extensive macrovascular disease before recruitment, defined by one or more of the following criteria: MI or stroke at least 6 months before entry to the trial, PCI or coronary artery bypass surgery at least 6 months before recruitment, acute coronary syndrome at least 3 months before recruitment, or objective evidence of coronary artery disease¹¹ or obstructive arterial disease in the leg.</p> <p>Exclusion criteria: Patients were excluded if they had T1D; were</p>				<p>intervention, or PCI, leg revascularization, and amputation above the ankle.</p> <p>Secondary endpoint: Death from any cause, nonfatal MI (excluding silent MI) or nonfatal stroke.</p> <p>Adverse events</p>	<p>RR=37%; p=0.035</p> <p>and the composite cardiac endpoint (nonfatal MI [excluding silent MI], coronary revascularization, ACS, or cardiac death) RR=19% P=0.034</p> <p>There were non significant differences in the primary or main secondary end points defined in the main PROactive study, and the individual endpoints of the primary composite .</p> <p>Adverse events As with the total PROactive study population, there were fewer patients with serious adverse evens in the pioglitazone group versus the placebo group (580 [47.2%] vs 620 [51.0%]) in the patients with T2D and previous MI.</p> <p>The incidence of HF was significantly higher in patient receiving pioglitazone (13.5 vs 9.6%; p= 0.003). The incidence of serious HF (requiring hospitalization) was also significantly higher in the pioglitazone group (7.5% vs 5.2%; p= 0.022)</p> <p>As expected, HF occurred in a</p>	
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			<p>taking only insulin; had planned coronary or peripheral revascularisation; had New York Heart Association class II heart failure or above; had ischaemic ulcers, gangrene, or rest pain in the leg; had had haemodialysis; or had greater than 2.5 times the upper limit of normal concentrations of alanine aminotransferase</p> <p>Patient characteristics, baseline laboratory data, and previous macrovascular morbidities were well balanced between the patients in the pioglitazone group and those in the placebo group.</p>				<p>greater proportion of patients in the MI subgroup (11.6%) than in those without previous MI (7.0% $p<0.0001$). The HR for any HF event in the previous-MI subgroup versus those who did not have a previous MI was 1.68 ($p<0.0001$)</p>	
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<p>Mattoo V, Eckland D, Widel M, Duran S, Fajardo C, Strand J et al. Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group study. <i>Clinical Therapeutics</i> 2005; 27(5):554-567. Ref ID: 30</p>	<p>RCT Double blind, multicentre. 1+</p>	<p>N= 289</p>	<p>Inclusion criteria: T2D patients , ≥30 years old at the time of diabetes diagnosis, using insulin therapy (with or without an oral antidiabetic medication) for ≥3 months, with an HbA1c ≥7.55 at screening.</p> <p>Exclusion criteria: T1D, previous glitazones use, clinical signs or symptoms of any chronic systemic condition (liver disease, diminished cardiac function, renal impairment, transplantation or dialysis, HIV infection), or signs or symptoms of drug or alcohol abuse.</p> <p>The two groups were well matched at baseline</p>	<p>Pioglitazone 30mg + Insulin¹² N= 142</p>	<p>Placebo + insulin N= 147</p>	<p>6 months</p>	<p>HbA1c FPG Lipid profile Adverse events</p>	<p>HbA1c At baseline the mean HbA1c value for the PIO+INS group was 8.85%. this improved to 8.11% at end point (p<0.002). In the PLB+INS group, the mean HbA1c value at baseline (8.79%) was unchanged at end point (8.66%). There was a significant difference between the two groups (-0.55; p<0.002)</p> <p>After 6 months, the % of patients who attained HbA1c values <7.0% was 18% with PIO+INS and 6.9% with PLB+INS.</p> <p><u>Subgroup analysis</u> PIO+INS improved HbA1c regardless of regimen (subgroup analysis of patients using ≤2 or ≥3 insulin injection/day revealed no differences in HbA1c)</p> <p>In addition, PIO+INS improved HbA1c regardless of OAM use before the study.</p> <p>a) Patients who used OAMs before study entry: PIO +INS (n=68), the mean HbA1c reduction from baseline was -0.90% (p<0.002) and for the PLB+INS group (N=76), the reduction from baseline was -</p>	<p>Eli Lilly</p>
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The study was composed of 3 period: lead-in (up to 14 days) , insulin intensification (3 months), and treatment (6 months). Being the latter the actual RCT

							<p>0..11% (p=NS). There was a significant difference between the treatment groups (p<0.002)</p> <p>b) Patients who did not use OAMs before study entry: PIO+INS (N=70), the mean HbA1c reduction from baseline was -0.65% (p<0.002) and for the PLB+INS group (N=67), the reduction from baseline was -0.2% (p=NS). There was a significant difference between the treatment groups (p<0.004)</p> <p>FPG The mean FPG level at baseline in the PIO+INS group (11.36 mmol/L) improved at end point (10.14 mmol/L), with a mean reduction of -1.45 (p<0.002). in the PLB+INS group, mean FPG at baseline (11.27 mmol/L) remained unchanged at end point (11.95 mmol/L). At end point the difference between the treatment meant for FPG was significant (1.80 mmol/L; p<0.002)</p> <p>Lipid profile HDL The mean HDL level of the PIO+INS group at baseline (1.23 mmol/L) increased significantly at end point (1.35 mmol/L; p<0.002). The mean HDL level of the PLB+INS group at baseline (1.24 mmol/L) was unchanged at</p>	
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							<p>end point (1.21 mmol/L). the difference between treatment groups was significant (0.13 p<0.002)</p> <p>LDL No changes. NS differences between groups.</p> <p>Tg No changes. NS differences between groups.</p> <p>Adverse events 263 patients (91.0%) completed the study. There were 330 AE in 109 patients in the PIO+INS group (7 AE caused patients to discontinue). In the PLB+INS group, there were 276 AE events in 98 patients (3 caused patients to discontinue)</p> <p><u>Hypo</u> There were 90 (63.4%) reported incidences of subjective hypoglycaemic episodes for PIO+INS and 75 (51.0%) for PLB+INS (p<0.05), but there was no difference between the treatment groups for clinical hypoglycaemia.</p> <p><u>Oedema</u> There were 20 cases of oedema with PIO+INS and 5 cases with PLB+INS</p> <p><u>Body weight</u></p>	
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									The mean increase in body weight with PIO+INS was 4.05 kg, and the mean increase with PLB+INS was 0.20 kg	
Hanefeld M. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. Diabetes Care 2004; 27(1):141-147. Ref ID: 396 ***** Charbonnel B, Scherthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes ¹³ . Diabetologia 2005;	RCT. Multicentre double-blind 1++	N= 639 From 91 centres in 12 European countries and Canada.	Inclusion criteria: Male and female patients with T2D, inadequately controlled with sulphonylurea monotherapy (at ≥50% of the maximal recommended dose or at the maximal tolerated dose for ≥ 3months) and with stable or worsening glycemic control for ≥ 3 months were eligible if the HbA1c was between 7.5 and 11.0% at screening.	Pioglitazone 15mg + SU at pre-study dose N= 319 12-weeks forced dose titration ¹⁴ pioglitazone dose was titrated to 30mg and 45mg 40-week maintenance period The dose of pioglitazone achieved at week 12 was maintained for	Metformin 850mg + SU at pre-study dose N=320 Metformin up to 2,550mg daily 40-week maintenance period The dose of metformin achieved at week 16 was maintained for the remaining 406 weeks.	52 weeks	HbA1c FPG Lipid profile	*HbA1c 52 weeks <u>NS difference between-treatment differences.</u> HbA1c was reduced by 1.20% in the SU plus pioglitazone group and 1.36% in the SU plus metformin group (p=0.065) The % of patients achieving an HbA1c <7.0% was similar in both groups (39% in the pioglitazone group; 40% in the metformin group) <i>Two year follow-up</i> <u>NS difference between-treatment differences</u> HbA1c was reduced by 1.03% with pioglitazone addition to SU and by 1.16% with metformin addition to SU (p=0.173) At week 104 the % of patients achieving an HbA1c <7.0% was similar in both groups (30.2% in the pioglitazone group; 28.4% in the	Takeda and Eli Lilly	

¹³ NB This is the 2 year follow-up for the Matthews study ID127 and the Hanefeld study (SEC 1 question) ID 396

¹⁴ Cessation of titration or down-titration was permitted only on the basis of tolerability issues, including actual hypoglycaemia or increased risk of hypoglycaemia. Patient continued to the next dose level, unless the investigator considered that the increase could put them at risk or hypoglycaemia

<p>48(6):1093-1104. Ref ID: 3137</p>				<p>the remaining 40 weeks.</p>			<p>metformin group) p=0.635</p> <p>*FPG 52 weeks <u>NS difference between-treatment differences</u> FPG was reduced by -2.2 mmol/l with SU plus pioglitazone and -2.3 mmol/l with SU plus metformin. P=0.528</p> <p><i>Two year follow-up</i> <u>NS difference between-treatment differences</u> From baseline to week 104, FPG was reduced by 2.0 mmol/l in the SU plus pioglitazone group and 1.9 mmol/l in the SU plus metformin. P=0.506</p> <p>*Lipid profile 52 weeks Triglycerides With SU plus pioglitazone triglycerides were reduced by 0.42 mmol/l and by 0.28 mmol/l in the SU plus metformin group (P<0.008)</p> <p>HDL In the SU plus pioglitazone group HDL was increased by 0.16 mmol/l in the SU plus pioglitazone and by 0.09 mmol/l in the SU plus metformin group (p<0.0001)</p> <p>LDL There was an increase of 0.08 mmol/l in LDL in the SU plus pioglitazone compared with a decrease of 0.16</p>	
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								<p>mmol/l in the SU plus metformin group p=0.0002</p> <p>TC/HDL ratio It was reduced to a similar extent in both groups from baseline to week 52</p> <p><i>Two year follow-up</i> Pioglitazone added to SU caused a significantly greater decreases in triglyceride levels and significantly greater increases in HDL level (p≤ 0.001)</p> <p>Decreases for LDL and TC were significantly greater in the Metformin addition to SU group compared to the pioglitazone addition to SU. (P<0.001 for LDL and p≤ 0.005 for TC)</p> <p>* Body weight 52 weeks Mean weight gain of 2.8kg was observed in the pioglitazone group compared with a reduction of 1.0 kg in the metformin group over the 52 weeks.</p> <p><i>Two year follow-up</i> At week 104, there was a mean weight increase of 3.7 kg when pioglitazone was added to SU compared to a decrease of 1.7kg when metformin was added to SU.</p>	
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							<p>*Adverse events AE occurred in similar proportions of patients in both treatment groups both at 52 and 104 weeks.</p> <p>GI <i>52 weeks</i> occurred more frequently in the metformin than in the pioglitazone arm (23.4 vs 12.2%) with diarrhoea, in particular occurring more frequently in the metformin group (12.5% vs 2.5%). <i>104 weeks</i> Occurred more frequently in the metformin than in the pioglitazone arm (19.4 vs 6.3%)</p> <p>CV <i>52 weeks</i> There was no difference in the incidence of cardiac disorders between groups (3.1% in the SU plus Pio and 4.1% in the SU plus metformin group), and no relationship to edema was noted in either treatment groups. <i>104 weeks</i> 2 cases in the pioglitazone group (0.6%) vs 3 cases in the metformin group (0.9%)</p> <p>HYPOs <i>52 weeks</i> Hypo events were the most frequently occurring AD in both groups with a slightly higher incidence in the SU plus metformin group (14.1 vs 10.7%) <i>104 weeks</i> a slightly higher incidence was seen in</p>	
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								the SU plus metformin group (15.6 vs 11.3%) OEDEMA 52 weeks Mild to moderate edema was the most commonly reported AE in the SU plus pioglitazone group (6.9 vs 1.6%) 104 weeks More frequent in the pioglitazone group (10.7 vs 2.8%)	
Jain R, Osei K, Kupfer S, Perez AT, Zhang J, Lannon MM. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. <i>Pharmacotherapy</i> 2006; 26(10):1388-1395. Ref ID: 4854	RCT double blind, multicentre 1-	N= 502	Inclusion criteria: patients with recently (≤ 2 yrs) diagnosed T2D unsuccessfully treated with diet and exercise. Treatment-naïve men and nonpregnant, nonlactating women 18-80 years of age, from the United States or Puerto Rico, were eligible for enrolment. At screening, patients were required to have HbA1c between 7.5% and 11.5%, fasting C-	Pioglitazone ¹⁵ N= 251	Glyburide N= 251	56 weeks - 16-week titration period and - 40-week maintenance period	HbA1c	HbA1c After 56 weeks no difference in HbA1c was observed between the two treatments (mean treatment difference -0.05%, $p = 0.669$). Body weight At the final visit, mean \pm SD weight increase from baseline was significantly greater in the pioglitazone group than the glyburide group (3.66 ± 6.138 kg vs 1.95 ± 5.354 kg, $p < 0.001$). Adverse events Overall, hypoglycaemia was the most common adverse event; treatment with glyburide produced a significantly greater rate of hypoglycaemia (24.3%)	Takeda

¹⁵ At visit 1, all patients were instructed to take one tablet (pioglitazone or placebo) and one capsule (glyburide or placebo) each morning. During a 16-week titration period, glucose control was optimized by achieving and maintaining fasting plasma glucose levels between 69 and 141 mg/dl. Pioglitazone or glyburide dosages could be increased every 4 weeks in increments of 15 or 5 mg/day, respectively, to a maximum of pioglitazone 45 mg/day or glyburide 15 mg/day. After titration, patients began 40-week double-blind treatment in which the optimal study drug dosage was maintained for each patient. Patients were required to bring study drug containers to each visit, and tablets were counted to assess treatment compliance.

¹⁶ During the 40-week maintenance period, the range of mean \pm SD daily doses at each visit was 9.9 ± 4.33 to 10.5 ± 4.31 mg for glyburide and 34.9 ± 11.64 to 37.6 ± 11.30 mg for pioglitazone. The median daily dose at each visit was 10 mg for glyburide and 45 mg for pioglitazone

		<p>peptide level of 1.0 ng/ml or greater, and fasting plasma glucose level above 120 mg/dl.</p> <p>Exclusion criteria: Any patient whose treatment had previously failed due to lack of efficacy or signs of intolerance, or who had recently (< 3 mo) undergone treatment with rosiglitazone, pioglitazone, or troglitazone could not participate in the study.</p> <p>Patients were also excluded if they had a chronic condition expected to require recurrent glucocorticoid use, New York Heart Association class III or IV heart failure, an acute cardiovascular event within 6 months before screening including MI, Cerebrovascular accident, evidence of an ongoing cardiac disturbance, evidence of acute or unstable chronic pulmonary</p>				<p>than that with pioglitazone (4.4%, $p < 0.001$)</p> <p>Edema occurred in 7.9% of patients (20 patients) taking pioglitazone and 4.8% of patients (12 patients) taking glyburide ($p = 0.1443$); these occurrences were constituted primarily by lower extremity edema</p> <p>Drop-out Of the 251 patients in each treatment group, 128 (51.0%) glyburide-treated patients and 134 (53.4%) pioglitazone-treated patients completed the study. <u>Overall dropout = 48%</u></p>	
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			disease or lesions at chest radiography, or a history of cancer not in remission for at least 5 years. Baseline demographic characteristics such as age, sex, and weight were comparable between groups. In addition, no clinically relevant differences were noted between treatment groups in type of drugs taken or percentage of patients taking any concomitant drugs						
Raz I, Stranks S, Filipczak R, Joshi P, Lertoft B, Rastam J et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: An 18-week, randomized, open-label study. Clinical Therapeutics 2005; 27(9):1432-1443. Ref ID: 586	RCT 1+	N=283 (27 sites in 8 countries)	Patients with type 2 diabetes Inclusion criteria: Treatment with SU therapy ≥ 3 months before screening and insufficient glycaemic control (HbA _{1c} 7.4%-14.7%) Whether the patients were previously on a maximum or stable dose of SU was not assured Age ≥ 18 yrs BMI ≤ 40 kg/m ² Exclusion criteria Patients with a significant disease or	N=93 BIAsp 30 plus pioglitazone (PIO) BIAsp 30 twice daily with and PIO mg once daily. The BIAsp dose was titrated individually to achieve target blood glucose levels of 5 to 8 mmol/L (90-144 mg/dL) for fasting, preprandial and nighttime	N=91 Glibenclamide (GLIB) plus PIO GLIB up to 15 mg daily (some patients exceeded this dose). PIO as for intervention N=97 BIAsp 30 As for intervention	18 weeks	HbA _{1c} FPG PPG Lipid profile Adverse events	HbA_{1c} After the 18-week treatment period, HbA _{1c} levels in the BIAsp 30 plus PIO group were significantly lower than in the GLIB plus PIO group (mean [SD], -0.64%[0.23%]; p = 0.005) and the BIAsp 30 monotherapy group (-0.60%[0.22%]; p = 0.008). Mean (SD) end-of-trial Hb1AC values were 8.4% (1.2%) for the BIAsp 30 monotherapy group, and 9.0% (2.1%) for the GLIB plus PIO group. From baseline to end of trial, HbA _{1c} values decreased in all three treatment groups but the reductions were not significant Fasting blood glucose (FBG) The reductions seen in FBG at the end of trial compared with baseline were not significant.	Novo Nordisk A/S

Comment [JD2]: Study was included in the INS6 question

			<p>condition likely to effect trial or health outcomes</p> <p>The study population (means) was: age 55.9 yrs BMI 29.5 kg/m², duration of diabetes 9.7 yrs HbA_{1c} 9.5%.</p>	<p>measurements, and 5 to 10 mmol/L (90-180 mg/dL) for postprandial readings</p>				<p>PPG At the end of trial, the mean prandial increment (postprandial glucose minus preprandial glucose) after breakfast, lunch, and dinner for BIAsp 30 plus PIO was significantly lower than seen for GLIB plus PIO (-14 mg/dL; p = 0.012).</p> <p>Lipid profile LDL NS differences</p> <p>Tg Triglyceride values in patients who received BIAsp 30 monotherapy were 30 mg/dL lower than those who received GLIB (p < 0.05), while those receiving BIAsp 30 plus PIO showed a 39 mg/dL difference compared with the GLIB plus PIO (p < 0.01).</p> <p>TC NS differences</p> <p>HDL At end-of-trial HDL cholesterol levels were significantly higher in the groups receiving BIAsp 30 plus PIO than in the other two groups (mean [SD], 4 [1] mg/dl via BIAsp 30 monotherapy [P ≤ 0.001]; 3 [1] mg/dL vs GLIM plus PIO [P < 0.01]).</p> <p>Adverse events (AEs) The most commonly reported AEs (incidence >5%) were upper</p>
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								<p>respiratory tract infections (13%-21% of exposed patients), headaches (4%-10%), edema (12%-9%), and weight increase (2%-8%). More patients experienced product-related AEs in the BIAsp 30 plus PIO group (28%) compared with patients received BIAsp monotherapy (20%) or GLIM plus PIO (16%).</p> <p>Edema BIAsp 30 plus PIO was associated with a higher proportion of patients experiencing peripheral edema (6%) compared with GLIM plus PIO (1%) and BIAsp 30 (0%).</p> <p>Body weight More patients in the BIAsp 30 plus PIO experienced an increase in weight (8%; mean weight gain 4.0 kg) compared with those in the BIAsp monotherapy group (3%; mean weight gain, 2.2 kg) and the GLIM plus PIO group (2%; mean weight , 2.2 kg).</p> <p>Hypos Fewer minor hypoglycaemic episodes were experienced in the GLIM plus PIO group (3 episodes) versus the BIAsp 30 plus PIO group (15 episodes) and the BIAsp 30 monotherapy group (47 episodes). The incidence of all hypoglycaemic episodes was significantly higher in the BIAsp 30 monotherapy group than in the other treatment groups:</p>
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