

Evidence Tables

Glit1 a: Is Rosiglitazone 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	Source of funding
Bailey CJ, Bagdonas A, Rubes J, McMorn SO, Donaldson J, Biswas N et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clinical Therapeutics 2005; 27(10):1548-1561. Ref ID: 3134	RCT 1++	N=569 randomised N=551 in the ITT analysis (at least one on-therapy efficacy measurement). 90 centres in 14 European countries	Inclusion criteria: 18 to 70 years old with type 2 diabetes. Patients must have been treated with metformin 1 to 2 g/d alone or in combination with an oral insulin secretagogue or acarbose for at least 8 weeks before screening. FBG levels greater than or equal to 126mg/dL and less than or equal to 216mg/dL. Previous exposure to insulin or thiazolidinediones within 6 mths was an exclusion. Patients were mean age 58 years and 58% were male. Mean weight was 90kg with a mean BMI of 32kg/m ² . Mean HbA1c was 7.5% and mean FBG was 168 mg/dL.	N=280 MET For the first 8 weeks patients received metformin 2.5g/d. At week 8 this was escalated to metformin 3g/d.	N=288 RSG / MET For the first 8 weeks patients received rosiglitazone combined with metformin 4mg/2g per day. At week 8 this was escalated to rosiglitazone combined with metformin 8mg/2g per day.	24 weeks	Mean change in HbA1c after 24 weeks of treatment. Mean change from baseline in FPG. Proportion of patients achieving target HbA1c and FPG levels. Lipid profile, weight, adverse events.	<p>*HbA1c There was a reduction in mean (SD) HbA1c in the RSG/MET group from 7.4% (1%) to 7.1% (1.1%) compared with a reduction from 7.5% (1%) to 7.4% (1.1%) with MET. After adjusting for baseline HbA1c, country and sex the treatment difference was -0.22% (95%CI -0.36 to -0.09, p=0.001).</p> <p>*FPG Mean (SD) FPG was reduced from 166.2 (29) to 144.1 (33) mg/dL in patients treated with RSG/MET at week 24 and from 169.3 (33) to 164.0 (37) mg/dL in patients treated with MET (treatment difference, -18.3 mg/dL 95%CI -23.5 to -13.2; p<0.0001).</p> <p>* Proportion of patients achieving target levels The proportion of patients achieving target levels of glycaemia at week 24 was significantly greater in the RSG/MET group compared with the MET group (54% in the RSG/MET group achieved HbA1c levels <7% and 32% achieved FPG <126 mg/dL, compared with 36% and 8% in the MET group respectively. The OR for achieving target HbA1c with RSG/MET compared to MET was OR=2.42 (95%CI 1.59 to 3.7; p<0.001). This</p>	GSK

								<p>was OR= 5.71 (95%CI 3.37 to 9.66; p<0.001) for FPG.</p> <p>*Weight There was a mean (SE) increase from baseline in weight in the RSG/MET group (1.3(0.22)kg) and a mean decrease in the MET group (-0.9(0.26)kg) .</p> <p>* Lipid profile (% change from baseline for MET and RSG/MET respectively) Total chol:-0.1 vs -10.7 HDL chol:-1.3 vs 4.1 LDL chol: 3.4 vs 14.5 Trig:-8.5 vs -1.2. No statistically comparison between groups were reported</p> <p>*Adverse events Adverse events led to study withdrawal in 4% in the RSG/MET group and 8% in the MET group. GI disorders were the most common leading to withdrawal in 5% of the MET group and 3% in the RSG/MET group. -Three patients (1%) in the RSG/MET group and 1 patient (0.4%) in the MET group reported on-therapy hypoglycaemia. -The incidence of diarrhoea was 14% in the MET group and 6% with RSG/MET. This was 9% and 6% for abdominal pain respectively. -Edema was reported in 8 patients (3%) who received RSG/MET and in 3 (1%) in the MET group.</p>	
Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J et al. A randomized	Multicentre double blind RCT conducted	N=319 (ITT population 313)	People with type 2 diabetes aged 18 to 80 were eligible if receiving more than or equal to 30U	N=104 I +PBO Insulin plus placebo	N=106 I + RSG 4mg/day Insulin plus	26 weeks (proceeded by	HbA1c FPG	I + RSG 4mg/day group had a decrease in HbA1c from baseline from 9.1 ± 1.3 to 8.5 ± 1.4 which was significantly better than the placebo group	GSK

<p>trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes.[see comment]. Diabetes Care 2001; 24(7):1226-1232. Ref ID: 172</p>	<p>in 38 US centres. 1++</p>		<p>insulin/day. Patients were excluded if they had elevated liver enzymes, serum creatinine >160 mmol/l, anaemia, BMI <22 or >42kg/m², angina, marked LVH or uncontrolled hypertension. Mean age 57years, 46% female, mean BMI 32kg/m², mean 12.5 years since diagnosis. Approximately 70% white, 20% black and 10% other.</p>	<p>In all groups insulin was standardised to twice daily injections. This could be adjusted during the run-in period but remained constant thereafter unless dose reduction was required to avoid hypoglycaemia</p>	<p>rosiglitazone N=103 I + RSG 8mg/day Insulin plus rosiglitazone</p>	<p>a 4 week insulin standardisation period & a 4 week placebo run-in period</p>	<p>Lipid profile Total daily insulin dose Adverse events.</p>	<p>(p<0.0001). I + RSG 8mg/day group had a decrease in HbA1c from baseline from 9.0 ± 1.3 to 7.9 ± 1.4 which was significantly better than the placebo group (p<0.0001). I + RSG 4mg/day group had a decrease in FPG from baseline from 11.8 ± 3.2 to 9.5 ± 3.2 which was significantly better than the placebo group (p<0.0001). I + RSG 8mg/day group had a decrease in FPG from baseline from 11.6 ± 3.2 to 9.1 ± 3.3 which was significantly better than the placebo group (p<0.0001). For the three groups percentage change from baseline for insulin dose was -0.6 ± 8.2 for I +PBO, -5.6 ± 15.9 for I + RSG 4mg/day and -12.0 ± 20.2 for I + RSG 8mg/day. Mean serum triglyceride levels did not significantly change from baseline in either I +RSG group compared with a significant increase in patients receiving I +PBO. Mean total cholesterol (4mg change from baseline 0.51 + 1.15, p<0.0001 and for 8mg, 0.75 + 1.36, p<0.0001) LDL cholesterol (4mg change from baseline median 0.28, p=0.0001 and for 8mg, median 0.38, p<0.0001) and HDL cholesterol (4mg change from baseline 0.17 + 0.36, p=0.067 and for 8mg, 0.16 + 0.46, p=0.0005) increased significantly in both RSG treatments groups. However, median total:HDL cholesterol and LDL:HDL cholesterol ratios were without changes from baseline in either I +RSG group and</p>	
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								<p>were similar across all treatment groups.</p> <p>The most common adverse event was symptoms consistent with hypoglycaemia which was reported in 53% of the I +RSG 4mg group and 67% of the I +RSG 8mg group compared with 38% in the placebo group. In all but 4 patients this was classified as mild or moderate.</p> <p>More patients in the I+RSG groups reported edema (13% in the I +RSG 4mg group, 16% in the I +RSG 8mg group compared with 5% in the placebo group).</p> <p>Body weight increased in all treatment groups (mean increase 0.9, 4.0 and 5.3kg in the I+PBO, I +RSG 4mg group and I +RSG 8mg group respectively).</p>	
<p>Baksi A, James RE, Zhou B, Nolan JJ. Comparison of uptitration of gliclazide with the addition of rosiglitazone to gliclazide in patients with type 2 diabetes inadequately controlled on half-maximal doses of a sulphonylurea. Acta Diabetologica 2004; 41(2):63-69. Ref ID: 3150</p>	<p>RCT double-blind, placebo-controlled conducted in seven European countries</p> <p>Level of evidence: 1+</p>	<p>473 patients (466 comprised the ITT population)</p>	<p>Inclusion criteria: patients were eligible if they were aged 35-80 and had T2D with FPG values ≥ 7.0 and ≤ 15.0 mmol/l while treated with gliclazide 160mg/day</p> <p>Patients were excluded from the study if they had symptomatic diabetic neuropathy requiring treatment, congestive heart failure grades III-IV according to NYHA classification, unstable angina or angina</p>	<p>gliclazide 160mg/day + rosiglitazone 4mg BID</p>	<p>Gliclazide uptitrated to a maximum of 320mg/day¹ + Placebo matched</p>	<p>26 weeks</p>	<p>HbA1c FPG Lipid profile Adverse events</p>	<p>*HbA1c A reduction of 1.3% (p=0.0001) was observed in the combination treatment group compared to the uptitrated gliclazide group after 26 weeks.</p> <p>HbA1c was reduced by $\geq 0.7\%$ in 141 patients (65%) in the combination treatment group compared to 48 patients (21%) in the uptitrated gliclazide group. P<0.0001</p> <p>The proportion of patients who achieved an HbA1c valued <7% was also greater in the combination group (48% vs.22%)</p> <p>*FPG</p>	<p>GSK</p>

¹ In the uptitrated gliclazide group, patients received 240mg/day gliclazide plus placebo-matched rosiglitazone from day 1. After 2 weeks, these patients had the gliclazide dosage increased to 320mg/day if their fasting capillary blood glucose was >5.0 mmol/l. Patients with a FCBG of 3.1-5.0 mmol/l remained on 240 mg/day and those with FCBG <3.1 received 160mg/day gliclazide. In the combination group, patients received 160mg/day gliclazide plus 4mg BID rosiglitazone throughout.

			<p>requiring continual nitrate relief, clinically significant hepatic disease, anaemia or hypertension.</p> <p>Demographic and metabolic baseline characteristics were comparable between the two treatment groups.</p>				<p>FPG was reduced by 3.0 mmol/l (p=0.0001) in the rosiglitazone plus gliclazide group compared to the uptitrated gliclazide group after 26 weeks.</p> <p>*Lipid profile The combination treatment led to increases in plasma lipoproteins</p> <p>Gliclazide final dose In the uptitrated gliclazide group, 229 of 241 patients (95%) remained on 320 mg/day gliclazide. In the rosi + gliclazide group, 213 of 225 patients (95%) remained on 160 mg/day until study end.</p> <p>*Body weight A significant increase in body weight was observed in patients receiving rosiglitazone plus gliclazide versus uptitrated gliclazide (3.4 kg; p= 0.0001)</p> <p>*Adverse events: The % of patients reporting on-therapy adverse events in the rosi + gliclazide group (164, 71%) was higher than in the uptitrated gliclazide group (143, 59%)</p> <p>Severe hypoglycaemia Rosi: 6% total; 1% severe Gliclazide: 2% total; 0.4% severe Definition: Inability to perform normal daily activities</p> <p>Oedema More patients in the combination group experienced oedema (11% vs 3%)</p> <p>Drop-out</p>	
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								<p>After randomization 106 patients withdrew before completing 26 weeks of treatment. 70 patients (29%) in the uptitrated gliclazide group and 36 patients (16%) in the rosi + gliclazide group.</p> <p>The proportion of patients who withdrew due to lack of efficacy was greater in the uptitrated gliclazide group (19%) than in the rosi + gliclazide group (2%)</p>	
<p>Derosa G, Gaddi AV, Piccinni MN, Ciccarelli L, Salvadeo S, Peros E et al. Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2 diabetes mellitus and metabolic syndrome. Pharmacotherapy 2005; 25(5):637-645. Ref ID: 3139</p>	<p>Multicentre double blind RCT conducted in Italy. 1+</p>	<p>N=99 randomised N=95 completed the study</p>	<p>Patients with type 2 diabetes were eligible if they had a diagnosis of diabetes for at least 6 months, fasting C-peptide level above 1.0ng/ml, inadequate glycaemic control with diet and oral hypoglycaemic agents such as sulfonylureas or metformin both at maximum tolerated dose and a diagnosis of metabolic syndrome.</p> <p>Exclusion criteria: history of ketoacidosis, unstable or rapidly progressive retinopathy, nephropathy or neuropathy, impaired liver or kidney function or anaemia, unstable cardiovascular or cerebrovascular conditions within 6 months. 50% male/female split, mean age 53 years, mean diabetes duration 5 years, mean BMI 27kg/m², mean HbA1c 8%.</p>	<p>N=47 Glimepiride 2mg once a day before lunch and metformin 500mg 3 times a day</p>	<p>N=48 Rosiglitazone 4mg once a day before lunch and metformin 500mg 3 times a day</p>	<p>12 months</p>	<p>HbA1c% FPG BMI Adverse events</p>	<p>Significant BMI decreases were observed in both groups at 12 months (glimepiride-metformin p>0.05, rosiglitazone-metformin p<0.01) but there was no between group difference.</p> <p>Significant HbA1c and FPG decreases were observed in both groups at 12 months (glimepiride-metformin p>0.05 for both, rosiglitazone-metformin p<0.01 for both) but there was no between group difference.</p> <p>Of the 95 patients who completed the study, 4 (9%) of the 47 patients in the glimepiride group and 6 (13%) of 48 patients in the rosiglitazone group had adverse effects; the difference was not significant.</p>	<p>Not reported</p>

<p>Kerenyi Z, Samer H, James R, Yan Y, Stewart M. Combination therapy with rosiglitazone and glibenclamide compared with upward titration of glibenclamide alone in patients with type 2 diabetes mellitus. Diabetes Research & Clinical Practice 2004; 63(3):213-223. Ref ID: 894</p>	<p>RCT multicentre, double-blind, placebo-controlled 1+</p>	<p>340 patients from 14 European countries and Israel) ITT population 335</p>	<p>Inclusion criteria: Male and female patients aged 35-80 years of age, with T2D and with baseline FPG of 7-15 mmol/l while receiving a half-maximal dose (7.5 mg/day) of glibenclamide.</p> <p>Exclusion criteria: Chronic use of insulin, systolic blood pressure >180mmHg or diastolic blood pressure >114 mmHg, congestive heart failure grades I-IV, unstable or severe angina and clinically significant hepatic, renal or haematological impairment.</p> <p>Baseline characteristics and demographic data were comparable between the two treatment groups. Baseline HbA_{1c} values: 7.9 ± 1.2 for the combination group and 8.1 ± 1.3 for uptitrated glibenclamide</p> <p>Duration of diabetes (years) 5.6± 4.7 for the combination group and 6.7± 5.9 for the uptitrated glibenclamide.</p>	<p>Glibenclamide 7.5mg/day + Rosiglitazone 8mg/day (4mg bid) N= 165</p>	<p>Glibenclamide uptitrated to a maximum of 15mg/day² N= 170</p>	<p>26 weeks</p>	<p>HbA1c FPG Lipid profile Adverse events</p>	<p>HbA1c Combination therapy reduced HbA1c by 0.81% compared with glibenclamide monotherapy (P < 0.0001)</p> <p>The proportion of patients responding to therapy with ≥ 0.7% reduction in HbA1c at week 26 was significantly greater in the rosi plus glibenclamide group compared with the uptitrated glibenclamide group (61.3% versus 24.0%, respectively; p<0.0001).</p> <p>FPG Combination therapy reduced FPG by 2.4 mmol/l compared with glibenclamide monotherapy (P < 0.0001)</p> <p>The maximal reduction in FPG with rosiglitazone added to glibenclamide was achieved by week 12 and was then maintained throughout the remaining 14 weeks of the study. In contrast, mean FPG levels remained close to baseline throughout the 26 week study period in the glibenclamide group despite increasing the dose from 7.5 to 15mg</p> <p>Lipid profile Combination treatment increased HDL, LDL and total cholesterol. HDL cholesterol also increased in the up-titrated glibenclamide group, although total cholesterol and LDL were reduced. There were small and comparable reductions in the total:HDL cholesterol and LDL:HDL cholesterol ratios in both treatment groups.</p> <p>*Adverse Events</p>	<p>GSK</p>
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² The dose of glibenclamide was increased to 10mg/day at randomisation. At week2, the dose was further increased to 15mg/day in all patients with fasting capillary blood glucose > 5.0 mmol/l. For patients with FCBG between 3.1 and 5.0 mmol/l, the glibenclamide dose was kept at 10mg/day, and the dose was reduced to 7.5mg/day in patients with FCBG < 3.1 mmol/l (in the combination group it was reduced to 5mg/day at week 2)

								<p>Hypoglycaemia Rosi + glibenclamide: 31 (18.5%) Uptitrated glibenclamide: 7 (4.1%)</p> <p>Oedema Rosi + glibenclamide: 16 (9.5%) Uptitrated glibenclamide: 5 (2.5%)</p> <p>Haemoglobin – hematocrit Combination therapy was associated with statistically significant reduction in Hb (-0.97g/dl, p< 0.0001) and haematocrit (-2.76%), p<0.0001) compared with uptitrated glibenclamide.</p> <p>Cardiac failure developed in 2 patients, both in the combination group.</p> <p>Body weight Treatment with rosi + glibenclamide increased body weight by a mean of 3.1kg. there was a small and non-significant increase in body weight of 0.14 kg compared with baseline in the uptitrated glibenclamide group.</p> <p>Drop-out The % of withdrawal was higher in the uptitrated glibenclamide group (26%, n=45) than in the rosiglitazone plus glibenclamide) (16%, n=27).</p> <p>The most common reason for withdrawal in the up-titrated glibenclamide groups was lack of sufficient therapeutic effect (10.5% compared with 0.6% for rosi plus glibenclamide).</p> <p>Adverse experiences were the leading cause of withdrawal in the rosi plus glibenclamide group (10% versus 6% with uptitrated glibenclamide). The</p>	
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								adverse event most commonly associated with withdrawal in this group was hypoglycaemia (6 patients, 4%). 3 patients withdrew from the study due to oedema, all of them in the combination group.	
Raskin P, McGill J, Saad MF, Cappleman JM, Kaye W, Khutoryansky N et al. Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. Diabetic Medicine 2004; 21(4):329-335. Ref ID: 123	RCT multicentre, open label. 1+	252 patients	<p>Inclusion criteria: Adults having Type 2 diabetes for at least 1 year, BMI \leq45 kg/m² with HbA_{1c} values > 7.0% and \leq12% after previous monotherapy (sulphonylurea or metformin, \geq 50% maximal dose) for at least 3 months.</p> <p>Prior therapy was withdrawn for 2 weeks, followed by randomization to repaglinide, rosiglitazone, or repaglinide/rosiglitazone</p> <p>At baseline, the groups were comparable in mean values of weight, HbA_{1c}, FPG and disease duration. Baseline HbA_{1c} values were comparable (9.3% for repaglinide, 9.0% for rosiglitazone, 9.1% for combination).</p> <p>Study treatments were</p>	Repaglinide monotherapy (n=63) Rosiglitazone monotherapy (n=63)	Repaglinide + rosiglitazone (n=127)	24 weeks (12-week dose-optimization period ³ ⁴ 12-week maintenance therapy)	Efficacy endpoints were changes in HbA _{1c} values (primary) or fasting plasma glucose values (secondary)	<p>*HbA_{1c} Mean changes in HbA_{1c} values at the end of treatment were greater for repaglinide/rosiglitazone therapy (-1.43%) than for repaglinide (-0.17%) or rosiglitazone (-0.56%) monotherapy. P<0.001 for combination vs. either monotherapy.</p> <p>In the repaglinide/rosiglitazone group, 39% of subjects achieved and HbA_{1c} value of \leq7% by week 24, compared with only 5% in the repaglinide monotherapy and 16% in the rosiglitazone monotherapy group.</p> <p>*FPG Reductions of fasting plasma glucose values relative to baseline were also greater for combination therapy (-5.2 mmol/l, -94 mg/dl) than for repaglinide monotherapy (-3.0 mmol/l, -54 mg/dl) or rosiglitazone monotherapy (-3.7 mmol/l, -67 mg/dl). P\leq0.001 for combination vs. either monotherapy</p> <p>Lipid profile For combination therapy median changes in values of lipid profile were</p>	Novo Nordisk

³ Repaglinide monotherapy was initiated at 0.5mg per meal if HbA_{1c} levels were \leq 8%, and at 1mg per meal for all other patients. The initial dosage of rosiglitazone monotherapy was 2 mg BID. Repaglinide/rosiglitazone combination therapy was initiated at 0.5mg or 1mg repaglinide per meal (adjusted according to HbA_{1c} as above), plus 2mf rosiglitazone BID.

⁴ All patients in groups treated with repaglinide could have dosage adjusted (weeks 4,8 and 12) up to a maximal dose of 4mg per meal. The rosiglitazone dosage could be doubled at week 12, up to a maximum dose not to exceed 4mg BID **

			<p>initiated with a 12-week dose optimization period (doses optimized according to labelling), followed by a 12-week maintenance period..</p>				<p>generally similar to median changes in these values observed for rosiglitazone monotherapy. (No statistical comparison reported)</p> <p>Median final dose (mg day) Repaglinide/rosiglitazone 6.0/4.0 Repaglinide 12.0 Rosiglitazone 8.00</p> <p>*Adverse Events Minor hypoglycaemic events occurred in 9% of combination therapy patients, vs. 6% for repaglinide and 2% for rosiglitazone. With non significant relative risk between the three arms</p> <p>Individual weight gains for combination therapy were correlated to HbA_{1c} response.</p> <p>Peripheral oedema was reported in 4% of repaglinide/rosiglitazone combination therapy patients and 3% of rosiglitazone monotherapy patients, with no cases reported for repaglinide monotherapy.</p> <p>Follow-up <u>Repaglinide</u> -Completed week 24 38 (60.3%) Reasons for discontinuation AE 4 (6.3%) <i>Lack of efficacy</i> 13 (20.6%) Non-compliance 1 (1.6%) Other 7 (11.1%)</p> <p><u>Rosiglitazone</u> -Completed week 24</p>	
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								37 (59.7%) Reasons for discontinuation AE 6 (9.7%) Lack of efficacy 13 (21.0%) Non-compliance 3 (4.8%) Other 3 (4.8%) <u>Repaglinide/Rosiglitazone</u> -Completed week 24 106 (83.5%) Reasons for discontinuation AE 4 (3.1%) Lack of efficacy 3 (2.4%) Non-compliance 4 (3.1%) Other 10 (7.9%)	
Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes RE, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006; 29(3):554-559. Ref ID: 3165	RCT Multicentre, open label 1+	217 patients from 42 U.S. centres	Inclusion criteria: Subjects >18 years of age with type 2 diabetes (A1C ≥ 7.5 and $\leq 11\%$) and a BMI of $>25\text{kg/m}^2$ were included in the study. Continuous oral hypoglycaemic treatment using stable daily doses of $\geq 50\%$ of the maximally labelled dose of a sulfonylurea and at least 1,000 mg metformin was required for ≥ 3 months before the screening visit. Exclusion criteria: Subjects were excluded	Sulfonylurea + metformin + Rosiglitazone 4mg/day N= 112 Rosiglitazone was increased to 8mg/day any time after 6weeks if FPG was >5.5 mmol/l	Sulfonylurea + metformin + Insulin glargine 10units/day N=105 Glargine was forced-titrated to target FPG ≤ 5.5 -6.7 mmol/l	24 weeks (preceded by a 4-week screening/titration phase) ⁵	HbA1c FPG Lipid profile Body weight Adverse events	* HbA1c Improvements from baseline were similar in both groups (-1.66% vs -1.51% for glargine and rosiglitazone respectively) with no significant difference between the groups (p=0.14) In patients with HbA1c glargine resulted in significantly greater A1C reduction compared with rosiglitazone (p<0.05) *FPG FPG decreased significantly from baseline to end point in both groups; however, greater reductions occurred in the insulin glargine group than in the rosiglitazone group (-3.60 \pm 0.23 vs -2.57 \pm 0.22 mmol/l) p=0.001	Aventis

⁵ During the screening/titration phase, patients not on the maximum metformin dose were titrated to 2,000 mg/day. Patients on 1,000 mg/day increased their dose to 1,500 mg/day immediately and to 2,000 mg/day 1 week later (or maximum tolerated dose), followed by a 2-week stabilization period. Patients on 1,500 mg/day increased their dose to 2,000 mg/day immediately followed by a 2-week stabilization period. Sulfonylurea and metformin doses remained unchanged during the treatment phase of the study.

			<p>for any of the following criteria: stroke, myocardial infarction, angina pectoris, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within the previous 12 months; history of congestive heart failure; treatment with nonselective B-blockers; hypoglycaemia unawareness; impaired renal function; active liver disease; substance or alcohol abuse; and malignancy and planned radiological examinations requiring administration of contrasting agents.</p>				<p>* Lipid profile Contrasting lipid effects at end point, from baseline, were demonstrated between insulin glargine versus rosiglitazone for total cholesterol (196 to 186mg/dl vs. 196 to 215 mg/dl [-4.4 vs. +10.1%], respectively; <i>P</i>=0.0001); LDL cholesterol (117 to 115 mg/dl vs. 106 to 120 mg/dl [-1.4 vs. +13.1%], respectively = 0.0004), and triglycerides (217 to 176 mg/dl vs. 241 to 252 mg/dl [-19.0 vs. +4.6%], respectively; <i>P</i>=0.0011). HDL cholesterol was unchanged, with insulin glargine but increased with rosiglitazone (+4.4%; <i>P</i> = 0.0407).</p> <p>* Body weight Rosiglitazone-treated patients gained more weight (3.0 ± 0.4 kg) than those on insulin glargine (1.7 ± 0.4 kg) (<i>P</i>=0.02)</p> <p>* Adverse events Adverse events possibly related to the study medication occurred significantly more among patients on rosiglitazone than on insulin glargine (28.6 vs. 6.7%, respectively; <i>P</i> < 0.0001)</p> <p>Peripheral edema occurred only in the rosiglitazone group, whereas no patient on insulin glargine reported edema (12.5 vs. 0%, respectively; <i>P</i> < 0.001)</p> <p>Hypoglycaemia Confirmed hypoglycaemic events at plasma glucose <3.9 mmol/l were slightly greater with insulin glargine (N=57) (rosiglitazone, N=47; <i>P</i> = 0.0528). Confirmed symptomatic hypoglycaemic</p>	
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							<p>events at plasma glucose <2.8 mmol/l were greater in the insulin glargine-treated group (insulin glargine, <i>N</i>=26; rosiglitazone, <i>N</i>=14; <i>P</i> <0.0165).</p> <p>More patients in the insulin glargine group had confirmed nocturnal hypoglycaemia of <3.9 mmol/l (insulin glargine, <i>N</i>=29; rosiglitazone, <i>N</i>=12; <i>P</i> = 0.02) and <2.8 mmol/l (insulin glargine, <i>N</i>=10; rosiglitazone, <i>N</i>=3; <i>P</i> < 0.05) than in the rosiglitazone group. The calculated average rate per patient-year of a confirmed hypoglycaemic event (defined as <70 mg/dl), after adjusting for BMI, was 7.7 (95% CI 5.4 to 10.8) and 3.4 (2.3 to 5.0) events for insulin glargine and rosiglitazone, respectively (<i>P</i> = 0.0073).</p> <p>The adverse events in the insulin glargine group included hypoglycaemia (related to the study medication) and gastrointestinal infection (unrelated to the study medication). In the rosiglitazone group, six of the nine adverse events, which included edema, nausea, hypoglycaemia, elevated liver function tests, and weight gain, were apparently related to the study medication.</p> <p>* Discontinuation rate Twenty- one subjects (18.8%) receiving rosiglitazone discontinued the study after beginning treatment versus eight (7.6%) receiving glargine (<i>P</i> = 0.0104). Two subjects (2%) in the insulin glargine group and nine (8%) in the rosiglitazone group withdrew due to adverse events.</p>	
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<p>Rosenstock J, Goldstein BJ, Vinik AI, O'Neill MC, Porter LE, Heise MA et al. Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. Sulphonylurea Titration (RESULT) study. Diabetes, Obesity & Metabolism 2006; 8(1):49-57. Ref ID: 14</p>	<p>RCT multicentre double blind 1+</p>	<p>227 patients from 48 centres in the US and Canada</p> <p>ITT population: 225</p>	<p>Inclusion criteria: Male and female patient aged ≥ 60 years, with document T2D, who had been treated with submaximal SU monotherapy for ≥ 3 months prior to screening, were eligible for inclusion in the study. Patients must have been on one-quarter to one-half of the maximum labelled SU dose for ≥ 2 months prior to screening with FPG ≥ 7.0 and ≤ 13.9 mmol/l at randomization.⁶</p> <p>Patient characteristics: Mean duration of diabetes was 6.8 years.</p> <p><u>Although patients with ischaemic heart disease could be included in the study, those with severe or unstable angina, coronary insufficiency or congestive heart failure (NYHA class III/IV) were excluded.</u></p> <p>Baseline demographics were similar between the groups. Mean baseline</p>	<p>Glipizide 10 mg BID + Rosiglitazone 4mg OD⁷</p> <p>N= 116</p>	<p>Glipizide 10 mg BID + Placebo OD</p> <p>N= 111</p>	<p>2 years</p>	<p>Primary endpoint: Disease progression⁸</p> <p>Secondary endpoints: Time to titration of maximum SU dose</p> <p>HbA1c FPG Lipid profile Insulin resistance Adverse events Hypoglycaemia</p>	<p>* Disease progression 27 of 110 SU-uptitrated patients (28.7%, adjusted for early withdrawals) compared with only 2 of 115 patients in the RSG + SU group (2.0% adjusted for early withdrawals) reached the primary endpoint of disease progression (p<0.0001)</p> <p>RSG + SU reduced the risk of losing glycaemic control by approximately 95% relative to uptitrated SU alone (hazard ratio 0.048, p<0.0001).</p> <p>* Time to titration of maximum SU dose Among the RSG + SU patients, 51.3% (59/115) remained on RSG 4mg/day plus the initial SU dose over the 2 years of the study. Only 11.3% (13/115) of RSG + SU group required titration to the maximum SU dose compared with 48.1% (53/110) with uptitrated SU alone.</p> <p>*HbA1c RSG + SU significantly decreased HbA1c by a mean of 0.65% from a baseline of 7.72% over 104 weeks (p<0.0001), whereas uptitrated SU alone produced no significant improvements from baseline (Difference +0.13%, baseline= 7.65%, p=0.1871).</p> <p>The HbA1c reduction with RSG + SU was significantly different from</p>	<p>GSK</p>
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⁶ All subjects were converted to glipizide (10mg BID) at study entry, then entered a 4-week run-in period

⁷ Although study medications could be adjusted at the discretion of the study physicians, step-wise up-titration to maximum approved doses of glipizide (40mg/day) and rosiglitazone (8mg/day, as divided doses) was required if FPG ≥ 180 mg/dl and recommended if FPG exceeded 140mg/dl. Patients who experienced disease progression could initiate insulin therapy and remain in the study. 11 patients required insulin therapy (all from the uptitrated SU group) and of these, four withdrew early from the study. No patient in the rosiglitazone SU group required insulin intervention.

⁸ Defined as the time at which FPG rose to ≥ 10 mmol/l, confirmed by a second FPG test within 3 days, for a patient who had been titrated to maximum doses of SU and study medication (rosiglitazone or placebo)

			<p>HbA1c , FPG and time since T2D diagnosis were well matched between groups. Concomitant illness at baseline were typical of those in older T2D patients and were similar in both treatment groups.</p>					<p>uptitrated SU alone (-0.79%, p<0.0001)</p> <p>RSG + SU produced maximal improvements in HbA1c by 24 weeks that were sustained over the 2 years of the study, with a mean HbA1c of <7% at study end.</p> <p>Specifically,50 and 32% of patients in the RSG + SU group achieved target HbA1c <7% and ≤6.5% respectively, compared with only 22 and 9% with uptitrated SU alone.</p> <p>*FPG FPG was reduced by a mean of 1.32 mmol/l (p<0.0001) from a baseline of 8.71 mmol/l over 104 weeks with RSG + SU. This compares with a significant increase of 0.78 mmol/l (p=0.0010) from baseline (8.84 mmol/l) with uptitrated SU alone.</p> <p>The difference between treatment groups was statistically significant (- 2.09 mmol/l, p<0.0001)</p> <p>*Lipid profile HDL- cholesterol +2.7 and +1.6%, LDL- cholesterol +3.3 and -1.3% for RSG+SU and uptitrated SU alone, respectively. Total cholesterol was reduced with uptitrated SU alone (-1.7%) but increased with RSG+SU (+6.2%). However the TC:HDL and LDL:HDL cholesterol ratios were unchanged in both treatment groups. Triglycerides increased with RSG+SU (+9.5%) but were reduced with uptitrated SU alone (-5.4%)</p> <p>*Insulin resistance RSG + SU decreased HOMA estimates</p>	
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								<p>of insulin resistance by 14% vs. baseline (p=0.001) compared with an increase of 18% with uptitrated SU alone (p= 0.0028).</p> <p>The difference between the two treatment groups was statistically significant (p<0.0001)</p> <p>*Adverse Events The overall incidence of AEs was comparable between the groups. The incidence of on-therapy AEs leading to withdrawal was similar in both groups: 11 (9.5%) with RSG + SU and 8 (7.2%) with uptitrated SU alone.</p> <p>Weight gain Body weight increased by 4.3 kg over 104 weeks with RSG+SU compared with a decrease of 1.2 kg with uptitrated SU alone.</p> <p>Oedema More frequent with RSG+SU (23 vs. 9%)</p> <p>There was no difference in the incidence of congestive heart failure between groups. (see inclusion criteria)</p> <p>*Hypoglycaemia The incidence of symptomatic hypoglycaemia was similar in the two treatment groups (32% for RSG + SU, 27% for uptitrated SU alone)</p> <p>Reasons for discontinuation <u>RSG + SU</u></p> <table border="0"> <tr> <td>Lack of efficacy</td> <td>3</td> </tr> <tr> <td>Adverse experiences</td> <td>11</td> </tr> <tr> <td>Deviation from protocol</td> <td>4</td> </tr> <tr> <td>Other</td> <td>6</td> </tr> </table>	Lack of efficacy	3	Adverse experiences	11	Deviation from protocol	4	Other	6	
Lack of efficacy	3																
Adverse experiences	11																
Deviation from protocol	4																
Other	6																

								<p>Total 24</p> <p><u>SU-uptitrated</u></p> <p>Lack of efficacy 32</p> <p>Adverse experiences 8</p> <p>Deviation from protocol 7</p> <p>Lost of follow-up 1</p> <p>Other 6</p> <p>Total 54</p> <p>Follow-up</p> <p>RSG + SU 77.5% (90)</p> <p>Placebo + SU 51.3% (57)</p>	
<p>St John SM, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care 2002; 25(11):2058-2064. Ref ID: 239</p>	<p>Open label multicentre RCT (19 sites in the US) 1+</p>	<p>N=203</p>	<p>Patients with type 2 diabetes aged 40 to 80 were eligible. Patients were excluded if they had clinically significant renal disease or hepatic disease, previous treatment for MI, coronary insufficiency or heart failure.</p> <p>Mean age was 55 years and approximately 25% were women. Mean BMI 85kg/m², duration of diabetes approximately 6 years, mean HbA1c 9.5%.</p>	<p>N=99</p> <p>Glyburide qid or bid which was titrated at the discretion of the investigator to optimal glycemic effect over the first 8 weeks and then held constant for the duration of the study period (the dose did not exceed 20mg/day). Median dose at 8 weeks was 10.5mg/day. In both groups previous oral antidiabetic medication was</p>	<p>N=104</p> <p>Rosiglitazone 4mg bid</p>	<p>52 weeks</p>	<p>Glycaemic control</p> <p>Lipid parameters</p> <p>Adverse events</p> <p>(Primary outcomes were cardiac function not reported here).</p>	<p>Both glyburide and rosiglitazone produced clinically significant reductions in HbA1c and FPG at week 52 compared with baseline values. Twice as many patients achieved HbA1c <7% at week 52 in the rosiglitazone group compared with glyburide (28% vs 13% - based on N=129 at week 52). Significance is not reported.</p> <p>The temporal pattern of decreases differed between the two treatment groups with the glyburide treatment resulting in a rapid reduction to 16 weeks after which control deteriorated. Progressive reductions in HbA1c were sustained with rosiglitazone such that HbA1c was comparable between treatment groups at 52 weeks.</p> <p>At week 52 FPG was 161.1mg/dl in the rosiglitazone group and 188.3mg/dl in the glyburide group (significance tests not reported).</p> <p>Triglyceride levels did not change significantly in either treatment group at week 52 compared to baseline</p> <p>Statistically significant median</p>	<p>GSK</p>

				discontinued.				<p>increases in both HDL and LDL cholesterol were observed in the rosiglitazone group (7.7mg/dl for each). LDL cholesterol increased from 140.2 to 146.5 mg/dl in the rosiglitazone group and decreased from 135.4 to 126.5 mg/dl in the glyburide group. The proportions of patients with LDL cholesterol >100mg/dl at week 52 was 89% in the rosiglitazone group and 77% in the glyburide group.</p> <p>The absolute number and percentage of patients with at least one adverse event was similar between the two groups. Signs and symptom of hypoglycaemia were reported more commonly in glyburide treated patients (7.1%) than in rosiglitazone treated patients (1.9%).</p>	
<p>Vongthavaravat V, Wajchenberg BL, Waitman JN, Quimpo JA, Menon PS, Ben KF et al. An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes. Current Medical Research & Opinion 2002; 18(8):456-461. Ref ID: 209</p>	<p>Open label multicentre RCT with centres in India, Brazil, The Philippines, Thailand, Argentina and Tunisia 1+</p>	<p>N=348 N=334 eligible after screening N=238 completed the trial</p>	<p>Patients with type 2 diabetes were eligible to enter the study if they had been receiving SU therapy for at least 6 months and if their SU dose had been constant for at least 2 months. They had to be between 40 and 80 years of age and to have a FPG 126 to 270mg/dl at screening.</p> <p>Patients were excluded if they had significant renal or hepatic impairment, hypertension or anaemia. Patients with diabetic retinopathy or neuropathy requiring treatment were excluded as were those with a BMI <22 or >38. Mean age 55, 55% female, mean BMI</p>	<p>N=175 Rosiglitazone (2mg before breakfast and one in the evening before a meal) and sulphonylurea at normal dose</p> <p>% of patients on: Glibenclamide 69% Glipizide 11% Gliclazide 10% Glimepiride 5% Chlorpropamide 3% Tolbutamide 0% Other 3%</p>	<p>N=173 Sulphonylurea alone at the patients normal dose.</p> <p>% of patients on: Glibenclamide 69% Glipizide 9% Gliclazide 12% Glimepiride 7% Chlorpropamide 4% Tolbutamide 1% Other 0%</p>	<p>26 weeks</p>	<p>HbA1c</p> <p>Fasting plasma glucose</p> <p>Lipid levels</p> <p>Adverse events and hypoglycaemia.</p>	<p>The RSG and SU group showed decreases in both mean FPG (199 to 166mg/dl, mean change -38.4, 95%CI -47.1 to -19.7) and HbA1c 9.1% to 7.9%, mean change -1.1, 95% CI -1.37 to -0.89) from baseline to 26 weeks. In contrast, mean FPG and HbA1c increased slightly in the control group. The difference between the treatment groups in both cases was significant (p=0.0001).</p> <p>Mean total cholesterol and LDL cholesterol concentrations increased after 26 weeks in the RSG and SU group (TC from 207 to 220mg/dl and LDL from 130 to 135mg/dl). However, this was accompanied by a rise in HDL cholesterol (41 to 45 mg/dl). As a result, the LDL/HDL ratio fell sharply and to a similar degree in both groups (3.4 to 3.1 for RSG and SU and 3.1 to 2.9 for SU alone. (No significance tests reported for lipid outcomes).</p>	<p>GSK</p>

			27kg/m ² , mean weight 69kg. Approximately 60% classified as oriental and 40% white.					<p>Hypoglycaemia occurred in 19 case in the RSG and SU group and 2 in the SU alone group(p<0.001). However of these 19 cases, 16 were mild, two moderate and one severe (none requiring hospitalisation).</p> <p>Seven patients in the RSG and SU group and two in the SU alone group withdrew from the study because of adverse events (p<0.001).</p>	
Weissman P, Goldstein BJ, Rosenstock J, Waterhouse B, Cobitz AR, Wooddell MJ et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Current Medical Research & Opinion 2005; 21(12):2029-2035. Ref ID: 3133	RCT 1-	N=766 randomised N=709 ITT population (at least one on therapy efficacy measurement). 63 centres in the US. NB primary HbA1c analysis only included those completing the study (N=573, 75%) thus not an ITT analysis.	Inclusion criteria: 18 to 75 years old with type 2 diabetes HbA1c of 6.5% to 8.5% for those receiving prior combination treatment (metformin and sulphonylurea) and 7% to 10% for drug naïve or prior monotherapy patients. FBG of 7 to 15 mmol/L and a BMI more than or equal to 27kg/m ² . Mean age was 56 years, weight 98 kg, BMI 34kg/m ² , HbA1c 8% and FBG 10 mmol/L.	N=358 (RSG +MET) Rosiglitazone 4mg/day plus metformin 1000 mg/day for 8 weeks. Then up-titrated to RSG 8mg/day plus MET 1000mg/day	N=351 (MET) Metformin 1500mg/day for 8 weeks. Then up-titrated to 2000mg/day.	24 weeks	Mean change in HbA1c after 24 weeks of treatment. Mean change from baseline in FBG. Lipid profile, weight, adverse events.	<p>There was a mean reduction in HbA1c of -0.93% (95%CI-1.06 to -0.80%) in the RSG + MET group and a reduction of -0.71 (95%CI -0.83 to -0/60%) in the MET group from baseline. This was a mean treatment difference of -20% (95%CI -0.36 to -0.04). NB only 75% of randomised patients were included in this analysis.</p> <p>The RSG + MET group had significantly greater reductions from baseline than the MET alone group in FBG with a treatment difference of -0.85 mmol/L (95%CI -1.23 to -0.47mmol/L (this analysis included 62% of those randomised).</p> <p>Lipid profiles (% change from baseline for RSG +MET and MET respectively) Total chol:10.4 vs -1.4 HDL chol:8.3 vs 2.8 LDL chol: 11.2 vs -4.3 Trig:1.3 vs 1.6</p> <p>The RSG + MET group had a mean weight gain of 1.79kg compared with a mean weight loss of 1.78kg in the MET group.</p> <p>20% of patients were withdrawn post-randomisation in the RSG + MET group before randomisation and 25% in the MET group. 7% in the RSG + MET group and 10% in the MET group was</p>	GSK

								due to adverse experience. Discontinuation due to GI disorders was 3.1% in the RSG + MET group and 6.8% in the MET group.	
G. A. Diamond, L. Bax, and S. Kaul. Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death.[see comment]. <i>Annals of Internal Medicine</i> 147 (8):578-581, 2007. ID 5096	MA (reanalyses of previous MA)	42 trials, N=27487 patients	As for ID 4978	Rosiglitazone (monotherapy or combination)	placebo or active comparator	Not mentioned	MI CV death	Authors' conclusions: the risk for M and death from CV disease for diabetic patients taking rosiglitazone is uncertain. They also advocate for long-term patient-oriented outcomes studies on rosiglitazone to clarify its safety.	None mentioned
ID 5097	MA 1+	4 trials (N=14,291 patients)	RCTs of at least 12 months; patients with impaired glucose tolerance or type 2 diabetes mellitus; only difference between treatment groups being rosiglitazone use.	Rosiglitazone	placebo or active comparator	At least 12 months	MI	MI RR 1.42 (95% CI 1.06 to 1.91), p=0.02 Among patients with Type 2 diabetes, rosiglitazone use for at least 12 months is associated with a significantly increased risk of heart failure without a significantly increased risk of CV mortality.	Not mentioned
ID 5098	MA 1++	7 trials (N=20,191 patients)	RCTs (double blind) of TZDs if reported risk estimates or frequency data for CHF and CV death. Excluded non-randomised studies.	Rosiglitazone or pioglitazone	placebo or active comparator	Between 1-2 years (mean 29.7 months)	CHF and CV death	Heart failure: significantly higher risk of developing heart failure in patients treated with rosiglitazone or pioglitazone compared to controls (RR 1.72, 95%CI 1.21 to 2.42, p=0.002). CV death: risk of CV death was not increased with either of the 2 glitazones	Not mentioned
ID 5099	MA	42 RCTs (N=14,237 patients) and some observational data	Double blind RCTs sponsored by GSK; patients with Type 2 diabetes mellitus	Rosiglitazone (monotherapy or combination)	placebo or active comparator	Short-term trials (most were 6 months)	MI	MI HR 1.31 (95% CI 1.01 to 1.72) p<0.05	GSK

ID 5001	Cochrane SR/MA 1++	18 trials N=3888 randomised to rosiglitazone	RCTs at least 24 weeks; Adults with type 2 diabetes mellitus	Rosiglitazone (monotherapy or combination)	placebo or active comparator	Median 26 weeks	HbA1c, oedema, mortality.	<p>HbA1c: Active glucose-lowering agents resulted in similar reductions in HbA1c compared to rosiglitazone treatment.</p> <p>Oedema: Oedema was significantly raised in patients receiving rosiglitazone (OR 2.27, 95% CI 1.83 to 2.81).</p>	
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