

Evidence Tables

MET1 Is metformin as monotherapy or in combination with oral antidiabetic drugs effective in the control of blood glucose in people with type 2 diabetes compared to other oral antidiabetic drugs regimens or placebo?

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%	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.	*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). *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). * 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 was OR= 5.71 (95%CI 3.37 to 9.66; p<0.001) for FPG. *Weight There was a mean (SE) increase from baseline in weight in the RSG/MET group	GSK

			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.					(1.3(0.22)kg) and a mean decrease in the MET group (-0.9(0.26)kg) . * 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 *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.	
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,	RCT. Multicentre double-blind 1++	N= 630 randomized ITT=620 (10 patients were not eligible due to missing HbA1c data)	Male and female patients with T2D, inadequately managed with metformin alone (at ≥505 of the maximum recommended dose or at the maximum	N=317 Pioglitazone 15mg o.d + Metformin at pre-study dose 16-weeks forced dose titration ²	N=313 Gliclazide 80mg o.d + Metformin at pre-study dose 16-weeks forced dose titration	52 weeks	Primary efficacy measure: Change in HbA1c from baseline to Week 52. Secondary endpoints: FPG Lipid profile Albumin/cre	*HbA1c 52 weeks No statistically significant between-group differences <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	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

<p>comparative study. Diabetes/Metabolism Research Reviews: 21: 167 - 174 REF ID: 127.</p> <p>*****</p> <p>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 ¹. Diabetologia 2005; 48(6):1093-1104. Ref ID: 3137</p>		<p>Patients from 75 centers in nine European countries and Australia.</p>	<p>tolerated dose for ≥3 months) were screened.</p> <p>Inclusion criteria : age between 35 and 75 years, inclusive; HbA1c of ≥7.5% or ≤11.0%; fasting C- peptide of ≥1.5ng/ml (0.5 nmol/l) and stable or worsening glycaemia control 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</p>	<p>pioglitazone dose was titrated to 30mg and 45mg</p> <p><u>At the end of the 16-week,</u> 70% of patients had been titrated to the maximum pioglitazone dose (45mg o.d.)³</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>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 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>atinine ratio Adverse events</p>	<p>0.76% with pioglitazone and gliclazide respectively, p=0.003).</p> <p>*FPG 52 weeks No statistically significant between-group differences</p> <p><i>Two year follow-up</i> 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 52 weeks 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). (No other data was reported)</p> <p>*LDL 52 weeks Met/Pio treatment was associated with a mean increase in LDL of 0.27 mmol/L compared to a decrease of 0.11 mmol/L in LDL with Met/Gli treatment</p> <p>The differences between groups were</p>	
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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

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>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±1.00, BMI 32.6±5.0, mean metformin dose 1726mg/day</p> <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>statistically significant favouring the Met/Gli treatment (p<0.001 log-transformed data). (No other data was reported)</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>*Body weight 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>*Adverse events 52 weeks AE occurred in similar proportions of patients in both treatment groups: <u>Met/Pio</u> 55.5% n=176; with a total of 533 events, of which 140 were study-related <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</p>	
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								<p>heart failure.</p> <p>Discontinuation</p> <p><u>Met/Pio</u></p> <p>Did not complete week 52 17.7%</p> <p>Adverse events 4.1%</p> <p><u>Met/Gli</u></p> <p>Did not complete week 52 13.4%</p> <p>Adverse events 4.5%</p> <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. 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>	
<p>Saenz A, Fernandez EI, Mataix A, Ausejo M, Roque M, and Moher D. 2005 Metformin monotherapy for type 2 diabetes mellitus. [Review] [165 refs]. Cochrane Database of Systematic Reviews: CD002966 REF ID: 128.</p>	<p>Cochrane systematic review</p> <p>1++</p>	<p>N=29 metformin RCTs with 37 arms of comparison involving 5259 participants. (search until Sept 03).</p>	<p>Patients with new or existing type 2 diabetes</p>	<p>Monotherapy with metformin</p>	<p>Placebo or any other active intervention</p>	<p>The median trial duration was five months (range 3-24 months), and 10.7 years the UKPDS</p>	<p>Mortality Morbidity glycaemic control, plasma lipids, fasting and post-load insulin, body weight, adverse effects.</p>	<p>MORTALITY & MORBIDITY (Relative Risk)</p> <p>UKPDS: Metformin vs sulfonylureas or insulin</p> <p><u>Statistically significant differences:</u></p> <p>* Any diabetes-related outcomes 0.78 (95% CI [0.65, 0.94]) p= 0.009</p> <p>* All-cause mortality 0.73 (95% CI [0.55, 0.97]) p= 0.03</p> <p><u>No statistically significant differences:</u></p> <p>* Diabetes-related death * Myocardial infarction * Stroke * Peripheral vascular disease</p>	N/A

							<p>* Microvascular</p> <p>UKPDS: metformin vs conventional</p> <p><u>Statistically significant differences:</u></p> <p>* Any diabetes-related outcomes 0.74 (95% CI [0.60, 0.90]) p= 0.004</p> <p>* Diabetes-related death 0.61 (95% CI [0.40, 0.94]) p= 0.03</p> <p>* All-cause mortality 0.68 (95% CI [0.49, 0.93]) p= 0.01</p> <p>* Myocardial infarction 0.64 (95% CI [0.45, 0.92]) p= 0.02</p> <p><u>No statistically significant differences:</u></p> <p>* Stroke * Peripheral vascular disease * Microvascular</p> <p>Non-UKPDS trials: metformin vs comparison.</p> <p><u>No statistically significant differences:</u></p> <p>* All-cause mortality * Ischaemic heart disease</p> <p>OTHER OUTCOMES (Standardized Mean Difference)</p> <p>Metformin vs placebo</p> <p><u>Statistically significant differences:</u></p> <p>*Change in HbA1C (%) -0.97 (95% CI [-1.25, -0.69])</p> <p>*Change in FPG (mmol/l) -0.87 (95% [-1.13, -0.61])</p>	
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								<p><u>No statistically significant differences:</u> *Change in BMI or weight *Change in total cholesterol *Change in HDL cholesterol *Change in LDL cholesterol *Change in Triglycerides</p> <p>Metformin vs diet <u>Statistically significant differences:</u> *Change in HbA1C (%) -1.06 (95% CI [-1.89, -0.22])</p> <p>*Change in total cholesterol -0.59 (95% CI [-0.90, -0.27])</p> <p><u>No statistically significant differences:</u> *Change in FPG (mmol/l) *Change in BMI or weight *Change in HDL cholesterol *Change in LDL cholesterol *Change in Triglycerides</p> <p>Metformin vs alpha-glucosidase inhibitors <u>Statistically significant differences:</u> *Change in total cholesterol (mmol/l) +1.32 (95% CI [0.77, 1.87])</p> <p><u>No statistically significant differences:</u> *Change in HbA1C *Change in FPG *Change in BMI or weight *Change in HDL cholesterol *Change in LDL cholesterol *Change in Triglycerides</p> <p>Metformin vs sulphonylureas <u>Statistically significant differences:</u> *Change in HbA1C (%) -0.14 (95% CI [-0.28, -0.01])</p> <p>*Change in FPG (mmol/l) -0.16 (95% CI [-0.27, -0.05])</p> <p>*Change in BMI or weight</p>	
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								<p>-0.45 (95% CI [-0.80, -0.10])</p> <p>*Change in LDL cholesterol (mmol/l) -0.29 (95% CI [-0.52, -0.07])</p> <p>*Change in Triglycerides (mmol/l) -0.22 (95% CI [-0.43, -0.02])</p> <p><u>No statistically significant differences:</u> *Change in total cholesterol *Change in HDL cholesterol</p> <p>Metformin vs meglitinides <u>Statistically significant differences:</u> *Change in FPG (mmol/l) -0.31 (95% CI [-0.51, -0.12])</p> <p><u>No statistically significant differences</u> *Change in HbA1C *Change in BMI or weight *Change in total cholesterol *Change in HDL cholesterol *Change in LDL cholesterol *Change in Triglycerides</p> <p>Metformin vs thiazolidinediones <u>Statistically significant differences:</u> *Change in HbA1C (%) -0.28 (95% CI [-0.52, -0.03])</p> <p><u>No statistically significant differences:</u> *Change in FPG *Change in BMI or weight</p> <p>Metformin vs insulin <u>Statistically significant differences:</u> *Change in BMI or weight -0.91 (95% CI [-1.44, -0.37])</p> <p>*Change in total cholesterol (mmol/l) -0.77 (95% CI [-1.29, -0.24])</p> <p>*Change in HDL (mmol/l) +0.65 (95% CI [0.13, 1.17])</p>	
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							<p>*Change in LDL (mmol/l) -0.83 (95% CI [-1.35, -0.30])</p> <p><u>No statistically significant differences</u> *Change in HbA1C (%) *Change in FPG *Change in triglycerides</p> <p>ADVERSE EVENTS (Relative Risk)</p> <p>Metformin vs placebo <u>Statistically significant differences:</u> *Diarrhea 3.09 (95% CI [1.58, 6.07])</p> <p><u>No statistically significant differences:</u> *Hypoglycaemia *Gastrointestinal discomfort</p> <p>Metformin vs diet <u>Statistically significant differences:</u> *Hypoglycaemia 4.21 (95% CI [1.40, 12.66])</p> <p>Metformin vs alpha-glucosidase inhibitors <u>Statistically significant differences:</u> *Gastrointestinal discomfort 0.26 (95% [0.07, 0.91])</p> <p>Metformin vs sulphonylureas <u>Statistically significant differences:</u> *Hypoglycaemia 0.49 (95% [0.25, 0.96])</p> <p>*Diarrhea 2.72 (95% [1.09, 6.77])</p> <p><u>No statistically significant differences:</u> *Gastrointestinal discomfort</p> <p>Metformin vs meglitinides <u>Statistically significant differences:</u> *Diarrhea 3.56 (95% [1.81, 7.00])</p>	
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								<p><u>No statistically significant differences:</u> *Hypoglycaemia *Gastrointestinal discomfort</p>	
<p>Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P, Quartet [corrected] Study Group. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial.[erratum appears in J Clin Endocrinol Metab. 2005 Feb;90(2):746]. Journal of Clinical Endocrinology & Metabolism 2004; 89(12):6068-6076. Ref ID: 161</p>	<p>RCT 1++</p>	<p>N=1199 randomise d. N=1194 included in the ITT analysis from 167 centres in 12 European countries.</p>	<p>Inclusion criteria: Patients aged 35-75yrs with Type 2 diabetes inadequately treated by diet alone, had HbA_{1c} between 7.5% and 11% with stable or worsening glycaemic control for at least 3 months.</p> <p>Mean age 56 yrs in the metformin group and 57yrs in the pioglitazone group. 58% and 53% were male in the metformin and pioglitazone groups respectively. Mean BMI was 31.4 and 31.2 kg/m² respectively and mean HbA_{1c} was 8.7% in both groups.</p>	<p>N=597 Metformin (850mg) + pioglitazone placebo, up to 3 times daily.</p> <p>In both groups corticosteroids and B-blockers were allowed if treatment commenced at least 4 weeks before screening. Anti-hypertensives (except thiazides) were allowed dependent on clinical need, lipid-lowering agents were also permitted.</p> <p>Both groups were instructed to adhere to a disease- and weight-orientated diet throughout the study.</p>	<p>N=597 Pioglitazone (up to 45mg) + metformin placebo once daily.</p> <p>Patients started with 30mg pioglitazone. Doses were increased, maintained or decreased at 4, 8 or 12 weeks according to tolerability. Dose reached at wk 12 was fixed for rest of study.</p>	<p>1 year (52 weeks).</p>	<p>Mean HbA_{1c}, fasting plasma glucose (FPG); Lipid profile (TG, total cholesterol, HDL and LDL cholesterol levels); mean body weight and adverse events (AEs).</p>	<p>There was no significant difference between the two groups for mean HbA_{1c} (2-sided 95% CI = -0.01 to 0.19) and TC/HDL-C ratio (8% decrease in both groups, p=0.9).</p> <p>Pioglitazone treatment was associated with a significantly greater reduction in FPG (mean difference -0.3 mmol/L, p=0.016) and Pioglitazone treatment was also associated with significantly greater increases in HDL-cholesterol than the metformin group (0.16 mmol/L vs. 0.08 mmol/L, p=0.001). Triglyceride levels were 0.61 mmol/L lower than baseline in the pioglitazone group compared with decreases of 0.3 mmol/L in the metformin group (p=0.001). For LDL-C there was a +0.27 mmol/L change from baseline for pioglitazone vs. -0.12 mmol/L for metformin (p=0.001). There was no significant difference between the groups for the TC/HDL-C ratio which was 8% lower than baseline in both groups.</p> <p>Mean body weight increased by 1.9 kg compared to a decrease of 2.5 kg with metformin. Mean waist circumference remained unchanged in the pioglitazone group compared to a loss of 3 cm with metformin.</p> <p>Compared to metformin, the pioglitazone group had a lower incidence of adverse events (53% vs. 58% respectively) and lower proportion of more severe AEs was (4.9% vs. 7.4% respectively).</p> <p>No statistical comparisons between groups *Diarrhoea Pioglitazone 19 (3.2%) Metformin 66 (11.1%)</p>	<p>Not mentioned</p>

								*Oedema Pioglitazone 27 (4.5%) Metformin 10 (1.7%)	
Cryer DR, Nicholas SP, Henry DH, Mills DJ, and Stadel BV. 2005. Comparative outcomes study of metformin intervention versus conventional approach the COSMIC Approach Study. Diabetes Care: 28: 539 - 543 REF ID: 134.	RCT Open label, parallel-group, multicentre. 1+ (postmarketing safety surveillance study requested by FDA)	N=9,000 Randomization, stratified by site, was in a 4:1 ratio to two primary treatment groups (five secondary groups)	Inclusion criteria: Eligible patients were men or women aged >18 years with a diagnosis of type 2 diabetes, with glycemia suboptimally controlled (at the discretion of the investigators) on diet or sulfonylurea monotherapy. Principal inclusion criteria included normal renal function (serum creatinine <1.5 mg/dl [men] and <1.4 mg/dl [women] or normal creatinine clearance), normal hepatic	N=7,227 <u>Metformin</u> Group 1: metformin only ⁷ Group 2: Metformin + SU only Group 3: Metformin + Non-SU oral agent Initial metformin treatment was 500 mg b.i.d., with meals, increased weekly in 500 mg steps if required (maximum 2,500 mg/day in three divided doses, with meals). All patients received diet counselling	N=1,505 <u>Usual care</u> Group 5: Non-metformin oral agent only Group 6 Insulin + non-metformin oral agent, or non-metformin oral agent combination	1-year	Serious Adverse Events ⁸ Plasma lactate levels	*SAE SAEs were reported by 10.3% (95% CI 9.6–11.1%) of the metformin group and by 11.0% (9.5–12.7%) of the usual care group (<i>P</i> =0.43), with a similar pattern of SAEs between groups according to body System <u>Lactic acidosis was not observed.</u> Reasons for switch from initial treatment By study end, 89.7% of the metformin group and 76.9% of the usual care group were still receiving their initial study treatment, while 5.4 and 18.9%, respectively, had switched to the alternative treatment arm. The most common reasons for switching from initial treatment (≥1% of patients) were lack of efficacy (1.5 vs. 14.4% in the metformin and usual care groups, respectively), SAEs (0.4 vs. 0.2%), or other AEs (5.6 vs. 2.7%). 3.2% of the metformin group and 1.9% of the usual care group discontinued prematurely *Plasma lactate levels Mean ± SD plasma lactate was 1.7 ± 0.6 mmol/l in the metformin group and 1.6 ± 0.6 mmol/l in the usual care group after 12 months of treatment (<i>P</i> = 0.137). Plasma lactate >3.0 mmol/l occurred in 4% of the metformin group and 1% of the usual care group (not significant between	Bristol-Myers Squibb

⁷ Patients who became uncontrolled on oral monotherapy (groups 1 and 5) could cross to the relevant secondary treatment group

⁸ SAEs comprised any experience that was fatal, life-threatening, permanently or substantially disabling, resulted in permanent or significant disability or incapacity, required or prolonged hospitalization, an important medical event that jeopardized the patient or required intervention to prevent a serious outcome, a congenital abnormality, a cancer, an overdose of medication, or a condition that resulted in the development of drug dependency or drug abuse.

			function (AST <2 X upper limit of normal), no history of metabolic acidosis. Demographic and other baseline characteristics were similar between groups					groups).	
Fujioka K, Pans M, and Joyal S. 2003. Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. Clinical Therapeutics: 25: 515 - 529 REF ID: 367.	RCT 1+	N=217 From 42 centres in the US	Inclusion criteria: Patients between the ages of 27 and 77 years who had T2D for > 2 months to <10 years Eligible patients had been receiving MIR 500mg BID for the treatment of T2D for at least 8 weeks. They were required to have a HbA1c ≤8.5% and FPG ≤200mg/dl ⁹ . Patients could not be receiving long-term insulin	1. MXR 1000mg QD administered with the evening meal N= 75 2. MXR 1000mg QD administered with the evening meal for 1 week, followed by an increase to 1500mg QD N= 71	3. MIR 500mg BID with the morning and evening meals N= 71 <u>Note:</u> after 12 weeks, the daily dose could be increased by 500mg in any group if HbA1c was ≥8% at that time.	24 weeks	HbA1c FPG Lipids Body weight	* HbA1c At week 24, the mean change from baseline in HbA1c was 0.06%, for MIR, 0.25%, for MXR 1000 mg, and 0.14%.for MXR 1500 mg. No statistical significant differences were observed between the groups. *FPG Mean FPG concentrations increased in all 3 treatment groups at week 24. The mean increases were smaller in the MXR groups compared with the MIR group. (Statistical significance not reported) * Lipids No clinically significant changes from baseline were seen in TC or HDL levels at week 24 in any treatment group LDL levels at week 24 decreased in all 3 groups, with a mean change of -4mg/dl with MIR and -6mg/dl in both MXR groups. (Statistical comparison between groups not reported) Whereas small increases from baseline in triglycerides levels were observed at week	Bristol-Myers-Squibb

⁹ The inclusion of patients who had achieved moderate of good glycemic control at moderated doses of MIR was intended to preselect patients who were likely to respond to once-daily MXR

			therapy or any other antihyperglycemic therapy apart from MIR. The groups were well balanced with respect to demographic and metabolic characteristics					24 in patients receiving MIR (mean change 1mg/dl; 95% CI, -14 to 17), statistically significant increases of 34mg/dl (95% CI, 15 to 53) and 42mg/dl (95% CI, 6 to 78) were seen at week 24 in the groups that received MXR 1000 and 1500 respectively. (Statistical comparison between groups not reported) * Adverse events Drug-related experiences were reported in 18 of 71 (25%) MIR recipients, 22 of 75 (29%) MXR 1000mg recipients, and 24 of 71 (34%) MXR 1500mg recipients. Only 2 hypoglycemic events were recorded, 1 with MIR and 1 with MXR 1000mg. For other adverse events (Metformin IR 500mg BD vs metformin XR 1000mg QD): Diarrhea: 3% vs 5% Flatulence: 1% vs 4% Abdominal pain: 1% vs 4% Nausea/vomiting: 4% vs 3% Headache: 4% vs 4% Dyspepsia/heartburn: 6% vs 3%	
Gerich J, Raskin P, Jean LL, Purkayastha D, and Baron MA. 2005 PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. Diabetes Care: 28: 2093 - 2099 REF ID: 83	RCT randomized, multicentre, double-masked (USA) 1+	428 patients	Inclusion criteria: Men and women with type 2 diabetes inadequately controlled by diet and exercise were eligible to participate if they met the following inclusion criteria: 1) drug-naive, 2) aged 18–77	4-week maintenance period 120 mg a.c. nateglinide ¹⁰ + 500 mg open-label metformin before the evening meal 12-week titration period ¹¹	4-week maintenance period 1.25 mg glyburide before breakfast + 500 mg open-label metformin before the evening meal 12-week titration period	104 weeks (Eligibility was assessed during a 2-week screening period)	- HbA1c - FPG - Post-prandial Glucose Excursion (PPGE) - Lipid Profile - Body weight - Adverse events	*HbA1c no significant difference *FPG At week 104, the mean change in FPG was -1.6±0.2 mmol/l in patients randomized to the Nate/Met group and -2.4± 0.2 mmol/l in patients randomized to the Glyb/Met group. The mean difference was -1.2 ±0.2 mmol/l in favor of Glyb/Met group (<i>P</i> 0.0078). *PPGE no significant difference *Lipid profile no significant difference	Novartis

¹⁰ The dose level was not adjusted during this 4 -week maintenance period, unless hypoglycemia required downward titration to dose level 0 (60mg a.c. nateglinide, all other medications as above)

¹¹ Titration for both arms was performed at biweekly visits if FPG ≥ 6.7mmol/l

¹² The dose level in both arms was increased to the next highest level or to the "rescue dose level 9" if FPG ≥13.3 mmol/l, A1C ≥9.0%, or the patient had symptomatic hyperglycemia.

			<p>years, 3) baseline A1C ≥ 7.0 and $\leq 11.0\%$, 4) FPG ≤ 15 mmol/l, and 5) BMI between 22 and 45 kg/m². (Eligibility was assessed during a 2-week screening period)</p> <p>The groups were well balanced with respect to demographic and metabolic characteristics, with baseline A1C averaging 8.35%.</p>	<p>120 mg a.c. nateglinide</p> <p>+ and open-label metformin (titrated in 500-mg increments to a maximum of 2,000 mg daily).</p> <p>88-week monitoring period</p> <p>the doses of study medication remained constant, unless protocol-specified criteria for rescue therapy were met.¹²</p> <p>At the end of study <u>Mean daily doses</u> nateglinide: 357mg metformin: 1,459 mg</p>	<p>glyburide (titrated in 1.25-mg increments to a maximum of 10 mg daily)</p> <p>+ and open-label metformin (titrated in 500-mg increments to a maximum of 2,000 mg daily).</p> <p>88-week monitoring period</p> <p>the doses of study medication remained constant, unless protocol-specified criteria for rescue therapy were met.</p> <p>At the end of study <u>Mean daily doses</u> glyburide: 5.1 mg metformin: 1,105 mg</p>		<p>*Body weight Body weight decreased slightly in patients randomized to the Nate/Met group (-0.4 \pm 0.4 kg) and increased slightly in patients randomized to the Glyb/Met group +0.8 \pm 0.5 kg). The between-group difference was statistically significant (Nate/Met - Glyb/Met = -1.2 kg, $P=0.0115$).</p> <p>* Adverse effects one or more adverse events was experienced by most of the subjects: 91.8% of those randomized to the Nate/Met group and 90.9% of patients randomized to the Glyb/Met group.</p> <p>The only AEs that occurred frequently (in 10% of patients) in a preponderance in one treatment group (more than a twofold difference in prevalence) was hypoglycemia. One or more episodes of confirmed hypoglycemia was reported by 17.7% of patients receiving glyburide/metformin vs. 8.2% of those receiving nateglinide/metformin (P 0.003).</p> <p>Reasons for discontinuation¹³ <u>Nateglinide/metformin</u></p> <table> <thead> <tr> <th>Adverse Events (any AE)</th> <th>n (%)</th> </tr> </thead> <tbody> <tr> <td>• Abdominal pain</td> <td>0</td> </tr> <tr> <td>• Diarrhea</td> <td>3 (1.4)</td> </tr> <tr> <td>• Hypoglycemia</td> <td>1 (0.5)</td> </tr> <tr> <td>Subject withdrew consent</td> <td>22 (10.1)</td> </tr> <tr> <td>Lost to follow-up</td> <td>15 (6.9)</td> </tr> <tr> <td>Protocol violation</td> <td>7 (3.2)</td> </tr> <tr> <td>Unsatisf. therapeutic effect</td> <td>3 (1.4)</td> </tr> <tr> <td>Abnormal lab value</td> <td>2 (0.9)</td> </tr> <tr> <td>Administrative problem</td> <td>1 (0.5)</td> </tr> <tr> <td>Death</td> <td>1 (0.5)</td> </tr> <tr> <td>Total</td> <td>78 (35.6)</td> </tr> </tbody> </table> <p><u>Glyburide/metformin</u></p>	Adverse Events (any AE)	n (%)	• Abdominal pain	0	• Diarrhea	3 (1.4)	• Hypoglycemia	1 (0.5)	Subject withdrew consent	22 (10.1)	Lost to follow-up	15 (6.9)	Protocol violation	7 (3.2)	Unsatisf. therapeutic effect	3 (1.4)	Abnormal lab value	2 (0.9)	Administrative problem	1 (0.5)	Death	1 (0.5)	Total	78 (35.6)	
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¹³ Specific AEs leading to premature discontinuation that occurred in three or more patients are detailed.

				<u>Rescue/level 0 doses</u> 17 (8.2%) were receiving the rescue dose, and 5 patients (2.4%) were receiving dose level 0.	<u>Rescue/level 0 doses</u> five patients (2.5%) were on the rescue dose and eight patients (4.0%) were receiving dose level 0.			<table border="0"> <tr> <td></td> <td style="text-align: right;">n (%)</td> </tr> <tr> <td>AE (any AE)</td> <td style="text-align: right;">28 (13.4)</td> </tr> <tr> <td> • Abdominal pain</td> <td style="text-align: right;">4 (1.9)</td> </tr> <tr> <td> • Diarrhea</td> <td style="text-align: right;">4 (1.9)</td> </tr> <tr> <td> • Hypoglycemia</td> <td style="text-align: right;">4 (1.9)</td> </tr> <tr> <td>Subject withdrew consent</td> <td style="text-align: right;">31 (14.8)</td> </tr> <tr> <td>Lost to follow-up</td> <td style="text-align: right;">16 (7.7)</td> </tr> <tr> <td>Protocol violation</td> <td style="text-align: right;">8 (3.8)</td> </tr> <tr> <td>Unsatisf therapeutic effect</td> <td style="text-align: right;">3 (1.4)</td> </tr> <tr> <td>Abnormal lab value</td> <td style="text-align: right;">0</td> </tr> <tr> <td>Administrative problem</td> <td style="text-align: right;">0</td> </tr> <tr> <td>Death</td> <td style="text-align: right;">1 (0.5)</td> </tr> <tr> <td>Total</td> <td style="text-align: right;">87 (41.6)</td> </tr> </table>		n (%)	AE (any AE)	28 (13.4)	• Abdominal pain	4 (1.9)	• Diarrhea	4 (1.9)	• Hypoglycemia	4 (1.9)	Subject withdrew consent	31 (14.8)	Lost to follow-up	16 (7.7)	Protocol violation	8 (3.8)	Unsatisf therapeutic effect	3 (1.4)	Abnormal lab value	0	Administrative problem	0	Death	1 (0.5)	Total	87 (41.6)	
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Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. <i>Diabetes, Obesity & Metabolism</i> 2006; 8(1):39-48. Ref ID: 3132	RCT 1+	N=341 randomised, patients from 11 countries in Europe.	<p>Inclusion criteria: patients with Type 2 diabetes. All patients had been receiving at least 850mg metformin/day for at least 1 month.</p> <p>Mean age 55 yrs in the BIAsp group, 56 yrs in the BIAsp + metformin and 58 yrs in the glibenclamide + metformin group. 47%, 49% and 46% were male in the groups respectively. Mean BMI was 30.9, 30.4 and 30.5 kg/m² respectively and mean HbA_{1c} was</p>	N=111 allocated (N=107 exposed) BIAsp 30, initial daily dose 0.3 U/kg body weight/day	N=116 allocated (N=108 exposed), BIAsp + metformin 0.2 U/kg body weight/day	16 weeks	<p>Mean HbA_{1c}; lipid profile (TG, HDL cholesterol levels); mean post-prandial glucose (based on average blood glucose after 3 meals/day); mean body weight and adverse events (AEs).</p>	<p>Patients in the BIAsp 30 + metformin group had significantly lower mean HbA_{1c} than those treated with BIAsp 30 alone (0.39%, p=0.007), but was not significantly different from glibenclamide + metformin (0.20%).</p> <p>There was no significant difference between the treatment groups for mean post-prandial blood glucose and for before-breakfast glucose.</p> <p>Body weight increased for all 3 treatment groups by the end of the study (1.6kg, 0.8 kg and 0.1 kg for BIAsp 30, BIAsp + metformin and Metformin + Glibenclamide groups respectively). There was no significant difference in end-of trial body weight compared to the BIAsp 30 + metformin group (-0.66 kg difference) and between BIAsp 30 + metformin compared to BIAsp 30 alone (-0.80 kg difference).</p> <p>However, end-of trial body weight was significantly higher for the BIAsp 30 group compared to the glibenclamide + metformin group (-1.46 kg difference).</p> <p>There was no significant difference in triglyceride (TG) reduction or HDL-cholesterol increase, between the three treatment groups.</p>																											

			9.6%, 9.3% and 9.4% respectively.	starting dose of glibenclamide was 2.33 rising to 6.58 mg by the end of the trial. Dose of metformin remained unchanged throughout the trial (approx. 1660 mg/day) and was similar between the two groups receiving it.				The proportions of patients who had at least one adverse event were: 42%, 31% and 24% in the BIAsp 30, BIAsp + metformin and Metformin + Glibenclamide groups respectively. 95% of the events were deemed to be unrelated to the trial.	
Marre M, Van GL, Usadel KH, Ball M, Whatmough I, and Guitard C. 2002 Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. Diabetes, Obesity & Metabolism: 4: 177 - 186 REF ID: 455.	RCT multicentre double-blind, parallel group trial 1+	467 patients from centres in North America, Europe and South Africa.	Inclusion criteria: Patients \geq 30 years of age with T2D of at least 6 months' duration. HbA1c in the range of 6.8% to 11% (mean of week -4 and -2 evaluations) was required for study entry, and patients were excluded if FPG values were \geq 15mmol/l at either time-point. Patients were required to have been treated with metformin for a	metformin 1000mg + nateglinide 60mg N= 155 metformin 1000mg + nateglinide 120mg N= 160	metformin 1000mg + placebo N= 152	24 weeks All patients entered a single-blind, 4-week run-in period and were treated with a maximally effective dose of metformin 1000mg b.i.d plus nateglinide placebo. Patients fulfilling the inclusion/exclusion criteria at week -4, -2 and 0	HbA1c FPG Lipid profile Weight Side effects	*HbA1c HbA1c was significantly reduced with nateglinide 60mg and 120mg plus metformin compared with metformin control (-0.36%, p = 0.003; -0.51%, p <0.001 respectively) *FPG There was no change in FPG levels from baseline in patients receiving nateglinide 60mg. Compared with metformin control, there was a reduction of -0.8 mmol/l (p= < 0.01) in patients receiving 120mg of nateglinide *Triglycerides Tg were reduced significantly with nateglinide 120mg-plus-metformin compared with the placebo-plus -metformin group at study end-point (-0.2 p= 0.042) * Weight Statistically significant increase (p <0.001) in mean weight of 0.9kg (over that in the metformin group) was observed in the nateglinide 120mg-combination therapy group vs. metformin. *Adverse events	Novartis

			<p>minimum of 3 months and stabilized at a dose of ≥ 1500 mg/day for at least 4 weeks before study entry</p> <p>The majority of patients were <65 years of age (73.9%) and 45% were clinically obese. The mean duration of know diabetes across all treatment groups was 6.8 years. HbA1c values were similar across the 3 groups.</p>			<p>study visits were then randomized to the 3 arms.</p>		<p>19 patients (4.1%) discontinued therapy because of adverse events: 5 in the placebo group, 8 in the nateglinide 60mg and 6 in the nateglinide 120 mg.</p> <p>The most commonly reported adverse events were events suggestive of hypoglycaemia (3.9% in the placebo group, 8.4% in the 60mg nateglinide, and 15.6% in the nateglinide 120mg group), upper respiratory tract infection (4.6%, 9.7% and 8.1%) and diarrhoea (7.9%, 5.8% and 5.6%). the incidence of gastrointestinal adverse events was low and similar in all treatment groups. Serious adverse effects were reported for 17 patients (3.6%) none of which was judged by the investigator to be drug-related.</p> <p>Symptomatic hypoglycaemic events were observed with greater frequency in the nateglinide-plus metformin groups than in the placebo-plus-metformin group. When analysed by baseline HbA1c level, the majority of hypoglycaemic symptoms occurred with nateglinide-120mg when administered to patients with a low HbA1c value of $\leq 8\%$</p>	
Roberts VL, Stewart J, Issa M, Lake B, and Melis R. 2005 Triple therapy with Glimpiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week,	RCT multicentre double-blind 1+	N=170 Of 170 randomized patients, 159 were included in the efficacy analysis and 168 ¹⁴	Inclusion criteria: men and women aged 18 to 80 years with a minimum 1-year history of T2D who had been performing self-monitored	N=84 Metformin + thiazolidinedione + 6 weeks of forced titration of glimepiride 2mg ¹⁵ then 20 weeks of dose maintenance	N=84 Metformin + thiazolidinedione + 6 weeks of forced titration of placebo then 20 weeks of dose maintenance	30 weeks 4-week stabilization & eligibility period Patients continued to take fixed	HbA1c FPG Lipid profile BMI & weight Proportion of responding patients (HbA1c $\leq 7\%$) Adverse	*HbA1c HbA1c was significantly improved at end point with glimepiride combination therapy compared with placebo (mean [SE], -1.31% [0.08] vs. -0.33% [0.08], respectively; P < 0.001) *FPG At end point, the adjusted mean differences between treatments significantly favoured the glimepiride combination in terms of	Sanofi-Aventis

¹⁴ one patient in each treatment group was discontinued before receiving study medication

¹⁵ Insulin secretory capacity was defined as a fasting C-peptide concentration ≥ 0.27 nmol/L

<p>randomized, double-blind, placebo-controlled, parallel-group study. Clinical Therapeutics: 27: 1535 - 1547 REF ID: 61.</p>		<p>were included in the safety analysis</p>	<p>blood glucose testing at home were eligible for participation. Patients had to be receiving a stable regimen of immediate-release metformin (1.0-2.5 g/d) or extended-release metformin (up to 2g/d) and a half-maximum to maximum dose of a thiazolidinedione (up to 8mg/d for rosiglitazone, 45mg/d for pioglitazone) for at least 3 months before study entry.</p> <p>At screening, HbA1c values had to be between 7.5% and 9.5%, and BMI had to be between 26 and 42 kg/m².</p> <p>In addition, patients were required to have insulin</p>			<p>doses of their current OAD therapy</p> <p>26-week treatment period -6-week titration phase -20-week maintenance period</p>	<p>events</p>	<p>fasting plasma glucose (-37.4 [4.0] mg/dl; P < 0.001)</p> <p>*BMI & body weight The adjusted mean changes in body mass index from baseline to end point were 1.26 (0.16) kg/m² with glimepiride and 0.17 (0.16) kg/m² with placebo (P < 0.001). Similarly, the mean change in weight was greater with glimepiride than with placebo (3.76 [0.54] vs. 0.45 [0.52] kg; P < 0.001).</p> <p>*Lipid profile No significant statistical difference</p> <p>*Responding patients The majority of patients (62.2%) who received glimepiride achieved an HbA1c value of ≤ 7%, compared with 26.0% of patients receiving placebo (P < 0.001 between groups).</p> <p>*Adverse events The overall incidence of hypoglycaemia was 51.2% in the glimepiride group and 8.3% in the placebo group (P < 0.001).</p> <p>Reasons for discontinuation</p> <table border="0"> <tr> <td colspan="2"><u>Glimepiride group</u></td> <td style="text-align: right;">n</td> </tr> <tr> <td colspan="2">Did not complete wk 30</td> <td style="text-align: right;">14(16.7%)</td> </tr> <tr> <td colspan="3">Reasons for discontinuation</td> </tr> <tr> <td>• Adverse event</td> <td></td> <td style="text-align: right;">7</td> </tr> <tr> <td>• Withdrawal of consent</td> <td></td> <td style="text-align: right;">4</td> </tr> <tr> <td>• Lost to follow-up</td> <td></td> <td style="text-align: right;">1</td> </tr> <tr> <td>• Site close by sponsor</td> <td></td> <td style="text-align: right;">1</td> </tr> <tr> <td>• No compliance</td> <td></td> <td style="text-align: right;">1</td> </tr> <tr> <td colspan="2"><u>Placebo group</u></td> <td style="text-align: right;">n</td> </tr> <tr> <td colspan="2">Did not complete wk 30</td> <td style="text-align: right;">23(27.4%)</td> </tr> <tr> <td colspan="3">Reasons for discontinuation</td> </tr> <tr> <td>• Adverse event</td> <td></td> <td style="text-align: right;">7</td> </tr> <tr> <td>• Withdrawal of consent</td> <td></td> <td style="text-align: right;">7</td> </tr> </table>	<u>Glimepiride group</u>		n	Did not complete wk 30		14(16.7%)	Reasons for discontinuation			• Adverse event		7	• Withdrawal of consent		4	• Lost to follow-up		1	• Site close by sponsor		1	• No compliance		1	<u>Placebo group</u>		n	Did not complete wk 30		23(27.4%)	Reasons for discontinuation			• Adverse event		7	• Withdrawal of consent		7	
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¹⁶ At biweekly visits, the dose of glimepiride or placebo was titrated in 2 steps (to 4 and then 8mg/d) as needed until the therapeutic goal of serum glucose <120mg/dl was achieved. The dose of glimepiride or placebo could be reduced once in the even of clinical signs of hypoglycaemia and an FPG level <70mg/dl, a random capillary blood glucose level <60mg/dl, or a mean of 3 consecutive SMBG concentrations <70 mg/dl before a study visit. **Patients reporting excessive hyperglycaemia were discontinued from the study**

			<p>secretory capacity¹⁵ during the stabilization phase and an FPG level between 130 and 235 mg/dl within 42 to 72 hours of randomization.</p> <p>Patients who required insulin therapy, were taking other sulfonylureas, or had a history of sulfonylurea hypersensitivity were excluded.</p> <p>The groups were well balanced with respect to demographic and metabolic characteristics,</p>					<ul style="list-style-type: none"> • <u>Lack of efficacy</u> 3 • Lost to follow-up 4 • Violated study protocol 2 	
Yki JH, Kauppinen MR, Tiikkainen M, Vahatalo M, Virtamo H, Nikkila K et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006; 49(3):442-451. Ref ID: 3	RCT (7 European study centres) 1+	N=110 insulin naïve type 2 diabetes patients.	Inclusion criteria: Age 35 to 75 years treated with a stable dose of sulfonylurea and metformin or with metformin alone for at least 3 months prior to enrolment. HbA1c greater	N=61 Bedtime insulin glargine with metformin (G+MET). The goal was to achieve an FPG of 4.0 to 5.5 mmol/l (72 to 100 mg/dl in both groups. The patients were taught to increase their insulin dose by	N=49 Bedtime NPH with metformin (NPH+MET).	36 weeks	Change in HbA1c, symptomatic hypoglycaemia, body weight, adverse events.	<p>At 36 weeks there was no significant difference between mean HbA1c in the G+MET group (7.14 ± 0.2%) and the NPH+MET group (7.16 ± 0.14%).</p> <p>During the last 12 weeks, FPGs averaged 5.75 ± 0.02 in the G+MET group and 5.96 ± 0.03 mmol/l in the NPH+MET group (<0.001).</p> <p>There was no significant difference in mean weight gain between the groups (2.6 ± 0.6 kg in the G+MET group and 3.5 ± 0.7 kg in the NPH+MET group)</p>	Grants from the Academy of Finland and from Aventis.

			<p>than or equal to 8% and a mean fasting plasma glucose (FPG) concentration of greater than 7 mmol/l. Exclusion criteria: Use of other oral antihyperglycemic agents, prior insulin use and non-compliance with daily measurement of FPG. 63% of patients were male, mean age 56 years, mean weight 93kg, mean BMI 32 kg/m², mean HbA1c 9.5% and mean FPG 13 mmol/l.</p>	<p>2IU if FPG >5.5 mmol/l (100mg/dl) and by 4 IU if FPG >10 mmol/l (180 mg/dl) on three consecutive mornings.</p>				<p>In the G+MET group 54% of patients experienced at least one adverse event and this was 49% in the NPH+MET group. Most common were infections and musculoskeletal and gastrointestinal disorders with no differences between the groups.</p> <p>During the entire study, the frequency of hypoglycaemia averaged 5.4 (5 confirmed symptomatic) and 8.0 (7.7) episodes/patient year in the G+MET and NPH+MET groups (p=0.12).</p>	
<p>Raskin P, Klaff L, McGill J, South SA, Hollander P, Khutoryansky N, Hale PM, and Repaglinide vs. Nateglinide Metformin Combination Study Group. 2003</p>	<p>Open-label, parallel-group, randomized, multicentre trial</p> <p>1+ **</p>	<p>N= 192 patients from 6 US-research centres.</p> <p>168</p>	<p>Inclusion criteria: adults (≥18 years old) who had type 2 diabetes for at least 3 months and BMI</p>	<p>N=96</p> <p>2-week titration period¹⁷</p> <p>The dosage of repaglinide was increased stepwise from</p>	<p>N=96</p> <p>2-week titration period</p> <p>Starting nateglinide dose was 120 mg per meal</p>	<p>16 weeks</p> <p>(4-week run-in period)²⁰</p>	<p>HbA1c</p> <p>FPG</p> <p>Glucose area under the time-concentration curve from 0 to 240min</p>	<p>*HbA1c</p> <p>Final HbA1c values were lower for repaglinide/metformin combination therapy than nateglinide/metformin treatment, but there was no significant difference between the two treatments</p> <p>Mean end-of-study changes in HbA1c</p>	<p>Novo Nordisk Pharmaceuticals</p>

¹⁷ Targets for glycemic control during the 2-week dose titration period were SMBG preprandial values of 80–140 mg/dl

¹⁸ Even during the maintenance period secretagogue dosage adjustment was still possible as needed.

¹⁹ For the nateglinide/metformin group, 82% of patients received the daily maximal dose of nateglinide, whereas only 7% of repaglinide-treated patients received the maximal daily dosage. In both groups, the median dose of metformin was 2,000 mg/day.

²⁰ Subjects previously treated with a sulfonylurea had a 4-week run-in period of metformin treatment (500 mg b.i.d. for 2 weeks, followed by metformin 1,000 mg b.i.d. for 2 weeks and thereafter doses taken with meals). Those previously treated with metformin or low-dose Glucovance received 1,000 mg metformin b.i.d. for 4 weeks.

<p>Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin.[see comment][erratum appears in Diabetes Care. 2003 Sep;26(9):2708]. Diabetes Care: 26: 2063 - 2068 REF ID: 350.</p>		<p>patients completed the study.</p> <p>Missing values of HbA1c and FPG (In the event of patient withdrawal or missing data after baseline) were substituted by imputed data (calculated by the incremental mean imputation [IMI] method)</p>	<p>values of 24–42 kg/m². Subjects were stratified by baseline HbA1c value (<9% or ≥9%). Enrolled patients had HbA1c values >7% and ≤12% in previous monotherapy with a sulfonylurea (at ≥25% of the maximum dose), metformin (>1,000 mg/day), or low-dose Glucovance (glyburide ≤2.5 mg and metformin ≤500 mg). In the Repa/Met group the mean age was 55.8± 10.7; 50% of patients were male; mean BMI was 32.9±5.7. HbA1c 8.4±1.3</p> <p>In the Nate/Met group the</p>	<p>1.0 to 2.0 and to 4.0 mg per meal at weekly visits based on the results of 8-point self-monitoring of blood glucose (SMBG) (maximum dose, 16 mg/day).</p> <p>+ 1,000 mg metformin b.i.d.</p> <p>14-week maintenance period¹⁸</p> <p>Repaglinide + 1,000 mg metformin b.i.d.</p> <p>At the end of study¹⁹ median final dose of repaglinide:5.0 mg/day</p>	<p>(the maximum daily dose), which could be reduced to 60 mg/meal in response to hypoglycemia episodes.</p> <p>+ 1,000 mg metformin b.i.d.</p> <p>14-week maintenance period</p> <p>Nateglinide + 1,000 mg metformin b.i.d.</p> <p>At the end of study median final dose of nateglinide: 360 mg/day</p>		<p>(AUC0-240min). Adverse Effects</p>	<p>values from baseline were significantly greater for the repaglinide/metformin combination regimen than for nateglinide/metformin (–1.28 vs. –0.67%; <i>P</i> = 0.001).</p> <p>*FPG Mean end-of-study reductions of FPG values from baseline were significantly greater for the repaglinide/metformin group (–39 vs. –21 mg/dl for nateglinide/metformin; <i>P</i> = 0.002)</p> <p>* Glucose AUC 0-240min. No significant differences</p> <p>*Adverse events <i>No statistical comparisons were reported</i></p> <p>The most frequent adverse event in both groups was upper respiratory tract infection (21% of Repa/Met group vs. 12% of Nate/Met group).</p> <p>Minor hypoglycemic episodes occurred in 7% of the patients of the Repa/Met group compared with 2% of the patients in the Nate/Met group.</p> <p>The Repa/Met group had 5% incidence of arthralgia and 5% incidence of chest pain, as compared with 1% for each in the Nate/Met group.</p> <p>Reasons for discontinuation</p> <table border="0"> <tr> <td><u>Repa/Met</u></td> <td>n (%)</td> </tr> <tr> <td>Did not complete week 16</td> <td>7 (7)</td> </tr> <tr> <td>Reasons for discontinuation</td> <td></td> </tr> <tr> <td>• Adverse event</td> <td>0</td> </tr> <tr> <td>• Lack of efficacy</td> <td>0</td> </tr> <tr> <td>• Noncompliance</td> <td>2 (2)</td> </tr> <tr> <td>• Other</td> <td>5 (5)</td> </tr> </table> <table border="0"> <tr> <td><u>Nate/Met</u></td> <td>n (%)</td> </tr> <tr> <td>Did not complete week 16</td> <td>17 (18)</td> </tr> <tr> <td>Reasons for discontinuation</td> <td></td> </tr> </table>	<u>Repa/Met</u>	n (%)	Did not complete week 16	7 (7)	Reasons for discontinuation		• Adverse event	0	• Lack of efficacy	0	• Noncompliance	2 (2)	• Other	5 (5)	<u>Nate/Met</u>	n (%)	Did not complete week 16	17 (18)	Reasons for discontinuation		
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			mean age was 55.0± 10.6; 60% of patients were male; mean BMI was 33.4±5.7. HbA1c 8.2±1.3					<ul style="list-style-type: none"> • Adverse event 1 (1) • Lack of efficacy 7(7) • Noncompliance 2 (2) • Other 7(7) 	
Derosa G, Franzetti I, Gadaleta G, Ciccarelli L, Fogari R. Metabolic variations with oral antidiabetic drugs in patients with Type 2 diabetes: comparison between glimepiride and metformin. Diabetes, Nutrition & Metabolism - Clinical & Experimental 2004; 17(3):143-150. Ref ID: 3141	RCT 1-	N=164 randomised, N=148 completers. Patients from 3 centres in Italy.	<p>Inclusion criteria: patients with Type 2 diabetes diagnosed in the last 6 months. All patients were normotensive, non-smokers with no coronary heart disease, at high risk of vascular disease (HbA1c >7.0 and LDL cholesterol >100 mg/dl).</p> <p>Mean age 56 yrs in the glimepiride group, 58 yrs in the metformin group. 47% and 51% were male in the groups respectively. Mean BMI was 27.6 kg/m² and 28.1 kg/m²</p>	<p>N=83 (N=75 completers) Metformin, max. dose 3000 mg/d (treatment period); mean final dose end of titration = 2500 mg/d.</p> <p>On entering the study both groups followed a controlled-energy diet (1400-1600 kcal/d) and undertook aerobic activity for at least 30 min 3-4 times/week. After randomisation all patients started on an 8-week titration period to allow the drug doses to be optimised to achieve fasting plasma</p>	<p>N=81 (N=73 completers) Glimepiride, Max. dose 4 mg/d (treatment period); mean final dose end of titration = 3 mg/d.</p>	12-months	<p>Mean HbA_{1c}; FPG; PPG (2 hrs after lunch); lipid profile (TG, total, LDL and HDL cholesterol levels); mean body weight and adverse events (AEs).</p>	<p>At 12 months there was no significant change from baseline in each group for BMI, total cholesterol, TG and HDL-cholesterol.</p> <p>There was a significant decrease from baseline after 12 months in mean HbA_{1c} (glimepiride -1.6 mg/dl, p<0.01; metformin -1.4 mg/dl, p<0.01); FPG (glimepiride -42 mg/dl, p<0.01; metformin -49 mg/dl, p<0.01); PPG (glimepiride -27 mg/dl, p<0.01; metformin -26 mg/dl, p<0.01).</p> <p>There were no between-group comparisons.</p> <p>Withdrawals: 10% non-completers in each group due to diarrhoea and nausea (N=2 metformin group), failure to appear at a visit (N=1 in each group) and unsatisfactory glycaemic control (N=5 and N=7 metformin and glimepiride groups respectively).</p>	Not mentioned

			respectively and mean HbA1c was 8.5% and 8.4% respectively.	glucose (FPG) <120 mg/dl and 2-hr post-prandial glucose (PPG) <160 mg/dl. Followed by a 12-month treatment period.					
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.	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. 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). 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 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. 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 due to adverse experience. Discontinuation due to GI disorders was 3.1% in the RSG + MET group and 6.8% in the MET group.	GSK
Salpeter S, Greyber	Cochrane systematic	N=206 Comparati	Inclusion criteria:	Metformin alone or in	Placebo or sulphonylurea,	At least one month	Death due to lactic	There were no cases of fatal or nonfatal lactic acidosis in 47,846 patient-years of	N/A

<p>E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus.[update in Cochrane Database Syst Rev. 2006;(1):CD002967; PMID: 16437448][update of Cochrane Database Syst Rev. 2002;(2):CD002967; PMID: 12076461]. [Review] [260 refs]. Cochrane Database of Systematic Reviews 2003;(2):CD002967. Ref ID: 275</p>	<p>review 2++</p>	<p>ve trials and cohort studies</p>	<p>Prospective clinical trials in patients with type 2 diabetes mellitus which evaluated metformin, alone or in combination with other treatments, compared to placebo or to any other glucose-lowering therapy. Trials were included even if they were not randomised or blinded. Observational cohort studies were also included.</p>	<p>combination with other treatments</p>	<p>thiazolidinedione, meglitinide, alpha glucosidase inhibitor, insulin, non-pharmacological intervention, any combination of the above,</p>		<p>acidosis Reported cases of nonfatal lactic acidosis.</p>	<p>metformin use or in 38,221 patients-years in the non-metformin group. Using Poisson statistics with 95% confidence intervals the upper limit for the true incidence of metformin related lactic acidosis was 6.3 cases per 100,000 patient years and the upper limit for the true incidence of lactic acidosis in the non-metformin group was 7.8 cases per 100,000 patient years.</p>	
<p>Fujioka²¹ K, Brazg RL, Raz I, Bruce S, Joyal S, Swanink R, and Pans M. 2005. Efficacy, dose-response relationship and safety of once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise:</p>	<p>RCT Protocol 1 1+</p>	<p>N=240</p>	<p>Inclusion criteria: diagnosis of T2D of 1-120 months' duration with inadequate glycaemic control despite diet and exercise therapy. Age (21-78 years) and BMI (≥ 21 kg/m² and \leq</p>	<p>Metformin XR 500mg²² - 1000mg N=79 After one week this was increased to two tablets daily, taken with the evening meal. At 12 weeks, patient with HbA1c 7-8%</p>	<p>Placebo N= 161</p>	<p>24 weeks</p>	<p>HbA1c Proportion of patients achieving HbA1c <7.0% FPG Lipid profile Body weight Adverse events.</p>	<p>*HbA1c once-daily metformin XR reduced HbA1c significantly (p<0.001) compared with placebo the treatment differences between metformin XR 1000mg QD and placebo were -0.7% at 12 weeks and -0.8% at 24 weeks. * % of patients achieving HbA1c <7.0% 29% and 35% of patients achieved HbA1c <7.0% after 12 and 24 weeks of metformin XR 1000mg</p>	<p>Bristol-Myers Squibb</p>

²¹ This paper reported two double blind, randomized, placebo-controlled studies of 24 and 16 weeks' duration, in T2D patients with inadequate glycaemic control despite diet and exercise. Protocol 1 provided an evaluation of metformin XR at a commonly used dosage. Protocol 2 evaluated different dosages of metformin XR

²² Patients were randomized in a 2:1 ratio to receive one tablet of extended-release metformin (metformin XR) 500mg or matching placebo once daily with the evening meals. After one week this was increased to two tablets daily, taken with the evening meal. At 12 weeks, patients with HbA1c 7-8% could receive an additional table (total daily dose of 1500mg metformin XR), while patients with HbA1c $\geq 8\%$ were withdrawn.

<p>results from two double-blind, placebo-controlled studies. Diabetes, Obesity & Metabolism: 7: 28 – 39 REF ID: 3169.</p>			<p>38 kg/m²). HbA1c 7-10%, FPG ≥ 7.0 mmol/l (126 mg/dl) and < 15 mmol/l (270mg/dl).</p> <p>The groups were well balanced with respect to demographic and metabolic characteristics.</p>	<p>could receive an additional table (total daily dose of 1500mg metformin XR), while patients with HbA1c ≥ 8% were withdrawn.</p>			<p>*FPG Change in FPG mirrored effects on HbA1c with significant reduction vs. placebo at all dosages in either study.</p> <p>*Lipid profile Significant effect on lipid parameters were not observed at 12 weeks; however, a significant reduction in LDL was observed in the metformin XR group compared with placebo at 24 weeks (placebo-corrected mean change of -9.0mg/dl, p=0.006)</p> <p>*Body weight at 24 weeks, the mean reduction in weight in the placebo group (-1.0kg), achieved statistical significance (p= 0.012) compared with the mean change in the metformin XR group (-0.2 kg)</p> <p>*Adverse events all-cause AE were reported by 59.5% of patients treated with placebo and by 63.5% of patients treated with metformin XR.</p> <p>GI adverse events (%) GI AEs (particularly nausea/vomiting and diarrhoea) were more common in metformin-treated patients.</p> <table border="0" data-bbox="1536 973 2040 1276"> <thead> <tr> <th></th> <th>Placebo (N=79)</th> <th>XR 1000mg (N=159)</th> </tr> </thead> <tbody> <tr> <td>Abdominal pain</td> <td>5.1</td> <td>7.5</td> </tr> <tr> <td>Diarrhoea</td> <td></td> <td>5.1</td> </tr> <tr> <td>6.9</td> <td></td> <td></td> </tr> <tr> <td>Nausea/vomiting</td> <td>3.8</td> <td>9.4</td> </tr> <tr> <td>URI</td> <td>13.9</td> <td>10.7</td> </tr> <tr> <td>Headache</td> <td>10.1</td> <td>8.2</td> </tr> <tr> <td>Influenza</td> <td>7.6</td> <td>7.5</td> </tr> <tr> <td>Dizziness</td> <td>6.3</td> <td>4.4</td> </tr> <tr> <td>UTI</td> <td>5.1</td> <td>3.8</td> </tr> </tbody> </table> <p><u>Reasons for discontinuation</u> Total 95 (39.6%)</p>		Placebo (N=79)	XR 1000mg (N=159)	Abdominal pain	5.1	7.5	Diarrhoea		5.1	6.9			Nausea/vomiting	3.8	9.4	URI	13.9	10.7	Headache	10.1	8.2	Influenza	7.6	7.5	Dizziness	6.3	4.4	UTI	5.1	3.8	
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Fujioka K, Brazg RL, Raz I, Bruce S, Joyal S, Swanink R, and Pans M. 2005. Efficacy, dose-response relationship and safety of once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies. Diabetes, Obesity & Metabolism: 7: 28 – 39 REF ID: 3169.	RCT Protocol 2 1+	N=742	Same as above but HbA1c 7-11% and FPG \geq 7.0 mmol/l (126 mg/dl) and < 15.6 mmol/l (280mg/dl). The groups were well balanced with respect to demographic and metabolic characteristics.	1) metformin XR 500mg QD ²³ N= 128 2) metformin XR 1000mg QD N=120 3) metformin XR 1500mg QD N=120 4) metformin XR 2000mg QD N=134 5) metformin XR 1000mg BID N=123	6) placebo N=117	16 weeks	HbA1c Proportion of patients achieving HbA1c <7.0% Lipid profile Body weight Adverse events	*HbA1c once-daily metformin XR reduced HbA1c significantly (p<0.001) compared with placebo A dose-relationship for the effects of once-daily metformin XR on HbA1c was evident: treatment differences vs. placebo of -0.6% (500mg QD), -0.7% (1000mg QD), -1.0% (1500mg QD), -1.0% (2000mg QD) and -1.2% (1000mg BID) * % of patients achieving HbA1c <7.0% once again, a dose-relationship for this parameter was observed in patients receiving once-daily treatment, with the maximal effects attained at metformin XR 1500mg QD and 2000mg QD (34% and 36% of patients respectively, vs. 10% with placebo) *FPG Change in FPG mirrored effects on HbA1c with significant reduction vs. placebo at all dosages in either study. *Lipid profile once-daily metformin XR significantly	Bristol-Myers Squibb

²³ Patients were randomized to receive one of the five metformin XR regimes or matching placebo. Double-blind therapy was initiated at a metformin XR dose of 500mg/day (one tablet) and increased at weekly intervals until target dosages were reached.

							<p>reduced LDL ($p < 0.05$ – $p < 0.001$), compared with placebo, at all dosages studied. In addition a significant reduction ($p < 0.05$) in total cholesterol was observed in the metformin XR 2000mg</p> <p>*Body weight NS</p> <p>*Adverse events all-cause AE were reported by 59.5% of patients treated with placebo and by 65.85% of patients treated any dosage of metformin XR.</p> <table> <thead> <tr> <th>%</th> <th>Placebo (N=116)</th> <th>XR 1000mg (N=622)</th> </tr> </thead> <tbody> <tr> <td>Abdominal pain</td> <td>2.6</td> <td>5.1</td> </tr> <tr> <td>Diarrhoea</td> <td></td> <td>3.4</td> </tr> <tr> <td>12.9</td> <td></td> <td></td> </tr> <tr> <td>Nausea/vomiting</td> <td>1.7</td> <td>8.2</td> </tr> </tbody> </table> <p><u>Reasons for discontinuation</u></p> <table> <thead> <tr> <th></th> <th>Total</th> </tr> </thead> <tbody> <tr> <td></td> <td>119 (16%)</td> </tr> </tbody> </table> <p>Placebo</p> <table> <tbody> <tr> <td>Lack of efficacy</td> <td>16.2%</td> </tr> <tr> <td>Subject request</td> <td>3.4%</td> </tr> <tr> <td>Adverse events</td> <td>0.9%</td> </tr> <tr> <td>Other</td> <td>3.4%</td> </tr> </tbody> </table> <p>Metformin XR 500mg QD</p> <table> <tbody> <tr> <td>Lack of efficacy</td> <td>10.2%</td> </tr> <tr> <td>Subject request</td> <td>6.3%</td> </tr> <tr> <td>Adverse events</td> <td>3.1%</td> </tr> <tr> <td>Other</td> <td>1.6%</td> </tr> </tbody> </table> <p>Metformin XR 1000mg QD</p> <table> <tbody> <tr> <td>Lack of efficacy</td> <td>5.0%</td> </tr> <tr> <td>Subject request</td> <td>2.5%</td> </tr> <tr> <td>Adverse events</td> <td>2.5%</td> </tr> <tr> <td>Other</td> <td>1.7%</td> </tr> </tbody> </table> <p>Metformin XR 1500mg QD</p> <table> <tbody> <tr> <td>Lack of efficacy</td> <td>5.8%</td> </tr> <tr> <td>Subject request</td> <td>5.0%</td> </tr> </tbody> </table>	%	Placebo (N=116)	XR 1000mg (N=622)	Abdominal pain	2.6	5.1	Diarrhoea		3.4	12.9			Nausea/vomiting	1.7	8.2		Total		119 (16%)	Lack of efficacy	16.2%	Subject request	3.4%	Adverse events	0.9%	Other	3.4%	Lack of efficacy	10.2%	Subject request	6.3%	Adverse events	3.1%	Other	1.6%	Lack of efficacy	5.0%	Subject request	2.5%	Adverse events	2.5%	Other	1.7%	Lack of efficacy	5.8%	Subject request	5.0%
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<p>Blonde L, Joyal S, Henry D, Howlett H. Durable efficacy of metformin/glibenclamide combination tablets (Glucovance) during 52 weeks of open-label treatment in type 2 diabetic patients with hyperglycaemia despite previous sulphonylurea monotherapy. International Journal of Clinical Practice 2004; 58(9):820-826. Ref ID: 3172</p>	<p>Retrospective chart review/cohort study (4 diabetes clinics in the US) 2+</p>	<p>N=471 (3 ineligible due to missing data)</p>	<p>Patient charts were identified by study investigators from a sites pharmacy prescription database from Oct 2001 to May 2002. All adult patients who were started on metformin XR or switched from metformin IR or other oral anti-diabetic agent to metformin XR within the previous 2 years were eligible for inclusion in the metformin XR cohort. Patients who were started on metformin IR within the past 2 years</p>	<p>N=158 Metformin IR (immediate release) Mean daily dose 1282 mg.</p>	<p>N=310 Metformin XR (extended release) (N=205 of this group had switched from immediate release to extended release metformin) Mean daily dose 1258 mg</p>	<p>N/A</p>	<p>Gastrointestinal tolerability</p>	<p>Overall Metformin XR vs metformin IR cohorts</p> <p>The frequency of any GI adverse event within the first year of treatment was similar between metformin XR and metformin IR (11.94% vs 11.39%, p=0.86). There was no significant difference between the cohorts for any individual GI adverse events.</p> <p>Diarrhea 6.77% vs 7.59%</p> <p>Nausea 2.26% vs 3.80%</p> <p>Dyspepsia 1.61% vs 1.27%</p> <p>Abdominal pain 1.61% vs 0.63%</p> <p>Constipation 0.97% vs 0.63%</p> <p>Vomiting 0.65% vs 0.63%</p> <p>Abdominal distension 0.32% vs 0%</p> <p>Fecal abnormality 0.32% vs 0.63%</p> <p>Blood in stool 0% vs 0.63%</p> <p>Flatulence 0% vs 0.63%</p> <p>Patients switched from metformin IR to Metformin XR</p> <p>In a cohort of 205 patients started on metformin IR and switched to metformin XR the frequency of any GI adverse event was 26.45% (while taking metformin IR) vs 11.71% after switching to metformin XR; p=0.0006). The frequency of diarrhea in this comparison was 18,05% vs 8.29%; p=0.0084).</p> <p>Comparison of patients new to metformin treatment with either metformin IR or</p>	<p>Bristol Myers Squibb</p>

			were eligible for inclusion in the metformin IR cohort. Mean age 56 years, mean BMI 33kg/m2.					metformin XR. A significantly greater percentage of patients reported a GI adverse event during the first year of treatment with metformin IR (19.83%, 72/363) than during the first year of therapy with metformin XR (9.23%, 6/65, p=0.0414). A significantly higher proportion of patients in the immediate release metformin group reported diarrhea in the metformin IR group (13.5% vs 3.08, p=0.0169).	
Yousseif A, Roberts S, Malik S, Packianathan S, Shotliff K. Patient reported side effects and compliance with glucophage SR. Diabetic Medicine 23 (Suppl 2), 111. 2006. Abstract P326 Ref ID: 3173	Abstract only							Introduction: Compliance with therapy is influenced by side effect profile and polypharmacy. Glucophage SR has been reported to have fewer gastrointestinal side effects, which potentially improves compliance. Aims: To assess tolerance and compliance reported by patients taking glucophage SR, after a 6-month period. Methods: Patients on glucophage SR were identified retrospectively from the pharmacy database. Patient demographics, compliance and side effects experienced on conventional metformin therapy were obtained from patient notes. Following a 6-month period on glucophage SR therapy, patients were questioned about side effects and compliance. Results: Of the 34 patients initially identified, 62% (21/34) completed the survey. Demographics: 11 male/10 female; age range: 31–78 years old (median age: 61 years old). On conventional metformin 76% (16/21) had documented gastrointestinal side effects: diarrhoea 52.4% (11/21); abdominal pain 5% (1/21), nausea 5% (1/21), unspecified 5% (1) and flatulence 10% (2/21). On glucophage SR 95.2% of patients (20/21) reported good compliance (one patient discontinued medication due to diarrhoea). Only 14.3% (3/21) experienced gastrointestinal side effects. Conclusion: In this survey patients reported good compliance and less gastrointestinal side effects with glucophage SR.	

								Glucophage SR is a useful therapeutic alternative for Type II diabetic patients unable to tolerate conventional metformin.
Thomas Z, Phillips SM, Hogan D, Whittingstall L, Wilson P, Almrayat M. The tolerability of prolonged-release metformin (Glucophage SR) in previously metformin intolerant patients - review of local experience. Diabetic Medicine 23 (suppl 2), 111. 2006. Abstract P325 Ref ID: 3174	Abstract only							Metformin is standard first line therapy for patients with Type 2 diabetes mellitus and obesity. Gastrointestinal side effects occasionally present barriers to its use. Recently available slow-release metformin (Glucophage SR) holds the promise of reduced gastrointestinal side effects compared to immediate-release metformin. Here we report our initial clinical experience of its use. Twenty-four Type 2 diabetes patients (12M, 12F; age 60.6 ± 0.6 year (mean ± SD); diabetes duration 6.5 ± 0.5 year) who were previously intolerant to standard metformin preparation were prescribed Glucophage SR. Duration of treatment was 4.7 ± 2.2 months; 15 patients (62%) tolerated the Glucophage SR, seven patients (30%) did not tolerate it. No follow up data on two patients were available at time of analysis. No significant changes were seen in either glycated haemoglobin (HBA1c; 8.9 ± 1.4 before vs. 8.8 ± 1.4% after), or body mass index (32.4 ± 6.8 before vs. 32.9 ± 7.1 kg/m2 after). Triglyceride levels in those who continued the treatment were not significantly changed (pre 2.3 ± 1.8 vs. after 1.9 ± 0.8 mmol/l). Our local experience suggests that slow release metformin is well tolerated in a significant proportion of patients who previously were intolerant to standard preparations and thus worth considering. The impact on glycaemic control is not significant at early stages.
Mohammad F, Fenna I, Leong K, Joseph P, Leach J, Raymond CJ et al. Audit of metformin sustained release (SR) in patients intolerant of immediate release	Abstract only							Background: The use of metformin in Type 2 diabetes mellitus is limited by its gastrointestinal side effects. Metformin SR is thought to be better tolerated and may improve compliance. Aims: To audit the impact of metformin SR in patients intolerant of metformin. Methods: Patients switched onto metformin SR who had previously been metformin intolerant were identified from the diabetes

<p>metformin. Diabetic Medicine 23 (supp 2), 111. 2006. Abstract P324 Ref ID: 3176</p>								<p>database at Clatterbridge General Hospital. Dosage of metformin and metformin SR, HbA1c, BMI and tolerability to metformin SR were analysed from the notes. Results: Data were available from 28 patients (17M, 11F, mean age: 61.2 years and mean duration of diabetes: 9.6 years). The mean dose of metformin and metformin SR was 1441 and 1303 mg daily and duration of treatment was 18.2 and 5.9 months respectively. The mean HbA1c (8.4% vs. 8.4%) and BMI (31 vs. 32.2) did not alter significantly pre and during metformin SR use. However 23 (82%) patients were able to tolerate metformin SR without Gastrointestinal problems and only two (7.1%) patients needed to discontinue metformin SR. Conclusion: Metformin SR was tolerated better but did not alter HbA1c or BMI significantly, this may be due to the short duration of treatment with metformin SR at present.</p>	
<p>Nagle A, Brake J, Hopkins M, Brame C, Spelman S, Prichard R. Glucophage SR. Can it really make a difference? Diabetic Medicine [23 (suppl 2)], 110. 2006. Abstract P319 Ref ID: 3175</p>	<p>Abstract only</p>							<p>Objectives: To establish whether patients unable to tolerate standard Metformin were given appropriate advice on administration and titration, and if Metformin sustained release (SR) was then tolerated and had beneficial effects on HbA1c, weight and insulin/sulphonylurea requirements. Design: Eleven Patients with Type 2 diabetes (nine on insulin therapy, two on sulphonylurea monotherapy) identified as not taking Metformin or taking less than 2 g under the outpatient care of a large teaching hospital in Liverpool were included in the study. Main results: All patients had been prescribed and taking Metformin correctly when not tolerated. Mean HbA1c was 9.0% this was significantly lower at 12 weeks (P = 0.03) 8.2%. A significant reduction in insulin dose in all insulin treated patients from 84 U/day to 75 U/day (P = 0.04). There was a significant increase in weight from 96.7 kg to 97.8 kg (P = 0.04). Eight patients (27%)</p>	

								<p>tolerated 2 g of metformin SR, three (27%) patients tolerated 1–1.5 g. Conclusions: Poor tolerability of immediate release Metformin in this group of patients was not due to their administration of the drug, and Metformin SR was well tolerated with benefits of reduction in HbA1c and insulin requirements, but also an increase in weight.</p>	
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