

**Evidence Tables
SEC 1**

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Charpentier G, Fleury F, Kabir M, Vaur L, and Halimi S. 2001. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabetic Medicine: 18: 828 - 834 REF ID: 988.	RCT Level of evidence: 1++	N= 372 from 34 hospital and general practice centres in France	Inclusion criteria: patients aged between 35 and 70 years with T2D inadequately controlled by metformin monotherapy 2550mg daily for at least 4 weeks ¹ and with a serum creatinine <110 µmol/l. Newly diagnosed patients (<1 year) were recruited provided that BMI was ≥ 23.9 kg/m ² for female patients or ≥ 25.0 kg/m ² for male patients There were no	1. metformin + glimepiride placebo N= 75 2. glimepiride + metformin placebo N= 150	3. metformin + glimepiride N= 147	20 weeks 12-week dose titration ² 8-week maintenance phase ³	HbA1c FBG PPBG Lipid profile BMI Adverse events	*HbA1c Combination treatment (glimepiride + metformin) was significantly more efficient in reducing HbA1c levels than: - glimepiride alone (difference in mean change 1.04% 95% CI 0.81 – 1.27%; p < 0.001) - metformin alone (difference in mean change 0.92% 95% CI 0.63 – 1.21%; P<0.001) there was no significant difference between metformin or glimepiride monotherapy in terms of HbA1c. * FPG combination treatment was significantly more effective than either monotherapy in reducing FBG (P<0.001) there was no significant difference between metformin or glimepiride monotherapy in terms of FPG *PPBG combination treatment was significantly more effective than either monotherapy in reducing PPBG (P<0.001) treatment with glimepiride was significantly	Hoechst Marion Roussel

¹ As defined by FBG criteria (7.8 mmol/L < FBG ≤ 13.9 mmol/L)

² Metformin dosage remained constant throughout the study at 850mg three times daily or matching placebo. At the end of the study, nearly twice as many patients in either monotherapy group than in the combination group (84% in the metformin group and 77% in the glimepiride group vs. 41% in the combination group) had been titrated to the highest dose level of glimepiride (or matching placebo)

³ In the maintenance phase dosages of study treatments had to be kept constant; however, in case of hypoglycaemic symptoms, glimepiride dosage was reduced to the previous level.

			<p>differences between the three groups with respect to demographic and baseline characteristics or diabetes history</p>				<p>more effective than metformin in reducing PPBG (P<0.001)</p> <p>*Total cholesterol the combination of glimepiride and metformin was significantly more effective than glimepiride alone (P<0.001) in reducing total cholesterol levels, although there was no significant difference between the combination and metformin alone.</p> <p>*Tg - LDL - HDL NS difference</p> <p>*BMI treatment with metformin resulted in a significant lower BMI than either glimepiride alone (P<0.001) or the combination treatment (P<0.002); however there was no significant difference between the glimepiride and combination treatment groups.</p> <p>*Adverse events AE were experienced by 105 patients</p> <table border="0"> <thead> <tr> <th></th> <th>n</th> <th>(%)</th> </tr> </thead> <tbody> <tr> <td>metformin</td> <td>22</td> <td>(29%)</td> </tr> <tr> <td>glimepiride</td> <td>38</td> <td>(25%)</td> </tr> <tr> <td>glimepiride + metformin</td> <td>45</td> <td>(31%)</td> </tr> </tbody> </table> <p>Hypoglycaemia: the incidence of symptomatic episodes was significantly higher in the combination treatment group than in either of the monotherapy groups (22% of patients vs. 11% of patients in the metformin group and 13% of patients in the glimepiride group, P=0.039)</p> <p>Diarrhoea was more commonly reported in the metformin group than in the other two treatment groups (7% of patients vs. 1% of patients in the glimepiride group and 3% of patients in the combination group)</p> <table border="0"> <thead> <tr> <th>Discontinuation</th> <th>n</th> <th>(%)</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> </tr> </tbody> </table>		n	(%)	metformin	22	(29%)	glimepiride	38	(25%)	glimepiride + metformin	45	(31%)	Discontinuation	n	(%)				
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Furlong NJ et al. 2003 Comparison of repaglinide vs. gliclazide in combination with bedtime NPH insulin in patients with Type 2 diabetes inadequately controlled with oral hypoglycaemic agents. Diabetic medicine: a journal of the British Diabetic Association: 20: 935 - 941 REF ID: 339.	RCT Open label Level of evidence: 1++	N=80 UK patients	Inclusion criteria: men and women aged over 18 years with T2D and inadequate glycaemic control (HbA1c >7.0% despite maximal oral therapy Baseline characteristics were similar for age, sex, weigh, BMI, FBG and HbA1c. HbA1c 9.4 ± 0.3% in the repaglinide group and 9.2 ± 0.3% in the gliclazide group.	Bedtime NPH insulin ⁴ + repaglinide 4mg t.i.d N= 41	Bedtime NPH insulin + gliclazide 160mg b.i.d. N= 39	13 weeks	-HbA1c -FPG -Post-prandial blood glucose excursions -Weight -Well-being and diabetes treatment satisfaction -Adverse events	* HbA1c HbA1c decreased by 1.0% from 9.2 to 8.2% (P=0.001) in the insulin/gliclazide and by 0.9%, from 9.4 to 8.5% in the insulin/repaglinide group (P=0.005). Change in HbA1c between the groups was not statistically different (P= 0.83) * FBG FBG improved by (mean) -3.5 mmol/l, from 10.1 to 6.7 mmol/l (P< 0.0001) in the insulin/gliclazide group and by -2.7 mmol/l, from 10 to 7.1 mmol/l (P<0.0001) in the insulin/repaglinide group. Change in FBG between the groups was not statistically different (P= 0.26) * Post-prandial blood glucose excursions No statistically significant differences were observed between the groups. * Body weight 4.1 ±0.5kg in the insulin/gliclazide group and 3.4 ±0.4kg in the insulin/repaglinide group (P<0.0001 for both groups from baseline). The difference in weight gain between the groups was not statistically significant (P=0.29)	Novo Nordisk Pharmaceuticals.

⁴ in both groups, NPH insulin (Insulatard®) was started at a dose of 0.5 units per kg bodyweight and increased after 1 week to 0.7 units per kg. Insulin doses were then titrated at the clinician's discretion, aiming for a target fasting blood glucose of 4.0 – 6.0 mmol/l.

							<p>* Well-being score Well-being scores improved by 3.8 ± 1.7 points, from 45.5 ± 2.2 to 50.5 ± 2.1 ($P=0.004$) in the insulin/repaglinide group. There was a small non-significant increase of 1.1 ± 1.2 points, from 46.4 ± 2.2 to 47.6 ± 2.1 in the insulin/gliclazide group.</p> <p>* diabetes treatment satisfaction score (DTSQ) Statistically significant improvements in DTSQ scores were observed in both groups. In the insulin/gliclazide group, by 4.9 ± 1.1 points from 28.4 ± 1.6 to 33.3 ± 0.6 ($P<0.0001$) and by 3.0 ± 0.9 points from 31 ± 0.9 to 34.6 ± 0.4 ($P=0.0006$).</p> <p>Comparing the changes in scores for both questionnaires revealed no statistically significant differences [$P=0.065$ (WBQ) and 0.29 (DTSQ)]</p> <p>* Adverse events a total of 70 adverse events were recorded throughout the study, 38 in the insulin/gliclazide and 32 in the insulin/repaglinide group.</p> <p>Serious Adverse events</p> <table> <tr> <td><u>Insulin/gliclazide</u></td> <td>3</td> </tr> <tr> <td>- MI</td> <td>2</td> </tr> <tr> <td>- chest pain</td> <td>1</td> </tr> <tr> <td><u>insulin/repaglinide</u></td> <td>3</td> </tr> <tr> <td>- dizziness</td> <td>1</td> </tr> <tr> <td>- diarrhoea + incontinence</td> <td>1</td> </tr> <tr> <td>- abnormal liver test</td> <td>1</td> </tr> </table> <p>- Hypoglycaemia 19 (49%) subjects in the insulin/gliclazide group and 16 (39%) of subjects in the insulin/repaglinide group remained free from hypoglycaemia throughout the study ($P=0.26$ between groups)</p>	<u>Insulin/gliclazide</u>	3	- MI	2	- chest pain	1	<u>insulin/repaglinide</u>	3	- dizziness	1	- diarrhoea + incontinence	1	- abnormal liver test	1	
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							<p>Over the 13-week study period, mean number of hypoglycaemic episodes experienced per patient was 2.95 ± 0.82 and 2.3 ± 0.52 for the insulin/gliclazide and insulin/repaglinide groups, respectively (P=0.81 between groups)</p> <p>Discontinuation</p> <table> <tr> <td><u>Insulin/repaglinide</u></td> <td>6</td> <td>(14.6%)</td> </tr> <tr> <td>- consent withdrawal</td> <td>1</td> <td></td> </tr> <tr> <td>- lack of efficacy</td> <td>2</td> <td></td> </tr> <tr> <td>- adverse events</td> <td>3</td> <td></td> </tr> <tr> <td><u>insulin/gliclazide</u></td> <td>0</td> <td></td> </tr> </table>	<u>Insulin/repaglinide</u>	6	(14.6%)	- consent withdrawal	1		- lack of efficacy	2		- adverse events	3		<u>insulin/gliclazide</u>	0			
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<p>Bengel FM, Abletshauser C, Neverve J, Schnell O, Nekolla SG, Standl E, and Schwaiger M. 2005. Effects of nateglinide on myocardial microvascular reactivity in Type 2 diabetes mellitus--a randomized study using positron emission tomography. Diabetic Medicine: 22: 158 - 163 REF ID: 3147</p>	<p>RCT Level of evidence: 1+</p>	<p>N=47</p>	<p>Inclusion criteria: HbA1c 6.5 – 9.5%, diagnosis of T2D at least 12 weeks prior to inclusion, treatment with diet alone or diet combined with a single oral antidiabetic agent for at least 12 weeks prior to inclusion, BMI 22-35 kg/m².</p> <p>A randomization ratio 2:1 (nateglinide: placebo) was selected to reduce the number of patients</p>	<p>Nateglinide 120mg N= 33</p>	<p>Placebo N= 14</p>	<p>16 weeks</p>	<p>HbA1c FPG Lipid profile Adverse events</p> <p>Main outcome (and what the study was powered for) was myocardial blood flow and microvascular reactivity (outcomes not considered here).</p>	<p>*HbA1c Nateglinide decreased HbA1c by 0.4% whereas it increased by 0.5% in the placebo group) P<0.05. The least squares mean for percentage change from baseline was – 3.6% (SE 2.9) for nateglinide vs 5.6% (SE 3.9) for placebo (p=0.02).</p> <p>*FPG NS</p> <p>*Lipid profile NS</p> <p>Discontinuation</p> <table> <tr> <td><u>Nateglinide</u></td> <td></td> <td></td> </tr> <tr> <td>Adverse events</td> <td>4</td> <td>(12%)</td> </tr> <tr> <td>Sub-dose</td> <td>2</td> <td>(6%)</td> </tr> <tr> <td><u>Placebo</u></td> <td></td> <td></td> </tr> <tr> <td>Adverse events</td> <td>0</td> <td></td> </tr> </table>	<u>Nateglinide</u>			Adverse events	4	(12%)	Sub-dose	2	(6%)	<u>Placebo</u>			Adverse events	0		<p>Novartis</p>
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			<p>receiving potentially inferior therapy.</p> <p>There was no significant difference between the groups with regard sex, age, BMI or duration of diabetes. The HbA1c baseline was 7.6± 0.9% in the nateglinide group and 7.9 ±0.8% in the placebo group.</p>																		
<p>Dashora UK, Sibal L, Ashwell SG, Home PD. Insulin glargine in combination with nateglinide in people with Type 2 diabetes: a randomized placebo-controlled trial. <i>Diabetic Medicine</i> 2007; 24: 344-349</p> <p>Ref ID: 4891</p>	RCT 1+	N=55 End point data not available on 25% of patients	<p>Inclusion criteria: type 2 diabetics on twice daily insulin therapy for at least 3 months, HbA1c 6.1-10%, BMI ≤ 42.0 kg/m², age 39-83 years</p> <p>Exclusion criteria: significant hepatic renal or renal dysfunction, active cardiovascular disease</p> <p>Baseline</p>	<p>Nateglinide + insulin glargine</p> <p>4 week run-in period of insulin glargine</p> <p>Metformin was continued if taken</p> <p>Randomisation and concealment methods not described.</p>	<p>Placebo + insulin glargine</p> <p>4 week run-in period of insulin glargine</p> <p>Metformin was continued if taken</p>	<p>16 weeks</p> <p>4 week run-in period and 12 weeks of treatment</p>	<p>Primary: HbA1c</p> <p>Secondary: Self-monitored glucose levels, body weight, insulin dose</p>	<p><u>Glycaemic control:</u> Baseline adjusted HbA1c was not significantly difference between groups: Nateglinide 7.8 ± 1.4 % Placebo 8.3 ± 1.3% Baseline adjusted difference in mean change (95% CI) -0.43% (-0.98 – 0.13)</p> <p>Self monitored blood glucose concentrations (mmol/l) were significantly lower in the nateglinide group only at certain times of the day.</p> <table border="1"> <thead> <tr> <th>Time</th> <th>Difference (95% CI)</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>After breakfast</td> <td>-2.3 (-4.4, -0.2)</td> <td>0.030</td> </tr> <tr> <td>Before lunch</td> <td>-2.5 (-4.6, -0.3)</td> <td>0.029</td> </tr> <tr> <td>After lunch</td> <td>-2.3 (-4.6, -0.4)</td> <td>0.021</td> </tr> </tbody> </table> <p>There was no difference in the proportion of</p>	Time	Difference (95% CI)	p-value	After breakfast	-2.3 (-4.4, -0.2)	0.030	Before lunch	-2.5 (-4.6, -0.3)	0.029	After lunch	-2.3 (-4.6, -0.4)	0.021	<p>Drugs provided by Sanofi-Aventis and Novartis</p>
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			<p>characteristics: HbA1c: Nateglinide 8.2 ± 1.0% Placebo 8.2 ± 1.0%</p> <p>BMI (kg/m²) Nateglinide 31.0 ± 4.0 Placebo 30.9 ± 5.5</p> <p>Insulin dose: Nateglinide 55 ± 28 U/day Placebo 58 ± 29 U/day</p> <p>Metformin use: Nateglinide 20/26 Placebo 19/29</p> <p>Duration of diabetes (Years) Nateglinide 12.3 ± 5.6 Placebo 13.2 ± 6.4</p> <p>Duration of insulin use (Years) Nateglinide 5.2 ± 3.8 Placebo 6.7 ± 4.1</p>				<p>patients experiencing hypoglycaemic episodes in either arm.</p> <p><u>Weight (kg)</u> There was no significant difference in mean change 0.78 (-0.45 – 2.01)</p> <p><u>Insulin dose at end of treatment period</u> Nateglinide group: 58 ± 30 U/day Placebo: 62 ± 31 U/day No significant difference between treatments</p> <p><u>Adverse events</u> There were no treatment-related serious adverse events.</p>		
Derosa, G., et al. "Comparison between repaglinide and	RCT Level of	N= 132 from a single	Inclusion criteria: Patients with	Repaglinide 1mg/d N=66	Glimepiride 1mg/d N=66	1 year ⁵	HbA1c FPG PPG	*HbA1c NS difference between repaglinide and glimepiride in terms of HbA1c	Not reported

⁵ The 12-month treatment period was preceded by an initial 4 -week placebo washout stage (prior randomisation), and an 8-week titration period.

<p>glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors." <u>Clinical Therapeutics</u> 25.2 (2003): 472-84. Ref ID 184</p>	<p>evidence: 1+</p>	<p>centre in Italy</p>	<p>T2D for ≥ 6 months, non-smokers, with normal BP, no coronary heart disease, and normal renal function. Patients were receiving no antidiabetic medications at the time of enrolment and had not achieved satisfactory glycaemic control (HbA1c >7.0%) with diet and exercise alone. All patients had LDL ≥ 100mg/dl. There were no significant differences in demographic and metabolic variables between groups.</p> <p>The mean ages was 56 years in the repaglinide group and 54 years in the glimepiride group</p>	<p>(Mean final doses 2.5 mg/d)</p>	<p>(Mean final doses 3 mg/d)</p>		<p>Lipid profile Body weight/BMI</p>	<p>*FPG NS difference between groups</p> <p>*PPG PPG levels were significantly lower with repaglinide compared with glimepiride (p<0.01)</p> <p>Repaglinide mg/dl (SD) Baseline: 194 (30) 12 months: 148 (27) Change from baseline: -46 (-64 to -12)</p> <p>Glimepiride mg/dl (SD) Baseline: 188 (32) 12 months 167 (28) Change from baseline: -21 (-48 to -13)</p> <p>* Lipid profile NS difference between groups</p> <p>* Body weight / BMI NS difference between groups</p> <p>* Safety data not reported</p> <table border="0"> <tr> <td>Discontinuation</td> <td>n</td> <td>(%)</td> </tr> <tr> <td><u>repaglinide</u></td> <td></td> <td></td> </tr> <tr> <td>Did not complete study</td> <td>4</td> <td>(6%)</td> </tr> <tr> <td>-lack of efficacy</td> <td>3</td> <td>(4.5%)</td> </tr> <tr> <td>-lost of follow-up</td> <td>1</td> <td>(1.5%)</td> </tr> <tr> <td><u>glimepiride</u></td> <td></td> <td></td> </tr> <tr> <td>Did not complete week 20</td> <td>4</td> <td>(6%)</td> </tr> <tr> <td>-lack of efficacy</td> <td>2</td> <td>(3%)</td> </tr> <tr> <td>-adverse events</td> <td>2</td> <td>(3%)</td> </tr> </table>	Discontinuation	n	(%)	<u>repaglinide</u>			Did not complete study	4	(6%)	-lack of efficacy	3	(4.5%)	-lost of follow-up	1	(1.5%)	<u>glimepiride</u>			Did not complete week 20	4	(6%)	-lack of efficacy	2	(3%)	-adverse events	2	(3%)	
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<p>K. Esposito, D. Giugliano, F. Nappo, and R. Marfella.</p>	<p>RCT, single-blind, multi-centred</p>	<p>N=175, 14 clinics in Italy</p>	<p>Inclusion criteria: type 2 diabetes</p>	<p>N=88 repaglinide</p>	<p>N=87 glibenclamide</p>	<p>13-14 months</p>	<p>HbA1c, fasting glucose</p>	<p>*HbA1c HbA1c levels decreased with both repaglinide -0.9±0.5 (-1.1 to -0.7) and</p>	<p>Not stated</p>																											

Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 110 (2):214-219, 2004.	1+	Control group N=150	between ≥6 months and <10 yrs, aged 35-70, BMI ≥24, HbA1c ≥6.5%, treated with oral drugs or diet Exclusion criteria: insulin use, concomitant chronic disease, uncontrolled hypertension, recent acute illness, or change in diet or treatment within the last 3 months.	1.5, 3, 6 or 12 mgs TID, before meals	5, 10, 15 or 20 mgs BD, before meals	6-8 week titration period for optimization of drug dosage and 12 month treatment period on fixed optimal dosage	level, peak glucose level, lipids	<p>glibenclamide -0.8±0.5 (-1.1 to -0.5); there was no significant difference between the treatments.</p> <p>*Fasting glucose The fasting glucose levels decreased significantly for glibenclamide which decreased by -32±25 (-42 to -22), compared with -24±18mg/dL (-38 to -10) for repaglinide, p<0.001.</p> <p>*Post prandial glucose peak The glucose peak (maximal increase in blood glucose obtained at any point after a meal). This level decreased significantly for the repaglinide group, -70±58 (-98 to -42) compared with the glibenclamide group, -51±43 (-75 to -27), p <0.001. Similarly the area under the curve (AUC) for glucose from 0-2hr point decreased significantly for the repaglinide group, -3998±1035 (-5340 to -2450) compared with the glibenclamide group, -2090±670 (-3100 to 980), p=0.01</p> <p>*Lipids Changes in total cholesterol, HDL cholesterol and triglycerides were non-significant.</p> <p>*Adverse events 9% of the repaglinide group and 13% of the glibenclamide group had hypoglycaemic events</p> <table border="0" data-bbox="1538 1117 2033 1228"> <tr> <td>*Discontinuation</td> <td>n</td> <td>(%)</td> </tr> <tr> <td>Repaglinide</td> <td>7</td> <td>8%</td> </tr> <tr> <td>Glibenclamide</td> <td>7</td> <td>8%</td> </tr> </table>	*Discontinuation	n	(%)	Repaglinide	7	8%	Glibenclamide	7	8%	
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Forst T, Eriksson JW, Strotmann HJ, Bai S,	RCT - Open Label	N= 143 form 19	Inclusion criteria:	N= 75	N= 68	26 weeks	*HbA1c *Post	*HbA1c Mean HbA1c levels were not significantly	Eli Lilly									

⁶ Hypoglycaemia was defined for this study as a blood glucose value <3mmol/L (54mg/dl)

<p>Brunelle R, Gulliya KS, Gack S, and Gudat U. 2003. Metabolic effects of mealtime insulin lispro in comparison to glibenclamide in early type 2 diabetes. Experimental & Clinical Endocrinology & Diabetes: 111: 97 - 103 REF ID: 927.</p>	<p>Evidence level: 1+</p>	<p>study centres (Germany, Sweden, US)</p>	<p>Patients with T2D receiving oral anti-diabetic therapy, but not insulin, aged between 35 and 70 years, HbA1c <1.7 fold of the upper-normal limit of the local laboratory, and a C-peptide response ≥ 0.4 nmol/L after intravenous administration of 1.0mg glucagon were included.</p> <p>There was no significant difference between the groups with regard sex, age, BMI or duration of diabetes. The baseline mean HbA1c was $7.5\% \pm 1.0\%$ in the insulin lispro treatment group and $7.7\% \pm 1.2\%$ in the glibenclamide group</p>	<p>Insulin lispro bolus therapy</p> <p>LP was given as 4 to 8 units per injection, usually three times per day for up to 26 weeks.</p> <p>The mean daily insulin dosage was 18.6 units. The insulin dose was adjusted to correspond with each patient's metabolic needs.</p>	<p>Glibenclamide</p> <p>Glibenclamide was supplied as 3.5mg tablets (micronized formulation), and given 3.5 to 10.5 mg/day,</p> <p>The mean daily dosage was 5.6mg</p>		<p>Prandial Blood Glucose Excursions *Body weight *AE</p>	<p>different between the treatment groups at any time during the study.</p> <p>*Blood Glucose Excursions In the lispro treated group, the postprandial increase in blood glucose was significantly smaller compared with the glibenclamide treated group at any time during the day.</p> <p>the change in mean overall BG excursions from baseline to endpoint was $-1.0 \geq 1.5$ mmol/L in the insulin lispro treatment group and -0.3 ± 1.5 mmol/L in the glibenclamide group, (P = 0.013)</p> <p>*Body weight NS differences in body weight between the two groups were observed at any time during the study.</p> <p>*Adverse Events No significant difference (P=0.794) in adverse events was observed between the treatment groups.</p> <p>AE were reported for 26 (34.7%) patients in the insulin lispro treatment group and 25 (36.8%) patients in the oral treatment group.</p> <p>No significant differences were observed between the treatment groups regarding hypoglycaemic episodes⁶.</p> <p>At 24 weeks, 4 patients (6.5%) in the insulin lispro treatment group and 8 patients (13.8%) in the oral treatment group reported hypoglycaemic episodes (P=0.264).</p> <p>No drop-out figures reported</p>	
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<p>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</p>	<p>RCT randomized, multicentre, double-masked (USA) 1+</p>	<p>428 patients</p>	<p>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-naïve, 2) aged 18–77 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,</p>	<p>4-week maintenance period 120 mg a.c. nateglinide⁷</p> <p>+ 500 mg open-label metformin before the evening meal</p> <p>12-week titration period⁸</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</p>	<p>4-week maintenance period 1.25 mg glyburide before breakfast</p> <p>+ 500 mg open-label metformin before the evening meal</p> <p>12-week titration period</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</p>	<p>104 weeks (Eligibility was assessed during a 2-week screening period)</p>	<p>- HbA1c - FPG - Post-prandial Glucose Excursion (PPGE) - Lipid Profile - Body weight - Adverse events</p>	<p>*HbA1c no significant difference</p> <p>*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 (P 0.0078).</p> <p>*PPGE no significant difference</p> <p>*Lipid profile no significant difference</p> <p>*Body weight Body weight decreased slightly in patients randomized to the Nate/Met group (-0.4 ± 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</p>	<p>Novartis</p>
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⁷ 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)

⁸ Titration for both arms was performed at biweekly visits if FPG ≥ 6.7 mmol/l

⁹ 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 $\geq 9.0\%$, or the patient had symptomatic hyperglycemia.

¹⁰ Specific AEs leading to premature discontinuation that occurred in three or more patients are detailed.

			with baseline A1C averaging 8.35%.	study medication remained constant, unless protocol-specified criteria for rescue therapy were met. At the end of study Mean daily doses nateglinide: 357mg metformin: 1,459 mg Rescue/level 0 doses 17 (8.2%) were receiving the rescue dose, and 5 patients (2.4%) were receiving dose level 0.	medication remained constant, unless protocol-specified criteria for rescue therapy were met. At the end of study Mean daily doses glyburide: 5.1 mg metformin: 1,105 mg Rescue/level 0 doses five patients (2.5%) were on the rescue dose and eight patients (4.0%) were receiving dose level 0.			hypoglycemia was reported by 17.7% of patients receiving glyburide/metformin vs. 8.2% of those receiving nateglinide/metformin (P 0.003). Reasons for discontinuation Nateglinide/metformin n (%) Adverse Events (any AE) 27(12.3) • 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) Glyburide/metformin 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)	
Horton ES, Foley JE, Shen SG, and Baron MA. 2004. Efficacy and tolerability of initial	RCT ¹¹ Level of evidence: 1+	N= 401 ¹²	Inclusion criteria: Patients aged ≥ 30 years,	1) nateglinide 120 mg (taken 1 -30 min before each of	3) 120 mg nateglinide (taken 1–30 min	24 weeks	HbA1c FPG Post load glucose	*HbA1c baseline and endpoint HbA1c data were available in 376 TN patients.	Novartis

¹¹ this study examined data from the treatment-naïve (TN) subgroup of patients who participated in a placebo-controlled prospective study comparing the efficacy and safety of nateglinide, metformin and the combination of nateglinide and metformin in patients with T2D (Horton 2000). This report focuses on comparisons between placebo and initial CT.

¹² in the entire cohort, a nearly equal number of patients were randomized to each treatment; however, a somewhat smaller percentage of patients randomized to CT were TN (52%) than those randomized to nateglinide (58%), metformin (58%), or placebo (60%)

<p>combination therapy with nateglinide and metformin in treatment-naive patients with type 2 diabetes. Current Medical Research & Opinion: 20: 883 - 889 REF ID: 112.</p>			<p>had T2D diagnosed at least 3 months previously, and were treated with diet and exercise for at least 4 weeks before entering a 4-week, single-blind, placebo run-in period. BMI between 20 – 35 kg/m², HbA1c between 6.8% and 11.0% and FPG level of ≤ 15 mmol/L.</p> <p>In the four randomized subgroups, the mean age was 55 to 59 years. Males outnumbered females by nearly 2 to 1. The TN patients had a mean HbA1c of 8.2% and an average FPG of slightly over 10 mmol/L</p>	<p>three main meals) N=104</p> <p>2) metformin titrated according to the approved package labeling to 500 mg (immediately after the start each of three main meals) N=104</p>	<p>before each of three main meals) plus 500 mg metformin (immediately after the start each of three main meals N= 89</p> <p>4) placebo N=104</p>		<p>Body weight Adverse events</p>	<p>HbA1c increased modestly but significantly in placebo-treated patients ($\Delta = +0.3 \pm 0.1\%$) and decreased significantly and to a similar extent in patients receiving nateglinide ($\Delta = -0.8 \pm 0.1\%$) or metformin ($\Delta = -0.8 \pm 0.1\%$). An additive effect was seen with CT ($\Delta = -1.6 \pm 0.1\%$), representing an adjusted mean change of $-1.9 \pm 0.2\%$ relative to placebo.</p> <p>A responder analysis determined that 70% of patients receiving CT achieved an endpoint HbA1c of < 7.0%. In contrast, 34% and 41% of the TN patients receiving nateglinide and metformin monotherapy, respectively, achieved this goal, and 17% of placebo-treated patients had an HbA1c at endpoint of <7.0%.</p> <p>*FPG baseline and endpoint HbA1c data were available in 389 TN patients.</p> <p>FPG did not change in the placebo-treated patients; it decreased significantly in patients receiving nateglinide ($\Delta = -1.1 \pm 0.3$) or metformin monotherapy ($\Delta = -1.2 \pm 0.3$ mmol/L), representing approximately 11% and 12% decreases, respectively. The decrease in FPG in patients receiving initial CT ($\Delta = -2.3 \pm 0.3$ mmol/L) representing a decrease of approximately 22%</p> <p>*Post load glucose excursion baseline and endpoint measures of the 2-hour PLGE were available in 310 TN patients.</p> <p>PLGE decreased in all groups, but only modestly though significantly in placebo-treated patients ($\Delta = -0.5 \pm 0.2$ mmol/L) and to a somewhat greater extent in patients receiving metformin monotherapy ($\Delta = -1.0 \pm 0.2$ mmol/L). The PLGE decreased more substantially in patients given nateglinide</p>	
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								<p>monotherapy ($\Delta = -1.9 \pm 0.2$) and to a still greater extent in those receiving CT ($\Delta = -2.3 \pm 0.2$ mmol/L).</p> <p>*Body weight there was no significant change in body weight in patients randomized to CT ($\Delta = +0.2 \pm 0.4$kg) or placebo ($\Delta = -0.2 \pm 0.4$kg)</p> <p>*Adverse events No serious adverse events judged to be related to study medication</p> <p>GI The percentage of patients randomized to CT experiencing one or more gastrointestinal AE (27%) was essentially identical to that of those receiving metformin monotherapy (27.9%), and approximately twofold that of patients receiving placebo and nateglinide monotherapy (14.4% and 16.3%, respectively)</p> <p>Hypoglycaemia Occurred in ~29% of patients receiving CT, the incidence of confirmed hypoglycaemia occurred in TN randomized to CT was 3.4%, with all considered to be mild.</p>	
<p>Lu CH, Chang CC, Chuang LM, Wang CY, Jiang YD, and Wu HP. 2006 Double-blind, randomized, multicentre study of the efficacy and safety of gliclazide-modified release in the treatment of Chinese type 2 diabetic patients. Diabetes, Obesity & Metabolism: 8: 184 - 191</p>	<p>RCT Level of evidence: 1+</p>	<p>N=63 Chinese patients</p>	<p>Inclusion criteria: male or female outpatients aged from 30-75 years with BMI ranging from 21 to 35 kg/m² with T2D known for at least 3 months (treated with diet for ≥ 3 months, or with</p>	<p>Gliclazide MR 30mg¹⁴ N=32 12-week titration period 8-week maintenance period</p>	<p>Gliclazide 80mg N=31 12-week titration period 8-week maintenance period</p>	<p>20 weeks</p>	<p>HbA1c FPG Lipid profile Weight BMI Adverse events</p>	<p>*HbA1c (N=58) gliclazide MR and gliclazide significantly decreased the values of HbA1c at week 20/last visit by $1.6 \pm 1.6\%$ ($P < 0.001$) and $1.6 \pm 1.4\%$ ($P < 0.001$), respectively, and there is no difference between treatment groups ($P = 0.947$)</p> <p>*FPG (N=61) Gliclazide MR decreased FPG over the treatment period by -40.8 ± 56.3 mg/dl ($P < 0.001$) and gliclazide by -24.5 ± 67.0 ($P = 0.059$). No significant differences between groups.</p>	<p>Not reported</p>

REF ID: 813.			<p>diet and alpha-glucosidase inhibitors or with diet and biguanide for ≥ 3 months at constant dosage, or with diet and a low dose of sulfonylurea for ≥ 3 months at a constant dosage before selection), having HbA1c values $\geq 7\%$ obtained within 1 month before study entry.¹³</p> <p>One of the exclusion criteria was T2D patients treated with insulin in the previous 3 months before selection</p> <p>The two treatment groups were comparable for all baseline characteristics.</p>					<p>*Lipids the changes from baseline to last value under treatment observed on all mean lipid parameter were small and with no clinical significance.</p> <p>*Body weight At the end of the study the treatment period the mean changes of body weight were 1.4 ± 2.7 kg in the gliclazide MR group and 1.4 ± 2.7kg in the gliclazide group.</p> <p>*Adverse events (N=61)¹⁵ In the gliclazide MR group, the most common adverse effects reported by patients were abdominal pain (9%) and pharyngitis (9%), while in the gliclazide group the most common adverse effect was neuropathy (14%).</p> <p>Only two adverse events (one for increase of aminotransferase level in the gliclazide MR group and one for skin rash in the gliclazide group) were considered as related to the study treatment.</p> <p>Hypoglycaemia 3 patients (9.3%) experienced five mild hypoglycaemic episodes in the gliclazide MR treatment group. No suspected hypoglycaemic episode was observed in the gliclazide treatment group</p>	
Madsbad S, Kilhovd B, Lager I et al.	Multicentre RCT.	N= 256	Diet or oral hypoglycaemic	Repaglinide ¹⁶ N= 175	Glipizide N= 81	12 months (preceded	HbA1c FPG	*HbA1c there was a statistically significant difference	Novo Nordisk

¹³ Patients on alpha-glucosidase inhibitor or acarbose continued their treatment without changing the dose all over the study duration. Patients on low dose of sulfonylurea were asked to stop their treatment during the study
¹⁴ from week 0 to week 12 the patient entered in a 12-week titration period. Patient started with the lowest dose (i.e. gliclazide 80mg or gliclazide MR 30mg) and the dosage was gradually increased at every 4-week visit to achieve an optimal glycaemic control (FPG ≤ 7.7 mmol/l or the maximum dose reached). During the maintenance period the dosage was maintained unchanged.

¹⁵ A total of 63 patients were evaluated for safety. 2 patients who were given study medication were lost to follow-up at week 0. As a consequence, all description of frequency on safety set was made on 61 patients

<p>Comparison between repaglinide and glipizide in Type 2 diabetes mellitus: a 1-year multicentre study. <i>Diabetic Medicine</i>. 2001; 18(5):395-401 REF ID: 71</p>	<p>Level of evidence: 1+</p>		<p>agents-treated T2D patients, aged 40-75 years with a BMI ≥ 21 and ≤ 35 kg/m² and HbA1c ≥ 6.5 and $\leq 10\%$</p> <p>The two groups were comparable for all baseline characteristics</p> <p>HbA1c: 7.3% in the repaglinide group and 7.2% in the glipizide group. BMI 28 kg/m² in both groups.</p>			<p>by a 6-week titration period)</p>	<p>Lipid profile Body weight Adverse events</p>	<p>between HbA1c changes from baseline in the two treatment groups in favour of repaglinide (0.19% vs 0.78%, Difference - 0.59%; P<0.05)</p> <p>Sub-group analysis HbA1c decreased in the OHA-naïve patients by 1.5% and 0.3% in the repaglinide and glipizide groups, respectively. (P<0.05)</p> <p>*FPG there was a statistically significant difference between FPG changes in the two treatment groups in favour of repaglinide (0.5 mmol/l vs 1.3 mmol/l. Difference -0.9 mmol/l; P<0.05)</p> <p>Sub-group analysis in the OHA-naïve patients, FPG decreased by 2.4 mmol/l in the repaglinide group and increased by 1.0 mmol/l in the glipizide group (P<0.05)</p> <p>*Lipid profile NS changes from baseline. NS difference between groups</p> <p>*Body weight body weight decreased by 0.7kg and 0.9kg in the repaglinide and glipizide groups, respectively, with no significant difference between groups.</p> <p>*Adverse Events Hypoglycaemia The number of patients experiencing minor hypoglycaemic events was similar in the repaglinide and glipizide groups (15% vs. 19% respectively)</p>	
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¹⁶ there were four dose levels in both groups. Dose level 1 was either repaglinide, 0.5mg with meals or glipizide, 5mg before breakfast; dose level 2 was either repaglinide, 1.0 mg with meals, or glipizide, 7.5 mg before breakfast; dose level 3 was either repaglinide, 2.0 mg with meals, or glipizide, 10mg before breakfast; and dose level 4 was either repaglinide. 4.0 mg with meals. or glipizide, 10 mg before breakfast plus 5mg before dinner. Oral-treated patients with FBG > 9.0 mmol/l on their previous treatment started at dose level 2. Otherwise all patients started at dose level 1. Slightly more than 50% of the patients in both groups received the highest dose level at the start of the maintenance period.

								<p>A total of 20 patients in the repaglinide group and 9 in the glipizide group reported adverse events other than hypoglycaemia. The most common were nausea and fatigue.</p> <table> <thead> <tr> <th>Discontinuation</th> <th>n</th> <th>(%)</th> </tr> </thead> <tbody> <tr> <td colspan="3"><u>Repaglinide</u></td> </tr> <tr> <td>Withdrawn</td> <td>35</td> <td>(20)</td> </tr> <tr> <td>- Adverse events</td> <td>25</td> <td>(14.2)</td> </tr> <tr> <td>- Lack of efficacy</td> <td>3</td> <td>(1.7)</td> </tr> <tr> <td>- Lost to follow-up</td> <td>0</td> <td></td> </tr> <tr> <td colspan="3"><u>Glipizide</u></td> </tr> <tr> <td>Withdrawn</td> <td>23</td> <td>(28.3)</td> </tr> <tr> <td>- Adverse events</td> <td>16</td> <td>(19.7)</td> </tr> <tr> <td>- Lack of efficacy</td> <td>3</td> <td>(2.4)</td> </tr> <tr> <td>- Lost to follow-up</td> <td>0</td> <td></td> </tr> </tbody> </table>	Discontinuation	n	(%)	<u>Repaglinide</u>			Withdrawn	35	(20)	- Adverse events	25	(14.2)	- Lack of efficacy	3	(1.7)	- Lost to follow-up	0		<u>Glipizide</u>			Withdrawn	23	(28.3)	- Adverse events	16	(19.7)	- Lack of efficacy	3	(2.4)	- Lost to follow-up	0		
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<p>Moses RG, Gomis R, Frandsen KB, Schlienger JL, Dedov I. Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. Diabetes Care 2001; 24(1): 11-15. Ref ID: 306</p>	<p>Double blind multicentre RCT (61 centres in 13 countries) 1+</p>	<p>N=408</p>	<p>Type 2 diabetes patients at least 40 years of age treated with diet alone but with suboptimal control. Those who had previously received oral antidiabetic agents were excluded. Patients whose HbA1c deteriorated by more than or equal to 1% during the study were withdrawn. In the repaglinide group mean age was 57.5 years and 47%</p>	<p>N=270 (ITT population N=260) Repaglinide One tablet was taken immediately before each main meal in accordance with the dietary pattern of the individual (two to four times daily). If a meal was skipped or postponed the trial medication for than meal was also skipped or postponed and if a meal was added trial medication was also</p>	<p>N=138 (ITT population N=134) Placebo Administration as for repaglinide</p>	<p>16 weeks</p>	<p>HbA1c FBG Adverse events including hypoglycaemic events and weight gain</p>	<p>*HbA1c HbA1c levels decreased from baseline by a mean of 1.14% in the repaglinide group (p<0.001) while in the placebo group a nonsignificant decline of 0.15% was recorded. At the end of the study mean HbA1c levels were 0.99% lower in the repaglinide group than in the placebo group (p<0.001). Improvement in HbA1c was independent of the recorded meal pattern.</p> <p>*FPG FPG levels decreased significantly in the repaglinide group during the study with a mean reduction of 1.80mmol/l (p<0.001). There was a mean 1.44mmol/l greater reduction in the repaglinide group compared with the placebo group (p<0.001).</p> <p>*Body weight There was no significant difference between groups in body weight change during the 12-week maintenance period.</p> <p>*Adverse events 17% of patients in the repaglinide group and 3% in the placebo group reported minor</p>	<p>Novo Nordisk</p>																																	

			were female. Mean BMI was 30kg/m ² with mean weight 84kg. Mean HbA1c was 7.8% and FBG was 9.9mmol/l. In the placebo group mean age was 57 years and 42.5% were female. Mean BMI was 30.9 kg/m ² with mean weight 86.6kg. Mean HbA1c was 7.6% and FBG was 9.6mmol/l.	added. Patients initially received a prandial dose of 0.5mg with the dose being doubled after 4 weeks if FPG exceeded 7.8mmol/l. Patients remained on this dose for a further 12 weeks.				episodes of hypoglycaemia. 3 repaglinide patients reported a total of 4 major hypoglycaemic events. Other adverse events were infrequent and similar in frequency between treatment groups. The overall tolerability of repaglinide was similar to placebo excluding hypoglycaemic events: 29% of patients in the repaglinide group and 30% in the placebo group reported and adverse event.	
Raskin P, Klaff L, McGill J, South SA, Hollander P, Khutoryansky N, Hale PM, and Repaglinide vs.Nateglinide Metformin Combination Study Group.2003 Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin.[see comment][erratum appears in Diabetes Care. 2003	Open-label, parallel-group, randomized, multicentre trial 1+ **	N= 192 patients from 6 US-research centres. 168 patients completed the study. Missing values of HbA1c and FPG (In the	Inclusion criteria: adults (≥18 years old) who had type 2 diabetes for at least 3 months and BMI values of 24–42 kg/m ² . Subjects were stratified by baseline HbA1c value (<9% or ≥9%). Enrolled	N=96 2-week titration period 17 The dosage of repaglinide was increased stepwise from 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)	N=96 2-week titration period Starting nateglinide dose was 120 mg per meal (the maximum daily dose), which could be reduced to 60 mg/meal in response to hypoglycemia episodes.	16 weeks (4-week run-in period) 20	HbA1c FPG Glucose area under the time-concentration curve from 0 to 240min (AUC0-240min). Adverse Effects	*HbA1c Final HbA1c values were lower for repaglinide/metformin combination therapy than nateglinide/metformin treatment, but there was no a significant difference between the two treatments Mean end-of-study changes in HbA1c values from baseline were significantly greater for the repaglinide/metformin combination regimen than for nateglinide/metformin (–1.28 vs. –0.67%; P = 0.001). *FPG Mean end-of-study reductions of FPG values from baseline were significantly	Novo Nordisk Pharmaceuticals

¹⁷ Targets for glycaemic 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>Sep;26(9):2708]. Diabetes Care: 26: 2063 - 2068 REF ID: 350.</p>		<p>event of patient withdrawal or missing data after baseline) were substituted by imputed data (calculated by the incremental mean imputation [IMI] method)</p>	<p>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 In the Nate/Met group the mean age was 55.0± 10.6; 60% of patients were male; mean BMI was 33.4±5.7. HbA1c 8.2±1.3</p>	<p>(maximum dose, 16 mg/day). + 1,000 mg metformin b.i.d. 14-week maintenance period 18 Repaglinide + 1,000 mg metformin b.i.d. At the end of study 19 median final dose of repaglinide:5.0 mg/day</p>	<p>+ 1,000 mg metformin b.i.d. 14-week maintenance period Nateglinide + 1,000 mg metformin b.i.d. At the end of study median final dose of nateglinide: 360 mg/day</p>		<p>greater for the repaglinide/metformin group (-39 vs. -21 mg/dl for nateglinide/metformin; P =0.002)</p> <p>* Glucose AUC 0-240min. No significant differences</p> <p>*Adverse events No statistical comparisons were reported</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>Repa/Met</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> <p>Nate/Met</p> <table border="0"> <tr> <td></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> <tr> <td>• Adverse event</td> <td>1 (1)</td> </tr> <tr> <td>• Lack of efficacy</td> <td>7(7)</td> </tr> <tr> <td>• Noncompliance</td> <td>2 (2)</td> </tr> <tr> <td>• Other</td> <td>7(7)</td> </tr> </table>	Repa/Met	n (%)	Did not complete week 16	7 (7)	Reasons for discontinuation		• Adverse event	0	• Lack of efficacy	0	• Noncompliance	2 (2)	• Other	5 (5)		n (%)	Did not complete week 16	17 (18)	Reasons for discontinuation		• Adverse event	1 (1)	• Lack of efficacy	7(7)	• Noncompliance	2 (2)	• Other	7(7)	
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<p>Ristic S, Collober-Maugeais C, Pecher E, Cressier F. Comparison of Nateglinide and Gliclazide in combination with Metformin, for treatment of patients with Type 2 diabetes mellitus inadequately controlled on maximum doses of Metformin alone. Diabetes medicine 2006; 23: 757-762</p> <p>Ref ID: 4902</p>	<p>RCT 1+</p> <p>Double blind, double dummy</p>	<p>Multi centre study</p> <p>N=262</p> <p>N= 133 Nateglinide + metformin</p> <p>N= 129 Gliclazide + metformin</p> <p>Loss to follow up 12.6%</p>	<p>Inclusion criteria: Type 2 diabetics for ≥ 6 months, on metformin therapy for ≥ 3 months with poor control, on a minimum metformin dose of 1000 mg/day for 2 months, baseline HbA1c of 6.8-9.0%, BMI 20-35 kg/m².</p> <p>Exclusion criteria: nil mentioned</p> <p>There were no significant differences between the groups at baseline.</p>	<p>Metformin and Nateglinide 60 mg tid titrated up to maximum of 180 mg before meals</p> <p>Titration: dose increased of fasting plasma glucose > 7 mmol/l, no confirmed hypoglycaemic events, and if the patient had not experienced more than three hypoglycaemic events in the past month.</p> <p>Glucose and insulin concentrations measured after a test meal.</p>	<p>Metformin and Gliclazide 80 mg daily titrated up to maximum of 240 mg daily</p> <p>Titration: dose increased of fasting plasma glucose > 7 mmol/l, no confirmed hypoglycaemic events, and if the patient had not experienced more than three hypoglycaemic events in the past month.</p> <p>Glucose and insulin concentrations measured after a test meal.</p>	<p>24 weeks</p>	<p>HbA1c</p> <p>Fasting plasma glucose (FPG)</p> <p>Percentage of patients reaching a treatment target (HbA1c < 7% &/ decrease $\geq 0.5\%$ HbA1c)</p> <p>Body weight</p>	<p><u>Glycaemic control</u></p> <p>Similar HbA1c and FPG reduction in nateglinide group and gliclazide group.</p> <table border="1" data-bbox="1547 256 2022 483"> <thead> <tr> <th></th> <th>Nateglinide + metformin</th> <th>Gliclazide + metformin</th> </tr> </thead> <tbody> <tr> <td>change in HbA1c (%)[*]</td> <td>-0.41 \pm 0.08</td> <td>-0.57 \pm 0.08</td> </tr> <tr> <td>change in FPG (mmol/l)[†]</td> <td>-0.63 \pm 0.17</td> <td>-0.82 \pm 0.18</td> </tr> </tbody> </table> <p>*p-value for treatment difference 0.099 † p-value for treatment difference 0.375</p> <p>Following the test meal: change from baseline measures of:</p> <table border="1" data-bbox="1547 651 2022 1270"> <thead> <tr> <th></th> <th>Nateglinide + metformin</th> <th>Gliclazide + metformin</th> </tr> </thead> <tbody> <tr> <td>Max postprandial plasma glucose excursion (mmol/l)</td> <td>-0.71 \pm 0.22 p = 0.037</td> <td>-0.10 \pm 0.23</td> </tr> <tr> <td>30-min postprandial insulin (pmol/l)</td> <td>98.9 \pm 12.1 p < 0.001</td> <td>32.5 \pm 12.56</td> </tr> <tr> <td>2-h postprandial insulin (pmol/l)</td> <td>83.9 \pm 16.6 P = 0.047</td> <td>39.6 \pm 17.8</td> </tr> <tr> <td>2-h postprandial insulin excursion (pmol/l)</td> <td>75.5 \pm 16.0 P = 0.033</td> <td>30.2 \pm 16.6</td> </tr> </tbody> </table> <p><u>Proportion of patients reaching a target HbA1c</u></p> <p>No significant difference between groups</p>		Nateglinide + metformin	Gliclazide + metformin	change in HbA1c (%) [*]	-0.41 \pm 0.08	-0.57 \pm 0.08	change in FPG (mmol/l) [†]	-0.63 \pm 0.17	-0.82 \pm 0.18		Nateglinide + metformin	Gliclazide + metformin	Max postprandial plasma glucose excursion (mmol/l)	-0.71 \pm 0.22 p = 0.037	-0.10 \pm 0.23	30-min postprandial insulin (pmol/l)	98.9 \pm 12.1 p < 0.001	32.5 \pm 12.56	2-h postprandial insulin (pmol/l)	83.9 \pm 16.6 P = 0.047	39.6 \pm 17.8	2-h postprandial insulin excursion (pmol/l)	75.5 \pm 16.0 P = 0.033	30.2 \pm 16.6	<p>Novartis Pharma, Basel.</p> <p>Authors are employees of the company.</p>
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<p>Rosenstock J, Hassman DR, Madder RD, Brazinsky SA, Farrell J, Khutoryansky N et al. Repaglinide versus nateglinide monotherapy: a randomized, multicentre study. Diabetes Care 2004; 27(6): 1265-1270. Ref ID: 3151</p>	<p>Multicentre, open label RCT 1+</p>	<p>N=150</p>	<p>Adult type 2 diabetes patients who had received only diet and exercise therapy in the previous 3 months with BMI values 24 to 42kg/m². In the repaglinide group mean age was 50.9 years, there were 41 men and 35 women with a mean BMI 33kg/m² and mean 3.5 years since diagnosis. In the nateglinide group mean age 54, 42 men/32 women, BMI 32.9 and 4.3 years since diagnosis. Baseline HbA1c was</p>	<p>N=76 Mealtime repaglinide monotherapy In both groups there was an initial 3-week dose titration with target glycaemic control during the 3 weeks of 80 to 140mg/dl by SMBG for preprandial values. Dose adjustment possible in the following 13 weeks. Patients initiated repaglinide treatment at doses of 0.5mg before each meal and doses were increased stepwise from 0.5 to 1.0, to 2.0 and to 4.0mg at</p>	<p>N=74 Mealtime nateglinide monotherapy</p> <p>Patients initiated treatment at doses of 60mg/meal and increased to 120mg/meal after 1 week if target glycaemic control was not achieved. This allowed for a maximum dose of 360mg/day corresponding to 3 meals at the maximum dose.</p>	<p>16 weeks</p>	<p>HbA1c FBG PPBG Adverse events including hypoglycaemic events and weight gain</p>	<p>*HbA1c Final HbA1c values were lower for repaglinide monotherapy than nateglinide monotherapy (7.3 vs 7.0%). Mean final reductions of HbA1c were significantly greater for repaglinide monotherapy than nateglinide monotherapy (-1.57 vs -1.04%; p=0.002).</p> <p>*FBG Mean changes in FBG demonstrated significantly greater efficacy for repaglinide than nateglinide (-57 vs -18 mg/dl; p<0.001)</p> <p>Median final doses were 6.0mg/day for repaglinide and 360mg/day for nateglinide.</p> <p>*Postprandial plasma glucose curve (ΔAUC_{E0-240 min}) were not significantly different for repaglinide and nateglinide.</p> <p>*Body weight Mean weight gains from baseline to study end were +1.8kg for repaglinide and +0.7kg for nateglinide, p=0.04).</p> <p>*Adverse events The most common adverse events (3-10% of patients in both groups) were upper respiratory tract infection, sinusitis, constipation, arthralgia, headache and</p>	<p>Novo Nordisk</p>

			8.9% in both groups.	weekly visits based on the results of SMBG (maximum dose 16mg/day).				vomiting but there were no notable differences in the pattern between the two groups. Hypoglycaemia There were 7% of repaglinide patients who had minor hypoglycaemic episodes and 0% for nateglinide (this is 0.016 events per patient per months for repaglinide vs 0 for nateglinide p=0.3, NS).	
Saloranta C, Hershon K, Ball M, Dickinson S, Holmes D. Efficacy and safety of nateglinide in type 2 diabetic patients with modest fasting hyperglycemia. J Clin Endocrinol Metab 2002; 87(9):4171-4176. Ref ID: 2	Double blind multicentre RCT (103 study centres in 12 countries) 1+	N=675	Type 2 diabetes patients at least 30 years of age maintained on diet alone. Patients who had received oral antidiabetic treatment during the previous 3 months or intense insulin treatment within 6 months were excluded. Patients had to have mean FPG of 7-8.3mmol/l (not <6.1 or >10mmol/l). Patients were 63% male, 96% white, 64% were under 65 years. Mean BMI was 29kg/m ² . Mean HbA1c	N=166 Nateglinide 30mg N=175 Nateglinide 60mg N=171 Nateglinide 120mg All taken up to 30 minutes before breakfast, lunch and dinner (preceded by a 4 week single blind run-in period).	N=163 Placebo (administered as for intervention)	24 weeks	HbA1c FBG Adverse events including hypoglycaemic events and weight gain	HbA1c *In placebo treated patients, glycaemic control deteriorated modestly over the 24 weeks (change in HbA1c =+0.16 ± 0.05%), whereas nateglinide produced a dose-related reduction of HbA1c. The least square mean changes of HbA1c from baseline relative to placebo (-0.26 ± 0.05, -0.31 ± 0.04, -0.39 ± 0.05 for 30mg, 60mg and 120mg respectively) were significant (p<0.001). *FPG Nateglinide treatment produced a modest but statistically significant and dose-related reduction of FPG relative to placebo (p<0.001 vs placebo for all dose strengths). *Body weight Body weight increased in each treatment group, ranging from +0.31kg in the placebo treated cohort to +0.65kg in the patients that received 30mg nateglinide although there were no significant differences between the four groups. *Adverse events Withdrawals due to adverse events were 4.3% in the placebo group, 5.4% in the nateglinide 30mg group, 3.4% for the 60mg group and 7.6% for the 120mg group. Hypoglycaemia There was a dose related increase in symptomatic hypoglycaemia but the	Novartis

			characteristics.					<p><u>Gliclazide MR</u></p> <p>Did not complete week 27 35 (8.6)</p> <p>Adverse events</p> <p>-other than hypoglycaemia 12 (3.0)</p> <p>-hypoglycaemia 1 (0.2)</p> <p>Lack of efficacy 1 (0.2)</p> <p>Nonmedical reason 16 (3.9)</p> <p>Protocol deviation 5 (1.2)</p> <p><u>Glimepiride</u></p> <p>Did not complete week 27 32 (8.3)</p> <p>Adverse events</p> <p>-other than hypoglycaemia 11 (2.5)</p> <p>-hypoglycaemia 9 (2.0)</p> <p>Lack of efficacy 1 (0.2)</p> <p>Nonmedical reason 9 (2.0)</p> <p>Protocol deviation 2 (0.4)</p>																			
<p>Wright AD, Cull CA, Macleod KM, Holman RR. Hypoglycaemia in type 2 diabetic patients randomised to and maintained on monotherapy with diet, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. Journal of Diabetes and its Complications 2006; 20: 395-401</p> <p>Ref ID: 4884</p>	Cohort study 2+	<p>N=5063</p> <p>Completion rates for patients remaining on allocated treatment for 6 years:</p> <p>Diet 756/949 (79%)</p> <p>Sulphonylurea 1418/1687 (84%)</p> <p>Metformin 290/336 (86%)</p>	<p>Inclusion criteria:</p> <p>For the UKPDS; 25-65 years, FPG>6.0 mmol/l on 2 occasions after being diagnosed diabetic.</p> <p>Exclusion criteria:</p> <p>ketonuria >3.0 mmol/l, serum creatinine >175 µmol/l, or severe previous illness that would limit life</p>	Conventional glucose control primarily with diet alone	Intensive glucose control primarily with sulphonylurea, metformin (overweight subjects only) or insulin therapy.	6 years	Incidence of hypoglycaemia ²³	<p>Annual percentage (95% CI) of patients reporting at least one hypoglycaemic episode in relation to therapy</p> <table border="1"> <thead> <tr> <th>Therapy</th> <th>Grades 1-4 hypoglycaemia</th> <th>Grades 2-4 hypoglycaemia</th> </tr> </thead> <tbody> <tr> <td>Diet alone</td> <td>0.8 (0.6 to 1.0)</td> <td>0.1 (0.1 to 0.2)</td> </tr> <tr> <td>Sulphonylurea</td> <td>7.9 (5.1 to 11.9)</td> <td>1.2 (0.4 to 3.4)</td> </tr> <tr> <td>Metformin</td> <td>1.7 (1.0 to 3.0)</td> <td>0.3 (0.1 to 1.1)</td> </tr> <tr> <td>Basal insulin alone</td> <td>21.2 (14.6 to 29.8)</td> <td>3.8 (1.2 to 11.1)</td> </tr> <tr> <td>Basal + prandial insulin</td> <td>32.6 (21.8 to 45.6)</td> <td>5.5 (2.0 to 14.0)</td> </tr> </tbody> </table> <p>The proportion of patients reporting grades 1-4 hypoglycaemia decreased with increasing HbA1c for those treated with diet, sulphonylurea, or metformin but appeared to</p>	Therapy	Grades 1-4 hypoglycaemia	Grades 2-4 hypoglycaemia	Diet alone	0.8 (0.6 to 1.0)	0.1 (0.1 to 0.2)	Sulphonylurea	7.9 (5.1 to 11.9)	1.2 (0.4 to 3.4)	Metformin	1.7 (1.0 to 3.0)	0.3 (0.1 to 1.1)	Basal insulin alone	21.2 (14.6 to 29.8)	3.8 (1.2 to 11.1)	Basal + prandial insulin	32.6 (21.8 to 45.6)	5.5 (2.0 to 14.0)	<p>UK MRC, British Diabetic Association, NIH, British Heart Foundation, Novo-Nordisk, Bayer, Bristol Myers Squibb, Hoechst, Lilly, Lipha, Farmitalia Carlo</p>
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²³ Hypoglycaemia was defined on the following scale: 1) transitory symptoms not affecting normal activity, 2) temporarily incapacitated but patient able to control symptoms without help, 3) incapacitated and required assistance to control symptoms without help, 4) required medical attention or glucagon injection. This was further divided into any hypoglycaemia (grades 1-4), substantive hypoglycaemia (grades 2-4), and major hypoglycaemia (grades 3-4).

		Insulin alone 1036+38/1 219 (88%)	or require extensive systemic treatment. Baseline characteristics: 59% male 83% white Caucasian Median HbA1c 6.9%					increase with increasing HbA1c in insulin treated patients (this relationship persisted after adjustment for concurrent daily insulin dose). The study also reported hypoglycaemic episodes in relation to demographic characteristics. These data were not relevant to this question and are not detailed here.	Erba.
Alvarsson et al 2003 Beneficial Effects of Insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients Ref ID 168	Multicentre RCT (6 centres in Sweden) 1-	N=51 randomised N=39 included in the analysis (76%)	Type 2 diabetes patients (diagnosed < 2 years) aged 35 to 70 years with BMI <35kg/m ² . FBG between 7 to 12 mmol/l when on diet alone for at least one month. Patients were excluded if pharmacologically treated for more than 6 months or showing low fasting plasma C-peptide concentrations (<2 nmol/l). The patients were middle-aged, moderately overweight (mean BMI 27) and in a fairly	N=21 Glibenclamide Initially at a dose of 1.75mg once daily and then adjusted by steps of 1.75 to 3.5mg with the aim of keeping HbA1c levels within target level (less than or equal to 1% above the upper normal level of HbA1c.	N=18 Insulin Given twice daily as premixed insulin (i.e. a combination of 30% soluble and 70% NPH insulin). The starting dose of insulin was 0.25 units kg ⁻¹ 24h ⁻¹ . Two thirds of the daily dose before breakfast and one third before supper. Doses were adjusted as follows: 1) increase of total dose by 10% if mean 24h capillary blood glucose was >12mmol/l, 2) decrease of total dose by	2 years	Glibenclamide and insulin dose Body weight Lipids HbA1c Side effects Glucagon tests: C peptide and IAPP (not reported here).	*HbA1c HbA1c decreased in both groups during the first year of treatment (p<0.01). At the end of the second year, HbA1c had increased in the glibenclamide group (p<0.01) but was still significantly lowered compared with baseline (p<0.005) in the insulin treated patients. The difference in the evolution of HbA1c between groups was significant (p=0.02). After 1 year, the glibenclamide group received 2.4 ± 0.4 mg/day of glibenclamide and the insulin group 20.6 ± 2.0 IU/day. After 2 years the dose of glibenclamide had increased significantly (p=0.03) whilst the insulin dose was essentially unchanged. *Body weight Body weight increased in both groups although this did not differ significantly between the groups *Lipid levels HDL cholesterol levels increased significantly during the study in the glibenclamide group (p=0.03) whilst levels were unchanged in the insulin treated patients. *Adverse events There were no obvious side effects of each	Novo Nordisk

			good metabolic control as assessed by HbA1c (mean 6.9% in the glibenclamide group and 7,3% in the insulin group.		10% if mean capillary blood glucose was <6mmol/l or 3) decrease of individual dose by 10% if blood glucose was <4.0mmol/l at a time point 2h or later after the last dose.			treatment and no severe hypoglycaemic episodes.													
Inukai K, Watanabe M, Nakashima Y, Sawa T, Takata N, Tanaka M, Kashiwabara H, Yokota K, Suzuki M, Kurihara S, Awata T, and Katayama S. 2005. Efficacy of glimepiride in Japanese type 2 diabetic subjects. Diabetes Research & Clinical Practice: 68: 250 - 257 REF ID: 849.	RCT Open label Level of evidence: 1-	N=172 Japanese patients	Inclusion criteria: Not clearly stated. Patients in whom glycemic control had been inadequate (HbA1c ≥7.0%) with a conventional SU (either gliclazide or glibenclamide), All had been on one of these SU for at least 6 months.	3 rd SU group Glimepiride N=120	2 nd SU group Gliclazide or Glibenclamide N=52	6 months	HbA1c FPG Lipid profile	*HbA1c NS change from baseline values. Not statistical difference reported between groups *FPG NS change from baseline values. Not statistical difference reported between groups *Lipid profile NS change from baseline values. Not statistical difference reported between groups *Body weight NS change from baseline values. Not statistical difference reported between groups. No safety data reported	Not reported												
Jibran R, Suliman MI, Qureshi F, Ahmed M. Safety and efficacy of repaglinide compared with Glibenclamide in the management of type 2 diabetic Pakistani patients. Pak J Med Sci. 2006; 22(4): 385-390	RCT 1-	N=100 N=50 in each arm	Inclusion criteria: Newly diagnosed type 2 diabetics uncontrolled on diet and exercise Exclusion criteria: type 1 diabetics, type	Repaglinide Starting dose 0.5 mg tid taken from 30 min to immediately before a meal Titrated to up to 2mg tid	Glibenclamide 5mg/day starting dose Titrated up to 15mg/day Individualised weight maintaining	1 year	Fasting blood glucose 2-hour post prandial blood glucose Weight (kg)	Outcomes: <table border="1"> <thead> <tr> <th></th> <th>Repaglinide</th> <th>Glibenclamide</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>Fasting Blood sugar (mg/dl)</td> <td>64 ± 53</td> <td>34.7 ± 53</td> <td>0.007</td> </tr> <tr> <td>2hr post prandial</td> <td>119 ± 66</td> <td>87.6 ± 74</td> <td>0.02</td> </tr> </tbody> </table>		Repaglinide	Glibenclamide	p-value	Fasting Blood sugar (mg/dl)	64 ± 53	34.7 ± 53	0.007	2hr post prandial	119 ± 66	87.6 ± 74	0.02	Not reported
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2hr post prandial	119 ± 66	87.6 ± 74	0.02																		

Ref ID: 160			<p>2 diabetics on insulin or on maximum or near maximum doses of sulphonylureas, or on any other drugs not included in this study. Also any patients with significant gastrointestinal, cardiovascular or renal disease or any serious concurrent medical illness.</p> <p>Baseline characteristics:</p> <table border="1" data-bbox="663 810 938 1153"> <tr> <td></td> <td>Glibenclamide</td> <td>Repaglinide</td> </tr> <tr> <td>N</td> <td>50</td> <td>50</td> </tr> <tr> <td>Age</td> <td>45.8 ± 8.8</td> <td>46.6 ± 10.5</td> </tr> <tr> <td>Sex F %</td> <td>80</td> <td>68</td> </tr> <tr> <td>Weight</td> <td>65.8 ± 9.4</td> <td>72.7 ± 17</td> </tr> <tr> <td>BMI</td> <td>30.4 ± 5.6</td> <td>27.1 ± 3.5</td> </tr> </table>		Glibenclamide	Repaglinide	N	50	50	Age	45.8 ± 8.8	46.6 ± 10.5	Sex F %	80	68	Weight	65.8 ± 9.4	72.7 ± 17	BMI	30.4 ± 5.6	27.1 ± 3.5	<p>based on blood glucose levels</p> <p>Individualised weight maintaining diet</p>	diet		HbA1c	<table border="1" data-bbox="1547 145 2022 371"> <tr> <td>blood sugar (mg/dl)</td> <td></td> <td></td> <td></td> </tr> <tr> <td>HbA1c (%)</td> <td>1.1 ± 0.3</td> <td>0.7 ± 0.5</td> <td>0.00</td> </tr> <tr> <td>Weight (kg)</td> <td>0.4 ± 3.2</td> <td>Not given</td> <td>Not significant</td> </tr> </table>	blood sugar (mg/dl)				HbA1c (%)	1.1 ± 0.3	0.7 ± 0.5	0.00	Weight (kg)	0.4 ± 3.2	Not given	Not significant	
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Tong et al 2002. The contribution of metformin to glycaemic control in patients with type 2 diabetes mellitus receiving combination therapy with insulin	Single centre RCT performed in China 1-	N=64 randomised N=51 included in the analysis	All patients with type 2 diabetes for more than 2 years, more than 20 years old, with secondary oral	N=24 Combination therapy of sulphonylurea and human isophane insulin. In both groups	N=27 Combination therapy of sulphonylurea, human isophane insulin and metformin.	36 weeks (plus 5 weeks when metformin was withdrawn from the	HbA1c FPG BMI Insulin dose Hypoglycaemia	*HbA1c Those who received metformin in the combination therapy from week 0 to 36 had a significantly lower HbA1c value following stabilisation at week 36 (metformin group: 8.13 ± 0.89% vs no metformin group: 9.05 ± 1.3% p=0.003). However, withdrawal of metformin caused a significant increase in	Novo Nordisk																														

Ref ID 244			hypoglycaemic agent failure. Mean BMI was 24kg/m ² , mean fasting glucose was 8mmol/l and mean HbA1c was 8.7%. The metformin group were significantly older, had longer duration of diabetes and longer duration of OHA therapy.	maximal doses of sulphonylurea were glibenclamide 20mg, glipizide 20mg and gliclazide 320mg. Human isophane insulin was initiated at an arbitrary dose of 6 units given 30 mins before retiring. The dose of insulin was adjusted by 2-4 U/week as determined by the fasting capillary blood glucose (target was less than or equal to 7.8 mmol/l on 2 consecutive occasions for either group).	Metformin was given at 1g twice daily. At the conclusion of the 36-week study metformin was withdrawn and the group assessed for a further 5 weeks.	metformin group).	<p>the HbA1c level to $9.69 \pm 1.29\%$ by the end of the study phase.</p> <p>*FPG At the end of the 5 weeks phase in which metformin was withdrawn, the plasma fasting glucose of the metformin group showed an increase compared with the metformin not given group. The change of FPG from baseline was different (metformin group: 3.56 ± 3.26 mmol/l vs metformin not given -0.51 ± 1.75 mmol/l, $p=0.0001$).</p> <p>The mean insulin dosage at week 36 in the metformin group was significantly less than the average dose of insulin used by patients not given metformin (metformin group: 13.7 ± 6.8 U/day, metformin not given: 23.0 ± 9.4 U/day, $p=0.001$).</p> <p>*BMI There was a slight increase in BMI in both groups at 36 weeks but there were no significant changes in either group.</p> <p>*Lipid profile Triglycerides, HDL and LDL cholesterol did not change significantly from baseline in either group.</p>	
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