

Evidence Tables

INS 5: Are long acting insulin analogues (insulin glargine (Lantus)) effective in the control of blood glucose compared to NPH insulin, biphasic insulins or multiple daily injections?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
<p>Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzner TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. <i>Cochrane Database of Systematic Reviews</i> 2007, Issue 2</p> <p>Ref ID: 4955</p>	<p>Systematic review and meta analysis 1++</p> <p>All included studies were RCT's, parallel trials, none were blinded.</p>	<p>N=9 studies</p> <p>Insulin glargine vs. NPH N=7 (Eliaschewitz 2006, Fritsche 2003, Massi 2003, Rosenstock 2001, Riddle 2003, Yki-Jarvinen 2006, Yokohama 2006¹)</p> <p>Insulin detemir vs. NPH N=2 (Haak 2005, Hermansen 2006)</p>	<p>Inclusion criteria: only patients with T2D, various other inclusion criteria including HbA1c levels, age, BMI ranges, pre-study treatment requirements.</p> <p>Exclusion criteria: various exclusion criteria including, in 2 studies patients with proliferative retinopathy or maculopathy requiring treatment, or in another study those who have recently received treatment. In addition in 2 studies recurrent major hypoglycaemia and hypoglycaemia unawareness.</p>	<p>Insulin glargine once daily, usually at bedtime, in 1 study it was given in the morning.</p> <p>Insulin Detemir once or twice daily.</p> <p>All other oral agents or insulins used had to be the same in both arms.</p>	<p>NPH once daily, usually at bedtime, in 1 study it could be given at bedtime or twice daily.</p> <p>All other oral agents or insulins used had to be the same in both arms.</p>	<p>6-12 months</p> <p>Most studies had 6 months follow up, 1 study had 9 months (Yki-Jarvinen 2006) and 1 had 12 month follow up (Massi 2003).</p>	<p>Primary outcomes: HbA1c change between baseline and endpoint, weighted mean differences (WMD)</p> <p>Secondary outcomes: rates of hypoglycaemia episodes (severe, nocturnal, symptomatic and overall) Peto-odds ratio was calculated.</p>	<p><u>Glycaemic outcomes:</u></p> <p>HbA1c: Glargine vs NPH WMD of change of HbA1c from baseline to study endpoint: Including 4 studies (Eliaschewitz 2006, Fritsche 2003, Rosenstock 2001, Yki-Jarvinen 2006): 0.1% (-0.1 to 0.2) p=0.49 Including all studies: 0.00% (-0.1 to 0.1) p=0.93</p> <p>Hypoglycaemia: Severe hypoglycaemia Peto-odds ratio: 0.70 (0.40 to 1.23) in favour of glargine. Symptomatic and overall hypoglycaemia (based on 3 studies Eliaschewitz 2006, Fritsche 2003, Rosenstock 2001): Relative risk 0.84 (0.75 to 0.95) p=0.005 in favour of insulin glargine Symptomatic nocturnal hypoglycaemia (based on 3 studies Eliaschewitz 2006, Fritsche 2003, Rosenstock 2001):</p>	

¹ Yokohama 2006 was mentioned but not used in the meta-analyses due to its study design.

		<p>N=1715 patients randomised to insulin glargine</p> <p>N=578 patients randomised to insulin detemir</p> <p>Total number of patients not reported.</p>						<p>Relative risk 0.66 (0.55 to 0.80) p< 0.0001 in favour of insulin glargine. All the other studies not included in the meta-analysis as they did not report hypoglycaemia consistently also found significant differences in favour of glargine.</p> <p>Mortality, cardiovascular morbidity, quality of life and costs were not reported on by any study. There were no reports on diabetic late complications in any of the trials.</p> <p>Adverse events: No meta-analysis. There were no significant differences in numbers of adverse events or serious adverse events between groups or in withdrawals due to adverse events.</p> <p>Detemir studies meta-analysis results not reported in this table, as not included in review.</p>	
<p>Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005; 28(4):950-955. Ref ID: 92</p>	<p>Meta analysis 1+</p>	<p>N=2304 patients from 4 clinical trials (318 study centres) Yki-Jarvinen 2000 and Massi Benedetti 2003, Rosenstock 2001 and Fonseca 2001,</p>	<p>Patients had had type 2 diabetes for at least 2 years, were aged <80 years, had HbA1c levels >7.5% but <12% and had BMI values <40kg/m2. 56% were men. Mean age was 58 years with a mean BMI of 30.5 kg/m2. Mean HbA1c at baseline was 8.8%. Mean fasting plasma glucose was 199 mg/dl. 71% were on oral</p>	<p>N=1142 Insulin glargine administered once daily at bedtime.</p>	<p>N=1162 NPH insulin once or twice daily. (In both groups in three of the four trials patients were also treated with oral antidiabetic drugs and in the other</p>	<p>One study of 24 weeks, two of 28 weeks and one of 52 weeks (the study used data from a 20 week interim analysis).</p>	<p>Percentage of patients reaching target HbA1c (less than or equal to 7%). Change in fasting plasma glucose and insulin dose. Incidences of</p>	<p>The proportion of patients achieving target end HbA1c (less than or equal to 7%) was similar between the insulin glargine and NPH insulin treated patients (30.8% and 32.1% respectively). Fasting plasma glucose levels were significantly lower at end point in the insulin glargine group than in the NPH insulin group 8 ± 0.1 vs. 9 ± 0.0 mmol/l (p=0.02). Insulin glargine and NPH insulin treated patients had similar mean basal and total insulin doses at endpoint (38 ± 25 IU in the glargine group and 37 ± 27 IU</p>	<p>Sponsored by Aventis Pharma</p>

		Riddle 2003 Fritsche 2003.	antidiabetic drugs only and 23% were on insulin only. Mean diabetes duration was 10 years.		trial with regular human insulin). In three trials NPH insulin was once daily whilst in the other it was once or twice daily.		hypoglycemia. Symptomatic hypoglycemia was defined as an event with clinical symptoms consistent with hypoglycemia. Severe episodes were defined as events where the patient required the assistance of another person and was associated with either a plasma glucose level less than or equal to 65mg/dl or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration	in the NPH group). There was an 11% risk reduction in all documented symptomatic hypoglycemia in the insulin glargine group compared with the NPH group(p=0.0006) and a 26% reduction in nocturnal hypoglycemia (<0.0001). There was no significant difference in terms of documented nonnocturnal hypoglycemia (49.6% vs. 51.7%). There was a 46% risk reduction in all documented severe hypoglycemia in the insulin glargine group compared with the NPH group(p=0.04) and a 59% reduction in severe nocturnal hypoglycemia (<0.02). There was no significant difference in terms of documented severe nonnocturnal hypoglycemia (0.8% vs. 0.9%). There were no statistically significant differences between the glargine and NPH groups (10.2% and 9.1% respectively) in the incidence of hypoglycemia reported as a serious event (only hypoglycemia related treatment-emergent adverse events are presented).	
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<p>Eliaschewitz FG, Calvo C, Valbuena H, Ruiz M, Aschner P, Villena J et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. Archives of Medical Research 2006; 37(4):495-501. Ref ID: 805</p>	<p>Open label multicentre RCT (56 centres in 10 South American countries) 1+</p>	<p>N=528 randomised N=481 randomised and treated</p>	<p>Type 2 diabetes patients aged up to 75 years with a BMI less than or equal to 35kg/m² who failed to achieve good metabolic control on OADs which they had taken for at least 6 months (HbA1c levels more than or equal to 7.5% and less than or equal to 10.5%; FBG levels more than or equal to 100mg/dL (5.5mmol/L). Patients were mean 56 years old with a mean BMI of 27kg/m² and 40% were male. Diabetes duration was 10 years. Mean HbA1c was 9.1% and mean FBG was 11mmol/L.</p>	<p>N=231 Insulin glargine at bedtime with once daily glimepiride 4mg a day. Insulin doses in both groups were titrated during the first 6 weeks of treatment using a predefined titration regimen in order to achieve a target FBG of less than or equal to 5.5mmol/L.</p>	<p>N=250 NPH insulin at bedtime with once daily glimepiride 4mg a day</p>	<p>24 weeks</p>	<p>n. Change in HbA1c from baseline Change in FBG from baseline Adverse events Hypoglycaemia: Symptomatic hypoglycaemic events were categorised as mild (blood glucose 2.8 to 4.2mmol/L), moderate (blood glucose < 2.8 mmol/L), or severe (blood glucose < 2.8 mmol/L and acquiring assistance from another person). Symptomatic nocturnal hypoglycaemia was defined as a</p>	<p>Although levels decreased from baseline to endpoint in both treatment groups there was no significant difference between the two groups (adjusted mean difference -0.029 (90%CI -0.210 to 0.153; p=0.795). In the insulin glargine group 50.4% were HbA1c responders (less than or equal to 7.5%) compared with 48% in the NPH insulin group (p=0.529).</p> <p>There was no significant difference in the change in FBG values from baseline to the end of the study between the insulin glargine and NPH groups (p=0.298).</p> <p>The number of patients with at least one symptomatic hypoglycaemic episode was significantly lower in the insulin glargine group than in the NPH insulin group (RR=1.27; 95%CI 1.03 to 1.57; p=0.042).</p> <p>The risk of nocturnal events in the NPH insulin group was 22% greater in the NPH group (RR=1.22; 95%CI 1.09 to 1.37; p<0.001) and 19% greater for nocturnal confirmed events (RR=1.19; 95%CI 1.07 to 1.31; p<0.01).</p> <p>Adverse events were reported by 137 patients (59%) in the insulin glargine group and 150 (60%) in the NPH insulin group.</p>	<p>Sanofi Aventis</p>
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							hypoglycaemic event that occurred while the patient was asleep between bedtime and getting up in the morning.																										
Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomised trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. Diabetic Medicine 2006; 23: 736-742 Ref ID: 4865	RCT 1+ Randomised, open trial (no blinding) ITT analysis but not specifically mentioned Study aimed at comparing a therapeutic policy of insulin introduction and self titration with a policy of oral agent adjustment	N=405 Multisite recruitment	Inclusion criteria: T2D for > 6 months, on 0/1/2 oral glucose-lowering agents (with at least 1 at or below half-maximal dose), no substantial change in oral agents for at least 3 months, HbA1c between 7.5 -11%, BMI 21-41 kg/m ² . Exclusion criteria: Need for or use of insulin or thiazolidinediones, intolerance to metformin, previous ketoacidosis, night-shift workers, pregnancy or not using contraception, significant co-morbid illnesses, history of alcohol abuse, serum creatinine ≥ 133 µmol/l in males and 124 µmol/l in females.	Insulin Glargine added to current therapy. Initial dose 10u, titrated up to achieve FPG of ≤ 5.5 mmol/l.	On oral glucose-lowering agents. Titrated and/or oral agents added to achieve FPG of ≤ 5.5 mmol/l and HbA1c of ≤ 7% until maximal doses of 2 oral agents used, then 3 rd agent added.	24 weeks	Primary outcome: first achievement of 2 consecutive HbA1c levels ≤ 6.5% Secondary outcomes: first achievement of 2 consecutive HbA1c levels ≤ 7%, the achieved HbA1c level, lipid profiles, quality of life, diabetes treatment satisfaction (measured by Diabetes Treatment	Primary endpoint of 2 consecutive HbA1c levels ≤ 6.5% : Unadjusted HR: 1.68 (1.00, 2.83; p=0.049) Adjusted HR ² : 1.71 (1.02, 2.88; p=0.043) Secondary endpoint of 2 consecutive HbA1c levels ≤ 7% : Unadjusted HR: 1.66 (1.21, 2.29; p=0.002) Adjusted HR ² : 1.75 (1.27, 2.41; p=0.001) Change in key parameters:	Aventis Canada																								
								<table border="1"> <thead> <tr> <th></th> <th>glargine</th> <th>control</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>Δ HbA1c %</td> <td>-1.55</td> <td>1.25</td> <td>0.005</td> </tr> <tr> <td>Δ FPG mmol/l</td> <td>-3.89</td> <td>-2.31</td> <td>0.0001</td> </tr> <tr> <td>Δ TG mmol/l</td> <td>-1.08</td> <td>-0.47</td> <td>0.02</td> </tr> <tr> <td>Δ Chol mmol/l</td> <td>-0.38</td> <td>-0.11</td> <td>0.015</td> </tr> <tr> <td>Δ non-HDL</td> <td>-0.37</td> <td>-0.13</td> <td>0.02</td> </tr> </tbody> </table>		glargine	control	p	Δ HbA1c %	-1.55	1.25	0.005	Δ FPG mmol/l	-3.89	-2.31	0.0001	Δ TG mmol/l	-1.08	-0.47	0.02	Δ Chol mmol/l	-0.38	-0.11	0.015	Δ non-HDL	-0.37	-0.13	0.02	
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								<p>Similar results were noted after adjustment for baseline level, site of recruitment and stratum.</p> <p>There was no difference in the effect of glargine in subgroups defined by gender, site of care, prior drug therapy, BMI, age or duration of diabetes</p> <p>Hypoglycaemia rates were the same in both groups.</p>									
Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, Al HA et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care 2005; 28(7):1568-1573. Ref ID: 51	RCT (2 centres, US) 1+	N=107 type 2 diabetes patients	Inclusion criteria: Patients had to be 60 years old or more with a clinical diagnosis of type 2 diabetes for at least a year and with at least one insulin injection per day for the past month (with or without oral antidiabetic medications) and have an HbA1c of equal to or more than 7%. Patients had a mean age of 66 years. 58% were male (although this was 72% in the CSII group and 44% in the MDI group). Mean BMI was 32 kg/m ² and mean HbA1c was 8.3%	N=53 CSII Continuous subcutaneous insulin infusion. Intensive therapy with preprandial insulin lispro and with basal insulin as continuous lispro infusion.	N=54 MDI Multiple daily injection. Intensive therapy with preprandial insulin lispro and with basal insulin as once daily insulin glargine. In both groups oral antidiabetics were discontinued and insulin targets were	12 months	HbA1c Insulin dose Hypoglycaemia (capillary glucose <65mg/dl or symptoms resolving with oral carbohydrates) and severe hypoglycaemia (symptoms with capillary glucose < 50mg/dl) Body weight Quality of life	<p>Mean HbA1c fell by 1.7 ± 1.0% in the CSII group to 6.6% and by 1.6 ± 1.2% in the MDI group to 6.4%. The difference in HbA1c between treatment groups was not statistically significant (p=0.2).</p> <p>At the end of the study, total daily insulin requirements were similar for the two groups. The mean total daily insulin requirement was 108 ± 63 units for CSII subjects and 108 ± 62 units for MDI subjects (p=0.998).</p> <p>81% of CSII patients and 90% of MDI patients experienced at least one episode of minor hypoglycaemia (P=0.49). Rates of severe hypoglycaemia were similarly low in the two groups (CSII 0.08 and MDI 0.23 events per person year, p=0.61).</p> <p>Weight gain did not differ between the two groups (2.1 vs 2.6 kg, p=0.70).</p>	The American Diabetes Assoc.								

² Adjusted for baseline HbA1c, number of oral agents used at baseline and site of recruitment.

					adjusted to achieve target blood glucose levels of 80 to 120 mg/dl before meals, 100 to 150 mg/dl at bedtime and HbA1c <5.6% without incurring unacceptable hypoglycaemia.			Treatment satisfaction improved significantly with both CSII and MMI (p<0.0001) but the difference between groups was not significant (p=0.58).																					
Jacober SJ, Scism-Bacon JL, Zagar AJ, for the IONW Study investigators. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naïve patients with type 2 diabetes receiving oral antidiabetic agents. <i>Diabetes, Obesity and Metabolism</i> 2006; 8: 448-455 Ref ID: 4879	RCT 1+ Multicentre, randomised open-label, cross over study 11 centres in the US	N=60 Drop out rate 16.7% Randomisation method not described.	Inclusion criteria: >30 years old, poor blood glucose control, on at least 2 oral agents of different classes for at least 2 months, HbA1c 1.2-2x the upper limit of normal reference range used by local laboratory. Exclusion criteria: Undergoing treatment for malignancy other than basal cell or squamous cell skin cancer, cardiac (class III or IV) or liver disease, renal transplantation or dialysis, haemoglobinopathy,	Intensive mixed therapy (IMT) for 4 months: Insulin lispro mixture 50/50 at breakfast and lunch Insulin lispro mixture 25/75 at evening meal Then cross over to alternate	Insulin glargine for 4 months: Once daily insulin glargine at bedtime Then cross over to alternate treatment sequence for 4 months.	8 months	Primary outcome: HbA1c change from pre-therapy (defined as the value at the beginning of the period during which the treatment regimen was used) Secondary outcome: Endpoint HbA1c, HbA1c	<u>Glycaemic outcomes:</u> <table border="1"> <thead> <tr> <th></th> <th>IMT</th> <th>Glargine</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>End of therapy HbA1c %</td> <td>7.08 ± 0.11</td> <td>7.34 ± 0.11</td> <td>0.003</td> </tr> <tr> <td>Change from pre-therapy HbA1c %</td> <td>-1.01 ± 0.10</td> <td>-0.75 ± 0.10</td> <td>0.0068</td> </tr> <tr> <td>Change from pre-study HbA1c %</td> <td>-1.98 ± 0.11</td> <td>-1.76 ± 0.11</td> <td>0.0083</td> </tr> <tr> <td>Proportion</td> <td>44</td> <td>31</td> <td>0.1026</td> </tr> </tbody> </table>		IMT	Glargine	p	End of therapy HbA1c %	7.08 ± 0.11	7.34 ± 0.11	0.003	Change from pre-therapy HbA1c %	-1.01 ± 0.10	-0.75 ± 0.10	0.0068	Change from pre-study HbA1c %	-1.98 ± 0.11	-1.76 ± 0.11	0.0083	Proportion	44	31	0.1026	
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			<p>chronic anaemia, known allergy to insulin, pregnant or intended to become pregnant, breastfeeding, BMI>40kg/m2, >1 episode of severe hypoglycaemia, or had any other condition that precluded following and completing the protocol, on rosiglitazone, long term insulin therapy, chronic systemic glucocorticoid therapy, fibric acid derivatives, niacin or bile acid sequestrant to treat hypertriglyceridaemia.</p> <p>Not stated if there were any differences between the groups at baseline.</p>	<p>treatment sequence for 4 months.</p> <p>Target fasting and pre-prandial blood glucose value was 6.7mmol/l.</p> <p>For lispro treatment target post-prandial glucose level (2hr after meal) was 10.0 mmol/l.</p>		<p>change from prestudy level, 8-point glucose profiles, rate of hypoglycaemia (episodes/patient/30 days), body weight and weight gain.</p>	<table border="1"> <tr> <td>on of patients with HbA1c ≤7%</td> <td></td> <td></td> <td></td> <td></td> </tr> </table> <p>FBG levels did not differ between the two regimens.</p> <p>BG values 2-h after breakfast, lunch and dinner were significantly lower for the IMT regimen than the glargine regimen.</p> <p>Pre-dinner BG also significantly lower for IMT regimen.</p> <p>Insulin Dose</p> <table border="1"> <thead> <tr> <th></th> <th>IMT</th> <th>Glargine</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>Mean insulin dose at the end of therapy</td> <td>0.353 ± 0.256 IU/kg</td> <td>0.276 ± 0.207 IU/kg</td> <td>0.0107</td> </tr> </tbody> </table> <p>Hypoglycaemia rates (episodes/patient/30days):</p> <table border="1"> <thead> <tr> <th></th> <th>IMT</th> <th>Glargine</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>Overall hypoglycaemia</td> <td>3.98 ± 4.74</td> <td>2.57 ± 3.22</td> <td>0.0013</td> </tr> <tr> <td>Nocturnal hypoglycaemia</td> <td>0.80 ± 2.12</td> <td>1.05 ± 1.59</td> <td>0.3604</td> </tr> </tbody> </table>	on of patients with HbA1c ≤7%						IMT	Glargine	p	Mean insulin dose at the end of therapy	0.353 ± 0.256 IU/kg	0.276 ± 0.207 IU/kg	0.0107		IMT	Glargine	p	Overall hypoglycaemia	3.98 ± 4.74	2.57 ± 3.22	0.0013	Nocturnal hypoglycaemia	0.80 ± 2.12	1.05 ± 1.59	0.3604
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								Mean body weight at the end of therapy	99.7 ± 18.6 kg	99.0 ± 19.1 kg	0.9106	
								Mean weight gain	1.98 ± 0.44 kg	1.52 ± 0.46 kg	0.457	
Janka HU, Plewe G, Riddle MC, Kliebe FC, Schweitzer MA, Yki JH. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes.[see comment]. Diabetes Care 2005; 28(2):254-259. Ref ID: 80	RCT 1+ (66 sites in 10 European countries).	N=371 type 2 insulin naïve patients	Inclusion criteria: Male or female patients aged 35 to 75 years with a type 2 diabetes duration of at least 1 year and treated with sulfonylurea and metformin for at least a month. BMI had to be less than or equal for 35 kg/m2, HbA1c levels between 7.5 and 10.5% and FBG levels greater than or equal to 120 mg/dl. The study population was 59% male, with mean age 60 years, mean weight 85kg, mean BMI 30 kg/m2, mean HbA1c of 8.8%, mean FBG 171 mg/dl (9.5 mmol/l).	N=177 Glargine plus OAD group: Insulin glargine given once daily in the morning (starting dose 10 IU) plus oral antidiabetic drugs (3 or 4mg glimepiride plus metformin at the same dose as before study entry). In both groups insulin doses were adjusted by	N=187 70/30 group: Human remixed insulin (30% regular, 70% NPH insulin) administered twice daily before breakfast (starting dose 10IU) and dinner (starting dose 10IU) while glimepiride and metformin were discontinued	24 weeks	Glycaemic control Insulin dose Hypoglycemia Weight gain Adverse events	Mean HbA1c decrease from baseline was significantly more pronounced (-1.64 vs. -1.31%, p=0.0003) with glargine plus OAD than with 70/30. An HbA1c level of less than or equal to 7% was achieved by 49.4% of patients in the glargine plus OAD group compared with 39% in the 70/30 group (p=0.0596). Significantly more patients on glargine plus OAD (45.5% than on 70/30 (28.6%) reached an HbA1c of less than or equal to 7% without an episode of confirmed nocturnal hypoglycaemia (p=0.0013). FBG decrease was greater with glargine plus OAD (adjusted mean difference -17mg/dl (-0.9 mmol/l) p<0.0001), and more patients reached target FBG of less than or equal to 100 mg/dl with glargine plus OAD than with 70/30 (31.6 vs 15.0%, p=0.0001). Patients received more than twice as much daily insulin with 70/30 than with glargine plus OAD (64.5 vs. 28.2 IU). 61.6% of those receiving glargine plus OAD and 67.2% of those receiving 70/30 experienced at least one	Supported by Aventis Pharma			

				a forced titration regimen calling for weekly adjustments for 8 weeks at 2 weekly intervals. The FBG target was 100 mg/dl and the before dinner blood glucose target for the 70/30 group was 100 mg/dl with a step-wise increase of insulin depending on blood glucose values.				hypoglycaemic event (p=0.2838). During treatment the rate of confirmed hypoglycaemic events expressed as episodes per patient years was significantly lower with glargine plus OAD for all hypoglycaemic events (4.07 vs 9.87, <0.0001) symptomatic events (2.62 vs 5.73, <0.0009) and nocturnal events(0.51 vs 1.04, <0.0449) . Severe hypoglycaemia was very uncommon in both groups. Mean weight gain did not significantly differ between the two groups (1.4 ± 3.3 vs 2.1 ± 4.2 kg, p=0.0805). The incidence of adverse events was similar with 50.3% in the glargine plus OAD group and 48.7% in the 70/30 group experiencing at least one adverse event.	
Kann PH, Wascher T, Zackova V, Moeller J, Medding J, Szocs A, Mokan M, Mrevlje F, Regulski M. Starting Insulin therapy in Type 2 diabetics: Twice daily biphasic Insulin Aspart 30 plus Metformin versus once-daily Insulin Glargine plus Glimepiride <i>Exp Clin</i>	RCT 1+ Multinational (European), multi centre, open label, randomised trial	N=255 Drop out rate 9.8%, similar in both groups.	Inclusion criteria: insulin naïve T2D, poor glycaemic control (HbA1c > 7 & ≤ 12%), BMI ≤ 40kg/m ² , currently on oral therapy including sulphonylureas (at least ½ maximum dose alone or in combination with metformin or metformin monotherapy (≥ 2g/day)	BIAsp 30 (30% soluble and 70% protamine d insulin aspart) 2x daily, 0.1 IU/kg before breakfast and dinner, titrated up to achieve PG	Insulin glargine once daily (at a preferred time of day), 0.2IU/kg/day titrated up to achieve pre-meal PG of 5-8mmol/l.	28 weeks 26 weeks after randomisation	Primary endpoint: mean difference in change in HbA1c from baseline Secondary endpoints: FPG, mean prandial	Mean total daily medication dose: BIAsp 30: 0.40IU/kg Glargine: 0.39 IU/kg p=0.65 Metformin: 2000mg Glimepiride: 4.0mg <u>Glycaemic control:</u> Mean difference in HbA1c from baseline: Greater in BIAsp 30/met than in the Glargine/glim group: -0.5 (-0.8, -0.2;	Novo Nordisk

<p><i>Endocrinol Diabetes</i> 2006; 114: 527-532</p>	<p>ITT analysis</p>		<p>Exclusion criteria: history of drug or alcohol abuse, impaired renal or hepatic function, cardiovascular problems, taking any other medication that may have interfered with glucose regulation, pregnant, breast-feeding or intending to become pregnant.</p> <p>Baseline characteristics: No significant differences between groups</p>	<p>5-8mmol/m pre-meal and 5-10mmol/l 90 min post meal</p> <p>Metformin 500 mg before breakfast and dinner titrated up to 2000 mg.</p>	<p>Glimepiride 1mg/daily titrated to a max of 4mg daily.</p>		<p>plasma glucose increment, seven point blood plasma profiles, hypoglycaemic episodes, adverse events.</p>	<p>p=0.0002) (corrected for baseline)</p> <p>End of trial HbA1c values: BIAsp 30/met: 7.5 ± 1.1% Glargine/glim: 7.9 ± 1.3% (p=0.01)</p> <p>Proportion of patients achieving HbA1c < 7%: BIAsp 30/met: 33.1% Glargine/glim: 26.2% NS difference between groups</p> <p>Mean prandial increment at trial end: BIAsp 30/met: 1.4 ± 1.4 mmol/l Glargine/glim: 2.2 ± 1.8 mmol/l (p=0.0002)</p> <p>FPG absolute change from baseline: BIAsp 30/met: -2.6 ± 0.24 mmol/l Glargine/glim: -2.2 ± 0.25 mmol/l NS difference between groups for mean change from baseline (p=0.23)</p> <p>Hypoglycaemic episodes: Proportion of patients experiencing minor hypoglycaemic episodes BIAsp 30/met: 20.3% Glargine/glim: 9% (p=0.0124)</p> <p>Adverse events: Greater number of adverse events in the BIAsp 30/met group but not statistically significant. 2 patients with hypoglycaemic coma in the BIAsp 30/met group</p> <p>Body weight increase: BIAsp 30/met: +0.7kg NS increase from baseline</p>	
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								Glargine/glim: significant increase from baseline +1.5 kg (0.84, 2.19; $p < 0.0001$) Not stated if there was a statistically significant difference between the groups.																																							
Kazda C, Hulstrunk H, Helsberg K, Langer F, Forst T, Hanefeld M. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture vs. basal therapy with insulin glargine: A randomised controlled trial in patients with type 2 diabetes beginning insulin therapy. <i>Journal of Diabetes and Its Complications</i> 2006; 20: 145-152 Ref ID: 4881	RCT 1+ Open label, randomised, parallel, three arm multicentre trial ITT and per protocol analyses	N=159 Recruited from 19 sites in Germany Drop out rate 12.6%	Inclusion criteria: T2D, duration 1-10 years, no insulin treatment in the last 3 months, BMI $< 40 \text{ kg/m}^2$, HbA1c 6.0-10.5% (within 4 weeks before screening) Exclusion criteria: nil mentioned Comparisons made between: Lispro vs. glargine MidMix vs. glargine	Insulin glargine 1x daily at bedtime Target was FBG $< 7 \text{ mmol/l}$ Oral hypoglycaemic agents discontinued	Insulin lispro 3x daily before breakfast, lunch, dinner Insulin lispro mid mixture (MidMix; 50% lispro/50% NPL) 3x daily before breakfast, lunch, dinner Target was 2-hr post prandial blood glucose $< 10 \text{ mmol/l}$ Oral hypoglycaemic agents discontinued	24 weeks	Primary outcome: postprandial glucose excursion (PPGE) 2 hours after breakfast Secondary outcome: changes in 2hr postprandial blood glucose from baseline to the end of the study, HbA1c, self monitored blood glucose profiles, hypoglycaemic episodes, body weight, patient satisfaction. Patient satisfaction measured	<table border="1"> <thead> <tr> <th colspan="4">Glycaemic control</th> </tr> <tr> <th></th> <th>Group</th> <th>Change from baseline</th> <th>P vs. glargine</th> </tr> </thead> <tbody> <tr> <td rowspan="3">FBG mmol/l</td> <td>Lispro</td> <td>-0.9 ± 2.2</td> <td>< 0.001</td> </tr> <tr> <td>MidMix</td> <td>0.9 ± 1.8</td> <td>< 0.001</td> </tr> <tr> <td>Glargine</td> <td>-2.6 ± 2.4</td> <td></td> </tr> <tr> <td rowspan="3">2hr PPGE mmol/l</td> <td>Lispro</td> <td>-2.1 ± 2.9</td> <td>< 0.001</td> </tr> <tr> <td>MidMix</td> <td>-1.8 ± 2.4</td> <td>0.001</td> </tr> <tr> <td>Glargine</td> <td>-0.1 ± 2.2</td> <td></td> </tr> <tr> <td rowspan="3">HbA1c %</td> <td>Lispro</td> <td>-1.1 ± 1.1</td> <td>0.001</td> </tr> <tr> <td>MidMix</td> <td>-1.2 ± 1.1</td> <td>< 0.001</td> </tr> <tr> <td>Glargine</td> <td>-0.3 ± 1.1</td> <td></td> </tr> </tbody> </table> <p>Mean daily insulin dose at endpoint: Glargine $0.43 \pm 0.22 \text{ IU/(kg day)}$ Lispro $0.50 \pm 0.23 \text{ IU/(kg day)}$ MidMix $0.59 \pm 0.30 \text{ IU/(kg day)}$ $p < 0.005$</p> <p>Proportion of patients reaching BG control targets: Lispro (target $< 10 \text{ mmol/l}$ after breakfast) 76.9% MidMix (target $< 10 \text{ mmol/l}$ after breakfast) 66.7% Glargine (target $< 7 \text{ mmol/l}$) 60.8%</p>	Glycaemic control					Group	Change from baseline	P vs. glargine	FBG mmol/l	Lispro	-0.9 ± 2.2	< 0.001	MidMix	0.9 ± 1.8	< 0.001	Glargine	-2.6 ± 2.4		2hr PPGE mmol/l	Lispro	-2.1 ± 2.9	< 0.001	MidMix	-1.8 ± 2.4	0.001	Glargine	-0.1 ± 2.2		HbA1c %	Lispro	-1.1 ± 1.1	0.001	MidMix	-1.2 ± 1.1	< 0.001	Glargine	-0.3 ± 1.1		Lilly Deutschland GmbH
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							using a non-validated 5 point Likert scale questionnaire	<p>Hypoglycaemia: Self reported episodes Lispro 1.4 per 100 patient days MidMix 1.5 per 100 patient days Glargine 1.0 per 100 patient days</p> <p><u>Mean change in body weight:</u></p> <table border="1"> <thead> <tr> <th></th> <th>Group</th> <th>Change from baseline</th> <th>P vs. glargine</th> </tr> </thead> <tbody> <tr> <td>Body weight</td> <td>Lispro</td> <td>2.3 ± 4.3 kg</td> <td></td> </tr> <tr> <td></td> <td>MidMix</td> <td>1.8 ± 3.4 kg</td> <td></td> </tr> <tr> <td></td> <td>Glargine</td> <td>0.7 ± 3.8 kg</td> <td></td> </tr> <tr> <td>BMI kg/m²</td> <td>Lispro</td> <td>0.9 ± 1.5</td> <td>0.048</td> </tr> <tr> <td></td> <td>MidMix</td> <td>0.6 ± 1.1</td> <td>0.19</td> </tr> <tr> <td></td> <td>Glargine</td> <td>0.2 ± 1.3</td> <td></td> </tr> </tbody> </table> <p><u>Adverse events:</u> NS difference between groups</p> <p><u>Treatment satisfaction:</u> Proportion of patients with high or very high treatment satisfaction per group: Lispro 65.4% MidMix 63.0% Glargine 50.9% Not stated if these differences were significant.</p>		Group	Change from baseline	P vs. glargine	Body weight	Lispro	2.3 ± 4.3 kg			MidMix	1.8 ± 3.4 kg			Glargine	0.7 ± 3.8 kg		BMI kg/m ²	Lispro	0.9 ± 1.5	0.048		MidMix	0.6 ± 1.1	0.19		Glargine	0.2 ± 1.3		
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Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH.	Crossover RCT (12 U.S. study centres)	N=105 type 2 diabetes patients with inadequate	Inclusion criteria: Patients aged 13 to 80 years with a BMI less than or equal to	N=52 Insulin lispro mix 75/25 before	N=53 The opposite treatment sequence.	32 weeks	HbA1c FBG Hypoglycaemia (blood	The mix 75/25 treatment group experienced a greater decrease in mean (SD) HbA1c (-3.1%(1.0%) vs. -0.9% (0.9); p=0.003) and a lower mean	First author employed by Eli																												

<p>Combined therapy with insulin lispro mix 75/25 plus metformin or insulin glargine plus metformin: A 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clinical Therapeutics 2004; 26(12):2034-2044. Ref ID: 1127</p>	<p>1+</p>	<p>control without insulin.</p>	<p>40kg/m². Inadequate glycaemic control as indicated by an HbA1c value between 1.3 and 2.0 times the upper limit of normal while using oral antihyperglycaemic medications. Mean age was 55 years and 63% were male. Mean BMI was 31kg/kg, mean FBG was 153 mg/dl and mean HbA1c was 8.7%</p>	<p>breakfast and dinner plus metformin 1500 to 2550 mg/d for 16 weeks and then insulin glargine at bedtime plus metformin 1500 to 2550 mg/d for an additional 16 weeks.</p>	<p>In both groups doses could be adjusted by the investigator to achieve an FBG and premeal blood glucose target of 90 to 126 mg/dL. For mix 75/25 there was also a 2 hour ppBG target of 144 to 180 mg/dL..</p>		<p>glucose <63 mg/dL or symptoms of hypoglycaemia). Severe hypoglycaemia (needing third party assistance) Total insulin dose Body weight Adverse events</p>	<p>(SD) HbA1c at end point compared with insulin glargine (7.4% (1.1%) vs 7.8% (1.1%); p=0.002). More patients using mix 75/25 achieved target HbA1c more than or equal to 7% (42% vs 18%, p=0.002). Mean end point FBG was significantly lower with insulin glargine (123.9 mg/dL vs 139.3 mg/dL; p<0.001. With mix 75/25 the mean (SD) 2 hour ppBG was similar after lunch but significantly lower after breakfast (156.4 (43.6) vs 171.1 (44.9) mg/dL;p=0.0012) and dinner (164.8 (42.65) vs 193.8 (51.0) mg/dL;p<0.001). The rise in mean (SD) blood glucose after meals was significantly smaller with Mix 75/25 in the morning (16.9 (47.0) vs 47.4 (34.8) mg/dL;p<0.001) and evening (14.2 (44.1) vs 45.9 (41.3) mg/dL;p<0.001) but did not differ after then noon meal. Gain in body weight was greater with Mix 75/25 than insulin glargine (2.3 (4.0) kg vs 1.6 (4.0) kg; p=0.006). The mean (SD) total daily insulin doses recorded at end point were 0.62 (0.37) U/kg for Mix 75/25 and 0.57 (0.37) U/kg for insulin glargine (P<0.001) respectively. No patients experienced severe hypoglycaemia. The overall hypoglycaemia rate was higher with mix 75/25 (mean 0.68 (1.38) vs 0.39 (1.24) episodes/patient per 30 days; p=0.041). There was no difference between treatments for the incidence (11% vs 12%) and rate (mean 0.41 vs 0.24 episodes/patient per 30 days) of nocturnal hypoglycaemia.</p>	<p>Lilly.</p>
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								There was no significant difference between treatments in the incidence of or type of adverse events and none were considered to be related to insulin treatment.	
Malone JK BSCBR. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association 2005; 22(4):374-381. Ref ID: 1128	Crossover RCT (12 European study centres) 1+	N=97 type 2 diabetes patients with inadequate glucose control.	Inclusion criteria: Inadequate glycaemic control as indicated by an HbA1c value between 1.3 and 2.0 times the upper limit of normal. Patients were required to be using NPH once or twice daily, alone or in combination with an oral antidiabetic agent(s), or a human insulin mixture with oral agent(s). (These patients were selected as they were expected to benefit from prandial control not provided by their previous insulin.) Patients had a mean age of 60 years. 44% were male. Mean weight was 77kg and mean BMI was 29 kg/m ² . Mean HbA1c was 8.5%.	N=50 Insulin lispro mixture (25% insulin lispro and 75% NPL) before breakfast and dinner plus metformin (1500 to 2550 mg per day) for 16 weeks followed by insulin glargine at bedtime plus metformin (1500 to 2550 mg per day) for 16 weeks.	N=47 The opposite treatment sequence. In both groups doses could be adjusted by the investigator to achieve an FBG and premeal blood glucose target of 90 to 126 mg/dL. For mix 75/25 there was also a 2 hour ppBG target of 144 to 180 mg/dL.	32 weeks	HbA1c Post prandial blood glucose . Body weight. Insulin and metformin doses Hypoglycaemia rates. Adverse events	At endpoint HbA1c was lower with the insulin lispro mixture plus metformin compared with glargine plus metformin (7.54% ± 0.87% vs 8.14% ± 1.03%, p<0.001). Change in HbA1c from baseline to endpoint was greater with the insulin lispro mixture plus metformin (-1.0% vs -0.42%; p<0.001). A higher percentage of patients treated with the insulin lispro mixture were at or below an HbA1c of 7% at endpoint (30% vs 12%; p=0.002). The FBG was higher at endpoint after treatment with Mix25 (7.9 vs. 7.39 mmol/l, p=0.007). Patients in the insulin lispro mixture plus metformin group experienced more weight gain than those treated with glargine plus metformin (Mean weight change 0.82 ± 2.56kg vs 0.06 ± 2.49kg, p=0.001) and required a slightly higher daily insulin dose (0.42 ± 0.20 vs 0.36 ± 0.18 U/kg, p<0.001). Metformin dose at endpoint was similar for the two treatments. Two hour post prandial BG was lower after morning, midday and evening meals (p<0.001) during treatment with the insulin lispro mixture and metformin. FBG was higher during treatment with the lispro mix plus metformin (7.90 ± 1.92 vs 7.39 ± 1.96 mmol/l, p=0.007). A greater proportion of patients treated	First author employed by Eli Lilly.

								<p>with the insulin lispro mixture plus metformin achieved the morning and evening 2 h post prandial BG targets of less than or equal to 10 mmol/l (66% vs 42% and 64% vs 40%, p<0.001 for both). A greater proportion of patients treated with glargine plus metformin achieved the FBG target (less than or equal to 7 mmol/l) (34% vs 51%, p=0.01). There was no difference between groups in the proportion of patients achieving the midday 2 h post prandial BG target.</p> <p>The overall hypoglycaemia rate was not different between treatments (0.61 ± 1.41 vs 0.44 ± 1.07 episodes/patient/30 days;p=0.477). Patients treated with the insulin lispro mixture plus metformin experienced a lower rate of nocturnal hypoglycaemia (0.41 ± 0.49 vs 0.34 ± 0.85 episodes/patient/30 days;p=0.002). Daytime hypoglycaemia rate was higher with the insulin lispro mixture plus metformin (0.46 ± 1.28 vs 0.10 ± 0.51 episodes/patient/30 days;p=0.003). No episodes of severe hypoglycaemia occurred in either group.</p> <p>There was no difference between treatments in the overall incidence of adverse events. Three serious adverse events were reported in each group but none were related to insulin or metformin treatment.</p>													
Pan CY, Sinnassamy P, Chung KD, Kim KW. Insulin glargine	RCT 1+ Randomised,	N= 443 Asian patients,	Inclusion criteria: Insulin naïve Asian age 40-80 years with T2D ³ , poorly controlled on oral	Insulin glargine at bedtime	NPH at bedtime Glimepiride	3-4 week screening phase	Primary outcome: change in HbA1c from	<table border="1"> <thead> <tr> <th colspan="4">Glycaemic control</th> </tr> <tr> <th></th> <th>Glargine</th> <th>NPH</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>Reduction</td> <td>-0.99%</td> <td>-0.77%</td> <td>0.031</td> </tr> </tbody> </table>	Glycaemic control					Glargine	NPH	p	Reduction	-0.99%	-0.77%	0.031	Sanofi Aventis
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<p>versus NPH insulin therapy in Asian Type 2 diabetes patients. Diabetes Research & Clinical Practice 2007; 76(1):111-118.</p> <p>Ref ID: 4883</p>	<p>parallel, open-label, non-inferiority study.</p>	<p>multinational study, 31 study centres in 10 countries (China, Hong Kong, Indonesia, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan, Thailand).</p> <p>Drop out rate 11%</p> <p>ITT and per-protocol analyses. Method of randomisation, allocation concealment not mentioned.</p>	<p>anti-diabetic agents for ≥ 3 months, BMI 20-35 kg/m², HbA1c 7.5-10.5%, FBG > 6.7mmol/l.</p> <p>Exclusion criteria: pregnancy, history of ketoacidosis, likelihood of requiring drugs prohibited in the study protocol (non-selective beta blockers, systemic corticosteroids).</p> <p>There were no significant differences between groups at baseline.</p>	<p>Glimepiride 3 mg once daily in the morning</p> <p>Insulin doses started at 0.15 IU/kg/day, titrated upward until target FBG (≤ 6.7 mmol/l) was reached.</p>	<p>3 mg once daily in the morning</p> <p>Insulin doses started at 0.15 IU/kg/day, titrated upward until target FBG (≤ 6.7 mmol/l) was reached.</p>	<p>24 weeks treatment period</p>	<p>baseline to endpoint</p> <p>Secondary outcomes: mean FBG level, mean daily BG and nocturnal BG profiles, Proportion of patients with FBG ≤ 6.7 mmol/l, proportion of patients with HbA1c < 7.5%, proportion of combined responders (FBG and HbA1c), insulin dose, change in BMI, proportion of patients with hypoglycaemia, adverse events.</p>	<table border="1"> <tr> <td>in mean HbA1c</td> <td></td> <td></td> <td>9</td> </tr> <tr> <td>Endpoint mean HbA1c</td> <td>7.90 \pm 1.16%</td> <td>8.13 \pm 1.19%</td> <td></td> </tr> <tr> <td>Reduction in FPG</td> <td>-106 mg/dL</td> <td>-104 mg/dL</td> <td></td> </tr> <tr> <td>Mean daily BG</td> <td>-94 mg/dL</td> <td>-80 mg/dL</td> <td>0.018</td> </tr> <tr> <td>Proportion of patients achieving HbA1c < 7.5%</td> <td>38.1%</td> <td>30.3%</td> <td>NS</td> </tr> <tr> <td>Proportion of patients achieving FBG < 6.7mmol/l</td> <td>62.3%</td> <td>58.7%</td> <td>NS</td> </tr> <tr> <td>Mean daily insulin dose at endpoint</td> <td>32.1 \pm 17.6 IU</td> <td>32.8 \pm 18.9 IU</td> <td>NS</td> </tr> </table>				in mean HbA1c			9	Endpoint mean HbA1c	7.90 \pm 1.16%	8.13 \pm 1.19%		Reduction in FPG	-106 mg/dL	-104 mg/dL		Mean daily BG	-94 mg/dL	-80 mg/dL	0.018	Proportion of patients achieving HbA1c < 7.5%	38.1%	30.3%	NS	Proportion of patients achieving FBG < 6.7mmol/l	62.3%	58.7%	NS	Mean daily insulin dose at endpoint	32.1 \pm 17.6 IU	32.8 \pm 18.9 IU	NS
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Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005; 28(2):260-265. Ref ID: 79	RCT (25 centres in the US) 1+	N=233 insulin naïve type 2 diabetes patients	Inclusion criteria: Insulin naïve type 2 diabetes patients who were 18 to 75 years old and had a BMI less than or equal to 40 and body weight <125kg, and an HbA1c value greater than or equal to 8%. All were previously treated with metformin at least 1000mg/day as a single agent or in combination therapy for at least 3 months. Mean age 52 years, 55% male, mean weight 90kg, mean BMI 31 kg/m ² , mean HbA1c 9.7% with 10% with an HbA1c >8.5% at baseline.	N=117 Twice daily BIAsp 70/30 (a biphasic insulin analog formulation of insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine). before breakfast and supper.	N=116 Once daily glargine at bedtime. In both groups metformin was optimised to 1500-2550 mg/day, secretagogues and alpha glucosidase inhibitors were discontinued. Pioglitazone was continued if taken pre-study. In both groups insulin therapy was initiated at a total daily dose of 10 units for those with FPG values <180mg/dl or 12 units for those with FPG values	28 weeks	Reduction in HbA1c FPG Insulin dose Body weight Hypoglycaemia episodes Adverse events	The mean HbA1c values were lower for the BIAsp 70/30 group compared with the glargine group (6.91 ± 1.17 vs. 7.41 ± 1.24%, p<0.01) and the overall reduction in HbA1c for those in the BIAso 70/30 group was significantly greater than for subjects in the glargine group (-2.79 ± 0.11 vs -2.36 ± 0.11% respectively, <0.01). More BIAsp 70/30 treated patients reached target HbA1c values than glargine treated subjects (HbA1c less than or equal to 6.5%: 42 vs 28%, p<0.05; HbA1c <7.0%: 66 vs 40%, p<0.001). FPG values were similar at baseline and at the end of the study in both groups. Insulin doses at the end of the study were greater for the BIAsp 70/30 group than for the glargine group (total units: 78.5 ± 39.5 vs 51.3 ± 26.7 units; for units by weight, 0.82 ± 0.40 vs. 0.55 ± 0.27 units/kg, p<0.05). Mean body weight increased in both groups although significantly more in the BIAsp 70/30 group (5.4 ± 4.8kg vs. glargine 3.5 ± 4.5kg. p<0.01). The overall rate of minor hypoglycaemia (documented plasma glucose <56mg/dl with or without symptoms) based on all patients was greater in the BIAsp 70/30 group than in the glargine group (3.4 ± 6.6 vs. 0.7 ± 2.0 episodes per patient year, respectively; p<0.05). Minor hypoglycaemia was reported by 43% of people in the BIA sp 70/30 group and by 16% in the glargine group (p<0.05).	Supported by Novo Nordisk

					greater than or equal to 180 mg/dl. Insulin doses were titrated weekly for the first 12 weeks and then every 2 weeks thereafter to achieve target FPG and pre-supper plasma glucose values of 80-110 mg/dl. All adjustments were made using specified algorithms.			The number and type of reported adverse events were similar for the two treatment groups and were not unexpected for the trial population.																
Raskin PR, Hollander PA, Lewin A, Gabbay RA, Bode B, Garber AJ. Basal insulin or premix analogue therapy in type 2 diabetes patients. European Journal of Internal Medicine 2007; 18(1):56-62.	RCT 1+ Randomised open-label, parallel group study	N=157 Sub-population of the INITIATE study, those not using thiazolidinediones (TZD). Recruited at 25 centres in USA.	Inclusion criteria: Insulin naïve T2D, 18-75 years old, BMI < 40kg/m2, body weight < 125 kg, HbA1c ≥ 8%, previously treated with metformin ≥ 1000 mg/day as mono- or combination therapy for > 3 months. Exclusion criteria: not described in this paper	N=79 Twice-daily BIAsp 30 before breakfast and dinner 4 week metformin run-in period, therapy	N=78 Insulin glargine at bedtime 4 week metformin run-in period, therapy optimised to 1500-2550	28 weeks	Primary outcome: reduction in mean HbA1c from baseline.	<p><u>Glycaemic outcomes:</u></p> <table border="1"> <thead> <tr> <th></th> <th>BIAsp</th> <th>Glargine</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>Reduction in mean HbA1c</td> <td>-2.89 ± 1.6%</td> <td>-2.46 ± 1.6%</td> <td>0.035</td> </tr> <tr> <td>Endpoint mean HbA1c</td> <td>7.0 ± 1.3%</td> <td>7.4 ± 1.3%</td> <td>0.035</td> </tr> <tr> <td>Proportion of patients achieving</td> <td>65%</td> <td>41%</td> <td>0.03</td> </tr> </tbody> </table>		BIAsp	Glargine	p	Reduction in mean HbA1c	-2.89 ± 1.6%	-2.46 ± 1.6%	0.035	Endpoint mean HbA1c	7.0 ± 1.3%	7.4 ± 1.3%	0.035	Proportion of patients achieving	65%	41%	0.03
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Roskamp R. Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in Type 2 diabetic patients. Diabetic Medicine 2003; 20(7):545-551. Ref ID: 1126	RCT (29 European study centres) 1++	N=204 patients with Type 2 diabetes in whom oral medication was inadequate.	Inclusion criteria: All patients were 40 to 80 years of age and had an HbAc1 level of 7% or greater and a BMI of 21 to 35kg/m2. None of the patients had received prior insulin. Across the 3 study groups the percentage of men ranged from 57 to 64%. Mean age was about 60 years. Mean fasting plasma glucose ranged from 11.7 to 12.4 mmol/l. Mean HbA1c ranged from 9.5 to 9.7%.	N=64 Insulin glargine once daily with 30 ug/ml zinc content. N=72 Insulin glargine once daily with 80 ug/ml zinc content.	N=68 NPH insulin once daily Patients in all groups continued to take their existing oral medication. During the initial 3 week titration phase, basal insulin doses were adjusted to achieve FBG values between 4 and 7 mmol/l the dose was increased if higher values were obtained in the absence of nocturnal hypoglycaemia. Dose increases were at least 10% of the total daily basal insulin dose and were not	4 weeks	Changes in FPG. Insulin dose Adverse events. Hypoglycaemia episodes defined as either symptomatic or asymptomatic in the context of a glucose level below 2.8 mmol/l.	NS differences in adverse events. No significant differences in values of adjusted mean FPG at study endpoint were found in the comparison between the two formulations of insulin glargine (9.00 vs. 8.68 mmol/l) or the pooled insulin glargine group and the NPH insulin group (8.74 vs. 8.62 mmol/l). However, within each group there were clinically and statistically significant decreases in FPG. Significant decreases in values within each group but with no differences between treatments were observed for mean FBG and HbA1c. 52 patients each had at least one episode of hypoglycaemia (25.5%). This was not significantly different between the groups (18.8% of insulin glargine (30) patients, 25% of insulin glargine (80) patients and 32.4% of NPH insulin patients). No cases of severe hypoglycaemia were reported and no episode was characterised as a serious adverse event. For comparisons all the glargine data was combined and compared with the NPH data. No significant difference was found between the glargine and NPH groups in terms of symptomatic (19.9% vs 29.4%) and asymptomatic (2.9% vs 7.4%) daytime hypoglycaemia. Significant differences were found between the groups in terms of symptomatic (7.3% vs 19.1% p=0.0123) and asymptomatic (0% vs 5.9% p=0.0116) nocturnal hypoglycaemic episodes.	Sponsored by Aventis Pharma
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					implemented more frequently than every 2 days. The basal insulin dose was reduced if FBG was <4 mmol/l and/or nocturnal hypoglycaemia occurred.			There were comparable increases in insulin dose in each group during the study. Median insulin dose by U/kg body weight increased from 0.11 to 0.17 U/kg in the insulin glargine (30) group, from 0.13 to 0.17 U/kg in the insulin glargine (80) group and from 0.11 to 0.15 U/kg in the NPH insulin group. Mean body weight increased by 0.31kg in the insulin glargine (30) group, by 0.64kg in the insulin glargie (80) group and by 0.68 in the NPH insulin group. Adverse events considered possibly related to study treatment occurred in 3 of the insulin glargine (30) patients (4.7%) 3 insulin glargine (80) patients (4.2%) and 2 NPH insulin patients (2.9%). One patient in each group experienced an injection site reaction.																						
Standl E, Maxeiner S, Raptis S. Once daily Insulin glargine administration in the morning compared to bedtime in combination with morning glimepiride in patients with Type 2 Diabetes: an assessment of treatment flexibility. Horm Metab Res 2006; 38: 172-177 Ref ID: 820	RCT 1+ Multinational, multicentre, controlled, open label study Non-inferiority study (equivalence region 10%)	N=624 Drop out rate 7%	Inclusion criteria: Age 18-80 years, T2D diagnosed at least 3 years prior to study entry, on AODs for ≥6 months (doses equivalent to glimepiride 2,3, or 4 mg), poor control (HbA1c ≥7.5% and ≤10.5%; FBG ≥6.7 mmol/l and BMI ≤35 kg/m ²) Exclusion criteria: No insulin treatment allowed 4 weeks prior to the study Baseline characteristics: there were no	Morning glargine (6-9am) + Glimepiride (6-9am) All previous OAD treatment stopped, glargine dose titrated according to a predefined schedule to target FBG levels of ≤ 5.5 mmol/l.	Evening glargine (9-11pm) + Glimepiride (6-9am) All previous OAD treatment stopped, glargine dose titrated according to a predefined schedule to target FBG levels of ≤ 5.5 mmol/l.	28 weeks 4 week screening period 24 week treatment period	Primary endpoint: Nocturnal hypoglycaemia ⁴ Secondary endpoints: Frequency of overall, symptomatic and severe Baseline to endpoint reductions in HbA1c, mean change in daily blood glucose	<table border="1"> <tr> <td></td> <td>Morning glargine</td> <td>Bedtime glargine</td> <td></td> </tr> <tr> <td>Nocturnal hypoglycaemia incidence</td> <td>13.0%</td> <td>14.9%</td> <td></td> </tr> <tr> <td>Between treatment difference</td> <td colspan="3">-1.9% (One-sided 95% CI -100%; 2.84%)</td> </tr> <tr> <td>Hypoglycaemia episodes per patient</td> <td>0.46 ± 1.99</td> <td>0.43 ± 1.58</td> <td></td> </tr> </table> <p>These are the results of the per-protocol analysis, the full analysis set yielded similar results.</p> <p>Secondary outcomes</p> <table border="1"> <tr> <td></td> <td>Morning glargine</td> <td>Bedtime glargine</td> <td>p</td> <td></td> </tr> </table>		Morning glargine	Bedtime glargine		Nocturnal hypoglycaemia incidence	13.0%	14.9%		Between treatment difference	-1.9% (One-sided 95% CI -100%; 2.84%)			Hypoglycaemia episodes per patient	0.46 ± 1.99	0.43 ± 1.58			Morning glargine	Bedtime glargine	p		Aventis pharma (company of Sanofi-Aventis)
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			<p>significant differences between treatment groups for sex, age, BMI, duration of diabetes, age at onset of diabetes, duration of oral therapy (results were controlled for country/region)</p> <p>Assessment of bias: open-label study, dose of glimepiride at physicians discretion prior to randomisation, ITT analysis</p>				(BG) and fasting blood glucose (FBG), response rates of HbA1c and FBG.	Overall hypoglycaemia (%)	43.1	38.4	0.24	
								Severe hypoglycaemia (%)	1.3	0.7	0.49	
								Symptomatic hypoglycaemia (%)	42.8	38.1	0.24	
								Mean HbA1c change %	-1.65 ± 1.21	-1.57 ± 1.16	0.42	
								Proportion of patients with HbA1c < 7 %	48%	47%	0.66	
								Mean change in FBG (mmol/l)	-4.25 ± 2.82	-4.48 ± 2.75	0.08	
								Mean change in nocturnal BG (mmol/l)	-3.81 ± 3.25	-3.89 ± 3.15	0.52	
								Change in mean daily BG (mmol/l)	-4.08 ± 3.14	-3.80 ± 3.03	0.13	
								Mean daily insulin dose (IU)	34.7 ± 17.4	32.4 ± 17.0	0.15	
								Mean body	2.1	1.8	0.39	

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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	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	N=61 Bedtime insulin glargine with metformin (G+MET). The goal was to	N=49 Bedtime NPH with metformin (NPH+MET).	36 weeks	Change in HbA1c, diurnal glucose concentrations, symptomatic hypoglycaemia	<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) and insulin doses were 68 ± 5 and 70 ± 6 IU/day respectively (NS).. At 36 weeks there was no significant difference between mean HbA1c in the</p>	Grants from the Academy of Finland and from Aventis.														

2006; 49(3):442-451. Ref ID: 3			<p>greater than or equal to 8% and a mean fasting plasma glucose (FPG) concentration of greater than 7 mmol/l.</p> <p>Exclusion criteria: Use of other oral anihyperglycaemic agents, prior insulin use and non-compliance with daily measurement of FPG.</p> <p>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>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 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>a, body weight and insulin dose. Patients monitored glucose values when they thought they experienced symptoms of hypoglycaemia. Biochemical hypoglycaemia was defined as a plasma glucose equal to or more than 4mmol/l. Severe hypoglycaemia was an event with symptoms consistent with hypoglycaemia during which the patient required the assistance of another person and which were associated</p>	<p>G+MET group (7.14 ± 0.2%) and the NPH+MET group (7.16 ± 0.14%). Symptomatic, but not confirmed symptomatic hypoglycaemia was significantly lower during the first 12 weeks in the G+MET group (4.1 ± 0.8 episodes/patient year) than in the NPH+MET group (9.0 ± 2.3 episodes/patient year, p<0.05) but not significantly different thereafter. The frequency of confirmed symptomatic hypoglycaemia during the first 12 weeks was 2.4 vs 5.6 episodes per patient which was not significantly different. 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). Of the confirmed symptomatic hypoglycaemia, 98% and 93% in the G+MET and NPH+MET groups were nocturnal. There were no differences in biochemical hypoglycaemia and there were no episodes of severe hypoglycaemia. Glucose levels before dinner were higher in the NPH+MET group (10.1 ± 0.3 mmol/l) than in the G+MET group (8.6 ± 0.3 mmol/l, p=0.002) throughout the 36 week study. 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) 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</p>	
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							with either a plasma glucose level of <3.1mmol/l or with prompt recovery after oral carbohydrate.	and musculoskeletal and gastrointestinal disorders with no differences between the groups.																								
Yokoyama H, Tada J, Kamikawa F, Kanno S, Yokota Y, Kuramitsu M. Efficacy of conversion from bedtime NPH insulin to morning insulin glargine in type 2 diabetic patients on basal-prandial insulin therapy. Diabetes Research & Clinical Practice 2006; 73(1):35-40. Ref ID: 4880	RCT 1-	N=62 Methods of randomisation not stated, nor is loss to follow up, allocation concealment or ITT analysis. Blinding of clinicians was not possible due to the treatments used.	Inclusion criteria: T2D of >2 years, age > 35 years, negative anti-GAD antibody test, no episodes of ketoacidosis, BMI ≤ 40kg/m ² , HbA1c ≤ 10%, previous poor glycaemic control (HbA1c ≥ 8%) despite optimal sulphonylureas, diet and exercise therapy, >1 year on basal prandial insulin therapy with aspart/lispro and NPH at bedtime with or without anti-diabetic oral agents. Exclusion criteria: Impaired hepatic, renal or cardiac function, major hypoglycaemia. No differences between groups were found at baseline.	Insulin glargine in the morning while continuing aspart/lispro at each meal. Glargine dose increased to meet target FBG 6-7.8 mmol/l; mealtime insulin reduced to maintain total daily dose of insulin unchanged. 3-month run-in period during which previous	NPH insulin at bedtime while continuing aspart/lispro at each meal. 3-month run-in period during which previous insulin therapy was continued.	3 month run-in period 6 months treatment period	HbA1c	Glycaemic control <table border="1"><thead><tr><th></th><th>Glargine</th><th>NPH</th><th>p</th></tr></thead><tbody><tr><td>Mean HbA1c at 6 months *</td><td>6.6 %</td><td>7.0 %</td><td>0.007</td></tr><tr><td>FPG at 6 months</td><td>6.3 ± 1.1 mmol/l</td><td>7.6 ± 0.7 mmol/l</td><td><0.01</td></tr><tr><td>Total insulin dose</td><td>42 ± 18 IU/day</td><td>38 ± 16 IU/day</td><td>NS</td></tr><tr><td>Post-prandial glucose</td><td>8.1 ± 3.0 mmol/l</td><td>8.6 ± 2.7 mmol/l</td><td>NS</td></tr></tbody></table> Body weight <table border="1"><thead><tr><th>BMI kg/m²</th><th>26.4 ± 5.0</th><th>25.6 ± 3.2</th><th>NS</th></tr></thead></table> *Similar decline in HbA1c seen even when baseline HbA1c adjusted for. Hypoglycaemic events No episodes of severe hypoglycaemia		Glargine	NPH	p	Mean HbA1c at 6 months *	6.6 %	7.0 %	0.007	FPG at 6 months	6.3 ± 1.1 mmol/l	7.6 ± 0.7 mmol/l	<0.01	Total insulin dose	42 ± 18 IU/day	38 ± 16 IU/day	NS	Post-prandial glucose	8.1 ± 3.0 mmol/l	8.6 ± 2.7 mmol/l	NS	BMI kg/m ²	26.4 ± 5.0	25.6 ± 3.2	NS
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