

Evidence Tables

INS 2 Are the biphasic insulin preparations (pre-mixes) effective in the control of blood glucose compared to NPH in people with type 2 diabetes?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding																																
<p>Ceriello A, Del Prato S, Bue-Valleskey J, Beattie S, Gates J, De la Pena A, Malone J. Premeal insulin lispro plus bedtime NPH or twice-daily NPH in patients with type 2 diabetes: acute postprandial and chronic effects on glycaemic control and cardiovascular risk factors. <i>Journal of Diabetes and its Complications</i> 2007; 21: 20-27</p> <p>Ref ID: 4870</p>	<p>RCT 1+</p> <p>Open-label, multicentre cross over trial conducted at 4 clinical centres in Italy</p>	<p>N=30</p> <p>Loss to follow up 5/30</p>	<p>Inclusion criteria: T2D, inadequate glycaemic control (HbA1c =7-9.5%), treatment with other OADs (except thiazolidinediones) or insulin for at least 30 days before the study.</p> <p>Exclusion criteria: BMI > 35 kg/m², TG >400 mg/dl, >1 episode of severe hypoglycaemia within 6 months prior to study entry, pregnant or breastfeeding women, use of systemic glucocorticoids for >2 weeks, history of drug or alcohol</p>	<p>8-week lead in period; all OADs discontinued, patients on twice daily NPH.</p> <p>12 weeks insulin lispro three times daily before each meal + NPH at bedtime</p> <p>12 weeks of twice daily NPH</p>	<p>8-week lead in period</p> <p>12 weeks of twice daily NPH</p> <p>12 weeks insulin lispro three times daily before each meal + NPH at bedtime</p>	24 weeks	<p>Glycaemic control: HbA1c, PPGE, fasting blood glucose, serial blood and insulin samples after a standard test meal.</p> <p>Lipid control: FFA, lipid profile</p> <p>Inflammatory markers: factor VII, prothrombin fragments 1 and 2, C-reactive protein, nitrotyrosine, D-glucitol</p>	<p>Acute post prandial effects observed during the test meal studies: Insulin lispro arm had a lower and earlier peak mean SG concentration, with a faster return to mean baseline glucose levels. Post prandial glucose excursion (PPGE) was significantly lower in the lispro arm.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th>Lispro + NPH</th> <th>Twice daily NPH</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>PPGE (AUC mM/h)</td> <td>43.5</td> <td>57.6</td> <td><0.001</td> </tr> </tbody> </table> <p>There were significant differences in some lipid measures between the groups at the start of the test meal.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th>Lispro + NPH</th> <th>Twice daily NPH</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>Cholesterol (mM)</td> <td>5.26 ± 0.16</td> <td>5.58 ± 0.16</td> <td>0.053</td> </tr> <tr> <td>LDL-C (mM)</td> <td>3.30 ± 0.15</td> <td>3.64 ± 0.16</td> <td>0.035</td> </tr> <tr> <td>LDL-C/HDL-C</td> <td>2.73 ± 0.15</td> <td>3.05 ± 0.16</td> <td>0.024</td> </tr> </tbody> </table> <p>At 5-hrs after the test meal, LDL-C and HDL-C was significantly higher in the lispro/NPH arm than the NPH arm.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th>Lispro + NPH</th> <th>Twice daily NPH</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>LDL-C</td> <td>3.12 ±</td> <td>2.88 ±</td> <td>0.012</td> </tr> </tbody> </table>		Lispro + NPH	Twice daily NPH	p	PPGE (AUC mM/h)	43.5	57.6	<0.001		Lispro + NPH	Twice daily NPH	p	Cholesterol (mM)	5.26 ± 0.16	5.58 ± 0.16	0.053	LDL-C (mM)	3.30 ± 0.15	3.64 ± 0.16	0.035	LDL-C/HDL-C	2.73 ± 0.15	3.05 ± 0.16	0.024		Lispro + NPH	Twice daily NPH	p	LDL-C	3.12 ±	2.88 ±	0.012	Eli-Lilly and company
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abuse, any other severe disease.

Baseline characteristics:
 Mean age 60.7 ± 7.9 years
 Sex 40% female
 Origin 100% Caucasian
 Body weight 75.4 ± 10.4 kg
 BMI 27.1 ± 3.1 kg/m²
 HbA1c 8.37 ± 0.94%

(mM)	0.08	0.09	
HDL-C (mM)	1.15 ± 0.02	1.07 ± 0.02	0.004

No significant difference was shown during postprandial period for nitrotyrosine, factor VII, C-reactive protein, D-glucitol, chylomicron remnants. Prothrombin fragments 1 and 2 were not analysed due to technical difficulties.

Chronic effects observed after 12 weeks of treatment:

	Lispro + NPH	Twice daily NPH	p
HbA1c %	7.63 ± 0.15	8.24 ± 0.22	<0.001
Total daily insulin dose (U/kg)	0.45 ± 0.06	0.53 ± 0.07	0.052
Mean 2-hr PPBG (mM)	9.18 ± 0.37	11.36 ± 0.38	<0.001
Cholesterol (mM)	5.49 ± 0.17	5.76 ± 0.17	0.049
LDL-C (mM)	3.47 ± 0.16	3.70 ± 0.16	0.053
Oxidised LDL (U/l)	77.5 ± 6.0	88.0 ± 6.1	0.043

There was no significant treatment difference for weight, HDL, TG, FFA, factor VII activity and nitrotyrosine.

Safety:
 There was no significant difference between regimens for either overall or nocturnal hypoglycaemia.

<p>Christiansen J.S et al. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. <i>Diabetes, Obesity and Metabolism</i>, 5, 2003, 446-454 ID 3179</p>	<p>RCT multinational parallel-group, double-blind trial.</p> <p>Evidence grading 1+</p>	<p>403 patients from thirty-four trials in nine countries.</p>	<p>Inclusion criteria: men and women aged ≥ 18 years with T2D, HbA1c $\leq 11.0\%$ and BMI $\leq 35\text{kg/m}^2$. Patients taking insulin were included only if their daily dose was <1.8 IU/kg. Participants represented a typical cross-section of people with T2D, including insulin naïve and those receiving OHA therapy and/or once or twice daily NPH insulin monotherapy.</p> <p>The groups were well balanced with respect to demographic, metabolic characteristics and previous treatment.</p> <p><u>Insulin aspart:</u></p>	<p>Insulin aspart 30¹ (BIAsp30®) n=201</p>	<p>NPH Insulin n=202</p>	<p>16 weeks</p>	<p>HbA1c self-recorded daily blood glucose FBG PPBG Insulin dose adverse events</p>	<p>*HbA1c HbA1c concentration decreased linearly and statistically significantly in both treatment groups (reductions of 0.67% and 0.61% in aspart30 and NPH groups respectively; $p < 0.0001$ vs. baseline)</p> <p>Pre-trial therapy was a highly significant predictor of HbA1c at 16 weeks ($p = 0.002$), the most marked reductions in HbA1c were observed in patients previously taking NPH insulin monotherapy and in those who were insulin naïve.</p> <p>*Daily blood glucose Mean daily BG concentration decreased significantly in both groups between baseline (11.2 and 11.3 mmol/l in aspart30 and NPH insulin groups, respectively) and study completion (9.4 mmol/l in both groups; $p < 0.0001$ vs. baseline), as did BG range (reductions of -1.55 and -1.57 mmol/l from baseline in aspart30 and NPH groups respectively, both with no significant difference between treatments.</p> <p>*FBG FBG levels decreased by similar amounts in both groups (1.4 and 1.5 mmol/l in aspart30 and NPH groups, respectively), but final values were 0.95 mmol/l higher in the aspart30 group ($p < 0.0001$)</p> <p>*PPBG PPBG control improved in both groups during the 16-week treatment phase. Post-breakfast values decreased by -2.3 and -2.2 mmol/l in the aspart30 and NPH groups, respectively; post-lunch values by -1.9 and -2.1 mmol/l, respectively and post-dinner values by -2.3 and -2.1 mmol/l, respectively.</p>	<p>Novo Nordisk</p>
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¹ The starting dose in previously insulin naïve patients was 8-16U/day, at the discretion of the attending physician; patients taking NPH insulin before the study commenced on a dose that reflected their pre-trial requirement
All OHA therapies were discontinued at randomization

² Three subjects were withdrawn due to AE; the only event related to medication was one case of protamine allergy in the NPH group.

			<p>BMI 28.0± 3.7, duration of diabetes (years) 10.5± 6.8, baseline HbA1c 8.8± 1.3</p> <p><u>NPH:</u> BMI 28.4± 3.7, duration of diabetes (years) 10.5± 6.8, baseline HbA1c 8.8± 1.2</p>				<p>Mean prandial glucose increment over the three main meals was significantly lower in the aspart30 group (0.69 mmol/l lower; p< 0.0001, between groups)</p> <p>* Insulin dose Mean daily insulin dose increased in both groups throughout the treatment period, without stabilizing at completion of the study. A greater mean dose increase was required in the aspart30 group (0.23 IU/kg) than the NPH group (0.15 IU/kg; p=0.004)</p> <p>*Adverse Events Hypoglycaemia Less than 2% of patients in either group experienced a major hypoglycaemic event. Minor hypoglycaemic were numerically more frequent in the aspart30 group (341 events in 77 patients vs. 285 events in 68 patients, respectively), but the relative risk was not statistically significant different between treatments (RR= 1.21 [95% CI: 0.77 to 1.90]; p= 0.40)</p> <p>Other AE A similar number of AE occurred in both groups (141 events in 72 patients in the aspart30 group vs. 141 events in 76 patients in the NPH insulin group), most of which were mild or moderate in severity and considered unrelated to the study medications.²</p> <p>Less than 5% of patients in either group experienced serious adverse events, although a slightly greater number were observed in the NPH group (8 events in 7 patients); all were considered unrelated to the study medication. There was no clinically relevant alteration in biochemical or haematological parameters.</p>	
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<p>Kilo C. et al. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. Journal of Diabetes and its complications 17 (2003) 307-313 ID 31</p>	<p>RCT open label Evidence grading 1+</p>	<p>140 patients from 25 centres in the US</p>	<p>Inclusion criteria: men or women, ≥ 18 years, with T2D and a body weight ≤ 100kg and BMI ≤ 40kg/m². The patients were naïve to insulin treatment and had inadequate glycemic control (HbA1c ≥ 7.5%) on a regimen of ≥ 3 months of metformin as monotherapy or in combination with a sulphonylurea or repaglinide.</p> <p>The three treatment groups were similar with regard to demographic and baseline characteristics</p>	<p>Insulin aspart³(NovoLog Mix 70/30) + Metformin (N=46)</p>	<p>NPH insulin (Novolin N) + Metformin (N=47)</p> <p>Biphasic human insulin (Novolin 70/30) + Metformin (N=47)</p>	<p>12 weeks⁴</p>	<p>HbA1c FPG SMBG assessments Insulin dose Body weight Safety</p>	<p>The patients entered the study in poor glycemic control, with average HbA1c values or approx 9.5% and FPG values of more than 200mg/dl. Each of the insulin combinations regimes was effective in providing improved glycemic control.</p> <p>*HbA1c HbA1c levels decreased over the 12-week treatment period by 1.3% in the biphasic aspart group, by 1.2% in the NPH insulin group, and by 1.1% for patients in the biphasic human insulin group. <u>NS</u> difference among the treatment groups.</p> <p>*FPG FPG values decreased (mean ± SD) from baseline to the end of the study by 31% for the biphasic aspart group (-75 ± 72.3 mg/dl), by 37% (-91± 72.0 mg/dl) for the NPH group, and by 28% (-63± 86.2 mg/dl) for the biphasic human insulin group. <u>NS</u> difference among the treatment groups.</p> <p>*SMBG assessments Improved glycemic control was also observed in the results of the SMBG assessments. Mean values for the 8-point SMBG profile at week 12 were decreased from baseline values by approx 50mg/dl at each of the assessment times.</p> <p>Although there were no overall significant differences between the treatment groups, SMBG values for before breakfast and before lunch values tended to be lower for the NPH insulin group, while after dinner and 10pm, values tended to be higher for</p>	<p>Novo Nordisk</p>
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³ The starting insulin dose was 0.16 U/kg for each insulin formulation. During the first 4 weeks of treatment, the insulin dosage was adjusted by 2-6 U to achieve FBG levels of 90-126 mg/dl. The dose adjustments were based on twice-weekly self-monitored blood glucose (SMBG) assessments. After the dose-adjustment period, the insulin dosage was maintained for the remaining 8 weeks of the study.

⁴ It was preceded by a 4-week run-in period in which patients were treated with 500 to 2550 mg/day of metformin divided into one to three doses. The dose was adjusted during the first 3 weeks of the run-in to achieve and maintain target FBG levels of 90-126 mg/dl, or the maximally tolerated dose, or a maximum daily dose of 2550 mg. The patient's metformin dose was not changed after the fourth week of the run-in period, unless a dose reduction was necessary for clinical reasons. At the end of the run-in period, patients who were not able to achieve the FBG target of 90-126 mg/dl on metformin only were randomized to one of the three insulin treatment regimes.

							<p>the NPH insulin group as compared to the biphasic insulin aspart and biphasic human insulin groups.</p> <p>*Insulin dose Insulin dose (mean \pm SD) was titrated from an initial daily dose of approximately 12 U/day for each group to 26 ± 13.6 U/day for the biphasic aspart group, 28 ± 15.8 U/day for the NPH insulin group, and 29 ± 16.2 U/day for the biphasic human insulin group.</p> <p>*Metformin dose The average daily metformin dose for each group was approximately 2200 mg.</p> <p>*Body weight Subjects treated with biphasic insulin aspart or biphasic human insulin gained slightly more weight (an average of 0.7 and 1.0 kg, respectively) than did patients who were treated with NPH insulin (average gain of 0.1 kg) (between treatment p value= 0.25)</p> <p>*Adverse Events A total of 203 AE were reported for 87 (62%) patients during the insulin treatment period. Upper respiratory track infection was the most commonly reported event (21 patients). The number and type of AE were similar for each of the treatment groups.</p> <p>Minor symptoms of hypoglycaemia were reported by slightly more patients in the biphasic insulin aspart group as compared to the NPH insulin and biphasic human insulin groups.</p> <p>No major hypoglycaemic events were reported. Nocturnal hypoglycaemia (midnight – 6am) was less frequently reported for patients receiving biphasic insulin aspart (7 patients) as compared to patients in the NPH insulin and biphasic human insulin groups (11 patients in each</p>	
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								group)		
								Total Drop-out	N 9	% (6.4)
								* Aspart 70/30	4	(2.9)
								-AE	2	
								- no compliance	2	
								* NPH insulin	4	(2.9)
								- no compliance/other	4	
								* Human insulin	1	(0.7)
								- ineffective therapy	1	