

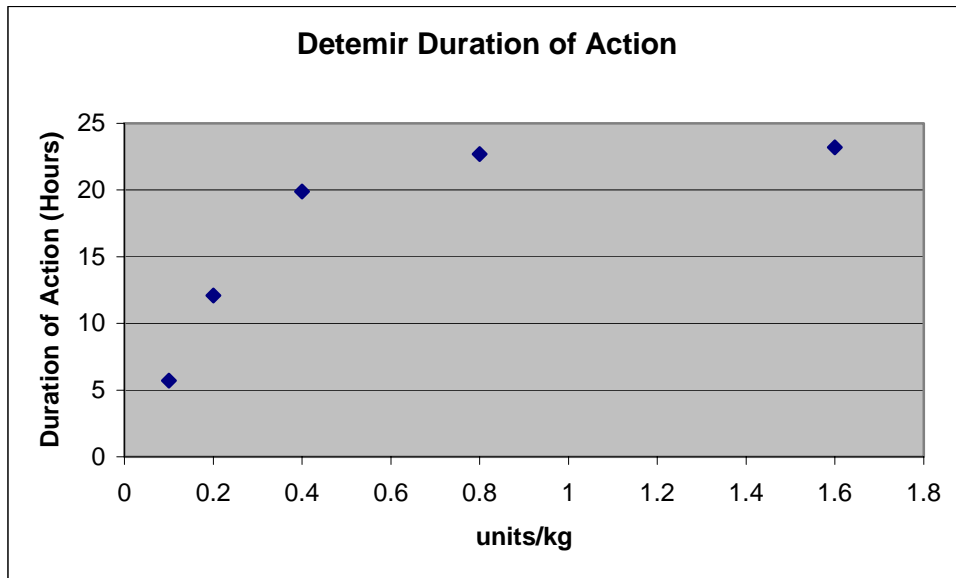
Bon Secours Richmond
Pharmacy and Therapeutics Committee
Levemir® (detemir)
5/2006

Detemir is being marketed as a long acting insulin for once or twice-daily administration, with more predictable absorption than NPH and glargine, and less hypoglycemia.

Recommendations:

- Detemir is not recommended for formulary inclusion at this time as:
 - Package insert studies demonstrated similar outcomes (HbA_{1c}, fasting plasma glucose reductions, and hypoglycemia) for detemir, NPH and glargine (see graphics below).
 - The package insert rates for hypoglycemia are not lower with detemir. The event rate for all studies included in the package insert are: minor events/subject/month 1.76 detemir, 1.72 NPH; major events/subject/month 0.03115 detemir, 0.025 NPH.
 - Detemir's duration of action is dose dependent, doses less than 0.4 units/kg do not allow for once daily dosing (see graphic below). Determination of the proper once daily dose requires that the patient be started on twice daily dosing with dosage titration to an effective dose. The total daily dose can then be converted to once daily. The dose response curve for once daily dosing is not flat and is not comparable to glargine, which may cause higher rates of hypoglycemia (see graphic below).
 - There is only one published study comparing detemir to glargine [Pieber 2005 Diabetologia 2005;48(suppl1):A92]
 - Most studies have compared detemir twice daily dosing to NPH twice daily, usually in type 1 DM.
 - Detemir is 4.4 times as expensive as NPH insulin
 - Caution: Detemir and glargine are colorless solutions for SC injection only
 - Detemir and glargine should not be mixed with any other insulin
 - Detemir levels are higher and occur earlier when mixed with other insulins
- Patients using detemir at home will be asked to continue their own supply when possible
- More predictable absorption may make detemir an option for patients requiring intensive self-monitoring of blood glucose and multiple daily injections who have demonstrated erratic blood glucose levels on stable insulin therapy.

Cost Comparison for Levemir® , Lantus®, NPH			
	Levemir®	Lantus®	NPH
Concentration	100 U/ml	100 U/ml	100 U/ml
Vial size	10 ml	10 ml	10 ml
Cost per vial	\$48.79	\$59.91	\$10.98



Plank J, Diabetes Care 2005;28(5):1107-1112

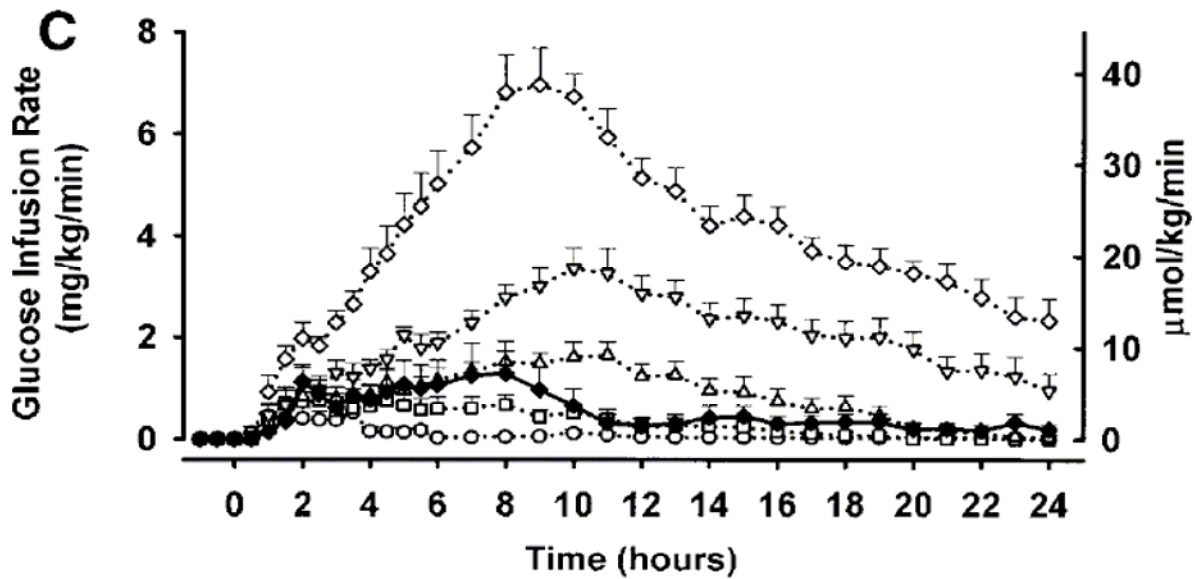


Figure 1—Time profiles for intravenous insulin infusion rates (A), plasma glucose levels (B), and GIRs (C) for after subcutaneous injection of NPH insulin (0.3 IU/kg) and insulin detemir (ID; 0.1, 0.2, 0.4, 0.8, and 1.6 units/kg) in 12 patients with type 1 diabetes. Data are means \pm SE.

Plank J, Diabetes Care 2005;28(5):1107-1112

Table 1: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus - Adult

	<u>Study A</u>	
	16 weeks	
Treatment duration	NovoLog® (insulin aspart)	
Treatment in combination with	<u>LEVEMIR</u>	<u>NPH</u>
Number of subjects treated	276	133
HbA_{1c} (%)		
Baseline	8.64	8.51
End of study adjusted mean	7.76	7.94
Mean change from baseline	-0.82	-0.60
Fasting Plasma Glucose (mg/dL)		
End of study adjusted mean	168	202
Mean change from baseline	-42.48	-10.80
Daily Basal Insulin Dose (U/kg)		
Prestudy mean	0.36	0.39
End of study mean	0.49	0.45
Daily Bolus Insulin Dose (U/kg)		
Prestudy mean	0.40	0.40
End of study mean	0.38	0.38

Baseline values were included as covariates in an ANCOVA analysis.

Table 2: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus - Pediatric

	<u>Study D</u>	
	26 weeks	
Treatment duration	NovoLog® (insulin aspart)	
Treatment in combination with	<u>LEVEMIR</u>	<u>NPH</u>
Number of subjects treated	232	115
HbA_{1c} (%)		
Baseline	8.75	8.77
End of study adjusted mean	8.02	7.93
Mean change from baseline	-0.72	-0.80
Fasting Plasma Glucose (mg/dL)		
End of study adjusted mean	151.92	172.44
Mean change from baseline	-45.00	-19.98
Daily Basal Insulin Dose (U/kg)		
Prestudy mean	0.48	0.49
End of study mean	0.67	0.64
Daily Bolus Insulin Dose (U/kg)		
Prestudy mean	0.52	0.47
End of study mean	0.52	0.51

Table 3: Efficacy and Insulin Dosage in Type 2 Diabetes Mellitus

Treatment duration Treatment in combination with	Study E	
	24 weeks	
	OAD	
	<u>LEVEMIR</u>	<u>NPH</u>
Number of subjects treated	237	239
HbA_{1c} (%)		
Baseline	8.61	8.51
End of study adjusted mean	6.58	6.46
Mean change from baseline	-1.84	-1.90
Proportion achieving HbA _{1c} ≤ 7%	70%	74%
Fasting Plasma Glucose (mg/dL)		
End of study adjusted mean	119.16	113.40
Mean change from baseline	-75.96	-74.34
Daily Insulin Dose (U/kg)		
End of study mean	0.77	0.52

In a 22-week, non-blinded, randomized, clinical study (Study F, n=395) in adults with Type 2 diabetes, LEVEMIR and NPH human insulin were given once- or twice-daily as part of a basal-bolus regimen. As measured by HbA_{1c} or FPG, LEVEMIR had efficacy similar to NPH human insulin.

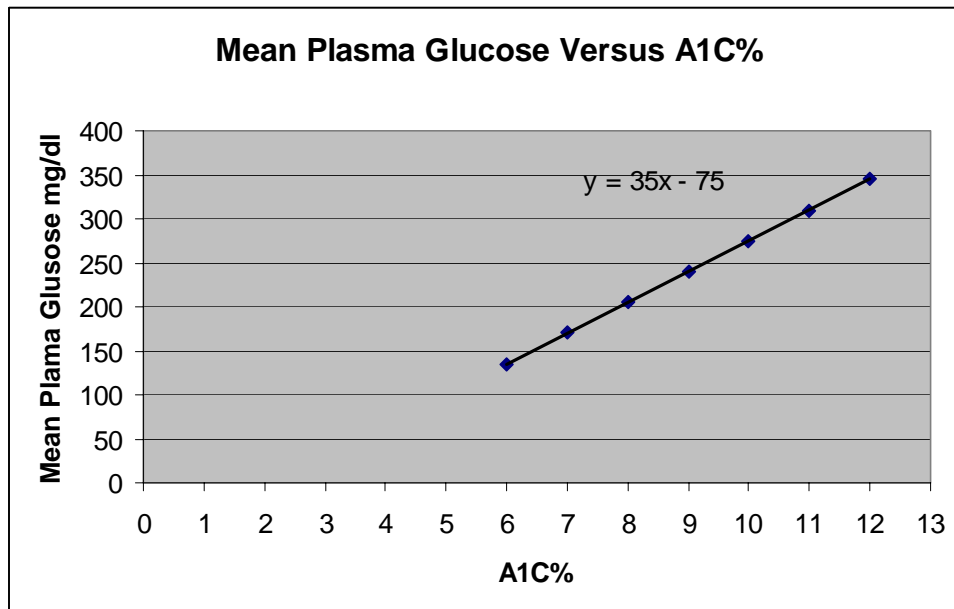
Table 4: Safety Information on Clinical Studies*

Treatment	# of subjects	Weight (kg)		Hypoglycemia (events/subject/month)	
		Baseline	End of treatment	Major**	Minor***
Type 1					
<u>Study A</u>					
LEVEMIR	N=276	75.0	75.1	0.045	2.184
NPH	N=133	75.7	76.4	0.035	3.063
<u>Study C</u>					
LEVEMIR	N=492	76.5	76.3	0.029	2.397
NPH	N=257	76.1	76.5	0.027	2.564
<u>Study D Pediatric</u>					
LEVEMIR	N=232	N/A	N/A	0.076	2.677
NPH	N=115	N/A	N/A	0.083	3.203
Type 2					
<u>Study E</u>					
LEVEMIR	N=237	82.7	83.7	0.001	0.306
NPH	N=239	82.4	85.2	0.006	0.595
<u>Study F</u>					
LEVEMIR	N=195	81.8	82.3	0.003	0.193
NPH	N=200	79.6	80.9	0.006	0.235

* See CLINICAL STUDIES section for description of individual studies

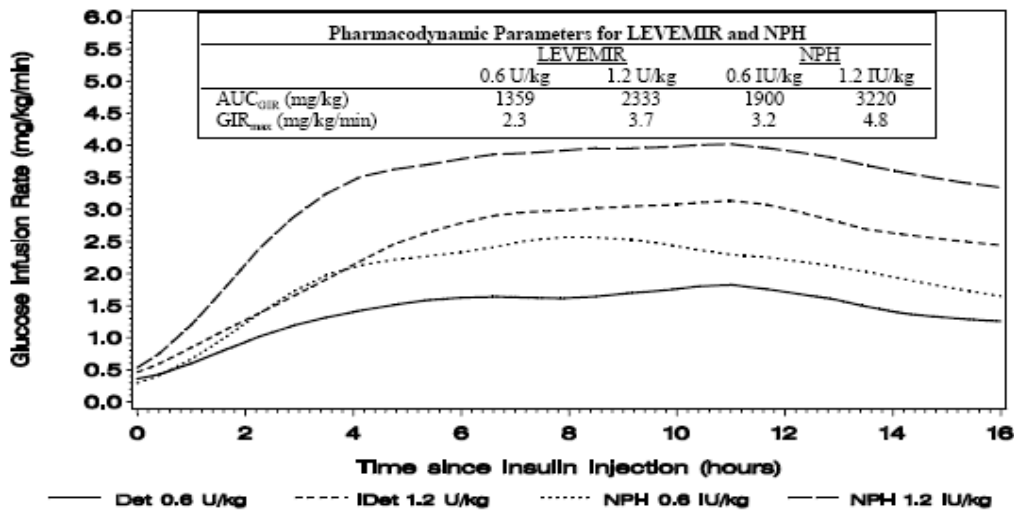
** Major = requires assistance of another individual because of neurologic impairment

*** Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself



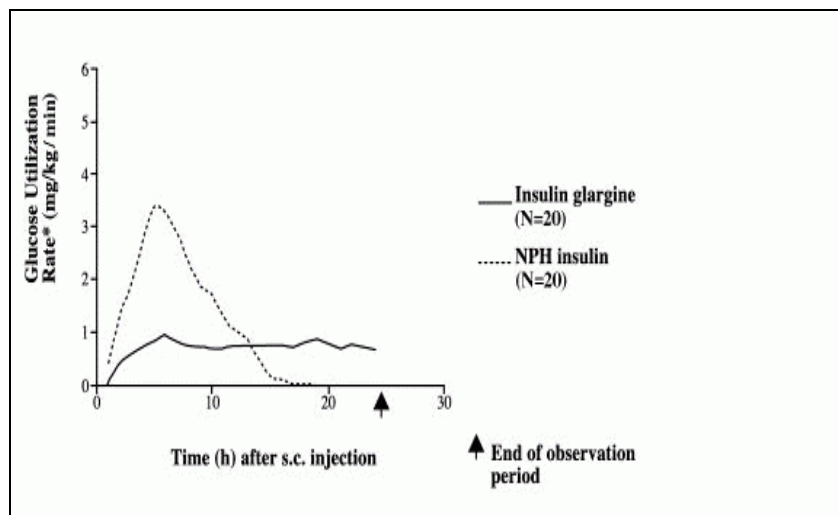
	Levemir® (detemir)	NPH	Lantus® (glargine)
Description	Produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of <i>Saccharomyce cerevisiae</i> . Long acting basal insulin analog, which has a C14 fatty acid chain attached to the B29 position, which induces albumin binding. MW 5916,	Produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of <i>Saccharomyce cerevisiae</i> .	Produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of <i>Escherichia coli</i> (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. MW 6063
Mechanism of action	Regulates glucose metabolism, through it's ability to bind to insulin receptors. Extended duration of action due to molecule self association and albumin binding	Insulin is a naturally occurring hormone secreted by the pancreas. Insulin is required by the cells of the body in order for them to remove and use glucose from the blood.	Regulates glucose metabolism and lowers blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production.
Chemistry	Is a clear, colorless, aqueous, neutral sterile solution, pH 7.4	It is a cloudy or milky suspension of human insulin with protamine and zinc.	The solution is clear and colorless with no particles visible, pH 4
Duration of action (hours)	5.7 – 23.2 (Dose dependent)	18 - 24	10.8 - 24
Unit to nmol/l ratio	1 unit = 24 nmol/l	1 unit= 6 nmol/l	1 unit= 6 nmol/l
Potency Ratio (insulin/NPH)	1.48	1	1
Dosage ranges (U/kg)	0.1 – 1.6		0.03 – 1.4
Time to reach Cmax (hours)	6 – 8	4 -12	5
Absorption	Slow due to self-association of the molecules		Microprecipitates form after injection, which are slowly absorbed
Absolute bioavailability	60 %		
Volume of distribution	0.1 L/kg		
Protein Binding	98 % bound to albumin		
Half – life (hours)	5 – 7		
Contraindications	Hypersensitivity to insulin detemir or one of its incipients	Tolerated well by most people	Hypersensitive to insulin glargine or the excipients.
Common adverse reactions	Hypoglycemia, allergic reactions, lipodystrophy, pruitus, rash, injection site reactions, and weight gain	Local reaction, Hypoglycemia	Allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, hypoglycemia
Monitor	HbA _{1c} and glucose testing		
Pregnancy category	C	B	C
Dose	Administer once or twice daily. Doses individualized according to blood glucose measurements. Twice daily dosing should be administered with evening meal, at bedtime, or 12 hours after the morning dose.	Patient based. Based on blood glucose levels	Lantus may be administered at any time during the day. Lantus should be administered subcutaneously once a day at the same time every day.
Precautions	Do not be diluted or mixed with any other insulin preparation. Only for SC injection.	Ok to mix, but always draw up clear before cloudy.	Do not be diluted or mixed with any other insulin preparation. Only for SC injection.

- Levemir® can be administered once or twice daily.
 - Once daily dosing should be administered with the evening meal or at bedtime
 - Twice daily dosing should be administered with evening meal, at bedtime, or 12 hours after the morning dose. Studies indicate that dosing Levemir® in the morning and at bedtime result in better diabetic outcomes.
 - Most detemir studies used twice daily dosing especially when it was compared to Lantus®. Once a day dosing was used in studies comparing detemir to NPH. These studies had results that show no significant difference between detemir and NPH.
- Dose determination for Levemir®:
 - Changing basal insulin to Levemir® can be done on a unit-to-unit basis. In some patients with type 2 diabetes, more Levemir® may be required than NPH insulin. In a clinical study, the mean dose at end of treatment was 0.77 U/kg for Levemir® and 0.52 IU/kg for NPH human insulin.
 - For patients currently receiving only basal insulin, changing the basal insulin to Levemir® can be done on a unit-to-unit basis.
 - For patients not controlled on oral meds, Levemir® should be started at a dose of 0.1 to 0.2 U/kg once daily in the evening or 10 units once to twice daily.



- Levemir® is a subcutaneous injection, which can be administered in the thigh, abdominal wall, or upper arm. Studies have suggested that administering the injection in the abdominal wall or upper arm result in better glycemic control.
- Studies were conducted comparing the consistency of Levemir® pharmacokinetics across 3 different age groups. The data suggested that insulin detemir is associated with a consistent pharmacokinetic profile across children, adolescents, and adults. NPH showed significant differences between children and adults.

- Lantus® is administered at any time during the day, and is given SQ once daily at the same time each day.
 - The average dose is 10 IU once daily, and adjusted according to the patient's need to a total daily dose range from 2 to 100 IU.
- Dose determination for Lantus®:
 - Transferring from once-daily NPH human insulin or ultralente human insulin to once-daily Lantus®, the initial dose is usually not changed.
 - Transferring from twice-daily NPH human insulin to Lantus® once daily, to reduce the risk of hypoglycemia, the initial dose (IU) is usually reduced by approximately 20% (compared to total daily IU of NPH human insulin).



Between-patient variability (CV, coefficient of variation); insulin glargine, 84% and NPH, 78%. Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values); indicative of insulin activity.

Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin.

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AIMS: This trial investigated the efficacy and safety of two different administration-time regimens with insulin detemir (IDet) to that of a conventional basal insulin regimen with NPH insulin (NPH). **METHODS:** This multinational, 16-week, open, parallel group trial included 400 people with Type 1 diabetes mellitus (DM) randomized to IDet either morning and before dinner (IDet_{morn+din}) or morning and bedtime (IDet_{morn+bed}), or to NPH morning and bedtime (NPH_{morn+bed}), all in combination with mealtime insulin aspart (IAsp). **RESULTS:** HbA1c was comparable between the three groups after 16 weeks ($P = 0.64$), with reductions of 0.39-0.49% points. Lower fasting plasma glucose (FPG) was observed with IDet_{morn+din} and IDet_{morn+bed} compared with NPH_{morn+bed} (9.8 and 9.1 vs. 11.1 mmol/l, $P = 0.006$), whereas the IDet groups did not differ ($P = 0.15$). Within-person variation in self-measured FPG was significantly lower for both IDet regimens (sd IDet_{morn+din} 2.5, IDet_{morn+bed} 2.6 mmol/l) than for NPH_{morn+bed} (sd 3.1 mmol/l, $P < 0.001$), but was comparable between the IDet groups ($P = 0.48$). Ten-point plasma glucose profiles were lower between dinner and breakfast in the IDet_{morn+din} group ($P = 0.043$), compared with the two other groups. Risk of overall and nocturnal hypoglycaemia was similar for the three groups. Lower mean bodyweight was observed with IDet compared with NPH after 16 weeks (difference: (IDet_{morn+din})-1.3 kg, $P < 0.001$, (IDet_{morn+bed})-0.6 kg, $P = 0.050$). **CONCLUSIONS:** Both IDet regimens were well tolerated and provided lower and less variable glucose levels with no, or less, weight gain than NPH at comparable HbA1c. IDet can be administered either at dinner or bedtime, with similar glycaemic control according to the need of the individual person.

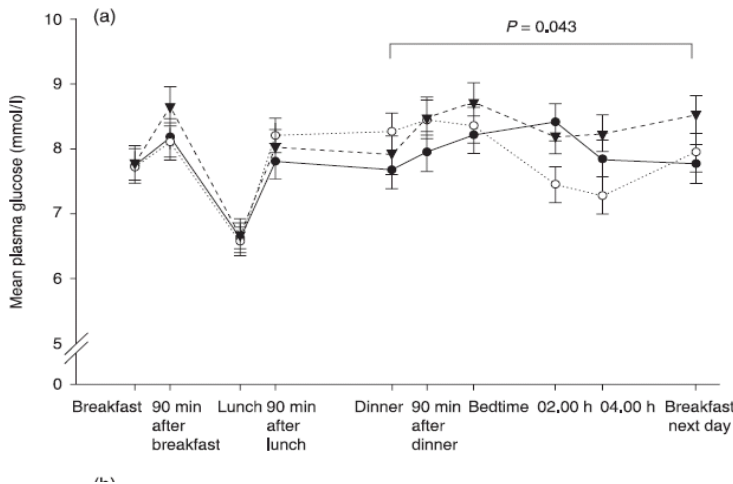


Figure 1 (a) Self-measured mean 10-point plasma glucose profiles after 16 weeks of treatment. Values are means, bars represent se. The overall shape of the glucose profiles differed between the three treatments in the period before dinner and until breakfast the next day as indicated by the P -value of 0.043. IDet_{morn+bed} (●), IDet_{morn+din} (○), NPH_{morn+bed} (▼). (b) Mean 24-h CGMS profiles after 16 weeks of treatment. The plot is based on mean 24-h glucose profiles starting at 23.00 h. The plots have been redrawn starting before breakfast to ease comparison with (a). Because of the impact of meals, insulin administration, etc., interpretation of the profiles during the daytime should be made with caution. IDet_{morn+bed} (—), IDet_{morn+din} (···), NPH_{morn+bed} (- - -).

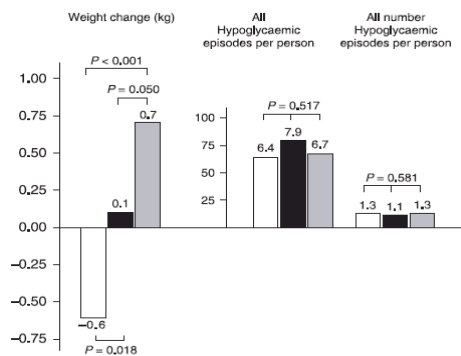


Figure 2 Change in bodyweight and incidence of hypoglycaemia. Change in bodyweight adjusted for baseline and change in HbA_{1c}. P -values represent pair-wise comparisons. Hypoglycaemic episodes: depicted is the number of hypoglycaemic episodes per person during the last 12 weeks of treatment. P -values represent a test of the risk in the three treatment groups. IDet_{morn+din} (□), IDet_{morn+bed} (■), NPH_{morn+bed} (▒).

Table 3 Hypoglycaemic episodes during the last 12 weeks of treatment

Treatment group	IDer _{morn+dn} (139)	IDer _{morn+bed} (132)	NPH _{morn+bed} (129)	P-value*
	Episodes (n)	Episodes (n)	Episodes (n)	
All episodes	876 (100)	1005 (92)	842 (100)	0.52
Nocturnal	184 (60)	142 (51)	167 (60)	0.58
All major episodes	12 (5)	6 (5)	5 (4)	NA
Nocturnal	4 (3)	2 (1)	2 (2)	NA
All minor episodes	420 (88)	458 (78)	411 (89)	0.77
Nocturnal	87 (40)	77 (35)	80 (44)	0.90
All symptoms only	444 (69)	541 (64)	426 (68)	0.54
Nocturnal	93 (31)	63 (31)	85 (37)	0.55

n, Number of persons having at least one hypoglycaemic episode.

NA, not applicable. Because of the low number of major hypoglycaemic episodes it was not possible to obtain a valid estimate for the risk between treatments.

* P-value, overall test for similar risk of hypoglycaemia between the three treatments.

Diabetes Care. 2005 May;28(5):1107-12.

A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir.

Plank J, Bodenlenz M, Sinner F, Magnes C, Gorzer E, Regittnig W, Endahl LA, Draeger E, Zdravkovic M, Pieber TR.

Department of Internal Medicine, Medical University Graz, Auenbruggerplatz 15, A-8036 Graz, Austria.

OBJECTIVE: To investigate the pharmacodynamic profile and duration of action for five subcutaneous doses of insulin detemir (0.1, 0.2, 0.4, 0.8, and 1.6 units/kg; 1 unit = 24 nmol) and one subcutaneous dose of NPH insulin (0.3 IU/kg; 1 IU = 6 nmol). **RESEARCH DESIGN AND METHODS:** This single-center, randomized, double-blind, six-period, crossover study was carried out as a 24-h isoglycemic clamp (7.2 mmol/l) in 12 type 1 diabetic patients. **RESULTS:** Duration of action for insulin detemir was dose dependent and varied from 5.7, to 12.1, to 19.9, to 22.7, to 23.2 h for 0.1, 0.2, 0.4, 0.8, and 1.6 units/kg, respectively. Interpolation of the dose-response relationships for AUC(GIR) (area under the glucose infusion rate curve) revealed that a detemir dose of 0.29 units/kg would provide the same effect as 0.3 IU/kg NPH but has a longer duration of action (16.9 vs. 12.7 h, respectively). Lower between-subject variability was observed for insulin detemir on duration of action (0.4 units/kg insulin detemir vs. 0.3 IU/kg NPH, $P < 0.05$) and GIR(max) (maximal glucose infusion rate) (0.2 and 0.4 units/kg insulin detemir vs. 0.3 IU/kg NPH, both $P < 0.05$). Assessment of endogenous glucose production (EGP) and peripheral glucose uptake (PGU) resulted in an AOC(EGP) (area over the EGP curve) of 636 mg/kg (95% CI 279-879) vs. 584 (323-846) and an AUC(PGU) (area under the PGU curve) of 173 (47-316) vs. 328 (39-617) for 0.29 units/kg detemir vs. 0.3 IU/kg NPH, respectively. **CONCLUSIONS:** This study shows that insulin detemir provides a flat and protracted pharmacodynamic profile. Note: the GIR required to maintain a stable blood sugar shows a pronounced peak at higher detemir doses.

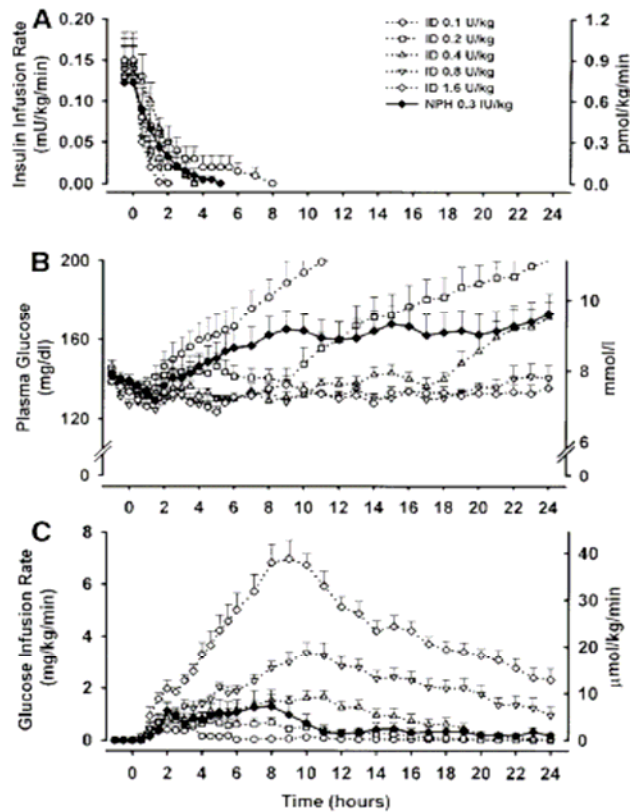


Figure 1—Time profiles for intravenous insulin infusion rates (A), plasma glucose levels (B), and GIRs (C) for after subcutaneous injection of NPH insulin (0.3 IU/kg) and insulin detemir (ID; 0.1, 0.2, 0.4, 0.8, and 1.6 units/kg) in 12 patients with type 1 diabetes. Data are means \pm SE.

Table 1—Pharmacodynamic parameters after subcutaneous injection of NPH insulin and insulin detemir

	NPH insulin (0.3 IU/kg)	Insulin detemir				
		0.1 units/kg	0.2 units/kg	0.4 units/kg	0.8 units/kg	1.6 units/kg
Onset of action (h)	1.8 \pm 1.2	2.0 \pm 1.8	2.0 \pm 2.5	1.6 \pm 1.1	1.1 \pm 0.7	0.8 \pm 0.3
End of action (h)	15.3 \pm 9.0	7.6 \pm 6.1	14.0 \pm 5.3	21.5 \pm 3.3	23.7 \pm 0.9	23.9 \pm 0.2
Clamps where end of action was truncated at 24 h (%)	33.3	9.1	9.1	41.7	90.9	90.9
Duration of action (h)	12.7 \pm 9.9	5.7 \pm 6.6	12.1 \pm 6.2*	19.9 \pm 3.2†	22.7 \pm 1.2	23.2 \pm 0.3
AUC _{GIR} (mg/kg)	743 (180–1,306)	101 (–204 to 405)†	419 (24–814)	1,184 (667–1,701)	2,879 (2,084–3,675)	5,703 (4,939–6,466)
GIR _{max} (mg \cdot kg ^{–1} \cdot min ^{–1})	1.6 (0.5–2.6)	0.8 (0.4–1.1)†	1.1 (0.8–1.4)†	1.7 (1.2–2.1)†	3.3 (2.6–4.0)	7.0 (5.8–8.2)
Time to GIR _{max} (h)	6.1 (2.7–9.5)	3.2 (1.5–5.0)	6.2 (4.1–8.3)	8.6 (6.9–10.3)	9.3 (8.6–10.0)	8.7 (7.3–10.2)

Data are means \pm SD or estimate (95% CI). Between-subject variability for duration of action, AUC_{GIR}, and GIR_{max} for 0.1, 0.2, and 0.4 units/kg insulin detemir vs. 0.3 IU/kg NPH: * P < 0.07; † P < 0.05. All other comparisons not significant. Note that a higher percentage of truncated clamps underestimates variability for the respective insulin dose.

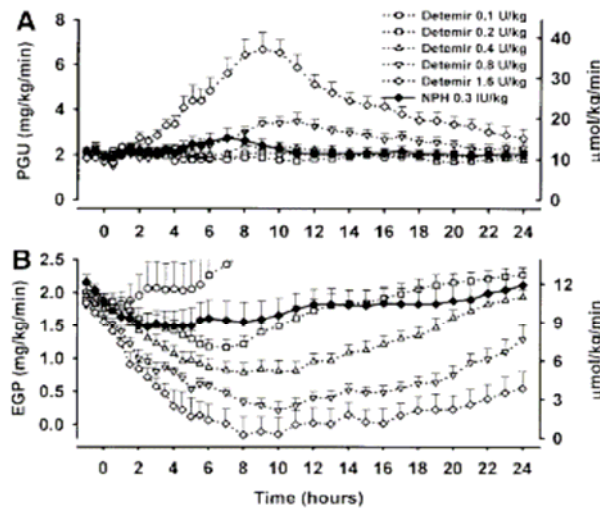


Figure 2—Time profiles for PGU (A) and EGP (B) after subcutaneous injection of NPH insulin (0.3 IU/kg) and insulin detemir (0.1, 0.2, 0.4, 0.8, and 1.6 units/kg) in 12 patients with type 1 diabetes. Data are means \pm SE.

Diabetes Care. 2004 May;27(5):1081-7.

Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial.

Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg JE, Abrams P, Landin-Olsson M, Hylleberg B, Lang H, Draeger E; Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group.

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OBJECTIVE: Insulin detemir is a soluble long-acting basal insulin analog designed to overcome the limitations of conventional basal insulin formulations. Accordingly, insulin detemir has been compared with NPH insulin with respect to glycemic control (HbA1c, prebreakfast glucose levels and variability, and hypoglycemia) and timing of administration. **RESEARCH DESIGN AND METHODS:** People with type 1 diabetes ($n = 408$) were randomized in an open-label, parallel-group trial of 16-week treatment duration using either insulin detemir or NPH insulin. Insulin detemir was administered twice daily using two different regimens, either before breakfast and at bedtime (IDet(morn+bed)) or at a 12-h interval (IDet(12h)). NPH insulin was administered before breakfast and at bedtime. Mealtime insulin was given as the rapid-acting insulin analog insulin aspart. **RESULTS:** With both insulin detemir groups, clinic fasting plasma glucose was lower than with NPH insulin (IDet(12h) vs. NPH, -1.5 mmol/l [95% CI -2.51 to -0.48], $P = 0.004$; IDet(morn+bed) vs. NPH, -2.3 mmol/l (-3.32 to -1.29), $P < 0.001$), as was self-measured prebreakfast plasma glucose ($P = 0.006$ and $P = 0.004$, respectively). The risk of minor hypoglycemia was lower in both insulin detemir groups (25%, $P = 0.046$; 32%, $P = 0.002$; respectively) compared with NPH insulin in the last 12 weeks of treatment, this being mainly attributable to a 53% reduction in nocturnal hypoglycemia in the IDet(morn+bed) group ($P < 0.001$). Although HbA1c for each insulin detemir group was not different from the NPH group, HbA1c for the pooled insulin detemir groups was significantly lower than for the NPH group (mean difference -0.18% [-0.34 to -0.02], $P = 0.027$). Within-person between-day variation in self-measured prebreakfast plasma glucose was lower for both detemir groups (both $P < 0.001$). The NPH group gained weight during the study, but there was no change in weight in either of the insulin detemir groups (IDet(12h) vs. NPH, -0.8 kg [-1.44 to -0.24], $P = 0.006$; IDet(morn+bed) vs. NPH, -0.6 kg [-1.23 to -0.03], $P = 0.040$). **CONCLUSIONS:** Overall glycemic control with insulin detemir was improved compared with NPH insulin. The data provide a basis for tailoring the timing of administration of insulin detemir to the individual person's needs.

Table 2 —Outcome measures using insulin detemir or NPH insulin as basal insulin therapy in type 1 diabetes

	IDet _{12h}	IDet _{mor+bed}	NPH	P
HbA _{1c} (%)	7.75 ± 0.07	7.78 ± 0.07	7.94 ± 0.07	0.082
Clinic FPG (mmol/l)	9.75 ± 0.37	8.94 ± 0.37	11.24 ± 0.38	<0.001
Self-monitored prebreakfast plasma glucose (mmol/l)				
Mean	8.28 ± 0.20	8.26 ± 0.20	9.05 ± 0.21	0.005
Within-patient SD	2.95 (2.80–3.10)	2.91 (2.76–3.05)	3.49 (3.31–3.68)	<0.001
Body weight change (kg)	0.02 ± 0.22	0.24 ± 0.22	0.86 ± 0.23	0.018
CGMS glucose profiles deviation from average (mmol/l · h)				
>24 h	54.9 ± 2.95	63.7 ± 2.92	59.7 ± 2.92	0.092
Overnight	15.9 ± 0.98	17.7 ± 1.01	16.2 ± 1.00	NS
Hypoglycemia in final 12 weeks				
Minor				
Anytime				
n (%)	114 (84)	114 (83)	107 (84)	
Events	842	780	1,074	0.020
Nocturnal				
n (%)	59 (44)	47 (34)	64 (50)	
Events	125	82	166	0.002
Major				
Anytime				
n (%)	6 (4)	11 (8)	10 (8)	
Events	9	24	12	NS
Nocturnal				
n (%)	3 (2)	5 (4)	4 (3)	
Events	4	9	4	NS
Insulin dose (units/day)				
Basal	36.7 ± 16.4	36.3 ± 16.5	34.8 ± 13.5	NS
Mealtime	27.9 ± 15.0	29.4 ± 12.2	29.4 ± 12.5	NS

Data are means ± SE, estimate (95% CI) for within-patient SD, mean ± SD for insulin doses, or n (%). n = 130–132 for the IDet_{12h} group, n = 131–135 for the IDet_{mor+bed} group, and n = 119–125 for the NPH group, except for GCMS, where n = 58–60 for 24 h and 62–69 for overnight. Differences and confidence intervals for pairs of treatments are given in Table 3. n for hypoglycemia is number of people having at least one episode. P value for ANOVA comparison of the three treatment groups together.

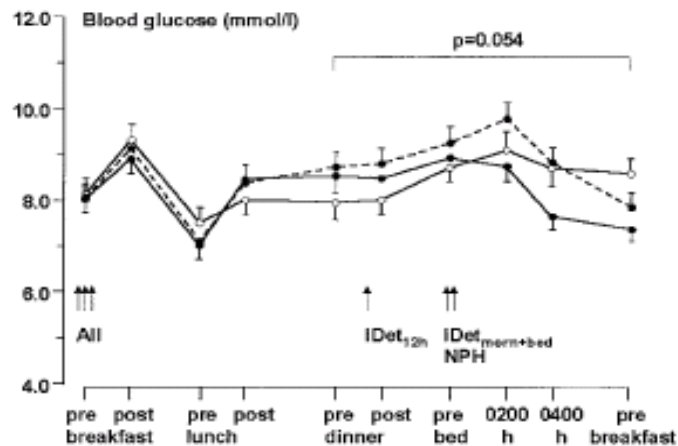


Figure 1—Mean 10-point self-measured plasma glucose profiles after 16 weeks of treatment with insulin detemir or NPH insulin as basal insulin. Arrows indicate time of first and second basal insulin dose. IDet_{12h} (●—●), insulin detemir administered at 12-h intervals; IDet_{mor+bed} (●—●), insulin detemir administered morning and bedtime; NPH (○—○), NPH insulin morning and bedtime.

Diabetes Res Clin Pract. 2004 Nov;66(2):193-201.

Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes.

Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N.

Metabolic Center, Institute of Preventive and Clinical Medicine, Limbova 14, 833 01 Bratislava, Slovak Republic.
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This trial compared the efficacy and safety of basal-bolus therapy using either the soluble basal insulin analogue insulin detemir (IDet) in combination with meal-time rapid-acting analogue insulin aspart (IASp), or NPH insulin (NPH) in combination with meal-time regular human insulin (HSI). This was a 22-week, multinational, open-labelled, symmetrically randomised, parallel group trial including 395 people with type 2 diabetes (IDet + IASp: 195, NPH + HSI: 200). At 22 weeks, HbA_{1c} was comparable between

treatments (IDet + IAsp: 7.46%, NPH + HSI: 7.52%, $P = 0.515$) with decreases from baseline of 0.65% and 0.58%, respectively. Treatment with IDet + IAsp was associated with a significantly lower within-person variation in self-measured fasting plasma glucose (FPG) (SD:1.20 versus 1.54 mmol/L, $p < 0.001$), as well as a lower body weight gain (0.51 versus 1.13 kg, $p = 0.038$) than with NPH + HSI. The risk of nocturnal hypoglycaemia was 38% lower with IDet + IAsp than with NPH + HSI, but statistical significance was not attained ($P = 0.14$). The overall safety profile was similar between the two treatments. Basal-bolus treatment with IDet + IAsp is an effective and well tolerated insulin regimen in people with type 2 diabetes, resulting in glycaemic control comparable to that of NPH + HSI, but with the advantages of less weight gain and a lower day-to-day within-person variation in FPG.

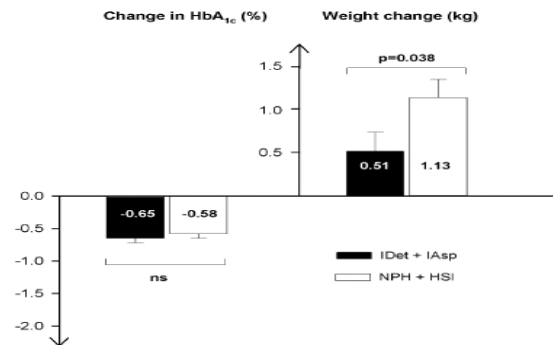


Fig. 1. Effects of IDet + IAsp and NPH + HSI on change in HbA_{1c} and body weight after 22 weeks of treatment. Values are means, bars represent S.E. The weight change was adjusted for change in HbA_{1c}.

K. Ražlová et al. / *Diabetes Research and Clinical Practice* 66 (2004) 193–201

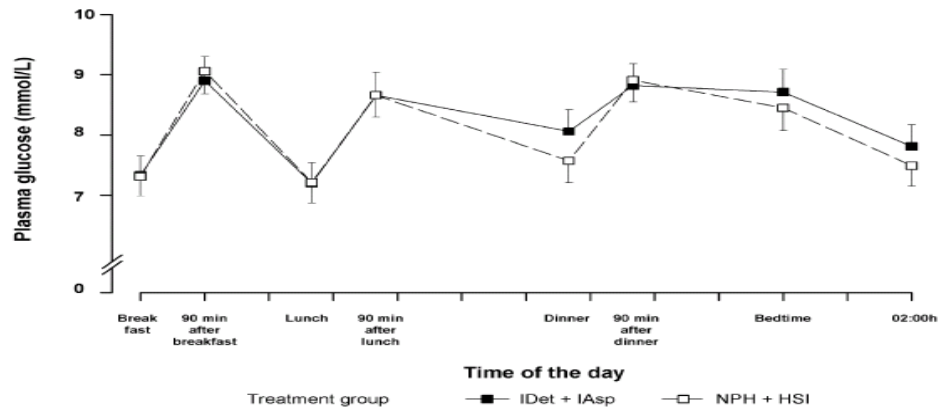


Fig. 2. Estimated means of 8-point plasma glucose profiles (± 2 S.E.) at 22 weeks.

Diabetes. 2004 Jun;53(6):1614-20.

Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes.

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The aim of this randomized double-blind study was to compare the within-subject variability of the glucose-lowering effect of a novel insulin analog, insulin detemir, with that of insulin glargine and NPH insulin in people with type 1 diabetes. Fifty-four subjects (32 males and 22 females, age 38 \pm 10 years [mean \pm SD], BMI 24 \pm 2 kg/m²), HbA_{1c} 7.5 \pm 1.2%, diabetes duration 18 \pm 9 years) participated in this parallel group comparison. Each subject received four single subcutaneous doses of 0.4 units/kg of either insulin detemir (n = 18), insulin glargine (n = 16), or human NPH insulin (n = 17) under euglycemic glucose clamp conditions (target blood glucose concentration 5.5 mmol/l) on four identical study days. The pharmacodynamic (glucose infusion rates [GIRs]) and pharmacokinetic (serum concentrations of insulin detemir, human insulin, and insulin glargine) properties of the basal insulin preparations were recorded for 24 h postdosing. Insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine, as assessed by the coefficient of variation (CV) for the pharmacodynamic end points studied [GIR-AUC((0-12 h)) 27% (detemir) vs. 59% (NPH) vs. 46% (glargine); GIR-AUC((0-24 h)) 27 vs. 68 vs. 48%; GIR(max) 23 vs. 46 vs. 36%; $P < 0.001$ for all comparisons]. Insulin detemir also provided less within-subject variability in the pharmacokinetic end

points: maximal concentration (C(max)) 18 vs. 24 vs. 34%; INS-AUC((0- infinity)) 14 vs. 28 vs. 33%. The results suggest that insulin detemir has a significantly more predictable glucose-lowering effect than both NPH insulin and insulin glargine. Note: This was not a cross over trial.

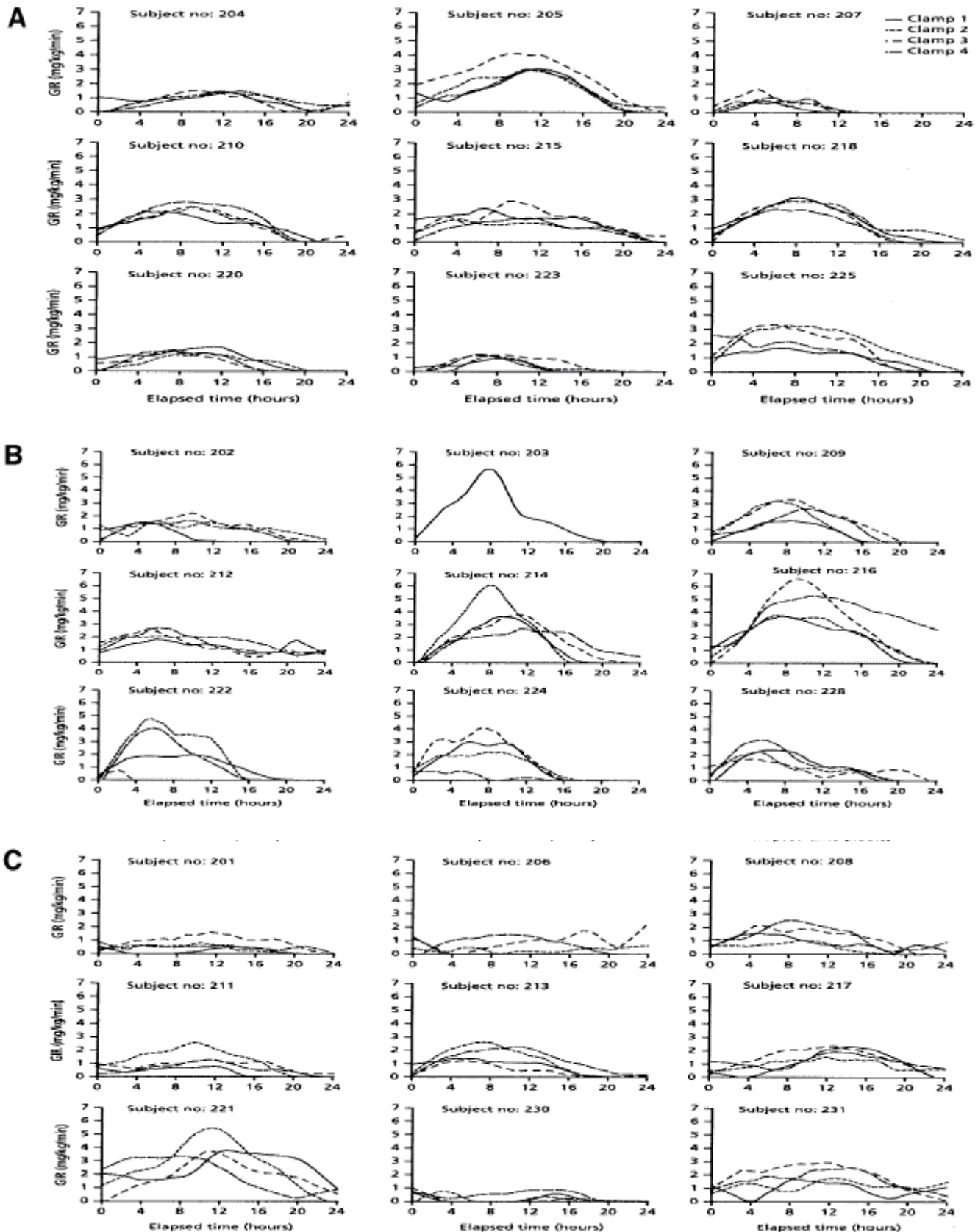
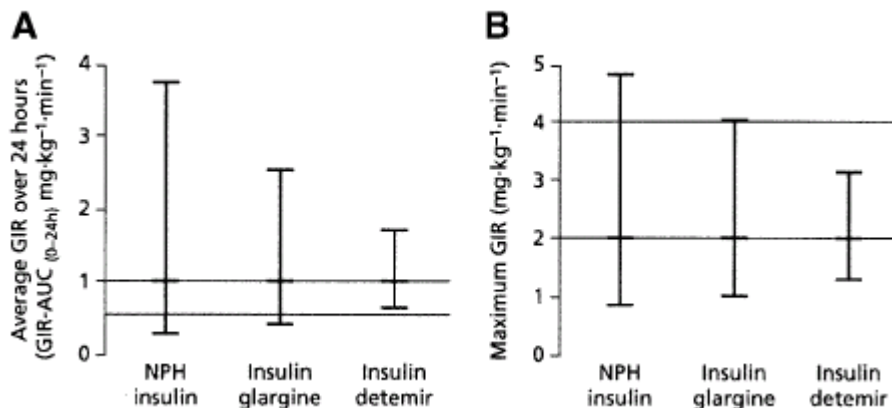


FIG. 1. Individual time-action profiles (glucose infusion rates over time) of the first nine patients randomized to insulin detemir (A), NPH insulin (B), or insulin glargine (C). The four clamps in one subject are summarized in one plot. A low within-subject variability is indicated by the four lines in one plot being close to each other (e.g., subject no. 204), whereas major deviations between the time-action profiles in one subject (e.g., subject no. 224) shows a high within-subject variability.



Diabetologia. 2004 Apr;47(4):622-9.

Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes.

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AIMS/HYPOTHESIS: The aim of the trial was to compare the efficacy and tolerability of two types of basal-bolus therapy, using either the soluble long-acting basal insulin analogue, insulin detemir, in combination with the rapid-acting analogue, insulin aspart, or NPH insulin in combination with mealtime regular human insulin. **METHODS:** In this 18-week, 1:1 randomised, open-labelled, parallel trial, 595 patients with Type 1 diabetes mellitus received insulin detemir or NPH insulin in the morning and at bedtime in combination with mealtime insulin aspart or regular human insulin respectively. **RESULTS:** Glycaemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA1c: 7.88% vs 8.11%; mean difference: -0.22% point [95% CI: -0.34 to -0.10]; $p < 0.001$). Self-measured 8-point plasma glucose profiles differed between the groups ($p < 0.001$), with lower postprandial plasma glucose levels in the insulin detemir/insulin aspart group. Within-person day-to-day variation in plasma glucose was lower with insulin detemir/insulin aspart than with NPH insulin/regular human insulin (SD: 2.88 vs 3.12 mmol/l; $p < 0.001$). Risk of overall and nocturnal hypoglycaemia (23.00-06.00 hours) was, respectively, 21% ($p = 0.036$) and 55% ($p < 0.001$) lower in the insulin detemir/insulin aspart group than in the NPH insulin/regular human insulin group. Body weight (adjusted for baseline and change in HbA1c) was 1 kg lower with insulin detemir/insulin aspart than with NPH insulin/regular human insulin ($p < 0.001$). **CONCLUSIONS/INTERPRETATION:** Basal-bolus therapy using insulin detemir/insulin aspart offers a better balance of control and tolerability than with NPH insulin/regular human insulin. The low variability and more physiological action profiles generated with these insulin analogues resulted in improved glycaemic control with lower risk of hypoglycaemia and no concomitant body weight increase. Note: the use of fast acting versus rapid acting insulin would cause the post meal glucose differences.

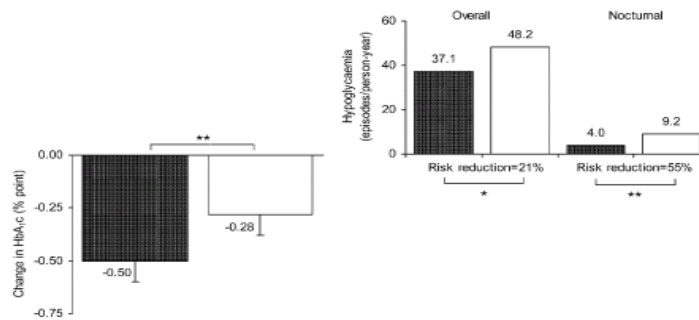


Fig. 1. Change in HbA_{1c} and hypoglycaemic episodes with insulin detemir/insulin aspart (■) and NPH/regular human insulin (□). Data are means, or means ± SE. **p*=0.036, ***p*<0.001

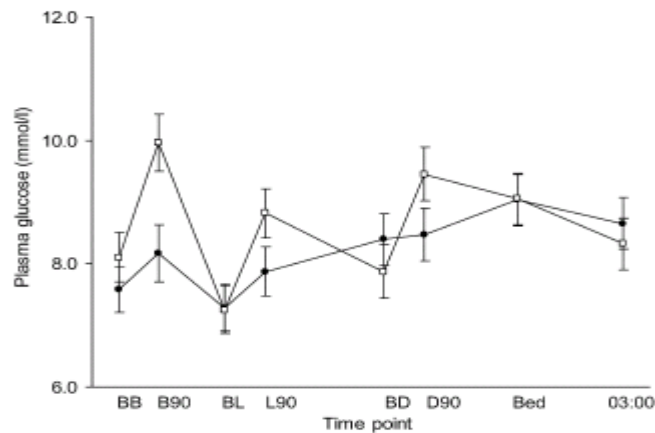


Fig. 2. 8-point plasma glucose profiles for insulin detemir/insulin aspart (●) and NPH insulin/regular human insulin (□). Data are means ± 2SE. BB, before breakfast; B90, 90 min after breakfast; BL, before lunch; L90, 90 min after lunch; BD, before dinner; D90, 90 min after dinner; Bed, bedtime

Table 4. Hypoglycaemia during the last 12 weeks of treatment

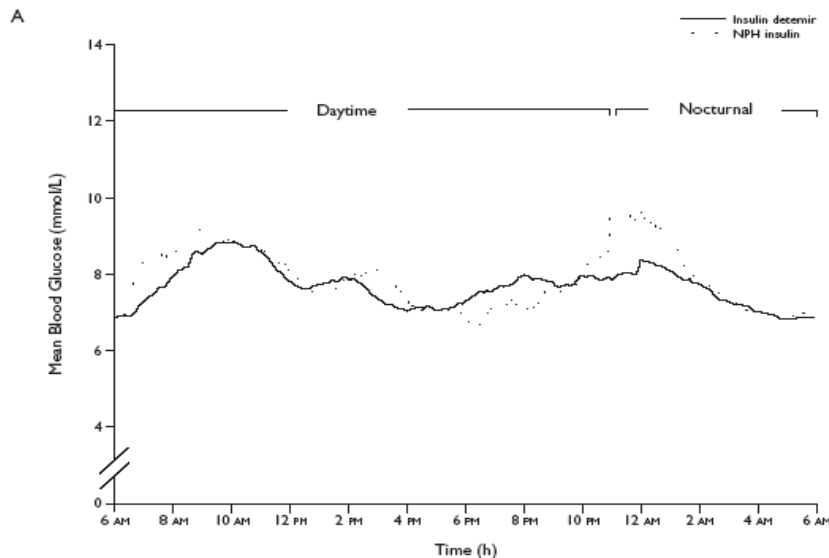
	Insulin detemir/insulin aspart			NPH insulin/regular human insulin			[Insulin detemir/insulin aspart]/ [NPH insulin/regular human insulin]		
	<i>n</i>	(%)	Events	<i>n</i>	(%)	Events	Relative risk	95% CI	<i>p</i> value
Hypoglycaemia (24 h)									
All	219	(75.0)	2497	238	(82.9)	3192	0.79	[0.63 to 0.98]	0.036
Major	19	(6.5)	40	18	(6.3)	45	0.89	[0.35 to 2.22]	0.796
Minor	202	(69.2)	1780	222	(77.4)	2282	0.79	[0.62 to 0.99]	0.045
Symptoms only	121	(41.4)	677	148	(51.6)	865	0.79	[0.56 to 1.12]	0.182
Nocturnal hypoglycaemia (23.00–06.00 hours)									
All	113	(38.7)	271	173	(60.3)	608	0.45	[0.35 to 0.58]	<0.001
Major	3	(1.0)	4	12	(4.2)	24	0.17	[0.04 to 0.63]	0.008
Minor	98	(33.6)	196	142	(49.5)	427	0.46	[0.35 to 0.61]	<0.001
Symptoms only	41	(14.0)	71	72	(25.1)	157	0.46	[0.30 to 0.71]	<0.001

Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen.

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OBJECTIVE: The purpose of this trial was to compare the effects of QD basal insulin replacement using insulin detemir versus neutral protamine Hagedorn (NPH) insulin in basal-bolus therapy in combination with regular human insulin (HI) in patients with type 1 diabetes mellitus (DM). **METHODS:** This was a 6-month, prospective, randomized, open-label, controlled, parallel-group trial conducted at 92 sites in Europe and Australia. The trial population included men and women with type 1 DM for at least 1 year aged ≥ 18 years with glycosylated hemoglobin (HbA(1c)) $\leq 12\%$ already taking QD basal-bolus treatment with an intermediate- or long-acting insulin and a fast-acting human insulin or insulin analogue as bolus insulin. Patients were randomly assigned (2:1) to 6 months of treatment with insulin detemir or NPH at bedtime in combination with HI with main meals. Main outcome measures were blood glucose control as assessed by HbA(1c), fasting plasma glucose (FPG), 9-point self-monitored blood glucose (SMBG) profiles, 24-hour continuous blood glucose profiles, hypoglycemia, weight gain, and adverse events. **RESULTS:** Of the 749 patients randomized to treatment, 747 were exposed to trial products and included in the intent-to-treat analysis set. Seven hundred patients completed the trial: 465 (94.7%) in the insulin detemir group and 235 (91.8%) in the NPH group. After 6 months, FPG was lower with insulin detemir than with NPH (-1.16 mmol/L difference; $P = 0.001$), whereas HbA(1c) did not differ significantly between treatments (-0.12% [95% CI, -0.25 to 0.02]; $P = \text{NS}$). Day-to-day variability in self-measured fasting blood glucose was lower with insulin detemir (SD, 2.82 vs 3.60 mmol/L; $P < 0.001$). The overall shape of the 9-point SMBG profiles differed significantly between treatments ($P = 0.006$), with lower glucose levels before breakfast with insulin detemir than with NPH ($P < 0.001$). There was a 26% reduction in the relative risk of nocturnal hypoglycemia with insulin detemir compared with NPH ($P = 0.003$). Gain in body weight was significantly lower after 6 months with insulin detemir than with NPH (-0.54 kg difference; $P = 0.024$). The frequency and type of adverse events were similar between treatment groups. **CONCLUSIONS:** In this study, QD administration of insulin detemir at bedtime resulted in lower fasting blood glucose levels with less day-to-day variability and less fluctuation from ean blood glucose levels over 24 hours than NPH insulin, combined with an overall reduction in the risk of nocturnal hypoglycemia. These findings suggest that evening administration of insulin detemir may provide an opportunity to further improve fasting blood glucose targets.



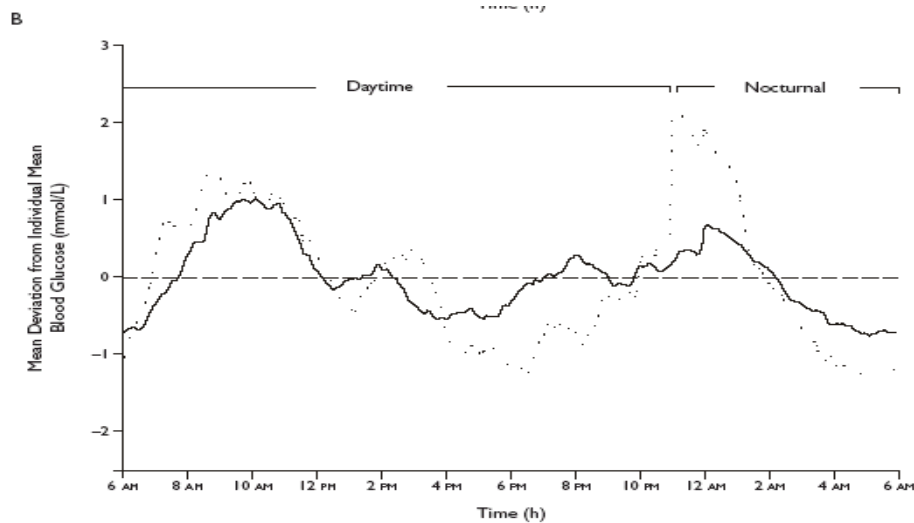


Figure 1. Continuous Glucose Monitoring System (CGMS; Medtronic MiniMed, Northridge, California) profiles among patients with type 1 diabetes mellitus after 5 months of treatment with insulin detemir (n = 99) or neutral protamine Hagedorn (NPH) insulin (n = 39). (A) Mean 24-hour CGMS blood glucose profile. (B) Mean fluctuation from individual mean blood CGMS glucose level over the same period.

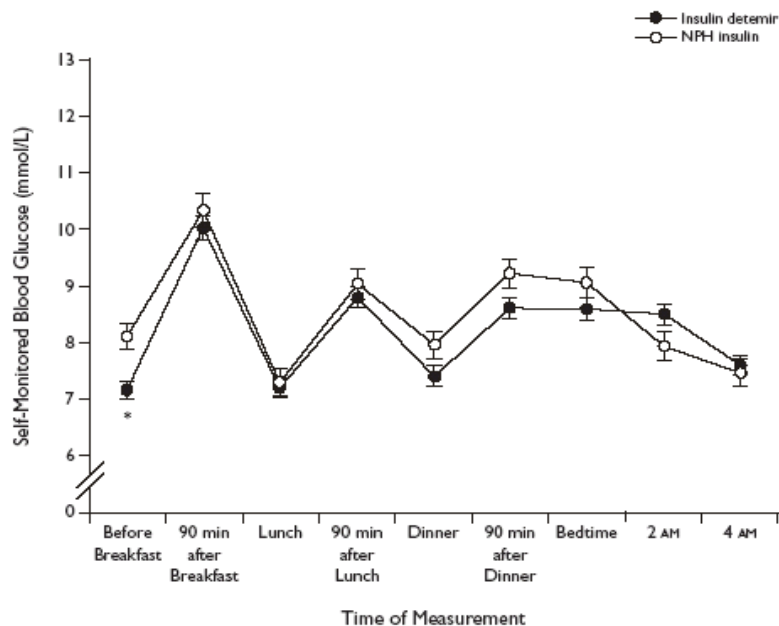


Figure 2. Mean (SE) 9-point self-measured blood glucose profiles among patients with type 1 diabetes mellitus after 6 months of treatment with insulin detemir (n = 491) or neutral protamine Hagedorn (NPH) insulin (n = 256) as basal insulin. *P < 0.001.

Drugs. 2004;64(22):2577-95.

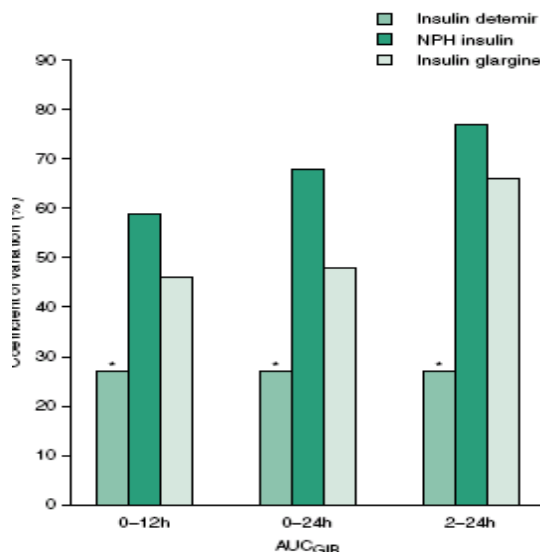
Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus.

Chapman TM, Perry CM.

Adis International Limited, Auckland, New Zealand.

Insulin detemir (Levemir) is a soluble long-acting human insulin analogue acylated with a 14-carbon fatty acid. The fatty acid modification allows insulin detemir to reversibly bind to albumin, thereby providing slow absorption and a prolonged and consistent metabolic effect of up to 24 hours in patients with type 1 or type 2 diabetes mellitus. Insulin detemir has a more predictable, protracted and consistent effect on blood glucose than neutral protamine Hagedorn (NPH) insulin, with less inpatient variability in glycaemic

control, compared with NPH insulin or insulin glargine. Insulin detemir, administered once or twice daily, is at least as effective as NPH insulin in maintaining overall glycaemic control, with a similar or lower risk of hypoglycaemia, especially nocturnal hypoglycaemia, compared with NPH insulin in patients with type 1 or type 2 diabetes. Insulin detemir also provides the added clinical benefit of no appreciable bodyweight gain in patients with type 1 diabetes and less bodyweight gain than NPH insulin in patients with type 2 diabetes. Insulin detemir is, therefore, a promising new option for basal insulin therapy in patients with type 1 or 2 diabetes.



g. 1. Coefficients of variation (%) showing inpatient variability the glucose-lowering effect (assessed by the area under the glucose infusion rate curve [AUC_{GIR}] measured over 0-12 hours, 0-24 hours and 2-24 hours) of insulin detemir, neutral protamine Hagedorn (NPH) insulin and insulin glargine.^[24] Evaluable patients with type 1 diabetes mellitus received insulin detemir (n = 18), NPH insulin (n = 17) or insulin glargine (n = 16) in a single-centre, randomised, double-blind trial. Each insulin preparation was administered as four single subcutaneous doses (0.4 U/kg) on four identical study days under euglycaemic clamp conditions. The target blood glucose level was 5.5 mmol/L. * p < 0.001 vs comparators.

Diabetes Care. 2003 Nov;26(11):3087-92.

Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes.

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Kinderkrankenhaus auf der Bult, Hannover, Germany. danne@hka.de

OBJECTIVE: This trial aimed to characterize for the first time the pharmacokinetic profile of insulin detemir, the novel soluble basal insulin analog, in children and adolescents compared with adults. Comparisons were also made with NPH insulin to determine any between-treatment difference in the effect of age on pharmacokinetic profile. **RESEARCH DESIGN AND METHODS:** This single-center, open-label, randomized, crossover trial included children (aged 6-12 years, n = 13), adolescents (aged 13-17 years, n = 10), and adults (aged 18-65 years, n = 11) of both sexes. Subjects were given single doses of 0.5 units/kg s.c. insulin detemir or 0.5 IU/kg NPH insulin on 2 separate days. Serial blood sampling was performed for 24 h for analysis of serum insulin detemir, human insulin, and glucose concentrations. **RESULTS:** The mean pharmacokinetic profile of insulin detemir was similar across all three age-groups. This was determined by statistical analyses of the data, which showed no overall age effect or between-group differences when pairwise comparisons were made between children (or adolescents) and adults on the parameters of the area under the curve (AUC), AUC from zero to infinity, AUC from 0 to 24 h [AUC((0-24 h))], and the maximum concentration measured during the 24 h after dosing. No overall age effect for AUC((0-24 h)) and C(max) was detected for NPH insulin, but data were only analyzable from seven adults and pairwise comparisons did indicate that children and adults had different pharmacokinetic profiles. Less total variability in the pharmacokinetics of insulin detemir than NPH insulin was indicated by lower coefficients of variation in AUC, C(max), and time to maximum concentration in all three age-groups. **CONCLUSIONS:** The data suggest that insulin detemir can be used in children and adolescents with type 1 diabetes using titration guidelines similar to those used in adults. Moreover, insulin detemir may offer the advantage of greater predictability of response in comparison to NPH insulin due to lower total variability and a lesser degree of kinetic disparity across age-groups.

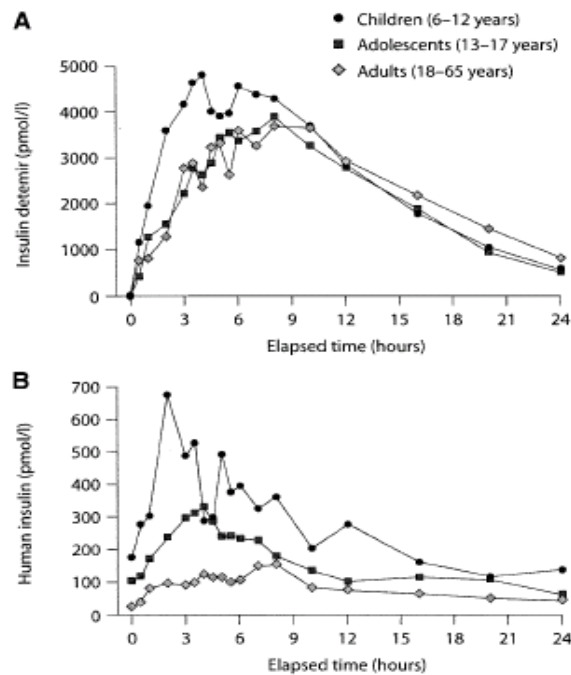


Figure 1—Mean serum concentration–time profile of insulin detemir and NPH insulin by age-group. A: Insulin detemir. B: NPH insulin.

Table 2—Pharmacokinetic parameters of insulin detemir and NPH insulin for children, adolescents, and adults with type 1 diabetes

	Age-group		
	6–12 years	13–17 years	18–65 years
Insulin detemir			
n	10	10	9
AUC _(0–03) (pmol · l ⁻¹ · min ⁻¹)	4,078,672 ± 1,789,975	3,373,627 ± 754,187	3,896,543 ± 1,516,217
AUC _(0–24h) (pmol · l ⁻¹ · min ⁻¹)	3,764,915 ± 1,574,934	3,082,003 ± 607,080	3,382,071 ± 1,419,125
C _{max} (pmol/l)	5,907 ± 3,229	4,456 ± 1,073	4,641 ± 2,299
t _{max} (min)	309 ± 137	426 ± 122	483 ± 206
t _{1/2} (min)	302 ± 100	301 ± 107	425 ± 78
Cl/F (l · min ⁻¹ · kg ⁻¹)	3.43 ± 1.36	3.74 ± 0.98	3.41 ± 1.00
MRT (min)	653 ± 162	705 ± 182	827 ± 140
NPH insulin			
n	9	10	7
AUC _(0–24h) (pmol · l ⁻¹ · min ⁻¹)	411,003 ± 483,066	207,974 ± 153,624	111,941 ± 77,941
C _{max} (pmol/l)	595 ± 504	355 ± 347	140 ± 121
t _{max} (min)	363 ± 247	318 ± 267	480 ± 237

Data are means ± SD.

Best Pract Res Clin Gastroenterol. 2002 Jun;16(3):475-92.

New insulins in the treatment of diabetes mellitus.

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Landmark studies have confirmed the importance of intensified insulin treatment for minimizing long-term diabetic complications. Human insulin is still first-line treatment. However, even the most intensive of human insulin-based regimens can only poorly reproduce physiologically desirable insulin release, which includes rapid outbursts of insulin at mealtimes coupled with relatively low and stable basal levels between meals. Encouragingly, there are now four available or soon-to-be-available insulin analogues that offer the potential for more physiological insulin profiles. Insulin lispro and insulin aspart are rapid-acting insulin analogues intended for immediate pre-meal administration in type 1 or type 2 diabetes. Compared with injected human insulin, they improve post-prandial glucose control and reduce late post-meal and night-time hypoglycaemic episodes. Two basal insulin analogues, insulin glargine and insulin detemir, have also shown beneficial profiles with regard to night-time hypoglycaemia. Some, but not all, studies with the two rapid-acting insulins have shown improvement in overall glucose control, as assessed by HbA(1c), in comparison to human insulin.

These results are encouraging and provide hope that entirely analogue-based regimens may improve overall glycaemic control and ease of use of insulin. Copyright 2002 Elsevier Science Ltd.

Table 1. Insulin preparations and their pharmacokinetics following subcutaneous injection^a.

Insulin	Onset of action (minutes or hours)	Peak of action (hours)	Duration of action (hours)
Soluble human insulin	1/2–1	2–4	5–8
Insulin lispro	0.1–0.25	1–2	4–5
Insulin aspart	0.1–0.25	1–2	4–5
Human NPH-insulin	1–2	5–7	13–18
Lente insulin	1–3	4–8	13–20
Ultralente insulin	2–4	8–10	18–30
Insulin glargine	1–2	4–5	> 24
Insulin detemir	1–2	6–8	10–18

^aAdapted from Hermans MP et al (1999, *Acta Clinica Belgica* 54-5: 233–240) with permission.

Diabet Med. 1999 Apr;16(4):332-8.

Time-action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304.

Heinemann L, Sinha K, Weyer C, Loftager M, Hirschberger S, Heise T.

Department of Metabolic Diseases and Nutrition, WHO Collaborating Centre for Diabetes, Heinrich-Heine-University Dusseldorf, Germany.

AIMS: To compare the pharmacokinetic and pharmacodynamic properties of subcutaneously injected NN304, a novel long-acting insulin analogue, to NPH-insulin during euglycaemic glucose clamps in 11 healthy volunteers. **METHODS:** On three study days NN304 was injected in three different doses (0.15, 0.3, 0.6 U/kg body weight), while NPH-insulin (0.3 U/kg) was injected in identical dose on two other days. **RESULTS:** Injection of NN304 resulted in a linear and proportional increase in total NN304 concentrations (AUC_{0-1440 min}: 0.15 U/kg: 344±43, 0.3 U/kg: 666±82, 0.6 U/kg: 1295±210 nmol/l; P<0.001). Maximal concentrations (609±140, 1046±283, 2033±460 pmol/l; P<0.001) were reached after 4–6 h. The metabolic response (expressed as maximal glucose infusion rates (GIR)) induced by subcutaneous injection of NN304 did not show the pronounced peak seen with NPH-insulin in an identical dose: GIR_{max} 3.2±1.1 vs. 4.4±1.8 mg/kg/min (P<0.05 for 0.3 U/kg NN304 vs. NPH-insulin; mean of both study days with NPH-insulin, all others not significant). NN304 also showed a slower onset of action, as indicated by a significantly higher t_{max} (446±162 vs. 359±175 min) and lower AUC_{0-240min} (0.5±0.3 vs. 0.8±0.4 g/kg/240min; P<0.05, respectively). The three different doses of NN304 induced a significantly different glucose consumption in the first 720 min after injection (AUC_{0-720 min} 1.1±0.6, 1.9±0.8, 1.7±0.8 g/kg; P<0.05 for 0.15 U/kg), but not over the whole study period (AUC_{0-1440 min} 1.8±1.1, 3.1±1.3, 2.8±1.4 g/kg). **CONCLUSIONS:** Injection of NN304 at different doses resulted in an increase in total NN304 concentration in a linear dose-response effect and a more even metabolic effect than NPH-insulin. However, we found no clear dose-response in its metabolic effect.

J Pharm Sci. 1997 Dec;86(12):1365-8.

Effect of fatty acids and selected drugs on the albumin binding of a long-acting, acylated insulin analogue.

Kurtzhals P, Havelund S, Jonassen I, Markussen J.

Novo Research Institute, Novo Nordisk A/S, Bagsvaerd, Denmark.

NN304 (LysB29-tetradecanoyl, des(B30)-insulin) is a new soluble, long-acting insulin analogue that is tightly bound to human serum albumin differentiating it from human insulin. In the present study, we investigate the effect of fatty acids and selected drugs on the

binding of NN304 to human serum albumin *in vitro*. Binding of the first fatty acid equivalent to albumin does not affect the binding of NN304. None of the tested drugs compete with the binding of NN304 at drug-to-albumin concentration ratios of < 1 . The binding of NN304 is shown to be independent of binding of drugs in the two major binding pockets that are located in domains IIA and IIIA of the albumin molecule. Tolbutamide and glibenclamide do not compete with NN304 for binding to albumin at therapeutic drug-to-albumin concentration ratios. High concentrations of acetylsalicylic acid and ibuprofen decrease the affinity of NN304 for albumin, but these interactions occur at drug-to-albumin concentration ratios that are higher than clinically relevant. In conclusion, NN304 is unlikely to be involved in clinically significant drug interactions at the albumin binding level. The unique ligand binding properties of serum albumin and its abundance in the extracellular fluids makes fatty acid acylation and albumin binding an attractive protraction principle for insulin and potentially also for other peptide drugs.

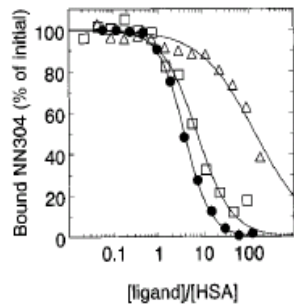


Figure 1—Competition between NN304 and fatty acids for binding to HSA: octanoic acid (Δ); dodecanoic acid (\bullet); hexadecanoic acid (\square). The results for dodecanoic acid are from ref 6.

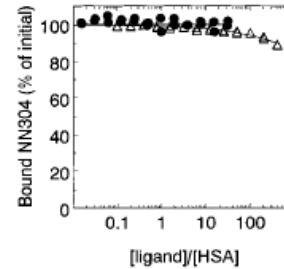


Figure 2—Displacement of NN304 from HSA by ligands bound in domain IIA of the albumin molecule: warfarin (\bullet); phenylbutazone (Δ). ^{125}I -Labeled NN304 (2.5 nmol/L) was equilibrated with immobilized HSA ($\approx 15 \mu\text{mol/L}$) and various concentrations of the competing drugs, and the fraction of bound NN304 was determined. [Ligand]/[HSA] refers to the ratio between the total concentrations of ligand and of HSA.

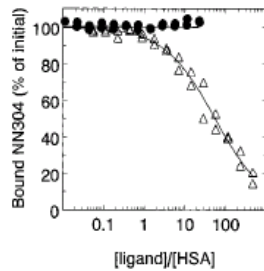


Figure 3—Displacement of NN304 from HSA by drugs bound in domain IIIA of the albumin molecule: diazepam (\bullet); ibuprofen (Δ). Conditions were as described in Figure 2.

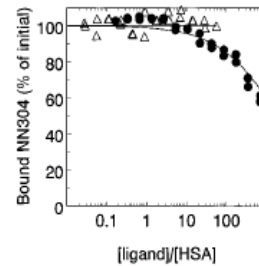


Figure 4—Displacement of NN304 from HSA by the high dose drugs acetylsalicylic acid (\bullet) and valproate (Δ). Conditions were as described in Figure 2.

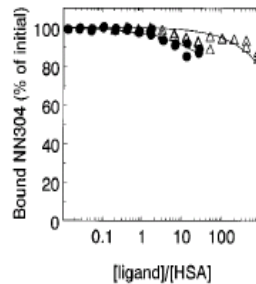


Figure 5—Displacement of NN304 from HSA by sulfonylureas: glibenclamide (\bullet); tolbutamide (Δ). Conditions were as described in Figure 2.

Diabetes Technol Ther. 2004 Oct;6(5):579-88.

The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes.

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BACKGROUND: This trial compared the long-term safety and efficacy of the basal insulin preparations, insulin detemir and NPH insulin, in basal-bolus therapy for patients with type 1 diabetes. **METHODS:** This multinational open, parallel-group trial randomized patients to receive insulin detemir or NPH insulin twice daily in addition to mealtime human soluble insulin. Doses were titrated

towards predefined glycemic targets. After an initial 6-month treatment period, patients were invited to participate in a 6-month extension period. A total of 289 from 421 elected to continue in the trial, of which 252 completed. **RESULTS:** Glycemic control as assessed by hemoglobin A1c (insulin detemir, 7.88%; NPH insulin, 7.78%; difference not significant) and fasting plasma glucose (insulin detemir, 10.1 mmol/L; NPH insulin, 9.84 mmol/L; difference not significant) was similar in both treatment groups at end point, with hemoglobin A1c little changed from baseline and fasting plasma glucose slightly decreased. There was some evidence for a risk reduction for hypoglycemia in association with insulin detemir, although this was not statistically significant (relative risk overall hypoglycemia, 0.71, $P = 0.139$; relative risk nocturnal hypoglycemia, 0.71, $P = 0.067$), and hypoglycemic events were fewer in each of the 12 months. There was a significant treatment difference with regard to weight outcome; NPH insulin was associated with weight gain (1.4 kg), but there was no mean weight gain (-0.3 kg) in the insulin detemir cohort (baseline-adjusted between-group difference at 12 months, 1.66 kg, $P = 0.002$). There were no obvious between-group differences in other safety parameters. **CONCLUSIONS:** Glycemic control is maintained with insulin detemir during long-term treatment. At equivalent glycemic control to NPH insulin, insulin detemir is associated with a lack of weight gain and a trend towards a reduced risk of nocturnal hypoglycemia when used in basal-bolus therapy with mealtime soluble human insulin.

Diabetes Care. 2003 Mar;26(3):590-6.

Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart.

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OBJECTIVE: Insulin detemir is a soluble basal insulin analog with a unique mechanism of protracted action designed to reduce the variability associated with conventional basal insulins. This trial compared the glycemic control, risk of hypoglycemia, and effect on body weight of insulin detemir and NPH insulin in patients with type 1 diabetes treated with rapid-acting insulin aspart at meals. **RESEARCH DESIGN AND METHODS:** This study was a 6-month multinational open parallel-group comparison conducted at 46 centers in five countries and included 448 patients with type 1 diabetes randomized 2:1 to insulin detemir or NPH insulin, respectively. **RESULTS:** After 6 months, comparable HbA(1c) levels were found between the two treatment groups. Fasting plasma glucose tended to be lower in patients treated with insulin detemir, but this difference was not statistically significant (-0.76 mmol/l, $P = 0.097$). Within-subject variation in self-measured fasting blood glucose was lower with insulin detemir than with NPH insulin (SD 3.37 vs. 3.78 mmol/l, $P < 0.001$). Risk of hypoglycemia was 22% lower with insulin detemir than with NPH insulin ($P < 0.05$) and 34% lower for nocturnal (2300-0600) hypoglycemia ($P < 0.005$). Nightly plasma glucose profiles were smoother and more stable with insulin detemir ($P = 0.05$). Body weight was significantly lower with insulin detemir at the end of the trial ($P < 0.001$). **CONCLUSIONS:** Treatment with insulin detemir resulted in more predictable glycemic control, with smoother plasma glucose profiles than NPH insulin and a significant reduction in the risk of hypoglycemia. The reduction in body weight with insulin detemir is a potential additional advantage. Regimens optimized for insulin detemir may be able to improve glycemic control beyond that possible with NPH insulin.

Table 2—Selected efficacy and safety data after 6 months of treatment with insulin detemir or NPH insulin

	Insulin detemir	NPH insulin	Difference (detemir-NPH)	Relative risk (detemir/NPH)	P
Glycemic control					
HbA _{1c} (%)* (n = 280 and 139)	7.60 ± 0.09	7.64 ± 0.10	-0.04 (-0.218 to 0.128)		0.61
FPG (mmol/l)* (all patients; n = 274 and 138)	9.19 ± 0.44	9.94 ± 0.52	-0.76 (-1.65 to 0.14)		0.09
Daily insulin dose [nmol (U/IU)]†					
Basal	710 (59.2 U)	190 (31.7 IU)			
Bolus	184 (30.7 U)	156 (26.0 U)			
Variability (fasting SMBG)					
Mean fasting SMBG (mmol/l) (n = 271 and 137)	8.80	9.23			
Within-subject variation (SD) (n = 271 and 137)	3.37	3.78			<0.001
Body weight					
Final weight (kg)‡ (n = 282 and 138)	70.9 ± 0.28	71.8 ± 0.33	-0.98		0.001
Hypoglycemia (episodes over the last 5 months; proportion of patients with ≥1 episode)					
All events	7,522; 271; 5.188	4,820; 138; 6.70		0.78 (0.62 to 0.97)	0.029
Major	56; 24; 0.04	41; 21; 0.06		0.65 (0.28 to 1.50)	0.312
Minor	3,184; 259; 2.19	2,180; 129; 3.03		0.72 (0.56 to 0.93)	0.011
Symptoms only	4,271; 236; 2.94	2,595; 121; 3.61		0.83 (0.62 to 1.11)	0.213
Nocturnal (any)	923; 198; 0.64	689; 110; 0.96		0.66 (0.50 to 0.87)	<0.005

Data are means ± SE except where indicated. 95% CIs are shown for the difference between groups. *Estimated means with correction for baseline values. †Insulin detemir: 1 unit (U) = 12 nmol, NPH insulin: 1 unit (IU) = 6 nmol, IAsp: 1 unit (U) = 6 nmol. ‡The analysis is based on an ANCOVA model with treatment as fixed effect and weight at baseline as covariate. Only those patients who provided information for the analysis of weight are included in the table. §Data are number of episodes; number of patients with at least one hypoglycemic episode; events per subject month.

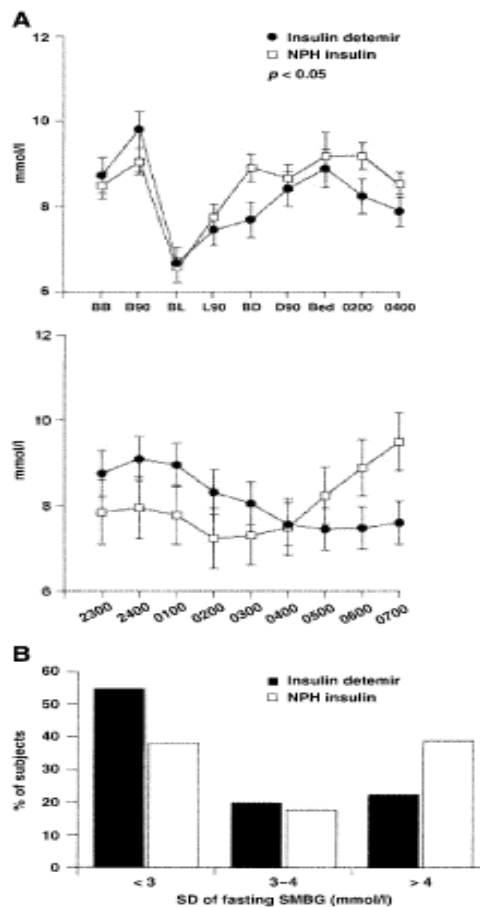


Figure 1—A: Daytime and night-time 8-h plasma glucose profiles. **B:** Distribution of individual within-subject SDs. BB, before breakfast; B90, 90 min after breakfast; BL, before lunch; L90, 90 min after lunch; LD, before dinner; D90, 90 min after dinner.

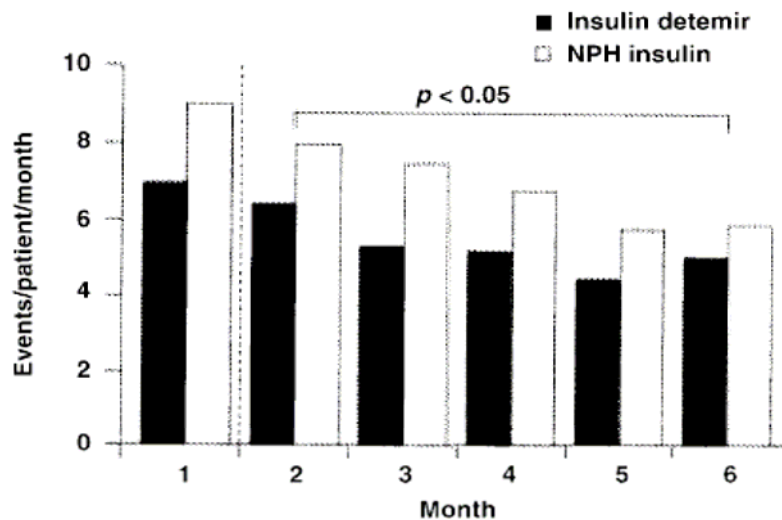


Figure 2—Hypoglycemic episodes. All hypoglycemic episodes are pooled for the entire treatment period. Month 1 is the titration phase; months 2–6 are the maintenance phase.

Diabetes Care. 2001 Feb;24(2):296-301.

Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy.

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OBJECTIVE: Insulin detemir (NN304) is a soluble basal insulin analog developed to cover basal insulin requirements. This trial aimed to compare the blood glucose-lowering effect of insulin detemir with that of NPH insulin (NPH) and to evaluate the two treatments with regard to intrasubject variation of fasting blood glucose, incidence of hypoglycemia, dose requirements, and safety. **RESEARCH DESIGN AND METHODS:** This multicenter open randomized crossover trial in 59 type 1 diabetic subjects comprised a 2-week run-in period on a basal-bolus regimen with NPH insulin once daily, followed by two 6-week periods of optimized basal-bolus therapy with either once-daily insulin detemir or NPH insulin. **RESULTS:** The area under the curve, in the time interval 23:00-8:00, derived from 24-h serum glucose profiles, was not statistically significantly different for the two treatment periods (insulin detemir:NPH ratio 89.2:83.5, $P = 0.59$). The intrasubject variation in fasting blood glucose during the last 4 days of treatment was lower for insulin detemir compared with NPH ($P < 0.001$). Mean dose requirements of insulin detemir were 2.35 times higher (95% CI 2.22-2.48) compared with NPH. During the last week of treatment, fewer subjects experienced hypoglycemic episodes on insulin detemir (60%) compared with NPH treatment (77%) ($P = 0.049$). **CONCLUSIONS:** Insulin detemir was as effective as NPH in maintaining glycemic control when administered at a higher molar dose. The results indicate that insulin detemir may provide more predictable fasting blood glucose with lower intrasubject variation and reduced risk of hypoglycemia compared with NPH.

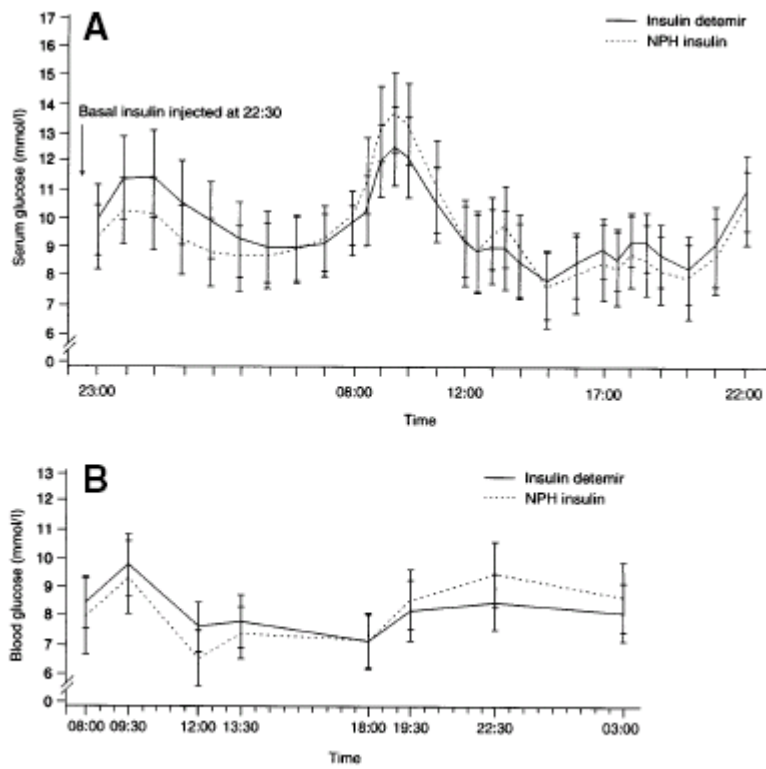


Figure 1—Blood glucose profiles. A: Mean 24-h serum glucose profiles. B: Home-monitored mean eight-point blood glucose profiles during the last week of treatment. Values are means $\pm 2 \times$ SEM.

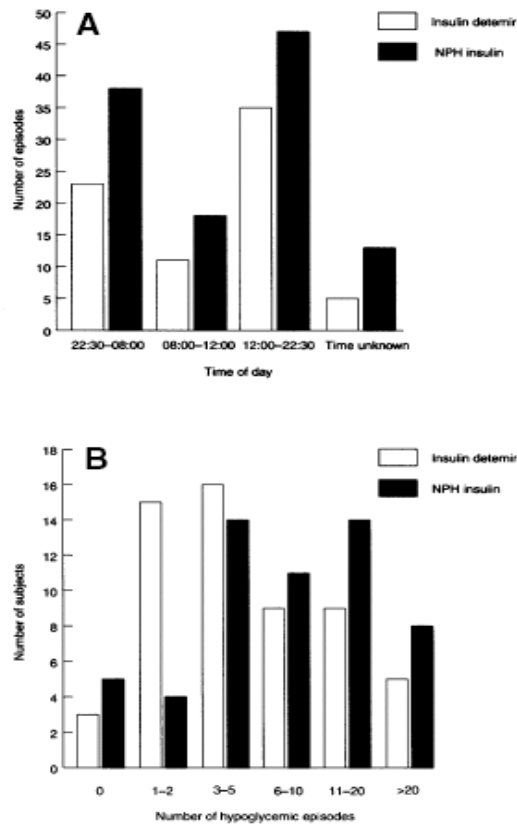


Figure 2—Hypoglycemic episodes during the last week of treatment versus time of day (A) and distribution by treatment during the 6-week treatment period (B).

Exp Clin Endocrinol Diabetes. 2000;108(2):100-5.

Pharmacokinetic and pharmacodynamic properties of long-acting insulin analogue NN304 in comparison to NPH insulin in humans.

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NN304 is a long-acting insulin analogue that is acylated with a 14-C-fatty acid chain. Protraction of action of this novel insulin analogue is due not to slow absorption after subcutaneous administration but to reversible binding to albumin. We investigated the pharmacokinetic and pharmacodynamic properties of insulin analogue NN304 (0.3 and 0.6 U/kg) in comparison to NPH insulin (0.3 and 0.6 IU/kg) in 10 healthy volunteers performing a randomised, double-blind, cross-over, placebo-controlled glucose clamp study. During the observation period of 24 hours the areas under the insulin curve for NPH[0.3 IU/kg] vs. NPH[0.6 IU/kg] were 60 vs. 102 nmol min l(-1) (p<0.01) and for insulin analogue NN304[0.3 U/kg] vs. NN304[0.6 U/kg] 490 vs. 932 nmol min l(-1) (p <0.001), suggesting a clear dose-response relationship for both NPH insulin and NN304. The amount of disposed glucose (area under the curve of glucose infusion) differed with statistical significance between the five treatments and was highest with NPH[0.6 IU/kg] (2671 mg/kg) and lowest with placebo (265 mg/kg). However, area under the curve of glucose infusion after treatment with NN304 was only 36% (dose of 0.3 U/kg) and 24% (dose of 0.6 U/kg) of that observed with corresponding doses of NPH insulin. Moreover, increasing dosages of NN304 failed to demonstrate a significant dose-response with regard to the area under the curve of glucose infusion. This study demonstrates that the principle of protracted insulin action of NN304 by reversible binding to albumin is effective in humans albeit at a much lower rate of glucose utilisation when compared to NPH insulin. Thus, in contrast to animal studies NN304 and NPH insulin can not be considered equipotent in humans.

Diabet Med. 1999 Apr;16(4):332-8.

Time-action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304.

Heinemann L, Sinha K, Weyer C, Loftager M, Hirschberger S, Heise T.

Department of Metabolic Diseases and Nutrition, WHO Collaborating Centre for Diabetes, Heinrich-Heine-University Dusseldorf, Germany.

AIMS: To compare the pharmacokinetic and pharmacodynamic properties of subcutaneously injected NN304, a novel long-acting insulin analogue, to NPH-insulin during euglycaemic glucose clamps in 11 healthy volunteers. **METHODS:** On three study days NN304 was injected in three different doses (0.15, 0.3, 0.6 U/kg body weight), while NPH-insulin (0.3 U/kg) was injected in identical dose on two other days. **RESULTS:** Injection of NN304 resulted in a linear and proportional increase in total NN304 concentrations (AUC_{0-1440 min}: 0.15 U/kg: 344+/-43, 0.3 U/kg: 666+/-82, 0.6 U/kg: 1295+/-210 nmol/l; P<0.001). Maximal concentrations (609+/-140, 1046+/-283, 2033+/-460 pmol/l; P<0.001) were reached after 4-6 h. The metabolic response (expressed as maximal glucose infusion rates (GIR)) induced by subcutaneous injection of NN304 did not show the pronounced peak seen with NPH-insulin in an identical dose: GIR_{max} 3.2+/-1.1 vs. 4.4+/-1.8 mg/kg/min (P<0.05 for 0.3 U/kg NN304 vs. NPH-insulin; mean of both study days with NPH-insulin, all others not significant). NN304 also showed a slower onset of action, as indicated by a significantly higher t_{max} (446+/-162 vs. 359+/-175 min) and lower AUC_{0-240min} (0.5+/-0.3 vs. 0.8+/-0.4 g/kg/240min; P<0.05, respectively). The three different doses of NN304 induced a significantly different glucose consumption in the first 720 min after injection (AUC_{0-720 min} 1.1+/-0.6, 1.9+/-0.8, 1.7+/-0.8 g/kg; P<0.05 for 0.15 U/kg), but not over the whole study period (AUC_{0-1440 min} 1.8+/-1.1, 3.1+/-1.3, 2.8+/-1.4 g/kg). **CONCLUSIONS:** Injection of NN304 at different doses resulted in an increase in total NN304 concentration in a linear dose-response effect and a more even metabolic effect than NPH-insulin. However, we found no clear dose-response in its metabolic effect.

Diabetologia. 2005 Oct;48(10):1988-95. Epub 2005 Sep 14.

Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique.

Scholtz HE, Pretorius SG, Wessels DH, Becker RH.

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AIMS/HYPOTHESIS: This single-dose, double-blind, randomised, parallel-group study evaluated the reproducibility in systemic exposure and glucodynamic effect of insulin glargine, NPH insulin (NPH) and insulin ultralente (ultralente) using the manually adjusted euglycaemic clamp technique. **METHODS:** In total, 36 healthy volunteers received two consecutive s.c. injections (0.4 IU/kg) of glargine, NPH or ultralente with a wash-out period of 7 days between treatments. **RESULTS:** In healthy volunteers, glargine presented well-reproduced flat concentration profiles and no pronounced peaks in activity. NPH, by contrast, showed well-defined peaks in concentration and glucose disposal, while ultralente had highly variable profiles. Within-subject variability (ANOVA) for insulin exposure over 24 h was 15% for glargine and 19% for NPH, compared with 67% for ultralente ($p < 0.05$, glargine and NPH vs ultralente). The 49% within-subject variability in total glucose disposal (glucose infusion rate [GIR]-AUC_{0-24 h}) with ultralente was about twice as large as the 22% with NPH ($p < 0.05$), but was intermediate with glargine at 31% ($p = \text{NS}$). By contrast, variability in the diurnal time-action profile (SD of diurnal day-to-day differences in GIR) for glargine was 30% ($p < 0.05$) and 50% ($p < 0.05$) less than with NPH and ultralente, respectively. No serious adverse events were reported. **CONCLUSIONS/INTERPRETATION:** Although representing insulins of different profiles, glargine and NPH showed a high and similar reproducibility of total absorption and glucodynamic effect, whereas ultralente proved to have poor reproducibility. However, while NPH yields peaks in concentration and activity, glargine shows flat and non-fluctuating profiles resulting in less variation in day-to-day 24-h activity.

Diabetes Res Clin Pract. 2005 Oct;70(1):1-7. Epub 2005 Mar 2.

Therapy with insulin glargine (Lantus) in toddlers, children and adolescents with type 1 diabetes.

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OBJECTIVE: To determine the efficacy and safety of insulin glargine (IG) in children and adolescents with type 1 diabetes. In a prospective, 6-month study, 80 patients, aged 2-19 years, received IG once daily plus insulin regular or rapid analogue before meals. The data of body mass index, frequency of severe hypoglycaemia, daily mean blood glucose, fasting blood glucose, haemoglobin A1c and total daily insulin dosage before and after institution of glargine therapy were collected. **RESULTS:** After 6 months, the average HbA1c level in the entire cohort dropped from 7.63 ± 0.81 to $7.14 \pm 0.70\%$ ($p < 0.001$). Fasting blood glucose decreased from 161 ± 37 to 150 ± 35 mg/dl ($p < 0.05$) in the total group. Severe hypoglycaemic episodes were reduced from 0.18 events per patient in the 6 months before IG therapy to 0.11 events per patient in the 6 months after IG therapy. The total daily insulin dose was reduced in the entire group from 0.90 ± 0.32 to 0.83 ± 0.29 u/kg/day ($p < 0.05$). Body mass index (BMI) remained unchanged. In the 14 preschooler children, the HbA1c dropped from 7.54 ± 0.60 to $6.96 \pm 0.57\%$ ($p < 0.05$). **CONCLUSIONS:** Insulin glargine is an efficacious treatment to improve metabolic control in children and adolescents with type 1 diabetes. It also improved the metabolic control in preschool-age children, without increasing the number of hypoglycaemic events.

Intern Med J. 2005 Sep;35(9):536-42.

Glargine is superior to neutral protamine Hagedorn for improving glyated haemoglobin and fasting blood glucose levels during intensive insulin therapy.

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AIM: To compare glycaemic control and symptomatic hypoglycaemia rates with glargine versus neutral protamine Hagedorn (NPH) in poorly controlled type 1 diabetes patients. **METHODS:** Patients ($n = 125$) received preprandial insulin lispro and either glargine (n

= 62) or NPH (n = 63) at bedtime for 30 weeks in a multicentre, randomized, single-blind (a blinded investigator made titration decisions) study. Basal insulin dosage was titrated to achieve fasting blood glucose (FBG) values < 5.5 mmol/L. RESULTS: Baseline characteristics were similar for the two groups (mean diabetes duration 17.5 +/- 10.1 years) except mean glycated haemoglobin (HbA(1c)), which was lower in the glargine versus NPH group (9.2 +/- 1.1% vs 9.7 +/- 1.3%; P < 0.02). At end-point, mean HbA(1c) was 8.3 versus 9.1% for the glargine versus NPH groups. Adjusted least-squares mean (LSM) change from baseline was -1.04 versus -0.51%, a significant treatment benefit of 0.53% for HbA(1c) in favour of glargine (P < 0.01). Mean baseline FBG were similar for the glargine and NPH groups (11.2 vs 11.4 mmol/L). The means for end-point FBG were 7.9 versus 9.0 mmol/L. Adjusted LSM change from baseline was -3.46 versus -2.34 mmol/L, with a significant difference of 1.12 mmol/L in favour of glargine (P < 0.05). There were similar total numbers of daytime mild, moderate or severe hypoglycaemia episodes in the two treatment arms. However, significantly fewer moderate or severe nocturnal hypoglycaemic episodes were observed in the glargine group (P = 0.04 and P = 0.02). CONCLUSION: Glargine is superior to NPH for improving HbA(1c) and FBG levels during intensive insulin therapy in patients with type 1 diabetes, and is associated with less severe nocturnal hypoglycaemia.

Diabetes Metab Res Rev. 2005 Nov-Dec;21(6):545-53.

A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes.

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BACKGROUND: To compare insulin glargine with NPH human insulin for basal insulin supply in adults with type 1 diabetes. **METHODS:** People with type 1 diabetes (n = 585), aged 17-77 years, were randomized to insulin glargine once daily at bedtime or NPH insulin either once- (at bedtime) or twice-daily (in the morning and at bedtime) according to their prior treatment regimen and followed for 28 weeks in an open-label, multicentre study. Both groups continued with pre-meal unmodified human insulin. **RESULTS:** There was no significant difference between the two insulins in change in glycated haemoglobin from baseline to endpoint (insulin glargine 0.21 +/- 0.05% (mean +/- standard error), NPH insulin 0.10 +/- 0.05%). At endpoint, self-monitored fasting blood glucose (FBG) had decreased similarly in each group (insulin glargine -1.17 +/- 0.12 mmol/L, NPH insulin -0.89 +/- 0.12 mmol/L; p = 0.07). However, people on >1 basal insulin injection per day prior to the study had a clinically relevant decrease in FBG on insulin glargine versus NPH insulin (insulin glargine -1.38 +/- 0.15 mmol/L, NPH insulin -0.72 +/- 0.15 mmol/L; p < 0.01). No significant differences in the number of people reporting >or=1 hypoglycaemic episode were found between the two groups, including severe and nocturnal hypoglycaemia. Insulin glargine was well tolerated, with a similar rate of local injection and systemic adverse events versus NPH insulin. **CONCLUSIONS:** A single, bedtime, subcutaneous dose of insulin glargine provided a level of glycaemic control at least as effective as NPH insulin, without an increased risk of hypoglycaemia. Copyright (c) 2005 John Wiley & Sons, Ltd.

Diabetes Care. 2005 Jun;28(6):1282-8.

Improvement of glycaemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine.

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OBJECTIVE: Large prospective studies have demonstrated that optimum glycaemic control is not routinely achieved in clinical practice. Barriers to optimal insulin therapy include hypoglycaemia, weight gain, and suboptimal initiation and dose titration. This study compared two treatment algorithms for insulin glargine initiation and titration: algorithm 1 (investigator led) versus algorithm 2 (performed by study subjects). **RESEARCH DESIGN AND METHODS:** A prospective, multicenter (n = 611), multinational (n = 59), open-label, 24-week randomized trial in 4,961 (algorithm 1, n = 2,493; algorithm 2, n = 2,468) suboptimally controlled type 2 diabetic subjects. **RESULTS:** At baseline, mean diabetes duration was 12.3 +/- 7.2 years, and 72% of subjects were pretreated with insulin. At end point, there was no significant difference in the incidence of severe hypoglycaemia between algorithms 1 and 2 (0.9 vs. 1.1%). There was a significant reduction in HbA(1c) from 8.9 +/- 1.3 to 7.8 +/- 1.2%, with a greater decrease (P < 0.001) with algorithm 2 (-1.22%) versus algorithm 1 (-1.08%). Fasting blood glucose decreased from 170 to 110 mg/dl, with a greater decrease (P < 0.001) with algorithm 2 (-62 mg/dl) versus algorithm 1 (-57 mg/dl). Mean basal insulin dose increased from 22.9 +/- 15.5 to 43.0 +/- 25.5 IU, with a significant difference (P < 0.003) between algorithm 2 (21.6 IU) and algorithm 1 (18.7 IU). **CONCLUSIONS:** Glargine is safe and effective in improving glycaemic control in a large, diverse population with longstanding type 2 diabetes. A simple subject-

administered titration algorithm conferred significantly improved glycemic control with a low incidence of severe hypoglycemia compared with physician-managed titration.

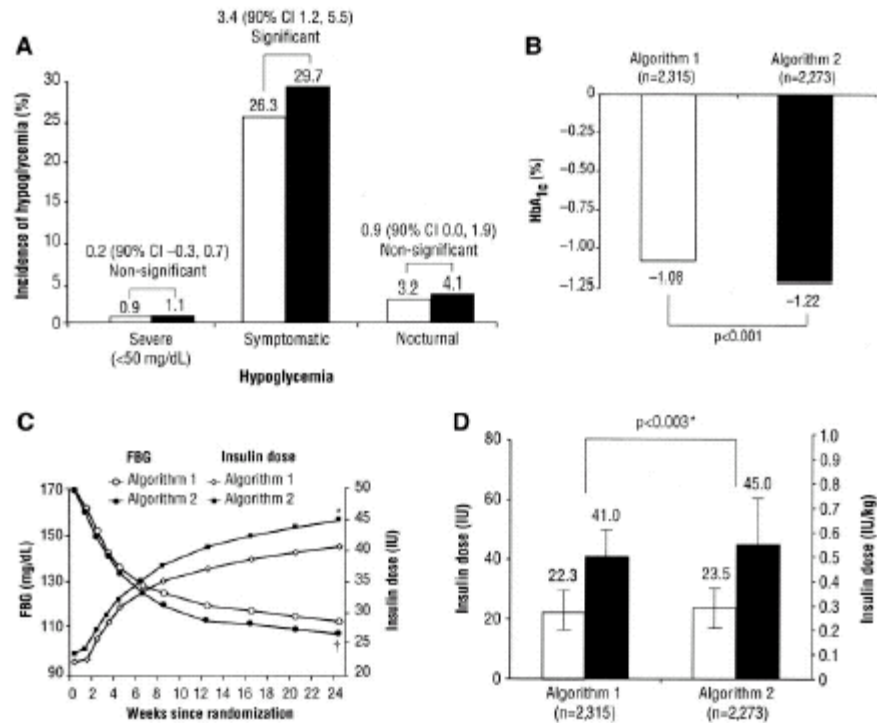


Figure 1—A: Incidence of hypoglycemia in the per-protocol population receiving insulin glargine algorithm 1 (□; n = 2,315) or algorithm 2 (■; n = 2,273). B: Mean reduction in HbA_{1c} levels from baseline to end point in the per-protocol population receiving insulin glargine algorithm 1 or algorithm 2. C: Mean FPG throughout the study compared with mean insulin glargine dose (IU) in the per-protocol population receiving algorithm 1 or algorithm 2. The decrease in FPG and increase in insulin dose from baseline to end point was significant for both algorithms (P < 0.001). *P < 0.003 between algorithms at end point; †P < 0.001 between algorithms at end point. D: Insulin dose at baseline (□) and end point (■) in the per-protocol population receiving insulin glargine algorithm 1 or algorithm 2.

Diabetes Care. 2005 Mar;28(3):560-5.

Effects of exercise on the absorption of insulin glargine in patients with type 1 diabetes.

Peter R, Luzio SD, Dunseath G, Miles A, Hare B, Backx K, Pauvaday V, Owens DR.

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OBJECTIVE: To study the effects of exercise on the absorption of the basal long-acting insulin analog insulin glargine (Lantus), administered subcutaneously in individuals with type 1 diabetes. **RESEARCH DESIGN AND METHODS:** A total of 13 patients (12 men, 1 woman) with type 1 diabetes on a basal-bolus insulin regimen were studied. (125)I-labeled insulin glargine at the usual basal insulin dose was injected subcutaneously into the thigh on the evening (2100) before the study day on two occasions 1 week apart. Patients were randomly assigned to 30 min intense exercise (65% peak oxygen uptake [Vo(2peak)]) on one of these visits. The decay of radioactive insulin glargine was compared on the two occasions using a thallium-activated NaI gamma counter. Blood samples were collected at regular intervals on the study days to assess plasma glucose and insulin profiles. **RESULTS:** No significant difference was found in the (125)I-labeled insulin glargine decay rate on the two occasions (exercise vs. no exercise; repeated-measures ANOVA, P = 0.548). As expected, a significant fall in plasma glucose was observed over the exercise period (area under curve above fasting [DeltaAUC] glucose: -0.39 +/- 0.11 vs. -1.30 +/- 0.16 mmol . l(-1) . h(-1); nonexercise vs. exercise; P = 0.001), but insulin levels did not differ significantly on the two occasions (DeltaAUC insulin: -2.1 +/- 3.9 vs. 1.5 +/- 6.2 pmol . l(-1) . h(-1); nonexercise versus exercise; P = 0.507). **CONCLUSIONS:** An intense 30-min period of exercise does not increase the absorption rate of the subcutaneously injected basal long-acting insulin analog insulin glargine in patients with type 1 diabetes.

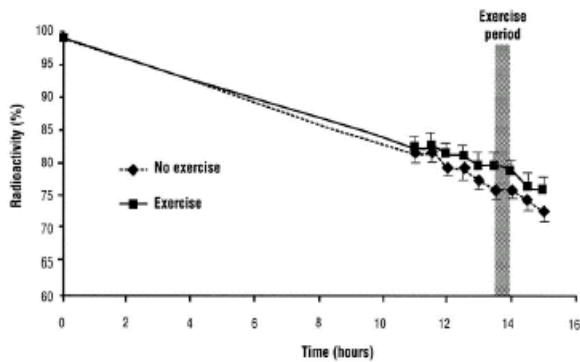


Figure 1—Mean (\pm SE) radioactive disappearance.

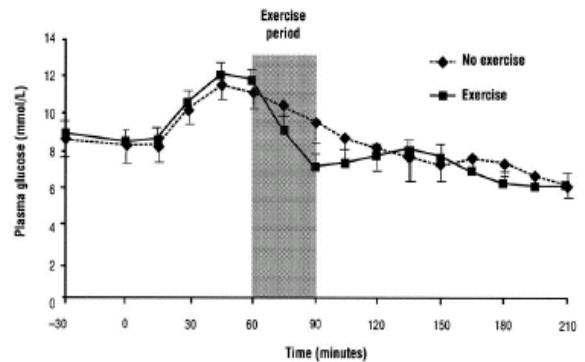


Figure 2—Mean (\pm SE) plasma glucose.

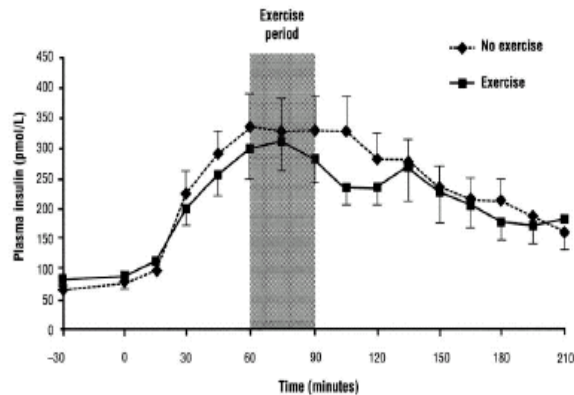


Figure 3—Mean (\pm SE) plasma insulin.

Diabetes Care. 2005 Feb;28(2):260-5.

Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs.

Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A; INITIATE Study Group.

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OBJECTIVE: Safety and efficacy of biphasic insulin aspart 70/30 (BIAsp 70/30, prebreakfast and presupper) were compared with once-daily insulin glargine in type 2 diabetic subjects inadequately controlled on oral antidiabetic drugs (OADs). **RESEARCH DESIGN AND METHODS:** This 28-week parallel-group study randomized 233 insulin-naïve patients with HbA(1c) values $\geq 8.0\%$ on $>1,000$ mg/day metformin alone or in combination with other OADs. Metformin was adjusted up to 2,550 mg/day before insulin therapy was initiated with 5-6 units BIAsp 70/30 twice daily or 10-12 units glargine at bedtime and titrated to target blood glucose (80-110 mg/dl) by algorithm-directed titration. **RESULTS:** A total of 209 subjects completed the study. At study end, the mean HbA(1c) value was lower in the BIAsp 70/30 group than in the glargine group (6.91 \pm 1.17 vs. 7.41 \pm 1.24%, $P < 0.01$). The HbA(1c) reduction was greater in the BIAsp 70/30 group than in the glargine group (-2.79 \pm 0.11 vs. -2.36 \pm 0.11%, respectively; $P < 0.01$), especially for subjects with baseline HbA(1c) $>8.5\%$ (-3.13 \pm 1.63 vs. -2.60 \pm 1.50%, respectively; $P < 0.05$). More BIAsp 70/30-treated subjects reached target HbA(1c) values than glargine-treated subjects (HbA(1c) $\leq 6.5\%$: 42 vs. 28%, $P < 0.05$; HbA(1c) $<7.0\%$: 66 vs. 40%, $P < 0.001$). Minor hypoglycemia (episodes/year) was greater in the BIAsp 70/30 group than in the glargine group (3.4 \pm 6.6 and 0.7 \pm 2.0, respectively; $P < 0.05$). Weight gain and daily insulin dose at study end were greater for BIAsp 70/30-treated subjects than for glargine-treated subjects (weight gain: 5.4 \pm 4.8 vs. 3.5 \pm 4.5 kg, $P < 0.01$; insulin dose: 78.5 \pm 39.5 and 51.3 \pm 26.7 units/day, respectively). **CONCLUSIONS:** In subjects with type 2 diabetes poorly controlled on OADs, initiating insulin therapy with twice-daily BIAsp 70/30 was more effective in achieving HbA(1c) targets than once-daily glargine, especially in subjects with HbA(1c) $>8.5\%$.

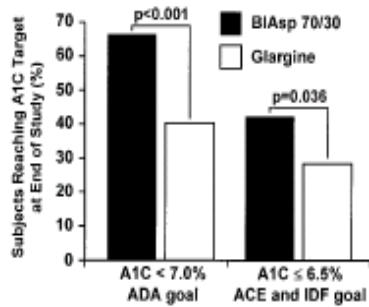


Figure 1—Percentage of subjects achieving HbA_{1c} target values at the end of the study. P values were calculated from Fisher's exact test. ADA, American Diabetes Association; ACE, American College of Endocrinology; IDF, International Diabetes Federation.

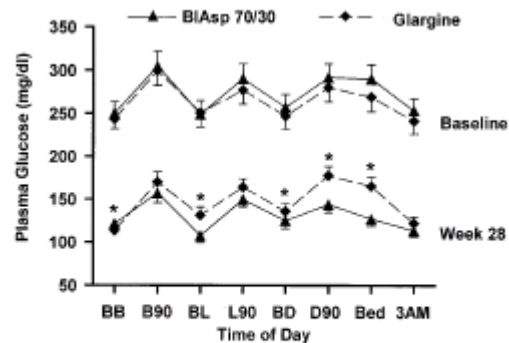


Figure 2—Eight-point SMPG readings before breakfast, lunch, and supper [BB, BL, and BD] and 90 min after breakfast, lunch, and supper [B90, L90, and D90]; at bedtime [Bed]; and at 3:00 A.M. Number of data points at each time point at baseline, 114–116; at week 28, BIAsp 70/30, 97–99; glargine, 105–106. Statistically significant differences ($P < 0.05$) between treatment groups at specific time points are indicated with an asterisk. Error bars represent 2 SE.

Diabetes Care. 2005 Feb;28(2):254-9.

Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes.

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OBJECTIVE: To compare the efficacy and safety of adding once-daily basal insulin versus switching to twice-daily premixed insulin in type 2 diabetic patients insufficiently controlled by oral antidiabetic agents (OADs). **RESEARCH DESIGN AND METHODS:** In a 24-week, multinational, multicenter, open, parallel group clinical trial, 371 insulin-naïve patients with poor glycemic control (fasting blood glucose [FBG] ≥ 120 mg/dl, HbA(1c) 7.5–10.5%) on OADs (sulfonylurea plus metformin) were randomized to once-daily morning insulin glargine plus glimepiride and metformin (glargine plus OAD) or to 30% regular/70% human NPH insulin (70/30) twice daily without OADs. Insulin dosage was titrated to target FBG ≤ 100 mg/dl (both insulins) and predinner blood glucose ≤ 100 mg/dl (70/30 only) using a weekly forced-titration algorithm. **RESULTS:** Mean HbA(1c) decrease from baseline was significantly more pronounced (-1.64 vs. -1.31%, $P = 0.0003$), and more patients reached HbA(1c) $\leq 7.0\%$ without confirmed nocturnal hypoglycemia (45.5 vs. 28.6%, $P = 0.0013$) with glargine plus OAD than with 70/30. Similarly, FBG decrease was greater with glargine plus OAD (adjusted mean difference -17 mg/dl [-0.9 mmol/l], $P < 0.0001$), and more patients reached target FBG ≤ 100 mg/dl with glargine plus OAD than with 70/30 (31.6 vs. 15.0%, $P = 0.0001$). Glargine plus OAD patients had fewer confirmed hypoglycemic episodes than 70/30 patients (mean 4.07 vs. 9.87/patient-year, $P < 0.0001$). **CONCLUSIONS:** Initiating insulin treatment by adding basal insulin glargine once daily to glimepiride plus metformin treatment was safer and more effective than beginning twice-daily injections of 70/30 and discontinuing OADs in type 2 diabetic patients inadequately controlled with OADs.

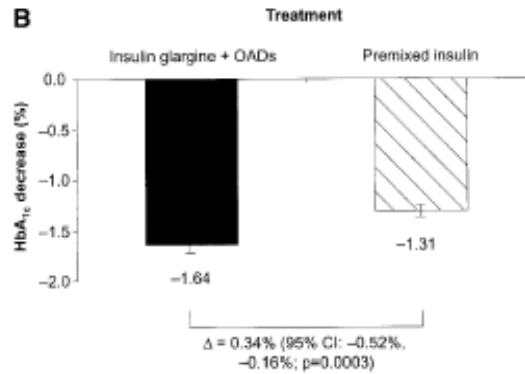
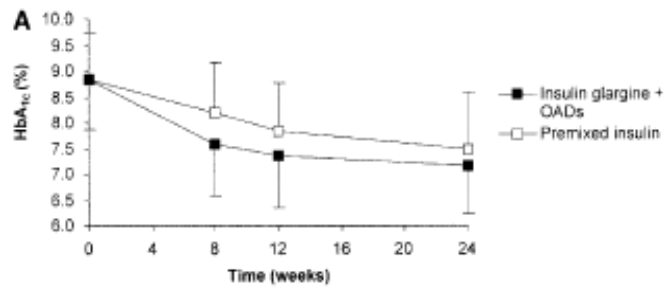


Figure 1—A: Change in HbA_{1c} over 24 weeks (mean \pm SD) in insulin glargine plus glimepiride and metformin (insulin glargine + OADs) and premixed insulin treatment groups. B: Improvement in HbA_{1c} (adjusted mean decrease from baseline [before insulin initiation] to end point \pm SE).

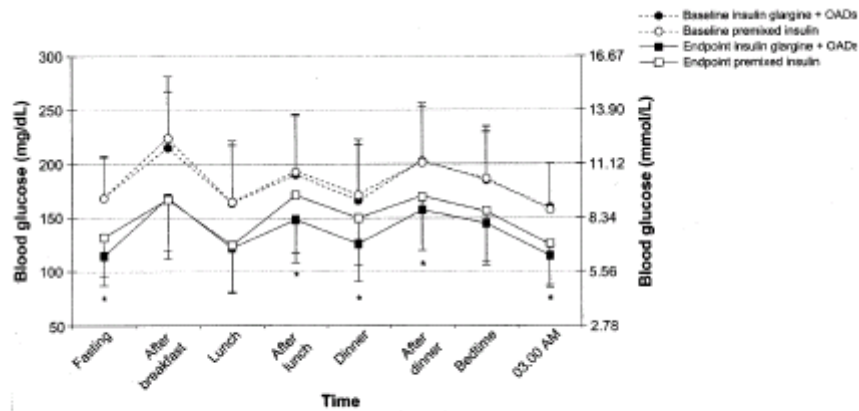


Figure 2—Twenty-four-hour eight-point blood glucose profiles at baseline (before insulin initiation) and end point in insulin glargine plus glimepiride and metformin (insulin glargine + OADs) and premixed insulin treatment groups (* $P < 0.05$ for treatment comparison of changes from baseline to end point).

Diabetes Technol Ther. 2004 Oct;6(5):589-95.

Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes.

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BACKGROUND: The goal of new therapies introduced for type 1 diabetes should be to decrease hypoglycemic episodes while improving glycemc control. **METHODS:** A database was used to computer match the baseline A1C values in 196 subjects with type 1 diabetes receiving multiple daily injections (MDI) consisting of four or more injections per day. There were 98 patients transferred from NPH to insulin glargine (Lantus, Aventis Pharmaceuticals, Bridgewater, NJ), and 98 patients remained on NPH throughout the study. The gender distribution and mean age (approximately 32 years), duration of diabetes (approximately 16 years), and duration of treatment (approximately 13 months) were not significantly different between the groups. The majority of patients were well controlled (>50% in both groups had an A1C <7%). **RESULTS:** The mean A1c values were not significantly different in the groups at baseline or at follow-up. Severe hypoglycemic episodes per patient per year were significantly lower in the glargine group compared with the NPH group (0.5 vs. 1.2, respectively; $P = 0.04$). The mean end-of-study total ($P = 0.03$) and long-acting ($P = 0.0001$) doses were significantly reduced from baseline in the group that switched to glargine, but not in the group that remained on NPH, with no change in the short-acting dose in either group. The weight gain was significantly higher in the NPH group at the end of the study ($P = 0.004$) with no significant change in the glargine group. **CONCLUSIONS:** Transfer to glargine treatment from NPH in MDI regimens

significantly reduces severe hypoglycemic episodes despite a decline in long-acting basal insulin without significant weight gain.

Diabetes Care. 2005 Jan;28(1):10-4.

Randomized controlled clinical trial of glargine versus ultralente insulin in the treatment of type 1 diabetes.

Kudva YC, Basu A, Jenkins GD, Pons GM, Quandt LL, Gebel JA, Vogelsang DA, Smith SA, Rizza RA, Isley WL.

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OBJECTIVE: Multiple daily insulin injection programs are commonly accompanied by considerable glycemic variation and hypoglycemia. We conducted a randomized crossover design clinical trial to compare glargine with ultralente insulin as a basal insulin in type 1 diabetes. **RESEARCH DESIGN AND METHODS:** To determine whether the use of glargine insulin as a basal insulin would result in a comparable HbA_{1c} and less glycemic variation and hypoglycemia than ultralente insulin, 22 individuals (aged 44 +/- 14 years [+/-SD], 55% men) with type 1 diabetes who were experienced with multiple daily insulin injections and had an HbA_{1c} of <7.8% were randomized in a crossover design to receive either glargine or ultralente as the basal insulin for 4 months. Aspart insulin was used as the prandial insulin. Physicians providing insulin dose adjustment advice were masked to the type of basal insulin. **RESULTS:** Treatment with glargine resulted in lower mean HbA_{1c} (6.82 +/- 0.13 vs. 7.02 +/- 0.13, difference: 0.2 +/- 0.08, P = 0.026), less nocturnal variability (plasma glucose 49.06 +/- 4.74 vs. 62.36 +/- 5.21 mg/dl, P = 0.04), and less hypoglycemia (24.5 +/- 2.99 vs. 31.3 +/- 4.04 events, P = 0.05), primarily due to less daytime hypoglycemia (P = 0.002). On the other hand, serious hypoglycemia and average glucose concentration measured with continuous subcutaneous glucose monitoring did not differ. **CONCLUSIONS:** We conclude that while use of either ultralente or glargine as a basal insulin can result in excellent glycemic control, treatment with glargine is associated with slightly but significantly lower HbA_{1c} and less nocturnal glycemic variability and hypoglycemia.

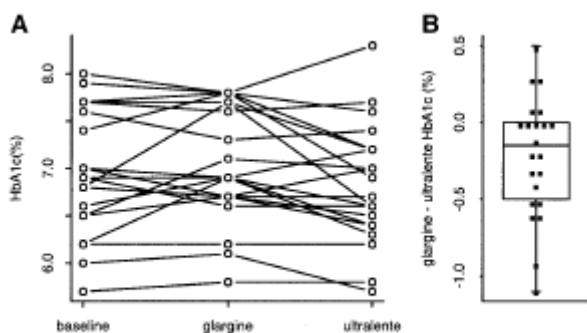


Figure 2—HbA_{1c} during the trial. Difference indicates the difference of HbA_{1c} at the end of the glargine phase and at the end of the ultralente phase.

Am J Med Sci. 2004 Nov;328(5):274-80.

A comparison of bedtime insulin glargine with bedtime neutral protamine hagedorn insulin in patients with type 2 diabetes: subgroup analysis of patients taking once-daily insulin in a multicenter, randomized, parallel group study.

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BACKGROUND: Basal insulin is frequently administered once daily. This subgroup analysis of a multicenter, randomized, parallel study compared insulin glargine (Lantus Aventis Pharmaceuticals, Bridgewater, NJ) with neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes, evaluating only patients treated previously with once-daily NPH insulin. **METHODS:** Patients received bedtime insulin glargine or NPH insulin, with preprandial regular insulin. One hundred patients (mean age, 57.9 years; mean glycohemoglobin, 8.4%; mean fasting blood glucose, 167 mg/dL) were treated for up to 28 weeks. **RESULTS:** Patients treated with insulin glargine (n = 52) and NPH insulin (n = 48) achieved similar reductions from baseline in glycohemoglobin (-0.41% versus -0.46%) and fasting blood glucose (-22 mg/dL versus -22 mg/dL) at week 28. The proportion of patients reaching target fasting blood glucose (<120 mg/dL) at 28 weeks was 34.2% with insulin glargine and 24.4% with NPH insulin. Similar proportions of patients

achieved glycohemoglobin less than 7% and less than 8% in both groups. Baseline and week-28 mean daily doses of insulin glargine (27.3 IU versus 36.4 IU) were similar to NPH insulin doses (25.5 IU versus 30.2 IU). However, significantly fewer patients reported one or more episodes of hypoglycemia with insulin glargine (46.2%) versus NPH insulin (60.4%; $P < 0.05$). Significantly fewer patients also reported one or more symptomatic episodes confirmed by blood glucose less than 50 mg/dL with insulin glargine (17.3%) versus NPH insulin (31.3%; $P < 0.005$). **CONCLUSION:** Bedtime insulin glargine is as effective as bedtime NPH insulin in improving glycemic control, with significantly less hypoglycemia.

Diabet Med. 2004 Nov;21(11):1213-20.

Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin.

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BACKGROUND: Glargine is a long-acting insulin analogue potentially more suitable than NPH insulin in intensive treatment of Type 1 diabetes mellitus (T1 DM), but no study has proven superiority. The aim of this study was to test superiority of glargine on long-term blood glucose (BG) as well as on responses to hypoglycaemia vs. NPH. **METHODS:** One hundred and twenty-one patients with T1 DM on intensive therapy on four times/day NPH and lispro insulin at each meal, were randomized to either continuation of NPH four times/day ($n = 60$), or once daily glargine at dinner-time ($n = 61$) for 1 year. Lispro insulin at meal-time was continued in both groups. In 11 patients from each group, responses to stepped hyperinsulinaemic-hypoglycaemia were measured before and after 1 year's treatment. **RESULTS:** Mean daily BG was lower with glargine [7.6 ± 0.11 mmol/l (137 ± 2 mg/dl)] vs. NPH [8.1 ± 0.22 mmol/l (146 ± 4 mg/dl)] ($P < 0.05$). HbA(1c) at 4 months did not change with NPH, but decreased with glargine (from 7.1 ± 0.1 to $6.7 \pm 0.1\%$), and remained lower than NPH at 12 months ($6.6 \pm 0.1\%$, $P < 0.05$ vs. NPH). Frequency of mild hypoglycaemia [self-assisted episodes, blood glucose ≤ 4.0 mmol/l (72 mg/dl)] was lower with glargine vs. NPH (7.2 ± 0.5 and 13.2 ± 0.6 episodes/patient-month, $P < 0.05$). After 1 year, NPH treatment resulted in no change of responses to hypoglycaemia, whereas with glargine plasma glucose, thresholds and maximal responses of plasma adrenaline and symptoms to hypoglycaemia improved ($P < 0.05$). **CONCLUSIONS:** The simpler glargine regimen decreases the percentage of HbA(1c) and frequency of hypoglycaemia and improves responses to hypoglycaemia more than NPH. Thus, glargine appears more suitable than NPH as basal insulin for intensive treatment of T1 DM.

Diabetes Res Clin Pract. 2004 Oct;66(1):49-56.

Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine.

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OBJECTIVE: To see if insulin glargine improves glycemic control in a clinical setting. **Research design and methods:** A questionnaire and electronic database were used to assess glycemic parameters for 292 type 1 diabetic subjects taking $> \text{ or } = 4$ injections per day and receiving glargine as their only long-acting basal insulin for at least 6 months. Sixty-three subjects were taking glargine in the morning, 125 were taking glargine in the evening, and 104 were splitting the glargine dose between the morning and evening. **RESULTS:** The mean (\pm S.D.) age and duration of diabetes were 32 ± 10 years and 15.9 ± 10.3 years, respectively. The mean (\pm S.E.M.) durations of treatment with glargine were 13.1 ± 0.6 months, 12.2 ± 0.4 months, and 14.3 ± 0.5 months for the morning, evening, and split treatment groups, respectively ($P < 0.01$). The A1C values improved significantly from baseline for the evening and the split dosage groups or when all groups were combined. The mean basal insulin dose was significantly reduced at the end of the study in all the three groups from baseline with no change in the short-acting insulin dose. The number of severe hypoglycemic episodes decreased from 379 in the year prior to glargine treatment to 167 in the post-glargine year. The weight gain was significantly higher in the group that took the split glargine dose ($P < 0.01$). **CONCLUSIONS:** Similar or improved glycemic control was achieved by administering glargine in the morning, evening, or using a split dose without any further increase in severe hypoglycemic episodes. Splitting the glargine dose did not offer any advantages in glycemic control parameters.

Diabetes Res Clin Pract. 2004 Oct;66(1):49-56.

Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes.

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OBJECTIVE: To present the findings in a randomized, parallel-group study, comparing once-daily insulin glargine with twice-daily NPH insulin in patients with type 1 diabetes previously treated with multiple daily injections of basal and regular insulin. **METHODS:** Of 394 patients with type 1 diabetes treated for up to 28 weeks, 195 received insulin glargine and 199 received NPH insulin, in addition to preprandial regular insulin. Glycemic control and hypoglycemic episodes were assessed. **RESULTS:** A greater mean decrease in fasting blood glucose (FBG) was achieved at endpoint with insulin glargine than with NPH insulin (-21 mg/dL versus -10 mg/dL [-1.17 mmol/L versus -0.56 mmol/L]; $P = 0.015$), and a greater percentage of patients treated with insulin glargine reached the target FBG (32.6% versus 21.3%; $P = 0.015$). Similar percentages of patients in both treatment groups achieved glycosylated hemoglobin values of 7.0% or less at endpoint (insulin glargine, 35.8%; NPH insulin, 35.4%). After the 1-month titration phase, the percentage of patients who reported at least one symptomatic hypoglycemic event confirmed by a blood glucose value of less than 50 mg/dL (2.8 mmol/L) was significantly lower with insulin glargine than with NPH insulin (73.3% versus 81.7%; $P = 0.021$). Furthermore, the percentage of patients who reported at least one symptomatic hypoglycemic event confirmed by a blood glucose value of less than 36 mg/dL (2.0 mmol/L) was significantly lower with insulin glargine than with NPH insulin (36.6% versus 46.2%; $P = 0.033$). **CONCLUSION:** Once-daily insulin glargine was at least as effective as twice-daily NPH insulin in improving fasting glycemic control and resulted in fewer reported symptomatic hypoglycemic events.

Diabetes Nutr Metab. 2004 Apr;17(2):84-9.

Effect of continuous subcutaneous insulin infusion vs multiple daily insulin injection with glargine as basal insulin: an open parallel long-term study.

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UO Diabetologia, AO Ospedali Riuniti di Bergamo, Largo Barozzi 1, I-24128 Bergamo, Italy. glepore@ospedaliriuniti.bergamo.it

Aim of this 1-yr open parallel study was to evaluate the efficacy of two regimens of intensive insulin treatment: continuous s.c. insulin infusion (CSII) and multiple daily insulin injection (MDI) treatment with lispro plus glargine in 48 Type 1 diabetic patients that had been treated with MDI (regular or lispro insulin before each meal plus NPH) for at least 1 yr. Twenty-four patients treated with CSII, receiving lispro at multiple basal infusion rates plus boluses at meal (CSII group), were compared to 24 patients, matched for age, duration of diabetes and metabolic control, treated with MDI with lispro at each meal combined with glargine (glargine group). In the CSII group, compared to traditional MDI treatment, there was a decrease in HbA1c (9.0 +/- 1.3% during traditional MDI vs 8.0 +/- 1.0% during CSII, $p < 0.001$), severe hypoglycaemic episodes (0.42 vs 0.17 per patient/yr, $p < 0.05$), insulin requirement (48 +/- 11.7 vs 35.9 +/- 8.5 U/day, $p < 0.001$). In the glargine group, compared to MDI traditional treatment, there was a decrease in HbA1c (8.6 +/- 1.1 vs 7.9 +/- 1.2%, $p < 0.001$) and severe hypoglycaemic episodes (0.46 vs 0.21 per patient/yr, $p < 0.05$). No significant difference between the CSII group and the glargine group was present in the degree of improvement in HbA1c and severe hypoglycaemic episodes. However, in the CSII group there was a significantly greater reduction in mean amplitude of glycaemic excursions (MAGE) and insulin requirement than in the glargine group. In conclusion, despite a similar improvement in metabolic control, CSII improves blood glucose variability when compared to MDI with glargine as basal insulin.

Diabetes Care. 2004 Feb;27(2):632-3.

Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetic patients using basal/bolus therapy.

Albright ES, Desmond R, Bell DS.

Acta Diabetol. 2003 Dec;40(4):156-62.

Equipotency of insulin glargine and regular human insulin on glucose disposal in healthy subjects following intravenous infusion.

Scholtz HE, Pretorius SG, Wessels DH, Venter C, Potgieter MA, Becker RH.

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The absolute glucose disposal of insulin glargine (Lantus) was compared to that of regular human insulin in healthy subjects (n=20) using the euglycaemic clamp technique in a single-dose, double-blind, randomized, two-way crossover design. Subjects received 30-minute intravenous infusions of insulin glargine (0.1 IU/kg) or human insulin (0.1 IU/kg) and a 20% glucose solution infused at a variable rate to maintain euglycaemia at the subject's baseline glucose level. At equal baseline blood glucose levels (4.42 mmol/l [range, 4.00-5.16 mmol/l] and 4.42 mmol/l [range, 4.01-4.94 mmol/l], respectively), the area under the glucose infusion rate (GIR) time curves from 0-6 hours (AUC(0-6h)) was within the bioequivalence range (insulin glargine, 663.92 mg/kg; human insulin, 734.85 mg/kg). Both the time to maximum GIR and the suppression of serum C-peptide were similar with insulin glargine and human insulin. The resulting maximum serum insulin concentrations (C_{max}) were 151.16 microIU/ml and 202.23 microIU/ml, and the time to C_{max} (T_{max}) was 30 minutes (the duration of the infusion). The observed differences in the C_{max} (the mean value for insulin glargine was about 25% lower than that of human insulin) could be explained by lower cross-reactivity of insulin glargine in the human insulin radioimmunoassay. The employed intravenous route, though definitely not the intended clinical use of insulin glargine, provided the clinical evidence in healthy subjects that on a molar basis insulin glargine is equipotent to regular human insulin regarding glucose disposal.

Arterioscler Thromb Vasc Biol. 2004 Feb;24(2):325-30. Epub 2003 Dec

3.5 years of insulin therapy with insulin glargine improves in vivo endothelial function in type 2 diabetes.

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OBJECTIVE: To determine long-term effects of insulin glargine on vascular function in patients with type 2 diabetes. **METHODS AND RESULTS:** A total of 49 in vivo endothelial function tests, intrabrachial artery infusions of endothelium-dependent (acetylcholine [ACh]) and endothelium-independent (sodium nitroprusside [SNP]) vasoactive agents, were performed in 11 patients with type 2 diabetes (age: 59+/-2 years; BMI: 29.7+/-0.9 kg/m²; fasting plasma glucose: 226+/-14 mg/dL) and 16 matched normal subjects. The tests in the type 2 diabetic patients were performed before and after 6 months and 3.5 years of combination therapy with insulin glargine and metformin. A control group of type 2 diabetic patients not treated with insulin was studied twice at 6-month intervals. Before treatment, blood flow during infusions of low and high doses of ACh were significantly lower in the type 2 diabetic patients than in the normal subjects (P=0.021 for ANOVA). In the patients with type 2 diabetes, blood flow during infusion of the low dose of ACh averaged 7.1+/-0.8 mL/dL per minute at baseline, 8.8+/-1.0 mL/dL per minute at 6 months (NS), and then increased compared with baseline by 87+/-29% to 11.6+/-1.4 mL/dL per minute at 3.5 years (P<0.02 versus baseline). Blood flow during infusion of the high dose of ACh increased from 8.8+/-0.9 at baseline to 13.0+/-1.9 mL/dL per minute at 6 months (P<0.05) and by 86+/-25% to 14.7+/-1.6 mL/dL per minute at 3.5 years (P<0.01 versus baseline), which was not different from normal subjects. Blood flow during infusion of low (blood flow at 0 months: 7.7+/-0.5; at 6 months: 9.9+/-0.6; P<0.01 for 6 versus 0 months; and 3.5 years: 11.6+/-1.1 mL/dL per minute; P<0.02 for 3.5 years versus 0 months) and high (blood flow at 0 months: 10.7+/-0.9; 6 months: 13.4+/-1.0; P<0.05 for 6 versus 0 months; and 3.5 years: 16.6+/-1.5 mL/dL per minute; P<0.05 for 3.5 years versus 0 months) doses of SNP also increased significantly during insulin therapy. **CONCLUSIONS:** We conclude that insulin glargine therapy improves endothelium-dependent and endothelium-independent vasodilatation. These data support the idea that long-term insulin therapy has

beneficial rather than harmful effects on vascular function in type 2 diabetes.

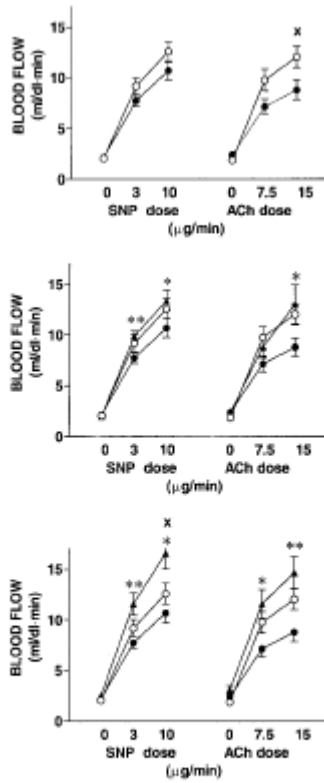


Figure 1. Forearm blood flow responses to intra-arterial SNP and ACh infusions in the type 2 diabetic patients before (●) and after (▲) insulin glargine therapy, and in the normal subjects (O) at baseline (upper panel), 6 months (middle panel), and 3.5 years (lower panel). $^{\#}P < 0.05$ for type 2 diabetic patients versus normal subjects. $^*P < 0.05$ and $^{**}P < 0.01$ for type 2 diabetic patients before versus after insulin therapy.

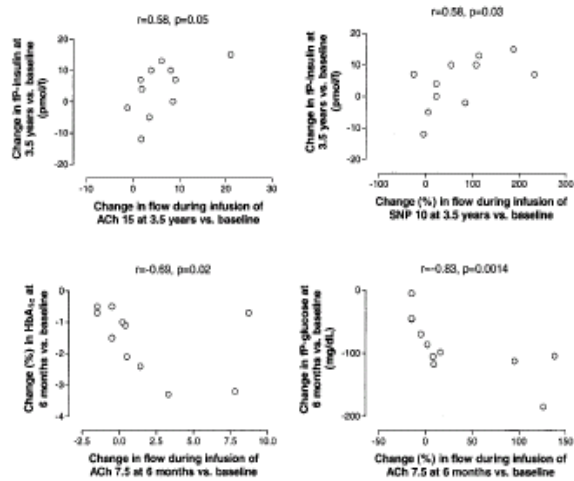


Figure 2. Relationships (Spearman non-parametric correlation coefficient) between changes in fasting plasma insulin and blood flow during infusion of the high dose of acetylcholine at 3.5 years versus baseline (upper left panel), changes in fasting plasma insulin and blood flow (%) during infusion of the high dose of sodium nitroprusside at 3.5 years versus baseline (upper right panel), changes (%) in glycosylated hemoglobin and blood flow during infusion of the low dose of acetylcholine at 6 months versus baseline (lower right panel), and changes in fasting plasma glucose and blood flow (%) during infusion of the low dose of acetylcholine at 6 months versus baseline (lower left panel). SNP 10 indicates sodium nitroprusside at a rate of 10 μg/min; ACh 7.5, acetylcholine at a rate of 7.5 μg/min; ACh 15, acetylcholine at a rate of 15 μg/min; IP, fasting plasma; HbA_{1c}, glycosylated hemoglobin.

J Pediatr. 2003 Dec;143(6):737-40.

Reduced hypoglycemic episodes and improved glyceemic control in children with type 1 diabetes using insulin glargine and neutral protamine Hagedorn insulin.

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OBJECTIVE: The purpose of this study was to evaluate the use of a new long-acting basal insulin, insulin glargine (IG), in children with type 1 diabetes. Study design Data from 114 subjects, age 2 to 18 years (mean, 12.2 years; 54 boys, 60 girls), were collected for 9 months before and 9 months after IG treatment. During IG therapy, all subjects received morning neutral protamine Hagedorn insulin (given with insulin lispro; Humalog) to provide daytime insulin coverage. The numbers of nonsevere and severe hypoglycemic events, hemoglobin A1c values, body weight, and daily insulin dose were recorded at each clinic visit. **RESULTS:** The mean (+/-1 SEM) frequency of nonsevere hypoglycemic events per week decreased from 2.0+/-0.1 to 1.3+/-0.1 (P<.001). Severe hypoglycemic episodes were reduced from a total of 22 in the 9 months before IG to nine in the 9 months after IG. Severe nocturnal events were similarly reduced from 14 to four episodes. The mean (+/-1 SEM) hemoglobin A1c levels were 9.6+/-0.1% (baseline), 9.4+/-0.1% at 3 months (P=.18), 9.3+/-0.1% at 6 months (P=.03), and 9.3+/-0.1% at 9 months (P=.01). **CONCLUSION:** Insulin glargine therapy can reduce hypoglycemic episodes in children and adolescents with suboptimal glucose control without jeopardizing glyceemic control.

Diabetes Care. 2003 Nov;26(11):3080-6.

The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients.

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OBJECTIVE: To compare the abilities and associated hypoglycemia risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA(1c). **RESEARCH DESIGN AND METHODS:** In a randomized, open-label, parallel, 24-week multicenter trial, 756 overweight men and women with inadequate glyceemic control (HbA(1c) >7.5%) on one or two oral agents continued prestudy oral agents and received bedtime glargine or NPH once daily, titrated using a simple algorithm seeking a target fasting plasma glucose (FPG) \leq 100 mg/dl (5.5 mmol/l). Outcome measures were FPG, HbA(1c), hypoglycemia, and percentage of patients reaching HbA(1c) \leq 7% without documented nocturnal hypoglycemia. **RESULTS:** Mean FPG at end point was similar with glargine and NPH (117 vs. 120 mg/dl [6.5 vs. 6.7 mmol/l]), as was HbA(1c) (6.96 vs. 6.97%). A majority of patients (approximately 60%) attained HbA(1c) \leq 7% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia (\leq 72 mg/dl [4.0 mmol/l]) with glargine (33.2 vs. 26.7%, P < 0.05). Moreover, rates of other categories of symptomatic hypoglycemia were 21-48% lower with glargine. **CONCLUSIONS:** Systematically titrating bedtime basal insulin added to oral therapy can safely achieve 7% HbA(1c) in a majority of overweight patients with type 2 diabetes with HbA(1c) between 7.5 and 10.0% on oral agents alone. In doing this, glargine causes significantly less nocturnal hypoglycemia than NPH, thus reducing a leading barrier to initiating insulin. This simple regimen may facilitate earlier and effective insulin use in routine medical practice, improving achievement of recommended standards of diabetes care.

Horm Metab Res. 2003 Jul;35(7):434-8.

Comparison of the subcutaneous absorption of insulin glargine (Lantus) and NPH insulin in patients with Type 2 diabetes.

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The aim of this study was to compare the subcutaneous absorption characteristics of insulin glargine with NPH insulin in patients with

Type 2 diabetes. In this single-dose, double-blind, randomized, two-way crossover study, 14 patients with Type 2 diabetes (aged 40-70 years) previously untreated with insulin were randomized to receive in a fasting state either a single subcutaneous injection of 0.3 U/kg 125I-insulin glargine or 0.3 U/kg 125I-NPH insulin. The disappearance of radioactivity was monitored for forty-eight hours. The median time for 25%, 50% and 75% of the radioactivity to disappear from the injection site was significantly longer for insulin glargine compared with NPH insulin (T75% 15.0 and 6.5 h, $p=0.009$; T50% 26.3 and 13.4 h, $p=0.009$; T25% 42.4 and 26.6 h, $p=0.019$, respectively). The mean residual radioactivity remaining at 24, 36 and 48 h after injection remained significantly higher than NPH insulin (54.4 and 27.9%, $p=0.0001$; 35.0 and 17.0%, $p=0.003$; 19.2 and 9.2%, $p=0.01$, respectively). Mean plasma glucose levels reached a minimum after 14.6 and 9 h in response to insulin glargine and NPH insulin, respectively. The subcutaneous absorption of insulin glargine in fasting Type 2 diabetes patients was significantly (2-3 times) slower compared with NPH insulin in patients with Type 2 diabetes. The slower absorption of insulin glargine correlated with the fall in plasma glucose levels over a 24 h period compared with the faster insulin absorption and more rapid decrease in plasma glucose levels observed in response to NPH insulin. Both insulin glargine and NPH insulin were well tolerated.

Drugs. 2003;63(16):1743-78.

Insulin glargine: an updated review of its use in the management of diabetes mellitus.

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Insulin glargine is a human insulin analogue prepared by recombinant DNA technology. Modification of the human insulin molecule at position A21 and at the C-terminus of the B-chain results in the formation of a stable compound that is soluble at pH 4.0, but forms amorphous microprecipitates in subcutaneous tissue from which small amounts of insulin glargine are gradually released. The plasma concentration versus time profile of insulin glargine is therefore relatively constant in relation to conventional human insulins, with no pronounced peak over 24 hours. This allows once-daily administration as basal therapy. Early randomised trials with insulin glargine generally showed greater reductions in fasting blood or plasma glucose levels and a reduced frequency of nocturnal hypoglycaemia relative to neutral protamine Hagedorn (NPH) insulin in patients with type 1 diabetes mellitus. In addition to this basal therapy, patients continued to use the regular mealtime insulin regimen to which they were accustomed. More recent data with insulin glargine have included evidence of improved glycaemic control, with improvements in satisfaction with treatment over NPH insulin. Furthermore, the time of day at which insulin glargine is injected has no clinically relevant effect on glycaemic control in these patients. There are also data from small, nonblind studies to suggest comparable glycaemic control with insulin glargine and continuous subcutaneous insulin infusion. Results from comparative studies and meta-analyses in individuals with type 2 diabetes show lower incidences of nocturnal hypoglycaemia with insulin glargine than with NPH insulin, with two studies showing a significantly greater improvement in glycosylated haemoglobin levels with insulin glargine than with NPH. Insulin glargine is well tolerated, and is not associated with greater immunogenicity or increases in bodyweight than NPH insulin. Long-term data show maintenance of glycaemic control with insulin glargine for up to 39 months in adults and children with type 1 and adults with type 2 diabetes. In conclusion, insulin glargine is an effective and well tolerated basal insulin therapy when given as a single daily subcutaneous injection to patients with diabetes, with benefits in terms of glycaemic control and reduced frequency of hypoglycaemia over regimens based on conventional basal insulins. Accumulating data and official recommendations show the suitability of insulin glargine for first-line use in selected patients with type 2 diabetes who require insulin treatment, as well as in patients with type 1 disease, and confirm its use in children and adolescents.

Diabetes Care. 2003 Jun;26(6):1738-44.

A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes.

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OBJECTIVE: Insulin glargine (Lantus), a long-acting human insulin analog, provides effective glycemic control when administered at

bedtime. This open-label, randomized, parallel group, multicenter study investigated whether insulin glargine is equally effective if administered before breakfast, before dinner, or at bedtime. **RESEARCH DESIGN AND METHODS:** Patients with type 1 diabetes on basal-bolus therapy (n = 378, 18-68 years, HbA(1c) 5.5-9.8%) were treated with once-daily individually titrated insulin glargine in combination with prandial insulin lispro for 24 weeks. **RESULTS:** Baseline characteristics were similar in the three groups (overall age 40.9 +/- 11.9 years, diabetes duration 17.3 +/- 11.5 years). Median total daily insulin dose was similar at baseline (0.65, 0.65, and 0.66 IU/kg for breakfast, dinner, and bedtime, respectively) and remained relatively constant over the study period; however, the insulin glargine-to-total insulin dose ratio increased more in the breakfast group than in the dinner and bedtime groups. A similar reduction of adjusted mean HbA(1c) from baseline to end point occurred in all patients (7.6-7.4, 7.6-7.5, and 7.6-7.5% for breakfast, dinner, and bedtime, respectively), and a similar percentage achieved HbA(1c) <7.0% at end point in all groups (29.5, 29.8, and 25.8%, respectively). The 24-h blood glucose profiles in relation to injection time were similar in all groups. The incidences of total symptomatic and severe hypoglycemia did not differ between the three treatment groups; however, nocturnal hypoglycemia occurred in significantly fewer patients in the breakfast group (59.5%) compared with the dinner (71.9%) and bedtime (77.5%) groups (P = 0.005). **CONCLUSIONS:** These data suggest that insulin glargine, in combination with insulin lispro, is safe and effective when administered before breakfast, before dinner, or at bedtime.

Horm Metab Res. 2003 Mar;35(3):189-96.

A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes.

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AIMS: The aim of the trial was to compare the efficacy and safety of the new, long-acting basal insulin, insulin glargine (LANTUS(R)), with NPH human insulin, each administered in a combination regimen with oral antidiabetic drugs in patients with Type 2 diabetes. **METHODS:** In a multicentre, open, randomised study, 570 patients with Type 2 diabetes, aged 34 - 80 years, were treated for 52 weeks with insulin glargine or NPH insulin given once daily at bedtime. Previous oral antidiabetic therapy was continued throughout the study. **RESULTS:** There was a clinically relevant decrease in glycosylated haemoglobin (GHb) values from baseline to endpoint with both drugs (insulin glargine: - 0.46 %; NPH insulin: - 0.38 %; p = 0.415); also, this difference was statistically significant in the subgroup of overweight patients with BMI > 28 kg/m² (insulin glargine: - 0.42 %, NPH insulin: - 0.11 %; p = 0.0237). Over the entire treatment period, NPH insulin-treated patients (41 %) and insulin glargine-treated patients (35 %) experienced a similar level of symptomatic hypoglycaemia. A statistically significant difference was observed in the number of patients treated with NPH insulin who reported at least one episode of nocturnal hypoglycaemia compared with those treated with insulin glargine in the overall population and in the overweight subgroup (overall: 24 % vs. 12 %, p = 0.002; overweight: 22.2 % vs. 9.5 %, p = 0.0006), using the Cochran-Mantel-Haenszel test. These differences were most pronounced in insulin-naive and overweight (BMI > 28 kg/m²) sub-groups. The incidence of adverse events was similar for the two treatments. **CONCLUSIONS:** This study demonstrated that insulin glargine is as effective as NPH insulin in achieving glycaemic control in patients with Type 2 diabetes, and is associated with fewer episodes of symptomatic hypoglycaemia, particularly nocturnal episodes.

Diabetes Care. 2003 May;26(5):1490-6.

Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime.

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OBJECTIVE: To establish differences in blood glucose between different regimens of optimized basal insulin substitution in type 1 diabetic patients given lispro insulin at meals, i.e., NPH injected four times a day versus glargine insulin once daily at dinner or at bedtime. **RESEARCH DESIGN AND METHODS:** A total of 51 patients with type 1 diabetes on intensive therapy (NPH four times/day and lispro insulin at each meal) were randomized to three different regimens of basal insulin substitution while continuing lispro insulin at meals: continuation of NPH four times/day (n = 17), once daily glargine at dinnertime (n = 17), and once daily glargine at bedtime (n = 17) for 3 months. Blood glucose targets were fasting, preprandial, and bedtime concentrations at 6.4-7.2 mmol/l and 2 h after meals at 8.0-9.2 mmol/l. The primary end point was HbA(1c). **RESULTS:** Mean daily blood glucose was lower with dinnertime glargine (7.5 +/- 0.2 mmol/l) or bedtime glargine (7.4 +/- 0.2 mmol/l) versus NPH (8.3 +/- 0.2 mmol/l) (P < 0.05). A

greater percentage of blood glucose values were at the target value with glargine at dinner and bedtime versus those with NPH ($P < 0.05$). HbA(1c) at 3 months did not change with NPH but decreased with glargine at dinnertime (from 6.8 ± 0.2 to $6.4 \pm 0.1\%$) and glargine at bedtime (from 7.0 ± 0.2 to $6.6 \pm 0.1\%$) ($P < 0.04$ vs. NPH). Total daily insulin doses were similar with the three treatments, but with glargine there was an increase in basal and a decrease in mealtime insulin requirements ($P < 0.05$). Frequency of mild hypoglycemia (self-assisted episodes, blood glucose ≤ 4.0 mmol/l) was lower with glargine (dinnertime 8.1 ± 0.8 mmol/l, bedtime 7.7 ± 0.9 mmol/l) than with NPH (12.2 ± 1.3 mmol/l) (episodes/patient-month, $P < 0.04$). In-hospital profiles confirmed outpatient blood glucose data and indicated more steady plasma insulin concentrations at night and before meals with glargine versus NPH ($P < 0.05$). There were no differences between glargine given at dinnertime and at bedtime. **CONCLUSIONS:** Regimens of basal insulin with either NPH four times/day or glargine once/day in type 1 diabetic patients both result in good glycemic control. However, the simpler glargine regimen decreases the HbA(1c) level and frequency of hypoglycemia versus NPH. In contrast to NPH, which should be given at bedtime, insulin glargine can be administered at dinnertime without deteriorating blood glucose control.

Diabetes Care. 2003 Mar;26(3):799-804.

Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens.

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OBJECTIVE: To compare blood glucose control and incidence of nocturnal hypoglycemia in adolescents with type 1 diabetes on multiple injection regimens managed with either an insulin analog combination or NPH insulin plus regular human insulin. **RESEARCH DESIGN AND METHODS:** In a randomized cross-over study, 28 adolescents with type 1 diabetes on multiple injection therapy received either insulin glargine prebedtime plus lispro preprandially (LIS/GLAR) or NPH insulin prebedtime plus regular human insulin preprandially (R/NPH). During each 16-week treatment arm, subjects completed home blood glucose profiles, and at the end of each treatment arm, they were admitted for an overnight metabolic profile. A total of 25 subjects completed the study. **RESULTS:** Compared with R/NPH therapy, LIS/GLAR was associated with lower mean blood glucose levels (LIS/GLAR versus R/NPH): fasting (8.0 vs. 9.2 mmol/l, $P < 0.0001$), 2 h postbreakfast (8.1 vs. 10.7 mmol/l, $P < 0.0005$), prelunch (8.9 vs. 10.1 mmol/l, $P < 0.01$), and 2 h postlunch (8.0 vs. 9.5 mmol/l, $P < 0.002$). However, there was no difference in mean blood glucose levels before or after the evening meal. Incidence of nocturnal hypoglycemia on overnight profiles was 43% lower on LIS/GLAR compared with R/NPH therapy; however, there was no difference in rates of self-reported symptomatic hypoglycemia. Total insulin dose required to achieve target blood glucose control was lower on LIS/GLAR (1.16 IU/kg) compared with R/NPH therapy (1.26 IU/kg, $P < 0.005$), but there was no significant difference in HbA(1c) levels (LIS/GLAR versus R/NPH: 8.7 vs. 9.1% , $P = 0.13$). **CONCLUSIONS:** Combination therapy with insulin glargine plus lispro reduced the incidence of nocturnal hypoglycemia and was at least as effective as R/NPH insulin therapy in maintaining glycemic control in adolescents on multiple injection regimens.

J Pediatr Endocrinol Metab. 2002 Apr;15(4):369-76.

Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus.

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The objective of this study was to compare the efficacy and safety of insulin glargine, a long-acting insulin analog, with NPH insulin in children and adolescents with type 1 diabetes mellitus (T1DM). In a multicenter, open-label, randomized, 6-month study, 349 patients with T1DM, aged 5-16 years, received insulin glargine once daily or NPH insulin either once or twice daily, based on their prior treatment regimen. Although there was no significant difference between the NPH insulin and insulin glargine treatment groups with respect to baseline to endpoint change in HbA1c levels, fasting blood glucose (FBG) levels decreased significantly more in the insulin glargine group (-1.29 mmol/l) than in the NPH insulin group (-0.68 mmol/L, $p = 0.02$). The percentage of symptomatic hypoglycemic events was similar between groups; however, fewer patients in the insulin glargine group reported severe hypoglycemia (23% vs 29%) and severe nocturnal hypoglycemia (13% vs 18%), although these differences were not statistically significant ($p = 0.22$ and $p = 0.19$, respectively). Fewer serious adverse events occurred in the insulin glargine group than in the NPH insulin group ($p < 0.02$). A once-daily subcutaneous dose of insulin glargine provides effective glycemic control and is well tolerated in children and adolescents with T1DM.

Diabet Med. 2001 Aug;18(8):619-25.

Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes.

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AIMS: To assess satisfaction with treatment and psychological well-being associated with insulin glargine and Neutral Protamine Hagedorn (NPH). Insulin glargine, a new long-acting insulin analogue, provides constant, peakless insulin release following once-daily administration and is associated with fewer hypoglycaemic episodes, despite metabolic control equivalent to that achieved with NPH human basal insulin. **METHODS:** The Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Well-being Questionnaire (W-BQ) were completed at baseline and at weeks 8, 20 or 28 by 517 patients with Type 1 diabetes participating in a randomized, controlled European trial comparing insulin glargine and NPH. Analysis of covariance was performed on change from baseline scores (main effects: treatment and pooled site; covariate: baseline scores). **RESULTS:** Treatment satisfaction improved with insulin glargine at all time points, including endpoint, but deteriorated slightly with NPH. These differences were significant throughout the study (change from baseline to endpoint: +1.27 vs. -0.56; $P = 0.0001$). Outcomes were better with insulin glargine for the DTSQ items, Perceived Frequency of Hyperglycaemia and Hypoglycaemia, with statistically significant differences at week 28 and endpoint for hyperglycaemia ($P = 0.0373$ and 0.0379) and at week 20 for hypoglycaemia ($P = 0.0024$). There was no difference in psychological well-being between the treatment groups, with mean scores increasing in both. **CONCLUSIONS:** Study participants had treatment-independent improvements in General Well-being. Advantages for insulin glargine were seen in significantly improved Treatment Satisfaction throughout the study, together with lower Perceived Frequency of Hyperglycaemia than for patients on NPH, without a significant increase in Perceived Frequency of Hypoglycaemia.

Diabetes Care. 2001 Apr;24(4):631-6.

Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin.

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OBJECTIVE: To determine the safety and efficacy of the long-acting analog insulin glargine compared with NPH insulin in patients with type 2 diabetes who were previously treated with insulin alone. **RESEARCH DESIGN AND METHODS:** A total of 518 subjects with type 2 diabetes who were receiving NPH insulin with or without regular insulin for postprandial control were randomized to receive insulin glargine (HOE 901) once daily ($n = 259$) or NPH insulin once or twice daily ($n = 259$) for 28 weeks in an open-label, multicenter trial. Doses were adjusted to obtain target fasting glucose <6.7 mmol/l. At study end point, the median total daily insulin dose in both treatment groups was 0.75 IU/kg. **RESULTS:** The treatment groups showed similar improvements in HbA1c from baseline to end point on intent-to-treat analysis. The mean change (means \pm SD) in HbA1c from baseline to end point was similar in the insulin glargine group ($-0.41 \pm 0.1\%$) and the NPH group ($-0.59 \pm 0.1\%$) after patients began with an average baseline HbA1c of approximately 8.5%. The treatments were associated with similar reductions in fasting glucose levels. Overall, mild symptomatic hypoglycemia was similar in insulin glargine subjects (61.4%) and NPH insulin subjects (66.%) However, nocturnal hypoglycemia in the insulin glargine group was reduced by 25% during the treatment period after the dose-titration phase (26.5 vs. 35.5%, $P = 0.0136$). Subjects in the insulin glargine group experienced less weight gain than those in the NPH group (0.4 vs. 1.4 kg, $P < 0.0007$). **CONCLUSIONS:** In patients with type 2 diabetes, once-daily bedtime insulin glargine is as effective as once- or twice-daily NPH in improving and maintaining glycemic control. In addition, insulin glargine demonstrates a lower risk of nocturnal hypoglycemia and less weight gain compared with NPH insulin.

Diabetes. 2000 Dec;49(12):2142-8.

Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro.

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To compare the pharmacokinetics/dynamics of the long-acting insulin analog glargine with NPH, ultralente, and continuous subcutaneous (SC) infusion of insulin lispro (continuous subcutaneous insulin infusion [CSII]), 20 C-peptide-negative type 1 diabetic patients were studied on four occasions during an isoglycemic 24-h clamp. Patients received SC injection of either 0.3 U/kg glargine or NPH insulin (random sequence, crossover design). On two subsequent occasions, they received either an SC injection of ultralente (0.3 U/kg) or CSII (0.3 U x kg⁻¹ x 24 h⁻¹) (random sequence, crossover design). After SC insulin injection or CSII, intravenous (IV) insulin was tapered, and glucose was infused to clamp plasma glucose at 130 mg/dl for 24 h. Onset of action (defined as reduction of IV insulin >50%) was earlier with NPH (0.8 +/- 0.2 h), CSII (0.5 +/- 0.1 h), and ultralente (1 +/- 0.2 h) versus glargine (1.5 +/- 0.3 h) (P < 0.05) (mean +/- SE). End of action (defined as an increase in plasma glucose >150 mg/dl) occurred later with glargine (22 +/- 4 h) than with NPH (14 +/- 3 h) (P < 0.05) but was similar with ultralente (20 +/- 6 h). NPH and ultralente exhibited a peak concentration and action (at 4.5 +/- 0.5 and 10.1 +/- 1 h, respectively) followed by waning, whereas glargine had no peak but had a flat concentration/action profile mimicking CSII. Interindividual variability (calculated as differences in SD of plasma insulin concentrations and glucose infusion rates in different treatments) was lower with glargine than with NPH and ultralente (P < 0.05) but was similar with glargine and CSII (NS). In conclusion, NPH and ultralente are both peak insulins. Duration of action of ultralente is greater, but intersubject variability is also greater than that of NPH. Glargine is a peakless insulin, it lasts nearly 24 h, it has lower intersubject variability than NPH and ultralente, and it closely mimics CSII, the gold standard of basal insulin replacement.

Diabetes Care. 2000 Nov;23(11):1666-71.

A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes.

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OBJECTIVE: To determine the safety and efficacy of the long-acting insulin analog, insulin glargine, as a component of basal bolus therapy in patients with type 1 diabetes. **RESEARCH DESIGN AND METHODS:** Patients with type 1 diabetes receiving basal-bolus insulin treatment with NPH human insulin and insulin lispro were randomized to receive insulin glargine (HOE 901), a long-acting basal insulin analog, once a day (n = 310) or NPH human insulin (n = 309) as basal treatment with continued bolus insulin lispro for 16 weeks in an open-label study. NPH insulin patients maintained their prior schedule of administration once or twice a day, whereas insulin glargine patients received basal insulin once a day at bedtime. **RESULTS:** Compared with all NPH insulin patients, insulin glargine patients had significant decreases in fasting blood glucose measured at home (means +/- SEM, -42.0 +/- 4.7 vs. -12.4 +/- 4.7 mg/dl [-2.33 +/- 0.26 vs. -0.69 +/- 0.26 mmol/l]; P = 0.0001). These differences were evident early and persisted throughout the study. More patients in the insulin glargine group (29.6%) than in the NPH group (16.8%) reached a target fasting blood glucose of 119 mg/dl (< 6.6 mmol/l). However, there were no differences between the groups with respect to change in GHb. Insulin glargine treatment was also associated with a significant decrease in the variability of fasting blood glucose values (P = 0.0124). No differences in the occurrence of symptomatic hypoglycemia, including nocturnal hypoglycemia, were observed. Overall, adverse events were similar in the two treatment groups with the exception of injection site pain, which was more common in the insulin glargine group (6.1%) than in the NPH group (0.3%). Weight gain was 0.12 kg in insulin glargine patients and 0.54 kg in NPH insulin patients (P = 0.034). **CONCLUSIONS:** Basal insulin therapy with insulin glargine once a day appears to be as safe and at least as effective as using NPH insulin once or twice a day in maintaining glycemic control in patients with type 1 diabetes receiving basal-bolus insulin treatment with insulin lispro.

Diabetes Care. 2000 Aug;23(8):1130-6.

Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group.

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OBJECTIVE: Available basal insulin formulations do not provide a constant and reliable 24-h insulin supply. We compared the efficacy and safety of glargine (a long-acting insulin analog) and NPH insulins in insulin-naive type 2 diabetic patients treated with oral antidiabetic agents. **RESEARCH DESIGN AND METHODS:** There were 426 type 2 diabetic patients (age 59 +/- 9 years, BMI 28.9 +/- 4.3 kg/m², mean +/- SD) with poor glycemic control on oral antidiabetic agents randomized to treatment for 1 year with bedtime insulin glargine or bedtime NPH insulin. Oral agents were continued unchanged. The fasting blood glucose (FBG) target was 6.7 mmol/l (120 mg/dl). **RESULTS:** Average glycemic control improved similarly with both insulins (HbA_{1c}, [reference range <6.5%] 8.3 +/- 0.1 vs. 8.2 +/- 0.1% at 1 year, glargine vs. NPH, mean +/- SEM, P < 0.001 vs. baseline for both). However, there was less nocturnal hypoglycemia (9.9 vs. 24.0% of all patients, glargine vs. NPH, P < 0.001) and lower post-dinner glucose concentrations (9.9 +/- 0.2 vs. 10.7 +/- 0.3 mmol/l, P < 0.02) with insulin glargine than with NPH. Insulin doses and weight gain were comparable. In patients reaching target FBG, HbA_{1c} averaged 7.7 and 7.6% in the glargine and NPH groups at 1 year. **CONCLUSIONS:** Use of insulin glargine compared with NPH is associated with less nocturnal hypoglycemia and lower post-dinner glucose levels. These data are consistent with peakless and longer duration of action of insulin glargine compared with NPH. Achievement of acceptable average glucose control requires titration of the insulin dose to an FBG target < or =6.7 mmol/l. These data support use of insulin glargine instead of NPH in insulin combination regimens in type 2 diabetes.

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Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo.

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OBJECTIVE: To study the pharmacodynamic properties of the subcutaneously injected long-acting insulin analog HOE901 (30 microg/ml zinc) in comparison with those of NPH insulin and placebo. **RESEARCH DESIGN AND METHODS:** In this single-center double-blind euglycemic glucose clamp study, 15 healthy male volunteers (aged 27 +/- 4 years, BMI 22.2 +/- 1.8 kg/m²) received single subcutaneous injections of 0.4 U/kg body wt of HOE901, NPH insulin, or placebo on 3 study days in a randomized order. The necessary glucose infusion rates (GIRs) to keep blood glucose concentrations constant at 5.0 mmol/l were determined over a 30-h period after administration. **RESULTS:** The injection of HOE901 did not induce the pronounced peak in metabolic activity observed with NPH insulin (GIR_{max} 5.3 +/- 1.1 vs. 7.7 +/- 1.3 mg x kg(-1) x min(-1)) (P < 0.05); after an initial rise, metabolic activity was rather constant over the study period. This lack of peak was confirmed by a lower glucose consumption in the first 4 h after injection (area under the curve from 0 to 4 h [AUC(0-4 h)] 1.02 +/- 0.34 vs. 1.48 +/- 0.34 g/kg) (P < 0.001) with HOE901, as compared with NPH insulin. In this single-dose study, the metabolic effect measured over a period of 30 h was lower with HOE901 than with NPH insulin (AUC(0-30 h) 7.93 +/- 1.82 vs. 9.24 +/- 1.29 g/kg) (P < 0.05). **CONCLUSIONS:** This study shows that the soluble long-acting insulin analog HOE901 induces a smoother metabolic effect than NPH insulin, from which a better substitution of basal insulin requirements may follow.

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Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes.

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OBJECTIVE: Insulin glargine (21A-Gly-30Ba-L-Arg-30Bb-L-Arg-human insulin) is a biosynthetic insulin analog with a prolonged duration of action compared with NPH human insulin. This study compared insulin glargine with NPH human insulin in subjects with type 1 diabetes who had been previously treated with multiple daily injections of NPH insulin and regular insulin. **RESEARCH DESIGN AND METHODS:** This study was a multicenter randomized parallel-group study in which subjects were randomized to receive premeal regular insulin and either insulin glargine (at bedtime) or NPH insulin (at bedtime for patients on once-daily therapy

and at bedtime and in the morning for patients on twice-daily therapy) for up to 28 weeks. Dose titration of both basal insulins was based on capillary fasting whole blood glucose (FBG) levels; the goal was a premeal blood glucose concentration of 4.4-6.7 mmol/l.

RESULTS: A total of 534 well-controlled type 1 diabetic subjects (mean GHb 7.7%, mean fasting plasma glucose [FPG] 11.8 mmol/l) were treated. A small decrease in GHb levels was noted with both insulin glargine (-0.16%) and NPH insulin (-0.21%; $P > 0.05$). Significant reductions in median FPG levels from baseline (-1.67 vs. -0.33 mmol/l with NPH insulin, $P = 0.0145$) and a trend for a reduction in capillary FBG levels were achieved with insulin glargine. After the 1-month titration phase, significantly fewer subjects receiving insulin glargine experienced symptomatic hypoglycemia (39.9 vs. 49.2%, $P = 0.0219$) or nocturnal hypoglycemia (18.2 vs. 27.1%, $P = 0.0116$) with a blood glucose level < 2.0 mmol/l compared with subjects receiving NPH insulin.

CONCLUSIONS: Lower FPG levels with fewer episodes of hypoglycemia were achieved with insulin glargine compared with once- or twice-daily NPH insulin as part of a basal-bolus regimen in patients with type 1 diabetes.
