

# 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<sub>1c</sub> 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.

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**Abbreviations:** DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; IAsp, insulin aspart; SMBG, self-measured blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The Diabetes Control and Complications Trial (DCCT) (1,2) and the Stockholm Trial (3) have shown that intensive insulin therapy with resulting tight glycemic control reduces the incidence and delays the progression of late diabetic complications associated with type 1 diabetes, albeit with the expense of a substantially increased incidence of hypoglycemia (4–6).

Traditional basal insulin preparations such as NPH insulin and ultralente do not accurately reproduce physiological serum insulin levels and are characterized by peaks in plasma concentration that may result in hypoglycemia during the night (7). Furthermore, differences in crystal size and inadequate resuspension make absorption kinetics and dosing precision with NPH insulin variable and result in unpredictable glucose levels (8,9).

More recently, the basal insulin analogs insulin glargine and insulin detemir have been developed to enable patients with diabetes to maintain more stable and predictable basal glucose levels with less within-subject day-to-day variation. Compared with NPH insulin, basal-bolus treatment with insulin glargine led to similar glycemic control with a flatter pharmacokinetic profile and lower risk of hypoglycemia (10–13). However, insulin glargine is presented in an acidic formulation, limiting its ability to be mixed with other insulins and possibly also accounting for increased injection pain (14). Insulin detemir is soluble and has a neutral pH. It is an acylated derivative of human insulin [Lys<sup>B29</sup>(N<sup>ε</sup>-tetradecanoyl) des(B30) human insulin], with protracted action (15). When injected subcutaneously, insulin detemir binds to albumin via the fatty acid chain leading to a substantial reduction in the free insulin detemir con-

centration. At steady state, only a small fraction of insulin detemir is present in the free and unbound form (16).

By combining the basal soluble analog insulin detemir and the rapid-acting analog insulin aspart (IAsp) in a basal-bolus treatment regimen, it may be possible to more closely mimic near-normal insulin profiles, with resulting improvement in glycemic control compared with more conventional insulin therapy (17). The aim of this trial was to evaluate the metabolic control, risk of hypoglycemia, and other potential effects of treatment with insulin detemir in patients with type 1 diabetes on such a basal-bolus regimen.

## RESEARCH DESIGN AND METHODS

### Design

Forty-six investigational sites in Europe participated in this open parallel trial, which consisted of a 3-week screening period and a 26-week treatment period in which patients were randomized (in a 2:1 ratio) to insulin detemir or NPH insulin treatment before breakfast and bedtime, with rapid-acting IAsp at main meals. Randomization was performed using a telephone randomization system: the Interactive Voice Response System.

### Subjects

Patients with a history of type 1 diabetes for at least 1 year who had received basal (once or multiple times daily) bolus insulin treatment for at least 2 months were included in the trial. Only patients with an HbA<sub>1c</sub> level  $\leq 12\%$ , a BMI  $\leq 35$  kg/m<sup>2</sup>, and a total basal insulin dosage of  $\leq 100$  IU/day were included. Selection criteria excluded patients with proliferative retinopathy, impaired hepatic or renal function, severe cardiac problems, uncontrolled hypertension, recurrent major hypoglycemia, or allergy to insulin. Pregnant or breast-feeding women were also excluded. The trial was carried out in accordance with the Declaration of Helsinki (18) and was approved by local ethics committees and health authorities according to local regulations. Written informed consent was obtained from each subject before trial entry.

### Procedures

Patients were instructed to administer either insulin detemir (1,200 nmol/ml) or NPH insulin (600 nmol/ml Isophane hu-

man insulin; Novo Nordisk, Bagsvaerd, Denmark) before breakfast and bedtime, and IAsp (NovoRapid; Novo Nordisk) before each main meal as subcutaneous injections using the NovoPen 3 device (Novo Nordisk). During the first 2 weeks, basal insulin doses were optimized following instructions of the investigator based on the patients' self-measured blood glucose (SMBG) profiles. In the following weeks, the dose ratio between rapid-acting and basal insulin was adjusted. The first month of the trial was regarded as a titration phase, whereas the last 5 months were considered the maintenance phase.

Patients were instructed to aim for blood glucose targets (fasting/preprandial, 4–7 mmol/l; postprandial,  $<10$  mmol/l; from 0200 to 0400, 4–7 mmol/l). They recorded insulin dose, concomitant medication, and hypoglycemia in diaries and were encouraged to measure blood glucose whenever symptoms of hypoglycemia occurred. Hypoglycemic episodes were classified as "major" if assistance to treat was required, as "minor" if blood glucose was  $<2.8$  mmol/l and the patients dealt with the episode themselves, and as "symptoms" if not confirmed by a blood glucose measurement.

At trial entry and after 13 and 26 weeks of treatment, HbA<sub>1c</sub> and fasting plasma glucose (FPG) were measured and patients recorded SMBG profiles. In addition, patients measured fasting SMBG during the last 7 days of treatment. On the last day of treatment, all patients (88 on detemir and 41 on NPH) from selected sites, chosen on the basis of their ability to conduct the procedure, were hospitalized, and an 8-h plasma glucose profile was recorded between 2300 and 0700. Patients were fasted from 2300 and samples were taken by intravenous access; thus, patients were not awakened during sampling. Any hypoglycemic episodes occurring during the monitoring period were treated according to standard procedures. The demographic characteristics of this subset of patients were not different from that of the whole study population.

### Analytical methods

HbA<sub>1c</sub> (reference range of assay, 4.0–6.0%) was determined by high-performance liquid chromatography on a Bio-Rad Diamat. FPG was determined by an enzymatic hexokinase method. These and additional standard safety analyses

related to hematology, biochemistry, and lipids were performed by Clinical Research Laboratories, Zaventem, Belgium. All patients measured SMBG using One-Touch Profile blood glucose meters (LifeScan).

### Statistical analyses

The primary end point was the HbA<sub>1c</sub> level after 6 months of treatment. HbA<sub>1c</sub> and FPG levels after 6 months were analyzed by an ANOVA model, with treatment and country as fixed effects and covariate adjustment for baseline values. Within-subject day-to-day fluctuations in fasting SMBG during the past 7 days of treatment were compared between the two groups using variance-component models. Nightly 8-h plasma glucose profiles at 6 months were evaluated using a baseline adjusted repeated-measures ANOVA model. To estimate the relative risk of hypoglycemia, all hypoglycemic episodes occurring during the maintenance period were analyzed as recurrent events using a  $\gamma$  frailty model. Nocturnal episodes (from 2300 to 0600) were analyzed separately. Weight at 6 months was analyzed using an ANOVA model, with treatment group as fixed effect and weight at baseline as covariate.

**RESULTS**— A total of 448 patients were randomized and 447 were exposed to trial products. All results are based on the intention-to-treat population, which included all exposed patients. Of these, 284 (94.4%) of 301 patients on insulin detemir and 141 (96.6%) of 146 on NPH insulin completed the trial. In the insulin detemir group, a total of five patients were withdrawn: three patients because of ineffective therapy, noncompliance, and other reasons, respectively, and two patients because of adverse events. Five patients were also withdrawn in the NPH insulin group: two patients because of ineffective therapy and three patients because of other reasons. Baseline characteristics were similar between the two treatment groups (Table 1). Patients used a wide variety of insulin preparations, and the daily dosage insulin regimen differed to a large extent. Mean daily doses of insulin were similar between treatment groups at baseline (Table 1).

### HbA<sub>1c</sub> and glycemic control

Mean HbA<sub>1c</sub> decreased slightly in both treatment groups (0.55% point) and was

**Table 1—Baseline characteristics for all patients receiving treatment**

	Insulin detemir	NPH insulin
n	301	146
Age (years)	38.9 ± 13.3	41.8 ± 14.2
Sex		
M	162 (53.8)	74 (50.7)
F	139 (46.2)	72 (49.3)
Weight (kg)	71.5 ± 11.9	71.2 ± 11.5
BMI (kg/m <sup>2</sup> )	24.5 ± 3.2	24.6 ± 3.4
Diabetes duration (years)	17.1 ± 9.9	17.4 ± 11.0
FPG (mmol/l)	11.6 ± 5.21	11.6 ± 5.27
HbA <sub>1c</sub> (%)	8.18 ± 1.14	8.11 ± 1.12
Total daily insulin dose (units)*		
Basal	27.4 ± 12.5	25.2 ± 13.7
Bolus	30.9 ± 15.5	29.6 ± 15.8

Data are means ± SD or n (%). \*Does not include patients using premix insulin at study start: insulin detemir group, 27 IU/U (n = 1); NPH insulin group, 40 IU/U (n = 1).

comparable after 6 months (Table 2). Mean FPG after 6 months tended to be lower in patients treated with insulin detemir than in patients treated with NPH insulin (Table 2), but this difference was not statistically significant (−0.76 mmol/l, P = 0.097). Plasma glucose was lower in the morning and until lunch in

the insulin detemir group than in the insulin NPH group, whereas lower plasma glucose levels were reported during the afternoon, evening, and early night in the NPH insulin group than in the insulin detemir group (Fig. 1A).

The day-to-day fluctuation in fasting SMBG within a subject, based on home-

measured blood glucose during the past 7 days of treatment, was statistically significantly lower with insulin detemir than with NPH insulin (P < 0.001) (Fig. 1B and Table 2).

Nightly 8-h plasma glucose profiles were significantly different between the two treatments (P = 0.05), and a smoother and more stable profile was observed with insulin detemir (Fig. 1A). The area under the curve was similar between the two treatments, with the insulin detemir/NPH insulin ratio being 1.02 (95% CI 0.86–1.21, P = 0.8). The effect of insulin detemir appeared to be longer lasting than that of NPH insulin and was still evident at 0700, when plasma glucose concentrations in insulin detemir-treated patients were significantly lower (7.6 vs. 9.5 mmol/l, P < 0.05). The effect of NPH insulin decreased markedly after 0400.

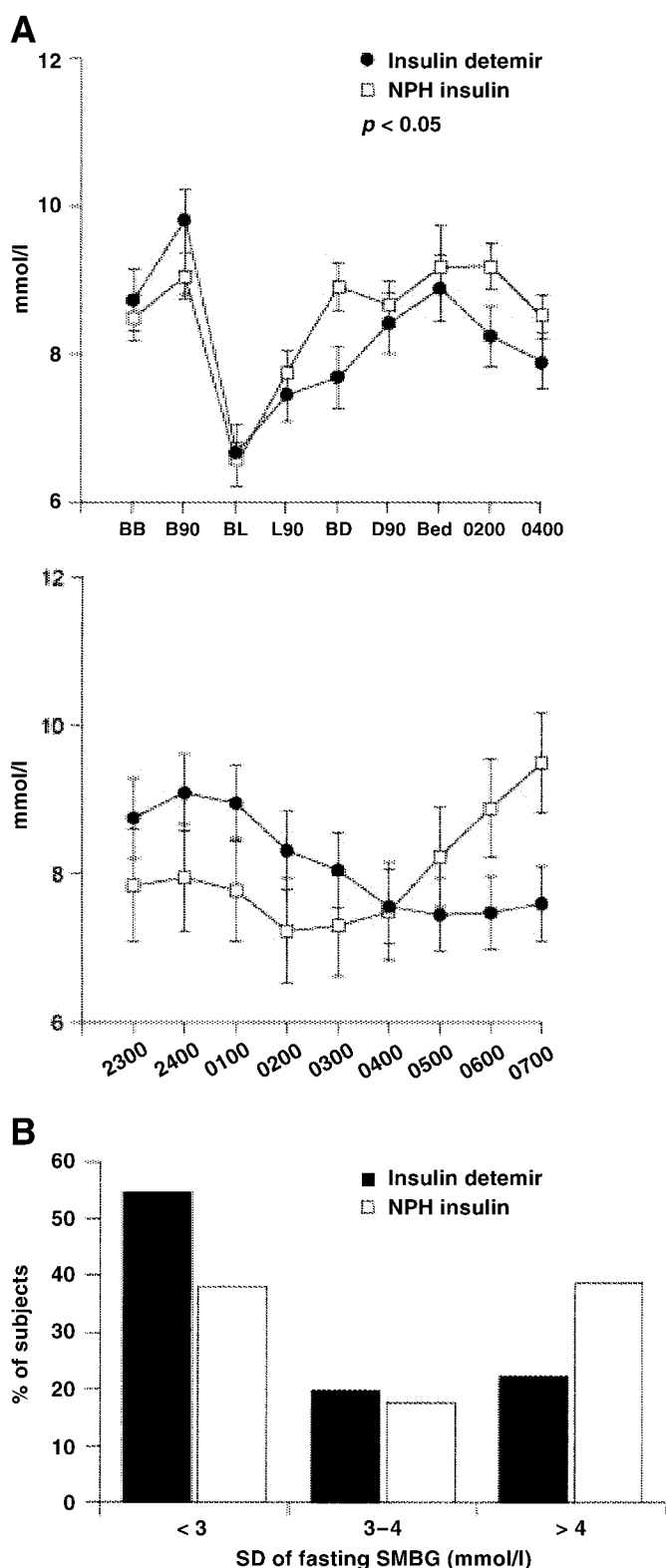
**Body weight**

A statistically significant difference was observed in mean body weight between the two treatment groups after 6 months of treatment (P < 0.001, Table 2). Based on the raw data obtained at baseline and

**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 <sub>1c</sub> (%)* (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/U)]†					
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 ANOVA 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; BD, before dinner; D90, 90 min after dinner.

after 6 months of treatment, patients in the detemir group had a slight weight loss of 0.2 kg during the trial, whereas patients in the NPH insulin group gained 0.7 kg.

### Hypoglycemic episodes

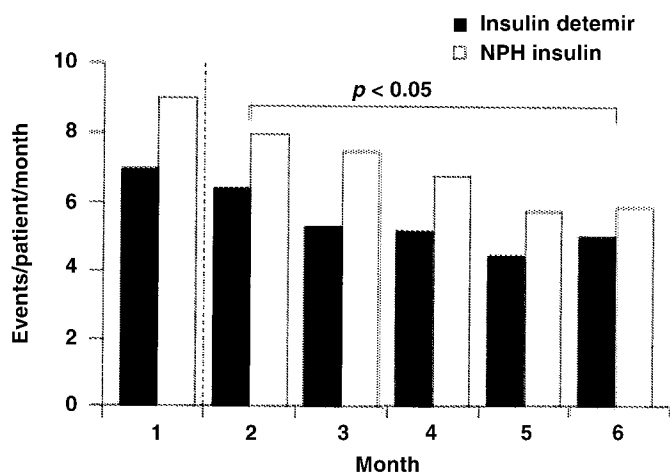
The risk of hypoglycemia during the maintenance period (the last 5 months of treatment) was 22% lower in the detemir group than in the NPH insulin group, with an estimated hazard ratio (detemir/NPH insulin) of 0.78 ( $P < 0.05$ , Table 2). Adjustment for HbA<sub>1c</sub> did not change this result significantly. The reduced risk of hypoglycemia in the detemir group was maintained throughout the entire treatment period (Fig. 2). The risk of nocturnal hypoglycemic episodes was 34% lower for the detemir group with a hazard ratio of 0.66 ( $P < 0.005$ , Table 2).

### Insulin dose requirements

After 6 months of treatment, the mean daily molar dose requirement of basal insulin was ~3.8 times higher in the detemir group than in the NPH insulin group, corresponding to 29.6 units of insulin detemir in the formulation to be marketed versus 31.7 IU of NPH insulin. The mean daily dose of IAsp was 30.7 units in the detemir group compared with 26.0 units in the NPH insulin group.

### Adverse events

The overall incidence and pattern of adverse events was similar between treatments, and the majority of events were mild and considered unrelated to trial products. Two patients in the detemir group and none in the NPH insulin group withdrew because of adverse events (one because of uterine carcinoma and one because of headache, vomiting, and malaise). None of the events were considered related to the trial product. About 70% of patients in both treatment groups had one or more adverse events, of which the most common were headache, upper respiratory tract infection, and rhinitis. Less than 10% of all events were evaluated as having a probable or possible relation to the trial products, and <5% of patients in either group reported serious adverse events. This proportion of patients included two cases of severe hypoglycemia in the detemir group and one in the NPH insulin group. Three patients treated with insulin detemir and one subject treated with NPH insulin developed injection site reactions. These were characterized as pain and my-



**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.

algia, redness, or lipodystrophy around the injection site after administration of insulin detemir and as itching around the injection site with NPH insulin. One potentially allergic reaction (mild itching rash) was judged as having a possible relation to insulin detemir.

## CONCLUSIONS

### Glycemic control

Patients in both the insulin detemir and NPH insulin group experienced a decrease of ~0.55% in HbA<sub>1c</sub> during the 6 months of treatment, with no significant difference in final HbA<sub>1c</sub> between groups. The decrease in HbA<sub>1c</sub> may partly be explained by participation in the study or it may be related to the switch to IAsp at trial entry and is consistent with findings from a previous study using this insulin (17). FPG also decreased in both groups during the trial and was most pronounced in the detemir group.

Comparable glycemic control was observed between treatment groups in a similar trial investigating treatment with insulin detemir and NPH insulin in patients with type 1 diabetes, with human regular insulin as meal-related insulin (19). In both studies, these results were obtained with a three to four times higher molar dose of insulin detemir compared with NPH insulin, which is consistent with the lower receptor affinity and potency demonstrated for insulin detemir compared with human insulin in early preclinical studies (20,21). As discussed below, it is likely that further optimization of the basal insulin regimen would be

possible using insulin detemir, which would hopefully provide superior glycemic control.

### Variability of glycemic control

Administration of insulin detemir resulted in more predictable blood glucose levels, with significantly lower day-to-day within-subject variation in fasting SMBG than with NPH insulin. This finding is consistent with findings from other trials in patients with type 1 diabetes (19,22). The lower within-subject variation may be attributed to the soluble formulation and unique method of protraction of insulin detemir. These have been shown to result in more reproducible insulin absorption compared with basal insulins such as NPH (23), which rely on thorough resuspension of the insulin suspension and dissolution of crystals at the injection site for reproducible prolonged action (8,9). Indeed, although a lower intersubject variability has been demonstrated for insulin glargine than for NPH (24), it was shown to be less variable than ultralente but similar to NPH in terms of intrasubject variability (25). The predictable and stable glycemic response observed with insulin detemir is likely to make it easier for patients to adjust basal insulin doses. Furthermore, because patients can more accurately predict their glycemic response to an injection, they will be more likely to aim for tighter glycemic targets without the worry of increasing their risk for hypoglycemia.

This trial also provided evidence for a longer duration of action of insulin detemir than NPH insulin: smoother and

more stable plasma glucose levels were maintained throughout the night. This prolonged duration of action complements findings from kinetic studies showing that insulin detemir has a flatter time-action profile than NPH (26), reaching a peak effect almost 90 min later than NPH (26). From these profiles, the duration of action of insulin detemir appears to be long enough to cover nighttime basal insulin requirements. The effect of insulin detemir was most pronounced during the early morning hours, reflected in the lower FPG levels with insulin detemir compared with NPH insulin. The optimal effect of insulin detemir coincided with the “dawn phenomenon” between 0500 and 0800, where blood glucose tends to rise because of decreased insulin sensitivity and secretion of growth hormone (27).

### Hypoglycemia and body weight

A 22% lower risk of overall hypoglycemia was observed with insulin detemir compared with NPH insulin during the previous 5 months of treatment, and a 34% lower risk of nocturnal hypoglycemia was observed. This result is consistent with a tendency toward a lower incidence of nocturnal hypoglycemia observed in another study with insulin detemir in basal-bolus therapy with human regular insulin (19). In the DCCT, 61 hypoglycemic episodes per 100 subject-years were reported in the intensive treatment group, in which assistance was required (1,4,5). Expressed in this way, we found 46 episodes in the detemir group and 68 episodes in the NPH insulin group. However, in the DCCT, mean HbA<sub>1c</sub> was slightly lower (7.2%) compared with our trial, and human regular insulin was used as bolus insulin. The reduced risk of hypoglycemia with insulin detemir can be ascribed in part to its lower within-subject variability, which would be expected to reduce the number of occasions in which glucose levels fall into the hypoglycemic range. In addition, the pronounced reduction in nocturnal hypoglycemia can also be ascribed to the smoother nighttime glycemic profile observed with insulin detemir, which tended to have a less extreme glucose nadir later in the night.

As well as reduced hypoglycemia, a significant difference in body weight was observed in the insulin detemir group compared with the NPH group during this trial. The difference in body weight

after treatment with insulin detemir and NPH insulin was consistent with findings from a parallel trial that investigated treatment with insulin detemir in basal-bolus therapy with human regular insulin (19). The reason for the weight loss observed with insulin detemir treatment is not known, but if confirmed in subsequent studies, this may be of additional clinical benefit because weight gain is a common problem associated with intensive insulin treatment (4).

Investigators and patients in this trial may have been reluctant to aggressively increase the dose of a new basal insulin preparation such as insulin detemir because of the fear of hypoglycemia, especially during the night, and may have compensated for this by injection of bolus insulin late in the evening. In fact, the molar ratio of bolus insulin increased slightly in the detemir group relative to the NPH-treated group, partly because of inappropriate dosing with bolus insulin before bedtime during the titration period. An approximately three- to fourfold higher molar dose of insulin detemir was required (resulting in an approximately twofold ratio by volume using the formulation in this trial). This result may have further discouraged upward titration of dose, a factor that would not be an issue with the more concentrated and bioequivalent preparation of insulin detemir to be marketed (which has a four times higher molar concentration than that of NPH insulin in order to establish unit-to-unit conversion).

Taken together, the properties emerging as characteristics of insulin detemir—low within-subject variability, smooth time-action profile, and reduced risk of hypoglycemia—are promising. These results suggest that a basal-bolus insulin regimen with insulin detemir may allow tighter glycemic control than that possible with NPH insulin, especially when used in combination with a rapid-acting analog such as IAsp, without increasing the burden of hypoglycemia.

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## References

1. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes and the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Diabetes Control and Complications Trial Research Group: The absence of a glycemic threshold for the development of long-term complications: the perspective of the diabetes control and complications trial. *Diabetes* 45:1289–1298, 1996
3. Reichard O, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment in the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304–309, 1993
4. Diabetes Control and Complications Trial Research Group: Adverse events and their association with treatment regimens in the diabetes control and complications trial. *Diabetes Care* 18:1415–1427, 1995
5. Diabetes Control and Complications Trial Research Group: Hypoglycemia in the diabetes control and complications trial. *Diabetes* 46:271–286, 1997
6. Diabetes Control and Complications Trial Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med* 90:450–459, 1991
7. Starke A, Heinemann L, Hohlmann A, Berger M: The action profiles of human NPH insulin preparations. *Diabet Med* 6:239–244, 1989
8. Kølendorf K, Bojsen J, Deckert T: Clinical factors influencing the absorption of <sup>125</sup>I-NPH insulin in diabetic patients. *Horm Metab Res* 15:274–278, 1983
9. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO: Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens. *Lancet* 354:307–335, 1999
10. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA: Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes: U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care* 23:639–643, 2000
11. Pieber TR, Eugene-Jolchine I, Derobert E: Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes: the European Study Group of HOE 901 in type 1 diabetes. *Diabetes Care* 23:157–162, 2000
12. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T: A 16-week comparison of the novel insulin analog insulin glargine. *Diabetes Care* 23:1666–1671, 2000
13. Rosenstock J, Park G, Zimmerman J: Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens: U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. *Diabetes Care* 23:1137–1142, 2000
14. Lindholm E: New insulins in the treatment of diabetes mellitus. *Best Pract Res Clin Gastroenterol* 16:475–492, 2002
15. Kurtzhals P, Havelund S, Jonassen I, Kiehr B, Larsen UD, Ribell U, Markussen J: Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo. *Biochem J* 312:725–731, 1995
16. Markussen J, Havelund S, Kurtzhals P, Andersen AS, Halstrøm J, Hasselager E, Larsen UD, Ribell U, Schäffer L, Vad K, Jonassen I: Soluble, fatty acid acylated insulins bind to albumin and show protracted action in pigs. *Diabetologia* 39:281–288, 1996
17. Home P, Lindholm A, Riis A: Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomised controlled trial. *Diabet Med* 17:762–771, 2000
18. Declaration of Helsinki: Recommendations guiding medical physicians in biomedical research involving human patients. *JAMA* 277:925–926, 1997
19. Roberts A, Bayer T, Munksgaard E, Lang H, Standl E: Efficacy and safety of 6-month treatment with insulin detemir in type 1 diabetic patients on a basal/bolus regimen (Abstract). *Diabetes* 50 (Suppl. 2):A129, 2001
20. Kurtzhals P, Schaffer L, Sorensen A, Kristensen C, Jonassen I, Schmid C, Trub T: Correlations of receptor binding and metabolic and mitogenic potencies of insulin

- analogs designed for clinical use. *Diabetes* 49:999–1005, 2000
21. Brunner GA, Hirschberger S, Sendlhofer G, Wutte A, Ellmerer M, Balent B, Schaupp L, Krejs GJ, Pieber TR: Postprandial administration of the insulin analogue insulin aspart in patients with type 1 diabetes mellitus. *Diabet Med* 17:371–375, 2000
  22. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M: Comparison of the soluble basal insulin analog insulin detemir with NPH insulin. *Diabetes Care* 24:296–301, 2001
  23. Strange P, McGill J, Mazzeo M: Reduced pharmacokinetic (PK) variability of a novel, long-acting insulin analog (Abstract). *Diabetes* 48 (Suppl. 1):A103, 1999
  24. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: 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. *Diabetes* 49:2142–2148, 2000
  25. Scholtz HE, van Niekerk, Meyer BH, Rosenkranz B: An assessment of the variability in the pharmacodynamics of HOE901 compared to NPH insulin and ultralente human insulins using the euglycaemic clamp technique. *Diabetologia* 42 (Suppl. 1):A235, 1999
  26. Heinemann L, Sinha K, Weyer C, Loftager M, Hirschberger S, Heise T: Time-action profile of the soluble, fatty acid acylated, long-acting insulin analog NN304. *Diabet Med* 16:332–338, 1999
  27. Perriello G, De Feo P, Torlone E, Fanelli C, Santeusano F, Brunetti P, Bolli GB: Nocturnal spikes of growth hormone secretion cause the dawn phenomenon in type 1 (insulin-dependent) diabetes mellitus by decreasing hepatic (and extrahepatic) sensitivity to insulin in the absence of insulin waning. *Diabetologia* 33:52–59, 1990