Insulin Detemir Offers Improved Glycemic Control Compared With NPH Insulin in People With Type 1 Diabetes

A randomized clinical trial

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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 (HbA_{1c}, 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 HbA_{1c} for each insulin detemir group was not different from the NPH group, HbA_{1c} 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.

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This trial formed part of the clinical development program for insulin detemir by Novo Nordisk, Denmark. The investigators or their institutions were remunerated appropriately for their activity in this study and in some cases for other activities undertaken together with Novo Nordisk.

Abbreviations: CGMS, continuous glucose monitoring system; FPG, fasting plasma glucose.

Landmark studies show that intensive diabetes management delays progression of the late complications of type 1 diabetes (1,2). Although the introduction of rapid-acting insulin analogs has given improvement in postprandial blood glucose control, these analogs are not ideal for use with NPH insulin, which has inadequate duration of action to cover nighttime requirements and an undesirable peak effect ~5 h after administration (3). These problems, together with the high day-to-day variability in absorption (4,5), present a major barrier to achieving appropriate targets of blood glucose control.

These limitations have stimulated the development of a soluble basal insulin analog that does not require resuspension before injection nor forms a precipitate (which must redissolve) after injection. It is designed to give constant basal levels of circulating insulin and a smooth and predictable action profile. Insulin detemir is such an insulin analog, created by acylation of the lysine-B29 amino acid residue (6). Prolonged action results from a combination of increased self-association and albumin binding at the injection site (7–9). These mechanisms also provide more reproducible absorption.

These characteristics suggest that insulin detemir might provide improved glycemic control compared with NPH insulin in a mealtime + basal insulin regimen. The sustained glucose-lowering effect and attenuated peak of action (10) suggest that administration earlier than bedtime could provide adequate insulin supply during the night without increased risk of nocturnal hypoglycemia. Furthermore, administration at fixed intervals rather than at breakfast and bedtime could provide more stable daily basal insulin profiles and eliminate regimen-inherent source of variation, thereby further improving blood glucose control.

The current study therefore investigated whether insulin detemir provides

improved glycemic control compared with NPH insulin, regardless of administration time, when used in a mealtime + basal treatment regimen. A morning and bedtime regimen was used for NPH insulin because this is overwhelmingly the most common conventional accompaniment to rapid-acting insulin analogs in routine clinical practice. This regimen was also used for one insulin detemir group, whereas the second insulin detemir group used fixed 12-h dosing intervals.

RESEARCH DESIGN AND METHODS

— A total of 52 trial sites in Australasia and Europe participated in this open-label three-arm parallel-group trial, which consisted of a 2-week screening period and a 16-week treatment period (six visits in all). Because insulin detemir is a clear solution and injection timing varied in one arm, the study could not be blinded without using dummy injections.

Insulin

People were randomized to twice-daily treatment with either insulin detemir (100 units/ml; Novo Nordisk, Bagsværd, Denmark) or NPH insulin (Novo Nordisk). The insulin detemir group was further randomized into two groups, using insulin detemir either before breakfast and at bedtime ($IDet_{morn+bed}$) or at 12-h intervals ($IDet_{12h}$). NPH insulin was administered before breakfast and at bedtime. Mealtime insulin requirements were supplied by the rapid-acting insulin analog insulin aspart (NovoRapid/NovoLog; Novo Nordisk). All insulin preparations were administered as subcutaneous injections using a NovoPen 3.0 device. Randomization was initiated by the investigator using remote telephone allocation. The starting dose for all basal insulins was 70% of basal insulin dose at trial entry. The dose for people switching from once-daily basal insulin was split one-third/two-thirds morning and evening. Basal insulin doses were titrated to optimal levels over the first 4 weeks, or longer if necessary, based on self-monitored plasma glucose levels and the targets for blood glucose control (prebreakfast/night 4.0–7.0 mmol/l; postprandial ≤10.0 mmol/l), which were identical for both insulin types. Both the basal evening and morning doses were adjusted according to the following algorithm: prebreakfast/predinner blood glucose >7.0 mmol/l, no change; 7.0–10.0 mmol/l, +10% change in dose; 10.0–15.0 mmol/l, +20% change in basal dose; and >15.0 mmol/l, +25% change in basal dose (with allowance for hypoglycemia, patient preference, and clinician judgment).

Patients

Eligible people were men and women >18 years old with type 1 diabetes for >1 year who were already using a mealtime + basal regimen for >2 months, with basal insulin dose <100 units/day, HbA_{1c} ≤12.0%, and BMI ≤35.5 kg/m^2. Basal insulin at entry was once daily in 47%, more than once daily in 46%, and premix in 7%. People with significant medical problems (including proliferative retinopathy, recurrent major hypoglycemia, impaired hepatic or renal function, or uncontrolled cardiovascular problems) or using medication known to interfere with glucose metabolism were excluded, as were pregnant or breast-feeding women.

Written informed consent was obtained from each person before trial entry. The trial was carried out in accordance with good clinical (research) practice guidelines (11) and was approved by ethics committees and health authorities according to local regulations.

Measurements

HbA_{1c} and fasting plasma glucose (FPG) were measured at randomization and after 8 and 16 weeks. Participants were asked to measure prebreakfast self-monitored plasma glucose on each of the last 7 days of treatment and to perform a 10-point blood glucose profile during the week before randomization and at week 16, using a Precision QID meter (MediSense; Abbott, Abbott Park, IL). Also, 24-h blood glucose profiles were measured using a continuous glucose monitoring system (CGMS; Medtronic MiniMed, Northridge, CA) for 72 h in all people at selected centers (n = 206) after 12 weeks of treatment.

Hypoglycemic episodes and adverse events were recorded at each visit. Hypoglycemic episodes were classified as major (requiring assistance from another person), minor (glucose measurement <2.8 mmol/l, with or without symptoms), or symptomatic only (no glucose measurement or glucose >2.8 mmol/l). Nocturnal hypoglycemia was taken as any episode between 2300 and 0600. Body weight was measured at randomization and after 16 weeks of treatment.

HbA_{1c} (reference range 4.3–6.1%) was determined by high-performance liquid chromatography (Bio-Rad Variant; Bio-Rad, Hercules, CA). Clinic FPG was determined by a hexokinase method. These and standard safety analyses were performed by Laboratorium für Klinische Forschung (Raisdorf, Germany).

Statistical analyses

Results presented are based on the intention-to-treat group, consisting of all people randomized and exposed to trial medication. Missing data were handled by an interpolation method. The primary end point was HbA_{1c}. The sample size calculation was based on an individually relevant difference in HbA_{1c} of 0.4%, a power of 80%, and a baseline-adjusted SD of 1.0%, suggesting 366 people needed to complete the study.

HbA_{1c}, FPG, and prebreakfast self-monitored plasma glucose were analyzed using baseline-adjusted ANOVA, with treatment and country as fixed effects. Within-person day-to-day fluctuation in prebreakfast self-monitored plasma glucose during the last 7 days was compared using variance-component models, and within-person SD is given as estimate (95% CI). Ten-point self-monitored plasma glucose profiles were evaluated using a repeated-measures ANOVA model. Total and nocturnal (2300–0600) excursions in the CGMS profiles were calculated as the area between the profile and the individual's average glucose level over the same period. These excursions from the mean were then analyzed by repeated-measures ANOVA.

The relative risk of hypoglycemia was estimated from its incidence over the 12-week maintenance period. Episodes were analyzed as recurrent events using a γ-frailty model with treatment and HbA_{1c} after 8 weeks as the covariate. The model handles the recurrent aspect of episodes appropriately (12). Change in body weight was analyzed by baseline-adjusted ANOVA with HbA_{1c} change as a covariate.

For all analyses, an overall three-way test between groups was performed. If the overall comparison of the three treatment groups was statistically significantly different, the treatment groups were compared pairwise. If the overall comparison was not statistically significant, the two insulin detemir groups were pooled (on

Table 1 —*Baseline characteristics of the people randomized and receiving treatment*

	$IDet_{12h}$	$IDet_{morn+bed}$	NPH
n	137	139	132
Age (years)	40.9 ± 13.0	41.3 ± 11.4	38.3 ± 12.4
Sex (M/F)	71/66	79/60	70/62
Weight (kg)	74.2 ± 12.6	75.0 ± 12.3	75.5 ± 14.0
BMI (kg/m^2)	25.1 ± 3.3	25.2 ± 3.6	25.2 ± 3.7
Diabetes duration (years)	17.1 ± 10.6	17.6 ± 10.7	15.1 ± 10.6
FPG (mmol/l)	11.57 ± 4.65	11.65 ± 4.61	12.20 ± 5.49
HbA_{1c}	8.55 ± 1.20	8.74 ± 1.20	8.52 ± 1.19
Insulin dose (units/day)*			
Basal	26.4 ± 10.8	28.1 ± 12.5	29.5 ± 13.7
Mealtime	30.9 ± 12.9	29.4 ± 13.4	30.5 ± 13.4

Data are means ± SD. *Does not include people using premix insulin at study start.

the expectation of lack of independence of effect of a true basal insulin given at different times only 3–5 h apart in the evening) and compared with the NPH insulin group. Adverse events were evaluated by summary statistics, and the two insulin detemir groups were combined for these evaluations.

RESULTS

Characteristics and withdrawals

A total of 441 people were entered as possibly eligible. Of the 409 people randomized, 408 were exposed to trial drugs during the trial period from October 2001 to April 2002. Of these, 135 (97%) of 139 people on $IDet_{morn+bed}$, 132 (96%) of 137 on $IDet_{12h}$, and 124 (93%) of 132 on NPH insulin completed the trial. There were no differences in baseline characteristics between the three groups (Table 1). In the 17 people who withdrew from the trial, the reasons were adverse events (2 people), ineffective therapy (3 people), protocol noncompliance (9 people), and other (3 people), including fear of hypoglycemic event, withdrawal of informed consent, and pregnancy.

Insulin doses

At 16 weeks, the morning/evening dose distribution was 39/61% in the two insulin detemir groups, and it was 34/66% in the NPH insulin group (P = NS) (Table 2). Injection times of the morning doses of basal insulin were very similar (data not shown). Evening injection time of the NPH and bedtime detemir groups was very similar (around 2230), but it was 2.5 h earlier (at 1956) in the $IDet_{12h}$ group.

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

	$IDet_{12h}$	$IDet_{morn+bed}$	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 $IDet_{morn+bed}$ 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.

Table 3 —*Outcome measures (pairwise comparisons) using insulin detemir or NPH insulin as basal insulin therapy in type 1 diabetes*

Measure	Group 1	Group 2	Mean difference (95% CI)	*P*
HbA_{1c} (%)	$IDet_{combined}$	NPH	−0.2 (−0.34 to −0.02)	0.027
Clinic FPG (mmol/l)	$IDet_{12h}$	NPH	−1.5 (−2.51 to −0.48)	0.004
	$IDet_{morn+bed}$	NPH	−2.3 (−3.32 to −1.29)	<0.001
	$IDet_{12h}$	$IDet_{morn+bed}$	0.8 (−0.18 to 1.80)	NS
Self-monitored fasting blood glucose				
Mean	$IDet_{12h}$	NPH	−0.8 (−1.32 to −0.22)	0.006
	$IDet_{morn+bed}$	NPH	−0.8 (−1.34 to −0.25)	0.004
	$IDet_{12h}$	$IDet_{morn+bed}$	0.0 (−0.51 to 0.56)	NS
Within-patient SD*	$IDet_{12h}$	NPH		<0.001
	$IDet_{morn+bed}$	NPH		<0.001
	$IDet_{12h}$	$IDet_{morn+bed}$		NS
Body weight change (kg)	$IDet_{12h}$	NPH	−0.8 (−1.44 to −0.24)	0.006
	$IDet_{morn+bed}$	NPH	−0.6 (−1.23 to −0.03)	0.040
	$IDet_{12h}$	$IDet_{morn+bed}$	−0.2 (−0.80 to 0.37)	NS
CGMS glucose profiles deviation from average (mmol/l · h)				
>24 h	$IDet_{combined}$	NPH	−6.45 (−13.3 to 0.40)	0.065
Overnight	$IDet_{combined}$	NPH	−1.72 (−4.05 to −0.62)	NS
Hypoglycemia in final 12 weeks [RR (95% CI)]†				
Minor–any time	$IDet_{12h}$	NPH	0.75 (0.56–1.00)	0.046
	$IDet_{morn+bed}$	NPH	0.68 (0.56–0.84)	0.002
Minor–nocturnal	$IDet_{12h}$	NPH	0.74 (0.50–1.08)	NS
	$IDet_{morn+bed}$	NPH	0.47 (0.36–0.62)	<0.001

Pairwise testing was only performed where allowed by the protocol (see RESEARCH DESIGN AND METHODS); accordingly only limited comparisons are given. *Data distribution did not allow calculation of mean difference and CIs for within-patient variability; †estimates of the relative risk of hypoglycemic episodes during the maintenance period calculated using a recurrent event γ-frailty model. $IDet_{combined}$, insulin detemir groups combined.

Glycemic control

Mean HbA_{1c} decreased by 0.85% (0.07) (Table 2) in the $IDet_{12h}$ group, by 0.82% (0.07) in the $IDet_{morn+bed}$ group, and by 0.65% (0.07) in the NPH insulin group (baseline-adjusted ANOVA, $P = 0.082$) (Table 2). The improvement in HbA_{1c} for the two insulin detemir groups combined was greater than that observed with NPH insulin (difference −0.18% [95% CI −0.34 to −0.02], $P = 0.027$).

At end point, clinic FPG levels were statistically significantly lower between groups ($P < 0.001$) (Table 2), as were prebreakfast self-monitored plasma glucose levels in the previous week ($P < 0.005$) (Table 2). Both insulin detemir groups compared with the NPH group were also very statistically significantly lower (Table 3) for the two measurements.

Within-person between-day variation in fasting self-monitored plasma glucose was also lower in the detemir groups ($P < 0.001$) (Tables 2 and 3), with no difference between the insulin detemir groups. The apparently lower fluctuation of the CGMS profiles from individual days means that the two insulin detemir groups combined, compared with the NPH insulin group, did not reach statistical significance ($P = 0.065$) (Table 3).

Self-monitored plasma glucose profiles

At end point the shape of the three 10-point self-monitored plasma glucose profiles were similar between treatments during the daytime (Fig. 1). In the interval between dinner and breakfast (when timing of the basal insulin injections differed), the difference was close to conventional statistical significance ($P = 0.054$).

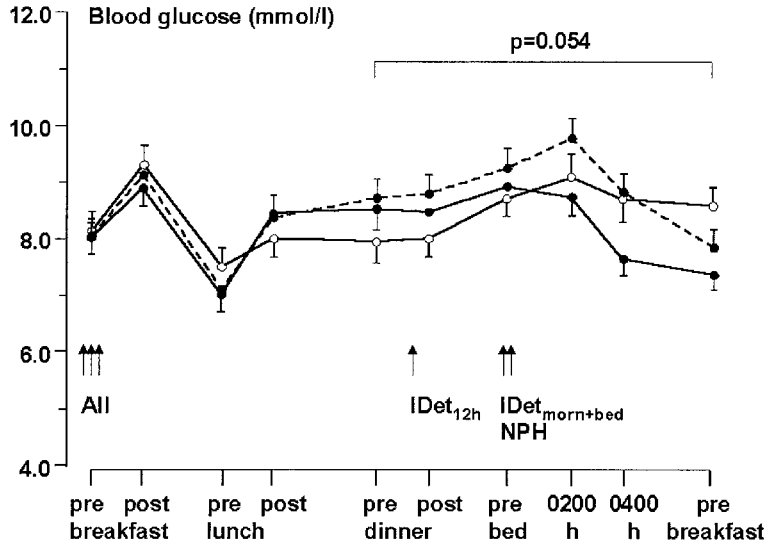

Figure 1—*Mean 10-point self-measured plasma glucose profiles after 16 weeks of treatment with insulin detemir or NPH insulin as basal insulin. Arrows indicate time of first and second basal insulin dose. $IDet_{12h}$ (●—●), insulin detemir administered at 12-h intervals; $IDet_{morn+bed}$ (● - - ●),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

However, inspection of the profile suggests the $IDet_{12h}$ group was lower on average than the $IDet_{morn+bed}$ and NPH insulin groups after bedtime (Fig. 1).

Hypoglycemic episodes

The incidence of minor hypoglycemic episodes differed between the three groups (Table 2). This was mostly attributable to a highly significant reduction in the risk of nocturnal hypoglycemia in the $IDet_{morn+bed}$ group compared with the NPH insulin group ($P < 0.001$) (Table 3), although the anytime risk reduction in the $IDet_{12h}$ group did reach statistical significance (Table 3). The difference in minor nocturnal hypoglycemia between the insulin detemir groups was statistically significant ($P = 0.035$). The incidence of all symptomatic hypoglycemia (including episodes refuted or unconfirmed by blood glucose testing) showed similar trends, but with less statistical power (data not shown). Very few severe hypoglycemic episodes were recorded (Table 2), giving no statistical differences between the groups.

Body weight

Body weight increased in the NPH insulin group over the study period (Table 2) but was unchanged in the two insulin detemir groups ($P = 0.018$), despite adjustment for the improvement in HbA_{1c}.

Adverse events

The adverse event profile was similar for the combined insulin detemir groups and the NPH insulin group. Serious adverse events were reported for 14 (5%) people in the pooled insulin detemir group and for 4 (3%) people in the NPH insulin group. Except for hypoglycemia, none of the events was judged by investigators as possibly related to treatment.

CONCLUSIONS — The present study has a number of strengths and weaknesses, many in common with pivotal phase 3 studies performed with other new insulin preparations. Notable among these, the study was performed in a large number of centers in a number of different countries, resulting in a small number of people with diabetes being studied in each center. Thus, the investigators would have little opportunity to learn and optimally implement the different pharmacodynamic characteristics of insulin detemir. Furthermore, the comparator basal insulin, NPH insulin, was being used by a majority of participants before the study started, so the experience of the users and investigators would be biased toward advantage for the NPH insulin. These factors may partly account for the statistically unchanged insulin doses and dose distribution found between insulin detemir– and NPH insulin–treated participants. With other insulin analogs, phase 3 studies conducted at an equivalent time in the clinical development program were somewhat disappointing (13–15), only for the new insulin analogs to later gain widespread clinical acceptance, as subsequent studies, having benefited from learned experience, have given evidence of further gains in blood glucose control.

Despite this, the present study suggests that insulin detemir is superior to NPH insulin in a number of ways when used in a mealtime + basal insulin regimen with insulin aspart. This includes overall blood glucose control, prebreakfast hyperglycemia, variability of prebreakfast blood glucose concentrations, nocturnal hypoglycemia, and body weight change.

Interpretation of HbA_{1c} data are problematic for insulins that reduce biochemical nocturnal hypoglycemia, because this will mitigate any improvement due to reduction in hyperglycemia at the other times of the day. Nevertheless, the improvement of the combined detemir groups compared with NPH insulin (an acceptable analytical procedure because the detemir groups would not be independent of each other) reached statistical significance ($P = 0.027$) with a difference that, by Diabetes Control and Complications Trial (DCCT) figures, would give a useful reduction in retinopathy risk if maintained for some years (1). This is consistent with earlier findings (16,17), reproduced in the current study for both insulin detemir treatment regimens, showing improved prebreakfast blood glucose control compared with NPH insulin, as measured by clinic fasting plasma glucose levels (which tend to be high because of stress and delays involved in attending for blood sampling) and by self-monitored plasma glucose levels (Tables 2 and 3). The greater improvement in clinic rather than self-monitored levels is to be expected for better basal insulin when compared with NPH because the latter's glucose-lowering effect is rapidly waning around breakfast time, an effect clinically familiar as the Sunday morning lie-in phenomenon.

The more optimal basal insulin profile is also evidenced by the combination of lower prebreakfast blood glucose levels with less nocturnal hypoglycemia. The reduction in minor hypoglycemia (biochemically confirmed) seems mainly to have been due to the 53% reduction in risk in the $IDet_{morn+bed}$ group at night compared with the NPH group, although the power of the study is such that a useful 25% reduction in minor anytime hypoglycemia in the $IDet_{12h}$ group could not be confirmed as being due to the measured 26% fall in risk in minor hypoglycemia at night.

In other studies glucose profiles obtained by CGMS technology have shown a trend to less within-day variation with insulin detemir than with NPH insulin (18,19). This was also the case for the combined insulin detemir findings in the current study (Table 3), consistent with the findings for hypoglycemia and prebreakfast plasma glucose levels.

Uniquely for a basal insulin, detemir has been reported as showing reduced within-person variability in glucose clamp studies when compared with NPH insulin, although insulin glargine is somewhat less variable than human ultralente insulin (20,21). This is confirmed as having clinical significance in the current study, with lower within-person between-day variability observed in both insulin detemir groups compared with NPH insulin (Tables 2 and 3). The size of the reduction (SD of 0.5–0.6 mmol/l) would suggest that mean prebreakfast blood glucose levels could be lowered by ~1.0 mmol/l or more while retaining the same risk of hypoglycemia at that time, crudely consistent with the reduction reported for self-monitored plasma glucose concentration (0.8 mmol/l). This reduction in variability of effect might be related to insulin detemir being an entirely soluble preparation throughout the absorption process, its unique mechanism of protraction of action (22), and some buffering of variability of absorption by albumin once in the circulation.

Regardless of whether it was administered at equal 12-h intervals or with a longer interval during the day than overnight, insulin detemir provided similar overall blood glucose control. Other studies have tested detemir injection before the main evening meal with similar con-

clusions (19), although none have tested the alternative of a fixed interval after the evening rapid-acting insulin analog.

The studies would appear to suggest that the timing of the evening injection could be adjusted to best suit the needs of the individual concerned. The more marked decrease in fasting clinic plasma glucose in the $IDet_{morn+bed}$ group, together with the lower risk of nocturnal hypoglycemic events compared with the $IDet_{12h}$ group, suggests that a morning and bedtime treatment regimen might be better suited for those people with a higher risk of hypoglycemia. Alternatively, the lower blood glucose levels of the $IDet_{12h}$ group during the night, which were not associated with more nocturnal hypoglycemic episodes than NPH insulin (and possibly less), would make a treatment regimen with earlier evening injection preferable for those who are not prone to nocturnal hypoglycemia and are thus able to seek the best possible control overnight. This flexibility in individual treatment regimen is supported by the findings of the other insulin detemir trial (19), where no difference in HbA_{1c} was observed between morning and dinner and morning and bedtime administration.

During the trial, body weight increased in the NPH insulin group but was unchanged in the two insulin detemir groups, despite improved overall glucose control (HbA_{1c}). These differences compared with NPH insulin have been found consistently in insulin detemir studies, with larger changes seen with increased duration of study (17,19,23). The reason why insulin detemir does not induce weight gain, compared with NPH insulin, is not clear. Possible mechanisms include, but are not limited to, an indirect or direct effect on the hypothalamus or less caloric consumption to treat and prevent hypoglycemia. This property of insulin detemir could be of long-term advantage, weight gain being a common problem in association with intensive diabetes management (24).

In conclusion, insulin detemir offers improved overnight control with better prebreakfast plasma glucose levels and/or nocturnal hypoglycemia rates than NPH insulin. Overall blood glucose control also seems to be improved. The more consistent glycemic control with improved predictability of prebreakfast blood glucose levels might be a particular advantage to some people with erratic control. Uniquely, there is a clear advantage over NPH insulin in body weight control. Thus, treatment with insulin detemir is superior to NPH insulin when used in combination with the rapid-acting insulin analog insulin aspart. Additionally, the differences in findings between the two detemir arms provide evidence on how timing of administration can be varied to suit individual needs. Studies comparing insulin detemir with other means of basal insulin delivery, notably insulin glargine and insulin pump therapy, would be of interest.

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APPENDIX

Members of The Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group are: Australia: T. Donnelly, A. Roberts, D. Wilson, S. Colagiuri, K. Stanton, and T. Davis; Belgium: K. Van Acker, H. De Leeuw, L. Van Gaal, J. Tits, C. Vercammen, and S. Van Imschoot; France: J.-J. Altman, J. Bringer, G. Charpentier, J. Cheikel, J.-P. Courreges, P. Duvezin Caubet, D. Gouet, Y. Lorcy, R.A. Marechaud, M. Marre, and J.-L. Selam; New Zealand: H. Lunt, S. Young; Sweden: F. Norstrom, O. Norrhamn, E. Bjork, M. Carlsson, M. Gutniak, B. Berger, and Dr. Fagerberg-Arvidsson; the Netherlands: K. Hoogenberg, C. Brouwer, J. de Sonnaville, R. van Leendert, and Dr. van Ouwerkerk; and the U.K.: B. Frier, A. Jaap, R. Jones, B. Millward, M. Page, M. Sampson, I. Scobie, A. Scott, K. Shaw, M. Small, and T. Wheatley.

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