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ORIGINAL ARTICLE

Effect of insulin degludec versus insulin glargine U100 on nocturnal glycaemia assessed by plasma glucose profiles in people with type 1 diabetes prone to nocturnal severe hypoglycaemia

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Abstract

Aim: To compare nocturnal glucose profiles according to hourly plasma glucose measurements during treatment with insulin degludec and insulin glargine U100 in a cohort of people with type 1 diabetes prone to nocturnal severe hypoglycaemia.

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Materials and methods: The HypoDeg trial is a 2-year investigator-initiated, randomized, controlled crossover trial in 149 participants randomized to treatment with insulin degludec and insulin glargine U100 for 12 months each. The 51 participants in this predefined substudy stayed at least one night in hospital during each treatment arm for plasma glucose samples to be taken. Endpoints were glucose profiles, including mean plasma glucose, glycaemic variability and risk of hypoglycaemia.

Results: There were no differences between treatments regarding mean plasma glucose. We saw a flatter glucose profile during insulin degludec compared with insulin glargine U100 treatment, which had a nadir at 4:00 AM, with a subsequent rise. During treatment with insulin degludec, the participants had lower glycaemic variability, with an estimated treatment difference of −4.3% (95% confidence interval [CI] −8.1 to −0.5; $P < 0.05$). Participants treated with insulin degludec were less likely to experience nocturnal hypoglycaemia below 3.0 mmol/L (hazard ratio 0.36 [95% CI 0.17-0.73; $P < 0.05$]).

Conclusion: Based on nocturnal plasma glucose measurements, treatment with insulin degludec compared with insulin glargine U100 administered in the evening results in lower glycaemic variability and lower risk of nocturnal hypoglycaemia without differences in mean plasma glucose.

KEYWORDS
basal insulin, clinical trial, glycaemic control, hypoglycaemia, insulin analogues, type 1 diabetes

1 | INTRODUCTION

Achieving glycaemic control during the night with a low risk of hypoglycaemia is of utmost importance to people with type 1 diabetes, as recurrent symptomatic hypoglycaemia at night may compromise overall glycaemic control.[1] Long-acting insulin analogues, including insulin degludec, lower the risk of nocturnal hypoglycaemia in people with type 1 diabetes and recurrent nocturnal severe hypoglycaemia.[2-5]

The HypoDeg trial investigated whether insulin degludec U100 compared with insulin glargine U100 reduces the occurrence of nocturnal symptomatic hypoglycaemia, as evaluated by blood glucose monitoring (BGM) in people with type 1 diabetes and recurrent nocturnal severe hypoglycaemia.[6] The study showed a clinically significant reduction in nocturnal symptomatic hypoglycaemia during treatment with insulin degludec compared with insulin glargine U100[3] and similar reductions in nocturnal asymptomatic hypoglycaemia as recorded by continuous glucose monitoring (CGM).[7] BGM mainly captures nocturnal symptomatic events and provides no insight into plasma glucose profiles during the night. CGM provides comprehensive glycaemic data during daily life, but these are considered less precise than BGM data and have not yet been accepted as valid endpoints at the regulatory level. In particular, nocturnal CGM data obtained by early CGM systems with a mean absolute relative difference (MARD) greater than 10%, such as the Medtronic iPro (Enlite sensor; Medtronic Minimed, Northridge, California) used in this study with a MARD of 12.9% to 18.9%,[8] have been viewed with scepticism regarding their precision.[9] Furthermore, concerns have been raised about the occurrence of hypoglycaemic events due to the risk of artefacts caused by sensor insertion site compression during sleep.[10] This predefined HypoDeg substudy was specifically designed to address these limitations, with the aim of assessing nocturnal glucose trajectories for comparison of pharmacodynamics and risk of hypoglycaemia between insulin degludec and insulin glargine U100 according to laboratory standard plasma glucose measurements in this population of people with type 1 diabetes and at high risk of nocturnal severe hypoglycaemia.

2 | RESEARCH DESIGN AND METHODS

2.1 | Trial design and procedures

The HypoDeg trial is a Danish investigator-initiated, controlled, 2-year, multicentre, crossover trial conducted in a PROBE (prospective, randomized, open trial, blinded endpoint adjudication) design. In the trial, the effect of insulin degludec compared with insulin glargine U100 on hypoglycaemic events in people with type 1 diabetes prone to nocturnal severe hypoglycaemia was reported. Nocturnal severe hypoglycaemia was defined as an event of hypoglycaemia that required the assistance of another person and occurred during sleep at night. Participants were randomized 1:1 to receive basal-bolus treatment with insulin degludec and insulin aspart for 12 months, followed by insulin glargine U100 and insulin aspart, or the reverse order. The primary endpoint of the HypoDeg trial was the incidence

TABLE 1 Baseline characteristics of participants.

Characteristic		(N = 149)	Participation in overnight substudy (N = 51)	Non-participation in overnight substudy (N = 98)
Age[a], years		54 ± 14	58 ± 13	52 ± 13
Male sex, n (%)		105 (71)	34 (67)	71 (72)
Body mass index[b], kg/m^2		26.9 ± 4.2	27.3 ± 5.0	25.4 ± 3.5
Duration of diabetes, years		28 ± 14	28 ± 14	28 ± 14
HbA1c, mmol/mol		61.7 ± 9.8	62.1 ± 8.8	61.5 ± 10.3
HbA1c, %		7.8 ± 0.9	7.8 ± 0.8	7.8 ± 0.9
Late diabetic complications, n (%)				
Retinopathy	Simplex	55 (37)	19 (35)	36 (37)
	Laser-treated	23 (15)	11 (22)	23 (24)
Nephropathy	Microalbuminuria	19 (13)	3 (6)	16 (17)
	Macroalbuminuria	6 (4)	3 (6)	3 (3)
Peripheral neuropathy		42 (28)	23 (24)	19 (37)
Autonomic neuropathy		32 (22)	11 (22)	21 (21)
Macrovascular complications[c]		17 (11)	7 (14)	10 (10)
Hypertension		80 (54)	29 (57)	51 (52)
C-peptide negative[d], n (%)		124 (87)	44 (86)	80 (88)
Hypoglycaemia awareness, n (%)				
Clarke[21]	Aware	39 (26)	16 (32)	23 (24)
	Unclassifiable	47 (32)	16 (32)	31 (32)
	Reduced awareness	59 (41)	18 (36)	41 (42)
Gold[22]	Aware	94 (63)	31 (61)	63 (64)
	Impaired	52 (35)	19 (37)	33 (34)
Pedersen-Bjergaard[11]	Aware	25 (17)	10(20)	15 (15)
	Impaired	94 (63)	31 (61)	63 (64)
	Unaware	27 (18)	10 (20)	17(18)
Nocturnal severe hypoglycaemia in the preceding 2 years, episodes/patient				
Mean ± SD		2.3 ± 2.2	2.6 ± 2.4	2.1 ± 2.1
Median (range)		1 (1-15)	1 (1-12)	1 (1-15)
Weekly alcohol consumption[e], units		8 ± 7	8 ± 8	8 ± 7
Smokers, n (%)		41 (28)	8 (16)	33 (34)
Insulin dose, IU/d				
Total basal insulin dose at baseline		28 ± 18	32 ± 23	25 ± 12
Total overall insulin dose at baseline		57 ± 27	65 ± 36	53 ± 20

Note: Data are mean ± SD or number (%) unless indicated otherwise.
[a]Significant difference $P = 0.007$ by Mann-Whitney *U*-test for non-normal distribution.
[b]Significant difference $P = 0.005$ by independent samples *t*-test.
[c]Macrovascular complications: hypertension, ischaemic heart disease, heart failure, stroke, transient cerebral ischaemia, and/or peripheral vascular surgery.
[d]C-peptide negative = below detection limit (<20 pmol/L).
[e]One unit = 8 g of alcohol.

of nocturnal symptomatic hypoglycaemia as evaluated by BGM during the 2-year study. The trial protocol and primary outcomes have been described in detail elsewhere.[3,6]

We invited the participants to take part in an optional overnight substudy of four nights—two nights in each treatment arm after 6, 12, 18 and 24 months of participation. On the day of the overnight stay, participants arrived in the late afternoon at the Clinical Research Unit at Copenhagen University Hospital—Nordsjælland, Hillerød, where they were offered a standard evening meal and followed their usual evening routine, including administration of bolus insulin. There were

no restrictions on the timing of the last bolus of insulin. Participants administered bolus and basal insulin in the same manner during the substudy visits as during the main trial. The long-acting insulin analogues were administered at the evening meal. At bedtime, they had a venous line inserted in the cubital vein. During the night, a study nurse or physician observed the participants and took blood samples for blinded plasma glucose measurements every hour from 11:00 PM to 7:00 AM while the participants were asleep. Plasma glucose samples were analysed by photometry at the laboratory the following day using a Siemens Dimension Vista 1500 (Siemens Medical Solutions, Malvern, Pennsylvania) analyser. The plasma glucose measurements, thus, were not used to control glycaemic levels during the trial.

If participants experienced symptomatic hypoglycaemia, the personnel noted this, took a point-of-care blood glucose measurement, and took action to restore the glucose level. The event was recorded as symptomatic hypoglycaemia if the plasma glucose at the time was ≤3.9 mmol/L.

The trial was approved by the Regional Committee on Biomedical Research Ethics (#H-3-2014-101) and the Danish Medicines Agency (#201407615), and the Danish Data Protection Agency (I-suite no: 02945; #NOH-2014-018). The trial is registered at www.eudract.ema.europ.eu (#2014-001942-24) and www.clinicaltrials.gov (#NCT02192450). It was conducted according to the Helsinki Declaration and Good Clinical Practice standards monitored by the Danish Agency for Good Clinical Practice. All participants provided written informed consent.

2.2 | Participants

Adults (≥18 years) diagnosed with type 1 diabetes for more than 5 years and with one or more episodes of nocturnal severe hypoglycaemia within the last 2 years were eligible for participation. We randomized 149 people in the main trial. Recruitment and screening have been described previously.[6]

The participants in the overnight substudy were characterized by a long duration of diabetes, a mean glycated haemoglobin (HbA1c) level of 62.1 mmol/mol (7.8%), C-peptide levels below the detection limit (<20 pmol/L), and a high prevalence of impaired or absent awareness (Pedersen-Bjergaard method[11]). The mean number of nocturnal severe hypoglycaemic events (previous 2 years) was 2.6 per patient (Table 1). No clinically relevant differences were found between participants and non-participants.

2.3 | Outcomes

To assess differences in treatment effects on mean plasma glucose, we calculated overall mean plasma glucose levels and mean plasma glucose at distinct timepoints. Next, the variability of nocturnal glucose profiles was assessed using the coefficient of variation (CV). To evaluate the risk of nocturnal hypoglycaemia according to treatment, we collected data on the number of nights with at least one episode of hypoglycaemia during the night. Furthermore, we collected data on the number of measures of low plasma glucose and the number of nights with consecutively low measures of low plasma glucose.

2.4 | Definitions of hypoglycaemia

We reviewed the plasma glucose measurements for hypoglycaemic events, classified according to international consensus by the International Hypoglycaemia Study group (IHSG)[12]: level 1: a glucose alert value of ≤3.9 mmol/L (≤70 mg/dL) and level 2: a plasma glucose of <3.0 mmol/L (<54 mg/dL), which is sufficiently low to indicate serious, clinically important hypoglycaemia.

Because level 1, according to the IHSG, covers all hypoglycaemic events equal to and below 3.9 mmol/L, we added an intermediary level of glucose values (3.9 to 3.0 mmol/L) to differentiate whether differences in level 2 hypoglycaemia solely drove a difference in level 1 hypoglycaemia.

There were no events of severe hypoglycaemia during this substudy.

2.5 | Statistical analysis

According to data distribution, we performed baseline comparisons between groups for continuous variables using an independent samples *t*-test or the Mann-Whitney *U*-test. For categorical variables, we compared differences in proportions between groups using Pearson's chi-squared test.

We defined the overall mean total plasma glucose concentration as the mean of all plasma glucose values from 11:00 PM to 7:00 AM and calculated the mean plasma glucose for every distinct timepoint during the night. In the analysis of mean plasma glucose at 7:00 AM (as an indicator of fasting plasma glucose), participants with symptomatic hypoglycaemia during the night were left out, as these episodes were treated with the ingestion of carbohydrates.

The CV was calculated as a percentage to quantify the glycaemic variability during the night (CV = [(SD of glucose)/(mean glucose)] × 100). A mixed linear regression model was applied to assess the effect of the two different insulin regimens on mean plasma glucose levels and the CV. Treatment and visit numbers were fixed effects, and the participant numbers were random effects. When applying the mixed model and assigning participant numbers as a random effect, the model accounts for the repeated-measure and crossover design. We included the interaction between treatment and visit in the model to account for a possible effect between visits. Hence the results are the CV for single nights.

The linear mixed model provided the estimated treatment differences, and standard descriptive statistics were used to indicate the mean values of variables.

In a Poisson log-linear model with fixed effects of treatment, treatment sequence, and visit, we modelled the number of measures of low plasma glucose to compare rates of hypoglycaemia between groups. The same model was used to compare the number of nights

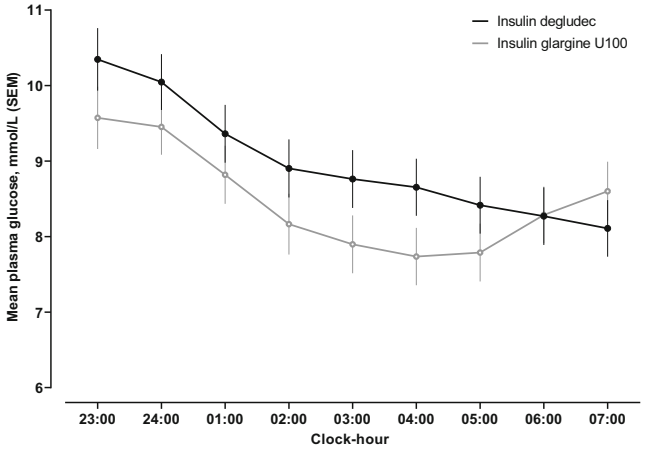

FIGURE 1 Mean plasma glucose mmol/L (SEM) during the night according to treatment. The insulin analogues were administered at 6:30 PM

with hypoglycaemia and consecutively low measures of plasma glucose.

Due to the crossover design, the hypoglycaemia rate is presented as a percentage of the total number of nights with a hypoglycaemic episode where participants were treated with either insulin analogue. So, regardless of the number of episodes on a given night, the hypoglycaemia rate includes nights with a minimum of one episode of hypoglycaemia. Hypoglycaemia rates in the two treatment groups were compared using hazard ratios (HRs) and 95% confidence intervals (CIs) from a Cox proportional hazards regression analysis. We used time-to-event during the night and Kaplan-Meier plots to illustrate the proportion of participants who experienced hypoglycaemia at different levels during the night.

The level of statistical significance was set at 5% (two-sided). The statistical software SPSS (IBM SPSS statistics 25) was used for all analyses.

3 | RESULTS

A subgroup of 61 people agreed to participate in the overnight substudy. The predefined criterion for including participants in our analyses was available data from at least one night in each treatment arm, leaving 51 participants and 196 nights for inclusion in the final analysis. Forty-five participants (88%) completed all four nights, four (8%) participants completed three nights, and two (4%) participants completed two nights (one in each treatment arm). Valid data were obtained for 196 nights in 51 participants, 97 nights during treatment with insulin degludec, and 99 nights with insulin glargine U100.

3.1 | Plasma glucose profiles

The overall mean (SD) plasma glucose concentration in the insulin degludec arm was 9.0 (3.3) mmol/L and was 8.5 (3.3) mmol/L in the insulin glargine U100 arm. The mixed model analysis showed no differences between treatments in overall mean plasma glucose. We evaluated mean plasma glucose concentration at the specific timepoints (11:00 PM, 12:00 AM, 1:00 AM, 2:00 AM, 3:00 AM, 4:00 AM, 5:00 AM, 6:00 AM and 7:00 AM). There were no differences between treatments, including fasting plasma glucose at 7:00 AM. Figure 1, showing the plasma glucose profiles according to treatment, illustrates that treatment with insulin degludec results in a steady decline in plasma glucose throughout the night. In contrast, treatment with insulin glargine U100 declined to a nadir at approximately 4:00 AM, with a subsequent rise.

3.2 | Coefficient of variation

The mean (SD) CV at night during treatment with insulin degludec and insulin glargine U100 were 22.1% (12.0%) and 27.5% (14.9%), respectively. In the linear mixed model, the difference in CV between treatments was statistically significant (estimated treatment difference −4.3% [95% CI −8.1 to −0.5]; $P < 0.05$). The CV shown is for single nights, as we included the interaction between visit and treatment in the statistical model, which was insignificant. Hence, the difference between treatment effects on CV during the single visit was influenced only by the treatment.

3.3 | Hypoglycaemia

We recorded hypoglycaemia on 57 (29%) out of 196 nights, 19 nights during insulin degludec treatment and 38 nights during insulin glargine U100 treatment, and this difference was significant ($P < 0.05$ [95% CI 0.3 to 0.8]). During insulin degludec treatment, we recorded 68 measures of low plasma glucose and 109 measures during insulin glargine U100 treatment. There was no difference between treatments in level 1 (≤3.9 mmol/L) measures; however, there were significantly fewer level 2 (<3.0 mmol/L) measures during insulin degludec treatment ($P < 0.05$ [95% CI 0.2 to 1.0]).

Eighteen participants (35%) did not experience any hypoglycaemia, 17 (33%) experienced one night with hypoglycaemia (plasma glucose ≤3.9 mmol/L), eight (16%) experienced two nights with hypoglycaemia, and five (10%) experienced three nights with hypoglycaemia. Three participants (6%) experienced hypoglycaemia during all four nights. Symptomatic hypoglycaemic events were recorded in 18 participants (35%)—six events during insulin degludec treatment and 16 events during insulin glargine U100 treatment.

Twenty-eight participants had more than one measure of hypoglycaemia during the night. These measures were consecutive during most nights (38 out of 45). The mean nadir and number of consecutive measures of hypoglycaemia were the same between treatments. The number of nights with consecutive measures of hypoglycaemia differed numerically between treatments. During insulin degludec treatment, there were consecutive hypoglycaemia measures for

TABLE 2 Hazard ratios (95% CI) of hypoglycaemia based on event rates of hypoglycaemia.

Level of hypoglycaemia	Insulin degludec (97 nights) nights with an event (%)	Insulin glargine U100 (99 nights) nights with an event (%)	Hazard ratio	95% CI	*P* value
Level 1 (≤3.9 mmol/L)	19 (20)	38 (38)	0.46	0.27–0.77	0.0034
Level 2 (<3.0 mmol/L)	8 (8)	22 (22)	0.36	0.17–0.73	0.011
Intermediary (3.9-3.0 mmol/L)	16 (16)	36 (36)	0.40	0.23–0.69	0.001
Symptomatic (≤3.9 mmol/L)	5 (5)	13 (15)	0.38	0.15–0.95	0.055
Asymptomatic (≤3.9 mmol/L)	18 (19)	35 (35)	0.48	0.28–0.82	0.0076
Asymptomatic (<3.0 mmol/L)	6 (6)	17 (17)	0.35	0.15–0.79	0.021

Abbreviation: CI, confidence interval.

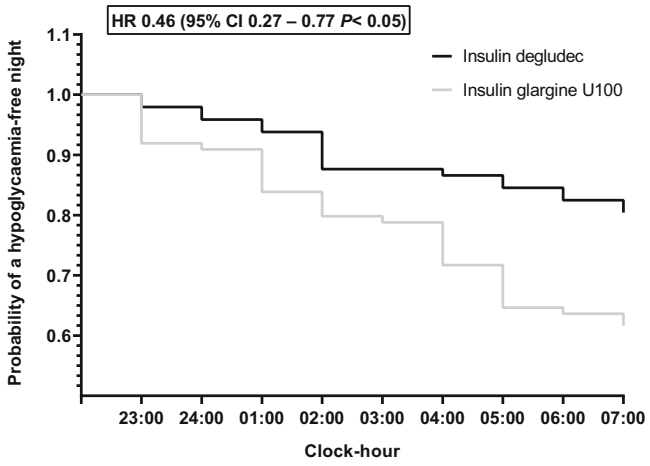

FIGURE 2 Probability of a hypoglycaemia-free night at level 1 (≤3.9 mmol/L) according to treatment and clock-hour during the night in 51 people with type 1 diabetes and recurrent nocturnal severe hypoglycaemia. The insulin analogues were administered at 6:30 PM. CI, confidence interval; HR, hazard ratio

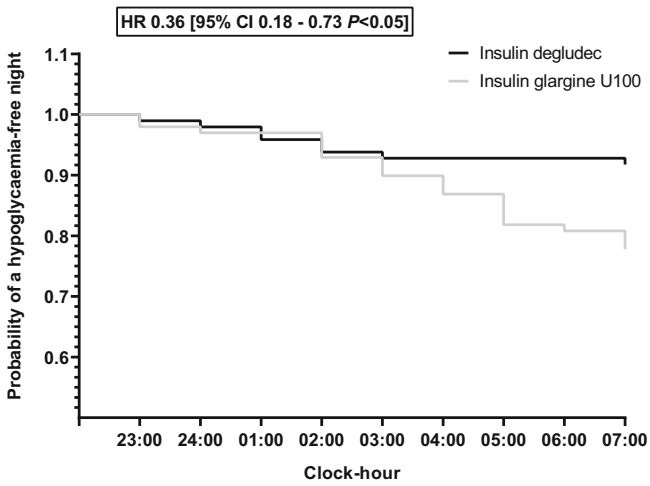

FIGURE 3 Probability of a hypoglycaemia-free night at level 2 (<3.0 mmol/L) according to treatment and clock-hour during the night 51 people with type 1 diabetes and recurrent nocturnal severe hypoglycaemia. The insulin analogues were administered at 6:30 PM. CI, confidence interval; HR, hazard ratio

14 nights and during insulin glargine U100 for 25 nights. The difference was not significant.

3.4 | Level 1: plasma glucose ≤3.9 mmol/L

The rate of hypoglycaemia expressed as nights with a minimum of one episode of level 1 hypoglycaemia was lower during insulin degludec treatment (20% vs. 38%; HR 0.46 [95% CI 0.27 to 0.77]; $P < 0.05$ [Table 2]). This translates into a 54% lower risk of experiencing level 1 hypoglycaemia during the night when treated with insulin degludec than with insulin glargine U100. The Kaplan-Meier survival curve illustrates the probability of a hypoglycaemia-free night at each timepoint during the night in Figure 2.

A possible influence of evening meal insulin aspart administration was tested by excluding nights with episodes at bedtime (11:00 PM). Even after excluding these nights, the hypoglycaemia rate in the insulin degludec arm remained lower (18% vs. 33%; HR 0.51 [95% CI 0.28 to 0.92]; $P < 0.05$ [Table 2]). Repeated Cox regression analysis, including only the participants (n = 45) who completed all four nights, confirmed the results, with a lower rate of nights with a minimum of one episode of level 1 hypoglycaemia in the insulin degludec arm (20% vs. 37%; HR 0.49 [95% CI 0.28 to 0.87]; $P < 0.05$ [Table 2]).

3.5 | Level 2: plasma glucose <3.0 mmol/L

The rate of nights with a minimum of one episode of level 2 hypoglycaemia was 64% lower during treatment with insulin degludec as compared with treatment with insulin glargine U100 (8% vs. 22%; HR 0.36 [95% CI 0.18-0.73]; $P < 0.05$ [Table 2]). The Kaplan-Meier survival curve illustrates the distribution of hypoglycaemic episodes and the probability of a hypoglycaemia-free night at this level (Figure 3).

3.6 | Intermediary level of hypoglycaemia: plasma glucose 3.9 mmol/L to 3.0 mmol/L

At the intermediary level, we found a 60% lower rate of nights with a minimum of one episode of hypoglycaemia during treatment with

insulin degludec (16% vs. 36%; HR 0.40 [95% CI 0.23 to 0.69]; $P = 0.001$ [Table 2]).

3.7 | Symptomatic and asymptomatic hypoglycaemia

During treatment with insulin degludec, the rate of nights with a minimum of one episode of symptomatic hypoglycaemia was 62% lower than during insulin glargine U100 treatment (5% vs. 15%; HR 0.38 [95% CI 0.15 to 1.0]; $P = 0.053$ [Table 2]).

Leaving out episodes of symptomatic hypoglycaemia at both levels also resulted in significant differences between treatments. At hypoglycaemia levels 1 and 2, the rate of nights with a minimum of one episode of asymptomatic hypoglycaemia during the night was lower during treatment with insulin degludec than insulin glargine U100 (19% vs. 35%; HR 0.48 [95% CI 0.28 to 0.82], $P = 0.05$ and 6% vs. 17%; HR 0.35 [95% CI 0.15 to 0.79], $P = 0.05$, respectively [Table 2]).

The survival analyses were repeated according to visits to estimate the effect of the duration of treatment. The results were as follows. After 6 months of maintenance treatment (insulin degludec compared with insulin glargine U100, an HR below 1 indicates less hypoglycaemia during insulin degludec treatment): level 1 hypoglycaemia (≤3.9 mmol/L): HR 0.39 [95% CI 0.15-1.03], nonsignificant; level 2 hypoglycaemia (<3.0 mmol/L): HR 0.46 [95% CI 0.17-1.2], nonsignificant.

After 12 months of maintenance treatment (insulin degludec compared with insulin glargine U100; an HR below 1 indicates less hypoglycaemia during degludec treatment): level 1 hypoglycaemia (≤3.9 mmol/L): HR 0.65 [95% CI 0.31 to 1.37], nonsignificant; level 2 hypoglycaemia (<3.0 mmol/L): HR 0.32 [95% CI 0.11 to 0.95], $P = 0.0430$.

4 | DISCUSSION

This analysis of nocturnal plasma glucose profiles in people with type 1 diabetes experiencing recurrent nocturnal severe hypoglycaemia provides mechanistic insight into the beneficial effect of insulin degludec on the risk of nocturnal hypoglycaemia. Thus, we found a significantly lower glycaemic variability during the night for treatment with insulin degludec than treatment with insulin glargine U100. At comparable mean nocturnal glucose levels, the treatment with insulin degludec resulted in a 54% reduction in the risk of nocturnal hypoglycaemia. Because the HypoDeg Trial participants were hypoglycaemia-prone, this finding is essential as it may be directly applied in a clinical setting with patients experiencing nocturnal hypoglycaemia.

At night, hypoglycaemia risk depends primarily on the basal insulin's pharmacokinetic and pharmacodynamic profile. Euglycaemic clamp studies of insulin degludec show that the pharmacodynamic profile is uniform across a 24-hour dosing interval, with low within-subject variability in the glucose-lowering effect.[13] The half-life of insulin degludec is 25 hours, compared with 12.5 hours for insulin glargine U100. Compared with insulin glargine U100, the within-subject variability in the glucose-lowering effect of insulin degludec is one-quarter that of insulin glargine U100.[14] In day-to-day variability, insulin degludec results in a stable variability, whereas insulin glargine U100 results in a peak in variability at 14 to 16 hours post-dosing.[14]

These properties of insulin degludec may explain the results in the present study. The present results correspond well with the main result of the HypoDeg trial showing a relative rate reduction of 28% in nocturnal symptomatic hypoglycaemia at level 1 (≤3.9 mmol/L) and 37% at level 2 (≤3.0 mmol/L) hypoglycaemia with insulin degludec.[3] As most episodes of nocturnal hypoglycaemia are asymptomatic,[15] we also applied CGM in another predefined substudy of the HypoDeg trial that showed a relative rate reduction of 32% at level 1 nocturnal asymptomatic hypoglycaemia and 52% at level 2. During the main trial, asymptomatic hypoglycaemia could only be captured during the day. Asymptomatic hypoglycaemia on CGM may be overestimated due to CGM imprecisions in the low blood glucose range[9,16] and erroneous hypoglycaemic recordings due to physical pressure on the CGM device during the night.[10] By using plasma glucose measurements, these concerns were eliminated in this study. Because the plasma glucose measures were blinded and not analysed until the following day, they did not influence treatment decisions. Hence, the results of the present study confirm that differences found in nocturnal hypoglycaemia by CGM are reliable when controlled with laboratory standard plasma glucose measurements.

As this trial includes people with type 1 diabetes and a high risk of nocturnal hypoglycaemia, it expands the results of the BEGIN and SWITCH trials. These previous trials found similar relative reductions in nocturnal hypoglycaemia during treatment with insulin degludec compared with insulin glargine U100[17,18] in people with type 1 diabetes with no or an intermediary risk of hypoglycaemia.

The major strength of this trial is the use of plasma glucose measurements every hour during sleep and the complete recording of symptomatic hypoglycaemia by study personnel. These are state-of-the-art glucose measurements and are considered more accurate than CGM, particularly in the hypoglycaemic range. Another strength is that the inclusion of people at high risk of hypoglycaemia makes the findings representative of the hypoglycaemia rates that will occur in clinical practice in people with type 1 diabetes and problematic hypoglycaemia; previous trials comparing insulin degludec to insulin glargine U100 have excluded or not specifically included people with a high risk of nocturnal hypoglycaemia. A third strength is the study's crossover design, which eliminates the random effects of participants with extreme rates of hypoglycaemia. The in-hospital setting may have impacted nocturnal glycaemia, although we tried to normalize the situation as much as possible by allowing participants to follow their usual routines. A minor limitation of this substudy is that we only took plasma glucose once every hour, which is less extensive than CGM.

Today, there are two ultra-long-acting basal insulins available. Only two studies have compared insulin glargine U300 and insulin

degludec.[19,20] As both studies included people at low risk of hypoglycaemia, it is difficult to say whether the similarities between the two insulins in these studies would apply to people with type 1 diabetes who are at high risk of hypoglycaemia. A study similar in methodology to the one presented here in a similar patient population would be desirable.

In conclusion, in people with type 1 diabetes and recurrent nocturnal severe hypoglycaemia, treatment with insulin degludec compared with insulin glargine U100 administered at the evening meal significantly reduces nocturnal glycaemic variability assessed by laboratory plasma glucose measurements during two in-hospital nights during each treatment and as a consequence, also consistently reduces the rate of nights with hypoglycaemia. There was no difference between treatments in mean plasma glucose, overall or at specific timepoints during the night.

AUTHOR CONTRIBUTIONS

Ulrik Pedersen-Bjergaard, Rikke M. Agesen, Lise Tarnow and Birger Thorsteinsson initiated and designed the trial. Rikke M. Agesen, Amra Ciric Alibegovic, Henrik Ullits Andersen, Henning Beck-Nielsen, Peter Gustenhoff, Troels Krarup Hansen, Christoffer G. R. Hedetoft, Tonny Jensen, Charlotte Røn Stolberg, Claus Bogh Juhl, Susanne Søgaard Lerche, Kirsten Nørgaard, Hans-Henrik Parving, Lise Tarnow, Birger Thorsteinsson, and Ulrik Pedersen-Bjergaard participated in the coordination of the study and data collection. Julie M. Bøggild Brøsen, Peter Lommer Kristensen and Ulrik Pedersen-Bjergaard planned and executed the statistical analyses. Julie M. Bøggild Brøsen was responsible for the development of the manuscript. All authors contributed to, read, and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Julie Maria Bøggild Brøsen, Henning Beck-Nielsen, Troels Krarup Hansen, Christoffer Georg Riber Hedetoft, Tonny Joran Jensen, Charlotte Røn Stolberg, Susanne Søgaard Lerche, Hans-Henrik Parving, Lise Tarnow and Birger Thorsteinsson have no competing financial interests. Ulrik Pedersen-Bjergaard has served on advisory boards for Novo Nordisk and Sanofi, and has received lecture fees from Abbott, Sanofi, and Novo Nordisk. Amra Ciric Alibegovic and Rikke Mette Agesen have been employed by Novo Nordisk A/S since September 2019 (after the finalization of the study). Henrik Ullits Andersen is on advisory boards for Abbott Laboratories, Astra Zeneca and Novo Nordisk, has received lecture fees from Nordic Infucare and owns stock in Novo Nordisk. Peter Gustenhoff has served on advisory boards for Abbott Laboratories, Astra Zeneca, Boehringer Ingelheim, Novo Nordisk and Sanofi. Claus Bogh Juhl serves on advisory boards for Novo Nordisk. Kirsten Nørgaard serves as an advisor to Abbott Laboratories, Medtronic and Novo Nordisk and has received fees for speaking from Bayer, Medtronic, Novo Nordisk, Roche Diabetes Care, Rubin Medical, Sanofi, and Zealand Pharma, and owns stock in Novo Nordisk. Peter Lommer Kristensen has received speakers fee from Sanofi A/S, Novo Nordisk A/S and AstraZeneca A/S.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Wild D, Von Maltzahn R, Brohan E, Christensen T, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. *Patient Educ Couns*. 2007;68(1):10-15.
2. Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. *Lancet Diabetes Endocrinol*. 2014;2(7):553-561.
3. Pedersen-Bjergaard U, Agesen RM, Brøsen JMB, et al. Comparison of treatment with insulin degludec and glargine U100 in patients with type 1 diabetes prone to nocturnal severe hypoglycaemia: the HypoDeg randomized, controlled, open-label, crossover trial. *Diabetes Obes Metab*. 2021;1–11:257-267.
4. Agesen RM, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogs on frequency of non–severe hypoglycemia in patients with type 1 diabetes prone to severe hypoglycemia: much higher rates detected by continuous glucose monitoring than by self-monitoring of blood glucose—the HypoAna trial. *Diabetes Technol Ther*. 2018;20(3):247-256.
5. Agesen RM, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: the HypoAna trial. *Diabetes Metab*. 2016;42(4):249-255.
6. Agesen RM, Alibegovic AC, Andersen HU, et al. The effect of insulin degludec on risk of symptomatic nocturnal hypoglycaemia in adults with type 1 diabetes and high risk of nocturnal severe hypoglycaemia (the HypoDeg trial): study rationale and design. *BMC Endocr Disord*. 2019;19(1):78.
7. Bøggild Brøsen JM, Agesen RM, Alibegovic AC, et al. Continuous glucose monitoring-recorded hypoglycemia with insulin degludec or insulin glargine U100 in people with type 1 diabetes prone to nocturnal severe hypoglycemia. *Diabetes Technol Ther*. 2022;24(9):643-654.
8. Heinemann L, Schoemaker M, Schmelzeisen-Redecker G, et al. Benefits and limitations of MARD as a performance parameter for

continuous glucose monitoring in the interstitial space. *J Diabetes Sci Technol*. 2020;14:135-150.
9. Bailey TS, Alva S. Landscape of continuous glucose monitoring (CGM) and integrated CGM: accuracy considerations. *Diabetes Technol Ther*. 2021;23(S3):S5-S11.
10. Mensh BD, Wisniewski NA, Neil BM, Burnett DR. Susceptibility of interstitial continuous glucose monitor performance to sleeping position. *J Diabetes Sci Technol*. 2013;7(4):863-870.
11. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. *Diabetes Metab Res Rev*. 2003;19(3):232-240.
12. Amiel SA, Aschner P, Childs RNB, et al. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of diabetes. *Diabetologia*. 2017;60:3-6.
13. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. *Clin Pharmacokinet*. 2014;53(9):787-800.
14. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab*. 2012;14:859-864.
15. Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symptomatic hypoglycemia in 411 type 1 diabetic patients. *Diabet Med*. 1991;8:217-222.
16. Hornborg Svensson C, Henriksen MM, Thorsteinsson B, Pedersen-Bjergaard U. Continuous glucose monitoring (CGM) readings during patient-reported symptomatic hypoglycemia: assessment of the advanced technologies and treatments for diabetes consensus definition of CGM-recorded hypoglycemia. *Diabetes Technol Ther*. 2022;24(2):130-135.
17. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN basal-bolus type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1489-1497.
18. Lane W, Bailey TS, Gerety G, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes the SWITCH 1 randomized clinical trial. *JAMA*. 2017;4(318):33-44.
19. Miura H, Sakaguchi K, Otowa-Suematsu N, et al. Effects of insulin degludec and insulin glargine U300 on glycaemic stability in individuals with type 1 diabetes: a multicentre, randomized controlled crossover study. *Diabetes Obes Metab*. 2020;22(12):2356-2363.
20. Battelino T, Danne T, Edelman SV, et al. CGM-based time-in-range using insulin glargine 300 units/ml versus insulin degludec 100 units/-ml in type 1 diabetes: the head-to-head randomized controlled InRange trial. *Diabetes Obes Metab*. 2022;25(2):545-555.
21. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care*. 1995;18(4):517-522.
22. Gold AE, Macleod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care*. 1994;17(7):697-703.

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