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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

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Abstract

Aim: To investigate whether the long-acting insulin analogue insulin degludec compared with insulin glargine U100 reduces the risk of nocturnal symptomatic hypoglycaemia in patients with type 1 diabetes (T1D).

Methods: Adults with T1D and at least one episode of nocturnal severe hypoglycaemia during the last 2 years were included in a 2-year prospective,

randomized, open, multicentre, crossover trial. A total of 149 patients were randomized 1:1 to basal-bolus therapy with insulin degludec and insulin aspart or insulin glargine U100 and insulin aspart. Each treatment period lasted 1 year and consisted of 3 months of run-in or crossover followed by 9 months of maintenance. The primary endpoint was the number of blindly adjudicated nocturnal symptomatic hypoglycaemic episodes. Secondary endpoints included the occurrence of severe hypoglycaemia. We analysed all endpoints by intention-to-treat.

Results: Treatment with insulin degludec resulted in a 28% (95% CI: 9%-43%; $P = .02$) relative rate reduction (RRR) of nocturnal symptomatic hypoglycaemia at level 1 (≤3.9 mmol/L), a 37% (95% CI: 16%-53%; $P = .002$) RRR at level 2 (≤3.0 mmol/L), and a 35% (95% CI: 1%-58%; $P = .04$) RRR in all-day severe hypoglycaemia compared with insulin glargine U100.

Conclusions: Patients with T1D prone to nocturnal severe hypoglycaemia have lower rates of nocturnal symptomatic hypoglycaemia and all-day severe hypoglycaemia with insulin degludec compared with insulin glargine U100.

KEYWORDS

basal insulin, hypoglycaemia, insulin analogues, phase IV study, randomized trial, type 1 diabetes

1 | INTRODUCTION

Hypoglycaemia is the primary side effect of insulin therapy in type 1 diabetes and a daily source of concern for patients and their relatives.[1,2] Nocturnal hypoglycaemia, in particular, is feared by many patients, and their effort to reduce the risk may result in overnight hyperglycaemia, which is a significant contributor to poor glycaemic control, and ultimately a potential driver of microvascular complications.[3-6] Therefore, reducing nocturnal hypoglycaemia is a cornerstone to improve overall glycaemic control and treatment outcomes in type 1 diabetes.

During the night, a significant cause of hypoglycaemia is inappropriate nocturnal insulin action because of an unphysiological action profile and variable absorption of basal insulin. Even although the first-generation long-acting insulin analogues glargine U100 and detemir, in comparison with NPH insulin, consistently reduce the risk of nocturnal hypoglycaemia in patients with type 1 diabetes, nocturnal hypoglycaemia remains a significant clinical problem.[7-9] The newer long-acting insulin analogue degludec displays a further 25% relative rate reduction (RRR) of nocturnal hypoglycaemia compared with insulin glargine U100 in the phase 3 trials in patients with type 1 diabetes at a low risk of hypoglycaemia.[10] This reduction is confirmed in a trial including subgroups of patients at an increased risk of hypoglycaemia.[11] However, no data exist on patients specifically prone to nocturnal severe hypoglycaemia.

Therefore, the HypoDeg trial aims to investigate whether the rate of nocturnal symptomatic hypoglycaemia is lower with insulin degludec U100 compared with insulin glargine U100 in patients with type 1 diabetes prone to nocturnal severe hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The HypoDeg trial was an investigator-initiated, 2-year, crossover study conducted in a prospective, randomized, open, blinded endpoint (PROBE) design, carried out at 10 centres in Denmark. Each 1-year treatment period consisted of 3 months of run-in or crossover, used for insulin dose adjustment and stabilization of treatment regimens, followed by 9 months of maintenance. A detailed description of the study design has been published previously.[12]

Patients were eligible if they had been diagnosed clinically with type 1 diabetes for more than 5 years, were aged 18 years or older, and reported one or more episodes of nocturnal severe hypoglycaemia in the previous 2 years (defined by the need for treatment assistance from another person). Pertinent exclusion criteria were: history of primary and secondary adrenal insufficiency, growth hormone deficiency or untreated hypothyroidism, unstable macrovascular disease, history of malignancy, drug or alcohol abuse, and HbA1c more than 86 mmol/mol (>10%).[12] Because the use of continuous glucose monitoring (CGM) was very limited in Denmark at this time we decided only to include people using self-monitored blood glucose (SMBG) as control of glycaemia.

We identified participants by either a screening questionnaire, which was mailed to the patients, or completed by the patients in the outpatient clinics, or by opportunistic screening in the clinics.

The study was approved by the Regional Committee on Biomedical Research Ethics (#H-3-2014-101), the Danish Medicines Agency (#2014071615), and the Danish Data Protection Agency (I-suite no: 02945; #NOH-2014-018), and was registered at www.

eudract.ema.europe.eu (#2014-001942-24) and at www.clinicaltrials.gov (#NCT02192450). All participants gave written informed consent.

2.2 | Randomization and procedures

We randomized patients to start basal-bolus therapy with insulin degludec/insulin aspart (Tresiba/NovoRapid) or insulin glargine U100/insulin aspart (Lantus/NovoRapid). A web-based electronic case report form generating site-specific randomization lists in blocks of four patients randomized 73 patients to receive insulin degludec first, and 76 patients to receive insulin glargine U100 first.[12]

Insulin degludec or insulin glargine U100 were administered subcutaneously by insulin pen once daily with the evening meal. This timing provides more consistent overnight glucose control with insulin glargine U100 than administration in the morning.[13] A stringent treat-to-target design was not considered feasible in these hypoglycaemia-prone patients. We set the glycaemic target to maintain baseline glycaemic control in both treatment periods at the investigators' discretion. We reduced both basal and prandial insulin doses by 20% at entry into both treatment arms and uptitrated to the patients' usual fasting and preprandial glucose targets to prevent increased rates of severe hypoglycaemia during the run-in and crossover periods.

We instructed patients to perform and record four-point SMBG profiles twice-weekly (before breakfast, before lunch, before dinner, and at bedtime) throughout the study. Patients were seen at their local outpatient clinic every third month, nine visits in total. At every visit, blood pressure, pulse, and weight were recorded, and HbA1c was measured. At the randomization, crossover, and end-of-study visits, we measured fasting blood glucose and C-peptide.[12] Furthermore, we assessed hypoglycaemia awareness by three validated methods.[14-16]

Adverse events were recorded and graded according to current good clinical practice guidelines.[12]

2.3 | Outcomes

The primary endpoint is the number of episodes of nocturnal symptomatic hypoglycaemia reported by the patients during the maintenance periods, that is, the last 9 months of each treatment arm. We defined symptomatic hypoglycaemia at two levels as a plasma glucose of 3.9 mmol/L or less (level 1) or of 3.0 mmol/L or less (level 2). The protocol of the study was written before the current International Hypoglycaemia Study Group recommendations concerning hypoglycaemia reporting were established.[17] Therefore, we report level 2 hypoglycaemia as 3.0 mmol/L or less, and not as less than 3.0 mmol/L.[12]

Night time is defined conventionally in two ways: 12:00 AM-05:59 AM and 11:00 PM-06:59 AM.[12] Furthermore, we applied an exploratory 'real-life' definition from 4 hours after evening prandial or corrective bolus insulin administration until actual morning prandial insulin administration to exclude any influence of coincidental correction with rapid-acting insulin. This definition is referred to as individual night time in the article.

The secondary endpoints are the incidence of severe hypoglycaemia (total, night time, daytime) as defined by the American Diabetes Association as an event requiring the assistance of another person to actively administer carbohydrates, glucagon, or to take other corrective actions.[18] Overall glycaemic control, as assessed by the last three HbA1c values in each treatment arm and insulin doses at the end of each treatment period, are accommodated in the secondary endpoints.[12]

We instructed patients to report all nocturnal symptomatic hypoglycaemia and any severe episodes by telephone to a call centre within 24 hours or on the first upcoming workday after the event. A structured interview questionnaire was applied to all possible severe hypoglycaemic episodes to validate severity and document causality according to Whipple's triad.[19] In accordance with the PROBE design, all potential primary endpoints and severe hypoglycaemic events were adjudicated by a review committee blinded to the treatment regimen.

Furthermore, the patients were instructed and encouraged to keep a diary of hypoglycaemic events, including the date and time of each episode, accompanying measurement of plasma glucose, symptoms, waking state (or sleep), and last prandial or corrective bolus insulin administration time.

2.4 | Statistical analyses

Baseline characteristics of the participants are summarized by mean and standard deviation for continuous data, and frequencies and proportions for categorical data. Summary statistics for the outcome event rates per year are summarized by mean and standard deviation, or by median and range. Mixed effects Poisson regression models are fitted to model the difference in incidence rates of hypoglycaemia. We included a subject-level normal random effect to account for the crossover design. As all count outcomes show signs of overdispersion, we used an observation-level normal random effect.

The dependent variable in a Poisson regression varies among individuals and over time, and is why a key fixed effect is follow-up time. Fixed effects also include treatment, and we adjusted for the period, study site, and an average of HbA1c levels, respectively. The average of HbA1c measurements is calculated as an average of the last three HbA1c levels by the end of the specific treatment period. If one or two measures are missing, we calculated the average from the remaining non-missing observations. Each outcome is furthermore tested for treatment by period interaction. We quantified treatment comparisons as unadjusted and adjusted incidence rate ratios (IRRs). The IRR can be interpreted as a RRR, and we present it as such.

We performed goodness-of-fit and tests for overdispersion using a simulation-based approach. Average absolute rate reductions (ARRs) are estimated using the regression parameter estimates, and the associated 95% confidence intervals are estimated using a parametric bootstrap with 10 000 replications. Treatment-dependent differences in HbA1c levels and weight from baseline to the end of the first and second periods are analysed using linear regression models. Differences in dosage of basal, prandial/corrective bolus, and total insulin depending on treatment are estimated using linear mixed effects models with a subject-specific normal random effect. We set the level of statistical significance at 5% (two-sided). No adjustment for multiple testing was performed. We used the statistical software R for all analyses. Packages

TABLE 1 Baseline characteristics of participants

Characteristic		(N = 149)
Age (y)		54 (14)
Male, n (%)		105 (71)
Body mass index (kg/m^2)		26 (4)
Body weight (kg)		80.6 (14)
Duration of diabetes (y)		28 (14)
HbA1c	mmol/mol	62 (10)
	(%)	7.8 (0.9)
Fasting plasma glucose (mmol/L)		10.5 (5)
Retinopathy, n (%)	Background	55 (37)
	Laser-treated	23 (15)
Nephropathy, n (%)	Microalbuminuria	19 (13)
	Macroalbuminuria	6 (4)
Peripheral neuropathy, n (%)		42 (28)
Autonomic neuropathy, n (%)		32 (21)
Macrovascular complications,[a] n (%)		17 (11)
Hypertension, n (%)		80 (54)
C-peptide negative,[b] n (%)		124 (83)
Hypoglycaemia awareness (%)		
Aware/impaired awareness[14] (%)		64/36
Aware/unclassified/reduced awareness[15] (%)		27/32/41
Aware/impaired/unaware[16] (%)		17/64/19
Rate of nocturnal severe hypoglycaemia in the preceding 2 y (episodes/patient)	Mean (SD)	2.3 (2.2)
	Median (range)	1 (1-15)
Weekly alcohol consumption, units[c] (%)		
1-7		62 (16)
8-14		31 (42)
>14		22 (15)
Smokers, n (%)		41 (27)
Pretrial basal insulin, n (%)		
Insulin detemir		59 (40)
Once daily		19 (32)
Twice daily		40 (68)
Insulin glargine U100		52 (35)
Once daily		35 (67)
Twice daily		17 (33)
NPH		25 (17)
Once daily		18 (72)
Twice daily		7 (28)
Premixed insulin		1 (1)
Insulin degludec		6 (4)
Insulin glargine U300		2 (1)
Insulin dose (units/kg/d)		0.7 (0.5)

[a]Macrovascular complications: hypertension, myocardial infarction, ischaemic heart disease, heart failure, stroke, transient cerebral ischemia (TCI), and/or peripheral vascular surgery.
[b]C-peptide negative = below detection limit (<20 pmol/L).
[c]One unit = 15 g of alcohol.

used were lme4 for continuous outcomes, glmmTMB for count outcomes, and overdispersion was assessed using DHARMa.[20-23]

3 | RESULTS

Screening of potential candidates was performed from December 2015 to March 2017, resulting in the identification of 149 patients who fulfilled the criteria, and they were randomized (73 to receive insulin degludec first, and 76 to receive insulin glargine U100 first) from 20 January 2015 to 10 March 2017. The last patient's last visit was on 21 February 2019.

Baseline characteristics of the 149 participants are summarized in Table 1 and include long duration of diabetes, high prevalence of absent endogenous insulin production and reduction of hypoglycaemia awareness (83%, Pedersen-Bjergaard method),[16] and a mean rate of nocturnal severe hypoglycaemic events in the preceding 2 years of 2.3 ± 2.2 (median [range]: 1 [1-15]).

We included all 149 randomized patients in the intention-to-treat (ITT) cohort. Seventeen patients (11%) dropped out or discontinued before the predefined cut-off point for inclusion in the per-protocol (PP) analysis (18 months on treatment), leaving 132 participants for inclusion in the PP cohort (Figure 1). Another four patients discontinued later during the trial. An equal number of participants in the randomized cohort (n = 149) dropped out for various reasons while receiving insulin degludec or insulin glargine U100 (eight [5%] and seven [5%] participants, respectively). Four patients (3%) did not wish to receive insulin glargine U100 and did not crossover in the study. Two patients died, one in each treatment arm; no relation to the insulin products or trial procedures was identified (Figure 1).

3.1 | Nocturnal symptomatic hypoglycaemia

3.1.1 | Level 1 hypoglycaemia

A total of 727 episodes of level 1 symptomatic hypoglycaemia occurred during 12:00 AM-05:59 AM (Table 2). Events were reported by 79 and 94 patients in the insulin degludec and insulin glargine U100 arms, respectively. During 11:00 PM-06:59 AM, 1379 events were reported by 96 and 108 patients in the insulin degludec and insulin glargine U100 arms, respectively (Table 2). During individual

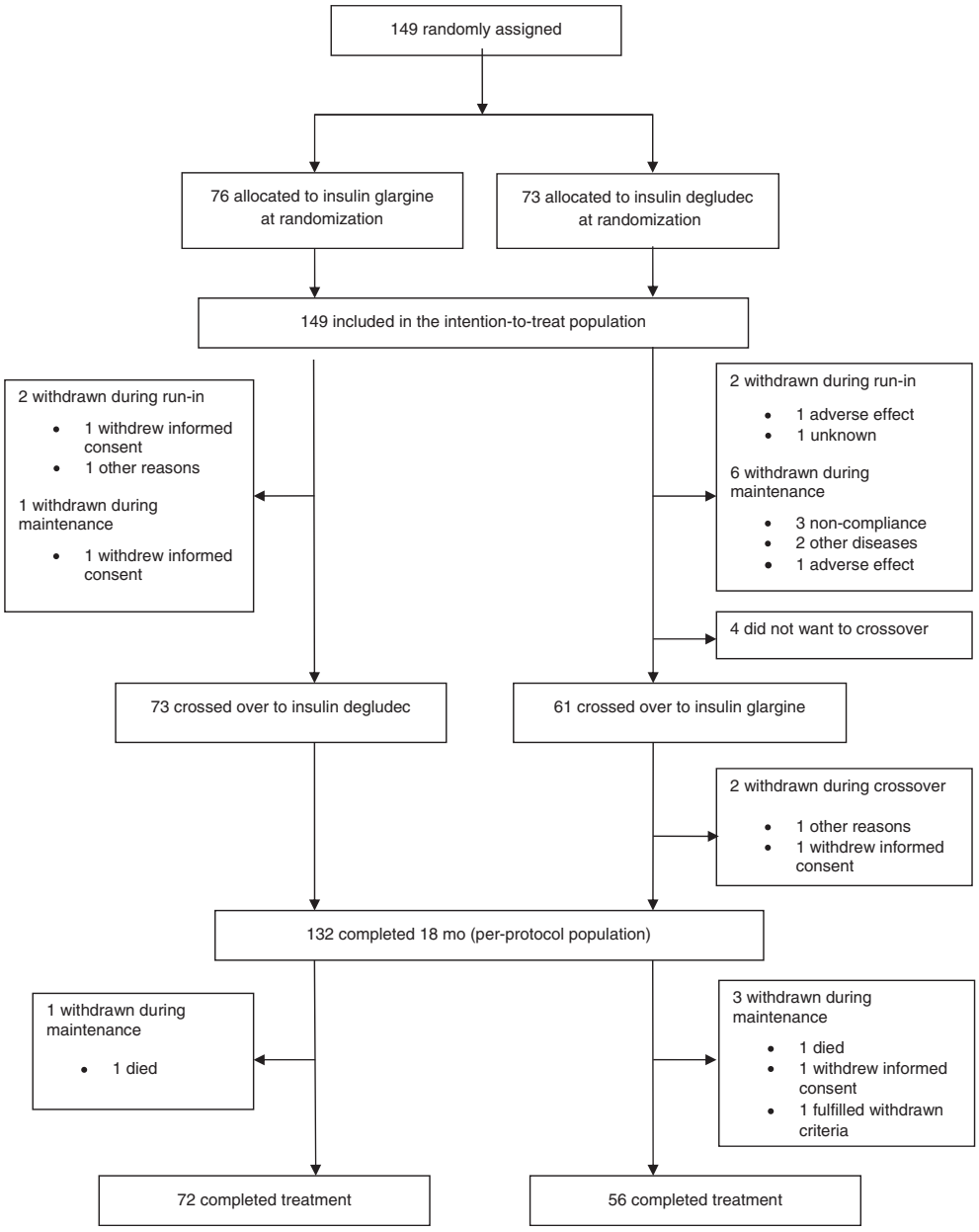

FIGURE 1 CONSORT patient flow diagram

night time, 2589 events were reported. One hundred and twelve patients reported events during treatment with insulin degludec and 117 patients during treatment with insulin glargine U100.

The ITT analyses of level 1 symptomatic hypoglycaemia occurring both during 12:00 AM-05:59 AM and during 11:00 PM-06:59 AM showed a significant RRR of 28% with insulin degludec, corresponding to ARRs of 1.0 and 1.7 episodes per patient-year, respectively (Table 2 and Figure 2A). The ITT analysis on level 1 symptomatic hypoglycaemic episodes occurring during individual night time showed a non-significant RRR of 16% with insulin degludec (Table 2).

3.1.2 | Level 2 hypoglycaemia

During 12:00 AM-05:59 AM, 447 episodes of symptomatic level 2 hypoglycaemia were reported by 62 patients in the insulin degludec arm and 85 patients in the insulin glargine U100 arm (Table 2). During 11:00 PM-06:59 AM, 743 events were reported by 78 and 98 patients during treatment with insulin degludec and insulin glargine U100, respectively. During individual night time, 1113 events were reported by 96 and 109 patients during treatment with insulin degludec and glargine U100, respectively (Table 2).

The ITT analyses resulted in significant RRRs of 37%, 34%, and 29% with insulin degludec, corresponding to ARRs of 0.8, 1.3, and 1.5 episodes per patient-year during 12:00 AM-05:59 AM, 11:00 PM-06:59 AM, and individual night time, respectively (Table 2 and Figure 2A).

The distribution of symptomatic hypoglycaemia illustrated in 4-hour time periods in Figure SS1 reveals consistent reduction throughout the night, with a greater impact during the early night, with insulin degludec.

TABLE 2 Nocturnal symptomatic hypoglycaemia maintenance periods: the overall number of episodes and according to treatment

Nocturnal symptomatic hypoglycaemia	Total		Insulin degludec		Insulin glargine		RRR (%) with insulin degludec	*P* value	ARR (E/year [95% CI]) with insulin degludec
	E	E/year	E	E/year	E	E/year			
Level 1 (≤3.9 mmol/L)									
12:00 AM-05:59 AM	727		319		408				
Mean (SD)		3.36 (5.50)		2.88 (5.14)		3.87 (5.84)	28 (9-43)	.02	1.04 (0.54-1.55)
Median (range)		1.31 (0.00-35.73)		1.24 (0.00-35.73)		1.34 (0.00-34.60)			
11:00 PM-06:59 AM	1379		622		757				
Mean (SD)		6.51 (9.01)		5.69 (8.68)		7.39 (9.31)	28 (4-45))	.01	1.75 (1.05-2.45)
Median (range)		2.65 (0.00-50.43)		2.39 (0.00-50.43)		3.17 (0.00-38.57)			
Individual night time	2589		1229		1360				
Mean (SD)		12.20 (18.20)		11.18 (17.70)		13.30 (18.73)	16 (−5-32)	.12	1.94 (0.99-2.90)
Median (range)		5.71 (0.00-119.27)		5.55 (0.00-119.27)		5.71 (0.00-116.68)			
Level 2 (≤3.0 mmol/L)									
12:00 AM-05:59 AM	447		186		261				
Mean (SD)		2.06 (3.95)		1.68 (3.61)		2.47 (4.26)	37 (16-53)	.002	0.84 (0.44-1.23)
Median (range)		0.00 (0.00-28.19)		0.00 (0.00-27.79)		1.16 (0.00-28.19)			
11:00 PM-06:59 AM	743		316		427				
Mean (SD)		3.45 (5.80)		2.87 (5.36)		4.14 (6.18)	34 (17-48)	<.001	1.31 (0.79-1.82)
Median (range)		1.30 (0.0-34.41)		1.13 (0.00-34.41)		1.38 (0.00-31.34)			
Individual night time	1113		491		622				
Mean (SD)		5.21 (8.74)		4.45 (8.03)		6.03 (9.41)	29 (8-45)	.01	1.55 (0.92-2.18)
Median (range)		2.19 (0.00-53.15)		1.43 (0.00-53.15)		2.66 (0.00-50.73)			

Note: Intention-to-treat population (n = 149).

Abbreviations: ARR, absolute rate reduction; E, episodes; E/year, episodes per patient-year; RRR, relative rate reduction.

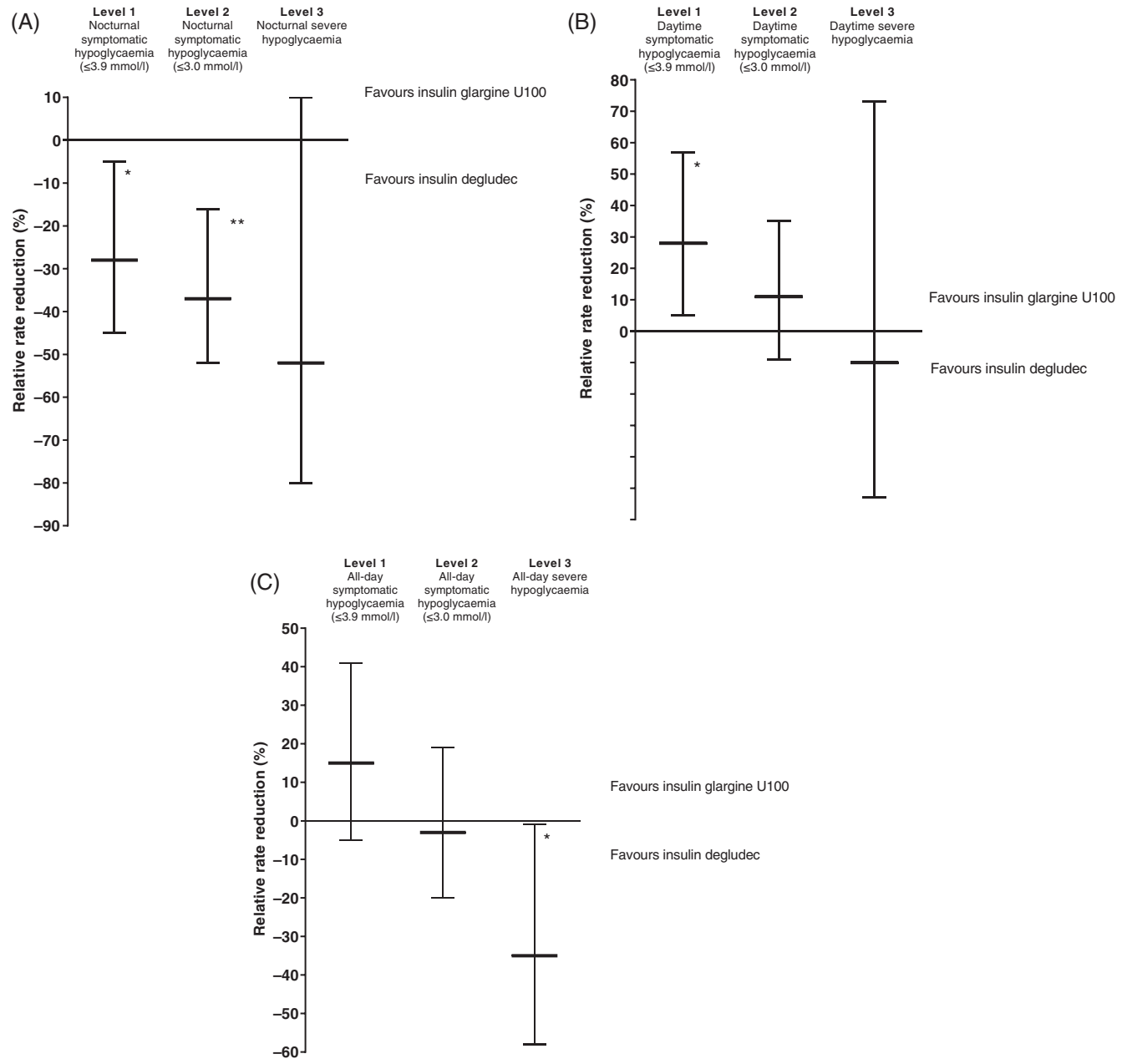

FIGURE 2 Relative rate reduction with 95% CI of A, nocturnal (12:00 AM-05:59 AM), B, daytime (06:00 AM-11:59 PM), C, and all-day (24 h) hypoglycaemia with insulin degludec according to severity. Significant difference between treatment arms (*$P < .05$; **$P < .01$)

Analyses of the 132 patients in the PP cohort replicated the findings from the ITT analyses. For details, see Table S1.

Adjusting for HbA1c, treatment period, and the site did not change the treatment effect estimates (data not shown).

3.2 | Severe hypoglycaemia

During the trial, participants reported 223 events of severe hypoglycaemia. At blinded endpoint adjudication, 17 events did not meet the severity criterion concerning treatment assistance from another person, thus leaving 206 events for further analysis. According to Whipple's triad, 129 (63%) events were definite. A total of 70 events were reported during run-in or crossover periods, leaving 136 events reported by 55 (37%) of the randomized patients for the analysis. The all-day (24 hours) mean rate corrected for observation time in the maintenance periods was 0.7 ± 1.5 episodes per patient-year (Table 3).

Fifty-six (41%) episodes were reported during treatment with insulin degludec, and 80 (59%) episodes were reported during treatment with insulin glargine U100. The ITT analysis showed a statistically significant RRR of 35%, corresponding to an ARR of 0.3 episodes per patient-year with insulin degludec compared with insulin glargine U100 (Table 3 and Figure 2C). The difference was primarily a result of a lower rate of nocturnal events, whereas there was no difference during daytime (Table 3 and Figure 2).

TABLE 3 Severe hypoglycaemia in maintenance periods: the overall number of episodes and according to treatment

Severe hypoglycaemia	Total		Insulin degludec		Insulin glargine		RRR (%) with insulin degludec	*P* value	ARR (E/year [95% CI]) with insulin degludec
	E	E/year	E	E/year	E	E/year			
All-day (24 h) severe hypoglycaemia	136		56		80				
Mean (SD)		0.68 (1.54)		0.52 (1.26)		0.85 (1.78)	35 (1-58)	.04	0.27 (0.05-0.48)
Median (range)		0.00 (0.00-10.44)		0.00 (0.00-9.07)		0.00 (0.00-10.44)			
Daytime severe hypoglycaemia 06:00 AM-11:59 PM	87		41		46				
Mean (SD)		0.41 (1.13)		0.38 (1.02)		0.45 (1.23)	10 (−73-53)	.75	0.07 (−0.10-0.25)
Median (range)		0.00 (0.00-9.20)		0.00 (0.00-6.69)		0.00 (0.00-9.20)			
Daytime severe hypoglycaemia 07:00 AM-10:59 PM	78		36		42				
Mean (SD)		0.37 (1.09)		0.34 (0.96)		0.41 (1.21)	13 (−86-59)	.72	0.08 (−0.09-0.24)
Median (range)		0.00 (0.00-9.20)		0.00 (0.00-6.69)		0.00 (0.00-9.20)			
Nocturnal severe hypoglycaemia 12:00 AM-05:59 AM	47		14		33				
Mean (SD)		0.26 (0.93)		0.13 (0.42)		0.40 (1.26)	52 (−10-79)	.08	0.19 (0.06-0.32)
Median (range)		0.00 (0.00-10.44)		0.00 (0.00-2.59)		0.00 (0.00-10.44)			
Nocturnal severe hypoglycaemia 11:00 PM-06:59 AM	56		19		37				
Mean (SD)		0.30 (0.99)		0.17 (0.54)		0.43 (1.30)	51 (−15-79)	.08	0.19 (0.05-0.33)
Median (range)		0.0 (0.00-10.44)		0.00 (0.00-3.89)		0.00 (0.00-10.44)			

Note: Intention-to-treat population (n = 149).
Abbreviations: ARR, absolute rate reduction; E, episodes; E/year, episodes per patient-year; RRR, relative rate reduction.

We showed the same tendencies in reduction during treatment with insulin degludec in the PP population. For details, see Table S2. Adjusting for HbA1c, treatment period, and the site did not change the treatment effect estimates (data not shown).

3.3 | All-day and daytime hypoglycaemia

No differences between treatments were shown in all-day (24 hours) symptomatic hypoglycaemia occurrence (Figure 2C). Treatment with insulin degludec resulted in a significant 23%-28% increased rate of level 1 symptomatic hypoglycaemia during daytime compared with insulin glargine U100. However, we observed no differences between treatments in level 2 daytime hypoglycaemia. For further details, see Tables S3 and S4.

3.4 | HbA1c

At baseline, the mean HbA1c was 62 ± 10 mmol/mol (7.8% ± 0.9%). We maintained this overall level of glycaemic control throughout the study. Thus, in the first maintenance period, the mean HbA1c was 63 ± 10 mmol/mol (7.9% ± 0.9%) and 61 ± 9 mmol/mol (7.7% ± 0.9%) with insulin degludec and glargine U100, respectively, and in the second maintenance period, 61 ± 10 mmol/mol (7.7% ± 1.0%) and 64 ± 11 mmol/mol (8.0% ± 1.0%) for insulin degludec and glargine U100, respectively, without any statistically significant difference between treatments ($P = .2$).

3.5 | Four-point profiles (SMBG)

There was no difference in fasting plasma glucose or bedtime glucose between the treatments (Table S6). Significantly lower prelunch and predinner SMBG values were recorded during treatment with insulin degludec.

3.6 | Body weight

During the first maintenance period, we found no differences in mean (SD) weight changes between treatment groups from baseline (0.3

[3.8] kg insulin degludec vs. 0.9 [2.6] kg insulin glargine U100; difference −0.6 kg, 95% CI −1.6-0.49; $P = .3$). In the second maintenance period, however, we noted a difference in mean (SD) weight change between treatment groups from baseline (−0.6 [4.3] kg insulin glargine U100 vs. 1.2 [4.1] kg insulin degludec; difference 1.8 kg, 95% CI 0.35-3.19; $P = .02$).

3.7 | Insulin dose

At the end of the first maintenance period, the mean (SD) total insulin dose during treatment with insulin degludec was 42.7 (19.3) U. During treatment with insulin glargine U100, the mean (SD) total insulin dose was 42.5 (24.2) U. At the end of the second maintenance period, the mean (SD) total insulin doses were 49.2 (22.4) and 48.1 (30.1) U during treatment with insulin degludec and glargine U100, respectively. In a linear mixed effects model, the difference between total insulin doses was statistically significantly lower with insulin degludec (difference −1.4 U [95% CI: −2.3-0.1]; $P = .04$).

At the end of the first maintenance period, the mean (SD) basal insulin doses were 21.3 (10.5) and 19.4 (13.7) U during treatment with insulin degludec and glargine U100, respectively. At the end of the second maintenance period, the mean (SD) basal insulin doses were 24.6 (11.9) and 24.1 (18.0) U during treatment with insulin degludec and glargine U100, respectively. The difference in basal insulin doses was significantly lower with insulin degludec (difference −0.8 U [95% CI: −1.6-0.8]; $P = .03$).

We showed no difference in mean bolus insulin doses (difference −0.7 U [95% CI: −1.6-0.26]; $P = .16$) between treatment groups. Insulin doses according to treatment and treatment periods can be found in Table S5. As the differences are calculated based on the subject-specific random effects model, they differ slightly from the overall average.

4 | DISCUSSION

In this study specifically addressing patients with type 1 diabetes prone to nocturnal severe hypoglycaemia, treatment with insulin degludec at a comparable level of glycaemic control resulted in 28% to 37% lower rates of level 1 and level 2 nocturnal symptomatic hypoglycaemia, respectively, and a 35% lower rate of all-day severe hypoglycaemia compared with insulin glargine U100.

Previously, the BEGIN basal bolus type 1 study compared insulin degludec with insulin glargine U100 and excluded patients with recurrent severe hypoglycaemia or impaired hypoglycaemia awareness. The study reported a 27% lower rate of nocturnal confirmed hypoglycaemia (plasma glucose <3.1 mmol/L or severe hypoglycaemia) with insulin degludec at a comparable level of glycaemic control and no difference in the rate of severe hypoglycaemia between the treatments.[24]

The SWITCH 1 study was a randomized, double-blind, crossover, treat-to-target study comparing insulin degludec and insulin glargine U100 in patients with type 1 diabetes and at least one risk factor for developing hypoglycaemia.[11] The number of patients in the SWITCH 1 trial with previous severe nocturnal hypoglycaemia cannot be deduced but is probably low (10%-15%). The rate of nocturnal severe or blood glucose-confirmed symptomatic hypoglycaemia of less than 3.1 mmol/L was found to be 36% lower in the maintenance periods during treatment with insulin degludec compared with insulin glargine U100. A significant reduction of 35% in severe hypoglycaemia in favour of insulin degludec was also reported.[11] Thus, the relative treatment differences between insulin degludec and glargine U100 in risk of nocturnal hypoglycaemia are consistent between the BEGIN, the SWITCH 1, and the HypoDeg studies, as are the relative differences between the treatments on severe hypoglycaemia in the SWITCH 1 and the HypoDeg studies.

Despite comparable relative treatment differences in the three studies, ARRs in nocturnal symptomatic hypoglycaemia with insulin degludec were higher in the current study, 0.8 episodes per patient-year, compared with 0.6 episodes per patient-year in SWITCH 1 using the same definition of night time. For severe hypoglycaemia there was more than a 2-fold greater ARR with insulin degludec in the HypoDeg trial than in the SWITCH 1 study.

We found no difference between the treatments in all-day hypoglycaemia, which is in accordance with the BEGIN study, but differs from SWITCH 1. The differences could be explained by differences in prandial insulin titration between the studies. Thus, in BEGIN and SWITCH 1, the intervention included prandial insulin titration in addition to the basal insulin intervention, which was not the case in the current study. However, there was an increased risk of level 1 hypoglycaemia with insulin degludec during daytime, which did not translate into clinically significant level 2 or severe hypoglycaemia. As judged from SMBG data (Table S6) showing higher glucose levels before lunch and dinner in the glargine U100 arm, this could be explained by waning of the glargine U100 effect, which was not fully compensated for by uptitration of prandial insulin.

The major strength of the HypoDeg trial is the specific inclusion of type 1 diabetes patients with recurrent nocturnal severe hypoglycaemia and hence at the greatest risk of experiencing future nocturnal hypoglycaemia. The vast majority of insulin trials specifically exclude hypoglycaemia-prone people to facilitate tight titration and avoid the major random impact of a few patients with very high rates of hypoglycaemia. The latter is the reason for the crossover design in the HypoDeg trial, which enables contribution to both treatment arms by all patients, no matter their rate of hypoglycaemia.[25] Furthermore, the long duration, and pragmatic treatment goals, avoid the incremental risk of hypoglycaemia. The treat-to-target design has been raised as a concern regarding the SWITCH 1 trial.[26-28] In SWITCH 1, the HbA1c level was reduced to 51-52 mmol/mol (6.8%-6.9%) compared with the maintenance of a level of 61-64 mmol/mol (7.7%-8.0%) in our study. Thus, the magnitude of the observed treatment differences in our study probably represents those expected in clinical practice in this category of patients. Furthermore, the crossover design reduces the influence of confounding covariates and between-patient variability, which is particularly important because of the considerably

skewed distribution of hypoglycaemic events in a high-risk population.[19] Another important strength is the long duration of both the run-in and crossover periods, minimizing the carryover effect, which is an inherent risk of a crossover design. The long maintenance periods (as opposed to the 16-week maintenance phase in SWITCH 1) further minimize the risk of intrapatient variability.

We analysed the primary endpoint according to different definitions of night time. In addition to conventional definitions, we applied an exploratory real-life definition from 4 hours after evening prandial or corrective bolus insulin administration until morning prandial insulin administration. We did this to eliminate the possible influence of coincidental correction with rapid-acting insulin administered in the evening and to isolate the treatment difference caused by the basal insulins. This definition turned out to be challenging to use in practice and did not provide additional information.

The main limitation of this study is the open-label design, which is partly compensated by blinded adjudication of endpoints. Blinding would have required a double-dummy method using vials and syringes, which is not feasible in a 2-year study in a pen-based diabetes environment such as Denmark. Another limitation could be consistent and required dosing of insulin degludec and insulin glargine U100 at the evening meal. However, a study comparing once-daily treatment in type 1 diabetes with glargine U300 and U100 administered either in the morning or in the evening in a crossover design presented flatter nocturnal CGM curves, suggesting more consistent overnight glucose control with evening administration of U100 compared with morning injection.[13] A variable dosing schedule in terms of timing and frequency would have hampered the direct comparison between insulin degludec and glargine U100.

Since the planning of this study, insulin glargine U300 has been introduced to clinical practice. To date, only one head-to-head comparison with insulin degludec in type 1 diabetes has been performed.[29] This two x 4-week crossover study in 46 patients showed no difference in severe or confirmed hypoglycaemia.[29] Insulin glargine U300 and other new insulin interventions should be studied in patients with type 1 diabetes at an increased risk of nocturnal and severe hypoglycaemia. This will clarify the maximum potential benefit of the therapies, as has previously also been performed to compare multiple daily injection therapy based on insulin detemir and aspart with regular and NPH human insulin.[7-9]

In conclusion, insulin degludec, compared with insulin glargine U100, in patients with type 1 diabetes prone to nocturnal severe hypoglycaemia, provides a clinically significant reduction of nocturnal symptomatic and severe hypoglycaemia. The ARRs are greater than previously appreciated from studies of patients at a low or intermediate risk of hypoglycaemia.

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CONFLICT OF INTEREST

JMBB, HBN, TKH, CH, TJ, AEK, SSL, HHP, ALS, LT, and BT have no competing financial interests. UPB has served on advisory boards for AstraZeneca/Bristol Myers Squibb, Novo Nordisk, Sanofi, and Zealand Pharma, and has received lecture fees from Astra Zeneca/Bristol Myers Squibb, Sanofi and Novo Nordisk. ACA and RMA has by September 2019 (after the finalization of the study), been employed by Novo Nordisk. HUA 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. PG has served on advisory boards for Abbott Laboratories, Astra Zeneca, Boehringer Ingelheim, Novo Nordisk and Sanofi. CBJ serves on advisory boards for Novo Nordisk. KN 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, Zealand Pharma, and owns stock in Novo Nordisk.

AUTHOR CONTRIBUTIONS

UPB, RMA, LT, and BT initiated and designed the trial. RMA, ACA, HUA, HBN, PG, TKH, CH, TJ, CBJ, SSL, KN, HHP, LT, BT, and UPB participated in the coordination of the study and data collection. AEK and ALS planned and executed the statistical analyses. UPB was responsible for, and JMBB participated in the development of the manuscript. All authors contributed to, read, and approved the final manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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