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ORIGINAL ARTICLE

Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: insulin glargine versus neutral protamine Hagedorn insulin in insulin-naïve people with type 2 diabetes

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Aims: To examine whether insulin glargine can lead to better control of glycated haemoglobin (HbA1c) than that achieved by neutral protamine Hagedorn (NPH) insulin, using a protocol designed to limit nocturnal hypoglycaemia.

Methods: The present study, the Least One Oral Antidiabetic Drug Treatment (LANCELOT) Study, was a 36-week, randomized, open-label, parallel-arm study conducted in Europe, Asia, the Middle East and South America. Participants were randomized (1 : 1) to begin glargine or NPH, on background of metformin with glimepiride. Weekly insulin titration aimed to achieve median prebreakfast and nocturnal plasma glucose levels ≤5.5 mmol/l, while limiting values ≤4.4 mmol/l.

Results: The efficacy population (n = 701) had a mean age of 57 years, a mean body mass index of 29.8 kg/m^2, a mean duration of diabetes of 9.2 years and a mean HbA1c level of 8.2% (66 mmol/mol). At treatment end, HbA1c values and the proportion of participants with HbA1c <7.0 % (<53 mmol/mol) were not significantly different for glargine [7.1 % (54 mmol/mol) and 50.3%] versus NPH [7.2 % (55 mmol/mol) and 44.3%]. The rate of symptomatic nocturnal hypoglycaemia, confirmed by plasma glucose ≤3.9 or ≤3.1 mmol/l, was 29 and 48% less with glargine than with NPH insulin. Other outcomes were similar between the groups.

Conclusion: Insulin glargine was not superior to NPH insulin in improving glycaemic control. The insulin dosing algorithm was not sufficient to equalize nocturnal hypoglycaemia between the two insulins. This study confirms, in a globally heterogeneous population, the reduction achieved in nocturnal hypoglycaemia while attaining good glycaemic control with insulin glargine compared with NPH, even when titrating basal insulin to prevent nocturnal hypoglycaemia rather than treating according to normal fasting glucose levels.

Keywords: hypoglycaemia-sensitive algorithm, insulin glargine, NPH insulin

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Introduction

Basal insulin, as neutral protamine Hagedorn (NPH) insulin or a long-acting analogue such as insulin glargine, is often recommended for starting insulin therapy in the ambulatory care of people with type 2 diabetes [1–4]. The long-acting insulin analogues have more favourable time–action profiles after evening injection and, accordingly, lead to fewer nocturnal hypoglycaemic events in treat-to-target studies based on prebreakfast glucose testing [5,6]. A meta-analysis of individual patient data suggested a risk reduction of ~50% for nocturnal hypoglycaemia when using insulin glargine compared with NPH insulin [7].

It has been suggested that head-to-head treat-to-target clinical trials do not reflect the tendency in routine clinical practice to limit titration to near-normal prebreakfast glucose levels, because of the need to prevent nocturnal hypoglycaemia. If insulin dosage is limited by observed or anticipated hypoglycaemia, this practice could lead to earlier cessation of titration of NPH insulin and hence higher glycated haemoglobin (HbA1c) levels. Published binomial regression analyses from the treat-to-target studies suggest that this effect on HbA1c

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might be quite large and thus clinically relevant [5,8]. A meta-regression analysis of combined HbA1c and hypoglycaemia outcomes confirms this approach [9]; however, no clinical trial has attempted to show whether basal insulin analogues are superior to NPH for HbA1c when the hypoglycaemia rate with NPH is reduced to the same level as with insulin glargine.

In the present paper, we report the results of the LAntus versus NPH: Comparison in insulin-naïve people not adequately controlled with at Least One Oral Antidiabetic Drug Treatment (LANCELOT) Study. This study attempted to show the superiority of insulin glargine over NPH insulin on the change in HbA1c from baseline after 36 weeks, by applying a new concept for titrating basal insulin based on nocturnal as well as fasting glucose values, with specific focus on the prevention of nocturnal hypoglycaemia.

Methods

Study Participants

Eligible candidates for this study were insulin-naïve men and women with type 2 diabetes diagnosed for >1 year, aged 30–70 years, with a body mass index (BMI) <40.0 kg/m^2, and an HbA1c level ≥7.0–10.5% (>54–90 mmol/mol). Oral glucose-lowering drug doses [metformin (≥1000 mg/day), sulfonylurea, glinide or α-glucosidase inhibitor] had to be stable for ≥3 months. Pregnancy or anticipated pregnancy, use of incretin therapies within 3 months or thiazolidinedione monotherapy were exclusion criteria, as were clinically active cardiovascular, eye, liver, renal, neurological, endocrine or other major diseases.

Written informed consent was obtained from all participants, and institutional review board/independent ethics committee approval was obtained for each participating study centre or country.

Study Design

This study was registered at ClinicalTrials.gov (NCT00949442) and European Union Drug Regulating Authorities Clinical Trials (EudraCT 2007-006640-22). This 36-week, randomized, open-label, parallel-arm study was conducted at 74 sites in 16 countries in Europe (nine), Asia (three), the Middle East (two) and South America (two) between July 2009 and July 2012. A 2-week run-in period was followed by a 36-week treatment period, with randomization using an interactive voice-response/interactive web response system. Safety data were collected for a further week. Three study visits were required after baseline in the first 8 weeks, then four more up to 36 weeks. These were supplemented by nine (or more, as required) further telephone contacts. At the start of the run-in period, all people not on glimepiride were started on it; other oral glucose-lowering drugs except metformin were discontinued. The glimepiride dose was 2 mg once daily, or less if this was not tolerated. There were no protocol-specified changes to metformin dosage.

Insulins and Dose Titration

Randomization was in equal numbers to either insulin glargine or NPH insulin, to be given once daily in the evening between 20:00 and 22:00 hours. Insulin glargine was injected using a Lantus SoloSTAR insulin pen (Sanofi, Paris, France), NPH insulin with a prefilled Insuman Basal Optiset pen (Sanofi). The recommended starting insulin dose was 0.2 U/kg.

Self-monitored plasma glucose (SMPG) assessment was performed daily with a sponsor-supplied meter and reagent strips (AccuChek®; Roche, Mannheim, Germany). Nocturnal tests taken ~5–6 h after insulin administration were recommended before each titration.

A systematic dose-titration regimen was advised based on both prebreakfast [fasting plasma glucose (FPG)] and nocturnal SMPG levels (Table 1), with a goal of 4.4–5.5 mmol/l at both times. The insulin dose was to be adjusted weekly during weeks 1–4, twice weekly during weeks 5–12, and then weekly up to week 36. The median of the last three prebreakfast glucose measurements (unless one value was ≤4.4 mmol/l) was used for dose titration, together with the last nocturnal glucose measurement. A measurement <4.4 mmol/l at either time called for reduction of insulin by two units. Additionally if prebreakfast glucose was <2.8 mmol/l the dose was to be decreased by 2 U and remain at the lower dose for 1, 2 or 3 weeks, depending if this was the first, second or third such occurrence. In the event of severe hypoglycaemia or HbA1c ≤ 6.0% (42 mmol/mol) no insulin dose increase was allowed for the remainder of the study. An international dose-titration committee reviewed SMPG values and insulin doses on an ongoing basis via a website and the study investigators were contacted by e-mail if titration was inadequate.

Table 1. Insulin dose-titration algorithm used for both insulins throughout the study.

	Fasting plasma glucose			
	≤4.4 mmol/l or symptomatic hypoglycaemia	>4.4 to ≤5.5 mmol/l	>5.5 to ≤7.8 mmol/l	>7.8 mmol/l
Nocturnal plasma glucose				
≤4.4 mmol/l or symptomatic hypoglycaemia	−2 U	−2 U	−2 U	−2 U
>4.4 to ≤5.5 mmol/l	−2 U	0	0	0
>5.5 to ≤7.8 mmol/l	−2 U	0	+2 U	+2 U
>7.8 mmol/l	−2 U	0	+2 U	+4 U

All data are dose change per injection. In the event of severe hypoglycaemia or HbA1c ≤ 6.0% (42 mmol/mol), no insulin dose increase was allowed for the remainder of the study.

In participants with HbA1c >8.5% despite FPG <5.5 mmol/l, a prandial insulin could be added from week 24 onward as rescue medication.

Assessments and Measurements

Blood samples for HbA1c were collected at screening, baseline and weeks 12, 24 and 36, and measured in a central laboratory. In addition to the measurements taken to guide insulin titration, prebreakfast SMPG measurements were required for 6 consecutive days before baseline and at the week 12, 24 and 36 visits, and the participants performed an eight-point SMPG profile twice during the week before these visits: before and 2 h after main meals, at bedtime and 5–6 h after the insulin injection.

Hypoglycaemic episodes and adverse events were recorded throughout the study. Documented symptomatic hypoglycaemia was defined as an event with clinical symptoms that were considered to have resulted from hypoglycaemia and that was confirmed by SMPG ≤3.9 mmol/l or ≤3.1 mmol/l. Severe symptomatic hypoglycaemia was defined as an event with clinical symptoms that were considered to have resulted from hypoglycaemia, requiring the assistance of another person, and that was either confirmed by plasma glucose <2.0 mmol/l (<36 mg/dl) or prompt recovery after oral carbohydrate, i.v. glucose or glucagon administration. Nocturnal events are those that occurred after bedtime and before getting up in the morning; daytime events occurred during the normal awake period.

Outcomes and Statistical Analysis

The primary objective of the study was to show the superiority of insulin glargine over insulin NPH in terms of the change in HbA1c from baseline to the end of the treatment period. The main secondary objectives were to compare the following between treatment groups: time profile of HbA1c, FPG, nocturnal SMPG, and eight-point SMPG profiles, percentage of participants achieving HbA1c <7.0 or <6.5% (<53 or <47 mmol/mol), daily dose of insulin, prandial insulin use at 6 months as rescue medication, change in body weight from baseline, incidence and rate of hypoglycaemia (symptomatic diurnal and nocturnal, asymptomatic and severe), overall safety and treatment satisfaction. The last was measured using the Diabetes Treatment Satisfaction Questionnaire, maximum score 36 points [10].

It was estimated that at least 568 evaluable participants (670 were randomized with 15% not assessable) needed to be randomized to detect a difference in change of HbA1c of 0.3% (3.3 mmol/mol) at the 5% significance level with 90% power. This assumes a standard deviation (s.d.) of change of HbA1c of 1.1% (12 mmol/mol).

Efficacy analyses (which did not include hypoglycaemia) were assessed in the modified intent-to-treat (ITT) population; namely, all randomized participants who received study medication and had at least one postbaseline assessment of any primary or secondary efficacy variable. Additional efficacy analyses were performed for the per protocol population, a subset of the modified ITT population that excluded those with a major protocol violation. Other analyses, including hypoglycaemia, were performed for the safety population, comprising all randomized and treated individuals. Missing efficacy and safety values were imputed with the last observation carried forward method for the end of treatment value, defined as the last postbaseline value available during the on-treatment period.

Change from baseline in HbA1c, FPG, eight-point plasma glucose profiles, mean daily plasma glucose level and body weight was accessed using analysis of covariance (ANCOVA), with treatment as a fixed effect and baseline value as a covariate. For those with incomplete data at 36 weeks, the last study observation was used. The proportion of participants having at least one episode of hypoglycaemia was compared between treatments using Pearson's chi-squared test or Fisher's exact test. The event rate for each type of hypoglycaemia was analysed using a generalized linear model based on Poisson or negative binomial distributions.

Univariate and multivariate analyses (stepwise regression model) were performed to identify potential factors that predict a successful primary outcome. The candidate explanatory variables were gender, country, age, BMI and number of glucose-lowering medications at screening, and diabetes duration and HbA1c at baseline.

Results

Participant Flow and Characteristics

Of 1102 people screened, 708 were randomized (Table S1), four of whom did not receive study treatment, while three others did not have a further measurement (Figure S1), yielding 352 on insulin glargine and 349 on NPH insulin in the modified ITT population. In the NPH insulin group, 22 participants (6.3%) prematurely discontinued study treatment as did 19 participants (5.4%) in the insulin glargine group.

Baseline characteristics of the randomized participants were similar between the two treatment groups (Table 2), except for a small imbalance in those receiving metformin and glimepiride in addition to basal insulin, and in retinopathy and duration of diabetes. The majority of participants (glargine group, 93%; NPH group, 90%) received combination therapy of metformin and glimepiride in addition to basal insulin. The mean (s.d.) daily dose of metformin at randomization was 2015 (582) mg with insulin glargine and 2098 (564) mg with NPH insulin; the corresponding daily dose of glimepiride was 2.0 (0.3) and 2.0 (0.2) mg, respectively.

Insulin Dose

Insulin dose increased steadily over 36 weeks, with the last recorded dose being 32.4 U (0.39 U/kg) for glargine and 30.7 U (0.36 U/kg) for NPH (p value non-significant; Figure 1). No participant on glargine and four participants on NPH insulin started prandial insulin during the study.

Plasma Glucose Control

In the modified ITT population, the mean (s.d.) HbA1c declined from 8.2 (0.8)% [66 (9) mmol/mol] at baseline in both groups to 7.1 (0.9)% [54 (10) mmol/mol] at the end of

Table 2. Demographic and baseline characteristics of the people with type 2 diabetes in the modified ITT population.

	Insulin glargine	NPH insulin
No. participants	352	349
Mean (s.d.) age, years	57.3 (8.3)	57.2 (7.8)
Female, n (%)	198 (56.2)	195 (55.9)
Mean (s.d.) body weight, kg	81.2 (16.0)	82.7 (15.5)
Mean (s.d.) body mass index, kg/m^2	29.7 (4.5)	30.1 (4.5)
Mean (s.d.) duration of diabetes, years	9.1 (5.5)	9.4 (5.7)
Mean (s.d.) duration of OGLD use, years	7.5 (5.1)	7.9 (5.5)
Mean (s.d.) HbA1c		
%	8.2 (0.8)	8.2 (0.9)
mmol/mol	66 (9)	66 (10)
Mean (s.d.) FPG, mmol/l	9.2 (2.1)	9.0 (2.0)
Diabetes complications, n (%)		
Retinopathy	56 (15.9)	45 (12.9)
Nephropathy	24 (6.8)	25 (7.2)
Neuropathy	97 (27.6)	83 (23.8)
OGLD treatment at study entry, n (%)		
Metformin	338 (96.0)	331 (94.8)
Sulfonylurea	321 (91.2)	316 (90.5)
Repaglinide	5 (1.4)	5 (1.4)
α-glucosidase inhibitor	5 (1.4)	7 (2.0)
Thiazolidinedione	29 (8.2)	28 (8.0)
OGLD treatment at randomization, n (%)		
Metformin alone	9 (2.6)	15 (4.3)
Metformin overall, including combination	335 (95.2)	329 (94.3)
Glimepiride alone	17 (4.8)	19 (5.4)
Glimepiride overall*, including combination	343 (97.4)	333 (95.4)
Thiazolidinediones†	6 (1.7)	6 (1.7)
Metformin + sulfonylurea (glimepiride)	326 (92.6)	314 (90.0)

FPG, fasting plasma glucose; ITT, intent-to-treat; OGLD, oral glucose-lowering drug; s.d., standard deviation.
*93% (glargine) and 92% (NPH) of participants received daily dose of 2 mg glimepiride during the study.
†All but one participant (major protocol violation) stopped thiazolidinediones within a few days.

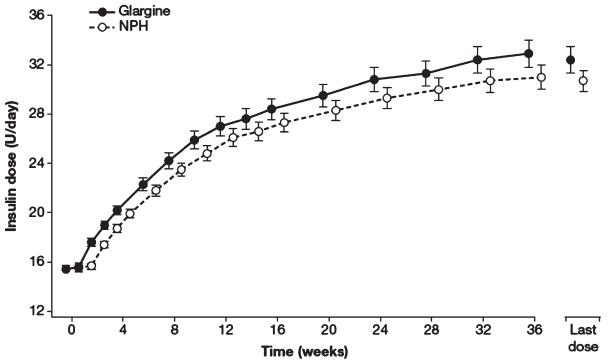

Figure 1. Time course of change of insulin dose (U/day) in the safety population. Values are mean ± standard error.

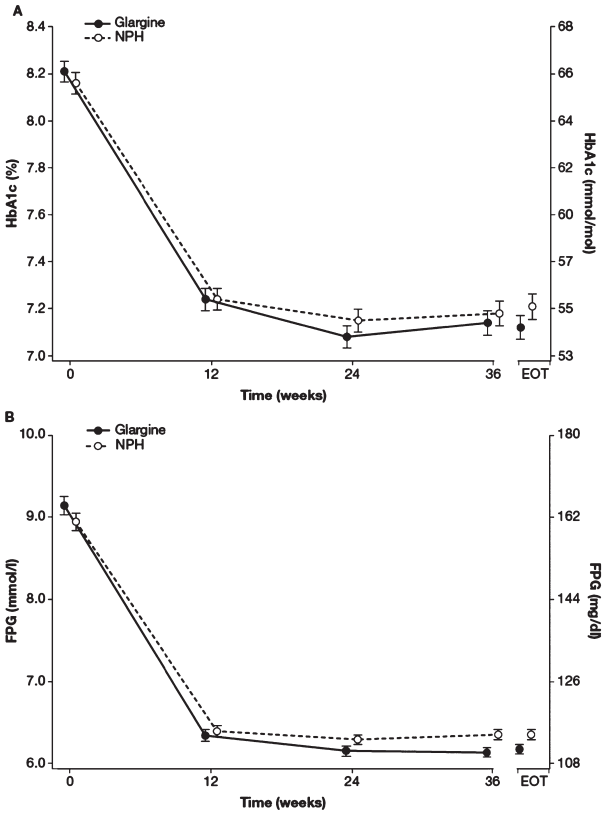

Figure 2. Time course of change in (A) mean glycated haemoglobin (HbA1c) and (B) fasting plasma glucose (FPG) in the modified intent-to-treat population (all randomized, treated and with one efficacy endpoint measurement). Values are mean ± standard error. EOT, end of treatment.

treatment on glargine and to 7.2 (1.0)% [55 (11) mmol/mol] on NPH, with an adjusted mean change of −1.1 (0.5)% [−12 (5) mmol/mol] and −1.0 (0.5)% [−11 (5) mmol/mol (Table 3)]. The estimated treatment difference was −0.10% (95% CI −0.23, 0.03) or −1.1 mmol/mol (95% CI −2.5, 0.3; p = 0.11). Glargine was not found to be superior in this population or in the per protocol population, where the estimated treatment difference was −0.11% (95% CI −0.25, 0.02) or −1.2 mmol/mol (95% CI −2.7, 0.2; p = 0.10). A similar proportion of participants in the glargine and NPH insulin groups (50.3 vs. 44.3%, respectively; p value non-significant) achieved HbA1c <7.0% (<53 mmol/mol) and 22.1 vs. 23.3%, respectively (p value non-significant) achieved HbA1c <6.5% (<47 mmol/mol) by the end of treatment.

Both HbA1c and fasting SMPG had reached a nadir by 12 weeks, a level maintained up to 36 weeks (Figure 2). At 36 weeks, fasting mean (s.d.) SMPG declined from 9.2 (2.1) mmol/l on glargine and from 8.9 (1.9) mmol/l on NPH to 7.1 (0.9) and 7.2 (1.0) mmol/l, respectively (Table 3). The estimated treatment difference was −0.17 [−0.35; 0.00] mmol/l. When non-completers were excluded, this difference −0.23 (−0.40, −0.06) mmol/l favoured insulin glargine (p = 0.009). Nocturnal SMPG at the end of treatment declined from 9.1 (2.7) mmol/l on glargine and 8.8 (2.5) mmol/l on NPH to 6.3 (1.7) and 6.3 (1.7) mmol/l, respectively (Table 3). The adjusted mean change was −2.7 (0.1) mmol/l in both groups.

The eight-point SMPG profiles were broadly similar in pattern for glargine and NPH at the end of treatment (Figure S2); however, the estimated treatment difference significantly

Table 3. Change in insulin dose, glycaemic control measures and body weight.

	Glargine group: n = 352	NPH insulin group: n = 349
Mean (s.d.) insulin dose		
Day 1		
U	15.4 (3.7)	15.5 (3.7)
U/kg	0.19 (0.03)	0.19 (0.03)
End of treatment		
U	32.4 (20.5)	30.7 (17.6)
U/kg	0.39 (0.22)	0.37 (0.19)
Change from baseline		
U	16.9 (19.0)	15.0 (16.3)
U/kg	0.20 (0.21)	0.17 (0.18)
HbA1c level		
Baseline, mean (s.d.)		
%	8.2 (0.8)	8.2 (0.9)
mmol/mol	66 (9)	66 (10)
End of treatment, mean (s.d.)		
%	7.1 (0.9)	7.2 (1.0)
mmol/mol	54 (10)	55 (11)
Adjusted mean (s.e.) change from baseline		
%	−1.07 (0.05)	−0.97 (0.05)
mmol/mol	−12 (0.5)	−11 (0.5)
HbA1c <7.0%, %	50.3	44.3
FPG, mmol/l		
Baseline, mean (s.d.)	9.2 (2.1)	8.9 (1.9)
End of treatment, mean (s.d.)	6.2 (1.2)	6.4 (1.2)
Adjusted mean (s.e.) change from baseline	−2.85 (0.06)	−2.68 (0.06)
Daily plasma glucose, mmol/l		
Baseline, mean (s.d.)	10.2 (2.2)	9.8 (2.0)
End of treatment, mean (s.d.)	7.6 (1.5)	7.8 (1.4)
Adjusted mean (s.e.) change from baseline	−2.46 (0.07)	−2.17 (0.07)
Nocturnal plasma glucose, mmol/l		
Baseline, mean (s.d.)	9.1 (2.7)	8.8 (2.5)
End of treatment, mean (s.d.)	6.3 (1.7)	6.3 (1.7)
Adjusted mean (s.e.) change from baseline	−2.66 (0.09)	−2.66 (0.09)
Body weight, kg		
Baseline, mean (s.d.)	81.2 (16.0)	82.6 (15.5)
End of treatment, mean (s.d.)	82.5 (15.6)	83.7 (15.7)
Adjusted mean (s.e.) change from baseline	1.26 (0.16)	1.05 (0.16)

FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; s.d., standard deviation; s.e., standard error.

favoured glargine before (−0.3 mmol/l; p = 0.003) and 2 h after breakfast (−0.4 mmol/l; p = 0.038), before (−0.3 mmol/l; p = 0.031) and 2 h after lunch (−0.3 mmol/l; p = 0.048), and 2 h after dinner (−0.4 mmol/l; p = 0.030). Accordingly the adjusted mean change from baseline in daily average plasma glucose was greater with glargine than with NPH insulin (−2.5 vs. −2.2 mmol/l; Table 3), with a small estimated treatment difference of −0.3 (−0.5, −0.1) mmol/l (p = 0.006).

Hypoglycaemia

The proportion of participants who reported ≥1 hypoglycaemic event at any time, confirmed by plasma glucose ≤3.1 mmol/l, was similar with glargine (36.4%) and NPH insulin (36.0%), and the study prevalence of ≥1 confirmed nocturnal hypoglycaemic event was 16.1 and 19.7% (all non-significant; Table 4). Using plasma glucose ≤3.9 mmol/l, results were 64.7 and 61.1% for any event, and 34.7 and 38.0% for nocturnal events. Three participants in the glargine group and one in the NPH group reported severe hypoglycaemia.

The estimated event rates [standard error (s.e.)] of confirmed anytime hypoglycaemia (plasma glucose ≤3.1 mmol/l) were 1.74 (0.12) and 2.21 (0.12) events/person-year with glargine and NPH insulin, respectively, while the rate of confirmed nocturnal hypoglycaemia was 0.35 (0.16) and 0.66 (0.14) events/person-year. For events with plasma glucose ≤3.9 mmol/l anytime, the rates were 7.67 (0.09) and 8.04 (0.09) events/person-year with glargine and NPH, respectively, while for nocturnal hypoglycaemia the rates were 1.59 (0.12) and 2.23 (0.12) events/person-year.

The risk of having a hypoglycaemic event was significantly lower with glargine than with NPH insulin for symptomatic confirmed nocturnal hypoglycaemia [plasma glucose ≤3.1 mmol/l: relative risk 0.52 (0.34, 0.80), p = 0.003; plasma glucose ≤3.9 mmol/l: relative risk 0.71 (0.51, 0.99), p = 0.042]. The results reflect lower cumulative event rates with glargine for symptomatic nocturnal hypoglycaemia which diverged from those with NPH starting from baseline (Figure 3). There was no statistically significant difference in relative risk for anytime or daytime confirmed symptomatic hypoglycaemia (Table 4).

No differences between treatment groups were found for the percentage of participants (glargine group 26.3% vs. NPH group 26.3%) who achieved HbA1c levels <7.0% (<53 mmol/mol) without any confirmed (plasma glucose ≤3.1 mmol/l) symptomatic hypoglycaemia or without any confirmed nocturnal symptomatic hypoglycaemia (40.5 vs. 35.3%).

Body Weight

The mean (s.d.) body weight increased in both the glargine [baseline 81.2 (16.0) kg, end of treatment 82.5 (15.6) kg] and the NPH [82.6 (15.5) kg to 83.7 (15.7) kg] groups. The mean treatment difference (change from baseline) did not differ [0.2 (−0.2, 0.7) kg].

Treatment Satisfaction

Mean (s.d.) overall treatment satisfaction improved with both treatments, from 25.5 (7.4) points at baseline to 31.8 (4.7) scale points at the end of treatment with glargine, and from 24.6 (7.6) to 31.0 (5.7) scale points with NPH. The estimated treatment difference was 0.7 (95% CI −0.1, 1.4) scale points (p = 0.097).

Predictors of Glucose Control

Multivariate analysis identified only baseline HbA1c (p < 0.001), number of oral glucose-lowering drugs at screening (p = 0.002) and country (p = 0.001) as strong and significant predictors of HbA1c <7.0 % (<53 mmol/mol), but not age, duration of diabetes or BMI. For hypoglycaemia, country (p < 0.001), longer duration of diabetes (p = 0.024) and lower BMI (<30 kg/m^2, p = 0.002) were identified as significant predictors of anytime hypoglycaemia confirmed at plasma

Table 4. Anytime, nocturnal and daytime hypoglycaemia confirmed by plasma glucose ≤3.9 or ≤3.1 mmol/l in the safety population.

	Insulin glargine group n = 354	NPH insulin group n = 350	Rate ratio [95% CI]	p
With confirmation plasma glucose ≤3.9 mmol/l				
Anytime				
Events*, n	1879	1847	—	
Prevalence, %	64.7	61.1	—	0.330
Events/person-year, estimated rate (s.e.)	7.67 (0.09)	8.04 (0.09)	0.95 (0.74, 1.23)	0.716
Nocturnal				
Events*, n	378	515	—	
Prevalence, %	34.7	38.0	—	0.369
Events/person-year, estimated rate (s.e.)	1.59 (0.12)	2.23 (0.12)	0.71 (0.51, 0.99)	0.042
Daytime				
Events*, n	1365	1198	—	
Prevalence, %	55.9	50.0	—	0.115
Events/person-year, estimated rate (s.e.)	5.51 (0.10)	5.15 (0.10)	1.07 (0.81, 1.43)	0.637
With confirmation plasma glucose ≤3.1 mmol/l				
Anytime				
Events*, n	424	513	—	
Prevalence, %	36.4	36.0	—	0.903
Events/person-year, estimated rate (s.e.)	1.74 (0.12)	2.21 (0.12)	0.79 (0.56, 1.10)	0.158
Nocturnal				
Events*, n	84	155	—	
Prevalence, %	16.1	19.7	—	0.211
Events/person-year, estimated rate (s.e.)	0.35 (0.16)	0.66 (0.14)	0.52 (0.34, 0.80)	0.003
Daytime				
Events*, n	326	339	—	
Prevalence, %	29.9	27.4	—	0.461
Events/person-year, estimated rate (s.e.)	1.33 (0.13)	1.43 (0.14)	0.93 (0.64, 1.35)	0.691

s.e., standard error.
*Some events had missing information on the time of occurrence.

glucose ≤3.9 mmol/l. Country ($p < 0.001$), longer duration of diabetes ($p = 0.021$), and a trend for lower BMI ($p = 0.052$) were predictors for events confirmed at plasma glucose ≤3.1 mmol/l. Only country ($p < 0.001$) was a predictor of nocturnal hypoglycaemia confirmed at plasma glucose ≤3.1 mmol/l.

Adverse Events

The mean (s.d.) proportion of participants experiencing ≥1 treatment-emergent adverse event was similar for those on glargine [113 (31.9)%] and NPH insulin [107 (30.6)%]. Very few participants had treatment-emergent adverse events leading to permanent treatment discontinuation [glargine group, 6 (1.7)%; NPH group, 4 (1.1)%]. There were five deaths in the glargine group (myocardial infarction, n = 3; traumatic intracranial haemorrhage, n = 1; metastatic renal cancer, n = 1) and two deaths in the NPH group (thoracic haemorrhage resulting from shooting, n = 1; subarachnoid haemorrhage, n = 1).

Discussion

The aim of the present study was to examine the change from baseline to end of treatment in HbA1c using an algorithm designed to reduce the rate of nocturnal hypoglycaemia with NPH insulin to values no different from those with insulin glargine. Various algorithms for dose titration have been used and published, and indeed recently reviewed [11]. Our approach in the present paper used some of the common and less common approaches espoused by these algorithms, with the intention of emphasizing the effect of hypoglycaemia and low nocturnal values in limiting dose titration, as against more aggressive titration to FPG targets; thus, the protocol requested nocturnal measurements before titration, which was performed at weekly intervals, with lower values resulting both in dose reduction and suspension of further dose increases, for longer intervals if recurrent. Severe hypoglycaemia and HbA1c ≤6.0% (42 mmol/mol) also led to dose increment suspension for the remainder of the study, but are unlikely to have a significant effect on the study population as a whole.

Despite this dose-titration algorithm intended to be sensitive to low plasma glucose testing (including at night) and the occurrence of hypoglycaemic events, the risk of nocturnal hypoglycaemia remained notably higher with NPH insulin than with glargine. This is in the context of relatively modest final insulin doses compared with some studies, but with FPG, HbA1c and HbA1c-to-target results similar or only marginally worse than the 'best' studies [11]. Accordingly, it remains unanswered whether treatment to an individually tolerated rate of hypoglycaemia would lead to a greater reduction in HbA1c levels with insulin glargine in routine clinical practice. Meanwhile the results are consistent with treat-to-target studies with insulins glargine and detemir, where HbA1c levels were

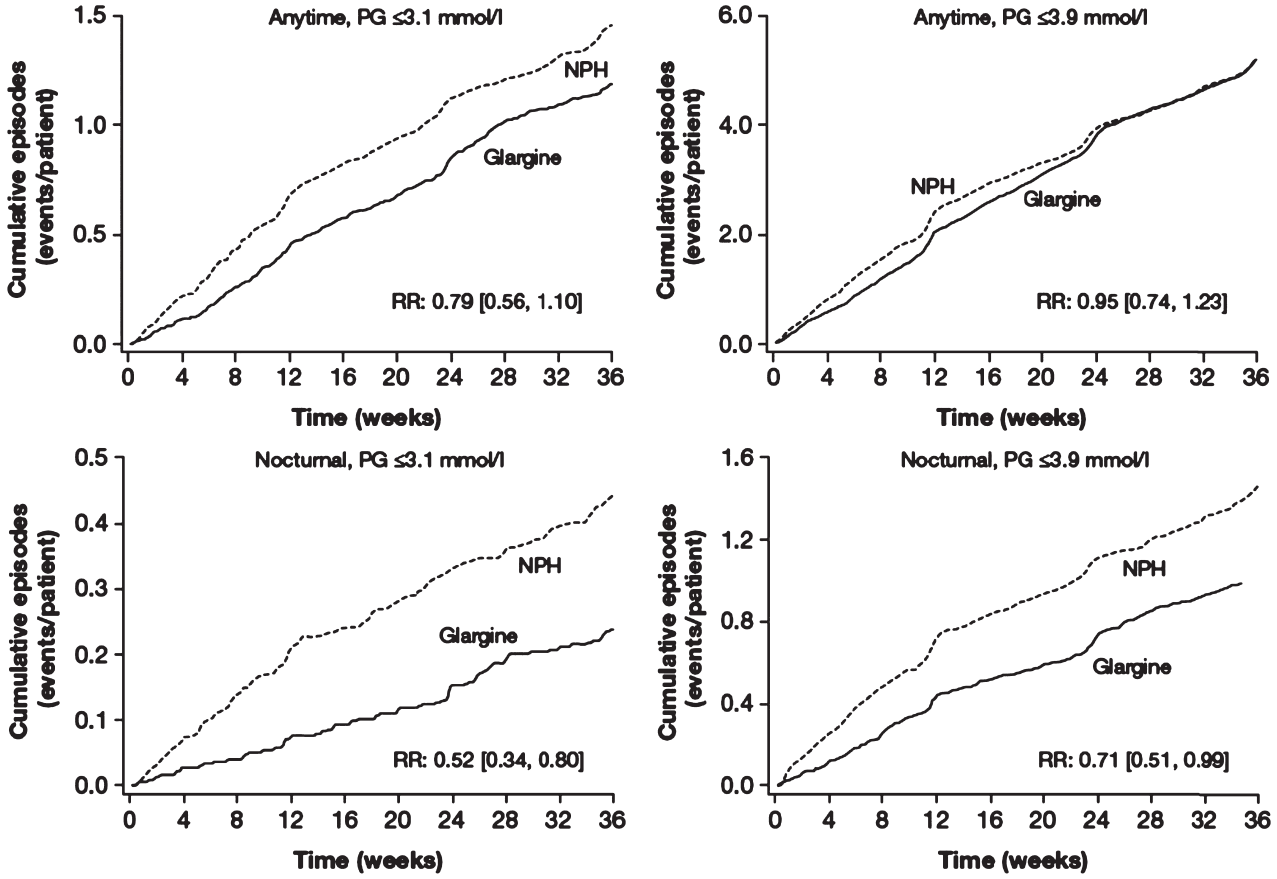

Figure 3. Cumulative events per person of anytime and nocturnal symptomatic hypoglycaemia confirmed by plasma glucose ≤3.9 mmol/l or plasma glucose ≤3.1 mmol/l in the safety population. PG, plasma glucose; RR, relative risk.

similar but nocturnal hypoglycaemia was lower than with NPH insulin [5,6].

The question is clinically important, as relevant differences in HbA1c levels would be expected to drive differences in vascular complications in the longer term, and thus the cost-effectiveness of the basal insulin analogues. The binomial regression relationships between hypoglycaemia and HbA1c, for insulins glargine and detemir, do suggest the opportunity for hypoglycaemia to modulate HbA1c to advantage compared with NPH in insulin starters [5,8].

There are several possible reasons for the persistence of an excess of nocturnal hypoglycaemia with NPH. In the present study, >90% of the participants were taking sulfonylureas and it is possible that participants on NPH retained a greater risk for nocturnal hypoglycaemia in this setting. Other reasons include limitations of the algorithm itself, the unpredictable variability of the effect of NPH leading to unpredictable glucose patterns at night or lower than anticipated power for hypoglycaemia to modulate basal insulin dose adequately, given that as many as 36% of people still reported confirmed nocturnal hypoglycaemia. The 36-week study duration might be a factor for the last three possibilities, suggesting that a longer study may be needed to provide a definitive answer. This is of course relevant to the development of further new basal insulin analogues.

The HbA1c levels achieved in the present study were very similar with the two insulins, but it appeared that FPG was beginning to separate by 36 weeks (completer population), although the difference was small. This too suggests that duration of such a treat-to-hypoglycaemia study needs to be longer. Numerically the HbA1c levels achieved were a little above those in the original treat-to-glucose-target studies [5,6], so it is also possible that tighter glucose control is necessary to show differences between insulin types in the short term. The argument, however, is limited by FPG being numerically lower in the present study than in the earlier studies, suggesting that although the final insulin dose was not high (31–32 U/day), it was not inappropriate in this study population, and that the algorithm and monitoring by the titration committed were successful. One useful result of this study is verification that the findings of the original treat-to-target studies can be reproduced globally; that is, the reduction in nocturnal hypoglycaemia with insulin glargine appears independent of geographic region and cultural influences. Determination of efficacy and safety across global populations is relevant to the development of future insulin products.

Our predictor analysis confirmed previous evidence that baseline HbA1c is the major determinant of achievement of HbA1c targets, while country as an influence independent of that is likely to reflect differences in medical attitudes and

resources. Less obvious is why number of previous oral agents might predict achievement of target, independent of these in particular, as combination metformin + sulfonylurea therapy was continued in >90% of participants from randomization (Table 2). One possibility is that use of more oral agents reflected more active glucose management, and this continued in respect of insulin dose adjustment during the study. The fact that hypoglycaemia should be predicted by duration of diabetes might reflect less stable glucose control as endogenous insulin secretion wanes with time, an effect presumably overcome for prediction of HbA1c to target by the application of the dose-titration algorithm. In clinical practice it is generally observed that people with a higher BMI have less susceptibility to hypoglycaemia when on insulin, as is confirmed in the present study, although the reasons are unknown.

In conclusion, superiority of insulin glargine over NPH insulin in the reduction of HbA1c after 36 weeks of treatment was not observed; however, the study confirmed that insulin glargine and NPH insulin were similar in this regard and showed, in a diverse, globally distributed population, that safe and effective titration of glargine resulted in lower rates of nocturnal hypoglycaemia despite an algorithm designed to reduce the rate with the comparator insulin. Further treat-to-hypoglycaemia studies might be of longer duration, and perhaps limited to the subpopulation experiencing hypoglycaemia in the first months after starting insulin.

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Conflict of Interest

P. D. H., G. B. B., C. M., C. D., V. P. and M. R. C. contributed to study design and conduct/data collection, analysis and writing. W. L. and M.-P. D. contributed to the study design, analysis and writing. C. C. contributed to the analysis and writing. P. D. H., or institutions with which he is associated, receives funding from all major insulin manufacturers including Sanofi for his educational, research and advisory activities. G. B. B. has served on advisory panels for Bristol-Myers Squibb, Eli Lilly, Novartis Pharmaceuticals and Sanofi and received research support from Sanofi. C. M. has served on advisory panels for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, MannKind Corporation, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk, Pfizer and Sanofi and on the speaker's bureau for Eli Lilly, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk and Sanofi. She has received research support from Eli Lilly, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk and Sanofi. C. D. served on advisory panels and speaker's bureaus for Abbott, Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk, Pfizer and Sanofi. M. C. R. has served as a consultant to and on the speaker's bureau for Amylin Pharmaceuticals, Elcelyx Therapeutics, Eli Lilly, Hoffmann La Roche, Sanofi and Valeritas. He has received research support from Amylin Pharmaceuticals, Eli Lilly, Elcelyx Therapeutics, Sanofi and Valeritas. W. L., C. C., V. P. and M.-P. D. are employees of Sanofi. This duality of interest has been reviewed and managed by Oregon Health & Science University.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Participant disposition.

Figure S2. Eight-point PG profiles at baseline and end of treatment for insulin glargine and NPH insulin.

Table S1. Summary of patients screened and randomly assigned, overall and by country – all screened patients.

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