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Assessment of hypoglycaemia during basal insulin therapy: Temporal distribution and risk of events using a predefined or an expanded definition of nocturnal events

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A B S T R A C T
Aim. – To describe in type 2 diabetes the 24-hour distribution of hypoglycaemia and compare the frequency of nocturnal events based on a predefined nocturnal window or an expanded interval, using illustrative data for two insulin glargine formulations.

Methods. – Temporal distribution of hypoglycaemic events was assessed descriptively and by profile using participant-level data from three randomized trials comparing insulin glargine 300 U/mL (Gla-300) and 100 U/mL (Gla-100). Risk of hypoglycaemia and annualized event rates were compared for the predefined nocturnal interval (00:00 to 05:59 h) and an expanded window (22:00 h to the pre-breakfast glucose measurement).

Results. – Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic events were reported most frequently between 06:00 and 10:00 h with both insulins. Nearly threefold more events were identified using the expanded nocturnal interval. Risk of ≥ 1 nocturnal event was 25% lower with Gla-300 than Gla-100 with the predefined, and 16% lower with the expanded interval; annualized event rates were 31% and 24% lower with the predefined and expanded window, respectively. The between-insulin difference in number of nocturnal events depended markedly on the chosen nocturnal interval (556 vs. 1145 fewer events with Gla-300 using the predefined vs. expanded interval).

Conclusions. – The predefined 00:00–05:59 h nocturnal interval excluded many hypoglycaemic events occurring during the actual overnight interval. While Gla-300 reduced hypoglycaemic events versus Gla-100 [regardless of the interval considered], the results obtained using the expanded window better reflect the clinical experience of people treated with basal insulin.

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Introduction

Hypoglycaemia is a leading barrier to attaining glycaemic goals with insulin therapy [1]. Nocturnal hypoglycaemia may be particularly alarming to individuals with diabetes and providers, and disruptive to medical management [2–4]. Recent clinical trials investigating the use of new long-acting insulin preparations in type 2 diabetes (T2DM) have examined the frequency of nocturnal hypoglycaemia to determine whether this unwanted effect is reduced with the newer products. Nocturnal hypoglycaemia has usually been defined as occurring between 00:00 and 05:59 h, to limit the inclusion of hypoglycaemia potentially related to mealtime insulin taken after wakening. However, this 6-hour window may not include all events occurring during the period between waking and breakast, during which fasting continues and glucose is still regulated by basal insulin; it also does not include the period between an evening injection of basal insulin and midnight. Thus, many events of hypoglycaemia related to basal insulin during the night will be ignored when assessing differences between insulins.
Here we report the temporal (24-hour) distribution of hypoglycaemic events using participant-level data available from three trials of insulin glargine (EDITION 1–3) in T2DM [5–7]. In addition to the number and timing of hypoglycaemic events, the times of evening insulin injections and of pre-breakfast self-measured glucose tests were routinely collected in the EDITION trials, and assessments were made of the incidence and rate of hypoglycaemia meeting the primary hypoglycaemia definition and an alternative definition of < 3.0 mmol/L (< 54 mg/dL). Using this information, we examined the effect of including events occurring in a wider nocturnal window, defined as the interval between 22:00 h and the pre-breakfast glucose test for each participant, as compared with the 00:00–05:59 h interval that was predefined as “nocturnal” in these trials. Because the trials were randomized comparisons of treatment with insulin glargine 300 U/mL (Gla-300) or insulin glargine 100 U/mL (Gla-100), our analysis allowed evaluation of the effect of the nocturnal interval chosen on the observed differences between these insulins.

**Materials and methods**

**Data sources and participants**

EDITION 1, 2, and 3 were multicentre, randomized, open-label, two-arm, parallel-group, phase 3a trials (NCT01499082, NCT01499095, NCT01676220) of similar designs that have been described previously [5–7]. In EDITION 1, participants had previously followed a regimen of basal insulin therapy with either Gla-100 or neutral protamine Hagedorn (NPH) insulin (≥ 42 U/day), together with mealtime insulin therapy, with or without metformin, for at least 1 year. In EDITION 2, participants had used basal insulin (Gla-100 or NPH insulin; ≥ 42 U/day) for more than 6 months, combined with oral anti-hyperglycaemic drugs (OADs) within the previous 4 weeks. Participants in EDITION 3 were insulin-naïve and were required to have used OADs for at least 6 months before screening. In addition, sulfonylureas were to be discontinued in EDITION 2 (2 months prior to screening) and in EDITION 3 (at baseline). All participants provided written, informed consent. All three protocols were approved by the appropriate ethics committees and the trials were conducted according to Good Clinical Practice and the principles of the Declaration of Helsinki.

After a 2-week screening phase, each trial included a 6-month main on-treatment period; data from this are included in the present analysis. No participants were < 18 years of age or had glycated haemoglobin (HbA1c) < 7.0% (53 mmol/mol), or > 10.0% (86 mmol/mol) for EDITION 1 and 2, and > 11.0% (97 mmol/mol) for EDITION 3. Further details of inclusion and exclusion criteria have been reported previously [5–7] and are summarized in Table S1 (see supplementary materials associated with this article online).

**Therapy**

Participants were randomized (1:1) to receive once-daily subcutaneous injections of either Gla-300 or Gla-100 (both Sanofi, Paris France) as described previously [6–8]. The basal insulin injection was administered in the evening from before dinner to bedtime, and at the same time for everyone during the 6 months of randomized therapy. Basal insulin injection time was recorded by all participants. Basal insulin dosage was adjusted seeking a fasting, pre-breakfast, self-monitored plasma glucose (SMGP) target of 4.4–5.6 mmol/L (80–100 mg/dL), using specific titration algorithms [5–7].

**Outcomes**

The pre-specified hypoglycaemia endpoints were the same for each trial [5–7]. Briefly, all hypoglycaemic events were categorized according to the American Diabetes Association definitions [8]:

- severe hypoglycaemia (an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions);
- documented symptomatic hypoglycaemia (an event during which typical symptoms of hypoglycaemia are confirmed by an SMGP measurement of ≤ 3.9 mmol/L (≤ 70 mg/dL));
- and asymptomatic hypoglycaemia identified by an SMGP measurement of ≤ 3.9 mmol/L (≤ 70 mg/dL).

The main analysis of hypoglycaemic events used the combination of the confirmed (with or without symptoms) and severe categories. Hypoglycaemic events with a plasma glucose measurement of < 3.0 mmol/L (< 54 mg/dL) were also analysed and reported.

**Data analysis and statistics**

All analyses included all participants randomized and exposed to ≥ 1 dose of trial drug. In each trial’s protocol, hypoglycaemic events reported between 00:00 h and 05:59 h were defined as nocturnal events (“predefined definition”). In the current post hoc analysis, an expanded window of nocturnal hypoglycaemia was defined using a fixed start time (22:00 h), and a pre-breakfast time defined for everyone by the median value of all pre-breakfast times collected on pre-breakfast, 4- or 8-point SMGP (“expanded definition”).

Hypoglycaemic events were reported as the number and percentages of participants having ≥ 1 hypoglycaemic event over 6 months, the total number of events, and the annualized rate of events (events per participant-year). Relative risk for participants to have ≥ 1 hypoglycaemic event was estimated using the Cochran–Mantel–Haenszel method. The rates of hypoglycaemia were analysed using an over-dispersed Poisson regression model with treatment and randomization strata of screening HbA1c (< 8.0 and > 8.0% [< 64 and > 64 mmol/mol]) and trial as fixed effects, and logarithm of the duration of the treatment period as offset.

Although the EDITION 1, 2, and 3 studies were conducted in different populations, the consistent study designs and endpoints allowed a pooled analysis to be performed. The main analysis used pooled patient-level data from the EDITION 1, 2, and 3 studies (EDITION 1 + 2 + 3). In addition, to examine the data without the potentially confounding effect of the mealtime insulin used in EDITION 1, pooled patient-level data from the EDITION 2 and 3 studies (EDITION 2 + 3) were included in a secondary analysis. Data from each individual trial are also given as supportive information.

**Results**

**Study population**

Taken together, the EDITION 1, 2, and 3 trials randomized 2496 participants of whom 2488 were treated with study insulin and are included here. Baseline characteristics of participants in the pooled populations are provided in Table 1; those for participants in each trial have been previously reported [5–7] and are provided in Table S2 (see supplementary materials associated with this article online). Important differences between the trial populations are evident. Notably, participants in EDITION 1 (who were all users of basal and mealtime insulin) were approximately 2 years older on average and had ~3–6 years longer duration of diabetes than those in EDITION 2 and 3. Participants in EDITION 1 also had used insulin for longer than those in EDITION 2.
Timing of evening insulin injections and pre-breakfast glucose tests

The temporal distributions of basal insulin injections and of SMPG tests before breakfast are shown separately for each trial in Fig. S1 (see supplementary materials associated with this article online), and the pooled data are provided in Table S3 (see supplementary materials associated with this article online). Despite the differences in clinical characteristics between the trial populations, the distributions of times of basal insulin injections and pre-breakfast SMPG testing were similar. For all three trials combined, the median time of the glucose test was 07:30 h and that of insulin injection was 21:30 h. However, there was considerable variation, with some individuals doing the glucose test before 05:00 h or after 10:00 h and some taking the injection before 18:00 h or after 01:00 h.

Pattern of hypoglycaemic events by time of day

The 24-h temporal patterns of hypoglycaemic events that were confirmed or severe are shown in Fig. 1A–1D. By inspection, both the percentage of participants with ≥1 events and the event rates were lowest in the early morning hours and highest between 06:00 and 10:00 h. The patterns for the individual studies are similar (Fig. 1B, 1D), except for the period after 10:00 h in EDITION 1, in which mealtime insulin was given and more hypoglycaemic events were reported than in EDITION 2 and 3.

Number of hypoglycaemic events by nocturnal interval

The numbers of events identified between 00:00 and 05:59 h and between 22:00 h and the pre-breakfast SMPG are shown in Table 2. With data pooled from all three trials, 3026 events were reported in the predefined interval, and 8315 in the expanded interval (Table 2). Nocturnal events constituted 15.7% of the daily total using the predefined 00:00–05:59 h interval, and 43.1% of events using the expanded interval. The increase in the percentage of daily events classified as nocturnal with the expanded interval was especially prominent in EDITION 2 and 3, in which mealtime insulin was not used. In those two trials, the percentage of events identified as nocturnal increased from 17.5% to 50.5% with the expanded definition.

Risk of experiencing various categories of hypoglycaemia with Gla-300 and Gla-100, by treatment and nocturnal interval and glucose confirmation level

In the analysis of data pooled from all three trials, the percentage of participants experiencing ≥1 nocturnal event was lower with Gla-300 than Gla-100 using both the 00:00–05:59 h interval (relative risk [RR] 0.75, 95% confidence interval [CI] 0.68 to 0.83) and the 22:00 h to pre-breakfast SMPG window (RR 0.84, 95% CI 0.78 to 0.89) (Fig. 2A). A consistent pattern of lower risk for Gla-300 compared with Gla-100 was also observed for both nocturnal intervals when < 3.0 mmol/L (< 54 mg/dL) was used as the defining glycaemic threshold or with other categories of hypoglycaemia (Fig. 3A). While the differences between the upper and lower confidence limits narrowed with the higher numbers in the expanded interval versus the predefined nocturnal window, the shifts in the central estimates did not fall outside the paired confidence interval and, in general, were small (Fig. 2A, 3A).

From the analysis of EDITION 2 + 3 together, which excludes the potential confounding effect of mealtime insulin, there was also a lower risk of hypoglycaemia for Gla-300 compared with Gla-100 for confirmed (< 3.5 mmol/L [< 62 mg/dL]) or severe hypoglycaemic events for both nocturnal intervals (Fig. 2A). Similar patterns were observed in each of these trials separately and for other categories of hypoglycaemia (Fig. 2A, Table S4; see supplementary materials associated with this article online).

Rate of hypoglycaemic events by treatment, nocturnal window, and glucose confirmation level

Event rates (event per participant-year) were lower with Gla-300 than Gla-100 in analysis of data from all three trials using both the predefined interval (rate ratio [RR] 0.69, 95% CI 0.57 to 0.84) and the expanded window (RR 0.76, 95% CI 0.66 to 0.87) (Fig. 2B). Similar patterns were seen for each trial separately, for data from EDITION 2 + 3 only, for the other glycaemic threshold (< 3.0 mmol/L (< 54 mg/dL)), and for other definitions of hypoglycaemia (Fig. 3B).

The total numbers of events reported during therapy with each glargine formulation in each of the nocturnal intervals are shown in Table 2. In all three trials together, 1791 confirmed or severe events occurred with Gla-100 in the predefined interval and 1235 with Gla-300, a difference of 556 events. In the expanded nocturnal interval, there were 4730 events with Gla-100 and 3585 with Gla-300, a difference of 1145 events.
Discussion

These post hoc analyses of data from EDITION 1, 2, and 3 provide new information about the temporal distribution of hypoglycaemic events during daily life in a broad range of people with T2DM on insulin (basal only, and basal-bolus). The most important observation was that events were reported most frequently between 06:00 and 10:00 h, and this was observed with both basal insulin preparations. The fasting glucose measurement, which was to be taken immediately before breakfast, was typically measured close to 07:30 h. Consequently, many nocturnal events were excluded from computation of risk for the overnight fasting period when the predefined nocturnal window (00:00–05:59 h) was used. The difference in numbers of events identified in the predefined versus the expanded nocturnal window is important. Almost three times as many events (8315 vs. 3026) were reported as nocturnal, and most likely related to basal insulin treatment, with the expanded definition. In those not using mealtime insulin (only basal insulin), the percentage of all events in a 24-hour observation period defined as ‘nocturnal’ was about 18% with the predefined interval versus 51% with the expanded definition. This finding suggests specificity of the expanded definition in detecting hypoglycaemia induced by basal insulin even in participants on basal-bolus insulin. Thus, the expanded definition of nocturnal events may provide a more complete description of the risk of nocturnal hypoglycaemia.

Fig. 1. Percentage of participants with ≥1 confirmed (≤3.9 mmol/L ≤70 mg/dL) or severe hypoglycaemic events (A, B), and annualized rate of confirmed (≤3.9 mmol/L ≤70 mg/dL) or severe hypoglycaemia events (C, D) by time during the 6-month treatment period in (A, C) EDITION 1 + 2 + 3 safety population and (B, D) individual EDITION 1, 2, and 3 trial safety populations.

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attributable to basal insulin use and, through greater number, more statistical power.

The high incidences of hypoglycaemia and event rates reported in EDITION 1, 2, and 3 in the intervals 06:00–08:00 h and 08:00–10:00 h may have several explanations. Firstly, SMPC measurements are more likely to be made at these times than during the midnight time and early-morning hours, and the definition of hypoglycaemia utilized required confirmation for both symptomatic and asymptomatic events by such measurements. Secondly, sleep is known to suppress awareness of hypoglycaemia [9], including adrenergic symptoms, so it is more likely to be detected after normal waking. In addition, long-acting basal insulin preparations may increase the risk of hypoglycaemia during prolonged fasting, and it seems likely that people who waken later and delay breakfast longer may risk hypoglycaemia more than those who arise earlier and have shorter duration of overnight fasting. Regardless of the explanation, the pattern of nocturnal hypoglycaemia with long-acting insulin glargine, both GLA-100 [10] and GLA-300 (present study) is different from that reported with NPH insulin [10], for which the risk of hypoglycaemia increases sharply in the earlier hours of the night, presumably related to differences in pharmacokinetics [11].

The increased power of the broader definition of nocturnal hypoglycaemia can be seen in Fig. 2, where the confidence intervals are much narrower than for the original predefined definition. However, as the original confidence intervals generally do not cross 1.00, the qualitative conclusion of a hypoglycaemia advantage for GLA-300 over GLA-100 from prior analyses is not changed [5–7]. While it is evident from Fig. 1 that the direction of advantage for the intervals 06:00–08:00 h and 08:00–10:00 h is the same as the two prior intervals after 02:00 h, there is a trend in the data presented in Fig. 2 for the relative risk and rate ratios to be closer to 1.00 (although still mostly statistically significant) using the expanded definition that extends past 06:00 h. This observation might suggest a downside to the expanded definition, namely that more events after 06:00 h were not amenable to an improvement with a better basal insulin, but rather reflect the lack of minute-to-minute control of insulin delivery when using subcutaneous injections.

It has recently been suggested that the glucose confirmation level for hypoglycaemia reported in clinical trials should be lowered to < 3.0 mmol/L (< 54 mg/dL) [12,13]. Like nearly all phase 3 trials of the newer longer-acting insulins, the EDITION 1–3 trials were not specifically powered to verify differences in the risk of hypoglycaemia, and suffer further in this respect with the lower numbers of hypoglycaemic events confirmed below 3.0 mmol/L. Allowing for this context, analyses performed using that lower glycaemic cut-off do not lead to different conclusions regarding risks between the two definitions of nocturnal hypoglycaemia than were found using the more traditional threshold (Table S4; see supplementary materials associated with this article online).

The findings of these analyses build upon and extend those of two other studies [10,14]. The original Treat-to-Target Trial defined nocturnal hypoglycaemia as occurring after the bedtime injection and before the routine pre-breakfast glucose test, breakfast itself, or administration of any OAD in the morning. Both the percentages of participants affected and event rates peaked sharply between 02:00 and 07:00 h, with significant between-treatment differences (GLA-100 versus NPH insulin) favouring the basal analog throughout that interval. At 10:00 h hypoglycaemia was slightly more common with GLA-100 than NPH. In the EDITION trials, the risk of hypoglycaemia appeared to extend later into the morning than in this earlier trial, consistent with the longer durations of action of GLA-100 and GLA-300 compared with NPH, thereby exposing the limitation of the predefined 00:00–05:59 h interval in recognizing events after 06:00 h but prior to breakfast.

More recently, an analysis of experience with GLA-100 versus insulin degludec was reported using the conventional nocturnal interval (00:00–05:59 h) and two expanded intervals, 21:59–05:59 h and 00:01–07:59 h [14]. Data were pooled from three trials enrolling insulin-naive participants and one enrolling participants on mealtime and basal insulin therapy. The results of most analyses were consistent across all three definitions of the nocturnal interval, showing significantly less hypoglycaemia with the new analog. This result confirms our finding that the definition used, in the context of current clinical trial design, does not alter the conclusion that hypoglycaemia during overnight fasting is
reduced by longer-acting insulin analogs, but our findings additionally define the degree to which the 00:00–05:59 h nocturnal window misses clinically important hypoglycaemic events.

Despite highlighting important limitations of using the 00:00–05:59 h window in assessing the risk of nocturnal hypoglycaemia during treatment with insulin, our analyses do not overcome other difficulties in the interpretation of data from clinical trials. These include the potential for under-reporting of nocturnal events during sleep that do not awaken the individual, and increased ascertainment of asymptomatic events before breakfast when pre-breakfast glucose tests are done frequently. Use of continuous glucose monitoring devices in future studies would allow collection of data that are less confounded by such factors [15]. Another problem, both for clinical practice and clinical research, is that posed by people with diabetes who have widely varying daily schedules for sleep and meals, or reversed day–night schedules compared with the general population. The few but widely displaced outliers in their time of basal insulin injection or pre-breakfast glucose testing in this dataset illustrate this concern.

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For individuals with unusual or highly variable daily schedules, the concept of nocturnal as distinguished from daytime hypoglycaemia may be less useful, and assessment of the full 24-hour risk of hypoglycaemia more relevant. In summary, these analyses demonstrate that, in different populations of people with T2DM treated with regimens including basal insulin, many hypoglycaemic events occurring during the overnight fasting period were not identified by use of the predefined 00:00–05:59 h definition of nocturnal hypoglycaemia. Expanding this definition to include the time between late evening and breakfast time (i.e., a fasting temporal interval during which people with T2DM treated with basal insulin may be at risk of hypoglycaemia regardless of it being night or day) increased the number of events identified by up to threefold and may provide a more clinically relevant assessment of risk during titration of basal insulin. However, the relative risk and rate ratio for nocturnal hypoglycaemic events with Gla-300 versus Gla-100 were confirmed to be significantly lower with Gla-300 using both definitions of the nocturnal window.

**Author contributions**

Sanofi was the sponsor of the original studies contributing to this analysis and was responsible for the design and coordination of those trials, monitoring clinical sites, collecting and managing data, and performing all statistical analyses. Matthew C. Riddle, Philip D. Home, Ana Merino-Trigo, and Geremia B Bolli developed the initial concept for this analysis. Matthew C. Riddle, Philip D. Home, Angelo Avogaro, Margarita Giménez Álvarez, Ana Merino-Trigo, and Geremia B Bolli participated in interpreting the findings as well as writing, reviewing, and editing the manuscript. Emmanuelle Boélle-Le Corfec participated in data analysis and in writing, reviewing, and editing the manuscript. All authors had
full access to all the data in the study and have approved the decision to submit this article for publication.

Disclosure of interest

The authors report the following dualities of interest:
Matthew C. Riddle--Consultant: AstraZeneca, Biodel, Elcelyx, GlaxoSmithKline, Sanofi, Valeritas; Research support: AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi. These dualities have been reviewed and managed by Oregon Health & Science University.

Philip D. Home--Consultant: AntriaBio, AstraZeneca, GlaxoSmithKline, Hanmi, JanssenPharmaceutical Companies of Johnson & Johnson, Merck (MSD), Novo Nordisk, Roche Diagnostics, Sanofi, Skypharma; Research support: GlaxoSmithKline, Novo Nordisk, Sanofi; Acted as a speaker for: AstraZeneca, Biocon, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck (MSD), Novo Nordisk, Sanofi.

Angelo Avogaro--Advisory panel: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly; Board member: Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Novo Nordisk, Sanofi, Takeda; Research support: Boehringer Ingelheim, Bristol-Myers Squibb; Speakers bureau: AstraZeneca, Eli Lilly, Novartis, Novo Nordisk, Sanofi, Servier, Takeda.

Margarita Giménez Álvarez--Acted as a speaker for: Eli Lilly, Medtronic, Merck (MSD), Novo Nordisk, Sanofi.

Ana Merino-Trigo--Employee: Sanofi; Stocks/shares: Sanofi.

Emmanuelle Boîlle-Le Corf--Employee: Sanofi; Stocks/shares: Sanofi.

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Appendix A. Supplementary material

Supplementary materials (Fig. S1 and Tables S1–S4) associated with this article can be found at http://www.sciencedirect.com at https://doi.org/10.1016/j.diabete.2017.12.001.

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