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BRIEF REPORT

A *post-hoc* pooled analysis to evaluate the risk of hypoglycaemia with insulin glargine 300 U/mL (Gla-300) versus 100 U/mL (Gla-100) over wider nocturnal windows in individuals with type 2 diabetes on a basal-only insulin regimen

Geremia B. Bolli MD[1] | Carol Wysham MD[2] | Miles Fisher MD[3] | Soazig Chevalier MS[4] | Anna M. G. Cali MD[4] | Bruno Leroy MD[4] | Matthew C. Riddle MD[5]

[1]Department of Medicine, University of Perugia, Perugia, Italy

[2]Diabetes and Endocrinology Center, Rockwood Clinic, Spokane, Washington

[3]Glasgow Royal Infirmary, University of Glasgow, Glasgow, UK

[4]Sanofi, Paris, France

[5]Oregon Health and Science University, Portland, Oregon

Correspondence
Geremia B. Bolli, MD, Section of Endocrinology and Metabolism, Department of Medicine, Hospital S.M. della Misericordia, Piazzale Gambuli, 1, 06129 Perugia PG, Italy.
Email: geremia.bolli@unipg.it

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The EDITION trials in type 2 diabetes demonstrated comparable glycaemic control with less nocturnal and anytime (24-hour) hypoglycaemia for insulin glargine 300 U/mL (Gla-300) versus glargine 100 U/mL (Gla-100). However, the predefined nocturnal window (0:00–5:59 AM) may not be the most relevant for clinical practice. This *post-hoc* analysis compared expansions of the predefined nocturnal interval during basal insulin treatment without prandial insulin. Patient-level, 6-month data, pooled from the EDITION 2 and 3 trials and the EDITION JP 2 trial (*N* = 1922, basal insulin only) were analysed. Accompanying hypoglycaemia during treatment with Gla-300 was compared to that during treatment with Gla-100, using predefined (0:00–5:59 AM) and expanded (10:00 PM–5:59 AM, 0:00–7:59 AM, 10:00 PM to pre-breakfast SMPG) windows. Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemic events were reported most frequently between 6:00 AM and 8:00 AM. Windows expanded beyond 6:00 AM included more events than other windows. The percentage of participants with at least one event was lower with Gla-300 than Gla-100 in all windows examined. Expanding the nocturnal interval allows better assessment of the risk of hypoglycaemia associated with basal insulin. The risk of nocturnal hypoglycaemia was consistently lower with Gla-300 versus Gla-100 using all four windows.

KEYWORDS

basal insulin, hypoglycaemia, type 2 diabetes

1 | INTRODUCTION

Basal insulin is an essential component of the management strategy for individuals with type 2 diabetes (T2DM),[1] and is often required when lifestyle interventions and non-insulin glucose-lowering agents fail to achieve target glycaemic control. However, basal insulin treatment is often delayed, and/or dose titration is not optimized, resulting in poor glucose control despite initiation of insulin. Studies have identified fear of hypoglycaemia as one of the dominant reasons for sub-optimal use of basal insulin.[2] Hypoglycaemic events often occur at night, when warning symptoms are physiologically blunted, and may result in both acute and long-term clinical consequences.[3] As such, these nocturnal events elicit fear, in both the individuals with T2DM and the healthcare practitioners. Long-acting basal insulin analogues have been developed to deliver constant and predictable glucose-lowering effects over 24 hours, providing improved glycaemic control and reduced risk of nocturnal hypoglycaemia because of a rather flat pharmacodynamic (PD) profile.[4]

Insulin glargine 300 U/mL (Gla-300) has more stable and prolonged pharmacokinetic (PK) and PD profiles than insulin glargine 100 U/mL (Gla-100).[5] The EDITION treat-to-target clinical trials showed that the improved PK and PD properties of Gla-300 translate

into clinical benefits such as glycaemic control equivalent to that of Gla-100 with less hypoglycaemia in individuals with T2DM, primarily, but not exclusively, at night (defined as 0:00–05:59 AM).[6–8]

The value of extending time intervals beyond 00:00–5:59 AM when assessing nocturnal hypoglycaemia has been shown in a patient-level meta-analysis of the global EDITION trials in T2DM (EDITION 1, 2 and 3), in which a clinically defined window from 10:00 PM to the time of pre-breakfast self-monitored plasma glucose (SMPG) measurement (median, 7:30 AM) resulted in the inclusion of many more hypoglycaemic events compared to the predefined 0:00–5:59 AM window, and confirmed a clinically relevant reduction in the risk of hypoglycaemia with Gla-300 during the overnight fasting period.[9] However, the EDITION 1 trial[7] examined individuals using prandial insulin in addition to basal insulin; thus, the results may not be specifically attributed to basal insulin alone.

The present *post-hoc* analysis was designed to evaluate the risk of nocturnal hypoglycaemia with Gla-300 vs Gla-100 by using data pooled from three trials in which participants with T2DM used only basal insulin (EDITION 2, 3 and JP 2) without the confounding effects of the prandial insulin used in EDITION 1. Hypoglycaemia at night was analysed using the predefined 0:00–5:59 AM nocturnal interval and three expansions thereof.

2 | METHODS

2.1 | Trial design

EDITION 2, EDITION 3 and EDITION JP 2 were multicentre, randomized, open-label, two-arm, parallel-group, phase 3a studies in different populations of adults with T2DM (NCT01499095, NCT01676220, NCT01689142) and have been described previously.[6,8,10] In EDITION 2 and EDITION JP 2, participants must have used basal insulin treatment (≥ 42 U/d in EDITION 2) for more than 6 months, in combination with non-insulin antihyperglycaemic agents within the previous 4 weeks. For the EDITION 2 trial, exclusion criteria included recent (within the past 2 months) use of sulphonylureas. In the EDITION JP 2 trial, concomitant sulphonylurea and/or glinide treatment was permitted, with doses adjusted if at least two symptomatic or at least one severe hypoglycaemic episode(s) occurred. Overall, 63% of participants in the EDITION JP 2 trial received sulphonylureas and/or glinides, with a similar proportion of participants in the Gla-300 (62%) and Gla-100 (64%) groups.[11] Participants in the EDITION 3 trial were insulin-naïve and were required to have used non-insulin antihyperglycaemic agents for at least 6 months before screening; if participants were receiving sulphonylureas/glinides, these medications were discontinued.

Participants were randomized (1:1) to receive once-daily injections of Gla-300 (Toujeo, Sanofi, Paris, France) using a modified SoloSTAR (Sanofi) pen-injector in the EDITION 2 trial or a modified Tactipen (Sanofi) injector in the EDITION 3 and JP 2 trials, or Gla-100 (Lantus, Sanofi) using a SoloSTAR pen. Basal insulin was titrated, seeking a pre-breakfast SMPG target of 4.4–5.6 mmol/L (80–100 mg/dL).

Basal insulin injections were to be administered in the evening, defined as the time immediately before the evening meal until bedtime, at the same time every day. All participants recorded time of injection.

2.2 | Outcomes

Pre-specified hypoglycaemia endpoints, categorized according to American Diabetes Association definitions,[12] were the same for all studies and have been reported previously.[6,8,10] Confirmed or severe hypoglycaemia was defined as any event that was documented and symptomatic, was asymptomatic with a plasma glucose measurement of ≤3.9 mmol/L (≤70 mg/dL) or was severe. Hypoglycaemic events with more stringent plasma glucose measurements of <3.0 mmol/L (<54 mg/dL) were also analysed. During the main 6-month treatment period, hypoglycaemic events were reported by time of day, as percentage of participants with at least one event and as annualized rates (events per participant-year).

2.3 | Definitions of nocturnal hypoglycaemia

Four windows were used for evaluation of nocturnal hypoglycaemia:

1. Predefined window as per study protocol, with events occurring between 0:00–5:59 AM classified as nocturnal.
2. Expansion of predefined window by 2 hours in the evening (10:00 PM–5:59 AM).
3. Expansion of predefined window by 2 hours in the morning (0:00–7:59 AM).
4. Individualized final window, defined by a fixed start time and an end time that varied by participant (10:00 PM to each individual's recorded time of pre-breakfast SMPG).

2.4 | Data analysis

While the EDITION 2, 3 and JP 2 trials were conducted in different populations, all three trials had a similar design, and the consistent study designs and endpoints allowed a pooled analysis. Hypoglycaemia over 6 months was assessed in safety populations by analysing patient-level data pooled from the EDITION 2, 3 and JP 2 trials. Point estimates for the relative risk and 95% confidence intervals (CIs) for the percentage of participants with at least one hypoglycaemic event were estimated using the Cochran–Mantel–Haenszel method, while rates of hypoglycaemia (events per participant-year) were analysed using an over-dispersed Poisson regression model to determine rate ratios and 95% CIs.

3 | RESULTS

Baseline characteristics (Table S1) were, in general, similar between the trials, with the exception of BMI, which was lower in the EDITION JP 2 trial (mean [SD]: Gla-300, 25.7 [4.0]; Gla-100, 24.8 [3.6] kg/m^2) than in the EDITION 2 trial (mean [SD]: Gla-300, 34.8 [6.6]; Gla-100, 34.8 [6.1] kg/m^2) and the EDITION 3 trial (mean [SD]: Gla-300, 32.8 [6.9]; Gla-100, 33.2 [6.6] kg/m^2). Distribution, by time of day, of the time of the pre-breakfast SMPG and basal insulin injection was

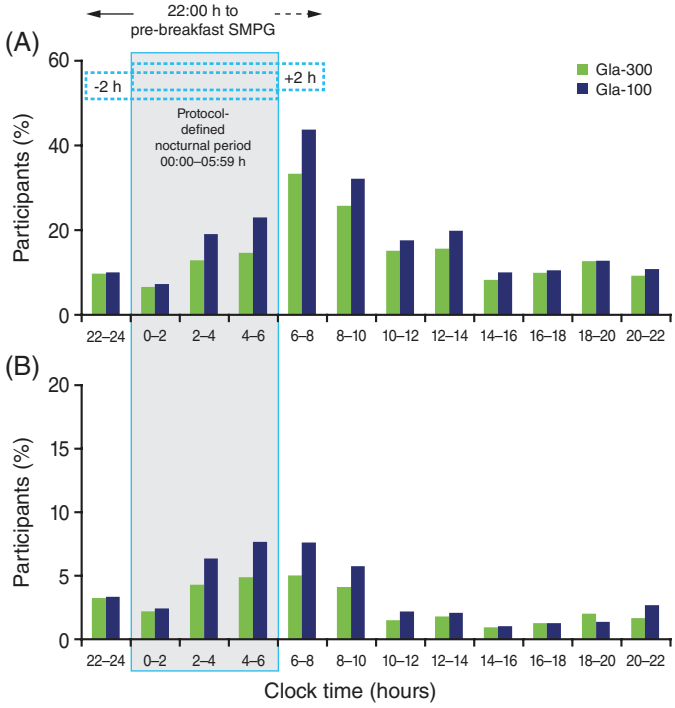

FIGURE 1 Percentage of participants with at least one confirmed or severe hypoglycaemic event at both the (A) ≤ 3.9 mmol/L (≤70 mg/dL) threshold and the (B) < 3.0 mmol/L (<54 mg/dL) threshold (safety population†) – Pool of results from the EDITION 2, EDITION 3 and EDITION JP 2 trials. †Gla-300 N = 958, Gla-100 N = 964. Abbreviation SMPG, self-monitored plasma glucose

comparable for the Gla-300 and Gla-100 groups and between studies (Figure S1). For the pooled analysis, the overall median time of pre-breakfast SMPG was 7:30 AM (interquartile range [IQR]: 6:55–8:16 AM) and the median time of basal insulin injection was 9:17 PM (IQR: 8:00–10:05 PM).

At every time point analysed, fewer participants reported confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia with Gla-300 than with Gla-100 (Figure 1A). This finding was consistent with those of the individual EDITION 2, 3 and JP 2 trials, in which, for the majority of time points, fewer participants reported confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia with Gla-300 than with Gla-100 (Figure S2). For confirmed (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia (Figure 1B) a similar pattern was observed. A greater percentage of 24-hour events were defined as nocturnal when using windows that extended past 6:00 AM (Table 1).

Percentage of participants with ≥ one confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemic event almost doubled when using nocturnal window definitions that extended past 5:59 AM (0:00–7:59 AM and 10:00 PM to pre-breakfast SMPG) vs the predefined window (0:00–5:59 AM) (Table 1). This was consistent with results from the individual EDITION trials (S2). The risk of at least one confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe event was consistently lower with Gla-300 than with Gla-100, regardless of the nocturnal window used (Figure S3). Approximately two to three times more hypoglycaemic events were identified during nocturnal windows that extended past 5:59 AM vs the predefined window in the pooled analyses (Table 1), consistent with results from the individual EDITION 2, 3 and JP 2 trials (Table S2). Annualized rates of hypoglycaemia also increased approximately two-fold when using extended nocturnal windows, for all definitions of hypoglycaemia (Table 1 and S4).

4 | DISCUSSION

The aim of this *post-hoc* study was to more fully explore the 24-hour time course and the clinical significance of hypoglycaemic events occurring during treatment of T2DM with basal insulin only by comparing the risk of hypoglycaemia during the predefined nocturnal window commonly used in clinical trials with expanded windows.

This analysis of pooled, patient-level data from the EDITION 2, 3 and JP 2 studies demonstrates that the incidence of reported hypoglycaemia with both Gla-300 and Gla-100 was highest during the 6:00–8:00 AM interval, outside the standard, predefined 0:00–5:59 AM window. The number of hypoglycaemic events reported was more than doubled by including this 2-hour period, suggesting that a window incorporating this time interval is of clinical relevance when examining the role of basal insulin. The pattern of findings from pooled data was also seen in the individual EDITION studies. The high number of events during the 6:00–8:00 AM interval may be related to the protocol-mandated measurement of pre-breakfast SMPG, but the fact that this interval, which is approximately 8–11 hours after basal insulin injection, near dawn and often before the first meal of the day, includes more events is compatible with the pharmacodynamics of basal insulin in T2DM during nocturnal fasting.[13] In clinical reality, up-titration of basal insulin would increase the dose until the dawn phenomenon was overcome, and euglycaemia would ideally be achieved without risk of hypoglycaemia.

Lower risk of hypoglycaemia with Gla-300 vs Gla-100 extends past the predefined nocturnal window (0:00–5:59 AM), in line with the flatter and more evenly distributed PK and PD profiles of Gla-300 compared with Gla-100. The observation in the present study of a higher risk of hypoglycaemia during waking hours may not inspire the fear of events that occur during sleep; however, these events are still important and clinically relevant, and efforts should be made to minimize the frequency of their occurrence.

Recently, a comparable analysis using pooled data from three trials of Gla-300 (EDITION 1, 2 and 3) in T2DM was reported,[9] with results similar to those presented here, including the finding that, while the relative risk and rate ratios move closer to 1.00 with the extended intervals, the conclusion of a reduced risk of hypoglycaemia with Gla-300 vs Gla-100 remains. However, only the present study indicates that the peak of hypoglycaemia incidence at 6:00–8:00 AM is specifically the result of basal insulin, as, in the previous study,[9] the prandial insulin at breakfast in the EDITION 1 trial might have confounded the risk of hypoglycaemia occurring almost 12 hours after evening injection of Gla-300 or Gla-100. Together, the previous study[9] and the current, more specific, analysis provide strong evidence that evening injections of basal insulin confer the greatest risk of hypoglycaemia during the 6:00–8:00 AM time interval.

Interestingly, the results observed in the EDITION JP 2 trial, which investigated Japanese participants, were similar to those

TABLE 1 Nocturnal hypoglycaemia by window (safety population) – Pool of results from the EDITION 2, EDITION 3 and EDITION JP 2 trials

Nocturnal window	0:00–5:59 AM (predefined window in EDITION studies)			10:00 PM–5:59 AM			0:00–7:59 AM			10:00 PM to pre-breakfast SMPG		
	Gla-300 (*N* = 958)	Gla-100 (*N* = 964)	Difference	Gla-300 (*N* = 958)	Gla-100 (*N* = 964)	Difference	Gla-300 (*N* = 958)	Gla-100 (*N* = 964)	Difference	Gla-300 (*N* = 958)	Gla-100 (*N* = 964)	Difference
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe												
Participants with ≥1 hypoglycaemic event (%)	23.6	33.2	9.6	28.6	36.6	8.0	40.9	52.4	11.5	44.9	57.1	12.2
Total number of events	754	1275	521	925	1412	487	2173	3132	959	2260	3210	950
Events per participant, y	1.7	2.8	1.1	2.1	3.1	1.0	4.8	6.9	2.1	5.0	7.1	2.1
Percentage of events in 24 h defined as nocturnal	16.4	20.6	4.2	20.2	22.8	2.6	47.4	50.7	3.3	49.3	51.9	2.6
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe												
Participants with ≥1 hypoglycaemic event (%)	7.2	10.0	2.8	8.6	11.7	3.1	10.4	14.7	4.3	12.2	17.0	4.8
Total number of events	112	191	79	140	214	74	209	317	108	251	357	106
Events per participant, y	0.3	0.4	0.1	0.3	0.5	0.2	0.5	0.7	0.2	0.6	0.8	0.2
Percentage of events in 24 h defined as nocturnal	26.0	34.2	8.2	32.6	38.4	5.8	48.6	56.8	8.2	58.4	64.0	5.6
Documented symptomatic (≤ 3.9 mmol/L [≤ 70 mg/dL])												
Participants with ≥ hypoglycaemic event (%)	17.1	23.4	6.3	19.9	25.7	5.8	26.4	33.1	6.7	29.3	35.9	6.6
Total number of events	468	721	253	529	782	253	1029	1351	322	1075	1445	370
Events per participant, y	1.0	1.6	0.6	1.2	1.7	0.5	2.3	3.0	0.7	2.4	3.2	0.8
Percentage of events in 24 h defined as nocturnal	23.1	28.1	5.0	26.2	30.4	4.2	50.9	52.6	1.7	53.2	56.2	3.0
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])												
Participants with ≥1 hypoglycaemic event (%)	5.8	8.6	2.8	6.8	9.6	2.8	8.2	11.4	3.2	9.6	13.2	3.6
Total number of events	83	162	79	100	177	77	138	239	101	178	272	94
Events per participant, y	0.2	0.4	0.2	0.2	0.4	0.2	0.3	0.5	0.2	0.4	0.6	0.3
Percentage of events in 24 h defined as nocturnal	28.8	41.4	12.6	34.7	45.3	10.6	47.9	61.1	13.2	61.8	69.6	7.8

Abbreviation: SMPG, self-monitored plasma glucose.
Difference, Gla-100 minus Gla-300 (please also see Figures S3 and S4 for results of specific analysis of the differences between Gla-300 and Gla-100, including relative risk, rate ratios and associated confidence intervals).

observed in the EDITION 2 and 3 trials, which investigated Western populations, despite lower BMI and lower doses of insulin in the EDITION JP 2 trial. In theory, the use of sulphonylureas and/or glinides in the EDITION JP 2 trial might have confounded the results of the present pooled analysis, as sulphonylureas increase the risk of hypoglycaemia[11] and were not allowed in the EDITION 2 and 3 trials.[6,8] However, such confounding seems unlikely because a similar percentage of participants using sulphonylureas and/or glinides were allocated to the Gla-300 and Gla-100 groups in the EDITION JP 2 trial,[11] and because the 24-hour distribution of hypoglycaemia in the EDITION JP 2 trial was similar to that seen in the EDITION 2 and 3 trials. Thus, inclusion of the EDITION JP 2 trial, which is representative of an Asian population, enriches and strengthens the present pooled analysis of the 24-hour distribution of hypoglycaemia.

A similar study analysing rates of nocturnal hypoglycaemia with insulin degludec vs Gla-100 also demonstrated that adding 2 hours to the conventional, predefined 0:00–5:59 AM nocturnal window resulted in a two- to three-fold increase, with both insulins, in the number of hypoglycaemic episodes per 100 patient-years of exposure.[14]

These results highlight contrasts between nocturnal hypoglycaemia, as defined for regulatory submission, and wider definitions which appear to be of more clinical relevance. Use of a wider window may be particularly relevant in examining the risk of hypoglycaemia that is specifically the result of basal insulin in individuals with diabetes, especially in those with a higher risk of hypoglycaemia. In the recently published clinical trial of Gla-300 vs Gla-100 in older individuals with T2DM, the SENIOR study,[15] intervals of 10:00 PM–8:59 AM and 0:00–5:59 AM were both used to categorize nocturnal hypoglycaemia,[16] although only data for the latter interval were reported.[15]

Limitations of the present study include the potential underreporting of nocturnal events that do not awaken the individual. Use of continuous glucose monitoring devices for future studies would provide a more accurate description of the number and timing of hypoglycaemic events. In addition, the pooled analyses presented here were not pre-specified. However, the EDITION studies were designed from the outset with consistent study designs and endpoints that allowed analysis of pooled data.

In conclusion, this study has demonstrated that hypoglycaemic events that are specifically induced by basal insulin are most frequently reported between 6:00 and 8:00 AM, with the time of breakfast being varied, but most often between 7:00 and 8:00 AM. Broader windows of observation for hypoglycaemia during a nocturnal/fasting period that extends beyond 6:00 AM allow identification of more affected individuals and more events induced by basal insulin. It would be useful if future studies comparing basal insulins could report results of hypoglycaemic events that occurred within this wider window as well as the predefined window. The lower incidence and rate of nocturnal hypoglycaemia with Gla-300 vs Gla-100 was confirmed using all analysed time windows, showing a consistently reduced risk with Gla-300 compared to Gla-100.

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Conflict of interests

G. B. B. is a consultant to Menarini and Sanofi; has provided research support to Sanofi; and is a member of the speakers bureau for Menarini and Sanofi. C. W. serves on advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk and Sanofi; is a consultant to AstraZeneca, Eli Lilly, Janssen and Sanofi; and is a member of the speakers bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Insulet, Janssen, Novo Nordisk and Sanofi. M. F. serves on advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mylan, NAPP, Novo Nordisk, Sanofi and Servier; and is a member of the speakers bureau for MSD. S. C. is an employee of and a stock/shareholder in Sanofi. A. M. G. C. is an employee of Sanofi. B. L. is an employee of and a stock/shareholder in Sanofi. M. C. R. is a consultant to AstraZeneca, Biodel, Elcelyx, GlaxoSmithKline, Sanofi and Valeritas; and has provided research support to AstraZeneca, Eli Lilly, Novo Nordisk and Sanofi.

Author contributions

Sanofi was the sponsor of the studies analysed and was responsible for the design and coordination of the trials, the monitoring of clinical sites, the collection and managment of data and the performance of all statistical analyses. G. B. B., A. M. G. C., S. C. and M. C. R. developed the initial concept for this analysis. G. B. B., C. W., M. F., S. C., A. M. G. C., B. L. and M. C. R. participated in interpreting the findings as well as writing, reviewing and editing the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

ORCID

Geremia B. Bolli https://orcid.org/0000-0003-4966-4003
Matthew C. Riddle https://orcid.org/0000-0003-1169-3036

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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