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BRIEF REPORT

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Hypoglycaemia risk with insulin glargine 300 U/mL compared with glargine 100 U/mL across different baseline fasting C-peptide levels in insulin-naïve people with type 2 diabetes: A post hoc analysis of the EDITION 3 trial

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Abstract

The relationship between baseline fasting C-peptide (FCP) and glucose control was examined in insulin-naïve people with type 2 diabetes inadequately controlled with oral antihyperglycaemic drugs commencing basal insulin glargine 300 U/mL (Gla-300) or 100 U/mL (Gla-100) in the absence of sulfonylurea/glinides. Participants with FCP measurement from the EDITION 3 trial (n = 867) were stratified according to baseline FCP (≤0.40, >0.40-1.20, >1.20 nmol/L); 11.0%, 70.9% and 18.1% contributed to each group. Glycaemic control, body weight, insulin dose and hypoglycaemia were determined at 26 weeks. Glycaemic control (HbA1c, FPG) at 26 weeks was similar in each FCP group between insulins. However, end-of-study insulin dose was greater with higher FCP for both insulins. More people with lower baseline FCP experienced hypoglycaemia with both insulins, but with numerically lower incidence for Gla-300 versus Gla-100 across all FCP groups for all definitions (time periods and levels) of hypoglycaemia. This suggests that Gla-300 might be particularly advantageous for people who are at higher risk of hypoglycaemia.

KEYWORDS

basal insulin, beta cell function, clinical trial, hypoglycaemia, type 2 diabetes

1 | INTRODUCTION

People with type 2 diabetes (T2D) represent a heterogenous population and recent cluster analyses have proposed five different diabetes phenotypes using age, body mass index (BMI), glycaemia, homoeostasis model estimates and islet autoantibodies.[1,2] Based on phenotype, people have a different risk for hypoglycaemia during insulin therapy and a different risk for developing diabetic complications.[1,3] Among the predictive factors of the hypoglycaemia risk when starting basal insulin, lower BMI and sulfonylurea use are well established.[4,5] Fasting C-peptide(FCP), a surrogate biomarker of ß-cell function, has been reported as an additional predictive biomarker for hypoglycaemia risk in insulin-naïve people with T2D commencing insulin glargine 100 U/mL (Gla-100) as add-on therapy to oral antihyperglycaemic drugs (OADs) including sulfonylurea.[6]

Insulin glargine 300 U/mL (Gla-300), a 3-fold more concentrated formulation of Gla-100 with improved pharmacokinetic and pharmacodynamic properties compared with Gla-100 at bioequivalent doses,[7] reduced the risk of hypoglycaemia at similar levels of glycaemic control compared with Gla-100 in different T2D study populations enrolled in the EDITION clinical trial programme.[8] The aim of the present post hoc analysis was to explore the risk of hypoglycaemia on basal insulin treatment with Gla-300 or Gla-100 in the insulin-naïve T2D population not receiving sulfonylurea/glinides in the EDITION 3 trial,[9] analysed according to baseline FCP levels.

2 | MATERIALS AND METHODS

2.1 | Study and participant selection

Participant-level data from the 26-week EDITION 3 trial of insulin-naïve people with T2D inadequately controlled (HbA1c > 53 mmol/mol; >7.0%) on OADs (metformin or/and dipeptidyl peptidase-4 inhibitors but not using sulfonylurea/glinides) were analysed. The study used a forced titration algorithm with once-weekly dose adjustments by 2-8 U/day based on patient's self-measured blood glucose, targeting a fasting plasma glucose (FPG) of 4.4 to 5.6 mmol/L (80-100 mg/dL).[9]

2.2 | Outcomes

Clinical characteristics were determined at baseline and after the introduction and titration of the basal insulins (Gla-300 and Gla-100, Sanofi, Paris, France). These were administered once-daily at the same time between dinner and bedtime. All clinical outcomes were assessed over the 26-week study period according to three predefined baseline FCP groups (≤0.40, >0.40-1.20, >1.20 nmol/L). As FCP cut-offs often vary across studies we used the same FCP cut-offs for subgroups as those used in our previous study analysing insulin-naïve people with T2D commencing Gla-100,[6] but with the two highest groups merged, as the >2.00 nmol/L group was small and similar to the group below it. The aim was to approximate subpopulations ranging from dominant insulin deficiency to dominant insulin resistance. Hypoglycaemia was defined as a confirmed plasma glucose (PG) of ≤3.9 or <3.0 mmol/L (≤70 or <54 mg/dL), or severe hypoglycaemia requiring third-party assistance. Nocturnal hypoglycaemia was defined as an event occurring from midnight to 05:59 AM.

2.3 | Statistical analysis

Analyses used descriptive statistics, and results are shown as mean (SD) unless stated otherwise. Hypoglycaemia incidences and event rates were compared as described in the primary study paper.[9] Plots displaying the relationship between hypoglycaemia frequency and baseline FCP levels were derived from negative binomial regression analysis.

3 | RESULTS

3.1 | Participant characteristics and demographic variables

From a total of 878 people who participated in the EDITION 3 trial, 867 had baseline FCP measured and were included in the analysis. Baseline demographic and clinical characteristics according to baseline FCP groups are given in Table S1. The majority (70.9%) had FCP levels of >0.40 to 1.20 nmol/L, 11.0% had levels of ≤0.40 nmol/L, and 18.1% had FCP > 1.20 nmol/L. Mean age and glycaemic variables were similar across all three FCP and insulin groups, whereas body weight and BMI were lowest in the ≤0.40 nmol/L FCP groups and highest in the FCP > 1.20 nmol/L groups. Participants in the highest FCP groups had lower estimated glomerular filtration rates (eGFR) than those in the lowest FCP groups; the distribution of race groups also differed.

3.2 | Glycaemic control

The mean reductions in HbA1c observed at week 26 ranged from 1.35% to 1.67% (14.8 to 17.7 mmol/mol) across FCP groups with numerically greater reductions with Gla-100 versus Gla-300 in the two lowest FCP groups (Table 1). The percentage of people achieving the target HbA1c level of <7.0% (<53 mmol/mol) at week 26 was comparable across all FCP groups (42%-48%), except for Gla-100 in the ≤0.40 nmol/L FCP group (35%) (Figure S1).

From similar baseline FPG levels in each FCP group, the mean FPG changes after 26 weeks ranged from −3.0 to −4.2 mmol/L (Table 1). There was a trend of smaller FPG reductions with higher baseline FCP, particularly observed in Gla-300 groups (from −3.7 to −3.0 mmol/L), resulting in the highest FPG levels at 26 weeks for Gla-300 and Gla-100 (7.1/6.8 mmol/L) in the >1.20 nmol/L FCP groups. The percentage of participants achieving target FPG of ≤5.6 mmol/L (≤100 mg/dL) at 26 weeks was highest in the ≤0.40 nmol/L FCP groups and steadily decreased in the higher FCP groups (Gla-300: from 29% to 27% and 19%; Gla-100: from 33% to 31% and 24%) (Figure S1).

3.3 | Insulin doses

The mean Gla-300 and Gla-100 starting doses ranged from 0.19 to 0.20 U/kg/day across the three FCP groups, but daily doses were thus higher in the highest FCP groups given the body weight differences. Both insulins were steadily titrated during 26 weeks in each FCP group reaching highest mean doses per kilogram in the >1.20 nmol FCP group for Gla-300 (0.71 U/kg) and Gla-100 (0.66 U/kg), and lowest doses in the ≤0.40 nmol/L FCP group (Gla-300: 0.43 U/kg; Gla-100: 0.35 U/kg) (Table 1, Figure S2). The mean Gla-300 dose increments were consistently higher in each FCP group compared with Gla-100, with the highest end of study ratio of doses in the ≤0.40 nmol/L group, and lowest in the >1.20 nmol/L FCP group (Table 1).

TABLE 1 Outcome measures at 26 weeks and change from baseline according to baseline fasting C-peptide groups

	Fasting C-peptide group					
	≤0.40 nmol/L		>0.40-1.20 nmol/L		>1.20 nmol/L	
	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100
HbA1c	n = 52	n = 43	n = 308	n = 298	n = 69	n = 83
Baseline (%)	8.68 (1.20)	8.65 (1.22)	8.49 (1.01)	8.59 (1.05)	8.47 (1.07)	8.45 (1.09)
Week 26, %	7.12 (0.95)	7.03 (0.61)	7.08 (0.96)	7.01 (0.93)	6.99 (0.97)	7.10 (1.09)
Change from baseline, % unit	−1.45 (1.09)	−1.67 (1.22)	−1.40 (1.07)	−1.57 (1.16)	−1.35 (1.24)	−1.39 (1.21)
Baseline (mmol/mol)	71.4 (13.1)	71.0 (13.3)	69.3 (11.0)	70.4 (11.5)	69.1 (11.7)	68.9 (11.9)
Week 26, mmol/mol	54.3 (10.4)	53.3 (6.6)	53.9 (10.5)	53.1 (10.1)	52.9 (10.6)	54.1 (11.9)
Change from baseline, mmol/mol	−15.9 (11.9)	−17.7 (13.3)	−15.3 (11.7)	−17.2 (12.6)	−14.8 (13.5)	−15.2 (13.2)
FPG, mmol/L	*n = 42*	*n = 34*	*n* = 258	*n = 232*	*n* = 53	*n* = 70
Baseline	10.0 (3.6)	10.1 (2.6)	9.9 (2.8)	10.1 (2.8)	10.3 (2.8)	11.0 (3.5)
Week 26	6.4 (1.9)	6.1 (1.8)	6.6 (2.2)	6.2 (1.7)	7.1 (2.2)	6.8 (2.0)
Change from baseline	−3.7 (3.8)	−4.2 (2.4)	−3.3 (3.2)	−3.8 (2.9)	−3.0 (3.2)	−4.0 (3.1)
Insulin dose	n = 45	n = 35	n = 259	n = 233	n = 56	n = 69
Week 26, U/kg	0.43 (0.25)	0.35 (0.21)	0.63 (0.29)	0.53 (0.23)	0.71 (0.28)	0.66 (0.24)
Change from baseline, U/kg	0.23 (0.25)	0.15 (0.22)	0.44 (0.29)	0.33 (0.22)	0.52 (0.27)	0.47 (0.23)
Hypoglycaemia incidence	n = 52	n = 43	n = 310	n = 303	n = 70	n = 86
Anytime (≤3.9 mmol/L or severe), % people	65.4	76.7	47.1	53.8	28.6	34.9
Relative risk	0.86 (0.66-1.10)		0.87 (0.75-1.02)		0.82 (0.51-1.31)	
Anytime (<3.0 mmol/L or severe), % people	17.3	27.9	8.7	16.5	8.6	10.5
Relative risk	0.62 (0.29-1.34)		0.53 (0.34-0.82)		0.82 (0.31-2.18)	
Nocturnal (≤3.9 mmol/L or severe), % people	36.5	46.5	17.4	22.8	7.1	14.0
Relative risk	0.79 (0.49-1.27)		0.76 (0.56-1.05)		0.52 (0.19-1.43)	
Nocturnal (<3.0 mmol/L or severe), % people	11.5	14.0	3.2	6.9	1.4	2.3
Relative risk	0.83 (0.29-2.38)		0.46 (0.22-0.97)		0.77 (0.12-4.86)	
Severe, n people[a]	0	0	3	4	1	0
Body weight, kg	n = 47	n = 36	n = 267	n = 248	n = 57	n = 73
Baseline	78.5 (19.5)	75.6 (17.0)	94.7 (22.0)	95.8 (21.3)	109.8 (22.9)	105.8 (23.1)
Week 26	79.5 (20.8)	76.0 (18.1)	95.2 (21.6)	96.0 (22.0)	108.5 (24.0)	106.2 (23.2)
Change from baseline	0.7 (3.4)	1.1 (3.6)	0.7 (3.8)	0.8 (4.0)	−1.1 (3.8)	0.1 (3.2)

Note: Values are means (SD) or as stated. Group numbers vary with missing values.

[a]third party assistance required; Gla-300, glargine 300 U/mL; Gla-100, glargine 100 U/mL; relative risk (95% CI) for Gla-300 compared with Gla-100.

3.4 | Hypoglycaemia

The incidence and event rate of anytime (PG ≤ 3.9 mmol/L or severe) and nocturnal (PG ≤ 3.9 mmol/L or severe) hypoglycaemia decreased with each higher FCP step in both insulin groups, being lowest in the >1.20 nmol/L FCP group (Tables 1 and S2). However, in Gla-300 participants, the incidence was numerically and consistently lower versus Gla-100 across all FCP groups with relative risk reductions of 13%-18% for anytime (PG ≤ 3.9 mmol/L or severe) hypoglycaemia and 21%-48% for nocturnal hypoglycaemia. The incidence and event rate of severe hypoglycaemia over 26 weeks was very low with both insulin treatments, such that no meaningful differences could be expected.

Analyses using a more stringent PG cut-off(PG < 3.0 mmol/L; <54 mg/dL) yielded similar findings as observed with PG ≤ 3.9 mmol/L (Tables 1 and S2). However, in the >0.40-1.20 nmol/L FCP group, with higher participant numbers, the relative risk reductions were greater and more statistically certain for Gla-300 versus Gla-100.

Binomial regression analysis revealed a strong negative relationship between both anytime and nocturnal hypoglycaemia event rate and baseline C-peptide for both insulins, irrespective of the PG cut-off definition used (Figure 1). Furthermore, the plots show a consistently lower hypoglycaemia risk with Gla-300 versus Gla-100 across different FCP levels, predominantly with decreasing FCP levels.

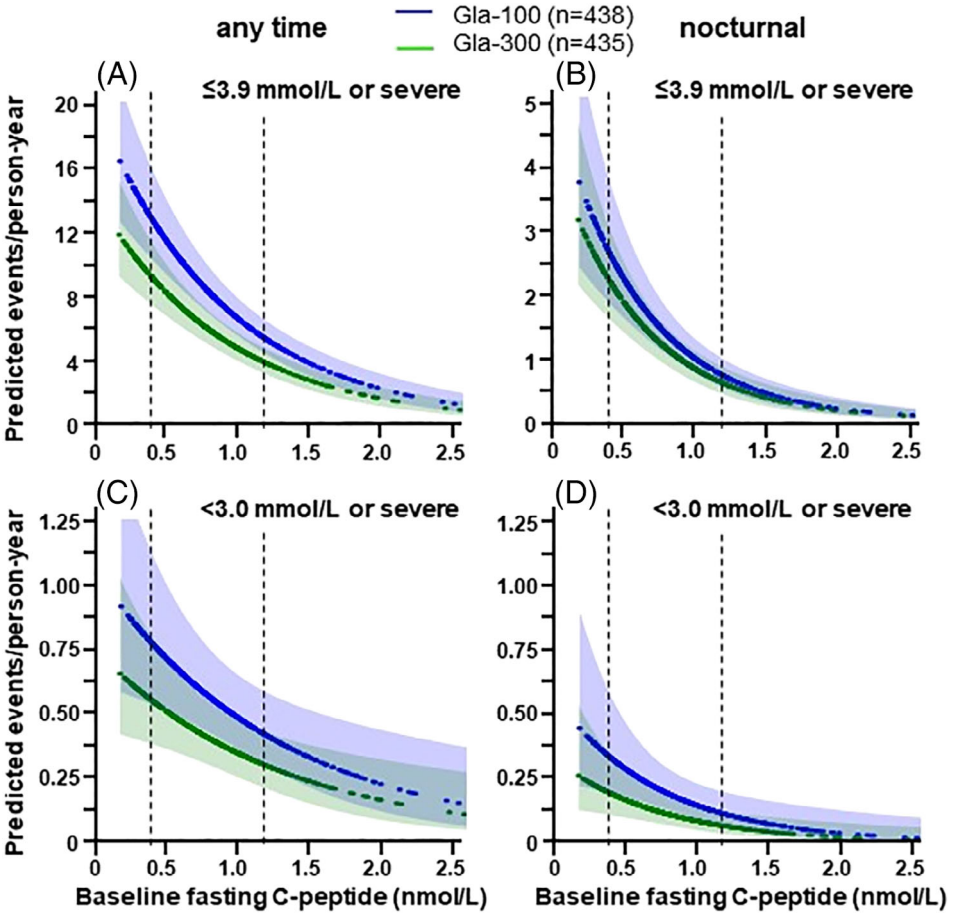

FIGURE 1 Relationship of frequency of confirmed hypoglycaemia (events/person-year) at anytime with PG ≤ 3.9 mmol/L or severe (A), and PG <3.0 mmol/L or severe (C), nocturnal with PG ≤3.9 mmol/L or severe (B), and PG <3.0 mmol/L or severe (D), according to baseline fasting C-peptide levels. Plots are derived from negative binomial regression analysis and displayed with 95% confidence intervals. Vertical dotted lines indicate FCP cut-offs used for the stratification of groups. Gla-300, glargine 300 U/mL; Gla-100, glargine 100 U/mL; PG, plasma glucose

3.5 | Body weight

Baseline and 26-week mean body weights were least in people with the lowest FCP values compared with higher FCP (Table 1). Mean gain in body weight was greatest in ≤0.40 nmol/L FCP groups at 26 weeks, 0.7 kg with Gla-300 and 1.2 kg with Gla-100, and least in the >1.20 nmol/L FCP groups (0.1 kg with Gla-100), whereas reduction was found with Gla-300 (−1.1 kg).

4 | DISCUSSION

This post hoc analysis of the EDITION 3 trial using participant-level data of 867 insulin-naïve T2D people identified individuals at different risk of hypoglycaemia over 6 months of basal insulin treatment when stratified by baseline FCP, confirming recent findings from a larger pooled analysis of nine studies with Gla-100.[6] Moreover, at similar glycaemic control with both insulins across different baseline FCP levels, Gla-300 treatment appeared to be associated with a lower risk of hypoglycaemia compared with Gla-100. However, a significant relative risk reduction was only found for anytime and nocturnal clinically important hypoglycaemia with PG < 3.0 mmol/L (level 2; ADA/EASD[10]) in people with FCP levels 0.40-1.20 nmol/L, representing the largest group of study participants. For the other smaller FCP groups (<0.40 and >1.20 nmol/L) we found a similarly consistent and clear trend of relative risk reduction with Gla-300 lacking significance, presumably because of the limited number of people in each FCP group. With regression analysis (Figure 1), the advantage of Gla-300 over Gla-100 appeared even more marked for absolute rate reduction, suggesting that people with T2D and lower FCP who have higher event rates might benefit more than those with higher FCP and lower event rates, most probably representing people with insulin resistance.

As observed in other glargine T2D studies,[6] the current post hoc analysis of the EDITION 3 trial re-emphasizes that the differences in baseline FCP levels and associated phenotypes between groups largely account for the heterogeneity of outcome responses observed at 26 weeks after beginning basal insulin therapy and supports the recently proposed cluster classification of diabetes.[1,3] About 11% of people in the EDITION 3 trial had a low baseline FCP (≤0.40 nmol/L). As expected, this minority group had a tendency for longer duration of known diabetes (9-11 years) and a slightly higher baseline HbA1c (+0.2% units; +2 mmol/mol) compared with those with higher FCP levels (Tables 1 and S1). Notably, those participants had the lowest body weight/BMI, both at baseline and 26 weeks, and experienced the highest incidence and number of hypoglycaemia events. By contrast, participants in the highest FCP group are obese, probably more insulin-resistant, with lower eGFR levels at baseline and lower risk of

hypoglycaemia. Cluster analyses have confirmed a strong association between the presence of insulin resistance and the development of nephropathy in T2D.[1,3]

The heterogeneity of study participants with T2D in the EDITION 3 trial was further shown by their different insulin dose requirements to achieve similar glycaemic control. The final basal insulin doses for Gla-300 and Gla-100 were least in the lowest FCP group, suggesting that this insulin-deficient group was more insulin-sensitive[1,3,11,12] and almost doubled in the highest FCP group. The need for higher doses of Gla-300 versus Gla-100 to achieve similar glycaemic control has been previously discussed.[6] Using a predefined FCP cut-off(e.g. >0.40 nmol/L) and measurement of other biomarkers such as anti-GAD 65 antibodies as inclusion criteria could reduce the level of heterogeneous people in T2D studies, excluding people with LADA or MODY diabetes.[13,14]

EDITION 3 included insulin-naïve people with T2D. Even in this typically low-risk population for hypoglycaemia, FCP identified a non-negligible subgroup (11%) at a higher risk of hypoglycaemia. Further, the effects of Gla-300 on risk reduction of hypoglycaemia were clearly not confounded by sulfonylurea/glinides, as these drugs were excluded from use in this study.

A limitation of this post hoc analysis is that it describes observations associated with retrospectively defined baseline FCP subgroups and by necessity has used a descriptive analysis; confounding factors other than fasting C-peptide levels may also have contributed to the difference in hypoglycaemia risk with Gla-300 and Gla-100.

In summary, this post hoc analysis in insulin-naïve people with T2D commencing basal insulin as either Gla-300 or Gla-100 after inadequate glycaemic control on oral therapy indicates that a notable minority of people (11%) with lower FCP are at higher risk of hypoglycaemia compared with those with higher FCP. The study also suggests that Gla-300 is associated with a lower relative hypoglycaemia risk compared with Gla-100, clearly shown for FCP levels of >0.40 to 1.20 nmol/L and by consistent trends in favour of Gla-300 in the other FCP groups. Our findings reaffirm that in the subgroup with low FCP, basal insulin should be carefully titrated to limit hypoglycaemia.

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CONFLICT OF INTEREST

G.B.B. is a consultant for Eli Lilly and Sanofi; has received research support from Sanofi; and is on the speakers' bureau for Eli Lilly, Menarini and Sanofi. W.L. is an employee of Sanofi, Germany, and a Sanofi shareholder. Z.B. is an employee of Sanofi, France, and a Sanofi shareholder L.M.-M. is an employee of the IVIDATA Group, providing consultancy to Sanofi. P.D.H. has received funding for self or affiliated institutions from AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Janssen/J&J, Merck, Novo Nordisk, Roche Diagnostics, Roche Pharma, Sanofi and Takeda.

AUTHOR CONTRIBUTIONS

G.B.B. was involved in interpretation, critical revision and final approval of the manuscript. W.L. was involved in designing the study, data acquisition, data analysis and interpretation, critical revision, and final approval of the manuscript. Z.B. was involved in interpretation, critical revision and final approval of the manuscript. L.M.-M. was involved in data acquisition, data analysis and interpretation, critical revision, and final approval of the manuscript. P.D.H. was involved in interpretation, critical revision and final approval of the manuscript. All authors take responsibility for the accuracy and integrity of the data presented in this paper.

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SUPPORTING INFORMATION

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

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