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Hypoglycemia as a function of HbA_{1c} in type 2 diabetes (T2DM): insulin glargine 300 U/mL in a patient-level meta-analysis of EDITION 1, 2 and 3

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INTRODUCTION

- Basal insulin therapy often involves a compromise between achieving glycemic targets and avoiding hypoglycemia, dependent on how insulin use is optimized. Fear of hypoglycemia can lead to sub-optimal insulin dosing,[1] which may impair glycemic control.
- Insulin glargine 300 U/mL (Gla-300) provides more stable and prolonged pharmacokinetic and pharmacodynamic profiles compared with insulin glargine 100 U/mL (Gla-100).[2] This translates into Gla-300 providing equivalent glycemic control to Gla-100 with less hypoglycemia in people with type 2 diabetes (T2DM), as demonstrated in a previous patient-level meta-analysis of data from the phase 3a EDITION 1, 2 and 3 studies.[3]
- Here, data from the EDITION 1, 2 and 3 studies (**Table 1**) were further investigated to determine the relationship between HbA_{1c} achieved at month 6 and the hypoglycemia benefit of Gla-300 versus Gla-100.

OBJECTIVE

To explore the relationship between hypoglycemia over 6 months and HbA_{1c} at month 6 in T2DM clinical trials comparing Gla-300 with Gla-100.

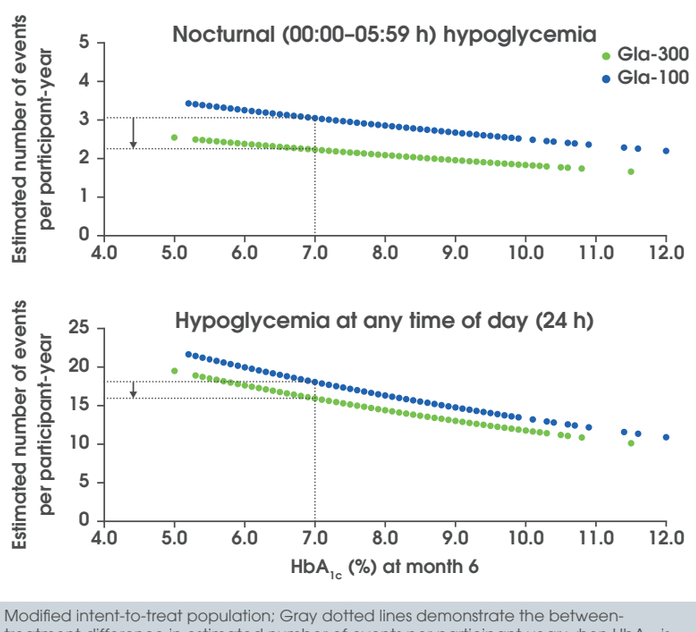
METHODS

- **Design:** EDITION 1, 2 and 3 were multicenter, randomized, open-label, two-arm, parallel-group, phase 3a studies (NCT01499082, NCT01499095, NCT01676220),[4–6] each including a main 6-month treatment period.
- **Treatment:** Participants were randomized (1:1) to once-daily evening injections of Gla-300 or Gla-100 titrated to a fasting self-monitored plasma glucose (SMPG) target of 80–100 mg/dL (4.4–5.6 mmol/L).
- **Outcomes:** Hypoglycemia, defined as the annualized rate of confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe events (ADA definitions[7]) at any time of day (24 h) and during the night (00:00–05:59 h), and HbA_{1c} (%) at month 6.
- **Data analysis and statistics:** A meta-analysis was performed on patient-level data, and analyses were also performed on data from individual studies. The estimated annualized rates (number of events per participant-year) as a function of HbA_{1c} at month 6 were derived using a negative binomial model with the total number of events that occurred from baseline to month 6 as the response variable, treatment and HbA_{1c} at month 6 as covariates, and log-transformed period duration (from baseline to month 6) as an offset variable. A model including a treatment-by-HbA_{1c} interaction term was also implemented.

RESULTS

- **Study population:**
  - In total, 1055 and 1048 participants with available hypoglycemia and HbA_{1c} data from the Gla-300 and Gla-100 groups, respectively, were included in the meta-analysis. Baseline characteristics for the randomized population are shown in **Table 1**.
- **Hypoglycemia as a function of HbA_{1c} at month 6:**
  - People treated with Gla-300 consistently experienced a lower rate of confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemia at night (00:00–05:59 h) and at any time of day (24 h) compared with those treated with Gla-100, regardless of HbA_{1c} at month 6 (**Figure 1**).

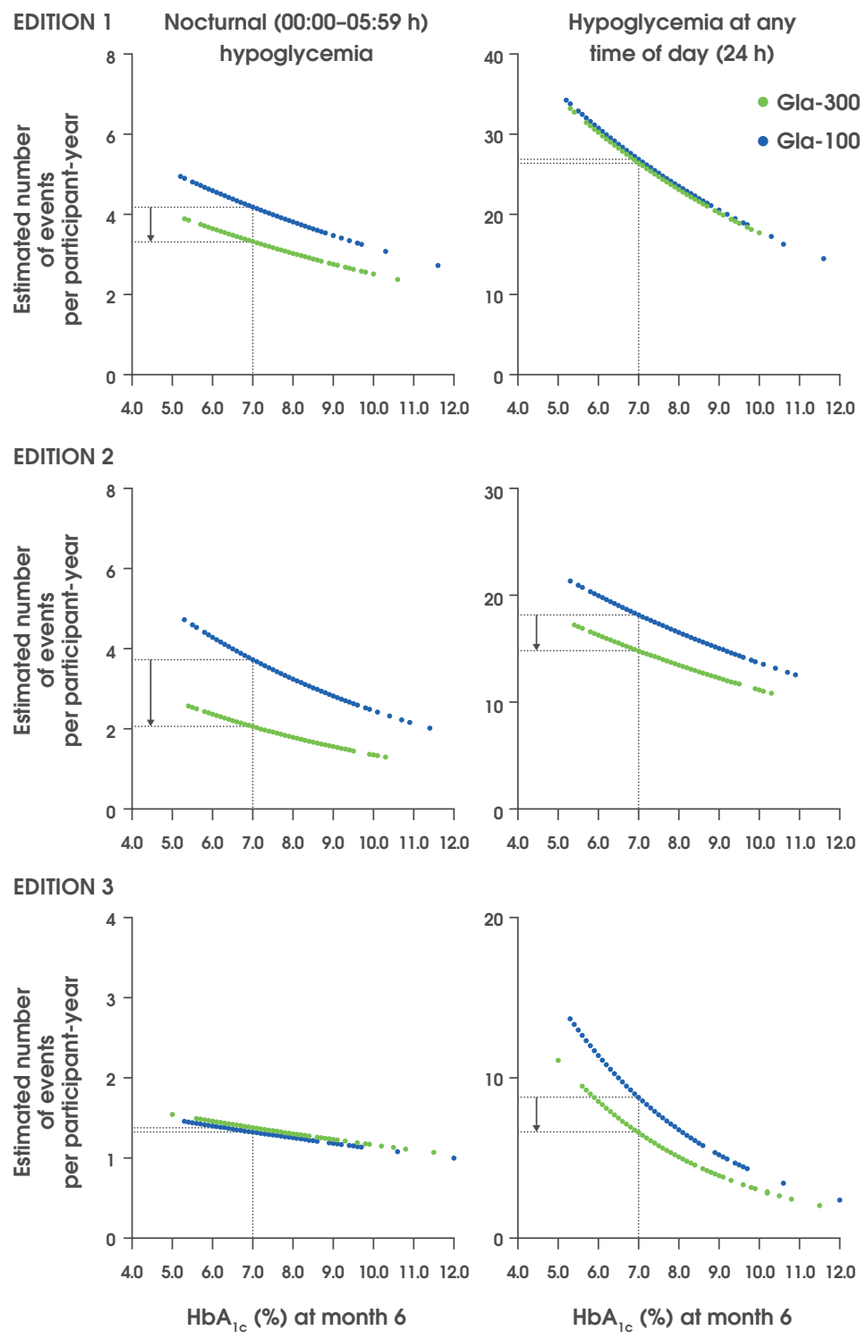
Figure 1: Estimated annualized rates of confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemia over 6 months of treatment with Gla-300 or Gla-100 in a patient-level meta-analysis of the T2DM EDITION 1, 2 and 3 studies, as a function of HbA_{1c} at month 6



Modified intent-to-treat population; Gray dotted lines demonstrate the between-treatment difference in estimated number of events per participant-year when HbA_{1c} is 7.0 % at month 6

  - Adding a treatment-by-HbA_{1c} interaction term to the model (graphs not shown) did not significantly improve the goodness of fit (interaction p-value 0.829 and 0.937 for nocturnal (00:00–05:59 h) hypoglycemia and anytime (24 h) hypoglycemia, respectively). Therefore, the model without interaction describes the data accurately.
  - Presenting data by individual EDITION study showed that the estimated rates were clearly lower with Gla-300 compared with Gla-100, regardless of HbA_{1c} at month 6. Exceptions to this were events at any time of day (24 h) in EDITION 1 and nocturnal (00:00–05:59 h) events in EDITION 3 (**Figure 2**); rates of these events were comparable between treatments, which could be linked to the specific population and background therapy:
    - In the EDITION 1 study, rates of hypoglycemia were likely confounded by the fact that participants were taking mealtime insulin in addition to basal insulin.[4]
    - Participants in EDITION 3 were insulin naïve prior to the study and experienced fewer hypoglycemic events than those in EDITION 1 and 2.[4–6] It is possible that this affected the ability to detect differences in the rates of hypoglycemia between the Gla-300 and Gla-100 groups in the EDITION 3 study, although further investigation may be warranted.

Figure 2: Estimated annualized rates of confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemia over 6 months of treatment with Gla-300 or Gla-100 in the T2DM EDITION 1, 2 and 3 studies, as a function of HbA_{1c} at month 6



Modified intent-to-treat population; Gray dotted lines demonstrate the between-treatment difference in estimated number of events per participant-year when HbA_{1c} is 7.0 % at month 6

SUMMARY

In T2DM, when evaluating hypoglycemia it is important to consider glycemic control; achieving glycemic targets with minimal hypoglycemia could promote adherence to therapy and reduce the risk of long-term micro- and macrovascular complications.[7,8] The analysis of the relationship between hypoglycemia rates and HbA_{1c} at month 6 demonstrated that:

- In the patient-level meta-analysis, annualized rates of confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemia at night (00:00–05:59 h) and hypoglycemia at any time of day (24 h) were lower with Gla-300 compared with Gla-100, regardless of HbA_{1c} values at month 6.
- The results of this meta-analysis were generally consistent with those seen in the individual EDITION 1, 2 and 3 studies.

CONCLUSION

- **In this meta-analysis of people with T2DM, treatment with Gla-300 resulted in a lower rate of hypoglycemia versus Gla-100, regardless of HbA_{1c} at month 6; this was generally consistent with the individual EDITION studies, across people with a broad range of characteristics and disease stages.**
- **The results of this analysis suggest that treatment with Gla-300 could allow people with T2DM to achieve comparable glycemic control with less hypoglycemia versus Gla-100.**

Table 1: Summary of studies (including baseline characteristics) in patient-level meta-analysis of people with T2DM

Study description and treatment	EDITION 1		EDITION 2		EDITION 3		Patient-level meta-analysis	
Number of participants								
Gla-300	404		404		439		1247	
Gla-100	403		407		439		1249	
Glucose-lowering therapy at screening	Basal + mealtime insulin ± Met*		Basal insulin + OADs†		Insulin naïve + OADs‡		N/A	
Inclusion criteria								
Basal insulin dose	≥42 U/day		≥42 U/day				N/A	
HbA_{1c}	≥7.0 %, ≤10.0 %		≥7.0 %, ≤10.0 %		≥7.0 %, ≤11.0 %			
Age	≥18 years		≥18 years		≥18 years			
Mean baseline characteristics	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**
Age, years	60.1	59.8	57.9	58.5	58.2	57.2	58.7	58.5
BMI, kg/m²	36.6	36.6	34.8	34.8	32.8	33.2	34.7	34.8
Duration of diabetes, years	15.6	16.1	12.7	12.5	10.1	9.6	12.7	12.6
HbA_{1c}, %	8.15	8.16	8.26	8.22	8.51	8.57	8.31	8.32

Randomized population; *Use of OADs other than Met prohibited within 3 months prior to screening and during the study; †Use of sulfonylureas prohibited within 2 months prior to screening and during study; ‡Except sulfonylureas, glinides and other OADs not approved for use with insulin. BMI, body mass index; Met, metformin; N/A, not applicable; OAD, oral antihyperglycemic drug; T2DM, type 2 diabetes

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