Lower Glucose Variability and Risk for Hypoglycaemia on Insulin Glargine 300 U/mL Versus Insulin Glargine 100 U/mL, Evaluated by the Low Blood Glucose Index in Randomized Phase III Clinical Trials

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INTRODUCTION

- It has been repeatedly shown that risk analysis of glucose variability (GV), introduced 20 years ago[1] and reviewed this year[2], is instrumental in detecting risk for hypo- and hyperglycaemia in diabetes. In particular, the Low Blood Glucose Index (LBGI) – a GV-based metric of the risk for hypoglycaemia – was confirmed as a powerful predictor of severe events[3].
- EDITION 2 (NCT01499095) and EDITION 3 (NCT01676220) were 12-month studies comparing Glargine 300 Units/ml (Gla-300) to Glargine 100 Units/ml (Gla-100) in prior insulin-treated and -naive people with type 2 diabetes (T2D), respectively[4,5].

OBJECTIVE

The objective of this reanalysis of EDITION 2 and EDITION 3 data is two-fold:

(1) To assess differences between Gla-300 and Gla-100 in glucose variability and the associated risk for hypoglycaemia throughout the day;

(2) To test whether the LBGI identifies T2D patients at risk for hypoglycaemia, e.g. those who reported documented symptomatic hypoglycaemia confirmed by BG readings below 3 mmol/L.

METHODS

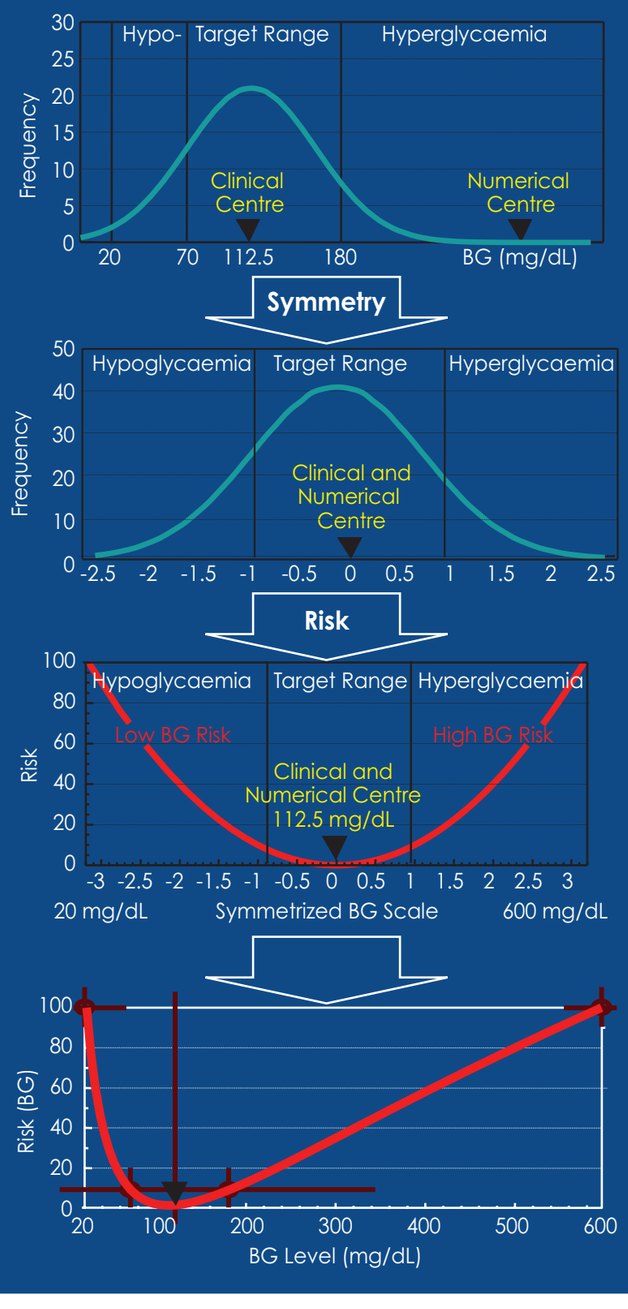
Self-monitoring (SMBG) daily profiles including BG readings pre- and 2-hr post each meal, at bedtime and at 3AM, were available across the study period together with records of documented symptomatic hypoglycaemia (DSH, confirmed by BG readings below 3 mmol/L [54 mg/dL]), as follows:

- EDITION 2: N=796 insulin users, 39,388 SMBG readings, 639 DSH episodes[4];
- EDITION 3: N=839 insulin naive patients, 41,548 SMBG readings, 235 DSH episodes[5].

Both studies randomized their participants to Gla-300 or Gla-100. For both studies, GV and the LBGI were computed using SMBG daily profiles, using the risk analysis structures presented below:

Risk Analysis of Blood Glucose Data
(introduced 1997[1]; reviewed 2017[2])

- The variance carried by hypoglycaemic and hyperglycaemic readings is equalized.
- Excursions into extreme hypoglycaemia and hyperglycemia get progressively increasing risk values.
- The variance within the safe euglycaemic range is attenuated, which reduces noise during data analysis.



ANALYSIS

The LBGI was used to compare GV and risk for hypoglycaemia on Gla-300 vs. Gla-100 throughout the day, and to identify patients who experienced frequent DSH.

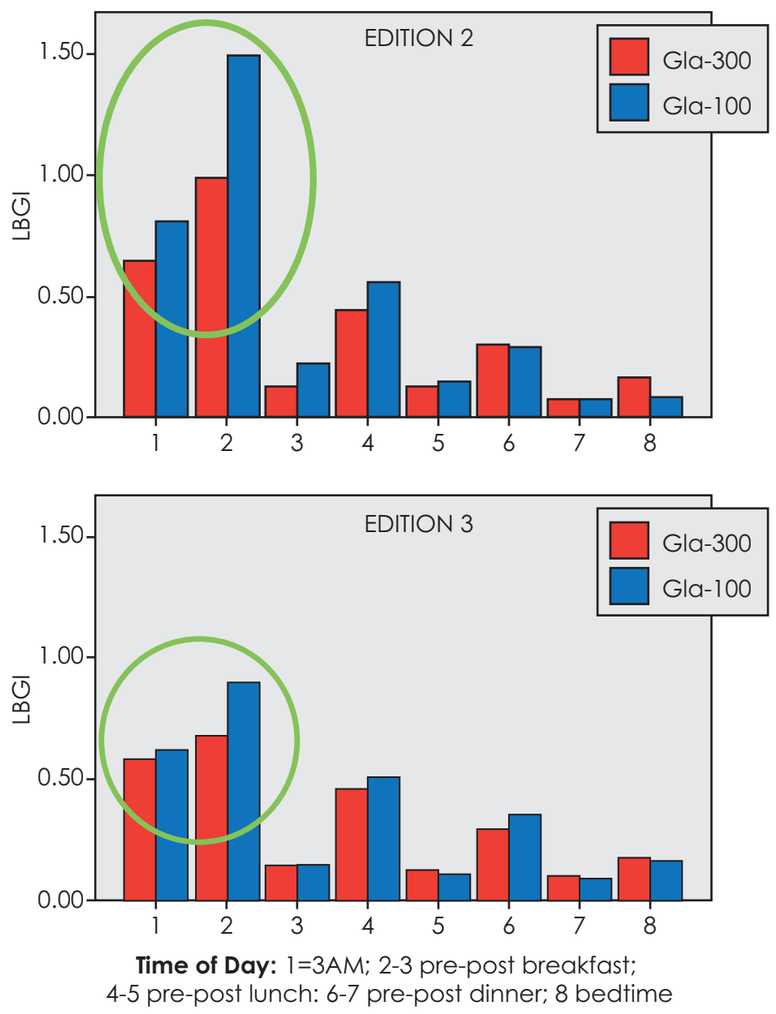
RESULTS

RISK COMPARISON OF GLA-300 VS. GLA-100

The LBGI and night time LBGI were lower on Gla-300 compared to Gla-100. These differences were evident throughout both studies, and more apparent during the titration phases. The largest differences were observed in night time:

Risk Index	EDITION 2		EDITION 3	
LBGI	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**
Titration	0.333	0.507	0.241	0.300
Maintenance	0.410	0.498	0.376	0.410
P-value	0.002		0.090	
Night LBGI	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**
Titration	0.707	1.292	0.496	0.593
Maintenance	0.987	1.241	0.731	0.924
P-value	<0.001		0.020	

The daily profiles of risk for hypoglycaemia are presented below:



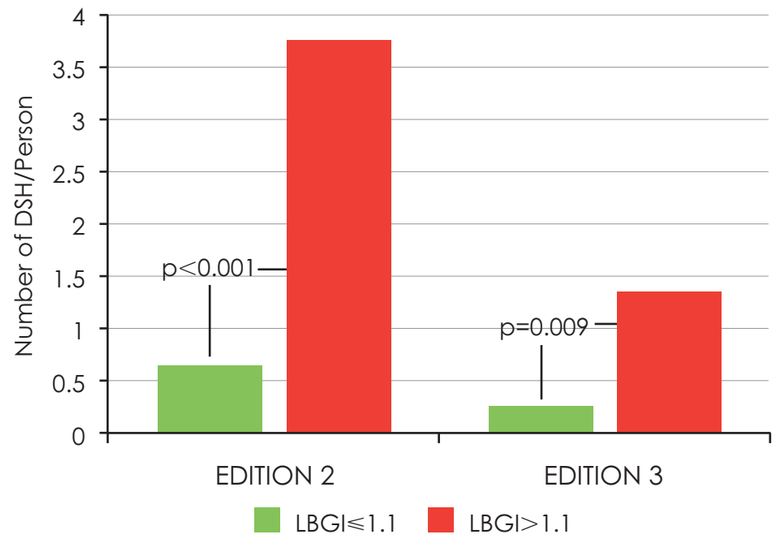
Time of Day: 1=3AM; 2-3 pre-post breakfast; 4-5 pre-post lunch: 6-7 pre-post dinner; 8 bedtime

IDENTIFYING SUBJECTS AT RISK FOR HYPOGLYCAEMIA

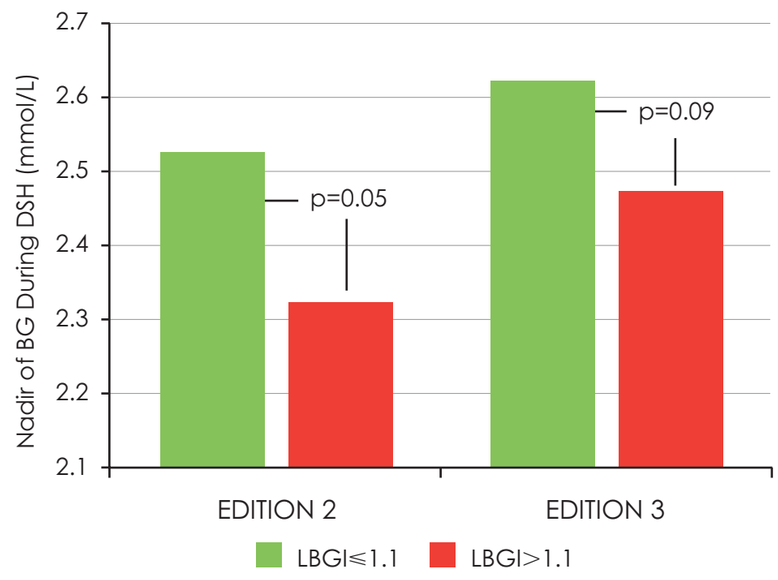
In both studies, the LBGI correlated with the observed number of documented hypoglycaemic episodes:

Correlation	EDITION 2	EDITION 3
LBGI with #DSH episodes/patient	r=0.35 p<0.001	r=0.26 p<0.001

Participants who were at moderate risk (defined as LBGI > 1.1) experienced several-fold more frequent DSH than those at minimal risk (LBGI ⩽ 1.1):



Participants who were at moderate risk (defined as LBGI > 1.1) experienced lower nadir of blood glucose during DHS than those at minimal risk (LBGI ⩽ 1.1):



SUMMARY

- For both Gla-300 and Gla-100, GV decreases over the course of treatment and is higher during the titration period.
- Among several other traditional metrics of GV tested in this reanalysis, the coefficient of variation (CV) was the only measure that detected a difference between Gla-300 and Gla-100; but, this was observed only in the EDITION 2 study and the result was not confirmed by EDITION 3.
- The most consistent difference between treatments was lower risk for (and frequency of) nocturnal hypoglycaemia on Gla-300 compared with Gla-100. This difference was substantial and was evident throughout both EDITION 2 and EDITION 3 trials.
- Out of all GV measures tested, the LBGI was the best predictor of hypoglycaemia – it correlated with the observed number of documented hypoglycaemic episodes.
- LBGI > 1.1 identified patients who reported higher frequency of DHS. These patients report several-fold higher incidence of hypoglycaemia compared to the rest of the population, in both EDITION 2 and EDITION 3 studies.

CONCLUSION

- The Low Blood Glucose Index, a risk-based metric of glucose variability in the hypoglycaemic range, demonstrated statistically significant glucose variability and hypoglycaemia risk reductions on Gla-300 compared with Gla-100.
- These risk differences were most prominent overnight and were consistent across the titration and maintenance periods for both EDITION 2 and EDITION 3 studies.

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DISCLOSURES

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