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Hypoglycemia risk associated with basal insulin use in type 2 diabetes (T2DM): the LIGHTNING study

Luigi Meneghini[1], Fang Liz Zhou[2], Zsolt Bosnyak[3], Rachele Berria[2], Javier Jimenez[2], Timothy Bailey[4]

[1]University of Texas Southwestern Medical Center, Dallas, USA; [2]Sanofi, Bridgewater, USA; [3]Sanofi, Paris, France; [4]AMCR Institute, Escondido, USA

INTRODUCTION

- There is growing interest in the use of real-world evidence to support clinical decision making, which has increased the use of data sources other than randomized controlled trials (RCTs).[1]
- This approach recognizes that while RCTs provide a gold standard for testing treatment hypotheses, generalizing the findings to larger, more diverse, populations can be difficult.[2]
- Two second-generation basal insulin (BI) analogs, insulin glargine 300 U/mL (Gla-300) and insulin degludec (IDeg), have a smoother action profile and a lower risk of hypoglycemia compared with first-generation BI analogs.[3]
- However, the outcomes of switching from BI analogs to Gla-300 or IDeg in routine real-world clinical practice settings require further investigation.

OBJECTIVE

The LIGHTNING study utilized real-world electronic health record (EHR) data, representative of the general population and real-life practice, to assess hypoglycemia rates in patients with T2DM prescribed first- (glargine 100 U/mL [Gla-100], detemir [IDet]) or second-generation (IDeg, Gla-300) BI analogs. This preliminary analysis focuses on patients switching BIs, to validate findings from previous real-world Gla-300 studies.

METHODS

- **Data source:** LIGHTNING used the Humedica database (www.optum.com), which includes >5 million people with diabetes and >10 years of longitudinal data.
- Humedica combines data from more than 50 US healthcare systems, and includes more than 700 hospitals and 7000 clinics.
  - LIGHTNING included all data collected from January 1, 2007 to March 31, 2017.
- **Study population:**
  - Inclusion criteria
    - Confirmed diagnosis of T2DM (presence of ≥1 International Classification of Diseases [ICD]-9 or 10 diagnosis codes [ICD-9: 250.x0; 250.x2; ICD-10: E11] or ≥1 prescriptions for an antihyperglycemic drug any time during the study window).
    - Age ≥18 years at the time of first known prescription of a BI in EHR database.
  - Exclusion criteria
    - Likely predominant diagnosis of type 1 diabetes (T1DM) at any time during the study window.
    - Individuals with >10 BI switches within the study window were excluded as they likely represent unusual clinical behavior.
- **Study design:**
  - The unit of analysis was "patient-treatment", the period on which a patient was on a particular kind of BI treatment (e.g. the period between a treatment index and a treatment end). Hypoglycemic events were to be counted only within the patient-treatment period.
  - Treatment index date was defined as the date of the very first prescription of BI, or the change of prescription from one BI to another.
  - Treatment end was defined as the earliest occurring of the following three options: the end of follow-up period in the dataset (December 31, 2016), the change of prescription from the index BI to another, or 1 year after treatment index date.
  - "Duration" for determining hypoglycemia rates was taken to be the duration of the patient-treatment period minus that of all inpatient stays during this period (as admission often results in a switch to an institution-preferred BI).
  - This preliminary analysis included data collected between April 1, 2015 and December 31, 2016, and individuals who switched to the following BI treatments: Gla-300, Gla-100, IDet, and IDeg.
- **Target outcomes:**
  - Severe hypoglycemia was defined as hypoglycemic events (ICD-9 or 10 code identified or plasma glucose ≤70 mg/dL) related to inpatient or emergency department encounter.
  - HbA_{1c} change was defined as change from baseline to 76–180 days' follow-up, for the subgroup of patients with HbA_{1c} in both time windows.
- **Statistical analysis:**
  - Propensity score matching (PSM), using variables including those shown in **Table 1** and the index date, was used to match cohorts for potentially confounding characteristics, allowing for between-treatment comparison.

RESULTS

- **Study population:**
  - The dataset includes 779,813 people with T2DM receiving BI (**Figure 1**).
  - A total of 130,155 BI treatments complied with inclusion/exclusion criteria (**Figure 1**). This number represents both new BI starts and switches from one BI to another. The rest of our analysis will focus only on patient-treatments representing a switch from one BI to another.

Figure 1: LIGHTNING study population – patient selection

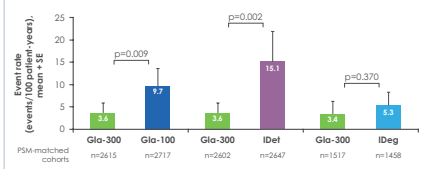
Patient numbers	
Individuals in Humedica database	74,389,932
Individuals with T2DM	4,978,173
Individuals with T2DM receiving BI	779,813
Number of patient-treatments	
BI treated T2DM	1,050,697
Using Gla-100, IDet, IDeg or Gla-300	930,869

	Gla-300	Gla-100	IDet	IDeg	Total
No co-prescriptions on index date	12,070	628,733	215,005	11,454	867,262
Participant age ≥18 years at first known prescription of BI	12,061	624,871	214,198	11,421	862,551
<10 BI switches within study window	11,582	613,523	210,886	11,359	847,350
Started after April 1, 2015	11,577	145,344	76,005	11,358	244,284
Without multiple BIs[a]	10,687	140,292	71,573	10,560	232,112
No inactivity >270 days in the 365 days prior to index date[a]	9680	95,761	52,388	9756	167,585
With baseline HbA_{1c} values	7053	73,997	40,700	8405	130,155

[a]Multiple treatments defined as those that have another treatment start within 1 week (before or after) of specified basal insulin start; [b]Inactivity defined as the lack of any time-stamped data.
BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; IDet, insulin detemir

- **Baseline characteristics:**
  - After PSM, most baseline characteristics were similar across BI treatment groups (**Table 1**) with the exception of the following: Years since diabetes diagnosis: Gla-100 vs Gla-300 and IDet vs Gla-300, both p≤0.05; insulin experience: IDeg vs Gla-300, p<0.01; CV heart failure: IDeg vs Gla-300, p=0.01; CV abnormal heart rhythm: Gla-100 vs Gla-300, p=0.04.
  - However, the statistical differences in baseline characteristics may reflect the large sample size as the actual differences are very small and unlikely to be clinically relevant.
  - Time (days) from the beginning of the study period to treatment index dates was similar: Gla-300 349.2 vs Gla-100 353.5, p=0.13; Gla-300 348.7 vs IDet 349.6, p=0.75; Gla-300 440.0 vs IDeg 438.6, p=0.54.
- **Severe hypoglycemia:**
  - Severe hypoglycemia rates were significantly lower in patients switching from any BI to Gla-300 vs those switching to Gla-100 (p=0.009) or IDet (p=0.002), and comparable vs those switching to IDeg (p=0.370) (**Figure 2**). Rates for Gla-300 were consistent regardless of the comparator treatment (~3–4 events/100 patient-years).

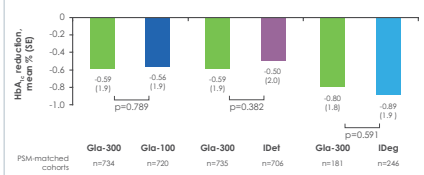
Figure 2: Comparing rates of severe hypoglycemia following a switch to either Gla-300 or comparator BI



BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; IDet, insulin detemir; PSM, propensity score matching; SE, standard error

- **HbA_{1c} reduction:**
  - HbA_{1c} reductions were similar in all three comparison groups (0.50 % to 0.89 %), with no statistically significant between-group differences (**Figure 3**).

Figure 3: HbA_{1c} reduction following a switch to either Gla-300 or comparator BI



BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; IDet, insulin detemir; PSM, propensity score matching; SE, standard error

DISCUSSION

- LIGHTNING indicates that switching to Gla-300 is associated with significantly lower rates of severe hypoglycemia versus IDet and Gla-100, while maintaining comparable HbA_{1c} reductions.
- Switching to Gla-300 was comparable to IDeg in terms of both severe hypoglycemia rates and glycemic control.
- These findings are in line with DELIVER D, a retrospective study utilizing EHR from the Predictive Health Intelligence Environment database that assesses clinical outcomes when switching from Gla-100 to Gla-300 or IDeg.[4] LIGHTNING, however, includes a much larger real-world population.
- The limitations of this preliminary analysis include the following:
  - Previous BI dose and the reason for switching to a different BI may have been a potential confounder, however, this information is not available in the EHR database.
  - Currently, baseline characteristics are only available for the whole cohort after PSM, not specifically those who switched BIs.
  - Sample size for the Gla-300 v IDeg HbA_{1c} comparison is small.

CONCLUSIONS

- **LIGHTNING indicates significantly lower rates of severe hypoglycemia for Gla-300 vs first-generation BIs and comparable rates vs IDeg, without compromising HbA_{1c} reduction, in patients with T2DM switching from any previous BI.**
- **Results are consistent with previous RCTs and other real-world analyses of Gla-300.**

Table 1: Baseline characteristics after propensity score matching (PSM)

	Gla-100 vs Gla-300		IDet vs Gla-300		IDeg vs Gla-300	
BI cohort	Gla-300	Gla-100	Gla-300	IDet	Gla-300	IDeg
Patient-treatments, N	7044	7044	7020	7020	4228	4228
Age, years	60.6 (12.3)	60.6 (13.1)	60.6 (12.4)	60.6 (13.2)	60.0 (12.6)	59.7 (12.3)
Gender, male, %	51	50	51	51	50	50
Years since diabetes diagnosis in database	4.4 (2.4)	4.4 (2.6)	4.3 (2.4)	4.4 (2.6)	4.5 (2.5)	4.5 (2.5)
Insulin experience, AU	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)
Non-compliance proxy, %	25	26	25	26	30	31
Coprescription: GLP-1 RA, %	23	22	23	22	24	24
Most recent HbA_{1c}, %-unit	9.1 (2.0)	9.1 (2.1)	9.1 (2.0)	9.1 (2.2)	9.2 (2.0)	9.2 (1.9)
Severe hypoglycemia (prior 12 months), events PHPY	10.5 (52.1)	9.3 (44.4)	10.5 (52.2)	10.2 (44.1)	12.7 (61.9)	14.1 (59.6)
Comorbidities, %						
CV heart failure	8	7	8	7	9	9
CV abnormal heart rhythm	13	12	13	12	14	14
CV other	17	17	17	16	21	20
Cancer	7	7	7	7	8	8
Chronic renal disease	28	27	28	26	32	31
Diabetic neuropathy	28	29	28	28	32	31
Thyroid disease	19	18	19	19	22	22

Data are mean (SD) unless otherwise stated. Insulin experience is a measure of "insulin memory" of a patient (value between 0 and 1); it has a value of 1 with an insulin prescription and starts to decay 90 days after prescription, with a half-life of 30 days, resetting to 1 upon new prescription. Non-compliance defined as the time interval between subsequent basal insulin prescriptions being greater than 120 days within 1 year prior to index date. AU, arbitrary unit; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDeg, insulin degludec; IDet, insulin detemir; PHPY, per 100 patient-years; PSM, propensity score matching

Disclosures: The data were presented previously at the 15th Annual World Congress Insulin Resistance Diabetes & Cardiovascular Disease (WCIRDC), November 30 – December 2, 2017, Los Angeles, CA, USA
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Contact details: Luigi Meneghini, University of Texas Southwestern Medical Center, Dallas, USA; Luigi.Meneghini@UTSouthwestern.edu

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