REAL-WORLD EVIDENCE DEMONSTRATES COMPARABLE CLINICAL OUTCOMES OF SWITCHING FROM INSULIN GLARGINE 100 U/ML (GLA-100) TO INSULIN GLARGINE 300 U/ML (GLA-300) VS INSULIN DEGLUDEC (IDEG) IN PATIENTS WITH TYPE 2 DIABETES (T2D)

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ABSTRACT

Background: This study compared clinical outcomes of T2D patients switched from using Gla-100 to Gla-300 or IDeg in a real-world clinical setting.

Methods: This retrospective, observational study used electronic medical records (EMRs) from the Predictive Health Intelligence Environment database. Inclusion criteria: adults with T2D; switched to Gla-300 or IDeg from using Gla-100 during 6 months before the switch (index date: first switch between 03/01/2015-12/31/2016); active in EMR for ≥12 months prior to index date and followed for 6 months after; A1C measures during 6 months before switching (Gla-300, n=2,893; IDeg, n=853). Gla-300 and IDeg switchers were propensity score matched 1:1 on baseline characteristics. Endpoints were A1C change, hypoglycemia (ICD-9/ICD-10 and/or plasma-glucose level ≤70 mg/dL) incidence, and event rate (all hypoglycemia and hypoglycemia associated with hospitalization/emergency department service [hospitalization/ED-related]) during follow-up. A1C change was analyzed in a patient subgroup with A1C measures at both baseline and 3-6 months' follow-up in the matched cohorts.

Results: During follow-up, switching to Gla-300 (n=810) and IDeg (n=810) showed comparable hypoglycemia incidence (all: 11.9% vs 12.7%, respectively, *P*=0.45; hospitalization/ED-related: 4.4% vs 3.8%, respectively, *P*=0.80). Adjusted for baseline hypoglycemia, Gla-300 and IDeg showed similar hypoglycemia event rate during follow-up (all: *P*=0.88; hospitalization/ED-related: *P*=0.82). A1C decreased significantly from 8.95% to 8.46% for Gla-300 (n=364) and from 8.98% to 8.49% for IDeg (n=370) (both cohorts: *P*<0.01) during follow-up (comparable A1C reduction in both groups, *P*=0.97).

Conclusion: In a real-world setting, T2D patients on Gla-100 switching to Gla-300 or IDeg showed comparable glycemic control, hypoglycemia incidence, and hypoglycemia event rate.

INTRODUCTION

- Patients with type 2 diabetes (T2D) that are uncontrolled on metformin-only or on metformin plus additional oral antidiabetes drugs (OADs) may initiate basal insulin therapy according to the 2017 recommendations from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE).[1,2]
- Two new second-generation basal insulins, Gla-300 and IDeg, have recently been approved; these have a smoother action profile and a reduced risk of hypoglycemia compared with first-generation basal insulins.[3-5]
- Insulin glargine 300 U/mL (Gla-300) became available in the US in February 2015. The EDITION randomized controlled trial (RCT) program demonstrated that the use of Gla-300 leads to glycemic control comparable with that of insulin glargine 100 U/mL (Gla-100), with less hypoglycemia, in a wide range of T2D patients.[6]
- Insulin degludec (IDeg) became available in the US in September 2015; the BEGIN RCT program showed that a lower rate of nocturnal confirmed hypoglycemia was seen in T2D patients treated with IDeg compared with Gla-100.[4]
- The interest in comparative effectiveness research, and a growing demand for real-world data to support decision making, has increased the use of data sources other than RCTs.[7]
- The outcomes of switching from basal insulin to Gla-300 compared with switching to IDeg in routine real-world clinical practice settings have not been well characterized.

OBJECTIVE

- To evaluate clinical outcomes in patients with T2D using Gla-100 who switched to either Gla-300 or IDeg in real-world clinical practice.

METHODS

Study Design

- The Differentiate Gla-300 clinical and Economic in reaL-world Via EMR data with IDeg study (DELIVER D) is a retrospective cohort study.
- Data were collected from the Predictive Health Intelligence Environment (PHIE) database (IBM Explorys data) of electronic medical records (EMRs) representing 39 integrated health delivery networks.
- Patients were selected based on the inclusion and exclusion criteria defined in the study protocol; data analysis was conducted according to a statistical analysis plan.

Patient Selection

- All patients with ≥ 1 diagnosis record of T2D in the database at any time were identified by ICD-9-CM/ICD-10-CM codes.[8]
- Patients had initiated either Gla-300 or IDeg (100 U/mL or 200 U/mL); the index date was the first prescription date during the period March 1, 2015 to December 31, 2016.
- Patients had ≥ 1 Gla-100 prescription within 6 months before the index date (6-month baseline period); they must not have had any other basal insulin prescriptions within this period.
- Patients must have had records in the EMR 12 months prior to the index date (12-month baseline period) and at least 6 months after the index date (follow-up).
- Patients were age ≥ 18 years on the index date.
- All patients had ≥ 1 measurement of glycated hemoglobin A_{1c} (A1C) level recorded during the 6-month baseline period.
- Patients with type 1 diabetes or using > 1 basal insulin on the index date were excluded.

Propensity Score Matching

- Patients switching to Gla-300 and to IDeg were matched at a 1:1 ratio on a propensity score based on baseline demographics and clinical characteristics.[9]
- Baseline patient characteristics used in the matching process were:
  - demographics (age, gender, race, insurance type, geographic region)
  - clinical characteristics 12 months prior to the index date (body mass index [BMI], Charlson comorbidity index [CCI] score, prevalence of comorbidities, concomitant medication use)
  - clinical characteristics within the 6-month baseline period (A1C level, hypoglycemia, incidence of all-cause health care utilization)
- Statistical tests (χ^2 test /2-sample Student t-test) were performed, and standardized mean difference (SMD) was calculated, to assess any imbalance before and after matching on individual baseline characteristics.

Outcome Assessments

- The study endpoints included:
  - in the matched cohorts:
    - hypoglycemia (identified by ICD-9-CM/ICD-10-CM code and/or plasma glucose level ≤ 70 mg/dL) incidence and event rate (events/per patient per year [PPPY], adjusted for baseline hypoglycemia event) during the 6-month follow-up period
  - in a subgroup of patients in the matched cohorts with A1C measurements at both the 6-month baseline and 3-6 months' follow-up:
    - A1C change: A1C level reduction from baseline (closest to index date) to follow-up (latest available value during the follow-up period)
    - A1C goal attainment: the proportion of patients reaching a prespecified A1C target < 7.0% (53 mmol/mol) and < 8.0% (64 mmol/mol) during a 3-6 month follow-up period

Statistical Analysis

- Differences between baseline and follow-up hypoglycemia incidence were tested by McNemar's tests within each cohort; adjusted odds ratios (aORs) (adjusted for baseline hypoglycemia incidence) were calculated for follow-up hypoglycemia incidence to compare risks between the 2 cohorts.
- Adjusted mean and least-squares means (LSM) difference were calculated for follow-up hypoglycemia event rates in the 2 cohorts controlled for baseline hypoglycemia event.
- Differences between baseline and follow-up A1C were tested by paired Student t-tests within each cohort, and A1C change from baseline to follow-up was compared between Gla-300 and IDeg cohorts by a 2-sample Student t-test.

RESULTS

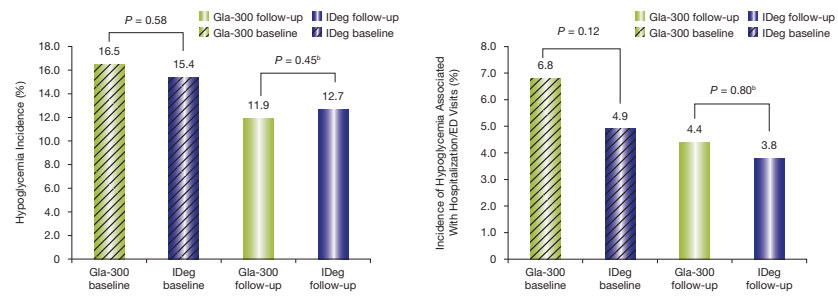
Patient Selection and Matching

- The final cohort consisted of 2,893 patients using Gla-100 who switched to Gla-300 and 853 who switched to IDeg (**Figure 1**); the population differed significantly on demographics (e.g. age, race, insurance type) and on a few clinical characteristics (e.g. nephropathy comorbidity).
- After matching, each cohort comprised 810 patients; all baseline characteristics (except the percentages of other race) had an SMD < 0.1, demonstrating balance in baseline values between the treatment groups (see **Table**).
- In the matched cohorts, 364 and 370 patients in the Gla-300 and IDeg cohorts, respectively, had A1C measurements at both the 6-month baseline and after 3-6 months of follow-up; these patients were included in the analysis of A1C change and goal attainment.

Patient Baseline Characteristics

- In the matched cohorts, 47.4% and 47.3% of patients in the Gla-300 and IDeg cohorts, respectively, were male; mean age was 58 years.
- In the IDeg cohort, 404 (49.9%) and 293 (36.2%) patients used 100 U/mL and 200 U/mL formulations, respectively; the remaining 113 (13.9%) patients used formulation of unknown strength.
- The mean number of OADs was 1.1 in both cohorts; approximately 15% of Gla-300 and IDeg switchers used a glucagon-like peptide-1 receptor agonist; 14% used sodium glucose co-transporter 2 inhibitors.
- The mean CCI scores were similar in the 2 cohorts: 1.19 and 1.22 in the Gla-300 cohort and IDeg cohorts, respectively.
- Patients in both cohorts had a high A1C level at the 6-month baseline: 9.15% and 9.13% in the Gla-300 cohort and IDeg cohorts, respectively.
- Hypoglycemia incidence during the 6-month baseline period was 16.5% and 15.4% in the Gla-300 cohort and IDeg cohorts, respectively.

Figure 2. Hypoglycemia During the 6-Month Follow-Up Period.



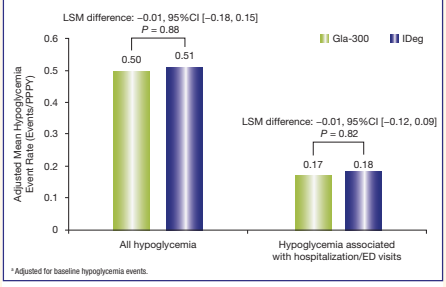
[a] Incidence reduction from baseline to follow-up: Gla-300, *P* < 0.01; IDeg, *P* = 0.05. [b] Adjusted for baseline hypoglycemia incidence. [c] Incidence reduction from baseline to follow-up: Gla-300, *P* = 0.02; IDeg, *P* = 0.23.

Table. Baseline Patient Characteristics Before and After Propensity Score Matching (Key Variables).

	Before Matching				After Matching			
	Gla-300 Switchers (n = 2,893)	IDeg Switchers (n = 853)	*P* Value	SMD	Gla-300 Switchers (n = 810)	IDeg Switchers (n = 810)	*P* Value	SMD
Age, mean (SD), years	58.8 (12.2)	57.8 (12.4)	0.03	0.09	58.2 (12.2)	57.8 (12.5)	0.57	0.03
Gender, male, n (%)	1,468 (50.7)	395 (46.3)	0.11	0.09	384 (47.4)	383 (47.3)	0.97	< 0.01
Race, n (%)								
African American	502 (17.4)	113 (13.3)	0.01	0.11	122 (15.1)	110 (13.6)	0.43	0.04
Caucasian	2,117 (73.2)	654 (76.7)	0.30	0.08	610 (75.3)	616 (76.1)	0.86	0.02
Other (multiracial, Native American or Alaskan Native, other)	123 (4.3)	56 (6.6)	0.01	0.10	36 (4.4)	55 (6.8)	0.05	0.10
Unknown	151 (5.2)	30 (3.5)	0.05	0.08	42 (5.2)	29 (3.6)	0.12	0.08
Insurance type, n (%)								
Commercial	1,054 (36.4)	352 (41.3)	0.04	0.10	304 (37.5)	340 (42.0)	0.16	0.09
Medicaid	265 (9.2)	51 (6.0)	< 0.01	0.12	50 (6.2)	48 (5.9)	0.84	0.01
Medicare	893 (30.9)	215 (25.2)	0.01	0.13	220 (27.2)	206 (25.4)	0.50	0.04
Others (military, workers' compensation, other public)	145 (5.0)	43 (5.0)	0.97	0.00	34 (4.2)	41 (5.1)	0.42	0.04
Unknown	536 (18.5)	192 (22.5)	0.02	0.10	202 (24.9)	175 (21.6)	0.16	0.08
Baseline A1C, mean (SD), %	9.09 (1.91)	9.13 (1.89)	0.63	0.02	9.15 (1.83)	9.13 (1.90)	0.79	0.01
Baseline BMI, mean (SD), kg/m²	35.3 (7.4)	34.7 (7.6)	0.07	0.07	34.9 (7.4)	34.7 (7.6)	0.45	0.04
Number of baseline OADs, mean (SD)	1.2 (0.8)	1.1 (0.8)	0.45	0.04	1.1 (0.8)	1.1 (0.8)	0.81	0.02
Baseline treatments, n (%)								
GLP-1 RA	507 (17.5)	128 (15.0)	0.12	0.07	124 (15.3)	120 (14.8)	0.80	0.01
RAI	1,569 (54.2)	477 (55.9)	0.56	0.03	459 (56.7)	455 (56.2)	0.89	0.01
OADs	1,927 (66.6)	541 (63.4)	0.31	0.07	510 (63.0)	511 (63.1)	0.98	< 0.01
CCI score, mean (SD)	1.2 (1.6)	1.2 (1.7)	0.35	0.04	1.2 (1.7)	1.2 (1.7)	0.69	0.02
Comorbidities and/or diabetic complications, n (%)								
Hypertension	2,383 (82.4)	675 (79.1)	0.36	0.08	645 (79.6)	635 (78.4)	0.78	0.03
Hyperlipidemia	2,357 (81.5)	689 (80.8)	0.84	0.02	638 (78.8)	656 (81.0)	0.62	0.06
Neuropathy	828 (28.6)	271 (31.8)	0.14	0.07	238 (29.4)	253 (31.2)	0.50	0.04
Nephropathy	223 (7.7)	101 (11.8)	< 0.01	0.14	87 (10.7)	82 (10.1)	0.70	0.02
Retinopathy	311 (10.8)	106 (12.4)	0.20	0.05	98 (12.1)	100 (12.4)	0.89	0.01
Obesity	1,214 (42.0)	356 (41.7)	0.93	< 0.01	330 (40.7)	332 (41.0)	0.94	0.01
Depression	549 (19.0)	158 (18.5)	0.79	0.01	153 (18.9)	147 (18.2)	0.73	0.02
Patients with hypoglycemia events within 6 months prior to switch, n (%)	463 (16.0)	133 (15.6)	0.79	0.01	134 (16.5)	125 (15.4)	0.58	0.03
All-cause health care utilization within 6 months prior to switch, n (%)								
Patients requiring hospitalization	470 (16.3)	129 (15.1)	0.47	0.03	142 (17.5)	123 (15.2)	0.24	0.06
Patients requiring ED service	760 (26.3)	243 (28.5)	0.27	0.05	221 (27.3)	231 (28.5)	0.64	0.03
Patients requiring endocrinological outpatient service	527 (18.2)	175 (20.5)	0.17	0.06	164 (20.3)	162 (20.0)	0.91	0.01

ED, emergency department; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RAI, rapid acting insulin; SD, standard deviation.

Figure 3. Adjusted Mean Hypoglycemia Event Rate (Events/PPPY).[a]

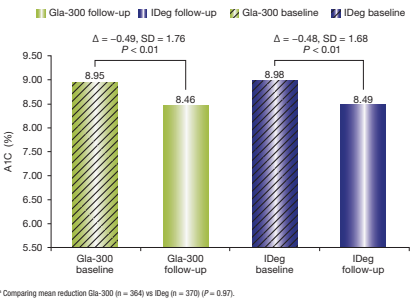


[a] Adjusted for baseline hypoglycemia events.

Hypoglycemia

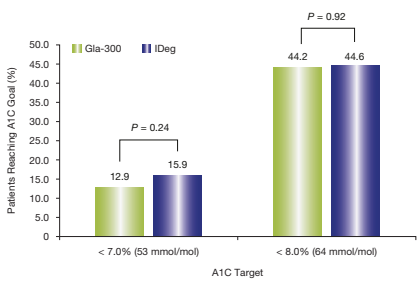
- In both Gla-300 and IDeg switcher cohorts, incidence of hypoglycemia decreased after switching:
  - in the Gla-300 cohort, this decreased from 16.5% at baseline to 11.9% during the follow-up period (*P* < 0.01) (**Figure 2A**)
  - in the IDeg cohort, this decreased from 15.4% at baseline to 12.7% during the follow-up period (*P* = 0.05) (**Figure 2A**)
- During the 6-month follow-up period, a comparable proportion of patients switching to Gla-300 experienced hypoglycemia compared with those switching to IDeg (aOR 0.89, 95% confidence interval [CI] [0.65, 1.21]; *P* = 0.45) controlled for baseline hypoglycemia incidence (**Figure 2A**).
- After adjusting for baseline hypoglycemia, Gla-300 and IDeg switchers showed comparable hypoglycemia event rates during the 6-month follow-up period; adjusted mean was 0.50 events/PPPY and 0.51 events/PPPY for Gla-300 and IDeg, respectively; LSM difference −0.01 events/PPPY, 95% CI [−0.18, 0.15]; *P* = 0.88 (**Figure 3**).

Figure 4. Change in A1C From Baseline to Follow-Up.[a]



[a] Comparing mean reduction Gla-300 (n = 364) vs IDeg (n = 370) (*P* = 0.97).

Figure 5. A1C Goal Attainment.



- Gla-300 and IDeg switchers also showed reduced incidence from baseline to follow-up for hypoglycemia associated with hospitalization or ED visits; in Gla-300 switchers, this decreased from 6.8% at baseline to 4.4% at follow-up (*P* = 0.02); in IDeg switchers, this decreased from 4.9% at baseline to 3.8% at follow-up (*P* = 0.23) (**Figure 2B**).
- The incidence and event rate of hypoglycemia associated with hospitalization or ED visits during the 6-month follow-up period were also comparable between the 2 cohorts: aOR = 1.07, 95% CI [0.64, 1.77], *P* = 0.80; LSM difference in event rate −0.01 events/PPPY, 95% CI [−0.12, 0.09], *P* = 0.82 (**Figures 2B** and **3**).

A1C Change

- Mean baseline A1C was 8.95% in the Gla-300 cohort (n = 364) and 8.98% in the IDeg cohort (n = 370), and A1C levels decreased significantly to 8.46% and 8.49%, respectively, during 3-6 months of follow-up (*P* < 0.01 for both) (**Figure 4**).
- A1C reductions were comparable in both cohorts (0.49% for Gla-300 vs 0.48% for IDeg; *P* = 0.97).

A1C Goal Attainment

- Patients on Gla-300 and those on IDeg were equally likely to attain A1C < 7.0% (12.9% vs 15.9%, respectively; *P* = 0.24) and A1C < 8.0% (44.2% vs 44.6%, respectively; *P* = 0.92) during 3-6 months' follow-up (**Figure 5**).

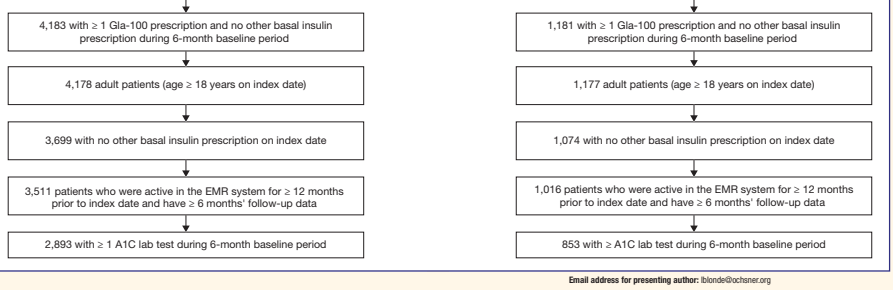
STRENGTHS AND LIMITATIONS

- To our knowledge, this is the first study to compare the 2 novel second-generation basal insulins, Gla-300 and IDeg, with matched cohorts in a real-world setting; the patients included in this study represent a real-life US population.
- Although head-to-head RCTs are still ongoing, this study provides a first insight into clinical effectiveness of the new basal insulins.
- While the findings represent actual treatment-use patterns and outcomes outside the confines of clinical trials, several limitations should be noted:
  - PHIE EMR data mostly came from northwest and southern states, thus might not be representative of US national landscape; patients included in the study were early users of second-generation basal insulins, therefore their demographics and clinical characteristics might be different from basal insulin experienced patients in general
  - hypoglycemia may have been underreported in the study, as only the clinically significant events were likely to be captured (i.e. there were no self-monitoring-blood-glucose or continuous-blood-glucose-monitoring data)
  - switching treatment regimen can be a complex decision, with both clinical and socioeconomic considerations; EMR data may not reveal the reason why patients switched basal insulins
  - EMR data capture medication prescription, not dispensing or consumption; the prescription information may not reflect the actual drug use in real life
  - dosage data were missing in a high percentage of the EMRs; dose information could, therefore, not be addressed in this study
  - the follow-up period for this study was relatively short, and patients could switch from basal insulins other than Gla-100 (e.g. insulin detemir) in a real-world clinical setting; comparative effectiveness of Gla-300 and IDeg in a broader patient population or with longer follow-up warrants further research

CONCLUSION

- In this first head-to-head analysis between the two second-generation basal insulin analogs in a real-world setting, switching from Gla-100 to either Gla-300 or IDeg in T2D patients with elevated A1C levels resulted in comparable improvements in glycemia and reduced risk of hypoglycemia.

Figure 1. Patient Selection.



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