



Effectiveness and Safety of Insulin Glargine 300 U/ml in Comparison with Insulin Degludec 100 U/ml Evaluated with Continuous Glucose Monitoring in Adults with Type 1 Diabetes and Suboptimal Glycemic Control in Routine Clinical Practice: The OneCARE Study

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ABSTRACT

Introduction: Data regarding efficacy of second-generation basal insulins (BI) using continuous glucose monitoring (CGM) come from clinical trials. We evaluated the effectiveness of insulin glargine 300 U/ml (Gla-300) compared to insulin degludec 100 U/ml (IDeg-100) in

terms of percentage of time in range (TIR); 70–180 mg/dl was obtained from CGM in sub-optimally controlled patients with type 1 diabetes (T1D) in routine clinical practice.

Methods: This observational, multicenter, cross-sectional study included patients with T1D (> 3 years diabetes duration, HbA_{1c} ≥ 7.5%) who had switched from first-generation BI to Gla-300/IDeg-100 within the past 24 months according to physician discretion. Clinical and laboratory data were obtained from

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clinical records and during study visit, and CGM data were collected prior to the visit.

Results: One hundred ninety-nine people with T1D were included [42.6 ± 13.4 (mean \pm SD) years, 18.4 ± 10.4 years diabetes duration]; 104 received Gla-300, 95 IDeg-100. TIR 70–180 throughout whole day was similar in both groups, 52.4 ± 14.0 vs. $49.3 \pm 13.9\%$ Gla-300/IDeg-100, respectively. At night, TIR 70–180 and TIR 70–140 were significantly higher in the Gla-300 group compared to the IDeg-100 (52.4 vs. 46.2 and 31.8 vs. 26.9% , respectively, $p = 0.0209$ and $p = 0.0182$), and time above range (180) was significantly lower in the Gla-300 group (40.1% vs. 47.2% , $p = 0.0199$). Additional CGM glucometric data were comparable in both groups. Patient treatment satisfaction score assessed through the Diabetes Treatment Satisfaction Questionnaire (DTSQ) was high and similar for both insulins.

Conclusion: This real-world study shows the effectiveness and safety of Gla-300 are more similar to than different from IDeg-100, with a slightly better nocturnal glucose profile, in sub-optimally controlled T1D patients switching from a first-generation BI.

Keywords: CGM; Gla-300; Glycemic control; T1D

Key Summary Points

Why carry out this study?

Effectiveness of Gla-300 compared to other basal insulins evaluated with continuous glucose monitoring (CGM) is unknown in sub-optimally controlled persons with type 1 diabetes (T1D)

Most of the information available on the efficacy of using new insulins and CGM comes from clinical trials conducted under optimal conditions or in highly selected groups of patients

OneCARE is a real-world study with time in range as primary endpoint

What was learned from the study?

The effectiveness and safety of Gla-300 are more similar to than different from IDeg-100, with a slightly better nocturnal glucose profile, in persons with long-standing sub-optimally controlled T1D switching from first-generation BI in routine clinical practice

Switch from first- to second-generation basal analogs led to a significant reduction in confirmed hypoglycemia and severe hypoglycemia episodes with no significant differences between Gla-300 and IDeg-100

INTRODUCTION

Diabetes mellitus (DM) is one of the leading causes of mortality and major morbidities, including cardiovascular disease (CVD), kidney disease (diabetic nephropathy), amputations and blindness. Such complications can be avoided if blood glucose levels remain close to normal glycemic levels [1]. Hypoglycemia is the complication most frequently associated with the treatment of type 1 diabetes (T1D) and one of the main challenges to achieving treatment goals. Achieving glycemic objectives recommended by scientific societies is accomplished in less than a third of patients with T1D [2]. Use of the second-generation basal insulin analogs [3] with a longer duration of action (up to 24 h), flatter action profiles and less day-to-day variability [4] and the incorporation of technology for monitoring glucose profiles can be an advantage for improving glycemic targets without increasing the risk of hypoglycemia.

There are currently two different second-generation basal insulins: insulin glargine 300 U/ml (Gla-300) and insulin degludec (IDeg). Gla-300 uses subcutaneous precipitation as a retarding principle providing consistent activity and extended duration of action. All these properties provide a more constant and

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prolonged pharmacokinetic and pharmacodynamic profile, > 24 h blood glucose control with less glycemic variability, a lower risk of hypoglycemia and reduction in glycosylated hemoglobin A_{1c} (HbA_{1c}), as observed in clinical trials [5–12] and real-world studies [13–15], versus Gla-100.

IDeg has an ultralong duration of action and a long half-life with a flatter and stable glucose-lowering effect. IDeg's effect is based on the formation of soluble multi-hexamers in subcutaneous tissues. This creates a reservoir from which monomers are released continuously and slowly to be finally absorbed into the blood flow. It has been demonstrated to have a stable pharmacodynamic profile, which leads to lower fluctuations in glucose levels as also observed in clinical trials [16] and real-world studies [17, 18].

Since the beginning of the century, it has been possible to measure glucose concentration using portable and minimally invasive continuous glucose monitoring (CGM) systems for 24 h. Within the different types of CGM, those called interactive or “real-time CGM” can allow patients and healthcare professionals to have access to glucose levels, fluctuations in glucose levels and real-time alerts about impending hypo- or hyperglycemia. There are two types of real-time CGM systems: those that provide glucose information continuously and those that provide the same information intermittently whenever the reading monitor approaches the transmitter (intermittent-like, on demand or “flash”-like). Use of these devices has shown benefits in terms of glycemic control, improving the quality of life and helping to reduce HbA_{1c} and mean glucose in patients with DM [19–22].

Limited evidence is available in the T1D population using CGM and about the comparison between first- and second-generation basal insulins and between the two second-generation basal insulins. A current study conducted by Miura et al. comparing the effects of IDeg and Gla-300 on glycemic stability in T1D patients using CGM concluded that both insulins were comparable in terms of glucose-stabilizing effects [23]. These results were also observed in terms of glycemic control in the type 2 diabetes (T2D) population when

comparing Glar-300 and IDeg using a CGM device [24]. However, most of the evidence on the efficacy of using second-generation basal insulins and CGM comes from clinical trials and real-world studies conducted under optimal conditions or in highly selected groups of patients.

The main objective of the ONECARE study was to describe the effectiveness and safety of Gla-300 versus Degludec 100U (IDeg-100), defined as the percentage of time in range (TIR) (glucose 70–180 mg/dl) during 14 consecutive days within a 4-week period measured using CGM in patients with suboptimally controlled T1D in routine clinical practice in Spain.

METHODS

Study Design

This was an observational, retrospective, cross-sectional, multicenter study conducted in endocrinology departments of 21 hospitals in Spain (Supplementary Material Table S1), including adults with T1D who had switched from a first-generation basal insulin (BI) analog (insulin glargine 100 U/ml or detemir) to a second-generation basal insulin, either Gla-300 or IDeg-100, within 24 months of the study visit. The study comprised two phases (Fig. 1): (1) the period in which patients were treated with basal bolus (BB) insulin (first generation BI) for a minimum of 3 months [patients on intermediate acting (NPH) and premixed insulin were excluded]; (2) the period when the patients, as per physician criteria, switched the BI, within the last 24 months before the study visit, to either Gla-300 or IDeg-100. CGM was performed using the Freestyle Libre[®] CGM system (Abbott Diabetes Care, Witney, UK), and data from 14 consecutive days within the last month were analyzed, the period recommended by international consensus to assess the glycemic profile and enable decision-making in clinical practice [25].

The inclusion criteria were adults diagnosed with T1D at least 3 years prior to study enrollment; switched from ≥ 3 months of treatment with BB insulin treatment (first-generation BI)

(TAR) > 180 mg/dl and > 250 mg/dl; time below range (TBR): < 70 mg/dl and < 54 mg/dl, mean glucose profile over 24-h period, percentage of estimated HbA_{1c}, coefficient of variation (CV), interquartile range (IR), area under the curve (AUC), average daily risk range (ADRR), high blood glucose index (HBGI) and low blood glucose index (LBGI) [29], mean amplitude of glycemic excursions (MAGE) and mean daily difference (MODD) in glucose. A hypoglycemic episode was defined as a period of > 15 min duration below a specific threshold. Likewise, a hyperglycemic episode was defined as a period of > 15 min duration above a specific threshold.

Other secondary endpoints collected through medical data were the percentage of patients with hypoglycemic events in the 12 months before the switch versus events after the switch to study visit, mean HbA_{1c} and fasting plasma glucose (FPG), and number of adverse events. A confirmed hypoglycemia event was defined as an episode of symptomatic or asymptomatic hypoglycemia with plasma glucose < 54 mg/dl or < 70 mg/dl, and a severe hypoglycemia event was defined as an episode of hypoglycemia at any time of the day (24 h) and during the night that requires assistance from another person administering carbohydrates, glucagon, or any other corrective measure.

Statistical Analyses

The sample size of 214 patients (107 patients per group) allowed comparison of TIR 70–180 mg/dl between patients with Gla-300 and those with IDeg-100. A minimum difference of 3.3% was considered (difference between mean percentage of time within a glucose range of 70–180 mg in Gla-300 and other basal insulin of 57.8% and 54.5%, respectively, in the Bergenstal et al. study [5]) with a significance level of 0.05 and a statistical power of 0.80.

The analysis of the primary and some secondary objectives (those related to data obtained from the FreeStyle Libre[®] device) was performed by the HealthPartners Institute,

International Diabetes Center (IDC), in Minnesota. The comparison of results between the two study groups, facilitated by the IDC, was performed using IQVIA Information S.A.

Percentage of time in TIR was compared between groups with Student's *t*-test. The secondary endpoints were tested for significance as intergroup differences of normally or non-normally distributed data with the unpaired Student's *t*-test or Mann-Whitney *U*-test, respectively. A two-sided *p* value of < 0.05 was considered statistically significant for all other analyses. Percent of patients with hypo- and hyperglycemic episodes was compared between groups with the chi-square test, and McNemar's Test was used for the comparison between serious events before and after the treatment.

Continuous variables were described by the number of patients with valid observations, mean and standard deviation (SD). Categorical variables were described by number and percentages of patients per response category.

Statistical analyses were generated using SAS software, version 7.15, Enterprise Guide or above.

RESULTS

Patients and treatment characteristics

A total of 220 participants were included in the study, and 21 were excluded for not having 70% CGM data from the Freestyle Libre[®] device for 14-consecutive days within the last month prior to inclusion in the study. Of the 199 valid patients, 104 (52.3%) switched to Gla-300 and 95 (47.7%) to IDeg-100.

Sociodemographic and clinical characteristics (BMI, height, blood pressure and heart rate) were similar between the two groups, as shown in Table 1 and in the Supplementary Material Table S2. Hypercholesterolemia (23.6%), hypertension (12.1%) and diabetic retinopathy (20.6%) were the most frequent comorbidities observed in both groups, the proportion of patients with retinopathy being statistically higher in the IDeg-100 group than in the Gla-300 group (27.4% vs. 14.4%, *p* = 0.0241). Mean time since T1D diagnosis was 18.4 ± 10.4 years

Table 1 Participant characteristics

	Total N = 199	GLA-300 N = 104	IDEG-100 N = 95	p value
Age years	42.6 ± 13.4	43.5 ± 14.3	41.7 ± 12.3	0.3500
Women, <i>n</i> (%)	100 ± 50.3	46 ± 44.2	54 ± 56.8	0.0755
BMI, kg/m ²	26.0 ± 3.8	26.2 ± 4.0	25.7 ± 3.6	0.4425
Time since T1D diagnosis, years	18.4 ± 10.4	16.8 ± 10.1	20.2 ± 10.5	0.0218
Comorbidities Associated to T1D, <i>n</i> (%)	99.0 ± 49.7	45 ± 43.3	54 ± 56.8	0.0558
Dyslipidemia	47 ± 23.6	23 ± 22.1	24 ± 25.3	0.6015
Hypertension	24 ± 12.1	14 ± 13.5	10 ± 10.5	0.5254
Retinopathy	41 ± 20.6	15 ± 14.4	26 ± 27.4	0.0241
Nephropathy	12 ± 6.0	5 ± 4.8	7 ± 7.4	0.4485
Hypothyroidism	19 ± 9.5	9 ± 8.7	10 ± 10.5	0.6535
Total daily insulin dose, U/kg/day	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.1456
Fast-acting insulin, <i>n</i> (%)				
Lispro (Humalog [®])	51.2 ± 5.6	23 ± 22.1	28 ± 29.5	0.5310
Aspart (Novorapid [®])	106 ± 53.3	56 ± 53.8	50 ± 52.6	
Glulisina (Apidra [®])	36 ± 18.1	22 ± 21.2	14 ± 14.7	
Regular (Actrapid [®] , Humulina regular [®])	6 ± 3.0	3 ± 2.9	3 ± 3.2	
Basal insulin, <i>n</i> (%)				
Detemir (Levemir [®])	18 ± 9.0	7 ± 6.7	11 ± 11.6	0.2758
Glargine 100 U/ml (Lantus [®])	180 ± 90.5	97 ± 93.3	83 ± 87.4	
Glargine 100 U/ml (Abasaglar [®])	1 ± 0.5	0	1 ± 1.1	

Data are mean ± SD unless otherwise stated

BMI: body mass index; T1D, type 1 diabetes

overall, but it was significantly shorter in the Gla-300 group than in the IDeg-100 group: 16.8 ± 10.2 vs. 20.2 ± 10.5 years ($p = 0.0218$), respectively.

No significant differences were observed in the number of months that the patients were on the BI, either Gla-300 or IDeg-100, at the time of the study, with time elapsed between the change in insulin and the study visit being 14.5 ± 6.6 months (14.3 ± 6.6 vs. 14.7 ± 6.6 months for Gla-300 and IDeg-100, respectively; $p = 0.6908$). BI was most often administered in the evening in both study

groups (in 58% of participants before the switch vs. 60% after the switch). There were no significant changes in the daily time schedule of BI administration after changing BI in both groups. The most frequent reasons why physicians decided to change the patient's BI were a suboptimal HbA_{1c} in 52.3% of patients and recurrent hypoglycemia in 49.2%, and no differences were observed between the two groups.

Before the switch, 90.5% of T1D patients were treated with Gla-100, 25.4 ± 12.5 UI/day, 9.0% with Detemir and 0.5% (1 patient) with

Table 2 Glucometric data of patients using either GLA-300 OR IDEG-100

	Total n = 199	Gla-300 n = 104	IDeg-100 n = 95	p value
Mean glucose over 24-h period (mg/dl)	175.1 ± 31.6	171.6 ± 31.6	178.9 ± 31.3	0.1032
Estimated HbA1c (%)	7.7 ± 1.1	7.6 ± 1.1	7.9 ± 1.1	0.1032
TIR (%)				
70–180 mg/dl	50.9 ± 14.0	52.4 ± 14.0	49.3 ± 13.9	0.1191
70–140 mg/dl	30.9 ± 10.7	31.9 ± 11.0	29.7 ± 10.2	> 0.05
TAR (%)				
> 180 mg/dl	42.8 ± 15.9	41.0 ± 16.1	44.8 ± 15.6	0.0935
> 250 mg/dl	16.8 ± 13.4	15.4 ± 13.0	18.2 ± 13.8	0.1453
TBR (%)				
< 54 mg/dl	2.3 ± 3.2	2.5 ± 3.7	2.2 ± 2.7	0.4433
< 70 mg/dl	6.3 ± 5.4	6.6 ± 6.0	5.9 ± 4.7	0.3663
SD (mg/dl)	69.5 ± 15.0	67.8 ± 15.4	71.3 ± 14.4	0.0934
CV of glucose levels (%)	39.9 ± 6.8	39.8 ± 7.1	40.1 ± 6.5	
< 36% (stable)	29.1%	32.7%	25.3%	0.6903
≥ 36% (unstable)	70.9%	67.3%	74.7%	0.2494
AUC (mg/dl) complete day	4098.3 ± 780.7	4008.4 ± 773.8	4196.7 ± 780.5	0.0893
LBGI	1.5 ± 1.4	1.6 ± 1.6	1.4 ± 1.2	0.3076
HBGI	4.6 ± 2.4	4.4 ± 2.4	4.9 ± 2.5	0.1215
ADRR	48.4 ± 11.8	47.4 ± 12.2	49.5 ± 11.3	0.1980
MAGE 24 h (mg/dl)	153.1 ± 33.2	149.4 ± 34.4	157.2 ± 31.6	0.1006
MODD in glucose (mg/dl)	68.4 ± 16.7	66.4 ± 18.0	70.5 ± 14.9	0.0822

Data are mean ± SD unless otherwise stated. Glucometric data analyzed in the full day period

TIR: time in range, *TAR*: time above range, *TBR*: time below range, *SD*: standard deviation, *CV*: coefficient of variation, *AUC*: area under the curve, *LBGI*: low blood glucose Index, *HBGI*: high blood glucose index, *ADRR*: average daily risk range, *MAGE*: mean amplitude of glycemic excursions, *MODD*: mean of daily difference

Gla-100 biosimilar (Abasaglar®). The total daily insulin dose per kilogram body weight was similar between study groups at the time of the study visit (0.7 U/kg/day for Gla-300 vs. 0.6 U/kg/day for IDeg-100; $p = 0.1465$). At the study visit, mean Gla-300 dose was significantly higher, 28.5 ± 12.6 UI/day compared to IDeg-

100, 22.8 ± 10.7 ($p = 0.0010$). No difference in prandial insulin dose was observed between Gla-300 and IDeg-100 (22.2 ± 13.8 vs. 21.8 ± 11.6 ; $p = 0.8199$) respectively.

The proportion of patients with normal hypoglycemia awareness measured using Clarke's questionnaire was not different

between the study groups (65% of the participants).

ENDPOINTS OBTAINED FROM CGM

Primary Endpoint

Effectiveness Measured as TIR 70–180 mg/dl

The CGM device was active a mean time percentage of 93.5% for both arms. The mean percentage of time within TIR 70–180 mg/dl within the last 14-consecutive days for the full day period was similar between the Gla-300 and IDeg-100 groups: $52.4 \pm 14.0\%$ versus $49.3 \pm 13.9\%$ (Table 2 and Supplementary Material Figure S1). The same was observed in TIR 70–140 mg/dl.

Secondary Endpoints

Time at Glucose Target Levels Measured Through CGM

There was no significant difference in TIR, TBR and TAR for the full day period between the two treatment groups, as shown in Fig. 2a, b and Table 2.

When analyzing the day and night periods, significant differences between the two groups were observed in TIR 70–140 mg/dl, TIR 70–180 mg/dl and TAR > 180 mg/dl in the nocturnal period (24:00–06:00), as shown in Fig. 2c, with no significant differences observed in the day period. Those patients treated with Gla-300 presented a higher percentage in the recommended range of 70–180 mg/dl (52.4% Gla-300 vs. 46.2% IDeg-100, $p = 0.0182$) and 70–140 mg/dl (31.8% Gla-300 vs. 26.9% IDeg-100, $p = 0.0209$) and a lower percentage in TAR > 180 mg/dl (40.1% Gla-300 vs. 47.2% IDeg-100, $p = 0.0199$).

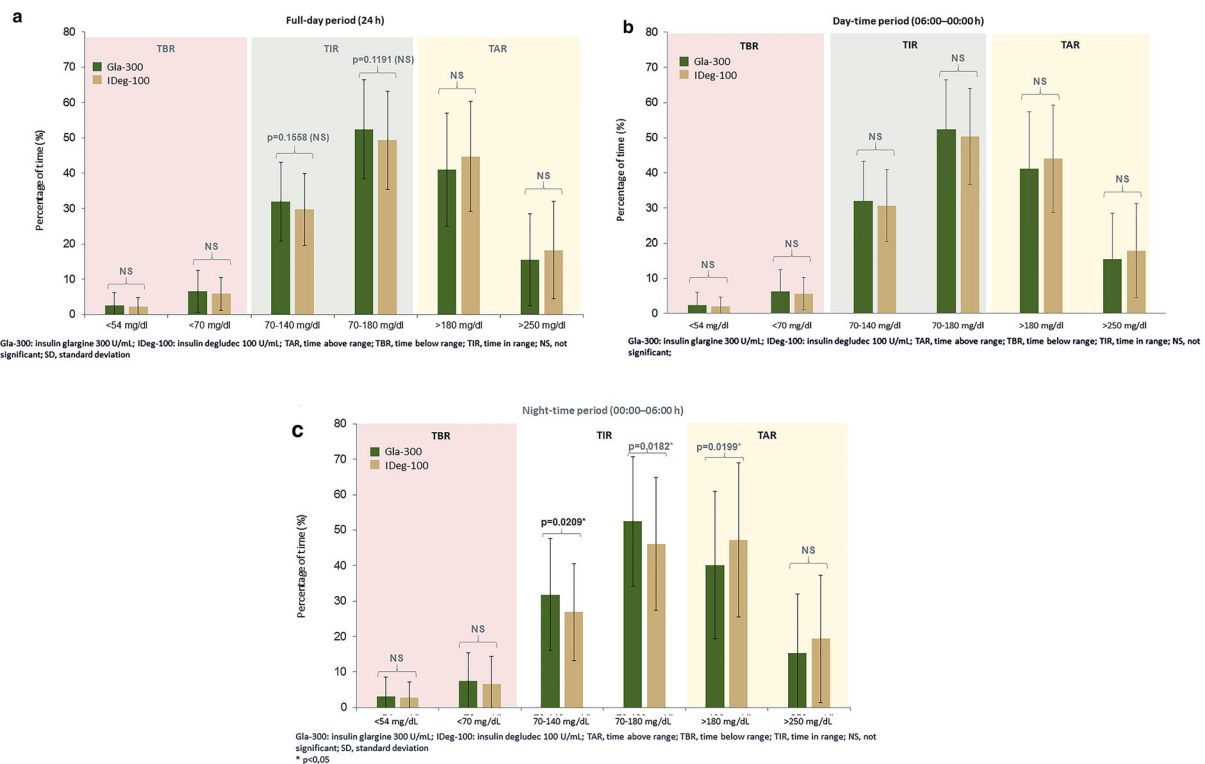


Fig. 2 Percentage of time at glucose target levels for different periods during 24 h

Additional Glucometric Values from CGM

No significant differences between groups in the full day period were observed in additional data obtained from CGM including glycemic variability metrics, as shown in Table 2. Mean 24-h glucose curves for the Gla-300 group were significantly lower (lower glycemic excursions) at night than for IDeg-100 patients (170.4 mg/dl vs. 181.9 mg/dl; $p < 0.05$) (data not shown).

Number of Episodes and Minutes in Hypoglycemia

No significant differences in the average number of hypoglycemic episodes and in the average minutes per day spent in hypoglycemia (< 70 and < 54 mg/dl) in the 14 consecutive days of CGM prior to study visit were observed between study groups in any of the periods analyzed (complete day, night or day period) (Fig. 3a).

Number of Episodes and Minutes in Hyperglycemia

No significant differences in the number of hyperglycemic episodes and in the average minutes per day spent in hyperglycemia (> 180 mg/dl) in the 14-consecutive days prior to study visit were observed between study groups in either the complete day or daytime period. This remained the same when the number and minutes of hyperglycemia episodes (> 250 mg) were analyzed for these same periods of time. Nevertheless, during the nighttime period, the number of episodes (> 250 mg/dl) per day was significantly lower in the Gla-300 group (Fig. 3b). Likewise, in terms of average minutes per day spent > 180 mg/dl, it was observed that Gla-300-treated patients spent fewer minutes per day in hyperglycemia during the nighttime period (Fig. 3b).

ENDPOINTS OBTAINED FROM CLINICAL RECORDS AND AT THE STUDY VISIT

HbA_{1c} and FPG values obtained in the 4 months prior to the study visit were available in 88.0% of the study population: 74.9% in the last 2 months and 13.1% in the 2–4 months prior to

the visit. The mean HbA_{1c} value closest to the study visit was similar in both groups: $7.8\% \pm 1.0$ in Gla-300 and $8.0\% \pm 0.9$ in IDeg-100 ($p = 0.2529$). The proportion of patients achieving a HbA_{1c} $< 7\%$ was higher in Gla-300 compared with the IDeg-100 group (Table 3).

In the total population, it was observed that patients with HbA_{1c} < 7 had a better nocturnal TIR (TIR 70–180 mg/dl and TIR 70–140 mg/dl) than patients with HbA_{1c} $\geq 7\%$ (59.4% of the time in TIR 70–180 mg/dl vs. 47.5% of the time in TIR 70–180 mg/dl, $p = 0.0028$ and 38.21% of the time in TIR 70–140 mg/dl vs. 27.7% of the time in TIR 70–140 mg/dl, $p = 0.0010$).

A relation was observed in the Gla-300 group between a better nocturnal TIR (70–140 mg/dl and 70–180 mg/dl) and lower HbA_{1c} $< 7\%$ level, indicating that Gla-300 has a better nocturnal profile in CGM and confers better glycemic results in real-life clinical practice.

Patients with HbA_{1c} $< 7\%$ in the Gla-300 group had a better nocturnal TIR (70–140 mg/dl and 70–180 mg/dl) than patients with HbA_{1c} $\geq 7\%$ (60.3% of the time in TIR 70–180 mg/dl vs. 50.2% of time in TIR 70–180 mg/dl, $p = 0.0324$, and 40.3% of the time in TIR 70–140 mg/dl vs. 29.8% of the time in TIR 70–140 mg/dl, $p = 0.0103$). This relation was not observed in the IDeg-100 group.

Confirmed hypoglycemic events (< 70 mg/dl, < 54 mg/dl and severe hypoglycemia) were obtained during the 12 months prior to switch and in the period from switch to the study visit [median time elapsed between switch and the study visit of 14.5 (percentile 8.3–20.6 months)]. Data regarding confirmed hypoglycemic events < 70 mg/dl and < 54 mg/dl in medical records were available in 40.0% of patients; this figure increased to 82.0% in the case of severe hypoglycemia. A decrease in the number of confirmed hypoglycemia and severe hypoglycemia events after the switch from first-generation BI to second-generation BI was observed, without significant differences between the study groups. Fewer patients had an episode of severe hypoglycemia when treated with a second-generation BI (3.1% vs. 12.9%, second vs. first generation BI, respectively; $p = 0.0003$).

Likewise, more patient-reported hypoglycemic events were observed (< 70 mg/

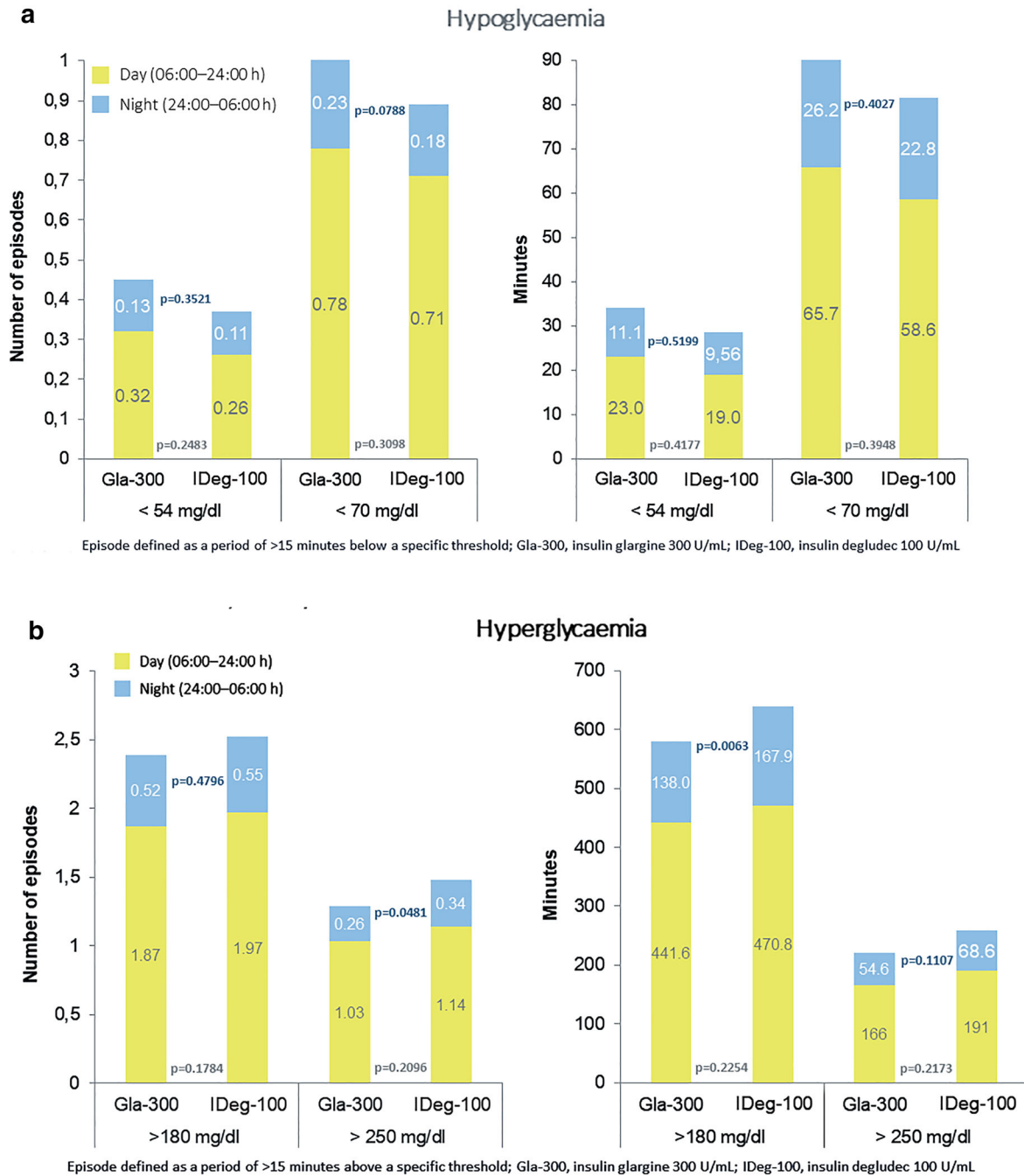


Fig. 3 Average number of episodes per day and average minutes per day of episodes in **a** hypoglycemia and **b** hyperglycemia

dl, < 54 mg/dl and severe hypoglycemia) in the 12 months before the change of BI compared to the period from the switch to the study visit. No

differences between groups were observed (Table 3).

Table 3 HbA_{1c}, FPG and hypoglycemic events according to the medical record

	Before the switch			At the study visit			<i>p</i> value
	Total	Gla-300	IDeg-100	Total	Gla-300	IDeg-100	
HbA _{1c} % (1)	8.4 ± 1.1	8.3 ± 0.9	8.6 ± 1.2	7.8 ± 1.0	7.8 ± 1.0	8.0 ± 0.9	0.2529
HbA _{1c} < 6.5%, %	0	0	0	2.7	4.2	1.1	0.2112
HbA _{1c} < 7%, %	0	0	0	13.7	18.8	8.0	0.0352
Mean FPG, mg/dl (1)	172.9 ± 70.2	177 ± 70.7	168.5 ± 69.9	151.3 ± 67	155.9 ± 65.4	146.1 ± 68.9	0.3519
Hypoglycemic events* < 70 mg/dl, <i>n</i> (2)	10.5 ± 13.6	11.8 ± 16.1	8.4 ± 7.8	7.9 ± 10.1	8.3 ± 11.8	7.3 ± 6.9	0.3488
Hypoglycemic events* < 54 mg/dl, <i>n</i> (2)	4.9 ± 8.1	4.7 ± 8.1	5.2 ± 8.4	3 ± 5.6	2.9 ± 5.3	3.2 ± 6.2	0.7544
Severe hypoglycemic events**, <i>n</i> (2)	0.3 ± 1.4	0.5 ± 1.9	0.2 ± 0.7	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	0.6327

Data are mean ± SD unless otherwise stated

HbA_{1c} hemoglobin A_{1c}, FPG fasting plasma glucose

*Confirmed hypoglycemia defined as an episode of symptomatic or asymptomatic hypoglycemia with plasma glucose < 54 mg/dl (3.0 mmol/l) or < 70 mg/dl (3.9 mmol/l)

**Severe hypoglycemia is defined as an episode of hypoglycemia at any time of the day (24 h) and during the night that requires assistance from another person administering carbohydrates, glucagon, or any other corrective measure

(1) HbA_{1c} and FPG were collected in the 4 months prior to the switch to Gla-300 or IDeg-100 and in the 4 months prior to study visit

(2) Hypoglycemic events were collected in the 12 months before the switch and in the period from switch to study visit [time elapsed between switch and the study visit of 14.5 months (6.6)]

Results on Diabetes Treatment Satisfaction Questionnaire and Insulin Treatment Satisfaction Questionnaire

The mean global score for DTSQs was 27.8, reflecting high treatment satisfaction with both insulins, without any difference between them (Supplementary Material Figure S2). The same result was obtained from the ITSQ questionnaire, with a mean global score of 67.2 ± 21.5 .

DISCUSSION

The OneCARE study provides, for the first time to our knowledge, information regarding the comparison of effectiveness of second-generation basal insulin analogs, Gla-300 and IDeg-100, in terms of CGM-related metrics in patients with T1D previously sub-optimally controlled with first-generation basal insulin analogs. Our real-world study suggests that both BIs are similar in achieving CGM targets according to international consensus, mainly 24-h TIR 70–180 mg/dl. The recent RESTORE real-world retrospective study has also shown that switching from a first-generation BI to Gla-300 or IDeg-100 provided similar improvements in glycemic control and a significant decrease in hypoglycemia [30].

To date, very scarce evidence comparing Gla-300 and IDeg-100 in the T1D population is available. Direct comparison of both insulins is limited to two studies that did not use CGM information [31, 32]. The results regarding pharmacodynamics vary. Recently, Miura et al. reported the effects of both insulins on glycemic stability in c-peptide-negative T1D patients using CGM [23]. In a multicenter randomized crossover design including 46 patients, the authors suggested that Glarg-300 and IDeg-100 have comparable stabilizing effects on the glucose profile. They did not find any significant difference in the percentage of CGM readings in the target glucose ranges with the exception of a decrease in TBR < 70 mg/dl in those patients switched from IDeg-100 to Gla-300.

In this context, and as has been mentioned in a recent review [33], there is a need for studies utilizing CGM in a head-to-head

comparison of second-generation BI in T1D. As both types of studies are deemed complementary, this need applies not only to randomized clinical trials but also to real-world pragmatic studies. In this context, a few months ago, Battelino et al. published the study design of the InRange open-label, randomized, parallel trial comparing Gla-300 and IDeg-100 in sub-optimally controlled patients with T1D using CGM and TIR consensus group recommendations for the primary outcome [33]. The hypothesis being tested is that Gla-300 is non-inferior to IDeg-100 concerning the percentage TIR after 12-week follow-up. While we wait for the results of the InRange trial, we think that the information obtained in OneCare is worth of attention.

In the real-world clinical practice scenario, Gla-300 is comparable to IDeg in terms of the overall TIR and safety profile, similar to those found in published studies [34, 35]. However, Gla-300 showed more nocturnal time periods in the TIR range at night in suboptimally controlled T1D patients switching from first-generation BI compared with IDeg.

Our hypothesis is aligned with results observed in the study by Carral et al. [36]. In this retrospective observational study, a higher percentage of patients in the Gla-300 group reached the target of $HbA_{1c} \leq 7\%$ and more patients treated with IDeg-100 presented $HbA_{1c} > 8\%$. In addition, in a subgroup of 71 patients (17%) who used CGM (FreeStyle Libre), a significant difference was observed in $TIR > 180$ mg/dl not only in the nighttime period but also throughout the study period.

The reason why Gla-300 has better results could be explained by the different pharmacodynamic profiles of the two drugs. As stated by Bailey et al., Gla-300 provides fewer fluctuating steady-state pharmacodynamic profiles (lower within-day variability) and more evenly distributed pharmacokinetic profiles compared with IDeg-100 [31].

These similar effects on the glucose profile are achieved using more units of Gla-300 than IDeg-100. As previously shown, this is not the result of the lower potency of Gla-300 but of its lower bioavailability after subcutaneous injection [10, 37]. Related to its nature, there were

some differences in the clinical characteristics of the two groups of patients receiving the two second-generation insulin analogs. The duration of T1D and presence of retinopathy were longer and higher, respectively, in patients using insulin IDeg-100. However, we think that in a population with, on average, nearly 2 decades since the diagnosis of T1D, the impact of a sparse difference of 3 years could be considered almost negligible. The rest of the clinical, laboratory and treatment characteristics, including pre-switch HbA_{1c}, and the reasons for the switch from a first-generation BI were comparable in the two groups.

Regarding the results achieved by both insulins in terms of CGM-based targets, it should be underlined that in neither TIR nor TBR were the recommendations of the ATTD consensus for CGM utilization achieved [38]. However, this is not surprising considering the clinical characteristics of the participants in the real-world One-Care study: T1D patients with longstanding disease, with poor metabolic control in which may be less stringent A1C goals might be applied [39]. In addition, at the time of inclusion of participants in our study, there was no reimbursement for CGM by the national health care provider. Thus, the use of self-financing CGM by participants could be related to their additional difficulties in obtaining optimal metabolic control despite using BB treatment including second-generation BI. Moreover, this use could also create a bias in the process of patient selection, including patients with more complications and more difficulties managing their glycemic control having more interest in participating in the study and not all of the T1D population being included [40].

Regarding the result obtained from clinical records, in fact, results of the real-world One-CARE study show that both second-generation BIs, Gla-300 and IDeg, performed better than first-generation BI in terms of glucose control and hypoglycemic events, supporting data obtained in the clinical program from both second-generation BIs. In the DELIVER-2 [13] and DELIVER-3 [14] study, Gla-300 showed greater improvements in glycemic control and reduced the risk of hypoglycemia in T2D when switching from Gla-100. Similar effects were

found with the IDeg switching as observed in the prospective real-world study of Fadine et al., in which the switch to degludec from another BI was associated with significantly lower rates of hypoglycemia and improved glycemic control [41].

Our study has limitations; we are well aware of them, and some have already been mentioned. The lack of randomization, lack of a centralized laboratory and lack of intensive control and monitoring of all aspects of usual clinical practice are some of the weaknesses of real-world studies that undermines the internal validity of the results. Also, although the diabetes duration difference was only 3 years between groups, the IDeg-100 group presented a more severe course of the disease, (higher rates of retinopathy). Nevertheless, a post-hoc analysis has been performed aiming to assess the effect of T1D duration and the presence or absence of retinopathy in both arms of the study, and it was observed that the equivalent effectiveness of Gla-300 and IDeg-100 in sub-optimally controlled T1D patients switching from a first-generation basal insulin seems not to be affected by either the duration of the disease or the presence or absence of retinopathy (data not shown). The results of this analysis are in line with the results observed in the main results of the study. However, the strength of the study is, to the best of our knowledge, that this is one of the first studies comparing head-to-head Gla-300 and IDeg-100 effectiveness in clinical practice in a large sample size of sub-optimally controlled T1D patients using CGM metrics demonstrating the similarities of both insulins after the assessment of outcomes based on objectively collected data.

CONCLUSION

In summary, in terms of the achievement of CGM-based targets from the last consensus recommendations, this real-world study suggests that the effectiveness and safety of Gla-300 insulin is similar to those obtained with IDeg-100 in patients with long-standing sub-optimally controlled T1D switching from first-generation BI.

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had a cross-sectional design, and all patients provided written informed consent for participation in this study and publication of their clinical data for research purpose.

Data Availability. All data generated or analyzed during this study are included in this published article as supplementary information files.

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