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ORIGINAL RESEARCH

Clinical Outcomes of Switching to Insulin Glargine 300 U/ml from Other Basal Insulins in People with Type 2 Diabetes in Italy: A Real-World Study

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ABSTRACT

Introduction: Primary aim was to provide real-world evidence of the outcomes after the switch to glargine 300 U/ml (Gla-300) from other basal insulins (first or second generation) in Italy.
Methods: Multicenter, observational, retrospective study based on electronic medical records.
Results: Overall, 953 T2DM insulin ± OAD treated people switched to Gla-300 or Gla-100 from January 2015 to July 2018. Three clinically relevant cohorts were identified: patients switching to Gla-300 from first-generation basal insulin (cohort 1), patients switching to Gla-300 from degludec-100 (Deg-100) (cohort 2), and those switching to Gla-100 from any basal insulin (cohort 3). The three cohorts differed in terms of age, diabetes duration, and metabolic control. HbA1c changes after 6 months from the switch were − 0.27% (95% CI − 0.38; − 0.16), − 0.06% (95% CI − 0.31; 0.19), and − 0.30% (95% CI − 0.51; − 0.09) in the three cohorts, respectively. FPG significantly decreased in cohort 1 (− 14.07 mg/dl, 95% CI − 20.25; − 7.89), while body weight significantly decreased in cohort 2 (− 1.47 kg, 95% CI − 2.55; − 0.39). Doses of insulin marginally changed during the follow-up (+ 0.89 U in basal insulin daily dose in cohort 1 and + 2.07 U in short-acting insulin daily dose in cohort 2).
Conclusions: Switching to Gla-300 from first-generation basal insulin in the real world is associated with improvements in metabolic control despite a suboptimal titration of both basal and short-acting insulins. Inertia in insulin titration documented in the Gla-100 cohort is also observed with the second-generation basal insulin. The switch to Gla-300 from Deg-100 was associated with a decrease in body weight of − 1.47 kg despite a slight increase in short-acting insulin daily doses of about + 2 U.

Keywords: Basal insulin; Degludec; Glargine 100; Glargine 300; Switch; Type 2 diabetes

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Key Summary Points

Why carry out this study?

Second generation basal insulins provide similar or improved efficacy compared to first generation ones with better safety profile.

Real world evidence is important to assess the use and the impact of these recent basal insulins in clinical practice.

Primary aim of the study was to provide real-world evidence of the outcomes after the switch to the second generation basal insulin glargine 300 U/mL (Gla-300) in Italy.

What was learned from the study?

A relevant number of people with type 2 diabetes and different clinical profiles switch basal insulin in clinical practice.

Switching to Gla-300 from 1st generation basal insulin is associated with improvements in metabolic control despite a suboptimal titration of both basal and short acting insulin.

Switching to Gla-300 from the other available 2nd generation basal insulin (degludec 100 U/ml) is associated with a decrease in body weight.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by relative insulin deficiency and eventual need for supplemental insulin therapy [1, 2]. Appropriate initiation and titration of insulin therapy are essential to enhance adherence to therapy and to reach glycemic targets [3]. However, Italian real-life data show that T2DM people treated with insulin are uncontrolled in 50% of cases [4].

New-generation basal insulins provide similar or improved efficacy compared to first-generation (i.e., insulin glargine 100 U/ml or detemir) with a better safety profile [3].

Insulin glargine 300 units/ml (Gla-300) is a second-generation basal insulin analog available in Italy since January 2017. Gla-300 has distinct pharmacokinetic (PK) and pharmacodynamic (PD) profiles compared to glargine 100 units/ml (Gla-100). This new formulation allows for the formation of a more compact subcutaneous depot after injection that results in a more gradual release of insulin providing a more constant and smoother PK profile and longer duration of action on the PD profile versus Gla-100 [5, 6].

In the treat-to-target studies from the EDITION phase 3 clinical program, Gla-300 has been shown to be non-inferior to Gla-100 with respect to glycated hemoglobin (HbA1c) reduction [7–9]. Furthermore, a significantly lower percentage of people with T2DM experienced confirmed hypoglycemic events on Gla-300 compared to Gla-100 [7–9].

Insulin degludec 100 U/ml (Deg-100) is another second-generation basal insulin available in Italy since 2015. PK-PD data of Deg-100 showed a more stable kinetic profile than Gla-100 [10]. The BEGIN clinical program showed comparable glycemic control vs. Gla-100 in most trials, with lower nocturnal hypoglycemic episodes during the maintaining phase, but a frequency of diurnal hypoglycemia higher with Deg-100 than with Gla-100 [11–13]. The new formulation insulin degludec 200 U/ml (Deg-200) provides comparable levels of glycemic control with similar rates of hypoglycemia to Deg-100, but it is not available in Italy [14].

Recently, a PK-PD clinical study of Gla-300 vs. Deg-100 has shown a lower within-day variability of Gla-300 compared to Deg-100 in a once-daily morning dosing regimen of 0.4 U/kg/day [6]. A trial-level meta-analysis using data from BEGIN (Deg-100) and EDITION (Gla-300) suggested that despite greater reductions in fasting plasma glucose, Deg-100 was associated with less improvement in HbA1c versus Gla-100, with an hypoglycemia benefit only evident at night; Gla-300 showed similar HbA1c reduction to Gla-100, accompanied by lower risk of

hypoglycemia both at night and at any time of day [15]. The head-to-head BRIGHT trial in a naïve T2DM population has recently documented that Gla-300 and Deg-100 provided similar glycemic control improvements with comparable hypoglycemia incidence during the full study period but lower in favor of Gla-300 during the titration period [16]. A trial involving individuals with T2DM treated with basal insulin showed there was no significant difference in the rate of overall symptomatic hypoglycemia between Deg-200 and Gla-300 in the maintenance period in insulin-treated individuals [17, 18]. In a real-world setting, switching from Gla-100 or detemir to Gla-300 or Deg-100 was associated with similar improvements in glycemic control and hypoglycemia in adult people with T2DM [19].

Starting from these premises, real-world evidence is particularly important to assess the use and the impact of these recent basal insulins in clinical practice. In this respect, retrospective review of electronic medical records (EMRs) represents a new frontier in epidemiologic and clinical research, offering the potential for low-cost, high-volume data on clinical effectiveness [20].

Particularly, no clinical data are available relative to the Italian diabetic population that has switched from other basal insulins to Gla-300 in real-life conditions.

In the Lazio region, a network of seven diabetes centers (ACISMOM) cares for 40% of people with diabetes referred to specialist care. One center of the same network is in the Puglia region. All the centers share the same EMRs system.

The principal aim of this study, which was based on the retrospective review of EMRs adopted in the ACISMOM network, was to assess the clinical outcomes of switching to Gla-300 from first- or other second-generation basal insulins. Secondary endpoints were to assess the most frequent types of switch to Gla-300 or Gla-100, patients' characteristics associated to the different types of switch and potential reasons for switching.

METHODS

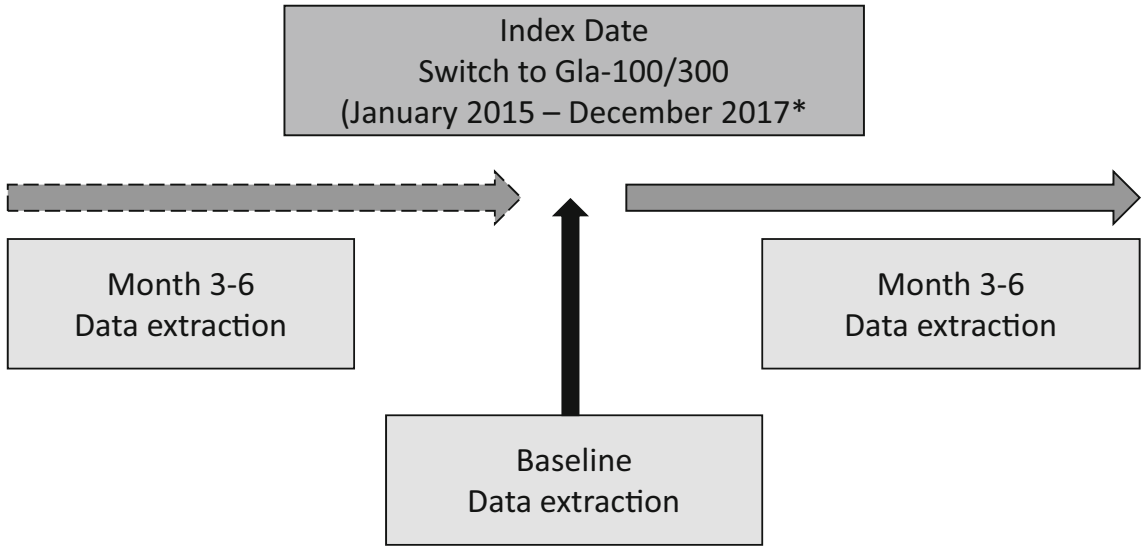
This was a multicenter, observational, longitudinal, retrospective study based on pre-existing data derived from EMRs. The study involved eight diabetes clinics of the ACISMOM network.

Eligible patients were those with a diagnosis of T2DM, aged $\geq$ 18 years, switched to Gla-300 or Gla-100 from other basal insulins (first or second generation) in the time period from January 2015 through December 2017, using the previous basal insulin analogs for at least 6 months before initiating insulin Gla-300 or Gla-100, with availability of a follow-up of at least 3 months after initiating insulin Gla-300 or Gla-100, not switching to another basal insulin analog after the switch to Gla-300 or Gla-100 during the study period.

Study endpoints included within-group changes after 3 and 6 months from the switch in the following parameters: glycated hemoglobin (HbA1c), fasting blood glucose (FBG), body weight, total insulin daily dose, total basal insulin daily dose and total short-acting insulin daily dose. In addition, the number of severe hypoglycemic episodes reported on EMRs and average number of visits during 6 months were assessed. Although the study protocol also included the evaluation of the incidence of non-severe hypoglycemia, this information was not available for most of the patients, since the routine download of self-monitoring of blood glucose (SMBG) values from glucose meters on EMRs was not common practice in participating centers.

To explore the main reasons for switching basal insulin, a site questionnaire was administered to principal investigators of all participating centers. Possible reasons for switching basal insulin in their everyday practice included: better metabolic control, less hypoglycemia, less glycemic variability, better adherence, easier titration, less weight gain, greater flexibility of administration, cost of treatment, frequency of administration, and adverse events.

All centers adopted the same EMRs (MyStar Connect®, Meteda srl, San Benedetto del Tronto, Italy) and an ad hoc software, which



*estimated extraction data end. A longer timeframe could be evaluated on the basis of the actual start-up date of the retrospective data extraction.

Fig. 1 Graphical study design

was developed for the standardized and anonymous extraction of the following data: age, gender, diabetes duration, diabetes therapy, type of insulin, insulin dose, number of insulin injections/day, HbA1c, FBG, hypoglycemia, body weight, body mass index (BMI), lipid profile (triglycerides, total cholesterol, high-density and low-density lipoprotein), blood pressure, renal function (albuminuria and glomerular filtration rate), antihypertensive and lipid-lowering treatment, and history of major diabetes complications.

Classification of diabetes complications was based on the International Classification of Diseases, 9th revision-Clinical Modification (ICD-9 CM); pharmacologic treatments were based on the Anatomical Therapeutic Chemical Classification System (ATC). Severe hypoglycemia was defined as an episode requiring the assistance of the patient by other persons. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national-Ethics Committee of the ACISMOM network) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Statistical Analysis

Being an exploratory, descriptive study, no formal sample size estimation was performed.

Study outcomes have been investigated on three clinically relevant cohorts, i.e., patients switching to Gla-300 from first-generation basal insulin (cohort 1), patients specifically switching to Gla-300 from second-generation basal insulin, i.e., Deg-100 (cohort 2), and patients switching to Gla-100 from any other basal insulin (first or second generation) (cohort 3).

Patients' characteristics were summarized by cohort as mean and standard deviation (continuous variables) or counts and percentages (categorical variables). Given the descriptive nature of the study and the substantial differences of patient characteristics in the different cohorts, no between-group comparison was performed.

Within-group changes after 3 (T + 3) and 6 months (T + 6) from the switch in levels of HbA1c, FBG, body weight, and insulin dose

Table 1 Baseline patient characteristics by cohort

Variable	Category	Cohort 1 Switch to Gla-300 from any basal insulin	Cohort 2 Switch to Gla-300 from insulin degludec	Cohort 3 Switch to Gla-100 from any basal insulin
No. group		691	122	262
Age (years)		70.0 ± 10.9	69.6 ± 8.9	73.3 ± 10.9
Sex (%)	Women	41.0	46.7	46.9
	Men	59.0	53.3	53.1
Diabetes duration (years)		19.6 ± 22.1	16.8 ± 21.6	16.5 ± 13.5
Weight (kg)		85.8 ± 17.8	88.7 ± 18.4	83.2 ± 17.8
BMI (kg/m^2)		30.9 ± 5.8	31.7 ± 6.3	30.7 ± 5.7
HbA1c (%)		8.3 ± 1.4	8.5 ± 1.3	8.1 ± 1.5
HbA1c ≤ 7%		12.6	8.3	20.6
Fasting blood glucose (mg/dl)		174.3 ± 59.9	177.4 ± 63.6	171.0 ± 64.3
Systolic blood pressure (mmHg)		130.5 ± 13.5	128.9 ± 14.2	130.6 ± 14.6
Diastolic blood pressure (mmHg)		77.6 ± 13.0	76.9 ± 7.1	76.2 ± 8.1
Total cholesterol (mg/dl)		173.7 ± 46.4	179.6 ± 40.2	173.9 ± 43.5
LDL cholesterol (mg/dl)		95.6 ± 36.4	103.3 ± 35.7	94.1 ± 33.7
HDL cholesterol (mg/dl)		47.8 ± 13.9	48.3 ± 13.4	48.7 ± 12.7
Triglycerides (mg/dl)		143.2 ± 72.4	138.8 ± 68.6	146.0 ± 85.1
eGFR (MDRD formula, ml/min*1.73m^2)		75.6 ± 31.2	75.6 ± 24.1	72.7 ± 24.7
eGFR ≤ 60 ml/min*1.73 m^2		33.0	24.6	29.3
Albuminuria (mg/l)		65.5 ± 151.6	47.3 ± 157.4	101.1 ± 315.2
Micro-/macroalbuminuria (%)		33.9	22.0	35.8
Diabetes complications (%)	Coronary heart disease	9.4	7.4	11.1
	Myocardial infarction	2.2	0	2.3
	Stroke	1.0	2.5	1.9
	Coronary by-pass	1.9	3.3	1.1
	Coronary revascularization	5.5	5.7	3.1
	Heart failure	0.6	2.5	1.1

Table 1 continued

Variable	Category	Cohort 1 Switch to Gla-300 from any basal insulin	Cohort 2 Switch to Gla-300 from insulin degludec	Cohort 3 Switch to Gla-100 from any basal insulin
	Lower limb complications	7.4	2.5	8.8
Insulin treatment:				
Total daily insulin dose (U)		59.6 ± 28.3	72.1 ± 36.7	51.2 ± 35.6
Per-kg insulin dose (U)		0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.3
Total daily basal insulin dose (U)		25.4 ± 14.6	32.6 ± 23.6	18.6 ± 12.2
Number of basal insulin administrations/day (%)	1	100	100	96.6
	2	0	0	3.4
Patients treated with short-acting insulin, irrespective of no. of injections (%)		76.6	86.9	64.5
Total daily short-acting insulin dose (U)		32.7 ± 17.9	38.5 ± 19.7	31.0 ± 24.9
Number of short-acting insulin administrations/day (%)	0	23.4	13.1	35.5
	1	2.9	2.4	5.7
	2	11.3	5.7	8.0
	3	62.4	78.7	50.8
Treatment scheme	Insulin + other glucose-lowering drugs	57.9	63.1	61.1
	Insulin only	42.1	36.9	38.9
Concomitant glucose-lowering drugs	Metformin	7.7	42.6	14.9
	Sulphonylureas	7.7	7.4	14.9
	Glinides	6.5	2.5	14.9
	Glitazones	1.0	0.8	2.3
	Acarbose	1.2	3.3	1.5
	DPPIV inhibitors	11.3	7.4	13.7
	GLP1-RAs	5.4	6.6	2.3

Table 1 continued

Variable	Category	Cohort 1 Switch to Gla-300 from any basal insulin	Cohort 2 Switch to Gla-300 from insulin degludec	Cohort 3 Switch to Gla-100 from any basal insulin
	SGLT2 inhibitors	17.4	24.6	6.5

Data are means and standard deviations or proportions

were assessed using mixed models for repeated measurements. Results were expressed as estimated mean at each time point with their 95% confidence intervals (95% CI) and estimated mean difference and 95% CI from T0 (switch date) to T + 3 and T + 6. In addition, rate of severe hypoglycemia, proportion of patients with HbA1c < 7.0% and < 8.0%, and mean number of visits after the switch were assessed.

RESULTS

Overall, 953 T2DM insulin ± OAD treated people switched to Gla-300 or Gla-100 from January 2015 to July 2018 (study flow chart is shown in Fig. 1). Characteristics of the patients of each cohort at the time of the basal insulin switch are reported in Table 1. Patients treated with basal and short-acting insulin were 76.6% in cohort 1, 86.9% in cohort 2, and 64.5% in cohort 3, while those treated with basal-bolus insulin scheme (i.e., basal and 3 injections of short-acting insulin) were 62.4%, 78.7%, and 50.8%, respectively. Furthermore, about 60% of patients used insulin in association with other glucose-lowering agents with marked differences in the prevalence of use of the different classes of drugs (Table 1).

Patients in cohort 1 (from first-generation basal insulin to Gla-300) were 59% men and had mean age of 70 years, diabetes duration of 19.6 years, HbA1c of 8.3%, and BMI of 30.9 kg/m^2.

Mean total daily dose of insulin prescribed was of 59.6 U (average daily dose of basal insulin of 25.4 U and average daily dose of short-acting insulin of 32.7 U) (Table 1).

Patients in cohort 2 (from Deg-100 to Gla-300) were 53.3% men and had mean age of 69.6 years, diabetes duration of 16.8 years, HbA1c of 8.5%, and BMI of 31.7 kg/m^2. Mean total daily dose of insulin prescribed was 72.1 U (average daily dose of basal insulin 32.6 U and average daily dose of short-acting insulin 38.5 U) (Table 1).

Patients in cohort 3 (from any basal insulin to Gla-100) were 53.1% men and had mean age of 73.3 years, diabetes duration of 16.5 years, HbA1c of 8.1%, and BMI of 30.7 kg/m^2. Mean total daily dose of insulin prescribed was of 51.2 U (average daily dose of basal insulin 18.6 U and average daily dose of short-acting insulin 31.0 U) (Table 1).

At longitudinal analyses, in cohort 1 HbA1c levels significantly decreased from baseline by − 0.28% (95% CI − 0.38; − 0.18) after 3 months and by − 0.27% (95% CI − 0.38; − 0.16) after 6 months. FBG significantly decreased during 6 months. A slight, non-significant reduction in body weight was also found (Table 2 and Fig. 2).

In cohort 2, HbA1c levels were significantly reduced by − 0.21% (95% CI − 0.43; − 0.01) after 3 months but were unchanged after 6 months. FBG levels did not change after 3 months and were reduced after 6 months, without reaching the statistical significance. In terms of body weight, the switch from Deg-100 to Gla-300 was associated with a statistically significant weight loss of − 1.05 kg (95% − 1.92; − 0.18) after 3 months and − 1.47 kg (95% − 2.55; − 0.39) after 6 months (Table 2 and Fig. 2).

In cohort 3, HbA1c levels significantly decreased by − 0.31% (95% CI − 0.50; 0.12) after 3 months and by − 0.30% (95% CI − 0.51;

Table 2 Changes in estimated mean levels of continuous endpoints during the follow-up by cohort and within-group comparisons

Change in	Visit	Cohort 1 Switch from any basal insulin to Gla-300			Cohort 2 Switch from insulin degludec to Gla-300			Cohort 3 Switch from any basal insulin to Gla-100		
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value
HbA1c (%)	T0	8.26 (8.16; 8.36)	–	–	8.47 (8.24; 8.70)	–	–	8.09 (7.91; 8.27)	–	–
	T + 3	7.98 (7.86; 8.10)	− 0.28 (− 0.38; − 0.18)	**< 0.0001**	8.26 (8.01; 8.51)	− 0.21 (− 0.43; 0.01)	**0.05**	7.78 (7.58; 7.98)	− 0.31 (− 0.50; − 0.12)	**0.002**
	T + 6	7.99 (7.87; 8.11)	− 0.27 (− 0.38; − 0.16)	**< 0.0001**	8.41 (8.13; 8.69)	− 0.06 (− 0.31; 0.19)	0.64	7.79 (7.57; 8.01)	− 0.30 (− 0.51; − 0.09)	**0.007**
FBG (mg/dl)	T0	173.71 (169.09; 178.33)	–	–	178.26 (167.13; 189.39)	–	–	170.87 (162.51; 179.23)	–	–
	T + 3	164.93 (159.34; 170.52)	− 8.78 (− 14.59; − 2.97)	**0.003**	174.97 (162.08; 187.86)	− 3.29 (− 16.97; 10.39)	0.64	156.29 (146.72; 165.86)	− 14.5 (− 24.80; − 4.36)	**0.005**
	T + 6	159.64 (153.69; 165.59)	− 14.07 (− 20.25; − 7.89)	**< 0.0001**	162.74 (147.48; 178.00)	− 15.52 (− 31.37; 0.33)	0.06	161.88 (150.83; 172.93)	− 9.00 (− 20.59; 2.59)	0.13
Body weight (kg)	T0	84.62 (82.92; 86.32)	–	–	86.36 (82.41; 90.31)	–	–	82.21 (78.83; 85.59)	–	–
	T + 3	84.27 (82.55; 85.99)	− 0.36 (− 0.90; 0.18)	0.19	85.31 (81.34; 89.28)	− 1.05 (− 1.92; − 0.18)	**0.02**	82.30 (78.88; 85.72)	0.09 (− 1.08; 1.26)	0.88

Table 2 continued

Change in	Visit	Cohort 1Switch from any basal insulin to Gla-300			Cohort 2Switch from insulin degludec to Gla-300			Cohort 3Switch from any basal insulin to Gla-100		
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value
	T + 6	84.13 (82.40; 85.86)	− 0.49 (− 1.07; 0.09)	0.10	84.89 (80.88; 88.90)	− 1.47 (− 2.55; − 0.39)	**0.009**	82.54 (79.07; 86.01)	0.34 (− 0.99; 1.67)	0.62

Paired *t* test derived from linear mixed models for repeated measurements
Statistically significant *p* values ($p < 0.05$) are in bold

− 0.09) after 6 months. FBG significantly decreased after 6 months. Body weight was unchanged during the follow-up (Table 2 and Fig. 2).

Changes during the follow-up in total, basal, and short-acting insulin daily doses for the three cohorts are reported in Table 3. In cohort 1, a small increase in basal insulin dose of 0.89 U (95% CI 0.15; 1.63) was found after 6 months, while the short-acting and total daily dose remained unchanged. In cohort 2, the dose of short-acting insulin significantly increased by 2.07 U (95% CI 0.37; 3.77) during 6 months after the switch, while the dose of Gla-300 did not significantly change. In cohort 3, a small increase in basal insulin dose of 1.32 U (95% CI 0.03; 2.61) was found after 3 months, but not after 6 months. No significant changes in short-acting and total daily doses were documented during the follow-up.

The average number of visits after the switch was 2.5 ± 1.3 in cohort 1 and 2.2 ± 1.0 in the other two cohorts.

The site questionnaires highlighted the main reasons for switching in the different cohorts:

- Hypoglycemia concern, less glucose variability, and better control/efficacy were ranked as the three main reasons for the switch from Deg-100 to Gla-300 and from any other basal insulin to Gla-300.
- Better control, hypoglycemia concern, efficacy, adverse events, and cost were ranked as the main reasons for the switch from any basal insulin to Gla-100.

Overall, only three severe hypoglycemia episodes were registered in EMRs; all occurred in cohort 1. For this reason, incidence rates of severe hypoglycemia could not be calculated.

DISCUSSION

This study shows that a relevant number of people with T2DM switch basal insulin in clinical practice. Specifically, the study adds important insights for the understanding of the clinical profile of patients switching to Gla-300 from other basal insulins.

Key differences emerged between patients who switched to Gla-300 and Gla-100 and

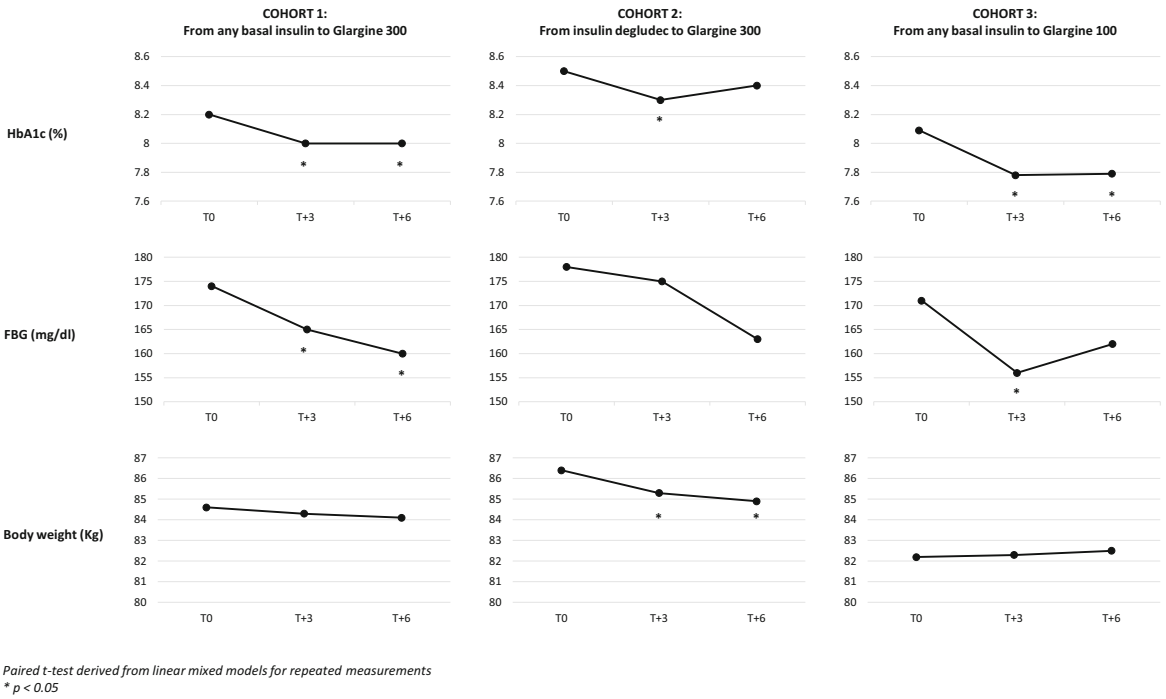


Fig. 2 Changes in estimated mean levels of continuous endpoints during the follow-up by cohort and within-group comparisons (graphical representation)

between patients who switched from Deg-100 to Gla-300.

Patients switching to Gla-300 from any first-generation basal insulin had the longest diabetes duration (19.6 years vs. about 16.5 years in the other two cohorts), while patients switching to Gla-100 from any other basal insulin were the oldest ones (73.3 years vs. about 70 years in the other two cohorts). As safety and efficacy of Gla-300 vs. Gla-100 in people with T2DM aged $\geq$ 65 years were demonstrated in the SENIOR and DELIVER 3 study, where comparable reductions in HbA1c and benefit in hypoglycemia risk with Gla-300 were documented, it would be expected that second-generation basal insulins would be used more often in the oldest people [21, 22].

Data on the cohort switching from Deg-100 to Gla-300 are particularly interesting. These patients showed the worst metabolic control (HbA1c 8.5 $\pm$ 1.3% vs. 8.3 $\pm$ 1.4% in cohort 1 and 8.1 $\pm$ 1.5% in cohort 3) although they were more often treated with four or more insulin injections/day and with the highest insulin doses (72 U/day of total insulin vs. 50–60 U/day in the other two cohorts), identifying a particularly complex patient phenotype. After the switch, metabolic control improved (especially in terms of FBG) and weight decreased although the total insulin dose was slightly increased. No severe hypoglycemic episodes occurred in this cohort.

It is important to underline that observed changes in metabolic control were reasonably due to insulin therapy, since it is recognized that changes in lifestyle (diet and physical activity) seldom occur in the elderly T2DM population [4]. However, we cannot exclude that some reinforcement of education on lifestyle may have occurred together with the switch of basal insulin.

Regarding the Gla-300 titration, the dose increase observed in clinical practice is particularly low (< 1 U during 6 months in all cohorts) with respect to what could be expected based on data from clinical trials and a summary of characteristics of the product. This attitude of participating diabetologists seems to indicate that the therapeutic inertia in terms of insulin titration documented in the Gla-100 cohort is

Table 3 Insulin titration during the follow-up by cohort

Insulin dose	Visit	Cohort 1 Switch from any basal insulin to Gla-300			Cohort 2 Switch from insulin degludec to Gla-300			Cohort 3 Switch from any basal insulin to Gla-100		
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value
Total daily dose (U)	T0	59.5 (57.15; 61.99)	–	–	72.00 (65.31; 78.69)	–	–	50.45 (45.51; 55.39)	–	–
	T + 3	60.08 (57.58; 62.58)	0.51 (− 0.73; 1.75)	0.42	71.62 (64.76; 78.48)	− 0.38 (− 3.95; 3.19)	0.83	52.33 (47.25; 57.41)	1.88 (− 1.01; 4.77)	0.20
	T + 6	60.58 (58.04; 63.12)	1.01 (− 0.31; 2.33)	0.13	74.69 (67.60; 81.78)	2.68 (− 1.29; 6.65)	0.19	50.18 (44.87; 55.49)	− 0.27 (− 3.53; 2.99)	0.87
Basal daily dose (U)	T0	25.47 (24.45; 26.49)	–	–	32.58 (29.24; 35.92)	–	–	18.65 (17.15; 20.15)	–	–
	T + 3	25.94 (24.86; 27.02)	0.47 (− 0.22; 1.16)	0.19	31.67 (28.12; 35.22)	− 0.91 (− 3.60; 1.78)	0.51	19.96 (18.36; 21.56)	1.32 (0.03; 2.61)	**0.05**
	T + 6	26.36 (25.25; 27.47)	0.89 (0.15; 1.63)	**0.02**	33.36 (29.58; 37.14)	0.78 (− 2.20; 3.76)	0.61	19.64 (17.91; 21.37)	0.99 (− 0.45; 2.43)	0.18
Short-acting daily dose (U)	T0	32.79 (31.22; 34.36)	–	–	38.45 (34.55; 42.35)	–	–	30.52 (27.06; 33.98)	–	–

Table 3 continued

Insulin dose	Visit	Cohort 1Switch from any basal insulin to Gla-300			Cohort 2Switch from insulin degludec to Gla-300			Cohort 3Switch from any basal insulin to Gla-100		
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	*p* value
	T + 3	32.98	0.18	0.65	39.49	1.04	0.18	31.15	0.63	0.53
		(31.35; 34.61)	(− 0.61; 0.97)		(35.53; 43.45)	(− 0.49; 2.57)		(27.60; 34.70)	(− 1.32; 2.58)	
	T + 6	32.97	0.18	0.68	40.52	2.07	**0.02**	29.06	− 1.46	0.19
		(31.32; 34.62)	(− 0.66; 1.02)		(36.49; 44.55)	(0.37; 3.77)		(25.37; 32.75)	(− 3.67; 0.75)	

Paired *t* test derived from linear mixed models for repeated measurements
Statistically significant *p* values ($p < 0.05$) are in bold

also observed with the new-generation Gla-300 basal insulin. This finding is particularly relevant, as the prompt efficacy of Gla-300 mainly depends on an appropriate and timely dose titration because of its known pharmacologic characteristics and PK/PD profile.

Two recently published prospective real-life comparative studies (REACH and REGAIN) showed no differences in glycemic control with Gla-300 versus standard-of-care basal insulin over 12 months. However, suboptimal insulin titration occurred in both treatment arms suggesting that additional titration instruction/support may be required for patients to fully derive the benefits from newer basal insulin formulations [23].

Short-acting insulin optimization after the switch also seems to be sub-optimal in most patients treated with Gla-300. Thus, the sub-optimal titration of insulin doses observed under real-life conditions suggests the lack of adequate education for both patients and physicians.

The paucity of data on SMBG available in EMRs, as also previously documented [24], suggests poor attention to the collection of the data regarding hypoglycemia and glycemic profiles in clinical practice at least in people with T2DM.

The site questionnaire emphasized the role of risk of hypoglycemia, glucose variability, and inadequate metabolic control as the main reasons for switching from any other basal insulin to Gla-300.

Real-world studies provide information that is complementary to randomized clinical trials and may be more generalizable and pertinent to clinicians and healthcare systems.

Data obtained in the DELIVER program [19, 21, 22, 25–27] with comparative data in propensity-matched cohorts show that people with T2DM who switched to Gla-300 from other basal insulin analog regimens improved their glycemic control with fewer hypoglycemia events, confirming and complementing the results of the EDITION registration clinical program [7–9]. Particularly, the DELIVER 2 and 3 study showed that switching basal insulins in T2DM people with elevated HbA1c levels to Gla-300 was associated with significantly lower risk of hypoglycemia than switching to other basal insulins (mainly first-generation basal insulin), with comparable glycemic control; the lower risk of hypoglycemia-related, diabetes-related, and all-cause emergency room services translates into lower costs in patients using Gla-300 [22, 24].

The non-comparative EU-TREAT study demonstrated that switching patients to Deg-100 from first-generation basal insulins improved glycemic control and significantly reduced the risk of hypoglycemia in routine clinical practice [28]. In the DELIVER D + comparative US study on T2DM high-risk insulin-treated patients, switching from a first- (Gla-100 or detemir) second-generation (Gla-300 or Deg-100) basal insulin analog resulted in similar improvements in glycemic control and in a similar or better effect on hypoglycemia with Gla-300 compared with Deg-100 [19].

Compared to these studies, data from this real-world study confirm the effectiveness and safety of the switch to Gla-300 from other basal insulins, although a major effort regarding timely and efficient titration is needed.

This study has strengths and limitations. Among the strengths, this study provides important complementary information about the effectiveness of Gla-300 in clinical practice. Compared to other studies based on EMRs, this study was able to provide an accurate description of T2DM patient characteristics switched to Gla-300 in real life, data on insulin doses, and physician attitudes towards insulin therapy in Italy.

As for the limitations, the inclusion of a network of centers with homogeneous clinical approaches could limit the generalizability of the results. Furthermore, information about causes and treatment of severe hypoglycemia and data on non-severe hypoglycemia were not found in the database, suggesting the need to improve the systematic revision of SMBG data through EMRs. The overall duration of insulin therapy and other concomitant treatments before the switch was also not available in the database. Finally, the limited number of observations did not allow for propensity score matching, thus precluding the possibility to perform a comparative effectiveness analysis

among the cohorts. Therefore, this study has a purely descriptive nature. However, methods applied in this study including EMRs data retrospective review and secure anonymous data transfer represented a pilot phase, used to design two ongoing, larger studies in T1DM and T2DM in European populations, evaluating the switch to Gla-300 or Deg-100 from other basal insulins and comparing their effectiveness and safety after the application of propensity score matching.

CONCLUSION

In conclusion, this regional, multicenter, non-interventional study based on the retrospective analysis of real-world data from Italy shows that switching to Gla-300 from previous first-generation basal insulins is associated with improvements in HbA1c levels of about − 0.3% despite a suboptimal titration of both basal and short-acting insulin, without an increase in the risk of severe hypoglycemia. The switch from Deg-100 to Gla-300 is associated with a decrease in body weight of − 1.47 kg, despite a slight increase in total insulin daily doses. The study emphasizes the urgent need for optimization of insulin titration to maximize the benefits of basal insulins in these patients, since the therapeutic inertia documented in the Gla-100 cohort is also found with the new-generation Gla-300 basal insulin.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national - Ethics Committee of the ACISMOM network) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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