



Glycaemic Control in People with Type 2 Diabetes Mellitus Switching from Basal Insulin to Insulin Glargine 300 U/ml (Gla-300): Results from the REALI Pooled Database

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ABSTRACT

Introduction: Using pooled data from the REALI European database, we evaluated the impact of previous basal insulin (BI) type on real-life effectiveness and safety of switching to insulin glargine 300 U/ml (Gla-300) in people with suboptimally controlled type 2 diabetes.

Methods: Patient-level data were pooled from 11 prospective, open-label, 24-week studies. Participants were classified according to the type of prior BI. Of the 4463 participants, 1282 (28.7%) were pre-treated with neutral protamine Hagedorn (NPH) insulin and 2899 (65.0%) with BI analogues (BIAs), and 282 (6.3%) had undetermined prior BI.

Results: There were no meaningful differences in baseline characteristics between subgroups, except for a higher prevalence of diabetic neuropathy in the NPH subgroup (21.6% versus 7.8% with BIAs). Mean \pm standard deviation haemoglobin A1c (HbA1c) decreased from $8.73 \pm 1.15\%$ and $8.35 \pm 0.95\%$ at baseline to $7.71 \pm 1.09\%$ and $7.82 \pm 1.06\%$ at week 24 in the NPH and BIA subgroups, respectively. Least squares (LS) mean change in HbA1c was -0.85% (95% confidence interval -0.94 to -0.77) in NPH subgroup and -0.70% (-0.77 to -0.64) in BIA subgroup, with a LS mean absolute difference between subgroups of 0.16 (0.06 – 0.26 ; $p = 0.002$). Gla-300 mean daily dose was slightly increased at week 24 by 0.07

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U/kg/day (approximately 6 U/day) in both subgroups. Incidences of symptomatic and severe hypoglycaemia were low, without body weight change.

Conclusions: Irrespective of previous BI therapy (NPH insulin or BIAs), switching to Gla-300 improved glycaemic control without weight gain and with low symptomatic and severe hypoglycaemia incidences. However, a slightly greater glucose-lowering effectiveness was observed in people pre-treated with NPH insulin.

Keywords: Basal insulin analogues; Basal insulin switching; Insulin glargine 300 U/ml; Neutral protamine Hagedorn insulin; Pooled database; Routine clinical practice; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

Switching basal insulin (BI) in people with type 2 diabetes mellitus (T2DM) is motivated by several factors including suboptimal glucose control, unacceptable frequency of hypoglycaemia, fear of weight gain, titration difficulties, or low treatment adherence

By using the REALI database to pool patient-level data from 11 prospective studies reflecting routine clinical practice in different European countries, we sought to expand knowledge regarding the real-life effectiveness and safety of switching to Gla-300 in people with T2DM uncontrolled on NPH insulin or on BI analogues

What was learned from the study?

Gla-300 can improve glycaemic control without weight gain and with a low hypoglycaemia incidence, regardless of the nature of prior BI therapy

People with suboptimally controlled T2DM who switch to Gla-300 from NPH insulin show slightly greater haemoglobin A1c reduction than those who switch from BI analogues

INTRODUCTION

Based on clinical practice guidelines, people with type 2 diabetes mellitus (T2DM) who are unable to reach target haemoglobin A1c (HbA1c) levels with oral antidiabetic drugs (OADs) may be initiated on basal insulin (BI) therapy [1, 2]. BI options include neutral protamine Hagedorn (NPH) insulin, first-generation BI analogues (BIAs), namely insulin detemir and insulin glargine 100 U/ml (Gla-100), and second-generation BIAs namely insulin glargine 300 U/ml (Gla-300) and insulin degludec [1]. Long-acting BIAs (i.e., insulin detemir, Gla-100, Gla-300, and insulin degludec) may however be preferred over the intermediate-acting NPH insulin, since they show comparable glycaemic control with a reduced risk of hypoglycaemia [1, 2].

Gla-300 has several advantages when compared with NPH insulin and first-generation BIAs. These include a more prolonged half-life and a smoother pharmacokinetic/pharmacodynamic profile, coupled with low fluctuation and high reproducibility, resulting in evenly distributed glucose-lowering activity beyond 24 h [3, 4]. This extended and more stable coverage of Gla-300 may translate into reduced treatment burden and improved adherence, which could in turn improve treatment outcomes [5, 6].

In the EDITION phase III clinical trial programme performed in a large population with a broad clinical spectrum of T2DM, patients who switched to Gla-300 from another BI, either Gla-100 or NPH insulin, demonstrated comparable glycaemic control with consistently fewer hypoglycaemic events at any time of the day and nocturnally compared with those who switched to Gla-100 [7]. Real-world evidence concerning switching to Gla-300 has also been encouraging, with real-life prospective studies from different countries across Europe showing that a direct switch to Gla-300 from other BIs resulted in improved glycaemic control and a reduced risk of hypoglycaemia without weight gain [8–13]. However, there are very limited prospective real-world data evaluating the switch from NPH insulin to Gla-300, with only

one published study from Poland prospectively assessing the effectiveness of switching from NPH insulin to Gla-300 in a total of 469 people with T2DM [8]. Hence, by using the REALI database to pool patient-level data from 11 observational/low-interventional, prospective studies reflecting routine clinical practice in different European countries, we sought to expand knowledge regarding the real-life effectiveness and safety of switching to Gla-300 in people with T2DM suboptimally controlled on a non-Gla-300 BI regimen.

METHODS

Study Design and Participants

This REALI analysis included pooled data from 11 multicentre, prospective, open-label studies of a minimum duration of 24 weeks conducted between June 2015 and April 2019 in Germany, Austria, Switzerland, the Netherlands, Spain, France, the Czech Republic, Greece, Poland, Denmark, Slovenia, Slovakia, Croatia, the UK, Belgium, Serbia, Bulgaria, and Hungary [9–19]. The methodology of the REALI project and previous analyses from the REALI database have been presented elsewhere [20–22].

Patients included in this analysis were adults with T2DM inadequately controlled (HbA1c $\geq 7.0\%$) on previous BI therapy (\pm prandial and/or premixed insulin) with or without OADs who switched to Gla-300 therapy. In the pooled studies, patients were switched to Gla-300 upon the treating physician-investigator's decision because of suboptimal glucose control, titration difficulties, frequent hypoglycaemic episodes, or fear of hypoglycaemia. Gla-300 treatment was applied according to its approved label [23]. Gla-300 was administered subcutaneously once daily, at the same time of the day ± 3 h if needed.

All pooled studies were conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines and were approved by the relevant institutional review boards/ethics committees. All participants gave written informed consent. Before data pooling, all patient information was de-

identified. Consequently, no ethical approval was required for this pooled analysis.

Assessments

Data were collected at baseline, 12 weeks, and 24 weeks. At baseline, recorded data included demographics, body weight and/or body mass index (BMI), T2DM duration, diabetic complications and cardiovascular comorbidities, previous antidiabetic therapy (OADs and insulins), and glycaemic parameters. At follow-up visits, current glycaemic variables, body weight, Gla-300 daily dose, and hypoglycaemic events were recorded.

Efficacy outcomes evaluated in the pooled analysis were the changes in HbA1c and fasting plasma glucose (FPG) from baseline to week 12 and week 24 of Gla-300 treatment as well as the proportion of patients achieving HbA1c targets of $< 7.0\%$ (< 53 mmol/mol), $< 7.5\%$ (< 58.5 mmol/mol), and $< 8.0\%$ (< 63.9 mmol/mol) at week 24.

Safety outcomes included hypoglycaemia incidence and annualised rate (events per patient-year), calculated for symptomatic and severe hypoglycaemic events occurring at any time of the day (24 h) and during the night (00:00–05:59 h). Symptomatic hypoglycaemia was defined as any event with clinical symptoms with or without documented blood glucose measurement. Severe hypoglycaemia was defined as any event requiring assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions. Other hypoglycaemic events (e.g., asymptomatic hypoglycaemia, symptomatic confirmed hypoglycaemia, daytime hypoglycaemia) were not reported across all individual studies and were hence not included in the REALI analysis. Likewise, hypoglycaemia during the 4-week period before Gla-300 initiation was not reported in most of the individual studies.

The pooled analysis also evaluated changes in body weight and the daily dose of Gla-300 (expressed in both U/day and in U/kg/day) from baseline to weeks 12 and 24.

Statistical Analysis

To evaluate the impact of prior BI regimens on the effectiveness and safety of Gla-300, patients were classified into two subgroups: those treated with prior NPH insulin and those previously treated with BIAs (i.e., Gla-100, insulin detemir, insulin degludec).

The change in HbA1c from baseline to weeks 12 and 24 of Gla-300 treatment was evaluated using a mixed model for repeated measures (MMRM), with fixed categorical effects of study, visit, subgroup category, and subgroup category-by-visit interaction as well as continuous fixed covariates of baseline HbA1c, baseline HbA1c value-by-visit interaction, age, age value-by-visit interaction, BMI, and BMI value-by-visit interaction. Based on this MMRM, we estimated the least squares (LS) mean changes in HbA1c from baseline to week 24 in the two subgroups and the corresponding 95% confidence intervals (CIs). All other efficacy and safety endpoints as well as baseline characteristics were summarised descriptively, with categorical variables presented as counts and percentages and continuous variables as mean \pm standard deviation (SD) or as median (quartile 1–quartile 3).

Effectiveness and safety analyses were performed on all included patients who received at least one Gla-300 dose. No imputation of missing data was performed. All statistical tests were two-sided, with a p value of < 0.05 considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Participants

A total of 4463 participants were included in this REALI pooled analysis, of whom 4372 (98.0%) received at least one Gla-300 dose and

were hence part of the effectiveness and safety analyses. Of the 4463 included participants, 282 (6.3%) had undetermined prior BI type. Among the remaining 4181 participants, 1282 (28.7%) switched to Gla-300 from NPH insulin and 2899 (65.0%) from BIAs, namely Gla-100 (1947/2899; 67.2%), insulin detemir (615/2899; 21.2%), insulin degludec (316/2899; 10.9%), and other insulins (21/2899; 0.7%). Baseline characteristics were overall comparable between the two BI pre-treated subgroups (Table 1). The mean \pm SD age of the 4463 participants was 64.1 ± 9.6 years, with slightly more male patients enrolled (53.5%). The mean \pm SD BMI was 32.7 ± 5.7 kg/m², with most participants (64.9%) having a baseline BMI ≥ 30 kg/m². Median diabetes duration was 12.0 years, with most participants receiving at baseline biguanides (73.0%), followed by dipeptidyl peptidase-4 inhibitors (25.5%) and sulphonylureas (18.2%). The mean \pm SD baseline HbA1c in the 4463 included participants was $8.46 \pm 1.05\%$, while the mean \pm SD baseline FPG was 175.6 ± 52.7 mg/dl.

Glycaemic Control

In the efficacy population ($N = 4372$), mean \pm SD HbA1c decreased from $8.47 \pm 1.05\%$ at baseline to $7.78 \pm 1.08\%$ at week 24, corresponding to a LS mean change in HbA1c from baseline to week 24 of -0.76% (95% CI -0.81 to -0.70). In the NPH and BIA subgroups, mean \pm SD HbA1c decreased from $8.73 \pm 1.15\%$ and $8.35 \pm 0.95\%$ at baseline to $7.71 \pm 1.09\%$ and $7.82 \pm 1.06\%$ at week 24, respectively. Accordingly, the LS mean decrease in HbA1c from baseline was statistically significantly higher in patients previously treated with NPH insulin than in those previously treated with BIAs (Fig. 1) at both week 12 ($p = 0.02$) and week 24 ($p = 0.002$). At week 24, the LS mean decrease in HbA1c from baseline was 0.85% in the NPH insulin subgroup and 0.70% in the BIA subgroup, for a between-group

Table 1 Baseline characteristics according to previous basal insulin (BI) used

	Previous NPH insulin (<i>N</i> = 1282)	Previous BIAs (<i>N</i> = 2899)	Total (<i>N</i> = 4463 ^a)
Age (years), mean ± SD	63.3 ± 9.4	64.6 ± 9.8	64.1 ± 9.6
Male, <i>n</i> (%)	676 (52.8)	1593 (54.9)	2388 (53.5)
Body mass index (kg/m ²), mean ± SD	32.5 ± 5.8	32.8 ± 5.7	32.7 ± 5.7
Diabetes duration (years), median (Q1–Q3)	12.0 (7.0–17.0)	13.0 (8.0–17.0)	12.0 (8.0–17.0)
Duration of prior BI therapy (years) ^b , median (Q1–Q3)	1.2 (0.5–3.4)	1.6 (0.6–3.7)	1.7 (0.7–3.8)
Prior BI dose (U/day), mean ± SD	32.4 ± 24.6	37.5 ± 23.0	36.1 ± 23.5
Prior non-insulin glucose-lowering drugs, <i>n</i> (%) ^c	1042 (81.3)	2379 (82.1)	3421 (76.7)
Biguanides	743 (71.3)	1756 (73.8)	2499 (73.0)
Sulphonylureas	211 (20.2)	412 (17.3)	623 (18.2)
DPP-4 inhibitors	183 (17.6)	689 (29.0)	872 (25.5)
SGLT-2 inhibitors	113 (10.8)	407 (17.1)	520 (15.2)
GLP-1 receptor agonists	50 (4.8)	224 (9.4)	274 (8.0)
Number of prior non-insulin glucose-lowering drugs, <i>n</i> (%) ^c			
1	667 (64.0)	1253 (52.7)	1920 (56.1)
≥ 2	375 (36.0)	1126 (47.3)	1501 (43.9)
Patients with ≥ 1 diabetic complication, <i>n</i> (%)			
Diabetic neuropathy	277 (21.6)	225 (7.8)	657 (14.7)
Diabetic retinopathy	120 (9.4)	213 (7.3)	404 (9.1)
Diabetic nephropathy	95 (7.4)	266 (9.2)	406 (9.1)
Patients with ≥ 1 cardiovascular risk factor, <i>n</i> (%)			
Hypertension	773 (60.3)	2031 (70.1)	3031 (67.9)
Dyslipidaemia	328 (25.6)	1071 (36.9)	1620 (36.3)
HbA1c (%), mean ± SD	8.70 ± 1.16	8.35 ± 0.95	8.46 ± 1.05
Fasting plasma glucose (mg/dl), mean ± SD	186.3 ± 56.8	171.3 ± 49.3	175.6 ± 52.7

BIA basal insulin analogue, *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1, *HbA1c* haemoglobin A1c, *NPH* neutral protamine Hagedorn, *Q* quartile, *SD* standard deviation, *SGLT-2* sodium-glucose cotransporter-2

^aA total of 282/4463 (6.3%) patients had missing data on the type of previously used BI

^bData on duration of prior BI therapy were available for only 1589/4463 (35.6%) patients

^cThe total number of patients who were previously treated with glucose-lowering drugs in each subgroup was used as the denominator to calculate the percentages of patients in each drug class as well as the percentages of patients receiving 1 or ≥ 2 glucose-lowering drugs

difference of 0.16 (95% CI 0.06–0.26). Consistently, the proportion of patients achieving HbA1c targets of < 7.0%, < 7.5%, and < 8.0% at week 24 was numerically higher in patients previously treated with NPH insulin than in those previously treated with BIAs (Fig. 2).

In line with changes in HbA1c, patients previously treated with NPH insulin showed a greater mean \pm SD decrease in FPG from baseline to week 24 than those previously treated with BIAs (change of -46.4 ± 64.4 mg/dl versus -22.5 ± 77.9 mg/dl). In both subgroups, the reduction in FPG happened mainly in the first 12 weeks of Gla-300 treatment (Fig. 3). In the overall efficacy population ($N = 4372$), the

observed mean \pm SD FPG decreased from 176.3 ± 52.5 mg/dl at baseline to 146.2 ± 60.5 mg/dl at week 24, corresponding to an observed mean \pm SD change of -29.8 ± 74.0 mg/dl.

Hypoglycaemia, Gla-300 Dose, and Body Weight

During the 24-week Gla-300 treatment period, 555/4372 (12.7%) patients experienced at least one hypoglycaemic episode. Incidences and event rates for symptomatic and severe hypoglycaemia occurring at any time of the day and during the night were low in both subgroups

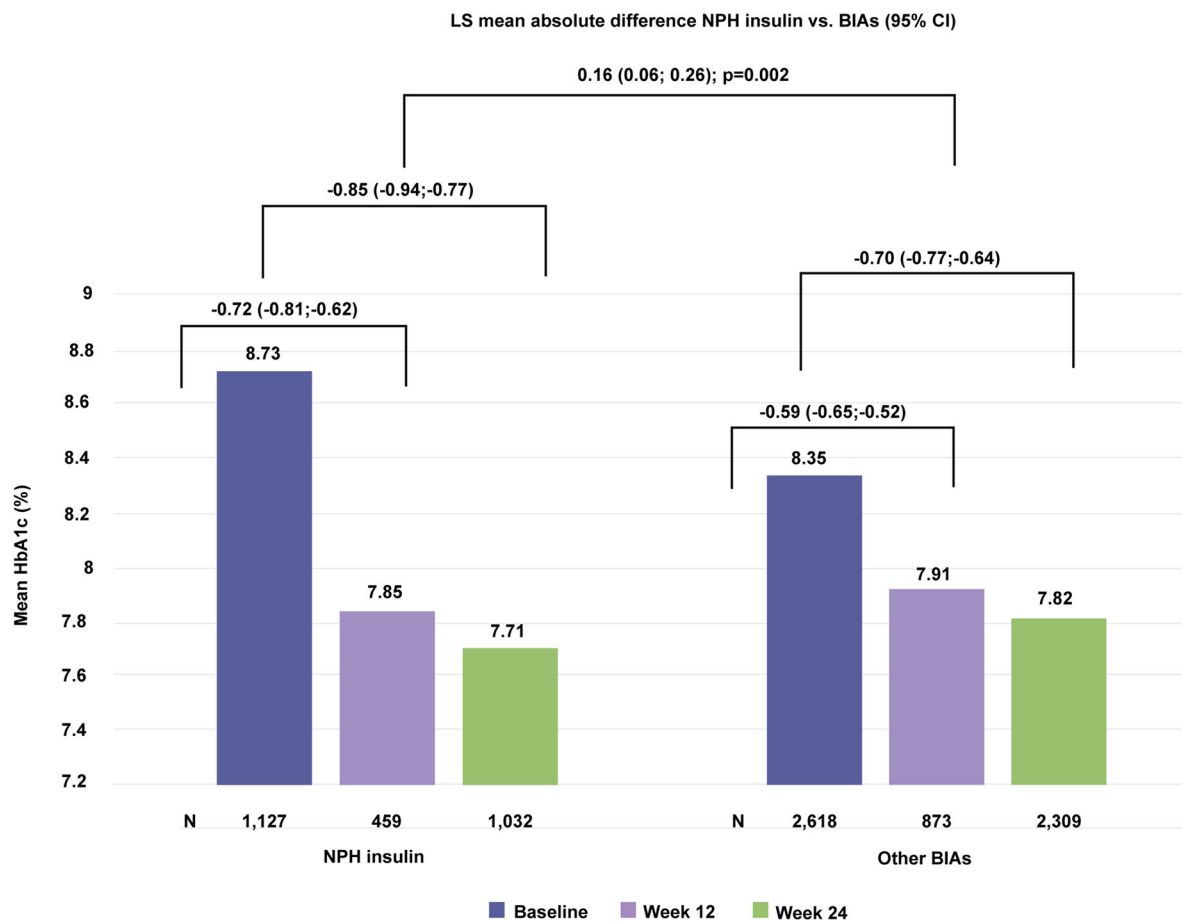


Fig. 1 Observed mean haemoglobin A1c (HbA1c) and least squares (LS) mean change (95% confidence interval [CI]) in HbA1c from baseline to weeks 12 and 24 according to previous basal insulin. N = number of

patients with available data at each time point. *BIA* basal insulin analogue, *NPH* neutral protamine Hagedorn

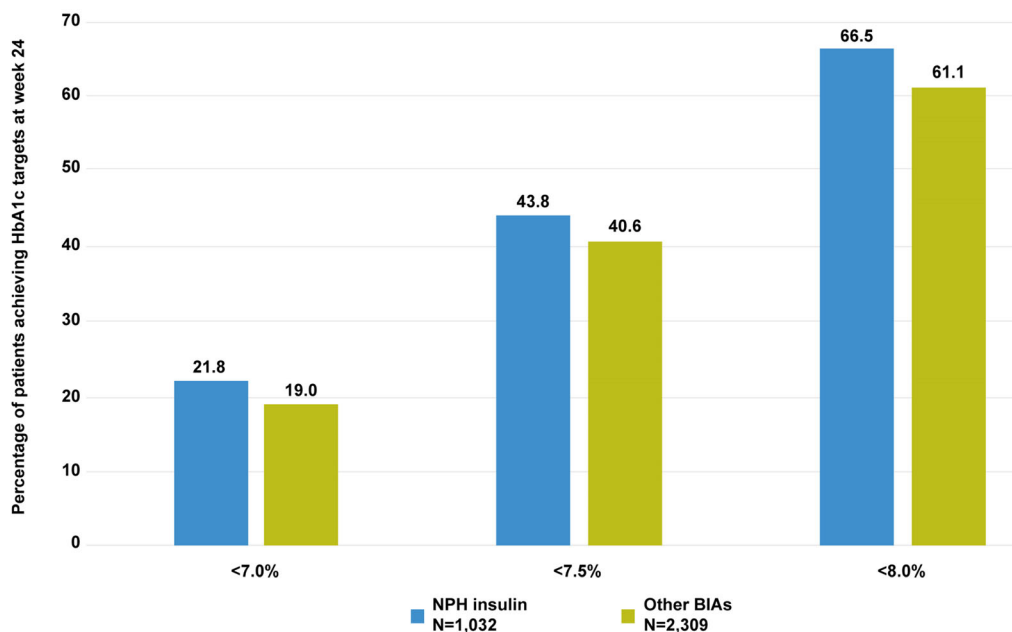


Fig. 2 Percentage (%) of patients achieving haemoglobin A1c (HbA1c) targets < 7.0%, < 7.5%, and < 8.0% at week 24 according to previous basal insulin. *BIA* basal insulin analogue, *NPH* neutral protamine Hagedorn

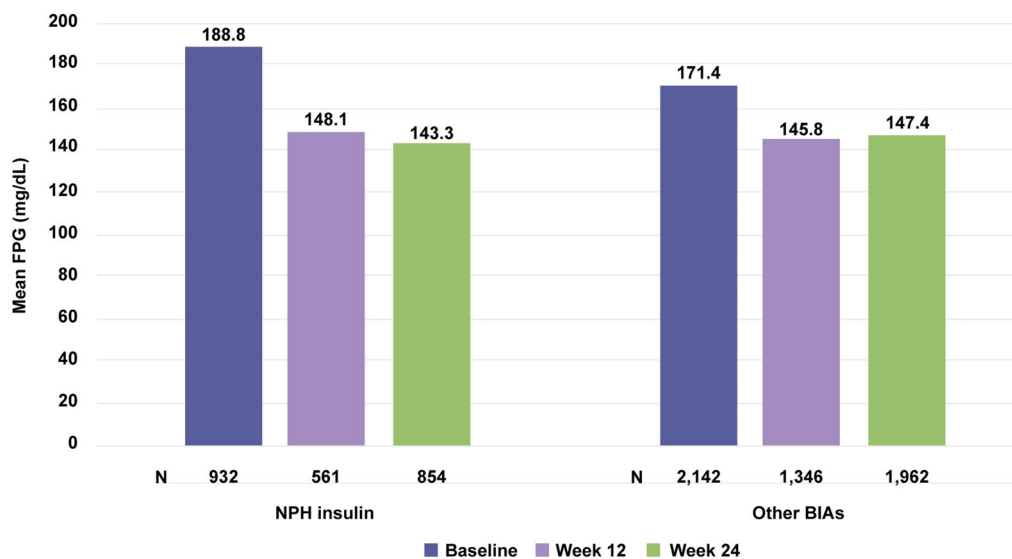


Fig. 3 Observed mean fasting plasma glucose (FPG) during the 24-week treatment period according to previous basal insulin. *N* = number of patients with available data

at each time point. *BIA* basal insulin analogue, *NPH* neutral protamine Hagedorn

(Table 2). The observed daily dose of Gla-300 slightly increased from baseline to week 24 by an overall mean change of 0.07 U/kg/day (approximately 6 U/day) in both subgroups, with the greatest dose increase during the initial

12 weeks of Gla-300 treatment (Table 3). Body weight remained stable throughout the 24-week Gla-300 treatment period (Table 3).

Table 2 Incidence and event rate of hypoglycaemic events according to previous basal insulin

	Previous NPH insulin (<i>N</i> = 1213)	Previous BIAs (<i>N</i> = 2877)	Total (<i>N</i> = 4372)
Total patient-year exposure	533.88	1225.75	1898.81
Any time of the day hypoglycaemia			
Symptomatic hypoglycaemia			
Patients with ≥ 1 event, <i>n</i> (%)	133 (11.0)	306 (10.6)	483 (11.0)
Total number of events (event rate)	589 (1.10)	1,599 (1.30)	2,278 (1.20)
Severe hypoglycaemia			
Patients with ≥ 1 event, <i>n</i> (%)	4 (0.3)	16 (0.6)	21 (0.5)
Total number of events (event rate)	6 (0.011)	29 (0.024)	36 (0.019)
Nocturnal hypoglycaemia			
Symptomatic hypoglycaemia			
Patients with ≥ 1 event, <i>n</i> (%)	42 (3.5)	80 (2.8)	130 (3.0)
Total number of events (event rate)	72 (0.13)	183 (0.15)	265 (0.14)
Severe hypoglycaemia			
Patients with ≥ 1 event, <i>n</i> (%)	1 (0.1)	6 (0.2)	7 (0.2)
Total number of events (event rate)	1 (0.002)	10 (0.008)	11 (0.006)

The event rate is calculated as the total number of events divided by total patient-years of exposure

BIA basal insulin analogue, *NPH* neutral protamine Hagedorn

DISCUSSION

Switching BI in people with T2DM is motivated by several factors including suboptimal glucose control, unacceptable frequency of hypoglycaemia, fear of weight gain, titration difficulties, or low treatment adherence resulting from a complex regimen and heavy injection burden [5, 11]. In this REALI pooled analysis conducted in a large and clinically diverse population with T2DM, switching to Gla-300 from another BI (i.e., NPH insulin, Gla-100, insulin detemir, insulin degludec) was associated with a clinically meaningful and continuous decrease in HbA1c, especially in those switching from NPH

insulin. These results are encouraging, particularly since patients previously treated with NPH insulin had higher levels of baseline HbA1c and FPG compared to those previously treated with BIAs, which may be related to a greater number and/or severity of hypoglycaemia episodes usually seen with NPH insulin compared to insulin glargine/detemir therapy, curbing the titration process [24].

The glycaemic improvement in the REALI analysis was achieved without any weight gain and with a low incidence of symptomatic and severe hypoglycaemia. Our results support the findings from randomised controlled trials (RCTs) and from other real-world studies not included in this REALI analysis conducted in

Table 3 Changes from baseline in observed Gla-300 daily dose and in observed body weight according to previous basal insulin

	Previous NPH insulin (<i>N</i> = 1213)	Previous BIAs (<i>N</i> = 2877)	Total (<i>N</i> = 4372)
Gla-300 daily dose (U/day)			
Baseline	29.4 ± 16.3	35.4 ± 19.6	33.5 ± 18.6
Week 12	33.7 ± 17.0	41.1 ± 23.0	38.6 ± 21.3
Change from baseline to week 12	4.7 ± 9.3	5.9 ± 11.7	5.5 ± 10.8
Week 24	35.6 ± 19.6	41.7 ± 23.7	39.6 ± 22.3
Change from baseline to week 24	5.8 ± 10.7	6.3 ± 14.4	6.0 ± 13.0
Gla-300 daily dose (U/kg/day)			
Baseline	0.31 ± 0.16	0.37 ± 0.19	0.36 ± 0.18
Week 12	0.38 ± 0.17	0.48 ± 0.24	0.44 ± 0.21
Change from baseline to week 12	0.06 ± 0.10	0.08 ± 0.13	0.07 ± 0.12
Week 24	0.38 ± 0.20	0.44 ± 0.22	0.42 ± 0.21
Change from baseline to week 24	0.07 ± 0.11	0.07 ± 0.16	0.07 ± 0.14
Body weight (kg)			
Baseline	92.9 ± 17.0	94.4 ± 17.7	93.3 ± 17.5
Week 24	93.3 ± 17.5	95.3 ± 18.1	94.1 ± 17.8

All data are expressed as mean ± standard deviation (SD)
BIA basal insulin analogue, *Gla-300* insulin glargine 300 U/ml, *NPH* neutral protamine Hagedorn

people with inadequately controlled T2DM, in which switching to Gla-300 from other BIs was

associated with an improved glycaemic control regardless of the nature or duration of prior BI therapy, a reduced incidence of hypoglycaemia, and a neutral or positive effect on body weight [6, 25–27]. The low incidence of symptomatic and severe hypoglycaemia after switching to Gla-300 from previous BIs can be attributed to the flat and stable pharmacokinetic/pharmacodynamic profile of Gla-300 and its 24-h duration of action that help to reduce the magnitude and frequency of blood glucose fluctuations [28].

Fear of hypoglycaemia is known to reduce patients' adherence to insulin regimens and decrease their quality of life, as it can promote compensatory behaviours to avoid hypoglycaemia, such as decreased or omitted insulin doses, resulting in poor glycaemic control and an increased risk of serious health consequences [29]. Hence, the reported low incidence of hypoglycaemia associated with Gla-300 is important to give people with T2DM the confidence to initiate and optimise their BI therapy and to better control their disease in the long term. The reduction of hypoglycaemia incidence by switching to Gla-300 from another BI regimen has also been found to have a positive economic impact by reducing healthcare utilisation such as inpatient hospitalisation rates and emergency department visits [26].

Insulin titration is another challenging issue in routine clinical practice. In the EDITION 1 and EDITION 2 RCTs, people with T2DM who switched from Gla-100 or NPH insulin to Gla-300 showed a mean dose increase of 0.28–0.36 U/kg/day from baseline to week 24 of Gla-300 therapy, with the greatest Gla-300 dose increase during the initial 12 weeks of treatment (of 0.25–0.31 U/kg/day) [6]. In the present REALI analysis, the dose of Gla-300 also increased until week 12 of treatment and then stabilised. However, in REALI, mean Gla-300 dose increased from baseline to weeks 12 and 24 of treatment by only 0.07 U/kg/day at both time points, suggesting that changes in insulin dosing in routine clinical practice are smaller than those seen in RCTs. Due to its stable pharmacokinetic/pharmacodynamic profile as well as its longer duration of action lasting up to 24 h, Gla-300 requires overall less frequent titration

than other BIs to reach steady state over the dosing period [30]. Nevertheless, the small increase in the mean daily dose of Gla-300 that was reported in REALI suggests that more efforts regarding timely and efficient BI titration are needed in routine clinical practice, with a well-defined and easy BI treatment algorithm as well as continuous patient education and empowerment [11, 12, 16, 27].

There are limitations to the current pooled analysis, such as the relatively short treatment duration and the presence of a potential reporting bias, which is inherent to observational studies. There is usually underreporting of hypoglycaemic events in real-world studies, which may lead to underestimation of absolute rates of hypoglycaemia. This underestimation is also possible in RCTs, in which patient-reported hypoglycaemic episodes are compared with glucometer records [31]. However, in the present analysis, the direction of changes in hypoglycaemia risk throughout the 24-week Gla-300 treatment period as well as between-group comparisons seems to be maintained, thereby lending confidence to the data reported herein. Of note, symptomatic and severe hypoglycaemias occurring at any time of the day (24 h) and during the night were the only types of hypoglycaemic events that were consistently reported across the individual pooled studies [9–19]. Other hypoglycaemic events (e.g., asymptomatic hypoglycaemia, symptomatic confirmed hypoglycaemia, daytime hypoglycaemia) were not reported across all individual studies and were hence not included in the REALI analysis. Likewise, assessment of hypoglycaemia during the 4-week period before Gla-300 initiation was not reported in most individual studies. In addition, this REALI analysis did not pool data on Gla-300-related adverse events/serious adverse events other than hypoglycaemia, since the individual studies did not identify new adverse events or safety signals during Gla-300 treatment. All reported adverse events in the individual studies [9–19] were consistent with Gla-300's established safety profile. Furthermore, although there is a diverse representation of countries across Europe in REALI, bias may exist in some data given the inclusion of different countries with

different healthcare systems and practices, which may impact T2DM management, particularly the choice of BI for insulin initiation as well as BI titration. For example, in some European countries (e.g., Serbia, Norway, Sweden, Hungary), NPH insulin is recommended by local guidelines as the first-line insulin over BIAs. Another limitation of this pooled analysis is the lack of a comparator arm versus Gla-300 inherent to the design of the individual studies [9–19].

This pooled analysis is nevertheless strengthened by its large sample size as well as the prospective nature of the evaluated studies increasing the reliability of data when compared to retrospective real-world data analyses. Additional strengths include the application of standardised endpoint definitions to reduce study-specific differences, the adoption of a MMRM analysis with adjustments for baseline factors, and the relatively high external validity of the included studies as a result of the lack of strict inclusion and exclusion criteria. Overall, this REALI analysis offers valuable insight regarding the effectiveness and safety of Gla-300 administered in routine clinical practice among people with T2DM suboptimally controlled on NPH insulin or other BIAs.

CONCLUSIONS

Irrespective of previous BI therapy, switching to Gla-300 was associated with improved glycaemic control without weight gain and with a low incidence of symptomatic and severe hypoglycaemia in people with T2DM suboptimally controlled on BI with or without OADs. However, a slightly greater glucose-lowering effectiveness was observed in people pre-treated with NPH insulin.

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

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