Diabetes Ther (2021) 12:1073–1097
https://doi.org/10.1007/s13300-021-01030-0

ORIGINAL RESEARCH

Impact of Age on the Effectiveness and Safety of Insulin Glargine 300 U/mL: Results from the REALI European Pooled Data Analysis

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Received: January 12, 2021 / Accepted: February 10, 2021 / Published online: March 1, 2021

ABSTRACT

Introduction: Patients aged ≥ 65 years continue to be underrepresented in clinical studies related to type 2 diabetes mellitus (T2DM). Accordingly, the REALI pooled analysis was performed to evaluate the effectiveness and safety of insulin glargine 300 U/mL (Gla-300) across different age subgroups, using data from 14 interventional and non-interventional studies.

Methods: Pooled efficacy and safety data were collected from 8106 European patients with uncontrolled T2DM who were initiated on or switched to Gla-300 injected once daily for 24 weeks. Patients were categorised into five age subgroups: < 50 (*N* = 727), 50–59 (*N* = 2030), 60–69 (*N* = 3054), 70–79 (*N* = 1847) and ≥ 80 years (*N* = 448).

Results: Mean baseline haemoglobin A1c (HbA1c) decreased linearly from the youngest (9.10%) to the oldest (8.46%) age subgroup. Following Gla-300 initiation, there were similar HbA1c reductions across age groups, with a least

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squares mean (95% confidence interval) change in HbA1c from baseline to week 24 of − 1.09% (− 1.18 to − 1.00), − 1.08% (− 1.14 to − 1.03), − 1.12% (− 1.17 to − 1.07), − 1.18% (− 1.24 to − 1.12) and − 1.11% (− 1.23 to − 0.99) in the < 50, 50–59, 60–69, 70–79 and ≥ 80 years subgroups, respectively. The incidences and event rates of reported hypoglycaemia were overall low. Compared to younger age subgroups, lower incidences of symptomatic hypoglycaemia occurring at any time of the day (5.9 vs. 7.6–9.4% for the younger subgroups) or during the night (0.5 vs. 1.6–2.5%) were recorded in patients aged ≥ 80 years. By contrast, the highest incidence of severe hypoglycaemia occurring any time of the day was reported in the subgroup aged ≥ 80 years (1.1 vs. 0.1–0.6% for the younger age subgroups).

Conclusion: Gla-300 initiated in patients with uncontrolled T2DM provides glycaemic improvement with a favourable safety profile across a wide range of ages.

Keywords: Age; Europe; Glycaemic control; Hypoglycaemia; Insulin glargine 300 U/mL; Older adults; Pooled analysis; Type 2 diabetes

Key Summary Points

Why carry out this study?

Treatment of uncontrolled type 2 diabetes mellitus (T2DM) in elderly patients is more challenging than in non-elderly patients because of age-related pathophysiological features, increased prevalence of comorbidities, polypharmacy and difficulties in adhering to complex self-care activities.

Considering the limited data focusing on T2DM care in older adults, the REALI pooled analysis was performed to evaluate the effectiveness and safety of insulin glargine 300 U/mL (Gla-300) across different age subgroups, using data from 14 interventional and non-interventional studies reflecting clinical practice in different European countries.

What was learned from the study?

Gla-300 therapy initiated in patients with uncontrolled T2DM is associated with clinically important and consistent reductions in haemoglobin A1c and fasting plasma glucose levels across a wide range of ages, with limited hypoglycaemia concerns.

The findings of the REALI pooled analysis indicate that Gla-300 might be a suitable therapeutic option in elderly patients who represent a vulnerable population prone to hypoglycaemia.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13808264.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing public health burden in older adults. Worldwide, an estimated 135.6 million people aged 65–99 years had diabetes in 2019, and this number is expected to increase to 276.2 million in 2045 [1]. Management of T2DM in elderly patients is challenging for clinicians due to the difficulty in individualising glycaemic targets and treatment strategies, as well as to the presence of coexisting comorbidities, polypharmacy and hypoglycaemic risk [2]. Indeed, older adults with T2DM have a higher risk of premature death, functional disability, accelerated muscle loss, depression, cognitive dysfunction, renal impairment and cardiovascular diseases, such as hypertension, coronary heart disease and stroke, than those without T2DM [3, 4]. At the same time, older adults with T2DM are more prone to hypoglycaemia than their younger counterparts for multiple reasons, such as potential difficulties with food ingestion,

insufficient adjustment of insulin dose, decreased renal function leading to slower clearance of drugs, reduced responses to counterregulatory hormones, lower blood glucose threshold for autonomic symptoms and higher blood glucose threshold for cognitive dysfunction [5, 6]. Furthermore, older adults with T2DM may either have elderly onset disease (diagnosed at age ≥ 65 years) or long-standing diabetes with onset in middle age or earlier years, adding to the complexity of T2DM management in the elderly [7].

Long-acting, once-daily basal insulin represents an effective and safe therapeutic option in older patients with T2DM not achieving glycaemic targets on oral glucose-lowering agents and/or glucagon-like peptide-1 (GLP-1) receptor agonists [3, 4, 6, 8]. Given the complexity of multiple-dose insulin regimens for older patients, once-daily basal insulin injection therapy is preferred in most elderly frail patients due to its ease of use and the limited risk of hypoglycaemia and disease-related distress [4, 6, 8–10]. Insulin glargine 300 U/mL (Gla-300) is a second-generation, long-acting basal insulin analogue, given as a once-daily subcutaneous injection, which has demonstrated comparable glycaemic control to that provided by insulin glargine 100 U/mL (Gla-100), with a reduced risk of hypoglycaemia at any time of the day and at night in a broad population of almost 2500 patients with T2DM enrolled in the EDITION phase III clinical trial programme [11]. A post-hoc analysis of the EDITION 1, 2 and 3 trials provided evidence of a comparable glycaemic control and a reduced risk of nocturnal hypoglycaemia for Gla-300 versus Gla-100 in both patients aged < 65 and ≥ 65 years [12]. SENIOR, a randomised controlled trial (RCT) comparing Gla-300 to Gla-100 in individuals with T2DM aged ≥ 65 years, showed comparable reductions in haemoglobin A1c (HbA1c) and a lower risk of documented symptomatic hypoglycaemia versus Gla-100, with a significant benefit on hypoglycaemic risk observed in participants aged ≥ 75 years [5].

With the exception of dedicated studies like SENIOR [5], patients aged ≥ 65 years continue to be underrepresented in clinical studies related to T2DM or to diabetes-associated conditions [13, 14], despite having the highest prevalence of diabetes of any age group (19.3%) [1]. In a descriptive analysis of 2484 diabetes-related interventional trials, very few trials (0.6%) selectively enrolled patients aged ≥ 65 years; specifically, patients > 65 years of age were excluded from 30.8% of studies and those aged > 75 years were excluded from 54.9% of studies [15]. Considering the limited data focusing on diabetes care in older adults, the REALI pooled analysis was performed to evaluate the effectiveness and safety of Gla-300 in different prespecified age subgroups, using data from 14 interventional and non-interventional studies reflecting clinical practice in different European countries.

METHODS

Study Selection and Population

Eligible studies for the REALI pooled analysis had to be prospective (interventional or observational) studies performed in European countries among patients with uncontrolled T2DM (i.e. in whom glycaemic targets have not been achieved) initiated on Gla-300 therapy, and had to have a duration of at least 24 weeks and individual participant-level data available for both efficacy and safety outcomes [16]. In the present analysis, 14 trials conducted between June 2015 and December 2018 were pooled (Table 1), ten of which are already published [17–27]. The rationale, methodology and a detailed description of the variables have been already provided in the published protocol of the REALI project [16].

In each study, Gla-300 was administered subcutaneously once daily, using a pre-filled insulin pen at the same time of the day ± 3 h if needed. Two of the included studies (Take Control [19] and ITAS [20]) were RCTs in which patients were allocated to a self- versus a physician-managed titration of Gla-300, whereas the other studies were single-arm, i.e. Gla-300 was administered using a physician-led titration algorithm. All studies, except COBALTA [25], were performed in the ambulatory care setting.

Table 1 Characteristics of the studies included in the REALI pooled analysis

Study name	Location(s)/ period of study	Study description	Key inclusion criteria	Sample (*N*)	Age range (years)	Age, years (mean ± SD)
Non-interventional studies						
Toujeo-Neo (ISRCTN number: ISRCTN93674355)	Germany/August 2015 to March 2017	52-week, observational, open-label, multicentre, prospective study to assess real-world effectiveness and safety of switching basal component of any BOTplus or any basal-bolus insulin regimen to Gla-300	Patients with T2DM previously treated with any basal insulin except Gla-300, and with an HbA1c $\geq$ 7.5% and $\leq$ 10.0% and a FPG > 130 mg/dL	1213	24–85	64.6 ± 10.6
OPTIN-D [27]	The Netherlands/ October 2015 to September 2017	24-week, multicentre, prospective, open-label, observational cohort study to document changes over time in PROs (e.g. emotional wellbeing, adherence, sleep quality and duration)	Patients with T2DM previously treated with insulin (basal ± prandial insulin) for $\geq$ 6 months prior to Gla-300 initiation	162	53–77	65.7 ± 6.9
To-Goal (Data on file)	Serbia/November 2017 to October 2018	15-month, prospective, observational study to evaluate real-life effectiveness and safety of Gla-300	Patients with T2DM previously treated with insulin (basal ± prandial insulin) without OADs	367	36–82	62.8 ± 8.4

Table 1 continued

Study name	Location(s)/ period of study	Study description	Key inclusion criteria	Sample (*N*)	Age range (years)	Age, years (mean ± SD)
TOP-2 [17]	Germany, Austria and Switzerland/ June 2015 to December 2016	52-week, observational, open-label, multicentre, prospective study to evaluate real-world effectiveness and safety of Gla-300 in patients uncontrolled on their previous BOT	Patients with T2DM previously treated with any basal insulin except Gla-300, and with an HbA1c $\geq$ 7.5% and $\leq$ 10.0%	1640	38–88	64.7 ± 10.1
Toujeo-BB [18]	Hungary/March 2016 to April 2017	24-week, single-arm, non-interventional, multicentre study aimed to evaluate real-world effectiveness of Gla-300 + insulin glulisine in patients uncontrolled on their previous basal-bolus regimen	Patients with T2DM previously treated with basal-bolus regimens (NPH + regular insulin), with an HbA1c $\geq$ 8.0% or $\geq$ 3 hypoglycaemic events per month requiring correction	229	44–75	61.6 ± 8.6

Table 1 continued

Study name	Location(s)/ period of study	Study description	Key inclusion criteria	Sample (*N*)	Age range (years)	Age, years (mean ± SD)
Toujeo-1 [21, 22]	Germany and Switzerland/ June 2015 to December 2017	52-week, non-interventional, multinational, multicentre, prospective study to evaluate real-world effectiveness and safety of initiating a BOT regimen with Gla-300	Insulin-naïve patients with T2DM previously treated with OADs, with an HbA1c $\geq$ 7.5% and $\leq$ 10.0%	1547	37–88	64.6 ± 11.1
TOPAZ [23]	Czech Republic/ May 2016 to March 2018	24-week, multicentre, prospective, observational, single-arm study to evaluate clinical effectiveness and safety of Gla-300	Patients with T2DM previously treated with basal insulin with or without OADs, and with an HbA1c > 7.6% or repeated hypoglycaemia	300	47–78	63.8 ± 7.5
MAGE [24]	Belgium/June 2016 to August 2018	12-month, multicentre, prospective, observational, single-arm study to assess treatment satisfaction, efficacy, and safety of Gla-300 in a real-world setting	Patients with T2DM for > 1 year, with an HbA1c $\geq$ 7.0% and $\leq$ 10.0%, previously treated with any basal insulin except Gla-300 plus mealtime insulin	93	45–77	63.7 ± 7.5

Table 1 continued

Study name	Location(s)/ period of study	Study description	Key inclusion criteria	Sample (*N*)	Age range (years)	Age, years (mean ± SD)
GOAL-Ro (Data on file)	Romania/ May 2017 to June 2018	24-week, prospective, observational study to evaluate real-life effectiveness and safety of Gla-300	Insulin-naïve patients with T2DM, with an HbA1c ≥ 7.0%	1048	45–72	60.2 ± 7.0
To UPGRADE (Data on file)	Bulgaria/July 2017 to December 2018	24-week, prospective, multicentre, non-interventional study to evaluate real-life effectiveness and safety of Gla-300	Patients with T2DM previously treated with NPH ± prandial insulin or premixed insulin with or without OADs	286	27–83	61.8 ± 9.5
Interventional, single-arm studies						
COBALTA [25] (EudraCT number: 2015–004,715-20)	Spain/June 2016 to July 2018	26-week, open-label, multicentre, single-arm study to evaluate efficacy and safety of Gla-300 during hospitalisation and therapy intensification at discharge	Hospitalised patients with T2DM who were ≥ 3 months on treatment with basal insulin with or without OADs, with an HbA1c ≥ 8.0% and ≤ 10.0%	112	53–88	72.3 ± 10

Table 1 continued

Study name	Location(s)/ period of study	Study description	Key inclusion criteria	Sample (*N*)	Age range (years)	Age, years (mean ± SD)
TRANSITION 2 [26] (ClinicalTrials.gov identifier: NCT02967237)	France/ January 2016 to July 2017	24-week, multicentre, prospective, open-label, single-arm study to evaluate efficacy and safety of Gla-300 in patients with suboptimal glucose control on another basal insulin for whom a therapeutic change was indicated	Patients with T2DM previously treated with basal insulin with or without other antidiabetics, HbA1c > 7.5%, and fasting SMPG > 130 mg/dL (mean of last 3 measures)	193	46–78	62.3 ± 8.0
Interventional, randomised controlled studies						
Take Control [19] (EudraCT number: 2015–001,626-42)	Greece, Spain, Czech Republic, Switzerland, Poland, Denmark, Slovenia, Slovakia, Croatia, UK/ February 2016 to June 2017	24-week, multinational, multicentre, open-label, randomised (1:1), two-arm, parallel-group study to compare efficacy and safety of self- versus physician-managed titration of Gla-300	Patients with T2DM for ≥ 1 year, who were for ≥ 6 months on treatment with ≥ 1 OAD, with or without a basal insulin, and with an HbA1c ≥ 7.0% and ≤ 10.0% for patients taking basal insulin, or ≥ 7.5% and ≤ 11.0% for insulin-naïve patients	631	41–81	63.9 ± 8.5

Table 1 continued

Study name	Location(s)/ period of study	Study description	Key inclusion criteria	Sample (*N*)	Age range (years)	Age, years (mean ± SD)
ITAS [20] (EudraCT Number: 2015–001,167-39)	Italy/September 2015 to October 2017	24-week, multicentre, open-label, randomised (1:1), parallel-group study to compare efficacy and safety of self- versus physician-managed titration of Gla-300	Insulin-naïve patients with T2DM for ≥ 1 year, with an HbA1c ≥ 7.5% and ≤ 10.0% on OADs	359	45–79	64.3 ± 8.4

BOT Basal insulin-supported oral therapy, *BOTplus* basal insulin-supported oral therapy plus a single or double dose of prandial insulin, *FPG* fasting plasma glucose, *Gla-300* insulin glargine 300 U/mL, *HbA1c* haemoglobin A1c, *NPH* neutral protamine Hagedorn, *OADs* oral antidiabetic drugs, *PROs* patient-reported outcomes, *SD* standard deviation, *SMPG* self-monitored plasma glucose, *T2DM* type 2 diabetes mellitus

Patients included within the REALI analysis were either insulin-naïve or previously treated with insulin (basal insulin ± prandial insulin) with or without non-insulin anti-hyperglycaemic agents. Exclusion criteria common for all studies included in this analysis were: the presence of cancer, a diagnosis of type 1 diabetes, pregnancy and/or breastfeeding, a history of alcohol or drug abuse, the presence of any clinically relevant somatic or mental disease, stage 5 chronic kidney disease, known hypersensitivity or intolerance to Gla-300 or any of its excipients and inability to self-measure blood glucose levels.

All pooled studies were conducted according to the principles of the Declaration of Helsinki and the requirements of Good Clinical Practice, 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.

Assessment of Outcomes

Glycaemic control was evaluated for age subgroups by determining the mean values of HbA1c and fasting plasma glucose (FPG) at initiation of Gla-300 (baseline) and subsequently at weeks 12 and 24 of Gla-300 therapy. Changes in HbA1c and FPG from baseline to weeks 12 and 24, as well as the percentages of patients achieving the HbA1c targets of < 7.0% (< 53 mmol/mol), < 7.5% (58.5 mmol/mol) and < 8.0% (63.9 mmol/mol) at week 24 of Gla-300 treatment were determined.

Safety endpoints included the percentage of patients with ≥ 1 hypoglycaemic event; the event rate of hypoglycaemic events; and the changes in daily insulin dose (in U/day and in U/kg/day) and body weight from baseline to weeks 12 and 24 of Gla-300 treatment. Hypoglycaemic events were reported according to their time of occurrence, during the night and at any time of the day. The definitions of

hypoglycaemia were predetermined in the present pooled analysis. Severe hypoglycaemia was defined as any event requiring assistance from another person to actively administer carbohydrates or glucagon or take other corrective actions. Symptomatic hypoglycaemia was defined as an event during which typical symptoms of hypoglycaemia occurred (e.g. sweating, hunger, shakiness, palpitations).

Statistical Analysis

Patients were categorised into five age subgroups: < 50, 50–59, 60–69, 70–79 and ≥ 80 years. Efficacy and safety outcomes were analysed using 10-year age strata to enable a detailed description of characteristics over a wide range of ages.

Baseline characteristics were reported as frequencies and percentages for categorical variables and as the mean, standard deviation (SD), median and first and third quartiles (Q1–Q3) for continuous variables. Mixed models for repeated measures (MMRM) in HbA1c and FPG were analysed to produce least squares (LS) mean estimates and 95% confidence intervals (CIs) for each age subgroup. All other endpoints were assessed descriptively. Hypoglycaemic event rates were calculated as the number of events per patient-year of exposure.

Given the exploratory nature of the investigation, there was no statistical adjustment for multiple comparisons. Missing patient baseline characteristics and missing outcome data were noted in some studies; no imputation of missing data was performed. All statistical tests were two-sided, with a p value of < 0.05 considered to be statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Study Population

In total, 8106 participants from 20 European countries were included in this patient-level pooled analysis, of whom 727 (9.0%) were aged < 50 years, 2030 (25.0%) were between the ages of 50 and 59 years, 3054 (37.7%) were between the ages of 60 and 69, 1847 (22.8%) were between the ages of 70 and 79 years and 448 (5.5%) were aged ≥ 80 years. Of the 8106 participants, 7929 (97.8%) were treated with at least one dose of Gla-300.

Overall, baseline characteristics were fairly comparable across the 14 pooled studies. Nevertheless, some differences were noted; for instance, participants in the interventional, single-arm COBALTA study [25] were of a substantially higher mean age (72.3 years) compared with participants in the other studies (mean age ranged from 60.2 to 65.7 years) (Table 1).

The baseline characteristics of the pooled study population (N = 8106) by 10-year age strata are summarised in Table 2. At baseline, the mean (± SD) age of the overall study population was 63.8 ± 9.7 years, with a mean (± SD) body mass index (BMI) of 32.0 ± 5.4 kg/m^2 and a median (Q1–Q3) T2DM duration of 10.0 (6.0–15.0) years. Slightly more than half of the patients (4323; 53.3%) were men.

Comparison of the five age subgroups revealed that the proportion of women was the highest in the subgroup aged ≥ 80 years (60.5 vs. 44.6–48.5% for the younger age subgroups) and that both baseline body weight and BMI decreased linearly with increasing age, with patients < 50 years having the highest mean BMI (33.5 vs. 29.9–32.6 kg/m^2 for the older age subgroups). Similarly, in studies reporting estimated glomerular filtration rate (eGFR) (N = 1698), baseline eGFR decreased with increasing age, with almost all patients aged ≥ 70 years experiencing some degree of renal impairment. As expected, the median diabetes duration of the 10-year age strata increased linearly from the youngest (6 years) to the oldest (14 years) age subgroup.

At baseline, most study participants were previously treated with insulin (4920/8106; 60.7%) and with Gla-100 in particular (1926/8106; 23.8%). In addition, 70.2% of the overall study population (N = 5687) was previously treated with at least one non-insulin anti-hyperglycaemic treatment. Compared to their

Table 2 Baseline characteristics by 10-year age strata

Characteristic	Age subroups (years)				
	< 50 (*N* = 727)	50–59 (*N* = 2030)	60–69 (*N* = 3054)	70–79 (*N* = 1847)	≥ 80 (*N* = 448)
Age (years)					
Mean ± SD	45.5 ± 3.7	55.2 ± 2.8	64.5 ± 2.9	73.9 ± 2.8	82.5 ± 2.3
Median (Q1–Q3)	47.0 (44.0–48.0)	56.0 (53.0–58.0)	65.0 (62.0–67.0)	74.0 (71.0–76.0)	82.0 (81.0–84.0)
Female, *n* (%)	334 (45.9)	906 (44.6)	1376 (45.1)	895 (48.5)	271 (60.5)
Body weight (kg)	96.6 ± 18.8	93.4 ± 16.8	91.6 ± 16.5	87.0 ± 15.5	81.3 ± 13.1
Body mass index (kg/m^2)	33.5 ± 6.2	32.6 ± 5.9	32.2 ± 5.1	31.0 ± 5.0	29.9 ± 4.3
eGFR (mL/min/1.73 m^2)	101.8 ± 19.1	90.2 ± 23.2	82.8 ± 43.5	73.0 ± 24.7	61.9 ± 23.1
Diabetes duration (years)	6.0 (3.0–10.0)	8.0 (5.0–13.0)	11.0 (7.0–16.0)	13.0 (9.0–19.0)	14.0 (9.0–20.0)
Previous insulin use, *n* (%)	371 (51.0)	1188 (58.5)	1864 (61.0)	1212 (65.6)	285 (63.6)
Prior basal insulin use, *n* (%)[a]	336 (46.2)	1065 (52.5)	1681 (55.0)	1077 (58.3)	241 (53.8)
Insulin glargine 100 U/mL	128 (38.1)	422 (39.6)	713 (42.4)	530 (49.2)	133 (55.2)
NPH insulin	114 (33.9)	319 (30.0)	501 (29.8)	276 (25.6)	52 (21.6)
Insulin detemir	48 (14.3)	162 (15.2)	231 (13.7)	142 (13.2)	24 (10.0)
Insulin degludec	30 (8.9)	83 (7.8)	99 (5.9)	82 (7.6)	23 (9.5)
Prior basal insulin dose (U/day)	38.3 ± 27.4	37.7 ± 24.2	36.8 ± 23.3	34.2 ± 22.6	28.7 ± 16.9
Prior rapid-acting insulin use, *n* (%)[b]	83 (11.4)	253 (12.5)	377 (12.3)	211 (11.4)	27 (6.0)
Insulin aspart	9 (10.8)	52 (20.6)	99 (26.3)	59 (28.0)	2 (7.4)
Insulin glulisine	6 (7.2)	30 (11.9)	29 (7.7)	22 (10.4)	2 (7.4)
Insulin lispro	8 (9.6)	23 (9.1)	44 (11.7)	26 (12.3)	12 (44.4)
Other insulin	48 (57.8)	99 (39.1)	134 (35.5)	72 (34.1)	9 (33.3)
Previous non-insulin anti-hyperglycaemic treatment, *n* (%)[c]	465 (64.0)	1420 (70.0)	2083 (68.2)	1395 (75.5)	324 (72.3)
Biguanides	368 (79.1)	1073 (75.6)	1585 (76.1)	988 (70.8)	170 (52.5)
Dipeptidyl peptidase-4 inhibitors	144 (31.0)	413 (29.1)	643 (30.9)	487 (34.9)	138 (42.6)
Sulphonylurea	100 (21.5)	264 (18.3)	532 (25.5)	351 (25.2)	54 (16.7)
SGLT-2 inhibitors	103 (22.2)	296 (20.8)	316 (15.2)	168 (12.0)	53 (16.4)
GLP-1 receptor agonists	45 (9.7)	117 (8.2)	145 (7.0)	54 (3.9)	3 (0.9)
Patients with ≥ 1 CV event or risk factor, *n* (%)	441 (60.7)	1494 (73.6)	2502 (81.9)	1532 (82.9)	386 (86.2)
Hypertension	355 (48.8)	1295 (63.8)	2266 (74.2)	1406 (76.1)	365 (81.5)

Table 2 continued

Characteristic	Age subroups (years)				
	< 50 (*N* = 727)	50–59 (*N* = 2030)	60–69 (*N* = 3054)	70–79 (*N* = 1847)	≥ 80 (*N* = 448)
Dyslipidaemia	243 (33.4)	796 (39.2)	1350 (44.2)	679 (36.8)	112 (25.0)
Peripheral arterial disease	31 (4.3)	248 (12.2)	546 (17.9)	390 (21.1)	100 (22.3)
Previous myocardial infarction	19 (2.6)	142 (7.0)	301 (9.9)	214 (11.6)	65 (14.5)
Previous stroke	3 (0.4)	92 (4.5)	225 (7.4)	184 (10.0)	44 (9.8)
Other ischaemic heart disease	15 (2.1)	140 (6.9)	336 (11.0)	210 (11.4)	31 (6.9)
Patients with ≥ 1 diabetic complication, *n* (%)	140 (19.3)	469 (23.1)	895 (29.3)	412 (22.3)	45 (10.0)
Diabetic neuropathy	107 (14.7)	340 (16.7)	639 (20.9)	249 (13.5)	14 (3.1)
Diabetic retinopathy	22 (3.0)	133 (6.6)	281 (9.2)	156 (8.4)	14 (3.1)
Diabetic nephropathy	22 (3.0)	112 (5.5)	211 (6.9)	154 (8.3)	12 (2.7)
HbA1c (%)	9.10 ± 1.37	8.90 ± 1.33	8.80 ± 2.08	8.49 ± 1.05	8.46 ± 0.94
FPG (mg/dL)	185.5 ± 59.8	183.5 ± 55.6	182.1 ± 54.4	177.6 ± 51.7	184.0 ± 56.1

Data are expressed as the mean ± SD or the median with first and third quartiles (Q1–Q3) in parentheses, unless otherwise indicated

N refers to all patients from the pooled REALI database included in the age subgroup mentioned; means and percentages are calculated based on data available for each variable

CV cardiovascular, *eGFR* estimated glomerular filtration rate, *GLP-1* glucagon-like peptide-1, *NPH* neutral protamine Hagedorn, *SGLT-2* sodium glucose co-transporter-2

[a] The total number of patients who were previously treated with basal insulin in each age subgroup was used as the denominator to calculate the percentages of patients who received prior insulin glargine, NPH, detemir, or degludec

[b] The total number of patients who were previously treated with rapid-acting insulin in each age subgroup was used as the denominator to calculate the percentages of patients who received prior insulin aspart, glulisine, lispro, or other

[c] The total number of patients who were previously treated with non-insulin anti-hyperglycaemic agents in each age subgroup was used as the denominator to calculate the percentages of patients in each drug class

younger counterparts, patients aged ≥ 70 years were more likely to be treated with Gla-100 at baseline (49.2–55.2% of those previously treated with basal insulin versus 38.1–42.4%, respectively). The use of biguanides, sodium glucose co-transporter-2 inhibitors, and GLP-1 receptor agonists decreased with increasing age, while the use of dipeptidyl peptidase-4 inhibitors increased with increasing age (Table 2).

The proportion of patients with at least one concomitant cardiovascular event or risk factor was higher with increasing age. By contrast, the proportion of patients with at least one diabetic complication was the highest in the subgroup aged 60–69 years (29.3%) and the lowest in the ≥ 80 years subgroup (10.0%).

Mean (± SD) baseline HbA1c decreased linearly from the youngest (9.10% ± 1.37) to the oldest (8.46% ± 0.94) age subgroup. By contrast, mean (± SD) baseline FPG values were higher in the < 50 (185.5 ± 59.8 mg/dL) and ≥ 80 years (184.0 ± 56.1 mg/dL) subgroups than in the other age subgroups (Table 2).

Glycaemic Control

The improvement in HbA1c levels from baseline to weeks 12 and 24 of Gla-300 therapy was notable in all five age subgroups, with comparable HbA1c reductions across subgroups (Table 3). At 12 weeks, the LS mean decrease in HbA1c from baseline ranged from − 0.88 to − 1.03% across the 10-year age strata. At 24 weeks, the LS mean (95% CI) change in HbA1c from baseline was − 1.09% (− 1.18 to − 1.00), − 1.08% (− 1.14 to − 1.03), − 1.12% (− 1.17 to − 1.07), − 1.18% (− 1.24 to − 1.12) and − 1.11% (− 1.23 to − 0.99) in the < 50, 50–59, 60–69, 70–79 and ≥ 80 years subgroups, respectively.

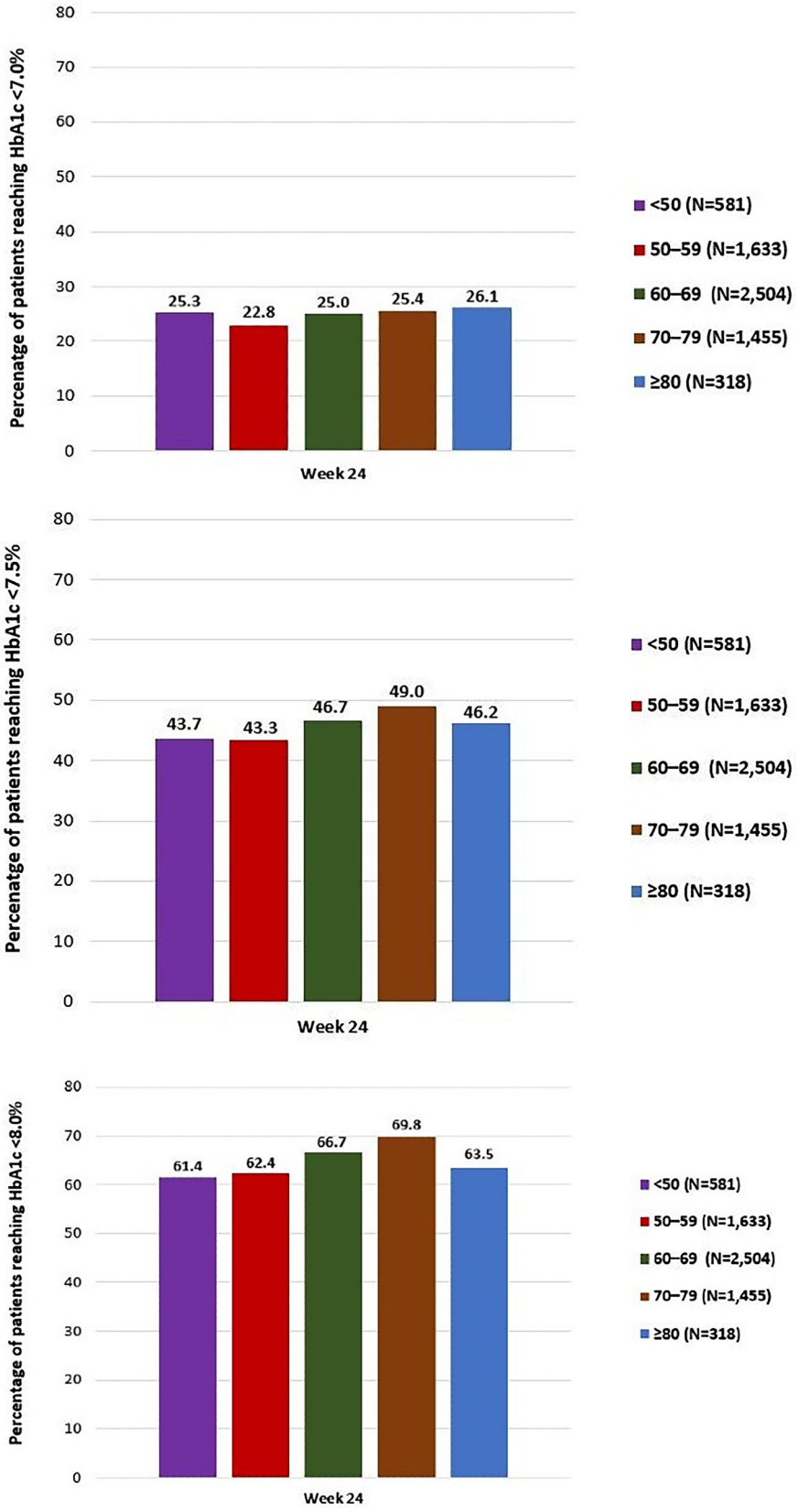
Table 3 Mean HbA1c and changes in HbA1c from baseline to weeks 12 and 24 of Gla-300 treatment by 10-year age subgroups

HbA1c (in %) parameters	Age subroups (years)				
	< 50 (*N* = 708)	50–59 (*N* = 1988)	60–69 (*N* = 2992)	70–79 (*N* = 1804)	≥ 80 (*N* = 437)
HbA1c at baseline, *n*	564	1583	2424	1390	297
Mean ± SD	9.13 ± 1.40	8.92 ± 1.34	8.81 ± 1.33	8.51 ± 1.08	8.45 ± 0.95
HbA1c at week 12, *n*	236	670	1155	556	59
Mean ± SD	7.80 ± 1.06	7.91 ± 1.08	7.87 ± 1.11	7.72 ± 0.97	7.61 ± 1.01
Change from baseline to week 12, *n*	233	657	1128	548	57
LS mean ± SE	− 0.92 ± 0.06	− 0.88 ± 0.03	− 0.89 ± 0.03	− 0.94 ± 0.04	− 1.03 ± 0.11
(95% CI)	(− 1.03; − 0.81)	(− 0.95; − 0.81)	(− 0.94; − 0.83)	(− 1.01; − 0.87)	(− 1.24; − 0.82)
LS mean ± SE difference[a]	–	0.04 ± 0.06	0.03 ± 0.06	− 0.02 ± 0.07	0.11 ± 0.12
(95% CI)	–	(− 0.09; 0.16)	(− 0.09; 0.15)	(− 0.15; 0.11)	(− 0.35; 0.12)
Associated *p* value	–	0.546	0.604	0.739	0.355
HbA1c at week 24, *n*	581	1633	2504	1455	318
Mean ± SD	7.78 ± 1.20	7.77 ± 1.16	7.68 ± 1.12	7.63 ± 0.98	7.58 ± 0.95
Change from baseline to week 24, *n*	554	1544	2362	1363	291
LS mean ± SE	− 1.09 ± 0.05	− 1.08 ± 0.03	− 1.12 ± 0.02	− 1.18 ± 0.03	− 1.11 ± 0.06
(95% CI)	(− 1.18; − 1.00)	(− 1.14; − 1.03)	(− 1.17; − 1.07)	(− 1.24; − 1.12)	(− 1.23; − 0.99)
LS mean ± SE difference[a]	–	0.01 ± 0.05	− 0.03 ± 0.05	− 0.09 ± 0.05	− 0.02 ± 0.08
(95% CI)	–	(− 0.09; 0.11)	(− 0.13; 0.06)	(− 0.19; 0.01)	(− 0.17; 0.13)
Associated *p* value	–	0.893	0.506	0.087	0.800

n refers to the number of patients with available data

CI confidence interval, *LS* least squares, *SE* standard error

[a] For the difference between the subgroups, the reference is the subgroup aged < 50 years


Percenatge of patients reaching HbA1c <7.0%
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50
40
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25.3
22.8
25.0
25.4
26.1
Week 24
<50 (N=581)
50–59 (N=1,633)
60–69 (N=2,504)
70–79 (N=1,455)
≥80 (N=318)
Percenatge of patients reaching HbA1c <7.5%
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Week 24
<50 (N=581)
50–59 (N=1,633)
60–69 (N=2,504)
70–79 (N=1,455)
≥80 (N=318)
Percentage of patients reaching HbA1c <8.0%
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61.4
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66.7
69.8
63.5
Week 24
<50 (N=581)
50–59 (N=1,633)
60–69 (N=2,504)
70–79 (N=1,455)
≥80 (N=318)

◀**Fig. 1** Percentage of patients achieving glycated haemoglobin (*HbA1c*) targets at week 24 of insulin glargine 300 U/mL (Gla-300) treatment, by 10-year age strata

The improvement in HbA1c across the 10-year age strata translated into similar HbA1c target achievements at 24 weeks of Gla-300 therapy (Fig. 1). Between 22.8 and 26.1% of patients across the five age subgroups achieved HbA1c < 7.0% at 24 weeks, and between 43.3 and 49.0% achieved HbA1c < 7.5%.

In line with changes in HbA1c, the LS mean change in FPG from baseline to weeks 12 and 24 of Gla-300 therapy was also comparable across the 10-year age strata (Table 4).

Safety

The incidence and rate of hypoglycaemic events reported over the 24-week Gla-300 treatment period were overall low, with the incidence of hypoglycaemia occurring at any time of day ranging from 8.9 to 12.4% and the incidence of nocturnal hypoglycaemia ranging from 0.7 to 3.1% across the five age subgroups (Table 5). Compared to the younger age subgroups, a lower incidence of symptomatic hypoglycaemia occurring at any time of the day or during the night was recorded in patients aged ≥ 80 years (5.9% vs. 7.6–9.4% or 0.5% vs. 1.6–2.5%, respectively). Very few severe hypoglycaemic episodes occurring at any time of the day were reported, but the highest incidence was observed in the subgroup aged ≥ 80 years (1.1 vs. 0.1–0.6% for the younger age subgroups). No nocturnal severe hypoglycaemic events were reported in the subgroup aged ≥ 80 years (Table 5).

The daily dose of Gla-300 (expressed in both U/day and in U/kg/day) increased over the 24-week Gla-300 treatment period in all five age subgroups (Table 6), but the mean increase was the highest in the subgroup aged < 50 years (+ 9.21 U/day and + 0.10 U/kg/day at 24 weeks) and the lowest in the subgroup aged ≥ 80 years (+ 5.12 U/day and + 0.07 U/kg/day at 24 weeks).

The mean (± SD) change in body weight from baseline to week 12 and week 24 of Gla-300 therapy was marginal across all age subgroups (Table 6).

DISCUSSION

Findings from the REALI pooled analysis demonstrated that treatment with Gla-300 initiated in patients with uncontrolled T2DM improved glycaemic control with a favourable safety profile across a wide range of ages. In daily practice, practitioners treating elderly patients with uncontrolled T2DM may face more challenges than with younger patients, due to age-related deterioration in glucose tolerance, a reduction in endogenous insulin secretion and difficulties in adhering to complex self-care activities [3, 4, 28]. Aging may also modify the counterregulatory and symptomatic responses to hypoglycaemia, which can lead to less intense symptoms of hypoglycaemia, consequently increasing the risk of hypoglycaemia in elderly patients due to hypoglycaemia unawareness [6, 29]. Finally, progressive renal impairment, as well as insulin deficiency requiring insulin therapy, may contribute to the higher risk of hypoglycaemia in older adults [4, 6].

Although a key objective in older people with uncontrolled T2DM is to minimise hypoglycaemia, achieving appropriate glycaemic goals remains important [3, 4, 12]. The Endocrine Society recommends individualised glycaemic targets ranging from ≥ 7.0% (53 mmol/mol) to < 8.5% (69 mmol/mol) in older adults tailored to overall health (e.g. number of comorbidities, degree of cognitive impairment) and to management strategies (e.g. where medication that can cause hypoglycaemia is used) [3]. Similarly, according to the most recent clinical practice recommendations of the American Diabetes Association (ADA), older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should adhere to a HbA1c target < 7.0–7.5%, while those with multiple coexisting chronic illnesses, cognitive impairment or functional dependence should have less stringent glycaemic goals (such as HbA1c < 8.0–8.5%) [4]. In the REALI pooled

analysis, approximately half of the patients, including those in the older age subgroups, achieved target HbA1c values < 7.5% at 24 weeks of Gla-300 therapy, and approximately two-thirds achieved an HbA1c target < 8.0%, which is mostly consistent with the level of glycaemic control recommended by the current clinical practice guidelines [3, 4, 8].

The clinically important and consistent reductions from baseline in HbA1c levels that were noted in REALI in different age subgroups are supported by the results of real-world studies and RCTs evaluating Gla-300 in patients aged ≥ 65 years with T2DM who were uncontrolled on their prior anti-hyperglycaemic regimen [5, 12, 30, 31]. In DELIVER 3 [31], a propensity-matched, retrospective, cohort

Table 4 Mean FPG and changes in FPG from baseline to weeks 12 and 24 of Gla-300 treatment by 10-year age subgroups

FPG (mg/dL) parameters	Age subroups (years)				
	< 50 (*N* = 708)	50–59 (*N* = 1988)	60–69 (*N* = 2992)	70–79 (*N* = 1804)	≥ 80 (*N* = 437)
FPG at baseline, *n*	358	1140	1704	1164	277
Mean ± SD	187.4 ± 58.7	184.1 ± 54.8	181.9 ± 54.2	177.8 ± 51.5	185.0 ± 52.0
FPG at week 12	260	838	1249	879	209
Mean ± SD	143.5 ± 40.7	145.2 ± 46.0	142.1 ± 43.8	138.5 ± 39.4	137.8 ± 39.9
Change from baseline to week 12, *n*	226	734	1118	769	159
LS mean ± SE	− 36.9 ± 2.7	− 33.8 ± 1.6	− 36.5 ± 1.3	− 38.5 ± 1.6	− 44.1 ± 3.2
(95% CI)	(− 42.2; − 31.6)	(− 36.9; − 30.7)	(− 39.1; − 33.9)	(− 41.5; − 35.4)	(− 50.5; − 37.8)
LS mean ± SE difference[a]	–	3.1 ± 3.0	0.4 ± 2.9	− 1.6 ± 3.0	− 7.3 ± 4.1
(95% CI)	–	(− 2.8; 9.0)	(− 5.2; 6.0)	(− 7.4; 4.2)	(− 15.2; 0.7)
Associated *p* value	–	0.298	0.889	0.592	0.0752
FPG at week 24, *n*	389	1215	1811	1253	321
Mean ± SD	145.3 ± 46.0	146.9 ± 47.1	140.4 ± 42.4	142.4 ± 76.0	136.7 ± 40.1
Change from baseline to week 24, *n*	343	1076	1621	1094	259
LS mean ± SE	− 37.1 ± 3.0	− 35.0 ± 1.8	− 40.1 ± 1.5	− 38.2 ± 1.8	− 45.3 ± 3.4
(95% CI)	(− 42.9; − 31.3)	(− 38.4; − 31.5)	(− 43.0; − 37.2)	(− 41.7; − 34.8)	(− 52.0; − 38.5)
LS mean ± SE difference[a]	–	2.1 ± 3.3	− 3.0 ± 3.2	− 1.1 ± 3.3	− 8.2 ± 4.4
(95% CI)	–	(− 4.3; 8.6)	(− 9.2; 3.2)	(− 7.6; 5.4)	(− 16.8; 0.5)
Associated *p* value	–	0.516	0.341	0.738	0.064

n refers to the number of patients with available data

[a] For the difference between the subgroups, the reference is the subgroup aged < 50 years

Table 5 Incidence and event rate of hypoglycaemic events, by 10-year age strata

Incidence/event rate of hypoglycaemia	Age subroups (years)				
	< 50 (*N* = 708)	50–59 (*N* = 1988)	60–69 (*N* = 2992)	70–79 (*N* = 1804)	≥ 80 (*N* = 437)
Total patient-year exposure	308.82	862.64	1313.51	770.21	174.16
Any time of the day hypoglycaemia					
Any hypoglycaemia					
Patients with ≥ 1 event, *n* (%)	63 (8.9)	179 (9.0)	332 (11.1)	224 (12.4)	44 (10.1)
Total number of events (event rate)[a]	277 (0.897)	790 (0.916)	1566 (1.192)	1128 (1.465)	317 (1.820)
Symptomatic hypoglycaemia[b]					
Patients with ≥ 1 event, *n* (%)	56 (7.9)	151 (7.6)	274 (9.2)	170 (9.4)	26 (5.9)
Total number of events (event rate)	243 (0.787)	614 (0.712)	1105 (0.841)	706 (0.917)	131 (0.752)
Severe hypoglycaemia[c]					
Patients with ≥ 1 event, *n* (%)	1 (0.1)	8 (0.4)	10 (0.3)	10 (0.6)	5 (1.1)
Total number of events (event rate)	1 (0.003)	8 (0.009)	22 (0.017)	15 (0.019)	6 (0.034)
Nocturnal hypoglycaemia					
Any hypoglycaemia					
Patients with ≥ 1 event, *n* (%)	13 (1.8)	47 (2.4)	92 (3.1)	46 (2.5)	3 (0.7)
Total number of events (event rate)	38 (0.123)	126 (0.146)	232 (0.177)	78 (0.101)	5 (0.029)
Symptomatic hypoglycaemiaa					
Patients with ≥ 1 event, *n* (%)	11 (1.6)	43 (2.2)	74 (2.5)	38 (2.)	2 (0.5)
Total number of events (event rate)	36 (0.117)	99 (0.115)	161 (0.123)	50 (0.065)	3 (0.017)
Severe hypoglycaemia					
Patients with ≥ 1 event, *n* (%)	0	4 (0.2)	3 (0.1)	2 (0.1)	0

Table 5 continued

Incidence/event rate of hypoglycaemia	Age subroups (years)				
	< 50 (*N* = 708)	50–59 (*N* = 1988)	60–69 (*N* = 2992)	70–79 (*N* = 1804)	≥ 80 (*N* = 437)
Total number of events (event rate)	0	4 (0.005)	8 (0.006)	2 (0.003)	0

[a] Event rates, which are based on total patient-year exposure, are expressed as the number of events per year

[b] Symptomatic hypoglycaemia was defined as an event during which typical symptoms of hypoglycaemia occurred (e.g. sweating, hunger, shakiness, palpitations)

[c] Severe hypoglycaemia was defined as any event requiring assistance from another person to actively administer carbohydrates or glucagon, or take other corrective actions

study examining clinical outcomes in 2352 patients with T2DM aged ≥ 65 years switching from basal insulin to Gla-300 or to a first-generation basal insulin (insulin detemir or Gla-100) in real-world clinical practice, HbA1c reductions were comparable in both cohorts, with significantly reduced hypoglycaemia incidences and event rates in the Gla-300 cohort [31]. Compared to REALI, patients in the Gla-300 cohort of DELIVER 3 (*N* = 1176) had higher mean HbA1c levels at the 3- to 6-months follow-up assessment (8.12% from a baseline HbA1c of 8.60% vs. 7.58–7.68% at week 24 from a baseline of 8.45–8.81% in patients aged ≥ 60 years in REALI). HbA1c target attainment was also lower in the Gla-300 cohort of DELIVER 3 [30] compared to REALI (< 7.0%: 19.3 vs. 25.0–26.1% in patients aged ≥ 60 years in REALI; < 8.0%: 50.9 vs. 63.5–69.8%). In the 26-week SENIOR RCT [5] conducted in 1014 patients aged ≥ 65 years with uncontrolled T2DM who received either Gla-300 (*N* = 508) or Gla-100 (*N* = 506), mean HbA1c decreased from 8.20% at baseline to 7.31% at week 26 among Gla-300-treated patients, with the proportion of Gla-300-treated patients reaching HbA1c targets of < 7.0% and < 7.5% of 33.3 and 60.6%, respectively. Among patients aged ≥ 75 years, who formed approximately 20% of the SENIOR study population, similar reductions in mean HbA1c from baseline to week 26 were observed, from 8.17 to 7.29% in Gla-300-treated patients (*N* = 135), with a significantly lower incidence of documented symptomatic hypoglycaemia occurring at any time of the day with Gla-300 compared with Gla-100 (1.5 vs. 10.4%; relative risk 0.33; 95% CI 0.12–0.88) [5]. Even though, compared to the present analysis, the study populations of SENIOR [5] and DELIVER 3 [30] were older (mean age of approx. 71 vs. 64 years in REALI), with a higher proportion of diabetic complications (approx. 50 vs. 24% in REALI), the results of the REALI analysis using 10-year age strata support the results of the SENIOR RCT [5] and the DELIVER three real-world analysis [30].

Overall, the REALI findings, along with the data from the aforementioned studies [5, 12, 30, 31], indicate that Gla-300 is a treatment option equally beneficial in both younger and older patients with T2DM, achieved through a sustained glycaemic control which contributes to minimising the risk of hypoglycaemia. Although insulin therapy, particularly intensive insulin therapy with basal insulin alone or with basal-bolus insulin, has been associated with weight gain in elderly patients [3], Gla-300 therapy had a weight-neutral effect in the present analysis across the evaluated age subgroups. This represents a practical advantage for both patients aged < 50 years who had the highest mean baseline BMI (33.5 kg/m^2) and those aged ≥ 80 years who had a lower mean baseline BMI (29.9 kg/m^2) and who were able to maintain a stable body weight.

Although elderly patients with T2DM are known to have a greater risk of hypoglycaemia compared to younger ones, Gla-300 therapy was associated with overall low incidence of hypoglycaemia in the present analysis across the

Table 6 Changes in Gla-300 daily dose and body weight from baseline to weeks 12 and 24 of treatment, by 10-year age strata

Gla-300 dose/body weight	Age subroups (years)				
	< 50 years (*N* = 708)	50–59 (*N* = 1988)	60–69 (*N* = 2992)	70–79 (*N* = 1804)	≥ 80 (*N* = 437)
Gla-300 daily dose (U/day)					
Baseline	28.41 ± 21.67	28.58 ± 18.77	28.61 ± 19.06	25.80 ± 17.07	21.03 ± 13.86
Week 12	37.27 ± 24.10	35.54 ± 20.00	35.70 ± 20.59	30.90 ± 16.91	26.26 ± 16.65
Change from baseline to week 12	8.68 ± 14.05	7.17 ± 12.14	7.10 ± 11.41	5.67 ± 10.15	5.86 ± 11.46
Week 24	38.45 ± 23.99	37.62 ± 21.78	36.60 ± 21.27	31.88 ± 19.73	26.36 ± 15.74
Change from baseline to week 24	9.21 ± 13.82	8.73 ± 13.97	7.87 ± 13.53	6.03 ± 13.45	5.12 ± 10.61
Gla-300 daily dose (U/kg/day)					
Baseline	0.30 ± 0.25	0.30 ± 0.18	0.30 ± 0.18	0.29 ± 0.17	0.26 ± 0.17
Week 12	0.44 ± 0.26	0.42 ± 0.20	0.41 ± 0.20	0.37 ± 0.16	0.34 ± 0.20
Change from baseline to week 12	0.12 ± 0.14	0.10 ± 0.14	0.09 ± 0.12	0.07 ± 0.11	0.03 ± 0.10
Week 24	0.40 ± 0.23	0.39 ± 0.20	0.39 ± 0.21	0.36 ± 0.20	0.33 ± 0.19
Change from baseline to week 24	0.10 ± 0.13	0.09 ± 0.14	0.09 ± 0.15	0.08 ± 0.15	0.07 ± 0.12
Body weight (kg)					
Baseline	96.56 ± 18.90	93.45 ± 16.80	91.58 ± 16.48	86.95 ± 15.52	81.16 ± 12.98
Week 12	90.47 ± 14.95	90.51 ± 14.38	88.86 ± 14.58	85.29 ± 14.47	73.35 ± 10.44
Change from baseline to week 12	-0.06 ± 2.76	0.01 ± 3.14	0.04 ± 2.38	0.00 ± 2.24	0.02 ± 1.59
Week 24	97.15 ± 18.81	94.96 ± 17.49	92.27 ± 16.83	87.50 ± 15.36	81.95 ± 13.55
Change from baseline to week 24	0.03 ± 5.01	0.12 ± 4.25	0.04 ± 3.67	-0.14 ± 3.82	-0.19 ± 3.33

All data are expressed as mean ± SD

evaluated age subgroups. In addition to its evenly distributed and stable pharmacokinetic exposure and pharmacodynamic profile [32], the simple, once-daily dosing regimen of Gla-300 may have contributed to this lower incidence of hypoglycaemia. Indeed, simplification of insulin regimens to match an individual's self-management abilities and their available social and medical support has been shown to reduce disease-related distress and hypoglycaemia risk without worsening glycaemic control [3, 4, 8]. A lower incidence and event rate of symptomatic hypoglycaemia occurring during the night or at any time of the day were recorded in patients aged ≥ 80 years compared to younger subgroups. We assume that this is

likely to be related to the impact of aging on counterregulatory and symptomatic responses, thereby reducing the intensity of hypoglycaemia symptoms [29]. A small study from the UK, which compared the responses to hypoglycaemia of young and elderly patients without diabetes, showed that autonomic and neuroglycopenic symptom scores were significantly lower in the older group [33]. Another small Canadian study similarly found diminished autonomic activation leading to attenuation of symptom intensity as a feature of aging, independent of any effects of diabetes [34]. In a more recent study from the USA among 40 patients aged ≥ 69 years with HbA1c values > 8.0%, 95 of the 102 (93.1%) hypoglycaemic episodes recorded were unrecognised by symptoms or by fingerstick glucose measurements performed four times a day [35]. The lower incidence of symptomatic hypoglycaemia occurring during the night or at any time of the day that was reported in REALI patients aged ≥ 80 years might also have been related to a more cautious use of Gla-300 in the oldest patients, as the Gla-300 dose change (expressed in U/kg/day) was approximately two-thirds the change observed in the youngest age subgroup.

Lack of hypoglycaemic symptoms recognition can render elderly patients more susceptible to severe hypoglycaemia [6], as reflected in the present pooled analysis by the higher incidence of severe hypoglycaemia occurring at any time of the day in patients aged ≥ 80 years compared to younger ones. The incidence of severe hypoglycaemia occuring at any time of the day remains, however, low in REALI (0.1–1.1% across age groups) and in the range of that observed in the SENIOR RCT (0.8% for all Gla-300 treated patients and 0% for patients aged ≥ 75 years) [5]. Overall, the low risk of hypoglycaemia with Gla-300 across a wide range of ages is an important finding, particularly for older adults with T2DM, given that clinical concern relating to hypoglycaemia and its associated adverse events is often a barrier to effective dose adjustment and attainment of target glycaemic control [32].

Using information from a U.S. electronic health records database, the real-world LIGHTNING study [36] predicted the rate of severe hypoglycaemia with Gla-300 across various patient subgroups with high hypoglycaemia risk, including both insulin-naïve patients aged ≥ 65 (N = 20885) and ≥ 75 years (N = 10325) and patients switching from another basal insulin analogue aged ≥ 65 (N = 15837) and ≥ 75 years (N = 5654). In all subgroup analyses, Gla-300 was associated with lower rates of severe hypoglycaemia compared to first-generation basal insulin analogues, such as Gla-100 and insulin detemir, irrespective of prior insulin therapy status [36]. Similarly, another post-hoc analysis, investigating the association of baseline patient characteristics with key outcomes reported from the EDITION 1, 2 and 3 trials, found that the comparable glycaemic control of Gla-300 versus Gla-100 with less hypoglycaemia seen in the EDITION studies was observed, irrespective of age, body mass index, age at T2DM onset or duration of T2DM [37]. In summary, the sustained glycaemic benefits of Gla-300 in the older adult population, as well as its reduced risk of hypoglycaemia compared to first-generation basal insulin analogues, support its use in older adults with T2DM. In addition, the flexibility and convenience of a once-daily injection of Gla-300 is advantageous in this population who may rely on caretakers to administer insulin [38].

Somewhat surprising was the inverse relationship between baseline glycaemic status and age, as indicated by the lower baseline mean HbA1c with increasing age. Nevertheless, several cross-sectional studies have reported a similar relationship between baseline HbA1c and age [39–41]. The reasons for such relationship need to be considered. The high baseline HbA1c levels seen in the youngest age subgroup may be related to the rapid changes in lifestyle that expose people, including those with diabetes, to increased biological and behavioural risk factors [39, 41]. It has also been speculated that older patients may have a different pathophysiological form of T2DM than younger ones, as found in a data-driven cluster analysis conducted among 8980 adults with newly diagnosed diabetes in which four subgroups of T2DM were identified with significantly different patient characteristics and risk of diabetic

complications [42]. One of these subgroups was labelled as mild age-related diabetes; patients in this cluster are older, with modest metabolic derangements and a lower HbA1c at diagnosis compared to patients in other clusters, such as severe autoimmune diabetes and severe insulin-deficient diabetes [42].

At baseline, more than two-thirds of the patients had been previously treated with at least one non-insulin anti-hyperglycaemic treatment. Interestingly, in a post-hoc analysis [43] of patient-level data from the EDITION 3 RCT and de-identified data from the Clinformatics real-world claims database, Gla-300 therapy initiated in insulin-naïve patients with T2DM uncontrolled on oral antidiabetic drugs (OADs) was associated with reductions in prior OAD therapy without compromising glycaemic control, while preserving the hypoglycaemic benefit of Gla-300 versus Gla-100 [43]. The ADA [4] currently recommends simplification of treatment regimens in older patients with T2DM to reduce the risk of hypoglycaemia and polypharmacy. Thus, since the post-hoc analysis [43] of data from EDITION 3 and from the Clinformatics real-world database suggests that patients treated with Gla-300 could step down OAD use without jeopardising glycaemic control and with a reduced hypoglycaemia risk, these findings, in line with those of REALI, could have important ramifications for clinical decision-making in older T2DM populations regarding regimen simplification.

Limitations of the REALI pooled analysis include the unbalanced and uncontrolled number of patients across the different age subgroups and the lack of assessments of cognitive function, functional capacity or frailty. REALI is also a post-hoc analysis, rather than a dedicated prospective trial in older individuals with T2DM. Another limitation is the lack of comparative data with another basal insulin. Moreover, the results of REALI may not have accounted for certain elderly individuals with T2DM, particularly in those aged $\geq$ 80 years, who were not accessible to enrolment in interventional or observational studies [44]. Furthermore, the REALI pooled analysis included the COBALTA study [25] conducted in 112 hospitalised patients, who represented less than 1.4% of the pooled study population. The inclusion of hospitalised patients does not influence the results of REALI, given their marginal number in the pooled analysis. However, we have also elected to pool the results of the Toujeo-Neo (ISRCTN number: ISRCTN93674355) and Toujeo-BB [18] studies conducted among patients with T2DM previously treated with basal-bolus regimens, since the main focus of REALI was to assess the effectiveness and safety of Gla-300 in a broad range of European patients with T2DM in daily clinical practice settings. The inclusion of patients on basal-bolus insulin regimens could have potentially impacted the results of REALI due to different hypoglycaemia risks than in insulin-naïve patients or in patients previously treated with basal insulin therapy only. Several strengths of this pooled analysis deserve to be noted, such as the inclusion of a large number of participants, including 2295 patients aged $\geq$ 70 years (28.3%), from several prospective studies, thereby increasing the statistical power of the analysis, which resulted in a more precise estimate of the therapeutic benefit and safety of Gla-300. In addition, the REALI pooled analysis applied standardised endpoint definitions to reduce study-specific differences. Most importantly, the REALI analysis provides valuable information regarding the safety and effectiveness of Gla-300 in an older group of individuals who are often excluded or underrepresented in clinical trials and includes data from non-interventional studies close to real-world clinical practice.

CONCLUSION

Gla-300 was found to be effective with a good safety profile in both younger and older patients with uncontrolled T2DM, indicating that it may be a suitable therapeutic option in elderly patients who represent a vulnerable population that is prone to hypoglycaemia.

ACKNOWLEDGEMENTS

The authors thank the participants, staff, and investigators of all pooled studies.

Funding. This study was funded by Sanofi (Paris, France). The article processing charges were also funded by Sanofi (Paris, France).

Medical Writing and Editorial Assistance. Medical writing support in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3) was provided by Thomas Rohban, MD, and Magalie El Hajj, PharmD, of Partner 4 Health (Paris, France), and was funded by Sanofi.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. All authors contributed to the project design and the analysis plan. Celine Mauquoi performed the statistical analysis of the data. All authors were involved in the interpretation of the data, writing and reviewing drafts of the manuscript, and approved the final version for submission.

Prior Presentation. Preliminary results were presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.

Disclosures. Riccardo C. Bonadonna has received funding for consulting or speaker fees from Sanofi, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Janssen, Eli Lilly and Johnson & Johnson. Didac Mauricio has received funding for consulting or speaker fees from Almirall, Ascensia, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Eli Lilly, Ferrer, Janssen, Menarini, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi. Dirk Müller-Wieland has received funding for consulting or speaker fees from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi. Nick Freemantle has received funding for consulting, research or speaker fees from Sanofi, Novo Nordisk, Allergan, Merck Sharp & Dohme, AstraZeneca, PCT, Ipsen, Takeda, Akcea and Accelovance. Gregory Bigot is an IVIDATA employee for Sanofi. Celine Mauquoi is an IDDI employee, and has acted as a biostatistics contractor for Sanofi. Alice Ciocca and Mireille Bonnemaire are Sanofi employees. Pierre Gourdy has received advisory board and speaker honoraria from Abbott, Amgen, AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Sanofi and Servier.

Compliance with Ethics Guidelines. This analysis did not involve primary data collection by the authors, and all post-hoc analysed data were anonymised; consequently, separate ethical approval was not required. Protocols for all included studies were approved by the appropriate ethics committees, and the studies were conducted according to Good Clinical Practice and the Declaration of Helsinki.

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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