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ORIGINAL RESEARCH

Glycaemic Control with Insulin Glargine 300 U/mL in Individuals with Type 2 Diabetes and Chronic Kidney Disease: A REALI European Pooled Data Analysis

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ABSTRACT

Introduction: Management of type 2 diabetes mellitus (T2DM) in patients with chronic kidney disease is complex. Using the REALI European pooled database, we determined the impact of baseline renal function on the effectiveness and safety of insulin glargine 300 U/mL (Gla-300) initiated in adults with inadequately controlled T2DM.

Methods: Data from 1712 patients with available estimated glomerular filtration rate (eGFR) at baseline were pooled from six 24-week prospective studies. Patients who received once-daily subcutaneous injections of Gla-300 were classified into four renal function subgroups, according to baseline eGFR: ≥ 90 (N = 599), 60–89 (N = 786), 45–59 (N = 219), and 15–44 mL/min/1.73 m^2 (N = 108).

Results: Compared to those with baseline eGFR ≥ 60 mL/min/1.73 m^2, patients with lower eGFR values tended to be older, had a longer T2DM duration, and were more likely to present diabetic complications. After 24 weeks of Gla-300 therapy, the least-squares mean (95% confidence interval) decrease in haemoglobin A1c (HbA1c) from baseline (− 1.14% [− 1.28 to − 1.00], − 1.21% [− 1.34 to − 1.08], − 1.19% [− 1.36 to − 1.01], and − 0.99%

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[− 1.22 to − 0.76]) and the proportion of patients achieving HbA1c < 7.5% (53.3%, 51.3%, 49.5%, and 51.5%) were comparable in the ≥ 90, 60–89, 45–59, and 15–44 mL/min/1.73 m^2 subgroups, respectively. Although the incidence of hypoglycaemia was overall low, more patients in the eGFR 15–44 mL/min/1.73 m^2 subgroup experienced hypoglycaemia at night or at any time of the day compared with higher eGFR subgroups. There were no notable differences between the renal function subgroups in the changes in Gla-300 daily dose and body weight from baseline to week 24.
Conclusion: Although an eGFR of 15–44 mL/min/1.73 m^2 was associated with a slightly increased risk of hypoglycaemia among patients with inadequately controlled T2DM, Gla-300 provided glycaemic improvement with an overall favourable safety profile regardless of baseline eGFR.

Keywords: Chronic kidney disease; Estimated glomerular filtration rate; Europe; Insulin glargine 300 U/mL; Pooled analysis; Type 2 diabetes

Key Summary Points

Why carry out this study?

Chronic kidney disease (CKD) is a common complication in individuals with type 2 diabetes mellitus (T2DM), and the level of renal function impacts on the choice and dosage of glucose-lowering therapies as well as on the individual's glycaemic target and the risk of hypoglycaemia

Since data on insulin glargine 300 U/mL (Gla-300) in patients with T2DM and CKD are limited in settings close to clinical practice, the REALI CKD analysis aimed to determine the impact of renal function on the effectiveness and safety of Gla-300 using pooled data from six 24-week, open-label, prospective studies including European patients with inadequately controlled T2DM who were initiated on or switched to Gla-300

What was learned from the study?

Renal function does not seem to affect the effectiveness and safety of Gla-300, as individuals with inadequately controlled T2DM and renal impairment achieved a clinically important improvement in glycaemic control with limited hypoglycaemia concerns during 24-week treatment with Gla-300

The findings of the REALI CKD pooled analysis support Gla-300 as a therapeutic option for individuals with T2DM and renal impairment

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.13809482.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) are common chronic comorbid conditions, with the prevalence of CKD among patients with diabetes estimated at 36% in the USA [1]. In Europe, the prevalence of end-stage renal disease among patients with diabetes is projected to increase approximately 3% per year from 2012 to 2025 [2]. CKD is an independent risk factor for hypoglycaemia, and increases the risk already present in patients with T2DM due to accumulation of uremic toxins leading to lower hepatic and renal insulin degradation, and as a result of decreased renal gluconeogenesis as well as deficient catecholamine release [3–5]. Unfortunately, the combination of hypoglycaemia and CKD is associated with increased morbidity and mortality, particularly from cardiovascular disease [4, 5], and T2DM was found to increase the risk of death from renal disease by threefold [6].

The management of T2DM in patients with CKD is especially difficult, in part because of treatment complexity and due to insufficient convincing data supporting the benefits of tight glycaemic control in this subset of patients [7]. In patients with T2DM and advanced CKD, basal insulin is considered the therapeutic option of choice, as oral glucose-lowering agents such as metformin, sulfonylureas, and sodium glucose co-transporter 2 inhibitors are less used because their glycaemic efficacy is reduced and/or the risk of hypoglycaemia or other adverse reactions is increased as a consequence of drug accumulation [4, 5, 7, 8]. Insulin requirements are generally lower in patients with T2DM and renal impairment due to a decreased insulin clearance; yet, there are no guidelines regarding insulin dose adjustment in this specific population [5, 9].

Insulin glargine 300 U/mL (Gla-300) is a second-generation basal insulin that was developed to optimise glycaemic control while minimising the risk of hypoglycaemia [10]. Gla-300 provides a more stable and prolonged pharmacokinetic/pharmacodynamic profile compared with the first-generation analogue insulin glargine 100 U/mL (Gla-100) owing to a more gradual and extended release of insulin glargine from the subcutaneous depot at the injection site, extending blood glucose control beyond 24 h [11].

Gla-300 was compared to Gla-100 in the randomised phase III EDITION 1, 2 and 3 studies [12] and to insulin degludec 100 U/mL (IDeg-100) in the head-to-head randomised BRIGHT trial [13], demonstrating equivalent glycaemic control with a lower hypoglycaemia risk at night and at any time of the day in a broad population of patients with T2DM, including patients with an impaired renal function. To further investigate the effectiveness and safety of Gla-300 in individuals with T2DM and CKD, we performed analyses on the REALI pooled database [14] including patient-level data from six prospective studies conducted in Europe.

METHODS

Pooled Studies

The REALI CKD analysis was based on pooled data from six multicentre, open-label, prospective, interventional or observational studies conducted over a minimum period of 24 weeks in European adult patients with inadequately controlled T2DM (i.e. in whom glycaemic targets have not been achieved) who were initiated on or switched to Gla-300 (Table 1) [10, 15–18]. Patients included in the REALI CKD analysis were either insulin-naïve or previously treated with basal insulin with or without oral glucose-lowering drugs. Common exclusion criteria included the presence of type 1 diabetes, pregnant or breastfeeding women, stage 5 CKD (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m^2), and any condition that could interfere with insulin requirements and/or haemoglobin A1c (HbA1c) levels.

In each study, Gla-300 was administered subcutaneously once daily, using a pre-filled insulin pen, at the same time of the day $\pm$ 3 h if needed. Two studies (Take Control [15] and ITAS [10]) were parallel-group trials in which patients were randomised (1:1) to a self- or physician-managed titration of Gla-300, whereas the other studies included only one study arm: Gla-300 prescribed according to the investigating physician's choice.

All studies included in this analysis were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements. All participants provided written informed consent prior to participation in the studies. Before data pooling, all patient information was de-identified. Consequently, no ethical approval was required for this pooled analysis.

Outcomes

The main efficacy endpoint for this pooled analysis was the change in HbA1c from baseline to week 24 of Gla-300 treatment. Other efficacy outcomes included the change in HbA1c from baseline to week 12 and week 24 of Gla-300

Table 1 Characteristics of studies included in the pooled analysis

Study	Location(s)	Study design	Number of patients	Inclusion criteria		
				Previous treatment status	HbA1c (%)	eGFR (mL/min/1.73 m^2)
Take Control [15]	Greece, Spain, Czech Republic, Switzerland, Poland, Denmark, Slovenia, Slovakia, Croatia, UK	24-week, multinational, open-label, randomised (1:1), two-arm, parallel-group study evaluating a self- versus physician-managed titration of Gla-300	620	≥ 6 months on treatment with ≥ 1 non-insulin anti-hyperglycaemic drug, with or without a basal insulin	≥ 7.0 and ≤ 10.0 for patients previously treated with basal insulin, or ≥ 7.5 and ≤ 11.0 for insulin-naïve patients	≥ 15
ITAS [10]	Italy	24-week, multicentre, open-label, pragmatic, randomised (1:1), parallel-group study evaluating a self- versus physician-managed titration of Gla-300	335	Insulin-naïve patients	≥ 7.5 and ≤ 10.0	≥ 15
TRANSITION 2 [16]	France	24-week, interventional, multicentre, open-label, single-arm study to evaluate switching from any basal insulin to Gla-300	154	≥ 6 months on treatment with basal insulin with or without non-insulin antidiabetic agents	> 7.5	≥ 15
TOPAZ [17]	Czech Republic	24-week, multicentre, observational, single-arm study to evaluate switching from any basal insulin to Gla-300	232	≥ 3 months on treatment with basal insulin with or without non-insulin antidiabetic agents	> 7.6	≥ 30

Table 1 continued

Study	Location(s)	Study design	Number of patients	Inclusion criteria		
				Previous treatment status	HbA1c (%)	eGFR (mL/min/1.73 m^2)
COBALTA [18]	Spain	26-week, interventional, multicentre, open-label, single-arm study to evaluate Gla-300 in a basal-bolus regimen during hospitalisation	109	Hospitalised patients with ≥ 3 months on treatment with basal insulin with or without non-insulin antidiabetic agents	≥ 8.0 and ≤ 10.0	≥ 30
To UPGRADE (Data on file)	Bulgaria	24-week, multicentre, observational, single-arm study to evaluate switching from NPH ± prandial insulin or premixed insulin to Gla-300	262	Previous treatment with NPH ± prandial insulin or premixed insulin with or without oral antidiabetic agents	≥ 7.0	No eGFR limitation

eGFR estimated glomerular filtration rate, *Gla-300* insulin glargine 300 U/mL, *HbA1c* haemoglobin A1c, *NPH* Neutral Protamine Hagedorn, *UK* United Kingdom

treatment; the change in fasting plasma glucose (FPG) from baseline to weeks 12 and 24 of Gla-300 treatment; and the percentage 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 weeks 12 and 24.

Safety endpoints included the percentage of patients with at least one hypoglycaemic event; the event rate of hypoglycaemic events; and the changes in daily insulin dose 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, 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). With the exception of COBALTA [18] in which capillary blood glucose monitoring was used to assess hypoglycaemia in hospitalised patients, the other pooled studies [10, 15–17] relied on the presence of typical symptoms of hypoglycaemia, confirmed or not by documented self-measured capillary glucose measurement.

Statistical Analyses

In the present analysis, study participants were pooled and results assessed across four renal

function subgroups, according to baseline eGFR: ≥ 90 (indicating normal kidney function), 60–89 (mild impaired kidney function), 45–59 (mild to moderate impaired kidney function), and 15–44 mL/min/1.73 m^2 (moderate to severe impaired kidney function). If not already determined in each individual study, eGFR was calculated using the Modification of Diet in Renal Disease equation without accounting for race, as this was not reported in the pooled studies.

The changes in HbA1c and FPG from baseline to weeks 12 and 24 of Gla-300 therapy were analysed using a mixed model for repeated measures (MMRM), including fixed categorical effects of visit and eGFR category as well as continuous fixed covariates of baseline HbA1c or FPG, baseline HbA1c or FPG value-by-visit interaction, and eGFR category-by-visit interaction. The least-square (LS) mean change from baseline to weeks 12 and 24 in HbA1c and FPG estimates and their corresponding 95% confidence intervals (CIs) were provided for each eGFR category. All other efficacy and safety endpoints as well as baseline demographic and disease characteristics were assessed descriptively, with categorical variables presented as counts and percentages, and continuous variables as mean, standard deviation (SD), median, and first and third quartiles. Hypoglycaemic event rates were calculated as the number of events per patient-year of exposure.

No imputation of missing data was performed. All statistical tests were two-sided, with a p value < 0.05 considered statistically significant. All analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Study Population

A total of 1712 patients from 13 European countries were included in the REALI CKD pooled analysis, of whom 108 (6.3%) had a baseline eGFR between 15 and 44, 219 (12.8%) between 45 and 59, 786 (45.9%) between 60 and 89, and 599 (35.0%) ≥ 90 mL/min/1.73 m^2. Of these 1712 patients, 1672 (97.7%) were treated with at least one dose of Gla-300 and were included in both efficacy and safety analyses.

Demographics and baseline characteristics of the four renal function subgroups are summarized in Table 2. Overall, compared to those with a baseline eGFR ≥ 60 mL/min/1.73 m^2, patients with lower eGFR values tended to be older, more often female, and had a longer duration of diabetes. With a decreasing baseline eGFR, patients were more likely to be pretreated with insulin, and to suffer from diabetic complications and from previous cardiovascular events such as myocardial infarction and stroke. With regards to previous non-insulin anti-hyperglycaemic treatments, patients in the 15–44 mL/min/1.73 m^2 subgroup were far less likely to be treated with biguanides compared to those in the other subgroups. Mean baseline HbA1c was slightly higher in patients with an eGFR of 15–44 mL/min/1.73 m^2 compared to the other eGFR subgroups.

Glycaemic Control

The LS mean decrease in HbA1c from baseline to weeks 12 and 24 of Gla-300 therapy was clinically meaningful in all four renal function subgroups, with overall similar HbA1c reductions across subgroups (Table 3). At 24 weeks, the LS mean (95% CI) change in HbA1c from baseline was − 1.14% (− 1.28 to − 1.00), − 1.21% (− 1.34 to − 1.08), − 1.19% (− 1.36 to − 1.01), and − 0.99% (− 1.22 to − 0.76) in the ≥ 90, 60–89, 45–59, and 15–44 mL/min/1.73 m^2 subgroups, respectively.

Over a quarter of patients with an eGFR ≥ 45 mL/min/1.73 m^2 reached HbA1c levels < 7.0% at 24 weeks of Gla-300 therapy versus 21.6% of patients in the eGFR 15–44 mL/min/1.73 m^2 subgroup. The achievements of HbA1c targets < 7.5% or < 8.0% were fairly comparable across the renal function subgroups at week 24 (Fig. 1).

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 similar across the four renal function subgroups (Table 4).

Table 2 Baseline characteristics, according to renal function

Baseline characteristic by baseline eGFR, mL/min/1.73 m^2	15–44 (*N* = 108)	45–59 (*N* = 219)	60–89 (*N* = 786)	≥ 90 (*N* = 599)
Female, *n* (%)	59 (54.6)	123 (56.2)	358 (45.5)	239 (39.9)
Age, years	69.8 ± 7.9	69.2 ± 7.3	64.4 ± 8.3	60.5 ± 8.6
Body weight, kg	90.9 ± 17.6	85.9 ± 14.3	87.5 ± 14.9	88.5 ± 16.8
Body mass index, kg/m^2	32.7 ± 5.4	31.6 ± 4.4	31.2 ± 4.8	31.5 ± 5.2
eGFR, mL/min/1.73 m^2	38.0 ± 5.8	53.4 ± 4.1	76.0 ± 8.3	110.0 ± 42.4
Diabetes duration, years	14.5 (10.5–20.5)	13.0 (8.0–17.0)	11.0 (7.0–16.0)	11.0 (6.0–15.0)
Previous insulin use, *n* (%)	88 (81.5)	168 (76.7)	548 (69.7)	334 (55.8)
Prior basal insulin use, *n* (%)[a]	69 (63.9)	145 (66.2)	484 (61.6)	312 (52.1)
Prior insulin glargine	34 (49.3)	59 (40.7)	196 (40.5)	156 (50.0)
Prior NPH insulin	25 (36.2)	65 (44.8)	202 (41.7)	97 (31.1)
Prior insulin detemir	9 (13.0)	21 (14.5)	81 (16.7)	51 (16.3)
Prior insulin degludec	1 (1.4)	0	1 (0.2)	8 (2.6)
Duration of basal insulin therapy, years	1.5 (0.7–4.3)	2.0 (0.8–4.1)	1.5 (0.7–3.7)	1.2 (0.7–3.6)
Prior basal insulin dose, U/day	33.9 ± 19.3	31.9 ± 16.8	33.3 ± 21.8	37.6 ± 26.2
Previous non-insulin anti-hyperglycaemic treatment, *n* (%)[b]	93 (86.1)	194 (88.6)	726 (92.4)	576 (96.2)
Biguanides	51 (54.8)	161 (83.0)	669 (92.1)	552 (95.8)
Sulfonylurea	28 (30.1)	84 (43.3)	312 (43.0)	230 (39.9)
Dipeptidyl peptidase 4 inhibitors	33 (35.5)	71 (36.6)	223 (30.7)	178 (30.9)
Glucagon-like peptide 1 receptor agonists	15 (16.1)	18 (9.3)	99 (13.6)	90 (15.6)
SGLT2 inhibitors	2 (2.2)	16 (8.2)	95 (13.1)	68 (11.8)
Patients with ≥ 1 diabetic complication, *n* (%)	50 (46.3)	93 (42.5)	258 (32.8)	149 (24.9)
Diabetic neuropathy	36 (33.3)	66 (30.1)	192 (24.4)	85 (14.2)
Diabetic retinopathy	17 (15.7)	24 (11.0)	88 (11.2)	53 (8.8)
Diabetic nephropathy	32 (29.6)	35 (16.0)	41 (5.2)	44 (7.3)
Patients with ≥ 1 cardiovascular event and/or risk factor, *n* (%)	93 (86.1)	195 (89.0)	661 (84.1)	451 (75.3)
Hypertension	91 (84.3)	183 (83.6)	601 (76.5)	382 (63.8)
Dyslipidaemia	61 (56.5)	146 (66.7)	479 (60.9)	336 (56.1)
Peripheral arterial disease	16 (14.8)	25 (11.4)	97 (12.3)	57 (9.5)
Previous myocardial infarction	21 (19.4)	21 (9.6)	67 (8.5)	40 (6.7)
Previous stroke	17 (15.7)	22 (10.0)	59 (7.5)	30 (5.0)

Table 2 continued

Baseline characteristic by baseline eGFR, mL/min/1.73 m^2	15–44 (*N* = 108)	45–59 (*N* = 219)	60–89 (*N* = 786)	≥ 90 (*N* = 599)
Haemoglobin A1c, %	8.89 ± 0.98	8.75 ± 0.98	8.77 ± 1.00	8.75 ± 0.96
Fasting plasma glucose, mg/dL	182.0 ± 61.0	187.3 ± 61.1	185.8 ± 61.4	178.4 ± 50.2

Data are expressed as mean ± standard deviation or median (first and third quartiles), unless otherwise indicated
N refers to all patients from the pooled REALI database included in the eGFR subgroup mentioned; means and percentages are calculated on the basis of data available for each variable
eGFR estimated glomerular filtration rate, *NPH* Neutral Protamine Hagedorn, *SGLT2* sodium glucose co-transporter 2
[a] The total number of patients who were previously treated with basal insulin in each eGFR 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 non-insulin anti-hyperglycaemic agents in each eGFR subgroup was used as the denominator to calculate the percentages of patients in each drug class

Safety

The incidences and event rates of hypoglycaemic events were overall low across the four renal function subgroups. However, compared with the higher eGFR subgroups, more patients in the eGFR 15–44 mL/min/1.73 m^2 subgroup experienced hypoglycaemia at night or at any time of the day during the 24-week treatment period with a hypoglycaemia event rate any time of the day of 4.4 versus 2.7, 2.5 and 2.8 episodes per patient-year in the 45–59, 60–89 and ≥ 90 mL/min/1.73 m^2 subgroups, respectively (Table 5).

The mean ± SD change in the daily dose of Gla-300 from baseline to weeks 12 and 24 was overall comparable across subgroups, with a slightly higher mean daily insulin dose increase in the eGFR ≥ 90 mL/min/1.73 m^2 subgroup at both time points (Table 6). The mean ± SD change in body weight from baseline to week 12 and week 24 of Gla-300 therapy was marginal across the four renal function subgroups (Table 6).

DISCUSSION

In the REALI CKD pooled analysis of six prospective studies conducted among patients with T2DM, Gla-300 provided glycaemic improvement with a favourable safety profile, regardless of baseline eGFR. Indeed, consistent and similar reductions from baseline to week 24 of Gla-300 therapy in HbA1c and FPG were recorded across the four eGFR subgroups, indicating that the efficacy of Gla-300 was not impacted by renal function status.

Our findings are in line with post hoc analyses of the EDITION 1, 2 and 3 trials [9] and of the BRIGHT study [8]. In the post hoc patient-level meta-analysis [9] of the EDITION trials conducted among 1247 patients with T2DM treated with once-daily evening injections of Gla-300 and who were classified into two baseline eGFR subgroups (208 patients with an eGFR < 60 mL/min/1.73 m^2 and 1039 with an eGFR ≥ 60 mL/min/1.73 m^2), the LS mean decrease in HbA1c after 6 months (− 0.98% and − 1.03% for those with an eGFR < 60 and ≥ 60 mL/min/1.73 m^2, respectively) and the proportion of patients achieving HbA1c target < 7.5% (54.9% and 54.0% for those with an eGFR < 60 and ≥ 60 mL/min/1.73 m^2, respectively) were similar in both renal function subgroups [9]. The meta-analysis [9] also found that the risk of confirmed (≤ 3.9 mmol/L) or severe hypoglycaemic events at any time of the day or at night was lower in Gla-300-treated patients (*n* = 1247) than in those who received Gla-100 therapy (*n* = 1249), regardless of baseline renal function. No heterogeneity of treatment effects was observed across renal function subgroups [9].

In the prespecified subgroup analysis [8] of the randomised BRIGHT trial conducted among

Table 3 Change in HbA1c (%) from baseline to weeks 12 and 24 of Gla-300 treatment, according to baseline eGFR (mL/min/1.73 m^2)

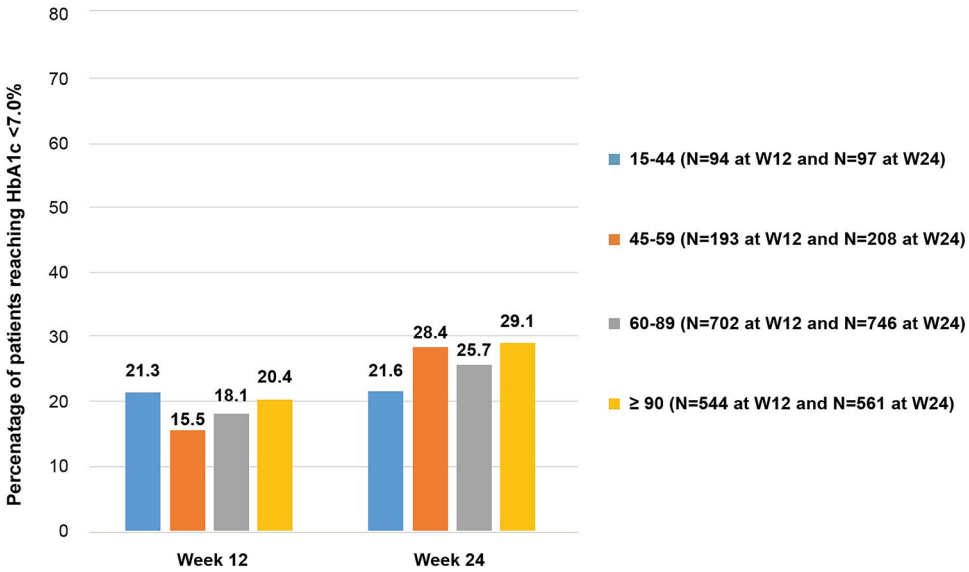
	15–44 (*N* = 104)	**45–59 (*N* = 214)**	**60–89 (*N* = 766)**	**≥ 90 (*N* = 588)**
Mean ± SD HbA1c at baseline	8.90 ± 0.98	8.76 ± 0.98	8.79 ± 0.99	8.77 ± 0.95
Mean ± SD HbA1c at week 12	7.89 ± 1.09	7.84 ± 1.00	7.76 ± 0.98	7.69 ± 0.95
Change from baseline to week 12	*n* = 94	*n* = 192	*n* = 696	*n* = 543
LS mean ± SE (95% CI)	− 0.83 ± 0.11 (− 1.06 to − 0.61)	− 0.90 ± 0.09 (− 1.07 to − 0.73)	− 0.98 ± 0.06 (− 1.11 to − 0.86)	− 1.00 ± 0.07 (− 1.14 to − 0.86)
LS mean ± SE difference* (95% CI)	0.17 ± 0.11 (− 0.05 to 0.38)	0.10 ± 0.08 (− 0.06 to 0.26)	0.02 ± 0.06 (− 0.09 to 0.13)	
p value	0.133	0.212	0.765	
Mean ± SD HbA1c at week 24	7.74 ± 1.17	7.59 ± 1.14	7.57 ± 0.96	7.58 ± 1.09
Change from baseline to week 24	*n* = 97	*n* = 205	*n* = 741	*n* = 559
LS mean ± SE (95% CI)	− 0.99 ± 0.12 (− 1.22 to − 0.76)	− 1.19 ± 0.09 (− 1.36 to − 1.01)	− 1.21 ± 0.07 (− 1.34 to − 1.08)	− 1.14 ± 0.07 (− 1.28 to − 1.00)
LS mean ± SE difference* (95% CI)	0.15 ± 0.11 (− 0.07 to 0.37)	− 0.05 ± 0.08 (− 0.21 to 0.12)	− 0.07 ± 0.06 (− 0.18 to 0.04)	
p value	0.194	0.558	0.219	

CI confidence interval, *eGFR* estimated glomerular filtration rate, *Gla-300* insulin glargine 300 U/mL, *HbA1c* haemoglobin A1c, *LS* least-squares, *SD* standard deviation, *SE* standard error

*For the difference between the subgroups, the reference is the ≥ 90 mL/min/1.73 m^2 subgroup

466 insulin-naïve patients with T2DM who received evening Gla-300, HbA1c reductions over 24 weeks were also similar in those with eGFR ≥ 90 (*n* = 246), between 60 and 89 (*n* = 172), and < 60 mL/min/1.73 m^2 (*n* = 47). However, heterogeneity of treatment effect across renal function subgroups was observed (*p* = 0.02), reflecting a significantly greater mean HbA1c reduction from baseline to week 24 (8.58% to 6.94%) among Gla-300-treated patients with eGFR < 60 mL/min/1.73 m^2 (*n* = 47) compared to patients with the same range of eGFR randomised to IDeg-100 therapy (*n* = 49) (8.30–7.28%) (LS mean difference of − 0.43%; 95% CI − 0.74 to − 0.12), while there were no differences in hypoglycaemia incidence or rates over 24 weeks in that subgroup [8].

With the exception of nocturnal severe hypoglycaemia which was rarely reported in REALI CKD (with an incidence ranging from 0% to 0.5% across the four eGFR subgroups), the incidences and event rates of hypoglycaemic events were higher in the eGFR 15–44 mL/min/1.73 m^2 subgroup compared with the other eGFR subgroups, which is not surprising and in line with the existing literature [8, 9, 19]. The observed differences between the eGFR 15–44 mL/min/1.73 m^2 subgroup and the other eGFR subgroups in the event rate and incidence of hypoglycaemia are unlikely to be related to


Percenatage of patients reaching HbA1c <7.0%
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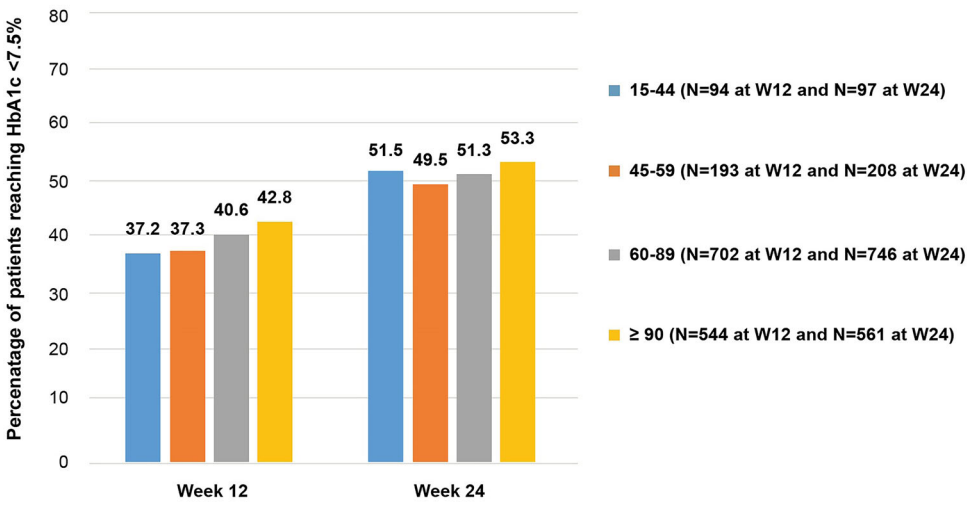
Week 12
Week 24
15-44 (N=94 at W12 and N=97 at W24)
45-59 (N=193 at W12 and N=208 at W24)
60-89 (N=702 at W12 and N=746 at W24)
≥ 90 (N=544 at W12 and N=561 at W24)


Percenatage of patients reaching HbA1c <7.5%
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40
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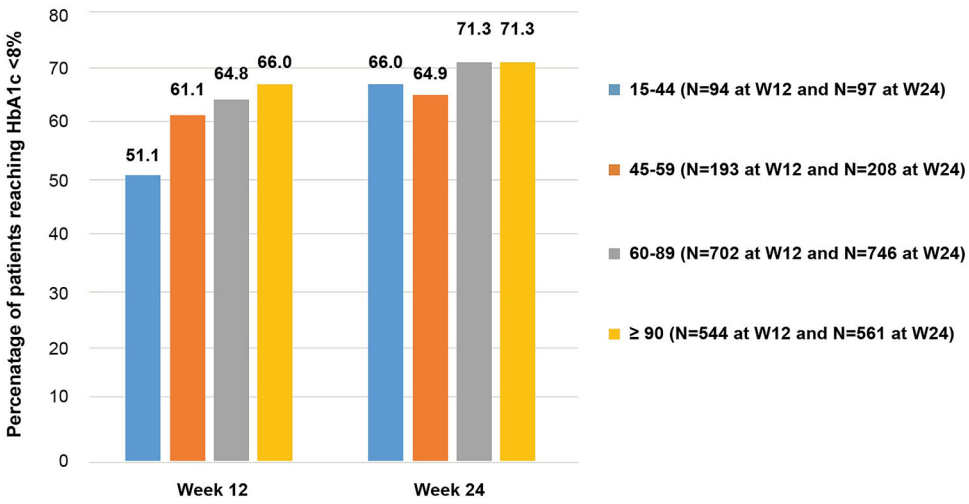
20
10
0
37.2
37.3
40.6
42.8
51.5
49.5
51.3
53.3
Week 12
Week 24
15-44 (N=94 at W12 and N=97 at W24)
45-59 (N=193 at W12 and N=208 at W24)
60-89 (N=702 at W12 and N=746 at W24)
≥ 90 (N=544 at W12 and N=561 at W24)


Percenatage of patients reaching HbA1c <8%
80
70
60
50
40
30
20
10
0
51.1
61.1
64.8
66.0
66.0
64.9
71.3
71.3
Week 12
Week 24
15-44 (N=94 at W12 and N=97 at W24)
45-59 (N=193 at W12 and N=208 at W24)
60-89 (N=702 at W12 and N=746 at W24)
≥ 90 (N=544 at W12 and N=561 at W24)

◀**Fig. 1** Percentage of patients achieving HbA1c targets during Gla-300 treatment, according to baseline eGFR (mL/min/1.73 m^2). *eGFR* estimated glomerular filtration rate, *Gla-300* insulin glargine 300 U/mL, *HbA1c* haemoglobin A1c, *W* week

Gla-300 dose increase throughout the 24-week treatment period, but are consistent with the higher risk for hypoglycaemia reported in people with CKD [9, 20].

Overall, the findings of the REALI CKD pooled analysis, along with the data from the aforementioned post hoc analyses [8, 9], support the use of Gla-300 in patients with renal impairment, given its sustained glycaemic control benefit and its overall low risk of hypoglycaemia in this challenging-to-treat population that is particularly vulnerable to hypoglycaemia. This vulnerability is due to multiple factors, including a reduced renal mass and therefore a reduced capacity for renal glucose release, especially when the eGFR falls below 45 mL/min/1.73 m^2 [4, 7, 21]. Hypoglycaemic events affect patients' lives profoundly, as they are associated with psychological distress, cardiovascular morbidity, and a significantly increased risk of death within 1 day of a hypoglycaemic event [4, 7, 20]. The overall low reported incidences of hypoglycaemia associated with Gla-300 in the present pooled analysis

Table 4 Change in fasting plasma glucose (mg/dL) from baseline to weeks 12 and 24 of Gla-300 treatment, according to baseline eGFR (mL/min/1.73 m^2)

	15–44 (*N* = 104)	**45–59 (*N* = 214)**	**60–89 (*N* = 766)**	**≥ 90 (*N* = 588)**
Mean ± SD FPG at baseline	185.6 ± 60.2	187.3 ± 60.1	186.7 ± 60.8	179.3 ± 49.4
Mean ± SD FPG at week 12	139.9 ± 44.7	144.5 ± 50.1	137.3 ± 43.5	132.4 ± 39.6
Change from baseline to week 12	*n* = 58	*n* = 125	*n* = 506	*n* = 443
LS mean ± SE (95% CI)	− 32.2 ± 5.8 (− 43.6 to − 20.9)	− 31.2 ± 4.4 (− 39.7 to − 22.6)	− 37.0 ± 3.1 (− 43.1 to − 30.9)	− 37.6 ± 3.2 (− 43.9 to − 31.3)
LS mean ± SE difference* (95% CI)	5.4 ± 5.6 (− 5.7 to 16.4)	6.4 ± 4.1 (− 1.5 to 14.4)	0.6 ± 2.6 (− 4.5 to 5.8)	
p value	0.340	0.114	0.815	
Mean ± SD FPG at week 24	134.1 ± 55.0	140.7 ± 41.4	135.1 ± 42.5	133.1 ± 41.7
Change from baseline to week 24	*n* = 61	*n* = 143	*n* = 555	*n* = 452
LS mean ± SE (95% CI)	− 40.3 ± 5.8 (− 51.7 to − 28.9)	− 33.0 ± 4.3 (− 41.4 to − 24.7)	− 40.8 ± 3.1 (− 46.8 to − 34.8)	− 38.4 ± 3.2 (− 44.6 to − 32.1)
LS mean ± SE difference* (95% CI)	− 1.9 ± 5.7 (− 13.0 to 9.2)	5.3 ± 4.0 (− 2.5 to 13.1)	− 2.5 ± 2.6 (− 7.6 to 2.7)	
p value	0.733	0.182	0.347	

CI confidence interval, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *Gla-300* insulin glargine 300 U/mL, *LS* least-squares, *SD* standard deviation, *SE* standard error

*For the difference between the subgroups, the reference is the ≥ 90 mL/min/1.73 m^2 subgroup

Table 5 Incidence and event rate of hypoglycaemic events, according to baseline eGFR (mL/min/1.73 m^2)

	15–44 (*N* = 104)	45–59 (*N* = 214)	60–89 (*N* = 766)	≥ 90 (*N* = 588)
Total patient-year exposure	46.92	99.39	355.58	267.60
Any time of the day hypoglycaemia				
Any hypoglycaemia				
Patients with ≥ 1 event, *n* (%)	36 (34.6)	58 (27.1)	217 (28.3)	165 (28.1)
Total number of events (event rate)	206 (4.39)	272 (2.74)	899 (2.53)	753 (2.81)
Symptomatic hypoglycaemia				
Patients with ≥ 1 event, *n* (%)	28 (26.9)	36 (16.8)	160 (20.9)	119 (20.2)
Total number of events (event rate)	97 (2.07)	94 (0.95)	513 (1.44)	414 (1.55)
Severe hypoglycaemia				
Patients with ≥ 1 event, *n* (%)	3 (2.9)	4 (1.9)	7 (0.9)	6 (1.0)
Total number of events (event rate)	5 (0.11)	5 (0.05)	11 (0.03)	13 (0.05)
Nocturnal hypoglycaemia				
Any hypoglycaemia				
Patients with ≥ 1 event, *n* (%)	10 (9.6)	11 (5.1)	54 (7.0)	39 (6.6)
Total number of events (event rate)	14 (0.30)	22 (0.22)	127 (0.36)	125 (0.47)
Symptomatic hypoglycaemia				
Patients with ≥ 1 event, *n* (%)	9 (8.7)	7 (3.3)	43 (5.6)	34 (5.8)
Total number of events (event rate)	12 (0.26)	9 (0.09)	94 (0.26)	76 (0.28)
Severe hypoglycaemia				
Patients with ≥ 1 event, *n* (%)	0	1 (0.5)	3 (0.4)	2 (0.3)
Total number of events (event rate)	0	1 (0.01)	4 (0.01)	5 (0.02)

Event rates, which are based on total patient-year exposure, are expressed as number of events per year
Symptomatic hypoglycaemia was defined as an event during which typical symptoms of hypoglycaemia occurred (e.g. sweating, hunger, shakiness, palpitations). Severe hypoglycaemia was defined as any event requiring assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions
eGFR estimated glomerular filtration rate

in both patients with reduced and preserved renal function are thus encouraging and are particularly beneficial during the early weeks of treatment, as they enable patients to titrate their basal insulin dose as intended to improve glycaemic control, without under- or delayed titration which often results from patients' fear of hypoglycaemia [13, 22].

Although not having issued specific guidelines on glycaemic goals for patients with T2DM and CKD, the American Diabetes Association (ADA) recommends individualised glycaemic targets according to age, comorbidities, and life expectancy [23]. For patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions,

Table 6 Gla-300 daily dose (U/day and U/kg/day) and body weight (kg) changes from baseline to weeks 12 and 24 of treatment, according to baseline eGFR (mL/min/1.73 m^2)

	15–44 (*N* = 104)	45–59 (*N* = 214)	60–89 (*N* = 766)	≥ 90 (*N* = 588)
Gla-300 daily dose (U/day)				
Baseline	26.0 ± 16.0	25.7 ± 13.1	25.9 ± 15.6	26.2 ± 18.2
Week 12	33.2 ± 16.0	34.2 ± 18.2	33.9 ± 18.8	37.3 ± 22.4
Change from baseline to week 12	7.8 ± 11.3	9.0 ± 12.7	8.7 ± 11.5	11.8 ± 13.7
Week 24	35.6 ± 18.0	35.6 ± 18.8	36.3 ± 20.3	39.4 ± 23.1
Change from baseline to week 24	10.4 ± 13.0	10.4 ± 13.0	10.5 ± 13.8	13.6 ± 16.2
Gla-300 daily dose (U/kg/day)				
Baseline	0.29 ± 0.16	0.29 ± 0.14	0.29 ± 0.16	0.28 ± 0.17
Week 12	0.37 ± 0.16	0.38 ± 0.17	0.38 ± 0.18	0.41 ± 0.21
Change from baseline to week 12	0.06 ± 0.11	0.09 ± 0.12	0.10 ± 0.13	0.13 ± 0.14
Week 24	0.40 ± 0.20	0.40 ± 0.18	0.41 ± 0.20	0.43 ± 0.21
Change from baseline to week 24	0.11 ± 0.16	0.11 ± 0.14	0.12 ± 0.15	0.15 ± 0.16
Body weight (kg)				
Baseline	91.0 ± 17.9	85.7 ± 14.3	87.5 ± 14.9	88.4 ± 16.9
Week 12	92.3 ± 16.6	86.1 ± 14.7	87.8 ± 15.0	88.8 ± 16.8
Change from baseline to week 12	− 0.5 ± 5.5	0.1 ± 2.0	− 0.08 ± 2.4	0.2 ± 2.6
Week 24	90.5 ± 17.5	85.6 ± 14.8	87.8 ± 14.8	88.8 ± 16.9
Change from baseline to week 24	− 0.7 ± 4.6	− 0.04 ± 2.3	0.1 ± 3.6	0.2 ± 3.7

All data are expressed as mean ± standard deviation
eGFR estimated glomerular filtration rate, *Gla-300* insulin glargine 300 U/mL

or longstanding diabetes, HbA1c goals that are less stringent than the general target of < 7.0% (i.e. < 8.0%) are suggested [23]. Similarly, the National Kidney Foundation (NKF) recommends that in patients at risk for hypoglycaemia, such as those with diabetes and impaired renal function, target HbA1c should be extended above 7.0% [24]. In this pooled analysis, approximately half of the patients in the four eGFR subgroups achieved target HbA1c values < 7.5% at 24 weeks of Gla-300 therapy, and approximately two-thirds achieved an HbA1c target < 8.0%, in line with the recommendations of the NKF [24] and the ADA [23]. Interestingly, the HbA1c targets achievement, particularly the achievement of HbA1c levels < 7.0% in the eGFR 15–44 mL/min/1.73 m^2 subgroup, occurred mainly in the first 12 weeks of Gla-300 treatment. This might be a result of the usual dose escalation during the early weeks of basal insulin therapy parallel to titration according to fasting glucose targets.

The present pooled analysis has several strengths including the prospective nature and the high completion rate (≥ 90%) of the evaluated studies. This pooled analysis also included a large, diverse population of patients with T2DM, with a variety of baseline characteristics that are typically encountered in a clinical setting. Most importantly, the REALI CKD pooled analysis provides valuable information supporting the use of Gla-300 in individuals with T2DM and renal impairment, a patient population that is generally understudied and for

which clinical study results are not necessarily similar to those reported for the general T2DM population. However, our findings should be interpreted in the context of certain limitations. The number of patients in the evaluated renal functions subgroups was not controlled, and subsequently there were substantially fewer patients in the 15–44 and 45–59 mL/min/1.73 m^2 groups than the 60–89 and $\geq$ 90 mL/min/1.73 m^2 groups. Other limitations include the post hoc nature of the analysis, the exclusion of data from participants with a baseline eGFR < 15 mL/min/1.73 m^2 (stage 5 CKD), and the lack of comparative data with another basal insulin. Furthermore, the fact that race was not taken into account in the calculations of eGFR might affect the accuracy of renal function assessment. However, given the geographical coverage of the studies, we assumed that a very small number of patients of African descent were enrolled. Longer-term assessment (beyond 24 weeks) would have also been helpful in evaluating the long-term effectiveness and safety of Gla-300 therapy according to renal function. Lastly, the results of REALI could have been potentially impacted by the concomitant administration of Gla-300 with oral antidiabetic drugs in some patients. Nevertheless, the findings of the REALI CKD pooled analysis support Gla-300 as a therapeutic option for individuals with T2DM and renal impairment.

CONCLUSIONS

Kidney function does not seem to affect the glycaemic effectiveness and safety of Gla-300, as individuals with inadequately controlled T2DM and renal impairment who were initiated on or switched to Gla-300 achieved a clinically important improvement in glycaemic control with a low hypoglycaemia risk, especially for severe hypoglycaemia.

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Compliance with Ethics Guidelines. This analysis did not involve primary data collection by the authors, and all pooled analysed data were de-identified; 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. All participants provided written informed consent prior to participation in the studies.

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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