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RESEARCH LETTER

WILEY

Real-life effectiveness of iGlarLixi (insulin glargine 100 U/mL and lixisenatide) in people with type 2 diabetes according to prior insulin use

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1 | BACKGROUND

Fixed-ratio combinations of a basal insulin and a glucagon-like peptide-1 receptor agonist (GLP-1RA) have recently been incorporated in the latest US and European guidelines for the management of people with inadequately controlled type 2 diabetes (T2D), and glycated haemoglobin (HbA1c) >2% above target or HbA1c value >10% (>85.8 mmol/mol).[1,2] In addition to their effect on glycaemic control,[3] the combination of a GLP-1RA and basal insulin in one injection mitigates the side effects of its individual components, such as the gastrointestinal adverse events (AEs), associated with GLP-1RAs[4,5] and the weight gain associated with insulin use.[3]

iGlarLixi is the fixed-ratio combination of insulin glargine 100 U/mL (iGlar) and the GLP-1RA lixisenatide (Lixi), administered subcutaneously once daily within 1 h before the most convenient meal.[6] Although treatment with iGlarLixi achieved favourable clinical results in randomized controlled trials (RCTs),[7–10] there are still limited data on the real-life effectiveness and safety of initiating iGlarLixi in insulin-naïve versus insulin-pretreated people with T2D.

We have pooled data, therefore, from two observational studies[11,12] to evaluate the treatment outcomes of iGlarLixi in people with T2D inadequately controlled on non-insulin glucose-lowering therapy, with or without basal insulin, in the real-life setting.

2 | METHODS

For our analysis, we pooled patient-level data from two real-life, prospective, observational studies,[11,12] part of the comprehensive European REALI programme.[13,14] The pooled studies included adults with inadequately controlled T2D, who initiated treatment with iGlarLixi (Suliqua®, Sanofi, Paris, France), with or without non-insulin

TABLE 1 Baseline characteristics according to prior insulin use.

Characteristic	Insulin-naïve ($N = 718$)	Insulin-pretreated ($N = 598$)	Overall ($N = 1316$)
Age, years			
Mean ± SD	60.2 ± 9.4	61.9 ± 8.5	61.0 ± 9.0
Median (Q1–Q3)	61.0 (53.0–67.0)	63.0 (56.0–68.0)	62.0 (55.0–67.0)
Female, *n* (%)	387 (53.9)	350 (58.5)	737 (56.0)
Body weight, mean ± SD kg	90.4 ± 17.2	90.1 ± 16.5	90.3 ± 16.9
BMI, mean ± SD kg/m^2	32.2 ± 5.6	32.3 ± 5.4	32.2 ± 5.5
BMI category, *n* (%)			
<30 kg/m^2	276 (38.4)	212 (35.5)	488 (37.1)
≥30 kg/m^2	442 (61.6)	386 (64.5)	828 (62.9)
Diabetes duration, median (Q1–Q3) years	8.0 (4.0–12.0)	10.0 (5.0–15.0)	9.0 (5.0–13.0)
Number of previous non-insulin glucose-lowering agents, *n* (%)	$n = 714$	$n = 592$	$n = 1306$
1	207 (29.0)	535 (90.4)	742 (56.8)
≥2	507 (71.0)	57 (9.6)	564 (43.2)
Previous non-insulin glucose-lowering agents, *n* (%)[a]	$n = 714$	$n = 598$	$n = 1306$
Biguanides	700 (98.0)	587 (99.2)	1287 (98.5)
Sulphonylureas	362 (50.7)	45 (7.6)	407 (31.2)
Dipeptidyl peptidase-4 inhibitors	144 (20.2)	12 (2.0)	156 (11.9)
Sodium-glucose cotransporter-2 inhibitors	79 (11.1)	11 (1.9)	90 (6.9)
Glucagon-like peptide-1 receptor agonists	7 (1.0)	0	7 (0.5)
Participants with ≥1 cardiovascular event or risk factor, *n* (%)[b]			
Hypertension	283 (39.4)	425 (71.1)	708 (53.8)
Dyslipidaemia	275 (38.3)	407 (68.1)	682 (51.8)
Other ischaemic heart disease	120 (16.7)	184 (30.8)	304 (23.1)
Peripheral arterial disease	58 (8.1)	107 (17.9)	165 (12.5)
Previous stroke	22 (3.1)	39 (6.5)	61 (4.6)
Previous myocardial infarction	19 (2.6)	30 (5.0)	49 (3.7)
Participants with ≥1 diabetic complication, *n* (%)[b]			
Diabetic neuropathy	226 (31.5)	307 (51.3)	533 (40.5)
Diabetic retinopathy	100 (13.9)	103 (17.2)	203 (15.4)
Diabetic nephropathy	91 (12.7)	49 (8.2)	140 (10.6)
Baseline HbA1c, % (mmol/mol)	9.40 ± 1.45 (79.2 ± 15.8)	8.76 ± 1.20 (72.3 ± 13.1)	9.11 ± 1.38 (76.1 ± 15.0)
Baseline FPG, mg/dL (mmol/L)	193.1 ± 56.5 (10.6 ± 3.1)	174.3 ± 46.3 (9.6 ± 2.6)	184.5 ± 53.0 (10.2 ± 2.9)

Abbreviations: BMI, body mass index; FPG, fasting blood glucose; HbA1c, glycated haemoglobin; SD, standard deviation; Q, quartile.
[a]The total number of participants who were previously treated with non-insulin glucose-lowering agents in each prior insulin use group was used as the denominator to calculate the percentages of participants in each drug class. For 10 participants, data on their non-insulin glucose-lowering agents were not available.
[b]A participant could be counted in more than one category.

glucose-lowering agents, for 24 weeks.[13] For the purpose of this pooled analysis, participants were classified into two main groups based on their prior insulin use: an insulin-naïve and an insulin-pretreated group. All participants provided written informed consent in the pooled studies, which were conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines and approved by the appropriate ethics committees. The primary endpoint of this analysis was the change in HbA1c from baseline to Week 24. Safety endpoints included the incidence of hypoglycaemic events and gastrointestinal AEs. We also evaluated changes in body weight and iGlarLixi dose. The changes in HbA1c and fasting plasma glucose (FPG) from baseline were analysed using a mixed model for repeated measures, with fixed effects of study, visit, prior insulin use category (insulin-naïve or insulin-pretreated), as well as continuous covariates of baseline HbA1c or FPG, age, baseline body mass index, and all associated interactions-by-visit. We estimated the least squares (LS) mean HbA1c and FPG changes from baseline to Weeks 12 and 24 with the corresponding 95% confidence

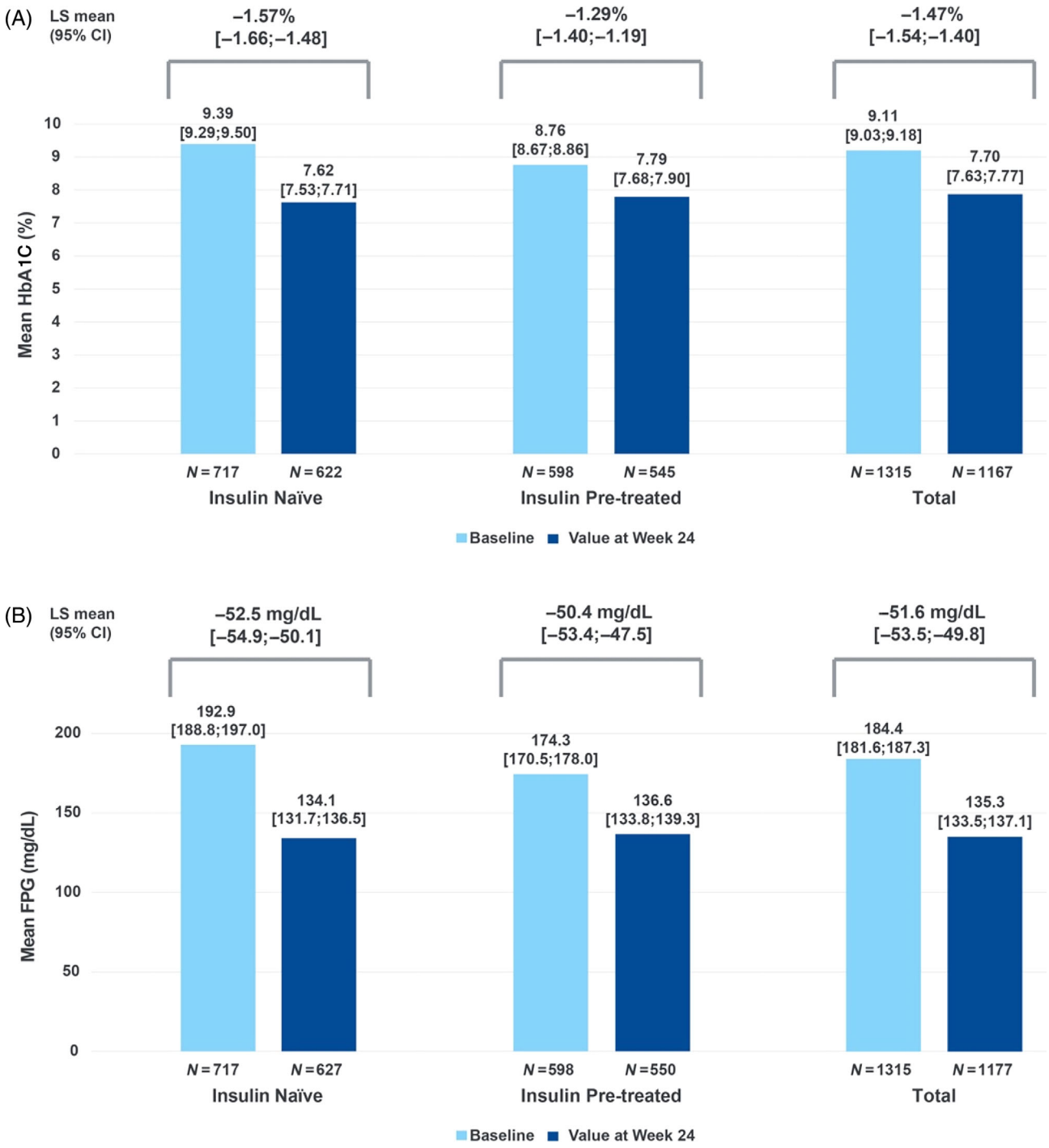

FIGURE 1 (A) Mean glycated haemoglobin and (B) mean fasting plasma glucose and the corresponding least squares mean change (95% confidence interval) from baseline to Week 24 of iGlarLixi (insulin glargine 100 U/mL and lixisenatide) treatment by prior insulin use. The LS mean changes in both HbA1c and FPG levels from baseline, along with their corresponding 95% CIs, were derived from a mixed models for repeated measures. These models incorporated an unstructured covariance matrix and included fixed categorical effects of visit, subgroup category, and subgroup category-by-visit interaction. Additionally, continuous fixed covariates such as baseline HbA1c or FPG, age, body mass index, baseline HbA1c or FPG value-by-visit interaction, age value-by-visit interaction, and body mass index value-by-visit interaction were accounted for. The bar graph values correspond to descriptive statistics for HbA1c and FPG values at baseline and Week 24. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least squares.

intervals (CIs) for each group. Hypoglycaemic event rates were reported as percentages of participants with at least one event and calculated as annualized rates. All other endpoints, as well as baseline characteristics, were summarized descriptively as mean ± standard deviation (SD) or as median (quartile 1–quartile 3) for continuous variables and as counts and percentages for categorical variables. There

was no imputation of missing data and no adjustment for multiple testing was made. A two-sided p value <0.05 was taken to indicate statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

The present patient-level pooled analysis included 1316 participants, 718 (54.6%) of whom were insulin-naïve and 598 (45.4%) were insulin-pretreated prior to iGlarLixi initiation, with a median insulin treatment duration of 2.5 years. Table 1 summarizes the demographics and baseline characteristics. The overall mean ± SD age of the study population was 61.0 ± 9.0 years, the mean ± SD body mass index was 32.2 ± 5.5 kg/m^2, and the median (interquartile range) diabetes duration was 9.0 (5.0–13.0) years. Insulin-naïve participants had a mean ± SD baseline HbA1c of 9.4% ± 1.5% compared to 8.8% ± 1.2% in insulin-pretreated participants (p < 0.001). The majority of insulin-pretreated participants had received insulin glargine 100 U/mL (408/598, 68.2%) as their basal insulin.

Treatment with iGlarLixi improved glycaemic control in both groups by an overall LS mean HbA1c change of −1.47% (95% CI −1.54 to −1.40) by Week 24 (Figure 1A). At Week 12, the LS mean HbA1c change was −1.33% (95% CI −1.42 to −1.25) in insulin-naïve participants and −0.96% (95% CI −1.07 to −0.85) in insulin-pretreated participants. Insulin-naïve participants experienced significantly greater LS mean reductions in HbA1c compared to insulin-pretreated participants at both Week 12 (LS mean difference of 0.37% [95% CI 0.23–0.51]; p < 0.001) and Week 24 (0.28% [95% CI 0.14–0.42]; p < 0.001). Similar proportions of insulin-naïve and insulin-pretreated participants reached HbA1c targets at Week 24 (Figure S1). LS mean change in FPG was −51.6 mg/dL (95% CI −53.5 to −49.8) in the overall population (Figure 1B). Figure S2 presents the mean change in HbA1c and FPG in mmol/mol and mmol/L units, respectively, and their corresponding LS mean changes from baseline to Week 24.

Treatment with iGlarLixi was well tolerated, with a low incidence of hypoglycaemia and gastrointestinal AEs. Among the 1315 evaluated participants, 36 out of 717 insulin-naïve (5.0%) and 12 out of 598 insulin-pretreated participants (2.0%) reported a total of 109 symptomatic hypoglycaemia events (event rate: 0.175).

Body weight decreased as of the first 12 weeks, with an overall mean ± SD change of −1.8 ± 4.6 kg at Week 24 in the overall population. A similar trend was observed for insulin-naïve participants (−1.7 ± 4.9 kg) and insulin-pretreated participants (−2.0 ± 4.3 kg) at Week 24.

In insulin-naïve participants, the mean iGlarLixi dose doubled from 0.16 U/kg/day (14.3 U/day) at baseline to 0.35 U/kg/day (30.7 U/day) at Week 24. In insulin-pretreated participants, the dose increased by 1.5-fold from 0.28 U/kg/day (24.4 U/day) at baseline to 0.42 U/kg/day (36.4 U/day) at Week 24 (Figure S3).

4 | CONCLUSIONS

This pooled analysis demonstrated the effectiveness and safety of initiating iGlarlixi in people with inadequately controlled T2D who were either insulin-pretreated or insulin-naïve. Treatment with iGlarLixi improved glycaemic control in the study population, with an overall LS mean HbA1c change of −1.47% at Week 24, as observed in various RCTs, in which iGlarLixi reduced HbA1c by 1.0%–1.6% over 30 weeks.[7,9,10] Insulin-naïve participants experienced a statistically greater HbA1c decrease than insulin-pretreated participants, yet the difference may be less clinically relevant, particularly since insulin-naïve participants had a significantly higher baseline HbA1c compared to insulin-pretreated participants (9.4% vs. 8.8%; p < 0.001).

Reports of hypoglycaemia events and gastrointestinal AEs were low in the current analysis; only 5.0% of insulin-naïve and 2.0% of insulin-pretreated participants reported symptomatic hypoglycaemia. The LixiLan trials have shown a higher incidence of documented symptomatic hypoglycaemia, ranging from 25.6% to 27.8% in insulin-naïve[7,9] and 40.0% in insulin-pretreated participants.[10] The difference between our analysis and LixiLan RCTs may be in part due to the less stringent method for reporting hypoglycaemic events encountered in observational studies.

iGlarLixi led to a clinically meaningful body weight loss, regardless of prior insulin use, with an overall reduction of −1.8 ± 4.6 kg, which is considered a major advantage in routine clinical practice, given that 62.9% of participants in our study population had obesity.

The main strengths of our pooled analysis are its large sample size (N = 1316) and the use of the mixed model for repeated measures, which is a robust analytical method that reduces the degree of bias in the results. Our pooled analysis may be limited by unmeasured confounding factors, potential reporting bias specific to observational studies, and the relatively short treatment duration, which may be insufficient for a full titration in real-life practice. Further investigation of the effectiveness and safety of iGlarLixi may provide additional insights into long-term iGlarLixi treatment.

In conclusion, this European pooled analysis confirms the effectiveness and safety of iGlarLixi in both insulin-naïve and insulin-pretreated people with inadequately controlled T2D in routine clinical practice.

AUTHOR CONTRIBUTIONS

All authors contributed to the project design and the analysis plan. Mathilde Tournay 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 approval of the final version for submission.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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