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Published in:
Diabetes, Obesity & Metabolism

DOI:
[10.1111/dom.14844](https://doi.org/10.1111/dom.14844)

Publication date:
2023

Licence:
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Document Version
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

McCrimmon, R., Cheng, A. Y. Y., Galstyan, G. R., Djaballah, K., Li, X., Coudert, M., & Frias, J. P. (2023). iGlarLixi versus Basal Plus Rapid-Acting Insulin in Adults with Type 2 Diabetes Advancing from Basal Insulin Therapy: The SoliSimplify Real-World Study. *Diabetes, Obesity & Metabolism*, 25(1), 68-77. <https://doi.org/10.1111/dom.14844>


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iGlarLixi versus basal plus Rapid-Acting insulin in adults with type 2 diabetes advancing from basal insulin therapy: The SoliSimplify Real-World study

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Funding information

Sanofi

Abstract

Aim: For people with suboptimally controlled type 2 diabetes (T2D) on basal insulin (BI), guidelines recommend several treatment advancement options. This study compared the clinical effectiveness of once-daily iGlarLixi versus a multiple-injection BI + rapid acting insulin (RAI) regimen in adults with T2D advancing from BI therapy in real-world clinical practice.

Materials and methods: Electronic medical records from the Observational Medical Outcomes Partnership (OMOP) database were analysed retrospectively using propensity score matching to compare therapy advancement with iGlarLixi or BI + RAI in US adults ≥ 18 years with T2D on BI who had ≥ 1 valid glycated haemoglobin (HbA1c) value at baseline and at the 6-month follow-up. The primary objective was non-inferiority of iGlarLixi to BI + RAI in HbA1c change from baseline to 6 months (margin 0.3%).

Results: Propensity score matching generated cohorts with balanced baseline characteristics (N = 814 in each group). HbA1c reduction from baseline to 6 months with iGlarLixi was non-inferior to BI + RAI [mean difference (95% confidence interval): 0.1 (−0.1, 0.2)%; one-sided $p = .0032$]. At 6 months, weight gain was significantly lower with iGlarLixi than with BI + RAI [−0.8 (−1.3, −0.2) kg; two-sided $p = .0069$]. Achievement of HbA1c <7% without hypoglycaemia and weight gain were similar between groups [odds ratio (95% confidence interval): 1.15 (0.81, 1.63); $p = .4280$]. Hypoglycaemia was low in both groups, probably because of underreporting.

Conclusions: In real-world clinical practice, glycaemic outcomes 6 months after treatment advancement from BI are similar for people with T2D using iGlarLixi versus BI + RAI, with iGlarLixi leading to less weight gain.

KEYWORDS

basal insulin, database research, glucagon-like peptide-1 analogue, glycaemic control, iGlarLixi, type 2 diabetes

This article has an accompanied Plain Language Summary in the Supporting Information [Data S1](#).

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1 | INTRODUCTION

Achieving recommended glycaemic targets for people with diabetes is critical to avoid short- and long-term vascular complications.¹ For people with type 2 diabetes (T2D) on basal insulin (BI) with elevated glucose levels, guidelines recommend either adding a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or a rapid-acting insulin (RAI) to an existing BI regimen, or switching to either a premixed insulin or a fixed-ratio combination (FRC) of BI + GLP-1 RA.²

These treatment options have all been shown to provide greater improvements in glucose levels compared with BI treatment,³⁻⁵ probably because of additional prandial glucose control. However, BI + RAI or premixed insulin regimens require multiple daily injections and more frequent self-measured blood glucose testing than BI regimens, while an FRC maintains a simpler, once-daily injection schedule. FRCs also have a lower risk of hypoglycaemia and weight gain compared with BI + RAI and premix regimens.^{6,7}

iGlarLixi, which combines insulin glargine 100 U/ml and lixisenatide, has previously been shown to provide better glycaemic control with less weight gain and less hypoglycaemia versus BIAsp 30 premix insulin for adults with T2D advancing from BI.⁶ However, while indirect evidence from randomized controlled trial (RCT) data supports the effectiveness of iGlarLixi as an alternative therapy to BI + RAI regimens,^{8,9} there are no published results directly comparing iGlarLixi with BI + RAI therapy.

SoliSimplify is a real-world study comparing the effectiveness of once-daily iGlarLixi with a BI + RAI treatment regimen prescribed in clinical practice to people with T2D advancing from BI therapy.

2 | MATERIALS AND METHODS

2.1 | Study objectives

The primary study objective was to show the non-inferiority of iGlarLixi to BI + RAI therapy in glycated haemoglobin (HbA1c) change from baseline to follow-up at 6 months. Key secondary objectives were to show superiority of iGlarLixi to BI + RAI in body weight change from baseline to 6-month follow-up; proportion of participants achieving HbA1c <7% without any recorded hypoglycaemia and without any body weight gain at the 6-month follow-up; and change in HbA1c from baseline to 6-month follow-up.

2.2 | Study design

SoliSimplify was a retrospective, observational, cohort study of anonymized patient data collected from the Observational Medical Outcomes Partnership (OMOP) US Ambulatory electronic medical records (EMRs) database comparing outcomes with iGlarLixi and BI + RAI in adults with T2D advancing therapy from BI. Data were collected between 1 July 2016 and 28 February 2021 (Figure 1). A participant's index date was defined by their first prescription of either iGlarLixi or RAI and their baseline period began 6 months (180 days) before their index date. The follow-up period duration was variable, starting from index date to the earliest date of death, health plan disenrollment, last record or 6 months (180 days) post-index.

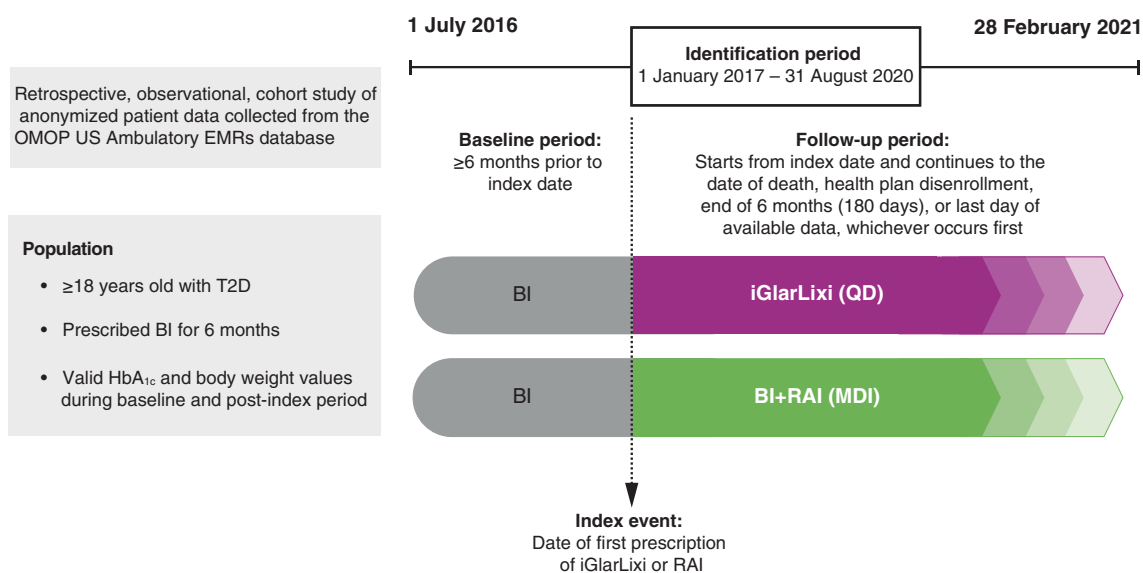


FIGURE 1 SoliSimplify study design. Eligible participants were identified as adults ≥18 years old, diagnosed with type 2 diabetes, prescribed basal insulin for 6 months, with a valid baseline HbA_{1c} record. Each participant received a propensity score and then treatment cohorts were created by PSM. BI, basal insulin; EMRs, electronic medical records; HbA_{1c}, glycated haemoglobin; iGlarLixi, insulin glargine 100 U/ml and lixisenatide; MDI, multiple daily injections; OMOP, Observational Medical Outcomes Partnership; PSM, propensity score matching; QD, once-daily; RAI, rapid-acting insulin

TABLE 1 Demographic and baseline characteristics for iGlarLixi versus BI + RAI cohort after PSM

| Variable | iGlarLixi (N = 814) | BI + RAI (N = 814) | STD DIFF |
|--|---------------------|--------------------|----------|
| Age, years; mean ± SD | 61.5 ± 11.0 | 61.6 ± 11.1 | 0.01 |
| Age group, years; n (%) | | | |
| 18-49 | 108 (13.3) | 107 (13.1) | 0.00 |
| 50-64 | 378 (46.4) | 368 (45.2) | 0.02 |
| 65-74 | 238 (29.2) | 249 (30.6) | 0.03 |
| ≥75 | 90 (11.1) | 90 (11.1) | 0.00 |
| Sex, female; n (%) | 392 (48.2) | 400 (49.1) | 0.02 |
| Race, n (%) | | | |
| Asian | 21 (2.6) | 19 (2.3) | 0.02 |
| African American | 94 (11.6) | 103 (12.7) | 0.03 |
| Caucasian | 573 (70.4) | 563 (69.2) | 0.03 |
| Other/unknown | 126 (15.5) | 129 (15.9) | 0.01 |
| T2D duration identified in database, years; mean ± SD ^a | 4.6 ± 3.1 | 4.8 ± 3.2 | 0.03 |
| Body weight, kg; mean ± SD ^b | 100.1 ± 22.7 | 99.0 ± 23.5 | 0.04 |
| HbA1c value ^b | | | |
| % mean ± SD | 9.2 ± 1.8 | 9.2 ± 1.7 | 0.01 |
| mmol/mol, mean ± SD | 77 ± 19 | 77 ± 19 | 0.01 |
| HbA1c group, n (%) ^c | | | |
| <7% | 53 (6.5) | 50 (6.1) | 0.02 |
| ≥7% and <8% | 144 (17.7) | 149 (18.3) | 0.02 |
| ≥8% and <9% | 236 (29.0) | 237 (29.1) | 0.00 |
| ≥9% and <11% | 248 (30.5) | 246 (30.2) | 0.01 |
| ≥11% | 133 (16.3) | 132 (16.2) | 0.00 |
| Baseline BI types, n (%) ^d | | | |
| Insulin glargine | 640 (78.6) | 643 (79.0) | 0.01 |
| Insulin detemir | 150 (18.4) | 150 (18.4) | 0.00 |
| Insulin degludec | 131 (16.1) | 119 (14.6) | 0.04 |
| NPH | 21 (2.6) | 19 (2.3) | 0.02 |
| OADs usage, n (%) | | | |
| 0 | 160 (19.7) | 148 (18.2) | 0.04 |
| 1 | 342 (42.0) | 353 (43.4) | 0.03 |
| 2 | 251 (30.8) | 258 (31.7) | 0.02 |
| ≥3 | 61 (7.5) | 55 (6.8) | 0.03 |
| OADs categories, n (%) ^e | | | |
| Metformin | 540 (66.3) | 550 (67.6) | 0.03 |
| Sulphonylureas | 266 (32.7) | 270 (33.2) | 0.01 |
| DPP-4i | 148 (18.2) | 144 (17.7) | 0.01 |
| Thiazolidinediones | 81 (10.0) | 74 (9.1) | 0.03 |
| CCI, mean ± SD | 2.16 ± 1.72 | 2.22 ± 1.67 | 0.03 |
| CCI category, n (%) | | | |
| 0 | 42 (5.2) | 33 (4.1) | 0.05 |
| 1 | 367 (45.1) | 358 (44.0) | 0.02 |
| ≥2 | 405 (49.8) | 423 (52.0) | 0.04 |
| Presence of common morbidities and diabetic complications of interest, n (%) | | | |
| Hypertension | 608 (74.7) | 605 (74.3) | 0.01 |
| Hyperlipidaemia | 525 (64.5) | 516 (63.4) | 0.02 |

(Continues)

TABLE 1 (Continued)

| Variable | iGlarLixi (N = 814) | BI + RAI (N = 814) | STD DIFF |
|--|---------------------|--------------------|----------|
| Neuropathy | 201 (24.7) | 192 (23.6) | 0.03 |
| Nephropathy | 145 (17.8) | 137 (16.8) | 0.03 |
| Retinopathy | 51 (6.3) | 56 (6.9) | 0.02 |
| Obesity | 220 (27.0) | 225 (27.6) | 0.01 |
| Depression | 108 (13.3) | 107 (13.1) | 0.00 |
| Chronic kidney disease | 93 (11.4) | 85 (10.4) | 0.03 |
| Systolic blood pressure value, mmHg; mean \pm SD ^{a,f} | 130.78 \pm 15.12 | 130.75 \pm 15.64 | 0.00 |
| Diastolic blood pressure value, mmHg; mean \pm SD ^{a,g} | 76.26 \pm 9.13 | 75.94 \pm 9.63 | 0.03 |

^aDuration of T2D listed in the database was limited by the length of time that participants were enrolled in the health care plan.

^bClosest to index date.

^cHbA1c: 7% = 53 mmol/mol, 8% = 64 mmol/mol, 9% = 75 mmol/mol, 11% = 97 mmol/mol.

^dParticipants could be prescribed more than one type of BI in the baseline period.

^eIt was not possible to identify SGLT2 inhibitor use from the database.

^fSystolic blood pressure before PSM was calculated on 814 participants on iGlarLixi and 7183 participants on BI + RAI.

^gDiastolic blood pressure before PSM was calculated on 814 participants on iGlarLixi and 7184 participants on BI + RAI.

Abbreviations: BI, basal insulin; CCI, Charlson Comorbidity Index; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; iGlarLixi, insulin glargine 100 U/ml and lixisenatide; NPH, neutral protamine Hagedorn; OAD, oral antihyperglycaemic drug; PSM, propensity score matching; RAI, rapid acting insulin; SD, standard deviation; SGLT2, sodium glucose co-transporter-2; STD DIFF, standardized mean difference; T2D, type-2 diabetes mellitus.

2.3 | Participants

Eligible adults (≥ 18 years) had a T2D diagnosis [International Classification of Diseases-10 Clinical Modification (ICD-10-CM) code E11] during the identification period, 1 January 2017 through 31 August 2020; at least one prescription for BI (NPH, insulin glargine 100 U/ml or 300 U/ml, insulin detemir, insulin degludec) at least 6 months before their index date; and ≥ 1 valid value for HbA1c [5-15% (31-140 mmol/mol)] and body weight in the baseline period (including index date) and between 90 and 210 days post index date.

Exclusion criteria included a diagnosis of any other type of diabetes and any prescription for a GLP-1 RA, RAI, iGlarLixi (insulin glargine 100 U/ml and lixisenatide), IDegLira (insulin degludec 100 U/ml and liraglutide), or premix insulin in the 90 days before their index date.

2.4 | Study endpoints

The primary endpoint was defined as the mean difference between the two treatment cohorts in change in HbA1c value from baseline value (record closest to or on the index date) to follow-up at 6 months (value closest to 180 days post-index, between 90 and 210 days). The key secondary endpoints were body weight change from baseline to 6-month follow-up; proportion of participants achieving HbA1c <7% without any hypoglycaemia and without any body weight gain at the 6-month follow-up (composite endpoint); and change in HbA1c from baseline to 6-month follow-up.

Additional endpoints included hypoglycaemia incidence and event rate at the 6-month follow-up, defined as (ICD-10-CM) code E16.2 and Systemized Nomenclature of Medicine (SNOMED) code 4154498, or blood glucose <70 mg/dl (<3.9 mmol/L) confirmed either

by laboratory testing or observation results. HbA1c and body weight values, demographic characteristics and health data (e.g. age, presence of common comorbidities) were also extracted and/or derived from the database.

2.5 | Statistical analyses

Analyses were performed in R (v 4.0.4) with open-source OHDSI R packages, including SkeletonComparativeEffectStudy, CohortMethod and Cyclops. A minimum sample size of 699 per group was calculated to provide 80% power to show non-inferiority of iGlarLixi to BI + RAI in terms of HbA1c change from baseline to follow-up with a margin of 0.3%; 3 mmol/mol [SD 2.0% (22 mmol/mol)]; $\alpha = 0.025$, one-sided t-test]. Individuals with missing values for covariates of interest were excluded from the analysis.

In brief, propensity scores were generated for each participant using logistic regression. Scores represented the probability that a patient received iGlarLixi based on their observed baseline demographics and clinical characteristics (listed in Table 1). Matched groups were created based on propensity scores on the logit scale using a greedy neighbour matching algorithm with a fixed calliper of 0.2 SDs of the propensity score on the logit scale. Based on their recorded treatment, participants were matched to iGlarLixi and BI + RAI groups 1:1. The balance between groups was assessed pre- and post-propensity score matching (PSM) using standardized mean differences (STDDIFF) and a threshold score of 0.1.

The primary endpoint of between-treatment difference in mean HbA1c change was assessed using a paired t-test (one-sided, $\alpha = 0.025$), with a non-inferiority margin of 0.3% (3 mmol/mol). Key secondary endpoints were assessed in hierarchical order (to control

overall type I error) to show superiority of iGlarLixi versus BI + RAI in: (a) body weight change; (b) composite target achievement; and (c) HbA1c change (two-sided, $\alpha = 0.05$). Testing was stopped when the null hypothesis could not be rejected. Paired t-tests were used to compare between-treatment differences in body weight, while the odds ratio of participants reaching the composite target endpoint between treatment cohorts was estimated by logistic regression.

Exploratory analyses were performed to evaluate the effects of baseline HbA1c $\geq 9\%$ (≥ 75 mmol/mol) or age ≥ 65 years on the primary and secondary endpoints.

Sensitivity analyses revealed that the results were not greatly influenced by slight variations in starting parameters or endpoint definitions. A restricted identification period (1 January 2017 and 30 June 2019) was used to explore possible impacts of COVID-19 on primary and key secondary endpoints. Primary and key secondary endpoints were also re-evaluated using participants who had ≥ 1 additional treatment prescription within 180 days post-index date, and participants who had ≥ 1 BI prescription within 120 days window from index date. The proportion of participants achieving HbA1c $< 8\%$ without any hypoglycaemia and without any body weight gain was analysed as a composite target endpoint.

3 | RESULTS

3.1 | Participants

The database contained 3 730 396 participants with T2D with records during the study period. After applying sample selection criteria, 819 individuals were eligible to be included in the iGlarLixi cohort and 7298 were eligible for the BI + RAI cohort (Table S1). Before PSM, cohorts differed in several baseline characteristics (STDDIFF > 0.1 ; Table S2).

After PSM, there were 814 participants in each cohort, with no differences observed between participant demographics and baseline characteristics (STDDIFF ≤ 0.1 for all; Table 1). Participants in both cohorts had a number of comorbidities, the two most common being hypertension ($\sim 75\%$ in each cohort) and hyperlipidaemia ($\sim 65\%$ in each cohort). Participants in each cohort had a mean age of ~ 60 years, a mean weight of ~ 100 kg, and almost 30% were obese. Mean baseline HbA1c was 9.2% (77 mmol/mol) in both cohorts. The most commonly prescribed BIs in the baseline period were insulin analogues and most participants were on one or two oral antihyperglycaemic drugs.

3.2 | Outcomes

The mean \pm SD HbA1c was reduced from a baseline of $9.2 \pm 1.8\%$ (77 ± 20 mmol/mol) to $8.5 \pm 1.7\%$ (69 ± 19 mmol/mol) with iGlarLixi and from $9.2 \pm 1.7\%$ (77 ± 19 mmol/mol) to $8.4 \pm 1.7\%$ (68 ± 19 mmol/mol) with BI + RAI at the 6-month follow-up (mean

change \pm SD, iGlarLixi: $-0.7 \pm 1.8\%$, 8 ± 20 mmol/mol; BI + RAI: $-0.8 \pm 1.7\%$, 9 ± 19 mmol/mol; Figure 2A). Mean HbA1c reductions with iGlarLixi were non-inferior to BI + RAI [non-inferiority margin: 0.3%; mean difference (95% CI): 0.1 ($-0.1, 0.2$)%, 1 ($-1, 2$) mmol/mol; one-sided $p = .0032$; Figure 2A]; therefore, the primary endpoint was met.

The first key secondary endpoint was also met, as mean body weight decreased from baseline to 6-month follow-up in the iGlarLixi cohort (mean \pm SD: -0.1 ± 4.6 kg) and increased in the BI + RAI cohort (0.7 ± 6.7 kg); the between-treatment difference was significant [mean difference (95% CI): -0.8 kg ($-1.3, -0.2$); two-sided $p = .0069$; Figure 2B]. The percentage of people with T2D who achieved HbA1c $< 7\%$ without any hypoglycaemia and without any body weight gain did not differ between the treatment groups [iGlarLixi: 9.2% (75 of 814); BI + RAI: 8.1% (66 of 814); odds ratio (95% CI): 1.15 (0.81, 1.63); $p = .4280$; Figure 2C]. As this composite endpoint was not achieved, superiority in HbA1c change from baseline to 6-month follow-up was not tested. The percentage of people with T2D who achieved HbA1c $< 7\%$ was 15.5% (126 of 814) with iGlarLixi and 16.0% (130 of 814) with BI + RAI.

At the 6-month follow-up, 2.7% (22 of 814) in the iGlarLixi cohort and 2.5% (20 of 814) in the BI + RAI cohort experienced hypoglycaemia, while rates of recorded hypoglycaemia were 8.60 and 7.37 events per 100 person-years, respectively. There was no significant between-treatment difference in hypoglycaemia incidence [odds ratio (95% CI): 1.1 (0.6, 2.1)] or rates [relative risk (95% CI): 1.2 (0.7, 1.9)].

3.3 | Subgroup analyses

In participants with baseline HbA1c $\geq 9\%$ (≥ 75 mmol/mol), iGlarLixi and BI + RAI were associated with similar HbA1c reductions from baseline to 6-month follow-up (mean change \pm SD, iGlarLixi: $-1.5 \pm 2.0\%$, -16 ± 22 mmol/mol; BI + RAI: $-1.5 \pm 1.9\%$, -16 ± 21 mmol/mol). Body weight was maintained in the iGlarLixi group (0.0 ± 4.5 kg), and an increase was seen with BI + RAI (1.2 ± 5.5 kg) (Table 2). A similar proportion of participants with high baseline HbA1c achieved HbA1c $< 7\%$ (< 53 mmol/mol) without hypoglycaemia and without weight gain in each treatment cohort [iGlarLixi: 19 of 381 (5.0%), BI + RAI: 17 of 378 (4.5%)] (Table 2).

In older participants (≥ 65 years of age at baseline), mean HbA1c reductions from baseline to 6-month follow-up were similar for those prescribed either iGlarLixi or BI + RAI (mean change \pm SD, iGlarLixi: $-0.7 \pm 1.7\%$, -8 ± 19 mmol/mol; BI + RAI: $-0.7 \pm 1.5\%$, -8 ± 16 mmol/mol; Table 2), and of a similar magnitude to that observed in the overall study population. The mean \pm SD body weight changes of -0.5 ± 4.1 kg and 0.4 ± 7.6 kg were seen with iGlarLixi and BI + RAI, respectively, and a numerically greater percentage of older participants on iGlarLixi achieved the HbA1c target of $< 7\%$ (< 53 mmol/mol) without hypoglycaemia and without body weight gain than with BI + RAI [iGlarLixi: 38 of 328 (11.6%), BI + RAI: 26 of 339 (7.7%); Table 2].

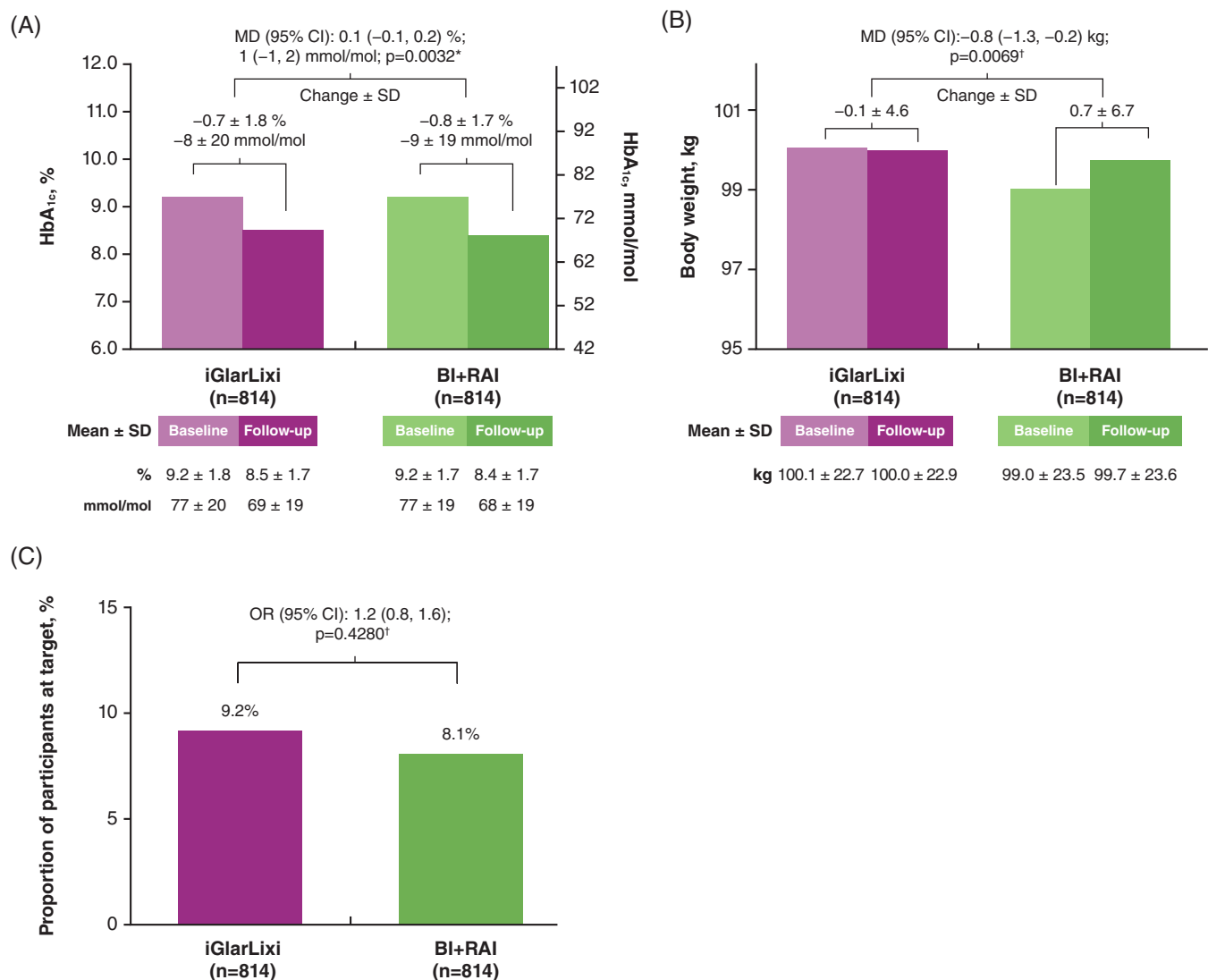


FIGURE 2 Efficacy outcomes in PSM-matched cohorts. (A) Mean HbA_{1c}; (B) mean body weight; (C) proportion of participants achieving HbA_{1c} <7% (<53 mmol/mol) without any hypoglycaemia and without body weight gain at the 6-month follow-up. *One-sided *p*-value assessing non-inferiority of iGlarLixi versus BI + RAI with non-inferiority margin = 0.3% (3 mmol/mol); †Two-sided *p*-value assessing superiority of iGlarLixi versus BI + RAI. BI, basal insulin; CI, confidence interval; HbA_{1c}, glycated haemoglobin; iGlarLixi, insulin glargine 100 U/ml and lixisenatide; MD, mean difference; OR, odds ratio; RAI, rapid-acting insulin; SD, standard deviation, SE, standard error

3.4 | Sensitivity analyses

Sensitivity analyses revealed that both treatments were associated with similar reductions in HbA_{1c} over the study period regardless of whether the study period fell before or during the COVID-19 pandemic, or whether the participants had been prescribed ≥1 additional treatment prescription during the 120 days before or 180 days after their index dates (Table S3). iGlarLixi showed a significant body weight reduction compared with BI + RAI whether the study period was before or during the COVID-19 pandemic, but small increases were seen with both treatments if the participants were prescribed at ≥1 additional treatment during the 120 days before (iGlarLixi: 0.1 ± 4.8 kg; BI + RAI: 0.7 ± 5.4 kg) or 180 days after (iGlarLixi: 0.1 ± 4.7 kg; BI + RAI: 0.7 ± 5.3 kg) their index dates. The proportion

of participants that achieved a target HbA_{1c} of <7% without any hypoglycaemia and without any body weight gain at the 6-month follow-up was similar in both treatment cohorts across these parameters. With the less-stringent composite target of HbA_{1c} <8% without any hypoglycaemia and without any body weight gain at the 6-month follow-up, the proportion of participants reaching this target was comparable between the cohorts (iGlarLixi: 196 of 814, 24.1%; BI + RAI: 175 of 814, 21.5%).

4 | DISCUSSION

Real-world data, such as electronic health records and health insurance claims datasets, are increasingly used as a complement to

TABLE 2 Exploratory analyses of iGlarLixi versus BI + RAI treatment in participants with high baseline HbA1c or ≥65 years of age

| | Baseline HbA1c ≥9% (≥75 mmol/mol) | | Age ≥65 years | |
|---|-----------------------------------|--------------------|---------------------|--------------------|
| | iGlarLixi (n = 381) | BI + RAI (n = 378) | iGlarLixi (n = 328) | BI + RAI (n = 339) |
| Change in HbA1c, % | | | | |
| Baseline, mean ± SD | 10.7 ± 1.4 | 10.6 ± 1.4 | 8.9 ± 1.5 | 8.8 ± 1.6 |
| 6 months follow-up, mean ± SD | 9.2 ± 1.8 | 9.1 ± 1.8 | 8.2 ± 1.4 | 8.1 ± 1.4 |
| Change from baseline to 6-month follow-up, mean ± SD | -1.5 ± 2.0 | -1.5 ± 1.9 | -0.7 ± 1.7 | -0.7 ± 1.5 |
| Change in HbA1c, mmol/mol | | | | |
| Baseline, mean ± SD | 93 ± 15 | 92 ± 15 | 74 ± 16 | 73 ± 17 |
| 6-month follow-up, mean ± SD | 77 ± 20 | 76 ± 20 | 66 ± 15 | 65 ± 15 |
| Change from baseline to 6-month follow-up, mean ± SD | -16 ± 22 | -16 ± 21 | -8 ± 19 | -8 ± 16 |
| Change in body weight, kg | | | | |
| Baseline, mean ± SD | 100.2 ± 21.8 | 97.6 ± 23.0 | 94.0 ± 19.8 | 92.9 ± 21.6 |
| 6-month follow-up, mean ± SD | 100.3 ± 22.0 | 98.9 ± 23.1 | 93.5 ± 20.4 | 93.3 ± 21.3 |
| Change from baseline to 6-month follow-up, mean ± SD | 0.0 ± 4.5 | +1.2 ± 5.5 | -0.5 ± 4.1 | 0.4 ± 7.6 |
| HbA1c <7% (53 mmol/mol) without hypoglycaemia and without body weight gain at the 6-month follow-up | | | | |
| Participants, n (%) | 19 (5.0%) | 17 (4.5%) | 38 (11.6%) | 26 (7.7%) |

Abbreviations: BI, basal insulin; HbA1c, glycated haemoglobin; iGlarLixi, insulin glargine 100 U/ml and lixisenatide; RAI, rapid-acting insulin; SD, standard deviation.

randomized clinical trials to inform health care and regulatory decision making.¹⁰ These data provide an index of interactions between patients and the health care system and as such provide a measure of the clinical courses of individual patients or effectiveness of a pharmacological intervention at scale.¹¹ SoliSimplify was designed to compare the real world effectiveness of iGlarLixi with a BI + RAI regimen in a propensity-matched population of people with T2D advancing treatment from BI using anonymized patient data collected from OMOP US Ambulatory EMRs. In this setting, we found that after 6 months, iGlarLixi was non-inferior to a BI + RAI regimen in terms of HbA1c reduction and did not result in weight gain, while weight gain was seen with BI + RAI. Sensitivity analyses revealed that the results were not greatly influenced by slight variations in starting parameters or endpoint definitions and similar findings were seen in two subgroup analyses (HbA1c ≥75 mmol/mol or age ≥65 years at baseline). There was no significant between-treatment difference in hypoglycaemia incidence.

For people with T2D not reaching their glycaemic targets with BI, guidelines recommend adding either a GLP-1 RA or an RAI to an existing BI regimen, or switching to either a premixed insulin or an FRC of BI + GLP-1 RA.² In the present study, we have used real world evidence (RWE) to compare an FRC with BI + RAI. Consistent with our findings, indirect evidence from a Bayesian network meta-analysis of eight published RCTs suggested that iGlarLixi was more effective than BI plus one daily injection of prandial insulin, provided similar glycaemic control versus BI plus prandial insulin three times daily, and provided similar weight profiles compared with both prandial insulin regimens.⁸ Using PSM, the LixiLan-L⁵ and the GetGoal Duo-2¹² studies suggested that iGlarLixi could provide significantly greater HbA1c reduction and favourable weight change alongside fewer episodes of

hypoglycaemia compared with basal-bolus therapy in participants with T2D advancing therapy from BI.⁹ Similarly, the DUAL-VII RCT study found the FRC, IDegLira, was non-inferior to basal-bolus therapy in terms of HbA1c reduction.⁷ Lower rates of hypoglycaemia were also observed in the IDegLira group than the basal-bolus treatment group, but this was in the context of more robust detection and confirmation of hypoglycaemia in the DUAL-VII RCT than the present analysis, including non-severe hypoglycaemia.⁷ Therefore, the results of the present RWE study complement findings from direct and indirect comparisons between FRCs and BI + RAI regimens from RCTs.

Individualization of therapy also requires the health care professional to be cognizant of other factors, including comorbidities, hypoglycaemia risk, patient preference² and how treatment complexity may affect adherence and persistence.¹³ In particular, increasing number of injections can be perceived as burdensome by people with T2D, and perceived burden of treatment can be a strong predictor of poor treatment adherence.¹⁴ In addition to more frequent daily injections, basal plus prandial regimens have the added complexity of more frequent self-monitoring of glucose, as well as carbohydrate counting, to the most appropriate dose of prandial insulin. iGlarLixi provides a simpler, once-daily injection regimen, versus multiple daily injections with BI + RAI, that in the real-world setting proved as efficacious in terms of glycaemic benefit. The SoliComplex observational RWE study in people with T2D advancing their therapy from BI showed that iGlarLixi was associated with higher treatment persistence, alongside similar HbA1c reductions compared with premixed and basal-bolus insulin regimens.^{15,16} Another major factor leading to non-compliance with insulin-based treatments is the fear of weight gain.¹⁷ As iGlarLixi is associated with less weight gain compared with premixed insulin, it could be a suitable option.⁶ The results from the

present study suggest that, where treatment complexity and adherence are a concern, iGlarLixi presents a suitable alternative to BI + RAI for advancing therapy from BI.

Both treatments showed HbA1c reductions of almost 1% (10.9 mmol/mol) over 6 months in a clinical practice setting. The proportion of people achieving a target HbA1c <7% without hypoglycaemia and without weight gain was ~8.5% overall, and ~15% reached HbA1c <7% overall. While the HbA1c reductions and target achievement seen in the present study are lower than observed in RCTs,^{4,5,18} results of other trials assessing antihyperglycaemic regimens have also shown less robust HbA1c reductions in RWE studies compared with RCTs.¹⁹ Indeed, two randomized pragmatic studies of insulin glargine (100 and 300 U/ml) efficacy reported HbA1c reductions in people with T2D of ~0.5 to 1.5% after 6 months.²⁰ These modest reductions were attributed to lack of standardized titration-to-target algorithms, which are typical in RCTs of antihyperglycaemic therapies, and less contact with health care professionals.²⁰ Furthermore, RCT participants may be more motivated to adhere to their therapy than those in clinical practice. Results of observational RWE studies of the fixed ratio combination, iDegLira (insulin degludec and liraglutide), showed similar results to the present study, with modest HbA1c reductions of approximately between 0.6% and 1.1% (6.6–12.0 mmol/mol).^{21,22} Furthermore, data from Zenari et al. showed little improvement from 6 months to 12 months, suggesting that extending the present study beyond 6 months would be unlikely to have improved target achievement.²²

Although epidemiological data show that many people with T2D do not achieve glycaemic targets outside of clinical trials,²³ the target achievement rates for iGlarLixi in the clinical setting are similar to those observed in a non-interventional RWE of iGlarLixi effectiveness²⁴ and for other antihyperglycaemic agents.^{21,25} RWE has also revealed low target HbA1c achievement for people with T2D following therapy advancement with BI.²⁶ EMR data from more than 40 000 individuals across six countries showed that only ±28.7% reached HbA1c levels of <7% (<53 mmol/mol) 2 years after initiating BI therapy.²⁶ In the eight studies comprising the DELIVER programme, which also utilized EMR data from the United States and PSM, between 15% and 27% of the participants treated with BI achieved HbA1c <7%.²⁷

As previously mentioned, there was a modest benefit for iGlarLixi versus BI + RAI for body weight change (<1 kg), with no weight gain seen in the iGlarLixi arm. Similarly, iDegLira (the other FRC of BI and GLP-1 RA) was associated with a small (<1 kg) but statistically significant benefit for body weight change compared with basal-bolus insulin, with no weight gain seen with iDegLira.⁷ This was in the context of an RCT with a treat-to-target treatment approach and scheduled participant follow-up.⁷ Other studies have also shown no weight gain when switching from a BI regimen to iGlarLixi.^{5,6} Concerns about body weight can be a barrier to intensification of a BI regimen²⁸ so it is encouraging that iGlarLixi did not result in weight gain.

In the present analysis, few hypoglycaemia events were recorded (iGlarLixi: 2.7%; BI + RAI: 2.5%), and the severity of these events is unknown. Because of factors such as impaired awareness, recall bias,

incorrect coding, or reticence of participants to report episodes to their physicians, hypoglycaemia tends to be underreported in retrospective RWE studies.^{29,30} Hypoglycaemic events recorded in EMRs are also more likely to be severe, that is, events requiring external assistance for recovery.³¹ In comparison, data from a survey-based study specifically designed to assess self-reported hypoglycaemia showed that >50% of 2706 Canadians receiving insulin and/or sulphonylureas reported at least one non-severe event in the last 30 days and/or severe event in the last year.³² This suggests many hypoglycaemia events are not captured in EMRs, which is a limitation of the study and means that conclusions about the effect of treatment on hypoglycaemia in SoliSimplify cannot be derived because of the low reported incidence of hypoglycaemia.

Clinical data from RWE studies can provide insight into the effectiveness of therapies in populations not typically included in RCTs. Unlike results derived from RCTs that have highly selected populations, a high degree of participant follow-up^{11,33} and, for studies comparing insulin-based therapies in particular, often employ a treat-to-target design using titration protocols, RWE results are more representative of clinical practice. In this study, treatment advancement with iGlarLixi was seen to be as effective as BI + RAI in participants with higher baseline HbA1c ($\geq 9\%$, ≥ 75 mmol/mol) and adults ≥ 65 years of age, two populations that may normally be excluded from RCTs. In particular, people ≥ 65 years of age with T2D are often excluded from RCTs,³⁴ yet it is important to assess clinical outcomes in these people, as they represent a substantial proportion of the T2D population.²³ Furthermore, there are additional treatment considerations for older adults because of their higher risk of hypoglycaemia and associated complications,³⁵ as well as the prevalence of comorbidities, polypharmacy and renal impairment in this population.³⁴ Consequently, guidelines recommend treatment simplification where possible for older individuals, which may suggest that iGlarLixi could provide a suitable option for older people with T2D who require therapy advancement.

Limitations of the present analysis include that the EMR database used is a repository for reimbursement claims and is not designed to support clinical research. Thus, the quality of the data depends on the information provided by the physicians¹¹ or on correct coding and many potentially-useful data are not available (e.g. medication dose); for example, in the present analysis limited data were available on hypoglycaemia events. The use of pre-defined codes to gather data precluded the identification of specific patient subgroups and the sodium-glucose co-transporter inhibitor (SGLT2i) use was not reliably captured. However, results from a recent RWE study assessing iGlarLixi efficacy with or without concomitant SGLT2i in people with T2D showed that HbA1c reductions and hypoglycaemia prevalence were similar for iGlarLixi users regardless of SGLT2i therapy.³⁶ In addition, levels of treatment adherence will probably be lower than those achieved in an RCT.¹¹ As with other RWE studies, lack of randomization may lead to bias from unknown confounders. Although PSM was used to minimize bias, this methodology matches individuals based on a pre-selected, known set of baseline covariates, and may not fully eliminate bias. It is also worth noting that a large proportion of the

BI + RAI population were eliminated from this analysis during PSM because of the smaller number of participants treated with iGlarLixi; thus, results may not be representative of the full BI + RAI population. A low level of adherence will impact the apparent effectiveness of both treatments, which, in turn, could minimize possible differences between the treatments. While this bias would favour non-inferiority in HbA1c, it would decrease the likelihood of observing the superiority in body weight change observed with iGlarLixi. In addition, it is not possible to determine whether all participants in the BI + RAI cohort continued BI post-index date. A pre-planned sensitivity analysis on participants with any BI prescription 30 days post-index was designed to address this, but was not performed as the sample sizes were very similar to the overall study population, suggesting few participants did not have post-index BI prescriptions.

In this RWE study, iGlarLixi showed similar glycaemic control to BI + RAI without weight gain in people with T2D in a clinical practice setting. These data, from the first direct comparison of these treatments in real-life clinical practice use, suggest that iGlarLixi could provide an effective and simpler, once-daily alternative therapy option to BI + RAI in people advancing from BI.

ACKNOWLEDGMENTS

We thank Ana Merino-Trigo, PhD (Sanofi) for coordinating the development, facilitating author discussions, and for providing a courtesy review of this manuscript. We also thank Xiaoyu Lin and Jing Li (IQVIA China) for analytical support. Editorial assistance was provided by Katey Glunt, PhD, and Hannah Brown, PhD, of Fishawack Communications Ltd, part of Fishawack Health.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to participant-level data and related documents. Participant-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at <http://www.vivli.org>.

AUTHORSHIP

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All authors participated in the interpretation of the data, the writing, reviewing, and editing of the manuscript, and had final responsibility for approving the published version.

DISCLOSURE OF INTERESTS

Rory J. McCrimmon has acted as an advisor and speaker for Sanofi and Novo Nordisk. Alice Y.Y. Cheng has received honoraria for speaking or consulting from Abbott, AstraZeneca, Bausch, Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, Insulet, Janssen, Merck, Novo Nordisk, Sanofi, HLS Therapeutics, Medtronic and Takeda; and has participated in clinical trials supported by Boehringer Ingelheim, Eli

Lilly, Sanofi and Applied Therapeutics. Gagik Galstyan has served on advisory boards for MSD, AstraZeneca, Novo Nordisk, Sanofi, Abbott and Pfizer; and has been a speaker for Eli Lilly, Novo Nordisk, Sanofi, Novartis, Berlin Chemie, MSD, Boehringer Ingelheim, AstraZeneca, Amgen, LifeScan, Servier and Takeda. Mathieu Coudert, Khier Djabalalah and Xuan Li are employees of Sanofi. Juan P. Frias has research support from Akero, AstraZeneca, Boehringer Ingelheim, BMS, 89bio, Eli Lilly, Intercept, IONIS, Janssen, Madrigal, Metacrine, Merck, North-Sea Therapeutics, Novartis, Novo Nordisk, Oramed, Pfizer, Poxel, Sanofi and Theracos; has participated in advisory boards and consulting with Akero, Altimmune, Axcella Health, Becton Dickenson, Boehringer Ingelheim, Carmot Therapeutics, Echosens, 89bio, Eli Lilly, Gilead, Intercept, Metacrine, Merck, Novo Nordisk, Pfizer and Sanofi; and is on Speakers' Bureaus for Eli Lilly, Merck and Sanofi.

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REFERENCES

1. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.
2. American Diabetes Association. 9. Pharmacologic approaches to glycaemic treatment: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45(Supplement 1):S125-S143.
3. Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F. GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2019;35(1):e3082.
4. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007; 357(17):1716-1730.
5. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. 2016; 39(11):1972-1980.
6. Rosenstock J, Emral R, Sauque-Reyna L, et al. Advancing therapy in suboptimally controlled basal insulin-treated type 2 diabetes: clinical outcomes with iGlarLixi versus premix BIAsp 30 in the SoliMix randomized controlled trial. *Diabetes Care*. 2021;44:2361-2370.
7. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin; DUAL VII randomized clinical trial. *Diabetes Care*. 2018;41:1009-1016.
8. Home P, Blonde L, Kalra S, et al. Insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) compared with premix or addition of meal-time insulin to basal insulin in people with type 2 diabetes: a systematic review and Bayesian network meta-analysis. *Diabetes Obes Metab*. 2020;22(11):2179-2188.
9. Tabák ÁG, Anderson J, Aschner P, et al. Efficacy and safety of iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide, compared with basal-bolus regimen in patients with type 2 diabetes: propensity score matched analysis. *Diabetes Ther*. 2020;11(1): 305-318.
10. Beaulieu-Jones BK, Finlayson SG, Yuan W, et al. Examining the use of real-world evidence in the regulatory process. *Clin Pharmacol Ther*. 2020;107(4):843-852.

11. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293-2297.
12. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 trial. *Diabetes Care*. 2016;39:1318-1328.
13. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
14. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. *J Gen Intern Med*. 2005;20(5):479-482.
15. Lajara R, Heller C, Pantalone KM, et al. iGlarLixi vs. premixed insulin initiation in adults with type 2 diabetes (T2D) advancing from basal insulin (BI) therapy: SoliComplex real-world study. *Diabetes*. 2022;71(Supplement_1):739-P.
16. Pantalone KM, Heller C, Lajara R, et al. Initiation of iGlarLixi vs. basal-bolus insulin (BB) in adults with type 2 diabetes (T2D) advancing from basal insulin (BI) therapy: the SoliComplex real-world study. *Diabetes*. 2022;71(Supplement_1):733-P.
17. Lee DSU, Lee H. Adherence and persistence rates of major antidiabetic medications: a review. *Diabetol Metab Syndr*. 2022;14(1):12.
18. Raccach D, Huet D, Dib A, et al. Review of basal-plus insulin regimen options for simpler insulin intensification in people with type 2 diabetes mellitus. *Diabet Med*. 2017;34(9):1193-1204.
19. Carls GS, Tuttle E, Tan RD, et al. Understanding the gap between efficacy in randomized controlled trials and effectiveness in real-world use of GLP-1 RA and DPP-4 therapies in patients with type 2 diabetes. *Diabetes Care*. 2017;40(11):1469-1478.
20. Freemantle N, Mauricio D, Giaccari A, et al. Real-world outcomes of treatment with insulin glargine 300 U/mL versus standard-of-care in people with uncontrolled type 2 diabetes mellitus. *Curr Med Res Opin*. 2020;36(4):571-581.
21. Egede LE, Bogdanov A, Fischer L, Da Rocha Fernandes JD, Kallenbach L. Glycemic control among patients newly prescribed IDegLira across prior therapy group in US real-world practice. *Diabetes Ther*. 2020;11(7):1579-1589.
22. Zenari L, Da Porto A, De Moliner L, et al. Real-world evaluation of glycemic outcomes and extra-glycemic parameters in diabetic patients treated with the combined formulation degludec-liraglutide (IDegLira). *Diabetes Ther*. 2021;12(1):197-209.
23. Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2020*. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2020.
24. Kis JT, Nagy G, Kovacs G. Effectiveness of iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide, in people with type 2 diabetes. *Diabetes Ther*. 2021;12(9):2517-2529.
25. Lautsch D, Boggs R, Wang T, et al. Individualized HbA1c goals, and patient awareness and attainment of goals in type 2 diabetes mellitus: a real-world multinational survey. *Adv Ther*. 2022;39(2):1016-1032.
26. Mauricio D, Meneghini L, Seufert J, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. *Diabetes Obes Metab*. 2017;19(8):1155-1164.
27. Blonde L, Bailey T, Sullivan SD, Freemantle N. Insulin glargine 300 units/mL for the treatment of individuals with type 2 diabetes in the real world: a review of the DELIVER programme. *Diabetes Obes Metab*. 2021;23(8):1713-1721.
28. Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. *Diabetes Obes Metab*. 2018;20(3):488-496.
29. Frier BM, Ratzki-Leewing A, Harris SB. Reporting of hypoglycaemia in clinical trials of basal insulins: a need for consensus. *Diabetes Obes Metab*. 2019;21(7):1529-1542.
30. Östenson CG, Geelhoed-Duijvestijn P, Lahtela J, Weitgasser R, Markert Jensen M, Pedersen-Bjergaard U. Self-reported non-severe hypoglycaemic events in Europe. *Diabet Med*. 2014;31(1):92-101.
31. Nunes AP, Yang J, Radican L, et al. Assessing occurrence of hypoglycemia and its severity from electronic health records of patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2016;121:192-203.
32. Ratzki-Leewing A, Harris SB, Mequanint S, et al. Real-world crude incidence of hypoglycemia in adults with diabetes: results of the InHypo-DM study, Canada. *BMJ Open Diabetes Res Care*. 2018;6(1):e000503.
33. Klonoff DC, Gutierrez A, Fleming A, Kerr D. Real-world evidence should be used in regulatory decisions about new pharmaceutical and medical device products for diabetes. *J Diabetes Sci Technol*. 2019;13(6):995-1000.
34. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care*. 2012;35(12):2650-2664.
35. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, Sinclair AJ. Hypoglycemia in older people - a less well recognized risk factor for frailty. *Aging Dis*. 2015;6(2):156-167.
36. Guja C, Giorgino F, Blonde L, et al. Concomitant iGlarLixi and sodium-glucose co-transporter-2 inhibitor therapy in adults with type 2 diabetes: LixiLan-G trial and real-world evidence results. *Diabetes Ther*. 2022;13(1):205-215.

SUPPORTING INFORMATION

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

How to cite this article: McCrimmon RJ, Cheng AYY, Galstyan G, et al. iGlarLixi versus basal plus Rapid-Acting insulin in adults with type 2 diabetes advancing from basal insulin therapy: The SoliSimplify Real-World study. *Diabetes Obes Metab*. 2022;1-10. doi:[10.1111/dom.14844](https://doi.org/10.1111/dom.14844)