Received: 14 May 2018 | Revised and accepted: 8 November 2018

DOI: 10.1111/dom.13580

WILEY

BRIEF REPORT

Insulin glargine/lixisenatide fixed-ratio combination improves glycaemic variability and control without increasing hypoglycaemia

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Funding information
The authors received writing/editorial support in the preparation of this manuscript provided by Pim Dekker, PhD, and Yasmin Issop, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

Maintaining optimal glycaemic control reduces the risk of micro- and macrovascular complications in patients with type 2 diabetes. Typically, glycaemic control is based on glycated haemoglobin (HbA1c) as a measure of mean glucose concentration; however, this marker does not accurately reflect glycaemic variability (GV), which is characterized by the amplitude, frequency and duration of hypo- and hyperglycaemic fluctuations. In the present study, we analysed data from the LixiLan-O trial, which compared iGlarLixi, a titratable fixed-ratio combination of the glucagon-like peptide-1 receptor agonist lixisenatide (Lixi) and long-acting basal insulin glargine 100 units/mL (iGlar), with its individual components, and the LixiLan-L trial, which compared iGlarLixi with iGlar. The GV features that were measured were mean and SD of self-measured plasma glucose (SMPG), high blood glucose index (HBGI) and low blood glucose index, area under the SMPG curve for each patient (AUCn), mean absolute glucose (MAG) and mean amplitude of glycaemic excursions (MAGE). By week 30, iGlarLixi improved all GV markers from baseline, with no increased hypoglycaemia risk. Significant improvements were observed in SMPG, SD of SMPG, HBGI, AUCn, MAG and MAGE compared with iGlar, and in SMPG, HBGI and AUCn, compared with Lixi.

KEYWORDS

antidiabetic drug, glycaemic control, type 2 diabetes

1 | INTRODUCTION

Glycated haemoglobin (HbA1c) is commonly used to estimate mean glucose exposure over 2 to 3 months to assess glycaemic control in patients with diabetes; however, HbA1c does not reflect daily excursions in blood glucose or glycaemic variability (GV).[1] Patients with type 2 diabetes (T2D), despite achieving within-target control of HbA1c, may still show substantial GV.[2,3] Increased GV correlates with increased hypoglycaemia,[4] may adversely affect endothelial function and oxidative stress, and probably contributes to cardiovascular complications in diabetes.[5]

One therapeutic option for reducing GV and persistent hyperglycaemia is treatment with a glucagon-like peptide-1 receptor agonist (GLP-1RA). Because they are known to reduce postprandial glucose (PPG) excursions, GLP-1RAs may have a unique benefit in the reduction of GV. Two recent studies of regimens that included GLP-1RAs reported significant reductions (improvements) in GV for such regimens compared with insulin alone and other injectable combination therapies.[2,3] iGlarLixi, a combination of the GLP-1RA lixisenatide (Lixi) and long-acting basal insulin (BI) glargine 100 units/mL (iGlar), is delivered through a single daily injection for T2D treatment. In phase III trials, iGlarLixi significantly reduced HbA1c values, with fewer gastrointestinal adverse events compared with Lixi alone, and without increasing hypoglycaemia compared with iGlar alone.[6,7] Additionally, significant improvements in 2-hour PPG values were observed with iGlarLixi compared with iGlar. In the present study, we investigated the effects of iGlarLixi compared with those of its individual components, iGlar and Lixi, on GV markers.

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2 | METHODS

2.1 | Study design and patients

In this post hoc analysis we assessed data from two phase III trials. The first, LixiLan-O (NCT02058147), compared iGlarLixi, iGlar and Lixi in 1170 patients with T2D inadequately controlled on metformin alone (HbA1c 58–86 mmol/mol [7.5–10%]) or with a second oral antidiabetes drug (OAD; HbA1c 53–75 mmol/mol [7.0–9.0%]). Patients discontinued the second OAD, optimized their metformin dose over 4 weeks, and were randomized to one of the three treatment groups for 30 weeks.[6]

The second, LixiLan-L (NCT02058160), compared iGlarLixi with iGlar in 736 patients with T2D inadequately controlled on BI with zero, one or two OADs.[7] Any therapy other than metformin was discontinued, and all patients transitioned to and/or optimized iGlar for 6 weeks. Patients with HbA1c values of 53 mmol/mol (7.0%) to 86 mmol/mol (10.0%), fasting self-measured plasma glucose (SMPG) values ≤7.8 mmol/L (140 mg/dL) and an iGlar dose of ≤50 units were randomized to iGlarLixi or iGlar for 30 weeks.

2.2 | Statistical analyses

2.2.1 | Assessments

During the 30-week trial period, patients recorded their SMPG at seven time points (pre-injection, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, 2 hours after dinner, and at bedtime) at baseline and week 30. The resulting seven-point SMPG profile differences were used to calculate mean SMPG, the SD of SMPG, high blood glucose index (HBGI), low blood glucose index (LBGI), area under the SMPG curve for each patient (AUCn), mean absolute glucose (MAG) rate of change, and mean amplitude of glycaemic excursions (MAGE). HBGI and LBGI incorporate logarithmic transformations to the glycaemic range to assess, respectively, hyper- and hypoglycaemic excursions.[1] AUCn is indicative of the magnitude and duration of PPG excursions, MAG provides information about the extent (or amplitude) of GV, and MAGE represents the excursions that exceed the SD of the glucose variation.[1]

Data from patients who provided complete seven-point SMPG profiles at baseline and week 30 were analysed. AUCn was based on the parameter-free trapezoidal rule using nominal times (8:00 AM, 10:00 AM, 1:00 PM, 3:00 PM, 6:00 PM, 8:00 PM and 10:00 PM). Paired *t* tests were used to test changes from baseline; two-sample *t* tests were used for comparisons between groups.

3 | RESULTS

3.1 | Baseline characteristics

Baseline patient characteristics are shown in Supporting Information Table S1. Patients enrolled in the two trials had similar mean HbA1c concentrations at baseline (64–66 mmol/mol [8.0–8.2%]), but those in the LixiLan-L trial had a longer diabetes duration and lower baseline fasting plasma glucose (FPG) values. There were some baseline differences between the trial populations in GV profile measures. In the LixiLan-L population, the mean SMPG, HBGI and AUCn were lower, while the SD of SMPG, LBGI (still <1.1), MAG and MAGE were higher. These values may reflect the fact that patients in the LixiLan-L trial were already using BI therapy at baseline.

3.2 | Glycaemic control

Compared with iGlar or Lixi alone, iGlarLixi resulted in lower mean SMPG concentrations (Table 1 and Supporting Information Figure S1), and significantly greater changes from baseline ($P < 0.0001$; Figure 1 and Table 1) at week 30. In the iGlarLixi group, mean SMPG decreased by 3.36 mmol/L (60.5 mg/dL) and 1.45 mmol/L (26.1 mg/dL) in LixiLan-O and LixiLan-L, respectively. These reductions were significantly greater than those obtained with iGlar alone (mean differences vs iGlarLixi: 0.87 mmol/L [15.6 mg/dL] in LixiLan-O and 1.08 mmol/L [19.5 mg/dL] in LixiLan-L) or with Lixi alone (mean difference vs iGlarLixi: 1.49 mmol/L [26.8 mg/dL]).

In the group who were at minimal hypoglycaemia risk (LBGI <1.1),[8] the proportion of patients who experienced hypoglycaemia was higher for iGlarLixi vs iGlar (27.7% vs 22.8%) in the LixiLan-O trial, but lower for iGlarLixi vs iGlar (36.4% vs 42.3%) in the LixiLan-L trial. In the higher risk group (LBGI ≥1.1), the proportion of patients who experienced hypoglycaemia was lower for iGlarLixi vs iGlar in both trials (27.3% vs 38.1% in LixiLan-O; 43.2% vs 55.6% in LixiLan-L). Of the Lixi-treated patients, the proportion who experienced hypoglycaemia was low in both LBGI groups (7.8% for LBGI <1.1; 0% for LBGI ≥1.1 [Supporting Information Table S2]). In both studies, ~10% of patients had LBGI ≥1.1. Differences in hypoglycaemia between the LixiLan-O and LixiLan-L trials may have arisen because of differences in study design. In the LixiLan-L trial there were patients uncontrolled on BI with or without other OADs, and in the LixiLan-O trial there were patients previously uncontrolled on metformin with or without other OADs.

3.3 | GV outcomes

Treatment with iGlarLixi significantly improved all GV measures from baseline to week 30 in both trials, and several measures also significantly improved with iGlar or Lixi alone (Table 1). Mean SMPG, AUCn and HBGI were significantly improved with iGlarLixi compared with either of its components alone. SDs of SMPG and MAG also improved to a greater degree with iGlarLixi compared with either of its individual components, reaching statistical significance in the comparisons with iGlar alone. MAGE improved significantly compared with iGlar.

4 | DISCUSSION

Data from these large phase III studies show that iGlarLixi treatment in patients with T2D reduces average glycaemia and GV to greater extents than either of its components (iGlar and Lixi) alone, with no increased hypoglycaemia risk. Specifically, HBGI decreased, accompanied by reductions in SMPG and glycaemic exposure (AUCn). LBGI remained below a threshold of 1.1, indicating no apparent increased hypoglycaemia risk for iGlarLixi compared with iGlar or Lixi alone.

TABLE 1 Glycaemic variability outcomes[a]

	LixiLan-O study			LixiLan-L study	
	iGlarLixi(n = 300)	iGlar(n = 284)	Lixi(n = 144)	iGlarLixi(n = 246)	iGlar(n = 238)
Mean SMPG (mmol/L)					
Week 30	7.0 (1.1)	7.7 (1.4)	8.5 (1.8)	7.7 (1.7)	8.6 (1.7)
Change vs baseline	−3.4 (2.1)	−2.5 (2.1)	−1.9 (2.2)	−1.4 (1.9)	−0.4 (1.8)
P	<0.0001	<0.0001	<0.0001	<0.0001	0.002
Mean (SE) difference vs iGlarLixi		−0.9 (0.2)	−1.5 (0.2)		−1.1 (0.2)
P		<0.0001	<0.0001		<0.0001
SD of SMPG (mmol/L)					
Week 30	1.5 (0.6)	1.8 (0.8)	1.7 (0.7)	1.8 (0.8)	2.2 (0.8)
Change vs baseline	−0.3 (0.8)	−0.1 (0.9)	−0.2 (0.8)	−0.4 (1.0)	0.1 (0.9)
P	<0.0001	0.178	0.016	<0.0001	0.042
Mean (SE) difference vs iGlarLixi		−0.2 (0.1)	−0.1 (0.1)		−0.5 (0.1)
P		0.004	0.226		<0.0001
HBGI					
Week 30	2.0 (2.1)	3.4 (3.6)	5.1 (5.3)	3.7 (4.2)	5.7 (5.0)
Change vs baseline	−8.3 (7.0)	−6.3 (6.8)	−5.3 (7.2)	−3.3 (5.2)	−0.6 (5.5)
P	<0.0001	<0.0001	<0.0001	<0.0001	0.116
Mean (SE) difference vs iGlarLixi		2.0 (0.6)	3.0 (0.7)		2.8 (0.5)
P		0.001	<0.0001		<0.0001
AUCn (mmol-h/L)					
Week 30	98.5 (16.2)	109.5 (20.6)	119.3 (25.8)	108.5 (23.5)	122.4 (25.4)
Change vs baseline	−47.6 (30.5)	−34.3 (29.9)	−27.3 (31.5)	−22.3 (27.0)	−5.0 (26.6)
P	<0.0001	<0.0001	<0.0001	<0.0001	0.004
Mean (SE) difference vs iGlarLixi		−13.2 (2.5)	−20.3 (3.1)		−17.3 (2.4)
P		<0.0001	<0.0001		<0.0001
MAG (mmol/L)					
Week 30	1.7 (0.8)	2.1 (1.0)	1.9 (0.9)	1.9 (0.9)	2.5 (1.1)
Change vs baseline	−0.6 (1.2)	−0.2 (1.2)	−0.4 (1.2)	−0.7 (1.3)	0.2 (1.2)
P	<0.0001	0.001	<0.0001	<0.0001	0.059
Mean (SE) difference vs iGlarLixi		−0.4 (0.1)	−0.2 (0.1)		−0.8 (0.1)
P		<0.001	0.178		<0.0001
MAGE (mmol/L)	**(n = 253)**	**(n = 246)**	**(n = 107)**	**(n = 230)**	**(n = 231)**
Week 30	2.9 (1.4)	3.5 (1.7)	3.0 (1.3)	3.5 (1.7)	4.3 (1.9)
Change vs baseline	−0.4 (1.9)	−0.1 (2.0)	−0.4 (1.6)	−1.0 (2.1)	0.3 (2.1)
P	<0.0001	0.657	0.004	<0.0001	0.049
Mean (SE) difference vs iGlarLixi		−0.4 (0.2)	0.0 (0.2)		−1.2 (0.2)
P		0.031	0.930		<0.0001

Abbreviations: AUCn, area under the SMPG curve for each patient; HBGI, high blood-glucose index; iGlar, insulin glargine 100 units/mL; iGlarLixi, fixed-ratio combination of insulin glargine 100 units/mL and lixisenatide; Lixi, lixisenatide; MAG, mean absolute glucose; MAGE, mean amplitude of glycaemic excursions; SMPG, self-measured plasma glucose.
All values are mean (SD) unless stated otherwise.
[a] Based on seven-point SMPG values (pre-injection fasting glucose, 2 h after breakfast, before lunch, 2 h after lunch, before dinner, 2 h after dinner, and at bedtime).

The greater improvement in GV seen with iGlarLixi may be attributable to the complementary reduction in PPG excursions seen with Lixi, combined with a reduction in glycaemic excursions during the basal period (the last 6-8 hours of expected action of iGlar).[9] It is also possible that hypoglycaemic excursions (and GV) fell because counter-regulatory processes are maintained during GLP-1RA therapy. Although short- and long-acting GLP-1RAs are beneficial with regard to both FPG and PPG, Lixi has been shown to have a pronounced PPG-lowering effect and to be suitable for combination therapy with BI.[10] The different modes of action and glucose-lowering effects of the two agents combine to address both FPG and PPG excursions.

Measures of GV have proven useful for the prediction of glycaemic outcomes and hypoglycaemia in previous studies. In patients with T2D undergoing treatment intensification, high pre-treatment GV correlates negatively with glycaemic outcomes. Patients with high baseline GV had persistently higher HbA1c levels after 24 weeks of treatment intensification.[11] Additionally, several GV measures have been correlated with hypoglycaemia: SD of SMPG, MAGE, MAG and

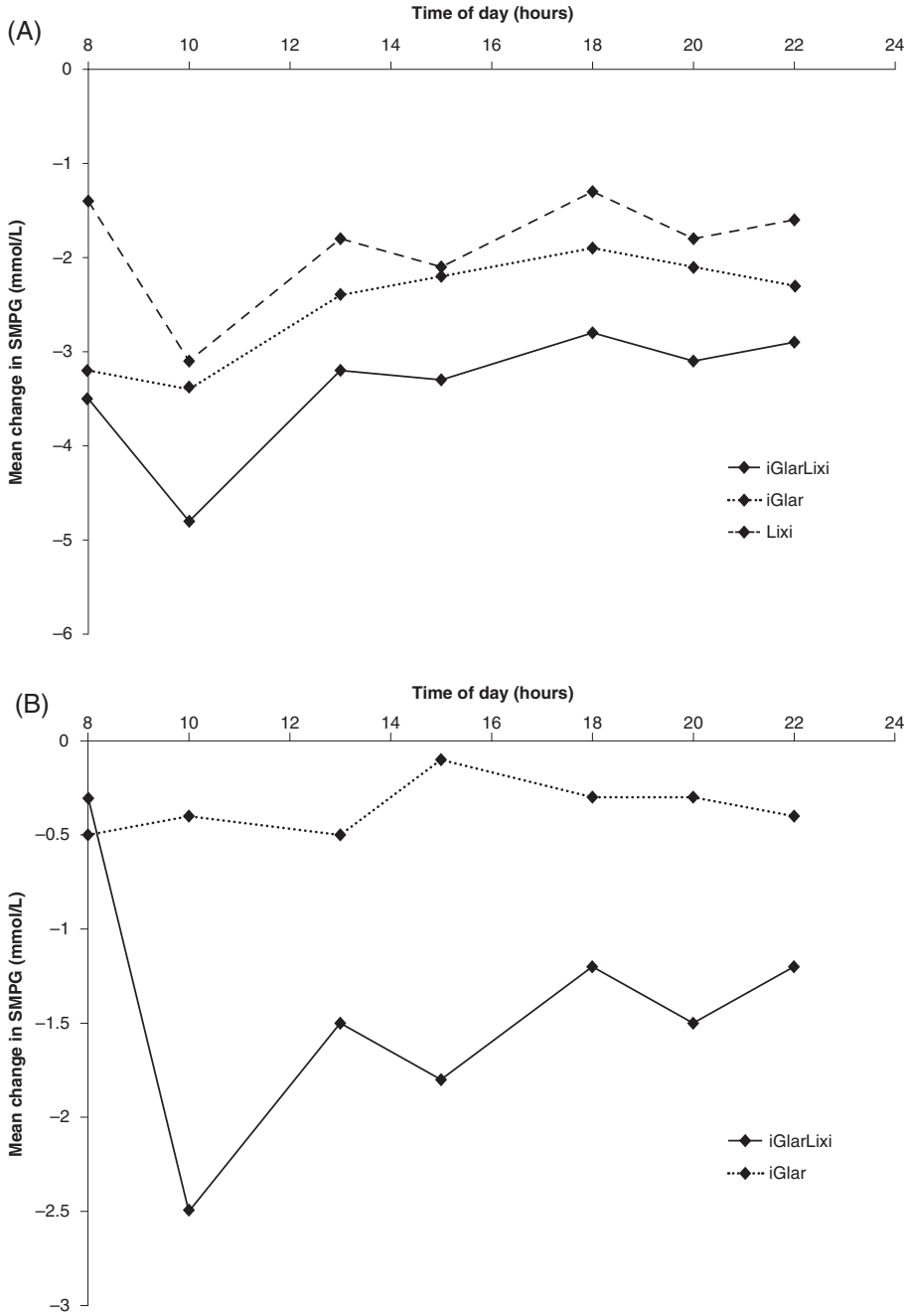

FIGURE 1 Mean change in self-measured plasma glucose (SMPG) seven-point profiles from baseline to week 30 in the A, LixiLan-O and B, LixiLan-L trials

coefficient of variation. In a different study in hospitalized patients with T2D, those with hypoglycaemic events had significantly higher GV (measured as mean Δ daily glucose, mean SD of SMPG, and MAGE) than those without hypoglycaemia ($P < 0.05$).[12] GV data have also proven effective in comparing therapies for T2D. Pooled data from three trials of Lixi as add-on therapy to BI showed a significant reduction in GV (measured as SD of SMPG, MAG, MAGE, HBGI, LBGI and AUC for fasting glucose) with Lixi, accompanied by no increase in hypoglycaemia risk.[13] A recent report investigating GV in four different therapy cohorts found that, in controlled T2D, the lowest GV and hypoglycaemia frequency were achieved with a regimen of BI plus the GLP-1RA liraglutide (Lira).[3] Similarly, modest improvements in only one measure of GV (coefficient of variation) were seen at 26 weeks in a study of basal-bolus insulin vs BI plus the GLP-1RA exenatide.[2] In a study that involved participants receiving the fixed-ratio combination therapy, insulin degludec and Lira (iDegLira), GV was assessed using continuous glucose monitoring (CGM) and a nine-point SMBG profile.[14] As with the present study, the fixed-ratio combination resulted in improved glycaemic control compared with the individual components, and a greater reduction in SMBG values. CGM data showed that the time out of range was lower for IDegLira vs Lira, despite duration of interstitial glucose <3.9 mmol/L (70 mg/dL) or <2.8 mmol/L (<50 mg/dL) not reaching statistical significance for differences between iDegLira or its constituents. It also demonstrated greater reduction of mean interstitial glucose with iDegLira compared with Lira, but not compared with IDeg, and similar day-to-day variability

compared with both IDeg or Lira. In the present study, CGM data were not available and thus not included in the seven-point SMPG profile.

Glycaemic variability has been identified as a risk factor for complications such as cardiovascular disease, independent of overall glucose control,[5] and CGM studies facilitate a real-time hypoglycaemia risk for patients.[15] While several trials of closed-loop insulin therapy in type 1 diabetes have shown that reductions in GV are associated with patient-perceived benefits, there is a lack of randomized controlled trials demonstrating clinical benefit from therapeutic strategies that target GV in patients with T2D independently of glycaemia (measured by HbA1c). GV is an important component of glycaemic control,[16] and the recent International Consensus on Use of Continuous Glucose Monitoring proposed that several GV metrics, including coefficient of variation, SD of SMPG, LBGI and HBGI, be included as standard output for clinical consideration.[17] There is growing support in achieving GV endpoint recognition by regulatory agencies, and their inclusion in clinical trials and in clinical practice[11,15]; however, further studies are warranted.

Limitations of the present study include the fact that data were obtained from SMPG rather than CGM, which means that the temporal resolution of the GV analyses is limited compared with other studies.[1,14] Furthermore, only patients with measurements at both baseline and week 30 visits were included in the study. Additionally, these data were drawn from studies of different patient populations; GV was not the primary endpoint of these trials, and our analysis was not prespecified.

In conclusion, in the LixiLan-O and LixiLan-L trials, iGlarLixi reduced GV by most measures to a greater extent than that achieved by each of its individual components alone. There was no increase in hypoglycaemia risk with iGlarLixi compared with iGlar in either trial.

ACKNOWLEDGMENTS

The authors received writing/editorial support in the preparation of this manuscript provided by Pim Dekker, PhD, and Yasmin Issop, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

Conflict of interest

R.A. has served as a consultant for AstraZeneca, Janssen, Medtronic, Novo Nordisk and Sanofi US, Inc. and on the advisory panel for AstraZeneca, Janssen, Medtronic, Novo Nordisk and Sanofi US, Inc., and has received research support from Abbvie, AstraZeneca, BD, Covance, Dexcom, Eli Lilly, Genkyotex, GSK, ICON, Inventiv Health, Janssen, Lexicon, Medtronic, Merck, Novo Nordisk, Parexel, Pfizer, PPD, Quintiles and Sanofi US, Inc. and unrestricted grants from Sanofi US, Inc. G.U. has had an advisory/consulting role for Novo Nordisk and Sanofi US, Inc., and has received research support for inpatient studies (to Emory University) from Sanofi, Novo Nordisk and Merck. W.S. is employed by Sanofi US, Inc. B.K. has had an advisory panel/consulting role for Dexcom and Sanofi, and has received research grant/material support from Dexcom, Roche Diagnostics, Sanofi and Tandem.

Author contributions

R.A. was involved in data acquisition, data analysis and interpretation, critical revision and final approval of the manuscript. G.U. was involved in data analysis and interpretation, critical revision and final approval of the manuscript. W.S. was involved in designing the study, data acquisition, data analysis and interpretation, critical revision and final approval of the manuscript. B.K. was involved in data analysis and interpretation, critical revision and final approval of the manuscript. All authors take responsibility for the accuracy and integrity of the data presented in this manuscript.

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SUPPORTING INFORMATION

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

How to cite this article: Aronson R, Umpierrez G, Stager W, Kovatchev B. Insulin glargine/lixisenatide fixed-ratio combination improves glycaemic variability and control without increasing hypoglycaemia. *Diabetes Obes Metab*. 2019;21:726–731. https://doi.org/10.1111/dom.13580