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ORIGINAL ARTICLE

Predictors of outcomes in patients with type 2 diabetes in the lixisenatide GetGoal clinical trials

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Aims: To explore the treatment outcomes in adult patients with type 2 diabetes (T2D) enrolled in the GetGoal trials of lixisenatide (LIXI), and the predictive effects of baseline characteristics on outcomes.

Methods: This study was a pooled analysis of patient-level data from the LIXI GetGoal studies comparing LIXI and placebo. Patients were divided into baseline therapy groups: those receiving oral antidiabetes drugs (OADs) at baseline (n = 2760) or those receiving basal insulin at baseline (n = 1198).

Results: Compared with placebo, LIXI treatment led to significantly greater reductions in glycated haemoglobin (HbA1c), and greater achievement of the composite endpoint of HbA1c <7.0% (53 mmol/mol) with no symptomatic hypoglycaemia and no weight gain in either the OAD (34% vs 18%; $P < .0001$) or the basal insulin groups (19% vs 10%; $P < .0001$). Treatment with LIXI was associated with a greater percentage of patients experiencing a symptomatic hypoglycaemic event compared with placebo in both the OAD (5% vs 3%; $P = .0098$) and basal insulin groups (27% vs 17%; $P < .0001$). In assessing baseline factors that were predictors of treatment outcomes, only baseline HbA1c and LIXI treatment were strong predictors of outcomes in both the OAD and basal insulin groups. No other baseline characteristic had such a large or consistent clinically relevant predictive effect across treatment outcomes.

Conclusions: The results from this study show that irrespective of baseline characteristics, LIXI treatment, as an add-on to OAD or basal insulin therapy, is effective in reducing HbA1c and achieving composite endpoints.

KEYWORDS

lixisenatide, outcomes, predictors

1 | INTRODUCTION

Type 2 diabetes (T2D) is a progressive metabolic disease characterized by elevated blood glucose levels attributable to insufficient insulin production and usually insulin resistance. Patients with early-stage disease may achieve glycated haemoglobin (HbA1c) glycaemic control targets (≤6.5% [48 mmol/mol; American Association of Clinical Endocrinologists] or <7.0% [53 mmol/mol; American Diabetes Association]) through lifestyle modifications; however, as the disease progresses, additional therapies, such as oral antidiabetes drugs (OADs), glucagon-like peptide-1 (GLP-1) receptor agonists and insulin, must often be added to maintain glycaemic control.[1–4] Different classes of agents vary in their effects on factors such as HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), body weight, insulin secretion and sensitivity, and potential for hypoglycaemia.[1] Current recommendations for the choice of initial and add-on therapies are therefore based on individual baseline patient characteristics, such as glycaemic profile, weight and comorbidities.[1–4]

Lixisenatide (LIXI) is a once-daily glucagon-like peptide-1 receptor agonist (GLP-1 RA) for the treatment of people with T2D that was recently approved by the US Food and Drug Administration and is also approved for use in several other countries. The GetGoal trial

programme is a series of international, multicentre, phase III clinical trials assessing the efficacy and safety of LIXI in adult patients with T2D on a range of background therapies. Data from these trials showed that LIXI as monotherapy or add-on therapy to OADs or basal insulin significantly improved HbA1c levels and was associated with pronounced PPG reductions, a low rate of hypoglycaemia, and beneficial effects on weight.[5–14] Ideally, it would be valuable to identify those patients who would most benefit from specific therapies, allowing more targeted treatment approaches. Identifying patient characteristics that are predictive of poorer outcomes may also allow clinicians to identify patients who may benefit from alternative approaches to meet their treatment goals, or additional support, in order to attain their goals. The objective of the present study was to explore the effects of baseline characteristics on end-of-treatment outcomes in patients with T2D initiating LIXI in the GetGoal trials.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a pooled analysis of patient-level data from LIXI GetGoal studies conducted by Sanofi. The GetGoal studies were phase III, prospective, randomized controlled trials of LIXI in adult patients with T2D. The studies included in the present analysis were the 24-week, placebo-controlled GetGoal trials in patients not reaching glycaemic targets with either OADs or basal insulin. Full details of the study methods in the eligible GetGoal trials have been published elsewhere.[5–10,12–14] Summaries of the included trials, patient populations and any treatment adjustments are given in Tables S1 and S2, Appendix S1. All of the included studies were conducted according to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Common inclusion criteria across the trials included duration of T2D ≥1 year and HbA1c levels of 7.0% to 10.0% (53-86 mmol/mol). Patient data were extracted from the intention-to-treat study populations. Patients were required to have both baseline and endpoint HbA1c measurements for inclusion in the analysis. Baseline demographic and clinical characteristics collected included age, height, weight, body mass index (BMI), sex, HbA1c, FPG and PPG levels, PPG excursion, known duration of diabetes, OAD use and insulin use.

2.2 | Efficacy and safety endpoints

Efficacy and safety endpoints included change from baseline in HbA1c, FPG and PPG levels, PPG excursion, patients achieving HbA1c <7.0% (53 mmol/mol), incidence of severe hypoglycaemia and symptomatic hypoglycaemia, and weight change. Severe hypoglycaemia was defined as a hypoglycaemic event requiring assistance. Symptomatic hypoglycaemia was defined as confirmed blood glucose <3.33 mmol/L (60 mg/dL) or hypoglycaemia with prompt recovery after oral carbohydrate administration. The following composite endpoints were also evaluated: endpoint HbA1c levels <7.0% (53 mmol/mol) with no weight gain (no weight gain was defined as change in weight [endpoint – baseline weight] ≤ 0); endpoint HbA1c levels <7.0% (53 mmol/mol) with no symptomatic hypoglycaemia; endpoint HbA1c levels <7.0% (53 mmol/mol) with no weight gain and no symptomatic hypoglycaemia.

2.3 | Statistical analysis

In these analyses, two distinct questions were addressed. Firstly, the effects of LIXI or placebo treatment and the impact of baseline therapy were investigated. Data were analysed by baseline therapy (OADs or basal insulin) and treatment group (LIXI or placebo). Continuous variables were assessed using count, mean ± standard deviation (s.d.) and median values. Safety and efficacy endpoints were assessed descriptively. HbA1c change was assessed according to quartiles of selected baseline factors. Composite endpoints were assessed using number and percentage of patients achieving the combined endpoint; *P* values were determined using a chi-squared test.

Secondly, predictors of patient responses to LIXI were investigated. Predictor analyses were carried out using multivariable regression analyses to control for key patient characteristics and assess the adjusted outcomes among patients with T2D treated with LIXI or placebo. Covariates in the regression analyses included baseline BMI, age, sex, known duration of diabetes, insulin history, OAD history, baseline FPG, PPG and HbA1c levels, baseline PPG excursions and basal insulin dose. The effect of interaction between treatment and baseline characteristics was also investigated. A sensitivity analysis was carried out using a generalized linear model to further evaluate the impact of LIXI vs placebo, after adjusting for baseline PPG level in addition to the above-described default covariates.

No additional *P* value adjustment was carried out for multiple comparisons. A *P* value of .05 was taken to indicate statistical significance. All statistical analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Patient baseline characteristics

Overall, pooled data for 2760 patients on baseline OAD therapy and 1198 on baseline basal insulin therapy were included in the analysis. There were no significant differences in mean baseline age, BMI, known duration of diabetes, and HbA1c levels between treatment groups (LIXI and placebo) in each of the study arms (Table 1). Patients in the basal insulin group tended to have a lower FPG and longer known duration of diabetes compared with the OAD group (Table 1).

3.2 | Effect of treatment on outcomes

Results were generally consistent between the OAD and basal insulin baseline therapy groups. Compared with placebo, LIXI was associated with significantly improved glycaemic outcomes in patients receiving either OADs or basal insulin. Decreases in HbA1c, PPG, PPG excursion, weight and BMI from baseline were significantly greater in the LIXI group compared with the placebo group in patients receiving OADs and those receiving basal insulin (Table 2). Decreases in FPG were significantly greater in the LIXI group compared with placebo in

TABLE 1 Patient demographics and baseline characteristics

	Baseline OAD therapy		Baseline basal insulin therapy	
Characteristics	LIXI N = 1828	Placebo N = 932	LIXI N = 665	Placebo N = 533
Age, n (%)				
<35 years	40 (2)	24 (3)	10 (2)	10 (2)
35 to 44 years	190 (10)	86 (9)	62 (9)	52 (10)
45 to 54 years	563 (31)	267 (29)	167 (25)	128 (24)
55 to 64 years	731 (40)	358 (38)	275 (41)	222 (42)
65 to 74 years	273 (15)	176 (19)	129 (19)	108 (20)
≥75 years	31 (2)	21 (2)	22 (3)	13 (2)
Mean (s.d.) age, years	55.5 (9.6)	56.3 (10.0)	57.4 (9.8)	56.9 (10.1)
Sex: female, n (%)	958 (52)	478 (51)	359 (54)	265 (50)
Baseline BMI, n (%)				
BMI <25 kg/m^2	257 (14)	147 (16)	133 (20)	129 (24)
BMI 25 to <30 kg/m^2	587 (32)	308 (33)	222 (34)	171 (32)
BMI 30 to <35 kg/m^2	515 (28)	232 (25)	166 (25)	120 (23)
BMI ≥35 kg/m^2	469 (26)	245 (26)	141 (21)	111 (21)
Mean (s.d.) HbA1c, %	8.12 (0.88)	8.05 (0.82)	8.15 (0.85)	8.10 (0.82)
Mean (s.d.) HbA1c, mmol/mol	65 (9.6)	64 (9.0)	66 (9.3)	65 (9.0)
Mean (s.d.) FPG, mmol/L	9.44 (2.22)	9.17 (2.13)	7.44 (2.34)	7.39 (2.33)
Mean (s.d.) FPG, mg/dL	170 (39.9)	165 (38.3)	134 (42.2)	133 (42.0)
Mean (s.d.) PPG[1], mmol/L	16.28 (4.09)	16.67 (3.99)	15.61 (4.37)	15.22 (4.32)
Mean (s.d.) PPG[1], mg/dL	293 (73.6)	300 (71.8)	281 (78.7)	274 (77.7)
Mean (s.d.) PPG excursion[2], mmol/L	NR	NR	7.72 (3.89)	7.67 (3.99)
Mean (s.d.) PPG excursion[2], mg/dL			139 (70.1)	138 (71.9)
Mean (s.d.) known duration of diabetes, years	7.3 (5.5)	7.6 (5.5)	11.8 (7.1)	11.4 (7.0)

NR, not reported; s.d., standard deviation.

[1] Measured by standardized meal test.

[2] 2-h PPG levels minus plasma glucose levels 30 minutes before the standardized meal test.

patients receiving OADs, but the difference was not significant for those in the basal insulin group (Table 2).

The proportion of patients experiencing ≥1 symptomatic hypoglycaemic event was significantly higher with LIXI vs placebo in patients treated with OADs or basal insulin (Table 2). The incidence of severe hypoglycaemia was low in all groups. In all, 1 patient (0.05%) in the OAD and LIXI group and 5 patients (0.75%) in the basal insulin and LIXI group experienced ≥1 severe hypoglycaemic event compared with no patients in any placebo group (*P* value not significant for comparison between treatment groups).

Significantly more patients treated with LIXI met composite endpoints of HbA1c <7.0% (53 mmol/mol) with no weight gain and no symptomatic hypoglycaemia compared with placebo (Table 2). This was highly significant (*P* < .0001), both when LIXI was added to basal insulin and to OADs.

3.3 | Predictors of outcomes

The change in HbA1c with LIXI or placebo was stratified by selected baseline characteristics in both the OAD (Figure 1) and basal insulin baseline therapy groups (Figure 2). Across strata, for all baseline characteristics in both the OAD and basal insulin groups, LIXI led to a significantly greater reduction in HbA1c than placebo (Figures 1 and 2). In the OAD group, age, baseline BMI, known duration of diabetes and sex had little effect on HbA1c change with either LIXI or placebo (Figure 1). Those with higher baseline HbA1c levels had greater reductions in HbA1c in both the LIXI and placebo groups, and those with higher PPG levels appeared to have greater reductions in HbA1c in the LIXI group (Figure 1). In the basal insulin group, baseline characteristics had a greater impact on HbA1c change; patients with increasing age and longer known duration of diabetes had a greater change in HbA1c with LIXI and placebo treatment, and patients with a higher BMI had a greater change in HbA1c in the placebo group (Figure 2). Those with higher baseline HbA1c levels had greater reductions in HbA1c in the LIXI and placebo groups, and those with higher baseline PPG levels had greater reductions in HbA1c in the LIXI group (Figure 2).

Regression analysis identified LIXI treatment and baseline HbA1c as strong predictors of a range of clinical endpoints (Table 3). Other baseline characteristics were generally weaker and variable predictors of outcomes (Table 3). LIXI treatment was a strong predictor of HbA1c change, PPG change, weight change, symptomatic hypoglycaemia and achievement of HbA1c <7.0% (53 mmol/mol) in both the OAD and basal insulin therapy groups (Table 3), and a greater likelihood of achieving composite endpoints of HbA1c <7.0% (53 mmol/mol) without weight gain and/or symptomatic hypoglycaemia compared with placebo (Table 3). Higher baseline HbA1c predicted a greater reduction in HbA1c in both the OAD and basal insulin groups (*P* < .0001 for both; Table 3). Lower baseline HbA1c level was, however, a predictor of achieving HbA1c <7.0% (53 mmol/

TABLE 2 Significance of assessed clinical outcomes in the LIXI and placebo groups across GetGoal programme (8 studies)

	Baseline OAD therapy (5 studies)			Baseline basal insulin therapy (3 studies)		
Endpoints	LIXI (n = 1828)	Placebo (n = 932)	*P*	LIXI (n = 665)	Placebo (n = 533)	*P*
Individual endpoints						
Mean (s.d.) change in HbA1c, %	−0.87 (0.95)	−0.33 (0.93)	**<.0001**	−0.68 (1.03)	−0.19 (0.88)	**<.0001**
Patients reaching HbA1c <7.0% (53 mmol/mol) at EOT, n (%)	797 (44)	223 (24)	**<.0001**	259 (39)	112 (21)	**<.0001**
Mean (s.d.) change in FPG, mmol/L	−1.00 (2.27)	−0.22 (2.03)	**<.0001**	−0.01 (2.86)	0.20 (2.73)	.1996
Mean (s.d.) change in PPG[1], mmol/L	−5.76 (5.30)	−0.86 (3.80)	**<.0001**	−5.28 (5.82)	−0.33 (4.26)	**<.0001**
Mean (s.d.) change in PPG excursion[2], mmol/L	NR	NR		−4.69 (5.22)	−0.23 (3.97)	**<.0001**
Mean (s.d.) change in weight, kg	−1.80 (3.19)	−1.15 (2.94)	**<.0001**	−0.71 (2.87)	0.30 (2.49)	**<.0001**
Mean (s.d.) change in BMI, kg/m^2	−0.66 (1.17)	−0.43 (1.07)	**<.0001**	−0.26 (1.05)	0.12 (0.91)	**<.0001**
Patients experiencing ≥1 symptomatic hypoglycaemic event[3], n (%)	94 (5)	28 (3)	**.0098**	182 (27)	91 (17)	**<.0001**
Composite endpoints						
Patients reaching HbA1c <7.0% (53 mmol/mol), no weight gain at EOT (composite), n (%)	655 (36)	176 (19)	**<.0001**	175 (26)	92 (17)	**.0002**
Patients reaching HbA1c <7.0% (53 mmol/mol), no symptomatic hypoglycaemia at EOT (composite), n (%)	747 (41)	214 (23)	**<.0001**	182 (27)	66 (12)	**<.0001**
Patients reaching HbA1c <7.0% (53 mmol/mol), no weight gain, no symptomatic hypoglycaemia at EOT (composite), n (%)	613 (34)	170 (18)	**<.0001**	123 (19)	52 (10)	**<.0001**

EOT, end of treatment; NR, not reported; s.d., standard deviation.

Values set in bold represent significant *P* values of < .05.

[1] Measured by standardized meal test.

[2] 2-h PPG levels minus plasma glucose levels 30 minutes prior to the standardized meal test.

[3] <3.33 mmol/L (60 mg/dL).

mol) or composite endpoints (HbA1c <7.0% [53 mmol/mol] with no symptomatic hypoglycaemia and no weight gain) in both the OAD and basal insulin baseline therapy groups (*P* < .0001 for all; Table 3).

Baseline HbA1c level was also a predictor of other clinical outcomes including FPG change, PPG change, weight change and composite endpoints, but was not a significant predictor of symptomatic hypoglycaemia for either treatment group (*P* = .2196 and *P* = .5434 for the OAD and basal insulin groups, respectively). Baseline BMI, baseline FPG level, baseline PPG level, baseline PPG excursion, age, sex and known duration of diabetes were predictive for some endpoints, but this varied between the OAD and basal insulin groups and tended to be small effects that were not clinically relevant (Table 3).

In additional regression analyses, age, sex and baseline BMI did not show a significant interaction with LIXI or placebo treatment (*P* > .05 for all in both the OAD and basal insulin baseline therapy groups). LIXI resulted in a greater response compared with placebo across all categories; however, there was also a significant interaction between treatment group and baseline HbA1c, showing that patients with more elevated baseline HbA1c levels had a greater treatment effect with LIXI.

4 | DISCUSSION

This pooled analysis shows that, compared with placebo, treatment with the GLP-1 RA LIXI resulted in significant improvements in clinically relevant endpoints in patients with T2D when added to either OAD or basal insulin therapy, supporting the results shown in the individual studies.[5,6,8–10,12–14] Treatment with LIXI was also associated with an increase in symptomatic, but not severe, hypoglycaemia compared with placebo on a background of basal insulin or OADs. Patients were significantly more likely to achieve the composite endpoint of HbA1c <7.0% (53 mmol/mol), no symptomatic hypoglycaemia and no weight gain when LIXI was added to either OADs or basal insulin, compared with placebo. This suggests that co-administration of LIXI with basal insulin may help some patients to achieve treatment goals without weight gain and without symptomatic hypoglycaemia, which would be of value because insulin treatment is often associated with an increase in weight and/or hypoglycaemia.

Treatment with LIXI and baseline HbA1c level were strong and consistent predictors of clinical endpoints. No other patient baseline characteristic investigated (age, BMI, sex, known duration of diabetes, baseline FPG level, baseline PPG level or baseline PPG excursion) had such large or consistent clinically relevant predictive effects on endpoints. LIXI led to a significantly greater reduction in HbA1c compared with placebo, irrespective of a range of baseline characteristics (baseline HbA1c, known duration of diabetes, sex, age, baseline PPG and baseline BMI) or whether LIXI was added to OADs or basal insulin. These analyses also showed no interaction of LIXI or placebo with age, sex or baseline BMI, in either the OAD or basal insulin group. Together these results suggest that LIXI benefits a wide range of patients regardless of their baseline characteristics or background therapy. However, LIXI

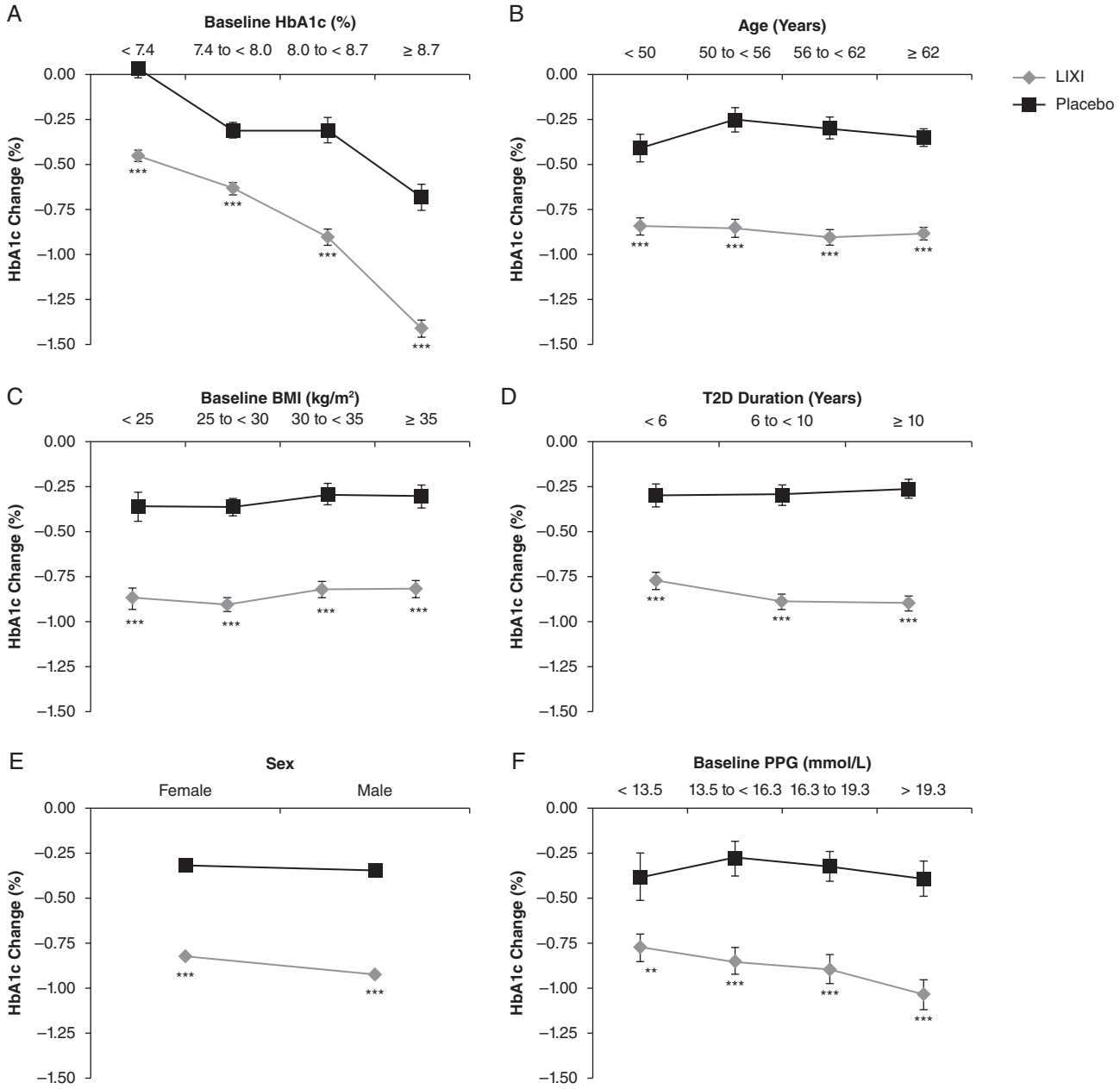

FIGURE 1 HbA1c change from baseline in the LIXI and placebo treatment groups, stratified by A, baseline HbA1c; B, age; C, baseline BMI; D, known duration of diabetes; E, sex and F, baseline PPG, in the GetGoal trials with baseline OAD therapy. *$P < .05$; **$P < .01$; ***$P < .001$ for placebo vs LIXI treatment. Error bars indicate standard errors.

treatment was also shown to be a predictor of symptomatic hypoglycaemia when added to either OADs or basal insulin.

Several studies of patients treated with GLP-1 RAs have investigated the predictive effects of baseline factors on outcomes. As in the present study, most of these studies indicated a significant correlation between baseline HbA1c and change in HbA1c, so that patients with higher baseline HbA1c levels had greater decreases in HbA1c.[15–20] Lower baseline HbA1c has been shown to be associated with greater target HbA1c achievement,[16] as was also shown in the present analysis.

The reported predictive value of other variables for outcomes in patients treated with GLP-1 RAs has been less consistent. For example, baseline weight was shown to be a determinant of HbA1c reduction in a study by Lapolla et al.,[18] but baseline weight and BMI were shown not to be predictive in other studies.[15,17,19,20] In the present study, baseline BMI had a minor, but significant, predictive value for HbA1c reduction in the basal insulin but not the OAD group; however, LIXI led to a significantly greater reduction in HbA1c than placebo irrespective of baseline BMI. Some studies have shown a correlation between weight change and baseline BMI[15] or baseline weight.[18] In the present study, baseline BMI was not predictive of weight change in patients treated with basal insulin, but had a small predictive value for weight change in the OAD group (treatment estimate 0.07 kg per 1 kg/m^2 increase in BMI; $P < .0001$). A recent analysis showed that treatment with a GLP-1 RA improved glycaemic parameters independently of weight change.[21] Although the degree

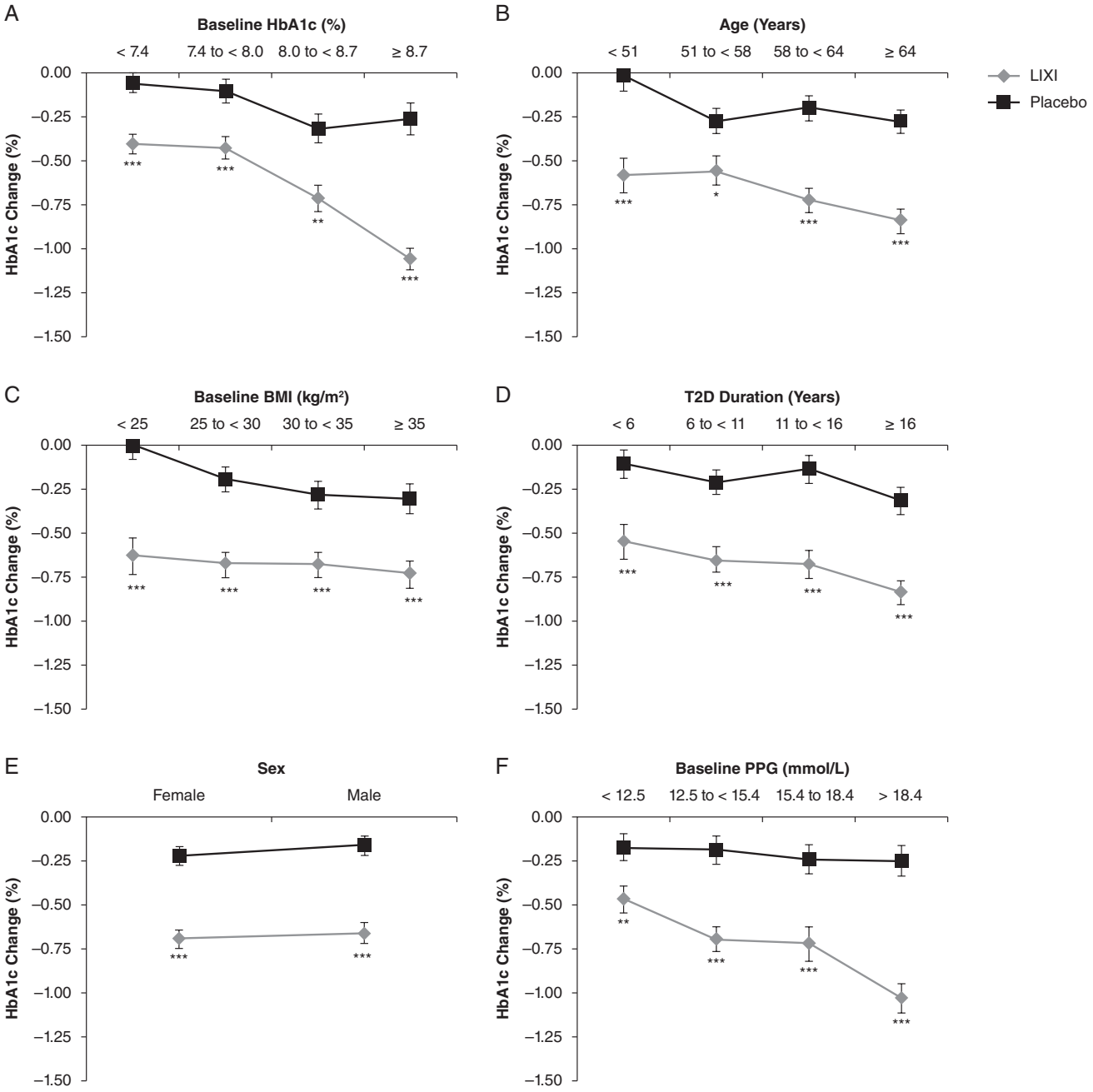

FIGURE 2 HbA1c change from baseline in the LIXI and placebo treatment groups, stratified by A, baseline HbA1c; B, age; C, baseline BMI; D, known duration of diabetes; E, sex and F, baseline PPG, in the GetGoal trials with baseline basal insulin therapy. **P* < .05; ***P* < .01; ****P* < .001 for placebo vs LIXI treatment. Error bars indicate standard errors.

of improvement increased with increased weight loss, reductions in median HbA1c and FPG were seen across all weight loss quartiles, including the quartile with modest weight gain; however, the correlation between change in weight and change in HbA1c was found to be weak overall.[21]

Because one of the mechanisms of action of GLP-1 RAs is increased insulin secretion, it has been postulated that the decline in β-cell function seen over time in diabetes may act to limit the action of GLP-1 RA. In our pooled analysis there was no evidence of smaller changes in HbA1c with longer known duration of diabetes, and this result is supported by many[15,17,19] but not all[18] other studies of GLP-1 RAs in T2D. The lack of association between disease duration and response to GLP-1 RAs may be attributable to improvements in β-cell function, shown in human studies using markers of function such as homeostasis model assessment (HOMA) score,[22–24] or relate to protection of β-cell mass after treatment with GLP-1 RAs, which has been shown in animals.[25,26] The study that showed a relationship between disease duration and diminished GLP-1 RA response proposed that this may have been related to higher failure in β-cell function as a result of previous long-duration sulphonylurea use.[18] Evidence suggests that the PPG reduction with LIXI is driven by slowed gastric emptying and reduced postprandial insulin secretion,[27,28] which may also explain why the efficacy of LIXI may be independent of the duration of diabetes. However, as there were no direct

TABLE 3 Significant predictors of selected outcomes in the GetGoal phase III clinical programme

	Baseline OAD therapy		Baseline basal insulin therapy	
Significant predictors	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Change in HbA1c as an outcome, %				
LIXI vs placebo	−0.54 (−0.61, −0.47)	**<.0001**	−0.45 (−0.57, −0.32)	**<.0001**
Baseline HbA1c, per 1.0%	−0.53 (−0.57, −0.48)	**<.0001**	−0.31 (−0.41, −0.21)	**<.0001**
Age, per year	−0.01 (−0.01, −0.00)	**<.0001**	−0.01 (−0.02, −0.01)	**.0012**
Known duration of diabetes, per year	0.01 (0.00, 0.02)	**.0254**	−0.01 (−0.02, −0.01)	**.0394**
Female vs male	0.09 (0.02, 0.15)	**.0104**	−0.05 (−0.17, 0.08)	.4485
Baseline FPG, mg/dL	0.01 (0.00, 0.01)	**<.0001**	0.01 (0.00, 0.01)	**.0226**
Baseline PPG[1], mg/dL	NR	NR	−0.01 (−0.01, −0.01)	**<.0001**
Baseline PPG excursion[2], mg/dL	NR	NR	0.01 (0.01, 0.01)	**.0019**
Change in FPG as an outcome, mg/dL				
LIXI vs placebo	−12.29 (−15.04, −9.54)	**<.0001**	−4.33 (−9.49, 0.83)	.0999
Baseline HbA1c, per 1.0%	2.02 (−0.24, 3.80)	**.0264**	5.36 (1.25, 9.47)	**.0107**
Age, per year	−0.20 (−0.34, −0.05)	**.0079**	−0.18 (−0.46, 0.10)	.2132
Baseline BMI, per 1 kg/m^2	0.39 (0.17, 0.60)	**.0005**	0.34 (−0.11, 0.80)	.1331
Known duration of diabetes, per year	0.09 (−0.21, 0.39)	.5517	−0.67 (−1.15, −0.19)	**.0066**
Female vs male	−2.99 (−5.60, −0.37)	**.0253**	−3.85 (−9.05, 1.35)	.1466
Baseline FPG, mg/dL	−0.52 (−0.56, −0.48)	**<.0001**	−0.77 (−0.84, −0.69)	**<.0001**
Change in PPG as an outcome (mg/dL)				
LIXI vs placebo	−88.28 (−100.38, −76.18)	**<.0001**	−80.84 (−91.09, −70.60)	**<.0001**
Baseline HbA1c, per 1.0%	−16.42 (−24.25, −8.58)	**<.0001**	11.47 (3.57, 19.36)	**.0045**
Age, per year	−0.83 (−1.47, −0.19)	**.0116**	0.01 (−0.56, 0.57)	.9865
Baseline BMI, per 1 kg/m^2	1.65 (0.71, 2.59)	**.0006**	0.52 (−0.35, 1.38)	.2415
Baseline FPG, mg/dL	−0.22 (−0.39, −0.04)	**.0180**	0.16 (0.01, 0.31)	**.0419**
Baseline PPG[1], mg/dL	NR	NR	−0.93 (−1.08, −0.78)	**<.0001**
Baseline PPG excursion[2], mg/dL	NR	NR	0.22 (0.07, 0.37)	**.0037**
Change in weight as an outcome, kg				
LIXI vs placebo	−0.67 (−0.91, −0.43)	**<.0001**	−0.96 (−1.34, −0.59)	**<.0001**
Baseline HbA1c, per 1.0%	0.28 (0.12, 0.43)	**.0005**	0.51 (0.21, 0.81)	**.0009**
Age, per year	−0.01 (−0.03, −0.01)	**.0288**	−0.01 (−0.03, 0.01)	.1709
Baseline BMI, per 1 kg/m^2	−0.07 (−0.09, −0.05)	**<.0001**	−0.02 (−0.06, 0.01)	.1706
Baseline FPG, mg/dL	−0.01 (−0.01, −0.01)	**<.0001**	0.01 (−0.01, 0.01)	.8730
Baseline PPG[1], mg/dL	NR	NR	−0.01 (−0.01, −0.01)	**.0148**
Baseline PPG excursion[2], mg/dL	NR	NR	0.01 (0.01, 0.01)	**.0303**
	Odds ratio (95% CI)	***P***	**Odds ratio (95% CI)**	***P***
Symptomatic hypoglycaemia (<3.33 mmol/L [60 mg/dL]) as an outcome				
LIXI vs placebo	1.91 (1.22, 3.00)	**.0050**	2.03 (1.42, 2.90)	**<.0001**
Known duration of diabetes, per year	1.03 (0.99, 1.07)	.1193	1.04 (1.01, 1.07)	**.0183**
Baseline FPG, mg/dL	0.99 (0.99, 1.00)	**.0019**	0.99 (0.98, 0.99)	**<.0001**
Baseline basal insulin dose/weight (U/kg)	NR	NR	2.59 (1.26, 5.31)	**.0095**
Patients reaching HbA1c <7.0% (53 mmol/mol) at EOT as an outcome				
LIXI vs placebo	3.37 (2.76, 4.11)	**<.0001**	3.05 (2.18, 4.30)	**<.0001**
Baseline HbA1c, per 1.0%	0.41 (0.35, 0.46)	**<.0001**	0.30 (0.22, 0.40)	**<.0001**
Age, per year	1.01 (1.00, 1.02)	**.0107**	1.02 (1.00, 1.03)	.0923
Baseline BMI, per 1 kg/m^2	0.99 (0.97, 1.00)	.0851	1.03 (1.00, 1.06)	**.0268**
Known duration of diabetes, per year	0.97 (0.95, 0.99)	**.0021**	1.04 (1.01, 1.07)	**.0185**
Baseline FPG, mg/dL	0.99 (0.99, 0.99)	**<.0001**	1.00 (0.99, 1.00)	.2921
Baseline PPG, mg/dL	NR	NR	1.01 (1.00, 1.01)	**.0114**
Baseline PPG excursion[2], mg/dL	NR	NR	0.99 (0.99, 1.00)	**.0264**

TABLE 3 Continued

	Baseline OAD therapy		Baseline basal insulin therapy	
Significant predictors	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Endpoint HbA1c <7.0% (53 mmol/mol) and no weight gain as an outcome				
LIXI vs placebo	3.13 (2.54, 3.85)	**<.0001**	2.63 (1.82, 3.80)	**<.0001**
Baseline HbA1c, per 1.0%	0.40 (0.35, 0.46)	**<.0001**	0.32 (0.24, 0.44)	**<.0001**
Age, per year	1.02 (1.01, 1,03)	**<.0001**	1.02 (1.00, 1.04)	.0592
Baseline BMI (kg/m^2)	1.00 (1.00, 1.02)	.9784	1.03 (1.01, 1.06)	**0.0381**
Known duration of diabetes, per year	0.97 (0.95, 1.00)	**.0189**	1.05 (1.02, 1.08)	**.0020**
Baseline FPG, mg/dL	1.00 (0.99, 1.00)	**.0019**	1.00 (0.99, 1.00)	.6382
Endpoint HbA1c levels <7.0% (53 mmol/mol) and no symptomatic hypoglycaemia as an outcome				
LIXI vs placebo	3.14 (2.57, 3.84)	**<.0001**	2.09 (1.46, 3.00)	**<.0001**
Baseline HbA1c, per 1.0%	0.41 (0.36, 0.47)	**<.0001**	0.27 (0.20, 0.38)	**<.0001**
Age, per year	1.01 (1.00, 1.02)	**.0207**	1.02 (1.00, 1.04)	**.0205**
Known duration of diabetes, per year	0.96 (0.94, 0.99)	**.0009**	1.00 (0.97, 1.04)	.8667
Baseline FPG, mg/dL	0.99 (0.99, 1.00)	**<.0001**	1.00 (0.99, 1.01)	.2577
Endpoint HbA1c <7.0% (53 mmol/mol), no symptomatic hypoglycaemia, no weight gain as an outcome				
LIXI vs placebo	2.93 (2.37, 3.62)	**<.0001**	2.27 (1.50, 3.44)	**.0001**
Baseline HbA1c, per 1.0%	0.41 (0.36, 0.48)	**<.0001**	0.28 (0.19, 0.40)	**<.0001**
Age, per year	1.02 (1.01, 1.03)	**.0017**	1.02 (1.01, 1.05)	**.0168**
Known duration of diabetes, per year	0.97 (0.95, 1.00)	**.0101**	1.00 (0.92, 1.10)	.9286
Female vs male	0.89 (0.74, 1.07)	.2008	1.56 (1.04, 2.35)	**.0319**
Baseline FPG, mg/dL	1.00 (0.99, 1.00)	**.0139**	1.00 (1.00, 1.01)	.1759

CI, confidence interval; EOT, end of trial; NR, not reported.

For comparisons of categorical variables, the first listed variable is the reference.

Values set in bold represent significant *P* values of < .05.

Only data for significant predictors are shown. Predictors evaluated were: LIXI vs placebo; baseline HbA1c (per 1%); age (per year); baseline BMI (per 1 kg/m^2); duration of diabetes (per year); female vs male; baseline FPG; baseline PPG; and baseline PPG excursion.

[1] Measured by standardized meal test.

[2] 2-h PPG levels minus plasma glucose levels 30 minutes before the standardized meal test.

measurements of β-cell function included in this analysis, it was not possible to address the question of how patients with longer diabetes duration and therefore low insulin reserves respond to LIXI.

A strength of the present analysis lies in the use of patient-level data from prospective, randomized controlled trials that used standardized treatment regimens and targets; however, despite pooling data from 8 clinical trials that analysed the results from almost 4000 patients, validation of the findings in prospective studies or randomized controlled trials is warranted. Finally, only studies of LIXI were included in this analysis and, as such, applicability of the findings to other GLP-1 RAs is unknown.

In conclusion, the results from this study show that LIXI treatment as an add-on to OAD or basal insulin therapies is effective in reducing HbA1c levels in patients regardless of their baseline characteristics. The addition of LIXI to either OADs or basal insulin also results in a higher proportion of patients achieving HbA1c <7.0% (53 mmol/mol) without symptomatic hypoglycaemia or weight gain.

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Conflict of interest

L. B. and his institution have received grant and research support from AstraZeneca, Janssen Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Inc., Merck & Co., Novo Nordisk and Sanofi. L. B. has received honoraria/speaker fees from AstraZeneca, Janssen Pharmaceuticals, Inc., Merck & Co., Novo Nordisk and Sanofi, and honoraria/consultant fees from AstraZeneca, GlaxoSmithKline, Intarcia Therapeutics, Inc., Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk and Sanofi. P. C. has received honoraria, and support and travel funds from Sanofi US, Inc. T. D. is an employee of Sanofi US. J. L. is an employee of Novosys Health, under contract with Sanofi US, Inc. E. N. is an employee of Artech Information Systems LLC, under contract with Sanofi US, Inc. R. G. has received research support from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Medtronic, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Takeda, is on an advisory panel for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novo Nordisk, Roche, Sanofi and Takeda, has received speaker fees from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novo Nordisk, Sanofi and Servier, and is a consultant to AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Novo Nordisk and Takeda.

Author contributions

L. B., P. C., and R. G. interpreted the data and critically reviewed the manuscript. T. D. and E. N. developed the concept for this analysis, interpreted the data and critically reviewed the manuscript. J. L. conducted the analyses, interpreted the data and critically reviewed the manuscript. All authors approved the final version for submission.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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