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Lixisenatide plus basal insulin in patients with type 2 diabetes mellitus: a meta-analysis

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ABSTRACT

Aims: The efficacy of the once-daily prandial GLP-1 receptor agonist lixisenatide plus basal insulin in T2DM was assessed by pooling results of phase III trials.
Methods: A meta-analysis was performed of results from three trials in the GetGoal clinical program concerning lixisenatide or placebo plus basal insulin with/without OADs. The primary endpoint was change in HbA_{1c} from baseline to week 24. Secondary endpoints were change in PPG, FPG, insulin dose, and weight from baseline to week 24. Hypoglycemia rates and several composite endpoints were assessed.
Results: Lixisenatide plus basal insulin was significantly more effective than basal insulin alone at reducing HbA_{1c} at 24 weeks. Composite and secondary endpoints were improved significantly with lixisenatide plus basal insulin, with the exception of FPG, which showed no significant difference between the groups. Lixisenatide plus basal insulin was associated with an increased incidence of hypoglycemia versus basal insulin alone.
Conclusions: Lixisenatide plus basal insulin resulted in significant improvement in glycemic control versus basal insulin alone, particularly in terms of controlling PPG. Prandial lixisenatide in combination with basal insulin is a suitable option for treatment intensification in patients with T2DM insufficiently controlled with basal insulin, as these agents have complementary effects on PPG and FPG, respectively.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by elevated blood glucose as a result of insulin resistance and β-cell dysfunction. Early T2DM can be controlled with lifestyle modifications and the use of oral antidiabetics (OADs) (Garber, Abrahamson, Barzilay, et al., 2013; Ryden, Standl, Bartnik, et al., 2007), while basal insulin as add-on to OADs is generally initiated in patients with more advanced diabetes or in patients who do not achieve glycemic control with OADs alone (American Diabetes Association, 2013). Basal insulin once daily is effective for the control of fasting plasma glucose (FPG); however, excursions in post-prandial plasma glucose (PPG) in patients with poor glycemic control are not addressed by basal insulin and may require prandial therapies. Basal–bolus and basal-plus regimens, combining once-daily basal insulin and mealtime administration of a rapid-acting insulin (RAI), or pre-mixed insulin, are commonly recommended in this regard (Inzucchi,

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Bergenstal, Buse, et al., 2012). However, insulin-based regimens, particularly those with a prandial component (Holman, Farmer, Davies, et al., 2009), are associated with weight gain and hypoglycemia, which can impact patient acceptance of treatment (Cryer, Davis, & Shamoon, 2003; Russell-Jones & Khan, 2007).

Incretin hormones secreted by the gastrointestinal tract stimulate glucose-dependent insulin secretion to ensure that PPG excursions are limited regardless of carbohydrate load (Holst, 2007; Crespo, González Matías, Lozano, et al., 2009). The incretin glucagon-like peptide-1 (GLP-1) is released post-prandially by the intestine but is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). The effects of GLP-1 in the pancreas (release of insulin and suppression of glucagon release) and in the stomach (delay of gastric emptying) have made GLP-1 a focus of research for T2DM pharmacotherapies. A number of GLP-1 receptor agonists (GLP-1 RAs) have been developed to take advantage of the 'incretin effect'. These agents include liraglutide and exenatide once weekly (longer acting GLP-1 RAs with a predominant effect on FPG), exenatide twice daily and lixisenatide (GLP-1 RAs with a predominant effect on PPG). The clinical efficacy of these agents in T2DM is now established, and the advantage of significant improvements in glycemic control together with a low risk of hypoglycemia and weight gain relative to other anti-diabetic agents has made GLP-1 RAs an attractive option for treatment intensification.

Lixisenatide (Lyxumia®; Sanofi, Paris, France) is a once-daily prandial GLP-1 RA for the treatment of T2DM that is based on the exendin-4 peptide with a glycine residue at position 2, prolonging its activity as it is less readily degraded by DPP-4 (Werner, Haschke, Herling, et al., 2010). Lixisenatide, as a monotherapy, in addition to OADs or basal insulin, demonstrated significant efficacy versus placebo in reducing glycated hemoglobin (HbA_{1c}) and regulating PPG with a beneficial effect on body weight in the phase III GetGoal clinical program (Ahrén, Leguizamo, Miossec, et al., 2013; Fonseca, Alvarado-Ruiz, Raccah, et al., 2012; Riddle, Aronson, Home, et al., 2013; Riddle, Forst, Aronson, et al., 2013; Seino, Min, Niemoeller, et al., 2012). The PPG-lowering effects of prandial GLP-1 RAs, such as lixisenatide, may be of particular benefit for patients uncontrolled on optimally titrated basal insulin, for whom PPG excursions are likely to be the predominant contributor to hyperglycemia (Riddle, Umpierrez, DiGenio, et al., 2011). Lixisenatide plus basal insulin versus basal insulin alone, in patients whose T2DM was insufficiently controlled with basal insulin or OADs, was assessed in three of the GetGoal trials (GetGoal-Duo1, GetGoal-L and GetGoal-L-Asia); herein, we report a meta-analysis of these trials in order to assess the efficacy and safety of lixisenatide plus basal insulin in a large and diverse patient population. In doing so, we aim to provide information to guide clinicians using lixisenatide in combination with basal insulin.

2. Materials and methods

2.1. Analysis design

This was a meta-analysis of data from patients with T2DM in the three phase III GetGoal trials in which lixisenatide 20 μg once daily was administered as add-on to basal insulin ± OADs and compared with placebo plus basal insulin ± OADs. All medications were self-administered according to the regimens of the individual trials.

The designs of these GetGoal trials have been reported previously (Riddle, Aronson, Home, et al., 2013; Riddle, Forst, Aronson, et al., 2013; Seino et al., 2012) (Supplementary Table 1). Briefly, the methodologies of these trials were as follows: GetGoal-Duo1 (NCT00975286) investigated lixisenatide as add-on to newly initiated insulin glargine in patients whose T2DM was insufficiently controlled with metformin ± thiazolidinediones; GetGoal-L (NCT00715624) assessed lixisenatide as add-on to basal insulin in patients whose T2DM was insufficiently controlled on basal insulin (insulin glargine, insulin detemir or neutral protamine Hagedorn) ± metformin; GetGoal-L-Asia (NCT00866658) assessed lixisenatide as add-on to basal insulin in Asian patients whose T2DM was insufficiently controlled on basal insulin (insulin glargine, insulin detemir or neutral protamine Hagedorn) ± sulfonylurea. Each of the trials was of 24 weeks' duration and had change in HbA_{1c} at trial end as the primary endpoint. The trials were conducted between July 2008 and August 2011 across 25 countries (the number of countries and enrolment/completion dates varied by trial). Patients were randomized to receive lixisenatide or placebo 1:1 in GetGoal-Duo1 and GetGoal-L-Asia, and 2:1 in GetGoal-L.

2.2. Inclusion criteria

All patients had inadequately controlled T2DM ($HbA_{1c} \geq 7\%$) and were randomized to receive either lixisenatide or placebo in addition to treatment with basal insulin ± OADs in one of the phase III GetGoal trials (thus three trials were included in this meta-analysis). Included patients were from the intent-to-treat population of their respective trial and were required to have HbA_{1c} measurements at baseline and at 24 weeks.

2.3. Endpoints

The primary endpoint of this meta-analysis (and of the three GetGoal trials) was change in HbA_{1c} from baseline to week 24. Secondary endpoints included change from baseline in the proportion of patients with HbA_{1c} <7% or ≥7% at week 24. In addition, sub-analyses were performed of HbA_{1c} change from baseline to week 24 in patients who were treated concomitantly with sulfonylureas versus patients who were not and in patients who were basal-insulin naïve at the beginning of treatment in the trials versus patients already receiving basal insulin. Other secondary endpoints were the first PPG measurement after injection of lixisenatide based on patients' 7-point self-monitored blood glucose profiles (mg/dL); 2-hour PPG levels (mg/dL) after the standardized meal test; change from baseline in FPG (mg/dL) at week 24; the proportion of patients with FPG <110 mg/dL (6.1 mmol/L) or ≥110 mg/dL at week 24; and insulin dose (U/kg) change at week 24. The standardized meal test consisted of a 600 kcal liquid meal (400 mL Ensure Plus, Abbott Nutrition, Columbus, OH, USA) comprising 53.8% carbohydrate, 16.7% protein and 29.5% fat, to be consumed within a 10-minute period.

Safety endpoints in this meta-analysis were: prevalence of per-protocol-defined symptomatic hypoglycemia at week 24; the annualized rate of symptomatic hypoglycemic events; and the number and proportion of patients with severe hypoglycemia. A sub-analysis of the occurrence of hypoglycemia was also performed in patients who were being treated concomitantly with sulfonylureas versus patients who were not. In common with trials of other GLP-1 RAs, symptomatic hypoglycemia was defined as an event with clinical symptoms consistent with an hypoglycemic episode (e.g. sweating, palpitations, hunger, fatigue, restlessness, anxiety, irritability, headache, loss of concentration, somnolence, psychiatric or visual disorders, transient sensory or motor defects, confusion, convulsions or coma) with documented plasma glucose <60 mg/dL (3.3 mmol/L). Severe hypoglycemia was defined as an hypoglycemic event during which patients required assistance from another person because they could not self treat due to acute neurological impairment resulting from hypoglycemia (The Diabetes Control & Complications Trial Research Group, 1991) and where the event was associated with plasma glucose <36 mg/dL (2.0 mmol/L) or where the event was associated with prompt recovery after oral carbohydrate, or intravenous glucose/glucagon.

This meta-analysis also assessed a number of composite endpoints at week 24 that comprised both efficacy and safety parameters; these were: HbA_{1c} levels <7% and no symptomatic hypoglycemia; HbA_{1c}

levels <7% and no weight gain; HbA_{1c} levels <7%, no weight gain and no symptomatic hypoglycemia.

2.4. Statistical methods

Descriptive statistics were used to measure and describe clinical characteristics and patient demographic data, as well as to measure and describe efficacy and safety outcomes. The number of patients and the associated percentage of the total number of patients with the relevant data reported were determined for dichotomous variables. The count, mean ± standard deviation (SD), and median were reported for continuous variables. Treatment arms within each group were compared with one another, with p-values calculated using a chi-square test or analysis of variance test where appropriate.

A meta-analysis was used to determine the overall efficacy and safety of lixisenatide as an add-on treatment to basal insulin. Standard meta-analytic techniques were applied to assess the overall outcome measures using a random-effects model with an inverse variance method to determine weighted mean differences with 95% confidence intervals (CIs) for continuous variables and Mantel–Haenszel odds ratios for all dichotomous outcome data. A p-value of 0.05 was used to determine the level of statistical significance. Quantification of heterogeneity was examined with I^2 to measure the degree of total variation across trials owing to heterogeneity and establish the consistency of evidence. I^2 values >50% indicate a substantial level of heterogeneity; if heterogeneity was observed, this was accommodated using a random-effect model. All descriptive statistical analyses were carried out using SAS®. The meta-analysis was carried out using RevMan 5.1.

3. Results

A total of 665 patients were treated with lixisenatide plus basal insulin, and 533 patients were administered placebo plus basal insulin. A summary of the results of each of the studies included is shown in Supplementary Table 1. Patient demographics and clinical characteristics in this meta-analysis were comparable in the lixisenatide and placebo groups (Table 1). At baseline, 84% of patients in each treatment arm were receiving OADs. In violation of the respective study protocols, eight patients in GetGoal-L (five patients in the lixisenatide arm and three patients in the placebo arm) and two patients in GetGoal-L-Asia (both in the placebo arm) received premix insulin instead of basal insulin prior to screening.

Table 1
Baseline characteristics.

Characteristic	Lixisenatide + basal insulin (n = 665)	Placebo + basal insulin (n = 533)
Mean age, years (SD)	57.4 (9.8)	56.9 (10.1)
Male, n (%)	306 (46.0)	268 (50.3)
Mean weight, kg (SD)	82.8 (21.2)	81.3 (21.2)
Mean BMI, kg/m^2	30.6 (6.5)	30.0 (6.5)
Mean diabetes duration, years (SD)	11.8 (7.1)	11.4 (7.0)
OAD use, n (%)	558 (83.9)	447 (83.9)
Metformin[a]	485 (68.8)	353 (64.5)
Sulfonylureas[a]	108 (15.3)	111 (20.3)
Thiazolidinediones[a]	27 (3.8)	27 (4.9)
Mean duration of OAD use, years (SD)	6.3 (5.4)	5.9 (4.9)
Insulin use at baseline, n (%)	437 (65.7)	306 (57.4)
Insulin use at screening, n (%)		
Insulin glargine[b]	260 (53.9)	175 (53.7)
Insulin detemir[b]	65 (13.5)	61 (18.7)
NPH[b]	152 (31.5)	85 (26.1)
Premix insulin[b,c]	5 (1.0)	5 (1.5)
Mean duration of insulin use, years (SD)	2.0 (3.2)	1.9 (3.5)
Mean HbA_{1c}, % (SD)	8.2 (0.9)	8.1 (0.8)
Mean FPG, mg/dL (SD)	134.4 (42.2)	133.2 (42.0)

BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic; SD, standard deviation.

[a] Safety population data for GetGoal-Duo1, GetGoal-L and GetGoal-L-Asia (lixisenatide arm, n = 705; placebo arm, n = 547).

[b] Safety population data for GetGoal-L and GetGoal-L-Asia (lixisenatide arm, n = 482; placebo arm, n = 326); patients from GetGoal-Duo1 are excluded as they were insulin-naïve at baseline.

[c] Patients receiving premix insulin at screening violated their respective study protocols.

3.1. Primary endpoint

Lixisenatide 20 μg once daily as add-on to basal insulin significantly reduced HbA_{1c} from baseline to week 24 compared with placebo plus basal insulin (p = 0.003; Fig. 1). The potential heterogeneity for the primary endpoint was high (I^2 = 90%), but this was accommodated using a random-effects model.

3.2. Secondary endpoints

Patients treated with lixisenatide plus basal insulin were almost four times more likely to achieve HbA_{1c} <7% than patients who were administered placebo plus basal insulin (HbA_{1c} <7% in 39.0% vs. 21.0% of patients, respectively; odds ratio [OR]: 3.67; p = 0.0016). In patients who were insulin-naïve at the start of lixisenatide treatment, lixisenatide plus basal insulin resulted in significantly greater reductions in HbA_{1c} at week 24 compared with placebo plus basal insulin (mean [SD] reductions of −0.60 [0.77]% and −0.30 [0.80]%, respectively; p < 0.0001; Table 2). Compared with insulin-naïve patients, reductions in HbA_{1c} at week 24 with lixisenatide treatment were greater in patients who were taking basal insulin at baseline (mean [SD] reduction with lixisenatide plus basal insulin, −0.72 [1.13]% versus placebo plus basal insulin, −0.11 [0.93]%, respectively; p < 0.0001; Table 2). Lixisenatide plus basal insulin treatment resulted in significant improvement in HbA_{1c} regardless of whether or not patients were receiving concomitant sulfonylureas. Mean (SD) week 24 HbA_{1c} changes from baseline in the sulfonylurea-treated patients were −0.91 (1.36)% with lixisenatide plus basal insulin and 0.04 (0.88)% with placebo plus basal insulin (p < 0.0001; Table 2). In patients who were not receiving concomitant sulfonylureas, mean (SD) HbA_{1c} changes from baseline were −0.64 (0.95)% and −0.25 (0.87)%, respectively (p < 0.0001; Table 2).

Compared with placebo plus basal insulin, lixisenatide plus basal insulin significantly improved control of 2-hour PPG over 24 weeks (p < 0.0001; Fig. 2A). Change in FPG at 24 weeks was not significantly different in the two treatment groups (Fig. 2B). Change with lixisenatide plus basal insulin was −0.24 mg/dL compared with +3.54 mg/dL for placebo plus basal insulin; p = NS).

Lixisenatide plus basal insulin significantly reduced body mass index by 0.26 kg/m^2 compared with an increase of 0.12 kg/m^2 with placebo plus basal insulin (p < 0.0001). Mean body weight loss was 0.83 kg greater with lixisenatide plus basal insulin compared with placebo plus basal insulin (p = 0.001; Fig. 2C).

Basal insulin dose by weight was significantly lower at week 24 with lixisenatide plus basal insulin compared with placebo plus basal insulin (−0.02 U/kg, 95% CI: −0.03, −0.01; p < 0.0001). At study end, the mean absolute change from baseline in basal insulin dose was −0.57 U for lixisenatide plus basal insulin and 2.42 U for placebo plus basal insulin (p < 0.0001).

3.3. Safety endpoints

Symptomatic hypoglycemia was significantly more common in patients treated with lixisenatide plus basal insulin than in patients treated with placebo plus basal insulin (OR: 1.82; 95% CI: 1.29, 2.57;

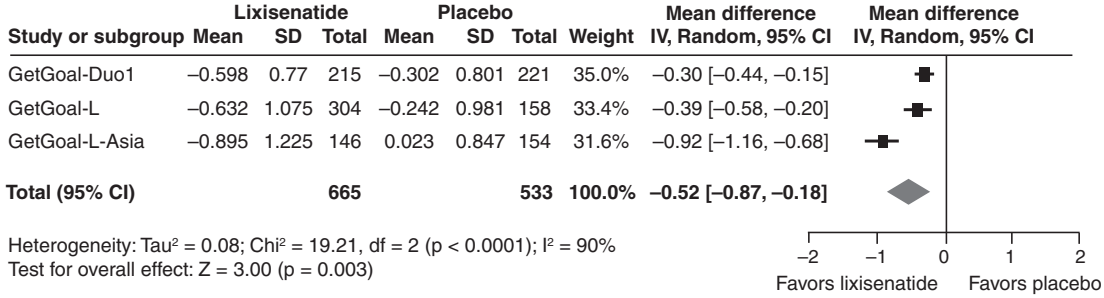

Fig. 1. Forest plot for meta-analysis of least squares mean difference between lixisenatide plus basal insulin and placebo plus basal insulin in terms of change in HbA_{1c}–ITT population. CI, confidence interval; df, degrees of freedom; HbA_{1c}, glycated hemoglobin; ITT, intent to treat; IV, inverse variance; SD, standard deviation.

$p < 0.001$). Overall, 182/665 (27.4%) and 91/533 (17.1%) patients in the lixisenatide plus basal insulin and placebo plus basal insulin groups, respectively, developed symptomatic hypoglycemia. There was a numerically higher rate of severe hypoglycemia in patients treated with lixisenatide plus basal insulin when compared with patients who were administered placebo plus basal insulin (5/665 [0.8%] and 0/533 patients, respectively).

Overall, 44/103 (42.7%) patients treated with a sulfonylurea and lixisenatide plus basal insulin experienced symptomatic hypoglycemia compared with 21/109 (19.3%) patients who were not treated with lixisenatide ($p < 0.001$). In those who were not administered a sulfonylurea (but were treated with basal insulin ± metformin ± a thiazolidinedione), 138/562 (24.6%) patients and 70/424 (16.5%) patients experienced symptomatic hypoglycemia in the lixisenatide and placebo groups, respectively ($p < 0.01$). No patients who were being treated concomitantly with a sulfonylurea experienced severe hypoglycemia. Overall, 5/562 (0.9%) non-sulfonylurea treated patients in the lixisenatide plus basal insulin group experienced severe hypoglycemia (versus no patients receiving placebo and basal insulin without a sulfonylurea).

Table 2
HbA_{1c} change from baseline to week 24 in subanalyses.

Subpopulation	Lixisenatide + basal insulin	Placebo + basal insulin	p-value versus placebo
Insulin-naïve at start of lixisenatide treatment			
n	215	221	
Mean (SD) baseline HbA_{1c}, %	7.56 (0.54)	7.60 (0.54)	
Week 24 mean (SD) HbA_{1c}, %	6.96 (0.81)	7.30 (0.85)	
Mean (SD) HbA_{1c} change from baseline, %	−0.60 (0.77)	−0.30 (0.80)	< 0.0001
Non-insulin-naïve at start of lixisenatide treatment			
n	450	310	
Mean (SD) baseline HbA_{1c}, %	8.44 (0.82)	8.46 (0.81)	
Week 24 mean (SD) HbA_{1c}, %	7.72 (1.20)	8.35 (1.14)	
Mean (SD) HbA_{1c} change from baseline, %	−0.72 (1.13)	−0.11 (0.93)	< 0.0001
Concomitant sulfonylurea use			
n	103	109	
Mean (SD) baseline HbA_{1c}, %	8.58 (0.72)	8.61 (0.77)	
Week 24 mean (SD) HbA_{1c}, %	7.67 (1.34)	8.65 (1.13)	
Mean (SD) HbA_{1c} change from baseline, %	−0.91 (1.36)	0.04 (0.88)	< 0.0001
No concomitant sulfonylurea use			
n	562	424	
Mean (SD) baseline HbA_{1c}, %	8.08 (0.85)	7.97 (0.78)	
Week 24 mean (SD) HbA_{1c}, %	7.44 (1.10)	7.72 (1.08)	
Mean (SD) HbA_{1c} change from baseline, %	−0.64 (0.95)	−0.25 (0.87)	< 0.0001

HbA_{1c}, glycated hemoglobin; SD, standard deviation.

3.4. Composite endpoints

Patients in the lixisenatide plus basal insulin group were significantly more likely to achieve each of the composite endpoints than patients who were administered placebo plus basal insulin. Patients treated with lixisenatide plus basal insulin were over three times more likely to achieve $HbA_{1c} < 7\%$ and no weight gain (OR: 3.35; 95% CI: 1.66, 6.77; $p = 0.0008$) and more than 2.5 times more likely to have $HbA_{1c} < 7\%$ and no symptomatic hypoglycemia (OR: 2.65; 95% CI: 1.30, 5.38; $p = 0.0007$) compared with patients treated with placebo plus basal insulin, after 24 weeks. Furthermore, patients in the lixisenatide plus basal insulin group were over 2.5 times more likely to have $HbA_{1c} < 7\%$, no weight gain and no symptomatic hypoglycemia ($p = 0.0009$; Fig. 3).

4. Discussion

This meta-analysis of over 1000 patients demonstrated that lixisenatide 20 μg once daily in combination with basal insulin was effective for the treatment of patients with T2DM inadequately controlled on basal insulin with or without OADs. Compared with placebo plus basal insulin, treatment with lixisenatide plus basal insulin resulted in significantly greater reductions in HbA_{1c} alongside significant reductions from baseline in the absolute basal insulin dose and the insulin dose by weight given at the end of 24 weeks of treatment. Lixisenatide plus basal insulin also significantly improved control of PPG and resulted in significant weight loss when compared with patients who were administered placebo plus basal insulin. Reductions in HbA_{1c} with lixisenatide treatment were robust and were found to be significant versus placebo in patients who: were receiving basal insulin at the start of lixisenatide treatment; initiated basal insulin with lixisenatide treatment; were receiving concomitant sulfonylureas; or who were not receiving concomitant sufonylureas. Importantly, patients who received lixisenatide plus basal insulin were significantly more likely than patients in the placebo group to achieve all of the composite endpoints assessed. It would appear that it is the magnitude of the reductions in body weight and the increased likelihood of achieving glycemic control with lixisenatide plus basal insulin that are driving the response in the composite endpoints in this meta-analysis, compensating for the increased occurrence of symptomatic hypoglycemia.

Symptomatic hypoglycemia was significantly more common in patients treated with lixisenatide plus basal insulin than in patients treated with placebo plus basal insulin (27.4% vs. 17.1%). Previous evidence has shown that the incidence of symptomatic hypoglycemia with lixisenatide monotherapy is less than 2% (Fonseca et al., 2012), while the combination of lixisenatide with sulfonylureas and/or insulin markedly increases its incidence (to between 15 and 43%) (Riddle, Aronson, Home, et al., 2013; Riddle, Forst, Aronson, et al., 2013; Seino et al., 2012; Rosenstock, Hanefeld, Shamanna, et al., 2014). Similar results have been reported for exenatide in

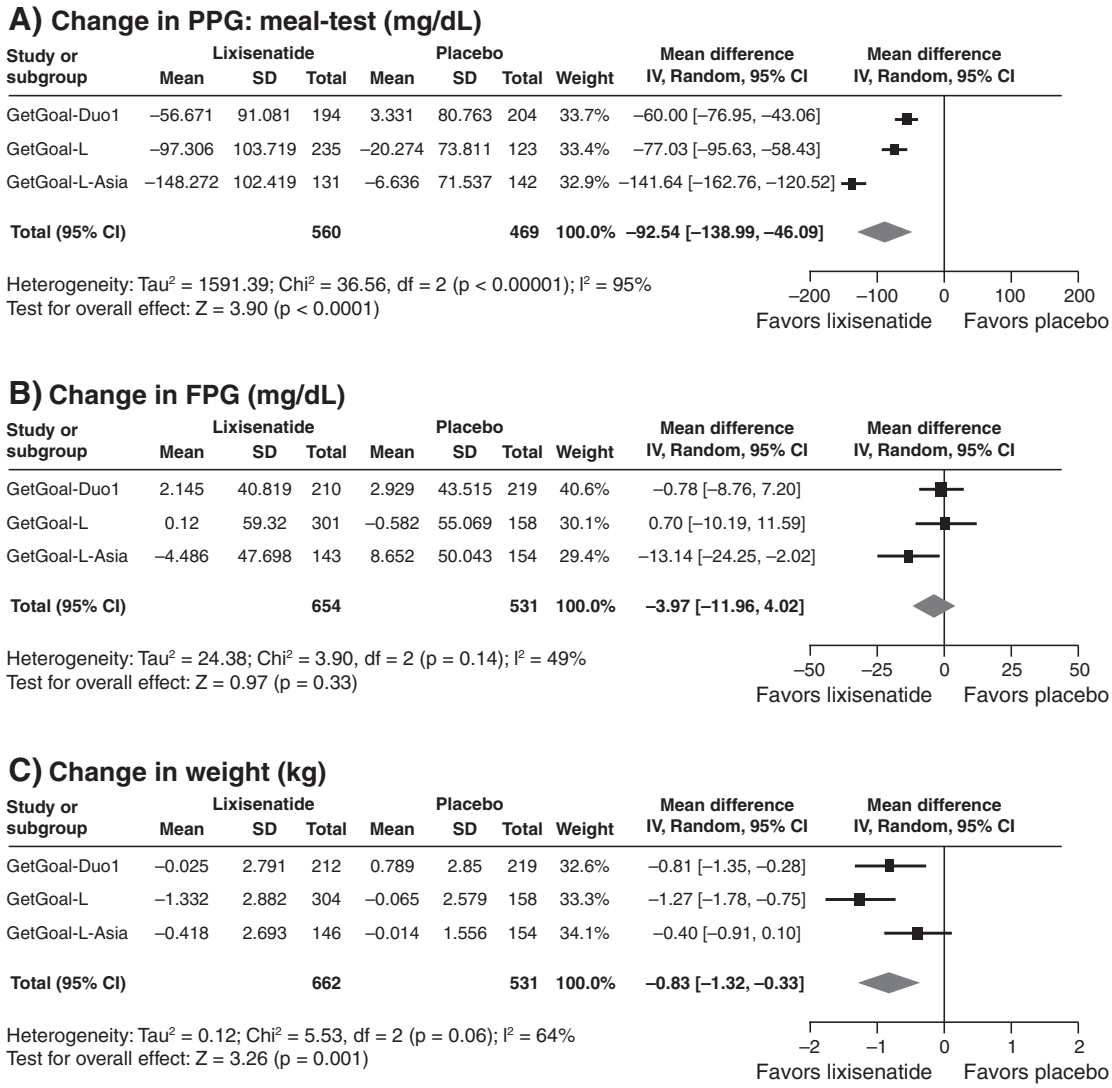

Fig. 2. Forest plots for lixisenatide versus placebo in terms of (A) change in PPG, (B) change in FPG and (C) change in weight—ITT population. CI, confidence interval; df, degrees of freedom; FPG, fasting plasma glucose; ITT, intent to treat; IV, inverse variance; PPG, post-prandial plasma glucose; SD, standard deviation.

combination with sulfonylureas and/or insulin (Buse, Henry, Han, et al., 2004; Buse, Bergenstal, Glass, et al., 2011; Gao, Yoon, Chuang, et al., 2009). The present analysis pooled cohorts of different ethnicities, with one of the trials being performed across multiple countries in Asia (GetGoal-L-Asia). As shown in Supplementary Table 1, the majority of patients participating in GetGoal-L-Asia were treated concomitantly with sulfonylureas, had longer disease duration and lower body mass index at baseline compared with patients in the other studies analyzed. Furthermore, patients in GetGoal-L-Asia experienced greater reductions in HbA_{1c} but less body weight loss compared with patients from the other trials. This should be taken into account when interpreting the results of this meta-

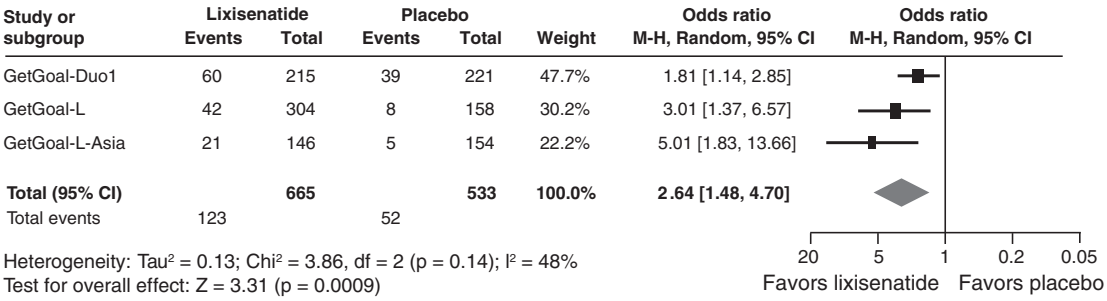

Fig. 3. Forest plot for meta-analysis of likelihood of patients achieving HbA_{1c} <7%, no weight gain and no symptomatic hypoglycemia—ITT population. CI, confidence interval; df, degrees of freedom; HbA_{1c}, glycated hemoglobin; ITT, intent to treat; M–H, Mantel–Haenszel test.

analysis as a high level of heterogeneity was evident ($I^2 = 90\%$ for the primary endpoint). In pooling substantially different cohorts, treatment effects may be diluted or exaggerated. Indeed, the rate of symptomatic hypoglycemia experienced by patients receiving concomitant sulfonylureas in GetGoal-L-Asia appears to have skewed the occurrence of hypoglycemia in the meta-analysis as a whole. A sub-analysis of patients treated concomitantly with sulfonylureas (i.e. most of the patients in GetGoal-L-Asia versus the rest of the meta-analysis population) indicated that rates of symptomatic hypoglycemia rose by 18% when sulfonylureas were added to the regimen, although no patients in this group experienced severe hypoglycemia. Sulfonylurea treatment is associated with an increased risk of hypoglycemia (Bodmer, Meier, Krahenbuhl, et al., 2008) and in the recent European Public Assessment Report of lixisenatide, it was concluded that hypoglycemia with lixisenatide was mainly seen in patients who were treated concomitantly with a sulfonylurea and/or basal insulin. For this reason, use of a sulfonylurea and basal insulin simultaneously in patients treated with lixisenatide was not recommended (European Medicines Agency). As noted above, the results with lixisenatide plus basal insulin for the composite endpoints indicated that patients were still significantly more likely to reach HbA_{1c} targets without experiencing hypoglycemia than were patients who received placebo plus basal insulin.

In this meta-analysis, treatment with lixisenatide plus basal insulin did not result in significant improvements over placebo plus basal insulin in terms of reductions in FPG. However, the addition of lixisenatide to basal insulin resulted in significant improvements compared with placebo in terms of PPG control. Many patients with T2DM who achieve FPG control experience large PPG excursions (Avignon, Radauceanu, & Monnier, 1997; Bouma, Dekker, de Sonnaville, et al., 1999; Soonthornpun, Rattarasarn, Leelawattana, et al., 1999; Verges, 2002) and there is, therefore, a strong clinical rationale for combining a treatment that addresses FPG (basal insulin) with a treatment that effectively controls PPG (e.g. a prandial GLP-1 RA, prandial insulin, or a DPP-4 inhibitor). The differing effects of lixisenatide on FPG and PPG are also observed for twice-daily exenatide and can be explained by the short-acting pharmacokinetic profile of these two agents (Meier, 2012). A head-to-head study comparing prandial GLP-1 RA therapy with once-daily lixisenatide versus twice-daily exenatide in patients uncontrolled on metformin demonstrated comparable reductions in HbA_{1c} and FPG in each group, although PPG levels were not reported. Mean weight loss was slightly higher with exenatide versus lixisenatide, but the incidence of symptomatic hypoglycemia and gastrointestinal adverse events was significantly lower with lixisenatide versus exenatide (Rosenstock, Raccah, Korányi, et al., 2013). A 4-week, pharmacodynamic study comparing prandial short-acting lixisenatide versus long-acting liraglutide in patients inadequately controlled on metformin further highlights the clinical consequences of GLP-1 RA pharmacokinetics (Kapitza, Forst, Coester, et al., 2013). The reduction in PPG with lixisenatide was significantly greater than with liraglutide, while the reduction in FPG with liraglutide was significantly greater than with lixisenatide. Overall, HbA_{1c} and body-weight reductions were slightly greater with liraglutide versus lixisenatide, the incidence of gastrointestinal events was slightly lower with lixisenatide versus liraglutide, and there were no reported events of symptomatic hypoglycemia in either group. Preliminary data have also recently been made available for an 8-week pharmacodynamic study comparing addition of lixisenatide versus liraglutide in patients not optimally controlled following systematic titration of insulin glargine (Meier, Rosenstock, Hincelin-Méry et al). PPG reductions were significantly greater with lixisenatide versus liraglutide, while clinically comparable reductions in HbA_{1c} were seen across the treatment groups. Symptomatic hypoglycemia was slightly more frequent with lixisenatide, and patients receiving liraglutide experienced more lower gastrointestinal tract events.

A number of prandial agents other than GLP-1 RAs have been shown to be effective in achieving HbA_{1c} targets when given in combination with basal insulin in patients with T2DM (Buse et al., 2011; Arnolds, Dellweg, Clair, et al., 2010; Leahy, 2012; Nayak, Govindan, Baskar, et al., 2010; Owens, Luzio, Sert-Langeron, et al., 2011; Riddle & Rosenstock, 2003; Rosenstock, Rodbard, Bain, et al., 2013). In patients with T2DM who are insufficiently controlled on basal insulin, treatment intensification with an RAI is commonly recommended for control of post-prandial hyperglycemia (Garber et al., 2013; Inzucchi et al., 2012). Results of the 4T study reported that approximately two-thirds of patients who received a basal–prandial insulin regimen, subsequent to loss of glycemic control on basal insulin plus OADs, achieved a target HbA_{1c} of <7% (Holman et al., 2009). However, while treatment intensification with prandial insulin can effectively reduce HbA_{1c}, pre-mixed insulin, basal–bolus and basal-plus regimens are associated with hypoglycemia and weight gain, resulting in poor treatment acceptance and compliance issues as a consequence of side effects and dosing complexity (Russell-Jones & Khan, 2007; Bonafede, Kalsekar, Pawaskar, et al., 2011; Farrokhi, Klindukhova, Chandra, et al., 2012; Odegard & Capoccia, 2007). Moreover, these side effects of hypoglycemia and weight gain are likely to be particularly impactful in elderly, frail, or obese patients.

GLP-1 RAs have demonstrable benefits in terms of weight loss. Effect on weight is an important consideration when selecting the most appropriate treatments to achieve glycemic control in T2DM. Patients are often unwilling to commence or intensify insulin-based treatments owing to associated weight gain. Treatment intensification with GLP-1 RAs may, therefore, present a useful alternative to prandial insulin in patients insufficiently controlled on basal insulin.

Indeed, recent results from the 4B study have indicated that HbA_{1c} reductions with twice-daily exenatide plus insulin glargine were non-inferior to those observed with mealtime bolus insulin lispro plus insulin glargine. Moreover, FPG and body weight were significantly lower, and the annualized rate of hypoglycemic events was reduced with exenatide plus insulin glargine (Diamant, Nauck, Shaginian, et al). GetGoal-Duo2, a study comparing lixisenatide once daily plus insulin glargine with the RAI insulin glulisine once or thrice daily plus insulin glargine, is ongoing with an estimated completion date of December 2014.

The findings of the current meta-analysis demonstrate that lixisenatide plus basal insulin is a favorable option for treatment intensification in patients with T2DM insufficiently controlled with basal insulin alone, as these agents have complementary effects on PPG and FPG, respectively. Evidence from the GetGoal-Duo1 study indicates that addition of lixisenatide can be beneficial within 12 weeks of basal insulin initiation for patients with HbA_{1c} >7% despite basal insulin being titrated systematically to control FPG levels (Riddle, Forst, Aronson, et al., 2013). Patients on basal insulin experiencing marked PPG excursions may benefit most from the addition of lixisenatide and future studies should investigate this and other potential identifiers of lixisenatide response to guide clinical decisions.

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