Lixisenatide as add-on to oral anti-diabetic therapy: an effective treatment for glycaemic control with body weight benefits in type 2 diabetes

Denis Raccah1*
Pierre Gourdy2
Luc Sagnard3
Antonio Ceriello4

1 Department of Diabetology, University Hospital Sainte-Marguerite, Marseille, France
2 Department of Diabetology, University Hospital Rangueil, Toulouse, France
3 Sanofi, Paris, France
4 Diabetes and Endocrinology, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

*Correspondence to:
Denis Raccah, Department of Diabetology, University Hospital Sainte-Marguerite, 270, Boulevard de Sainte-Marguerite, 13009 Marseille, France.
E-mail: denis.raccah@ap-hm.fr

Abstract

Background Achieving recommended glycated haemoglobin (HbA1c) targets in patients with type 2 diabetes mellitus (T2DM) requires effective control of fasting and post-prandial plasma glucose. As T2DM progresses, oral anti-diabetics are no longer sufficient to maintain glycaemic control. Five phase III studies in the GetGoal clinical trial programme assessed the efficacy of lixisenatide, a once-daily prandial glucagon-like peptide-1 receptor agonist, in combination with oral anti-diabetics in patients with T2DM insufficiently controlled using oral anti-diabetics.

Methods A meta-analysis was performed of the results of five 24-week clinical trials (comprising 2760 patients) concerning lixisenatide or placebo plus oral anti-diabetic therapy. The primary endpoint of these studies was change in HbA1c at week 24. Changes in fasting and post-prandial plasma glucose, and weight were also established as were the odds ratios for hypoglycaemia and composite safety and efficacy endpoints. Meta-analysis outcomes were assessed using a random effects model. All meta-analyses were performed using RevMan, version 5.1.

Results Lixisenatide was significantly better than placebo in terms of achieving all endpoints in this meta-analysis, including the primary endpoint change in HbA1c at week 24, with \( p < 0.0001 \) for all endpoints. The mean number of symptomatic hypoglycaemic events per patient year was increased for patients in the lixisenatide versus placebo groups (\( p = 0.04 \)). However, compared with patients in the placebo group, patients treated with lixisenatide were more likely to achieve composite efficacy and safety endpoints.

Conclusions This meta-analysis demonstrates that lixisenatide in combination with oral anti-diabetic therapy significantly improves outcomes combining efficacy and safety parameters in patients with T2DM. © 2014 The Authors. Diabetes/Metabolism Research and Reviews published by John Wiley & Sons, Ltd.

Keywords glycaemic control; lixisenatide; oral anti-diabetics; prandial; type 2 diabetes mellitus

Introduction

Early type 2 diabetes mellitus (T2DM) can be controlled with lifestyle measures and the use of oral anti-diabetic monotherapy, such as metformin or...
a sulfonylurea [1,2]. However, as T2DM progresses, beta-cell function declines, and insulin resistance increases, such that treatment with monotherapy is often no longer sufficient to maintain glycaemic control. As a result, additional agents, such as other oral anti-diabetics [dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors, sodium/glucose cotransporter 2 inhibitors, thiazolidinediones, and meglitinides (secretagogues)], insulin, or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are added to the patient’s regimen [1,2].

The efficacy of lixisenatide has been assessed across the full spectrum of the natural history of T2DM, by studying patients with uncontrolled glycaemia and exercise interventions, various oral anti-diabetics, and basal insulin. In the phase III GetGoal clinical trial programme, lixisenatide demonstrated significant efficacy versus placebo in reducing glycated haemoglobin (HbA1c) and in the improvement of post-prandial plasma glucose control after a test meal [3–7]. Lixisenatide add-on treatment to oral anti-diabetics has been assessed in comparison with placebo in five GetGoal trials (GetGoal-S, GetGoal-P, GetGoal-M, GetGoal-M-Asia, and GetGoal-F1); herein, we report a meta-analysis of these trials in order to assess the efficacy and safety of lixisenatide plus oral anti-diabetic treatment in a large and diverse patient population.

Materials and methods

Overall study design

This was a meta-analysis of data from the five phase III GetGoal studies in patients with T2DM in which lixisenatide 20 μg once daily was administered as add-on to oral anti-diabetics and compared with placebo plus oral anti-diabetics (Figure 1). Design and results for four of the five studies have been published in full [3,8–10]. Briefly, the methodologies were as follows: GetGoal-F1 (NCT00763451) was a one-step/two-step dose increase study of lixisenatide as add-on to metformin; GetGoal-M (NCT00712673) was a study assessing the effects of morning or evening dosing of lixisenatide, compared with placebo, as add-on to metformin; GetGoal-M-Asia (NCT01169779) assessed lixisenatide as add-on to metformin ± a sulfonylurea in Asian patients; GetGoal-P (NCT00763815) assessed lixisenatide as add-on to pioglitazone ± metformin; and GetGoal-S (NCT00713830) was a study of lixisenatide as add-on to a sulfonylurea ± metformin.

Each of the studies was of at least 24-week duration and had change in HbA1c from baseline to week 24 as the primary endpoint. The studies were conducted between June 2008 and December 2011 across 16 countries (the number of countries and enrollment/completion dates varied by study). Patients were randomized to receive lixisenatide plus oral anti-diabetics or placebo plus oral anti-diabetics 2:1 in these studies, with the exception of GetGoal-M-Asia in which patients were randomized 1:1 and GetGoal-M in which patients were randomized 3:1.

Inclusion criteria

Patients whose T2DM was inadequately controlled (HbA1c ≥7%) despite oral anti-diabetic treatment and who were in the intent-to-treat (ITT) populations of the five GetGoal phase III trials analysed here were included in this meta-analysis. The ITT population in these studies consisted of all randomized patients who received at least one dose of double-blind study treatment and had both a baseline and at least one post-baseline efficacy assessment.

Interventions

The interventions in this meta-analysis were lixisenatide 20 μg once daily as add-on to oral anti-diabetics (metformin, sulfonylurea, and pioglitazone) or placebo plus oral anti-diabetics. All medications were self-administered according to the regimens of the individual studies.

Endpoints

The primary endpoint in all of the studies (and in this meta-analysis) was change in HbA1c from baseline to week 24. Two-hour post-prandial plasma glucose level after a standardized meal test was assessed at baseline and week 24 as a secondary endpoint. A standardized meal test was performed in three of the five studies included in this meta-analysis (GetGoal-S, GetGoal-M, and GetGoal-M-Asia) and consisted of a 600-kcal liquid meal (400 mL of Ensure Plus; Abbott Nutrition, Columbus, OH) comprising 53.8% carbohydrate, 16.7% protein, and 29.5% fat, which was to be consumed within a 10-min period. Additional secondary endpoints across the five analysed studies included the following: the proportion of patients with HbA1c <7% or ≥7% at week 24, change from baseline in fasting plasma glucose at week 24, and the proportion of patients with fasting plasma glucose <110 mg/dL (6.1 mmol/L) or ≥110 mg/dL at week 24, and change in body weight from baseline to week 24.

Safety endpoints analysed in this meta-analysis were as follows: the prevalence of symptomatic hypoglycaemia at week 24, the number of symptomatic hypoglycaemia events per patient year (annualized rate), and the number

![Figure 1. Overall study design. OAD, oral anti-diabetic; R, randomized](image-url)
and proportion of patients with severe hypoglycaemia. Symptomatic hypoglycaemia was defined as an event with clinical symptoms consistent with a hypoglycaemic 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 an accompanying plasma glucose <60 mg/dL (3.3 mmol/L) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon injection if no plasma glucose value was available. Severe hypoglycaemia was defined as a hypoglycaemic event where the patient required assistance from another person because he or she could not self treat because of acute neurologic impairment resulting from hypoglycaemia, and where the event was associated with either plasma glucose <36 mg/dL (2.0 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or intramuscular glucagon administration.

In addition, composite safety/efficacy endpoints at 24 weeks that synthesized data from across the five studies were assessed only in this meta-analysis. These were as follows: HbA1c levels ≤7% and no symptomatic hypoglycaemia; HbA1c levels ≤7% and no weight gain; and HbA1c levels <7%, no weight gain, and no symptomatic hypoglycaemia.

### Statistical methods

#### Overall
Descriptive statistics were used to measure and describe clinical characteristics and patient demographics and to describe and measure the efficacy and hypoglycaemia outcome assessments. The number and proportion of patients were determined for dichotomous variables. The count, mean (standard deviation), and median were reported for continuous variables.

#### Meta-analysis statistical methods
For each outcome, the baseline and endpoint results for the lixisenatide and placebo treatment arms for each individual study group/clinical trial were compared with one another to determine the overall impact of lixisenatide treatment. Meta-analysis outcomes were assessed using a random effects model. Weighted mean differences with 95% confidence intervals (CIs) were determined for continuous data using the inverse variance method. Mantel–Haenszel odds ratios (ORs) for 95% CI were determined for all dichotomous outcome data. Quantification of heterogeneity was also examined with I² to measure the degree of total variation across studies due to heterogeneity and to establish the consistency of evidence. I² values >50% indicate a substantial level of heterogeneity. All meta-analyses were performed using RevMan, version 5.1, Copenhagen: Cochrane Collaboration. RevMan was also used to generate forest plots.

### Results

A total of 2760 subjects, composed of 1828 patients treated with lixisenatide plus oral anti-diabetics, and 932 patients who were administered placebo as add-on to oral anti-diabetics (comprising the sum of the ITT populations in the five studies) were included in this meta-analysis. Patient demographics and clinical characteristics were comparable in the lixisenatide plus oral anti-diabetics and placebo plus oral anti-diabetics groups (Table 1), except for the proportion of patients in each racial group, which differed between the lixisenatide and placebo arms (p < 0.0001).

#### Primary endpoint

In this meta-analysis, lixisenatide 20 µg once daily as add-on to oral anti-diabetics significantly reduced HbA1c compared with placebo plus oral anti-diabetics with an overall placebo-corrected treatment effect of −0.53% (p < 0.0001; Figure 2). Mean change at 24 weeks in HbA1c overall in the lixisenatide plus oral anti-diabetics and placebo arms (Table 1), except for the proportion of patients in each racial group, which differed between the lixisenatide and placebo arms (p < 0.0001).

### Table 1. Patient baseline demographics and clinical characteristics

| Parameter                          | Lixisenatide (n = 1828) | Placebo (n = 932) | p-value |
|------------------------------------|-------------------------|-------------------|---------|
| Age, mean (SD) years               | 55.5 (9.6)              | 56.3 (10.0)       | 0.0562  |
| Male, n (%)                        | 870 (47.6)              | 454 (48.7)        | 0.5777  |
| Race, n (%)                        | 1246 (68.2)             | 558 (59.9)        | 0.0001  |
| White                              | 1246 (68.2)             | 558 (59.9)        |         |
| Asian                              | 503 (27.5)              | 338 (36.3)        |         |
| Black/African American             | 44 (2.4)                | 22 (2.4)          |         |
| Other                              | 35 (1.9)                | 14 (1.5)          |         |
| BMI, mean (SD) kg/m²               | 31.6 (6.5)              | 31.3 (6.5)        | 0.2665  |
| BMI ≥30 kg/m², n (%)               | 984 (53.8)              | 477 (51.2)        | NA      |
| Weight, mean (SD) kg               | 86.5 (21.2)             | 85.8 (21.9)       | 0.4031  |
| OAD use, n (%)                     | 1685 (92.2)             | 863 (92.6)        | NA      |
| Metformin                          | 620 (33.9)              | 363 (39.0)        |         |
| Sulfonylurea                       | 308 (16.9)              | 148 (15.9)        |         |
| Thiazolidinedione                  | 1094 (56.9)             | 507 (52.3)        |         |
| Monotherapyb                       | 829 (43.1)              | 462 (47.7)        |         |
| Combination therapyb               | 8.1 (0.9)               | 8.1 (0.8)         | NA      |
| FPG, mean (SD) mg/dL              | 169.5 (39.9)            | 165.4 (38.3)      | NA      |

a Based on safety population data, lixisenatide n = 1923, placebo n = 969.

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Secondary endpoints

Treatment effects with lixisenatide plus oral anti-diabetics compared with placebo plus oral anti-diabetics in the key efficacy endpoints assessed in this meta-analysis are shown in Table 2. Compared with the placebo plus oral anti-diabetics group, a significantly higher proportion of patients treated with lixisenatide plus oral anti-diabetics achieved HbA1c <7% (23.9% and 43.6%, respectively; \( p < 0.0001 \)) (Table 3). Mean change from baseline to week 24 in 2-h post-prandial plasma glucose after a test meal was −103.71 mg/dL in the lixisenatide group versus −15.48 mg/dL in the placebo arm (\( p < 0.0001 \)). Change in fasting plasma glucose from baseline to week 24 was −18.10 mg/dL and −3.94 mg/dL for lixisenatide plus oral anti-diabetics and placebo plus oral anti-diabetics, respectively (\( p < 0.0001 \)). Mean body weight reduction from baseline at week 24 with lixisenatide plus oral anti-diabetics was 1.80 kg compared with 1.15 kg in patients who received placebo plus oral anti-diabetics (\( p < 0.0001 \)).

Hypoglycaemia

Overall, 94/1828 (5.1%) patients treated with lixisenatide plus oral anti-diabetics experienced symptomatic hypoglycaemia compared with 28/932 (3.0%) patients who were administered placebo as add-on to oral anti-diabetics [treatment effect OR: 1.6; 95% CI: 1.02, 2.50; \( p = 0.04 \)] . The mean (standard deviation) number of symptomatic hypoglycaemic events per patient year was 0.23 (1.37) versus 0.13 (0.88) for patients in the lixisenatide plus oral anti-diabetics versus placebo plus oral anti-diabetics groups (\( p = 0.04 \)). Severe hypoglycaemia occurred only in GetGoal-S (in which patients received lixisenatide or placebo as add-on to a sulfonylurea ± metformin), during which one event was reported in the group of patients treated with lixisenatide plus oral anti-diabetics compared with no event in the placebo plus oral anti-diabetics group (treatment effect OR: 1.52; 95% CI: 0.06, 37.32; \( p = 0.80 \)). Approximately 95% of patients treated with lixisenatide plus oral anti-diabetics did not experience symptomatic hypoglycaemia according to summated data in this meta-analysis.

Composite endpoints

Lixisenatide plus oral anti-diabetics was significantly more effective than placebo plus oral anti-diabetics at
achieving each of the composite endpoints \((p < 0.0001\) for all; Table 3). Patients treated with lixisenatide plus oral anti-diabetics were \(>2.5\) times more likely than those who were administered placebo plus oral anti-diabetics to achieve \(\text{HbA}_1c < 7\%\) with no weight gain, \(\text{HbA}_1c < 7\%\) with no symptomatic hypoglycaemia, and \(\text{HbA}_1c < 7\%\) with no weight gain or symptomatic hypoglycaemia (Figure 3).

### Discussion

Type 2 diabetes mellitus is a progressive disease, which necessitates treatment intensification with pharmacotherapies, additional to first-line oral anti-diabetics, to control rising glycaemia. Indeed, proactive treatment intensification is recommended \([1,11,12]\), but clinical inertia, patient resistance to change, and inadequate monitoring may mean that such intensification does not occur, resulting in periods of elevated plasma glucose \([13]\).

The efficacy of lixisenatide in combination with oral anti-diabetics has been assessed in five phase III studies in the GetGoal clinical programme. The results of this meta-analysis indicate that in patients with T2DM in whom treatment is insufficiently controlled with oral anti-diabetics, the addition of lixisenatide 20 \(\mu\)g once daily significantly reduced \(\text{HbA}_1c\) and fasting and post-prandial plasma glucose, and had a beneficial effect on body weight \textit{versus} placebo. Furthermore, lixisenatide plus oral anti-diabetics was \(>2.5\) times more likely to result in an \(\text{HbA}_1c < 7\%\) with no symptomatic hypoglycaemia and no weight gain \textit{versus} placebo plus oral anti-diabetics. A funnel plot was generated to investigate potential publication bias for the primary endpoint in this meta-analysis. The funnel plot indicated that the data in each study favoured lixisenatide. This finding is unsurprising, as trials included in this meta-analysis were taken from the phase III clinical trial programme for lixisenatide, in which lixisenatide demonstrated significant improvements \textit{versus} placebo in each of the large, randomized, controlled GetGoal trials.

There was a higher incidence of reported symptomatic hypoglycaemia with lixisenatide plus oral anti-diabetics \textit{versus} placebo plus oral anti-diabetics. GetGoal-M (an investigation of morning \textit{versus} evening dosing with lixisenatide) \([3]\) was the only study included in this meta-analysis where the increased occurrence of symptomatic hypoglycaemia approached significance, with the \(95\%\) CI just crossing the line of unity. The cause of the higher rates of hypoglycaemia with lixisenatide \textit{versus} placebo in GetGoal-M compared with the other trials included in this meta-analysis is unclear. However, in the GetGoal-X trial, in patients with T2DM receiving metformin, those receiving lixisenatide experienced significantly fewer incidences of symptomatic hypoglycaemia than those receiving exenatide (2.5\% \textit{vs} 7.9\%; \(p < 0.05\)) \([14]\). Out of all trials analysed, one patient in the lixisenatide group (in combination with a sulfonylurea) and none in the placebo group experienced severe hypoglycaemia.

One limitation of the current meta-analysis was the relatively short duration of the included GetGoal trials (24 weeks). Fifty-two-week extensions to a number of the GetGoal trials will provide data concerning long-term efficacy and safety of lixisenatide. Post-marketing studies are also underway in order to assess real-world efficacy and patient compliance with lixisenatide used in combination with oral anti-diabetics or basal insulin.

To our knowledge, this is the first meta-analysis of data concerning lixisenatide in combination with oral anti-diabetics, although a number of meta-analyses concerning other GLP-1 RAs as monotherapies or in combination with oral anti-diabetics have been performed previously in patients with T2DM \([15–17]\). To date, meta-analyses of

![Figure 3. Meta-analysis for HbA1c <7%, no weight gain, and no symptomatic hypoglycaemia for lixisenatide versus placebo (ITT population). CI, confidence interval; HbA1c, glycated haemoglobin; ITT, intent-to-treat; M–H, Mantel–Haenszel test; mITT, modified ITT.](image-url)
other GLP-1 RAs/OADs used in combination with metformin and sulfonylureas for treatment intensification have produced consistent findings. Meta-analyses of randomized controlled trials have revealed that therapy with metformin and a DPP-4 inhibitor results in better glycemic control [18,19] and greater reductions in fasting plasma glucose compared with metformin monotherapy [19]. Furthermore, although add-on treatment with sulfonylureas, glinides, thiazolidinediones, basal insulin, and biphasic insulin is associated with weight gain [20], DPP-4 inhibitors were weight neutral [15,20–22], and both alpha-glucosidase inhibitors [20–22] and GLP-1 RAs are commonly associated with some degree of weight loss [15,20–22]. Neither DPP-4 inhibitors nor GLP-1 RAs in combination with metformin were associated with an increase in the risk of hypoglycaemia [19,22]. Increased rates of the class-associated effect of gastrointestinal adverse events have been reported in meta-analyses of GLP-1 RAs plus oral anti-diabetics versus oral anti-diabetic monotherapy [15,17].

The choice of combination treatment used in patients with T2DM that can no longer be controlled with oral anti-diabetic monotherapy should be personalized towards the characteristics of their disease, taking into account pertinent factors such as their weight, the presence of comorbidities, and medication adverse event profiles. For example, extra-pancreatic adverse effects such as transient increased heart rate and acute renal injury have been reported with some GLP-1 RAs [23]. Treatment guidelines from both the American Diabetes Association and the American Association of Clinical Endocrinologists emphasize that medication selection for patients with T2DM should focus on reducing HbA1c to within guideline limits using individualization of treatment based on clinical characteristics [1,11,24].

The efficacy of the once-daily prandial agent lixisenatide plus oral anti-diabetics in the reduction of post-prandial plasma glucose excursions is notable; addressing both post-prandial and fasting plasma glucose is necessary to achieve sustained glycemic control, although the relative contributions of post-prandial and fasting plasma glucose to HbA1c change over time and vary with treatment [25,26]. A considerable proportion of patients with T2DM experience large post-prandial plasma glucose excursions, even if they have achieved fasting plasma glucose control; a prandial therapy is therefore important in these patients in order for them to achieve recommended HbA1c targets [27–30]. The once-daily prandial GLP-1 RA lixisenatide improves post-prandial plasma glucose excursions by slowing gastric emptying, which consequently prolongs absorption of meal-derived glucose [31], and by inhibiting post-prandial glucagon secretion. In the study of Kapitza et al. [32], lixisenatide was associated with greater improvements in post-prandial plasma glucose than liraglutide, with comparative reductions in both area under the curve (AUC) between 00:30–04:30 h and maximum post-prandial plasma glucose excursion (p < 0.0001 for both; 00:30 h = start of meal).

This meta-analysis demonstrated that lixisenatide in combination with oral anti-diabetic therapy had favourable effects on endpoints combining efficacy and safety parameters in patients with T2DM. These results indicate that lixisenatide plus oral anti-diabetics is a valuable treatment option for patients with T2DM inadequately controlled using oral agents alone. Future, directed studies in patients whose post-prandial plasma glucose excursions remain unaddressed by their current regimen would be useful to explore further the use of once-daily lixisenatide in these patients.

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**Conflicts of interest**

Denis Raccah has been a member of advisory boards and a speaker at symposia for Bristol-Myers Squibb, Eli Lilly, Medtronic, Merck Serono, MSD, Novartis, Novo Nordisk, and Sanofi. Pierre Gourdy has received consulting and lecture fees from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi, and a research grant from Sanofi. Luc Sagnard is a full-time employee of Sanofi. Antonio Cериello has acted on advisory boards for AstraZeneca/Bristol-Myers Squibb, Bayer Diagnostics, Medtronic, Sanofi, Takeda, Novartis, and Novo Nordisk and has received fees for consultancy from Eli Lilly, Bayer, Novo Nordisk, Sanofi, Novartis, AstraZeneca/Bristol-Myers Squibb, and Takeda.

**References**

1. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists’ comprehensive diabetes management algorithm 2013 consensus statement – executive summary. *Endocr Pract* 2013; 19: 536–557.

2. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive
summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD) (Suppl 1): S67–S74.

12. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364–1379.

13. Zinman B. Initial combination therapy for type 2 diabetes mellitus: is it ready for prime time? Am J Med 2011; 124: S19–S34.

14. Rosenstock J, Raccah D, Koranyi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin (GetGoal-L). Diabetes Care 2013; 36: 2489–2496.

15. Ravon CR, Mannucci E, Ahren B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes – a review and meta analysis. Diabetes Obes Metab 2012; 14: 762–767.

16. Esposito K, Mosca C, Brancario C, Chiodini P, Ceriello A, Giugliano D. GLP-1 receptor agonists and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Curr Med Res Opin 2011; 27: 1519–1528.

17. Wang Y, Li T, Yang M, Liu H, Boden G, Yang G. Glucagon-like peptide-1 receptor agonists versus insulin in inadequately controlled patients with type 2 diabetes mellitus: a meta-analysis of clinical trials. Diabetes Obes Metab 2011; 13: 972–981.

18. Poulsen N, Sukomboom N, Setwivattanakul W. Efficacy of various antidiabetic agents as add-on treatments to metformin in type 2 diabetes mellitus: systematic review and meta-analysis. ISRN Endocrinol 2012; 2012: 798146.

19. Wu D, Li L, Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Obes Metab 2014; 16: 30–37.

20. Phung OJ, Scholler JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010; 303: 1410–1418.

21. Gross DJ, Kramer CK, Leitao CB, et al. Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med 2011; 154: 672–679.

22. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycemic control, hypoglycemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes Obes Metab 2012; 14: 810–820.

23. Sequeira J, Gallwitz B. The extrapancreatic effects of GLP-1 receptor agonists: a focus on the cardiovascular, gastrointestinal and central nervous systems. Diabetes Obes Metab 2013. doi:10.1111/dom.12251.

24. Goldman-Levine JD. Beyond metformin: initiating combination therapy in patients with type 2 diabetes mellitus. Pharmacotherapy 2011; 31: 445–535.

25. Monnier I, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 2003; 26: 881–885.

26. Riddle M, Umpleyere G, DiGenio A, Zhou R, Rosenstock J. Contributions of basal and postprandial hyperglycemia over a wide range of A1C levels before and after treatment intensification in type 2 diabetes. Diabetes Care 2011; 34: 2508–2514.

27. Avignon A, Radauceanu A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. Diabetes Care 1997; 20: 1822–1826.

28. Bouma M, Dekker JH, de Sonnaville JJ, et al. How valid is fasting plasma glucose as a parameter of glycemic control in non-insulin-using patients with type 2 diabetes? Diabetes Care 1999; 22: 904–907.

29. Soonthornpun S, Rattarasarn C, Leelawattana R, Setasuban W. Postprandial plasma glucose: a good index of glycemic control in type 2 diabetic patients having near-normal fasting glucose levels. Diabetes Res Clin Pract 1999; 46: 23–27.

30. Verges B. The impact of prandial glucose regulation in practice. Diabetes Nutr Metab 2002; 15: 28–32.

31. Lorenz M, Pfeiffer C, Steinstrasser A, et al. Effects of lixisenatide once daily on gastric emptying in type 2 diabetes – relationship to postprandial glycaemia. Regul Pept 2013; 185C: 1–8.

32. Kapitza C, Forst T, Coester HV, Poiriers F, Ruus P, Hincelin-Mery A. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. Diabetes Obes Metab 2013; 15: 642–649.