Glucagon-like peptide-1 receptor agonists: Are they all the same?

Debbie Hicks, Jill Hill, June James, Anna Reid, Grace Vanterpool, on behalf of TREND-UK

Citation: Hicks D, Hill J, James J et al (2014) Glucagon-like peptide-1 receptor agonists: Are they all the same? *Diabetes & Primary Care* **16**: 254–8

Glucagon-like peptide-1 receptor agonists are proving useful for lowering blood glucose levels, especially when the target need is excessive postprandial hyperglycaemia. With four of these agents available in the UK, there is a choice as to which one to prescribe. This article examines the factors that might influence individual prescribing decisions.

Article points

1. Glucagon-like 1 (GLP-1) receptor agonists mimic the natural action of GLP-1 to stimulate insulin production, inhibit glucagon release, delay gastric emptying and increase satiety.
2. There are four GLP-1 receptor agonists currently available in the UK; all can be used to significantly lower both postprandial and, to some extent, fasting plasma glucose.
3. While their mechanism of action is similar, there are some differentiating points – including timing of administration and co-prescribing with other antidiabetes agents – that can help in making the right choice of GLP-1 receptor agonist for the individual.

Key words

- GLP-1 receptor agonists
- Incretin effect
- Postprandial hyperglycaemia

Authors

Debbie Hicks is a Nurse Consultant – Diabetes, Barnet, Enfield and Haringey Mental Health Trust. Jill Hill is a Diabetes Specialist Nurse, Shropshire. June James is a Nurse Consultant in Diabetes, University Hospitals of Leicester NHS Trust. Anna Reid is a Nurse Consultant – Diabetes, Guy's and St Thomas' NHS Foundation Trust. Grace Vanterpool is a Diabetes Nurse Consultant, London.

HbA_{1c} is the universally accepted marker of average blood glucose levels used to help diagnose type 2 diabetes, and to aid treatment adjustment if required (World Health Organization, 2011). Monnier et al (2003) demonstrated that fasting hyperglycaemia is the major contributor to HbA_{1c} with poorly controlled diabetes, while postprandial hyperglycaemia is the major contributor in people nearing HbA_{1c} goals. Therefore, separate measurements of fasting and postprandial glucose levels can provide guidance for which therapies are likely to benefit the individual, depending on need.

To improve glycaemic control to the near-normal range, people with type 2 diabetes are initially treated using oral antidiabetes agents, with lifestyle changes such as diet and exercise being an integral part of managing the condition. When these measures fail to control blood glucose levels adequately, the traditional approach has been to introduce insulin therapy into an individual's regimen; however, this regimen change may be delayed owing to psychological factors such as fear of hypoglycaemia and weight gain (Gherman et al, 2011). A relatively recent addition to the treatment armamentarium are the glucagon-like peptide-1 (GLP-1) receptor agonists.

GLP-1 receptor agonists: Incretin mimetics

In the 1960s, data suggested that oral glucose elicited a much greater secretion of insulin than when intravenously administered and that this potentiation by the gut of insulin secretion may be responsible for up to 70% of the insulin response to a meal (Elrick et al, 1964). This physiological activity was named the *in*testinal s*ecreti*on of *in*sulin, or *incretin*, effect and is much diminished or even lost in people with type 2 diabetes. Two hormones, gastric inhibitory polypeptide and GLP-1, are responsible for this effect (Drucker and Nauck, 2006).

GLP-1 receptor agonists mimic endogenous GLP-1 by interacting with GLP-1 receptors and stimulating insulin production from pancreatic beta-cells when blood glucose levels are increased. They also inhibit hepatic glucagon release, delay gastric emptying and increase satiety (Drucker and Nauck, 2006). These actions are glucose dependent and so will not be activated in the absence of carbohydrates or when blood glucose is within the normal range (Pratley and Gilbert, 2008).

While the primary effect of GLP-1 receptor agonists is attenuation of postprandial glucose excursions, they can also lower fasting plasma glucose (FPG) levels (Owens et al, 2013). In general, the continuously acting GLP-1 receptor agonists liraglutide and exenatide prolonged release have a greater ability to lower FPG than the shorter-acting agents exenatide (administered twice daily) and lixisenatide (Lund et al, 2014). Another beneficial aspect of GLP-1 receptor agonists is their potential to cause weight loss (Lund et al, 2014). This is in contrast to sulphonylureas, pioglitazone and insulin, which may encourage weight gain, a situation not ideal in those already overweight or obese (Inzucchi et al, 2012), and similar to sodium–glucose cotransporter 2 (SGLT2) inhibitors (Abdul-Ghani et al, 2012).

There is some debate about whether GLP-1 receptor agonists provide distinct cardiovascular

Table 1. Product characteristics of the glucagon-like peptide-1 receptor agonists currently available in the UK (electronic Medicines Compendium, 2014a; 2014b; 2014c; 2014d; 2014e).

Agent	Dosage and administration	Licensed* for use in combination with…	Renal/hepatic impairment	Cautions for each agent (see below for additional cautions covering all agents)
Exenatide twice daily (Byetta®)	• Prefilled pens for injection – 5 µg or 10 µg solution • Administer up to 60 minutes before eating • Do not give injections less than 6 hours apart	• Metformin, a sulphonylurea† or pioglitazone • Metformin + a sulphonylurea† or pioglitazone • Basal insulin +/- metformin and/or pioglitazone	• Careful dose escalation in moderate renal impairment (CrCl 30–50 mL/min) • Not recommended in severe renal impairment or end-stage renal disease (CrCl <30 mL/min) • No dose adjustment in hepatic impairment	• Dose of basal insulin may need evaluating and reducing in those at risk of hypoglycaemia • Use with caution, with careful dose escalation, in those aged >70 years • As exenatide can slow gastric emptying, may reduce extent/rate of absorption of oral medicinal products that require rapid GI absorption
Exenatide prolonged release (Bydureon®)	• 2 mg powder and solvent for injection • Administered once weekly, same day each week at any time • Leave at least 7 days between doses if day needs changing	• Metformin, a sulphonylurea† or pioglitazone • Metformin + a sulphonylurea† or pioglitazone	• Not recommended in those with moderate (CrCl 30–50 mL/min) or severe (CrCl <30 mL/min) renal impairment or end-stage renal disease • No dose adjustment in hepatic impairment	• If switching from exenatide twice daily, may experience transient blood glucose elevations that generally improve within first 2 weeks
Liraglutide (Victoza®)	• 6 mg/mL solution for injection in prefilled pen • Up to 1.8 mg administered once daily at any time (NICE does not recommend over 1.2 mg [NICE, 2010])	• Oral glucose-lowering products† • Basal insulin + oral glucose-lowering products†	• People with mild renal impairment (CrCl 60–90 mL/min) may experience more GI effects • Not recommended in those with moderate (CrCl 30–59 mL/min) or severe (CrCl <30 mL/min) renal impairment or end-stage renal disease • Therapeutic experience in those with mild, moderate or severe hepatic impairment currently too limited to recommend to such individuals	• Dose of basal insulin may need evaluating and reducing in those at risk of hypos • Patients aged >70 years may experience more GI effects • Not recommended in those with congestive heart failure, inflammatory bowel disease or diabetic gastroparesis • Use with caution in those with pre-existing thyroid disease
Lixisenatide (Lyxumia®)	• 10 µg or 20 µg solution for injection • Initiated at 10 µg, up to 20 µg administered once daily within the hour prior to any meal, preferably before the same meal each day	• Oral glucose-lowering products† • Basal insulin + oral glucose-lowering products (except a sulphonylurea)	• Use in caution in moderate renal impairment (CrCl 30–50 mL/min) • Not recommended in severe renal impairment (CrCl <30 mL/min) or end-stage renal disease • No dose adjustment in hepatic impairment	• Should not be used with a sulphonylurea + basal insulin owing to hypoglycaemia risk • Not recommended in those with gastroparesis • As lixisenatide can slow gastric emptying, may reduce extent/rate of absorption of oral medicinal products that require rapid GI absorption

Very common side effects (≥1/10):
- *With all*: nausea and diarrhoea (should reduce over time; and most are mild to moderate)
- *With all except liraglutide*: hypoglycaemia in some combined regimens and vomiting (both common [≥1/100 to <1/10] with liraglutide)
- *Only with exenatide prolonged release*: constipation and injection site pruritus
- *Only with lixisenatide*: headache

Clinical experience is very limited in people aged >75 years

If there is severe abdominal pain, seek urgent medical review to rule out acute pancreatitis

†Owing to increased risk of hypoglycaemia, reduction in sulphonylurea dose may be necessary if combined with a GLP-1 receptor agonist

Cautions for all:
- Monitor International Normalized Ratio during initiation of GLP-1 receptor agonists if on warfarin/cumarol derivative (plus during escalation of exenatide twice daily or ending of lixisenatide)
- Individuals should be advised of potential dehydration risk in relation to GI side effects and take precautions to avoid fluid depletion

Contraindicated in: type 1 diabetes; children; as treatment for diabetic ketoacidosis; history of pancreatitis; severe gastrointestinal disease; women planning pregnancy or not taking contraception; and during pregnancy and breastfeeding

*Licensed for use as part of combination therapy for adults who have not achieved adequate glycaemic control with these agents and diet and exercise. CrCl=creatinine clearance; GI=gastrointestinal.

Page points

1. There are four currently available glucagon-like peptide-1 receptor agonists in the UK, all of which are administered via subcutaneous injection.
2. A number of ongoing trials are looking specifically at cardiovascular outcomes, but no conclusions can currently by drawn.

benefits such as blood pressure decreases, lipid profile improvement and better endothelial and myocardial function. While clinical studies suggest that these agents can modestly but significantly lower systolic blood pressure (electronic Medicines Compendium [eMC], 2014a; 2014b; 2014c; 2014d; 2014e), results from randomised trials on cardiovascular mortality are not yet available. A number of ongoing trials are looking specifically at cardiovascular outcomes, but no conclusions can currently be drawn (Ryder, 2013). The positive impact on cardiovascular risk factors would certainly be advantageous for individuals with type 2 diabetes as the condition is often associated with hypertension, dyslipidaemia and obesity (Stranges and Khanderia, 2012).

The different agents

There are four currently available GLP-1 receptor agonists in the UK, all of which are administered via subcutaneous injection. They have a similar mode of action, with slight variations, but differ in their dosing schedules. Exenatide (Byetta®), the first in this class of drug to be launched in the UK (in 2007), is administered twice daily. This agent has since been joined in the class by exenatide prolonged release (Bydureon®), a once-weekly formulation, as well as the once-daily agents liraglutide (Victoza®) and lixisenatide (Lyxumia®; eMC 2014a; 2014b; 2014c; 2014d; 2014e). Albiglutide and dulaglutide, both with once-weekly formulations, are due to be launched in the near future (Lund, 2014).

Table 1 details some of the prescribing information for each of these agents. Choice of whether to use a GLP-1 receptor agonist, and which agent to use, may depend on: the other antidiabetes medications that a person is taking (all except exenatide prolonged release have a licence to be used with insulin); whether or not the person has renal impairment (and what stage it is); and whether there are any contraindicating factors.

The NICE (2009) type 2 diabetes guidelines only include exenatide twice daily (NICE, 2009), but the body has since published technology appraisals for liraglutide (NICE, 2010) and exenatide prolonged release (NICE, 2012) and an evidence summary for lixisenatide (NICE, 2013). *Table 2* summarises NICE recommendations on when each agent can be prescribed in relation to other antidiabetes drugs.

Table 2. Summary of NICE recommendations for glucagon-like peptide-1 receptor agonist prescribing (NICE, 2009; 2010; 2012; 2013).

Agent	Recommendation
Exenatide	• Third line after metformin and a sulphonylurea
Exenatide prolonged release Liraglutide	• Dual therapy with metformin or a sulphonylurea if intolerant of one or other agent and of pioglitazone and dipeptidyl peptidase-4 inhibitors, or if there are contraindications • Triple therapy with metformin plus a sulphonylurea or pioglitazone
Lixisenatide	• No specific guidance; effectiveness evaluated in combination with metformin, pioglitazone, or basal insulin with or without metformin

Glucagon-like peptide-1 receptor agonist therapy should only be considered when control of blood glucose remains inadequate with oral antidiabetes therapy and the person has:

- A BMI ≥35 kg/m² in people of European descent (with appropriate adjustment for other ethnic groups) and there are problems associated with high weight
- *OR* a BMI <35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities

The benefit of these agents should be evaluated after 6 months and they should only be continued if there is a reduction in HbA_{1c} of at least 11 mmol/mol (1 percentage point) *AND* in body weight of at least 3%

Efficacy

While all of the GLP-1 receptor agonists have been shown to significantly reduce HbA_{1c} compared with a placebo, it is interesting to also consider if there are differences when comparing between different agents. There have only been a handful of such studies, the majority of which have compared exenatide in one or other of its formulations. While no significant differences were found between exenatide twice-daily and lixisenatide (Rosenstock et al, 2013), two studies found liraglutide to lower HbA_{1c} to a significantly greater extent compared with either exenatide formulation (Buse et al, 2009; 2013). However, in the one comparing liraglutide with exenatide twice daily, there were no differences between the agents with regard to postprandial measures (Buse et al, 2009). Furthermore, while the study comparing liraglutide with exenatide prolonged release favoured the former (Buse et al, 2013), an independent meta-analysis of randomised controlled trials of GLP-1 receptor agonists did not identify any significant differences in lowering of HbA_{1c} between these agents, suggesting they led to similar glycaemic effects (Scott et al, 2013).

Safety and tolerability

The most frequently reported adverse events with GLP-1 receptor agonists are gastrointestinal,

including nausea, vomiting and diarrhoea; however, few people discontinue as a result of these events (Heine et al, 2005; Buse et al, 2011; 2013; Riddle et al, 2013a, 2013b; Rosenstock et al, 2013; eMC, 2014a; 2014b; 2014c; 2014d; 2014e; see *Table 3*). Nausea, the commonest adverse event, is most likely to occur after initiation and then typically subsides relatively quickly. For instance, in a study of lixisenatide and exenatide twice daily, nausea occurred most frequently in the first few weeks but was very limited by 8 weeks (Rosenstock et al, 2013).

In head-to-head studies, nausea was found to be higher with exenatide twice daily compared with the prolonged-release formulation (34.5% versus 26.4%; Drucker et al, 2008) or with lixisenatide (35.1% versus 24.5%; Rosenstock et al, 2013). In a study comparing exenatide twice daily and liraglutide, occurrences were similar initially (28.0% and 25.5%, respectively) but took longer to subside with exenatide (Buse et al, 2009). However, when comparing liraglutide with exenatide prolonged release, less nausea was found with the latter (21% versus 9%; Buse et al, 2013). Useful tips to help combat nausea are shown in *Box 1*.

Fear of hypoglycaemia can be a major concern for people commencing insulin therapy (Gherman et al, 2011). With GLP-1 receptor agonists, incidences of hypoglycaemia, especially major hypoglycaemia, are relatively low, when used as monotherapy or with some oral antidiabetes agents, including metformin (Heine et al, 2005; Buse et al, 2013; Rosenstock et al, 2013). However, the incidence of hypoglycaemia can increase when combined with a sulphonylurea or basal insulin (Buse et al, 2011; 2013; Riddle et al, 2013a; 2013b; see *Table 3*). If a GLP-1 receptor agonist is given in combination with a sulphonylurea, the dose should be at least temporarily reduced and the person monitored. When a GLP-1 receptor agonist is combined with basal insulin, the insulin dose should be evaluated and reduced if necessary (eMC, 2014a; 2014b; 2014c; 2014d; 2014e).

A potential relationship between treatment with GLP-1 receptor agonists and acute pancreatitis has been the subject of recent debate. The agents' summaries of product characteristics do report a risk of developing this condition, albeit a rare one (eMC, 2014a; 2014b; 2014c; 2014d; 2014e). In 2013, however, the European Medicines Agency (EMA) published an assessment on GLP-1-based therapies in which it examined the incidence of acute pancreatitis, as reported in a journal article, as well as other clinical data. They concluded that currently available data "do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines" (EMA, 2013).

The characteristic symptom of acute pancreatitis is persistent, severe abdominal pain. If an individual experiences this they should stop using the GLP-1 receptor agonist and urgently seek medical help. If it is acute pancreatitis then the person cannot be restarted on GLP-1 receptor agonist therapy. These agents are not suitable for someone with a history of pancreatitis (eMC, 2014a; 2014b; 2014c; 2014d; 2014e).

Another adverse event associated with injectable therapies are injection site reactions. With GLP-1 receptor agonists these are usually mild (see *Table 3*), with most individual nodules being asymptomatic and resolving. They are most frequently observed with exenatide prolonged release and are consistent with the known properties of poly(D,L-lactide-*co*-glycolide) polymer microsphere formulations, which allow the GLP-1 receptor agonist to be absorbed over a week's duration (eMC, 2014a). This should be discussed with all individuals suitable for prolonged-release formulations of GLP-1 receptor agonists.

Table 3. Selected adverse event data from summaries of product characteristics (electronic Medicines Compendium, 2014a; 2014b; 2014c; 2014d; 2014e).*

Agent	Hypoglycaemia (all levels combined unless otherwise stated)	Nausea, at least one episode	Injection site reaction
Exenatide	• + pioglitazone +/- metformin: 11% (PB: 7%) • + SU: 23.5% (PB: 12.6%) • + SU and metformin: 25.2% (PB: 3.3%) • + basal insulin: 25% (PB 29%)	• 40–50% • 4% withdrew	5.1%
Exenatide prolonged release	• Monotherapy: 2.2% • + SU: 15.9%	• 20% • <1% withdrew	16%
Liraglutide	• Monotherapy: no major episodes • + SU: 0.02 major events/subject-year • + basal insulin: 1.0 events/subject-year	• + metformin: 20.7% • 2.8 % withdrew	2%
Lixisenatide	• Monotherapy: 1.7% (PB: 1.6%) • Monotherapy severe: 0.4% (PB: 0.2%) • + SU: 22.7% (PB: 15.2%) • + SU and basal insulin: 47.2% (PB: 21.6%)	• 26.1% (PB: 6.2%) • 3.1% withdrew	3.9% (PB: 1.4%)

***Owing to variations in the nature of the various studies from which the data were collected, this table is presented for illustrative purposes as opposed to strict comparisons between the agents.**

SU=sulphonylurea; PB=placebo.

Box 1. Useful tips when using GLP-1 receptor agonist therapy.

The therapeutic response from GLP-1 receptor agonist therapy means that patients taking this medication may feel nauseous. There are some simple steps to alleviate this, including:

- Stop eating when you feel full; don't clear your plate out of habit
- Try using a smaller plate to encourage smaller portions
- Cut down on fatty foods
- Avoid foods and smells that make you feel worse; have someone else cook, if possible
- Food containing ginger may be helpful
- Wear comfortable clothes; tight waistbands can make you feel worse

GLP=glucagon-like peptide.

Other concerns include cardiovascular safety, but while current clinical trial results do not suggest adverse cardiovascular effects (eMC, 2014a; 2014b; 2014c; 2014d; 2014e), ongoing outcome studies will provide a more robust evaluation (Ryder, 2013). These outcome studies will also be reporting on incidences of pancreatic and thyroid cancer (Ryder, 2013). With regard to any potential malignancy, while rat studies have shown a link between long-term, very-high-dose GLP-1-receptor agonist administration and non-lethal thyroid C-cell tumours, current studies in humans do not suggest any such link (eMC, 2014a; 2014b; 2014c; 2014d; 2014e). There is also no direct evidence, from both animal and human studies, of a link between GLP-1 receptor agonists and the development of pancreatic cancer (Ryder, 2013).

Summary

GLP-1 receptor agonists are effective in improving glycaemic control, and while they are not clinically indicated for weight loss, this may be an additional benefit. The practice of using GLP-1 receptor agonists with insulin is becoming more common as this allows blood glucose levels to be reduced while potentially negating weight gain experienced with insulin therapy. Patients commenced on GLP-1 receptor agonist therapy need the right information and support to help ensure that they get the maximum benefit. ■

Abdul-Ghani MA, Norton L, DeFronzo RA (2012) Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. *Curr Diab Rep* **12**: 230–8

Buse JB, Rosenstock J, Sesti G et al (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group multinational, open-label trial (LEAD-6). *Lancet* **374**: 39–47

Buse JB, Bergenstal RM, Glass LC et al (2011) Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med* **154**: 103–12

Buse JB, Nauck M, Forst T et al (2013) Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* **381**: 117–24

Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* **368**: 1696–705

Drucker DJ, Buse JB, Taylor K et al (2008) Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* **372**: 1240–50

electronic Medicines Compendium (2014a) *BYDUREON 2 mg powder and solvent for prolonged-release suspension for injection*. eMC, Leatherhead. Available at: http://bit.ly/1AugZMe (accessed 14.08.14)

electronic Medicines Compendium (2014b) *Byetta 5 micrograms solution for injection, prefilled pen. Byetta 10 micrograms solution for injection, prefilled pen*. eMC, Leatherhead. Available at: http://bit.ly/1kR70N3 (accessed 14.08.14)

electronic Medicines Compendium (2014c) *Lyxumia 10 micrograms solution for injection*. eMC, Leatherhead. Available at: http://bit.ly/VBGL1o (accessed 14.08.14)

electronic Medicines Compendium (2014d) *Lyxumia 20 micrograms solution for injection*. eMC, Leatherhead. Available at: http://bit.ly/1sRv0lX (accessed 14.08.14)

electronic Medicines Compendium (2014e) *Victoza 6 mg/ml solution for injection in pre-filled pen*. eMC, Leatherhead. Available at: http://bit.ly/1jxhIYs (accessed 14.08.2014)

Elrick H, Stimmler L, Hlad Jr CJ et al (1964) Plasma insulin response to oral and intravenous glucose administration. *J Clin Endocrinol Metab* **24**: 1076–82

European Medicines Agency (2013) *Investigation into GLP-1 based diabetes therapies concluded. Press Release 26.July.2013*. Available at: http://bit.ly/1o8MiDy (accessed 12.08.14)

Gherman A, Veresiu IA, Sassu RA et al (2011) Psychological insulin resistance: a critical review of the literature. *Practical Diabetes International* **28**: 125–8

Heine RJ, Van Gaal LF, Johns D et al (2005) Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes. A randomized trial. *Ann Intern Med* **143**: 559–69

Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* **35**: 1364–79

Lund A, Knop FK, Vilsbøll T (2014) Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes: differences and similarities. *Eur J Intern Med* **25**: 407–14.

Monnier L, Lapinski H, Collette C et al (2003) Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycaemia of Type 2 diabetic patients. Variations with increasing levels of HbA_{1c}. *Diabetes Care* **26**: 881–5

NICE (2009) *Type 2 diabetes: The management of type 2 diabetes* (CG87). NICE, London. Available at: http://www.nice.org.uk/guidance/cg87 (accessed 14.08.14)

NICE (2010) *Liraglutide for the treatment of type 2 diabetes mellitus* (TA203). NICE, London. Available at: http://www.nice.org.uk/guidance/ta203 (accessed 14.08.14)

NICE (2012) *Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes* (TA248). NICE, London.Available at: http://www.nice.org.uk/guidance/ta248 (accessed 14.08.14)

NICE (2013) Type 2 diabetes: lixisenatide (ESNM26). NICE, London. Available at: http://www.nice.org.uk/advice/ESNM26 (accessed 14.08.14)

Owens DR, Monnier L, Bolli GB (2013) Differential effects of GLP-1 receptor agonists on components of dysglycaemia in individuals with type 2 diabetes mellitus. *Diabetes Metab* **39**: 485–96

Pratley RE, Gilbert M (2008) Targeting incretins in type 2 diabetes: role of GLP-1 receptor agonists and DPP-4 inhibitors. *Rev Diabet Stud* **5**: 73–94

Riddle MC, Aronson R, Home P, et al (2013a) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin. A 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care* **36**: 2489–96

Riddle MC, Forst T, Aronson R, et al (2013b) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine. A 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). *Diabetes Care* **36**: 2497–503

Rosenstock J, Raccah D, Korányi L et al (2013) Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin. A 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care* **36**: 2945–51

Ryder RE (2013) The potential risks of pancreatitis and pancreatic cancer with GLP-1-based therapies are far outweighed by the proven and potential (cardiovascular) benefits. *Diabet Med* **30**: 1148–55

Scott DA, Boye KS, Timlin L et al (2013) A network meta-analysis to compare glycaemic control in patients with type 2 diabetes treated with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily or placebo. *Diabetes Obes Metab* **15**: 213–23

Stranges P, Khanderia U (2012) Diabetes and cardiovascular disease: focus on glucagon-like peptide-1 based therapies. *Ther Adv Drug Saf* **3**: 185–201

World Health Organization (2011) *Use of glycated haemoglobin (HbA_{1c}) in the diagnosis of diabetes mellitus*. WHO, Geneva, Switzerland. Available at: http://bit.ly/1p944Mb (accessed 14.08.2014)