Incretin therapy for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors

Bo Ahrén, MD, PhD, Department of Clinical Sciences Lund, Lund University, Sweden

Correspondence to: Bo Ahrén, MD, PhD, Department of Clinical Sciences Lund, Lund University, B11 BMC, SE-221 84 Lund, Sweden; email: Bo.Ahren@med.lu.se

Received: 2 December 2012
Accepted: 5 December 2012

Summary

Incretin therapy is a glucose-lowering therapy which has attracted great interest during recent years. It is based on the antidiabetic action of the incretin hormone glucagon-like peptide-1 (GLP-1), which involves both stimulation of insulin secretion and inhibition of glucagon secretion. This results in lowering of both fasting and postprandial glycaemia. Incretin therapy is either with GLP-1 receptor agonists or with inhibitors of dipeptidyl peptidase-4 (DPP-4), which is the enzyme which inactivates endogenous GLP-1. The GLP-1 receptor agonists are injected subcutaneously once or twice daily or once weekly. The DPP-4 inhibitors are oral tablets taken once or twice daily. Both therapies reduce HbA_{1c} without weight gain, and for GLP-1 receptor agonists with a weight reduction. Incretin therapy is safe with very few adverse events and an additional value of the therapy is a very low risk for hypoglycaemia. Incretin therapy is efficient both in monotherapy and in combination with metformin, sulphonylureas, thiazolidinediones and insulin. Its main indication is as add-on to metformin in patients who are insufficiently controlled on metformin alone, and an important indication is also in combination with insulin therapy. The experienced value of incretin therapy for patient care will most likely result in increased use of this therapy during the coming years.

Eur Diabetes Nursing 2013; 10(1): 31–36

Key words

incretin hormones; GLP-1; DPP-4; treatment; type 2 diabetes

Introduction

Incretin therapy is an exciting novel glucose-lowering therapy in type 2 diabetes. It targets the dysfunction of the pancreatic islets, which is the pathophysiology of the disease, and it reduces both fasting and postprandial glucose with at the same time a very low risk for hypoglycaemia and no weight gain.

Incretin therapy is based on the incretin hormone glucagon-like peptide-1 (GLP-1), which is released from endocrine cells in the gut during and after meal ingestion. GLP-1 contributes to the incretin effect, which is the large insulin secretion after meal ingestion, and which is attributed to augmented glucose-stimulated insulin secretion by intestinal hormones.[1] GLP-1 stimulates insulin secretion and inhibits glucagon secretion through glucose-dependent mechanisms.[1,2] GLP-1 also causes a delay in gastric emptying[3] and induces satiety through a central effect in the hypothalamus.[4] All these effects are of potential value in the treatment of type 2 diabetes, which initiated the development of GLP-1 based therapy for the disease.[5]

The first study demonstrating that GLP-1 had the potential as an anti-diabetogenic agent showed, in 1992, that the hormone reduced insulin requirement after meal ingestion in type 2 diabetes.[6]

The antidiabetic action of GLP-1 was later confirmed in several other studies, including a six-week study using continuous subcutaneous infusion of GLP-1 in subjects with type 2 diabetes showing improved glycaemia and reduced body weight.[7] A challenge in the early development of GLP-1 as a therapy was that the hormone is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).[8] This enzyme is produced in the endothelial cells and rapidly inactivates GLP-1, making the circulating half-life of the native hormone only 1–2 minutes. To overcome this challenge, the two strategies for incretin therapy were developed: DPP-4 resistant GLP-1 receptor agonists and DPP-4 inhibitors.[9]

GLP-1 receptor agonists

Today, several GLP-1 receptor agonists exist.[10] The first to be approved for clinical use was exenatide, which is the synthetic recombinant form of the peptide exendin-4 having approximately 50% similarity to GLP-1. The original exenatide formulation (Byetta) is injected subcutaneously (SC) twice daily. Recently, a longer-acting formulation of exenatide has been developed (Bydureon) in which exenatide is incorporated into microspheres consisting of biodegradable polymers. These microspheres are slowly degraded after SC injection allowing exenatide to be slowly released, resulting in a stable concentration after once-weekly injections.[11]

The first GLP-1 analogue to be developed was liraglutide (Victoza). In liraglutide, a fatty acid is bound to a slightly modified GLP-1 molecule, which results in a delay in the absorption from the subcutaneous space resulting in a prolonged half-life allowing once-daily injection.[12]

Both exenatide and liraglutide reduce fasting and prandial glucose and body weight when used as add-on to metformin, sulphonylurea and thiazolidinedione, resulting in reduced HbA_{1c}.[11,12] In most studies, HbA_{1c} is reduced by ≈0.8–1.5% (8–15mmol/mol) from baseline

values of 7.5–8.5% (58–69mmol/mol). Furthermore, body weight is reduced by GLP-1 receptor agonists by approximately 3–5kg.

GLP-1 receptor agonists are safe and highly tolerable with a notable low risk for hypoglycaemia. The only consistent adverse events are nausea and vomiting, which are most common in the early weeks after start of therapy and subside thereafter. GLP-1 receptor agonists may also result in reactions at the site of injection, which is more common with the exenatide once weekly having a larger gauge-needle.

A few studies have directly compared the efficacy of different GLP-1 receptor agonists. One study showed that exenatide once weekly is more potent than exenatide twice daily in reducing HbA_{1c} when added to either drug-naïve patients or patients on oral antihyperglycaemic agents, whereas no difference was observed in the reduction of body weight.[13] Another study showed that liraglutide is more potent than exenatide once weekly in reducing HbA_{1c} when added to either drug-naïve patients or patients on oral antihyperglycaemic agents, whereas the body weight reduction is not different between them.[14] Another recent analysis of potential differentiation between various GLP-1 receptor agonists suggests that the short-acting forms are more potent in reducing postprandial glycaemia whereas the long-acting forms are more potent in reducing fasting glucose.[15] However, more direct head-to-head studies are required in order to establish differences between the various GLP-1 receptor agonists.

DPP-4 inhibitors

DPP-4 inhibitors prevent the inactivation of GLP-1, resulting in prolonged high postprandial GLP-1 levels.[9] This in turn results in higher insulin levels, in relation to circulating glucose, and reduced glucagon levels, which reduce fasting and postprandial glycaemia.

The first study showing the potential of using DPP-4 inhibition in the therapy of type 2 diabetes examined the DPP-4 inhibitor NVP-DPP728 over a four-week period and showed that both fasting and prandial glucose as well as HbA_{1c} were reduced.[16] Several DPP-4 inhibitors are now in clinical use in a number of countries, such as sitagliptin (Januvia), vildagliptin (Galvus), saxagliptin (Onglyza) and linagliptin (Trajenta). There are differences between them in chemical structure, pharmacokinetic properties, metabolism and mode of elimination.[17] From a practical point of view, this has implications for the dosing interval (either once or twice daily) and dosing in patients with renal impairment (with recommended dose reduction for DPP-4 inhibitors which are renally excreted).

DPP-4 inhibitors are indicated for use as monotherapy as well as in combination with metformin, sulphonylurea, thiazolidinedione and insulin. Under all these conditions, there is improvement in glycaemia without weight gain (or a slight weight reduction) and with a very low risk for adverse events, including hypoglycaemia. The reduction in HbA_{1c} is in most studies in the range of 0.6–1.1% (6–11mmol/mol) from baseline values of 7.5–8.5% (58–69mmol/mol).[18–20]

Variable	GLP-1 receptor agonists	DPP-4 inhibitors
Mode of administration	Subcutaneous injection	Oral tablet
Degree of GLP-1 stimulation	Pharmacological	Physiological
Insulin secretion	Stimulation	Stimulation
Glucagon secretion	Inhibition	Inhibition
Gastric emptying	Delay	No effect
Fasting and prandial glucose	Reduction	Reduction
HbA_{1c}	Lowered by ≈0.8–1.5% (8–15mmol/mol)*	Lowered by ≈0.6–1.1% (6–11mmol/mol)*
Body weight	Lowered by ≈3–5kg	No change or lowered by ≈1kg
Risk of hypoglycaemia	Low	Low
Adverse events	Nausea or vomiting in the beginning of therapy	Low risk

*Effect on HbA_{1c} dependent on the baseline HbA_{1c}.

Table 1. Summary of similarities and differences between GLP-1 receptor agonists and DPP-4 inhibitors

GLP-1 receptor agonists versus DPP-4 inhibitors

Table 1 shows the summarised experience when comparing GLP-1 receptor agonists and DPP-4 inhibitors. There are main similarities between the two strategies, e.g. both target the

	No. of patients	Baseline HbA_{1c}	Change in HbA_{1c}	Hypoglycaemia (% of patients)	Ref no.
Exenatide (10µg BID) Placebo	113 113	8.2% 8.2%	-0.8 -0.1	5.3 5.3	25
Exenatide QW (no placebo)	160	8.6%	-1.4	1.3	58
Liraglutide (1.8mg QD) Placebo	242 121	8.4% 8.4%	-1.2 -0.1	3.0 3.0	26
Sitagliptin (100mg QD) Placebo	453 224	8.0% 8.0%	-0.7 -0.0	1.3 2.1	27
Vildagliptin (50mg BID) Placebo	175 171	8.4% 8.3%	-0.5 +0.9	0.5 0.5	28
Saxagliptin (5mg QD) Placebo	186 175	8.1% 8.1%	-0.7 -0.1	0.5 0.6	29
Linagliptin (5mg QD) Placebo	484 163	8.1% 8.0%	-0.5 +0.2	0.6 2.8	30

BID = twice daily; QW = once weekly; QD = once daily.

Table 2. Changes in HbA_{1c} and number of patients with at least one hypoglycaemic episode in six-month placebo-controlled studies adding incretin therapy versus placebo to ongoing metformin in patients with type 2 diabetes. Note: the criteria for hypoglycaemia were different in the different studies and therefore do not allow between-study comparisons. No severe hypoglycaemia was observed in any of the studies

islet dysfunction in type 2 diabetes by stimulating insulin secretion and inhibiting glucagon secretion, and both efficiently reduce HbA_{1c} with a very low risk of hypoglycaemia. There are also differences. A main difference is that GLP-1 receptor agonists are injectables whereas DPP-4 inhibitors are oral tablets. Another difference is that the long-acting GLP-1 receptor agonists reduce HbA_{1c} more efficiently than DPP-4 inhibitors.[21]

Other differences between the two strategies of incretin therapy are that GLP-1 receptor agonists reduce body weight, whereas DPP-4 inhibitors are body weight neutral, or slightly reduce body weight, and that GLP-1 receptor agonists, but not DPP-4 inhibitors, are associated with nausea and vomiting in the beginning of therapy, a risk that can be reduced by dose escalation.

Hypoglycaemia

A main advantage with the use of incretin therapy is the low risk for hypoglycaemia which is not uncommon in type 2 diabetes.

Hypoglycaemia has a number of negative impacts, such as acute symptoms, including: cognitive dysfunction and coma; negative implications for social interactions and sport and other leisure activities; traffic accidents; fear of repeated hypoglycaemia resulting in deteriorated glycaemic control; increase in body weight due to defence eating; and reduced working capacity.[22] Hypoglycaemia has also an increased cost for the patient, the health care system and society, as it is associated with more frequent contact with the health care system, including emergency visits and hospitalisation, increased use of glucose monitoring strips, absence from work and reduced working capacity, and accidents. There is also a long-term negative impact on cardiovascular diseases, because hypoglycaemia is associated with ECG changes, endothelial dysfunction, inflammation, and coagulation defects.[23] This may result in increased risk of cardiovascular disease in patients having repeated episodes of hypoglycaemia.[24]

Table 2 shows the observed low rate of hypoglycaemia in six-month studies where different incretin therapy has been added to metformin in placebo-controlled trials. There are different rates of hypoglycaemia in different studies, because different criteria for hypoglycaemia have been used. The overall message is, however, that when comparing incretin therapy with placebo, there is no increased rate of hypoglycaemia even though HbA_{1c} levels are lower with incretin therapy.[25–30]

A mechanism of the low incidence rate of hypoglycaemia during treatment with incretin is that the islet effects of GLP-1 are glucose dependent, which means that when glucose levels are reduced to normal baseline level the islet effects of GLP-1 are reduced.[1] It has also been shown with vildagliptin that DPP-4 inhibition in addition sustains or even enhances the glucagon counter-regulation to hypoglycaemia, which is important in the prevention of hypoglycaemia.[31]

Safety

Incretin therapy is associated with a very low risk of adverse events or complications. For some years, a discussion has been ongoing as to whether there is an increased risk of acute pancreatitis as a result of incretin therapy. However, the occurrence of acute pancreatitis is by itself increased in type 2 diabetes and therefore may occur in all types of therapy, including incretin therapy. A large claims-based study

comparing the risk of acute pancreatitis with exenatide or sitagliptin versus metformin or the sulphonylurea glyburide (glibenclamide) showed no higher risk for acute pancreatitis with the incretin therapy.[32] Nevertheless, it is very important to follow patients on incretin therapy with regard to potential long-term complications, although at present there is no such indication.[33]

Cardiovascular effects

It is well known that hyperglycaemia is associated with the development of cardiovascular disease and it may therefore be expected that reduction in glycaemia by incretin therapy will improve cardiovascular complications in type 2 diabetes.[34] On top of the reduction in glycaemia, incretin therapy has been shown to have other effects which may add to the potential beneficial cardiovascular effects of the reduction in glycaemia. Thus, incretin therapy slightly reduces blood pressure and blood lipids and does not increase body weight, and GLP-1 has been shown to have positive direct cardiovascular effects on the heart and endothelial cells.[35–37] Therefore, it is possible that incretin therapy may have beneficial effects on cardiovascular outcome beyond what would be expected from the reduction in glycaemia. This is supported by meta-analyses of cardiovascular events during incretin therapy.[36,38] At present, a large number of cardiovascular outcome trials with many of the incretin-based therapies are ongoing, involving tens of thousands of patients and running over several years. When these studies report their results, which is expected to start in 2014, more robust evidence on potential cardiovascular effects of incretin therapy will be available.

Clinical positioning

Table 3 shows the present indications in Europe for the different incretin therapies. An important indication is as add-on to metformin in patients with insufficient glycaemic control when treated with metformin alone, in association with lifestyle changes. As add-on to metformin, incretin therapy has advantages over sulphonylureas by avoiding weight gain and with the very low risk for hypoglycaemia. This is clearly evident from studies comparing incretin therapy as add-on to metformin versus sulphonylurea, with regard to both GLP-1 receptor agonists[26] and DPP-4 inhibitors.[39] Figure 1 illustrates this in a study comparing add-on with the DPP-4 inhibitor vildagliptin to metformin versus add-on with the sulphonylurea glimepiride.[40] The two compounds reduced HbA_{1c} by a similar degree over the one-year study period, whereas in terms of body weight and degree of hypoglycaemia there were clear differences.

Incretin therapy has also been shown to be effective as add-on to insulin in patients treated with metformin and insulin and in whom the glycaemic control is insufficient on this therapy.[41–45] The combination of incretin therapy with insulin will probably become more common in the future and without the weight gain which is often seen during insulin therapy.

In most clinical guidelines, incretin therapy is placed as add-on to metformin in patients in whom metformin alone is insufficient for glycaemic control, and some guidelines in addition place incretin therapy as part of triple therapy. This was clearly seen in the recent joint ADA/EASD position statement on glucose-lowering therapy in type 2 diabetes which was published in 2012.[46] Incretin therapy has not been introduced earlier in guidelines due to the desire to observe long-term outcome of the therapies and the higher price of incretin therapy when compared with the other agents (such as sulphonylureas). Since the long-term experience is now accumulating and shown to be good, there is currently an increasing interest in introducing incretin therapies at earlier stages than those in previous guidelines. Furthermore, with regard to the cost of compounds within the incretin therapy class of drugs, it should be emphasised that health economic studies

	Mono-therapy	Combination therapy			Triple therapy		
		MET	SU	TZD	Insulin (± MET)	MET + SU	MET + TZD
Exenatide BID	–	√	√	√	√	√	√
Exenatide QW	–	√	√	√	–	√	√
Liraglutide	–	√	√	–	–	√	√
Sitagliptin	√*	√	√	√	√	√	√
Vildagliptin	√*	√	√	√	–	–	–
Saxagliptin	√*	√	√	√	√	–	–
Linagliptin	√*	√	–	–	–	√	–

*When metformin alone is unsuitable. MET = metformin; SU = sulphonylurea; TZD = thiazolidinedione; BID = twice daily; QW = once weekly.

Table 3. Approved indications for use of incretin therapy in Europe in 2012

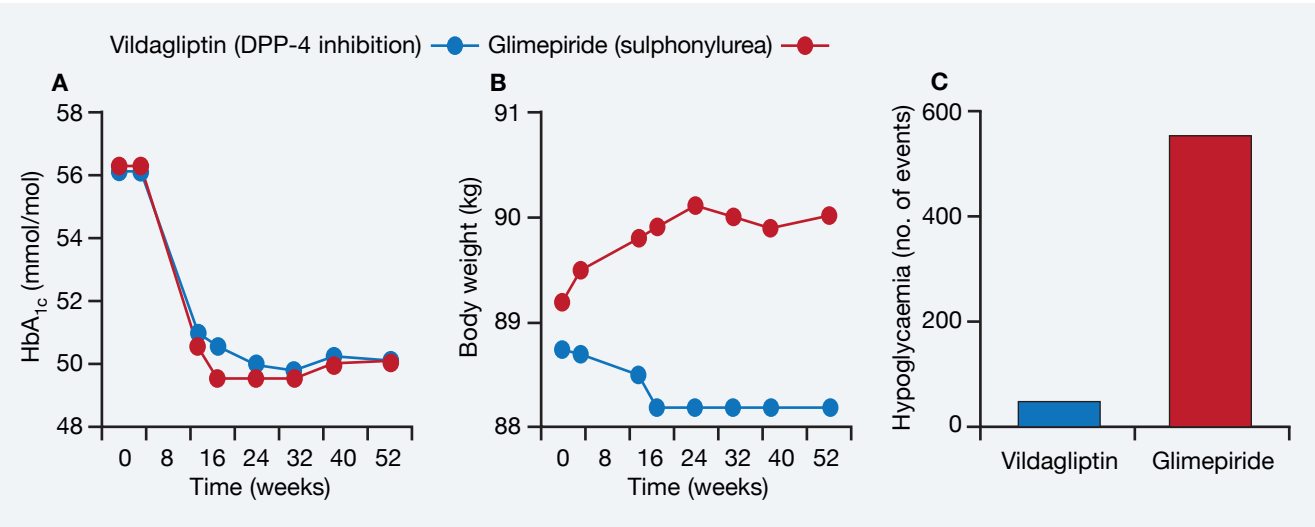

Figure 1. HbA_{1c} levels (A), body weight (B), and number of hypoglycaemic episodes (C) during 52-week treatment with vildagliptin 50mg twice daily (n=992 at week 52 per protocol population) or glimepiride up to 6mg/day (n=976 at week 52 per protocol population) added to metformin (≥1500mg/day). Means (±SE) are shown. (Adapted from: Ferrannini E, *et al. Diabetes Obes Metab* 2009:11:157–66,[40] with permission from John Wiley & Sons)

need to be performed in more detail and then take into account not only the cost of the compounds themselves, but also the cost of other aspects of therapy – e.g. the costs of hospital admission and of hypoglycaemia, which may be lower during incretin-based therapy.

Incretin therapy may thus be used in both the early and late stages of the disease. Because of the low risk of hypoglycaemia, incretin therapy may be particularly well suited for patients with an increased risk for hypoglycaemia – examples include those in employment or who have other conditions in which it is important to avoid hypoglycaemia, those who are elderly, and patients with renal impairment.[47–50]

Future aspects

Incretin therapy has gained much interest during recent years and its use will most likely increase because it is a safe therapy with good glucose-lowering action without weight gain and with a low risk for hypoglycaemia and other adverse events. Therefore, an important future aspect of the therapy is that more therapeutic experience will be acquired, with more long-term follow-up studies documenting, e.g. durability of effects, long-term safety, and long-term cardiovascular outcomes. This will result in a more definite positioning in algorithms and guidelines for glucose-lowering therapy.

Another future development is that more long-term incretin therapies are in development. This includes both weekly GLP-1 receptor agonists and once-weekly DPP-4 inhibitors.[10,51]

A further future development is the potential of using incretin therapy in the treatment of diseases other than type 2 diabetes. Since GLP-1 is a powerful inhibitor of glucagon secretion and hyperglucagonaemia is seen also in type 1 diabetes, a future indication of using incretin therapy in type 1 diabetes has been explored in several studies with encouraging results.[52,53] Furthermore, the weight reducing effect of GLP-1 may be further developed into GLP-1 receptor agonists as therapy of obesity without diabetes.[54] Finally, the cardioprotective effects of GLP-1 may be used for direct therapy of heart failure or acutely after myocardial infarction;[35] a neuroprotective effect may be used for therapy of neurodegenerative disorders;[55] and the potential anti-inflammatory actions of GLP-1 may be used in treatment of psoriasis.[56] We may thus be expecting an exciting future development of incretin therapy.[57]

Declaration of interests

The author has received honoraria for consulting and lecturing from: Boehringer Ingelheim, Bristol Myers Squibb/Astra Zeneca, GSK, Lilly, Novartis, Novo Nordisk, Merck and Sanofi, all of which produce GLP-1 receptor agonists or DPP-4 inhibitors.

References

1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006;368:1696–705.
2. Dunning BE, *et al.* Alpha-cell function in health and disease: influence of GLP-1. *Diabetologia* 2005;48:1700–13.
3. Nauck MA, *et al.* Glucagon-like peptide-1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 1997;273(5 Pt 1):E981–8.
4. Gutzwiller JP, *et al.* Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. *Am J Physiol* 1999;276:R1541–4.
5. Ahrén B. GLP-1 for type 2 diabetes. *Exp Cell Res* 2011;317:1239–45.
6. Gutniak M, *et al.* Antidiabetic effect of glucagon-like peptide-1 (7-36) amide in

normal subjects and patients with diabetes mellitus. *N Engl J Med* 1992;326:1316–22.
7. Zander M, *et al.* Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 2002;359:824–30.
8. Deacon CF, *et al.* Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2 terminus in type II diabetic patients and in healthy subjects. *Diabetes* 1995;44:1125–31.
9. Ahrén B. GLP-1-based therapy of type 2 diabetes: GLP-1 mimetics and DPP-IV inhibitors. *Curr Diabet Rep* 2007;7:340–7.
10. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 2012;109:728–42.
11. Scott LJ. Exenatide extended-release: a review of its use in type 2 diabetes mellitus. *Drugs* 2012;72:1679–707.
12. Keta R, Davies MJ. Treatment evaluation of liraglutide in type 2 diabetes. *Exp Opin Biol Ther* 2012;12:1551–6.
13. Drucker DJ, *et al.* Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. *Lancet* 2008;372:1240–50.
14. Buse JB, *et al.* Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 2013;381: 117–24.
15. Fineman MS, *et al.* GLP-1 based therapies: differential effects on fasting and postprandial glucose. *Diabetes Obes Metab* 2012;14:675–88.
16. Ahrén B, *et al.* Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4 week study period in type 2 diabetes. *Diabetes Care* 2002;25:869–75.
17. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab* 2011; 13:7–18.
18. Ahrén B. Use of DPP-4 inhibitors in type 2 diabetes: focus on sitagliptin. *Diabetes Obes Metab* 2010;3:31–41.
19. Ahrén B. Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin – diabetes control and potential adverse events. *Best Pract Res Clin Endocrinol Metab* 2009;23:487–98.
20. Deeks ED. Linagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2012;762:1793–824.
21. Deacon CF, *et al.* 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;14:762–7.
22. Barnett AH, *et al.* Key considerations around the risks and consequences of hypoglycaemia in people with type 2 diabetes. *Int J Clin Pract* 2010;64:1121–9.
23. Desouza CV, *et al.* Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care* 2010; 33:1389–94.
24. Zoungas S, *et al.* Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–8.
25. DeFronzo RA, *et al.* Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005;28:1092–100.
26. Nauck M, *et al.* Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009;32:84–90.
27. Charbonnel B, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006;29:2638–43.
28. Bosi E, *et al.* Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care* 2007;30: 890–5.
29. DeFronzo RA, *et al.* The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care* 2009;32:1649–55.
30. Taskinen MR, *et al.* Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab* 2011;13:65–74.
31. Ahrén B, *et al.* Vildagliptin enhances islet responsiveness to both hyper- and hypoglycemia in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2009;94:1236–43.
32. Dore DD, *et al.* Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* 2009;25: 1019–27.
33. Drucker DJ, *et al.* The safety of incretin-based therapies – review of the scientific evidence. *J Clin Endocrinol Metab* 2011;96:2027–31.
34. Stratton IM, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321:405–12.
35. Usscher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012;33:187–215.
36. Mannucci E, Dicembrini I. Incretin-based therapies and cardiovascular risk. *Curr Med Res Opin* 2012;28:715–21.
37. Lorber D. GLP-1 receptor agonists: effects on cardiovascular risk reduction. *Cardiovasc Ther* 2012 Jul 30. doi: 10.1111/cdr.12000. [Epub ahead of print.]
38. Monami M, *et al.* Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2013;15:112–20.
39. Ahrén B. Are sulfonylureas less desirable than DPP-4 inhibitors as add-on to metformin in the treatment of type 2 diabetes? *Curr Diabet Rep* 2011;11:83–90.
40. Ferrannini E, *et al.* Fifty-two week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. *Diabetes Obes Metab* 2009;11: 157–66.
41. Fonseca V, *et al.* Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia* 2007;50:1148–55.
42. Vilsbøll T, *et al.* Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2010;12:167–77.
43. Balena R, *et al.* Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. *Diabetes Obes Metab* 2012 Oct 15. doi: 10.1111/dom.12025. [Epub ahead of print.]
44. Berlie H, *et al.* Glucagon-like peptide-1 receptor agonists as add-on therapy to basal insulin in patients with type 2 diabetes: a systematic review. *Diabetes Metab Syndr Obes* 2012;5:165–74.
45. Barnett A, *et al.* Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin* 2012;28:513–23.
46. Inzucchi SE, *et al.* Management of hyperglycaemia 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). *Diabetologia* 2012;55: 1577–96.
47. Paolisso G, *et al.* Dipeptidyl peptidase-4 inhibitors in the elderly: more benefits or risks? *Adv Ther* 2012;29:218–33.
48. Mathieu C, Bollaerts K. Antihyperglycaemic therapy in elderly patients with type 2 diabetes: potential role of incretin mimetics and DPP-4 inhibitors. *Int J Clin Pract* 2007;154:29–37.
49. Sisson EM. Liraglutide: clinical pharmacology and considerations for therapy. *Pharmacother* 2011;31:896–911.
50. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head studies. *Diabetes Metab* 2012; 38:89–101.
51. Gantz I, *et al.* Effect of MK-3102, a novel once-weekly DPP-4 inhibitor, over 12 weeks in patients with type 2 diabetes mellitus. *Diabetologia* 2012;55(Suppl 1):S51.
52. Issa CM, Azar ST. Possible role of GLP-1 and its agonists in the treatment of type 1 diabetes mellitus. *Curr Diab Rep* 2012;12: 560–7.
53. Farngren J, *et al.* Vildagliptin reduces glucagon during hyperglycemia and sustains glucagon counterregulation during hypoglycemia in type 1 diabetes. *J Clin Endocrinol Metab* 2012;97:3799–806.
54. Astrup A, *et al.* Effects of liraglutide in the treatment of obesity: a randomized, double-blind, placebo-controlled study. *Lancet* 2009; 374:1606–16.
55. Harkavyui A, Whitton PS. Glucagon-like peptide 1 receptor stimulation as a means of neuroprotection. *Br J Pharmacol* 2010;159: 495–501.
56. Drucker DJ, Rosen CF. Glucagon-like peptide-1 (GLP-1) receptor agonists, obesity and psoriasis: diabetes meets dermatology. *Diabetologia* 2011;54:2471–4.
57. Ahrén B. The incretin-based therapy: novel avenues – novel targets. *Diabetes Obes Metab* 2011;13(Suppl 1):158–66.
58. Bergenstal RM, *et al.* Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 2010;376:431–9.