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Latest Insights into Incretin-based Therapies and the Importance of Cardiovascular Risk Factor Control: An Update Report from EASD, Stockholm, September 2010

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Target Audience

This activity is intended for non-US physicians, specifically diabetologists/endocrinologists, cardiologists, internists, primary care physicians, and other healthcare professionals involved in the management of patients with type 2 diabetes.

Goal Statement

The goal of this activity is to improve the understanding of the clinical benefits and potential risks of modern incretin-based therapies, in particular GLP-1 analogues, in the management of type 2 diabetes in the context of latest information presented at the annual EASD congress in Stockholm, September 2010.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Understand the principles of incretin-based therapies and the clinical differences between GLP-1 agonists and DPP-IV inhibitors

2. Identify tolerability issues and safety data of incretin-based therapies (including pancreatitis)

3. Describe the metabolic effects of GLP-1 agonists with a focus on beta-cell function, the central/neurological effects leading to increased satiety and weight loss, and potential cardiovascular benefits.

4. Outline ongoing outcome studies with GLP-1 agonists

5. Assess the safety and efficacy of GLP-1 agonists and their potential for long-term cardiovascular risk reduction in high-risk patients (eg, in diabetic patients with hypertension or pre-existing cardiovascular disease)

Incretin-based therapies, such as the injectable GLP-1 agonists exenatide and liraglutide, are the latest advance in the management of type 2 diabetes.

The advantages of GLP-1 agonists over alternative oral treatments are improved glycaemic control (HbA1c), and increased satiety, which often leads to substantial weight loss in these mostly overweight or obese patients. These GLP-1 agonists also positively affect other relevant cardiovascular risk markers, such as high blood pressure.

Preclinical data suggest that GLP-1 agonists may not only stop the continuous decline in beta-cell function, but may actually reverse this process, thereby reducing the risk for the serious long-term complications of diabetes.

Currently, 2 GLP-1 analogues are approved for use in patients with type 2 diabetes:

- Exenatide, which has to be self-injected twice daily before meals, and
- Liraglutide, for once-daily injection independent of meals.

Several once-weekly GLP-1 analogues are in late-stage clinical development, although recent clinical or regulatory set-backs have affected taspoglutide and the extended-release formulation of exenatide.
In the past few months, 2 major outcome trials were started to test the hypothesis of cardiovascular risk reduction by GLP-1 agonists:

- LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results); and
- EXSCEL (Exenatide Study of Cardiovascular Event Lowering) with extended-release exenatide.

Study results are expected in 2016 or 2017, respectively.

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Dr. Gault does intend to discuss **off-label** uses of drugs, mechanical devices, biologics, or diagnostics approved by the European Medicines Agency.

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Introduction

Type 2 diabetes is a chronic, degenerating metabolic disorder characterized by elevated levels of blood glucose (hyperglycaemia). The underlying condition is caused by insulin resistance and/or defective insulin secretion from pancreatic beta cells. Patients with type 2 diabetes generally have an increased cardiovascular risk, with the majority having raised blood pressure.[1, 2] Cardiovascular problems (heart attacks, angina, strokes, peripheral artery disease) are major causes of morbidity and mortality. Adequate control of blood pressure and cholesterol are paramount in the treatment of these patients and result in significant reductions in cardiovascular risk.[3-5] Problems with controlling hyperglycaemia also result in microvascular complications, including eye, kidney and nerve damage.[6-8]

The number of people with type 2 diabetes is increasing worldwide, due to a growing and aging population, and an increasing prevalence of obesity and sedentary lifestyles. The Centers for Disease Control and Prevention in the United States has described type 2 diabetes as an epidemic; the World Health Organization predicts that 366 million people worldwide will have type 2 diabetes by 2030, and that diabetes deaths will double between 2005 and 2030.[9]

Controlling hyperglycaemia reduces microvascular complications of type 2 diabetes; this is a major target in effective treatment.[7] A recent meta-analysis of over 30,000 patients in randomised controlled trials showed that intensive control of hyperglycaemia

also significantly reduces macrovascular complications (ie, coronary events).[4] Furthermore, intensive glycaemic control has a long-term legacy benefit in reducing cardiovascular morbidity and mortality, even if intensive therapy is not maintained.[10]

Glycated haemoglobin (HbA1c) is a measure of long term hyperglycaemia. The usual aim of therapy is to achieve an HbA1c level of less than 7.0% or 6.5%.[11] This goal should be tailored for the individual; it may not be achievable for all patients. Other factors, such as occurrence of hypoglycaemic events, duration of diabetes and other comorbid conditions should be taken into account when customising the HbA1c target.

Lifestyle changes (diet and increased physical exercise) are essential for patients with type 2 diabetes. Unfortunately, most patients cannot lose sufficient weight to lower their blood glucose and maintain good glycaemic control over the longer term.[12] Therefore, most patients will require the sequential addition of glucose-lowering medications. A generalized treatment algorithm for the management of type 2 diabetes is shown in Figure 1.[13] It should be noted that management algorithms for type 2 diabetes vary from country to country, depending on local approval of anti-diabetic therapies and clinical practice.

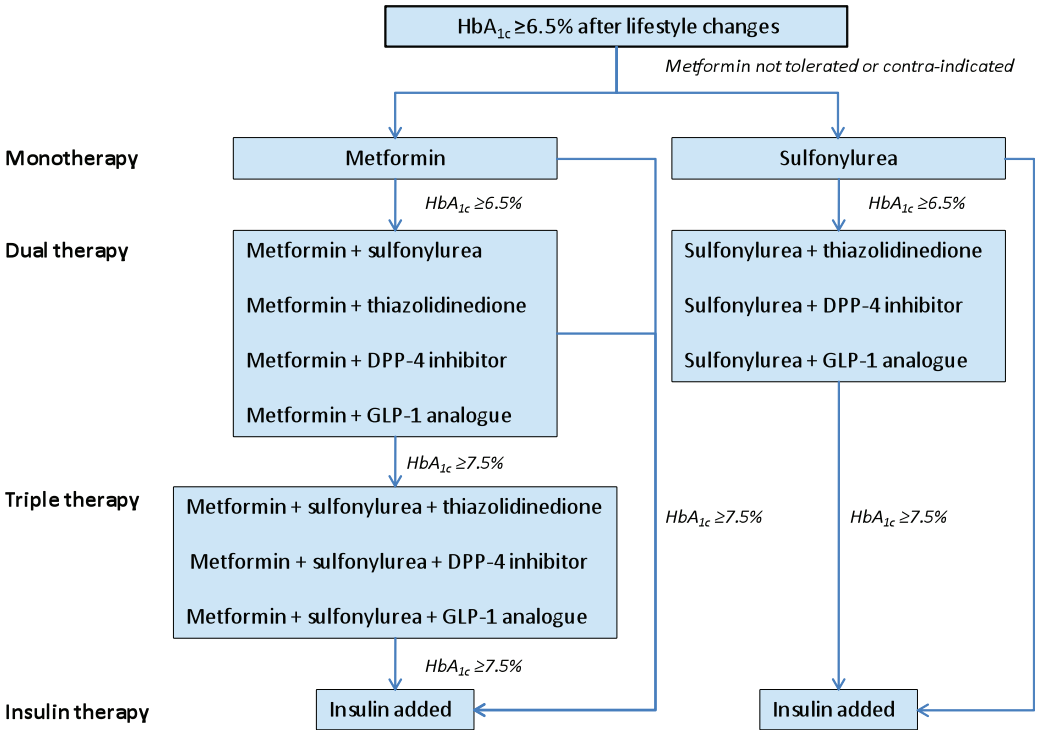


Figure 1. Blood glucose-lowering therapies recommended for treatment of type 2 diabetes. From: National Institute for Health and Clinical Excellence (NICE) short clinical guideline 87, Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes.[13]

Metformin is widely used as first-line therapy for newly diagnosed type 2 diabetes, with the addition of sulfonylurea as second-line therapy if glycaemic control remains poor or deteriorates. If metformin is not tolerated, or is contraindicated, sulfonylurea may be considered as initial monotherapy. Other agents for blood glucose control (eg, thiazolidinediones, DPP-4 inhibitors, or GLP-1 agonists) may also be used in second-line therapy with either metformin or sulfonylurea, or as third-line therapy in combination with both metformin and sulfonylurea. If HbA1c levels are still too high (≥ 7.5%), then insulin therapy will be required, in combination with other medications.

Current treatment regimens for type 2 diabetes do not stop the decline in pancreatic beta-cell function, and several medications (sulfonylureas, thiazolidinediones, and insulin) lead to increased weight, in a population of patients who are generally already obese. Thus, there is a need for new therapies to manage this complicated condition. Due to the increased cardiovascular risk (which has been observed with thiazolidinediones), and major underlying cardiovascular problems in these patients, long-term cardiovascular risk assessment for any new anti-diabetic therapy is now required by the Food and Drug Administration (FDA).

Glucagon-like peptide-1 (GLP-1)-based therapies may address these unmet needs in the management of type 2 diabetes. This review highlights how GLP-1 receptor agonists exert and maintain lower HbA1c levels, reduce body weight, and also have beneficial effects on the cardiovascular system.

Glucagon-like Peptide 1 (GLP-1)

Two key hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP; also known as gastric inhibitory polypeptide), are released from the gastrointestinal tract after eating; they induce insulin release in a glucose-dependent manner.[14-19] These hormones are known as incretins (ie, they augment insulin secretion in response to oral glucose compared to intravenous glucose). Together, GLP-1 and GIP account for up to 60% of the insulin secreted after a meal in healthy humans.[20]

Following release, both GLP-1 and GIP are broken down within minutes, primarily by the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4; also known as CD26). Di-peptidyl peptidase-4 is a serine protease that cleaves the two amino acids from peptides that have proline or alanine in the penultimate amino-terminal position [21, 22]; DPP-4 is widely distributed, but is found in particularly high concentrations in the vascular endothelium.[21, 22] Glucagon-like protein-1 and its metabolites are rapidly cleared via the kidneys.[23, 24]

Effects of GLP-1 are depicted in Figure 2. They can be largely considered under pancreatic and extrapancreatic actions.

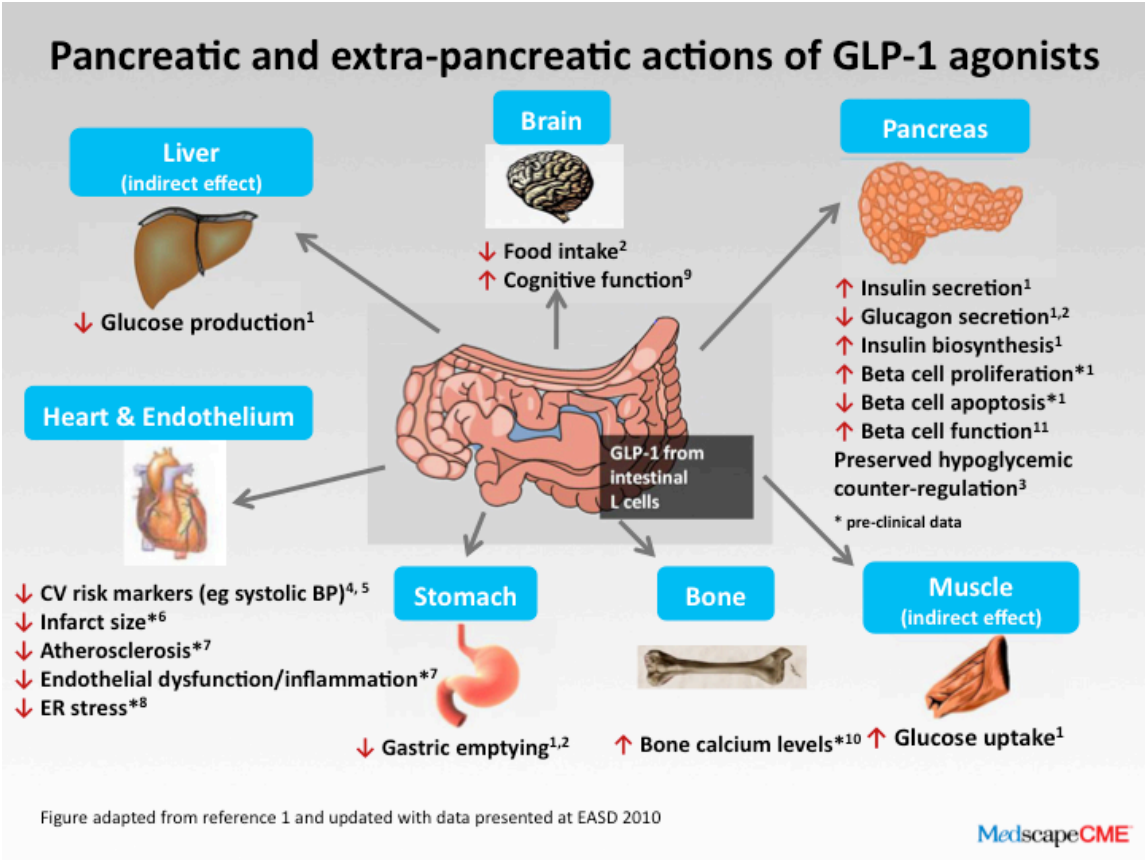


Figure 2. Physiological effects of GLP-1. 1Baggio LL, Drucker DJ. Gastroenterology. 2007;132:2131–2157. 2Drucker DJ. Diabetes Care. 2003;26:2929–2940. 3Drucker DJ, Nauck MA. Lancet. 2006;368:1696-1705. 4Nauck MA, et al. Diabetes Care. 2009;32:84-90. 5Zinman B, et al. Diabetes Care. 2009; 32:1224-1230. 6Bose AK, et al. Diabetes. 2005;54:146-151. 7Dear AE, et al. Diabetologia. 2010;53 (Suppl 1): S72. 8Schisano B, et al. Diabetologia. 2010;53 (Suppl 1): S518. 9Nauck MA, et al. J Clin Endocrinol Metab. 2002;87:1239-1246. 10Nuche-Berenguer B, et al. Diabetologia. 2010;53(Suppl 1):S337. 11Bunck MC, et al. Diabetologia. 2010;53(Suppl 1):S338.

Pancreatic actions of GLP-1

Glucagon-like protein-1 acts on the GLP-1 G-protein-coupled receptor of pancreatic beta-cells in a glucose-dependent manner, increasing the intracellular concentration of cyclic AMP.[18] The rise in cyclic AMP has several consequences, including an increase

in intracellular calcium and closure of the ATP-dependent potassium channel, which in turn induces insulin secretion.[25] Increased cyclic AMP also upregulates insulin synthesis,[26] which replaces insulin released from pancreatic beta-cells. Stimulation of GLP-1 receptors also increases pancreatic beta-cell mass by stimulating beta-cell proliferation[18, 27-30] and inhibiting apoptosis, as shown in various animal studies.[29, 30] Improved beta-cell function has been shown with GLP-1 analogues in clinical trials.[31]

Additionally, GLP-1 decreases glucagon concentrations, independently of its ability to release insulin.[32, 33] This appears to be both a direct effect via the GLP-1 receptors present on pancreatic alpha-cells and an indirect effect of stimulating the release of somatostatin, which in turn decreases glucagon release.[28] Importantly, the ability of GLP-1 to decrease glucagon concentrations is glucose-dependent; thus, the physiological feedback mechanism of raising glucagon to counteract low blood glucose levels is not affected.[16, 34]

Extrapancreatic actions of GLP-1

The GLP-1 receptor is widely distributed and can be found in the lung, brain, kidney, small and large intestine, stomach and heart, in addition to the pancreas.[35, 36]

GLP-1 stimulates the enteric nervous system, resulting in the slowing of gastrointestinal motility.[28, 37] It stimulates ascending vagal afferents to the brain, which feed back to reduce gastric emptying,[38] causing a central satiety effect and decreasing food intake. [39] GLP-1 may also directly regulate gastric acid secretion,[40] although its effect on gastric acid secretion is not present in vagotomised humans.[38] Stable analogues of GLP-1 result in clinically meaningful weight loss, which is beneficial to patients with type 2 diabetes, who are commonly overweight.

Many of the other actions of GLP-1 have been determined from use of long-acting GLP-1 peptides, particularly exenatide and liraglutide (details of these GLP-1 peptides can be found in Sections 4 and 5, respectively). Whether these actions also occur with endogenously released GLP-1 is uncertain. For example, stimulation of GLP-1 receptors with GLP-1 analogues has been shown to protect the heart and reduce infarction size against ischaemia, [41] and to increase acetylcholine-induced endothelium-dependent relaxations,[42, 43] which are important cardiovascular considerations. Recent data presented at the European Association for the Study of Diabetes (EASD) 2010 suggest that GLP-1 agonists have beneficial effects on the cardiovascular system, and also on the brain and bone.[44-49]

GLP-1 as a therapeutic target for type 2 diabetes

The incretin effect is diminished in patients with type 2 diabetes; some patients have significantly reduced plasma concentrations of GLP-1 compared to normal volunteers.[50] However, exogenous GLP-1 retains its insulinotropic activity in patients with type 2 diabetes, and also lowers glucagon concentration, whereas the activity of exogenous GIP is diminished.[15] Therefore, the development of incretin therapies for patients with type 2 diabetes has focused on GLP-1 rather than GIP.

There are 2 strategies for the development of incretin-based therapies:

- To enhance the half-life of endogenous incretins by inhibiting the activity of DPP-4; and
- To mimic the actions of GLP-1 with stable analogues which are not broken down by DPP-4.

Incretin-Mediated Therapies

DPP-4 inhibitors

Three DPP-4 inhibitors (sitagliptin, saxagliptin and vildagliptin) are currently approved for the treatment of type 2 diabetes. The main characteristics of these therapies are summarized in Table 1.

Table 1. Main Product Characteristics of DPP-4 Inhibitors

	Sitagliptin[51, 52]	**Saxagliptin**[53, 54]	**Vildagliptin**[55, 56]
Route	Oral	Oral	Oral
Dosage	100 mg once daily A lower dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia	5 mg once daily Dose of sulfonylurea should be lowered in combination treatment	50 mg twice daily 50 mg once daily in combination with a sulfonylurea
Approximate half-life	12.4 hours	2.5 hours	3 hours
Elimination	Metabolism is a minor pathway. Primarily eliminated unchanged in urine	Elimination by metabolism (cytochrome P450 3A4/5) and renal clearance	Elimination by metabolism (not CYP 450 enzymes) and renal clearance
HbA_{1c} reduction (monotherapy)	Moderate decrease Up to -0.8%	Moderate decrease Up to -0.8%	Moderate decrease Up to -0.8%
Effect on weight	Weight neutral	Weight neutral	Weight neutral
Indicated in combination with:	**Monotherapy** (when metformin is inappropriate) **Dual therapy** with metformin, a thiazolidinedione, or a sulfonylurea **Triple therapy** with sulfonylurea + metformin; thiazolidinedione + metformin **Insulin** with or without metformin	**Dual therapy** with metformin, a thiazolidinedione, or a sulfonylurea	**Dual therapy** with metformin, a thiazolidinedione, or a sulfonylurea
Contraindication and special warnings	Not recommended in patients with moderate to severe renal failure (creatinine clearance < 50 mL/min). No dose adjustment in mild to moderate liver impairment	Not recommended in patients with moderate to severe renal failure (creatinine clearance < 50 mL/min). No dose adjustment in mild to moderate liver impairment	Not recommended in patients with moderate to severe renal failure (creatinine clearance < 50 mL/min). Contraindicated in patients with liver impairment
Very common adverse events	Hypoglycaemia with sulfonylurea	Hypoglycaemia with sulfonylurea	Hypoglycaemia with sulfonylurea

The DPP-4 inhibitors reduce the proteolysis of GLP-1 and GIP and prolong their half-lives, thereby increasing the concentration of endogenously released incretins (eg, the GLP-1 concentration is increased 2- to 3-fold). This results in a modest reduction in HbA1c, up to approximately 0.8%.[57] Saxagliptin is the most potent DPP-4 inhibitor; although it has a relatively short half-life (2.5 hours), it is able to inhibit DPP-4 over 24 hours due to its high enzyme affinity. Both sitagliptin and saxagliptin are administered once daily, whereas vildagliptin is administered twice daily. DPP-4 inhibitors have no effect on body weight.

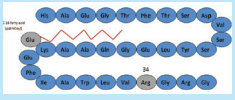
DPP-4 inhibitors generally have a low incidence of adverse events.[58] Sitagliptin, the first marketed DPP-4 inhibitor, demonstrated a good safety profile over a 2-year period in over 10,000 patients with type 2 diabetes.[59, 60] There are some post-marketing reports of pancreatitis in association with DPP-4 inhibitors,[61] but a causal link has not been established.[62]

At EASD 2010, updates were given on several other DPP-4 inhibitors in development (linagliptin,[63-65] dutogliptin,[66] and alogliptin[67, 68]). Interestingly, linagliptin is eliminated non-renally; renally impaired type 2 diabetes patients did not need dose adjustments (unlike other DPP-4 inhibitors).[64]

GLP-1 agonists

Two GLP-1 agonists (exenatide and liraglutide) are currently approved for the treatment of type 2 diabetes. The main characteristics of these therapies are summarized in Table 2, together with the characteristics of the natural hormone, GLP-1. More specific details on exenatide and liraglutide are provided in later sections.

Table 2. Main Product Characteristics of GLP-1 Agonists

	GLP-1	Exenatide[69-72]	Liraglutide[73-78]
Structure*			
Homology to GLP-1	100%	53%	97%
Antibody formation	-	Approximately 61% of patients	Approximately 3% of patients
Route	-	Subcutaneous	Subcutaneous
Dosage	-	Twice daily (BID) 1 month at 5 µg BID, then 10 µg BID	Once daily (QD) 1 week at 0.6 mg QD, then 1.2 mg QD. Can increase to 1.8 mg QD if required
Food interaction	-	Must take before meals	No food interaction
Approximate Half-life	1-2 minutes	2.4 hours	13 hours
Elimination	Proteolysis by DPP-4	Glomerular filtration with subsequent proteolytic degradation	No specific organ identified as major route of elimination
HbA_{1c} reduction	-	-0.8 to -0.9%	-1.0 % to -1.5%
Mean change in weight	-	-1.6 kg to -2.8 kg (over 30 weeks)	-0.2 kg to -2.8 kg (over 26 weeks)
Indicated in combination with:	-	Metformin and/or a sulfonylurea and/or a thiazolidinedione	Metformin and/or sulfonylurea; metformin and a thiazolidinedione
Contraindication and special warnings	-	Severe renal impairment and gastrointestinal disease	Inflammatory bowel disease and diabetic gastroparesis; thyroid adverse events
Very common adverse events	-	Nausea, vomiting, diarrhoea, Hypoglycaemia with sulfonylurea	Headache, nausea, vomiting, diarrhoea Hypoglycaemia with sulfonylurea

While DPP-4 inhibitors primarily enhance the effects of endogenously-produced GLP-1 (up to the maximum physiological levels of GLP-1), exogenous administration of a GLP-1 agonist provides much greater stimulation of the GLP-1 receptor. Pharmacological doses of GLP-1 agonists result in superior glycaemic control (ie, greater reduction of HbA1c which is sustained, unlike with a sulfonylurea) and weight loss, due to their ability to increase satiety and delay gastric emptying. A meta-analysis presented at EASD 2010 showed GLP-1 agonists to achieve greater reductions in HbA1c, fasting glucose and body weight compared to DPP-4 inhibitors, and that these effects were sustained.[80] Furthermore, pharmacological doses of GLP-1 analogues have wide-ranging effects, via GLP-1 receptors in a variety of other tissues and organs throughout the body, suggesting the potential for beneficial effects on various extra-pancreatic sites (eg, heart, endothelium, and brain).

Exenatide

Exenatide was the first marketed GLP-1 agonist. It is a synthetic peptide based on exendin-4, which is found in the saliva of the Gila monster lizard. It is 53% homologous to human GLP 1 (see structure in Table 2). It is a full agonist of the GLP-1 receptor but is resistant to proteolysis by DPP-4, due to replacement of alanine with glycine in the penultimate amino-terminal position. The main characteristics of exenatide are summarized in Table 2.

After subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2 hours; the mean terminal half-life is 2.4 hours. Therefore, exenatide requires twice daily (BID) dosing and must be given within 1 hour before morning and evening meals. Exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation.[69, 81]

Exenatide can be administered with metformin, and/or a sulfonylurea, and/or a thiazolidinedione. However, when exanatide was used in combination with a sulfonylurea in clinical studies, the incidence of hypoglycaemia was greater than that of placebo in combination with a sulfonylurea. Therefore, when exenatide is added to sulfonylurea therapy, a reduction in the sulfonylurea dose should be considered to reduce the risk of hypoglycaemia.[69]

In three pivotal, phase 3, randomized, double-blind, placebo-controlled clinical studies (AMIGO: Diabetes Management for Improving Glucose Outcomes), exenatide was shown to reduce HbA1c and body weight in patients treated for 30 weeks, whether exenatide was added to metformin, a sulfonylurea or a combination of both (Table 3). Extension studies showed that the HbA1c reduction was sustained, and the weight loss continued for at least 82 weeks of treatment.[82]

Table 3 Summary of Phase 3, Randomized, Double-Blind, Placebo-Controlled Studies of Exenatide in Patients with Type 2 Diabetes

Study	Other Anti-Diabetic Therapies Received	Duration of Treatment	Number Randomised	Treatments (BID)	Change in HbA_{1c} (%)	Change in Weight (kg)
AMIGO 1[70]	Metformin	30 weeks	336	Exenatide 5 µg	-0.40	-1.6
				Exenatide 10 µg	-0.78	-2.8
				Placebo	+0.08	-0.3
AMIGO 2[71]	Sulfonylurea	30 weeks	377	Exenatide 5 µg	-0.46	-0.9
				Exenatide 10 µg	-0.86	-1.6
				Placebo	+0.12	-0.6
AMIGO 3[72]	Metformin and sulfonylurea	30 weeks	733	Exenatide 5 µg	-0.6	-1.6
				Exenatide 10 µg	-0.8	-1.6
				Placebo	+0.2	-0.9
Pooled AMIGO Studies[69]	Metformin and/or sulfonylurea	30 weeks	1446	Exenatide 5 µg	-0.59	-1.41
				Exenatide 10 µg	-0.89	-1.91
				Placebo	+0.08	-0.65

Nausea, vomiting, and diarrhoea are the most common adverse events associated with exenatide. Hypoglycaemia occurs infrequently, and generally only when administered with sulfonylureas.

Cases of acute pancreatitis have been reported in patients treated with exenatide, but 2 studies using distinct analytic methods and data sets found that exenatide use was not associated with an increased risk of acute pancreatitis.[83] Further investigation suggests that patients with type 2 diabetes have a higher risk of developing pancreatitis.[84, 85] For both DPP 4 inhibitors (sitagliptin[62]) and GLP-1 agonists (exenatide [83]), there does not appear to be any increase or decrease in the risk of developing pancreatitis in patients with type 2 diabetes.

Exenatide also has a warning on possible links to kidney dysfunction, and post-marketing studies have been requested to investigate cases of pancreatitis, renal failure and thyroid and pancreatic cancer with exenatide.[86]

New findings for exenatide reported at EASD 2010

Data on the durability of exenatide, and its beneficial effects on pancreatic beta-cell function, were presented at EASD 2010. These new data show that both exenatide and insulin glargine sustained HbA1c reduction over a 3-year treatment period, while exenatide significantly reduced, and insulin glargine increased, body weight. Importantly, after 3 years of treatment, first-phase insulin secretion was sustained following a 4-week off-drug period with exenatide, but not with insulin glargine. This improvement cannot be explained by glucose lowering alone, and suggests increased pancreatic beta-cell function, which is only observed after long-term treatment.[87]

Part of the effect of exenatide on decreasing body weight could be due to its ability to restore the normal satiety response, which is lost in patients with type 2 diabetes. Using functional magnetic resonance imaging, it was reported that the ventral tegmental area of the brain of patients with diabetes showed activation even when patients were fed, but this did not occur in the presence of exenatide.[44]

A retrospective comparison of exenatide with other glucose-lowering agents on the relative incidence rates of first cardiovascular events was assessed in patients with type 2 diabetes using the LifeLink™ database.[45] Patients who were exposed to exenatide were more likely to have hyperlipidemia and hypertension prior to treatment than patients exposed to other agents. However, even in this high-risk population, patients on exenatide were 20% less likely to have a cardiovascular event or hospitalizations compared to patients on other glucose-lowering agents.

Exenatide is a peptide and patients do develop antibodies to this GLP-1 agonist. However, there is controversy regarding whether these antibodies have a neutralizing effect, and what the long-term clinical consequences of such antibodies may be. In one study reported at EASD 2010, antibody titres to exenatide were shown to peak early in treatment, and did not cross-react with GLP-1 or glucagon.[88] In contrast, in another study, 61% of patients were shown to have antibodies to exenatide after 26 weeks' treatment; patients with high antibody titres had smaller HbA1c reductions than patients with low titres.[89] This may suggest a reduced glucose-lowering efficacy in those patients developing antibodies to exenatide.

A once-weekly extended release formulation of exenatide (previously referred to as exenatide LAR) is under development; new findings regarding this formulation were reported at EASD 2010. When patients on exenatide 10 µg BID were transitioned to once-weekly treatment at a dose of 2 mg, HbA1c was reduced by a further 0.2%, suggesting a clinical advantage for prolonged exenatide exposure.[90] Furthermore, once-weekly exenatide resulted in greater improvements in glycaemic control and body weight compared to maximum approved doses of sitagliptin and pioglitazone. Improvements in systolic blood pressure also occurred in patients who switched from sitagliptin to once-weekly exenatide.[91] Compared to exenatide twice daily, treatment with the once-weekly formulation resulted in significantly greater decreases from baseline in HbA1c and fasting blood glucose. Both exenatide regimens reduced sitting systolic blood pressure. Nausea, the most frequent adverse event, occurred less frequently with once-weekly exenatide (14%) than with twice-daily therapy (35%), and was predominantly transient and mild or moderate in intensity. Injection-site reactions were infrequent and generally mild in intensity, but occurred more often with once-weekly exenatide. Both groups lost weight.[92]

Comparison of exenatide once-weekly with insulin glargine for 26 weeks demonstrated superior improvements in HbA1c and body weight reduction with exenatide. Furthermore, small but significant changes in different surrogate markers of cardiovascular risk were observed, particularly in patients with abnormal baseline CV risk factors.[49] The FDA has requested another clinical trial of exenatide once-weekly to gather further data on its effect on heart rate -- notably, a thorough QT study with exposures of exenatide higher than typical therapeutic levels. It is unlikely that extended-release exenatide will be on the market before the middle of 2012.[93]

Liraglutide

Liraglutide was the second GLP-1 therapeutic to be approved. It is 97% homologous to GLP-1, but with a fatty acid side chain attached (see structure in Table 2).[79] Following subcutaneous administration, prolonged activity is observed, which is based on three mechanisms: self-association (as heptameric aggregates of liraglutide within the injection depot) resulting in slow absorption; binding to albumin; and resistance towards DPP-4 and NEP degradation.[94] The main characteristics of liraglutide are summarized in Table 2.

The absorption of liraglutide following subcutaneous administration is slow, reaching maximum concentration 8 - 12 hours post-injection. The mean elimination half-life is approximately 13 hours, which means that liraglutide can be administered as a once-daily (QD) dose. Importantly, liraglutide can be given without regard to food, unlike exenatide which has to be given before a

meal. Liraglutide is metabolized in a similar way to other large proteins; no specific organ has been identified as the major route of elimination.

At present, liraglutide is approved to be administered with metformin and/or a sulfonylurea, or with metformin and a thiazolidinedione. Similar to exenatide, hypoglycaemia may occasionally occur in combination therapy with sulfonylurea and the dose of sulfonylurea should be reduced accordingly.[73]

In five phase 3, randomized, double-blind, controlled clinical studies (LEAD, Liraglutide Effect and Action in Diabetes), liraglutide was shown to reduce HbA1c, fasting plasma glucose and post-prandial glucose in patients treated for 26 weeks, whether liraglutide was added to metformin, a sulfonylurea, a combination of both or a combination of metformin and a thiazolidinedione (Table 4). Similarly, in a monotherapy study (LEAD-3), liraglutide treatment resulted in greater reductions in HbA1c, body weight and less hypoglycaemia than glimepiride after 52 weeks treatment (Table 4).

In a randomized open-label study (LEAD-6), liraglutide (1.8 mg QD) was compared with exenatide (10 µg BID).[95] After 26 weeks, liraglutide resulted in a significantly greater improvement than exenatide in glycaemic control (HbA1c 1.12% vs 0.79% respectively). Weight loss was not statistically different between groups (3.24 kg for liraglutide versus 2.87 kg for exenatide). Both drugs were well tolerated, but nausea was less persistent and minor hypoglycaemia less frequent with liraglutide than with exenatide.

In the majority of LEAD clinical trials with liraglutide, reductions in systolic blood pressure were observed, which occurred within the first few weeks of treatment and within a shorter time-frame than observed for weight loss, suggesting a weight-loss-independent mechanism of blood pressure reduction.[75, 77] The largest decrease in systolic blood pressure occurred in the LEAD-4 trial (combination with metformin and a thiazolidinedione). In this study, liraglutide at 1.2 mg and 1.8 mg decreased systolic blood pressure by 6.7 and 5.6 mm Hg, respectively, compared with 1.1 mm Hg for placebo. Diastolic blood pressure was not significantly decreased (-2.3 mm Hg for liraglutide 1. 2mg, -1.9 mm Hg for liraglutide 1.8 mg and -0.8 mm Hg for placebo). Interestingly, there were slight increases in pulse rate in the LEAD clinical trials, which could suggest activation of the baroreceptor reflex as a compensatory mechanism to counteract any fall in diastolic blood pressure.[77] Furthermore, significant decreases in LDL c holesterol, triglycerides and free fatty acids were reported in the LEAD-4 clinical trial compared with patients who received placebo, suggesting liraglutide could have long-term cardiovascular benefits. Data from a meta-analysis of 6 LEAD studies c onfirmed these findings and also indicated a reduction of the inflammatory markers high-sensitivity C-reactive protein (hsCRP) and brain natriuretic protein (BNP).[96]

Table 4 Summary of Phase 3, Randomized, Controlled Studies of Liraglutide in Patients with Type 2 Diabetes

Study	Other Anti-Diabetic Therapies Received	Duration of Treatment	Number Randomized	Treatments (QD)	Change in HbA_{1c} (%)	Change in Weight (kg)
LEAD-1[74] (dual therapy)	Sulfonylurea	26 weeks	1041	Liraglutide 0.6 mg	-0.60	+0.7
				Liraglutide 1.2 mg	-1.08	+0.3
				Liraglutide 1.8 mg	-1.13	-0.2
				Placebo	+0.23	-0.1
				Rosiglitazone 4mg	-0.44	+2.1
LEAD-2[75] (dual therapy)	Metformin	26 weeks	1091	Liraglutide 0.6 mg	-0.69	-1.8
				Liraglutide 1.2 mg	-0.97	-2.6
				Liraglutide 1.8 mg	-1.00	-2.8
				Placebo	+0.09	-1.5
				Glimepiride 4mg	-0.98	+1.0
LEAD-3[76] (mono-therapy)	None (patients with early type 2 diabetes)	52 weeks	746	Liraglutide 1.2 mg	-0.84	-2.1
				Liraglutide 1.8 mg	-1.14	-2.5
				Glimepiride 8mg	-0.51	+1.1
LEAD-4[77] (triple therapy)	Metformin and thiazolidinedione	26 weeks	533	Liraglutide 1.2 mg	-1.5	-1.0
				Liraglutide 1.8 mg	-1.5	-2.0
				Placebo	-0.5	+0.6
LEAD-5[78] (triple therapy)	Metformin and sulfonylurea	26 weeks	581	Liraglutide 1.8 mg	-1.33	-1.8
				Placebo	-0.24	-0.42
				Insulin glargine	-1.09	+1.6

The most frequently reported adverse events associated with liraglutide in clinical studies were gastrointestinal events (eg, nausea, diarrhoea, vomiting). These reactions usually diminished within a few days or weeks on continued treatment. Headache was also common.[73]

Patients with type 2 diabetes have a higher risk of developing pancreatitis[84, 85]; as with exenatide, monitoring for pancreatitis and thyroid cancer has been requested by the FDA.[97] Evidence presented at EASD 2010 suggests that liraglutide does not induce pancreatitis in rats or mice dosed for 2 years, or in non-human primates dosed for 87 weeks.[98]

New findings for liraglutide reported at EASD 2010

At EASD 2010 it was reported that liraglutide improves cardiovascular risk factors associated with type 2 diabetes, including systolic blood pressure and body weight.[77] Nausea, vomiting and diarrhoea are commonly reported class effects associated with GLP-1 agonists early in therapy; these adverse events could explain some of the weight loss in patients taking GLP-1 agonists. Sustained weight loss was reported to occur regardless of whether patients had adverse events of nausea, vomiting or diarrhoea.[99] Data in rats indicated that regulation of appetite signals in the brain, rather than delayed gastric emptying, is the main mechanism for liraglutide induced weight loss.[100,101]

Evidence for beneficial effects on the vascular endothelium was presented, which suggests that liraglutide may have the potential to ameliorate atherosclerosis in patients with type 2 diabetes. In vitro data showed liraglutide to down-regulate endoplasmic reticulum stress markers in endothelial cells exposed to high glucose levels.[102] In a mouse model of atherosclerosis (mice fed a high-fat diet), liraglutide inhibited induction of adhesion molecules and prevented endothelial dysfunction.[47] Further evidence for GLP-1 agonists improving pancreatic beta-cell function was presented from a meta-analysis of six liraglutide LEAD clinical trials.[31] Both the homeostasis model assessment for beta-cell function (HOMA-B), and the proinsulin-to-insulin ratio improved, suggesting that liraglutide may reduce or even reverse the long-term decline in beta-cell function in type 2 diabetes (similarly to exenatide).[87]

In a mouse model of traumatic brain injury, liraglutide therapy protected against cortical lesions, suggesting an anti-inflammatory action and neuroprotective properties.[46]

Finally, liraglutide was reported to significantly improve overall treatment satisfaction compared with a DPP-4 inhibitor (sitagliptin),[103] reflecting the superior HbA1c reduction and weight loss which was observed for liraglutide versus sitagliptin.[104]

Other GLP-1 Analogues in Development

Two GLP-1 analogues, taspoglutide and lixisenatide, are in the later stages of clinical development.

Taspoglutide is a long-acting GLP-1 analogue in which alanine at position 8 and glycine at position 35 have been replaced with aminoisobutyric acid to prevent DPP-4 and protease-mediated cleavage at the N- and C-terminus, respectively.[105] Due to a zinc-based sustained release formulation and its resistance to proteolysis, taspoglutide can be given subcutaneously once-weekly. Results from several phase 3 clinical trials of taspoglutide (T-emerge trials) were presented at EASD 2010. These studies compared taspoglutide with sitagliptin or placebo in patients inadequately controlled on metformin (T-emerge 4 trial) [106]; taspoglutide monotherapy vs placebo in drug-naive patients (T emerge 1 trial) [107]; taspoglutide vs exenatide in patients inadequately controlled on metformin, a thiazolidinedione, or both (T-emerge 2 trial) [108, 109]; or taspoglutide vs insulin glargine in patients inadequately controlled on metformin (T-emerge 5 trial).[110] The results were supportive of taspoglutide as a therapeutic agent for the treatment of type 2 diabetes. However, a higher than expected incidence of hypersensitivity reactions (associated with anti-drug antibodies[111]) was observed in patients receiving once-weekly therapy with taspoglutide and further clinical trials have been suspended.[112]

Lixisenatide (also known as AVE0010) is based on the structure of exendin-4, but is modified with six lysine residues at the C-terminal.[113] In a randomized, double-blind, placebo-controlled study, lixisenatide significantly improved glycaemic control in mildly hyperglycaemic patients who were inadequately controlled on metformin.[114] Dose-response relationships were seen for once- and twice-daily regimens, with a 20-µg once-daily dose of lixisenatide demonstrating the best efficacy-to-tolerability ratio. Data presented at EASD 2010 showed that lixisenatide also significantly improved glycaemic control when used as a monotherapy,[115] and restored insulin release and accelerated glucose disposition when administered to patients with type 2 diabetes (treated with metformin or diet and exercise alone).[116] Phase 3 trials of lixisenatide are ongoing.

A number of other GLP-1 analogues are in the early stages of clinical development, eg, albiglutide,[117, 118] LY2189265[119] and VRS-859.[120] These analogues have been specifically engineered to have a prolonged half-life, so that the frequency of subcutaneous injections can be reduced to weekly, or even monthly, intervals. Albiglutide was engineered by the genetic fusion of a DPP-4-resistant GLP-1 analogue dimer to human albumin,[118] LY2189265 by the fusion of a DPP-4-resistant GLP-1 analogue

to modified immunoglobulin G (IgG4),[121] and VRS-859 by the fusion of exenatide to a novel hydrophilic sequence of natural amino acids called XTEN.[122] The development of once-weekly formulations of liraglutide and/or the novel GLP-1 analogue semaglutide is also under consideration.[123] It will be interesting to follow the development of these novel agents with extended dosing intervals, to see if they are efficacious and safe in the treatment of patients with type 2 diabetes.

Future Developments

GLP-1 agonists have demonstrated sustained long-term glycaemic control, and importantly, this occurs in a glucose-dependent manner, so that the risk of hypoglycaemia is low. Intensive glycaemic control is known to reduce the microvascular complications associated with diabetes.[7] The decreases in body weight, systolic blood pressure, LDL cholesterol, triglycerides and free fatty acids found with liraglutide [77] suggest that in long term studies, there could be significant cardiovascular benefits.

Furthermore, the cardiovascular efficacy of the various GLP-1 agonists may differ; for example, in rat aortae, various GLP-1 peptides have shown different potency at inducing relaxations.[124] There may also be differences between the GLP-1 agonists depending on their proteolysis, as it has been suggested that the major DPP-4 cleavage product of GLP-1 ([9-36] amide) has vasodilator effects, possibly via a second GLP-1 receptor.[125]

Long-term clinical trials will help to answer which GLP-1 agonists have the greatest benefit in terms of cardiovascular risk reduction. Such trials have already commenced for liraglutide (LEADER: a long-term, multi-centre, international, randomized, double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events; estimated enrolment of 8754 patients with type 2 diabetes) and once-weekly exenatide (EXSCEL: a randomized, placebo-controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once-weekly; estimated enrolment of 9500 patients with type 2 diabetes). However, these trials evaluating cardiovascular risk are not due to complete until 2016 and 2017, respectively.[126, 127]

Patients with type 1 diabetes might also benefit from treatment with GLP-1 agonists. At EASD 2010, results for liraglutide in patients with type 1 diabetes with residual beta-cell function suggested that insulin treatment could be discontinued without impairment of glycaemic control.[128] Furthermore, the development of fixed-dose combinations of GLP-1 agonists and long-acting insulin analogues - eg, insulin degludec and liraglutide -- is being planned.[123] Non-injectable formulations are being developed, including nasal and transdermal, which may help to increase patient compliance.[129]

The significant weight loss induced by GLP-1 agonists, together with their beneficial effects on various cardiovascular risk factors, implies that they could prove to be of therapeutic benefit in the treatment of obesity. A clinical trial investigating the effects of liraglutide in healthy obese volunteers has started, as part of a full clinical development for the treatment of obesity.[126] Hypercholesterolaemia is associated with low bone density; results from a rat model of obesity presented at EASD 2010 suggest that GLP-1 agonists have the ability to both lower triglycerides and increase bone calcium levels, possibly involving a second GLP-1 receptor.[48]

Finally, evaluation of the effects of stimulating GLP-1 receptors in the brain presents the possibility of beneficial effects for both Alzheimer's[130] and Parkinson's[131] disease. A clinical trial to evaluate the effects of exenatide in Parkinson's disease is underway.[127]

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