

## The Incretin System and Type 2 Diabetes

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### Abstract

While antidiabetes therapies target glycemic control, most do not address the underlying problems of excess bodyweight and deteriorating pancreatic beta-cell function. Some therapies also provoke hypoglycemia and/or weight gain. Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the gut in response to nutrient intake and has a major role in the post-prandial insulin response in healthy individuals. The incretin response is, however, impaired in individuals with type 2 diabetes. There are two therapeutic approaches that target the incretin system: GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 receptor agonists provide pharmacological levels of GLP-1 activity, while DPP-4 inhibitors restore physiological levels. The pharmacological levels of GLP-1 induced by GLP-1 receptor agonists provide effective glycemic control and weight reduction. The DPP-4 inhibitors also improve glycemic control but are weight-neutral. Pre-clinical studies in animal models and *in vitro* systems suggest that incretin-based therapies have the potential to preserve beta-cell mass and improve their function. Initial clinical data show improvements in beta-cell function in patients treated with incretin-based therapies, supporting the pre-clinical observations. A further benefit of incretin-based therapies is that they provide glucose-dependent glucose control, which means that they have a low inherent risk of inducing hypoglycemia. These agents therefore look extremely promising in the management of type 2 diabetes, being efficacious and having positive benefits on weight, low risk of hypoglycemia, and the potential to improve pancreatic islet cell function in the long term.

### Keywords

Dipeptidyl peptidase-4 (DPP-4), DPP-4 inhibitor, exenatide, glucagon-like peptide-1 (GLP-1), GLP-1 receptor agonist, incretin, liraglutide, sitagliptin, saxagliptin, type 2 diabetes

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### The Impact of Diabetes and Patient Needs

With the increasing problem of obesity related to sedentary lifestyles and calorie-rich diets, the incidence and prevalence of type 2 diabetes are increasing at an alarming pace. Diabetes has a major impact in terms of patient quality of life and is associated with significant economic burden in terms of medical costs and lost productivity. In 2007, it was estimated that 57 and 24 million North Americans had pre-diabetes and diabetes, respectively.<sup>1</sup> Estimated annual costs for diabetes in 2007 were \$172 billion.<sup>1</sup> From a European perspective, it has been estimated that diabetes affects approximately 3–4 million 20–39-year-olds, 20 million 40–59-year-olds, and 30 million 60–79-year-olds.<sup>2</sup>

Pre-diabetes and type 2 diabetes are closely associated with obesity and other major cardiovascular risk factors, such as dyslipidemia and hypertension. Diabetes can also exacerbate the risks posed by other cardiovascular risk factors.<sup>1</sup> With the incidence of diabetes increasing in both older and younger age groups, society is facing a burden of diabetes-associated morbidity and mortality. In addition, with many treatments for

diabetes promoting weight gain, there is a need for treatments that do not exacerbate obesity and have a low risk for hypoglycemia.

### The Incretin System

The incretin effect is the greater increment in plasma insulin levels induced by an equivalent glucose load administered orally rather than intravenously. It is mediated via endocrine peptide hormones secreted by the intestine in response to nutrient exposure. The two major incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose insulinotropic polypeptide (GIP), which in healthy individuals may be responsible for around 70% of the post-prandial insulin response.<sup>3</sup>

There is a reduction of the incretin effect in individuals with type 2 diabetes, which can be rectified through the administration of exogenous native GLP-1.<sup>3,4</sup> Hence, continuous intravenous infusion of GLP-1 in subjects with type 2 diabetes increases insulin secretion, reduces glucagon secretion, and lowers plasma glucose.<sup>5</sup> The effect of GLP-1 is glucose-dependent, so despite ongoing infusion of GLP-1,

insulin levels return toward basal levels and plasma glucose stabilizes when normal fasting plasma glucose concentrations are reached.<sup>5</sup> This glucose dependence implies that drugs targeting the incretin system should have a low inherent risk of inducing hypoglycemia.

GLP-1 also has a number of other effects that could benefit individuals with type 2 diabetes. *In vitro* and animal studies have demonstrated that native GLP-1 promotes beta-cell neogenesis and preservation, so GLP-1 treatment could potentially help to preserve beta-cell mass and improve beta-cell function in patients with type 2 diabetes.<sup>6</sup> GLP-1 promotes satiety, slows gastric emptying, and is associated with reduced energy intake in humans,<sup>7</sup> suggesting that GLP-1 receptor agonists may support weight reduction. GLP-1 increases renal sodium excretion and has favorable effects on endothelial dysfunction, factors that can potentially explain the decrease in systolic blood pressure observed after long-term treatment with GLP-1 agonists.<sup>8,9</sup> GLP-1 also has beneficial effects on the heart, such as protecting myocardial cells in ischemic reperfusion injury models and improving cardiac function following acute myocardial infarction.<sup>6,10,11</sup> These actions could provide benefits for patients with type 2 diabetes and associated comorbidities.

While exogenous continuous administration of native GLP-1 showed therapeutic potential,<sup>5</sup> the use of recombinant human GLP-1 would not be clinically useful. Recombinant GLP-1 cannot be administered orally and the native peptide is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) following intravenous injection, giving it an *in vivo* half-life of only two minutes.<sup>12</sup> It has therefore been necessary to develop mimetics or analogs of human GLP-1 that are much more resistant to DPP-4 degradation than the native hormone. This strategy has produced the GLP-1 receptor agonists exenatide and liraglutide, which are administered by subcutaneous injection.

Another strategy has been to develop inhibitors of DPP-4 to enable concentrations of native GLP-1 to increase. This approach is less specific, however, as DPP-4 inhibitors also increase endogenous GIP concentrations. Two DPP-4 inhibitors, sitagliptin and saxagliptin, are currently approved in the US. Sitagliptin, vildagliptin, and saxagliptin are approved in the EU. Another DPP-4 agent, alogliptin, has postponed its US and EU approval submissions in order to carry out additional safety studies, as required by the US Food and Drug Administration (FDA).

One important difference between these two therapeutic approaches is that GLP-1 receptor agonists induce pharmacological levels of GLP-1 activity, while DPP-4 inhibitors preserve physiological levels. In addition, while GLP-1 receptor agonists act only through GLP-1, inhibition of DPP-4 is likely to affect concentrations of both GLP-1 and GIP, as these molecules are both substrates for the DPP-4 enzyme.<sup>13</sup>

While GLP-1 concentrations are reduced in individuals with type 2 diabetes, however, its insulinotropic action is relatively well preserved.<sup>13,14</sup> By contrast, while GIP concentrations are largely unaffected in type 2 diabetes, its insulinotropic action is impaired.<sup>13</sup> These characteristics of GLP-1 receptor agonists and DPP-4 inhibitors result in functional differences between the two approaches, which will now be discussed.

### Exenatide and Liraglutide— The Glucagon-like Peptide-1 Receptor Agonists Basic Properties

Exenatide (synthetic exendin-4) is a recombinant peptide based on a salivary product of the 'gila monster' lizard (*Heloderma suspectum*).<sup>15</sup> Exenatide is a 39-amino-acid peptide that has a 53% identical sequence to human GLP-1. Exenatide is a GLP-1 mimetic with similar potency to native GLP-1 but with partial resistance to DPP-4.<sup>16</sup>

Exenatide was approved in the US in 2005 as an add-on therapy to improve glycemic control in patients with type 2 diabetes who have not achieved adequate glycemic control with metformin, a sulfonylurea (SU), a thiazolidione (TZD), or combinations of metformin and an SU or TZD.<sup>15</sup> European marketing approval was gained in 2006 for combined therapy with metformin, SUs, TZDs, or combinations of oral antidiabetes drugs (OADs).<sup>17</sup>

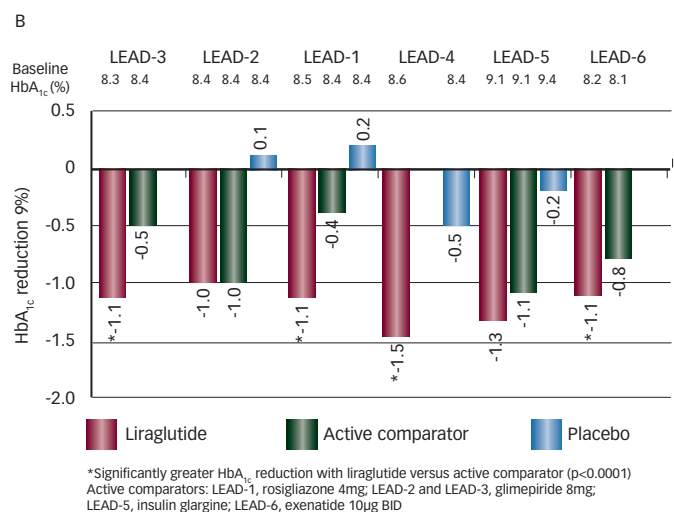
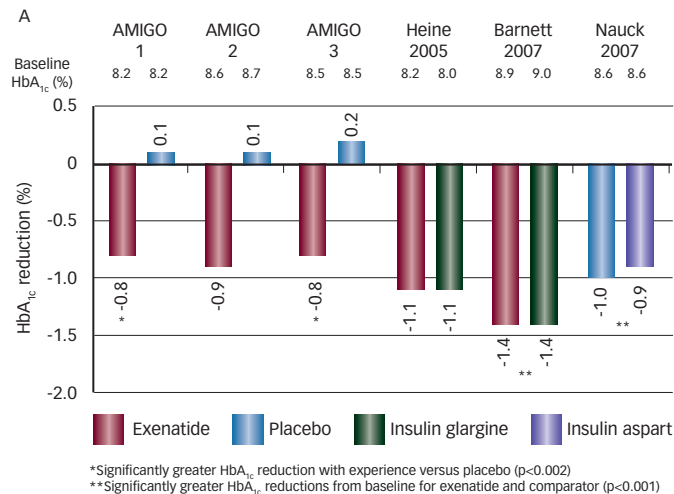
Following subcutaneous injection, exenatide reaches peak plasma levels at approximately two hours, has a plasma half-life of around three to four hours, and induces reductions in glucose concentrations for five to seven hours.<sup>18,19</sup> This means that exenatide requires twice-daily dosing 0–60 minutes before a meal and primarily acts to control post-prandial blood glucose after breakfast and dinner.<sup>19</sup> Exenatide is predominantly eliminated by glomerular filtration, therefore dosage escalation should be carried out cautiously in patients with moderate renal impairment and it is not recommended for individuals with end-stage renal disease or severe renal impairment.<sup>15</sup> A long-acting exenatide formulation requiring once-weekly dosing is also currently in clinical development.<sup>19–21</sup>

Liraglutide, the first once-daily human GLP-1 analog, is approved for use in the EU<sup>22</sup> and is still under FDA review in the US. It is a synthetic analog of human GLP-1 with a 97% identical amino acid sequence that has been modified by the addition of a fatty acid side chain and a glutamic acid spacer. This means that liraglutide self-associates into heptamers, which delays absorption from the injection site.<sup>23</sup> Once in the circulation, the fatty acid side chain may provide the molecule with partial resistance to DPP-4 via reversible binding to serum albumin. These attributes mean that following a single dose of liraglutide, peak plasma levels are reached after nine to 12 hours and the drug has a half-life of 13 hours.<sup>24</sup> In addition, liraglutide achieves increased plasma concentrations for up to 24 hours following a single subcutaneous injection and steady-state levels are achieved quickly, which supports once-daily dosing.<sup>24,25</sup> It can be administered at any time of day irrespective of meals, although individual users should inject at the same time each day. Liraglutide is metabolized in the same way as large endogenous proteins and there is no single organ responsible for elimination.<sup>22</sup> The European approval recommends that liraglutide can be used without dose adjustment in patients with mild renal impairment.<sup>22</sup> However, given limited therapeutic experience in patients with moderate renal impairment and a lack of therapeutic experience in patients with severe renal impairment, use in these populations is not recommended.<sup>22</sup>

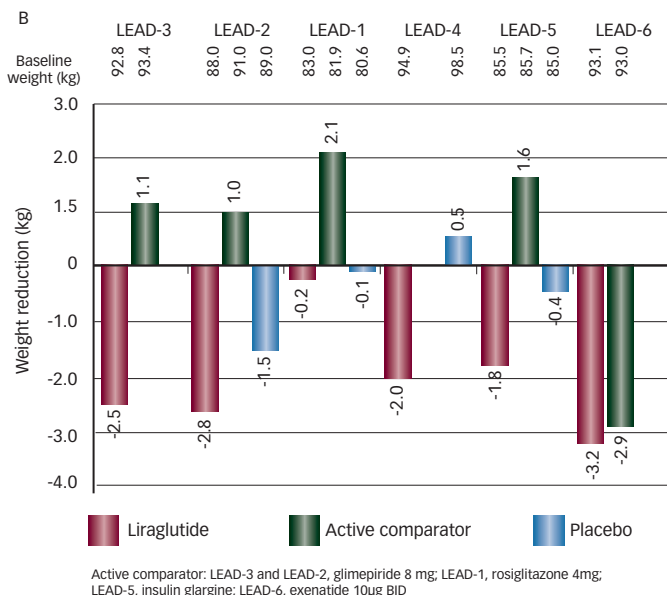
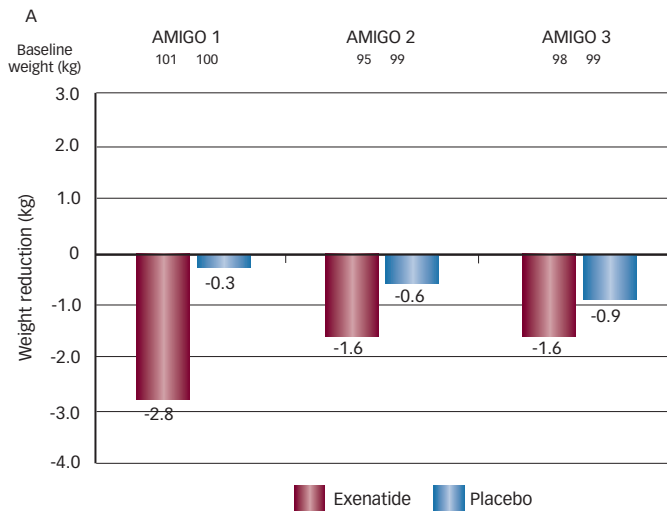
### Clinical Efficacy

The clinical efficacy of exenatide has been examined in a large number of clinical trials including the AMIGO (AC2993: Diabetes Management for Improving Glucose Outcomes) studies.<sup>26–28</sup> Glycated hemoglobin (HbA<sub>1c</sub>)

**Figure 1: HbA<sub>1c</sub> Reductions with Exenatide 10µg Twice Daily (A)<sup>26-31</sup> and Liraglutide 1.8mg Once Daily (B)<sup>34-39</sup>**



**Figure 2: Weight Reductions with Exenatide 10µg Twice Daily (A)<sup>26-28</sup> and Liraglutide 1.8mg Once Daily (B)<sup>34-39</sup>**



reductions of 0.80–0.86% were observed in the three AMIGO trials where exenatide treatment was added to various OAD combinations (see Figure 1).<sup>26-28</sup> Other trials have demonstrated that exenatide offers HbA<sub>1c</sub> reductions that are non-inferior to insulin glargine<sup>29-30</sup> or insulin aspart<sup>31</sup> (see Figure 1). Exenatide treatment was associated with weight reductions of 1.6–2.8kg (see Figure 2).<sup>26-28</sup> These data are in agreement with a meta-analysis of trials involving exenatide, which indicated an average reduction in HbA<sub>1c</sub> of approximately 1.0%, a reduction in fasting blood glucose of approximately 25mg/dl, and weight reductions of 2–3kg over 30 weeks.<sup>32</sup> Exenatide was associated with weight benefits versus insulin glargine (between-group difference -2.2kg; p<0.001)<sup>29</sup> and insulin aspart (-5.4kg; p<0.001).<sup>31</sup> Higher rates of gastrointestinal adverse events were observed with exenatide than with insulins.<sup>29-31</sup> A long-term evaluation of patients who continued exenatide treatment following the AMIGO studies has suggested that initial improvements in glycemic control and weight loss continued over a two-year period.<sup>33</sup> Of 1,446 individuals included in the original intention-to-treat population, however, only 283 completed the two-year extension, so loss of approximately 80% of the original study population may have introduced some bias in the study findings.<sup>33</sup>

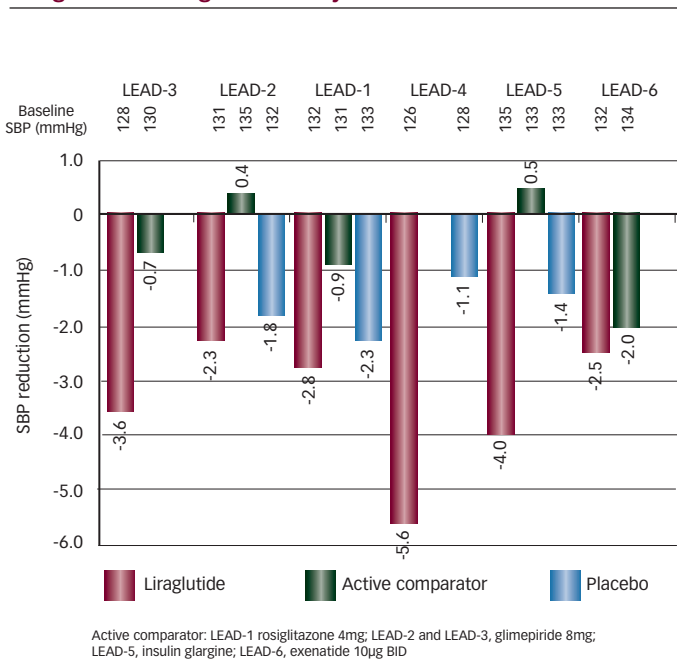
Liraglutide has been studied in the LEAD (Liraglutide Effect and Action in Diabetes) trials,<sup>34-39</sup> which were designed to investigate liraglutide as either monotherapy or in combination with one or two OADs and compare them against some commonly used therapies for type 2 diabetes (see Table 1).<sup>34-39</sup> Liraglutide treatment was associated with reductions in HbA<sub>1c</sub> of between 1–1.5% in the LEAD trials (see Figure 1).<sup>34-39</sup> Liraglutide induced significantly greater reductions in HbA<sub>1c</sub> than comparator treatment in all but the LEAD 2 trial,<sup>35</sup> in which it was similar. The LEAD 6 study compared liraglutide 1.8mg once daily and exenatide 10µg twice daily as add-ons to metformin and/or SU therapy.<sup>39</sup> In LEAD 6, mean HbA<sub>1c</sub> reduction was significantly greater with liraglutide treatment than with exenatide (-1.12 versus -0.79%; p<0.0001) and mean fasting plasma glucose was significantly lower with liraglutide (-29mg/dl) compared with exenatide (-10.8mg/dl; p<0.0001).<sup>39</sup> Both liraglutide and exenatide were well tolerated. Nausea was less persistent with liraglutide than with exenatide (p<0.0001). Minor

**Table 1: The LEAD Trials Examined the Role of Liraglutide Therapy Across a Range of Treatment Intensities**

Study	Liraglutide Group	Active Comparator	Placebo and Background Therapy
LEAD 1 <sup>34</sup>	Liraglutide + glimepiride	Rosiglitazone + glimepiride	Placebo and Glimepiride
LEAD 2 <sup>35</sup>	Liraglutide + metformin	Glimepiride + metformin	Metformin
LEAD 3 <sup>36</sup>	Liraglutide monotherapy	Glimepiride monotherapy	No placebo group
LEAD 4 <sup>37</sup>	Liraglutide + metformin and rosiglitazone	No active comparator group	Metformin + rosiglitazone
LEAD 5 <sup>38</sup>	Liraglutide + metformin and glimepiride	Insulin glargine + metformin + glimepiride	Metformin + glimepiride
LEAD 6 <sup>39</sup>	Liraglutide + metformin and/or glimepiride	Exenatide + metformin and/or glimepiride	No placebo group

Appropriate placebos for both liraglutide injections plus active comparators were included in all treatment groups.

**Figure 3: Systolic Blood Pressure Reduction with Liraglutide 1.8mg Once Daily<sup>34-39</sup>**



SBP = systolic blood pressure.

hypoglycemia was also less frequent with liraglutide than with exenatide (1.93 versus 2.60 events per patient per year;  $p=0.01$ ).<sup>39</sup> With the exception of LEAD 1, in which liraglutide plus glimepiride treatment was weight-neutral,<sup>34</sup> in the other studies liraglutide treatment was associated with weight reductions of approximately 2–3kg (see Figure 2).<sup>35-39</sup> Systolic blood pressure reductions of between 2.3 and 5.6mmHg were also observed with liraglutide treatment (see Figure 3). In the head-to-head comparison of liraglutide and exenatide (LEAD 6), the decrease in systolic blood pressure by 2.5 and 2.0mmHg, respectively, was not significantly different between the groups.<sup>39</sup>

### Beta-cell Effects

Studies in animal and *in vitro* models suggested that GLP-1 receptor agonists may promote pancreatic beta-cell neogenesis and preservation. These initial observations have been supported by data from the LEAD trials showing improvements in beta-cell function by a homeostatic model assessment (HOMA) index of beta-cell function (HOMA-B) of 27–35% from baseline following liraglutide treatment.<sup>34-39</sup> Similar improvements in HOMA-B were observed with exenatide.<sup>40,41</sup> Liraglutide and exenatide also improved other measures of beta-cell function, such as the pro-insulin to insulin ratio, as well as other non-beta-cell-related improvements in glycemic measures, such as the HOMA-index of insulin resistance. These results suggest that GLP-1 receptor agonists have the potential to improve beta-cell function, a key underlying pathology in type 2 diabetes. Whether this is reflected in improved durability of glycemic control needs to be tested in long-term clinical trials.

### Adverse Side Effects

As expected from the glucose-dependent glucose lowering of GLP-1, the GLP-1 receptor agonists are associated with low hypoglycemia rates in clinical studies. Hypoglycemia was most commonly reported when GLP-1 receptor agonists were combined with SUs, so prescribing information for exenatide and liraglutide both include a recommendation to reduce SU dosing when adding a GLP-1 receptor agonist. Individuals may also experience nausea when therapy is initiated, which in most cases ceases within four weeks. This probably relates to delayed gastric emptying. Gradual dose titration of both exenatide and liraglutide may help to avoid this potential side effect.<sup>41,42</sup>

### The Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors act by increasing endogenous GLP-1 and GIP activity. However, only GLP-1 retains insulinotropic activity in individuals with type 2 diabetes. There is evidence that DPP-4 inhibitors induce lower placebo-corrected HbA<sub>1c</sub> reductions (0.7–1.0%) compared with GLP-1 receptor agonists (1.0–1.5%),<sup>32,34-38,43</sup> but this needs to be confirmed in head-to-head trials. There are a number of DPP-4 inhibitors in development, including alogliptin and linagliptin; however, this section will concentrate on sitagliptin and saxagliptin, as these agents have received regulatory approval in the US.

### Sitagliptin

Sitagliptin is approved for use at a dose of 100mg/day as either monotherapy or in combination with metformin or TZDs in the US.<sup>44</sup> In patients with moderate or severe renal insufficiency the dose of sitagliptin should be reduced to 50 and 25mg/day, respectively.<sup>44</sup> In the EU, sitagliptin is approved for use as dual or triple combination therapy with metformin, SUs, or TZDs and as monotherapy where metformin is contraindicated or not tolerated. In addition, sitagliptin is indicated as an add-on to insulin ( $\pm$  metformin) when diet and exercise plus insulin do not achieve adequate glycemic control. At doses  $\geq 100$ mg, sitagliptin inhibits  $\geq 80\%$  of DPP-4 activity over 24 hours.<sup>45</sup> This results in at least a two-fold increase in post-meal levels of endogenous GLP-1 compared with placebo.<sup>45-47</sup> The greatest HbA<sub>1c</sub> reductions reported with sitagliptin have been observed when it has been used in combination with metformin in previously OAD-naïve patients (placebo-adjusted reductions of -0.83 and -1.57% for sitagliptin 100mg and sitagliptin 100mg plus metformin 1,000mg, respectively).<sup>48</sup> This

effect may reflect the fact that metformin increases GLP-1 secretion and sitagliptin prolongs its half-life.<sup>19</sup> Measures of beta-cell function such as HOMA-B (12% improvement, 95% confidence interval [CI] 9.45–14.60) and pro-insulin/insulin ratio (-0.06, 95% CI -0.08 to -0.04) were also significantly improved with sitagliptin versus placebo, although HOMA-B was not significantly improved versus active comparators (5.64%, 95% CI 0.38–10.90).<sup>49</sup>

### Saxagliptin

Saxagliptin has been studied as a monotherapy in treatment-naïve patients or as an add-on therapy to metformin or an SU.<sup>50–52</sup> The lower recommended dosage of saxagliptin (2.5mg/day) should be used in individuals with moderate or severe renal disease.<sup>53</sup> In treatment-naïve patients, 24 weeks of saxagliptin monotherapy (10mg dose) resulted in an HbA<sub>1c</sub> reduction from baseline (mean 7.9%) of -0.54 versus +0.19% for placebo (p<0.0001).<sup>50</sup> Adjusted mean fasting plasma glucose was significantly reduced from baseline at -17mg/dl with saxagliptin versus +6mg/dl for placebo (p<0.0001).<sup>50</sup> No cases of confirmed hypoglycemia were reported.<sup>50</sup> In patients failing with metformin monotherapy, saxagliptin (10mg/day) plus metformin demonstrated statistically significant adjusted mean decreases from baseline to week 24 versus placebo in HbA<sub>1c</sub> (-0.58 versus +0.13%; p<0.0001) and fasting plasma glucose (-20.50 versus +1.24mg/dl; p<0.0001).<sup>52</sup> Approximately 5% of patients reported hypoglycemic episodes in each treatment arm.<sup>52</sup> Weight reductions were 0.53kg for saxagliptin plus metformin and 0.92kg for placebo plus metformin.<sup>52</sup> A third study examined the efficacy of adding saxagliptin to suboptimal doses of glyburide (7.5mg/day) versus uptitration of glyburide (to a maximum of 15mg/day).<sup>51</sup> Saxagliptin 5mg reduced HbA<sub>1c</sub> by 0.64 versus +0.08% for uptitrated glyburide (p<0.0001) and fasting plasma glucose by -10 versus +1mg/dl for uptitrated glyburide.<sup>51</sup> Reported hypoglycemic events were comparable for saxagliptin (14.6%) and uptitrated glyburide (10.1%).<sup>51</sup>

### Comparison of the Two Drug Classes

Like GLP-1 receptor agonists, DPP-4 inhibitors are associated with a low risk of hypoglycemia. Few hypoglycemic events have been reported in clinical trials, although as with GLP-1 receptor agonists higher rates have been reported in combination therapy with SUs. In contrast to GLP-1 receptor agonists, DPP-4 inhibitors are weight-neutral. Adverse gastrointestinal events are less likely with DPP-4 inhibitors than with GLP-1 receptor agonists. These differences between the two drug classes may reflect the level of GLP-1 receptor stimulation. While the DPP-4 inhibitors can restore endogenous GLP-1 concentrations in individuals with type 2 diabetes, they do not raise GLP-1 to the pharmacological levels achieved by the GLP-1 receptor agonists.<sup>13,20</sup>

In addition to differences in GLP-1 activity, there is a potential concern with the specificity of action of DPP-4 inhibitors because DPP-4 is

involved in immunoregulation in addition to its role in the incretin system. The possibility of immunological effects has been suggested as increased rates of infections (nasopharyngitis and urinary tract infections) have been observed in some trials.<sup>32</sup> In addition, post-marketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported.<sup>44</sup> Overall, however, the DPP-4 inhibitors appear to be very well tolerated in the majority of patients.

### Conclusions

Incretin-based antidiabetes therapies offer patients the potential to target key pathogenic mechanisms in type 2 diabetes in addition to lowering blood glucose. Across trials, GLP-1 receptor agonists induced mean HbA<sub>1c</sub> reductions of approximately 0.8–1.5%. For DPP-4 inhibitors HbA<sub>1c</sub> reductions were around 0.7–1.0%. The GLP-1 receptor agonists also bring additional benefits, such as weight loss and blood pressure reduction. These treatments are simple for patients to self-administer and titrate and, for liraglutide, dosing is not dependent on food intake. The risks of serious adverse side effects, such as (particularly severe) hypoglycemia, are low; this, together with weight benefits and less/no necessity for daily blood glucose monitoring, is likely to facilitate improved patient adherence.

From a physician's perspective, therapies that target the incretin system may be a useful treatment option for patients with type 2 diabetes, due to their clinical efficacy, good tolerability, and low risk of hypoglycemia and their potential to improve beta-cell function. Incretin-based therapies offer a promising novel treatment modality for individuals with diabetes, with added benefits and the potential for beta-cell protection; the latter now requires study in long-term clinical trials. ■



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(including 'difficult-to-reach' groups). In addition to publishing over 500 original papers, Professor Barnett has written many books, review articles, and editorials on diabetes and has contributed chapters to major textbooks on the subject. He also regularly acts as adviser to the National Institute for Health and Clinical Excellence (NICE), the European Medicines Agency (EMA), and the National Prescribing Centre on diabetes-related therapies. For two years, he held the position of Medical Research Council Senior Fellow in Diabetes at King's College Hospital, London. He gained his MD from King's College, University of London, and subsequently trained at a number of hospitals and universities.

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