



## The Clinical Use of Incretin-Based Therapy in Type 2 Diabetes

### Learning Objectives

After completing this activity, participants should be better able to:

- Explain how the progressive pathophysiology of type 2 diabetes demands progressive therapeutic interventions to reach and maintain glycemic goals
- Describe the role of the incretin system on glucose homeostasis
- Compare the benefits and limitations of incretin-based therapies with other glucose-lowering agents
- Differentiate the clinical effects of the glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors

### Introduction

Among the pathophysiologic mechanisms involved in the etiology of type 2 diabetes mellitus (T2DM), the role of the incretin system is the least familiar to most clinicians. However, the incretin system has been the subject of clinical investigation over the last 4 decades.<sup>1</sup> The incretin system may be responsible for up to 70% of insulin secretion in response to oral glucose or a meal in healthy individuals.<sup>2</sup> A key incretin hormone, glucagon-like peptide-1 (GLP-1), is secreted in response to food ingestion, but is broken down within minutes through the action of the enzyme DPP-4. To overcome this degradation, the injectable GLP-1R agonists exenatide and liraglutide have been developed. In addition, the oral inhibitors of DPP-4—sitagliptin, saxagliptin, and linagliptin—have been developed to prolong the action of endogenous GLP-1. Both the GLP-1R agonists and DPP-4 inhibitors act to increase insulin release<sup>3-7</sup> and inhibit glucagon secretion,<sup>3,5,6,8-11</sup> both in a glucose-dependent manner (Table 1). The GLP-1R agonists, but not DPP-4 inhibitors, have been shown to slow gastric emptying<sup>5,12</sup> and to promote satiety.<sup>5,13,14</sup> Based upon preclinical investigation, the effects of GLP-1R agonists and DPP-4 inhibitors on pancreatic  $\beta$ -cell function have been investigated, with some trials demonstrating improvement of surrogate markers of  $\beta$ -cell function and others not.<sup>5,10,15-19</sup>

**Hypoglycemia risk is low with glucose-dependent incretin-based therapy.**

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**Table 1.**

### Actions of GLP-1R Agonists and DPP-4 Inhibitors in Regulating Glucose Homeostasis<sup>3,5,6,10</sup>

	Physiologic		Pharmacologic		
	↑ Insulin secretion (glucose-dependent)	↓ Glucagon secretion (glucose-dependent)	Promote satiety	Weight effect	↓ Gastric emptying rate
GLP-1R agonists	+	+	+	↓ 1-4 kg	+
DPP-4 inhibitors	+	+	No effect	↔	No effect

### Glycemic Efficacy

GLP-1R agonists lower glucose levels more than DPP-4 inhibitors as monotherapy, resulting in mean reductions in glycated hemoglobin (A1C) level ranging from 0.5% to 1.5%<sup>20-24</sup> for GLP-1R agonists, vs about 0.5% to 0.8% for DPP-4 inhibitors.<sup>\*15,18, 25</sup> When either of these classes is administered to patients on metformin or other glucose-lowering therapy, reductions in A1C level similar to or slightly greater than with monotherapy are observed.<sup>6,7,26-29</sup> A1C reductions of up to 1.5% have been reported with the GLP-1R agonist liraglutide.<sup>30,31</sup> Reductions in fasting plasma glucose (FPG) range from 11 to 44 mg/dL with the GLP-1R agonists and 4 to 29 mg/dL with the DPP-4 inhibitors.<sup>6,28,30-36</sup> Reductions in postprandial glucose (PPG) range from 29 to 49 mg/dL for the GLP-1R agonists and 23 to 68 mg/dL for the DPP-4 inhibitors.<sup>6,27,28,35,36</sup>

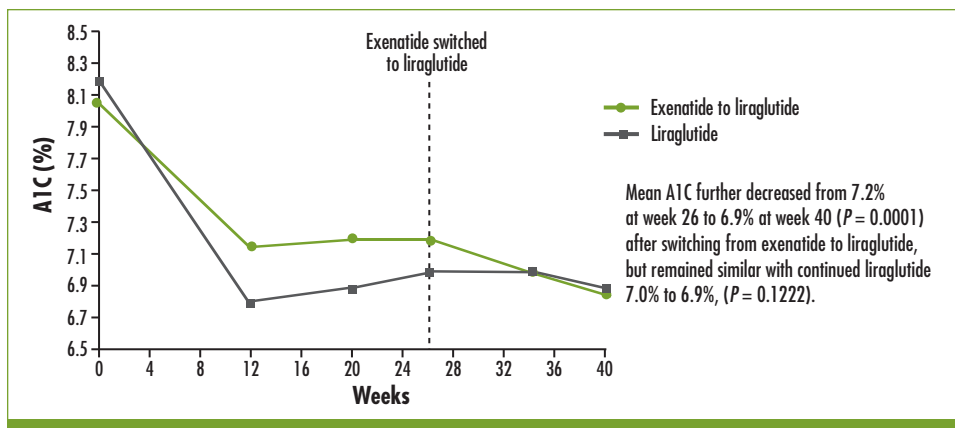
Patients with a baseline A1C level  $\geq 9.0\%$  appear to experience a greater A1C reduction with incretin-based therapy.<sup>16,28,32</sup> For example, in patients treated with exenatide, the A1C level decreased 0.6% in patients with a baseline A1C level  $< 8.0\%$  compared to a decrease of 1.5% in patients with a baseline A1C level  $\geq 9.0\%$ .<sup>16</sup> Furthermore, patients previously treated with diet and exercise alone have been observed to achieve a greater A1C reduction with liraglutide than those previously treated with glucose-lowering monotherapy (-1.6% vs -0.7%, respectively).<sup>22</sup>

### Head-to-Head Comparisons

Several trials have compared the addition to oral glucose-lowering therapy of 1 incretin-based therapy with another. A 26-week trial found that A1C level was reduced by 0.79% with exenatide 10 mcg twice daily compared to 1.12% with liraglutide once daily. The FPG decreased 11 mg/dL and 29 mg/dL, respectively.<sup>10</sup> Over an additional 14 weeks, A1C level decreased an additional 0.3% in patients switched from exenatide to liraglutide 1.8 mg once daily and 0.1% in those who continued liraglutide (Figure 1).<sup>37</sup>

A 6-week, double-blind, crossover trial compared exenatide 5 mcg twice daily for 1 week, followed by 10 mcg twice daily for 1 week, with sitagliptin 100 mg once daily for 2 weeks.<sup>5</sup> From a baseline FPG of 178 mg/dL, the FPG decreased to 163 mg/dL in patients treated with

\*Data cited in this section are not placebo-adjusted.



**Figure 1. Exenatide vs liraglutide as add-on therapy to metformin, sulfonyleurea, or the combination: A1C.** Diabetes Care by American Diabetes Association. Copyright 2011, Reproduced with permission of AMERICAN DIABETES ASSOCIATION in the format of internet posting via Copyright Clearance Center.<sup>37</sup>

exenatide and to 159 mg/dL in those treated with sitagliptin. From a baseline of 245 mg/dL, the PPG decreased to 133 mg/dL in patients treated with exenatide and 208 mg/L in those treated with sitagliptin. Following crossover, the PPG increased 73 mg/dL in those switched from exenatide to sitagliptin, but decreased 76 mg/dL in those switched from sitagliptin to exenatide.

In another 26-week trial, from a baseline of 8.4% to 8.5%, A1C decreased 1.2% and 1.5% in the liraglutide 1.2 and 1.8 mg once daily groups, respectively, and decreased 0.9% in the sitagliptin 100 mg once daily group.<sup>19</sup> Reductions of the FPG of 34 and 39 mg/dL were observed in the liraglutide 1.2 and 1.8 mg groups, respectively, and 15 mg/dL in the sitagliptin group. Including a 26-week extension, A1C level decreased from baseline to 52 weeks by 1.3% and 1.5% in the liraglutide 1.2 and 1.8 mg groups, respectively, and by 0.9% in the sitagliptin group.<sup>38</sup> The FPG decreased 31 and 37 mg/dL in the liraglutide 1.2 and 1.8 mg groups, respectively, and 11 mg/dL in the sitagliptin group.

An 18-week trial randomized patients with an A1C level of 6.5% to 10% on stable metformin doses to add-on therapy with sitagliptin 100 mg or saxagliptin 5 mg once daily.<sup>39</sup> From a baseline of 7.7%, similar reductions in A1C were observed (sitagliptin 0.6% vs saxagliptin 0.5%).

## Nonglycemic Effects

The GLP-1R agonists and DPP-4 inhibitors produce effects beyond lowering blood glucose that are clinically important.

## Weight

The ability of the GLP-1R agonists, but not the DPP-4 inhibitors, to promote satiety and reduce caloric intake<sup>5,14,40</sup> is thought to result in the 1 to 4 kg weight loss over several months that is observed in most patients on GLP-1R agonist therapy.<sup>20,22,29-34</sup> On the other hand, the DPP-4 inhibitors are considered weight-neutral.<sup>11,15,16,18,35,41</sup> The weight loss observed with

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the GLP-1R agonists results from loss of fat mass rather than lean body mass.<sup>42-45</sup> A decrease in fat mass of 11% and trunk fat mass of 13% has been observed following 1 year of treatment with exenatide as add-on therapy to metformin; lean body mass did not change.<sup>42</sup> One year of treatment with liraglutide also as add-on therapy to metformin resulted in a 16% to 17% decrease in visceral fat and 8% to 9% decrease in subcutaneous fat.<sup>45</sup>

The weight loss observed with the GLP-1R agonists has been a focus of much interest because of the contribution of weight gain in the pathogenesis of T2DM and increasing cardiovascular risk. The records of adults treated with exenatide, sitagliptin, or insulin for 60 days or more were reviewed to assess the potential impact of weight loss on glycemic control and cardiovascular biomarkers.<sup>46</sup> Patients treated with exenatide or sitagliptin lost weight (3.0 vs 1.1 kg, respectively), while patients treated with insulin gained weight (0.6 kg). Changes in body weight were significantly associated with reductions in A1C (exenatide 0.5%, sitagliptin 0.5%, insulin 1.0%) and FPG (exenatide 13 mg/dL, sitagliptin 14 mg/dL, insulin 27 mg/dL) for all 3 groups. However, a greater change in A1C and FPG occurred in those with weight loss treated with exenatide and in those with weight gain treated with sitagliptin or insulin. In terms of cardiovascular biomarkers, weight loss was significantly associated with reductions in both systolic (exenatide 2 mm Hg, sitagliptin 1 mm Hg, insulin 2 mm Hg) and diastolic (1 mm Hg in all 3 groups) blood pressure in all 3 groups. With respect to weight-associated changes in the lipid profile, patients treated with exenatide achieved significant reductions in total cholesterol (11 mg/dL), low-density lipoprotein cholesterol (LDL-C) (4 mg/dL), and triglycerides (26 mg/dL), while total cholesterol (9 mg/dL) and triglycerides (26 mg/dL) decreased in those treated with sitagliptin, and total cholesterol (12 mg/dL) in those treated with insulin. The short-term nature of the analysis precluded any assessment of the impact on cardiovascular events.

### Blood Pressure & Blood Lipids

Effects of GLP-1R agonists and DPP-4 inhibitors on blood pressure and the lipid profile have been investigated in other trials. Most studies show a 1- to 7-mm Hg reduction in systolic blood pressure with the GLP-1R agonists, while diastolic blood pressure and heart rate were unchanged.<sup>10,19,22,23,30,31,33,34,37,47-49</sup> Blood pressure also appears to be minimally affected by DPP-4 inhibitor therapy.<sup>19</sup>

In terms of the lipid profile, the greatest improvement is observed in the triglyceride level, which is reduced by 20 to 46 mg/dL with GLP-1R agonists, although no change has been observed in some studies.<sup>10,19,29,31,33,46</sup> The change in triglyceride level with the DPP-4 inhibitors appears more modest, with a reduction up to 20 mg/dL, although a number of studies report no change.<sup>15,38,50</sup> Small changes in LDL-C and high-density lipoprotein cholesterol (HDL-C) levels have been observed with both the GLP-1R agonists and DPP-4 inhibitors.

### Safety & Tolerability

While the current guidelines issued by the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) conclude that “placing greater emphasis on safety and ability to achieve an A1C goal of 6.5% will result in earlier and more frequent use of the incretin-based therapies,” their use is not without adverse events (Table 2).<sup>51-56</sup>

**Table 2.****Adverse Events<sup>a,52-56</sup>**

Exenatide	Nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, antiexenatide antibody formation
Liraglutide	Headache, nausea, diarrhea, antiliraglutide antibody formation
Sitagliptin	Upper respiratory tract infection, nasopharyngitis, headache
Saxagliptin	Upper respiratory tract infection, urinary tract infection, headache
Linagliptin	Nasopharyngitis

<sup>a</sup>Those with an incidence  $\geq 5\%$  and occurring more frequently than placebo.

**Hypoglycemia**

A key benefit of the GLP-1R agonists and DPP-4 inhibitors is a low incidence of hypoglycemia,<sup>28,48,57-59</sup> which results from the glucose-dependent manner of stimulation of insulin release and inhibition of glucagon secretion. As monotherapy, mild/moderate hypoglycemia has been observed in 4% to 9% with exenatide,<sup>20,23</sup> 0% to 12% with liraglutide,<sup>22,24</sup> 1% to 2% with sitagliptin,<sup>15-17</sup> 0% with saxagliptin,<sup>18,60</sup> and 0% with linagliptin.<sup>61</sup> In prospective head-to-head clinical trials, the incidence of mild/moderate hypoglycemia is similarly low and comparable among the GLP-1R agonists and DPP-4 inhibitors when added to metformin-based therapy.<sup>5,10,19,37-39,62</sup> In combination with a sulfonylurea, the incidence of hypoglycemia is increased with all GLP-1R agonists<sup>63,64</sup> and DPP-4 inhibitors,<sup>11,35,61</sup> which has led to the recommendation that the dose of sulfonylurea be reduced when the combination is used.<sup>52-56</sup>

**Nausea**

Transient nausea is the most common adverse event observed with the GLP-1R agonists,<sup>20,22-24</sup> peaking within 8 weeks with exenatide<sup>10,26</sup> and less than 4 weeks with liraglutide.<sup>10,22</sup> To reduce the incidence and severity of nausea, a dose escalation strategy is recommended. Exenatide should be started at 5 mcg twice daily within 1 hour of a meal for 1 month, then increased to 10 mcg twice daily.<sup>52</sup> Liraglutide should be initiated at 0.6 mg once daily without regard to meals and increased to 1.2 mg once daily after 1 week. If needed, liraglutide may thereafter be increased to 1.8 mg once daily.<sup>53</sup> Using these dose escalation strategies, nausea was experienced by 28% of patients treated with exenatide and 26% with liraglutide.<sup>10</sup> Compared to generally well-tolerated DPP-4 inhibitor therapy, nausea was experienced by 34% of patients treated with exenatide and 12% with sitagliptin in a 6-week crossover trial,<sup>5</sup> and 21% to 27% of patients treated with liraglutide and 5% treated with sitagliptin in a 26-week trial.<sup>19</sup>

**Acute Pancreatitis**

Acute pancreatitis has been reported with exenatide,<sup>52</sup> liraglutide,<sup>53</sup> sitagliptin,<sup>54</sup> and linagliptin.<sup>56</sup> The possible association of pancreatitis with incretin-based therapy is unclear, because persons with T2DM have an elevated risk of pancreatitis compared to persons without T2DM.<sup>65,66</sup> In addition, analyses of 2 insurance claims databases show that the risk of acute pancreatitis with GLP-1R agonist therapy is similar to other glucose-lowering therapies.<sup>66,67</sup> Further investigation is ongoing with all 5 incretin-based therapies currently available.

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### Hypersensitivity Reactions

Some type of hypersensitivity reaction has been reported with each of the 5 incretin-based therapies, although they appear to be more common with the DPP-4 inhibitors. Anaphylaxis and angioedema have been seen with exenatide<sup>52</sup> and an immunogenic reaction generally characterized by urticaria in less than 1% with liraglutide.<sup>53</sup> Serious allergic and hypersensitivity reactions, including Stevens-Johnson syndrome, have been described in postmarketing reports of sitagliptin.<sup>54</sup> A pooled analysis of 5 studies involving saxagliptin showed that hypersensitivity reactions, mainly urticaria and facial edema, occurred in 2% of patients.<sup>55</sup> Fewer than 1% of patients treated with linagliptin exhibited a hypersensitivity reaction, mainly urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity.<sup>56</sup> The Food and Drug Administration (FDA) has required further investigation of hypersensitivity reactions possibly associated with saxagliptin<sup>68</sup> and linagliptin.<sup>69</sup>

### Additional Safety Investigations

The FDA has required further investigations with incretin-based therapies to assess a possible association with thyroid medullary cancer or cardiovascular events.

#### Medullary Thyroid Cancer

Postmarketing reports with exenatide and rodent studies involving drug exposure levels of liraglutide many times those anticipated in humans led the FDA to conclude that there is a low risk of medullary thyroid cancer in humans requiring further investigation.<sup>70-72</sup> An association is unclear, because other investigation suggests that a GLP-1R mechanism may be involved in rodents but that GLP-1R expression in thyroid C-cells is low in humans.<sup>73</sup>

#### Cardiovascular Events

The FDA is also requiring further cardiovascular investigation as part of the approval requirements for liraglutide,<sup>71</sup> saxagliptin,<sup>68</sup> and linagliptin.<sup>69</sup> These requirements are in keeping with new standards adopted by the FDA for all glucose-lowering agents. The requirements were not completely met with the data submitted by the respective manufacturers prior to implementation of the new FDA standards.

### Use in Special Populations

#### Renal Dysfunction

Because of the common occurrence of renal dysfunction in patients with T2DM and the kidneys as a predominant clearance pathway of exenatide, sitagliptin, and saxagliptin, careful attention to dosing is needed to reduce the risk of hypoglycemia with these 3 agents (Table 3). Exenatide should not be used in patients with a creatinine clearance <30 mL/minute, and cautiously if the creatinine clearance is 30 to 50 mL/minute.<sup>52</sup> The dose of sitagliptin or saxagliptin should be reduced in patients with creatinine clearance ≤50 mL/minute.<sup>54,55</sup> Although dosage adjustment is not needed, liraglutide should be used cautiously in patients with renal dysfunction.<sup>53</sup> Patients treated with liraglutide with a creatinine clearance 60 to 89 mL/minute have been observed to not be at increased risk of minor hypoglycemia, nausea, or renal injury compared to placebo.<sup>74</sup> The dose of linagliptin does not need to be adjusted based on renal function, as approximately 80% of linagliptin is cleared via the enterohepatic system.<sup>56</sup>

**Table 3.****Use in Special Populations<sup>52-56</sup>**

Population	GLP-1R Agonists		DPP-4 Inhibitors		
	Exenatide	Liraglutide	Sitagliptin	Saxagliptin	Linagliptin
Kidney dysfunction/ ↓ CrCl (mL/min)	<30: CI 30-50: caution 50-80: no change in dose	Use with caution; no change in dose	<30: 25 mg once daily 30-49: 50 mg once daily 50-80: no change in dose	<50: 2.5 mg once daily	No change in dose
Pregnant	Category C		Category B		
Lactating	D/C nursing or D/C drug		Caution		
Elderly	Take care in dose selection based on renal function	No effect of age on phar- ma- cokinetics	Take care in dose selection based on renal function	Take care in dose selec- tion based on renal function	No change in dose

CI = contraindicated; CrCl = creatinine clearance; D/C = discontinue.

**Pregnancy & Lactation**

None of the GLP-1R agonists or DPP-4 inhibitors have been investigated in well-controlled studies involving pregnant or lactating women. Based upon animal studies, the GLP-1R agonists are classified as pregnancy category C; the DPP-4 inhibitors are classified as pregnancy category B (Table 3).<sup>52-56</sup> The GLP-1R agonists should be discontinued in a woman who is nursing or nursing discontinued.<sup>52,53</sup> The DPP-4 inhibitors should be used cautiously by a woman who is nursing.<sup>54-56</sup>

**Summary**

The incretin system plays an important role in glucose homeostasis, but is impaired in patients with T2DM. In addition to pharmacologic actions that differ from other glucose-lowering agents, there are important differences among the 5 incretin-based therapies currently available. These differences in glucose-lowering efficacy, weight, nonglycemic effects, safety, tolerability, and use in special populations are significant factors to consider in selecting therapy for an individual patient with T2DM.

## CASE: A 47-Year-Old Woman With Longstanding T2DM



### History and Presentation

A 47-year-old woman diagnosed with T2DM 5½ years ago was seen in the emergency department last night with a blood glucose of 47 mg/dL. This is the second time in 7 months that she has experienced symptomatic hypoglycemia. Current medications are metformin 1000 mg twice daily and glimepiride 4 mg once daily. She walks approximately 1¼ miles 3 to 4 days/week and belongs to a weekly bowling league.

### Physical Examination

- Blood pressure: 124/76 mm Hg
- Weight: 194 lb
- Body mass index: 29.6 kg/m<sup>2</sup>
- Waist: 37.4 in
- Height: 5 ft 9 in

### Laboratory Findings (1 week ago)

A1C: 7.9%

Lipid profile: Within normal limits except that her triglyceride level (now 177 mg/dL) has increased 19 mg/dL over the last 13 months.

### Clinical Decision Point

#### *What is your top priority at this visit?*

- Refer to a dietitian for dietary management
- Switch metformin to the extended-release formulation
- Discontinue glimepiride
- Review diabetes written action plan with patient

### Comment

The issue of greatest concern at the present time is the patient's recurring episodes of symptomatic hypoglycemia that require medical intervention. Therefore, addressing risks of hypoglycemia is of paramount importance, such as reviewing with the patient her eating habits and the written action plan, with consideration for referral to a dietitian. However, since glimepiride poses the greatest risk for hypoglycemia of the glucose-lowering medications she is currently taking, discontinuing glimepiride is the top priority. Replacement glucose-lowering therapy will be needed, especially since her A1C level is not 7% or less, which is the target for most patients.

### Clinical Decision Point

#### *What glucose-lowering medication would you add to metformin?*

- $\alpha$ -Glucosidase inhibitor (AGI)
- DPP-4 inhibitor
- GLP-1R agonist
- Thiazolidinedione (TZD)

### Comment

In weighing these options, important considerations to keep in mind are the need to lower the A1C by about 1.0% (possibly more with the discontinuation of glimepiride) and her body weight and body mass index. Cardiovascular risk is also an important consideration, especially given the rise in her triglyceride level. Potential issues that might affect adherence, including medication costs as well as administration requirements, should be discussed with the patient.

#### Option 1: Add an AGI

The complementary mechanism of action of an AGI makes it a good choice in combination with metformin. The A1C reduction to be expected with an AGI is 0.5% to 0.8%, which may be inadequate. The primary disadvantage of an AGI is gastrointestinal side effects.

#### Option 2: Add a DPP-4 inhibitor

The complementary mechanism of action of a DPP-4 inhibitor makes it a good choice in combination with metformin. The A1C reduction to be expected with a DPP-4 inhibitor is 0.5% to 0.8%, which may be inadequate. However, important advantages include weight neutral effects, low incidence of hypoglycemia, and modest reduction of the triglyceride level. Hypersensitivity reactions, cost, and long-term safety not established are the primary limitations.

#### Option 3: Add a GLP-1R agonist

The complementary mechanism of action of a GLP-1R agonist makes it a good choice in combination with metformin. The A1C reduction to be expected with a GLP-1R agonist is 0.5% to 1.5%, which should be adequate in this patient. Important advantages include an average weight loss of 1 to 4 kg, low incidence of hypoglycemia, and modest reduction of the triglyceride level. Transient nausea and vomiting, cost, long-term safety not established, and parenteral administration are the primary limitations.

#### Option 4: Add a TZD

The complementary mechanism of action of a TZD makes it a good choice in combination with metformin. The A1C reduction to be expected with a TZD is 0.5% to 1.4%, which should be adequate in this patient. Pioglitazone offers the potential to improve the lipid profile and decrease the risk of myocardial infarction, whereas rosiglitazone increases the risk of myocardial infarction. Preliminary evidence suggests that patients who take pioglitazone longer than a year are at increased risk of bladder cancer. Fluid retention, weight gain, and the risk of congestive heart failure and bone fractures are important limitations with TZDs.

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### Frequently Asked Questions About Incretins

**Q.** If you are going to prescribe a GLP-1R agonist, why wouldn't you just go straight to insulin?

**A.** While insulin is the most physiologic treatment available for patients with T2DM and provides dose-dependent lowering of the blood glucose, there are important limitations to its use—principally weight gain and a relatively high risk of hypoglycemia. This is in contradistinction to the GLP-1R agonists, which promote a 1 to 4 kg weight loss in most patients over several months. In addition, the GLP-1R agonists are associated with a low incidence of hypoglycemia, with rare reports of major hypoglycemia. As monotherapy, exenatide causes hypoglycemia in 4% to 9% of patients and liraglutide in 0% to 12% of patients.

**Q.** Why not initiate incretin-based therapy early in the management of patients with T2DM?

**A.** It can be. All 5 of the incretin-based therapies currently available (exenatide, liraglutide, sitagliptin, saxagliptin, linagliptin) have been approved by the FDA for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. In addition, the most recent guidelines issued by AACE/ACE indicate that the GLP-1R agonists and DPP-4 inhibitors can be used across the spectrum of A1C levels (ie, 6.5% and above). For a patient with an A1C level of 6.5% to 7.5%, a GLP-1R agonist or DPP-4 inhibitor is an alternative to metformin as initial therapy, particularly if the PPG is markedly elevated.

**Q.** How soon after a GLP-1R agonist or DPP-4 inhibitor is initiated should the FPG and A1C levels be checked to determine efficacy and guide titration?

**A.** First, it's important to note that the maintenance dose of exenatide, sitagliptin, saxagliptin, or linagliptin is not adjusted based on glycemic response, although adjustment is necessary based on renal function or concomitant use of a specific drug that interacts. For liraglutide, the dose can be increased from 1.2 mg to 1.8 mg once daily if necessary based on the glycemic response. The dose escalation strategies used for exenatide (5 mcg twice daily, then 10 mcg twice daily after 1 month) and liraglutide (0.6 mg once daily, then 1.2 mg once daily after 1 week) are used to reduce the incidence and severity of nausea and vomiting.

From an efficacy viewpoint, the blood glucose begins to decline after the first dose of the GLP-1R agonist or DPP-4 inhibitor and stabilizes after several weeks. Using the dose escalation strategy for liraglutide described above, Garber et al found that the FPG declined sharply by 2 weeks. Thereafter, the FPG stayed relatively unchanged in patients treated with 1.2 mg, but declined slightly further

through week 12 in patients treated with 1.8 mg. As expected, the decline in A1C lagged behind, reaching the lowest A1C by week 8 in patients treated with 1.2 mg and week 12 in patients treated with 1.8 mg once daily.

**Q. Are GLP-1R agonists and DPP-4 inhibitors contraindicated completely in anyone who has had pancreatitis in the past?**

**A.** None of the GLP-1R agonists or DPP-4 inhibitors have been studied in patients with a history of pancreatitis. In patients with a history of pancreatitis, the labeling for exenatide indicates that alternative glucose-lowering therapy should be considered, while liraglutide should be used with caution. At present, it is unclear if the GLP-1R agonists or DPP-4 inhibitors increase the risk of acute pancreatitis beyond the increased risk posed by T2DM. Retrospective analyses have not identified an association between incretin-based therapies and acute pancreatitis. To clarify this issue, the FDA has required further investigation with all 5 incretin-based therapies currently available. In the meantime, close monitoring and patient education are suggested.

**Q. Fear of injection is a significant barrier to initiating insulin. For the same reason, doesn't the oral route of administration of the DPP-4 inhibitors make them preferable to the GLP-1R agonists?**

**A.** The oral route of administration is an important advantage of the DPP-4 inhibitors. For patients who are truly unwilling to use an injectable medication despite patient education including self-injection with the new pen devices, a DPP-4 inhibitor allows us to address some of the incretin etiologies that contribute to T2DM. It's important to remember that the DPP-4 inhibitors typically lower A1C level 0.5% to 0.8%, which is less than with a GLP-1R agonist or insulin. Although the DPP-4 inhibitors are weight neutral, which is an important advantage compared to some other glucose-lowering therapies including insulin, the GLP-1R agonists promote weight loss in most patients. This is an important advantage of the GLP-1R agonists that often eliminates or at least reduces a patient's concerns about using an injectable medication.

**Q. Is there a situation in which a GLP-1R agonist and a DPP-4 inhibitor could be used together?**

**A.** The combination of a GLP-1R agonist and DPP-4 inhibitor has not been investigated in clinical trials and is not included in the approved indications. From a mechanism of action perspective, the combination would seem to offer no advantages over GLP-1R agonist therapy since the GLP-1R agonists cause more actions than the DPP-4 inhibitors. For example, the GLP-1R agonists promote satiety

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and delay gastric emptying. In addition, the GLP-1R agonists are resistant to the enzymatic action of DPP-4, so adding a DPP-4 inhibitor to a GLP-1R agonist would probably have minimal effect on the duration of action of the GLP-1R agonist.

### **Q.** Is there any experience using the combination of a GLP-1R agonist or DPP-4 inhibitor and insulin?

**A.** Although outside the approved labeling for exenatide and liraglutide, 2 clinical trials have investigated this use. In a 30-week study, patients were randomized to exenatide or placebo as add-on therapy to insulin glargine alone or in combination with metformin or pioglitazone (or both). The A1C level decreased from 8.3% to 6.6% (-1.7%) with exenatide and from 8.5% to 7.5% (-1.0%) with placebo ( $P < .001$ ). The hypoglycemia rate was similar between groups (1.4 vs 1.2 events/patient-year, respectively); adverse gastrointestinal events were more common in the exenatide group. The average insulin dose increased 13 and 20 units/day in the exenatide and placebo groups, respectively. Similar A1C reductions were observed in a 4-week open-label study comparing the addition of exenatide or placebo to the combination of insulin glargine and metformin, although the rate of hypoglycemia was much higher in the exenatide group (10.1 vs 1.6 events/patient-year, respectively).

The DPP-4 inhibitor sitagliptin is approved for use in combination with insulin. The addition of sitagliptin to long-acting, intermediate-acting, or premixed insulin has been shown to provide additional lowering of the A1C level over 24 weeks compared to placebo (-0.6% vs 0.0%, respectively), although the incidence of hypoglycemia was greater in patients treated with sitagliptin (16% vs 8%, respectively). Another 24-week study showed greater glucose-lowering with the addition of sitagliptin to the combination of once-daily insulin detemir and metformin compared to the addition of a sulfonylurea; the rates of hypoglycemia were low in both groups.