Incretin-Related Therapies in Type 2 Diabetes: A Practical Overview
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Abstract
Progressive deterioration of the incretin system has been shown to be a key component of the pathophysiology of type 2 diabetes. Improved understanding of the physiology underlying incretins has led to the development of new therapies that act through modulation of the incretin system. These agents offer some potential advantages over previous antidiabetes drugs and have been approved for use in type 2 diabetes. There are two broad classes of incretin-related therapies: dipeptidyl peptidase-4 inhibitors (sitagliptin and saxagliptin) and glucagon-like peptide-1 receptor agonists (exenatide and liraglutide). Although the two classes have some benefits in common—notably a low risk of hypoglycemia—they can be differentiated in terms of their pharmacology, efficacy and safety profiles, and clinical considerations.

Introduction
Type 2 diabetes is characterized by progressively declining β-cell function in the setting of insulin resistance, which, coupled with worsening glycemic control, results in the classic presentation of hyperglycemia-associated diabetes complications: diabetic retinopathy, nephropathy, and cardiovascular disease (CVD). Early initiation and prompt intensification of therapy, coupled with patient education to promote effective self-management, are advocated as key treatment objectives in type 2 diabetes. However, the limitations associated with many current therapies result in suboptimal treatment, both in terms of poor glycemic control (two-thirds of patients still do not meet current glycemic targets) and unwanted side effects of therapy. For example, insulin, thiazolidinediones, and sulfonylureas (SUs) frequently cause weight gain, which undermines efforts to encourage patients to achieve and maintain a healthier body weight. Furthermore, the risks of hypoglycemia associated with current therapies may reduce patient confidence and hinder adherence. Patients may also have adherence difficulties when therapies require multiple daily dosing or frequent blood glucose monitoring. All of these problems can act as barriers to treatment success.

Recently, a new class of drugs has emerged that derives from improved understanding of the incretin system. These drugs may help overcome some of the limitations described above. As a result, incretin-related therapies are now recognized by diabetes associations as valuable options.
within a stepped-care approach to type 2 diabetes management and have been incorporated into current treatment guidelines.²

However, the introduction of new therapeutics into everyday clinical use requires a clear understanding of the practical implications of their use. With regard to the incretin-related therapies, these considerations include how they fit into the current care options for type 2 diabetes, their associated benefits and risks, which patients will benefit most from their use, and in which patients their use should be avoided. This article addresses these issues.

Summary of Incretin-Related Therapies

Physiology of the incretin system
The gut secretes several hormones in response to food intake, of which glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are the most important in terms of glucose regulation. GLP-1 and GIP are collectively termed “the incretin hormones,” and their influence extends to several regulatory systems, including the endocrine pancreas.

GLP-1 and GIP both stimulate pancreatic β-cells to release insulin in response to glucose, and GLP-1 also suppresses postprandial glucagon output. Under normal physiological conditions, the actions of these hormones serve to limit rises in postprandial blood glucose, and in their absence, the pancreatic response to glucose is diminished. This phenomenon, termed the “incretin effect,” was first illustrated in the 1960s after observations that equivalent plasma glucose concentrations elicited greater insulin release when ingested than when delivered through direct intravenous infusion.³ It was later discovered that the incretin effect is compromised in type 2 diabetes,³ but not until recently have pharmacotherapies targeting this system become available.

Development of incretin-related therapies
Research suggests that the diminished incretin effect in type 2 diabetes reflects a greatly reduced pancreatic responsiveness to GIP that is not compensated by additional GIP secretion.⁴ This ruled out GIP as a candidate for drug development. However, GLP-1 was shown to be able to reduce hyperglycemia in type 2 diabetes when infused at supraphysiological levels.⁵

Native GLP-1 is rapidly degraded by the enzyme dipeptidyl-peptidase (DPP)-⁴. This enzyme, expressed in many tissues, rapidly cleaves peptides, including the incretins. As a result, native GLP-1 persists in the circulation for < 2 minutes.⁶ This means that human GLP-1 cannot be readily adapted for clinical use because it would need to be given by continuous infusion. Therapeutic exploitation of GLP-1 physiology therefore required GLP-1 analogs that were resistant to DPP-4 or drugs that could maximize the effects of endogenous GLP-1 by inhibiting DPP-⁴. Using this approach, DPP-⁴ inhibitors and DPP-⁴–resistant GLP-1 receptor agonists were developed.

Current incretin-related therapies: GLP-1 agonists and DPP-⁴ inhibitors
Exenatide and liraglutide are the two GLP-1 agonists currently approved for use in the United States. Exenatide is a synthetic version of exendin-⁴ (a salivary gland peptide from the Gila monster lizard), which has an amino acid sequence similar to that of human GLP-1 (53% homologous).⁷ Liraglutide is an analog of human GLP-1 with a primary amino acid sequence that is nearly identical (97%) to that of human GLP-1. There are also several drugs that target inhibition of DPP-⁴ as their mechanism of action; these include sitagliptin, vildagliptin, and saxagliptin. Vildagliptin is approved in Europe, but U.S. approval has been delayed indefinitely because of requirements for additional studies. Because sitagliptin and saxagliptin are currently approved for use in the United States, this review will focus on these two agents.

The results of phase III trials for these incretin therapies have been extensively reviewed elsewhere, and a full examination of their results is beyond the scope of this article. The major findings are summarized in Table 1.

Practical Considerations of Current Incretin-Related Therapies

Administration and dosing
As peptide-based therapies, exenatide and liraglutide would be broken down if ingested and are therefore administered by subcutaneous injection in the thigh, abdomen, or upper arm. Both are available in prefilled multi-dose pens.

Exenatide is available in 5- and 10-µg doses; each dose requires a specific pen, both of which contain 60 doses (the equivalent of 30 days of treatment). Exenatide is partially resistant to DPP-⁴ and exerts a blood glucose–lowering effect for about 7 hours after injection,⁸ which is why it must be dosed twice daily. The recommended dosing schedule, < 60 minutes before morning and evening meals, is designed to allow peak drug levels to coincide with postprandial glucose absorption.

Liraglutide is available in three doses: 0.6, 1.2, and 1.8 mg. The liraglutide pen can deliver all three doses and contains the equivalent of 30, 15, or 10 doses of liraglutide 0.6, 1.2, or 1.8 mg, respectively. The structure of liraglutide differs from that of native GLP-1 in that it has a fatty acid side chain that causes molecules to self-associate into heptameric aggregates, resulting in slow absorption following subcutaneous administration and facilitating albumin binding.⁹ The fatty acid side chain is also believed to contribute to resistance to degradation by DPP-⁴. Together these properties result in a circulating half-life of ~ 13 hours,¹⁰ allowing for once-daily dosing independent of mealtimes.

For both exenatide and liraglutide, it is recommended that patients initially start on the lower dose before progressing to higher doses after 1 month or 1 week, respectively. These incremental dosing regimens minimize the incidence and magnitude of nausea.

In contrast to the GLP-1 agonists, DPP-⁴ inhibitors can be administered orally and typically require once-daily dosing independent of food intake. They reach peak
Inhibition of DPP-4 confers a two- to threefold increase in postprandial plasma concentrations of endogenous GLP-1, thereby reducing postprandial hyperglycemia.\textsuperscript{19,20}

Concomitant therapies

The use of incretin-related therapies in patients with type 2 diabetes has been approved for both monotherapy and combination therapy approaches, and both GLP-1 agonists and DPP-4 inhibitors appear well suited for use in combination with current therapies (Table 1).

Because GLP-1 receptors mediate delayed gastric emptying, it is possible that GLP-1 receptor agonism could affect absorption of concomitant oral medications. For this reason, the prescribing information for exenatide advises that drugs required to reach threshold concentrations for efficacy (e.g.,

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Table 1. Summary of Findings From Trials Involving Incretin-Related Agents Used in Mono- and Combination Therapies

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>Duration (weeks)</th>
<th>A1C reductions from baseline (%)</th>
<th>Patients reaching target A1C of &lt;7.0% (%)</th>
<th>Mean weight change from baseline (kg)\textsuperscript{†}</th>
<th>Mean systolic blood pressure change from baseline (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1 Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide 1.2 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONO\textsuperscript{13}</td>
<td>—</td>
<td>52</td>
<td>−0.8</td>
<td>43</td>
<td>−2.1</td>
</tr>
<tr>
<td>COMBO\textsuperscript{34–38}</td>
<td>MET, SU, TZD, MET+SU, MET+TZD</td>
<td>26</td>
<td>−1.0 to −1.5</td>
<td>34–58</td>
<td>+0.3 to −2.6</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONO\textsuperscript{13}</td>
<td>—</td>
<td>52</td>
<td>−1.1</td>
<td>51</td>
<td>−2.5</td>
</tr>
<tr>
<td>COMBO\textsuperscript{34–38}</td>
<td>MET, SU, TZD, MET+SU, MET+TZD</td>
<td>26</td>
<td>−1.0 to −1.5</td>
<td>42–54</td>
<td>−0.2 to −3.24</td>
</tr>
<tr>
<td>Exenatide 5 µg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONO\textsuperscript{76}</td>
<td>—</td>
<td>24</td>
<td>−0.7</td>
<td>48</td>
<td>−2.8</td>
</tr>
<tr>
<td>COMBO\textsuperscript{30–32}</td>
<td>MET, SU, MET+SU</td>
<td>30</td>
<td>−0.4 to −0.6</td>
<td>27–33</td>
<td>−0.9 to −1.6</td>
</tr>
<tr>
<td>Exenatide 10 µg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONO\textsuperscript{76}</td>
<td>—</td>
<td>24</td>
<td>−0.9</td>
<td>46</td>
<td>−3.1</td>
</tr>
<tr>
<td>COMBO\textsuperscript{30–32}</td>
<td>MET, SU, MET+SU</td>
<td>30</td>
<td>−0.8 to −0.9</td>
<td>34–46</td>
<td>−1.6 to −2.8</td>
</tr>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin 100 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONO\textsuperscript{45,47,82}</td>
<td>—</td>
<td>12 to 24</td>
<td>−0.5 to −0.8</td>
<td>41</td>
<td>−0.2</td>
</tr>
<tr>
<td>COMBO\textsuperscript{46,48,50,77, 78,83}</td>
<td>MET, SU, MET+SU, TZD</td>
<td>18 to 30</td>
<td>−0.6 to −2.1*</td>
<td>17–66*</td>
<td>+1.1 to −1.3*</td>
</tr>
<tr>
<td>Saxagliptin 5 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONO\textsuperscript{40}</td>
<td>—</td>
<td>24</td>
<td>−0.5</td>
<td>38</td>
<td>Neutral</td>
</tr>
<tr>
<td>COMBO\textsuperscript{41–44}</td>
<td>MET, SU, TZD</td>
<td>24</td>
<td>−0.6 to −2.5*</td>
<td>23–60*</td>
<td>+0.8 to −1.6*</td>
</tr>
</tbody>
</table>

\textsuperscript{MET, metformin; MONO, monotherapy; NR, not reported; TZD, thiazolidinedione.}

\textsuperscript{*Achieved in combination with up to 2,000 mg metformin, suggesting additive effect.}

\textsuperscript{†Weight gain was typically observed when used in combination with an SU.}
oral contraceptives and antibiotics) should be taken ≥ 1 hour before exenatide.21

Similarly, although studies have shown that liraglutide does not affect the absorption of orally administered medications to a clinically relevant degree, its absorption insert advocates caution when liraglutide is used in patients receiving oral medications.22 However, in studies with liraglutide, its effect on gastric motility was not shown to have clinically meaningful interactions with drugs taken by mouth.23

Studies have also demonstrated that DPP-4 inhibitors have few clinically relevant interactions or effects on oral drugs.24,25 A slight increase in exposure to digoxin with sitagliptin has been reported and is thought to be the result of an increase in the bioavailability of digoxin. Increased monitoring is therefore recommended if these agents are used concomitantly.26–28 Saxagliptin is metabolized by the cytochrome 3A4 enzyme and, accordingly, its daily dose should be limited to 2.5 mg if given to patients already receiving strong 3A4 inhibitors (e.g., ketoconazole).29

**Side effects**

Hypoglycemia is uncommon with both GLP-1 agonists and DPP-4 inhibitors, and trial data indicate that it is most commonly reported in patients taking concomitant SUUs.30–50 The most commonly reported side effect of GLP-1 use is nausea. In the phase III trials for exenatide and liraglutide—known as the AC2993: diabetes Management for Improving Glucose Outcomes (AMIGO, Amylin Pharmaceuticals) and Liraglutide Effect and Action in Diabetes (LEAD, Novo Nordisk) trials, respectively—nausea was reported by 45–51% and 10.5–40% of patients, respectively, depending on dose and concomitant medication. The nausea was transient, however, and typically resolved after the first month.31–34 Increase in the frequency of headaches, sinusitis, nasopharyngitis, and urinary tract infections have also been reported with DPP-4 inhibitors.26,29

Because GLP-1 agonists are peptides, antibodies may develop during treatment with these agents. In the AMIGO trial series,30–32 38% of patients had low-titer anti-exenatide antibodies at 30 weeks, with high-titer antibodies in an additional 6% of patients, half of whom showed an attenuated glycemic response, posing the prospect of a declining glycemic effect in some individuals. Under these circumstances, an alternative therapy should be sought.

Liraglutide’s high degree of homology to native GLP-1 likely contributes to a low frequency of antibody formation seen in clinical trials.31 Therefore, liraglutide may be less antigenic than exenatide. In the LEAD-6 trial, which directly compared exenatide and liraglutide, 113 of 185 patients treated with exenatide for 26 weeks tested positive for antibodies, while only 4 of 154 patients who received liraglutide consistently had anti-liraglutide antibodies.32 However, how this affects glycemic control in a real-world clinical setting remains to be determined.

There has been concern about an increased risk of pancreatic effects with incretin-related therapies. However, because patients with type 2 diabetes have a 2.8-fold higher risk than the general population of developing pancreatitis,51 it has not been established whether the association between pancreatitis and incretins is causal or artifactual. Nevertheless, there have been reports of acute pancreatitis in patients receiving exenatide21 and sitagliptin.26,54

Although there were more instances of pancreatitis with liraglutide than with comparators in the LEAD trials (5/2,420 vs. 0/1,717),13–18 at 0.2% of patients, it still represents a frequency lower than that seen in the general population.55 Because of the possible association of incretins with pancreatitis, however, caution should be applied when prescribing incretin-related therapies to patients at higher risk for pancreatitis, such as those with a history of pancreatitis, gallstones, high triglycerides, or alcoholism. Furthermore, if patients present signs or symptoms of pancreatitis, such as unrelenting front-to-back abdominal pain, then incretin therapy should be discontinued until confirmatory tests are performed. If these tests are positive, incretin-based therapy should not be resumed.

Thyroid C-cell tumors have been associated with liraglutide in rodents. A recent study has shown this to be a class effect of GLP-1 receptor agonists;56 GLP-1 receptors are localized to rodent C-cells, and application of GLP-1 receptor agonists stimulated calcitonin release, upregulation of calcitonin gene expression, and C-cell hyperplasia in rat and mouse models. However, GLP-1 receptor expression in C-cells is comparatively low in humans and other primates; 20 months of treatment with liraglutide at doses > 60 times higher than those used clinically did not lead to C-cell hyperplasia in monkeys.56 Although the clinical relevance of these findings in humans has yet to be determined, it has been recommended that patients receiving liraglutide report any symptoms consistent with thyroid tumors (e.g., ongoing cough, hoarseness, or difficulty swallowing or breathing).

Liraglutide is also contraindicated in patients who have a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.22 For this reason, liraglutide includes a boxed warning in its prescribing information, and post-approval surveillance mandated by the U.S. Food and Drug Administration is being conducted for incidences of thyroid cancer with liraglutide use.

A potential safety concern with DPP-4 inhibitors is the possibility that these agents may compromise immune function. DPP-4 displays structural similarities to “sister” peptidase enzymes such as DPP-8 and -9. Therefore, DPP-4 inhibitors may also reduce the catalytic breakdown of other peptide substrates in addition to GLP-1, including immunomodulatory cytokines. It is therefore possible that DPP-4 inhibitors might interact to a greater or lesser extent (depending on enzyme selectivity) with the immune system.57 This possibility might account for the increased incidence of nasopharyngitis and respiratory tract infections seen with sitagliptin and saxagliptin, as well as some of the rare hypersensitivity
and allergic reactions observed with DPP-4 inhibitors.26,29 These reactions, which were observed in 1.5% of patients treated with saxagliptin, include anaphylaxis, angioedema, and exfoliative skin conditions such as Stevens-Johnson syndrome and require immediate discontinuation of treatment.29,58

A rare but potentially fatal adverse reaction has been observed with the combined formulation of sitagliptin and metformin, as a result of lactic acidosis resulting from metformin accumulation.27 This necessitates regular monitoring of renal function and immediate discontinuation of therapy if lactic acidosis is suspected. It is unclear whether the issue may present with other DPP-4 inhibitors that are co-administered with metformin.

Use in special populations
Patients with type 2 diabetes have an increased likelihood of developing renal impairment.20 Exenatide is renally metabolized and excreted, so the potential exists for accumulation in patients with reduced kidney function. No dose adjustment is required for mild to moderate renal impairment, but exenatide use is not recommended in patients with end-stage renal disease or severe renal impairment.21 On the other hand, liraglutide, like native GLP-1, is fully metabolized by endogenous enzymes, so its clearance does not depend on renal excretion.64 Although no dose adjustments are recommended for patients with impaired kidney function, limited therapeutic experience with liraglutide in such patients means liraglutide should be used cautiously in cases of mild, moderate, and severe renal impairment.

DPP-4 inhibitors are all cleared through the kidneys and are therefore likely to accumulate in patients with renal impairment.20,61 Results from a saxagliptin study in renally compromised patients are pending. However, it is recommended that renal function be tested before initiation of saxagliptin (with periodic tests thereafter) and that doses be limited to 2.5 mg/day for patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min). Similarly, it is recommended that renal function be tested before and periodically during therapy with sitagliptin, and dose reductions of 50 and 25 mg daily are recommended in moderate and severe renal impairment, respectively.62

Dose adjustment in cases of hepatic impairment is not recommended with either exenatide or liraglutide, although caution is advised.21,12 Studies have similarly indicated that DPP-4 inhibitors can be used without dose adjustment in mild to moderate hepatic impairment.24,63 All of the incretin-related therapies appear to be well suited for use in elderly populations, with no additional safety considerations directly attributable to age. Their use in pediatric populations has not been investigated and therefore is not recommended. Neither GLP-1 agonists nor DPP-4 inhibitors have been studied in pregnant or lactating women. Therefore, use of incretin-related therapies is cautiously recommended only when the benefits to the mother outweigh the potential risks to the fetus and is not recommended in mothers who are breastfeeding.

Comparative highlights of the above practical considerations, together with insights from clinical experience, are listed in Table 2.

Who Benefits Most From Incretin-Related Therapies?
The glucose-lowering effects of GLP-1 agonists and DPP-4 inhibitors make incretin-related therapies well suited to patients with poor glycemic control. However, as more has been learned about GLP-1, therapeutic potential beyond enhancing insulin secretion and lowering glucose has emerged. These class features may make incretin-related therapies particularly well suited for certain patients. For example, a key benefit of incretin-related therapies is that, similar to the SUs, they have the potential to increase insulin secretion but, unlike SUs, incretin-mediated insulin secretion (as well as inhibition of glucagon secretion) is glucose dependent.65 As such, incretin-stimulated insulin secretion only operates under hyperglycemic conditions, resulting in an inherently low risk of hypoglycemia. Incretin-related therapies therefore have a clear clinical utility in patients such as the elderly, who are at high risk of, or at extra risk from, hypoglycemia.64 GLP-1 also slows gastric motility and promotes satiety.65 That GLP-1 can reduce appetite even in fasting individuals suggests a satiety-increasing effect that is independent of delayed gastric emptying.66 In clinical trials, these effects translated into weight loss with GLP-1 agonists liraglutide and exenatide (2.5–3 kg) and modest weight reductions with DPP-4 inhibitors (0–0.2 kg) (Table 1). Incretin-related therapies, and GLP-1 agonists in particular, may therefore be of notable benefit to obese patients. In contrast, although nausea is typically transient with the GLP-1 agonists, it is possible that some patients may benefit from the comparative reduction in gastrointestinal effects seen with DPP-4 inhibitors.

Incretin-related therapies also promise therapeutic benefits with regard to the cardiovascular system. Potentially welcome effects have been demonstrated with GLP-1 and GLP-1 receptor agonists,67 including reductions in systolic blood pressure (Table 1), inflammatory markers of CVD (such as plasminogen activator inhibitor-1) and B-type natriuretic peptide (BNP), improved vasodilatory function, and protection against myocardial ischemia-reperfusion injury.

In a placebo-controlled analysis of pooled data from the liraglutide studies (LEAD 1–6, Novo Nordisk), 1.8 mg liraglutide significantly reduced several cardiovascular risk biomarkers, including total cholesterol (−5.1 mg/dl), LDL cholesterol (−7.8 mg/dl), triglycerides (−17.8 mg/dl), BNP (−12%), and high-sensitivity C-reactive protein (−23.1%) (all P < 0.01).68 Similarly, studies with exenatide have demonstrated benefits both in terms of improved cardiovascular biomarker profiles and reduced blood pressure.65,70 Observations such as these give hope that GLP-1–related therapies might be particularly beneficial to patients with type 2 diabetes who are at risk for CVD.
Notably, a recent retrospective analysis of clinical records from >12,000 patients treated with exenatide or sitagliptin demonstrated that the beneficial effects of incretins on cardiovascular biomarkers, as well as body weight and glycemic control, are observed outside of the clinical trial setting.71 Perhaps the most encouraging feature of incretin-based therapies is the possibility that they can help preserve β-cell function. Apoptotic β-cell loss appears to play a central role in the development of insulin deficiency and the onset and progression of type 2 diabetes, and β-cells function at up to 50% reduced capacity by the time type 2 diabetes is diagnosed.1,72 Animal and in vitro studies have shown that GLP-1 receptor stimulation can enhance β-cell proliferation and inhibit β-cell apoptosis;13,73,74 therefore, drugs that enhance GLP-1–mediated effects may be able to limit disease progression.

Clinical trial data have shown that both GLP-1 agonists and DPP-4 inhibitors are associated with improvements in parameters of β-cell function such as the proinsulin:insulin ratio and homeostasis model of assessment (HOMA-B).37,45,47,48,75–78 However, these effects are only observed while patients receive therapy, and the legacy of these effects and how they relate to the clinical progression of diabetes is only speculative at present.

Head-to-Head Comparisons of Incretin-Related Therapies
Few trials have directly compared the incretin-based therapies. As part of the liraglutide development program (LEAD-6 trial), 1.8 mg liraglutide once daily was compared with 10 µg exenatide twice daily.37 Both agents were added to metformin and/or SU in 464 patients for 26 weeks. In this study, liraglutide achieved a greater reduction in A1C (−1.1 vs −0.8%; P < 0.0001; baseline ~8.2%), with a greater proportion of patients reaching <7.0% (54 vs. 43%; P < 0.01). Weight loss did not differ significantly between liraglutide and exenatide (−3.2 and −2.9 kg, respectively), nor did systolic blood pressure reduction (−2.5 and −2.0 mmHg, respectively). HOMA-B assessment indicated a greater improvement in β-cell function with liraglutide (P < 0.0001). Liraglutide also showed better tolerability in this trial with less persistent nausea and a lower rate of minor hypoglycemia (1.9 vs. 2.6 events/patient/year; P = 0.013). Only two major hypoglycemic events occurred, both in patients taking exenatide with SUs.

In an extension of the LEAD-6 trial, patients were switched from exenatide to 1.8 mg once-daily liraglutide or continued on liraglutide for an additional 14 weeks. A1C (0.32%), fasting plasma glucose (FPG; 16.2 mg/dl), body weight (0.9 kg), and systolic blood pressure (3.8

### Table 2. Head-to-Head Comparison of GLP-1 Agonists and DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>GLP-1 Agonists</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulates pharmacological levels of GLP-1</td>
<td>GLP-1 levels dependent on endogenous incretin secretion</td>
</tr>
<tr>
<td>Injectable formulation once (liraglutide) to twice daily (exenatide)</td>
<td>Oral formulation once daily</td>
</tr>
<tr>
<td>Effective as both monotherapy and combination therapy</td>
<td>Effective as both monotherapy and combination therapy. Good choice for monotherapy in those intolerant to metformin or renally compromised</td>
</tr>
<tr>
<td>Suited for overweight patients; promotes significant amounts of weight loss</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Good glucose-lowering ability; can lower both postprandial and fasting levels</td>
<td>Moderate glucose-lowering ability; likely to work best in early disease on postprandial values</td>
</tr>
<tr>
<td>Improvements in cardiovascular markers</td>
<td>Minimal impact on cardiovascular markers</td>
</tr>
<tr>
<td>Low risk of hypoglycemia</td>
<td>Low risk of hypoglycemia</td>
</tr>
<tr>
<td>If SU, may need a lower dose</td>
<td>If SU, may need a lower dose</td>
</tr>
<tr>
<td>Higher incidence of side effects (nausea)</td>
<td>Increased headaches, infections, and dermatological effects</td>
</tr>
<tr>
<td>Caution if history of gall bladder disease, alcoholism, high triglycerides, or pancreatitis</td>
<td>Caution if history of gall bladder disease, alcoholism, high triglycerides, or pancreatitis</td>
</tr>
<tr>
<td>Advise patients to call if there are signs or symptoms of pancreatitis (severe, unrelenting abdominal pain front to back)</td>
<td>Advise patients to call if there are signs or symptoms of pancreatitis (severe, unrelenting abdominal pain front to back)</td>
</tr>
<tr>
<td>No dose titration relative to food intake or ambient blood glucose level</td>
<td>No dose titration relative to food intake or ambient blood glucose level</td>
</tr>
<tr>
<td>Typically tier 3 formulary coverage</td>
<td>Typically tier 3 formulary coverage</td>
</tr>
</tbody>
</table>
mmHg) were all further decreased among patients who switched from exenatide to liraglutide (all \( P < 0.0001 \).\(^7\)

Sitagliptin has been compared to exenatide in a small 2-by-2-week crossover trial.\(^8\) This was not long enough to evaluate A1C, and although both drugs had similar effects on FPG, 2-hour postprandial plasma glucose was lower with exenatide (133 vs. 208 mg/dl; \( P < 0.0001 \)). When patients switched from sitagliptin to exenatide, their postprandial plasma glucose decreased by a mean 76 mg/dl, but when the reverse switch was made, postprandial plasma glucose increased by 73 mg/dl. Exenatide also suppressed glucagon secretion and gastric emptying to a greater degree and reduced total caloric intake compared to sitagliptin (−134 vs. +130 kcal; \( P = 0.02 \)).

In a recent randomized active-controlled trial, liraglutide 1.2 and 1.8 mg (n = 221) were compared with 100 mg oral sitagliptin (n = 219) for 26 weeks in patients with type 2 diabetes.\(^9\) These treatments were added to ongoing therapy with metformin and/or a SU. However, because exenatide is given twice daily compared to the once-daily dose regimen of liraglutide, this trial was open label. Both the 1.2 mg (−1.24%) and the 1.8 mg (−1.50%) doses of liraglutide were significantly more effective than sitagliptin (−0.90%) in lowering mean A1C. These corresponded to estimated mean treatment differences for liraglutide 1.2 and 1.8 mg versus sitagliptin of −0.60% (\( P < 0.0001 \)) and −0.34% (\( P < 0.0001 \)), respectively. Mean weight loss was also significantly greater in both liraglutide arms than with sitagliptin (both \( P < 0.0001 \)). The estimated mean weight reductions in favor of liraglutide over sitagliptin were −1.90 kg for the 1.2-mg dose and −2.42 kg for the 1.8-mg dose. Nausea was more common with liraglutide (21–27%) than with sitagliptin (5%), whereas hypoglycemia was low and comparable between groups.

Conclusion
The incretin-related therapies are important new drugs that effectively lower blood glucose. Studies have demonstrated they can be safely used in combination with current oral therapies. However, studies of their use in combination with insulin are lacking. The corollary benefits of incretin-related therapies such as low hypoglycemic risk, blood pressure-lowering effects, and weight-lowering effects make them well-suited for patients who are at risk of hypoglycemia and those who are hypertensive or obese.

Because DPP-4 inhibitors require some endogenous GLP-1 secretion, it is likely that they are most suitable in patients who retain some β-cell activity. However, the potential β-cell loss-sparing effects of the incretin class of drugs suggests that patients may benefit from early use of either GLP-1 agonists or DPP-4 inhibitors.

Few studies have directly compared GLP-1 receptor agonists with DPP-4 inhibitors, but available evidence suggests that GLP-1 receptor agonists are more effective glucose-lowering therapies and have the additional potential advantages of weight and systolic blood pressure reduction. DPP-4 inhibitors have the advantage of oral administration and excellent tolerability, but their efficacy is somewhat more limited by their dependence on endogenous GLP-1 secretion. The best results are obtained when these agents are used in combination with metformin.

The range of incretin-related therapies available in the United States has already begun to increase, and their growing use in diabetes care makes understanding their clinical utility increasingly relevant.

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