The management of type 2 diabetes mellitus (T2DM) remains complex and challenging for patients and their physicians. Although the number of patients with T2DM who successfully achieve target levels of glycosylated hemoglobin (HbA₁c) is steadily increasing, a substantial number of patients continue to fall short of acceptable treatment goals, leaving them at high risk for development of diabetes mellitus–associated complications.¹,²

Traditional agents for the treatment of patients with T2DM include metformin, insulin secretagogues (ie, sulfonylureas and glinides), thiazolidinediones (TZDs), α-glucosidase inhibitors, and insulin. Unfortunately, these agents fail to adequately address the pathologic characteristics of T2DM, including insulin deficiency resulting from insufficient pancreatic insulin release, excess hepatic glucose output, and insulin resistance (which results in decreased glucose uptake in the liver and peripheral tissues [eg, muscle and fat]).³ In addition, many traditional agents are associated with increased incidence of hypoglycemia (eg, glinides, insulin, sulfonylureas) or with unwanted increase in body weight (eg, glinides, glitazones, insulin, sulfonylureas).⁴ Also, most traditional agents for managing T2DM have mechanisms that do not adequately control levels of postprandial glucose (PPG),⁵ which is a dominant contributor to overall glycemia when HbA₁c levels are below 8.5%. Elevated PPG levels increase cardiovascular risk.⁶

Two recent additions to the armamentarium of T2DM management are incretin-based therapies—glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. These agents, which were developed to meet the need for antihyperglycemic agents that exhibit improved efficacy and safety relative to traditional therapies, represent a major paradigm shift in management because they address unique pathophysiologic pathways in T2DM.

Alan J. Garber, MD, PhD, FACE

As knowledge of pathophysiologic mechanisms of diabetes mellitus has increased, clinical attention has shifted to the incretin system. Incretin hormones, including glucagon-like peptide-1, or GLP-1, and glucose-dependent insulinotropic polypeptide, are vital to the control of glucose homeostasis and pancreatic β-cell preservation. Novel strategies for the treatment of patients with type 2 diabetes mellitus (T2DM) engage the incretin system. Glucagon-like peptide-1 receptor agonists provide robust glycemic control as well as beneficial reductions in body weight. Dipeptidyl peptidase-4, or DPP-4, inhibitors exhibit beneficial glycemic effects and are weight-neutral. Incretin-based medications are becoming increasingly recognized in guidelines as early treatment options because of their efficacy and well-tolerated profiles. The author reviews the safety and efficacy of currently approved incretin-based agents, as well as the role of these medications in treatment paradigms for patients with T2DM. He also discusses investigational incretin-based agents.

J Am Osteopath Assoc. 2011;111(7 suppl 5):S20-S30

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Financial Disclosures: Dr Garber is a consultant, advisory board member, and speaker’s bureau member for GlaxoSmithKline PLC, Merck & Co Inc, Daiichi Sankyo Co Ltd, and Novo Nordisk Inc.

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This supplement is supported by an independent educational grant from Novo Nordisk Inc.
Physiologic Actions of Incretin Hormones

As knowledge of the pathophysiologic mechanisms of diabetes mellitus has increased, clinical attention has shifted to the incretin system. Hormones secreted from gastrointestinal endocrine cells play key roles in the control of energy balance by regulating the assimilation, storage, and metabolic processing of nutrients. Disruption of these endocrine cells disturbs the normal control of insulin production and body weight, contributing to the development of T2DM. Two incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are vital to the control of glucose homeostasis through their ability to increase the β-cell insulin response to ingested glucose. These hormones are responsible for more than 90% of the incretin effect observed after glucose ingestion.

Glucagon-like peptide-1 and GIP are released within minutes of glucose absorption to increase insulin secretion. Glucagon-like peptide-1 is synthesized in L cells in the distal small bowel and colon, whereas GIP is secreted by K cells in the duodenum and proximal jejunum. Both GLP-1 and GIP trigger insulinotropic actions by binding to β-cell receptors. Glucagon-like peptide-1 receptors are primarily expressed on pancreatic glucagon-containing α, β, and δ cells, though they are also widely expressed in the central nervous system (CNS), peripheral nervous system, lung, heart, and gastrointestinal tract. Glucagon-like peptide-1 and GIP exert multiple biologic effects (Figure 1). A key feature of GLP-1 action is the glucose-dependent stimulation of insulin secretion and concomitant suppression of glucagon.

The numerous metabolic effects of GLP-1 include the following: inhibiting gastric acid secretion; bioregulating fat metabolism in adipocytes; increasing glucagon secretion and fat deposition; increasing β-cell replication; and decreasing β-cell apoptosis. Under normal physiologic conditions, fasting plasma glucose (FPG) is managed by tonic insulin and glucagon secretion, but excursions of PPG are controlled by insulin and the incretin hormones. The biologic activities of GLP-1 and GIP are related to key pathophysiologic characteristics of T2DM.

Several key pathologic abnormalities characteristic of T2DM appear to be related to the functions of incretins. Patients with T2DM have impaired incretin function, impaired GLP-1 release, diminished insulinotropic response to GIP, glucoregulatory defects, and impaired glucose homeostasis. Figure 2 lists the effects of GLP-1 and GIP on defects in glucose metabolism, pancreas function, and energy uptake in patients with T2DM. Importantly, the incretin effect—in particular, postprandial production of GLP-1—is impaired in patients with T2DM. The insulin-secretory response, however, can be restored with pharmacologic doses of GLP-1.

Incretin-Based Treatment Options

Glucagon-like peptide-1 is rapidly metabolized by the enzyme DPP-4, resulting in the generation of an inactive compound that makes for a nonviable therapeutic agent. As a result, a number of receptor agonists of GLP-1 and inhibitors of DPP-4 have been developed as options for treating patients with T2DM. Glucagon-like peptide-1 receptor agonists can produce GLP-1 levels that are more than 5 times a patient’s physiologic levels, and DDP-4 inhibitors result in an approximate 2-fold increase in GLP-1 levels.

Figure 1. Multiple physiologic effects of glucagon-like peptide-1 (GLP-1). Reprinted with permission from Baggio and Drucker.
Defects in Type 2 Diabetes | Action of Incretins
---|---
Impaired glucose-stimulated insulin secretion and first-phase response | Restoration of glucose-dependent insulinotropic effect and lack of postprandial biphasic response
Hyperglucagonemia | Suppression of glucagon secretion
Defective hypoglycemia counter-regulation | Glucagon secretion, and loss of insulinotropic effect, when plasma glucose is low
Reduced β-cell mass and insulin content | Increased synthesis of proinsulin, possible increased β-cell mass or differentiation of islet precursor cells into β-cells
Accelerated β-cell apoptosis | Possible inhibition of toxin-induced β-cell apoptosis
Normal, retarded, or accelerated gastric emptying | Slowing of gastric emptying
Hypercaloric energy intake, obesity | Suppression of appetite/increased satiety, weight loss

Figure 2. Actions of the incretins glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide on pathophysiologic defects in patients with type 2 diabetes mellitus. Reprinted from Khoo J et al with permission from Dove Medical Press Ltd.

(FDA) for the treatment of patients with T2DM. It is a synthetic form of exenatide-4, a peptide that was discovered in the saliva of the Gila monster (*Heloderma suspectum*) in 1992. The amino acid sequence of exenatide is 53% identical with that of human GLP, allowing it to be a strong GLP-1 receptor agonist. Reductions in FPG and PPG levels caused by exenatide are mediated by the effects of glucose-dependent insulin secretion, suppression of glucagon secretion, slowing of gastric emptying, and reductions in food intake. In the short-term, exenatide decreases PPG levels by as much as 75%, primarily as a result of the substantial dose-dependent slowing of gastric emptying. The half-life of exenatide is 2.4 hours after subcutaneous (SC) injection, with peak action achieved after 2 to 3 hours. Exenatide is administered twice daily at any time within a 60-minute period before the morning meal and the evening meal (ie, before the 2 main meals of the day, approximately 6 h apart). As a result of the effect of exenatide on delayed gastric emptying, oral medications such as contraceptive pills and antibiotics (whose efficacy depends on reaching a threshold concentration) are best taken at least 1 hour before exenatide.

The efficacy of exenatide has been studied as monotherapy and in combination with oral hyperglycemic agents. In drug-naive patients with T2DM, exenatide 5 μg twice daily for 4 weeks, followed by 10 μg twice daily for 26 weeks, resulted in reduced mean HbA₁c level, FPG level, and body weight, compared to placebo. Clinical trials assessing the efficacy of adding exenatide (5 μg or 10 μg subcutaneously twice daily) to ongoing oral antihyperglycemic agents (ie, metformin, sulfonylureas, or TZDs) in patients with T2DM and suboptimal glycemic control demonstrated that exenatide substantially improved several glycemic and nonglycemic outcomes vs placebo. Two clinical studies of exenatide (5 μg or 10 μg once daily) demonstrated mean increases in the homeostasis model assessment-β-cell (HOMA-B) index, a commonly used measure of β-cell function, of 19% at 24 weeks and 32% at 30 weeks. In patients with T2DM, exenatide normalizes the loss of first-phase insulin secretion and the hypersecretion of glucagon from β cells, thereby reducing hepatic glucose production in the postprandial state.

The safety and tolerability of exenatide and other GLP-1 receptor agonists have been evaluated in various studies. Because of the effects of endogenous GLP-1 on glucose-dependent insulin secretion, hypoglycemia is uncommon in patients receiving GLP-1 receptor ago-
The rates of hypoglycemia observed in patients taking exenatide are largely dependent on the agents with which it is combined. When exenatide was used alone in a clinical trial reported by Moretto et al,28 low rates (about 5%) of mild hypoglycemia were observed in patients. These hypoglycemia rates were not significantly different from rates observed in participants given placebo, and no severe hypoglycemic events were reported.28

In other clinical trials, patients receiving exenatide with metformin or metformin with a TZD as background therapy had no increased risks of hypoglycemia.20,27 The incidence of hypoglycemia increased when exenatide was used in combination with a sulfonylurea but decreased with a reduction in sulfonylurea dose.16 The incidence of hypoglycemia was found to be similar with once-daily insulin glargine and with twice-daily exenatide 10 μg.29

Exenatide is excreted renally. Although no dosage adjustment is needed in patients with only mild to moderate renal impairment, exenatide is contraindicated in patients with creatinine clearance (CrCl) rates of less than 30 mL/min or with end-stage renal disease.12

Observational reports and clinical trial data suggest an association between use of GLP-1 agonists and acute pancreatitis.30 Six cases of hemorrhagic or necrotizing pancreatitis linked to exenatide use were reported to the FDA between October 2007 and August 2008.31 Patients with T2DM, regardless of treatment type, have 3 times the risk for pancreatitis compared with the general population.12 Conditions commonly associated with diabetes mellitus—including obesity, hypertriglyceridemia, and gallstones—are known risk factors for the development of pancreatitis.12 Nevertheless, in a case-controlled cohort study examining

<table>
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<th>Agent</th>
<th>ROA</th>
<th>Dosing Frequency</th>
<th>Change in HbA1c Level, %</th>
<th>Change in Body Weight, kg</th>
<th>Change in SBP, mm Hg</th>
<th>Adverse Effects</th>
<th>Limitations of Use</th>
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<tr>
<td><strong>GLP-1 Receptor Agonists</strong></td>
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<tr>
<td>☐ Exenatide14 SC</td>
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<td>-0.4 to -0.9</td>
<td>-0.9 to -3.1</td>
<td>-3.4 to -3.7</td>
<td>Transient nausea</td>
<td>Not for treatment of patients with T1DM or diabetic acidosis; do not use if CrCl &lt;30 mL/min or if patient has ESRD; potential risk of pancreatitis</td>
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<tr>
<td>☐ Liraglutide33 SC</td>
<td>Once daily</td>
<td>-1.4 to -1.9</td>
<td>-3.7 to -3.8</td>
<td>-4.7</td>
<td>Transient nausea</td>
<td>Not for treatment of patients with T1DM or diabetic acidosis; use with caution in patients with renal insufficiency; potential risk of pancreatitis</td>
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**DPP-4 Inhibitors**

| ☐ Sitagliptin47 PO | Once daily | -0.6 to -0.8 | Weight-neutral | NA | Headache, nasopharyngitis, URI | Not for treatment of patients with T1DM or diabetic acidosis; dosage adjustment with moderate to severe renal insufficiency/ESRD; risk of serious hypersensitivity reactions (eg, anaphylaxis, angioedema) |
| ☐ Saxagliptin55 PO | Once daily | -0.7 to -0.9 | Weight-neutral | NA | Arthralgia, cough, headache, nasopharyngitis, URI, UTI | Not for treatment of patients with T1DM or diabetic acidosis; dosage adjustment with moderate to severe renal impairment/ESRD |
| ☐ Linagliptin63 PO | Once daily | -0.4 to -0.5 | Weight-neutral | NA | Back pain, headache, hypertension | Not for treatment of patients with T1DM or diabetic acidosis |

Figure 3. Summary of the clinical effects and limitations of incretin-based agents approved by the US Food and Drug Administration. Adapted with permission from Garber AJ.3 Abbreviations: CrCl, creatinine clearance; DPP-4, dipeptidyl peptidase-4; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; NA, not available; PO, orally; ROA, route of administration; SBP, systolic blood pressure; SC, subcutaneously; T1DM, type 1 diabetes mellitus; URI, upper respiratory tract infection; UTI, urinary tract infection.
a large US commercial health insurance database, exenatide use was not associated with an increased risk of acute pancreatitis.35 Until this relationship is more clearly defined, patients who are prescribed exenatide should be monitored for signs of pancreatitis.12

The most common adverse events associated with exenatide have been gastrointestinal in nature (eg, diarrhea, nausea, vomiting). One review article35 found that between 33% and 57% of patients using exenatide reported mild to moderate nausea in several clinical trials. Exenatide is not recommended for patients with severe gastrointestinal disease, including gastroparesis.

Liraglutide—Liraglutide is the first human GLP-1 analog approved by the FDA.33 It has 2 modifications in the amino acid sequence compared to natural, human GLP-1, as well as a fatty acid side chain attached to the peptide—resulting in slow absorption into the circulatory system, increased reversible binding to albumin, and reduced susceptibility to DPP-4 degradation.34 Liraglutide improves glycemic control and increases insulin secretion in response to carbohydrate loads.5 The half-life of liraglutide is 11 to 15 hours after subcutaneous injection, making it suitable for once-daily administration, with peak action after 8 to 12 hours.5 It can be administered at any time of the day, irrespective of meals.

The glycemic and weight-reduction effects of liraglutide, alone or in combination with various therapeutic regimens, have been compared with placebo and active comparators in a series of 6 phase III clinical trials known as the Liraglutide Effect and Action in Diabetes [LEAD] studies.34-40 In drug-naïve patients previously treated with diet and exercise, liraglutide monotherapy reduced HbA1c levels by 1.6% over a 52-week period.35 Liraglutide in combination with 1 or 2 oral hyperglycemia agents produced HbA1c reductions of 0.6% to 1.5%.35,36

In the LEAD-5 study,40 the safety and efficacy of liraglutide oncedaily was compared with insulin glargine in participants receiving concomitant metformin and glimepiride. Treatment with liraglutide resulted in a statistically significant lower HbA1c level compared to insulin glargine (P=0.0015). In that study, patients treated with insulin glargine gained weight, as is commonly observed after transition to insulin. By contrast, patients treated with liraglutide lost weight.40

These data, along with a similar study of exenatide vs insulin glargine in patients using metformin and a sulfonylurea,29 suggest that GLP-1 receptor agonists may be attractive alternatives to insulin treatment in patients for whom oral combination therapy is not effective.34

In terms of nonglycemic outcomes, mean body weight reductions of 1.0 kg to 3.2 kg have been reported with liraglutide use. In addition, liraglutide is associated with reductions in systolic blood pressure of 0.6 mm Hg to 7.9 mm Hg (Figure 2).35-40 These changes in blood pressure were observed within 2 weeks of treatment initiation, suggesting that the reductions were independent of weight loss associated with more prolonged therapy.16

Beneficial effects on β-cell function have also been demonstrated with liraglutide.16 In both animal and in vitro studies, liraglutide decreased β-cell apoptosis and increased β-cell mass and differentiation.41 In three 26-week clinical studies36,38,39 of liraglutide, improvements in HOMA-B measurements of 23% to 32% were observed. Furthermore, the proinsulin-to-insulin ratio decreased by 0.1 in 2 of these studies and remained unchanged in the third, indicating a potential beneficial effect on insulin processing.36,38,39

The safety and efficacy of liraglutide vs exenatide were compared in the LEAD-6 trial.38 In this 26-week trial, patients were randomly assigned to receive either liraglutide 1.8 mg once daily (n=233) or exenatide 10 μg twice daily (n=231), in addition to maximally tolerated doses of metformin with or without sulfonylureas. Treatment with liraglutide resulted in a statistically significant greater reduction in HbA1c level compared to exenatide (1.12% vs 0.79%, respectively; P<.001). Fifty-four percent of liraglutide-treated patients and 43% of exenatide-treated patients achieved the HbA1c target of less than 7.0% (P=0.0015). Liraglutide and exenatide produced similar reductions in body weight (3.24 kg and 2.87 kg, respectively).38

Both liraglutide and exenatide were well tolerated in the LEAD-6 trial,38 but nausea and minor hypoglycemia occurred less frequently with liraglutide. In the LEAD-6 study,38 liraglutide once daily provided greater improvements in glycemic control compared to exenatide twice daily, and liraglutide was generally better tolerated than exenatide. Use of liraglutide may be preferred in patients with T2DM in whom minimizing weight gain or risk of hypoglycemia are major considerations.38

The Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION)-6 trial42 evaluated the safety and efficacy of liraglutide with those of exenatide long-acting release (LAR)—a once-weekly synthetic formulation of exendin-4—in phase III clinical trials. Over the 26-week trial period, patients treated with exenatide LAR 2 mg once weekly had a mean reduction in HbA1c level of 1.3%, while patients treated with liraglutide 1.8 mg once daily had a mean reduction in HbA1c level of 1.5%. Gastrointestinal adverse events occurred more frequently in patients treated with liraglutide (20% nausea, 13% diarrhea, 11% vomiting) than in patients treated with exenatide LAR (9% nausea, 6% diarrhea, 4% vomiting). However, injection-site nodules occurred more frequently among exenatide LAR users (10%) than among liraglutide users (1%). No major hypoglycemic events occurred in either treatment group.42

As with exenatide, the incidence of hypoglycemia with liraglutide is largely dependent on the particular combination of oral hyperglycemia agents administered with the GLP-1 receptor agonist.5 The incidence of minor hypoglycemia was low (3%-12%)—and comparable to the incidence with placebo—in patients taking liraglutide as monotherapy or in combination with metformin or a TZD.35,36,39 Liraglutide, when given in combination with a sulfonylurea, resulted in a higher incidence of hypoglycemia (5%-27%).37,38,40

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**Figure 2**

Effect of treatment with exenatide or liraglutide on HOMA-B measurements in 3 phase III clinical trials.36,38,39 Data are presented as mean ± SD. The difference between treatments was statistically significant (P<.001).
Data on the pharmacokinetic profile of liraglutide for cases of mild to moderate renal impairment show no alteration of the drug’s profile.43 Thus, it is not necessary to adjust the dose of liraglutide for patients with renal impairment. Before FDA approval of liraglutide, the LEAD trials were carefully reviewed for cases of pancreatitis. Among more than 3900 study participants, 7 cases of pancreatitis were reported in patients using liraglutide, including 1 case in a patient who was also using another diabetes medication.44 Although there may be a small risk of pancreatitis with liraglutide use (and the number of patients affected is small), the magnitude of risk is difficult to determine beyond the baseline risk from T2DM.43 Patients prescribed liraglutide should be made aware of the symptoms of pancreatitis.44

Long-term GLP-1 receptor agonist administration in rodents has been associated with increased serum calcitonin levels and C-cell tumor formation, raising concern that liraglutide might carry an increased risk of medullary thyroid cancer.8,45 However, whereas rodent C cells have a relatively high density of cell surface GLP-1 receptors and respond to GLP-1, human C cells have few to no cell surface GLP-1 receptors and apparently do not respond metabolically to GLP-1.

In primate studies consisting of 20 months of GLP-1 receptor agonist dosing at more than 60-fold the clinical exposure as well as in a 2-year observational study of treatment with liraglutide in more than 5000 patients with either T2DM or obesity without diabetes mellitus—data did not support an effect of GLP-1 receptor activation on serum calcitonin levels or on C-cell hyperplasia. Furthermore, no change in blood calcitonin levels have been noticed in any of the long-term trials involving liraglutide administration. Finally, long-term human C-cell stimulation with proton pump inhibitors, which raise gastrin levels, does not produce C-cell proliferation in humans.

Collectively, these data suggest that the adverse effects from liraglutide previously reported in rodents may not apply to humans.45 The long-term consequences of sustained GLP-1 receptor activation merit further investigation.

As with exenatide, the most common adverse effect reported from liraglutide use is nausea. The frequency of nausea in the LEAD trials44-46 ranged from 10.5% (when combined with a sulfonylurea) to 40% (when combined with a TZD). Liraglutide-associated nausea can be limited by gradual dosage titration.12

**DPP-4 Inhibitors**

**Sitagliptin**—Sitagliptin is an orally active, fully reversible inhibitor of DPP-4 and the first such agent approved for use in the United States.16,47 Inhibition of DPP-4 by sitagliptin slows the inactivation of GLP-1 and GIP, resulting in increased concentrations of the intact, active, endogenous incretin hormones and greater duration and magnitude of their actions. In addition, glucose-dependent insulin secretion is increased, and glucagon secretion and hepatic glucose production are decreased.2 Sitagliptin has been associated with an approximate 2-fold increase in postprandial GLP-1 plasma concentrations, compared to placebo, in healthy human study participants and in patients with T2DM.10,48

In clinical trials, sitagliptin produced the greatest reduction in HbA1c level when used in combination with metformin, suggesting an additive effect. In drug-naïve patients with T2DM, sitagliptin monotherapy (100 mg once daily) produced mean HbA1c reductions of 0.6% to 0.9%.49,50 When used in combination with metformin, sitagliptin 100 mg once daily reduced HbA1c level by a mean of 1.6% to 2.0%, depending on the dose of metformin used.51 In patients treated with combination sitagliptin and metformin, reductions in HbA1c and FPG levels have been sustained over 2 years.43

Unlike GLP-1 receptor agonists, DPP-4 inhibitors are weight-neutral. Body weight reductions of 0.1 kg to 0.6 kg have been reported with sitagliptin as monotherapy or in combination with metformin.49-51 Blood pressure reductions observed in sitagliptin clinical trials have not been clinically significant.52 Patients treated with sitagliptin or a combination of metformin and sitagliptin have shown improvements in β-cell function. In one evaluation of such combination therapy, an 18% improvement in HOMA-B measurement was observed.53

In safety and tolerability assessments in clinical trials, the incidence of hypoglycemia was low (<2%) among patients with T2DM who used sitagliptin.23 This rate was similar to the incidence of hypoglycemia in patients given placebo.

Because sitagliptin is cleared by the kidneys, dosage adjustments are recommended in patients with moderate to severe renal insufficiency and in patients undergoing dialysis. For patients with moderate renal insufficiency (CrCl, 30-50 mL/min), the sitagliptin dose should be reduced to 50 mg. For patients with severe renal insufficiency (CrCl <30 mL/min) or end-stage renal disease, a sitagliptin dose reduction to 25 mg is indicated.43

The most commonly reported adverse effects of sitagliptin in clinical trials were gastrointestinal in nature, including abdominal pain, nausea, and diarrhea. Other adverse events that occurred more frequently in sitagliptin-treated patients than in other study participants were arthralgia, back pain, headache, and pain in the extremities.15,35 A meta-analysis of pooled clinical trial data indicates an increased risk for infection (ie, nasopharyngitis, urinary tract infection) in patients treated with sitagliptin.34 Serious hypersensitivity reactions—including anaphylaxis, angioedema, and exfoliative skin conditions (eg, Stevens-Johnson syndrome)—have been noted in postmarketing reports.54 Rarely, hepatic enzyme elevations have also been reported.

**Saxagliptin**—Saxagliptin is another DPP-4 inhibitor approved by the FDA for the treatment of patients with T2DM.55 It is a potent, reversible, competitive agent that selectively inhibits DPP-4.56 As with sitagliptin, saxagliptin exerts its glucoregulatory actions through prevention of incretin degradation, leading to potentiation of GLP-1 and GIP action.56

The efficacy of saxagliptin has been studied as monotherapy and in combination with metformin, sulfonylureas, and TZDs. During 24 to 102 weeks of treatment with saxagliptin, glycemic efficacy has been demonstrated in patients.
with T2DM regardless of age, gender, race/ethnicity, or body weight.\textsuperscript{[58]} When used as monotherapy, saxagliptin 5 mg once daily produced mean HbA$_{1c}$ reductions of 0.5% to 0.7%.\textsuperscript{[56,57]} When used in combination with traditional oral hyperglycemic agents, saxagliptin 5 mg once daily (as add-on therapy or as initial combination therapy) provided clinically important reductions in HbA$_{1c}$ level.\textsuperscript{[56]}

Saxagliptin, when used with metformin, produced mean reductions in HbA$_{1c}$ levels of 0.7% to 2.5%\textsuperscript{[58,59]}, when used with a sulfonylurea, HbA$_{1c}$ mean reduction was 0.6%\textsuperscript{[60]}, and when used with a TZD, HbA$_{1c}$ mean reduction was 0.9%.\textsuperscript{[61]}

As with sitagliptin, the effects of saxagliptin on body weight are neutral. Improvements in β-cell function (as measured with HOMA-B assessment) have been observed when saxagliptin was used in combination with either metformin or a TZD.\textsuperscript{[56,61]} In treatment-naive patients with T2DM using an intravenous hyperglycemic clamp model, saxagliptin improved pancreatic β-cell responsiveness to glucose in the fasting and postprandial states, and it decreased postprandial glucagon concentrations.\textsuperscript{[56]}

The safety and tolerability of saxagliptin were assessed in 8 multicenter, randomized, phase III clinical trials in which this DPP-4 inhibitor was administered as monotherapy, as initial combination with metformin, or as add-on treatment in patients receiving metformin, glyburide, or a TZD.\textsuperscript{[56]} In all saxagliptin groups in these trials, the frequency of hypoglycemia was generally similar to that found with placebo.\textsuperscript{[56]}

Dosage adjustment of saxagliptin (2.5 mg once daily) is recommended in patients with moderate to severe renal impairment (CrCl <50 mL/min) or end-stage renal disease. A reduced saxagliptin dose of 2.5 mg daily is also recommended for patients taking strong CYP3A4/5 inhibitors, such as ketoconazole.\textsuperscript{[56]}

The most common adverse events observed with saxagliptin are similar to those of sitagliptin, such as headache, nasopharyngitis, upper respiratory tract infections, and urinary tract infections.\textsuperscript{[56]}

**Linagliptin**—In May 2011, linagliptin became the latest DPP-4 inhibitor to be approved by the FDA for the treatment of patients with T2DM.\textsuperscript{[58]} Similar to sitagliptin and saxagliptin, linagliptin is a potent, highly selective, DPP-4 enzyme inhibitor.\textsuperscript{[63]}

The efficacy of oral linagliptin, as monotherapy or in combination with other oral antihyperglycemic drugs, has been evaluated in several large, randomized, double-blind, multicenter trials, in both treatment-naive and treatment-experienced adult patients with inadequately controlled T2DM. In trials of 12 to 26 weeks’ duration, linagliptin produced clinically significant reductions in HbA$_{1c}$ levels.\textsuperscript{[63]} Linagliptin treatment has also been associated with improvements in β-cell function.\textsuperscript{[63]}

In approximately 4000 patients with T2DM in clinical trials, linagliptin as monotherapy or in combination with other oral antihyperglycemic drugs was generally well tolerated, with a low incidence of hypoglycemia.\textsuperscript{[63]}

Unlike other DPP-4 inhibitors, linagliptin undergoes minimal elimination via the renal route and, thus, it may be particularly useful in the treatment of patients with T2DM who have renal impairment.\textsuperscript{[63]}

**GLP-1 Receptor Agonists vs DPP-4 Inhibitors**

Various similarities and differences exist between GLP-1 receptor agonists and DPP-4 inhibitors.\textsuperscript{[2,36]}

Both classes of incretin-based medications exert beneficial effects on glycemic control, irrespective of the type of background oral agents. Both also complement the action of metformin, TZDs, and sulfonylureas. Importantly, GLP-1 receptor agonists and DPP-4 inhibitors are rarely, if ever, associated with severe hypoglycemia, provided that they are not used in combination with a sulfonylurea.\textsuperscript{[2]}

Among the differences between these 2 drug classes, GLP-1 receptor agonists are administered via subcutaneous injection, while DPP-4 inhibitors are delivered as oral tablets. Glucagon-like peptide-1 receptor agonists are probably more effective than DPP-4 inhibitors at reducing HbA$_{1c}$ levels. Glucagon-like peptide-1 receptor agonists help preserve β cells, which are diminished with DPP-4 inhibitors; induce weight loss, unlike DPP-4 inhibitors; and have beneficial effects on blood pressure—effects that have not been demonstrated with DPP-4 inhibitors.\textsuperscript{[2,36]}

**Treatment Guidelines**

Multiple guidelines exist for the treatment of patients with T2DM, including those put forth by the American Diabetes Association (ADA)\textsuperscript{[64]} and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE).\textsuperscript{[4]} Figure 4 provides a schematic of the AACE/ACE treatment guideline recommendations.\textsuperscript{[4]}

Before selection of a particular drug regimen, it is important to establish an appropriate individualized HbA$_{1c}$ goal for the patient. Several recent large-scale clinical trials have evaluated the effects of intensive lowering of glucose levels on macrovascular disease and major cardiovascular events.\textsuperscript{[65-67]} Results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD)\textsuperscript{[65]} the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation (ADVANCE) trial,\textsuperscript{[66] and the Veterans Affairs Diabetes Trial (VADT)\textsuperscript{[67]}} suggested that intensive glycemic control to near normoglycemia had no effect on cardiovascular outcomes. In addition, the ACCORD trial\textsuperscript{[65]} found increased mortality in patients undergoing tight glycemic control, though this finding was not replicated in the ADVANCE\textsuperscript{[66]} and VADT trials.\textsuperscript{[67]}

In the ACCORD study,\textsuperscript{[65]} randomization to the intensive treatment arm was associated with higher rates of severe hypoglycemia, which may be one possible explanation for the increased risk of cardiovascular outcomes observed in the study.\textsuperscript{[68]} In healthy individuals, acute hypoglycemia provokes sympathoadrenal activation and regulatory hormonal secretion that protects the brain from neuroglycopenia. Other metabolic changes also occur in healthy individuals to restore blood glucose to normal levels. However, in patients with T2DM who have endothelial dysfunction, acute hypoglycemia can lead to acute hemodynamic and hematologic changes, which can ultimately result, in turn, in increased tissue ischemia and...
major adverse vascular events, including myocardial infarction and stroke.60

These adverse changes might be further confounded by hypoglycemia unawareness, particularly in patients with coexisting cardiovascular autonomic neuropathy (a strong risk factor for sudden death). Because no anatomic features of hypoglycemia can be detected postmortem, death resulting from a hypoglycemic event may be mistakenly ascribed to coronary artery disease, especially if blood glucose measurements of the individual are not available.60,70

Other explanations proposed for the increased mortality observed in the ACCORD trial65 include adverse effects from increased exposure to particular antidiabetic medications, from rapid correction of hyperglycemia, and from weight gain, as well as differences in baseline characteristics. None of these explanations have been validated in post hoc trial analyses. Thus, the ultimate cause of the increased mortality remains unknown.68,70

The results of ACCORD and other trials65-70 suggest that in patients with T2DM, glycemic targets should be individualized based on the particular characteristics of individual patients, including the following: projected benefits from glycemic control; presence of comorbidities and complications; risks and consequences of hypoglycemic events; and presence of hypoglycemic unawareness.68,71,72 For most patients, the best treatment strategy is one targeted to an HbA1c level of less than 7%. Lower HbA1c levels may be indicated in younger patients and in patients with no history of cardiovascular disease. Conversely, less stringent HbA1c goals may be appropriate for patients with a history of severe hypoglycemia, advanced cardiovascular disease, or extensive comorbid conditions, or for individuals with advanced T2DM in whom an HbA1c value of less than 7% has been difficult to achieve.68

Consideration must also be given
to the choice of antihyperglycemic agent. Agents should be considered not only on the basis of their ability to achieve a patient’s HbA1c goal, but also for their effects on weight, glycemic durability, and cardiovascular protection, as well as their adverse-effect profiles and methods of delivery.27 Incretin-based medications are becoming increasingly recognized in guidelines as early treatment options because of their effects on glycemic and nonglycemic endpoints and their well-tolerated profiles.

The AACE/ACE guidelines4 clearly state that incretin-based options should not be limited to third-line or fourth-line therapies.35 In fact, one might argue that incretin-based agents could be used to replace the older insulin-secretory agents—sulfonylureas—in the treatment armamentarium for patients with T2DM. Although sulfonylureas have long been one of the most widespread treatment options for patients with T2DM, their use is associated with weight gain, risk of severe hypoglycemia, and a singular mechanism of action that often results in patients being treated with additional antihyperglycemic agents.73 Recent studies have also shown that sulfonylureas may be associated with increased β-cell apoptosis, suggesting that sulfonylureas may actually accelerate the progressive decrease in β-cell mass, thereby promoting the need for insulin replacement.73

Data from recent trials comparing sulfonylureas with DPP-4 inhibitors have demonstrated similar reductions in HbA1c level with either medication, but changes in body weight consistently favored DPP-4 inhibitors. Furthermore, superior effects on lipid profiles were observed in patients treated with DPP-4 inhibitors relative to those treated with sulfonylureas.74 Clinical trials also showed that severe hypoglycemia occurred at a rate of approximately 1.5% over 2 years with the use of sulfonylureas, but it was extremely rare with DPP-4 inhibitors.74 Thus, any financial savings incurred by using sulfonylureas in the treatment of patients with T2DM could be quickly negated by the need for additional physician visits or even hospital admissions to manage hypoglycemic episodes.

Importantly, incretin-based agents potentiate glucose-stimulated insulin secretion and may restore reduced glucose-induced insulin secretion in patients with T2DM. The insulinotropic effects of GLP-1 receptor agonists and DPP-4 inhibitors are glucose dependent, reducing the risk of hypoglycemia.

When an incretin-based medication is indicated, the choice of the particular agent to use is a joint decision between physician and patient. The only available incretin-based agents at the time of publication of the AACE/ACE guidelines (November 2009)4 were the GLP-1 receptor agonist exenatide and the DPP-4 inhibitors sitagliptin and saxagliptin. Since then, the GLP-1 receptor agonist liraglutide and the DPP-4 inhibitor linagliptin have been approved by the FDA, and these agents are now available for incorporation into the AACE/ACE algorithm (Figure 4).4

Patients at increased cardiovascular risk, including those who are overweight or have hypertension, may receive greater benefit from GLP-1 receptor agonists as a result of the effects of these drugs on body weight and blood pressure. Glucagon-like peptide-1 receptor agonists also offer more robust HbA1c reductions compared to DPP-4 inhibitors.75

Many patients may prefer to use DPP-4 inhibitors because these agents can be taken orally—in contrast to GLP-1 receptor agonists, which must be administered once or twice daily by subcutaneous injection with a prefilled pen. However, the reluctance that patients have at the prospect of self-administering injections can often be overcome by providing comprehensive instructions on how to use the pen devices. The physician should show the patient how to use the pen devices and demonstrate its use, with the patient then making a return demonstration. In many cases, the provider is able to make an injection without the patient realizing it, because the needles of modern pen devices have such fine gauges.75

Finally, it is worth noting that both GLP-1 receptor agonists and DPP-4 inhibitors have low risks for hypoglycemia, and research to date has found no long-term toxicities with either of these incretin-based treatments.

Investigational Incretin-Based Agents

Many new incretin-based agents are under investigation for the treatment of patients with T2DM. Albiglutide, exenatide LAR, and lixisenatide are investigational GLP-1 receptor agonists in late stages of clinical development.76

Among new classes of medications on the horizon for T2DM management, sodium-glucose cotransporter 2 (SGLT-2) inhibitors seem to be one of the most promising. The FDA recently accepted a New Drug Application for dapagliflozin, an investigational SGLT-2 inhibitor, for the treatment of patients with T2DM.77 Results of ongoing phase III and phase IV clinical trials will outline the role that these new agents may play in the management of T2DM.

Quick-release bromocriptine (bromocriptine-QR), a D2 dopamine receptor agonist, was approved by the FDA in 2008 as a treatment for patients with T2DM. Bromocriptine-QR has demonstrated efficacy as an adjunctive agent in the management of T2DM, though studies of longer duration are needed to further define its role in diabetes mellitus management.78,79

Colesevelam, a bile acid sequestrant, was also approved by the FDA in 2008, for use in combination with other antihyperglycemic agents to improve glycemic control in patients with T2DM.80 Recent data analysis has demonstrated that colesevelam improves HbA1c levels when used in combination with metformin in patients with T2DM.81

Conclusion

The treatment of patients with T2DM remains complex and challenging for physicians. Several GLP-1 receptor agonists and DPP-4 inhibitors have recently been added to the armamentarium of T2DM management, and several more agents are in late stages of clinical development. These incretin-based medications demonstrate improved efficacy and safety relative to traditional agents, and they represent a major paradigm shift in the treatment of patients with diabetes mellitus.


