Evidence-Based Practice Use of Incretin-Based Therapy in the Natural History of Diabetes

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Abstract: The incretin class of anti-hyperglycemic agents, including glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, is an important addition to the therapeutic armamentarium for the management of appropriate patients with type 2 diabetes mellitus as an adjunct to diet and exercise and/or with the agents metformin, sulfonylureas, thiazolidinediones, or any combination thereof. More recently, US Food and Drug Administration (FDA)-approved indications for incretins were expanded to include use with basal insulin. This review article takes an evidence-based practice approach in discussing the importance of aggressive treatment for diabetes, the principles of incretin physiology and pathophysiology, use of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, and patient types and contexts where incretin therapy has been found beneficial, from metabolic syndrome to overt diabetes.

Keywords: diabetes; dipeptidyl peptidase-4 inhibitors; glucagon-like peptide-1 receptor agonists; incretin

Introduction

The incretin class of anti-hyperglycemic agents is an important addition to the therapeutic armamentarium for the care of patients with type 2 diabetes mellitus (T2DM). Incretin-based therapies have been available since 2005 with the initial launch of glucagon-like peptide-1 (GLP-1) receptor agonists, followed by the launch of the dipeptidyl peptidase-4 (DPP-4) inhibitors. Although these agents were initially approved as an adjunct to diet and exercise and/or metformin, sulfonylureas, thiazolidinediones (TZDs), or any therapeutic combination of these agents in patients with T2DM, indications for incretin therapy have been recently expanded to include their use with basal insulin.

This review takes a broad view of the use of GLP-1 receptor agonists and DPP-4 inhibitors based on the concept of evidence-based practice, the philosophy that takes the principles of evidence-based medicine and combines them with patient-based experience, clinical expertise, expert opinions, and existing guidelines to treat any individual patient in the optimal fashion. The review provides a rationale for the need to treat patients aggressively, discusses principles of incretin physiology and pathophysiology, the incretin medications themselves (similarities and differences), and patient types and contexts where incretin therapy has proven to be useful, from metabolic syndrome (MetS) to overt diabetes.

Materials and Methods

The author’s clinical experience and expertise were used as the foundation for the article, supplemented by supportive literature related to the topic. Evidence-based
guidelines and an evidence-based practice approach are used for the recommendations.

**Treatment Rationale**

Today’s diabetes epidemic correlates directly with the obesity epidemic in the United States and worldwide. Estimates from 2010 indicated that 25.6 million (11.3%) US adults have diabetes, with an additional 79 million (35%) with prediabetes. The hyperglycemia of diabetes leads directly to complications that can be present well before a patient is diagnosed with overt diabetes. Both hyperglycemic spikes (ie, variability) and continuous glycemic elevations result in acute and chronic toxicity, which leads to both micro- and macrovascular complications. The presence of hyperglycemia, especially previously unrecognized hyperglycemia, correlates directly with adverse patient outcomes in the hospital setting.

Data from meta-analyses of large prospective, randomized trials show that in patients with T2DM, both early and late in the course of disease, aggressive glycemic control can reduce both micro- and macrovascular complications. Confusion has arisen from apparent negative results in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular Disease: Preterax and DiaMicon Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT). In the ACCORD trial (N = 10,251), intensive therapy (target glycated hemoglobin [HbA1c] level < 6.0%) increased patient mortality and did not significantly reduce major cardiovascular (CV) events compared with standard therapy (target HbA1c 7.0% to 7.9%). Patients who were older, with longer duration of diabetes, and with existing CV comorbidities had undue hypoglycemia and weight gain—results arguably accounting for the inability to reduce CV outcomes and increased patient mortality with aggressive treatment to lower HbA1c levels < 6.0% using hypoglycemia agents. It should be no surprise given that patient weight gain increases risk of CV disease and mortality, and that weight loss reduces cardiometabolic risk factors in patients with T2DM. Additionally, hypoglycemia has many negative CV consequences. In the ADVANCE trial (N = 11,140), intensive glucose control, defined as the use of gliclazide plus other drugs to achieve HbA1c level < 6.5%, resulted in a 10% relative reduction in the combined outcome of major macro- and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy, compared with standard glucose control. There were no significant differences between types of glucose control used on patient major macrovascular events, mortality from CV causes, or mortality from any cause. Severe hypoglycemia was uncommon, but was more prevalent in the intensive-control group compared with the standard-control group. In the VADT trial (N = 1791), intensive therapy (absolute reduction of 1.5% in HbA1c level compared with standard therapy group) in patients with poorly controlled T2DM had no significant effect on rates of major CV events, mortality, or microvascular complications. Thus, aggressive treatment is warranted, but agents that cause hypoglycemia and weight gain should be avoided, which is the logic for use of the new incretin classes of agents, which are either weight neutral or result in weight loss for patients, with no undue hypoglycemic risk in the absence of concurrent hypoglycemic agents.

**Natural History of T2DM**

Type 2 diabetes mellitus is a chronic, progressive disorder that occurs in genetically susceptible individuals exposed to an environmental trigger favoring insulin resistance. The disease can be exacerbated by factors including obesity, mental illness, sleep disorders, exposure to second-hand smoke, and lack of physical activity. Prediabetes (defined by the presence of impaired fasting glucose level or impaired glucose tolerance) reflects patient risk for future development of diabetes, as well as CV disease, and is associated with obesity, dyslipidemia, and hypertension. Early intensification of T2DM management has been proven to minimize patient risk of developing long-term micro- and macrovascular complications. In addition to the core pathophysiologic defects in T2DM of insulin resistance in muscle and the liver, and abnormal ß-cell function, other mechanisms of hyperglycemia include accelerated lipolysis of fat cells, decreased response to intestinal incretin hormones, hyperglucagonemia of the ß-cell, increased glucose reabsorption in the kidney, and insulin resistance in the brain.

**The Role of Incretin-Based Therapies**

The potential of incretin therapy is observed through glucoregulatory and other effects in the patient. Glucoregulatory effects include improvement in the incretin effect (by definition) and the function of both ß- and α-cells (especially a glucose-dependent release of insulin and suppression of glucagon) with both DPP-4 inhibitors and GLP-1 receptor agonists, as well as in reduction of insulin resistance in fat and muscle via direct and indirect effects on the liver. Additional actions and benefits of incretin therapy include reducing hepatic glucose output and weight reduction with
GLP-1 receptor agonists via inducing hypothalamic satiety and slowing the fast gastric emptying observed in patients with diabetes.

**Glucoregulatory Incretin Effects**

The incretin effect was initially described in 1964. It was recognized that the β-cell secreted 4 times more insulin when glucose was given to metabolically normal subjects orally rather than intravenously. The phenomenon, termed the *incretin effect* (due to gut-derived hormones secreted in response to nutrient ingestion that potentiate insulin secretion from β-cells), was found to be diminished in patients with diabetes. The hormone with the most therapeutic potential was identified as GLP-1. Secretion of GLP-1 may be reduced in patients with diabetes, but the most recent work suggests that GLP-1 resistance also exists and can be overcome by pharmacologic levels of the hormone. The key effects of GLP-1 are to produce glucose-dependent secretion of insulin (increasing both first- and second-phase insulin secretion) and suppress glucagon secretion with nutrient ingestion (with a low risk of hypoglycemia); it has been shown to normalize plasma glucose levels in patients with T2DM. Moreover, GLP-1 also has been shown to minimize suppression of insulin induced by therapeutic use of steroids and calmodulin inhibitors.

**Additional Actions and Benefits of Incretins**

The actions of GLP-1 extend beyond the glucoregulatory effects outlined. Additional benefits include slowing of the fast gastric emptying that exists in patients with T2DM, suppressing appetite in the hypothalamus, and multiple beneficial CV effects, as shown in clinical and preclinical studies. The reported CV effects included reduced total and low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, and triglyceride levels; increased high-density lipoprotein cholesterol (HDL-C); reduced high-sensitivity C-reactive protein; lowered systolic and diastolic blood pressure; improved endothelial function in patients with T2DM who had established coronary heart disease (CHD); improved left ventricular (LV) function in patients with acute myocardial infarction (MI); enhanced sodium excretion; improved cardiomyocyte viability after ischemia-reperfusion injury; improved systolic function; peripheral vasodilation; and reduced vascular inflammation.

Patients with acute MI with or without diabetes who received a 72-hour infusion of GLP-1 added to standard therapy after successful primary angioplasty showed significant improvements in LV ejection fraction (LVEF; from 29 ± 2% to 39 ± 2%; P < 0.01 vs controls). In addition, GLP-1 infusion peri-MI reduced infarct size. Improvements in LVEF also were observed after MI in patients with chronic heart failure with or without diabetes who received GLP-1 infusion for 5 weeks in addition to standard therapy (from 21 ± 3% to 27 ± 3%; P < 0.01 vs controls). In another study in patients with CHD and preserved LV function, a 48-hour infusion of GLP-1 initiated 12 hours before coronary artery bypass graft surgery reduced the need for vasopressors and anti-arrhythmic agents, and provided significantly better glycemic control pre- and perioperatively (95 ± 3 vs 140 ± 10 mg/dL; P = 0.02 vs controls). In addition, GLP-1 recipients required 45% less insulin than controls to achieve the same glycemic control during the postoperative period.

**Incretin-Based Therapies**

Attempts to use GLP-1 as a therapeutic agent in patients with T2DM have been limited by its short half-life in circulation, which is largely due to its inactivation by the enzyme DPP-4. These findings led to the development of incretin mimetics: GLP-1 analogs that are resistant to DPP-4 degradation, and DPP-4 inhibitors, agents that inhibit the proteolytic cleavage and inactivation of native GLP-1. The DPP-4 inhibitors increase concentration of endogenous GLP-1 approximately 2- to 4-fold, whereas GLP-1 receptor agonists, via their homology to native GLP-1, increase its effect 8- to 10-fold, with resultant different effects of the 2 classes of agents. Orally administered DPP-4 inhibitors improve the incretin effect and glucose-dependent secretion of insulin, as well as the suppression of glucagon with nutrient ingestion, which results in a low risk of hypoglycemia. In addition to these benefits, injectable GLP-1 receptor agonists decrease caloric intake and result in patient weight loss by slowing down the fast gastric emptying observed in patients with T2DM and by suppressing appetite through effect on the hypothalamus.

The primary principle in choosing the right class of incretin is matching the right drug with the right patient and vice versa. The choice of agent should be based on individualized comorbidities, compliance issues, and patient administration preference — injection (once or twice daily, or once weekly; needle size) or oral dosing — and all of the practical issues surrounding clinical judgment, along with use of a patient-centric approach, from matching the patient’s needs with regard to extent of reduction in HbA1c level and weight, to other effects achieved by the different incretin drug classes.
Table 1 summarizes key studies and reductions in patient HbA1c levels per US Food and Drug Administration (FDA)-approved agents currently available, including the DPP-4 inhibitors linagliptin,61–66 saxagliptin,67–72 sitagliptin,55–70 and alogliptin77–81; and the GLP-1 receptor agonists exenatide twice daily,82–87 exenatide once weekly,88–92 and liraglutide.93–98 As Bloomgarden et al99 noted for antihyperglycemic agents in general, the higher the baseline HbA1c level, the greater the reduction in HbA1c level when incretins are used.100 An interesting exception occurs when sodium-glucose cotransporter-2 (SGLT-2) inhibitors are added to both incretin classes of agents. Monotherapy efficacy is preserved completely with regard to patient glycemic benefit and weight loss,101 presumably because incretins reduce the compensatory increase in hepatic glucose production induced by SGLT-2 inhibition.102 The incretin therapies are effective when added to existing regimens, such as metformin and/or pioglitazone; and although incretin therapies have proven effective when added on to sulfonylureas, the combination can be associated with hypoglycemia — thus, incretins are used to discontinue sulfonylureas and glinides in patients, a major focus of our evidence-based practice approach in the use of incretins.

The weight neutrality of the DPP-4 inhibitors and the weight loss associated with the GLP-1 receptor agonists are important considerations for the approach. The DPP-4 inhibitors are weight neutral. Very importantly, the GLP-1 receptor agonists are associated with mean weight reductions whether used as monotherapy or in combination therapy,102 an effect that does not appear due to the nausea that some patients experience on GLP-1 receptor agonist therapy.95,104 The weight-loss effect is durable if the agent is continued.91,105

Tolerability and Notable Adverse Events

Hypoglycemia is infrequent and severe hypoglycemia is rare when using DPP-4 inhibitors and GLP-1 receptor agonists,91,106 in contrast to sulfonylureas.55–58 Cardiovascular safety is a major focus of the evidence-based practice approach in the use of incretins. All the incretins have met the less stringent CV safety requirements instituted by the FDA in 2008.107 Saxagliptin and alogliptin have demonstrated CV safety in large prospective, randomized, controlled trials reported in 2013108,109 and have met more stringent FDA criteria, while CV outcomes trials are in progress for other incretin agents. A meta-analysis of data from DPP-4 inhibitors110 suggested a modest reduction in CV events. The mechanism for the CV effects of DPP-4 inhibitors through modulation of endothelial progenitor cells, the inflammatory pathway, and the ischemic response, was reviewed by Fadini and Avogaro.111 Sitagliptin has been shown to have cardioprotective effects on ischemic segments and mitigated post-ischemic stunning in patients undergoing stress testing.112 A retrospective database analysis of claims during a 4-year period showed that patients treated with exenatide twice daily were 19% less likely to have a CV event than patients treated with other glucose-lowering agents.113

The most common adverse effects of DPP-4 inhibitors are upper respiratory tract infections, nasopharyngitis, and headache.114–117 The most common adverse effects of GLP-1 receptor agonists include nausea, vomiting, diarrhea, headache, and injection site reactions.118–120

In 3 placebo-controlled, 30-week clinical trials of exenatide twice daily as an add-on to metformin and/or sulfonylurea, the most common adverse events occurring in patients receiving exenatide (N = 963) compared with placebo (N = 483) were nausea (44% vs 18%), vomiting (13% vs 4%), and diarrhea (13% vs 6%).118 Of note, in a 2008, 24-week study of exenatide twice daily as monotherapy showed the rate of nausea to be 3% with exenatide 5 mcg (2 of 77 patients) and 13% with exenatide 10 mcg (10 of 78 patients).119 The lower nausea rates may have occurred because patients learned how to use exenatide and to stop eating when full. Moreover, the incidence of nausea with exenatide once weekly 2 mg (9% of 461 patients) was nearly one-third that with liraglutide 1.8 mg daily (21% of 450 patients) in a 26-week open-label study.89 Nausea decreases over time with both exenatide and liraglutide use.121–123 Some patients on GLP-1 receptor agonists have undue hypothalamic sensitivity resulting in nausea, even at low doses. It can account for the 1% dropout rates in many studies.86,89,118,121–125 but may be treated with metoclopramide or ondansetron.126

In patients exposed to GLP-1 receptor agonists, slower gastric emptying seems to be the cause of gastrointestinal upset, nausea, and even vomiting, especially if the patient continues eating after the first sense of fullness, has a high-fiber intake, consumes high-fat meals, or eats too quickly. Thus, patients should be taught that they will lose their appetite between meals and should not eat out of habit, to stop eating at the first sense of fullness, eat slowly, and avoid high-fat and very high-fiber meals. To reduce the risk of nausea, physicians may advise patients to slow the titration of exenatide twice daily118 and liraglutide,119 and administer exenatide twice daily closer to the start of a meal.118

With regard to renal safety with use of incretin-based therapies, there is no evidence of direct nephrotoxicity,114,118,119,127,128 but worsening renal function
Table 1. Reduction in HbA1c Levels in Key Monotherapy and Combination-Therapy Studies With GLP-1 Receptor Agonists and DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>N</th>
<th>Duration, Weeks</th>
<th>Treatments</th>
<th>Baseline HbA1c Level, %</th>
<th>HbA1c Change, (% or +%)</th>
<th>P Value vs Placebo</th>
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<td>Alogliptin</td>
<td>DeFronzo et al, 2008</td>
<td>77</td>
<td>329</td>
<td>Alogliptin 25 mg QD</td>
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<td>-0.59</td>
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<td></td>
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<td>Placebo</td>
<td>-0.02</td>
<td>-</td>
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<td></td>
<td>Pratley et al, 2009</td>
<td>500</td>
<td>26</td>
<td>Alogliptin 25 mg QD</td>
<td>8.1</td>
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<td>-</td>
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<td>Nauck et al, 2009</td>
<td>527</td>
<td>26 (add-on to metformin)</td>
<td>Alogliptin 12.5 mg QD</td>
<td>7.9</td>
<td>-0.6</td>
<td>&lt; 0.001</td>
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<td></td>
<td>Alogliptin 25 mg QD</td>
<td>7.9</td>
<td>-0.6</td>
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<td>Placebo</td>
<td>8.0</td>
<td>-0.1</td>
<td>-</td>
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<td>Pratley et al, 2009</td>
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<td>26 (add-on to pioglitazone)</td>
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<td>-</td>
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<td>Rosenstock et al, 2010</td>
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<td>26</td>
<td>Alogliptin 25 mg QD + pioglitazone 30 mg QD</td>
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<td>-1.71</td>
<td>&lt; 0.05 vs each component alone</td>
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<td>&lt; 0.0001 vs placebo; metformin 1000 mg alone</td>
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<td>Placebo</td>
<td>8.7</td>
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<td>-</td>
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(Continued)
### Table 1. (Continued)

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<td>−0.64</td>
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<td>Sitagliptin 100 mg QD</td>
<td>8.7</td>
<td>−0.6</td>
<td>&lt; 0.001</td>
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<td>Dobs et al, 2013(^4)</td>
<td>278</td>
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<td>Sitagliptin 100 mg QD</td>
<td>8.8</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>Exenatide Twice Daily</td>
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<td>Moretto et al, 2008(^6)</td>
<td>232</td>
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<td>7.9</td>
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<td>&lt; 0.001</td>
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<td>Zinman et al, 2007(^7)</td>
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<td>Heine et al, 2005(^4)</td>
<td>551</td>
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<tr>
<td>Russell-Jones et al, 2012(^7)</td>
<td>820</td>
<td>26</td>
<td>Exenatide 2 mg QW</td>
<td>8.5</td>
<td>−1.53</td>
<td>−</td>
</tr>
<tr>
<td>Bergenstal et al, 2010(^4)</td>
<td>491</td>
<td>26</td>
<td>Exenatide 2 mg QW</td>
<td>8.6</td>
<td>−1.5</td>
<td>−</td>
</tr>
</tbody>
</table>

\(^a\) Duration of treatment in weeks.
\(^b\) P values are for treatment effects compared to placebo or active comparator, as indicated.
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Agent Study</th>
<th>N</th>
<th>Duration, Weeks*</th>
<th>Treatments</th>
<th>Baseline HbA1c Level, %</th>
<th>HbA1c Change, (or +)%</th>
<th>P Value vs Placebob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamant et al, 2010</td>
<td>456</td>
<td>26 (add-on to metformin ± sulfonylurea)</td>
<td>Exenatide 2 mg QW</td>
<td>8.3</td>
<td>-1.5</td>
<td>0.017 vs insulin glargine</td>
</tr>
<tr>
<td>Drucker et al, 2008</td>
<td>295</td>
<td>30</td>
<td>Exenatide 2 mg QW</td>
<td>8.3</td>
<td>-1.9</td>
<td>0.0023 vs exenatide BID</td>
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<td>Buse et al, 2013</td>
<td>911</td>
<td>26 (add-on to oral agents)</td>
<td>Exenatide 2 mg QD</td>
<td>8.4</td>
<td>-1.48</td>
<td>0.02 vs exenatide</td>
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<td>Liraglutide</td>
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<td>Garber et al, 2009</td>
<td>746</td>
<td>52</td>
<td>Liraglutide 1.2 mg QD</td>
<td>8.3</td>
<td>-0.84</td>
<td>0.0014 vs glimepiride</td>
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<tr>
<td>Nauck et al, 2009</td>
<td>1087</td>
<td>26 (add-on to metformin)</td>
<td>Glimepiride 8 mg QD</td>
<td>8.4</td>
<td>-0.51</td>
<td>-</td>
</tr>
<tr>
<td>Pratley et al, 2010</td>
<td>658</td>
<td>26 (add-on to metformin)</td>
<td>Liraglutide 1.2 mg QD</td>
<td>8.3</td>
<td>-1.0</td>
<td>NR</td>
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<tr>
<td>Marre et al, 2009</td>
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<td>Liraglutide 1.2 mg QD</td>
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<td>-1.1</td>
<td>&lt; 0.0001 vs placebo; vs sitagliptin</td>
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<tr>
<td>Zinman et al, 2009</td>
<td>533</td>
<td>26 (add-on to metformin + rosiglitazone)</td>
<td>Rosiglitazone 4 mg QD</td>
<td>8.4</td>
<td>-0.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Russell-Jones et al, 2009</td>
<td>576</td>
<td>26 (add-on to metformin and glimepiride)</td>
<td>Insulin glargine</td>
<td>8.2</td>
<td>-1.09</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Measured in weeks unless otherwise noted.
*Compared with placebo unless otherwise noted.
*Frequency of dosing not reported.

Abbreviations: BID, twice daily; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; NR, not reported; QD, once daily; QW, once weekly; TZD, thiazolidinedione.

has been reported in some individuals taking exenatide, liraglutide, or sitagliptin. Exenatide should not be used in patients with severe renal impairment or end-stage renal disease, and should be used with caution in patients with renal transplantation, while liraglutide should be used with caution in patients with renal impairment. Assessment of renal function is recommended prior to initiating sitagliptin and alogliptin and periodically thereafter; dose adjustment is recommended in patients with moderate-to-severe renal insufficiency and in patients with end-stage renal disease. No dose adjustments are indicated for patients with renal impairment taking linagliptin. With saxagliptin therapy, the dose should be limited to 2.5 mg based on renal function, and assessment is recommended before initiation of saxagliptin and periodically thereafter.

Both longer duration formulations of GLP-1 receptor agonists carry black-box warnings for the risk of medullary thyroid cancer, however, this was observed in rodents and not humans, and 3 studies have shown no GLP-1 receptors on human C-cells. Nevertheless, in accordance with prescribing information, a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 in patients should be considered contraindications for liraglutide and exenatide once weekly use based on the findings in rodents. Routine calcitonin and/or ultrasound testing is not recommended, but referral to an endocrinologist is recommended for patients with thyroid
noodles or elevated serum calcitonin levels identified for other reasons.

Pancreatitis has been reported with use of DPP-4 inhibitors and GLP-1 receptor agonists, and warnings exist on all incretin labels – specifically, they should not be prescribed to patients with a history of pancreatitis. Incretin-based therapies should be discontinued if signs and symptoms arise, and in this regard, it is important to educate patients on the signs and symptoms of pancreatitis. Therapy should not be resumed if pancreatitis is confirmed.114–120,134,135

Current evidence, however, does not support a causal relationship between incretin-based therapies and pancreatitis. A large database analysis of patients taking exenatide twice daily and sitagliptin showed no increased risk compared with patients taking metformin or glyburide.136 Although there was a higher incidence of pancreatitis in liroglutide-treated patients than in those on an active comparator, it was smaller than expected given that patients with diabetes have a 1.5- to 3-fold higher risk of developing pancreatitis than nondiabetic patients.119,137 Furthermore, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) study, pancreatitis occurred infrequently, and the incidence of acute or chronic pancreatitis was similar in patients receiving saxagliptin or placebo.109 A recent review of the data by the FDA and European Medicines Agency (EMA) found no undue risk of pancreatitis or pancreatic cancer, and recommended continued scrutiny and maintenance of current warnings.138

**Clinical Applications for Incretin-Based Therapies**

Based on the characteristics of GLP-1 and the incretin drug classes discussed, it becomes evident how and for which clinical applications one might use incretin-based therapies across the natural history of the MetS and T2DM, and even for many patients with type 1 diabetes mellitus (T1DM) and latent autoimmune diabetes in adults (LADA)139 (Figure 1).

**Clinical Study Data**

Incretin therapies have proved effective in treating late-postprandial hypoglycemia in patients at risk of developing or who already have MetS due to loss of or decreased first-phase insulin secretion, resulting in slightly higher 1-hour postprandial blood glucose levels and higher initial insulin levels. As a result of loss of first-phase insulin release, a disproportion of blood glucose/insulin concentration 4 to 5 hours after eating is believed to result in hypoglycemia, with classic catechol symptoms, and occasionally, in neuroglycopenic symptoms. These patients are usually put on a no-concentrated-sweets diet, but some patients still have symptoms. Almeda-Valdes et al146 showed that patients with postprandial hypoglycemia treated with sitagliptin had significant improvement due to increased first-phase insulin release. In clinical experience, the same effect has been observed with the DPP-4 inhibitors and GLP-1 receptor agonists.

Next along the MetS treatment continuum are the GLP-1 receptor agonists, which generally reduce hypoglycemia (although concomitant use of insulin or insulin secretagogues may increase risk of hypoglycemia) and also promote weight loss. In a meta-analysis of 8 studies conducted in adults with T2DM, significant weight loss was observed with GLP-1 receptor agonist therapy versus comparators (weighted mean difference of –2.37 kg [95% CI, –3.95 to –0.78]), with a more pronounced difference when exenatide was compared with insulin (2 studies: –4.76 kg [95% CI, –6.03 to –3.49]).141 Weight loss with use of exenatide twice daily has been shown to be durable, with 84% of patients (182 of 217 patients) experiencing weight loss over 2 years.142 Treatment with exenatide twice daily for 16 weeks resulted in 77% of patients (229 of 299 patients) with MetS losing an average of 6% of their body weight.141 In a group of obese nondiabetic patients, 64% of the 186 patients receiving 2.4 or 3 mg of liroglutide once daily lost > 5% of their body weight over 1 year, and > 85% maintained this level of weight loss at 2 years.144

In a pilot study by Armato et al,145 56% of 25 patients with impaired fasting plasma glucose levels and 59% of 22 patients with impaired glucose tolerance returned to normal glucose tolerance when treated with exenatide twice daily plus pioglitazone and metformin. In the Diabetes Prevention Program Outcomes Study (N = 1990), the incidence of overt diabetes in patients with prediabetes was reduced 50% to only 5% per year; and, in those patients who had achieved normal glucose regulation, the incidence of future overt diabetes was only 3% per year.146

Both DPP-4 inhibitors and GLP-1 receptor agonists have demonstrated durability of glycemic control over 2 to 3 years.156,142,147,151 With exenatide, results are likely due to improved β-cell function, as evidenced by increased C-peptide secretion in patients during hyperglycemic clamp studies following 1 year of therapy with exenatide twice daily.152 The results can be contrasted to the marked monotherapy failure rates observed with sulfonylureas after 1 year of use.153–158 Many commentators contrast the low cost of individual doses of sulfonylureas with the higher cost of incretin
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classes of drugs, however, focusing solely on drug costs fails to recognize the greater expenses associated with older medications for increased patient emergency room visits, hospitalizations, mortality, under-recognized hypoglycemic unawareness, lifestyle restrictions, and self-monitoring of blood glucose testing, as well as diminished quality of life, worry for spouse, friends, and coworkers, fear of hypoglycemia leading to inadequate glycemic control, and severe hypoglycemia increasing the risk of dementia. In addition, given increased apoptosis (death) of β-cells with sulfonylurea use, patients will need more expensive drugs in 1 to 3 years, but with the disadvantage of having lost β-cell mass. In fact, various comparisons of sulfonylureas with incretin therapies have shown incretins to be cost-effective.162–168

Guideline Recommendations

The 2012 ADA guidelines note DPP-4 inhibitors and GLP-1 receptor agonists as therapeutic options, but sulfonylureas maintain a prominent role in the treatment paradigm, even as the guidelines advocate the importance of avoiding hypoglycemia and weight gain in patients with T2DM. There is concern regarding greater patient mortality associated with higher exposure to sulfonylureas and acute coronary events shown in large drug database studies, which may be contributed to by the loss of ischemic preconditioning observed with use of most sulfonylureas. In contrast, the incretin classes of therapy have shown CV safety and possible CV benefits, as discussed.

Early combination therapy of the incretin classes with other antidiabetic agents is supported, given the efficacy of such regimens and the known tissue damage caused by the mechanisms of complications of diabetes that can accrue with less aggressive treatment. In addition, combination therapy is supported by complementary mechanisms of action. There is a synergy with co-administration of DPP-4 inhibitors and metformin, as metformin increases endogenous active GLP-1 levels. In addition, there is a particular synergy with co-administration of DPP-4 inhibitors and GLP-1 receptor agonists with SGLT-2 inhibitors, as the increase in hepatic glucose production induced by SGLT-2 inhibitors is counteracted by reduced hepatic glucose production with use of DPP-4 inhibitors and GLP-1 receptor agonists.

Recent data presented by Abdul-Ghani et al demonstrated that early, triple antidiabetic therapy with metformin, pioglitazone, and exenatide twice daily, targeting the core metabolic defects responsible for hyperglycemia (insulin resistance and β-cell dysfunction) is more efficacious and better tolerated than therapy aimed simply at lowering patient plasma glucose concentration (escalating metformin, followed by sequential addition of glipizide, and then basal insulin), without correcting the underlying pathophysiologic disturbances present in T2DM, such as
step-by-step addition to metformin of sulfonylureas and insulin.

Additional concerns with regard to the 2012 ADA guidelines were recently published. The guidelines recommend less aggressive HbA1c level goals in patients who are older, have a longer duration of diabetes, and have important comorbidities (based upon the ACCORD, VADT, and ADVANCE trials, in which aggressive sulfonylurea and insulin use was associated with hypoglycemia and weight-gain complications). The guidelines now recognized that there are 9 classes of antidiabetic agents, including the DPP-4 inhibitors and GLP-1 receptor agonists, which are unlikely to cause hypoglycemia and, in my clinical opinion, allow clinicians to be as aggressive in these patients as in those who are younger, have a shorter duration of diabetes, and have no significant comorbidities.

The 2013 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) pharmacologic guidelines update, encompassing the broader care of patients with MetS through overt diabetes, recommends early use of combination therapy, consisting of metformin as the cornerstone of dual therapy for most patients (when metformin is contraindicated, TZDs may be used) and a GLP-1 receptor agonist or DPP-4 inhibitor. Additional combinations include metformin plus a TZD, an SGLT-2 inhibitor, basal insulin, colesevelam, bromocriptine-QR, or an alpha-glucosidase inhibitor. The insulin secretagogues (sulfonylureas or glinides) can be used in combination with metformin as a last dual therapy treatment option. Furthermore, the guidelines recommend choosing the right drug for the right patient and, most importantly, with regard to avoidance of hypoglycemia and weight gain in patients, the early use of DPP-4 inhibitors and GLP-1 receptor agonists.

Clinical Practice Experience

In my clinical practice experience, incorporation of additional principles into the diabetes-management approach maximizes control of as many mechanisms of hyperglycemia as possible, especially combining agents that address fasting and postprandial blood glucose levels, β-cell secretion, and insulin resistance. Measures include use of 3 to 4 non-insulin agents before considering insulin; not using sulfonylureas/glinides; incorporating the 2013 AACE/ACE first-tier/second-tier principle of using the most effective agents, ideally metformin, GLP-1 receptor agonists, DPP-4 inhibitors, α-glucosidase inhibitors, and now, SGLT-2 inhibitors. For patients who cannot take ≥1 of these agents, using second-line agents, such as pioglitazone, bromocriptine-QR, or colesevelam; combining agents that target or improve β-cell function, directly or indirectly, such as incretins/SGLT-2 inhibitors, pioglitazone; agents that improve insulin resistance, such as pioglitazone/metformin/bromocriptine-QR; and using insulin only if the patient is following a no-concentrated-sweets diet (otherwise the patient is positioned for weight gain and hypoglycemia). Patients are kept on non-insulin treatments when they start basal insulin. If the patient is already on insulin and is willing to follow a no-concentrated-sweets diet, the current insulin dose can be decreased ∼25% for agreeing to follow the diet; it can also be decreased an additional ∼25% if hypoglycemic episodes are occurring. The recalculated dose can be decreased ∼25% if an SGLT-2 inhibitor is added and ∼25% if a GLP-1 receptor agonist is added to the therapeutic regimen. Thus, when patients are on <40 units of insulin daily, without a restrictive diet and are experiencing hyperglycemic episodes, insulin treatment can be discontinued, as a no-concentrated-sweets diet is started along with a GLP-1 receptor agonist and/or SGLT-2 inhibitor. For patients on greater amounts of insulin, the same proportionate reductions in insulin and down-titrations are recommended initially; and as the patient loses weight, insulin therapy can be further decreased, and potentially stopped in many patients.

Weight reduction is an important clinical outcome in disease management. Incretin therapies are used in patients with MetS, as well as in those with diabetes. Treatments include using SGLT-2 inhibitors with GLP-1 receptor agonists to maximize weight loss; using incretins before pioglitazone to prevent weight gain; using SGLT-2 inhibitors with pioglitazone to reduce edema-related weight (personal observation); using GLP-1 receptor agonists as the preferred therapy over DPP-4 inhibitors in the “right patient”; using GLP-1 receptor agonists always before initiating insulin unless the patient is “sick” (ie, symptomatic) avoiding insulin if the patient is not following a no-concentrated-sweets diet; and keeping the patient on incretin/SGLT-2 inhibitor when adding basal insulin. Only ∼10% of patients need bolus insulins if non-insulin therapies are being administered as basal insulin therapy is initiated. Only analog insulins should be used per the AACE recommendations. The combination of incretin therapy with basal insulin is preferred, as 60% to 87% of patients on such a regimen achieve the ADA goal of HbA1c level <7%. Use DPP-4 inhibitors when reductions of <1.0% in HbA1c level are needed and use GLP-1 receptor agonists when reductions ≥1.0% are needed (patients may benefit from possible weight loss). Exenatide twice
Table 2. Reductions in Patient Body Weight in Key Monotherapy and Combination Therapy Studies With GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Agent Study</th>
<th>N</th>
<th>Duration, Weeks</th>
<th>Treatments</th>
<th>Baseline Body Weight, kg</th>
<th>Body Weight Change, (+ or −) kg</th>
<th>P Value (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exenatide Twice Daily</strong></td>
<td></td>
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<tr>
<td>Moretto et al, 2008&lt;sup&gt;8a&lt;/sup&gt;</td>
<td>232</td>
<td>24</td>
<td>Exenatide 5 mcg BID</td>
<td>85</td>
<td>−2.8</td>
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<td>−1.4</td>
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<td>Exenatide 5 mcg BID</td>
<td>100</td>
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<td>Exenatide 10 mcg BID</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
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<td>−0.3</td>
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<td>DeFronzo et al, 2005&lt;sup&gt;8b&lt;/sup&gt;</td>
<td>336</td>
<td>30 (add-on to metformin)</td>
<td>Exenatide 5 mcg BID</td>
<td>95</td>
<td>−0.9</td>
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<td>Exenatide 10 mcg BID</td>
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<td>Heine et al, 2005&lt;sup&gt;8c&lt;/sup&gt;</td>
<td>551</td>
<td>26 (add-on to metformin + sulfonylurea)</td>
<td>Titrated insulin glargine QD</td>
<td>88.3</td>
<td>+1.8</td>
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<td>87.0</td>
<td>−2.0</td>
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<td>Metformin 2000 mg/d</td>
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<td>0.892 vs exenatide</td>
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<td>Pioglitazone 45 mg/d</td>
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<td>+1.5</td>
<td>&lt; 0.001 vs exenatide</td>
</tr>
<tr>
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<td></td>
<td>Sitagliptin 100 mg/d</td>
<td></td>
<td>−0.8</td>
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<td>89</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>riterion insulin glargine QD</td>
<td>90.6</td>
<td>+1.4</td>
<td></td>
</tr>
<tr>
<td>Buse et al, 2013&lt;sup&gt;8h&lt;/sup&gt;</td>
<td>911</td>
<td>26 (add-on to oral agents)</td>
<td>Exenatide 2 mg QW</td>
<td>90.9</td>
<td>−2.68</td>
<td>—</td>
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<td></td>
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<td>Liraglutide 1.8 mg QD</td>
<td>91.1</td>
<td>−3.57</td>
<td>0.0005 vs exenatide</td>
</tr>
<tr>
<td><strong>Liraglutide</strong></td>
<td></td>
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<tr>
<td>Nauck et al, 2009&lt;sup&gt;8i&lt;/sup&gt;</td>
<td>1087</td>
<td>26 (add-on to metformin)</td>
<td>Liraglutide 1.2 mg QD</td>
<td>NR</td>
<td>−2.6</td>
<td>≤ 0.01 vs placebo; &lt; 0.0001 vs glimepiride</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Liraglutide 1.8 mg QD</td>
<td>NR</td>
<td>−2.8</td>
<td>≤ 0.01 vs placebo; &lt; 0.0001 vs glimepiride</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Glimepiride 4 mg QD</td>
<td>NR</td>
<td>+1.0</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>NR</td>
<td>−1.5</td>
<td>—</td>
</tr>
<tr>
<td>Pratley et al, 2010&lt;sup&gt;8j&lt;/sup&gt;</td>
<td>658</td>
<td>26 (add-on to metformin)</td>
<td>Liraglutide 1.2 mg QD</td>
<td>93.7</td>
<td>−2.86</td>
<td>&lt; 0.0001 vs sitagliptin</td>
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<td>Liraglutide 1.8 mg QD</td>
<td>94.6</td>
<td>−3.38</td>
<td>&lt; 0.0001 vs sitagliptin</td>
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<td>Sitagliptin 100 mg QD</td>
<td>93.1</td>
<td>−0.96</td>
<td>—</td>
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<tr>
<td>Marre et al, 2009&lt;sup&gt;8k&lt;/sup&gt;</td>
<td>1041</td>
<td>26 (add-on to glimepiride)</td>
<td>Liraglutide 1.2 mg QD</td>
<td>80.0</td>
<td>+0.3</td>
<td>&lt; 0.0001 vs rosiglitazone</td>
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<td>Liraglutide 1.8 mg QD</td>
<td>83.0</td>
<td>−0.2</td>
<td>&lt; 0.0001 vs rosiglitazone</td>
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<tr>
<td></td>
<td></td>
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<td>Rosiglitazone 4 mg QD</td>
<td>80.6</td>
<td>+2.1</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>81.9</td>
<td>−0.1</td>
<td>—</td>
</tr>
<tr>
<td>Zinman et al, 2009&lt;sup&gt;8l&lt;/sup&gt;</td>
<td>533</td>
<td>26 (add-on to metformin + rosiglitazone)</td>
<td>Liraglutide 1.2 mg QD</td>
<td>NR</td>
<td>−1.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liraglutide 1.8 mg QD</td>
<td>NR</td>
<td>−2.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>NR</td>
<td>+0.6</td>
<td>—</td>
</tr>
</tbody>
</table>

(Continued)
daily is approved for use with insulin glargine; however, exenatide once weekly is not. Liraglutide is approved for use with basal insulin analogs.

If an incretin is added to a patient already on insulin, it is likely that insulin doses will need to be lowered to avoid hypoglycemia. If needed, insulin doses can be up-titrated. When adding exenatide to insulin therapy, lower the basal insulin dose 10% and bolus insulin dose 50%. When adding liraglutide to insulin therapy, lower basal and bolus insulin doses 25% each. With the addition of exenatide once weekly, maximal effect is achieved over ~6 weeks, which reflects the delayed effect of the extended-release formulation; thus, it will be necessary to down-titrate insulin doses gradually as glucose numbers drop over time. Sitagliptin, saxagliptin, linagliptin, and alogliptin are approved for concurrent use with insulin. When adding a DPP-4 inhibitor to basal insulin, reduce patient basal insulin dose 10%, and reduce bolus insulin dose 30%.

Of great interest, when GLP-1 receptor agonists are added to insulin therapy in patients with T1DM, they have also been found efficacious. Once insulin doses are adjusted, incretins reduce the dawn effect and reduce variability, brittleness, and rates of hypoglycemia simply due to the reduction in glucagon secretion. Moreover, some studies have shown improvement in HbA1c level and weight reduction in patients with T1DM.196–198 Similar effects are observed with the use of DPP-4 inhibitors.199,200 Treatment with a GLP-1 receptor agonist or DPP-4 inhibitor may be implemented in patients with T1DM depending on the need for weight reduction. A special case seems to be efficacy of incretins in treating patients with LADA, based on findings from a study of the DPP-4 inhibitor sitagliptin.199

The use of incretins is advocated in cases of stress and steroid diabetes, especially for patients in the hospital and those with new-onset diabetes after transplantation, to exploit the benefits in reducing hypoglycemia caused by the reduction in insulin secretion resulting from use of steroids and calmodulin inhibitors.39,40,201 Additionally, incretins are effective in treating patients undergoing bariatric surgery. A GLP-1 receptor agonist is used preoperatively. In some patients, these agents may obviate the need for surgery, especially when combined with an SGLT-2 inhibitor; however, in others, any weight loss prior to bariatric surgery makes the procedure easier. In patients undergoing bariatric surgery, incretins may be initiated postoperatively to avoid hypoglycemia, engendered by the use of sulfonylureas and insulin, as the patients will have rapid drops in plasma glucose initially and then have rapid weight loss on discharge. Incretins are also used in those who develop late-postprandial hypoglycemia after bariatric surgery, reminiscent of the same syndrome seen prior to developing prediabetes or diabetes (restoring first-phase insulin release).202

Lastly, with the advent of 9 antihyperglycemic agents that do not cause hypoglycemia, patient treatment goals for glycemic control and HbA1c level have changed. The ADA goal of HbA1c level < 7% and even the AACE goal of HbA1c level ≤ 6.5%, were previously generated to avoid hyperglycemia. Now clinicians can aim for the lowest HbA1c level possible without undue hypoglycemia, even in the elderly (in whom the appropriate caution was applied by the ADA in 2013, given the results of the ACCORD, VADT, and ADVANCE trials on the aggressive use of sulfonylureas and insulin). It seems very appropriate to do so given the greater survival in patients aged > 75 years with low HbA1c levels,203 as long as antihyperglycemic agents that do not cause hypoglycemia, such as the incretins, are used.

### Conclusions

In summary, patients with MetS and T2DM are treated aggressively because of the epidemic of obesity and...
diabetes, and the potential for adverse patient outcomes. The physiology and pathophysiology of the incretin agents have been reviewed, and it has been noted that incretin agents, which normalize and correct incretin pathophysiology, have pleotropic effects in reducing weight gain, causing weight loss, and reducing the frequency of hypoglycemia in patients; use of incretin therapy will likely also have a benefit on CV outcomes. The right drug for the right patient should be chosen, but incretin agents, in general, can be therapeutically applied in patients across the whole continuum of the natural history of MetS and diabetes.

Finally, in seeking an approach to diabetes and glycemic control that aims to reduce patient blood sugar levels as low as possible, as early as possible, for as long as possible, as safely as possible, and especially, in as rational a manner as possible — the incretin classes of agents now allow us to do so.

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Conflict of Interest Statement

References


