Clinical Efficacy of GLP-1 Agonists and Their Place in the Diabetes Treatment Algorithm

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Incretin-based therapies (subcutaneously administered glucagon-like peptide-1 [GLP-1] agonists and oral dipeptidyl peptidase-4 inhibitors) represent a new mechanism of action with which to target the adverse effects of type 2 diabetes mellitus. Both classes of incretins are excellent choices for patients who have jobs that do not permit use of insulin therapy, who have hypoglycemic unawareness, or for whom hypoglycemia is an especially worrisome potential adverse effect. Glucagon-like peptide-1 agonists are an attractive choice for patients in whom promotion of weight loss is a major consideration and the glycated hemoglobin level is moderately elevated (<8.0%) (ie, insulin is not required). Short-acting exenatide has been available since 2005 and is administered twice a day before meals. Liraglutide is the first of the long-acting GLP-1 agonists to be approved in the United States and is administered once a day. The most common adverse effects of GLP-1 agonists are those related to the gastrointestinal system. Both exenatide and liraglutide are associated with weight loss when used as monotherapy or as part of combination-therapy strategies. Glucagon-like peptide-1 agonists also have beneficial effects on cardiovascular risk factors such as blood pressure and lipids.

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Understanding the features, benefits, and limitations of incretin-based therapies (glucagon-like peptide-1 [GLP-1] agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) has become important in light of recent trends in treatment recommendations for patients with type 2 diabetes mellitus.[1-3] Incretin-based therapies represent a new mechanism of action, which targets the adverse effects of type 2 diabetes. They may be used in a complementary fashion with more traditional agents as part of combination treatment strategies. Both classes of incretins are excellent choices for patients who have jobs that do not permit use of insulin therapy, who have hypoglycemic unawareness, or for whom hypoglycemia is an especially worrisome potential side effect.

The focus of this article is to review the actions and appropriate place in therapy for the available GLP-1 agonists, exenatide and liraglutide. A brief review of current treatment goals and recommendations for patients with type 2 diabetes is included.

Individualizing Therapy and Tailoring Treatment Goals

Each patient with diabetes should be approached comprehensively, based on the patient's unique medical history and risk factors, behaviors, and ethnocultural background and environment.

The results of the Diabetes Control and Complications Trial,[4] the United Kingdom Prospective Diabetes Study,[5] and the Kumamoto study[6] helped to establish glycemic goals of therapy for patients with type 2 dia-

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betes. Since then, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[7] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[8] and Veterans Affairs Diabetes Trial (VADT),[9] in which the goals for glycated hemoglobin (HbA_{1c}) were much more aggressive (<6% in ACCORD and VADT; ≤6.5% in ADVANCE), demonstrated that overly aggressive glucose reduction can result in adverse outcomes. The ACCORD trial was halted early due to an increased death rate for patients who underwent intensive glycemic control. In this study, hypoglycemia was 3 times more common in the intensive group. The results of ADVANCE and the VADT indicated no increase in death but no cardiovascular benefit either.

Glucose targets should be individualized and take into account the patient's age, duration of disease, presence or absence of microvascular complications, presence or absence of macrovascular disease (including risk factors for cardiovascular disease [CVD]), and risk for severe hypoglycemia. The general target of HbA_{1c} levels for patients with type 2 diabetes remains less than 7%. Fasting plasma glucose (FPG) targets should be between 90 mg/dL and 130 mg/dL. For patients not at target HbA_{1c} goals (despite having FPG levels at goal), a 2-hour postprandial glucose (PPG) goal of less than 180 mg/dL is recommended.[10]

In older individuals with established disease of many years' duration and evidence of CVD (or risk factors for CVD), a more relaxed approach toward glycemic control can be considered (HbA_{1c} ≥7%).[11] The evidence suggests that the clinical course of established CVD is not readily altered by strict glycemic control, although the progression of some microvascular complications may be retarded.[7-9] Patients recently diagnosed as having type 2 diabetes who do not have established atherosclerotic disease may receive cardiovascular benefit from more intensive glycemic control, bringing HbA_{1c} levels closer to normal (ie, 6%).[11]

For all patients with type 2 diabetes, CVD risk reduction is important. For lipids, the primary goal is to reduce low-density lipoprotein cholesterol (LDL-C) to less than 100 mg/dL in patients without coronary heart disease and less than 70 mg/dL in patients with CHD. Blood pressure goals for most patients with diabetes are less than 130/80 mm Hg.[10] Modest weight loss (5%-10% of body weight) provides benefit in improving hyperglycemia, dyslipidemia, and hypertension.[12] A summary of these recommendations is provided in the *Table*.

Treatment Approaches

Medical nutrition therapy continues to be the cornerstone of efforts to improve outcomes for patients with type 2 diabetes. Ongoing counseling with a registered dietitian and an individualized meal plan may help guide patients toward achieving their goals. Physicians should encourage moderate calorie restriction and carbohydrate intake along with a reduction in saturated fat and an increase in fiber intake. A program of

Table.
Treatment Goals for Patients With Type 2 Diabetes

Parameter	Treatment Goal
■ **Glucose**	
☐ Glycated hemoglobin, %	<7% for most; closer to normal for healthy; relaxed for those with limited life expectancy (individualize based on age, comorbidities, and duration of disease)
☐ Fasting plasma glucose, mg/dL	90-130
☐ 2-hour postprandial glucose, mg/dL	<180
■ **Lipids, mg/dL**	
☐ Low-density lipoprotein cholesterol	≤70 highest risk (established coronary artery disease); <100 high risk plus 2 risk factors*
☐ Non-high-density lipoprotein cholesterol	<100 highest risk; <130 high risk
☐ Apolipoprotein B levels	<80 highest risk; <90 high risk
☐ High-density lipoprotein	>40 in men; >50 in women
☐ Triglycerides	<150
■ **Blood Pressure, mm Hg**	
☐ Systolic	<130
☐ Diastolic	<80
■ **Weight**	
☐ Weight loss	Reduce by at least 5%-10%; avoid weight regain

* Risk factors are cigarette smoking; hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication); low high-density lipoprotein cholesterol (<40 mg/dL); family history of premature congestive heart failure; and age (men, ≥45 y; women, ≥55 y).

regular moderate-intensity physical activity for 30 to 60 minutes daily, at least 5 days weekly, is also recommended.[10]

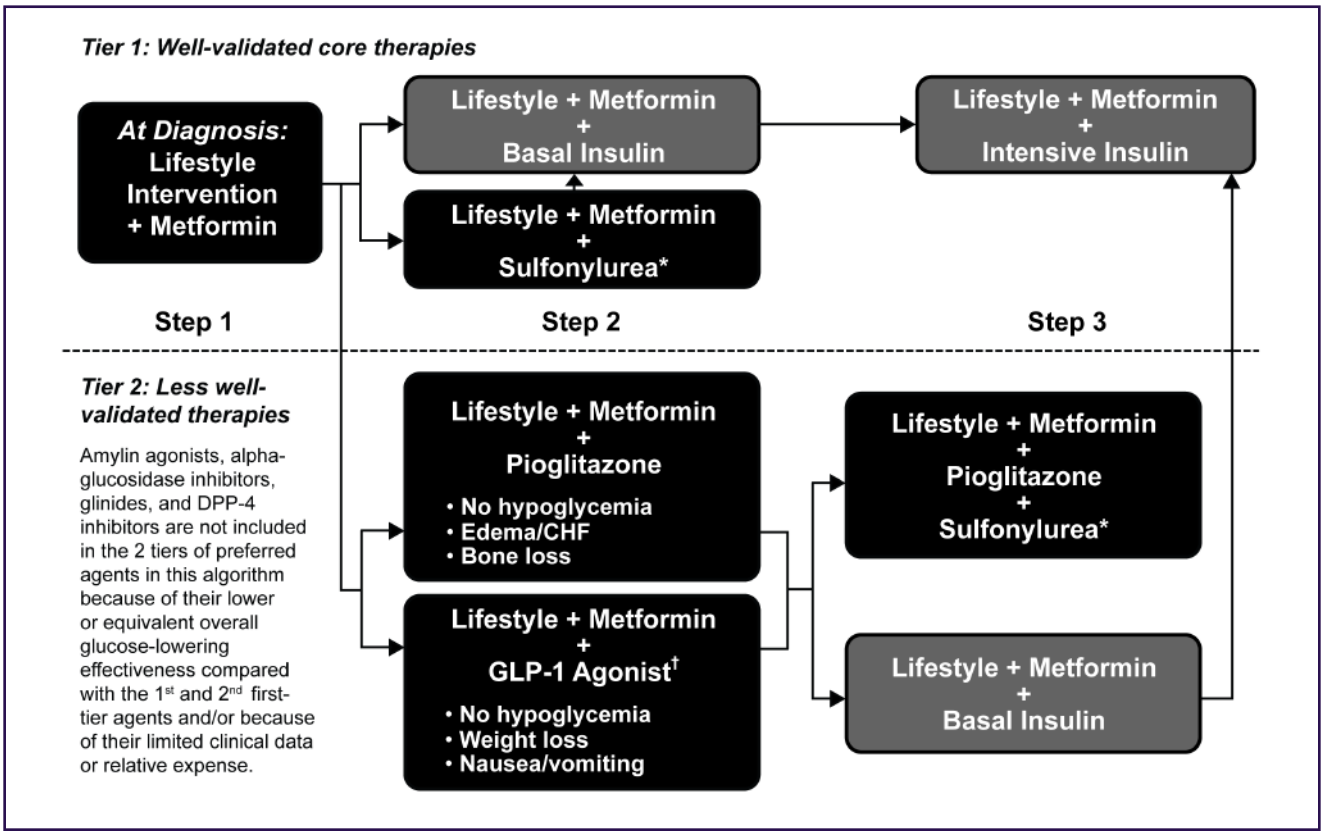
Recognizing that lifestyle interventions may not be durable enough for patients to achieve or maintain their HbA_{1c} goals, concurrent treatment with metformin is recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[3] Levels of HbA_{1c} above 7% are a "call to action" to add on to or change therapy to achieve desired HbA_{1c} levels. In such cases, the ADA/EASD treatment algorithm (*Figure 1*) goes on to recommend the rapid transition to combination therapy (ie, addition of sulfonylureas, insulin, thiazolidinediones, or GLP-1 agonists) when HbA_{1c} levels of less than 7% are not achieved or sustained.[3] Glucagon-like peptide-1 agonists are suggested as an alternative to sulfonylureas or insulin as add-on therapy to metformin. The ADA/EASD consensus statement emphasizes using agents that are "well validated" through extensive use and considering the degree to which those agents can lower HbA_{1c} levels.[3] At the time of publication, DPP-4 inhibitors were not included because of limited safety data and experience with these agents. This omission has recently been criticized because it leaves practicing physicians and their patients with too few options.[13] It is likely that the ADA will update the treatment guidelines in 2011.

The American Association of Clinical Endocrinologists and the American College of Endocrinology have recently issued updated treatment recommendations.[2] The AACE algorithm (*Figure 2*) emphasizes safety and efficacy vs costs of therapy and provides recommendations based on ambient HbA_{1c} levels. This algorithm for glycemic control has 2 important features: (1) It favors the higher-priority use of GLP-1 agonists and DPP-4 inhibitors because of their effectiveness and overall safety profiles. These agents are preferred for most patients in place of sulfonylureas and glinides; (2) It moves sulfonylureas to a lower priority because of their associated risk of hypoglycemia and weight gain and the failure of these agents to provide sustainable improvement in glycemic control.[14]

Figure 1. *The American Diabetes Association/European Association for the Study of Diabetes 2009 consensus algorithm for the management of hyperglycemia in patients with type 2 diabetes mellitus. *Excludes glyburide and chlopropamide. †Insufficient clinical use to be confident regarding safety.* ***Abbreviations:*** *CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1. Reprinted with permission from Nathan et al.[3] Copyright 2009 American Diabetes Association. From* Diabetes, *Vol. 32, 2009; 193-203. Reproduced by permission of the American Diabetes Association.*

Incretin-Based Therapies: Similarities and Differences

Incretin-based therapies (ie, GLP-1 agonists and DPP-4 inhibitors) represent a novel mechanism of action with which to target the adverse effects of type 2 diabetes.[15] They may be used in a complementary fashion with more traditional agents as part of combination treatment strategies. Both classes of incretin-based therapies are excellent choices for patients who have jobs that do not permit use of insulin therapy, who have hypoglycemic unawareness, or for whom hypoglycemia is an especially worrisome potential side effect.[1,2] Because their basis



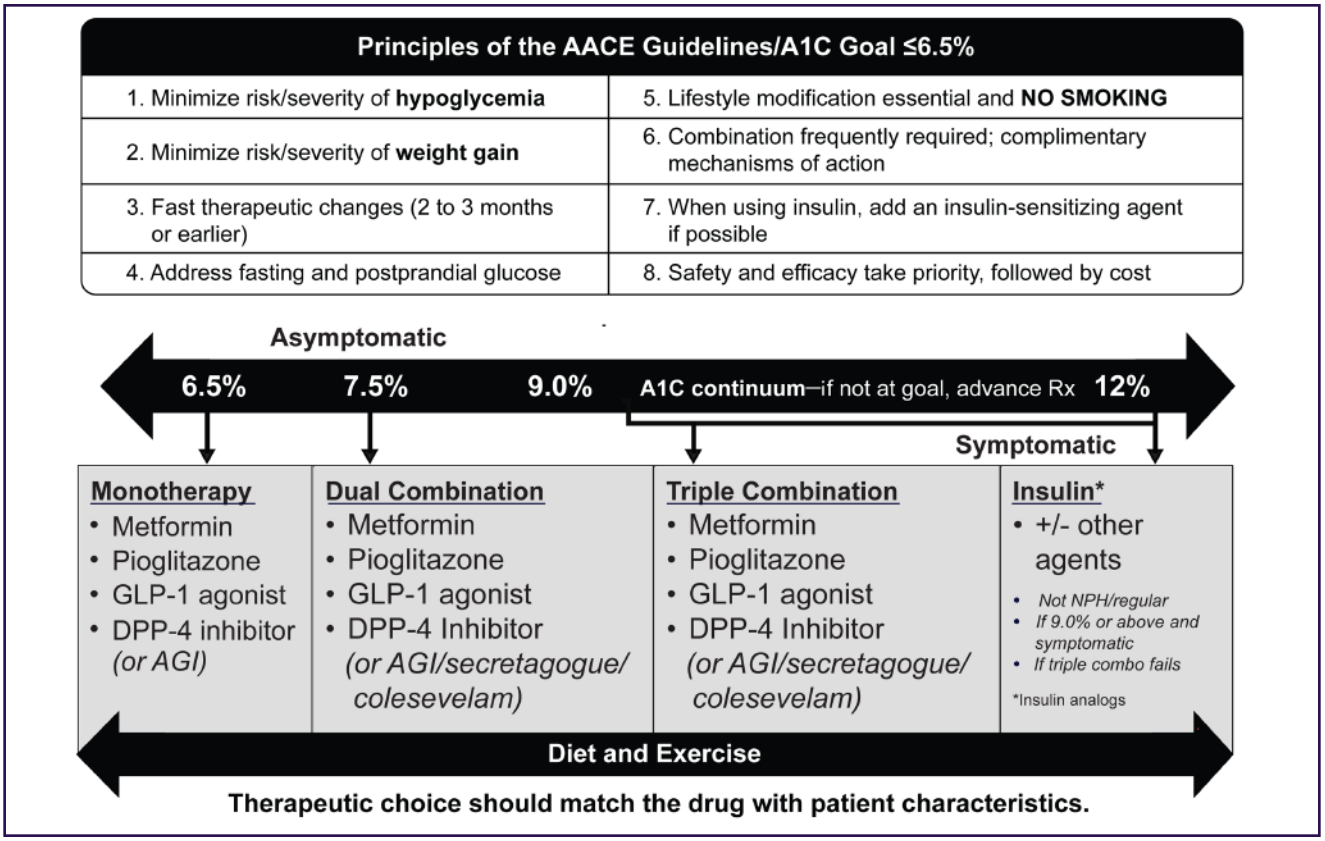


Figure 2. *The American Association of Clinical Endocrinologists algorithm for the pathophysiologic approach to treating patients who have diabetic hyperglycemia.* ***Abbreviations:*** *A1C, glycated hemoglobin; AGI, alphaglucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1. Reprinted with permission from Rodbard et al.*[2]

of action is similar, the use of GLP-1 agonists and DPP-4 inhibitors together is not recommended.

Dipeptidyl peptidase-4 inhibitors prevent the rapid degradation of endogenous GLP-1, a hormone that normally promotes the production and secretion of insulin from pancreatic β cells in a glucose-dependent manner, minimizes the release of glucagon from pancreatic α cells, induces satiety, slows gastric emptying, and reduces hepatic glucose production.[15] These inhibitors work by slightly increasing native GLP-1 levels above their normal physiologic levels.

Glucagon-like peptide-1 agonists work by binding to GLP-1 receptors located throughout the body, especially on pancreatic α and β cells. Glucagon-like peptide-1 receptors are activated equally by a GLP-1 agonist or native GLP-1. An injection of a GLP-1 agonist "floods" the binding sites of the receptors at pharmacologic levels to a much greater degree than the DPP-4 inhibitors; thus, these drugs tend to lower HbA_{1c} levels, reduce weight, slow gastric emptying, and lower glucagon levels more substantially than DPP-4 inhibitors.[16] Pharmacologic GLP-1 binding at the receptor site also increases the likelihood of adverse effects such as nausea, vomiting, and diarrhea.[17,18] Gradual dose titration can ameliorate these effects. Patients should be advised that eating beyond satiety may trigger nausea when using a GLP-1 agonist. Longer-acting GLP-1 agonists, such as liraglutide, have more profound effects on postprandial hyperglycemia as well as beneficial effects on FPG levels.[19,20]

Two head-to-head trials[16,19] of the GLP-1 agonists and the DPP-4 inhibitor sitagliptin helped identify differences between the 2 classes of agents. The first of these trials[16] was more pharmacologic in nature—it evaluated the effects of the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor sitagliptin on 2-hour postprandial glucose (PPG) levels, insulin and glucagon secretion, gastric emptying, and caloric intake in patients with type 2 diabetes.[16] Although the study was limited by the 2-week duration of exposure, the data demonstrate that exenatide had a greater effect than sitagliptin in lowering PPG levels (*Figure 3*), increasing insulin secretion, and reducing PPG secretion in patients with type 2 diabetes. Exenatide also slowed gastric emptying and reduced calorie intake while sitagliptin did not.

The second trial[19] was a large (N=665), 26-week randomized trial adding once-daily liraglutide or once-daily sitagliptin to metformin for patients with inadequate glycemic control while receiving metformin monotherapy. Major findings from the study were greater reductions in HbA_{1c} levels, FPG levels, and weight (*Figure 4*). Nausea initially occurred at higher rates with liraglutide 1.8 mg (27%) and 1.2 mg (21%) than with sitagliptin (5%). Nausea with liraglutide was transient. Most episodes occurred early, and few patients withdrew from the study. The median duration of nausea was 1 to 2 weeks; with continued administration, the prevalence of nausea was similar to that of sitagliptin.[19]

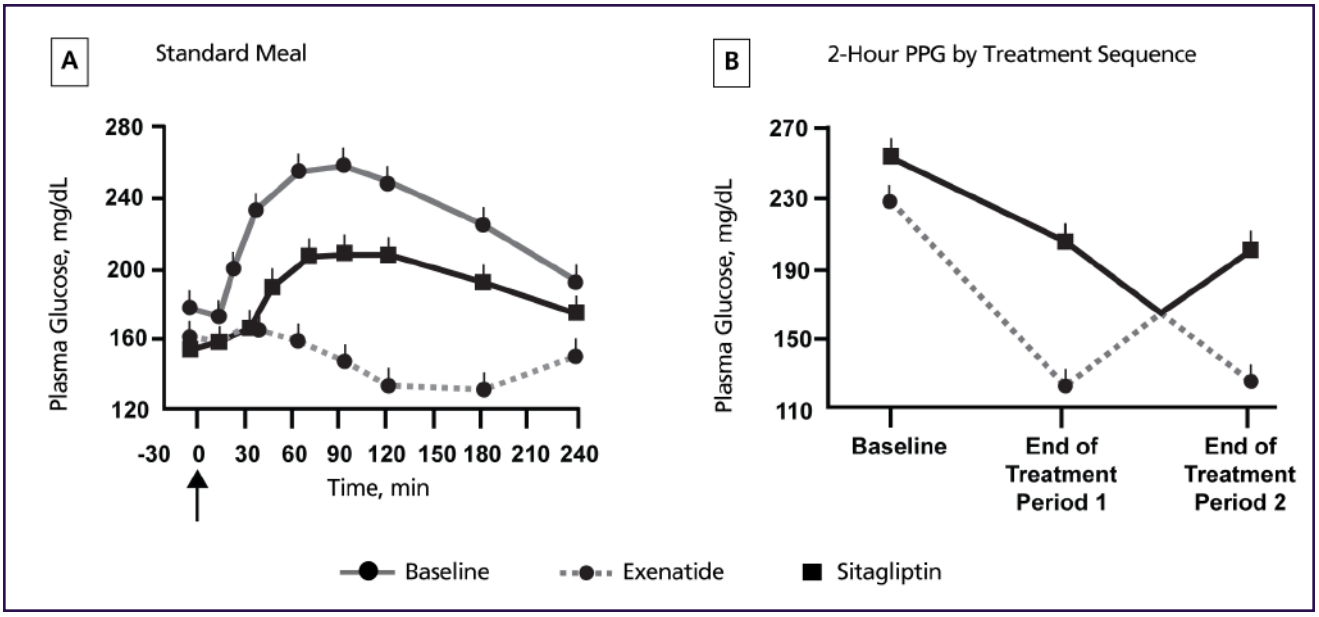


Figure 3. *Postprandial glucose (PPG) concentrations after treatment with exenatide or sitagliptin. (A) Comparison of postprandial glucose levels using exenatide, sitagliptin, and no medication (baseline). (B) Comparison of 2-hour postprandial glucose levels using exenatide and sitagliptin by treatment sequence. Reprinted with permission from DeFronzo et al.*[16]

GLP-1 Agonists

Combination Therapy

Short-acting exenatide has been available since 2005; it is approved for monotherapy or as part of combination therapy as an adjunct to diet and exercise. Clinical trials showed that exenatide 5 μg to 10 μg injected subcutaneously twice a day lowers HbA_{1c} by almost a percentage point (0.8%) and at the same time is associated with weight loss of 3 to 6 pounds over 30 weeks. The greatest weight loss was obtained when exenatide was used with metformin.[21] The most potent glucose-lowering effects occurred when exenatide was used in combination with metformin and a thiazolidinedione.[22] Subsequent studies have shown HbA_{1c} reductions of -1.3% and -1.6% at 9 and 12 months, respectively.[23] In a "real world study,"[24] a progressive reduction of weight (about 10 lb) was also observed. The primary effect of short-acting GLP-1 agonists such as exenatide is the lowering of PPG levels.[25] Exenatide is also being developed as a long-acting (once weekly) product. This formulation is still being investigated, but it shows that a more persistent GLP-1 agonist can result in greater effects on FPG levels, as well as PPG levels, leading to more profound overall HbA_{1c} reductions.[26] When higher HbA_{1c} levels (>9%) are involved, fasting plasma glucose levels are of particular importance because they make a substantially greater contribution to HbA_{1c}. When patients are switched from short-acting to long-acting exenatide, there may be a temporary deterioration in glucose control until blood concentrations of the longer-acting agent are achieved.

Liraglutide is the first of the long-acting GLP-1 agonists to be approved in the United States. This long-acting GLP-1 agonist is administered subcutaneously once a day. It has been studied in more than 65,000 patients internationally. Liraglutide has been studied in combination with metformin,[20,27] sulfonylureas,[28] thiazolidinediones plus metformin,[29] and metformin plus sulfonylureas.[20,30] As a longer-acting agent, more profound reductions in HbA_{1c} levels have been observed with liraglutide across clinical trials than were observed in the twice-a-day exenatide registration trials, reflecting an effect on both FPG and PPG levels. When compared directly with a long-acting insulin analog, liraglutide resulted in statistically significant better glucose-lowering without the risk of hypoglycemia or weight gain.[30]

Both exenatide and liraglutide are associated with weight loss when used as monotherapy or as part of combination-therapy strategies. Weight loss is more profound in patients with greater starting body mass indices.[31] Glucagon-like peptide-1 agonists also have beneficial effects on blood pressure.[24,28] Lipid effects are more mixed from study to study but are generally beneficial; some (but not all) of these effects may be related to weight loss. Significant improvements in very low-density lipoprotein, free fatty acids, and triglycerides have been observed.[32]

Head-to-head comparisons of liraglutide and exenatide show that liraglutide once a day provided statistically significant greater improvements in glycemic control than did exenatide twice a day (when used in combination with oral antidiabetic therapy).[20] In the open-label extension to this trial, patients on exenatide were switched to liraglutide, and further reductions in HbA_{1c} and weight were observed without an increased risk of hypoglycemia.[33] Further lowering of HbA_{1c} after switching from exenatide may be explained primarily by reductions in FPG levels by liraglutide.

Monotherapy

Exenatide is now approved for use as a stand-alone medication with diet and exercise to improve glycemic control in adults with type 2 diabetes. Previously, exenatide was approved for use only in patients who were also taking other common diabetes medications and had

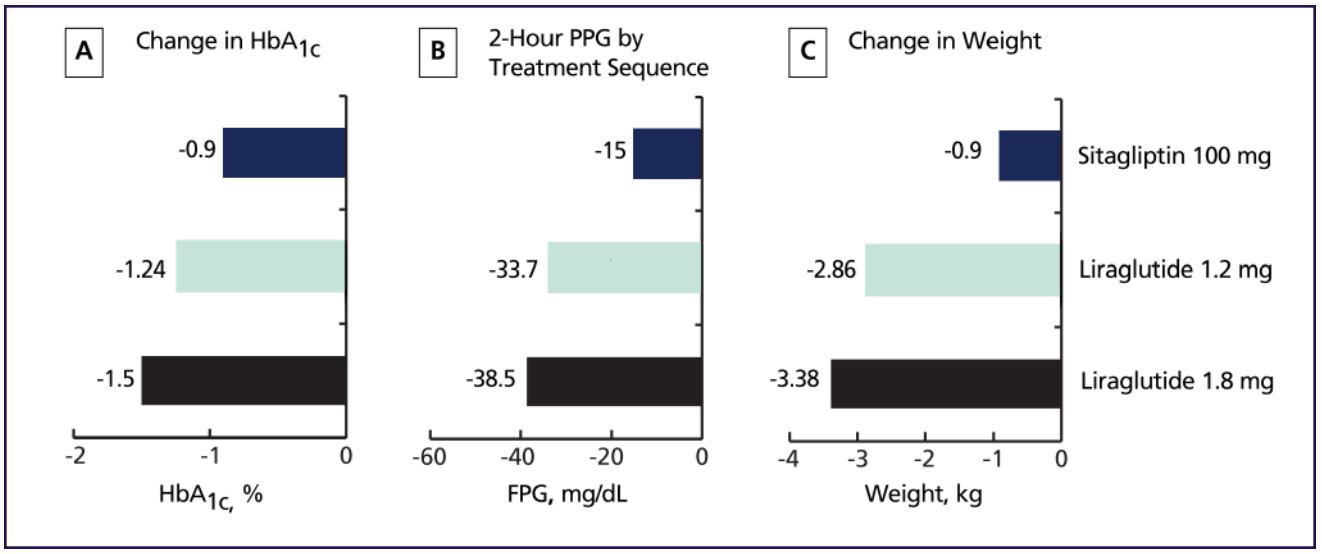


Figure 4. *Comparisons of changes in (A) glycated hemoglobin (HbA_{1c}), (B) fasting plasma glucose, and (C) weight loss in patients taking liraglutide vs those taking sitagliptin over 26 weeks. Adapted from Pratley et al.[19] Copyright 2009 American Diabetes Association. From* Diabetes, *Vol 58, 2009; 773-795. Reproduced by permission of the American Diabetes Association.*

not achieved adequate glycemic control. Patients treated with 5 μg or 10 μg of exenatide twice daily as monotherapy had HbA_{1c} reductions of 0.7% and 0.9%, respectively, and lost 6.0 and 6.4 pounds, respectively, in a 26-week study.[34]

The newer GLP-1 agonist, liraglutide, is not currently indicated as first-line therapy for patients inadequately controlled on diet and exercise; however, it may be used as monotherapy if other agents are not well tolerated or effective. A year-long randomized controlled trial conducted to compare liraglutide monotherapy with glimepiride monotherapy in treatment-naïve patients supported monotherapy use.[35] This study found that liraglutide was safe and effective as initial pharmacologic therapy for patients with type 2 diabetes and that it led to greater reductions in HbA_{1c}, weight, hypoglycemia, and blood pressure than glimepiride did alone.[35]

Safety Considerations

While associated with a low risk of hypoglycemia (due to glucose-dependent mechanisms of action) and with weight loss (due to effects on gastric emptying and satiety), GLP-1 agonists do have adverse effects that physicians should be aware of when selecting treatment candidates and when initiating therapy in appropriate patients. For liraglutide, this includes the need to assess the patient's risk for medullary thyroid carcinoma and multiple endocrine neoplasia type 2—personal or family history of such precludes liraglutide use.[36,37] For GLP-1 agonists and all incretin-based therapies, including DPP-4 inhibitors, there are precautions against using these drugs in patients with a history of pancreatitis.

Based on my experience performing multiple clinical trials on GLP-1 agonists and DPP-4 inhibitors, I feel that the US Food and Drug Administration's directive[38] to demonstrate that a new antidiabetic therapy is not associated with an unacceptable increase in cardiovascular risk can be helpful. When a patient who initiates therapy with an incretin drug has abdominal pain, nausea, and vomiting, he or she should immediately discontinue the incretin therapy. Serial measurements of amylase and lipase should be performed every other day for 6 days. If these titers are rising, patients should undergo a computed tomography scan of the pancreas, which may confirm the presence of pancreatitis. However, linking pancreatitis directly to the use of an incretin may be difficult. Risk factors for pancreatic dysfunction in patients with diabetes include obesity, alcohol abuse, hypertriglyceridemia, and gallstones, as well as use of medications such as angiotensin-converting enzyme inhibitors and diurectics.[37]

It is advisable to discuss the possible adverse effects of pharmacotherapeutic regimens with patients whenever prescribing a new therapy. As stated earlier, the most common adverse effects of GLP-1 agonists are those related to the gastrointestinal system. Patients should not confuse feelings of satiety (a desired effect) with that of nausea. Risk of nausea may be limited by advising the patient to eat slowly, titrating the dose, gradually escalating the dose, and, for exenatide, appropriately timing the administration of the dose in relation to mealtime (ie, <60 minutes before eating with less nausea anecdotally reported closer to the upper limit of the 60-minute interval). Liraglutide may be administered without regard to mealtimes. The longer-acting agents, such as liraglutide, appear to be associated with a lower incidence of gastrointestinal adverse effects.

Conclusion

Glucagon-like peptide-1 agonists represent an exciting addition to the treatment options for patients with type 2 diabetes—effective glucose-lowering without weight gain or substantial risk of hypoglycemia—when used in combination with lifestyle modification alone or as part of combination therapy strategies.

Case Study

Moshe is a 59-year-old Orthodox Jewish man who was diagnosed with type 2

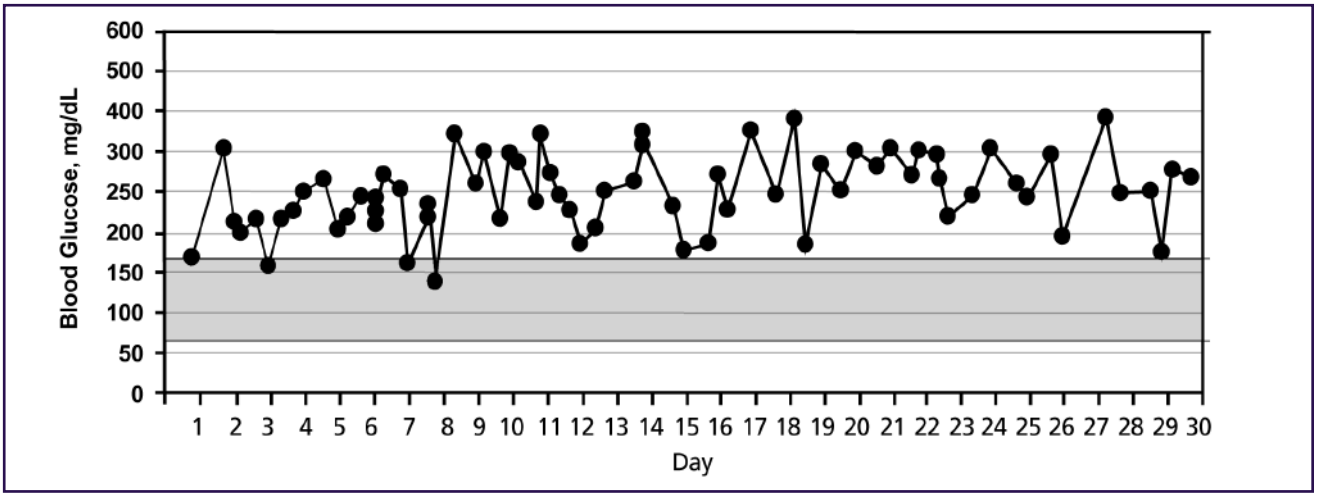


Figure 5. *Blood glucose levels of a 59-year-old man with type 2 diabetes mellitus. Glucose measurements were taken for a month before his most recent office visit.*

diabetes mellitus 8 years ago. His comorbidities are characteristic of patients with type 2 diabetes: he has stage 2 hypertension (current blood pressure is 162/94 mm Hg) and mixed dyslipidemia (low-density lipoprotein cholesterol, 124 mg/dL; high-density lipoprotein, 38 mg/dL; triglycerides, 244 mg/dL; non–high-density lipoprotein cholesterol, 172 mg/dL; apolipoprotein B, 124 mg/dL). He had 2 stents placed in his left anterior descending artery in 2009. He also has evidence of peripheral sensory neuropathy (loss of vibratory sense and ankle reflexes). Other medical problems include erectile dysfunction.

His medications include metformin hydrochloride, 850 mg twice daily (taken without regard to meal times); acarbose, 25 mg 3 times per day; aspirin, 81 mg once daily; lisinopril, 20 mg every day; and simvastatin, 40 mg every day. Moshe does not exercise frequently but does walk once a week. He is obese (body mass index, 38). Cardiovascular examination reveals orthostatic hypotension and no change in heart rate with inspiration, expiration, or valsalva (suggestive of autonomic cardiomyopathy). No retinopathy is evident on eye examination. Results of a spot urine test for microalbumin is negative; recent laboratory results show that serum creatinine is 1.1 mg/dL.

Because of his cardiovascular comorbidities and his existing microvascular complications, his treatment goals have been individualized as follows: FPG range, 90 mg/dL to 130 mg/dL (less strict because of the presence of heart disease); PPG range, less than 180 mg/dL; and an HbA_{1c} goal of 7.5%. His current HbA_{1c} is 8.5%. Review of his self-monitoring blood glucose level, taken for a month before his most recent office visit, show that virtually no measurements are at goal (*Figure 5*).

The patient is experiencing chronic hyperglycemia and requires intensification of his diabetes regimen. Neither his FPG nor PPG values are within the ADA-recommended target range (ie, FPG, 90-130 mg/dL; PPG, <180 mg/dL). Therefore, the patient was advised to increase his metformin to 1000 mg with breakfast and dinner, discontinue his acarbose, and begin liraglutide 0.6 mg/d. The patient was advised to check his blood glucose level daily upon rising. The dose will be increased to 1.2 mg after 1 week if the patient does not experience nausea. After 1 week at 1.2 mg/d, the patient's blood glucose meter will be downloaded. If the majority of his FPG levels are within the 90 mg/dL to 130 mg/dL range, the 1.2 mg dose will be continued. However, if his FPG levels are still higher than 130 mg/dL, the liraglutide dose will be increased to 1.8 mg/d.

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