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Tailoring treatment for type 2 diabetes: Uncovering the HOW and NOW of GLP-1 receptor agonist therapy

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Intended audience

This activity is intended for primary care physicians, osteopathic family physicians, nurses, diabetes educators, and other health care providers (HCPs) who treat patients with T2DM.

Educational objectives

At the conclusion of this activity, participants should be able to:

- Outline the current standards of glycemic control and potential opportunities for individualized treatment of T2DM with GLP-1 RA therapy.
- Summarize the benefits and limitations of current GLP-1 RAs.
- Assess the nonglycemic effects of GLP-1 RA therapy in patients with T2DM.
- Identify key patient characteristics that support or preclude the use of GLP-1 RA therapy for T2DM.
- Describe initiation strategies and potential dose adjustments for patients with comorbid conditions (e.g., cardiovascular disease, renal disease, diabetic neuropathy).

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Tailoring treatment for type 2 diabetes: Uncovering the HOW and NOW of GLP-1 receptor agonist therapy

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KEYWORDS:
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Glycemic control;
Nonglycemic effects

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease that results from multihormonal dysregulation and is frequently accompanied by a number of comorbidities and complications. Improved glycemic control has been associated with improved microvascular outcomes, but the relationship between glycemic control and macrovascular disease is more complex. Numerous studies evaluating glycemic control and its effect on long-term outcomes have altered the paradigm of treatment for this chronic disease. Today, treatment guidelines and algorithms recommend "tailoring" T2DM therapy to the individual needs of the patient. The incretin-based therapies, including the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, offer health care providers and patients expanded treatment options for T2DM. The GLP-1 RAs, with their multiple mechanisms of action, are uniquely suited to provide complementary T2DM therapy. In particular, GLP-1 RAs have been shown to provide improved glycemic control, as monotherapy or in combination with other antidiabetes agents, while exhibiting a low incidence of hypoglycemia. Furthermore, GLP-1 RAs demonstrate beneficial effects on nonglycemic markers such as body weight, lipids, and systolic blood pressure. The enhanced glycemic efficacy of GLP-1 RAs accompanied by the unique nonglycemic effects may facilitate a more "tailored" approach to therapy for many patients with T2DM.

The number of patients with type 2 diabetes mellitus (T2DM) is rising at an alarming rate. According to the most recent US Centers for Disease Control and Prevention statistics, 25.8 million American adults are afflicted with T2DM, although 7 million of these adults remain undiagnosed.[1] More concerning, the number of individuals with T2DM is expected to at least double by 2034.[2] Given that T2DM is associated with significant comorbidity, reduced quality of life, and reduced lifespan, these statistics are sobering and necessitate intensified efforts toward effective management of T2DM.[3]

T2DM is a chronic, progressive disease that often results from a mixture of genetic factors and cumulative years of poor lifestyle choices.[4,5] This combination frequently makes effective disease management difficult to achieve in many patients. Furthermore, pharmacologic therapy has limitations such as lack of durable glycemic control and undesirable side effects. Given that the incidence of T2DM is on the rise, and in recent years individuals are developing T2DM at a much younger age, the durability of agents has become increasingly important.[1,6,7] As a result, identifying effective therapeutic approaches for individual patients has become ever more complicated. Most patients require correction of multihormonal dysregulation, but the efficacy, safety, and complexity varies with each treatment option. For this reason, a "one size fits all" treatment approach is not likely to promote long-term success in patients with this complicated disease. In addition, generally applicable glycemic goals may be detrimental in some patients and several T2DM glucose-lowering therapies are contraindicated or require dose adjustments for patients with a history of cer-

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Table 1 List of FDA-approved T2DM drugs discussed

Generic Name	Brand Name
Acarbose	Precose
Exenatide	Byetta
Glimepiride	Amaryl
Glyburide	Diabeta
	Glynase
	Micronase
Insulin detemir	Levemir
Insulin glargine	Lantus
Linagliptin	Tradjenta
Liraglutide	Victoza
Metformin hydrochloride (HCl)	Glucophage
	Glumetza
	Riomet
	Fortamet
Miglitol	Glyset
Nateglinide	Starlix
Pioglitazone HCl	Actos
Repaglinide	Prandin
Rosuvastatin calcium	Crestor
Saxagliptin HCl	Onglyza
SitagliptinHCl	Januvia

tain medical comorbidities. Thus, individualization of therapy—"tailoring" treatment to the patient's level of glycemic dysfunction, clinical characteristics, and personal preferences—represents the current standard of care.[8]

Today, more than eight classes of agents are commonly used to assist in the attainment of optimal glycemic control in patients with T2DM (Table 1). Although each class of agents improves glycemic control, one single agent is unlikely to sustain glycemic control indefinitely.[9,10] In fact, at some point in their disease, most patients with T2DM will require additional or alternative pharmacologic therapy.[5,8]

The incretin-based therapies, including the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors offer providers and patients expanded treatment options for T2DM. These classes of medications affect hormonal deficiencies arising from the gastrointestinal (GI) tract that have profound effects on glucose homeostasis and hormonal end points throughout the body. The incretin-based therapies lower serum glucose levels but also provide some unique nonglycemic effects that may facilitate a more "tailored" approach to therapy for a large number of patients with T2DM. Notably, these "incretin effects" are not directly targeted by other available therapies. With their unique mechanism of action, improved ability to achieve glycemic control, beneficial nonglycemic effects, and low incidence of hypoglycemia, the GLP-1 RAs may serve to improve the lives of patients affected by T2DM. Accordingly, this article will focus on *how* the GLP-1 RAs fit into the spectrum of diabetes disease management as well as why they should be considered *now* in individualization of care in patients with T2DM. To illustrate the benefits of "tailoring" therapy to individual patients, case studies are included within this article to guide the application of current clinical evidence regarding the use of GLP-1 RAs for T2DM.

Pathophysiology of type 2 diabetes

Historically, T2DM was thought to be simply a disorder of insulin metabolism. However, more recent research has shown T2DM to be a much more complicated disorder. Multihormonal dysregulation frequently results in impaired glucose metabolism, and if left unchecked or untreated, it can result in frank hyperglycemia.[11] Although beta-cell dysfunction and demise over the course of T2DM is known to result in diminished insulin secretion, research has also identified additional pancreatic and extra-pancreatic hormones that are dysregulated in T2DM and contribute to inadequate glycemic control.[11,12]

The pancreatic hormones (glucagon, insulin, and amylin) play a central role in the regulation of glucose. In the 1950s, the discovery of glucagon, a hormone produced by the alpha cells of the pancreas, expanded the understanding of glucose regulation. In the healthy individual, glucagon is secreted during fasting conditions, leading to increased glucose production from the liver. In normal physiology, elevation of serum glucose after a meal suppresses glucagon and subsequent hepatic gluconeogenesis. Interestingly, in the diabetic state, postprandial glucagon levels are inappropriately high, resulting in excessive glucose production from the liver, further exacerbating postprandial hyperglycemia.[11] Amylin, a hormone produced with insulin by pancreatic beta cells, suppresses postprandial glucagon secretion and slows gastric emptying in the normal state. However, the effects of amylin are also blunted in the diabetic state.

Similar to pancreatic hormones, the intestinally-derived incretin hormones, are peptides that help maintain normal glucose levels.[11,12] In the healthy state, the incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are secreted from the intestinal cells in response to a meal, resulting in an increased level of insulin secretion from the beta cells of the pancreas. This effect, known as the *incretin effect,* is only seen with oral glucose ingestion and not intravenous administration. As is evident in Figure 1, the incretin effect is notably deficient in patients with T2DM.[12,13]

Because the insulinotropic effects of GLP-1 remain intact in individuals with T2DM, GLP-1 has become an important therapeutic target.[14] However, GLP-1 is rapidly degraded by the enzyme DPP-4, effectively limiting the half-life of exogenously administered GLP-1 to ~2 minutes.[15-17] Accordingly, two therapeutic strategies have been used to permit clinical use of GLP-1–targeted therapies: GLP-1 RAs, which are resistant to degradation by the DPP-4 enzyme; and the DPP-4 inhibitors, which increase endogenous GLP-1 levels via inhibition of the DPP-4 enzyme.[18] In addition to its effect on the beta cell, GLP-1 is

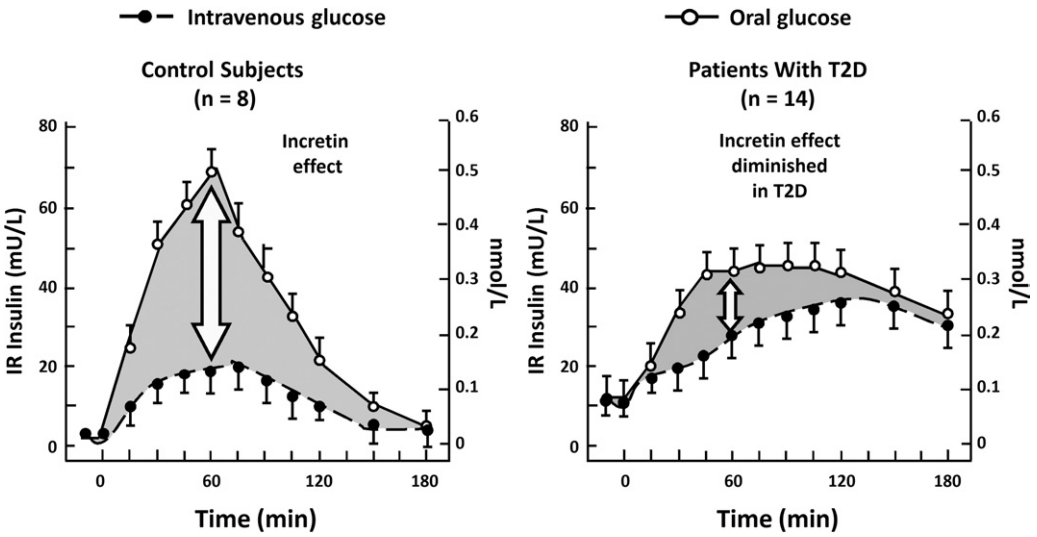


Figure 1 The incretin effect is blunted in T2DM. The difference between the insulin response to an intravenous glucose load compared with an oral glucose load is known as the *incretin effect*. This effect is diminished in T2DM. IR insulin = insulin immunoreactivity. (Adapted from Nauck MA, et al.[13])

known to decrease gastric emptying, suppress postprandial glucagon secretion, decrease appetite, and increase satiety.[12,14,16] These actions have been shown to improve glycemic control as well as promote weight loss in many patients.

Recognizing the varied physiologic effects associated with the pancreatic and extra-pancreatic hormones, investigators continue to explore the hormonal abnormalities related to T2DM while striving to better understand the factors leading to T2DM and the progressive decline of the beta cell.[19]

The progression of T2DM is complex

Genetic predisposition and sedentary lifestyles combined with energy-rich diets are thought to lead to the development of T2DM.[20,21] Insulin resistance and the persistence of hyperinsulinemia have been shown to have a toxic effect on the beta cell, even before glucose levels begin to rise (Figure 2).[22] Eventually, a combination of effects, including reduced beta-cell function, impaired incretin effect, and increased insulin resistance, lead to a relative insulin insufficiency.[23] When insulin production is inadequate to accommodate rising glucose levels, frank hyperglycemia occurs. This hyperglycemia results in subsequent damage to the beta cell, further propagating the hyperglycemia. Typically, postprandial abnormalities precede fasting hyperglycemia as a result of decreased first-phase insulin secretion and possibly because of the loss of incretin effect.[23] Unfortunately, by the time fasting blood glucose levels rise and a clinical diagnosis of T2DM is made, almost 50% of the beta-cell mass may have perished and insulin production is waning.[23] This information, taken together with evidence from several landmark diabetes trials, serves as the basis for a shifting treatment approach for patients with T2DM that includes a focus on early, aggressive treatment of hyperglycemia to improve long-term outcomes.[8]

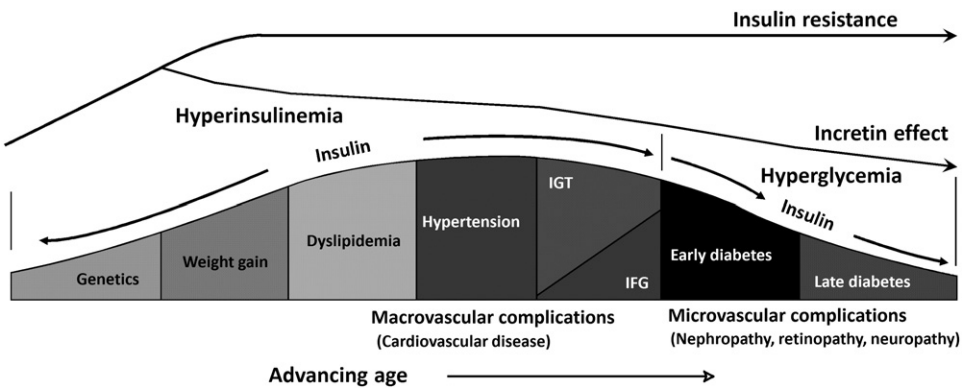


Figure 2 Pathophysiology of T2DM. T2DM is a progressive disease involving multiple hormonal abnormalities, many of which are present before the onset of hyperglycemia. IGT = impaired glucose tolerance; IFG = impaired fasting glucose. (Adapted from LaSalle[22] and Nathan et al.[33])

Type 2 diabetes: A new treatment paradigm emerges

The results of several landmark diabetes trials have changed the way T2DM is treated today. Although the effect on macrovascular complications (e.g., myocardial infarction, cerebrovascular disease) is not as clear, improved glycemic control has been shown to reduce the long-term risk of microvascular complications (e.g., nephropathy, neuropathy, retinopathy). The United Kingdom Prospective Diabetes Trial (UKPDS), a trial investigating the effects of intensive glycemic control (IGC) on T2DM complications, initially reported results in 1998.[9,10] In this study, 3867 *newly diagnosed* T2DM patients were randomized to receive conventional management of T2DM (i.e., diet) or IGC (i.e., pharmacologic therapy with a fasting plasma glucose [FPG] goal of <120 mg/dL). After 10 years of treatment, the intensive group achieved a mean A_{1c} of 7.0% compared with 7.9% in the conventional therapy group. However, more impressively, the intensive therapy group saw a 25% reduction in microvascular complications ($p = .0099$) accompanied by a 10% reduction in diabetes-related deaths ($p = .34$).[9] Although these initial findings favored *early* initiation of IGC for the reduction of microvascular risk, they did not reveal a significant, consistent reduction in macrovascular disease.[9]

In a UKPDS follow-up study, the principle of *early,* intensive treatment of T2DM was validated 10 years after the initial results were published. In this report, Holman et al. followed 3277 patients from the initial UKPDS trial. These individuals were no longer randomized to receive IGC or conventional therapy and therefore the between-group A_{1c} differences were lost after the first year of treatment.[24] Despite similar levels of glycemic control for the majority of the follow-up period, subjects in the initial intensive control group had a persistent reduction in microvascular risk (24%; $p = .001$) relative to the conventional group and were maintained over the10-year passage of time. In addition, a 15% reduction in myocardial infarction risk ($p = .01$) and a 13% reduction in risk of death from any cause ($p = .007$) emerged.[24] These follow-up findings suggest that IGC achieved *early* in the course of T2DM may offer not only a decreased long-term microvascular risk (a phenomenon referred to as the "legacy effect"), but also a reduction in macrovascular risk.

More recently, three landmark clinical trials attempted to further delineate the benefits of IGC regarding the prevention of macrovascular disease. Contrary to expectations, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, and the Veterans Affairs Diabetes Trial (VADT), failed to demonstrate a significant reduction in macrovascular risk in the IGC groups.[25,26] In fact, the ACCORD trial was terminated early because of an apparent increased risk of mortality, including cardiovascular (CV) causes in the IGC group.[25]

Numerous subsequent analyses have attempted to try to explain why IGC resulted in increased mortality in the ACCORD trial while failing to demonstrate the same risk in the ADVANCE or VADT trials. Calles-Escandon et al. identified three baseline patient characteristics that were associated with higher mortality within the intensive group of the ACCORD trial: A_{1c} >8.5%, the presence of neuropathy, and aspirin use.[27] Conversely, further evaluation of the VADT trial results revealed that CV benefit with IGC varies with disease duration; individuals with T2DM duration of <15 years and treated with IGC had a reduced risk of CV events, whereas individuals with T2DM >20 years showed an increased CV risk with IGC.[28] These data suggest that patients with advanced T2DM disease duration and/or the presence of comorbidities may benefit from less stringent glycemic control than patients early in the T2DM disease spectrum.

Hypoglycemia is presumed to contribute to the risk of increased mortality (or lack of reduction in mortality) with IGC. Two analyses of the ACCORD trial confirmed the postulated relationship between hypoglycemia and increased mortality in both arms of the study; however, this relationship failed to explain the increased mortality in the IGC group. In fact, the presence of symptomatic, severe hypoglycemia in individuals within the IGC group was associated with a lower risk of death than in the control group.[29,30] Of note, the ACCORD trial methods involved more intensive frequency of self-monitoring of blood glucose (SMBG) in the intensive arm (2–8 times per day) compared with the control group (<1–3 times per day), as well as more frequent clinical follow-up. Furthermore, individuals with a history of severe hypoglycemia in the previous 3 months were excluded from the study. Therefore, the methods used in this study may confound our ability to derive accurate information regarding a causal relationship between hypoglycemia, IGC, and mortality.[29] More recently, Zoungas et al. published data elucidating the relationship between hypoglycemia and mortality and CV events in the ADVANCE trial. The authors of this study found that even a single episode of severe hypoglycemia was associated with an increased incidence of macrovascular events (hazard ratio [HR] 2.88, 95% confidence interval [CI] 2.01–4.12), death from CV cause (HR 2.68, 95% CI 1.72–4.19), and death from any cause (HR 2.69; 95% CI 1.97–3.67).[31] Taken together, these data suggest hypoglycemia may have fatal consequences, imploring its avoidance and demanding vigilance from clinicians when initiating or intensifying T2DM regimens.

Tailoring therapy through proper selection of glycemic control agents for T2DM

Data from the landmark clinical trials discussed above suggest that a "one size fits all" approach to T2DM is not beneficial to *all* patients and has led to a shift in T2DM care.

In response to these findings, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recently updated their clinical guidelines regarding the treatment of T2DM. According to both sets of guidelines, *early* initiation of pharmacologic therapy upon diagnosis of T2DM is recommended to reduce the risk of long-term T2DM complications.[8,32]

Although these associations agree on the benefits of *early* initiation of T2DM therapy and the goal of individualizing therapy, they differ in terms of their definition of glycemic control.[5,8,33,34] The ADA currently recommends an A_{1c} target of $<7\%$.[32] However, it should be noted that more stringent A_{1c} goals may be considered in patients with a short duration of T2DM, long life expectancy, and the absence of concomitant coronary artery disease (CAD). On the other hand, less stringent goals should be considered for individuals with a history of severe hypoglycemia, long T2DM duration, limited life expectancy, significant CAD and/or microvascular complications, and extensive comorbidities. By contrast, the AACE/ACE treatment algorithm for T2DM, published in 2009, recommended an A_{1c} goal of $\leq 6.5\%$.[8] More recently, AACE published their guideline for "Developing a Diabetes Mellitus Comprehensive Care Plan," which continues to recommend a general A_{1c} goal of $\leq 6.5\%$ while specifically acknowledging that none of the trials to date have successfully established *one* optimal glycemic goal. In addition, the guideline discusses the risks associated with IGC in some individuals and recommends the consideration of other nonglycemic factors such as comorbidities, age, and risk for hypoglycemia when setting individual glycemic treatment goals.[5]

In addition to their recommendations regarding treatment goals, the ADA and AACE/ACE discuss how clinicians should proceed in attaining optimal glycemic control. According to the 2009 AACE/ACE treatment algorithm, T2DM therapy should be based on a patient's existing A_{1c} level, using specific monotherapy, dual therapy, or triple therapy regimens that are likely to attain euglycemia. Both the ADA/European Association for the Study of Diabetes (EASD) and AACE/ACE algorithms identify metformin (MET) as the "cornerstone" of T2DM therapy, but also recognize incretin-based therapies as preferred second-line agents.[8,33] The 2009 ADA/EASD guidelines recommend the use of GLP-1 RAs as second-tier therapy when weight and/or the risk of hypoglycemia is a concern,[33] whereas the AACE/ACE algorithm prefers GLP-1 RAs over DPP-4 inhibitors because of the potential for a greater reduction in A_{1c} as well as their common and beneficial effect on body weight.[8] In keeping with the previous 2009 algorithms, the 2011 AACE guidelines also emphasize consideration of both glycemic and nonglycemic effects of T2DM agents, including durability, effect on body weight, adverse events, and CV safety.[5,8] Finally, the AACE/ACE algorithm urges frequent treatment intensification using agents with complementary mechanisms of action (MOA) and the early use of combination therapy, including the GLP-1 RAs.[8]

As noted before, MET is considered by many diabetes experts to be the "cornerstone" of T2DM care. However, at some point in their disease, most patients with T2DM will require additional or alternative pharmacologic therapy.[8] The plethora of available agents offers a multitude of drug combinations to the clinician and the patient with T2DM. Yet at the same time, the sheer number of agents, along with their differing nonglycemic effects and safety profiles, may complicate intensification of T2DM therapy. Although current treatment guidelines offer algorithms for advancing pharmacologic T2DM therapy, it is expected that clinicians have a strong foundation regarding the MOA for each class of drugs combined with a comprehensive understanding of their complementary effects.[8] Table 2 outlines the various mechanisms by which T2DM agents improve glycemic control. The "secretagogues" increase insulin levels while the biguanides and thiazolidinediones (TZDs) increase insulin sensitivity. Several T2DM agents (insulin, biguanides, TZDs, GLP-1 RAs, DPP-4 inhibitors) contribute to improved glycemic control by suppressing inappropriate hepatic glucose production of T2DM. The biguanides, α-glucosidase inhibitors, and GLP-1 RAs also prevent the absorption of glucose from the gut, thereby limiting postprandial glucose (PPG) excursions. Although many of these agents offer multiple MOAs to lower blood glucose, good glycemic control is still difficult to achieve with a single agent.[9,10] Given their multiple significant MOAs, including stimulation of glucose-dependent insulin secretion, decreased hepatic glucose production, slowed gastric emptying, and increased satiety, the GLP-1 RAs provide additional clinical benefits that complement other T2DM therapies.[18,35,36] Specifically,

Table 2 Type 2 diabetes agents: mechanism of action[35,46,105,112-116]

Agent	↑ Insulin levels	↑ Insulin sensitivity	↓ Hepatic glucose production	↓ Glucose absorption	↑ Satiety
Insulins	✓		✓		
Sulfonylureas	✓				
Biguanides		✓	✓	✓	
α-glucosidase inhibitors				✓	
Thiazolidinediones		✓	✓		
Meglitinides	✓				
GLP-1 receptor agonists	✓		✓	✓	✓
DPP-4 inhibitors	✓		✓		

Table 3 FDA-approved incretin-based agents

GLP-1 receptor agonists	DPP-4 inhibitors
Exenatide BID (Byetta®)	Sitagliptin (Januvia®)
Liraglutide (Victoza®)	Saxagliptin (Onglyza®)
	Linagliptin (Tradjenta®)

their impact on glucose-dependent insulin secretion, reduced risk of hypoglycemia, and decreased appetite and increased satiety, with the potential for reduced body weight, are unique among T2DM agents, making GLP-1 RAs attractive treatment options.[37]

Incretin-based therapies: Rationale for use

As previously mentioned, the incretin effect is impaired in individuals with T2DM. However, it should be noted that the glucose-dependent, insulinotropic effect of GLP-1 remains intact. This knowledge has led researchers to explore the potential benefits of exogenous GLP-1 administration on glucose metabolism. Similar to native GLP-1, exogenous GLP-1 administration through continuous subcutaneous (sc) infusion was found to be associated with improved glycemic control, enhanced first-phase insulin secretion, decreased appetite, and reduced body weight.[38] As a result, novel methods of restoring the incretin effect in T2DM have been pursued: GLP-1 RAs, which are resistant to degradation by the DPP-4 enzyme; and the DPP-4 inhibitors, which increase endogenous GLP-1 levels via inhibition of the DPP-4 enzyme.[18] See Table 3 for a list of Food and Drug Administration (FDA)-approved incretin-based therapies.

Exendin-4, a biologically active peptide originating from the venom of the Gila monster lizard, was the basis for the first GLP-1 RA. Exenatide is a twice-daily (bid), synthetic form of exendin-4 administered by sc injection that was approved by the US FDA for use in patients with T2DM in 2006.[35] Exendin-4 shares ~50% homology with human GLP-1 and is resistant to degradation by the DPP-4 enzyme.[39,40] Since the initial approval of exenatide BID by the FDA, additional exendin-4 based GLP-1 RAs have undergone clinical investigation.[35] An application for a once-weekly (qw) formulation of exenatide has been submitted to the FDA for approval and a once-daily agent, lixisenatide, is currently in phase 3 clinical trials.[41,42]

In 2010, the FDA approved liraglutide, the first human GLP-1 analog indicated for use in T2DM by sc injection.[36] Disparate to exendin-4–based GLP-1 RAs, liraglutide is 97% homologous with native human GLP-1. Although liraglutide is also resistant to DPP-4 degradation, it exhibits a 13-hour half-life, allowing it to be administered on a once-daily basis vs twice a day.[36] Other long-acting human-based GLP-1 RAs are currently in phase 3 clinical trial development, including once-weekly formulations of albiglutide and dulaglutide.[43,44]

Another approach to increasing circulating levels of GLP-1 can be achieved by interfering with the action of the DPP-4 enzyme (i.e., DPP-4 inhibitors). At present, 3 DPP-4 inhibitors—sitagliptin, saxagliptin, and linagliptin—are FDA-approved for use in T2DM and are administered via an oral tablet.[45-48] Similar to the GLP-1 RA class, additional DPP-4 inhibitors are currently in phase 3 clinical development, including dutogliptin.[49-51] In addition, a new drug application was submitted in 2007 for the DPP-4 inhibitor alogliptin; trials of alogliptin are currently underway to provide additional data as requested by the FDA.[52]

Although both GLP-1 RAs and DPP-4 inhibitors are incretin-based, their glycemic and nonglycemic profiles vary considerably. A solid understanding of the similarities and differences between these two classes of therapies is essential to ensuring appropriate "tailoring" of an individual T2DM patient's regimen with these agents, and thus successful therapy initiation and intensification.

Incretin-based therapies: *How* do they compare?

Although both classes of incretin-based therapies, GLP-1 RAs and DPP-4 inhibitors, increase GLP-1 activity in patients with T2DM, they vary in their ability to do so.[18] The DPP-4 inhibitors increase circulating levels of endogenous GLP-1 within the "physiologic" range, whereas the GLP-1 RAs achieve much higher "supraphysiologic" levels of exogenous GLP-1.[18,53] As a result, the glycemic and nonglycemic profiles of these two classes of agents are not the same (Table 4). Several studies have directly compared the efficacy and tolerability of various incretin-based therapies, delineating the similarities and differences between these two classes of incretin-based therapies.

GLP-1 RAs compared with DPP-4 inhibitors

As previously mentioned, higher levels of GLP-1 activity are achieved with GLP-1 RAs compared with DPP-4 inhibitors. Therefore, it is not surprising that these agents are associated with a greater reduction in A_{1c} (Figure 3).[54-57] This was demonstrated in a 26-week trial in which treatment with liraglutide was compared with sitagliptin in a randomized, parallel group of T2DM patients who were inadequately controlled on MET therapy (mean baseline A_{1c} 8.5%).[57] During the trial, 665 individuals with T2DM were randomized to receive 1.2 mg liraglutide sc once daily, 1.8 mg liraglutide sc once daily, or 100 mg sitagliptin orally once daily in addition to MET. At the conclusion of the trial, greater A_{1c} reductions were attained with liraglutide 1.2 mg and 1.8 mg (–1.24% and –1.5%) compared with sitagliptin (–0.90%; $p < .0001$ for both liraglutide therapies compared with sitagliptin). In addition, the odds ratio for a patient achieving an A_{1c} <7.0% were 4.50 (95% CI 2.90–6.97) with liraglutide 1.8 mg and 2.75 (1.78–4.25) with liraglu-

Table 4 Comparison of incretin-based therapies[54]

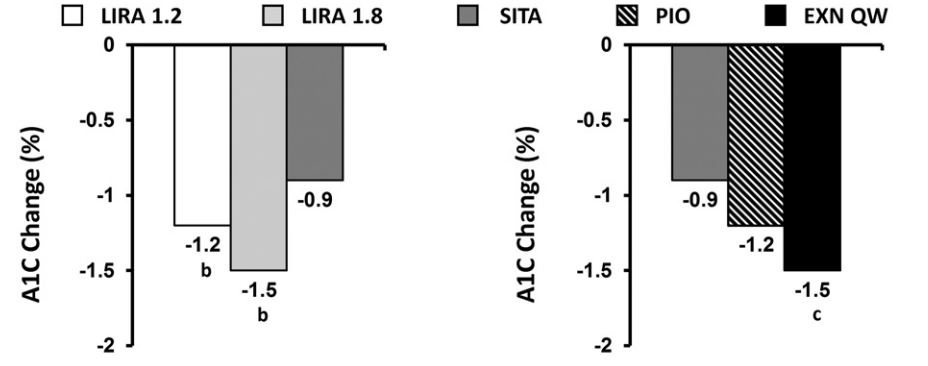
Characteristic	DPP-4 Inhibitors	GLP-1 RAs
Method of administration	Oral	Subcutaneous injection
Expected A_{1c} decrease	0.5–1.0%	0.7–1.9%
Weight effect	Neutral	Weight loss
Effect on CV risk factors*	Neutral	Beneficial
Common adverse events	Headache, URI/UTI	Nausea
Low risk of hypoglycemia?	Yes	Yes
Gastrointestinal adverse events?	No	Yes
Improve postprandial glucose levels?	Yes	Yes†

*Defined as blood pressure, lipids, weight
†Greater effect for this class.

tide 1.2 mg compared with sitagliptin. More recently, the authors of this study reported data for the one-year extension of this trial.[58] At one year, A_{1c} reductions were sustained with liraglutide (–1.29 and –1.51%) and were significantly greater than the reductions achieved with sitagliptin (–0.88; $p < .0001$). Notably, Diabetes Treatment Satisfaction Questionnaire results were more favorable regarding treatment with liraglutide when compared with sitagliptin ($p = .03$).[58]

The GLP-1 RAs are also associated with a beneficial effect on weight, whereas the DPP-4 inhibitors exhibit a neutral weight profile.[54,55,57] In this trial, a significant benefit of weight reduction was evident at the conclusion of the study; weight loss was significantly greater in patients treated with liraglutide 1.2 mg and 1.8 mg (–2.86 kg and –3.38 kg; $p < .0001$) than in patients treated with sitagliptin (–0.96 kg).[57] Higher GLP-1 activity has been associated with delayed gastric emptying, but in some patients this comes at the cost of a greater incidence of GI side effects, such as nausea and vomiting.[53,59]

In a similar way, exenatide qw and sitagliptin were compared in a 26-week trial involving patients with T2DM who were inadequately controlled on MET (mean baseline A_{1c} 8.5%).[55] In this trial, patients were randomized to receive exenatide qw 2 mg sc plus oral placebo, 100 mg sitagliptin orally once daily plus injected placebo once weekly, or 45 mg pioglitazone orally once daily plus injected placebo once weekly. At the conclusion of this study, exenatide qw reduced A_{1c} to a greater extent (least squares [LS] mean –1.5%) than sitagliptin (–0.9%) or pioglitazone (–1.2%; $p < .0001$). In addition, treatment with exenatide qw was associated with a greater degree of weight loss (–2.3 kg) than sitagliptin (difference of –1.5 kg) or pioglitazone (difference of –5.1 kg; $p < .0001$).[55]



Agent	Weight Loss
LIRA 1.2 mg	-3.38 kg[a]
LIRA 1.8 mg	-2.86 kg[a]
SITA 100 mg	-0.96 kg

Agent	Weight Loss
EXN QW	-2.3 kg[b]
SITA 100 mg	-0.8 kg
PIO 45 mg	+2.8 kg

[a] 26 week trial, all treatments in combination with MET.
[b] $P < .05$ vs sitagliptin.
[c] $P < .05$ vs sitagliptin and pioglitazone.

Figure 3 GLP-1 RAs compared with sitagliptin. GLP-1 RAs, liraglutide and exenatide QW, exhibit greater A_{1c} reductions and weight loss than the DPP-4 inhibitor, sitagliptin.[54-57] [a]$p < .05$ vs. sitagliptin; [b]$p < .05$ vs. sitagliptin and pioglitazone. MET = metformin; LIRA = liraglutide; EXN QW = exenatide once weekly; SITA = sitagliptin.

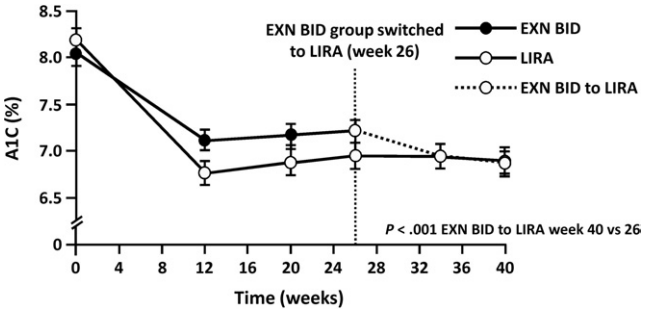


Figure 4 Comparing GLP-1 RAs. Switching from exenatide bid to liraglutide at week 26 results in additional A_{1c} improvements. EXN BID = exenatide twice daily; LIRA = liraglutide. (Adapted from Buse et al.[62])

Subsequently, a 26-week extension of this trial examined the effects of switching from sitagliptin or pioglitazone to exenatide qw compared with continuation of exenatide qw therapy.[60] Those patients who remained on exenatide qw for the 52-week study attained significant A_{1c} reductions (–1.6 ± .1%; 95% CI –1.9 to –1.3%). Patients who switched from sitagliptin to exenatide qw after the initial 26 weeks of treatment saw additional improvements in A_{1c} (–0.3%; p = .0010) and weight (–1.1 kg; p = .0006). Switching from pioglitazone to exenatide qw resulted in a maintenance of A_{1c} reduction along with a significant weight reduction (–3.0 kg; $p < .0001$).[60] These data demonstrate the glycemic efficacy of GLP-1 RAs compared with DPP-4 inhibitors, and also delineate the varying effects on body weight among the two therapeutic classes.

GLP-1 RAs: Head-to-head studies

The currently approved GLP-1 RAs, exenatide bid and liraglutide, have been evaluated in comparison with one another as well as with other classes of antidiabetes agents. In a series of six studies of liraglutide entitled the Liraglutide Effect and Action in Diabetes (LEAD), liraglutide was compared with exenatide bid in the 26-week LEAD-6 trial. In this study, 464 adults with inadequately controlled T2DM (mean baseline A_{1c} 8.2%) receiving MET and/or sulfonylurea (SU) were randomized to receive liraglutide 1.8 mg sc daily or exenatide 10 mcg sc bid. At the conclusion of the study, the A_{1c} reduction achieved with liraglutide (–1.12%) was significantly greater than that achieved with exenatide bid (–0.79%; $p < .0001$).[61] Liraglutide had a greater effect on FPG than exenatide bid, but exenatide bid achieved significantly greater PPG control after breakfast and dinner. Notably, the weight loss achieved with each agent was not statistically different; liraglutide resulted in a 3.24-kg weight loss and exenatide bid was associated with a 2.87-kg weight loss after 26 weeks of treatment.[61] In a 14-week extension of the LEAD-6 study, individuals receiving exenatide bid were switched to liraglutide 1.8 mg once-daily, resulting in further A_{1c} improvement (Figure 4).[62]

Exenatide bid has also been studied in comparison with exenatide qw in a 24-week trial involving patients with T2DM naïve to drug therapy or receiving oral antidiabetes agents.[63,64] At the conclusion of the study, exenatide qw reduced A_{1c} from baseline to a greater degree (–1.6%) than exenatide bid (–0.9%; $p < .0001$). Furthermore, 58% of patients using exenatide qw achieved an A_{1c} <7% compared with those using exenatide bid (30.1%; $p < .0001$).[63] In addition to reductions in A_{1c}, significant improvements in weight were achieved in 71% of patients receiving exenatide qw compared with 51% of patients receiving exenatide bid.[63] Another trial compared the two agents over a 30-week period and subsequently examined the effects of switching patients from exenatide bid to exenatide qw at week 30 of the 52-week study compared with exenatide qw use alone (n = 128 exenatide qw alone and n = 130 exenatide bid→qw).[64,65] Although both groups attained similar A_{1c} reductions over the 52-week study period (–2.0%), patients switching from exenatide bid to exenatide qw achieved further A_{1c} reductions (–0.2%) during the study period.[65]

Most recently, in a trial yet to be published, exenatide qw 2 mg was compared with liraglutide 1.8 mg. At the conclusion of the 26-week study, patients receiving exenatide qw achieved a reduction in baseline A_{1c} of 1.3% compared with a 1.5% reduction with liraglutide; however, further analyses of these data are still pending.[66]

Initiation of GLP-1 RA therapy in patients with T2DM

When a clinician is initiating pharmacologic therapy for T2DM, several factors should be considered. First, an individual patient's current health and comorbidities should be thoroughly evaluated and the degree of A_{1c} reduction required to bring a patient to goal should be elucidated. Once the A_{1c}-lowering requirements have been determined for a particular patient, appropriate agent selection should begin by choosing agents with the ability to bring a patient as close to their glycemic goal as possible. The incretin-based therapies have been studied not only in comparison with each other but also as monotherapy, combination therapy, and in comparison with many other classes of antidiabetes agents. Current data support the efficacy of GLP-1 RAs with regard to A_{1c} reduction.

Monotherapy

In addition to lifestyle modifications, liraglutide and exenatide bid are both currently FDA-approved as monotherapy for the treatment of T2DM. However, it should be noted that liraglutide is not presently indicated as *first-line* monotherapy for the treatment of T2DM and at this point, neither of the incretin-based agents are currently recommended as first-line monotherapy by the ADA or AACE/ACE treatment algorithms/guidelines which based a strong predilection for MET as first-line therapy.[5,8,34-36] Nevertheless, exenatide 10 mcg sc bid, when studied as monotherapy

over a 24-week period, demonstrated A_{1c} reductions from baseline of 0.9% compared with a −0.2% reduction with placebo; $p < .001$.[67] In addition, single-agent therapy with liraglutide 1.2 mg and 1.8 mg sc have demonstrated sustained A_{1c} reductions of 0.9% and 1.1%, respectively, compared with −0.6% with glimepiride; $p < .04$.[68]

Although the A_{1c} reductions achieved with these agents make GLP-1 RAs excellent choices for monotherapy consideration, clinicians should keep in mind that many patients with T2DM will require combination therapy, either initially or as their disease progresses. Accordingly, when initiating or intensifying therapy for patients with T2DM, several factors should be considered: the patient's A_{1c} level, their glycemic pattern (postprandial hyperglycemia vs fasting hyperglycemia), the patient's glycemic goal and comorbid conditions, and their current treatment regimen—all of which can influence selection of an appropriate agent.

Combination therapy

According to the most current treatment guidelines, clinicians should be cognizant of the MOA of the agents used to treat T2DM. When adding a new agent to an existing treatment regimen, it should provide complementary action to the prevailing drug(s) to address the multiple aspects of disease pathophysiology and maximize the glycemic-lowering effects. Given their multiple mechanisms for improving glycemic control, GLP-1 RAs offer the possibility to complement all other T2DM therapies.

Both of the currently available GLP-1 RAs have been studied extensively in combination with other antidiabetes agents, including SUs, MET, and TZDs. When used as combination therapy, both GLP-1 RAs have demonstrated similar A_{1c} reductions as in monotherapy. In a series of studies 16 weeks to 30 weeks in duration, exenatide bid achieved A_{1c} reductions of 0.8% to 0.9% in combination with SUs, MET, SU + MET, and TZD ± MET compared with 0.1% to 0.2% with placebo.[69-72] Similarly, in the LEAD trials, liraglutide was studied in combination with SU, MET, SU + MET, and TZD ± MET. Liraglutide 1.2 mg and 1.8 mg sc achieved A_{1c} reductions of 1.0% to 1.5% compared with A_{1c} changes of −0.5% to + 0.2% with placebo over 26 weeks when used in combination with these agents.[73-76] In addition, when used as combination therapy, liraglutide achieved similar A_{1c} reductions to MET (–1.0% for liraglutide 1.2 mg, 1.8 mg, and MET) while achieving significantly greater A_{1c} reductions compared with rosiglitazone (–0.4% with rosiglitazone and –1.1% with liraglutide 1.2 mg and 1.8 mg; $p < .05$), as well as insulin glargine (IG) (–1.3% with liraglutide 1.8 mg and –1.1% with IG; $p < .05$). These data establish the GLP-1 RAs as effective antidiabetes agents. Prescribed as either monotherapy or in combination therapy, meaningful reductions in A_{1c} with exenatide or liraglutide can be expected.

Intensifying T2DM therapy with insulin or a GLP-1 RA

As mentioned previously, the GLP-1 RAs have been studied in combination with oral T2DM agents, achieving significant A_{1c} reductions. Unfortunately, treatment options for intensification in many individuals (eg, case study No. 2) are limited by their current regimen, A_{1c} level, and comorbidities. As a result, clinicians may find themselves weighing the options of the injectable medications, GLP-1 RAs or insulin. Several studies have evaluated these therapies head-to-head.

Insulin therapy has been proven effective throughout the spectrum of T2DM.[20,33,77] It has great capability to reduce A_{1c} and can be tailored to match each individual's glycemic needs. However, insulin therapy is hampered by a higher risk of hypoglycemia compared with many oral agents and is also associated with weight gain. Interestingly, the incretin therapies are being explored as possible alternatives to insulin therapy as well as in combination with insulin therapy. Although the DPP-4 inhibitor sitagliptin is currently the only incretin-based therapy approved by the FDA for use with insulin, there is tremendous interest regarding the use of GLP-1 RAs to intensify glycemic control among patients who do not attain glycemic goals on insulin therapy alone and/or to offset the weight gain often associated with insulin therapy. Within the last year, two randomized trials of GLP-1 RAs used in conjunction with basal insulin analogues have been published and results from these studies lend support to the notion that positive effects can be achieved when a GLP-1 RA is used with basal insulin in patients unable to attain glycemic targets on oral therapies.[78,79] However, because the combination of GLP-1 RAs and insulin is not FDA-approved at this time, only the comparison studies are discussed in this article.

Liraglutide was compared with IG in a 26-week trial involving individuals with inadequately controlled T2DM (baseline A_{1c} 8.3%) on MET and an SU.[76] At the conclusion of the study, liraglutide achieved a significantly greater reduction in A_{1c} (1.3%) compared with IG (–1.1; $p < .0015$). In addition, mean weight loss with liraglutide was 1.8 kg compared with a 1.6-kg weight gain with IG. Hypoglycemic events were similar for both agents and although GI events were greater in the liraglutide group, serious adverse events (SAE) occurred less frequently (4%) in the liraglutide group compared with the IG group (7%).[76]

Similarly, in a 26-week trial comparing exenatide bid with IG, Heine et al. reported similar reductions in A_{1c} for these two agents (1.16% and 1.14%, respectively).[80] Yet, significant differences were observed. Compared with IG, exenatide bid reduced PPG excursions ($p < .03$). Furthermore, at week 26, exenatide bid was associated with a 2.3-kg weight loss compared with a 1.8-kg weight gain with IG. Although the occurrence of hypoglycemia was similar for both agents, GI side effects were significantly more common ($p < .001$) with exenatide bid (57.1%) than with IG (8.6%).[80] In addition, a meta-analysis of four clinical

trials evaluated exenatide bid and insulin (glargine or biphasic aspart) in 1423 patients with T2DM. At 26 weeks, similar A_{1c} reductions were observed with exenatide bid (–1.2%) compared with insulin (–1.1%; $p = .09$). However, exenatide bid was associated with significantly greater weight loss (–2 kg with exenatide bid and +1.8 kg with insulin; $p < .0001$), with 70% of exenatide bid users losing weight compared with 21% of patients using insulin.[81] These data regarding GLP-1 RAs illustrate the need to fully evaluate an agent's glycemic as well as nonglycemic profile when initiating or intensifying T2DM therapy.

HOW do the nonglycemic effects of GLP-1 RAs affect treatment selection?

Although improved glycemic control is paramount when considering T2DM agents, the entire profile of an agent is important to long-term success. Nonglycemic effects of an agent, such as an agent's impact on body weight and CV risk factors such as blood pressure (BP) and lipids, should be considered when selecting an agent for glycemic control because a negative effect on these parameters could affect adherence to therapy and long-term outcomes.[5,37,82] For example, an increase in weight can negatively influence a patient's adherence to therapy, which may consequently affect their glycemic control.[83] Because of the multiple actions of GLP-1, GLP-1 RAs have favorable nonglycemic effects, including a beneficial effect on body weight and CV risk factors.[54,59] Although GLP-1 RAs are not intended or indicated to treat conditions other than hyperglycemia, their effects on the body as a whole may prove beneficial for many T2DM patients.

Weight

As noted throughout this discussion, the GLP-1 RAs can decrease caloric intake and promote weight loss in patients with T2DM.[12,54] The LEAD-6 trial, comparing liraglutide and exenatide bid, illustrated this benefit with both agents achieving ~3 kg in weight loss over the course of the 26-week trial.[61] Additional trials indicate that the weight loss effect of exenatide bid and liraglutide can be maintained for years (>3.5 with exenatide bid and >2 years with liraglutide).[61,84,85] Although this moderate weight loss may not resolve a patient's weight issues, the effect is important, especially considering the associated impact of increased body weight on comorbidities such as heart disease, hypertension, and dyslipidemia, as well as the fact that many other agents contribute to weight gain.[86,87] Furthermore, in clinical trials of GLP-1 RAs used in combination with TZDs and/or SUs (2 classes shown to promote weight gain), individuals achieved significant weight losses compared with placebo.[72,73,75,88] This complementary action of the GLP-1 RAs, therefore, may serve to offset the weight gain typically associated with other T2DM agents in the clinical setting.

Table 5 LEAD-6: GLP-1 RA effects on CV risk factors[61]

Risk factor	Liraglutide	Exenatide BID
Systolic BP (mm Hg)	–2.51	–2.0
Diastolic BP (mm Hg)	–1.05	–1.98
Total cholesterol (mg/dL)	–7.7	–4.3
LDL cholesterol (mg/dL)	–17.0	–15.5
HDL cholesterol (mg/dL)	–1.5	–1.9
Triglycerides (mg/dL)	–15.9	–8.9
Free fatty acids (mg/dL)	–6.6	–3.9

Interestingly, the weight loss associated with GLP-1 RA therapy is not necessarily linked to the degree of A_{1c} reduction. For example, Schmidt et al. demonstrated that the A_{1c} reduction observed with liraglutide is independent of its weight loss effect.[89] Similarly, Klonoff et al. showed that although the majority of patients taking exenatide bid lost weight and achieved improved glycemic control (68%), 16% of patients experienced weight loss despite a rise in A_{1c}; 10% experienced a reduction in A_{1c} accompanied by an increase in weight; and a smaller proportion (6%) gained weight but also experienced a rise in A_{1c}.[89] As a result, it is important to provide patients with clear and realistic expectations regarding the weight effects of GLP-1 RA therapy.

Cardiovascular risk factors

As with all other antidiabetes agents, no studies to date have demonstrated that GLP-1 RAs lead to a reduction in long-term CV or macrovascular risk.[35,36] Figure 2 illustrates clearly the natural progression of T2DM, and it is reasonable to assume that macrovascular disease likely develops even before the diagnosis of T2DM.[22] At present, comparative studies of exenatide and liraglutide have failed to show an increased risk of CV events.[90-92] In August 2010, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results-A Long Term Evaluation (LEADER) trial began to evaluate the long-term CV safety of liraglutide, but the data are not expected to be complete until 2016.[93] Furthermore, as shown in Table 5, data from the LEAD-6 trial show that GLP-1 RAs have demonstrated a beneficial effect on CV risk factors, including systolic blood pressure, lipid levels, and, as discussed earlier, weight.[61,84,94] The recent T2DM guidelines emphasize the importance of comprehensive T2DM care, specifically addressing the treatment of hypertension, dyslipidemia, and body weight.[5] Although this information does not justify the use of GLP-1 RAs to treat blood pressure and cholesterol, one should consider an agent's effects on these parameters before selecting a T2DM therapy, particularly for a patient with significant CV risk.

HOW does the safety and tolerability of GLP-1 RAs affect patient selection?

Consideration of an agent's safety and tolerability profile is a principal aspect of initiating or intensifying T2DM therapy. More importantly, though, the agent should be evaluated in the context of the individual patient's medical profile. For example, a newly diagnosed T2DM patient may benefit from TZD therapy, whereas the same therapy could be detrimental to a patient with a history of congestive heart failure.[95,96] Furthermore, when initiating combination therapy, the likely side effects of the combination should be considered. The GLP-1 RAs exhibit a favorable side effect profile, further contributing to their use in T2DM care. However, a thorough understanding of the mechanism of action and tolerability of the GLP-1 RAs is essential to the proper use of these agents in the clinical setting.

Hypoglycemia is associated with higher mortality in patients with T2DM and its presence may affect the ability to achieve glycemic control with some agents.[29] Of particular interest, the use of GLP-1 RAs may be desirable in some patients because the incidence of hypoglycemia has been shown to be quite low (unless combined with SUs) because of its glucose-dependent MOA.[54] A 2009 meta-analysis of the GLP-1 RAs revealed a 4% to 11% incidence of hypoglycemia with exenatide as monotherapy or combination therapy. Similarly, the incidence of hypoglycemia with liraglutide monotherapy or combination therapy was 3% to 12%. In addition, no episodes of major hypoglycemia were documented for either agent.[54] To the contrary, SU therapy seems to increase the risk of hypoglycemia when used with GLP-1 RAs. Buse et al. demonstrated a similar low incidence of hypoglycemia with liraglutide (6%) and exenatide (11%) when they were combined with "non-SU" background therapy, but when used in combination with SUs, the incidence rose to 33% and 42% for liraglutide and exenatide, respectively.[61] Therefore, initiating therapy with a GLP-1 RA may require a dosage reduction or discontinuation of the SU.[35,36] In general, the GLP-1 RAs have demonstrated utility in patients who are prone to hypoglycemia with other agents. Therefore, GLP-1 RAs may be good candidates in patients who are at increased risk for hypoglycemia or who have experienced repeated episodes of hypoglycemia.

Because of their capacity to delay gastric emptying, nausea and/or vomiting is the most common adverse effect encountered with GLP-1 RAs.[54] Results from the LEAD-6 evaluation comparing liraglutide and exenatide bid demonstrated a similar incidence of nausea with liraglutide (25.5%) than exenatide bid (28%). However, it should be noted that the presence of nausea improved over time for both agents, but declined more rapidly in the liraglutide group.[61] By week 6, only 8.1% of liraglutide patients reported nausea compared with 15.8% of patients receiving exenatide bid.[61] In addition, Best et al. showed that the presence of nausea with exenatide bid or qw therapy did not affect quality of life scores.[97] On the basis of these findings, some experts suggest that patients should receive specific education regarding the effect on gastric emptying with GLP-1 RAs to avoid confusion between the symptom of newfound "satiety" vs. "nausea."[98] Regardless, caution should be exercised when prescribing these agents to patients with an already compromised gastric emptying rate (gastroparesis) because GLP-1 RAs may exacerbate the patient's symptoms. Moreover, patients should be instructed to report nausea that presents with abdominal pain because this may represent a more serious problem, including pancreatitis.

Although the occurrence of postmarketing cases of acute pancreatitis associated with exenatide bid and liraglutide have led to label warnings and precautions for both of these products, analyses of several large health insurance databases have revealed no increased risk for acute pancreatitis for exenatide bid compared with other antidiabetes agents.[35,36,99-102] Moreover, it is important to note that studies have shown that individuals with diabetes have a threefold higher incidence of acute pancreatitis compared with nondiabetic patients, suggesting that the mechanism may have more to do with the presence of T2DM than the agents used for treatment.[103] Notably, the DPP-4 inhibitors, sitagliptin and linagliptin, bear similar label warnings regarding pancreatitis.[45,46] Nevertheless, in patients with a history of pancreatitis, it is recommended that liraglutide be used with caution and an agent other than exenatide be considered in these patients.[35,36] If pancreatitis is confirmed in a patient taking a GLP-1 RA, the medication should be stopped immediately and should not be restarted.[35,36]

Chronic kidney disease (CKD) is common in patients with T2DM and may represent a barrier to optimal glycemic control because of the special attention to dosing and avoidance of hypoglycemia that is required when renal function is a concern.[104] When a drug is eliminated by the kidneys, the presence of a reduced glomerular filtration rate (GFR) can lead to elevated plasma levels of the drug or its active metabolites.[104] Specific to T2DM, accumulation of these therapeutic agents can lead to hypoglycemia and/or can be detrimental to the kidneys themselves.[104] As a result, some T2DM agents require special dosing in the presence of impaired renal function, whereas others (e.g., MET) are contraindicated as the impairment progresses.[105] Worthy of mention, the GLP-1 RAs differ from one another with regard to their renal clearance and renal dosing (Table 6).[35,36] Exenatide bid is primarily cleared by the kidneys and its use is not recommended for use in patients with severe renal failure (GFR <15 mL/min/1.73m^2).[35] In addition, caution is advised for use in patients with impaired renal function because the hypovolemia associated with nausea/vomiting can worsen renal function.[35] Liraglutide, however, is cleared primarily by proteolytic degradation and therefore does not require a dose adjustment as renal function worsens.[36] However, if a patient experiences GI side effects with liraglutide, hypovolemia is still a possibility and patients at risk for worsening renal function should be monitored.

Table 6 Renal dosing with GLP-1 RAs[35,36]

Degree of renal impairment (mL/min/1.73 m^2)	Exenatide BID	Liraglutide
Stage 3 (GFR 30–59)	May use	May use; no dose adjustment
Stage 4 (GFR 15–29)	Not recommended	May use; no dose adjustment
Stage 5 (GFR <15)	Not recommended	May use; no dose adjustment
Drug clearance		
Exenatide BID		Liraglutide
Primarily renal with subsequent proteolytic degradation		Proteolytic degradation; 6% excreted in urine

Finally, in rodent studies with high dosages of liraglutide, an increase in calcitonin levels was observed along with an increased occurrence of medullary thyroid tumors.[106,107] Importantly, analogous studies in primates (using liraglutide doses >60 times human exposure) have not resulted in C-cell hyperplasia or medullary thyroid tumors. Furthermore, liraglutide exposure in humans is not associated with elevated mean calcitonin levels, suggesting that this may be a species-specific effect.[61,106] Although the mechanism for formation of these tumors seems to be specific to rodents, the incidence of medullary thyroid tumors will continue to be monitored over the next 15 years using an established cancer database.[107] Currently, there are no recommendations to order additional screening tests such as calcitonin levels or thyroid ultrasounds to screen patients for thyroid cancer who are taking liraglutide. Still, at this time, it is recommended that liraglutide is not used in patients with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 syndrome (MEN-2).[36] Patients should be educated to report any symptoms of thyroid tumors (e.g., lump, change in voice, difficulty swallowing, or shortness of breath) to their health care provider.[36]

Overall, the GLP-1 RAs exhibit a favorable safety and tolerability profile. However, proper patient selection and education regarding the benefits and risks of GLP-1 RA therapy is vital to successful application of these agents in the clinical setting.

Strategies on *how* to manage cost-related concerns regarding GLP-1 RAs

For many patients, the cost of medications is a significant barrier to initiation and intensification of T2DM therapy. Many patients with financial constraints may not be compliant if they are worried about the expense of a drug or are unable to fill their medications regularly. Yet, others simply prefer to be treated with the most inexpensive option. There is no question that the direct costs of many brand-name medications are significantly higher than many generic options. However, recent data estimate that pharmaceutical expenses of T2DM represent only 30% of total diabetes costs.[108] Complications such as CVD, hypoglycemia, retinopathy, and limb amputations account for the majority of T2DM costs in the US today.[109,110] Therefore, the entire profile of an agent should be considered and an agent with the ability to limit the indirect costs of T2DM might be favored over agents without these characteristics. The GLP-1 RAs exhibit a low risk of hypoglycemia and favorable trends in CV risk factors, and these beneficial effects should be considered when making treatment choices.[54] For those patients with significant financial constraints, patient assistance programs exist for both FDA-approved GLP-1 RAs (Table 7). Patients should be educated about the long-term costs of T2DM as well as the direct costs of agents so they can make informed decisions about their care.

Case Studies

Case study #1: Initiating T2DM therapy *now* with GLP-1 RAs

A 44-year-old man presents to the office for a routine evaluation. He has a history of hypertension, osteoarthritis, and dyslipidemia. His weight continues to increase, he has gained 10 lbs over the last year, and the arthritis in his knees has kept him from walking as much as he has in the past.

Table 7 Patient assistance

Agent	Patient assistance program website
Exenatide	http://www.byetta.com/Pages/byetta_insurance_coverage.aspx
Liraglutide	http://www.victoza.com/starting/coverage-and-reimbursement.aspx

Noting the change in weight and physical activity, and upon reviewing that he has a family history of diabetes, his physician orders an A_{1c} measurement to screen for T2DM. Results reveal his A_{1c} to be 8.9%. He shares that he is frustrated by his inability to lose weight through lifestyle changes, and he is now open to speaking with a nutritionist to discuss meal planning and food choices, which he was reluctant to do in the past. His vital signs are: height, 69", weight 234 lbs, body mass index (BMI) 35 kg/m^2, blood pressure (BP) 122/70 mm Hg. His past medical history includes obesity, dyslipidemia, degenerative joint disease (DJD) in both knees, and hypertension. His current medications are: atorvastatin 20 mg orally once daily, lisinopril/hydrochlorothiazide 20/25 mg orally once daily, amlodipine 5 mg orally once daily, naproxen 500 mg twice daily orally prn for pain. His lab work reveals: total cholesterol 135 mg/dL, low-density lipoprotein (LDL) 88 mg/dL, high-density lipoprotein (HDL) 41 mg/dL, triglycerides (TGC) 49 mg/dL, A_{1c} 8.9%, glucose 160 mg/dL, creatinine 1.2 mg/dL, GFR $>$60 mL/min/1.73 m^2.

Faculty comments

This individual, a 44-year-old obese male with newly diagnosed T2DM, requires initiation of therapy to reduce his long-term risks. Given his limited comorbid conditions, long life expectancy, and short duration of diabetes, a more stringent A_{1c} goal would be appropriate.[111] Therefore, a glycemic goal as close to normal ($\sim$6.5%) would be most suitable for this patient, provided it can be achieved without significant hypoglycemia.[32]

According to the AACE/ACE treatment guidelines for T2DM, a patient with an A_{1c} of 8.9% should be considered for dual pharmacologic therapy using MET and a GLP-1 RA or DPP-4 inhibitor or TZD, or less favorably, a SU or glinide.[8] This individual requires more than a 2.0% reduction in his A_{1c} to achieve glycemic control and one therapeutic agent (with the exception of insulin) is unlikely to achieve this goal.[8] Although any of the aforementioned agents would likely improve the patient's glycemic control, other factors should also be considered. This particular patient is obese, with a BMI of 35 kg/m^2. Although he will have a consultation with a dietitian, which is an appropriate first step to understanding food choices and meal planning as a long-term strategy, because of this patient's individual characteristics, pharmacologic therapy may also be indicated. MET is a suitable first-line treatment option for this patient considering its glucose-lowering ability and neutral to positive effects on weight loss.[8] However, the choice of an additional agent is more challenging. Because of their propensity to cause weight gain and/or edema, TZDs may not be the best supplemental choice for this patient. Other potential treatment options for this patient include the DPP-4 inhibitors and the α-glucosidase inhibitors, both of which are oral agents and have minimal effect on weight. On the other hand, both the ADA/EASD guidelines and the AACE/ACE algorithm for T2DM currently recommend GLP-1 RAs as preferred second agents when weight loss is desired.[8,33] Furthermore, the use of a GLP-1 RA may complement the action of MET because it is likely to not only improve glycemic control and help achieve his target A_{1c} but may also promote weight loss, which may help with reducing discomfort from his osteoarthritis and improve his exercise patterns. However, one must also consider that both MET and GLP-1 RAs are commonly associated with GI side effects. Therefore, it may be prudent to initiate therapy with MET at this visit and, through close monitoring over the next 4 weeks, follow up by adding a GLP-1 RA to the therapy. Most importantly, the benefits of *early* initiation of therapy must be communicated to the patient to promote compliance with therapy.

Resolution

The patient's physician discussed his T2DM diagnosis with him and reviewed the causes and natural progression of the disease. Furthermore, the physician emphasized the importance of *early* glycemic control and its effect on long-term prognosis, engaging the patient in the discussion, gauging the patient's understanding of the topic, and recommending that the patient proceed with pharmacologic therapy to best treat his disease. Subsequently, the physician reviewed the benefits and risks as well as modes of administration of all classes of pharmacologic agents that may help this patient achieve his individual glycemic goal. Stating that the patient's current glycemic control is beyond the abilities of a single antidiabetes agent, the patient's physician recommended that they develop a strategy together for the patient to start MET combined with GLP-1 RA therapy to help improve glucose control and potentially promote weight loss.

The patient expressed an interest in improving his "sugar" and weight at the same time, and was receptive to initiating dual therapy. The patient left the office with a prescription for MET 500 mg once daily for two to three days to be increased to twice daily thereafter. Possible GI side effects were discussed with the patient along with the signs and symptoms of hypoglycemia. The provider explained that although a GLP-1 RA is more likely than MET to have a beneficial effect on weight loss, the patient may notice fewer side effects if the initiation of both medications was spaced over a few weeks. Ten days later, the patient returned to the office to meet with a diabetes educator to learn more about T2DM and the use of an injectable medication. The diabetes educator demonstrated the injection technique, followed by asking the patient to inject his first dose in the office to increase his level of confidence with this type of therapy. The patient left with a prescription for a GLP-1 RA, pen needles, and several educational materials to help answer any questions that may have arisen. Table 8 summarizes the current prescribing and storage recommendations for the currently available GLP-1 RAs.

Table 8 GLP-RAs: dosing and supply[35,36]

	Exenatide BID	Liraglutide
Dosing	5 mcg sc twice daily ×1 month, then 10 mcg sc twice daily before largest meals	0.6 mg sc once daily ×1 week, then 1.2 mg sc once daily. May increase to 1.8 mg sc once daily irrespective of meals if needed
Storage		
Before first use	Refrigerated	
After first use	Room temp (not to exceed 77°F) or refrigerated	Room temp (59–86°F) or refrigerated
Shelf life of open pen	30 days	30 days
Special precautions	Protect from sunlight Do not freeze Do not store with needle on pen	
How supplied	5 mcg/dose, 60+ dose, prefilled pen 10 mcg/dose, 60+ dose, prefilled pen	Multidose (0.6, 1.2, and 1.8 mg), prefilled pen 1.2 mg dose = 2 pens/month 1.8 mg dose = 3 pens/month

Case Study #2: Intensification of T2DM therapy *now* with GLP-1 RAs

A 68-year-old obese female with moderately severe renal impairment (GFR = 28 mL/min/2.73 m^2) and T2DM x7 years presents for a routine follow-up appointment. The patient has persistently maintained suboptimal glycemic control and states she just is not successful in limiting her dietary intake of carbohydrates and sweets. She expresses an interest in improving her glycemic control but is concerned about the safety of adding yet another drug to her daily list of medications. Her vital signs are: height 63", weight 246 lbs, BMI 44 kg/m^2, BP 124/80 mm Hg. Her past medical history includes dyslipidemia, tobacco abuse, hypertension, CAD, previous myocardial infarction (5 years prior), and depression. Her medications are: metformin 1000 mg orally twice daily, glimepiride 4 mg orally once daily, bupropion XL 300 mg orally once daily, pravastatin 40 mg orally once daily, lisinopril 20 mg orally once daily, triamterene/hydrochlorothiazide 37.5/25 mg orally once daily, and aspirin 81 mg orally once daily. Her lab work reveals: total cholesterol 193 mg/dL, LDL 107 mg/dL, HDL 31 mg/dL, TGC 179 mg/dL, A_{1c} 7.9%, FPG 141 mg/dL, creatinine 1.3 mg/dL, and GFR 18 mL/min/2.73 m^2.

Faculty comments

This case study illustrates a fairly common clinical scenario in the primary care office, a T2DM patient with CKD who has glucose levels inadequately controlled on a combination of glucose-lowering agents and who has been unsuccessful with weight loss attempts. Given her longer duration of T2DM, presence of comorbidities, and advancing age, this individual may require a less stringent glycemic goal than the patient described in Case Study #1.[32] For these reasons, an A_{1c} >7% may be appropriate for this individual. In addition, comprehensive care of T2DM entails more than just glycemic control.[32] The DPP-4 inhibitors might be considered for this patient from a glycemic control aspect, however they are unlikely to have any impact on the patient's weight.[54] In a similar way, although the addition of a basal insulin would likely help this individual achieve glycemic control, it may also promote further weight gain. In addition, this patient has suboptimal lipid and BP control and these factors should be considered when choosing an appropriate T2DM therapy. Although the GLP-1 RAs should not be substituted for well-validated antihypertensive and cholesterol-lowering therapies, they do have beneficial effects on CV risk factors. Furthermore, the GLP-1 RAs have been shown to promote weight loss and for this particular patient, a GLP-1 RA may improve her overall long-term outcomes without increasing her risk of hypoglycemia. However, it is prudent to decrease or discontinue the dose of SU that this patient is taking when considering adding a GLP-1 RA.

Resolution

The patient's physician explained to her that an elevated A_{1c} is associated with both microvascular and macrovascular complications. The patient voiced continued concern regarding the safety of multiple medications, which precipitated a discussion of the benefits and risks of insulin vs. GLP-1 RAs. The patient's physician reiterated the patient's increased risk for numerous medical complications including death caused by her uncontrolled disease states. The patient's reduced GFR (28 mL/min/2.73 m^2) was also considered in regard to the choice of therapy. Although GLP-1 RAs can be used in patients with CKD, clinicians need to be aware that the nausea and vomiting sometimes associated with GLP-1 RAs can lead to hypovolemia and therefore the GLP-1 RAs may be poorly tolerated depending on the degree of renal insufficiency. At this point, treatment with either GLP-1 RA is a therapeutic option for this patient;

however, variations in current recommendations should be noted between the two existing GLP-1 RAs. As outlined in Table 4, liraglutide can be used at all stages of renal function. Conversely, prescribing information for exenatide bid states that its use should be avoided in patients with stage 4 (GFR 15–29 mL/min/2.73 m^2) and stage 5 disease (GFR $\leq$15 mL/min/2.73 m^2) kidney disease.[35,46,105,112-116]

Also relevant to this discussion, a DPP-4 inhibitor may be an appropriate treatment option for this patient. Given that only 5% of the drug is excreted renally, linagliptin, a recently FDA-approved DPP-4 inhibitor, requires no dose adjustment in the presence of any degree of renal impairment.[45] Conversely, sitagliptin and saxagliptin require dosing adjustments when used in advanced stages of CKD.[46,47] Furthermore, worsening renal function during sitagliptin use has been reported in post-marketing experiences, although it should be noted that some of these cases involved patients receiving inappropriate dosages of the agent.[46]

After discussing the benefits and risks of all of the above therapies, the patient's physician recommended that she consider intensifying her T2DM therapy by adding a GLP-1 RA to the MET and SU. The patient agreed to start therapy with a GLP-1 RA and, consequently, her SU dose was decreased by one half. After demonstrating the injection technique and allowing her to inject her first dose in the office using a sample device, the patient left with a prescription for a GLP-1 RA, pen needles, and several educational materials to answer any questions that may arise.

Conclusion

T2DM is a chronic disease with many variables affecting its long-term course. Improved glycemic control has been associated with improved microvascular outcomes, but the relationship between glycemic control and macrovascular disease is complicated. Newer research supports a "tailored" or individualized approach to T2DM care to improve outcomes, that is to say, the whole patient should be considered when prescribing pharmacologic therapy for T2DM. Furthermore, effective and comprehensive T2DM care requires control of all CV risk factors, not just glycemia.

As a result, when selecting pharmacologic agents for initiation and intensification of T2DM therapy, one must consider both the glycemic and nonglycemic effects of the agent in addition to its MOA. Glucose-lowering agents, when used in combination, should complement each other to maximize benefit and minimize risk. The GLP-1 RAs, with their multiple MOAs, are uniquely suited to provide complementary T2DM therapy. Furthermore, they demonstrate glycemic efficacy in addition to many beneficial nonglycemic effects that lend themselves to simple, "tailored" initiation and intensification of T2DM therapy.

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