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Intensifying type 2 diabetes therapy:
Assessing the options
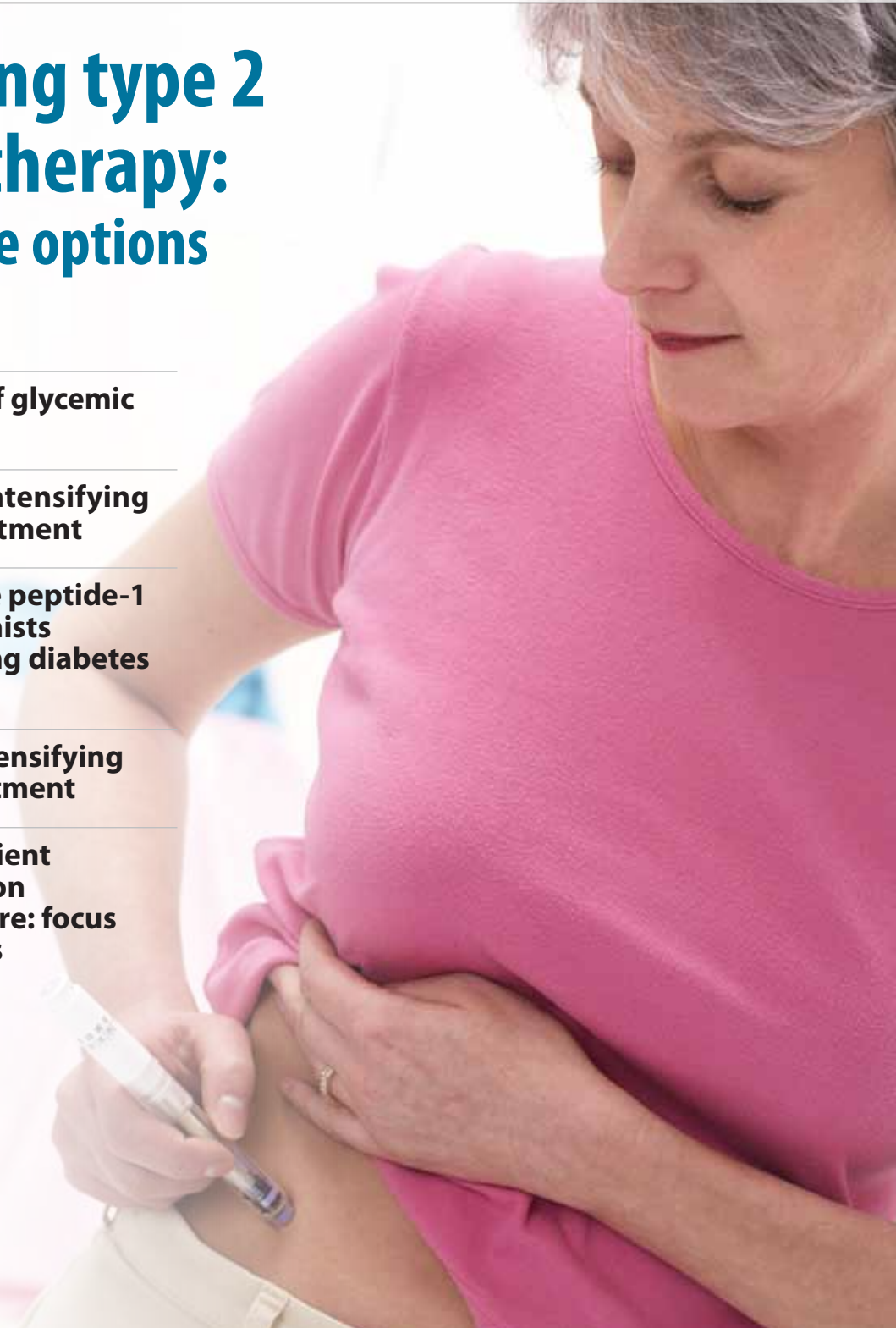
FACULTY

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LEARNING OBJECTIVES

After reading this supplement, the family physician should be better able to:
- Describe the importance of glycemic control in type 2 diabetes mellitus (T2DM).
- Compare the benefits and limitations of oral glucose-lowering agents.
- Describe the roles of glucagon-like peptide-1 receptor (GLP-1R) agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and insulin in managing patients with T2DM.
- Compare the benefits and limitations of GLP-1R agonists and DPP-4 inhibitors.
- Identify strategies to initiate and intensify insulin in patients with T2DM.
- Identify effective communication strategies to foster self-management with injectable glucose-lowering medications by patients with T2DM.

Introduction

Stephen A. Brunton, MD, FAAFP

This supplement is the fifth undertaken by the Primary Care Education Consortium (PCEC) that focuses on treatment of patients with type 2 diabetes mellitus (T2DM). Three of these supplements (September 2008, September 2009, and September 2010) focused on incretin-based therapies, ie, the glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. Surveys conducted by *The Journal of Family Practice* following publication of these 3 supplements and a fourth that focused on special issues in T2DM (May 2010), as well as information from other feedback mechanisms, show that family physicians have a basic familiarity regarding the incretin system and incretin-based therapies. They are, however, less familiar with differences among the incretin-based therapies and where these therapies may fit into treatment.

While the combination of lifestyle management and metformin is appropriate as initial therapy for most patients with T2DM,[1,2] at some point this combination will not provide the desired glycemic control. What then? As indicated in the current guidelines of the American Diabetes Association/European Association for the Study of Diabetes[1] and the American Association of Clinical Endocrinologists/American College of Endocrinology,[2] there is no uniform answer to this question.

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Treatment should be based on the relative efficacy, tolerability, safety, and cost of available options, as well as a patient's duration of T2DM and current glycemic control. The presence and extent of comorbidities such as obesity and cardiovascular disease must also be factored in. To promote patient self-management and improve adherence, treatment decisions must also include a patient's needs and capabilities.

The objective of this supplement is to answer the question posed above: how should treatment be intensified when the combination of lifestyle management and metformin does not provide the desired glycemic control? Because the choice of treatment must be individualized, this supplement discusses all treatment options available for T2DM. For each option, the benefits and limitations are presented and adverse events, particularly hypoglycemia and weight gain, are noted. Emphasis is placed on the GLP-1R agonists and insulin. The GLP-1R agonists are relatively new and less familiar to family physicians, but they are an option throughout the spectrum of treatment,[2] as is insulin, which is often viewed as late-stage therapy.[1,2]

Since individualizing treatment and promoting patient self-management require thoughtful problem solving, this supplement is designed to provide a practical discussion of the issues, including tips to improve physician-patient communication. Several case studies are presented to reinforce the key concepts. ■

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Importance of glycemic control

Edward J. Shahady, MD

Type 2 diabetes (T2DM) is characterized by increasing insulin resistance and declining ability of the β-cell to compensate.[1] By the time fasting hyperglycemia is present, β-cell secretory capacity is reduced by ≥50% and usually continues to decline despite treatment with glucose-lowering medications.[2] This environment of increasing insulin resistance and worsening glycemic control leads to the diabetes complications of neuropathy, retinopathy, nephropathy, and cardiovascular disease.[3] Accumulating evidence suggests, however, that the decline in β-cell function may be slowed or even reversed, particularly if addressed early in the course of the disease.[4] Long-term exposure to hyperglycemia, hyperlipidemia, and inflammatory cytokines may be factors that lead to β-cell decline and death. Early treatment to reduce that exposure may be the key to β-cell survival.[4,5] Several studies indicate that some medications, such as insulin, the thiazolidinediones, and incretin-based therapies, improve β-cell function and may prevent β-cell death.[6-9] Results of investigations with metformin and sulfonylureas have provided conflicting results,[10-14] perhaps as a result of differences in duration of T2DM or of unappreciated differences in the surrogate markers of β-cell function.[15,16] Furthermore, the Diabetes Prevention Program demonstrated a 58% reduction in the incidence of diabetes over 3 years with lifestyle changes in individuals with impaired glucose tolerance.[17]

Effect of glycemic control on cardiovascular disease in diabetes

Diabetes is considered a cardiovascular disease risk equivalent, as people with diabetes but no prior myocardial infarction (MI) have been shown to have a 3- to 4-fold greater risk of MI than those who do not have diabetes.[18] Reducing hyperglycemia has been associated with a reduction in cardiovascular events in some but not all clinical studies.

The United Kingdom Prospective Diabetes Study (UKPDS), which investigated newly diagnosed middle-aged patients with T2DM, revealed a reduction in cardiovascular events after 10 years in the group receiving intensive treatment.[19] This long-term benefit has been called the legacy effect, to emphasize the importance of intensive early treatment in patients newly diagnosed with T2DM. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[20-22] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study,[23] and the Veterans Affairs Diabetes Trial (VADT),[24,25] however, demonstrated either no effect or an increased incidence of cardiovascular events with intensive glucose-lowering therapy. These differences in outcomes may be explained by the fact that the patients in the ACCORD and VADT studies were older, had a longer duration of diabetes, and had had a prior cardiovascular event. Subanalyses of the 3 studies revealed a reduction in cardiovascular events in patients who were

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younger, had a relatively short duration of T2DM, and had no known cardiovascular disease.

These studies have led to current recommendations to individualize treatment, with aggressive lowering of glycosylated hemoglobin (A1C) to <7% for those with little comorbidity and a long life expectancy.[19,20] However, less aggressive lowering is recommended for patients who are older, have significant comorbidities, and have had diabetes for 10 to 15 years.[26,27] It is also important to remember that the duration of the ACCORD, ADVANCE, and VADT studies was 5 years or fewer, while the average follow-up in the UKPDS was 10.7 years. In addition, the UKPDS involved patients newly diagnosed with T2DM. This is an important distinction, since more aggressive lowering of blood glucose early in the disease has been shown to reduce the risk of cardiovascular events. It is also important to remember that reducing blood glucose levels reduces the incidence of microvascular complications in T2DM.[28]

Achieving glycemic goals

The target A1C goal recommended by the American Diabetes Association (ADA) is <7.0%,[26] whereas the A1C goal of the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) is ≤6.5%.[29] When selecting therapy to achieve the target A1C goal, it is important to keep in mind that A1C levels of 8.5% or higher are determined to a greater extent by the fasting plasma glucose (FPG) level than by the postprandial plasma glucose (PPG) level.[30] As the A1C level falls to <8.5%, it is the PPG level that becomes the determinant of the A1C level such that at an A1C level <7.3%, PPG contributes approximately 70% to the A1C level.[30] Therefore, while focusing on FPG reduction may be appropriate in most patients with T2DM when initiating treatment, PPG becomes an important treatment target as the A1C level declines.

Balancing treatment goals and barriers

Early identification and treatment of T2DM and effective use of medications can help reduce diabetes-related complications.[31-33] Empowerment of the patient and office team, as well as diabetes registries to measure success of treatment, can also promote reduction of diabetes-related complications.[34,35] However, patients and clinicians face multiple barriers when they attempt to establish this foundation. Lack of time, financial reimbursement issues, low health literacy and numeracy, and limitations associated with many current therapies often result in suboptimal treatment. Many patients do not achieve current glycemic, lipid, and blood pressure goals,[19] and treatment-related side effects such as hypoglycemia and weight gain can lead to nonadherence.[36] When the right medications are chosen for the right patient at the right time and are used in the right way, however, patient health outcomes can be significantly improved. Balancing treatment effectiveness, safety, and cost, and patient acceptance of the treatment regimen, comprise the cornerstones of successful treatment. ∎

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Options for intensifying diabetes treatment

Timothy S. Reid, MD

TAKE-HOME POINTS

- Glucose-lowering agents lose their effectiveness to lower blood glucose levels over time.

- Glycemic and extraglycemic effects and drug interactions are important considerations when selecting combination therapy.

- Current guidelines provide treatment road maps that work for most patients, but clinical judgment must be exercised to optimize treatment benefits and reduce risks.

When the combination of intensive lifestyle modification and a maximally tolerated dose of metformin does not provide the glycemic control desired, there are several options for combination pharmacologic therapy. However, as will be discussed in this article, several factors should be considered when selecting medications for combination therapy, such as the pathophysiology and duration of diabetes, baseline and current glycosylated hemoglobin (A1C) levels, current therapy, comorbidities, and other factors, including cost (**TABLE 1**), to meet the individual needs and capabilities of the patient. Duration of type 2 diabetes mellitus (T2DM) is important because of the progressive nature of the disease and the direct correlation with loss of pancreatic β-cell function. The A1C level is a key consideration because of the relative contribution of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels (as discussed in the previous article in this supplement, "Importance of glycemic control"). The higher the A1C level, the more likely it is that 2 or more pharmacologic agents will be necessary to reach the target A1C goal. The presence of symptoms due to hyperglycemia indicates the need for more rapid reduction of blood glucose, perhaps over several weeks, using insulin, an insulin secretagogue such as a sulfonylurea or glinide,[1] or a glucagon-like peptide-1 receptor (GLP-1R) agonist.[2]

Mechanisms, magnitude, and durability of glucose-lowering

A patient's current pharmacologic therapy is an important consideration when determining how to intensify therapy. In general, using combinations of pharmacologic agents that act by different mechanisms to target 1 or more pathophysiologic causes of T2DM (eg, insulin resistance, insulin deficiency, impaired incretin response) is considered to provide the best treatment synergy.[1] Since the mechanism of action of metformin, a biguanide, is relatively unique in that it lowers glucose primarily by decreasing hepatic glucose production, as well as by increasing peripheral glucose uptake and utilization,[3] use of metformin with most other agents provides good synergy.[3-23]

The different mechanisms of action among the glucose-lowering agents result in variable effects on FPG and PPG levels as well as on the A1C level (**TABLE 1**).[1,2,24,25] As monotherapy, the α-glucosidase inhibitors, the bile acid sequestrant colesevelam, the dipeptidyl peptidase-4 (DPP-4) inhibitors, and the synthetic amylin analog pramlintide provide mild glucose-lowering; the glinides, the GLP-1R agonists, and the thiazolidinediones (TZDs) provide moderate glucose-lowering; and metformin and the sulfonylureas provide moderate to marked glucose-lowering. Insulin provides the greatest glucose-lowering of all agents available, but with an increased risk of hypoglycemia and weight gain. A recent meta-analysis showed that efficacy of all non-insulin therapies added to metformin was similar, but that adverse effects such as weight gain

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TABLE 1 Costs and glucose-lowering effects of oral agents, insulin, GLP-1R agonists, and pramlintide as monotherapy[1,2,24,25]

	Metformin	AGI	Colesevelam	DPP-4I	Glinide	GLP-1R Agonist	Insulin	Pramlintide	SU	TZD
Cost*	$	$	$$$	$$$	$$ (N) $$$ (Re)	$$$	$-$$	–	$	$$$ (P) $$-$$$ (Ro)
FPG-Lowering	Moderate	Neutral	Mild	Mild	Mild	Mild	Moderate to marked	Mild	Moderate	Moderate
PPG-Lowering	Mild	Moderate	Mild	Moderate	Moderate	Moderate to marked	Moderate to marked	Moderate to marked	Moderate	Mild
A1C-Lowering	1%–2%	0.5%–0.8%	0.5%	0.5%–0.8%	0.5%–1.5%	0.5%–1.5%	1.5%–3.5%	0.4%–1.0%	1%–2%	0.5%–1.4%

*Based on an average daily maintenance dose of available products: $, ≤$3.00/day; $$, $3.01–5.00/day; $$$, ≥$5.01/day. Source: www.drugstore.com; accessed July 20, 2011.

AGI, α-glucosidase inhibitor; DPP-4I, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; GLP-1R, glucagon-like peptide-1 receptor; N, nateglinide; P, pioglitazone; PPG, postprandial plasma glucose; Re, repaglinide; Ro, rosiglitazone; SU, sulfonylurea; TZD, thiazolidinedione.

Adapted from Endocrine Practice, Volume 15(6), Rodbard HW, Jellinger PS, Davidson JA, et al., Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control, Pages 540-559. Copyright (2009), with permission from the American Association of Clinical Endocrinologists.

and hypoglycemia differed among these combinations.[26]

While the magnitude of glucose-lowering is an important consideration in selecting treatment, another is the durability of glucose-lowering. Likely due to the progressive nature of T2DM, perhaps the greatest limitation of glucose-lowering agents is that they lose their effectiveness for lowering blood glucose levels over time. This was clearly demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS)[27] and A Diabetes Outcome Progression Trial (ADOPT).[28] In ADOPT, the incidence of monotherapy failure at 5 years was 15% with the TZD rosiglitazone, 21% with metformin, and 34% with glyburide. The greater failure rate observed with glyburide may have resulted from its principal mechanism of action (ie, stimulation of insulin secretion) and the deterioration in pancreatic β-cell function over time, with rapid deterioration typically occurring within several years after diagnosis of T2DM.[29]

Oral agents

The extraglycemic benefits and side effects of diabetes medications should be considered when choosing therapy. In addition to drug interactions, there are important lipid, cardiovascular, gastrointestinal, renal, weight, and bone mineral issues that must be considered when oral medications are added to the treatment regimen or when they are discontinued. (Subsequent articles in this supplement focus on the GLP-1R agonists and insulin.) Among the extraglycemic benefits is the ability of the TZDs and the DPP-4 inhibitor sitagliptin to improve the lipid profile[1,24,30,31]; improvements with saxagliptin[32] and linagliptin[33] have not been observed. The greatest improvement in the lipid profile seen with sitagliptin is a reduction in the triglyceride level, although the magnitude of the effect is similar to

or less than that observed with the GLP-1R agonists.[34,35] While these improvements do not qualify pioglitazone or sitagliptin as primary therapy for dyslipidemia, the risk of atherosclerotic vascular disease may be reduced with their use,[31] although further investigation is needed to confirm this.

There are also limitations among the classes of oral glucose-lowering agents, some of which are summarized in **TABLE 2**.[24] The risks for hypoglycemia and weight gain are especially important limitations of many oral agents. While all glucose-lowering agents can cause hypoglycemia, it is most likely to occur with the insulin secretagogues, especially the long-acting sulfonylureas chlorpropamide and glyburide.[24] The secretagogues, as well as the TZDs, are the agents most likely to cause weight gain. Weight gain associated with the TZDs results from an increase in adipose tissue mass and fluid retention. The fluid retention tends to occur peripherally and is poorly responsive to loop diuretics and angiotensin-converting enzyme (ACE) inhibitors.[24] In fact, because both of the TZDs currently available, pioglitazone and rosiglitazone, may cause or exacerbate heart failure, they are contraindicated in patients with New York Heart Association class III or IV heart failure.[22,23]

Other limitations associated with the TZDs are worthy of discussion. Most but not all clinical trials have demonstrated an increased risk of myocardial infarction (MI) with rosiglitazone, although no association with MI has been observed with pioglitazone.[22,23] Consequently, the use of rosiglitazone is now restricted, and there is a warning in the prescribing information concerning the risk of MI with its use.[23] Another concern associated with the TZDs is a greater than 2-fold risk of fracture, primarily involving the lower limb and wrist. The risk appears to be the same or slightly higher in women than

TABLE 2 Risks/limitations of oral agents and pramlintide[24]

	Metformin	AGI	Colesevelam	DPP-4I	Glinide	Pramlintide	SU	TZD
Hypoglycemia	Neutral	Neutral	Neutral	Neutral	Mild	Neutral	Moderate	Neutral
GI symptoms	Moderate	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral
Risk of use with renal insufficiency	Severe	Neutral	Neutral	Reduce dosage	Neutral	Unknown	Moderate	Mild
CI in liver failure or predisposition to lactic acidosis	Severe	Neutral	Neutral	Neutral	Moderate	Neutral	Moderate	Moderate
Heart failure/ edema	CI in CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Mild/Moderate
								CI in NYHA Class III, IV CHF
Weight gain	Benefit	Neutral	Neutral	Neutral	Mild	Benefit	Mild	Moderate
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate
Drug-drug interactions	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Moderate	Neutral

AGI, α-glucosidase inhibitor; CHF, congestive heart failure; CI, contraindicated; DPP-4I, dipeptidyl peptidase-4 inhibitor; GI, gastrointestinal; NYHA, New York Heart Association; SU, sulfonylurea; TZD, thiazolidinedione.

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in men, but it is similar for pioglitazone and rosiglitazone and is independent of age and dose.[28,36,37]

Adverse gastrointestinal reactions have been observed with several classes of oral glucose-lowering agents. Among these, there is a small risk of impaired liver function with the glinides, sulfonylureas, and TZDs.[10,11,19-23] While the α-glucosidase inhibitors frequently cause diarrhea, the major side effect of the bile acid sequestrant colesevelam is constipation; therefore, colesevelam is contraindicated in patients with a history of bowel obstruction and is not recommended for those who may be at risk for bowel obstruction.[7]

Pramlintide

The synthetic amylin analog pramlintide slows gastric emptying and inhibits glucagon secretion in a glucose-dependent manner, with a predominant effect on PPG. Pramlintide, which is indicated as adjunctive treatment with mealtime insulin,[6] typically reduces the A1C level by 0.4% to 0.6%.[1] Because severe hypoglycemia may occur when pramlintide is added to insulin, a 50% reduction in the prandial insulin dose and close monitoring of glucose levels are recommended; subsequent insulin doses should be based on blood glucose monitoring.[6] Nausea occurs in about 30% of patients treated with pramlintide but lessens over time. An advantage of pramlintide is an average weight loss of 1 kg to 1.5 kg over 6 months.[1]

Current treatment guidelines for T2DM

In consideration of the unique profiles of currently available glucose-lowering agents, 2 treatment guidelines for patients with T2DM have recently been updated—those developed by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD)[1] and those developed by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE).[24] Although both guidelines affirm the importance of treatment individualization, the ADA/EASD guidelines are somewhat more prescriptive than the AACE/ACE guidelines, but they are based less on the patient's current A1C level.

For patients who do not achieve adequate glycemic control with initial therapy consisting of lifestyle modification plus metformin, the ADA/EASD guidelines recommend the addition of either insulin or a sulfonylurea as a tier 1 option.[1] Basal insulin is preferred if the A1C level is >8.5% or symptoms of hyperglycemia are present, although patients with newly diagnosed T2DM may achieve an adequate response with a sulfonylurea. Tier 2 treatment options include a TZD or a GLP-1R agonist, particularly if hypoglycemia is a concern. A GLP-1R agonist would also be a good choice if promotion of weight loss is important and the A1C level is <8.0%. The remaining pharmacologic options for lowering blood glucose are recommended by the ADA/EASD in limited situations.

The AACE/ACE guidelines focus on the patient's current A1C level and provide treatment recommendations based on 3 A1C ranges: 6.5% to 7.5%, 7.6% to 9.0%, and >9.0% (**TABLE 3**).[24,38] Treatment options within each of these ranges reflect the AACE/ACE recommendation for a target A1C level

TABLE 3 AACE/ACE recommendations: Intensifying therapy in patients not achieving glycemic control with lifestyle modification + metformin[24]

Lifestyle Modification + Metformin AND		
A1C 6.5%–7.5%	**A1C 7.6%–9.0%**	**A1C >9.0%**
Add:	*Add:*	*Insulin ± other agents:*
GLP-1R agonist if ↑↑PPG	GLP-1R agonist if ↑↑PPG	Discontinue secretagogue with multidose insulin
DPP-4I if ↑PPG and ↑FPG	DPP-4I if ↑PPG and ↑FPG	Can use pramlintide with prandial insulin
TZD	TZD	
Low-dose glinide or SU	Low-dose glinide if ↑PPG	
Colesevelam	Low-dose SU if ↑FPG	
AGI if ↑PPG		

A1C, glycosylated hemoglobin; AGI, α-glucosidase inhibitor; DPP-4I, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; GLP-1R, glucagon-like peptide-1 receptor; PPG, postprandial plasma glucose; SU, sulfonylurea; TZD, thiazolidinedione.

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<6.5% for most patients with T2DM, while recognizing the need to individualize treatment to minimize the risk for hypoglycemia.[24] For a patient with an A1C level of 6.5% to 7.5% despite lifestyle modification and metformin, the AACE/ACE recommends the addition of a GLP-1R agonist or DPP-4 inhibitor, with preference given to the GLP-1R agonists because of their greater effectiveness in reducing PPG and their weight loss effects.[24] Alternatively, a low-dose secretagogue could be used. An α-glucosidase inhibitor is an option if the PPG level is elevated, while colesevelam is a consideration in general. For a patient with an A1C level between 7.6% and 9.0%, the GLP-1R agonists, DPP-4 inhibitors, TZDs, or low-dose secretagogues are options. A sulfonylurea is an option if the FPG level is elevated, whereas a glinide can be considered if the PPG level is elevated. For a patient with an A1C level >9.0% despite lifestyle modification and metformin, insulin therapy should be initiated without delay.[24] ■

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Glucagon-like peptide-1 receptor agonists for intensifying diabetes treatment

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The glucagon-like peptide-1 receptor (GLP-1R) agonists have quickly become an important treatment option for patients with type 2 diabetes mellitus (T2DM). The development of the GLP-1R agonists is based on the discovery that the incretin system is integrally involved in regulating glucose homeostasis.[1] The actions of the incretin system have been shown to primarily result from the secretion of 2 gut peptides in response to oral food ingestion—glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. GLP-1, which is secreted by the L-cells of the small intestine, is more important as a clinical remedy, as patients with T2DM may be deficient or resistant to GIP.[2]

Clinical pharmacology

Administration of GLP-1 has been shown to result in a host of biological actions, including a glucose-dependent increase in insulin secretion and inhibition of glucagon secretion via effects on pancreatic β-and α-cells, respectively.[2-6] GLP-1 does not suppress glucagon secretion at plasma glucose levels <65 mg/dL or so, thus reducing the risk of hypoglycemia. GLP-1 also has been shown to promote proliferation, increase differentiation, and prolong survival of pancreatic β-cells.[7,8] Finally, GLP-1 slows gastric emptying[9] and promotes satiety, leading to reduced caloric intake.[10,11]

Although effective in regulating glucose homeostasis, GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in an elimination half-life for GLP-1of <2 minutes.[12] Consequently, administration of GLP-1 is an impractical approach to augment the level of circulating GLP-1. One strategy that can capitalize on the incretin effect, however, is to use analogs of GLP-1, which are resistant to the enzymatic actions of DPP-4. These GLP-1 analogs bind to the GLP-1 receptor on the pancreatic islet cells. Two GLP-1 analogs, hereafter referred to as GLP-1R agonists, exenatide and liraglutide, are currently available in the United States. Homology to native GLP-1 is 53% for exenatide and 97% for liraglutide.[13] Exenatide has a mean elimination half-life of 2.4 hours,[14] and liraglutide 13 hours[13]; consequently, exenatide is administered twice daily and liraglutide once daily.

Another strategy that can utilize the incretin pathway is to interfere with the rapid inactivation of GLP-1 by DPP-4. DPP-4 inhibitors (sitagliptin, saxagliptin, and linagliptin) block the enzymatic action of DPP-4, thereby increasing the elimination half-life of endogenous GLP-1. The modest increase in the physiologic level of GLP-1 with administration of a DPP-4 inhibitor (10 pmol/L)[15] compared to the higher, pharmacologic level of GLP-1 achieved with administration of a GLP-1R agonist

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TABLE 1 Overview of selected clinical trials involving the GLP-1R agonists

	Duration (wk)	Δ A1C (%)	Δ FPG (mg/dL)	Δ PPG (mg/dL)	% Patients Achieving A1C <7%
With lifestyle management					
Exenatide[19-21]	4–24	↓0.4–1.2	↓18–36	↓21–48	46–67
Liraglutide[22,23]	52–104	↓0.6–1.1	↓9–22	↓27–37	37–51
Add-on to metformin					
Exenatide[24-26]	20–32	↓0.4–1.4	↓7–52	NR	32–46
Liraglutide[27]	26	↓1.0	↓29–31	↓41–47	35–42
Add-on to metformin + another agent					
Exenatide[26,28,33]	16–52	↓0.6–1.7	↓9–32	↓28–52	27–62
Liraglutide[34,35]	26	↓1.3–1.5	↓28–48	↓33–49	54–58

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; GLP-1R, glucagon-like peptide-1 receptor; PPG, postprandial plasma glucose.

(60 pmol/L)[16] is thought to explain the better glucose-lowering efficacy and promotion of satiety and weight loss observed with GLP-1R agonists but not with DPP-4 inhibitors.

Role of GLP-1R agonists in treatment

In addition to exenatide and liraglutide, which were approved by the US Food and Drug Administration (FDA) in April 2005 and January 2010, respectively, other GLP-1R agonists are in development. Once-weekly exenatide was approved for marketing in Europe in June 2011 and is currently under FDA review.

Barely mentioned in previous guideline recommendations, the 2009 updates developed by consensus panels of the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD)[17] and the American Association of Clinical Endocrinology (AACE)/American College of Endocrinologists (ACE)[18] describe important roles for the GLP-1R agonists in treatment of patients with T2DM. The ADA/EASD recommendations list the GLP-1R agonists as an alternative to the thiazolidinediones (TZDs) for patients who do not achieve glycemic control with the combination of lifestyle management plus metformin and insulin or a sulfonylurea.[19] In addition, a GLP-1R agonist is a recommended treatment when the risk of hypoglycemia is especially worrisome or when weight loss is a major factor and the patient's glycosylated hemoglobin (A1C) level is <8.0%.[17]

The AACE/ACE guideline recommendations describe the GLP-1R agonists as a treatment option across the spectrum of A1C levels, ie, ≥6.5%.[18] For a patient with an A1C 6.5% to 7.5%, a GLP-1R agonist is an alternative to metformin as initial therapy, particularly if the postprandial plasma glucose (PPG) level is markedly elevated. If the patient does not achieve glycemic control with the combination of lifestyle management and metformin, the addition of a GLP-1R ago-

nist is one of the recommended options, as it is for a patient with an A1C of 7.6% to 9.0%. A GLP-1R agonist is also recommended in combination with metformin and a sulfonylurea or a TZD in drug-naïve patients with no symptoms and an A1C level >9.0%. Similarly, triple therapy involving a GLP-1R agonist is recommended for patients with an A1C level ≤9.0% who does not achieve glycemic control with dual therapy, except when dual therapy includes a DPP-4 inhibitor.

Clinical trials

The clinical profile of the GLP-1R agonists has been extensively investigated in clinical trials demonstrating moderate glucose-lowering (**TABLE 1**) and frequent adverse gastrointestinal events, as well as a low incidence of hypoglycemia, weight loss in most patients, and other favorable nonglycemic effects.[19-35]

GLP-1R agonists as monotherapy
Efficacy

As monotherapy in combination with lifestyle management, the GLP-1R agonists typically reduce the A1C level by 0.5% to 1.5%.[19,21,22] Reduction of the PPG level with a GLP-1R agonist is greater than that of the fasting plasma glucose (FPG) level.[19,22] Increasing the dose of exenatide from 5 μg to 10 μg twice daily and liraglutide from 1.2 mg to 1.8 mg once daily provides additional but modest improvement in glucose reduction. Patients who have not been treated with pharmacologic glucose-lowering therapy appear to achieve a greater reduction in blood glucose level compared to those previously treated with glucose-lowering pharmacotherapy. For example, use of liraglutide 1.2 mg or 1.8 mg once daily for 52 weeks led to a reduction in the A1C level of 1.2% and 1.6%, respectively, in patients previously managed with diet and exercise only compared to 0.5% and 0.7%, respectively, for patients previously treated with glucose-lowering monotherapy.[22]

Safety and tolerability

The observation that the actions of GLP-1R agonists to stimulate insulin secretion and inhibit glucagon secretion are dependent on the level of glucose suggests that the GLP-1R agonists should cause hypoglycemia infrequently. Indeed, mild to moderate hypoglycemia occurs in 4% to 9% of patients treated with exenatide monotherapy[19,20] and in 0% to 12% of those treated with liraglutide monotherapy.[22,36] These low rates of hypoglycemia are sustained, as shown during 2 years of follow-up, wherein 12% and 10% of patients treated with liraglutide 1.2 mg or 1.8 mg once daily, respectively, experienced minor hypoglycemia (self-reported plasma glucose <56 mg/dL).[26] By comparison, 26% of patients treated with glimepiride experienced minor hypoglycemia during the 2-year period. An episode of major hypoglycemia occurred in 1 patient treated with liraglutide 1.8 mg once daily after an insulin infusion.

Adverse gastrointestinal effects are commonly experienced by patients treated with a GLP-1R agonist. Of these, nausea is the most common, occurring in more than half of patients treated with exenatide[19,20] and nearly 30% of those treated with liraglutide.[22,36] Initiating GLP-1R therapy using the dose-escalation strategy described later in this article reduces the incidence of nausea such that nausea is experienced by 28% of patients treated with exenatide and 26% of those treated with liraglutide.[37]

Acute pancreatitis has been reported infrequently in patients treated with exenatide[38] or liraglutide.[39] During 2 years of monotherapy with liraglutide (N=498), 3 cases of pancreatitis occurred, of which none were judged to be treatment-related.[22,23] Two patients recovered (1 while continuing liraglutide therapy) and 1 patient died.[23] An association between acute pancreatitis and GLP-1R agonist therapy is usually difficult to assess, as patients with T2DM have a 2- to 3-fold increased risk of pancreatitis compared to persons without diabetes.[40,41] Furthermore, retrospective analyses of 2 insurance claims databases show a risk of acute pancreatitis with GLP-1R agonist therapy similar to those of other glucose-lowering therapies.[41,42] Nonetheless, clinical vigilance and patient education are needed.

Case Study

EC is a 53-year-old male building contractor with a 6-year history of T2DM, who is being seen for a regular follow-up. Physical examination and laboratory results show
- Blood pressure 125/75 mm Hg
- Body mass index (BMI) 32 kg/m^2
- A1C 6.9%
- Lipid profile within normal limits

EC reports that he takes his medications every day; review of the pharmacy claims database also indicates good adherence. EC has no history of cardiovascular disease. Current medications are metformin 1 g twice daily and rosiglitazone 4 mg once daily. He wants to discontinue rosiglitazone because of the reports of heart attacks that he has heard about on television.

As a first step, it would be appropriate to talk with the patient about his concerns regarding heart attacks due to rosiglitazone and to let him know that the evidence concerning this risk is mixed. You could then review with him the benefits and limitations of the other treatment options. Although it is uncertain how much his A1C level would increase if rosiglitazone were discontinued, it seems reasonable to consider replacing rosiglitazone with another agent with at least comparable glucose-lowering capability. Thus, choices for him would be insulin or a sulfonylurea, glinide, or GLP-1R agonist. The relatively high risk of hypoglycemia with insulin, the sulfonylureas, and glinide is a concern because of this patient's vocation and his irregular eating habits. It would be prudent to develop a written hypoglycemia action plan with the patient. Because of the concerns regarding hypoglycemia, a GLP-1R agonist is a better choice. In addition, the mechanism of action of the GLP-1R agonists is complementary to metformin.

GLP-1R agonists as add-on to metformin or with other agents

The efficacy of the GLP-1R agonists has also been extensively investigated when used as add-on therapy to metformin alone[24-27] or in combination with another agent.[26,28-35] These studies generally show that addition of a GLP-1R agonist provides further glucose reduction, similar to that observed with GLP-1R agonist monotherapy. Patients with an A1C level >9.0% achieve greater A1C reduction than those with an A1C level <9.0%.

A recent 30-week trial investigated exenatide as add-on therapy to insulin glargine given alone or in combination with metformin and/or pioglitazone. Patients in this study had A1C levels of 7.1% to 10.5%.[33] Exenatide was initiated at 5 μg twice daily before the morning and evening meals for 4 weeks, then increased to 10 μg twice daily. The A1C level decreased 1.7% in patients treated with exenatide and 1.0% in patients treated with placebo. The decrease in FPG was similar in the exenatide and placebo groups (-29 mg/dL vs -27 mg/dL, respectively), whereas the morning and evening, but not the midday, glucose excursions decreased significantly more in the exenatide group. For example, the morning glucose excursion decreased 36 mg/dL in exenatide patients and 4 mg/dL in placebo patients (P<.001). Body weight decreased 1.8 kg in exenatide patients and increased 1.0 kg in placebo

patients. Systolic and diastolic blood pressure decreased 2.7 and 1.7 mm Hg in exenatide patients, while both increased 1.7 mm Hg in placebo patients (*P*=.01 and *P*<.001, respectively). Heart rate increased 2.3 beats per minute in exenatide patients and decreased 0.7 beats per minute in placebo patients (P<.01). The number of hypoglycemic episodes per patient-year did not differ significantly between exenatide and placebo patients. Two episodes of major hypoglycemia were experienced by 1 patient in the placebo group. Adverse gastrointestinal events were observed more frequently with exenatide than with placebo. In these patients receiving insulin-based dual or triple glucose-lowering therapy, the addition of exenatide improved glycemic control and decreased body weight without causing significant hypoglycemia; adverse gastrointestinal events were common.

The efficacy and safety of exenatide as add-on therapy to metformin and a sulfonylurea has also been studied in comparison with premix insulin aspart. The adult patients in this study had A1C levels ≥8.0%.[43] Patients were randomized to receive exenatide 5 μg twice daily for 4 weeks, then increased to 10 μg twice daily for 20 weeks, or to premix insulin aspart 12 units daily given in 1 or 2 doses; the sulfonylurea was discontinued in patients treated with premix insulin aspart twice daily. From a baseline of 10.1% to 10.3%, the A1C level decreased to 8.5% in the exenatide group and to 7.8% and 7.6% in the premix insulin aspart once- and twice-daily groups, respectively (*P*<.0001 for both insulin groups vs exenatide). Reductions in FPG levels were significantly greater in the premix insulin aspart groups (*P*=.0002 and *P*<0001). Reductions in PPG levels were also greater after dinner in the insulin aspart groups than in the exenatide group, but not after breakfast or lunch. Minor hypoglycemia occurred significantly more frequently in the premix insulin aspart once-daily and twice-daily groups compared to exenatide (4.02 vs 5.25 vs 1.28 events/patient-year, respectively; *P*<.0001 for both insulin groups vs exenatide). Major hypoglycemia was experienced by 4 and 6 patients in the premix insulin aspart once-daily and twice-daily groups, respectively, and by no patients in the exenatide group. Patients in the premix insulin aspart once-daily and twice-daily groups gained 2.8 kg and 4.1 kg, respectively, while patients in the exenatide group lost 1.9 kg. Nausea occurred in 29% of patients in the exenatide group compared to 9% and 8% in the premix insulin aspart once-daily and twice-daily groups, respectively.

Head-to-head comparisons of a GLP-1R agonist with other incretin-based therapy

GLP-1R agonist add-on therapy has been compared to other incretin-based therapies in several randomized clinical trials. These trials have compared exenatide and liraglutide,[37,44]

exenatide and sitagliptin,[45,46] liraglutide and sitagliptin,[47] and liraglutide with the investigational extended-release form of exenatide that is administered once weekly.[48]

In the comparison of exenatide with liraglutide, adults with inadequately controlled glycemia despite maximally tolerated doses of metformin and/or sulfonylurea were randomized in open-label fashion to receive exenatide 10 μg twice daily (n=231) or liraglutide 1.8 mg once daily (n=233).[37] After 26 weeks, the baseline A1C of 8.1% decreased 0.8% with exenatide and 1.1% with liraglutide (*P*≤.0001). FPG levels decreased 11 mg/dL and 29 mg/dL, respectively (*P*≤.0001). On the other hand, patient-measured PPG levels decreased more with exenatide than with liraglutide after breakfast (estimated treatment difference [ETD]: 24 mg/dL; *P*<.0001) and after dinner (ETD 18 mg/dL; *P*=.0005); the ETD after lunch was not statistically significant. More patients in the liraglutide group than in the exenatide group achieved the target A1C level of <7.0% (54% vs 43%, respectively; *P*=.0015).[37] The treatment difference was greatest for patients with a baseline A1C ≥10% but was not affected by previous glucose-lowering therapy or baseline BMI. In the 14-week extension phase, further significant decreases in A1C (-0.3%; *P*<.0001) and FPG (-16 mg/dL; *P*<.0001) levels were observed in patients switched from exenatide to liraglutide; these levels decreased slightly in patients who remained on liraglutide.[44]

Three studies have compared exenatide or liraglutide with the DPP-4 inhibitor sitagliptin. In all 3 studies, the observed decrease in blood glucose was greater with the GLP-1R agonist than with sitagliptin. In the first study, a 6-week crossover trial (N=61), FPG levels decreased from 178 to 163 mg/dL in patients treated with exenatide and from 178 to 159 mg/dL in patients treated with sitagliptin (*P*=NS).[45] However, PPG levels decreased from 245 to 133 mg/dL in patients treated with exenatide and from 245 to 208 mg/dL in those treated with sitagliptin (*P*≤.0001). PPG level increased by 72 mg/dL following crossover from exenatide to sitagliptin, compared to a decrease of 76 mg/dL following crossover from sitagliptin to exenatide. The second study was an open-label trial (N=48) comparing addition of exenatide or sitagliptin to the combination of metformin and insulin glargine to achieve an FPG level ≤100 mg/dL.[46] At the end of 4 weeks, the 6-hour PPG excursion in the exenatide and sitagliptin groups was 606 and 612 mg/dL, respectively, compared to 728 mg/dL in the group treated with metformin and insulin glargine (*P*<.05 vs both exenatide and sitagliptin). The A1C level decreased in all 3 groups from baseline (*P*<.05), with a greater reduction in the exenatide group compared to the metformin plus insulin glargine group (*P*<.05). In the third trial, adult patients inadequately controlled with metformin were randomized to liraglutide 1.2 mg (n=225) or 1.8 mg (n=221) once daily or sitagliptin 100 mg once

daily (n=219) for 26 weeks. From a baseline of 8.4%, A1C level decreased by 1.2% and 1.5% in the liraglutide 1.2-mg and 1.8-mg groups, respectively, and from a baseline of 8.5% by 0.9% in the sitagliptin group (*P*≤.0001 vs both liraglutide groups). Reductions from baseline in FPG level showed a similar trend, decreasing by 34 mg/dL from 182 mg/dL in the liraglutide 1.2-mg group, by 39 mg/dL from 178 mg/dL in the liraglutide 1.8-mg group, and by 15 mg/dL from 180 mg/dL in the sitagliptin group (*P*≤.0001 vs both liraglutide groups).

Preliminary results of DURATION-6, the sixth study comparing once-weekly administration of extended-release exenatide with other glucose-lowering agents, were recently announced.[48] The 26-week study randomized patients who were not achieving glycemic control despite lifestyle management in conjunction with metformin, a sulfonylurea, metformin plus a sulfonylurea, or metformin plus pioglitazone. Patients treated with exenatide 2 mg once weekly (n=461) experienced a reduction in A1C of 1.3% compared to 1.5% for patients treated with liraglutide 1.8 mg once daily (n=451). Adverse gastrointestinal events were more common in patients treated with liraglutide compared to those treated with exenatide once weekly: nausea (20% vs 9%), vomiting (11% vs 4%), and diarrhea (13% vs 6%). Major hypoglycemia was not observed in either group.

In summary, these prospective head-to-head clinical trials show that the GLP-1R agonists exenatide and liraglutide provide comparable reductions in blood glucose levels, and that both provide greater glucose-lowering than the DPP-4 inhibitor sitagliptin.

Case Study

During a discussion with EC about GLP-1R agonist therapy, he expresses some anxiety about using an injectable drug. As well as providing patient education regarding self-injection and the available devices, you have EC self-inject in the office. In addition to easing his concerns, this allows you to ensure that EC uses the proper technique. You also discuss the nonglycemic benefits of GLP-1R agonist therapy, as these may serve to motivate EC to self-manage with a GLP-1R agonist.

Nonglycemic effects

The GLP-1R agonists exert clinically important effects beyond lowering blood glucose. These include effects on weight, blood pressure, blood lipids, and pancreatic β-cell function.

Weight

As noted above, the pharmacologic level of GLP-1 analog achieved with the GLP-1R agonists is thought to contribute to the satiety and reduced caloric intake observed with these agents[11,45,49] but not with the DPP-4 inhibitors. A 6-week

crossover trial comparing exenatide with sitagliptin showed a decreased caloric intake with exenatide (-134 kcal) during a standardized meal, but an increase of 130 kcal with sitagliptin (*P*=.0227).[45]

It is likely that this ability to promote satiety contributes to the average weight loss of 1 kg to 4 kg observed in most patients treated with a GLP-1R agonist.[19,22,28,29,32,34,35,50] Weight loss observed with the GLP-1R agonists appears to result predominantly from loss of fat rather than loss of lean body mass.[51-54] At the end of 1 year of treatment with exenatide, a decrease in fat mass of 11% and trunk fat mass of 13% has been observed, while lean body mass did not change.[51] Similarly, 1 year after the addition of liraglutide to metformin, visceral fat declined by 16% to 17% and subcutaneous fat by 8% to 9%.[54]

The effect of weight loss on glycemic control and cardiovascular biomarkers due to GLP-1R agonist therapy has been retrospectively investigated using the General Electric Centricity research database.[55] Adult patients treated for 60 days or more with exenatide (n=6280), sitagliptin (n=5861), or insulin (n=32,398) were studied. Treatment with other glucose-lowering therapy was not allowed from 3 months before to 12 months after receipt of the first prescription for exenatide, sitagliptin, or insulin. Patients in the exenatide and sitagliptin groups experienced significant weight loss (*P*<.0001 and *P*=.009, respectively), while patients in the insulin group experienced significant weight gain (*P*=.002) (**TABLE 2**). Changes in body weight were significantly associated with reductions in A1C (*P*<.0001 for all 3 groups) and FPG (*P*=.002, *P*=.008, and *P*<.0001 for exenatide, sitagliptin, and insulin, respectively). Weight loss was significantly associated with reductions in both systolic and diastolic blood pressure in all 3 groups (*P*<.0001 for each). With respect to weight-associated improvement in the lipid profile, there were significant improvements in total cholesterol (*P*<.001), low-density lipoprotein (LDL) cholesterol (*P*=.005), and triglycerides (*P*=.007) in patients treated with exenatide. Patients treated with sitagliptin experienced significant weight-associated improvement in total cholesterol (*P*<.001) and triglycerides (*P*=.001), while weight-associated improvement in total cholesterol (*P*=.02) was observed in patients treated with insulin. Overall, this real-world investigation demonstrated that the strongest weight benefit was observed with exenatide, followed by sitagliptin. Further investigation is needed to determine whether the observed improvements in cardiovascular biomarkers result in a reduction in cardiovascular events in patients with T2DM.

Blood pressure and blood lipids

Additional trials show similar effects on cardiovascular biomarkers with GLP-1R agonist therapy. These trials generally

TABLE 2 Effect of GLP-1R agonist therapy on weight and cardiovascular biomarkers[55]

Parameter	Exenatide (n=6280)	Sitagliptin (n=5861)	Insulin (n=32,398)
Weight, kg			
Baseline	110	97	96
Change	↓3.0	↓1.1	↑0.6
BMI, kg/m²			
Baseline	38.5	33.8	33.6
Change	NR	NR	NR
A1C, %			
Baseline	7.7	7.7	8.8
Change	↓0.5	↓0.5	↓1.0
FPG, mg/dL			
Baseline	157	159	187
Change	↓13	↓14	↓27
Systolic blood pressure, mm Hg			
Baseline	130	130	132
Change	↓2.3	↓1.1	↓1.8
Diastolic blood pressure, mm Hg			
Baseline	77	76	75
Change	↓1.2	↓0.6	↓1.3
Total cholesterol, mg/dL			
Baseline	177	175	183
Change	↓11	↓10	↓14
LDL cholesterol, mg/dL			
Baseline	95	96	100
Change	↓4	↓6	↓8
HDL cholesterol, mg/dL			
Baseline	43	44	45
Change	0	0	0
Triglycerides, mg/dL			
Baseline	209	188	223
Change	↓27	↓20	↓45

A1C, glycosylated hemoglobin; BMI, body mass index; FPG, fasting plasma glucose; GLP-1R, glucagon-like peptide-1 receptor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NR, not reported.

show a 1- to 7-mm Hg reduction in systolic blood pressure but no significant change in diastolic blood pressure or heart rate.[20,22,29,30,32,34,35,37,44,47,56,57] In addition, the lipid profile is often improved, notably the triglyceride level.[20,22,29,30,32,34,35,37,47] For example, addition of liraglutide 1.2 mg once daily, but not 1.8 mg once daily, to metformin and rosiglitazone led to significant (*P*<.05) reduction in LDL cholesterol (-11 mg/dL) and triglyceride (-34 mg/dL) levels compared to placebo.[35]

Preliminary data suggest other possible cardiovascular benefits with GLP-1R agonist therapy. Investigation indicates that liraglutide modulates expression of vascular adhesion molecules and plasminogen activator inhibitor-1 (PAI-1) in an in vitro model of endothelial cell dysfunction.[59] In humans, significant decreases in cardiovascular biomarkers such as PAI-1 (*P*=.018), B-natriuretic peptide (*P*=.048), and leptin (*P*=.0017) were observed in a subanalysis of a randomized clinical trial following 14 weeks of treatment with liraglutide

1.25 mg once daily.[59] Other markers, including adiponectin, high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-α, were not altered.

Pancreatic β-cell function

Finally, in addition to acting on alterations in the incretin system involved in glucose homeostasis, GLP-1R agonists may also address another pathophysiologic mechanism of T2DM: pancreatic β-cell dysfunction. Based on early clinical evidence indicating GLP-1 might actually improve β-cell function,[49] many studies have investigated the effect of exenatide or liraglutide on various markers of β-cell function. These studies show that some but not all measures of β-cell function were improved.[20,27,60,61] A direct comparison of exenatide and liraglutide in adults with inadequate glycemic control despite therapy with metformin and/or a sulfonylurea showed improvement in β-cell function, as determined

TABLE 3 Clinical effects observed with exenatide vs liraglutide after 26 weeks of treatment

	Exenatide vs Liraglutide[37]		Exenatide vs Liraglutide[44]	
	Exenatide 10 µg BID (n=231)	Liraglutide 1.8 mg QD (n=233)	Exenatide 10 µg BID → Liraglutide 1.8 mg QD (n=187)	Liraglutide 1.8 mg QD (n=202)
A1C, %				
Baseline	8.1	8.2	7.2	7.0
Change	↓ 0.8	↓1.1*	↓0.3†	↓ 0.1
FPG, mg/dL				
Baseline	171	176	160	147
Change	↓11	↓ 29*	↓16†	↓ 4
Weight, kg				
Baseline	93.0	93.1	NR	NR
Change	↓ 2.9	↓3.2	↓ 0.9†	↓0.4
ΔPancreatic β-cell function				
Fasting insulin, pmol/L	↓ 1.38	12.43‡	NC	NC
Fasting C-peptide, nmol/L	↓ 0.02	0.05	NC	NC
Fasting proinsulin:insulin ratio	↓ 0.02	0.00	NC	NC
HOMA-B, %	2.74	32.12*	14.5§	NR
HOMA-IR, %	NR	NR	NC	NC
Fasting glucagon, ng/L	↓12	↓ 19	NR	NR
ΔBlood pressure, mm Hg				
Systolic	↓ 2.0	↓ 2.5	↓3.8†	↓ 2.2
Diastolic	↓ 2.0	↓ 1.1	NC	NC
ΔLipids, mg/dL				
Total cholesterol	↓ 4	↓ 8	NR	NR
LDL cholesterol	↓ 16	↓ 17	NR	NR
HDL cholesterol	↓ 2	↓ 2	NR	NR
Triglycerides	↓ 20	↓ 36‡	NR	NR

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-B, homeostasis model assessment–β-cell function; HOMA-IR, homeostasis model assessment–insulin resistance; LDL, low-density lipoprotein; NC, data not reported but authors indicated no significant change from baseline to study end; NR, data not reported.

P value comparing the 2 agents: *$P \leq .0001$; ‡$P \leq .05$. P value compared to baseline: †$P < .0001$; §$P = .001$.

by the homeostasis model of assessment-B (HOMA-B).[37] Increases of 2.74% in patients treated with exenatide and 32.12% in patients treated with liraglutide ($P<.0001$) were observed after 26 weeks (**TABLE 3**) Similarly, compared to sitagliptin, liraglutide 1.2 mg and 1.8 mg once daily resulted in significant improvement in HOMA-B ($P<.0001$ vs sitagliptin), fasting C-peptide ($P<.005$), and fasting proinsulin-to-insulin ratio ($P<.05$).[46] Some other measures of β-cell function did not improve. Addition of exenatide to metformin with or without rosiglitazone has been shown to result in significant improvement in the disposition index, a gold standard measure of β-cell function.[26]

Additional safety considerations
Long-term safety of the GLP-1R agonists is an area of significant ongoing investigation to clarify concerns raised during clinical trials and postmarketing reports, as well as to ensure that unanticipated events are identified quickly should they occur.

Medullary thyroid cancer
Postmarketing reports involving exenatide[62] and preclinical and clinical studies of liraglutide[63] have raised the possibility of medullary thyroid neoplasms. Studies involving male rats treated with liraglutide revealed a significantly increased incidence of C-cell carcinomas, which led the FDA to express concern about a risk of such cancers in humans.[63] There is evidence to suggest, however, that such tumors may have a genetic basis, as rats not exposed to liraglutide have been observed to develop C-cell thyroid tumors.[64] In addition, development of C-cell tumors may be species-specific, as the GLP-1 receptor–mediated mechanism thought to be involved in rodents is not expressed in monkeys or humans. Monkeys

administered high levels of liraglutide for 20 months did not develop C-cell hyperplasia, and humans exposed to liraglutide for 2 years showed no evidence of calcitonin levels above the lower end of the normal range.[64] (Calcitonin is a biomarker for medullary thyroid cancer and C-cell hyperplasia.)

To determine if there is an association between GLP-1R agonists and medullary thyroid cancer, the FDA has required the manufacturers of exenatide and liraglutide to carry out further investigations and maintain a 15-year cancer registry for those treated with liraglutide.[62,65] In the meantime, the prescribing information for liraglutide includes a boxed warning concerning the risk of medullary thyroid cancer.[13]

Cardiovascular events

Subsequent to filing the new drug application (NDA) for liraglutide but before its approval by the FDA, the FDA adopted new cardiovascular safety standards for all glucose-lowering drugs. Since the data provided in the NDA for liraglutide did not meet these new standards and thus could not rule out the possibility of cardiovascular events, the FDA has required further clinical investigation to assess the risk of cardiovascular events with liraglutide.[65] It should be noted that a randomized, placebo-controlled, double-blind crossover study found that 7 days of liraglutide in doses as high as 1.8 mg once daily prolonged the QTc interval by less than 10 milliseconds.[66]

Case Study

After you give EC an overview of ongoing safety investigations with the GLP-1R agonists, he asks if there are any other safety issues or adverse events that he should know about. In addition to the low incidence of hypoglycemia with the GLP-1R agonists, you discuss strategies to minimize the incidence and severity of nausea and vomiting.

Further considerations

Selecting, initiating, and optimizing GLP-1R agonist therapy

During the discussion about treatment options for lowering blood glucose levels, the concerns, needs, and abilities of the patient should be investigated, as these all impact adherence. (See "Physician-patient communication in diabetes care" in this supplement)

An important issue to discuss with the patient is adverse gastrointestinal events, particularly nausea. As noted earlier, mild nausea commonly occurs with GLP-1R agonist therapy, probably from the pharmacologic levels of GLP-1 receptor activity. Nausea peaks within 8 weeks of initiating treatment with exenatide[24] and typically resolves within 14 to 16 weeks, while nausea peaks early during treatment with liraglutide, with fewer than 10% of patients experiencing nausea by week

4.[22] Nonetheless, clinical trial experience shows that reducing the initial dose and using a dose-escalation strategy reduces the incidence and severity of nausea.[37] Exenatide should be started at a dose of 5 µg twice daily and given within 60 minutes of the morning and evening meals. The dose of exenatide can be increased to a maximum dose of 10 µg twice daily after 1 month, if needed, to further lower the blood glucose level.[14] Similarly, liraglutide should be initiated at a dose of 0.6 mg once daily and increased to 1.2 mg once daily 1 week later. The dose of liraglutide can be increased to the maximum dose of 1.8 mg once daily, if needed, to further lower blood glucose. Liraglutide can be taken without regard to meals.[13]

Use in special populations

GLP-1R agonist therapy should be used cautiously, if at all, in selected populations. When GLP-1R agonist therapy is initiated in a patient already receiving a sulfonylurea, there is an increased risk of hypoglycemia. Therefore, the dose of the sulfonylurea should be reduced.[13,14]

In patients with severe renal impairment, ie, creatinine clearance <30 mL/min or end-stage renal disease, exenatide should not be used. Exenatide should be used cautiously in patients with a creatinine clearance of 30 to 50 mL/min.[14] A review of 6 randomized clinical trials of liraglutide showed that patients with a creatinine clearance of 60 to 89 mL/min were not at increased risk of minor hypoglycemia, nausea, or renal injury compared to placebo.[67] Nonetheless, cautious use of liraglutide in patients with renal impairment is recommended, although no dosage adjustment is recommended.[13]

The potential risks of exenatide and liraglutide to the fetus are unknown; therefore, their use during pregnancy should be considered only if potential benefit justifies potential risks to the fetus.[13,14] Similarly, exenatide and liraglutide should not be used by women who are nursing; alternatively, nursing should be discontinued.[13,14]

Current evidence indicates that age, gender, and race have no clinically significant effect on the pharmacokinetics of exenatide[14] or liraglutide.[13]

Conclusion

Incretin-based therapies represent a new and exciting way to treat T2DM. Whereas the magnitude of glucose-lowering with these agents is comparable to that seen with traditional glucose-lowering agents, the newer medications have considerably more attractive adverse effect profiles, including a low risk of hypoglycemia and, in the case of the GLP-1R agonists, a potential for weight loss. The spectrum of opportunity for the use of GLP-1R agonists is broad, from monotherapy to combination therapy with virtually every other diabetes

medication, allowing us to intensify control at almost any level by exploiting this novel pathway. Whether or not these medications will allow a better prognosis for our patients beyond that afforded by better glucose control is unknown. What is fascinating, though, is that they have given us an entirely new understanding of how the gastrointestinal tract educates the rest of the body about nutrient intake, suggesting that the future holds even more effective ways to modulate food intake and improve our patients' metabolisms. ∎

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Insulin for intensifying diabetes treatment

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TAKE-HOME POINTS

- Insulin remains an essential and appropriate option for the treatment of patients with T2DM and failing β-cell function.

- Insulin analogs may offer some benefits over human insulins.

- Insulin therapy is typically initiated with basal insulin because of its relative ease of use and lower incidence of hypoglycemia compared to prandial or premix insulin. It also results in less weight gain.

- Several options are available to intensify basal insulin therapy, including stepwise prandial or premix insulin or full basal-bolus replacement therapy.

- Fixed prandial doses might simplify insulin treatment for patients and clinicians, making basal-bolus insulin therapy a viable alternative for controling glycemia.

Introduction

Since its discovery in the 1920s, insulin has remained the most effective treatment option available to lower blood glucose levels, especially in the setting of failing β-cell function. There are 2 broad groups of synthetic insulins currently available. Biosynthetic human insulins have the same chemical structure as insulin secreted by the human pancreas, while insulin analogs have structural modifications that affect their pharmacokinetic and, by consequence, pharmacodynamic profile. As a result of these modifications, the rapid-acting insulin analogs (eg, aspart, glulisine, lispro) have a shorter onset and duration of action than short-acting regular human insulin and more closely mimic the prandial release of endogenous insulin in a person with normal glucose tolerance.[1-3] The long-acting insulin analogs (eg, detemir, glargine) have a longer onset and duration of action than intermediate-acting human neutral protamine Hagedorn (NPH) insulin and more closely mimic the basal release of endogenous insulin.[4-6]

Clinical implications of pharmacodynamics

The pharmacodynamic differences between the human and analog insulins are thought to have important clinical implications in patients with type 2 diabetes mellitus (T2DM). For example, evidence indicates that hypoglycemia occurs less frequently with comparable glycemic control with the use of basal insulin analogs than with human NPH insulin,[7-13] while weight gain is usually comparable with the basal insulin analogs and human NPH insulin.[13]

Based on reviews of more recent clinical trials, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) concluded in their updated treatment guidelines that "Use of NPH as a basal insulin has been superseded by the synthetic analogues insulin glargine and insulin detemir, which provide a relatively peakless profile for approximately 24 hours and yield better reproducibility and consistency, both between patients and within patients, and a corresponding reduction in the risk of hypoglycemia."[14] However, one meta-analysis found only marginal benefits with basal insulin analogs in terms of glycosylated hemoglobin (A1C) reduction compared with that seen with NPH insulin (weighted mean difference, -0.05% insulin glargine vs human NPH insulin; 0.13% insulin detemir vs human NPH insulin) and inconsistent benefits with respect to hypoglycemia.[15]

The same meta-analysis found minimal differences between rapid-acting insulin analogs and short-acting regular human insulin with respect to A1C reduction (weighted mean difference, -0.03% lispro vs regular human insu-

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lin; -0.09% aspart vs regular human insulin) and the risk of hypoglycemia in patients with T2DM.[15] Another meta-analysis found a significantly greater reduction in A1C overall with rapid-acting insulin analogs (0.10%; *P*=.037) compared to regular human insulin; the superiority was significant in patients treated with prandial insulin administered 3 times a day but not 2 times a day.[16]

No significant difference between rapid-acting analogs and regular human insulin was observed in the rate of severe hypoglycemia (odds ratio, 0.61, favoring analogs).[16] The updated AACE/ACE guidelines do not recommend the use of regular human insulin because its time course of action does not adequately mimic the normal physiologic profile. Improper timing of regular insulin administration can lead to suboptimal postprandial control, while stacking (ie, accumulation) of insulin, as might occur with frequent dosing to correct hyperglycemia, can result in hypoglycemia.[14] These issues are less apparent with rapid-acting insulin analogs, which have a faster onset and shorter duration of biological action than regular human insulin. The AACE/ACE guidelines state that "rapid-acting insulin analogues are superior to 'regular human insulin' and provide a better, safer alternative."[14]

Cost considerations

Cost is an important consideration in managing patients with T2DM. When considering the cost of medications, insulin analogs are more expensive than human insulin (approximately twice the cost), with the magnitude of difference dependent on the pharmacy where purchased. This may have important implications for a person with no insurance or a high copay. The discussion of cost is incomplete, however, without considering the relative impact of the different therapies on health outcomes.

Two analyses of the cost-effectiveness of insulin analogs versus human insulin in patients with T2DM have reported the incremental costs per quality-adjusted life-year (QALY). QALY is a measure of the monetary value of an intervention in reducing disease burden (ie, morbidity and mortality); 1 QALY reflects 1 year lived free of disease burden. In one of these analyses, when fear of hypoglycemia was considered, insulin aspart was associated with an incremental cost of Can$4429 per QALY compared to regular human insulin.[17] For insulin lispro, the incremental cost was Can$12,115 per QALY. Compared to NPH insulin, the incremental cost for insulin glargine was Can$73,989 per QALY and Can$234,606 for insulin detemir. Thus, it can be concluded that the insulin analogs improve quality of life compared to human insulins, but at a higher cost.

The second analysis estimated that for insulin glargine compared to NPH insulin, the QALY ranged from US$8578 over 36 years to US$39,052 over 40 years. For insulin detemir versus NPH, costs would be reduced by US$2020 over 10 years.[18] The difference with insulin detemir was attributed primarily to anticipated reductions in complications, primarily nephropathy and retinopathy.

Role of insulin therapy—guideline recommendations

The recommended role of insulin in treating patients with T2DM varies somewhat based on current guidelines. According to the guidelines developed by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD), insulin is 1 of 2 well-validated options for managing patients with T2DM who do not achieve glycemic control with the combination of lifestyle and metformin, especially those with an A1C level >8.5% or symptoms secondary to hyperglycemia.[19] The other option is a sulfonylurea. Insulin is also recommended in combination with lifestyle management for patients with severely uncontrolled diabetes with catabolism.

The AACE/ACE guidelines take a different approach, with recommended treatment options based on a patient's A1C level and previous therapy.[14] For patients with an A1C ≤9.0%, insulin alone or with other agents is recommended if glycemic control is not achieved with dual or triple oral therapy. For patients with an A1C >9.0%, insulin should be used alone or with other agents if the patient is treatment-naïve but symptomatic, or if triple oral therapy has failed.

Target A1C goals

The target A1C goal for most patients according to the ADA and the AACE/ACE is <7.0%[20] and 6.5%,[14] respectively. These recommendations are based on results of the Diabetes Control and Complications Trial[21] and United Kingdom Prospective Diabetes Study,[22] both of which demonstrated a curvilinear relationship between A1C and microvascular complications. This relationship indicates that the greatest benefit in reducing complications results from moving from very high blood glucose levels to only modestly elevated levels. Further reduction of blood glucose levels to an A1C level <7% further reduces the risk of microvascular complications, but to a smaller absolute degree. At the same time, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that attempting to lower A1C to <6% is associated with an increased risk of hypoglycemia and cardiovascular death.[23] These results, combined with the clinical challenge of achieving near normal blood glucose levels, indicate that A1C goals need to be individualized. Aggressive management may be more appropriate for patients with a short duration of diabetes, a long life expectancy, and no significant cardiovascular disease. A less stringent A1C goal might be appropriate for patients with long-duration T2DM, limited life expectancy, a history of severe hypoglycemia,

TABLE 1 Results of the Treating-to-Target in Type 2 Diabetes (4-T) trial[25,38]

	Biphasic	Prandial	Basal	P Value		
				Biphasic vs Prandial	Biphasic vs Basal	Prandial vs Basal
Baseline	N=235	N=239	N=234			
A1C, %	8.6	8.6	8.4			
Weight, kg	86.9	84.9	85.5			
Metformin + sulfonylurea, n	221	227	224			
1 Year	N=235	N=238*	N=234			
A1C, %	7.3	7.2	7.6	0.08	<.001	<.001
Δ A1C, %	-1.3	-1.4	-0.8	NR	NR	NR
Patients with A1C ≤7.0%, %	41.7	48.7	27.8	0.08	<.001	<.001
Δ Weight, kg	4.7	5.7	1.9	.005	<.001	<.001
Hypoglycemia requiring third-party assistance, %	4.7	6.7	1.7	NR	NR	NR
Hypoglycemia, events/patient-year	5.7	12.0	2.3	NR	NR	NR
3 Years	N=235	N=239	N=234			
A1C, median, %	7.1	6.8	6.9	0.28	0.67	0.52
Patients with A1C ≤7.0%, %	49.4	67.4	63.2	<.001	0.02	0.22
Δ Weight, kg	5.7	6.4	3.6	.21	.005	<.001
Insulin dose, units/kg/d	0.78	0.94	1.03	.05	<.001	.07
Hypoglycemia requiring third-party assistance, %	2.6	2.1	0.9	NR	NR	NR
Hypoglycemia, events/patient-year	3.0	5.5	1.7	NR	NR	NR

A1C, glycosylated hemoglobin.

*One patient had insufficient data.

advanced microvascular or macrovascular disease, or extensive comorbidities, and in whom an A1C <7.0% has been difficult to attain despite appropriate management.[24]

Initiating insulin therapy
Treating to Target in Type 2 Diabetes (4-T) trial
The benefits of adding insulin to existing glucose-lowering therapy were affirmed in the 4-T trial.[25] The 4-T trial was a 52-week open-label, controlled multicenter trial in which patients (N=708) with an elevated A1C level (7.0% to 10.0%) despite maximally tolerated doses of metformin and/or a sulfonylurea were randomized to treatment with biphasic insulin aspart twice daily, prandial insulin aspart 3 times daily before meals, or basal insulin detemir once or twice daily. Mean insulin doses increased steadily over the year, with most patients requiring the addition of a second type of insulin to achieve target glycemia by the end of 3 years. From a baseline of 8.4% to 8.6%, A1C levels at 52 weeks decreased most in the biphasic (-1.3%) and prandial (-1.4%) groups compared to the basal group (-0.8%) (**TABLE 1**). The proportion of patients with an A1C ≤7.0% was significantly higher in the biphasic and prandial groups (41.7% and 48.7%, respectively) than in the basal group (27.8%) (*P*<.001). Patients with a baseline A1C >8.5% were less likely to achieve an A1C ≤6.5% at 52 weeks in the basal group compared to the biphasic group (*P*=.007); there was no significant difference between the biphasic and prandial insulin groups. Weight gain and hypoglycemia frequency were lowest in the basal group. In summary, at 1 year, the initiation of biphasic or prandial insulin aspart reduced A1C levels more than the introduction of basal insulin detemir; however, the risks of hypoglycemia and weight gain were greater in the biphasic and prandial insulin groups than in the basal group.

Results of the 4-T trial at 3 years showed further reductions in median A1C level following intensification in all 3 groups, with no significant differences between treatments. However, significantly more patients in the intensified basal and prandial groups achieved an A1C level ≤7.0% (*P*<.001 vs biphasic). Body weight continued to increase after 1 year in all 3 groups, but the increase was significantly less in the basal group. Overall, hypoglycemia occurred most frequently in the

prandial group and least frequently in the basal group. Major hypoglycemia requiring third-party assistance occurred in 2.6% of patients in the biphasic group, 2.1% in the prandial group, and 0.9% in the basal group. Changes from baseline in systolic and diastolic blood pressure, low-density lipoprotein cholesterol, and triglycerides were not significant in any of the groups. However, high-density lipoprotein cholesterol increased significantly in all 3 groups (*P*=.03 between groups): biphasic, by 1.2 mg/dL; prandial, by 2.3 mg/dL; and basal, by 2.3 mg/dL. In contrast to results at 1 year, initiation and intensification of prandial insulin aspart or basal insulin detemir provided better blood glucose control than did biphasic insulin. Overall, patients initially treated with basal insulin detemir experienced fewer hypoglycemic episodes and less weight gain.

Case Study

DK is a 71-year-old retired female with a 7-year history of T2DM. Her current A1C is 9.1% (7.8% a year ago), body mass index is 29 kg/m² (27.5 kg/m² a year ago), and creatinine clearance is 65 mL/minute. She has taken metformin and glimepiride for many years (currently 1000 mg twice daily and 8 mg once daily, respectively). Acarbose 50 mg 3 times daily was added 7 months ago. DK reports that she occasionally forgets to take her medications; review of her pharmacy claims database indicates good adherence. DK has no history of cardiovascular disease. She had a hip fracture 9 months ago and resumed her normal activities within the past month or so, including a half-mile walk almost every day.

Options for use in combination with metformin include insulin, a glucagon-like peptide-1 receptor (GLP-1R) agonist, and a thiazolidinedione (TZD). Of these, only insulin would be expected to provide the necessary reduction in blood glucose. A GLP-1R agonist would be a consideration to promote weight loss and might be especially beneficial in conjunction with other efforts to improve her ambulation. A TZD would be a poor choice because of her history of hip fracture. The patient agrees to begin insulin therapy.

Selecting the type of insulin for initial treatment

In keeping with the results of the 4-T trial, the ADA/EASD guidelines recommend basal insulin when initiating insulin therapy.[19] The general concept is to first correct the fasting hyperglycemia with 1 injection of a basal insulin, and then address postprandial hyperglycemia, if needed, with other insulin options. Along with basal insulin, the AACE/ACE guidelines recommend other insulin options, such as biphasic, basal-bolus, or prandial (bolus) insulin.[14] Factors such as distribution of glycemic burden (fasting vs postprandial), physical activity, eating habits, and patient preference, including cultural issues, must be considered when selecting an insulin regimen. Considering all insulin options available, initiating insulin therapy with basal insulin is a relatively safe, easy, and less threatening option for patients with T2DM.

Initiating basal insulin

Basal insulin can be initiated using several approaches, including:

> 1. Treat-to-target approach: administer 10 units of basal insulin once daily.[9] If the initial pre-breakfast or pre-dinner plasma glucose level is <126 mg/dL or the patient's body mass index <26 kg/m², a lower starting dose of 6 units is appropriate.[11]
> 2. ADA/EASD recommendations: start with 0.2 units/kg.[19]

When insulin is begun, the patient's current therapies should be reviewed and adjusted to optimize glycemic control, minimize therapeutic side effects, and simplify the regimen.

Although basal insulin can be initiated twice daily (eg, before breakfast and dinner), once-daily administration at bedtime carries several advantages, such as simplifying the regimen and reducing the amount of weight gain, and it is by far the preferred option. Initial insulin doses need to be adjusted based on fasting plasma glucose (FPG) levels. The dose of basal insulin can be increased using any of a number of physician- or patient-driven titration algorithms[9,26,27] (**TABLE 2**).

Case Study

DK begins insulin therapy with basal insulin 10 units once daily at bedtime. Using the 303 algorithm[27] (**TABLE 2**) over 7 months, DK is now taking 31 to 34 units (0.43 units/kg) of basal insulin at bedtime. Her current A1C is 7.4%. Over the past 3 weeks, her FPG has ranged from 94 to 133 mg/dL, and her postprandial glucose (PPG) 2 hours after dinner from 162 to 224 mg/dL. She has not experienced any episodes of symptomatic hypoglycemia, although on 2 or 3 occasions her FPG has been 65 to 70 mg/dL. Her current weight is 80.2 kg (79 kg at the start of insulin therapy).

Despite her FPG level being well controlled, DK's A1C level is still above the target of ≤7.0%, due to her frequent postprandial hyperglycemia.

Intensifying insulin therapy

The effects of glucose-lowering therapy, including insulin, should be monitored with periodic A1C testing and self-monitoring of blood glucose (SMBG) to assess both distribution of glycemic burden and hypoglycemia risk. If the target A1C level has not been achieved within 2 to 3 months with optimal doses of current therapy, intensification is needed. In most

TABLE 2 Treat-to-target approaches to initiating basal insulin

Riddle et al[9]		Davies et al[26]			Meneghini et al[27]	
Start with 10 IU/d bedtime basal insulin and adjust weekly		Start with 10 IU/d* bedtime basal insulin and adjust weekly (physician-directed) OR Start with a dose equivalent to the highest FPG over the previous 7 days and adjust every 3 days (patient-managed)			Start with basal insulin once daily and adjust every 3 days	
Mean of self-monitored FPG values from preceding 2 days	↑Insulin dose (IU/d)	Mean of self-monitored FPG values from preceding 3 days	↑Insulin dose (IU/d) (physician-directed)	↑Insulin dose (IU/d) (patient-managed)	Mean of self-monitored FPG values from preceding 3 days	Change in insulin dose (IU/d)
≥180 mg/dL	8	≥180 mg/dL	6-8	2	>110 mg/dL	3
140–180 mg/dL	6	140–179 mg/dL	4	2	80–110 mg/dL	0
120–140 mg/dL	4	120–139 mg/dL	2	2	<80 mg/dL	-3
100–120 mg/dL†	2	100–119 mg/dL	0-2	0-2		

FPG, fasting plasma glucose.

*In insulin-naïve patients.

†Small insulin dose decreases (2–4 units/day per adjustment) were allowed if severe hypoglycemia (requiring assistance) or plasma-referenced glucose <56 mg/dL was documented in the preceding week.

treat-to-target studies using once-daily basal insulin, the dose of insulin averages between 0.4 and 0.6 units/kg per day.[9,26,28,29] Increasing basal insulin doses beyond this range might not be as effective as the addition of prandial insulin to cover 1 or more meals. There are several approaches for intensifying basal insulin therapy.

Addition of prandial insulin

When considering adding prandial (bolus) insulin to existing basal insulin therapy, the question is how many mealtime doses of prandial insulin should be started, and with which meal(s)? Recent investigations provide practical information about adding prandial insulin in a staged fashion beginning with 1 dose per day.[30-33]

Lankisch et al showed that in patients suboptimally controlled on basal insulin glargine, the addition of a single injection of insulin glulisine at breakfast or at the meal with the highest postprandial excursion was equally effective in reducing the A1C level.[30] In patients taking glulisine at breakfast, the A1C level decreased from 7.35% at baseline to 7.03% at 24 weeks; in those taking glulisine at the main meal, it decreased from 7.29% to 6.94%. The dose of glulisine increased from 4.6 units at baseline to 11.2 units at 24 weeks in the breakfast group and from 5.0 units to 12.0 units in the main meal group. Hypoglycemia occurred at similar rates in both groups.

A second study evaluated the administration of 1, 2, or 3 prandial injections of insulin glulisine in patients whose A1C values were still above target following 14 weeks of insulin glargine optimization.[31] The dose of insulin glargine after the

14-week run-in was similar between the group achieving the A1C target and the group remaining in suboptimal control (0.55 units/kg/day). The initial dose of glulisine administered before each meal was calculated as 10% of the basal insulin dose. While reductions in A1C at the end of the study were comparable among the 3 groups (-0.44%, -0.36%, and -0.43% in the 1-, 2-, and 3-injection[s]-per-day groups, respectively), 45% of patients in the 3-injection group achieved an A1C <7.0% compared to 29% in the once-daily and 33% in the twice-daily group. Severe hypoglycemia was more frequent in the group taking glulisine 3 times daily (16%) compared to the once-daily (7%) and twice-daily (8%) groups.

A third study explored the sequential addition and titration of 1, 2, or 3 prandial insulin doses using a simplified (SimpleSTEP) versus a more data-driven (ExtraSTEP) approach.[33] Following a 3-month optimization period with basal insulin detemir (mean dose 0.6 units/kg/day), insulin aspart was added to the first meal, starting with a dose of 4-6 units, with a second and third prandial insulin aspart injection added after 12 and 24 weeks if A1C values remained ≥7%. The SimpleSTEP group started prandial insulin aspart doses before the largest meal(s), as subjectively identified by patients, and adjusted the aspart dose based on the finger-stick glucose level before the subsequent meal or at bedtime for pre-dinner aspart. The ExtraSTEP group started prandial insulin aspart before the meal with the largest PPG increment, and adjusted the dose based on the 2-hour PPG level (**TABLE 3**). A1C reductions after 48 weeks averaged 1.2% and were similar between the 2 groups; most of the reduction

TABLE 3 Sequential addition and titration of 1, 2, or 3 prandial insulin doses using the SimpleSTEP or ExtraSTEP approaches[33]

Basal Insulin Detemir Titration		SimpleSTEP Prandial Aspart Titration			ExtraSTEP Prandial Aspart Titration	
Pre-breakfast PG level (mg/dL)	Insulin detemir adjustment (units)	Premeal PG level (mg/dL)	Bedtime PG level (mg/dL)	Insulin aspart adjustment (units)	2-hour post-meal PG level (mg/dL)	Insulin aspart adjustment (units)
<56*	-4	<72*	<72*	-2	<72*	-2
56–71*	-2	72-108	72-144	0	72-144	0
72–108	0	109-162	145-180	+2	145-180	+2
109–144	+2	>162	>180	+4	>180	+4
145–162	+4					
>162	+6					
Insulin detemir titrated based on average of 3 pre-breakfast PG measurements.		Insulin aspart added to largest self-reported meal. Titration based on pre-meal/bedtime PG levels; 4 daily PG measurements.			Insulin aspart added to meal with largest PG increment. Titration based on post-meal PG levels; 6 daily PG measurements.	

PG, plasma glucose. *One or more PG values <72 mg/dL without obvious explanation.

in A1C (~1.0%) was observed with the addition of the first 2 prandial insulin boluses. While there was no difference in hypoglycemic episodes or weight gain between the 2 groups, sequential addition of prandial insulin doses did increase the risk of nonsevere hypoglycemia.[33]

Case Study

DK adds 4 units of prandial insulin before dinner to her regimen, using the SimpleSTEP approach, and adjusts her pre-dinner insulin dose to 12 units, based on her bedtime plasma glucose; her bedtime PPG level over the past week has ranged from 115 to 156 mg/dL.

Switching to basal-bolus or premix insulin

The PREFER study compared intensification of therapy with either basal-bolus or biphasic premix insulin.[34] Patients with suboptimal glycemic control on oral glucose-lowering therapy ± once-daily basal insulin were randomized to basal-bolus therapy (n=537) or biphasic premix insulin (n=178). The basal-bolus group received insulin detemir once daily and insulin aspart 3 times daily before each meal, with the insulin aspart dose divided in 3:1:2 ratios among breakfast, lunch, and evening meals, respectively. Patients in the biphasic premix group received 0.2 units/kg insulin aspart 70/30 before breakfast and 0.1 units/kg before the evening meal. Oral glucose-lowering agents were discontinued in all patients. Insulin doses were titrated using a predefined algorithm.

At study end, prandial doses in the basal-bolus group were evenly distributed among the 3 meals (0.173, 0.140, and 0.176 units/kg before breakfast, lunch, and dinner, respectively), with the mean detemir dose at 0.353 units/kg. In the biphasic group, the breakfast and dinner doses also were evenly distributed, at 0.315 and 0.316 units/kg, respectively. The mean A1C reduction in the basal-bolus group was statistically greater than that seen in the premix group (8.52% to 6.96% vs 8.40% to 7.16%; *P*=.0052). Patients previously treated with basal insulin experienced relatively greater A1C reductions with basal-bolus insulin than with biphasic insulin (1.21% vs 0.75%, respectively; *P*=.0129). Insulin-naïve patients had similar A1C reductions with both regimens (1.69% vs 1.42%, respectively). Eleven episodes of major hypoglycemia requiring third-party assistance occurred in 5 patients in the basal-bolus group; none occurred in the biphasic group. Incidence rates for minor and nocturnal hypoglycemia were similar between groups. Body weight increased 2.4 kg in the basal-bolus group and 2.1 kg in the biphasic group. The results of this study suggest that patients previously treated with insulin may benefit more from basal-bolus insulin therapy, whereas insulin-naïve patients may benefit equally with both regimens, although biphasic insulin may be more convenient.

Calculating basal-bolus insulin doses

Switching to basal-bolus insulin therapy from basal insulin or premix insulin therapy requires a few simple steps. The first step is to estimate the total daily dose (TDD) of insulin the patient needs either by multiplying the patient's weight in kilograms by 0.5 units/kg/day if the patient is currently using basal insulin, or by calculating the total dose of premix insulin

currently being administered. Next, the TDD is divided in half. Of the TDD, 50% covers the basal insulin requirement and the other 50% the bolus (prandial) insulin requirement. For the prandial component, approximately one-third (or 10% to 20% of the TDD) is taken at each of the 3 daily meals. Finally, a supplemental (correction) scale is calculated, which estimates the fall in blood glucose per unit of rapid- or short-acting insulin.

The correction factor can be calculated by dividing 1800 for rapid-acting insulin or 1500 for regular human insulin by the TDD.[35] For example, if using a rapid-acting insulin analog and an estimated TDD of 60 units, 1 unit of insulin should lower the plasma glucose by approximately 30 mg/dL (1800 ÷ 60 units = 30 mg/dL). If the pre-meal target is set at 130 mg/dL, for every 30 mg/dL increment above 130 mg/dL, the patient would add 1 unit of a rapid-acting analog, usually to a meal bolus, to correct the hyperglycemia over the next 4 to 5 hours.

While the approach just described is reasonable to calculate initial basal and bolus (prandial) insulin doses, adjustment will be necessary based on the patient's glycemic response, as measured by SMBG. The FPG level measured before breakfast should be used to adjust the dose of basal insulin. The pre-lunch blood glucose level should be used to adjust the subsequent breakfast prandial insulin dose, the pre-dinner level to adjust the subsequent lunchtime prandial insulin dose, and the bedtime level to adjust the subsequent dinner prandial insulin dose.

Although carbohydrate counting and matching carbohydrate intake to the insulin dose remains the mainstay of prandial insulin management in type 1 diabetes mellitus, this approach requires a great deal of effort and might not be feasible for all patients with T2DM. A fixed (simple) versus flexible (based on carbohydrate counting) prandial insulin approach in patients with T2DM was evaluated in a 24-week open-label study. Doses of insulin glargine and insulin glulisine were adjusted weekly based on SMBG.[36] Participants were further randomized to either a simple algorithmic approach, using set doses of glulisine to be taken before each meal, or to an insulin-to-carbohydrate ratio, adjusting their glulisine dose at each meal based on the amount of carbohydrates they expected to consume; this latter group was also given a correction (supplemental) scale to correct hyperglycemia. At study end, the A1C level decreased similarly in both groups (8.1% to 6.7% in the fixed group and 8.3% to 6.5% in the flexible group). Weight gain was observed in both groups (3.6 kg and 2.4 kg, respectively). While the rates of hypoglycemia were low in both groups, significantly more patients in the flexible group experienced symptomatic hypoglycemia, measured as blood glucose <50 mg/dL (8.0 vs 4.9 events/patient-year; P=.02).

Another basal-bolus study in patients with poorly controlled T2DM (N=373) treated with oral glucose-lowering medications, long-acting or premix insulin, or a combination compared a simple fixed-dose regimen of prandial insulin with SMBG performed 1 to 2 days per week to a flexible regimen with extensive patient education, daily SMBG, carbohydrate counting, and patient supplemental dose adjustment.[37] Basal insulin detemir and metformin were added to either regimen based on clinical need as determined by the investigator. The mean total prandial insulin aspart dose, basal insulin detemir dose, and proportion of patients treated with insulin detemir were similar in both groups. A1C levels decreased from a baseline of 8.2% to 7.0% in the fixed group and 6.7% in the flexible group (P=.0074). The incidence of hypoglycemia was low and similar in both groups (0.08 vs 0.106 events/patient-week, respectively), with only 1 episode of severe hypoglycemia occurring in each group. ■

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Physician-patient communication in diabetes care: Focus on injectables

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The multifaceted nature of type 2 diabetes mellitus (T2DM), the myriad issues that patients encounter, and the fact that T2DM is primarily a chronic disease requiring patient self-management underscore the roles of the primary care physician as coach and facilitator. As a coach, it is vitally important that the physician communicates effectively and develops a strong partnership with the patient. As a facilitator, the physician can involve other members of the health care team to ensure that patients receive help and support to effectively manage this highly complex and demanding chronic illness. Because effective communication is a cornerstone of creating and sustaining partnerships with patients, this article provides insights about how to accomplish this goal both in general and specifically in the treatment of T2DM with insulin and the glucagon-like peptide-1 receptor (GLP-1R) agonists.

Strategies for effective communication

Improved health outcomes are increasingly emphasized, yet in T2DM these outcomes are largely in the hands of the patients themselves. As noted in a recent study, patient-related factors contribute 98% of the effects on glycemia, while physician-related factors contribute just 2%.[1] Although some patient factors, such as race or age, cannot be changed, it may be possible to influence other factors, such as patient knowledge and behavior, through effective physician-patient communication. In addition, discussion and education with other patients may be helpful.[2,3]

A physician's communication style has a strong impact on a patient's level of trust in her or him and directly correlates with better medication-taking behaviors.[4,5] Patient participants in the Diabetes Attitudes, Wishes, and Needs (DAWN) study reported that diabetes-related distress interfered with self-management and behavioral efforts and that patients want their physicians to help deal with these issues.[6] More than 80% of health care professionals who participated in the DAWN study agreed that psychosocial issues were the main source of self-management problems. Both groups indicated that these issues are rarely discussed during clinical care visits.

Strategies that enhance communication include showing empathy toward and actively listening to patients and using an open-ended rather than a closed-ended declarative communication style. Also, a collaborative style in lay language often facilitates discussion so that the patient is more willing to share information.[7] The Ask, Listen, Empathize approach is a nondirective communication style based primarily on active listening.[8,9] With this approach, the role of the provider is to ask questions to elicit the patient's concerns, barriers to treatment, or problems related to the disease; listen to the patient's

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TABLE 1 Resources for professionals

American Association of Clinical Endocrinologists http://www.aace.com
American Association of Diabetes Educators https://www.diabeteseducator.org/ProfessionalResources/ products/index.html
American Diabetes Association http://professional.diabetes.org/ResourcesForProfessionals. aspx?cid=60378&typ=17
National Diabetes Education Program http://ndep.nih.gov/
National Institute of Diabetes and Digestive and Kidney Diseases http://www2.niddk.nih.gov/HealthEducation/InteractiveTools/

responses without offering opinions, judgments, or advice; and then empathize and encourage further reflection and discussion. The goal is to help patients gain clarity about an issue and develop their own solutions.

A counseling strategy that has shown some success is motivational interviewing (MI).[10-13] MI is nonjudgmental, empathetic, and encouraging, without any attempt to motivate, convince, persuade, or advise the patient.[12,13] Training is generally required to use this method effectively. More information about MI can be found at http://www.motivationalinterview.org/.

A source of concern for many physicians is how to involve patients in their own care through effective communication and still accomplish the other tasks required during a routine, and often very short, visit. It may seem counterintuitive, but strategies such as addressing the patient's psychosocial needs can actually shorten the visit.[14] Communication strategies[8,9] to use throughout the visit are as follows:

At the start of the visit
- Establish the agenda. Begin by saying, "I have about 15 minutes to spend with you today, and there are some things I need to cover. I also want to make sure you get what you need from this visit, so what questions or concerns would you like to address today?"
- Another approach is to ask the patient to respond to a brief open-ended questionnaire, such as the Diabetes Concerns Assessment form,[15] while waiting to be seen. This form is found at http://www.med.umich.edu/mdrtc/profs/index.htm#conc.
- To ascertain the patient's fears and motivation for change, ask, "What is hardest for you in managing your diabetes?"

During the visit
- Elicit and respond to emotional issues related to diabetes by asking, listening, and empathizing.
- Avoid the temptation to set goals, offer advice, or solve prob-

lems *for* rather than *with* the patient.
- Solicit the patient's opinions on laboratory and other outcome measures before offering your own. Use discussion about the patient's experiences and your findings as teachable moments. For example, during a foot exam, point out areas that the patient needs to pay close attention to.
- Offer referrals for self-management education, nutritional therapy, and ongoing self-management support.

At the end of the visit
- Ask the patient to identify 1 thing to do differently to better manage diabetes, or ask the patient to set a more formal behavioral goal.
- Ask the patient to summarize the visit.
- Jointly jot down a brief list of decisions made during the visit.

When treatment changes
Making the move from lifestyle management and oral medications to injectable therapies is often difficult for patients.[16,17] One strategy to ease this transition is to present to the patient, at the time of diagnosis, all treatment options, including lifestyle management plus metformin, which is typically initiated first; other oral medications; and injectable medications.[18,19] Point out that changes in therapy are not signs that the patient is getting sicker or is a failure at self-managing, which can discourage the patient,[16,17] but rather that these changes are simply a response to the body's declining insulin production.

Insulin—new formulations and devices
Because many patients are concerned about the impact of insulin and injections on their lifestyle and quality of life, it may help to provide information about benefits of and issues related to the use of insulin, especially compared to other options, and how to manage common barriers and side effects.[16,17] This can help patients make informed treatment choices in the context of their own lifestyle, other priorities and demands, and diabetes care goals. Referring the patient to other members of the health care team (eg, a nurse, pharmacist, registered dietitian, or certified diabetes educator) for diabetes self-management education and support can be indispensable. Numerous educational resources are available online as well (**TABLE 1**).

Although true needle phobia is extremely rare,[16] a common initial patient comment about injectable therapies is, "I don't like needles."[18] The first step in addressing the patient's resistance is to better understand its true nature by asking, "What about needles or taking insulin bothers you?" Since some patients are unfamiliar with the pen devices and ultra-fine needles, showing them a pen device, demonstrating its use, and having them self-administer a dose in the office can be helpful.

Many diabetes patients have some familiarity with insu-

TABLE 2 Patient assistance programs

Glucagon-like receptor-1 agonists
• Exenatide http://www.amylin.com/products/patient-assistance-program.htm
• Liraglutide http://www.novomedlink.com/diabetes/patient-assistance-program.aspx
Rapid-acting insulin analogs
• Insulin aspart http://www.novomedlink.com/diabetes/patient-assistance-program.aspx
• Insulin glulisine https://patientassistanceprogram.sanofi-aventis.us/Faq.aspx
• Insulin lispro http://lillytruassist.com/Pages/Index.aspx
Short-acting regular human insulin
• Regular human insulin http://lillytruassist.com/Pages/Index.aspx
Intermediate-acting human insulin
• NPH insulin http://lillytruassist.com/Pages/Index.aspx
Long-acting insulin analogs
• Insulin detemir http://www.novomedlink.com/diabetes/patient-assistance-program.aspx
• Insulin glargine https://patientassistanceprogram.sanofi-aventis.us/Faq.aspx
All medications
• Partnership for Prescription Assistance http://www.pparx.org

lin preparations and devices from experiences with friends and family. This familiarity could lead them to perceive insulin treatment negatively; they may even believe that insulin causes long-term complications or death.[16,17] Even those with more positive perceptions may not know how currently available insulin preparations and devices compare to those of a decade ago or earlier. Based on an assessment of the patient's perceptions, points that may be worth emphasizing are the purity of today's synthetic insulin preparations and their low risk of allergic reactions. It also may be worth noting that insulin, particularly the insulin analogs, is the most effective, natural, and physiologically aligned glucose-lowering therapy available.

The GLP-1R agonists

Because the GLP-1R agonists are a relatively new class of agents, patients may benefit from learning how they work, their effect on blood glucose, and their expected effects. A potential benefit of the GLP-1R agonists is that less blood glucose monitoring may be needed than with insulin regimens, which require multiple injections and self-adjustments. Their low incidence of hypoglycemia, particularly severe hypogly-

cemia, should be highlighted.[16,17] Teaching patients how to prevent and manage hypoglycemia with whatever treatment regimen they are on can further ease their concerns.

Discussing the nonglycemic effects of GLP-1R agonists is also important to help patients make informed decisions regarding their treatment. For example, since fear of weight gain is common with insulin therapy,[16,17] the 1- to 4-kg weight loss often experienced by patients treated with a GLP-1R agonist will likely be viewed as a desirable benefit. Other nonglycemic effects of the GLP-1R agonists worth discussing include improvement in the lipid profile, particularly the triglyceride level, and possible benefits for pancreatic β-cell function. Insulin also improves the lipid profile, particularly high-density lipoprotein cholesterol and triglyceride levels.

Cost of therapy should be discussed before initiating any regimen. The cost of a GLP-1R agonist ranges from $6 to $14 per day (www.drugstore.com). Since a patient may hesitate to raise the issue of cost, ask about insurance coverage and if cost is a concern. Patient assistance programs exist for those who qualify (**TABLE 2**). ∎

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