Optimizing the Use of Glucagon-Like Peptide 1 Receptor Agonists in Type 2 Diabetes: Executive Summary

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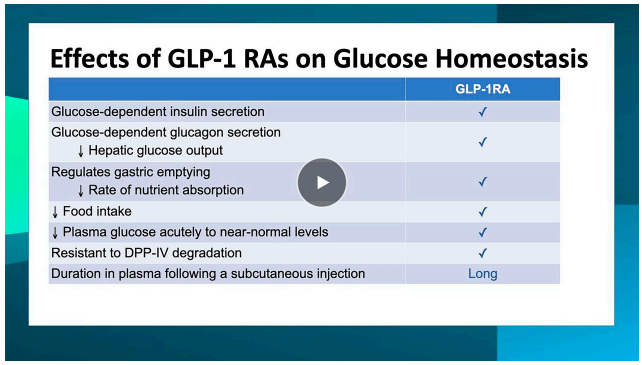
The type 2 diabetes treatment algorithm recommended by the American Diabetes Association (ADA) has undergone major changes in the past 5 years based on a greater understanding of the pathophysiology of diabetes and extensive investigation of the clinical profiles of glucose-lowering medications (1,2). As a consequence, the glucagon-like peptide 1 (GLP-1) receptor agonists are now recommended in several clinical situations for people with type 2 diabetes (2).

This article is intended to serve as an executive summary for a series of videos now available on the *Clinical Diabetes* website, in which the authors, who each provide care to people with type 2 diabetes, outline the clinical profile of GLP-1 receptor agonists, including the recent investigations regarding their cardiovascular (CV) safety and benefits on which the ADA's recommendations for their use are based. In addition, these clinicians provide insights into best practices to promote improved self-management by incorporating GLP-1 receptor agonist therapy into the treatment plan for people with type 2 diabetes. The video series described below is available in its entirety at https://diabetesjournals.org/clinical/pages/glp-1_receptor_agonists_in_type_2_diabetes.

Video Summaries

Clinical Profile (Video 1)



Video 1. The Unique Profile of GLP-1 Receptor Agonists. Available from https://bcove.video/3Ncvpvj.

The incretin system plays a central role in glucose homeostasis, largely because of the action of GLP-1, a gut-derived neuroendocrine hormone that stimulates insulin secretion in response to oral glucose. In people with type 2 diabetes, the incretin response is diminished (3). Administration of a GLP-1 receptor agonist restores the incretin effect, resulting in increased insulin secretion and lower blood glucose levels (4). Because the effects of GLP-1 receptor agonists on insulin and glucagon secretion are glucose dependent, these agents are associated with a low risk of hypoglycemia (2). This characteristic is a key difference in comparison with insulin and contributed to the ADA's recommendation that a GLP-1 receptor agonist be considered before insulin for people who require injectable therapy (2).

In addition to their unique glycemic profile, GLP-1 receptor agonists possess several nonglycemic benefits. Among these is their ability to promote satiety, thereby leading to a reduction in food intake (5). Consequently, these agents promote weight loss in most people with type 2 diabetes (2).

GLP-1 receptor agonists are categorized as short-acting (exenatide and lixisenatide) or long-acting (dulaglutide, exenatide extended-release, liraglutide, and semaglutide). Although all GLP-1 receptor agonists reduce

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https://doi.org/10.2337/cd22-0020

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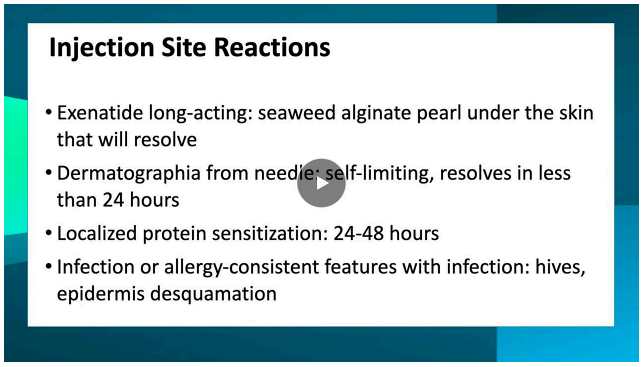
both fasting and postprandial blood glucose levels, the short-acting agents produce a greater reduction in postprandial glucose, whereas the long-acting agents result in greater reduction in fasting plasma glucose (6). Other differences among the GLP-1 receptor agonists (e.g., dosing frequency, route of administration, gastrointestinal [GI] side effects, and CV benefits) are considerations for treatment individualization.

Collectively, the numerous glycemic and nonglycemic characteristics of the GLP-1 receptor agonist class of medications provide a strong rationale for their use in the treatment of many people with type 2 diabetes, as recommended by the ADA.

Safety and Tolerability (Video 2)



Video 2. Safety and Tolerability of GLP-1 Receptor Agonists. Available from https://bcove.video/3FCeq2D.

Because GLP-1 is a gut-derived neuroendocrine hormone, it is not surprising that GI side effects—principally nausea and vomiting—are commonly observed in people treated with a GLP-1 receptor agonist (2). Fortunately, these GI effects occur most often at treatment initiation and are generally transient, although they may result in treatment discontinuation for some people. The GI side effects can be minimized in several ways, including initiating treatment at the lowest dose and titrating the dose based on tolerability. People taking a GLP-1 receptor agonist should be reminded to limit consumption of higher-fat and liquid carbohydrate foods and to stop eating when they begin to feel full.

Injection site reactions were reported when the GLP-1 receptor agonist class was introduced, specifically with exenatide (in its primary weekly formulation) (7). Fortunately, these reactions have been found to be unlikely with the other GLP-1 receptor agonists, although rare allergic reactions can occur (8).

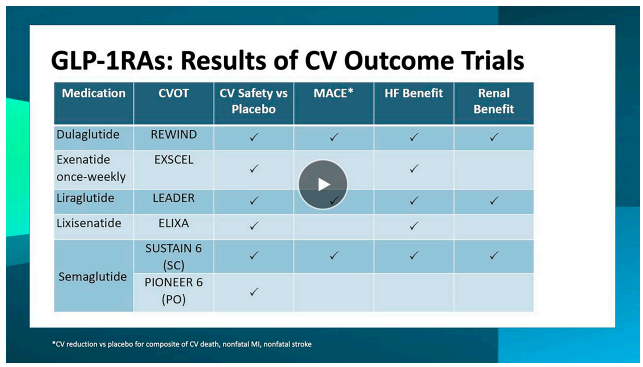
Medullary thyroid C-cell tumors were observed in preclinical trials involving nonprimate rodents administered a GLP-1 receptor agonist (9). The explanation for this finding was thought to be hyperstimulation of the GLP-1 receptors, which are found in much higher density in rodent than human thyroid C-cells, with administration of a GLP-1 receptor agonist (10). This observation led to the inclusion of a boxed warning in the prescribing information for all agents in this drug class.

Surveillance for medullary thyroid cancer has been ongoing since 2010, when the Medullary Thyroid Carcinoma Surveillance Study (11) was launched. A key goal of this study is to monitor the annual incidence of medullary thyroid cancer in the United States to identify any possible increase related to the introduction of long-acting GLP-1 receptor agonists. Current evidence indicates that GLP-1 receptor agonists do not increase the risks of other cancers (12).

There remains a lack of data demonstrating that GLP-1 receptor agonist therapy causes pancreatitis (13). In fact, ongoing investigations, including the numerous multiyear cardiovascular outcomes trials (CVOTs) that have been conducted in recent years, have demonstrated no increased risk of pancreatitis with GLP-1 receptor agonist use. It is important to point out that people with type 2 diabetes are at an increased risk of pancreatitis (14). It is unknown whether those with a history of pancreatitis are at higher risk for development of pancreatitis with GLP-1 receptor agonist use. If pancreatitis is suspected in a person treated with an agent from this drug class, the GLP-1 receptor agonist should be discontinued and appropriate management should be initiated.

Patient education resources related to safety may be found at the Association of Diabetes Care & Education Specialists and the Mayo Clinic websites (15,16).

Cardiovascular Safety and Benefits (Video 3)



Video 3. Cardiovascular Safety and Benefits of GLP-1 Receptor Agonists. Available from https://bcove.video/39lM2FV.

In 2008, the U.S. Food and Drug Administration (FDA) began to require that any new medication for lowering

blood glucose in people with type 2 diabetes demonstrate no increase in CV risk (17). The FDA end point requirement for these CVOTs was a three-point composite of major adverse cardiovascular events (MACE) that included CV death, nonfatal myocardial infarction, and nonfatal stroke. The three-point MACE was chosen to simplify the statistical analysis of CV safety and benefit using hard clinical end points. The CVOTs also included a variety of secondary end points involving heart failure and kidney events. It is important to recognize that the results of the CVOTs cannot be directly compared because of differences in study populations, including cardiovascular disease (CVD) history, and other factors.

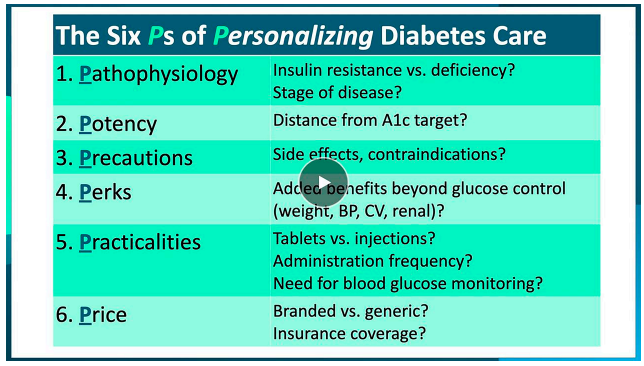
All of the GLP-1 receptor agonists have been shown to be noninferior to placebo as part of standard care with respect to their CV safety (18–23). In addition, dulaglutide, liraglutide, and injectable semaglutide were all shown to provide a CV benefit compared with placebo (i.e., superiority) as part of standard care, as demonstrated by a significant reduction in three-point MACE. Among the individual end points, dulaglutide and injectable semaglutide showed significant reductions in nonfatal stroke, and liraglutide was shown to reduce CV death. These three GLP-1 receptor agonists were also demonstrated to significantly reduce composite renal end points.

Recent evidence from the AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes) trial showed that the investigational exendin-based GLP-1 receptor agonist efpeglenatide significantly reduced MACE in people with type 2 diabetes and either a history of CVD or current kidney disease plus at least one other CV risk factor (24).

The CVOT results for the GLP-1 receptor agonists dulaglutide, liraglutide, and injectable semaglutide contributed to important shifts in the treatment of people with type 2 diabetes. First, the treatment goal has been modified from a focus on specific end points (i.e., blood glucose, blood pressure, blood lipids, and body weight) to a focus on CV risk reduction (2,25). Importantly, CV risk reduction relates to CV events (e.g., CV death, nonfatal MI, and nonfatal stroke) rather than surrogate end points. Second, treatment algorithms from the ADA and American Association of Clinical Endocrinologists/America College of Endocrinology now place GLP-1 receptor agonists in a prominent role for treating people with established CVD (2,26). In addition, other medical specialists, such as cardiologists and nephrologists, have also embraced the use of GLP-1 receptor agonists in treatment recommendations for people with type 2 diabetes (27). The prescribing information for dulaglutide, liraglutide, and injectable semaglutide all include an indication for use in people with established CVD.

Collectively, these changes promote a more person-centered approach to type 2 diabetes management.

Strategies to Resolve Barriers (Video 4)



Video 4. Strategies to Resolve Barriers to GLP-1 Receptor Agonist Use. Available from https://bcove.video/3w3pXoD.

Person-centered care encourages engagement and optimal long-term self-management by people with diabetes. Shared decision-making is recommended as a means of facilitating person-centered care because it provides a structured approach enabling partnership in making treatment decisions (28). Empowering people with diabetes to make treatment decisions based on their preferences and values, guided by clinician insight, is a key objective of shared decision-making. Using the "six Ps" of personalizing diabetes care can be helpful in this process. This includes discussing pathophysiology, potency, precautions, perks, practicalities, and price of treatment options (29). Once an informed person with diabetes makes a treatment decision, the clinician plays a crucial role in supporting that decision.

Most people treated with a GLP-1 receptor agonist experience one or more GI side effects—typically nausea and/or vomiting—early in the course of treatment. It is important to counsel people that GLP-1 receptor agonist therapy promotes early satiety, which may be misinterpreted as nausea. Consequently, people should be advised to stop eating immediately when initial feelings of satiety occur. As noted earlier, several other strategies, including dosage titration (except with exenatide extended-release), can be used to minimize the occurrence and severity of GI side effects. People who experience protracted GI side effects during GLP-1 receptor agonist therapy should be advised to contact their prescriber so that appropriate steps can be taken to adjust

therapy if indicated and prevent dehydration, especially in those with or at risk for kidney problems.

Although concerns about injectable medications are well established among both people with diabetes and clinicians (30), clinicians should strive to be a catalyst for overcoming, rather than propagating, any concerns on the part of people with diabetes. One helpful strategy is to have people self-administer their first dose of an injectable GLP-1 receptor agonist in the clinic and then ask if they have any concerns with the experience. If so, the clinician can provide additional education or take further action as appropriate.

People with type 2 diabetes must be engaged in and committed to taking responsibility for the multiple tasks required for optimal management of this complex disease. For clinicians, it is vital to work with and support people with diabetes in finding—and modifying, as needed—a treatment plan that is not perceived as overly complex and that they can manage to achieve their individualized treatment goals. Because type 2 diabetes is a chronic disease that typically also affects family members, it is important to involve family and others who provide support for people with diabetes in both education and care processes. When skillfully practiced, shared decision-making can contribute to treatment decisions with which people with diabetes are comfortable and better able to incorporate into their daily life.

ACKNOWLEDGMENTS

The production of this video series and associated materials was funded by an educational grant from Novo Nordisk, Inc. Writing and editorial support in the preparation of this digital publication and executive summary was provided by Gregory Scott, PharmD, RPh, on behalf of the Illinois Academy of Family Physicians, Primary Care Metabolic Group, and Primary Care Education Consortium. The content for this article and the associated video series was produced according to the policies of the Accreditation Council for Continuing Medical Education. Novo Nordisk had no input into the topic, forum discussion, or any content for this article or its accompanying videos.

DUALITY OF INTEREST

J.A. serves as an advisor, consultant, and/or speaker for Alfa Sigma, AstraZeneca, Abbott Diabetes Care, Bayer, Eli Lilly, Gelesis, Novo Nordisk, and Sanofi. J.R.G. serves on speaker's bureaus and/or as a consultant to Abbott Diabetes Care, Boehringer Ingelheim, Eli Lilly, Intuity Technology, Novo Nordisk, and Xeris. D.F.K. serves on advisory boards and/or speaker's bureaus for Abbott Diabetes Care, Cequr, Dexcom, Eli Lilly, Novo Nordisk, Sanofi, and Xeris and has stock options in Pendulum. E.M. serves on advisory boards and/or speaker's bureaus or is a consultant to Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, and Novo Nordisk and has received research support from Abbott Diabetes Care and Pendulum. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

J.A. organized and structured the data. J.R.G. and D.F.K. researched the data. E.M. researched the data and provided case study details and ambulatory glucose profile reports. J.A. is the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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