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# Pharmacotherapeutic Approaches to Decrease Complications in Type 2 Diabetes Part 1: Glucagon-Like Peptide-1 Receptor Agonists

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***Abstract***

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder contributing to substantial morbidity and mortality. As the most readily accessible healthcare providers, pharmacists can positively impact the health of patients with T2DM by recommending and counseling on evidence-based medications, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs). This continuing education activity will introduce the complex pathogenesis of type 2 diabetes, elucidate the GLP-1 RAs with cardiovascular trial evidence, and review pertinent counseling points on GLP-1 RAs.

***Goals and Objectives***

The goal of this application-based activity is to assist pharmacists in any setting to effectively counsel providers and patients on evidence-based recommendations related to the use of GLP-1 RAs in T2DM.

Upon completion, the learner will be able to:

1. Describe the complex pathogenesis of type 2 diabetes and identify how GLP-1 RAs attenuate pathogenic abnormalities to impact glucose control, satiety, contribute to weight loss, and prevent progression of the disease.
2. Compare and contrast cardiovascular outcome trials for the three GLP-1 RAs with proven cardiovascular benefit, liraglutide, injectable semaglutide, and dulaglutide to guide the selection of suitable evidence-based GLP-1 RAs.
3. Define the roles in therapy of GLP-1 RAs as suggested by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists Guidelines (AACE).
4. Discuss the tolerability and safety profiles of GLP-1 RAs.
5. Compare and contrast oral semaglutide to injectable GLP-1 RA therapy.
6. Discuss practical considerations guiding appropriate selection of therapy between liraglutide, injectable semaglutide, and dulaglutide.

***Introduction***

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder with substantial morbidity and mortality potential. In 2018, the Centers for Disease Control and Prevention (CDC) estimated diabetes affects nearly 27 million Americans – roughly an 8th of the United States' population. Diabetes is the 7th leading cause of death in the United States; adults with the disease are 2 to 4 times more likely to die from a cardiovascular event. Diabetes is also the number one cause of kidney failure, non-traumatic amputations, and adult blindness in the United States. The estimated total direct and indirect cost of diabetes to the U.S. health system in 2017 was $327 billion, and average annual expenditures attributed directly to diabetes management were approximately $9,600 per person.[1]

As the most readily accessible of healthcare providers, pharmacists have unique ability to positively impact these statistics through provision of evidence-based recommendations to patients and providers for the optimization of diabetes management and the

improvement of cardiovascular outcomes.[2] It has been well documented that quality of care and patient outcomes improve when pharmacists have an active role in interprofessional care for patients with diabetes.[3]

For years, diabetes practice guidelines have included pharmacotherapeutic recommendations centered around the reduction of surrogate glucose markers, such as hemoglobin $A_{1c}$ ($HBA_{1c}$), balanced against risks of potential side effects. In 2008, the U.S. Food and Drug Administration (FDA) began mandating that manufacturing companies of emerging diabetes medications prove cardiovascular safety of those medications. Resulting cardiovascular outcome trials (CVOTs) dramatically increased evidence to meaningfully direct diabetes management practices. In fact, based on CVOTs, 3 GLP-1 RAs have now gained FDA approval for indications to reduce cardiovascular events and have elevated the position of this drug class in both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) diabetes treatment algorithms.[4,5]

With increased priority placed on GLP-1 RAs in treatment algorithms, pharmacists can anticipate regularly recommending GLP-1 RAs and educating patients and providers on appropriate use of medications in this class. This continuing education activity will introduce the complex pathogenesis of type 2 diabetes, elucidate the myriad benefits of GLP-1 RAs through examination of both the novel mechanism of action of this drug class and the burgeoning pipeline of favorable evidence encircling this class of antidiabetic medications, compare and contrast CVOTs related to GLP-1 RAs, and evaluate the current ADA and AACE guidelines to define the role of the GLP-1 RAs in therapy. The common tolerability and safety concerns will also be discussed, in addition to the devices and dosage forms related to this class of antidiabetic drugs.

## ***Pathophysiology of T2DM***

T2DM is a complex heterogeneous metabolic disorder characterized by multiple pathophysiologic abnormalities, donned "the ominous octet." The core defects associated with T2DM include varying levels of hepatic and muscle insulin resistance, pancreatic β-cell failure, incretin deficiency/resistance, accelerated lipolysis, excessive glucagon secretion, increased renal glucose reabsorption, and neurotransmitter dysregulation in the brain (Table 1).[6]

Insulin resistance refers to the inability of cells to respond appropriately to endogenous insulin and occurs primarily in the liver and muscle tissues. The presence of increased insulin in the blood typically suppresses hepatic glucose production. However, in the setting of insulin resistance, this process is attenuated. Early in the progressive development of this disease, pancreatic β-cells compensate for insulin resistance by over-secretion of insulin. Prolonged supraphysiologic blood glucose levels damage pancreatic β-cells, resulting in decreased endogenous insulin production and promoting further glucose dysregulation.[7]

Additional evidence implicates modified adipocyte metabolism and altered fat topography in the pathogenesis of glucose intolerance in T2DM. Fat cells are resistant to insulin's antilipolytic effect, leading to chronically increased levels of free fatty acids, which stimulate gluconeogenesis, worsen hepatic and muscle insulin resistance, and impair insulin secretion further.[8] Fatty acid overflow from the filled adipose cells is toxic to hepatic, muscle, and pancreatic cells alike.[9]

Because obesity, especially with centralized fat distribution, is a powerful driver in the pathogenicity of diabetes, the brain and satiety center are important considerations in the progression of diabetes. When the brain detects altered energy stores via physiologic signals, it prompts the urge to eat. In the patient with T2DM, these signals are more difficult to attenuate because insulin resistance fosters an environment of perpetual cellular starvation, paradoxically in the setting of overabundant glucose. The lack of appropriate satiety signals leads to excess consumption, a primarily anabolic physiologic state, and ultimately, the deposition of more fat.[10]

Most recently implicated in the pathogenesis of T2DM is the increased renal threshold of glucose reabsorption. Under normal conditions, approximately 90% of filtered glucose is reabsorbed by the high capacity sodium-glucose cotransporter 2 (SGLT2) protein and the remaining 10% by the sodium-glucose cotransporter 1 (SGLT1) protein in the convoluted and proximal tubules of the kidney, respectively. In the setting of hyperglycemia, the kidneys compensate through spilling glucose into the urine when a threshold is reached. In the maladaptive diabetic kidney, this threshold is increased and, instead of correcting hyperglycemia through this compensatory mechanism, the kidneys instead retain glucose to satisfy the obligate energy needs of neural tissues, leading to prolonged hyperglycemia and its subsequent complications.[11,12]

Decreases in gastrointestinal (GI) secretions and functionality of incretin hormones in response to food are also complicit in the pathogenesis of T2DM. Glucose ingested orally elicits a more robust insulin response than glucose administered intravenously. This is known as the "incretin effect," the majority of which is due to 2 hormones, glucagon inhibitory polypeptide (GIP) and glucagon-like peptide-1(GLP-1). While the incretin effect typically accounts for approximately 70% of postprandial insulin secretion, it is largely absent in T2DM. Typically, GLP-1 is a potent inhibitor of glucagon secretion, yet this characteristic is also lost in the setting of T2DM. The mechanism for elevated glucagon may be synergistic between endogenous GLP-1 inactivity and pancreatic α-cell derangement.[13-15]

## ***Pharmacology of the GLP-1 Receptor Agonists***

While endogenous GLP-1 hormone is dysfunctional in the setting of T2DM, novel formulations of GLP-1 RAs directly stimulate GLP-1 receptors such that they induce supraphysiologic responses. The GLP-1 receptor is found throughout the body, including presence in β-cell of the pancreas, but also in the α cells, δ cells, and in the heart, kidney, nervous system, liver, and GI tract.[14,16,17] When activated, the β-cell GLP-1 receptor induces both glucose-dependent insulin secretion and glucose-dependent insulin biosynthesis. In addition, glucagon secretion by α-cells is decreased.[14,18,19] Furthermore, GLP-1 inhibits hepatic glucose production while increasing its metabolic clearance.[13,20,21] Endogenous GLP-1 is degraded by the dipeptidyl-peptidase 4 (DPP4) enzyme. Unlike this endogenous hormone, GLP-1 RAs are peptides that are not similarly degraded by DPP4. This characteristic combined with the ubiquity of the GLP-1 receptor lends the medication class its therapeutic effects in type 2 diabetes.[14,22]

Use of GLP-1 RAs restore the incretin effect, reducing unbridled insulin secretion and associated strain on the β-cells. This helps preserve β-cell insulin stores and consequently protects β-cell mass.[20,21,23]

GLP-1 RAs have a direct effect on the satiety center in the hypothalamus, leading to decreased appetite. Additionally, they decrease appetite indirectly through the slowing of gastric emptying. Decreasing the rate of gastric emptying leads to stomach distention and activation of gastric mechanoreceptors in the stomach. Consequently, satiety signals from the gut reinforce appetite suppression. This promotes weight loss in patients on GLP-1 RAs and further increases sensitivity, impacting another core defect in the pathogenesis of T2DM.[14,18,19]

Because of their novel pharmacology addressing multiple core defects associated with T2DM, GLP-1 RAs uniquely illicit improvement on multiple surrogate markers, including robust reductions in $HBA_{1c}$, decreasing fasting and post-prandial blood glucose levels, promoting weight reduction, and modestly lowering blood pressure. Ultimately, these multiple benefits aggregate in proven cardiovascular (CV) benefit, as evidenced in CVOTs.

***Cardiovascular Outcomes Data***

Starting in 2008, the FDA mandated CVOTs for all new diabetes medications to evaluate cardiovascular safety of diabetes medications. CVOTs are designed to demonstrate noninferiority of diabetes medications compared to placebo.[24] The required primary endpoint for CVOTs is a composite of 3 major adverse cardiac events (3P-MACE): CV death, nonfatal myocardial infarction (MI), or nonfatal stroke.[25] Seven long-term CVOTs have been published for GLP-1 RAs.[24]

Cardiovascular event reduction evidence for GLP1-RAs as a class is favorable. Based on meta-analyses of the CVOTs, the GLP-1 RAs collectively show a 13% relative risk reduction in the composite 3P-MACE compared to placebo.[24,25] Additionally, there are significant relative risk reductions in CV death (12%) and all-cause mortality (11%), fatal stroke (19%) and non-fatal stroke (15%), hospitalization for heart failure (9%), and in the composite renal endpoint (17%).[24-26]

Since there is limited evidence of direct CVOT comparison between GLP-1 RAs to establish the absolute best agent in this class, respective individual CVOT data is used to guide clinical choices. While all the GLP-1 RA CVOTs demonstrate CV safety, 3 available injectable agents (liraglutide, injectable semaglutide, and dulaglutide) have demonstrated statistically and clinically significant reductions in the 3P-MACE.[24-30] Of note, albiglutide also showed a CV benefit, enhancing the quality of evidence for this class, but it is no longer marketed. The pivotal CVOT leading to liraglutide's first-in-class indication to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease is the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) provides evidence that has secured the same indication for injectable semaglutide. While the majority of patients enrolled in the LEADER and the SUSTAIN-6 trials had a known history of cardiovascular disease, the CVOT for dulaglutide, Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND), enrolled a majority of patients with no prior history of CV events. Inspired by positive results in this trial, the FDA has approved a new indication for dulaglutide for not only treatment of adult patients for secondary prevention but also for primary prevention for those patients with risk factors without established disease.

While all 3 of evidence-based GLP-1 RAs cited above are recommended, effects on surrogate markers may further steer selection between agents. In the CVOTs, differences have been observed between agents in terms of $HBA_{1c}$ lowering, weight loss, and the rate and severity of adverse events. Table 2 compares and contrasts these 3 evidenced-based GLP-1 RA agents and outcomes from their respective CVOTs.

***Brief Summary of Guidelines***

**American Diabetes Association (ADA)**

The 2020 ADA Standards of Medical Care in Diabetes have expanded recommendations for the use of GLP-1 RAs. Along with the initiation of metformin and comprehensive lifestyle management, the ADA guidelines prefer a GLP-1 RA with an FDA labeled indication of reducing cardiovascular events in any patient with established atherosclerotic cardiovascular disease (ASCVD) or with indicators of high ASCVD risk. This recommendation is independent of baseline $HBA_{1c}$ or $HBA_{1c}$ target. This is a shift in approach to diabetes management, wherein therapy is guided by cardiovascular risk and not necessarily by surrogate markers of glucose control. The GLP-1 RAs are also an alternative to SGLT2 inhibitor agents for patients with reduced ejection fraction heart failure (HFrEF) or chronic kidney disease (CKD), especially if an SGLT2 inhibitor is not tolerated or its use is limited by poor renal function. The GLP-1 RAs are also recommended in any patient with $HBA_{1c}$ above their individualized target on metformin and lifestyle management with a compelling need to minimize the risk of hypoglycemic events or promote weight reduction.[4,28] For those patients who require injectable therapy to reduce $HBA_{1c}$, the guidelines now prefer GLP-1 RAs to insulin therapy. The guidelines also recommend considering patient-specific factors, such as affordability of medications as well as label contraindications and precautions, which are covered below in the section devoted to tolerability and safety of GLP-1 RAs.[4,28,31]

**American Association of Clinical Endocrinologists (AACE)**

The AACE stratify agents using evidence-based approaches into a hierarchy of recommended usage in their updated 2020 guidelines Glycemic Control Algorithm. The algorithm also expands their guidelines to include the use of GLP-1 RA therapy in any patient independent of glycemic control with established ASCVD, high risk for ASCVD, HFrEF or CKD. The AACE guidelines also place emphasis on the GLP-1 RAs with the highest level of evidence for decreasing cardiovascular endpoints. GLP-1 RAs are recommended as monotherapy in patients with entry $HBA_{1c}$ levels $\leq 7.5\%$ or as augmentation strategies for dual or triple-therapy in those patients with entry $HBA_{1c}$ levels $\geq 7.5 - 9\%$.[5] AACE also highlights contraindications and precautions consistent with class labeling, which are covered below in the section devoted to tolerability and safety of GLP-1 RAs.[5,31]

***Tolerability and Safety of GLP-1 RAs***

In addition to promising evidence on efficacy, randomized controlled trials for the GLP-1 RAs have also elucidated safety profiles for these medications. The most commonly reported adverse effects are gastrointestinal in nature, including nausea, diarrhea, and vomiting. Consistently throughout GLP-1 RA trials, GI adverse effects have been reported as mild, usually self-limiting, and, in

most cases, can be avoided altogether with properly managed titration. These GI side effects have accounted for less than 5% of study discontinuation in trials.[29,32]

Due to the mechanisms of action of GLP-1 RAs, patients with certain comorbidities may be at a higher risk for adverse effects and should be screened thoroughly to improve tolerability and safety. In patients with severe gastroparesis, gastroesophageal reflux disease, or gallbladder or biliary disease, the use of a GLP-1 RA is not recommended due to the risk of exacerbation of these conditions. Severe nausea and vomiting can lead to electrolyte derangement and dehydration in some patients, possibly exacerbating chronic kidney disease (CKD) or conceivably contributing to acute kidney injury.[33]

Due to the glucose-dependent mechanism of action of GLP-1 RAs, the risk of hypoglycemia with these agents is very low. Reports of hypoglycemia are usually associated with concomitant use of a sulfonylurea or insulin.[31]

During development, GLP-1 RAs displayed an increased risk for thyroid C-cell hyperplasia, C-cell tumors, and medullary thyroid carcinomas in murine models. However, this has not been regularly represented in either clinical trial or real-world data, most likely owing to species differences in the expression of GLP-1 in rodents versus humans.[34]

Post-marketing data and retrospective analysis drew attention to a possible association between GLP-1 RA therapy and pancreatitis. However, after independent review of the toxicological and observational data, the FDA could not identify a causal relationship between GLP-1 RA therapy and pancreatitis or pancreatic cancer. Furthermore, clinical trials reporting pancreatic events have shown no differences in the incidence of pancreatitis, and although there has been a reported numerical imbalance in pancreatic cancer in the LEADER trial, it is not statistically significant. Of note, many GLP-1 RA clinical trials have excluded patients with a history of pancreatitis, and this risk remains a warning and clinical consideration for the use of GLP-1 RAs.[34,35]

***Oral Semaglutide (Rybelsus)***

In late 2019, Novo Nordisk's newest GLP-1 RA, an oral dosage form of semaglutide (Rybelsus), was granted FDA approval to improve glycemic control in adult patients with T2DM. The approval was based on data from 10 clinical trials, each under the acronym "PIONEER," which stands for Peptide Innovation for Early Diabetes Treatment, collectively enrolling over 9500 patients and including a CVOT and head-to-head studies against sitagliptin, empagliflozin, and liraglutide 1.8 mg.[32] Results from the CVOT, PIONEER-6, demonstrate oral semaglutide CV safety, the rate of 3P-MACE not statistically different from placebo (3.8% vs. 4.8%).[36] In the PIONEER-2 & PIONEER-3 trials, oral semaglutide demonstrates more significant $HBA_{1c}$ lowering and weight reduction in comparison with sitagliptin and empagliflozin, respectively. When compared to liraglutide at its maximum dose of 1.8 mg daily, oral semaglutide is noninferior in $HBA_{1c}$ lowering and superior in weight reduction.[36-39] A study to assess possible superiority has also been initiated and is slated for completion in the year 2024.[40]

Oral semaglutide represents a novel non-injectable GLP-1 RA dosage option for those patients eligible for treatment with a GLP-1 RA. While the data from the PIONEER trials on $HBA_{1c}$ lowering and weight reduction are promising, administration concerns may prohibit its use in certain patients. Proper prescribing and counseling are required to minimize adverse GI adverse effects and maximize absorption and therapeutic effect. Oral semaglutide has extremely low bioavailability of 0.4 – 1%. In order to achieve acceptable blood levels, patients need to swallow the tablet whole, not broken or crushed, on an empty stomach, separated by at least 30 minutes from any food or other medications and with no more than 4 ounces of water. Additionally, patients naïve to GLP-1 RA therapy should be provided a starting sub-therapeutic 3mg dose of oral semaglutide daily for 1 month, solely administered as a low dose in order to reduce the incidence and severity of common GI adverse reactions. Once the first month is completed, patients are increased to 7 mg daily for at least an additional month, and eventually can be titrated to the 14 mg daily dose. Upwards of 80% of patients were able to tolerate the targeted 14 mg dose after proper titration in the PIONEER trials. It should also be noted the tablets are also extremely friable and hygroscopic, and as a result, should be kept in a cool, dry place and not removed from the blister pack until the time of administration.[36-39,41]

There is guidance in the package insert for patients changing from the oral to the injectable form of semaglutide or vice-versa. If changing from the injectable semaglutide 0.5mg to the oral dosage form, patients can be converted to the 7 mg or 14 mg oral dose 1 week following their last injection of 0.5 mg subcutaneous semaglutide. For patients changing from the oral form to the injectable, patients can inject 0.5 mg semaglutide a day after the last oral dose.[41]

***Practice Considerations***

The 3 GLP-1 RAs FDA approved to decrease CV complications are liraglutide, injectable semaglutide, and dulaglutide. These 3 agents comprise the mass majority of market share of GLP-1 agonists dispensed.[42] In considering their unique cardiovascular benefits and frequency of prescribing, it behooves pharmacists to be well-versed in the clinical applications and practical considerations associated with these 3 agents. Below, each agent is discussed further and important individual practical considerations for each is presented. All 3 of these drugs retail in the hundreds of dollars per month, so affordability for most patients is primarily based on insurance coverage.[43] With respect to cost, it is important to consider the availability of coupon cards from medication manufacturers to assist in reducing out-of-pocket expenses for privately insured patients as well as assistance programs for those patients who may be uninsured and meet income criteria.

**Liraglutide (Victoza)**

Liraglutide is a once daily injection. Appropriate use of the medication requires patients to apply a pen needle, dial to a patient-specific dose, and inject accordingly. Liraglutide is provided in a multidose pen, similar to traditional insulin pens. Each pen must be stored in a refrigerator prior to use and may be stored at room temperature for up to 30 days once the pen is in use. Each pen contains 18 mg of liraglutide. The pens are supplied in boxed packages of either 2 or 3 pens. Each package is anticipated to provide 30 days of therapy at the target doses of 1.2 mg daily or 1.8 mg daily respectively. Liraglutide uses the same standard pen needles as used with most insulin pens, and like most insulin pens, the pen needles are not included with the product and must be acquired separately. The pen has preset doses marked at 0.6 mg, 1.2 mg, and 1.8 mg and there are 10 clicks between each preset dose.[33]

The manufacturer recommends initiating liraglutide at 0.6 mg daily for 7 days then increasing to 1.2 mg daily. If the patient requires additional glycemic control, increase to 1.8 mg daily after a week of the 1.2 mg daily dose. The same pen is used regardless of what dose the patient is using. This is different from other GLP-1 RAs. For some patients, starting at the 0.6 mg dose induces bothersome GI adverse effects. Instead of discontinuing liraglutide altogether due to GI concerns, it may be reasonable to attempt a lower dose of 0.3 mg daily and slowly titrate in 0.3 mg increments instead of the larger, standard 0.6 mg increments. Though it is recommended against doing so in the manufacturer package insert, to achieve a 0.3 mg dose, a patient could dial the pen for 5 clicks and use this dose for 1 week and then increase to 0.6 mg for the following week, add 5 clicks more for a dose of 0.9 mg the following week, and then reach the goal dose of 1.2 mg the subsequent week.[33] As it is a once daily injection wherein once weekly injectables in this class also exist as options, liraglutide may be a more or less favorable option for patients depending on their preferences related to likely adherence. For those who are hesitant to use needles, liraglutide may be a less favorable option due to the requirement to manipulate needles on and off the pen on a daily basis.

Patients taking liraglutide for type 2 diabetes can expect an $HBA_{lc}$ reduction of 0.8%-1.1% and weight loss of 2.1-2.5 kg with liraglutide alone and can anticipate greater $HBA_{lc}$ reductions and weight loss in combination with other T2DM therapies, such as metformin.[33] See Table 2 and Table 3 for additional anticipated benefits as compared with other agents in this class.

**Injectable Semaglutide (Ozempic)**

Injectable semaglutide is administered once weekly. Injectable semaglutide is similar to liraglutide in regard to attaching standard pen needles prior to injection. However, unlike liraglutide, the pen needles for injectable semaglutide are included in the box with the medication and do not need to be acquired separately. Prior to use, pens should be kept refrigerated. After first use, each pen may be stored at room temperature for 56 days. There are 2 types of injectable semaglutide pens, which vary depending on the intended dose. A carton of 1 pen is available and delivers preset doses of 0.25 mg or 0.5 mg per injection. This carton comes with 6 pen needles. A carton of 2 pens is also available. The pens in this carton only dispense 1 mg doses and will deliver 2 doses of 1 mg per pen. This carton comes with 4 pen needles and is intended to last 28 days for maintenance treatment at the 1 mg dose.[44]

The manufacturer of injectable semaglutide recommends initiating the medication at a dose of 0.25 mg once weekly for 4 weeks and then increasing the dose to 0.5 mg once weekly. This therapy requires the carton of 1 pen that provides these dosing options. If additional glycemic control is warranted after 4 weeks, patients may increase the dose to 1 mg once weekly. If the dose is increased, then the injectable semaglutide 1 mg pen, which comes in the carton of 2 pens, will need to be prescribed.[44] As it is a once weekly dosing option, this may be preferable therapy for patients who wish to limit needle sticks or who may find once weekly dosing more convenient with regard to adherence.

With monotherapy of injectable semaglutide alone, $HBA_{lc}$ reductions of 1.4-1.6% and weight loss of 3.8-4.7 kg have been demonstrated in clinical trials.[44,45] Notably, injectable semaglutide provides superior $HBA_{1c}$ reduction and weight loss compared to other GLP-1 RAs, as expounded upon in Table 3. This makes injectable semaglutide an attractive option for those patients who are further away from $HBA_{lc}$ goals and in whom weight reduction is clinically necessary. See Table 2 and Table 3 for additional anticipated benefits as compared with other agents in this class.

**Dulaglutide (Trulicity)**

Dulaglutide is a once weekly injection. Unlike liraglutide and injectable semaglutide, patients do not have to attach external needles to the injection device for dulaglutide. Instead, the injection device is a single-dose auto-injecting pen with a hidden retractable needle. Dulaglutide comes in either 0.75 mg or 1.5 mg strengths of dulaglutide. The manufacturer provides packaged cartons for each dose with 4 single-dose pens per carton anticipated to provide a combined 28 days of therapy. Each pen should be kept refrigerated prior to use. If necessary, each single-dose pen can be kept at room temperature for a total of 14 days.[34]

Dulaglutide is initiated at the 0.75 mg once weekly dose. It is recommended to administer the dose on the same day each week at generally the same time without regard to meals. After 1 month, the dose can be increased to 1.5 mg once weekly for additional glycemic control. As with injectable semaglutide, the once weekly dosing of this medication may be preferable therapy for patients who wish to limit needle sticks or who may find once weekly dosing more convenient for adherence compared with daily injections. As the injection device for this medication is unique in having the needle preloaded and hidden from view from patients, dulaglutide is a particularly attractive option for those patients who are afraid of needles or lack the dexterity to attach small pen needles.[34]

Patients taking dulaglutide for type 2 diabetes can expect an $HBA_{lc}$ reduction of 0.7%-0.8% and weight loss of 1.4-2.3 kg with dulaglutide as monotherapy.[34] However, it is typically used as an adjunctive agent for $HBA_{1c}$ lowering and weight loss after an adequate trial of metformin monotherapy.[4,5,28,46] See Table 2 and Table 3 for additional anticipated benefits as compared with other agents in this class.

**Head-to-Head Data**

While limited in availability, some head-to-head studies on these 3 agents do exist. Ultimately, any of the 3 agents between liraglutide, injectable semaglutide, or dulaglutide are likely to be beneficial and reasonable options for indicated patients. Typically, formulary selection and costs will be the driving factor between the three. However, for those in whom any of these agents are affordable and otherwise accessible, there may be subtle reasons to pick one agent over another. For instance, when compared head-to-head with dulaglutide, liraglutide has demonstrated to offer similar reductions in $HBA_{lc}$ while offering slightly more weight reduction.[47] Similarly, when compared head-to-head with dulaglutide, injectable semaglutide demonstrates both better $HBA_{lc}$ reduction and weight loss.[30] When factoring in data from non-head-to-head studies, injectable semaglutide does appear to offer the greatest benefits in terms of $HBA_{lc}$ lowering and weight reduction overall. See Table 2 and Table 3 for more side-by-side comparisons of these agents. Despite the subtle differences between these agents in beneficial performance, it should be reiterated that product availability, cost, and practical considerations, including daily versus weekly dosing preferences and concerns related to pen needles, will often factor into appropriate selection between these agents for specific patients.

**GLP-1 RAs and Other Medications for the Treatment of Type 2 Diabetes**

Most patients diagnosed with type 2 diabetes should start therapy with comprehensive lifestyle management followed by the initiation of metformin as the first-line pharmacological therapy. Although practical considerations, such as cost, comorbidities, and contraindications must guide individual therapy, most patients with diabetes in need of more intervention could benefit significantly from the addition of a GLP-1 RA with proven CV benefit. Specifically, this is recommended for any patients with established ASCVD or high ASCVD risk, independent of $HBA_{1c}$. It is possible that an SGLT2 inhibitor may be uniquely preferred in the setting of heart failure or chronic kidney disease, though a GLP-1 RA remains the preferred acceptable alternative to SGLT2 inhibitors regardless of $HBA_{1c}$ in these patient populations in the setting of SGLT2 inhibitor intolerance or contraindication. For most patients who need three agents for management of their diabetes, the combination of metformin, a GLP-1 RA with proven CV benefit, and an SGLT2 inhibitor with proven CV benefit would be preferred, as long as there are no contraindications or practically prohibitive concerns.[4,5,28] Each of these medication classes have unique mechanisms of action and the synergistic combinations of these agents have been studied and are supported in study data.[47,48]

When compared with insulin glargine, GLP-1 RAs have demonstrated similar reduction of $HBA_{1c}$ with lower risks for hypoglycemia or weight gain, making them the preferred injectable therapy over insulin for most patients. Where it is deemed necessary, a GLP-1 RA may also be used in conjunction with insulin, though this requires more aggressive monitoring of hypoglycemic risks with this combination.[4,28,49] As aforementioned, while GLP-1 RAs have low hypoglycemic risks as a class themselves, these risks are increased when used in combination with insulins or sulfonylureas.

Compared with DPP4 inhibitors, GLP-1 RAs are more efficacious in managing blood glucose.[50] The combination of GLP-1 RAs and DPP4 inhibitors would be redundant with regard to mechanisms of action and is generally not recommended.[4,28]

***Conclusion***

The management of diabetes is challenging; its effects can be far-reaching, produce financial burden, impact organ function, and even lead to death. GLP-1 RAs are effective agents for the treatment of T2DM and confer myriad metabolic benefits including the comprehensive reductions of blood glucose, weight, and blood pressure, while maintaining a very low risk of hypoglycemia. Three specific agents (liraglutide, injectable semaglutide, and dulaglutide) have proven reduction in 3P-MACE outcomes and have obtained FDA indications to reduce cardiovascular events. Both ADA and the AACE guidelines endorse these GLP-1 RAs as preferred second-line agents, added to metformin and lifestyle modifications, for improving glucose targets to goal, for primary prevention of CV events in high risk patients, and for secondary CV prevention. The most common adverse effects are gastrointestinal and include nausea, vomiting and diarrhea, but can be successfully mitigated by slowly titrating the drug and screening patients with moderate to severe GERD or gastroparesis. Additional patient-centered considerations are insurance coverage, dosing frequency preferences (daily vs weekly), and device ease of use. Pharmacists knowledgeable in GLP-1 RA therapy can readily improve provider prescribing and patient use necessary to achieve optimal metabolic and cardiovascular outcomes.

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**Table 1.** Summary of Core Defects in T2DM[6]

| Location | Defects |
|---|---|
| **Muscle** | decreased glucose uptake |
| **Pancreatic beta cell** | dysfunctional (hyper and hypo) insulin secretion in response to food |
| **Pancreatic alpha cell** | increased glucagon secretion stimulates hepatic glucose production |
| **Liver** | increased hepatic glucose production |
| **Gastrointestinal tract** | decreased incretin effect – multifactorial impact on blood glucose |
| **Adipose tissue** | increased lipolysis and free fatty acid levels, which increase insulin resistance |
| **Kidney** | increased glucose reabsorption |
| **Brain** | neurotransmitter dysfunction leading to increased appetite |

**Table 2.** CVOT data for 3 GLP-1 RA products with CV reduction indications vs placebo

| | liraglutide (*Victoza*)[51] | injectable semaglutide (*Ozempic*)[52] | dulaglutide (*Trulicity*)[27] |
|---|---|---|---|
| **CVOT (year published)** | LEADER (2016)[a] | SUSTAIN-6 (2016)[b] | REWIND (2019)[c] |
| **Average Trial Duration** | 3.8 years | 2.1 years | 5.4 years |

| | | | |
|---|---|---|---|
| **Treatment Dose and Frequency** | 1.2 mg up to 1.8 mg daily | 0.5 or 1.0 mg weekly | 1.5 mg weekly |
| **3P-MACE**<br>**active drug vs placebo**<br>*# of events* | 608 vs 694<br>13.0% vs 14.9%<br>NNT: 53 | 108 vs 146<br>6.6% vs 8.9%<br>NNT: 45 | 594 vs 693<br>12.0% vs 13.4%<br>NNT: 73 |
| **Cardiovascular Death %** | 4.7% vs 6.0%<br>NNT: 77 | 2.7% vs 2.8%<br>Non-statistical difference | 6.4% vs 7.0%<br>Non-statistical difference |
| **Nonfatal Myocardial Infarction** | 6.0% vs 6.8%<br>Non-statistical difference | 2.9% vs 3.9%<br>Non-statistical difference | 4.1% vs 4.3%<br>Non-statistical difference |
| **Nonfatal Stroke** | 3.4% vs 3.7%<br>Non-statistical difference | 1.6% vs 2.7%<br>NNT: 90 | 2.7% vs 3.5%<br>NNT: 125 |
| **New or Worsening Nephropathy** | 5.7% vs 7.2%<br>NNT: 67 | 3.8% vs 6.1%<br>NNT: 44 | 17.1% vs 19.6%<br>NNT: 40 |
| **Blood Pressure Reduction** | 1.2 mmHg | 2.6 mmHg | 1.7 mmHg |
| **Mean Baseline $HBA_{1c}$**<br>**and $HBA_{1c}$ Reduction** | 8.7%<br>0.4% | 8.7%<br>0.5mg: 1.1%<br>1mg: 1.4% | 7.3%<br>0.61% |
| **Weight Loss** | 2.3kg | 0.5mg: 3.6kg<br>1mg: 4.9kg | 1.46kg |
| **GI Adverse Effects** | Reported individually<br>N: 1.6% vs 0.4 %<br>V: 0.7% vs 0.1%<br>D: 0.6 vs 0.1% | Composite GI<br>50.7% vs 52.3% | Composite GI:<br>47.4% vs 34.1%<br>NNH: 8 |
| **Unique Adverse Effects** | Acute gallstone disease<br>3.1% vs 1.9%<br>NNH: 83 | Retinopathy complications<br>3.0% vs 1.8%<br>NNH: 83 | - |

Abbreviations: CVOT, cardiovascular outcome trials; 3P-MACE, composite of 3 major adverse cardiac events including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; NNT, number needed to treat for the average duration of the study to prevent 1 event; $HBA_{1c}$, hemoglobin $A_{1c}$; GI, gastrointestinal; N, nausea; V, vomiting; D, diarrhea; NNH, number needed to harm for the average duration of the study to cause 1 event.
[a] Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
[b] Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes
[c] Researching Cardiovascular Events with a Weekly Incretin in Diabetes

**Table 3.** Comparison of GLP-1 RA Titration Schedules, Expectations for $HBA_{1c}$ Reductions, and Weight Loss

| | **liraglutide (*Victoza*)[33]** | **injectable semaglutide (*Ozempic*)[44]** | **dulaglutide (*Trulicity*)[34]** |
|---|---|---|---|
| **Titration Schedule** | - (0.3mg once daily for 7 days if patient has intolerable GI adverse effects)<br>- Start with 0.6mg once daily for 7 days<br>- Increase to 1.2mg once daily<br>- If greater glycemic control or weight loss is need after 12 weeks, could try to increase to 1.8mg once daily | - Start with 0.25mg once weekly for 4 weeks<br>- Increase to 0.5mg once weekly<br>- If greater glycemic control is needed after 12 weeks, increase to 1.0mg once weekly | -0.75 mg weekly for 1 month<br>-option to increase to 1.5 mg weekly dose after 1 month for maximum glycemic control |
| **Average $HBA_{1c}$ Reduction with GLP-1 RA Monotherapy** | 0.8% (1.2mg)<br>1.1% (1.8mg) | 1.4% (0.5mg)<br>1.6% (1.0mg) | 0.7% (0.75mg)<br>0.8% (1.5mg) |

| | | | |
|---|---|---|---|
| **Average Weight Loss with GLP-1 RA Monotherapy** | 2.1kg (1.2mg)<br>2.5kg (1.8mg) | 3.8kg (0.5mg)<br>4.7kg (1.0mg) | 1.4kg (0.75)<br>2.3kg (1.5) |

Abbreviations: GI, gastrointestinal; $HBA_{1c}$, hemoglobin $A_{1c}$; GLP-1 RA, glucagon-like peptide-1 receptor agonist

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***Self-Assessment Question #1***

PP is a 51-year-old male with T2DM and a history of angina. He has been taking metformin for 5 years at the recommended maximum dose and tolerates it well. He has improved his lifestyle habits, but his most recent $HBA_{1c}$ has come back at 8%. He says he is not afraid of needles, but he would really prefer not to start insulin any earlier than necessary. The patient also wants the product to be easy to use, and since he is on a lot of medicine, he would prefer once weekly dosing compared to daily. Through discussion with the physician and the patient, it is determined that a GLP-1 RA is a good drug class to consider, especially if the drug has positive CVOT data. You recommend:

a) exenatide IR (Byetta)
b) exenatide ER (Bydureon)
c) liraglutide (Victoza)

***Self-Assessment Question #2***

SK is a 59-year-old white male diagnosed with T2DM 9 years ago. He is currently taking metformin 1000 mg two times daily. His $HBA_{1c}$ is 8.1% and his provider has foregone the titration and started liraglutide at 1.2mg daily injected subcutaneously to improve his blood glucose control. Of the following, which adverse effect is most likely when starting this new medication, especially at this dose?

a) Edema and weight gain
b) Pancreatitis
c) UTI's and yeast infections
d) Nausea

***Self-Assessment Question #3***

A nurse practitioner asks you how semaglutide works. A good explanation would be the following:

a) It works primarily on insulin resistance in the muscles
b) It decreases glucagon secretion, causes insulin secretion in response to meals, and enhances satiety
c) It causes a delay in the absorption of carbohydrates
d) It causes the pancreas to secrete insulin throughout the day

***Self-Assessment Question #4***

You are describing the benefits of GLP-1 RAs to a patient. Which of the following would be correct?

a) These injectable drugs are indicated in both type 1 and type 2 diabetes
b) Every drug in this class has proven to decrease cardiovascular events and death
c) Both the oral and injectable versions of semaglutide have proven to decrease cardiovascular events and death
d) These drugs produce robust blood glucose lowering and they also positively affect cardiovascular risk factors, such as blood pressure reduction and weight, and some have proven to decrease the chance of cardiovascular events and death

***Self-Assessment Question #5***

A physician is asking about the recommended starting dose and titration for the injectable semaglutide. You respond with:

a) Start with 0.75mg weekly for 4 weeks and then titrate to 1.5 mg
b) Start with 0.6 mg daily for 1 week and then titrate to 1.2 mg
c) Start with 0.25 mg weekly for 4 weeks and then titrate to 0.5mg weekly for at least 4 weeks. If additional glycemic control is needed, can increase the dose a max of 1 mg
d) Start with 3 mg daily for 30 days and titrate to 7 mg daily for at least 30 more days. Dose may then be increased to a max of 14 mg daily

*Self-Assessment Question #6*

RW is a 64-year-old white male with a history of uncontrolled type 2 diabetes and newly established diabetic retinopathy. Which of the following GLP-1 RAs has documented risks of increasing retinopathy complications?

a) liraglutide
b) dulaglutide
c) injectable semaglutide
d) oral semaglutide

*Self-Assessment Question #7*

MJ is a 56-year-old, obese female with type 2 diabetes and a history of poor adherence primarily due to inability to pay for medications. She has had a long-standing hyperglycemia with the following complications: peripheral neuropathy, autonomic neuropathy with severe gastroparesis, stage 3 diabetic nephropathy with an albumin to creatinine ratio greater than 200 mg/g and eGFR at 66 ml/min. She returned to clinic 3 months ago newly enrolled in SC Medicaid. Her $HBA_{1c}$ at that time was 12% and her $HBA_{1c}$ today is 9% with 90% adherence to new medications metformin ER 1000 mg BID and insulin glargine 60 units QAM. Her primary care provider has written an initial prescription for dulaglutide 0.75 mg once weekly, 4 pens and no refills and a prescription for 1.5 mg pens to start a week after the last 0.75 mg pen. What concerns do you have?

a) The patient is likely to have significant nausea and vomiting with a GLP-1 RA because of gastroparesis and is not recommended in this patient
b) Dulaglutide is contraindicated in patients with chronic kidney disease
c) Dulaglutide increases the risk of distal amputations in patients with peripheral neuropathy
d) The dosing of the dulaglutide is incorrect

*Self-Assessment Question #8*

A patient with a history of a myocardial infarction and well controlled diabetes (A1c 6.4%) currently taking metformin, sitagliptin, and glimepiride. The patient agreed with the provider to start liraglutide for cardiovascular protection as long as some of the other medications could be stopped. What recommendations do you recommend for the other medications?

a) He could stop the metformin since liraglutide provides excellent cardioprotection
b) He could stop the sitagliptin because the mechanism of action of liraglutide already causes a supraphysiologic effect on the GLP-1 receptor
c) He could stop the glimepiride because liraglutide provides a specific physiologic insulin secretion in response to food intake and stopping the glimepiride would decrease the incidence of hypoglycemia
d) Both B and C are correct