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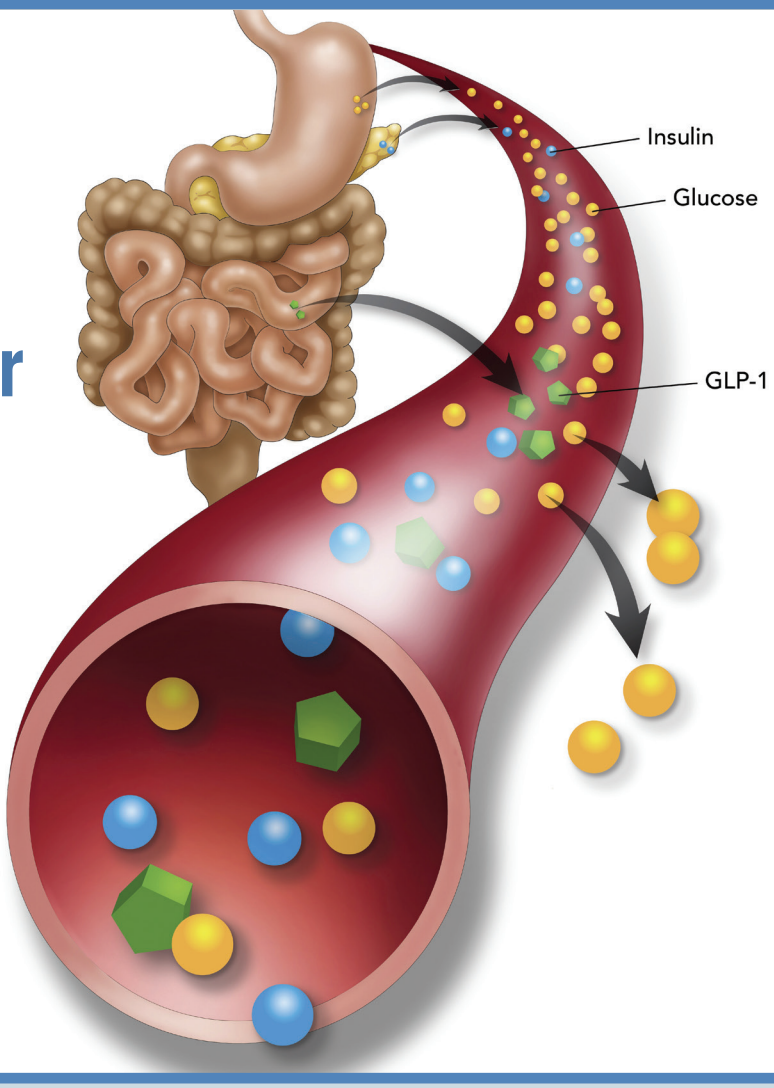

A Clinical Overview of Once-weekly Glucagon-like Peptide-1 Receptor Agonists

Jeff Unger, MD, FAAFP, FACE

Of the US population, 9.4% (approximately 30 million people) have diabetes,[1,2] and 90% of those affected are managed within a primary care setting. The rates of diabetes-related complications (eg, acute myocardial infarction, stroke, lower-extremity amputation, end-stage renal disease, and death from hyperglycemia) have declined sharply (by approximately 28% to 68%) over the past 20 years. However, the increasing prevalence of diabetes and prediabetes will have a profound effect on the socioeconomic stability of the US healthcare system for years to come.[3]

Recent data from the 2011–2014 National Health and Nutrition Examination Survey (NHANES) indicate that only 51% of US adults with diabetes achieve a hemoglobin A_{1c} (HbA_{1c}) level less than 7%. Despite the approval and marketing of new agents for diabetes in several classes (eg, glucagon-like peptide-1 receptor agonists [GLP-1 RAs], sodium–glucose cotransporter-2 [SGLT-2] inhibitors, and longer-acting basal insulins) and disposable insulin pumps, improvement of HbA_{1c} nationally has actually declined since NHANES 2007–2010, when 52% of patients achieved their targeted HbA_{1c}.[4]

Randomized, controlled clinical trials of diabetes therapies conducted under US Food and Drug Administration (FDA) guidance (for regulatory approval purposes) consistently demonstrate success in achieving an HbA_{1c} level less than 7%—as low as 6.5%. However, real-world studies suggest that suboptimal adherence to prescribed medications might mitigate a patient's ability to achieve the glycemic target.[5] Patients in the real world might be concerned about adverse events associated with drugs, the complexity of treatment regimens, potential weight gain, and the risk of hypoglycemia. Television advertisements that mention the risk of thyroid cancer, amputation, and hypoglycemia associated with these agents can hinder one's desire to begin taking a new drug.

Former US Surgeon General C. Everett Koop said: "Drugs don't work in patients who don't take them."[6] Medication adherence plays an essential role in overall glycemic control and helps reduce the risk of complications, prevent premature mortality, and lower overall health care costs. Unfortunately, the adherence rate among patients with type 2 diabetes (T2D) is as low as 45%; nearly one-third of patients with T2D fail to fill even their first prescription of a glucose-lowering agent.[7,8]

Nonadherence increases the likelihood of long-term complications, more frequent hospitalizations, higher health care costs, and rates of mortality. In patients younger than 65 years, the risk of hospitalization over 12 months was found to be 30% at the lowest quintile (1% to 19%) of adherence to antidiabetes medications, compared to 13% at the highest quintile (80% to 100%).[9]

Poor adherence to T2D medication regimens has been associated with important non-patient factors (eg, suboptimal health care system integration and clinical inertia among practitioners); patient demographics (eg, low socioeconomic level and young age); misconceptions and lack of patient-directed education regarding prescribed medications; and patient burden relating to procuring and taking medication (eg, out-of-pocket expenses and treatment complexity).[10] Certainly, improved communication between patients and prescribers related to drug risks and benefits should mitigate fears, while facilitating shared decision-making. Although these factors, particularly medication cost, can reduce treatment adherence, a study by Kurlander et al demonstrated that nonfinancial factors such as disease-state comprehension, satisfaction with medication-related information, and comorbid major depression, can influence patient behaviors.[11]

Clinicians should consider therapeutic interventions that can improve adherence and minimize the risk of treatment-emergent adverse events, such as weight gain and hypoglycemia. The American Diabetes Association and the European Association for the Study of Diabetes emphasize the importance of considering patients' preference for such treatment-related factors when clinical decisions are made regarding management of T2D.[12] Decisions that are patient-centered

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are likely to improve adherence and, consequently, clinical outcomes.[13]

This supplement to *The Journal of Family Practice* provides an overview of the role of once-weekly GLP-1 RA therapy in T2D. Agents in this therapeutic class vary considerably in dosing regimens, frequency of administration, and metabolic effects (eg, lowering glucose and blood pressure). Recently published cardiovascular outcome studies suggest that the reduced risk of death from cardiovascular causes observed with liraglutide and semaglutide is unique to each agent. Patient-centered prescribing, therefore, should take into consideration the patient's baseline HbA_{1C} level, weight, blood pressure, dosing preferences, and cardiovascular risk profile.

The outstanding authors–educators profiled in this supplement address the burden of disease of T2D, the mode of action, efficacy, safety, and the impact on cardiovascular outcomes of the 4 FDA-approved once-weekly GLP-1 RAs[14-17]:

- albiglutide
- dulaglutide
- exenatide extended-release
- semaglutide.

Because albiglutide is due to be withdrawn from the market in July 2018,[18] the supplement will focus primarily on the other 3 GLP-1 RAs. Understanding patient preferences while addressing safety concerns and treatment-emergent adverse events will, ultimately, extend the longevity and benefit the quality of life of our patients with T2D.

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An Overview of the Burden of Illness and the Role of Once-Weekly Glucagon-like Peptide-1 Receptor Agonists in the Treatment of Type 2 Diabetes

Stephen A. Brunton, MD, FAAFP

Abstract

Type 2 diabetes (T2D) is a debilitating condition and more people are being diagnosed each year. T2D increases patients' risk of developing disabling micro- and macrovascular complications, significantly reduces patients' quality of life, and is a substantial global economic burden. The efficacy and safety of antihyperglycemic therapies have improved over the years and have increased the lifespan for these patients. Consequently, patients are living longer with the condition and the associated comorbidities, but with a lowered quality of life. Therefore, therapies should aim to provide both optimal glycemic control and improve quality of life. Glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy improves glycemic control, reduces body weight, and has a low risk for hypoglycemia. GLP-1 RAs are available as once-daily (OD), twice-daily (BD), or once-weekly (OW) injectable formulations; OW injections may increase patients' satisfaction and improve treatment adherence. In the last decade, concern has been raised about the cardiovascular (CV) safety of antihyperglycemic therapies. Clinical data have been limited on CV outcomes among OW GLP-1 RAs. However, a post hoc analysis of the SUSTAIN-6 trial suggested that semaglutide, the most recently US Food and Drug Administration (FDA)-approved OW GLP-1 RA therapy, may offer cardioprotection, addressing this previously unmet clinical need.

Introduction

Diabetes is a debilitating condition that is characterized by systemic hyperglycemia and is one of the leading causes of death worldwide. Currently, diabetes leads to 1 death every 6 seconds and accounts for more annual mortalities than HIV/AIDS, malaria, and tuberculosis combined.[1]

T2D is the most common form of diabetes and is estimated to affect 87% to 91% of the total population living with diabetes in high-income countries. It predominantly affects adults; however, the numbers of adolescents and children being diagnosed with the condition are increasing.[1] T2D can develop at any point during a person's life as a consequence of numerous factors. The primary risk factors for T2D are overweight, a sedentary lifestyle, age older than 45 years, and a family history of diabetes.[2] The number of people with T2D is increasing rapidly alongside cultural and societal changes, such as an aging population, increased urbanization, increased sugar consumption, reduced fruit and vegetable intake, and an increase in sedentary lifestyle.[1,3]

Incidence and prevalence

In 2015, an estimated 415 million adults worldwide had diabetes, approximately 8.8% of the adult population. Of these, 193 million people remain undiagnosed; 318 million had impaired glucose tolerance, indicating they are at risk of developing T2D. Of the total population with diabetes in 2015, the numbers are evenly split among men and women (215.2 million vs 199.5 million, respectively) but the numbers of people living with diabetes in urban communities are higher compared with rural areas (269.7 vs 145.1 million, respectively).

Currently, the United States has the third highest number of adults with diabetes (29.3 million), after China and India (with 109.6 million and 69.2 million, respectively). Globally, the number of people with diabetes is predicted to rise to 642 million by 2040 and the number of diabetes-related mortalities is also expected to increase.[1]

Comorbidities

Chronic hyperglycemia has debilitating systemic effects owing to its association with the aberrant activation of pathological intracellular signaling cascades. This activation has deleterious

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effects on cells and results in tissue and organ damage and dysfunction.[4] Duration of diabetes increases the risk for disabling systemic complications such as retinopathy, nephropathy, cardiovascular disease (CVD), peripheral neuropathy, and lower-extremity ulcerations resulting in amputations, as well as pregnancy complications. The risk for these complications is further increased with poor glycemic control.[5,6] Currently there are no global estimates of the prevalence of diabetes complications, and the data that are available have been collected mostly from high-income countries.[7]

Retinopathy

Retinopathy can lead to impaired vision and is responsible for 2.6% cases of blindness worldwide.[8] It affects 35% of patients with T2D, and proliferative retinopathy (the most severe form that can cause blindness) affects 7% of patients with T2D.[9] Diabetic retinopathy is the leading cause of vision loss in adults aged 20 to 74 years and, between 1999 and 2010, was ranked as the fifth most common cause of moderate to severe visual impairment.[8,10]

Nephropathy

Nephropathy occurs in up to one-third of people with diabetes and can progress to end-stage renal disease (ESRD).[11] Pooled data from 54 countries show that at least 80% of cases of ESRD are caused by diabetes or hypertension, or a combination of both; the proportion of ESRD attributable to diabetes alone ranges from 12% to 55%.[7] Between 4% and 17% of people with diabetes develop ESRD 20 years after diabetes diagnosis, and 18% to 22% develop ESRD 30 years after their diabetes diagnosis.[12,13]

Cardiovascular disease

CVDs are the most prevalent cause of mortality and morbidity among people with both type 1 diabetes (T1D) and T2D.[14] CVD includes angina, myocardial infarction (MI), stroke, peripheral artery disease, and congestive heart failure (CHF). CVD occurs 2 to 4 times more frequently in people with diabetes than in people without diabetes.[14,15] Given that the risk of CVD in patients with diabetes is increased with elevated plasma glucose,[16] it is understandable that in the United States, adults with diabetes have increased CVD mortality rates (1.7-fold) and an increased relative risk for CVD morbidity and mortality (1–3 in men, 2–5 in women) compared with US adults without diabetes. Among men with diabetes in the United States, 12.2% have had an MI, 11.2% have coronary heart disease (CHD), 7.9% have CHF, and 6.8% have had a stroke; in women these values were reported to be 7.1%, 6.7%, 7.7%, and 6.3%, respectively.[17]

Neuropathy

Neuropathy occurs in up to 30% to 50% of people with diabetes, with the most common form being chronic sensorimotor distal symmetric polyneuropathy, a form of peripheral neuropathy.[18,19] People with peripheral neuropathy initially report paresthesias, dysesthesias, numbness in the extremities, muscle weakness, and neuropathic pain. Neuropathic pain is chronic, severe, and debilitating, and occurs in 11% to 32% of people with diabetes and peripheral neuropathy.[6] As the duration of diabetes increases, peripheral neuronal terminals are gradually lost and symptoms progress to a complete loss of sensory perception, which subsequently increases the risk of foot ulceration.[20]

Lower-extremity amputations

Nonhealing foot ulceration can occur in people with diabetes and is a common cause of lower-extremity amputations (LEAs). Globally, foot ulceration has been reported in 6.3% of people with diabetes, with a higher prevalence in men than women (4.5% vs 3.5%, respectively), and higher in people with T2D than with T1D (6.4% vs 5.5%, respectively).[21] People with diabetes are 10 to 20 times more likely to require LEAs than people without diabetes,[7] and people 65 years of age or older account for 55% of individuals requiring LEAs.[22]

Pregnancy complications

Pregnancies in women with preexisting diabetes have a higher risk for complications for both mother and fetus.[23] For the mother, preexisting T2D increases the risk of pregnancy-induced hypertension, preeclampsia, polyhydramnios, premature rupture of membranes, and preterm delivery (less than 37 weeks), and is associated with greater blood loss at birth.[23,24] For the fetus, preexisting T2D in the mother increases the risk of the fetus developing neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress; affected fetuses have a 4- to 5-fold increase in perinatal death, and a 4- to 6-fold increase in stillbirths compared with fetuses in the general population.[25,26] These potentially devastating pregnancy complications have been partly attributed to both poor glycemic control and obesity, which often coexist in people with T2D.[23]

Cancers and dementia

T2D is also considered to be a risk factor for the development of certain types of cancers and dementia. A meta-analysis of population-based studies identified that the relative risk of developing cancers was higher in patients with T2D than those without. Compared with people without T2D, people with T2D had a 2-fold greater risk of developing cancers of the liver, pancreas, and endometrium; and a 1.5-fold greater risk for cancers of the colon, rectum, breast, and bladder[27]; people with T2D, however, were at no greater risk for developing lung cancers.[28]

Dementia comes in many forms, with vascular dementia (VD) and Alzheimer's disease (AD) being the most common.[29] The relative risk of developing VD and AD is higher in patients with T2D than patients without T2D.[30] Reports indicate that in patients with T2D, the relative risk for VD ranges from 2.3 to 2.5 and for AD ranges from 1.5 to 3.8.[31-33]

Quality of life

Quality of life (QoL) was first introduced by the World Health Organization in 1997 as a broad multidimensional estimate of well-being as well as a measurement of health and the effects of health care.[34] Overall, people with T2D report a lower QoL than people without T2D, an observation that has been attributed to a reduction in health-related QoL (HRQoL).[35] HRQoL scores, which are affected by physical and mental well-being, are significantly lower in people with T2D than people without T2D. HRQoL scores were also found to be lower among people at high risk of developing T2D than people at lower risk.[36] Among people with diabetes, HRQoL scores were lowest in people with comorbidities, women, older patients, and patients taking insulin. Across all of these subsets, the lowest HRQoL scores were reported in people with macro- and microvascular complications, which is unsurprising as all such complications are associated with physical deterioration and intensification of treatment strategies.[35]

The prevalence of depression was found to be 7% higher in people with diabetes than in people without. Comorbid depression increases the risk of treatment nonadherence, development of complications, and a further reduction in HRQoL.[37] Severe depression increases the lifetime risk of suicidal ideation and suicide attempts, with these occurring at rates of 24.2% and 13.3% in cohorts of people with diabetes vs 16.5% and 3.5% in people without diabetes, respectively.[38,39]

Economic impact

Health care expenditures

In 2015, most countries worldwide spent between 5% and 20% of their total health budget on diabetes-related illnesses, with a total global expenditure of US $673 billion. As the incidence and prevalence of diabetes and survival rates for people with diabetes increase, the global expenditure on diabetes is predicted to rise 19% by 2040. Globally, the United States had the highest total diabetes-related expenditures in 2015—US $320 billion—almost half of the worldwide costs that year.[1]

Health care expenditures for people with diabetes have been found to be 2- to 3-fold higher than for people without diabetes.[1] Costs associated with T2D increase with age, disease severity, and the presence of comorbidities.[40] In the US, overall medical costs for people with diabetes are increased by 10% to 50% if patients have peripheral vascular disease, proliferative retinopathy, neuropathy, or hypertension; by 70% to 150% if patients have CHD, CHF, hemiplegia, or amputation; and by 300% to 500% if patients have ESRD.[40]

Effect in the workplace

In the workplace, T2D is associated with a reduction in work quality, decreased productivity, increased fatigue, loss of concentration, and increased absenteeism; in 2007, these losses cost the United States an estimated US $58.2 billion.[41] The probability of being employed is lower among people with diabetes,[3,42] and more people with diabetes require government financial aid than people without diabetes.[41]

People with diabetes who are employed report lower annual salaries than counterparts without diabetes, although significant effects have been observed only for men, with a reduction in wages of up to 20%.[3] Patients have substantial health care costs, including consultation fees, hospitalizations, medical transportation, medication, dietary requirements, and glucose monitoring. Although these costs can be covered by insurance, many lower-income families do not have access to insurance plans. Lower annual salaries combined with a reduced access to health insurance can lead to a substantial economic burden on patients and their families, and can further reduce QoL.[42]

Potential benefits of OW GLP-1 RA treatment in alleviating the burden of illness

GLP-1 RA therapy

Because of the complex multifactorial pathophysiology of T2D, an effective therapeutic approach should combine positive lifestyle changes with efficacious therapeutic agents. Upon initial diagnosis, first-line therapy often includes metformin. However, as the disease progresses, beta-cell function declines progressively and additional add-on therapies are required to achieve adequate glycemic control. Achieving adequate glycemic control as early as possible after diagnosis is paramount to the prevention of health deterioration and reduction in the risk for diabetes-associated comorbidities.[41]

GLP-1 RAs have been shown to reduce glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose levels and aid in weight loss.[43] GLP-1 is an incretin hormone that is secreted from L cells of the distal small intestine in response to luminal stimulation and exerts widespread systemic effects. GLP-1 RAs reduce plasma glucose levels through an increase in insulin and a decrease in glucagon secretion in a glucose-dependent manner, delaying gastric emptying, and assisting in weight loss through appetite suppression and increasing postprandial satiation.[44] In a review of preclinical and clinical studies, Kawanami et al described that incretin-based therapies can protect against diabetes-associated complications, including vascular disease, nephropathy, retinopathy, and neuropathy, and these effects have been attributed to their antihyperglycemic, anti-inflammatory, and antioxidant properties.[45] A more detailed account of the pharmacokinetic properties of GLP-1 RAs and their mode of action can be found in a dedicated article in this supplement (See "The Pharmacokinetic Properties of Glucagon-like Peptide-1 Receptor Agonists and Their Mode and Mechanism of Action in Patients with Type 2 Diabetes" on page S8).

GLP-1 RAs are administered as subcutaneous injections and were originally developed as daily treatments, including exenatide (BD) and liraglutide (OD). More recently, OW formulations

have been made available and include exenatide extended release, albiglutide, dulaglutide, and semaglutide.[46] However, albiglutide is scheduled to be discontinued as of July 2018.[47] No current American Diabetes Association guidelines distinguish between the use of OD and OW GLP-1 RA therapies. When clinicians are selecting treatments to achieve better glycemic control, a patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include the efficacy, risks of hypoglycemia, impact on weight, potential adverse effects, and the costs of treatment.[41]

Research findings indicate that reduced treatment adherence among patients with diabetes is influenced by a combination of complex dosing regimens, increased dosing, high costs, adverse events, weight gain, and poor health care provider–patient relationships. Suboptimal treatment adherence needs to be minimized because of the association with reduction in glycemic control and increased risk of complications.[48,49] Therefore, although some patients may favor OD therapies, the incorporation of OW GLP-1 RAs may potentially increase treatment adherence and QoL for people with T2D by reducing treatment complexity and the number of injections.

OW GLP-1 RAs

In clinical trials, all OW GLP-1 RAs currently approved in the US have demonstrated efficacy in people with T2D for reducing HbA_{1c} and for weight loss. All have similar common adverse events and have low occurrence rates of hypoglycemia.[50-60] Trials of individual GLP-1 RAs, comparing OW (exenatide, dulaglutide, albiglutide) with the OD active comparator (liraglutide) or BD active comparator (exenatide), and OW semaglutide with OD insulin glargine and oral sitagliptin placebo found that all drugs have efficacy in reducing HbA_{1c}, the primary endpoint of the studies.[50-53,58,59] A detailed account of the efficacy and safety of OW GLP-1 RAs can be found in dedicated articles in this supplement (See "Clinical Efficacy of Once-weekly Glucagon-like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes" on page S14; See "Safety of Once-weekly Glucagon-like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes" on page S25).

Of the head-to-head trials, 2 evaluated patients' satisfaction of therapy with a Diabetes Treatment Satisfaction Questionnaire. Patient satisfaction was reported to be similar among patients taking albiglutide and liraglutide. Patient satisfaction was significantly greater with OW exenatide than twice-daily exenatide, and rates of treatment adherence were similar in both arms; the authors hypothesized the difference in satisfaction to be due to the reduced number of required injections.[46] The findings in a study from the United Kingdom support this hypothesis, specifically reporting that "dosing frequency" is ranked as being more important to patients than fluctuations in weight, nausea, or reductions in HbA_{1c} when rating their GLP-1 RA therapy.[61]

Other studies have identified that OW exenatide is associated with lower monthly medical costs than liraglutide and may be a more cost-effective therapy, although Wang et al concluded that results arising from cost-effectiveness studies vary and the results are dependent on the chosen source of clinical data. Therefore, although indicated, the potential financial benefit of OW drugs over daily drugs is still uncertain.[62-64]

Concern has been raised about the CV safety of antihyperglycemic therapies,[65] and the CV profiles of drugs should be considered carefully. Until recently, few positive CV outcomes have been reported with FDA-licensed OW GLP-1 RAs. However, the most recently FDA-approved OW GLP-1 RA, semaglutide, has been associated with a reduced risk of death from CV causes, nonfatal MI, or nonfatal stroke in patients at high risk of CVD.[66] To date, semaglutide is the first OW injectable GLP-1 RA therapy that has been associated with positive CV outcomes (based on a post hoc analysis of the SUSTAIN-6 trial), and may be a suitable mono- or add-on therapy for glycemic control and to reduce the burden of illness in people with T2D. A detailed account of the CV outcomes of OW GLP-1 RAs is available in a dedicated article within this supplement (See "Implications of Cardiovascular Outcomes Trials in Type 2 Diabetes for Primary Care" on page S35).

Conclusion

T2D is associated with debilitating comorbidities and is a substantial burden on both the economy and patients' QoL. The prevalence of T2D keeps increasing and as treatments for diabetes improve, patients are living longer, leading to an increased risk of developing comorbidities. Thus, treatments should aim to improve both glycemic control and QoL. Current GLP-1 RA–based therapies provide options for the treatment of T2D by enabling the intensification of glycemic control while reducing body weight. They are associated with a low risk for hypoglycemia and may reduce the risk of complications associated with diabetes. OW GLP-1 RA therapies may be preferable to OD and twice-daily GLP-1 RA drugs in that they could potentially increase treatment adherence and QoL by reducing the number of required injections. Semaglutide, the most recent FDA-approved OW GLP-1 RA, is the first drug of its class to demonstrate positive CV outcomes and can be considered a useful option when developing treatment regimens for patients with T2D. ●

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The Pharmacokinetic Properties of Glucagon-like Peptide-1 Receptor Agonists and Their Mode and Mechanism of Action in Patients with Type 2 Diabetes

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Abstract

Once-weekly (OW) glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated improved glycemic control in patients with type 2 diabetes (T2D), and some have a number of other benefits, including weight loss, improvements in blood pressure and lipid profiles, and cardiovascular protection. They also provide a therapy option with a low risk of hypoglycemia, an attractive choice for many patients. Molecular structure and pharmacokinetic properties vary among GLP-1 RAs, with some more closely related than others to native glucagon-like peptide-1 (GLP-1). OW GLP-1 RAs have various modifications to their molecular structure that make the molecules resistant to degradation by dipeptidyl peptidase-4 (DPP-4), increasing the half-life of these drugs and making them suitable for OW administration. These differences in the molecular structures and pharmacokinetic properties between the various OW GLP-1 RAs help to explain the differences in efficacy, mechanisms, and safety profiles among the drugs, and these considerations can help primary care physicians to optimize prescribing practices.

Introduction

GLP-1 RAs are established options for the management of T2D in adults, often as an add-on to metformin monotherapy in patients with inadequate glycemic control.[1,2] A range of GLP-1 RAs has been developed that differ in their molecular structure and size, pharmacokinetic properties, and pharmacodynamic effects, including options with a half-life that supports OW administration.[3-5]

This narrative review will discuss the pharmacokinetics of GLP-1 RAs and the possible mechanisms underlying their pharmacodynamic effects, as well as consider the implications of these properties for patients and health care practitioners.

GLP-1 RAs differ in their molecular structure and pharmacokinetic properties

Native GLP-1 is a 30-amino acid peptide hormone associated with, among other characteristics, enhanced glucose-dependent insulin secretion and decreased glucose-dependent glucagon secretion, as well as inhibition of gastrointestinal motility and regulation of appetite and satiety.[6] In a review of preclinical and clinical studies of both DPP-4 inhibitors and GLP-1 RAs, Kawanami et al. demonstrated that incretin agents, including GLP-1 RAs, also protect against diabetes-associated complications, including atherosclerosis, nephropathy, retinopathy, and neuropathy. These effects have been attributed to downregulation of inflammation, oxidative stress, and macrophage activation.[7] The widespread systemic effects of GLP-1 are summarized in **TABLE 1**. Native GLP-1 has a half-life of only 1 to 2 minutes, owing to the rapid actions of the enzyme DPP-4, which metabolizes and degrades incretin hormones, including GLP-1.[6]

To utilize the glycemic properties of native GLP-1, GLP-1-based therapies with a longer half-life than those of native GLP-1 were developed, as either GLP-1 direct-acting or GLP-1 indirect-acting therapies.[5] GLP-1 direct-acting therapies—GLP-1 RAs—act to supplement GPL-1 in supraphysiologic doses, and are associated with a strong reduction in hemoglobin A1c (HbA_{1c}), weight loss, and a low risk of hypoglycemia.[17-20] GLP-1 indirect-acting therapies—DPP-4 inhibitors—act to inhibit the DPP-4 enzyme and prevent it from degrading GLP-1. DPP-4 inhibitors are associated with a modest reduction in HbA_{1c}, weight neutrality, and a low risk of hypoglycemia.[21,22]

GLP-1 RAs have been developed based on exendin-4 (a lizard peptide with 53% homology to human GLP-1) and human incretin hormone GLP-1, and act in a glucose-dependent manner to stimulate the secretion of insulin and reduce the secretion

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TABLE 1 Systemic effects of GLP-1

Target	GLP-1 effect
Pancreas	Increased insulin secretion[8]
	Decreased glucagon secretion[8]
	Increased insulin biosynthesis[8]
	Increased beta-cell proliferation[9]
	Decreased beta-cell apoptosis[10]
Gastrointestinal tract	Decreased gastric emptying[11]
	Decreased gastric motility[11]
	Decreased gastric secretions[11]
Brain	Increased neuroprotection[12]
	Decreased appetite[13]
Liver	Decreased glucose production[14]
Heart	Increased cardioprotection[15]
	Increased cardiac function[15]
Skeletal muscle	Increased glucose uptake and storage[16]

Abbreviation: GLP-1, glucagon-like peptide-1.

of glucagon.[5,6] GLP-1 RAs can be categorized as short-acting or long-acting, based on their pharmacokinetic and pharmacodynamic properties.

Short-acting GLP-1 RAs have a half-life of 2 to 4 hours, and this increased half-life (compared with native GLP-1) is due to modifications in the structure of the molecule, resulting in once- (OD) or twice-daily (BD) administration.[5,6] For example, exenatide BD is a synthetic version of exendin-4.[23] It is an incretin mimetic, with an amino-acid substitution of serine rather than alanine on the N-terminus of exendin-4, which makes the molecule resistant to degradation by DPP-4. Exenatide BD is approved for BD administration, within 1 hour of breakfast and dinner.[5,24,25] Similarly, lixisenatide, an injectable GLP-1 RA, is also derived from exendin-4, but has a modified C-terminus consisting of 6 additional lysine residues that act to resist degradation by DPP-4, increasing the half-life to 3 hours. This molecule is approved for OD administration within 1 hour of breakfast.[5,26,27]

Longer-acting GLP-1 RAs have a half-life greater than 12 hours (eg, 13 hours with liraglutide), with some having a half-life of as long as 14 days.[24] Indeed, GLP-1 RAs such as albiglutide, dulaglutide, exenatide extended-release (ER), and semaglutide each have a half-life that supports OW administration (**TABLE 2**). (Note: Albiglutide is scheduled to be withdrawn from the market in July 2018.[32])

Incorporating the exenatide molecule into a poly(D,L-lactic-co-glycolic acid) matrix provides controlled delivery of the active substance, allowing a steadystate concentration to be achieved in 6 to 10 weeks and increasing the half-life of exenatide from approximately 2.4 hours to 2 weeks. This OW formula can be administered at any time, irrespective of mealtimes.[33,34]

Both albiglutide and dulaglutide are larger macromolecules than native GLP-1, consisting of a DPP-4-resistant human GLP-1 dimer fused to a bulky side group consisting of recombinant human albumin (albiglutide) and a modified human immunoglobulin G4 heavy chain (dulaglutide). These large side groups, along with the DPP-4 resistance, allow for an extended half-life of approximately 5 and 4 days, respectively, compatible with OW dosing.[29,35]

Semaglutide is a human GLP-1 analog that has 94% homology to native human GLP-1. The 3 modifications to GLP-1 that increase the half-life of semaglutide and make it suitable for OW dose administration are (1) an amino acid substitution (alanine to α-aminoisobutyric acid) at position 8; (2) an amino acid substitution (lysine to arginine) at position 34; and 3) acylation of lysine in position 26 with the addition of a spacer and a C-18 fatty diacid side chain. The fatty diacid and the spacer mediate strong binding to albumin, and the amino acid substitution at position 8 makes semaglutide less susceptible to degradation by DPP-4, leading to a half-life of 7 to 8 days.[30,31]

GLP-1 RAs improve glycemic control with a low risk of hypoglycemia

The ability of native GLP-1 to stimulate insulin secretion and suppress glucagon secretion in a glucose-dependent manner acts to normalize plasma glucose in people with T2D.[36,37] This ability does not impair overall hypoglycemia counter-regulation in healthy volunteers, except for a reduction in growth hormone responses.[37]

The mode of action of GLP-1 RAs on glycemic control differs between short-acting and long-acting therapies. Short-acting GLP-1 RAs (including exenatide BD and lixisenatide) primarily lower postprandial the glucose level and insulin concentration, due to their ongoing impact on gastric emptying.[5,24] Conversely, long-acting GLP-1 RAs primarily lower the fasting blood glucose level by stimulating insulin secretion and reducing the glucagon level,[24] and appear to have limited effect on gastric motility, probably due to tachyphylaxis.[5] This difference in mode of action, as well as the differing half-lives, may contribute to variability in efficacy. Indeed, long-acting exenatide ER has been shown to provide greater reduction in HbA_{1c} than the short-acting exenatide BD formulation, and dulaglutide has also demonstrated superiority over exenatide BD.[38,39] Patients with T2D treated with OW semaglutide experienced superior glycemic control when compared with those treated with exenatide ER[40] or dulaglutide,[41] but the mechanism of this effect is yet to be elucidated, and may be multifactorial.

OW GLP-1 RAs are also associated with greater glycemic control and weight loss reductions compared with the DPP-4 inhibitor sitagliptin, a GLP-1 indirect-acting therapy, [21,22,42,43] as well as other antihyperglycemic agents in various patient populations.[21,44-47]

TABLE 2 Overview of once-weekly GLP-1 RAs

Therapy	Molecular structure	Half-life	Approved dosage	Time to steady state
Albiglutide[28]	DPP-4-resistant GLP-1 dimer fused to human albumin	6-7 days	30 mg, SC once weekly (increase to 50 mg once weekly if required)	Not reported
Dulaglutide[29]	DPP-4-resistant GLP-1 fused to Fc fragment of human immunoglobulin G4	5 days	0.75 mg, SC once weekly; can increase to 1.5 mg, SC once weekly, for additional glycemic control	2 weeks
Exenatide extended-release[24]	DPP-4-resistant GLP-1 encapsulated in PLGA microspheres	2 weeks	2 mg, once weekly	6-10 weeks
Semaglutide[30,31]	Human GLP-1 homolog with 2 amino acid substitutions and a C18 fatty acid side chain at the position of aminoisobutyric acid	7 days	0.5 mg, SC once weekly, increasing to 1 mg, SC once weekly	Not reported

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; OW, once-weekly; PLGA, poly(d,l-lactic-co-glycolic acid); SC, subcutaneous.

GLP-1 RAs are associated with weight loss

Weight loss of 5% to 10% in patients with T2D is associated with significant, clinically relevant reduction in cardiovascular (CV) risk factors, with further benefit observed in patients who lose more than 10% of body weight.[48]

GLP-1 RAs are associated with body-weight reduction in patients with T2D; the extent of this weight loss is affected by concomitant medications.[17-19,49] Native GLP-1 acts as a physiologic regulator of appetite and energy intake.[50] The physiologic actions of GLP-1 include slowing gastric emptying, which may contribute to lower energy intake and weight loss; however, this effect is attenuated during continued exposure and is therefore more strongly associated with the short-acting GLP-1 RAs.[51]

GLP-1 receptors have been found in the brain,[52,53] and brain activity related to highly desirable food cues was reduced in patients with T2D treated with liraglutide, compared with placebo-treated controls.[53] These data are supported by another study, which also demonstrated a reduction in appetite in patients with T2D treated with liraglutide[54]; similar effects have been observed in male subjects without diabetes who were treated with exenatide.[55] A reduction in appetite has also been observed with semaglutide treatment in people with obesity and HbA_{1c} less than 6.5%.[56]

Nonclinical studies in mice have shown that semaglutide enters the hypothalamus, where it indirectly inhibits the orexigenic peptides neuropeptide Y and agouti-related peptide.[57] Administration of semaglutide also leads to cell activation in brain regions associated with reward and food intake,[58] which may contribute to the weight-loss effect.

GLP-1 RAs reduce mean systolic and diastolic blood pressure

T2D is a major risk factor for CV disease; in particular, hypertension in patients with T2D is a major driver of excess CV risk.[59] OW GLP-1 RAs have been shown to decrease mean systolic and diastolic blood pressure (BP) in patients with T2D.[60-64]

Animal studies have suggested the involvement of several different pathways for this ability, including effects on the vascular, myocardial, renal, and central nervous systems; however, further mechanistic studies are required to elucidate the mechanism in humans, because it is unclear whether the same pathways are used.[60] A better understanding of the effects of GLP-1 RAs on BP may help provide explanations for the influence of GLP-1 therapies on CV risk in patients with T2D.

GLP-1 RAs improve lipid profiles

Lipid abnormalities are a particular marker for T2D—though they are also present in other conditions—further contributing to the risks of CV events. Studies have observed improvement in fasting and postprandial lipid profiles with the GLP-1 RAs liraglutide and semaglutide in patients with T2D, including a significant decrease in postprandial hypertriglyceridemia.[66,67] Exenatide ER has also demonstrated a positive effect on lipid profiles,[68] and a number of studies with dulaglutide have demonstrated favorable effects on cholesterol levels.[69]

Possible mechanisms underlying the effects of GLP-1 and GLP-1 RAs on lipids include reduced intestinal absorption of dietary lipids; inhibition of intestinal chylomicron output; regulation of hepatic very-low-density lipoprotein production; and enhanced hepatic fatty acid oxidation or autophagy. However, further studies are required to reveal fully the mechanisms of action of GLP-1 RAs in the intestine and liver to improve the lipid profile.[70]

Short- and long-acting GLP-1 RAs differentially increase mean heart rate

The short-acting GLP-1 RAs, exenatide BD and lixisenatide, are associated with a transient (less than 12) 1 to 3 beats per minute

(bpm) increase in mean heart rate measured over 24 hours, whereas the long-acting GLP-1 RAs, exenatide ER, liraglutide, and dulaglutide, are associated with more pronounced (3 to 10 bpm) increases in heart rate over the same period.[71] The GLP-1 receptor has been localized to sinoatrial node (SAN) myocytes in monkeys and human heart tissue.[72] A randomized 12-week parallel group trial of patients with T2D treated with exenatide compared with placebo indicated that direct SAN stimulation might be involved in the observed mean increase in heart rate.[73] The relationship between increased heart rate and effects on CV risk is complex, and may be mitigated by other improvements in CV risk factors, including improved glycemic control, reduction in weight and BP, and improved lipid profile.

Some long-acting GLP-1 RAs improve CV outcomes

CV outcome trials with liraglutide, semaglutide, exenatide and lixisenatide have published results:

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial reported superior reduction in the primary outcome of major adverse CV events (MACE) (time from randomization to first occurrence of CV death, nonfatal myocardial infarction [MI], nonfatal stroke) in patients with T2D and established CV disease or at high risk of CV disease who were treated with liraglutide, compared with those receiving placebo (P<0.001 for noninferiority and P=0.01 for superiority).[67] These data resulted in a recent update to the indications in the prescribing information for liraglutide (Victoza; Novo Nordisk A/S, Bagsværd, Denmark), to reduce the risk of MACE in adult patients with T2D and established CV disease.[74]

The SUSTAIN-6 trial of OW semaglutide vs placebo (when both were added to standard care) in patients with T2D at high CV risk met its primary endpoint of noninferiority of semaglutide compared with placebo in MACE. A post hoc (nonprespecified) analysis also reported a significantly superior reduction in the risk of MACE with semaglutide.[64] The mechanisms underlying these effects of semaglutide and liraglutide are unclear, but several hypotheses have been proposed, including: beneficial effect on weight and lipid profiles; anti-inflammatory effects; direct effect on the myocardium; and lowering of insulin resistance.[66]

To date, there are no CV outcome trials showing a similar benefit for other GLP-1 RAs. However, data from the Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) demonstrated noninferiority of exenatide ER vs placebo for MACE (composite endpoint of CV death, nonfatal MI, or nonfatal stroke), and fell just short of statistical significance for superiority.[75] OD lixisenatide was also shown to be noninferior to placebo in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial.[76] Trials evaluating CV outcomes with albiglutide and dulaglutide are ongoing (HARMONY Outcomes [estimated completion date, March 2018; clinicaltrials.gov NCT02465515]; and REWIND [estimated completion date, July 2018; clinicaltrials.gov NCT01394952]).[77]

Conclusions and perspectives

As a drug class, the GLP-1 RAs have proven efficacy for decreasing HbA_{1c} and for weight loss in T2D, with a reduced risk of hypoglycemia compared with insulin or sulfonylureas.[65] These characteristics underlie the inclusion of GLP-1 RAs in many clinical practice guidelines.[65,78]

The various chemical modifications of individual GLP-1 RAs underlie their pharmacokinetic and pharmacodynamic properties. Notably, the longer half-life of long-acting GLP-1 RAs may have important benefits for treatment. Conversations about starting injectable therapy can become easier when OW options are available to the patient; when given the choice between an OW and daily injection, many prefer the OW option.[79-81] For some patients, the option of less-frequent injection may reduce reluctance to initiate therapy and improve adherence.[82] Furthermore, missed doses of approved long-acting GLP-1 RAs can be adjusted if patients miss an injection, provided that there are at least 3 days until the next scheduled dose (exenatide ER83 or dulaglutide[28]). Some patients find it helpful to mark the calendar to remind them when to take the next dose.

In addition to improving glycemic control, GLP-1 RAs have extra-pancreatic effects that reduce a number of key CV risk factors. Weight loss, reduced BP, improved lipid profile, and improved endothelial and myocardial function have all been reported in preclinical and clinical studies of GLP-1 RAs.[24] Conversely, whereas GLP-1 RAs are associated with an increased heart rate and pulse,[5,60,70,73] recent CV outcome trials demonstrating CV benefit in patients with T2D would suggest that it is unlikely that this increased heart rate has any negative effect on CV risk factors.[64,67,84].

In addition to favorable efficacy, OW GLP-1 RAs may also be associated with less frequent gastrointestinal side effects, such as nausea, diarrhea, and vomiting,[85] a feature that is appreciated by patients and can help to maintain adherence to therapy.[82]

OW GLP-1 RAs have a good tolerability profile in practice, mitigating the burden associated with adverse effects. The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) place GLP-1 RAs second, immediately after metformin, in the hierarchy of recommended medications for glycemic management, owing to their robust HbA_{1c}-lowering efficacy, low risk of hypoglycemia, and usual association with weight and BP reductions.[2]

When selecting a GLP-1 RA for an individual patient, the medical history, including risk of CV disease, should be considered. Guidelines from the American Diabetes Association recommend consideration of liraglutide or empagliflozin (a sodium–glucose cotransporter-2 inhibitor), in patients with longstanding, suboptimally controlled T2D and established atherosclerotic CV disease, because these medications reduce CV and all-cause mortality when added to standard care. Weight loss may also be considered when treating patients who

are overweight (body mass index; BMI, * at least 25 to 29.9) with T2D.[2] Limiting the use of GLP-1 RAs to obese patients (BMI, at least 30) precludes overweight patients (BMI at least 25–29.9) with T2D from the associated weight-loss benefits.

It is therefore important to consider key patient factors when prescribing GLP-1 RAs. Unlike metformin and thiazolidinediones, GLP-1 RAs are not contraindicated in patients with significant heart failure, which, along with the low risk of hypoglycemia, may address an unmet need for older patients with T2D. However, administration of GLP-1 RAs requires motor, visual, and cognitive skills, which may make them unsuitable for some patients. The weight loss associated with GLP-1 RAs may also be undesirable—in older patients with cachexia, for example.[65] Because GLP-1 RAs are not substitutes for insulin, they should not be considered for use in patients with type 1 diabetes or diabetic ketoacidosis.[65]

The variability in molecular structure, pharmacokinetic properties and half-life within the OW GLP-1 RA class may provide evidence to explain the inconsistency in efficacy, mechanisms, and safety profiles among the drugs; this requires further study. The differences in efficacy and safety should be considered by healthcare practitioners, alongside the aforementioned patient factors, to fully optimize prescribing practices. ●

**Calculated as weight in kilograms divided by height in meters squared.*

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Clinical Efficacy of Once-weekly Glucagon-like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are indicated for restoring normoglycemia in patients with type 2 diabetes (T2D). This review analyzed and compared the efficacy results from 30 trials with the once-weekly (OW) GLP-1 RAs albiglutide, dulaglutide, exenatide extended-release (ER) and semaglutide. The 4 OW GLP-1 RAs showed a higher reduction in glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and body weight, when compared to placebo. Semaglutide significantly reduced the HbA_{1c} level (estimated treatment difference [ETD]: –0.62%; 95% confidence interval [CI], –0.79 to –0.44; *P*<0.0001), FPG (ETD: –15 mmol/L; 95% CI, –22 to –8.3; *P*<0.0001) and body weight (ETD: –3.73 kg; 95% CI, –4.53 to –2.93; *P*<0.0001) compared with exenatide ER. A direct comparison between OW, once-daily (OD), and twice-daily (BD) GLP-1 RAs indicated some trends in efficacy, for example, with OD liraglutide, providing a significant reduction in body weight vs albiglutide (ETD: 1.55 kg; 95% CI, 1.05-2.06; *P*<0.0001 for albiglutide), dulaglutide (ETD: 0.71 kg; 95% CI, 0.17 -1.26; *P*=0.011 for dulaglutide), and exenatide ER (ETD: 0.90 kg; 95% CI, 0.39-1.40; *P*=0.0005 for exenatide ER). OW GLP-1 RAs also offered improved glycemic control when compared with the dipeptidyl peptidase-4 inhibitor sitagliptin. In conclusion, OW GLP-1 RAs offer a valid therapeutic option for T2D.

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DISCLOSURES

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Introduction

GLP-1 RAs are glucose-lowering agents for the treatment of T2D that act on the GLP-1 receptor of beta-cells in the pancreas to increase insulin secretion, help decrease glucagon secretion, slow gastric emptying, and increase satiety[1] (See "The Pharmacokinetic Properties of Glucagon-like Peptide-1 Receptor Agonists and Their Mode and Mechanism of Action in Patients with Type 2 Diabetes" on page S8). GLP-1 RAs have also demonstrated weight loss and decreases in some cardiovascular risk factors in clinical trials vs placebo/active comparators.[1]

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have recommended GLP-1 RAs as a combination therapy for those patients who despite intensive therapy still have a glycated hemoglobin (HbA_{1c}) level above the recommended target.[2] Moreover, in the recently published guidelines, ADA recommended GLP-1 RAs as first-line therapy, and in combination with metformin and lifestyle management, in those patients with HbA_{1c} at least 9% and atherosclerotic cardiovascular disease.[3] In their recent consensus statement, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) recommended the use of GLP-1 RAs as second-line therapy for patients with HbA_{1c} less than 7.5%, and as second agent in addition to metformin (or substitute first-line agent) for those with HbA_{1c} at least 7.5%.[4]

In addition to those formulations that require daily dosing, 4 GLP-1 RAs with an OW dosing are approved in the United States (albiglutide [scheduled to be discontinued July 2018],[5] dulaglutide,[6] exenatide ER,[7] and semaglutide[8]). OW therapies might reduce the burden of frequent injections as well as increase adherence.[9] As efficacy is 1 of many aspects to consider when prescribing treatments for patients,[3] awareness of any differences between these 4 OW GLP-1 RAs is important. Data on safety, including CV outcomes, will be discussed in separate manuscripts in this supplement (See "Safety of Once-weekly Glucagon-like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes" on page S25).

Methods

This review compares the relative efficacy of OW GLP-1 RAs from a total of 30 randomized, controlled trials, focusing on glycemic

control (HbA_{1c}, fasting plasma glucose [FPG] or fasting serum glucose [FSG], post-prandial glucose [PPG]), and weight. These trials include the pivotal sponsor-led investigations supporting the efficacy and safety of the 4 OW GLP-1 RAs, some of the data from which supported their original 'new drug applications' to the US Food and Drug Administration. A CV safety trial[10] reported efficacy data, but as this was on a background of standard care, the results cannot be compared with standard efficacy designs, and thus was not included in this review.

Results

OW GLP-1 RAs vs placebo

Results from 11 randomized, controlled trials of GLP-1 RAs from 24 to 104 weeks' duration that included a placebo arm are summarized in **TABLE 1**; 4 used albiglutide,[11-14] 3 used dulaglutide,[15-17] 2 used exenatide ER,[17-19] and 3 used semaglutide.[20-22] All trials showed statistically significant and clinically meaningful reductions in HbA_{1c} for the antidiabetic treatments tested, with mean treatment differences ranging from –0.66% to –1.76% (**TABLE 1**). This was true across a variety of allowed background therapies (ie, diet and exercise alone, metformin, sulfonylureas, other oral antidiabetes drugs [OADs], and basal insulin).

Where reported, GLP-1 RAs also showed statistically significant reductions in mean FPG/FSG, with mean treatment differences ranging from –20.5 to –43 mg/dL vs placebo.[11-13,15,18,20,21] Results for PPG control are difficult to compare directly, as a variety of measures were reported (eg, 6-point self-monitored blood glucose [SMBG],[18] 7-point self-measured plasma glucose [SMPG],[20] 7-point SMPG and post-prandial increment).[20] All of the trials showed a numerically greater reduction in body weight for the OW GLP-1 RAs vs placebo, although these differences varied in magnitude and only some were reported as statistically significant.[10,16,18,20,21]

OW GLP-1 RAs vs dipeptidyl peptidase-4 (DPP-4) inhibitors

All 6 trials that compared an OW GLP-1 RA with a DPP-4 inhibitor (sitagliptin) (**TABLE 2**) demonstrated that OW GLP-1 RAs were associated with significantly greater decreases in HbA_{1c} vs sitagliptin (range of treatment differences, –0.38% to –1.06%).[11,18,23-26] For the 5 trials reporting treatment differences for FPG, those results also significantly favored the OW GLP-1 RA over sitagliptin (range of treatment differences, –10.1 mg/dL to –26.8 mg/dL).[11,18,23-26]

Five of the 6 trials demonstrated that treatment with an OW GLP-1 RA resulted in a favorable effect on weight compared with sitagliptin (range of treatment differences, –1.07 kg to –4.20 kg).[11,18,23-26] One trial showed no significant difference in weight between the treatments (treatment difference, 0.1 kg [95% CI, –0.7 to 0.9], P=0.86).[18]

OW GLP-1 RAs compared with other treatments

Results from randomized trials or arms of randomized trials comparing OW GLP-1 RAs with other treatments not discussed above are shown in **TABLE 3**. These include metformin,[25,27] the sulfonylurea glimepiride,[11] the sodium-glucose co-transporter (SGLT)-2 inhibitor dapagliflozin,[34] thiazolidinediones,[12,24,25] and insulin.[28,30-32] Some of these trials have been mentioned above because they included a placebo arm (**TABLE 1**), or an arm with a DPP-4 inhibitor (**TABLE 2**). Head-to-head comparisons between OW GLP-1 RAs will be discussed later (**TABLE 4**).

Oral agents

ADA guidelines state that metformin is the first-line monotherapy to consider in patients with T2D and HbA_{1c} less than 9%, with dual or triple combination therapy to be considered under specific circumstances.[3] For this reason, many of the trials included in this review allowed the use of metformin as a baseline treatment, in addition to the OW GLP-1 RAs under investigation. Direct comparisons of OW GLP-1 RAs as monotherapies to metformin were less common. It was evident from the majority of the trial data that when used in combination with metformin, OW GLP-1 RAs are efficacious for glucose control and weight loss. Just 2 trials investigated OW GLP-1 RAs as monotherapy versus metformin (dulaglutide in AWARD-3[27] and exenatide ER in DURATION-4[25]), and in those cases, OW GPL-1 RAs were more effective than metformin.

Three trials compared an OW GLP-1 RA with pioglitazone, 2 involving exenatide ER,[24,25] and 1 involving albiglutide.[14] Exenatide ER was shown to improve glycemic control relative to pioglitazone in both studies (26 weeks; DURATION-2 and DURATION-4).[24,25] Also, patients using exenatide ER lost a mean of –2.3 kg and –2.0 kg, respectively, whereas patients using pioglitazone gained a mean of 2.8 kg and 1.5 kg, respectively (both treatment differences: P<0.001).[24,25] By comparison, in the 52-week study using albiglutide, patients experienced a small but statistically significant increase in HbA_{1c} relative to pioglitazone (treatment difference, 0.25% [0.10; 0.40], P=0.001) while simultaneously losing a significant amount of body weight (treatment difference, –4.85 kg [95% CI, –5.51 to –4.20], P<0.001).[12]

A single 104-week trial (HARMONY-3) compared a sulfonylurea (glimepiride) with albiglutide.[11] Results indicated that albiglutide improved glycemic control and was associated with a mean weight loss of 1.21 kg, whereas patients taking glimepiride experienced a mean weight gain of 1.17 kg.

SGLT-2 inhibitors

Only 1 trial (DURATION-8) compared an OW GLP-1 RA (exenatide) in combination with an SGLT-2 inhibitor, ie dapagliflozin (**TABLE 3**).[34] These 2 treatments improve glycemic control and reduce weight via different mechanisms, so it was logical to see if their use in combination might be more effective than either one used alone. As shown in **TABLE 3**, the combination of these 2 treatments was superior to monotherapy.

TABLE 1 Results from trials where OW GLP-1 RAs were compared with placebo

Data are estimated treatment differences expressed in mean (95% CI) unless stated otherwise.

				Treatment difference (OW GLP-1 RA–placebo) or other characterization			
Trial name and time to primary endpoint*	**Current therapies allowed**	**OW GLP-1 RA**	**Comparator(s) other than placebo**	**HbA_{1c}, %**	**FPG/FSG, mg/dL**	**Other glycemic results, mg/dL**	**Body weight, kg**
HARMONY-1;[14] 52 weeks	Pioglitazone ± metformin	Albiglutide 30 mg		–0.8 (–1.0; –0.6); *P*<0.0001	–29 (–40; –20); *P*<0.0001	NR	–0.2 kg; *P*=0.72
HARMONY-2;[13] 52 weeks	Metformin, insulin	Albiglutide 30 mg Albiglutide titrated to 50 mg at week 12		–0.84 (–1.11; –0.58); *P*<0.0001 –1.04 (–1.31; –0.77); *P*<0.0001	–34.0 (–45.9; –22.0); *P*<0.0001 –42.8 (–54.9; –30.8); *P*<0.0001	NR	Albiglutide (both doses) NS different from placebo
HARMONY-3;[11] 104 weeks	Metformin	Albiglutide 30 mg (titrated as needed up to 50 mg)	Sitagliptin, glimepiride	–0.9 (–1.2; –0.7); *P*<0.0001	–28; *P*<0.0001	NR	**Δ from baseline** Albiglutide: –1.21 Placebo: –1.0
HARMONY-5;[12] 52 weeks	Metformin, glimepiride	Albiglutide 30 mg	Pioglitazone	–0.87 (–1.07;–0.68); *P*<0.001	–23.9 (–34.0; –13.7); *P*<0.001	NR	–0.03 (–0.88; 0.82) *P*=0.95
AWARD-1;[18] 26 weeks	At least 1 OAD (± pioglitazone ± metformin)	Dulaglutide 1.5 mg Dulaglutide 0.75 mg	Exenatide BD	–1.05 (–1.22; –0.88); *P*<0.001 –0.84 (–1.01; –0.67); *P*<0.001	**Δ from baseline** Dulaglutide 1.5 mg: –43 ± 2 Dulaglutide 0.75 mg: –34 ± 2 Placebo: –5 ± 3	NR	**Δ from baseline** Dulaglutide 1.5 mg: –1.30 ± 0.29 Dulaglutide 0.75 mg: –0.20 ± 0.29
AWARD-8;[15] 24 weeks	Glimepiride	Dulaglutide 1.5 mg		–1.3 (–1.6: –1.0); *P*<0.001	–33.54 (–46.55; –20.53); *P*<0.001	NR	–0.68 (–1.53; 0.18); NS
AWARD-9;[16] 28 weeks	Insulin glargine ± metformin	Dulaglutide 1.5 mg		–0.77 (–0.97;–0.56); *P*<0.001	NR	NR	–2.41 (–3.19; –1.64); *P*<0.001
DURATION-NEO-2;[18] 28 weeks	Metformin	Exenatide OWS-AI 2. mg	Sitagliptin	–0.72 (–1.15; –0.30); *P*=0.001	–30.9 (–46.7;–15.1); *P*<0.001	**6-point SMBG** –18.8 (–28.3; –9.3); *P*=0.001‡	–1.3 (–2.3; –0.2); *P*=0.020‡
DURATION-7;[19] 28 weeks	Metformin	Exenatide ER + insulin glargine	Placebo + insulin glargine	–0.7 (–0.9; –0.5); *P*<0.001	–10 (–18;–1); *P*=0.021	**2-h PPG** –28 (–39; –17); *P*<0.001	–1.5 (–2.1; –0.8); *P*<0.001
SUSTAIN-1;[21] 30 weeks	Metformin	Semaglutide 1 mg Semaglutide 0.5 mg		–1.53 (–1.81;–1.25); *P*<0.0001 –1.43 (–1.71;–1.15); *P*<0.0001	–32.2 (–41.6; –22.7); *P*<0.0001 –35.3 (–44.8; –25.7); *P*<0.0001	**7-point SMPG** –13.3 (–21.4; –5.22); *P*=0.0014 –7.4 (–16; 0.9); *P*=0.0807	–3.56 (–4.74; –2.38); *P*<0.0001 –2.75 (–3.92; –1.58); *P*<0.0001

SUSTAIN-5;[20] 30 weeks	Basal insulin ± metformin	Semaglutide 1 mg Semaglutide 0.5 mg		–1.76; *P*<0.0001 –1.36; *P*<0.0001	–33.7 (–44.5; –22.9); *P*<0.0001 –20.5 (–31.3;–9.72); *P*=0.0002	**7-point SMPG** –40.9 (–50.9; –30.6); *P*<0.0001 –31.5 (–41.6; –21.2); *P*<0.0001	–5.03; *P*<0.0001 –2.28; *P*<0.0001
SUSTAIN-6;[10] 104 weeks	Non-incretin-based therapies	Semaglutide 0.5 mg Semaglutide 1 mg		–0.66 (–0.80; –0.52); *P*<0.0001 –1.05 (–1.19; –0.91); *P*<0.0001	NR	NR	–2.87 (–3.47; –2.28); *P*<0.0001 –4.35 (–4.94; –3.75); *P*<0.0001

Abbreviations: AWARD, A Study in Participants With Type 2 Diabetes Mellitus; DURATION-NEO-2, Comparison Study of the Glycemic Effects, Safety, and Tolerability of Exenatide Once Weekly Suspension to Sitagliptin and Placebo in Subjects With Type 2 Diabetes Mellitus; ER, extended release; FPG, fasting plasma glucose; FSG, fasting serum glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HARMONY, Effect of Albiglutide when added to Standard Blood glucose lowering therapies, on major cardiovascular events in subjects with type 2 diabetes mellitus; HbA_{1c}, glycated hemoglobin; NR, not reported; NS, not significant; OADs, oral antidiabetic medications; OW, once weekly; OWS-AI, once weekly suspension for autoinjection; PPG, post-prandial glucose; SMBG, self-measured blood glucose; SMPG, self-measured plasma glucose; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes.

The conversion factor used to convert FPG/FSG and other glycemic values from mmol/L to mg/dL is 18.

*All studies are randomized, phase 3, double-blind trials, where the primary endpoint was change from baseline at the end of the trial in HbA_{1c}, unless stated otherwise.

†Phase 2 trial

‡Nominal *P*-value; formal hypothesis testing was stopped after FPG analysis.

Insulin

Six trials (HARMONY-4, HARMONY-6, AWARD-2, AWARD-4, SUSTAIN-4, DURATION-3) examined an OW GLP-1 RA vs OD basal insulin glargine[28,30-33,42] with 1 involving a basal–bolus regimen that also included the bolus insulin lispro thrice daily (**TABLE 3**).[30]

When comparing the different study results, it is important to consider the stringency to which the basal insulin arm was titrated to the FPG goal. In the 52-week trial comparing albiglutide with a basal-only insulin regimen, there was no significant difference in HbA_{1c} between the 2 treatments (0.11% [95% CI, –0.04 to 0.27]).[30] However, there was more than a 2-fold reduction in FPG (–37 vs –16 mg/dL; *P*<0.0001) for patients using insulin glargine, achieved with adjustments made to insulin doses if FPG increased by 20 mg/dL or more over 2 consecutive days or decreased by at least 20 mg/dL over the preceding week.[30] Two 52-week trials looked at dulaglutide at both 1.5 and 0.75 mg OW.[28,31] HbA_{1c} was lowered to a significantly greater extent at both doses in each trial compared with insulin glargine (uptitration of insulin followed a standard algorithm, eg dose adjustment of 0 to 2 units for FPG of 100 to 119 mg/dL).[28,31] At the higher dose (1.5 mg), there was also a modest weight loss with dulaglutide, whereas patients using insulin glargine gained weight. In the semaglutide trial (30 weeks)[32] and the exenatide trial (26 weeks)[29] changes in HbA_{1c}, FPG, and weight all significantly favored the OW GLP-1 RA over insulin glargine (uptitration based on the lowest pre-breakfast SMPG of the preceding 3 days[32] or instructions provided to the patients, but details not published[29]). Finally, in the 28-week trial comparing OW albiglutide with a full basal–bolus insulin regimen in patients inadequately controlled on a basal-only regimen plus OADs, there were small but statistically significant improvements in HbA_{1c} and body weight vs the insulin lispro/insulin glargine regimen (insulin uptitration based on previous 2 days and at the investigator's discretion).[33]

Head-to-head trials of GLP-1 RAs

Of the trials included in this review, only 2 directly compared two OW GLP-1 RAs. These trials compared semaglutide with exenatide ER (SUSTAIN-3, 56 weeks), and semaglutide with dulaglutide (SUSTAIN-7, 40 weeks), respectively.[35,36] In these trials, patients receiving semaglutide had significantly greater reductions in HbA_{1c}, FPG, 7-point SMPG, and postprandial increment of the 7-point SMPG compared with those receiving exenatide ER or dulaglutide, respectively (**TABLE 4**).[35,36] There were 3 head-to-head trials directly comparing an OW GLP-1 RA with an OD GLP-1 RA, and 3 comparing an OW-GLP-1 RA with a BD GLP-1 RA (**TABLE 4**), with no clear trend in the glycemic control data. Comparisons were difficult due to differing dosages and titration even for some of the same treatments. When considering the effect on weight, in the single OW head-to-head trial, treatment with semaglutide resulted in greater weight loss compared with exenatide ER.[35] When comparisons were made between OW, OD, and BD GLP-1 RAs, it appeared that the OD GLP-1 RA liraglutide had an increased beneficial effect on weight compared with albiglutide (estimated treatment difference [ETD]: –1.55 kg, *P*<0.0001),[37] dulaglutide (ETD: –0.71 kg, *P*<0.011),[38] and exenatide ER (ETD: –0.90 kg, *P*=0.0005; **TABLE 4**).[39]

One 30-week trial compared the same product, exenatide, in both a BD and OW administration.[40] The OW formulation, which is considered

TABLE 2 **Results from trials of OW GLP-1 RAs vs DPP-4 inhibitors**

Data are estimated treatment differences expressed in mean (95% CI) unless stated otherwise.

				Treatment differences (OW GLP-1 RA – comparator DPP-4 inhibitors) or other characterization		
Trial name and time to primary endpoint*	**Current therapies allowed**	**OW GLP-1 RA** **Comparator DPP-4 inhibitors**	**Other comparator(s)**	**HbA_{1c},%**	**FPG/FSG, mg/dL**	**Body weight, kg**
HARMONY-3;[11] 104 weeks	Metformin	Albiglutide 30 mg OW (titrated as needed up to 50 mg), Sitagliptin 100 mg OD	Placebo, glimepiride	–0.4 (–0.5; –0.2); *P*=0.0001	–16; *P*=0.0002	**Δ from baseline** –1.21 –0.86 *P*<0.0001
AWARD-5;[23] 52 weeks	Metformin	Dulaglutide 1.5 mg OW Dulaglutide 0.75 mg OW, sitagliptin 100 mg OD		–0.71 (–0.87; –0.55) –0.75 (–0.63; –0.31)	–26; *P*<0.001 –13; *P*<0.001	–1.50; *P*<0.001 –1.07; *P*<0.001
DURATION-2;[24] 26 weeks	Metformin	Exenatide ER 2 mg OW, sitagliptin 100 mg OD	Pioglitazone	–0.6 (–0.9; –0.4), *P*<0.0001	–16 (–5; –25); *P*=0.0038	–1.5 (–2.4; –0.7), *P*=0.0002
DURATION-4;[25] 26 weeks	None	Exenatide ER 2 mg OW, sitagliptin 100 mg OD	Metformin, pioglitazone	**Δ from baseline** –1.53 –1.15 (–0.62; –0.13); *P*<0.001†	**Δ from baseline** –41 –20; *P*<0.001	**Δ from baseline** –2.0 –0.8; *P*<0.001
DURATION-NEO-2;[18] 28 weeks‡	Metformin	Exenatide OWS-AI 2 mg, Sitagliptin 100 mg OD	Placebo	–0.38 (–0.70; –0.06); *P*=0.021	–10.1 (–21.8; 1.7); *P*=0.092	0.1 (–0.7; 0.9); *P*=0.86§
SUSTAIN-2;[26] 56 weeks	Metformin, pioglitazone Rosiglitazone	Semaglutide 1 mg OW Semaglutide 0.5 mg OW Sitagliptin 100 mg OD	None	–1.06 (–1.21; –0.91); *P*<0.0001 –0.77 (–0.92; –0.62); *P*<0.0001	–26.8 (–31.9; –21.8); *P*<0.0001 –17 (–22.7; –12); *P*<0.0001	–4.20 (–4.91; –3.49); *P*<0.0001 –2.35 (–3.06; –1.63); *P*<0.0001

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; ER, extended release; FPG, fasting plasma glucose; FSG, fasting serum glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; OD, once daily; OW, once weekly; OWS-AI, once weekly suspension for autoinjection.

The conversion factor used to convert FPG/FSG values from mmol/L to mg/dL is 18.

*All studies are randomized, phase 3, double-blind trials, where the primary endpoint was change from baseline in HbA_{1c} at the end of the trial, unless stated otherwise.

†98.3% confidence interval reported.

‡This trial was open-label.

§Nominal *P*-value; formal hypothesis testing was stopped after FPG analysis.

to be more convenient for patients, provided significantly better glycemic control as measured by HbA_{1c} (ETD: –0.33%, *P*<0.0023) and FPG (ETD: –23 mg/dL, *P*<0.0001) than the BD formulation, without an increased risk of hypoglycemia and comparable reductions in body weight. In a 22-week extension of that trial, those glycemic improvements were sustained in the OW group, and glycemic control further improved when patients formerly in the BD group switched to the OW formulation.[43] However, change from baseline in 2-h PPG was greater when exenatide was used BD rather than OW (124 vs 95 mg/dL, respectively). Gastric emptying delay during the meal tolerance test was also more pronounced with BD use.

Discussion

The estimated treatment differences of the 4 OW GLP-1 RAs against placebo demonstrated significantly reduced HbA_{1c} at their

TABLE 3 Results from trials of OW GLP-1 RAs vs other treatments

(Data are estimated treatment differences expressed in mean (95% CI) unless stated otherwise.)

				Treatment differences (OW GLP-1 RA – comparator treatment) or other characterization			
Trial name and time for treatment period*	**Other therapies allowed**	**OW GLP-1 RA Comparator treatment(s)**	**Other comparator(s)**	**HbA_{1c},%**	**FPG/FSG, mg/dL**	**Other glycemic results, mg/dL**	**Body weight, kg**
OW GLP-1 RA used as single agent vs other therapies							
AWARD-3;[27] 52 weeks†	None	 Dulaglutide 1.5 mg OW Dulaglutide 0.75 mg OW Metformin OD	None	 –0.22 (–0.36; –0.08) *P*=0.002 –0.15 *P*=0.020	**Δ from baseline** –29 ± 2 –26 ± 2 –24 ± 2 *P*=0.025 for dulaglutide 1.5 mg vs metformin	NR	**Δ from baseline** –2.29 ± 0.24 –1.36 ± 0.24 –2.22 ± 0.24; *P*=0.001
DURATION-4;[25] 26 weeks	None	 Exenatide ER 2 mg OW, Metformin 2000 mg OD Pioglitazone 45 mg OD	Sitagliptin	**Δ from baseline** –1.53 –1.48 (–0.26; 0.17)‡ *P*=0.620 –1.63 (–0.15; 0.35)‡ *P*=0.328	**Δ from baseline** –41 –36 *P*=0.155 for metformin vs exenatide ER 2 mg	NR	**Δ from baseline** –2.00 –2.00 *P*=0.892 +1.5 *P*<0.001
AWARD-4;[28] 52 weeks†,§	Insulin OADs	 Dulaglutide 1.5 mg OW Dulaglutide 0.75 mg OW Insulin glargine OD	None	 –0.22 (–0.38; –0.07) *P*=0.005 –0.17 (–0.33; –0.02) *P*=0.015	**Δ from baseline** –4.9 4.0 –28.4	**Δ from baseline 2-h post meals** –70.9 –73.1 –67.7	**Δ from baseline** –0.87 (–1.40; –0.34) 0.18 (–0.35; 0.71) 2.33 (1.80; 2.86)
DURATION-3;[29] 26 weeks§	Metformin SUs	Exenatide 2 mg OW Insulin glargine OD	None	–0.16 (–0.29; –0.03) *P*=0.017	11 (4; 18) *P*=0.001	NR	–4.0 (–4.6; –3.5) *P*<0.0001
OW GLP-1 RAs used in combination with other therapies							
DURATION-2;[24] 26 weeks	None	Exenatide ER 2 mg OW + metformin, Pioglitazone 45 mg OD + metformin	Sitagliptin	–0.3 (–0.6; –0.1), *P*=0.0165	–3.6 (–14; –5.4), *P*=0.3729	NR	–5.1 (–5.9; –4.3), *P*<0.0001

TABLE 3 Results from trials of OW GLP-1 RAs vs other treatments (*continued*)

(Data are estimated treatment differences expressed in mean (95% CI) unless stated otherwise.)

				Treatment differences (OW GLP-1 RA – comparator treatment) or other characterization			
Trial name and time for treatment period*	**Other therapies allowed**	**OW GLP-1 RA** **Comparator treatment(s)**	**Other comparator(s)**	**HbA_{1c},%**	**FPG/FSG, mg/dL**	**Other glycemic results, mg/dL**	**Body weight, kg**
HARMONY-5;[12] 52 weeks	Glimepiride	Albiglutide 30 mg OW (titration to 50 mg allowed) + metformin Pioglitazone 30 mg OD (titration to 45 mg allowed) + metformin	Placebo	0.25 (0.10; 0.40) *P*=0.001	18.9 (11.0; 26.8) *P*<0.001	NR	–4.85 (–5.51; –4.20), *P*<0.001
HARMONY-3;[11] 104 weeks	None	Albiglutide 30 mg OW titrated to 50 mg + metformin Glimepiride 2 mg OD titrated to 4 mg + metformin	Sitagliptin, placebo	–0.3 (–0.5; –0.1); *P*=0.0033	–10; *P*=0.0133	NR	**Δ from baseline** –1.21 +1.17 *P*<0.0001 for albiglutide vs glimepiride
HARMONY-4;[30] 52 weeks§	SUs	Albiglutide 30 mg OW (titration to 50 mg allowed after week 4) + metformin Insulin glargine OD + metformin	None	0.11 (–0.04; 0.27)	**Δ from baseline** –16 –37 *P*<0.0001	NR	–2.61 (–3.20; –2.02) *P*<0.0001
AWARD-2;[31] 78 weeks§,‖	None	Dulaglutide 1.5 mg OW + metformin + glimepiride Dulaglutide 0.75 mg OW + metformin + glimepiride Insulin glargine OD + metformin + glimepiride	None	–0.45 (–0.60; –0.29); *P*<0.001 –0.13 (–0.29; 0.02); *P*<0.001	**Δ from baseline Pre-breakfast** –27 ± 3 mg/dL –16 ± 3 mg/dL –32 ± 3 mg/dL	**Δ from baseline 2-h post meals** –35 ± 2 mg/dL –30 ± 2 mg/dL –29 ± 2 mg/dL	**Δ from baseline** –1.87 ± 0.24 *P*<0.001 vs glargine –1.33 ± 0.24 *P*<0.001 vs glargine +1.44 ± 0.24
SUSTAIN-4;[32] 30 weeks§	SUs	Semaglutide 1 mg OW + metformin Semaglutide 0.5 mg OW + metformin Insulin glargine OD + metformin	None	–0.81 (–0.96; –0.67) *P*<0.0001 –0.38 (–0.52; –0.24) *P*<0.0001	–11 (–17; –5.2) *P*=0.0002 1.4 (–4.3; 7.2) *P*=0.6243	**8-point SMPG** –10 (–15; –5.6); *P*<0.0001 –0.72 (–5.4; 4.1); *P*=0.7816	–6.33 (–6.99; –5.67) *P*<0.0001 –4.62 (–5.27; –3.96) *P*<0.0001

HARMONY-6;[33] 52 weeks†§	Metformin Pioglitazone Alpha glucosidase inhibitors	Albiglutide (titration to 50 mg allowed after week 8) with insulin glargine Three times daily lispro with insulin glargine	None	–0.16 (–0.32; 0.00) $P<0.0001$¶	–18 –13 $P=0.2366$ for albiglutide vs lispro	NR	–1.5 (–2.1; –1.0) $P<0.0001$
DURATION-8;[32] 28 weeks	None	Exenatide + dapagliflozin + metformin Exenatide 2 mg OW + metformin Dapagliflozin 10 mg OD + metformin	None	–0.4 (–0.6; –0.1); $P=0.004$ –0.6 (–0.8; –0.3); $P<0.001$	–20.0 (–27.9; –12.1); $P<0.001$ –16 (–24.3; –8.6); $P<0.001$	**2-h PPG** –7.7 (–15 to –0.54); $P=0.036$ –10.4 (–18; –3.2); $P=0.005$	–1.87 (–2.66; –1.08); $P<0.001$ –1.22 (–2.00; –0.44); $P=0.002$

Abbreviations: ER, extended release; FPG, fasting plasma glucose; FSG, fasting serum glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; NR, not reported; OD, once daily; OW, once-weekly.

The conversion factor used to convert FPG/FSG and other glycemic values from mmol/L to mg/dL is 18.

*All studies are randomized, phase 3, double-blind trials, where the primary endpoint was change from baseline in HbA_{1c} at the end of the trial, unless stated otherwise.

†The primary endpoint was change from baseline in HbA_{1c} at 26 weeks.

‡98.3% confidence interval.

§This was an open-label trial.

‖The primary endpoint was change from baseline in HbA_{1c} at 52 weeks.

¶Non-inferiority *P*-value.

respective primary endpoints in all 10 trials; 8 also reported data showing significant reductions in FPG (**TABLE 1**).[10-16,18,20,21] It is important to recognize that these trials were heterogeneous with respect to duration, dose, prior diabetes treatment history, and background therapies allowed. Despite these limitations, differences have been demonstrated among these agents (**TABLE 4**). While greater efficacy might be expected with OW GLP-1 RAs due to the potentially increased adherence, this has not always been found to be true (HARMONY-7,[37] AWARD-6,[38] and DURATION-6[39]). One OW GLP-1 RA with perceived lesser efficacy (albiglutide) is no longer marketed in the United States.

The most relevant clinical information comes from 8 head-to-head trials comparing GLP-1 RAs trials (**TABLE 4**), with only 2 trials directly comparing 2 OW GLP-1 RAs (semaglutide vs exenatide ER, and semaglutide vs dulaglutide).[35,36] Results from these trials indicated that better glycemic control was achieved with semaglutide compared with exenatide ER or dulaglutide. The other 6 head-to-head trials either compared an OW GLP-1 RA with a GLP-1 RA taken OD or BD, or in 1 case, compared an OW with a BD formulation of the same drug (exenatide ER vs exenatide).[41] In AWARD-6, HbA_{1c} was significantly noninferior and not superior for dulaglutide vs liraglutide;[38] in DURATION-5, HbA_{1c} was significantly lower for exenatide ER vs exenatide BD;[41] in HARMONY-7, HbA_{1c} was not significantly different between albiglutide and liraglutide,[37] and, finally, in DURATION-6, HbA_{1c} was significantly higher for the OW treatment, exenatide ER.[39] FPG results mirrored those for HbA_{1c}. The comparative effect of daily vs weekly dosing on PPG is important to understand. Only 1 trial compared these 2 dosing regimens for the same product (exenatide ER vs exenatide BD)[40] and those results indicated that there was a greater change in PPG from baseline for BD dosing (–124 vs –95 mg/dL, $P=0.0124$). The 2 other trials compared the OW GLP-1 RA (dulaglutide) against either exenatide BD[17] or liraglutide OD,[38] with the former showing a lower mean PPG with dulaglutide 1.5 mg and the latter showing no significant difference.

Results from trials comparing OW GLP-1 RAs vs sitagliptin were very consistent, with both HbA_{1c} and fasting glucose values being significantly lower with the GLP-1 RAs (**TABLE 2**). For both sitagliptin as well as other treatments (**TABLE 3**), there was a clear trend for OW GLP-1 RAs to have significantly greater weight loss vs the comparators.

Although this was not a systematic review, we have no reason to believe that any randomized trials of OW GLP-1 RAs were not included, and thus the findings should be an accurate reflection of the current literature. Additional trials are needed to better answer questions about comparative efficacy and optimal dosing of OW GLP-1 RAs.

What does this mean for clinicians? In response to data from a large number of randomized trials, particularly those

TABLE 4 Results from trials with head-to-head comparisons of OW GLP-1 RAs

Data are estimated treatment differences expressed in mean (95% CI) unless stated otherwise.

			Treatment differences (OW GLP-1 RA–comparator treatment) or other characterization			
Trial name and time to primary endpoint*	**Current therapies allowed**	**OW GLP-1 RA Comparator treatment(s)**	**HbA_{1c}, %**	**FPG/FSG, mg/dL**	**Other glycemic results, mg/dL**	**Body weight, kg**
OW GLP-1 RA trials						
SUSTAIN-3;[36] 56 weeks	NR	Semaglutide 1 mg OW, exenatide ER 2 mg OW	–0.62 (–0.80; –0.44); *P*<0.0001	–15.1 (–21.8; –8.5); *P*<0.0001	**7-point SMPG** –13.1 (–18.4; –7.9); *P*<0.0001 **PPG increment** –4.3 (–7.9; –0.7); *P*=0.0189	–3.78 (–4.58; –2.98); *P*<0.0001
SUSTAIN-7,[36] 40 weeks	Metformin	Semaglutide 0.5 mg OW, dulaglutide 0.75 mg OW	–0.40 (–0.55; –0.25); *P*<0.0001	–5.6 (–11.3; 0.2); *P*=0.0603	**7-point SMPG** –7.9 (–12.8; –3.1); *P*=0.0014 **PPG increment** –5.9 (–9.9; –1.8); *P*=0.0053	–2.26 (–3.02; –1.51); *P*<0.0001
		Semaglutide 1 mg, dulaglutide 1.5 mg OW	–0.41 (–0.57; –0.25); *P*<0.0001	–10.4 (–16.4; –4.7); *P*=0.0005	**7-point SMPG** –11.3 (–16.2; –6.3); *P*<0.0001 **PPG increment** –5.4 (–9.5; –1.1); *P*=0.013	–3.55 (–4.32; –2.78); *P*<0.0001
OW vs OD GLP-1 RA trials						
HARMONY-7;[37] 32 weeks	At least 1 OAD (Metformin, TZDs, SUs)	Albiglutide 30 mg OW titrated to 50 mg at week 6, Liraglutide 0.6 mg OD titrated to 1.2 mg at week 1 and 1.8 mg at week 2	0.21 (0.08; 0.34); *P*=0.0846	8.3 (2.5; 14); *P*=0.0048	NR	1.55 (1.05; 2.06); *P*<0.0001
AWARD-6;[38] 26 weeks	Metformin	Dulaglutide 1.5 mg OW, liraglutide OD uptitrated from 0.6 mg in week 1, to 1.2 mg in week 2, then to 1.8 mg in week 3	–0.06 (–0.19; 0.07); *P*<0.0001†	–0.5 (–5.8; 4.5); *P*=0.83	**Mean PPG** –2.3 (–6.5; 1.8); *P*=0.26	0.71 (0.17; 1.26); *P*=0.011
DURATION-6;[39] 26 weeks	Metformin, SUs, metformin + SUs, metformin + pioglitazone	Exenatide ER 2 mg OW, liraglutide uptitrated from 0.6 mg OD to 1.8 mg OD	0.21 (0.08; 0.33); *P*=0.0018	6.5 (0.9; 12)	NR	0.90 kg (0.39; 1.40); *P*=0.0005

OW vs BD GLP-1 RA trials						
AWARD-1;[17] 26 weeks	At least 1 OAD (± pioglitazone ± metformin)	Dulaglutide 1.5 mg OW, Dulaglutide 0.75 mg OW, exenatide 5 µg BD for 4 weeks then 10 µg BD	Dulaglutide 1.5 mg: –0.52 (–0.66; –0.39) Dulaglutide 0.75 mg: –0.31 (–0.44; –0.18) NR	Dulaglutide 1.5 mg: –18; *P*<0.001 Dulaglutide 0.75 mg: –10; *P*<0.001	Mean of all PPG values were significantly lower for dulaglutide 1.5 mg (*P*=0.047) than exenatide	Weight loss was similar for dulaglutide 1.5 mg and exenatide but weight gain for dulaglutide 0.75 mg vs exenatide –0.24; *P*=0.474‡
DURATION-1;[40] 30 weeks	SUs	Exenatide ER 2 mg OW, exenatide 10 µg BD	–0.33 (–0.54; –0.12) *P*<0.0023	(–23; –9.4 mmol/L) *P*<0.0001	Change from baseline in 2-h PPG was greater for BD dosing (–124 vs –95 mg/dL) *P*=0.0124	(–1.3; 1.1) *P*=0.89
DURATION-5;[41] 24 weeks	Metformin, SUs, TZDs	Exenatide ER 2 mg OW, exenatide 5 µg BD 4 weeks, then 10 µg BD 20 weeks	–0.7 (–0.9; –0.4); *P*<0.0001	NR	NR	–0.95 (–1.9; 0.01)

Abbreviations: BD, twice daily; CI, confidence interval; ER, extended release; FPG, fasting plasma glucose; FSG, fasting serum glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; NR, not reported; OD, once daily; OW, once weekly; PPG, post-prandial glucose; SUs, sulfonylureas; TZDs, thiazolidinediones.

The conversion factor used to convert FPG/FSG and other glycemic values from mmol/L to mg/dL is 18.

*All studies are randomized, phase 3, open-label trials, where the primary endpoint was change from baseline in HbA_{1c} at the end of the trial, unless stated otherwise.

†*P* value for non-inferiority.

‡AWARD-1 was a double-blind trial, where the primary endpoint was change from baseline in HbA_{1c} at week 26.

where they are dosed OD or BD, the GLP-1 RA agents are now favored earlier (second-line) in combination with metformin in T2D by the most recent treatment guidelines.[2] Readers are referred to 2 recent meta-analyses for an overview of these trials.[44,45] The growing amount of data from trials where drugs of this class are dosed OW indicates that they remain effective with much less frequent dosing, and compare favorably to a variety of other diabetes treatments. Furthermore, the single trial showing that an OW GLP-1 RA (exenatide ER) in combination with another OAD (dapagliflozin) was superior to either medication used alone[34] suggests that there may be even more opportunities to intensify therapy and improve glycemic control in T2D. Hopefully, future trials will help refine our understanding of these opportunities.

In summary, the efficacy of OW GLP-1 RAs combined with the convenience and flexibility of less frequent dosing offers additional options for clinicians treating patients with T2D who are not adequately controlled with lifestyle modifications and metformin. Of course, safety and side effects must also be considered when individualizing treatment. This will be discussed in other articles in this supplement.

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Safety of Once-weekly Glucagon-like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been found efficacious in the treatment of type 2 diabetes (T2D), demonstrating the ability to lower HbA_{1c}, and having the potential for inducing weight loss and reducing the risk of hypoglycemia, compared with other antihyperglycemic agents. Currently, 4 once-weekly (OW) GLP-1 RAs are approved: albiglutide, dulaglutide, exenatide ER, and recently, semaglutide. This review compares the relative safety of OW GLP-1 RAs, as well as their safety in comparison to other antihyperglycemic agents, using safety data reported in key sponsor-led phase 3 studies of the 4 OW GLP-1 RAs. The favorable safety profiles of OW GLP-1 RAs, added to their efficacy and the favorable weekly dosing regimen, make these agents appropriate options for patients with T2D. However, there are key differences within this class of drugs in macrovascular, microvascular, gastrointestinal and injection-site reaction adverse events, and these should be considered when healthcare providers are prescribing therapy.

Introduction

GLP-1 RAs are glucose-lowering agents with multiple mechanisms of actions, including the enhancement of glucose-stimulated insulin secretion, decrease of glucagon secretion, slowing of gastric emptying, and increase in satiety.[1] The mode of action of GLP-1 RAs is discussed in more detail in a dedicated article in this supplement (See "The Pharmacokinetic Properties of Glucagon-like Peptide-1 Receptor Agonists and Their Mode and Mechanism of Action in Patients with Type 2 Diabetes" on page S8). GLP-1 RAs have been found efficacious in the treatment of type 2 diabetes (T2D), demonstrating the ability to lower HbA_{1c}, and having the potential for inducing weight loss and reducing the risk of hypoglycemia, when compared with other antihyperglycemic agents such as sulfonylureas and insulins. Efficacy is also discussed in more detail in a separate article in this supplement (See "Clinical Efficacy of Once-weekly Glucagon-like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes" on page S14). When choosing treatment options, the combined glycemic control, low risk of hypoglycemia, and propensity for decreasing body weight is a key consideration for patients with T2D.

OW GLP-1 RAs albiglutide, dulaglutide, exenatide extended release (ER), and semaglutide are currently approved in patients with T2D in the United States, by the US Food and Drug Administration (FDA). The aim of this review is to compare the relative safety of GLP-1 RAs with an OW dosing regimen, as well as the safety of OW GLP-1 RAs with once-daily (OD) GLP-1 RAs and other classes of antihyperglycemic agents.

Methods

This is a review of the literature available on the safety of OW GLP-1 RAs, including randomized controlled trials, meta-analyses, and systematic reviews. Data from the key sponsor-led phase III studies of the four OW GLP-1 RAs were included in this review: 7 trials related to albiglutide, 8 to dulaglutide, 9 to exenatide and 7 to semaglutide (See "Clinical Efficacy of Once-weekly Glucagon-like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes" on page S14). The study designs and primary endpoints of all key trials have been described elsewhere and the principal outcome of this review is the effect of OW GLP-1 RAs on key safety outcomes.

Results

Thirty phase III randomized trials were identified. Trial duration varied from 24 to 104 weeks, included between 124 and 1648 patients randomized to the drug under investigation, and included different patient populations (**TABLE 1**). As only 1 of these trials involves 2 OW GLP-1 RAs head-to-head comparisons, there is limited capacity to compare the treatments directly in terms of relative safety and tolerability.

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DISCLOSURE

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TABLE 1 Trial designs and effects on cardiovascular risk factors with OW GLP-1 RAs

(All values presented are mean (SD) unless otherwise stated.)

Trial name	Comparator	Background therapies allowed	Patients, n (ID dose)	EOT change from baseline in SBP (mm Hg)	EOT change from baseline in DBP (mm Hg)	EOT change from baseline in blood lipids (mmol/L)		
						EOT change from baseline in total cholesterol	EOT change in LDL cholesterol	EOT change in triglycerides
Albiglutide								
HARMONY-1[2]	Placebo	+/- MET	150 (30 mg OW)	NR	NR	NR	NR	NR
HARMONY-2[3]	Placebo	+/- MET	101 (30 mg OW) 99 (50 mg OW)	–2.8 (12.14) –1.3 (13.37)	–0.8 (8.21) –0.8 (8.95)	–0.312 (0.8948) –0.101 (0.6237)	–0.278 (0.6999) –0.130 (0.5928)	–0.379 (2.5157) 0.014 (0.8548)
HARMONY-3[4]	Placebo, sitagliptin, glimepiride	+ MET	302 (30 mg OW)	–1.0 (14.2)	–0.7 (9.3)	–0.07 (0.9)	–0.03 (0.8)	–0.20 (1.3)
HARMONY-4[5]	Insulin glargine	MET +/- SU	504 (30 mg OW)	–1.4 (14.4)	–0.8 (10.0)	–2.1 (27.8)	–1.8 (22.6)	–17.3 (102.5)
HARMONY-5[6]	Placebo, pioglitazone	MET, SU	271 (30 mg OW)	NR	NR	NR	NR	NR
HARMONY-6[7]	Three times daily insulin lispro	IGlar, detemir/NPH, +/- OADs	285 (30 mg OW)*	NR	NR	NR	NR	NR
HARMONY-7[8]	Liraglutide	OADs	404 (30 mg OW)	<1	<1	NR	NR	NR
Dulaglutide								
AWARD-1[9]	Exenatide, placebo	Pioglitazone, MET	280 (0.75 mg OW) 279 (1.5 mg OW)	1.62 ± 0.85† 0.83 ± 0.87†	0.76 ± 0.57† 0.89 ± 0.57†	–0.09 (0.84) –0.12 (0.86)	–0.08 (0.77) –0.06 (0.69)	–0.04 (0.95) –0.26 (1.23)
AWARD-2[10]	Insulin glargine	MET, glimepiride	272 (0.75 mg OW) 273 (1.5 mg OW)	–0.59 ± 0.85† –0.70 ± 0.85†	–0.36 ± 0.52† –0.44 ± 0.52†	0.03‡ 0.02‡	–0.02‡ 0.0‡	0.03‡ 0.05‡
AWARD-3[11]	Metformin	None	270 (0.75 mg OW) 269 (1.5 mg OW)	–2.7 ± 0.88† –0.1 ± 0.8†	–1.4 ± 0.56† 0.3 ± 0.60†	–1 (% change)‡ –2 (% change)‡	–2 (% change)‡ –2 (% change)‡	–1 (% change)‡ –4 (% change)‡
AWARD-4[12]	Insulin glargine	Insulin lispro, +/- MET	293 (0.75 mg OW) 295 (1.5 mg OW)	1.04 –0.26	0.15 –0.01	0.94 0	–1.02 –1.95	5.73 2.96
AWARD-5[13]	Sitagliptin, placebo + sitagliptin	MET	302 (0.75 mg OW) 304 (1.5 mg OW)	–0.5 ± 0.7† –0.8 ± 0.7†	0.2 ± 0.5† 0.3 ± 0.5†	–0.03‡ –0.03‡	0.02‡ –0.06‡	–0.15‡ –0.16‡
AWARD-6[14]	Liraglutide	MET	299 (1.5 mg OW)	–3.36 ± 0.7†	–0.22 ± 0.4†	–0.13 ± 0.05†	–0.11 ± 0.04†	–0.18 ± 0.08†
AWARD-8[15]	Placebo	Glimepiride	239 (1.5 mg OW)	–0.52 ± 0.96†	–0.03 ± 0.61†	NR	NR	NR
AWARD-9[16]	Placebo	IGlar	150 (1.5 mg OW)	NR	NR	NR	NR	NR
Exenatide ER								
DURATION-1[17]	n/a	SU	128 (2 mg OW)	–6.2†	–2.8†	–9.6†	–3.4†	–15% (geometric LS mean)

DURATION-2[18]	Sitagliptin, pioglitazone	MET +/- SU	160 (2 mg OW)	–4†	NR	NR	NR	–5%†
DURATION-3[19]	Insulin glargine	IGlar	233 (2 mg OW)	–3 ± 1†	–1 ± 1†	–0.12 ± 0.06†	–0.05 ± 0.05†	0.96§
DURATION-4[20]	Metformin, pioglitazone, sitagliptin	None	248 (2 mg OW)	–1.3 ± 0.8†	NR	NR	NR	NR
DURATION-5[21]	Exenatide BID	MET, SU, TZD	129 (2 mg OW)	–2.9 ± 1.1†	0.2 ± 0.7†	–15.4 ± 2.6†	–6.4 ± 2.1†	0.94 ± 0.3†
DURATION-6[22]	Liraglutide	MET +/- SU/ pioglitazone	461 (2 mg OW)	–2.48 ± 0.56†	–0.49 ± 0.37†	–0.06 ± 0.04†	–0.05 ± 0.03†	NR
DURATION-7[23]	Placebo	IGlar +/- MET	233 (2 mg OW)	NR	NR	NR	NR	NR
DURATION-8[24]	Dapagliflozin	MET	231 (2 mg OW exen + dapa) 230 (2 mg OW)	–4.2† –1.3†	–0.0 (9.3) 0.8 (7.8)	0.05† –0.09†	0.15† 0.07†	–0.28† –0.18†
DURATION-NEO-2[25]	Exenatide (autoinjection), sitagliptin, placebo	MET	181 (2 mg OW AI)	1.2 ± 0.9†	1.0 ± 0.6†	NR	NR	NR
Semaglutide								
SUSTAIN-1[26]	Placebo	MET, OADs (excl. GLP-1 RA/DPP-4i)	128 (0.5 mg OW) 130 (1 mg OW)	–2.58 –2.74	–0.50 0.18	0.98§ 0.93§	1.00§ 0.92§	0.92§ 0.91§
SUSTAIN-2[27]	Sitagliptin	MET, TZD	409 (0.5 mg OW) 409m (1 mg OW)	–5.1 –5.6	–2.0 –1.9	NR	NR	NR
SUSTAIN-3[28]	Exenatide ER	NR	404 (1 mg OW)	–4.6	–1.0	NR	NR	NR
SUSTAIN-4[29]	Insulin glargine	MET, SU	362 (0.5 mg OW) 360 (1 mg OW)	–4.65 –5.17	–1.38 –0.98	0.95§ 0.95§	0.96§ 0.95§	0.89§ 0.87§
SUSTAIN-5[30]	Placebo	Basal insulin +/- MET	132 (0.5 mg OW) 131 (1 mg OW)	–4.3 –7.3	NR	NR	NR	NR
SUSTAIN-6[31]	Placebo	None	826 (0.5 mg OW) 822 (1 mg OW)	–3.44 –5.37	–1.37 –1.57	0.97§ 0.97§	0.97§ 0.98§	0.93§ 0.92§
SUSTAIN-7[32]	Dulaglutide	Metformin	301 (0.5 mg OW) 300 (1 mg OW)	–2.4 –4.9	–0.6 –2.0	NR	NR	NR

Abbreviations: AI, autoinjector; BID, twice daily; dapa, dapagliflozin; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; EOT, end of trial; ER, extended release; exen, exenatide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ID, investigated drug; IGlar, insulin glargine; LDL, low-density lipoprotein; LS, least squares; MET, metformin; NPH, Neutral Protamine Hagedorn; NR, not reported; OAD, oral antidiabetic drug; OW, once weekly; SD, standard deviation; SE, standard error; SBP, systolic blood pressure; SU, sulfonylurea; TZD, thiazolidinedione.

*Albiglutide was uptitrated to 50 mg OW if necessary to maintain HbA_{1c} <7.5%.

†LS mean ± SE (if SE was reported).

‡Median values only.

§Data are estimated ratios to baseline.

The primary endpoint was change from baseline in HbA_{1c} in all trials except Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN)-6, which had a primary composite outcome of first occurrence of cardiovascular (CV) death, nonfatal myocardial infarction, or non-fatal stroke, collectively known as major adverse cardiovascular events (MACE). Of note, the duration of SUSTAIN-6 was 104 weeks, included more patients than any other trial in this review (1648 randomized to semaglutide 0.5 mg or 1 mg OW), and only included patients with T2D over the age of 50 years, at high risk of CV disease.[31]

Macrovascular, including CV safety with GLP-1 RAs

OW GLP-1 RAs have been shown to reduce HbA_{1c} and body weight, and these are both key considerations in the benefit of GLP-1 RAs on CV risk factors. CV safety data, including MACE, with all GLP-1 RAs in comparison to each other and to other antihyperglycemic agents, will be discussed in further detail elsewhere in this supplement (See "Implications of Cardiovascular Outcomes Trials in Type 2 Diabetes for Primary Care" on page S35), but briefly, SUSTAIN-6 demonstrated noninferiority of semaglutide to placebo, both on a background of standard of care, in reducing MACE, and the post hoc analysis also demonstrated superiority in patients with T2D at high risk for CV disease.[31] Exenatide ER demonstrated noninferiority, but not superiority, to placebo in MACE in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial,[33] and liraglutide, a long-acting once daily (OD) GLP-1 RA, demonstrated superior CV protection compared with placebo, both in addition to standard therapy, in the Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial.[34]

Here, we focus on other CV risk factors of interest with OW GLP-1 RAs, including blood pressure, cholesterol and triglyceride profiles (**TABLE 1**). Overall, GLP-1 RAs reduce systolic blood pressure (SBP), and improve lipid profiles (**TABLE 1**). Semaglutide appears to show the greatest improvement in SBP and diastolic blood pressure (DBP) when compared with other OW GLP-1 RAs (**TABLE 1**). Exenatide ER appears to exert the largest reductions in blood lipids, though all OW GLP-1 RAs improve total cholesterol and low-density lipoprotein (LDL)-cholesterol. The change from baseline in triglycerides is less clear, but the general trend appears to be a reduction in blood triglycerides for all OW GLP-1 RAs (**TABLE 1**).

Microvascular safety with GLP-1 RAs

While the currently licensed OW GLP-1 RAs do not present any evidence of an increased risk for diabetic retinopathy, the SUSTAIN-6 trial reported that 50 patients (3%) treated with semaglutide experienced diabetic retinopathy complications, compared with 29 patients (1.8%) in the placebo group (hazard ratio [HR] 1.76; [95% confidence interval [CI] 1.11;2.78], $P = 0.02$).[31] Speculation remains as to the etiology of retinopathy complications in SUSTAIN-6, and it is possible that a rapid decline in HbA_{1c} in patients with long-standing disease may lead to a higher risk of progression of diabetic retinopathy.[35] As patients who experienced diabetic retinopathy in SUSTAIN-6 were characterized by pre-existing diabetic retinopathy, a longer mean diabetes duration, higher mean HbA_{1c} at baseline, and greater proportion of patients receiving insulin treatment at baseline[36], these data should be interpreted with caution.

Subgroup analyses in a recent review found that GLP-1 RAs, with the exception of semaglutide, presented a lower risk for retinopathy when compared with sulfonylureas, but not in comparison with placebo or any other active drug.[37] This review also found that GLP-1 RAs significantly reduced the incidence of nephropathy when compared with placebo (odds ratio [OR] 0.77, [95% CI 0.67; -0.88], $P = 0.005$). The difference in nephropathy events was not statistically significant when OW GLP-1 RAs were compared with any active comparator drugs, except in the case of semaglutide, which demonstrated significant benefit (OR 0.61 [95% CI 0.44; -0.84], $P = 0.002$).[37,38]

Other adverse events (AEs) of special interest with GLP-1 RAs

Other AEs of special interest with OW GLP-1 RAs are presented in **TABLE 2**.

Heart rate

All trials of OW GLP-1 RAs that reported mean change from baseline in heart rate reported an increase of between 0.6 and 4.1 beats per minute (**TABLE 2**). This effect is more pronounced in OW GLP-1 RAs and liraglutide, compared with short-acting OD GLP-1 RAs, exenatide BD, and lixisenatide.[1]

Gastrointestinal (GI) AEs

The proportion of patients experiencing any GI AE, specifically nausea, is high among all GLP-1 RA therapies, and appears to be higher with semaglutide than those in other trials (**TABLE 2**). When compared with placebo, there is variability within the GLP-1 RA class for the risk of GI side effects. It is worth noting that the percentages reported in **TABLE 2** do not list transient nausea separately, and this is the most common GI AE for patients treated with GLP-1 RAs, including semaglutide.[39]

Pancreatitis

Within the OW GLP-1 RAs phase III trials, the proportion of patients experiencing pancreatitis events was 1% or less for all investigated drugs (**TABLE 2**). While some studies show an increase in lipase and amylase levels in a small number of patients, a recent sub-analysis of the LEADER trial concluded that this increase does not predict an increased risk of pancreatic events in patients treated with liraglutide.[40] This may also apply to other GLP-1 RAs, given the elevated lipase and amylase

TABLE 2 Adverse events of special interest from GLP-1 RA trials

(Data are n (%), unless otherwise stated.)

Trial name, dose	GI AEs			Pancreatitis events	Increased lipase or amylase levels*	EOT change from baseline in heart rate, bpm	Hypoglycemic events			Injection-site reactions	Malignant neoplasms‡	Deaths
	Nausea	Vomiting	Diarrhea				Symptomatic events	Asymptomatic events†	Severe events			
Albiglutide (all 30 mg OW unless otherwise stated)												
HARMONY-1[2]	16 (10.7)	6 (4.0)	17 (11.3)	0	NR	NR	5 (3.3)	0	2 (1.3)	17 (11.3)	NR	0
HARMONY-2[3]	10 (9.9)	3 (3.0)	10 (9.9)	0	NR	2.5	1 (1.0)	NR	0	18 (17.8)	0	0
50 mg OW	9 (9.1)	3 (3.0)	13 (13.1)	0		0.8	0		0	22 (22.2)	2 (2)	3 (3)
HARMONY-3[4]	10.3%	5.6%	12.6%	2 (<1)§	NR	1.3	9 (3.0)	4 (1.3)	0	52 (17.2)	1 (<1)	NR
HARMONY-4[5]	50 (9.9)	3.8%	38 (7.5)	0	NR	1.0	88 (17.5)	32 (6.3)	2 (<1)	70 (13.9)	0	3 (<1)
HARMONY-5[6]	26 (9.6)	7 (2.6)	24 (8.9)	1 (<1)	NR	NR	37 (13.7)	9 (3.3)	1 (<1)	35 (12.9)	0	0
HARMONY-6‖[7]	11.2%	6.7%	13.0%	0	NR	NR	45 (15.8)	19 (6.7)	0	9.5%	1 (<1)	NR
HARMONY-7[8]	40 (9.9)	20 (5.0)	60 (14.9)	1§	L: 12	1.0	42 (10.4)	15 (3.7)	0	28 (6.9)¶	0	NR
Dulaglutide												
AWARD-1,[9]												
0.75 mg OW	47 (17)	17 (6)	26 (9)	0	NR	1.56 ± 0.55**	1.10 events/pt/yr	NR	0	NR	NR	1 (<1)
1.5 mg OW	81 (29)	47 (17)	36 (14)	1		1.68 ± 0.56**	0.45 events/pt/yr		0			1 (<1)
AWARD-2,[10]												
0.75 mg OW	21 (7.7)	10 (3.7)	25 (9.2)	1	L: 23 (8.6) A: 1 (0.4)	0.61 ± 0.50**	106 (39.0)	121 (44.3)	0	2 (<1)	NR	0
1.5 mg OW	42 (15.4)	18 (6.6)	29 (10.6)	2	L: 45 (16.7) A: 4 (1.5)	1.31 ± 0.50**	110 (40.3)	118 (44.3)	2 (0.7)	2 (<1)		0
AWARD-3,[11]												
0.75 mg OW	31 (11.5)	20 (7.4)	21 (7.8)	0	L: 3 (1.5) A: 0	1.6 ± 0.57**	11.1%	NR	0	6 (2.2)	0	0
1.5 mg OW	53 (19.7)	26 (9.7)	30 (11.2)	0	L: 1 (0.5) A: 0	1.8 ± 0.57**	12.3%		0	10 (3.7)	0	0
AWARD-4,[12]						mean		NR				
0.75 mg OW	52 (18)	31 (11)	46 (16)	0	L: 5 (2.1) A: 1 (0.4)	2.3	250 (85.6)		8 (3)	4 (1)	0	1 (<1)
1.5 mg OW	76 (26)	36 (12)	49 (17)	0	L: 8 (3.5) A: 0	2.4	235 (80.8)		10 (3)	1 (<1)	0	1 (<1)

TABLE 2 Adverse events of special interest from GLP-1 RA trials (*continued*)

(Data are n (%), unless otherwise stated.)

Trial name, dose	GI AEs			Pancreatitis events	Increased lipase or amylase levels*	EOT change from baseline in heart rate, bpm	Hypoglycemic events			Injection-site reactions	Malignant neoplasms‡	Deaths
	Nausea	Vomiting	Diarrhea				Symptomatic events	Asymptomatic events†	Severe events			
AWARD-5,[13]				0								
0.75 mg OW	42 (14)	23 (8)	30 (10)		L: 26 (8.7)	2.1 ± 0.5**	5.3%	NR	0	NR	0	0
1.5 mg OW				0	A: 4 (1.3)							
	53 (17)	39 (13)	44 (15)		L: 22 (7.3)	2.4 ± 0.5**	10.2%		0		0	1 (<1)
					A: 2 (0.7)							
AWARD-6,[14]	61 (20)	21 (7)	36 (12)	0	L: 11 (4)	2.4 ± 0.4**	26 (9)	NR	0	1 (<1)	0	0
1.5 mg OW					A: 1 (<1)							
AWARD-8,[15] 1.5 mg OW	25 (10.5)	NR	20 (8.4)	0	L: 7 (3.0)	2.9 ± 0.67**	27 (11.3)	NR	0	0	0	1 (<1)
					A: 0							
AWARD-9,[16] 1.5 mg OW	18 (12.0)	9 (6.0)	17 (11.3)	0	L: 2 (1.3)	NR	82 (54.7)	NR	1 (<1)	1 (<1)	0	0
					A: 0							
Exenatide ER (all 2 mg OW, unless otherwise stated)												
DURATION-1[17]	7%	6.3%	8.6%	0	NR	NR	10.2	NR	0	4 (8)	NR	NR
DURATION-2[18]	38 (24)	18 (11)	29 (18)	0	NR	NR	2 (1)	NR	0	16 (10)	0	NR
DURATION-3[19]	30 (13)	10 (4)	20 (9)	1 (<1)	L + A:5 (2.1)	4 ± 1**	19 (8)	NR	3 (1.3)	30 (13)	NR	0
DURATION-4[20]	28 (11.3)	12 (4.8)	27 (10.9)	0	NR	1.5 ± 10**	18 (7.2)	NR	0	26 (10.5)††	NR	0
DURATION-5[21]	18 (14.0)	6 (4.7)	12 (9.3)	1 (<1)	NR	4.1**	5 (3.9)	NR	0	13%	0	NR
DURATION-6[22]	43 (9)	17 (4)	28 (6)	1 (<1)	1 (<1)‡‡	NR	51 (19)	NR	0	48 (10)††	1 (<1)	2 (0.4)
DURATION-7[23]	14.7% total			NR	NR	NR	29.7%	NR	0	7.8%	NR	NR
DURATION-8[24]												
2 mg OW exen + dapa	12 (5)	NR	10 (4)	1 (<1)	NR	NR	8 (3)	NR	0	28 (12)	0	3 (1)
2 mg OW exen	17 (7)		13 (6)	1 (<1)			3 (1)		0	27 (12)	0	1 (<1)
DURATION-NEO-2§§ [25]	16 (8.8)	6 (3.3)	5 (2.8)	0	NR	2.7 ± 0.7**	4 (2.2)	NR	0	34 (18.8)	0	NR
Semaglutide												
SUSTAIN-1,[26]					NR					NR		
0.5 mg OW	26 (20)	5 (4)	16 (13)	0		2.4	0	0	0		2 (2)	0
1 mg OW	31 (24)	9 (7)	14 (11)	0		2.4	0	0	0		2 (2)	0

SUSTAIN-2,[27] 0.5 mg OW 1 mg OW	73 (18) 72 (18)	33 (8) 41 (10)	54 (13) 53 (13)	3 (1) 1 (<1)	NR	1.6 1.8	7 (2) 2 (<1)	NR	0	NR	0 2 (<1)	2 (<1) 1 (<1)
SUSTAIN-3,[28] 1 mg OW	41.8% total			NR	NR	2.1	NR	NR	NR	1.2%	2 (<1)	2 (<1)
SUSTAIN-4 [29] 0.5 mg OW 1 mg OW	77 (21) 80 (22)	24 (7) 37 (10)	59 (16) 69 (19)	2 (1) 0	NR	mean 2.3 3.1	4 (1)‖‖ 3 (1)‖‖	NR	2 (<1) 5 (1)	NR	4 (1) 0	4 (1) 0
SUSTAIN-5 [30] 0.5 mg OW 1 mg OW	NR	NR	NR	NR	NR	mean 0.8 4.0	NR	NR	8.3% 10.7%	NR	NR	NR
SUSTAIN-6 [31] 0.5 mg OW 1 mg OW	143 (17.3) 180 (21.9)	87 (10.5) 122 (14.8)	148 (17.9) 151 (18.4)	6 (0.7) 3 (0.4)	L: 12.7% A: 1.6% (for sema total)	mean 2.1 2.4	NR	NR	191 (23.1)¶¶ 178 (21.7)¶¶	8 (1.0) 9 (1.1)	26 (3.1) 40 (4.9)	62 (3.8) for sema total
SUSTAIN-7 [32] 0.5 mg OW 1 mg OW	68 (23) 63 (21)	31 (10) 31 (10)	43 (14) 41 (14)	0 0	NR	mean 2.1 (0.51) 4.0 (0.51)	NR	NR	3 7	4 (1) 6 (2)	3 (1) 3 (1)	1 (<1) 1 (<1)

Abbreviations: A, amylase; AE, adverse events; AI, autoinjector; dapa, dapagliflozin; EOT, end of trial; ER, extended release; exen, exenatide; GI, gastrointestinal; HbA_{1c}, glycated hemoglobin; L, lipase; n, number of patients with an event; NR, not reported; OW, once weekly; pt, patient; SBP, systolic blood pressure; sema, semaglutide; ULN, upper limit of normal; yr, year.

*Patients experiencing increased lipase or total amylase >3x ULN.

†Where non-severe hypoglycemia was reported without reference to whether symptoms were present, these data were entered into the symptomatic column and NR entered into the asymptomatic column.

†Some publications reported specific malignant neoplasms only (eg thyroid cancer), but others reported a broad range of neoplasms. This column provides the total number of neoplasms reported in the publications.

§Probable pancreatitis possibly related to study drug.

‖Albiglutide was uptitrated to 50 mg OW if necessary to maintain HbA_{1c} <7.5%.

¶Includes only events for which injection-site reaction was the preferred term.

**LS mean ± SE (if SE was reported).

††Injection-site nodules only.

‡‡Patient discontinued due to increased amylase levels; actual level not reported and may not have been >3x ULN.

§§Exenatide 2 mg OW was administered via AI.

‖‖Includes nocturnal severe or blood glucose-confirmed hypoglycemia.

¶¶Number of episodes of hypoglycaemia (rather than number of patients).

levels observed in other trials, regardless of pancreatic events **(TABLE 2)**, though this required further study.

Gallbladder disorders

SUSTAIN-6 is the only trial in this review that reported gallbladder disorders with the investigated drug (data not shown). A similar number of patients in both the semaglutide and placebo arms of the trial experienced disorders associated with the gallbladder; 58 (7.1%) and 61 (7.4%) patients with semaglutide and placebo, respectively,[31] and this may be related to the nature of the patient population.

Hypoglycemia

GLP-1 RAs reduce the potential for hypoglycemic episodes compared with prandial insulin, sulfonylureas, and meglitinides, in combination with the potential for better HbA_{1c} control.[41]

The proportion of patients experiencing severe hypoglycemic events is generally less than 1% across all OW GLP-1 RAs, except in Impact of LY2189265 Versus Insulin Glargine in Combination With Insulin Lispro for the Treatment to Target of Type 2 Diabetes Mellitus trial (AWARD 4), SUSTAIN-5, and SUSTAIN-6, which allowed patients to continue with background insulins **(TABLE 2)**.[12,30,31] Patients experienced more non-severe hypoglycemic events (either symptomatic or asymptomatic) in trials allowing insulins, thiazolidinediones or sulfonylureas, compared with trials that did not allow these background therapies **(TABLE 1, TABLE 2)**.

Injection-site reactions (ISRs) and hypersensitivity

The proportion of patients experiencing ISRs appears to vary across trials. Dulaglutide and semaglutide appeared to cause fewer ISRs than exenatide ER in their respective phase 3 trials (**TABLE 2**). The Safety and Efficacy of Exenatide Once Weekly Injection Versus Metformin, Dipeptidyl Peptidase-4 Inhibitor, or Thiazolidinedione as Monotherapy in Drug-Naive Patients With Type 2 Diabetes (DURATION)-4 and DURATION-6 trials with exenatide ER report injection-site nodules only,[20,22] and so the proportion of patients experiencing any ISRs is likely to be even higher than the relatively high percentages already reported (**TABLE 2**).

All licensed OW GLP-1 RAs are contraindicated in patients with hypersensitivity to the drugs.[42-44]

Malignant neoplasms and multiple endocrine neoplasia syndrome type 2 (MEN 2)

The number of patients experiencing malignant neoplasms or MEN 2 was very low in all trials with OW GLP-1 RAs, and this paucity of data limits any meaningful comparison between the drugs (**TABLE 2**). GLP-1 RAs have demonstrated an increase in the incidence of thyroid C-cell tumors in rodents, and it is unknown whether this risk is relevant to humans.[42-44] However, there are concerns surrounding the issue, and most GLP-1 RAs are contraindicated in patients with a personal or family history of MEN 2.[42,44-46]

Renal impairment

The guidelines from the American Association of Clinical Endocrinologists (AACE) and exenatide ER prescribing information (PI) confirm that exenatide should not be used if creatinine clearance is less than 30 mL/min.[43,47] However, the dulaglutide PI suggests no dose adjustment in patients with renal impairment, including end-stage renal disease,[44] and of note, a recently updated PI for OD liraglutide states that no dose adjustment is required for patients with mild, moderate, or severe renal impairment. A recent pharmacokinetic study demonstrated that dose adjustments of semaglutide may not be required in patients with renal impairment, including end-stage renal disease.[48]

Discussion

The American Diabetes Association (ADA) guidelines highlight GI side effects, elevated heart rate, possible acute pancreatitis, and C-cell hyperplasia and medullary thyroid carcinoma in rodents as key adverse events attributable to the GLP-1 RA class. AACE guidelines emphasize that these drugs should not be used in patients with the rare condition medullary thyroid carcinoma MEN 2, and highlight the increased risks of pancreatitis in patients with a history of pancreatic events.[47]

Evidence from clinical trials demonstrates that a high proportion of patients experience mild or moderate GI adverse events, but many of the patients may only experience transient nausea, for whom the nausea may be manageable. A recent review demonstrated that albiglutide had the lowest risk for nausea and diarrhea within the class, while OW exenatide had the lowest risk of vomiting. Patients in the DURATION-6 trial treated with exenatide ER experienced fewer GI AEs than did those treated with OD liraglutide (9% vs 21%, respectively),[22] and patients in the Effect of Albiglutide when Added to Standard Blood glucose lowering Therapies, on Major Cardiovascular Events in subjects with Type 2 Diabetes mellitus (HARMONY 7) trial treated with albiglutide experienced fewer nausea events than did those treated with liraglutide (9.9% vs. 29.2%, respectively, $P<0.0001$).[8] However, albiglutide is due to be removed from the market (July 2018).[49] These data suggest that OW GLP-1 RAs may be favorable over short-acting OD GLP-1 RAs in patients at risk of GI side effects. However, patients in the AWARD-6 trial treated with dulaglutide and liraglutide experienced similar rates of nausea (20% vs 18%, respectively).[14]

GLP-1 RAs may impede gastric emptying,[1] and because of this, AACE guidelines recommend that patients with gastroparesis or severe gastroesophageal reflux disease require careful monitoring and possible dose adjustments when receiving

some GLP-1 RA therapies.[47] This effect appears to be reduced in OW GLP-1 RAs, compared with OD.[1]

Large epidemiological trials have demonstrated a link between elevated resting heart rate and CV risk, including all-cause mortality.[50,51] While all OW GLP-1 RAs are associated with increased heart rate, data in the LEADER, EXSCEL, and SUSTAIN-6 trials suggest that this increase bears no relation to an increased incidence of CV events with these therapies.[31,33,34]

For patients with a personal or family history of MEN 2, a rare form of thyroid cancer, AACE guidelines state that GLP-1 RAs should not be used,[47] and albiglutide, dulaglutide and exenatide ER, as well as OD liraglutide are contraindicated in these patients.[42-44,46] However, the daily GLP-1 RAs exenatide BD and lixisenatide carry no such contraindication.[52,53]

The issue of pancreatitis and pancreatic cancer is a complex one. No studies have confirmed that GLP-1 RAs increase the risk of pancreatic events, and a recent review concluded that the available evidence from clinical trials does not suggest any relevant increase in the risk of pancreatitis.[54] The AACE guidelines recommend that GLP-1 RAs should be used cautiously in patients with a history of pancreatitis, and discontinued if acute pancreatitis develops.[47] The ADA lists acute pancreatitis as a possible disadvantage to the GLP-1 RA class, but does not explicitly provide guidance on the use of GLP-1 RAs in patients experiencing these events. However, post-marketing reports of exenatide submitted to the FDA Adverse Event Reporting System led the FDA to insist on adding pancreatitis to the label for exenatide.[55] As the patient numbers are so low, it is difficult to draw any simple conclusion on the issue, and all other licensed GLP-1 RAs now carry a warning regarding the potential risks.[42-44,52,56,57] Large-scale observational studies may provide further clarity on this matter.

To conclude, the favorable safety profiles including low rates of hypoglycemia with OW GLP-1 RAs, added to the efficacy benefits of reduced HbA_{1c} and body weight, as well as the favorable dosing regimen, make them appropriate options for patients with T2D. There are key differences within the class in macrovascular, microvascular, gastrointestinal, and injection-site reaction adverse events, and these should be considered when primary care physicians are prescribing therapy. Further safety investigations including real-world evidence studies with OW GLP-1 RAs will provide further clarity on the differentiation of the safety of the drugs.

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Implications of Cardiovascular Outcomes Trials in Type 2 Diabetes for Primary Care

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Abstract

Patients with type 2 diabetes (T2D) are at a greater risk of cardiovascular (CV) morbidity and mortality than their counterparts without diabetes. Worsening glycemic control is associated with increasing risk of CV events and mortality, but glycemic control alone does not appear sufficient to improve CV outcomes. Furthermore, some glucose-lowering drugs have been associated with an increased risk of CV events. As a result, the US Food and Drug Administration (FDA) issued guidance in 2008 for the investigation of CV risk with new diabetes therapies. Numerous CV outcomes trials have since been initiated for drugs in the dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide-1 receptor agonist (GLP-1 RA) classes. CV safety has been confirmed for a number of drugs. More recently, CV benefits have been shown for some SGLT-2 inhibitors and GLP-1 RAs. Primary care physicians should consider medications that can lower CV risk alongside favorable efficacy and safety profiles for treatment of patients with T2D at high CV risk.

T2D and CV risk

T2D is considered a CV risk equivalent disease. In 1998, Haffner and colleagues reported that Finnish patients with T2D had a risk for future major coronary events similar to that of patients with previous myocardial infarction (MI).[1] Patients with diabetes are at approximately 2-fold greater risk of death from CV causes than their counterparts without diabetes.[2] The most vulnerable patients are those with a prior history of ischemic events such as MI and stroke.[3] Over the past 20 years, the incidence of MI in patients with T2D has declined by 68%, due in part to increased use of statins, aspirin, antihypertension therapies, and improved glycemic control.[4] Unfortunately, the prevalence of diabetes is increasing in the United States; by 2030, an estimated 15% of the population will have diabetes, placing an ominous strain on healthcare resources.[5]

CV risk and T2D therapies

Increased hemoglobin A_{1c} (HbA_{1c}) is associated with an increased risk of CV disease (CVD).[6] Therefore, improved glycemic control would be expected to reduce the risk of CV events. However, there remains some controversy, and achieving HbA_{1c} targets alone may not be sufficient to independently reduce CV events and mortality rates.[7] Improvements in other risk factors such as blood pressure, cholesterol, and insulin resistance are also needed for optimal management. Early trials of the impact of intensive glucose control on long-term outcomes showed improvements in microvascular complications,[8-10] with benefits in macrovascular disease and mortality emerging after long-term follow-up[11] and meta-analysis.[12] However, initial results from 2 trials – Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) and Veterans Affairs Diabetes Trial (VADT) – suggested higher overall rates of mortality with intensive therapy (not statistically significant in VADT).[13,14] Although the increased risks diminished with long-term follow-up,[15,16] the initial results brought long-term outcomes under increased scrutiny.

CV outcomes trials in T2D

Prior to 2008, drugs for T2D were approved based on their ability to reduce HbA_{1c}—as a surrogate marker for diabetes complications—and short-term safety profile; approval trials were typically run for 6 months for efficacy assessment, though often with an extension period for longer-term safety follow-up.[17] Patients with existing CVD were considered high risk and therefore excluded from these trials assessing efficacy.[17] A new drug's impact on CV safety was assessed through investigator-initiated adverse event reports during approval trials, with no adjudication or systematic, prespecified analysis.[17]

In 2007, Nissen and Wolski published a meta-analysis suggesting that the thiazolidinedione drug rosiglitazone—widely used at that time—increased nonfatal MI by 43% and increased CV death by 64%.[18] This analysis had far-reaching implications,

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and the FDA received public and legislative criticism that questioned its ability to protect the public from potentially harmful drugs. As a result, the FDA issued guidance to sponsors of clinical trials involving glucose-lowering agents for evaluating the CV safety of these therapies, and now requires a demonstration that any new diabetes therapy does not result in an unacceptable increase in CV risk.[19]

The FDA proposes that CV events are prospectively adjudicated by independent and blinded committees during all phase 2 and 3 trials, and approval of a new drug can be granted if CV safety is shown using data from the phase 2–3 clinical trial program. However, in case of any uncertainty, approval may be granted in conjunction with a mandatory post-approval CV outcomes trial (CVOT).[19]

Nearly all diabetes therapies approved since 2008 have been subject to post-approval CVOTs, and there are numerous ongoing CVOTs across a range of drug classes (**TABLE**). In line with the FDA guidance, most of these CVOTs use a 3-component composite endpoint of major adverse CV events (MACE) including CV death, nonfatal MI, and nonfatal stroke as the primary endpoint, while some use a 4-component primary endpoint (4-point MACE), which also includes hospitalization for unstable angina.[19]

To ensure that events are captured over a reasonable timescale and that results provide meaningful estimates of CV risk, CVOTs include patients with T2D at high risk of CVD.[19] Trials are typically designed to capture a designated number of events in order to assess CV safety (event-driven trials), but some also include a minimum follow-up period to detect any longer-term effects.[37] To isolate the CV impact of the drug under investigation from treatment effects, CVOTs aim to achieve the same glycemic target in both treatment groups, supported by the best available care for other CV risk factors including anti-hypertensive, lipid management, and anti-platelet aggregation therapies (standard-of-care treatment). Thus, CVOTs are designed to detect CV risk associated with the use of a given medication, and not to demonstrate overall improvements in glycemic control.

While there are obvious limitations in comparing results across trials, the use of common MACE endpoints allows some comparisons. In this article, we review the primary results reported from trials initiated after the FDA guidance in 2008 with DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 RAs, with a particular focus on once-weekly (OW) GLP-1 RAs.

Results from CVOTs with DPP-4 inhibitors

Among the first post-2008 CVOTs to report results were those involving the DPP-4 inhibitors saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction; SAVOR TIMI 53), alogliptin (Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care; EXAMINE), and sitagliptin (Trial Evaluating Cardiovascular Outcomes with Sitagliptin; TECOS).[21-23] While these trials included patients at high risk of CVD, the specific patient populations differed: SAVOR TIMI 53 enrolled patients with established CVD or multiple CV risk factors, TECOS enrolled only patients with established CVD, and EXAMINE enrolled patients with acute coronary syndrome.[21-23] All 3 trials met their primary endpoint by demonstrating noninferiority for 3-point (SAVOR TIMI 53 and EXAMINE) or 4-point (TECOS) MACE, with each DPP-4 inhibitor compared with placebo on a background of standard-of-care therapy in high risk patients (**TABLE**).[21-23] Overall, DPP-4 inhibitor CVOTs have demonstrated neither an elevated nor reduced risk of ischemic events in patients with T2D at high risk for CV events. However, patients treated with saxagliptin, and patients without a history of heart failure treated with alogliptin experienced a small yet statistically significant increase in hospitalization for congestive heart failure.[38,39]

Results from CVOTs with SGLT-2 inhibitors

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA REG OUTCOME) study results were of great interest in 2015, with the publication showing that not only did the SGLT-2 inhibitor empagliflozin meet the requirement for no unacceptable increased risk (noninferiority), it reduced the risk of CV events compared with placebo (14% risk reduction for MACE vs placebo) in patients with T2D and established CVD (**TABLE**).[25] This reduction was driven by a significant reduction in CV death, with no significant differences for nonfatal MI or nonfatal stroke with empagliflozin vs placebo.[25] The cardioprotection demonstrated with empagliflozin in EMPA REG OUTCOME occurred within weeks of the onset of drug use, suggesting a mechanism independent of improved glycemic control.[25] In addition, after a median follow-up of approximately 3 years, patients treated with empagliflozin vs placebo had a 35% reduced risk of hospitalization for heart failure (2.7% vs 4.1%) and a 39% reduced risk for progression of renal disease (12.7% vs 18.8%).[25,40]

The CANVAS Program comprised 2 CVOTs (CANagliflozin cardiovascular Assessment study; CANVAS, and Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with T2DM; CANVAS-R) with similar designs to allow pooled analysis of the CV safety of canagliflozin in patients with established CVD or multiple CV risk factors.[28] Results showed that canagliflozin is the second SGLT-2 inhibitor to show a CV benefit with a reduced risk of CV events after treatment, compared with placebo (14% risk reduction for MACE vs placebo) (**TABLE**).[28] In contrast to results from the EMPA-REG OUTCOME trial, no significant differences were identified for individual primary endpoints. Thus, CV death was not the key driver of this result for canagliflozin.[25,28]

Additional clinical trials are planned to determine whether SGLT-2 inhibitors can improve outcomes in patients with heart failure and renal insufficiency.

Results from CVOTs with GLP-1 RAs

The first CVOT of a GLP-1 RA was the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study, which examined CV outcomes among patients with T2D and acute coronary syndrome treated with lixisenatide once-daily (OD). Results from ELIXA showed that lixisenatide was noninferior to placebo with respect to the risk of major CV events (including hospitalization for unstable angina) (**TABLE**).[24]

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial, published in 2016, showed that OD liraglutide was the first GLP-1 RA to provide CV risk reduction (13% risk reduction for MACE vs placebo) in patients with T2D (**TABLE**).[26] Patients in the LEADER trial had established CVD or CV risk factors, and the beneficial effect on the primary endpoint (MACE) was driven by reductions in all 3 components, albeit with nonsignificant reductions in nonfatal MI and nonfatal stroke.[26] The improvement in CV outcomes appeared independent of overall glycemic control: although HbA_{1c} was 0.4 percentage points lower in the liraglutide cohort compared with the placebo cohort, changes in HbA_{1c} of similar magnitude in other contemporary CVOTs have not resulted in beneficial CV outcomes.[26, 41,42]

CVOTs of OW GLP-1 RAs

The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN)-6 trial was a pre-approval CVOT comparing the risk of MACE with the OW GLP-1 RA semaglutide (0.5 or 1 mg) vs placebo (in addition to standard-of-care therapy) in approximately 3300 patients with T2D and at high risk for CVD.[27] Eligibility criteria were similar to the LEADER trial with the OD GLP-1 RA liraglutide, and SUSTAIN-6 included 2 years of follow-up data for patients with established CVD (83%) or multiple CV risk factors (17%).[27] In addition to the use of concomitant medications to achieve glycemic targets in both the semaglutide and placebo treatment groups, most patients were also treated with antihypertensive (94% of patients), lipid-lowering (77%), and anti-thrombotic medications (76%) at baseline.[27]

The SUSTAIN-6 trial met its primary endpoint, showing that there was no increased risk of CV events with semaglutide (pooled doses) compared with placebo: the primary MACE outcome occurred in 7% of patients in the semaglutide group and 9% of patients in the placebo group (**TABLE**).[27] Similar results were observed when both the 0.5 mg and 1 mg doses of semaglutide were analyzed separately.[27] While the trial was designed to assess noninferiority (no increased risk) of semaglutide vs placebo, a post hoc analysis prompted by the primary endpoint result suggested that semaglutide *reduced* the risk of CV events. The 26% risk reduction for MACE after treatment with semaglutide compared with placebo was statistically significant for superiority (**TABLE**).[27] The limitations of these results from a post hoc analysis of a relatively small and short-term (regarding CVOTs) pre-approval trial must be appreciated.[27] In addition to the results for macrovascular disease, SUSTAIN-6 also showed that patients treated with semaglutide had a 36% reduced risk for new or worsening nephropathy compared with placebo-treated patients (3.8% vs 6.1%), but an increased risk for diabetic retinopathy complications (3.0% vs 1.8%).[33] Furthermore, glycemic equipoise was not achieved—a greater reduction in HbA_{1c} was observed with semaglutide compared with placebo—despite the use of other glucose-lowering drugs. This suggests that the current standard of care treatment for patients at high risk of CVD can be improved.[33]

Results from CVOTs with other OW GLP-1 RAs are beginning to emerge. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial was designed to assess the CV safety and efficacy of exenatide extended release (ER) compared with placebo in a large patient population (approximately 14,000 patients) with T2D at a broad range of CV risk (the trial aimed to recruit approximately 30% of the study population without prior CV events).[29] The results show no increased CV risk (noninferiority) with exenatide ER compared with placebo, but the trial did not show a CV benefit with exenatide ER (**TABLE**).[29] CVOTs are ongoing for dulaglutide (Researching Cardiovascular Events With a Weekly Incretin; REWIND)[31] and albiglutide (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; HARMONY OUTCOMES).[36] While the results from HARMONY OUTCOMES will be viewed with interest, the direct impact on clinical practice will be limited by the manufacturer's decision to withdraw albiglutide from the market in 2018.[43]

Discussion

Of the CVOTs with GLP-1 RAs that have reported results to date, 2 have demonstrated CV safety (for lixisenatide and exenatide ER), 1 has shown CV risk reduction (for liraglutide), and 1 suggests via post hoc analysis a reduction in CV risk (for semaglutide). Two SGLT-2 inhibitors have also demonstrated CV risk reduction; consistent results across both trials suggest that this may be a class effect for these drugs.

The different CVOT designs and populations complicate the comparison of results from the GLP-1 RA class, but semaglutide is currently the only OW medication in this class with results supporting a CV benefit. The results of a meta-analysis of short-term trials examining the effect of GLP-1 RAs (not limited to OW dose forms) on mortality and CV events indicated that this class of drugs appeared to reduce all-cause mortality, CV mortality, and the incidence of MI.[44] However, the mixed results from longer duration CVOTs with GLP-1 RAs (including the OW forms) currently make a class effect appear unlikely.

Empagliflozin received CV indications from the FDA in December 2016. The emplagliflozin label states that the drug can be used to reduce the risk of CV death in adults with T2D. The liraglutide label, which was amended in August 2017, states that

TABLE **Overview of CVOTs in diabetes started after the 2008 FDA guidance[20]**

Trial	Study status	Drug class	Intervention	Primary outcomes	N	Follow-up (years)	Primary result: risk of outcome with study drug vs placebo (hazard ratio [95% CI])	CV safety (non-inferiority) of study drug confirmed?	CV benefit (superiority) of study drug shown?
SAVOR-TIMI53[21]	Completed	DPP-4 inhibitor	Saxagliptin vs placebo	CV death, MI, or stroke	16,492	2.1	1.00 (0.89;1.12)	Yes	No
EXAMINE[22]	Completed	DPP-4 inhibitor	Alogliptin vs placebo	CV death, MI, or stroke	5380	1.5	0.96 (≤1.16)*	Yes	No
TECOS[23]	Completed	DPP-4 inhibitor	Sitagliptin vs placebo	CV death, MI, UA, or stroke	14,671	3.0	0.98 (0.88;1.09)	Yes	No
ELIXA[24]	Completed	GLP-1 RA OD	Lixisenatide vs placebo	CV death, MI, UA, or stroke	6068	2.1	1.02 (0.89;1.17)	Yes	No
EMPA-REG OUTCOME[25]	Completed	SGLT-2 inhibitor	Empagliflozin 10 mg vs empagliflozin 25 mg vs placebo	CV death, MI, or stroke	7028	3.1	0.86 (0.74;0.99)†	Yes	Yes
LEADER[26]	Completed	GLP-1 RA OD	Liraglutide vs placebo	CV death, MI, or stroke	9340	3.8	0.87 (0.78;0.97)	Yes	Yes
SUSTAIN-6[27]	Completed	GLP-1 RA OW	Semaglutide 0.5 mg vs semaglutide 1 mg vs placebo	CV death, MI, or stroke	3297	2.1	0.74 (0.58;0.95)	Yes	Yes‡
CANVAS Program[28]	Completed	SGLT-2 inhibitor	Canagliflozin 100 mg vs canagliflozin 300 mg vs placebo	CV death, MI or stroke	10,142	3.6	0.86 (0.75;0.97)	Yes	Yes
EXSCEL[29]	Completed	GLP-1 RA OW	Exenatide once weekly vs placebo	CV death, MI, or stroke	14,752	3.2	0.91 (0.83;1.00)	Yes	No
CAROLINA[30]	Ongoing, not recruiting	DPP-4 inhibitor	Linagliptin vs glimepiride	CV death, MI, or stroke	6072	-	-	-	-
REWIND[31]	Ongoing, not recruiting	GLP-1 RA OW	Dulaglutide vs placebo	CV death, MI, or stroke	9622	-	-	-	-
DECLARE-TIMI58[32]	Ongoing, not recruiting	SGLT-2 inhibitor	Dapagliflozin 10 mg vs placebo	CV death, MI, or stroke	17,276	-	-	-	-
CARMELINA[33]	Ongoing, not recruiting	DPP-4 inhibitor	Linagliptin 5 mg vs placebo	CV death, MI, or stroke	7003	-	-	-	-
MK-3102-018[34]	Terminated	DPP-4 inhibitor	Omarigliptin vs placebo	CV death, MI, UA, or stroke	4202	-	-	-	-

CONTINUED

TABLE Overview of CVOTs in diabetes started after the 2008 FDA guidance[20] *(continued)*

Trial	Study status	Drug class	Intervention	Primary outcomes	N	follow-up (years)	Primary result: risk of outcome with study drug vs placebo (hazard ratio [95% CI])	CV safety (non-inferiority) of study drug confirmed?	CV benefit (superiority) of study drug shown?
VERTIS CV[35]	Ongoing, not recruiting	SGLT-2 inhibitor	Ertugliflozin 5 mg vs ertugliflozin 15 mg vs placebo	CV death, MI, or stroke	8000	-	-	-	-
HARMONY OUTCOMES[36]	Ongoing, not recruiting	GLP-1 RA OW	Albiglutide 30 mg vs albiglutide 50 mg vs placebo	CV death, MI, or stroke	9400	-	-	-	-

Abbreviations: CAROLINA, Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes trial; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus trial; CI, confidence interval; CV, cardiovascular; DECLARE-TIMI58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events Trial; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MI, myocardial infarction; MK-3102, Cardiovascular Outcomes Following Treatment With Omarigliptin (MK-3102) in Participants With Type 2 Diabetes Mellitus trial; SGLT-2, sodium-glucose co-transporter-2; UA, unstable angina; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

Adapted from: Schnell et al. *Cardiovasc Diabetol.* 2016;15:139.

*Upper boundary of the one-sided repeated CI, at an alpha level of 0.01.

†95.02% CI.

‡Post hoc analysis.

the drugs can reduce the risk of MACE including CV death, non-fatal MI and non-fatal stroke in adults with T2D and established CV disease.

The mechanisms underpinning the additional cardioprotective effects of glucose-lowering drugs are unclear. For SGLT-2 inhibitors, hemodynamic effects such as reductions in blood pressure and intravascular volume involving osmotic diuresis may provide a rationale.[45] Several hypotheses have been proposed for GLP-1 RAs, including beneficial effects on risk factors such as glycemia, weight, blood pressure, and lipid profiles, as well as direct effects on inflammation, platelets, vasculature, and immune cells.[46]

Implications for primary care physicians

GLP-1 RA prescribing decisions in primary care tend to be led by glycemic efficacy and weight loss, but given the importance of CVD within diabetes, the CV benefits highlighted in recent CVOTs should also be considered. However, high-risk patients similar to those included in CVOTs represent a minority of patients seen in primary care.

CVOTs allow identification of patients who benefit most from particular treatments, but benefits in lower-risk patients remain to be established. With the inclusion of high-risk patients in trials, a reduction in CV risk with a drug would not necessarily apply to patients with lower CV risk.[20] However, the absence of harm would be expected to also apply to patients with lower CV risk.

Adherence to medication is likely to be better in a controlled clinical trial setting than in routine clinical practice, and may represent another barrier to applying the CVOT results reported to primary care. In a retrospective study of real-world practice, the CVD REAL study showed that treatment with SGLT-2 inhibitors (dapagliflozin, canagliflozin or empagliflozin) vs other glucose-lowering drugs was associated with a lower risk of hospitalization for heart failure (39% risk reduction) and death (51% risk reduction). This suggests that the benefits observed with empagliflozin and canagliflozin in randomized trials may be a class effect that applies to patients with T2D in real-world practice.[47] These findings offer reassurance that the results from CVOTs can be translated to real-world practice.

A growing body of evidence, including several of the CVOTs covered in this article, supports the management of T2D beyond glycemic control.[25-28,48] Primary care physicians who manage high-risk patients with T2D and CVD should strongly consider prescribing medications that are proven to reduce the risk of stroke, CV death, and nonfatal MIs.

Conclusion

Following FDA guidance issued in 2008 for assessment of CV safety of new diabetes drugs, CVOTs have demonstrated CV safety for a number of new therapies. The GLP-1 RA liraglutide has been shown to improve CV outcomes for patients with T2D at high risk for CV events, while post hoc analysis of the SUSTAIN-6 trial suggests that semaglutide may also offer cardioprotection. Renal inhibition of SGLT-2 in patients with established CVD or

high CV risk has also been shown to improve CV outcomes, and slow the progression of chronic kidney disease. Primary care physicians should target therapy for patients at high CV risk to include medications that can lower CV risk and improve overall glycemic control without increasing risk of weight gain and hypoglycemia.

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