The Clinical Impact of GLP-1 Receptor Agonists in Type 2 Diabetes: Focus on the Long-Acting Analogs

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Abstract

GLP-1 receptor agonists (GLP-1 RAs), introduced for clinical use in 2005, have excellent potency in reducing HbA_{1c} and mean glucose, improving fasting plasma glucose, inducing weight loss or protecting against the weight gain associated with insulin therapy, reducing appetite, and delaying gastric emptying. Two of these medications, liraglutide and semaglutide, appear to have cardioprotective effects as reflected in cardiovascular outcomes studies. The GLP-1 RAs are associated with gastrointestinal side effects that tend to diminish over time. They have very low risk of hypoglycemia unless used in conjunction with insulin or insulin secretagogues. Two coformulations of GLP-1 RAs together with long-acting basal insulin are available for daily use. The original GLP-1 RA, exenatide, requires twice-daily injections; two short-acting analogs are given once daily. Three currently available long-acting GLP-1 RAs are injected once weekly, providing greater convenience and potentially improving patient adherence. Semaglutide appears to be the most effective in terms of HbA_{1c} reduction and weight loss. GLP-1 RAs can be combined with all classes of antihyperglycemic agents except DPP-4 inhibitors. Current studies are exploring the use of an implantable osmotic pump for long-term administration of a rapid acting analog (exenatide), an oral preparation of semaglutide, benefits for management of obesity and nonalcoholic steatohepatitis, and mechanisms of cardioprotective effects.

Keywords: Type 2 diabetes, GLP-1 receptor agonists, Clinical trials, Cardiovascular outcome trials, Pharmacotherapy.

Introduction

GLP-1 RECEPTOR AGONISTS (GLP-1 RAs) are an important, well-established therapeutic option for management of patients with type 2 diabetes,^{1,2} and may be used alone, with oral antihyperglycemic agents, with insulin, or as coformulations with long-acting insulins. These agents are highly effective in terms of reduction of HbA_{1c}, weight reduction (or to minimize weight gain when coadministered with insulin or sulfonylureas), appetite suppression, reduced glycemic variability, and have low risk of hypoglycemia. GLP-1 RAs can be classified as rapid or long acting and in terms of homology to GLP-1 or to exendin-4. Table 1 summarizes their pharmacokinetic properties.

Of particular interest when treating people with diabetes is cardiovascular safety. The risk of death from any cause in people with diabetes is up to twice that of the general population³ and the risk of death from cardiovascular causes is up

to fourfold that of people without diabetes.⁴ Liraglutide and semaglutide have beneficial effects in cardiovascular outcome trials.

Exenatide

Exenatide was the first GLP-1 RA approved for clinical use in the United States in 2005. The original formulation of exenatide is a short-acting medication and requires injections twice per day (Table 1). Subsequently, liraglutide was introduced; it has longer duration of action so that it can be used once daily (Table 1). Another short acting GLP-1 RA, lixisenatide, was approved for once-daily therapy (Table 1). Three longer lasting preparations that can be given once weekly are currently available in the United States: exenatide extended release (ER), dulaglutide, and semaglutide (Table 1). Another long-acting preparation, albiglutide, was withdrawn from the market in the United States, possibly

TABLE 1. GLP-1 RECEPTOR AGONISTS: PHARMACOKINETIC PROFILES

Agent	Half-life ($T_{1/2}$)	T_{max}
Short Acting		
Exenatide <i>bid</i>	2.4 h	2 h
Lixisenatide <i>qd</i>	3 h	1–3.5 h
Liraglutide <i>qd</i>	13 h	8–12 h
Long Acting		
Dulaglutide <i>qw</i>	~4 days	24–48 h
Exenatide <i>qw</i>	7–14 days	6–7 weeks
Semaglutide <i>qw</i>	~7 days	1–3 days

due to limited efficacy. A once-daily oral preparation of semaglutide is currently undergoing clinical trials⁵ in a development program known as PIONEER. An alternative approach, now being explored in clinical trials, is to administer a short-acting agonist, exenatide, using an implantable osmotic pump.⁶

The structure of exenatide is based on exendin-4, a peptide from Gila monster saliva with limited homology with human GLP-1. Accordingly, it may have a higher incidence of allergic reactions and neutralizing antibodies than medications with a higher degree of homology with GLP-1. Subsequently, several GLP-1 RA analogs were developed with increased potency and increased duration of action.⁷ Tables 2–4 summarize the effectiveness of exenatide ER and the other GLP-1

RAs used for management of people with diabetes. There is a small increased risk of mildly elevated pancreatic lipase and amylase and a small increased risk of pancreatitis that is weakly associated with all of the GLP-1 RA preparations. However, there is no credible evidence of increased risk of pancreatic or other malignancies in people receiving either short- or long-acting GLP-1 RAs.

Exenatide can be continuously infused using a small implantable osmotic minipump that continuously delivers exenatide for 3–6 months.^{8,9} In a randomized, open-label, phase 2 study, patients with poorly controlled type 2 diabetes receiving metformin were treated using ITCA 650 delivering 20 μ g of exenatide/day for 12 weeks followed by 60 μ g/day for 12 weeks. These patients experienced significant reductions in HbA_{1c} of –1.4% and reductions in body weight of –3.1 kg during the initial 24-week treatment period, and these effects were maintained during a 24-week extension.¹⁰ In another recent study, 60 patients with longstanding, uncontrolled type 2 diabetes (HbA_{1c} 10%–12%) were enrolled in a 39-week, open-label, phase 3 trial. The initial exenatide dose was 20 μ g/day for 13 weeks, then 60 μ g/day for 26 weeks. At the end of the trial there was a mean reduction of HbA_{1c} of –2.8% and body weight was reduced by –1.2 kg, and 25% of patients achieved HbA_{1c} <7%. The most common side effects, typical of the entire GLP-1 RA class, were nausea, vomiting, and diarrhea. Discontinuation of treatment related to side effects was low (7%).

TABLE 2. EFFECTIVENESS OF LONG-ACTING GLP-1 RECEPTOR AGONISTS: EXENATIDE EXTENDED RELEASE

Study	Duration	Comparators	HbA _{1c} Change (%)	Weight Change (kg)
DURATION-1 ^a	30 weeks (N=295)	Exenatide ER	–1.9%	–4.0
Background meds.:	30 weeks (N=295)	Exenatide <i>bid</i>	–1.5%	
1 or 2 of the following: Metformin, Sulfonylurea, or Thiazolidinedione	6-year extension (N=136)	Exenatide ER	–1.6%	–4.2
DURATION-2 ^b	26 weeks	Exenatide ER	–1.6%	–2.7
Background meds.:		Sitagliptin	–1.0%	–1.0
Metformin		Pioglitazone	–1.4%	+3.3
N=491				
DURATION-3	3-year extension	Exenatide ER Insulin glargine	–1.0%	–2.6
Background meds.:			–0.8%	+1.4
Metformin $\pm$ sulfonylurea				
N=456				
DURATION-4 ^b	26 weeks	Exenatide ER	–1.5%	–2.0
Background meds.:		Metformin	–1.5%	–2.0
Drug Naïve		Pioglitazone	–1.6%	+1.5
N=820		Sitagliptin	–1.2%	–0.8
DURATION-5	24 weeks	Exenatide ER	–1.6%	–2.3
Background meds.:		Exenatide <i>bid</i>	–0.9%	–1.4
Drug naïve, or oral agents				
N=252				
DURATION-6	26 weeks	Exenatide ER	–1.3%	–2.7
Background meds.:		Liraglutide	–1.5%	–3.6
Metformin		1.8 mg/day		
N=911				

^aDURATION: DIABETES THERAPY UTILIZATION: RESEARCHING CHANGES IN A1C, WEIGHT, AND OTHER FACTORS THROUGH INTERVENTION WITH EXENATIDE ONCE WEEKLY^{27–36}

^bDURATION-2 and DURATION-4 were double blind; other studies were open label.

TABLE 3. EFFECTIVENESS OF LONG-ACTING GLP-1 RECEPTOR AGONISTS: DULAGLUTIDE³⁷⁻⁴⁴

Study	Treatment arms	Study duration (weeks)	A _{1c} change (%)	Weight change (kg)
AWARD-1: background metformin and pioglitazone	Dulaglutide 1.5 mg qw	52	-1.51	-1.3
	Exenatide twice daily (10-μg)		0.99	-1.3
AWARD-2: metformin	Dulaglutide 0.75 mg qw	78	-0.59	-1.33
	Dulaglutide 1.5 mg qw		-0.90	-1.87
	Insulin glargine qd		-0.62	+1.28
AWARD-6: background liraglutide 26 weeks	Dulaglutide 1.5-mg qw	26	-1.42	-2.9
	Liraglutide 1.8-mg qd		-1.36	-3.6
AWARD 10: 24 weeks	Dulaglutide 0.75 mg qw + empagliflozin	24	-1.21	-2.6
	Dulaglutide 1.5 mg qw + empagliflozin		-1.34	-3.1
	Placebo qw + empagliflozin		-0.54	-2.1

Liraglutide

Liraglutide was the second GLP-1 RA to become available in the United States. Its major advantage was longer half-life and hence greater effectiveness when administered as a once-daily injection. It was generally more effective than exenatide and has much higher homology (97%) with human GLP-1, and therefore, a lower risk of immunogenicity and allergic reactions.

Liraglutide was evaluated in a phase 3 clinical program known as LEAD (Liraglutide Effect and Action in Diabetes), using monotherapy and combination therapy, with multiple comparators.¹¹⁻¹⁶ Liraglutide administered once daily demonstrated significant HbA_{1c} reductions ranging from -0.8% to -1.1% with the lower dose (1.2 mg/day), and from -1.0% to -1.5% with the higher dose (1.8 mg/day). Significant weight reductions were demonstrated with weight loss in these studies ranging from -2.2 to -5.9 lbs with the lower dose (1.2 mg/day) and from -4.0 to -7.3 lbs with the higher dose (1.8 mg/day).

Insulin Degludec/Liraglutide Coformulation

Because of the attractiveness of simultaneous initiation of therapy with a GLP-1 RA and a long-acting basal insulin, a coformulation of liraglutide and insulin degludec was developed and found to be both effective and well tolerated. It is administered as one injection per day, thereby providing convenience and hopefully resulting in better compliance. Its

use markedly reduces the weight gain associated with insulin therapy and the gastrointestinal side effects of a GLP-1 RA. For patients who require more than 50 U of insulin per day, one can use the separate preparations of the two medications so that they can be titrated independently.

In a development program known as DUAL, the efficacy and safety of the coformulation of insulin degludec and liraglutide were evaluated.¹⁷⁻²² In a 52-week comparison of IDegLira with insulin degludec or liraglutide alone,²² the mean HbA_{1c} at 52 weeks was reduced by 1.84% in the IDegLira group, 1.40% in the insulin degludec group, and 1.21% in the liraglutide group. Seventy-eight percent of the patients on IDegLira achieved an HbA_{1c} of <7% compared with 63% of patients receiving insulin degludec and 57% of those receiving liraglutide. The mean fasting plasma glucose at the end of the trial was similar for patients receiving IDegLira or insulin degludec but higher in the liraglutide group. At 52 weeks, the daily insulin dose was 37% lower with IDegLira than with insulin degludec. IDegLira was associated with a greater decrease in body weight of 2.8 kg, and a 37% lower rate of hypoglycemia compared with insulin degludec.²²

Lixisenatide

Lixisenatide is another GLP-1 RA available for once-daily use. Its half-life is shorter than that of liraglutide (Table 1).

TABLE 4. EFFECTIVENESS OF LONG-ACTING GLP-1 RECEPTOR AGONISTS: SEMAGLUTIDE⁴⁵⁻⁵³

Study	Dose (mg)	Study duration (weeks)	HbA _{1c} (%) change	Weight change (pounds)
SUSTAIN-1: semaglutide (monotherapy)	0.5	30	-1.4	-8.4
	1.0		-1.6	-10.4
	Placebo		-0.1	-2.6
SUSTAIN-2: semaglutide (vs. sitagliptin)	0.5	56	-1.3	-9.3
	1.0		-1.5	-12.1
	Sitagliptin 100 mg		-0.7	-3.7
SUSTAIN-3 (vs. exenatide ER qw)	1.0	56	-1.4	10.6
	Exenatide ER 2 mg qw		-0.9	-4.4
SUSTAIN-4: semaglutide+insulin (vs. glargine U100)	0.5	30	-1.2	-7.1
	1.0		-1.5	-10.4
	Insulin glargine U100		-0.9	+2.0
SUSTAIN-5: semaglutide added to basal insulin (vs. placebo)	0.5	30	-1.3	-7.7
	1.0		-1.7	-13.2
	Placebo		-0.2	-2.6

SUSTAIN, Semaglutide Unabated Sustainability in Treatment of type 2 diabetes.

Lixisenatide is less effective than liraglutide in reducing HbA_{1c}, fasting plasma glucose, and body weight, after 24 weeks of therapy,²³ but it has greater efficacy in reducing the postprandial glucose levels both at 28 days and 24 weeks of therapy.^{23–25} HbA_{1c} was reduced by 0.5% with morning injection and 0.4% with evening injection (placebo corrected). The 2-h postprandial glucose was reduced by 4.5 mmol/L (placebo corrected), and body weight was reduced by 0.9 kg (morning) or 0.6 kg (evening injection, placebo corrected).²³ When lixisenatide was administered to people inadequately controlled with basal insulin alone, there was an average reduction in HbA_{1c} of 0.4%, the percentage of subjects achieving an HbA_{1c} <7% increased from 12% for placebo to 28%, the postprandial glucose was reduced by 3.8 mmol/L, average body weight decreased by 1.3 kg, and total insulin dose per day decreased by an average of 3.7 U/day from a baseline of 55 U/day.²⁵

Lixisenatide/Insulin Glargine Coformulation

Lixisenatide was introduced as a coformulation with insulin glargine, for the same reasons as for liraglutide combined with insulin degludec: convenience (one injection per day), reducing the extent of weight gain associated with insulin therapy, and a reduced risk of gastrointestinal side effects, as the doses of GLP-1 RA and insulin glargine are gradually escalated. This can be an effective manner to intensify therapy after failing to achieve goal with a mono- or combination oral therapy.

The LixiLan-L study evaluated 736 patients inadequately controlled on basal insulin alone or in combination with 1 or 2 oral agents.²⁶ Patients treated with iGlarLixi showed reductions in HbA_{1c} of –1.1% and with iGlar of –0.6%. A higher percentage of patients achieved the HbA_{1c} target level of <7% ($P < 0.0001$): 55% of iGlarLixi patients reached HbA_{1c} <7% compared with 30% of iGlar patients. iGlarLixi also demonstrated significant reductions in 2-h postprandial glucose (PPG) following a standardized liquid breakfast meal compared with iGlar. Mean body weight decreased by 0.7 kg with iGlarLixi and increased by 0.7 kg with iGlar ($P < 0.0001$). These improvements were accompanied by no increased risk of hypoglycemia.

Long-Acting GLP-1 RAs for Weekly Administration

Short-acting GLP-1 RAs require either twice-daily or daily administration. Currently, three long-acting agents are available, permitting administration on a weekly basis: exenatide ER, dulaglutide, and semaglutide. These offer greater convenience and therefore are expected to improve adherence.

There appears to be increased potency both in terms of HbA_{1c} reduction and weight loss in the longer acting preparations, semaglutide, dulaglutide, and exenatide ER, compared with the short-acting preparations.

Exenatide ER

Exenatide ER was the first weekly agent to become available. It consists of the same exenatide molecule that is absorbed slowly because it is encapsulated into a polymeric matrix of microspheres. This preparation is associated with a greater incidence of local reactions at the injection site that resolve spontaneously with time. The gastrointestinal side

effects are less frequent and mild than for the other GLP-1 RAs, presumably because the final therapeutic blood level is achieved relatively slowly due to the gradual accumulation of the peptide over a period of up to 6–7 weeks. The phase 3 clinical trials of exenatide ER, consisting of six studies, were designated as the DURATION studies,^{27–36} (Table 2). These included two randomized placebo-controlled trials^{27,31} and four open-label studies. The studies used several comparators and several different types of background medications and included subjects with HbA_{1c} ranging from 6% to 12%. Most studies were 24–30 weeks in duration, but DURATION-1 was extended (open label) to 6 years and DURATION-3 was extended to 3 years. In all six studies, HbA_{1c} levels were reduced by 1.3%–1.6%. The extent of HbA_{1c} reduction was linearly related to the baseline HbA_{1c} level, which is characteristic of nearly all medications for type 2 diabetes. Benefits in terms of HbA_{1c} and weight loss persisted through 6 years of follow-up in the open-label study although the number of subjects showed major attrition. The major side effects were gastrointestinal, as is characteristic for this entire class of therapeutic agents, both short and long acting. Minor reactions at the injection site were common for this agent, in contrast to all of the other GLP-1 RAs, presumably due to the polymeric microspheres. In the DURATION development program, exenatide ER was found to be superior in terms of its ability to lower HbA_{1c} to all agents studied, metformin, pioglitazone, sitagliptin, exenatide bid, and insulin glargine, with the exception of liraglutide. In DURATION-6, liraglutide 1.8 mg/day was found to be more efficacious than exenatide ER.³⁶

Dulaglutide

Dulaglutide is a long-acting GLP-1 analog suitable for once-weekly use. Dulaglutide shows considerably greater potency than the short-acting analogs discussed above and greater potency than exenatide ER. It has been evaluated in a series of 10 phase 3 clinical trials. The Assessment of Weekly Administration or AWARD clinical trials included ten phase 3 trials with multiple comparators.^{37–44} (Tables 2–4) The comparators included placebo, a sulfonylurea, exenatide, insulin glargine, and liraglutide in a variety of settings and patient populations.

When dulaglutide was added to prior therapy with the SGLT₂ inhibitor empagliflozin, it resulted in additional improvement in HbA_{1c} and greater weight loss.⁴⁴

The AWARD-1 trial compared dulaglutide 1.5 mg versus exenatide (10 µg) twice daily with background therapy of metformin and pioglitazone. Participants receiving dulaglutide (1.5 mg/week) experienced dose-dependent reduction in HbA_{1c} level of 1.51%, while those receiving exenatide showed a 0.99% reduction. Both groups experienced similar weight loss, 1.3 kg, and similar incidence of gastrointestinal side effects.³⁸ Thus, in subjects with metformin and pioglitazone background therapy, once-weekly dulaglutide therapy shows superior efficacy compared with exenatide, with similar tolerability.

The AWARD-2 trial³⁹ compared dulaglutide (0.75 and 1.5 mg/week) with insulin glargine titrated using a fasting blood glucose target of 100 mg/dL, with both groups also receiving metformin treatment. The dulaglutide-treated participants exhibited an average 0.59% reduction in HbA_{1c} with the 0.75 mg dose or a 0.9% reduction with the 1.5-mg dulaglutide

dose, compared with a 0.62% reduction in the group receiving insulin glargine. Dulaglutide demonstrated a dose-dependent weight loss while the insulin glargine-treated group showed a +1.28 kg weight gain. Thus, dulaglutide (1.5 mg/week) was superior to insulin glargine and a 0.75 mg dose was noninferior.

The AWARD-6 trial⁴³ compared dulaglutide (1.5 mg/week) versus liraglutide (1.8 mg daily), both with concomitant metformin, for 26 weeks. The dulaglutide and liraglutide groups showed nearly identical decreases in HbA_{1c} levels of 1.42% and 1.36%, respectively. The liraglutide group demonstrated significantly greater weight loss (3.6 kg) compared with the dulaglutide group (2.9 kg). Adverse events were similar in the two groups.

Additional AWARD studies compared dulaglutide with several other comparators.^{40–44}

Semaglutide

Semaglutide is a GLP-1 RA that has recently become available for treatment of type 2 diabetes using once-weekly injection at dosages of 0.5 or 1.0 mg/week. The molecule has 94% amino acid sequence homology to native GLP-1. Structural modifications render semaglutide more resistant to degradation by dipeptidyl peptidase-4, confer strong binding to albumin, and extend its half-life to ~1 week (Table 1). To minimize gastrointestinal side effects, therapy should be initiated at 0.25 mg/week for 4 weeks and subsequently at 0.5 mg/week.

Semaglutide is the latest addition to the once-weekly GLP-1 RA class of therapies. It has been extensively studied in the SUSTAIN clinical trials—Semaglutide Unabated Sustainability in Treatment of type 2 diabetes (Table 4)^{45–51} and found to be more effective in terms of HbA_{1c} reduction and weight loss than placebo, sulfonylureas, exenatide, DPP-4 inhibitors, or basal insulin (glargine), either in the presence or absence of oral agents such as metformin. Semaglutide results in HbA_{1c} reduction and weight loss that are statistically and clinically significant. The combination of HbA_{1c} reduction and weight loss was seen in more than 75% of subjects in a series of five clinical trials (SUSTAIN-1 through SUSTAIN-5).^{45–51} There is a modest increase in potency of the higher 1.0 mg/week dose compared with 0.5 mg/week. Gastrointestinal side effects are comparable to those of the other GLP-1 RAs and tend to become milder after continued use.

The phase 3a development program for semaglutide included subjects across the entire spectrum of diabetes progression (Table 4). There were five trials in the SUSTAIN 3a program. SUSTAIN-1 enrolled drug-naïve patients with shorter duration of diabetes; SUSTAIN-2 enrolled patients receiving metformin and/or thiazolidinediones and the comparator was sitagliptin; in SUSTAIN-3, subjects had been receiving one or two oral antidiabetic agents and the comparator was once-weekly exenatide ER; in SUSTAIN-4, patients were receiving metformin with or without sulfonylureas and insulin, and in SUSTAIN-5, the patients had longer duration of diabetes and were being treated with basal insulin in both the semaglutide treatment and the placebo groups.

HbA_{1c} reduction

Reduction in HbA_{1c} was dose dependent with modest improvement as dose was increased from 0.5 to 1.0 mg/week.

The reduction in HbA_{1c} was nearly maximal by 16 weeks and highly statistically significant. The odds ratio for achieving an HbA_{1c} of 7.0% with semaglutide compared with placebo was ~15 for the 0.5 mg/week dosage and ~30 for the 1.0 mg/week dosage. Similar odds ratios were observed when using a target HbA_{1c} of 6.5%. Weight loss was also dose dependent: –3.7 kg at the 0.5 mg/week dosage and –5.4 kg at 1.0 mg/week after 30 weeks.⁴⁵

Composite endpoint

HbA_{1c} reduction and weight loss. In an analysis of subjects achieving any degree of HbA_{1c} reduction ≥1% and any degree of weight loss ≥5% using data from all five SUSTAIN 3a clinical trials, significantly more subjects receiving semaglutide achieved this dual composite endpoint than any of the comparators. The proportion of subjects achieving this endpoint was generally greater with semaglutide 1.0 versus 0.5 mg, suggesting a dose-dependent effect. Semaglutide was well tolerated with a safety profile similar to that of the other GLP-1 RAs.⁴⁵ SUSTAIN-6 was a cardiovascular outcome trial.⁵²

SUSTAIN-7 was a phase 3b clinical trial that compared the effectiveness of semaglutide (0.5 or 1.0 mg/week dose levels) and dulaglutide (0.75 mg or 1.5 mg/week) when added to previous therapy with empagliflozin. The lower dose of semaglutide was more effective than the higher dose of dulaglutide in reducing HbA_{1c} and achieving weight loss. The higher dose of semaglutide (1.0 mg/week) reduced mean A_{1c} by 1.8% and average weight by 6.5 pounds, in comparison with an average 1.4% reduction in HbA_{1c} and 3.0 pounds weight loss for the group receiving the higher dose of dulaglutide 1.5 mg/week.⁵³

Potential Mechanisms for Cardiovascular Protection

GLP-1 exerts direct and indirect actions on the cardiovascular system, including effects on cardiomyocytes, blood vessels, and adipocytes.⁵⁴ The GLP-1 RAs have beneficial effects on blood pressure⁵⁵ and reduce postprandial lipoprotein levels.⁵⁶ GLP-1 RAs have cardioprotective actions in preclinical models of cardiovascular ischemia, and short-term studies in humans have shown beneficial effects on cardiac function in people with ischemic heart disease. GLP-1 receptor activation in the hypothalamus reduces appetite and contributes to weight loss.⁵⁷ Obesity is a significant risk factor for atherosclerotic cardiovascular disease and increased risk of heart failure. Therefore, weight loss associated with the use of GLP-1 RA may contribute to potential cardioprotective effects. Furthermore, weight loss is associated with increased plasma adiponectin levels, which have been shown to protect against acute myocardial infarctions and cardiac hypertrophy.⁵⁸

Cardiovascular Outcome Trials for GLP-1 RAs

Large randomized placebo-controlled trials have been conducted in patients with type 2 diabetes with high cardiovascular risk to evaluate the cardiovascular safety of four GLP-1 RAs: liraglutide and lixisenatide for daily administration, and semaglutide and exenatide ER for weekly administration (Table 5).

ELIXA: The Evaluation of Lixisenatide in Acute Coronary Syndrome

The ELIXA trial compared lixisenatide with placebo in 6068 patients with type 2 diabetes who had an acute coronary event within 180 days and had a mean HbA_{1c} of 7.7%, followed up for a median of 2.1 years. The primary outcome was a 4-point major adverse cardiovascular event (MACE) that added hospitalization for unstable angina. The hazard ratio (HR) for the primary outcome was 1.02 (noninferior) with $P < 0.001$ for noninferiority and $P = 0.81$ for superiority.⁵⁹

LEADER: Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results

This study compared liraglutide 1.8 mg once daily with placebo in 9340 patients with type 2 diabetes and established cardiovascular disease (81%) or cardiovascular risk factors and a mean HbA_{1c} of 8.7%, followed up for a median of 3.8 years. The HR for the primary outcome was 0.87 with $P < 0.001$ for noninferiority and $P = 0.01$ for superiority.⁶⁰

SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with type 2 Diabetes

SUSTAIN-6 compared semaglutide (0.5 and 1.0 mg once per week) with placebo in 3297 patients with type 2 diabetes and established cardiovascular disease (83%) or cardiovascular risk factors and a mean HbA_{1c} of 8.7%, followed up for a median of 2.1 years. The HR was 0.74 with $P < 0.001$ for noninferiority and $P = 0.02$ for superiority.⁵²

EXSCEL: Exenatide study of cardiovascular event lowering

EXSCEL was the cardiovascular trial with once-weekly exenatide ER. This study compared exenatide extended-release (2 mg once per week) with placebo in 14,752 patients with type 2 diabetes and established cardiovascular disease (73%) or without previous cardiovascular events and a me-

dian HbA_{1c} of 8.0% followed up for a median of 3.2 years. The HR was 0.91 with $P < 0.001$ for noninferiority and $P = 0.06$ for superiority.⁶¹

A meta-analysis of the four cardiovascular trials reported to date evaluating cardiovascular safety of the GLP-1 RA included ELIXA, LEADER, SUSTAIN-6, and EXSCEL.⁶² These trials demonstrated cardiovascular safety, with findings from two trials (LEADER and SUSTAIN-6) showing significant reductions in the primary endpoint, a 3-point MACE outcome, including cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke. Only liraglutide was associated with significant reductions in all-cause mortality and cardiovascular mortality, and only semaglutide was associated with a significant reduction in nonfatal stroke. The authors concluded that drugs in the class of GLP-1 RA can reduce the 3-point MACE, cardiovascular mortality, and all-cause mortality risk, although to varying degrees for individual drugs and without safety concerns. If one assumes that all of the GLP-1 RAs were to show a class effect for cardioprotection and average the results of the LEADER, ELIXA, SUSTAIN-6, and EXSCEL studies, then the HR would be 0.90.⁶²

Discussion

The following considerations apply to commercially available GLP-1 RA class of therapies (Tables 2–4).

Use of GLP-1 RAs alone or as part of combination therapy with oral agents or insulin greatly improves the ability to achieve an HbA_{1c} target of either 6.5% or 7.0%. GLP-1 RAs are synergistic with metformin, SGLT₂ inhibitors, insulins, and have been used in conjunction with pioglitazone.

GLP-1 RAs have been shown to be safe, effective, and well tolerated. The gastrointestinal side effects—nausea, vomiting, and diarrhea—generally decline in frequency and severity within a matter of weeks. Slower titration of dose of the GLP-1 RA can reduce the risk of these side effects.

HbA_{1c} reduction and weight loss are largely accomplished within 15 weeks and can be expected to have reached maximal

TABLE 5. CARDIOVASCULAR OUTCOME TRIALS FOR FOUR GLP-1 RECEPTOR AGONISTS^{52,59–62}

<i>Trial</i>	<i>Patient population</i>	<i>Median follow-up</i>	<i>HR</i>
Lixisenatide ELIXA ⁵⁹	T2D with acute cardiovascular event ≤ 180 days; $N = 6058$	25 Months	HR = 1.02. No significant difference versus placebo for 4-point MACE (3-point MACE; or unstable angina requiring hospitalization), nor all-cause mortality.
Liraglutide LEADER ⁶⁰	T2D, age ≥ 50 years; CVD or CKD; or age ≥ 60 years with one risk factor; $N = 9340$	3.8 Years	HR = 0.85 for all-cause death. HR = 0.87 for 3-point MACE. HR = 0.78 for CVD death.
Exenatide qw EXSCEL ⁶¹	T2D, 70% with prior cardiovascular event; $N = 14752$	3.2 Years	HR = 0.91 for 3-point MACE
Semaglutide qw SUSTAIN-6 ⁵²	T2D, age ≥ 50 years with CVD, HF, or CKD, or ≥ 60 years with one risk factor; $N = 3297$	2.1 Years	HR = 0.74 for 3-point MACE

CKD, chronic kidney disease; CVD, cardiovascular disease; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HF, heart failure; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, major adverse cardiovascular event; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with type 2 Diabetes; T2D, type 2 diabetes.

effectiveness by 30 weeks. The reduction in HbA_{1c} and weight loss is dose dependent.

In addition to the reduction of HbA_{1c} and weight loss, the GLP-1 RAs reduce glycemic variability measured by several standard metrics (% coefficient of variation, standard deviation, mean amplitude of glycemic excursions) and accompanied by an increase in the percentage of time in the target range.^{63–66}

If the HbA_{1c} is <8%, or if the patient is at high risk for hypoglycemia for any reason (e.g., hypoglycemia unawareness, or history of severe or frequent hypoglycemia), it is advisable to reduce the dosage of insulin and/or other antihyperglycemic agents by a moderate amount to reduce the risk of hypoglycemia when adding another highly effective agent.

GLP-1 RAs are highly effective and even better tolerated when coformulated with insulin (liraglutide with insulin degludec, lixisenatide with insulin glargine U-100)). This ensures that dosage is escalated slowly and gradually.

Cardiovascular protection has been observed for liraglutide in the LEADER study. A smaller effect with borderline statistical significance was observed for exenatide ER in the EXSCEL trial but not for lixisenatide in the ELIXA. A cardiovascular outcome trial for dulaglutide is ongoing. It is worth noting that the curves for both liraglutide and semaglutide in the cardiovascular outcome trials (CVOTs) separate from placebo after more than 1 year. This is in contrast to the results reported in the EMPA-REG CVOT for empagliflozin, in which separation of the curves occurs within 3 months of initiation of the medication. This suggests that the mechanisms of cardiovascular benefit are distinctive for these two classes of medications.

For people with type 2 diabetes experiencing unacceptable levels of hypoglycemia while receiving insulin therapy, it may be possible to reduce or even eliminate the use of insulin by addition of highly effective therapies such as GLP-1 RAs.

Ongoing research and development can be expected to clarify the effectiveness and safety of the implantable osmotic pump for administration of exenatide or other relatively rapidly cleared analogs, the potential clinical utility of an oral preparation of semaglutide,⁶⁷ and the effectiveness of GLP-1 RAs for management of obesity^{57,68} and of nonalcoholic hepatosteatosis.⁶⁹

Conclusions

GLP-1 RAs are one of the most effective and well-tolerated class of therapies for type 2 diabetes. These medications are usually more effective in terms of HbA_{1c} reduction and weight loss than metformin, sulfonylureas, and DPP-4 inhibitors. The GLP-1 RA class of medications has a low risk of hypoglycemia, but adjustments of the doses of other medications are advisable, especially if the initial baseline HbA_{1c} is <8%, or if the patient is receiving insulin or sulfonylureas.

The effects of GLP-1 RAs appear to be additive with basal insulin. Lixisenatide is available as a fixed dose-ratio coformulation with insulin glargine U-100 and liraglutide is available as a fixed dose-ratio coformulation with insulin degludec. These coformulations facilitate slow and systematic titration of dose, which has the benefit of reduced gastrointestinal side effects related to the GLP-1 RA, reduced risk of hypoglycemia related primarily to the insulin, and often permit use of smaller doses for both medications than when they are used alone. Liraglutide has been demonstrated

to be cardioprotective with respect to the prespecified 3-component MACE.

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