

Clinical potential of liraglutide in cardiovascular risk reduction in patients with type 2 diabetes: evidence to date

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Abstract: Metformin is the first-line therapy for the management of type 2 diabetes. After 3 months of metformin, add-on therapy can be considered if an individual's glycemic control has not been achieved for hemoglobin A1c, fasting blood glucose levels, and postprandial blood glucose levels. Liraglutide is a potential second-line option for the management of type 2 diabetes mellitus, particularly for those who are or may be at a high risk of cardiovascular disease. It can also be used as an add-on therapy for those individuals with established cardiovascular disease. Liraglutide has additional benefits, such as no to minimal risk of hypoglycemia and promotion of weight loss through its mechanism of action. This particular article summarizes evidence on cardiovascular biomarkers and surrogate endpoints, along with macrovascular events, with liraglutide therapy. Overall, liraglutide has extensive cardiovascular evidence based on which it could be used as a desirable agent for glycemic control while lowering the risk of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization from heart failure.

Keywords: glucagon-like peptide-1, glucagon-like peptide-1 receptor agonist, liraglutide, cardiovascular

Introduction

The landscape and management of type 2 diabetes mellitus (T2DM) have changed dramatically over the past 5–10 years. One of the reasons for this change includes newly developed, extensively studied, and approved agents. Based on the American Diabetes Association and European Association for the Study of Diabetes consensus guidelines, metformin remains to be the first-line therapy for the treatment of T2DM, as long as there is no contraindication. For a patient that does not achieve a target hemoglobin A1c (HbA1c) after 3 months of metformin, an additional oral or injectable agent can be initiated for glycemic control.¹ When considering dual therapy, the patient's history of clinical cardiovascular disease should be assessed and determined. An agent that reduces major cardiovascular events and death would be preferred over another agent that has shown neutral effects.¹ Cardiovascular evidence has been extensively studied and published among glucagon-like peptide-1 receptor agonists (GLP-1 RA). Table 1 lists the current US Food and Drug Administration (US FDA)-approved agents.

Agents within the class of GLP-1 RA have several mechanisms of actions in order to promote glycemic control and improve other metabolic effects. In order to control glucose levels, these particular agents help to promote insulin secretion from the beta cells and suppress glucagon secretion from the alpha cells of the pancreas. In addition, GLP-1 RA will slow gastric emptying within the intestines and promote

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Table 1 Current US FDA-approved GLP-1 receptor agonists for type 2 diabetes mellitus

Brand name	Generic name	Maximum dose	Frequency	Drug company	Date of approval	Indication
Byetta ²⁸	Exenatide	10 µg	Twice daily	AstraZeneca	2005	T2DM
Bydureon ²⁹	Exenatide XR	2 mg	Once weekly	AstraZeneca	2005	T2DM
Victoza ³	Liraglutide	1.8 mg	Once daily	Novo Nordisk	2010	T2DM
Trulicity ³⁰	Dulaglutide	1.5 mg	Once weekly	Eli Lilly	2014	T2DM
Adlyxin ³¹	Lixisenatide	20 µg	Once daily	Sanofi-Aventis	2016	T2DM
Ozempic ³²	Semaglutide	1 mg	Once weekly	Novo Nordisk	2017	T2DM

Abbreviations: T2DM, type 2 diabetes mellitus; FDA, Food and Drug Administration; GLP-1, glucagon-like peptide-1; XR, extended release.

satiety society in the brain. These medications mimic one of the body's incretin hormones, GLP-1, by binding to the appropriate receptor; however, GLP-1 is degraded by the enzyme, dipeptidyl peptidase-IV (DPP-IV).² Short-acting GLP-1 RA, such as exenatide immediate-release and lixisenatide, can target postprandial values due to short half-life. In comparison, long-acting GLP-1 RA can target fasting blood glucose values and, therefore, show a greater HbA1c reduction. Overall, these non-insulin injectable agents are highly effective in targeting glycemic levels with no risk of hypoglycemia and additional benefit of weight loss.^{1,2}

Liraglutide (marketed as Victoza in the US, Novo Nordisk) was approved by the US FDA in 2010 for the treatment of T2DM when used in conjunction with diet and exercise.³ Another liraglutide product was approved in 2014, marketed as Saxenda in the US (Novo Nordisk) for weight management.⁴ The indication and product label were updated in August 2017 and October 2018, respective to each branded product, to include evidence on liraglutide's efficacy in reducing cardiovascular events and deaths among those with T2DM and established cardiovascular disease.^{3,4} In this clinical review article, the evolving literature has been summarized regarding the efficacy and safety of liraglutide on various cardiovascular markers, endpoints, and events, particularly among patients with T2DM and cardiovascular disease.

Pharmacology

Liraglutide was the second GLP-1 RA developed and is 97% homologous to the native incretin hormone, with modifications occurring in two places (26th and 34th positions) and the addition of a fatty-acid chain to the 16th carbon position.^{3,5} The fatty-acid chain lengthens the duration of action of liraglutide, permitting once-daily administration.⁵ As mentioned in the introduction, the mechanism of action for GLP-1 RA is multifaceted, similar to the endogenous hormone, and

includes increasing insulin secretion, decreasing glucagon secretion, prolonging gastric emptying, and bolstering satiety.⁵ Glycemic reduction due to liraglutide is mediated by an increase in insulin secretion, decrease in glucagon secretion, and delayed gastric emptying. Insulin secretion is glucose-dependent, which lowers the risk of hypoglycemic episodes.⁵

Despite liraglutide slowing gastric emptying, studies have shown that it has no to minimal effect on other medications when taken concomitantly.³ Common adverse effects are ephemeral nausea and vomiting, which are generally mitigated by dose titration.³ The results of the Liraglutide Effect and Action in Diabetes (LEAD) trials yielded positive clinical results for liraglutide in regard to HbA1c improvement and weight reduction, but the trials failed to show that liraglutide could be utilized as a first-line pharmacotherapy option in patients with diabetes.^{7–12} Based on its mechanism of action, it is a possible pharmacologic agent for weight management in the appropriate patient population based on the Satiety and Clinical Adiposity Liraglutide Evidence in Nondiabetic and Diabetic people trials.^{13,14}

Pharmacokinetics and pharmacodynamics

After subcutaneous administration, liraglutide gets slowly absorbed and a maximum drug concentration level is reached within 8–12 hours with an absolute bioavailability of around 55%.^{3,6} The average steady-state concentration was estimated to be 128 ng/mL with 1.8 mg subcutaneous dose. Exposure of liraglutide is comparable between all three administration sites (ie, upper arm, abdomen, and thigh). It is highly bound to plasma protein (>98%) with an estimated clearance range of 0.6–1.2 L/h. Clearance remained similar among all doses, ages, injection sites, and races. The elimination half-life is about 13 hours with no findings of unmetabolized liraglutide found in the urine or feces. It is metabolized similar to other large proteins by degradation into peptides, amino acids, and

fatty acid fragments within the body; therefore, the drug has a low chance of interactions with CYP/CYP450 metabolized drugs.^{3,6} Table 2 summarizes the pharmacokinetic profile of liraglutide in comparison to other GLP-1 RA.

No dose adjustments are needed for renal and/or hepatic impairment.^{15,16} However, it should be used with caution in patients with end-stage renal disease due to limited studies in this population.³

Methods

PubMed and EBSCO searches were conducted using terms *liraglutide*, *cardiovascular*, *type 2 diabetes mellitus*, and *GLP-1 receptor agonists*. Results were further narrowed down by searching for clinical trials and meta-analyses that focused on liraglutide in regard to cardiovascular risk reduction and outcomes among patients with T2DM. Any relevant articles focusing on cardiovascular endpoints or outcomes, even in special populations, were utilized for this review article. While there were no selection criteria for the vast amount of evidence, the focus was on clinical trials or meta-analyses evaluating liraglutide and its effect on cardiovascular markers, endpoints, or events.

Clinical evidence

Cardiovascular markers

Heart failure

A trial in 2014 examined the use of liraglutide on peritoneal dialysis (PD) among Japanese patients with type 2 diabetes for 12 months.¹⁷ The trial enrolled 30 patients whose blood glucose levels were not controlled on current regimen, which included oral antidiabetic agents and/or insulin therapy. Patients were excluded if there was a history of type 1 diabetes, diabetic ketoacidosis, serum C peptide <2.0 ng/mL, insulin doses >20 units per day, or severe hepatic or cardiac failure. The purpose of the trial was to determine the efficacy and safety of liraglutide in patients undergoing PD with

type 2 diabetes. Fifteen patients received liraglutide while the other patients (n=15) continued their current regimen. Among the 15 patients who received liraglutide, ten started liraglutide while in an inpatient setting while the other five started liraglutide in an outpatient setting. Prior to starting liraglutide, 11 patients were taking insulin and five were taking oral antidiabetic agents. Liraglutide dose was increased, based on the dose required for glycemic control, over 14 days to a final dose of 0.6–0.9 mg subcutaneously daily. One patient discontinued liraglutide due to nausea and anorexia. For the patients who started liraglutide as inpatients, blood glucose levels were monitored prior to and after 2 hours of each meal and at bedtime. This glucose monitoring regimen was preformed 1 week before and 2–3 weeks after starting liraglutide. For patients who started liraglutide as outpatients, blood glucose levels were monitored prior to and after 2 hours of meal for two times. Echocardiographic measurements were taken upon starting PD and after 12 months. Parameters such as left ventricular mass index (LVMI), left ventricular ejection fraction, and left ventricular eccentric hypertrophy were assessed using the Devereux and Reicheck formula. SBP and DBP upon awakening were significantly decreased in the liraglutide group after 6 and 12 months ($P=0.022$ and 0.002 , retrospectively). Also, LVMI was decreased in the liraglutide group at 12 months ($P=0.044$). Liraglutide was shown to have positive outcomes for blood glucose control and blood pressure control. Also, PD patients with DM may tolerate liraglutide with few adverse drug reactions.¹⁷

Hyperlipidemia

Chylomicron and intestinal ApoB48 secretion have been documented to increase in patients with T2DM. This increase is associated with postprandial hyperlipidemia, which plays a main role in the reduction of cardiovascular risks associated with T2DM.¹⁸ Liraglutide has also been shown to decrease postprandial triglycerides.¹⁹ A trial published in 2018

Table 2 Pharmacokinetic properties of US FDA-approved GLP-1 receptor agonists

Brand name	Generic name	Half-life	Volume of distribution	Elimination
Byetta ²⁸	Exenatide	2.4 hours	28.3 L	Glomerular filtration
Bydureon ²⁹	Exenatide XR	2 weeks	28.3 L	Glomerular filtration
Victoza ³	Liraglutide	13 hours	13 L	Urine and feces (metabolite)
Trulicity ³⁰	Dulaglutide	5 days	9.3–33 L	–
Adlyxin ³¹	Lixisenatide	1–3.5 hours	100 L	Glomerular filtration
Ozempic ³²	Semaglutide	1 week	12.5 L	Urine and feces

Abbreviations: L, liters; T2DM, type 2 diabetes mellitus; FDA, Food and Drug Administration; GLP-1, glucagon-like peptide-1; XR, extended release.

examined the *in vivo* kinetics of ApoB48, and the production and catabolism of ApoB48, in patients with T2DM treated with liraglutide for 6 months.¹⁸ In addition, the trial also examined the animal and *in vitro* studies that focused on the effects of liraglutide in producing chylomicrons. The study enrolled ten patients with T2DM and hyperlipidemia. Inclusion criteria were triglycerides >150 mg/dL or high-density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women and HbA1c above 7%. Patients had to have a stable HbA1c for 6 months prior to the start of the study and had to be treated with oral antidiabetic agents (metformin monotherapy [n=5]; metformin plus sulfonylurea [n=4]; metformin plus acarbose [n=1]). Liraglutide was initiated at 0.6 mg per day and titrated to 1.2 mg per day after 1 week as a subcutaneous injection. The dose was maintained at 1.2 mg per day throughout the study. Pharmacokinetic studies were performed prior to starting liraglutide and 6 months after treatment. Patients were instructed to avoid strenuous exercise 3 days prior to the kinetic study; one day prior to the kinetic study, patients underwent a 12-hour fast for physical exam and blood tests. On the day of the kinetic study, the patients' food intake was 1,700 kcal (55% carbohydrate, 39% fat, and 7% protein). Meals were split up into small amounts (every 2 hours, starting 6 hours before the tracer infusion up to the end of the study). Tracing of ApoB48 was done by administration of L-D8-Valine mixed in normal saline with infusion of 0.7 mg/kg intravenously and then immediately followed by a 16-hour constant infusion of 0.7 mg/kg per hour. Blood samples were collected before and after infusion according to the scheduled intervals (ie, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 15, and 16 hours). Body weight, fasting glucose, HbA1c, homeostasis model assessment-insulin resistance, fasting triglycerides, total cholesterol, and ApoB all were reduced with statistical significance ($P<0.05$). The HDL and low-density lipoprotein (LDL) concentrations showed no statistical significance. The total amount of ApoB48 pool was reduced ($P=0.005$) related to the decrease in ApoB48 production rate ($P=0.009$) and increase in ApoB48 fractional catabolic rate ($P=0.005$).¹⁸ In conclusion, liraglutide showed a decrease in ApoB48, by reducing the production of ApoB48 and increasing its catabolism. The reduction of ApoB48, caused by liraglutide, in DM patients may improve dyslipidemia and cardiac outcomes.

Additional evidence

Heart rate variability (HRV) is seen in patients with T2DM and can indicate autonomic imbalance. Standard deviation of beat-to-beat intervals (SDNN) from 24-hour heart monitoring

measures HRV for autonomic reflex balance. Autonomic imbalance with reduced SDNN and increased HRV has been associated with coronary artery disease (CAD), heart failure, and cardiovascular death.²⁰ A study, published in 2017, examined liraglutide's effect on HRV in patients who were overweight and had stable CAD and who were newly diagnosed with T2DM.²⁰ The study was a randomized, double-blinded, placebo-controlled 24-week crossover study with a 2-week washout period. Patients who took antidiabetic agent had a minimum 2-week washout period prior to the start of the trial. Liraglutide was initiated at 0.6 mg subcutaneously daily plus 500 mg metformin orally twice daily. The regimen was increased after 14 days to 1.2 mg subcutaneously daily plus 1,500 mg metformin orally daily. At 28 days, liraglutide and metformin were maximized to 1.8 mg subcutaneously once daily and 1,000 mg orally twice daily, respectively. All patients had 48 hours Holter monitoring before and after each intervention during weeks 0, 12, 14, and 26. Physical activity was restricted to prevent variability in heart rate (HR) and mean, minimum, and maximum HR were assessed, along with diurnal variation in HR. Diurnal HR variation was analyzed using full recording time, and hourly HR was calculated as the average from two consecutive days, when available. Forty patients underwent randomization and only 30 patients completed all visits. Full data were available for only 26 patients. Liraglutide treatment decreased mean HR (6.9 ± 8.6 vs -1.2 ± 7.1 beats per min [bpm]; $P=0.003$) and minimum HR (7.0 ± 5.9 vs -0.7 ± 5.2 bpm; $P<0.001$). Maximum increase in HR was statistically significant ($P=0.057$). SD of beat-to-beat intervals was decreased with liraglutide (-33.9 ms; $P<0.001$, paired analysis); however, there was an increase in HR during the day ($P=0.083$) and at night ($P=0.026$). The changes noted suggest that liraglutide plays a role in sympathovagal balance.²⁰

Surrogate cardiovascular endpoints

The effects of liraglutide on microvascular and macrovascular outcomes have been evaluated in several studies. In the first study, which was conducted for 22 weeks in Denmark, the objective was to determine whether the use of liraglutide could improve microvascular function.²¹ The trial was a randomized, single-blinded, cross over trial that involved two sequences: 10 weeks of liraglutide followed by a 2-week washout period and 10 weeks of normal diabetic therapy (sequence 1) and 10 weeks of normal diabetic therapy followed by 10 weeks of liraglutide therapy (sequence 2). The primary endpoint was coronary flow reserve (CFR) measurement, which is believed to have a positive correlation to

coronary microcirculation. Secondary endpoints included peripheral endothelial function, body weight, waist circumference, blood pressure, HR, HbA1c, fasting C-peptide, plasma glucose level, and serum insulin. A total of 24 patients were randomized, but only 20 patients (ten per sequence) completed the full treatment duration and obtained the maximum dose of liraglutide 1.2 mg subcutaneously once daily. The analysis of baseline characteristic in each group yielded no significant differences, and no statistically significant differences were seen between groups for the primary outcome and several secondary outcomes. CFR yielded a hazard ratio of 0.16 with 95% CI (−0.08 to 0.40; $P=0.18$); endothelial function also lacked statistically significant results with a hazard ratio of 0.09 (95% CI −0.17 to 0.36; $P=0.49$) between groups. Statistically significant secondary outcomes included decreases in HbA1c ($P=0.01$), plasma glucose ($P<0.001$), weight ($P=0.03$), and SBP ($P=0.01$). Additional secondary outcomes that yielded no statistically significant results were DBP, HR, and waist circumference. While some statistically significant results were achieved, the investigators pondered whether the trial duration and/or liraglutide dose prevented the study from obtaining significant results for the primary endpoint.²¹

A second study focused on the utilization of liraglutide in patients following an acute coronary event, specifically a myocardial infarction, in both efficacy and safety. The study was a non-randomized, prospective, open-label, single-arm, single-center pilot trial, which assessed the variations in multiple cardiovascular biomarkers prior to liraglutide initiation to week 24.²² The cardiovascular biomarkers included were high-sensitive C-reactive protein, cystatin-C, malondialdehyde-modified LDL, remnant-like lipoprotein particle cholesterol, and 1,5 anhydroglucitol. Additional secondary parameters were also studied, including alterations in glycemic parameters, left ventricular function, diastolic function, and occurrence of adverse events. Only eight patients were enrolled in this study and all were able to tolerate the maximum dose of the intervention, liraglutide 0.9 mg subcutaneously once daily. The only biomarker yielding statistical significance was 1,5 anhydroglucitol ($P=0.08$). In addition, other statistically significant results identified were reduction in body weight ($P=0.003$), body mass index ($P=0.005$), LDL concentration ($P=0.029$), and non-HDL concentrations ($P<0.013$). The authors stated that changes in lipid levels were caused by the introduction of statin therapy. There was also a statistically significant increase in SBP levels ($P<0.001$) and DBP levels ($P<0.001$) by the week 24 of therapy, regardless of the patients receiving treatment

with a renin–angiotensin system inhibitor. While half of the patients reported constipation within the first weeks of the study, no other adverse events were disclosed. This study differs in comparison to others based on there being no clear link to a decrease in macrovascular effects, per the authors; however, it did not yield deterioration in the patients' well-being. It is also noted that this study utilized a lower dose than that approved for use within the US which may have affected the results.²²

Cardiovascular events

The main cardiovascular trial involving liraglutide was the LEADER trial (Liraglutide in Action for Diabetes: Evaluation of Cardiovascular Outcomes).²³ For this particular study, adult patients with T2DM were included if they had at least one cardiovascular condition or one cardiovascular risk factor. In this multicentered, double-blinded, placebo-controlled trial, patients were randomized in a 1:1 fashion to liraglutide or to placebo. Liraglutide was given subcutaneously once daily at a dose of 1.8 mg or at a lower dose based on tolerance. The primary outcome was a composite of time to event in which the authors evaluated the first occurrence of death from cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke. For this particular trial, the primary composite outcome was statistically significant between liraglutide (13%) and placebo (14%, 95% CI 0.78–0.99, $P<0.01$). There was a 13% reduction in this primary composite outcome. Within the composite outcome, liraglutide reduced death from any cause by 15% (0.85, 95% CI 0.74–0.97, $P=0.02$). This specific outcome was highly influenced by death from cardiovascular cause. In addition, there was a 14% reduction in myocardial infarction ($P=0.046$). Other outcomes were not statistically significant except for a 16% reduction in microvascular events, which was greatly influenced by nephropathy as fewer people in the liraglutide group had this type of an event compared with placebo ($P=0.003$).²³

A follow-up study to the LEADER trial was published to investigate the various myocardial infarction subtypes and determine the differences between liraglutide and placebo.²⁴ This publication was a post hoc hike analysis, in which there were 781 first and recurrent myocardial infarctions that had been reported in both groups. Overall, there were fewer events in the liraglutide ($n=359$) vs placebo ($n=421$) groups ($P=0.022$). It should be noted that more people in the liraglutide group had a history of coronary artery bypass graft but fewer people had a history of peripheral arterial disease. Overall, from the LEADER trial in the post hoc analysis, it

has been observed that liraglutide had a significant impact on reducing the risk of myocardial infarction and other cardiovascular events in patients with established cardiovascular disease or in those at high risk of cardiovascular diseases.^{23,24} The LEADER trial is the major publication that has led to changes in guidelines regarding liraglutide for the management of T2DM. Based on this particular study, the package insert and product information for liraglutide, as Saxenda, have been updated to indicate its efficacy in reducing cardiovascular events.^{3,4}

An additional trial was carried out in Chinese patients who had T2DM and CAD to determine the efficacy of liraglutide alone and in combination with metformin on metabolic and cardiovascular outcomes.²⁵ Similar to other trials, liraglutide improved fasting blood glucose levels, HbA1c, weight, total cholesterol, LDL, C-reactive protein, and blood pressure measurements, along with injection fraction. These results showed that liraglutide is an effective agent in improving these surrogate endpoints in a high-risk patient population.²⁵

Meta-analyses

In addition to the numerous studies analyzed, two meta-analyses were reviewed, concentrating on the cardiovascular outcomes with use of GLP-1 RA.^{26,27} In the first meta-analysis, 45 randomized controlled trials were examined, with several trials including liraglutide. The primary objective of these trials was composite cardiovascular safety outcome, which included cardiovascular mortality, ischemic heart disease, nonfatal heart failure, and stroke. Eighteen trials evaluated the efficacy of liraglutide on cardiovascular outcomes (n=9, compared to placebo; n=9, compared to active comparator drug). Among these, none of the trials produced statistically significant results, except for HbA1c reduction.²⁶

The second meta-analysis investigated cardiovascular effects of both GLP-1 RA and DPP-IV inhibitors by reviewing 28 articles, among which nine trials analyzed GLP-1 RA only.²⁷ Within these publications, the cardiovascular outcomes included stroke, myocardial infarction, death due to cardiovascular issues, and hospitalization due to acute coronary syndrome or heart failure. The primary endpoint was to assess the risk reduction in cardiovascular-related events while the patient was receiving a GLP-RA or DPP-IV inhibitor. Among the various studies that were evaluated, only one study – LEADER trial – revealed statistically significant evidence and related evidence for the cardiovascular effects of GLP-1 RA in reducing major adverse cardiovascular events within patients, as summarized earlier.²⁷

Adverse drug events

Clinical trials of liraglutide, dosed at either 1.2 mg per day or 1.8 mg per day, have reported adverse drug reactions of gastrointestinal upset, injection site reaction, and hypoglycemia. The most common ($\geq 5\%$) gastrointestinal complaints reported were nausea, vomiting, diarrhea, dyspepsia, and decreased appetite.^{3,7–12,23} Withdrawal related to these adverse events was 4.3% in liraglutide group compared to 0.5% in placebo group. However, the gastrointestinal side effects were noted to resolve after 2–3 months with continuation of therapy. Injection site reactions were reported in 2% of liraglutide group compared to 0.2% of placebo group. Hypoglycemia, requiring assistance from another person, was reported in one 26-week trial, in which seven patients that had this type of event were simultaneously taking a sulfonylurea drug.^{3,7–12,23}

The LEADER trial examined the cardiovascular effects of liraglutide.²³ There was no difference in any adverse events between groups ($P=0.12$). Rates of neoplasms were higher in the liraglutide group but were not statistically significant. Adverse drug reactions leading to discontinuation were higher in the liraglutide group ($P<0.001$), which was largely due to gastrointestinal adverse events. As for serious adverse events, liraglutide group had more injection site reactions ($P=0.002$) and acute gallstone disease ($P<0.001$), whereas placebo group had more severe hypoglycemic events ($P=0.02$).²³

Limitations of clinical trials

Liraglutide has been examined for cardiovascular events in varying populations in both randomized controlled trials and meta-analyses.^{23,26,27} Although a vast amount of evidence is available, limitations should be noted. Many of the studies had a smaller sample size; with the exclusion of the LEADER trial, the majority of the trials enrolled <100 patients. The outcome(s) would have been potentially different if a larger population had been tested. In addition, majority of the studies had minimal racial diversity. Applying the trial outcomes to some races is questionable. Finally, the duration of cardiovascular outcomes is unknown past 5 years. Most of the studies examined the effects of liraglutide for <6 months. The LEADER study followed up patients only from 3.5 to 5 years. Liraglutide has unknown benefit for cardioprotection after 5 years. Further studies are needed to determine length of time and possible variations among race.^{23,26,27}

Therapeutic considerations

Within the past decade, liraglutide has been approved by the US FDA for treatment of both T2DM and obesity.^{3,4} When being utilized for T2DM treatment, liraglutide is not consid-

ered a first-line option; however, it can be used as an adjunctive therapy for patients with cardiovascular disease or who are at risk of cardiovascular diseases.¹ With the recent consensus guidelines, liraglutide is recommended and preferred over semaglutide and exenatide extended-release for patients with cardiovascular diseases.¹ Older individuals (those 65 years of age or older) have shown no variation in clinical response.³

Liraglutide was the first once-daily GLP-1 RA, dosed 0.6 mg for 1 week, then titrated to 1.2 mg and potentially to a maximum dose of 1.8 mg as Victoza.³ If liraglutide is given for weight management, then Saxenda should be initiated at 0.6 mg once daily, and then titrated by 0.6-mg increments to a maximum dose of 3 mg once daily.⁴ If a patient is not able to tolerate the titrated dose due to gastrointestinal adverse events, then the titration can be prolonged. If one dose of liraglutide is missed, the patient should be encouraged to maintain the current dose of liraglutide. Liraglutide should be restarted at 0.6 mg once daily, if a patient misses more than three consecutive doses.^{3,4} Liraglutide can be injected any time of the day as long as it is a consistent time for the patient. Liraglutide comes in a pre-filled, multi-dose pen, which is similar to a pre-filled insulin pen requiring patient education on proper storage, preparation, and administration. It can be injected within the abdomen, thigh, and upper arm.^{3,4}

Summary

Liraglutide has a pharmacokinetic profile, allowing for once-daily administration among patients with T2DM or obesity. It has been proven to be an effective agent in reducing glycemic concentrations, particularly fasting blood glucose levels and HbA1c. In addition, it is an effective option to promote weight loss with no to minimal risk of hypoglycemia. It is an appropriate option for patients with T2DM who have or are at risk of cardiovascular events, requiring add-on therapy for glycemic control.

Author contributions

All authors contributed to data analysis, drafting and revising of the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2018;61(12):2461–2498.
2. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care*. 2011;34(Supplement 2):S279–S284.
3. Victoza® [package insert]. Plainsboro Township, NJ: Novo Nordisk, 2018.
4. Saxenda® [package insert]. Plainsboro, NJ: Novo Nordisk; 2014.
5. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs Context*. 2015;4:212283.
6. Jacobsen LV, Flint A, Olsen AK, Ingwersen SH. Liraglutide in type 2 diabetes mellitus: clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2016;55(6):657–672.
7. Marre M, Shaw J, Brändle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26(3):268–278.
8. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care*. 2009;32(1):84–90.
9. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *The Lancet*. 2009;373(9662):473–481.
10. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32(7):1224–1230.
11. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulphonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52(10):2046–2055.
12. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *The Lancet*. 2009;373(9683):39–47.
13. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the scale diabetes randomized clinical trial. *JAMA*. 2015;314(7):687–699.
14. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11–22.
15. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. *Br J Clin Pharmacol*. 2009;68(6):898–905.
16. Flint A, Nazzari K, Jagielski P, Hindsberger C, Zdravkovic M. Influence of hepatic impairment on pharmacokinetics of the human GLP-1 analogue, liraglutide. *Br J Clin Pharmacol*. 2010;70(6):807–814.
17. Hiramatsu T, Ozeki A, Asai K, et al. Liraglutide improves glycemic and blood pressure control and ameliorates progression of left ventricular hypertrophy in patients with type 2 diabetes mellitus on peritoneal dialysis. *Ther Apher Dial*. 2015;19(6):598–605.
18. Vergès B, Duvillard L, Pais de Barros JP, et al. Liraglutide reduces postprandial hyperlipidemia by increasing apoB48 (apolipoprotein B48) catabolism and by reducing apoB48 production in patients with type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2018;38(9):2198–2206.
19. Hermansen K, Bækdal TA, Düring M, et al. Liraglutide suppresses postprandial triglyceride and apolipoprotein B48 elevations after a fat-rich meal in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, cross-over trial. *Diabetes Obes Metab*. 2013;15(11):1040–1048.
20. Kumarathurai P, Anholm C, Larsen BS, et al. Effects of liraglutide on heart rate and heart rate variability: a randomized, double-blind, placebo-controlled crossover study. *Diabetes Care*. 2017;40(1):117–124.

21. Faber R, Zander M, Pena A, Michelsen MM, Mygind ND, Prescott E. Effect of the glucagon-like peptide-1 analogue liraglutide on coronary microvascular function in patients with type 2 diabetes – a randomized, single-blinded, cross-over pilot study. *Cardiovasc Diabetol*. 2015;14(1):1–11.
22. Kajiwaru M, Tanaka A, Kawasaki T, et al. Safety and efficacy of liraglutide treatment in Japanese type 2 diabetes patients after acute myocardial infarction: a non-randomized interventional pilot trial. *J Cardiol*. 2017;69(3):511–517.
23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–322.
24. Marso SP, Nauck MA, Monk Fries T, et al. Myocardial infarction subtypes in patients with type 2 diabetes mellitus and the effect of liraglutide therapy (from the leader trial). *Am J Cardiol*. 2018;121(12):1467–1470.
25. Liu Y, Jiang X, Chen X. Liraglutide and metformin alone or combined therapy for type 2 diabetes patients complicated with coronary artery disease. *Lipids Health Dis*. 2017;16(1):227.
26. Sun F, Yu K, Wu S, et al. Cardiovascular safety and glycemic control of glucagon-like peptide-1 receptor agonists for type 2 diabetes mellitus: a pairwise and network meta-analysis. *Diabetes Res Clin Pract*. 2012;98(3):386–395.
27. Mannucci E, Monami M. Cardiovascular safety of incretin-based therapies in type 2 diabetes: systematic review of integrated analyses and randomized controlled trials. *Adv Ther*. 2017;34(1):1–40.
28. Byetta® [package insert]. Wilmington, ED: AstraZeneca; 2015.
29. Bydureon® [package insert]. Wilmington, ED: AstraZeneca; 2017.
30. Trulicity® [package insert]. Indianapolis, IN: Eli Lilly; 2018.
31. Adlyxin™ [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2016.
32. Ozempic® [package insert]. Plainsboro, NJ: Novo Nordisk; 2017.

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