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The role of GLP-1 receptor agonists in managing type 2 diabetes

ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists improve glycemic control in patients with type 2 diabetes mellitus, have cardioprotective and renoprotective effects, and do not cause weight gain or significant hypoglycemia. In fact, they have been found to be effective for weight loss in patients with obesity with and without diabetes. They are now the preferred drugs to add to the regimen when oral metformin by itself is not enough to meet the patient's hemoglobin A1c goal.

KEY POINTS

Long-acting GLP-1 receptor agonists control glycemia a little better than short-acting agents and better than insulin, lowering hemoglobin A1c by about 1%.

Large, randomized clinical trials of GLP-1 receptor agonists have had positive or at worst neutral results in terms of preventing major adverse cardiovascular events in patients with type 2 diabetes who either had cardiovascular disease at baseline or were at high risk of it.

GLP-1 receptor agonists have a protective effect on the kidneys, reducing the risk of macroalbuminuria, but perhaps do not help preserve the glomerular filtration rate as much as sodium-glucose transporter-2 inhibitors.

GLP-1 receptor agonists are recommended as either first-line or second-line therapy regardless of baseline hemoglobin A1c in patients who have established atherosclerotic cardiovascular disease, high risk of atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure.

TWO NEW CLASSES OF DRUGS have brought on a major shift in how we manage type 2 diabetes mellitus: glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. We discussed SGLT-2 inhibitors in an earlier article in this *Journal*.¹ Here, we review the evidence regarding the benefits and adverse effects of GLP-1 receptor agonists, aiming to help guide primary care clinicians in using these agents while taking care of their patients who have type 2 diabetes mellitus or obesity.

■ HOW THE GUT TALKS TO THE PANCREAS

In healthy people without diabetes, glycemic homeostasis is regulated by pancreatic hormones such as insulin, amylin, and glucagon, as well as by incretin hormones released from the gastrointestinal cells, eg, GLP-1 and glucose-dependent insulinotropic polypeptide.

In response to ingestion of glucose, the L and K intestinal cells release incretin hormones that stimulate pancreatic beta cells, leading to insulin secretion. This mechanism is mainly activated after oral ingestion of glucose rather than intravenous administration, and may be impaired in patients with impaired glucose tolerance or non-insulin-dependent diabetes, leading to hyperglycemia.² Incretin's role in reducing hyperglycemia is also mediated by glucagon suppression and delayed gastric emptying.^{3,4}

■ LONG-ACTING AGENTS LOWER HEMOGLOBIN A1c ABOUT 1%

Several GLP-1 receptor agonists are approved by the US Food and Drug Administration

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TABLE 1
Glucagon-like peptide-1 receptor agonists approved for use in the United States

Drug	Available doses	Frequency and route	Dose approved for weight management
Exenatide	5 µg, 10 µg	Twice daily subcutaneously	Not approved
Liraglutide	0.6 mg, 1.2 mg, 1.8 mg	Once daily subcutaneously	0.6 mg once daily for 1 week, increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily
Exenatide extended-release	2 mg	Once weekly subcutaneously	Not approved
Dulaglutide	0.75 mg, 1.5 mg, 3 mg, 4.5 mg	Once weekly subcutaneously	Not approved
Semaglutide	0.25 mg, 0.5 mg, 1 mg, 2 mg	Once weekly	Titrate every 4 weeks: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg once weekly
Semaglutide, oral	3 mg, 7 mg, 14 mg	Once daily by mouth	Not approved
Liraglutide-insulin degludec	0.36 mg-10 U 0.5 mg-16 U	Once daily subcutaneously	Not approved
Lixisenatide-insulin glargine	5 µg-15 U 10 µg-30 U	Once daily subcutaneously	Not approved
Tirzepatide	2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Once weekly subcutaneously	Not approved

(FDA) for use in patients with type 2 diabetes mellitus, with various formulations intended for use as short-acting monotherapy, long-acting monotherapy, and in combination with basal insulin (Table 1).

Huthmacher et al⁵ performed a meta-analysis of 14 clinical trials and calculated that overall, the change in hemoglobin A1c with GLP-1 receptor agonists was -0.7% (95% confidence interval [CI] -1.2 to -0.2 , $P = .006$), and that the reduction was somewhat smaller with short-acting agents (-0.5% , 95% CI -0.7 to -0.3 , $P < .0001$) and greater with long-acting agents (-1.0% , 95% CI -1.2 to -0.8 , $P < .0001$). Notably, more patients achieved their hemoglobin A1c targets ($< 7\%$ or $\leq 6.5\%$, depending on the trial) if they received long-acting agents.⁵

Abd El Aziz et al⁶ performed a meta-analysis of 19 clinical trials comparing the addition of GLP-1 receptor agonists vs insulin treatment in patients already receiving oral glucose-lowering agents. GLP-1 receptor agonists lowered hemoglobin A1c by 0.12% more than insulin did ($P < .0001$), with the difference being entirely due to the longer-acting agents. On the other hand, insulin lowered fasting plasma glucose by 32.4 mg/dL more than GLP-1 receptor agonists did ($P < .0001$).⁶

For these reasons, guidelines from the American Diabetes Association (ADA) have shifted.⁷ For patients with type 2 diabetes who have atheroscle-

rotic cardiovascular disease or are at high risk for it or who have kidney disease or heart failure, either a GLP-1 receptor agonist or an SGLT-2 inhibitor with demonstrated cardiovascular benefit with or without metformin is recommended, independent of the hemoglobin A1c level (level of evidence A).⁷

■ PROTECTING THE HEART AND BRAIN

GLP-1 receptor agonists interfere with several molecular and cellular steps of the atherogenesis process. GLP-1 plays key roles in reducing the production of reactive oxygen species, reducing platelet activation, reducing activation of macrophages and monocytes and their consecutive accumulation in the vascular wall, and inhibiting endothelin production, which in turn, leads to vasodilation. GLP-receptor agonists boost the effects of GLP-1, enhancing these desirable actions.⁸⁻¹¹ Furthermore, these drugs stabilize endothelial cells and reduce plaque hemorrhage and rupture.¹²⁻¹⁴ The result of these actions is a slower progression of atherosclerosis.

Results of randomized trials

Six large randomized trials and a post hoc analysis¹⁵⁻²¹ have investigated the safety and efficacy of GLP-1 receptor agonists in patients with type 2 diabetes who also either had known cardiovascular disease or were at high risk of it, using a composite of major adverse

TABLE 2

Effects of glucagon-like peptide-1 receptor agonists on major adverse cardiovascular events in clinical trials

Trial	Number of patients	Median follow-up	Cardiovascular disease at baseline ^a	Treatment	Number needed to treat ^b
REWIND ¹⁵	9,901	5.4 years	31.5%	Dulaglutide 1.5 mg subcutaneously weekly	323
SUSTAIN-6 ¹⁶	3,297	2.1 years	2.1 years 60.5%	Semaglutide 0.5 or 1 mg subcutaneously weekly	83
LEADER ¹⁷	9,340	3.8 years	81.3%	Liraglutide 1.6 mg subcutaneously daily	200
ELIXA ¹⁸	6,068	2.1 years	100%	Lixisenatide 10 or 20 µg subcutaneously daily	No benefit
EXSCEL ¹⁹	14,752	3.2 years	70%	Exenatide extended-release 2 mg subcutaneously weekly	No benefit
PIONEER-6 ²¹	3,183	1.3 years	85%	Semaglutide 14 mg by mouth daily	No benefit

^a All patients had longstanding type 2 diabetes and also either had a history of cardiovascular disease or were at risk of it.

^b Number of patients needed to be treated for 1 year to prevent 1 major adverse cardiovascular event (myocardial infarction, stroke, or death from cardiovascular causes, plus, in the ELIXA trial, hospitalization for heart failure), calculated as the inverse of the absolute risk reduction.

ELIXA = Lixisenatide in Patients With Type 2 Diabetes and Acute Coronary Syndrome; EXSCEL = Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PIONEER-6 = Oral Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes; REWIND = Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6 = Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes

cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) as the primary end point (Table 2).^{15–19,21}

The **REWIND trial** (Researching Cardiovascular Events With a Weekly Incretin in Diabetes)¹⁵ reported statistically significant reductions in major adverse cardiovascular events (relative risk reduction 12%, with a number needed to treat [NNT] of 323, ie, the number of patients who would need to be treated for 1 year to prevent 1 event) and nonfatal stroke (relative risk reduction 24%, NNT 588) in patients who received dulaglutide 1.5 mg once a week compared with placebo. Differences in the rates of nonfatal myocardial infarction and death from cardiovascular causes were not statistically significant. Notably, the REWIND trial had the lowest proportion of randomized patients who had established cardiovascular disease at baseline (only 31%) of the 6 major trials of GLP-1 receptor agonists.^{15–21}

The **SUSTAIN-6 trial** (Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes)¹⁶ showed a significant relative risk reduction of 26% (NNT 83) in major adverse cardiovascular events in those who received semaglutide 0.5 or 1 mg compared

with placebo. This difference was primarily driven by a significant relative risk reduction of 39% (NNT 196) in nonfatal stroke in the semaglutide group.¹⁶

The **LEADER trial** (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results)¹⁷ showed a relative risk reduction in major adverse cardiac events of 13% (NNT 200) and in cardiovascular death of 22% (NNT 250) in patients with type 2 diabetes who received liraglutide compared with placebo. Rates of nonfatal myocardial infarction and nonfatal stroke were lower in the liraglutide group than in the placebo group, but these differences were not statistically significant.¹⁷

The trial was criticized for differences in the use of cardioprotective medication between the treatment groups. More patients with established cardiovascular disease in the liraglutide group were using beta-blockers, statins, angiotensin-converting enzyme inhibitors, and platelet aggregation inhibitors than in the placebo group, which might have skewed the results in favor of liraglutide.

The **ELIXA trial** (Lixisenatide in Patients With Type 2 Diabetes and Acute Coronary Syndrome)¹⁸ failed to show the same benefit. The ELIXA trial did not have

the between-group differences for baseline cardioprotective medications as in the LEADER trial, and the trial population included patients with type 2 diabetes with a history of either myocardial infarction or hospitalization for unstable angina within the previous 180 days.

The EXSCEL trial (Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes)¹⁹ compared 2-mg weekly doses of exenatide with placebo. The incidence of major adverse cardiovascular outcomes was 9% lower in the exenatide group than in the placebo group, but the difference was not statistically significant ($P = .06$).¹⁹ A post hoc analysis of the EXSCEL trial showed that use of SGLT-2 drugs in the placebo group led to a lower incidence of all-cause mortality, which consequently confounded the effect of exenatide in the treatment group.²⁰

The PIONEER 6 trial (Oral Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes)²¹ found that the incidence of major adverse cardiovascular events was 21% lower with oral semaglutide than with placebo, but the difference was not statistically significant ($P = .17$).

A meta-analysis found that SGLT-2 inhibitors protected the kidney better than GLP-1 receptor agonists

■ PROTECTING THE KIDNEYS

The mechanisms underlying the renal protective effects of GLP-1 receptor agonists are not completely understood. What is known is that these drugs lower hemoglobin A1c, weight, and blood pressure, thereby modifying traditional risk factors for progression of chronic kidney disease and diabetic nephropathy.^{22,23} Moreover, GLP-1 receptors can be found in the renal proximal convoluted tubular cells and preglomerular vascular smooth muscle cells in the kidneys, and direct stimulation of these receptors inhibits the sodium-hydrogen exchanger 3 at the brush border of the proximal convoluted tubular cells. This leads to increased natriuresis and consequently reduced blood pressure.

The AWARD-7 trial²⁴ was an open-label multicenter trial that randomized 577 patients with stage 3 and 4 chronic kidney disease and type 2 diabetes to receive dulaglutide 0.75 mg once a week, dulaglutide 1.5 mg once a week, or daily insulin glargine, in combination with insulin lispro for 1 year. The estimated glomerular filtration rate declined more slowly in the 2 dulaglutide groups than in the insulin group, but the

urine albumin-creatinine ratio did not differ between the 3 groups.

Post hoc analysis of some of the large cardiovascular outcome trials of GLP-1 receptor agonists confirmed the renal protective effects:

The LEADER trial,²⁵ in further analysis, showed a relative risk reduction in nephropathic events of 22% (NNT 25) in the liraglutide group compared with placebo. This difference was mainly due to a statistically significant relative risk reduction in new-onset persistent macroalbuminuria of 26% (NNT 32).

The REWIND trial,²⁶ in an exploratory analysis, similarly showed that patients receiving dulaglutide had a relative risk reduction of 15% (NNT 167) in the composite renal outcome and 23% in new macroalbuminuria compared with placebo.

Zelniker et al²⁷ performed a meta-analysis and found that SGLT-2 inhibitors protected the kidney better than GLP-1 receptor agonists did. The relative risk reduction in the composite kidney outcome (new-onset macroalbuminuria, sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal causes) was 18% with GLP-1 receptor agonists compared with 38% with SGLT-2 inhibitors ($P < .001$). This benefit was mainly driven by a reduction in macroalbuminuria. GLP-1 receptor agonists did not demonstrate the same renal benefits of SGLT-2 inhibitors with regard to reducing the risks of worsening estimated glomerular filtration rate, end-stage renal disease, and renal death.²⁷

■ EFFECT ON WEIGHT

In studies in rats, stimulation of GLP-1 receptors in the hypothalamus by GLP-1 receptor agonists prevented meal initiation and induced meal termination.^{28,29} Evidence of reduced energy intake, suppressed appetite, and reduced food-craving was also noted in human studies, and patients receiving GLP-1 receptor agonists have had modulated taste preference, with lower preference for fatty and energy-dense food, and less pleasure in eating.³⁰⁻³² These hypothalamic effects are thought to vary among patients treated with GLP-1 receptor agonists.

Clinical trials of GLP-1 agonist for weight loss

Numerous observational and interventional studies of the glycemic effects of GLP-1 receptor agonists in patients with type 2 diabetes have noted that patients receiving these drugs lose weight. Subsequently, several studies evaluated their weight-loss effect in patients without diabetes:

The SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals) Obesity and Prediabetes trial³³ confirmed the efficacy of high-dose liraglutide (3 mg) in combination with lifestyle modifications for weight reduction over 56 weeks.

Frias et al³⁴ found that patients lost more weight with higher doses of dulaglutide, ie, 3 mg and 4.5 mg, than with 1.5 mg.

The STEP 1 trial (Semaglutide Treatment Effect in People With Obesity)³⁵ showed that semaglutide in a high weekly dose (2.4 mg) in addition to lifestyle intervention yielded a statistically significant weight reduction of 14.9% from baseline, compared with 2.4% with placebo.

O'Neil et al³⁶ compared the effects of semaglutide in various doses, liraglutide 3 mg daily, and placebo on weight loss in a head-to-head trial. Patients lost more weight with the active agents than with placebo and lost significantly more weight with semaglutide 0.2 mg or more than with liraglutide 3 mg.

Semaglutide is approved for weight loss in patients without diabetes

High-dose semaglutide is the most effective of the available weight-loss drugs thus far. Of all these drugs, only semaglutide 2.4 mg has been shown to cause a mean weight reduction of at least 10% compared with placebo. Moreover, the weight-reduction plateau noted with other antiobesity medications between 30 and 40 weeks was not seen in the STEP 1 trial.^{37–39}

In light of the results of the STEP 1 trial, a weekly subcutaneous dose of semaglutide of 2.4 mg, which is higher than the 1 mg weekly currently approved for diabetes, was recently approved by the FDA for chronic obesity management in patients without diabetes.

ADVERSE EFFECTS OF GLP-1 RECEPTOR AGONISTS

Gastrointestinal effects

Nausea, vomiting, and diarrhea are the most commonly reported adverse effects of GLP-1 receptor agonists. These effects are dose-dependent, often spontaneously resolve with continued treatment, and are more frequent with the short-acting agents than with the long-acting ones. Slow titration of these agents is helpful in increasing their gastrointestinal tolerability.⁴⁰

Pancreatitis

Acute pancreatitis has been linked to the use of exenatide in postmarketing reports submitted to the FDA Adverse Event Reporting System and in observational studies.⁴¹ But large randomized controlled trials did not

confirm this linkage. The LEADER and SUSTAIN-6 trials showed significantly higher levels of amylase and lipase in patients receiving liraglutide and semaglutide compared with placebo, but without a concomitant higher incidence of acute pancreatitis. Similarly, other cardiovascular outcome trials did not show any difference in the rates of acute pancreatitis between patients receiving GLP-1 receptor agonists vs placebo. Furthermore, 2 large meta-analyses revealed that the incidence of acute pancreatitis and pancreatic cancer with GLP-1 receptor agonists was not statistically different from that observed in the comparator groups.^{42,43}

The current guidelines of the American Association of Clinical Endocrinologists⁴⁴ recommend using GLP-1 receptor agonists with caution if they are needed in patients with type 2 diabetes who have a history of pancreatitis. GLP-1 receptor agonists should be discontinued if patients develop acute pancreatitis while using them.

Retinopathy

Retinopathy has been reported to occur at higher rates in patients treated with semaglutide, liraglutide, dulaglutide, and albiglutide, but this difference was statistically significant only for patients who received semaglutide.^{15,17,18} Most of these patients had retinopathy at baseline, and worsening of retinopathy was similarly reported when insulin was started. This suggests that retinopathy could be attributable to rapid glucose lowering rather than to a drug class effect.¹⁸

Hypoglycemia

Hypoglycemia has occurred at similar rates in patients receiving GLP-1 receptor agonists compared with placebo in the major cardiovascular outcome trials.⁴⁵

Medullary thyroid cancer, pancreatic cancer

Medullary thyroid cancer and pancreatic cancer have occurred in higher rates in studies of rats receiving GLP-1 receptor agonists, but not in human trials.^{46,47} Nevertheless, the FDA requires GLP-1 receptor agonists to carry a black-box warning regarding the risk of thyroid C-cell tumors, and it recommends against using them in patients with a personal or family history of medullary thyroid cell cancer or multiple endocrine neoplasia syndrome type 2a or 2b.⁴⁸

FUTURE DIRECTIONS

Reversing fatty liver disease

GLP-1 receptor agonists could, in theory, play a role in slowing and reversing the progression of nonalcoholic fatty liver disease (NAFLD).⁴⁹

In the Lira-NAFLD trial,⁵⁰ patients who received liraglutide 1.2 mg daily for 6 months experienced a reduction in liver fat content of 31% ($P < .0001$). Multivariate analysis showed that the reduction in liver fat was associated with baseline liver fat content, age, and reductions in body weight, triglycerides, and hemoglobin A1c. Patients who lost no weight had no reduction in liver fat content.

Newsome et al⁵¹ performed a phase 2 clinical trial that revealed significant resolution of nonalcoholic steatohepatitis (NASH) in 59% of patients treated with semaglutide 0.4 mg for 72 weeks compared with only 17% in patients who received placebo ($P < .001$). The trial found no difference in fibrosis between patients treated with semaglutide compared with placebo.

The current recommended management of NASH and NAFLD remains limited to lifestyle modification, vitamin E supplementation, and pioglitazone in selected patients.⁵² GLP-1 receptor agonists are expected to be recommended in the future for treating NAFLD and NASH, if more trials confirm their benefits in treating this condition.

Use in polycystic ovary syndrome

Studies in patients with polycystic ovary syndrome showed a significant drop in testosterone levels and body mass index in those receiving liraglutide or exenatide compared with placebo or metformin.^{53,54} Neither of the GLP-1 receptor agonists had effects on menstrual frequency or the levels of sex hormone-binding globulin, fasting glucose, or fasting insulin. Further studies are still needed to evaluate the benefits of GLP-1 receptor agonists in patients with polycystic ovary syndrome.

Use in type 1 diabetes

The ADJUNCT ONE trial (Efficacy and Safety of Liraglutide as Adjunct Therapy to Insulin in the Treatment of Type 1 Diabetes),⁵⁵ the ADJUNCT TWO trial,⁵⁶ and a large meta-analysis⁵⁷ found reductions in hemoglobin A1c, body weight, and total daily dose of insulin, but also highlighted an increase in hyperglycemia with ketosis in patients with type 1 diabetes mellitus receiving liraglutide or exenatide in combination with insulin. This might have been due to insulin dose reductions when liraglutide was initiated. No significant changes in C-peptide were reported in these studies.^{55–57}

Currently, GLP-1 receptor agonists are neither recommended nor FDA-approved for use in type 1 diabetes.^{7,44} However, in our opinion, adding them off-label to insulin in patients with type 1 diabetes can help the patients lose weight and stabilize their blood sugar levels.

Use in combination with glucose-dependent insulinotropic polypeptide

Evidence is emerging on the benefit of adding glucose-dependent insulinotropic polypeptide (GIP) to boost and complement the efficacy of GLP-1 receptor agonists in multiple ways. GIP has a glucose-dependent effect, stimulating insulin secretion when blood glucose levels are high and increasing glucagon secretion when they are low, hence improving glycemic control without increasing hypoglycemia.

Tirzepatide is an injectable combination GIP and GLP-1 receptor agonist that is currently being investigated as a treatment for type 2 diabetes mellitus. Studies have shown greater reductions in hemoglobin A1c and weight in patients receiving tirzepatide compared with placebo or weekly subcutaneous semaglutide 1 mg.⁵⁸ The FDA approved tirzepatide for use in treating type 2 diabetes mellitus on May 13, 2022.⁵⁹

REVIEW OF THE GUIDELINES

According to the ADA 2022,⁷ for patients with type 2 diabetes who also have established or a high risk of atherosclerotic cardiovascular disease, established kidney disease, or heart failure, an SGLT-2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular benefit with or without metformin is recommended. For patients with heart failure or chronic kidney disease, initiating an SGLT-2 inhibitor first is preferred. Of note, this recommendation is independent of baseline hemoglobin A1c level or individualized A1c target and needs to take into account efficacy, hypoglycemia risk, impact on weight, high cost, risk of side effects, and patient preferences.

The ADA guidelines also suggest prioritizing adding a GLP-1 receptor agonist over initiating basal insulin in patients who need potent injectable therapy for glucose control. However, basal insulin remains the first injectable treatment option in patients with evidence of ongoing catabolism or symptomatic hyperglycemia when hemoglobin A1c is higher than 10%, blood glucose levels are 300 mg/dL or higher, or type 1 diabetes is suspected.

Similarly, the 2020 guidelines of the American Association of Clinical Endocrinologists⁴⁴ recommend long-acting GLP-1 receptor agonists or SGLT-2 inhibitors in patients with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease with or without chronic kidney disease, regardless of glycemic control.

THE BOTTOM LINE

GLP-1 receptor agonists are recommended as either first-line or second-line therapy regardless of baseline hemoglobin A1c in patients who have established atherosclerotic cardiovascular disease, high risk of atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure. Some agents are also approved

for weight management in patients with a body mass index of 27 kg/m² or higher with weight-related comorbidities or a body mass index of 30 kg/m² or higher. ■

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing type 2 diabetes. *Cleve Clin J Med* 2021; 99(1):47–58. doi:10.3949/ccjm.88a.20088. Published correction appears in *Cleve Clin J Med* 2021; 88(4):205.
2. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol* 2016; 4(6):525–536. doi:10.1016/S2213-8587(15)00482-9
3. Nauck MA, Klein M, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1993; 36(8):741–744. doi:10.1007/BF00401145
4. Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci* 1993; 38(4):665–673. doi:10.1007/BF01316798
5. Huthmacher JA, Meier JJ, Nauck MA. Efficacy and safety of short- and long-acting glucagon-like peptide 1 receptor agonists on a background of basal insulin in type 2 diabetes: a meta-analysis. *Diabetes Care* 2020; 43(9):2303–2312. doi:10.2337/dc20-0498
6. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes Metab* 2017; 19(2):216–227. doi:10.1111/dom.12804
7. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, Bakris G, et al. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2022. *Diabetes Care* 2022; 45(suppl 1):S125–S143. doi:10.2337/dc22-5009
8. Ku HC, Chen WP, Su MJ. DPP4 deficiency exerts protective effect against H2O2 induced oxidative stress in isolated cardiomyocytes. *PLoS One* 2013; 8(1):e54518. doi:10.1371/journal.pone.0054518
9. Barale C, Buracco S, Cavalot F, Frascaroli C, Guerrasio A, Russo I. Glucagon-like peptide 1-related peptides increase nitric oxide effects to reduce platelet activation. *Thromb Haemost* 2017; 117(6):1115–1128. doi:10.1160/TH16-07-0586
10. Arakawa M, Mita T, Azuma K, et al. Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. *Diabetes* 2010; 59(4):1030–1037. doi:10.2337/db09-1694
11. Ding L, Zhang J. Glucagon-like peptide-1 activates endothelial nitric oxide synthase in human umbilical vein endothelial cells. *Acta Pharmacol Sin* 2012; 33(1):75–81. doi:10.1038/aps.2011.149
12. Tang ST, Tang HQ, Su H, et al. Glucagon-like peptide-1 attenuates endothelial barrier injury in diabetes via cAMP/PKA mediated down-regulation of MLC phosphorylation. *Biomed Pharmacother* 2019; 113:108667. doi:10.1016/j.biopha.2019.108667
13. Rakipovski G, Rolin B, Nöhr J, et al. The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE^{-/-} and LDLr^{-/-} mice by a mechanism that includes inflammatory pathways. *JACC Basic Transl Sci* 2018; 3(6):844–857. doi:10.1016/j.jacbs.2018.09.004
14. Burgmaier M, Liberman A, Möllmann J, et al. Glucagon-like peptide-1 (GLP-1) and its split products GLP-1(9-37) and GLP-1(28-37) stabilize atherosclerotic lesions in ApoE^{-/-} mice. *Atherosclerosis* 2013; 231(2):427–435. doi:10.1016/j.atherosclerosis.2013.08.033
15. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; 394(10193):121–130. doi:10.1016/S0140-6736(19)31149-3
16. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; 375(19):1834–1844. doi:10.1056/NEJMoa1607141
17. 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. doi:10.1056/NEJMoa1603827
18. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015; 373(23):2247–2257. doi:10.1056/NEJMoa1509225
19. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017; 377(13):1228–1239. doi:10.1056/NEJMoa1612917
20. Clegg LE, Heerspink HJL, Penland RC, et al. Reduction of cardiovascular risk and improved estimated glomerular filtration rate by SGLT2 inhibitors, including dapagliflozin, is consistent across the class: an analysis of the placebo arm of EXSCEL. *Diabetes Care* 2019; 42(2):318–326. doi:10.2337/dc18-1871
21. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019; 381(9):841–851. doi:10.1056/NEJMoa1901118
22. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358(24):2560–2572. doi:10.1056/NEJMoa0802987
23. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015; 313(6):603–615. doi:10.1001/jama.2014.18574
24. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; 6(8):605–617. doi:10.1016/S2213-8587(18)30104-9
25. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017; 377(9):839–848. doi:10.1056/NEJMoa1616011
26. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019; 394(10193):131–138. doi:10.1016/S0140-6736(19)31150-X
27. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation* 2019; 139(17):2022–2031. doi:10.1161/CIRCULATIONAHA.118.038868
28. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest* 2014; 124(10):4473–4488. doi:10.1172/JCI75276
29. Gabery S, Salinas CG, Paulsen SJ, et al. Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight* 2020; 5(6):e133429. doi:10.1172/jci.insight.133429
30. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly

- semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes Obes Metab* 2017; 19(9):1242–1251. doi:10.1111/dom.12932
31. Kadoh H, Chedid V, Halawi H, et al. GLP-1 analog modulates appetite, taste preference, gut hormones, and regional body fat stores in adults with obesity. *J Clin Endocrinol Metab* 2020; 105(5):1552–1563. doi:10.1210/clinem/dgz140
32. Schlögl H, Kabisch S, Horstmann A, et al. Exenatide-induced reduction in energy intake is associated with increase in hypothalamic connectivity. *Diabetes Care* 2013; 36(7):1933–1940. doi:10.2337/dc12-1925
33. 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. doi:10.1056/NEJMoa1411892
34. Frias JP, Wynne AG, Matyjaszek-Matuszek B, et al. Efficacy and safety of an expanded dulaglutide dose range: a phase 2, placebo-controlled trial in patients with type 2 diabetes using metformin. *Diabetes Obes Metab* 2019; 21(9):2048–2057. doi:10.1111/dom.13764
35. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021; 384(11):989. doi:10.1056/NEJMoa2032183
36. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018; 392(10148):637–649. doi:10.1016/S0140-6736(18)31773-2
37. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012;95(2):297–308. doi:10.3945/ajcn.111.024927
38. Garvey WT, Birkenfeld AL, Dicker D, et al. Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial. *Diabetes Care* 2020; 43(5):1085–1093. doi:10.2337/dc19-1745
39. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013; 21(5):935–943. doi:10.1002/oby.20309
40. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metab* 2017; 19(3):336–347. doi:10.1111/dom.12824
41. US Food and Drug Administration. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm>. Accessed July 12, 2022.
42. Monami M, Nreu B, Scatena A, et al. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): data from randomized controlled trials. *Diabetes Obes Metab* 2017; 19(9):1233–1241. doi:10.1111/dom.12926
43. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Glucagon-like peptide-1 receptor agonists and pancreatitis: a meta-analysis of randomized clinical trials. *Diabetes Res Clin Pract* 2014; 103(2):269–275. doi:10.1016/j.diabres.2014.01.010
44. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2020 executive summary. *Endocr Pract* 2020; 26(1):107–139. doi:10.4158/CS-2019-0472
45. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; 7(10):776–785. doi:10.1016/S2213-8587(19)30249-9
46. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 2010; 151(4):1473–1486. doi:10.1210/en.2009-1272
47. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* 2013; 62(7):2595–2604. doi:10.2337/db12-1686
48. US Food and Drug Administration. Questions and answers—safety requirements for Victoza (liraglutide). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm198543.htm>. Accessed July 12, 2022.
49. Liu J, Wang G, Jia Y, Xu Y. GLP-1 receptor agonists: effects on the progression of non-alcoholic fatty liver disease. *Diabetes Metab Res Rev* 2015; 31(4):329–335. doi:10.1002/dmrr.2580
50. Petit JM, Cercueil JP, Loffroy R, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes: the Lira-NAFLD study. *J Clin Endocrinol Metab* 2017; 102(2):407–415. doi:10.1210/jc.2016-2775
51. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021; 384(12):1113–1124. doi:10.1056/NEJMoa2028395
52. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; 67(1):328–357. doi:10.1002/hep.29367
53. Niafar M, Pourafkari L, Porhomayon J, Nader N. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. *Arch Gynecol Obstet* 2016; 293(3):509–515. doi:10.1007/s00404-015-3976-7
54. Han Y, Li Y, He B. GLP-1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis. *Reprod Biomed Online* 2019; 39(2):332–342. doi:10.1016/j.rbmo.2019.04.017
55. Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE Treat-To-Target randomized trial. *Diabetes Care* 2016; 39(10):1702–1710. doi:10.2337/dc16-0691
56. Ahrén B, Hirsch IB, Pieber TR, et al. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. *Diabetes Care* 2016; 39(10):1693–1701. doi:10.2337/dc16-0690
57. Wang W, Liu H, Xiao S, Liu S, Li X, Yu P. Effects of insulin plus glucagon-like peptide-1 receptor agonists (GLP-1RAs) in treating type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Ther* 2017; 8(4):727–738. doi:10.1007/s13300-017-0282-3
58. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021; 385(6):503–515. doi:10.1056/NEJMoa2107519
59. US Food and Drug Administration. FDA news release. FDA approves novel, dual-targeted treatment for type 2 diabetes. May 13, 2022. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes>. Accessed July 12, 2022.

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The role of GLP-1 receptor agonists in managing type 2 diabetes

In the August 2022 issue, an error appeared in Nachawi N, Rao PP, Makin V. *The role of GLP-1 receptor agonists in managing type 2 diabetes*. *Cleve Clin J Med* 2022; 89(8):457–464. doi:10.3949/ccjm.89a.21110. In **Table 1**, the frequency of administration of tirzepatide is once weekly, not once daily. Additional available tirzepatide doses have also been added. The corrected **Table 1** appears below:

TABLE 1
Glucagon-like peptide-1 receptor agonists approved for use in the United States

Drug	Available doses	Frequency and route	Dose approved for weight management
Exenatide	5 µg, 10 µg	Twice daily subcutaneously	Not approved
Liraglutide	0.6 mg, 1.2 mg, 1.8 mg	Once daily subcutaneously	0.6 mg once daily for 1 week, increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily
Exenatide extended-release	2 mg	Once weekly subcutaneously	Not approved
Dulaglutide	0.75 mg, 1.5 mg, 3 mg, 4.5 mg	Once weekly subcutaneously	Not approved
Semaglutide	0.25 mg, 0.5 mg, 1 mg, 2 mg	Once weekly	Titrate every 4 weeks: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg once weekly
Semaglutide, oral	3 mg, 7 mg, 14 mg	Once daily by mouth	Not approved
Liraglutide-insulin degludec	0.36 mg-10 U 0.5 mg-16 U	Once daily subcutaneously	Not approved
Lixisenatide-insulin glargine	5 µg-15 U 10 µg-30 U	Once daily subcutaneously	Not approved
Tirzepatide	2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Once weekly subcutaneously	Not approved

This is now correct on ccjm.org.