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Review

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Pulse of Progress: A Systematic Review of Glucagon-Like Peptide-1 Receptor Agonists in Cardiovascular Health

Michael Sabina[a, b], M. Mrhaf Alsamman[a]

Abstract

According to the World Health Organization (WHO), the prevalence of type 2 diabetes mellitus (T2DM) and obesity has increased globally over the past 50 years, affecting over 500 million adults worldwide in 2023. A novel class of drugs known as glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as a beacon of hope in treating the pandemic of diabetes and obesity. This analysis' objective was to draw comparisons of how these medications reduce cardiovascular outcomes. The review revealed unique differences in GLP-1s, highlighting some of their strengths and weaknesses and which populations they can cater to preferentially. Even though all drugs in question of this review are proven to be efficacious for diabetes and obesity, differences in their cardiovascular safety profiles and efficacy were noted. The analysis recognized the potential of drugs like semaglutide and tirzepatide, as leaders in the space. Although this current assessment of where GLP-1 receptor agonists stand in regard to cardiovascular outcomes may still be premature, the space is extremely active, and there are trials that are highly anticipated to transform the landscape of diabetes and obesity management in patients with more established cardiovascular comorbidities in the near future.

Keywords: Cardiovascular; Diabetes; Obesity; GLP-1 agonist

Introduction

According to the World Health Organization (WHO), the prevalence of type 2 diabetes mellitus (T2DM) and obesity has increased globally over the past 50 years, affecting over 500 million adults worldwide in 2023. This population has an increased risk of adverse cardiac events and stroke [1, 2]. While both T2DM and obesity are being considered by many experts around the globe as a "pandemic", there has been a recent upsurge of relentless research to find effective treatments. In the midst of all this new research, a new class of drugs amongst others, known as glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as a beacon of hope. Their unique method of action affects glucose control via several different mechanisms. They promote delayed gastric emptying, they increase insulin secretion while inhibiting glucagon release, but only when glucose levels are elevated via the incretin effect, thus reducing the likelihood of hypoglycemia [3]. These agents are proven to provide glycemic and weight loss benefits which in theory, present as potential cardiovascular benefits. This review attempts to critically analyze the most up-to-date evidence from trials and offer a detailed analysis in how they rank amongst each other in terms of cardiovascular safety and efficacy. The GLP-1 receptor agonists in question are lixisenatide, exenatide, albiglutide, efpeglenatide, semaglutide, liraglutide, dulaglutide, and the novel tirzepatide (dual GLP-1 and GIP agonist). It will attempt to dissect each drug's unique aspects, strengths and weaknesses, and offer recommendations on what needs to be done in the future to solidify their role in the cardiovascular space. Lastly, it will discuss the emerging trends and future directions in this rapidly evolving field.

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[a]Internal Medicine Program, GME, Lakeland Regional Health Medical Center, Lakeland, FL 33805, USA
[b]Corresponding Author: Michael Sabina, Internal Medicine Program, GME, Lakeland Regional Health Medical Center, Lakeland, FL 33805, USA.
Email: Michael.Sabina@mylrh.org

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Current state of GLP-1s in the management of diabetes and weight management

Prior studies have already compared the efficacy of these drugs in head-to-head trials in regard to A1c lowering and weight loss management [4]. The LEAD-6 trial showed that long-acting liraglutide had significantly greater improvements in glycemic control when compared to short-acting exenatide [5]. The DURATION-6 trial showed that liraglutide daily was also superior to exenatide weekly in A1c lowering [6]. In the GETGOAL-X trial, lixisenatide once daily demonstrated noninferior improvements in glycosylated hemoglobin A1c (HbA1c) compared with exenatide twice daily [7]. Another trial by Nauck et al showed liraglutide was more effective than lixisenatide as an add-on to metformin in improving glycemic control. Body weight reductions and gastrointestinal (GI) adverse event profiles were similar [8]. The AWARD-1 and AWARD-6 trial demonstrated dulaglutide had superior glycemic control versus exenatide but was noninferior to liraglutide [9, 10]. In the SUSTAIN-3 trial, semaglutide was superior to exenatide in improving glycemic control and reducing body weight after 56 weeks of treatment; the drugs had comparable safety profiles [11]. The SUSTAIN-7 trial showed at low

and high doses, semaglutide was superior to dulaglutide in improving glycemic control and reducing body weight [12]. In the SUSTAIN-10 trial, semaglutide was superior to liraglutide in reducing HbA1c and body weight. There were higher rates of GI adverse effects with semaglutide vs. liraglutide [13]. In PIONEER-4 trial, oral semaglutide was noninferior to subcutaneous liraglutide in decreasing HbA1c but was superior in decreasing bodyweight compared with liraglutide. Safety and tolerability of oral semaglutide were similar to subcutaneous liraglutide [14]. The PIONEER-10 trial showed once-daily oral semaglutide significantly reduced HbA1c and bodyweight versus weekly subcutaneous dulaglutide in Japanese patients with type 2 diabetes [15]. In the HARMONY-7 trial, patients who received once-daily liraglutide had greater reductions in HbA1c than did those who received once-weekly albiglutide, however, weight loss was not assessed [16]. In an exploratory analysis comparing double-blind treatment with efpeglenatide with open-label liraglutide as a reference found that efpeglenatide 4-mg dose was noninferior to open-label liraglutide treatment in reducing HbA1c levels, and body weight reductions with efpeglenatide 3 mg or 4 mg were comparable to those seen with liraglutide 1.8 mg [17]. The SURPASS-2 trial showed tirzepatide at the same three weekly doses (5, 10, and 15 mg) was superior against weekly injections of semaglutide 1.0 mg at all doses for A1c lowering and weight loss [18]. Tirzepatide was superior compared with dulaglutide for glycemic control and reduction in bodyweight, in the SURPASS J-MONO [19] trial (Table 1) [5-19].

A previous study done by Trujillo et al provided a detailed meta-analysis of GLP-1 receptor agonists and ranked them in A1c lowering, weight loss efficacy, and GI side effects when comparing head-to-head trial data [4]. Three drugs, albiglutide, efpeglenatide, and tirzepatide were not mentioned in the rankings. We updated the table to account for these three drugs (Table 2).

When comparing A1c lowering efficacy, these agents could be ranked (from highest to lowest) in the following order: tirzepatide > semaglutide (subcutaneous) = semaglutide (oral) > dulaglutide = liraglutide = efpeglenatide > exenatide extended release (ER) > exenatide (twice daily) = lixisenatide = albiglutide.

When comparing weight loss, these agents could be ranked (from most to least) in the following order: tirzepatide > semaglutide (subcutaneous) = semaglutide (oral) > liraglutide = efpeglenatide > dulaglutide > exenatide ER = exenatide (twice daily) = lixisenatide.

In regard to the treatment of type 2 diabetes and obesity, tirzepatide has the strongest evidence for being a leader in the GLP-1 community. This review attempts to further expand on GLP-1s and their current standings when taking into consideration cardiovascular outcomes.

Study Analysis

Lixisenatide

The ELIXA trial (2015)

This study assessed the cardiovascular effects of lixisenatide in 6,068 patients with type 2 diabetes who had experienced a myocardial infarction (MI) or had been hospitalized for unstable angina within the previous 180 days and were assigned to receive either lixisenatide or a placebo, in addition to the standard care. The primary composite endpoint included cardiovascular death, MI, stroke, or hospitalization for unstable angina. The results showed that a primary endpoint event occurred in 13.4% of the patients in the lixisenatide group compared to 13.2% in the placebo group. Importantly, lixisenatide was not associated with a higher rate of serious adverse events, severe hypoglycemia, pancreatitis, pancreatic neoplasms, or allergic reactions compared to the placebo. In conclusion, lixisenatide did not demonstrate superiority over a placebo in reducing cardiovascular events; however, it was deemed safe for patients with acute coronary events within the previous 180 days. In conclusion, the results support that lixisenatide is safe for cardiovascular disease but does not show clear cardiovascular benefits [20].

Exenatide

The EXSCEL trial (2017)

The study's primary focus was to assess whether adding once-weekly exenatide ER treatment to standard care in patients with T2DM was noninferior or superior to placebo in cardiovascular safety. This trial involved 14,752 patients, of whom 73.1% had previous cardiovascular disease, randomized to receive 2 mg of ER-exenatide or placebo once weekly. The primary outcome of the EXSCEL trial was defined as the first occurrence of any component of a composite outcome, which included death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The results showed that 11.4% in the exenatide group experienced a primary composite outcome event, compared to 12.2% in the placebo group ($P < 0.001$ for noninferiority and $P = 0.06$ for superiority). Notably, there were no significant differences between the two groups in terms of death from cardiovascular causes, fatal or nonfatal MI, fatal or nonfatal stroke, hospitalization for heart failure, hospitalization for acute coronary syndrome, incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events. The trial's findings suggest that exenatide can be a safe addition to the therapeutic regimen for these patients without increasing their cardiovascular risk. However, the study also puts in question the efficacy in improving cardiovascular outcomes [21].

Albiglutide

HARMONY trial (2018)

This trial aimed to determine the safety and efficacy of albiglutide in preventing cardiovascular death, MI, or stroke in a population with established cardiovascular disease. A total of 9,463 participants were randomly assigned to receive either a

Table 1. Summary of Head-to-Head Trials Comparing GLP-1 Agonists in A1c Lowering, Weight Reduction, and GI Side Effects

Trial	Drugs compared	Results of A1c lowering	Results of weight reduction	Results of GI side effects: nausea/vomiting/diarrhea
LEAD-6 [5]	Liraglutide (1.8 mg SC daily)	1.12%	3.24 kg	25.5%/6.0%/12.3%
	Exenatide (10 µg SC twice daily)	0.79%	2.87 kg	28%/9.9%/12.1%
DURATION-6 [6]	Liraglutide (1.8 mg SC daily)	1.48%	3.57 kg	20.7%/10.7%/13.1%
	Exenatide ER (2.0 mg SC weekly)	1.28%	2.68 kg	9.3%/3.7%/6.1%
GETGOAL-X [7]	Lixisenatide (20 µg SC daily)	0.79%	2.96 kg	24.5%/10.1%/10.4%
	Exenatide ER (2.0 mg SC weekly)	0.96%	3.98 kg	35.1%/13.3%/13.3%
Trial by Nauck et al [8]	Liraglutide (1.8 mg SC daily)	1.8%	4.3 kg	21.8%/6.9%/12.4%
	Lixisenatide (20 µg SC daily)	1.20%	3.7 kg	21.8%/8.9%/9.9%
AWARD-1 [9]	Dulaglutide (1.5 mg SC weekly)	1.51%	1.3 kg	28%/16.8%/11.1%
	Dulaglutide (0.75 mg SC weekly)	1.30%	Gained 0.2 kg	16.1%/6.1%/7.9%
	Exenatide (10 µg SC twice daily)	0.99%	1.07 kg	25.7%/10.9%/5.8%
AWARD-6 [10]	Dulaglutide (1.5 mg SC weekly)	1.42%	2.9 kg	20.4%/7.0%/12.0%
	Liraglutide (1.8 mg SC daily)	1.36%	3.61 kg	18.0%/8.3%/12.0%
SUSTAIN-3 [11]	Semaglutide (1.0 mg SC weekly)	1.5%	5.6 kg	22.3%/7.2%/11.4%
	Exenatide ER (2.0 mg SC weekly)	0.90%	1.9 kg	11.9%/6.2%/8.4%
SUSTAIN-7 [12]	Semaglutide (0.5 mg SC weekly)	1.5%	4.6 kg	23%/10%/14%
	Semaglutide 1.0 mg SC weekly	1.8%	6.5 kg	21%/19%/14%
	Dulaglutide (0.75 mg SC weekly)	1.1%	2.3 kg	13%/4%/8%
	Dulaglutide (1.0 mg SC weekly)	1.4%	3.0 kg	20%/10%/18%
SUSTAIN-10 [13]	Semaglutide (1.0 mg SC weekly)	1.7%	5.8 kg	21.8%/10.4%/15.6%
	Liraglutide (1.2 mg SC daily)	1.0%	1.9 kg	15.7%/8%/12.2%
PIONEER-4 [14]	Semaglutide (14 mg oral daily)	1.2%	1.5 kg	20%/9%/15%
	Liraglutide (1.8 mg SC daily)	1.1%	0.9 kg	18%/5%/11%
PIONEER-10 [15]	Semaglutide (3 mg oral daily)	0.9%	0 kg	5%/2%/2%
	Semaglutide (7 mg oral daily)	1.4%	0.9 kg	8%/1%/2%
	Semaglutide (14 mg oral daily)	1.7%	1.6 kg	9%/7%/8%
	Dulaglutide (0.75 mg SC weekly)	1.4%	1.0 kg	9%/2%/6%
HARMONY-7 [16]	Albiglutide (30 - 50 mg SC weekly)	0.78%	N/A	Total: 35.9%
	Liraglutide (0.6 - 1.0 mg SC daily)	0.99%	N/A	Total: 49%
Rosenstock et al [17]	Efpeglenatide (0.3, 1.0, 2.0, 3.0, or 4.0 mg SC weekly)	0.56%, 0.95%, 1.19%, 1.41%, 1.61%	1.21 kg	11%/0/14%
			2.01 kg	8%/3%/3%
			1.52 kg	27%/12%/9%
			2.73 kg	22%/11%/11%
			3.31 kg	33%/22%/5%
	Liraglutide (1.8 mg SC daily)	1.38%	3.21 kg	33%/11%/14%
SURPASS-2 [18]	Tirzepatide (5 mg SC weekly)	2.01%	7.96 kg	17.4%/13.2%/5.7%
	Tirzepatide (10 mg SC weekly)	2.24%	9.3 kg	19.2%/16.4%/8.5%
	Tirzepatide (15 mg SC weekly)	2.30%	11.2 kg	22.1%/13.8%/9.8%
	Semaglutide (1 mg SC weekly)	1.86%	5.7 kg	17.9%/11.5%/8.3%
SURPASS J-MONO [19]	Tirzepatide (5 mg SC weekly)	2.4%	5.8 kg	12%
	Tirzepatide (10 mg SC weekly)	2.6%	8.5 kg	20%
	Tirzepatide (15 mg SC weekly)	2.8%	10.7 kg	20%
	Dulaglutide (0.75 mg SC weekly)	1.3%	0.5 kg	8%

GLP-1: glucagon-like peptide-1; SC: subcutaneous; ER: extended release; GI: gastrointestinal.

Table 2. Updated Ranking and Side Effects of GLP-1 Receptor Agonists When Comparing A1c Lowering and Weight Reduction

Drug (dose)	Within class comparability of A1c lowering efficacy	Within class comparability of effect on weight	Within class comparability of side effects
Albiglutide (30 - 50 mg SC weekly)	Lowest	N/A	Low
Exenatide (10 µg SC twice daily)	Lowest	Lowest	Highest
Lixisenatide (20 µg SC daily)	Lowest	Lowest	Intermediate
Exenatide ER (2.0 mg SC weekly)	Low	Lowest	Low
Dulaglutide (0.75 mg and 1.5 mg SC weekly)	Intermediate	Low	Intermediate/high
Liraglutide (1.8 mg SC daily)	Intermediate	Intermediate	Intermediate
Efpeglenatide (0.3, 1.0, 2.0, 3.0, or 4.0 mg SC weekly)	Intermediate	Intermediate	High
Semaglutide (0.5 mg and 1.0 mg SC weekly)	High	High	High
Semaglutide (7 mg and 14 mg oral daily)	High	High	Intermediate/high
Tirzepatide (5 mg, 10 mg, 15 mg SC weekly)	Highest	Highest	High

GLP-1: glucagon-like peptide-1; GI: gastrointestinal.SC: subcutaneous; ER: extended release; N/A: not available.

subcutaneous injection of albiglutide (30 - 50 mg, adjusted based on glycemic response and tolerability) or a matched dose of placebo once a week, alongside their standard care. In the albiglutide group, the primary composite outcome occurred in 7% compared to 9% in the placebo group, indicating both noninferiority and superiority of albiglutide ($P < 0.0001$ and $P = 0.0006$, respectively). Notably, the incidence of other serious adverse events, including acute pancreatitis, pancreatic cancer, and medullary thyroid carcinoma, did not significantly differ between the two groups. However, there were moderate glycemic differences between groups, limiting the assessment of cardiovascular effects independent of glucose-lowering [22]. Nonetheless, the data are strongly in favor of albiglutide and its ability to reduce cardiovascular outcomes.

Efpeglenatide

The AMPLITUDE-O trial (2021)

This study focused on the cardiovascular and renal effects of efpeglenatide in patients with type 2 diabetes who were also at high risk for adverse cardiovascular events. Participants either had a history of cardiovascular disease or current kidney disease, defined as an estimated glomerular filtration rate (eGFR) of 25.0 to 59.9 mL/min/1.73 m^2 of body-surface area, plus at least one other cardiovascular risk factor. A total of 4,076 patients were randomized; 1,359 participants were assigned to receive the 4-mg dose of efpeglenatide, 1,358 to receive the 6-mg dose of efpeglenatide, and 1,359 to receive placebo. The primary outcome of the study was the occurrence of major adverse cardiovascular events (MACEs), which included nonfatal MI, nonfatal stroke, or death from cardiovascular or undetermined causes. The key secondary outcomes included an expanded MACE composite outcome (incorporating coronary revascularization or hospitalization for unstable angina) and a composite renal outcome (encompassing incident macroalbuminuria, a significant increase in the urinary albumin-to-creatinine ratio, a sustained decrease in the eGFR of $\geq 40\%$ for ≥ 30 days, renal-replacement therapy for ≥ 90 days, or a sustained eGFR of < 15 mL/min/1.73 m^2 for ≥ 30 days). In the efpeglenatide group, an incident MACE occurred in 7.0% compared to 9.2% in the placebo group, showing noninferiority ($P < 0.001$) and superiority ($P = 0.007$) of efpeglenatide compared to placebo. Additionally, a composite renal outcome event occurred in 13.0% compared to 18.4% in the placebo group, indicating a significant renal benefit ($P < 0.001$). However, GI side effects like diarrhea, constipation, nausea, vomiting, or bloating were more frequently reported with efpeglenatide than with placebo ($P = 0.03$). However, there was no evidence of pancreatic, thyroid, or malignancy-related adverse effects. Efpeglenatide improves cardiovascular outcomes and provides renal benefits, critical considerations in managing patients with type 2 diabetes [23].

Dulaglutide

REWIND trial (2019)

The REWIND trial compared dulaglutide to placebo in patients with T2DM and increased cardiovascular risk with the aim to measure incidence of cardiovascular death, MI, and stroke. The results showed a significant reduction in the composite outcome for the dulaglutide group compared to the placebo group (12.0% vs. 13.4%). The subgroups in the composite had varying results, however. Specifically, cardiovascular death and nonfatal MI did not show significant differences. Only nonfatal strokes showed a significant reduction (2.7% vs. 3.5% $P = 0.017$). Notably, eye or kidney microvascular outcome showed a significant difference in the semaglutide group versus placebo (18.4% vs. 20.6%) ($P = 0.002$), concerning retinopathy as a side effect. On the other hand, dulaglutide demonstrated a moderate effect on macroalbuminuria (2.5% lower than placebo), a marker of kidney health. Dulaglutide is in a great position when comparing renal outcomes in GLP-1s, however, its efficacy in cardiovascular outcomes, although positive, does not appear to be as strong as other competitors [24].

Liraglutide

The LEADER trial (2016)

This trial was a significant double-blind study evaluating the cardiovascular effects of liraglutide in 9,340 patients with type 2 diabetes and a high risk of cardiovascular disease. The primary objective was to assess whether liraglutide was noninferior to placebo regarding major cardiovascular events, defined as death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The results demonstrated that liraglutide was noninferior and superior to placebo in reducing the incidence of the primary composite outcome. Specifically, 13.0% of patients in the liraglutide group experienced a primary outcome event compared to 14.9% in the placebo group. Furthermore, liraglutide was associated with lower rates of death from cardiovascular causes and death from any cause. However, the differences in rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure between the two groups were not statistically significant. Compared to placebo, there was also a reduction in systolic and diastolic blood pressure in the liraglutide group. Notably, there was a significant increased incidence rate of gallbladder disease, nausea, vomiting, diarrhea, and adverse events in the liraglutide group in comparison to placebo. In conclusion, the LEADER trial provided evidence of cardiovascular benefits of liraglutide in patients with type 2 diabetes and high cardiovascular risk, although not as strong as other competitors. Also, the increased risk of GI side effects is of concern [25].

Semaglutide

SUSTAIN-6 (2016)

The SUSTAIN-6 trial assessed semaglutide's cardiovascular safety in type 2 diabetes patients. It involved 3,297 participants with established cardiovascular disease or chronic kidney disease (CKD). Participants were randomized to receive weekly semaglutide (0.5 mg or 1 mg) or placebo alongside standard care for 104 weeks; the trial's primary composite outcome was the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke. The outcome occurred in 6.6% of the semaglutide group versus 8.9% of placebo ($P \leq 0.001$). Nonfatal MI was 2.9% in the semaglutide group and 3.9% in placebo ($P = 0.12$); nonfatal stroke was 1.6% versus 2.7%, respectively ($P = 0.04$). Nephropathy rates were lower in the semaglutide group (3.8% vs 6.1% in placebo). Semaglutide groups had more significant systolic blood pressure reduction (1.3 mm Hg in 0.5 mg group and 2.6 mm Hg in 1 mg group, $P < 0.001$) than placebo. On the downside, retinopathy complications were higher (3% vs. 1.8% in placebo, $P = 0.02$). GI side effects led to more treatment discontinuations; they occurred in 50.7% and 52.3% in the 0.5 mg and 1 mg semaglutide groups, respectively, compared to 35.7% and 35.2% in placebo. The main GI side effects were diarrhea, nausea, and vomiting. The pulse rate increase was higher in the semaglutide group, particularly 2.0 beats per minute (bpm) in the 1.0 mg group. Incidence of acute pancreatitis, gallbladder disorders, pancreatic cancer, and hypoglycemia episodes were comparable between groups. No medullary thyroid carcinomas were confirmed. In summary, the trial provided evidence for the cardiovascular safety of semaglutide in type 2 diabetes patients, although not as strong as other competitors, due to findings in nonfatal MI subgroup showing no significant difference. The higher rates of retinopathy complications and significant GI side effects in the semaglutide group highlighted potential safety concerns [26].

The PIONEER 6 trial (2019)

This trial compared oral semaglutide to placebo in patients with T2DM with the aim of assessing its cardiovascular safety by measuring MACEs, which include cardiovascular death, nonfatal MI, and nonfatal stroke. It enrolled 3,183 patients with established CKD or cardiovascular disease. The results showed there was a 21% reduction in major adverse cardiovascular outcomes in the oral semaglutide group in comparison to placebo. However, rates of nonfatal MI and stroke were similar between both groups. There was also a significant increase in GI side effects in the semaglutide group. In summary, this trial approves of oral semaglutide in use with patients with established cardiovascular disease or CKD; however, its efficacy may not be up to par as its competitors or subcutaneous formulas [27].

SELECT trial (2023)

The SELECT trial, assessing semaglutide once a week subcutaneously at 2.4 mg for 33 months in overweight or obese (body mass index (BMI) 27 or greater) patients without diabetes, randomized 17,604 participants (8,803 to semaglutide, 8,801 to placebo) to evaluate cardiovascular risk reduction. The primary endpoint (a composite of cardiovascular death, nonfatal MI, or stroke) occurred in 6.5% of the semaglutide group versus 8.0% of the placebo group over 39.8 months, demonstrating a 20% risk reduction with semaglutide. Additionally, semaglutide led to a 9.39% weight reduction compared to 0.88% in the placebo group over 104 weeks. Glycated hemoglobin level above 6.5% was seen in 3.5% of the semaglutide group and 12% in the placebo group. These findings are significant as they demonstrate the cardioprotective effects of semaglutide at higher doses. However, its renal protective effects highlighted in the SUSTAIN-6 trial were not apparent, as 1.8% in the semaglutide group reached the endpoint versus 2.2% in the placebo. Notably, GI disorders caused discontinuation in 9.39% of semaglutide participants versus 2.0% of placebo participants. It also showed a miniscule difference that was significant for gallbladder-related disorders, more present in the semaglutide group (2.8%) versus placebo (2.3%) ($P = 0.04$). The study also presents with its limitations. It has a narrow patient profile with a limited enrollment of women (27.7%) and black individuals (3.8%). Also, patients with already established atherosclerotic cardiovascular disease (AS-

CVD) were excluded from the study, which might be a more realistic generalizable population to consider [28]. In summary, this trial showed the increased semaglutide dose subcutaneously (2.4 mg) did improve efficacy in cardiovascular outcomes, glycemic control, and weight loss, however, at the price of renal benefit previously provided in the lower doses of the SUSTAIN-6 trial. Also, GI side effects were still present along with an increase in gallbladder-related disorders not previously seen.

STEP-HFPEF trial (2023)

This study was recently completed and contributes immensely to the potential use-case of GLP-1s in patients with heart failure and obesity. In this trial, 529 patients with heart failure with preserved ejection fraction (HFpEF) and a BMI of 30 or higher were randomized to receive either semaglutide 2.4 mg once weekly or a matching placebo. The results showed a mean change of 16.6 points in the clinical summary score (CSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is a scoring system that provides a measure of symptoms and physical limitations associated with heart failure, in favor of semaglutide compared to placebo. The 6-min walk distance change averaged 21.5 m with semaglutide versus only 1.2 m with placebo. Notably, unlike past trials that highlighted possible side effects of semaglutide, serious adverse events were lower in the semaglutide group (13.3%) compared to the placebo group (26.7%). This indicates that in this particular patient population, semaglutide appears to have an improved safety profile. In conclusion, the study demonstrates that semaglutide can have a considerable role in managing obese patients with HFpEF, providing considerable improvements in symptoms, exercise function, reducing physical limitations, and promoting significant weight loss [29].

SOUL trial (anticipated completion in 2025)

This trial is expected to be completed sometime in 2025 and aims to establish oral semaglutide's efficacy in reducing cardiovascular outcomes, specifically those with ASCVD and CKD. The primary endpoint focuses on the time to the first occurrence of MACEs, including cardiovascular death, nonfatal MI, or nonfatal stroke. Secondary outcomes encompass a range of cardiovascular and kidney-related events. The study also includes cognitive assessments, considering the potential links between GLP-1 receptor agonists and cognitive decline. This is a highly anticipated trial, which has the potential to solidify semaglutide amongst the top of GLP-1s [30].

Tirzepatide

SURPASS-CVOT trial (anticipated completion in 2024)

The SURPASS-CVOT trial is a significant research study evaluating the cardiovascular safety and efficacy of tirzepatide compared to dulaglutide in individuals with type 2 diabetes and established ASCVD. Participants were randomized to receive either tirzepatide or dulaglutide once weekly by subcutaneous injection in addition to their standard care. The trial's primary goal is to assess the effect of time on the first occurrence of MACEs, defined as cardiovascular death, MI, or stroke. The primary analysis includes noninferiority and superiority assessments of tirzepatide versus dulaglutide and a putative placebo. The study population was high-risk, with 65% having coronary disease, 47.3% reporting prior MI, 57.4% having undergone coronary revascularization, 19.1% with a history of stroke, and 25.3% with peripheral artery disease. In summary, the SURPASS-CVOT trial aims to establish definitive evidence of the cardiovascular safety and efficacy of tirzepatide. Its first trial in doing so will be in comparison to dulaglutide, a drug with known cardiovascular benefits. An ambitious goal has been set for the novel dual agonist drug [31].

SUMMIT trial (anticipated completion in 2024)

This is a randomized, double-blind, placebo-controlled, phase 3 study comparing the efficacy and safety of tirzepatide versus placebo in patients with HFpEF and obesity. The primary outcome measure is a hierarchical composite of all-cause mortality, nonfatal MI, or nonfatal stroke. Secondary outcomes include the percent change from baseline in body weight loss at 104 weeks and changes in glycemic control markers. Scheduled for completion in July 2024, this study will attempt to join semaglutide's current standing amongst GLP-1s and cardiovascular benefits in patients with HFpEF [32].

Discussion

This review of GLP-1 receptor agonists comprehensively analyzes their role in cardiovascular outcomes and presents a streamlined discussion and conclusion of these drugs' current state and potential future.

Efficacy and safety in cardiovascular management

Each GLP-1 receptor agonist exhibits unique characteristics regarding efficacy, safety, and suitability for specific patient needs. Lixisenatide and exenatide ER, although both deemed safe, have not been conclusively shown to reduce cardiovascular outcomes, as shown by the ELIXA and EXSCEL trials [20, 21]. Conversely, albiglutide, efpeglenatide, semaglutide, liraglutide, and dulaglutide have established roles in reducing cardiovascular outcomes. The HARMONY trial highlighted albiglutide's potential in this regard. Although its poor glycemic control in comparison to other GLP-1s is of concern, the HARMONY trial showed it has cardiovascular benefits with superiority over placebo [22]. Efpeglenatide and dulaglutide, in particular, also offer renal benefits, a significant factor in type 2 diabetes management. Efpeglenatide showed superiority over placebo in reducing cardiovascular outcomes, at the

Table 3. Results of Head-to-Head Trials When Comparing CV Outcomes in GLP-1 Receptor Agonists

Trial	Drug (dose) vs. placebo	Results in CV outcome reduction (CV death/nonfatal MI/nonfatal stroke)	P value	Results of side effects that were significant
ELIXA [20]	Lixisenatide (10 µg SC daily)	21%/62.8%/13.3%	0.81	N/A
	Placebo	23.3%/61.9%/12.3%		
EXSCEL [21]	Exenatide ER (2.0 mg SC weekly)	4.6%/6.6%/2.5%	0.06	Increased HR by 2.51 bpm
	Placebo	7.9%/6.7%/2.9%		
HARMONY [22]	Albiglutide (30 - 50 mg)	7%	P < 0.0006	None were significant.
	Placebo	9%		
AMPLITUDE [23]	Efpeglenatide (4 or 6 mg SC weekly)	7%	P = 0.007	Increased GI side effects (constipation, diarrhea, nausea, vomiting, bloating)
	Placebo	9.20%		Significantly fewer decreases in kidney function
REWIND [24]	Dulaglutide (1.5 mg SC weekly)	12%	P = 0.026	Increased GI side effects
	Placebo	13.40%		
LEADER [25]	Liraglutide (1.8 mg SC weekly)	13%	P = 0.01	Decreased incidence of renal or retinal microvascular events
	Placebo	14.90%		
SUSTAIN-6 [26]	Semaglutide (0.5 and 1.0 mg SC weekly)	6.60%	P = 0.02	Increased incidence of retinopathy
				Decreased incidence of new or worsening nephropathy
	Placebo	8.90%		Decreased blood pressure by 2.6 mm Hg
PIONEER-6 [27]	Semaglutide (14 mg oral daily)	0.9%/2,3%/0.8%	P < 0.001	Increased GI side effects
	Placebo	1.9%/1.9%/1.0%		
SELECT [28]	Semaglutide (2.4 mg SC weekly)	6.50%	P < 0.001	Increased incidence of gallbladder disorders
	Placebo	8%		
STEP HFPEF [29]	Semaglutide (2.4 mg SC weekly)	+7.8 difference in KCCQ-CSS score, +20.3 m difference in 6-min walk distance change	P < 0.001	Improved symptom and physical limitations in HFpEF
	Placebo			

CV: cardiovascular; GLP-1: glucagon-like peptide-1; GI: gastrointestinal.SC: subcutaneous; ER: extended release; N/A: not available, bpm: beat per minute; HFpEF: heart failure with preserved ejection fraction.

price of increased GI side effects [23]. Dulaglutide showed evidence of reduced cardiovascular outcomes although not as strong as others, and despite some setbacks in head-to-head trials, it remains a valuable option, especially for patients requiring renal protection. Notably, patients did have increased incidence of retinopathy [24]. Liraglutide appears to have similar cardiovascular benefits as dulaglutide, however does not offer renal protection, instead, it showed to offer reductions in systolic blood pressure [25]. Semaglutide, available in subcutaneous and oral formulations, has emerged as a significant therapeutic agent. Its efficacy extends beyond glycemic control, demonstrating cardiovascular and renal benefits in diverse patient populations, including those with diabetes, prediabetes, obesity, and HFpEF. While the therapeutic advantages of semaglutide are clear, it is not without side effects. In low dose subcutaneous injection, there is a renal and blood pressure benefit. In high dose subcutaneous injection (2.4 mg), the cardiovascular benefits are apparent and strong, however, the renal benefit is lost. GI disturbances are a notable concern, and there is a potential risk of retinopathy and gallbladder disorders at the higher dose. The SOUL trial is currently underway, which intends to compare efficacy in

Table 4. Ranking of GLP-1 Receptor Agonists When Comparing CV Outcomes

Drug (dose)	Within class comparability of A1c lowering efficacy	Within class comparability of effect on weight	Within class comparability of cardiovascular safety/efficacy	Strengths and weaknesses
Albiglutide (30 - 50 mg)	Lowest	Unknown	High	Poor glycemic control
Exenatide (10 µg SC twice daily)	Lowest	Lowest	Unknown	
Lixisenatide (10 µg SC daily)	Lowest	Lowest	Lowest	No significant difference from placebo
Exenatide ER (2.0 mg SC weekly)	Low	Lowest	Lowest	No significant difference from placebo
Dulaglutide (1.5 mg SC weekly)	Intermediate	Low	Intermediate	Renal benefit Increased GI side effects
Liraglutide (1.8 mg SC weekly)	Intermediate	Intermediate	Intermediate	Renal benefit BP lowering
Efpeglenatide (4 mg or 6 mg SC weekly)	Intermediate	Intermediate	High	Renal benefit
Semaglutide (14 mg oral daily)	High	High	Low	Increased GI side effects
Semaglutide (0.5 mg and 1.0 mg SC weekly)	High	High	Intermediate	Renal benefits, BP lowering Increased retinopathy Increased GI side effects
Semaglutide (2.4 mg SC weekly)	Highest	Highest	High	HFpEF benefits Increased incidence of gallbladder disorders
Tirzepatide	Highest	Highest	Unknown	No studies completed yet

CV: cardiovascular; GLP-1: glucagon-like peptide-1; GI: gastrointestinal.SC: subcutaneous; ER: extended release; HFpEF: heart failure with preserved ejection fraction; BP: blood pressure.

reducing cardiovascular outcomes in those with established ASCVD in a 3.5 - 5-year long-term follow-up and will also look into cognitive assessments to answer questions about cognitive decline and its associations with GLP-1s [26-30]. Tirzepatide, with its dual-acting mechanism, has shown impressive results in A1c reduction and weight loss, challenging semaglutide's leadership in these areas. However, its cardiovascular safety and efficacy are still under investigation in the SURPASS-CVOT and SUMMIT trials. These trials, testing tirzepatide against dulaglutide in patients with ASCVD and evaluating its impact on obese patients with HFpEF, respectively, are highly anticipated. Their outcomes are intended to challenge semaglutide's current hold on T2DM and obesity when considering cardiovascular outcomes. We have summed up the results of each trial discussed in this analysis in Table 3 [20-29].

After analysis of these trials, we have also established an updated ranking system that takes into consideration cardiovascular outcomes and other benefits that were found (Table 4).

In terms of cardiovascular safety and efficacy, the ranks are as follows: semaglutide (subcutaneous (SC) 2.4 mg) = efpeglenatide = albiglutide > semaglutide (0.5 mg and 1 mg SC) = dulaglutide = liraglutide > semaglutide (oral) > lixisenatide = exenatide ER.

Future prospects and research needs

There is a pressing need for long-term data on the efficacy and safety of GLP-1 receptor agonists, particularly for periods extending beyond 3 years. Such data are essential for

Table 5. Anticipated Trials of GLP-1 Agonists

Trial (expected year of completion)	Objective
SOUL (2025)	Semaglutide's efficacy in reducing cardiovascular outcomes in those with atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD).
SURPASS-CVOT (2024)	Tirzepatide compared to dulaglutide in individuals with type 2 diabetes and established (ASCVD).
SUMMIT (2024)	Tirzepatide versus placebo in patients with heart failure with preserved ejection fraction and obesity.

GLP-1: glucagon-like peptide-1.

understanding the sustainability of benefits and long-term risks. Head-to-head trials have been established when comparing obesity and A1c-lowering management, but there is a gap in the literature when comparing cardiovascular outcomes head-to-head. Observational studies and registries could provide valuable insights into the performance of these drugs in more diverse and real-world patient populations. Most, if not all, studies are industry driven, providing a risk of bias. Furthermore, cost-effectiveness analysis and patient-centered outcomes research are vital to inform policy decisions and enhance patient care. It is important to cater to patient needs, even when considering economic feasibility. One particular study has already shown tirzepatide to be more cost-effective than semaglutide [33]. The potential introduction of new drugs, like the triple agonist retatrutide, shows promise, especially in obesity management [34]. We are still in the early stages of the development and unfolding of a new class of medications that are highly anticipated to answer the increasingly worsening pandemic of T2DM, obesity, and its cardiovascular implications in the world. The next couple of years plan to catapult GLP-1s into the world of everyday care of cardiologists and their patients.

We have summed up below trials that are highly anticipated (Table 5) to add to the discussion of GLP-1s and their safety and efficacy in reducing cardiovascular outcomes.

Conclusions

The landscape of GLP-1 receptor agonists is dynamic and competitive, with each drug contributing uniquely to cardiovascular outcomes in patients with type 2 diabetes. The coming years are critical for determining the most effective and safe treatments, with the potential for new therapies to revolutionize this field further. The continued focus on comprehensive, long-term, and patient-centered research will be pivotal in shaping the future of diabetes and cardiovascular disease management.

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Conflict of Interest

None to declare.

Author Contributions

Michael Sabina conducted a comprehensive systematic review, encompassing the identification, screening, eligibility, and inclusion of relevant studies, performed an extensive literature search, ensuring the inclusion of pertinent publications and data sources, executed a thorough analysis of the collected data, interpreting findings with a focus on relevance and impact, designed and compiled all tables presented in the manuscript, ensuring clarity and accuracy of the data displayed, and authored the discussion and conclusions sections, synthesizing the findings into coherent insights and recommendations. M Mrhaf Alsamman provided overall oversight for the project, ensuring adherence to research objectives and academic standards, performed critical final edits to the manuscript, enhancing its clarity, coherence, and overall quality, ensured that the paper was comprehensive and accurate, with particular attention to the verification of data and information presented, and supplied essential resources necessary for the successful completion of the research and preparation of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. Lee SH, Nam K, Lee GR, Nam YU, Lee JSH, Joo YH, Han SW. SAT-199 association between serum lipid profiles and progression of CKD: know-CKD study. Kidney International Reports. 2019;4(7):S90-S91. doi
2. Panuganti KK, Nguyen M, Kshirsagar RK. Obesity. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/books/NBK459357/.
3. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of

randomised controlled trials. BMJ. 2012;344:d7771. doi pubmed pmc
4. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. doi pubmed pmc
5. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, 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). Lancet. 2009;374(9683):39-47. doi pubmed
6. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, Hoogwerf BJ, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013;381(9861):117-124. doi pubmed
7. Rosenstock J, Raccah D, Koranyi L, Maffei L, Boka G, Miossec P, Gerich JE. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013;36(10):2945-2951. doi pubmed pmc
8. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. Diabetes Care. 2016;39(9):1501-1509. doi pubmed
9. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, Kuhstoss D, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care. 2014;37(8):2159-2167. doi pubmed
10. Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384(9951):1349-1357. doi pubmed
11. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41(2):258-266. doi pubmed
12. Pratley RE, Aroda VR, Lingvay I, Ludemann J, Andreassen C, Navarria A, Viljoen A, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6(4):275-286. doi pubmed
13. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Verges B, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020;46(2):100-109. doi pubmed
14. Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, Pedersen KB, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. 2019;394(10192):39-50. doi pubmed
15. Yabe D, Nakamura J, Kaneto H, Deenadayalan S, Navarria A, Gislum M, Inagaki N, et al. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2020;8(5):392-406. doi pubmed
16. Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, Ye J, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol. 2014;2(4):289-297. doi pubmed
17. Rosenstock J, Sorli CH, Trautmann ME, Morales C, Wendisch U, Dailey G, Hompesch M, et al. Once-weekly efpeglenatide dose-range effects on glycemic control and body weight in patients with type 2 diabetes on metformin or drug naive, referenced to liraglutide. Diabetes Care. 2019;42(9):1733-1741. doi pubmed
18. Frias JP, Davies MJ, Rosenstock J, Perez Manghi FC, Fernandez Lando L, Bergman BK, Liu B, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503-515. doi pubmed
19. Inagaki N, Takeuchi M, Oura T, Imaoka T, Seino Y. Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2022;10(9):623-633. doi pubmed
20. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, Lawson FC, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373(23):2247-2257. doi pubmed
21. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228-1239. doi pubmed pmc
22. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr., Granger CB, Jones NP, Leiter LA, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519-1529. doi pubmed
23. Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, Lam CSP, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med. 2021;385(10):896-907. doi pubmed
24. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, 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 pubmed
25. Marso SP, Poulter NR, Nissen SE, Nauck MA, Zinman B, Daniels GH, Pocock S, et al. Design of the liraglu-

tide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. Am Heart J. 2013;166(5):823-830.e825. doi pubmed
26. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, Lingvay I, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-1844. doi pubmed
27. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841-851. doi pubmed
28. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232. doi pubmed
29. Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, Hovingh GK, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389(12):1069-1084. doi pubmed
30. McGuire DK, Busui RP, Deanfield J, Inzucchi SE, Mann JFE, Marx N, Mulvagh SL, et al. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: Design and baseline characteristics of SOUL, a randomized trial. Diabetes Obes Metab. 2023;25(7):1932-1941. doi pubmed
31. Nicholls SJ, Bhatt DL, Buse JB, Prato SD, Kahn SE, Lincoff AM, McGuire DK, et al. Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics. Am Heart J. 2024;267:1-11. doi pubmed
32. Frias JP, et al. Tirzepatide and cardiovascular outcomes in patients with type 2 diabetes and established atherosclerotic cardiovascular disease. Circulation. 2022.
33. Azuri J, Hammerman A, Aboalhasan E, Sluckis B, Arbel R. Tirzepatide versus semaglutide for weight loss in patients with type 2 diabetes mellitus: A value for money analysis. Diabetes Obes Metab. 2023;25(4):961-964. doi pubmed
34. Rosenstock J, Frias J, Jastreboff AM, Du Y, Lou J, Gurbuz S, Thomas MK, et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. Lancet. 2023;402(10401):529-544. doi pubmed