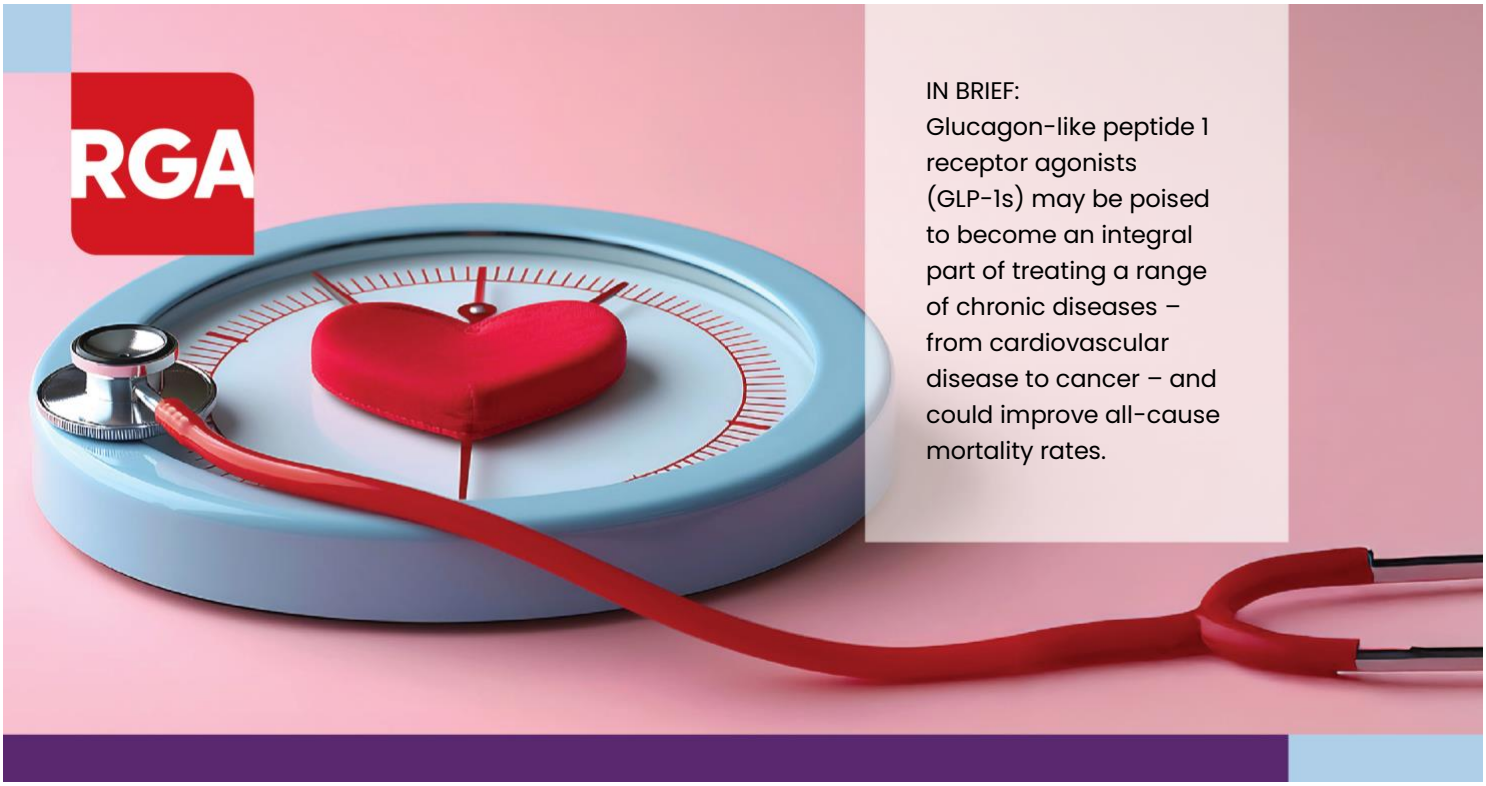


GLP-1 Receptor Agonists: Changing the scales of human health

By Hilary Henly

KEY TAKEAWAYS

- GLP-1s, initially developed to help manage and treat diabetes and later used to treat obesity, are now showing significant potential to help prevent and treat other conditions.
- Studies show that GLP-1s could potentially be used to treat CVD, mental health disorders, liver and kidney disorders, neurodegenerative disorders, addiction disorders, and cancer.
- Insurers should carefully monitor these trials and consider GLP-1s' potential impact on disease incidence, prevalence, and mortality outcomes in the future.

Originally developed to improve diabetic control, glucagon-like peptide 1 receptor agonists (GLP-1s) have emerged as a successful treatment for weight management, but their potential applications may extend much further.

Growing evidence suggests the introduction of GLP-1s in the management of multiple diseases and disorders could help reduce the lifetime burden of chronic diseases on the healthcare system and improve patients' overall wellbeing, thereby benefiting insurers.

Studies show that this class of drugs can be used to treat heart failure, liver disease, anxiety and depression, neurodegenerative disorders, kidney disease, sleep apnea, and addiction disorders. GLP-1s may be poised to become an integral part of treating certain chronic diseases and could improve all-cause mortality rates. A meta-analysis of initial research showed that GLP-1s reduced the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes (T2D) by 14%, all-cause mortality by 12%, hospital admissions for heart failure by 11%, and the composite kidney outcome by 21%.[1]

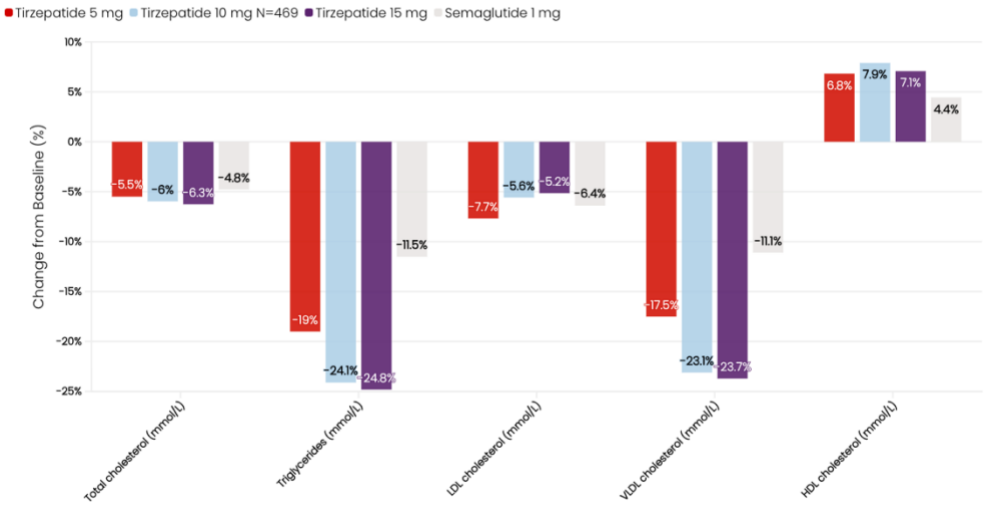
Beyond diabetes and obesity

Cardiovascular disease

In March 2024, the US Food and Drug Administration (FDA) approved Wegovy (semaglutide) for adults with cardiovascular disease (CVD) and either obesity and overweight to reduce the risk of cardiovascular death, heart attack, and stroke.[2] Semaglutide, liraglutide, and tirzepatide have all shown cardiovascular protective effects, such as reducing lipid and blood pressure levels. Notable findings include:

- In the SURMOUNT-1 trial of tirzepatide for the treatment of obesity, secondary findings showed improvements in the GLP-1 treatment group in systolic blood pressure (-7.2mm Hg), diastolic blood pressure (-4.8mm Hg), triglycerides (-24.8mg/dl), fasting insulin (-42.9mIU liter), and total cholesterol (-4.8mg/dl).[3]
- In the STEP-1 trial of semaglutide for the treatment of obesity, secondary findings showed improvements in the GLP-1 treatment group in systolic blood pressure (-6.16mm Hg) and diastolic blood pressure (-2.83mm Hg).[4]
- In the SURPASS-2 trial, the percentage change from baseline at 40 weeks for total cholesterol (-5.49%), triglycerides (-19%), and low-density lipoprotein (-7.68%) levels were lower, and the HDL (good) cholesterol (+6.82%) levels were higher in patients on tirzepatide 5mg versus those who used semaglutide 1mg. [5]

Figure 1: Effect of once-weekly tirzepatide, compared with semaglutide, on lipid profile[5]



GLP-1s are also being investigated for the prevention and treatment of heart failure. There are currently no approved targeted therapies for left ventricular ejection fraction (EF)-preserved heart failure (HFpEF) associated with obesity. The SELECT trial of nearly 18,000 individuals showed that 2.4mg of semaglutide reduced heart attacks, strokes, and mortality due to CVD, with 73% fewer patients progressing to diabetes compared to the control group. Key findings included:

- Semaglutide improved all outcome measures in patients with heart failure (MACE HR 0.72, cardiovascular death HR 0.76, all-cause mortality HR 0.81), compared with those without heart failure.
- Semaglutide improved outcomes in both the heart failure with reduced EF group (MACE HR 0.65) and the heart failure with preserved EF group (MACE HR 0.69).
- Semaglutide reduced MACE by 20% (HR 0.80) in patients with pre-existing atherosclerotic cardiovascular disease and overweight or obesity compared with placebo.[6]

Nervous system

Insulin resistance is a common feature in neurodegenerative disease, and research shows that T2D is a risk factor for Alzheimer's disease (AD) and Parkinson's disease (PD). In addition to reducing insulin resistance, GLP-1s can reduce neuroinflammation and subsequent motor and cognitive impairment in patients suffering from neurodegenerative disorders, such as PD and AD.

Trials of lixisenatide in persons with PD have found the treatment improved non-motor symptoms, mobility, and quality of life, but longer and larger trials are now needed to determine the effects and safety of lixisenatide in persons with PD.[7]

Exenatide is the most prevalent GLP-1 in clinical trials for AD and PD treatments. A phase 2 trial of exenatide in treating AD showed that patients displayed reduced amyloid-β 42 concentrations, the abnormal accumulations that are a primary driver of AD. In a separate trial of 62 patients with moderate-severity PD, exenatide had positive and sustained effects on motor function after 12 weeks.[8]

The EVOKE phase III trial is studying the effect of semaglutide in AD, with preliminary results due in September 2025. Additional clinical trials are in progress, including the investigation of GLP-1s to treat glaucoma, Friedreich ataxia, and multiple sclerosis.[7]

RGA life and health insurance experts are actively engaging with insurers to help determine optimal paths forward in addressing GLP-1 challenges and other emerging issues. Ready to join the conversation?

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Addictive disorders

One unexpected finding in GLP-1 users has been a reduction in alcohol consumption and addictive behaviors. This may be related to the impact on the brain's reward system, as GLP-1s are expressed in areas of the brain influenced by addictive drugs, such as nicotine, opioids, and alcohol. The brain's reward system triggers the release of dopamine, but this response is muted in the presence of drugs such as semaglutide.[9]

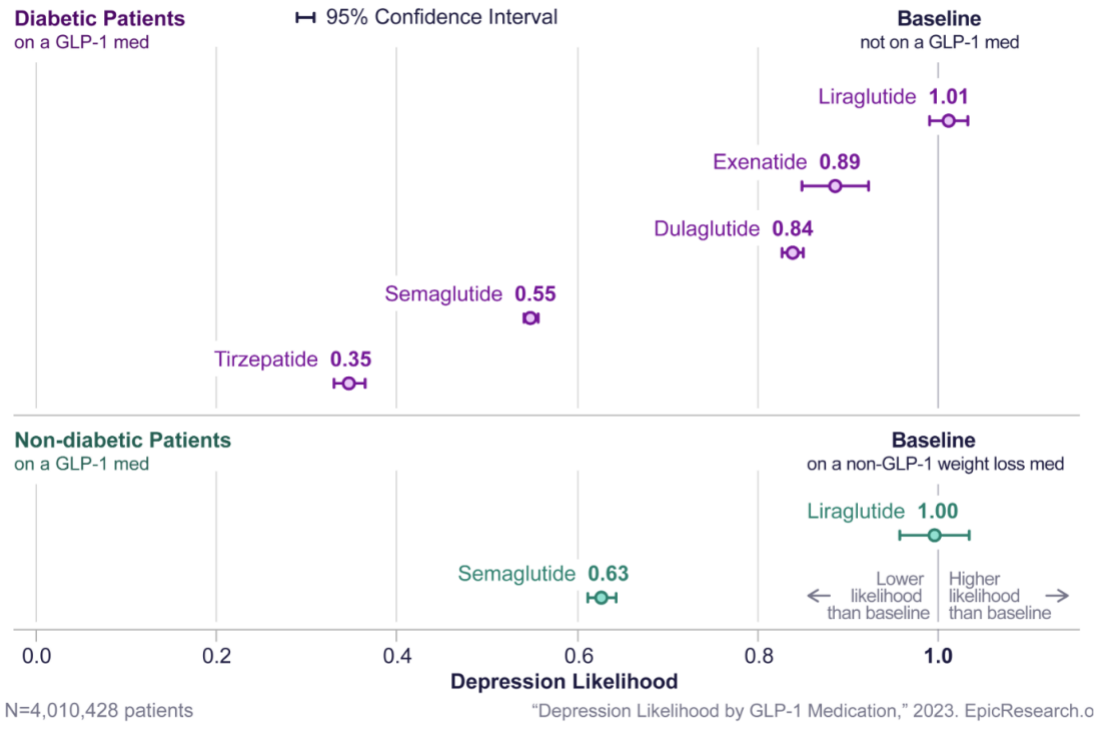
Studies to date have shown that semaglutide, liraglutide, and dulaglutide can reduce alcohol consumption and combat addiction. In one study of over 83,000 patients, semaglutide was associated with a 50%-56% lower risk for both incidence and recurrence of alcohol use disorder over a 12-month follow-up compared with other anti-obesity medications.[10]

Ongoing trials are currently studying semaglutide and tirzepatide for alcohol use disorder, semaglutide for opioid use and cannabis use disorder, liraglutide for opioid use disorder, and semaglutide and exenatide to achieve smoking cessation.[9]

Mental health

Diabetic patients treated with tirzepatide, semaglutide, dulaglutide, and exenatide are less likely to be diagnosed with depression and anxiety. A recent study using 233 million patient records found significantly lower depression and anxiety scores for patients that were treated with GLP-1s, particularly with tirzepatide.[11]

Figure 2: The likelihood of patients being diagnosed with depression after a GLP-1 prescription compared to those on a non-GLP-1 medication[11]



Initial studies on the risk of suicide in individuals taking GLP-1s indicate that these drugs may increase suicidal thoughts and ideation. However, in a retrospective study of nearly half a million patients, semaglutide was associated with lower risk for incident (HR = 0.27) and recurrent (HR = 0.44) suicidal ideation compared with non-GLP-1 anti-obesity medications.[12] A separate study of people with T2D treated with GLP-1s found the rate of suicide attempts was more than 53% lower in the GLP-1 group compared to patients treated with DPP-4 inhibitors (oral hypoglycemics).[9]

Kidney Disease

Diabetes is a known risk factor for acute kidney disease (AKD), which is associated with the risk of end-stage kidney disease and mortality. Trials to date have shown that GLP-1s may have beneficial effects on kidney function, especially relevant for T2D patients with chronic kidney disease (CKD).[13]

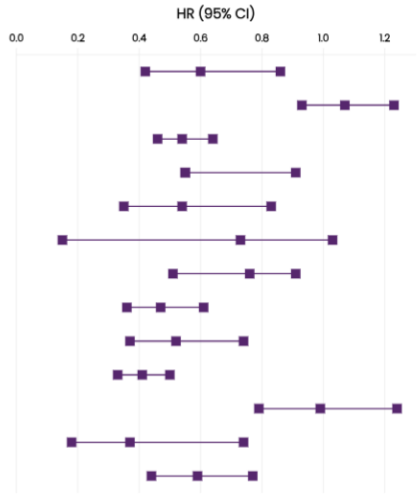
- In a recent study of T2D patients with AKD, the mortality rate was significantly lower in the GLP-1 user group compared to the non-user group (HR 0.57). The user group had lower risk of major adverse cardiovascular events (MACE) (HR 0.88), as well as a lower risk of major adverse kidney events (MAKE) (HR 0.73).[13]
- In the SURPASS-4 trial (phase III), participants taking tirzepatide showed a much lower occurrence of composite kidney endpoint (time to first occurrence of eGFR decline of at least 40% from baseline, end-stage kidney disease, death due to kidney failure, or new onset albuminuria) compared with those who received insulin glargine (HR 0.58).[14]
- In the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial, the risk of a primary outcome event – major kidney disease event, onset of kidney failure (dialysis, transplant, eGFR <15 ml/min per 1.73 m2), < 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes = in patients with T2D and chronic kidney disease was 24% lower in the 1mg semaglutide group compared to the placebo group. The risk of MACE was 18% lower, and the risk of death was 20% lower in the semaglutide group compared to the placebo group.[15]

Cancers

GLP-1s have been investigated for their impact in reducing the risk of obesity-related cancers (OACs) such as colorectal cancer, esophageal, breast, colorectal, endometrial, gallbladder, stomach, kidney, ovarian, pancreatic, and thyroid cancer, as well as hepatocellular carcinoma, meningioma, and multiple myeloma. In a study of more than 1.6 million patients with T2D and no prior diagnosis of OACs, patients treated with GLP-1s had a significantly lower risk for 10 of the listed cancers.[16]

Figure 3: Risk of OACs in patients on GLP-1s versus patients on insulin

Outcome (N =1651 452)	Group prescribed GLP-IRAsbut not insulin. No (%) (n= 48983)	Group prescribed insulin but not GLP-IRAs, No (%) (n= 1044745)	HR (95% CI)
Esophageal cancer (n=48437)	49 (0.10)	77 (0.16)	0.60 (0.42-0.86)
Breast cancer (n=13768)	427 (3.08)	379 (2.94)	1.07 (0.93-1.23)
Colorectal cancer (n=48443)	223 (0.46)	391 (0.81)	0.54 (0.46-0.64)
Endometrial cancer (n=25750)	160 (0.62)	210 (0.82)	0.74 (0.60-0.91)
Gallbladder cancer (n=48587)	<10 (<0.02)	19 (0.04)	0.35 (0.15-0.83)
Stomach cancer (n=48449)	56 (0.12)	75 (0.16)	0.73 (0.51-1.03)
Kidney cancer (n=48322)	223 (0.46)	284 (0.59)	0.76 (0.64-0.91)
Hepatocellular carcinoma (n=48397)	79 (0.16)	167 (0.35)	0.47 (0.36-0.61)
Ovarian cancer (n=25739)	51 (0.20)	94 (0.37)	0.52 (0.37-0.74)
Pancreatic cancer (n=48490)	123 (0.25)	290 (0.60)	0.41 (0.33-0.50)
Thyroid cancer (n=48527)	154 (0.32)	149 (0.31)	0.99 (0.79-1.24)
Meningioma (n=48518)	11 (0.02)	29 (0.06)	0.37 (0.18-0.74)
Multiple myeloma (n=48527)	80 (0.17)	131 (0.27)	0.59 (0.44-0.77)



Conclusion

GLP-1s, initially developed to help manage and treat diabetes and later used to treat obesity, are now showing significant potential to help prevent and treat CVD, mental health disorders, liver and kidney disorders, neurodegenerative disorders, addiction disorders, and cancer. Studies have shown improvements in CVD and all-cause mortality in diabetic patients on GLP-1s. Additional clinical trials are required to evaluate the efficacy, safety, and tolerability of the different GLP-1s for disease management and for reducing cause-specific and all-cause mortality.

This research could have significant implications for the life and health industry. Insurers should carefully monitor these trials and consider GLP-1s' potential impact on disease incidence, prevalence, and mortality outcomes in the future.

RGA life and health insurance experts are actively engaging with insurers to help determine optimal paths forward in addressing GLP-1 challenges and other emerging issues. Ready to join the conversation?
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