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Commentary

The expanding benefits of GLP-1 medicines

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GLP-1 medicines, initially developed for blood glucose and weight control, improve outcomes in people with cardiovascular, kidney, liver, arthritis, and sleep apnea disorders, actions mediated in part through anti-inflammatory and metabolic pathways, with some benefits partly independent of the degree of weight loss achieved.

Modern GLP-1 receptor agonists and co-agonists (GLP-1 medicines) such as liraglutide, dulaglutide semaglutide, and the GLP-1R/glucose dependent insulinotropic polypeptide receptor (GIPR) co-agonist tirzepatide, were initially developed for the treatment of type 2 diabetes (T2D) due to their actions to increase insulin and decrease glucagon secretion and slow gastric emptying through effects on the pancreas and brain. GLP-1R/GIPR receptor activation in the brain also reduces appetite and promotes satiety, supporting development of liraglutide, semaglutide, and tirzepatide for weight loss. Liraglutide, semaglutide, and tirzepatide are currently approved for people with obesity and for those who are overweight with one or more weight-related comorbidities.[1]

Beyond their well-characterized effects to lower blood glucose and body weight, GLP-1 medicines reduce rates of chronic kidney disease (CKD), myocardial infarction, stroke, and cardiovascular death in people with type 2 diabetes (T2D) (Figure 1). GLP-1 medicines also improve symptoms and outcomes in people with heart failure with preserved ejection fraction (HFpEF), the majority with concomitant obesity and often T2D. Benefits have also been demonstrated in separate trials of people with metabolic dysfunction associated liver disease (MASLD), the majority with T2D and obesity; sleep apnea (concomitant obesity but not T2D); and osteoarthritis (obesity with or without T2D) (Table 1). This commentary summarizes evidence demonstrating beneficial effects of GLP-1 medicines on conditions other than T2D or obesity, including cardiovascular disease (CVD), CKD, MASLD, osteoarthritis (OA), obstructive sleep apnea (OSA), and peripheral artery disease (PAD) (Figure 1A).

Cardiovascular disease and CKD

In 2024, semaglutide was approved by the FDA as the first weight-loss medication to reduce the risk of major adverse cardiovascular events (MACE) in adults with obesity or who are overweight, without T2D and stablished CVD, when prescribed with a reduced-calorie diet and increased physical activity. This approval was based on results of the SELECT trial, which studied 17,604 patients with BMI >27 and a history of myocardial infarction, stroke, or symptomatic PAD. Subcutaneous semaglutide 2.4 mg weekly reduced the primary composite outcome of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (6.5% vs. 8%, semaglutide vs. placebo, respectively, HR 0.8; CI 95%; 0.72–0.90; $p < 0.001$) at a mean follow-up of 34.2 months.[2] Additionally, semaglutide reduced the secondary outcome of all-cause mortality (4.3% vs. 5.2%; HR 0.81; CI 95%; 0.71–0.93). Notably, these effects were independent of the extent of weight loss.

In a pooled analysis of clinical trials assessing patients with heart failure with preserved ejection fraction (HFpEF), including the STEP HFpEF and STEP HFpEF DM trials, as well as in the FLOW and SELECT trials, semaglutide improved New York Heart Association (NYHA) class II–IV symptoms, physical limitations, exercise function, associated with a 30% reduction of N-terminal pro-brain natriuretic peptide and a 31% reduction in the composite endpoint of cardiovascular death and the need for treatment intensification or hospitalization for heart failure-related events (HR 0.69; CI 95%; 0.53–0.89; $p = 0.0045$).[3]

The FLOW trial studied 3,533 adults with a mean BMI of 32, T2D, and CKD. After 3.4 years of follow-up, subcutaneous semaglutide 1 mg weekly reduced rates of a composite outcome that included kidney failure events (long-term dialysis, kidney transplantation, or sustained eGFR <15 mL/min/1.73 m^2 for ≥28 days), a sustained ≥50% reduction in eGFR, or death from kidney-related or cardiovascular causes (23.2% with placebo vs. 18.7% with semaglutide; HR 0.76; CI 95%; 0.66–0.88; $p < 0.001$).[4] Based on these results, in January 2025, the FDA expanded the prescribing indications for semaglutide to reduce the risk of kidney disease progression, kidney failure, and death due to CVD in adults with T2D and CKD.

The SOUL clinical trial evaluated the cardiovascular safety of oral semaglutide in people with T2D. The results further supported the cardiorenal benefits of GLP-1 medicines with or without concomitant use of sodium-glucose co-transporter 2 inhibitors (SGLT2i). In this placebo-controlled trial enrolling over 9,600 individuals with T2D and established atherosclerotic cardiovascular disease, CKD, or both, treatment with oral semaglutide at maximal dose of 14 mg daily resulted in a 14% relative risk reduction in the primary MACE outcome compared with placebo (HR 0.86; CI 95%; 0.77–0.96; $p = 0.006$) over a mean follow-up of 47.5 ± 10.9 months (Table 1). Participants were analyzed according to baseline use of SGLT2i (use of SGLT2i $n = 2,596$; no use of SGLT2i $n = 7,054$) and subsequently for any use

Table 1. Clinical trials expanding the benefits of GLP-1 medicines in cardiovascular disease, chronic kidney disease, metabolic-associated liver disease, osteoarthritis, obstructive sleep apnea, and peripheral artery disease

Trial	Drug	Dose	Duration	Condition treated	Primary endpoint	Key results
SELECT	Semaglutide (subcutaneous)	2.4 mg/week	40 months	Obesity with cardiovascular risk	Reduction in MACE (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke)	20% reduction in MACE events (HR 0.80; CI 95%; 0.72 to 0.90; $p < 0.001$)
STEP HFpEF	Semaglutide (subcutaneous)	2.4 mg/week	52 weeks	HFpEF and obesity	Improvement in KCCQ-CSS score and change in body weight	16.6-point improvement in KCCQ-CSS with semaglutide vs. 8.7 with placebo; +21.5 m in 6-min walk test; 13.3% weight loss.
STEP HFpEF DM	Semaglutide (subcutaneous)	2.4 mg/week	52 weeks	HFpEF with T2D and obesity	Improvement in KCCQ-CSS score and change in body weight	13.7-point improvement in KCCQ-CSS with semaglutide vs. 6.4 with placebo; +12.7 m in 6-min walk test; 9.8% weight loss.
SUMMIT	Tirzepatide (subcutaneous)	Maximal dose 15 mg/week	52 weeks	HFpEF and obesity	Reduction in CV death and heart-failure events and improvement in KCCQ-CSS	38% reduction in the composite endpoint of CV death or worsening heart-failure events compared to placebo (HR 0.62; CI 95%; 0.41–0.95; $p = 0.026$); 6.9-point improvement in KCCQ-CSS compared to placebo
FLOW	Semaglutide (subcutaneous)	1 mg/week	3.4 years	Chronic kidney disease with T2D	Reduction in major kidney disease events (kidney failure, at least a 50% reduction in eGFR from baseline, or death from kidney related or CV causes)	24% reduction in the composite primary outcome; trial stopped early due to significant benefit
SOUL	Semaglutide (oral)	Maximal dose 14 mg/day	47.5 months	T2D with cardiovascular risk, atherosclerotic CVD, CKD, or both.	Reduction in MACE (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke)	14% reduction in MACE events (HR 0.86; CI 95%; 0.77 to 0.96; $p = 0.006$)
ESSENCE	Semaglutide (subcutaneous)	2.4 mg/week	240 weeks	MASH with fibrosis F2-F3	Resolution of steatohepatitis without worsening of liver fibrosis and reduction in liver fibrosis without worsening of steatohepatitis	MASH resolution in 62.9% vs. 34.3% with placebo; fibrosis improvement in 36.8% vs. 22.4% with placebo after 72 weeks of treatment
Survodutide in MASH	Survodutide (subcutaneous)	2.4, 4.8, 6.0 mg/week	48 weeks	MASH with fibrosis F1-F3	Resolution of steatohepatitis without worsening of liver fibrosis and reduction in liver fibrosis without worsening of steatohepatitis	MASH resolution in 62% vs. 14% with placebo; ≥30% liver fat reduction in 67% vs. 14%; fibrosis improvement in 36% vs. 22%
Tirzepatide in MASH	Tirzepatide (subcutaneous)	5, 10, 15 mg/week	52 weeks	MASH with fibrosis F2-F3	Resolution of steatohepatitis without worsening of liver fibrosis	MASH resolution in up to 62% with tirzepatide vs. 10% with placebo
STEP 9	Semaglutide (subcutaneous)	2.4 mg/week	68 weeks	Knee osteoarthritis with obesity	Change in body weight and in the WOMAC pain score	−41.7 point in the WOMAC pain score with semaglutide vs. −27.5 points with placebo; 13.7% weight loss vs. 3.2% with placebo.

(*Continued on next page*)

Table 1. *Continued*

Trial	Drug	Dose	Duration	Condition treated	Primary endpoint	Key results
SURMOUNT-OSA	Tirzepatide (subcutaneous)	10 mg or 15 mg/week	52 weeks	Obstructive sleep apnea with obesity	Change in AHI	Trial 1: −25.3 events/h with tirzepatide vs. −5.3 events/hour with placebo; trial 2: −29.3 events/h with tirzepatide vs. −5.5 events/h with placebo
STRIDE	Semaglutide (subcutaneous)	1 mg/week	52 weeks	Peripheral artery disease with T2D	Ratio to baseline of the maximum walking distance at week 52 measured on a constant load treadmill in the full analysis set	Maximum walking distance was significantly greater in trial participants randomized to semaglutide

of SGLT2i during the trial (use of SGLT2i n = 4,718; no use of SGLT2i n = 4,932). An analysis of MACE by SGLT2i use showed no evidence of heterogeneity in the effects of oral semaglutide with evidence for significant benefit in subjects taking SGLT2i. Treatment with oral semaglutide also reduced rates of several prespecified secondary outcomes, including cardiovascular death (HR 0.93; CI 95%; 0.80–1.09), a five-composite major kidney disease events (HR 0.91; CI 95%; 0.80–105), and a two-composite major adverse limb events (HR 0.71; CI 95%; 0.52–0.96), although these findings did not all reach statistical significance. Notably, the overall safety profile of oral semaglutide was consistent with previous trials. The observed cardiorenal benefits, regardless of SGLT2i use, reinforce the therapeutic value of GLP-1 medicines, exemplified by semaglutide, as part of comprehensive cardiometabolic care in individuals with T2D.[5]

Metabolic liver disease

In a 240-week phase 3 clinical trial of 1,200 adults with metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis stages F2-F3 (mean BMI 34.6), semaglutide 2.4 mg weekly improved liver histology (Non-alcoholic Fatty Liver Disease Activity Score, inflammation, and ballooning and steatosis) in the first 800 participants over 72 weeks. Compared to placebo, semaglutide increased rates of steatohepatitis resolution without worsening liver fibrosis (63% vs. 34%) and reduced liver fibrosis without worsening of steatohepatitis (37% vs. 23%).[6] Additional safety and efficacy results are anticipated in 2029. As hepatocytes do not express the GLP-1R, the benefits of semaglutide may be secondary to weight loss or indirect reflecting local or systemic actions of semaglutide to improve hepatic metabolism and inflammation (Figure 1B).

Survodutide, a single peptide targeting both the glucagon receptor (GCGR) and the GLP-1R also improved MASH with no worsening of fibrosis in 293 participants with a mean BMI of ∼36 by up to 62% vs. 14%, for survodutide vs. placebo, in a 48-week phase 2 clinical trial.[7] Adverse events noted with survodutide were predominantly gastrointestinal in nature, consistent with the class of GLP-1 medicines. Additionally, treatment with the GIPR-GLP-1R co-agonist tirzepatide reduced body weight (mean starting BMI 36.5) and decreased the extent of steatohepatitis without worsening of fibrosis in a phase 2 clinical trial over 52 weeks.[8] Greater weight loss was associated with a higher incidence of MASH resolution without worsening of fibrosis, but this association with weight loss was less evident for reduction in fibrosis without worsening of MASH.

Osteoarthritis

The STEP 9 trial of 407 participants with a clinical and radiologic diagnosis of moderate knee osteoarthritis who had at least moderate pain and BMI ≥30 reported that semaglutide 2.4 mg weekly over 68 weeks improved the WOMAC pain score (range 0–100, with a higher score indicating more pain) by −41.7 points compared to −27.5 points with placebo (CI 95%; −20.0 to −8.3; $p < 0.001$).[9] Semaglutide reduced weight by 13.7%, compared to 3.2% with placebo, which likely underlies some of the observed benefits.

Obstructive sleep apnea

In 2024, tirzepatide was approved for adults with moderate-to-severe OSA and obesity, based on results of the phase 3 SURMOUNT-OSA clinical trials.[10] Trial 1 included 234 adults not receiving positive airway pressure (PAP) at baseline and trial 2 enrolled 235 adults who were receiving PAP therapy at baseline. Participants in both trials were randomized in a 1:1 ratio to receive the maximum tolerated weekly dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks. At 52 weeks of follow-up, compared to placebo, tirzepatide reduced the primary outcome of the apnea hypopnea index, with −25.3 events per h (CI 95%; −29.3 to −21.2) with tirzepatide and −5.3 events per h with placebo, for an estimated treatment difference vs. placebo of −20.0 events per h in trial 1. In trial 2, the change in AHI at week 52 was −29.3 events per h (CI 95%; −33.2 to −25.4) with tirzepatide vs. −5.5 events per h (CI 95%; −9.9 to −1.2) for placebo, for an estimated treatment difference of −23.8 events per h (CI 95%; −29.6 to −17.9).[10]

Peripheral artery disease (PAD)

The STRIDE trial studied the efficacy of semaglutide 1 mg qw in people with

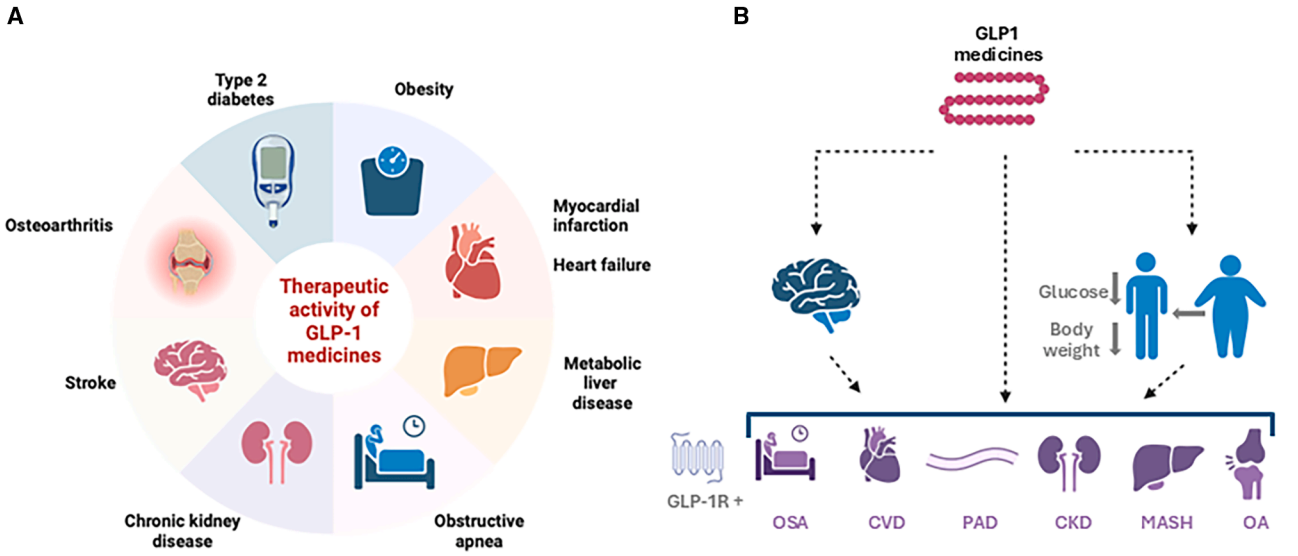

Figure 1. Clinical indications for and mechanisms for GLP-1 medicines

(A) Therapeutic activity of GLP-1 medicines. Clinical benefits for GLP-1 medicines demonstrated in phase 3 randomized controlled trials.

(B) Direct and indirect mechanisms through which GLP-1 medicines reduce disease complications, including reduction of inflammation through inter-organ communication via the brain, direct activation of GLP-1 receptors within multiple organs, and lowering of blood glucosae and body weight.

OSA, obstructive sleep apnea; CVD, cardiovascular disease; PAD, peripheral artery disease; CKD, chronic kidney disease; MASH, metabolic-associated steaohepatitis; OA, osteoarthritis.

PAD, characterized by intermittent claudication and hemodynamic evidence of impaired peripheral limb blood flow, in subjects age 18 years and older with T2D. Maximum walking distance at 52 weeks was significantly greater in trial participants randomized to semaglutide. Notably, semaglutide use was associated with ~4 kg placebo-subtracted weight loss, with a modest correlation between increases in walking distance and the extent of achieved weight loss.[11]

Neuroprotective effects

GLP-1 medicines reduce stroke incidence, as shown in major cardiovascular outcome trials including SELECT, SUSTAIN-6, REWIND, and PIONEER 6. These effects may result from metabolic improvements; direct actions in the central nervous system, including modulation of neuroinflammation; attenutation of platelet aggregation; reduced atherosclerosis; protection of vascular integrity; and reduced oxidative stress. GLP-1 medicines are also associated with a lower risk of all-cause dementia, including Alzheimer's disease (AD), in individuals with T2D.[2] The ongoing EVOKE and EVOKE+ trials are testing the disease-modifying potential of oral semaglutide (14 mg/day) in early symptomatic, biomarker-confirmed AD. Each trial is enrolling 1,840 participants for 156 weeks of treatment. The primary endpoint is change in the CDR Sum of Boxes score at week 104. Results are expected in 2025, with an extension phase continuing into 2026.

Biological pathways affected by GLP-1 medicines

How GLP-1 medicines confer benefits partially independent of weight loss remains incompletely understood. A unifying feature across many of the chronic conditions targeted by GLP-1 medicines, including CVD, CKD, MASLD, osteoarthritis, PAD, and obstructive sleep apnea, is dysregulated inflammation, occurring frequently in the context of insulin resistance and obesity. Insulin resistance itself plays a central role in the pathophysiology of these diseases and is closely linked to chronic low-grade inflammation. Whether the clinical efficacy of GLP-1 medicines in these conditions is primarily mediated by weight loss or by additional mechanisms such as improved insulin sensitivity, restoration of metabolic control and reduced inflammation remains an open question (Figure 1B), since most large clinical trials are not designed to elucidate the underlying molecular mechanism. Furthermore, the results of major outcome trials have not been consistently analyzed according to the degree of weight loss achieved. Notably, a preliminary report from the SELECT trial investigators suggested that the 20% reduction in the primary outcome was not dependent on the extent of weight loss achieved (https://easo.org/semaglutide-4-year-weight-loss-and-cardiovascular-benefits/). GLP-1 medicines consistently reduce biomarkers of inflammation in clinical trials and dampen inflammatory responses in both animal models and humans, partly independent of weight loss.[12] These immunomodulatory effects are reflected by reductions of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), serum amyloid A (SAA), and interleukin-6 (IL-6) and other inflammatory cytokines and markers of oxidative stress. Notably, the semaglutide-regulated circulating proteome reveals modulation of inflammation-linked proteins, partly independent of weight loss.[13]

At least three complementary mechanisms of action contribute to the anti-inflammatory effects of GLP-1 medicines. These include direct effects on GLP-1R + cells within joints, the heart, kidney, liver, and immune cells[14] and indirect actions

through weight reduction and blood glucose control, as well as through inter-organ communication to dampen inflammation via activation of GLP-1R in subsets of central nervous system neurons[15] (Figure 1B). GLP-1 may also improve organ health via targeting endothelial and vascular smooth muscle cells within multiple organs, cell types that control local blood flow as well as local immunomodulatory actions. However, the exact molecular mechanisms linking the clinical actions of GLP-1 medicines to improved health outcomes for a range of expanding outcomes (Figures 1A and 1B) require further investigation.

CONCLUSIONS AND FUTURE DIRECTIONS

The unexpectedly broad benefits of GLP-1 medicines now extend to reduction in rates of heart failure, stroke, myocardial infarction, diabetic kidney disease, metabolic liver disease, osteoarthritis peripheral vascular disease, and obstructive sleep apnea (Table 1; Figure 1). Ongoing trials are exploring the use of GLP-1 medicines in people with substance use disorders, psychiatric disorders, and neurodegenerative disorders.[2] More detailed elucidation of the actions and benefits of GLP-1 medicines that might be partly independent of weight loss and glucose metabolism may provide new therapeutic opportunities to precisely target and further expand the use of GLP-1 therapeutics, perhaps, where weight loss may not be paramount, using lower doses that are less costly and associated with fewer adverse events.

While effective dosing ranges for GLP-1 medicines such as semaglutide and tirzepatide are well established for treatment of T2D and obesity, the dose-response relationships for reduction of inflammation or for conditions such as substance abuse or neurodegenerative disorders like Alzheimer's remain unclear. Notably, in some people with neuropsychiatric conditions, weight loss may not desirable. Hence understanding dose-response relationships for GLP-1 medicines in conditions beyond T2D or obesity, delineation of optimal treatment durations, and identification of key GLP1-regulated circuits that produce weight loss-independent benefit may open up new avenues for use of these medicines, ideally optimizing both efficacy and tolerability.

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DECLARATION OF INTERESTS

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