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Review Article

GLP-1-Based Therapies Beyond Weight Loss: Cardiovascular, Renal and Metabolic Applications

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 agonist tirzepatide were developed for type 2 diabetes and later for chronic weight management. A growing body of randomised evidence now shows organ-level benefits that extend beyond glycaemia and weight.

Objective: To review the cardiovascular, renal and metabolic applications of GLP-1-based therapies, their safety and limitations, emerging agents, and the role of the pharmacist in safe and effective use.

Methods: Narrative review of randomised controlled trials, meta-analyses, guidelines and mechanistic literature.

Findings: Cardiovascular outcome trials in type 2 diabetes and in obesity without diabetes show reductions in major adverse cardiovascular events, with a pooled reduction of about 14% in diabetes. Semaglutide and tirzepatide improve symptoms and outcomes in obesity-related heart failure with preserved ejection fraction. Semaglutide slows kidney disease progression in diabetic kidney disease, and both semaglutide and tirzepatide improve histological outcomes in metabolic dysfunction-associated steatohepatitis; tirzepatide reduces the severity of obstructive sleep apnoea. Gastrointestinal adverse events are the main tolerability issue, and rare events (pancreatitis, gallbladder disease, ocular events) require vigilance. Weight regain after discontinuation, loss of lean mass, access, cost and unregulated compounded products are practical limitations.

Conclusion: GLP-1-based therapies are best viewed as cardio-renal-metabolic medicines. Pharmacists are well placed to support appropriate selection, titration, adverse-effect management, monitoring and adherence.

Keywords: GLP-1 receptor agonists; semaglutide; tirzepatide; cardiovascular outcomes; chronic kidney disease; heart failure; metabolic dysfunction-associated steatohepatitis; obesity; pharmacist

1. Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that enhances glucose-dependent insulin secretion, suppresses glucagon, slows gastric emptying and promotes satiety through central pathways.1,2 Long-acting GLP-1 receptor agonists (GLP-1 RAs) such as liraglutide, dulaglutide and semaglutide, and the dual GIP/GLP-1 agonist tirzepatide, have transformed the management of type 2 diabetes and obesity.[3–5]

Public attention has focused on weight loss, but GLP-1 receptors are expressed in the heart, vasculature, kidney, liver and brain, and dedicated outcome trials now show clinical benefit in several organ systems.[2,6] This reframes these agents from glucose- or weight-lowering drugs to treatments for cardio-renal-metabolic disease, and it has implications for prescribing, guidelines and pharmacy practice. This review summarises the current evidence, safety considerations, emerging advances and the pharmacist's role.

2. Methodology / Literature Search Strategy

This narrative review was prepared by searching PubMed/MEDLINE, Embase and ClinicalTrials.gov for English-language publications [confirm search period, e.g. January 2015 to October 2026] using combinations of the terms "GLP-1 receptor agonist", "semaglutide", "liraglutide", "dulaglutide", "tirzepatide", "cardiovascular outcomes", "heart failure", "chronic kidney disease", "steatohepatitis" and "sleep apnoea". Priority was given to phase 3 randomised controlled trials, cardiovascular and kidney outcome trials, systematic reviews and meta-analyses, and current clinical practice guidelines. Mechanistic and observational studies were included where randomised data were unavailable. Study selection was by consensus and no formal risk-of-bias assessment or meta-analysis was undertaken.

3. Background

3.1 Physiology and pharmacology

Native GLP-1 is secreted by intestinal L-cells and is degraded within minutes by dipeptidyl peptidase-4, which prompted the development of enzyme-resistant, long-acting analogues.[1] Currently used agents differ in structure, half-life and receptor activity: liraglutide (daily), dulaglutide and semaglutide

(weekly subcutaneous; semaglutide also available orally) and tirzepatide (weekly, dual GIP/GLP-1 agonism).[3,5]

3.2 Mechanisms of organ protection

Cardiovascular and renal benefits probably arise from weight loss, lower blood pressure and improved glycaemia and lipids, combined with direct actions including anti-inflammatory and anti-atherosclerotic effects, and natriuresis and haemodynamic effects in the kidney.[6,7] The early separation of event curves in several trials suggests that mechanisms beyond weight loss contribute.[6]

4. Current Evidence

4.1 Atherosclerotic cardiovascular disease

Cardiovascular outcome trials in people with type 2 diabetes showed significant reductions in major adverse cardiovascular events (MACE) with liraglutide, subcutaneous semaglutide, dulaglutide and albiglutide.[8–11] Oral semaglutide also reduced MACE in the SOUL trial.[12] A meta-analysis of randomised trials reported about a 14% reduction in MACE, a 12% reduction in all-cause mortality and a 21% reduction in a composite kidney outcome.[13] In SELECT, weekly semaglutide reduced MACE in adults with overweight or obesity and established cardiovascular disease without diabetes (6.5% vs 8.0%; hazard ratio 0.80), extending the indication beyond diabetes.[14] Key trials are summarised in Table 1 and Figure 1.

4.2 Heart failure

In STEP-HFpEF, semaglutide 2.4 mg produced larger improvements in symptoms and physical function and greater weight loss than placebo in obesity-related heart failure with preserved ejection fraction (HFpEF).[15] The benefit was confirmed in people with type 2 diabetes.[16] In SUMMIT, tirzepatide reduced the composite of cardiovascular death or worsening heart-failure events and improved health status in obesity-related HFpEF.[17]

4.3 Chronic kidney disease

Kidney effects of GLP-1 RAs include reduced albuminuria and slower decline in estimated glomerular filtration rate, supported by renal secondary outcomes from LEADER.[7,18] The dedicated FLOW trial, stopped early for efficacy, showed that semaglutide reduced major kidney disease events, cardiovascular death and MACE in people with type 2 diabetes and chronic kidney disease.[19] A post-hoc analysis of SURPASS-4 suggested slower eGFR decline with tirzepatide than with insulin glargine, but dedicated kidney outcome data for tirzepatide are still awaited.[20]

4.4 Metabolic dysfunction-associated steatohepatitis (MASH)

Phase 2 studies of liraglutide and semaglutide first showed resolution of steatohepatitis.[21,22] In the phase 3 ESSENCE trial, semaglutide improved both steatohepatitis resolution and fibrosis compared with placebo,[23] and in a phase 2 trial tirzepatide produced dose-dependent MASH resolution in participants with fibrosis.[24] Long-term clinical outcomes such as cirrhosis and liver-related events remain to be shown.

4.5 Obstructive sleep apnoea and other metabolic effects

Tirzepatide reduced the apnoea–hypopnoea index and body weight in adults with obesity and moderate-to-severe obstructive sleep apnoea.[25] Weight reductions of roughly 15% with semaglutide 2.4 mg and up to about 21% with tirzepatide 15 mg underpin many of these effects.[26,27] Because obesity management improves glycaemia and may allow de-intensification of other therapy, it has been proposed as a primary treatment goal in type 2 diabetes.[28]

4.6 Neurological applications

Evidence outside cardio-renal-metabolic disease is preliminary. A small randomised trial of lixisenatide in early Parkinson's disease reported less motor progression than placebo over 12 months, but gastrointestinal adverse effects were common and clinical relevance remains unproven.[29]

5. Clinical Applications

Guidelines now recommend GLP-1 RAs or dual agonists with proven benefit for people with type 2 diabetes and established atherosclerotic cardiovascular disease or high risk, and for those with chronic kidney disease, largely independent of baseline HbA1c or background metformin.[30–33] Practical applications include:

- **Type 2 diabetes with ASCVD or high risk:** select an agent with proven cardiovascular benefit (e.g. semaglutide, liraglutide, dulaglutide).[30,32]
- **Type 2 diabetes with CKD:** semaglutide is supported by FLOW, often alongside an SGLT2 inhibitor and renin–angiotensin blockade.[19,31,33]
- **Obesity with established cardiovascular disease:** semaglutide 2.4 mg for secondary prevention, even without diabetes.[14]
- **Obesity-related HFpEF:** semaglutide or tirzepatide to improve symptoms and reduce events.[15,17]
- **MASH with fibrosis and obstructive sleep apnoea:** consider according to local labelling and specialist input.[23–25]

Treatment should start at the lowest dose with stepwise titration to limit gastrointestinal effects, and doses of insulin or sulfonylureas often need reduction to avoid hypoglycaemia.[30,34] Regulatory approvals and reimbursement criteria differ between countries and should be checked locally.

6. Safety & Limitations

6.1 Safety

- **Gastrointestinal:** nausea, vomiting, diarrhoea and constipation are most frequent, usually during dose

escalation; gradual titration, smaller meals and avoiding high-fat foods help.[34] A large cohort study in people using these agents for weight loss reported higher risks of pancreatitis, gastroparesis and bowel obstruction than with an alternative weight-loss drug, although observational data cannot prove causation.[35]

- **Diabetic retinopathy:** SUSTAIN-6 showed more retinopathy complications with semaglutide, which appeared linked to rapid HbA1c reduction in people with pre-existing retinopathy; screening is advised.[9,36]
- **Ocular:** an association with non-arteritic anterior ischaemic optic neuropathy has been reported in observational data and is under continuing evaluation.[37]
- **Thyroid:** these agents are contraindicated in personal or family history of medullary thyroid carcinoma or MEN2 based on rodent C-cell findings; a large cohort study found no overall increase in thyroid cancer but a possible rise with longer use.[38]
- **Other:** gallbladder disease, dehydration-related acute kidney injury and hypoglycaemia in combination therapy are described in product labelling; use in pregnancy is not recommended.

6.2 Limitations

- **Weight regain:** much of the weight and cardiometabolic benefit is lost after withdrawal, implying long-term treatment.[39]
- **Body composition:** a proportion of weight lost is lean mass, and mitigation strategies (resistance exercise, adequate protein) need prospective testing.[40]
- **Evidence gaps:** many outcome trials enrolled select populations; cardiovascular outcome data for tirzepatide are still emerging.[5,13]
- **Access and quality:** cost, supply shortages and unapproved compounded products create safety concerns, including dosing errors.[41]

7. Emerging Advances

Oral small-molecule GLP-1 agonists such as orforglipron may expand access by avoiding injections and cold-chain storage.[42] Triple agonists targeting GLP-1, GIP and glucagon receptors, such as retatrutide, achieved substantial weight loss in phase 2.[43] Ongoing outcome trials will clarify cardiovascular, renal and hepatic benefits of tirzepatide and next-generation agents, and combination approaches with amylin analogues and SGLT2 inhibitors are under investigation.

8. Pharmacist's Role

Pharmacists can contribute across the care pathway:

- **Appropriate selection:** screen for contraindications (medullary thyroid carcinoma, MEN2, pregnancy), pancreatitis history and retinopathy, and match the agent to evidence-based indications.[30,31]
- **Titration and tolerability:** counsel on dose escalation, missed doses, meal size, hydration and when to seek help for severe abdominal pain or persistent vomiting.[34]
- **Medication review:** adjust insulin and sulfonylureas, and consider delayed gastric emptying on absorption of oral medicines, narrow-therapeutic-index drugs and oral contraceptives (tirzepatide), per labelling.
- **Monitoring:** HbA1c, weight, blood pressure, renal function and retinal screening; support adherence, because discontinuation leads to weight regain.[31,39]
- **Medication safety:** teach injection technique and storage; warn against unregulated or compounded products and verify supply sources.[41]
- **Lifestyle and body composition:** reinforce nutrition, protein intake and resistance activity.[40]

9. Research Gaps

- Long-term cardiovascular, kidney and hepatic outcomes for tirzepatide and newer agents.[20,24]
- Outcomes after discontinuation, optimal maintenance dosing and de-escalation strategies.[39]
- Effects on lean mass, bone and function, particularly in older adults.[40]
- Causality and absolute risk of rare adverse events (NAION, pancreatitis, thyroid cancer).[35,37,38]
- Efficacy in under-represented groups and real-world cost-effectiveness, including pharmacist-led care models.
- Benefit in neurological and psychiatric conditions, currently investigational.[29]

10. Future Perspectives

GLP-1-based therapies are likely to become foundational pillars of cardio-renal-metabolic care, used alongside statins, SGLT2 inhibitors and renin–angiotensin blockade. Future practice will depend on oral and less frequent formulations, multi-receptor agonists and risk-stratified selection tools, together with reimbursement frameworks that reflect long-term, organ-protective benefit.[4,42,43] Pharmacists will increasingly act as medication-safety leaders, adherence supporters and educators in this expanding field.

11. Conclusion

Evidence from large randomised trials supports GLP-1-based therapies as treatments that reduce cardiovascular events, improve outcomes in obesity-related HFpEF, slow kidney disease progression and improve liver and sleep-related outcomes, in addition to lowering weight and glucose.[13,14,19,23,25] Gastrointestinal tolerability, rare safety signals, lean-mass loss, weight regain on withdrawal and access remain important

limitations. Pharmacist-supported, guideline-concordant use offers the best route to maximising benefit and minimising harm.

Tables and Figures

Table 1. Major cardiovascular outcome trials of GLP-1 receptor agonists.

Trial (agent)	Population	Primary outcome	Result (HR, 95% CI)
LEADER (liraglutide)[8]	T2D, high CV risk	3-point MACE	0.87 (0.78–0.97)
SUSTAIN-6 (semaglutide s.c.)[9]	T2D, high CV risk	3-point MACE	0.74 (0.58–0.95)
REWIND (dulaglutide)[10]	T2D, ± CVD	3-point MACE	0.88 (0.79–0.99)
Harmony Outcomes (albiglutide)[11]	T2D with CVD	3-point MACE	0.78 (0.68–0.90)
SOUL (oral semaglutide)[12]	T2D with CVD and/or CKD	3-point MACE	0.86 (0.77–0.96)
SELECT (semaglutide 2.4 mg)[14]	Overweight/obesity with CVD, no diabetes	4-point MACE	0.80 (0.72–0.90)
Meta-analysis of T2D trials[13]	T2D	MACE	0.86 (0.80–0.93)

CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.

Table 2. Key evidence for heart-failure, kidney, hepatic, sleep and weight outcomes.

Domain / trial	Agent	Population	Main finding
Heart failure: STEP-HFpEF[15]	Semaglutide 2.4 mg	HFpEF, BMI ≥30	Greater improvement in symptoms/function and weight loss vs placebo
Heart failure: SUMMIT[17]	Tirzepatide	HFpEF, obesity	Lower risk of CV death or worsening HF (HR 0.62)
Kidney: FLOW[19]	Semaglutide 1.0 mg	T2D with CKD	24% lower risk of major kidney disease events (HR 0.76)
Liver: ESSENCE[23]	Semaglutide 2.4 mg	MASH, stage F2–F3	Higher MASH resolution and fibrosis improvement vs placebo
Liver: SYNERGY-NASH[24]	Tirzepatide	MASH, F2–F3 (phase 2)	Dose-dependent MASH resolution vs placebo
Sleep: SURMOUNT-OSA[25]	Tirzepatide	OSA with obesity	Significant reduction in apnoea–hypopnoea index
Weight: STEP 1 / SURMOUNT-1[26,27]	Semaglutide / tirzepatide	Obesity, no diabetes	Mean weight loss ≈15% (semaglutide 2.4 mg) and up to ≈21% (tirzepatide 15 mg)

CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; MASH, metabolic dysfunction-associated steatohepatitis; OSA, obstructive sleep apnoea.

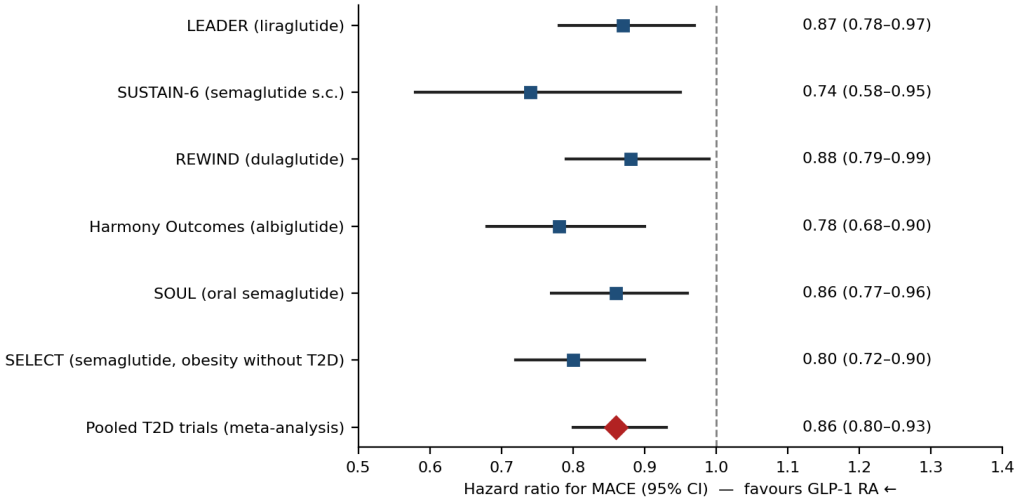


Figure 1. Hazard ratios for major adverse cardiovascular events (MACE) in GLP-1 receptor agonist outcome trials. Values as reported in the original publications.[8–1]

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