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REVIEW ARTICLE

# Cardiovascular effects of GLP-1 receptor agonists: atherosclerotic outcomes, obesity, HFpEF, and kidney disease – a narrative review

**Marcel Gisal[1,A-D], Julia Koźlak[1,A,C-D] ✉, Magdalena Sokół[1,B-C], Katarzyna Wróblewska[2,B-C], Filip Leszczyński[2,B-C], Lidia Stopyra[3,E-F]**

[1] *Student Scientific Circle at the Department of Infectious and Tropical Diseases, Andrzej Frycz Modrzewski University, Krakow, Poland*
[2] *Medical College, Andrzej Frycz Modrzewski University, Krakow, Poland*
[3] *Department of Infectious and Tropical Diseases, Andrzej Frycz Modrzewski Krakow University, Medical College, Krakow, Poland*
*A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article*

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## Abstract

**Introduction and Objective.** Cardiovascular disease (CVD) is a major cause of morbidity and mortality, especially in type 2 diabetes mellitus (T2DM). Selected glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide cardiovascular benefit beyond glucose lowering. The aim of the review is to summarize compound-specific cardiovascular evidence and data in obesity, heart failure with preserved ejection fraction (HFpEF), and chronic kidney disease (CKD).

**Review Methods.** A narrative review used PubMed, Scopus, and supplementary Google Scholar searches from database inception to 6 August 2026, with reference to SANRA. Landmark cardiovascular outcome trials (CVOTs), randomized trials, meta-analyses, guidelines, and selected mechanistic studies were included. Thirty-two publications were analyzed.

**Brief description of the state of knowledge.** CVOTs show heterogeneous results across GLP-1RAs, ranging from cardiovascular safety to reductions in major adverse cardiovascular events (MACE). SELECT demonstrated secondary-prevention benefit with semaglutide 2.4 mg in adults with overweight or obesity, without diabetes, but with established cardiovascular disease. In obesity-related HFpEF, semaglutide improved symptoms, physical function, and body weight, while effects on mortality and heart-failure hospitalization remain uncertain. Kidney benefits are supported by pooled analyses and FLOW. Gastrointestinal and biliary adverse effects remain relevant safety considerations.

**Summary.** GLP-1RAs reduce cardiovascular risk in selected patients with T2DM, but effects are not uniform across the class. Evidence beyond T2DM remains compound- and population-specific, and further studies should clarify long-term safety, hard heart-failure outcomes, comparative effectiveness, and optimal patient selection.

## Key words

glucagon-like peptide-1 receptor agonists, cardiovascular diseases, diabetes mellitus

## INTRODUCTION AND OBJECTIVE

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide, particularly among patients with type 2 diabetes mellitus (T2DM). In this population, the risk of major cardiovascular events, including myocardial infarction, stroke, and heart failure, is markedly increased compared with the general population. This elevated risk is further amplified by the frequent coexistence of obesity, hypertension, dyslipidaemia, and chronic low-grade inflammation, all of which contribute to accelerated atherosclerosis and progression of cardiometabolic disease [1, 2].

In recent years, the pharmacological management of T2DM has increasingly incorporated cardiovascular risk reduction alongside glycaemic control. Consequently, greater attention has been directed toward glucose-lowering therapies with demonstrated cardiovascular effects, including selected glucagon-like peptide-1 receptor agonists (GLP-1RAs) [1, 2]. GLP-1RAs were initially developed to improve glycemic control by enhancing glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying. However, subsequent studies have demonstrated that these agents exert a range of pleiotropic effects, including significant body weight reduction, blood pressure lowering, and improvement in lipid profiles. These effects contribute to changes in the overall metabolic profile and may contribute to cardiovascular risk reduction [3, 4]. Evidence from large randomized cardiovascular outcome trials (CVOTs) and subsequent meta-analyses has confirmed that selected GLP-1RAs significantly reduce the risk of major adverse cardiovascular events (MACE), particularly in patients with T2DM and high cardiovascular risk [5]. More recent trials have extended the evidence to selected populations with obesity and obesity-related heart failure with preserved ejection fraction (HFpEF) [6–9], while dedicated and pooled analyses have strengthened the evidence for kidney protection in T2DM and chronic kidney disease (CKD) [10,11].

Beyond clinical outcomes, growing experimental and translational evidence suggests that the cardioprotective effects of GLP-1RAs may involve multiple biological

Address for correspondence: ✉ Julia Koźlak, Student Scientific Circle at the Department of Infectious and Tropical Diseases, Andrzej Frycz Modrzewski Krakow University, 30-705 Krakow, Poland
E-mail: juliak594@interia.eu

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pathways. These include improvement of endothelial function, attenuation of inflammatory processes, reduction of oxidative stress, and modulation of atherosclerotic plaque development, highlighting their complex and multifactorial mechanism of action [13–15].

Given the rapidly expanding body of evidence and the evolving concept of cardiometabolic medicine, a comprehensive and up-to-date synthesis of available data is warranted. Therefore, the aim of this review is to present current evidence on the effects of GLP-1RAs on the cardiovascular system, with particular emphasis on underlying biological mechanisms, clinical trial findings, and emerging cardiometabolic applications.

Unlike reviews focusing primarily on pooled class-level cardiovascular effects, this narrative review integrates compound-specific CVOT findings with the strength of mechanistic evidence and critically distinguishes established cardiovascular outcomes from emerging, population-specific evidence in obesity, HFpEF, and CKD.

## REVIEW METHODS

A narrative literature review was conducted to summarize and critically evaluate the evidence on the cardiovascular effects of GLP-1RAs. The review was prepared with reference to the Scale for the Assessment of Narrative Review Articles (SANRA) [12]. PubMed and Scopus were searched, and Google Scholar was used as a supplementary source to identify additional relevant publications and clinical guidelines. PubMed and Scopus were searched from database inception to 6 August 2026. The complete PubMed search strategy was as follows: ('Glucagon-Like Peptide-1 Receptor Agonists' [Mesh] OR 'GLP-1 receptor agonist' [Title/Abstract] OR 'GLP-1 receptor agonists' [Title/Abstract] OR GLP-1RA [Title/Abstract] OR GLP-1RAs [Title/Abstract] OR liraglutide [Title/Abstract] OR semaglutide [Title/Abstract] OR dulaglutide [Title/Abstract] OR exenatide [Title/Abstract] OR lixisenatide [Title/Abstract] OR albiglutide [Title/Abstract] OR efpeglenatide [Title/Abstract]) AND ('Cardiovascular Diseases'[Mesh] OR 'cardiovascular outcome' [Title/Abstract] OR 'cardiovascular outcomes' [Title/Abstract] OR 'major adverse cardiovascular event' [Title/Abstract] OR 'major adverse cardiovascular events' [Title/Abstract] OR MACE [Title/Abstract] OR atherosclerosis [Title/Abstract] OR stroke [Title/Abstract] OR 'myocardial infarction' [Title/Abstract] OR 'cardiovascular mortality' [Title/Abstract] OR 'cardiovascular death' [Title/Abstract] OR 'heart failure' [Title/Abstract] OR HFpEF [Title/Abstract] OR obesity [Title/Abstract] OR 'chronic kidney disease' [Title/Abstract] OR 'renal outcome' [Title/Abstract] OR 'kidney outcome' [Title/Abstract] OR inflammation [Title/Abstract] OR 'endothelial function' [Title/Abstract] OR 'oxidative stress' [Title/Abstract].

No lower publication-date restriction was applied to pivotal cardiovascular outcome trials, as earlier landmark studies were necessary to describe the chronological development of evidence and distinguish cardiovascular superiority from cardiovascular safety. For mechanistic studies, meta-analyses, clinical guidelines, and emerging applications, priority was given to publications from 2018 onward, while earlier studies were included when clinically or historically relevant.

Eligible publications included randomized cardiovascular outcome trials, other relevant randomized clinical trials, systematic reviews, meta-analyses, clinical guidelines, and selected mechanistic or translational studies. Full-text English-language articles directly related to cardiovascular, cardiorenal, metabolic, or functional outcomes of GLP-1RAs were included. Conference abstracts, case reports, duplicate publications, and studies not directly related to the review objective were excluded. In total, 32 publications were included in the final narrative synthesis.

## DESCRIPTION OF THE STATE OF KNOWLEDGE

**Mechanisms of cardiovascular protection.** GLP-1RAs exert beneficial effects on the cardiovascular system through complex and multifactorial biological mechanisms. Although their therapeutic role was initially associated with glycemic control in patients with T2DM, accumulating experimental and clinical evidence indicates that their cardioprotective effects extend beyond glucose lowering and may involve direct actions on the vascular wall, inflammatory pathways, and metabolic factors associated with cardiovascular risk [13, 16, 17].

Importantly, the evidence supporting these proposed mechanisms varies in strength and origin. Some effects have been documented in clinical studies in humans, whereas others are derived primarily from translational research, *in vitro* experiments, or animal models, and their contribution to cardiovascular risk reduction in clinical practice remains uncertain.

The proposed mechanisms include improvement of endothelial function, anti-inflammatory activity, reduction of oxidative stress, inhibition of atherosclerosis progression, and favourable modulation of metabolic and haemodynamic parameters [13, 14, 18]. The vascular endothelium plays a central role in maintaining cardiovascular homeostasis by regulating vascular tone, inflammatory responses, platelet aggregation, and antithrombotic functions. Endothelial dysfunction represents one of the earliest stages of atherosclerosis and is a key contributor to CVD in patients with T2DM [13, 14, 18].

*In vitro* studies and animal models suggest that GLP-1RAs may directly influence endothelial cells via activation of GLP-1 receptors (GLP-1Rs) expressed in vascular tissues. These experimental effects may include increased bioavailability of nitric oxide (NO), a critical mediator of vasodilation and vascular protection against pro-inflammatory and prothrombotic processes [15]. In preclinical studies, GLP-1RAs have been shown to reduce the production of reactive oxygen species, attenuate oxidative stress, and decrease the expression of adhesion molecules and leukocyte adhesion to the endothelium, thereby potentially inhibiting early stages of atherogenesis [14, 18]. However, the extent to which these direct vascular effects contribute to cardiovascular event reduction in humans has not been fully established.

Anti-inflammatory effects of GLP-1RAs have been observed in experimental studies and are supported by translational and clinical findings, although the type and strength of evidence differ between individual pathways. Chronic low-grade inflammation plays a pivotal role in the pathogenesis of atherosclerosis and cardiovascular complications in patients with T2DM and obesity [13, 14].

Experimental and translational studies suggest that GLP-1RAs may reduce the expression or circulating concentrations of pro-inflammatory mediators, including interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), and modulate signalling pathways involved in inflammatory responses [13, 14]. Reductions in circulating inflammatory markers have been observed in human studies, whereas effects on macrophage infiltration and immune-cell function have been demonstrated predominantly in preclinical models. These experimental findings suggest that GLP-1RAs may promote a more stable vascular environment and limit the progression of atherosclerotic lesions.

Emerging evidence also indicates that GLP-1RAs may affect multiple stages of the atherosclerotic process. Experimental studies have demonstrated reduced lipid accumulation in macrophages, decreased formation of foam cells, and modulation of vascular smooth muscle cell proliferation. In addition, GLP-1RAs may contribute to plaque stabilization through attenuation of inflammatory activity and reduced activity of proteolytic enzymes involved in extracellular matrix degradation, thereby potentially lowering the risk of plaque rupture and acute cardiovascular events [13, 14]. However, direct clinical evidence demonstrating that these plaque-related effects mediate reductions in cardiovascular events in humans remains limited.

The cardioprotective effects of GLP-1RAs are also closely linked to their impact on metabolic and haemodynamic parameters. These agents improve glycaemic control through glucose-dependent insulin secretion and suppression of glucagon release [16]. Importantly, their use is associated with significant body weight reduction, which is particularly relevant in patients with obesity and T2DM. Weight loss contributes to improved insulin sensitivity, reduced systemic inflammation, and lower blood pressure [4]. Clinical studies have also demonstrated beneficial effects of GLP-1RAs on lipid profiles and modest reductions in systolic blood pressure, further contributing to overall cardiovascular risk reduction [4].

In recent years, increasing attention has been directed toward the cardiorenal metabolic axis. CKD and T2DM are closely interconnected with CVD, and declining renal function further amplifies cardiometabolic risk [19]. Meta-analyses and clinical studies suggest that GLP-1RAs may exert renoprotective effects, including reduction in the progression of albuminuria and slowing of renal function decline in patients with T2DM [5,19]. These effects may be mediated through improved metabolic control, changes in inflammatory pathways, and modulation of renal haemodynamics; however, the relative contribution of these mechanisms remains uncertain.

Overall, clinically documented effects such as weight reduction, improved glycaemic control, modest blood-pressure lowering, and changes in selected renal and inflammatory markers, coexist with several proposed direct vascular and cellular mechanisms. However, many of the latter remain supported mainly by preclinical or translational evidence, and their independent contribution to cardiovascular outcome reduction in humans remains uncertain [16, 17, 20].

**Evidence from cardiovascular outcome trials.** Large randomized cardiovascular outcome trials (CVOTs) have substantially expanded the evidence regarding the cardiovascular safety and efficacy of individual GLP-1RAs in patients with T2DM. Most trials evaluated a three-point MACE endpoint comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. However, endpoint definitions were not entirely uniform; notably, ELIXA used a four-point composite that additionally included hospitalization for unstable angina. The results of these trials ranged from confirmation of cardiovascular safety without significant cardiovascular benefit to demonstration of superiority for MACE. Therefore, the cardiovascular findings should be interpreted at the level of individual compounds and studies rather than assumed to be uniform across the entire GLP-1RA class [21–29].

The chronological development of evidence began with ELIXA, which evaluated lixisenatide in 6,068 patients with T2DM following a recent acute coronary syndrome. Lixisenatide was non-inferior to placebo for the primary four-point cardiovascular endpoint but did not demonstrate superiority (hazard ratio (HR) 1.02; 95% confidence interval (CI) 0.89–1.17), thereby confirming cardiovascular safety without demonstrating a significant reduction in the primary cardiovascular endpoint [21]. In contrast, the LEADER trial subsequently demonstrated that liraglutide significantly reduced three-point MACE in patients with T2DM at high cardiovascular risk (HR 0.87; 95% CI 0.78–0.97). This benefit was accompanied by significant reductions in cardiovascular death (HR 0.78; 95% CI 0.66–0.93) and all-cause mortality, whereas the reductions in non-fatal myocardial infarction and non-fatal stroke were not individually statistically significant [22].

SUSTAIN-6 provided evidence for subcutaneous semaglutide in patients with T2DM at high cardiovascular risk. The primary MACE endpoint occurred less frequently with semaglutide than with placebo (HR 0.74; 95% CI 0.58–0.95), with a significant reduction in non-fatal stroke (HR 0.61; 95% CI 0.38–0.99), while cardiovascular mortality was similar between the study groups [23]. However, SUSTAIN-6 was primarily designed as a pre-approval cardiovascular safety trial to establish non-inferiority rather than as a trial prospectively powered and pre-specified to demonstrate superiority. Its favourable efficacy findings should therefore be interpreted in the context of its statistical design, relatively short follow-up, and limited number of cardiovascular events. The subsequent EXSCEL trial confirmed the cardiovascular safety of once-weekly exenatide but did not demonstrate superiority for MACE (HR 0.91; 95% CI 0.83–1.00; p=0.06 for superiority) [24].

Further evidence of cardiovascular superiority was provided by Harmony Outcomes, in which albiglutide reduced three-point MACE among patients with T2DM and established CVD (HR 0.78; 95% CI 0.68–0.90) [25]. In this trial, the benefit was particularly apparent for myocardial infarction, illustrating that myocardial infarction may contribute importantly to the cardiovascular effect of an individual GLP-1RA. In REWIND, dulaglutide reduced MACE in a broader population of patients with T2DM, of whom approximately 31% had established CVD at baseline (HR 0.88; 95% CI 0.79–0.99) [26]. The most apparent component-specific benefit was observed for stroke. The long follow-up and inclusion of a large proportion of participants without established CVD distinguished REWIND from earlier CVOTs, although the study population remained at elevated cardiovascular risk and should not be considered a general low-risk primary-prevention population.

PIONEER 6 subsequently confirmed the cardiovascular safety of oral semaglutide but did not demonstrate superiority for MACE (HR 0.79; 95% CI 0.57–1.11) [27]. Although cardiovascular death was less frequent in the semaglutide group, the short follow-up, small number of events, and wide confidence intervals limited conclusions regarding cardiovascular efficacy. In AMPLITUDE-O, efpeglenatide significantly reduced MACE in patients with T2DM and established CVD or CKD accompanied by at least one additional cardiovascular risk factor (HR 0.73; 95% CI 0.58–0.92), demonstrating cardiovascular superiority despite being structurally based on exendin-4 [28]. More recently, the SOUL trial provided evidence of cardiovascular efficacy for oral semaglutide in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD), CKD, or both. Oral semaglutide significantly reduced three-point MACE compared with placebo (HR 0.86; 95% CI 0.77–0.96), thereby demonstrating superiority in a formal event-driven trial [29].

The relative contribution of individual MACE components varied across compounds and studies. Cardiovascular mortality contributed prominently to the benefit observed with liraglutide in LEADER, non-fatal stroke was significantly reduced with subcutaneous semaglutide in SUSTAIN-6, stroke reduction was particularly apparent with dulaglutide in REWIND, and myocardial infarction contributed importantly to the effect observed with albiglutide in Harmony Outcomes. By contrast, ELIXA and EXSCEL did not demonstrate significant reductions in the composite cardiovascular outcome. Consequently, the cardiovascular benefits observed across the GLP-1RA trial programme cannot be characterized uniformly as being driven primarily by stroke and cardiovascular mortality [21–26].

A clear distinction should therefore be maintained between compounds with demonstrated cardiovascular superiority and those for which only cardiovascular safety has been established. Liraglutide, albiglutide, dulaglutide, efpeglenatide, and oral semaglutide in SOUL demonstrated superiority for MACE. Lixisenatide, once-weekly exenatide, and oral semaglutide in PIONEER 6 confirmed cardiovascular safety without demonstrating superiority. Subcutaneous semaglutide was associated with a statistically significant reduction in MACE in SUSTAIN-6; however, this finding should be interpreted in the context of a trial primarily designed and powered to establish non-inferiority [21–29].

These differences do not necessarily establish that one GLP-1RA is superior to another, because the trials were not designed as head-to-head comparisons. They differed substantially in cardiovascular risk profiles, prevalence of established CVD and chronic kidney disease, endpoint definitions, duration of follow-up, statistical power, treatment discontinuation, and background therapy. Meta-analytic findings may support an overall cardiovascular benefit associated with GLP-1RA therapy, but they should not be interpreted as evidence that all individual compounds provide identical reductions in MACE or its components. Accordingly, the term 'class effect' should be used cautiously, with recognition of clinically relevant heterogeneity among individual agents and trial populations.

**Evidence from meta-analyses.** Meta-analyses of randomized cardiovascular outcome trials provide more precise estimates of the overall cardiovascular and kidney effects associated with GLP-1RA therapy. Nevertheless, pooled estimates should be interpreted cautiously because the included trials differed in the investigated compounds, baseline cardiovascular and kidney risk, prevalence of established CVD, duration of follow-up, endpoint definitions, statistical design, and background therapy [5,30].

Across major meta-analyses, GLP-1RA therapy has been associated with an approximately 13–14% relative reduction in three-point MACE compared with placebo [5, 10, 30]. Pooled reductions have also been reported for cardiovascular death, nonfatal stroke, and all-cause mortality, whereas the effect on nonfatal myocardial infarction has generally been smaller or less consistent [5,30]. However, class-level estimates should not be interpreted as indicating that cardiovascular benefit is uniformly driven by the same MACE component or that all individual agents have equivalent cardiovascular efficacy. The contribution of cardiovascular death, myocardial infarction, and stroke varies according to the drugs, trials, and populations included in each analysis.

The interpretation of an overall class effect is further limited by pharmacological and clinical heterogeneity among individual GLP-1RAs. These agents differ in molecular structure, duration of action, route of administration, effects on body weight, and the strength of cardiovascular and kidney evidence available for each compound. Meta-analyses have not consistently demonstrated statistically significant differences between structural subgroups, such as human GLP-1 analogues and exendin-4–based agents; however, the absence of a subgroup interaction does not establish equivalent efficacy of all individual drugs [5]. In addition, between-trial variability may partly reflect differences in age, body mass index, kidney function, baseline cardiovascular risk, treatment discontinuation, and duration of follow-up [31]. Because adequately powered head-to-head cardiovascular outcome trials are lacking, indirect comparisons cannot determine whether one GLP-1RA is superior to another.

Subgroup analyses have generally shown cardiovascular benefit both in participants with established CVD and in those enrolled on the basis of cardiovascular risk factors alone [5]. Formal interaction analyses have not consistently demonstrated a significant difference in relative treatment effect between these groups. Nevertheless, participants without established CVD in cardiovascular outcome trials frequently had multiple risk factors and should not be considered representative of a low-risk primary-prevention population. Moreover, because event rates are higher among patients with established CVD, a comparable relative risk reduction may translate into a greater absolute clinical benefit in secondary-prevention populations.

Meta-analyses have also reported modest reductions in hospitalization for heart failure, although this effect has generally been less pronounced than the reduction in atherosclerotic cardiovascular events [5, 32]. These pooled findings should not be interpreted as evidence of a uniform therapeutic effect in established heart failure, particularly because most cardiovascular outcome trials were not primarily designed to assess heart-failure treatment and included heterogeneous or incompletely characterized heart-failure populations. This cardiovascular profile differs from that of sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have demonstrated more pronounced effects on heart-failure hospitalization; however, comparisons between the two classes are predominantly indirect and should therefore be interpreted cautiously [32].

Evidence regarding kidney outcomes has become more clinically relevant with the inclusion of trials reporting harder kidney endpoints. Earlier meta-analyses of cardiovascular outcome trials suggested that reductions in broad kidney composites were driven largely by a lower incidence or progression of macroalbuminuria [5,19]. In a recent meta-analysis of 11 randomized trials involving 85,373 participants, GLP-1RA therapy reduced the risk of a composite kidney outcome comprising kidney failure, sustained worsening of kidney function, or death from kidney disease by 18% among participants with T2DM. The same analysis found reductions in kidney failure, MACE, and all-cause mortality [10]. Nevertheless, the strength of kidney evidence is not identical across individual agents. Most earlier trials evaluated kidney outcomes as secondary or exploratory endpoints, whereas FLOW was specifically designed to assess clinically important kidney outcomes with semaglutide in patients with T2DM and CKD [11]. Differences in endpoint definitions, baseline estimated glomerular filtration rate (eGFR) and albuminuria, follow-up duration, and the availability of dedicated kidney outcome trials should therefore be considered when interpreting pooled estimates.

Overall, meta-analytic evidence supports a moderate reduction in MACE and all-cause mortality with GLP-1RA therapy, together with a reduction in clinically relevant kidney outcomes [5,10]. However, these pooled estimates represent an average effect across heterogeneous drugs, populations, and trial designs. They should not be interpreted as evidence of identical cardiovascular or kidney efficacy for every GLP-1RA, and treatment selection should remain informed by the evidence available for the individual compound and the patient's predominant cardiovascular, metabolic, and kidney risk profile.

**Cardiovascular evidence beyond type 2 diabetes.** Research on GLP-1RAs has expanded beyond glucose-lowering treatment in T2DM, particularly toward the management of obesity and obesity-related cardiovascular conditions. However, evidence obtained with a specific drug, dose, and clinical population should not automatically be extrapolated to the entire pharmacological class or to individuals with different cardiovascular risk profiles. The principal areas of clinical investigation beyond glucose-lowering therapy in T2DM, together with the corresponding evidence and its limitations, are summarized in Table 1.

Obesity is associated with an increased risk of ASCVD and heart failure and is accompanied by multiple metabolic and haemodynamic abnormalities. GLP-1RAs approved for weight management can produce substantial weight loss and improve selected cardiometabolic risk factors, including blood pressure, glycaemic measures, and lipid parameters [3, 4]. Nevertheless, improvements in body weight or surrogate cardiometabolic markers should not by themselves be interpreted as evidence of reduced cardiovascular morbidity or mortality. Such conclusions require trials specifically designed to evaluate clinical cardiovascular events.

The SELECT trial provided direct cardiovascular outcome evidence in individuals without diabetes. The trial included 17,604 adults aged 45 years or older with a body mass index (BMI) of at least 27 kg/m$^2$ and pre-existing CVD who were randomly assigned to once-weekly subcutaneous semaglutide 2.4 mg or placebo. During a mean follow-up of 39.8 months, three-point MACE occurred in 6.5% of participants receiving semaglutide and 8.0% receiving placebo (HR 0.80; 95% CI 0.72–0.90). These findings demonstrate cardiovascular benefit with semaglutide in patients with overweight or obesity who did not have diabetes but already had established CVD [6]. They should therefore be interpreted as evidence relevant to secondary cardiovascular prevention and should not be extrapolated to a general population with obesity but without pre-existing CVD. Moreover, the result was established for semaglutide 2.4 mg and does not demonstrate an equivalent effect for every GLP-1RA. Permanent discontinuation due to adverse events was also more frequent with semaglutide than with placebo, emphasizing the need to consider tolerability alongside cardiovascular benefit [6].

Semaglutide has also been evaluated in the obesity-related HFpEF phenotype. In the Semaglutide Treatment Effect in People with Obesity and HFpEF (STEP-HFpEF) trial, which included patients with HFpEF and obesity but without diabetes, semaglutide 2.4 mg produced greater improvement than placebo in the Kansas City Cardiomyopathy Questionnaire clinical summary score, greater weight reduction, and an increase in six-minute walk distance after 52 weeks [7]. Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus (STEP-HFpEF DM) demonstrated directionally consistent improvements in patients with obesity-related HFpEF and T2DM, although the magnitude of weight reduction was smaller than in the trial excluding diabetes [8]. These studies support improvements in heart-failure-related symptoms, physical limitations, exercise capacity, and body weight in the populations studied.

These patient-reported and functional outcomes should be distinguished from hard cardiovascular endpoints. Neither STEP-HFpEF nor STEP-HFpEF DM was primarily designed or powered to demonstrate reductions in cardiovascular mortality or heart failure hospitalization. A pooled analysis reported fewer adjudicated heart failure events with semaglutide; however, the total number of events was limited, and the finding should be considered supportive rather than definitive evidence of reduced mortality or hospitalization risk [9]. Larger and longer event-driven trials are required to establish whether the observed symptomatic and functional improvements translate into consistent reductions in major heart failure outcomes.

Overall, current evidence beyond T2DM is clinically relevant but remains indication-, compound-, and population-specific. SELECT supports cardiovascular risk reduction with semaglutide 2.4 mg in individuals with overweight or obesity, without diabetes, and with established CVD. The STEP-HFpEF programme supports symptomatic, functional, and weight-related benefits in patients with obesity-related HFpEF, both with and without T2DM, but does not yet provide definitive evidence of reduced cardiovascular mortality. These distinctions are important to avoid treating improvements in surrogate, functional, and health-status measures as equivalent to reductions in major cardiovascular events.

**Safety and tolerability.** The cardiovascular and metabolic benefits of GLP-1RAs should be considered together with their tolerability and potential adverse effects. Gastrointestinal symptoms, particularly nausea, vomiting, diarrhea, constipation, and abdominal discomfort, are the

**Table 1.** Clinical evidence for GLP-1RAs in selected cardiometabolic conditions beyond glucose-lowering treatment in T2DM

| Clinical condition and population | Main findings | Clinical interpretation | References |
|---|---|---|---|
| Obesity or overweight | Clinically relevant weight loss and improvement in selected cardiometabolic risk factors. | Improvements in body weight and surrogate risk markers do not by themselves demonstrate reduced cardiovascular events. | [3,4] |
| Overweight or obesity without diabetes, with established CVD | In SELECT, semaglutide 2.4 mg reduced three-point MACE compared with placebo. | Evidence applies to secondary prevention in the population studied and should not be extrapolated to primary prevention or the entire GLP-1RA class. | [6] |
| Obesity-related HFpEF, with or without T2DM | Semaglutide improved symptoms, physical limitations, six-minute walk distance, and body weight. | These trials support symptomatic and functional benefits but do not provide definitive evidence of reduced cardiovascular mortality or HF hospitalization. | [7–9] |
| T2DM and CKD | Reductions in albuminuria progression and clinically relevant composite kidney outcomes. | The strength of evidence differs among agents; dedicated kidney outcome evidence is currently strongest for semaglutide. | [10,11] |

Abbreviations: CVD, cardiovascular disease; CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular events; T2DM, type 2 diabetes mellitus.

most frequently reported treatment-related events. They are usually mild to moderate and occur most commonly during treatment initiation or dose escalation, but they may lead to treatment discontinuation, especially at higher doses used for weight management [3, 6].

Gallbladder and biliary disorders, including cholelithiasis and cholecystitis, have been reported more frequently with GLP-1RAs than with control treatment, although the absolute risk remains relatively low. Acute pancreatitis remains a clinical concern, but randomized trials and pooled analyses have not consistently demonstrated a significant increase in risk. Because the number of events is small, treatment should be discontinued and appropriate evaluation undertaken when pancreatitis is suspected [5, 6, 33].

The risk of hypoglycaemia is low when GLP-1RAs are used alone, but it increases when they are combined with insulin or sulfonylureas [3]. Diabetic retinopathy complications were more frequent with semaglutide than placebo in SUSTAIN-6, supporting closer ophthalmological monitoring in selected patients with pre-existing diabetic retinopathy [23].

Overall, GLP-1RAs have demonstrated an acceptable safety profile in large trials, although gastrointestinal tolerability, gallbladder-related events, treatment discontinuation, and selected population-specific risks should be considered when individualizing therapy [6, 33].

**Research gaps and future directions.** Several important research gaps remain. First, the cardiovascular and kidney effects observed across individual trials should not be assumed to apply uniformly to all GLP-1RAs. Adequately powered head-to-head outcome trials are lacking, and further comparative studies are needed to determine whether clinically relevant differences exist among individual agents, doses, and molecular structures [5, 31].

Second, evidence beyond T2DM remains strongly population- and compound-specific. SELECT demonstrated cardiovascular benefit with semaglutide 2.4 mg in individuals with overweight or obesity and established CVD, but evidence for primary prevention in people without diabetes or previous CVD remains limited [6]. Similarly, the STEP-HFpEF programme demonstrated symptomatic and functional benefits, whereas definitive evidence regarding cardiovascular mortality and heart-failure hospitalization is still insufficient [7–9].

Further studies should also clarify the long-term durability of cardiovascular and kidney benefits, the consequences of treatment discontinuation and weight regain, and the safety of prolonged treatment, particularly at higher doses. Additional evidence is needed in older adults, patients with frailty, advanced kidney disease, and other populations that remain underrepresented in randomized trials.

Finally, future research should focus on identifying clinical and biological markers that may help predict which patients are most likely to derive cardiovascular, kidney, or functional benefit from individual GLP-1RAs.

## SUMMARY

Evidence from cardiovascular outcome trials and meta-analyses indicates that selected GLP-1RAs reduce the risk of major adverse cardiovascular events in patients with T2DM and elevated cardiovascular risk. However, the magnitude and components of benefit differ among individual agents and study populations. Therefore, cardiovascular effects should be interpreted according to the evidence available for each compound rather than assumed to represent a uniform class effect.

Current guidelines support the use of GLP-1RAs with demonstrated cardiovascular benefit in selected patients with T2DM. The 2023 European Society of Cardiology (ESC) Guidelines recommend these agents in patients with T2DM and established ASCVD to reduce cardiovascular events, independently of baseline or target glycated haemoglobin (HbA1c) and concomitant glucose-lowering medication (Class I, Level of Evidence A). In patients with T2DM without established ASCVD or severe target-organ damage but with a calculated 10-year cardiovascular risk of at least 10% according to SCORE2-Diabetes, treatment with a GLP-1RA and/or an SGLT2 inhibitor may be considered for cardiovascular risk reduction (Class IIb, Level of Evidence C) [2]. The American Diabetes Association (ADA) Standards of Care recommend a GLP-1RA with demonstrated cardiovascular benefit for patients with T2DM and established ASCVD or multiple ASCVD risk factors to reduce MACE; this recommendation is supported by level A evidence [1]. In the ADA framework, the letter grade reflects the quality of supporting evidence rather than a formal class of recommendation. These recommendations concern defined populations with T2DM and should not be interpreted as supporting unrestricted treatment irrespective of diabetes status or approved indications.

Evidence beyond T2DM is currently strongest for semaglutide in selected populations. SELECT demonstrated

a reduction in MACE in adults with overweight or obesity, without diabetes, but with established CVD, and therefore supports secondary rather than general primary prevention. In obesity-related HFpEF, semaglutide improved symptoms, physical limitations, exercise capacity, and body weight; however, these outcomes should be distinguished from definitive reductions in cardiovascular mortality or heart-failure hospitalization [6–9].

Overall, GLP-1RAs have an established role in cardiovascular risk reduction in selected patients with T2DM, while evidence for additional cardiometabolic applications continues to evolve. Future studies should clarify long-term safety, durability of benefit, comparative effectiveness among individual agents, effects on hard outcomes in heart failure and populations without established CVD, and the optimal selection of patients most likely to benefit.

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