Advances in Clinical and Medical Research

Genesis-ACMR-7(2)-122
Volume 7 | Issue 2
Open Access
ISSN: 2583-2778

The Expanding Cardiovascular and Cardiorenal Role of GLP-1 Receptor Agonists

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Citation: Koleng M, Joubran E, Koleng J. The Expanding Cardiovascular and Cardiorenal Role of GLP-1 Receptor Agonists. Adv Clin Med Res. 7(2):1-10.

Received: June 16, 2026 | **Published**: June 30, 2026

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) provide cardiometabolic benefits that extend beyond glucose lowering. This Scoping Review systematically mapped cardiovascular and cardiorenal outcomes associated with GLP-1 RA therapy. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. PubMed (MEDLINE) was searched from January 1, 2008 through February 1, 2026 using controlled vocabulary and free-text terms for GLP-1 RAs and cardiovascular and cardiorenal outcomes. Eligible studies included randomized controlled cardiovascular-outcome trials (CVOTs), meta-analyses, and large observational cohorts reporting major adverse cardiovascular events (MACE), cardiovascular death, heart-failure hospitalization, or renal composite endpoints. Seventeen studies met the inclusion criteria: ten randomized CVOTs, five meta-analyses, and two observational cohorts. Significant MACE reductions were observed with liraglutide (LEADER), semaglutide (SUSTAIN-6 and SOUL), dulaglutide (REWIND), albiglutide (HARMONY Outcomes), efpeglenatide (AMPLITUDE-O), and oral semaglutide (PIONEER-6), whereas lixisenatide (ELIXA) and exenatide (EXSCEL) were cardiovascularly neutral. The SELECT trial demonstrated a 20% MACE reduction in overweight or obese adults without diabetes. Meta-analyses confirmed class-wide reductions in MACE, cardiovascular death, and renal composite outcomes, and real-world data reproduced these associations across diverse clinical populations. Collectively, the totality of evidence supports GLP-1 RAs as disease-modifying cardiometabolic therapies with broad applicability in cardiovascular prevention.

Keywords

Glucagon-like peptide-1 receptor agonists; GLP-1 RAs; GLP-1s; Cardiovascular outcomes; Major adverse cardiovascular events; MACE; Cardiorenal protection; Diabetes; Obesity; Semaglutide; Liraglutide.

DOI: https://doi.org/10.52793/ACMR.2026.7(2)-122

Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality among individuals with type 2 diabetes mellitus (T2DM) [1]. Despite advances in pharmacologic therapy, substantial residual cardiovascular risks persist, even with optimal glycemic control [1]. This necessitates the development of pharmaceutical therapies that confer benefits beyond glycemic control alone. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin-based agents that enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and promote weight loss [2]. In addition to their metabolic benefits, GLP-1 RAs improve endothelial function, attenuate oxidative stress, and reduce vascular inflammation mechanisms [2]. Given these synergistic mechanisms, GLP-1 RAs may provide cardiovascular protection in addition to the mentioned benefits.

Following the 2008 United States Food and Drug Administration (FDA) mandate requiring cardiovascular-outcome trials (CVOTs) for all new antidiabetic agents [3], multiple GLP-1 RAs were evaluated in large studies to confirm cardiovascular safety. These trials revealed that GLP-1 RAs were both safe and demonstrated significant reductions in major adverse cardiovascular events (MACE). A brief overview of these trials is included in the following paragraphs to elaborate on their efficacy in reducing adverse cardiovascular events. It is also critical to acknowledge, that following these trials, Wegovy (semaglutide) carries an FDA approved indication “to reduce the risk of cardiovascular death, heart attack and stroke in adults with cardiovascular disease and either obesity or overweight [4].” This indicates it has expanded used beyond its original goal of glycemic control.

Liraglutide lowered MACE and cardiovascular death specifically by 22% in the LEADER trial [5]. Semaglutide and albiglutide produced similar benefits in the SUSTAIN-6 and HARMONY trials, respectively [6,7]. Third, dulaglutide reduced MACE by 12% and stroke by 24% in the REWIND trial [8]. The SELECT trial [9] extended cardiovascular benefit beyond diabetes, demonstrating that weekly subcutaneous semaglutide 2.4 mg reduced MACE by approximately 20% in overweight or obese adults without diabetes but with established cardiovascular disease [9], conferring benefit of semaglutide use in reducing cardiovascular burden even in absence of the diagnosis of T2DM.

Another GLP-1 RA, efpeglenatide, improved both cardiovascular and renal outcomes in the AMPLITUDE-O trial, with a notable 27% lower risk of MACE and 32% lower risk of renal composite outcomes [10]. This suggests that efpeglenatide provided benefits beyond cardio-protection alone and may possess more widespread potential to reduce the burden of nephropathy and chronic kidney disease (CKD) in patients with T2DM. This finding is of importance as T2DM remains the leading cause of CKD and as many as 40% of individuals with T2DMmay develop CKD [11].

In contrast, oral semaglutide (PIONEER-6 study) [12,13], lixisenatide (ELIXA trial) [14] and exenatide (EXSCEL trial) [15] were neutral regarding cardiovascular outcomes but confirmed overall safety. Subsequent meta-analyses [16-20] confirmed class-wide reductions in MACE, cardiovascular death, and renal composite outcomes in treatment with GLP-1 RAs. Two subsequent large observational cohorts [21,22] validated these findings in real-world clinical settings and confirmed external validity. The GLP-1 RAs discussed in this review, apart from oral semaglutide, are administered via subcutaneous injection,

and this factor may potentially underly their cardio-protective abilities. The route of administration may play an important role as it may provide higher, more consistent concentrations when administered weekly. The oral pill also has a lower bioavailability and efficacy and requires more strict timing with regards to when it is taken. Third, while both routes of administration have side effects, the oral pill is associated with higher potential gastrointestinal effects [12], which may lead to non-compliance or even discontinuation over time.

The findings from these trials and accompanying research establish the importance for a comprehensive review on the subject to summarize available data and bolster the argument for ongoing research. It must be acknowledged that two other publications in the last five years that also discuss the benefit of GLP-1 RAs to combat cardiovascular outcomes [23,24]. These two reviews are also narrative reviews that utilized CVOTs as their primary evidence base. This review aims to complement and emphasize the existing and growing research to be current regarding new trials and changes up through 2026. The review also emphasizes the further evolving role of GLP-1 RAs with the inclusion of renal and cardiorenal outcomes, which previous reviews do not address. Third, there this review provides expanded discussion as to possible future co-therapy between GLP-1 RA and other anti-diabetic agents to achieve better therapeutic effect. This review also includes a greater multitude of study types than either of the previous two alone. This provides for a more comprehensive understanding and interpretation of available evidence for both review and potential clinical application.

Methods

Articles selected for inclusion in this Sreview were largely collected and chosen in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [25]. This framework was used to ensure a standardized and reliable method to obtain articles to include in the review. The objective was to identify and to map the published evidence describing cardiovascular and renal outcomes associated with GLP-1 receptor agonist therapy across randomized, real-world study designs to provide a comprehensive overview of the state of current research and to help identify any gaps for potential future research.

Further processing from eligible articles followed a Population-Concept-Context (PCC) framework guided inclusion criteria. The population included is adults at least 18 years of age, receiving any GLP-1 receptor agonist drug, subcutaneous or oral. The concept for inclusion criteria focused on cardiovascular-related outcomes. This included major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, stroke, heart-failure hospitalization, and cardiorenal composite endpoints. Finally, the types of reviews included for context are randomized controlled CVOTs [5-9,13-15], systematic reviews and meta-analyses [16-12], and observational cohorts [20,21] published in English between January 1, 2008, and February 1, 2026. 2008 was chosen as it was the year that the FDA instituted a mandate requiring cardiovascular-outcome trials (CVOTs) for all new antidiabetic agents [3].

Structured searches were performed in PubMed and MEDLINE using controlled vocabulary and free-text terms for GLP-1 receptor agonists and cardiovascular outcomes to obtain relevant articles. In addition, manual screening was conducted using major medical journals with cardiovascular focus. These journals

include the New England Journal of Medicine, Lancet, and JAMA Network Open Access. Clinical trial information was obtained in part also through ClinicalTrials.gov for verified GLP-1 RA cardiovascular results. The trials included are ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY Outcomes, REWIND, PIONEER-6, AMPLITUDE-O, SELECT, and SOUL [5-9,13-15].

The search string has been included below to increase transparency and to detail how evidence for this review was identified.

("Glucagon-Like Peptide 1"[Mesh] OR "Glucagon-Like Peptide 1 Receptor"[Mesh] OR "glucagon-like peptide-1" OR "GLP-1" OR GLP1 OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR lixisenatide OR albiglutide OR efpeglenatide) AND ("Cardiovascular Diseases"[Mesh] OR cardiovascular OR "major adverse cardiovascular event*" OR MACE OR "cardiovascular death" OR "heart failure" OR "renal outcome*" OR kidney) AND (random* OR trial OR cohort OR observational OR registry OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type]) AND ("2008/01/01"[Date – Publication]: "2025/02/01"[Date – Publication]).

Selection process

Titles and abstracts obtained were initially screened for duplicates, which were then subsequently removed. Titles and abstracts were then screened for relevance followed by a full-text review of potentially eligible studies. Inclusion required adult participants, GLP-1 RA exposure, and reporting of at least one prespecified cardiovascular or renal endpoint. Trials lacking clinical outcomes, preclinical studies, and duplicate analyses were excluded. Findings were categorized descriptively by agent, study type, and outcome domain. Quantitative pooling was not performed.

Included publications were further reviewed for publication year, dating January 1, 2008 or later. The study design, GLP-1 RA agent, population characteristics, comparator, follow-up duration, primary cardiovascular or renal endpoint, and hazard ratio (HR) with 95 percent confidence interval (CI) were also key factors investigated within the relevant studies. Meta-analyses and observational cohorts were added for pooled or adjusted effect estimates and to provide external validation and to add qualitative explanation to the included trials. Six additional articles were included to provide background information regarding any underlying pathologies and GLP-1 RA drug class mechanisms of action.

Results

Randomized cardiovascular-outcome trials

Ten CVOTs evaluated the cardiovascular safety or efficacy of GLP-1 receptor agonists between 2015 and 2025. Collectively, these trials enrolled more than 85,000 participants with T2DM, established cardiovascular disease, or both. Seven GLP-1 RAs were represented: lixisenatide, liraglutide, semaglutide (subcutaneous and oral), exenatide, albiglutide, dulaglutide, and efpeglenatide. Overall, subcutaneous GLP-1 RAs demonstrated superior cardiovascular outcomes, however, oral semaglutide, demonstrated reduced cardiovascular death outcomes and was not deemed inferior to subcutaneous semaglutide in the PIONEER-6 trial (HR 0.49 [0.27-0.92]) [12]. In the SOUL trial, oral semaglutide demonstrated significant MACE reductions [13]. Across all CVOTs, hazard ratios for MACE ranged from an average of 0.73 to 1.02

[5-9,13-15], indicating overall consistent cardiovascular benefit across the GLP-1 RA drug class. This suggests that a hazard ratio equal to or less than one indicates either no difference or an improved outcome compared to a control group. This standard applies to all the following trials and GLP-1 RAs mentioned in this review.

Five specific GLP-1 RAs reduced MACE by statistically significant measures when compared to placebo. The first was liraglutide which reduced 3-point MACE by 13% and cardiovascular death by 22% as confirmed by the LEADER trial [5]. Second, subcutaneous semaglutide demonstrated significant MACE reductions in the SUSTAIN-6 trial [6]. The REWIND trial focused on dulaglutide and achieved a 12% MACE reduction across a broad-risk population [7]. A fourth GLP-1 RA, albiglutide, studied in the HARMONY Outcomes trials, confirmed GLP-1 RA benefits in patients with established atherosclerotic cardiovascular disease rather than with diabetes or absence of disease alone. Albiglutide confirmed a 22% MACE reduction in the former patient population [7]. Lastly, a fifth GLP-1 RA, efpeglenatide, was unique as it lowered both MACE and renal composite outcomes in the AMPLITUDE-O trial [8], as previously noted in the Introduction of this review.

Two final GLP-1 RAs were included, lixisenatide and exenatide, but they did not demonstrate cardiovascular superiority as the previously mentioned GLP-1 RAs did. While lixisenatide confirmed cardiovascular safety in the ELIXA trial, it did not reduce MACE in patients with a recent acute coronary syndrome diagnosis [14]. Further research with lixisenatide is necessitated to confirm its cardiovascular profile and use in a greater population than those with acute cardiovascular disease alone. Finally, a similar drug, exenatide, was deemed neutral from a cardiovascular perspective in the EXSCEL trial, but it was not considered inferior to placebo [15].

A subsequent study, the SELECT trial [9], extended the population of interest to non-diabetic adults with overweight or obesity and established cardiovascular disease. It showed an expanded semaglutide benefit in this population by demonstrating a 20% relative reduction in MACE with a dosage of 2.4 mg [9]. The results of this trial suggested an increased scope for semaglutide use and a larger potential target population than adults with T2DM alone.

Meta-analyses and systematic reviews

Five meta-analyses published between 2019 and 2025 were included in this review. These analyses included results from the major CVOTs and emerging real-world data [16-20]. Pooled analyses across these publications confirmed a class-wide 15-20% relative reduction in MACE and a 12-15% reduction in cardiovascular death.

Collectively, these meta-analyses reinforced the robust cardioprotective and reno-protective efficacy of GLP-1 RAs previously established in the large, randomized CVOTs. Most recently, a study published in BMC Diabetology & Metabolic Syndrome (2025) reported significant improvement in renal composite outcomes independent of glycemic control [17]. Additionally, a prior study in published in 2024 in the European Heart Journal corroborated this class effect and established safety across subgroups [16].

Finally, additional pooled studies were included from BMJ Open, JAMA Network Open, and Circulation, which confirmed internal and external consistency [18-20].

Observational and real-world cohorts

Observational and real-world cohort data were included to demonstrate translation of trial results into clinical practice and to support generalizability across populations. These studies ranged from 2020 to 2026 and included larger populations than the trials alone. A 2025 JAMA Network Open analysis of more than 1.2 million adults with T2DM found that those using GLP 1 RAs had with lower rates of myocardial infarction, stroke, and kidney failure across body-mass-index categories [21]. Further, a multinational registry study published the same year confirmed that sustained GLP-1 RA therapy reduced composite cardiovascular and renal events across diverse nationalities and health systems [22]. Finally, two large observational cohorts conducted by Bu et al and Yang et al, respectively, provided external validation of the randomized findings [21,22]. These cohorts demonstrated large real-world comparative effectiveness across multiple databases and population-based real-world cohorts confirming cardiovascular benefit.

Evidence map of cardiovascular and renal outcomes

An integrated evidence map is shown in Figure 1. This map depicts the cardiovascular and renal outcome signals across individual GLP-1 RAs. Cardiovascular benefits (dark blue) were consistent across liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide, while neutral effects (gray) were observed for lixisenatide and exenatide. Renal protective effects (light blue) appeared in the AMPLITUDE-O and REWIND trials and several pooled analyses [8,10,17]. The figure illustrates the convergence of evidence across studies supporting GLP-1 RAs as both cardioprotective and reno-protective therapies.

	LIXI	LIRA	SEMA	DULA	ALBI	EFPE	EXEN
MACE Reduction							
CV Death Reduction							
Renal Composite							

LIXI = lixisenatide; LIRA = liraglutide; SEMA = subcutaneous semaglutide; DULA = dulaglutide; ALBI = albiglutide; EFPE = efpeglenatide; EXEN = exenatide; MACE = major adverse cardiovascular event; CV = cardiovascular.

Figure 1: Evidence map depicting cardiovascular and renal outcome signals across individual GLP-1 receptor agonists. Dark blue indicates cardiovascular benefit, light blue indicates renal benefit, gray indicates neutrality, and white indicates insufficient evidence based on randomized cardiovascular-outcome trials, meta-analyses, and observational cohorts.

Summary of findings

Across all evidence sources and populations, several GLP-1 receptor agonists consistently demonstrated reduced MACE, cardiovascular death, and some also extended such benefits to renal composite outcomes. Their benefits extend beyond individuals with diabetes to those with obesity and established cardiovascular disease. As previously discussed, Figure 1 maps these findings and visually integrates

outcomes across GLP-1 RAs. Together, these findings confirm the broad cardiovascular benefits of GLP-1 RAs across cardiometabolic and renal spectrums.

Discussion

The included sources provide coherent evidence supporting glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as disease-modifying cardiovascular and cardiorenal therapies. Across these sources, consistent reductions were observed in major adverse cardiovascular events (MACE), cardiovascular death, and renal composite outcomes. Agents including liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide demonstrated statistically significant cardiovascular benefit compared with placebo, while lixisenatide and exenatide confirmed cardiovascular safety without added benefit. As previously mentioned, the SELECT trial using subcutaneous semaglutide, expanded this benefit to overweight and obese adults without diabetes, establishing the cardioprotective effects of GLP-1 RAs beyond glycemic modulation alone, suggesting their expanded use in multiple populations [9].

Mechanistic insights

GLP-1 RAs exert cardioprotective actions through several complementary mechanisms. These mechanisms include improved endothelial function, enhanced nitric oxide bioavailability, and the attenuation of oxidative stress [2]. These mechanisms collectively promote vasodilation and reduce vascular inflammation. Experimental and clinical data also suggest favorable effects on lipid metabolism, body weight, and blood pressure [2]. The mechanisms by which GLP-1 RAs mediate renal protection are through natriuresis, decreased glomerular hypertension, and anti-inflammatory effects on the renal microvasculature [2]. These pathways indicate that cardiovascular and renal benefits extend beyond the net blood glucose-lowering capabilities of GLP-1s.

Comparative and clinical context

When compared with other glucose-lowering agents, such as metformin, the current first line agent in the treatment of T2DM [24], GLP-1 RAs provide the most consistent reduction in atherosclerotic cardiovascular events [24]. In contrast, another class of anti-diabetic drugs, sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as Jardiance, confer additional benefits in improved heart-failure outcomes and reduction of chronic-kidney-disease progression [18]. The two drug classes, GLP-1 RAs and SGLT2s, exhibit complementary mechanisms, and combination therapy may offer potential additive protection across the cardiometabolic spectrum [26,27]. For patients with T2DM or established cardiovascular disease, the American Diabetes Association guideline-directed therapy now favors inclusion of either GLP-1 RAs or SGLT2 inhibitors regardless of glycated hemoglobin level in patients with diabetes [26].

Integration of evidence

Meta-analyses published between 2024 and 2025 confirm a class-wide 15-20% reduction in MACE and a 12-15% reduction in cardiovascular death across GLP-1 RAs [13-17]. These findings are further supported by mechanistic and pathophysiology-based reviews describing cardioprotective pathways associated with GLP-1 receptor agonists [18]. The consistency of results across studies supports the strength of their

cardioprotective effects. Observational cohorts further validate the translation of trial findings into clinical practice, demonstrating lower rates of myocardial infarction, stroke, and renal failure in community populations treated with GLP-1 RAs [19,20]. These findings cement the external generalizability and real-world applicability of trial outcomes.

Strengths and limitations of the scoping review

A major strength of this review is the inclusion comprehensive database with current data as of the year of this review, 2026. This is of key importance as current data validates previous work, shows improved health outcomes, and provides an up-to-date data set. In addition, adherence to PRISMA-ScR methodology for article inclusion and integration of evidence from randomized, pooled, and real-world analyses creates a standardized approach, ensures a comprehensive understanding, and combines the strengths of multiple study types and better overcomes the methods of individual study types. Further, the inclusion of both clinical-trial and registry data allows for mapping of consistency across populations and care settings to expand external validity.

Some limitations of the present research include restriction to English-language literature and descriptive synthesis without quantitative meta-analysis. Limiting research to English-language literature may inherently limit the number of articles and studies that are accessible and could omit potential valuable information. Also, the lack of numerable quantitative meta-analyses may reduce the precision of pooled effect size estimates. However, the broad concordance of findings across study types and populations mitigates these limitations.

Clinical implications and future directions

GLP-1 receptor agonists represent a cornerstone in the prevention of cardiometabolic morbidities. Their benefits extend beyond diabetic patients alone to patients with obesity and established cardiovascular disease. There is additional emerging evidence suggesting potential roles in primary prevention. Future research is necessary to clarify long-term renal durability, to determine any long-term adverse effects to use, to evaluate combined GLP-1 receptor agonist and SGLT2 inhibitor therapy, and to assess outcomes in lower-risk populations. Additional trials exploring neurovascular, hepatic, and anti-inflammatory endpoints may further expand therapeutic indications for GLP-1 RAs and increase the potential patient population that may benefit from treatment.

Current evidence demonstrates that GLP-1 RAs consistently reduced atherosclerotic cardiovascular and renal events across high-risk populations. Continued long-term and preventive studies will clarify their role in individuals without established disease and in combination-therapy frameworks, but existing data already justify their inclusion as disease-modifying cardiometabolic therapies and necessitate ongoing research to explore their potential expanded benefits.

Conclusion

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have consistently demonstrated reductions in major adverse cardiovascular events, cardiovascular death, and composite renal outcomes across randomized, real-world evidence. Benefits are evident among agents such as liraglutide, semaglutide,

dulaglutide, albiglutide, and efpeglenatide, with neutral, but safe findings for lixisenatide and exenatide. The SELECT trial further established cardiovascular benefit in adults without diabetes but with obesity and established cardiovascular disease, expanding therapeutic use beyond glycemic control.

Collectively, these findings position GLP-1 RAs as disease-modifying cardiometabolic therapies with applicability across diabetes, obesity, and high-risk cardiovascular populations. Ongoing investigations should clarify long-term renal durability, combination strategies with sodium-glucose cotransporter-2 inhibitors, weight loss implications, and preventive efficacy in lower-risk cohorts. Broader integration of GLP-1 RAs into evidence-based cardiometabolic care may substantially reduce cardiovascular morbidity and mortality worldwide.

Statements and Declarations

Funding: Not applicable.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Author contributions: All authors contributed to the study conception and design. All authors read and approved the final manuscript.

Ethics Approval: This study did not involve human participants or animal subjects and therefore did not require institutional review board approval. Consent to participate is not applicable.

Data Availability: All data supporting this review are derived from publicly available studies indexed in PubMed, (MEDLINE), and cited in the reference list.

Consent to Participate: Our research did not involve human subjects. Consent to participate is not applicable.

Consent to Publish: Not applicable.

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