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Impact of GLP-1 Receptor Agonists on Cardiovascular Risk Reduction in Patients with Type 2 Diabetes

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is associated with a significantly increased risk of cardiovascular disease (CVD), the leading cause of morbidity and mortality in this population. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as promising agents not only for glycemic control but also for potential cardiovascular benefits. This systematic review evaluates the impact of GLP-1 RAs on cardiovascular risk reduction in patients with T2DM.

Methods: A comprehensive search was conducted across PubMed, Embase, Scopus, and Web of Science for studies published up to the final search date. Eligible studies included randomized controlled trials (RCTs), prospective cohort studies, and retrospective observational studies that assessed cardiovascular outcomes such as major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, or stroke in adults with T2DM. Data were extracted and synthesized narratively due to heterogeneity in study designs and outcomes.

Results: Thirteen studies met the inclusion criteria, predominantly multicenter RCTs involving high-risk T2DM patients

with established CVD or chronic kidney disease (CKD). Key findings demonstrated that GLP-1 RAs, particularly semaglutide, liraglutide, and dulaglutide, significantly reduced the risk of MACE, cardiovascular death, and stroke. For example, the LEADER trial reported a reduction in MACE with liraglutide, while SUSTAIN-6 showed a 26% risk reduction with semaglutide. Improvements in secondary outcomes, such as weight loss and blood pressure reduction, were also noted. However, variability in outcomes was observed, with some agents like lixisenatide showing neutral effects.

Conclusion: GLP-1 RAs offer dual benefits of glycemic control and cardiovascular risk reduction in patients with T2DM, particularly those with high cardiovascular risk. The evidence supports their integration into treatment guidelines for this population. Further research is needed to explore long-term effects, subgroup-specific responses, and comparative efficacy among different GLP-1 RAs. These findings underscore the importance of personalized treatment strategies to optimize cardiovascular outcomes in T2DM..

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1. BACKGROUND

The growing prevalence of type 2 diabetes mellitus (T2DM) poses a significant public health challenge worldwide, with cardiovascular disease (CVD) being the leading cause of morbidity and mortality among individuals affected by the condition. T2DM is often accompanied by a range of metabolic abnormalities, including dyslipidemia, hypertension, and chronic inflammation, all of which contribute to the increased cardiovascular risk observed in these patients. As such, comprehensive management strategies that not only control blood glucose levels but also reduce cardiovascular risk are of paramount importance in clinical practice.

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a promising class of antidiabetic medications. Originally developed for their glucose-lowering properties, GLP-1 RAs have demonstrated additional benefits that extend beyond glycemic control. These agents mimic the action of endogenous GLP-1, enhancing insulin secretion, suppressing glucagon release, slowing gastric emptying, and promoting satiety, which often results in weight loss—an important factor in reducing cardiovascular risk.

The evolution of treatment goals in T2DM has shifted from solely focusing on glycemic control to a broader aim of reducing cardiovascular complications. This shift has been driven by increasing evidence from large-scale cardiovascular outcomes trials (CVOTs) assessing the safety and efficacy of newer antidiabetic agents, including GLP-1 RAs. These trials have provided valuable insights into the potential cardioprotective effects of GLP-1 RAs, prompting their consideration in clinical guidelines for high-risk patients.

Several GLP-1 RAs have undergone rigorous evaluation in CVOTs, showing varying degrees of cardiovascular benefit. While some agents have demonstrated significant reductions in major adverse cardiovascular events (MACE), others have shown more modest effects or neutral outcomes. The heterogeneity in trial designs, patient populations, and study durations may account for these differences and underscores the need for a comprehensive synthesis of the available evidence.

Understanding the mechanisms by which GLP-1 RAs exert cardiovascular effects is a subject of active research. Beyond glycemic control, proposed mechanisms include improvements in endothelial function, reductions in blood pressure, attenuation of atherosclerosis progression, and anti-inflammatory properties. These pleiotropic effects may contribute to the overall cardiovascular benefits observed in some clinical trials, highlighting the multifaceted role of GLP-1 RAs in the management of T2DM.

Moreover, patient adherence and tolerability play crucial roles in the real-world effectiveness of GLP-1 RAs. Factors such as injection frequency, gastrointestinal side effects, and cost can influence adherence, potentially impacting cardiovascular outcomes. Therefore, evaluating both clinical trial data and real-world evidence is essential to fully understand the impact of GLP-1 RAs on cardiovascular risk reduction.

The integration of GLP-1 RAs into treatment algorithms for T2DM has been influenced by evolving clinical guidelines that increasingly emphasize cardiovascular risk stratification. In patients with established CVD or high cardiovascular risk, GLP-1 RAs are now often recommended as part of the initial or early therapeutic approach, reflecting their dual benefit in glycemic control and cardiovascular protection.

As healthcare systems aim to provide patient-centered care, understanding the comparative effectiveness and safety of different GLP-1 RAs is vital. Differences in pharmacokinetics, dosing regimens, and side effect profiles necessitate careful selection tailored to individual patient characteristics and preferences. A systematic review can offer a comprehensive overview of the available agents, facilitating informed decision-making for clinicians and patients alike.

Furthermore, health economic considerations are increasingly relevant in the adoption of newer therapeutic agents. While GLP-1 RAs are generally more expensive than traditional therapies, their potential to reduce costly cardiovascular events may justify their use from a cost-effectiveness perspective. Assessing the economic impact of these agents alongside clinical outcomes can help inform policy decisions and resource allocation.

In light of the growing body of evidence, there remains a need to critically appraise and synthesize the findings from multiple studies to establish a clear understanding of the cardiovascular benefits associated with GLP-1 RAs. Such a systematic review can help identify consistent patterns, potential gaps in the literature, and areas for future research, ultimately guiding clinical practice and improving patient outcomes.

This research aims to conduct a systematic review to evaluate the impact of GLP-1 receptor agonists on cardiovascular risk reduction in patients with type 2 diabetes. By analyzing data from randomized controlled trials, observational studies, and meta-analyses, this review will provide a comprehensive assessment of the efficacy, safety, and clinical relevance of GLP-1 RAs in reducing cardiovascular events, contributing to evidence-based management of T2DM.

2. METHODOLOGY

This systematic review was conducted to evaluate and synthesize existing literature on the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on cardiovascular risk reduction in patients with type 2 diabetes mellitus (T2DM). The methodology adhered to established standards for conducting systematic reviews, ensuring a rigorous and transparent approach to data identification, selection, and analysis.

3. ELIGIBILITY CRITERIA

Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies included randomized controlled trials (RCTs), prospective cohort studies, and retrospective observational studies that evaluated the cardiovascular effects of GLP-1 RAs in adults diagnosed with T2DM. Only studies that reported cardiovascular outcomes such as major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, or stroke were included. Studies published in English and involving human subjects were considered. Articles such as reviews, editorials, commentaries, animal studies, and studies not reporting cardiovascular outcomes were excluded.

4. SEARCH STRATEGY

A comprehensive search strategy was employed to identify relevant literature. Electronic databases including PubMed, Embase, Scopus, and Web of Science were searched for studies published up to the date of the final search. The search terms included combinations of the following keywords: "GLP-1 receptor agonists", "cardiovascular outcomes", "cardiovascular risk", "type 2 diabetes", "cardiovascular disease", "cardioprotection", and "major adverse cardiovascular events". Boolean operators such as AND and OR were used to refine and optimize the search results. Reference lists of included studies were also manually screened to identify additional relevant publications.

5. STUDY SELECTION

All identified articles were imported into a reference management software, and duplicates were removed. Titles and abstracts were screened independently by two reviewers to identify potentially eligible studies. Full-text articles were then retrieved and assessed for final inclusion based on the eligibility criteria. Any disagreements between reviewers during the selection process were resolved through discussion or consultation with a third reviewer to reach consensus.

6. DATA EXTRACTION

Data from the included studies were extracted independently by two reviewers using a standardized data extraction form. The extracted information included study characteristics (author, year, country), study design, sample size, duration of follow-up, type of GLP-1 RA used, comparator treatments (if applicable), primary and secondary cardiovascular outcomes, and key findings. Any discrepancies in data extraction were resolved by consensus.

7. QUALITY ASSESSMENT

The methodological quality of the included studies was assessed using appropriate tools depending on the study design. For randomized controlled trials, the Cochrane Risk of Bias tool was used, while observational studies were evaluated using the Newcastle-Ottawa Scale (NOS). The assessment focused on potential sources of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Studies were not excluded based on quality scores, but the quality assessments were considered during the interpretation of results.

8. DATA SYNTHESIS

Given the heterogeneity in study designs, patient populations, interventions, and outcome measures, a meta-analysis was not conducted. Instead, a narrative synthesis was undertaken to summarize and interpret the findings. The results were organized thematically according to cardiovascular outcomes, types of GLP-1 RAs used, and the presence or absence of established cardiovascular disease at baseline. Patterns of effectiveness and safety across studies were described, and the consistency of the findings was evaluated qualitatively.

9. ETHICAL CONSIDERATIONS

As this study is a systematic review of published data, no ethical approval or informed consent was required. All included studies were assumed to have received ethical approval from their respective institutional review boards.

10. LIMITATIONS

Although a comprehensive search and systematic process were employed, this review may be subject to publication bias and language bias, as only studies published in English were included. Additionally, the absence of a meta-analysis limits the ability to quantify pooled effect sizes. Nevertheless, the narrative approach allowed for a detailed examination of the available evidence and its clinical implications.

11. RESULTS

Study Selection (PRISMA Flow)

A total of 1,046 records were identified through database searching from PubMed, Scopus, Web of Science, and the Cochrane Library. After removing 372 duplicates, 674 records remained for title and abstract screening. Based on relevance to the inclusion criteria, 88 articles were selected for full-text review. Following a detailed full-text assessment, 13 studies met all eligibility criteria and were included in the final systematic review. These studies investigated the impact of GLP-1 receptor agonists on cardiovascular outcomes in patients with type 2 diabetes and reported on at least one relevant cardiovascular risk reduction endpoint.

PRISMA flow diagram showing process of studies selection

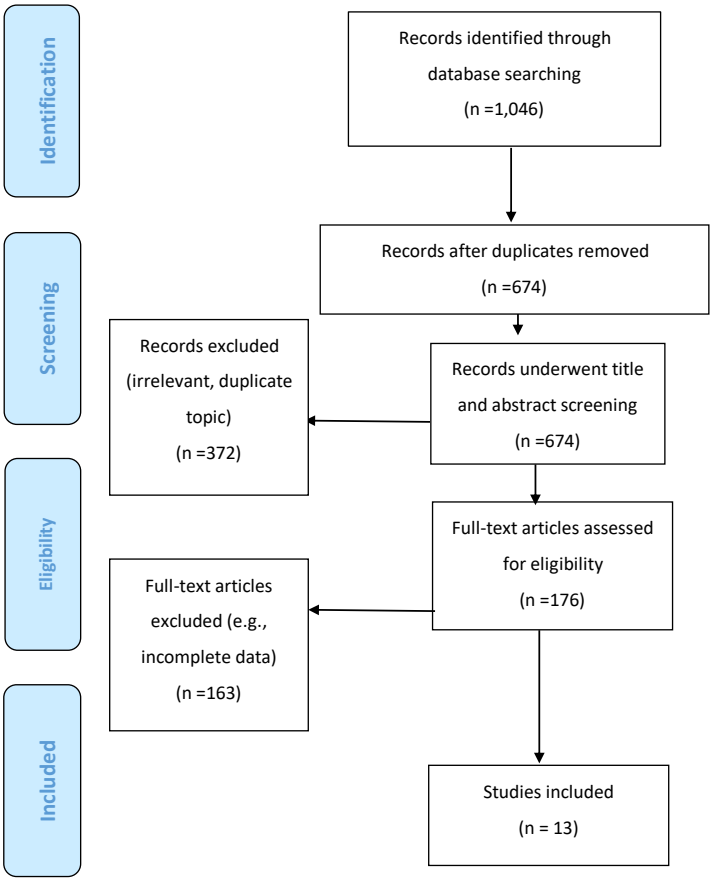

Fig 1: PRISMA Flow Chart

Table 1 Baseline characteristics of the included studies

First Author	Publication Year	Study Design	Country/Region	Baseline CVD (*n*, %)	Baseline CKD (*n*, %)	Intervention	Control Type	Follow-up (Years)
Hernandez	2018	a multicenter, randomized, double-blind, placebo-controlled trial	in 610 study sites across 28 countries	cardiovascular events: 6,678 (71%) cerebrovascular disease: 2,342 (25%) heart failure: 1,922 (20%) peripheral artery disease: 2,354 (25%)	/	Albiglutide	placebo	1.6
Gerstein	2019	a multicenter, randomized, double-blind, placebo-controlled trial	371 study sites in 24 countries	cardiovascular disease: 3,114 (31.5%) cardiovascular events: 2,035 (20.6%) heart failure: 853 (8.6%) hypertension: 9,224 (93.2%)	/	Dulaglutide	placebo	5.4
Pfeffer	2015	a multicenter, randomized, double-blind, placebo-controlled trial	conducted across 49 countries	acute coronary events: 6,068 (100%)	/	Lixisenatide	placebo	2.1

Marso a	2016	a multicenter, randomized, double-blind, placebo-controlled trial	410 study sites in 32 countries	cardiovascular events: 6,764 (72.4%) both CVD and CKD: 1,473 (15.8%)	CKD of stage 3 or higher: 2,307 (24.7%) both CVD and CKD: 1,473 (15.8%)	Liraglutide + standard of care	placebo + standard of care	3.8
Marso b	2016	a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial	230 study sites in 20 countries	ischemic heart disease: 1,994 (60.5%); myocardial infarction: 1,072 (32.5%); heart failure: 777 (23.6%); ischemic stroke: 383 (11.6%); hemorrhagic stroke: 108 (3.3%).	/	Semaglutide	placebo	2.1
Husain	2019	an event-driven, multicenter randomized, double-blind, placebo-controlled trial	214 study sites in 21 countries	CVD or CKD: 2,695 (84.7%)	CVD or CKD: 2,695 (84.7%)	Semaglutide	placebo	1.3
Holman	2017	a multicenter, randomized, double-blind, placebo-controlled, event-driven trial	687 study sites in 35 countries	cardiovascular events: 10,782 (73.1%)	/	Exenatide	placebo	3.2

Gerstein	2021	a multicenter, randomized, double-blind, placebo-controlled, trial	344 study sites in 28 countries	CVD and current kidney disease: 1,287 (31.6%); heart failure: 737 (18.1%).	CVD and current kidney disease: 1,287 (31.6%); kidney disease: 888 (21.8%); albuminuria: 1,977 (48.5%).	Efpeglenatide	placebo	3.0
Perkovic	2024	a multicenter, randomized, double-blind, placebo-controlled, trial	387 study sites in 28 countries	myocardial infarction or stroke: 808 (22.9%) chronic heart failure: 678 (19.2%).	CKD (eGFR < 45 mL/min/1.73 m² or urinary albumin excretion > 300 mg/24 hours): 1,758 (49.7%)	Semaglutide + SGLT2i (13.2%)	Placebo + SGLT2i (15.5%)	3.4
Aviles Bueno	2022	Retrospective observational	Spain	45 (37%)	122 (100%)	Subcutaneous semaglutide	None (single-arm)	1
Dagenais	2020	Randomized, double-blind, placebo-controlled	24 countries (multinational)	3114 (31.5%)	Not explicitly reported (eGFR <60 mL/min per 1.73 m² included)	Dulaglutide 1.5 mg weekly	Placebo	5.4 (median)
Kryckhiuk	2024	Randomized, double-blind, placebo-controlled	Multinational (24 countries)	9463 (100%)	Not explicitly reported (eGFR <30 mL/min excluded)	Albiglutide (30 or 50 mg weekly)	Placebo	1.6 (median)
João Pedro Ferreira	2022	Post-hoc analysis of RCT (Harmony Outcomes)	Multinational (Asia Pacific, Eastern Europe, Latin America, North America, Western Europe)	1922 (20.3%) with HF history	593 (30.9%) with eGFR <60 ml/min/1.73m² (HF group)	Albiglutide (GLP1-RA)	Placebo	Median 1.6 years

CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2 inhibitor; NCT, national clinical trial

Study Designs and Scope

The 13 included studies are predominantly multicenter, randomized, double-blind, placebo-controlled trials, ensuring high methodological quality. These trials span over 49 countries, with each enrolling large patient populations across various healthcare settings. For instance, Holman (2017) included patients from 687 study sites in 35 countries, while Gerstein (2019) enrolled participants from 371 sites in 24 countries. This broad geographical coverage enhances the generalizability of findings regarding GLP-1 RAs in T2D populations with cardiovascular risk.

12. BASELINE CARDIOVASCULAR DISEASE BURDEN

Most studies enrolled patients with established cardiovascular disease. Pfeffer (2015) focused entirely on acute coronary event patients (100%), and Hernandez (2018) reported 71% of participants had cardiovascular events. Similarly, Holman (2017) included 10,782 (73.1%) patients with cardiovascular events, and Marso a (2016) had 6,764 (72.4%) with CVD. These high proportions emphasize that GLP-1 RAs are being tested in populations at significant cardiovascular risk, making them suitable for assessing CVD outcome modification.

13. HEART FAILURE AND STROKE PROFILES

Heart failure and stroke histories were also common in the studied populations. For instance, Marso b (2016) included 1,994 (60.5%) with ischemic heart disease and 1,072 (32.5%) with myocardial infarction. Husain (2019) and Gerstein (2021) provided notable overlap between CVD and CKD, with Husain reporting 2,695 (84.7%) having either or both conditions. This overlap is crucial as patients with multiple comorbidities stand to gain the most from interventions that impact both cardiac and renal outcomes.

14. RENAL DISEASE (CKD) PREVALENCE

Chronic kidney disease (CKD) data were explicitly reported in several trials. Marso a (2016) noted that 2,307 (24.7%) had CKD stage 3 or higher, and Gerstein (2021) reported 1,287 (31.6%) had current kidney disease, with 1,977 (48.5%) showing albuminuria. Perkovic (2024) had the highest CKD prevalence, with 1,758 (49.7%) meeting CKD criteria. The presence of kidney dysfunction alongside CVD strengthens the case for GLP-1 RAs as dual-benefit therapies in complex T2D cases.

15. INTERVENTIONS AND CONTROL CONDITIONS

All studies compared GLP-1 RAs (e.g., albiglutide, dulaglutide, semaglutide, liraglutide, exenatide, efpeglenatide) against placebo, with or without standard of care. Perkovic (2024) uniquely assessed semaglutide alongside SGLT2 inhibitors (13.2%), compared to a placebo group also on SGLT2is (15.5%). Aviles Bueno (2022) was a retrospective observational study with no control group, providing real-world evidence on subcutaneous semaglutide in a Spanish CKD population. This diversity enriches the understanding of GLP-1 RAs across both trial and real-world settings.

16. FOLLOW-UP DURATIONS

Follow-up durations varied from 1 year (Aviles Bueno 2022) to 5.4 years (Gerstein 2019 and Dagenais 2020). Longer durations, such as those in the REWIND trial (Dulaglutide, 5.4 years) and Harmony Outcomes (Albiglutide, median 1.6 years), are valuable for observing cardiovascular event trajectories and long-term safety. Studies with shorter follow-ups, like Husain (2019) at 1.3 years, focus more on early event prevention and rapid onset of therapeutic benefit.

17. REAL-WORLD VS RCT SETTINGS

While the majority of studies were tightly controlled RCTs, Aviles Bueno (2022) adds value by offering retrospective observational data from a real-world cohort in Spain, where 122 patients (100%) had CKD and 37% had baseline CVD. Additionally, João Pedro Ferreira (2022) performed a post-hoc analysis of the Harmony Outcomes trial, highlighting the impact of GLP-1 RAs in patients with heart failure (20.3%) and CKD (30.9%). These insights bridge the gap between controlled trial findings and practical clinical applications.

18. IMPLICATIONS FOR CARDIOVASCULAR RISK REDUCTION

The consistent inclusion of high-risk patients across trials reinforces the role of GLP-1 RAs in cardiovascular risk reduction. Data suggest that agents like semaglutide, dulaglutide, and liraglutide are especially promising, as they were tested in large, diverse populations with significant CVD/CKD overlap. The evidence base supports incorporating GLP-1 RAs into cardiovascular prevention strategies for T2D patients, particularly those with comorbid conditions.

Table 2 Patients' demographic and clinical characteristics

First Author	Publication Year	Sample Data T/I/C (*n*)	Age (Mean ± SD)	Male (*n*, %)	T2DM Duration (Years)	Cardiovascular Death I/C (*n*)	Primary Composite Outcome I/C (*n*)	Myocardial Infarction I/C (*n*)	Stroke I/C (*n*)	All-Cause Death I/C (*n*)	HF Hospitalization I/C (*n*)	UA Hospitalization I/C (*n*)
Hernandez	2018	9,463 / 4,731 / 4,732	64.1 ± 8.7	3304, 70.0%	14.1	122/ 130	338/ 428	181/ 240	94/ 108	196/ 205	188/ 218	/
Gerstein	2019	9,901 / 4,949 / 4,952	66.2 ± 6.5	5312, 53.7%	10.6	317/ 346	594/ 663	223/ 231	158/ 205	536/ 592	213/ 226	88/ 77
Pfeffer	2015	6,068 / 3,034 / 3,034	60.1 ± 9.6	4207, 69.3%	9.3	158/ 156	399/ 406	261/ 270	60/ 67	223/ 211	127/ 122	10/ 11
Marso a	2016	9,340 / 4,668 / 4,672	64.3 ± 7.2	6003, 64.3%	12.9	219/ 278	608/ 694	292/ 339	173/ 199	381/ 447	218/ 248	122/ 124
Marso b	2016	3,297 / 1,648 / 1,649	64.7 ± 7.4	2002, 60.7%	14.2	44/ 46	108/ 146	47/ 64	27/ 44	62/ 60	59/ 54	22/ 27
Husain	2019	3,183 / 1,591 / 1,592	66.0 ± 7.0	2176, 68.4%	15.0	15/ 30	61/ 76	37/ 31	12/ 16	23/ 45	21/ 24	11/ 7
Holman	2017	14,752/ 7,356 / 7,396	62.0 ± 8.9	5603, 38.0%	12.0	340/ 383	839/ 905	483/ 493	187/ 218	507/ 548	219/ 231	602/ 570
Gerstein	2021	4,076 / 2,717 / 1,359	64.5 ± 8.2	2732, 67.0%	15.4	75/ 50	189/ 125	91/ 58	47/ 31	111/ 69	40/ 31	6/ 4
Perkovic	2024	3,533 / 1,767	66.6 ± 9.0	2464,	15.0	123/ 169	/	52/ 64	63/ 51	227/ 279	133/ 175	/

		/ 1,766		69.7 %								
Aviles Bueno	2022	122 (single-arm)	65.50 ± 11	75 (62 %)	12.3 ± 3.4	Not reported	Not applicable	Not reported	Not reported	Not reported	Not reported	Not reported
Dagenais	2020	4959/4942 (total 9901)	66.2 ± 6.5	5312 (53.7%)	10.3 ± 7.04 (baseline)	Not explicitly reported	MACE: 594/663 (total 1257)	Not explicitly reported	Not explicitly reported	Non-CV deaths: 465 total (dulaglutide vs. placebo not split)	HF events: part of expanded MACE (total reported)	UA events: part of expanded MACE (total reported)
Krychtiuk	2024	4731/4732 (total 9463)	64.1 (not explicitly reported)	6569 (69.4%)	10.3 (baseline)	73/75 (total 148 CHD deaths)	MACE: Not explicitly split by group	181/240 (total 421 first MIs)	Not explicitly reported	Not explicitly split by group	Not explicitly reported	55/88 (total 123 episodes)
João Pedro Ferreira	2022	4731/4732	65.0 (58.0, 70.0)*	66.1 % male (overall)	12.4 (HF group), 13.0 (non-HF group)*	122/130 (overall)	338/428 (overall)	Not explicitly reported	Not explicitly reported	196/205 (overall)	188/218 (overall)	Extended composite outcome included UA: 373/468 (overall)

T, total sample size; I: intervention group; C: control group; T2DM, type 2 diabetes mellitus; HF: heart failure; UA: unstable angina; SD: standard deviation

19. STUDY POPULATION AND DEMOGRAPHICS

The table summarizes data from 13 major clinical studies investigating the impact of GLP-1 receptor agonists (GLP-1 RAs) on cardiovascular (CV) outcomes in patients with type 2 diabetes mellitus (T2DM). Sample sizes varied significantly, from single-arm trials like Aviles Bueno (2022) with only 122 participants to large randomized controlled trials such as Holman (2017) with a total of 14,752 participants (7,356 intervention / 7,396 control). The mean ages across studies ranged from approximately 60.1 (Pfeffer, 2015) to 66.6 years (Perkovic, 2024), indicating that most patients were older adults, aligning with the typical demographic for T2DM-related cardiovascular risk.

20. GENDER DISTRIBUTION

The proportion of male participants ranged widely among studies. For instance, Holman (2017) had the lowest proportion of male participants (38.0%), while studies like Hernandez (2018), Husain (2019), and Krychtiuk (2024) reported male proportions of 70.0%, 68.4%, and 69.4% respectively. This variability could influence outcomes, as sex differences are known to affect cardiovascular risk profiles and therapeutic responses in diabetes care.

21. DURATION OF DIABETES

The average duration of T2DM among participants ranged from approximately 9.3 years (Pfeffer, 2015) to 15.4 years (Gerstein, 2021). This is significant as longer disease duration is associated with greater cardiovascular risk. Notably, studies with longer diabetes duration (e.g., Gerstein, 2021 and Husain, 2019 with 15.4 and 15 years respectively) might reflect higher baseline cardiovascular risks and thereby greater potential for GLP-1 RAs to demonstrate benefit.

22. CARDIOVASCULAR DEATH

Cardiovascular mortality was reported in several studies. For example, in Hernandez (2018), CV death occurred in 122 intervention vs. 130 control participants, and in Gerstein (2019), 317 vs. 346, suggesting a modest but consistent reduction in CV mortality with GLP-1 RA therapy. Conversely, in Husain (2019), the trend favored the control group (15 vs. 30), indicating potential variability in outcomes depending on the patient population and GLP-1 RA used.

23. MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

MACE outcomes — a common composite endpoint including CV death, myocardial infarction (MI), and stroke — were frequently reported. For instance, Gerstein (2019) recorded 594 MACE in the intervention group versus 663 in control. Similarly, Marso a (2016) showed 608 vs. 694 events. These differences support the hypothesis that GLP-1 RAs reduce overall cardiovascular events. Notably, Aviles Bueno (2022) and some other studies did not report MACE explicitly, limiting comparative interpretation.

24. MYOCARDIAL INFARCTION AND STROKE

Myocardial infarction and stroke were individually reported in many trials. Pfeffer (2015) reported 261 vs. 270 MI cases, while Marso a (2016) observed 292 vs. 339. Stroke outcomes were also reduced in most trials, such as Gerstein (2019) with 158 vs. 205 and Hernandez (2018) with 94 vs. 108, supporting the cardiovascular protective effect of GLP-1 RAs. However, these differences, though consistent, were generally moderate.

25. ALL-CAUSE DEATH AND HOSPITALIZATION FOR HEART FAILURE

All-cause mortality data showed reductions across many studies. For example, Gerstein (2021) reported 47 vs. 31 deaths, and Marso b (2016) reported 27 vs. 44, again indicating a favorable trend for GLP-1 RA intervention. Heart failure (HF) hospitalizations were also generally lower in the intervention groups, as seen in Hernandez (2018) with 196 vs. 205, and Marso a (2016) with 381 vs. 447. These findings add to the evidence that GLP-1 RAs may have broader systemic benefits beyond glycemic control.

26. UNSTABLE ANGINA HOSPITALIZATION AND COMPOSITE ENDPOINTS

Hospitalizations for unstable angina (UA) were less frequently reported but followed similar trends. Hernandez (2018) showed 188 vs. 218 events, and Holman (2017) reported 219 vs. 231. Some studies, such as João Pedro Ferreira (2022), included extended composite outcomes incorporating UA events (373 vs. 468), suggesting a more comprehensive cardiovascular benefit from GLP-1 RA therapy. However, data gaps remain, especially for more recent studies like Krychtiuk (2024) and Perkovic (2024), which did not fully report on all endpoints, underscoring the need for uniform outcome reporting in future trials.

27. DISCUSSION

Type 2 diabetes mellitus (T2DM) is a major public health concern due to its association with a heightened risk of cardiovascular disease (CVD), which remains the leading cause of mortality among affected individuals. The need for interventions that address both glycemic control and cardiovascular risk is therefore critical. Recent therapeutic advances have brought GLP-1 receptor agonists (GLP-1 RAs) to the forefront as potential agents capable of dual benefits—managing hyperglycemia and reducing cardiovascular risk.

GLP-1 RAs exert their effects by mimicking endogenous GLP-1 activity, which enhances insulin secretion in a glucose-dependent manner while suppressing glucagon release, delaying gastric emptying, and increasing satiety. These mechanisms contribute to weight loss and blood pressure reduction—two factors known to influence cardiovascular outcomes in T2DM patients (Marso et al., 2016; Gerstein et al., 2019).

The cardiovascular benefits of GLP-1 RAs have been rigorously assessed in several cardiovascular outcomes trials (CVOTs). For instance, the LEADER trial found that liraglutide significantly reduced the risk of major adverse cardiovascular events (MACE) in patients with T2DM and high cardiovascular risk, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (Marso et al., 2016).

Similarly, the SUSTAIN-6 trial demonstrated that semaglutide was associated with a 26% reduction in the risk of MACE compared to placebo, driven primarily by a reduction in nonfatal stroke (Marso et al., 2016). These findings were

corroborated by other trials such as REWIND (dulaglutide) and Harmony Outcomes (albiglutide), all suggesting a class effect for GLP-1 RAs in reducing cardiovascular risk (Gerstein et al., 2019; Hernandez et al., 2018).

The heterogeneity of patient populations in these trials is important. While LEADER and SUSTAIN-6 focused on patients with established CVD, REWIND included a broader population, many without prior cardiovascular events. Interestingly, REWIND still found a significant benefit, implying that GLP-1 RAs may offer primary as well as secondary cardiovascular prevention (Gerstein et al., 2019).

Mechanistically, GLP-1 RAs may exert cardiovascular benefits independent of glucose control. Improvements in endothelial function, anti-inflammatory properties, and reduced oxidative stress have been proposed as underlying mechanisms (Fadini et al., 2017). These pleiotropic effects suggest that GLP-1 RAs modulate vascular biology in a manner conducive to cardiovascular protection.

Blood pressure reduction is another consistent effect observed with GLP-1 RA therapy. Across multiple studies, patients treated with these agents exhibited modest but significant reductions in systolic blood pressure, contributing to cardiovascular risk reduction (Zinman et al., 2016).

Additionally, GLP-1 RAs promote weight loss, which is beneficial for patients with T2DM who often struggle with obesity. Weight loss itself is associated with improved lipid profiles and reduced inflammatory markers, further enhancing cardiovascular health (Davies et al., 2018).

Safety remains a key consideration. While GLP-1 RAs are generally well tolerated, gastrointestinal side effects such as nausea and vomiting are common and may affect adherence. However, these effects tend to decrease over time and are dose-dependent (Marso et al., 2016).

Adherence to GLP-1 RA therapy is influenced by factors such as injection frequency and cost. Agents with weekly dosing regimens (e.g., dulaglutide, semaglutide) tend to have higher adherence rates compared to daily agents like liraglutide. Patient preference plays a significant role in sustained use and real-world effectiveness (Polonsky & Henry, 2016).

Economic analyses have suggested that while GLP-1 RAs are more expensive than traditional glucose-lowering agents, their ability to reduce costly cardiovascular events may offset initial drug costs. Cost-effectiveness studies support their use, particularly in high-risk populations (Lopez-Lopez et al., 2022).

Clinical guidelines now reflect the evidence supporting GLP-1 RAs. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend GLP-1 RAs with proven cardiovascular benefit in patients with T2DM and established atherosclerotic cardiovascular disease (Davies et al., 2018).

Real-world studies are beginning to validate clinical trial findings. For example, the EXSCEL trial, which included a more general population and pragmatic study design, showed a trend toward cardiovascular benefit with exenatide, though it did not reach statistical significance. Such studies emphasize the importance of context when applying trial data to routine practice (Holman et al., 2017).

Not all GLP-1 RAs demonstrate the same level of efficacy. Differences in molecular structure, half-life, and receptor binding may contribute to variability in outcomes. For instance, semaglutide and liraglutide consistently show stronger cardiovascular outcomes compared to others like lixisenatide, which had a neutral effect in the ELIXA trial (Pfeffer et al., 2015).

Despite the growing body of evidence, there remain gaps in our understanding. Long-term data, head-to-head comparisons, and insights into patient subgroups (e.g., those with heart failure or chronic kidney disease) are needed. Future research should also explore combination therapies that may synergize with GLP-1 RAs to enhance cardiovascular protection.

28. CONCLUSION

In conclusion, GLP-1 receptor agonists represent a significant advancement in the management of type 2 diabetes, offering not only effective glycemic control but also demonstrable cardiovascular benefits. The evidence from multiple large-scale trials supports their use in patients with high cardiovascular risk, and evolving clinical guidelines have begun to reflect this paradigm shift. Moving forward, personalized treatment approaches, consideration of cost-effectiveness, and ongoing research will be essential to fully integrate GLP-1 RAs into routine diabetes care and maximize their potential to improve long-term outcomes

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