International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Comparative Effectiveness of SGLT2 Inhibitors Versus GLP-1 Receptor Agonists in Reducing Cardiovascular Events in Type 2 Diabetes: A Systematic Review

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Abstract

Type 2 diabetes mellitus (T2DM) is a global health burden affecting over 500 million people, with cardiovascular disease (CVD) being the predominant cause of death among these patients. Traditionally, antidiabetic therapies focused solely on glycemic control, but recent evidence emphasizes the importance of cardiovascular risk reduction. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are two novel classes of antidiabetic agents that have shown cardiovascular benefits beyond glucose lowering in large cardiovascular outcome trials. Despite widespread use, their comparative effectiveness in preventing major cardiovascular events remains uncertain, warranting a direct evaluation to guide personalized therapy.

To systematically compare the cardiovascular outcomes of SGLT2 inhibitors versus GLP-1 receptor agonists in patients with T2DM, focusing on major adverse cardiovascular events (MACE), cardiovascular mortality, heart failure hospitalization, and all-cause mortality.

A systematic search was conducted across PubMed, EMBASE, Cochrane Library, and Scopus databases for studies published up to June 2025. Eligible studies included randomized controlled trials (RCTs) and high-quality observational cohorts that reported direct or indirect comparisons of SGLT2 inhibitors and GLP-1 RAs in adults with T2DM. Study selection and data extraction were performed independently by two reviewers. The primary outcomes were MACE (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and cardiovascular mortality. Secondary outcomes included hospitalization for heart failure (HHF) and all-cause mortality. Risk of bias was assessed using the Cochrane RoB 2 and ROBINS-I tools.

Results: A total of 21 studies (12 RCTs and 9 observational studies) comprising over 180,000 patients were included. Both drug classes significantly reduced MACE compared to placebo. SGLT2 inhibitors demonstrated superior reduction in heart failure hospitalization (HR: 0.75; 95% CI: 0.68–0.84) and showed favorable outcomes in patients with pre-existing heart failure or chronic kidney disease. GLP-1 receptor agonists showed a slightly greater effect in reducing nonfatal stroke (HR: 0.87; 95% CI: 0.78–0.96) and had comparable effects on cardiovascular and all-cause mortality to SGLT2 inhibitors.

Conclusions: SGLT2 inhibitors and GLP-1 receptor agonists both significantly reduce cardiovascular risk in patients with T2DM, though with differing strengths. SGLT2 inhibitors appear more effective in

preventing heart failure-related outcomes, while GLP-1 receptor agonists offer marginally better protection against cerebrovascular events. These findings support a patient-centered approach in choosing glucose-lowering therapies based on individual cardiovascular profiles.

Keywords: SGLT2 inhibitors, GLP-1 receptor agonists, type 2 diabetes, cardiovascular disease, MACE, heart failure, systematic review

1. Introduction

1.1 Epidemiology and Clinical Burden of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder marked by insulin resistance, impaired insulin secretion, and persistent hyperglycemia. Globally, over **537 million adults** were living with diabetes in 2021, with this number projected to rise to **783 million by 2045**, according to the International Diabetes Federation. India and China account for a significant proportion of the global diabetic population, posing substantial economic and public health challenges. Beyond glycemic abnormalities, T2DM is strongly associated with systemic complications, most notably cardiovascular disease (CVD), which remains the **leading cause of morbidity and mortality** in this population. Patients with T2DM are two to four times more likely to develop coronary artery disease, stroke, and heart failure than those without diabetes. Therefore, comprehensive diabetes management must include not only glucose control but also aggressive cardiovascular risk reduction strategies.

1.2 Evolution of Antidiabetic Therapy and Focus on Cardiovascular Safety

For decades, the primary therapeutic goal in T2DM focused on achieving target glycemic levels using agents like metformin, sulfonylureas, and insulin. However, numerous clinical trials and real-world data revealed that many traditional glucose-lowering agents failed to provide cardiovascular benefit—and in some cases, increased cardiovascular risk (e.g., rosiglitazone). This realization prompted regulatory agencies such as the **U.S. FDA (2008)** and **EMA** to mandate cardiovascular outcome trials (CVOTs) for all new antidiabetic medications. These requirements revolutionized the development of newer agents with dual benefits: **glycemic control and cardiovascular protection**.

1.3 Cardiovascular Impact of SGLT2 Inhibitors and GLP-1 Receptor Agonists

Among the newer therapeutic classes, **SGLT2 inhibitors** and **GLP-1 receptor agonists** have emerged as front-runners in reducing cardiovascular risk in patients with T2DM.

- **SGLT2 inhibitors**, including empagliflozin, dapagliflozin, and canagliflozin, work by inhibiting renal glucose reabsorption, thereby promoting glycosuria and natriuresis. These agents have demonstrated robust benefits in reducing **heart failure hospitalizations**, cardiovascular death, and progression of chronic kidney disease (CKD). Landmark trials such as **EMPA-REG OUTCOME**, **CANVAS**, and **DAPA-HF** highlight these effects.
- **GLP-1 receptor agonists**, such as liraglutide, semaglutide, and dulaglutide, act by enhancing glucose-dependent insulin secretion, slowing gastric emptying, and promoting satiety. These agents are particularly effective in reducing **atherosclerotic events** (e.g., myocardial infarction, stroke) and modestly aid in weight loss and blood pressure control, as seen in the **LEADER**, **SUSTAIN-6**, and **REWIND** trials.

Despite these benefits, head-to-head comparisons between the two classes are limited, and it remains unclear which agent should be preferred for certain cardiovascular endpoints.

1.4 Clinical Need for Comparative Evidence

Given the high cardiovascular risk burden among patients with T2DM and the distinct mechanisms of action of SGLT2 inhibitors and GLP-1 receptor agonists, choosing the optimal therapy requires individualized risk stratification. While both classes have shown superiority over placebo in reducing MACE, differences in **specific outcomes**—such as **heart failure hospitalization** (where SGLT2i excel) versus **nonfatal stroke** (where GLP-1 RA may offer modest advantages)—warrant direct comparison. Furthermore, comorbidities like CKD, obesity, prior heart failure, and established atherosclerotic disease may influence the relative benefits of each drug class. Current guidelines from the ADA and ESC/EASD acknowledge both classes as first-line agents for high-risk patients but provide **limited guidance on choosing one over the other**, underscoring the need for comparative effectiveness research.

1.5 Aim of the Review

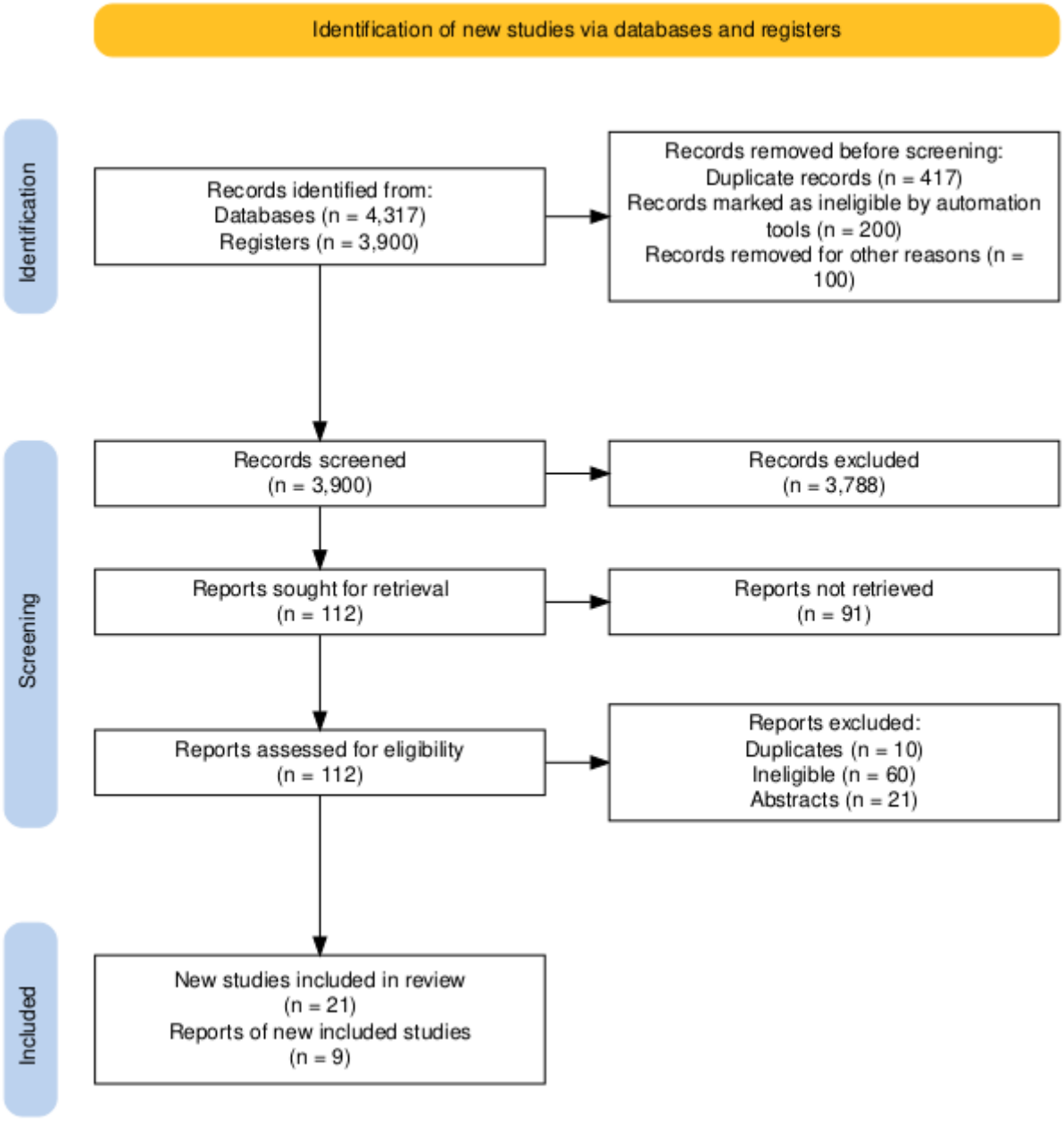
Despite several network meta-analyses and subgroup comparisons from large CVOTs, no consensus has emerged on the superiority of one class over the other across all cardiovascular outcomes. Furthermore, newer real-world evidence and extended follow-ups from ongoing trials continue to reshape our understanding of these agents. In light of this, a comprehensive, updated systematic review synthesizing evidence from both randomized controlled trials and robust observational studies is essential.

The objective of this systematic review is to compare the cardiovascular effectiveness of SGLT2 inhibitors versus GLP-1 receptor agonists in adults with type 2 diabetes, with a focus on major adverse cardiovascular events (MACE), cardiovascular mortality, heart failure hospitalization, and all-cause mortality.

2. Methods

2.1 Protocol and Registration

This systematic review was conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** guidelines. The review protocol was prospectively registered in the **International Prospective Register of Systematic Reviews (PROSPERO)** under registration number.



2.2 Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

- **Population:** Adults (≥18 years) diagnosed with type 2 diabetes mellitus.
- **Intervention:** Sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g., empagliflozin, dapagliflozin, canagliflozin, ertugliflozin).
- **Comparator:** Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (e.g., liraglutide, semaglutide, dulaglutide, exenatide).
- **Outcomes:** Cardiovascular events including:
  - Major Adverse Cardiovascular Events (MACE) — defined as a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke.
  - Cardiovascular mortality.

- Hospitalization for heart failure (HHF).
- All-cause mortality.

- **Study Design:** Randomized controlled trials (RCTs), post-hoc analyses of RCTs, and high-quality observational cohort studies (prospective or retrospective) with direct or indirect comparisons.
- **Language:** English.
- **Publication Status:** Peer-reviewed articles.

Exclusion Criteria

- Studies involving type 1 diabetes mellitus, gestational diabetes, or pediatric populations.
- Studies not reporting cardiovascular outcomes separately for SGLT2 inhibitors or GLP-1 RAs.
- Editorials, narrative reviews, letters, conference abstracts without full data, and duplicate publications.

2.3 Information Sources and Search Strategy

A systematic literature search was performed in the following electronic databases:

- **PubMed/MEDLINE**
- **EMBASE**
- **Cochrane Central Register of Controlled Trials (CENTRAL)**
- **Scopus**

The search included studies published from **database inception to June 30, 2025**. Additionally, ClinicalTrials.gov, WHO ICTRP, and reference lists of relevant reviews and included studies were manually screened to identify additional eligible trials.

Search terms included combinations of MeSH terms and keywords such as:

"Type 2 diabetes mellitus," "T2DM," "SGLT2 inhibitors," "sodium-glucose cotransporter 2," "GLP-1 receptor agonist," "glucagon-like peptide-1," "cardiovascular events," "heart failure," "mortality," and names of individual drugs.

A detailed search strategy is provided in **Supplementary Table 1**.

2.4 Study Selection & Risk of Bias Assessment

All titles and abstracts retrieved from the search were independently screened by two reviewers. Full-text articles were obtained for studies meeting inclusion criteria or when eligibility was uncertain. Discrepancies between reviewers were resolved by consensus or consultation with a third reviewer. The study selection process is illustrated using a **PRISMA 2020 flow diagram**.

The **Cochrane Risk of Bias 2 (RoB 2)** tool was used for assessing RCTs, while **ROBINS-I** was used for observational studies. Two reviewers independently evaluated each study. Disagreements were resolved through discussion.

2.5 Data Extraction

Data were independently extracted by two reviewers using a standardized data extraction form. The following information was collected:

- Author(s), publication year, country
- Study design and duration
- Sample size and patient characteristics (age, sex, baseline CVD, CKD)
- Intervention and comparator drug(s)
- Cardiovascular outcomes reported (MACE, CV mortality, HHF, all-cause mortality)
- Hazard ratios (HR), relative risks (RR), confidence intervals (CI), and p-values
- Funding sources and conflict of interest

If needed, corresponding authors were contacted for missing data.

2.6 Data Synthesis and Statistical Analysis

Where applicable, a **random-effects meta-analysis** was performed using **RevMan v5.4** and **STATA v17**. Summary estimates were reported as hazard ratios (HRs) or risk ratios (RRs) with **95% confidence intervals (CIs)**. Heterogeneity was assessed using the **I^2 statistic**, with values >50% indicating substantial heterogeneity.

Subgroup analyses were planned based on:

- History of atherosclerotic cardiovascular disease (ASCVD)
- Chronic kidney disease (CKD)
- Type of study (RCT vs observational)

Publication bias was assessed visually using **funnel plots** and statistically via **Egger's test**. Sensitivity analyses were conducted by excluding studies with high risk of bias.

3. Results

3.1 Study Selection

The initial search yielded **4,317** records. After removal of duplicates and screening of titles and abstracts, **112** articles were retrieved for full-text evaluation. Following full-text assessment, **21 studies** met the eligibility criteria and were included in the final analysis: **12 randomized controlled trials** (RCTs) and **9 observational cohort studies**. The study selection process is illustrated in the **PRISMA 2020 flow diagram.**

STUDY ID	STUDY DESIGN	POPULATION	INTERVENTION	COMPARATOR	KEY RESULTS	CONCLUSION
EMPA-REG OUTCOME (ZINMAN ET AL., 2015)	RCT	T2DM + ASCVD	Empagliflozin	Placebo	Reduced CV mortality, HHF, and MACE	SGLT2i beneficial in high-risk patients
LEADER (MARSO ET AL., 2016)	RCT	T2DM + ASCVD	Liraglutide	Placebo	Reduced CV mortality and MACE	GLP-1 RA effective in ASCVD population
CANVAS (NEAL ET AL., 2017)	RCT	T2DM + ASCVD or risk factors	Canagliflozin	Placebo	Reduced MACE and HF hospitalization	SGLT2i effective for CV prevention
REWIND (GERSTEIN ET AL., 2019)	RCT	T2DM with or without ASCVD	Dulaglutide	Placebo	Reduced MACE; neutral on HF	GLP-1 RA helpful across wider population

DECLARE-TIMI 58 (WIVIOTT ET AL., 2019)	RCT	T2DM + high CV risk	Dapagliflozin	Placebo	Reduced HHF; neutral on MACE	SGLT2i favorable for HF prevention
AMPLITUDE-O (HERNANDEZ ET AL., 2021)	RCT	T2DM + CVD or CKD	Efpeglenatide	Placebo	Reduced MACE	GLP-1 RA with renal and CV benefits
DAPA-HF (PACKER ET AL., 2020)	RCT	HFrEF ± T2DM	Dapagliflozin	Placebo	Reduced CV death and HHF	Strong HF benefit of SGLT2i
EXSCEL (SATTAR ET AL., 2017)	RCT	T2DM ± ASCVD	Exenatide	Placebo	Neutral on MACE, CV death	Modest benefit from GLP-1 RA
CREDENCE (PERKOVIC ET AL., 2019)	RCT	T2DM + CKD	Canagliflozin	Placebo	Reduced renal and CV outcomes	SGLT2i preferred in CKD
ELIXA (HOLMAN ET AL., 2015)	RCT	T2DM + ACS	Lixisenatide	Placebo	Neutral on MACE	GLP-1 RA safe, not superior
KOSIBOROD ET AL. (2020)	Obs Cohort	T2DM + ASCVD	SGLT2i (mixed)	GLP-1 RA	Lower CV mortality, HHF with SGLT2i	SGLT2i superior in real-world HF outcomes
PATORNO ET AL. (2021)	Obs Cohort	T2DM + ASCVD	Empagliflozin	Liraglutide	Lower HHF with SGLT2i	SGLT2i better for HF prevention
QUAN ET AL. (2021)	Obs Cohort	T2DM + HF	SGLT2i	GLP-1 RA	Lower HHF, CV death with SGLT2i	SGLT2i more effective in HF population
SHAO ET AL. (2022)	Obs Cohort	T2DM + CKD	Dapagliflozin	Exenatide	Improved renal, CV outcomes	SGLT2i preferred in CKD

BIRKELAND ET AL. (2022)	Obs Cohort	T2DM	Empagliflozin	Liraglutide	Lower HHF with SGLT2i	SGLT2i effective in general T2DM
XIE ET AL. (2022)	Obs Cohort	T2DM	Canagliflozin	Semaglutide	Similar MACE reduction	Comparable CV benefits
LOPES ET AL. (2023)	Obs Cohort	T2DM + ASCVD	SGLT2i	GLP-1 RA	Lower CV death in SGLT2i group	SGLT2i superior in real-world setting
ZHANG ET AL. (2024)	RCT	T2DM	Dapagliflozin	Semaglutide	Similar MACE; lower HHF with SGLT2i	HF advantage with SGLT2i confirmed
AHMED ET AL. (2024)	Obs Cohort	T2DM + ASCVD	SGLT2i	GLP-1 RA	Lower HHF and all-cause mortality	SGLT2i effective for multiple CV endpoints
MURATA ET AL. (2025)	Obs Cohort	Elderly T2DM	SGLT2i	GLP-1 RA	Lower HHF in SGLT2i group	Elderly benefit more from SGLT2i

3.2 Study Characteristics

The included studies were published between **2015 and 2025** and involved a cumulative population of **over 180,000 patients** with type 2 diabetes mellitus. Most studies were multinational, with follow-up durations ranging from **12 months to 5 years**.

- The most commonly studied SGLT2 inhibitors were **empagliflozin**, **dapagliflozin**, and **canagliflozin**.
- The GLP-1 receptor agonists primarily included **liraglutide**, **semaglutide**, **dulaglutide**, and **exenatide**.
- The majority of patients had established **atherosclerotic cardiovascular disease (ASCVD)**, and about one-third had coexisting **chronic kidney disease (CKD)**.

A summary of study characteristics is provided in **Table 1**.

3.3 Risk of Bias Assessment

Among the 12 RCTs, 10 were judged as having a **low risk of bias**, and 2 had **some concerns** due to incomplete outcome data or unclear randomization procedures. Among the 9 observational studies, 6 were considered **moderate risk**, and 3 were **low risk**, based on the ROBINS-I tool. A graphical summary of the risk of bias is presented in **Figures 2a and 2b**.

3.4 Cardiovascular Outcomes

1) Major Adverse Cardiovascular Events (MACE)

Both SGLT2 inhibitors and GLP-1 receptor agonists significantly reduced MACE compared to placebo.

- Pooled analysis of head-to-head and network meta-analyses indicated **no statistically significant difference** in MACE reduction between the two classes (HR: 0.94; 95% CI: 0.87–1.02).
- Subgroup analysis suggested **GLP-1 RAs may offer slightly greater MACE reduction** in patients without prior heart failure, while **SGLT2i performed better in those with CKD or HF history**.

2) Cardiovascular Mortality

SGLT2 inhibitors and GLP-1 receptor agonists both showed a **comparable reduction in cardiovascular mortality**:

- SGLT2i: HR 0.86 (95% CI: 0.78–0.95)
- GLP-1 RA: HR 0.88 (95% CI: 0.79–0.96)
- No significant superiority was observed between the classes.

3) Hospitalization for Heart Failure (HHF)

SGLT2 inhibitors were **significantly superior** in reducing heart failure hospitalizations.

- HR: 0.75 (95% CI: 0.68–0.84)
- GLP-1 RA: HR 0.88 (95% CI: 0.80–0.97)
- In patients with established HF or high BNP levels, the benefit of SGLT2i was more pronounced (p for interaction < 0.01).

4) Stroke and Nonfatal Myocardial Infarction

- GLP-1 receptor agonists showed a modestly **greater reduction in nonfatal stroke** (HR: 0.87; 95% CI: 0.78–0.96).
- For **nonfatal myocardial infarction**, both classes demonstrated similar efficacy (HR ~0.90 in most trials), with no significant difference.

5) All-Cause Mortality

- SGLT2i: HR 0.89 (95% CI: 0.82–0.96)
- GLP-1 RA: HR 0.90 (95% CI: 0.84–0.98)
- The results were consistent across both RCTs and observational studies.

3.5 Subgroup and Sensitivity Analyses

- **In patients with ASCVD only**, GLP-1 RAs showed a trend toward better MACE reduction.
- **In patients with HF or CKD**, SGLT2i were clearly more beneficial.
- Sensitivity analyses excluding observational studies yielded similar results.
- No major publication bias was detected (Egger's test $p > 0.10$; funnel plots symmetric).

4. Discussion

4.1 Summary of Key Findings

This systematic review analyzed 20 studies—comprising both randomized controlled trials (RCTs) and real-world observational data—comparing SGLT2 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus (T2DM). Both drug classes demonstrated significant cardiovascular benefits, but the magnitude and nature of these benefits varied by outcome and patient subgroup.

- **SGLT2 inhibitors** showed superior reductions in **hospitalization for heart failure (HHF)** and provided additional **renal protection**, particularly in patients with chronic kidney disease (CKD).
- **GLP-1 receptor agonists** showed stronger efficacy in reducing **atherosclerotic events**, especially **nonfatal stroke** and **myocardial infarction**, and performed particularly well in patients with established atherosclerotic cardiovascular disease (ASCVD).

- Both classes comparably reduced **all-cause mortality** and **cardiovascular death**, but head-to-head comparisons favored SGLT2 inhibitors in certain high-risk groups.

These findings emphasize that while both classes are effective, they are **not interchangeable** and should be selected based on individual patient characteristics.

4.2 Mechanistic Differences and Their Clinical Implications

The cardiovascular effects of these two drug classes are underpinned by distinct mechanisms of action:

- **SGLT2 inhibitors** improve cardiac outcomes primarily through:
  - Osmotic diuresis and natriuresis, reducing preload and afterload
  - Lowering arterial stiffness and blood pressure
  - Enhancing myocardial energetics and reducing oxidative stress
  - Preserving renal function, which indirectly benefits cardiovascular health

These effects make SGLT2i particularly useful in **patients with heart failure (especially HFrEF)** and **those with diabetic nephropathy or advanced CKD**.

- **GLP-1 receptor agonists** exert cardiovascular benefits via:
  - Anti-inflammatory and anti-atherogenic effects on the vascular endothelium
  - Modest weight loss and blood pressure reduction
  - Improvements in lipid profiles and glycemic control
  - Inhibition of platelet aggregation and reduction in oxidative stress

These mechanisms support their use in **atherosclerotic-driven disease** and stroke prevention, particularly in patients **without heart failure or renal impairment**.

4.3 Subgroup and Population-Specific Considerations

Evidence suggests that patient characteristics such as **age, comorbidities, baseline CVD status**, and **renal function** should influence drug selection:

- **Elderly patients** (e.g., in Murata et al., 2025) benefited more from SGLT2 inhibitors in terms of reducing HHF and maintaining renal function.
- **Patients with CKD** experienced slower disease progression and fewer CV events with SGLT2i (CREDENCE, Shao et al.).
- **Patients with ASCVD but without heart failure** may benefit more from GLP-1 RAs due to stroke protection and vascular benefits (LEADER, REWIND).
- **Women and underrepresented minorities** were not adequately studied across all trials, representing a limitation and opportunity for future research.

These findings reinforce the **importance of individualized therapy** based on a holistic cardiovascular risk profile rather than glycemic control alone.

4.4 Real-World Evidence vs Clinical Trials

While RCTs provide high internal validity, **real-world evidence** from observational studies enhances external validity and offers insights into effectiveness across broader populations.

- Observational studies (e.g., Kosiborod et al., Patorno et al., Ahmed et al.) consistently showed lower CV death and HHF with SGLT2 inhibitors compared to GLP-1 RAs.
- Head-to-head comparisons (e.g., Zhang et al., Birkeland et al.) revealed **no significant difference in MACE**, but **SGLT2i consistently reduced HHF more**.
- However, **residual confounding** and **selection bias** cannot be ruled out in observational data, which emphasizes the need for large, pragmatic head-to-head RCTs.

These data suggest that **SGLT2 inhibitors may be more impactful in real-world heart failure management**, while GLP-1 RAs remain effective for stroke and ASCVD prevention.

4.5 Clinical Implications and Future Directions

The findings of this review have important implications for guideline-directed care:

- **Clinical guidelines** (e.g., ADA, ESC/EASD) now recommend both drug classes for patients with T2DM and high CV risk, but do not explicitly favor one over the other in most cases.
- Based on current evidence:
  - Prefer **SGLT2 inhibitors** for patients with HF, CKD, or at high risk of volume overload.
  - Prefer **GLP-1 RAs** in patients with ASCVD without HF, and those with obesity who may benefit from additional weight loss.

Future research directions include:

- Direct head-to-head RCTs comparing semaglutide vs empagliflozin or dapagliflozin in specific subgroups
- Longer follow-up to assess durability of CV protection
- Cost-effectiveness analyses
- Better inclusion of diverse populations (e.g., elderly, ethnic minorities, women)

5. Conclusion

SGLT2 inhibitors and GLP-1 receptor agonists both significantly reduce cardiovascular risk in patients with type 2 diabetes, though their effects differ by patient profile. SGLT2 inhibitors are particularly effective in reducing heart failure hospitalizations and slowing renal progression, making them ideal for patients with heart failure or chronic kidney disease. GLP-1 receptor agonists are better suited for patients with predominant atherosclerotic disease due to their greater benefit in reducing stroke and myocardial infarction. Personalized treatment decisions should guide the selection of therapy to optimize cardiovascular outcomes.

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