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Comparative effectiveness of cardiovascular, renal and safety outcomes of second-line antidiabetic drugs use in people with type 2 diabetes

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Abstract

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by insulin resistance and impaired glucose regulation, which often leads to serious complications involving multiple organ systems. The main objective of this meta-analysis is to find the Comparative effectiveness of cardiovascular, renal, and safety outcomes of second-line antidiabetic drug use in people with type 2 diabetes. Search strategies included combinations of keywords such as "type 2 diabetes," "second-line antidiabetic drugs," "cardiovascular outcomes," "renal outcomes," "safety outcomes," "SGLT2 inhibitors," "GLP-1 receptor agonists," "DPP-4 inhibitors," "sulfonylureas," and "meta-analysis." The initial literature search identified 1,524 studies from various databases. After removing duplicates and applying inclusion and exclusion criteria, 42 studies were deemed eligible for inclusion in the meta-analysis. The pooled hazard ratio (HR) for MACE with SGLT2 inhibitors was 0.84 (95% CI: 0.78-0.90), indicating a 16% reduction in cardiovascular events, while the HR for GLP-1 RAs was 0.88

(95% CI: 0.81-0.94). This meta-analysis demonstrates that SGLT2 inhibitors and GLP-1 receptor agonists provide superior cardiovascular and renal benefits compared to traditional second-line therapies like sulfonylureas and DPP-4 inhibitors in people with type 2 diabetes.

Introduction

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by insulin resistance and impaired glucose regulation, which often leads to serious complications involving multiple organ systems. The global burden of T2D continues to rise, with millions of individuals affected, contributing significantly to morbidity, mortality, and healthcare costs [1].

The main objective of this meta-analysis is to find the Comparative effectiveness of cardiovascular, renal, and safety outcomes of second-line antidiabetic drugs use in people with type 2 diabetes.

Methodology

The meta-analysis was based on a systematic search of major medical and clinical databases, including:

- **PubMed**
- **Embase**
- **Cochrane Central Register of Controlled Trials (CENTRAL)**
- **ClinicalTrials.gov**
- **Medline**

Search strategies included combinations of keywords such as “type 2 diabetes,” “second-line antidiabetic drugs,” “cardiovascular outcomes,” “renal outcomes,” “safety outcomes,” “SGLT2 inhibitors,” “GLP-1 receptor agonists,” “DPP-4 inhibitors,” “sulfonylureas,” and “meta-analysis.” Studies published in English from January 2020 to June 2024 were considered for inclusion.

The inclusion criteria were as follows:

Only RCTs and large-scale observational studies that examined the cardiovascular, renal, or safety outcomes of second-line antidiabetic drugs were included. Adults diagnosed with T2D

who were prescribed second-line antidiabetic drugs, including SGLT2 inhibitors, GLP-1 RAs, DPP-4 inhibitors, and sulfonylureas.

Studies were excluded if they:

- Were conducted on animal models or in vitro.
- Did not report relevant cardiovascular, renal, or safety outcomes.
- Were single-arm studies with no comparator groups.

Data Extraction and Quality Assessment

Two independent reviewers extracted data from the eligible studies using a predefined data extraction form. The extracted information included:

- Study characteristics (authors, publication year, study design, sample size, follow-up duration).
- Patient demographics (age, sex, duration of T2D, comorbidities).
- Intervention details (type of second-line antidiabetic drugs, dose, duration of treatment).
- Outcome measures (cardiovascular, renal, and safety outcomes).
- Comparator interventions (placebo, metformin, or other second-line drugs).

To ensure the quality of included studies, we used Cochrane's Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies. Each study was rated for potential biases in randomization, allocation concealment, blinding, and outcome reporting. Only high-quality studies (low or moderate risk of bias) were included in the final analysis.

Statistical Analysis

The meta-analysis employed random-effects models to account for heterogeneity across studies, assuming that true effects might vary between studies due to clinical and methodological differences. Pooled relative risks (RRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for each outcome. The primary outcomes were cardiovascular events, renal events, and safety profiles, with separate analyses conducted for each drug class.

Results

The initial literature search identified 1,524 studies from various databases. After removing duplicates and applying inclusion and exclusion criteria, 42 studies were deemed eligible for inclusion in the meta-analysis. These studies included a mix of randomized controlled trials (RCTs) and observational cohort studies, with sample sizes ranging from 500 to over 20,000 participants. The final dataset consisted of studies evaluating the cardiovascular, renal, and safety outcomes of four major classes of second-line antidiabetic drugs: SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), DPP-4 inhibitors, and sulfonylureas.

Cardiovascular Outcomes

A pooled analysis of 22 studies focusing on cardiovascular outcomes showed significant differences between drug classes in reducing cardiovascular events. SGLT2 inhibitors and GLP-1 RAs were associated with a reduced risk of major adverse cardiovascular events (MACE) compared to sulfonylureas and DPP-4 inhibitors. The pooled hazard ratio (HR) for MACE with SGLT2 inhibitors was 0.84 (95% CI: 0.78-0.90), indicating a 16% reduction in cardiovascular events, while the HR for GLP-1 RAs was 0.88 (95% CI: 0.81-0.94).

Table 1: Summary of Cardiovascular Outcomes by Drug Class

Drug Class	MACE (HR, 95% CI)	Heart Failure (HR, 95% CI)	Cardiovascular Mortality (HR, 95% CI)
SGLT2 Inhibitors	0.84 (0.78-0.90)	0.72 (0.65-0.80)	0.88 (0.81-0.94)
GLP-1 RAs	0.88 (0.81-0.94)	0.85 (0.78-0.92)	0.90 (0.84-0.96)
DPP-4 Inhibitors	1.02 (0.94-1.11)	0.98 (0.90-1.06)	1.01 (0.92-1.10)
Sulfonylureas	1.10 (1.03-1.18)	1.15 (1.05-1.25)	1.12 (1.02-1.20)

Renal Outcomes

Renal outcomes were assessed in 15 studies, with a focus on the progression of chronic kidney disease (CKD) and the need for dialysis. SGLT2 inhibitors demonstrated the most substantial renal benefits, with a pooled HR for CKD progression of 0.70 (95% CI: 0.62-0.79). This represented a 30% reduction in the risk of CKD progression compared to other second-line

therapies. GLP-1 RAs also showed modest renal protective effects, though to a lesser extent than SGLT2 inhibitors (HR: 0.82, 95% CI: 0.75-0.90).

- Studies on sulfonylureas revealed no significant benefit in slowing renal decline (HR: 1.05, 95% CI: 0.96-1.15).
- DPP-4 inhibitors exhibited neutral effects on renal outcomes (HR: 1.01, 95% CI: 0.91-1.10).
- Table 2: Summary of Renal Outcomes by Drug Class

Drug Class	CKD Progression (HR, 95% CI)	ESRD or Dialysis (HR, 95% CI)
SGLT2 Inhibitors	0.70 (0.62-0.79)	0.65 (0.58-0.73)
GLP-1 RAs	0.82 (0.75-0.90)	0.78 (0.72-0.85)
DPP-4 Inhibitors	1.01 (0.91-1.10)	1.05 (0.95-1.14)
Sulfonylureas	1.05 (0.96-1.15)	1.12 (1.03-1.22)

Safety Outcomes

Safety profiles varied across the drug classes, with notable differences in adverse event rates:

- SGLT2 inhibitors were associated with an increased risk of genitourinary infections, with a pooled relative risk (RR) of 1.52 (95% CI: 1.30-1.78).
- GLP-1 RAs were more frequently linked to gastrointestinal side effects, including nausea and vomiting (RR: 1.45, 95% CI: 1.25-1.68).
- Sulfonylureas posed the highest risk of hypoglycemia, with an RR of 3.56 (95% CI: 3.02-4.19), particularly in older adults or those with impaired renal function.
- DPP-4 inhibitors had the most favorable safety profile, with minimal increases in adverse event rates compared to other drug classes.

Table 3: Summary of Safety Outcomes by Drug Class

Drug Class	Hypoglycemia (RR, 95% CI)	Genitourinary Infections (RR, 95% CI)	Gastrointestinal Events (RR, 95% CI)
SGLT2 Inhibitors	1.15 (1.08-1.25)	1.52 (1.30-1.78)	1.12 (1.05-1.20)

GLP-1 RAs	1.05 (0.98-1.10)	1.02 (0.95-1.08)	1.45 (1.25-1.68)
DPP-4 Inhibitors	0.95 (0.88-1.02)	0.98 (0.89-1.06)	1.05 (0.92-1.15)
Sulfonylureas	3.56 (3.02-4.19)	1.08 (0.95-1.15)	1.02 (0.94-1.12)

Subgroup Analysis

Subgroup analyses based on patient characteristics, such as age, sex, and duration of diabetes, revealed consistent cardiovascular and renal benefits for SGLT2 inhibitors and GLP-1 RAs across most subgroups. However, the efficacy of sulfonylureas was diminished in older adults, with higher rates of hypoglycemia and cardiovascular events observed in this population.

Heterogeneity and Publication Bias

The overall heterogeneity between studies was moderate, with an I^2 statistic of 42% for cardiovascular outcomes and 35% for renal outcomes, suggesting some variability across study designs and populations. Sensitivity analyses, excluding studies with high risk of bias, did not significantly alter the pooled results, confirming the robustness of the findings.

Table 4: Subgroup Analysis of Cardiovascular and Renal Outcomes by Patient Characteristics

Subgroup	**SGLT2 Inhibitors (HR, 95% CI)**	**GLP-1 RAs (HR, 95% CI)**	**Sulfonylureas (HR, 95% CI)**
Younger Patients (<65 years)	0.82 (0.76-0.89)	0.86 (0.80-0.92)	1.12 (1.05-1.20)
Older Patients (≥65 years)	0.88 (0.80-0.95)	0.91 (0.85-0.97)	1.25 (1.15-1.35)
Shorter Diabetes Duration (<10 years)	0.75 (0.69-0.82)	0.80 (0.75-0.85)	1.08 (1.02-1.15)
Longer Diabetes Duration (≥10 years)	0.90 (0.82-0.97)	0.92 (0.86-0.98)	1.15 (1.08-1.23)

Discussion

The findings from this meta-analysis provide valuable insights into the comparative effectiveness of second-line antidiabetic drugs, particularly regarding their cardiovascular, renal, and safety outcomes. The results highlight the substantial benefits of newer drug classes, especially SGLT2 inhibitors and GLP-1 receptor agonists (GLP-1 RAs), over traditional therapies like sulfonylureas and DPP-4 inhibitors in managing type 2 diabetes (T2D) [13,1`4,15]. The analysis shows that SGLT2 inhibitors and GLP-1 RAs significantly reduce the risk of major adverse cardiovascular events (MACE), with SGLT2 inhibitors demonstrating the most substantial benefit, particularly in reducing heart failure hospitalizations [16]. These findings align with previous large clinical trials such as the EMPA-REG and CANVAS trials for SGLT2 inhibitors and the LEADER trial for GLP-1 RAs, which established the cardioprotective effects of these drug classes. The heart failure benefits of SGLT2 inhibitors are particularly noteworthy, as heart failure is a leading cause of hospitalization and death in people with T2D [17]. By reducing heart failure risk, SGLT2 inhibitors provide a dual advantage of managing blood glucose while offering cardiovascular protection. GLP-1 RAs, on the other hand, demonstrated a notable reduction in cardiovascular mortality, suggesting they are particularly effective in patients with established cardiovascular disease [18].

DPP-4 inhibitors did not show a significant reduction in cardiovascular events, reinforcing their role as a safer but less effective option in cardiovascular risk management. Sulfonylureas were associated with an increased risk of cardiovascular events, consistent with the long-standing concern regarding their association with hypoglycemia and adverse cardiovascular outcomes, especially in older adults [19]. The renal protective effects of SGLT2 inhibitors were also evident in the meta-analysis, with a 30% reduction in the progression of chronic kidney disease (CKD) compared to other second-line therapies. This confirms the findings of trials like CREDENCE and DAPA-CKD, which established SGLT2 inhibitors as important agents in slowing renal decline, particularly in patients with diabetic kidney disease [20] . The ability of SGLT2 inhibitors to protect against both cardiovascular and renal complications underscores their role as a first-line choice in patients with T2D and high cardiovascular or renal risk. GLP-1 RAs also showed renal benefits, though to a lesser extent than SGLT2 inhibitors, making them a viable alternative for patients who may not tolerate SGLT2 inhibitors[21]. In contrast, DPP-4 inhibitors and sulfonylureas had neutral or even negative effects on renal outcomes, suggesting they may not offer additional benefits in patients with kidney disease. The safety profiles of second-line antidiabetic drugs varied, with SGLT2 inhibitors being associated with a higher risk of genitourinary infections, a known side effect related to their mechanism of

increasing urinary glucose excretion. While this adverse effect is manageable, it emphasizes the need for careful monitoring in patients with a history of urinary tract infections [22]. GLP-1 RAs were more frequently linked to gastrointestinal side effects, such as nausea and vomiting, which may limit their use in some patients despite their cardiovascular and renal benefits. These side effects are often dose-dependent and may diminish with continued use or with dose adjustments [23]. Sulfonylureas posed the highest risk of hypoglycemia, particularly in older adults or those with impaired kidney function. Hypoglycemia is a significant concern as it can lead to cardiovascular events and reduce treatment adherence. This supports the growing consensus that sulfonylureas should be used cautiously, especially in populations at high risk for hypoglycaemia [24,25]. DPP-4 inhibitors showed a favorable safety profile with low adverse event rates, making them a good option for patients who prioritize safety over cardiovascular and renal benefits. However, their neutral effects on critical outcomes like MACE and CKD progression limit their broader utility in high-risk patients [26,27].

Limitations

While this meta-analysis provides a comprehensive review of the available evidence, some limitations should be noted. First, the inclusion of both RCTs and observational studies introduces potential heterogeneity, although random-effects models were used to account for this. Additionally, the follow-up durations varied across studies, which may influence the assessment of long-term outcomes such as CKD progression or cardiovascular mortality. Finally, the possibility of publication bias, particularly in safety outcomes, cannot be entirely ruled out despite the use of statistical tests for bias.

Conclusion

This meta-analysis demonstrates that SGLT2 inhibitors and GLP-1 receptor agonists provide superior cardiovascular and renal benefits compared to traditional second-line therapies like sulfonylureas and DPP-4 inhibitors in people with type 2 diabetes. These newer drugs should be prioritized in clinical practice for patients at high cardiovascular or renal risk, while safety profiles must be considered in individualized treatment decisions.

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