Systematic Review/Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

A meta-analytic review of the safety and efficacy of semaglutide in type 2 diabetes mellitus and chronic kidney disease patients

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Background: Type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) frequently coexist, posing a significant challenge due to increased risks of cardiovascular disease and mortality. Glucagon-like peptide-1 receptor agonists, such as semaglutide, have demonstrated potential for enhancing glucose control and reducing cardiovascular and renal risks.

Methods: Randomized controlled trials (RCTs) were taken to compare semaglutide with placebo or standard care in adults with T2DM and CKD. Key outcomes assessed included cardiovascular mortality, major adverse cardiovascular events (MACE), kidney-related adverse events, all-cause mortality, and hospitalization rates.

Results: Three RCTs involving 10 013 patients were included. Semaglutide demonstrated a 29% reduction in cardiovascular mortality (risk ratio [RR]: 0.71; 95% confidence interval [CI]: 0.52–0.97; $P = 0.03$; $I^2 = 59\%$) and a 20% reduction in MACE (RR: 0.80; 95% CI: 0.71–0.91; $P = 0.0007$; $I^2 = 0\%$). A significant 20% decrease in kidney-related adverse events was observed (RR: 0.80; 95% CI: 0.71–0.89; $P < 0.0001$; $I^2 = 0\%$), and semaglutide also reduced the need for cardiovascular medications (RR: 0.86; 95% CI: 0.81–0.91; $P < 0.00001$; $I^2 = 13\%$).

Conclusion: Semaglutide shows promise as a therapeutic option for T2DM patients with CKD, significantly improving cardiovascular and renal outcomes. Its integration into treatment regimens for high-risk patients may enhance clinical outcomes and reduce treatment complexity. However, more extensive and longer-term studies are needed to confirm these findings.

Keywords: cardiovascular events, chronic kidney disease, GLP-1 receptor agonist, kidney events, meta-analysis, mortality, semaglutide, type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is a growing global health issue. More than 536 million people have T2DM, which is expected to rise to 783 million by 2045[1]. Among the complications of T2DM, CKD is the most common, with nearly 40% of those diagnosed with diabetes affected[2,3]. The combination of T2DM and CKD not only accelerates progression to ESRD but also increases the risk of CVD and mortality[4–6]. Patients with T2DM and CKD are more than twice as likely to die from CVD; indeed, they account for 60% of years of life lost due to diabetes[7,8]. Patients with T2DM and CKD, although they have many treatment options, are at extremely high risk for both cardiovascular and renal morbidity and mortality[9]. Most traditional glucose-lowering agents cannot provide all-around cardiorenal protection; thus, the limitation is a need for effective therapy[10]. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1 RAs) appeared recently, and their glycemic effects also benefit the cardiovascular

HIGHLIGHTS

- Semaglutide significantly improves key cardiovascular and renal outcomes in T2DM-CKD patients.
- Moderate heterogeneity was noted for certain endpoints, but sensitivity analyses supported the robustness of the findings.
- Further large-scale trials are needed to confirm long-term safety and efficacy in diverse populations.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2025) 87:2278–2285

Received 25 November 2024; Accepted 25 February 2025

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 27 March 2025

http://dx.doi.org/10.1097/MS9.0000000000003126

Table 1

Baseline characteristics of patients included in the meta-analysis

Study	Total sample (N)	Semaglutide (n)	Placebo (n)	Age (years) semaglutide/ placebo	Gender (M/F) semaglutide/ placebo	Body weight (kg) semaglutide/ placebo	BMI semaglutide/ placebo	HbA1c (%) semaglutide/ placebo	SBP (mm Hg) semaglutide/ placebo	DBP (mm Hg) semaglutide/ placebo	MI—no. (%) semaglutide/ placebo	Heart failure —no. (%) semaglutide/ placebo	Estimated GFR (mL/min/1.73 m²) semaglutide/ placebo
Perkovic *et al*[25]	3533	1767	1766	66.6 ± 9.0/ 66.7 ± 9.0	1248/519/ 1216/550	89.5 ± 19.8/ 89.8 ± 21.2	31.9 ± 6.1/ 32.0 ± 6.5	7.8 ± 1.3/ 7.8 ± 1.3	138.9 ± 16.1/ 138.4 ± 15.4	76.8 ± 10.0/ 76.1 ± 10.0	405 (22.9) / 403 (22.8)	342 (19.4) /336 (19.0)	46.9 ± 15.6/ 47.1 ± 14.7
Marso *et al*[15]	3297	1648	1649	64.65 ± 7.2/ 64.6 ± 7.55	1013/635/ 989/660	92.35 ± 20.7/ 91.85 ± 20.55	—/—	8.7 ± 1.45/ 8.7 ± 1.5	135.95 ± 17.5/ 135.3 ± 16.85	77 ± 10.0/ 77.1 ± 10.05	530 (32.15) / 542 (32.85)	381 (23.1) /396 (24.05)	—/—
Husain *et al*[26]	3183	1591	1592	66 ± 7/66 ± 7	1084/507/ 1092/500	91.0 ± 21.4/ 90.8 ± 21.0	32.3 ± 6.6/ 32.3 ± 6.4	8.2 ± 1.6/ 8.2 ± 1.6	135 ± 18/ 136 ± 18	76 ± 10/ 76 ± 10	—/—	—/—	74 ± 21/74 ± 21

and renal front[11–13]. Recent KDIGO (Kidney Disease: Improving Global Outcomes) and ADA (American Diabetes Association) guidelines recommend additional treatment for patients with T2DM at increased risk for atherosclerotic cardiovascular disease, heart failure, or progression of CKD namely SGLT2i and GLP-1 RA[14,15].

Among the GLP-1 RAs, semaglutide has shown particularly notable efficacy for glycemic control, weight reduction, and cardiometabolic risk reduction – surpassing many other agents in its class. It has demonstrated significant effects on glycemic parameters, major adverse cardiovascular events, mortality, hospitalization for heart failure, and slowing renal function decline[16,17]. This distinction is a primary reason semaglutide has garnered special interest in the context of T2DM and CKD, where weight management and robust cardiovascular/renal protection are critical factors. Given the overlapping risks and complexities in managing patients with T2DM and CKD, a comprehensive safety and efficacy assessment of semaglutide in this high-risk population is not just appropriate – it is necessary.

For this purpose, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing semaglutide with placebo or standard care in T2DM and CKD. We aimed to leave no stone unturned in understanding if semaglutide contributed to kidney adverse events and cardiovascular outcomes and whether its overall safety profile was affected. The thoroughness of our research should provide reassurance about the validity of our findings, while also addressing a research gap that specifically examines semaglutide in T2DM-CKD populations.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[18], also the work has been reported in line with Assessing the methodological quality of systematic reviews Guidelines and is registered on PROSPERO under the ID CRD42024610029. We performed a comprehensive search to identify relevant studies assessing the safety and efficacy of semaglutide in patients with T2DM and chronic kidney disease (CKD), with or without cardiovascular disease (CVD).

Data sources and search strategy

Electronic databases, including MEDLINE, Embase, and Cochrane CENTRAL, were systematically searched from their inception until May 2024. We used a combination of Medical Subject Headings and keywords, such as "semaglutide," "type 2 diabetes mellitus," "chronic kidney disease," "cardiovascular disease," "randomized controlled trial," and "placebo." Boolean operators (AND, OR) were applied to refine search results, and database-specific filters (e.g. limiting to RCTs in humans, English language) were used to ensure methodological rigor. Reference lists of relevant systematic reviews and meta-analyses were examined to identify additional studies. We also searched clinical trial registries and conference abstracts for potentially unpublished or ongoing trials. The detailed search strategy is given in Supplemental Digital Content Table 1, available at:. http://links.lww.com/MS9/A760.

Inclusion and exclusion criteria

We included RCT studies involving adults aged 18 years or older diagnosed with T2DM and CKD. Eligible studies compared

semaglutide with placebo or standard care and reported on at least one predetermined clinical outcome. These outcomes encompassed major kidney adverse events, major adverse cardiovascular events (MACE), cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, all-cause mortality, serious adverse events, hospitalization due to unstable angina or heart failure, and the use of cardiovascular medications.

Studies were excluded if they were observational, such as cohort or case-control studies, case reports, case series, reviews, editorials, or lacked a control group. We also excluded studies that did not report relevant clinical outcomes or were published in languages other than English.

Study selection and data extraction

Two independent reviewers screened the titles and abstracts of all retrieved articles to assess eligibility. Full-text articles were obtained for studies that appeared to meet the inclusion criteria or when eligibility was uncertain. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer. Data extracted included study characteristics, patient demographics, interventions, outcomes, and assessments of risk of bias, using a standardized data extraction form.

Risk of bias assessment

The quality of the included RCTs was assessed using the Cochrane Risk-of-Bias tool for Randomized Trials (RoB 2.0)[19]. This tool evaluates potential bias in five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as "low risk," "some concerns," or "high risk" of bias. Any discrepancies were resolved by consensus among the reviewers.

Statistical analysis

Statistical analyses were conducted using Review Manager (RevMan) software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). For dichotomous outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs) using a random-effects model to account for potential heterogeneity among studies. Heterogeneity was assessed with the Chi-squared test and quantified using the $I2$ statistic, where $I2$ values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively[20]. A P-value less than 0.05 was considered statistically significant. Due to the limited number of studies (fewer than 10), we did not assess publication bias through funnel plots. Several studies followed this methodology[21–24]

Results

After applying the inclusion and exclusion criteria, three RCTs involving a total of 10 013 patients with T2DM and CKD were included in the meta-analysis[15,25,26]. The study selection process is illustrated in the PRISMA flowchart (Fig. 1A). 1750 records were identified (1640 from databases and 110 from registers), 400 duplicates were removed, 1350 titles/abstracts were screened (811 excluded), and after assessing 340 full-text articles, three studies met all eligibility criteria and were included in the final analysis. Table 1 summarizes the detailed characteristics of the included studies. All studies were assessed to have a low risk of bias based on the Cochrane Risk-of-Bias tool (Fig. 1B and C and Supplemental Digital Content Table 2, available at: http://links.lww.com/MS9/A760).

Primary outcomes

Cardiovascular mortality

Semaglutide was associated with a statistically significant reduction in cardiovascular mortality compared to placebo (RR: 0.71; 95% CI: 0.52–0.97; P = 0.03; $I2$ = 59%) (Fig. 2). This corresponds to a 29% relative risk reduction in death from cardiovascular causes. However, the moderate heterogeneity ($I2$ = 59%) indicates some variability among the studies, but its nonsignificant P-value (0.09) mitigates it.

Major adverse cardiovascular events

Semaglutide also significantly decreased the incidence of MACE (RR: 0.80; 95% CI: 0.71–0.91; P = 0.0007; $I2$ = 0%) (Fig. 3), suggesting a 20% reduction in the risk of MACE among patients with T2DM and CKD.

Secondary outcomes

Major kidney adverse events

The meta-analysis revealed that patients treated with semaglutide experienced a significant reduction in major kidney adverse events compared to those receiving a placebo (RR: 0.80; 95% CI: 0.71–0.89; P < 0.0001; $I2$ = 0%) (Fig. 4). This indicates a 20% relative risk reduction in significant kidney adverse events with semaglutide treatment.

Nonfatal myocardial infarction

The incidence of nonfatal myocardial infarction was lower in the semaglutide group compared to placebo, but this difference did not reach statistical significance (RR: 0.86; 95% CI: 0.66–1.12; P = 0.27; $I2$ = 24%) (Fig. 5). The 14% relative risk reduction suggests a potential benefit, but the wide CI crossing unity indicates uncertainty in the effect estimate. The low heterogeneity among studies ($I2$ = 24%) suggests consistent findings.

Nonfatal stroke

Semaglutide did not significantly reduce the incidence of nonfatal stroke compared to placebo (RR: 0.86; 95% CI: 0.53–1.40; P = 0.54; $I2$ = 64%) (Supplemental Digital Content Figure 1, available at: http://links.lww.com/MS9/A760). The high heterogeneity ($I2$ = 64%) indicates substantial variability among studies, but its non-significance (P-value: 0.06) suggests no effect of heterogenicity.

All-cause mortality

With semaglutide treatment, a nonsignificant trend toward reduced all-cause mortality was observed (RR: 0.79; 95% CI: 0.59–1.07; p = 0.12; $I2$ = 61%) (Supplemental Digital Content Fig. 2, available at: http://links.lww.com/MS9/A760). This represents a 21% relative risk reduction, although the CI includes 1,

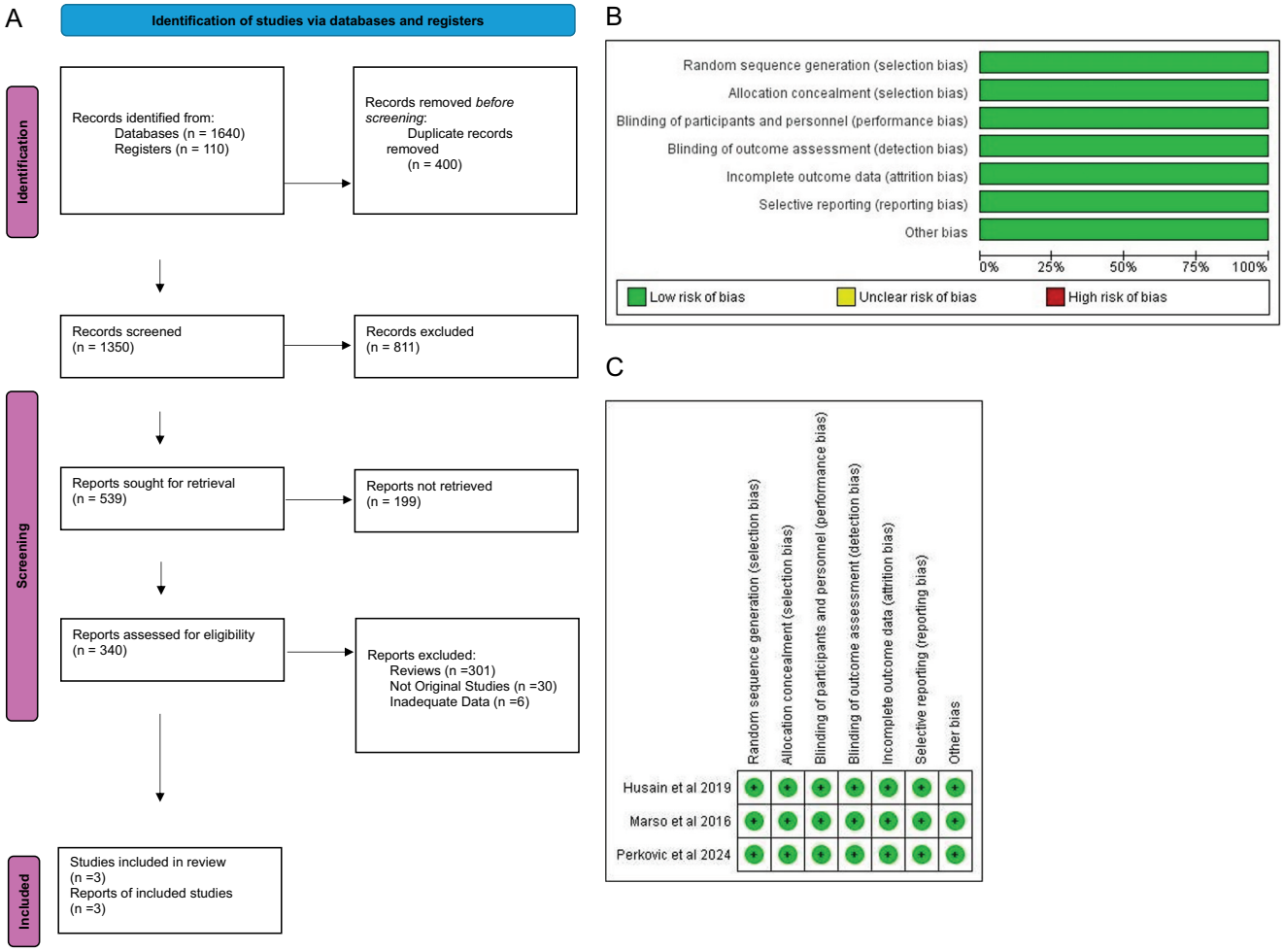

Figure 1. A: Prisma flowchart. B: Risk of bias graph. C: Risk of bias summary.

indicating that the result is not statistically significant. Moderate heterogeneity is also seen, which is insignificant (*P*-value: 0.08).

Serious adverse events

Semaglutide significantly reduced the occurrence of serious adverse events compared to placebo (RR: 0.92; 95% CI: 0.86–0.99; *P* = 0.03; *I2* = 38%) (Supplemental Digital Content Figure. 3, available at: http://links.lww.com/MS9/A760). This 8% relative risk reduction highlights a favorable safety profile for semaglutide in this patient population. The moderate heterogeneity indicates some variability but does not compromise the overall finding as it is insignificant (*P*-value: 0.20).

Hospitalization for unstable angina

There was no significant difference between semaglutide and placebo groups regarding hospitalizations due to unstable angina (RR: 1.01; 95% CI: 0.55–1.85; *P* = 0.98; *I2* = 28%) (Supplemental Digital Content Figure 4, available at: http://links.lww.com/MS9/A760). The RR close to 1 suggests no effect, and the wide CI reflects limited precision due to low event rates. The low heterogeneity indicates consistent results across studies.

Hospitalization for heart failure

Similarly, semaglutide did not significantly affect the rate of hospitalizations for heart failure (RR: 1.03; 95% CI: 0.76–1.40; *P* = 0.86; *I2* = 0%) (Supplemental Digital Content Figure 5, available at: http://links.lww.com/MS9/A760). The lack of heterogeneity (*I2* = 0%) suggests that the findings are consistent among the included studies. The RR indicates no significant difference between groups.

Use of cardiovascular medications

The use of cardiovascular medications was significantly reduced in the semaglutide group compared to placebo (RR: 0.86; 95% CI: 0.81–0.91; *P* < 0.00001; *I2* = 13%) (Supplemental Digital Content Figure 6, available at: http://links.lww.com/MS9/A760). This 14% relative risk reduction suggests that patients treated with semaglutide may require fewer additional cardiovascular therapies, potentially due to improved cardiovascular outcomes. The low heterogeneity supports the reliability of this finding.

Figure 2. Cardiovascular mortality.

Assessment of heterogeneity and sensitivity analyses

Heterogeneity was moderate to high for some outcomes, such as cardiovascular mortality and nonfatal stroke. Sensitivity analyses (including leave-one-out approaches) did not significantly alter the overall effect estimates, suggesting that the findings remain robust. Nevertheless, possible sources of variability may include differences in baseline severity of CKD or T2DM, variations in follow-up durations, and heterogeneity in patient demographics. Further subgroup or sensitivity analyses in larger datasets could help clarify these differences.

Publication bias

Due to the inclusion of fewer than 10 studies, assessment of publication bias using funnel plots was not feasible. Therefore, the possibility of publication bias cannot be entirely excluded. Given the small number of included RCTs, this limitation could influence the robustness of our conclusions and underscores the need for additional research.

Meta-regression

A meta-regression was impossible because fewer than five studies were included in the analysis. The limited number of studies restricts the statistical power required to draw meaningful conclusions from such an analysis. Consequently, the findings may not accurately reflect the broader trends or relationships that could be observed in a more substantial dataset. This limitation underscores the necessity for further research to enhance the body of evidence on this topic.

Discussion

This systematic review and meta-analysis evaluated the safety and efficacy of semaglutide in patients with T2DM and CKD, with or without CVD. Data from three RCTs encompassing 10 013 patients were analyzed. Our findings indicate that semaglutide significantly reduces the risk of significant kidney adverse events and MACE compared to placebo. Additionally, semaglutide was associated with a reduction in cardiovascular mortality and serious adverse events. While reductions in nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality did not achieve statistical significance, the observed trends favored semaglutide. Furthermore, the use of cardiovascular medications was significantly decreased in the semaglutide group.

Our results align with previous studies that have underscored the cardiovascular and renal benefits of GLP-1 RAs in patients with T2DM[27]. For instance, the SUSTAIN-6 trial demonstrated a significant reduction in MACE among semaglutide-treated patients, consistent with our findings[28]. Similarly, the PIONEER trials highlighted the renal protective effects of semaglutide, corroborating our observation of reduced major kidney adverse events[15]. However, unlike some earlier studies, our meta-analysis did not find a statistically significant reduction in nonfatal myocardial infarction or stroke. This discrepancy may be attributed to the limited number of included studies, variations in study populations, differences in follow-up durations, or heterogeneous baseline characteristics across trials. Despite the lack of statistical significance, the clinical implications remain noteworthy for patient care and may inform future research, particularly as semaglutide could still offer important benefits in broader populations or with longer follow-up[26].

The beneficial effects of semaglutide can be attributed to its multifaceted mechanisms of action. Semaglutide enhances glycemic control and induces weight loss, both pivotal in mitigating the progression of CKD and reducing cardiovascular risk[28]. Additionally, semaglutide exhibits anti-inflammatory and anti-atherogenic properties, contributing to the stabilization of atherosclerotic plaques and improvement in endothelial function[29,30].

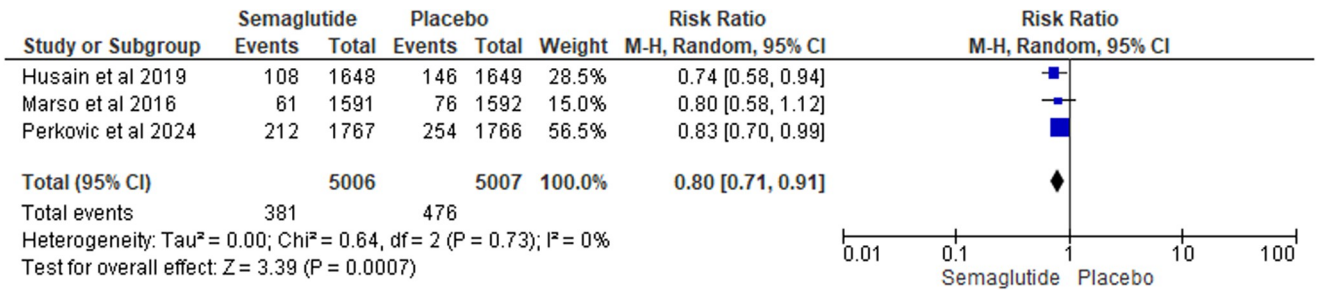

Figure 3. Major adverse cardiovascular events.

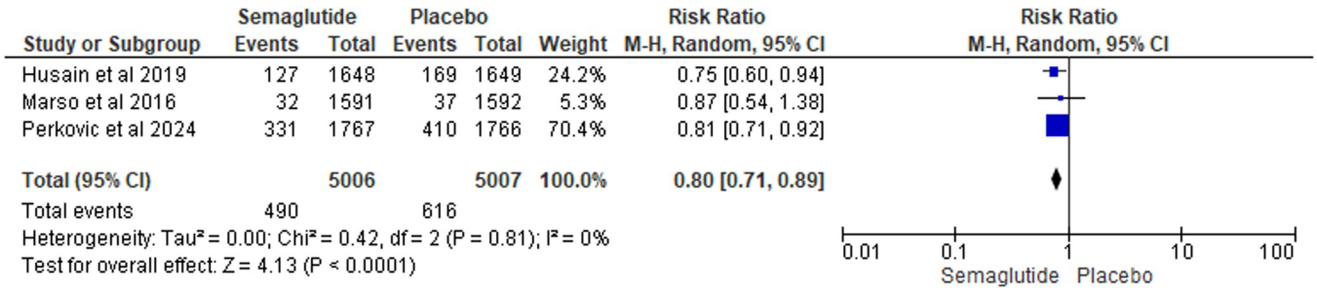

Figure 4. Major kidney adverse events.

These combined effects likely underpin the observed reductions in major kidney adverse events and MACE. Furthermore, semaglutide may improve lipid profiles and reduce oxidative stress, which are critical factors in cardiovascular health and renal function[31,32]. The significant decrease in cardiovascular medications suggests semaglutide may facilitate better managing cardiovascular risk factors, thereby reducing the need for additional pharmacotherapy and simplifying treatment regimens.

Despite the positive outcomes, this meta-analysis exhibited moderate heterogeneity in particular outcomes, such as cardiovascular mortality ($I2 = 59\%$) and all-cause mortality ($I2 = 61\%$). Possible sources of variability include differences in patient comorbidities, baseline kidney function, or follow-up durations among the included RCTs. Future studies might employ additional sensitivity or subgroup analyses (e.g. stratifying patients by CKD stage or baseline body mass index) to isolate and understand these factors more thoroughly. Indeed, the lack of detailed BMI variation data in the included RCTs is an important consideration given semaglutide's weight-dependent effects.

Clinically, our findings advocate for the integration of semaglutide into treatment regimens for patients with T2DM and CKD, particularly those at high risk for cardiovascular events. The significant reduction in adverse events in the primary kidney and cardiovascular system positions semaglutide as a valuable therapeutic option for improving patient outcomes[33,34]. Additionally, the decrease in the use of cardiovascular medications suggests potential simplification of treatment protocols and enhanced patient adherence, which can lead to better overall management of comorbid conditions. This is especially relevant in clinical settings where polypharmacy is a concern, as reducing the number of medications can improve patient quality of life and reduce the risk of medication-related adverse effects[29,35]. Also, it is an important consideration in healthcare systems, where polypharmacy is common and cost-effectiveness must be evaluated. Further economic evaluations or real-world adherence studies would offer valuable insights into whether semaglutide's benefits extend to cost savings or improvement in patient compliance. Future research should focus on large-scale, long-term, RCTs to confirm these benefits and explore the potential synergistic effects of semaglutide with other cardioprotective agents such as SGLT2i. Moreover, studies investigating the impact of semaglutide in diverse patient populations and varying stages of CKD would provide more comprehensive insights into its efficacy and safety[36].

However, this study is subject to several limitations. The small sample size (three RCTs) and limited follow-up durations restrict the generalizability of our findings and may affect the capacity to detect significant differences in certain endpoints (e.g. nonfatal stroke, and long-term mortality). Additionally, the inability to thoroughly assess publication bias (due to fewer than 10 included studies) raises caution regarding the robustness of the results. The reliance on published aggregate data rather than individual patient data restricts our ability to perform detailed subgroup analyses or adjust for confounding factors. Furthermore, the absence of long-term outcome data means that the enduring safety and efficacy of semaglutide remain to be fully established. Finally, all included studies were conducted by the same research group, which may introduce a risk of bias and affect the robustness of the findings. These considerations underscore the need for cautious interpretation and future research refinement.

Conclusion

In conclusion, semaglutide significantly reduces primary kidney and cardiovascular events in patients with T2DM and CKD and has a favorable safety profile. These findings advocate for

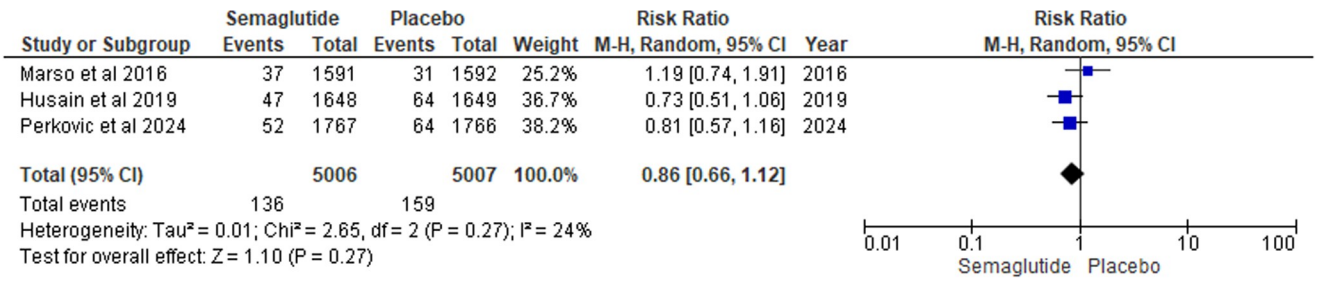

Figure 5. Nonfatal myocardial infarction.

considering semaglutide as part of the therapeutic strategy for managing T2DM and CKD to improve cardiovascular and renal outcomes. Nevertheless, the limited number of available studies and relatively short follow-up periods hamper capturing long-term safety and efficacy data. Larger, more diverse patient cohorts and longer trial durations are warranted to confirm these results and to explore specific directions, such as investigating optimal dosing, targeting particular patient subgroups (e.g. varying stages of CKD or higher BMI ranges), or designing new RCTs with distinct methodologies. As the evidence base grows, clinicians will be better equipped to determine semaglutide's precise role and cost-effectiveness in managing T2DM and CKD.

Ethical approval

Not applicable as we have used de-identified data available online.

Consent

Not applicable as it's a meta-analysis.

Sources of funding

No funding was provided for research.

Author's contribution

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Conflicts of interest disclosure

There was no conflict of interest among authors.

Research registration unique identifying number (UIN)

It is registered on Prospero CRD42024610029. The registration details can be reached at the following link: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=610029.

Guarantor

Salih Abdella Yusuf.

Provenance and peer review

No, it was not invited.

Data availability statement

The dataset supporting the conclusions of this article is included in this article.

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