Carbovascular and Renal Outcomes with SGLT-2 Inhibitors Versus GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis

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Original investigation

Keywords: SGLT2 inhibitors, GLP-1 receptor agonist, meta-analysis, Cardiovascular disease, renal outcomes, diabetes mellitus, chronic kidney disease

DOI: https://doi.org/10.21203/rs.3.rs-58029/v1

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Abstract

Background

Both sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are known to reduce cardiovascular and renal events in type 2 diabetes mellitus (DM) patients. However, no study to date has compared the effect of SGLT-2 inhibitors with that of GLP-1 RAs in type 2 DM patients with chronic kidney disease (CKD). We herein investigated the benefits of SGLT-2 inhibitors and GLP-1 RAs in CKD patients.

Methods

We performed a systematic literature search through July 2020. We selected randomized control trials that compared the risk of major adverse cardiovascular events (MACE) and a composite of renal outcomes. We performed a network meta-analysis to compare SGLT-2 inhibitors with GLP-1 RA indirectly. Risk ratios (RRs) with corresponding 95% confidence interval (CI) were synthesized.

Results

Fifteen studies were selected with a total of 20,947 patients. SGLT-2 inhibitors led to a risk reduction in MACE (RR [95% CI]; 0.80 [0.70-0.91]), but GLP-1 RAs did not (RR 0.89 [0.78-1.00]). Compared to GLP-1 RAs, SGLT-2 inhibitors did not demonstrate a significant difference (RR 0.90 [0.75-1.08]). Similarly, SGLT-2 inhibitors significantly decreased renal events (RR 0.66 [0.58-0.75]), but GLP-1 RAs did not (RR 0.80 [0.90-1.00]). SGLT-2 inhibitors were also associated with a lower risk of renal events compared to GLP-1 RAs (RR 0.73 [0.62-0.87]).

Conclusions

In patients with type 2 DM and CKD, SGLT-2 inhibitors were associated with a decreased risk of cardiovascular and renal events, but GLP-1 RA were not. SGLT-2 inhibitors significantly decreased the risk of renal events compared to GLP-1 RAs.

Background

Diabetes mellitus (DM) is a major public health problem with a high prevalence. The International Diabetes Federation estimated that 351.7 million people of working age (20–64 years) had DM in 2019, and this number is expected to increase to 417.3 million by 2030. Type 2 DM is the leading cause of chronic kidney disease (CKD); it accounts for about 36% of adult CKD in the United States. CKD with DM can progress to end-stage renal disease (ESRD), which confers a poor overall prognosis. Moreover, type 2 DM and CKD increase the risk of cardiovascular disease. Therefore, the prevention of CKD progression and cardiovascular events is essential for the management of patients with type 2 DM and CKD.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of glucose-lowering agents. SGLT2 inhibitors function through reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release. Several randomized controlled trials (RCTs) have demonstrated favorable cardiovascular and renal outcomes associated with SGLT2 inhibitors. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) decrease hemoglobin A1c by both stimulating glucose-dependent insulin secretion and reducing glucagon secretion. GLP-1 RAs are known to reduce blood pressure and body weight. A meta-analysis demonstrated that GLP-1 RAs improve cardiovascular outcomes. The American Diabetes Association recommends SGLT2 inhibitors or GLP-1 RAs in type 2 DM patients who have atherosclerotic cardiovascular disease or kidney disease. However, it remains unclear if GLP-1 RAs are beneficial to type 2 DM patients with CKD as well.

To date, no study has compared the effect of SGLT2 inhibitors on renal and cardiovascular diseases with that of GLP-1 RAs in CKD patients. We herein investigated the benefits of SGLT-2 inhibitors and GLP-1 RAs in CKD patients by network meta-analysis.

Methods

Literature search

The search strategy was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [14]. We performed a systematic search of PubMed, Medline, EMBASE, and the Cochrane Library from inception to July 31, 2020. The following keywords were applied: (sodium-glucose cotransporter-2 inhibitors) AND (SGLT-2 inhibitor) OR SGLT-2 OR 'empagliflozin' OR 'dapagliflozin' OR 'canagliflozin' OR 'luseogliflozin' OR 'ertugliflozin' OR (GLP-1 OR 'glucagon-like peptide-1 receptor' [MeSH] OR 'glucagon-like peptide-1 receptor agonist' OR 'exenatide' OR 'liraglutide' OR 'lixisenatide' OR 'semaglutide' OR 'dulaglutide' OR 'albiglutide') AND ('diabetes mellitus, type 2' [MeSH] OR 'diabetes mellitus type 2' OR 'type 2 diabetes mellitus' OR DM or diabetes) AND ('renal insufficiency, chronic' [MeSH] or CKD or 'chronic kidney disease' or 'kidney disease' or 'kidney failure' or CKF or 'chronic kidney failure' or 'renal failure' or CRF or CRD or 'chronic renal disease') AND ('myocardial infarction' [MeSH] OR MI or 'coronary artery disease' [MeSH] OR 'cardiovascular disease' [MeSH] OR 'cerebrovascular disorders' [MeSH] OR 'stroke' [MeSH] OR CVA OR 'cerebrovascular accident' [MeSH] OR MACE OR 'major adverse cardiovascular event' OR 'death' OR mortality [MeSH] OR 'all-cause mortality' OR 'cardiovascular mortality' OR 'heart failure' OR 'end stage renal disease' OR 'renal failure' OR 'kidney failure' OR ESRD OR 'renal death' OR 'albuminuria' OR 'urine albumin' OR 'proteinuria' OR 'urine protein').

We restricted the search to human studies. Reference lists included in meta-analysis studies were reviewed to minimize missing relevant studies. Two independent and blinded authors (TY and AB) reviewed the search results separately to select studies based on inclusion and exclusion criteria. When a consensus was not reached between the two authors, a third author (MW) was consulted to reach a decision.
Study selection

Studies were selected if they met the following criteria: (1) they were published in peer-reviewed journals; (2) they included adult patients (≥ 18 years old) with type 2 DM; (3) they were RCTs that compared SGLT2 inhibitors or GLP-1 RAs with placebo; (4) they compared the risk of major adverse cardiovascular events (MACE) between treatment and placebo groups; (5) they compared the risk of renal outcomes; and (6) they showed an incidence of MACE and a composite of renal outcomes in patients with CKD (defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m²). There was no restriction on publication language. Studies were excluded if (1) they included non-human subjects and (2) there was insufficient data for estimating the risk ratio (RR) even after contacting the authors.

Outcomes

The primary efficacy outcome of this analysis was 3-point MACE (MACE-3), including cardiovascular death, myocardial infarction (MI), and stroke. The secondary outcome was a composite of renal outcomes, including ESRD, a decline in kidney function (such as ≥40 % decrease in eGFR or doubling creatinine), albuminuria, and renal death.

Data extraction and quality assessment

All data from eligible studies were abstracted independently by two investigators (TY and AB). Any conflicts in data extraction or quality assessment were resolved by a third reviewer (MW). For each study, data regarding the incidence of MACE and a composite of renal outcomes in each group were abstracted. We used the Cochrane risk of bias assessment to explore sources of bias in the RCTs included in this analysis.\[15\] According to this scale, we evaluated the risk of bias in random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, selective reporting, incomplete outcome data, and other metrics.

Statistical analysis

We performed a network meta-analysis using “netmeta” package (version 1.1-0) and R programming language (R Foundation for Statistical Computing, Vienna, Austria). The RRs and 95 % confidence intervals (CIs) were estimated using Mantel-Haenszel methods. A random-effects model was used for the analysis. Heterogeneity was assessed by the probability value of the \( I^2 \) variable \[16, 17\]. We regarded an \( I^2 \) of < 40 % as “heterogeneity might not be important” and >50 % as “may represent substantial heterogeneity” based on the suggestion of the Cochrane Handbook for Systemic Review of Interventions \[18\].

Results

Literature search and included studies

A diagram of the study selection is shown in Figure 1. Initially, a total of 861 studies were obtained in the primary search from databases, and seventeen studies were identified through references. We removed 112 duplicate studies; 766 studies were screened. By screening titles and abstracts, 740 papers were excluded because they did not meet the inclusion criteria. By assessing full-text articles, eleven studies were excluded due to missing data. Finally, fifteen studies published up to July 31, 2020 were selected for our meta-analysis according to the inclusion criteria.\[8, 19-32\] Out of fifteen studies, eight studies were RCTs that compared SGLT2 inhibitors (Canagliflozin, \[8, 19, 25\] Dapagliflozin, \[20, 24\] Empagliflozin, \[21, 22\] and Luseogliflozin \[23\]) with placebo; seven studies compared GLP-1 RAs (Albiglutide, \[27\] Dulaglutide weekly, \[26, 32\] Exenatide weekly, \[28\] Liraglutide, \[30\] Semaglutide subcutaneously weekly, \[31\] and Semaglutide oral \[29\]) with placebo. The pooled population consisted of 8,926 patients in SGLT2 inhibitors studies (4,993 in the group treated with SGLT2 inhibitors and 3,933 in the control group) and 12,021 patients in GLP-1 RA studies (6,092 in the group treated with GLP-1 RAs and 5,929 in the control group). Hemoglobin A1c ranged from 6.5 % to 12 %. eGFR ranged from 15 to 59 ml/min/1.73m² in one study \[32\] and from 30 to 59 ml/min/1.73m² in other studies, with one study that did not mentioned its lower limit \[20\]. The median length of follow-up ranged from 6 months to 50.4 months in SGLT2 inhibitor studies and 12.0 months to 64.8 months in GLP-1 RA studies. All studies defined MACE-3 as a composite outcome comprised of cardiovascular death, myocardial infarction, and stroke. For renal outcomes, all studies included ESRD; all studies except one included renal death; \[32\] four studies included macroalbuminuria; \[21, 26, 28, 30\] one study defined reduced kidney function as a decrease in eGFR ≥ 30 %, \[26\] four as a decrease in eGFR ≥ 40 %, \[19, 20, 28, 32\] and three as a doubling creatinine. \[8, 21, 30\]

Study characteristics and quality assessment

The definitions of terms, including a composite of renal outcomes, and characteristics of the included studies are listed in Table 1 and Table 2, respectively. All studies defined CKD as eGFR < 60 ml/min/1.73m². The quality evaluation of the included studies is shown in Figure 2.

Network meta-analysis of treatment groups compared with placebo

MACE-3

Network plots were shown in Figure 3. SGLT-2 inhibitors were associated with a decreased risk of MACE-3 compared with placebo (RR [95 % CI]; 0.80 [0.70-0.91]), but GLP-1 RAs were not (RR 0.89 [0.78-1.00]). Compared to GLP-1 RAs, SGLT-2 inhibitors did not show a significant difference in the risk of MACE-3 (RR 0.90 [0.75-1.08]) (Figure 4). There was no heterogeneity (\( I^2 = 19.5 \), \( p = 0.25 \)).

Renal outcomes
We also performed a network meta-analysis of the risk of renal events. Network plots were shown in Figure 5. SGLT-2 inhibitors significantly decreased renal events (RR 0.66 [0.58-0.75]), but GLP-1 RAs did not (RR 0.80 [0.90-1.00]). SGLT-2 inhibitors were also associated with lower risk compared to GLP-1 RAs (RR 0.73 [0.62-0.87]) (Figure 6). There was no heterogeneity ($I^2 = 0\%$, $p = 0.82$).

**Discussion**

Our study revealed that SGLT-2 inhibitors decrease the risk of cardiovascular and renal events in type 2 DM patients with CKD. On the other hand, GLP-1 RAs did not lead to significantly lower cardiovascular or renal endpoints although they showed numerically better results. An indirect comparison of SGLT-2 inhibitors with GLP-1 RAs revealed that SGLT-2 inhibitors significantly decrease the risk of renal outcomes.

Various hypotheses have emerged explaining the positive impact of SGLT-2 inhibitors. The pathophysiology seems to be a combination of several mechanisms. First, SGLT-2 inhibitors have mild natriuretic and diuretic effects that lead to BP reduction. [33] BP reduction is an important factor that confers cardiovascular benefits and renoprotective effects. Second, SGLT-2 mitigates low-grade inflammation. SGLT-2 inhibitors prevent glucose entry into proximal tubular cells, which limits glucotoxicity, potentially leading to oxidative stress. [34]

Since SGLT-2 inhibitors antagonize glucose reabsorption in the renal tubule, we can anticipate that the effect of SGLT-2 inhibitors is dependent on eGFR. However, a pooled analysis of clinical trials revealed that SGLT-2 inhibitors decrease body weight, BP, and albuminuria regardless of eGFR, although glucose-lowering effects decreased as eGFR declined. [35] We hypothesize that the mechanisms of SGLT-2 inhibitors on cardiovascular and renal diseases are beneficial in patients with CKD as well.

In addition to glycemic control, several mechanisms explain the beneficial effects of GLP-1 RAs. First, GLP-1 RAs lead to BP reduction, [10] which can be attributed to natriuresis. [36] Other possible mechanisms are the reduction of reactive oxygen species and inflammation [37] and improvement of endothelial function. [38] However, our study did not find a significant difference between GLP-1 RAs and placebo. A prior study revealed that daily liraglutide and weekly semaglutide demonstrated significant superiority in reducing MACE, while lixisenatide was neutral in reducing cardiovascular risk. [39] We can hypothesize that there may be a class effect for cardiovascular and renal risk reduction.

The major strength of our analysis is that this is the first study that investigates the effect of SGLT-2 inhibitors and GLP-1 RAs on cardiovascular and renal events in type 2 DM patients with CKD. In the context of lacking RCTs directly comparing SGLT-2 inhibitors and GLP-1 RAs, our study provides evidence that it can be plausible to use SGLT-2 inhibitors over GLP-1 RAs for patients with DM and CKD. We included 8,926 patients in SGLT-2 inhibitors studies and 12,021 patients in GLP-1 RAs studies. Large sample size could be strong enough to reveal a statistically significant difference.

Our meta-analysis has several limitations. First, there is still a concern that CKD patients may not be fully randomized since the studies included are subgroup analyses of RCTs. Second, baseline hemoglobin A1c, follow-up duration, and medications and doses varied among studies, which can be a risk of heterogeneity. However, no significant heterogeneity was observed in this analysis. Third, the patients included in each trial may have achieved different levels of hemoglobin A1c, which may be subject to bias as well. Lastly, we defined CKD as eGFR < 60 ml/min/1.73m$^2$; we did not included patients with albuminuria. Therefore, we were not able to investigate the effects of SGLT-2 inhibitors and GLP-1 RAs for those who have albuminuria and eGFR > 60 ml/min/1.73m$^2$.

**Conclusion**

In patients with type 2 DM and CKD defined as eGFR <60 ml/min/1.73m$^2$, SGLT-2 inhibitors were associated with decreased risk of cardiovascular and renal events. GLP-1 RAs did not lead to significantly lower cardiovascular or renal endpoints although they showed numerically better results. SGLT-2 inhibitors significantly decrease the risk of renal events compared to GLP-1 RAs.

**Abbreviations**

DM: Diabetes mellitus; CKD: chronic kidney disease; ESRD: end-stage renal disease; Sodium-glucose cotransporter-2: SGLT-2; RCT: randomized controlled trial; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; BP: blood pressure; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MACE: major adverse cardiovascular events; eGFR: estimated glomerular filtration rate; RR: risk ratio; 3-point MACE: MACE-3; MI: myocardial infarction; CI: confidence interval;

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**
The authors declare that they have no competing interests.

Funding

The author (KT) received a fund from the Japan Society for the Promotion of Science, and Japan Agency for Medical Research and Development (AMED). The funding agency had no role in designing the study, conducting the analysis, interpreting the data or writing the manuscript.

Acknowledgments

Financial Support: This work was supported by grants from the Japan Society for the Promotion of Science, Salt Science Research Foundation (20C4), and Japan Agency for Medical Research and Development (AMED).

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Tables

Table 1: Definitions of terms in included studies

SGLT2i, sodium-glucose cotransporter-2; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RCT, randomized control study; eGFR, estimated glomerular filtration rate; Hgb A1c, hemoglobin A1c; ESRD, end-stage renal disease.
| Study design | Setting | Drug dose (mg/day) | Median follow up (months) | eGFR (ml/min/1.73m²) | Range of HgbA1c | Renal outcome |
|--------------|---------|-------------------|--------------------------|-----------------------|-----------------|--------------|
| SGLT2i vs placebo |         |                   |                          |                       |                 |              |
| CANVAS Program RCT | Multinational | Canagliflozin 300/100 | 29.0 | 30-59 | 7.0-10.5 | ≥ 40% eGFR decline, ESRD, renal death |
| CREDENCE RCT | Multinational | Canagliflozin 100 | 31.4 | 30-59 | 6.5-12.0 | Doubinc creatinine, ESRD, renal death |
| DECLARE-TIMI 58 RCT | Multinational | Dapagliflozin 10 | 50.4 | <60 | 6.5-12.0 | ≥ 40% eGFR decline, ESRD, renal death |
| EMPA-REG OUTCOME RCT | Multinational | Empagliflozin 10/25 | 37.2 | 30-59 | 7.0-9.0 | Macroalbuminuria, doubling creatinine, ESRD, death |
| EMPA-REG RENAL RCT | Multinational | Empagliflozin 25 | 12.0 | 30-59 | 7.0-9.0 | N/A |
| Haneda 2016 RCT | Multicenter | Luseogliflozin 2.5 | 12.0 | 30-59 | 6.5-10 | N/A |
| Kohan 2014 RCT | Multinational | Dapagliflozin 5/10 | 24.0 | 30-59 | 7.0-11.0 | N/A |
| Yale 2013 RCT | Multinational | Canagliflozin 300/100 | 6.0 | 30-59 | 7.0-10.5 | N/A |
| GLP-1 RA vs placebo |         |                   |                          |                       |                 |              |
| AWARD-7 RCT | Multinational | Dulaglutide 0.75/1.5 (weekly) | 12.0 | 15-59 | 7.5-10.5 | ≥ 40% eGFR Decline or ESRD |
| EXSCEL RCT | Multinational | Exenatide 2 (weekly) | 38.4 | 30-59 | 6.5-10 | Macroalbuminuria, ≥ 40% eGFR decline, ESRD, renal death |
| HARMONY Outcomes RCT | Multinational | Albiglutide 30/50 (weekly) | 19.2 | 30-59 | >7 | N/A |
| LEADER RCT | Multinational | Liraglutide 1.8 | 45.6 | 30-59 | >7 | Macroalbuminuria, doubling of serum creatinine, ESRD, renal death |
| PIONEER-6 RCT | Multinational | Semaglutide 14 (oral) | 15.9 | 30-59 | N/A | N/A |
| REWIND RCT | Multinational | Dulaglutide 1.5 (weekly) | 64.8 | 15-59 | <9.5 | Macroalbuminuria, ≥ 30% eGFR decline, ESRD, renal death |
| SUSTAIN-6 RCT | Multinational | Semaglutide 0.5/1 (weekly) | 25.2 | 30-59 | >7 | N/A |

Table 2: Baseline characteristics of included studies

SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; BMI, body mass index; Hgb A1c, hemoglobin A1c; DPP-4i, dipeptidyl peptidase-4 inhibitors; SU, sulfonylurea; BB, beta blocker; CCB, calcium channel blocker; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
| Author (year) | Number | Age | Male (%) | BMI | HgbA1c (%) | Insulin (%) | Biguanides (%) | DPP-4i (%) | SU (%) | BB (%) | CCB (%) | ACEi/ARB (%) | Loop diuretics (%) | Statin (%) | Asp (%) |
|--------------|--------|-----|----------|-----|------------|-------------|----------------|-----------|--------|--------|--------|-------------|-------------------|------------|--------|
| **SGLT2i vs placebo** | | | | | | | | | | | | | | |
| CANVAS Program | 2039 | 63.3 | 64.2 | 32 | 8.2 | 61 | 57.0 | 13.9 | 37.2 | 62.5 | N/A | 81.2 | 59.9 | 78.0 | N/A |
| CREDENCE | 2592 | 63 | 66.1 | 31.3 | 8.3 | 65.5 | 57.8 | 17.1 | 28.8 | 40.2 | N/A | 99.9 | 46.7 | 69.0 | N/A |
| DECLARE-TIMI 58 | 1265 | 64 | 63.0 | 32 | 8.3 | 40.9 | 82.0 | 16.8 | 42.7 | 52.6 | N/A | 81.3 | 40.6 | 74.9 | 61.0 |
| EMPA-REG OUTCOME | 1819 | 66.2 | 69.6 | 30.8 | 8.1 | 48.2 | 74.0 | 11.3 | 42.8 | 64.9 | 33.0 | 80.7 | 29.0 | 77.0 | 82.7 |
| EMPA-REG RENAL | 448 | 64.1 | 56.4 | 30.2 | 8.0 | 58.1 | 59.4 | N/A | 39.3 | 68.4 | 37.0 | 84.3 | 58.5 | 78.4 | 81.1 |
| Haneda 2016 | 242 | 66.9 | 71.3 | 25.1 | 7.7 | 0 | 12.7 | 16.6 | 37.6 | N/A | N/A | 66.3 | 1.9 | N/A | N/A |
| Kohan 2014 | 252 | 67.0 | 65.1 | N/A | 8.3 | 65.1 | N/A | N/A | 25.0 | N/A | N/A | N/A | N/A | N/A | N/A |
| Yale 2013 | 269 | 68.5 | 60.6 | 33 | 8.0 | 74.0 | 1.5 | 7.4 | 31.2 | 56.1 | 41.6 | 87.4 | N/A | 78.8 | N/A |
| **GLP-1 RAs vs placebo** | | | | | | | | | | | | | | | |
| AWARD-7 | 577 | 64.6 | 52.3 | 32.5 | 8.6 | 100 | N/A | N/A | N/A | 62.3 | 56.3 | 92.0 | 74.7 | 70.1 | N/A |
| EXSCEL | 3177 | 62.0 | 62.0 | 32.7 | 8.1 | 46.3 | 76.6 | 14.9 | 36.6 | 55.7 | 31.9 | 79.9 | 43.7 | 73.5 | 63.4 |
| HARMONY Outcomes | 2222 | 64.0 | 69.0 | 32.3 | 8.7 | 59.3 | 73.9 | 15.2 | 28.9 | 66.9 | 30.3 | 81.9 | 19.0 | 84.3 | 77.2 |
| LEADER | 2158 | 64.0 | 64.2 | 32.5 | 8.7 | 44.6 | 76.5 | 0.06 | 50.7 | 55.5 | 33.4 | 82.9 | 17.8 | 72.2 | 62.5 |
| PIONEER-6 | 856 | 66.0 | 68.0 | 32.3 | 8.2 | 60.6 | 77.4 | 0.06 | 32.3 | N/A | N/A | N/A | N/A | N/A | N/A |
| REWIND | 2199 | 66.2 | 53.7 | 32.3 | 7.3 | 23.9 | 81.2 | 5.7 | 46.0 | 45.6 | N/A | 81.5 | N/A | 66.2 | 53.4 |
| SUSTAIN-6 | 832 | 65.0 | 61.0 | 32.8 | 8.7 | 58.0 | 73.2 | 0.2 | 42.8 | 57.4 | 32.0 | 83.5 | 16.9 | 72.8 | 63.4 |

**Figures**
Figure 1
Flow diagram for study selection
Figure 2

Quality assessment (Cochrane risk of bias tool) for included RCTs RCT; randomized control study.
Figure 3
Network plot for MACE. SGLT-2, sodium-glucose cotransporter 2; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events.

Figure 4

| Treatment          | Comparison: other vs 'Placebo' | RR      | 95%-CI   |
|--------------------|--------------------------------|---------|----------|
| SGLT-2 inhibitors  | (Random Effects Model)         | 0.80    | [0.70; 0.91] |
| GLP-1 RA           |                                | 0.89    | [0.78; 1.00] |

| Treatment          | Comparison: other vs 'GLP-1 RA' | RR      | 95%-CI   |
|--------------------|---------------------------------|---------|----------|
| SGLT-2 inhibitors  | (Random Effects Model)         | 0.90    | [0.75; 1.08] |
| Placebo            |                                | 1.13    | [1.00; 1.28] |

| Treatment          | Comparison: other vs 'SGLT-2 inhibitors' | RR      | 95%-CI   |
|--------------------|------------------------------------------|---------|----------|
| GLP-1 RA           | (Random Effects Model)                  | 1.11    | [0.93; 1.33] |
| Placebo            |                                           | 1.25    | [1.10; 1.43] |
Network meta-analysis reporting risk ratio (RR) for MACE (A) in comparison with placebo, (B) in comparison with GLP-1 RA, (C) in comparison with SGLT-2 inhibitors in CKD patients. SGLT-2, sodium-glucose cotransporter 2; GLP-1 RA; glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; CKD, chronic kidney disease.

Figure 5

Network plot for renal events. SGLT-2, sodium-glucose cotransporter 2; GLP-1 RA; glucagon-like peptide-1 receptor agonist.
Network meta-analysis reporting risk ratio (RR) for renal outcomes (A) in comparison with placebo, (B) in comparison with GLP-1 RA, (C) in comparison with SGLT-2 inhibitors in CKD patients. SGLT-2, sodium-glucose cotransporter 2; GLP-1 RA, glucagon-like peptide-1 receptor agonist; CKD, chronic kidney disease.

**Supplementary Files**

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