Network Meta-Analysis on the Effects of Finerenone Versus SGLT2 Inhibitors and GLP-1 Receptor Agonists on Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease

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Research Article

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Abstract

Objective: To evaluate the cardiovascular and renal benefits of finerenone, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagonlike peptide-1 receptor agonists (GLP-1 RA) in patients with Type 2 Diabetes Mellitus (T2DM) and chronic kidney disease (CKD) with network meta-analysis.

Methods: Systematic literature searches were conducted of PubMed, Cochrane Library, Web of Science, Medline and Embase covering January 1, 2000 to December 30, 2021. Randomized control trials (RCTs) comparing finerenone, SGLT-2i and GLP-1 RA in diabetics with CKD were selected. We performed a network meta-analysis to compare the three drugs indirectly. Results were reported as risk ratio (RR) with corresponding 95% confidence interval (CI).

Results: In all, 17 RCTs were selected, including 51,496 patients. Finerenone reduced the risk of renal events and hospitalization for heart failure (HHF) (RR [95%CI]; 0.86 [0.79–0.93], 0.79 [0.67,0.92], respectively). SGLT-2i were associated with reduced risks of major adverse cardiovascular events (MACE) (RR [95%CI]; 0.84 [0.78–0.90]), renal events (RR [95%CI]; 0.67 [0.60–0.74], HHF (RR [95%CI]; 0.60 [0.53–0.68]), all-cause death (ACD) (RR [95%CI]; 0.89 [0.81–0.91]) and cardiovascular death (CVD) (RR [95%CI]; 0.86 [0.77–0.96]) compared to placebo. GLP-1 RA were associated with a lower risk of MACE (RR [95%CI]; 0.88 [0.80–0.97]). As for renal outcomes and HHF, SGLT2i had significant effect in comparison to finerenone (RR [95%CI]; 1.29 [1.13–1.47], 1.31 [1.07–1.61], respectively) and GLP-1 RA (RR [95%CI]; 1.36 [1.16–1.59], 1.49 [1.18–1.89], respectively). Compared with placebo, there was a trend toward reduction in ACD with finerenone (RR [95%CI]; 0.90 [0.80–1.00]). GLP-1 RA did not reduce the risk of renal events, HHF, CVD and ACD, but the analysis based on chemical structure showed that a GLP-1 analogues, liraglutide (RR [95%CI]; 0.79 [0.67–0.92], 0.69 [0.52–0.90], 0.76 [0.62–0.93], respectively) showed significant effect in HHF, CVD and ACD, while an exendin-4 analogues, exenatide (RR [95%CI]; 1.10 [0.83–1.46], 1.19 [0.84–1.69], 1.10 [0.87–1.39], respectively), did not.

Conclusions: In patients with T2DM and CKD, finerenone led to a risk reduction in renal events and HHF, SGLT2i were associated with a decreased risk of cardiovascular and renal events. GLP-1 RA were associated with a decreased risk of MACE. Among GLP-1 RA, GLP-1 analogues showed significantly reduced cardiovascular events compared with exendin-4 analogues.

Background

Globally, diabetes has become more prevalent within the recent years as more than 536.6 million people are currently suffering from Diabetes Mellitus(DM). By 2045, it is estimated that at least 783.2 million adults will be affected by diabetes.1]. Patients with diabetes are at high risk for adverse outcomes from atherosclerotic cardiovascular disease (ASCVD) [2,3], heart failure and renal disease [4,5]. With the increasing prevalence of Type 2 Diabetes Mellitus (T2DM) during recent decades, it has gradually become one of the primary factors accounting for the substantial global increase in end-stage renal disease (ESRD). Even with current therapies [6-10], patients with T2DM and chronic kidney disease (CKD) still experience significant residual cardiovascular and renal morbidity and mortality, the risk of patients developing cardiovascular and renal events increase as DM and CKD progresses [11]. Diabetes with CKD can progress to ESRD [12], and increase the risk of cardiovascular disease such as heart failure, myocardial infarction (MI), stroke, or dying from cardiovascular causes. [13, 14]. These factors contribute to a poor prognosis overall. Therefore, the prevention of CKD progression and cardiovascular events is essential for the management of patients with T2DM and CKD.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA) are one of the hotspots in the research field of diabetes. Several large cohort studies and randomized controlled trials (RCTs) have demonstrated favorable cardiovascular and renal outcomes associated with the two types of hypoglycemic agents in patients with diabetes or kidney disease. Moreover, the American Diabetes Association (ADA) recommends these two drug classes for individuals with T2DM with or at high risk for ASCVD, heart failure, and/or CKD [15].

Finerenone is a nonsteroidal and selective mineralocorticoid receptor antagonist. According to two large randomized placebo-controlled trials targeted at T2DM and CKD patients, finerenone demonstrated that it can significantly reduce the occurrences of composite renal outcome (defined as a composite of a sustained decrease of at least 40% in the estimated glomerular filtration rate (eGFR) from the baseline, kidney failure, or death from renal causes) and composite cardiovascular outcome (defined as a composite of nonfatal MI, nonfatal stroke, death from cardiovascular causes, or hospitalization for heart failure [HHF]), regardless of patients with or without established cardiovascular disease [16,17]. Consequently, in renin-angiotensin-aldosterone system (RAAS) inhibitions, finerenone represents a new frontier in the treatment of diabetic kidney disease [18]. ADA suggest that in patients with T2DM and CKD who are at increased risk for cardiovascular events or CKD progression or are unable to use a SGLT2i, finerenone is recommended to reduce CKD progression and cardiovascular events, they also suggest the use of GLP-1 RA for individuals with T2DM with or at high risk of ASCVD, and/or CKD [19].

Although all three drugs offer cardiovascular or renal benefits to patients with T2DM and CKD, currently no study has compared their effects on cardiovascular and renal outcomes.

In the absence of head-to-head trials comparing finerenone with SGLT2i or GLP-1 RA in cardiovascular and renal outcomes, performing network meta-analysis based on indirect comparisons is an efficient method of determining the relative cardiorenal efficacy of finerenone, SGLT2i, and GLP-1RA. Therefore, we herein investigate the effectiveness of finerenone, SGLT2i and GLP-1 RA in patients with T2DM and CKD by performing network meta-analysis based on RCTs.

Methods

Registration

We prospectively registered this systematic review in the International Prospective Register of Systematic Reviews database (PROSPERO) (registration number: CRD42022301457).

Literature search

Our search strategy was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension statement for network meta-analysis [20, 21]. We performed a systematic search of PubMed, Cochrane Library, Web of Science, Medline and Embase from January 1, 2000 to December 30, 2021.

The following keywords were applied:((“Glucagon-Like Peptide 1 receptor[MeSH]” OR “GLP-1” OR “GLP1 receptor agonist” OR “glucagon-like peptide-1 receptor agonist” OR “Exenatide[MeSH]” OR “Liraglutide[MeSH]” OR “Lixisenatide” OR “Albiglutide” OR “Dulaglutide” OR “Semaglutide”) OR (“Sodium-Glucose Transporter 2 Inhibitors[MeSH]” OR “SGLT-2 inhibitor” OR “SGLT-2” OR “Canagliflozin[MeSH]” OR “Dapagliflozin” OR “Sotagliflozin” OR “empagliflozin” OR “Ertugliflozin” OR “Luseoglifozin”) OR “Finerenone”) AND ((“Renal Insufficiency, Chronic[MeSH]” OR “chronic kidney disease” OR “CKD” OR “kidney disease” OR “kidney failure” OR “chronic kidney failure” OR “renal failure” OR “chronic renal disease” OR “chronic renal failure” OR “CRF”) AND (“Diabetes Mellitus[MeSH]” OR “Diabetes Mellitus type 2” OR “type 2 Diabetes Mellitus”)).

The search results were screened separately by two blinded and independent authors (Z and J) to identify studies according to inclusion and exclusion criteria. When the two authors encountered the inconsistencies, a third author (W) was consulted to reach a decision. In addition, we reviewed the list of references included in the meta-analysis studies to minimize missing relevant studies.

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 T2DM and(or) CKD; (3) they were RCTs that compared finerenone, SGLT2i or GLP-1 RA with a placebo; (4) they compared the risk of cardiovascular and renal outcomes between treatment and placebo groups; (5) they published in English. Studies were excluded if data for estimating risk ratio (RR) was insufficient even after contact with the authors.

Outcomes

There were five outcomes were assessed in this study, which were MACE, Renal outcome, HHF, all-cause death (ACD) and CVD. The definition of MACE was a composite of CVD, nonfatal MI, or nonfatal stroke. If nonfatal MI and stroke data were unavailable, the total MI and stroke were used instead. Renal outcome was defined as a composite of a sustained decrease of at least 40% in the eGFRfrom the baseline or a doubling of the serum creatinine level, kidney failure (a composite of end-stage kidney disease or sustained decrease in eGFR to <15 ml/min/1.73 m^2), or renal death. A similar renal outcome was used instead when this composite outcome was unavailable.

Data extraction and quality assessment

Two researchers (Z and J), independently performed data abstraction and risk of bias assessment from eligible studies. Risk of bias assessment was performed according to the Cochrane risk of bias assessment tool (RoB 2.0) [22]. Any discrepancies in data extraction or quality assessment were resolved by a third reviewer (W). Data regarding cardiovascular and renal outcomes were abstracted from each study group. In this study, we also applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method in order to assess the quality of the evidence for each outcome, GRADE method can be found and accessed in GRADEpro GDT software [23]. Evidence quality was graded into four grades, these categories are labelled as High, Moderate, Low, and Very low. To prevent any other factors that may alter the result such as bias and inaccuracies, we have also referred to the five criteria, which are the risk of bias, the inconsistency, the indirectness, the imprecision and the publication bias. The application of these criteria is used as an evaluation to create the summary of evidence table. [24, 25]. In addition to the five criteria, this network meta-analysis has also taken intransitivity and incoherence in to consideration, as they are vital when it comes to assess the quality of evidence for each outcome. In parallel, the quality of treatment effect estimates was rated based on the quality ratings of direct and indirect comparisons compliant to the GRADE Working Group approach [26].

Statistical analysis

We performed a network meta-analysis using Stata (version 15.0). Risk ratio (RR) and 95% confidence interval (CI) were used to present the efficacy of treatments. The probability value of the I^2 variable was calculated to assess heterogeneity, which was considered to be unimportant (0%< I^2 <40%), moderate heterogeneity (30%< I^2 <60%), substantial heterogeneity (50%< I^2 <90%), considerable heterogeneity (75%< I^2 <100%) [27]. We conducted a sensitivity analysis excluding “Cherney 2021”, as Cherney 2021 only included diabetics with severe CKD (eGFR: 15-30 ml/min/1.73 m^2). In this network meta-analysis, none of the 5 outcomes had a closed loop. Therefore, it means that there was only indirect evidence in all three drugs. Consequently, there was no need to test inconsistency for this network meta-analysis.

Results

Literature search and included studies

The detailed study filtering process is shown in Fig 1. In brief, we retrieved a total of 5163 articles from PubMed(n=977), Cochrane Library(n=74), Web of science(n=1022), Medline(n=1470) and Embase(n=1620) in primary search, during the processanother 12 articles were identified through references. A total of 2232 duplicate articles were removed. After review by title and abstract, 94 articles remained and entered into full-text assessing section. By assessing full text, 56 additional articles with missing data were excluded. Finally, 38 articles (included 17 randomized controlled trials) were included in this network meta-analysis [7,16,17,28-62]. Out of 17 studies, 3 studies were compared finerenone [16,17,28-30] with placebo; 8 studies were compared SGLT2i (Empaglifozin [31-35], Canaglifozin [7,36-42], Dapaglifozin [43-47], Ertuglifozin [48-50], and Sotaglifozin [51,52]) with placebo; 6 studies compared GLP-1 RA (Dulaglutide [53,54], Albiglutide [55], Exenatide [56,57], Semaglutide [58,59] and Liraglutide [60-62]) with placebo.

Baseline characteristics of included studies in patients with T2DM and CKD

The characteristics of the included studies are presented in Table 1. The pooled population consisted of 51,496 patients with T2DM and CKD, 14,847 of them were in finerenone studies (7246 in the intervention group and 7601 in control group), 25,098 patients in SGLT-2i studies (13,260 in the intervention group and 11,838 in control group) and 11,551 patients in GLP-1 RA studies (5355 in the group treated with GLP-1 RA and 5796 in the control group). The definition of MACE in the included trials was consistent, except for three of them, EMPA-REG, DECLARE–TIMI 58 and EXSCEL trials (data for nonfatal MI and stroke were not available, so we used total MI and stroke instead). Whereas renal events were defined slightly different across included trials, but they were similar enough that can be used in analysis. The detailed definitions of renal events in different trials are shown in Table 2.

Table 2

Definitions of terms in included studies

Trial	Study design	Patients enrolled in trials	Patients included in this study	Setting	Drug dose (mg/day)	Median follow up	eGFR	Range of HbA1c (%)	Definitions of ren events among included trials in patients with T2D and CKD
Finerenone vs placebo									
FIDELIO-DKD	RCT	T2DM and CKD	T2DM and CKD	Multinational	Finerenone 10/20	2.6years	25 to <75	≤12	≥40% eGFR decl renal death, ESRD eGFR<15 ml/min m^2
FIGARO-DKD	RCT	T2DM and CKD	T2DM and CKD	Multinational	Finerenone 10/20	3.4years	25 to 90	≤12	≥40% eGFR decl renal death
ARTS-DN	RCT	DN	DN	Multinational	Finerenone 1.25/2.5/5/7.5/10/15/20	90 days	≥30	≤12	≥40% eGFR decl
SGLT2i vs placebo									
EMPA-REG	RCT	T2DM	T2DM and CKD	Multinational	Empagliflozin 10/25	3.1 years	≥30	7 to 10	Macroalbuminuri doubling of serur creatinine, eGFR<45 ml/min m^2, renal-replace therapy; renal dea
CANVAS	RCT	T2DM	T2DM and CKD	Multinational	Canagliflozin 100/300	188.2weeks	≥30	7 to 10.5	ESRD, renal death ≥40% eGFR decl doubling of serur creatinine.
DECLARE–TIMI 58	RCT	T2DM	T2DM and CKD	Multinational	Dapagliflozin 10	4.2 years	CrCl≥60ml/min	6.5 to 12	≥40% eGFR decl renal death, ESRD
CREDENCE	RCT	T2DM and CKD	T2DM and CKD	Multinational	Canagliflozin 100	2.62years	30 to <90	6.5 to 12	ESRD, doubling o serum creatinine renal death
VERTIS CV	RCT	T2DM	T2DM and CKD	Multinational	Ertugliflozin 5/15	3.5years	≥30	7 to 10.5	N/A
DAPA-CKD	RCT	CKD	T2DM and CKD	Multinational	Dapagliflozin 10	2.4 years	25 to 75	N/A	≥50% eGFR decl ESRD, renal-replacement ther eGFR<15 ml/min m^2, renal death
SCORED	RCT	T2DM and CKD	T2DM and CKD	Multinational	Sotagliflozin 400	16 months	25 to 60	≥7	≥50% eGFR decl renal-replacemen therapy, eGFR<15 ml/min m^2
Cherney 2021	RCT	T2DM and CKD	T2DM and CKD	Multinational	Sotagliflozin 200/400	52weeks	15 to <30	7 to 11	≥50% eGFR decl renal-replacemen therapy, eGFR<15 ml/min m^2, renal death
GLP-1 RA vs placebo									
LEADER	RCT	T2DM	T2DM and CKD	Multinational	Liraglutide 1.8	3.84years	N/A	≥7	Macroalbuminuri doubling of serur creatinine, eGFR<45 ml/min m^2, renal-replace therapy, renal dea
REWIND	RCT	T2DM	T2DM and CKD	Multinational	dulaglutide 1.5 weekly	5.4years	≥15	≤9.5	Macroalbuminuri ≥30% eGFR decl renal-replacemen therapy,
HARMONY	RCT	T2DM	T2DM and CKD	Multinational	Albiglutide 30/50	1.5years	≥30	>7	N/A
EXSCEL	RCT	T2DM	T2DM and CKD	Multinational	Exenatide 2 weekly	3.2years	≥30	6.5 to 10	≥40% eGFR decl renal-replacemen therapy, renal dea
PIONEER-6	RCT	T2DM	T2DM	Multinational	Semaglutide 14 oral	15.9months	≥30	N/A	N/A

			and CKD						
SUSTAIN-6	RCT	T2DM	T2DM and CKD	Multinational	Semaglutide 0.5/1 weekly	109weeks	N/A	≥7	N/A

Note: DN: Diabetic Nephropathy; N/A: not available; CrCl: creatinine clearance; eGFR (ml/min/1.73m^2)

Risk of bias

We assess the risk of bias in those trials using the Revised Cochrane Risk of Bias Tool (RoB 2.0). The quality evaluation of the included studies is shown in Fig 2. All trials were evaluated as low risk in 5 outcomes. Detailed evaluations are as shown in Additional file 1 (RoB-2 evaluation) for each study.

GRADE assessment

In terms of reducing the MACE, there were 14 direct comparisons in the original articles and they were estimated high quality. In terms of reducing the renal outcomes, there were 13 direct comparisons in the original articles whose estimated results were high quality. In terms of reducing the HHF and CVD, there were 12 direct comparisons in the original articles and they were rated as high quality. In terms of reducing the ACD, there were 11 direct comparisons in the original articles and they were rated as high quality. The detail was shown in Table 3. Fig 3 shows the network graph.

According to recommendation of GRADE working group, we presented a four-step approach to rate the quality of evidence in each of the direct, indirect, and network meta-analysis estimates based on methods developed by the GRADE working group [26]. In this network meta-analysis, none of the 5 outcomes had a closed loop. Meaning that that no outcomes from both direct and indirect comparisons are included. Thus, rendering incoherence assessment unnecessary. The studies that are included had slightly different definitions of renal outcomes, and the baseline eGFR of patients in the “cherney 2021” was different from other studies. For direct comparisons, “cherney 2021” included only 1% of patients in SGLT2i (277/25098). Therefore, risk of bias was not taken in to consideration. As for intransitivity, there was only indirect evidence in the intercomparison of the three drugs. The GRADE working group recommends in such situation issues regarding intransitivity may warrant particular attention, and the threshold for rating down for intransitivity may be lower [26]. Therefore, we downgraded the quality of evidence for the comparison between SGLT2i and the two other drugs. The detail was shown in Table 4.

Table 3

GRADE assessment

Certainty assessment							№ of patients		Certainty	Importa
Intervention of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention group	Control group		
MACE (№ of studies: 14)					CRITICAL					
SGLT2i vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	1255/13143 (9.5%)	1266/11688 (10.8%)	High	
GLP-1 RA vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	633/4674 (13.5%)	721/4678 (15.4%)	High	
Finerenone vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	228/2833 (8.0%)	258/2841 (9.1%)	High	
Renal outcomes (№ of studies: 13)										CRITICAL
SGLT2i vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	586/11731 (5.0%)	700/10981 (6.4%)	High	
GLP-1 RA vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	428/3754 (11.4%)	474/3780 (12.5%)	High	
Finerenone vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	861/7234 (11.9%)	997/6600 (15.1%)	High	
HHF (№ of studies: 12)										IMPORTANT
SGLT2i vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	395/13144 (3.0%)	561/11689 (4.8%)	High	
GLP-1 RA vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	174/2673 (6.5%)	191/2662 (7.2%)	High	
Finerenone vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	256/6519 (3.9%)	325/6507 (5.0%)	High	
ACD (№ of studies: 11)					IMPORTANT					
SGLT2i vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	706/12128 (5.8%)	720/10898 (6.6%)	High	
GLP-1 RA vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	339/2673 (12.7%)	378/2662 (14.2%)	High	
Finerenone vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	552/6519 (8.5%)	614/6507 (9.4%)	High	
CVD (№ of studies:12)					IMPORTANT					
SGLT2i vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	623/13144 (4.7%)	597/11689 (5.1%)	High	
GLP-1 RA vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	213/2673 (8.0%)	235/2662 (8.8%)	High	
Finerenone vs Placebo	randomised trials	not serious	not serious	not serious	not serious	none	322/6519 (4.9%)	364/6507 (6.0%)	High	

Table 4

Estimates of effects and quality ratings for comparison of drugs to prevent cardiorenal outcomes

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	RR [95% CI]	Quality of evidence	RR [95% CI]	Quality of evidence	RR [95% CI]	Quality of evidence
MACE						
SGLT2i vs Placebo	0.83 (0.77,0.90)	High	Not estimable▲	—	0.84 (0.78,0.90)	High
GLP-1 RA vs Placebo	0.88 (0.80,0.97)	High	Not estimable▲	—	0.88 (0.80,0.97)	High
Finerenone vs Placebo	0.89 (0.75,1.05)	High	Not estimable▲	—	0.89 (0.75,1.05)	High
GLP-1 RA vs SGLT2i	—	—	1.05 (0.93,1.19)	Moderate*	1.05 (0.93,1.19)	Moderate*
Finerenone vs SGLT2i	—	—	1.06 (0.88,1.28)	Moderate*	1.06 (0.88,1.28)	Moderate*
Finerenone vs GLP-1 RA	—	—	1.01 (0.83,1.23)	High	1.01 (0.83,1.23)	High
Renal outcomes						
SGLT2i vs Placebo	0.67 (0.60,0.74)	High	Not estimable▲	—	0.67 (0.60,0.74)	High
GLP-1 RA vs Placebo	0.90 (0.80,1.02)	High	Not estimable▲	—	0.90 (0.80,1.02)	High
Finerenone vs Placebo	0.86 (0.79,0.93)	High	Not estimable▲	—	0.86 (0.79,0.93)	High
GLP-1 RA vs SGLT2i	—	—	1.36 (1.16,1.59)	Moderate*	1.36 (1.16,1.59)	Moderate*
Finerenone vs SGLT2i	—	—	1.29 (1.13,1.47)	Moderate*	1.29 (1.13,1.47)	Moderate*
Finerenone vs GLP-1 RA	—	—	0.95 (0.82,1.10)	High	0.95 (0.82,1.10)	High
HHF						
SGLT2i vs Placebo	0.60 (0.53,0.68)	High	Not estimable▲	—	0.60 (0.53,0.68)	High
GLP-1 RA vs Placebo	0.90 (0.74,1.09)	High	Not estimable▲	—	0.90 (0.73,1.09)	High
Finerenone vs Placebo	0.79 (0.67,0.92)	High	Not estimable▲	—	0.79 (0.67,0.92)	High
GLP-1 RA vs SGLT2i	—	—	1.49 (1.18,1.89)	Moderate*	1.49 (1.18,1.89)	Moderate*
Finerenone vs SGLT2i	—	—	1.31 (1.07,1.61)	Moderate*	1.31 (1.07,1.61)	Moderate*
Finerenone vs GLP-1 RA	—	—	0.88 (0.68,1.14)	High	0.88 (0.68,1.14)	High
CVD						
SGLT2i vs Placebo	0.86 (0.77,0.96)	High	Not estimable▲	—	0.86 (0.77,0.96)	High
GLP-1 RA vs Placebo	0.90 (0.75,1.08)	High	Not estimable▲	—	0.90 (0.75,1.08)	High
Finerenone vs Placebo	0.88 (0.76,1.02)	High	Not estimable▲	—	0.88 (0.76,1.02)	High
GLP-1 RA vs SGLT2i	—	—	1.04 (0.85,1.29)	Moderate*	1.04 (0.85,1.29)	Moderate*
Finerenone vs SGLT2i	—	—	1.02 (0.85,1.23)	Moderate*	1.02 (0.85,1.23)	Moderate*
Finerenone vs GLP-1 RA	—	—	0.98 (0.78,1.23)	High	0.98 (0.78,1.23)	High
ACD						
SGLT2i vs Placebo	0.90 (0.81,0.99)	High	Not estimable▲	—	0.89 (0.81,0.99)	High
GLP-1 RA vs Placebo	0.89 (0.78,1.02)	High	Not estimable▲	—	0.89 (0.77,1.02)	High
Finerenone vs Placebo	0.90 (0.80,1.00)	High	Not estimable▲	—	0.90 (0.80,1.00)	High
GLP-1 RA vs SGLT2i	—	—	0.99 (0.84,1.18)	Moderate*	0.99 (0.84,1.18)	Moderate*
Finerenone vs SGLT2i	—	—	1.00 (0.86,1.16)	Moderate*	1.00 (0.86,1.16)	Moderate*
Finerenone vs GLP-1 RA	—	—	1.01 (0.85,1.20)	High	1.01 (0.85,1.20)	High

▲Cannot be estimated because the drug was not connected in a loop in the evidence network *Intransitivity

Network meta-analysis of treatment groups

MACE

The results showed that in patients with T2DM and CKD, compared with placebo, SGLT-2i (RR [95% CI]; 0.84 [0.78–0.90]) and GLP-1 RA (RR [95% CI]; 0.88 [0.80–0.97]) were associated with a decreased risk of MACE, while finerenone (RR [95% CI]; 0.89 [0.75–1.05]) did not. Finerenone didn`t show a significant difference in the risk of MACE compared with SGLT-2i (RR [95% CI]; 1.19 [0.92–1.53]) and GLP-1 RA (RR [95% CI]; 1.02 [0.78–1.32]). There was also no significant difference in the risk of MACE between SGLT-2i and GLP-1 RA (RR [95% CI]; 1.17 [0.93–1.47]). There was no heterogeneity (I^2=3.3%, p=0.409). The detail is shown in Fig.4.

Renal outcome

Finerenone (RR [95% CI]; 0.86 [0.79–0.93]) and SGLT-2i (RR [95% CI]; 0.67 [0.60–0.74]) significantly decreased the morbidity of renal events, while GLP-1 RA (RR [95% CI]; 0.90 [0.73–1.02]) did not. Compared with finerenone (RR [95% CI]; 1.31 [1.07–1.61]) and GLP-1 RA (RR [95% CI]; 1.49 [1.18–1.89]), SGLT-2i were associated with a decreased morbidity of renal events. Finerenone was comparable to GLP-1 RA (RR [95% CI]; 0.95 [0.82–1.10]). There was moderate heterogeneity (I^2=37.4%, p=0.085). The detail is shown in Fig.5.

HHF

Compared with placebo, finerenone (RR [95% CI]; 0.79 [0.67–0.92]) was associated with a decreased risk of HHF while GLP-1 RA (RR [95% CI]; 0.90 [0.73–1.09]) did not. But there was no significant difference in the risk of HHF between the two drugs (RR [95% CI]; 0.88 [0.68–1.14]). Compared with finerenone (RR [95% CI]; 1.31 [1.07–1.61]), GLP-1 RA (RR [95% CI]; 1.49 [1.18–1.89]) and placebo (RR [95% CI]; 0.60 [0.53–0.68]), SGLT-2i were shown to be significantly more effective in reducing HHF. There was moderate heterogeneity (I^2=44.9%, p=0.046). The detail is shown in Fig.6.

ACD

Finerenone (RR [95% CI]; 0.90 [0.80–1.00) had a tendency to decrease the risk of ACD and SGLT-2i (RR [95% CI]; 0.89 [0.81–0.99]) were associated with a decreased risk of ACD, while GLP-1 RA (RR [95% CI]; 0.89 [0.77–1.02]) did not. And there was no significant difference among the three drugs (RR 0.99, 95% CI 0.84–1.18; RR 1.00, 95% CI 0.86–1.16; RR 1.01, 95% CI 0.85–1.20, respectively). This analysis showed no heterogeneity (I^2=0.0%, p=0.554). The detail is shown in Fig.7.

CVD

As for CVD, compared with placebo, only SGLT-2i were associated with a decreased events (RR [95% CI]; 0.86, [0.77–0.96]). There was no significant difference between the other two drugs and placebo, or among the three drugs (Fig.8). The analysis of CVD showed no heterogeneity (I^2=4.4%, p=0.402). The detail is shown in Fig.8.

Specific drugs' Pairwise comparison and analysis

In order to provide more specific recommendations for clinical drug selection, we further evaluated the efficacy of specific drugs based on its component. Compared to placebo, canagliflozin(RR [95% CI]; 0.78 [0.68–0.89]) , sotagliflozin(RR [95% CI]; 0.76 [0.66–0.87]) and liraglutide(RR [95% CI]; 0.69 [0.58–0.82]) displayed significantly lower risk of MACE，while finerenone (RR [95% CI]; 0.89 [0.75–1.05]), empagliflozin(RR [95% CI]; 0.89 [0.71–1.12]), dapagliflozin(RR [95% CI]; 0.92 [0.77–1.11]), ertugliflozin(RR [95% CI]; 1.09 [0.87–1.36]), , albiglutide(RR [95% CI]; 0.93 [0.73–1.18]), exenatide(RR [95% CI]; 1.03 [0.89–1.20]) and semaglutide(RR [95% CI]; 0.83 [0.60–1.13])were not. Compared to ertugliflozin or exenatide, canagliflozin, sotagliflozin and liraglutide were associated with a decreased risk of MACE. Liraglutide had a tendency to reduce MACE compared to finerenone (RR [95% CI]; 0.78 [0.61–1.00]) and albiglutide (RR [95% CI]; 0.74 [0.55–1.00]), it also showed more positive influence when compared with dapagliflozin (RR [95% CI]; 0.75 [0.58–0.96]). The detail is shown in Table 5a.

In renal outcome, finerenone (RR [95% CI]; 0.86 [0.79–0.93]), empagliflozin (RR [95% CI]; 1.55 [1.01–2.39]), canagliflozin (RR [95% CI]; 1.55 [1.01–2.39]) and dapagliflozin (RR [95% CI]; 1.55 [1.01–2.39]) reduced renal events significantly compared to placebo. The results of comparison showed that empagliflozin (RR [95% CI]; 0.76 [0.63–0.93]), canagliflozin (RR [95% CI]; 0.81 [0.67–0.99]) and dapagliflozin (RR [95% CI]; 0.70 [0.55–0.87]) significantly reduced the morbidity of renal events compared to finerenone. The detail is shown in Table 5b.

Finerenone(RR [95% CI]; 0.79 [0.67–0.92]), empagliflozin(RR [95% CI]; 0.59 [0.40–0.88]), canagliflozin(RR [95% CI]; 0.60 [0.48–0.75]), dapagliflozin(RR [95% CI]; 0.56 [0.41–0.76]), ertugliflozin(RR [95% CI]; 0.51 [0.34–0.76]), sotagliflozin(RR [95% CI]; 0.67 [0.52–0.85]) and liraglutide(RR [95% CI]; 0.73 [0.56–0.97]) reduced HHF significantly, but exenatide(RR [95% CI]; 1.10 [0.83–1.46]) did not. At the same time, all of the 7 drugs mentioned above significantly reduced HHF compared to exenatide (Table 5a). Another discovery worth noting is that canagliflozin (RR [95% CI]; 0.76 [0.58–1.00]) and dapagliflozin (RR [95% CI]; 0.71 [0.50–1.00]) had a tendency to decrease HHF compared to finerenone, and finerenone was associated with a higher risk of HHF than ertugliflozin (RR [95% CI]; 1.55 [1.01–2.39]). The detail is shown in Table 5a.

When it comes to ACD, dapagliflozin (RR [95% CI]; 0.81 [0.66–0.98]) and liraglutide (RR [95% CI]; 0.76 [0.62–0.93]) had significant effect than placebo. And finerenone (RR [95% CI]; 0.90 [0.80–1.00]) tended to reduce the risk of ACD when compared with placebo. As for CVD, liraglutide (RR [95% CI]; 0.69 [0.52–0.90]) was better than placebo, while other drugs were not. The detail is shown in Table 5c.

Table 5a

Pairwise league table of MACE and HHF.

Table 5a - Comparisons for MACE (bottom left) of the 10 drugs and HHF (upper right) of the 8 drugs. RR with 95%CI

EM	1.01 (0.65,1.59)	0.94 (0.57,1.55)	0.85 (0.49,1.50)	1.12 (0.71,1.78)	1.33 (0.87,2.03)		1.85 (1.14,3.01)	1.24 (0.76,2.00)	1.68 (1.14,2.50)
1.14 (0.88,1.49)	CA	0.93 (0.64,1.35)	0.84 (0.53,1.33)	1.11 (0.80,1.53)	1.31 (1.00,1.71)		1.83 (1.28,2.61)	1.22 (0.86,1.74)	1.66 (1.34,2.06)
0.96 (0.72,1.29)	0.84 (0.67,1.06)	DA	0.91 (0.55,1.51)	1.19 (0.81,1.76)	1.41 (1.00,2.00)		1.97 (1.30,2.99)	1.31 (0.87,1.99)	1.79 (1.32,2.44)
0.81 (0.59,1.13)	0.71 (0.54,0.93)	0.84 (0.63,1.13)	ER	1.32 (0.82,2.10)	1.55 (1.01,2.39)		2.17 (1.33,3.54)	1.45 (0.89,2.36)	1.97 (1.32,2.95)
1.17 (0.90,1.53)	1.02 (0.85,1.24)	1.22 (0.97,1.52)	1.44 (1.10,1.89)	SO	1.18 (0.89,1.58)		1.65 (1.14,2.39)	1.10 (0.76,1.59)	1.50 (1.18,1.91)
1.00 (0.76,1.33)	0.88 (0.71,1.09)	1.04 (0.81,1.34)	1.24 (0.92,1.65)	0.86 (0.69,1.06)	FI		1.40 (1.01,1.93)	0.93 (0.68,1.29)	1.27 (1.08,1.49)
0.96 (0.69,1.33)	0.84 (0.64,1.10)	1.00 (0.74,1.34)	1.18 (0.85,1.65)	0.82 (0.62,1.07)	0.96 (0.71,1.28)	AL			
0.86 (0.66,1.13)	0.75 (0.62,0.92)	0.89 (0.71,1.13)	1.06 (0.80,1.40)	0.74 (0.60,0.90)	0.86 (0.68,1.08)	0.90 (0.68,1.19)	EX	0.67 (0.45,0.99)	0.91 (0.69,1.21)
1.08 (0.73,1.58)	0.94 (0.67,1.32)	1.12 (0.78,1.60)	1.32 (0.89,1.96)	0.92 (0.65,1.29)	1.07 (0.75,1.53)	1.12 (0.76,1.66)	1.25 (0.88,1.77)	SE	
1.29 (0.97,1.72)	1.13 (0.90,1.41)	1.34 (1.04,1.73)	1.59 (1.18,2.13)	1.10 (0.88,1.38)	1.29 (1.00,1.65)	1.35 (1.00,1.81)	1.50 (1.19,1.89)	1.20 (0.84,1.72)	LI
0.89 (0.71,1.12)	0.78 (0.68,0.89)	0.92 (0.77,1.11)	1.09 (0.87,1.38)	0.76 (0.66,0.87)	0.89 (0.75,1.05)	0.93 (0.73,1.18)	1.03 (0.89,1.20)	0.83 (0.60,1.13)	0.69 (0.58,0.82)

Note: EM: empagliflozin; CA: canagliflozin, DA: dapagliflozin, ER: ertugliflozin, SO: sotagliflozin, FI: finerenone, AL: albiglutide, EX: exenatide,

SE: semaglutide, LI: liraglutide, PL: placebo

Table 5b

Pairwise league table of renal outcomes.

Table 5b – Comparisons for renal outcome of the 8 drugs. RR with 95%CI

empagliflozin	1.07 (0.83,1.37)	0.91 (0.69,1.20)	1.26 (0.84,1.87)	1.31 (1.08,1.59)	1.38 (1.09,1.75)	1.50 (1.02,2.19)	1.34 (1.02,1.76)	1.53 (1.28,1.83)
0.94 (0.73,1.20)	canagliflozin	0.85 (0.65,1.13)	1.18 (0.79,1.76)	1.23 (1.01,1.50)	1.30 (1.02,1.65)	1.40 (0.96,2.06)	1.25 (0.95,1.65)	1.44 (1.20,1.72)
1.10 (0.83,1.45)	1.17 (0.89,1.55)	dapagliflozin	1.38 (0.91,2.09)	1.44 (1.14,1.81)	1.52 (1.16,1.98)	1.64 (1.10,2.45)	1.47 (1.09,1.98)	1.68 (1.36,2.08)
0.80 (0.53,1.19)	0.85 (0.57,1.27)	0.72 (0.48,1.10)	sotagliflozin	1.04 (0.72,1.51)	1.10 (0.74,1.63)	1.19 (0.73,1.95)	1.06 (0.70,1.61)	1.22 (0.85,1.74)
0.76 (0.63,0.93)	0.81 (0.67,0.99)	0.70 (0.55,0.87)	0.96 (0.66,1.39)	finerenone	1.06 (0.88,1.26)	1.14 (0.81,1.62)	1.02 (0.82,1.28)	1.17 (1.08,1.27)
0.72 (0.57,0.92)	0.77 (0.61,0.98)	0.66 (0.51,0.86)	0.91 (0.61,1.35)	0.95 (0.79,1.14)	dulaglutide	1.08 (0.75,1.57)	0.97 (0.74,1.26)	1.11 (0.94,1.30)
0.67 (0.46,0.98)	0.71 (0.49,1.04)	0.61 (0.41,0.91)	0.84 (0.51,1.37)	0.87 (0.62,1.24)	0.92 (0.64,1.34)	exenatide	0.89 (0.60,1.33)	1.02 (0.73,1.43)
0.75 (0.57,0.98)	0.80 (0.61,1.05)	0.68 (0.51,0.92)	0.94 (0.62,1.42)	0.98 (0.78,1.23)	1.03 (0.79,1.34)	1.12 (0.75,1.66)	liraglutide	1.14 (0.93,1.41)
0.65 (0.55,0.78)	0.70 (0.58,0.83)	0.59 (0.48,0.74)	0.82 (0.57,1.18)	0.86 (0.79,0.93)	0.90 (0.77,1.06)	0.98 (0.70,1.37)	0.87 (0.71,1.08)	placebo

Table 5c

Pairwise league table of ACD and CVD.

Table 5c – Comparisons for ACD (bottom left) and CVD (upper right) of the 8 drugs. RR with 95%CI								
empagliflozin	1.11 (0.74,1.65)	1.09 (0.70,1.70)	1.12 (0.71,1.77)	1.14 (0.76,1.72)	1.13 (0.77,1.65)	1.40 (0.92,2.14)	0.88 (0.56,1.37)	1.28 (0.90,1.81)
1.02 (0.67,1.56)	canagliflozin	0.99 (0.71,1.38)	1.02 (0.72,1.44)	1.03 (0.77,1.37)	1.02 (0.80,1.30)	1.27 (0.94,1.72)	0.79 (0.57,1.11)	1.16 (0.95,1.40)
1.06 (0.69,1.62)	1.04 (0.78,1.37)	dapagliflozin	1.03 (0.69,1.54)	1.04 (0.74,1.48)	1.03 (0.76,1.41)	1.28 (0.89,1.84)	0.80 (0.54,1.18)	1.17 (0.89,1.54)
0.73 (0.41,1.30)	0.72 (0.45,1.16)	0.70 (0.43,1.12)	ertugliflozin	1.01 (0.71,1.46)	1.00 (0.72,1.39)	1.25 (0.86,1.81)	0.78 (0.52,1.16)	1.14 (0.85,1.52)
0.86 (0.57,1.31)	0.85 (0.65,1.10)	0.82 (0.63,1.06)	1.18 (0.74,1.87)	sotagliflozin	0.99 (0.76,1.28)	1.23 (0.90,1.69)	0.77 (0.54,1.09)	1.12 (0.91,1.39)
0.95 (0.64,1.41)	0.93 (0.74,1.16)	0.90 (0.72,1.13)	1.29 (0.83,2.02)	1.10 (0.90,1.35)	finerenone	1.24 (0.94,1.64)	0.78 (0.57,1.06)	1.13 (0.98,1.31)
0.84 (0.55,1.28)	0.82 (0.63,1.08)	0.79 (0.61,1.04)	1.14 (0.71,1.83)	0.97 (0.76,1.25)	0.88 (0.71,1.10)	exenatide	0.62 (0.43,0.90)	0.91 (0.72,1.15)
1.13 (0.73,1.73)	1.11 (0.83,1.47)	1.07 (0.80,1.42)	1.53 (0.95,2.48)	1.31 (1.00,1.70)	1.19 (0.94,1.50)	1.34 (1.02,1.77)	liraglutide	1.46 (1.11,1.92)
0.85 (0.58,1.24)	0.83 (0.69,1.02)	0.81 (0.66,0.98)	1.16 (0.75,1.79)	0.99 (0.83,1.17)	0.90 (0.80,1.00)	1.01 (0.84,1.22)	0.76 (0.62,0.93)	placebo

3.6. Conclusions from Minimally Contextualized Framework

The Minimally Contextualized Framework was developed to classify interventions in groups from the most to the least effective or harmful. The placebo was most closely connected to the other interventions and selected as the reference group, with an ineffective value, i.e. a relative effect value of 1, as the decision threshold. Based on the cardiovascular and renal outcomes we used the 95% CI of the estimate of effect comparing each of the interventions against the placebo. If this interval crosses the decision threshold, then the intervention can remain in the same group as the placebo. On the other hand, if the interval did not cross the decision threshold, then depending on which side of the threshold the interval lies on, the intervention could be classified as more effective or less effective than the placebo. Based on comparisons between pairs of interventions, if any intervention proves to be more effective than another category 1 intervention, then that corresponding intervention can be moved to a higher rated group (category 2) [63]. After evaluating the certainty of the evidence fromall11 interventions, the interventions were classified again into two broad categories: high certainty (moderate to high certainty evidence) and low certainty (low to very low certainty evidence). After checking consistency with pairwise comparisons and rankings, the intervention at the highest classification level could be considered as the most effective choice currently available, while low certainty as might be among the most effective. As was presented in Table 6.

Table 6

Final classification of 11 interventions, based on NMA of interventions for patients with T2DM and CKD

Certainty of the evidence	Category	Intervention	Intervention vs placebo RR (95% CI)	Surface under the cumulative ranking curve
MACE				
High certainty (moderate to high certainty evidence)	Category 1: among the most effective	liraglutide	0.69 (0.58,0.82)	0.940
		sotagliflozin	0.76 (0.66,0.87)	0.817
		canagliflozin	0.78 (0.68,0.89)	0.772
	Category 0: among the least effective	semaglutide	0.83 (0.60,1.13)	0.624
		finerenone	0.89 (0.75,1.05)	0.508
		empagliflozin	0.58 (0.25,1.36)	0.497
		dapagliflozin	0.92 (0.77,1.11)	0.418
		albiglutide	0.93 (0.73,1.18)	0.411
		exenatide	1.03 (0.89,1.20)	0.173
		ertugliflozin	1.09 (0.87,1.38)	0.113
Low certainty (low to very low certainty evidence)	Category 1: might be among the most effective	—	—	—
	Category 0: might be among the least effective	—	—	—
Renal outcome				
High certainty (moderate to high certainty evidence)	Category 2: among the most effective	dapagliflozin	0.59 (0.48,0.74)	0.941
		empagliflozin	0.65 (0.55,0.78)	0.847
		canagliflozin	0.70 (0.58,0.83)	0.765
	Category 1: inferior to the most effective, or superior to the least effective	dapagliflozin	0.59 (0.48,0.74)	0.941
		empagliflozin	0.65 (0.55,0.78)	0.847
		canagliflozin	0.70 (0.58,0.83)	0.765
		finerenone	0.86 (0.79,0.93)	0.437
	Category 0: among the least effective	sotagliflozin	0.82 (0.57,1.18)	0.489
		liraglutide	0.87 (0.71,1.08)	0.386
		dulaglutide	0.90 (0.77,1.16)	0.321
		exenatide	0.98 (0.70,1.37)	0.216
Low certainty (low to very low certainty evidence)	Category 1: might be among the most effective	—	—	—
	Category 0: might be among the least effective	—	—	—
HHF				

High certainty (moderate to high certainty evidence)	Category 2: among the most effective	ertugliflozin	0.51 (0.34,0.76)	0.863
	Category 1: inferior to the most effective, or superior to the least effective	empagliflozin	0.59 (0.40,0.88)	0.702
		ertugliflozin	0.51 (0.34,0.76)	0.863
		dapagliflozin	0.56 (0.41,0.76)	0.785
		canagliflozin	0.60 (0.48,0.75)	0.703
		sotagliflozin	0.67 (0.52,0.85)	0.557
		liraglutide	0.73 (0.56,0.97)	0.427
		finerenone	0.79 (0.67,0.92)	0.327
	Category 0: among the least effective	exenatide	1.10 (0.83,1.46)	0.040
Low certainty (low to very low certainty evidence)	Category 1: might be among the most effective	—	—	—
	Category 0: might be among the least effective	—	—	—
ACD				
High certainty (moderate to high certainty evidence)	Category 1: among the most effective	liraglutide	0.76 (0.62,0.93)	0.872
		dapagliflozin	0.81 (0.66,0.98)	0.769
	Category 0: among the least effective	canagliflozin	0.83 (0.69,1.02)	0.700
		empagliflozin	0.85 (0.58,1.42)	0.624
		finerenone	0.90 (0.80,1.00)	0.553
		sotagliflozin	0.99 (0.83,1.17)	0.315
		exenatide	1.01 (0.84,1.22)	0.258
		ertugliflozin	1.16 (0.75,1.79)	0.156
Low certainty (low to very low certainty evidence)	Category 1: might be among the most effective	—	—	—
	Category 0: might be among the least effective	—	—	—
CVD				
High certainty (moderate to high certainty evidence)	Category 1: among the most effective	liraglutide	0.69 (0.52,0.90)	0.907
	Category 0: among the least effective	empagliflozin	0.78 (0.55,1.11)	0.704
		dapagliflozin	0.85 (0.65,1.13)	0.565
		canagliflozin	0.87 (0.71,1.05)	0.554
		finerenone	0.88 (0.76,1.02)	0.510
		ertugliflozin	0.88 (0.66,1.18)	0.507
		sotagliflozin	0.89 (0.72,1.10)	0.484
		exenatide	1.10 (0.87,1.39)	0.091

Low certainty (low to very low certainty evidence)	Category 1: might be among the most effective	—	—	—
	Category 0: might be among the least effective	—	—	—

Sensitivity analyses

The results of sensitivity analyses are summarized in Table 7. We conducted a sensitivity analysis excluding “Cherney 2021”, as Cherney 2021 only included diabetics with severe CKD (eGFR: 15-30 ml/min/1.73 m^2). In MACE, renal outcomes and ACD, the results of sensitivity analyses were comparable to non-exclusion of “Cherney 2021”. Compared to sotagliflozin, liraglutide (RR [95% CI]; 0.76 [0.58–0.99]) was associated with a decreased risk of ACD. Whereas the previous results showed liraglutide had a trend towards a reduction in CVD compared to sotagliflozin.

Table 7

The summary of sensitivity analyses

Outcomes	Finerenone		SGLT-2i		GLP-1 RA		Comparison	Risk ratio	95%CI	I^2(%)	P
	I	C	I	C	I	C					
MACE	2833	2841	12959	11595	4674	4678	SGLT-2i vs placebo	0.84	0.78-0.91	26.8	0.174
							GLP-1 RA vs placebo	0.88	0.80-0.97		
							Finerenone vs placebo	0.89	0.75-1.05		
							GLP-1 RA vs SGLT-2i	1.04	0.92-1.18		
							Finerenone vs SGLT-2i	1.05	0.87-1.27		
							Finerenone vs GLP-1 RA	1.01	0.83-1.23		
HHF	6519	6507	12960	11596	2673	2662	SGLT-2i vs placebo	0.60	0.53-0.68	49.9	0.030
							GLP-1 RA vs placebo	0.90	0.73-1.09		
							Finerenone vs placebo	0.79	0.67-0.92		
							GLP-1 RA vs SGLT-2i	1.49	1.18-1.89		
							Finerenone vs SGLT-2i	1.31	1.07-1.61		
							Finerenone vs GLP-1 RA	0.88	0.68-1.14		
Renal outcome	7234	6600	11547	10888	3754	3780	SGLT-2i vs placebo	0.66	0.59-0.73	39.2	0.079
							GLP-1 RA vs placebo	0.90	0.80-1.02		
							Finerenone vs placebo	0.86	0.79-0.93		
							GLP-1 RA vs SGLT-2i	1.37	1.17-1.61		
							Finerenone vs SGLT-2i	1.30	1.14-1.49		
							Finerenone vs GLP-1 RA	0.95	0.82-1.10		
CVD	6519	6507	12960	11596	2673	2662	SGLT-2i vs placebo	0.87	0.78-0.97	0.0	0.658
							GLP-1 RA vs placebo	0.90	0.75-1.08		
							Finerenone vs placebo	0.88	0.76-1.02		
							GLP-1 RA vs SGLT-2i	1.04	0.84-1.28		
							Finerenone vs SGLT-2i	1.02	0.85-1.22		
							Finerenone vs GLP-1 RA	0.98	0.78-1.23		
ACD	6519	6507	11944	10805	2673	2662	SGLT-2i vs placebo	0.90	0.81-0.99	0.0	0.537
							GLP-1 RA vs placebo	0.89	0.77-1.02		
							Finerenone vs placebo	0.90	0.80-1.00		
							GLP-1 RA vs SGLT-2i	0.99	0.83-1.17		
							Finerenone vs SGLT-2i	1.00	0.86-1.16		
							Finerenone vs GLP-1 RA	1.01	0.85-1.20		

Note: I: intervention; C: control

Discussion

In the absence of RCT directly comparing to nonsteroidal and selective mineralocorticoid receptor antagonists, SGLT2i and GLP-1 RA, this network meta-analysis evaluated the relative efficacy of three drugs on cardiovascular and renal outcomes in patients with T2DM and CKD. This network meta-analysis was based on 17 large trials, which included 51,496 patients randomly assigned to three kinds of drugs or placebo. Our results revealed that finerenone can decrease the risk of renal events and HHF, alongside with the tendency to reduce ACD in patients with T2DM and CKD. Our study did not find an advantage of finerenone in reducing the risk of MACE. SGLT2i was found to be comprehensive in reducing the risk of MACE, renal events, HHF, CVD and ACD. It was also noted that SGLT-2i outperformed finerenone when it comes to reducing the risk of renal events. These findings suggests that amongst population who are susceptible to renal events, the use of SGLT-2i for risk reduction is more advantageous compared to finerenone.

This study revealed that GLP-1 RA decrease the risk of MACE compared with placebo. The result varied with a recent network meta-analysis [64]. The cause of such result may be due to the exclusion of ELIXA trail, as its definition of MACE included unstable angina. Unfortunately, GLP-1 RA did not show any significant benefit aside from reducing the risk of MACE, although they showed an advantage in numbers. Our study also revealed that SGLT-2i were associated with a decreased risk of renal events and HHF compared with finerenone and GLP-1 RA. This seems to imply that GLP1-RA has no advantage over SGLT2i, but analysis between specific drugs showed different results. Liraglutide, one of GLP-1 RA, was associated with a decreased risk of MACE, ACD, CVD and HHF. Of all the drugs included in this study, liraglutide was the only drug that showed efficacy in CVD compared with placebo. In addition, it showed a trend superior to finerenone in reducing the incidence of MACE. As shown in minimally contextualized framework, liraglutide also ranked first in MACE, ACD and CVD among all drugs included in this study.

Several mechanisms have been proposed for the positive impact of finerenone. As a nonsteroidal, selective mineralocorticoid receptor antagonist, finerenone has been shown to have potent anti-inflammatory and antifibrotic effects while reducing the urinary albumin-to-creatinine ratio, which may be related to its benefits in renal events and HHF [65-68].

As for the morbidity renal events and HHF, it was clear that SGLT-2i had more significant impact than finerenone, the result can be explained with the characteristics of SGLT-2i that are not found in finerenone, such as reducing blood glucose, reducing Oxidative stress, weight loss, reducing uric acid, controlling blood pressure, it can act as natriuretic and diuretic, improving renal ultrafiltration and hypoxia, all which should be taken into account. [69-78]. This may also be one of the reasons why finerenone has not been shown to reduce the incidence of MACE among the patients with T2DM and CKD.

Our results showed an interesting phenomenon, in the three observed outcomes of ACD, HHF and CVD, GLP-1 RA did not show a significant advantage over placebo, but liraglutide, a GLP-1 RA did. In addition, liraglutide had a significant effect than exenatide in the morbidity of MACE, ACD, HHF, and CVD. Based on chemical structure, GLP-1 RA can be divided into two groups: incretin-mimetics (exendin-4 analogs) and human GLP-1 analogues. Exenatide is a synthetic exendin-4 analogue and liraglutide is an acylated analogue of GLP-1.

To this day, no research has yet identified the drug elimination pathway of GLP-1 analogues, but so far it is believed that GLP-1 analogues is metabolized in target tissues via the common proteolytic pathway of large proteins. Their large molecular size or noncovalent attachment to albumin can prevent them from being eliminated by the kidneys. However, exendin-4 analogues are metabolized and eliminated by the kidneys. Moreover, exendin-4 analogues are resistant to inactivation of dipeptidyl peptidase-4, while GLP-1 analogues are partially metabolized to metabolites, which may be related to the better benefits in cardioprotective effects of liraglutide than exenatide [79,80].

A major strength of this network meta-analysis is that this is the first study which investigates the effect of finerenone, SGLT-2 inhibitors and GLP-1 RA on cardiovascular and renal outcomes in patients with T2DM and CKD. Secondly, the number of included studies and sample size was large and the statistical efficiency was reliable, which provided evidence for individualized drug administration in clinical practice of patients with T2DM and CKD. Last but not least, in the Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes-2022[19], ADA preferably recommends SGLT-2 inhibitors and finerenone over GLP-1 RA in vulnerable population who are at increased risk for cardiovascular events or CKD progression, they also suggests the use of GLP-1 RA or SGLT-2i for individuals with T2DM with or at high risk for ASCVD, and/or CKD in the Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022[15]. Our study supports their recommendations, with additional evidence that GLP-1 analogues could reduce the risk of MACE, HHF, CVD, especially ACD, suggesting that GLP-1 analogues can be an alternative option in patients with T2DM and CKD. GLP-1 RA may be suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of cardiovascular events appear to possibly slow CKD progression. While there is clear cardiovascular risk reduction associated with GLP-1 RA use in patients with T2DM and CKD, the proof of benefit on renal outcome will come with the results of the ongoing FLOW (A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide [81].

However, this study is not without limitations. Firstly, we conducted this network meta-analysis on the basis of indirect comparisons. Therefore, our results require validation by head-to-head trials comparing finerenone with SGLT2i and GLP-1 RA. Secondly, partial studies that are included in this paper are subgroup analysis of RCTs, there is still a concern that patients with T2DM and CKD may not be completely randomized. Thirdly, there were more patients involved in SGLT2i than GLP-1 RA and Finerenone. In addition, the baseline eGFR of patients in “Cherney 2021” was different from other studies. Although we did not observe high heterogeneity, these imbalances may limit the statistical capabilities of network meta-analysis. Finally, we did not pay attention to albuminuria, so we could not investigate the effects of three drugs for albuminuria in diabetics with CKD.

Conclusion

In patients with T2DM and CKD, finerenone led to a risk reduction in renal events and HHF, SGLT2i were associated with a decreased risk of cardiovascular and renal events. Finerenone had a tendency to decrease the risk of ACD. GLP-1 RA were associated with a decreased risk of MACE. As for renal outcomes and

HHF, SGLT2i had significant effect than finerenone and GLP-1 RA. Among GLP-1 RA, GLP-1 analogues showed significantly reduced cardiovascular events compared with exendin-4 analogues.

Abbreviations

SGLT2i: Sodium-glucose cotransporter-2 inhibitors; GLP-1 RA: Glucagonlike peptide-1 receptor agonists; T2DM: Type 2 diabetes mellitus; CKD: Chronic kidney disease; RCTs: Randomized control trials; RR: Risk ratio; CI: Confidence interval; HHF: Hospitalization for heart failure; MACE: Major adverse cardiovascular events; ACD: All-cause death; CVD: Cardiovascular death; DM: Diabetes mellitus; ASCVD: Atherosclerotic cardiovascular disease; ESRD: End-stage renal disease; MI: Myocardial infarction; ADA: American Diabetes Association; eGFR: Estimated glomerular filtration rate; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; CrCl: creatinine clearance.

Declarations

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Authors' contributions

Yaofu Zhang, Li Jiang and Tongxin Wang designed and monitored the whole analysis. Junheng Wang and Weijun Huang contributed to study selection. Yaofu Zhang, Li Jiang and Tongxin Wang contributed to data extraction. Chieh Chien provided the methodological support. Yonghua Xiao, Yaofu Zhang, Qiang Fu and Xiaozhe FU contributed to the data analysis and paper writing. Shidong Wang and Jinxi Zhao provided the project fund. Jinxi Zhao and Shidong Wang were responsible for the data review. All authors provided critical review and approved this manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table

Table 1 is available in the Supplementary Files section

Figures

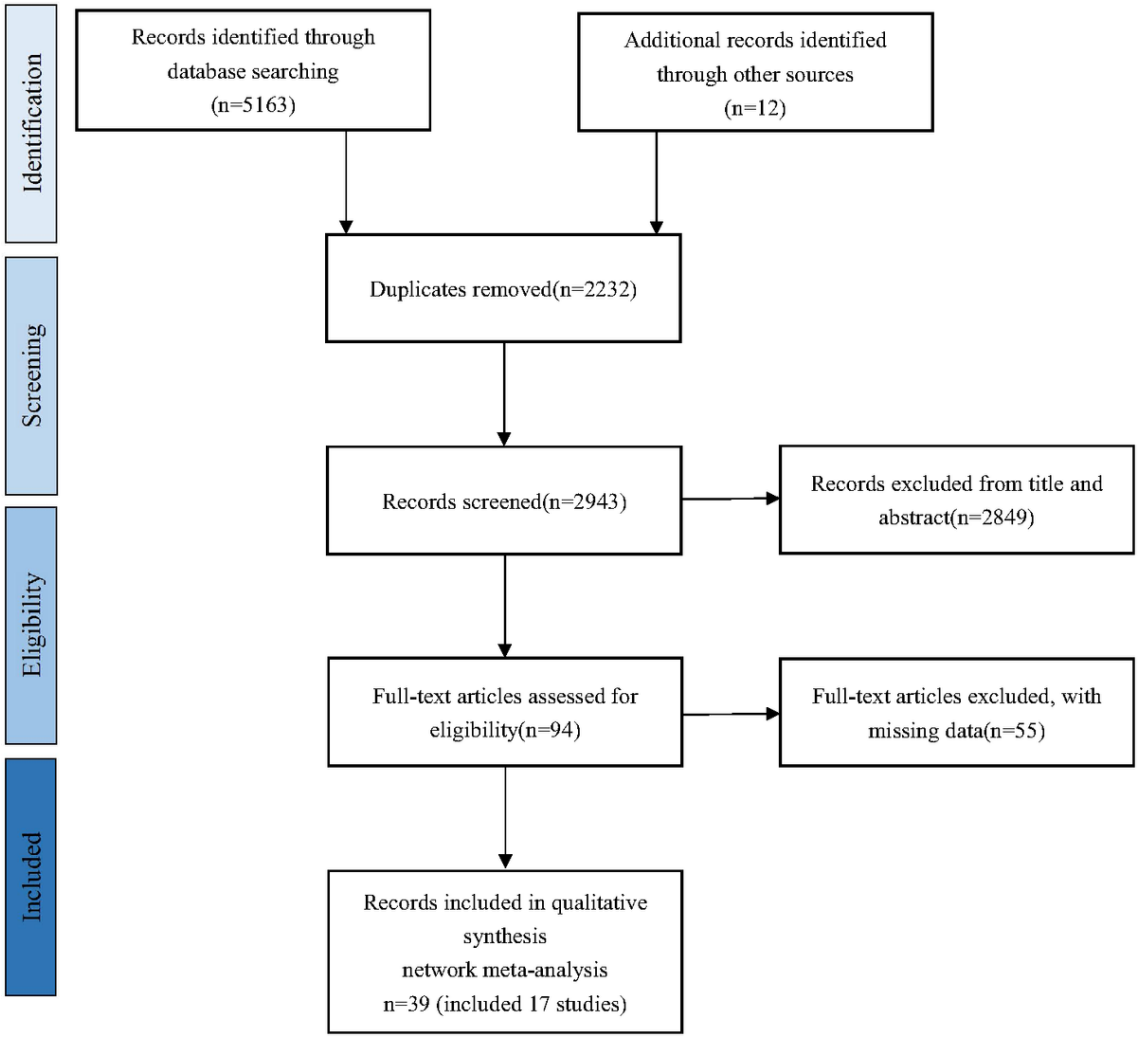

Figure 1

PRISMA flowchart.

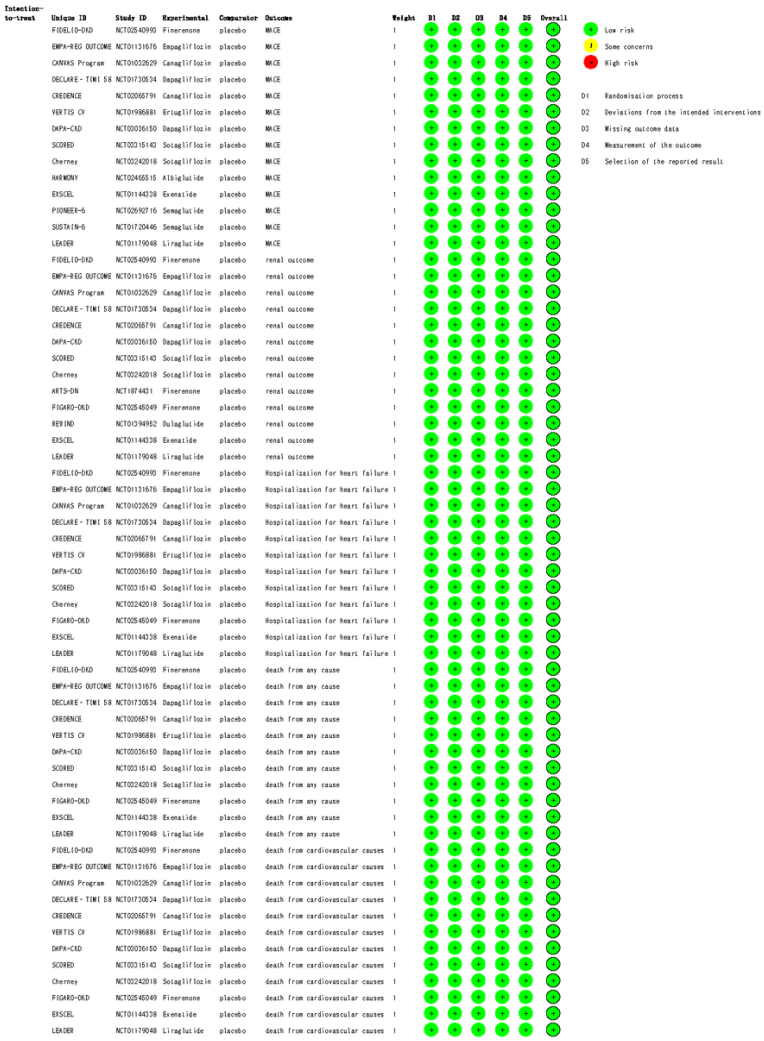

Figure 2

Detailed risk of bias in each study.

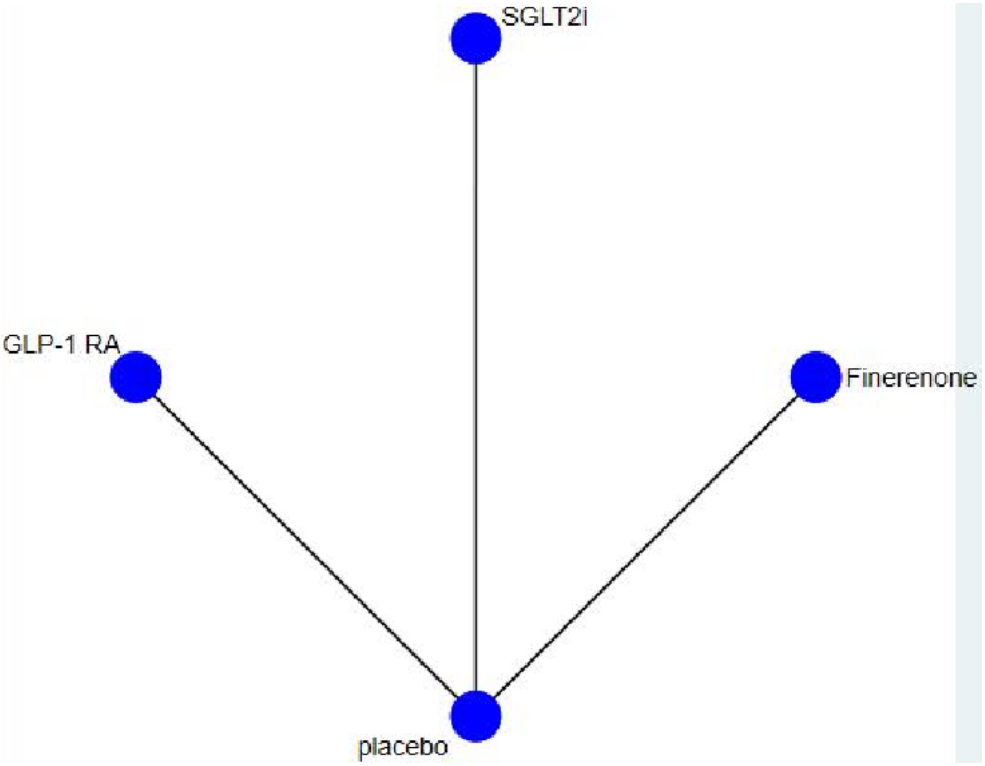

Figure 3

network graph.

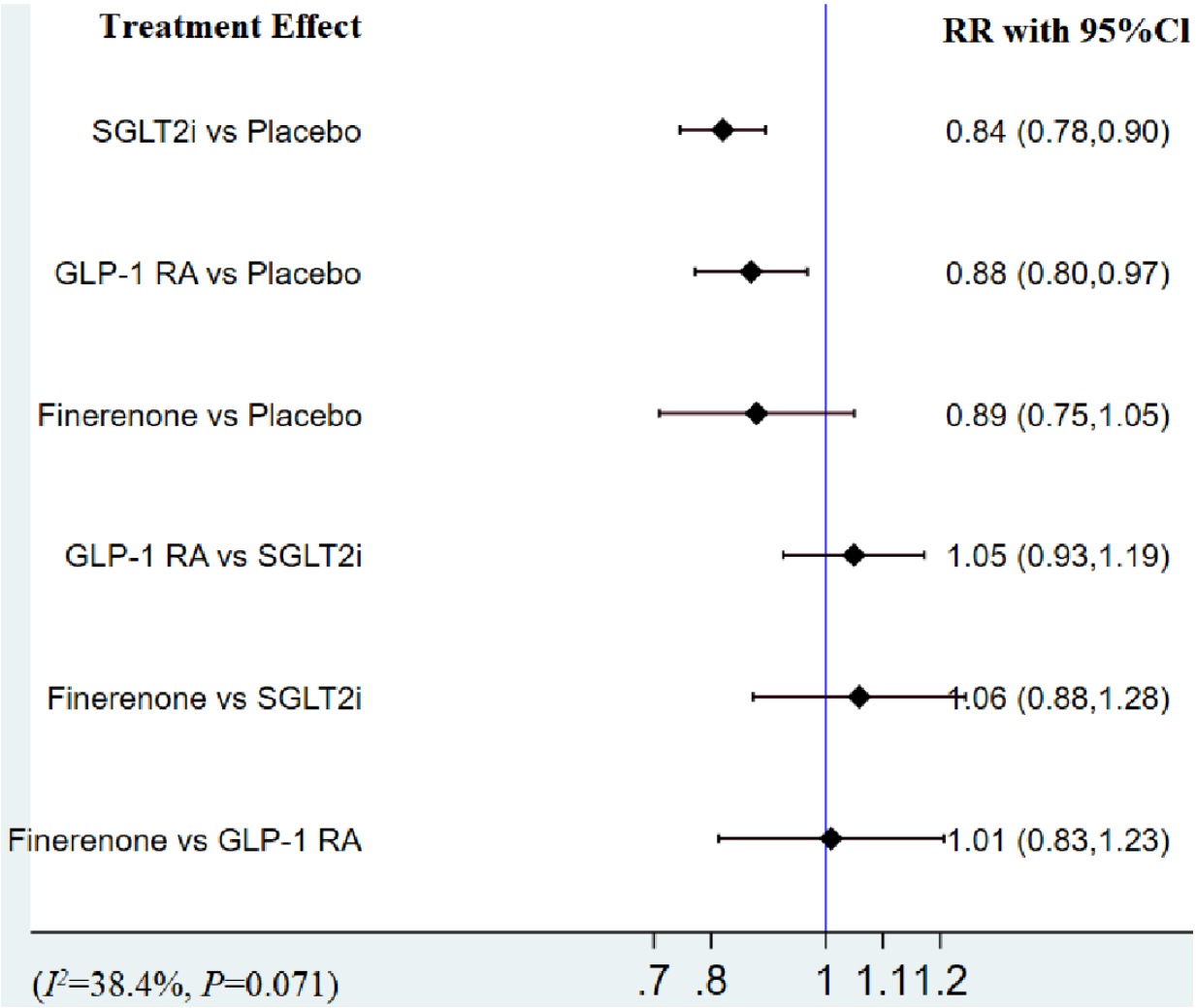

Figure 4

Network meta-analysis reporting RR for MACE in patients with T2DM and CKD.

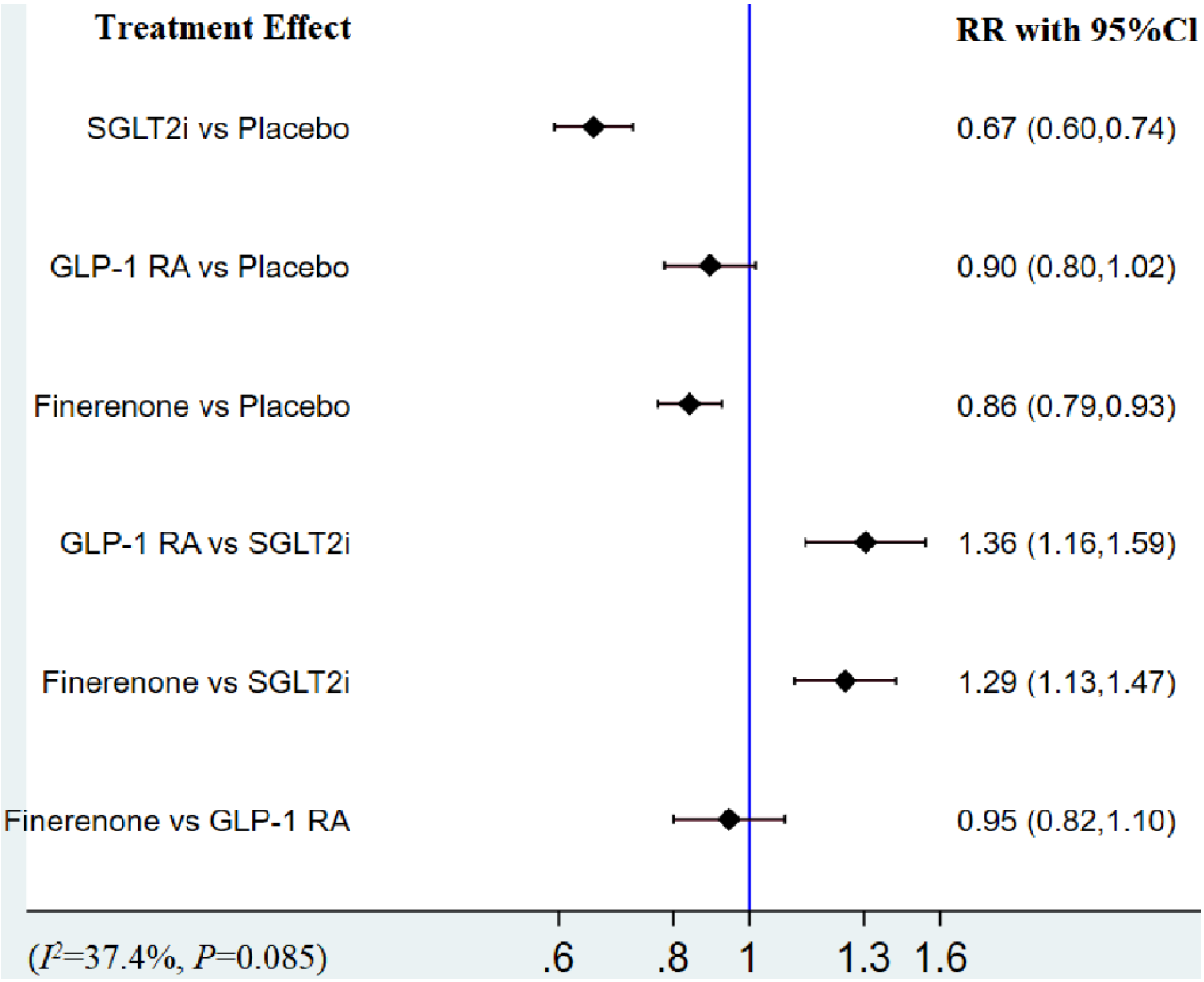

Figure 5

Network meta-analysis reporting RR for renal outcome in patients with T2DM and CKD.

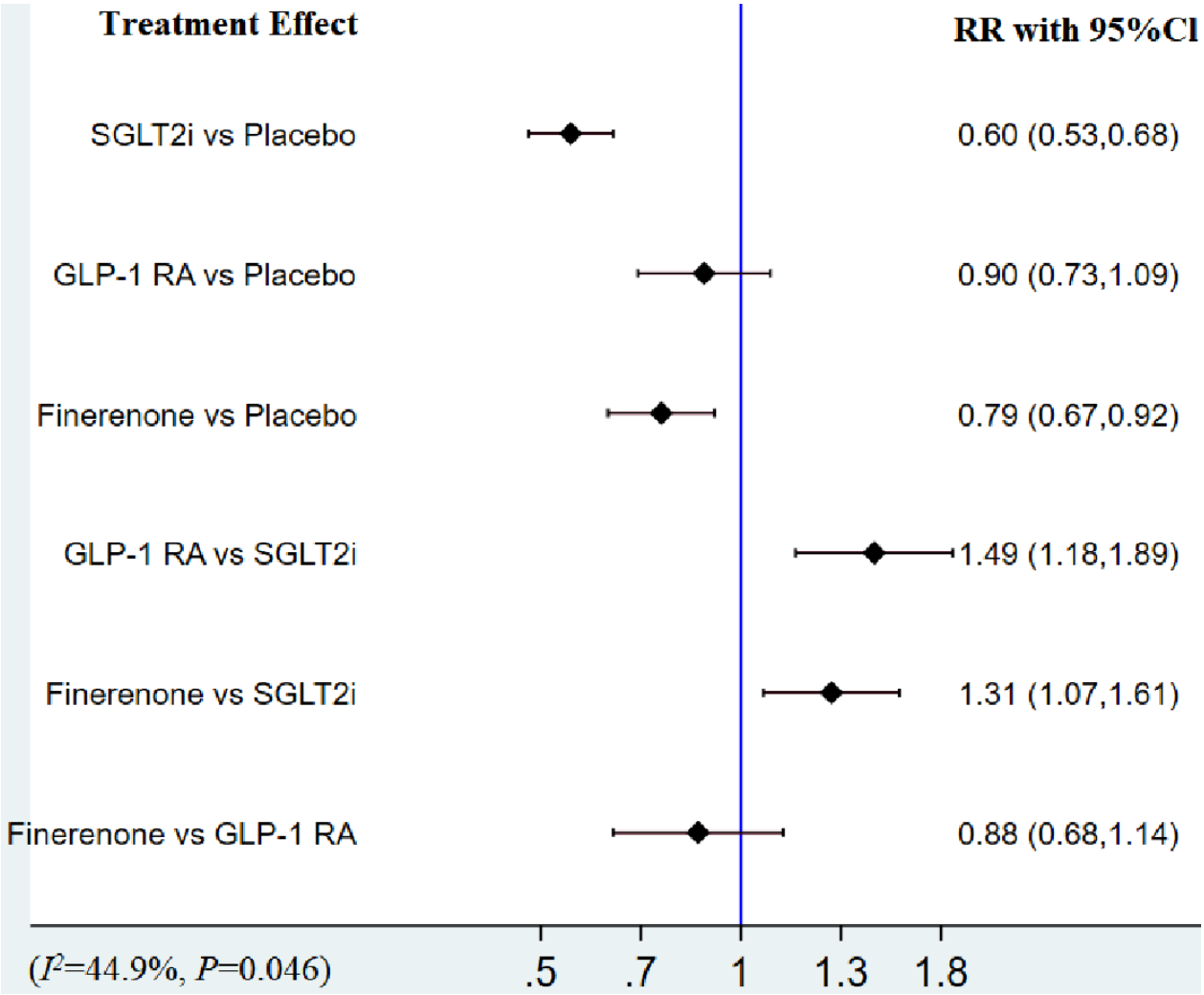

Figure 6

Network meta-analysis reporting RR for HHF in patients with T2DM and CKD.

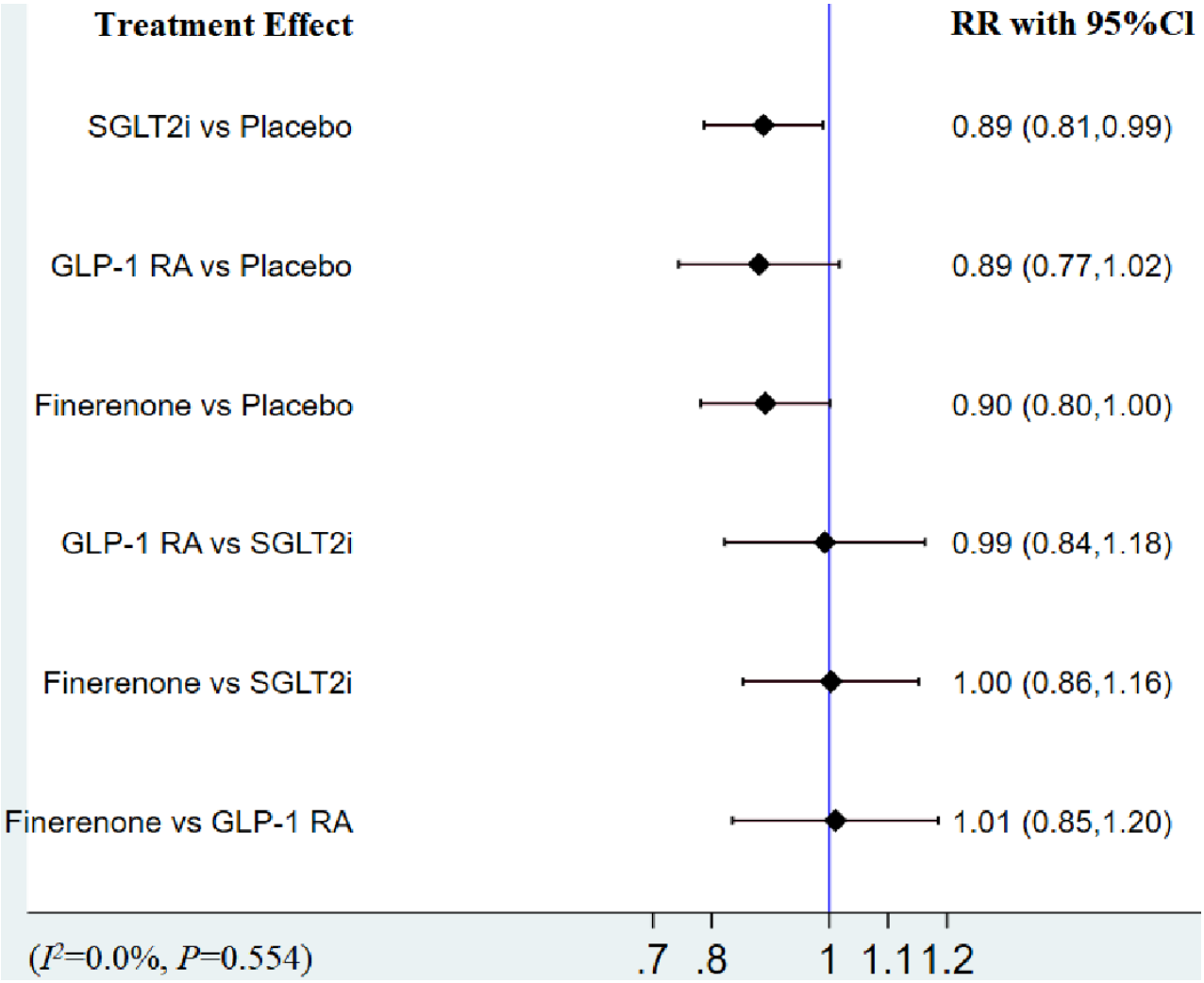

Figure 7

Network meta-analysis reporting RR for ACD in patients with T2DM and CKD.

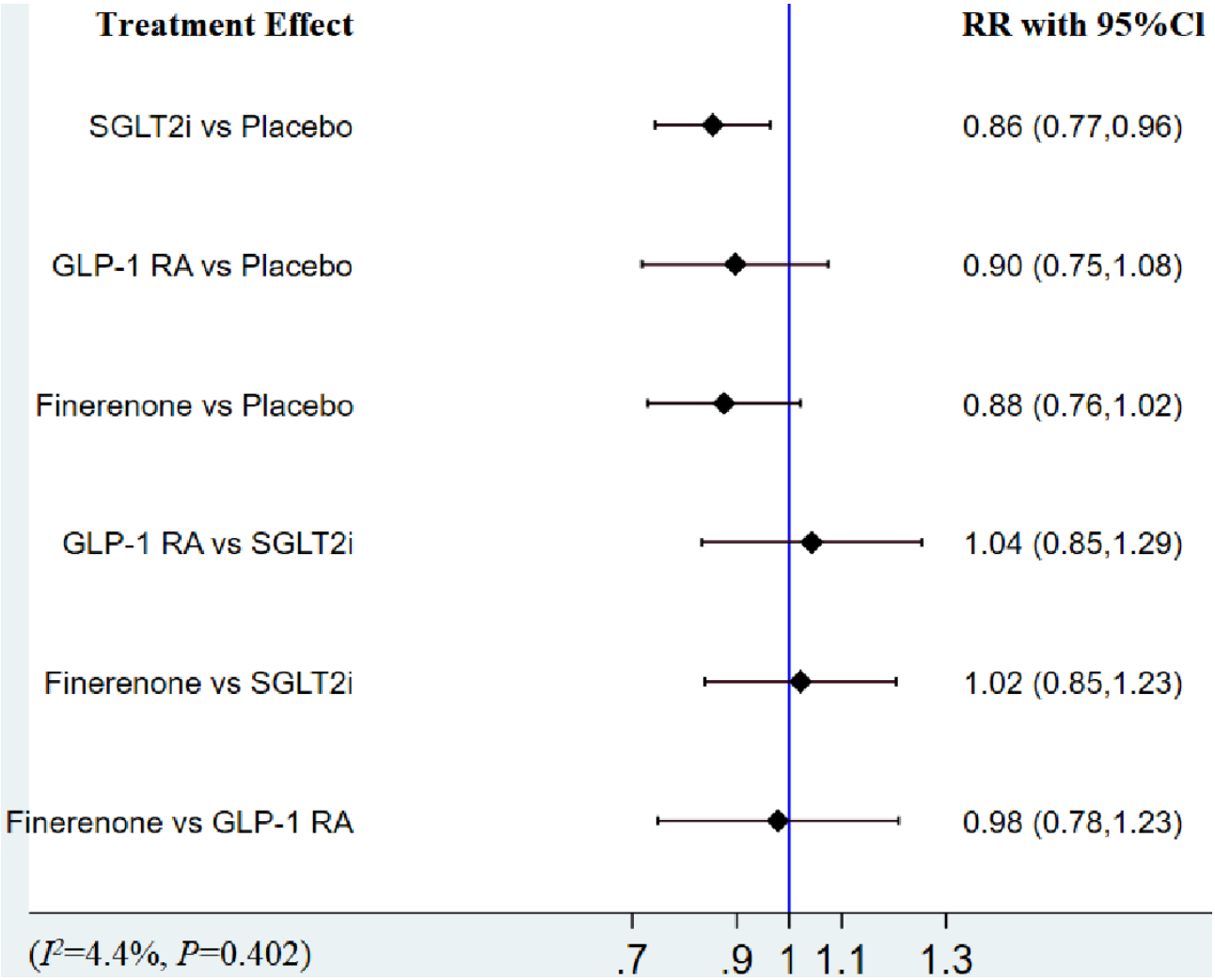

Figure 8

Network meta-analysis reporting RR for CVD in patients with T2DM and CKD.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1ROB2evaluation.xls
- Table1.docx