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META-ANALYSIS

Renal effects and safety of tirzepatide in subjects with and without diabetes: A systematic review and meta-analysis

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Abstract

BACKGROUND

Type 2 diabetes (T2D), as well as obesity, are risk factors for chronic kidney disease (CKD) and end-stage renal disease. The renal impacts of glucose-lowering

and weight-lowering drugs and their potential benefits in preventing CKD often guide clinicians in choosing them appropriately. Only limited data based on randomized controlled trials (RCTs) is currently available on the renal effects and safety profile of tirzepatide.

AIM

To explore the renal benefits and safety of tirzepatide *vs* controls.

METHODS

RCTs involving patients receiving tirzepatide for any indication in the intervention arm and placebo or active comparator in the control arm were searched through multiple electronic databases. The co-primary outcomes were percent change from baseline (CFB) in urine albumin-to-creatinine ratio (UACR) and absolute CFB in estimated glomerular filtration rate (eGFR; in mL/min/1.73 m^2); the secondary outcome was tirzepatide's renal safety profile. RevMan web was used to conduct meta-analysis using random-effects models. Outcomes were presented as mean differences (MD) or risk ratios with 95% confidence intervals.

RESULTS

Fifteen RCTs (n = 14471) with mostly low risk of bias (RoB) were included. Over 26-72 weeks, tirzepatide 10 mg [MD -26.95% (-40.13, -13.76), P < 0.0001] and 15 mg [MD -18.03% (-28.58, -7.47), P = 0.0008] were superior to placebo in percent reductions of UACR. Tirzepatide, at all doses, outperformed insulin in percent reductions of UACR. Compared to the placebo, the percent UACR reduction was greater in subjects with T2D than those with obesity but without T2D (MD -33.25% *vs* -7.93%; P = 0.001). The CFB in eGFR with all doses of tirzepatide was comparable [5 mg: MD 0.36 (-1.41, 2.14); 10 mg: MD 1.17 (-0.22, 2.56); 15 mg: MD 1.42 (-0.04, 2.88)]; P > 0.05 for all] *vs* insulin. Tirzepatide (pooled and separate doses) did not increase the risks of adverse renal events, urinary tract infection, nephrolithiasis, acute kidney injury, and renal cancer compared to the placebo, insulin, and glucagon-like peptide-1 receptor agonists.

CONCLUSION

Short-term data from RCTs with low RoB suggests that tirzepatide positively impacts UACR without detrimental effects on eGFR in subjects with T2D and obesity without T2D, with a reassuring renal safety profile. Larger RCTs are warranted to prove the longer-term renal benefits of tirzepatide, which might also prevent eGFR decline and worsening of CKD.

Key Words: Tirzepatide; Type 2 diabetes; Obesity; Urine albumin creatinine ratio; Estimated glomerular filtration rate; Renal safety; Acute kidney injury; Chronic kidney disease

Core Tip: It is important to appraise the renal impacts and safety profile of Tirzepatide for optimal use of this molecule by clinicians for managing patients with type 2 diabetes (T2D), the most common cause of chronic kidney disease across the globe. Based on 15 randomized controlled trials (RCTs) with mostly low risk of bias involving 14471 participants, this systematic review identified that Tirzepatide significantly reduces urine albumin-to-creatinine ratio compared to placebo and insulin, with a neutral impact on estimated glomerular filtration rate (eGFR) in individuals with T2D and obesity without T2D. Moreover, tirzepatide does not appear to increase the risks of renal adverse events. Larger and longer-term RCTs are warranted to prove the renal benefits of tirzepatide and its potential to prevent eGFR decline in patients.

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INTRODUCTION

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate (eGFR) persistently < 60 mL/min/1.73 m^2 and/or elevated urinary albumin excretion > 30 mg/day[1]. CKD in diabetes, often referred to as diabetic kidney disease (DKD), results from prolonged hyperglycemia, which causes glomerular hyperfiltration, thickening of the glomerular basement membrane, and mesangial expansion. This impairs glomerular filtration and leads to proteinuria, inflammation, and fibrosis, ultimately resulting in chronic kidney failure[2]. About 50% of people with type 2 diabetes (T2D) may experience CKD, one of the most prevalent microvascular complications of the disease, at some point during their T2D journey[1]. Obesity is also an independent risk factor for the new onset and progression of CKD; however, the

link is unclear. Obesity may cause renal dysfunction directly through obesity-related glomerulopathy (ORG) and indirectly through comorbidities like atherosclerosis, hypertension, and T2D. Adipocytokines are linked to glomerular inflammation, oxidative stress, endothelial dysfunction, glomerular hyperfiltration, and, ultimately, proteinuria[3]. The true prevalence of ORG is unknown, although the prevalence of significant proteinuria [≥ 1+ by urine dipstick or urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/mmol] is 4%-10% amongst patients with obesity. Moreover, obesity, which is an important risk factor for T2D and very common in these patients, accelerates the progression of both diabetic and non-diabetic CKD[4]. Both eGFR and UACR (normal < 30 mg/g) are recommended for risk assessment of DKD[2]. Currently, there are no specific well-established criteria for diagnosing ORG; such a diagnosis is primarily based on the presence of obesity and abdominal obesity, proteinuria, and typical microscopic appearance with the exclusion of secondary causes[5].

Optimizing control of glycemia, blood pressure, and lipids reduces the risk and slows down DKD progression and, thereby, the cardiovascular risk, which are the cornerstones of managing patients with DKD[6]. However, the benefits of intensive glycemic control rest upon reducing albuminuria only; it does not affect eGFR decline[7]. Drugs acting on the renin-angiotensin-aldosterone system (RAAS) are the specific therapeutic options for DKD; either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) is recommended to prevent the progression of DKD and reduce cardiovascular events in this condition[6]. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has demonstrated significant cardiovascular and kidney protection for patients with proteinuric kidney disease due to T2D when used with maximally tolerated ACEi or ARB[8]. However, in contrast to other microvascular complications, DKD hasn't decreased as a complication of T2D in recent years, even with the increased screening rate[9]. A definite treatment recommendation for ORG is lacking. Weight loss and RAAS blockers have a protective effect on obesity-related CKD, but even so, a significant proportion of patients eventually progress to end-stage renal disease (ESRD) despite treatment. Weight loss and RAAS blockers have a protective effect on obesity-related CKD. However, many patients still develop ESRD[8].

Some glucose-lowering drugs positively impact renal function, and their renal effects should be considered when choosing a treatment regime for a patient with diabetes. Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce renal tubular glucose reabsorption, intraglomerular pressure, and albuminuria and slow down the glomerular filtration rate decline[10]. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA) also have direct effects on the kidney and have been found to reduce albuminuria, decline in eGFR, and delay the onset of ESRD irrespective of their glycemic benefits [11]. Tirzepatide is a novel first-in-class dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors[12]. Tirzepatide effectively reduces blood glucose, body weight, insulin resistance, blood pressure, and atherogenic dyslipidemia. Such metabolic actions of tirzepatide may benefit CKD through improved hemodynamics and reduced inflammation, atherosclerosis, oxidative stress, and fibrosis[13]. No ongoing or available trials specifically investigate the effects of tirzepatide on patients with CKD. A post hoc analysis of the SURPASS-4 clinical trial found tirzepatide to reduce albuminuria, total eGFR slopes and nearly halved the risk of a composite kidney endpoint (eGFR decline ≥ 40%, renal death, kidney failure, or new-onset macroalbuminuria) in patients with T2D with high cardiovascular risk compared to insulin glargine[14]. A systematic review and meta-analysis (SRM) examining the effects of tirzepatide on albuminuria and renal function in patients with T2D mellitus has recently been published[15]. However, the SRM has several shortcomings; for example, it only included clinical trials conducted among subjects with T2D (not those with obesity and without T2D) and did not analyze its safety outcomes. Hence, it is imperative to conduct an updated SRM, including all relevant randomized controlled trials (RCTs) of tirzepatide in T2D and obesity without T2D, reporting the renal effects and safety of tirzepatide to inform better clinical practice decisions by healthcare professionals.

MATERIALS AND METHODS

Ethical compliance

This SRM complied with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA checklists[16,17]. It was registered with PROSPERO (CRD42024584102), and the protocol summary is accessible online.

Search strategy

A comprehensive search was performed across various databases and registries, including MEDLINE (*via* PubMed), Scopus, Cochrane Central Register, and ClinicalTrials.gov. The search investigated these sources from their inception to June 30, 2024. The search strategy utilized a Boolean approach with the terms "tirzepatide" OR "LY3437943"; the search terms were applied to titles only. A thorough and careful search was conducted to find any recently published or unpublished clinical trials in English. The search also included examining references within the retrieved clinical trials included in this study and relevant journals.

Study selection

The selection of clinical trials for this meta-analysis was based on the PICOS criteria. The patient population (P) consisted of individuals treated with tirzepatide for any clinical indication; the intervention (I) was the administration of tirzepatide; the control (C) included individuals receiving either a placebo or any other active comparator; the outcomes (O) included the renal effects and safety of tirzepatide; and the study type (S) included the RCTs. This analysis included RCTs with a minimum 12-week duration with study subjects aged ≥ 18 years. The trials had a minimum of two treatment groups, one administering tirzepatide either as monotherapy or in conjunction with other medications, while the other

group received a placebo or another active comparator, either alone or in combination with additional medications. Exclusions were clinical experiments using animals or healthy humans, nonrandomized trials, RCTs lasting less than 12 weeks, retrospective studies, pooled analyses of clinical trials, conference proceedings, letters to editors, case reports, and articles devoid of relevant outcome data.

Outcomes analyzed

The co-primary outcomes of this SRM were the percent change from baseline (CFB) in UACR and the absolute CFB in eGFR (calculated using CKD epidemiology collaboration, CKD-EPI formula) at the end of the trial. The secondary outcome was tirzepatide's renal safety profile. The safety profile included renal events (events classified as severe or serious adverse events), urinary tract infection (UTI), nephrolithiasis, acute kidney injury (AKI), and renal cancer. The terminologies for the adverse events were coined per the descriptions of the included studies.

Data extraction and handling of missing data

Four review authors independently performed data extraction utilizing standardized forms, with further details available elsewhere[18]. The handling of missing data has also been detailed in the same source[18].

Risk of bias assessment

Four authors independently performed the risk of bias (RoB) assessment using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) in the Review Manager (RevMan) computer program, version 7.2.0[19,20]. The domains included in RoB 2 cover all types of bias currently understood to affect the results of RCTs, *e.g.*, bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome; and bias in the selection of the reported result. The risk-of-bias judgment assigned one of three levels to each domain: Low risk of bias, some concerns, or high risk of bias. The least favorable assessment across the domains of bias was considered the overall risk of bias for the result[19]. The Risk-of-bias VISualization (robvis) web app was used to create risk-of-bias plots[21].

Statistical analysis

The results of the outcomes were expressed as mean differences (MDs) for continuous variables and as risk ratios (RRs) for dichotomous variables with 95% confidence intervals (CIs). Forest plots were created using the RevMan computer program, version 7.2.0[20], which portrayed the comparison of RR for primary and secondary outcomes, with the left side favouring tirzepatide and the right side favouring the control group(s). Random effects analysis models were applied while generating forest plots to address the anticipated heterogeneity resulting from population characteristics and study length variations among the included RCTs. The inverse variance statistical approach was utilized in all instances. Forest plots incorporating data from at least two RCTs were included in the results. A significance level of $P < 0.05$ was employed.

Assessment of heterogeneity

The assessment of heterogeneity was initially conducted through the analysis of forest plots. Afterward, a χ^2 test was conducted with N-1 degrees of freedom and a significance level of 0.05 to ascertain the statistical significance. The I^2 test was also utilized in the further analysis[22]. The interpretation of I^2 values has been previously discussed in detail[18].

Grading of the results

The GRADE methodology assessed the quality of evidence about each meta-analysis outcome[23]. The process of creating the summary of findings (SoF) table and evaluating the quality of evidence as "high", "moderate", "low", or "very low" has been previously described[18].

RESULTS

Search results

The study selection process is illustrated in Figure 1. The preliminary search yielded 1092 publications; after screening titles and abstracts and doing full-text reviews, the studies included in this meta-analysis were reduced to 30. Detailed evaluation led to the inclusion of 15 RCTs with 16 published reports involving 14471 subjects that met all the inclusion criteria[14,24-38]. Fifteen studies were excluded; eight were sub-studies or post hoc analyses of an included trial[39-46]; six studies have not reported the outcomes of interest[47-52]; and in another study, an open-label tirzepatide lead-in period followed by a double-blind, placebo-controlled period[53].

Characteristics of included studies

Two of the 15 RCTs included in this meta-analysis were phase 2 trials[24,38], and the other 13 were phase 3 trials[25-37]. Ten RCTs included individuals with T2D[24,26,30-37], four included obese/overweight subjects without diabetes[25,27-29], and one included those with biopsy-confirmed metabolic dysfunction associated steatohepatitis and stage F2 or F3 fibrosis, with or without diabetes[38], as the study population. Eight of the included RCTs used matching placebos[25-34,38], four used insulin[32,33,35,36], two used GLP-1RA[31,37], and one trial used both placebo and GLP-1RA in the control groups[24]. Most of the RCTs had three tirzepatide (5 mg, 10 mg, and 15 mg)[25,30-38], one had an additional arm of 1

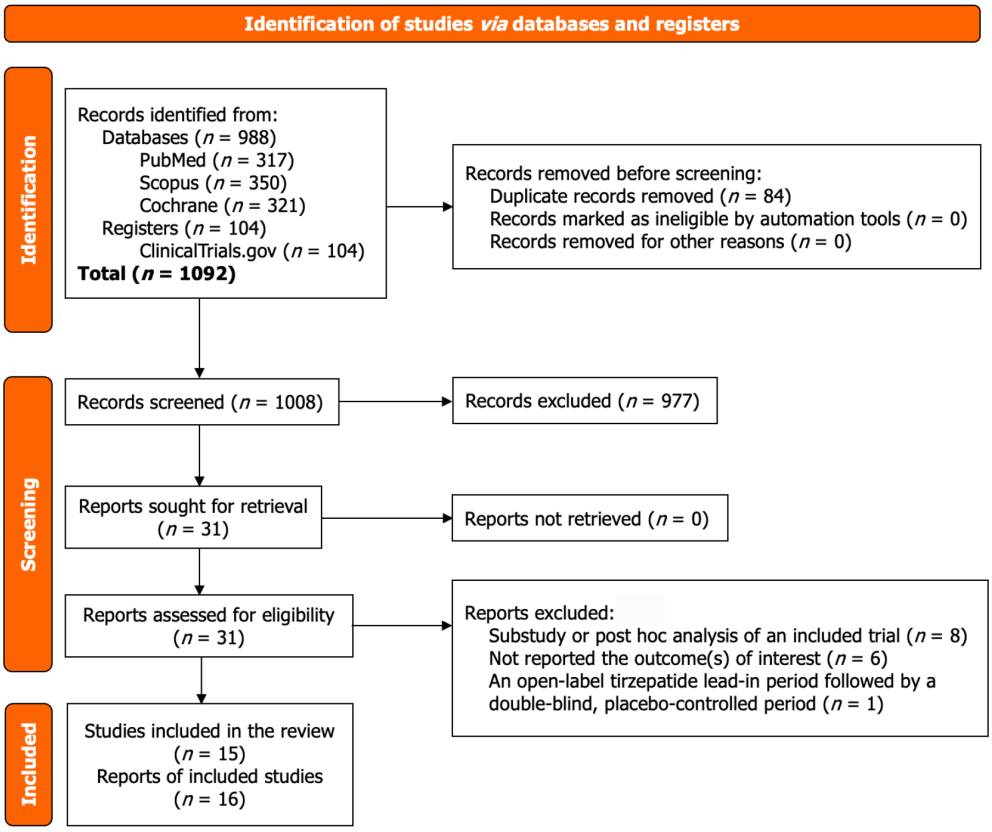


Figure 1 Flowchart on study retrieval and inclusion in the meta-analysis.

mg[24], two had two arms of 10 mg and 15 mg[26,28], and one trial had only single tirzepatide arm of maximum tolerated dose (MTD, 10 or 15 mg)[27]. SURMOUNT-OSA had two different trial populations, each with tirzepatide MTD (10 or 15 mg) and placebo arms; outcome results of tirzepatide MTD and placebo groups in Trials 1 and 2 were pooled into single groups of tirzepatide MTD and placebo[29]. All tirzepatide MTD arms were analyzed as tirzepatide 15 mg. One trial had a 26-week duration[24], four had 40-week durations[30,31,34,36], seven had 52-week durations[28,29,32,33,35,37,38], and the other three spanned 72 weeks[25-27]. The baseline characteristics of the included study subjects were matched throughout the trial arms in all of the included RCTs. Supplementary Table 1 presents the details of the baseline characteristics of the included studies. The proportions of study subjects with eGFR < 60 and UACR ≥ 30 in the overall study population are shown in Supplementary Table 2. Supplementary Table 3 summarizes the characteristics of the excluded RCTs.

Risk of bias in the included studies

Figure 2 depicts the bias risk across the 15 RCTs included in the meta-analysis. The overall risk of bias was low in most (60%) trials. One study (SURMOUNT-3) had 'some concerns' about attrition bias due to missing outcome data. Five (33.3%) studies had high risks for overall bias, which reflected the bias due to deviations from intended interventions. Publication bias was not assessed due to the inadequate number of RCTs (at least 10) in forest plots[54].

Grading of the results

The SoF table (Supplementary Table 4) provides the grades for the certainty of the evidence supporting the primary outcomes of this meta-analysis.

Effect of tirzepatide on UACR

Tirzepatide *vs* placebo: Tirzepatide 10 mg and 15 mg, but not 5 mg, was superior to placebo in percent reductions of UACR [for tirzepatide 5 mg: MD -20.68%, 95%CI (-45.43, 4.08), I^2 = 89%, P = 0.10, low certainty of the evidence; for 10 mg: MD -26.95% (-40.13, -13.76), I^2 = 81%, P < 0.0001, low certainty of the evidence; for 15 mg: MD -18.03% (-28.58, -7.47), I^2 = 72%, P = 0.0008, moderate certainty of the evidence] (Figure 3A). In subgroup analysis, according to the presence of T2D, tirzepatide (pooled dose) was superior to placebo in percent UACR reduction both in subjects with T2D [MD -33.25% (-47.56, -18.94), I^2 = 38%, P < 0.00001] and without T2D [MD -7.93% (-13.60, -2.26), I^2 = 0%, P = 0.006]; the UACR reduction was greater in subjects with T2D (P = 0.001 for subgroup difference) (Supplementary Figure 1). Furthermore, in a subgroup of subjects with T2D having baseline UACR ≥ 30 mg/g, the percent UACR reductions were greater with tirzepatide than with placebo [for tirzepatide 5 mg: MD -41.38% (-63.95, -18.81), I^2 = 0%, P = 0.0003; for 10 mg: MD -56.43% (-73.22, -39.65), I^2 = 0%, P < 0.00001; for 15 mg: MD -61.56% (-77.55, -45.57), I^2 = 0%, P < 0.00001] (Supplementary Figure 2). In another subgroup analysis, Subjects with T2D achieved significant reductions in percent UACR with

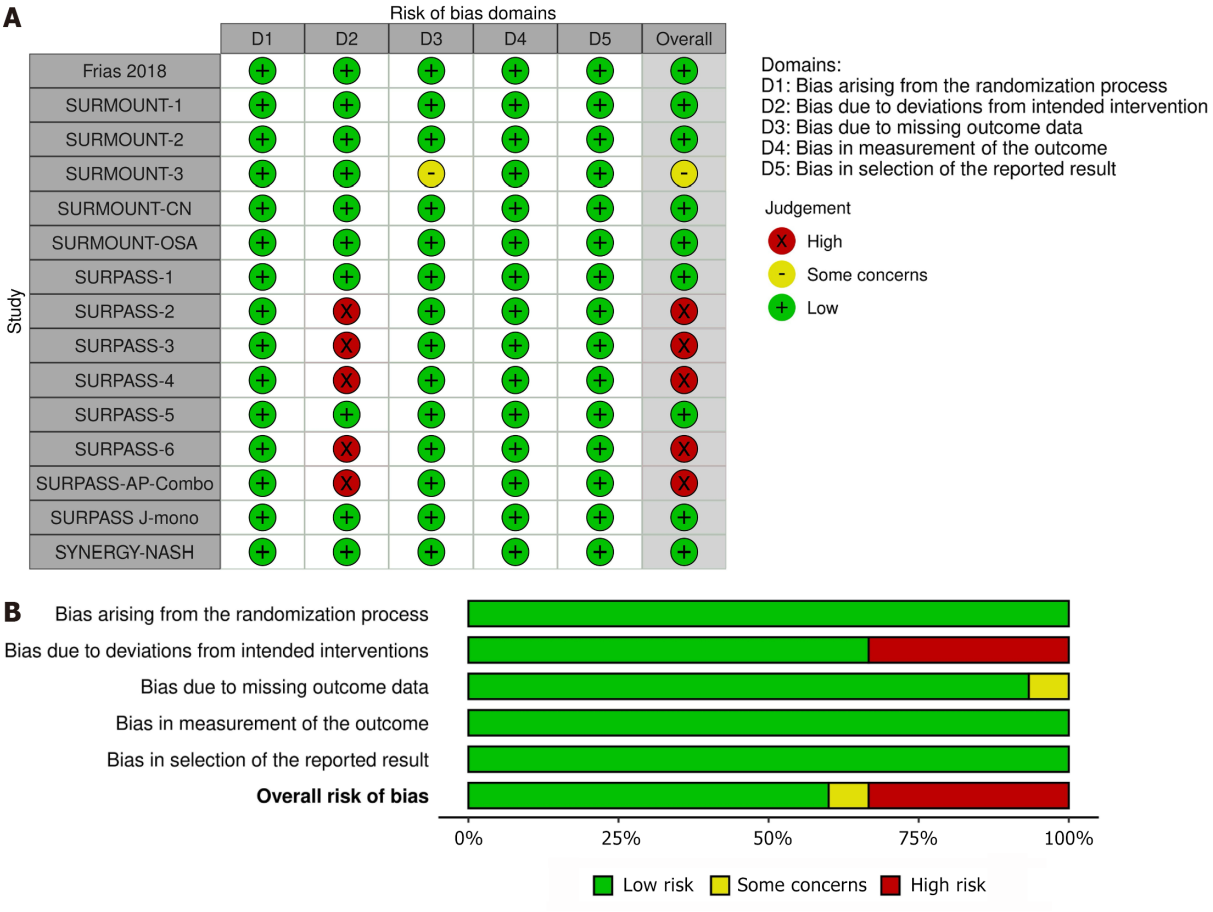


Figure 2 The risk of bias. A: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study; B: Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

tirzepatide *vs* control group (placebo or insulin) in the RCTs with mean baseline eGFR < 90 [MD -33.20% (-44.23, -22.17), I^2 = 48%, P < 0.00001] and ≥ 90 mL/min/1.73 m^2 [MD -28.19% (-44.78, -11.61), I^2 = 73%, P = 0.0009]; the UACR reduction was comparable in the two eGFR groups (P = 0.62 for subgroup difference) (Supplementary Figure 3).

Tirzepatide *vs* Insulin: Tirzepatide, at all doses, outperformed insulin in percent reductions of UACR [for tirzepatide 5 mg: MD -25.74% (-33.79, -17.70), I^2 = 55%, P < 0.00001, very low certainty of the evidence; for 10 mg: MD -30.36% (-42.13, -18.59), I^2 = 81%, P < 0.00001, very low certainty of the evidence; for 15 mg: MD -29.65% (-37.62, -21.68), P < 0.00001, very low certainty of the evidence] (Figure 3B). In subjects with baseline UACR ≥ 30 mg/g, greater percent UACR reductions were achieved with tirzepatide than with insulin [for tirzepatide 5 mg: MD -33.17% (-46.88, -19.46), I^2 = 0%, P < 0.00001; for 10 mg: MD -43.34% (-54.55, -32.13), I^2 = 0%, P < 0.00001; for 15 mg: MD -50.56% (-65.89, -35.24), I^2 = 52%, P < 0.00001] (Supplementary Figure 2).

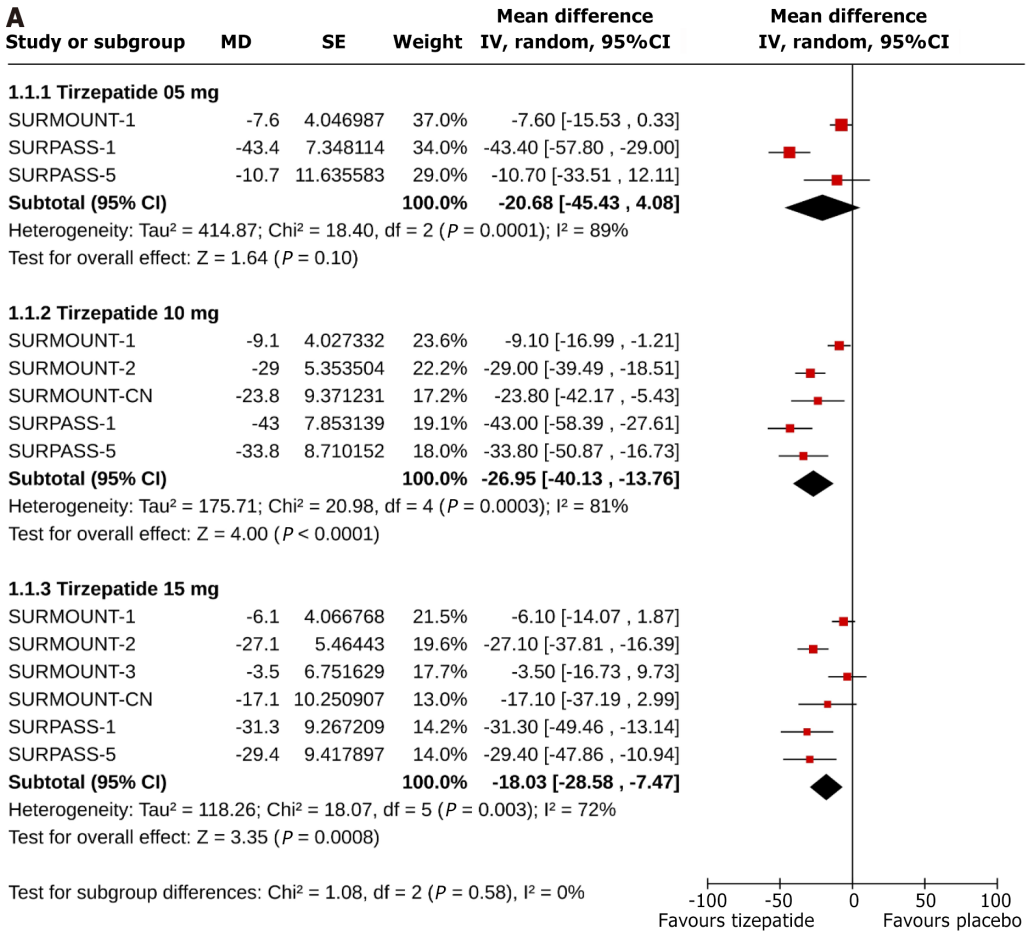
Tirzepatide *vs* GLP-1RA: Only one study, SURPASS-2, evaluated CFB in UACR in tirzepatide *vs* GLP-1RA. Percent CFB in UACR was statistically similar in the tirzepatide and semaglutide arms [for tirzepatide 5 mg: MD -4.4% (-15.0, 7.5), for 10 mg: MD 3.0% (-8.5, 15.9), for 15 mg: MD -8.9 (-19.1, 2.5), P < 0.05 for all][31]. In the same study, a greater percent UACR reduction than GLP-1RA was achieved with tirzepatide 15 mg [MD -28.70% (-51.54, -5.86), P = 0.01] but not with 5 and 10 mg (Supplementary Figure 2).

Effect of tirzepatide on eGFR

Tirzepatide *vs* placebo: One study, SURPASS 5, evaluating the CFB in eGFR in tirzepatide *vs* placebo found comparable CFB in eGFR in the two groups [for tirzepatide 5 mg: MD -2.0 mL/min/1.73 m^2 (-4.5, 0.4), for 10 mg: MD -0.4 mL/min/1.73m^2 (-2.9, 2.0), for 15 mg: MD 0.4 mL/min/1.73 m^2 (-2.0, 2.8), P > 0.05 for all][34].

Tirzepatide *vs* Insulin: The CFB in eGFR was comparable with all doses of tirzepatide *vs* insulin [for tirzepatide 5 mg: MD 0.36 mL/min/1.73 m^2 (-1.41, 2.14), I^2 = 82%, P = 0.69, very low certainty of the evidence; for 10 mg: MD 1.17 mL/min/1.73 m^2 (-0.22, 2.56), I^2 = 70%, P = 0.10, very low certainty of the evidence; for 15 mg: MD 1.42 mL/min/1.73 m^2 (-0.04, 2.88), P = 0.06, very low certainty of the evidence] (Figure 4).

Tirzepatide *vs* GLP-1RA: Only one study, SURPASS 2, evaluated CFB in eGFR in tirzepatide *vs* GLP-1RA. CFB in eGFR was comparable in the tirzepatide and semaglutide arms [for tirzepatide 5 mg: MD -0.2 mL/min/1.73 m^2 (-1.5, 1.2), for 10 mg: MD -0.3 mL/min/1.73 m^2 (-1.6, 1.0), for 15 mg: MD -0.6 mL/min/1.73 m^2 (-1.9, 0.8), P > 0.05 for all][31].



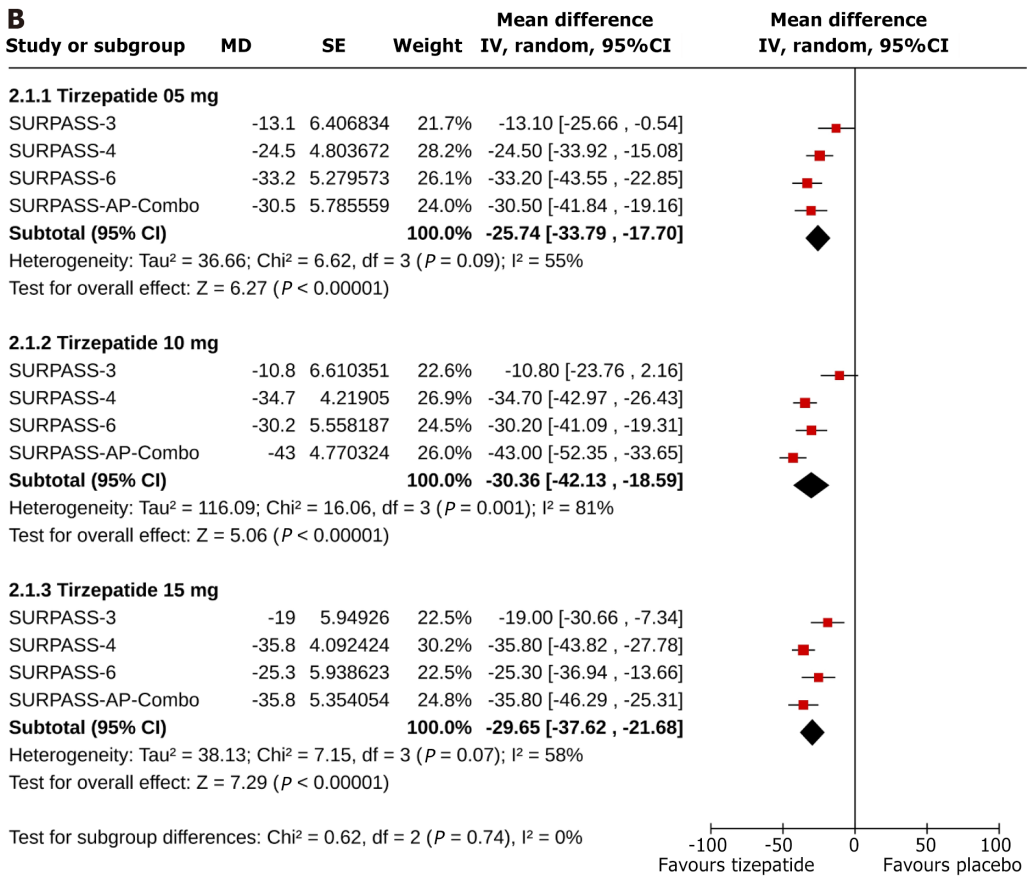


Figure 3 Forest plot highlighting the percent change from baseline in urine albumin-to-creatinine ratio. A: Tirzepatide *vs* Placebo groups; B:

Tirzepatide *vs* Insulin groups.

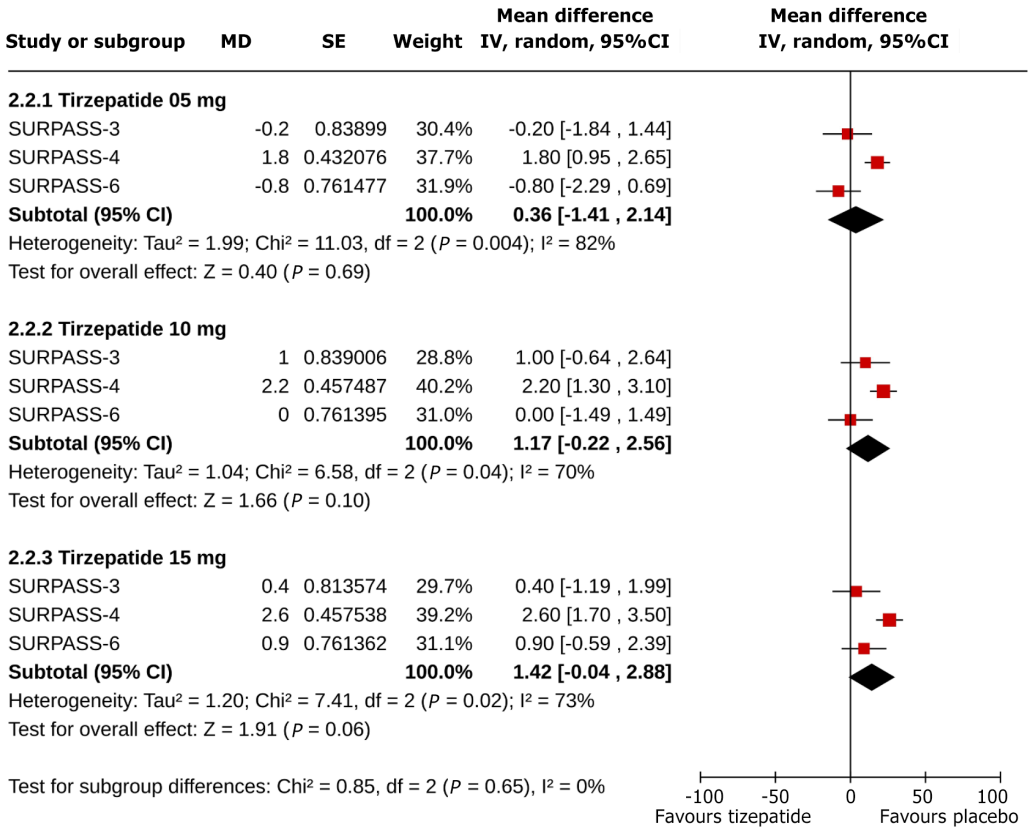


Figure 4 Forest plot highlighting the change from baseline in estimated glomerular filtration rate in Tirzepatide *vs* Insulin groups.

Sensitivity analyses

Leave-one-out sensitivity analyses were performed for UACR and eGFR in the tirzepatide *vs* placebo and tirzepatide vs. insulin groups to detect any changes in the statistical significance and heterogenicity (Supplementary Table 5). The statistical significance levels for percent UACR changes at any dose of tirzepatide *vs* placebo or insulin remained unaltered after omitting any of the included studies except for the omission of the SURPASS-1 and SURPASS-3 studies. The omission of the SURPASS-1 study reduced the heterogeneities among the studies for UACR change, and the differences between such changes in tirzepatide 5 mg *vs* placebo became statistically significant. The heterogeneity among the included studies comparing the UACR changes between tirzepatide (all doses) and insulin was also reduced when the SURPASS-3 study was omitted. The omission of the SURPASS-4 study reduced the heterogeneities among the studies for eGFR changes in tirzepatide (all doses) vs. insulin. A greater increment in eGFR was observed with tirzepatide 15 mg than with insulin if SURPASS-6 was omitted from the analysis.

Renal safety profile

In the pooled tirzepatide group, the placebo-adjusted risks for renal events [RR 2.00 (0.61, 6.55)], UTI [RR 0.76 (0.42, 1.36)], nephrolithiasis [RR 0.75 (0.21, 2.70)], AKI [RR 1.39 (0.38, 5.11)], and renal cancer [RR 0.71 (0.11, 4.72)] were not increased. The risks for UTI [RR 0.54 (0.07, 4.19)], nephrolithiasis [RR 1.49 (0.20, 11.28)], AKI [RR 0.91 (0.17, 4.95)], and renal cancer [RR 3.00 (0.31, 28.85)] in tirzepatide-treated patients were also not higher than in those on insulin. Moreover, tirzepatide and GLP-1RA had identical risks for UTI [RR 1.08 (0.12-9.72)], nephrolithiasis [RR 1.67 [0.20, 14.26]), AKI [RR 1.02 (0.11, 9.71)], and renal cancer [RR 1.00 (0.10, 9.61)]. In subgroup analysis, according to the tirzepatide doses, the risks of the specific adverse events with tirzepatide were comparable to those of the control groups (Table 1).

DISCUSSION

Main findings from the review

This review, including 15 RCTs with mostly low risk of bias and involving 14471 participants, examined the renal effects of Tirzepatide with study durations ranging from 26 to 72 weeks. The results suggest that tirzepatide treatment is associated with statistically significant reductions in albuminuria compared to placebo/insulin at all three doses of the

Table 1 Summary of the safety outcome findings

Outcome variables	Control group	Tirzepatide dose	No. of participants with outcome/participants analyzed		Pooled effect size, RR (95%CI)	I^2 (%)	*P* value
			Tirzepatide arm	Control arm			
Renal events	Placebo	Pooled	12/3180	2/1553	2.00 (0.61-6.55)	0	0.25
		10 mg	5/1018	2/1027	2.51 (0.48-12.96)	0	0.27
		15 mg	5/1552	2/1553	1.83 (0.48-6.89)	0	0.37
UTI	Placebo	Pooled	28/2980	20/1223	0.76 (0.42-1.36)	0	0.35
		5 mg	5/848	4/862	1.10 (0.28-4.33)	5	0.90
		10 mg	5/923	5/931	0.97 (0.31-3.03)	0	0.96
		15 mg	18/1209	20/1223	0.81 (0.43-1.54)	0	0.52
	Insulin	Pooled	3/2399	4/1928	0.54 (0.07-4.19)	37	0.56
		5 mg	1/802	4/1928	1.03 (0.13-7.84)	22	0.98
		10 mg	1/794	4/1928	0.69 (0.11-4.38)	0	0.70
		15 mg	1/803	4/1928	1.03 (0.13-8.06)	24	0.98
	GLP-1RA	Pooled	9/2045	1/682	1.08 (0.12-9.72)	37	0.94
		5 mg	2/684	1/682	1.35 (0.10-18.81)	31	0.82
		10 mg	3/678	1/682	1.81 (0.30-11.07)	0	0.52
		15 mg	4/683	1/682	1.87 (0.07-48.28)	56	0.71
Nephrolithiasis	Placebo	Pooled	5/3666	3/1533	0.75 (0.21-2.70)	0	0.65
		5 mg	2/914	0/926	2.96 (0.31-28.07)	0	0.35
		10 mg	1/1235	0/1241	3.03 (0.12-74.06)	NA	0.50
		15 mg	2/1517	3/1533	1.01 (0.13-7.74)	22	0.99
	Insulin	Pooled	4/2072	1/1360	1.49 (0.20–11.28)	0	0.70
		5 mg	2/687	1/1360	3.03 (0.37-24.57)	0	0.30
		10 mg	1/688	1/1360	1.74 (0.18-16.74)	0	0.63
		15 mg	1/697	1/1360	1.72 (0.18-16.51)	0	0.64
	GLP-1RA	Pooled	4/1886	0/628	1.67 (0.20-14.26)	0	0.64
		5 mg	1/629	0/628	2.99 (0.12-73.30)	NA	0.50
		10 mg	1/627	0/628	3.00 (0.12-73.45)	NA	0.50
		15 mg	2/630	0/628	4.97 (0.2-102.69)	0	0.64
Acute kidney injury	Placebo	Pooled	8/2965	2/1301	1.39 (0.38-5.11)	0	0.62
		5 mg	2/685	1/694	2.04 (0.19–22.45)	NA	0.56
		10 mg	5/999	2/1009	2.16 (0.47-10.00)	0	0.32
		15 mg	1/1281	2/1301	0.71 (0.11-4.47)	0	0.71
	Insulin	Pooled	5/2789	4/2068	0.91 (0.17-4.95)	30	0.91
		5 mg	2/930	4/2068	1.32 (0.28–6.28)	0	0.73
		10 mg	2/926	4/2068	1.33 (0.25-7.00)	6	0.74
		15 mg	1/933	4/2068	1.04 (0.13-8.05)	23	0.97
	GLP-1RA	Pooled	2/1568	0/523	1.02 (0.11-9.71)	0	0.99
		5 mg	0/525	0/523	Not estimable	NA	NA
		10 mg	1/520	0/523	3.17 (0.13-76.16)	NA	0.48
		15 mg	1/523	0/523	2.99 (0.12-73.30)	NA	0.50

Renal cancer	Placebo	Pooled	2/2538	1/1055	0.71 (0.11-4.72)	5	0.72
		5 mg	1/746	1/763	1.03 (0.11-9.86)	0	0.98
		10 mg	0/755	1/763	0.34 (0.01-8.26)	NA	0.51
		15 mg	1/1037	1/1055	1.02 (0.11-9.78)	0	0.99
	Insulin	Pooled	2/1702	0/1708	3.00 (0.31-28.85)	0	0.34
		5 mg	1/562	0/1708	9.38 (0.38-229.79)	NA	0.17
		10 mg	0/566	0/1708	Not estimable	NA	NA
		15 mg	1/574	0/1708	8.97 (0.37-219.56)	NA	0.18
	GLP-1RA	Pooled	2/1886	0/628	1.00 (0.10-9.61)	0	1.00
		5 mg	1/629	0/628	3.00 (0.12-73.09)	NA	0.50
		10 mg	1/627	0/628	3.00 (0.12-73.45)	NA	0.50
		15 mg	0/630	0/628	Not estimable	NA	NA

CI: Confidence interval; GLP-1RA: Glucagon-like peptide-1 receptor agonists; NA: Not applicable; RR: Risk ratio; UTI: Urinary tract infection.

drug used in the RCTs we assessed (except with the 5 mg dose when compared to placebo). The drug intervention was associated with a reduction in albuminuria of 18.03%, 26.95%, and 20.68%, respectively, with 15 mg, 10 mg, and 5 mg weekly doses of Tirzepatide, compared to placebo. The corresponding reduction in albuminuria in the Tirzepatide group compared to insulin was 29.65%, 30.36%, and 25.74%, respectively (all comparisons statistically significant). Subgroup analyses also indicated higher percentage reductions in albuminuria occurred in those with higher baseline UACR. The only one RCT comparing Tirzepatide with GLP-1RA (SURPASS 2) showed that a significant percentage UACR reduction was achieved only with tirzepatide 15 mg [MD -28.70% (-51.54, -5.86), P = 0.01] but not with 5 and 10 mg doses[31]. When the effects on kidney function were assessed on follow-up (*i.e.*, the changes in eGFR), any dose of tirzepatide administered (5 mg/10mg/15mg) showed an effect in comparison to the placebo or insulin, which reassures the renal safety of the drug intervention. Moreover, there was no excess incidence of renal adverse events such as nephrolithiasis, AKI, UTI, and renal cancer with Tirzepatide *vs* any comparator.

Clinical implications of the study results

Significant improvement in albuminuria with Tirzepatide treatment observed in the SRM has multiple important clinical implications. Albuminuria is the earliest and most important indicator of DKD, which reflects a microvascular compromise in diabetes, a forerunner of most diabetes-related end-organ complications, including cardiovascular disease (CVD)[55-57]. Every 10-fold increase in baseline UACR is associated with a 2.5-fold multivariable-adjusted hazard ratio (HR) for CVD[57]. Therefore, our finding of higher percentage reductions of UACR among those with higher baseline UACR is especially important in choosing the most appropriate candidate for tirzepatide treatment, even in resource-poor settings considering the high treatment costs associated with the drug. Better UACR reduction compared to semaglutide in the Tirzepatide 15 mg treatment group is also noteworthy.

Persistent albuminuria is one of the very important independent risk factors for steady decline in kidney function in patients with diabetes. A 16-year follow-up study including 1984 subjects with T2D exploring eGFR trajectories revealed that the mean annual decline in the first 10 years was 1.9, 2.1, and 3.0 mL/min/1.73 m^2 for patients with normo-, micro- and macroalbuminuria respectively[58]. Another short-term study with UACR data at a 2-year follow-up, involving 19897 patients (61% diabetics), showed a 3.08-fold [2.59 to 3.67] excess risk of developing ESRD at 2 years with a 4-fold increase in UACR, while a 4-fold reduction in UACR was associated with 0.34 [0.26 to 0.45] times the risk of ESRD at 2 years[59]. These observations again reinforce the importance of timely use of Tirzepatide, at least in those with higher baseline UACR, as those patients are most likely to benefit the best with the drug therapy.

Obesity is another important risk factor for the development of CKD among patients with T2D. Analyses of the ADVANCE trial follow-up data revealed that a "major renal event", defined as a doubling of baseline creatinine levels, new onset macroalbuminuria, ESRD, or renal death, was proportionately higher among those with higher body mass index (BMI)[60]. The multivariate-adjusted HR for higher BMI class compared to T2D patients with normal body weight were 0.91 [0.72 to 1.15], 1.03 [0.77 to 1.37], 1.42 [0.98 to 2.07] and 2.16 [1.34 to 3.49] for overweight, class 1 obesity, class 2 obesity, and class 3 obesity respectively (P for trend: 0.006) in this study. Tirzepatide, having excellent weight loss benefits, is therefore ideal for nephroprotection in obese subjects with T2D, with the best benefits anticipated in those with more severe grades of adiposity.

Although we observed no difference in the eGFR outcomes for the group of subjects on Tirzepatide compared to placebo, insulin, or GLP-1RA, presumably due to the short follow-up period of the RCTs included in this SRM, we would expect a slower decline in eGFR in the Tirzepatide group if followed up longer term based on the study results reported above[58-60]. The lack of significant renal adverse events in the Tirzepatide intervention group also reassures us about the safety of using this drug molecule in our day-to-day clinical practice.

Last but not least, we need to consider the excess mortality risk associated with albuminuria in T2D patients. The higher degree of albuminuria increases the mortality risk, and every 4-fold increase in UACR was associated with a 1.5-fold excess risk of mortality at a 2-year follow-up among patients with T2D[60]. Therefore, the observed renal protection conferred by Tirzepatide treatment in this SRM can be expected to offer a survival advantage if we follow up with these participants on a longer-term basis. The reduction in albuminuria and total eGFR slopes observed in the post hoc analysis of the SURPASS-4 trial with tirzepatide[14] and the remarkable risk reductions in composite kidney endpoints (eGFR decline ≥ 40%, renal death, kidney failure, or new-onset macroalbuminuria) in T2D patients with high baseline CVD risk compared to insulin glargine can be taken as a surrogate marker of this trend.

Limitations of the study

We acknowledge several limitations to this study. Firstly, for a lifelong disease with very high global prevalence, such as obesity and T2D, the duration of follow-up and participant numbers were too small to make definite conclusions regarding the long-term beneficial effects. However, we could extrapolate the therapeutic implications based on previous study results. Secondly, the heterogeneity of the study population in the included trials in terms of study place, baseline UACR, eGFR, and diabetes duration might introduce variability in the studied outcomes. We used random-model effects to analyze outcomes and performed sensitivity analyses for the primary outcomes. Despite these, the results still may not be generalizable. Thirdly, the between-group heterogeneity among the studies was significant due to variable sample sizes and follow-up algorithms. Fourthly, comparator groups were very different in their pharmacological properties, which would have impacted the study results. Moreover, the certainty of evidence generated by this study was mostly very low or low, questioning its wide acceptability in clinical practice. Despite these limitations, our results should empower clinicians with a better knowledge base and researchers to plan longer-term studies with more participants to generate a more robust evidence base.

CONCLUSION

Based on short-term follow-up data from 26 to 72 weeks, mostly with low risks of bias, it appears that tirzepatide improves UACR more effectively than placebo, insulin, and the highest dose of semaglutide. Tirzepatide use had no detrimental effect on eGFR, with a reassuring renal safety profile. However, high heterogenicity limits the generalizability of the findings. The cardiovascular implications, potential for renal protection (by reduction of eGFR), and mortality benefit conferred by albuminuria reduction with the drug need further validation in larger and longer-term studies with the appropriate involvement of diverse ethnic groups.

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