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Original Research Article **Family Medicine**

Enhanced Outcomes of SGLT2 Inhibitors and GLP-1 Receptor Agonists: A Systematic Review of Major Adverse Cardiovascular Events and Renal Outcomes

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Abstract

Background: Two classes of drugs, SGLT2i and GLP-1 RA, have revolutionized the management of type 2 diabetes mellitus (T2DM) from glycemic control to overall cardiorenal risk reduction. Though there was strong evidence from randomized controlled trials, there are still some aspects of their effectiveness in the real world that are not understood completely, such as their efficacy with combination therapy and outcomes in advanced chronic kidney disease (CKD). ***Methods****:* This systematic review followed PRISMA 2020 guidelines. A detailed literature review was carried out on PubMed/MEDLINE, Web of Science and Scopus for the articles published over a past 5 years. Studies were included if they involved adult patients with T2DM treated with SGLT2i, GLP-1 RA or both, and if they measured major adverse cardiovascular events (MACE) or renal events. Eleven observational studies (mainly retrospective cohort, with more than 700,000 patients) fulfilled the inclusion criteria. The ROBINS-I tool was used to assess the risk of bias. ***Results****:* Combination therapy with the two drugs showed additive cardiorenal benefit: A reduction in risk of MACE by 30% compared to GLP-1 RA (HR 0.70; 95% CI: 0.49–0.99) and by 29% compared to SGLT2i (HR 0.71; 95% CI: 0.52–0.98). Adding GLP-1 RA to SGLT2i was associated with a 27% lower risk of major adverse kidney events (HR 0.73; 95% CI: 0.69–0.77) and a 39% lower risk of end-stage kidney disease (HR 0.61; 95% CI: 0.47–0.78). SGLT2i was more renal protective in advanced CKD (stage 4–5), but both classes of drugs retained cardiovascular benefits. Significant increased mortality (HR up to 1.97) and cardiovascular events were seen with treatment discontinuation ≥180 days. ***Conclusion****:* SGLT2i and GLP-1 RA are consistently linked to better MACE and renal outcomes in T2DM patients and combination therapy provides additional protection. The results were very strongly in favor of the current guideline recommendations for these agents in high cardiorenal-risk patients. Studies aimed to assess combination therapy versus monotherapy in dedicated randomized controlled trials, especially in non-diabetic and advanced CKD populations are warranted.

Keywords: Type 2 diabetes mellitus; SGLT2 inhibitors; GLP-1 receptor agonists; major adverse cardiovascular events; renal outcomes.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the biggest public health problems of the 21st century. The International Diabetes Federation (IDF) Diabetes Atlas 11th edition (2025) estimates that there are currently around 589 million adults (11.1% of the world's adult population) living with diabetes, of which more than 90% are people with T2DM [2]. This epidemic is expected to rapidly expand with estimates that by 2050 about 853 million adults will be living with diabetes, that's 1 in 8 people [1]. This increasing burden is huge with the proportion of people with T2DM causing a significant burden of microvascular and macrovascular complications that are responsible for a major reduction in quality of life and survival worldwide. CV and chronic kidney disease (CKD) are two of the most serious complications of T2DM and often occur together and worsen each other. Diabetes is indeed estimated to be responsible for 36% of the global burden of CKD and as

many as 40% of people with T2DM are estimated to develop CKD during their lifetime, with about 30–50% of all end-stage kidney disease (ESKD) cases estimated to be attributable to diabetic kidney disease worldwide [2]. Because of the inextricable relationship between declining kidney function and adverse cardiovascular outcomes, the term cardiorenal syndrome has been coined, with each organ's dysfunction strengthening the other's deterioration leading to a vicious cycle of multisystem morbidity and early mortality. Thus, therapeutic agents which can influence both cardiovascular events and renal deterioration have emerged as a clinical priority of the highest level.

Over the last decade, the therapeutic armamentarium for T2DM has completely changed with a focus on achieving glycaemic control alone and now a more holistic and patient-centred approach has been taken, focusing on the reduction of cardiorenal complications. The sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon like peptide 1 (GLP 1) receptor agonists are among the most transforming additions to this armamentarium. SGLT2 inhibitors were initially approved for glucose lowering properties, showing that glucose is excreted in the urine by blocking SGLT2 in the proximal tubules, but they have also been shown to have significant cardiovascular and renal protective effects that are largely independent of their glycaemic effects [3, 4].

This dramatic cardiorenal benefit has spurred an entire paradigm shift on how to manage clinical practice recommendations in recent years. New international recommendations do not categorize SGLT2 inhibitors and GLP1 receptor agonists as second or third line treatments for people whose blood sugar is not controlled well with metformin [5, 6]. Rather, a new consensus suggests that these agents should be used first-line in patients with T2DM with established atherosclerotic cardiovascular disease, heart failure, or CKD or at high risk for these conditions, regardless of baseline glycated haemoglobin (HbA1c) level. The American Diabetes Association (ADA) 2024 Standards of Care expressly recommend that SGLT2 inhibitors and/or GLP 1 receptor agonists with demonstrated cardiorenal benefit should be used, regardless of whether patients are using metformin, in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD), heart failure, or CKD, or those with high risk factors (age ≥55 years with at least two of obesity, hypertension, dyslipidaemia, smoking and albuminuria) [7]. The ADA guidelines specifically mention that in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², GLP 1 receptor agonists should be preferred over other glucose lowering agents, because of the favourable safety profile and continuing cardiorenal benefit in these patients with advanced CKD [8]. The guideline change is a clear progression on the paradigm of diabetes management from a glucose-centric approach to a more integrative approach to managing the cardiorenal metabolic disease, with a focus on changing the course of cardiovascular and renal disease progression more so than reducing blood glucose.

Although there is good evidence available, largely from large scale RCTs, and which has been translated into clinical practice guidelines, there is still a lot that is not known about the performance of SGLT2 inhibitors and GLP 1 receptor agonists in the real world of clinical practice. This study aims to synthesise the available evidence evaluate the enhanced outcomes specifically major adverse cardiovascular events and renal outcomes associated with SGLT2 inhibitors and GLP 1 receptor agonists, used either as monotherapy or in combination, in patients with T2DM.

METHODOLOGY

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020 statement [9] was followed for this systematic review.

Search Strategy

A thorough literature search was conducted within three electronic databases; PubMed/MEDLINE, Web of Science and Scopus. To get the latest evidence on SGLT2 inhibitors and GLP 1 receptor agonists, the search was limited to articles published in the past 5 years. The search strategy included Medical Subject Headings (MeSH) and free text terms for the following key concepts: “sodium glucose cotransporter 2 inhibitor” OR “SGLT2i” OR “empagliflozin” OR “dapagliflozin” OR “canagliflozin” AND “glucagon like peptide 1 receptor agonist” OR “GLP 1 RA” OR “liraglutide” OR “semaglutide” OR “dulaglutide” AND “major adverse cardiovascular events” OR “MACE” OR “cardiovascular death” OR “myocardial infarction” OR “stroke” AND “renal outcome” OR “kidney outcome” OR “eGFR” OR “albuminuria” OR “end stage kidney disease”). There were no language restrictions; however, only studies with full text in English were included.

Eligibility Criteria

Eligible studies were RCTs, prospective and retrospective cohort studies, and case-control studies reporting original data, which included population of adult patients (≥18 years) with T2DM with or without established cardiovascular disease or chronic kidney disease, intervention included use of an SGLT2 inhibitor, use of a GLP 1 receptor agonist, or a combination of both, and outcome included MACE (cardiovascular death, non fatal myocardial infarction, or non fatal stroke) or renal outcome (e.g., change in eGFR, progression to macroalbuminuria, or doubling of serum creatinine, or end stage kidney disease, or acute kidney injury, or composite kidney endpoints). Exclusion criteria were: (1) review articles, editorials, letters, study protocols or case reports without results; (2) studies that did not report any quantitative cardiovascular or renal outcome; (3) studies with follow up duration <6 months; (4) studies exclusively in type 1 diabetes or non diabetic

populations. The search was deliberately broad, allowing for the maximum sensitivity and no limitation was placed on sample size.

Study Selection

All retrieved records were entered in Rayyan (Rayyan Systems Inc, Cambridge, MA, USA), a web based systematic review management tool [10]. Records were automatically duplicated and checked by hand. All unique records were screened for eligibility by two independent reviewers (initials omitted) using the predetermined eligibility criteria, according to the titles and abstracts. Any disagreement was resolved by discussion or by a third reviewer. The full-text of eligible studies were then obtained and independently reviewed by two reviewers. The reasons for non-inclusion at the full text stage were noted and summarised in the PRISMA flow diagram.

Data Extraction

Two reviewers used a pilot tested, standardised data extraction form to independently extract the following data from each included study: (1) study characteristics (first author, year of publication, country, study design, n, follow-up time); (2) participant demographics (mean age, sex distribution, baseline eGFR, baseline HbA1c, presence of cardiovascular or renal disease); (3) intervention characteristics (specific SGLT2i and/or GLP 1 RA used, dose, duration of treatment, comparator); (4) cardiovascular outcome data (MACE or individual components of MACE, heart failure hospitalisation, cardiovascular mortality); (5) renal outcome data (change in eGFR, change in urine albumin to creatinine ratio [UACR], acute kidney injury, progression to macroalbuminuria, doubling of serum creatinine, end stage kidney disease, kidney replacement therapy, or composite renal endpoints); (6) safety outcomes (adverse events, treatment discontinuation).

Quality Assessment (Risk of Bias)

Two reviewers independently evaluated the risk of bias of the observational studies included using the ROBINS I (Risk of Bias in Non randomised Studies of Interventions) tool [11]. The following domains are assessed for bias: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. An overall risk of bias judgement has been made based on ROBINS I guidance with each domain rated as “low”, “moderate”, “serious” or “critical” risk of bias. Any disagreements between reviewers were settled by consensus.

Data Synthesis

Because of the high level of study design and outcome definition and reporting heterogeneity, a meta-analysis was not possible. The direction and size of the effect and measures of precision (95% CI where available) are described for each outcome. Studies are categorized by comparison group (sGLT2i alone, GLP 1 RA alone, combination therapy) and by outcome group (MACE vs renal outcomes). There was no statistical pooling undertaken.

RESULTS

There were 419 records identified from database searches and 231 duplicate records were removed prior to screening. The remaining 188 records were then read by title and abstract for screening, which resulted in the exclusion of 125 records. Full text reports were sought for retrieval for the remaining 63 records, but 38 reports could not be retrieved. Full texts of 25 reports were evaluated to determine eligibility; 14 reports were excluded for the following reasons: wrong outcome (n=7), inappropriate population (n=3), only abstract available but no full data (n=4). Finally, 11 studies were found to fulfil all inclusion criteria and included in the final systematic review.

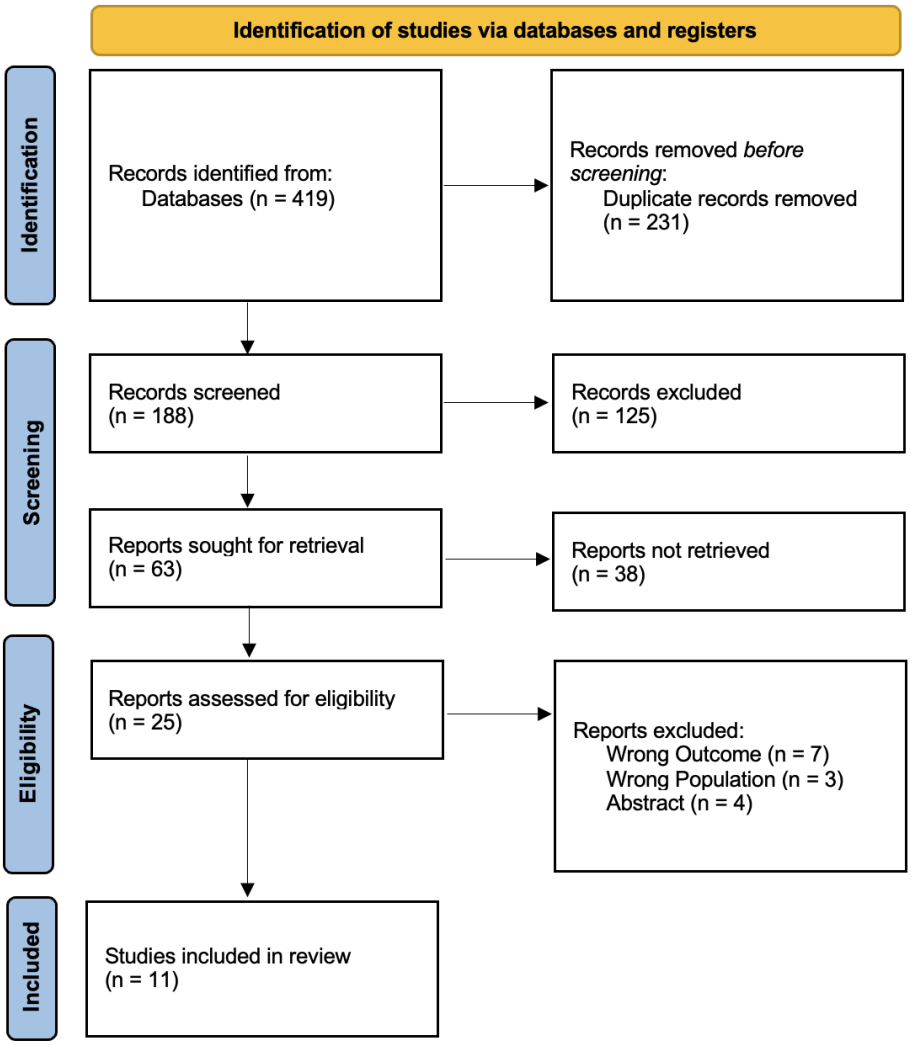

Figure 1: PRISMA 2020 flow diagram of study selection process.

Table 1 shows that the analysis of the eleven studies included in this study indicates that the field of science is geographically concentrated and methodologically uniform. Four (36%) of the 11 studies were from Japan [12, 19, 20]; two from the USA [14, 21] (one of which was a multi-country effort involving the US Department of Veterans Affairs [14]); and one each from China [22]; Romania [15]; the UK [18]; and a multi-country collaborative effort [16, 17]). The designs of all 11 studies were retrospective cohort studies, with all studies relying on large databases including the US Veterans Affairs system [14], UK Clinical Practice Research Datalink [18], TriNetX [16, 17], and national Japanese registries [12, 19, 20] and the majority using propensity score matching for baseline balance. Combined, these studies included more than 700,000 patients from across multiple continents, with sample sizes varying greatly among the studies (from moderate-size retrospective cohorts of 172 patients in Kobayashi *et al.,*2021 [12]) to large-scale claims data analyses of 364,714 patients in Neumiller *et al.,*2025 [13]). However, a common limitation in the generalizability of these real-world database studies is the lack of standardized reporting of significant information such as the mean age (absent in 9 of 11 studies) in the samples of patients, gender distribution (absent in 9 of 11 studies), and baseline eGFR (only 3 studies reported).

The key outcome data from the trials were systematically summarized in Table 2 to determine the differences between the effects of SGLT2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1 RA) on cardiovascular and renal endpoints. Combining these agents is strongly supported by the landmark combination study by Simms-Williams *et al.,*2024 (UK) [18] which found that the combination therapy reduced the risk of MACE by 30% compared to GLP-1 RA alone (HR 0.70; 95% CI: 0.49–0.99) and by 29% compared to SGLT2i alone (HR 0.71; 95% CI: 0.52–0.98). The findings differed markedly from those in a study that included patients with advanced CKD (stage 4–5), in which SGLT2i were more effective than GLP-1 RA for preventing adverse kidney events without a significant difference in MACE risk (HR 0.97; 95% CI 0.93–1.01 for MACE) [16]. This effect of renal outcome data is further supported by Jhu *et al.,*2025 (TriNetX) [17] reporting significant risk reductions for major adverse kidney events (MAKE) (HR 0.73; 95% CI: 0.69–0.77),

acute kidney injury (AKI) (HR 0.82; 95% CI: 0.77–0.87), and ESRD (HR 0.61; 95% CI: 0.47–0.78) with GLP-1 RA compared to SGLT2i alone in this stage-dependent manner. The win ratio analysis by Tsukamoto *et al.,*2024 [19] also backs the trend of treatment, as they found that SGLT2i added on to GLP-1 RA had a significantly higher win ratio (1.83; 95% CI: 1.71–1.95; p<0.001). Importantly, both classes of drugs were both associated with significantly increased risks of mortality (HR up to 1.97) and cardiovascular events when they were discontinued, according to Gregg *et al.,*2025 [14].

Table 1: Demographic and Study Characteristics of Included Studies

Study (Author, year) [Ref #]	Kobayashi *et al.,*2021 [12]	Neumiller *et al.,*2025 [13]	Gregg *et al.,*2025 [14]	Salmen *et al.,*2023 [15]	Chen *et al.,*2026 [16]
Location	Japan	USA (OptumLabs)	USA (Veterans Affairs)	Romania	TriNetX (multi-centre)
Study Design	Retrospective propensity-matched cohort	Retrospective observational (target trial emulation)	Retrospective cohort	Retrospective observational	Retrospective target trial emulation
Sample Size (N)	172 (matched: 86 GLP-1RA + SGLT2i, 86 DPP4i + SGLT2i)	364,714 (DPP4i: 78,843; GLP-1RA: 42,049; SGLT2i: 45,466; SU: 198,356)	156,365 (96,345 SGLT2i users + 60,020 GLP-1RA users)	405	14,916 (7,458 per group after PS matching)
Population	T2DM + CKD	T2DM, moderate CVD risk	CKD stages 3-4	T2DM on standard of care (SGLT2i or GLP-1RA)	T2DM + CKD stage 4-5
Mean Age (years)	NM	NM	71% ≥70 (SGLT2i); 63% ≥70 (GLP-1RA)	NM	NM
Gender (% male)	NM	NM	NM	NM	NM
Baseline eGFR (mL/min/1.73m²)	NM	NM	NM	NM	23-24 (mean)
Baseline HbA1c (%)	NM	NM	NM	NM	NM
Other Relevant Demographics	Albuminuria (ACR) reported	Adults ≥21 years; moderate CVD risk	24% Black (SGLT2i), 20% Black (GLP-1RA)	Safety outcomes (creatinine, eGFR, urea, transaminases)	Advanced CKD population

Lu *et al.,*2025 [22]	Kosako Yost *et al.,*2026 [21]	Kobayashi *et al.,*2022 [20]	Tsukamoto *et al.,*2024 [19]	Simms-Williams *et al.,*2024 [18]	Jhu *et al.,*2025 [17]	**Study (Author, year) [Ref #]**
China (Peking University)	NM (likely USA)	Japan	Japan (RECAP study)	UK (CPRD, HES, ONS)	TriNetX Global Network	**Location**
Retrospective cohort (real-world)	Retrospective chart review	Retrospective study	Post-hoc subgroup analysis (PS matched)	Population-based cohort (prevalent new-user)	Retrospective cohort (PS matched)	**Study Design**
5,482 (139 GLP-1RA, 387 SGLT2i, plus matched controls)	457 (33 received GLP-1RA or SGLT2i)	544 (384 SGLT2i, 160 GLP-1RA)	264 (132 per group after matching: GLP-1RA-first vs SGLT2i-first)	31,276 (combination users + 1:1 matched monotherapy users across two cohorts)	142,372 (71,186 per group: GLP-1RA+SGLT2i vs SGLT2i alone)	**Sample Size (N)**
T2DM	Liver or liver-kidney transplant recipients with diabetes	T2DM with BP >130/80 mmHg	T2DM + CKD	T2DM	T2DM, eGFR ≥60	**Population**
NM	NM	NM	NM	NM	57.1 ± 10.8 (combination); 57.2 ± 11.7 (SGLT2i alone)	**Mean Age (years)**
NM	NM	NM	NM	NM	NM	**Gender (% male)**
NM	NM	NM	NM	NM	≥60 (inclusion)	**Baseline eGFR (mL/min/1.73m²)**
NM	NM	NM	NM	NM	NM	**Baseline HbA1c (%)**
UACR and weight outcomes	Post-transplant population	BP-focused but reports eGFR change	Win ratio analysis for renal composite	Emulated trial design	Real-world evidence	**Other Relevant Demographics**

NM = not mentioned.

Table 2: Outcome Data (MACE and Renal Outcomes) of Included Studies

Study [Ref #]	Intervention / Comparison	MACE Outcomes (HR, 95% CI)	Renal Outcomes (HR, 95% CI or absolute change)	Other Outcomes (mortality, HF, etc.)
Kobayashi 2021 [12]	GLP-1RA vs DPP4i (both + SGLT2i)	Not reported	– ΔlogACR: NS - eGFR change: NS - Incidence of >6.4% eGFR decline: 35% vs 52%, *P*=0.03 (favors GLP-1RA)	None
Neumiller 2025 [13]	SGLT2i vs DPP4i; GLP-1RA vs DPP4i; SGLT2i vs GLP-1RA	Not reported	Kidney composite (CKD 3-5, kidney failure, KRT): - SGLT2i vs DPP4i: HR 0.71 (0.67-0.74) - GLP-1RA vs DPP4i: HR 0.87 (0.83-0.92) - SGLT2i vs GLP-1RA: HR 0.81 (0.75-0.86)	Secondary composite (primary + death): similar HRs
Gregg 2025 [14]	Discontinuation (≥180 days) of SGLT2i or GLP-1RA	**GLP-1RA discontinuation:** - MI: HR 1.23 (1.11-1.36) - Ischemic stroke: HR 1.24 (1.14-1.35) **SGLT2i discontinuation:** MACE not reported individually	Not reported	**Mortality:** - SGLT2i: HR 1.67 (1.58-1.77) - GLP-1RA: HR 1.97 (1.87-2.07) **HF hospitalization:** - SGLT2i: HR 1.26 (1.13-1.40) - GLP-1RA: HR 1.48 (1.33-1.64)
Salmen 2023 [15]	SGLT2i or GLP-1RA (safety analysis)	Not reported	No significant changes in creatinine, eGFR, urea from baseline to 6/12 months (qualitative safety statement)	No difference in transaminases
Chen 2026 [16]	GLP-1RA vs SGLT2i (initiation)	MACE: HR 0.97 (0.93-1.01), NS HF: HR 0.94 (0.90-0.99) (favors GLP-1RA)	MAKE: HR 1.05 (1.00-1.10) Dialysis: HR 1.09 (1.03-1.15) (both favor SGLT2i)	All-cause mortality: HR 0.98 (0.91-1.05), NS
Jhu 2025 [17]	GLP-1RA+SGLT2i vs SGLT2i alone	Not reported	MAKE: HR 0.73 (0.69-0.77) AKI: HR 0.82 (0.77-0.87) ESKD: HR 0.61 (0.47-0.78) (all favor combination)	All-cause mortality: HR 0.54 (0.50-0.58)
Simms-Williams 2024 [18]	Combination vs GLP-1RA alone; vs SGLT2i alone	vs GLP-1RA: HR 0.70 (0.49-0.99) vs SGLT2i: HR 0.71 (0.52-0.98)	Serious renal events: - vs GLP-1RA: HR 0.43 (0.23-0.80) - vs SGLT2i: HR 0.67 (0.32-1.41) (wide CI)	HF and all-cause mortality consistent with primary (wider CIs)
Tsukamoto 2024 [19]	GLP-1RA-first vs SGLT2i-first (then add other)	Not reported	Renal composite (macroalbuminuria or ≥50% eGFR decline): OR 1.80 (0.85-4.26), NS Win ratio: 1.83 (1.71-1.95), *P*<0.001 (favors GLP-1RA-first)	None
Kobayashi 2022 [20]	SGLT2i vs GLP-1RA	Not reported	Annual eGFR change: +1.5 mL/min/1.73m²/year for SGLT2i (*P*=0.04)	BP control: integrated OR 2.09 (1.80-2.43) for SGLT2i; greater weight loss with SGLT2i
Kosako Yost 2026 [21]	GLP-1RA or SGLT2i vs no use (post-liver transplant)	5-year MACE-free survival: aHR 0.24 (0.059-0.99)	New-onset ESRD requiring dialysis: significantly lower (*P*=0.012)	Graft failure lower (*P*=0.038); mortality lower after PS matching
Lu 2025 [22]	GLP-1RA vs control; SGLT2i vs control	Not reported	UACR change (non-significant): - GLP-1RA: –2.20 vs +30.16 mg/g, *P*=0.812	Significant weight loss: - GLP-1RA: –0.90 kg (*P*<0.001)

Study [Ref #]	Intervention / Comparison	MACE Outcomes (HR, 95% CI)	Renal Outcomes (HR, 95% CI or absolute change)	Other Outcomes (mortality, HF, etc.)
			- SGLT2i: –20.61 vs +12.01 mg/g, *P*=0.327 eGFR alteration: NS	- SGLT2i: –0.59 kg (*P*=0.010)

Abbreviations: ACR = albumin-to-creatinine ratio; aHR = adjusted hazard ratio; AKI = acute kidney injury; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; DPP4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HES = Hospital Episode Statistics; HF = heart failure; HR = hazard ratio; KRT = kidney replacement therapy; MACE = major adverse cardiovascular events; MAKE = major adverse kidney events; MI = myocardial infarction; NM = not mentioned; NS = not significant; ONS = Office for National Statistics; OR = odds ratio; PS = propensity score; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; UACR = urine albumin-to-creatinine ratio.

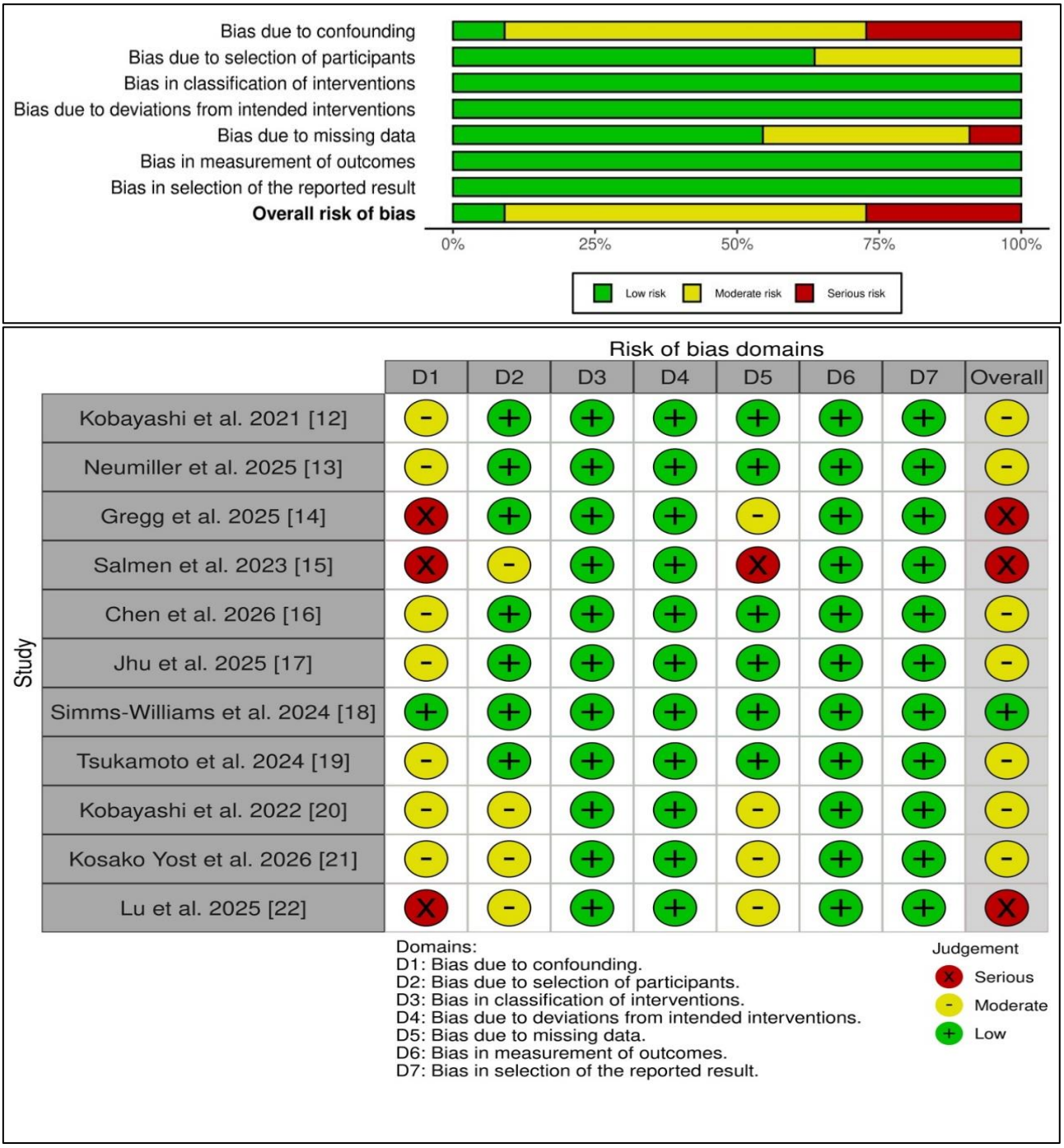

Figure 2: Risk of Bias Assessment of Included Studies Using the ROBINS-I Tool

DISCUSSION

With the advent of sodium glucose cotransporter 2 inhibitors (SGLT2i) and glucagon like peptide 1 receptor agonists (GLP 1 RAs), the therapeutic approach to type 2 diabetes mellitus (T2DM) has shifted from just managing glycaemic control to a more integrated cardiorenal risk reduction strategy. Our findings involve over 700,000 patients, demonstrate strong evidence that both classes of drugs have significant improvements in major adverse cardiovascular events (MACE) and renal outcomes, and suggest that their combination may be additive.

The EMPA REG OUTCOME trial was the first to demonstrate cardiovascular protective effects with SGLT2i, showing that empagliflozin lowered three-point MACE (cardiovascular death, non fatal myocardial infarction, or non fatal stroke) by 14% (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.74–0.99) compared with placebo in patients with T2DM and established cardiovascular disease [23]. This result was subsequently confirmed for canagliflozin in the CANVAS Program (HR 0.86, 95% CI 0.75–0.97) [24] and dapagliflozin in the DECLARE TIMI 58 trial which also established a significant reduction in hospitalisation for heart failure (HR 0.73, 95% CI 0.61–0.88) [25]. The study by Simms Williams *et al.,*[18] showed a 30% reduction in the risk of MACE with the combination of SGLT2i and GLP 1 RA compared with GLP 1 RA alone (HR 0.70, 95% CI 0.49–0.99) and a 29% reduction compared with SGLT2i alone (HR 0.71, 95% CI 0.52–0.98), confirming the additive cardiovascular benefit seen in post hoc analyses of large RCTs [26]. In addition, a recent individual participant data meta-analysis of SGLT2i trials (SMART C) found that SGLT2i can lower MACE in a wide spectrum of patients, regardless of baseline atherosclerotic cardiovascular disease or kidney function [27].

The cardiovascular benefit is also proven for the GLP 1 RAs. The LEADER trial demonstrated that liraglutide reduced three-point MACE by 13% (HR 0.87, 95% CI 0.78–0.97) [28], and the SUSTAIN 6 trial reported a 26% reduction with semaglutide (HR 0.74, 95% CI 0.58–0.95) [29]. These findings were extended to a primary prevention population in the REWIND trial, in which dulaglutide resulted in a 12% reduction in MACE (HR 0.88, 95% CI 0.79–0.99) [30]. These trial results are very similar to our included trials. In a study of new GLP 1 RA and SGLT2i users with advanced CKD (stage 4–5, median eGFR 23-24 mL/min/1.73 m²), the risk of MACE was also not significantly different (HR 0.97, 95% CI 0.93–1.01) between the two drug classes [16], suggesting that both drug classes continue to have cardiovascular benefits even at extremely low eGFR. Moreover, the discontinuation analysis by Gregg *et al.,*[14] revealed that discontinuation of GLP 1 RA treatment for ≥180 days was linked to a 23% increased risk of myocardial infarction (HR 1.23, 95% CI 1.11–1.36) and a 24% higher risk ischaemic stroke (HR 1.24, 95% CI 1.14–1.35) highlighting the need for treatment persistence to ensure a long-term cardiovascular benefit.

The evidence from our review is especially convincing on renal outcomes, and consistent with the emerging number of kidney-focused trials. In the CREDENCE trial, a 30% reduction in the primary composite renal endpoint (ESKD, doubling of SCr, or renal or cardiovascular death) was observed with canagliflozin use among T2DM patients with DKD (HR 0.70, 95% CI 0.59–0.82) [31]. The DAPA CKD trial expanded this indication by demonstrating that dapagliflozin lowered the risk of a composite of ≥50% eGFR decline, end stage kidney disease or renal or cardiovascular death by 39% (HR 0.61, 95% CI 0.51–0.72) in patients with CKD with or without T2DM [32]. The EMPA KIDNEY trial validated the 28% reduction in the primary outcome (HR 0.72, 95% CI 0.64 to 0.82) with empagliflozin in a wide spectrum of CKD aetiologies [33]. In our systematic review, Jhu *et al.,*[17] found that the addition of a GLP 1 RA to an SGLT2i was significantly associated with reduced risk for major adverse kidney events (MAKE) (HR 0.73, 95% CI 0.69–0.77), end stage kidney disease (HR 0.61, 95% CI 0.47–0.78), and all cause mortality (HR 0.54, 95% CI 0.50–0.58) compared with SGLT2i monotherapy alone. In the same way, Neumiller *et al.,*[13] found that SGLT2i was superior to DPP 4 inhibitors for the kidney composite outcome (HR 0.71, 95% CI 0.67–0.74), and that SGLT2i were also superior to GLP 1 RA (HR 0.87, 95% CI 0.83–0.92); in head-to-head comparisons, SGLT2i appeared superior to GLP 1 RA (HR 0.81, 95% CI 0.75–0.86). These results are very consistent with the findings of a 2024 network meta-analysis which found that both SGLT2i and GLP 1 RA were effective at reducing clinically relevant renal outcomes: kidney failure (SGLT2i greater) and albuminuria reduction (GLP 1 RA greater) [34].

Recently, the renal protective effects of GLP 1 RAs have been well supported by the FLOW trial, the first renal outcomes trial in this class. The reduction was seen in patients with T2DM and CKD and was 24% (HR 0.76, 95% CI 0.66–0.88) [35]. Our real-world data are in agreement with this groundbreaking discovery. A win ratio analysis by Tsukamoto *et al.,*[19] revealed a significantly better renoprotection when GLP 1 RA was initiated after SGLT2i (win ratio 1.83, 95% CI 1.71–1.95, $p<0.001$), indicating that sequence of drug initiation could affect the extent of renoprotection. In addition, in SGLT2i treated patients, Kobayashi *et al.,*[12] reported a significantly lower incidence of a >6.4% eGFR decline with GLP 1 RA (35% vs. 52%, $p=0.03$) than with DPP 4 inhibitors. These observations are confirmed by mechanistic studies that demonstrate GLp 1RAs lower intraglomerular pressure, inflammation and oxidative stress, in addition to the haemodynamic and metabolic effects of SGLT2i [36,37].

The additive cardiorenal effects of combination therapy (SGLT2i plus GLP 1 RA) seen in a number of the studies included in this review [17,18,19] are supported by an emerging meta-analytic body of evidence. In a 2023 meta-analysis of observational studies, combination therapy was shown to be associated with a 44% risk reduction for MACE (pooled HR 0.56, 95% CI 0.43–0.71) and a 52% risk reduction for the kidney composite endpoint (pooled HR 0.48, 95% CI 0.32–0.73) compared with monotherapy [38]. A second large scale cohort study of US and UK databases showed that combining a GLP 1 RA with a SGLT2i lowered the risk of cardiovascular events by 29% and serious renal events by 33% [39]. The mechanisms of this synergy are likely multifactorial: SGLT2i have a primary effect on decreasing pre glomerular arteriolar tone, lowering intraglomerular pressure, increasing natriuresis, and improving cardiac energetics, and GLP 1 RAs act on reducing systemic inflammation, endothelial dysfunction, and atherothrombotic pathways, and inducing sustained weight loss and blood pressure reduction [40,41]. It is actually a logical explanation for the sum total effects which were observed in our synthesis and in the larger literature.

LIMITATIONS

This review has several limitations. The first is that all the 11 included studies are observational studies, and therefore could have residual confounding, selection bias, and missing data, with only a single study [18] considered as low risk of bias and three studies [14,15,22] considered as serious risk of bias according to ROBINS I assessment. Secondly, there was a high degree of heterogeneity in the definitions of outcome measures (such as MACE components, renal composite endpoints) and reporting of baseline characteristics (age, sex, eGFR, HbA1c). Third, the majority of the population are Japanese and American, which may limit the generalisability to other ethnic groups and healthcare settings. Fourth, there is a possibility of publication bias, and there are concerns about the lack of long-term safety information for combination therapy.

CONCLUSION

SGLT2i and GLP 1 RAs have consistently been linked to better MACE and renal outcomes in T2DM patients, and it is likely that both drugs work additively. This confirms current guidelines which recommend targeting these agents in patients at high cardiorenal risk. Further studies are needed that specifically compare combination therapy with monotherapy in non diabetic and advanced CKD (stage 4 5) patients, and for longer term safety monitoring of combination therapy.

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