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Cardiovascular and renal effects of the combination therapy of a GLP-1 receptor agonist and an SGLT2 inhibitor in observational real-life studies

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Short title : Outcomes with GLP-1RA/SGLT2i combination in real-life

Abstract

Background

Combining a glucagon-like peptide-1 receptor agonist (GLP-1RA) and an sodium-glucose cotransporter 2 inhibitor (SGLT2i) improved cardiovascular (and renal) prognosis compared to either monotherapy in several post-hoc exploratory analyses of randomised controlled trials (RCTs) versus placebo carried out in patients with type 2 diabetes (T2DM) and high cardiovascular/renal risk. The aim of the present work is to verify if such a benefit of the combined therapy is also present in real-life clinical practice.

Methods

An extended search of the literature was performed to select observational retrospective studies that compared cardiovascular and/or renal outcomes in patients with T2DM treated with a GLP-1RA/SGLT2i combination versus patients treated with either GLP-1RA monotherapy or SGLT2i monotherapy, in addition to standard of care therapy.

Results

Nine observational studies showed that a GLP-1RA/SGLT2i combination is associated with a greater reduction in major adverse cardiovascular events (MACEs), hospitalisation for heart failure and all-cause-mortality when compared to either GLP-1RA alone or SGLT2i alone, without obvious differences between the two monotherapies, including regarding heart failure. Results were obtained in different populations, including patients with atherosclerotic cardiovascular disease and/or heart failure. Only three observational studies gave information on renal outcomes, with a greater benefit when the GLP-1RA/SGLT2i combination was compared with GLP-1RA alone or SGLT2i alone.

Conclusion

In real-life conditions, the GLP-1RA/SGLT2i combination reduced cardiovascular and renal outcomes compared with both GLP-1RA monotherapy and SGLT2i monotherapy. Overall, observational studies confirm the results reported in post-hoc exploratory analyses of RCTs versus placebo.

Key-words : Cardiovascular outcome – Combined therapy – GLP-1 receptor agonist – Renal outcome – SGLT2 inhibitor

Highlights

- Patients with type 2 diabetes (T2DM) are at increased risk of atherosclerotic cardiovascular disease, heart failure and chronic kidney disease
- Both GLP-1RAs and SGLT2is have proven their efficacy in reducing the risk of cardiovascular and renal complications
- Post-hoc analyses of randomised controlled trials reported a better prognosis with a GLP-1RA/SGLT2i combination compared with either monotherapy
- Several observational retrospective cohort studies confirm that this benefit can also be obtained in real-fife conditions
- GLP-1RA/SGLT2i combined therapy is already recommended for the management of at risk patients with T2DM in international guidelines/expert consensus statements.

Introduction

Both sodium-glucose cotransporter type 2 inhibitors (SGLT2is) [1, 2] and glucagon-like peptide-1 receptor agonists (GLP1-RAs) [3, 4] have demonstrated favourable cardiovascular and renal outcomes, including reduced all-cause mortality, in patients with type 2 diabetes (T2DM) at high risk. They are now included in the guidelines from scientific societies in diabetes [5], cardiology [6] and nephrology [7] fields to offer organ protection to at risk patients. Because the mechanisms of action of these two pharmacological classes are at least partly different and potentially additive [8], a combination of both drugs in high-risk patients may appear attractive [9, 10]. Indeed, a combined therapy improved surrogate endpoints such as better glucose control, reduction in bodyweight and correction of several cardiovascular risk factors (for instance systolic blood pressure and inflammatory biomarkers) [11-14].

Post-hoc analyses of several placebo-controlled randomised clinical trials (RCTs) [GLP-1RA added to background SGLT2i [15-17] ; SGLT2i added to background GLP-1RA [18-21]] and several subsequent meta-analyses of such RCTs [22-25] have demonstrated a better cardiovascular and renal prognosis among patients with T2DM treated with a combined GLP-1RA/SGLT2i therapy compared with those treated with either SGLT2i monotherapy or GLP-1RA monotherapy. However, whether positive results obtained in selected populations recruited in RCTs would be confirmed in real-life conditions is less documented. A recent systematic review and meta-analysis of observational studies confirmed that a GLP-1RA/ SGLT2i combination is more efficacious concerning surrogate endpoints such as glycated haemoglobin, body weight and arterial blood pressure [26]. This paper also suggested a reduced mortality rate with the combined therapy but this conclusion was only based upon two cohort studies, and no data regarding major cardiovascular and renal outcomes were mentioned.

Thus, the aim of the present work was to analyze the results of observational studies that compared the effects of a combined GLP-1RA/SGLT2i therapy versus either monotherapy on clinically relevant outcomes, i.e. major cardiovascular adverse events (MACEs : cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke), hospitalisation for heart failure (HF), a composite renal outcome including an aggravation of chronic kidney disease (CKD), and all-cause mortality.

Methods

Literature search

We searched PubMed, Scopus, Embase and the Cochrane Database of Systematic Reviews to identify English-language studies published between January 2015 and October 2024. The search was limited to studies evaluating the efficacy of a GLP-1RA/SGLT2i combination versus GLP-1RA or SGLT2i monotherapies on cardiovascular and/or renal outcomes in adult patients with T2DM enrolled in observational cohort studies. In a first step, the terms used for the research were "GLP-1 receptor agonist" (including each individual compound of this pharmacological family) AND "SGLT2 inhibitor" (including each individual compound of this family), combined with "combined therapy". In a second step, the terms "cardiovascular outcomes" OR "renal outcomes" AND "real-life" OR "observational study" were used. The reference lists of previously published systematic reviews and meta-analyses were also scrutinized to identify any further reports of potential interest.

Statistical analysis

In the literature, results are presented in two different ways : either as hazard ratio (HR) with 95% confidence interval (CI) in each treatment arm (without specific statistical comparison between the ARGLP-1/SGLT2i combination and each monotherapy) [27-30], or as HR with the combination therapy versus the reference monotherapy (SGLT2i alone or GLP-1RA alone) [31-35]. In order to minimize potential inclusion biases, propensity score matching (PSM) was used in five studies [30-32, 34, 35].

In the present work, results are expressed as HR with 95 % CI of the occurrence of the specified outcome (first event of MACE, hospitalisation for HF or all-cause mortality) between patients treated with a GLP-1RA/SGLT2i combination versus either GLP-1RA monotherapy or SGLT2i monotherapy.

Results

Cardiovascular outcomes

Overall, nine cohort studies were collected in the literature (Table 1). Six compared a combination GLP-1RA/SGLT2i versus either monotherapy [27-29, 32-34], among which one gave a direct statistical comparison [34]; two compared the combination with SGLT2i alone [31, 35] and one compared the addition of an SGLT2i (versus a sulphonylurea) on top on GLP-1RA alone [30]. Six studies analyzed the effects on MACEs [27, 28, 30-33], seven studies analyzed the effects on hospitalisation for HF [28-32, 34, 35] and six studies analyzed the effects on all-cause mortality [27, 29-32, 34]. Only four studies investigated the three outcomes simultaneously [30-32]. Some studies investigated a special population with T2DM, for instance patients after an acute myocardial infarction [33] or patients with HF : any type (ASCVD or HF) [28], HF with reduced ejection fraction (HFrEF) in patients with ASCVD [31] or HF with preserved ejection fraction (HFpEF) in overweight/obese patients [35]. Observational retrospective studies were carried out in different countries, in United States of America [30, 31], in United Kingdom [28, 32] and in European countries, Denmark [27], Spain [34] and Italy [33] while two studies used worldwide registries (Global Collaborative Network and TriNexT) [29, 35]. In all studies, the pharmacological therapy of interest (combination or either monotherapy) was added to background medications corresponding to standard of care (antidiabetic agents, lipid-lowering drugs and/or antihypertensive agents).

The three studies that tested the addition of a GLP-1RA on top of a SGLT2i reported lower HRs in patients treated with the combination compared with SGLT2i monotherapy whatever the clinical outcome: MACEs, hospitalisation for HF (except in one study that recruited patients with HFrEF [31]) and/or all-cause mortality [31, 34, 35] (Table 1). The study that compared the addition of an SGLT2i versus a sulphonylurea in patients treated with a GLP-1RA showed a highly significant reduction in hospitalisation for HF, whereas the effects on MACEs were less pronounced and the effect on all-cause mortality not significant [30] (Table 1).

Although some differences may vary across tested populations according to the considered outcome, overall the positive results with a GLP-1RA/SGLT2i combination compared with monotherapy were observed independently of the baseline characteristics of the participants with T2DM: patients after an acute myocardial infarction [33], patients with ASCVD or HF [28], patients with ASCVD and HFrEF [31], overweight/obese patients with HFpEF (Table 1) [35].

The largest study gave more detailed information especially regarding the different components of MACE-3P [29]. In this retrospective cohort analysis of 2.2 million people with T2DM receiving insulin across 85 US health care organizations, three intervention cohorts - SGLT2is (n = 143 600), GLP-1RAs (n = 186 841) and GLP-1RA/ SGLT2i combination (n = 108 504) - were compared after PSM against a control group. Interestingly, a sub-analysis showed a significant and almost similar risk reduction in all-cause mortality over 5 years for the combination therapy versus either SGLT2is alone (HR 0.53; 95% CI 0.50, 0.55) or GLP-1RAs alone (HR 0.56; 95% CI 0.54, 0.59) [29]. When compared with the SGLT2i monotherapy cohort, the combination cohort showed a modest reduction in risk for ischaemic heart disease (HR 0.91; 95% CI 0.88, 0.94), HF (HR 0.81; 95% CI 0.78, 0.84), stroke (HR 0.90; 95% CI 0.85, 0.94) and acute myocardial infarction (HR 0.83; 95% CI 0.79, 0.88) When compared with the GLP-1RA monotherapy cohort, the combination cohort showed a modest reduction in risks of HF (HR 0.84; 95% CI 0.80, 0.87), stroke (HR 0.92; 95% CI 0.88, 0.96) and acute myocardial infarction (HR 0.93; 95% CI 0.89, 0.98) [29].

Renal outcomes

Observational retrospective studies that reported renal outcomes in patients treated with a GLP-1RA/SGLT2i combination versus either monotherapy are far less numerous than those that focused on cardiovascular outcomes. Results are summarized in Table 2.

In a study that used the results of the Global Collaborative Network, a GLP-1RA/SGLT2i combination showed a modest, yet significant, reduction (- 8%) in risk for CKD when compared with the PSM SGLT2i cohort, while when compared with the PSM GLP-1RA cohort, the combination cohort showed greater reduction (- 20%) in the risk of CKD over 5 years [29] (Table 2).

Compared with GLP-1RAs, a GLP-1RA/ SGLT2i combination was associated with a 57% lower risk of serious renal events in a UK population-based cohort study [32]. Compared with SGLT2i monotherapy, the dual therapy was associated with numerically lower incidence of serious renal events (- 33%), but with a much wider confidence interval [32] (Table 2).

In overweight/obese patients with T2DM and HFpEF (PSM, n = 7044 in each group), compared with SGLT2i monotherapy, a GLP1RA/SGLT2i combination was associated with significant reductions in the risk of acute renal injury (-30%) and renal replacement therapy (-53%) (Table 2), besides already mentioned reductions in hospitalization for HF and all-cause mortality (Table 1) (35).

In the Japanese RECAP study, a retrospective analysis extracted T2DM patients who had received both SGLT2i and GLP-1RA treatment for at least 1 year in order to evaluate the effects of the preceding drug type on the renal outcome in clinical practice. The incidences of the renal composite outcome (either progression of the albuminuria status and/or a >/=30% decrease in the estimated glomerular filtration rate [eGFR]) in the SGLT2i- and GLP-1RA-preceding groups were 28% and 25%, respectively; results suggested that the preceding drug did not affect the renal outcome with GLP-1RA/SGLT2i combination therapy [36]. Nevertheless, other recent data issued from the same RECAP study suggested a slower annual eGFR decline after the addition of GLP-1RAs to SGLT2i-treated patients when compared to the addition of SGLT2is to GLP-1RA-treated patients, a finding that, however, deserves further confirmation [37].

Discussion

Retrospective observational studies showed that a GLP-1RA/SGLT2i combination is more efficacious than either monotherapy with an SGLT2i or a GLP-1RA on clinically relevant clinical outcomes. Not only a combined therapy reduces all-cause mortality, as already shown in a previous meta-analysis of only two studies (OR 0.49; 95% CI 0.41, 0.60) [26], but it also reduces the risk of MACEs, hospitalisation for HF and renal endpoints related to CKD. Thus, these results confirm in real-life conditions what was already reported in post-hoc analyses of RCTs - GLP-1RA added to SGLT2i [15-17]; SGLT2i added to GLP-1RA [18-21] -, findings that were summarized in several meta-analyses [22-25]. Of note, in a prespecified dedicated analysis of the recent FLOW trial carried out in patients with T2DM and CKD, the benefits of injectable semaglutide in reducing cardiovascular and kidney outcomes were not significantly different in participants with and without baseline SGLT2i use, even if the investigators considered statistical power was limited to detect smaller but clinically relevant effects [38].

Of note, in most studies, patients were already on a background glucose-lowering therapy with metformin, less often sulphonylureas or basal insulin. The findings in favour of the combined therapy are concordant with those of observational studies that have also observed a decreased risk of MACEs when comparing the GLP-1RA/SGLT2i combination with different types of combined therapies used as comparators: sulfonylurea/GLP-1RA combination (HR 0.67; 95% CI 0.59, 0.89) [30], metformin-sulfonylurea combination (HR 0.53; 95% CI 0.35, 0.80) [27], and other combination regimens (odds ratio [OR] 0.70; 95% CI 0.50, 0.98) [28]. In a large-scale, multinational, federated analysis of the LEGEND-T2DM study that compared the effectiveness of second-line antihyperglycaemic agents for cardiovascular outcomes in patients with T2DM and established ASCVD, a comparable cardiovascular risk reduction was observed with SGLT2is and GLP1-RAs, with both agents being more effective than dipeptidyl peptidase-4 inhibitors (DPP4is) and sulphonylureas [39]. However, a GLP-1AR/SGLT2i combination was not tested in this huge cohort. In a survey from Danish nationwide registries (results only reported as abstracts), the 5-year risk ratio (RR) of a dual GLP-1RA/SGLT2i therapy compared to a reference (dual therapy among DPP-4i/sulphonylurea/thiazolidinedione) was significantly reduced for HF (RR 0.93; 95% CI 0.87, 1.00), for MACE (RR 0.91; 95% CI 0.87, 0.95) and for all-cause death (RR 0.78; 95% CI 0.74, 0.82) [40]. Favourable results were also reported for >50% decrease in eGFR (RR 0.52; 95 % CI 0.45, 0.59) and end-stage renal disease (ESKD : RR 0.12; 95 % CI 0.09, 0.15), but surprisingly not for so-called chronic renal disease (however, precise definition not specified in the abstract) (RR 1.03; 95 % CI 0.97, 1.08) [41].

These positive results on hard clinical endpoints are in agreement with the favourable effects already reported with the GLP-1AR/SGLT2i combination on surrogate endpoints classically considered as cardiorenal risk factors (glycated haemoglobin, body weight, arterial blood pressure) as recently reported in a systematic review and meta-analysis of observational studies [26]. Positive results were consistently observed regarding the effects of a GLP-1RA/SGLT2i combination versus a monotherapy in patients with ASCVD and/or HF : patients with ASCVD or any type of HF [28], patients with ASCVD and HFrEF [31], overweight/obese patients with HFpEF [35]. While the interest for a better management of HF in patients with T2DM is increasing in recent years [42], potential benefits of a GLP-1RA/SGLT2i combined therapy in patients with HF remain to be better investigated [43], as extensively discussed in a recent editorial for HFpEF [44].

The findings of a 57% lower risk of serious renal events with a GLP-1RA/ SGLT2i combination compared with GLP-1RA monotherapy [32] are in agreement with the previously reported reduction of acute kidney injury episodes with SGLT2i therapy [45], especially in real-world studies [46]. Using a population-based database in Hong Kong, a real-world retrospective observational study compared renal outcomes in patients who started on SGLT2i with those who started on GLP1RA, with one-to-one PSM. After a median follow-up of 13 months, SGLT2i users had a lower risk of composite kidney outcomes (HR 0.77; 95% CI 0.62, 0.96, p = 0.02), mainly driven by a reduction in ESKD (HR 0.53, p = 0.01) [47]. Similarly, in a multicentre retrospective observational study on new users of diabetes medications carried out in Italy in individuals with T2DM, treatment with SGLT2i was associated with better preservation of renal function compared with GLP-1RA, as evidenced by slower decline in eGFR and lower rates of worsening CKD class during a median follow-up of 2.1 years [48]. Such finding was confirmed in a retrospective observational Japanese study using PSM [49]. These results of real-world studies are concordant with a better renal protection with SGLT2is compared with GLP-1ARs derived from indirect comparisons of RCTs [50]. However, in a meta-analysis of 20 observational studies, when compared to GLP-1RAs, SGLT2is were not associated with a statistically significant difference in the risk of kidney failure (HR 0.93, 95% CI 0.80, 1.09) [51]. Data from the present analysis suggest that adding a GLP-1RA in patients already treated with a SGLT2i results in a further improvement in renal prognosis, findings concordant with the results of the recent trial FLOW with semaglutide [38]. Nevertheless, further studies focusing on renal outcomes with the GLP-1AR/SGLT2i combination are needed.

Several limitations should be pointed out. All studies included in the present analysis were retrospective with quite different numbers of patients across reports. Furthermore, the mode of presentation of the results was rather heterogeneous. Whereas observational studies came from various countries, none of them were specifically carried out in Asian countries, which might limit any extrapolation. Observational studies that investigated the add-on value of a GLP-1AR/SGLT2i combination on renal outcomes are still scarce and further studies are required before drawing any firm conclusion. Finally, no studies properly investigated yet the cost-effectiveness of such a more expensive combination therapy, especially according to the baseline individual risk profile. The demonstration of the efficacy of a GLP-1RA/SGLT2i combination arose only from post-hoc subgroup analyses of CVOTs or from retrospective observational studies, yet both pieces of information have their own limitations. The superiority of the combined therapy should now be proven in a dedicated RCT. PRECIDENTD ("PREvention of CardIovascular and DiabEtic kidNey Disease in Type 2 Diabetes" : ClinicalTrials.gov Identifier: NCT05390892) is an ongoing open-label, pragmatic clinical trial that randomly assigns 9,000 patients with established T2DM and ASCVD or high-risk for ASCVD in a 1:1:1 allocation to a GLP-1RA, a SGLT2i or a GLP-1RA/SGLT2i combination. The primary outcome is a composite of total number (first and recurrent) of episodes of cardiovascular and renal major complications, and mortality. As patients will be followed up to 5 years, results are not expected before 2028.

Conclusion

In real-life conditions, the GLP-1RA/SGLT2i combination reduced cardiovascular and renal outcomes compared with GLP-1RA monotherapy or SGLT2i monotherapy in patients with T2DM, especially among those with comorbidities such as ASCVD and/or HF. Even if the studies that reported renal outcomes are less numerous, preliminary results were also in favour of the combined therapy. Thus, observational studies confirm the results reported in post-hoc exploratory analyses of RCTs versus placebo. Overall, these results confirm the recommendations of using a GLP-1RA/SGLT2i combined therapy in patients with T2DM at high/very high risk of cardiovascular and/or renal complications.

Table 1 : Cardiovascular outcomes in patients treated with a GLP-1RA/SGLT2i combination versus monotherapy in observational retrospective studies.

Results are expressed as hazard ratio (95% confidence interval).

				MACEs			Hospitalization for HF			All-cause mortality		
Reference (*)	Country	Patients	Follow-up years	SGLT2is	GLP-1RAs	Combination	SGLT2is	GLP-1RAs	Combination	SGLT2is	GLP-1RAs	Combination
Jensen et al 2020 [27]	Denmark	T2DM	5	N=3405 HR=0.67 (0.48, 0.94)	N=6515 HR=0.51 (0.43, 0.60)	N=1823 HR=0.53 (0.35, 0.80)	NA	NA	NA	N=3405 HR=0.30 (0.22, 0.40)	N=6515 HR=0.41 (0.30, 0.46)	N=1823 HR=0.18 (0.11, 0.28)
Dave et al 2021 [30]	US	T2DM	0.9		N=12584 (+ SUs)	N=12584 (PSM) HR=0.76 (0.59, 0.98) vs GLP-1RA		N=12584 (+ SUs)	N=12584 (PSM) HR=0.65 (0.50, 0.82) vs GLP-1RA		N=12584 (+ SUs)	N=12584 (PSM) HR=0.68 (0.40, 1.14) vs GLP-1RA
Wright et al 2022 [28]	UK	T2DM with ASCVD or HF	3.3-4.0	N=599 HR=0.82 (0.73, 0.92)	N=469 HR=0.93 (0.81, 1.06)	N=53 HR=0.70 (0.50, 0.98)	N=599 HR=0.49 (0.42, 0.58)	N=469 HR=0.82 (0.71, 0.95)	N=53 HR=0.43 (0.28, 0.64)	NA	NA	NA
Lopez et al 2022 [31]	US	T2DM with ASCVD and HFrEF	2.4	N=343		N=343 (PSM) HR=0.372 (0.240, 0.574) vs SGLT2i	N=343		N=343 29 events vs 28 events HR=0.366 (NS) vs SGLT2i	N=343		N=343 HR = 0.28 (0.171, 0.460) vs SGLT2i
Riley et al 2023 [29]	Worldwide (Global Collaborative Network)	T2DM	5	NA	NA	NA	N=143740 HR=0.73 (0.71, 0.75)	N=186844 HR=0.73 (0.81, 1.06)	N=108507 HR=0.60 (0.58, 0.62)	N= 143740 HR=0.49 (0.48, 0.50)	N= 186844 HR=0.47 (0.46, 0.48)	N=108507 HR=0.25 (0.24-0.26) HR=0.53 (0.50, 0.55) vs SGLT2i HR=0.56,

												(0.54, 0.59) vs GLP-1RA
Simms-Williams et al 2024 [32]	UK	T2DM	0.75	N=8942 Used as reference	N=6696 Used as reference	N=8942/N =6696 (PSM) HR=0.71 (0.52, 0.98) vs SGLT2i HR=0.70 (0.49, 0.99) vs GLP-1RA	N=8942 Used as reference	N=6696 Used as reference	N=8942/N =6696 (PSM) HR=0.70 (0.40, 1.23) vs SGLT2i HR=0.57 (0.35, 0.91) vs GLP-1RA	N=8942 Used as reference	N=6696 Used as reference	N=8942/N=6696 (PSM) HR=0.73 (0.52, 1.01) vs SGLT2i HR=0.71 (0.49, 1.02) vs GLP-1RA
Marfella et al 2024 [33]	Italy	T2DM post-acute MI	2	N=99	N=130	N=214 HR=0.170 (0.046, 0.633) vs SGLT2i HR=0.154 (0.038,0.622) vs GLP-1 RA						
Garcia-Vega et al 2024 [34]	Spain	T2DM	1.6	NA	NA	NA	N=12029	NA	N=2449 (without PSM) HR=0.69 (0.56, 0.87) vs SGLT2i	N=12029	NA	N=2449 (without PSM) HR=0.68 (0.54, 0.86) vs SGLT2i
							N=2449 Used as reference		N=2449 (with PSM) HR=0.72 (0.53, 1.00) vs SGLT2ii	N=2449 Used as reference		N=2449 (with PSM) HR=0.48 (0.35, 0.66) vs SGLT2i
Patel et al 2024 [35]	Worldwide (TriNexT)	OW/OB with T2DM	1				N=7044 (PSM)		N=7044 (PSM)			N=7044 (PSM)

		and HFpEF							HR=0.62 (0.58, 0.66) vs SGLT2i			HR=0.64 (0.54-0.75) vs SGLT2i

(*) : Listed by date of publication.

ASCVD : atherosclerotic cardiovascular disease. GLP-1RA : glucagon-like peptide-1 receptor agonist. HF : heart failure. HFpEF : heart failure with preserved ejection fraction. HFrEF : heart failure with reduced ejection fraction. MACEs : major cardiovascular adverse events. MI : myocardial infarction. NA : not available. OB : obese. OW : overweight. PSM : propensity score matching. SGLT2i : sodium-glucose cotransporter 2 inhibitor. SUs : sulphonylureas. T2DM : type 2 diabetes.

Table 2 : Renal outcomes in patients treated with a GLP-1RA/SGLT2i combination versus monotherapy in observational retrospective studies.

Results are expressed as hazard ratio with 95% confidence interval.

Reference	Renal endpoint	SGLT2i monotherapy	GLP-1RA monotherapy	SGLT2i + GLP-1RA combination	HR combination versus SGLT2i	HR combination versus GLP-1RA
Riley et al 2023 [29]	CKD	N = 109460 vs 109621 controls (*) 0.79 (0.77, 0.81) P< 0.001	N = 148850 vs 149130 controls (*) 0.90 (0.88, 0.92) P< 0.001	N = 85946 vs 86154 controls (*) 0.72 (0.70, 0.74) P< 0.001	N = 75576 vs 76092 0.92 (0.89, 0.95) P< 0.001	N = 85145 vs 85823 0.80 (0.77, 0.83) P < 0.001
Simms-Williams et al 2024 [32]	Serious renal events	N = 8942	N = 6696	N = 8942 vs SGLT2is N = 6696 vs GLP-1RAs	0.67 (0.32, 1.41) NS	0.43 (0.23, 0.80) P< 0.001
Patel et al 2024 [35]	New onset AKI Renal replacement therapy	N=7044 (PSM)	NA	N=7044 (PSM)	N=7044 (PSM) 0.70 (0.65, 0.75) P< 0.001 0.47 (0.34, 0.66) P< 0.001	NA

AKI : acute renal injury. CKD : chronic kidney disease. GLP-1RA : glucagon-like peptide-1 receptor agonist. NA : not available. NS : not significant. PSM = propensity score matching. SGLT2i : sodium-glucose cotransporter 2 inhibitor.

(*) Therapy for T2DM excluding SGLT2i and/or GLP-1RA

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