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Kidney Outcomes With Glucagon-Like Peptide-1 Receptor Agonists Versus Other Glucose-Lowering Agents in People With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Real-World Data

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ABSTRACT

Aims: Randomized placebo-controlled clinical trials showed that glucagon-like peptide-1 receptor agonists (GLP-1 RA) reduce kidney risk in patients with type 2 diabetes (T2D), prominently in those with chronic kidney disease. It is unclear whether these findings may apply to broader populations of patients with T2D treated in real-world settings and compared to active controls. We summarised real-world data of adverse kidney outcomes among patients with T2D initiating GLP-1 RA versus other glucose-lowering agents.

Materials and Methods: We searched PubMed and Embase for observational cohort studies (April 2005–January 2025; PROSPERO CRD42023405356). Initiators of GLP-1 RA were compared to sodium-glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl-peptidase 4 inhibitors (DPP4i), sulfonylureas, or basal insulin. Outcomes included risks of albuminuria progression, ≥ 40 or $\geq 50\%$ eGFR reduction from baseline, acute kidney injury (AKI), kidney-related hospitalizations, and end-stage kidney disease (ESKD), per data availability. We synthesised the data using inverse variance-weighted averages of logarithmic hazard ratios (HR)s in random-effect models.

Results: Thirty-one studies were eligible, encompassing 1,601,389 patients (mean age 49–78 years, 5%–64% women), with 21, 6, 5, and 1 of them using SGLT2i, DPP4i, basal insulin, and sulfonylureas as a comparator, respectively. Compared with SGLT2i, GLP-1 RA initiators had higher risks for AKI (HR [95% CI] 1.12 [1.05–1.20]), kidney-related hospitalizations (1.66 [1.01–2.73]), and $\geq 40\%$ reduction in eGFR (1.40 [1.27–1.53]), without evidence for differences in risks of $\geq 50\%$ eGFR reduction or ESKD. Compared to DPP4i, GLP-1 RA initiators had lower risks for experiencing $\geq 50\%$ eGFR reduction (0.84 [0.76–0.92]), kidney-related hospitalizations (0.73 [0.65–0.83]), and ESKD (0.70 [0.63–0.78]). Similar benefits were observed when comparing GLP-1 RA to sulfonylureas. Compared to basal insulin, GLP-1 RA initiation was associated with a lower risk of albuminuria progression (0.89 [0.80–0.99]), with inconsistent data regarding possible benefits in reducing ESKD risk.

Alisa Fishkin and Aliza Rozenberg share joint first authorship.

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Conclusions: In patients with T2D, initiation of GLP-1 RA in real-world settings may be associated with improved kidney outcomes compared to DPP4i, sulfonylureas, and basal insulin, and worse kidney outcomes compared to SGLT2i.

1 | Introduction

Type 2 diabetes (T2D) is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide [1–3]. The risk for CKD onset and progression in patients with T2D remains high even under optimal evidence-based treatment, which includes lifestyle modification, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and non-steroidal mineralocorticoid receptor antagonists (MRAs) [4].

Emerging data support the role of glucagon-like peptide-1 receptor agonists (GLP-1 RA) in improving kidney outcomes in patients with T2D. The FLOW trial has demonstrated that semaglutide improves kidney outcomes in patients with T2D and CKD with albuminuria [5]. Most trials that compared GLP-1 RA and placebo in patients with T2D at high cardiovascular risk and mostly preserved kidney function found that GLP-1 RAs improve cardiovascular outcomes [6] and prevent the onset of new macroalbuminuria [7]. Whether treatment with GLP-1 RAs mitigates the loss of estimated glomerular filtration rate (eGFR) in these populations was less certain – some studies [8, 9], but not others [10], found a preservation of kidney function with GLP-1 RA versus placebo. Further investigation is needed to determine whether these kidney effects can be extrapolated from randomized controlled trials (RCT)s to real-world settings, often including patients with lower cardiovascular and kidney risk profiles. Furthermore, these studies assessed the treatment effects of GLP-RA compared with placebo; it is unclear whether such kidney effects exist when compared with an active comparator.

This systematic review and meta-analysis assessed the association between initiating GLP-1 RA, versus other glucose-lowering agents (GLAs), and adverse kidney outcomes, in patients with T2D treated in real-world settings.

2 | Materials and Methods

2.1 | Search Strategy and Selection Criteria

We searched ‘PubMed’ and ‘Embase’ on January 1, 2025, for observational cohort studies assessing the risk of kidney outcomes among patients with T2D who initiated GLP-1 RA versus other GLAs – SGLT2i, dipeptidyl peptidase 4 inhibitors (DPP4i), sulfonylureas, or basal insulin. We included manuscripts that used real-world data, such as healthcare databases or insurance claims, and excluded randomized control trials, meta-analyses, and systematic reviews. The search was performed using keywords regarding the study types, populations, interventions, and kidney outcomes (Supporting Information S1). The search was conducted by two independent researchers and was restricted from April 1, 2005 (when the first GLP-1 RA received approval in the United States to treat patients with T2D) to January 1,

2025. Disagreements between the non-blinded assessors were resolved by consensus. All abstracts were screened, and relevant manuscripts underwent a full-text and supplementary evaluation. No contact was made with the authors. We screened the references of the identified manuscripts for additional relevant papers.

The included studies had to include only patients with T2D and apply a new-initiator active-comparator design to minimise the risk of confounding by indication and time-related bias. We included manuscripts that balanced the treatment groups by either inverse probability treatment weighting (IPTW) or propensity score (PS) matching. We excluded studies that combined different classes of GLAs in one control group or those that included patients treated with GLP-1 RA within 6 months before the index date. We excluded studies in languages other than English. A PRISMA flow chart was used to present the selection process in detail (Figure 1).

2.2 | Data Collection Process

We collected pre-specified data from each study related to the study characteristics, interventions and comparisons, patient characteristics, statistical approaches, and kidney-related outcomes (Supporting Information S1: Table S1). Categorical outcomes included incidence of new macroalbuminuria, categorical albuminuria progression, categorical albuminuria regression (indicating improvement), a decline in eGFR from baseline by $\geq 30\%$, $\geq 40\%$, $\geq 50\%$, or $\geq 57\%$ (representing doubling of serum creatinine), new onset CKD, worsening in CKD class, dialysis or kidney transplant, new ESKD, hospitalizations due to kidney event, acute kidney injury (AKI), or kidney-related death. When available, we presented data on composite kidney outcomes. We also collected data on continuous outcomes, such as the change in eGFR and UACR over time.

We included only studies that received approval from ethical committees. In addition, this systematic review and meta-analysis followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Supporting Information S2). To evaluate the risk of bias in each of the manuscripts included in the meta-analysis, we used the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) assessment tool (Supporting Information S1: Table S2). The protocol for this study was submitted to PROSPERO (CRD42023405356).

2.3 | Statistical Analysis

We present population sizes, number of events, hazard ratios, confidence intervals, and p -values depending on data availability. In addition, we specify the method used for balancing the cohorts (IPTW or PS). We present adjusted data, as available

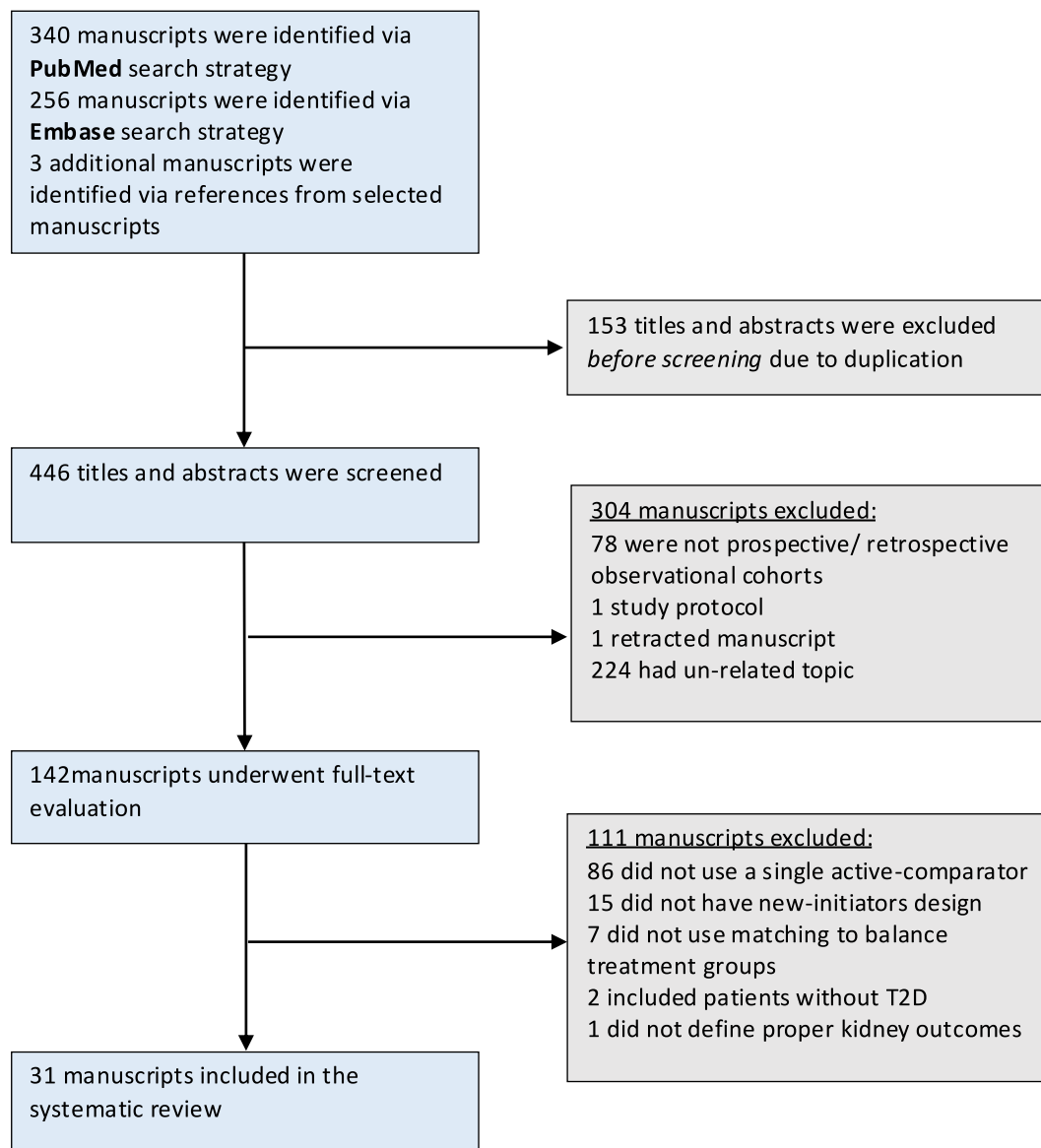


FIGURE 1 | PRISMA flow-chart. The search was conducted via PubMed and Embase between April 1, 2005, and January 1, 2025. Eligible manuscripts included observational cohort studies examining kidney outcomes in patients with T2D initiating GLP-1 RA versus other GLAs (SGLT2i, DPP4i, sulfonylureas, and basal insulin). DPP4i, dipeptidyl peptidase-4 inhibitors; GLAs, glucose-lowering agents; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose transporter 2 inhibitor; T2D, type 2 diabetes.

in the source manuscripts. We primarily collected intention-to-treat (ITT) follow-up data, in which follow-up continued until an effectiveness outcome (for the specific endpoint), end of data availability, or death. We also collected as-treated (AT) follow-up data, in which follow-up was terminated at study treatment discontinuation or the initiation of the comparator.

A pooled analysis was conducted for categorical outcomes with at least two manuscripts analysing the same group of GLA comparators. This analysis was carried out using inverse variance-weighted averages of logarithmic HRs, using random effect models, and applying the residual maximum likelihood method. We selected random models as the main analysis due to the conceptual, and observed, heterogeneity that are common when combining real-world studies, but we also fitted fixed effect models as a sensitivity analysis. Composite kidney outcomes

were not pooled because their definitions significantly varied across the studies. Heterogeneity was assessed using the I^2 statistic. Statistical analyses were conducted using R version 3.5.1 Austria.

2.4 | Risk of Bias Assessment

Overall, the risk of bias was moderate for most studies included in the meta-analysis. No study was evaluated as having a critical risk of bias (Supporting Information S1: Table S2). The risks of bias were mainly influenced by the confounding domain, as expected for real-world studies. When the number of available studies allowed ($N \geq 5$ studies), we created a funnel plot to inspect for potential publication biases.

TABLE 1 | Baseline characteristics of the participants in the included manuscripts.

GLP-1 RA versus SGLT2i																			
Manuscript	Population (origin)	PS/IPTW	N			Follow-up duration- median years (IQR)				Age- mean years (SD)			Sex- female (%)			eGFR mL/min/1.73 m ² (mean, SD)			GLP-1 RA type (%)
			GLP-1 RA	SGLT2i		GLP-1 RA	SGLT2i		GLP-1 RA	SGLT2i		GLP-1 RA	SGLT2i		GLP-1 RA	SGLT2i			
Ueda 2018 [11]	Sweden and Denmark	PS	17,213	17,213		0.87 (0.40–1.64)	0.65 (0.32–1.18)	61 (10)	61 (10)		39	39	eGFR (mL/min) ≥ 90-3533 (34) ≥ 60 to 89-3284 (31) < 60-1111 (11) Missing-2584 (25)	eGFR (mL/min) ≥ 90- 3721 (35) ≥ 60 to 89- 3366 (32) < 60- 683 (6) Missing-2742 (26)		NA			
Longato 2020 [12]	North-East Italy	PS	4298	4298		1.08 (0.58–1.83)		62.8 (9.7)	62.7 (9.2)		36.9	37	NA	NA		Exenatide- (14) Liraglutide- (34) Lixisenatide- (4) Dulaglutide- (48)			
Xie 2020 [13] ^a	United States veterans	PS	23,711	18,544		1.34 (0.76–2.05)	0.99 (0.58–1.69)	65.23 (3.65)	65.41 (3.65)		5.55	5.58	75.17 (7.01)	75.12 (7.01)		Liraglutide- (56.3) Dulaglutide- (22.1) Semaglutide- (12.9) Albiglutide- (4.4) Exenatide- (4.2)			
Patorno 2021 [14]	United States	PS	45,047	45,047		0.42 (0.24–0.87)	0.48 (0.24–0.98)	71.56 (5.03)	71.56 (5.01)		54	54.4	NA	NA		Albiglutide- (3.0) Dulaglutide- (14.8) Exenatide- (23.5) Liraglutide- (58.7)			
Lugner 2021 [15]	Sweden	IPTW	9648	12,097		1.7	1.1	60.23 (11.00)	60.82 (10.92)		38.1	37.0	91.32 (24.58)	92.05 (24.07)		Liraglutide- (75.1) Dulaglutide (16.3) Exenatide once weekly (6.4)			
Tang 2021 [16]	Hong Kong	IPTW	303	2541		2.13	1.04	Mean ± SE 54.9 ± 1.1	Mean ± SE 55.7 ± 0.2		48.2	49.5	Mean ± SE 110.0 ± 3.3	Mean ± SE 111.3 ± 0.6		Exenatide- (30.0) Liraglutide- (56.8) Lixisenatide- (13.2)			
Ueda 2022 [17]	Sweden, Denmark, and Norway	IPTW	63,921	87,525		2.2 (1.0–3.8)	1.6 (0.7–2.8)	61.4 (10.6)	61.4 (10.7)		39	39.1	NA	NA		Liraglutide- (84.1) Exenatide- (6.1) Dulaglutide- (7.1) Lixisenatide- (2.7) Semaglutide- (0.1)			
Zhuo 2022 [18]	United States	PS	71,477	71,477		0.45 (0.24–0.93)	0.49 (0.24–1.03)	71.9 (5.2)	71.9 (5.1)		53.6	53.6	NA	NA		NA			
Lui 2022 [19]	Hong Kong, China	PS	2551	2551		1 (0.33–1.0)	1.17 (0.5–2.5)	56.0 (12.3)	56.3 (13.3)		44	44	77.9 (28.6)	78.2 (28.1)		Liraglutide- (47.1) Dulaglutide (29.7) Exenatide (18.9) Lixisenatide (4.4)			
Baviera 2022 [20]	Lombardy, Italy	PS	20,762	20,762		Mean- years (SD) 2.78 (1.30)	Mean- years (SD) 2.77 (1.37)	66.30 (8.60)	66.36 (8.25)		40.1	40.1	NA	NA		NA			
Fu 2023 [21]	United States	PS	28,847	28,847		Mean- years (SD) 0.63 (0.33)		72 (7)	72 (7)		44	44	43.06 (14.45)	45.69 (15.50)		Albiglutide- (1.3) Liraglutide- (33) Lixisenatide- (0.7) Dulaglutide- (39.6) Semaglutide- (12.7) Exenatide- (12.5)			
Alkas 2023 [22]	Stockholm, Sweden	IPTW	17,082	13,645		2.5 (0.96–4.84)		Median [IQR] 63 [55–71]	Median [IQR] 64 [56–72]		38.0	39.0	Median [IQR] 90 [74–100]	Median [IQR] 87 [69–99]		NA			

(Continues)

TABLE 1 | (Continued)

GLP-1 RA versus SGLT2i											
Manuscript	Population (origin)	PS/IPTW	Follow-up duration- median years (IQR)				Age- mean years (SD)				GLP-1 RA type (%)
			GLP-1 RA	SGLT2i	N	GLP-1 RA	SGLT2i	GLP-1 RA	SGLT2i	Sex- female (%)	
Suzuki 2024 [23] ^b	Japan	1:4 PS	432	1728	NA	NA	NA	NA	NA	NA	Liraglutide (NA)
											Dulaglutide (NA)
Sohn 2024 [24]	South Korea	1:3 PS	528	1584	2.00 (0.90–3.86)	55.6 (13.1)	56 (13.6)	47.2	43.9	88.8 (26.8)	90.1 (26.0)
											Liraglutide (26.1)
Riester 2024 [25]	United States	IPTW	7659	3284	NA ^c	77.4 (7.7)	78.2 (7.8)	64.4	61.5	NA	NA
											Exenatide (4.2)
Edmonston 2024 [26]	United States	PS overlap weighting	47,268	35,004	1.2 (1.1–2.0)	Mean, median (IQR)	Mean, median (IQR)	52.4	52.4	Mean, median (IQR)	Mean, median (IQR)
						58.4, 59.0 (51.0–67.0)	58.4, 59.0 (51.0–67.0)			80.6, 81.8 (65.3–96.3)	80.6, 81.8 (65.3–96.3)
Hsiao 2024 [27] ^d	Taiwan	PS	22,506 ^e	22,506 ^e	2.43 (1.68–3.14)	NA	NA	NA	NA	NA	NA
											Exenatide (NA)
Htoo 2024 [28] ^f	United States	PS	10,837	10,837	0.5 (0.25–0.83)	NA	NA	NA	NA	NA	NA
											Liraglutide (NA)
Chan 2024 [29] ^g	AF	Taiwan	PS stabilised weight	561.63	11,404.06	68.73 (8.35)	69.27 (11.05)	38.2	36.6	NA	NA
											Liraglutide (51.7)
Fadini 2024 [30]	Italy	PS and 10 imputed dataset	5705	5705	2.1 (1.1–3.34)	60.8 (9.5)	60.9 (9.2)	40.3	39.3	85.8 (18.5)	85.9 (17.1)
											Liraglutide (30.8)
Morello 2024 [31]	United States	PS	14,573	14,573	3	66.5 (10.2)	66.4 (9.5)	5.5	5.2	73.2 (23.1)	74.7 (19.8)
											Exenatide (8.1)

(Continues)

TABLE 1 (Continued)

GLP-1 RA versus DPP4i										
Manuscript	Population (origin)	PS/PTW Age, sex, and PS	Follow-up duration- median years (IQR)				Age- mean years (SD)			
			GLP-1 RA	DPP4i	Mean- years (SD)	Mean- years (SD)	GLP-1 RA	DPP4i	Sex- female (%)	eGFR mL/min/1.73 m ² (mean, SD)
							GLP-1 RA	DPP4i	GLP-1 RA	DPP4i
Pasternak 2020 [32]	Sweden, Denmark, and Norway		38,731	38,731	3.1 (1.7)	3.0 (1.7)	59.3 (10.4)	59.4 (10.5)	43.1	NA
										Liraglutide- (92.5) Exenatide- (6.2) Lixisenatide- (0.7) Dulaglutide- (0.6)
Xie 2020 ^a [13]	United States veterans	PS	23,711	39,399	1.34 (0.76–2.05)	1.47 (0.78–2.23)	65.23 (3.65)	65.46 (3.65)	5.55	75.17 (7.01)
										75.04 (7.01)
										Liraglutide- (56.29) Dulaglutide- (22.14) Semaglutide- (12.90) Albiglutide- (4.44) Exenatide- (4.23)
Xu 2022 [33]	Stockholm, Sweden	PS weighted cox regression	5625	14,152	2.2 (1.0–4.3)	3.3 (1.5–6.2)	63 (11)	63 (12)	38.2	Median (IQR) 89.0 [70.2, 100.7]
										Exenatide- (6.4) Dulaglutide- (6.2) Unspecified- (1.5) Lixisenatide- (1.0) Semaglutide- (0.2)
Lin 2023 [34]	Taiwan, China	PS	602	1479	2.2 (2.0)	2.1 (2.1)	65.9 (11.5)	66.3 (11.0)	49.3	20.7 (15.2)
										20.6 (16.3)
										Liraglutide (NA) Dulaglutide (NA)
Alkas 2023 [22]	Stockholm, Sweden	IP*TW	17,082	17,573	2.5 (0.96–4.84)		Median [IQR] 63 [55–71]	Median [IQR] 63 [54–72]	38.0	Median [IQR] 89 [72–100]
Zhang 2024 [35]	US	PS	16,076	16,076	Mean- years (SD) 2.2 (1.9)		71.9 (8.1)	71.8 (8.7)	5.0	48.5 (11.7)
										48.5 (11.8)
										Liraglutide (34.5) Dulaglutide (25.7) Exenatide (6.6) Semaglutide (30.2) Albiglutide (3.1) Lixisenatide (0.02)

(Continues)

TABLE 1 (Continued)

GLP-1 RA versus sulfonylureas												
Manuscript	Population (origin)	PS/IPTW	Follow-up duration- median years (IQR)			Age- mean years (SD)			eGFR mL/min/1.73 m ² (mean, SD)			
			GLP-1 RA	SU		GLP-1 RA	SU		GLP-1 RA	SU	GLP-1 RA type (%)	
Xie 2020 [13] ^a	United States veterans	PS	23,711	134,904	1.34 (0.76–2.05)	1.69 (0.97–2.42)	65.23 (3.65)	65.62 (3.65)	5.55	75.17 (7.01)	74.98 (7.01)	Liraglutide- (56.29) Dulaglutide- (22.14) Semaglutide- (12.90) Albiglutide- (4.44) Exenatide- (4.23)

GLP-1 RA versus basal insulin												
Manuscript	Population (origin)	PS/IPTW	Follow-up duration- median years (IQR)			Age- mean years (SD)			eGFR mL/min/1.73 m ² (mean, SD)			
			GLP-1 RA	Insulin		GLP-1 RA	Insulin		GLP-1 RA	Insulin	GLP-1 RA type (%)	
Pawaskar 2014 [36]	United States	PS	2683	2683	1.0		58 (11)	58 (12)	55	79	79	Exenatide BID
Loughlin 2018 [37] ^b	United States	PS	2008	4016	NA	NA	NA	NA	NA	NA	NA	Exenatide once weekly
Longato 2021 [38]	Italy	PS	4063	4063	2.0 (1.0–3.0)		63.3 (9.1)	63.1 (11.2)	39.5	82.7 (18.0) ^j	82.4 (22.5) ^j	Dulaglutide (43) Liraglutide (35) Exenatide (18) Lixisenatide (4)
Schechter 2023 [39]	Israel	PS	3424	3424	6.95 (4.17–9.37)	6.64 (4.3–8.88)	59.5 (9.5)	59.3 (10.8)	44.7	90.1 (18.8)	91.2 (19.8)	Exenatide extended release (NA) Dulaglutide (NA) Lixisenatide (NA) Liraglutide (NA) Semaglutide (NA)
Peng 2023 [40]	Taiwan	PS	7279	7279	Mean 2.64		49.1 (12.4)	49.2 (13.4)	49.5	NA	NA	Dulaglutide (53.5) Liraglutide (46.5)

Note: The bold values represent the categories (ranges) under which the corresponding individual values fall.
Abbreviations: AF, atrial fibrillation; DPP4i, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse Probability Treatment Weighting; IQR, interquartile range; NA, not available; PS, propensity score; SD, Standard deviation; SE, standard error; SU, sulfonylureas; SGLT2i, Sodium-glucose cotransporter-2 inhibitor.
^aData about population size (N) and follow-up durations were taken from the main baseline characteristics table (Table 1- Xie Y, 2020), while the rest of the data was taken from the key characteristics after adjustment for propensity scores table (Supplemental Table 4- Xie Y, 2020).
^bBaseline characteristics are not available separately for patients with type 2 diabetes and are only available for the whole cohort that also includes patients with type 1 diabetes. The presented data are from a sensitivity analysis that included only patients with type 2 diabetes.
^cReason for end of follow-up and observed follow-up times are presented in Supplementary eTable 7: Table S7 of the original referenced paper.
^dIn the original manuscript, baseline characteristics data were divided into subgroups according to frailty status (fit, mild frailty, and moderate or severe frailty). There are no data regarding the characteristics of the whole cohort; therefore, we couldn't present them here.
^eN represents the whole cohort of patients across three sub-groups of patients initiating GLP-1 RA or SGLT2i, divided by Frailty status.
^fFor the ESKD outcome presented in this meta-analysis, the study included only patients with CKD stages 3–4. The baseline characteristics for this subpopulation were not provided.
^gIn the original manuscript, baseline characteristics data were divided into two sub-groups stratified by the presence of atrial fibrillation (AF) at baseline.
^hIn the original manuscript, baseline characteristics data were divided into sub-groups by age and kidney function; therefore, we weren't able to present them here.
ⁱOnly 710 and 731 initiators of GLP-1 RA and basal insulin, respectively, out of 4063 patients in each arm, had available clinical-laboratory data at baseline. Therefore, eGFR levels are reported only for these subsets of patients from the matched cohorts.

TABLE 2 | Kidney outcomes in each study that compared patients with type 2 diabetes who initiated GLP-1 RA versus another glucose-lowering agent.

GLP-1 RA versus SGLT2i									
Manuscript	GLP-1 RA			SGLT2i			GLP-1 RA versus. SGLT2i HR [95% CI]	p value	
	N	n	%	N	n	%			
Incident of macroalbuminuria									
Lugner 2021 [15]	9648	403	4.18	12,097	349	2.89	1.12 [0.96–1.30] ^a	0.1408	
Lui 2022 [19]	2551	NA	NA	2551	NA	NA	1.54 [0.14–16.67]	0.721	
Sohn 2024 [24]	528	5	0.95	1584	20	1.26	0.95 [0.36–2.56]	0.928	
Fadini 2024 [30]	2175	23.6 ^b		2320	26.5 ^b		0.87 [0.66–1.15]	0.327	
Albuminuria progression ^c									
Sohn 2024 [24]	528	13	2.46	1584	54	3.41	0.91 [0.50–1.67]	0.768	
Albuminuria regression ^c									
Sohn 2024 [24]	528	26	4.92	1584	133	8.40	0.64 [0.42–0.97]	0.036	
≥ 30/40/50/57% reduction in eGFR									
Lugner 2021 [15]	≥ 30%	9648	105	1.09	12,097	87	0.72	1.09 [0.80–1.47] ^a	0.5863
Lugner 2021 [15]	≥ 40%	9648	56	0.58	12,097	45	0.37	1.06 [0.70–1.61] ^a	0.7718
Sohn 2024 [24]	≥ 40%	528	13	2.46	1584	22	1.39	2.17 [1.09–8.33]	0.023
Fadini 2024 [30]	≥ 40%	NA	20.7 ^b		NA	16.2 ^b		1.28 [0.98–1.67]	0.076
Morello 2024 [31]	≥ 40%	14,573	3.1 ^d		14,573	4.5 ^d		1.43 [1.33–1.54] ^e	< 0.001
Lugner 2021 [15]	≥ 50%	9648	40	0.41	12,097	28	0.23	1.25 [0.74–2.13] ^a	0.4007
Xie 2020 [13]	> 50%	23,711	1043	4.40	18,544	491	2.65	1.15 [1.02–1.28] ^f	NA
Lui 2022 [19]	≥ 50%	2551	NA	NA	2551	NA	NA	0.96 [0.78–1.19]	0.726
Sohn 2024 [24]	≥ 50%	528	8	1.52	1584	9	0.57	3.33 [1.28–8.33]	0.013
Doubling of serum creatinine									
Sohn 2024 [24]		528	7	1.33	1584	6	0.38	4.55 [1.54–14.29]	0.006
Fadini 2024 [30]		4155	7.6 ^b		4182	4.9 ^b		1.56 [1.01–2.44]	0.047
New onset CKD ^g									
Fadini 2024 [30]		NA	33.6 ^b		NA	29.1 ^b		1.16 [0.99–1.37]	0.069
Worsening in CKD class ^h									
Fadini 2024 [30]		5701	255.5 ^b		5701	233.9 ^b		1.09 [1.01–1.16]	0.027
Hospitalisation for kidney events									
Ueda 2022 [17]		63,921	552	0.86	87,525	339	0.39	1.33 [1.14–1.54] ⁱ	NA
Baviera 2022 [20]		20,762	72	0.35	20,762	32	0.15	2.23 [1.48–3.43] ^j	NA
Acute kidney injury									
Ueda 2018 [11]		17,213	76	0.44	17,213	55	0.32	1.11 [0.79–1.59]	NA
Patorno 2021 [14] (365days)		45,047	1658	3.68	45,047	1536	3.41	1.08 [1.01–1.16]	NA
Zhuo 2022 (365days) [18]		71,477	1636	2.29	71,477	1455	2.04	1.12 [1.05–1.20]	NA
Baviera 2022 [20]		20,762	12	0.06	20,762	2	0.01	NA	NA
Fu 2023 [21]		28,847	2744	9.51	28,847	2466	8.55	1.10 [1.04–1.15] ^k	NA
Alkas 2023 [22]		4448 ^l	277	6.23	2354 ^l	64	2.72	1.35 [0.84–2.17] ^m	NA
Riester 2024 [25] (365days)		7659	NA	NA	3284	NA	NA	0.93 [0.85–1.02]	NA
End-stage kidney disease									
Xie 2020 [13]		23,711	401	1.69	18,544	88	0.47	1.11 [0.88–1.39] ^f	NA
Tang 2021 [16]		303	7 ⁿ	2.31	2541	11 ⁿ	0.43	1.95 [0.41–9.17] ^o	NA
Ueda 2022 [17]		63,921	196	0.31	87,525	107	0.12	1.35 [1.03–1.79] ⁱ	NA
Lui 2022 [19]		2551	NA	NA	2551	NA	NA	0.84 [0.61–1.15]	0.266

(Continues)

TABLE 2 | (Continued)

GLP-1 RA versus SGLT2i										
Manuscript		GLP-1 RA			SGLT2i			GLP-1 RA versus. SGLT2i	p value	
		N	n	%	N	n	%	HR [95% CI]		
Sohn 2024 [24]		528	7	1.33	1584	5	0.32	5.26 [1.64–16.67]	0.002	
Morello 2024 [31]		14,573	0.2 ^d		14,573	0.4 ^d		1.85 [1.43–2.38] ^e	< 0.001	
Dialysis or kidney transplant										
Hsiao 2024 [27]		Fit	11,882	158	1.33	11,882	62	0.52	2.43 [1.82–3.23] ^p	< 0.0001
		Mild frailty	7210	274	3.80	7210	70	0.97	3.93 [3.03–5.09] ^p	< 0.0001
		Moderate-severe frailty	3414	223	6.53	3414	87	2.55	2.60 [2.03–3.31] ^p	< 0.0001
Death due to kidney causes										
Ueda 2022 [17]		63,921	40	0.06	87,525	21	0.02	1.33 [0.74–2.44] ⁱ	NA	
Sohn 2024 [24]		528	0	0	1584	0	0	NA	NA	
GLP-1 RA versus DPP4i										
Manuscript		GLP-1 RA			DPP4i			GLP-1 RA versus DPP4i	p value	
		N	n	%	N	n	%	HR [95% CI]		
≥ 30/40/50/57% reduction in eGFR										
Xie 2020 [13]		> 50%	23,711	1043	4.4	39,399	1376	3.49	0.84 [0.76–0.92] ^f	NA
Xu 2022 [33]		≥ 57% ^q	5699	56	0.98	14,067	213	1.51	NA	NA
Progression of albuminuria ^r										
Zhang 2024 [35]			16,076	1662	10.34	16,076	1737	10.80	0.95 [0.89–1.02] ^s	0.17
Regression of albuminuria ^r										
Zhang 2024 [35]			16,076	809	5.03	16,076	742	4.62	1.10 [0.99–1.12] ^s	0.08
Hospitalisation for kidney events										
Pasternak 2020 [32]			38,731	444	1.15	38,731	583	1.51	0.73 [0.65–0.83]	NA
Acute kidney injury										
Alkas 2023 [22]			4448 ^l	277	6.23	10,605 ^L	1070	10.09	0.98 [0.82–1.18] ^m	NA
End-stage kidney disease										
Pasternak 2020 [32]			38,731	223	0.58	38,731	291	0.75	0.73 [0.62–0.87]	NA
Xie 2020 [13]			23,711	401	1.69	39,399	579	1.47	0.68 [0.59–0.79] ^f	NA
Xu 2022 [33]			5699	20	0.35	14,067	129	0.92	NA	NA
Death due to kidney causes										
Pasternak 2020 [32]			38,731	39	0.1	38,731	51	0.13	0.72 [0.48–1.10]	NA
Xu 2022 [33]			5699 ^t	0	0	14,067 ^t	8	0.06	NA	NA
GLP-1 RA versus sulfonylureas										
Manuscript		GLP-1 RA			Sulfonylureas			GLP-1 RA versus SU	p value	
		N	n	%	N	n	%	HR [95% CI]		
≥ 30/40/50/57% reduction in eGFR										
Xie 2020 [13]		> 50%	23,711	1043	4.4	134,904	4850	3.6	0.76 [0.69–0.83] ^f	NA
End-stage kidney disease										
Xie 2020 [13]			23,711	401	1.69	134,904	1594	1.18	0.72 [0.62–0.84] ^f	NA
GLP-1 RA versus basal insulin										
Manuscript		GLP-1 RA			Insulin			GLP-1 RA versus insulin	p value	
		N	n	%	N	n	%	HR [95% CI]		
New macroalbuminuria										
Schechter 2023 [39]			3424	190	5.55	3424	195	5.7	0.95 [0.78–1.16]	0.627

(Continues)

TABLE 2 | (Continued)

GLP-1 RA versus basal insulin									
Manuscript	GLP-1 RA			Insulin			GLP-1 RA versus insulin HR [95% CI]	p value	
	N	n	%	N	n	%			
Categorical progression of UACR									
Schechter 2023 [39]	3424	629	18.37	3424	685	20.01	0.89 [0.80–0.99]	0.036	
≥ 30/40/50/57% reduction in eGFR									
Schechter 2023 [39] 30%	3424	513	14.98	3424	504	14.72	0.98 [0.87–1.11]	0.786	
Schechter 2023 [39] 40%	3424	312	9.11	3424	311	9.08	0.96 [0.82–1.12]	0.583	
Schechter 2023 [39] 50%	3424	192	5.61	3424	165	4.82	1.11 [0.91–1.37]	0.303	
Schechter 2023 [39] 57%	3424	122	3.56	3424	112	3.27	1.04 [0.80–1.34]	0.783	
Acute kidney injury									
Longato 2021 [38]	4063	35	0.86	4063	43	1.06	0.82 [0.52–1.28]	0.379	
End-stage kidney disease									
Schechter 2023 [39]	3424	53	1.55	3424	55	1.61	0.92 [0.64–1.32]	0.634	
Peng 2023 [40]	7279	35	0.48	7279	119	1.63	0.29 [0.20–0.43] ^P	NA	
Death due to kidney causes									
Peng 2023 [40]	7279	13	0.18	7279	47	0.65	0.28 [0.15–0.51] ^P	NA	

Abbreviations: CI, confidence interval; DPP4i, Dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IPTW, Inverse probability of treatment weighting; NA, Not available; SGLT2i, sodium-glucose transporter two inhibitor; SU, Sulfonylurea; UACR, urinary albumin to creatinine ratio.

^aIPTW adjusted cox regressions.

^bCrude rates/1000 Person years.

^cAlbuminuria progression refers to worsening urinary albumin category (e.g., normoalbuminuria to microalbuminuria) confirmed twice with a 20% change of albuminuria and 30-day gaps, including increases in two stages for the last observation. Albuminuria regression refers to improvement (e.g., macroalbuminuria to microalbuminuria or normoalbuminuria) under similar conditions, with decreases in two stages considered for the last observation.

^dIncidence rate per 1000 person-year.

^eAdjusting for baseline covariates.

^fEstimated through IPTW with 0.1% truncation of stabilised weights.

^gThe occurrence of two eGFR values < 60 mL/min per 1.73 m² at least 90 days apart, among those who had a baseline eGFR > 60 mL/min per 1.73 m².

^hStage I eGFR ≥ 90 mL/min per 1.73 m²; stage II 60–90 mL/min per 1.73 m²; stage IIIa 45–60 mL/min per 1.73 m²; stage IIIb 30–45 mL/min per 1.73 m²; stage VI 15–30; stage V < 15 mL/min per 1.73 m².

ⁱThe covariates used for adjustment are not specified in the manuscript.

^jAdjusted for variables with an SDM ≥ 0.10.

^kSensitivity analysis applying a 365-day intention-to-treat follow-up.

^lNumber of participants Before IPTW.

^mThe analysis was weighted for 60 variables using inverse probability treatment weighting.

ⁿEvents (n) before IPTW, as presented in the original manuscript (Table 1 Tang EHM, 2021).

^oAdjustment for IPTW.

^pSubdistribution hazard ratio (95% CI).

^q≥ 57% reduction in eGFR = sustained doubling of serum creatinine.

^rProgression/Regression of albuminuria was defined as a stepwise categorical increase /decrease in albuminuria (< 30; ≥ 30 to < 300; ≥ 300 to < 3000; or > 3000) compared to mean albuminuria at baseline.

^sOdds ratio adjusted to propensity score.

^tPopulation size (N) before IPTW, as presented in the original manuscript (Table 1 Xu Y, 2022).

3 | Results

3.1 | Baseline Characteristics

A total of 446 unique titles and abstracts were screened, and 31 were found eligible (Table 1, Supporting Information S1: Table S3, and Figure 1). These studies reported data of 1,601,389 patients who initiated new GLAs; 542,278 of them initiated GLP-1 RA, most commonly liraglutide. The mean age at baseline ranged between 49 and 78 years, and 5%–64% of the participants were women. Baseline eGFR and UACR levels were reported in 17 and 9 of these manuscripts, respectively (Table 1, Supporting Information S1: Table S3). Thirty studies had a mean or median follow-up of ≤ 3 years, and one had a median

follow-up of up to 7 years [39]. There were 21, 6, 5, and 1 studies that used SGLT2i, DPP4i, basal insulin, and sulfonylureas as comparators, respectively (Table 1, Supporting Information S1: Table S3).

3.2 | Initiation of GLP-1 RA Compared With SGLT2i

In 21 studies, 444,705 and 775,359 initiated treatment with GLP-1 RA and SGLT2i, respectively. The risk for ESKD was reported in five studies [13, 16, 17, 19, 24], without evidence for a difference between GLP-1 RA versus SGLT2i initiators in a pooled

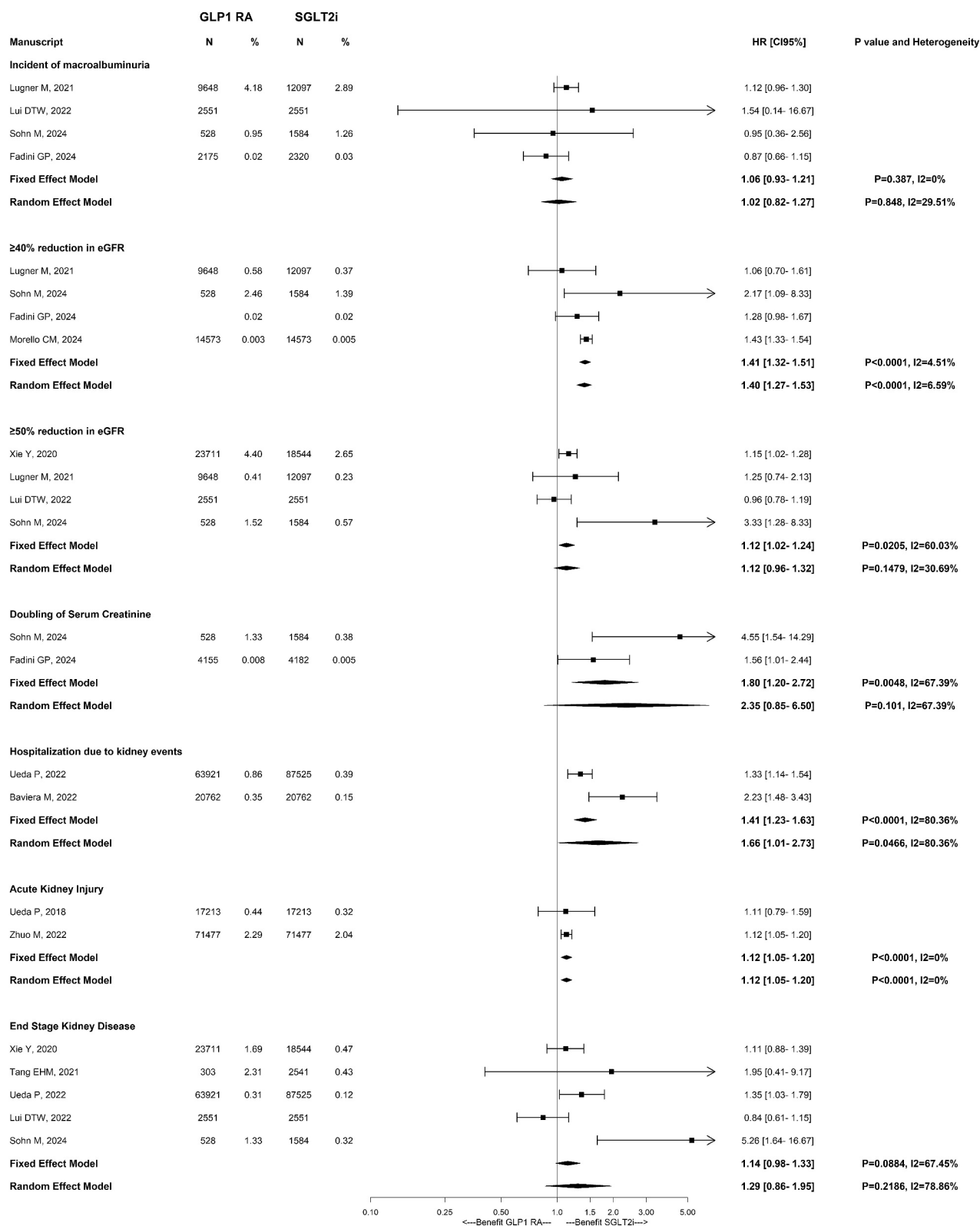


FIGURE 2 | Meta-analysis of kidney outcomes in patients with type 2 diabetes initiating GLP-1 RA versus SGLT2i in real-world studies. We assessed categorical kidney outcomes (new incident of macroalbuminuria, ≥ 40 or 50% reduction from baseline eGFR, doubling of serum creatinine, hospitalizations due to kidney events, AKI, and ESKD) among initiators of GLP-1 RA versus initiators of SGLT2i. Data were synthesised using inverse variance-weighted averages of logarithmic hazard ratios (HR)s in random- and fixed-effect models, presented as HR [95% CI] including p -value and studies heterogeneity (I^2). We selected random models as the main analysis because of the heterogeneity that is common when combining real-world studies. Four studies [14, 21, 22, 25] that assessed the risk of AKI and one study [31] that assessed the risk of ESKD were not synthesised in the meta-analysis due to an overlap between the datasets (see Table 2). AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; N, Population size; SGLT2i, sodium-glucose transporter 2 inhibitor.

TABLE 3 | Composite kidney outcomes in each study that compared patients with type 2 diabetes who initiated GLP-1 RA versus another glucose-lowering agent.

GLP-1 RA versus SGLT2i									
Manuscript	Composite outcome definition	GLP-1 RA			SGLT2i			HR [95% CI]	p value
		N	n	%	N	n	%		
Xie 2020 [13]	eGFR decline > 50%, ESKD, or ACM	23,711	1588	6.7	18,544	753	4.06	1.05 [0.96–1.15] ^a	NA
Lugner 2021 [15]	Micro/macrolbuminuria, eGFR ≥ 50% reduction or lower than < 60 mL/min per 1.73 m ² , dialysis, kidney transplantation, kidney failure, kidney death	9648	1864	19.32	12,097	1882	15.56	1.02 [0.95–1.09] ^b	0.5676
Ueda 2022 [17]	Kidney replacement therapy, hospitalisation for kidney events, and death from kidney causes	63,921	679	1.06	87,525	418	0.48	1.32 [1.15–1.52] ^c	NA
Lui 2022 [19]	Sustained ≥ 50% eGFR decline, ESKD, incident macroalbuminuria, and kidney-related mortality	2551	NA	NA	2551	NA	NA	1.12 [0.95–1.33]	0.157
Sohn 2024 [24]	Sustained ≥ 40%reduction in eGFR, progression to ESKD, new onset of macroalbuminuria, and kidney-related mortality	528	18	3.41	1584	42	2.65	1.59 [0.92–2.78]	0.097
Edmonston 2024 [26]	40% eGFR decline, incident ESKD, or ACM	47,268	28.80 ^d		35,004	26.89 ^d		1.08 [0.98–1.18]	0.141
Chan 2024 [29]	Dialysis, kidney transplantation, death from kidney causes, or hospitalisation for kidney events (AT analysis)	561.63	8.28	1.47	11,404.06	73.66	0.65	2.13 [1.04–4.35]	0.040
Morello 2024 [31]	Decline of ≥ 40% in eGFR, ESKD event, and ACM	14,573	6.9 ^d		344,160.23	641.16	0.19	1.89 [1.56–2.33]	< 0.001
Morello 2024 [31]	Decline of ≥ 40% in eGFR, ESKD event, and ACM (AT analysis)	12,896	7.2 ^d		14,573	10.7 ^d		1.54 [1.47–1.61] ^e	< 0.001
					12,071	4.6 ^d		1.52 [1.45–1.61] ^e	< 0.001
GLP-1 RA versus DPP4i									
Manuscript	Composite outcome definition	GLP-1 RA			DPP4i			HR [95% CI]	p value
		N	n	%	N	n	%		
Pasternak 2020 [32]	Kidney replacement therapy (dialysis or kidney transplantation), death from kidney causes, and hospitalisation for kidney events	38,731	570	1.47	38,731	722	1.86	0.76 [0.68–0.85]	NA
Xie 2020 [13]	eGFR decline > 50%, ESKD, or ACM	23,711	1588	6.7	39,399	2662	6.76	0.79 [0.74–0.85] ^a	NA
Xu 2022 [33]	Sustained doubling of serum creatinine, kidney failure (initiation of dialysis or transplantation or a sustained eGFR of < 15 mL/min per 1.73 m ²) or kidney death	5699 ^g	76	1.33	14,067 ^g	350	2.49	0.72 [0.53–0.98] ^f	NA
Lin 2023 [34]	Decline in eGFR> 50%, ESKD with dialysis, and cardiovascular death (AT analysis)	602	134	22.26	1479	393	26.57	0.75 [0.61–0.93] ^h	0.009
Zhang 2024 [35]	CKD progression: Doubling of serum creatinine or incident stage 5 CKD during follow up period	16,076	359	2.23	16,076	557	3.46	0.64 [0.56–0.73] ⁱ	< 0.001

(Continues)

TABLE 3 | (Continued)

GLP-1 RA versus DPP4i											
Manuscript	Composite outcome definition	GLP-1 RA			DPP4i			HR [95% CI]	p value		
		N	n	%	N	n	%				
Zhang 2024 [35]	CKD progression: Doubling of serum creatinine or incident stage 5 CKD during follow up period (AT analysis)	16,076	214	1.33	16,076	347	2.16	0.61 [0.52–0.73] ⁱ	< 0.001		
GLP-1 RA versus sulfonylureas											
Manuscript	Composite outcome definition	GLP-1 RA			Sulfonylureas			HR [95% CI]	p value		
		N	n	%	N	n	%				
Xie 2020 [13]	eGFR decline > 50%, ESKD, or ACM	23,711	1588	6.7	134,904	9609	7.12	0.72 [0.67–0.77] ^a	NA		
GLP-1 RA versus basal insulin											
Manuscript	Composite outcome definition	GLP-1 RA			Insulin			HR [95% CI]	p value		
		N	n	%	N	n	%				
Schechter 2023 [39]	Sustained ≥ 40% eGFR reduction or ESKD	3424	315	9.2	3424	316	9.23	0.96 [0.82–1.11]	0.566		
Schechter 2023 [39]	Sustained ≥ 40% eGFR reduction or ESKD (AT analysis)	3424	81	2.4	3424	113	3.3	0.71 [0.54–0.95]	0.020		
Peng 2023 [40]	Kidney insufficiency (eGFR < 15 mL/min/1.73 m ²), dialysis dependent ESKD, and kidney death	7279	79	1.09	7279	199	2.73	0.39 [0.30–0.51] ^j	NA		
Peng 2023 [40]	Kidney insufficiency (eGFR < 15 mL/min/1.73 m ²), dialysis dependent ESKD, and kidney death (AT analysis)	7279	35	0.48	7279	100	1.37	0.36 [0.25–0.53] ^j	NA		

Note: All analyses are presented with ITT definition except when specified otherwise.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IPTW, inverse probability treatments weighting; NA, not available; SGLT2i, sodium-glucose transporter two inhibitor.
^aAdjusted for generalised propensity score.
^bIPTW adjusted cox regressions.
^cThe adjustment used was not specified in the manuscript.
^dIncidence rate per 1000 patient-year.
^eAdjusting for baseline covariates.
^fThe IPTW was used to adjust.
^gN before IPTW, as presented in the original manuscript (Table 1 - Xu Y, et al. 2022).
^hPresented as HR/SHR (hazard ratio/subdistribution hazard ratio) [95% CI] of GLP-1 RA.
ⁱOdds ratio adjusted to propensity score.
^jSubdistribution hazard ratio (95% CI).

analysis ($N_{\text{GLP-1 RA}} = 91,014$, $N_{\text{SGLT2i}} = 112,745$; pool HR [95% CI] 1.29 [0.86–1.95]; Table 2, Figure 2, Supporting Information S1: Figure S1). One study [27] found a higher risk for dialysis or kidney transplant between GLP-1 RA initiators versus SGLT2i initiators across three subgroups of patients stratified by their frailty status (Table 2).

Two studies [24, 30] assessed the risk for $\geq 57\%$ eGFR decline; while each found an increased risk with GLP-1 RA versus SGLT2i initiators, these studies had high inter- and intra-study variability without evidence of between-group differences when pooling them (pool HR [95% CI] 2.35 [0.85–6.50]; Table 2 and Figure 2). There was no evidence for a difference in the risk of $\geq 50\%$ eGFR decline between the groups in four pooled studies [13, 15, 19, 24] ($N_{\text{GLP-1 RA}} = 36,438$, $N_{\text{SGLT2i}} = 34,776$; pool HR [95% CI] 1.12 [0.96–1.32], Table 2 and Figure 2). Pooling four studies [15, 24, 30, 31] we found an increased risk of $\geq 40\%$ decline in eGFR among initiators of GLP-1 RA versus SGLT2i (pool HR [95% CI] 1.40 [1.27–1.53], Table 2 and Figure 2). One study [15] analysed the risk of $\geq 30\%$ eGFR decline from baseline without a significant difference between the treatment groups (Table 2).

Pooling data of two studies demonstrated a higher risk for kidney-related hospitalisation with GLP-1 RA versus SGLT2i [17, 20] ($N_{\text{GLP-1 RA}} = 84,683$, $N_{\text{SGLT2i}} = 108,287$; pool HR [95% CI] 1.66 [1.01–2.73], Table 2 and Figure 2). Two studies [11, 18] found a higher risk of AKI with GLP-1 RA versus SGLT2i in an ITT follow-up approach ($N_{\text{GLP-1 RA}} = 88,690$, $N_{\text{SGLT2i}} = 88,690$; pool HR [95% CI] 1.12 [1.05–1.20]; Table 2 and Figure 2) and in AT analysis (Supporting Information S1: Table S4 and supplementary results).

One study [30] found a higher risk of worsening in the CKD class among GLP-1 RA initiators versus SGLT2i initiators (HR [95% CI] 1.09 [1.01–1.16]) without a significant difference between the treatment groups in the risk for new onset CKD (Table 2).

Pooling four studies [15, 19, 24, 30] that assessed the risk of incident of macroalbuminuria (UACR > 300 mg/g), we did not find evidence for a difference between initiators of GLP-1 RA versus SGLT2i (pool HR [95% CI] 1.02 [0.82–1.27]). One study [24] found that compared to SGLT2i, GLP-1 RA initiators were less likely to experience albuminuria improvement (0.64 [0.42–0.97]), with no difference found in albuminuria progression between groups (Table 2).

Six [16, 19, 23, 26, 30, 31] and two [30, 31] studies reported the change over time in eGFR and UACR, respectively, with GLP-1 RA versus SGLT2i initiators. The data are summarised in the Supporting Information S1: Table S5 and supplementary results.

Eight studies [13, 15, 17, 19, 24, 26, 29, 31] reported the risk of a composite kidney outcome; three [17, 29, 31] but not the others [13, 15, 19, 24, 26] found evidence for an increased risk with GLP-1 RA versus SGLT2i (Table 3).

3.3 | Initiation of GLP-1 RA Compared With DPP4i

Six studies [13, 22, 32–35] compared together 101,827 and 127,410 initiators of GLP-1 RA and DPP4i, respectively (Table 2 and Figure 3). Pooling two studies [13, 32], we found a lower risk for ESKD, with GLP-1 RA versus DPP4i ($N_{\text{GLP-1 RA}} = 62,442$, $N_{\text{DPP4i}} = 78,130$; pool HR [95% CI] 0.70 [0.63–0.78], Table 2 and Figure 3). One study [13] found a reduced risk for $\geq 50\%$ decline in eGFR among initiators of GLP-1 RA compared with DPP4i (HR [95% CI] 0.84 [0.76–0.92], Table 2). In another study [32], the risk of hospitalisation due to kidney events was lower with GLP-1 RA compared with DPP4i (HR [95% CI] 0.73 [0.65–0.83]; Table 2). The risk of AKI [22] and kidney-related death [32] were assessed by one study each, without evidence of a difference between the groups (Table 2). Another study [33] found a slower eGFR decline in initiators of GLP-1 RA versus DPP4i (mean between-groups difference 0.65 mL/min/1.73

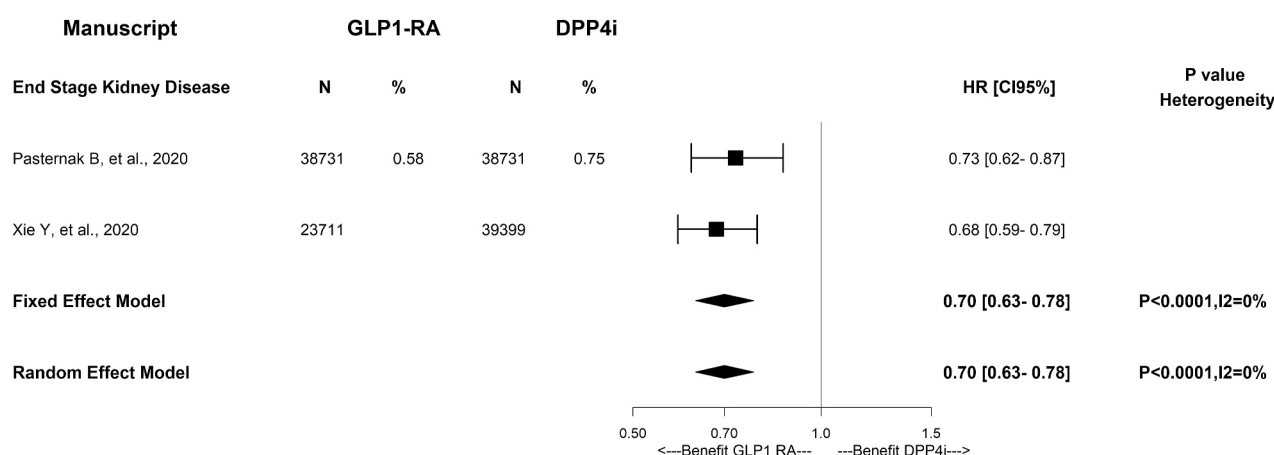


FIGURE 3 | Meta-analysis of kidney outcomes in patients with T2D initiating GLP-1 RA versus DPP4i in real-world studies. We assessed the risk for ESKD among initiators of GLP-1 RA versus initiators of DPP4i. Data were synthesised using inverse variance-weighted averages of logarithmic hazard ratios (HR)s in random- and fixed-effect models. Presented as HR [95% CI] including p -value and studies heterogeneity (I^2). We selected random models as the main analysis because of the heterogeneity that is common when combining real-world studies. CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; (N), Population size.

m2/year [95% CI 0.61–0.69]). One study [35] assessed the risks for albuminuria progression or albuminuria regression and did not find significant differences between GLP-1 RA and DPP4i initiators. Five studies [13, 32–35] separately found 21%–36% lower risk of composite kidney outcomes with GLP-1 RA compared with DPP4i (Table 3).

3.4 | Initiation of GLP-1 RA Compared With Sulfonylureas

One study [13] found a lower risk (HR [95% CI] 0.72 [0.67–0.77]) for a composite kidney outcome of > 50% eGFR decline, ESKD, or all-cause mortality, among 23,711 versus 134,904 initiators GLP-1 RA versus sulfonylureas, respectively. Similar findings were observed in each kidney component of this composite outcome (Table 2 and Table 3).

3.5 | Initiation of GLP-1 RA Compared With Basal Insulin

Five studies [36–40] compared together 19,457 and 21,465 patients who initiated GLP-1 RA and basal insulin, respectively (Table 2). One study [39], with a median follow-up of 7 years, found a lower risk for sustained categorical albuminuria progression (HR [95% CI] 0.89 [0.80–0.99] (Table 2)) among initiators of GLP-1 RA versus basal insulin. This study did not find evidence for a between-group difference in the risk of new macroalbuminuria, eGFR loss of $\geq 30\%$, $\geq 40\%$, $\geq 50\%$, or $\geq 57\%$ from baseline, new ESKD, or a composite outcome of $\geq 40\%$ eGFR loss or ESKD in ITT analysis (Table 2, Table 3). A shorter study [40] (mean follow-up 2.6 years) found a lower risk for ESKD

and kidney-related death among GLP-1 RA initiators versus basal insulin initiators (HR [95% CI] 0.29 [0.20–0.43], 0.28 [0.15–0.51], respectively, Tables 2 and 3). One study [38] did not find evidence for a difference in the risk of AKI between initiators of GLP-1 RA compared with basal insulin (Table 2). Another study [36] did not find a difference in the continuous change in UACR after 1 year of treatment with GLP-1 RA versus basal insulin. One study [39], but not two others [36, 37], found that the eGFR decline with GLP-1 RA was smaller compared to basal insulin until 30 months from treatment initiation, but not later.

4 | Discussion

Thirty-one manuscripts comprising 1,601,389 patients with T2D reported real-world kidney outcome data in initiators of GLP-1 RA versus other classes of GLAs (Figure 4). Most data originated from studies comparing GLP-1 RA versus SGLT2i, where initiating GLP-1 RA was associated with an increased risk of $\geq 40\%$ reduction in eGFR, kidney-related hospitalizations, AKI, and CKD class worsening, but not in end-stage kidney disease (ESKD). Compared with DPP4i and sulfonylureas, initiating GLP-1 RA was associated with reduced risk of ESKD, among other kidney outcomes. Compared with basal insulin, GLP-1 RA was associated with a lower risk of albuminuria progression and death due to kidney causes, with inconsistent data regarding benefits in reducing ESKD risk. The limited amount of granular high-quality data demands further research (Figure 4).

A meta-analysis of cardiovascular outcome trials (CVOTs) found that compared with a placebo, GLP-1 RA reduce the risk of cardiovascular outcomes, mortality, and the risk of

		Outcome												
		Macro-albuminuria	UACR/ albuminuria progression	Albuminuria regression	% reduction in eGFR				New onset CKD	CKD class worsening	Hospitalization for kidney events	AKI	ESKD	Death due to kidney causes
					≥30	≥40	≥50	≥57						
Comparator	SGLT2i	1.02 [0.82 – 1.27] (4 studies)	0.91 [0.50 – 1.67]	0.64 [0.42 – 0.97]	1.09 [0.80 – 1.47]	1.40 [1.27–1.53] (4 studies)	1.12 [0.96 – 1.32] (4 studies)	2.35 [0.85 – 6.50] (2 studies)	1.16 [0.99 – 1.37]	1.09 [1.01 – 1.16]	1.66 [1.01 – 2.73] (2 studies)	1.12 [1.05 – 1.20] (2 studies)	1.29 [0.86 – 1.95] (5 studies)	1.33 [0.74 – 2.44]
	DPP4i		0.95 [0.89 – 1.02] †	1.10 [0.99 – 1.12] †			0.84 [0.76 – 0.92]	‡			0.73 [0.65 – 0.83]	0.98 [0.82 – 1.18]	0.70 [0.63 – 0.78] (2 studies)	0.72 [0.48 – 1.10]
	Sulfonylureas						0.76 [0.69 – 0.83]						0.72 [0.62 – 0.84]	
	Insulin	0.95 [0.78 – 1.16]	0.89 [0.80 – 0.99]		0.98 [0.87 – 1.11]	0.96 [0.82 – 1.12]	1.11 [0.91 – 1.37]	1.04 [0.80 – 1.34]					0.82 [0.52 – 1.28]	0.92 [0.64 – 1.32] 0.29 [0.20 – 0.43]

† Odds Ratio

‡ No HR available, numbers of events are shown in Table 2.

	GLP-1 RA advantage
	Comparator advantage
	No significant difference
	No data available

FIGURE 4 | Kidney outcomes among patients with type 2 diabetes who initiated GLP-1 RA versus other GLAs in real-world studies. The colour represents the advantage/disadvantage of GLP-1 RA versus the comparator: green, GLP-1 RA advantage; red, comparator advantage; yellow-no significant difference; grey, unavailable data. A hazard ratio (HR) with a 95% confidence interval is presented when available. Some data represent pooled HR from this meta-analysis, while others correspond to individual studies, as noted. AKI, acute kidney injury; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SGLT2i, sodium-glucose transporter two inhibitors; UACR, urinary albumin to creatinine ratio.

composite kidney outcomes that included incident macroalbuminuria, in patients with T2D and high cardiovascular risk [41]. The FLOW trial (NCT03819153) further demonstrated that semaglutide reduced the risk of major kidney disease events or cardiovascular death and mitigated eGFR slope in people with T2D and CKD with albuminuria [5]. The current systematic review and meta-analysis adds new insight into the kidney effects of GLP-1 RA in people with T2D. The RCTs' settings include high-quality, strict follow-up conditions by multidisciplinary teams of healthcare experts that often cannot be achieved in the real world. Furthermore, real-world populations are more diverse than those recruited to RCTs and often include populations with lower baseline kidney and cardiovascular risks. For example, the FLOW trial included only patients with eGFR of 50–75 mL/min/1.73 m² and a UACR > 300–< 5000 mg/g, or an eGFR of 25–< 50 mL/min/1.73 m² with a UACR > 100–< 5000 mg/g [5]. Finally, all completed CVOTs with GLP-1 RA used a placebo comparator, while real-world studies often utilise active comparators, enabling a more pragmatic view. Thus, while RCTs provide a higher level of proof, real-world data provide complementary and required evidence [42].

In CVOTs, DPP4i was found to be generally neutral concerning cardiovascular and kidney outcomes compared with placebo [43–46] or sulfonylurea [47], except for one study showing a reduction in albuminuria [43]. Both GLP-1 RA and DPP4i target the incretin system and are not used together, supporting the comparison between these two classes of medications. Although only six studies were available, GLP-1 RAs were superior to DPP4i in several kidney-related outcomes, including the risk of $\geq 50\%$ eGFR decline or the risk of ESKD.

While most available glucose-lowering agents are used orally, GLP-1 RAs tested so far in real-world studies were mostly injectable, increasing the likelihood of selection bias, and making injectable basal insulin a reasonable comparator. In the AWARD-7 trial, once-weekly dulaglutide was not inferior to basal insulin in achieving glycaemic control and was associated with mitigation of eGFR loss in patients with T2D and CKD [48, 49]. We found that GLP-1 RAs were superior to basal insulin with respect to albuminuria progression and death due to kidney causes, with inconsistent data regarding possible benefits in preventing ESKD [39, 40]. One [39] study found that in patients with T2D, most of them with preserved kidney function, GLP-1 RA initiation, compared with basal insulin, was associated with lower risk of adverse kidney outcomes and eGFR loss in patients on active treatment (as-treated analysis) but less so in the intention-to-treat analysis. These findings support the hypothesis that patients' adherence to treatment may explain, at least partially, the differences between the results of AWARD-7 trial and real-world data.

In RCTs that included patients with T2D, SGLT2i consistently and robustly reduced the risk of CKD progression and AKI by estimates of 38% and 21%, respectively [50]. These beneficial effects were further supported by real-world evidence comparing SGLT2i with other GLAs [51, 52]. We found that compared with SGLT2i, initiation of GLP-1 RA was associated with increased risk for $\geq 40\%$ eGFR decline, hospitalizations due to kidney events, AKI, and CKD class worsening. These

findings can be explained by the robust kidney protective effects of SGLT2i [4, 5]. There was not sufficient evidence of a difference between GLP-1 RA and SGLT2i in the risk of $\geq 50\%$ eGFR decline or the risk of ESKD, supporting the hypothesis that the magnitude of kidney protection by SGLT2i versus GLP-1 RA is smaller than the effects observed compared to a placebo comparator.

The 2024 American Diabetes Association (ADA) guidelines recommended using GLP-1 RA in patients with T2D and CKD who have not achieved individualised glycaemic targets despite using metformin and SGLT2i or cannot use SGLT2i [3, 53]. Following the cardiovascular and kidney benefits of semaglutide observed in the FLOW trial, the 2025 guidelines noted that semaglutide can also be used as a first-line agent for people with T2D and CKD [54]. Relying on accumulating data that adding GLP-1 RA to SGLT2i may offer additional kidney and cardiovascular benefits [55, 56], several guidelines now recommend using both disease/diabetes-modifying drugs (DMDs) together in many groups of patients with type 2 diabetes [56–58]. No randomized controlled kidney outcome trial has directly compared kidney outcomes between GLP-1 RA versus SGLT2i; thus, it is not clear which one is more beneficial, especially in low-resource settings where patients may not have simultaneous access to both DMDs. This systematic review and meta-analysis indicated that GLP-1 RAs appeared to be associated with lower kidney risk compared to other glucose-lowering agents but were inferior or not superior compared with SGLT2i. However, in addition to kidney protection, GLP-1 RAs have additional benefits such as lowering blood glucose, body weight, blood pressure, and risk of atherosclerotic cardiovascular disease [41, 59]. The differential mechanisms of action, clinical benefits, and side effects of GLP-1 RAs and SGLT2i, should be taken into consideration in the treatment choice to allow personalised tailoring of treatment.

This study has several limitations. A limited number of studies have reported kidney outcomes following initiation of GLP-1 RA compared to a single class of GLAs in real-world. We excluded studies that compared GLP-1 RA against cohorts that combined several classes of GLAs due to the large heterogeneity in kidney outcomes among the GLAs' classes, as observed in our analysis. Real-world data are limited by selection bias, as physicians aim to tailor treatment to patients' characteristics and preferences. Partially addressing these limitations, we included only studies that applied a statistical approach to balance the cohorts (e.g., inverse probability treatment weighting or propensity score), although no statistical method can completely emulate randomisation. Additional challenges in real-world studies include variable duration of follow-up, study populations, frequency of laboratory measurements, and baseline medications, among others.

5 | Conclusion

A meta-analysis of data collected in real-world settings suggests that treatment with GLP-1 RA is associated with improved kidney outcomes compared with DPP4i, sulfonylureas, and basal insulin, and worse kidney outcomes compared with SGLT2i.

Author Contributions

M.S. and O.M. conceived the idea. A.F., A.R., M.S., D.R.S.S., I.Y. and O.M. developed the protocol and were responsible for the study design. A.F. and O.M. performed the systematic literature search and extracted data. A.R. and I.Y. performed the data analysis. AF and OM wrote the first draft, and A.R., M.S., D.R.S.S., G.A.H., G.L. and I.Y. revised the article for important intellectual content. All authors participated in critically reviewing the final manuscript and have approved the final version.

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Conflicts of Interest

A.F. and D.R.S. have no conflict of interest to declare. I.Y. and A.R. received hourly payments from AstraZeneca through Hadassah Medical Centre and from Novo Nordisk. M.S. reports travel support from Novo Nordisk and AstraZeneca through Hadassah Medical Centre and lecturing fees from AstraZeneca (2022). O.M. reports Advisory Board membership for Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp and Dohme, Boehringer Ingelheim, AstraZeneca and BOL Pharma, research grant support through Hadassah Hebrew University Hospital from Novo Nordisk and AstraZeneca, and Speaker's Bureau participation for AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp and Dohme, and Boehringer Ingelheim. From May 1st, 2023, Ofri Mosenzon has been an employee of Regeneron Pharmaceuticals Inc. G.A.H. reported previous Advisory Board: Sanofi and Eli Lilly. She is a current PI in several RCTs conducted by Novo Nordisk, Eli Lilly, Sanofi, AstraZeneca and Bayer, including the Confidence study, through Hadassah Medical Centre. G.A.H. reports travel support from Novo Nordisk and Medtronic through Hadassah Medical Centre and AstraZeneca through Sheba medical centre. Speakers Bureau: AstraZeneca, Novo Nordisk, Eli Lilly and Sanofi. G.L. reports participation in previous Advisory Boards: Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp and Dohme, Boehringer Ingelheim, AstraZeneca and Medtronic. He reports travel support from Novo Nordisk, Boehringer Ingelheim and AstraZeneca through Hadassah Medical Centre. Speakers Bureau: AstraZeneca, Novo Nordisk, Eli Lilly, Boehringer Ingelheim.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.70066>.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.