

Renal Outcomes of GLP-1 Receptor Agonists and Tirzepatide Across CKD Stages and Metabolic Phenotypes (Type 2 Diabetes and/or Overweight/Obesity): A scoping review

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Supplementary material

Supplementary Table 1. Search strategy

Source	Strategy	Results	Date
MEDLINE (Pubmed)	("Glucagon-Like Peptide 1 Receptor Agonists"[Mesh] OR "glucagon-like peptide 1 receptor agonist*" [tiab] OR "GLP-1 receptor agonist*" [tiab] OR GLP1RA* [tiab] OR GLP-1RA* [tiab] OR tirzepatide [tiab] OR mounjaro [tiab] OR zepbound [tiab] OR ("GIP" [tiab] AND ("GLP-1" [tiab] OR "glucagon-like peptide-1" [tiab])) AND (agonist* [tiab] OR co-agonist* [tiab] OR dual [tiab])) AND ("Kidney Diseases" [Mesh] OR "Renal Insufficiency, Chronic" [Mesh] OR "Diabetic Nephropathies" [Mesh] OR "Acute Kidney Injury" [Mesh] OR "Proteinuria" [Mesh] OR "Albuminuria" [Mesh] OR "Glomerular Filtration Rate" [Mesh]) AND ("Diabetes Mellitus, Type 2" [Mesh] OR "type 2 diabet*" [tiab] OR T2D [tiab] OR obesity [tiab] OR obese [tiab] OR "Chronic Kidney Disease" [tiab] OR CKD [tiab])	566	October/2025
EMBASE	1. exp glucagon like peptide 1 receptor agonist/ 2. (glucagon-like peptide 1 receptor agonist* or "GLP-1 receptor agonist*" or glp1ra* or glp-1ra*).ti. 3. exp tirzepatide/ 4. (tirzepatide or mounjaro or zepbound).ti. 5. ((GIP adj3 (GLP-1 or "glucagon-like peptide-1")) adj3 (agonist* or co-agonist* or dual)).ti. 6. 1 or 2 or 3 or 4 or 5 7. exp kidney disease/ 8. exp chronic kidney disease/ 9. exp diabetic nephropathy/ 10. exp acute kidney injury/ 11. exp proteinuria/ 12. exp albuminuria/ 13. exp glomerular filtration rate/ 14. 7 or 8 or 9 or 10 or 11 or 12 or 13 15. exp type 2 diabetes mellitus/ 16. diabet*.ti. 17. T2D.tikw. 18. exp obesity/ 19. obese.ti. or overweight.ti. 20. exp chronic kidney disease/ 21. CKD.ti. 22. 15 or 16 or 17 or 18 or 19 or 20 or 21	25	October/2025

	23. 6 and 14 and 22		
Cochrane	#1 MeSH descriptor: [Glucagon-Like Peptide 1 Receptor Agonists] explode all trees #2 (glucagon-like peptide 1 receptor agonist* OR "GLP-1 receptor agonist*" OR glp1ra* OR glp-1ra*):ti,ab,kw #3 MeSH descriptor: [Tirzepatide] explode all trees #4 (tirzepatide OR mounjaro OR zepbound):ti,ab,kw #5 (GIP NEAR/3 (GLP-1 OR "glucagon-like peptide-1") NEAR/3 (agonist* OR co-agonist* OR dual)):ti,ab,kw #6 #1 OR #2 OR #3 OR #4 OR #5 #7 MeSH descriptor: [Kidney Diseases] explode all trees #8 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees #9 MeSH descriptor: [Diabetic Nephropathies] explode all trees #10 MeSH descriptor: [Acute Kidney Injury] explode all trees #11 MeSH descriptor: [Proteinuria] explode all trees #12 MeSH descriptor: [Albuminuria] explode all trees #13 MeSH descriptor: [Glomerular Filtration Rate] explode all trees #14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 #15 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees #16 (type 2 diabet* OR T2D OR obesity OR obese OR "Chronic Kidney Disease" OR CKD):ti,ab,kw #17 #15 OR #16 #18 #6 AND #14 AND #17	16	October/2025

Supplementary Table 2. Studies characteristics

Study (year)	Design / N	Population	Intervention (dose/duration)	Comparator	Baseline eGFR (mL/min/1.73 m ²)	Renal outcomes (HR [95% CI])
McGuire et al (14)	Double-blind, multicenter RCT; n = 9,650 (33 countries)	T2D ≥50 years with ASCVD or CKD (eGFR <60); BMI 31; HbA1c 8%; 29% women	Oral semaglutide 14 mg qd (titration 3→7→14 mg) × 47.5 months	Placebo + standard care (SGLT2i 26.9%, RAS >80%)	74 ± 22.6	Major renal events HR 0.91 (0.80–1.05), NS
Colhoun et al (18)	Double-blind, placebo-controlled RCT; n = 17,604 (8,803 semaglutide, 8,801 placebo)	Adults ≥45 y with overweight/obesity (BMI ≥ 27 kg/m ²) and established cardiovascular disease, without diabetes; median follow-up 182 weeks	Semaglutide 2.4 mg s.c. weekly (dose escalation to 2.4 mg) × median 3.5 years	Placebo + standard care (ACEi/ARB ~75%)	Mean baseline eGFR ≈ 74 mL/min/1.73 m ² ; 22% had eGFR < 60 mL/min/1.73 m ² or UACR ≥ 30 mg/g	Composite kidney endpoint (death from kidney disease, chronic kidney replacement therapy, eGFR < 15, ≥50% decline in eGFR, or new macroalbuminuria): HR 0.78 (0.63–0.96); P = 0.02. On-treatment HR: 0.75 (0.59–0.94). eGFR change at 104 wks = +0.75 (0.43–1.06); subgroup eGFR < 60 = +2.19 (1.00–3.38); P < 0.001. UACR change –10.7% (–13.2, –8.2); P < 0.001. By UACR ≥ 30–<300 mg/g: –27.2% (–35.3, –18.1); P < 0.001.
Vernstrøm et al (15)	RCT (partly open / partly double-blind), 4 arms, 32 weeks, n=80 (of 120 total)	T2D with high CV risk or mild–moderate CKD (eGFR 81–91); mean age 68; 75–85% men; BMI 32; HbA1c 7.5%	1) Semaglutide s.c. 1 mg/week 16 wk + placebo 16 wk; 2) Empagliflozin 10 mg/day 32 wk; 3) Semaglutide +	Oral placebo or empagliflozin tablet according to group	81–91 (mean ≈87)	No significant change in measured GFR or UACR vs placebo; total kidney volume (TKV) decreased –3% (95% CI –5%, –0.3%; p=0.04); TKV reduction

			empagliflozin; 4) Placebo			correlated with decreases in GFR, UACR, and HbA1c
Long et al (17)	Retrospective cohort (EMR), CKD G4–G5/dialysis; n=76	Age 66.8±11.5; 54% men; T2D 96%; BMI 36.2±7.5; 63 CKD G4, 1 G5, 12 on dialysis	Semaglutide (s.c. 0.25→1 mg/week; or oral 3→14 mg/day); median 17.4 months	No active control group (pre–post comparison)	CKD G4: eGFR 24.5±4.8	eGFR (G4) 24.8→24.7 (NS); UACR –301 mg/g (NS); 4/63 started dialysis during follow-up
Perkovic et al (13)	Event-driven, double-blind, multicenter RCT; n=3,533; median 3.4 years	T2D + high-risk CKD: eGFR 25–75 + UACR >300 (if eGFR ≥50) or >100 (if eGFR 25–<50); stable RAS dose	Semaglutide 1.0 mg s.c. weekly (titration 0.25→0.5→1.0 over 8 weeks)	Placebo + standard care (RAS; SGLT2i and finerenone allowed)	eGFR 47.0±15.2; median UACR 568 mg/g; A3 68.5%; SGLT2i use 15.6%	Primary (major kidney disease events): kidney failure (RRT/transplant/sustained eGFR <15), ≥50% sustained eGFR decline, or renal/CV death → HR 0.76 (0.66–0.88), p=0.0003. Kidney component: HR 0.79 (0.66–0.94). eGFR slope difference +1.16 mL/min/1.73 m ² /year favoring semaglutide
Marso et al (4)	Double-blind, placebo-controlled CV outcomes RCT; n = 3,297; median follow-up 104 weeks	Adults with T2D ≥50 y and established cardiovascular disease (83%) or ≥60 y with ≥1 CV risk factor; HbA1c 8.7%; mean BMI 33 kg/m ² ; 72% on RAS blockade	Semaglutide s.c. 0.5 mg or 1.0 mg once weekly × 104 weeks	Placebo + standard care	Mean baseline eGFR ≈ 80 (range 30–>90); 24% had CKD stage ≥3	Prespecified secondary renal composite (“new or worsening nephropathy”: persistent macroalbuminuria, doubling of serum creatinine, need for chronic renal replacement therapy, or renal death): HR 0.64 (0.46–0.88); p = 0.005. Driven mainly by ↓ new-onset persistent macroalbuminuria (HR 0.54 [0.37–0.77]). No

						adverse effect on eGFR trajectory; consistent benefit across subgroups.
García de Lucas et al (16)	Multicenter ambispective observational; 9 hospitals in Spain; n=486 (296 without CKD; 190 with CKD [KDIGO moderate/high/very high]); 12 months	Adults with T2D; mean age 58 (no CKD) vs 67 (CKD); BMI ~36; greater CV burden and insulin use in CKD	Semaglutide s.c. 1 mg/week (clinical titration; switching from other GLP-1RAs allowed); follow-up at 6 and 12 months	No parallel control group; comparison between no CKD vs CKD and KDIGO subgroups	No CKD: eGFR 90 (81–98), UACR 6 mg/g; CK	
Apperloo et al (19)	Randomized double-blind placebo-controlled trial; n=101	Adults ≥18 y, overweight/obesity (BMI ≥27), CKD without diabetes; eGFR ≥25; UACR 30–3500 mg/g	Semaglutide 2.4 mg SC weekly × 24 weeks (titrated 0.25→0.5→1.0→1.7→2.4 mg)	Placebo + standard of care (86% RASi; 19% SGLT2i)	65 ± 25 mL/min/1.73 m ²	UACR ↓52.1% vs placebo (95% CI –65.2 to –34.1; p<0.0001); no difference in eGFR (Δ –1.1 mL/min/1.73 m ² , p=0.57); no change in cystatin-C eGFR; mGFR difference –1.9 (NS)
Oe et al (24)	Prospective, two-arm observational study (single-center); 6 months; n=55 enrolled, 48 analyzed (PPS: TZP n=23, Dula n=25)	Adults with T2D + CKD (eGFR ≤60), pretreated ≥3 months with dulaglutide 0.75 mg/week; mean age ~72–73; mainly G3a–G3b, A2–A3; increased visceral obesity	Switch to tirzepatide 2.5→5.0 mg/week	Continue dulaglutide 0.75 mg/week	eGFR _{cr} 43.5±10.6 (TZP) vs 42.6±12.1 (Dula); median UACR 279 vs 142 mg/g (NS)	eGFR: stable over 6 months; UACR: no change in TZP (median –3.5 mg/g), significant increase in Dula (+76.5 mg/g); between-group difference p<0.05
Packer et al (23)	Double-blind RCT; n=731; median 104 weeks	HFpEF (LVEF ≥50%) + obesity (BMI ≥30); CKD-enriched population; subgroups	Tirzepatide s.c. weekly, titrated 2.5→15 mg (maximum tolerated)	Placebo + standard therapy	Baseline eGFR-creat 64.4±22.4; eGFR-cys 55.3±22.4 (≈9 mL/min/1.73 m ² lower);	eGFR: initial 12-week dip with eGFR-creat (–3.0 mL/min/1.73 m ²), but improvement at 52 weeks

		by eGFR-cys <60 vs ≥60			CKD by eGFR-cys in 61%; higher UACR in CKD	vs placebo (+1.9 creat; +2.9 cys). UACR: –25% at 24 weeks and –15% at 52 weeks (p≈0.051); similar effect in CKD and non-CKD
Apperloo (22)	Post hoc analysis using individual data from 5 RCTs (duration 40/42 weeks)	Adults with T2D; majority with normal eGFR; subgroups with UACR ≥30 mg/g and/or eGFR <60; RASi use ~65–71%, SGLT2i 14–18%	Tirzepatide 5/10/15 mg s.c. weekly	Comparators: placebo (SURPASS-1,-5), semaglutide 1 mg (SURPASS-2), insulin degludec (SURPASS-3), insulin glargine (SURPASS-4)	Mean eGFR ~90–96 mL/min/1.73 m ² ; median UACR 11–12 mg/g (macroalbuminuria 5–7%)	UACR at week 40/42: vs comparators –19.3% (5 mg), –22.0% (10 mg), –26.3% (15 mg); in UACR ≥30 mg/g subgroup: –31.3%, –42.2%, –47.3%; eGFR: no overall difference at 40/42 weeks; mediation of UACR effect by HbA1c/weight ≈46%
Karakasis et al (25)	Meta-analysis of RCTs with follow-up ~40–52 weeks; total N=9,533	Adults with T2D, mostly with preserved eGFR; subgroups with UACR ≥30 mg/g and eGFR <60	Tirzepatide 5/10/15 mg s.c. weekly	Placebo / semaglutide 1 mg / insulin (per individual trial)	High mean eGFR (predominantly non-CKD population); low median UACR with albuminuric subgroups	Significant UACR reduction vs comparators; greater effect in UACR ≥30 mg/g subgroup. eGFR stable short-term (~40–52 weeks); no renal safety signal (exact values in article)
Heerspink et al (20)	Post hoc analysis of open-label, active-controlled RCT; n=1,995 (TZP n=995 vs n=1,000 iGlar); 52 weeks	T2D with high CV risk; BMI 32.6; HbA1c 8.5%; RAS use 80%, SGLT2i 25%	Tirzepatide 5/10/15 mg s.c. weekly (pooled dose analysis)	Titrated insulin glargine	eGFR-creat 81 vs 81.5 mL/min/1.73 m ² ; eGFR-cys 72.9 vs 73.5; median UACR 15.9 vs 14.0 mg/g; albuminuria ≥30 mg/g: 36%	Change at 52 weeks: eGFR-creat –2.5 vs –3.9 → Δ +1.4 (95% CI 0.3–2.4); eGFR-cys –3.5 vs –5.3 → Δ +1.8 (0.8–2.8); combined creat+cys Δ +1.8 (0.8–2.7). Effect consistent across subgroups (age, HbA1c, SGLT2i, weight, albuminuria, eGFR). No correlation between eGFR

						change and weight; weak correlation with HbA1c (r≈0.14)
Heerspink et al (21)	Open-label, active-controlled RCT; renal post-hoc analysis; n=1,995 (TZP n=995, iGlar n=1,000); up to 104 weeks (median 85 weeks)	T2D with high CV risk across 14 countries; HbA1c 7.5–10.5%; BMI ≥25; on metformin/SU/±SGLT2i	Tirzepatide 5/10/15 mg s.c. weekly (titration 2.5→target dose)	Insulin glargine U100 daily titrated to FPG <100 mg/dL	Mean eGFR 81.3 mL/min/1.73 m ² ; median UACR 15 mg/g; RAS 81%, SGLT2i 25%	eGFR slope –1.4 vs –3.6 mL/min/1.73 m ² /year → Δ +2.2 (95% CI 1.6–2.8); greater benefit if eGFR <60 (Δ +3.7 [2.4–5.1]). UACR % change: –6.8% vs +36.9% → Δ –31.9% (–37.7 to –25.7). Renal composite (≥40% ↓eGFR, ESKD, renal death or new macroalbuminuria): HR 0.58 (0.43–0.80)
Tsuchida et al (30)	Retrospective observational study with inverse probability weighting (IPW) by propensity score; CoDiC–JDDM database; n=255 (Dula n=125 vs n=130 non-Dula); 3 years	T2D + CKD G3–G4 (eGFR 15–59); Japan; mean age ~70 years; HbA1c 8.4–8.5%; concomitant RAS and SGLT2i use ~40%	Dulaglutide 0.75 mg s.c. weekly ≥6 months, with no prescription changes during the first 6 months	No dulaglutide (standard care without GLP-1RA), no prescription changes during first 6 months	eGFR 47.9 vs 47.7; UACR 218 vs 251 mg/g; stages: G3a 66%, G3b 27%, G4 6%	eGFR slope (primary, 3 years): Dula +0.11 (–0.34, 0.56) vs no-Dula –1.29 (–1.64, –0.94) mL/min/1.73 m ² /year → Δ +1.40 (0.83, 1.97); greater effect in macroalbuminuria and with SGLT2i; UACR: no sustained change
Tuttle et al (27)	Multicenter open-label RCT (dose-blinded for Dula); exploratory event analysis at 52 weeks; total AWARD-7 n=576 (Dula 1.5 mg n=192;	T2D + CKD G3–G4 (eGFR 15–<60); all on RAS if tolerated; HbA1c 7.5–10.5%	Weekly dulaglutide 0.75 or 1.5 mg + prandial insulin lispro	Daily insulin glargine + prandial insulin lispro	Mean eGFR (creatinine) ~34–44 depending on subgroup; macroalbuminuria median UACR ~1,043–1,372 mg/g	Composite: ≥40% decline in eGFR (creat), ESKD or renal death. Dula 1.5 mg vs iGlar: HR 0.45 (0.20–0.97); event rate 5% vs 11%. In macroalbuminuria: HR 0.25 (0.10–0.68); 7% vs

	Dula 0.75 mg n=190; iGlar n=194)					22%. No renal deaths. Similar results with cystatin-C eGFR.
Gerstein et al (26)	Double-blind multicenter RCT; n=9,901; median 5.4 years	T2D ≥50 years with prior CVD or risk factors; mean eGFR 76.9; albuminuria 35%	Dulaglutide 1.5 mg s.c. weekly	Placebo + standard care (RAS ~81%; SGLT2i very low)	eGFR 76.9±22.7; median UACR 1.80 mg/mmol; eGFR <60: 22%	Renal composite (new macroalbuminuria, ≥30% sustained ↓eGFR, RRT): HR 0.85 (0.77–0.93), p=0.0004. Components: macroalbuminuria HR 0.77 (0.68–0.87); ≥30% ↓eGFR HR 0.89 (0.78–1.01); RRT HR 0.75 (0.39–1.44). Sensitivity: ≥40% ↓eGFR HR 0.70; ≥50% HR 0.56. UACR: proportional LSM ratio 0.82 (0.78–0.86) (≈–18%). eGFR: mean difference +0.42 (NS).
Tuttle et al (28)	Multicenter open-label RCT (dose-blinded for Dula); 99 sites/9 countries; n=577 (Dula1.5 n=193; Dula0.75 n=190; iGlar n=194); 52 weeks	T2D + CKD G3–G4; HbA1c 7.5–10.5%; all on maximally tolerated RAS; basal-bolus insulin with lispro	Dulaglutide s.c. weekly 1.5 or 0.75 mg + prandial insulin lispro	Basal daily insulin glargine + prandial insulin lispro, titrated per protocol	eGFR CKD-EPI (creat) ~38; eGFR (cysC) ~37; median UACR ~214–234 mg/g; macroalbuminuria 44–46%	eGFR at 52 weeks higher with Dula vs iGlar (cysC 34.0 and 33.8 vs 31.3; p=0.005 and 0.009). eGFR decline smaller with Dula (creat and cysC). UACR decreased within groups; no global difference vs iGlar; in macroalbuminuria: Dula1.5 –43% (26 wk) and –29% (52 wk) vs iGlar (p=0.008 and 0.020). ESKD 4–8% (NS).

Tuttle et al (29)	Post hoc integrated analysis of 9 RCTs (6 with renal outcomes); total N=6,005; duration 26–104 weeks	Adults with T2D; eGFR <60 in 4.4%; macroalbuminuria 3%; RAS use ~68–70% in placebo groups; central laboratory	Dulaglutide s.c. weekly 0.75/1.5 mg	Placebo, active comparators (exenatide bid, metformin, sitagliptin, insulin glargine)	Mean eGFR ~86–90; low median UACR (mostly non-CKD population)	eGFR: no difference vs placebo, active comparators, or glargine at 26–104 weeks ($p \geq 0.075$). UACR: lower with Dula vs placebo/actives/glargine at 26 weeks ($p=0.023$; 0.013; 0.029). $\geq 40\%$ eGFR decline: fewer with Dula vs glargine (0.26% vs 1.25%; $p=0.012$).
von Scholten et al (32)	Double-blind, placebo-controlled, cross-over RCT; 12 weeks per period + 4-week washout; n=32 randomized, 27 completed	T2D with persistent albuminuria (UACR ≥ 30 mg/g), eGFR ≥ 30 ; stable RAS therapy	Liraglutide 0.6→1.2→1.8 mg/day s.c. (titration over 2 weeks; maintenance 10 weeks)	Placebo	After placebo: geometric mean UAER 199 mg/24 h (IQR 81–531); mGFR 75 mL/min/1.73 m ² ; 24-h BP 145/80 mmHg; HbA1c 61 mmol/mol	Primary (24-h UAER): –32% vs placebo (95% CI 7–50; $p=0.017$). mGFR: Δ –5 (95% CI –11; 2) mL/min/1.73 m ² (NS). 24-h SBP: Δ –5 mmHg (95% CI –10; 0; $p=0.07$). Multivariate: change in UAER correlated with 24-h SBP ($p=0.025$), not with HbA1c/weight/mGFR. Regression of albuminuria category observed in some participants.
von Scholten et al (33)	Open-label, single-center, before–after trial; n=35 (31 completed); 7 weeks + 21-day washout	Adults with T2D and hypertension (eGFR >60); 87% on RAS blockade; mean age 64 $\pm$ 7 years; 26% women	Liraglutide (0.6→1.2→1.8 mg/day s.c.), weekly titration for 7 weeks	No comparator (within-subject control)	mGFR 99.5, eGFR 89.7 mL/min/1.73 m ² , UAER 32.7 mg/day (42% micro/macroalbuminuria)	UAER –30% ($p=0.003$); FEalb –29% ($p=0.032$); mGFR –11 mL/min/1.73 m ² ($p<0.001$, reversible after washout); eGFR followed parallel trend.

Marso (31)	Multicenter, double-blind RCT; 410 sites/32 countries; n=9,340; median 3.8 years	T2D with high CV risk; age ≥50 with established CVD/CKD3–5/HF or ≥60 with ≥1 risk factor (e.g., microalbuminuria or HTN+LVH)	Liraglutide 1.8 mg/day s.c. (or maximum tolerated dose)	Placebo + standard care	Stratified by eGFR <30 vs ≥30; CKD ≥G3 in 24.7% at baseline	Nephropathy (pre-specified composite): new macroalbuminuria, doubling of serum creatinine + eGFR ≤45, need for RRT, or renal death → HR 0.78 (0.67–0.92); benefit driven by macroalbuminuria reduction.
Davies et al (32)	Double-blind, randomized, placebo-controlled trial; n = 279; 26 weeks	Adults with T2D and moderate CKD (eGFR 30–59); CKD G3a–G3b; older cohort; ~55% on insulin at baseline (stage 3B ≈43%)	Liraglutide 1.8 mg s.c. qd, uptitrated from 0.6 → 1.2 → 1.8 mg weekly over the first weeks; total treatment 26 weeks	Placebo + stable background glucose-lowering therapy (including insulin/SU per protocol)	~45 mL/min/1.73 m ² (geometric mean 45.4 vs 45.5); G3b 43%, G3a 56%	Not an event-HR trial for renal endpoints; change analyses showed stable kidney function: eGFR ETR 0.98 (95% CI 0.94–1.02; P=0.36); UACR ETR 0.83 (95% CI 0.62–1.10; P=0.19); no increase in hypoglycemia (30.47 vs 40.08 events/100 PYE; P=0.54) and no renal safety signal
Imamura et al (35)	Prospective, single-arm before–after series; n=23; 12 months	T2D with overt diabetic nephropathy (proteinuria >0.5 g/gCr in ≥3 samples) despite RAS therapy and salt restriction; mean age 58±2.3; 78% on insulin	Liraglutide s.c. daily 0.3→0.6→0.9 mg (weekly titration to 0.9 mg) for 12 months	No control group	eGFR 58.2±6.4; proteinuria 2.53±0.48 g/gCr; SBP 140 mmHg	Proteinuria decreased to 1.47±0.28 g/gCr at 12 months (p=0.002); eGFR slope improved from –6.6±1.5 to –0.3±1.9 mL/min/1.73 m ² /year (p=0.003); HbA1c 7.4→6.9% (p=0.04); BMI 27.6→26.5 kg/m ² (p<0.001); SBP unchanged.

Selvarajah et al (37)	Phase 2b multicenter double-blind RCT vs placebo; open-label semaglutide 1 mg/week arm; randomization 1:1:1:1:1 (cotadutide 100/300/600 µg daily, placebo, semaglutide); n=248, 26 weeks (co-primaries at week 14)	T2D + CKD (eGFR 20–<90, UACR >50 mg/g); mean age 67; 19% female; DKD 93.5%; RAASi 97%, SGLT2i 46.8%	Cotadutide daily s.c. (titrated 50→100/300/600 µg) × 26 weeks	Placebo (blinded) and open-label semaglutide 1 mg/week	Mean eGFR 55.3; geometric mean UACR 205.5 mg/g (CV 270%)	UACR vs placebo: –43.9% (300 µg) and –49.9% (600 µg) at week 14, maintained at week 26; category regression (micro→normo with 300 µg; macro→micro/normo with 600 µg); in subgroup eGFR ≤60 + UACR ≥300: –45.9% (300 µg) and –65.2% (600 µg) at week 26; eGFR slope improved with 600 µg (P=0.016)
Parker et al (34)	Phase 2a double-blind RCT, 1:1 cotadutide vs placebo, 32 days; multicenter (UK/Germany); N=41 (21 cotadutide, 20 placebo)	T2D + stage 3 CKD (eGFR 30–59); BMI 25–45; HbA1c 6.5–10.5%; ≥50% on insulin ≥20 U/day; mean age 71; 49% female	Cotadutide s.c. 50→300 µg/day titrated in 4 steps (50, 100, 200, 300 µg) over 32 days	Placebo (1:1)	Mean eGFR 44.7 vs 47.6; UACR assessed (micro/macroalbuminuria in 18 participants)	UACR ↓51% vs placebo in micro/macroalbuminuria subgroup (p=0.0504); no significant change in eGFR (Δ +1.17 vs –1.10 mL/min/1.73 m², p=0.268); effect independent of HbA1c
Gerstein et al (36)	Multicenter double-blind CVOT; 344 sites/28 countries; 1:1:1 randomization (efpeglenatide 4 or 6 mg weekly vs placebo); n=4,076 (efpeg n=2,717; placebo n=1,359); median 1.81 years	T2D with established CVD (89.6%) or CKD (eGFR 25–59.9) + ≥1 CV risk factor; baseline SGLT2i use 15.2%; albuminuria 48.5%	Efpeglenatide s.c. weekly (titration 2→4 mg or 2→4→6 mg), added to standard care	Placebo + standard care; stratified by baseline SGLT2i use	Mean eGFR 72.4; median UACR 28.3 mg/g; 31.6% with eGFR <60	Renal composite (incident macroalbuminuria + ≥30% ↑UACR, ≥40% sustained ↓eGFR, RRT ≥90 days, or sustained eGFR <15): HR 0.68 (0.57–0.79); UACR ↓21% (LSM); mean eGFR change +0.9 mL/min/1.73 m²

Wang et al (39)	Open-label, parallel, multicenter RCT (China, 4 sites), 24 weeks; n=92 (46/46)	T2D with macroalbuminuric DKD; eGFR ≥ 30 ; UACR >0.3 g/24 h; mean age 56 ± 8 ; 30% female	Exenatide 5 $\rightarrow$ 10 μ g b.i.d. + basal insulin glargine for 24 weeks	Prandial lispro + basal glargine (basal-bolus)	eGFR 70.4 ± 23.4	No HR reported; primary outcome (% change): UACR -29.7% ($p=0.0255$); UACR -28.4% ($p=0.0395$); absolute UACR -607.8 mg/g ($p=0.0209$); Δ eGFR $+6.64$ mL/min (PPS, $p=0.0369$)
van der Aart et al (40)	Post hoc analysis of EXSCEL RCT; EQW vs placebo; median follow-up 3.3 years; n=14,752 (3,503 with UACR, 13,826 with serial eGFR)	T2D with or without CVD; renal subgroup (23.7% of total). UACR $\geq 0 \rightarrow >200$ mg/g; mean eGFR ≈ 76	Exenatide once weekly (EQW 2 mg s.c., median 3.3 years)	Placebo + standard therapy	≈ 76 (estimated from UACR subgroup)	eGFR slope: neutral overall (Δ 0.02 [-0.18 to 0.22]); in UACR >100 mg/g $\rightarrow \Delta +0.79$ [0.24 – 1.34]; in >200 mg/g $\rightarrow \Delta +1.32$ [0.57 – 2.06]; UACR $\downarrow -28.2\%$ (>30 mg/g), -34.5% (>200 mg/g)
Muskiet et al (42)	Exploratory analysis of double-blind multicenter RCT (49 countries); total n=6,068; baseline UACR data in 5,978 (normo 4,441; micro 1,148; macro 389); median follow-up 108 weeks	T2D with recent acute coronary syndrome; subgroups by baseline albuminuria: normo <30 , micro 30–300, macro >300 mg/g	Lixisenatide 10–20 μ g s.c. daily added to standard care; titration after 2 weeks; ~ 108 weeks	Placebo + standard glycemic care	Stratified by baseline UACR (mean): normo ~ 78 , micro ~ 73 , macro ~ 61 ; 77% eGFR <90 ; 23% <60	New-onset macroalbuminuria: HR 0.808 (0.660–0.991) adjusted for baseline HbA1c; HR 0.815 (0.665–0.999) adjusted for baseline + on-trial HbA1c. Doubling of creatinine: HR 1.163 (0.741–1.825) NS; eGFR slope: no differences across UACR strata
van der Aart et al (41)	Post hoc analysis of EXSCEL, double-blind multicenter global RCT; n=3,503 with eGFR data; 2,828 with UACR data	T2D with high CV risk, subgroups by albuminuria: UACR >30 , >100 , >200 mg/g	Exenatide once weekly (EQW) 2 mg s.c. weekly; ~ 3 years duration (EXSCEL)	Placebo + standard care	Global mean ≈ 76 (by subgroup)	EQW improved eGFR slope vs placebo in UACR >100 mg/g: $+0.79$ (95% CI 0.24 – 1.34) mL/min/year; UACR >200 mg/g: $+1.32$ (0.57 – 2.06); UACR reduction -28.2% (>30

						mg/g), -22.5% (>100 mg/g), -34.5% (>200 mg/g)
Muta et al (43)	Retrospective post-hoc cohort with IPW-PS and PS-matching. Two comparisons: (A) SGLT2i-first vs GLP-1RA-first (n=266 vs 194); (B) dulaglutide vs liraglutide (n=246 vs 214). Combined follow-up ≥12 months of dual therapy	T2D treated with combined SGLT2i + GLP-1RA (dulaglutide or liraglutide). Exclusions: T1D, dialysis, severe liver disease, terminal cancer, pregnancy, or early discontinuation	(B) Dulaglutide 0.75–1.5 mg s.c. weekly (standard clinical use); ≥12 months of exposure in combination	(B) Liraglutide 0.9–1.8 mg s.c. daily; ≥12 months of exposure in combination. For analysis (A): sequence SGLT2i→GLP-1RA vs GLP-1RA→SGLT2i	Mean ≈76–78 (balanced after IPW); baseline albuminuria: median ACR ~30–40 mg/g (wide IQR)	Renal composite (albuminuria progression and/or ≥30% ↓eGFR): no difference by sequence (OR 1.13 [95% CI 0.68–1.88]). ≥30% ↓eGFR more frequent with liraglutide vs dulaglutide: OR 2.63 (1.07–6.45; p=0.04). Greater albuminuria reduction with liraglutide: OR 0.44 (0.04–0.85; p=0.03). Results consistent after PS-matching.
Dai et al (44)	Multicenter retrospective new-user cohort (CGRD, Taiwan); IPTW with generalized boosted models; weighted mean follow-up ≈2.4 years; n: liraglutide 3,210, dulaglutide 5,068 (weighted 7,604 vs 7,949)	Adults with T2D initiating liraglutide or dulaglutide (2016–2022); exclusions: T1D, pregnancy, other GLP-1RA/combo, follow-up <30 days; extensive covariate adjustment (demographics, HbA1c, eGFR, UACR, comorbidities, concomitant drugs)	Liraglutide s.c. daily (routine clinical dosing); ITT analysis with IPTW until event/drug change/end of follow-up	Dulaglutide s.c. weekly (routine clinical dosing)	CKD stage distribution after IPTW: ≥60 ~63%, 45–59 ~8%, 30–44 ~8%, 15–29 ~5%, <15 ~1%, dialysis ~5%; mean creatinine ~1.1 mg/dL; UACR available in subsample (normo/micro/macro)	Renal composite (new macroalbuminuria, >50% ↓eGFR, serum creatinine doubling, or dialysis): SHR 1.07 (0.995–1.16) (liraglutide vs dulaglutide); >50% ↓eGFR HR 1.04 (0.94–1.15); creatinine doubling HR 1.03 (0.92–1.15); dialysis HR 1.08 (0.90–1.30); macroalbuminuria SHR 1.05 (0.95–1.16). All NS.
Clegg et al (45)	Post-hoc of CVOT (EXSCEL), 1:1 propensity-matched. Two	T2D with broad CV risk; SGLT2i use in 8.7% of EQW arm; cohorts balanced for	Exenatide once-weekly (EQW) 2 mg s.c. + open-label SGLT2i; SGLT2i start	Placebo or EQW alone (without SGLT2i), standard of care	At matching: mean eGFR ~81 vs ~80; <60 in 16–23%; balanced between cohorts	Renal composites (≥40% ↓eGFR/dialysis/transplant ± macroalbuminuria): nonsignificant reductions;

	comparisons: EQW+SGLT2i vs Placebo (n=572/572) and EQW+SGLT2i vs EQW alone (n=575/575). Median follow-up ≈13–15 months from matching	clinical and lab variables	defined by first recorded visit; median SGLT2i exposure ≈9.3–9.8 months			eGFR slope improved with EQW+SGLT2i vs placebo (+1.94 [0.94–2.94] mL/min/year) and vs EQW alone (+2.38 [1.40–3.35]).
Cai et al (46)	Retrospective cohort (CGRD, Taiwan) 2011–2019; n=1,572 (liraglutide 945; dulaglutide 627); analysis by CKD stage; multivariable adjustment (age, sex, BMI)	Adults with T2D initiating liraglutide or dulaglutide; exclusion: prior ESRD; ≥60 days of prescription within 90-day index window	Liraglutide s.c. daily; follow-up from initiation to MACE event/end of data	Dulaglutide s.c. weekly; same follow-up criteria	Overall mean eGFR 79.8±40.2 (liraglutide) vs 75.5±37.4 (dulaglutide); median UACR 89.5 vs 73.5 mg/g (wide IQR)	Renal function decline (eGFR slope): slower with dulaglutide over time (p<0.05); no difference in absolute renal function or global renal safety between drugs. No “hard” renal HRs reported.

Abbreviations: ACR, albumin-to-creatinine ratio; AE, adverse event; BMI, body mass index; CKD, chronic kidney disease; CGRD, Chang Gung Research Database (Taiwan); CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcome trial; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; EQW, exenatide once weekly; ESKD/ESRD, end-stage kidney disease/renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IPW, inverse probability weighting; ITT, intention-to-treat; IQR, interquartile range; LSM, least squares mean; MACE, major adverse cardiovascular event; NS, not significant; OR, odds ratio; PS, propensity score; RAASi, renin–angiotensin–aldosterone system inhibitor; RCT, randomized controlled trial; RECAP, Retrospective Evaluation of Combination Antidiabetic Pathways; SHR, subdistribution hazard ratio; S.C., subcutaneous; SGLT2i, sodium–glucose cotransporter-2 inhibitor; T1D/T2D, type 1/type 2 diabetes mellitus; Tx, transplant; UACR, urine albumin-to-creatinine ratio; UAER, urinary albumin excretion rate.

Supplementary Table 3. Matrix of renal outcome evidence by CKD stage and metabolic phenotype

CKD stage (baseline)	Diabetes, non-obese	Diabetes, overweight/obese	Non-diabetes, overweight/obese	Non-diabetes, non-obese
G1–G2	NR (obesity-stratified renal outcomes generally not reported in T2D RCTs)	A/E/H available in broad T2D populations (often overweight/obese on average), but not stratified by BMI : SUSTAIN-6 A/H (4); SOUL H (14); EXSCEL post hoc A/E in albuminuria subgroups (40,41); ELIXA exploratory A/H (macroalbuminuria) (42); AMPLITUDE-O A/H (36).	A/E/H available in overweight/obesity without diabetes with mixed CKD status: SELECT kidney analysis A/E/H (18) (CKD subgroup present but not CKD-stage-stratified).	NR
G3a–G3b	NR (BMI-stratified renal outcomes rarely reported within CKD strata)	A/E/H available in CKD-enriched or CKD subgroup analyses (not BMI-stratified): FLOW A/E/H (13); AWARD-7 A/E/H (27,28); SURPASS-4 renal analyses A/E/H (21); Oe et al switch cohort (TZP vs Dula) A/E (24); LIRA-RENAL A/E (Davies) (32); mechanistic liraglutide trial in albuminuric T2D A/E (von Scholten crossover) (32).	A available; E mostly neutral; H limited : Semaglutide 2.4 mg in CKD without diabetes A/E (no eGFR difference at 24 wks) (19).	NR / very limited
G4	NR	Limited direct evidence ; mostly CKD G3–G4 combined or small cohorts: AWARD-7 includes G3–G4 (27,28) but not consistently separable as G4-only; semaglutide retrospective G4–G5/dialysis cohort A/E (pre–post; H limited) (17).	NR (no robust G4-only non-diabetic obesity-CKD RCT evidence in dataset provided)	NR
G5 / dialysis	NR	Very limited (observational only): semaglutide cohort includes G5/dialysis E (stability), H limited (17).	NR	NR

This table summarizes the availability of renal outcome reporting (albuminuria [A], eGFR slope/trajectory [E], and hard kidney outcomes/composite kidney endpoints [H]) across CKD stages and metabolic phenotypes (type 2 diabetes and overweight/obesity status). Cells marked NR (not reported) indicate that the primary studies did not provide renal outcomes stratified for the corresponding phenotype within that CKD stage, highlighting evidence gaps rather than implying absence of effect.

CKD stage classification in this table is based on eligibility criteria and baseline eGFR strata reported in each study; many trials report CKD as eGFR <60 or G3–G4 combined, limiting granularity at G4–G5. Obesity/non-obesity strata (within T2D or within CKD stages) are frequently not reported as effect modifiers for renal outcomes; therefore, “Diabetic, non-obese” and “Non-diabetic, non-obese” cells are predominantly NR, reflecting an evidence gap rather than omission. “Hard kidney outcomes (H)” includes composite kidney endpoints, kidney failure events, sustained eGFR decline thresholds, need for kidney replacement therapy, or adjudicated kidney endpoints as reported in each trial.

Supplementary Figure S1

