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Supplementary Table S1: Characteristics of Included Studies

Study ID	Author (Year)	Country/Region	Study Design	Population Characteristics	Sample Size (n)	Intervention (Drug/Treatment)	Comparator	Primary Outcomes	Secondary Outcomes	Results (Key Findings)	Adverse Events/Side Effects	Study Limitations
1	Cannon et al. (2020)	Multinational	Randomized, double-blind trial	Age: 62-64 years, Duration of T2D: ~14-16 years, CKD (eGFR 30-90 mL/min/1.73 m²), HbA1c: 6.5%-12%	4401	Canagliflozin 100 mg daily	Placebo	Composite of end-stage kidney disease, doubling of serum creatinine, or renal/cardiovascular death	Major adverse CV events, HF hospitalization	Significant reduction in primary outcome, similar risk reduction across HbA1c levels	Hypoglycemia, acute kidney injury, and amputation events noted but not significantly different from placebo	Observational limitations on specific safety outcomes. Lack of multiplicity adjustments.
2	Kahl et al. (2020)	Germany	Randomized, double-blind, placebo-controlled trial	Age: 18–75 years, BMI <45 kg/m², T2D duration <7 years, HbA1c: 6–8%	84	Empagliflozin 25 mg daily	Placebo	Liver fat content (LFC) reduction	Weight loss, uric acid, and adiponectin levels	22% relative reduction in LFC, weight loss (placebo-corrected: -2.5 kg), increased adiponectin	None significant; gastrointestinal discomfort was mild and transient	Short duration and limited generalizability. Primarily well-controlled T2D.
3	Yabe et al. (2020)	Japan	Open-label, randomized, active-controlled trial	Age: ~58 years, BMI: ~26 kg/m², HbA1c: 7-10.5%, T2D duration ~9 years	458	Oral semaglutide (3 mg, 7 mg, 14 mg daily)	Dulaglutide 0.75 mg weekly	HbA1c reduction at 52 weeks	Body weight reduction, safety (adverse events)	HbA1c reduction: up to -1.7% (14 mg), body weight reduction up to -1.6 kg	Dose-dependent gastrointestinal effects, mainly mild/moderate constipation	Open-label design and lack of multiplicity control for secondary outcomes.
4	Ali et al. (2020)	USA	Randomized controlled trial	Age 57.7 ± 7.4 years; BMI 33.3 ± 6.1 kg/m²; poorly controlled T2DM (HbA1c 7–11%); stable metformin ± sulfonylurea	45	Canagliflozin + Liraglutide (CANA/LIRA)	Canagliflozin (CANA), Liraglutide (LIRA)	HbA1c reduction; EGP changes	Weight loss, blood pressure reduction	CANA/LIRA resulted in greater weight loss but no additive effect on HbA1c compared to monotherapies.	None reported	Limited sample size; short duration of treatment (16 weeks); did not include long-term cardiovascular outcomes.
5	Quast et al. (2020)	Germany	Randomized, parallel-group trial	Age 18–70 years; BMI 18–40 kg/m²; T2DM for ≥3 months; on stable metformin ± other oral agents	57	Lixisenatide, Liraglutide	None	Gastric emptying, esophageal reflux	Gastric acid secretion, motility parameters	Lixisenatide delayed gastric emptying more than liraglutide but neither affected esophageal	Minor gastrointestinal events	Short study duration (10 weeks); esophageal reflux effects were not linked to glycemic control outcomes.

				or insulin.						reflux significantly.		
6	Lee et al. (2021)	Scotland	Multicenter, randomized trial	Mean age 68.7 years; 78% diabetes; NYHA class II/III heart failure; LVEF ≤40%; HbA1c 7.2 ± 1.5%.	105	Empagliflozin	Placebo	LV volume reduction (remodeling)	NT-proBNP levels, glycemic control	Empagliflozin reduced LV volumes and NT-proBNP; suggested cardiac remodeling may lower heart failure risks.	Two deaths (one pancreatic cancer)	Underpowered for rare outcomes; results limited to T2DM and prediabetes; unclear long-term cardiovascular mortality benefits.
7	Frias et al. (2021)	Multinational	Randomized, double-blind, parallel-arm	Adults with Type 2 Diabetes on Metformin (Mean age, BMI: 8.6%, 34.2 kg/m²)	1842	Dulaglutide 3.0 mg, 4.5 mg weekly	Dulaglutide 1.5 mg	HbA1c reduction at 36 weeks	Body weight change, safety at 52 weeks	Dulaglutide 4.5 mg superior for HbA1c reduction (-1.77%) and weight loss (-4.6 kg)	Nausea: 16.4%; Vomiting: 9.3%	Small dose-response differences for 3.0 mg vs. 1.5 mg
8	Davies et al. (2021)	Multinational	Randomized, double-blind, placebo-controlled	Adults with Type 2 Diabetes and Obesity (Mean BMI: 35.7 kg/m²; HbA1c: 8.1%)	1210	Semaglutide 2.4 mg weekly	Semaglutide 1.0 mg, placebo	% Bodyweight change, HbA1c <7%	Cardiometabolic risk factors, physical health scores	Semaglutide 2.4 mg achieved 9.6% weight loss, significant HbA1c improvement	Gastrointestinal events: 63.5% for 2.4 mg	Limited generalizability beyond studied population
9	Jongs et al. (2021)	Multinational	Randomized, double-blind, placebo-controlled	CKD patients with/without Type 2 Diabetes (Median UACR: 949 mg/g)	4304	Dapagliflozin 10 mg daily	Placebo	Change in UACR, kidney outcomes	Cardiovascular death, mortality	UACR reduced by 29.3% overall; greater reduction with diabetes (-35.1%)	No significant safety concerns reported	Secondary analysis; reliance on surrogate outcomes
10	Heerspink et al. (2021)	Multinational	Randomized, double-blind, placebo-controlled	Mean age: 62 years; 33.1% female; 67.5% had T2DM; baseline eGFR: 25–75 mL/min/1.73m²; UACR: 200–5000 mg/g	4304	Dapagliflozin 10 mg daily	Placebo	Rate of eGFR decline	Reduction in kidney failure risk; outcomes in patients with and without T2DM	Dapagliflozin significantly slowed eGFR decline compared to placebo; effect more pronounced in patients with higher	Not specifically reported	Potential bias from acute eGFR decline and measurement sensitivity. Focus on chronic effects might dilute the long-term treatment benefits.

										HbA1c/UACR.		
11	Shaman et al. (2022)	Multinational	Pooled analysis of RCTs	Median age: ~62 years; HbA1c ≥7%; subset with eGFR <60 mL/min/1.73m²; stratified by albuminuria levels	12,637	Semaglutide/Liraglutide (varied doses)	Placebo	Albuminuria reduction; eGFR slope changes	Risk reduction for persistent eGFR decline (30%, 40%, 50%, 57%)	GLP-1 agonists reduced albuminuria by 24%; slowed eGFR decline (larger effect in those with baseline eGFR <60); lower risks of substantial eGFR reductions.	Few adverse effects reported	Heterogeneity in trial durations and variations in population (different baseline CKD risks); secondary kidney outcomes in original trials.
12	Cheng et al. (2022)	China	Randomized, double-blind, placebo-controlled	Patients inadequately controlled with metformin; aged 40–75 years; HbA1c: 7–10%; BMI ≥25 kg/m²	36	Liraglutide 1.8 mg/day	Dapagliflozin, Acarbose	Cognitive and brain activation changes	Changes in metabolic parameters, waist circumference, and insulin levels	Liraglutide improved hippocampal activation and delayed memory; no significant changes observed with dapagliflozin or acarbose.	Mild, not detailed	Small sample size and short duration; focus on specific cognitive and olfactory neural measures; limited to patients on stable metformin therapy.
13	Tamborlane et al. (2022)	Multinational (Hungary, Israel, Mexico, Russia, USA)	Randomized, parallel-group, Phase 3	Mean age: 16 years; HbA1c: 6.5%-11%; Mix of metformin/insulin users	72	Dapagliflozin (SGLT-2 inhibitor)	Placebo	Change in HbA1c from baseline	Glycemic rescue, % achieving HbA1c <7%	HbA1c decreased by 0.75% (p=0.101) in ITT analysis; significant -1.13% reduction in per-protocol analysis.	69.2% experienced AEs, including hypoglycemia (28.2%); genital infections (one discontinuation due to this).	Limited sample size and recruitment challenges.
14	Tuttle et al. (2022)	Multinational	Pooled analysis of 19 placebo-controlled trials	Moderate-to-severe CKD; HbA1c ~8%; majority with hypertension	15,081	Empagliflozin (10/25 mg, SGLT-2 inhibitor)	Placebo	Safety of treatment in CKD patients	Adverse event frequency and kidney outcomes	No new safety concerns; lower risks for hyperkalemia and edema; consistent AE	Increased risk of genital infections; consistent SAE rates except slightly higher	Low patient numbers in CKD G4 subgroup, limiting statistical power.

										profile across CKD categories.	in CKD G4 group.	
15	Tamborlane et al. (2022)	Multinational (27 sites in 6 countries)	Randomized, parallel-group, Phase 3	Age: 10–17 years; severe obesity common; HbA1c: 6.5%-11%	83	Once-weekly Exenatide (GLP-1 agonist)	Placebo	HbA1c reduction at 24 weeks	Changes in fasting glucose, body weight, BP	HbA1c reduced by 0.85% (p=0.012) vs placebo; non-significant trends in fasting glucose and weight reduction.	61% experienced AEs; vomiting led to discontinuation for one participant.	Limited generalizability due to pediatric focus; short duration for chronic disease study.
16	Arslanian et al. (2022)	Multinational	Randomized, placebo-controlled trial	Youth (10–17 years), BMI > 85th percentile, HbA1c 6.5–11%, treated with/without metformin/insulin	154	Once-weekly Dulaglutide (0.75 mg/1.5 mg)	Placebo	HbA1c reduction at 26 weeks	Glycemic target (<7% HbA1c), fasting glucose, BMI changes	Dulaglutide reduced HbA1c significantly (−0.6 to −0.9 percentage points), superior to placebo. No effect on BMI. Increased proportion achieving HbA1c < 7%	Higher incidence of gastrointestinal events in Dulaglutide group. Consistent safety profile with adults.	Limited to 26 weeks; no long-term effects; not fully representative of diverse global youth populations.
17	Mosenzon et al. (2022)	Multinational	Post hoc analysis of RCT	Adults with T2D, moderate to high CV risk, HbA1c 6.5–12%, CrCl ≥ 60 mL/min	17,160	Dapagliflozin 10 mg/day	Placebo	eGFR decline and kidney disease progression	Cardiovascular outcomes, reduction in albuminuria	Dapagliflozin significantly reduced kidney disease progression risk across all KDIGO categories. eGFR slopes favored treatment group. Reduced albuminuria in treated group.	No significant difference in acute kidney injury incidence compared to placebo.	Hypothesis-generating nature of post hoc analyses; limited to participants with baseline CV risks.

18	Curovic et al. (2022)	Denmark	Randomized, crossover trial	Adults with T2D, albuminuria (UACR ≥ 30 mg/g), on stable RAS inhibitors	40	Dapagliflozin 10 mg/day	Placebo	Reduction in urinary proteomic classifier CKD273	Change in UACR, BP, eGFR	Significant improvement in CKD273 scores and regression from high- to low-risk CKD273 profile. UACR and HbA1c reduced significantly with treatment.	Minimal side effects reported; adherence >80%.	Small sample size, crossover design may introduce residual treatment effects. Limited generalizability.
19	Pratley et al. (2023)	Multinational	Randomized Controlled Trial	Older adults (≥40 years) with T2D and ASCVD; mean age: ≥65 years, 70% male, mean HbA1c: 8.1%	8,246	Ertugliflozin 5 mg/15 mg	Placebo	Cardiovascular and kidney safety outcomes	Slower eGFR decline, urine albumin-to-creatinine improvements	No increase in major adverse cardiovascular events; reduced risk of heart failure hospitalization; improved kidney outcomes	Genital infections, hypovolemia, and hypoglycemia more frequent in ertugliflozin group	Limited to T2D with ASCVD; underrepresentation of some ethnic groups
20	Schechter et al. (2023)	Multinational	Randomized Controlled Trial	Adults with T2D (mean age: 63.9 years); 39.8% with no ASCVD; median HbA1c: 8.1%	17,160	Dapagliflozin 10 mg	Placebo	Reduction in all-cause hospitalizations	Reduced hospitalizations for infections, cardiac, renal causes	11% reduction in non-elective hospitalizations; consistent benefits regardless of ASCVD status	Increased genital infections, volume depletion, and rare ketoacidosis cases	Post-hoc analysis; no specific subgroup analysis for rare side effects
21	Aroda et al. (2023)	Multinational	Randomized, double-blind, phase 3b trial	Adults with T2D, HbA1c 8-10.5%, BMI ≥25	1606	Oral semaglutide (14 mg, 25 mg, 50 mg)	Lower dose of semaglutide (14 mg)	HbA1c reduction	Bodyweight loss and safety profile	Higher doses (25 mg, 50 mg) achieved better HbA1c and weight reductions than 14 mg	Gastrointestinal issues, dose-dependent and mostly mild/moderate	Higher cost, adherence challenges for higher doses
22	Manubolu et al. (2024)	USA	Double-Blind Randomized Trial	Adults with T2D and coronary artery disease; mean BMI 28.5 kg/m²; HbA1c: 7.2–8.5%	115	Semaglutide	Placebo	Reduction in epicardial adipose tissue volume and density	Weight loss, improved HbA1c and triglycerides	9% reduction in EAT volume, 5% increase in EAT density; potential mechanisms for cardiovascular benefits of	Minimal reported; imaging quality and selection bias due to participant exclusions	Small sample size; single-center study; no long-term cardiovascular outcome measures available

										semaglutide		
23	Rosengren et al. (2024)	Sweden	Randomized open-label trial	Adults with type 2 diabetes, SIDD and SIRD subgroups, mean age 63-69 years, BMI 28-34	239	Semaglutide vs. dapagliflozin	None	HbA1c reduction	Bodyweight and postprandial glucose improvement	Semaglutide reduced HbA1c significantly more than dapagliflozin. Greater effects observed in SIDD subgroup.	Gastrointestinal symptoms with semaglutide; urinary tract symptoms with dapagliflozin	Limited to SIDD and SIRD pathophysiological subgroups
24	Mann et al. (2024)	Multinational	Randomized, double-blind trial	Adults with T2D and CKD, baseline eGFR ~47, median HbA1c ~7.8%	3533	Semaglutide (with/without SGLT2i)	Placebo	Composite kidney failure and CV outcomes	HbA1c reduction, weight loss, and eGFR decline mitigation	Semaglutide reduced kidney and CV outcomes; benefits consistent regardless of SGLT2i baseline use	Gastrointestinal events and minor discontinuations; no severe new safety issues	Limited power for smaller effects in SGLT2i users