SUPPLEMENTARY MATERIAL

Table S1. Systematic review inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Study type	Study conducted in humans	Study conducted in plants or animals
Treatment	Intervention includes a DPP-4 inhibitor	Intervention does not include a DPP-4 inhibitor
Publication type	Clinical trial	Review Case report Cost-benefit analysis Meta-analysis Conference abstract Editorial/letter to editor Full text not available
Study design	Randomized-controlled trial	Study not controlled/single arm Study not randomized/observational study Cross-over study Not double blind Pre-clinical or phase 1 study Time-to-event analysis
Study population	Type 2 diabetes mellitus with renal impairment	No type 2 diabetes mellitus Healthy individuals/volunteers No renal impairment
Outcomes	Study includes ≥1 of the following outcome measures: HbA1c, FPG, weight, hypoglycemia, lipid profile	Study does not include any of the following outcome measures: HbA1c FPG Weight Hypoglycemia Lipid profile (total cholesterol, triglycerides, VLDL, LDL, HDL, non-HDL)
Trial length	≥12-week long	<12-week long
Sample size	≥50 patients in the study	<50 patients in the study
Comparator arm	DPP-4 inhibitor trial has a common comparator arm to a vildagliptin trial	DPP-4 inhibitor trial lacks a common comparator arm to a vildagliptin trial

DPP-4 dipeptidyl peptidase-4, *HbA1c* glycated hemoglobin, *FPG* fasting plasma glucose, *VLDL* very low-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *non-HDL* non-high density lipoprotein-cholesterol.

Table S2. DPP-4 inhibitor studies included in systematic literature review.

Study no.	Study description	Randomization (no. of patients)	Treatment duration (weeks)	Renal definition	Publication
1	Efficacy/safety of sitagliptin versus placebo (first 12 weeks), followed by the active treatment with glipizide (for 42 weeks) in T2DM patients (HbA1c, 6.5–10%) with moderate to severe RI	Sitagliptin 50 mg qd or 25 mg qd: 65 patients Placebo (first 12 weeks) followed by glipizide 5 mg daily uptitrated to 10 mg bid (last 42 weeks): 26 patients	12 (placebo-controlled phase) 42 (active treatment phase)	Patients were stratified based on baseline renal function (CrCl) as estimated by the Cockcroft–Gault equation: stratum 1 – moderate renal insufficiency (CrCl, 30 to <50 mL/min and not on dialysis); stratum 2 – severe renal insufficiency (CrCl, <30 mL/min and not on dialysis or ESRD on dialysis)	[1]
2	Placebo-controlled 24-week study (efficacy/safety) of vildagliptin in drug-naïve or previously treated T2DM patients (HbA1c, 6.5–10%) with moderate to severe RI	Vildagliptin • Moderate RI: 165 patients • Severe RI: 124 patients Placebo • Moderate RI: 129 patients • Severe RI: 97 patients	24	Estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula ≥30 to <50 mL/min/1.73 m^2 – moderate RI and <30 mL/min/1.73 m^2 – severe RI	[2]

3	Placebo-controlled 24-week study (efficacy/safety) of vildagliptin in drug-naïve or previously treated T2DM patients (HbA1c, 6.5–10%) with moderate to severe RI 52-week extension of study 2 [2]	Vildagliptin: • Moderate RI: 122 patients • Severe RI: 94 patients Placebo: • Moderate RI: 89 patients • Severe RI: 64 patients	52	Estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula ≥30 to <50 mL/min/1.73 m^2 – moderate RI and <30 mL/min/1.73 m^2 – severe RI	[3]
4	Placebo-controlled 12-week study (efficacy/safety) of saxagliptin in T2DM patients with moderate to severe RI inadequately controlled (HbA1c, 7–11%) on previous treatment with anti-diabetes drugs	Saxagliptin 2.5 mg qd: 85 patients Placebo: 85 patients	12	Documented history of CrCl <50 mL/min within the previous three months. The degree of RI was categorized based on the estimated CrCl determined by the Cockcroft–Gault equation as moderate (CrCl, ≥30 to <50 mL/min), severe (CrCl, <30 mL/min and not on dialysis) or ESRD (receiving hemodialysis)	[4]
5	Efficacy/safety of saxagliptin versus placebo in T2DM patients with moderate to severe RI inadequately controlled (HbA1c, 7–11%) on previous treatment with anti-diabetes drugs 52-week extension of study 4 [4]	Saxagliptin 2.5 mg qd: 85 patients Placebo: 85 patients	52	Documentation of CrCl <50 mL/min (estimated by the Cockcroft–Gault equation) as moderate (CrCl, ≥30 to <50 mL/min), severe (CrCl, <30 mL/min and not on dialysis) or ESRD (receiving hemodialysis)	[5]
6	Placebo-controlled 52-week study (efficacy/safety) of linagliptin in T2DM patients with severe RI inadequately controlled (HbA1c, >7% to ≤10%) on previous treatment with anti-diabetes drugs	Linagliptin 5 mg qd: 68 patients Placebo: 65 patients	52	Participants fulfilled the criteria for severe RI (CKD stage 4/5) at screening, having an estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease study equation of 30 mL/min/1.73 m^2 (while not receiving chronic dialysis)	[6]

7	Efficacy/safety of linagliptin versus placebo (first 12 weeks), followed by the active treatment with glimepiride (for 40 weeks) in T2DM patients (HbA1c, 7.0–10%) with moderate to severe RI	Linagliptin 5 mg qd: 113 patients Placebo (first 12 weeks) followed by glimepiride 1–4 mg daily (for 40 weeks): 122 patients	12 (placebo-controlled phase) 42 (active treatment phase)	Estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula <60 mL/min/1.73 m^2	[7]

bid twice daily, *CrCl* creatinine clearance, *CKD* chronic kidney disease, *DPP-4* dipeptidyl peptidase-4, *HbA1c* glycated hemoglobin, *qd* once daily, *RI* renal impairment, *T2DM* type 2 diabetes mellitus.

REFERENCES

1. Chan JC, Scott R, Arjona Ferreira JC, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes Obes Metab. 2008;10(7):545–55.
2. Lukashevich V, Schweizer A, Shao Q, et al. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. Diabetes Obes Metab. 2011;13(10):947–54.
3. Kothny W, Shao Q, Groop PH, Lukashevich V. One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment. Diabetes Obes Metab. 2012;14(11):1032–9.
4. Nowicki M, Rychlik I, Haller H, et al. Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes Obes Metab. 2011;13(6):523–32.
5. Nowicki M, Rychlik I, Haller H, et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract. 2011;65(12):1230–9.
6. McGill JB, Sloan L, Newman J, et al.: Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. Diabetes Care. 2013;36(2):237–44.
7. Laakso M, Rosenstock J, Groop PH, et al. Treatment with the dipeptidyl peptidase-4 inhibitor linagliptin or placebo followed by glimepiride in patients with type 2 diabetes with moderate to severe renal impairment: a 52-week, randomized, double-blind clinical trial. Diabetes Care. 2015;38(2):e15–7.