REVIEW

Efficacy and Safety of the Utilization of Dipeptidyl Peptidase IV Inhibitors in Diabetic Patients with Chronic Kidney Disease: A Meta-Analysis of Randomized Clinical Trials

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Aim: To assess the efficacy and safety of Dipeptidyl Peptidase IV (DPP-4) inhibitors in patients with Type-2 Diabetes Mellitus (T2DM) and chronic kidney disease (CKD) using level 1 evidence.

Methods: The Cochrane and PubMed databases were searched from inception until January 1, 2022. RCTs that studied the efficacy and safety of DPP-4 inhibitors in diabetic patients with CKD were included. The primary efficacy outcome was assessed as the mean difference between HbA1c at the beginning and the end of each study for each arm, and the primary safety outcome was assessed as the incidence of adverse events and severe adverse events in each study.

Results: Twenty-one studies satisfied the pre-defined eligibility criteria. In assessing the efficacy of DPP-4 inhibitors in the treatment of T2DM and CKD, a total of 2917 patients under the DPP-4 inhibitors group and 2377 patients under the control group were included; The mean difference between the HbA1c of DPP-4 Inhibitor and the control group was -0.5295 with a 95% CI of -0.5337 to -0.5252. The included studies had high heterogeneity $p < 0.00001$ and $I^2 = 99\%$. In assessing the safety outcome and tolerability of DPP-4 inhibitors, a total of 8138 patients under the DPP-4 inhibitors group and 7517 patients under the control group were included; the odds ratio of adverse events between both groups was 0.9967 with a 95% CI of 0.9967 to 1.1047. The included studies had low heterogeneity $p = 0.25$ and $I^2 = 15\%$. The overall effect, $Z = 0.06$ ($p = 0.95$), was insignificant.

Conclusion: Patients suffering from both T2DM and CKD exhibited a significantly enhanced glycemic control when treated with DPP-4 inhibitors in comparison to the control group. Furthermore, no significant difference in the incidence of adverse events was observed between the DPP-4 inhibitors and the control group.

Keywords: diabetes, dipeptidyl peptidase IV, efficacy, safety, chronic kidney disease

Introduction

The past few years have seen a tremendous increase in type 2 diabetes mellitus (T2DM) cases and chronic kidney disease (CKD). Diabetic kidney disease (DKD), which is a major complication of long-lasting diabetes mellitus, is one of the main factors leading to end-stage renal diseases (ESRD) affecting approximately 30% of the diabetic population.[1,2] It has been proven that maintaining good glycemic control plays an important role in preventing the progression of deteriorating kidney function.[3] Nevertheless, the use of anti-hyperglycemic drugs in patients with T2DM with CKD is still controversial pertaining to their efficacy and safety.

Metformin, a well-known anti-hyperglycemic drug, for instance, might no longer be the first choice for CKD patients because of the risk of lactic acidosis.[4] Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral anti-diabetic agents that work by decreasing the inactivation of incretins such as glucagon-like peptide 1 and glucose-dependent insulino-tropic polypeptide to stimulate the release of insulin in a glucose-dependent manner.[5,6] By inhibiting DPP-4, these medications can help to lower blood sugar levels and improve glycemic control in people with T2DM.[7] Most of the DDP-4 inhibitors are excreted by the kidney; thus, a decrease in the dose given is essential for patients with ESRD, with the exception of Linagliptin due to its relatively low renal metabolism.[8]

DPP-4 inhibitors have been used safely in CKD patients; however, their impact on kidney outcomes is still questionable. Preclinical studies have implied that the pleiotropic effects of DPP-4 inhibition might actually be beneficial for the kidney, while clinical trials results were inconsistent.[9–11] Giorda et al[12] conducted a systematic review assessing the efficacy and safety of DPP-4 inhibitors in patients with T2DM with renal impairment, and their results suggest that it is safe and appropriate to use. Nevertheless, their study did not include enough clinical trials, and accordingly further meta-analysis is needed. The aim of our study is to conduct a meta-analysis of randomized controlled trials to investigate the efficacy and safety of Dipeptidyl peptidase-4 inhibitors in diabetic patients with CKD. This review provides a more comprehensive and reliable overview of the evidence than any single study[7] and could help identify areas where further research is needed.[13] The finding of the review could also inform clinical practice and policy,[7] helping to guide treatment decisions for patients with T2DM (American Diabetes Association).

Methods

This review was performed in accordance with the checklist and guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Data Sources and Searches

Our aim was to find randomized controlled trials (RCTs) assessing the efficacy and safety of DPP-4 therapy in patients with T2DM and chronic kidney disease (CKD). KDIGO (Kidney Disease Improving Global Outcomes) criteria were used to define CKD, which defines it as an eGFR <60 mL/min/1.73 m2 for 3 months or more, regardless of the attributed cause. The search strategy was developed by (M.Q., M.H., and W.M.) and conducted by (M.Q. and M.H.). The Cochrane and PubMed databases were searched using this strategy from inception until January 1, 2022. The following mesh terms were used "chronic kidney disease" AND "hypoglycemic agents" to screen the databases (PubMed and Cochrane). A limitation to RCTs only was applied to the search engines.

Study Selection

Two independent reviewers (M.Q. and M.H.) screened articles as abstracts and then in full text. Disagreements were resolved with a third reviewer (W.M.). Studies were included if they were RCTs studying the efficacy and safety of DPP-4 inhibitors in T2DM patients with CKD. Studies that either did not report Hba1c or used fasting/random blood glucose instead were excluded. Also, studies that did not report the mean difference in Hba1c at the beginning and at the end for both arms were excluded. Preliminary RCTs that were extended were excluded and the extension period publication was included if it met the exclusion/inclusion criteria. If data on the CKD subgroup of the RCT were inadequately reported, the authors of the RCT were contacted. Studies that met all selection criteria had their data abstracted.

Data Extraction and Quality Assessment

Information on study characteristics collected from eligible RCTs included basic study information (author identification, year of publication, National Clinical Trial number, sample size for each group, duration of intervention); participants' baseline characteristics (mean age, mean Hemoglobin A1C [HbA1C] at baseline, and pre-specified out-comes of efficacy and safety). Our primary outcome was glycemic control efficacy as measured by the difference in HbA1C from baseline to the end point of the intervention. Safety outcomes extracted included hypoglycemia, death, occurrence of any adverse event, and discontinuation rate from adverse events.

Risk of Bias Assessment and Grading the Quality of the Evidence

We synthesized selected articles and then assessed them using a modified version of the Quality Assessment Checklist for Prevalence Studies Risk of Bias tool. The analysis was done using the Cochrane tool also known as RoB 2. The RoB 2 tool offers a framework for evaluating the risk of bias in a single result from any form of randomized trial (an estimate of the impact of an experimental intervention compared with a comparator intervention on a specific outcome).[14] Randomized intervention studies were evaluated for risk of bias. The majority of the articles[15] had an overall low judgment; 2 articles had some concerns as an overall judgment and 3 articles had a high overall judgment. Summary plot [Figure 1] and Traffic light [Figure 2] were generated.

Data Synthesis and Statistical Analysis

A meta-analysis was performed to determine whether the difference in HbA1C between the baseline and the end of the intervention differed between groups using DPP-4-inhibitors comparing both placebo and controls, and whether the adverse events differed in the DPP-4-inhibitor arm. Aggregate estimates were presented both as a fixed effects model and as a random effects model. For each comparison, a Cochran's Q test was conducted to assess heterogeneity, and an I^2 statistic was calculated to estimate the percentage of total between study variations. All analyses were conducted using review manager software version 5.4.1 from the Cochrane collaboration.

Results

Search Outcomes

The database search yielded 317 studies. A total of 214 articles were retrieved from PubMed, and 103 from Cochrane Library. Thirty-two studies were duplicates and were eliminated. The remaining 285 studies were subjected to title and abstract screening where 259 studies were eliminated. The remaining 26 studies were assessed in full, where 21 satisfied the predefined eligibility criteria.

Figure 3 shows the PRISMA flow diagram summarizing the selection criteria outlined above.

Study Characteristics

Table 1 shows the description of each study that was included in this meta-analysis and it gives an insight of each included paper.

DPP-4 inhibitors play a significant role in the stimulation of insulin secretion and inhibition of glucagon secretion by elevating endogenous GLP-1 concentrations. DPP-4 inhibitors explored in the included studies are trelagliptin, omarigliptin, tenegliptin, sitagliptin, saxagliptin, linagliptin, and vildagliptin.

This meta-analysis aims to find out the Efficacy and Safety of DPP-4 inhibitors in the treatment of T2DM and renal insufficiency. It included 21 RCTs. The patients were categorized into two groups: DPP-4 inhibitors group and the control group. Three different variables were meta-analyzed, which are efficacy (changes from baseline in HbA1c), Adverse Events (AE), and Severe Adverse Events (SAE).
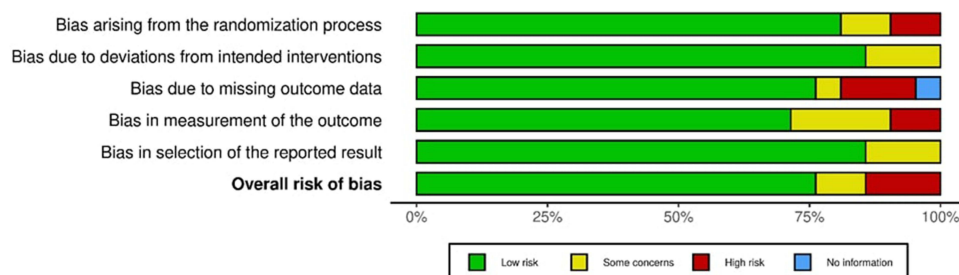

Figure 1 A summary plot that summarizes the risk of bias for all the included studies.
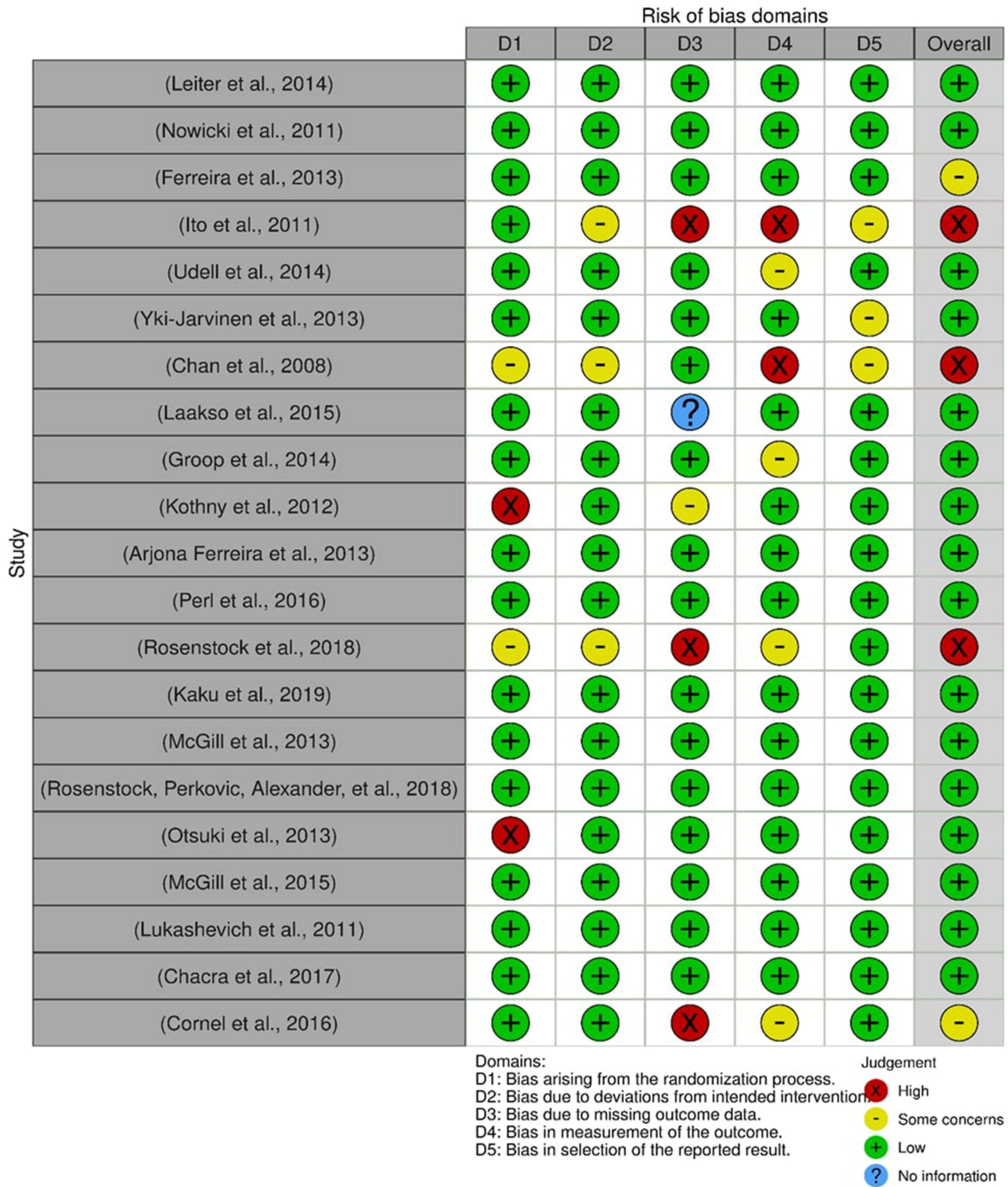
Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
(Leiter et al., 2014)	+	+	+	+	+	+
(Nowicki et al., 2011)	+	+	+	+	+	+
(Ferreira et al., 2013)	+	+	+	+	+	-
(Ito et al., 2011)	+	-	X	X	-	X
(Udell et al., 2014)	+	+	+	-	+	+
(Yki-Jarvinen et al., 2013)	+	+	+	+	-	+
(Chan et al., 2008)	-	-	+	X	-	X
(Laakso et al., 2015)	+	+	?	+	+	+
(Groop et al., 2014)	+	+	+	-	+	+
(Kothny et al., 2012)	X	+	-	+	+	+
(Arjona Ferreira et al., 2013)	+	+	+	+	+	+
(Perl et al., 2016)	+	+	+	+	+	+
(Rosenstock et al., 2018)	-	-	X	-	+	X
(Kaku et al., 2019)	+	+	+	+	+	+
(McGill et al., 2013)	+	+	+	+	+	+
(Rosenstock, Perkovic, Alexander, et al., 2018)	+	+	+	+	+	+
(Otsuki et al., 2013)	X	+	+	+	+	+
(McGill et al., 2015)	+	+	+	+	+	+
(Lukashevich et al., 2011)	+	+	+	+	+	+
(Chacra et al., 2017)	+	+	+	+	+	+
(Cornel et al., 2016)	+	+	X	-	+	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low
? No information

Figure 2 Traffic Plot figure that illustrates the risk of bias in all the domains in each included study.

Efficacy (Changes from Baseline in HbA1c): Meta-Analysis Results

The efficacy of DPP-4 inhibitors was evaluated by measuring the changes from baseline in HbA1c in the included studies [Figure 4]. In assessing the outcome of the efficacy of DPP-4 in the treatment of Type Two Diabetes (T2D) and renal insufficiency, a total of 2917 patients under the DPP-4 inhibitors group and 2377 patients under the control group were
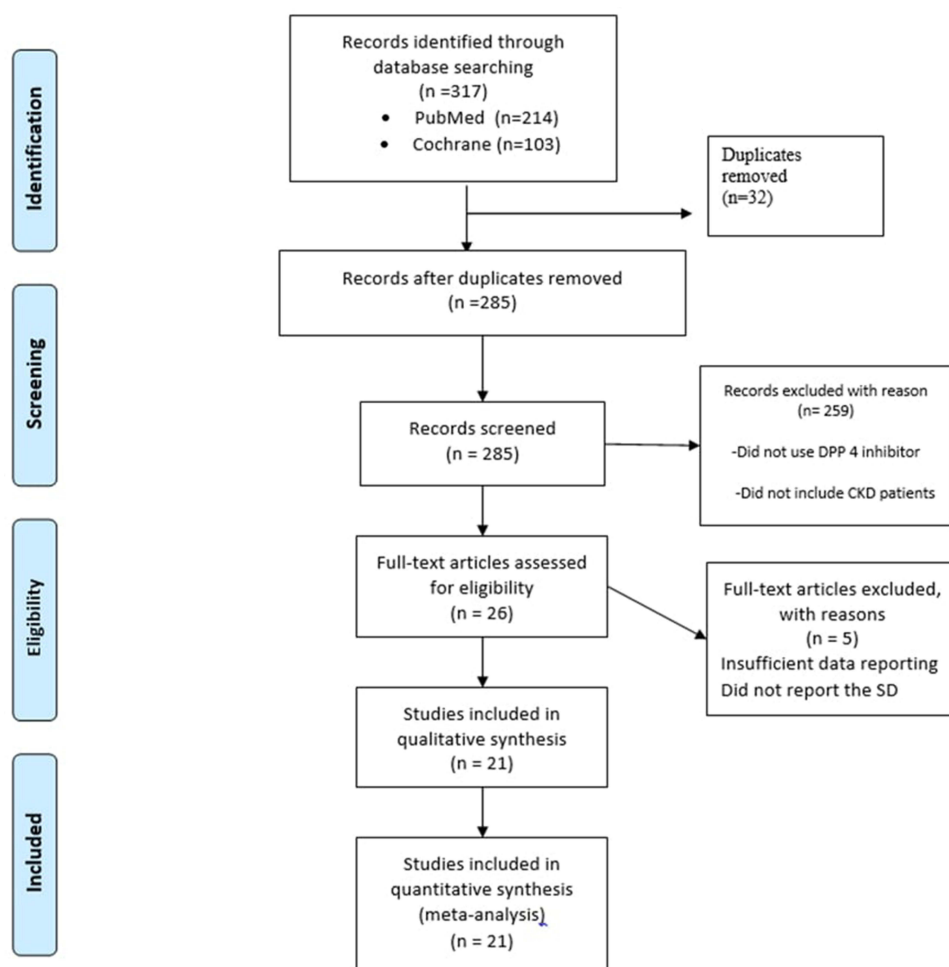
Figure 3 PRISMA flow chart showing how the studies were identified.
Abbreviations: CKD: Chronic Kidney Disease, DPP-4 Inhibitors: Dipeptidyl peptidase-4 inhibitor, SD: Standard Deviation.

included. All studies did not cross the line of zero effect, and therefore all studies were individually significant (p< 0.05). A study by Yki-Jarvinem et at, 2013 had the highest precision (58.8%), while Shira Perl et al, 2016 had the lowest precision (0%). A fixed effect model was used, and the pooled summary effect was −0.5295 and the 95% CIs were −0.5337 and −0.5252. The included studies had high heterogeneity p < 0.00001 and I^2 = 99%. Since the CI did not cross the line of no effect, the overall effect was significant. Overall effect Z = 242.02 (p < 0.00001). The results favour patients in the DPP-4 group. Therefore, patients in the DPP-4 inhibitors group had improved glycemic control.

Adverse Events (AE): Meta-Analysis Results

The safety and tolerability of DPP-4 inhibitors in the treatment of T2DM and renal insufficiency were evaluated by assessing the occurrence of Adverse Events [Figure 5]. In assessing the outcome of the safety and tolerability of DPP-4 inhibitors, a total of 8138 patients under the DPP-4 inhibitors group and 7517 patients under the control group were included. Only two studies (Udell et al and Shira et al) did not cross the line of zero effect and therefore were individually significant (p < 0.05). The remaining studies crossed the line of no effect and were individually not significant. A study by Rosenstock 2016 had the highest precision (24.2%), while Chan 2008, Kaku 2020, and McGill 2014 Severe had the lowest precision (0.2%). A random effect model was used, and the pooled summary effect was 0.9967 and the 95% CIs were 0.9967 and 1.1047. The included studies had relatively low heterogeneity p = 0.25 and I^2 = 15%. Since the CI crossed the line of no effect, the overall effect was not significant. Overall effect Z = 0.06 (p = 0.95).

Table 1 Study Descriptor Table

Author	Study design	Mean/Media Age (Experimental, Control)	Sample Size	Male	Female	Study Duration	Intervention	Outcome	Major Findings
(Udell et al, 2014)[16]	RCT	70,70	16,492	11,037	5455	2 yrs	Saxagliptin	Saxagliptin neither increased nor decreased the risk of the primary and secondary composite end points compared with placebo, irrespective of renal function	Saxagliptin do not affect the risk of ischemic cardiovascular events, increased the risk of heart failure hospitalization, and reduced progressive albuminuria, irrespective of baseline renal function.
(Chan et al, 2008)[15]	RCT	68.5, 65.3	91	47	44	54 weeks	Sitagliptin	The mean change [95% confidence interval (CI)] from baseline in HbA1c was 0.6% (0.8, 0.4) in the sitagliptin group compared with 0.2% (0.4, 0.1) in the placebo group	Sitagliptin was generally well tolerated and provided effective glycaemic control in patients with type 2 diabetes and moderate to severe renal insufficiency, including patients with ESRD on dialysis.
(Otsuki et al, 2014)[17]	Non-randomized study	69.8,66	51	31	12	28 weeks	Teneligliptin	Blood glucose level showed a 36.7 mg/dl decrease in the teneligliptin group. The differences in glycated albumin (at 28 w) and HbA1c (at 24 w) between the teneligliptin group and the control group were −3.1% and −0.57% respectively	Teneligliptin 20 mg is well tolerated, safe, and significantly improves glycemic control in diabetic patients with end-stage renal disease
(Chacra et al, 2017)[18]	RCT	69.5,64.5	213	131	82	24 weeks	Omarigliptin	After 24 weeks, the incidences of subjects with symptomatic hypoglycaemia, one or more adverse event (AE), drug-related AE, serious AE and discontinuation due to an AE were similar in the omarigliptin and placebo groups.	In this study in subjects with T2DM and RI, relative to placebo, omarigliptin provided clinically meaningful reductions in HbA1c, had a similar incidence of symptomatic hypoglycaemia and was generally well tolerated

(McGill et al, 2014)[19]	RCT	63.9, 70.2	91	57	34	54 weeks	Dipeptidyl peptidase-4 inhibitor linagliptin added to sulphonylurea	There was a similar incidence of overall adverse events (linagliptin: 79.3%, placebo: 75.8%) and hypoglycaemia (linagliptin: 37.9%, placebo: 39.4%). Severe hypoglycaemia was more common with placebo (linagliptin: 1.7%, placebo: 6.1%)	These data suggest that linagliptin is a safe and effective glucose-lowering treatment in T2DM patients with moderate-to-severe RI for whom sulphonylurea treatment is no longer sufficient.
(Lukashevich et al, 2011)[20]	RCT	64,64	515	294	221	24 Weeks	vildagliptin	After 24 weeks, the between-treatment difference in the adjusted mean change in A1C was −0.5 ± 0.1% in moderate RI (baseline A1C = 7.9%) and −0.6 ± 0.1% in severe RI (baseline A1C = 7.7%)	T2DM and moderate or severe RI, vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo. Further, relative to placebo, vildagliptin elicited a statistically and clinically significant decrease in A1C in patients with moderate or severe RI.
(Arjona Ferreira et al, 2013)[21]	RCT	64.5,58.5	139	77	52	54 weeks	Monotherapy with sitagliptin or glipizide	The incidences of symptomatic hypoglycemia and severe hypoglycemia were 6.3% versus 10.8% (between-group difference, 4.8% [95% CI, 15.7% to 5.6%]) and 0% versus 7.7% (between-group difference, 7.8% [95% CI, 17.1% to 1.9%]) in the sitagliptin and glipizide groups, respectively.	Treatment with sitagliptin or glipizide monotherapy was effective and well tolerated over 54 weeks in patients with type 2 diabetes and ESRD who were receiving dialysis

Table 1 (Continued).

Author	Study design	Mean/Media Age (Experimental, Control)	Sample Size	Male	Female	Study Duration	Intervention	Outcome	Major Findings
(Rosenstock et al, 2018)[22]	RCT	68.5,68.5	6980	4390	2590	July 2013 and August 2016	Linagliptin	A total of 5148 patients (73.8%) had prevalent kidney disease and 3990 patients (57.2%) had established CV disease with increased albuminuria	Compared with the spectrum of CV outcome trials conducted in patients with T2D to date, linagliptin has the highest number of individuals with prevalent kidney disease, including a large proportion of patients with severe kidney impairment
(Groop et al, 2014)[23]	RCT	60.11,60.11	2143	1069	1081	24 Weeks	linagliptin	The incidence of hypoglycaemia with linagliptin and placebo was 11.1 versus 6.9%, 11.9 versus 9.0% and 15.9 versus 12.0% in the normal, mild RI and moderate RI categories, respectively	Linagliptin is an effective, well-tolerated and convenient treatment in subjects with T2DM and mild or moderate RI.
(Laakso et al, 2015)[24]	RCT	66.6, 66.6	235	Unspecified	Unspecified	52 Week	Linagliptin	No results	Unspecified
Yki-Jarvinem et at, 2013[25]	RCT	59.7,60.4	1261	329	932	August 2009 and September 201	Adding Linagliptin to Basal Insulin Regimen	At week 24, HbA1c changed from a baseline of 8.3% (67 mmol/mol) by 20.6% and by 0.1% with linagliptin and placebo respectively.	Linagliptin added to basal insulin therapy significantly improved glycemic control relative to placebo without increasing hypoglycemia or body weight

| (Kothny et al, 2012)[26]	RCT	65.4, 67.35	369	207	162	52 Weeks	Dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin	In patients with moderate RI, similar proportions of patients experienced any adverse event (AE) (84 vs 85%), any serious adverse event (SAE) (21 vs 19%), any AE leading to discontinuation (5% vs 6%) and death (1% vs 0%) with vildagliptin and placebo, respectively. This was also true for patients with severe RI: AEs (85% vs 88%), SAEs (25% vs 25%), AEs leading to discontinuation (10% vs 6%) and death (3% vs 2%).	In patients with T2DM and moderate or severe RI, vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo during 1-year observation. Furthermore, relative to placebo, a clinically significant decrease in A1C was maintained throughout 1-year treatment with vildagliptin.
(Kaku et al, 2019)[27]	RCT	65.8,65.8	107	77	30	40 weeks	trelagliptin	The least square mean change (95% confidence interval [CI]) from baseline in hemoglobin A1c at the end of the double-blind phase was −0.71% (95% CI −0.885, −0.542) and 0.01% (95% CI −0.170, 0.183) in the A/A and P/A groups, respectively	Once-weekly trelagliptin 25 mg was efficacious, with no major safety concerns, and represents a meaningful treatment option in this patient population.
McGill et al, 2015[19]	RCT	63.8,64.8	811	431	379	52 Weeks	Combination of the dipeptidyl peptidase-4 inhibitor linagliptin with insulin-based regimens	Placebo-adjusted mean HbA1c changes from baseline were −0.59% (mild renal impairment) and −0.69% (moderate renal impairment) after 24 weeks and −0.43% (severe renal impairment) after 12 weeks	Adding linagliptin to insulin in type 2 diabetes mellitus patients with chronic kidney disease improved glucose control and was well tolerated.

(Continued)

Table 1 (Continued).

Author	Study design	Mean/Media Age (Experimental, Control)	Sample Size	Male	Female	Study Duration	Intervention	Outcome	Major Findings
(Cornel et al, 2016)[28]	RCT	Unspecified	14,671	Unspecified	Unspecified	December 2008 and July 2012	Sitagliptin therapy	Sitagliptin therapy was not associated with cardiovascular outcomes for any eGFR stage Kidney function declined at the same rate in both treatment groups, with a marginally lower but constant eGFR difference in those participants who were assigned to sitagliptin.	Impaired kidney function is associated with worse cardiovascular outcomes. Sitagliptin has no clinically significant impact on cardiovascular or CKD outcomes, irrespective of baseline eGFR
(Ito et al, 2011)[29]	RCT	67,68	51	35	16	24 Weeks	Administration of Vildagliptin	Vildagliptin had decreased average HbA1c levels from 6.7% baseline to 6.1%, average GA levels from 24.5% baseline to 20.5% and average postprandial plasma glucose levels from 186 mg/dL baseline to 140 mg/dL No changes in the control group.	Vildagliptin is effective for the treatment of diabetic patients on HD therapy
(Ferreira et al, 2013)[21]	RCT	Unspecified	426	Unspecified	Unspecified	54 weeks	Sitagliptin and Glipizide	There was a lower incidence of symptomatic hypoglycemia adverse events (AEs) with sitagliptin versus glipizide (6.2 and 17.0%, respectively and a decrease in body weight with sitagliptin (20.6 kg) versus an increase (1.2 kg) with glipizide (difference, 21.8 kg)	In patients with T2DM and chronic renal insufficiency, sitagliptin and glipizide provided similar A1C-lowering efficacy. Sitagliptin was generally well-tolerated, with a lower risk of hypoglycemia and weight loss versus weight gain, relative to glipizide.

Rosenstock, Perkovic, Alexander et al, 2018[22]	RCT	65.9	6991	23,390	4601	Unspecified	Linagliptin,	Adverse events occurred in 2697 (77.2%) and 2723 (78.1%) patients in the linagliptin and placebo groups; 1036 (29.7%) and 1024 (29.4%) had 1 or more episodes of hypoglycemia; and there were 9 (0.3%) vs 5 (0.1%) events of adjudication-confirmed acute pancreatitis.	Among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite CV outcome over a median 2.2 years.
(Nowicki et al, 2011)[30]	RCT	67	170	53	97	12 weeks	Saxagliptin	The adjusted mean decrease from baseline to week 12 in HbA1c was statistically significantly greater in the saxagliptin group than in the placebo group	Saxagliptin 2.5 mg once daily is a well-tolerated treatment option for patients with inadequately controlled T2DM and renal impairment.
Leiter et al, 2014[31]	RCT	63.3	771	458	313	52 week	Weekly subcutaneous albiglutide versus daily sitagliptin	Decreases in HbA1c, FPG, and weight were seen through week 52. Time to hyperglycemic rescue through week 52 was significantly longer for albiglutide than sitagliptin (P = 0.0017). Results of safety assessments were similar between groups, and most adverse events (AEs) were mild or moderate. Th	Once-weekly albiglutide therapy in renally impaired patients with type 2 diabetes provided statistically superior glycemic improvement with almost similar tolerability compared with daily sitagliptin therapy.
(Perl et al, 2016)[32]	RCT	62.6,62.9	188	77	111	24 Weeks	Saxagliptin	Mean change from baseline in A1C was significantly greater with saxagliptin 2.5 (–0.6%, P = 0.036 vs placebo) and 5 mg/day (–0.9%, P\0.001 vs placebo) compared with placebo (–0.2%).	These results suggest that saxagliptin 2.5 and 5 mg/day improve glycemic control and are generally well tolerated in patients with T2D and moderate CKD.

Abbreviations: RCT, Randomized Control Trial; CKD, Chronic Kidney disease; T2DM, Type 2 diabetes mellitus; RI, Renal Impairment; ESRD, End-Stage Renal Disease; CV, Cardiovascular; DPP-4 inhibitors, Dipeptidyl peptidase-4 inhibitor; FBG, Fasting Blood Glucose; HbA1c, Hemoglobin A1C; HD, Hemodialysis; eGFR, Estimated Glomerular Filtration Rate.
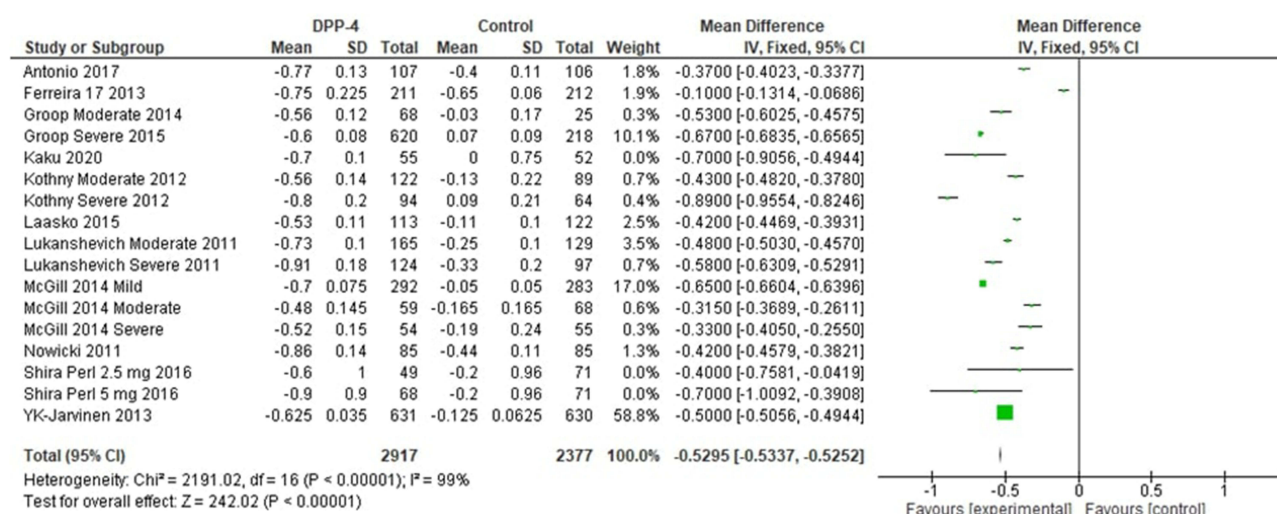
Figure 4 Forest plot of comparison: DPP-4 inhibitors vs control group (efficacy).
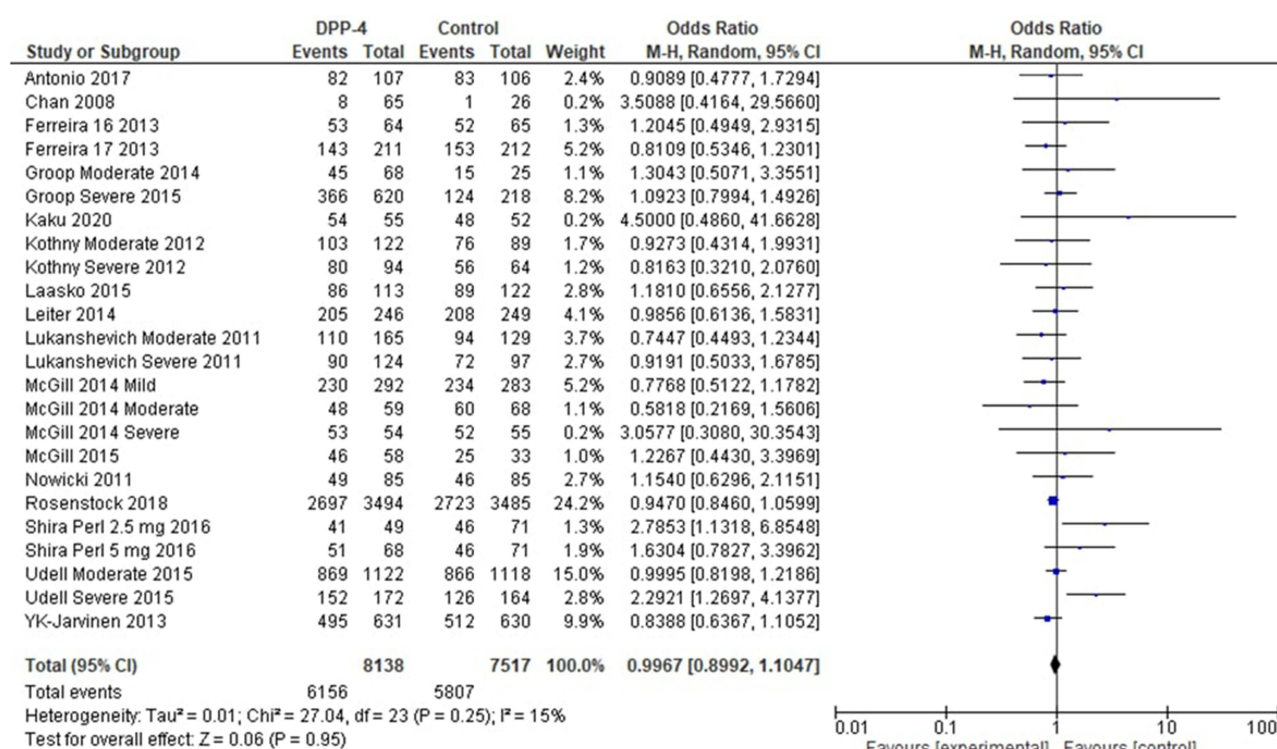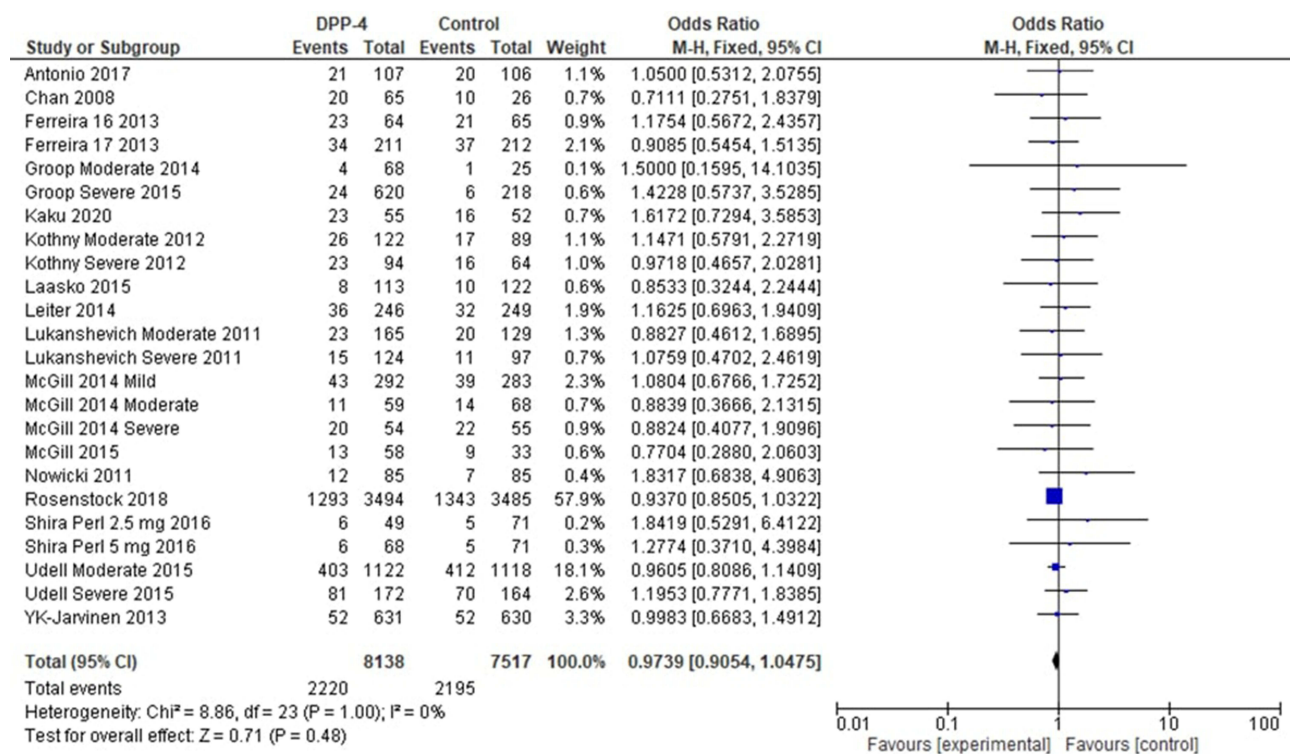

Figure 5 Forest plot of comparison: DPP-4 inhibitors vs control (Adverse Events).

The results show that there is no significant difference in the number of patients who suffered adverse events between the DPP-4 and the control group. Therefore, DPP-4 inhibitors are safe and well tolerated by patients.

Severe Adverse Effects (SAE)

The safety and tolerability of DPP-4 inhibitors in the treatment of T2DM and renal insufficiency were also evaluated by assessing the occurrence of severe adverse events [Figure 6]. In assessing the outcome of the safety and tolerability of DPP-4 inhibitors, a total of 8138 patients under the DPP-4 inhibitors group and 7517 patients under the control group were included. All studies crossed the line of no effect and were individually not significant p > 0.05. A study by

Figure 6 Forest plot of comparison: DPP-4 inhibitors vs control (Severe Adverse Effects).

Rosenstock et al had the highest precision (57.9%) (reference), while Groop et al had the lowest precision (0.1%) (reference). A fixed effect model was used, and the pooled summary effect was 0.9739 and the 95% CIs were 0.9054 and 1.0475. The included studies had low heterogeneity p = 1 and I^2 = 0%. Since the CI crossed the line of no effect, the overall effect was not significant. Overall effect Z = 0.71 (p = 0.48). The results show that there is no significant difference in the number of patients who suffered severe adverse events between the DPP-4 and the control group. Therefore, DPP-4 inhibitors are safe and well tolerated by patients.

Discussion

This meta-analysis aimed to assess the efficacy and safety of Dipeptidyl peptidase-4 inhibitors in patients with T2DM who had renal impairment. Patients with T2DM frequently have impaired renal function, particularly those older than 65, and these conditions are independently linked to higher death rates, cardiovascular events, and hospitalizations.[32]

Few treatment alternatives are available for managing hyperglycemia in patients with type 2 diabetes mellitus with ESRD receiving dialysis.[21] In order to gather more knowledge on DPP-4 inhibitors in patients with ESRD, the current study was built on a prior clinical study. It indicated that treatment with several DPP-4 inhibitors led to a reasonable improvement in glycemic control compared to a placebo. Antihyperglycemic therapy options are scarce and frequently linked with adverse side effects in patients with type 2 diabetes and CKD. Newer antihyperglycemic medications like DPP-4 inhibitors and incretin mimics may be used more frequently in people with type 2 diabetes with CKD.[15] Patients with T2DMoften have CKD, which is linked to a higher risk of hypoglycemia. Impaired renal glucose release and abnormal medication metabolism are additional risk factors for hypoglycemia brought on by CKD. Due to their lower risk of hypoglycemia, given their mechanism of action, DPP-4 inhibitors are thought to have the potential to solve several issues with hypoglycemic medications in patients with CKD.[27]

Patients in this research who received saxagliptin 2.5 mg compared favorably to those who received a placebo for the adjusted mean change in HbA1c from baseline to week 12. In individuals with moderate or severe renal impairment, analyses by baseline renal impairment category demonstrated that saxagliptin produced statistically higher adjusted mean

decreases in HbA1c than placebo. The adjusted mean reduction in HbA1c caused by saxagliptin in the ESRD subgroup was equivalent to gains made in the subgroups of patients with other forms of renal impairment. Still, it was comparable to increases made by placebo.[30] This investigation's efficacy findings align with further research in which linagliptin, combined with popular OADs, dramatically improved HbA1c levels in patients with T2DM and normal renal function. The placebo-adjusted mean decreases in HbA1c from baseline in the current group are comparable to glycaemic improvements seen in studies of other DPP-4 inhibitors in renal impairment patients.[19] The present investigation, however, is the first to precisely evaluate the use of exogenous insulin and DPP-4 inhibitor in patients with T2DM and CKD. Therefore, we think this research has therapeutically applicable applications given that most CKD patients require insulin therapy.

Without raising the risk of hypoglycemia or weight gain, linagliptin 5 mg once daily helped with glycemic management, was well-tolerated, had a favorable safety profile, and when combined with background therapy already in situ, reduced HbA1c by a factor adjusted for placebo.[23] The concurrent use of OADs, the kind of basal insulin, the patient's age, or the degree of renal impairment had no impact on these benefits. Low rates of hypoglycemia were observed when linagliptin was added to basal insulin, suggesting that a basal insulin dosage decrease may not be required to prevent hypoglycemia when linagliptin is also administered. The extension period offered new data on linagliptin's use in clinical practice, even though its primary goal was to provide long-term safety data for the drug. Linagliptin has a largely nonrenal route of elimination, like other DPP-4 inhibitors; hence, individuals with compromised renal function can change their dosage.[25]

Teneligliptin, a DPP-4 inhibitor, dramatically enhances glycemic control in diabetic patients with ESRD. Teneligliptin-related hypoglycemia or significant adverse effects were not observed during the research. Teneligliptin, a novel DPP-4 inhibitor, is effective, safe, and well tolerated in diabetic and hemodialysis patients. Teneligliptin significantly lowers blood glucose levels in diabetic ESRD patients.[17] Since hypoglycemia is closely monitored, vildagliptin is safe for treatment in diabetic patients undergoing HD.[29]

DPP-4 inhibitors have a low frequency of AEs and a minimal risk of hypoglycemia.[23] In patients with moderate-to-severe RI or ESRD, the usual clinical dose of saxagliptin, sitagliptin, and vildagliptin must be lowered. Lower doses of these DPP-4 inhibitors enhanced glycemic control in these participants. With the exception of a lower rate of hypoglycemia seen for patients in the DDP-4 inhibitors group compared with those in the placebo group, the incidences of adverse experiences overall, specific clinical adverse experiences, laboratory adverse experiences, and discontinuations because of a negative experience were comparable between the DDP-4 inhibitors and placebo groups. Patients on DDP-4 inhibitors who had type 2 diabetes and normal renal function had a low incidence of hypoglycemia in the past.[15] In general, saxagliptin was well tolerated. Individuals with moderate and severe renal impairment experienced more adverse events (AEs) when treated with saxagliptin than patients in the placebo group. Still, equal AE rates were observed in patients with end-stage renal disease (ESRD).[30] However, the total AE incidence was comparable across the two treatment groups when examined by therapy and background insulin use. There may be a misconception that saxagliptin medication is linked to more frequent AEs because insulin use was more prevalent in the saxagliptin group, despite the possibility that the imbalance is due to insulin use. Notably, all individuals taking background insulin therapy had their study drug discontinued due to AEs.

This long-term study found no brand-new safety signal or unexpected risk. There was generally no indication of hepatic, cutaneous, or pancreatitis-related safety associated with DPP-4 inhibitors when used for a year in patients with moderate or severe renal impairment, regardless of the specific focus areas for these drugs. Patients with severe renal impairment who received DPP-4 inhibitors experienced more adverse events (AEs) than those who received a placebo, primarily due to an increase in the number of mild instances of influenza.[26] Hypoglycemia and constipation are the two main side effects of teneligliptin, according to the pharmaceutical manufacturer that supplied details on domestic clinical studies.[17] Both in patients with moderate renal impairment (RI) and those with severe RI, the frequencies of any AE, any SAE, discontinuations due to AEs, and deaths with vildagliptin were comparable to those happening in patients receiving placebo.[20] Additionally, linagliptin therapy did not significantly increase body weight in patients with mild, moderate, and severe RI. This conclusion is relevant since taking insulin has been linked to extreme weight gain.[19]

This study had some limitations. Although sitagliptin and saxagliptin have been studied in patients with T2DM and moderate-to-severe RI, and no safety signals have been found for either drug, the relatively small sample size and brief (12 weeks) duration of the placebo-controlled study period of the prior studies limit conclusions about the safety of DPP-4 inhibitors in patients with T2DM and moderate or severe RI. Second, there was heterogeneity between the parent studies, and some analyses were post hoc. Third, observations during the extension are hypothesis-generating only due to the study design. Third, the trial's duration, which might have been too brief to affect kidney-related clinical outcomes like ESRD, could be a possible obstacle to correctly interpreting any renal effects. Fourth, although information on the introduction of treatments after the baseline period was available, it was not stated if linagliptin was associated with patients using fewer additional therapies. The timing of the blood sample is another limitation. Three days after the previous hemodialysis, a blood sample was collected when the dialysis procedure began. The interval following meals varied depending on the patient.

Conclusion

Patients with T2DM and CKD are among the most at risk for failure to achieve glycemic goals. The findings of this meta-analysis reveal that individuals with comorbid T2DM and CKD demonstrated significantly improved glycemic control when administered with DPP-4 inhibitors compared to the control group. Additionally, no significant disparity in the occurrence of adverse events was noted between the DPP-4 inhibitor-treated group and the control group.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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