Effects of DPP4 Inhibitors on Renal Outcomes in Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Objectives: This meta-analysis of randomized clinical trials (RCT) intends to evaluate the efficacy of DPP4 Inhibitors (DPP4I) compared with placebo, other antidiabetics (or DPP4I) on renal outcomes, adverse events (AEs), and all-cause mortality. **Methods:** We searched relevant scientific database for RCTs with DPP4I and prespecified renal end point. The effect size (mean difference or risk ratio) was reported with its 95% confidence interval. **Results:** Eight RCTs (n = 39040 participants) were included in the analysis. The rate of change in eGFR was not different in DPP4 inhibitor and control group. DPP4I use beyond 52 weeks did not worsen albuminuria progression (RR 0.88; 95% CI 0.80 to 0.96; high quality evidence) compared to placebo. The risk of AEs within 52 weeks (RR 0.93; 95% CI 0.80 to 1.08; moderate quality evidence), beyond 52 weeks (RR 0.98; 95% CI 0.97 to 1.00; low quality evidence), and all-cause mortality (RR 1.04; 95% CI 0.96 to 1.12; very low quality evidence) were similar to placebo. In head-to-head comparison between two DPP4I studies, no significant differences were found between alogliptin and vildagliptin for improvement in eGFR, UACR, or AE at 24 weeks. **Conclusions:** DPP4I do not seem to provide persuasive benefit in the renal outcomes or all-cause mortality in diabetes mellitus, though there was no evidence for increased AEs.

Keywords: Albuminuria, dipeptidyl peptidase-4 inhibitors, eGFR, meta-analysis, systematic review, T2DM, urinary albumin creatinine ratio

Introduction

Diabetes mellitus is one of the leading global public health problems among non-communicable diseases (NCD) targeted for action by world leaders. The disease prevalence has witnessed steady increase over the past few decades.[1] Among the microvascular complications associated with diabetes mellitus, diabetic kidney disease (DKD) is one of the leading causes of end-stage renal disease (ESRD). Globally, DKD accounts for approximately one-third of all patients initiating renal replacement therapy (RRT).[2] The past decade has witnessed introduction of several new medications in the armamentarium against diabetes mellitus. Notable among these, the incretin-based therapies (glucagon like peptide 1 receptor agonists and dipeptidyl peptidase 4inhibitors) have essentially paved a shift in the approach from focusing only on lowering glucose levels to strategies targeting the underlying patho-physiological processes.[3]

The DPP4I or gliptins, first introduced in 2006, represent a novel class of antidiabetic agents that inhibits the degradation of the incretin hormones—glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) leading to increased postprandial glucose-dependent insulin secretion and decreased glucagon secretion.[4] GLP-1 agonists have proven superiority in head-on comparisons with DPP4 inhibitors, and glinides are much weaker antidiabetic agents with no data to show comparability with DPP4 inhibitors. Nonclinical studies have suggested pleiotropic effects of

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DPP4 inhibition on kidney and some degree of clinical evidence insinuates possible nephroprotective effects beyond the mitigated renal risk conferred by glycemic control.[5] Although DPP4I have been used in elderly patients and in the presence of chronic kidney disease, their potential independent effects on renal outcomes have been largely undefined.[6]

Enforcement by regulatory agencies has led to the evaluation of cardiovascular safety of novel glucose-lowering drugs in large-scale clinical trials.[7] Few of these cardiovascular outcome trials have in addition identified potential drug-specific renoprotective benefits associated with the use of DPP4I, although some of the trials have reported inconsistent results on renal outcomes.[8] It is also noteworthy that the renal outcomes were secondary or additional endpoints in some landmark trials.[9] It is also difficult to presume whether the potential renoprotection encompasses all patients, as many of these studies were essentially performed in patients with an established cardiovascular disease or high cardiovascular risk.[10] Current evidence is suggestive of potential, yet questionable independent renoprotection of DPP4I beyond the benefit bestowed by glycemic control in diabetics. To address this uncertainty, we conducted this systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effects of DPP4I on renal outcomes compared with placebo or other antidiabetic drugs in patients with diabetes mellitus.

Methods

Study design

This systematic review and meta-analysis was performed according to a pre-specified protocol developed by the authors [Appendix 1]. The methods employed aligned to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for the conduct and reporting of this systematic review and meta-analysis [Appendix 2]. The protocol for this review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) for registration before the analyses were initiated (on March 18, 2019) and the protocol was registered before the analyses was completed (PROSPERO registration number CRD42019128775). To address our study objective, the primary outcomes of the study were changes in eGFR (estimated glomerular filtration rate), UACR (urine albumin creatinine ratio) at 24 weeks and 52 weeks and the secondary outcomes were incidence of adverse events and all-cause mortality within 52 weeks and end of treatment.

Data sources and search strategy

We performed systematic literature search in several electronic databases—the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE to identify RCT of DPP4I published from inception to February 2021, with no restriction of language. The search terms used were dipeptidyl peptidase 4 inhibitors, DPP4I, and the names of individual DPP4I. The detailed search strategy including search words for renal outcomes and term string strategies is provided [Appendix 3]. To capture unpublished data of included trials, the US clinical trial registry platform www.clinicaltrials.gov was searched.

Inclusion and exclusion criteria

Trials meeting the following criteria were included: (1) randomized controlled clinical trials (2) patients aged ≥18 years with diabetes with HbA1c of ≥6.5% at enrolment (3) reported primary outcome measures in terms of either eGFR or UACR, or both (4) reported secondary outcome measures in terms of incidence of all-cause mortality or adverse effects. Exclusion criteria were: (1) full text of published trials in language other than English (2) trials without full text (3) different publications from same set of original RCT data published earlier.

Risk of bias assessment

Two authors (SC, SKD) independently assessed the quality and risk of bias for each included study, using the Cochrane's risk of bias tool[11] based on six attributes of trials: sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other sources of bias. Attributes were assessed as low risk, high risk, or unclear risk. Any disagreements were resolved by discussion with two other authors (SP, KP).

Data extraction

Two authors (SKD and RC) independently extracted data using pre-validated data extraction forms according to the registered protocol. For our pre-specified primary renal outcomes of interest, namely changes in UACR and eGFR, mean changes from baseline along with standard deviations were extracted for continuous variables in the intervention DPP4I and control (placebo or other antidiabetic drugs) groups. In studies reporting UACR, extent of progression or regression of albuminuria and the number (proportion) of patients experiencing such deterioration were extracted. For the secondary outcomes of interest, namely incidence of adverse effects and all-cause mortality, we extracted the number (proportion) of patients reporting these pre-specified outcomes, the data being dichotomous in nature. Information was collected about the study authors, year of publication, number of randomized participants, study duration, intervention and comparator arms, background therapy for glycemic control, baseline UACR and eGFR, and the history of cardiovascular disease, heart failure, and CKD (eGFR <60 mL/min/1.73 m^2). For multiple-dose studies, we combined the different dose groups of the same drug into a single group. Wherever possible, data was extracted to allow an intention-to-treat analysis. In case of insufficient or missing data, the authors were contacted for additional information. All relevant data was analysed using Review Manager Version 5.3.5 software.[12] The reliability of data extraction and data entry was examined throughout the process.

Data synthesis and analysis

Mean differences (MD) with 95% confidence interval (CI) were calculated to measure the effect size for eGFR (24 weeks and 52 weeks) and UACR for pre-specified timeframes (24 weeks

and 52 weeks) and more than 52 weeks for long-term effects. Relative risks (RR) with 95% CI were computed to estimate the effect size for incidence of adverse effects, albuminuria progression, and all-cause mortality within 52 weeks and up to end of study. We pooled the effect size (MD or RR) across applicable included studies using the fixed-effects model. Random-effects model was explored whenever statistical heterogeneity was significant. Statistical heterogeneity was estimated using the χ^2 test and I^2 statistics. P value of <0.10 and $I^2 > 50\%$ were regarded as significant for statistical heterogeneity, whereas for treatment effect, P value of <0.05 was considered statistically significant. Reporting bias, especially publication bias was evaluated by asymmetry in the funnel plot for renal outcomes. Statistical analysis was performed using Review Manager Version 5.3 software (Cochrane Library Software, Oxford, UK).[12]

Sensitivity analysis

Among the included RCTs, some trials had a 2–4 week run-in period prior to the study intervention. The placebo and/or active drug run-in period represents a potential source of bias since it may select participants who are more compliant and/or less likely to experience AE. Therefore, a sensitivity analysis was conducted to explore the effect of pre-intervention run-in period on the effect size for various outcomes.

Quality of evidence analysis

The overall quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, which takes into account five criteria not only related to the internal validity such as study limitations (risk of bias), inconsistency, imprecision, and publication bias, but also to external validity like indirectness of results.[13] For each comparison, two review authors SKD and NY independently rated the quality of evidence for each outcome as 'high,' 'moderate,' 'low,' or 'very low' using GRADE pro GDT.[14] Discrepancies were resolved by the other review authors SC and SP.

Results

Retrieval and characteristics of included studies

Figure 1 depicts the study screening and selection process. Of 897 records retrieved through the database search, eight studies from seven publications[9,10,15-19] were included in the systematic review. One publication[18] was segregated into two studies (a, b) as per protocol, thereby computing to a total of eight included studies. Consistent with our pre-specified protocol, we grouped the included studies to allow for the following comparisons: a) DPP4I versus placebo b) DPP4I versus active control, and c) DPP4I versus DPP4I for each of the outcome measures. The characteristics of the included studies and their participants are described in Table 1, and Figure 1 enlists selection of studies for the systematic review.

Risk of bias assessment

The Cochrane risk of bias tool[11] for randomized controlled clinical trials in Revman 5.3.5[12] was used for the assessment

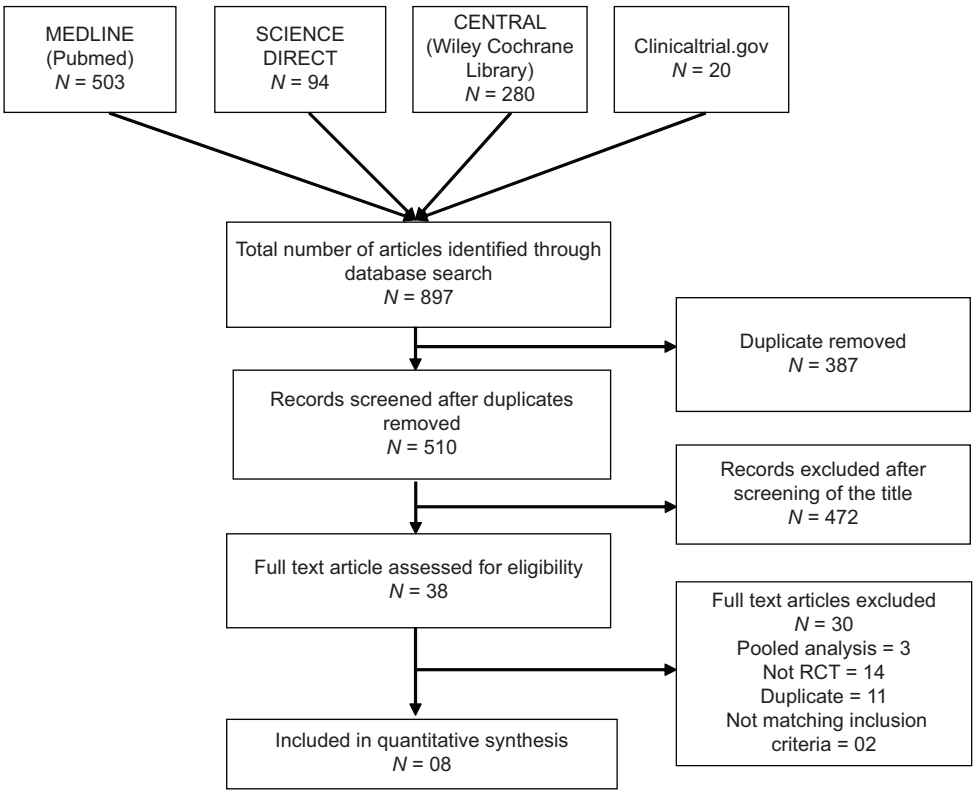

Figure 1: Selection of studies for the systematic review

Table 1: Characteristics of included studies

Study ID	Intervention (Dose)	Control (Dose)	Study duration	Follow-up	Outcomes Reported	Patient population				
						Baseline eGFR	Treatment naïve (N)/ experienced (E)	Background treatment	Co-morbidities	Total sample size
Cornel2016	Sitagliptin (100 mg OD to 25 mg OD) n=7332	Placebo n=7339	3 yrs	52 wks; EOT	eGFR, UACR, AE, All-cause mortality	>30	E only	metformin, pioglitazone, sulfonylurea, insulin	myocardial infarction coronary artery disease cerebrovascular disease peripheral arterial disease heart failure, dyslipidemia	14671
Chacra2017	Omarigliptin (25 mg once weekly to 12.5 mg once weekly) n=107	Placebo n=106	24 wks	24 wks	eGFR, AE	<60	N and E both	insulin other oral hypoglycemic agents	obesity	213
Groop 2017	Linagliptin (5 mg OD) n=182	Placebo n=178	24 wks	24 wks	eGFR, UACR, AE	>30	N only	N. A	obesity, hypertension	360
McGill 2012	Linagliptin (5 mg OD) n=68	Placebo n=65	52 wks	12 wks; 52 wks	eGFR, AE	<30	E only	insulin, sulfonylurea, meglitinides, pioglitazone, alpha glucosidase inhibitor	hypertension, diabetic nephropathy, diabetic retinopathy, metabolic syndrome	133
Mosenzon 2016	Saxagliptin (2.5 to 5 mg OD) n=8280	Placebo n=8212	2.1 yrs	52 wks EOT	eGFR, UACR, AE, All-cause mortality	≤ 50	N and E both	metformin, sulfonylurea, thiazolidinediones, insulin	established CVD, prior heart failure, hypertension, hyperlipidemia.	16492
Rosenstock 2018	Linagliptin (5 mg OD) n=3499	Placebo n=3492	1.7 yrs	12 wks; 52 wks; EOT	eGFR, UACR, AE, All-cause mortality	≥15	E only	insulin, metformin, sulfonylurea	hypertension, ischemic heart disease, heart failure, atrial fibrillation, chronic kidney disease, obesity	6991
Tanaka 2016a	Alogliptin (25 mg OD) n=25	Vildagliptin (50 mg BD) n=23	24 wks	12 wks; 24 wks	eGFR, UACR, AE	≥60	N and E both	metformin, sulfonylurea, pioglitazone, alpha glucosidase inhibitor		48
Tanaka 2016b	Alogliptin (25 mg OD) n=64	Vildagliptin (50 mg BD) n=68	24 wks	12 wks; 24 wks	eGFR, UACR, AE	≥60	E only	metformin, sulfonylurea, pioglitazone, alpha glucosidase inhibitor, sitagliptin		132

EOT = End of treatment; eGFR = Estimated glomerular filtration rate (ml/min); UACR = Urinary albumin creatinine ratio (mg/gm); AE = Adverse event

of risk of bias. Two review authors (SKD, NY) independently assessed them without blinding to authorship or journal. The summary of the risk of bias is presented in Figure S1. ROB for the interventional studies showed that there was low risk of bias in two RCTs,[9,10] whereas the remaining ones had moderate risk of bias.

Effects of interventions

DPP4I versus placebo

Short-term (up to 52 weeks) efficacy and safety of DPP4I compared to placebo

Six RCTs assessed the effects of DPP4I compared to placebo for short-term use (up to 52 weeks).

Primary outcomes

Changes in eGFR

Results were noted at 24 weeks; the rate of change in eGFR was not different in DPP4 inhibitor and control group, and the quality of evidence was considered as low [MD -1.53; 95% CI -3.34 to 0.29, 3 trials; n = 652; Figure 2a, Table 2A]. At 52 weeks, the observed effects [MD: 0.08; 95% CI -3.40 to 3.55; 2 trials; n = 14661; Figure 2b] were similar to that of earlier time points but the quality of evidence was very low [Table 2A]. The quality of evidence for this outcome at different time points had to be downgraded due to imprecision, inconsistency, and indirectness of results.

For changes in eGFR at 52 weeks, subgroup analysis showed no improvement in eGFR with sitagliptin (MD -1.30 with 95% CI -1.93 to 0.67, 1 trial; n = 10097) and linagliptin (MD 2.36 with 95%CI -1.24 to 5.96, 1 trial; n = 133).

Changes in UACR

Four out of six included placebo-controlled trials reported this outcome. Pooled analysis for changes in UACR was not feasible, as summary measures represented in the individual studies for this outcome were essentially not amenable for quantitative data synthesis. Groop 2017[16] (linagliptin vs. placebo) reported non-significant changes in the median UACR and 24 weeks post treatment, respectively. Cornel 2016[9] (sitagliptin versus placebo) reported mean changes of UACR from baseline, which were not significant compared to placebo at 4 months (-2.1 ± 27.5 vs. -1.4 ± 24.1), 8 months (2.1 ± 39.4 vs. 0.5 ± 44.5) and 12 months (1.3 ± 30.2 vs. 1.2 ± 32.3).

Secondary outcomes

Adverse effects

Compared with placebo, DPP4I treatment was not associated with increased AE rates (RR 0.93; 95% CI 0.80 to 1.08; 3 trials; n = 700; Figure 3). In our analysis, this corresponded to 337 less AEs per 1000 participants (95% CI: 1077 less to 403 more). However, the quality of the evidence was found to be moderate as the quality of evidence of this outcome was downgraded due to imprecision and inconsistency of results [Table 2A].

All-cause mortality

None of the studies reported mortality data.

Long-term (beyond 52 weeks) efficacy and safety of DPP4I compared to placebo

Primary outcomes

Changes in eGFR

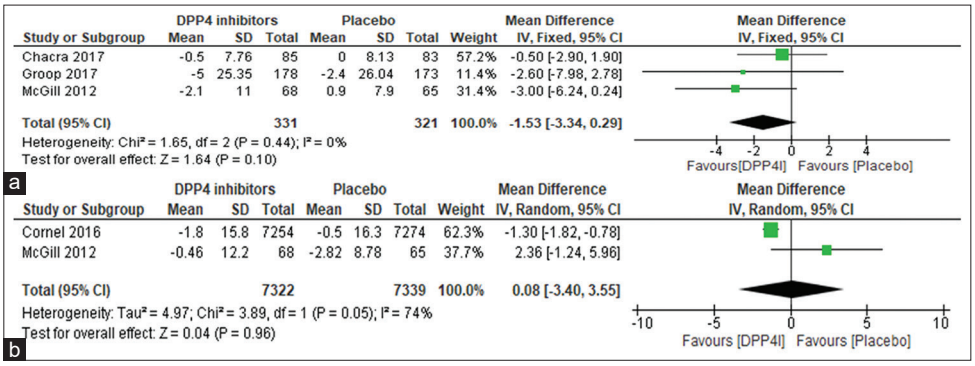

Figure 2: Short-term effects (within 52 weeks) of DPP4I versus placebo. (a) Changes of eGFR at 24 weeks; (b) Changes of eGFR at 52 weeks

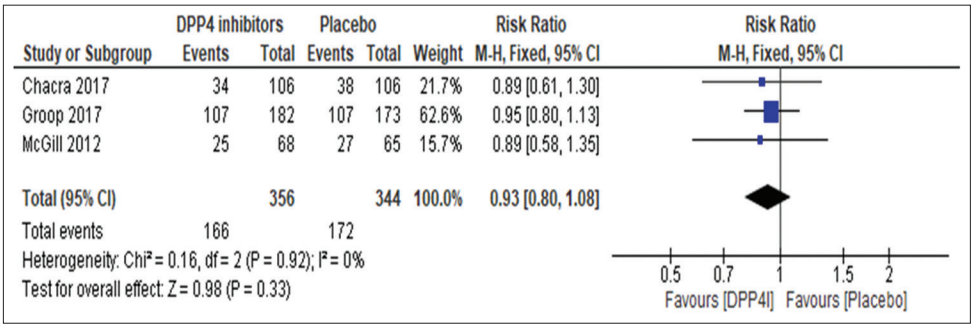

Figure 3: Relative risk of adverse events of short-term use (within 52 weeks) of DPP4I versus placebo

Quantitative synthesis was forsaken as we failed to obtain the continuous data. Mosenzon 2016[10] reported a non-significant doubling of serum creatinine with saxagliptin. Rosenstock 2018[15] reported renal outcomes in terms of sustained decrease ≥40% in eGFR from baseline and found no significant differences with linagliptin.

Cornel 2016[9] showed significant changes in eGFR (sitagliptin versus placebo) from baseline compared to placebo at 2 years (-3.2 ± 17.9 vs. -1.7 ± 17.7) and 3 years (-3.8 ± 18.1 vs. -1.6 ± 18.7), but the changes were not significant at 4 years (-4.0 ± 18.4 vs. -2.8 ± 18.3), and 5 years (-4.2 ± 17.4 vs. -5.7 ± 17.2).

Changes in UACR

DPP4I may retard albuminuria progression [RR 0.88; 95% CI 0.80 to 0.96; 2 trials; n = 14741; Figure 4a] and the quality of the evidence was high [Table 2A]. This corresponds to 30 less participants developing progression of albuminuria per 1000 participants (95% CI: 43 less to 17 less). Cornel 2016[9] showed consistently non-significant changes in mean UACR values from baseline compared to placebo at the end of 2 years (0.5 ± 33.1 vs. 3.1 ± 30.7), 3 years (2.6 ± 25.8 vs. 3.9 ± 30.3), 4 years (1.9 ± 16.3 vs. 1.6 ± 24.5), and 5 years (-2.5 ± 9.7 vs. 6.4 ± 16.4).

On subgroup analysis, delay in albuminuria progression was observed with both linagliptin (RR 0.92; CI 0.85 to 0.99; 1 trial; n = 4291) and saxagliptin (RR 0.84; CI 0.76 to 0.91; 1 trial; n = 10450).

Secondary outcomes

Adverse effects

The relative risk of adverse events with DPP4I was 0.98 compared to that of placebo [95% CI 0.97 to 1.00; 3 trials; n = 38011; Figure 4b] and the quality of evidence was low [Table 2A]. This corresponds to 7 less AE per 1000 participants (95% CI: 17 less to 2 more).

All-cause mortality

DPP4I do not appear to improve mortality [RR 1.04; 95% CI 0.96 to 1.12; 3 trials; n = 38142; Figure 4c]. This corresponds to two more deaths per 1000 participants (95% CI: 2 less to 7 more). We downgraded the quality of evidence of this outcome to be very low due to indirectness, imprecision, and inconsistency of results [Table 2A].

DPP4Is versus active control

None of the included studies have reported efficacy and safety data beyond 12 weeks.

Head-to-head comparison of DPP4I

Only two studies compared alogliptin to vildagliptin.

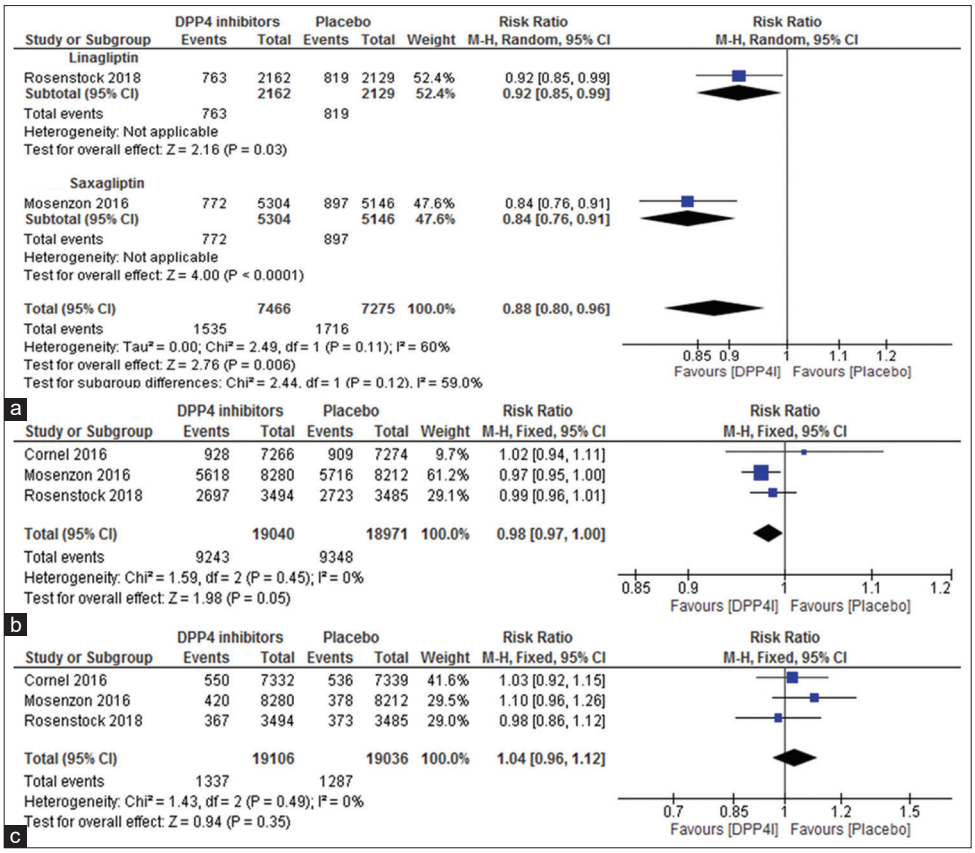

Figure 4: Long-term effects (beyond 52 weeks) of DPP4I versus placebo. (a) Relative risk of albuminuria progression; (b) Relative risk of adverse events; (c) Relative risk of all-cause mortality

Table 2: Summary of findings of the results

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Plain language summary
	Risk with intervention	Risk with comparator				
A: Intervention: DPP4 inhibitors, Comparator: Placebo						
Changes in eGFR at 24 weeks from baseline	MD 1.53 lower (3.34 lower to 0.29 higher)	The mean changes in eGFR at 24 weeks from baseline was 0	-	652 (3 RCTs)	⊕⊕◯◯ LOW[b,c]	We are uncertain of the effect of DPP4I on changes of eGFR at 24 weeks from baseline
Changes in eGFR at 52 weeks	MD 0.08 higher (3.4 lower to 3.55 higher)	The mean changes in eGFR at 52 weeks was 0	-	14661 (2 RCTs)	⊕◯◯◯ VERY LOW[a,b,c,d,e]	We are very uncertain of the effect of DPP4I on changes of eGFR at 52 weeks from baseline
Adverse events within 1 year	465 per 1,000	500 per 1,000	RR 0.93 (0.80 to 1.08)	700 (3 RCTs)	⊕⊕⊕◯ MODERATE[b]	Probably there is little or no difference in adverse events within 1 year
Albuminuria progression at EOT (more than 1 year)	208 per 1,000 (189 to 226)	236 per 1,000	RR 0.88 (0.80 to 0.96)	14741 (2 RCTs)	⊕⊕⊕⊕ HIGH	We are certain that DPP4I results in delayed progression of albuminuria at more than 1 year
Adverse events – long-term	483 per 1,000 (478 to 493)	493 per 1,000	RR 0.98 (0.97 to 1.00)	38011 (3 RCTs)	⊕⊕◯◯ LOW[b,e]	There may be little or no difference in adverse events
All-cause mortality	70 per 1,000 (65 to 76)	68 per 1,000	RR 1.04 (0.96 to 1.12)	38142 (3 RCTs)	⊕◯◯◯ VERY LOW[b,e,f]	We are very uncertain of the effect of DPP4I on all-cause mortality
B: Intervention: Alogliptin, Comparator: Vildagliptin						
Changes in eGFR at 24 weeks	MD 0.21 lower (2.53 lower to 2.1 higher)	The mean eGFR changes at 24 weeks was 0	-	180 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,e,g]	We are very uncertain of the effects of alogliptin compared to vildagliptin on changes of eGFR at 24 weeks from baseline
Changes inUACR at 24 weeks	MD 19.45 higher (7.68 lower to 46.58 higher)	The mean UACR changes at 24 weeks was 0	-	180 (2 RCTs)	⊕⊕◯◯ LOW[a,b,g]	We are uncertain of the effects of alogliptin compared to vildagliptin on changes of UACR at 24 weeks from baseline
AE at 24 weeks	22 per 1,000 (4 to 128)	22 per 1,000	RR 1.00 (0.17 to 5.81)	180 (2 RCTs)	⊕⊕◯◯ LOW[b,e,g]	We are uncertain about the difference in adverse events between alogliptin and vildagliptin at 24 weeks

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; RR: Risk ratio a. CI of studies did not overlap with each other b. CI includes null effect c. eGFR is a surrogate marker d. High I^2 value e. Variation in effect size of the studies f. It does not reflect the actual number of deaths due to renal causes g. Small sample size h. Bias was detected in studies

Short-term (up to 52 weeks) efficacy and safety of DPP4I compared to other DPP4I

The effect of DPP4I compared to other DPP4I was assessed in short-term use of 24 weeks in 2 RCTs.

Primary outcomes

Changes in eGFR

There was no difference between alogliptin and vildagliptin on eGFR changes at 24 weeks [MD: -0.21; 95% CI -2.53 to 2.10; 2 trials; n = 180; Figure 5a. However, the quality of evidence was very low Table 2B]. We downgraded the quality of evidence of this outcome due to imprecision, inconsistency, and indirectness of results.

Changes in UACR

There was no difference between alogliptin and vildagliptin for change in UACR at 24 weeks of treatment (MD: 19.45; 95% CI -7.68 to 46.58; 2 trials; n = 180; Figure 5b. The quality of evidence was low due to imprecision and inconsistency of results [Table 2B]. Heterogeneity is possibly due to active run-in period present in one trial.

Secondary outcomes

Adverse effects

AE reported with alogliptin [RR 1.0; 95% CI 0.17 to 5.81; 2 trials; n = 180; Figure 5c] were similar to vildagliptin. We downgraded the quality of evidence of this outcome to low due to imprecision and inconsistency of results [Table 2B].

All-cause mortality

None of the studies presented mortality data.

Long-term (beyond 52 weeks) efficacy and safety of DPP4Is compared to other DPP4 inhibitors

None of the included studies have reported long-term (beyond 52 weeks) efficacy and safety data.

Discussion

Summary of main results

Current treatment guidelines of diabetes mellitus target not merely on glycemic control but also recommend measures aimed for slowing or prevention of complications of diabetes. Interestingly, newer pharmacological therapies for diabetes have been reported to have potential benefit beyond glycemic control in diabetics. We conducted this systematic review and meta-analysis of randomized controlled trials (RCTs) to explore the effects of DPP4I on renal outcomes compared with placebo or other antidiabetic drugs in patients with diabetes mellitus. Parameters such as eGFR and UACR are generally used as endpoints of disease progression in assessing renal outcomes in the context of clinical trials. Though there is no consensus as to whether these are truly surrogate or indirect endpoints of renal outcome, it is preferable to consider them so, as true clinical endpoints often may not be assessed due to various logistic constraints, notable among which is the short duration of most studies.

Data extracted from the eligible RCTs were analysed for three comparisons. The results of the included studies mostly pertain to short time-horizon of 52 weeks of treatment, whereas results of long-term effects (beyond 52 weeks) are largely insufficient. The preponderance of evidence pertains to the use of DPP4I compared to placebo. Though DPP4I does not improve eGFR compared to placebo over short-term and long-term use, progression of albuminuria appears to be reduced with DPP4I compared to placebo on long-term use. On long-term use, the rates of AE were not high with DPP4I and there was no evidence of mortality benefit with DPP4I. Compared with active control, DPP4I does not improve eGFR but incidence of AE appears to be less. However, data for long-term safety and efficacy is deficient. Rates of AE are similar with the use of both DPP4I. All the study results are limited to treatment duration of 24 weeks and data are lacking for long-term safety and efficacy.

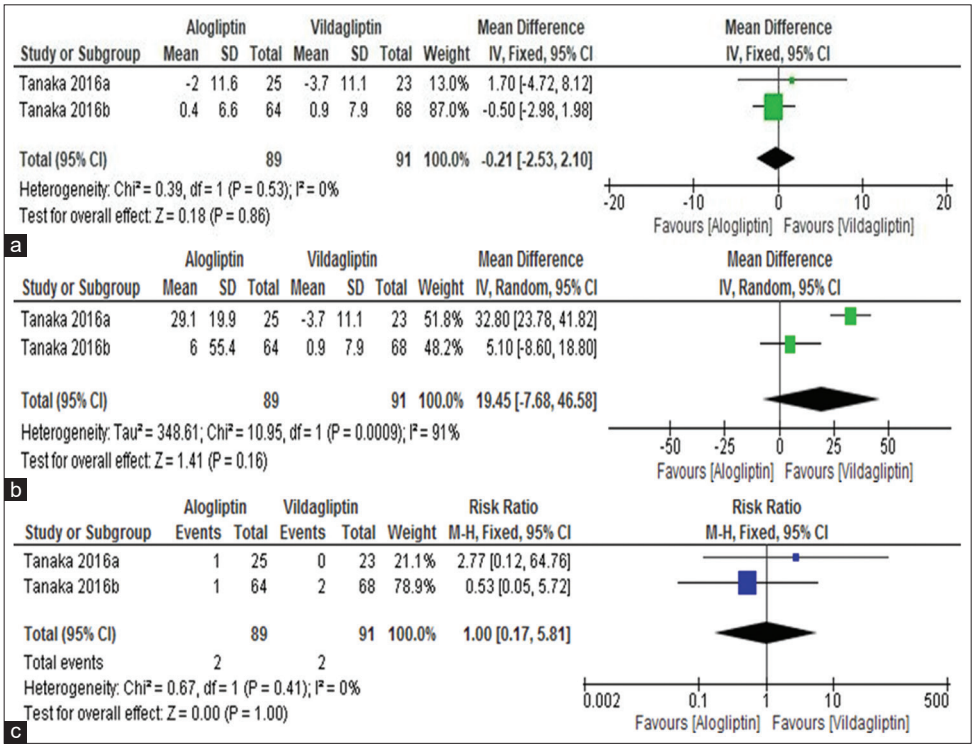

Figure 5: Short-term effects (within 52 weeks) of alogliptin versus vildagliptin. (a) Changes of eGFR at 24 weeks; (b) Changes of UACR at 24 weeks; (c) Relative risk of adverse events

Overall completeness and applicability of evidence

The review included a total of eight RCTs comparing DPP4I to placebo in diabetic participants (n = 39,040). Five studies were short-duration efficacy studies (maximum of 52 weeks) and three studies provided evidence for long-term efficacy. The rate of change in eGFR was not different in DPP4 inhibitor and control group. Observations among different DPP4Is have revealed that vildagliptin appears to be similar to alogliptin in eGFR changes but there is a lack of long-term efficacy data. Therefore, the current evidence is not sufficient to derive conclusions regarding efficacy of various other DPP4I on eGFR.

In this context it is appropriate to state that as yet, there is no consensus on the extent to which slowing of eGFR decline can be considered clinically meaningful to confer renoprotection by pharmacotherapy. Therefore, there is need for generating more evidence in appropriately designed studies to detect clinically meaningful differences in eGFR.

DPP4I may not worsen albuminuria progression as noted in changes in UACR compared with placebo on long-term use. However, adequate data comparing different DPP4I were not available for generating evidence for this parameter.

All included studies reported adverse events and serious adverse events.[9,10,15-19] While majority of the studies[10,15-18] reported safety profile of the drugs as treatment-emergent adverse events, the rest did not explicitly state the causality. The risk of adverse events and the all-cause mortality with DPP4I was similar to placebo. Head-to-head comparison of alogliptin and vildagliptin did not reveal any meaningful differences in AE.

Quality of the evidence

We included eight RCTs for the three comparisons as planned. The quality of evidence was high for progression of albuminuria but ranged from moderate to very low for all other outcomes.

Potential bias in the review process

During the conduct of the review, some deviations were made from the protocol, namely inclusion of only RCT reorganizing the objectives, dropping a few secondary outcomes, and subgroups as in the absence of sufficient data, we could not perform these analyses. These modifications were done to reduce the length, improve the readability, and to focus on the patient-oriented outcomes that are important for clinical practice. This is unlikely to introduce bias in the process of conducting this systematic review.

Extensive literature search was conducted. Certain limitations were noted during the review process like the challenges of excluding non-English language studies. Another limitation was with respect to the detection of serious and/or rare AE. This review included only the RCTs, and other nonrandomized studies were excluded. Therefore, it may jeopardize the scope for comprehensive detection of AE that are encountered in population-based studies.

This review included data from the RCTs and there was some information represented graphically in some of the included studies. With repeated attempts to obtain the data from two RCTs,[15,17] we failed. We imputed some data from the different graphs and figures published in those studies.

Agreements and disagreements with other studies or reviews

There is only one meta-analysis, which has been conducted prior to the present one for evaluating the emerging evidence comparing the effects of DPP4I to placebo and other active comparators with respect to renal outcomes.

Bae *et al*. 2019[20] reported a small reduction in eGFR levels with DPP4I use compared to placebo. Their findings must be interpreted cautiously as the eGFR data was pooled across all time points for analysis and not at specified time points. Our study showed no significant decrease in eGFR levels with DPP4I use compared to placebo at 52 weeks. Unlike Bae *et al.* 2019, we only included studies that reported our studied pre-specified renal outcomes as their primary endpoints. Disagreements of our study results with Bae *et al.* 2019 may partly be due to pooling of data across time intervals unlike our study. No significant differences were detected in the incidence of adverse events within 1 year, as well as beyond 1 year following treatment with DPP4I compared to placebo. Addition of DPP4I does not offer mortality benefit in patients with diabetes over one year of use. Our study also focused on the progressive changes in albuminuria exhibited by DPP4I compared to placebo whereas the previous meta-analysis tracked regression in albuminuria.

Our study has some limitations. First, we collected data of eGFR and UACR as continuous variables, although KDIGO considers a 40% decrease in eGFR from baseline as a clinically more meaningful endpoint. Second, some missing data had to be imputed from figures using Web-plot Digitizer; hence the values were close estimates of the actual values. Third, we could not evaluate the renal effects of DPP4I stratified by cardiovascular risk, notable among which is hypertension. Lack of availability of data in the included studies, stratified by duration of hypertension, nature of antihypertensive drug therapy and, extent of control of hypertension with such therapy did not permit us to address this pertinent issue.

The aforesaid factors make our review to stand out and reinforce the methodological rigor on the basis of a published protocol *a priori* in the PROSPERO platform, a comprehensive literature search of the published and unpublished literature irrespective of language, and the use of GRADE on a per outcome basis.

Conclusions

DPP4I did not show any significant improvement in eGFR or mortality compared to placebo, though there is an indication for retarding albuminuria progression with 52 weeks of use in

patients with type 2 diabetes mellitus. The available evidence for supporting the use of DPP4I for improving renal outcomes and mortality in type 2 diabetes mellitus patients seem rather inconsistent and weak. Therefore, there is need for further good quality randomized controlled trials to substantiate claims of benefit with its usage on renal endpoints. A head-to-head comparison of different DPP4Is is required to generate conclusive evidence of the effects of individual agents on the above investigated outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix

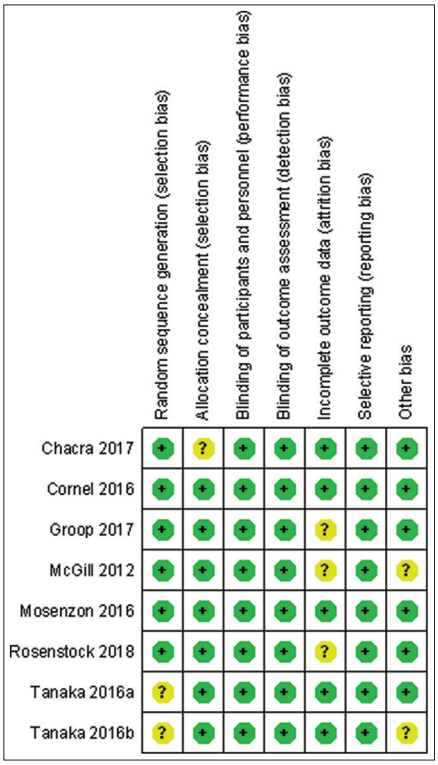

Figure S1: Risk of bias assessment for included studies. Red = High risk, Yellow = Unclear risk, Green = Low risk

Supplementary File

Appendix 1: Study Protocol

1. Title: DPP4 inhibitors for renoprotective effects in diabetic patients
2. Objectives: To evaluate the effects of dipeptidyl peptidase-4 (DPP-4) inhibitors on renal outcomes in patients with type 2 diabetes (T2D) compared with placebo within DPP-4 inhibitors or other antidiabetic agents.
3. Protocol and registration: The protocol for this review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) for registration prior to analysis (on March 18, 2019 registration number CRD42019128775)
4. Reporting: This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.
5. Eligible criteria

- Study characteristics
  - (1) Population: patients with diabetes
  - (2) Intervention: DPP-4 inhibitors
  - (3) Comparison: placebo or other antidiabetic agents
  - (4) Outcomes of interests
    1. Changes in estimated glomerular filtration rate (eGFR) from baseline
    2. Changes in urine albumin-to-creatinine ratio (UACR) from baseline
    3. Progression of albuminuria, defined as the development of microalbuminuria or macroalbuminuria from normoalbuminuria; development of macroalbuminuria from microalbuminuria
    4. Incidence of adverse events
    5. Incidence of all-cause mortality
  - (5) Time: at 24 weeks, at 52 weeks, and at the end of treatment (When study duration is more than 52 weeks)
  - (6) Study design: randomized controlled trials (RCTs)
  - (7) Length of follow-up: at least 24 weeks of study duration
- Report characteristics
  - (1) Years considered: published from inception to February 2021
  - (2) Language: no limitation of language
- Inclusion criteria: (1) Randomized and quasi-randomized controlled clinical trials (2) patients aged ≥18 with diabetes with HbA1c of ≥6.5% at enrolment (3) the intervention included any DPP-4 inhibitor as monotherapy or add-on therapy versus placebo or any other antidiabetic including other DPP-4 inhibitors for at least 24 weeks (4) reported primary outcome measures in terms of either eGFR or UACR, or both (5) reported secondary outcome measures in terms of incidence of all-cause mortality or adverse effects.
- Exclusion criteria were: (1) trials published full text in language other than English (2) trials without full text (3) duplicate publications of original RCT.

6. Information sources: We searched electronic databases of MEDLINE and the Cochrane Central Register of Controlled Trials.
7. Search strategy: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and Science Direct to identify RCTs of DPP-4 inhibitors published from inception to February 2021 with no restriction of language. The search terms used for DPP-4 inhibitors were dipeptidyl peptidase 4 inhibitors, DPP-4 inhibitors, and the names of individual DPP-4 inhibitors. To detect unpublished data of included trials, the US clinical trial registry platform was searched.
8. Study selection: All identified records were screened and evaluated for eligibility by two reviewers independently. We reviewed titles, abstracts, and full texts of the studies thoroughly. Any disagreements were resolved by consensus among investigators of this study.
9. Data extraction: For the primary renal endpoints of interest, namely changes in UACR and eGFR, mean changes from baseline along with standard deviations were extracted for continuous variables in the intervention (DPP-4 inhibitors) and control (placebo or other antidiabetic drugs) groups. In studies reporting UACR in terms of progression of albuminuria, the number of patients experiencing such deterioration was extracted. For our secondary outcomes of interest, namely incidence of adverse effects and all-cause mortality, we extracted the number of patients reporting these prespecified outcomes, the data being dichotomous in nature. Information was collected about the first author, year of publication, number of randomized participants, study duration, intervention and comparator arms, background therapy for glycemic control, baseline UACR and eGFR, and the history of cardiovascular disease, heart failure, and CKD (eGFR <60 mL/min/1.73 m^2).
10. Assessment of study quality and risk bias: We assessed quality and risk of bias of included studies using the Cochrane Risk of Bias Tool. Two reviewers independently evaluated each study based on the following aspects of trials:
    1) Random sequence generation

2) Allocation concealment
3) Blinding
4) Incomplete outcome data
5) Selective reporting
6) Other sources of bias.

Study quality was assessed using GradePro independently by two authors.

11. Data synthesis

Mean differences (MD) with 95% confidence intervals (CIs) were calculated to measure the effect size for UACR and eGFR for prespecified timeframes (up to 1 year and greater than 1 year). Relative risks (RRs) with 95% CIs were used to estimate the effect size for incidence of adverse effects (within 1 year and long term), albuminuria progression at the end of treatment and all-cause mortality.

Appendix 2: PRISMA Statement

Section/topic	Serial no	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3,4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating what were prespecified.	4
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5

Contd...

Appendix 2: Contd...

Section/topic	Serial no	Checklist item	Reported on page
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity, meta-regression [see Item 16]).	N. A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Appendix 2: PRISMA Statement

Appendix 3: Search Terms, Method and Identification of Studies

The following sources were searched extensively for eligible study reports:

1. Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2008) were searched using the following terms:
   "diabetes mellitus AND (dipeptidyl peptidase 4 inhibitors OR DPP-4 inhibitors) AND (renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR)" term string strategies were:
2. MEDLINE (2006 to present) electronic searches (provided by PubMed).
   For MEDLINE, we used the following search terms: "diabetes mellitus AND (dipeptidyl peptidase 4 inhibitors OR DPP-4 inhibitors) AND (renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR)". We tagged terms to Title/Abstract.
   In addition, individual name of the drugs were also used:
   "sitagliptin and diabetes mellitus", "sitagliptin AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR", "sitagliptin AND diabetes mellitus AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR", "saxagliptin AND diabetes mellitus", "saxagliptin AND renal outcomes", "saxagliptin AND diabetes mellitus AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR", "omarigliptin AND diabetes mellitus", "omarigliptin AND renal outcomes", "omarigliptin AND diabetes mellitus AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR ", "alogliptin AND diabetes mellitus", "alogliptin AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR", "alogliptin AND diabetes mellitus AND renal outcomes", "linagliptin AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR", "linagliptin AND diabetes mellitus AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR", "vildagliptin AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR", "vildagliptin AND diabetes mellitus AND renal outcomes, renal endpoints, kidney outcomes, kidney endpoints, e GFR, UACR".
3. Clinical Trials Registry (www.clinicaltrials.gov) For ongoing or unpublished trials, the database of clinical trial registry platformwas searched.