INPLASY

Dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes mellitus: protocol for an updated systematic review of evidence from 2006 to May 2026

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - The authors declare no conflicts of interest in relation to the subject matter of this review. None of the authors has received consultancy fees, honoraria, research grants, or other financial or non-financial support from manufacturers of dipeptidyl peptidase-4 inhibitors or from any other pharmaceutical company with a commercial interest in the outcomes reported. The review was conceived and conducted independently. Any future potential conflicts identified during the review process will be disclosed at the time of manuscript submission to the target journal.

INPLASY registration number: INPLASY202650164

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 May 2026 and was last updated on 28 May 2026.

INTRODUCTION

Review question / Objective The primary objective of this review is to appraise and synthesise the totality of published evidence on the clinical use of dipeptidyl peptidase-4 (DPP-4) inhibitors — sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, teneligliptin, omarigliptin, trelagliptin, anagliptin, gemigliptin, and evogliptin — in adults with type 2 diabetes mellitus, covering the full period from the class's introduction in 2006 through May 2026. The review addresses four specific questions: (1) What is the glycaemic efficacy of DPP-4 inhibitors as monotherapy and in combination with other antihyperglycaemic agents? (2) What cardiovascular outcomes are associated with their use, and how does the 2022 re-adjudication of the TECOS trial affect the class's heart failure risk profile? (3) What renal effects, including changes in urinary albumin-to-creatinine ratio and eGFR, are attributable to DPP-4 inhibitors, and which agent is appropriate in patients with advanced chronic kidney disease? (4) What adverse effects — particularly bullous pemphigoid, pancreatitis, and fractures — have been characterised or mechanistically described in the period since the most recent major review of the class (Deacon,

2020)? Using the PICOS framework: — Population: adults aged 18 years or older with type 2 diabetes mellitus — Intervention: any approved DPP-4 inhibitor at standard therapeutic dose — Comparator: placebo, active antihyperglycaemic comparator, or no treatment — Outcomes: HbA1c, major adverse cardiovascular events, hospitalisation for heart failure, eGFR slope, urinary albumin-to-creatinine ratio, hypoglycaemia, bullous pemphigoid, pancreatitis, fractures, all-cause mortality — Study designs: randomised controlled trials of at least 12 weeks' duration, systematic reviews and meta-analyses, large observational studies, pharmacovigilance analyses, conference proceedings, and clinical trial registry records.

Rationale DPP-4 inhibitors have been available for clinical use since 2006 and are among the most widely prescribed oral antihyperglycaemic agents worldwide. The most recent authoritative review of the class — Deacon (2020) in Nature Reviews Endocrinology — provided a detailed overview with a literature horizon of approximately September 2020. Several developments since that date justify an updated, independent appraisal. First, a data-lock error in the TECOS cardiovascular outcome trial (sitagliptin versus placebo) was identified and corrected in 2022. The re-adjudicated analysis by Scirica and colleagues, published in Clinical Cardiology, revised the hazard ratio for hospitalisation for heart failure from an equivocal 1.00 to a clearly neutral 0.95 (95% CI 0.81–1.11). This finding materially changes the class's heart failure risk narrative and has not been incorporated into any existing systematic review. Second, work published between 2021 and 2023 has both confirmed and mechanistically explained the bullous pemphigoid signal. A meta-analysis of 165 randomised trials calculated a Mantel-Haenszel odds ratio of 4.44 for the condition, while a 2023 mechanistic study in JCI Insight traced the phenomenon to CXCL12/SDF-1α accumulation and downstream BP180 autoantibody targeting — findings with direct prescribing implications, particularly in elderly patients. Third, updated network meta-analyses comparing DPP-4 inhibitors with GLP-1 receptor agonists and SGLT-2 inhibitors on cardiovascular and renal endpoints now encompass over 79,000 participants from completed cardiovascular outcome trials, providing a far more stable estimate than was available in 2020. Fourth, ADA guidelines updated in 2025 and 2026 have explicitly repositioned DPP-4 inhibitors in the treatment hierarchy, and the 2026 edition introduced a formal recommendation against concurrent use with GLP-1 receptor agonists — a clinically important change not previously codified. Finally, generic sitagliptin and alogliptin entered major markets in 2023–2024, changing the cost-effectiveness calculus for the class globally. This review also covers conference proceedings and clinical trial registry data not captured in prior syntheses, and is designed as a living document with a scheduled 2027 update.

Condition being studied Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by progressive insulin resistance and relative insulin deficiency, resulting in sustained hyperglycaemia. It accounts for approximately 90–95% of all diabetes cases and carries a substantial burden of microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular disease (coronary artery disease, stroke, peripheral arterial disease). The International Diabetes Federation estimated that 537 million adults were living with diabetes globally in 2021, with T2DM comprising the large majority; projections indicate this will exceed 643 million by 2030 and 783 million by 2045. Management of T2DM requires long-term pharmacological treatment in most patients. Glycaemic control, assessed primarily through HbA1c, remains the central therapeutic target, but contemporary treatment guidelines increasingly incorporate cardiovascular risk reduction and renal protection as co-equal goals. This has led to a stratified approach in which the choice of glucose-lowering agent is guided by the presence of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, not solely by glycaemic burden. DPP-4 inhibitors represent one of the main oral antihyperglycaemic drug classes used in T2DM. They are prescribed across a wide range of clinical settings and patient profiles, and their safety and efficacy have been examined in some of the largest cardiovascular outcome trials conducted in this disease area.

METHODS

Search strategy Electronic databases: PubMed/MEDLINE, Embase, Cochrane CENTRAL (Cochrane Database of Systematic Reviews and Central Register of Controlled Trials), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (WHO ICTRP). Date range: January 1, 2006 (year of first regulatory submission preceding sitagliptin's FDA approval) through May 28, 2026 (literature lock). Primary MeSH term: 'Dipeptidyl-Peptidase IV Inhibitors' [MeSH Major Topic]. Free-text terms (agent-level): sitagliptin OR vildagliptin OR saxagliptin OR alogliptin OR linagliptin OR teneligliptin OR omarigliptin OR trelagliptin OR anagliptin OR

gemigliptin OR evogliptin. Free-text terms (class-level): 'DPP-4 inhibitor*' OR 'DPP4 inhibitor*' OR 'dipeptidyl peptidase-4 inhibitor*' OR 'dipeptidyl peptidase IV inhibitor*' OR gliptin*. Disease filter: 'Diabetes Mellitus, Type 2' [MeSH] OR 'type 2 diabetes' [tiab] OR 'T2DM' [tiab] OR 'non-insulin-dependent diabetes' [tiab]. Outcome-specific supplementary searches (combined with the above using AND): cardiovascular outcomes OR major adverse cardiovascular events OR MACE OR heart failure OR hospitalisation for heart failure; chronic kidney disease OR diabetic nephropathy OR albuminuria OR eGFR; bullous pemphigoid; pancreatitis; pancreatic cancer; hypoglycaemia; fracture*; glycaemic variability OR time in range. Conference proceedings (hand-searched): American Diabetes Association Scientific Sessions (2006–2025); European Association for the Study of Diabetes Annual Meetings (2006–2025); European Society of Cardiology and ESC Heart Failure Congress (2013–2025); European Renal Association Annual Congress (2015–2025); Endocrine Society Annual Meeting (2006–2025); International Diabetes Federation World Congress (2006–2025). Pharmacovigi sources: FDA Adverse Event Reporting System (FAERS) public dashboard; EMA EudraVigilance; WHO VigiAccess — searched using agent names and class terms. Filters: English language; human studies. No restriction by publication type.

Participant or population Adults aged 18 years or older with a confirmed diagnosis of type 2 diabetes mellitus, as defined by the treating physician or by the diagnostic criteria used in each primary study. No restriction is placed on HbA1c at enrolment, duration of diabetes, body mass index, or co-existing medical conditions. Sub-populations of specific clinical interest — elderly patients (aged 65 years or above), those with chronic kidney disease (any stage), those with established atherosclerotic cardiovascular disease, and those with co-existing heart failure — are addressed separately in subgroup analyses. Studies enrolling both type 1 and type 2 diabetes patients are included if T2DM data are reported separately; studies restricted to type 1 diabetes are excluded. Studies in paediatric and adolescent populations (under 18 years) are excluded.

Intervention Any approved dipeptidyl peptidase-4 inhibitor at any approved or clinically studied dose, administered orally, as monotherapy or in combination with other antihyperglycaemic agents. This includes sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, teneligliptin, omarigliptin, trelagliptin, anagliptin, gemigliptin, and evogliptin. Fixed-dose combination formulations are included. Both standard-frequency (once or twice daily) and extended-interval (once-weekly) formulations are eligible.

Comparator Placebo; no treatment; metformin; sulfonylureas (glimepiride, gliclazide, glipizide, glibenclamide); thiazolidinediones (pioglitazone, rosiglitazone); SGLT-2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin); GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide, exenatide, tirzepatide); basal, bolus, or premixed insulin; alpha-glucosidase inhibitors; or a different DPP-4 inhibitor. Network meta-analyses comparing multiple agents simultaneously are eligible.

Study designs to be included Randomised controlled trials (minimum 12 weeks' duration); systematic reviews and meta-analyses of 5 or more randomised trials; observational studies (cohort, case-control) with a minimum of 500 participants and formal confounding adjustment; pharmacovigilance signal detection analyses; conference abstracts from completed trials; clinical trial registry records with primary completion date from 2020 onward. Case reports and case series accepted for bullous pemphigoid only (minimum 5 cases).

Eligibility criteria Inclusion criteria (additional to PICOS): — English-language publications — Studies reporting at least one of the defined primary or secondary outcomes (see items 18 and 19) — For pharmacovigilance analyses: studies using disproportionality methods (PRR, ROR, BCPNN, or equivalent) on FAERS, EudraVigilance, VigiAccess, or national drug safety databases — For conference abstracts: abstracts from completed trials with quantitative results; abstracts reporting interim or preliminary data are excluded — For registry records: entries with primary completion date on or after January 1, 2020, to capture recently completed studies not yet in the published literature Exclusion criteria: — Animal studies and in vitro experiments — Studies restricted to participants under 18 years of age — Studies restricted to type 1 diabetes mellitus without a separable T2DM subgroup — Case reports and case series with fewer than 5 participants (except bullous pemphigoid: minimum 5 cases accepted) — Duplicate publications: when multiple reports describe the same study population, the most recent or complete version is included and earlier versions are excluded — Editorials, letters, and commentaries that do not report original outcome data — Studies for which the full text cannot be retrieved after a reasonable attempt to contact the corresponding author —

Studies with a follow-up duration below 12 weeks for randomised efficacy trials (safety-focused trials of any duration are eligible) — Studies using investigational DPP-4 inhibitors not approved by at least one major regulatory authority (FDA, EMA, or an equivalent national authority) Handling of multiple publications from the same dataset: the most complete published analysis is included as the primary record; sub-studies and secondary publications are cross-referenced and their additional data extracted where they report outcomes not covered in the primary paper.

Information sources Electronic databases: PubMed/MEDLINE, Embase, Cochrane CENTRAL, ClinicalTrials.gov, WHO ICTRP. These represent the five primary peer-reviewed and registry sources for clinical research in this field. Conference proceedings: American Diabetes Association Scientific Sessions; European Association for the Study of Diabetes Annual Meetings; ESC Heart Failure Congress; European Renal Association Annual Congress; Endocrine Society Annual Meeting; IDF World Congress — all for the period 2006 to 2025. Abstract archives are accessed through the official conference websites and proceedings supplements in relevant journals. Pharmacovigi databases: FDA Adverse Event Reporting System (FAERS) public dashboard (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard); EMA EudraVigilance (https://www.adrreports.eu); WHO VigiAccess (https://www.vigiaccess.org). Searched using DPP-4 inhibitor class terms and individual agent names. Grey literature: Reference lists of all included systematic reviews and meta-analyses will be screened for additional eligible studies not captured by the database searches. Authors of recent large trials will be contacted if relevant data are not available in the published record.

Main outcome(s) 1. HbA1c reduction from baseline: weighted mean difference or standardised mean difference, expressed as percentage points and mmol/mol, at the latest available follow-up. 2. Major adverse cardiovascular events (MACE): composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; reported as hazard ratio or odds ratio with 95% confidence interval. 3. Hospitalisation for heart failure: hazard ratio or odds ratio with 95% confidence interval; analysed separately for saxagliptin and for the remainder of the class given the established agent-specific signal. 4. All-cause mortality: hazard ratio or odds ratio with 95% confidence interval. 5. Urinary albumin-to-creatinine ratio (UACR): change from baseline, standardised mean difference. 6. eGFR slope: change from baseline, weighted mean difference.

Additional outcome(s) Fasting plasma glucose: change from baseline (mmol/L or mg/dL). Postprandial glucose and glucagon AUC. Glycaemic variability: mean amplitude of glycaemic excursions (MAGE); coefficient of variation; time in range (where CGM data available). Body weight: change from baseline (kg). Hypoglycaemia: overall, severe, and nocturnal rates; odds ratio versus comparator. Bullous pemphigoid: Mantel-Haenszel odds ratio; pharmacovigilance disproportionality ratios (PRR, ROR). Pancreatitis: Peto odds ratio; pharmacovigilance disproportionality. Pancreatic cancer: Mantel-Haenszel odds ratio. Fracture risk: relative risk. Urinary tract infection rate. QTc prolongation (sitagliptin): mean change in milliseconds at therapeutic and supratherapeutic doses. Acute kidney injury outcomes (post-dialysis subgroup).

Data management Records identified from electronic database searches will be exported to Mendeley Reference Manager and deduplicated automatically, with manual verification of any ambiguous cases. The deduplicated library will then be imported into Rayyan (rayyan.ai) for the title-and-abstract screening phase. Rayyan's blinding feature will be activated so that neither reviewer can see the other's decisions during screening. For full-text screening and data extraction, a pre-specified data extraction form will be used, developed in Microsoft Excel. The form will capture: study identifier, publication year, study design, sample size, treatment duration, patient characteristics (age, sex, HbA1c at baseline, eGFR at baseline, cardiovascular risk category), DPP-4 inhibitor studied, dose, comparator, and all primary and secondary outcomes with their effect measures and confidence intervals. All source data and extraction files will be retained by the corresponding author and made available on request to any researcher seeking to verify or update the analysis.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using three validated tools, matched to study design: — Randomised controlled trials: Cochrane Risk of Bias tool version 2 (RoB2). Each trial will be assessed across five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. An overall risk of bias judgement of low, some concerns, or high will be assigned. —

Systematic reviews and meta-analyses: AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews, second edition). Sixteen items covering the review's methods, including a priori protocol registration, search strategy, risk of bias assessment in primary studies, and adequacy of the meta-analysis. — Observational studies: Newcastle-Ottawa Scale (NOS), assessing selection, comparability, and outcome ascertainment. — Pharmacovigilance analyses: assessed for appropriate use of signal detection methodology and whether confounding factors such as stimulated reporting or Weber effect are acknowledged. Evidence certainty for each primary outcome will be rated using the GRADE framework (high, moderate, low, very low), taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Strategy of data synthesis For continuous outcomes (HbA1c, UACR, eGFR, body weight, fasting glucose), pooled estimates will be expressed as weighted mean differences (WMD) or standardised mean differences (SMD) with 95% confidence intervals, using random-effects models (DerSimonian-Laird method). For time-to-event outcomes (MACE, HHF, all-cause mortality), hazard ratios with 95% confidence intervals will be pooled using random-effects meta-analysis. For rare binary outcomes (bullous pemphigoid, pancreatitis, pancreatic cancer, fractures), Peto odds ratios will be used in preference to Mantel-Haenszel odds ratios, given their superior performance when event rates are low. Heterogeneity will be assessed using the I^2 statistic, with thresholds of less than 25% (low), 25–50% (moderate), and above 50% (substantial). Potential sources of heterogeneity will be explored through pre-specified subgroup analyses (see item 23) and meta-regression where sufficient studies permit. For outcomes where pooled quantitative synthesis is not appropriate — for example, where the body of evidence consists predominantly of narrative reports or where heterogeneity is unacceptably high — results will be summarised narratively with tabulation of individual study results. Publication bias will be examined using funnel plot asymmetry (Egger's test) for meta-analyses incorporating ten or more studies. For smaller pools, visual assessment of funnel plots will be used with acknowledgement of its limitations. All statistical analyses will be performed using Review Manager 5 (RevMan, Cochrane Collaboration) and R (metafor package). Results will be presented as forest plots for each primary outcome.

Subgroup analysis Pre-specified subgroup analyses will be conducted for the following variables, where sufficient data are available: 1. Individual agent (sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin) — to determine whether outcomes differ across agents within the class. 2. Renal function at baseline (eGFR ≥60 ml/min/1.73m² versus eGFR 30–59 versus eGFR below 30) — given the importance of CKD in prescribing decisions. 3. Age group (below 65 years versus 65 years and above) — given the differential tolerability considerations in older patients. 4. Presence of established cardiovascular disease at baseline (yes versus no) — relevant to interpreting MACE and HHF outcomes. 5. Background antihyperglycaemic therapy (monotherapy versus combination with metformin versus combination with sulfonylurea versus combination with insulin). 6. Study duration (below 52 weeks versus 52 weeks and above) — to assess whether short-term and long-term outcomes are consistent. 7. Geographic region (Western versus East Asian populations) — given evidence that incretin responses differ between these groups. Subgroup analyses will be interpreted cautiously, with formal testing for interaction (Q test for subgroup differences) and a pre-specified threshold of P less than 0.05 for declaring a meaningful subgroup effect.

Sensitivity analysis The following sensitivity analyses are pre-specified: 1. Restricting the analysis to studies rated as low risk of bias by RoB2 — to determine whether inclusion of studies with methodological concerns influences the pooled estimate. 2. Excluding single large trials that account for more than 30% of the total weight in any meta-analysis — to assess whether results are driven by one dominant study. 3. Fixed-effects model in place of random-effects — to examine whether the choice of model alters conclusions, particularly for outcomes with low heterogeneity. 4. Restricting cardiovascular outcome analyses to the five pre-registered CVOTs only, excluding post-hoc analyses and sub-studies — to preserve the integrity of the intention-to-treat population. 5. For the bullous pemphigoid outcome: repeating the analysis after excluding individual agents with fewer than three contributing studies — to assess whether the class-level estimate is stable across agents. 6. Restricting renal outcome analyses to studies with a minimum follow-up of 24 weeks — to exclude very short-term changes that may not reflect sustained renal effects.

Language restriction English only. This restriction is acknowledged as a potential source of language bias and is noted as a limitation in the manuscript.

Country(ies) involved Saudi Arabia (primary affiliation — University of Hail).

Other relevant information Living review framework: this protocol is designed for an initial submission covering January 2006 through May 2026, with a formally pre-planned update in May 2027 using identical search terms, databases, and eligibility criteria. The 2027 update will be registered as a separate INPLASY protocol at that time. Relationship to the Deacon (2020) review: the present review is independent of and not affiliated with the 2020 narrative review by Deacon published in Nature Reviews Endocrinology. It draws on the same pharmacological subject matter but applies a systematic methodology with pre-specified eligibility criteria and formal quality assessment. Studies published before Deacon's September 2020 cutoff form the historical evidence base; studies published from September 15, 2020 onward are highlighted as new evidence in the manuscript text and tables. Target journal: Endocrine Practice (American Association of Clinical Endocrinology / Elsevier; ISSN 1530-891X). The manuscript will be submitted as a Review Article under the subscription model (no article processing charge). PRISMA 2020 compliance: the final manuscript will include a completed PRISMA 2020 checklist (all 30 items) and a PRISMA flow diagram submitted as a separate figure. Data availability: the data extraction form and the complete list of included studies will be made available as supplementary files with the published manuscript. Raw extraction data are available from the corresponding author on request.

Keywords DPP-4 inhibitors; gliptins; sitagliptin; linagliptin; type 2 diabetes; cardiovascular outcomes; bullous pemphigoid; chronic kidney disease; systematic review; ADA guidelines.

Dissemination plans The completed review will be submitted to Endocrine Practice, the official journal of the American Association of Clinical Endocrinology, as a Review Article. Findings relevant to the 2022 TECOS re-adjudication and the updated bullous pemphigoid mechanism will be highlighted in the abstract to maximise their visibility to practicing endocrinologists. The review is designed as a living document; a 2027 update will be submitted to the same journal. The INPLASY registration number will be cited in the Methods section of the published manuscript to allow readers to verify the pre-specified protocol.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceived and designed the review; developed the search strategy; conducted title-and-abstract screening; performed full-text eligibility assessment; led data extraction and quality assessment; drafted the manuscript; registered the protocol on INPLASY.
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Author 2 - Basmah Alanazi - Conducted independent title-and-abstract screening; performed full-text eligibility assessment; participated in data extraction; critically reviewed and revised the manuscript for important intellectual content.