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# Effectiveness in clinical practice versus efficacy of dipeptidyl peptidase-4 inhibitors in clinical trials for type 2 diabetes: protocol for systematic review

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## ABSTRACT

**Introduction** Data supporting the use of oral antidiabetic drugs mainly rely on data from premarketing clinical trials. Real-world data studies are crucial to evaluate effectiveness of drugs. The aim of this systematic review is to compare the results obtained for efficacy and effectiveness endpoints on clinical trials and those obtained from routine clinical practice of dipeptidyl peptidase-4 inhibitors.

**Methods and analysis** This systematic review will include randomised controlled trials and observational studies evaluating the efficacy and effectiveness of dipeptidyl peptidase-4 inhibitors, respectively. A literature search will be performed at Medline, Embase, Cochrane Controlled Register of Trials and ClinicalTrials.gov. Search terms comprised the drug name (including the pharmacotherapeutic class and the international non-proprietary name). Data on haemoglobin A1C, blood glucose and body weight will be retrieved. The risk of bias will be independently assessed according to the checklist proposed by Downs and Black. Data will be analysed using descriptive statistics and meta-analysis when applicable.

**Ethics and dissemination** Ethical approval is not required as no primary data are collected. This systematic review will be disseminated through a peer-reviewed publication and at conference meetings.

## Strengths and limitations of this study

- The Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare and the Preferred Reporting Items for Systematic Review and Meta-Analysis statement will be followed.
- Data from clinical trials will be compared with those from routine clinical practice.
- This study will provide evidence on both external validity of the results of clinical trials and on the extent to which patient with diabetes benefit from antidiabetic drugs.

## INTRODUCTION

Diabetes affects more than 400 million people worldwide.[1] Its prevalence among adults has been increasing over the years.[1] The WHO estimated that diabetes is the seventh cause of death.[1]

Several pharmacological interventions, such as oral antidiabetic drugs (OAD), are available to achieve and maintain a good glycaemic control.[2–4] Metformin, thiazolidinediones, sulfonylureas, glinides, α-glucosidase inhibitors, oral dipeptidyl peptidase-4 (DPP4) inhibitors and sodium-glucose transport protein 2 inhibitors are some examples of pharmacological therapeutic options for the control of type 2 diabetes mellitus.[2–4] They differ on mechanism of action and safety.[2–4] Nevertheless, their common goal is to control blood glucose, glycated haemoglobin and body weight.[2–4]

Data supporting the use of OAD mainly rely on data from premarketing clinical trials.[5] Despite randomised controlled trials (RCTs) being well-designed studies, they had limited duration and strict inclusion/exclusion criteria, which results in a homogeneous set of patients.[5]

Real-world data studies are crucial to evaluate effectiveness of drugs approved on the basis of premarketing RCT.[6 7] These observational studies can be retrospective, prospective or registries.[6] They provide data from routine clinical practice, including patients with heterogeneous characteristics.[6 7] These data can support benefit–risk ratio evaluation to make informed decisions in routine clinical practice.[6 7] It is, therefore, of clinical and scientific importance to compare the results obtained from RCT and those obtained from routine clinical practice.

The aim of this systematic review is to compare the results obtained for efficacy and effectiveness endpoints on clinical trials and those obtained from routine clinical practice of DPP4 inhibitors.

## METHODS

This protocol is in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[8] This systematic review will follow the Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare[9] and will be reported in accordance with the PRISMA statement.[10] As this work is a systematic review of published work, ethical approval is not required.

### Eligibility criteria

Studies will be assessed against the eligibility criteria described in the following sections.

- Study design: Premarketing phase III RCT will be selected to assess data on premarketing studies and postmarketing phase IV RCT along with observational studies will be selected to assess real-world data. The observational studies could be prospective or retrospective, cohort studies or case–control studies. Case series and case reports will be excluded. Meta-analysis of the above considered designs will also be included.
- Population: Studies assessing patients for whom a DPP4 inhibitors was administered/ prescribed will be included.
- Intervention: We will include studies assessing DPP4 inhibitors approved in Portugal (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin).
- Comparators: Included studies could assess the intervention against placebo, active treatment (such as other DPP4 inhibitor or other antidiabetic medicine) or no treatment.
- Outcomes: Studies must report results for the efficacy endpoints: mean change from baseline in haemoglobin A1C (HbA1c), number of patients achieving HbA1c<7%, mean change from baseline in fasting plasma glucose, mean change from baseline glucose and mean change from baseline in body weight; and for the effectiveness endpoints: all-cause mortality, cardiovascular-related mortality, acute myocardial infarction, stroke, hospitalisations, emergency department visits, amputations, nephropathy and retinopathy.
- Timing: No follow-up time restrictions will be applied.
- Setting: No setting restrictions will be applied for RCT and observational studies.
- Language: We will only include studies reported in English and Portuguese.

### Information sources

A literature search will be performed at Medline (https://www.ncbi.nlm.nih.gov/pubmed/), Embase (https://www.embase.com/), Cochrane Controlled Register of Trials (https://www.cochranelibrary.com/central) and ClinicalTrials.gov (https://clinicaltrials.gov/) since its inception until June 2019. In addition, the websites of the manufacturers of drugs will also be searched for studies with available results. The reference lists of studies selected for inclusion will also be reviewed for relevant additional studies. We will not search in grey literature, since we intend to extract the results of the outcomes assessed in the studies.

**Table 1** Draft search strategy in Medline

| Search | Equation |
|---|---|
| #1 | alogliptin (Supplementary Concept) |
| #2 | alogliptin |
| #3 | #1 OR #2 |
| #4 | "Linagliptin"(Mesh) |
| #5 | linagliptin |
| #6 | #4 OR #5 |
| #7 | "saxagliptin"(Supplementary Concept) |
| #8 | saxagliptin |
| #9 | #7 OR #8 |
| #10 | "Sitagliptin Phosphate"(Mesh) |
| #11 | sitagliptin |
| #12 | #10 OR #11 |
| #13 | "Vildagliptin"(Mesh) |
| #14 | vildagliptin |
| #15 | #13 OR #14 |
| #16 | "Dipeptidyl-Peptidase IV Inhibitors"(Mesh) |
| #17 | Dipeptidyl-Peptidase IV Inhibitors |
| #18 | Dipeptidyl-Peptidase 4 Inhibitors |
| #19 | #16 OR #17 OR #18 |
| #20 | #3 OR #6 OR #9 OR #12 OR #15 OR #19 |
| #21 | #20; Filters: Clinical Trial, Phase III; Clinical Trial, Phase IV |
| #22 | #20; Filters: Observational Study |

### Search strategy

Search terms will comprise the drug name (including the pharmacotherapeutic class and the international non-proprietary name). A combination of thesaurus terms and free terms will be used. The filters 'Clinical Trial, Phase III' and 'Observational Study' will be applied to the literature search. No language filters will be applied. The search will be updated at the end of the systematic review. A draft search strategy (Medline) is presented in table 1.

### Study records

Two researchers will independently screen by hand the titles and abstracts and selected full articles for inclusion in accordance with the prespecified eligibility criteria. Disagreements will be resolved by discussion and consensus with a third researcher.

### Data items

The following data will be extracted from each study: reference, year of publication, type of study, study design, duration of the clinical study, intervention (name, dosage, frequency and duration of treatment), comparators and data on HbA1c, blood glucose and body weight. Data will

be extracted from each included study by two researchers independently to a predeveloped form.

### Risk of bias individual studies

The risk of bias of the retrieved studies will be independently assessed. The checklist proposed by Downs and Black[11] will be applied, since it can assess both experimental and non-experimental studies. Studies' methodological quality will be assessed as good, fair or poor according to the total score as ≥20, from 15 to 19 and ≤14, respectively. When more than one reference is found for the same study, the methodological quality evaluation will be based on the total set of information. The methodological quality of the meta-analysis will be assessed using the instrument 'A MeaSurement Tool to Assess systematic Reviews' 2.[12] The instrument consists of 16 domains assessing the risk of bias that may have arisen through poor conduct of the systematic reviews of both RCTs and non-randomised studies.[12]

### Data synthesis

To compare the efficacy results of the DPP4 inhibitors when used in clinical trials context with their effectiveness in routine clinical practice, meta-analyses will be carried out for premarketing and postmarketing data.

For continuous outcomes (ie, HbA1c%, fasting plasma glycaemia and body weight), the weighted mean differences between the intervention group (DPP-4 inhibitors) and the comparator group, with their 95% CI, will be estimated using a random effects model. If a study does not report the SD, this will be calculated from the sample size and the SE or the 95% CI. The risk ratios and the 95% CI will be estimated for dichotomous outcomes (ie, endpoints: number of patients achieving HbA1c<7%, all-cause mortality, cardiovascular-related mortality, acute myocardial infarction, stroke, hospitalisations, emergency department visits, amputations, nephropathy and retinopathy), also using a random effects model.

Between studies, heterogeneity will be assessed using the $I^2$ statistic.[13] An $I^2$ estimate >50% will be considered indicative of substantial heterogeneity. The publication bias will be examined through visual inspection of a funnel plot and statistically evaluated by Egger's regression asymmetry test.[14] All reported p values will be two sided with significance being set as less than 0.05. Stata V.13.1 will be used to perform statistics.

### Patient and public involvement

No patients will be involved in this study. This is a protocol for a systematic review. Data supporting this study is openly available.

## DISCUSSION

This systematic review will compare data obtained from RCT with those obtained from real-world data.

Two types of evidence will be included: RCT and observational studies (cohort and case–control studies). We will evaluate the methodological quality of these studies. However, interpretation of their results should take in account the methodological quality of these designs.

The vast majority of the premarketing RCTs assessing antidiabetic drugs are designed to assess surrogated endpoints, like glycaemia, HbA1c% or weight changes. Data provided by RCTs may be scarce for some of the definitive outcomes, such as mortality, cardiovascular events, amputations, nephropathy and retinopathy. Therefore, if the event rates are low or the data are unavailable, it will be difficult to establish the comparison between premarketing and postmarketing scenarios for some outcomes. Another potential limitation of this study is that the scarcity of data may prevent conducting separate analyses for each DPP4 inhibitor to identify differences among the drugs in this class.

The most relevant contribution of this study is providing evidence on both external validity of the results of clinical trials and on the extent to which diabetic patient benefit from antidiabetic drugs in clinical practice. Recent antidiabetic drugs, such as DPP4 inhibitors are expensive and their widely use has been subject to discussion. Portuguese drug regulation authority started with the ex-post re-evaluations of added therapeutic value and the study of the economic impact of these drugs.

It is, therefore, important for clinicians, regulators and policymakers the availability of evidence to support their decisions.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The data that support the findings of this study are openly available in Medline, Embase, Cochrane Library and ClinicalTrials.gov. This systematic review will be disseminated through a peer-reviewed publication and at conference meetings.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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