NEW ENGLAND CEPAC
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COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value

Research Protocol

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Institute for Clinical and Economic Review

ICER
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Background, Objectives, and Research Questions

Background

In the US, approximately 30 million individuals have diabetes mellitus, of which 95% have the Type 2 form.[1] Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, a condition in which the body does not respond to insulin appropriately. Insulin is a hormone produced by beta cells in the pancreas that helps to control blood glucose levels; patients with T2DM have elevations in blood glucose (hyperglycemia). With chronic hyperglycemia, patients with T2DM are at increased risk for damage to blood vessels both large (macrovascular disease) and small (microvascular disease). Many of the complications of diabetes are the result of vascular disease, including microvascular damage to the eyes and kidneys, and macrovascular complications including myocardial infarction, stroke, limb ischemia, and cardiovascular (CV) death.[2] In 2014, 7.2 million hospital discharges were reported among individuals with diabetes, including hospitalizations for major CV disease and lower-extremity amputation.[1] The annual cost of managing diabetes is approximately $245 billion, including both direct medical costs and lost productivity resulting from complications.[1]

T2DM management includes close monitoring of blood sugar and glycated hemoglobin (HbA1c) levels – a measure of average blood sugar control over several months – as well as other aspects such as ophthalmic care, podiatric care, and managing risk factors for CV disease.[2] Levels of HbA1c are generally used as "glycemic targets" in patients with T2DM, with somewhat less intense control being accepted for older patients or for patients with a history of severe hypoglycemia, shorter life expectancy, established vascular complications, important comorbid conditions, or long-standing diabetes.[3] Improving glycemic control may reduce the risk or delay progression of microvascular complications, but the impact on macrovascular complications is less certain and may only manifest in individuals with longer life-expectancy. Healthy lifestyle changes (e.g., improved diet and increased exercise) are generally a standard part of T2DM management, and they may be sufficient to achieve healthy blood glucose levels or delay the onset of complications in some individuals. However, many individuals with T2DM will require antihyperglycemic medications to achieve and sustain glycemic control.[2,4]

Metformin is currently the most effective first-line medication option and has a favorable safety profile in that it does not increase weight or the risk of hypoglycemia (low blood sugar).[2,4] If lifestyle changes (e.g., diet and exercise) and metformin do not achieve a desired glycemic target, another glucose-lowering drug may be added.[2,4] Additional management options include oral administrations of sulfonylureas, thiazolidinediones, sodium-glucose cotransporte-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as injectable administrations of glucagon-like peptide 1 (GLP-1) receptor agonists, and insulin.[2,4]

The focus on glucose control has raised concerns that although some therapies may lower blood glucose, they may also increase the risk for adverse CV events which emerge more slowly. In 2008, the Food and Drug Administration (FDA) issued recommendations for the evaluation of CV risk for new antihyperglycemic therapies, which include the conduct of randomized trials that include patients at high risk for CV events.[5,6] Since then, several CV outcome trials have been conducted, and this evidence has allowed for greater certainty in considering the relative benefits and risks of each therapy.[5]

A new, oral GLP-1 receptor agonist, semaglutide (Novo Nordisk) is currently in development to treat patients with T2DM.[7] The manufacturer filed for FDA approval of oral semaglutide in March 2019 for two indications. A decision is expected by September 2019 for the first indication – to control blood glucose in patients with T2DM – and by January 2020 for the second indication – to reduce major CV events in adults with T2DM and established CV disease.[8] If approved, oral semaglutide would be the first oral formulation of a GLP-1 receptor agonist.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of oral semaglutide for the treatment of T2DM. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan for details on the proposed methodology and model structure that will be used for the economic evaluation (expected publication date July 29, 2019).

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts and patient groups:

1. In patients with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s), what is the comparative efficacy, safety, and effectiveness in terms of macrovascular outcomes (e.g., CV death), microvascular outcomes (e.g., retinopathy), quality of life, adverse events, and other key outcomes of add-on therapy with:
    - Oral semaglutide versus sitagliptin, a DPP-4 inhibitor?
    - Oral semaglutide versus empagliflozin, a SGLT-2 inhibitor?
    - Oral semaglutide versus liraglutide, an injectable GLP-1 receptor agonist?

2. In patients with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s), what is the comparative efficacy, safety, and effectiveness of adding oral semaglutide to current treatment versus continuing current treatment without add-on therapy in terms of macrovascular outcomes (e.g., CV death), microvascular outcomes (e.g., retinopathy), quality of life, adverse events, and other key outcomes?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Populations

The population of interest for this review is adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). Data permitting, we intend to examine subgroups including, but not limited to, the following:

1. Patients at high risk for CV events
2. Patients with moderate-to-severe renal impairment
3. Patients requiring a second antihyperglycemic agent (i.e., second-line therapy)
4. Patients requiring a third antihyperglycemic agent (i.e., third-line therapy)

Intervention

Our intervention of interest for this review is oral semaglutide (Novo Nordisk) added to current antihyperglycemic treatment.

Comparators

We plan to compare add-on oral semaglutide to ongoing background treatment (e.g., metformin with or without sulfonylureas) alone and to each of the following add-on agents:

- Sitagliptin (Januvia®, Merck), a DPP-4 inhibitor
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), a SGLT-2 inhibitor
- Liraglutide (Victoza®, Novo Nordisk), an injectable GLP-1 receptor agonist

These three agents were chosen in part because they were active comparators in the trials of oral semaglutide.

Outcomes

We will look for evidence on the following outcomes listed below.

Efficacy

Intermediate Outcomes

- HbA1c
- Fasting plasma glucose
- Body weight
- Blood pressure
- Lipids levels
- Estimated glomerular filtration rate (eGFR)
- Use of rescue medication (e.g., additional glucose-lowering medication)

Key Measures of Benefit

- Macrovascular outcomes including:
    - CV mortality
    - Stroke
    - Myocardial infarction
    - Heart failure
    - Other CV events
- Microvascular outcomes including:
    - Retinopathy
    - Nephropathy
    - Neuropathy
    - Other renal or eye events (e.g., chronic kidney disease progression, visual deterioration)
- All-cause mortality
- Hospitalization
- Health-related quality of life and activities of daily living
- Patient-reported outcomes

Safety

- Adverse events including:
    - Hypoglycemia
    - Weight gain
    - Pancreatitis
    - Urogenital infections
    - Gastrointestinal effects
    - Fractures
    - Renal effects
    - CV events
    - Other treatment-emergent adverse events

- Discontinuation (all-cause, due to adverse events)
- Serious adverse events

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least three months' duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

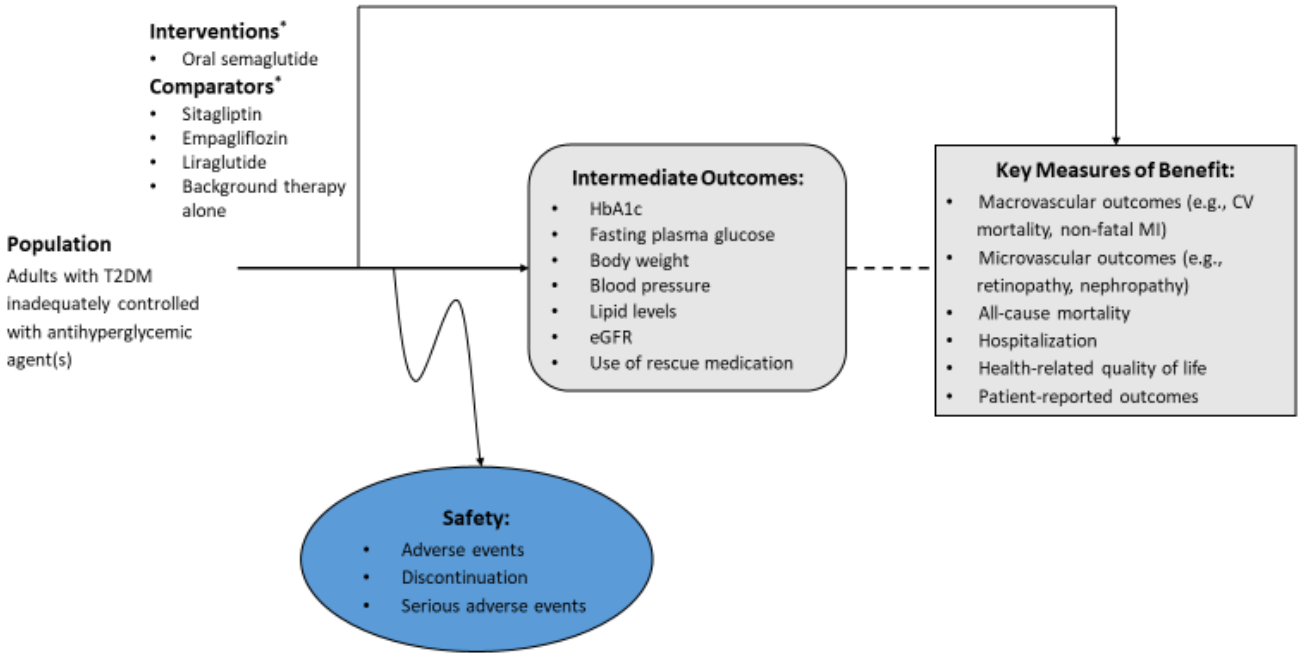
Study Eligibility Criteria

We will include randomized controlled trials (RCTs), non-randomized comparative studies, and single-arm trials of oral semaglutide with any sample size. We will also seek RCTs comparing our active comparators of interest to each other or ongoing background treatment in order to assess the feasibility of conducting a network meta-analysis (see Synthesis of Results for more details). If a network meta-analysis is found to not be feasible, we may include evidence from trials of the comparator therapies for context only. We will exclude studies that were conducted entirely in an Asian population due to differences in clinical characteristics (e.g., body mass index), standards of care, and dietary patterns.[9]

Analytic Framework

The proposed analytic framework for this project is depicted below:

Figure 1. Analytic Framework: Oral Semaglutide for Type 2 Diabetes Mellitus



CV: cardiovascular, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, MI: myocardial infarction, T2DM: type 2 diabetes mellitus

*Oral semaglutide, sitagliptin, empagliflozin, and liraglutide will be evaluated as add-on therapies to current antihyperglycemic treatment(s).

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., HbA1C levels), and those within the squared-off boxes are key measures of benefit (e.g., death). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[10]

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on oral semaglutide for T2DM will follow established best methods.[11,12] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies of oral semaglutide, sitagliptin, empagliflozin, and liraglutide. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings that were published in 2017 and later. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below. We will also search MEDLINE for recent systematic reviews of the other DPP-4 inhibitors, SGLT-2 inhibitors, or GLP-1 receptor agonists to provide context around how the comparator treatments compare to other agents within the same drug class. The proposed search strategy is presented in Appendix Table C1.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 1. Search Strategy of MEDLINE* and Cochrane Central Register of Controlled Trials (via Ovid)

	Search Terms
1	exp Diabetes Mellitus, Type 2/
2	(((adult or ketosis-resistant or matur* or late or "non-insulin depend*" or "noninsulin depend*" or slow or stable or "type 2" or "type II" or lipoatrophic) adj3 diabet*) or T2D* or MODY or NIDDM).ti,ab.
3	(semaglutide or "nn 9924" or nn9924).ti,ab.
4	exp Sitagliptin Phosphate/
5	(sitagliptin or "mk 0431" or mk0431 or januvia).ti,ab.
6	(empagliflozin or "BI 10773" or BI10773 or jardiance).ti,ab.
7	exp Liraglutide/
8	(liraglutide or "NN 2211" or NN2211 or victoza).ti,ab.
9	3 or 4 or 5 or 6 or 7 or 8
10	1 or 2
11	9 and 10
12	(address or autobiography or bibliography or biography or case reports or clinical trial phase i or comment or conference review or congress or consensus development conference or duplicate publication or dictionary or directory or editorial or guideline or interview or lecture or legal case or legislation or letter or meta analysis or news or newspaper article or note or patient education handout or periodical index or personal narrative or portrait or practice guideline or review or systematic review or video-audio media).pt.
13	conference abstract.pt.
14	limit 13 to yr="1946-2016"
15	11 not (12 or 14)
16	(clinical and trial).ti,ab. or exp 'clinical trials as topic'/ or clinical trial.pt. or random*.ti,ab. or exp 'random allocation'/ or tu.xs
17	15 and 16
18	limit 17 to english language
19	(animals not (human and animals)).sh.
20	18 not 19
21	remove duplicates from 20

*Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

Table 2. Search strategy of EMBASE

	Search Terms
1	'non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'
2	(((adult OR 'ketosis resistant' OR matur* OR late OR 'non-insulin depend*' OR 'noninsulin depend*' OR slow OR stable OR 'type 2' OR 'type ii' OR lipoatrophic) NEAR/3 diabet*):ti,ab) OR t2d*:ti,ab OR mody:ti,ab OR niddm:ti,ab
3	'semaglutide'/exp
4	semaglutide:ti,ab OR 'nn 9924':ti,ab OR nn9924:ti,ab
5	'sitagliptin'/exp
6	sitagliptin:ti,ab OR 'mk 0431':ti,ab OR mk0431:ti,ab OR januvia:ti,ab
7	'empagliflozin'/exp
8	empagliflozin:ti,ab OR bi10773:ti,ab OR 'bi 10773':ti,ab OR jardiance:ti,ab
9	'liraglutide'/exp
10	liraglutide:ti,ab OR nn2211:ti,ab OR 'nn 2211':ti,ab OR victoza:ti,ab
11	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	#1 OR #2
13	#11 AND #12
14	#13 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'network meta-analysis'/de OR 'nonhuman'/de OR 'phase 1 clinical trial (topic)'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'systematic review'/de OR 'systematic review (topic)'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
15	#14 NOT ('conference abstract'/it AND [1950-2016]/py)
16	('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk OR 'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp
17	#15 AND #16
18	#17 AND [english]/lim
19	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
20	#18 NOT #19
21	#20 NOT [medline]/lim

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into evidence tables. The basic design and elements of the extraction forms are presented in Appendix B. Elements include a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[14]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exist: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "semaglutide" and "NN 9924." We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

We will assess the feasibility of conducting a network meta-analysis (NMA) under a Bayesian framework. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)).[15,16] For continuous outcomes (e.g., HbA1C), the NMA model corresponds to a generalized linear model with identity link. For binary outcomes (e.g., CV death), the NMA model corresponds to a generalized linear model with a logit link. For all analyses, we will include random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) will be assumed constant across all treatment comparisons. We will use noninformative prior distributions for all model parameters. We will initially discard the first 40,000 iterations as "burn-in" and base inferences on an additional 40,000 iterations using 3 chains. Convergence of chains will be assessed with the Gelman-Rubin statistic and visually using trace plots. If the chains do not converge, an additional 10,000 iterations will be run, sequentially, until convergence.

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated. If there is evidence of inconsistency, the results will be presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

All NMAs will be conducted in R using the *gemtc* package.[17] Data included in each analysis along with the corresponding code will be included in an appendix of the Evidence Report. Results for all pairwise comparisons will be presented tabularly in terms of a point estimate and 95% credible intervals.

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include HbA1c levels, duration of diabetes, risk for CV events at baseline, presence of renal impairment, and background treatments (e.g., metformin with or without a sulfonylurea). If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[13] Additional explanation of each item can be found in Liberati et al. 2009.[18]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
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.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
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.	
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.	
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.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
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.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
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.	
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.	
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).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
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., health care providers, users, and policy makers).	
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).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
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.	

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Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes

Appendix C. Search Strategy for Recent Systematic Reviews

Table C1. Search Strategy of MEDLINE* and Cochrane Database of Systematic Reviews (via Ovid)

	Search Terms
1	exp Diabetes Mellitus, Type 2/
2	(((adult or ketosis-resistant or matur* or late or "non-insulin depend*" or "noninsulin depend*" or slow or stable or "type 2" or "type II" or lipoatrophic) adj3 diabet*) or T2D* or MODY or NIDDM).ti,ab.
3	Dipeptidyl-Peptidase IV Inhibitors/
4	((DPP4 or DPP 4 or DPPIV or DPP IV or dipeptidyl-peptidase IV or dipeptidyl-peptidase 4) adj2 inhibitor*).ti,ab.
5	Linagliptin/
6	exp Sitagliptin Phosphate/
7	(alogliptin or sitagliptin or saxagliptin or linagliptin).ti,ab.
8	Sodium-Glucose Transporter 2 Inhibitors/
9	((sodium glucose transporter 2 or sodium glucose cotransporter 2 or sodium glucose co-transporter 2 or SGLT 2 or SGLT2) adj2 inhibitor*) .ti,ab.
10	Canagliflozin/
11	(canagliflozin or dapagliflozin or empagliflozin or ertugliflozin).ti,ab.
12	Glucagon-Like Peptide 1/
13	Glucagon-Like Peptide-1 Receptor/
14	((glucagon like peptide 1 or GLP 1 or GLP1 or GLP 1R or GLP1R) adj2 (agonist* or receptor* or analog* or RA*)).ti,ab.
15	Liraglutide/
16	Exenatide/
17	(liraglutide or exenatide or albiglutide or dulaglutide or lixisenatide or semaglutide).ti,ab.
18	or/3-17
19	18 and (1 or 2)
20	(systematic review or meta-analysis).pt. or Network Meta-Analysis/
21	((systematic* adj2 review*) or meta analys* or metaanalys* or (indirect adj2 comparison*) or ((evidence or quantitative) adj2 synthes*)).ti,ab
22	19 and (20 or 21)
23	(cardiovascular or isch?emic or macrovascular or stroke or myocardial infarction or heart failure or renal or kidney* or microvascular or retinopathy or nephropathy or neuropathy or safety or adverse event* or mortality or death or hospitalization* or quality of life or patient reported outcome* or a1c or (glycemic adj2 control) or hyperglycemi* or weight or glomerular filtration rate or hypoglycemia).ti,ab
24	22 and 23
25	(animals not (human and animals)).sh.
26	24 not 25

	Search Terms
27	limit 26 to English language
28	limit 27 to yr="2013-Current"

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