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Adverse effects with semaglutide: a protocol for a systematic review with meta-analysis and trial sequential analysis

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ABSTRACT

Introduction Semaglutide is increasingly used for the treatment of type 2 diabetes mellitus, overweight and other conditions. It is well known that semaglutide lowers blood glucose levels and leads to significant weight loss. Still, a systematic review has yet to investigate the adverse effects with semaglutide for all patient groups.

Methods and analysis We will conduct a systematic review and search major medical databases (Cochrane Central Register of Controlled Trials, Medline, Embase, Latin American and Caribbean Health Sciences Literature, Science Citation Index Expanded, Conference Proceedings Citation Index—Science) and clinical trial registries from their inception and onwards to identify relevant randomised clinical trials. We expect to conduct the literature search in July 2024. Two review authors will independently extract data and perform risk-of-bias assessments. We will include randomised clinical trials comparing oral or subcutaneous semaglutide versus placebo. Primary outcomes will be all-cause mortality and serious adverse events. Secondary outcomes will be myocardial infarction, stroke, all-cause hospitalisation and non-serious adverse events. Data will be synthesised by meta-analyses and trial sequential analysis; risk of bias will be assessed with Cochrane Risk of Bias tool—version 2, an eight-step procedure will be used to assess if the thresholds for statistical and clinical significance are crossed, and the certainty of the evidence will be assessed by Grading of Recommendations, Assessment, Development and Evaluations.

Ethics and dissemination This protocol does not present any results. Findings of this systematic review will be published in international peer-reviewed scientific journals.

PROSPERO registration number CRD42024499511.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Both risks of random and systematic errors will be taken into account by using a predefined detailed Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols compliant methodology, risk-of-bias assessments using the Cochrane Risk of Bias tool—version 2, an eight-step assessment of the statistical and clinical significance, and trial sequential analysis.

⇒ The involvement of two independent investigators for data extraction and risk-of-bias assessments enhances the review's credibility.

⇒ The adverse effects of semaglutide might not be disease or dose specific, and pooling all patient groups and types of semaglutide increase the statistical power.

⇒ Statistical heterogeneity may be expected as the review includes trials with all types of study participants and all types of semaglutide.

⇒ We expect a lack of relevant data, as we expect that a large proportion of the available trials have not focused on assessing adverse effects.

INTRODUCTION

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are relatively new drugs that mimic the effects of incretin.[1] Glucagon-like peptide 1 is produced by enteroendocrine L cells in the gastrointestinal tract.[1] Some metabolic effects of glucagon-like peptide 1 are enhancement of glucose-dependent stimulation of insulin secretion, inhibition of glucagon secretion, reduction of gastrointestinal motility and reduction of gastric emptying, thus enhancing satiety and reducing food intake.[2] Treatment with GLP-1 RAs entails supraphysiological stimulation of the glucagon-like peptide receptor, and therefore, treatment with GLP-1 RAs results in supraphysiological effects of glucagon-like peptide 1.

One type of GLP-1 RAs is semaglutide. Since 2017, semaglutide has been approved by the U.S. Food & Drug Administration for treating patients with type 2 diabetes mellitus.[3] In 2021, semaglutide was approved by the U.S. Food & Drug Administration for

treating overweight and obesity.[3] Semaglutide is widely and increasingly used for the treatment of overweight or type 2 diabetes mellitus.

Semaglutide is available in both peroral and subcutaneous formulas:

- The peroral semaglutide is Rybelsus used for the treatment of type 2 diabetes mellitus in the following doses: 3 mg, 7 mg and 14 mg one time a day.[4]
- Subcutaneous Ozempic is used for treating type 2 diabetes mellitus and off-label usage for treating overweight and obesity in the following doses: 0.25 mg, 0.5 mg, 1 mg or 2 mg one time a week.[5]
- Subcutaneous Wegovy is used for treating overweight and obesity in the following doses: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg one time a week.[4]

Previous evidence

Several previous systematic reviews have shown that semaglutide lowers blood glucose levels and leads to significant weight loss compared with placebo. Most of these systematic reviews have also assessed some of the adverse effects of semaglutide.[4 6–14] Generally, the most frequent serious and non-serious adverse events have been related to the gastrointestinal tract (see online supplemental material). Animal studies have indicated an association between treatment with GLP-1 RA and pancreatitis, pancreatic cancer and thyroid cancer.[15] Recently, concerns have been raised regarding suicidal behaviour due to semaglutide.[16] The results of previous reviews are conflicting, and none of the systematic reviews included all relevant patient groups. Moreover, the latest published trials investigating semaglutide versus placebo (the 'Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity' (SELECT) trial[17] and the 'Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity' (STEP-HFpEF) trial[18]) have not been included in the previous reviews.[4 6–14] A detailed description of the previous reviews may be found in online supplemental material.

Why is this review important?

The results of previous reviews assessing the effects of semaglutide are conflicting, and no previous review has included all patient groups treated with semaglutide. The effects of semaglutide on blood glucose levels and weight loss might differ between the different patient groups being treated, but the adverse effects with semaglutide might be comparable. Including all patient groups in the analyses will increase the statistical power if meta-analyses are deemed warranted. There is a lack of a systematic review including all relevant trials assessing the adverse effects with semaglutide.

METHODS AND ANALYSES

The protocol is reported following the reporting guideline provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement[19 20] and is registered in the PROSPERO database (CRD42024499511).

Criteria for considering studies for this review

Types of trials

We will include randomised clinical trials, irrespective of publication status, publication year and language. We will not include quasi-randomised studies (ie, trials with inappropriate allocation strategies for interventions[21]), non-randomised studies (eg, case-control studies) or observational studies.

Types of participants

All patients treated with oral or subcutaneous semaglutide irrespectively of the indication for the treatment (eg, type 2 diabetes mellitus, obesity, chronic kidney disease, patients with a high risk of a cardiovascular event, women with polycystic ovary syndrome, etc).

Types of interventions

We will accept all dosages of oral and subcutaneous semaglutide.

We will accept placebo or 'no intervention' as control interventions.

Cointerventions

We will accept any cointervention, if the cointervention is intended to be delivered similarly in the intervention and control groups.

Outcome measures

Primary outcomes

1. All-cause mortality.
2. Proportion of participants with one or more serious adverse events. We will use the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, and resulted in persistent or significant disability or jeopardised the participant.[22] If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term "serious adverse event". If the trialists do not use the ICH-GCP definition or the term serious adverse event, we will also include the data if the event clearly fulfils the ICH-GCP definition of a serious adverse event. We will exploratorily assess each type of serious adverse event separately.

Secondary outcomes

1. Myocardial infarction (as defined by trialists).
2. Stroke (as defined by trialists).
3. All-cause hospitalisation (as defined by trialists).
4. Non-serious adverse events. Each type of adverse event will be analysed and presented separately.

Exploratory outcomes

1. Pancreatitis (as defined by trialists).
2. Any type of cancer (as defined by trialists).
3. Suicides or suicide attempts (as defined by trialists).
4. Composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke (as defined by trialists).
5. Vision changes (blurred vision, retinopathy or macular complications) (as defined by trialists).

Assessment time points

We will assess all outcomes at maximum follow-up.

Search methods for identification of studies

Electronic searches

We will search Cochrane Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online (Medline) (Medline Ovid), Excerpta Medica database (Embase) (Embase Ovid), Latin American and Caribbean Health Sciences Literature (VHL Regional Portal), Science Citation Index Expanded (Web of Science) and Conference Proceedings Citation Index—Science (Web of Science) to identify relevant trials. We will search all databases from their inception to the present. Trials will be included irrespective of language, publication status, publication year and publication type. For a detailed search strategy for all electronic searches, see online supplemental material.

We expect to conduct the literature search in July 2024.

Searching other resources

The reference lists of relevant trial publications will be checked for any unidentified randomised clinical trials. To identify unpublished trials, we will search clinical trial registries (eg, clinicaltrials.gov, clinicaltrialregister.eu, who.int/ictrp, chictr.org.cn) of the World.

We will also include unpublished trials if we identify these and assess relevant retraction statements and errata for included trials. We will also try to obtain clinical study reports from regulatory authorities as these are known to be more transparent in reporting adverse events.[23–28] We will also search preprint servers (bioRxiv, medRxiv) for unpublished trials.

Data collection

We will perform and report the review as recommended by the PRISMA statement.[29] Analyses will be performed using Stata V.16 (StataCorp LLC)[30] and trial sequential analysis.[31 32]

Selection of randomised clinical trials

Two review authors will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publications, and two review authors will independently screen the full-texts and will record reasons for the exclusion of the ineligible studies. The same two review authors will resolve any disagreements through discussion, or if required, they will consult a third author (JJ).

Data extraction and management

Two review authors will independently extract data from included trials in a predefined form. Disagreements will be resolved by discussion with a third author (JJ). The two review authors will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). Each trial will be named after the first author and year of the primary publication, and all secondary publications will be classified under that name. We will contact the trial authors by email to specify any missing data, which may not be reported sufficiently or at all in the publication.

Trial characteristics

We will extract the following data: bias risk components (as defined below), trial design (parallel, factorial or crossover), number of intervention groups, length of follow-up, estimation of sample size, and inclusion and exclusion criteria.

Participant characteristics

We will extract the following data: number of randomised participants, number of analysed participants, number of participants lost to follow-up/withdrawals/crossover, age range (mean or median), sex ratio, primary diagnosis (eg, type 2 diabetes mellitus, obesity, hypertension, chronic kidney disease, etc), haemoglobin A1c (mean and SD) and body mass index (mean and SD).

Experimental intervention characteristics

We will extract the following data: type of semaglutide (oral or subcutaneous), dosage and length of treatment period.

Control intervention characteristics

We will extract the following data: type of control (placebo, matching placebo, 'active' placebo, or no intervention), dosage and length of treatment period.

Outcomes

All outcomes listed above will be extracted from each randomised clinical trial. For each outcome, we will identify if there are deviations from intended interventions, if outcomes are missing, inappropriately measured, or selectively reported according to the criteria described later in the 'missing outcome data' bias domain, the 'risk of bias in measurement of the outcome' bias domain and the 'risk of bias in selection of the reported result' bias domain.

Notes

We will search for information regarding industry funding of either personal or academic activities for each trial author. We will judge a publication at high risk of for-profit bias if a trial is sponsored by the industry or if just one author has affiliation to the industry.[33] We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Two review

authors will independently transfer data into the Stata file.[30] Disagreements will be resolved through discussion, or if required, we will consult with a third author (JJ).

Assessment of risk of bias in the included trials

Our bias risk assessment will be based on the Cochrane Risk of Bias tool—version 2 (RoB 2) as recommended in The Cochrane Handbook of Systematic Reviews of Interventions.[21] We will evaluate the methodology in respect of the following bias domains:

- Bias arising from the randomisation process.
- Bias due to deviation from intended interventions (effect of assignment to intervention).
- Bias due to missing outcome data.
- Bias in measurement of outcomes.
- Bias arising from selective reporting of results.
- Overall assessment of risk of bias.

We will assess the domains 'deviations from intended interventions', 'missing outcome data', 'risk of bias in measurement of the outcome' and 'risk of bias in selection of the reported result' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. The overall risk of bias of a result or trial will be judged to be low if all domains are assessed at low risk of bias. If one or more domains are assessed at either some concerns or high risk of bias, the overall risk of bias will be assessed at high. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.

Differences between the protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between the protocol and the review' section of the systematic review.

Measurement of treatment effect

Dichotomous outcomes

We will calculate risk ratios with 95% CI for dichotomous outcomes, as well as the trial sequential analysis-adjusted CIs (see below).

Dealing with missing data

We will use intention-to-treat data if provided by the trialists.[34] We will, as the first option, contact all trial authors to obtain any relevant missing data (ie, for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see paragraph below), we will impute data.

Assessment of heterogeneity

We will primarily visually investigate forest plots for signs of heterogeneity. We will second assess the presence of statistical heterogeneity using I^2 statistic (ie, the percentage of total variation across trials apart from random variation, with 0% indicating no observed heterogeneity and increasing percentages indicating increasing heterogeneity)[21 35 36] and restricted maximum likelihood method to estimate the heterogeneity variance.[37 38] We will only conclude that the heterogeneity is high if the between trial variance translates to differences important to patients (based on the effect sizes defined by in the trial sequential analyses, see below). We will investigate heterogeneity through subgroup analyses (see 'Subgroup analyses and integration of heterogeneity' section below). We may ultimately decide that a meta-analysis should be avoided if heterogeneity is high.[21]

Assessment of reporting biases

We will use a funnel plot to assess reporting bias if 10 or more trials are included.[21] We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (ie, a funnel plot assesses small study bias).[21] From this information, we will assess possible reporting bias. For dichotomous outcomes, we will test asymmetry with the Harbord test[39] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1.[21] In addition, we will assess possible reporting bias for dichotomous outcomes with Egger and Begg tests.[40 41]

Unit of analysis issues

We will only include randomised clinical trials. For trials using crossover design, only data from the first period will be included,[21 42] so there will be no unit of analysis issues. We will not include cluster randomised trials.

Meta-analysis

We will undertake the meta-analyses in accordance with the *Cochrane Handbook of Systematic Reviews of Interventions*,[21] Keus *et al*[43] and the eight-step assessment suggested by Jakobsen *et al*.[44] We will use the statistical software Stata to analyse data.[30] We will assess our intervention effects with both a random-effect meta-analysis[45] and a fixed-effect meta-analysis for each treatment comparison separately.[46] We will primarily report the most conservative point estimate of the two (highest p-value) and consider the less conservative result a sensitivity analysis.[44]

We will assess a total of two primary outcomes and consider a p value of 0.03 (adjustment per recommendations by Jakobsen *et al*) or less as the threshold for statistical significance.[44] We will investigate possible heterogeneity through subgroup analyses. We will use the eight-step procedure to assess if the thresholds for significance are crossed.[44] We will include only the relevant intervention groups (arms) where multiple trial arms are reported in a single trial. If two comparisons are combined in the same meta-analysis, we will split the control group to avoid double counting .

Trial sequential analysis

We wish to control the risks of type I and type II errors. We will, therefore, perform trial sequential analysis on all outcomes, to calculate the required information size (that

is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries.[31 32 47–53] A more detailed description of trial sequential analysis can be found in the trial sequential analysis manual[31] and at http://www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction or a relative risk increase of 25%, an alpha of 3% for all outcomes (including exploratory outcomes), a beta of 10% and the observed diversity as suggested by the trials in the meta-analysis.

Subgroup analyses and integration of heterogeneity

Subgroup analyses

We will perform the following subgroup analyses when analysing the primary outcomes (all-cause mortality and serious adverse events).

1. Subgroup analyses of each patient group (eg, type 2 diabetes mellitus, obesity, hypertension, chronic kidney disease, etc).
2. Subgroup analyses of subcutaneous semaglutide compared with oral semaglutide.
3. Subgroup analyses of trials at high risk of bias compared with trials at low risk of bias.
4. Subgroup analyses of different doses of semaglutide (at or above the median compared with below the median).
5. Subgroup analyses of different lengths of intervention (at or above the median compared with below the median).
6. Subgroup analyses of different levels of treatment compliance (high degree of compliance compared with low degree of compliance (as defined by trialistis)).

We will use the formal test for subgroup interactions in Stata.[30] We will perform relevant unanticipated subgroup analyses, if we identify these.

Sensitivity analysis

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on all primary and secondary dichotomous outcomes.

- 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group survived, had no serious adverse events, had no non-serious adverse events and was not hospitalised, and that all those participants lost to follow-up in the control group did not survive, had a serious adverse event, had a non-serious adverse event and was hospitalised.
- 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group did not survive, had a serious adverse event, had a non-serious adverse event, and was hospitalised, and that all those participants lost to follow-up in the control group survived, had no serious adverse events, had no non-serious adverse events and was not hospitalised.

We will present the results of both scenarios in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.[44]

Summary of findings table

We will create a summary of findings table, including each of the prespecified outcomes. We will use the five Grading of Recommendations, Assessment, Development and Evaluations (GRADE) considerations (bias risk of the trials, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence.[44 54–56] We will assess imprecision using trial sequential analysis by downgrading three levels if the accrued sample is less than 33% of diversity-adjusted required information size (DARIS); two levels if between 33% and 66% of DARIS; one level if more than 66% of DARIS; and no downgrade if the cumulative Z-curve crosses the boundary for benefit, futility or harm. We will justify all decisions to downgrade the certainty of the evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. First, we will present our results in the summary of findings table based on the results from the trials at overall low risk of bias, and second, we will present the results based on all trials.[57]

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION

This systematic review does not require ethical approval and informed consent, as it does not use identifiable patient data. Findings of this systematic review will be published in international peer-reviewed scientific journals.

DISCUSSION

This systematic review with aggregate data meta-analyses and trial sequential analyses aims to assess the adverse effects of semaglutide versus placebo (both beneficial and harmful effects) on hard binary outcomes, including all patient groups. Primary outcomes will be all-cause mortality and serious adverse events. Secondary outcomes will be myocardial infarction, stroke, all-cause hospitalisation and non-serious adverse events.

This protocol has several strengths. The predefined detailed methodology follows the PRISMA-P statement, the eight-step assessment suggested by Jakobsen *et al*,[44]

trial sequential analysis,[31 32] and GRADE assessments.[54] Thus, this protocol considers both risks of design errors, random errors and systematic errors. The adverse effects of semaglutide might not be disease or dose specific, and pooling all patient groups and types of semaglutide increase the statistical power.

Our protocol also has limitations. The primary limitation is the risk of potential statistical heterogeneity as we include all types of participants and all types and doses of semaglutide. Furthermore, we anticipate that a large proportion of the available trials will investigate the effects of semaglutide on either glycaemic control or weight loss as the primary outcome and have less focus on the adverse effects with semaglutide. Insufficient data may complicate the systematic assessments of the adverse effects with semaglutide so we cannot draw definitive conclusions. Some randomised trials will presumably only focus on short-term effects of semaglutide (down to 12 weeks of treatment and then follow-up), which may reduce the likelihood of clinical events occurring within the treatment period.

Undetected low adherence to semaglutide and, thus, undetected lower exposure to semaglutide may be an issue, especially in trials with long treatment period. This may be a potential limitation.

Last, it is a limitation that we will only be able to include aggregate data and not individual patient data.

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Contributors The study idea, design and conduct were conceived by CDBS and JJ. CDBS authored the initial draft and worked closely with JJ on crafting the first version of the manuscript. Subsequently, CBK, JJP, PF, FS, JG, HD, AF, PHG, CG and OM assisted in refining the study design, critically revised the manuscript and approved the submitted version. CDBS is the guarantor. CDBS, FS, JJP and PF will be responsible for data collection. Analyses will be conducted by CDBS, JJP, FS, PF and JJ.

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Competing interests PG has received lecture fees for Novo Nordisk, AstraZeneca, Eli Lilly, Bayer, MSD and has served in Advisory Boards for Novo Nordisk, AstraZeneca, Bayer.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note We are anticipating to start the data analysis in 6 months (ie, July 2024).

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