BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005378
Article Type:	Protocol
Date Submitted by the Author:	02-Apr-2014
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Type 2 diabetes, meta-analysis, sodium-glucose co-transporter 2 inhibitor, ORAL MEDICINE

The effects of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: protocol for a systematic review with meta-analysis of randomised trials

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Keywords: sodium-glucose co-transporter 2 inhibitors, type 2 diabetes, meta-analyses, oral medicine

Word count (excluding title page, abstract and references): 1752

Abstract

Introduction: Sodium glucose co-transporter 2 inhibitors (SGLT-2i) increase urinary glucose excretion through a reduced renal glucose reabsorption. We plan to perform a systematic review of SGLT-2i for treatment of type 2 diabetes.

Methods and analysis: A systematic review with meta-analyses of randomised clinical trials on SGLT-2i versus placebo, other oral glucose lowering drugs or insulin for patients with type 2 diabetes will be performed. The primary endpoint will be HbA1c. Secondary endpoints will include changes in body weight, body mass index, fasting plasma glucose, plasma cholesterol, kidney and liver blood tests, blood pressure, and adverse events. Electronic (The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index) and manual searches will be performed. Meta-analyses will be performed and the results presented as mean differences for continuous outcomes and risk differences for dichotomous outcomes, both with 95% confidence intervals (CI). Subgroup, sensitivity, regression and sequential analyses will be performed to evaluate inter-trial heterogeneity, bias and the robustness of the results due to cumulative testing.

Ethics and dissemination: The study will contribute to the knowledge regarding the beneficial and harmful effects of SGLT-2i in patients with type 2 diabetes. We plan to publish the study irrespective of the results.

Results: The study will be disseminated by peerreview publication and conference presentation.

Protocol registration: PROSPERO CRD42014008960

ARTICLE SUMMARY

Article focus

Impact of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) on glycaemic control (hbA1c), effects on fasting plasma glucose, body weight (body mass index, BMI), lipids, liver and kidney blood tests, blood pressure and adverse events in patients with type 2 diabetes.

Key messages

A systematic review with meta-analysis on the glucose-lowering effect and safety of SGLT-2i in patients with type 2 diabetes in clinically relevant daily doses is lacking. Individualised treatment is recommended and new and safe drugs with alternative modes of action are needed for patients with type 2 diabetes to reach their treatment goals.

Strengths and limitations of this study

We have the knowledge and experience within our group on how to conduct a systemic review and meta-analysis. A possible limitation might be the access to data from the randomised clinical trials we plan to include in the study.

INTRODUCTION

Type 2 diabetes is a metabolic disease associated with obesity, dyslipidaemia and hypertension. Patients with type 2 diabetes are characterised by defective insulin secretion, insulin resistance, inappropriate glucagon secretion and an impaired incretin effect resulting in fasting and postprandial hyperglycaemia [1]. Hyperglycaemia with elevated levels of glycated haemoglobin A_{1c} (HbA_{1c}) predicts micro- and macrovascular complications [2]. Although improved metabolic control is associated with reduced morbidity and mortality [3], recent studies show that intensive glucose lowering treatments may harm some patients [4–7]. As a consequence the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends individualisation of the treatment [8]. Drugs with complementary mechanisms of action are recommended with metformin as first-line therapy. As β cell function declines, a number of patients fail to achieve their glycaemic target and maintenance of glucose control often necessitates several add-on therapies [8]. Current oral medications endorsed by ADA and EASD treatment algorithms for treating patients with type 2 diabetes i.e. metformin, sulphonylureas, dipeptidyl peptidase 4 inhibitors and thiazolidinediones act by increasing insulin secretion or sensitizing tissues to insulin action. Treatment strategies with insulin-independent pathways could therefore be advantageous.

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) represent a new class of drugs that inhibit glucose reabsorption in the proximal tubules of the kidneys. As a result, urinary glucose excretion is increased, which in turn reduces the amount of circulating glucose and improves glycaemic control. The effect is not associated with insulin secretion or action [9].

In clinical trials, SGLT-2i (in monotherapy or combined with metformin, sulphonylureas, pioglitazone, or insulin) seems to improve glycaemic control in type 2 diabetes [10–14]. In 2013 and 2014, two STGL-2i, canagliflozin and dapagliflozin, were approved by the United States Food and Drug Administration (FDA) [15,16] and the European Medicine Agency (EMA) for the treatment of patients with type 2 diabetes [17,18]. None of the individual clinical trials on SGLT-2i provide definite conclusions regarding efficacy and safety and so far current guidelines for the management of type 2 diabetes do not include SGLT-2i [8]. In order to provide robust evidence for the efficacy and safety of SGLT-2i we plan to perform a systematic review with meta-analyses of randomised controlled trials (RCTs). Unlike previous systematic reviews, we plan to include focus on trials assessing on STLG-2i in doses that are recommended for clinical practice.

OBJECTIVES

The primary objective of this systematic review is to evaluate the effects of SGLT-2i that are approved (dapagliflozin and canagliflozin) or is in late clinical development (empagliflozin). To increase external validity, we plan to only include trials with clinically relevant daily doses (canagliflozin 300 mg, dapagliflozin 10 mg and empagliflozin 25 mg). Our primary objective will be to assess the impact on glycaemic control (HbA_{1c}).

METHODS

The reporting of the review will follow the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [19] .

Criteria for considering studies for this review

Studies. The review will include RCTs irrespective of blinding and language..

Participants. Adult patients (at least 18 years of age) of both genders with type 2 diabetes will be included.

Interventions. The intervention comparisons will constitute SGLT-2i (dapagliflozin, canagliflozin and empagliflozin) versus placebo, other anti-diabetic drugs or insulin. Co-interventions with other anti-diabetic agents will be allowed if administered to both the intervention and control group.

Types of outcome measures

The following outcome measures will be assessed

Primary outcome measure

- HbA_{1c}

Secondary outcome measures

- Body weight and BMI
- Fasting plasma glucose
- Low density lipoprotein (LDL)-cholesterol

- Systolic and diastolic blood pressure
- Liver and kidney blood tests
- Adverse events

Search methods for identification of studies

All authors will participate in the identification and selection of trials. Excluded trials will be listed with the reason for exclusion. Authors will extract data in an independent manner. Eligible trials will be identified through electronic and manual searches. Electronic searches will be performed in MEDLINE ((Sodium-glucose [All Fields] AND co-transporter [All Fields]) OR ("2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [All Fields] OR "dapagliflozin" [All Fields]) OR ("canagliflozin"[Supplementary Concept] OR "canagliflozin" [All Fields]) OR ("empagliflozin" [Supplementary Concept] OR "empagliflozin" [All Fields]) OR Remogliflozin [All Fields] OR ("sergliflozin" [Supplementary Concept] OR "sergliflozin" [All Fields]) OR ("6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [All Fields] OR "tofogliflozin" [All Fields])), Cochrane Library, Embase and Web of science. Additional manual searches will be performed in reference lists of relevant papers, correspondence with experts, the pharmaceutical companies producing SGLT-2i and the World Health Organisation Trial Search Database [20].

Data collection and analysis

Two authors (HS and MC) will independently extract data and resolve disagreements through discussion before analysis. In the case of unresolved matters, a third party (TV, FK or LLG) will be involved. If necessary data are not included in the published trial reports, authors of included trials will be contacted for additional information.

Selection of studies

Trials identified through the searches will be listed and selected for inclusion according to the above mentioned criteria.

Data extraction

Extraction forms developed for the study will be used and the following data will be extracted: Trial characteristics (number of clinical sites, country of origin and funding), intervention characteristics (type, dose and duration of interventions applied), patient characteristics (inclusion criteria, background treatment, mean age, proportion of men, duration of type 2 diabetes, body weight, BMI, baseline systolic and diastolic blood pressure baseline HbA_{1c}, baseline blood tests, fasting plasma glucose, LDL-cholesterol, alanine amino transferase, alkaline phosphatase, creatinine and urate.

Assessment of risk of bias in included studies

The bias risk assessment will follow the recommendations described in the Cochrane Handbook for Reviews of Interventions and includes:

- Randomisation (selection bias): the randomisation methods will be extracted as the primary measure of bias control [21]. Methodological quality in the randomisation methods will be based on the allocation sequence generation (adequate if based on a table of random numbers, computer-generated random numbers or similar) and allocation concealment (adequate if randomisation was performed through serially numbered opaque sealed envelopes, a central independent unit, identically appearing coded drug containers or similar).

- Blinding (performance and detection bias): we will extract data on whether single of double blinding was performed, the method of blinding (e.g., use of placebo) and the persons who were blinded with regard to the interventions assessed (e.g., health care providers or patients).

- Incomplete outcome data (attrition bias): the extent to which all patients lost to follow-up are accounted for.

- Outcome reporting (reporting bias): the extent to which clinically relevant outcome measures are reported and differences between trial protocols and subsequent reports will be evaluated as a marker of reporting bias.

- Other bias: any other apparent biases will be evaluated.

Statistical analyses

The analyses will be performed in RevMan [22] and Stata Version 13 (STATA Corp, College Station, Texas, US). Analyses will be based on individual patient data when available or on published data. I^2 will be used as a measure of heterogeneity. I^2

values below 30% will be defined as unimportant, 30-50% as moderate heterogeneity, 50-75% as substantial heterogeneity and I^2 values >75% will be defined as considerable heterogeneity. Irrespective of the statistical heterogeneity, both fixed effect and random effects models will be used to test the robustness of the results. We will only report the results of the random effects meta-analyses if the results differ from the fixed effect models. Publication bias and other small study effects will be evaluated based on regression analysis (Egger's or Harbord's test).

Subgroup analyses will be performed to evaluate sources of heterogeneity. Differences between subgroups will be explored using tests for subgroup differences expressed as *p* values. The subgroup analyses will evaluate the influence of the type of data (individual patient data or published data), the control groups, collateral interventions, glycaemic control at baseline, duration of diabetes, baseline bodyweight (outcomes will be recalculated for patients who are normal weight defined as a maximum BMI of 25 kg/m^2 at the time of randomisation) and publication status and bias control.

Measures of treatment effect. Dichotomous data will be analysed using risk differences (RD) and continuous data using mean differences, both with 95% CIs. The number needed to treat will be calculated as the inverse of the RD for statistically significant outcome measures.

Unit of analyses issues. For trials presenting data from more than one treatment period (e.g. 26 and 52 weeks), data from the longest treatment period will be used. Based on the primary outcome measure, only data from the first period of cross-over trials will be used.

Dealing with missing data. Intention-to-treat analyses including all patients randomised will be performed. In the case of patients with missing outcome data, carry forward of the last observed response will be used. Individual patient data will be sought from the original source or from the published trial reports where individual patient data are unavailable.

ETHICS AND DISSEMINATION

The study will evaluate the clinical effect of SGLT-2i in patients with type 2 diabetes based on the available published and unpublished clinical trial data and thereby potentially improve the clinical knowledge on and management of type 2 diabetes.

CONTRIBUTORS

HS, LLG, MC and TV participated in the conception and design of this protocol including search strategy development. LLG provided statistical advice for the design. HS prepared the draft and all authors reviewed the manuscript and approved the final version.

FUNDING

TV and FKK are supported by unrestricted grants from Novo Nordisk Foundation. The research did not otherwise receive specific grant from any funding agency in the

public, commercial of not-for-profit sectors. No sponsor was involved in the study design, and no sponsor will have authority in collection, management, analysis and interpretation of data.

COMPETING INTERESTS

The authors declare no conflict of interests in relation to the present article.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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Journal:	*BMJ Open*
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Article Type:	Protocol
Date Submitted by the Author:	11-Jun-2014
Complete List of Authors:	Storgaard, Heidi; Gentofte Hospital, University of Copenhagen, Center for Diabetes Research, Department of Internal Medicine Gluud, Lise; Department of Gastroenterology, Christensen, Mikkel; Bispebjerg Hospital, University of Copenhagen, Department of Clinical Pharmacology Knop, Filip; Gentofte Hospital, University of Copenhagen, Center for Diabetes Research, Department of Internal Medicine Vilsbøll, Tina; Gentofte Hospital, University of Copenhagen, Center for Diabetes Research, Department of Internal Medicine
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Abstract

Introduction: Sodium glucose co-transporter 2 inhibitors (SGLT-2i) increase urinary glucose excretion through a reduced renal glucose reabsorption. We plan to perform a systematic review of SGLT-2i for treatment of type 2 diabetes.

Methods and analysis: A systematic review with meta-analyses of randomised clinical trials on SGLT-2i versus placebo, other oral glucose lowering drugs or insulin for patients with type 2 diabetes will be performed. The primary endpoint will be HbA1c. Secondary endpoints will include changes in body weight, body mass index, fasting plasma glucose, plasma cholesterol, kidney and liver blood tests, blood pressure, and adverse events. Electronic (The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index) and manual searches will be performed. Meta-analyses will be performed and the results presented as mean differences for continuous outcomes and risk differences for dichotomous outcomes, both with 95% confidence intervals (CI). Subgroup, sensitivity, regression and sequential analyses will be performed to evaluate inter-trial heterogeneity, bias and the robustness of the results due to cumulative testing.

Ethics and dissemination: The study will contribute to the knowledge regarding the beneficial and harmful effects of SGLT-2i in patients with type 2 diabetes. We plan to publish the study irrespective of the results.

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Key messages

A systematic review with meta-analysis on the glucose-lowering effect and safety of SGLT-2i in patients with type 2 diabetes in clinically relevant daily doses is lacking. Individualised treatment is recommended and new and safe drugs with alternative modes of action are needed for patients with type 2 diabetes to reach their treatment goals.

Strengths and limitations of this study

We have the knowledge and experience within our group on how to conduct a systemic review and meta-analysis. A possible limitation might be the access to data from the randomised clinical trials we plan to include in the study.

INTRODUCTION

Type 2 diabetes is a metabolic disease associated with obesity, dyslipidaemia and hypertension. Patients with type 2 diabetes are characterised by defective insulin secretion, insulin resistance, inappropriate glucagon secretion and an impaired incretin effect resulting in fasting and postprandial hyperglycaemia [1]. Hyperglycaemia with elevated levels of glycated haemoglobin A_{1c} (HbA_{1c}) predicts micro- and macrovascular complications [2]. Although improved metabolic control is associated with reduced morbidity and mortality [3], recent studies show that intensive glucose lowering treatments may harm some patients [4–7]. As a consequence the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends individualisation of the treatment [8]. Drugs with complementary mechanisms of action are recommended with metformin as first-line therapy. As β cell function declines, a number of patients fail to achieve their glycaemic target and maintenance of glucose control often necessitates several add-on therapies [8]. Current oral medications endorsed by ADA and EASD treatment algorithms for treating patients with type 2 diabetes i.e. metformin, sulphonylureas, dipeptidyl peptidase 4 inhibitors and thiazolidinediones act by increasing insulin secretion or sensitizing tissues to insulin action. Treatment strategies with insulin-independent pathways could therefore be advantageous.

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) represent a new class of drugs that inhibit glucose reabsorption in the proximal tubules of the kidneys. As a result, urinary glucose excretion is increased, which in turn reduces the amount of circulating glucose and improves glycaemic control. The effect is not associated with insulin secretion or action [9].

In clinical trials, SGLT-2i (in monotherapy or combined with metformin, sulphonylureas, pioglitazone, or insulin) seems to improve glycaemic control in type 2 diabetes [10–14]. In 2013 and 2014, two STGL-2i, canagliflozin and dapagliflozin, were approved by the United States Food and Drug Administration (FDA) [15,16] and the European Medicine Agency (EMA) for the treatment of patients with type 2 diabetes [17,18]. None of the individual clinical trials on SGLT-2i provide definite conclusions regarding efficacy and safety and so far current guidelines for the management of type 2 diabetes do not include SGLT-2i [8]. In order to provide robust evidence for the efficacy and safety of SGLT-2i we plan to perform a systematic review with meta-analyses of randomised controlled trials (RCTs). Unlike previous systematic reviews, we plan to include focus on trials assessing on STLG-2i in doses that are recommended for clinical practice.

OBJECTIVES

The primary objective of this systematic review is to evaluate the effects of SGLT-2i that are approved (dapagliflozin and canagliflozin) or is in late clinical development (empagliflozin). To increase external validity, we plan to only include trials with clinically relevant daily doses (canagliflozin 300 mg, dapagliflozin 10 mg and empagliflozin 25 mg). Our primary objective will be to assess the impact on glycaemic control (HbA_{1c}).

METHODS

The reporting of the review will follow the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [19] .

Criteria for considering studies for this review

Studies. The review will include RCTs irrespective of blinding and language..

Participants. Adult patients (at least 18 years of age) of both genders with type 2 diabetes will be included.

Interventions. The intervention comparisons will constitute SGLT-2i (dapagliflozin, canagliflozin and empagliflozin) versus placebo, other anti-diabetic drugs or insulin. Co-interventions with other anti-diabetic agents will be allowed if administered to both the intervention and control group.

Types of outcome measures

The following outcome measures will be assessed

Primary outcome measure

- HbA_{1c}

Secondary outcome measures

- Body weight and BMI
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All authors will participate in the identification and selection of trials. Excluded trials will be listed with the reason for exclusion. Authors will extract data in an independent manner. Eligible trials will be identified through electronic and manual searches. Electronic searches will be performed in MEDLINE ((Sodium-glucose [All Fields] AND co-transporter [All Fields]) OR ("2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [All Fields] OR "dapagliflozin" [All Fields]) OR ("canagliflozin"[Supplementary Concept] OR "canagliflozin" [All Fields]) OR ("empagliflozin" [Supplementary Concept] OR "empagliflozin" [All Fields]) OR Remogliflozin [All Fields] OR ("sergliflozin" [Supplementary Concept] OR "sergliflozin" [All Fields]) OR ("6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [All Fields] OR "tofogliflozin" [All Fields])), Cochrane Library, Embase and Web of science. Additional manual searches will be performed in reference lists of relevant papers, correspondence with experts, the pharmaceutical companies producing SGLT-2i and the World Health Organisation Trial Search Database [20].

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- Blinding (performance and detection bias): we will extract data on whether single of double blinding was performed, the method of blinding (e.g., use of placebo) and the persons who were blinded with regard to the interventions assessed (e.g., health care providers or patients).

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The analyses will be performed in RevMan [22] and Stata Version 13 (STATA Corp, College Station, Texas, US). Analyses will be based on individual patient data when available or on published data. I^2 will be used as a measure of heterogeneity. I^2

values below 30% will be defined as unimportant, 30-50% as moderate heterogeneity, 50-75% as substantial heterogeneity and I^2 values >75% will be defined as considerable heterogeneity. Irrespective of the statistical heterogeneity, both fixed effect and random effects models will be used to test the robustness of the results. We will only report the results of the random effects meta-analyses if the results differ from the fixed effect models. Publication bias and other small study effects will be evaluated based on regression analysis (Egger's or Harbord's test).

Subgroup analyses will be performed to evaluate sources of heterogeneity. Differences between subgroups will be explored using tests for subgroup differences expressed as *p* values. The subgroup analyses will evaluate the influence of the type of data (individual patient data or published data), the control groups, collateral interventions, glycaemic control at baseline, duration of diabetes, baseline bodyweight (outcomes will be recalculated for patients who are normal weight defined as a maximum BMI of 25 kg/m^2 at the time of randomisation) and publication status and bias control.

Measures of treatment effect. Dichotomous data will be analysed using risk differences (RD) and continuous data using mean differences, both with 95% CIs. The number needed to treat will be calculated as the inverse of the RD for statistically significant outcome measures.

Unit of analyses issues. For trials presenting data from more than one treatment period (e.g. 26 and 52 weeks), data from the longest treatment period will be used. Based on the primary outcome measure, only data from the first period of cross-over trials will be used.

Dealing with missing data. Intention-to-treat analyses including all patients randomised will be performed. In the case of patients with missing outcome data, carry forward of the last observed response will be used. Individual patient data will be sought from the original source or from the published trial reports where individual patient data are unavailable.

ETHICS AND DISSEMINATION

The study will evaluate the clinical effect of SGLT-2i in patients with type 2 diabetes based on the available published and unpublished clinical trial data and thereby potentially improve the clinical knowledge on and management of type 2 diabetes.

CONTRIBUTORS

HS, LLG, MC and TV participated in the conception and design of this protocol including search strategy development. LLG provided statistical advice for the design. HS prepared the draft and all authors reviewed the manuscript and approved the final version.

FUNDING

TV and FKK are supported by unrestricted grants from Novo Nordisk Foundation. The research did not otherwise receive specific grant from any funding agency in the public, commercial of not-for-profit sectors. No sponsor was involved in the study design, and no sponsor will have authority in collection, management, analysis and interpretation of data.

COMPETING INTERESTS

The authors declare no conflict of interests in relation to the present article.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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The effects of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: protocol for a systematic review with meta-analysis of randomised trials

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Keywords: sodium-glucose co-transporter 2 inhibitors, type 2 diabetes, meta-analyses, oral medicine

Word count (excluding title page, abstract and references): 1806

ARTICLE SUMMARY

Article focus

Impact of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) on glycaemic control (hbA1c), effects on fasting plasma glucose, body weight (body mass index, BMI), lipids, liver and kidney blood tests, blood pressure and adverse events in patients with type 2 diabetes.

Key messages

A systematic review with meta-analysis on the glucose-lowering effect and safety of SGLT-2i in patients with type 2 diabetes in clinically relevant daily doses is lacking. Individualised treatment is recommended and new and safe drugs with alternative modes of action are needed for patients with type 2 diabetes to reach their treatment goals.

Strengths and limitations of this study

We have the knowledge and experience within our group on how to conduct a systemic review and meta-analysis. A possible limitation might be the access to data from the randomised clinical trials we plan to include in the study.

ABSTRACT

Introduction: Sodium glucose co-transporter 2 inhibitors (SGLT-2i) increase urinary glucose excretion through a reduced renal glucose reabsorption. We plan to perform a systematic review of SGLT-2i for treatment of type 2 diabetes.

Methods and analysis: A systematic review with meta-analyses of randomised clinical trials on SGLT-2i versus placebo, other oral glucose lowering drugs or insulin for patients with type 2 diabetes will be performed. The primary endpoint will be HbA_{1c}. Secondary endpoints will include changes in body weight, body mass index, fasting plasma glucose, plasma cholesterol, kidney and liver blood tests, blood pressure, and adverse events. Electronic (The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index) and manual searches will be performed. Meta-analyses will be performed and the results presented as mean differences for continuous outcomes and risk differences for dichotomous outcomes, both with 95% confidence intervals (CI). Subgroup, sensitivity, regression and sequential analyses will be performed to evaluate inter-trial heterogeneity, bias and the robustness of the results due to cumulative testing.

Ethics and dissemination: The study will contribute to the knowledge regarding the beneficial and harmful effects of SGLT-2i in patients with type 2 diabetes. We plan to publish the study irrespective of the results.

Results: The study will be disseminated by peerreview publication and conference presentation.

Protocol registration: PROSPERO CRD42014008960

INTRODUCTION

Type 2 diabetes is a metabolic disease associated with obesity, dyslipidaemia and hypertension. Patients with type 2 diabetes are characterised by defective insulin secretion, insulin resistance, inappropriate glucagon secretion and an impaired incretin effect resulting in fasting and postprandial hyperglycaemia [1]. Hyperglycaemia with elevated levels of glycated haemoglobin A_{1c} (HbA_{1c}) predicts micro- and macrovascular complications [2]. Although improved metabolic control is associated with reduced morbidity and mortality [3], recent studies show that intensive glucose lowering treatments may harm some patients [4–7]. As a consequence the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends individualisation of the treatment [8]. Drugs with complementary mechanisms of action are recommended with metformin as first-line therapy. As β cell function declines, a number of patients fail to achieve their glycaemic target and maintenance of glucose control often necessitates several add-on therapies [8]. Current oral medications endorsed by ADA and EASD treatment algorithms for treating patients with type 2 diabetes i.e. metformin, sulphonylureas, dipeptidyl peptidase 4 inhibitors and thiazolidinediones act by increasing insulin secretion or sensitizing tissues to insulin action. Treatment strategies with insulin-independent pathways could therefore be advantageous.

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) represent a new class of drugs that inhibit glucose reabsorption in the proximal tubules of the kidneys. As a result, urinary glucose excretion is increased, which in turn reduces the amount of circulating glucose and improves glycaemic control. The effect is not associated with insulin secretion or action [9].

In clinical trials, SGLT-2i (in monotherapy or combined with metformin, sulphonylureas, pioglitazone, or insulin) seems to improve glycaemic control in type 2 diabetes [10–14]. In 2013 and 2014, two STGL-2i, canagliflozin and dapagliflozin, were approved by the United States Food and Drug Administration (FDA) [15,16] and the European Medicine Agency (EMA) for the treatment of patients with type 2 diabetes [17,18]. None of the individual clinical trials on SGLT-2i provide definite conclusions regarding efficacy and safety and so far current guidelines for the management of type 2 diabetes do not include SGLT-2i [8]. In order to provide robust evidence for the efficacy and safety of SGLT-2i we plan to perform a systematic review with meta-analyses of randomised controlled trials (RCTs). Previous systematic reviews on SGLT2i [19–24] used a pragmativ approach and included trials irrespective of the dosing or duration of follow up. We restricted our analyses to 'clinically relevant' trials, i.e., trials assessing doses and interventions that we use in clinical practice. We therefore limit our analyses to include trials on the recommended daily dose, clinical relevant compounds, and with sufficient follow up to assess the clinical effects. This approach means that smaller trials such as dose finding trials will not be included. We believe that this approach will give the evidence-based clinician a clearer and more useful answer. Doses that are not clinical relevant may under- or overestimate beneficial and potential harmful effects of SGLT-2i. Therefore, our results provide a more answer that may be used in clinical practice.

OBJECTIVES

The primary objective of this systematic review is to evaluate the effects of SGLT-2i that are approved (dapagliflozin and canagliflozin) or is in late clinical development (empagliflozin) in Europe and the United States of America. To increase external validity, we plan to evaluate doses that are currently recommended by FDA and/or EMA [17,25,26] as maximum daily dose and therefore only include trials with these daily doses (canagliflozin 300 mg, dapagliflozin 10 mg and empagliflozin 25 mg). Our primary objective will be to assess the impact on glycaemic control (HbA_{1c}).

METHODS

The reporting of the review will follow the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [27] .

Criteria for considering studies for this review

Studies. The review will include RCTs irrespective of blinding and language..

Participants. Adult patients (at least 18 years of age) of both genders with type 2 diabetes will be included.

Duration. Because red blood cells survive for 8 – 12 weeks, the trials should last for at least 12 weeks to evaluate the effect of SGLT-2i on HbA_{1c}

Interventions. The intervention comparisons will constitute SGLT-2i (dapagliflozin, canagliflozin and empagliflozin) versus placebo, other anti-diabetic drugs or insulin. Co-interventions with other anti-diabetic agents will be allowed if administered to both the intervention and control group.

Types of outcome measures

The following outcome measures will be assessed

Primary outcome measure

- HbA_{1c}

Secondary outcome measures

- Body weight and BMI
- Fasting plasma glucose
- Lipid profile (Low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholestrol, triglyceride)
- Systolic and diastolic blood pressure
- Liver and kidney blood tests (creatinine, uric acid)
- Urinary albumin
- Adverse events (Any adverse events, urinary tract infections, genital tract infections, hypoglycaemia, hypotension, total withdrawals)

Search methods for identification of studies

All authors will participate in the identification and selection of trials. Excluded trials will be listed with the reason for exclusion. Authors will extract data in an independent manner. Eligible trials will be identified through electronic and manual searches. Electronic searches will be performed in MEDLINE ((Sodium-glucose [All Fields] AND co-transporter [All Fields]) OR ("2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [All Fields] OR "dapagliflozin" [All Fields]) OR ("canagliflozin"[Supplementary Concept] OR "canagliflozin" [All Fields]) OR ("empagliflozin" [Supplementary Concept] OR "empagliflozin" [All Fields]) OR Remogliflozin [All Fields] OR ("sergliflozin" [Supplementary Concept] OR "sergliflozin" [All Fields]) OR ("6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [All Fields] OR "tofogliflozin" [All Fields])), Cochrane Library, Embase and Web of science. Additional manual searches will be performed in reference lists of relevant papers, correspondence with experts, the pharmaceutical companies producing SGLT-2i and the World Health Organisation Trial Search Database [28].

Data collection and analysis

Two authors (HS and MC) will independently extract data and resolve disagreements through discussion before analysis. In the case of unresolved matters, a third party (TV, FK or LLG) will be involved. If necessary data are not included in the published trial reports, authors of included trials will be contacted for additional information.

Selection of studies

Trials identified through the searches will be listed and selected for inclusion according to the above mentioned criteria.

Data extraction

Extraction forms developed for the study will be used and the following data will be extracted: Trial characteristics (number of clinical sites, country of origin and funding), intervention characteristics (type, dose and duration of interventions applied), patient characteristics (inclusion criteria, background treatment, mean age, proportion of men, duration of type 2 diabetes, body weight, BMI, baseline systolic and diastolic blood pressure baseline HbA_{1c}, baseline blood tests, fasting plasma glucose, LDL-cholesterol, alanine amino transferase, alkaline phosphatase, creatinine and urate.

Assessment of risk of bias in included studies

The bias risk assessment will follow the recommendations described in the Cochrane Handbook for Reviews of Interventions and includes:

- Randomisation (selection bias): the randomisation methods will be extracted as the primary measure of bias control [29]. Methodological quality in the randomisation methods will be based on the allocation sequence generation (adequate if based on a table of random numbers, computer-generated random numbers or similar) and allocation concealment (adequate if randomisation was performed through serially numbered opaque sealed

envelopes, a central independent unit, identically appearing coded drug containers or similar).

- Blinding (performance and detection bias): we will extract data on whether single of double blinding was performed, the method of blinding (e.g., use of placebo) and the persons who were blinded with regard to the interventions assessed (e.g., health care providers or patients).
- Incomplete outcome data (attrition bias): the extent to which all patients lost to follow-up are accounted for.
- Outcome reporting (reporting bias): the extent to which clinically relevant outcome measures are reported and differences between trial protocols and subsequent reports will be evaluated as a marker of reporting bias.
- Other bias: any other apparent biases will be evaluated.

Statistical analyses

The analyses will be performed in RevMan [30] and Stata Version 13 (STATA Corp, College Station, Texas, US). Analyses will be based on individual patient data when available or on published data. I^2 will be used as a measure of heterogeneity. I^2 values below 30% will be defined as unimportant, 30-50% as moderate heterogeneity, 50-75% as substantial heterogeneity and I^2 values >75% will be defined as considerable heterogeneity. Irrespective of the statistical heterogeneity, both fixed effect and random effects models will be used to test the robustness of the results. We will only report the results of the random effects meta-analyses if the

results differ from the fixed effect models. Publication bias and other small study effects will be evaluated based on regression analysis (Egger's or Harbord's test).

We plan to perform subgroup and meta-regression analyses based on treatment combinations as well as baseline patient characteristics.. Differences between subgroups will be explored using tests for subgroup differences expressed as *p* values. The subgroup analyses will evaluate the influence of the type of data (individual patient data or published data), the control groups (stratified by the type of intervention allocated to the control group), collateral interventions (interventions administered to both allocation groups), We will also perform meta-regression analyses to evaluate the potential influence of glycaemic control at baseline, duration of diabetes, and baseline bodyweight. In sensitivity analyses, we will evaluate the intervention effect in patients who are normal weight (defined as a maximum BMI of 25 kg/m^2 at the time of randomisation), trials published as full paper articles and trials with a low risk of bias.

Measures of treatment effect. Dichotomous data will be analysed using risk differences (RD) and continuous data using mean differences, both with 95% CIs.

Unit of analyses issues. For trials presenting data from more than one treatment period (e.g. 26 and 52 weeks), data from the longest treatment period will be used. Based on the primary outcome measure, only data from the first period of cross-over trials will be used.

Dealing with missing data. Intention-to-treat analyses including all patients randomised will be performed. For patients with missing data, we will perform

sensitivity analyses with simple imputation (counting patients as failures or successes).

ETHICS AND DISSEMINATION

The study will evaluate the clinical effect of SGLT-2i in patients with type 2 diabetes based on the available published and unpublished clinical trial data and thereby potentially improve the clinical knowledge on and management of type 2 diabetes.

CONTRIBUTORS

HS, LLG, MC and TV participated in the conception and design of this protocol including search strategy development. LLG provided statistical advice for the design. HS prepared the draft and all authors reviewed the manuscript and approved the final version.

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