Project Title
The effects of SGLT-2 inhibitors in patients with type 2 diabetes: a systematic review with meta-analysis of randomised trials

Research Proposal

Scientific Abstract:
Background: 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.

Objective, study design and participants: 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.

Main outcomes and statistics: 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.

Brief Project Background and Statement of Project Significance:
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 A1c (HbA1c) 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 pragmatic 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. We believe that this approach will give the evidence-based clinician a clearer and more useful answer.

Specific Aims of the Project:

The primary objective of this systematic review is to evaluate the effects of SGLT-2i that are approved (dapagliflozin and canagliflozin and 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 (HbA1c).

Types of outcome measures

The following outcome measures will be assessed

Primary outcome measure

• HbA1c

Secondary outcome measures

• Body weight and BMI
• Fasting plasma glucose
• Lipid profile (Low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglyceride)
• Systolic and diastolic blood pressure, heart rate
• Liver and kidney blood tests (creatinine, ALAT)
• Urinary albumin
• Adverse events (Any adverse events, serious adverse events, drug related adverse events, adverse events leading to discontinuation, mortality, all cancers, breast cancer, bladder cancer, urinary tract infections, genital tract infections, hypoglycaemia, hypotension, total withdrawals)

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety
Summary-level data meta-analysis
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

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 HbA1c

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.

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 ("surgery" [All Fields]) OR "surgery" [All Fields]) OR ("6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-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'-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 HbA1c, baseline blood tests, fasting plasma glucose, HDL- and LDL-cholesterol, triglyceride, 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].
• Blinding (performance and detection bias).
• Incomplete outcome data (attrition bias).
• Outcome reporting (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. I2 will be used as a measure of heterogeneity. I2 values below 30% will be defined as unimportant, 30-50% as moderate heterogeneity, 50-75% as substantial heterogeneity and I2 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/m2 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).

Narrative Summary:
The study will evaluate the 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.

Project Timeline:
Project start date: October 2013
Completion date: December 2014
Date manuscript drafted: March and April 2015
Date manuscript submitted for publication: April and May 2015
Date results reported back to the YODA project: April and May 2015

Dissemination Plan:
Anticipated products:
Two manuscripts
1. Glycemic control, blood pressure, lipids and adverse events
2. Liver and kidney data

Anticipated audience:
Diabetologists, endocrinologists, general practitioners and policymakers

Suitable journals for submission:
Manuscript 1; JAMA or BMJ-Open
Manuscript 2; BMJ-Open or Diabetes Care

Bibliography:

Supplementary Material: bmj_open-2014-storgaard-.pdf
Associated Trial(s):  
NCT00642278 - A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally Administered SGLT2 Inhibitor
NCT01106625 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control
NCT01064414 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled
NCT01081834 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled
NCT01106677 - A Randomized, Double-Blind, Placebo and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control
NCT00968812 - A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimpiride in the Treatment of Subjects With Type 2 Diabetes Mellitus
NCT01106651 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled
NCT01106690 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control
NCT01137812 - A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control

What type of data are you looking for?: Full CSR

General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

Conflict of Interest

COI Upload: [denmark_team_coi.pdf]

Certification

Certification: Yes
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training