DiEtary Sodium Intake effects on ertugliflozin-induced changes in GFR, reNal oxygenation and systemic hemodynamics: the DESIGN study, a randomized, placebo-controlled, cross-over study with ertugliflozin in people with type 2 diabetes

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This study has been transitioned to CTIS with ID 2023-510257-42-01 check the CTIS register for the current data. Sodium-glucose cotransporter 2 (SGLT2) inhibitors lead to a lowering of blood pressure and confer cardiovascular and renal protection in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON53765

Source
ToetsingOnline

Brief title
DESIGN

Condition

- Diabetic complications
- Nephropathies
- Vascular hypertensive disorders

Synonym
Type 2 Diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Merck,MSD (NB VUMC is verrichter;want het gaat om een investigator-initiated study)

Intervention

Keyword: Diabetic kidney disease, Hemodynamics, SGLT2-inhibition, Sodium intake

Outcome measures

Primary outcome

To investigate the modifying effects of WHO-recommended sodium intake (90 mmol per day) vs. high sodium intake (targeted at 250 mmol per day) on the effect of ertugliflozin 15 mg daily, versus placebo, on 24-hour blood pressure in overweight/obese adults with type 2 diabetes.

Secondary outcome

To investigate the efficacy of ertugliflozin 15 mg daily, versus placebo, in overweight/obese adults with type 2 diabetes to reduce the hypertensive effects of a high-sodium diet (250 mmol per day) versus 24-hour blood pressure measurement during participant*s normal diet (170 mmol/per day) obtained at screening visit.

Study description

Background summary

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) and dialysis in the developed world, and a major cause of premature mortality. Sodium-glucose cotransporter 2 (SGLT2) inhibitors lead to a lowering of blood pressure and confer cardiovascular and renal protection in many, but not all people with type 2 diabetes (T2D). The mechanisms of these salutary cardiorenal benefits remain unclear, and are incompletely explained by the modest improvements in glycemic control, body weight, and serum uric acid (2). An important hypothesis by which SGLT2 inhibitors could improve cardiorenal outcomes is renal sodium handling. Therefore, the efficacy of the drug may be mediated by sodium intake of the patient/participant. A better understanding of the mechanism of cardio-renal protection in response to SGLT2 inhibition is therefore needed to determine which patients would see the greatest benefit from this drug class and also how to augment the beneficial effects with complimentary drugs and/or lifestyle changes such as changes in dietary sodium intake.

Study objective

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors lead to a lowering of blood pressure and confer cardiovascular and renal protection in many, but not all people with type 2 diabetes (T2D), possibly due to a difference in sodium intake. with this mechanistic study we will have the ability to increase our understanding of the interaction between SGLT2-inhibitors and sodium intake and maximize the treatment response. In addition, we will be able to investigate if differences in dietary habits might contribute to the differences in the cardiovascular en renal protective function of SGLT2 inhibitors observed among different ethnicities.

Study design

The study is a bi-center randomized, placebo-controlled, crossover intervention study. Total number of included participants is 34, which undergo 4 conditions in randomized order. Rrandomization list generated by computer and supervised by pharmacy; blinded to investigator. While the treatment will be blinded for all participants, the sodium interventions are open-label.

The 4 conditions are:
1) low-sodium diet; placebo
2) low-sodium diet; ertugliflozin 15 once daily
3) high-sodium diet; placebo
4) high-sodium diet; ertugliflozin 15 mg once daily

A 24-hr blood pressure measurement as well 24-hr sodium excretion is measured

prior to the dietary blocks. Than, for each condition there is a 10-day diet run in period, followed by a 10-day intervention period, followed by the test visit. Between conditions there is a 4-week wash out.

Intervention

The interventions of the study consist of a low-sodium diet versus a high sodium diet and a placebo versus ertugliflozin 15 once daily

Study burden and risks

Risks
All participants within the study group will receive ertugliflozin, an SGLT-2 inhibitor which is approved for the for blood-glucose lowering treatment in T2DM patients and based on currently available data is considered to be safe. The most common adverse effects for ertugliflozin are genital mycotic- and urinary tract infections, pruritus, polyuria, frequent voiding and nycturia. As in all drug intervention trials, in this study, we will closely monitor patients for adverse drug and study events.. Participants can contact the research staff 24 hours a day. As for the testing agents, at our research centre at Amsterdam UMC we have done > 500 iohexol and PAH clearances in the last 5 years and not encountered a single problem.

Benefits
Moreover, SGLT-2 inhibitors may have beneficial effects in general and are associated with a decrease in blood pressure and body weight, as well as a reduction in kidney function decline and hospitalisation forhesrt failure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Adults with previously diagnosed T2DM according to American Diabetes Association (ADA) criteria
• HbA1c 6.5-10%
• Age 18 - 85 years of age
• Overweight or obese with BMI: >25 kg/m2
• We will make every effort to enrol participants of all races/ethnicities.*
• Both sexes (females must be post-menopausal; no menses >1 year; in case of doubt, Follicle-Stimulating Hormone (FSH) will be determined with cut-off defined as >31 U/L)
• Ability to provide signed and dated, written informed consent prior to any study procedures
• Estimated GFR 60-90 ml/min/1.73m2 by CKD-EPI matching the eGFR range of most participants in VERTIS-CV
• Sodium intake at baseline < 200 mmol/day
• UACR < 30 mg/mmol
• All participants need to be on a stable dose of diabetes medication, including Metformin, SU, DPP4-inhibitors, or insulin.
• Participants suffering from hypertension need to be on a stable dose of RAS inhibitors. In case RAS inhibition is not tolerated, the participant should to be on a stable dose of other antihypertensive treatment.

Exclusion criteria

• History of unstable or rapidly progressing renal disease
• Estimated GFR <60 mL/min/1.73m2 or eGFR > 90 mL/min/1.73m2 determined by

CKD-EPI
• UACR > 30 mg/mmol
• Current/chronic use of the following medication: SGLT2 inhibitors, TZD, GLP-1RA, glucocorticoids, immune suppressants, antimicrobial agents, chemotherapeutics Participants should be on a stable dose of antipsychotics, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Subjects on diuretics will only be excluded when these drugs cannot be stopped for the duration of the study.
• Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) will not be allowed, unless used as incidental medication (1-2 tablets) for non-chronic indications (i.e. sports injury, headache or back ache). However, no such drug can be taken within a timeframe of 2 weeks prior to renal testing
• History of diabetic ketoacidosis (DKA) requiring medical intervention (e.g. emergency room visit and/or hospitalization) within 1 month prior to the Screening visit.
• Current urinary tract infection and active nephritis
• Recent (<6 months) history of cardiovascular disease, including:
o Acute coronary syndrome
o Chronic heart failure (New York Heart Association grade II-IV)
o Stroke or transient ischemic neurologic disorder
• Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3x ULN
• Active malignancy. History of malignancy is allowed unless the participant still has active treatment other than hormonal therapy.
• History of or actual severe mental disease
• Substance abuse (alcohol: defined as >4 units/day)
• Allergy to any of the agents used in the study
• Individuals who are investigator site personnel, directly affiliated with the study, or are immediate (spouse, parent, child, or sibling, whether biological or legally adopted) family of investigator site personnel directly affiliated with the study
• Inability to understand the study protocol or give informed consent

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-07-2023
Enrollment:	22
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Ertugliflozin
Generic name:	Steglatro
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-06-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-510257-42-01
EudraCT	EUCTR2021-005474-25-NL
CCMO	NL80772.029.22