A phase 4, monocenter, randomized, double-blind, placebo-controlled, 4-armed cross-over mechanistic intervention study to assess the renal hemodynamic effect of mono- and combination therapy with empagliflozin (SGLT-2 inhibitor) and losartan (RAS inhibitor) in metformin and/or SU-treated patients with type 2 diabetes mellitus

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Investigate the effects of 7 (+-1) days of of mono- and combination therapy with the SGLT2 inhibitor empagliflozin (10 mg QD) and RAS inhibitor losartan (50 mg QD) on renal hemodynamics, (glomerular filtration rate (GFR) / effective renal plasma…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON49031

Source
ToetsingOnline

Brief title
RECOLAR: Renohemodynamic Effects of Combined empagliflOzin and LosARtan

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Nephropathies
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
adult-onset diabetes, Type 2 Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Boehringer Ingelheim,industrie

Intervention

Keyword: Diabetes, RAAS inhibition, Renoprotection, SGLT-2 inhibition

Outcome measures

Primary outcome

Renal hemodynamics (defined as GFR and effective renal plasma flow; ERPF),

measured by combined iohexol/para-aminohippurate acid; PAH) clearance

techniques, based on timed urine sampling (Day 7+-1)

Secondary outcome

* Estimated intra-renal hemodynamic functions (i.e. glomerular hydrostatic

pressure and afferent / efferent arteriolar resistance), which will be assessed

by the Gomez formulae

* Renal damage markers, measured as:

o 24-hour urinary albumin excretion (glomerular)

o Albumin-creatinine ratio (glomerular)

* Renal tubular function, measured as:

o Fractional and cumulative (24-hour urine collection) sodium and glucose excretion

* GFR trajectory, measured by:

o Creatinine clearance (24-hour urine collection)

* Systemic hemodynamics, measured by:

o Week 0, 1, 5, 10, 15, 16: SBP, DBP, MAP and heart rate, measured by automated oscillometric blood pressure monitor (Dinamap®)

o Week 0, 1, 5, 10, 15, 16: SBP, DBP, MAP, heart rate (HR), stroke volume (SV), cardiac output (CO)/-index (CI), and total systemic vascular resistance (TSVR)) derived from non-invasive beat-to-beat finger blood pressure measurements (Finger photoplethysmography, Nexfin®)

* Autonomic nervous system activity (Week 0, 8, 16), measured by:

o Heart rate variability derived from automated, beat-to-beat finger blood pressure and ECG recording monitor (Finger photoplethysmography, Nexfin®)

* Vascular function (Week 0, 8, 16), measured as:

o Arterial stiffness (Pulse Wave Analysis), measured by radial artery applanation tonometry (SphygmoCor®)

* Metabolic biomarkers

o Fasting glucose, lipid profile, insulin, glucagon. HbA1c at V1 only.

* Body anthropometrics

o Height, weight, BMI and waist/hip circumference

o Body fat content, total body water (TBW) and body cell mass (BCM) measured by body impedance analysis (BIA) (Soft Tissue Analyzer®)

Study description

Background summary

Diabetic kidney disease (DKD), characterized by reduced whole-kidney glomerular filtration rate (GFR) and/or urinary protein leakage, is a feared complication of type 2 diabetes (T2D). With severe consequences such as endstage kidney disease (ESKD) and renal death, and strongly linked to cardiovascular (CV) morbidity and mortality, optimal treatment of DKD is vital. Still, even with multifactorial treatment of renal risk factors, including hyperglycemia, hypertension, obesity, dyslipidemia and albuminuria, residual risk remains high worldwide. Since the introduction of blockers of the renin-angiotensin-aldosteron system (RAS), no other renoprotective drug for T2D has been successfully developed, highlighting the need for novel strategies or new therapeutic drugs to improve renal outcome in T2DM.
In this regard, the introduction of the sodium glucose cotransporter (SGLT)2 inhibitors has been met with great enthusiasm. Designed to inhibit glucose reabsorption in the proximal tubule they induce glycosuria which indeed reduces hyperglycemia. More importantly, these drugs have shown remarkable benefits on CV disease and renal outcome in large CV safety trials in T2D patients with high risk of or established atherosclerotic cardiovascular disease (CVD) as well as in patients with DKD. The first of these trials, the EMPAgliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients* Removing Excess Glucose (EMPA-REG OUTCOME), was reported in 2015 and demonstrated, next to risk reductions in CV outcomes, impressive reductions in the prespecified secondary renal outcome (1). In two subsequently reported CV safety trials conducted with canagliflozin (CANVAS-Program) and dapagliflozin (DECLARE-TIMI 58), these promising results indicating renal benefit were further strengthened (2,3). Recently, the results of a dedicated placebo-controlled trial with canagliflozin (CREDENCE) in DKD patients were reported (4). The study was terminated early due to overwhelming beneficial effects. Yet, at this point in time, the renoprotective mechanisms involved with SGLT2 inhibition still remain speculative, though a consistent finding is that SGLT2 inhibitors reduce estimated GFR after first dosing, which is reversible after treatment cessation. This *dip* indicates a renal hemodynamic phenomenon reminiscent of the RAS blockers and is thought to reflect a reduction in intraglomerular pressure (5). From studies in rodent models of type 1 diabetes and humans with type 1 diabetes it is hypothesized that SGLT2 inhibition leads to urinary sodium excretion by inhibiting in the proximal tubule, which influences renal hemodynamics through a mechanism known as tubuloglomerular feedback. In short, reduced sodium reabsorption at the level of the proximal tubule leads to increased sodium chloride delivery at the downstream located macula densa, which in turn increases afferent arteriolar resistance and reduces glomerular (hyper)filtration and hydrostatic pressure (5). In a recent trial at our department RED (NCT02682563) we investigated

whether this is also true in T2D. To our surprise, this study showed that the renohemodynamic actions of SGLT2 inhibition in T2D are not due to afferent vasoconstriction but rather efferent vasodilation. This is also the proposed working mechanism of inhibitors of the RAS system in T2D, although dedicated studies in humans are scarcely done. Indeed, people with T2D that do not respond to RAS blockers in terms of albuminuria reduction, also do not respond to SGLT2 inhibitor treatment (6).
In our opinion, we are left with several questions regarding the combination of SGLT2 and RAS inhibitors. Especially with the recent results of CREDENCE, it is very likely that the combination of these agents will become standard of care in patients with T2D and DKD. Both agents dilate the postglomerular arteriole, which might lead to relevant interactions or even synergistic effects. Since the majority of the population in the cardiovascular outcome trials used RAS inhibition, we know the renoprotective effect of SGLT2 inhibition is present with concurrent RAS inhibition. However, to what extend these agents interact and which of the various complex pathways involved in blood pressure and plasma volume control are affected by mono or combination therapy with these agents is unknown. It is important to emphasize that in the large trials, RAS blockade was not randomized and that the participants not on RAS blockade were small in numbers, making additional analyses on this topic difficult.
In conclusion: Despite multifactorial treatment approaches, residual risk for the development and progression of DKD remains high, and novel therapies or strategies to halt renal burden in T2DM are urgently needed. SGLT2 inhibitors and RAS inhibitors both induce glucose-independent renoprotective effects and improve renal outcome, seemingly via an at least partly equal mechanism, the dilation of the efferent glomerular arteriole resulting in an eGFR dip. The use of combination therapy with these agents could lead to an additive or even synergistic renoprotective effect in T2DM. As such, combined use of an SGLT2 inhibitor and RAS inhibitor may enhance individual benefits (e.g. reduction of glomerular pressure, activation of tubuloglomerular feedback, proximal and distal natriuresis, plasma volume contraction and reduction of blood pressure).

Study objective

Investigate the effects of 7 (+-1) days of of mono- and combination therapy with the SGLT2 inhibitor empagliflozin (10 mg QD) and RAS inhibitor losartan (50 mg QD) on renal hemodynamics, (glomerular filtration rate (GFR) / effective renal plasma flow (ERPF)) in metformin and/or SU-treated T2DM patients.

Study design

A single-center, prospective, placebo-controlled, double-blind, randomized, 4-arm cross-over mechanistic intervention study in 24 metformin and/or SU-treated patients with T2DM.

Intervention

24 T2DM patients will be randomized 1:1:1:1 to receive either empagliflozin and losartan, or empagliflozin and placebo, or losartan and placebo, or placebo and placebo.

Study burden and risks

Participants will be randomized for a four times 7 (+-1) days treatment with two different active study agents. Consequently, independent of treatment allocation, beneficial effects can be expected, as SGLT-2 inhibitors improve glycemic control and RAS inhibitors lower blood pressure. All study medications have been approved for blood-glucose lowering or hypertension treatment in T2DM and hypertensive patients and, based on currently available data, are considered to be safe. Furthermore, SGLT-2 inhibitors in general may also decrease blood pressure and body weight. It is important to stress that the patients have suboptimal glycemic control and an indication to receive additional glucose lowering medication.
The most common adverse effects for empagliflozin are genital mycotic- and urinary tract infections, pruritus, polyuria, frequent voiding and nycturia. When used in combination with a SU derivative or insulin (which is not the case in our study) hypoglycemia can occur. In addition, a slight empagliflozin-induced increase in LDL-cholesterol and increased hematocrit have been reported. Long-term (adverse) effects of SGLT-2 inhibitors are currently under investigation in large-scaled outcome trials, however the SGLT2-inhibitior empagliflozin has shown to reduce mortality and heart and renal failure in the EMPA-REG OUTCOME Trial (Bernard Zinman et al., 2015) (B. Zinman et al., 2015) and the SGLT2-inhibitior canagliflozin showed similar results in the more recent CANVAS trial (Neal et al., 2017).

With regard to the used testagents, the Infusion of Iohexol can lead to a warm, sometimes painful sensation. Most common but rare adverse effects are headache, stiffness, nerve pain, nausea, vomiting, fever, hives, stomach pain, hallucinations and neurological changes. In patients with an allergy for iodide it can elicit hypersensitive reactions, therefore we specifically check a for this allergy at screening.

As in all drug intervention trials, in this study, we will closely monitor patients for adverse drug and study events during the follow-up visit and by telephone consultation according to GCP (see Appendix A). Participants can contact the research staff 24 hours a day.

Possible benefits for participants
Participants are extensively tested and monitored, and receive high-quality care with many contact moments without any costs. In addition, this study is ideal to futher detail the effects of mono- and combination therapy with the SGLT-2 inhibor empagliflozin and RAS inhibitor losartan on renal hemodynamics. The patient has the opportunity to gain experience with these agents at no cost and might benefit from it later (when intensification of therapy is necessary).

In addition, former studies have shown that the use of SGLT2-inhibitors has a beneficial effect on stabilization of GFR and the lowering of blood pressure and weight.

Possible inconvenience for participants
Over the last 10 years, we have gained ample experience with similarly demanding mechanistic drug intervention studies in T2DM patients on renal hemodynamics (SAFEGUARD 2012.391, RENALIS 2013.459, ELIXIRS 2014.275, RED 2015.421, RACELINES 2017.336). Based on the positive feedback from our participants, the low drop-out rate (max 5%) and the large proportion of participants that returns to participate in yet another (similarly demanding) study, we are confident that the burden on participants is perceived as not being too high. Indeed, we have built in different ways to alleviate the burden for participants, including clear, repeated communication, frequent contacting, intensified (diabetes) care, 24-hour availability of research staff, study and travel reimbursement, enabling participants to receive the newest study medication (that for most of them would not be reimbursed in daily practice) and offering follow-up care in our out-patient clinic. Finally, it should be noted that several tests are similar to currently or previously performed in patient care for diagnostic purposes (e.g. iohexol/PAH-clearance).
We are aware of the fact that in the current study participants will undergo multiple tests that demand a considerable time investment from their end. The total duration of visits is 2 hours (V1) and 16 hours (visit 2, 3, 4, 5). These renal / cardiovascular test-days may be perceived as demanding that amongst others involves frequent blood and urine collection, infusions, blood pressure and heart rate. As mentioned above, all possible measures will be taken to minimize the discomfort for the participants during the tests (e.g. comfortable beds are available which allow a semi-recumbent position).

Safety issues
The study examinations/tests are considered to be safe. No invasive procedures (besides intravenous peripheral catheters) are involved. During the study tests, two *diagnostic agents* (i.e. iohexol and PAH) need to be administered; both agents are inert and have no side effects.

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

* Caucasian, Asian or Middle Eastern (sub-Saharan patients are not eligible);
* Both genders (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)
* Age: 45 - 80 years
* BMI: >25 kg/m2
* HbA1c: 6.5 * 10.5% Diabetes Control and Complications Trial (DCCT) or 48 - 91 mmol/mol International Federation of Clinical Chemistry (IFCC)
* Treatment with a stable dose of metformin and/or SU therapy for at least 3 months prior to inclusion
* Written informed consent

Exclusion criteria

* History of unstable or rapidly progressing renal disease
* Macroalbuminuria; defined as ACR of 300mg/g.
* Estimated GFR <60 mL/min/1.73m2 (determined by the Modification of Diet in Renal Disease (CKD-EPI) study equation)
* Only use of alpha blockers and/or beta blockers are allowed as antihypertensive background therapy. Patients using an antihypertensive agent will be considered if this agent can be stopped (i.e. blood pressure adequate

to stop at screening) or replaced by an alpha or beta blocker. In these patients, a 4 week wash-out/run-in period will be observed prior to visit 2.
* Current/chronic use of the following medication: SGLT2 inhibitors, RAS inhibitors, TZD, GLP-1RA, DPP-4 inhibitors, glucocorticoids, immune suppressants, antimicrobial agents, chemotherapeutics, 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.
* Volume depleted patients. Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status.
* 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, head-ache or back ache). However, no such drug can be taken within a time-frame 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
* Complaints compatible with neurogenic bladder and/or incomplete bladder emptying (as determined by ultrasonic bladder scan)
* 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
* (Unstable) thyroid disease; defined as fT4 outside of laboratory reference values or change in treatment within 3 months prior to screening visit
* History of or actual malignancy (except basal cell carcinoma)
* 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
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-11-2020
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Empagliflozin
Generic name:	Jardiance
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Losartan
Generic name:	Cozaar
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2020

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2021
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
EudraCT	EUCTR2019-003141-15-NL
ClinicalTrials.gov	NCT04238702
CCMO	NL71049.029.19