A phase 4, monocenter, randomized, double-blind, comparator-controlled, 3-armed parallel mechanistic intervention trial to assess the effect of 8-week empagliflozin (SGLT-2 inhibitor) monotherapy, followed by 8-week empagliflozin and linagliptin (DPP-4 inhibitor) combination therapy versus 8-week linagliptin monotherapy, followed by 8-week linagliptin and empagliflozin combination therapy versus 8-week gliclazide (Sulfonylurea derivate), followed by 8-week gliclazide intensification therapy on r

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To examine the effects of mono- and combination therapy with linagliptin and empagliflozine on renal hemodynamics

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

Summary

ID

NL-OMON48622

Source
ToetsingOnline

Brief title
Renal Actions of Combined Empagliflozin and LINagliptin in type 2 diabetES

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, DPP4, Renoprotection, SGLT2

Outcome measures

Primary outcome

To determine the effects of 8-week empagliflozin (SGLT-2 inhibitor) monotherapy (10 mg QD), followed by 8-week empagliflozin and linagliptin (DPP-4 inhibitor) combination therapy (10/5 mg QD) versus 8-week linagliptin monotherapy (5 mg QD), followed by 8-week linagliptin and empagliflozin combination therapy (5/10 mg QD) versus 8-week gliclazide (Sulfonylurea) monotherapy (30 mg QD), followed by 8-week gliclazide intensification (30 mg BID) on renal hemodynamics in both the fasting and postprandial state in metformin-treated T2DM patients, measured as:

* GFR (measured by the iohexol-clearance technique)

* Effective renal plasma flow (ERPF; measured by the para-aminohippurate acid (PAH) clearance technique)

Secondary outcome

To investigate the effects of the above-indicated interventions on:

* Renal damage markers (Week 0, 2, 8, 10, 16):

o 24-hour urinary albumin excretion (glomerular)

o Albumin-creatinine ratio (glomerular)

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

o Fractional and cumulative (24-hour urine collection) sodium-, potassium-, chloride-, calcium-, magnesium-, phosphate-, uric acid, bicarbonate-, ammonium- and urea excretion

o Urinary glucose excretion

o Urine osmolality

o Urinary pH

* GFR trajectory (Week 0, 2, 8, 10, 16), measured by:

o Creatinine clearance (24-hour urine collection)

* Systemic hemodynamics, measured by:

o Week 0, 2, 8, 10, 16: SBP, DBP, MAP and heart rate, measured by automated oscillometric blood pressure monitor (Dinamap®)

o Week 0, 8, 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 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 Glycated hemoglobin (HbA1c), and fasting and postprandial glucose, lipids (triglycerides (TG), total-cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and free fatty acids (FFA)), insulin, glucagon.

* 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®)

Exploratory Objectives

(The extent of these complementary measurements is conditional to feasibility and available budget)

To investigate the effects of the above-indicated interventions on:

* Complementary markers of renal function / damage (NGAL, KIM-1, plasma

cystatin C, fibroblast growth factor -23 (FGF-23), parathyroid hormone (PTH), soluble Klotho, urinary transforming growth factor-*1 (TGF-*1), collagen type IV, nephrin, podocin, urinary microparticles, 8-hydroxy-2' -deoxyguanosine (8-OHdG), Calcitriol, Monocyte Chemoattractant Protein-1 (MCP-1), tumor necrosis factor alpha (TNF-*))

* (Cardiovascular)-biomarkers (N-terminal pro-B-Type Natriuretic Peptide (NT-proBNP), Brain Natriuretic Peptide (BNP), Atrial Natriuretic Peptide (ANP), plasma renin activity (PRA), angiotensin II, angiotensin 1-7, aldosterone, urinary angiotensinogen, endothelin, catecholamines, soluble receptor for advanced glycation end products (sRAGE), zonulin, fructosamine, uric acid, ketone bodies, FGF-21, isoprostanes, urinary adenosine, plasma co-peptin, urinary cortisol, urinary dopamine

* Additional markers of inflammation (hsCRP, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1))

* Deoxyribonucleic acid (DNA) (to study the influence of genetic factors on the parameters measured and the response to DPP-4 inhibitor and / or SGLT-2 inhibitor) This will only be performed after specific and separate consent by the participant.

* DDP-4 substrates (GLP-1, GIP, substance-P, Neuropeptide Y (NPY), Stromal cell-derived factor 1 (SDF-1*), erythropoietin) and DPP-4 activity.

* 24h ambulatory blood pressure monitor (not mandatory, assed only when feasible (i.e. extra visit to pick up monitor; distance to CRU and willingness participant. Office blood pressure will also be measured after 1 hour rest in semi-recumbent position)

* Gut microbiome composition from fecal samples

* Insulin sensitivity (M-value) as derived from the glucose infusion rate

during the euglycemic clamp

* Insulin sensitivity (OGIS, Matsuda index) as derived from the meal tolerance

test

* Beta-cell function measures as derived from HOMA-B, insulinogenic index and

ratio of postprandial glucose and C-peptide area under the curve

Safety Objectives

* To evaluate the safety and tolerability of empagliflozin, linagliptin and

their combination, compared to gliclazide, in the target patient population

(Hb, Ht, erythrocytes, leucocytes, thrombocytes, sodium, potassium, AST, GGT,

creatinine and urine screening).

Study description

Background summary

Worldwide, diabetic nephropathy or diabetic kidney disease (DKD), is the most common cause of chronic and end stage kidney disease. With the increasing rates of obesity and type 2 diabetes (T2DM), many more patients with DKD may be expected in the coming years. DKD is a multi-factorial condition, involving factors such as obesity, chronic hyperglycemia, advanced glycation end products, oxidative stress, pro-inflammatory cytokines, systemic- and glomerular hypertension. Large-sized prospective randomized clinical trials suggest that intensified glucose and blood pressure control, the latter especially by using agents that interfere with the renin-angiotensin-aldosterone system (RAAS), may halt the progression of DKD, both in type 1 diabetes and T2DM. However, despite the wide use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, a

considerable amount of patients develop DKD during the course of diabetes, indicating an unmet need for renoprotective therapies. Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose linked transporters (SGLT-2) inhibitors are novel glucose-lowering drugs for the treatment of T2DM. These agents seem to exert pleiotropic actions *beyond glucose control*. SGLT-2 inhibitors decrease proximal sodium reabsorption and decrease glomerular pressure and albuminuria in rodents and type 1 diabetes patients. In addition, SGLT-2 inhibitors reduce blood pressure, urine acid and body weight. In rodents, SGLT-2 inhibitors also improved histopathological abnormalities associated with DKD. DPP-4 inhibitors are considered weight neutral, improve lipid profiles and slight reductions in blood pressure have been reported. To date, the potential renoprotective effects and mechanisms of these agents have not been sufficiently detailed in human type 2 diabetes. The current study aims to explore the clinical effects and mechanistics of mono- and combination therapy with SGLT-2 inhibitors and the DPP-4 inhibitors on renal physiology and biomarkers in metformin-treated T2DM patients with normal kidney function.

Hypothesis: Mono- and combination therapy with SGLT-2 inhibitor empagliflozin and DPP-4 inhibitor linagliptin, as compared to sulfonylurea (SU) derivate gliclazide may confer renoprotection by improving renal hemodynamics.

Study objective

To examine the effects of mono- and combination therapy with linagliptin and empagliflozine on renal hemodynamics

Study design

A phase 4, monocenter, randomized, double-blind, comparator-controlled, 3-armed parallel mechanistic intervention trial to assess the effect of 8-week empagliflozin (SGLT-2 inhibitor) monotherapy, followed by 8-week empagliflozin and linagliptin (DPP-4 inhibitor) combination therapy versus 8-week linagliptin monotherapy, followed by 8-week linagliptin and empagliflozin combination therapy versus 8-week gliclazide (Sulfonylurea), followed by 8-week gliclazide intensification therapy on renal physiology and biomarkers in metformin-treated patients with type 2 diabetes mellitus

Intervention

8-weeks of empagliflozin 10 mg QD monotherapy, followed by 8-weeks of empagliflozin and linagliptin 10/5 mg QD combintation therapy versus 8-weeks of linagliptin 5 mg QD monotherapy, followed by 8-weeks of linagliptin and empagliflozin 5/10 mg QD combination therapy versus 8-weeks of gliclazide 30 mg QD treatment, followed by 8-weeks of gliclazide 30 mg BID

Study burden and risks

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 1-2 hours (screening- and control visit) and 21 hours (visit 2, 3, 4, 5, 6) or 32 hours (visits 2, 2c, 3, 4, 4c, 5, 6). The total amount of drawn blood will be 602 mL (subgroup surplus 196 mL, subgroup total 798 mL) during a total period of 22 weeks. Visit 2 & Visit 2c and Visit 4 & 4c are scheduled in one week, which makes the maximum amount of blood drawn in one week 277 mL. The total amount of blood loss is approximately similar to the volume drawn with regular blood donations, which amounts 500 mL per donation and is allowed every 2.5 months for men and every 4 months for women. Female participants within the subgroup will lose a maximum of 787 mL in 16 weeks (~50 mL/week), similar to 2 blood donations in 5 months (~50 mL/week). Participants with a history of recent blood donation (< 6 months) are excluded from this study. In addition, the renal/cardiovascular test-days may be perceived as demanding: in particular, the combined renal/cardiovascular physiology test, that amongst others involves frequent blood and urine collection, infusions, blood pressure, heart rate and microvascular measurements. During the cardiac autonomous nervous system function tests participants may experience transient dizziness or lightheadedness.
However, we have gained ample experience with similarly demanding mechanistic drug intervention studies in T2DM patients. 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 and offering follow-up care in our out-patient clinic.
The study examinations/tests are considered to be safe. No invasive procedures (besides intravenous peripheral catheters) are involved. During the study tests, one *diagnostic agent* (i.e. iohexol and PAH) need to be administered; these agent are inert and have no side effects.
All study medications (empagliflozin, linagliptin and gliclazide) have been approved (FDA, EMA) for blood-glucose lowering treatment in T2DM patients and, based on currently available data, are considered to be safe. 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 empagliflozin has shown to reduce mortality and heart and renal failure in the EMPA-REG OUTCOME Trial (12). For linagliptin, nasopharyngitis and a cough are the most common adverse effects. The adverse effects of both these drugs are usually mild and transient. For gliclazide, hypoglycemia and blurred vision in the initiation

phase of treatment (due to changes in blood glucose levels) are the most common adverse effects. Also, albeit incidental, gastrointestinal adverse-effects (nausea, vomiting, diarrhea or constipation) have been reported. Of note, to compensate for the dose of gliclazide that will be used in this study (i.e. 30-60 mg per day) for a relatively short treatment duration (16 weeks), inclusion criteria for HbA1C will be at 7.0-9.5%. Therefore, also given the other inclusion- and exclusion criteria of the study participants, the overall risk of hypoglycemia is believed to be low to moderate.
Patients will be provided with a self-monitoring blood glucose (SMBG) device and instructed to perform ambulatory blood glucose checks in case of symptoms, during the course of the study. Also, they will receive standardized diabetes education, including information regarding carbohydrate use and self-management / resolution of hypoglycemia. 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. As in all drug intervention trials, in this study, we will closely monitor patients for adverse drug and study events

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Main study
* Caucasian*
* 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: 35 - 75 years
* BMI: >25 kg/m2
* HbA1c: 7.0 * 9.5% Diabetes Control and Complications Trial (DCCT) or 53 - 80 mmol/mol International Federation of Clinical Chemistry (IFCC)
* Treatment with a stable dose of metformin monotherapy for at least 3 months prior to inclusion
* Hypertension should be controlled, i.e. *140/90 mmHg, and treated with an ACE-I or ARB (unless prevented by side effect) for at least 3 months.
* Albuminuria should be treated with a RAAS-interfering agent (ACE-I or ARB) for at least 3 months.
* Written informed consent, * In order to increase homogeneity

Sub study
* Treatment with a stable dose of oral antihyperglycemic agents for at least 3 months prior to inclusion
* Metformin monotherapy
* Combination of metformin and low-dose SU derivative

Exclusion criteria

Main study:
* Estimated GFR <45 mL/min/1.73m2 (determined by the Modification of Diet in Renal Disease (MDRD) study equation)
* Hemoglobin level < 7.0 mmol/L
* Current urinary tract infection and/or active nephritis
* History of unstable or rapidly progressing renal disease
* Macroalbuminuria; defined as ACR of >300 mg/g.
* Current/chronic use of the following medication: thiazolidinediones, sulfonylurea derivatives, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitor, oral glucocorticoids, immune suppressants, antimicrobial agents, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs) and

monoamine oxidase inhibitors (MOAIs).
* Patients on diuretics will only be excluded when these drugs cannot be stopped 3 months prior randomization and 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, head-ache or back ache). However, no such drugs can be taken within a time-frame of 2 weeks prior to renal-testing
* Pregnancy
* History of or actual severe mental disease
* History of or actual severe somatic disease (e.g. systemic disease)
* History of or actual malignancy (except basal cell carcinoma)
* History of or actual pancreatic disease
* (Unstable) thyroid disease
* Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3x upper limit of normal (ULN)
* Recent (<6 months) history of cardiovascular disease, including
o Acute coronary syndrome
o Stroke or transient ischemic neurologic disorder or chronic heart failure (NYHA grade II-IV)
* Complaints compatible with or established neurogenic bladder and/or incomplete bladder emptying (as determined by ultrasonic bladder scan)
* Substance abuse (alcohol: defined as >3 units alcohol/day)
* History of diabetic ketoacidosis (DKA) requiring medical intervention (e.g., emergency room visit and/or hospitalization) within 1 month prior to the Screening visit.
* Recent blood donation (< 6 months)
* Allergy to any of the agents used in the study
* Inability to understand the protocol and/or give informed consent
* 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

Sub study:
Exclusion criteria
* History of gout
* Current/chronic use of the following medication: diuretics, SGLT-2 inhibitor, uric acid lowering medication, pyranizamide, vitamin K antagonists, salicylates, thiazide diuretics.
* Estimated GFR <60 mL/min/1.73m2 (determined by the Modification of Diet in Renal Disease (MDRD) study equation)
* Current urinary tract infection and active nephritis
* Recent (<6 months) kidney stones
* History of unstable or rapidly progressing renal disease
* Macroalbuminuria; defined as ACR of >300 mg/g.
* 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 drugs can be taken within a time-frame of 2 weeks prior to renal-testing
* Pregnancy
* History of or actual malignancy (except basal cell carcinoma)
* (Unstable) thyroid disease
* Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3x upper limit of normal (ULN)
* Recent (<6 months) history of cardiovascular disease, including
o Acute coronary syndrome
o Stroke or transient ischemic neurologic disorder or chronic heart failure (NYHA grade II-IV)
* History of diabetic ketoacidosis (DKA) requiring medical intervention (e.g., emergency room visit and/or hospitalization) within 1 month prior to the Screening visit.
* Allergy to any of the agents used in the study
* Inability to understand the protocol and/or give informed consent
* 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
*

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2017
Enrollment:	66

Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Benzbromaron
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Diamicron MR
Generic name:	Gliclazide MR
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Jardiance
Generic name:	Empagliflozine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Trajenta
Generic name:	Linagliptine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-11-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2020
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	EUCTR2017-001547-12-NL
CCMO	NL61691.029.17
Other	U1111-1195-3269