A phase 4, monocenter, randomized, double-blind, comparator-controlled, parallel-group, mechanistic intervention trial to assess the effect of 12-week treatment with the sodium-glucose linked transporters (SGLT)-2 inhibitor dapagliflozin versus the sulfonylurea (SU) derivative gliclazide on renal physiology and biomarkers in metformin-treated patients with type 2 diabetes mellitus (T2DM)

Published: 10-11-2015
Last updated: 19-04-2024

To gain more knowledge about the effects of SGLT2 inhibition on renal hemodynamics and the underlying mechanisms.

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

Summary

ID

NL-OMON47241

Source
ToetsingOnline

Brief title
RED: Renoprotective Effects of Dapagliflozin in Type 2 Diabetes

Condition

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

Synonym
adult-onset diabetes, Diabetes Mellitus Type 2

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Astra Zeneca,AstraZeneca

Intervention

Keyword: Dapagliflozin, Diabetes, Kidney, SGLT2

Outcome measures

Primary outcome

Primary objective: what are the long-term effects (i.e. after 12-week drug exposure) of the SGLT-2 inhibitor dapagliflozin versus the SU gliclazide on renal hemodynamics (glomerular filtration rate (GFR)/ effective renal plasma flow (ERPF)) in metformin-treated T2DM patients?

Secondary outcome

Secondary objectives: renal tubular function, renal damage markers, blood pressure, heart rate, body anthropometrics, body fat, markers of inflammation, glycemic variables, lipid spectrum, microvascular function, arterial stiffness, systemic hemodynamics, cardiac autonomic nervous system function.

Exploratory objectives: additional markers of renal function/damage,

inflammation and (cardiovascular)-biomarkers, deoxyribonucleic acid (DNA), gut

microbiome, insulin sensitivity and measures of beta-cell function.

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 maybe 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, indicatingan unmet need for renoprotective therapies. 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*, including reduction of blood pressureand body weight. In addition, SGLT-2 inhibitorsdecrease proximal sodium reabsorption and decrease glomerular pressure and albuminuria in rodents and type 1 diabetespatients. In rodents, SGLT-2 inhibitors alsoimproved histopathologicalabnormalities associated withDKD. 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 SGLT-2 inhibitors on renal physiology and biomarkers inmetformin-treated T2DM patients with normal kidney function.

Hypothesis: Treatment with the SGLT-2 inhibitor dapagliflozin, as compared to the sulfonylurea (SU) derivative gliclazide, may confer renoprotection by improving renal hemodynamics, and decreasing blood pressure and body weight in type 2 diabetes.

Study objective

To gain more knowledge about the effects of SGLT2 inhibition on renal hemodynamics and the underlying mechanisms.

Study design

Study Design: A phase 4, monocenter, randomized, double-blind, comparator-controlled, parallel-group, mechanistic intervention trial to assess the effect of 12-week treatment with the sodium-glucose linked transporters (SGLT)-2 inhibitor dapagliflozin versus the SU gliclazide on renal physiology and biomarkers in metformin-treated patients with type 2 diabetes mellitus (T2DM)

Study Endpoints and methods:
-Renal hemodynamics, i.e. GFR and ERPF will be measured by the gold-standard inulin- or iohexol and para-aminohippurate clearance methods, respectively, during both euglycemic- and hyperglycemic clamp;
-Renal tubular function will be measured by 24-hour urine sodium, potassium, chloride, calcium, magnesium, phosphate and urea and glucose;
-Markers of renal damage will include urinary albumin excretion, neutrophil gelatinase-associated lipocalin and kidney injury molecule-1;
-Blood pressure will be measured using an automated oscillometric blood pressure device (Dinamap®);
-Body anthropometrics, including body weight, height, body-mass index and waist circumference, and body fat contents (by bio-impedance analysis) will be measured; blood samples will be obtained to determine glycemic variables, lipids and markers of inflammation; systemic hemodynamic variables (including stroke volume, cardiac output and total peripheral resistance) will be measured by continuous beat-to-beat hemodynamic monitor (NexFin®);
-Heart rate will be determined by oscillometric blood pressure device;
-Microvascular function will be measured by capillary videomicroscopy and Laser Doppler;
-Arterial stiffness will be assessed by applanation tonometry, (SphygmoCor®);
-Additional urine, blood and feces will be collected for conditional determination of various markers of renal damage/function, inflammation, oxidative stress and (cardiovascular)-biomarkers and DNA;
-CANS will be measured by electrocardiography and NexFin®;
Insulin sensitivity will be measured by glucose infusion during the euglycemic clamp (M-value);
-Beta-cell function will be measured by quantification of insulin secretion during the hyperglycemic clamp.

Intervention

12 weeks of dapagliflozin 10mg QD versus gliclazide 30mg QD treatment

Study burden and risks

The subjects will visit the clinical research unit (CRU) for a screening of approximately 2 hours, 2 testing days of approx. 9 hours and a safety visit of

about 1 hour. During the treatment period they need to take one capsule.

Patients will have to remain fasted for the screening and testing visits. After these days they will get a meal and during the testing days they will quickly get glucose infused. Blood glucose levels will be checked frequently, therefore the chance of hypo- or hyperglycemia including the concomitant symptoms is small. Nevertheless, the absence of oral intake will probably be an unpleasant experience. However, subjects from our recents studies don't mention this as an issue.

Blood will be drawn once during the screening and once during the safety visit by venapuncture. During the testing days blood will be drawn frequently, but from an intravenous cathether which only has to be inserted once. The total amount of blood drawn will be 500ml and therefore not to much of a burden. Venapunctures and placement of catheters can cause haematomas and there is a small chance of tromboflebitis.

The methods used to measure our endpoints include the infusion of registered (diagnostic) substances (PAH/Inulin or iohexol) and glucose/insulin during the clamps. Hypersensitivity reactions liks anaphylaxis, angio-edema, flushing, nausea of stomach cramps can occur during the infusion of PAH and inuline or iohexol, but are extremely rare and never occured in our CRU.

During the clamps there is a risk of hypo- or hyperglycemia. We minimize this risk by checking blood glucose levels every 5 minutes and adjust the glucose infusion rate. We'll keep on checking blood glucose levels till at least 30 minutes after the end of a clamp to see whether glucose regulation recovered properly. Infusion of glucose 20% solution increases the risk of (trombo)flebitis, we'll try to prevent this by adding NaHCO3 to the solution. Our CRU has done thousands of clamps in recent years withour hypo- or hyperglycemia. Some patients have developed a tromboflebitis.

The most common side effects of dapagliflozin are hypoglycemia (mainly in combination with and SU derivative or insulin) and genital of urinary tract (fungal) infections. These adverse effects were usually mild and transient. Dehydration, hypovolemia and serious hypoglycemia have rarely been reported. Gliclazide can lead to hypoglycemia and, during the initial phase of treatment, blurred vision. Gastro-intestinal side effects like nausea, vomiting, diarrhea have been reported. Since gliclazide will be used in relatively small doses during this study for a relatively short duration.
Taking the in- and exclusion criteria into account the risk of hypoglycemia is low. Nevertheless, patients will be educated about hypoglycemia and carbohydrate intake to prevent or overcome an episode. They will also be provided with a blood glucose measuring device when they experience any symptoms of hypoglycemia.

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

Inclusion criteria
* 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: 6.5 * 9.0% Diabetes Control and Complications Trial (DCCT) or 48 - 86 mmol/mol International Federation of Clinical Chemistry (IFCC)
* 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**

* 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
** In order to accelerate inclusion, patients using combined metformin/SU derivative will be considered. In these patients, a 12 week wash-out period of the SU derivative will be observed, only when combined use has led to a HbA1c <8% at screening. Subsequently, patients will be eligible to enter the study, now using metformin monotherapy, provided that HbA1c still meets inclusion criteria.

Exclusion criteria

Exclusion criteria
* History of unstable or rapidly progressing renal disease
* Estimated GFR<60 mL/min/1.73m2 (determined by the Modification of Diet in Renal Disease (MDRD) study equation)
* Current/chronic use of the following medication: TZD, SU derivative, GLP-1RA, DPP-4I, SGLT-2 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 drugs can be taken within a time-frame of 2 weeks prior to renal-testing
* History of diabetic ketoacidosis (DKA) requiring medical intervention (eg, 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:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-02-2016
Enrollment:	44
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diamicron MR
Generic name:	Gliclazide MR
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Forxiga/Farxiga
Generic name:	Dapagliflozin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-11-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2018
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	EUCTR2015-003818-24-NL
CCMO	NL54965.029.15
Other	U1111-1173-7074