Treating microalbuminuria over 24 weeks in subjects with or without type 2 diabetes or hypertension

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To assess the albuminuria lowering effects of dapagliflozin in subjects with and without diabetes or hypertension and persistent elevated albuminuria.

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

Summary

ID

NL-OMON50643

Source
ToetsingOnline

Brief title
TIMOTHY

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Nephropathies

Synonym
early stage kidney disease, microalbuminuria

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Astra Zeneca,AstraZeneca funds the study and delivers the study drugs

Intervention

Keyword: albuminuria, chronic kidney failure, microalbuminuria, sglt2 inhibitor

Outcome measures

Primary outcome

Change in albuminuria from baseline

Secondary outcome

Changes from baseline in:

• Systolic / diastolic blood pressure

• Body weight

• Hba1c

• eGFR

• Number of patients with >=30%, 40%, 50% reduction in UACR from baseline at

week 24

Study description

Background summary

During the last three decades, elevated albuminuria has been shown to be relatively common in the general population (5-9%) and has been independently associated with poor cardiovascular and renal prognosis.

Drugs proven to be renal and cardiovascular protective, such as ACE inhibitors and angiotensin receptor blockers (ARBs), reduce albuminuria. Clinical practice guidelines recommend ACE inhibitors and ARBs to optimize blood pressure control and decrease albuminuria in patients with hypertension and diabetes. Although ACE inhibitors and ARBs reduce albuminuria by approximately 30%, albuminuria is not optimally controlled in all individuals and high albuminuria persists in a significant proportion of individuals. In addition, among individuals with elevated albuminuria but without diabetes or hypertension (isolated albuminuria), there are no guidelines-recommended therapies available to reduce albuminuria, despite the fact that individuals with isolated albuminuria are at

increased risk for progressive loss of renal or cardiovascular function. To further optimize cardiovascular and renal prognosis, additional treatments that reduce albuminuria are desirable for patients with isolated albuminuria and for patients with diabetes or hypertension and persistent albuminuria despite treatment with ACEi or ARB.

Sodium Glucose co Transporter 2 (SGLT2) inhibitors lower blood pressure, body weight and albuminuria. Importantly, these agents also reduce cardiovascular and renal outcome risks in large cardiovascular outcome studies in patients with type 2 diabetes. In addition, the DAPA-CKD study recently reported that dapagliflozin also reduced the risk of renal failure and heart failure, as well as mortality in patients with chronic kidney disease with and without type 2 diabetes. Whether the effect of SGTL2i extends to a broad group of individuals with and without type 2 diabetes or hypertension in earlier stages of renal disease than recruited in the DAPA-CKD trial is unknown. This is clinically important to note as early intervention in the course of CKD has been shown to be more effective in delaying the time to dialysis compared to intervention in advanced stages of the disease (Schievink et al. DOM 2016).

Study objective

To assess the albuminuria lowering effects of dapagliflozin in subjects with and without diabetes or hypertension and persistent elevated albuminuria.

Study design

The TIMOTHY study consists of a screening period, double blind treatment period and a follow-up period. Potential eligible participants will be recruited via general practitioners or through a general population screening program for increased albuminuria and risk factors for progressive chronic kidney disease and cardiovascular disease.

Subjects with type 2 diabetes or hypertension have to be on a stable dose (no changes in dose or type of drug) of ACEis or ARBs for at least 6 weeks prior to the screening visit to be eligible to proceed to the randomization visit. These subjects will maintain their stable doses of commercially available ACEis or ARBs. ACEi or ARBs are not required for subjects without type 2 diabetes or hypertension per clinical practice guidelines.

The randomization visit will occur 2 week after the subject*s screening visit. Participants will be assigned in a 1:1 ratio to double blind treatment with dapagliflozin 10 mg/d or matched placebo. At the randomization visit, three consecutive first morning void urine samples will be collected and blood samples taken for clinical chemistry measurements.

In patient follow-up visits take place after 2 weeks, 8 weeks, 16 weeks and 24

weeks. At each visit participants will be asked to collect 2 first morning void urine samples for assessment of UACR. Vital signs (i.e. blood pressure and body weight) and adverse events will be recorded at each visit and a blood sample will be taken for clinical chemistry assessment. Blood and urine will be stored for future biomarker studies.

Study medication will be discontinued at week 24 and patients will proceed in a 4 weeks wash-out period to assess off drug effects. Participants are asked to collect three consecutive first morning void urine samples after 4 weeks and visit the out-patient clinic where blood samples will be taken for clinical chemistry measurements.

Intervention

Dapagliflozine 10mg/day for a duration of 24 weeks is the intervention

Study burden and risks

Side effects may occur as a result of the study medication. An allergic reaction may occur as a result of the study medication. Subjects may experience minor pain, local irritation, bleeding or bruising at the puncture site as a result of venipuncture. There is a small chance of feeling light-headed and/or fainting. In rare cases, the puncture site may also become infected or nerves may be damaged. Patients are expected to follow the investigators' instructions for 28 weeks as necessary for the study.

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

• Age 45 to 80 years
• Persistent urinary albumin:creatinine ratio (UACR) >= 2.5 mg/mmol (~25 mg/g)
• Willing to sign informed consent

Exclusion criteria

• Diagnosis of type 1 diabetes mellitus
• eGFR < 25 ml/min/1.73m2
• UACR > 3500 mg/g
• Concurrent treatment with SGLT2 inhibitor
• Receiving immunosuppressive therapy within 6 months prior to enrollment
• History of diabetic ketoacidosis
• Active malignancy aside from treated squamous cell or basal cell carcinoma of the skin.
• Initiation or changes in the dose of interventions in the renin-angiotensin-aldosterone-system, diuretics, GLP-1 receptor agonists within 6 weeks of screening will not be allowed.
• Any medication, surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of medications including, but not limited to any of the following:
o History of active inflammatory bowel disease within the last six months;
o Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
o Gastro-intestinal ulcers and/or gastrointestinal or rectal bleeding within last six months;
o Pancreatic injury or pancreatitis within the last six months;
o Evidence of hepatic disease as determined by any one of the following: ALT or

AST values exceeding 3x ULN at the screening visit, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt;
o Evidence of urinary obstruction or difficulty in voiding at screening
• History of severe hypersensitivity or contraindications to dapagliflozin
• Subjects who, in the assessment of the investigator, may be at risk for dehydration or volume depletion that may affect the interpretation of efficacy or safety data
• Participation in any clinical intervention study within 3 months prior to initial dosing.
• History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during the screening.
• History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
• Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
• Pregnancy or breastfeeding

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-02-2022
Enrollment:	340
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Forxiga
Generic name:	dapagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-09-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-01-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2021-004073-31-NL
CCMO	NL78752.042.21

Study results

Date completed: 02-02-2023

Results posted: 26-07-2024

First publication
26-07-2024