ERtugliflozin triAl in DIabetes with preserved or reduced ejeCtion FrAcTion;mEchanistic evaluation in Heart Failure: "ERADICATE-HF"

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The systematic understanding of the effects of SGLT2i in the setting of HF will enable the design of rational physiology based strategies to decrease the burden of HF, which could have major clinical and research implications internationally.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON50595

Source
ToetsingOnline

Brief title
ERADICATE-HF

Condition

- Heart failures
- Glucose metabolism disorders (incl diabetes mellitus)
- Nephropathies

Synonym
diabetes mellitus type 2, heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Toronto General Hospital/University Health Network
Source(s) of monetary or material Support: industrie,Merck

Intervention

Keyword: Diabetes Mellitus type 2, Heart failure, SGLT2-inhibitor

Outcome measures

Primary outcome

Our primary goal is to determine if SGLT2i causes a persistent proximal renal tubular natriuretic effect (see below). We will capture acute (1 week) and chronic (12 weeks) responses, since physiological effects of SGLT2i agents may change over time. As an extension of our primary aim, we will assess whether ertugliflozin-related effects on proximal tubule natriuresis lead to a reduction in plasma volume and extracellular body water (see below). FENa and FELi excretion were calculated according to FE(electrolyte) = 100 X ([(electrolyte urine) X (creatinine plasma)]/[(electrolyte plasma) X (creatinine urine)]). FELi will used as a surrogate to measure proximal tubular sodium reabsorption, whereas FENa assesses total overall (proximal and distal) tubular sodium handling. Distal sodium handling is calculated by total-proximal sodium reabsorption, as described elsewhere. As in previous work, plasma and urine lithium levels will be measured using inductively with coupled spectroscopy.

Secondary outcome

Secondary:

1. We will determine if volume contraction leads to a decline in hormones that

are activated in HF patients such as B*type natriuretic peptides

(BNP/NT-pro-BNP), without activating the SNS7;

2. We will determine the impact of ertugliflozin on: renal hemodynamic function

(GFRiohexol/ERPFpah) measured at 1 week and 12 weeks as a measure of safety;

3. Blood pressure, echocardiographic measures of cardiac output (and derived

systemic vascular resistance) arterial stiffness and systemic vascular

resistance to better understand the blood pressure lowering effect in this

patient population;

4. Heart rate and heart rate variability, to assess effects on SNS activation;

5. Urinary natriuretic modulators, such as angiotensin converting enzyme-29 and

adenosine10;

6. To characterize the safety of ertugliflozin vs. placebo by determining the

number of hypoglycemic episodes between groups, and serious adverse events.

Study description

Background summary

Patients with T2D-HF have >50% 5-year mortality, leading to substantial societal and financial costs to Canadians. The identification of new therapies is essential to improve the quality of life and survival of T2D-HF patients. In EMPA-REG OUTCOME there was a significant decrease in the rate of hospitalization for HF after therapy for only 3 months. Despite this beneficial effect, the impact of SGLT2i in patients with overt HF remains unknown. The current gap in knowledge around SGLT2i effects in patients with existing HF highlights the urgent need for human mechanistic studies in this area. The renal and cardiovascular function effects of SGLT2i on natriuresis-related endpoints in patients with T2D and HF is not known. Our study will provide needed insights into physiological effects of SGLT2i agents on natriuresis, hemodynamic function and neurohormones in HF patients.

Study objective

The systematic understanding of the effects of SGLT2i in the setting of HF will enable the design of rational physiology based strategies to decrease the burden of HF, which could have major clinical and research implications internationally.

Study design

This study will use a double blind, stratified randomization trial approach involving 36 T2D-HF patients taking standard HF therapies.

Measurements:
• During the double blind treatment period, patients will collect a 24-hour urine collection at each visit for measurement of 24-hour protein, albumin, glucose, sodium, potassium, creatinine, and urea excretion. Twenty-four hour urine collections will be performed at: Visits 3, 4 and 8. Routine biochemistry and safety labs will be drawn at screening, during each physiological assessment and at each the specified office safety visits (see visit schedule table below).
• Office systolic and diastolic blood pressure measurements, heart rate, weight, and waist circumference will be performed at screening and at each subsequent physiological testing day and at each office visit (see visit schedule table below).
• Blood will be drawn for measurement of renal function tests, HbA1c, glucose, complete blood count, plasma albumin, RAAS biomarkers, natriuretic peptides, and neurohormones on visits 3, 4 and 8.
• Blood and urine samples will be stored for future exploratory biomarker analyses to study the effect of ertugliflozin in this study population.

Intervention

Patients will be randomized to 15 mg (1x 15mg tablets) PO ertugliflozin daily or a matched placebo.

Study burden and risks

Patients visit the outpatient clinic on a more regular basis than standard patient care -
i.e. at study inclusion and at each study visit for clinical assessment. Blood work for physiological assessments, renal function tests and cardiovascular assessments will be obtained as described in the protocol. 24hr urine will be collected one day prior to the hospital visit. No other invasive measurements will be executed. Patients receive restitution of all travel costs. Patients receive no priority in treatment of other diseases in the clinic during this study. There are no direct benefits for the patients to be included and participation is on a voluntary basis.

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

Men and women with type 2 diabetes > 12 months, eGFR > 30 ml/min/1.73m2, age > 18 years, HbA1c 6.5 - 10.5%, BMI 18.5-45.0 kg, blood prssure < 160/110 and > 90/60 at screening, heart failure NYHA 2-3 with ejection fraction > 20%, ACE/ARB-inhibition > 30 days, if diuretics are use then > 30 days before baseline, BNP levels at baseline >100 pg/ml (no atrial fibrillation), >200 pg/ml if in atrial fibrillation, if NT-pro-BNP is used then a cut-off baseline of >300ng/L (no atrial fibriallation) or >600 ng/L (in atrial fibrillation) should be used

Exclusion criteria

1. Type 1 Diabetes;2. Leukocyte and/or nitrite positive urinalysis that is untreated;3. Severe hypoglycaemia within 2 months prior to screening;4. History of brittle diabetes or hypoglycaemia unawareness based on investigator judgement;5. Unstable coronary artery disease with acute coronary syndrome, percutaneous intervention or bypass surgery within 3 months;6. Clinically significant valvular disease;7. Congestive heart failure secondary to an infiltrative cardiomyopathic process (for example amyloid) or pericardial constriction;8. Uncontrolled systemic hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure >110) or systemic hypotension(systolic blood pressure < 90/60 mmHg);9. Bariatric surgery or other surgeries that induce chronic malabsorption;10. Anti-obesity drugs or diet regimen and unstable body weight three months prior to screening;11. Treatment with systemic corticosteroids;12. Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells;13. Pre-menopausal women who are nursing, pregnant, or of childbearing potential and not practicing an acceptable method of birthcontrol;14. Participation in another trial with an investigational drug within 30 days of informed consent;15. Alcohol or drug abuse within three months prior to informed consent that would interfere with trial participation or any ongoing clinicalcondition that would jeopardize subject safety or study compliance based on investigator judgement;16. Liver disease, defined by serum levels of alanine transaminase, aspartate transaminase, or alkaline phosphatase >3 x upper limit ofnormal as determined during screening;17. Active malignancy at the time of screening;18. Allergy to iodine-based substances if receiving iohexol for GFR measureseen stenose > 30% vertoont;
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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:	Recruiting
Start date (anticipated):	15-05-2019
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Steglatro
Generic name:	Ertugliflozin

Ethics review

Approved WMO Date:	22-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2021
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:	23-02-2021
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	EUCTR2017-001840-37-NL
ClinicalTrials.gov	NCT03416270
CCMO	NL66121.029.18