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Cardiovascular effects of empagliflozin in diabetes mellitus

Submission date 08/10/2018	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 16/10/2018	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 25/08/2022	**Condition category** Circulatory System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
The prevalence of type 2 diabetes in the UK has more than doubled in the past 20 years and is expected to continue to rise. Despite improvements in diagnosis and treatment, the life expectancy of patients with type 2 diabetes remains significantly lower than that of the general population. Type 2 diabetes is associated with an increased cardiovascular (heart disease) risk compared to the general population, even after adjustment for other risk factors, and this risk has proved difficult to modify. Older medications aimed at improving blood sugar control, including sitagliptin, have shown no significant improvement in cardiovascular outcomes. Recently, a new medication, empagliflozin, has been shown to decrease both cardiovascular and all-cause mortality and decrease heart failure admissions in patients with type 2 diabetes and known cardiovascular disease. The mechanisms by which empagliflozin causes this reduction in heart failure and cardiovascular mortality are as yet unknown. The aim of this study is to determine the effects of empagliflozin on the heart in a population of patients with similar characteristics as studied in recent clinical trials.

Who can participate?
Patients aged 18-84 with known cardiovascular disease and recent heart attack (myocardial infarction), and with known type 2 diabetes

What does the study involve?
Participants receive sitagliptin and empagliflozin over two periods of 3 months and undergo tests including cardiac magnetic resonance imaging (MRI) of scar (extracellular fibrosis) and blood flow to the heart muscle, as well as assessment of diabetes status including blood tests. The aim is to find out whether empagliflozin treatment has any effects on the heart that are measurable with MRI.

What are the possible benefits and risks of participating?
There will be no direct clinical benefit to individual patients. This will be made clear at the start of the study. However, the results may show which diabetic medication is best for the control of their blood sugars, informing long-term prescribing. There are no direct risks to the patient from participating in this study. Some patients can find blood tests painful or may experience claustrophobia in the MRI scanner. Every effort will be made to reduce these sensations, as per

normal clinical routine in MRI scanning, but if a participant cannot tolerate the procedure, the scan will be stopped immediately.

Where is the study run from?
Leeds General Infirmary (UK)

When is the study starting and how long is it expected to run for?
April 2018 to June 2022

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Dr Kathryn Richards
K.H.Richards@leeds.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Kathryn Richards

ORCID ID
http://orcid.org/0000-0001-9539-3123

Contact details
LICAMM
LIGHT Laboratories
University of Leeds
6 Clarendon Way
Leeds
United Kingdom
LS2 9LU
+44 (0)113 3928250
K.H.Richards@leeds.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number
241152

ClinicalTrials.gov number

Secondary identifying numbers
38480, IRAS 241152

Study information

Scientific Title
Cardiovascular effects of empagliflozin in diabetes mellitus

Acronym
CEED

Study objectives
The trialists hypothesise that empagliflozin treatment is associated with changes in myocardial blood flow and myocardial fibrosis as measured by CMR, independently of blood sugar control.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Yorkshire & Humber- South Yorkshire Research Ethics Committee, 19/06/2018, ref: 18/YH/0190

Study design
Randomised; Both; Design type: Treatment, Drug, Validation of investigation/therapeutic procedures

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Heart disease in patients with type 2 diabetes and previous myocardial infarction

Interventions
This is a crossover study to characterise the cardiac effects of sitagliptin and empagliflozin on CMR imaging biomarkers and glycaemic status in patients with type 2 diabetes with a history of myocardial infarction. The trialists plan to recruit 60 patients with a diagnosis of diabetes and known heart disease. All participants will have HbA1c (a monitor of blood sugar control) levels within a range where an additional medication for diabetes would usually be considered. They will continue on their current diabetes medications throughout the trial.

All participants will undergo three CMR scans. A baseline scan will be carried out, followed by randomisation to either sitagliptin (100 mg once daily) or empagliflozin (10 mg once daily) by

mouth for 3 months, then a second CMR scan, followed by 3 months therapy with the other medication and a final CMR scan. In addition, blood tests and blood glucose monitoring with a Libre Pro will be carried out 2 weeks before each CMR scan.

The Libre Pro is a small patch that sticks to the patient's skin, usually the upper arm, and remains in place for up to 2 weeks. It provides results for continuous blood sugar monitoring over that time, then this information is downloaded after removal.
Blood tests will include fasting glucose and insulin levels, HbA1c (a marker of diabetes control), a full blood count (FBC) and eGFR (a marker of kidney function).

In total, this would amount to 7 visits for each participant. The entire visit will take around 2 hours when a CMR scan takes place (3 visits). Visits for blood tests and blood sugar monitoring would take approximately 30 minutes. Patients will be asked to record on a patient diary that they have taken the study medication each day.

These scans will be for research purposes only. However, the results of blood sugar control and HbA1c with each medication will be available to the GP and could help chose which medication to continue in the long term.

CMR scans will involve use of adenosine as a stress agent to assess perfusion reserve, and the use of standard contrast agent to assess the amount of scarred myocardium.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Sitagliptin, empagliflozin

Primary outcome measure
Myocardial perfusion reserve in remote myocardium, measured by cardiac MRI at baseline, 12 and 24 weeks

Secondary outcome measures
1. Myocardial perfusion reserve in infarcted territory
2. Extracellular volume fraction
3. Capillary permeability
4. Relationship between glycaemic markers and LV perfusion parameters
5. Aortic distensibility
Secondary outcome measures will be measured by cardiac MRI at baseline and at weeks 12 and 24. Secondary outcome measure 4 will also be measured at approximately 2 weeks before baseline and at weeks 10 and 22.

Overall study start date
16/04/2018

Completion date
30/06/2022

Eligibility

Key inclusion criteria
1. Type 2 diabetes mellitus
2. Metformin as single or dual therapy
3. Recent heart attack (<12 months)
4. HbA1c >48mmol/ml
5. 18-84 years old
6. Ability to provide informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
84 Years

Sex
Both

Target number of participants
Planned Sample Size: 60; UK Sample Size: 60

Total final enrolment
36

Key exclusion criteria
1. Previous coronary artery bypass grafting (CABG)
2. Need for further revascularisation
3. Contra-indication to CMR scanning (some pacemakers, intraorbital debris, intraauricular implants, intracranial clips etc)
4. Contra-indication to Adenosine
5. Known allergy to contrast medium (gadolinium)
6. Renal dysfunction with eGFR< 60
7. Obesity where girth exceeds the scanner bore
8. Pregnancy or breastfeeding
9. Inability to lie flat for CMR scan

Date of first enrolment
29/08/2018

Date of final enrolment
03/01/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Sponsor information

Organisation
University of Leeds

Sponsor details
Faculty Research Office
Room 9.29 Level 9 Worsley Building
Clarendon Way
Leeds
England
United Kingdom
LS2 9NL
+44 (0)113 3437587
governance-ethics@leeds.ac.uk

Sponsor type
University/education

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation; Grant Codes: RG/16/1/32092

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/12/2022

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.2	19/06/2018	16/10/2018	No	Yes
Participant information sheet	version v1.3	17/01/2019	06/09/2019	No	Yes
Protocol file	version v1.2	17/01/2019	06/09/2019	No	No
Protocol article		01/05/2021	13/08/2021	Yes	No
HRA research summary			28/06/2023	No	No