ISRCTN12589919 https://doi.org/10.1186/ISRCTN12589919

NLRP3 and SASP in early SGLT2i therapy in patients with diabetes who have had a heart attack

Submission date
26/01/2023

Recruitment status
No longer recruiting

Registration date
24/04/2023

Overall study status
Completed

Last Edited
18/12/2024

Condition category
Circulatory System

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
People with type 2 diabetes (T2DM) are at increased risk of major complications such as heart and kidney damage, which are responsible for the majority of deaths in patients with diabetes. This damage develops because of increased inflammation, damage which also intensifies as we get older. Inflammation has significant detrimental effects on an individual's health. If we can reduce or treat this damage, we can enhance both the quality of life and longevity of people with T2DM. A new class of drugs called sodium-glucose co-transporter-2 inhibitors (SGLT2 inhibitors) are prescribed to help control blood sugar levels in T2DM. These drugs, which are safe and well tolerated, have also shown an ability to protect the heart and kidneys from damage induced by inflammation. Exactly how they do this is currently unknown, a question this study aims to answer. The researchers will study if these drugs protect the heart and kidneys by blocking a specific form of inflammation linked to poor heart and kidney health in T2DM.

Who can participate?
Patients aged 18 years and over with T2DM, presenting with a heart attack, and eligible for SGLT2 inhibitors

What does the study involve?
Blood samples will be taken at specific intervals from discharge to examine the underlying biological mechanisms of how the SGLT2 inhibitors work in protecting patients.

What are the possible benefits and risks of participating?
The researchers aim to study how the SGLT2 inhibitor empagliflozin may target and blunt a specific form of inflammation, which may reduce cell degeneration, senescence and sustained tissue damage, and also affect specific immune-inflammatory cell behaviour and signalling. Although SGLT2 inhibitors are already prescribed for T2DM to reduce blood sugar, understanding how these drugs work will not only inform on how to use them better and will also help develop new therapies in combatting heart and kidney complications in T2DM. Empagliflozin is a licenced medication, already recommended for use in patients with the above conditions as per international guidelines. This study is not a clinical trial to prove the

effectiveness or safety of an investigational medical product. This has already been established for the SGLT2is. It is a study which seeks to examine and understand the underlying biological mechanisms of how this benefit occurs, how these drugs work, and to help inform us of how to better use it. Empagliflozin is well tolerated amongst patients, with urinary and genital tract infections being the most common side effects associated with it. These are easily treatable with oral medications and do not have any long-lasting effects. Participants enrolled in the study will be monitored for such events. They will also need to attend follow-up visits over a 6-month period. Moreover, they will undergo a blood sampling procedure at each visit. To minimise any delays and unsuccessful attempts at the blood sampling process, and therefore any associated discomfort from needle pricks, we have dedicated research clinics run by experienced clinicians who are experts in blood sampling. Participants will also be reimbursed for travel expenses to avoid any additional burden for participating in the study.
In addition to the usual review and follow-up as part of the standard NHS care, patients will have increased clinical access during their participation in the study and more regular and frequent contact with the clinical team members (the doctors in the research team are also the same doctors in the clinical team). This would allow early assessment, review, investigation or referral as appropriate.

Where is the study run from?
1. Lincoln County Hospital (UK)
2. University of Lincoln (UK)

When is the study starting and how long is it expected to run for?
August 2022 to December 2024

Who is funding the study?
1. European Association for the Study of Diabetes (EFSD) (Germany)
2. Boehringer Ingelheim (USA)

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
319343

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 54499, IRAS 319343

Study information

Scientific Title
The cardio-renal-metabolic role of NLRP3 and SASP in early SGLT2i therapy in diabetics with myocardial infarction

Study objectives
The SGLT2i empagliflozin provides anti-inflammatory protection via (i) inhibiting the NLRP3 inflammasome, (ii) blocking aberrant Cx-hemichannel activity and (iii) suppressing the senescence-associated secretory phenotype, and this benefits patients with type 2 diabetes mellitus (T2DM) and acute myocardial infarction (AMI) when early therapy is initiated prior to discharge.

Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 01/12/2022, East of Scotland Research Ethics Service (EoSRES) (Tayside Medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK; +44 (0)1382 383848; tay.eosres@nhs.scot), ref: LR/22/ES/0047

Study design
Observational; Design type: Case-controlled study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Diabetics with myocardial infarction

Interventions
This is a single-centre, prospective pilot study, limited to working with human blood samples and data with randomisation of patients into one of the two usual prescribing pathways to ensure no selection bias into either group for blood sampling in this study.

The study will be performed at Lincoln County Hospital, where the cardio-metabolic in-reach clinical team will identify appropriate patients who will then be approached by the cardiology research team (of whom the doctors in the research team are also part of the cardio-metabolic clinical team) for their consent to take part in the study. Such participants would be those that are known to have T2DM, admitted with a heart attack and who are eligible for the SGLT2i empagliflozin therapy, as recommended as part of their best standard of care.

This is not a clinical trial of an investigational medical product, or to prove its efficacy or safety. This has already been established for the SGLT2i's. Empagliflozin is an SGLT2i class of medication with licensed indication and is already prescribed and used to treat patients with T2DM, cardiovascular disease and myocardial infarction. Patients in this study will have been started on some medications already as part of guideline-directed medical therapy and established standard of care after their heart attack. One of the medications in consideration is the SGLT2i called empagliflozin which may benefit them.
There are two established prescribing pathways for empagliflozin for patients with type 2 diabetes after a heart attack:
- to start empagliflozin just prior to their discharge with their heart attack (Group A), or

- to start empagliflozin at the cardio-metabolic post-myocardial infarction (MI) follow-up clinic 3 months after discharge (Group B).

Patients who are indicated and eligible for empagliflozin therapy as part of their recommended best standard of care, AND are eligible for either one of the prescribing pathways with no specific preference for either pathway (ie. no specific clinical reason or otherwise) will be invited to take part in this study. Consented patients will be randomised to one of the 2 established prescribing pathways for the purpose of the study – to ensure no selection bias into either group for the blood sampling in the study.
This study does not affect any of the patient's treatment and usual prescribing practice in any way; ALL eligible patients will receive SGLT2i therapy after their heart attack via one of the established usual prescribing pathways, as well as other medicines recommended and indicated in the management of their condition.
The researchers will only be collecting blood samples for analysis in the study. They will collect blood samples at set intervals over 6 months. About 35-40 ml of blood will be taken at each interval in the study. Patients will have study blood samples taken at the start of the study whilst they are still in hospital prior to discharge. And again when they are seen in routine follow-up in the cardio-diabetes post-MI follow-up clinic in 3 months' time. These are timed to their usual review as part of their standard of care, to minimise any inconvenience or disruption.

There will also be a few additional study visits for blood sampling in the study depending on which group the patient have been randomized to:
Group A (empagliflozin prescribed prior to discharge): will have two additional study visits for blood sampling at 1 and 6 months.
Group B (empagliflozin prescribed at the follow-up clinic): will have three additional study visits for blood sampling at 1, 4 and 6 months.
The researchers have made arrangements for reimbursement for travel expenses for any additional visits incurred as a result of participation. After the last study visit at 6 months, the study patient will have completed their participation in the study.

Pseudo-anonymised coded patient data, demographics, clinical data, and specific clinical results and measurements of interest and relevance will be collected for correlation and analysis in the study. The blood samples will be transferred, via an approved cold chain process, to the University of Lincoln research laboratories, where further analysis will take place, as per predetermined and validated protocols, to assess for levels of various pro-inflammatory biochemicals known to lead to cell degeneration, aging and death, and the study of inflammatory cell behaviour and signalling.

Key aspects of the study design:
1. A total of 66 patients with completed blood sampling and analysis will be recruited for the study. This would include our target of 60 patients but will aim to over-recruit by 10% to ensure an adequate number of participants in case of rare events of dropout or withdrawal from the study.
2. Each patient's participation will be approximately 6 months from consent to the final visit.
3. Patients are randomized to one of the two established prescribing pathways to ensure no selection bias into either group for the blood sampling in the study.
4. The study does not affect any of the patient's treatment, usual prescribing practice, clinical management and follow-up as per their standard of care in any way.
5. Patients in the study will be commenced on guideline-directed medical therapy as per established recommendations and guidelines, and established standard of care. Therefore, no investigational medication will be introduced. Any AEs or SAEs identified in this study will be managed as part of the usual standard of care.

6. In addition to the usual review and follow-up of the standard of care, patients will have increased clinical access during their participation in the study and more regular and frequent contact with the clinical team members (the doctors in the research team are also the same doctors in the clinical team). This would allow early assessment, review, investigation, referral, or management of any AEs or SAEs as appropriate.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Empagliflozin

Primary outcome measure
1: Priming/activation of specific inflammatory biomarkers and proteins in the blood (the NLRP3 inflammasome) measured using qRT-PCR, Caspase 1 (Glo) and IL1b assay at Group A t = 0, t = 30, t = 90 and t = 180 days and Group B t = 90, t = 120 and t = 180 days, plus appropriate controls (t=0 and t = 30 days)
2. Cell ageing and tissue damage (senescent cell accumulation and secretory proteins [SASP]), measured using qRT-PCR, Western blotting and ELISA at Group A t = 0, t = 30, t = 90 and t = 180 days. and Group B t = 90, t = 120 and t = 180 days, plus appropriate controls (t = 0 and t = 30 days)
3. Cell behaviour (Cx43 hemichannel-mediated ATP release), measured using carboxyfluorescein dye uptake studies and ATP release assays at Group A t = 0, t = 30, t = 90 and t = 180 days. and Group B t = 90, t = 120 and t = 180days, plus appropriate controls (t = 0 and t = 30 days)

Secondary outcome measures
1. The difference in the baseline of activity and the magnitude of the effect of the primary outcome measures NLRP3, Cx43, and SASP correlated to the onset of empagliflozin therapy in AMI, measured using qRT-PCR, Caspase 1 (Glo) and IL1b assays, Western blotting, ELISA, carboxyfluorescein dye uptake studies and ATP release assays on blood samples taken from patients who received empagliflozin prior to discharge; Empa-earlier (Group A, blood sampled at t = 0, 30 and 90 days) vs patients who received empagliflozin at 3 months in follow-up clinic; Empa-later (Group B, blood sampled at t = 90, 120 and 180 days)
2. NLRP3, Cx43 and SASP measured using qRT-PCR, Caspase 1 (Glo) assays, IL1b assays, Western blotting, ELISA, carboxyfluorescein dye uptake studies and ATP release assays at 180 days

Overall study start date
15/08/2022

Completion date
31/12/2024

Eligibility

Key inclusion criteria
1. Male and female patients aged 18 years and over
2. Patients with known or new type 2 diabetes mellitus and newly diagnosed acute myocardial infarction

3. Eligible for SGLT2i therapy AND not on an SGLT2i yet
4. The patient is eligible for both prescribing pathways for starting SGLT2i:
4.1. Starting SGLT2i prior to discharge, or
4.2. Starting SGLT2i at follow-up clinic
5. The patient has no preference for a specific prescribing pathway and consents to be randomised
6. Able to provide informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
66

Total final enrolment
66

Key exclusion criteria
1. Pregnancy or breastfeeding
2. Severe end-stage kidney
3. Severe end-stage liver disease
4. other conditions that would reduce the expected life span of a patient to less than 2 years
5. Unable to provide informed consent
6. Patients who have an indication for early start of, or already prescribed, empagliflozin/other SGLT2i, separate from the above conditions (e.g. patients with known symptomatic heart failure with reduced ejection fraction [EF <40%])
7. Acute renal failure
8. Cardiogenic shock
9. Severe valvular heart disease
10. Surgical revascularisation
11. Inflammatory related conditions, including infection, cancer, or autoimmune disease

Date of first enrolment
27/02/2023

Date of final enrolment
31/05/2024

Locations

Countries of recruitment

England

United Kingdom

Study participating centre
University of Lincoln
School of Life Sciences
Joseph Bank Laboratories
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Study participating centre
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Sponsor type
University/education

Website
http://www.lincoln.ac.uk/home/

ROR

https://ror.org/03yeq9x20

Funder(s)

Funder type
Charity

Funder Name
European Foundation for the Study of Diabetes

Alternative Name(s)
The European Association for the Study of Diabetes, EFSD

Funding Body Type
Private sector organisation

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

Location
Germany

Funder Name
Boehringer Ingelheim

Alternative Name(s)
Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, BI, BIPI

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal once the study concludes, analyses are completed and the final manuscript is approved by all authors. This will likely be in autumn 2025. In addition, the results will be presented at national and international conferences.

Intention to publish date
01/09/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Profs C. Hills (Chills@lincoln.ac.uk), P. Squires (psquires@lincoln.ac.uk) and K. Lee (kelvin.lee@ulh.nhs.uk) (The data shared will depend on the requests. Formal, written consent was obtained from all participants for involvement in the study and the data is stored in a pseudonymised form.)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No