Study Title: Cardiovascular Effects of Empagliflozin and Sitagliptin in Diabetes Mellitus: A crossover study

Version Number: Version 1.2

Date: January 17 2019

Chief Investigator: Professor Sven Plein

Sponsor: University of Leeds

Funder: British Heart Foundation

REC reference: 18/YH/0190

IRAS ID: 241152

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Background

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 therapy, 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 risk compared to the general population, even after adjustment for other risk factors, and this risk has proved difficult to modify. Older therapies aimed at improving glycaemic control, including the promising class of dipeptidyl peptidase-4 (DPP-4) inhibitors, which include the drug sitagliptin, have shown no significant improvement in cardiovascular outcomes. Recently, the sodium-glucose cotransporter 2 inhibitor, empagliflozin, has been shown to decrease both cardiovascular and all-cause mortality and a decrease in HF 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 physiological effects of empagliflozin on the heart in a population of patients with similar characteristics as studied in recent clinical trials[1] and compare it with the effects of sitagliptin.

We will invite patients with type 2 diabetes and known cardiovascular disease or previous myocardial infarction (MI) to take part in this study. In a cross-over study patients will receive both sitagliptin and empagliflozin and undergo serial physiological assessment, including cardiac magnetic resonance (CMR) imaging of extracellular fibrosis and quantitative adenosine stress perfusion imaging as well as assessment of diabetes status including HbA1c and fasting glucose/insulin levels. Blood sugar control will be closely monitored using a Libre Pro® – which measures sugars over a fortnight. We will be using the blinded version of the Libre Pro®, to avoid bias by the participant being able to access their results during the trial and potentially modifying their behaviour.

We aim to determine whether empagliflozin treatment in patients with recent myocardial infarction has any physiological effects in the heart that are measurable with CMR.

Project Hypothesis

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

Study Design

Overview

We will recruit patients who have been diagnosed with an MI or who have a diagnosis of coronary artery disease as specified in the inclusion criteria. Recruitment will take place at the Leeds Teaching Hospitals and the Mid Yorkshire Hospitals NHS Trusts. Patients will be approached in person during their hospital admission or in outpatient clinics. Once discharged they may be approached with an initial telephone call followed by written information sent by post or email.

Each patient will undergo a comprehensive CMR study and blood tests at baseline. The first CMR scan will take place at least 2 months after the patient's **MI, angiography +/- PCI, or unstable angina**. Participants will be randomised as to the order of treatment and receive 3 months therapy with empagliflozin and with sitagliptin. They will have a further CMR scan and blood tests at the end of each 3-month period (3 scans in total). All study interventions will take place in Leeds. The study timeline and interventions are outlined below:

Study Visits

Overview - table of visits

	Baseline				Randomisation				
VISIT	1A	1B	2	3		4	5	6	7
Week			-2 weeks (±7 days)	0	Day 0 **at least 2 months MI, angiography +/- PCI, or unstable angina**	Week 10 (±7 days)	Week 12 (±7 days)	Week 22 (±7 days)	Week 24 (±7 days)
Assessments									
Identification and initial approach	X								
Eligibility criteria checked	X								
Written informed consent	X								
Imaging criteria met (echo or CMR)		X		X					
Venepuncture			X			X		X	
Libre Pro fitting			X			X		X	
Clinical history (medical history, CVS risk factors			X						
Medication list			X	X			X		X
Cardiac MRI				X			X		X

Randomisation					X				
Study medication prescribed and dispensed					X		X		
Study medication compliance checks						X	X	X	X

Visit 1A

The following procedures and assessments will be carried out at the screening visit:

- Written informed consent

1B

- Check clinical echocardiogram for left ventricular function if required – patients excluded at this stage if ejection fraction (EF) ≤40%, or dysfunction is severe (where not assessed quantitatively). Ejection fraction is a measure of ventricular function and likely related to the amount of scar present.

Visit 2 (week -2 ±7 days)

The following procedures and assessments will be carried out:

- Venepuncture: 15mls (Serum insulin and glucose, FBC, U&E, HbA1c). Fasting sample.
- Libre Pro fitting.
- Clinical history: relevant medical history and risk factors, current medication list.

Visit 3 (week 0) – at least 2 months after MI, angiography +/- PCI, or unstable angina

The following procedures and assessments will be carried out:

- Removal of Libre Pro
- CMR scan 1
- Review of CMR to assess degree of scar and determine whether to continue in study (>25% transmural infarcted myocardium to be excluded).
- Check current medication list
- Randomization
- Prescribe medication by CI/co-investigator
- Dispense study medication and issue patient diary

Visit 4 (week 10 ±7 days)

The following procedures and assessments will be carried out:

- Venepuncture: 15mls (Serum insulin and glucose, FBC, U&E, HbA1c). Fasting sample.
- Libre Pro fitting
- Check current medication list and patient clinical status
- Check study medication compliance (diary review)

Visit 5 (week 12 ±7 days)

The following procedures and assessments will be carried out:

- Removal of Libre Pro
- CMR scan 2
- Check current medication list and patient clinical status
- Prescribe medication by CI/co-investigator
- Dispense study medication
- Check study medication compliance (diary review)

Visit 6 (week 22 ±7 days)

The following procedures and assessments will be carried out:

- Venepuncture: 15mls (Serum insulin and glucose, FBC, U&E, HbA1c). Fasting sample.
- Libre Pro fitting.
- Check current medication list and patient clinical status
- Check study medication compliance (diary review)

Visit 7 (week 24 ±7 days)

The following procedures and assessments will be carried out:

- Removal of Libre Pro
- CMR scan 3
- Check study medication compliance (diary review)

Primary Outcome

1. Myocardial perfusion reserve in remote myocardium

Secondary Outcome

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

Patient Selection

Inclusion criteria

- Type 2 diabetes mellitus
- Metformin as single or dual therapy
- Presence of at least one out of the below four high risk cardiovascular events:
    - Previous heart attack
    - Evidence of multi-vessel coronary artery disease (≥2 major coronary arteries or the left main coronary artery), documented by any of the following:
        - – Presence of significant stenosis: ≥50% luminal narrowing during angiography
        - – Previous revascularization
        - – The combination of revascularization in one major coronary artery and significant stenosis (≥50% luminal narrowing) in another major coronary artery
    - • Evidence of single-vessel coronary artery disease, ≥50% luminal narrowing during angiography, not subsequently successfully revascularized, with at least 1 of the following:
        - – A positive non-invasive stress test for ischemia
        - – Hospital discharge for unstable angina ≤12 months prior to consent
    - • Unstable angina with evidence of single- or multi-vessel coronary artery disease

- HbA1c >48mmol/mol (>58 mmol/mol if on a sulphonylurea) within 3 months of recruitment
- 18-84 years old
- Ability to provide informed consent

Exclusion criteria

- Previous coronary artery bypass grafting (CABG)
- Need for further revascularisation
- Type 1 diabetes mellitus or previous diabetic keto-acidosis
- Current treatment with sitagliptin or empagliflozin
- Contra-indication to CMR scanning (some pacemakers, intraorbital debris, intraauricular implants, intracranial clips etc.)
- Contra-indication to Adenosine (severe asthma)
- Known allergy to contrast medium (gadolinium)
- Renal dysfunction with eGFR<60
- Obesity where girth exceeds the scanner bore
- Pregnancy or breast-feeding
- Inability to lie flat for CMR scan

For all patients recruited to the study basic demographic data, cardiovascular risk factors, current medications, duration of diabetes and presences of diabetes microvascular complications will be collected. Following inclusion in this study, clinical echo will be checked if required, and the participant will not progress further in the study if there is severe LV dysfunction, or EF <40%. If there is a large proportion of transmural infarction of the initial CMR scan (>25%), these participants will not proceed to randomisation.

CMR Protocol

CMR will be performed on a dedicated cardiovascular 3.0 Tesla Siemens Prisma system. As per routine clinical imaging, an intravenous cannula will be inserted, and heart rate, blood pressure and ECG monitored. The CMR scan takes approximately 60 minutes and comprises:

1. Scout images to determine left ventricular short axis.

2. LV function (cine) imaging in standard long and short axis planes using a fast gradient echo sequence; 10-12 slices; 30 phases; 10/0mm; to assess regional and global LV function (free-breathing with MOCO or breath-holds of 5 seconds depending on individual patients)

3. Native T1 mapping; 5s3s MOLLI; 3 slices; (breathhold 11 seconds)

4. Adenosine stress perfusion imaging; 140mcg/kg/min will be administered through a peripheral intravenous cannula for 3 minutes, as per routine clinical practice; Blood pressure recorded every two minutes and continuous ECG monitoring; when heart rate increased >10% and symptoms of adenosine are observed, a bolus of 0.05mmol/kg non-ionic gadolinium based contrast (Gadovist®) is given. Myocardial perfusion will be assessed with a T1-weighted saturation-recovery-prepared gradient echo sequence in 3-4 short axis slices; 60-90 dynamic images per slice acquired; free-breathing with MOCO.

5. Right ventricle (RV) function (cine) imaging in the axial plane; using a fast gradient echo sequence; 22-26 slices; 30 phases; 6/0mm (free-breathing with MOCO or breath-holds of 5 seconds depending on individual patients)

6. Rest perfusion imaging; pulse sequence and geometry identical to stress imaging described above without administration of adenosine

7. Top up of further 0.05 mmol/kg non-ionic gadolinium based contrast (Gadovist®)

8. Late gadolinium enhancement using a T1-weighted, segmented inversion-recovery sequence in multiple planes 6 minutes after contrast (free-breathing with MOCO)

9. Post-contrast T1 maps exactly 15 minutes after contrast administration; 4s3s2s MOLLI (breathold 12 seconds)

10. In some patients, additional images may be acquired to obtain the required information.

CMR interpretation

From CMR data, the following quantitative measurements will be obtained:

1. LV/RV volumes and ejection fraction, and LV mass.

2. Segmental measurement of native T1 and extracellular volume

3. Quantitative assessment of myocardial blood flow at stress and rest for calculation of global and segment myocardial blood flow (MBF) and MPR.

4. Segmental quantification of presence of and percentage of focal scarring on late gadolinium enhancement

5. Aortic dimensions and distensibility

Blood samples

Fasting blood samples will be taken for the measurement of serum insulin and glucose and calculation of HOMA-IR. These will be frozen, and analysed at the end of the study in a batch. FBC, U&Es and HbA1c will be measured prior to the CMR scan to confirm diabetes status, and ensure there is no contraindication to contrast agent administration.

Statistical analysis

Statistical analysis will be performed by the investigating team and health statisticians at the University of Leeds. This is a pilot study. Change, or degree of change, in MBF, MPR and tissue characteristics following treatment with empagliflozin are not known. A sample size of 40 would allow us to detect a change in MBF or 12% with a power of 80% and an alpha error of 0.05 in a normal healthy population. This change would be higher than the known within subject variation for MBF. Variation within the CAD population is likely to be higher and to allow for this and dropout, we estimate a sample size of 60 would be required.

Study Drug Treatment

Empagliflozin

Empagliflozin is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise or in addition to other medicinal products for the treatment of diabetes.

Contraindications

Diabetic ketoacidosis. Hypersensitivity to the active substance or to any of the other ingredients.

Side effects

Genital infection; hypoglycaemia (in combination with insulin or sulfonylurea); polyuria; pruritus; urinary tract infection (interruption of treatment in complicated UTI), dysuria; volume depletion

Frequency and duration

Empaglifozin 10mg once daily

Sitagliptin

For adult patients with type 2 diabetes mellitus, sitagliptin is indicated to improve glycaemic control as dual oral therapy in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.

Contraindications

Hypersensitivity to the active substance or to any of the other ingredients.

Side effects

Gastro-intestinal disturbances; nasopharyngitis; pain; peripheral oedema; upper respiratory tract infection, anorexia; dizziness; drowsiness; dry mouth; headache; hypoglycaemia; osteoarthritis, cutaneous vasculitis; pancreatitis (discontinue in acute pancreatitis); rash; Stevens-Johnson syndrome.

Frequency and duration

Sitagliptin 100 mg once daily

Administration / handling of the trial drugs

The study drug will be prescribed and dispensed by the study centre. Instructions as to how and when to take the prescribed medication in its licensed dose will be issued at the time of enrolment. A diary will be issued at the time of enrolment for subjects to record taking the medication, to assess compliance with treatment.

Monitoring and Dose Modifications

Recommended monitoring for both empagliflozin and sitagliptin is to check renal function prior to initiation and periodically throughout administration – stated as at least yearly for empagliflozin and periodically for sitagliptin. We will check U&Es prior to initiating medication and prior to each CMR scan; each visit, therefore prior to initiation and after 10 weeks of treatment (2-3 weeks before each scan).

Patients would be advised regarding potential side effects listed above as per usual clinical practice.

Drug Supply

The study drugs will be prescribed and dispensed by the study centre.

Withdrawal of Treatment

Treatment will be withdrawn if contra-indications to continued administration develop. Unexpected reactions to the medication will be recorded and may lead to the patient being withdrawn from the study.

Serious Adverse Events Procedures

General Definitions

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this treatment and can include;

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

An **adverse reaction (AR)** or **adverse drug reaction (ADR)** is any untoward or unintended responses to a study drug related to any dose administered to that subject. All AEs judged by either the reporting investigator or the Sponsor as having reasonable causal relationship to a medicinal product

qualify as adverse reactions. The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship.

An **unexpected adverse reaction (UAR)** is any adverse reaction the nature and severity of which is not consistent with the information about the study medication in question set out in the listed side effects.

A **suspected, unexpected serious adverse reaction (SUSAR)** is an adverse reaction that is both unexpected and serious. An adverse reaction is “unexpected” if its nature or severity is not consistent with the Reference Safety Information.

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study and will be classified as **expected adverse reactions**. For a full list of expected side effects of sitagliptin and empagliflozin, please refer to the lists previously in this document (4.1.2 and 4.2.2).

In addition the following criteria may be used in order to collect protocol-defined reportable adverse events which do not meet the criteria for serious (below):

- requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to body structure.

A **serious adverse event (SAE)** or **serious adverse reaction (SAR)** is defined in general as “any untoward medical occurrence or effect that:

- results in death,
- is life-threatening*,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- consists of a congenital anomaly or birth defect,
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

**the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.*

A SAE occurring to a research participant, where in the opinion of the Chief Investigator the event is Related and Unexpected will be reported to the main Research Ethics Committee (REC). The National Research Ethics Service (NRES) defines Related and Unexpected SAEs (RUSAEs) as follows:

- *Related*: that is, it resulted from administration of any research procedures; and
- *Unexpected*: that is, the type of event is not listed in the protocol as an expected occurrence.

Causality

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to the trial medications (i.e. definitely, probably or possibly related) are considered to be adverse reactions. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the REC and other bodies will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Severity

Severity of all AEs and ARs will be graded on a three-point scale of intensity (mild, moderate, severe):

Mild	Discomfort is noticed, but there is no disruption of normal daily activities.
Moderate	Discomfort is sufficient to reduce or affect normal daily activities.
Severe	Discomfort is incapacitating, with inability to work or to perform normal daily activities.

Note: An AE or AR may be severe but not serious

Operational definition and reporting period for AEs and SAEs

Expected AEs/SAEs – Not reportable

Due to the nature of CHD and its treatment, and diabetes, patients are likely to experience several adverse events throughout the course of the disease. The patient population may also have co-morbid disease and as such in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected.

In recognition of this, events fulfilling the definition of an adverse event or serious adverse events will not be reported in this study unless they are classified as 'expected' (section 5.2.2) or 'unexpected' and 'related' (section 5.2.3).

Expected AEs/SAEs – Reported within standard CRFs

The following SAEs are expected within the study population and will be reported by the clinical research team using standardised test and follow-up CRFs including:

- Complications related to any study test that requires a specific treatment or hospital admission
- Acute Coronary Syndrome
- Unplanned revascularisation procedure (PCI with or without stenting, CABG)
- Any admission for CV cause including heart failure, cardiac arrhythmia, suspected cardiac event, acute CHD hospitalisation, stroke/TIA (cerebrovascular)
- Hypoglycaemia
- Other known side effects of study medications
- Any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration
- Routine treatment or monitoring of the studied indication (i.e. diabetes and coronary artery disease), not associated with any deterioration in condition
- Elective or scheduled treatment for pre-existing conditions that did not worsen during the study
- Death

These events are expected within the study population and will not be subject to expedited reporting to the main REC. All non-serious or expected adverse events will be recorded on the study CRF at the follow-up visits 5 and 7. They will however, be included in the annual safety report provided to the main REC.

Related and Unexpected SAEs – Expedited Reporting

In keeping with HRA guidelines, reports of Serious Adverse Events (SAEs) or Serious Adverse Reactions (SARs) that are:

- related to the study (i.e. they resulted from administration of any of the research procedures) and
- unexpected (i.e. not listed in the protocol as an expected occurrence)

will be submitted to the REC using the HRA Non-CTIMP safety report to REC form within 15 days of the chief investigator becoming aware of the event and will be reported to the sponsor within 1 working day of the research team becoming aware of the event.

Events will be followed up until the event has resolved or a final outcome has been reached.

References

1. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. Zinman et al. NEJM 2015; 373: 2117-2128