

Cardiovascular Effects of Empagliflozin in Diabetes Mellitus

V 1.3 January 17 2019

CI: Professor Sven Plein

PARTICIPANT INFORMATION SHEET

Dear Participant,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Purpose of the study

In this study, we are looking at the effects of diabetes medication on the structure and function of the heart. We know some of these medications seem to reduce the risk of patients having heart problems, but we do not know how they do this. We are asking patients with diabetes who have had a heart attack or have heart artery disease to take two different medications that are already widely in use, and we will use MRI to look at the heart after the treatment.

Magnetic Resonance Imaging (MRI) is a test which produces detailed pictures of your internal organs by putting you within a strong magnetic field. With Cardiac MRI we are able to detect several important abnormalities that are caused by heart disease, for example the scarring of the heart from heart attacks and the restrictions of blood flow to the heart muscle that lead to angina. Also, MRI produces pictures of the heart with much greater detail than with other types of heart scans. Importantly, MRI is also a safer test than most other heart

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scans, because it does not expose patients to any harmful radiation and pictures of the heart can be taken “from the outside”. Because of all of these qualities, MRI has become an important test in patients who suffer with different types of heart disease. We have been doing MRI scans of the heart in Leeds since 1995. We are continuously carrying out research into improving the images and thereby improving patient care.

Why have I been chosen?

This study is looking at people like you, who have a diagnosis of diabetes, and have had a heart attack or a diagnosis of coronary artery disease. We are hoping to recruit 60 participants into this study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive from the NHS. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

What will happen to me if I take part?

All the study visits take place at the Leeds General Infirmary. All patients in this study will have three MRI scans. If you have had a heart attack or a stent fitted, we will do the first scan no earlier than 2 months after this. Prior to the MRI scan, you will need a set of blood tests. We will ask you some questions about your diabetes and medical history. We will also review any heart ultrasound scan you may have had as part of your clinical care. In the event that you are not able to take part in the study because of your blood or ultrasound results we will inform you by telephone and/or letter.

After the first scan we will add another diabetes medication to your current treatment. This will be either empagliflozin or sitagliptin. Both are established diabetes medications that are commonly used. This will only be done if your blood tests show that your diabetes could be better controlled and if doctors would usually recommend an additional medication.

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We may use the blood tests from your hospital admission or follow up to decide this; but otherwise will use blood tests taken on your first visit for this study.

We want to compare the effect of different treatments on how well the heart works, so you will have received a 3 month treatment period on each of 2 different diabetes medications. The order in which you receive these medications will be randomised, but everyone taking part will receive both; this is called a crossover study. At the end of each 3 month treatment, you will have another MRI scan (3 scans in total during this study). During the treatment we will ask you to keep a record (which we supply you with) that you are taking your medication each day.

We will take blood samples to be analysed as part of the research, this will be 10mls (2 teaspoons) on 3 occasions. We will ask you to come fasting for these tests. We will measure your blood count, diabetes status and renal function. We will store part of these samples and analyse them at the end of the study for additional markers of your diabetes.

Your blood sugars will also be monitored using a patch that is stuck to your skin and remains there for up to 2 weeks. You would need to attend hospital for this to be attached and removed, but we would coordinate this with your other blood tests and MRI scans to minimise any inconvenience. A table of the visits and your involvement in this study is included below.

The MRI scans will each take approximately 60 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of magnetic fields and radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images of your heart, though we do protect your ears with headphones. You can listen to the radio, or to one of your own CDs. We will remain in communication with you throughout the scan. During the scan, we will inject an MRI contrast medication into a vein in your arm. At one point, we will also inject a medication (Adenosine) into a vein in your other arm, which is a drug to increase the blood flow to your heart. This medication is used routinely in many heart tests. For the injections, we will insert two small tubes (cannulae) into a vein in your arm.

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Visit	What will happen	Time point in study
1/2	Written consent to take part in study. Research team will check the result of your clinical echo scan Blood tests and fit blood sugar monitor.	Week minus 2
3	Remove blood sugar monitor First CMR scan Prescription for medication (if blood tests and CMR result show you meet the criteria for this study)	Week 0
4	Blood tests and fit blood sugar monitor.	Week 10
5	Remove blood sugar monitor Second CMR scan Prescription for medication	Week 12
6	Blood tests and fit blood sugar monitor.	Week 22
7	Remove blood sugar monitor Final CMR scan	Week 24

Risks and discomforts

Magnetic Resonance Imaging (MRI) at 3 Tesla is safe and no x-rays or radiation is used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning. The contrast medication we use during the scan is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort, these are symptoms we expect to happen. However,

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all of these feelings usually subside within one or two minutes or even more quickly when the medication is stopped. In a small number of people (about 7 in 100) adenosine can cause temporary changes in heart rhythm, if this happens stopping the adenosine will bring the heart rhythm back to normal immediately. A doctor is present all the time during the MRI scan to make sure you are comfortable.

All medications can cause side effects, so it is possible you will experience these with the new diabetes medications. Both medications that we are using are used commonly in medical practice, they are not experimental medications. We are using them in the same way they would normally be prescribed; the only difference is that you will be more closely monitored by being part of this research. As usual, these tablets will come with information on how to take them and possible side effects to look out for. We will ask you to fill in a form each day to confirm that you have taken the tablet.

Wearing a Libre Pro monitor (blood sugar monitor) should not cause any discomfort, although occasionally patients may find this annoying. We would position it in a location where it would cause the least problems. It is not recommended that the Libre Pro monitor is kept underwater for longer than 30 minutes, or worn during strenuous exercise, so we would advise you to avoid these during the 2 week period you wear it. You will not be able to see immediate results of the blood sugar monitoring, they will be available to us at the end of the trial when we analyse all your results.

Benefits to you

This study does not form part of your normal clinical care and is done solely for research purposes.

At the end of the trial we will be able to tell you and your GP which of these diabetes medications gave you better blood sugar control, so that you can discuss this and continue to take the medication that worked best for you.

Abnormal & Incidental Findings

It is unlikely that the scan will detect clinically significant cardiac abnormalities. However, should this occur your GP will be informed in writing and they will be able to arrange further

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investigation and treatment if necessary. If you have private medical insurance it is possible the finding of significant cardiac abnormalities could have an impact on your cover.

Expenses

We will provide reasonable travel expenses should this be necessary for you to attend the MRI scan. We are also happy to arrange transport to the hospital and return you home if needs be.

Will my taking part be kept confidential?

All information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored, electronically on the Leeds Teaching Hospitals NHS Trust secure server, and on paper, under the provisions of the 2018 Data Protection Act. The data collected will be coded and your personal details will be kept separately. You will not be identified in any publication that may result from this research. We will not retain your personal details after the end of this study. If we keep any of your serum samples these will be stored in -80°C freezers in a secure environment, in Leeds Teaching Hospitals NHS Trust Research laboratories, these will only be stored for the duration of this study.

With your permission, we will inform your GP of your participation in the study. If any unexpected abnormality or condition were found we would inform your GP.

If you withdraw consent from further study follow-up, or if you were to become incapacitated, any data collected about you up to that point will remain on file and will be included in the final study analysis.

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Leeds Teaching Hospitals NHS Trust, on behalf of the University of Leeds, will keep identifiable information about you for the purpose of the study for 15 years after the study has finished. This information will not be held by the University of Leeds.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already

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obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at http://www.leeds.ac.uk/secretariat/data_protection.html

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the [UK Policy Framework for Health and Social Care Research](#).

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

What will happen to the results of the research study?

When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

Indemnity/Compensation

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

The research organisation

This is a research project of the Cardiac MRI department at the Leeds General Infirmary and the University of Leeds.

Who has reviewed the study?

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The study has been reviewed and approved both by a nationally approved Research Ethics Committee and your hospital Research and Development Office. More details can be provided, on request, by your study doctor.

Contact details:

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CONSENT FORM v 1.3 January 17 2019

Chief Investigator: Professor Sven Plein

Subject Study Number:

Subject Initials.....

Please initial boxes

1. I have read the Participant Information Sheet dated January 17 2019 (version 1.3) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason. ☐
3. I give my consent for my General Practitioner and other doctors looking after me to be informed. ☐
4. I understand that data and images collected will be stored on an NHS computer system, and, after my personal details have been removed, may be sent to participating study centres or to an independent laboratory, and may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA.

Yes	No
<input data-bbox="1217 1227 1340 1301" type="checkbox"/>	<input data-bbox="1353 1227 1476 1301" type="checkbox"/>
5. I understand that relevant sections of my medical notes and data collected during the study (including personal data) may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
6. If I were to lose capacity or withdraw consent for further follow-up I understand that identifiable data already collected will be kept and used for the purposes of the study. ☐
7. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

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8. I am willing to be contacted again in the future to receive information about the publication of this study.

Yes

No

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9. I would like to receive a summary of the final results when they are available.

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10. I give my permission for my data to be used in future related studies

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Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date.....

1 copy for patient, 1 copy for medical records and 1 copy for Investigator Site File

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