EMPA-KIDNEY Magnetic Resonance Imaging Substudy Protocol Supplement

Study Title: A multicentre international randomized parallel group double-blind placebo-controlled clinical trial of EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease

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Summary

This document is a substudy protocol supplement which provides the rationale, design and key operation details of an EMPA-KIDNEY substudy to image a subset of participants' hearts and kidneys using multi-parametric magnetic resonance imaging. This protocol substudy document is only relevant to sites participating in the substudy and does not alter the main protocol in any respect. The procedures in the main protocol should be followed irrepsective of whether a participant joins this substudy or not.

Background

The EMPA-KIDNEY study is investigating whether empagliflozin 10 mg daily reduces the risk of a cardiorenal composite outcome among patients with established chronic kidney disease. Trials in other populations indicate that sodium-glucose co-transporter-2 inhibitors (SGLT-2i, like empagliflozin) do reduce the risk of progression of kidney disease and heart failure (including cardiovascular death) among people with diabetes, diabetic kidney disease and – more recently – heart failure with reduced ejection fraction (including patients with and without diabetes). However, substantial uncertainty remains for many types of patients with chronic kidney disease (CKD) and diabetes excluded from these trials and for patients with CKD but without diabetes.

EMPA-KIDNEY and the other SGLT-2i trials will provide clear evidence of the clinical safety and efficacy of SGLT-2i, but the mechanisms by which these effects occur remain uncertain. Many different mechanisms have been proposed to explain the observed benefits to date, but much of this work relies on animal models and whether these mechanisms operate in humans has not been confirmed. Magnetic resonance imaging (MRI) offers an opportunity to assess the effects on structure and function of the heart and kidneys in patients with CKD.

MRI allows detailed imaging of organs without ionizing radiation. Cardiac MRI is well-established both in research and clinical care and provides accurate assessment of cardiac structure and function. It has frequently been used to assess the effects of treatments on cardiac structure (e.g. left ventricular mass) and function (e.g. cardiac output) for patients with cardiac disease. Patients with CKD develop abnormal cardiac structure and function early in their disease and it is likely that such abnormalities underlie some of the large excess risk of cardiovascular morbidity and mortality observed in this population. However, few studies to date have tested the effect of treatment in a randomized comparison on cardiac MRI among patients with CKD.

MRI of the kidney is a newer discipline and is currently a research tool only. There are many different MRI methods that can visualize different aspects of kidney structure and function and their combination is called “multiparametric” MRI. Examples of methods and what they assess are shown in Table 1.

MRI method	Target measure
Volumetry	Kidney size, cortical thickness
T1 mapping	Fibrosis (scarring) and inflammation of kidney
Blood oxygen level dependent (BOLD)	Kidney oxygenation
Arterial spin labelling (ASL)	Kidney perfusion
Diffusion-weighted imaging (DWI)	Fibrosis of kidney
Modified Dixon (mDIXON)	Fat content

Table 1: Examples of MRI methods and what they assess

Small studies have demonstrated that kidneys in healthy volunteers have different measurements to kidneys in patients with CKD. For example, one study found that the mean T1 time among healthy volunteers was 1432 (SD 87) ms, whereas among patients with CKD it was 1574 (SD 74) ($p<0.001$).[1] Cortical perfusion (measured by arterial spin labelling) was lower among patients with CKD (71 [SD 49] mL/100g/min) than healthy volunteers (200 [SD 56] mL/100g/min) ($p<0.001$). It is therefore plausible that treatments that retard the progression of kidney disease may also delay changes in MRI parameters. Furthermore, such MRI parameters could be used to either stratify risk or provide additional early data on new drugs during their development. MRI is safe and none of the planned measurements require injection of any contrast or other agents.

UK capability

The UK has a Renal Imaging Network (RIN; https://kidneyresearchuk.org/research/research-networks/uk-renal-imaging-network/) which is funded by the UK Medical Research Council and is undertaking a project to standardize approaches to renal MRI. This collaboration of centres (most of

whom are collaborating in the EMPA-KIDNEY trial) mean the UK is ideally placed to host this research. This proposal has been written by a collaboration of EMPA-KIDNEY investigators and members of the UK RIN. In addition, it may be possible to involve some other international centres although this has not been discussed yet.

Aims

The primary aim of this substudy is to use multiparametric MRI to assess, in a subset of EMPA-KIDNEY participants, the effect of empagliflozin 10mg versus matching placebo on kidney cortical T1 at 18 months after randomization.

Secondary aims are to use multiparametric MRI to assess:

1. The effects of empagliflozin 10mg versus matching placebo at 18 months on:
    - Kidney size and cortical thickness
    - Kidney perfusion (measured by arterial spin labelling)
    - Kidney oxygenation (measured by BOLD)
    - Kidney fat content (measured by mDIXON)
    - Cardiac structure (left ventricular mass, standard volumes)
    - Cardiac function (left ventricular ejection fraction, cardiac output)
    - Cardiac fibrosis (measured by T1)
2. Whether any effects of empagliflozin 10mg versus matching placebo on kidney fibrosis are modified by baseline factors, in particular by level of kidney function, glycosylated haemoglobin, body mass index, age, sex and RAS inhibitor use

Exploratory aims are to assess the effects of empagliflozin 10mg versus matching placebo at 18 months on less well-established MRI measurements (for example diffusion tensor imaging) which may only be measured in a subset of participants.

Sample size estimates

The original plan was to perform two scans in each participant: one at baseline and one at about 18 months after Randomization. Because of the COVID-19 pandemic it was not possible to perform baseline scans and recruitment to the main trial is now very nearly complete. However, it is still feasible to make the planned comparisons using a single scan during Follow-up (at least 18 months after Randomization). Instead of using the planned ANCOVA analysis (where the 18 month measurements are adjusted for baseline), we will use unadjusted measurements. This reduces the precision somewhat so a larger sample size is required.

It was estimated that at least 64 (of the 6000) EMPA-KIDNEY participants with baseline and 18 months follow-up MRI data will provide ample power (>90%, 2p=0.05) to detect at least a 50 ms difference in T1 (assumed reference range in healthy adults is 1500 ms with a standard deviation of 100 ms and intra-individual correlation of 0.8) based on analysis of covariance (ANCOVA). By changing the design to a single scan, approximately 172 participants are required for equivalent statistical power.

Data Analysis Plan

The primary analysis will estimate the differences in cortical T1 between treatment groups at ~18 months, regardless of whether a participant received all, some or none of their allocated treatment (i.e. intention-to-treat analyses). Secondary outcomes include kidney volumes, perfusion and oxygenation and cardiac structure and function. Differences in cortical T1 and the secondary outcomes between treatment groups will be adjusted (or stratified) for the elements included in the main trial's minimization algorithm. Missing measurements will be imputed. Results from the imputed analyses will be compared with those from equivalent "complete-case" analyses, but primary emphasis will be placed on the results after multiple imputation. More complete details of statistical methods, including definitions of subgroups, methods of any imputation, approaches to adjustments and weighting of averages will be set out in a separate full Data Analysis Plan which will be consistent with the main study Data Analysis Plan.

Flowchart of Substudy Activities

INVITATION
• Invite potential participants after Screening visit complete and participant has entered pre-randomization Run-in phase; OR • Invite potential participants around time of 18 or 24 month Follow-up visit (when a baseline scan was not possible)
INFORMED CONSENT AND BASELINE SCAN
• Written informed consent is sought from willing individuals when they attend for first MRI scan
18 MONTHS OF FOLLOW-UP
• Second MRI scan performed around time of 18-24 month follow-up visit

Design

Eligibility: In selected regions, EMPA-KIDNEY Local Clinical Centres (LCCs) with access to an appropriate MRI scanner will be invited to join this optional substudy. The only exclusion criteria are those for a standard MRI scan:

- Cardiac pacemaker
- Any unfixed metallic implant or metallic fragments
- Excessive tattoos
- Fear of closed spaces or claustrophobia
- Absence of one kidney

Invitation: Potential participants will be invited to join this substudy before the time of their Randomization Visit. If baseline scans were not possible (eg, due to COVID-19), participants will be invited around the time of their 18 or 24 month Follow-up visit for a single scan. If participants are interested the Research Coordinator will explain the substudy to potential participants using the Participant Information Leaflet and Consent Form. Consenting participants will then have an appointment made to attend for their MRI scan.

Methods: The MRI scanning staff will double-check the suitability of the patient for an MRI scan and explain what it will involve. The participant will need to hold their breath at certain points during the process. The planned MRI scans take about 1 hour to complete.

Analysis: The MRI data from all sites will be uploaded to an online secure platform (as used by other NHS services such as the Dementias Platform UK) and analysed by a standard pipeline. No participant data are required to be transferred with the scan (except for their de-identified unique study ID). The results will then be provided to the study statisticians at the University of Oxford for analysis. Patients from Oxford may have some of their MRI data also transferred to Perspectum Diagnostics who will process the data and provide results to University of Oxford staff. Basic demographic, medical history and laboratory details will be provided to staff at the University of Oxford and Perspectum Diagnostics to facilitate analysis of the exploratory aims. The primary analyses will not be conducted until the end of the main trial because only at this time will the unblinded treatment allocation become available.

References

1. Buchanan CE, Mahmoud H, Cox EF et al. *Nephrol Dial Transplant* 2019; doi 10.1093/ndt/gfz219