Author’s response to reviews

Title: Does Dapagliflozin Regress Left Ventricular Hypertrophy in Patients with Type 2 Diabetes? A Prospective, Double-blind, Randomised, Placebo-Controlled Study

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[05/08/2017]

Dear Editor

Thank you for your positive review of our manuscript. We wish to resubmit our manuscript entitled “Does Dapagliflozin Regress Left Ventricular Hypertrophy in Patients with Type 2
We can confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere.

We submit a revised manuscript addressing the reviewer’s comments as detailed below.

Reviewer 1

1. Patients included in the study will be diabetic normotensives (without antihypertensive drugs) and well-controlled hypertensives (with antihypertensive drugs). This should be better specified. A run-in period to optimize blood pressure control should be considered before starting the study and a 24h not 16h ABPM should be used to confirm a good blood pressure control. Specify protocol for in-office blood pressure measurement.

At screening, blood pressure will be taken using a Omron M10-IT blood pressure monitor and eligible patients will have a blood pressure of 145/90mmHg averaged over three readings. Such patients who require optimisation of their blood pressure will do so but will have to be stable on their antihypertensive medications for three months prior to enrolment. Patients with borderline office blood pressure will undergo ambulatory blood pressure measurement (AMBP) This will be performed using a Spacelab 90217 ambulatory blood pressure monitor. Inclusion will be possible with a twenty-four hour mean blood pressure <140/85 mmHg.

2. Are new onset diabetic patients included? How author will manage therapy in these patients?

New onset diabetic patients are not included in this study as sodium glucose linked transporter 2 inhibitors are currently only licensed as second line therapy. Patients in this study are therefore known diabetic patients who have already been established on another oral hypoglycaemic agent such as metformin.
3. Screening for left ventricular hypertrophy should be performed also with ECG criteria that should be indicated. Also author should specify ASE criteria for diagnosing LVH (echocardiographic method, indexing for body surface area, for height, etc.)

Whilst the electrocardiogram (ECG) is relatively specific it lacks sensitivity in diagnosing LVH hence echocardiography is more of a gold standard than ECG and will be used in this study to screen for LVH. Echocardiographic LV hypertrophy will be defined as either an LV mass index of >115g/m2 for men and >95g/m2 for women indexed to body surface area or > 48g/m2.7 or 44g/m2.7 when indexed to height2.7. This is specified in the inclusion criteria within the manuscript

4. In the paper study will end in May 2017! In clinicaltrial.gov this end is in December 2018. Please specify a correct study end date.

We have amended the trial end date in the manuscript to May 2019 and have also updated clinicaltrial.gov following our recent protocol amendment

5. Describe in detail how will you perform ABPM measurements: protocol, daytime and nighttime hours and blood pressure cut-off values, number of valid measures for an acceptable exam, etc.

Participants enrolled in the trial will be asked to undergo 24 hour ambulatory BP monitoring using a Spacelab 90217 ambulatory monitor. Examinations with greater than 50% successful readings will be deemed an acceptable examination.

6. Specify in detail laboratory methods for measuring analytes for research purposes. Specify what FRI means and how it is measured. Specify how will you assess eGFR and if 60 ml/min will be also indexed for 1.73 m2
FIRI is fasting insulin resistance index and is a simple well accepted index of insulin resistance.

The biomarker samples will be centrifuged and decanted into an aliquot which will be stored at -80°C. Uric acid will be analysed with an elisa method using SIGMA-ALDRICH assay, UK. BNP will be measured by a MULTI-ARRAY system. The kit is from MESO SCALE DISCOVERY, USA. FIRI will be analysed with an elisa method using an ALPCO assay. UK eGFR will be assessed using an abbreviated MDRD equation and will be indexed to 1.73m2.

7. Specify magnetic resonance protocol to assess LVH in patients

Short axis images from the atrio-ventricular ring to the LV apex will be acquired using a 2D ECG-gated breath hold segmented SSFP cine sequence with retrospective gating. Quantitative measurement of LV mass, ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (SV) will be derived by region of interest contours placed around endocardial and epicardial LV borders at end systole and end diastole.

8. Specify protocol for measuring CMRI visceral and subcutaneous abdominal fat mass

For measurement of subcutaneous adipose tissue (SCAT) and visceral adipose tissue (VAT) two successive axial 3D DIXON volume interpolated breath hold examination sequences will be acquired. These sequences will cover an anatomical area from the diaphragm to the pelvic floor, with a slice thickness of 3mm and up to 88 slices (dependent on patient size) collected within a single 3D block.

For image analysis the 'fat only' DIXON MR images will be segmented using Analyze (Mayo Clinic) software, and the SCAT and VAT compartments are defined using a signal intensity threshold method with manual correction where required. Epicardial fat structures and fat associated with the vertebrae will both be omitted from the final calculated volumes.
9. Specify details of instruments that you use for echocardiography, magnetic resonance, office blood pressure, and ABPM.

Echocardiography will be performed using a Philips Epiq 7 machine by a fully trained operator.

Cardiac MRI will be performed using a 3T Magnetrom Trio scanner [Siemens, Erlangen, Germany]

Office blood pressure will be taken using an Omron M10-IT blood pressure monitor

Ambulatory blood pressure measurements will be carried out using a Spacelab 90217 ambulatory monitor

10. What's the meaning of matching placebo? Is this a matched pair randomization design?

In the trial the patients will be randomised to either dapagliflozin or placebo. Matching placebo refers to the fact that the placebo arm will receive a tablet which appears identical to dapagliflozin but will be made up of lactose as described in the manuscript.

11. Specify units of measurement of body mass index

The units for body mass index are kg/m2 and this has been added to the manuscript

12. I further suggest authors to check and state whether the study is in agreement with the CONSORT guidelines for enhancing the quality and transparency of health research.

We can confirm that the study is in agreement with the CONSORT guideline for enhancing the quality and transparency of health research
Reviewer 2

I suggest that the definition of a significant reduction in LV mass is pre-specified in the methods

As requested this information is now in the sample size section of the methods section.

In addition to the changes made as detailed above we have also included the changes to our study protocol following a recent substantial amendment. These include;

1. Increasing our age limit to 80 years old

2. Reducing our HbA1c cut off for inclusion to 48mmol/mol

3. Increasing our weight limit to 150kg

4. In addition to indexing LV mass to body surface area we now will also index to height$^2.7$. This will overcome the increasing problem of the underestimation of LV mass using body surface area which is well recognised in the literature due to the increasing levels of obesity.

We hope these changes meet with your approval and we look forward to your response.

Yours Sincerely

Dr Alex Brown