Metformin and its effects on myocardial dimension and left ventricular hypertrophy in normotensive patients with coronary heart disease (MET-REMODEL study)

Analysis Plan

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MET-REMODEL study is a double blinded placebo controlled trial, funded by British Heart Foundation (Grant number: PG/14/4/30539). In this pragmatic "proof of concept" study, we will investigate the efficacy of Metformin to cause a favourable effect on left ventricular hypertrophy (LVH), either regression or less increase in left ventricular mass in non-diabetic patients with documented coronary artery disease and who are insulin resistant and/or prediabetic. Further information regarding the MET-REMODEL study can be found in the approved trial protocol and also from the published rationale and design paper (1). This analysis plan relates to the MET-REMODEL trial protocol Version 5.4 dated 20th October 2016.

Background

Left ventricular hypertrophy (LVH) is a common and independent risk factor for cardio-vascular events in patients with coronary artery disease (CAD) [2]. Controlling blood pressure is the standard approach to the management of LVH, but this is only partially effective as LVH also persists in normotensive patients [3]. Apart from blood pressure (BP), other main risk factors associated with LVH are insulin resistance (IR) and central obesity [1]. The diabetic medication, Metformin, reduces IR and aids weight loss and may therefore regress LVH [4].

In this single-centre, phase IV, double-blind, randomized, placebo-controlled trial, we propose to investigate the efficacy of Metformin to regress LVH in patients with a 68 non-diabetic patients with CAD who are insulin resistant and/or prediabetic. Participants will be randomized into two groups to receive, either Metformin XL or placebo.

The primary end-point of this trial is to investigate any change in left ventricular mass index (LVMI) measured using cardiac magnetic resonance imaging (cMRI). Secondary endpoints include changes to LV mass (LVM) and function measured using cMRI, insulin resistance measured using fasting insulin resistance index (FIRI), changes in glycaemic index measured using HbA1c, abdominal obesity measured using MRI, improvement in endothelial function assessed using flow mediated dilatation (FMD) and blood-borne biomarkers such as IL-6 (inflammation), NT-pro BNP (wall stress), Soluble ST2 (wall stress & fibrosis) and TBARs (oxidative stress). As blood-borne biomarkers can offer objective and biologically relevant and mechanistic insights that complements the findings of study specific end points, we propose to include these 4 biomarkers of distinct mechanisms that contribute to the pathophysiology of left ventricular hypertrophy.

A positive result will assist clinicians to identify a new mechanism for LVH regression by administering Metformin XL. This may also lead to investigating the mortality benefit of Metformin in patients with CAD and LVH.

Research question

Compared to placebo, does metformin improve cardiac parameters such as LVH regression, LV ejection fraction, LV systolic and diastolic volumes, endothelial function, blood-borne biomarkers, insulin resistance/glycaemic index and abdominal obesity?

Study Objectives

Primary Objective

To study the efficacy of metformin to cause regression of left ventricular mass index (LVMI) in participants with coronary artery disease (CAD) who are insulin resistant/pre-diabetes and on optimal current evidence based therapy for IHD.

Secondary Objectives

- To assess if metformin has effects on cardiac parameters LVM, LVEF, LVSV, LVEDV, LVESV as measured by cardiac MRI.
- To study whether metformin improves insulin resistance/HbA1c in patients with CAD.
- To assess whether metformin will reduce abdominal obesity in this patient group as measured by MRI
- To examine any differences following treatment with metformin in blood borne biomarkers such as NT pro BNP, IL-6, Soluble ST2, TBARs and any other markers of interest.
- To assess whether metformin will improve endothelial function as assessed by flow mediated dilatation.

STATISTICS AND DATA ANALYSIS

SAMPLE SIZE CALCULATIONS

For the primary outcome of LVMI regression using cardiac MRI, the study has been powered for an absolute change in LV mass based on previous studies conducted in the department of Clinical Pharmacology, Ninewells Hospital. In this group's recently published study of LVH regression using allopurinol in patients with ischaemic heart disease it was found that allopurinol significantly reduced LV mass by -5.2± 5.8 grams compared to placebo -1.3±4.5 grams ($p<0.007$) [5]. For an 80% power at a 5% significance level ($\alpha=0.05$), to detect a similar change in LV mass, 29 subjects per group (N=58) will be required. Previous studies have shown a 15% dropout rate. Therefore, accounting for this, a total of 68 participants will be required (34 per group).

Although we have shown above that this study has the potential sample size to achieve an adequate statistical power to detect a reasonable change in LVMI, we acknowledge that the overall sample size of the study is small. Furthermore, a limitation of our sample size calculation is that it is based on a single outcome and may not reflect the effects on other study endpoints. If the observed effect sizes for other end points in this study are small (i.e. less than ES of 0.4) then we acknowledge we will not have adequate statistical power to detect such effects in this study. In summary, given the relatively small sample size of this study, inferential between group comparisons are likely to be exploratory rather than definitive

Outcomes

Variables	Baseline	12-13 months follow-up
Cardiac Parameters		
LV Mass Index & LV mass (LVMI&LVM)	X	X
LV end systolic volume(LVESV)	X	X
LV end diastolic volume(LVEDV)	X	X
LV Ejection fraction (LVEF)	X	X
LV Stroke Volume (LVSV)		
Abdominal Obesity (Subcutaneous Abdominal Tissue [SAT] & Visceral Adipose Tissue [VAT])	X	X
Endothelial Function		
Flow mediated dilation	X	X
Research Biomarkers		
IL-6	X	X
NT pro BNP	X	X
Soluble ST2	X	X
TBARs	X	X
Biochemical Analysis		
Fasting Insulin Resistance Index	X	X
HbA1c	X	X

PROPOSED DATA ANALYSES

The primary analysis will be based on a between-group, intention-to-treat principle using the outcome data collected at baseline and 12-13 months' follow-up. The primary outcome comparison will be based on modified intention-to-treat analysis, i.e. all participants who had baseline measurements and took at least one dose of IMP will be analysed as part of the group to which they were randomized. Missing post-baseline values will be imputed using the baseline observation carried forward (BCOF) approach. However, to provide a true estimate of the efficacy of intervention, a per-protocol analysis was also performed.

Descriptive statistics in the form of means and standard deviations for continuous variables and percentages and denominators for categorical variables will be tabulated at baseline and for each visit. As outcomes are continuous, the comparison between arms of the trial will be assessed using the 2-tailed *t* test while categorical variables were analysed using chi-square test. Continuous variables not normally distributed are presented as medians with their interquartile ranges (IQRs). If normality could not be assumed, data underwent log transformation to convert it to a normal distribution. Correlation will be performed using Pearson's or Spearman's method. A sensitivity analysis using ANCOVA (analysis of covariance) will be performed adjusted for relevant covariates to evaluate the robustness of the effect of treatment on the outcome parameters. All between group outcome results will be presented as means and 95% confidence internals. A p value <0.05 will be considered significant.

MISSING DATA

The primary analysis will be based on the modified intention-to-treat. The extent of missing data will be examined and the reason for drop-out ascertained. Missing post-baseline values

will be imputed using the baseline observation carried forward (BCOF) approach.. Given the relatively small sample size of this study, we regard the results of the between group inferential analyses as exploratory and hypothesis generating. All analyses will be conducted by the trial statistician blinded to group allocation, using R Software (version 3.3.2, R core development team) or SPSS 22.0 (IBM Corp, Armonk, NY, USA).

References

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