Proposal

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Study Synopsis

Title of study	The effects of dapagliflozin compared with placebo on left ventricular remodelling in patients with asymptomatic left ventricular systolic dysfunction after myocardial infarction: a randomised, double-blinded, placebo-controlled, cardiac-MR based trial
Study centre	Queen Elizabeth University Hospital Clinical Research Facility
Primary endpoint	Change in indexed left ventricular end-systolic volume (LVESVI), from baseline to 12 months, measured using cardiac MR.
Secondary endpoints	• Changes in other CMR based metrics of LV remodelling (LVEDVI, LVEF, LV mass) from baseline to 12 months Changes in haematocrit from baseline to 12 months • Changes in plasma ketones from baseline to 12 months • Changes in haematocrit from baseline to 12 months • Changes in NT-proBNP from baseline to 12 months
Tertiary endpoints	• Changes in biomarkers of LV remodelling (sST2, Galectin 3, TIMP-1, MMP-9, Type III Procollagen Peptide and GDF-15) from baseline to 12 months • Changes in neurohormonal levels (BNP, MR-proANP, C-terminal ANP, CNP, MR-proADM, cGMP, endothelin-1, neprilysin antigen, renin and aldosterone) from baseline to 12 months
Rationale	The sodium glucose cotransporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin have been shown to reduce the risk of developing heart failure in patients with type 2 diabetes, with the greatest benefit in patients with prior atherosclerotic cardiovascular disease (ASCVD). More recently, in the DAPA-HF trial, dapagliflozin was shown to reduce the risk of worsening heart failure and of death in patients with established heart failure and reduced ejection fraction. These beneficial effects were observed in patients with and without type 2 diabetes. However, the mechanisms underlying the benefits are unknown. One possibility is that dapagliflozin prevents the progressive adverse cardiac “remodelling” that characterizes heart failure (e.g. progressive dilatation and decline in systolic function) of the left ventricle. It is important to determine whether this is the case in humans. However, it is difficult to know how to study this question. It is expected that the results of DAPA-HF will lead to a recommendation to use SGLT2 inhibitors in patients with HFrEF, meaning it will not be possible to study patients with HFrEF. On possibility would be to study individuals with *asymptomatic* left ventricular systolic dysfunction after myocardial infarction (MI). However, even here there is a limitation. New guidelines for treatment of patients with type 2 diabetes now recommend use of

	SGLT2 inhibitors in patients with ASCVD (which would obviously mean diabetes patients with prior MI). Consequently, the study proposed is in patients with residual left ventricular systolic dysfunction (ejection fraction ≤40%) after prior acute MI who do not have type 2 diabetes. Arguably, this, in any case, reflects the key clinical question about SGLT2 inhibitors i.e. are they just a treatment for diabetes or are they really a potential treatment for all patients with cardiovascular disease?
Methodology	Prospective, randomised, active-comparator, double-blinded study.
Sample size	80
Screening	Patients with EF ≤40% measured by trans-thoracic echocardiography post myocardial infarction without evidence of clinical heart failure and without type 2 diabetes.
Inclusion criteria	• Acute myocardial infarction (AMI) at least 3 months prior to recruitment • Left ventricular ejection ≤40% as measured by transthoracic echocardiography • Ability to provide written, informed consent • Age ≥18 years • Treatment with a beta-blocker and ACE inhibitor/ARB unless not tolerated or contraindicated.
Exclusion criteria	• History of type 2 diabetes • Contraindication to CMR (ferrous prosthesis, implantable cardiac device or severe claustrophobia) • Clinical and/or radiological heart failure (NYHA≥2) • Symptomatic hypotension and/or systolic blood pressure <95mmHg • eGFR < 30 mL/min/1.73m^2 • Persistent/permanent atrial fibrillation • History of AMI within last 3 months • Known hypersensitivity to the active study drug substances, contrast media or any of the excipients • Severe obesity (where body girth exceeds MRI scanner diameter) • Pregnancy, planning pregnancy, or breast feeding • Inability to give informed consent or comply with study protocol • Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 2 x ULN at Visit 1, history of hepatic encephalopathy, history of oesophageal varices, history of portacaval shunt, biliary cirrhosis and cholestasis • Participation in another intervention study involving a drug or device within the past 90 days (co-enrolment in observational studies is permitted)
Study drugs	Patients will be randomised in a 1:1 fashion to dapagliflozin 10mg once daily or matched placebo.
Duration of treatment:	9 months
Statistical analysis	The primary outcome will be compared between randomised groups using a linear regression model adjusted for baseline LVESVI value, and whether taking diuretics or not at baseline. Similar methods will be used for other outcomes. The Robertson Centre for Biostatistics will manage and analyse trial data. All statistical analyses will be conducted according to a Statistical Analysis Plan, which will be authored by the Trial Statistician and agreed by the Trial Steering Committee prior to unblinding of randomised groups.

Value for research fellow	This study will provide clinically important information from patients about the mechanisms of action of dapagliflozin in patients with left ventricular systolic dysfunction. It will not only allow the fellow to conduct patient-based research but will also provided experience in cardiac MRI. The fellow will be part of a team that have conducted similar studies in the past and who have expertise in clinical trials.