


# BMJ Open Sodium glucose co-transporter 2 inhibition with empagliflozin on metabolic, cardiac and renal outcomes in recent cardiac transplant recipients (EMPA-HTx): protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Cardiac transplantation (CTx) is a life-saving operation that can improve the quality and length of a recipient's life. Immunosuppression medication, required to prevent rejection, can result in adverse metabolic and renal effects. Clinically significant complications include metabolic effects such as diabetes and weight gain, renal impairment, and cardiac disease such as allograft vasculopathy and myocardial fibrosis. Sodium glucose co-transporter 2 (SGLT2) inhibitors are a class of oral medication that increase urinary excretion of glucose. In patients with type 2 diabetes, SGLT2 inhibitors improve cardiovascular, metabolic and renal outcomes. Similar benefits have been shown in patients with heart failure and reduced ejection fraction irrespective of diabetes status. In patients with post-transplant diabetes mellitus, SGLT2 inhibitors improve metabolic parameters; however, their benefit and safety have not been evaluated in randomised prospective studies. This study will potentially provide a novel therapy to improve or prevent complications (diabetes, kidney failure and heart fibrosis) that occur with immunosuppressive medications.

**Methods** The EMPA-HTx study is a randomised, placebo-controlled trial of the SGLT2 inhibitor empagliflozin 10 mg daily versus placebo in recent CTx recipients. One hundred participants will be randomised 1:1 and commence the study medication within 6–8 weeks of transplantation with treatment and follow-up until 12 months after transplantation. Demographic information, anthropomorphic measurements, pathology tests and cardiac magnetic resonance (CMR) scan will be recorded at baseline and follow-up. Patients will be reviewed monthly during the study until 12 months post-CTx and data will be collected for each patient at each study visit. The overall aim of the study is to assess the safety and efficacy of empagliflozin in CTx recipients. The primary outcome is glycaemic improvement measured as change in glycated haemoglobin and/or fructosamine. Key secondary outcomes are cardiac interstitial fibrosis measured by CMR and renal function measured by estimated glomerular filtration rate.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A randomised placebo controlled design testing a novel use of an approved medication for diabetes and heart failure.
- ⇒ Use of state of the art metabolic and cardiac measures.
- ⇒ Conducted in an adult Australian population at a single site, the study findings may not be applicable to other populations.
- ⇒ The requirement of renal function with estimated glomerular filtration rate >30 mL/min/1.73 m<sup>2</sup> may disproportionately limit the potential benefit on the outcome of renal function.
- ⇒ Given the immunosuppressed state of transplant recipients, potential infection risks such as genitourinary infection will be closely monitored.

**Ethics and dissemination** This study has been approved by St Vincent's Hospital Human Research Ethics Committee (2021/ETH12184). The findings will be presented at national and international scientific meetings and published in peer-reviewed journals.

**Trial registration number** ACTRN12622000978763.

## INTRODUCTION

Cardiac transplantation (CTx) is standard of care for the treatment of end-stage cardiac failure. Graft survival rates continue to improve with advances in post-transplant care and current 5-year survival rates approximate 85%–90%.<sup>1</sup> Immunosuppressive medications such as corticosteroids and tacrolimus effectively prevent and treat graft rejection. However, these same medications can also result in adverse metabolic and renal effects. Hence, the management of long-term CTx-related complications has become



increasingly important and are a significant cause of morbidity and mortality in CTx recipients. Clinically significant CTx-associated complications include metabolic effects such as diabetes and weight gain, renal impairment and cardiac disease such as allograft vasculopathy and myocardial fibrosis. Effective treatments to prevent or delay onset of chronic transplant-related complications are currently lacking.

Sodium glucose co-transporter 2 (SGLT2) inhibitors are oral medications that increase urinary excretion of glucose by inhibiting reabsorption from the renal proximal tubules.<sup>2</sup> The use of SGLT2 inhibitors in patients with type 2 diabetes mellitus (T2DM) improves composite cardiovascular and renal outcomes and is associated with reduced left ventricular end-diastolic volume measured by cardiac magnetic resonance (CMR), suggesting favourable effects on left ventricular remodelling.<sup>3,4</sup> The cardiac benefits of SGLT2 inhibition with empagliflozin are not limited to patients with T2DM.<sup>5</sup> Similar benefits of reduced risk of worsening heart failure or cardiac death in patients with heart failure with reduced ejection fraction, as well as preserved ejection fraction, have been shown irrespective of diabetes status.<sup>6–8</sup> As in patients with T2DM, SGLT2 inhibitor use in patients with heart failure and normal glucose tolerance improves left ventricular volume, mass and systolic function.<sup>9</sup>

Post-transplant diabetes mellitus (PTDM) is defined as new-onset diabetes following transplantation. Screening and diagnosis of PTDM is assessed at least 45 days after transplantation, as post-transplant hyperglycaemia often resolves following rationalisation of immunosuppression regimens.<sup>10</sup> PTDM affects up to 40% of patients post-CTx.<sup>11,12</sup> In addition to adverse cardiovascular effects, PTDM also increases the risk of other complications such as opportunistic infection and all-cause mortality.<sup>12,13</sup> As we and others have demonstrated, empagliflozin, a potent SGLT2 inhibitor, is safe and effective in cardiac and renal transplant recipients with PTDM, without significant increase in genitourinary infections.<sup>14–16</sup> Studies of CTx recipients followed for up to 1-year suggest empagliflozin is associated with significant reductions in body weight, blood pressure and diuretic requirement.<sup>14</sup> In renal transplant recipients with PTDM, empagliflozin improved estimated glomerular filtration rate (eGFR), waist circumference and total body fluid after 4 weeks of therapy.<sup>17</sup> Additionally, 24 weeks of empagliflozin in renal transplant recipients with PTDM improved glycaemic control.<sup>16</sup> In animal models of tacrolimus-associated diabetes, empagliflozin improved glycaemic outcomes and delayed progression of renal dysfunction and albuminuria.<sup>18</sup> Empagliflozin demonstrated a dose dependent improvement in cardiac functional recovery in animal model donor hearts, suggesting cardioprotective benefits and potential for donor heart preservation.<sup>19</sup>

SGLT2 inhibitors have well-established cardiac and non-cardiac benefits in patients with and without diabetes. Efficacy in the transplant setting is less clear. Retrospective cohort studies have implied safety and efficacy of

empagliflozin in patients with PTDM, but there are no randomised prospective studies to guide treatment.

This study will fill an evidence gap and have the potential to significantly advance the field of post-transplant care. The results of this study will determine the efficacy of empagliflozin in reducing the metabolic, cardiac and renal complications in CTx recipients. If successful, our data could support the use of a new class of medications (SGLT2 inhibitors) with pleiotropic effects in the prevention of transplant-related complications and would guide therapeutic decision making to improve outcomes in patients following CTx.

## METHODS AND ANALYSIS

### Study design and setting

The EMPA-HTx study is a double-blinded randomised placebo controlled trial of empagliflozin therapy (10 mg daily) in adults with recent cardiac transplant. The study aims to recruit 100 participants with 1:1 ratio, 50 will be randomised to empagliflozin and 50 to placebo. Cardiac transplant recipients will be recruited within 6–8 weeks from the date of cardiac transplant, and will receive the trial drug and be monitored until 12 months after transplant. Participants will be recruited from St Vincent's Hospital, Sydney. The main study visits will be conducted at the Garvan Institute of Medical Research and St Vincent's Hospital.

### Study outcomes

The overall aim of this project is to study the safety and efficacy of empagliflozin in CTx recipients. The specific aims and hypotheses of this project focus on the metabolic, cardiac and renal effects of empagliflozin in recent CTx recipients (table 1).

### Primary endpoint

The primary aim is to compare the effect of empagliflozin 10 mg daily to placebo on glycaemia measured as change of HbA1c and/or fructosamine from baseline to 12 months post-transplantation.

### Key secondary outcomes

The key secondary outcomes are the cardiac, renal and further metabolic effects of empagliflozin in CTx. First, to compare the effect of empagliflozin 10 mg daily to placebo on degree of cardiac interstitial fibrosis measured at 12 months post-transplantation with the endpoint of mean change in left ventricular interstitial fibrosis and mass as assessed by CMR from baseline. Second, to compare the effect of empagliflozin 10 mg daily to placebo on renal function measured at 12 months post-transplantation, with the endpoint of mean change in eGFR from baseline. Third, to compare the effect of empagliflozin 10 mg daily to placebo on development of diabetes at 12 months post-transplantation, in those who did not have diabetes diagnosed prior to cardiac transplant with the end point of development of diabetes defined as HbA1c  $\geq 6.5\%$ ,

**Table 1** Study end points

Change from baseline	Method of assessment
Primary ▶ Glycaemia	Change of HbA1c and/or fructosamine
Key secondary ▶ Cardiac interstitial fibrosis ▶ Renal function ▶ Development of diabetes	Change of left ventricular interstitial fibrosis and mass as assessed by CMR Mean change in eGFR HbA1c $\geq 6.5\%$ , and/or FPG $\geq 7.0$ mmol/L; or clinically diagnosed by treating physician
Other prespecified ▶ Number of hospitalisations for any reason ▶ All cause mortality ▶ Weight ▶ Waist circumference ▶ Dose of diuretic medication ▶ Dose of insulin ▶ Dose of metformin ▶ Dose of gliclazide ▶ Albumin creatinine ratio ▶ Cholesterol and triglyceride ▶ Measures of myocardial tissue characterisation and performance on CMR ▶ Oral glucose tolerance test (optional), area under the curve	
Safety The following will be assessed and recorded at each study visit: ▶ Early discontinuation of study drug due to adverse events ▶ Incidence of diabetic ketoacidosis ▶ Incidence of urinary tract or mycotic genital infection ▶ Occurrence of hypoglycaemia	
CMR, cardiac MR; eGFR, estimated glomerular filtration; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin.	

and/or fasting plasma glucose  $\geq 7.0$  mmol/L; or clinically diagnosed by treating physician.

Other prespecified end points and safety outcomes are listed in [table 1](#).

### Patient and public involvement

Heart transplant recipients were consulted about the concept of the study. Patients and/or the public were not involved in the conduct, or reporting, or dissemination plans of this research.

### Eligibility

Adults (over 18 years old) who have received a cardiac transplant within 6–8 weeks, are free from major rejection and have a baseline estimated glomerular filtration (eGFR)  $>30$  mL/min/1.73 m<sup>2</sup> will be recruited ([table 2](#)). Participants who have had exposure to an SGLT2 inhibitor in the last 30 days or have had a previous adverse event related to SGLT2 inhibitor use will be excluded. Participants with a history of diabetic ketoacidosis or fasting beta hydroxybutyrate  $>1.7$  mmol/L at baseline will be excluded. In the context of possible interference with excretion or metabolism of the study medication, known major organ dysfunction including eGFR  $<30$  mL/min/1.73 m<sup>2</sup>, liver disease transaminases  $>5$  times the upper limit of normal, current cancer or uncontrolled thyroid dysfunction are grounds for exclusion. These

**Table 2** Inclusion and exclusion criteria

Inclusion criteria	<ul style="list-style-type: none"> <li>▶ Men and women over 18 years of age</li> <li>▶ Cardiac transplant recipients recruited within 6–8 weeks from the date of cardiac transplant</li> <li>▶ Free from major rejection at enrolment</li> <li>▶ Baseline eGFR <math>&gt;30</math> mL/min/1.73 m<sup>2</sup></li> <li>▶ Willingness to give written informed consent and willingness to participate to and comply with the study</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>▶ Exposure to an SGLT2 inhibitor within the last 30 days</li> <li>▶ Previous adverse event related to SGLT2 inhibitor use</li> <li>▶ History of diabetic ketoacidosis</li> <li>▶ History of urosepsis</li> <li>▶ Fasting beta hydroxybutyrate <math>&gt;1.7</math> mmol/L at baseline.</li> <li>▶ Known major organ dysfunction (eGFR <math>&lt;30</math> mL/min/1.73m<sup>2</sup>, liver disease transaminases <math>&gt;5</math> times the upper limit of normal, current cancer or uncontrolled thyroid dysfunction). These conditions either interfere with the excretion or metabolism of the test medication, or would interfere with measurement of the study outcome.</li> <li>▶ Women lactating, pregnant or of childbearing potential who are not willing to avoid becoming pregnant during the study.</li> </ul>
eGFR, estimated glomerular filtration rate; SGLT2, sodium glucose co-transporter 2.	

conditions either interfere with the excretion or metabolism of the test medication, or would interfere with measurement of the study outcome. Women lactating, pregnant or of childbearing potential who are not willing to avoid becoming pregnant during the study will be excluded ([table 2](#)).

### Recruitment

Participants will be identified from St Vincent's Hospital Heart Transplant Unit. Participants will be referred and approved by treating cardiologist based on clinical status and blood test results. Potential participants will be approached by the study coordinator and will be briefed regarding the rationale for the study, and brief study procedure. If the potential participant indicates interest then they will be asked a brief history to check relevant inclusion and exclusion criteria. If no clear exclusion criterion are met, then the study procedure, and risks will be discussed in further detail and the participant will be provided with the study participant information consent form (online supplemental material) and the screening blood test request form. If participants have performed the relevant results recently, then we will seek permission to retrieve these results rather than duplicate the tests. Participants will be contacted with the results of screening blood tests to advise if they have met inclusion criteria. They will be invited to discuss any further consent queries during the first face-to-face visit.

**Table 3** Schedule of visits and data collection

Visits	Baseline (prior to randomisation, 6–8 weeks post CTx)	Months after cardiac transplant						Completion (12 months post- CTx)
		3	4 and 5*	6	7 and 8*	9	10 and 11*	
Medication history	+	+	+	+	+	+	+	+
Medical history and AEs monitoring	+	+	+	+	+	+	+	+
Weight and waist circumference	+	+		+		+		+
Blood pressure	+	+		+		+		+
Laboratory tests	+	+	+	+	+	+	+	+
HbA1c and fasting glucose	+	+		+		+		+
Fructosamine	+	+	+	+	+	+	+	+
Lipids	+			+				+
Urine albumin creatinine ratio	+	+		+		+		+
Beta hydroxybutyrate	+	+		+		+		+
Cardiac magnetic resonance 75g-OGTT (optional)	+			+				+

\*Visits at months 4, 5, 7, 8, 10 and 11 months can be via telehealth at patient request.  
AEs, adverse events; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test.

### Randomisation

Participants will be randomised using the minimisation programme for allocation of patients to parallel groups, modified from Saghaei and Saghaei.<sup>20</sup> Participants will be randomised to placebo or empagliflozin using minimisation (Minitable program) modified from Saghaei and Saghaei.<sup>20</sup> The factors include history of diabetes (yes or no), body mass index (BMI) (<27 kg/m<sup>2</sup>, ≥27 kg/m<sup>2</sup>), gender (men, women) and age (<50 years, ≥50 years). These four prognostic factors will be weighted at 40%, 20%, 20% and 20%, respectively. This will be supervised by a physician not involved with the study. Allocations will be communicated directly to St Vincent's Hospital clinical trials pharmacy. Research staff (including those involved with recruitment and outcome assessors), participants, care providers and data analysts are blinded to the treatment allocation.

### Study timeline

Time points, data and samples to be collected as listed in table 3.

### Data collection

Baseline and follow-up visits will include physical examination. Blood pressure will be measured in a seated position after a 5 min rest using a mercury sphygmomanometer. Weight will be measured to the nearest 0.1 kg in a hospital gown. Height will be measured to nearest 0.01 m by stadiometer with the participant barefoot. Waist circumference will be measured as the narrowest circumference between the lowest aspects of the ribs and anterior superior iliac crests. Detailed history will be recorded at baseline and include record of cardiac history that led to cardiac transplant, comorbidities, medication history

and family history. An updated history will be taken at follow-up visits and include any change to medications, any hospitalisations, any adverse events. Pathology results as part of routine care will be recorded. As part of workup for cardiac transplant, patients have pathology tests that include full blood count, biochemistry, glucose, lipids, liver function and HbA1c. Patients with recent cardiac transplant have routine blood tests, at least monthly, to review general health and immunosuppressant levels. Results of creatinine level, eGFR, urea, protein, albumin, sodium, and full blood count will be recorded. Additional pathology tests specific for the study will be collected through a private pathology company. The study-specific pathology tests are HbA1c, fructosamine, fasting glucose, lipid profile (low-density lipoprotein, high-density lipoprotein, triglycerides), beta hydroxybutyrate, and urine-albumin-creatinine ratio. Participants will be asked to have fasting pathology test between 8:00 and 10:00 hours, with last food or non-water drink before 22:00 hours the night prior. An oral glucose tolerance test, including fasting glucose level blood test, followed by consumption of 75 g oral glucose, with measurement of glucose level via blood test at 60 min and 120 min, will be offered to participants who are not known to have a history of diabetes at the time of transplant. CMR will be performed using a 3-T whole-body MR imaging unit (Prisma-Siemens, Germany) in the Advanced Cardiac Imaging Facility at St Vincent's Hospital.

### Statistical analysis

#### Sample size and power calculation

Sample size of 100 was determined based on previous studies that report an improvement of 0.6% or 7 mmol/

mol in HbA1c over 12 months in cardiac transplant cohort of 20 patients,<sup>14</sup> and an improvement of 0.2% or 2.0 mmol/mol in HbA1c over 24 weeks in a renal transplant cohort of 44 patients (22 empagliflozin, 22 placebo).<sup>16</sup> A clinically significant reduction is defined as reduction in HbA1c of  $\geq 0.5\%$ , and/or reduction in fructosamine of  $\geq 20$   $\mu\text{mol/L}$ . Assuming  $\leq 10\%$  rate of withdrawal, this study will be at least 80% powered to demonstrate an effect size of 0.6 (Cohen's d) in primary endpoint between empagliflozin and placebo with a two-sided significance level of 0.05. Based on these projections, 100 patients will be randomly assigned in a 1:1 ratio to receive empagliflozin 10 mg daily or placebo during the study period.

### Statistical plan

Summary statistics for categorical measures will include sample size, frequency and percentages. For continuous measures, summary statistics will include sample size, mean, and SD or median and IQR. A likelihood-based mixed effect regression model approach will be used for the primary efficacy analysis. The HbA1c measure at baseline and all post baseline measurements will be the dependent variable, and treatment by visit interaction will be the fixed effect of interest. The primary comparison will be the difference in mean change of HbA1c at 12 months from baseline between treatment and control groups.  $\chi^2$  test will be used to examine the association between treatment arm and the categorical outcomes. Logistic regression and ordinal logistics regression models will be used to examine the intervention effect on the binary or ordinal outcome measures, with controlling for key patients baseline characteristics such as pretransplant diabetic status. The Kaplan-Meier method will be used for estimation of cumulative event-free survival rates and Cox proportional hazards regression analysis will be used to compare hazard rates between empagliflozin and placebo.

### Confounding factors and potential bias

There may be volunteer bias skewing towards more engaged and health literate individuals, but the bias would be shared between both groups. History of diabetes, age, gender and BMI will be balanced in participants and controls to reduce confounding from those factors.

### ETHICS AND DISSEMINATION

This study has been approved by St Vincent's Hospital Human Research Ethics Committee (2021/ETH12184). Site Specific Ethics and Governance has been approved at both St Vincent's Hospital Sydney and the Garvan Institute of Medical Research. Deidentified data are stored electronically via REDCap software hosted at the Garvan Institute.<sup>21</sup>

The EMPA-HTx study is registered at the Australian New Zealand Clinical Trials Registry (ACTRN12622000978763, registered 11 July 2022), universal trial registration number U1111-1278-3639.

The results of this trial will be published in peer-reviewed journals, as well as presented at national and international conferences. The results will be communicated directly to the study population through an information sheet and video.

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