Empagliflozin to prevent worsening of left ventricular volumes and systolic function after myocardial infarction

Jaclyn Elizabeth Carberry
BSc(Hons), MB ChB, PGCert(HPE), MRCP

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School of Cardiovascular and Metabolic Health
College of Medical, Veterinary and Life Sciences
University of Glasgow

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Abstract

Background

Heart failure following an acute myocardial infarction (MI) is associated with significant morbidity and mortality, making its prevention a key therapeutic goal. Progressive adverse ventricular remodelling, characterised by ventricular dilation and declining systolic function, is a key precursor to the development of heart failure after MI.

Early reperfusion therapy and medications that reduce mortality and heart failure post-MI, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers, also prevent adverse remodelling. The mineralocorticoid receptor antagonist (MRA) eplerenone improved outcomes post-MI but showed a significant anti-remodelling effect only after adjusting for baseline covariates. Sacubitril/valsartan did not reduce the risk of developing heart failure or cardiovascular mortality in high-risk post-MI patients and had minimal impact on remodelling.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors lower the risk of heart failure progression and mortality in patients with chronic heart failure across all ranges of left ventricular ejection fraction (LVEF). One of their key mechanisms of benefit in heart failure with reduced ejection fraction (HFrEF) is a positive effect on ventricular remodelling. Empagliflozin did not significantly reduce the primary outcome of heart failure hospitalisation or all-cause mortality in high-risk post-MI patients, but did lower the incidence of first and total heart failure hospitalisations and other adverse heart failure events. Whether this is related to a remodelling effect remains uncertain. In lower-risk post-MI patients, dapagliflozin improved cardiometabolic outcomes but did not significantly impact the composite outcome of cardiovascular death or heart failure hospitalisation.

I conducted the EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction (EMPRESS-MI) randomised, placebo-controlled trial, which was designed to test the hypothesis that empagliflozin, when added to standard care, would mitigate adverse left

ventricular remodelling in high-risk post-MI patients, as assessed using cardiovascular magnetic resonance (CMR) imaging.

Aims and methods

The aim of the EMPRESS-MI trial was to examine the effect of empagliflozin on left ventricular remodelling in patients with left ventricular systolic dysfunction after an acute MI using the gold-standard method, CMR.

I performed a randomised, placebo-controlled trial comparing empagliflozin 10mg once daily with placebo, in addition to standard care, in patients within 12 hours and 14 days of an acute type 1 MI and an LVEF<45% by CMR. Key exclusion criteria were a history of HFrEF or contraindications to SGLT2 inhibitors. Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (measured using the modification of diet in renal disease formula) were excluded. Patients with permanent or persistent atrial fibrillation or an implanted cardiac device were excluded to avoid potential CMR image degradation. The primary outcome was the change in left ventricular end-systolic volume index (LVESVI) from baseline to 24 weeks as measured by CMR. The secondary outcomes, measured as change from baseline to 24 weeks, were: left ventricular end-diastolic volume index (LVEDVI), LVEF, left atrial volume index (LAVI), left ventricular mass index (LVMI), N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin I (hs-TnI), and infarct size measured using CMR. Exploratory outcomes included the change in biomarkers relevant to the actions of empagliflozin (uric acid, glycated haemoglobin, and haematocrit), kidney function, and body weight. I also examined the relationship between intramyocardial haemorrhage (IMH) and left ventricular remodelling and the effect of empagliflozin.

Results

In 104 patients included in the final analysis set, mean±standard deviation age was 63.0±11.2 years and 90 (86.5%) patients were male. The median time from MI to randomisation was 3.0 days (interquartile range 2.0-5.0). 92 (88.5%) patients had an ST-elevation MI (STEMI) and 12 (11.5%) had a non-STEMI (NSTEMI). 83 (79.8%) MIs were in the anterior location. Nearly all patients (103

[99.0%]) had percutaneous coronary intervention (PCI) or thrombolysis. At randomisation, 97 (93.2%) patients were taking an ACE inhibitor or an ARB, 89 (85.6%) a beta blocker, 66 (63.5%) an MRA, and 30 (28.8%) were on a loop diuretic. 46 (44.2%) patients received a loop diuretic at any point during the index admission before randomisation. The mean LVEF by echocardiography was 35.0±4.9% and by CMR was 34.8±6.0%.

In the placebo group, LVESVI decreased by 7.8±16.3 mL/m^2, LVEDVI did not change (-0.3±18.7 mL/m^2) and LVEF increased by 8.5±7.4% from baseline to 24 weeks. Empagliflozin had no effect compared with placebo on the change in LVESVI from baseline to 24 weeks; adjusted between-group difference 0.3 mL/m^2 (95% confidence interval [CI] -5.2 to 5.8); P=0.92. Empagliflozin had no effect on the change in LVEDVI, LVEF, LAVI, LVMI, NT-proBNP, hs-TnI or infarct size but did increase haematocrit (P=0.006) and reduced uric acid (P=0.006) and body weight (P=0.006).

At baseline, of 93 patients with complete data, 45 (48.4%) patients had IMH and 48 (51.6%) did not. In patients with IMH, LVESVI did not change between baseline and 24 weeks whereas in patients without IMH LVESVI decreased (-0.9±11.4 mL/m^2 vs. 14.7±14.7 mL/m^2; P<0.001). In patients with IMH, LVEDVI increased whereas in patients without IMH LVEDVI decreased (9.1±12.7 mL/m^2 vs. -7.8±16.8 mL/m^2; P<0.001). LVEF improved in patients with and without IMH but to a lesser degree in those with IMH (7.4±7.1% vs. 10.7±7.7%; P=0.004). Empagliflozin had no effect on remodelling in patients with and without IMH at baseline.

Conclusion

In patients with left ventricular systolic dysfunction after an acute MI treated with contemporary reperfusion and medical therapy, the addition of empagliflozin to standard care did not have any effect on improving left ventricular volumes or function compared with placebo, and did not reduce biomarkers of left ventricular wall stress (NT-proBNP) or myocardial injury (hs-TnI). Progressive adverse cardiac remodelling did not occur in the majority of patients.

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Publications relating to this work

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outcomes in ST-elevation myocardial infarction patients without standard modifiable risk factors - A multicenter cardiac magnetic resonance study. Eur J Intern Med. 2024 Jan;119:78-83.

Presentations relating to this work

European Society of Cardiology Congress August 2024 (Late-breaking clinical trial – oral presentation). Empagliflozin to prevent worsening of left ventricular volumes and systolic function after myocardial infarction.

European Society of Cardiology Congress August 2024 (Moderated poster presentation). Long-term prognosis after ST-elevation Myocardial Infarction according to the Canadian Cardiovascular Society Classification of tissue injury severity in acute myocardial infarction.

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Finally, and above all, I thank the patients and their families for their time and placing their trust in me. Many travelled long distances to attend study visits and endured CMR scans within days of one of the most significant health events of their lives. It was a pleasure and a privilege to be even a small part of their health journey.

Author's declaration

The work presented in this thesis was performed during my employment as a Clinical Research Fellow at the School of Cardiovascular and Metabolic Health, University of Glasgow, under the supervision of Dr Kieran Docherty, Professor Mark Petrie and Professor Colin Berry.

The design of the work presented in this thesis was that of me and my supervisors. I performed screening and recruitment, including obtaining informed consent, of all patients who participated in the study. I, with the help of Sister Barbara Meyer, performed all study follow-up visits.

I coordinated and attended all cardiac magnetic resonance (CMR) scans, which were performed by radiographers at the Golden Jubilee National Hospital. Analysis of CMR scans for the purposes of the primary and secondary trial outcomes was performed by Dr Matthew Lee. Analyses for any exploratory outcomes were performed by me. Biomarker sample processing and analysis were performed by the staff of the Glasgow Biomarker Research Unit at the School of Cardiovascular and Metabolic Health, University of Glasgow under the supervision of Dr Paul Welsh. Statistical analyses for the primary and secondary outcomes of the trial were performed by Ms Bethany Stanley and Dr Alex McConnachie of the Robertson Centre for Biostatistics according to a pre-specified Statistical Analysis Plan. Any additional analyses were performed by me.

I confirm that this thesis has been composed by me solely and that it has not been submitted for any other degree at the University of Glasgow or any other institution. The writing of this thesis is entirely my own work. All sources of information within this thesis are specifically acknowledged.

Jaclyn Elizabeth Carberry

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Abbreviations

ACE	angiotensin-converting enzyme
AE	adverse event
AESI	adverse event of special interest
AIRE	Acute Infarction Ramipril Efficacy
ALT	alanine transaminase
AR	adverse reaction
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
ASCVD	atherosclerotic cardiovascular disease
ASPIRE	Aliskiren Study in Post-MI Patients to Reduce Remodelling
AST	aspartate aminotransferase
BHF	British Heart Foundation
BNP	brain natriuretic peptide
BSA	body surface area
CAD	coronary artery disease
CANVAS	Canagliflozin Cardiovascular Assessment Study
CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction
CCS	Canadian Cardiovascular Society
CHI	Community Health Index
CI	confidence interval
CKD	chronic kidney disease
CMR	cardiovascular magnetic resonance
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CRP	c-reactive protein
CTFG	Clinical Trial Facilitation Group
CTIMP	clinical trial of an investigational medicine product
CV	cardiovascular
CVOT	cardiovascular outcome trial
DACAMI	The Impact of Dapagliflozin on Cardiac Function Following Anterior Myocardial Infarction in Non-diabetic Patients
DAPA ACT HF-TIMI 68	Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure -Thrombolysis in Myocardial Infarction 68
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DAPA-LVH	Does Dapagliflozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes?
DAPA-MI	Dapagliflozin in Patients with Myocardial Infarction
DAPA-VO2	Short-term Effects of Dapagliflozin on Peak Oxygen Consumption in HFrEF

DAPACARD	The Effects of Dapagliflozin on Cardiac Substrate Uptake, Myocardial Efficiency and Myocardial Contractile Work in Type 2 Diabetes Patients
DAPAPROTECTOR	Dapagliflozin To Attenuate Cardiac Remodelling After Acute Myocardial Infarction
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
DELIVER	Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure
DKA	diabetic ketoacidosis
DOXY-STEMI	Doxycycline to Protect Heart Muscle After Heart Attacks
EACVI	European Association of Cardiovascular Imaging
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMBODY	Effects Of Empagliflozin Versus Placebo On Cardiac Sympathetic Activity In Acute Myocardial Infarction Patients With Type 2 Diabetes Mellitus
EMI-STEMI	Empagliflozin Effects in Patients with ST-Elevation Myocardial Infarction Undergoing Primary PCI
EMMY	EMpagliflozin in patients with acute Myocardial infarction
EMPA-CARD	The effect of EMPAgliflozin on markers of inflammation in patients with concomitant type 2 diabetes mellitus and Coronary ARtery Disease
EMPA-HEART	Effects of Empagliflozin on Cardiac Structure in Patients with Type 2 Diabetes
EMPA-KIDNEY	Study of Heart and Kidney Protection with Empagliflozin
EMPA-PCI	Empagliflozin for No-reflow Phenomenon in PCI for STEMI
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
EMPA-RESPONSE-AHF	Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure
EMPA-TROPISM	Are the “Cardiac Benefits” of Empagliflozin Independent of Its Hypoglycaemic Activity?
EMPA-VISION	Assessment of Cardiac Energy Metabolism, Function and Physiology in Patients With Heart Failure Taking Empagliflozin
EMPACT-MI	Study to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction
EMPASHOCK	Effect At 3 Months of Early Empagliflozin Initiation in Cardiogenic Shock Patients on Mortality, Rehospitalization, Left Ventricular Ejection Fraction and Renal Function
EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction
Empire HF	Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction

EMPRESS-MI	EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction
EMPULSE	Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized
EPHESUS	Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FLASH	fast low-angle shot
GISSI	Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico
GJNH	Golden Jubilee National Hospital
GNA	grounds for non-acceptance
HbA1c	glycated haemoglobin
HEART	Healing and Early Afterload Reducing Therapy
HF	heart failure
HF-REVERT	Study to Assess Efficacy and Safety of CDR132L in Patients With Reduced Left Ventricular Ejection Fraction After Myocardial Infarction
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
IL	interleukin
IMH	intramyocardial haemorrhage
IMP	investigational medicinal product
IQR	interquartile range
IRONMAN	Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency
ISIS-2	Second International Study of Infarct Survival
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAV	left atrial volume
LAVI	left atrial volume index
LGE	late gadolinium enhancement
LVEDV	left ventricular end-diastolic volume
LVEDVI	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVESVI	left ventricular end-systolic volume index
LVGLS	left ventricular global longitudinal strain
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
MDRD	modification of diet in renal disease
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MIRON-DFP	CMR-guided Deferiprone Therapy for Acute Myocardial Infarction Patients

MMP	matrix metalloproteinases
MR-MI	Detection and Significance of Heart Injury in STEMI
MRA	mineralocorticoid receptor antagonist
MVO	microvascular obstruction
Myocardial-IRON	Noninvasive Imaging Estimation of Myocardial Iron Repletion Following Administration of Intravenous Iron
NHS	National Health Service
NSTEMI	non-ST-elevation MI
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
OMEGA-REMODEL	Omega-3 Acid Ethyl Esters on Left Ventricular Remodelling After Acute Myocardial Infarction
OPTIMAAL	Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan
PARADISE-MI	Prospective Angiotensin Receptor-Neprilysin Inhibitor versus Angiotensin-converting Enzyme Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction
PCI	percutaneous coronary intervention
PIS	patient information sheet
PITRI	Platelet Inhibition to Target Reperfusion Injury
PREGICA	Predisposition Génétique à l'Insuffisance Cardiaque
PRESTIGE-MI	Peri-treatment of SGLT2 Inhibitor on Myocardial Infarct Size and Remodelling Index in Patients With Acute Myocardial Infarction and High Risk of Heart Failure Undergoing PCI
PV	pharmacovigilance
RAAS	renin-angiotensin-aldosterone system
REC	Research Ethics Committee
REFORM	Safety and Effectiveness of SGLT-2 Inhibitors in Patients With Heart Failure and Diabetes
RSI	reference safety information
SAE	serious adverse event
SAR	serious adverse reaction
SAVE	Survival and Ventricular Enlargement
SCORED	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
SD	standard deviation
SGLT1	sodium-glucose co-transporter 1
SGLT2	sodium-glucose co-transporter 2
SIMPLE	Effects of SGLT2 Inhibitor on Myocardial Perfusion, Function and Metabolism in Type-2 diabetes patients at high cardiovascular risk
SNS	sympathetic nervous system
SOCOGAMI	SOdium-glucose CO-transporter inhibition in patients with newly detected Glucose Abnormalities and a recent Myocardial Infarction

SOLOIST-WHF	Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure
SSFP	steady-state free precession
STEMI	ST-elevation myocardial infarction
sTFR	serum transferrin receptor
SUGAR-DM-HF	Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure
SUSAR	sudden unexpected serious adverse reaction
T-TIME	Trial of Low-dose Adjunctive alTeplase During prIMary PCI
T2DM	type 2 diabetes mellitus
TGF-ß1	transforming growth factor ß1
TIMP	tissue inhibitors of metalloproteinase
TRACE	Trandolapril Cardiac Evaluation
TSAT	transferrin saturations
UK	United Kingdom
VALIANT	Valsartan in Acute Myocardial Infarction
VERTIS-CV	Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial
VIBE	volume-interpolated breath-hold examination
WOCBP	women of childbearing potential

Chapter 1 Introduction

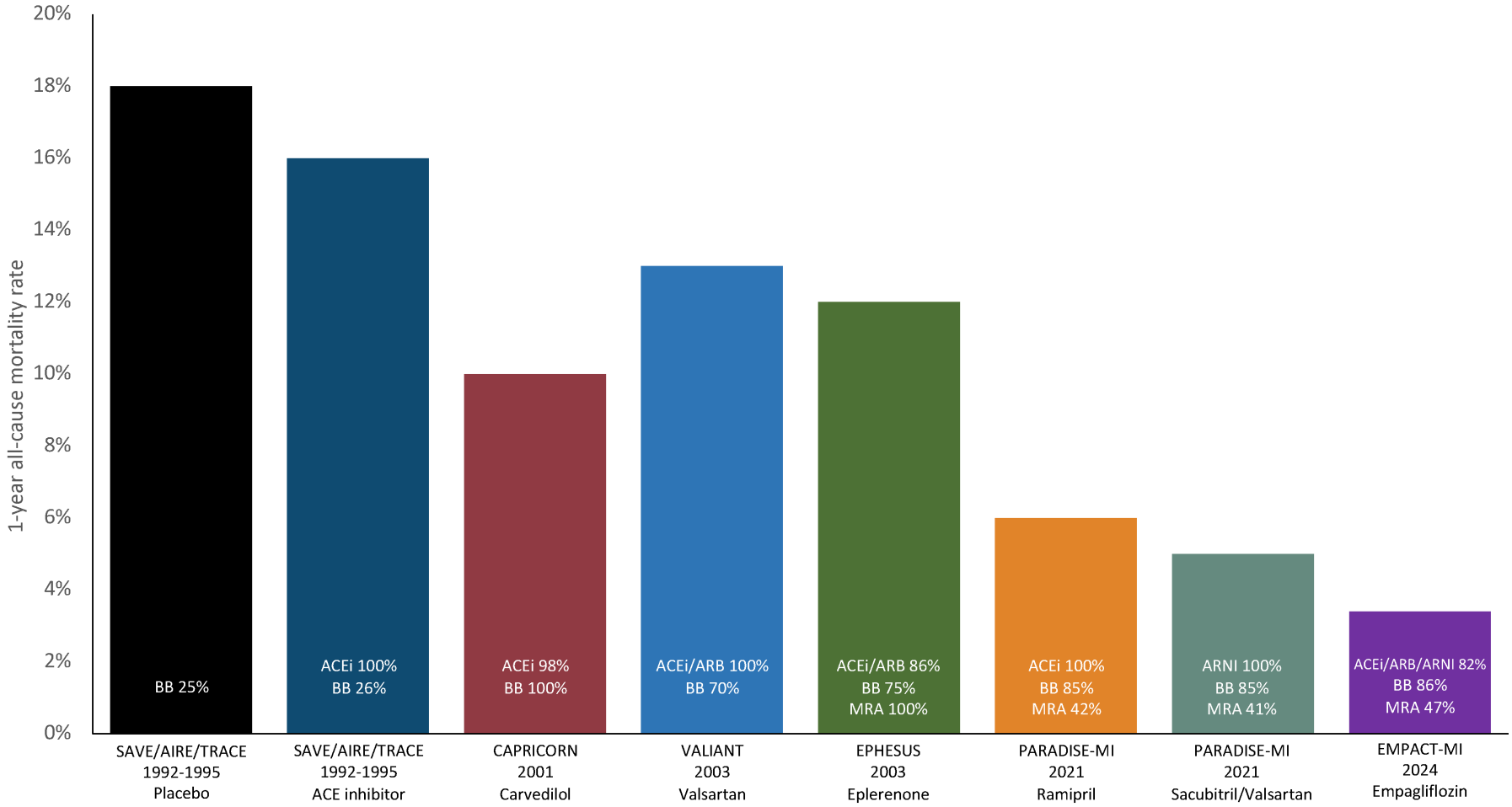
1.1 Background

In Scotland, there are around 10,000 admissions to hospital every year for myocardial infarction (MI).[1] Survival from MI has improved substantially over the past 3 decades as a result of advances in reperfusion and secondary prevention therapies. The 1-year mortality rate in clinical trials of high-risk post-MI patients has declined from approximately 18% to approximately 4% (Figure 1-1).[2] A recent analysis of high-risk post-MI patients recruited to the Valsartan in Acute Myocardial Infarction (VALIANT) (2003) and Prospective Angiotensin Receptor-Neprilysin Inhibitor (ARNI) versus Angiotensin-Converting Enzyme (ACE) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction (PARADISE-MI) (2021) clinical trials revealed a substantial reduction in all-cause mortality from 9.4 to 4.2 per 100 patient-years (adjusted hazard ratio [HR] 0.68 [95% confidence interval [CI] 0.58 to 0.80]; P<0.001).[3]

The British Heart Foundation (BHF) estimates that in the 1960s 7 out of 10 people with a heart attack would die, and today 7 out of 10 people with a heart attack will survive.[1] It might be anticipated that, with an expanding population of post-MI survivors, the incidence of post-MI heart failure would also increase. Surprisingly, the opposite is true.[4] In an analysis of over 175 thousand patients in Scotland between 1991 and 2015 discharged alive from a first acute MI event and without a previous diagnosis of heart failure, the risk of all-cause mortality decreased by 46% and heart failure hospitalisations by 53%.[4] Similar trends have been seen in analyses in other global regions.[5–14] The proportion of patients developing heart failure during the index admission with MI has also decreased.[15]

Despite the reduction in the incidence of post-MI heart failure, its development remains associated with a 3- to 4-fold increased risk of mortality.[4,7,15,16] This underpins the importance of the prevention of heart failure following an MI.

Figure 1-1 Changing risk of mortality at 1 year post-MI in randomised trials



Mortality rates were estimated from visual inspection of each trial's Kaplan-Meier estimates of mortality at 1 year.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AIRE, Acute Infarction Ramipril Efficacy; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; EMPACT-MI, Study to Evaluate the Effect of Empagliflozin on Hospitalisation for Heart Failure and Mortality in Patients with Acute Myocardial Infarction; EPHESUS, Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; MRA, mineralocorticoid receptor antagonist; PARADISE-MI, Prospective Angiotensin Receptor–Neprilysin Inhibitor versus Angiotensin-converting Enzyme Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction; SAVE, Survival and Ventricular Enlargement; TRACE, Trandolapril Cardiac Evaluation; VALIANT, Valsartan in Acute Myocardial Infarction.

1.2 Left ventricular remodelling following myocardial infarction

The pathological precursor to the development of chronic heart failure following an MI is ventricular dilation and a reduction in systolic function, a process known as progressive adverse left ventricular remodelling.

1.2.1 Pathophysiology of left ventricular remodelling following myocardial infarction

1.2.1.1 Early remodelling

Following an acute MI, the infarcted area becomes hypo- or akinetic, due to the loss of functional myocytes, disrupting the loading and mechanics of the left ventricle. This sudden change increases ventricular mechanical loading, contributing to ventricular dilation. Increased pressure in the ventricular cavity leads to increased wall stress (the law of Laplace), which further drives adverse remodelling.[17]

1.2.1.2 Infarct expansion and scar formation

At a structural level, thinning and dilation of the infarct zone occurs. The extent of ventricular dilation following MI has consistently been linked to higher mortality and adverse long-term outcomes.[18] An influx of inflammatory cells increases the local production of matrix metalloproteinases (MMPs), which break down collagen within the extracellular matrix. Combined with acute mechanical wall stress, this process leads to myocyte slippage. Subsequently, MMP activity is balanced by tissue inhibitors of metalloproteinases (TIMPs). This dynamic MMP/TIMP interplay initially causes collagen breakdown, leading to infarct zone thinning and dilation, followed by the accumulation of collagen and formation of an infarct scar. This scar tissue lacks the contractile properties of healthy myocardium and further compromises ventricular wall function. The loss of functional myocardium and the presence of scar tissue result in a progressive increase in ventricular volume and dilation.[17]

1.2.1.3 Inflammatory response

There is an immediate influx of inflammatory cells into the myocardium, triggering a local inflammatory response along with neurohormonal activation and oxidative stress.[17] The extracellular matrix undergoes significant change in both the infarct and remote zones as a reaction to the acute injury. Immune cells release growth factors, such as transforming growth factor ß1 (TGF-ß1), and express ACE, resulting in a local rise in angiotensin II levels. These processes promote fibroblast activation, leading to extracellular matrix fibrosis.[17]

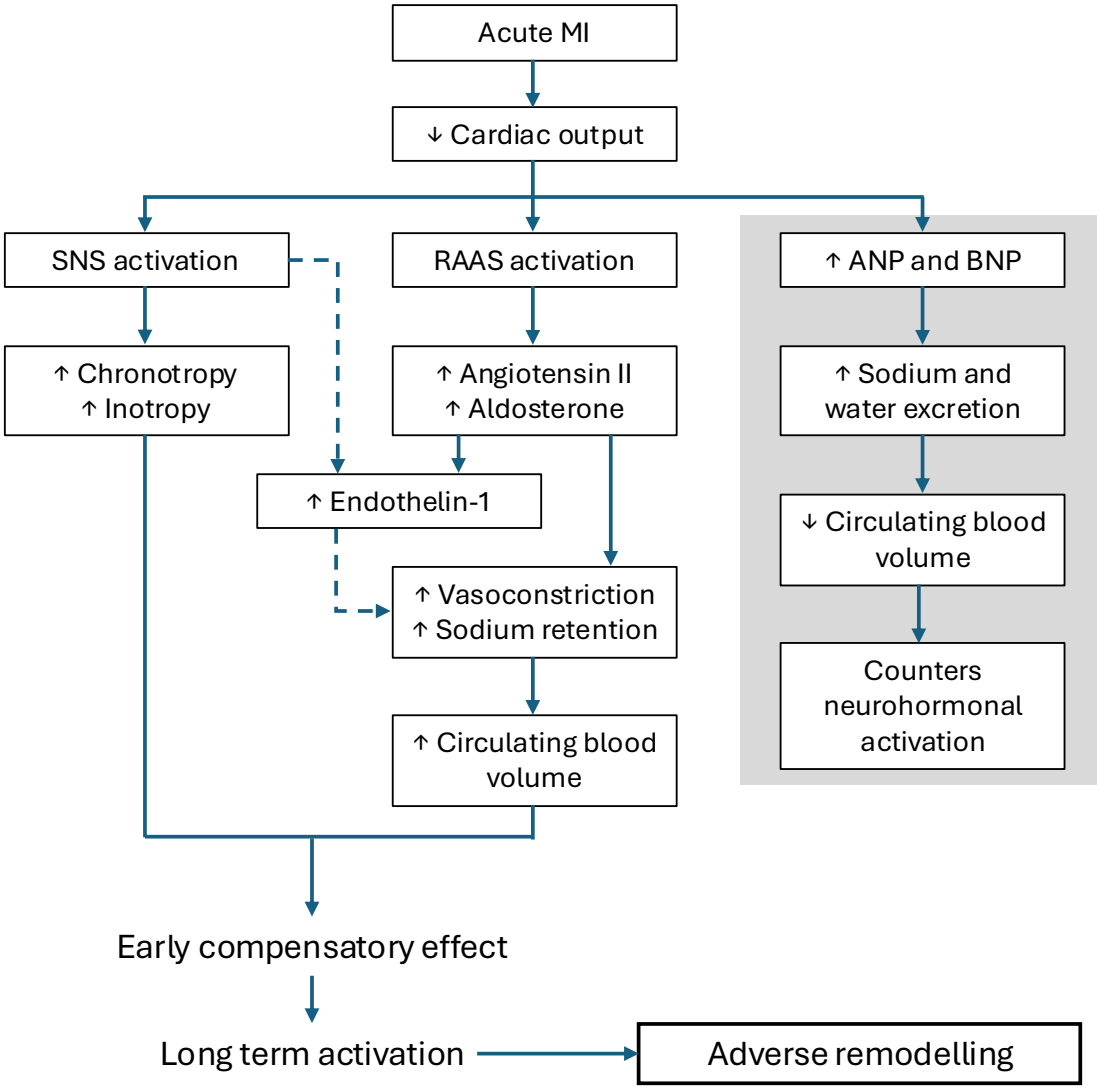
1.2.1.4 Neurohormonal activation

Immediately after an MI, the rapid decline in cardiac output activates neurohormonal systems, including the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) (Figure 1-2). Early SNS activation has a compensatory effect, increasing chronotropy and inotropy to maintain stroke volume despite a reduced cardiac output. The SNS also stimulates the RAAS, leading to the release of endothelin-1, a vasoconstrictor that increases afterload and promotes MMP activity. RAAS activation increases angiotensin II and aldosterone production, which maintain perfusion through vasoconstriction and sodium retention, thereby increasing circulating blood volume.[19]

Activation of the SNS and the RAAS can persist in the long term, driving myocardial hypertrophy, oxidative stress, inflammation, and apoptosis in both the infarct and remote myocardial regions. These processes amplify adverse remodelling and ventricular dysfunction.[19] To counteract maladaptive neurohormonal effects, atrial and B-type natriuretic peptides are released, which reduce intravascular volumes and systemic vascular resistance.[19]

Over time, these effects culminate in progressive impairment of left ventricular systolic function. The ejection fraction declines, and the ability of the ventricle to generate adequate contractile force is further compromised. This persistent systolic dysfunction underpins the development of clinical heart failure and increases the risk of mortality.

Figure 1-2 Neurohormonal activation post-MI



Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; MI, myocardial infarction; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

1.2.1.5 Ischaemia-reperfusion injury

Ischaemia-reperfusion injury, manifesting as microvascular obstruction (MVO), is a prognostically significant complication for which no effective treatment currently exists.[20,21] MVO occurs in approximately half of patients presenting with ST-elevation MI (STEMI).[22] MVO is best revealed by cardiovascular magnetic resonance (CMR) imaging, appearing as a hypointense core within the infarct zone on late gadolinium enhancement (LGE) imaging.[21]

MVO reflects microvascular damage and impaired tissue perfusion. If perfusion is not restored, capillary degradation transitions to intramyocardial haemorrhage (IMH), further exacerbating adverse left ventricular remodelling and adverse cardiac outcomes.[22] Despite its impact, there are currently no established interventions to prevent MVO at the time of primary percutaneous coronary intervention (PCI) or to treat it afterwards.

1.2.2 Epidemiology of left ventricular remodelling following myocardial infarction

Left ventricular remodelling is a major determinant of outcome post-MI.[18,23-25] Historical data from the pre-PCI era showed higher incidences of left ventricular systolic dysfunction due to limited treatments compared to contemporary populations receiving advanced therapies. In the echocardiographic sub-study of the Survival and Ventricular Enlargement (SAVE) trial, 41% of patients had received thrombolysis and 17% received PCI.[18] By 1 year, increases in left ventricular end-diastolic and end-systolic areas were observed in the overall cohort, and left ventricular enlargement was associated with adverse cardiac events.[18] At 2 years, 36% had left ventricular diastolic dilation and 40% had left ventricular systolic dilation defined as an increase >1.96 times the standard deviation (SD) of reproducibility for each measurement above baseline.[24]

In a sub-study of patients with anterior Q wave infarcts who had reperfusion therapy in the Healing and Early Afterload Reducing Therapy (HEART) study (65% had thrombolysis, 15% had PCI, 8% had both), the majority of patients had some recovery in left ventricular function by 90 days.[26] 23% had complete recovery, defined as left ventricular ejection fraction (LVEF) >55% and no regional akinesis or dyskinesis, and 58% had partial recovery, defined as improved LVEF and decreased extent of regional akinesis or dyskinesis.[26] The majority of improvement was seen in the first two weeks (13% with complete recovery at 14 days and 22% with complete recovery at 90 days).[26] In an analysis of an Italian registry of patients between 1995 and 1997 who had primary PCI for acute MI, and in whom 70% were taking an ACE inhibitor at discharge, 30% had evidence of adverse remodelling at 6 months, defined as an increase in left ventricular end-diastolic volume (LVEDV) ≥20%.[27] Adverse

remodelling was associated with cardiac death and hospitalisation for heart failure at 61 months follow-up.[27]

In the contemporary era with high rates of the use of secondary preventative and emergency reperfusion therapy, left ventricular remodelling occurs in approximately half of patients with STEMI at one year.[28] In an analysis of a Dutch registry left ventricular remodelling was defined as an increase in LVEDV≥20%. ACE inhibitors/angiotensin receptor blockers (ARBs) and beta-blockers were prescribed in 97% and 95%, respectively. At one year, 48% of patients had adverse remodelling, and most of these (87%) occurred within the first 6 months post-MI.[28] Patients with left ventricular remodelling were more likely to be admitted to hospital for heart failure during follow-up.[28] In the French Predisposition Génétique à l'Insuffisance Cardiaque (PREGICA) cohort, LVEDV was increased by ≥20%, ≥15% and ≥10% in 42%, 49% and 56%, respectively, at 6 months post-MI.[29] All patients were treated with PCI and there were high rates of ACE inhibitor/ARB prescriptions (97%) and beta-blocker prescriptions (98%) as well as mineralocorticoid receptor antagonists (MRAs) (27%).[29] Adverse remodelling was associated with the composite of all-cause death or heart failure.[29]

In CMR studies, criteria used to define adverse remodelling remain controversial. Traditional thresholds, such as increase in LVEDV≥20%, were initially based on echocardiographic reproducibility data.[27] Cut-off values of a 12% or greater increase in left ventricular volumes by CMR have been proposed.[30] When these definitions were applied to a contemporary registry of revascularised STEMI patients in Glasgow, 26% had adverse remodelling.[31] Those exhibiting increases in both LVEDV and left ventricular end-systolic volume (LVESV) had higher risks of mortality and heart failure hospitalisation.[31] An analysis of 37 CMR studies published between 2010 to 2019 included 4209 patients, 93% of whom had had PCI.[32] Definitions of adverse remodelling varied widely between the studies, and the prevalence of remodelling was between 11% and 48%, with a pooled prevalence of 23%.[32]

The data presented suggest that, despite advanced treatments, a substantial proportion of patients continue to develop progressive adverse left

ventricular remodelling after MI, which is associated with worse outcomes. Preventing this remodelling should be a clinical focus.

1.2.3 Prevention of left ventricular remodelling following myocardial infarction

One of the key advances in the treatment of MI was the demonstration that pharmacological attenuation of adverse remodelling was associated with a reduction in the risk of heart failure and mortality. By inhibiting the maladaptive neurohormonal activation which promotes adverse remodelling, ACE inhibitors or ARBs, beta-blockers, and MRAs reduce the risk of heart failure and mortality following MI.[18,25,33–41]

1.2.3.1 Coronary reperfusion therapy

The pivotal role of coronary reperfusion in reducing infarct size and mitigating the subsequent risk of heart failure is now well established. Coronary artery occlusion is the initial event in a cascade leading to adverse left ventricular remodelling and impaired systolic function. The effects of reperfusion were first described by Maroko and Braunwald in 1973, who demonstrated in a canine model that reperfusion reduces infarct size.[42] This work laid the foundation for the “open artery hypothesis”, derived from observations in a rat model of STEMI, and which proposed that early reperfusion of the infarct-related artery improves survival and preserves left ventricular systolic function.[43,44]

The survival benefits of thrombolytic therapy in patients with STEMI were demonstrated in two landmark randomised-controlled trials; Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico (GISSI) and Second International Study of Infarct Survival (ISIS-2).[45,46] One meta-analysis confirmed that prehospital thrombolysis, enabling earlier reperfusion, was associated with a more substantial reduction in mortality.[47] Adequate restoration of flow was recognised as being critical for the preservation and recovery of left ventricular function.[48]

Building on the striking decrease in mortality from thrombolysis, advances in percutaneous techniques, including balloon angioplasty and coronary stenting, emerged as superior methods for restoring coronary flow.[49] PCI has

been shown to yield greater improvements in left ventricular function and a more pronounced reduction in infarct size compared with thrombolysis.[50] Additionally, delays to PCI are correlated with worsening left ventricular function and an increased risk of heart failure.[51] PCI accounted for 46% of the attenuation observed in all-cause death between the VALIANT and PARADISE-MI trials.[3] Accordingly, urgent revascularisation with primary PCI is now the standard of care for patients with STEMI.[52,53]

1.2.3.2 Renin angiotensin system

Three major trials have evaluated the long-term effects of ACE inhibitors in high-risk patients post-MI; the SAVE, Acute Infarction Ramipril Efficacy (AIRE) and Trandolapril Cardiac Evaluation (TRACE) trials. Collectively, these studies demonstrated a 28% reduction in mortality, MI and heart failure hospitalisation for patients with left ventricular dysfunction post-MI.[54] An echocardiographic sub-study of the SAVE trial revealed that captopril mitigated increases in left ventricular end-diastolic and end-systolic areas at one year in patients with an LVEF<40% post-MI, compared to placebo.[18] Subsequently, the VALIANT trial established that valsartan, an ARB, achieved similar outcomes and effects on left ventricular remodelling as captopril.[25,37]

1.2.3.3 Sympathetic nervous system

In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, which included 1959 post-MI patients with an LVEF≤40%, there was a 20% relative reduction in all-cause mortality over a mean follow-up of 1.3 years with the addition of carvedilol to ACE inhibitor therapy.[38] Patients receiving carvedilol also showed less adverse left ventricular remodelling compared to those on placebo.[39]

1.2.3.4 Mineralocorticoid receptor antagonists

The Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) examined the impact of the MRA eplerenone in high-risk patients following acute MI.[40] Among patients with LVEF≤40% and either type 2 diabetes mellitus (T2DM) or signs/symptoms of heart failure, eplerenone reduced the risk of all-cause death and a composite of death, heart failure hospitalisation, MI, stroke, and arrhythmia.[40] However, the anti-

remodelling effect of MRAs appear less pronounced compared to ACE inhibitors and beta-blockers. In a CMR trial of post-MI patients with LVEF<40% by echo and without T2DM, eplerenone had a minimal remodelling effect, reaching statistical significance only after covariate adjustment.[41]

1.2.3.5 Neprilysin inhibition

The PARADISE-MI trial evaluated sacubitril/valsartan compared with the ACE inhibitor ramipril in patients following acute MI complicated by left ventricular systolic dysfunction, pulmonary congestion, or both.[55] There was no difference in the primary outcome of cardiovascular death or heart failure events (outpatient symptomatic heart failure or heart failure hospitalisation) (HR 0.90 [95% CI 0.78 to 1.04]; p=0.17).[55] However, exploratory analyses showed sacubitril/valsartan reduced the total number of heart failure events and investigator-reported events.[56] Sacubitril/valsartan was associated with higher rates of hypotension, and this, with the neutral primary outcome, has precluded its routine recommendation in guidelines for high-risk patients post-MI.[55] Furthermore, in a subset of patients in the PARADISE-MI trial who had serial echo assessments, and in a randomised-controlled trial of remote survivors of MI, sacubitril/valsartan had only a minimal anti-remodelling effect.[57,58]

1.3 Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of drug derived from phlorizin, a non-specific SGLT1 and SGLT2 inhibitor first sourced from the root bark of the apple tree by French chemists in 1835.[59] SGLT2 is a transporter protein primarily found in the proximal collecting duct of the kidneys, and is responsible for the reabsorption of approximately 90% of glucose from the renal filtrate.[60] By inhibiting SGLT2, glucose is excreted in the urine.

Whilst the mechanism of action of SGLT2 inhibitors was initially targeted at glucose excretion, these medications have additional cardiovascular and renal benefits in populations with and without T2DM, vascular disease, heart failure across the range of ejection fraction and chronic kidney disease (CKD). These beneficial effects are mediated through mechanisms beyond

their glucose-lowering effects. A summary of all landmark cardiovascular outcome trials (CVOTs) for SGLT2 inhibitors is shown in Table 1-1.

1.3.1 Clinical evidence of benefits of SGLT2 inhibitors

1.3.1.1 Type 2 diabetes mellitus

The first CVOTs for SGLT2 inhibitors were conducted in patients with T2DM and at high risk for cardiovascular events. These assessments were mandated by the United States Food and Drug Administration and European Medicines Agency, following concerns for cardiovascular safety raised by the association with rosiglitazone and an increased risk of heart failure.[61,62]

The first CVOT, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME), enrolled 7020 patients with T2DM and at high risk for cardiovascular events.[63] Patients were randomised to empagliflozin 10mg or 25mg once daily, or placebo. Treatment with empagliflozin reduced the primary outcome of cardiovascular death, MI or stroke, and was associated with a marked reduction in the risk of hospitalisation for heart failure.[63]

Building on these findings, 5 additional landmark CVOTs were conducted in patients with T2DM – Canagliflozin Cardiovascular Assessment Study (CANVAS), CANVAS Renal, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS-CV).[64–67] In a meta-analysis of these six trials, totalling 46,969 patients, there was a reduced risk of major adverse cardiovascular events (HR 0.90 [95% CI 0.85 to 0.95]; Q statistic P=0.27) and a consistent, substantial reduction in hospitalisation for heart failure across all trials (HR 0.68 [95% CI 0.61 to 0.76]; I^2=0.0%).[68]

The proportions of patients with a history of MI were reported for EMPA-REG OUTCOME (47%), DECLARE-TIMI 58 (21%) and VERTIS-CV (48%).[67,69,70] Subgroup analyses revealed higher baseline event rates in patients with a history of MI.[69,70] In EMPA-REG OUTCOME, reductions in death and hospitalisation for

heart failure were consistent across subgroups with and without prior MI.[69] However, in DECLARE-TIMI 58, the primary outcome of cardiovascular death, MI or stroke was reduced only in patients with a history of prior MI (P for interaction=0.048).[70] It is important to note that all of these trials excluded patients within 8–12 weeks of an acute MI.[63-67]

1.3.1.2 Heart failure

SGLT2 inhibitors reduce the risk of worsening heart failure and mortality in patients with chronic heart failure across the full spectrum of LVEF.[71-75] Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) established the benefits of SGLT2 inhibitors for reducing cardiovascular death and heart failure worsening in patients with chronic heart failure with reduced ejection fraction (HFrEF), while Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) demonstrated the same in patients with heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).[71-74]

In a patient-level pooled analysis of the DAPA-HF and DELIVER trials, to which I contributed as a co-author, 44% of patients with LVEF≤40% and 26% of those with LVEF>40% had a history of MI.[76] Patients with prior MI were at a higher risk of worsening heart failure events or cardiovascular death across the spectrum of LVEF.[76] Notably, dapagliflozin consistently reduced the risk of cardiovascular death or heart failure worsening in patients with and without a prior MI.[76] However, none of the CVOTs in chronic heart failure included patients within approximately 12 weeks of an acute MI.[71-74]

Two major CVOTs have evaluated the effects of SGLT2 inhibitors in patients hospitalised for acute heart failure.[77,78] The first, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF), recruited patients with T2DM, regardless of LVEF.[77] Sotagliflozin, a dual SGLT1/2 inhibitor, reduced the total number of cardiovascular deaths and hospitalisations and urgent visits for heart

failure.[77] Empagliflozin in Patients Hospitalised With Acute Heart Failure Who Have Been Stabilized (EMPULSE) included patients hospitalised for acute heart failure regardless of T2DM status or LVEF.[78] Empagliflozin reduced the primary hierarchical endpoint of all-cause death, heart failure events, time to first heart failure event and achieving a ≥5 point improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) analysed using a win ratio approach.[78] Additionally, a subgroup analysis of the DELIVER trial showed that the benefits of dapagliflozin were consistent for patients randomised during an acute hospitalisation or within 30 days of discharge.[79] Across these 3 trials, approximately one-quarter of patients had a history of MI, although no specific subgroup analyses have been performed.[77-79] The ongoing Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure-Thrombolysis in Myocardial Infarction 68 (DAPA ACT HF-TIMI 68) (NCT04363697) trial is assessing the effects of dapagliflozin in patients hospitalised for acute heart failure, across the spectrum of LVEF and irrespective of T2DM status, with the exclusion of patients within 30 days of a STEMI.

1.3.1.3 Chronic kidney disease

In two landmark trials, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY), SGLT2 inhibitors prevented the progression of renal disease and renal and cardiovascular death in patients with CKD.[80,81] In a pre-specified secondary analysis of the DAPA-CKD trial, patients with cardiovascular disease had a consistent benefit with dapagliflozin than those without.[82] 37% of the trial population had cardiovascular disease, encompassing coronary, cerebrovascular and peripheral arterial disease as well as heart failure and device therapy, with 24% of these patients having a history of prior MI.[82]

The Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial further supported these findings, showing that in 10,584 patients with T2DM, CKD and cardiovascular risk factors, of whom 20% had a history of MI, sotagliflozin reduced the total number of cardiovascular deaths, heart failure hospitalisations and urgent visits for

heart failure.[83] However, as observed in the SOLOIST-WHF trial, sotagliflozin was associated with higher rates of diarrhoea, likely reflecting its SGLT1 inhibiting effects in the intestines.[83]

1.3.1.4 Acute myocardial infarction

The necessity to evaluate evidence-based medical therapy for chronic heart failure in the acute MI setting is highlighted by the PARADISE-MI trial. Sacubitril/valsartan, which improves outcomes in chronic HFrEF, did not reduce cardiovascular death or heart failure in high-risk patients following acute MI.[55,84] The clinical scenario following acute MI differs significantly from chronic HFrEF, as it involves a sudden, sometimes transient reduction in LVEF, emergency coronary interventions, and the initiation of multiple secondary prevention therapies. Establishing the efficacy and safety of novel agents in the acute MI setting is crucial, rather than extrapolating evidence from chronic HFrEF.

At the time of starting my PhD, there were no data to support the initiation of SGLT2 inhibitors early following acute MI, as the CVOTs discussed above in patients with T2DM, heart failure and CKD excluded patients who were less than 8-12 weeks following acute MI (Table 1-1). Now, there are two completed large CVOTs, Dapagliflozin in Patients with MI (DAPA-MI) and the Study to Evaluate the Effect of Empagliflozin on Hospitalisation for Heart Failure and Mortality in Patients with Acute Myocardial Infarction (EMPACT-MI).[85,86]

The DAPA-MI trial randomised 4017 patients without T2DM who had an acute MI and any degree of left ventricular systolic dysfunction or Q waves to receive either dapagliflozin 10mg once daily or placebo.[85] Initially, the primary outcome was a composite of cardiovascular death or heart failure hospitalisation, but due to a lower-than-predicted event rate, this outcome was changed to a hierarchal win ratio assessment of death, hospitalisation for heart failure, non-fatal MI, the occurrence of atrial fibrillation/flutter, new-onset diabetes, New York Heart Association (NYHA) class at the final trial visit, and a decrease in body weight of ≥5% from baseline. Patients in the dapagliflozin arm of the trial were 34% more likely to have a favourable outcome than those randomised to placebo. However, this benefit was due to

effect on cardiometabolic components, with no effect on death or heart failure hospitalisation.[85]

The EMPACT-MI trial randomised 6522 patients within 14 days of acute MI, with an LVEF<45% and/or signs or symptoms of congestion and at least one additional heart failure risk factor, to empagliflozin 10mg once daily or placebo.[86] Over a median follow-up of 17.9 months, there was no difference in the primary composite outcome of first hospitalisation for heart failure and all-cause mortality (HR 0.90 [95% CI 0.76 to 1.06]; P=0.21). In an exploratory analysis assessing the individual components of the primary endpoint, empagliflozin reduced the risk of hospitalisation for heart failure (HR 0.77 [95% CI 0.60 to 0.98]; P=0.031).[86] Those in the empagliflozin group had a lower number of total heart failure hospitalisations, investigator-defined heart failure events, and outpatient heart failure worsening events.[87]

Table 1-1 Cardiovascular outcome trials of SGLT2 inhibitors

Trial Author/year	Population	SGLT2 inhibitor	Primary outcome	Heart failure outcome	Time window MI exclusion	% with prior MI	Prior MI/ischaemic/CVD subgroup analyses
T2DM							
EMPA-REG OUTCOME[63] Zinman 2015	n=7020 T2DM + ASCVD	Empa	CV death, MI or stroke HR 0.86 (0.74-0.99); P=0.04	HHF HR 0.65 (0.50-0.85); P=0.002	<2 months	46.6%	Prior MI CV death, all-cause death and HHF reduction consistent across groups with/without prior MI[69]
CANVAS Program[64] Neal 2017	n=10,142 T2DM + ASCVD/RFs	Cana	CV death, MI or stroke HR 0.86 (0.75-0.97); P=0.02	HHF HR 0.67 (0.52-0.87); P value NR	<3 months	NR	NR
DECLARE-TIMI 58[65] Wiviott 2019	n=17,160 T2DM + ASCVD/RFs	Dapa	CV death, MI or stroke HR 0.93 (0.84-1.03); P=0.17 CV death or HHF HR 0.83 (0.73-0.95); P=0.005	HHF HR 0.73 (0.61-0.88); P value NR	<8 weeks	20.9%	Prior MI CV death, MI or stroke in patients with prior MI P=0.039, without prior MI P=0.97; P for interaction=0.048.

							Consistent reduction in CV death or HHF[70]
CREDENCE[66] Perkovic 2019	n=4401 T2DM + CKD	Cana	ESKD, 2x creatinine, renal or CV death HR 0.70 (0.59-0.82); P<0.001	HHF HR 0.61 (0.47 – 0.80); P<0.001	<12 weeks	NR	NR
VERTIS-CV[67] Cannon 2020	n=8246 T2DM + ASCVD	Ertu	CV death, MI or stroke HR 0.97 (0.85-1.11); P<0.001 for noninferiority	HHF HR 0.70 (0.54-0.90); P value NR	<3 months	48.0%	NR
Heart failure							
EMPEROR-Reduced[71] Packer 2020	n=3730 Chronic HF LVEF≤40%	Empa	CV death or HHF HR 0.75 (0.65-0.86); P<0.001	HHF HR 0.69 (0.59-0.81); P value NR	<90 days	NR 51.7% with ischaemic cause of HF	Ischaemic HF Primary outcome consistent across ischaemic/non-ischaemic subgroups
EMPEROR-Preserved[72] Anker 2021	n=5988 Chronic HF LVEF>40%	Empa	CV death or HHF HR 0.79 (0.69-0.90); P<0.001	HHF HR 0.71 (0.60-0.83); P value NR	<90 days	NR 35.4% with ischaemic cause of HF	Ischaemic HF Primary outcome consistent across ischaemic/non-ischaemic subgroups
DAPA-HF[73] McMurray 2019	n=4744 Chronic HF LVEF≤40%	Dapa	CV death or worsening HF HR 0.74 (0.65-0.85); P<0.001	HHF HR 0.70 (0.59-0.83); P value NR	<12 weeks	44.1%	Prior MI Primary outcome consistent across groups with/without prior

							MI (pooled DAPA-HF/DELIVER analysis)[76]
DELIVER[74] **Solomon 2022**	n=6263 Chronic HF LVEF>40%	Dapa	CV death or worsening HF HR 0.82 (0.73-0.92); P<0.001	HHF HR 0.77 (0.67-0.89); P value NR	<12 weeks	26.2%	Prior MI Primary outcome consistent across groups with/without prior MI (pooled DAPA-HF/DELIVER analysis)[76]
SOLOIST-WHF[77] **Bhatt 2021**	n=1222 Hospitalised HF + T2DM	Sota	CV death, HHF and urgent HF visits HR 0.67 (0.52-0.85); P<0.001	Total HHF and urgent HF visits HR 0.64 (0.49-0.83); P<0.001	<3 months	24.1% (of subgroup of 1113 with KCCQ-12[88]) 58.3% with ischaemic cause of HF	Ischaemic HF Primary outcome consistent across ischaemic/non-ischaemic subgroups
EMPULSE[78] **Voors 2022**	n=530 Hospitalised HF	Empa	All-cause death, number of HFEs, time to first HFE, ≥5 point change in KCCQ Win ratio 1.36 (1.09-1.68); P=0.0054	NR	<90 days	24.2%	NR
CKD							

DAPA-CKD[80] **Heerspink 2020**	n=4304 CKD	Dapa	≥50% decline in eGFR, ESKD, renal or CV death HR 0.61 (0.51-0.72); P<0.001	HHF HR 0.51 (0.34-0.76); P value NR[89]	<12 weeks	9.6%	CVD Primary outcome consistent across subgroups with/without CVD[82]
SCORED[83] **Bhatt 2021**	n=10,584 CKD, T2DM + RFs	Sota	CV death, HHF and urgent HF visits HR 0.74 (0.63-0.88); P<0.001	Total HHF and urgent HF visits HR 0.67 (0.55-0.82); P<0.001	Not stated	19.9%	CVD Primary outcome consistent across subgroups with/without CVD
EMPA-KIDNEY[81] **2023**	n=6609 CKD	Empa	Progression of kidney disease or CV death HR 0.72 (0.64-0.82); P<0.001	NR	8-12 weeks	NR 26.7% with CVD	CVD Primary outcome consistent across subgroups with/without CVD
Acute MI							
DAPA-MI[85] **James 2023**	n=4017 Acute MI without T2DM	Dapa	Death, HHF, AFF, T2DM, NYHA at last visit, ≥5% decrease in body weight Win ratio 1.34 (1.20-1.50); P<0.001	HHF HR 0.83 (0.50-1.39); P value NR	NA	NA	NA
EMPACT-MI[86] **Butler 2024**	n=6610 Acute MI + LVEF<45% or congestion	Empa	Death or HHF HR 0.90 (0.76-1.06); P=0.21	HHF HR 0.77 (0.60-0.98); P=0.031[87]	NA	NA	NA

Abbreviations: AFF, atrial fibrillation/flutter; ASCVD, atherosclerotic cardiovascular disease; Cana, canagliflozin; CANVAS, Canagliflozin Cardiovascular Assessment Study; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established

Nephropathy Clinical Evaluation; CV, cardiovascular; CVD, cardiovascular disease; Dapa, dapagliflozin; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DAPA-MI, Dapagliflozin in Patients with Myocardial Infarction; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; EMPACT-MI, Study to Evaluate the Effect of Empagliflozin on Hospitalisation for Heart Failure and Mortality in Patients with Acute Myocardial Infarction; EMPA-KIDNEY, Study of Heart and Kidney Protection with Empagliflozin; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPULSE, Empagliflozin in Patients Hospitalised With Acute Heart Failure Who Have Been Stabilized; Ertu, ertugliflozin; ESKD, end-stage kidney disease; HF, heart failure; HFE, heart failure event; HHF, hospitalisation for heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NR, not reported; NYHA, New York Heart Association; RFs, risk factors; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SGLT2, sodium-glucose co-transporter 2 inhibitor; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; Sota, sotagliflozin; T2DM, type 2 diabetes mellitus; VERTIS-CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

1.3.2 Clinical evidence for an anti-remodelling effect of SGLT2 inhibitors

1.3.2.1 Heart failure

Both the progression of existing HFrEF and the development of heart failure after an MI are driven by adverse left ventricular remodelling. As such, neurohormonal inhibitors, such as beta-blockers and RAAS inhibitors, are recommended for treating both conditions. These therapies improve outcomes in established HFrEF, and have a beneficial effect on remodelling.[90–97] They also show similar positive effects in patients with post-MI systolic dysfunction, including the prevention of progressive adverse remodelling and the onset of HFrEF.[18,25,33–41] SGLT2 inhibitors, which improve outcomes in HFrEF, also demonstrate an anti-remodelling effect in patients with established chronic HFrEF. Three randomised, placebo-controlled trials have demonstrated that empagliflozin reduces left ventricular volumes in chronic HFrEF; Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction (Empire HF), Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycaemic Activity? (EMPA-TROPISM) and Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure (SUGAR-DM-HF).[98–100]

The Empire HF trial echocardiographic sub-study evaluated the impact of empagliflozin on left ventricular function and volumes in 190 patients with HFrEF, regardless of T2DM status, over 12 weeks of treatment.[99] Patients receiving empagliflozin had reductions in LVESV index (LVESVI), LVEDV index (LVEDVI) and left atrial volume index (LAVI), while no differences were observed in LVEF.[99] In the primary analysis, empagliflozin had no effect on the change in N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) over 12 weeks.[101]

The EMPA-TROPISM trial randomised 84 patients with HFrEF and without T2DM to empagliflozin or placebo for 6 months.[100] Empagliflozin reduced CMR-derived LVEDV, LVESV and left ventricular mass, and improved LVEF. Additional benefits included enhanced functional capacity, measured by

cardiopulmonary exercise testing and 6-minute walk test, as well as improved health status reflected in KCCQ-12 scores.[100]

The SUGAR-DM-HF trial, conducted in Glasgow, enrolled 105 patients with symptomatic HFrEF and either T2DM or prediabetes.[98] Patients were randomised to receive empagliflozin 10mg or placebo for 36 weeks. The co-primary outcomes were changes in LVESVI and left ventricular global longitudinal strain (LVGLS), assessed by CMR. There was a greater reduction in LVESVI with empagliflozin compared to placebo, although there was no difference in LVGLS. Furthermore, empagliflozin resulted in a greater reduction in LVEDVI, but no differences were observed in LVEF, left ventricular mass index (LVMI) or LAVI. Additionally, NT-proBNP levels were reduced in the empagliflozin group.[98]

The Assessment of Cardiac Energy Metabolism, Function and Physiology in Patients With Heart Failure Taking Empagliflozin (EMPA-VISION) trial explored the effects of empagliflozin on cardiac energetics in patients with nonischaemic chronic heart failure (36 with HFrEF and 36 with HFpEF).[102] In the HFrEF cohort, there was a 4.5 g/m^2 reduction in LVMI (95% CI -8.4 to -0.5; P=0.03) with empagliflozin compared to placebo, along with reductions in native T1 and cell volume. No differences were seen in LVEF or LVEDV. No differences in any CMR measure were observed in the HFpEF cohort. The EMPA-VISION trial is limited by its small sample size, and it was not powered to show differences in left ventricular remodelling parameters which were exploratory outcomes.[102]

Three trials have reported on the effect of dapagliflozin in HFrEF. The Safety and Effectiveness of SGLT-2 Inhibitors in Patients With Heart Failure and Diabetes (REFORM) trial showed no effect of dapagliflozin on left ventricular remodelling in patients with T2DM and a history of heart failure with previously documented LVEF reduction.[103] This trial was limited by its small sample size (n=56) and mild severity of heart failure.[103] The Short-term Effects of Dapagliflozin on Peak Oxygen Consumption in HFrEF (DAPA-VO2) trial showed no difference in any echocardiographic endpoints of left ventricular remodelling in patients with HFrEF with or without T2DM after only 3 months of treatment with dapagliflozin.[104] Finally, in 60 patients with

HFrEF and T2DM, 1 year of treatment with dapagliflozin improved LVEF and reduced LVEDV and LVESV.[105]

1.3.2.2 Type 2 diabetes mellitus

SGLT2 inhibitors have been extensively studied in populations with T2DM without heart failure for their effects on left ventricular remodelling, although outcomes vary depending on patient populations and study design.[106–114] The Effects of Empagliflozin on Cardiac Structure in Patients with Type 2 Diabetes (EMPA-HEART) CardioLink-6 randomised placebo-controlled trial, evaluated 97 patients with T2DM and coronary artery disease. Over 6 months, treatment with empagliflozin reduced LVMI, but had no effect on left ventricular volumes, function or NT-proBNP levels.[106] In contrast, the EMPA-HEART 2 CardioLink-7 trial assessed the effects of empagliflozin in patients without T2DM or heart failure but at risk of left ventricular remodelling. The study found no impact on remodelling parameters, suggesting the benefits of SGLT2 inhibitors may be more pronounced in patients with existing metabolic or cardiac conditions.[115] The SOdium-glucose CO-transporter inhibition in patients with newly detected Glucose Abnormalities and a recent Myocardial Infarction (SOCOGAMI) trial examined the effect of empagliflozin on LVEDV in 42 patients with T2DM or impaired glucose tolerance and within 6 months of an MI or unstable angina event.[116] There was no effect on left ventricular volumes or function, though the small sample size and unreported time from index event to randomisation limits application to acutely post-MI populations.[116]

1.3.2.3 Acute myocardial infarction

These findings underscore the potential for SGLT2 inhibitors to influence cardiac structure and function, particularly in heart failure populations. There are three randomised, placebo-controlled clinical trials, outlined below, which assess the effect of SGLT2 inhibitors on adverse remodelling acutely post-MI.

The EMpagliflozin in patients with acute Myocardial infarction (EMMY) trial examined the effect of empagliflozin versus placebo on NT-proBNP concentrations in 476 patients within 72 hours of a large acute MI, defined by

creatine kinase >800 IU/L or troponin >10 times the upper limit of normal.[117] The primary outcome was the change in NT-proBNP from randomisation to 26 weeks. Treatment with empagliflozin resulted in a 15% reduction in NT-proBNP (95% CI −4.4 to −23.6; P=0.026) compared to placebo. Additionally, secondary echocardiographic outcomes showed favourable placebo-corrected changes in LVEF (+1.5% [95% CI 0.2 to 2.9]; P=0.014), LVESV (−7.5 ml [95% CI -11.5 to -3.4]; P=0.0003), and LVEDV (−9.7 ml [-15.7 to -3.7]; P=0.0015). However, in a *post hoc* subanalysis of centrally analysed echocardiograms of 313 patients, there was no change in LVEF, and the changes LVESV and LVEDV just reached statistical significance (LVEDV P=0.048, LVESV P=0.044).[118]

The Impact of Dapagliflozin on Cardiac Function Following Anterior Myocardial Infarction in Non-diabetic Patients (DACAMI) trial assessed the impact of dapagliflozin on cardiac function in 100 patients with anterior STEMI and without T2DM.[119] Patients were randomised to receive dapagliflozin or placebo for 12 weeks, with the primary outcomes being changes in NT-proBNP and echocardiographic markers of remodelling. NT-proBNP was reduced more in the dapagliflozin group, but only LVMI showed a difference in echocardiographic measures.[119] The trial was powered for NT-proBNP, and the shorter duration and limitations of echocardiography may explain the lack of observed remodelling benefits.

Finally, the Empagliflozin Effects in Patients with ST-Elevation Myocardial Infarction Undergoing Primary PCI (EMI-STEMI) trial enrolled patients with STEMI undergoing PCI without T2DM.[120] 106 patients were randomised to empagliflozin or placebo, administered immediately before PCI and continued for 40 days. The mean change in LVEF was greater in the empagliflozin group compared to the placebo group (4.6% vs 1.3%; P=0.001). Despite prompt reperfusion and high rates of secondary prevention therapy, the control group exhibited minimal improvement in LVEF (38.0% at baseline vs 39.2% at 40 days) and an unexpectedly high heart failure hospitalisation rate of 21.5% (compared to 4.16% of high-risk post-MI patients in the EMPACT-MI trial across 17.9 months follow-up).[120] These findings may have limited generalisability.

1.3.3 Potential mechanisms of action of SGLT2 inhibitors following myocardial infarction

The mechanisms of action underlying the clinical benefits of SGLT2 inhibitors are not completely understood. However, some suggested mechanisms could theoretically contribute to a favourable remodelling effect in the specific pathophysiological conditions arising in the post-MI period. These mechanisms are summarised in Figure 1-3.

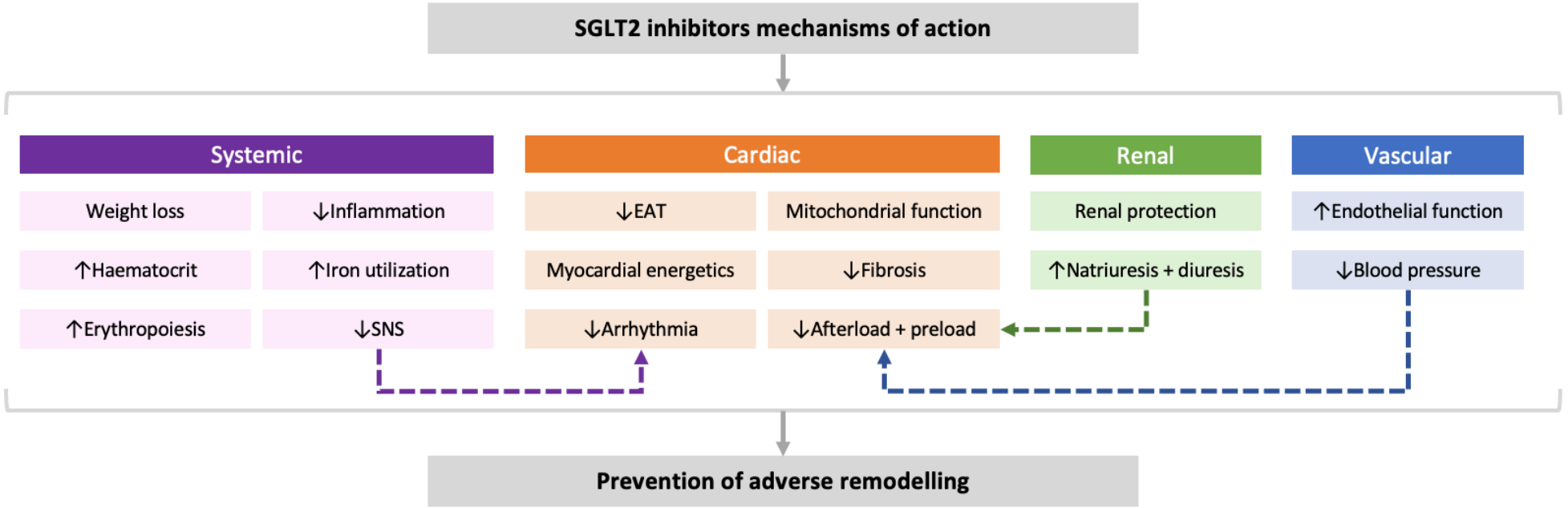
1.3.3.1 Ventricular loading and haemodynamic effects

In patients with heart failure, SGLT2 inhibition reduces invasively measured pulmonary pressure, NT-proBNP and LAVI all suggesting these agents reduce left ventricular filling pressure.[121–125] In the Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure (EMPA-RESPONSE-AHF) trial, involving 80 patients with acute heart failure, urinary output over 4 days was greater in the empagliflozin group.[126] However, in the EMPACT-MI trial, the reduction in risk of heart failure events with empagliflozin was consistent across groups with and without congestion at baseline, suggesting a diuretic effect is not the primary mechanism of benefit.[127] Furthermore, there was no difference in volume depletion events between the empagliflozin and placebo groups.[86]

1.3.3.2 Sympathetic nervous system and arrhythmias

One of the proposed mechanisms of action of SGLT2 inhibitors is a sympatholytic effect. However, in the Effects Of Empagliflozin Versus Placebo On Cardiac Sympathetic Activity In Acute Myocardial Infarction Patients With Type 2 Diabetes Mellitus (EMBODY) trial - a small, randomised trial of empagliflozin compared with placebo in patients with T2DM and acute MI - there was no benefit of empagliflozin compared with placebo on measures of cardiac sympathetic and parasympathetic nerve activity.[128] In an analysis of the DAPA-HF trial, dapagliflozin reduced the risk of serious ventricular arrhythmia, cardiac arrest, or sudden death in patients with HFrEF.[129]

Figure 1-3 Potential mechanisms of action of SGLT2 inhibitors post-MI



Abbreviations: EAT, epicardial adipose tissue; SGLT2, sodium-glucose co-transporter 2; SNS, sympathetic nervous system.

1.3.3.3 Weight loss and adipose tissue

SGLT2 inhibitors cause glucosuria and urinary loss of calories resulting in weight loss. In the DAPA-HF trial, dapagliflozin was associated with a small reduction in body weight.[130] Similarly, in the DAPA-MI trial, the cardiometabolic benefits of dapagliflozin included a ≥5% reduction in body weight from baseline.[85]

SGLT2 inhibition reduces epicardial adipose tissue and subcutaneous adipose tissue volume in HFrEF patients without diabetes.[131] A reduction in pro-inflammatory biomarkers is also seen, which may contribute to a favourable effect on attenuating adverse remodelling post-MI.

1.3.3.4 Increased erythropoiesis and iron utilisation

Empagliflozin had notable effects on erythropoiesis in the Empire HF trial, increasing erythropoietin production and altering red blood cell morphology.[132] Additionally, treatment with empagliflozin enhanced myocardial iron content as measured by CMR in the EMPA-TROPISM trial.[133] In the small number of patients receiving empagliflozin in the Noninvasive Imaging Estimation of Myocardial Iron Repletion Following Administration of Intravenous Iron (Myocardial-IRON) trial, improvements in myocardial iron content were more pronounced with intravenous iron compared to those not receiving empagliflozin.[134]

The DAPA-HF trial showed that patients with baseline anaemia were more likely to achieve anaemia correction with dapagliflozin compared to placebo.[135] Dapagliflozin also induced changes in biomarkers of iron mobilisation, including reductions in hepcidin, ferritin, and transferrin saturation (TSAT), and an increase in serum transferrin receptor (sTFR), likely driven by increased erythropoiesis.[136] In the EMPEROR-Reduced trial, new-onset anaemia in those without anaemia at baseline was reduced with empagliflozin.[137]

An analysis of the Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency (IRONMAN) trial revealed a numerical trend towards a greater haemoglobin increase with intravenous ferric derisomaltose in iron-deficient heart failure patients

concurrently on an SGLT2 inhibitor, although the small sample size limited the robustness of these findings.[138]

In patients with heart failure and iron deficiency, intravenous iron replenishment increases cardiac contractility, myocardial iron content and has favourable remodelling effects.[139,140] It is possible that the improved iron utilisation and myocardial iron content seen with SGLT2 inhibition may be associated with beneficial remodelling effects following acute MI.

1.3.3.5 Kidney-protective effects

Patients who are post-MI are vulnerable to multifactorial renal insults (acute haemodynamic instability, reduced cardiac output, contrast agents, initiation of nephrotoxic drugs). Patients with worse kidney function immediately following MI are at increased risk of cardiovascular death and development of heart failure.[141]

Reassuringly, in the EMPACT-MI trial, there was no increase in kidney-related adverse events with empagliflozin, and in the DAPA-MI trial there was no difference in the change in estimated glomerular filtration rate (eGFR) between dapagliflozin and placebo groups.[85,86] In patients with HFrEF, initiation of an SGLT2 inhibitor causes an initial decline in eGFR, followed by recovery and then a slower rate of decline when compared with placebo.[71,142] Importantly, this pattern was also observed in high-risk post-MI patients in the EMPACT-MI trial.[143]

A greater degree of kidney dysfunction also precludes the prescription and up-titration of medical therapy, e.g., RAAS inhibitors and MRAs. As well as attenuating the decline in kidney function over time, SGLT2 inhibitors may also have other kidney-protective effects in patients following acute MI. For example, in recent analyses of trials of SGLT2 inhibitors in HFrEF, SGLT2 inhibitors reduce the risk of hyperkalaemia associated with MRA and the rate of MRA discontinuation.[144,145]

1.3.3.6 Myocardial metabolome

A shift in the myocardial metabolome from the preferential breakdown of glucose to the more energy efficient metabolism of ketone bodies has been

considered a potential mechanism contributing to the clinical benefits of SGLT2 inhibitors in heart failure.[146] Empagliflozin, in a porcine model of MI, increased ketone metabolism and myocardial adenosine triphosphate concentrations and reduced adverse remodelling compared with control.[147]

In the EMPA-VISION trial of chronic heart failure patients, empagliflozin had no effect on in vivo measurements of cardiac energetics or metabolomic profiles.[102] Furthermore, in the EMMY trial of patients acutely post-MI, empagliflozin increased serum ß-hydroxybutyrate (3-ßOHB) levels over 26 weeks. Increasing 3-ßOHB levels were associated with measures of reverse left ventricular remodelling, including improved LVEF and reduced LVESV and LVEDV. However, this relationship was not modified by empagliflozin treatment.[148]

In humans, SGLT2 inhibitors increase hepatic ketone production and circulating ketone body concentrations, with a lesser effect in patients without diabetes.[149] Given the differential effect of SGLT2 inhibition on ketonaemia in patients with and without diabetes and the consistent benefit of SGLT2 inhibitors on outcomes regardless of the presence or not of diabetes, it is unlikely that increased ketones are a major contributor to their benefits.

1.3.3.7 Inflammation

A consistent effect of SGLT2 inhibitors in clinical trials has been a reduction in uric acid, a marker of oxidative stress.[150] In a proteomic analysis of the EMPEROR trials, there was a differential expression of proteins associated with reduced oxidative stress in patients treated with empagliflozin as compared with placebo.[151] There were increases in several proteins associated with a reduction in myocardial fibrosis, a key driver of progressive adverse left ventricular remodelling and the development of heart failure following MI.[151] There were increases in proteins associated with autophagy, the process of cellular housekeeping which clears cells of dysfunctional organelles that are a source of inflammation and oxidative stress.[151]

In the Empire HF Biomarker sub-study of 187 patients with HFrEF, there was an increase in plasma growth differentiation factor-15, an inflammatory

cytokine, with empagliflozin, which was inversely correlated with decreases in LVESV and LVEDV.[152] There was no change in plasma high-sensitivity c-reactive protein (CRP).[152] In 60 patients with T2DM and left ventricular hypertrophy in the Does Dapagliflozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes? (DAPA-LVH) trial, dapagliflozin reduced CRP compared to placebo, but there was no change in other inflammatory markers (tumour necrosis factor-α, interleukin [IL]-1β, IL-6, IL-10, eosinophil-lymphocyte ratio, and neutrophil-lymphocyte ratio).[153] In the EMMY trial of patients with acute MI, there were no between-group differences in the change in IL-6, high-sensitivity CRP, neutrophils, leukocytes, neutrophil-lymphocyte ratio or platelet-lymphocyte ratio, suggesting the inflammatory response following an MI may not be altered by SGLT2 inhibitors.[154]

1.4 Conclusion

Despite major advances in the treatment of acute MI, adverse left ventricular remodelling and the subsequent risk of heart failure remain prevalent challenges. SGLT2 inhibitors reduce heart failure events in patients at high risk after acute MI, whether this benefit is linked to remodelling was unknown at the beginning of my PhD. To address this, I conducted the EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction (EMPRESS-MI) clinical trial. This trial aimed to provide new insights through multiparametric cardiac imaging and circulating biomarker data on the effect of empagliflozin in patients at high risk of heart failure following acute MI. In Chapter 2, I will detail the methods and design of the EMPRESS-MI trial.

Chapter 2 Methods of a trial examining the effect of empagliflozin to prevent worsening of left ventricular volumes and systolic function after myocardial infarction

2.1 Introduction

As described in Chapter 1, patients with a reduced LVEF following an acute MI are at risk of progressive adverse cardiac remodelling. Whether the remodelling benefit of SGLT2 inhibitors seen in chronic HFrEF extends to high-risk patients with left ventricular systolic dysfunction following MI is unknown.

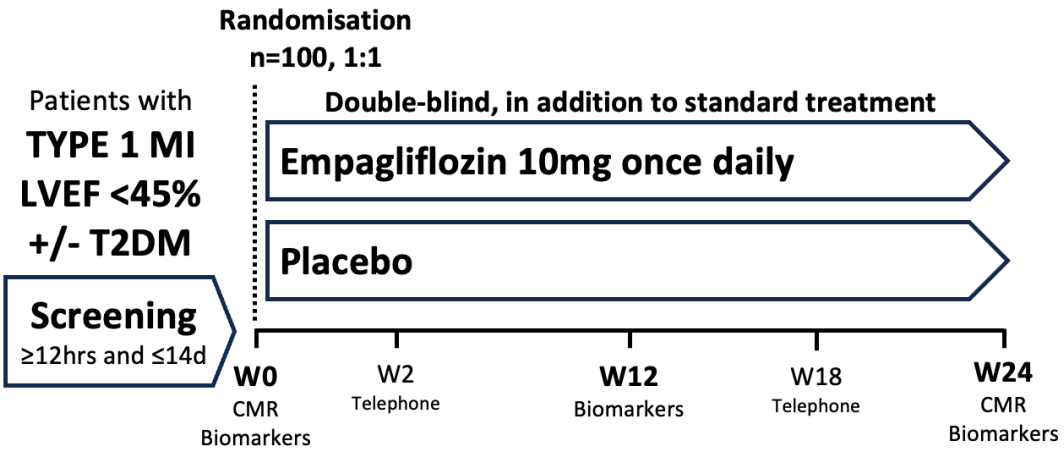
2.2 Trial design

I performed a multi-centre, randomised, double-blind, placebo-controlled trial to investigate the effect of empagliflozin, compared with placebo, on left ventricular volumes in patients with left ventricular systolic dysfunction following an MI - EMPRESS-MI. The trial was designed and conceived by the Trial Steering Committee. EMPRESS-MI was registered at ClinicalTrials.gov (NCT05020704). A summary of the trial is shown in Figure 2-1.

2.2.1 Trial setting

The main study centre was the Golden Jubilee National Hospital (GJNH). The Queen Elizabeth University Hospital and Glasgow Royal Infirmary were patient identification centres.

Figure 2-1 Trial design summary



Abbreviations: CMR, cardiovascular magnetic resonance; LVEF, left ventricular ejection fraction; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.

2.3 Trial outcomes

The primary, secondary and exploratory outcomes were measured as change from baseline to 24 weeks of follow-up. The between-treatment differences in these changes were analysed.

2.3.1 Primary outcome

The primary outcome was the change in LVESVI measured by CMR.

2.3.2 Secondary outcomes

The secondary outcomes were as follows:

- Change in other CMR measures of cardiac remodelling.
  - LVEDVI
  - LVEF
  - LAVI
  - LVMI
- Change in NT-proBNP
- Change in high-sensitivity troponin I (hs-TnI)
- Change in infarct size as measured by CMR

2.3.3 Exploratory outcomes

The exploratory outcomes were as follows:

- Change in other CMR biomarkers of adverse remodelling: including left ventricular circumferential strain using feature-tracking, extracellular volume in the remote and infarct regions, MVO, IMH, myocardial salvage index, remote zone native T1, right ventricular end-diastolic volume index, right ventricular ejection fraction, resting myocardial blood flow and cardiac biomechanics derived from mathematical modelling
- The proportion of patients in remodelling groups at 24 weeks, defined as; group 1: reverse left ventricular remodelling (≥12% decrease in LVESVI); group 2: no left ventricular remodelling (change in LVEDVI and LVESVI<12%); group 3: adverse left ventricular remodelling with compensation (≥12% increase in LVEDVI only); and group 4: adverse left ventricular remodelling (≥12% increase in both LVESVI and LVEDVI)[31]
- Change in circulating and urinary biomarkers reflecting neurohormonal activation, kidney function, tissue remodelling, inflammation, haematopoiesis (including ferritin, hepcidin, iron), and other pathways relevant to the underlying conditions of the patients and the actions of empagliflozin (including glycated haemoglobin [HbA1c] and uric acid).
- Change in patient-reported health status measured using EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire
- Change in circulating biomarkers of kidney function and injury including serum creatinine and eGFR (modification of diet in renal disease [MDRD] formula)
- Change in CMR biomarkers of renal fibrosis and inflammation; native T1 relaxation time and T2 relaxation time

2.4 Trial population

2.4.1 Identification of patients

As a member of the routine clinical care team, I prospectively screened all patients with a primary diagnosis of a type 1 acute MI and an LVEF≤40% on

transthoracic echocardiography performed ≥12 hours and ≤14 days after the index MI.

A type 1 acute MI, according to the Fourth Universal Definition of MI, was defined as:

Detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit and with at least one of the following:

- Symptoms of acute myocardial ischaemia
- New ischaemic electrocardiogram (ECG) changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.[155]

I used the transthoracic echocardiogram performed as part of routine clinical care to identify potentially eligible patients who would be suitable to undergo screening CMR. If an echocardiogram had not been performed as part of routine clinical care at the time of screening, then I performed the echocardiogram for the purposes of clinical care in my role as a member of the routine clinical team. I reviewed the echocardiography images offline to estimate the LVEF, either by using Simpson's biplane rule or visual estimation of LVEF. Patients with insufficient endocardial definition to allow accurate planimetry or visual assessment of LVEF were excluded from recruitment.

For patients who were transferred between hospital sites, the time from admission to the first hospital was used for the purposes of eligibility assessment.

I approached all patients without obvious contraindications to enrolment and verbal consent to discuss participation in research in addition to review of case-notes. I provided eligible patients with a patient information sheet (PIS)

(Appendix 1) detailing the trial and gave them the opportunity to ask questions prior to screening.

2.4.2 Inclusion criteria

The inclusion criteria were as follows:

- Male or female ≥18 years of age
- Informed consent
- Diagnosis of a type 1 acute MI meeting the Fourth Universal Definition of MI (STEMI or non-STEMI [NSTEMI])
- LVEF<45% as measured by CMR performed ≥12 hours and ≤14 days following hospital admission with an acute type 1 MI (changed from an LVEF≤40% by an amendment to the trial protocol on 23rd February 2023).
- For patients with an in-hospital MI as qualifying event, randomisation must still occur within 14 days of hospital admission
- eGFR≥30 ml/min/1.73m^2 at the time of randomisation (calculated using the MDRD formula)

Additional criteria for randomisation:

- Eligibility was assessed using LVEF≤40% measured by echocardiography during screening
- Patients who met the inclusion criteria proceeded to CMR scan
- CMR is considered a more accurate measure of LVEF therefore if the results of the CMR show ≥45% then the patients were no longer eligible and did not proceed to randomisation

2.4.3 Exclusion criteria

- Inability to give informed consent e.g. due to significant cognitive impairment
- Diagnosis of chronic HFrEF prior to admission with acute MI
- Systolic blood pressure <90 mmHg at randomisation measured after 5 minutes in a supine or sitting position.

- Cardiogenic shock or use of intravenous inotropes in last 24 hours before randomisation
- Coronary artery bypass graft surgery planned at time of randomisation
- Type 2 acute MI
- Any current severe stenotic valvular heart disease
- Diagnosis of Takotsubo cardiomyopathy
- Type I diabetes mellitus
- History of ketoacidosis
- Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy device
- Permanent or persistent atrial fibrillation
- Enrolment in another randomised clinical trial involving medical or device-based interventions (co-enrolment in observational studies is permitted)
- Currently pregnant, planning pregnancy, or currently breastfeeding
- History of allergy to SGLT2 inhibitor
- Current or planned use of an SGLT2 inhibitor at time of randomisation
- Active genital tract infections
- Anyone who, in the investigators' opinion, was not suitable to participate in the trial for other reasons
- Contraindication to contrast-enhanced CMR i.e. claustrophobia, metallic foreign object unsuitable for CMR

Eligibility waivers to the inclusion and exclusion criteria were not permitted.

2.4.4 Consent

If patients were agreeable to taking part in the trial after reading the PIS, I sought informed, written consent. I took informed consent according to Good Clinical Practice standards and using a formal informed consent form (Appendix 2). Enrolled patients (signed study consent) were allocated a unique patient identifying number which lasted for the duration of the entire trial. Informed, written consent was necessary prior to randomisation. I gave a copy of the consent form to the patient, and another was filed in the patient's electronic health records. The original consent form was filed in the

study file and scanned and uploaded into a secure study database for each consented patient.

I completed a log of all patients screened for eligibility. Anonymised information was collected including:

- Age
- Gender
- Ethnicity
- Whether the patient is recruited or not recruited to the study

I also recorded the following information for screened patients who were not recruited either because they were ineligible or because they decline participation:

- The reason not eligible for study participation OR
- Where eligible, reason declined

The right of the patient to refuse consent without giving reasons was always respected.

2.4.5 Screening

Patients who had provided written, informed consent went on to have a screening CMR scan. I personally accompanied all patients to the screening CMR scan and supervised all scans to ensure immediate assessment of LVEF for the purposes of eligibility and identification of any issues requiring immediate clinical review and expedited reporting. If patients had an LVEF of ≥45% on CMR, they did not proceed to randomisation and their involvement in the study did not continue. The methods I used for measuring LVEF by CMR are detailed in Chapter 2.5.6.1. This information was included in the study specific electronic case report form (eCRF). I obtained screening blood tests for the purposes of determining eGFR eligibility. If this had already been performed as part of clinical care within the preceding 24 hours, then they did not have to be repeated. A pregnancy test was performed in women of childbearing potential. I was assisted by Sister Barbara Meyer, an experienced clinical research nurse. Patients who initially failed screening may have been

re-screened once more for reasons other than LVEF. Re-screened patients would have been allocated a new patient number.

2.5 Trial procedures

2.5.1 Pre-randomisation investigations

I performed the following investigations prior to randomisation and recorded all results in the study specific eCRF.

- Physical examination including measurement of height and weight, auscultation of the heart and lungs and examination of the lower limbs for evidence of peripheral oedema
- Vital signs including blood pressure and heart rate
- 12-lead ECG
- Venepuncture – withdrawal of approximately 45mls of blood for full blood count, urea and electrolytes, liver function tests and HbA1c and for biomarker analysis
- Urine sample for biomarker analysis
- EQ-5D-5L questionnaire
- A full review of the patient's past medical history
- Prescribed medication

2.5.2 Randomisation

Once baseline measurements were collected, I randomised patients to empagliflozin 10mg or matched placebo in a 1:1 ratio. The randomisation schedule was computer-generated by the method of randomised permuted blocks, with random block length of 4 and 6. Randomisation was stratified by LVESVI measured at CMR (≤45 ml/m^2 or >45 ml/m^2), use of diuretics at the time of randomisation and presence/absence of T2DM (established diagnosis or an HbA1c≥48 mmol/mol at the index admission). Randomisation occurred within 24 hours of the CMR scan. Treatment allocation was blinded to all patients and trial staff.

On the day of randomisation, I provided all patients with a patient alert card (Appendix 3). This provided important information relating to specific side

effects, emergency unblinding and 24/7 contact details for the study team. I kept a dedicated trial mobile phone available 24/7 throughout the duration of the study for patients and clinical care teams.

I sent all patients' general practitioners formal written correspondence on the day of randomisation to provide important study details, including the date on which the study drug was started (Appendix 4). At the end of the trial, I provided formal correspondence to inform the patients' general practitioners of the patients' completion in the trial and the date the study drug was stopped.

2.5.3 Follow-up visits

Details of all study visits are summarised in Table 2-1. Patients were seen for all visits within the designated time window or as close to this as possible.

Table 2-1 Schedule of assessments

Study procedure	Screening (≥12 hours and ≤14 days after acute MI)	Visit 1 Randomisation (Day 0 - ≥12 hours and ≤14 days after acute MI)	Visit 2 (Week 2±4 days)	Visit 3 (Week 12± 7 days)	Visit 4 (Week 18± 7 days)	Visit 5 (Week 24± 4 weeks)
Face-to-face visit	X	X		X*		X
Telephone visit			X		X	
Review inclusion/exclusion criteria	X	X				
Echocardiogram	X†					
Obtain informed consent	X					
CMR	X‡					X
Physical examination		X				X
Medical history		X				
Medication history		X	X	X	X	X
Vital Signs (blood pressure/heart rate)	X	X		X		X
12-lead ECG		X				
Urine sample		X		X		X
Venepuncture (full blood count/urea and electrolytes/liver function tests/HbA1c)	X§	X		X		X

Venepuncture (biomarker analysis)		X		X		X
EQ-5D-5L questionnaire		X				X
Pregnancy testing in WOCBP	X			X		X
IMP dispensing		X		X		
Adverse event reporting			X	X	X	X
Study completion						X

*Visit 3 took place as a face-to-face visit unless not possible due to restrictions due to the COVID-19 pandemic in which case it was a telephone call. †Echocardiography performed by the clinical care team was reviewed for purposes of screening. ‡In eligible patients. §Results from the most recent local laboratory test within the preceding 24 hours were used. If not available, then performed by investigator who was part of the clinical care team.

Abbreviations: CMR, cardiovascular magnetic resonance; ECG, electrocardiogram; EQ-5D-5L, EuroQol 5-Dimension 5-Level; HbA1c, glycated haemoglobin; IMP, investigational medicinal product; MI, myocardial infarction; WOCBP, women of childbearing potential.

2.5.4 End-of-trial

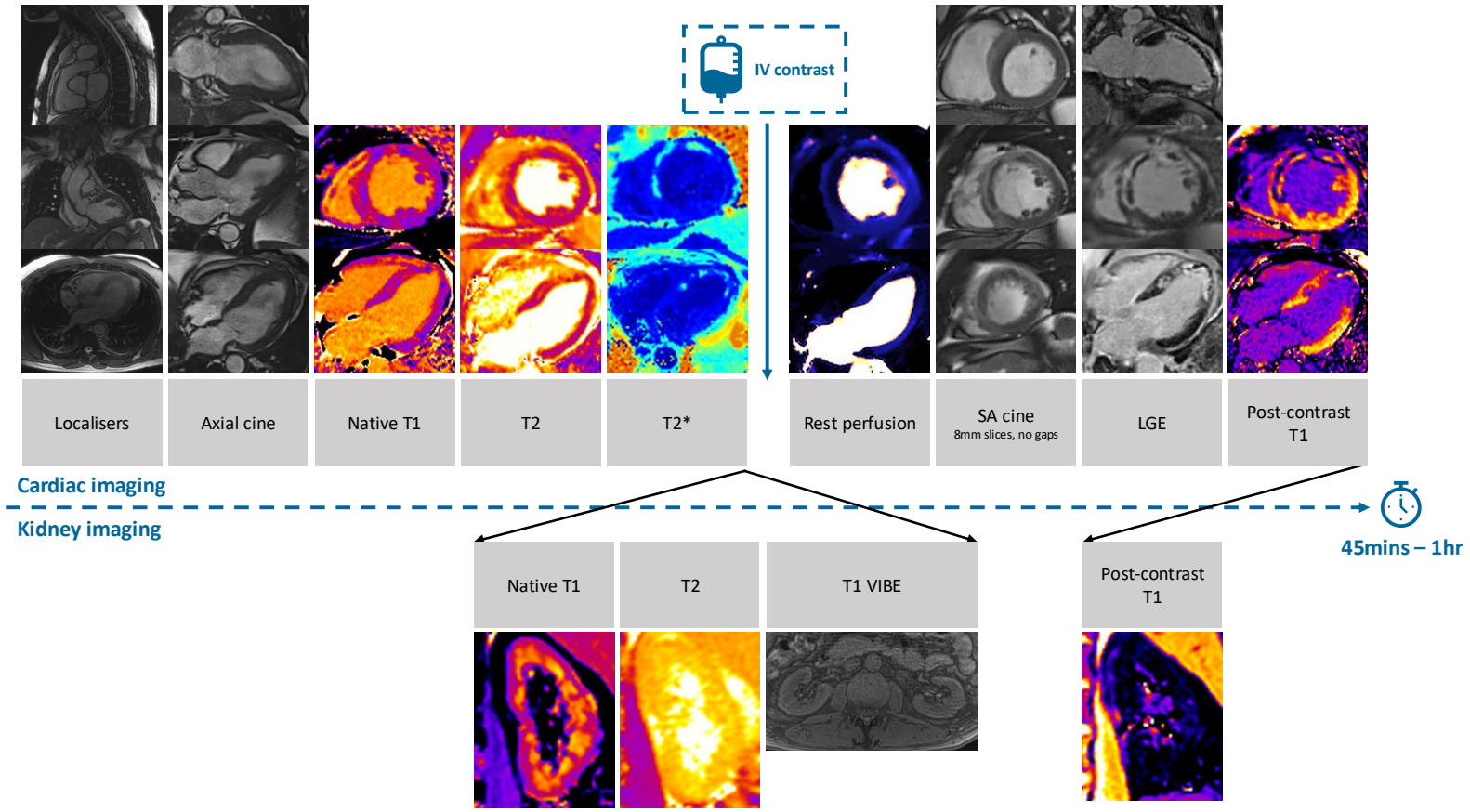
The end of the trial was defined as the date of the last patient's 24-week study visit (+/- 4 weeks) plus an additional 30 days of event reporting.

2.5.5 Cardiovascular magnetic resonance protocol

CMR was performed prior to randomisation and 24 weeks following randomisation on a single 1.5 Tesla Siemens MAGNETOM Avanto scanner at the GJNH. Images were obtained using a 12-element phased array cardiac surface coil and a 12-element phased array body surface coil for kidney imaging. CMR acquisition was performed by CMR radiographers at the GJNH who adhered to a standardised protocol for image acquisition. Typical imaging parameters for CMR and kidney imaging are detailed in Appendix 5 and Appendix 6, respectively.

The imaging protocol is outlined in Figure 2-2, and included steady-state free precession (SSFP) sequencing to acquire left ventricular axial cine images (2- 3- and 4-chamber) and a short-axis cine stack from pulmonary veins to left ventricular apex (8 mm slices, no gaps). Native and post-contrast T1 mapping of the 4-chamber and mid short-axis slice were acquired using a modified Look-Locker inversion-recovery sequence. T2 mapping of the 4-chamber and mid short-axis was acquired using an SSFP sequence. T2* mapping of the 4-chamber and mid short-axis was acquired using gradient echo acquisition and free-breathing motion corrected technique. Rest perfusion imaging of the 4-chamber and three short-axis slices (base, mid and apex) was acquired following intravenous injection of half-dose gadolinium-based contrast (Gadovist 0.05 mmol/kg at 4 mL/s with 30 mL saline flush). Full-dose contrast was then administered (Gadovist 0.1 mmol/kg at 4 mL/s with 30 mL saline flush) 10-15 minutes before LGE imaging (3 long-axis views, and short-axis stack) was acquired using phase-sensitive inversion recovery pulse sequence and free-breathing motion corrected technique. T1 modified Look-Locker inversion recovery pre- and post-contrast and T2 fast low-angle shot (FLASH) coronal imaging of the kidneys were acquired. T1 volume-interpolated breath-hold examination (VIBE) FLASH imaging in the axial plane of the kidneys was also acquired.

Figure 2-2 Outline of CMR protocol



Abbreviations: IV, intravenous; LGE, late gadolinium enhancement; SA, short-axis; VIBE, volume-interpolated breath-hold examination.

If the scan was being poorly tolerated, then the protocol was amended to prioritise acquisition of images necessary for primary and secondary outcome analysis (SSFP axial and short-axis cine stack, LGE imaging, no kidney imaging and no mapping).

2.5.6 Cardiovascular magnetic resonance analysis

I prepared a clinical report (linked to each individual patient by Community Health Index [CHI] number recorded on the randomisation log) for each patient following each scan. These were co-reported by Professor Colin Berry (Consultant Cardiologist, Professor of Cardiovascular Imaging and European Association of Cardiovascular Imaging [EACVI] Level 3 accredited in CMR) or Dr Ross Campbell (Consultant Cardiologist, Clinical Senior Lecturer and EACVI Level 2 accredited in CMR). Incidental findings were managed according to standard care, liaising with Radiology as appropriate. The final clinical report was uploaded by Professor Colin Berry or Dr Ross Campbell to Scottish National PACS for governance purposes as part of the permanent imaging health record for the patient. The clinical reports were not used for the purposes of endpoint measurement.

I pseudonymised all scans for the purposes of research analysis. Unlike the clinical reports, the research reports were prepared at the end of each patient's involvement in the trial. Dr Matthew Lee (Consultant Cardiologist and Clinical Senior Lecturer) performed analysis of both the baseline and 24-week follow-up scans for the primary and secondary CMR endpoints, in a paired fashion, to reduce intra-observer variability using the methods described below. Dr Lee was blinded to treatment assignment.

Primary and secondary CMR outcomes were measured using the commercially available software package (Circle CVI42, Circle Cardiovascular Imaging, Canada) using standard techniques according to the Society for Cardiovascular Magnetic Resonance guidelines for reporting CMR examinations.[156]

2.5.6.1 Left ventricular volumes and function

SSFP short-axis cine images from the mitral valve plane through to the apex were used to calculate ventricular volumes and ejection fraction. Specifically, left ventricular volumes were calculated by tracing the endocardial border (excluding papillary muscle and trabeculations) in end-systole and end-diastole. The basal left ventricular slice was defined as the most basal slice with >50% myocardium present. Left ventricular outflow tract volume was included in volumetric analysis. End-diastole was defined as the frame in which the blood pool of the mid ventricular slice is at its largest, and end-systole was defined as the frame in which the blood pool of the mid ventricular slice is at its smallest. Values for both volumes were indexed to body surface area (BSA), measured at the time of the scan and calculated using the Mosteller formula. Ejection fraction (%) was then calculated within the software package (ejection fraction = (LVEDV – LVESV) / LVEDV * 100). I used this technique for estimation of LVEF for the purposes of screening with regards to eligibility for randomisation and LVESVI for the purposes of randomisation (which was stratified by LVESVI≤45 ml/m^2 or >45 ml/m^2). The results I obtained were for screening purposes only and were not used for the purposes of outcome measurements.

2.5.6.2 Left ventricular mass index

The left ventricular epicardial border was traced manually in end-diastole and end-systole. Left ventricular mass was calculated as the total difference between the inner and outer circumferences of the left ventricular myocardium in end-diastole, multiplied by the myocardial density (1.05 g/cm^3), indexed to BSA.

2.5.6.3 Left atrial volume index

The left atrial volume was initially intended to be calculated by manually tracing the left atrium endocardial volume in end-systole on a short-axis stack contiguous with the left ventricular stack. However, it became clear during the analysis that the entire left atrium had not been adequately imaged in a proportion of cases. The imaging Standard Operating Protocol was revised such that left atrial volume was calculated using the biplane area-length method by manually tracing the left atrium endocardial volume

in end-systole. This method is widely accepted for accurate left atrial volume measurement.[156] Left atrial volume was indexed to BSA (calculated using the Mosteller formula).

2.5.6.4 Infarct size

Infarct size, measured in mass and as a percentage of myocardium, was calculated by manually drawing around the epicardial and endocardial border of the late enhancement short-axis images, then drawing an area of interest in normal myocardium (180 degrees from area of infarction). An auto-threshold of 5 SD from this normal myocardium was used to identify areas of late enhancement.

2.5.6.5 Microvascular obstruction

I performed analysis of the CMR scans for the purposes of measurement of the CMR exploratory outcomes. MVO was defined as a hypointense core within the hyperintense infarct core on LGE imaging and was included in the measurement of the infarct size.[157]

2.5.6.6 Intramyocardial haemorrhage

IMH was defined as a region of reduced T2* signal intensity <20 ms within the infarcted area.[157]

2.5.7 Biomarker sampling

I collected venous blood and urine samples before randomisation, at 12 weeks and 24 weeks following randomisation, for biomarker analysis. I was assisted by Sister Barbara Meyer. Samples were collected and processed at the Clinical Research Facility at the GJNH according to a Sample Handling Manual which I prepared. After completion of the trial, all samples were transferred to the central laboratory for batch analysis.

HbA1c and haematocrit were measured as part of routine care in National Health Service (NHS) GJNH biochemistry labs. NT-proBNP (Roche e411, Roche Diagnostics, Burgess Hill, United Kingdom [UK]), hs-TnI (i1000SR ARCHITECT, Abbott Laboratories, Maidenhead, UK), uric acid and creatinine for eGFR (Roche c311, Roche Diagnostics, Burgess Hill, UK) were batch measured after

study completion. All non-routine assays were performed at a central lab (GlasBRU, University of Glasgow) using the manufacturers' calibrators and quality controls.

2.5.8 Patient reported outcome measures

Patients were asked to complete an EQ-5D-5L questionnaire before randomisation and at 24 weeks after randomisation to assess the effect of empagliflozin on quality of life (Appendix 7).

2.6 Study drug

Following randomisation and at 12 weeks, I provided patients with 4 bottles of 30 tablets of either empagliflozin 10mg or matched placebo. They were instructed to take one tablet once a day. No dose modifications were permitted. The dose of empagliflozin (10mg once daily) in EMPRESS-MI was based on the dose used in licensed indications and the clinical benefit and safety results seen with this dose in EMPEROR-Reduced and EMPA-REG OUTCOME.[61,69] The same dose was studied in the EMPACT-MI trial.[86]

2.6.1 Monitoring of potential side effects

2.6.1.1 Monitoring of hypotension

A potential side effect of empagliflozin is symptomatic hypotension. At each study visit, I asked patients if they had experienced any symptoms of hypotension or volume depletion, including syncope, presyncope and falls and/or systolic blood pressure <85 mmHg. If felt necessary, the study drug could be discontinued if patients experienced any of these symptoms.

2.6.1.2 Monitoring of urinary tract and genital infections

Empagliflozin can cause urinary tract and genital infections. At each study visit, I asked patients if they had experienced any symptoms of urinary tract or genital infections. If felt necessary, the study drug could be discontinued if these occurred.

2.6.1.3 Monitoring of renal dysfunction and hyperkalaemia

Empagliflozin can cause renal dysfunction, therefore renal function was monitored for the duration of the trial. I checked renal function (including urea, creatinine and electrolytes) at Visit 1 (pre-randomisation), Visit 3 (12 weeks ± 7 days), and Visit 5 (24 weeks ± 4 weeks). Additional measurements were taken if clinically indicated. If the creatinine value showed a ≥2-fold increase from baseline (i.e. acute kidney injury stage 2 or 3) and was above the upper limit of normal, the study drug could be temporarily discontinued if clinically indicated as part of usual clinical care. If the eGFR was <20 mL/min/1.73m^2 on two consecutive blood samples then the study drug could be discontinued if clinically indicated as part of usual clinical care. I checked potassium levels and hyperkalaemia was defined as any lab measure ≥5.5 mmol/L. If a sample indicated the presence of hyperkalaemia this was rechecked. If potassium levels were persistently ≥6.0 mmol/L the study medication could be stopped and reversible causes of hyperkalaemia investigated. If potassium levels normalised to <5.5 mmol/L, the study medication could be restarted.

2.6.1.4 Monitoring of requirement of renal replacement therapy

If patients developed the requirement for renal replacement therapy at any point during the trial (e.g. haemodialysis, haemofiltration, kidney transplant), the study drug was discontinued. Utilisation of renal replacement therapy was assessed for at each study visit.

2.6.1.5 Monitoring of hepatic injury

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (alanine transaminase [ALT], aspartate aminotransferase [AST], total bilirubin) available, I made sure these parameters were analysed, if necessary, in an unscheduled blood test. Hepatic injury was defined by the following alterations of liver parameters after randomisation at Visit 1 - elevation of AST and/or ALT≥3-fold upper limit of normal combined with an elevation of total bilirubin ≥2-fold upper limit of normal measured in the same blood draw sample, OR an isolated elevation of AST and/or ALT≥5-fold upper limit of normal irrespective of any

bilirubin elevation. With respect to liver function, these laboratory findings constituted a hepatic injury alert and the patients showing these abnormalities were followed up according to medical judgement.

2.6.1.6 Monitoring of ketoacidosis

I discontinued the study medication if patients developed a confirmed diagnosis of ketoacidosis. I advised patients on how to recognise signs and symptoms of ketoacidosis. These included nausea and vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. I checked blood ketones if a patient had signs and/or symptoms and/or I had a clinical suspicion of ketoacidosis. Study medication was withheld immediately (at least temporary discontinuation; but permanent discontinuation if ketoacidosis was confirmed by biochemistry). Study medication was interrupted if ketones were >1.0 mmol/L on two separate measurements and not restarted until <0.6 mmol/L on two separate measurements. Study medication was permanently discontinued if any value was >1.5 mmol/L.

Diabetic ketoacidosis (DKA) was defined by the diagnostic criteria as described by the American Diabetes Association.[158] The same diagnostic criteria apply in the event of ketoacidosis occurring in a non-diabetic patient. Not all criteria need to apply for the diagnosis of DKA, and clinical judgement was taken into consideration. Due to its mechanism of action, empagliflozin can modify the clinical presentation of DKA, which may occur at lower plasma glucose levels.

2.6.1.7 Monitoring of major hypoglycaemic events

A major hypoglycaemic event was defined as an event that requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. At each study visit, I asked patients if they had experienced any major hypoglycaemic events.

2.6.1.8 Monitoring of lower limb amputations

I assessed for the occurrence of lower limb amputations at each study visit. Study medication was permanently discontinued if this occurred.

Consideration was also given to stopping study medication if patients developed foot complications such as infection, skin ulcers, osteomyelitis, or gangrene.

2.6.2 Development of heart failure and study drug discontinuation during follow-up

I assessed patients at each study visit for the development of symptomatic heart failure (symptoms and/or signs of heart failure, NT-proBNP measurement). Patients who developed symptomatic heart failure during the study were offered an open-label SGLT2 inhibitor outside of the trial, via standard care. I asked patients starting an open-label SGLT2 inhibitor or withdrawing from study medication or follow-up ≥12 weeks after randomisation to undergo an end-of-study CMR examination (patients withdrawing before 12 weeks were not asked to have a second CMR as an effect of left ventricular remodelling is unlikely to be detected before this time point).

2.6.3 Withdrawal criteria

Participants were free to stop participating at any point during the trial, but they were encouraged to remain under trial follow-up if they opted to discontinue the study medication. They were also able to withdraw consent for any further participation. Any patient enrolled in the trial was free to withdraw from the study at any time without giving a reason and without prejudicing any further treatment or care. Following their involvement in the trial any patient withdrawing continued standard treatment for MI as per local practice guidelines. Data collected up to withdrawal of consent was included in the study unless the patient insisted otherwise; similarly, stored clinical samples were retained, but were destroyed at the patient's request.

I asked patients these safety questions at every study visit after visit 1 (randomisation). If the answer to any of the safety questions below:

1. Any symptoms of hypotension/volume depletion including presyncope/syncope and falls and/or systolic blood pressure <85 mmHg
2. Any urinary tract infection episodes
3. Any genital infections

4. Major hypoglycaemic event
5. Renal dysfunction/hyperkalaemia
6. Ketoacidosis signs and symptoms
7. Lower limb amputation
8. Hepatic injury
9. Renal replacement therapy utilisation (haemodialysis, hemofiltration, kidney transplant)
10. Death

at any visit was Yes, I assessed the need for discontinuation of study medication according to the following parameters. # 1, 2, 3, 4 may not require discontinuation, # 5, 6 at least temporary discontinuation (if ketoacidosis confirmed by biochemistry, then permanent discontinuation), # 7, 8, 9, 10 permanent discontinuation. I also considered stopping study medication if patients develop foot complications such as infection, skin ulcers, osteomyelitis, or gangrene

I also considered discontinuing the study medication (if clinically indicated as part of usual clinical care) in any participant who developed any of the following during the study:

- eGFR<20 mL/min/1.73m^2 on two consecutive blood samples
- Clinical instability likely to require the addition of intravenous vasoactive drugs including vasodilators and/or inotropic agents and/or mechanical circulatory support devices
- Confirmed symptomatic hypoglycaemia (plasma glucose <2.5 mmol/L) that could not be rectified by alteration of other background antidiabetic agents. A major hypoglycaemic event was defined as an event that required assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.

I discontinued the study medication (if clinically indicated as part of usual clinical care) in any participant who developed hypersensitivity to the study medication or a confirmed diagnosis of ketoacidosis.

I scheduled additional study visits as clinically indicated, even if not meeting adverse event (AE)/serious adverse event (SAE)/adverse event of special

interest (AESI) criteria. Alternatively, patients' routine clinical care team (with their prior agreement) were asked to update clinically indicated blood tests, if patients preferred this, to minimise inconvenience.

2.7 Trial documents

2.7.1 Protocol and amendments

Protocol versions and amendments are listed in Table 2-2. I prepared study documents, assisted by trial managers Katriona Brooksbank and Joanne O'Donnell, trial administrator Liz Coyle, and supervised by the Trial Management Group.

2.7.2 Amendment to increase left ventricular ejection fraction criterion

The LVEF cut-off for eligibility as assessed by CMR was increased from ≤40% to <45% by an amendment to the protocol on the 23rd February 2023. This decision was made due to a substantial number of patients being ineligible for randomisation based on the original CMR criteria (14 of 88 patients who underwent screening CMR before the protocol amendment). In the EMMY trial, which included patients with higher baseline LVEF, empagliflozin had a remodelling benefit, supporting the rationale for this adjustment. Amending the LVEF cut-off to <45% aligned EMPRESS-MI with the large outcome trial EMPACT-MI, ensuring a consistent assessment of the effects of empagliflozin in a comparable population. To implement this change, I prepared the necessary trial documents and successfully submitted them to Research Ethics Committee (REC) and Medicines and Healthcare products Regulatory Agency (MHRA) for approval.

Table 2-2 Protocol and amendments

Amendment number	Version number	Protocol date	Submitted to	Details
REC approved version	1.0	17/12/2021	REC and MHRA	Approved by REC GNA from MHRA
MHRA approved version	2.0	11/02/2022	MHRA	Response to GNA from MHRA Revision of contraception section in line with CTFG guidelines Further clarification added as to the supply chain for IMP, and quality, manufacturer and supply chain of the placebo
SAm01	3.0	16/05/2022	REC and MHRA	Revised text to reflect all research activities taking place at the Golden Jubilee National Hospital with Queen Elizabeth University Hospital and Glasgow Royal Infirmary and Patient Identification Centres Revision of contraception section to include age-specific requirement for follicle-stimulating hormone testing Removal of physical examination from visit 3
SAm02	4.0	23/02/2023	REC and MHRA	Increase the LVEF inclusion criteria by the CMR scan from ≤40% to <45%. Early experience in trial recruitment suggested that excluding patients with an LVEF>40% and <45% at CMR was limiting recruitment. The EMMY trial had been published which showed empagliflozin improved left ventricular volumes by echocardiography at 6 months in patients with large MI. The mean ejection fraction for the participants was close to 50%. This amendment brought the

				inclusion criteria in line with those of the EMPACT-MI trial.[86,117]
SAm03	5.0	27/11/2023	REC and MHRA	Reflect change to summary of product characteristics for empagliflozin stating that, ketoacidosis, although less likely to occur, had been reported in patients without diabetes. The adverse effect term of 'diabetic ketoacidosis' was revised to 'ketoacidosis'
NSA05	-	-	NHS GGC R&I	Extended the trial end date from 02/01/2024, as documented in the initial IRAS form, to 31/08/2024. This allowed me to meet all end of study criteria as specified in protocol.

Abbreviations: CMR, cardiovascular magnetic resonance; CTFG, Clinical Trial Facilitation Group; EMMY, EMpagliflozin in patients with acute Myocardial infarction; EMPACT-MI, Study to Evaluate the Effect of Empagliflozin on Hospitalisation for Heart Failure and Mortality in Patients with Acute Myocardial Infarction; GNA, grounds for non-acceptance; IMP, investigational medicinal product; LVEF, left ventricular ejection fraction; MHRA, Medicines and Healthcare products Regulatory Agency; NHS GGC R&I, National Health Service Greater Glasgow and Clyde Research and Innovation; NSA, non-substantial amendment; REC, Research Ethics Committee; SAm, substantial amendment.

2.8 Data handling

2.8.1 Electronic case report form

A study specific eCRF developed by the Robertson Centre for Biostatistics and me was used to collect all study data.

Access to the eCRF was restricted, via a study-specific web portal, and only authorised site-specific personnel were able to make entries to patients' data via the web portal. Data were stored in a Microsoft SQL Server database.

2.8.2 Worksheets

I designed paper worksheets which formed the source data and aided data entry input into the eCRF. I completed paper worksheets at each visit, assisted by Sister Barbara Meyer.

2.9 Funding of the trial

The trial was funded by Boehringer Ingelheim. Boehringer Ingelheim had no role in the trial design, trial conduct, and was not involved in data analysis or interpretation. The funding of the trial was secured by Mark Petrie.

2.10 Approvals and timelines

2.10.1 Research Ethics Committee

The trial received formal ethical approval from the North East - Newcastle and North Tayside 2 REC (IRAS project ID 302654, REC reference 22/NE/0030) on the 22nd February 2022.

2.10.2 Medicines and Healthcare products Regulatory Agency

The trial received formal approval from the MHRA on 1st March 2022 and is registered on the European Union clinical trials register (EudraCT 2021-006086-38).

2.10.3 Research and Development

The trial was approved by the local research and development team in NHS GJNH on 6th September 2022 (GJNH reference number 22/CARD/03). The NHS Greater Glasgow and Clyde and University of Glasgow Co-Sponsor Regulatory Green Light was obtained on the 16th September 2022.

2.11 Pharmacovigilance

2.11.1 Definitions

Definitions of pharmacovigilance (PV) terms are detailed in Table 2-3.

Table 2-3 Pharmacovigilance terms and definitions

Term	Definition
Adverse event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse reaction (AR)	An untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the trial medication qualify as ARs.
Adverse event of special interest (AESI)	An AE or AR that is of particular interest to the trial whether for the analysis of trial endpoints, to provide further information on selected events, or more closely monitor patient safety due to the potential severity of such an event.
Serious adverse event (SAE)	A SAE is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was

	at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious adverse reaction (SAR)	An AE that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected unexpected serious adverse reaction (SUSAR)	A SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the SmPC for that product • in the case of any other IMP, in the investigator's brochure relating to the trial in question

Abbreviations: AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; IMP, investigational medicinal product; SAE, serious adverse event; SAR, serious adverse reaction; SmPC, summary of product characteristics; SUSAR, suspected unexpected serious adverse reaction.

2.11.2 Recording and reporting of adverse events, serious adverse events, and adverse events of special interest

All AEs occurring during the trial that were observed by the study team (me, Sister Barbara Meyer) or reported by the participant were recorded in the participant's medical records whether attributed to trial medication or not. All AEs were assessed to determine whether they met the definition of an AESI or met the seriousness requirements necessary to require reporting as a SAE. I assessed patients for AEs at each study visit from the date of randomisation until 30 days following the date of Visit 5.

All suspected adverse reactions (ARs) that occurred during this time period were recorded in the eCRF. Any AEs that met the criteria of an AESI were reported to the Sponsor as per SAEs

All SAEs and AESIs occurring between the date of randomisation and 30 days following the date of Visit 5 were recorded in the eCRF as soon as was reasonably practicable and within 24 hours of first becoming aware of the event. Any follow-up information was recorded as soon as this became available. If recording in the eCRF was not possible a paper SAE form was completed. The SAE form was downloaded from the Glasgow Clinical Trials Unit website: www.glasgowctu.org, printed off, completed and signed. The form was then faxed or emailed to the Glasgow Clinical Trials Unit PV Office. If the website was unavailable a paper copy of the SAE form was filed in the

Study Site File. If necessary, a verbal report could be given by contacting the PV Office by telephone. This was followed up as soon as possible with an electronic or written report.

Any SAE occurring outside of the time period defined above that was suspected to be related to study medication was subject to recording within the eCRF and reporting to the Sponsor. Elective procedures planned prior to trial entry were not reported as SAEs.

2.11.3 Assessment of adverse events

All SAEs were assessed for severity, causality and expectedness with reference to the study protocol and the reference safety information (RSI).

AEs were assessed for seriousness as per the definitions in Table 2-3; those which met the criteria for an SAE were subject to expedited reporting to the sponsor.

All SAEs were assessed for causality i.e. does the event have a “reasonable causal relationship” with trial medication. A binary Yes/No decision was used for the assessment of causality. I submitted SAEs with a provisional assessment of causality. Following this initial submission SAEs were reviewed for causality by the Principal Investigator (Professor Colin Berry), or their medically qualified designee(s) (Dr Kieran Docherty) as soon as possible and within 5 days of the site becoming aware of the event for fatal or life-threatening SAEs and 10 days for all other SAEs. In addition, the Chief Investigator (Professor Colin Berry) carried out an assessment of causality secondary to that of the local investigator/medically qualified designee. Where the Chief Investigator and local investigator/medically qualified designee disagreed regarding the causality of an event both opinions were captured within the eCRF. The Chief Investigator could upgrade events but could not downgrade the local clinician’s assessment of causality.

If the event was considered to be related (possibly, probably or definitely) to the study medication, an assessment was made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication. The expectedness of an AR was assessed against the RSI. If the event was

consistent with the relevant product information documented in the RSI, then it was considered expected. If the event was not consistent with the relevant product information documented in the RSI, then it was considered unexpected. The assessment of expectedness was carried out by the Chief Investigator (Professor Colin Berry), a delegated clinical member of the Trial Management Group or the Sponsor PV manager. The local investigator could provide an opinion regarding expectedness, but the Chief Investigator/Sponsor had overall responsibility.

Severity was assessed and described using the following categories:

- Mild – awareness of event but easily tolerated
- Moderate – discomfort enough to cause some interference with usual activity
- Severe – inability to carry out usual activity.

2.11.4 Reporting to Sponsor (Pharmacovigilance Office)

All SAEs were reported to the University of Glasgow PV Office and were subject to expedited review. The PV office forwarded copies of each SAE to Boehringer Ingelheim as per agreements in place between the parties.

2.11.5 Reporting to the MHRA and REC

Any SAEs assigned by the Principal Investigator or delegate and by the Chief Investigator (on behalf of the Sponsor) or Sponsor, as both suspected to be related to the study treatment and unexpected (i.e. not documented as an expected reaction to the investigational medicinal product in the RSI) were classified as a sudden unexpected serious adverse reaction (SUSAR) and were subject to expedited reporting to the MHRA and the REC. If the Chief Investigator disagreed with the Principal Investigator/delegate's causality assessment both opinions were provided on the report.

The Sponsor informed the MHRA and the REC of SUSARs within the required expedited reporting timescales:

- Fatal or life-threatening SUSARs: not later than 7 days after the sponsor had information that the case fulfilled the criteria for a fatal

or life-threatening SUSAR, and any follow-up information within a further 8 days.

- All other SUSARs: not later than 15 days after the sponsor had information that the case fulfilled the criteria for a SUSAR.

2.12 Statistical analysis

2.12.1 Sample size

The sample size was 120 patients based on the calculation that 50 patients in each group would provide >90% power (α level=0.05) to detect a mean between-group difference in change in LVESVI from baseline of 6 mL/m^2 (SD of change=7.8 mL/m^2), and allowing for a 10% screen failure rate for LVEF and a 10% drop out rate for loss to follow-up and death.[41] The sample size calculation for the primary outcome was selected as it represents a minimally important difference.[41,159]

2.12.2 Statistical analysis

As this was a clinical trial of an investigational medicinal product (CTIMP), statistical analyses were conducted at the study data centre (Clinical Trials Unit, Robertson Centre for Biostatistics, University of Glasgow) according to a prespecified Statistical Analysis Plan. The Statistical Analysis Plan was drafted by me, Bethany Stanley, Kieran Docherty and Colin Berry before it was finalised prior to unblinding (V1.0 dated 19th July 2024). Efficacy analyses were performed according to the intention-to-treat principle, including all randomly assigned participants without major protocol deviations, and with post-randomisation data available for the outcome of interest at any given time point, irrespective of their subsequent participation in the study and their adherence to randomised treatment. The safety analysis included all randomised patients who took at least one dose of study medication. Data were summarised descriptively for each randomised treatment group, using counts and percentages for categorical variables, and mean±SD or median (interquartile range [IQR]) depending on the distribution of the data. Each outcome was analysed using a linear regression analysis model adjusted for the randomised treatment group, the baseline value of the outcome in question, diuretic use at baseline, and diabetes status. The regression model

treatment effect estimates were reported with 95% CI and P values. A P value of <0.05 was considered statistically significant. All analyses were conducted by Bethany Stanley (Clinical Trials Unit, Robertson Centre for Biostatistics, University of Glasgow), and replicated by myself, using R Studio and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

The model noted above for the primary outcome was extended to include interaction terms to estimate the treatment effects within subgroups of the population. The subgroups of interest were:

- Age at Visit 1 (< vs. ≥ median)
- Sex (male vs. female)
- Baseline diuretic use (yes vs. no)
- T2DM status (yes vs. no)
- Baseline LVESVI (< vs. ≥ median)
- Baseline LVEF on CMR (< vs. ≥ median)
- MI type (NSTEMI vs. STEMI)
- NT-proBNP (< vs. ≥ median)
- Peak troponin (if available) (< vs. ≥ median)

2.13 Conclusion

This trial was designed to provide detailed insight into the effects of SGLT2 inhibition, in addition to standard care, in high-risk patients acutely post-MI. SGLT2 inhibitors reduced heart failure events in patients at high risk following acute MI. Whether this was due to a remodelling benefit was unknown. EMPRESS-MI provided novel multiparametric cardiac imaging and circulating biomarker data on the effect of empagliflozin in patients at high risk of heart failure following acute MI.

Chapter 3 Recruitment and baseline characteristics

3.1 Introduction

This chapter will describe the recruitment and baseline characteristics of the EMPRESS-MI clinical trial. The trial was designed to investigate the effect of empagliflozin, compared with placebo, on left ventricular volumes in patients with left ventricular systolic dysfunction following an MI.

3.2 Methods

EMPRESS-MI was a multi-centre, randomised, double-blind, placebo-controlled trial designed to investigate the effect of empagliflozin, compared with placebo, on left ventricular volumes in patients with left ventricular systolic dysfunction following an MI. Full details of the study protocol are outlined in Chapter 2.

3.2.1 Screening and recruitment

Eligible patients were those with a primary diagnosis of a type 1 acute MI and an LVEF≤40% on transthoracic echocardiography, and <45% on CMR, performed ≥12 hours and ≤14 days after the index MI. Eligible patients had an eGFR of ≥30 mL/min/1.73m^2. Key exclusion criteria included a diagnosis of chronic HFrEF prior to the index admission, systolic blood pressure <90 mmHg, a history of type 1 diabetes or permanent or persistent atrial fibrillation. Full inclusion and exclusion criteria are detailed in Chapter 2.4.

Admission transthoracic echocardiograms, performed ≥12 hours from admission as part of routine clinical care, were reviewed to identify patients with LVEF≤40%, measured by Simpson's Biplane or estimated by visual assessment. Those who met the inclusion and exclusion criteria were approached for consent. Consenting patients then had a baseline CMR scan. Patients with an LVEF<45% by CMR proceeded to randomisation (changed from an LVEF≤40% by an amendment to the trial protocol on 23rd February 2023), and those with LVEF≥45% were excluded from randomisation. Patients were randomised in a 1:1 ratio to receive either empagliflozin 10mg once

daily, or matching placebo. The full randomisation procedure is detailed in Chapter 2.5.

3.2.2 Cardiovascular magnetic resonance protocol and analysis

CMR was performed prior to randomisation and at 24 weeks following randomisation on a single 1.5 Tesla Siemens MAGNETOM Avanto scanner at the GJNH. The imaging protocol is outline in Chapter 2.5.5. All scans were analysed by Matthew Lee (Consultant Cardiologist and Clinical Senior Lecturer) for the purposes of primary and secondary outcome analysis. I analysed all scans for exploratory outcome analysis. All analyses were performed according to standard techniques as detailed in Chapter 2.5.6.

3.2.3 Statistical analysis

Statistical analyses were conducted by Bethany Stanley at the study data centre (Clinical Trials Unit, Robertson Centre for Biostatistics, University of Glasgow) and replicated by myself according to a prespecified Statistical Analysis Plan as detailed in Chapter 2.12.2. Analyses were performed according to the intention-to-treat principle, including all randomly assigned participants without major protocol deviations, and with post-randomisation data available for the outcome of interest at any given time point, irrespective of their subsequent participation in the study and their adherence to randomised treatment. The safety analysis included all randomised patients who took at least one dose of study medication. Data were summarised descriptively for each randomised treatment group, using counts and percentages for categorical variables, and mean±SD or median (IQR) depending on the distribution of the data.

3.3 Results

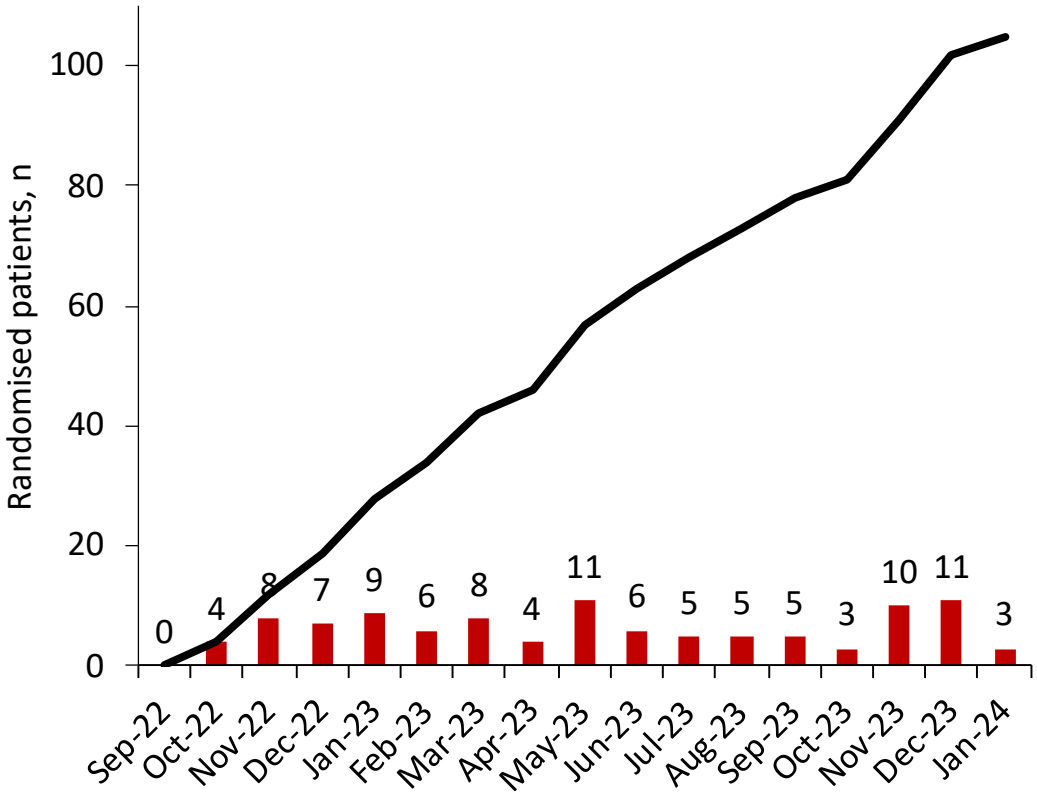
3.3.1 Screening and recruitment

Target recruitment was 120 which allowed a 10% dropout rate for reasons of LVEF eligibility and 10% for loss to follow-up and death. Screening began on 28th September 2022 and ended on the 11th January 2024. The first patient was randomised on the 6th October 2022 and the last patient was randomised on the 8th January 2024. A total of 131 patients were consented, and 105

(80.2%) patients were randomised (51 to empagliflozin, 54 to placebo). The recruitment timeline is detailed in Figure 3-1. Of the 26 (19.8%) who were not randomised, 16 (12.2%) were excluded due to LVEF being above the inclusion criteria on the baseline CMR scan (14 before 23rd February 2023 amendment, 2 following the amendment), 3 (2.2%) did not tolerate the baseline CMR scan due to claustrophobia, 2 (1.5%) were found to have contraindications to CMR after providing consent (history of penetrating eye injury), 2 (1.5%) had no evidence of acute MI on CMR, 1 (0.8%) had poor scan quality due to frequent premature ventricular complexes, 1 (0.8%) had cardiogenic shock and did not proceed to CMR and 1 (0.8%) had persisting systolic blood pressure <90 mmHg and did not proceed to CMR. Recruitment was completed after 105 patients were randomised, rather than continuing until 110 patients were randomised to account for the planned 10% drop out rate for loss to follow-up and death. This decision was based on a higher than anticipated dropout rate for LVEF eligibility (12.2%) and a lower than expected dropout rate for loss to follow-up and death. At that point, 69 participants had completed follow-up, 3 (4.3%) of whom did so without paired primary outcome data. The CONSORT flow diagram for the trial, including completeness of follow-up, is shown in Chapter 4.3.1.

Following randomisation one participant in the placebo group had a diagnosis of cardiac amyloid. After discussion with the Trial Steering Committee and Trial Management Group, and prior to unblinding, this randomisation was classified as a major protocol deviation, as the presence of cardiac amyloid would have met the exclusion criterion stating, “Anyone who, in the investigators’ opinion, is not suitable to participate in the trial for other reasons”. This participant was excluded from the efficacy analysis.

Figure 3-1 Trial recruitment timeline



3.3.2 Baseline characteristics

The baseline characteristics summarised by randomised treatment allocation for all 104 patients included in the efficacy analysis are displayed in Table 3-1. The mean±SD age was 63.0±11.2 years and 90 (86.5%) were male. A history of coronary artery disease was recorded in 14 (13.5%) patients, hypertension in 35 (33.7%), stroke in 3 (2.9%), chronic obstructive pulmonary disease in 5 (4.8%) and asthma in 7 (6.7%). 9 (8.6%) patients had a history of T2DM. 36 (34.6%) were current smokers, 27 (26.0%) were ex-smokers and 41 (39.4%) were non-smokers.

The median time from index MI to randomisation was 3.0 days (IQR 2.0-5.0). 92 (88.5%) patients had a STEMI and 12 (11.5%) had an NSTEMI. 83 (79.8%) MIs were in the anterior location.

Nearly all patients (103 [99.0%]) had PCI or thrombolysis. 102 (98.1%) had PCI performed and 5 (4.8%) received thrombolytic therapy. Of those with a STEMI, 86 (93.5%) had primary PCI with a median time from symptom onset to PCI of 5.6 hours (IQR 2.8-19.4). At randomisation, 97 (93.2%) patients were

taking an ACE inhibitor or an ARB, 89 (85.6%) a beta blocker, 66 (63.5%) an MRA, and 30 (28.8%) were on a loop diuretic. 46 (44.2%) patients received a loop diuretic at any point during the index admission before randomisation. Medication use during trial follow-up is detailed in Table 3-2.

The mean LVEF by echocardiography was 35.0±4.9% and by CMR was 34.8±6.0%. The mean infarct size as a percentage of myocardial mass was 36.3±13.4%. MVO was present in 77 (74.0%) patients and IMH in 47 of the 97 with interpretable T2* maps (48.5%). The median baseline NT-proBNP was 2109 pg/mL (IQR 1128-3375). The median peak troponin T was 4853 ng/L (IQR 2570-7945) (available in 86 [82.7%] patients).

Table 3-1 Baseline characteristics

Characteristic	Empagliflozin (n=51)	Placebo (n=53)
Age, years	63.4 (10.8)	62.6 (11.7)
Male, n (%)	44 (86.3)	46 (86.8)
Systolic blood pressure, mmHg	114.6 (16.5)	113.9 (17.5)
Heart rate, beats/min	77.9 (13.0)	73.5 (13.8)
eGFR, mL/min/1.73m^2	78.3 (20.3)	79.3 (20.2)
Peak troponin T, ng/L*	5585 (2604, 8132)†	4514 (2578, 7884)†
NT-proBNP, pg/mL	2316 (1110, 3375)†	2017 (1286, 3175)†
CMR LVEF, %	33.7 (6.0)	35.8 (5.8)
Time from symptom onset to reperfusion (STEMI patients only), mins	431 (171, 1339)†	280 (163, 550)†
MI type:		
STEMI, n (%)	46 (90.2)	46 (86.8)
NSTEMI, n (%)	5 (9.8)	7 (13.2)
Infarct location:		
Anterior, n (%)	41 (80.4)	42 (79.2)
Inferior, n (%)	6 (11.8)	9 (17.0)
Lateral, n (%)	4 (7.8)	2 (3.8)
PCI or thrombolysis, n (%)	50 (98.0)	53 (100)
PCI, n (%)	49 (96.1)	53 (100)
Thrombolysis, n (%)	2 (3.9)	3 (5.7)
Medical history:		
Hypertension, n (%)	20 (39.2)	15 (28.3)
T2DM, n (%)	4 (7.8)	5 (9.4)
Stroke, n (%)	1 (2.0)	2 (3.8)
Medications at randomisation		
Dual antiplatelet therapy, n (%)	51 (100)	53 (100)
Anticoagulant, n (%)	3 (5.9)	6 (11.3)
Statin, n (%)	50 (98.0)	53 (100)
ACE inhibitor or ARB, n (%)	50 (98.0)	47 (88.7)
Beta-blocker, n (%)	42 (82.4)	47 (88.7)
MRA, n (%)	33 (64.7)	33 (62.3)
Loop diuretic, n (%)	15 (29.4)	15 (28.3)
Loop diuretic at any point from admission to randomisation, n (%)	22 (43.1)	24 (45.3)

Baseline characteristics are presented for all randomised patients included in the efficacy analysis. Data presented as mean (SD) unless otherwise stated. eGFR was calculated using the modification of diet in renal disease formula. *Available in 86 (83%) patients. †Median (interquartile range).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CMR, cardiovascular magnetic resonance; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NSTEMI, non-ST-elevation myocardial infarction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus.

Table 3-2 Medication use during trial follow-up

	Randomisation		Visit 2		Visit 3		Visit 4		Visit 5	
	Empa n=51	Placebo n=53	Empa n=50	Placebo n=53	Empa n=50	Placebo n=53	Empa n=50	Placebo n=53	Empa n=50	Placebo n=53
Aspirin, n (%)	51 (100)	53 (100)	50 (100)	53 (100)	47 (94.0)	47 (88.7)	46 (92.0)	46 (86.8)	44 (88.0)	45 (84.9)
P2Y12 inhibitor, n (%)	51 (100)	53 (100)	50 (100)	53 (100)	50 (100)	52 (98.1)	49 (98.0)	51 (96.2)	46 (92.0)	47 (88.7)
Anticoagulation, n (%)	3 (5.9)	6 (11.3)	7 (14.0)	8 (15.1)	6 (12.0)	8 (15.1)	6 (12.0)	8 (15.1)	6 (12.0)	8 (15.1)
Statin, n (%)	50 (98.0)	53 (100)	49 (98.0)	53 (100)	49 (98.0)	53 (100)	49 (98.0)	53 (100)	49 (98.0)	53 (100)
ACE inhibitor, n (%)	46 (90.2)	41 (77.4)	44 (88.0)	41 (77.4)	41 (82.0)	41 (77.4)	40 (80.0)	38 (71.1)	39 (78.0)	36 (67.9)
ARB, n (%)	4 (7.8)	6 (11.3)	5 (10.0)	6 (11.3)	7 (14.0)	8 (15.1)	8 (16.0)	8 (15.1)	9 (18.0)	8 (15.1)
ARNI, n (%)	0 (0)	0 (0)	0 (0)	2 (3.8)	2 (4.0)	3 (5.7)	2 (4.0)	6 (11.3)	2 (4.0)	7 (13.2)
Beta-blocker, n (%)	42 (82.4)	47 (88.7)	44 (88.0)	47 (88.7)	46 (92.0)	49 (92.5)	48 (96.0)	49 (92.5)	49 (98.0)	48 (90.6)
MRA, n (%)	33 (64.7)	33 (62.3)	33 (66.0)	36 (67.9)	41 (82.0)	42 (79.2)	43 (86.0)	42 (79.2)	45 (90.0)	41 (77.4)
Diuretic, n (%)	15 (29.4)	15 (28.3)	15 (30.0)	19 (35.8)	13 (26.0)	18 (34.0)	13 (26.0)	17 (32.1)	13 (26.0)	14 (26.4)
Loop, n (%)	15 (29.4)	15 (28.3)	15 (30.0)	19 (35.8)	13 (26.0)	18 (34.0)	13 (26.0)	17 (32.1)	13 (26.0)	13 (24.5)
Thiazide, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.9)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI; angiotensin receptor-neprilysin inhibitor; empa, empagliflozin; MRA, mineralocorticoid receptor antagonist.

3.3.3 Baseline imbalances

The treatment groups were generally well-matched at baseline, though some imbalances in characteristics were noticed. There was a numerically longer symptom-to-reperfusion time and a larger infarct size in the empagliflozin group however in *post hoc* analyses these differences were not statistically significant (reperfusion time P=0.309, infarct size P=0.267). I performed exploratory adjusted analyses for these characteristics to assess their impact on the primary outcome (Chapter 4.3.8).

3.4 Discussion

3.4.1 Study population

EMPRESS-MI was designed to enrol patients at high risk of progressive adverse remodelling. Several of the baseline characteristics deserve further consideration.

The mean age in the EMPRESS-MI trial was 63, with 87% of the participants being male. These demographics align with those observed in previous trials involving high-risk post-MI patients. For example, in a recent remodelling trial of patients with an LVEF<45% on echocardiography immediately following an anterior MI the mean age was 58, and 88% of patients were male.[160] Similarly, in the DACAMI trial, which investigated dapagliflozin in patients immediately following reperfused anterior STEMI with an LVEF<50%, the mean age was 56, and 83% of patients were male.[119] Demographics were similar across three large randomised clinical trials of ACE inhibitors in high-risk patients post-MI (SAVE, AIRE and TRACE mean age 63 years, 76% male).[54] In The High-Risk Myocardial Infarction Database Initiative of four large randomised clinical trials including 28,771 patients (VALIANT, EPHESUS, Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan [OPTIMAAL] and CAPRICORN), the mean age was 65 years and 70% were male.[161] Contemporary large CVOTs, though utilizing enrichment criteria that may limit comparisons and generalisability, showed similar demographics to EMPRESS-MI (PARADISE-MI mean age 64 years and 76% male, EMPACT-MI mean age 64 years and 75% male).[162,163] In unselected non-trial populations, demographics were similar to the EMPRESS-MI trial. In a Danish cohort of

18,818 STEMI patients treated with primary PCI between 2003-2018, the mean age was 64 years and 74% were male.[164]

The majority of patients in the EMPRESS-MI population presented with an anterior STEMI as the index MI. Anterior MI is associated with a higher risk of adverse remodelling and heart failure due to the larger infarct size as compared to other MI locations.[165] Patients with anterior STEMI typically have a lower baseline LVEF than those with STEMI in other locations.[165] In an analysis of the PARADISE-MI trial, patients with STEMI were shown to have a lower baseline LVEF compared to those with NSTEMI.[166]

The mean infarct size as measured by CMR in the EMPRESS-MI population was substantial at 36%, larger than in other recent STEMI populations. A larger infarct size is associated with a higher risk of adverse remodelling.[165] In A Trial of Low-dose Adjunctive alTeplase During prIMary PCI (T-TIME), which evaluated intracoronary alteplase in patients presenting with a proximal-mid occlusion of a major coronary artery, the mean infarct size at baseline was 27%.[167] The BHF Detection and Significance of Heart Injury in STEMI (MR-MI) all-comers STEMI cohort study, reported a mean infarct size of 18%.[22] Another contemporary remodelling trial reported a median infarct size of 34% in the control group and 29% in the intervention group.[160]

In the EMPRESS-MI trial the prevalence of MVO and IMH was 74% and 48%, respectively. In a patient-level pooled analysis of randomised primary PCI trials which assessed MVO by CMR, the MVO incidence ranged from 37% to 78%.[20] Patients with MVO had a larger infarct size and were at higher risk of all-cause mortality and heart failure hospitalisation.[20] A meta-analysis of 18 studies evaluating IMH following STEMI observed an average IMH prevalence of 39%.[168] Patients with IMH had larger infarct sizes, lower LVEF and an increased risk of major adverse cardiovascular events.[168]

3.4.2 Comparison to remodelling trials

It is essential to highlight the key similarities and differences in baseline characteristics between the EMPRESS-MI population and other post-MI remodelling trials.

Baseline characteristics of three trials investigating the effect of SGLT2 inhibitors on adverse left ventricular remodelling post-MI are summarised in Table 3-3. The EMMY trial randomised 476 patients to empagliflozin or placebo within 72 hours of PCI for an acute MI with creatine kinase >800 IU/L or a troponin >10 times higher than the upper local laboratory limit of normal.[117,169] Unlike EMPRESS-MI, there was no eligibility requirement for low LVEF. Mean age and percentage of patients who were male and percentage of patients who were diabetic were comparable between EMPRESS-MI and EMMY (Table 3-3). However, the mean systolic blood pressure was higher in EMMY, which also had a higher blood pressure cut-off for eligibility (≥110/70 mmHg vs. systolic ≥90 mmHg in EMPRESS-MI).[169] Similarly, the mean eGFR in EMMY was higher (eligibility cut-off - EMPRESS-MI ≥30 mL/min/1.73m^2, EMMY >45 mL/min/1.73m^2).[169] In EMMY, the baseline troponin T and NT-proBNP were lower. MI location and type have not been reported for the full EMMY cohort. However, in a subset analysis of ECG parameters (181/472 patients), 88% had a STEMI, a proportion comparable to EMPRESS-MI.[170] Medication use also differed between the trials. Beta-blocker prescription rates at baseline were lower in EMPRESS-MI, possibly reflecting a greater prevalence of post-MI pulmonary congestion. There were higher prescription rates of MRAs and diuretics in EMPRESS-MI. In EMMY the ventricular volumes were almost half of those in EMPRESS-MI and LVEF was substantially higher. Taken together, these differences suggest a more clinically unwell post-MI cohort at higher risk of adverse remodelling in the EMPRESS-MI trial, compared to the EMMY trial.

Two smaller trials have investigated the effect of SGLT2 inhibitors on remodelling post-MI and baseline characteristics are compared in Table 3-3. The DACAMI trial randomised 100 patients with anterior STEMI and without T2DM to dapagliflozin or placebo for 12 weeks.[119] The EMI-STEMI trial randomised 101 patients with STEMI and without T2DM to empagliflozin or placebo immediately before primary PCI.[120] The baseline characteristics of these two smaller trials are similar to the EMMY trial, and are lower risk populations than that recruited to EMPRESS-MI.

Table 3-4 reports baseline characteristics of EMPRESS-MI and other randomised trials investigating non-SGLT2 inhibitor therapies for left ventricular remodelling in post-MI patients. Patient demographics are

generally similar across the trials. The percentage of patients with T2DM in EMPRESS-MI was lower than in previous trials. Given that patients with T2DM are at higher risk of time to heart failure hospitalisation and mortality post-MI, they have the potential to derive benefit from novel therapies.[171] PARADISE-MI and EMPACT-MI used T2DM as an enrichment factor, resulting in a higher prevalence of T2DM compared to other post-MI trials.[55,86] The T2DM prevalence in EMPRESS-MI was broadly similar to that in EMMY, likely reflecting the exclusion of many patients already prescribed an SGLT2 inhibitor for T2DM at the time of their acute MI.[117] The time from index MI to assessment of LVEF is shortest in EMPRESS-MI. Reperfusion and secondary prevention therapy use increases across trials. What is striking is the large left ventricular volumes in the EMPRESS-MI trial, indicating a greater degree of acute remodelling and a cohort at high risk of adverse remodelling.

Table 3-3 Randomised trials of SGLT2 inhibitors for left ventricular remodelling post-MI

	EMPRESS-MI (n=104)	**EMMY**[117] **(n=476)**	**DACAMI**[119] **(n=100)**	**EMI-STEMI**[120] **(n=101)**
Main inclusion criteria	LVEF<40%	Large MI defined as creatinine kinase >800 U/l + troponin >10x ULN	Anterior STEMI + LVEF<50% + no T2DM	STEMI + no T2DM
Intervention	Empagliflozin	Empagliflozin	Dapagliflozin	Empagliflozin
Imaging modality	CMR	Echo	Echo	Echo
Follow-up duration	24 weeks	26 weeks	12 weeks	40 days
Age, years	63	57	55/57	59/62
Male, %	87	82	83	78
Systolic blood pressure, mmHg	114	125*	NR	138/134
T2DM, %	9	13	0	0
eGFR, mL/min/1.73m^2	78	92	83/85	78/77
Troponin T, ng/L	4853*	3039*	3127/3088*	NR
NT-proBNP, pg/mL	2109*	1294*	291/289*	NR
STEMI, %	89	88†	100	100
Anterior, %	80	NR	100	61
Reperfusion, %	99	100	100	100
ACEi/ARB/ARNI, %	93	98	100	94
Beta-blocker, %	86	96	100	97
MRA, %	63	38	8	58
Loop diuretic, %	29	11	8	11
LVEF, %	35	48*	43/43	39/38

*Median. †From a subset analysis of electrocardiogram parameters (181 of 472 patients). Data are reported as treatment group/placebo group where values were provided separately.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CMR, cardiovascular magnetic resonance; DACAMI, The Impact of Dapagliflozin on Cardiac Function Following Anterior Myocardial Infarction in Non-diabetic Patients; eGFR, estimated glomerular filtration rate; EMI-STEMI, Empagliflozin Effects in Patients with ST-Elevation Myocardial Infarction Undergoing Primary PCI; EMPRESS-MI, EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction; EMMY, EMpagliflozin in patients with acute Myocardial infarction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NR, not reported; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal.

Table 3-4 Randomised trials of other therapies for left ventricular remodelling post-MI

	EMPRESS-MI (n=104)	**PARADISE-MI[57] (n=544)**	**Boyle et al[160] (n=147)**	**ASPIRE[172] (n=820)**	**Weir et al[41] (n=100)**	**VALIANT[25] (n=603)**	**CAPRICORN[39] (n=127)**	**SAVE[18] (n=512)**
Year	2024	2022	2021	2011	2009	2005	2004	1994
Main inclusion criteria	LVEF<45%	LVEF≤40% or pulmonary congestion and 1 risk-augmenting factor	Anterior STEMI and LVEF<45%	LVEF<45%	LVEF<40%	LVEF≤35% or HF or both	LVEF≤40%	LVEF≤40% without HF
Intervention	Empagliflozin	Sacubitril/ Valsartan	NP202	Aliskiren	Eplerenone	Valsartan	Carvedilol	Captopril
Comparator	Placebo	Ramipril	Placebo	Placebo	Placebo	Captopril or Valsartan + Captopril	Placebo	Placebo
Imaging modality	CMR	Echo	CMR	Echo	CMR	Echo	Echo	Echo
Time to LVEF assessment, days	3	5	5	43	4	NR	9	11
Follow-up duration	24 weeks	8 months	90 days	36 weeks	24 weeks	20 months	6 months	1 year
Age, years	63	64	58	60	61/57	64	61	60/58
Male, %	87	74	88	83	77	70	81	81
Systolic blood pressure, mmHg	114	119	NR	122/122	115/112	121	114/114	NR
T2DM, %	9	43	NR	22	0	23	21	20

eGFR, mL/min/1.73m^2	78	71	NR	80/81	67/73	NR	NR	NR
STEMI, %	89	75	100	NR	89	NR	NR	NR
Anterior, %	80	68	100	79	55	59	57	NR
Reperfusion, %	98% PCI 5% thromb	90% PCI 2% thromb	100% PCI	75% reperfusion therapy	27% PCI 54% thromb	17% PCI 39% thromb	42% PTCA/thromb	16% PTCA 41% thromb
ACEi/ARB/ARNI, %	93	100	87	99	94	100	92	49
Beta-blocker, %	86	84	90	96	93	73	47	NR
MRA, %	63	48	24	27	50	NR	NR	NR
Loop diuretic, %	29	47	NR	NR	21	NR	NR	NR
LVEF, %	35	42	42/43	38	52/46	40/39/39	39	31/31

Data are reported as treatment group/placebo group where values were provided separately.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASPIRE, Aliskiren Study in Post-MI Patients to Reduce Remodelling; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CMR, cardiovascular magnetic resonance; eGFR, estimated glomerular filtration rate; EMPRESS-MI, EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NR, not reported; PARADISE-MI, Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SAVE, Survival and Ventricular Enlargement; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus; thromb, thrombolysis; VALIANT, Valsartan in Acute Myocardial Infarction.

3.4.3 Comparison to cardiovascular outcome trials of SGLT2 inhibitors post-MI

As described in Chapter 1.3.1.4, two large CVOTs, DAPA-MI and EMPACT-MI, have investigated SGLT2 inhibitors in the acute post-MI setting.[85,86] The baseline characteristics for these trials are summarised in Table 3-5. The mean age in both trials was similar to that in EMPRESS-MI, and the majority of patients across all three trials were male. DAPA-MI excluded patients with T2DM, while EMPACT-MI defined the presence of T2DM as an enrichment factor, leading to a higher percentage of patients with T2DM in EMPACT-MI. Across the three trials, EMPRESS-MI included the highest percentage of STEMI patients.

There were notable differences in baseline treatments. Nearly all patients in EMPRESS-MI had PCI or thrombolysis, compared to 89% in DAPA-MI and EMPACT-MI. RAAS inhibitor prescription rates were lower in EMPACT-MI than in the other two trials, while MRA prescription rates varied in line with the populations studied, being lowest in DAPA-MI and highest in EMPRESS-MI. A significant proportion of EMPACT-MI participants (38%) were prescribed loop diuretics at discharge, compared to 30% of EMPRESS-MI participants at randomisation, possibly reflecting a greater prevalence of congestion in EMPACT-MI (which recruited patients with either LVEF<45% or congestion). However, 45% of patients in the EMPRESS-MI trial received diuretics at any point from admission to randomisation. Of note, the EMPACT-MI trial reported medications at discharge whilst EMPRESS-MI recorded medications at randomisation. Baseline LVEF in the EMPRESS-MI trial was lower than both outcome trials (40% in EMPACT-MI, <50% in 73% in DAPA-MI [mean not reported]).

Altogether, patients recruited to the EMPRESS-MI trial had more high-risk characteristics than those recruited to the DAPA-MI trial. Although EMPACT-MI used enrichment criteria to ensure a high-risk population, the baseline characteristics are comparable to EMPRESS-MI, with the exception of T2DM.

Table 3-5 Randomised cardiovascular outcome trials of SGLT2 inhibitors post-MI

	EMPRESS-MI (n=104)	**DAPA-MI[85] (n=4017)**	**EMPACT-MI[163] (n=6522)**
Main inclusion criteria	LVEF<40%	Any LV systolic dysfunction or Q-waves + no T2DM	LVEF<45% +/- congestion + ≥1 risk factor for heart failure
Intervention	Empagliflozin	Dapagliflozin	Empagliflozin
Age, years	63	63	64
Male, %	87	70	75
T2DM, %	9	0	32
STEMI, %	89	72	74
Reperfusion, %	99	89	89
ACEi/ARB/ARNI, %	93	92	83
Beta-blocker, %	86	90	87
MRA, %	63	23	48
Loop diuretic, %	29	NR	38
LVEF, %	35	<50 in 73%	40

Abbreviations: ACEi, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; DAPA-MI, Dapagliflozin in Patients with Myocardial Infarction; EMPACT-MI, Study to Evaluate the Effect of Empagliflozin on Hospitalisation for Heart Failure and Mortality in Patients with Acute Myocardial Infarction EMPRESS-MI, EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NR, not reported; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus.

3.4.4Limitations

The study population was majority white. Whilst this limits generalisability to more diverse populations, it reflects the demographic composition of the West of Scotland. Similarly, the majority of participants were male, although this is consistent with other similar trials. The percentage of female patients in the pre-screened population was comparable to that of the recruited cohort. Most patients recruited presented with a STEMI, therefore, the applicability of the results to patients with NSTEMI is limited. Most patients recruited did not have T2DM, limiting applicability of the results in this high-risk population.

Medications at the time of randomisation, rather than at the time of discharge, were recorded. The post-MI period is characterised by rapid initiation and titration of secondary prevention therapy, and medications at

randomisation may not fully reflect those prescribed at discharge from the index admission. However, I collected medication information at Visit 2 (2 weeks ± 4 days post-randomisation), which were broadly consistent with the medications recorded at randomisation.

Baseline differences between the groups were noted, including a numerically but not statistically longer median symptom-to-reperfusion time and a larger mean infarct size in the empagliflozin group. Such subtle baseline differences are expected in small mechanistic trials. Importantly, baseline left ventricular volumes were identical between the groups, suggesting similar acute adverse remodelling between the groups.

3.4.5 Conclusion

The baseline characteristics of the EMPRESS-MI trial indicate a population at high risk of adverse remodelling, and likely to benefit from additional anti-remodelling therapy. When compared to other trials investigating SGLT2 inhibitors post-MI, the EMPRESS-MI population has more higher risk features than most, with the exception of EMPACT-MI, which specifically selected for a high-risk population through the use of enrichment criteria.

Chapter 4 The effect of empagliflozin on cardiovascular magnetic resonance remodelling outcomes in patients with left ventricular systolic dysfunction following myocardial infarction

4.1 Introduction

In this chapter I will describe the effect of empagliflozin on CMR remodelling outcomes in the EMPRESS-MI clinical trial. The primary outcome was the change in LVESVI from baseline to 24 weeks. LVESVI is a major determinant of outcome post-MI.[23] Secondary CMR outcomes included changes in LVEDVI, LVEF, LAVI, LVMI and infarct size from baseline to 24 weeks. CMR is the gold standard method of assessment of left ventricular volumes and function and allows estimation of infarct size.[157]

4.2 Methods

4.2.1 Cardiovascular magnetic resonance protocol and analysis

The full CMR protocol and analysis methods are detailed in Chapter 2.5.5 and Chapter 2.5.6, respectively. Briefly, the CMR protocol included SSFP cine imaging for the measurement of left ventricular volumes, mass and function and left atrial volume. Late gadolinium enhancement imaging was included for the measurement of infarct size. CMR scans were analysed in a paired fashion and blinded to treatment assignment by Dr Matthew Lee (Consultant Cardiologist and Clinical Senior Lecturer) for the primary and secondary outcomes. Left ventricular volumes were calculated by tracing the endocardial border (excluding papillary muscle and trabeculations) in end-systole and end-diastole in the short-axis cine images from the mitral valve plane through to the apex. The basal left ventricular slice was defined as the most basal slice with >50% myocardium present. Left ventricular outflow tract volume was included in volumetric analysis. Left ventricular mass was calculated as the total difference between the inner and outer circumferences of the left ventricular myocardium in end-diastole, multiplied by the myocardial density (1.05 g/cm^3). Left atrial volume was calculated using the biplane area-length method by manually tracing the left atrium

endocardial volume in end-systole. Infarct size, measured in mass and as a percentage of myocardium, was calculated by manually drawing around the epicardial and endocardial border of the LGE short-axis images, then drawing an area of interest in normal myocardium (180 degrees from area of infarction). An auto-threshold of 5 SD from this normal myocardium was used to identify areas of late enhancement. Indexed values were indexed to BSA, measured at the time of the scan.

4.2.2 Statistical analysis

All statistical analyses were conducted by Bethany Stanley (Clinical Trials Unit, Robertson Centre for Biostatistics, University of Glasgow) and replicated by myself using R Studio and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and is described in detail in Chapter 2.12. Efficacy analyses were performed according to the intention-to-treat principle, including all randomly assigned participants without major protocol deviations, and with post-randomisation data available for the outcome of interest at any given time point, irrespective of their subsequent participation in the study and their adherence to randomised treatment.

Data were summarised descriptively for each randomised treatment group, using counts and percentages for categorical variables, and mean±SD or median (IQR), depending on the distribution of the data. Each outcome was analysed using a linear regression analysis model adjusted for the randomised treatment group, the baseline value of the outcome in question, diuretic use at baseline, and diabetes status. The regression model treatment effect estimates were reported with 95% CI and P values. A P value of <0.05 was considered statistically significant.

4.3 Results

4.3.1 Completeness of follow-up

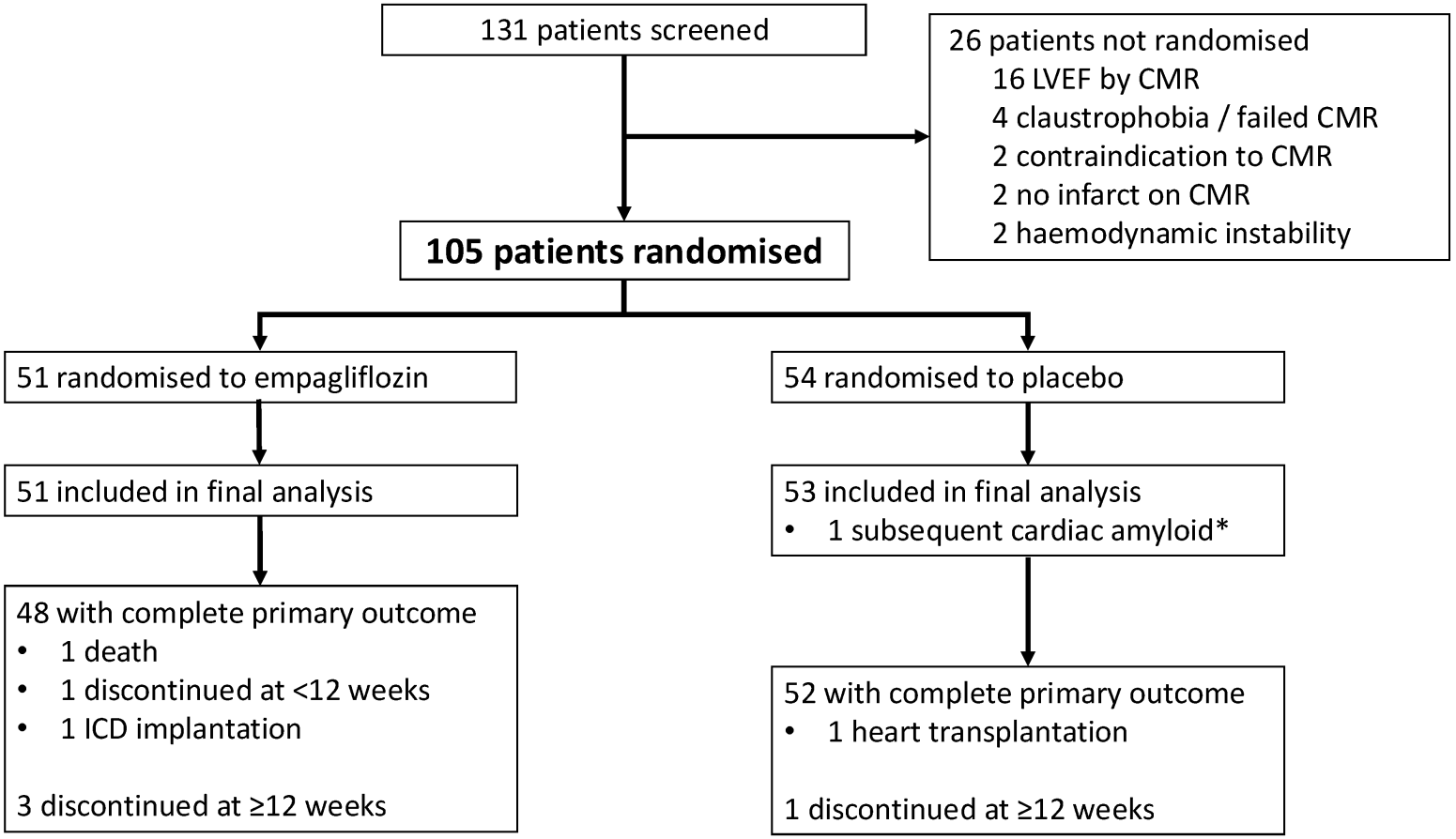
As described in Chapter 3.3.1, 105 patients were randomised to the EMPRESS-MI trial. The CONSORT diagram is shown in Figure 4-1.

51 patients were randomised to empagliflozin. 49 of the 51 remained on randomised therapy and 48 had complete primary outcome data. There was 1

death (sudden cardiac death) in the empagliflozin group. 1 patient in the empagliflozin group discontinued randomised treatment before at least 12 weeks of treatment exposure and did not undergo follow-up CMR as per the trial protocol. 1 patient in the empagliflozin group remained on randomised therapy but did not have complete primary outcome data. This patient received an implantable cardioverter defibrillator following randomisation, therefore did not attend for follow-up CMR but remained on randomised treatment and attended for all other outcome data collection.

54 patients were randomised to placebo. 1 patient randomised to the placebo group had a diagnosis of cardiac amyloid and the randomisation was classified as a major protocol deviation. This patient was excluded from the efficacy analysis. Of the 53 patients randomised to placebo and included in the efficacy analysis, 52 remained on randomised therapy and had complete primary outcome data. 1 patient in the placebo group discontinued randomised treatment before at least 12 weeks of treatment exposure and did not undergo follow-up CMR as per the trial protocol. There were no deaths in the placebo group.

Figure 4-1 CONSORT diagram



*This participant had a subsequent diagnosis of cardiac amyloid following randomisation. After discussion with the Trial Steering Committee and Trial Management Group, and prior to unblinding, this randomisation was classified as a major protocol deviation, as the presence of cardiac amyloid would have met the exclusion criterion “Anyone who, in the investigators’ opinion, is not suitable to participate in the trial for other reasons”.

Of the 16 patients who did not meet inclusion criteria by CMR LVEF, 10 had an LVEF≥45%.

6 patients discontinued the study drug early: 4 in the empagliflozin group and 2 in the placebo group.

In the empagliflozin group, 1 discontinued treatment before 12 weeks due to recurrent genital infections, and, per study protocol, did not attend for follow-up CMR but participated in all other outcome analysis. 3 discontinued therapy after at least 12 weeks of treatment and attended for follow-up CMR: 1 due to patient concern about side effects, 1 due to recurrent genital tract infection, and 1 following the development of symptomatic heart failure. Additionally, 1 patient received an ICD after randomization, remained on therapy, and attended all outcome analyses except the follow-up CMR.

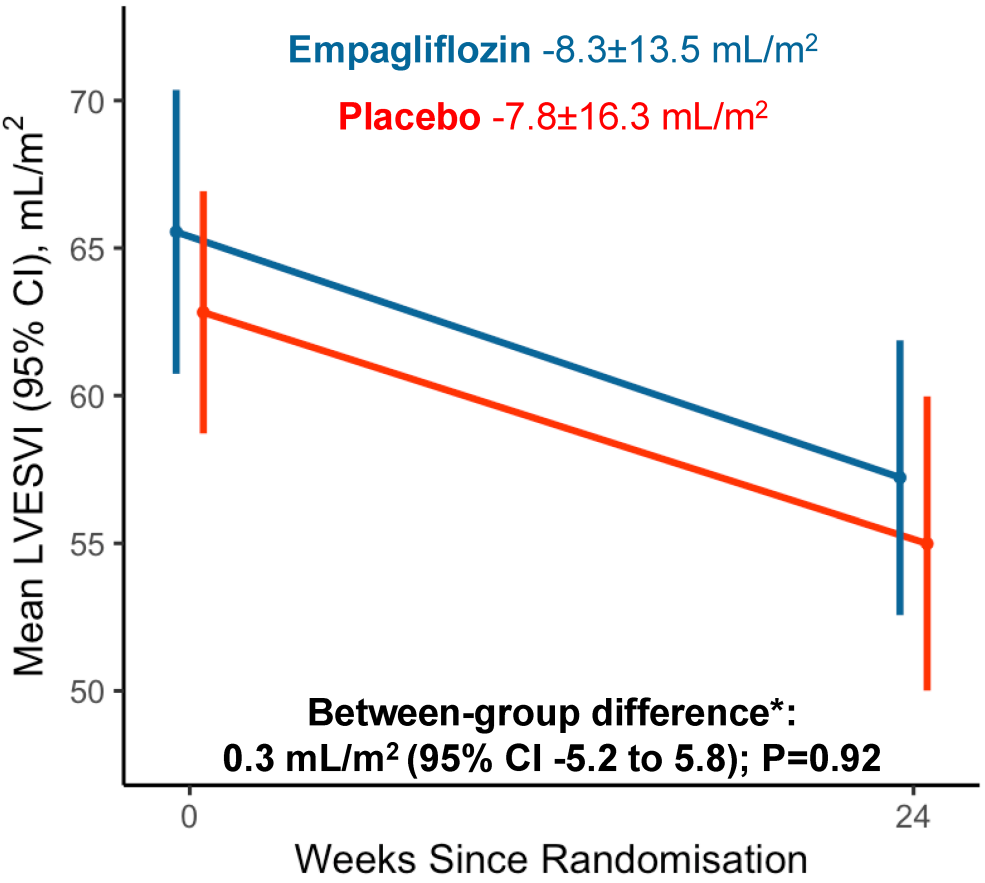
In the placebo group, 1 patient stopped treatment before 12 weeks due to receiving a heart transplant and did not attend the follow-up CMR but participated in all other outcome analyses. 1 discontinued therapy after at least 12 weeks of treatment, due to symptomatic heart failure, and attended for follow-up CMR.

Abbreviations: CMR, cardiovascular magnetic resonance; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction.

4.3.2 Effect of empagliflozin on left ventricular end-systolic volume index

Mean±SD LVESVI at baseline was 65.6±17.0 mL/m^2 in those randomised to empagliflozin with follow-up CMR data (n=48) and 62.8±15.1 mL/m^2 in those randomised to placebo (n=52). LVESVI decreased by 8.3±13.5 mL/m^2 between baseline and 24 weeks in the empagliflozin group and by 7.8±16.3 mL/m^2 in the placebo group: adjusted between-group difference 0.3 mL/m^2 (95% CI -5.2 to 5.8); P=0.92 (Figure 4-2 and Table 4-1).

Figure 4-2 Change in LVESVI from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval, LVESVI, left ventricular end-systolic volume index.

Table 4-1 Change in primary and secondary CMR outcomes with empagliflozin or placebo from baseline to 24 weeks

	Empagliflozin				Placebo				Between-group difference (95% CI)*	P value
	n	Baseline	24 weeks	Change	n	Baseline	24 weeks	Change		
Primary Outcome										
LVESVI, mL/m^2	48	65.6 (17.0)	57.2 (16.5)	-8.3 (13.5)	52	62.8 (15.1)	55.0 (18.3)	-7.8 (16.3)	0.3 (-5.2, 5.8)	0.92
Secondary Outcomes										
LVEDVI, mL/m^2	48	97.8 (19.8)	98.3 (17.3)	0.6 (16.3)	52	97.6 (18.3)	97.3 (22.2)	-0.3 (18.7)	0.8 (-5.5, 7.0)	0.81
LVEF, %	48	33.4 (6.0)	42.7 (8.6)	9.4 (7.5)	52	36.0 (5.8)	44.4 (7.6)	8.5 (7.4)	0.0 (-2.9, 3.0)	0.98
LAVI, mL/m^2	48	34.3 (12.7)	37.3 (13.4)	3.0 (14.4)	52	36.2 (11.2)	39.2 (13.0)	3.0 (13.3)	-1.0 (-5.9, 3.8)	0.67
LVMI, g/m^2	48	62.2 (13.7)	52.2 (9.6)	-10.0 (7.8)	52	59.1 (11.0)	50.4 (9.4)	-8.7 (6.4)	-0.3 (-2.4, 1.8)	0.78
Infarct size, %	47	37.9 (11.8)	28.7 (10.7)	-9.1 (7.7)	49	33.9 (15.2)	24.0 (13.1)	-9.9 (9.3)	2.1 (-0.9, 5.2)	0.16

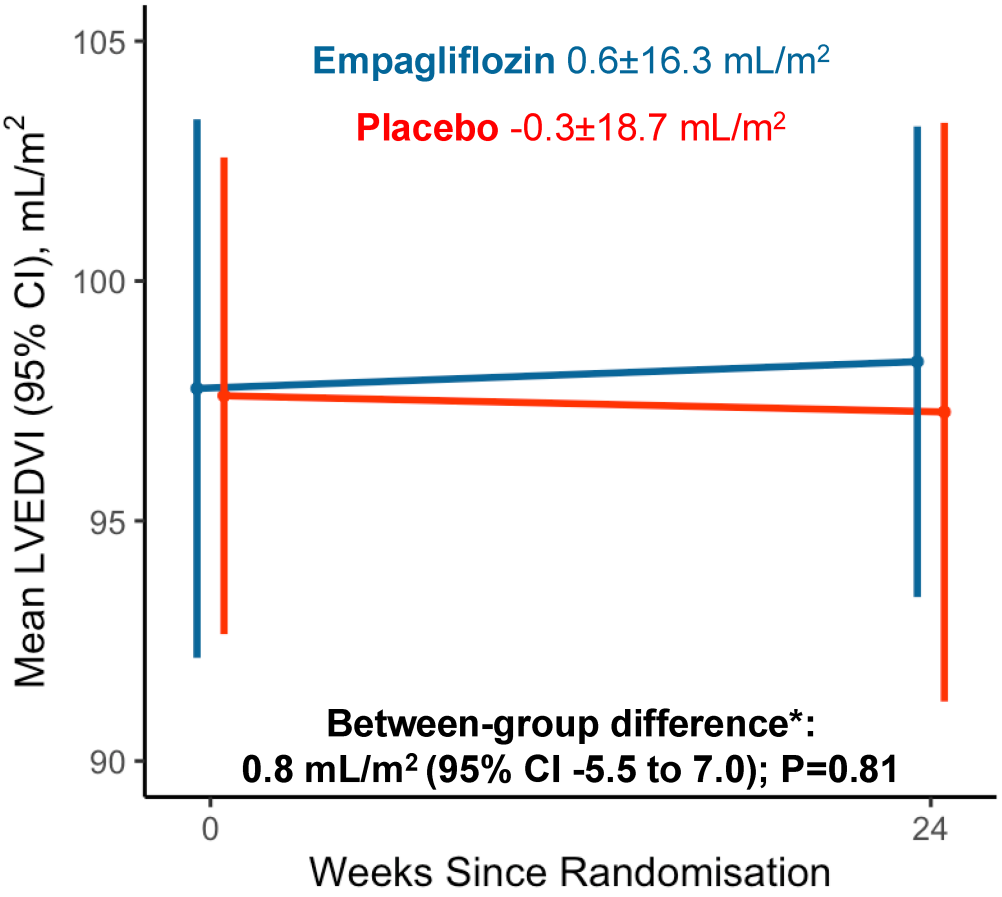
Data presented as mean (SD) unless otherwise stated. Results are reported for those with data available at baseline and 24 weeks.
*Calculated using a linear model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status. All outcomes are reported as adjusted mean differences (95% CI).

Abbreviations: CI, confidence interval; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index.

4.3.3 Effect of empagliflozin on left ventricular end-diastolic volume index

Mean±SD LVEDVI at baseline was 97.8±19.8 mL/m^2 in those randomised to empagliflozin with follow-up CMR data (n=48) and 97.6±18.3 mL/m^2 in those randomised to placebo (n=52). LVEDVI increased by 0.6±16.3 mL/m^2 between baseline and 24 weeks in the empagliflozin group and decreased by 0.3±18.7 mL/m^2 in the placebo group: adjusted between-group difference 0.8 mL/m^2 (95% CI -5.5 to 7.0); P=0.81 (Figure 4-3 and Table 4-1).

Figure 4-3 Change in LVEDVI from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

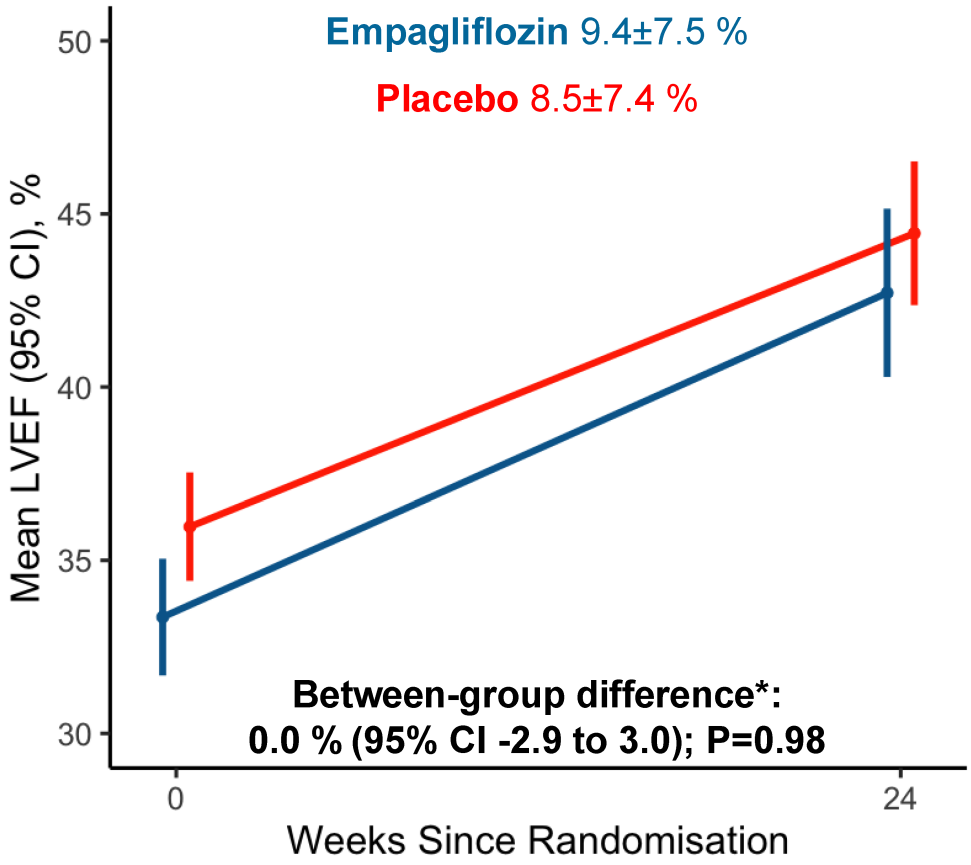
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval, LVEDVI, left ventricular end-diastolic volume index.

4.3.4 Effect of empagliflozin on left ventricular ejection fraction

Mean±SD LVEF at baseline was 33.4±6.0% in those randomised to empagliflozin with follow-up CMR data (n=48) and 36.0±5.8% in those randomised to placebo (n=52). LVEF increased by 9.4±7.5% between baseline and 24 weeks in the empagliflozin group and by 8.5±7.4% in the placebo group: adjusted between-group difference 0.0% (95% CI -2.9 to 3.0); P=0.98 (Figure 4-4 and Table 4-1).

Figure 4-4 Change in LVEF from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

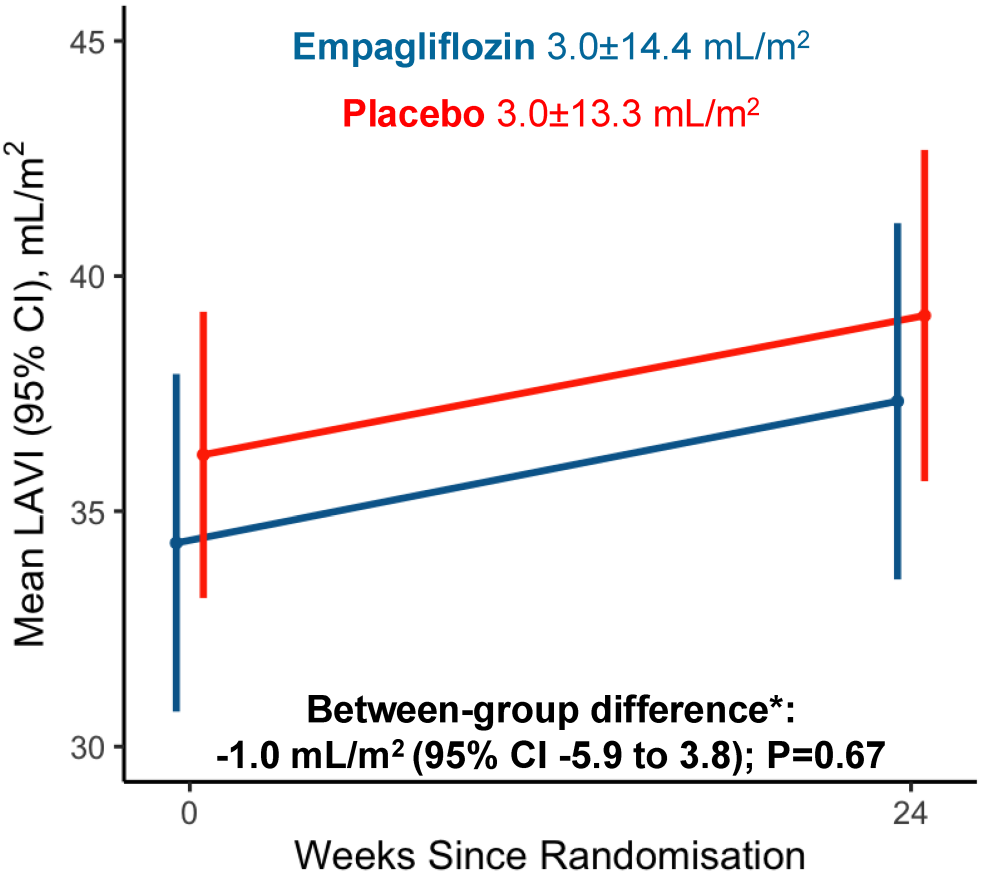
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval, LVEF, left ventricular ejection fraction.

4.3.5 Effect of empagliflozin on left atrial volume index

Mean±SD LAVI at baseline was 34.3±12.7 mL/m^2 in those randomised to empagliflozin with follow-up CMR data (n=48) and 36.2±11.2 mL/m^2 in those randomised to placebo (n=52). LAVI increased by 3.0±14.4 mL/m^2 between baseline and 24 weeks in the empagliflozin group and by 3.0±13.3 mL/m^2 in the placebo group: adjusted between-group difference -1.0 mL/m^2 (95% CI -5.9 to 3.8); P=0.67 (Figure 4-5 and Table 4-1).

Figure 4-5 Change in LAVI from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

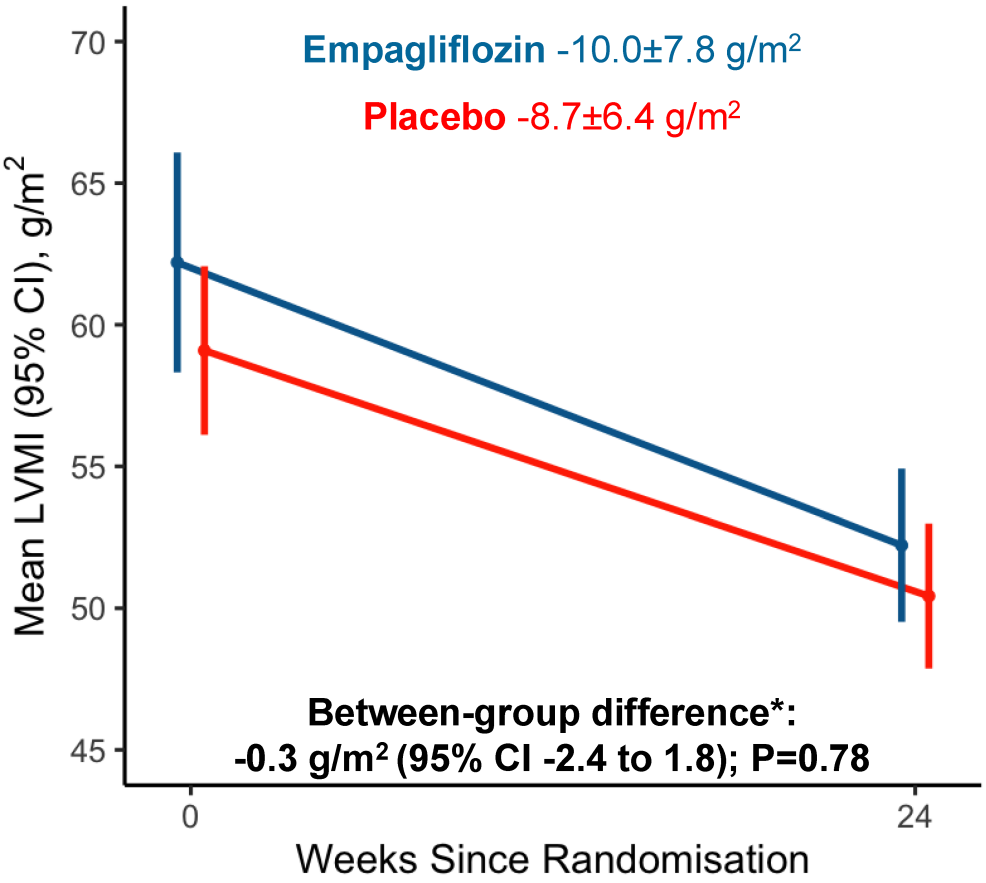
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval, LAVI, left atrial volume index.

4.3.6 Effect of empagliflozin on left ventricular mass index

Mean±SD LVMI at baseline was 62.2±13.7 g/m^2 in those randomised to empagliflozin with follow-up CMR data (n=48) and 59.1±11.0 g/m^2 in those randomised to placebo (n=52). LVMI decreased by 10.0±7.8 g/m^2 between baseline and 24 weeks in the empagliflozin group and by 8.7±6.4 g/m^2 in the placebo group: adjusted between-group difference -0.3 g/m^2 (95% CI -2.4 to 1.8); P=0.78 (Figure 4-6 and Table 4-1).

Figure 4-6 Change in LVMI from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

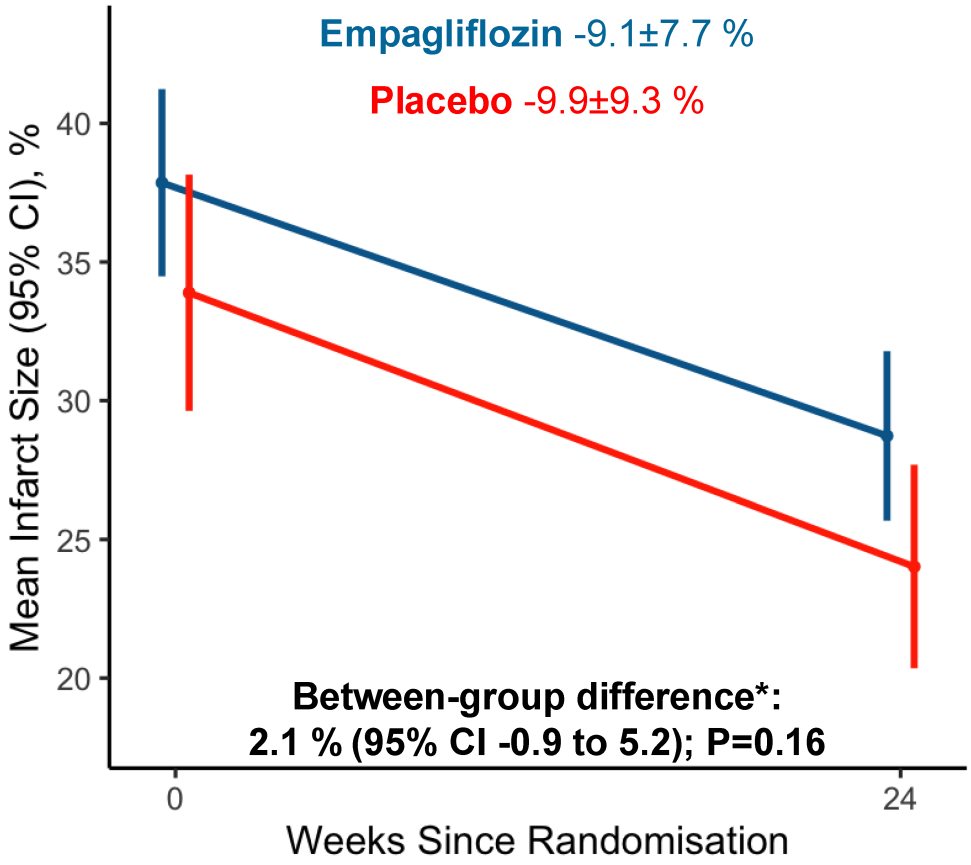
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval, LVMI, left ventricular mass index.

4.3.7 Effect of empagliflozin on infarct size

4 patients had no infarct size data at follow-up (1 technical issue with the CMR scanner, 2 incomplete LGE stack reconstruction, 1 gadolinium contrast not administered due to hypersensitivity reaction at the baseline scan). Mean±SD infarct size at baseline was 37.9±11.8% in those randomised to empagliflozin with infarct size data at follow-up (n=47) and 33.9±15.2% in those randomised to placebo (n=49). Infarct size decreased by 9.1±7.7% between baseline and 24 weeks in the empagliflozin group and by 9.9±9.3% in the placebo group: adjusted between-group difference 2.1% (95% CI -0.9 to 5.2); P=0.16 (Figure 4-7 and Table 4-1).

Figure 4-7 Change in infarct size from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval.

4.3.8 *Post hoc* analyses

A *post hoc* analysis of non-indexed CMR values yielded similar results (Table 4-2).

As discussed in Chapter 3.3.3, given potential imbalances in time from symptom-to-reperfusion and infarct size, additional *post hoc* adjustments were made for these variables. There was no difference in the primary outcome when adjusted for time to first reperfusion therapy (P=0.87), or infarct size (P=0.55).

Table 4-2 Change in non-indexed CMR values with empagliflozin or placebo from baseline to 24 weeks

	Empagliflozin				Placebo				Between-group difference (95% CI)*	P value
	n	Baseline	24 weeks	Change	n	Baseline	24 weeks	Change		
LVESV, mL	48	131.8 (45.4)	113.8 (40.9)	-18.0 (28.1)	52	123.3 (30.4)	109.1 (40.0)	-14.2 (31.6)	-2.1 (-13.3, 9.2)	0.71
LVEDV, mL	48	196.1 (56.0)	194.4 (49.3)	-1.8 (34.5)	52	191.4 (36.4)	192.7 (50.8)	1.3 (37.3)	-2.5 (-15.9, 11.0)	0.72
LAV, mL	48	69.1 (29.7)	73.8 (30.3)	4.7 (28.4)	52	70.8 (21.7)	77.2 (26.7)	6.4 (27.4)	-2.6 (-12.6, 7.4)	0.61
LVM, g	48	125.2 (37.7)	103.4 (27.3)	-21.8 (17.0)	52	116.9 (27.6)	99.8 (22.0)	-17.1 (14.1)	-2.3 (-6.8, 2.1)	0.30

Data presented as mean (SD) unless otherwise stated. Results reported for those with data available at baseline and 24 weeks. *Calculated using a linear model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status. Between-group differences are reported as adjusted mean differences (95% CI).

Abbreviations: CI, confidence interval; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass.

4.4 Discussion

In this population of patients with left ventricular systolic dysfunction after an acute MI, empagliflozin, compared with placebo, did not change left ventricular volumes or systolic function over 24 weeks of treatment. The majority of patients did not display features of progressive adverse remodelling over 24 weeks.

4.4.1 Absence of progressive adverse left ventricular remodelling

The eligibility criteria for EMPRESS-MI required patients to have a reduced LVEF both by echocardiography at least 12 hours after MI and by CMR prior to randomisation. The purpose of this design was to exclude patients with ventricular "stunning" who would rapidly recover systolic function. Notably, EMPRESS-MI is the only remodelling trial to incorporate this additional CMR criterion; two other CMR randomised controlled trials relied solely on echocardiography to define LVEF.[41,160] In those trials, LVEF measured by CMR was higher than by echocardiography, with minimal evidence of adverse remodelling at follow-up.[41,160] In contrast, in EMPRESS-MI the average LVEF was identical by both modalities (35%), and the left ventricular volumes and function were the largest amongst recent remodelling trials (Table 3-4 and Table 4-3). These data highlight that the EMPRESS-MI cohort was at high risk for adverse remodelling. Why, then, was there no evidence of progressive adverse remodelling?

Despite efforts to minimise the inclusion of patients with myocardial stunning, a proportion of patients may have had some myocardial stunning which improved following prompt revascularisation and comprehensive medical therapy. The mean infarct size was substantial (36% of left ventricular mass), and a 10% absolute reduction in infarct size was observed as well as a 9 g/m^2 reduction in LVMI. These data suggest that there may have been a substantial degree of myocardial oedema at baseline that contributed to transient myocardial stunning. Whether we would have seen a different pattern of remodelling - and potentially a treatment effect - had we recruited patients with persistent systolic dysfunction at a later time following acute MI is unknown. In an echocardiographic study of 261 patients

with a Q wave MI, most of whom had reduced LVEF or akinesis or dyskinesis, the majority of improvement in LVEF was seen by day 14.[26] In the Aliskiren Study in Post-MI Patients to Reduce Remodelling (ASPIRE) trial of 820 patients with LVEF<45% post-MI, baseline LVEF was assessed between 2-8 weeks following the index event and the median time to randomisation was 43 days. Similar to the EMPRESS-MI trial, left ventricular volumes decreased over 36 weeks and LVEF increased, but the changes were smaller (LVESV -3.5 ml, LVEDV -1.7 ml, LVEF +2.3% in the placebo group).[172] There was no treatment effect with aliskiren therapy.[172]

A second potential explanation for the lack of adverse remodelling in the EMPRESS-MI trial is the high numbers of patients who received pharmacological therapies known to prevent this process. At randomisation, nearly all patients were receiving an ACE inhibitor or ARB and over 80% were prescribed a beta blocker. Additionally, almost all patients underwent revascularisation. The observed improvements in left ventricular volumes and function observed in EMPRESS-MI align with findings from the echocardiography sub-study of the PARADISE-MI trial, where the mean changes in LVESVI, LVEDVI and LVEF in the ramipril group were -2.6 mL/m^2, +2.9 mL/m^2 and +6.6%, respectively (Table 4-3).[57] Utilisation of reperfusion and secondary prevention therapies was similarly high in the PARADISE-MI trial.[57] Collectively, these findings suggest that in the contemporary era of widespread use of reperfusion and neurohormonal antagonists, most patients do not experience progressive adverse remodelling in the months following acute MI. This contrasts with earlier remodelling analyses from trials such as CAPRICORN and SAVE, where left ventricular volumes would typically increase over time (Table 4-3).[18,39]

Various definitions have been proposed for adverse left ventricular remodelling post-MI. Recently, a 12% change in LVESV or LVEDV measured using CMR has been proposed as a cut-off indicating adverse (≥12% increase in volumes) or reverse remodelling (≤12% decrease in volumes).[30] While the overall trend in EMPRESS-MI was that of improvement, 15 (15%) patients had a ≥12% increase in LVEDVI, and 13 (13%) had a ≥12% increase in both LVEDVI and LVESVI. These rates are comparable to a Glasgow all-comers STEMI CMR cohort, where 14% and 11% of patients met these criteria, respectively.[31] In

Chapter 6, I will explore the relationship between infarct characteristics and remodelling patterns in the EMPRESS-MI cohort, and the identification of higher-risk populations in the contemporary era who may benefit from additional remodelling therapies.

4.4.2 Comparison to post-MI remodelling trials

The findings of the EMPRESS-MI trial should be considered in the context of previous trials that have examined left ventricular remodelling following MI. Table 4-3 summarises remodelling outcomes in the placebo groups of all previous post-MI randomised controlled trials.

The EMMY trial randomised 476 patients to empagliflozin or placebo within 72 hours of PCI for an acute MI with creatine kinase >800 IU/L or a troponin >10 times higher than the upper local laboratory limit of normal.[117] Empagliflozin reduced NT-proBNP, increased echocardiography-derived LVEF by 1.5%, and reduced LVESVI and LVEDVI by 3.2 mL/m^2 and 3.9 mL/m^2, respectively. Several characteristics suggest that the EMMY cohort was at a lower risk of adverse remodelling compared to EMPRESS-MI. Baseline ventricular volumes in EMMY were nearly half of those in EMPRESS-MI, LVEF was higher (49% vs. 36% in the placebo groups, respectively) and both troponin T and NT-proBNP were lower. Despite this, the remodelling patterns differed between EMMY and EMPRESS-MI; in EMMY the placebo group exhibited progressive adverse remodelling, with LVESVI and LVEDVI increasing by 2.3 mL/m^2 and 7.1 mL/m^2, respectively.[117]

The reason for this apparent discordance in ventricular remodelling trajectories between EMMY and other recent contemporary trials, including EMPRESS-MI, is unclear.[57,117] Background secondary prevention therapy and key clinical characteristics such as age, sex, and diabetes prevalence were similar between EMMY and EMPRESS-MI (Table 3-3).[117] One potential explanation is the timing of LVEF assessment, as delayed evaluation in EMMY may have captured less reversible myocardial stunning; however time from index event to LVEF assessment has not been reported in the EMMY trial. Given the treatment effect of empagliflozin on attenuating progressive remodelling in EMMY, but not in EMPRESS-MI, it is possible that empagliflozin exerts beneficial effects on left ventricular structure and function in patients

in whom the natural history is one of progressive adverse remodelling. However, this pattern was not observed in EMPRESS-MI.

Two smaller trials, DACAMI and EMI-STEMI, have evaluated the effects of SGLT2 inhibitors on left ventricular volumes and function.[119,120] These are discussed in detail in Chapter 1.3.2.3, with baseline characteristics compared in Table 3-3. In the DACAMI trial, no differences were observed in LVEF or left ventricular end-diastolic diameter at 12 weeks.[119] The LVEF at baseline was higher in DACAMI than in EMPRESS-MI (43% vs. 35%), and baseline NT-proBNP and troponin were lower. In the EMI-STEMI trial, LVEF after 90 days was higher in the empagliflozin group.[120] A key difference in the EMI-STEMI trial, compared to EMPRESS-MI, was the administration of empagliflozin immediately before PCI, raising the possibility of a protective effect during reperfusion. The ongoing Peri-treatment of SGLT2 Inhibitor on Myocardial Infarct Size and Remodelling Index in Patients With Acute Myocardial Infarction and High Risk of Heart Failure Undergoing PCI (PRESTIGE-MI) trial (NCT04899479) is investigating whether SGLT2 inhibitors, when given pre-PCI, influence infarct size and remodelling in acute MI. Whether SGLT2 inhibitors confer additional protection against ischaemia-reperfusion injury is unknown.

In a trial evaluating the calcium/calmodulin-dependent protein kinase II inhibitor, NP202, in 147 patients with anterior STEMI and LVEF<45%, NP202 had no effect on remodelling indices, including LVESVI, LVEDVI, LVEF and infarct size.[160] The inclusion criteria for this trial specified LVEF<45% by echocardiography only. LVEF at baseline was 37% and 38% by echocardiography and 43% and 42% by CMR in the placebo and treatment groups, respectively. Baseline left ventricular volumes were smaller than those in the EMPRESS-MI trial (Table 4-3), despite the similar high-risk characteristics of the population. Remodelling patterns were also distinct, with little change in LVESVI and a 6 ml/m^2 increase in LVEDVI in the placebo group, although this was after only 90 days of follow-up. There were similar rates of reperfusion and secondary prevention therapy in this trial with the exception of a lower rate of MRA prescription (24% vs. 63%).[160] In a similar CMR trial of 100 patients with LVEF<40% (assessed by echocardiography only), remodelling patterns were almost identical in the placebo group despite

longer follow-up at 24 weeks.[41] Eplerenone therapy in this trial only had an effect on remodelling after adjustment for baseline covariates.[41]

Omega-3 Acid Ethyl Esters on Left Ventricular Remodelling After Acute MI (OMEGA-REMODEL), another CMR trial, assessed the effect of omega-3-fatty acids on adverse left ventricular remodelling post-MI, but without LVEF eligibility criteria.[159] The mean LVEF at baseline was 54%, and left ventricular volumes were smaller compared to those in EMPRESS-MI (Table 4-3). The presenting characteristics of the OMEGA-REMODEL population differed to the EMPRESS-MI population, with only 58% of patients presenting with a STEMI and 27% of MIs in the anterior location. Furthermore, less than 1% of patients in this trial were prescribed an MRA, likely due to higher baseline ejection fractions. Omega-3 fatty acid reduced LVESVI by 5.4%, compared to a small 1.2% increase with placebo (P=0.0068). LVEDVI was not reported.[159]

Table 4-3 Baseline and change in left ventricular volumes in placebo groups of randomised trials of therapies for left ventricular remodelling post-MI

Trial, year Intervention vs. comparator	n	Imaging modality and follow-up	Baseline LVESVI (ml/m^2)	Change in LVESVI (ml/m^2)	Baseline LVEDVI (ml/m^2)	Change in LVEDVI (ml/m^2)
EMPRESS-MI, 2024 **Empagliflozin vs. placebo**	104	CMR 24 weeks	62.8 (15.1)	-7.8 (16.3)	97.6 (18.3)	-0.3 (18.7)
EMMY, 2022[117] **Empagliflozin vs. placebo**	476	Echo 26 weeks	29 (23, 36)	2.3 (0.7, 3.9)	56 (48, 65)	7.1 (4.7, 9.5)
PARADISE-MI, 2022[57] **Sacubitril/valsartan vs. ramipril**	544	Echo 8 months	41.3 (20.3)	-2.6 (16.0)	67.2 (22.1)	2.9 (17.5)
Boyle et al, 2021[160] **NP202 vs. placebo**	147	CMR 90 days	41.3	-0.6 (-9.3, 6.0)	72 (60, 84)	6.0 (-4.4, 14.3)
ASPIRE, 2011[172] **Aliskiren vs. placebo**	820	Echo 36 weeks	84.2 (25.5)*	-3.5 (16.3)*	133.5 (31.6)*	-1.7 (19.6)*
Weir et al, 2009[41] **Eplerenone vs. placebo**	100	CMR 24 weeks	48.6 (17.7)	0.1 (16.1)	89.0 (21.3)	6.1
VALIANT, 2005[25] **Valsartan vs. Captopril vs. Valsartan + Captopril**	603	Echo 20 months	73.9 (24.7)*	-0.94 (15.4)*	119.8 (33.5)*	2.5 (16.9)*
CAPRICORN, 2004[39] **Carvedilol vs. placebo**	127	Echo 6 months	82.5 (38.0)*	4.5 (2.8)*	133.2 (47.3)*	8.4 (3.3)*
SAVE, 1994[18] **Captopril vs. placebo**	512	Echo 1 year	52.2 (12.6)†	3.7†	71.6 (12.8)†	3.8†

*Non-indexed values. †Ventricular area, cm^2.

Abbreviations: ASPIRE, Aliskiren Study in Post-MI Patients to Reduce Remodelling; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CMR, cardiovascular magnetic resonance; EMMY, Empagliflozin in patients with acute Myocardial infarction;

EMPRESS-MI, EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; PARADISE-MI, Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction; SAVE, Survival and Ventricular Enlargement; VALIANT, Valsartan in Acute Myocardial Infarction.

4.4.3 Comparison to SGLT2 inhibitor remodelling trials

SGLT2 inhibitors reduce the risk of worsening heart failure and mortality in patients with HFrEF and one of the possible mechanisms of action is a favourable effect on adverse left ventricular remodelling.[75,98-100] Trials analysing the effect of SGLT2 inhibitors in different disease states are listed in Table 4-4. In patients with HFrEF, all trials have recently been pooled in a meta-analysis which demonstrated the beneficial effects of SGLT2 inhibitors for reverse remodelling.[173]

The main hypothesis of the EMPRESS-MI trial was that the remodelling benefits seen with SGLT2 inhibitors in established HFrEF would be mirrored in patients at high risk of developing heart failure as a result of an acute MI complicated by left ventricular systolic dysfunction. Since empagliflozin reduces heart failure hospitalisations and adverse heart failure events in high-risk patients post-MI, I hypothesised that a reduction in adverse remodelling would be a mechanistic explanation.[86] However, as EMPRESS-MI showed no evidence of a remodelling benefit, the clinical benefits of empagliflozin in this population may be driven by non-remodelling mechanisms.

A similar pattern is seen in T2DM. SGLT2 inhibitors reduce cardiovascular death and heart failure hospitalisations in patients with T2DM.[68] However, across 5 trials of patients with T2DM but no heart failure, SGLT2 inhibitors had no effect on left ventricular volumes (Table 4-4).[106,107,109,111,116] While SGLT2 inhibitors improve clinical outcomes in HFrEF, post-MI, and T2DM, reduced adverse remodelling does not appear to be the primary driver in all populations. In HFrEF, remodelling plays a role, but in T2DM and post-MI, other mechanisms may be responsible for their benefits.

Table 4-4 Baseline and change in left ventricular volumes and treatment effect in randomised trials of SGLT2 inhibitors for left ventricular remodelling in different disease states

Trial, year Population SGLT2 inhibitor	n	Imaging modality and follow-up	Baseline LVESVI (ml/m^2)	Change in LVESVI (ml/m^2)	Treatment effect	Baseline LVEDVI (ml/m^2)	Change in LVEDVI (ml/m^2)	Treatment effect
EMPRESS-MI, 2024 **Acute MI** **Empagliflozin**	104	CMR 24 weeks	66/63	-8/-8	0.3 (-5.2, 5.8); P=0.92	98/98	1/0	0.8 (-5.5, 7.0); P=0.81
HFrEF								
EMPA-VISION, 2023[102] **HFrEF** **Empagliflozin**	36	CMR 12 weeks	NR	NR	NR	242/225*	NR	-7.00 (-21.98, 8.85); P=0.39*
Fu et al, 2023[105] **HFrEF + T2DM** **Dapagliflozin**	60	Echo 1 year	126/122*	-18/-7*	P<0.001	182/179*	-12/-3*	P<0.001
DAPA-VO2, 2022[104] **HFrEF** **Dapagliflozin**	90	Echo 3 months	48/50	NR	-4.84 (-11.16, 1.48); P=0.166	72/76	NR	-3.36 (-11.00, 4.29); P=0.545
Empire HF, 2021[99] **HFrEF** **Empagliflozin**	190	Echo 12 weeks	54/49	-4/0	-4.3 (-8.5, -0.1); P=0.04	81/75	-4/1	-5.5 (-10.6, -0.4); P=0.03
EMPA-TROPISM, 2021[100] **HFrEF no T2DM** **Empagliflozin**	84	CMR 6 months	72/68	-13/0	P<0.001	111/107	-12/-1	P<0.001
SUGAR-DM-HF, 2021[98] **HFrEF + T2DM** **Empagliflozin**	105	CMR 36 weeks	81/77	-8/-2	-6.0 (-10.8, -1.2); P=0.015	115/111	-9/0	-8.2 (-13.7, -2.6); P=0.004

REFORM, 2020[103] **HFrEF + T2DM** **Dapagliflozin**	56	CMR 1 year	49/54	-5/-11	2.49 (-6.30, 11.28); P=0.571	86/95	-4/-13	3.9 (-7.05, 14.85); P=0.478
T2DM								
SOCOGAMI, 2022[116] **MI/UA within 6mo + T2DM** **Empagliflozin**	42	Echo and CMR 7 months	35/31	NR	NS	70/71	NR	NS
SIMPLE, 2021[111] **T2DM + ASCVD/RFs** **Empagliflozin**	91	Echo 13 weeks	37/36*	-1/-1*	P=0.92	83/84*	-5/-4*	P=0.80
DAPA-LVH, 2020[107] **T2DM + LVH** **Dapagliflozin**	66	CMR 12 months	37/34*	-2/-1*	-1.12 (-3.50, 1.25); P=0.348*	128/121*	0/1*	-1.59 (-7.06, 3.87); P=0.562*
DAPACARD, 2020[109] **T2DM** **Dapagliflozin**	53	CMR 6 weeks	33/28	1/2	-0.55 (-2.51, 1.41); P=0.57	83/74	0/-1	0.77 (-3.24, 4.78); P=0.70
EMPA-HEART, 2019[106] **T2DM + CAD** **Empagliflozin**	97	CMR 6 months	27/32	-1/0	-1.2 (-3.8, 1.4); P=0.36	63/71	-2/-2	-1.2 (-5.0, 2.7); P=0.55
Risk of remodelling								
EMPA-HEART 2, 2023[115] **No HF or T2DM, at risk of remodelling** **Empagliflozin**	169	CMR 6 months	31/33	-2/-1	-1.4 (-3.2, 0.4); P=0.13	74/76	-3/-2	-1.3 (-4.3, 1.7); P=0.41

*Non-indexed values. Data are reported as treatment group/placebo group.

Abbreviations: ASCVD/RFs, atherosclerotic cardiovascular disease/risk factors; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; DAPA-LVH, Does Dapagliflozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes?; DAPA-VO2, Short-term Effects of Dapagliflozin on Peak Oxygen Consumption in HFrEF; DAPACARD, The Effects of Dapagliflozin on Cardiac Substrate Uptake, Myocardial Efficiency and Myocardial Contractile Work in Type 2 Diabetes Patients; EMPA-HEART, Effects of Empagliflozin on Cardiac Structure in Patients with Type 2 Diabetes; EMPA-TROPISM, Are the “Cardiac Benefits” of Empagliflozin Independent of Its Hypoglycaemic Activity?; EMPA-VISION, Assessment of Cardiac Energy Metabolism, Function and Physiology in Patients With Heart Failure Taking Empagliflozin; Empire HF, Empagliflozin in Heart Failure Patients with Reduced Ejection Fraction; EMPRESS-MI, EMpagliflozin to PREvent worSening of left ventricular volumes and Systolic function after Myocardial Infarction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVH, left ventricular hypertrophy; MI, myocardial infarction; NR, not reported; NS, not significant; REFORM, Safety and Effectiveness of SGLT2 Inhibitors in Patients With Heart Failure and Diabetes; SGLT2, sodium-glucose co-transporter 2; SIMPLE, Effects of SGLT2 Inhibitor on Myocardial Perfusion, Function and Metabolism in Type-2 diabetes patients at high cardiovascular risk; SOCOGAMI, SOdium-glucose CO-transporter inhibition in patients with newly detected Glucose Abnormalities and a recent Myocardial Infarction; SUGAR-DM-HF, Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure; T2DM, type 2 diabetes mellitus; UA, unstable angina.

4.4.4 Limitations

Several limitations must be highlighted. Patients only received treatment for 24 weeks, and a remodelling effect may be seen to continue over a longer period.[28] As with all small mechanistic studies, the EMPRESS-MI trial was limited by a small sample size. The SD of the change in LVESVI was higher than we had initially powered for. Given that there was almost no between-group difference, a larger sample size would have been unlikely to show any clinically meaningful change.

4.4.5 Conclusion

In patients with left ventricular systolic dysfunction after an acute MI treated with contemporary reperfusion and medical therapy, the addition of empagliflozin to standard care did not have any effect on improving left ventricular volumes or function compared with placebo. The majority of patients did not display features of progressive adverse remodelling over 24 weeks.

Chapter 5 The effect of empagliflozin on circulating biomarkers and body weight in patients with left ventricular systolic dysfunction following myocardial infarction

5.1 Introduction

Left ventricular remodelling following an acute MI is influenced by multiple physiological processes, including neurohormonal activation, cardiac injury, metabolic and renal dysfunction, and volume regulation. Several biomarkers and clinical parameters serve as key indicators of these processes and may provide insight into the effects of SGLT2 inhibitors post-MI.

NT-proBNP is a well-established biomarker of neurohormonal activation and increased cardiac wall stress. The beneficial cardiorenal actions counteract the harmful activation of the RAAS and SNS by promoting diuresis and natriuresis. Plasma levels play a diagnostic role in heart failure and are prognostic for cardiovascular events. Elevated NT-proBNP values post-MI are associated with adverse remodelling and worse outcomes.[174–179] SGLT2 inhibitors reduce NT-proBNP in patients with HFrEF, but their effects in high-risk post-MI patients remain uncertain.[180] Several small post-MI trials have assessed the effect of SGLT2 inhibitors on NT-proBNP, with mixed results. The EMMY trial demonstrated a significant reduction in NT-proBNP with empagliflozin.[117] In contrast, the DACAMI and EMBODY trials showed no impact of SGLT2 inhibitors on NT-proBNP.[119,128] A recent meta-analysis concluded no clear benefit of SGLT2 inhibitors on NT-proBNP post-MI, though limitations in its design complicate interpretation.[181]

Troponin is an established diagnostic biomarker for acute coronary syndrome.[52] Higher levels immediately post-MI are associated with infarct size, left ventricular function and long-term outcome.[182–188] In the CANVAS and CREDENCE trials, the SGLT2 inhibitor canagliflozin reduced the increase in troponin T.[189,190] Similarly, in The effect of EMPAgliflozin on markers of inflammation in patients with concomitant T2DM and Coronary ARtery Disease (EMPA-CARD) trial of 95 patients with T2DM and coronary artery disease, empagliflozin reduced hs-TnI.[191] The effect of SGLT2 inhibitors post-MI,

however, remains unclear. The EMI-STEMI trial found no effect of empagliflozin on serial troponins within 72 hours post-MI.[120]

Elevated uric acid is associated with worse outcomes post-MI with reduced LVEF or heart failure.[192] SGLT2 inhibitors consistently lower uric acid across various conditions.[193,150,194–197] Empagliflozin reduced uric acid in patients with MI and T2DM in the EMBODY trial.[128]

HbA1c at the time of acute MI is associated with both short- and long-term prognosis.[198,199] Whilst SGLT2 inhibitors lower HbA1c in T2DM and HFrEF, their impact post-MI remains unclear.[71,73,117,128,200,201] In SOCOGAMI, fasting and 2-hour post-load glucose were reduced in the empagliflozin group.[116] In the DAPA-MI trial, dapagliflozin reduced new diagnoses of T2DM in patients with acute MI and without T2DM at baseline, although absolute HbA1c values were not reported.[85]

As described in Chapter 1.3.3.5, SGLT2 inhibitors have kidney-protective effects in HFrEF, a benefit mirrored in high-risk post-MI patients in the EMPACT-MI trial.[71,142,143] As described in Chapter 1.3.3.4, SGLT2 inhibitors also enhance erythropoiesis, increasing haematocrit and haemoglobin, the key mediators of benefit in the EMPA-REG OUTCOME trial.[132,135,136,202,203] In the EMBODY trial, empagliflozin prevented a decline in eGFR and haematocrit was increased in the empagliflozin group.[128,204]

As described in Chapter 1.3.3.3, SGLT2 inhibitors cause weight loss. In the DAPA-MI trial, the cardiometabolic benefits of dapagliflozin included a ≥5% reduction in body weight from baseline.[85] The EMBODY trial also reported weight loss with empagliflozin.[128]

In this chapter I will describe the effects of empagliflozin on circulating biomarkers of remodelling, NT-proBNP and hs-TnI, in the EMPRESS-MI trial. I will also describe the effects of empagliflozin on uric acid, HbA1c, eGFR, haematocrit, and body weight.

5.2 Methods

5.2.1 Biomarker sampling

I collected venous blood before randomisation, at 12 weeks and 24 weeks following randomisation, for biomarker analysis. I was assisted by Sister Barbara Meyer. Samples were collected and processed at the Clinical Research Facility at the GJNH according to a Sample Handling Manual. After completion of the trial, all samples were transferred to the central laboratory for batch analysis.

HbA1c and haematocrit were measured as part of routine care in NHS GJNH biochemistry labs. NT-proBNP (Roche e411, Roche Diagnostics, Burgess Hill, UK), hs-TnI (i1000SR ARCHITECT, Abbott Laboratories, Maidenhead, UK) and uric acid (Roche c311, Roche Diagnostics, Burgess Hill, UK) were batch measured after study completion. All non-routine assays were performed at a central lab (GlasBRU, University of Glasgow) using the manufacturers' calibrators and quality controls.

Measurements for body weight were taken before randomisation, at 12 weeks and 24 weeks following randomisation.

5.2.2 Statistical methods

All statistical analyses were conducted by Bethany Stanley (Clinical Trials Unit, Robertson Centre for Biostatistics, University of Glasgow) and replicated by myself using R Studio and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and are described in detail in Chapter 2.12. Efficacy analyses were performed according to the intention-to-treat principle, including all randomly assigned participants without major protocol deviations, and with post-randomisation data available for the outcome of interest at any given time point, irrespective of their subsequent participation in the study and their adherence to randomised treatment.

Data were summarised descriptively for each randomised treatment group, using counts and percentages for categorical variables, and mean±SD or median (IQR), depending on the distribution of the data. Each outcome was analysed using a linear regression analysis model adjusted for the randomised

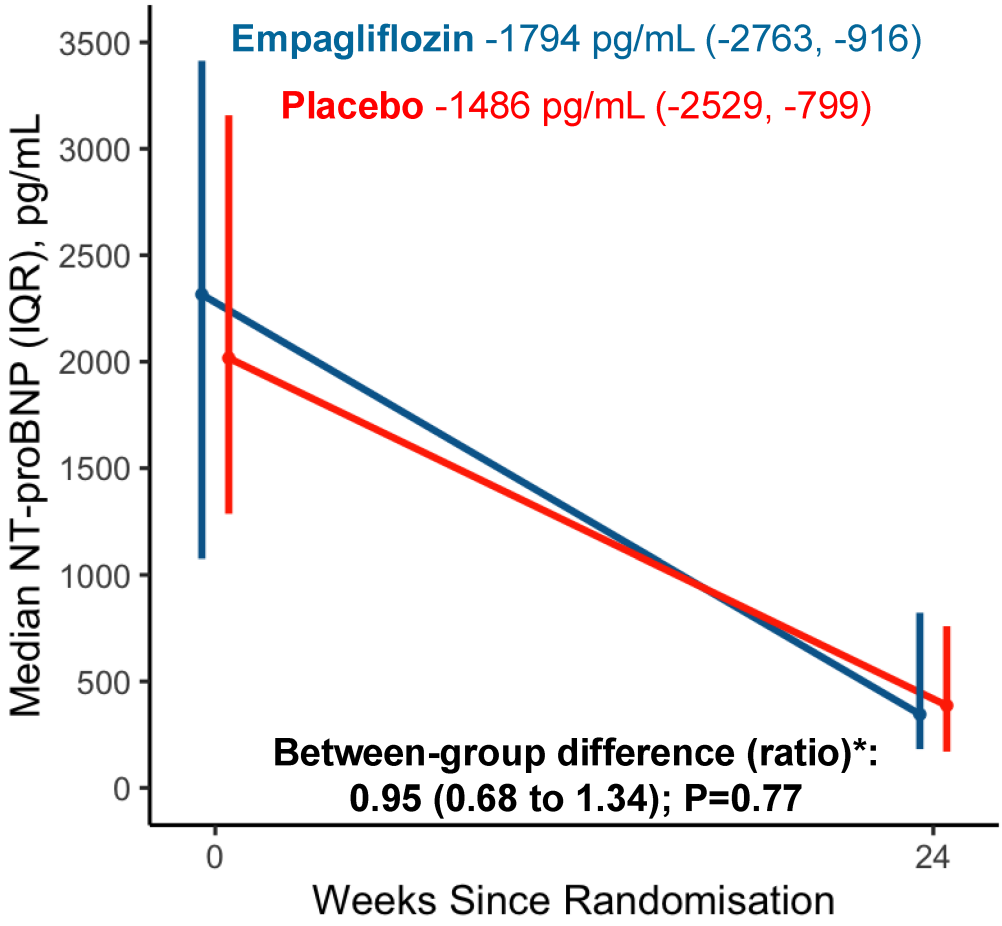
treatment group, the baseline value of the outcome in question, diuretic use at baseline, and diabetes status. The regression model treatment effect estimates were reported with 95% CI and P values. If required to satisfy modelling assumptions, log transformations were performed, and regression coefficients were back transformed and presented as relative differences. A P value of <0.05 was considered statistically significant.

5.3 Results

5.3.1 Effect of empagliflozin on NT-proBNP

Median NT-proBNP at baseline was 2316 pg/mL (IQR 1075-3413) in those randomised to empagliflozin with follow-up NT-proBNP data (n=49) and 2017 pg/mL (IQR 1286-3157) in those randomised to placebo (n=52). Empagliflozin had no effect on the change in NT-proBNP from baseline to 24 weeks. Median change in NT-proBNP was -1794 pg/mL (IQR -2763, -916) between baseline and 24 weeks in the empagliflozin group and -1486 pg/mL (IQR -2529, -799) in the placebo group: ratio of adjusted geometric means 0.95 (95% CI 0.68 to 1.34); P=0.77 (Figure 5-1 and Table 5-1). Similar results were seen at 12 weeks (P=0.34).

Figure 5-1 Change in NT-proBNP from baseline to 24 weeks



Data presented as median and error bars represent interquartile range.

*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status and reported as ratios of adjusted geometric means from models using log-transformed values.

Abbreviations: IQR, interquartile range; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Table 5-1 Change in circulating biomarkers and body weight with empagliflozin or placebo from baseline to 24 weeks

	Empagliflozin				Placebo				Between-group difference (95% CI)*	P value
	n	Baseline	24 weeks	Change	n	Baseline	24 weeks	Change		
NT-proBNP, pg/mL	49	2316 (1075, 3413)†	346 (182, 822)†	-1794 (-2763, -916)†	52	2017 (1286, 3157)†	387 (170, 759)†	-1486 (-2529, -799)†	0.95 (0.68, 1.34)	0.77
hs-TnI, ng/L	50	17552 (8417, 34473)†	8 (5, 15)†	-17547 (-34362, -8408)†	53	16047 (6529, 31040)†	7 (5, 14)†	-16040 (-31033, -6511)†	1.10 (0.81, 1.50)	0.54
Uric acid, umol/L	49	5.6 (4.6, 6.6)†	4.7 (4.0, 6.3)†	-0.6 (-1.9, 0.2)†	53	5.6 (4.5, 6.6)†	5.6 (4.4, 6.4)†	-0.1 (-0.9, 1.3)†	0.85 (0.75, 0.95)	0.006
HbA1c, mmol/mol	50	39.6 (11.6)	40.0 (5.1)	0.4 (10.0)	53	39.3 (7.7)	40.0 (6.1)	0.7 (3.4)	-0.1 (-1.7, 1.6)	0.94
eGFR, mL/min/1.73m^2	50	78.5 (20.5)	73.6 (17.5)	-4.8 (13.0)	53	79.3 (20.2)	72.3 (17.0)	-7.1 (15.1)	1.8 (-2.8, 6.5)	0.42
Haematocrit, L/L	48	0.40 (0.05)	0.42 (0.05)	0.02 (0.05)	52	0.41 (0.05)	0.40 (0.05)	-0.01 (0.04)	0.02 (0.01, 0.04)	0.006
Body weight, kg	48	84.0 (19.5)	81.5 (18.2)	-2.5 (6.0)	52	82.0 (15.6)	82.5 (17.1)	0.5 (4.2)	-2.9 (-5.0, -0.9)	0.006

Data presented as mean (SD) unless otherwise stated. Results are reported for those with data available at baseline and 24 weeks.
*Calculated using a linear model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status. Between-group differences are reported as ratios of adjusted geometric means for NT-proBNP, hs-TnI and uric acid from

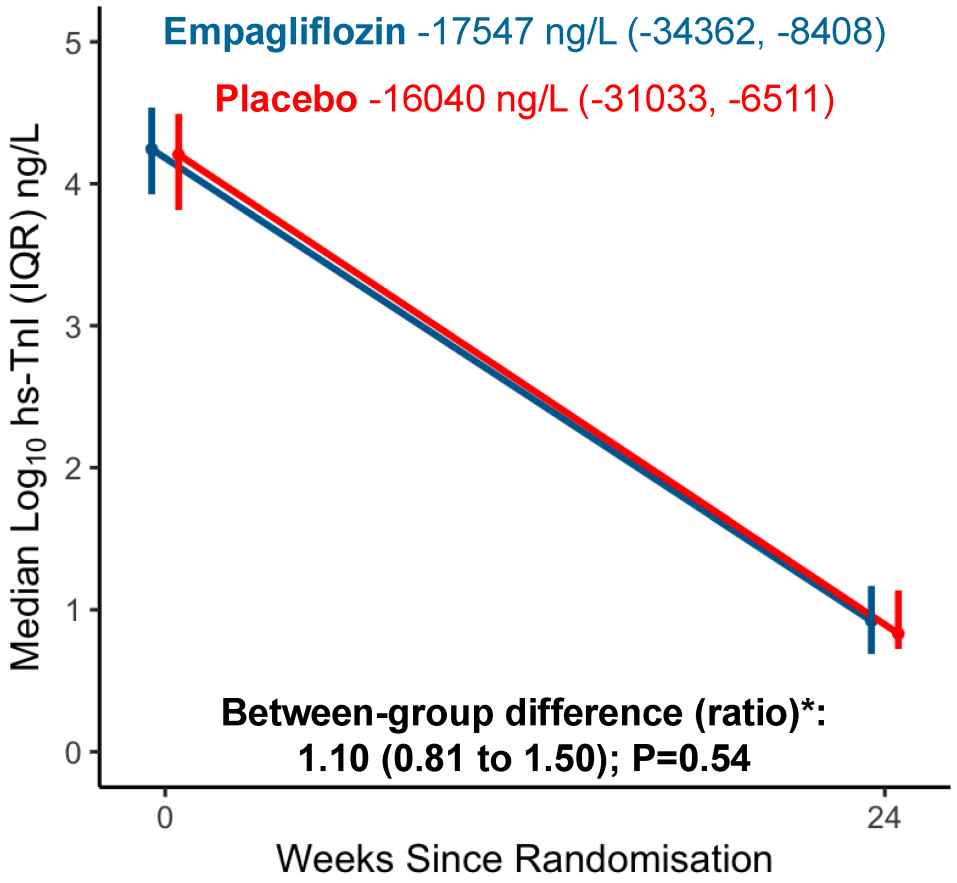
models using log-transformed values. All other outcomes are reported as adjusted mean differences (95% CI). †Median (interquartile range).

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin, hs-TnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

5.3.2 Effect of empagliflozin on hs-TnI

Median hs-TnI at baseline was 17552 ng/L (IQR 8417-34473) in those randomised to empagliflozin with follow-up hs-TnI data (n=50) and 16047 ng/L (IQR 6529-31040) in those randomised to placebo (n=53). Empagliflozin had no effect on the change in hs-TnI from baseline to 24 weeks. Median change in hs-TnI was -17547 ng/L (IQR -34362, -8408) between baseline and 24 weeks in the empagliflozin group and -16040 ng/L (IQR -31033, -6511) in the placebo group: ratio of adjusted geometric means 1.10 (95% CI 0.81 to 1.50); P=0.54 (Figure 5-2 and Table 5-1). Similar results were seen at 12 weeks (P=0.54).

Figure 5-2 Change in hs-TnI from baseline to 24 weeks



Data presented as median and error bars represent interquartile range. Graphical data are presented on a $\log_{10}$ scale for clarity.

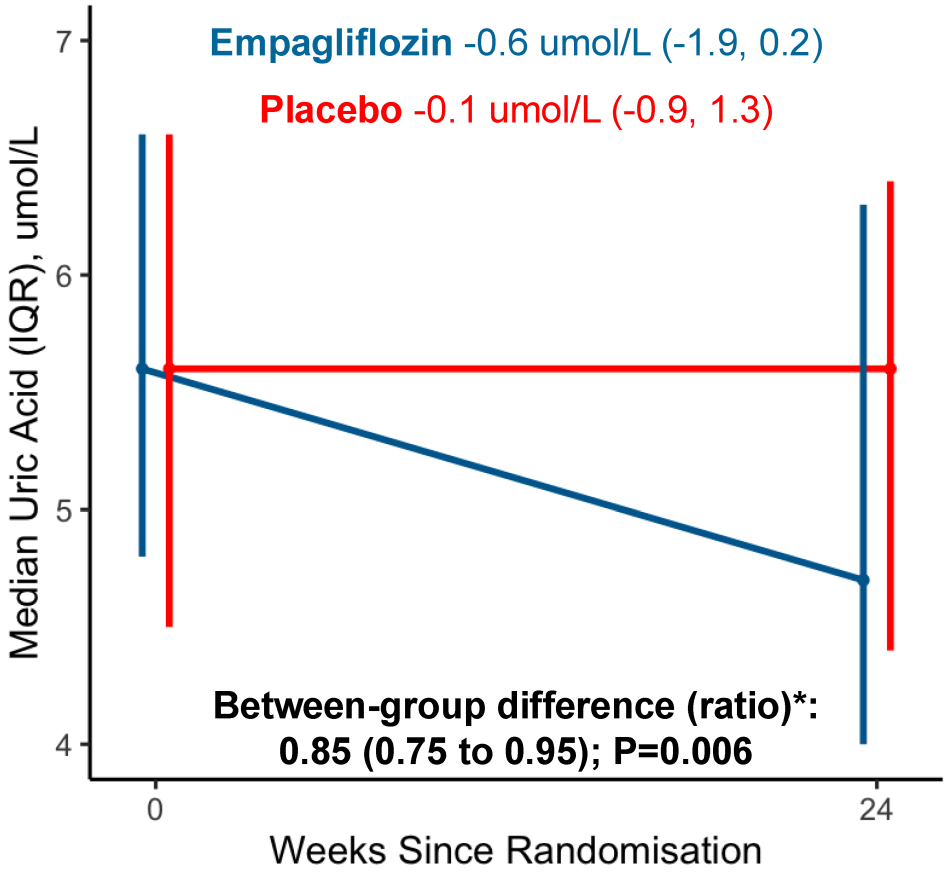
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status and reported as ratios of adjusted geometric means from models using log-transformed values.

Abbreviations: hs-TnI, high-sensitivity cardiac troponin I; IQR, interquartile range.

5.3.3 Effect of empagliflozin on uric acid

Median uric acid at baseline was 5.6 umol/L (IQR 4.6-6.6) in those randomised to empagliflozin with follow-up uric acid data (n=49) and 5.6 umol/L (IQR 4.5-6.6) in those randomised to placebo (n=53). Empagliflozin, compared to placebo, decreased uric acid from baseline to 24 weeks. Median change in uric acid was -0.6 umol/L (IQR -1.9-0.2) between baseline and 24 weeks in the empagliflozin group and -0.1 umol/L (IQR -0.9-1.3) in the placebo group: ratio of adjusted geometric means 0.85 (95% CI 0.75 to 0.95); P=0.006 (Figure 5-3 and Table 5-1). Similar results were seen at 12 weeks (P<0.001).

Figure 5-3 Change in uric acid from baseline to 24 weeks



Data presented as median and error bars represent interquartile range.

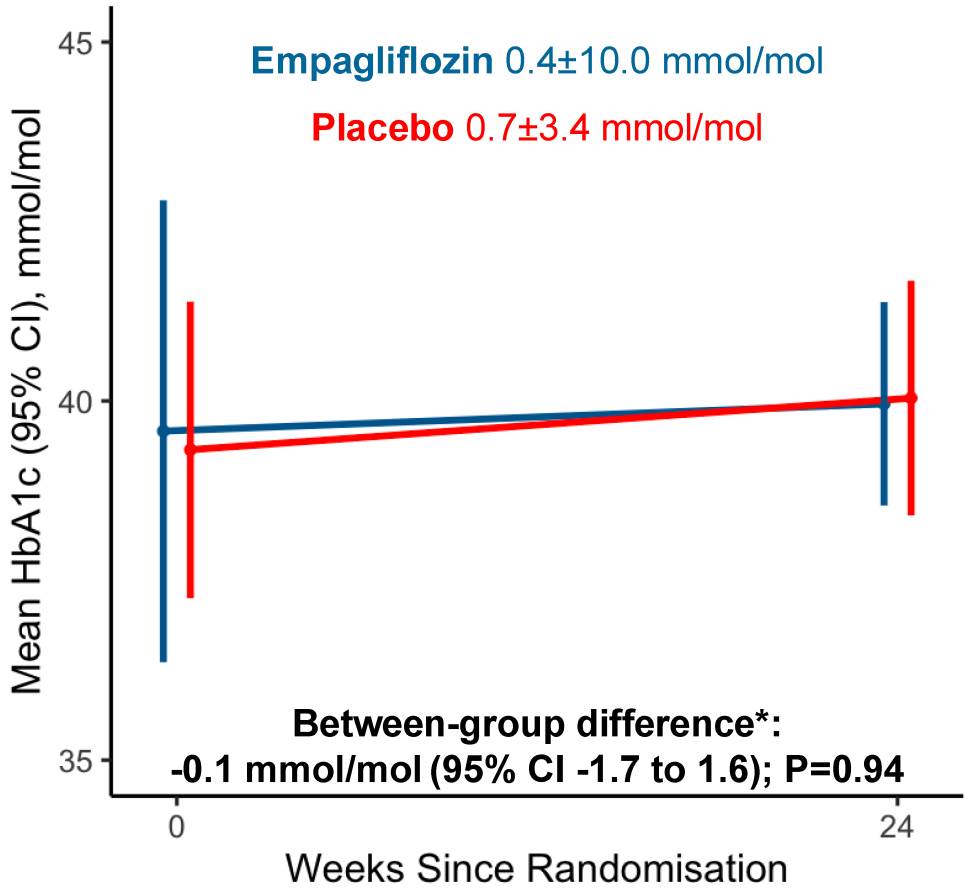
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status and reported as ratios of adjusted geometric means from models using log-transformed values.

Abbreviations: IQR, interquartile range.

5.3.4 Effect of empagliflozin on HbA1c

Mean±SD HbA1c at baseline was 39.6±11.6 mmol/mol in those randomised to empagliflozin with follow-up HbA1c data (n=50) and 39.3±7.7 mmol/mol in those randomised to placebo (n=53). Empagliflozin had no effect on the change in HbA1c from baseline to 24 weeks. Mean±SD change in HbA1c was 0.4±10.0 mmol/mol between baseline and 24 weeks in the empagliflozin group and 0.7±3.4 mmol/mol in the placebo group: adjusted between-group difference -0.1 mmol/mol (95% CI -1.7 to 1.6); P=0.94 (Figure 5-4 and Table 5-1). The change in HbA1c was greater in the empagliflozin group at 12 weeks (P=0.03); however, this difference was no longer significant by 24 weeks.

Figure 5-4 Change in HbA1c from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

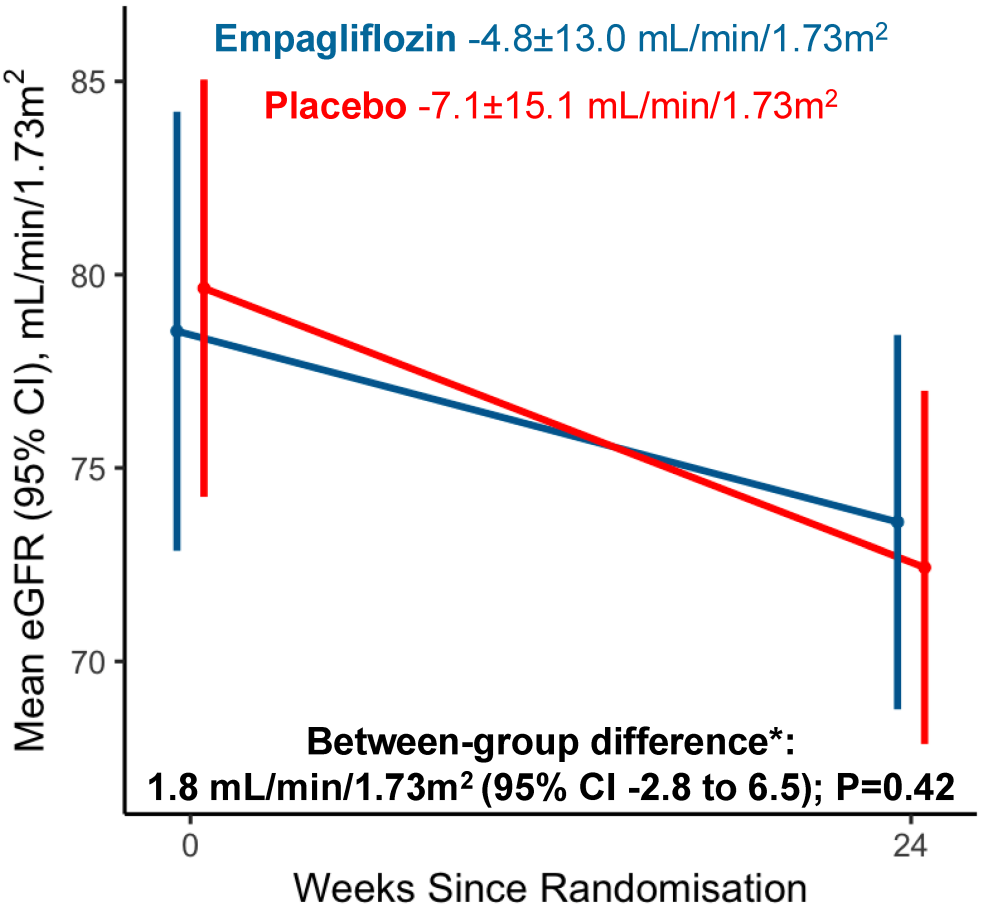
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin.

5.3.5 Effect of empagliflozin on eGFR

Mean±SD eGFR at baseline was 78.5±20.5 mL/min/1.73m^2 in those randomised to empagliflozin with follow-up eGFR data (n=50) and 79.3±20.2 mL/min/1.73m^2 in those randomised to placebo (n=53). Empagliflozin had no effect on the change in eGFR from baseline to 24 weeks. Mean±SD change in eGFR was -4.8±13.0 mL/min/1.73m^2 between baseline and 24 weeks in the empagliflozin group and -7.1±15.1 mL/min/1.73m^2 in the placebo group: adjusted between-group difference 1.8 mL/min/1.73m^2 (95% CI -2.8 to 6.5); P=0.42 (Figure 5-5 and Table 5-1). Similar results were seen at 12 weeks (P=0.87).

Figure 5-5 Change in eGFR from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

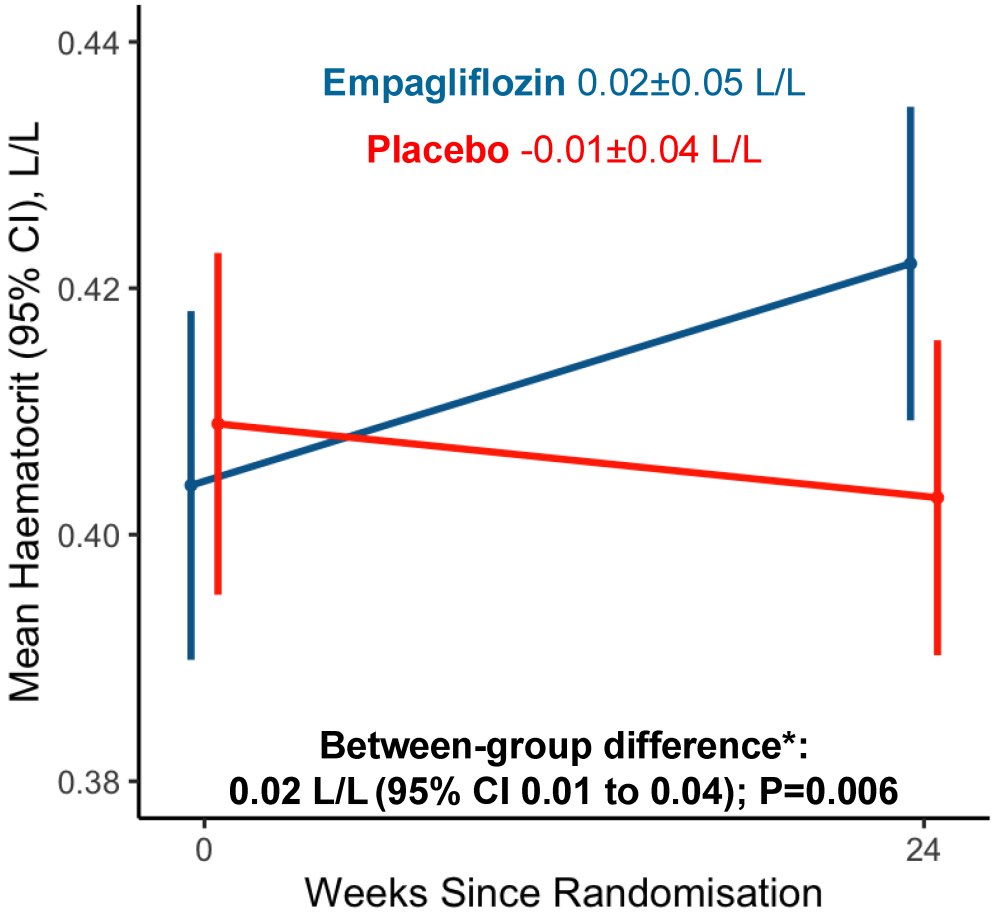
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

5.3.6 Effect of empagliflozin on haematocrit

Mean±SD haematocrit at baseline was 0.40±0.05 L/L in those randomised to empagliflozin with follow-up haematocrit data (n=48) and 0.41±0.05 L/L in those randomised to placebo (n=52). Empagliflozin, compared to placebo, increased haematocrit from baseline to 24 weeks. Mean±SD change in haematocrit was 0.02±0.05 L/L between baseline and 24 weeks in the empagliflozin group and -0.01±0.04 L/L in the placebo group: adjusted between-group difference 0.02 L/L (95% CI 0.01 to 0.04); P=0.006 (Figure 5-6 and Table 5-1).

Figure 5-6 Change in haematocrit from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

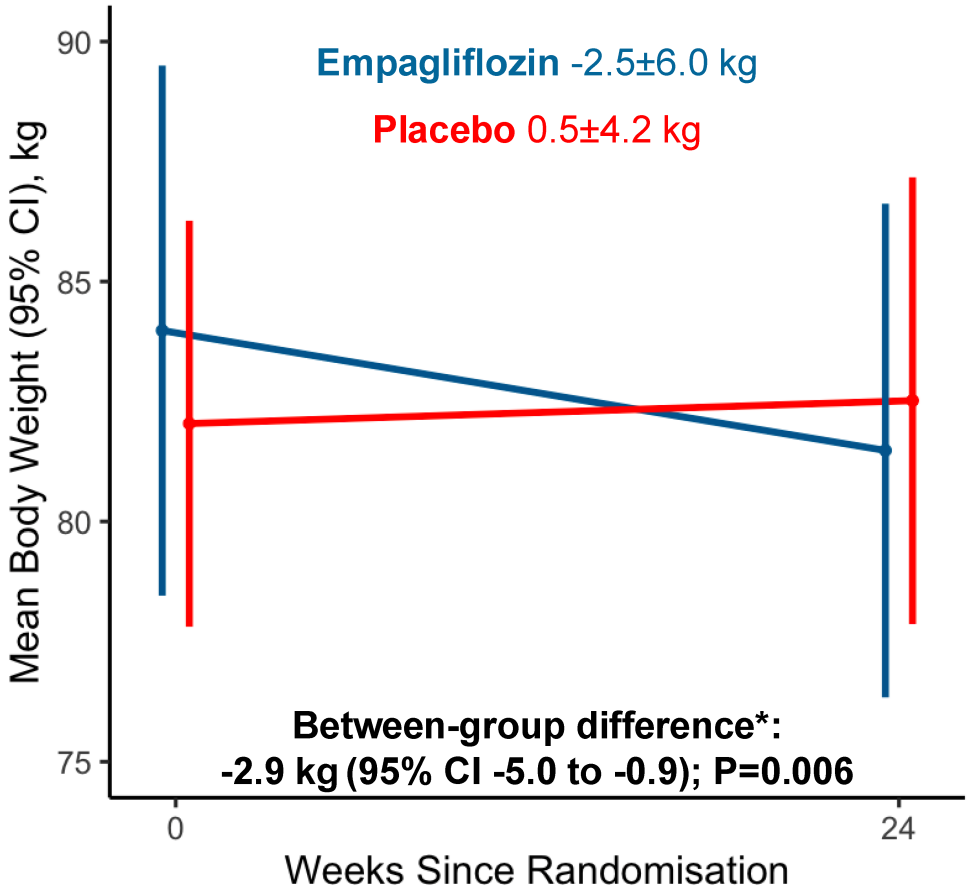
*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval.

5.3.7 Effect of empagliflozin on body weight

Mean±SD body weight at baseline was 84.0±19.5 kg in those randomised to empagliflozin with follow-up body weight data (n=48) and 82.0±15.6 kg in those randomised to placebo (n=52). Empagliflozin, compared to placebo, decreased body weight from baseline to 24 weeks. Mean±SD change in body weight was 2.5±6.0 kg between baseline and 24 weeks in the empagliflozin group and 0.5±4.2 kg in the placebo group: adjusted between-group difference -2.9 kg (95% CI -5.0 to -0.9); P=0.006 (Figure 5-7 and Table 5-1). Similar results were seen at 12 weeks (P=0.03).

Figure 5-7 Change in body weight from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals.

*Calculated using a linear regression model adjusted for randomised treatment, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CI, confidence interval.

5.4 Discussion

The effects of empagliflozin on circulating biomarkers of remodelling in the EMPRESS-MI trial are consistent with the lack of an effect on left ventricular volumes. NT-proBNP and hs-TnI declined over time in both treatment groups, with no treatment effect of empagliflozin. Given that NT-proBNP reflects cardiac wall stress, this parallel trajectory aligns with the absence of an effect of empagliflozin on left ventricular volumes.

In the EMMY trial, baseline NT-proBNP for the whole cohort was lower than that in EMPRESS-MI, reflecting a lower-risk post-MI population (1294 pg/mL vs. 2109 pg/mL). NT-proBNP decreased in both study groups but to a greater extent in the empagliflozin group in the EMMY trial (-15% (95% CI -4.4 to -24); P=0.026). This is in line with the observed effect of empagliflozin on left ventricular volumes seen in the EMMY trial.[117]

In contrast, the DACAMI trial, which enrolled patients with anterior STEMI and LVEF<50%, reported a lower baseline NT-proBNP than both EMMY and EMPRESS-MI (median 291 pg/mL in the dapagliflozin group and 289 pg/mL in the placebo group).[119] While NT-proBNP was reduced more in the dapagliflozin group, there was no effect on left ventricular volumes, likely due to the small sample size and short duration, limiting the ability to show an effect on echocardiographic measures.

Similar to the EMPRESS-MI trial, the EMBODY trial, in which 105 patients 2 weeks post-MI with T2DM were randomised to empagliflozin or placebo, showed no difference in the change in NT-proBNP between empagliflozin and placebo.[128] Baseline NT-proBNP was lower than in EMPRESS-MI (mean 1029 pg/mL in the empagliflozin group and 1271 pg/mL in the placebo group) and the LVEF was higher (58% in the empagliflozin group and 48% in the placebo group).[205] As in EMPRESS-MI, empagliflozin reduced uric acid and body weight and increased haematocrit, consistent with the known effects of SGLT2 inhibitors.[128] These results support the robustness of the EMPRESS-MI trial despite its smaller sample size and confirm patient adherence to medication.

In the SOCOGAMI trial, which included 42 patients with impaired glucose tolerance or T2DM and a history of MI or unstable angina within 6 months,

there was no effect of empagliflozin on NT-proBNP. The trial did not specify the time from index event to randomisation, making direct comparisons to other post-MI studies difficult.[116]

A recent meta-analysis of SOCOGAMI, EMBODY and DACAMI concluded no evidence of a beneficial effect of SGLT2 inhibitors on the reduction in NT-proBNP post-MI. However, the analysis had notable limitations, include the inclusion of SOCOGAMI, which did not recruit patients immediately post-MI, and the exclusion of EMMY, the largest trial, due to the absence of reported absolute change in NT-proBNP.[181]

There was no effect of empagliflozin on eGFR in the EMPRESS-MI trial. In contrast, the EMPACT-MI trial demonstrated a kidney-protective effect similar to that seen in heart failure, with an initial decline in eGFR followed by sustained improvement over 24 months in the empagliflozin group compared to placebo.[143] The lack of an observed effect in EMPRESS-MI may be due to the shorter follow-up duration and smaller sample size.

5.4.1 Limitations

The EMPRESS-MI trial was limited by the sample size. A larger sample size may have provided greater statistical power to detect small differences between the treatment groups. Troponin levels change dynamically post-MI reflecting infarct evolution and the myocardial injury process. Measuring troponin at a single time point limited the ability to assess peak levels more comprehensively. Serial measurements could have provided a clearer picture of the effect of empagliflozin on troponin levels post-MI over time.

5.4.2 Conclusion

In patients with left ventricular systolic dysfunction following an acute MI, empagliflozin had no effect on biomarkers relating to myocardial stress (NT-proBNP) and injury (hs-TnI). There was no effect of empagliflozin on HbA1c and eGFR in this cohort. Consistent with the known effects of empagliflozin, uric acid and body weight were reduced in the empagliflozin group, and the haematocrit was increased.

Chapter 6 The relationship between intramyocardial haemorrhage and left ventricular remodelling and the effect of empagliflozin in patients with left ventricular systolic dysfunction following myocardial infarction

6.1 Introduction

In this chapter, I will explore the relationship between IMH and left ventricular remodelling patterns in the EMPRESS-MI trial and the effect of empagliflozin. Exploratory outcomes of the EMPRESS-MI trial included the identification of IMH. EMPRESS-MI is the only post-MI remodelling trial of SGLT2 inhibitors to utilise CMR imaging. The effect of SGLT2 inhibitors in patients with infarct core pathology identified by CMR remains unknown. This trial provides novel mechanistic insights into the direct myocardial effects of SGLT2 inhibition using state-of-the-art imaging techniques.

As discussed in Chapter 3, the prevalence of IMH at baseline in the EMPRESS-MI trial was 48%, higher than the average 39% reported in a recent meta-analysis of 18 CMR STEMI studies, indicating a population at high risk for adverse left ventricular remodelling.[168] However, as outlined in Chapter 4, there was no evidence of progressive adverse remodelling in the overall EMPRESS-MI population. Given that IMH at baseline is a known predictor of adverse left ventricular remodelling, I hypothesised that this subgroup might exhibit distinct remodelling patterns within the EMPRESS-MI population.[206]

The recently proposed Canadian Cardiovascular Society (CCS) classification of acute MI describes 4 stages of tissue injury identified by CMR; 1) oedema without infarct by LGE; 2) infarct without MVO; 3) MVO; and 4) IMH.[207] Patients with MVO have a similar prognosis to patients without MVO, with IMH being the key factor for predicting prognosis.[208] At the European Society of Cardiology Congress 2024, I presented a poster abstract highlighting the association between the presence of IMH (CCS stage 4) and adverse outcome at 12 years post-MI in the BHF MR-MI STEMI cohort. Patients with CCS stage 4 had a higher risk of heart failure hospitalisation and all-cause mortality at 12 years, whilst there was no association between MVO and outcome.[209] These

findings highlight the importance of T2* imaging in post-MI CMR protocols in order to identify IMH as a prognostically important biomarker.

In this chapter, I aimed to determine whether, in a cohort treated with prompt reperfusion and high rates of secondary prevention therapy, the presence of IMH still confers a risk of adverse remodelling and identifies a subgroup more likely to benefit from novel anti-remodelling therapies. I assessed the effect of empagliflozin on remodelling in groups of patients with and without IMH. Additionally, I assessed the differences in remodelling across CCS stages to determine the impact of MVO alone on adverse remodelling.

6.2 Methods

6.2.1 Cardiovascular magnetic resonance protocol and analysis

The full CMR protocol and analysis methods are detailed in Chapter 2.5.5 and Chapter 2.5.6, respectively. Briefly, the CMR protocol included LGE for the identification of MVO and T2* mapping of the 4-chamber and mid short-axis for the identification of IMH. I analysed all CMR scans in a paired fashion and blinded to treatment allocation for the exploratory outcomes. MVO was defined as a hypointense core within the hyperintense infarct zone on LGE imaging.[157] IMH was defined as a region of reduced T2* signal intensity <20 ms within the infarcted area.[157] CMR scans were analysed in a paired fashion and blinded to treatment assignment by Dr Matthew Lee (Consultant Cardiologist and Clinical Senior Lecturer) for the primary and secondary outcomes, which included left ventricular volumes and function.

6.2.2 Biomarker sampling

I collected venous blood for NT-proBNP and hs-TnI measurement before randomisation, at 12 weeks and 24 weeks following randomisation, for biomarker analysis. I was assisted by Sister Barbara Meyer. Samples were collected and processed at the Clinical Research Facility at the GJNH according to a Sample Handling Manual. After completion of the trial, all samples were transferred to the central laboratory for batch analysis. NT-proBNP (Roche e411, Roche Diagnostics, Burgess Hill, UK) and hs-TnI (i1000SR

ARCHITECT, Abbott Laboratories, Maidenhead, UK) were batch measured after study completion. All non-routine assays were performed at a central lab (GlasBRU, University of Glasgow) using the manufacturers' calibrators and quality controls.

6.2.3 Statistical analysis

All statistical analyses in this chapter were conducted by myself using R Studio and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). Analyses were performed according to the intention-to-treat principle, including all randomly assigned participants without major protocol deviations, and with post-randomisation data available for the outcome of interest at any given time point, irrespective of their subsequent participation in the study and their adherence to randomised treatment.

Data were summarised descriptively for each randomised treatment group, using counts and percentages for categorical variables, and mean±SD or median (IQR), depending on the distribution of the data.

Baseline characteristics were compared between groups with and without IMH using the two-sample t-test and Wilcoxon rank-sum test for normal and non-normal continuous variables, respectively. For the effect of IMH on primary and secondary outcome measures, each outcome was analysed using a linear regression analysis model adjusted for IMH, the baseline value of the outcome in question, diuretic use at baseline, and diabetes status.

The treatment effect of empagliflozin on primary and secondary outcomes according to IMH was analysed using linear regression analysis models adjusted for IMH, baseline value of the outcome, use of diuretics at baseline and diabetes status and extended to include an interaction term to estimate the treatment effects within subgroups defined by randomised treatment.

Baseline characteristics were compared across CCS stages using linear regression analysis. For the effect of CCS stage on left ventricular remodelling, each outcome was analysed using a linear regression analysis model adjusted for CCS stage, the baseline value of the outcome in question, diuretic use at baseline, and diabetes status. Pairwise comparisons were

assessed to evaluate differences between CCS stage 2 and 3 and between CCS stage 2 and 4. Regression model effect estimates were reported with 95% CI and P values. A P value of <0.05 was considered statistically significant.

6.3 Results

6.3.1 Baseline values

Of 93 patients with complete data, 45 (48.4%) had IMH and 48 (51.6%) had no IMH.

At baseline, LVEF was lower in patients with IMH compared to those without IMH (33.5±5.6% vs. 36.1±6.1%; P=0.03) (Table 6-1). Patients with IMH had higher hs-TnI levels and larger infarct sizes than those without IMH (hs-TnI 24340 ng/L [IQR 14179-38399] vs. 9495 ng/L [IQR 3045-19533]; P<0.001, infarct size 44.1±11.4% vs. 27.4±10.9%; P<0.001) (Table 6-1).

At baseline, LVESVI, LVEDVI, LAVI, LVMI and NT-proBNP were similar between patients with and without IMH (all P>0.05) (Table 6-1).

6.3.2 Left ventricular remodelling and intramyocardial haemorrhage

Remodelling patterns in patients with and without IMH at baseline were divergent (Figure 6-1).

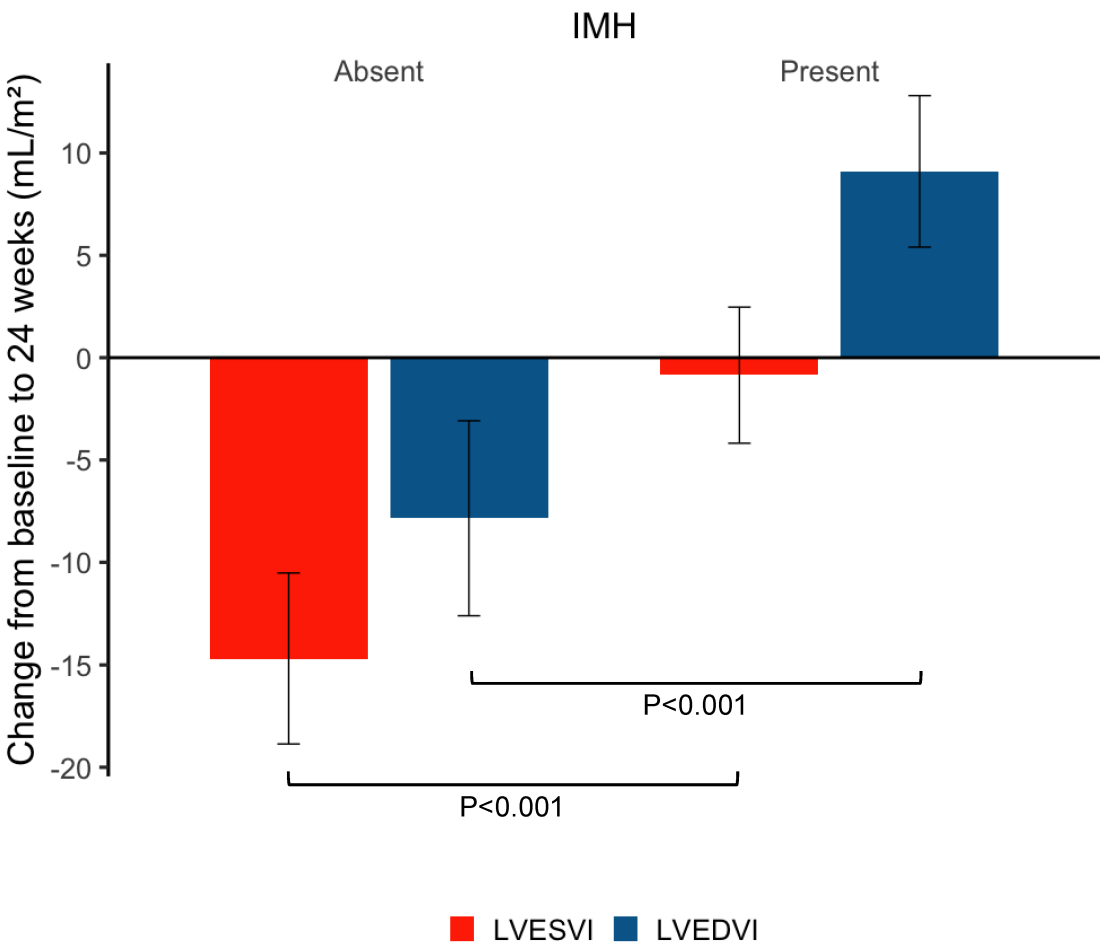
LVESVI decreased by 0.9±11.4 mL/m^2 between baseline and 24 weeks in patients with IMH at baseline and decreased by 14.7±14.7 mL/m^2 in patients without IMH: adjusted between-group difference 13.3 mL/m^2 (95% CI 8.2 to 18.3); P<0.001 (Figure 6-1 and Table 6-1).

LVEDVI increased by 9.1±12.7 mL/m^2 between baseline and 24 weeks in patients with IMH at baseline and decreased by 7.8±16.8 mL/m^2 in patients without IMH: adjusted between-group difference 15.4 mL/m^2 (95% CI 9.7 to 21.2); P<0.001 (Figure 6-1 and Table 6-1).

LVEF increased by 7.4±7.1% between baseline and 24 weeks in patients with IMH at baseline and by 10.7±7.7% in patients without IMH: adjusted between-group difference -4.4% (95% CI -7.4 to -1.4); P=0.004 (Table 6-1).

There was no difference in the change in LAVI, LVMI, NT-proBNP, hs-TnI or infarct size between baseline and 24 weeks in patients with and without IMH at baseline (Table 6-1).

Figure 6-1 Change in LVESVI and LVEDVI with the presence or absence of IMH from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals. P values were derived from a linear regression model adjusted for IMH, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: IMH, intramyocardial haemorrhage; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

Table 6-1 Change in primary and secondary outcomes with the presence or absence of IMH from baseline to 24 weeks

	No IMH				IMH				Between-group difference (95% CI)*	P value
	n	Baseline	24 weeks	Change	n	Baseline	24 weeks	Change		
LVESVI, mL/m²	48	64.1 (18.0)	49.4 (14.9)	-14.7 (14.7)	45	63.7 (12.8)	62.9 (18.2)	-0.9 (11.4)	13.3 (8.2, 18.3)	<0.001
LVEDVI, mL/m²	48	99.4 (20.0)	91.6 (17.8)	-7.8 (16.8)	45	95.7 (16.8)	104.8 (21.2)	9.1 (12.7)	15.4 (9.7, 21.2)	<0.001
LVEF, %	48	36.1 (6.1)	46.8 (7.2)	10.7 (7.7)	45	33.5 (5.6)	40.8 (8.1)	7.4 (7.1)	-4.4 (-7.4, -1.4)	0.004
LAVI, mL/m²	48	35.6 (10.3)	36.2 (11.9)	0.6 (11.2)	45	34.6 (13.4)	40.5 (14.5)	5.9 (15.5)	4.6 (-0.3, 9.6)	0.07
LVMI, g/m²	48	60.3 (14.0)	50.5 (11.1)	-9.9 (7.0)	45	60.8 (10.5)	52.4 (7.8)	-8.5 (7.1)	1.5 (-0.8, 3.7)	0.19
NT-proBNP, pg/mL	47	1970 (1055, 2924)†	306 (126, 529)†	-1509 (-2595, -812)†	47	2316 (1264, 3862)†	449 (251, 892)†	-1794 (-2782, -914)†	1.41 (0.99, 2.01)	0.06
hs-TnI, ng/L	49	9495 (3045, 19533)†	7 (5, 11)†	-9490 (-19524, -3042)†	47	24340 (14179, 38399)†	7 (5, 15)†	-24338 (-38390, -14118)†	1.23 (0.87, 1.75)	0.24
Infarct size, %	47	27.4 (10.9)	20.6 (11.1)	-6.8 (9.2)	42	44.1 (11.4)	31.7 (11.0)	-12.4 (7.1)	-0.6 (-4.0, 2.8)	0.78

Data presented as mean (SD) unless otherwise stated. Results are reported for those with data available at baseline and 24 weeks.
*Calculated using a linear regression model adjusted for IMH, baseline value of the outcome, use of diuretics at baseline and diabetes

status. Between-group differences are reported as ratios of adjusted geometric means for NT-proBNP and hs-TnI from models using log-transformed values. All other outcomes are reported as adjusted mean differences (95% CI). †Median (interquartile range).

Abbreviations: CI, confidence interval; hs-TnI, high-sensitivity cardiac troponin I; IMH, intramyocardial haemorrhage; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

6.3.3 Effect of empagliflozin on left ventricular remodelling according to intramyocardial haemorrhage

The effects of empagliflozin, compared with placebo, on left ventricular remodelling in patients with and without IMH at baseline are shown in Table 6-2. Empagliflozin had no effect on any of the primary and secondary outcomes in either group (Table 6-2).

Table 6-2 Change in primary and secondary outcomes with empagliflozin or placebo, grouped by the presence or absence of IMH, from baseline to 24 weeks

	No IMH (n=48)		IMH (n=45)		Interaction P value
	Empagliflozin	Placebo	Empagliflozin	Placebo	
LVESVI					
Baseline, mL/m^2	64.3 (20.7)	64.0 (16.3)	64.6 (11.8)	62.6 (14.1)	
24 weeks, mL/m^2	49.6 (15.5)	49.3 (14.8)	62.5 (15.7)	63.4 (21.3)	
Change, mL/m^2	-14.7 (12.5)	-14.7 (16.2)	-2.7 (10.6)	0.8 (12.4)	
Between-group difference (95% CI)*	0.1 (-7.1, 7.3)		-2.6 (-10.0, 4.8)		0.61
LVEDVI					
Baseline, mL/m^2	98.3 (23.5)	100.1 (17.7)	95.9 (14.3)	95.5 (20.0)	
24 weeks, mL/m^2	91.1 (17.9)	91.9 (18.1)	104.4 (16.0)	105.4 (26.8)	
Change, mL/m^2	-7.2 (14.8)	-8.27 (18.3)	8.47 (11.4)	9.88 (14.3)	
Between-group difference (95% CI)*	0.7 (-7.5, 8.8)		-1.5 (-9.8, 6.9)		0.72
LVEF					
Baseline, %	35.2 (6.1)	36.7 (6.1)	32.7 (5.8)	34.4 (5.3)	
24 weeks, %	46.5 (6.4)	47.0 (7.8)	40.8 (9.2)	40.9 (6.6)	
Change, %	11.3 (7.3)	10.3 (8.0)	8.1 (7.6)	6.4 (6.4)	
Between-group difference (95% CI)*	0.3 (-3.8, 4.5)		1.0 (-3.3, 5.3)		0.83
LAVI					
Baseline, mL/m^2	34.6 (12.0)	36.2 (9.2)	33.3 (13.3)	36.1 (13.7)	
24 weeks, mL/m^2	36.5 (14.0)	36.1 (10.5)	38.3 (13.9)	43.2 (15.2)	
Change, mL/m^2	1.9 (9.5)	-0.2 (12.2)	5.0 (16.4)	7.1 (14.6)	
Between-group difference (95% CI)*	1.3 (-5.9, 8.4)		-3.5 (-10.8, 3.8)		0.35
LVMI					
Baseline, g/m^2	60.8 (16.5)	59.9 (12.3)	62.3 (11.3)	59.0 (9.3)	
24 weeks, g/m^2	50.4 (11.7)	50.4 (11.0)	53.6 (8.1)	50.8 (7.4)	

Change, g/m^2	-10.4 (7.7)	-9.5 (6.6)	-8.7 (7.7)	-8.2 (6.4)	
Between-group difference (95% CI)*	-0.6 (-3.8, 2.6)		0.2 (-3.2, 3.5)		0.74
NT-proBNP					
Baseline, pg/mL	2007 (1105, 3236)†	1970 (1011, 2898)†	2502 (1500, 3502)†	2068 (1286, 4174)†	
24 weeks, pg/mL	321 (130, 710)†	209 (125, 422)†	382 (251, 956)†	474 (265, 818)†	
Change, pg/mL	-1625 (-2934, -943)†	-1432 (-2087, -801)†	-1936 (-2425, -1213)†	-1528 (-3698, -802)†	
Between-group difference (95% CI)*	0.92 (0.55, 1.54)		0.95 (0.57, 1.58)		0.93
hs-TnI					
Baseline, ng/L	9008 (3142, 15688)†	10624 (2091, 21824)†	28138 (16960, 42093)†	22495 (10632, 36351)†	
24 weeks, ng/L	7 (4, 10)†	7 (6, 13)†	8 (5, 17)†	6 (5, 15)†	
Change, ng/L	-8997 (-15680, -3137)†	-10610 (-21819, -2086)†	-28133 (-42089, -16900)†	-22491 (-36343, -10626)†	
Between-group difference (95% CI)*	0.88 (0.55, 1.40)		1.27 (0.79, 2.04)		0.27
Infarct size					
Baseline, %	29.1 (9.5)	26.4 (11.7)	43.8 (9.7)	44.5 (13.9)	
24 weeks, %	22.1 (9.1)	19.7 (12.3)	32.9 (9.7)	30.0 (12.8)	
Change, %	-7.0 (8.7)	-6.7 (9.7)	-10.9 (6.8)	-14.5 (7.2)	
Between-group difference (95% CI)*	0.6 (-3.9, 5.2)		3.6 (-1.2, 8.4)		0.38

Data presented as mean (SD) unless otherwise stated. Results are reported for those with data available at baseline and 24 weeks.
*Calculated using a linear regression model adjusted for IMH, baseline value of the outcome, use of diuretics at baseline and diabetes status and extended to include an interaction term to estimate the treatment effects within subgroups defined by randomised treatment. Between-group differences are reported as ratios of adjusted geometric means for NT-proBNP and hs-TnI from models using log-

transformed values. All other outcomes are reported as adjusted mean differences (95% CI). Interaction P value presented to assess for differences in treatment effect between subgroups. †Median (interquartile range).

Abbreviations: CI, confidence interval; hs-TnI, high-sensitivity cardiac troponin I; IMH, intramyocardial haemorrhage; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

6.3.4Left ventricular remodelling and CCS stage

Of 93 patients with complete data, 27 (29.0%) were CCS stage 2, 21 (22.6%) were CCS stage 3 and 43 (48.4%) were CCS stage 4. No patients were CCS stage 1.

At baseline, LVEF differed across CCS stages (Table 6-3). Hs-TnI and infarct size were higher with increasing CCS stages (Table 6-3). There were no differences in LVESVI, LVEDVI, LAVI, LVMI or NT-proBNP across CCS stages (Table 6-3).

Change in LVESVI, LVEDVI and LVEF were different across CCS stages (Figure 6-2 and Table 6-4). Pairwise comparisons revealed changes in these parameters were significantly different between CCS stage 4 and CCS stage 2 (all $P<0.001$), while no significant differences were observed between CCS stage 3 and CCS stage 2 (all $P>0.05$) (Table 6-4).

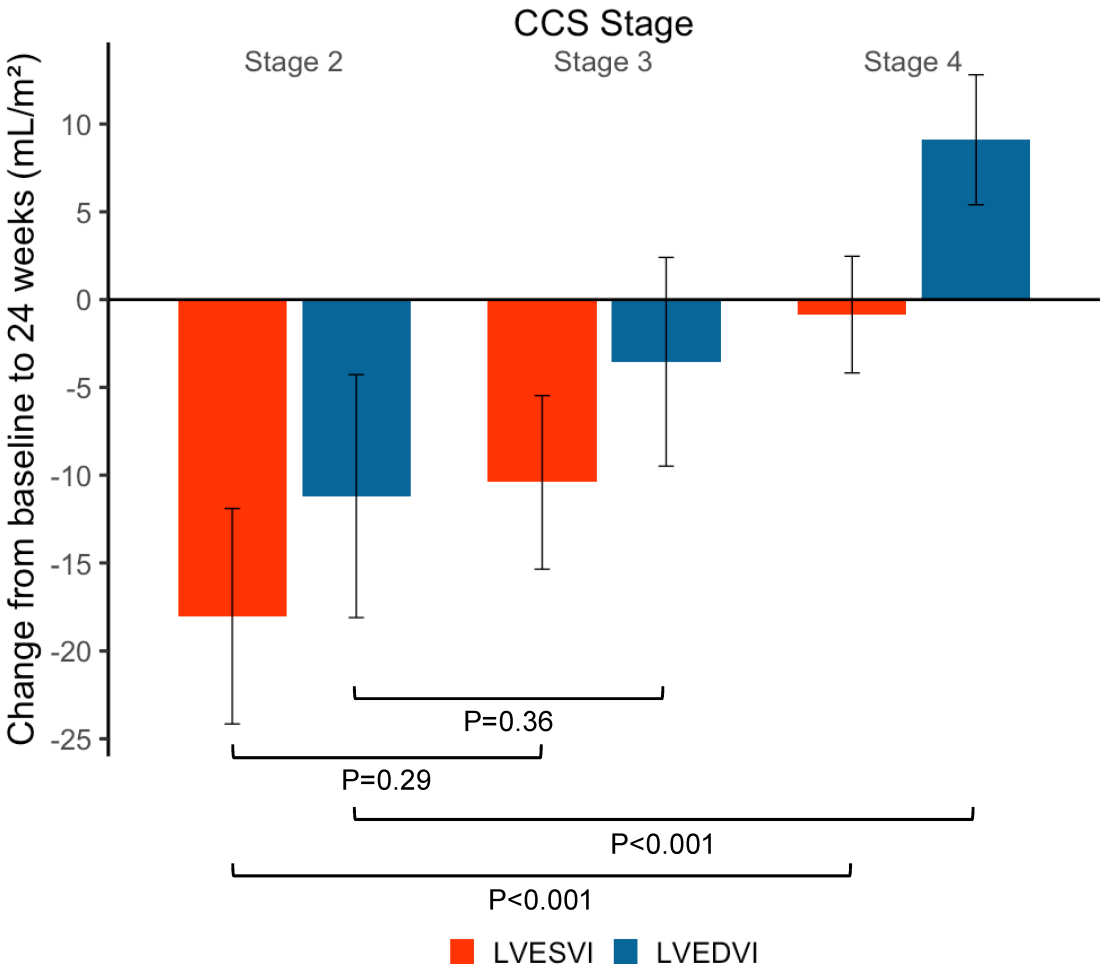
Table 6-3 Baseline values for primary and secondary outcomes with CCS stage

	CCS stage 2		CCS stage 3		CCS stage 4		P value*
	n		n		n		
LVESVI, mL/m^2	27	68.3 (20.6)	21	58.7 (12.2)	45	63.7 (12.8)	0.10
LVEDVI, mL/m^2	27	104.0 (22.8)	21	93.6 (14.0)	45	95.7 (16.8)	0.10
LVEF, %	27	34.9 (6.9)	21	37.6 (4.6)	45	33.5 (5.6)	0.03
LAVI, mL/m^2	27	38.1 (11.3)	21	32.4 (8.1)	45	34.6 (13.4)	0.24
LVMI, g/m^2	27	62.8 (16.0)	21	57.0 (10.3)	45	60.8 (10.5)	0.27
NT-proBNP, pg/mL	26	2008 (1035, 2602)†	22	1953 (1546, 3020)†	47	2316 (1264, 3862)†	0.29
hsTnI, ng/L	27	8357 (1648, 17218)†	22	13350 (7040, 21824)†	47	24340 (14179, 38399)†	<0.001
Infarct size, %	26	23.4 (10.8)	21	32.4 (9.0)	42	44.1 (11.4)	<0.001

Data presented as mean (SD) unless otherwise stated. Results are reported for those with data available at baseline and 24 weeks.
*Calculated using a linear regression model adjusted for CCS stage. †Median (interquartile range).

Abbreviations: CCS, Canadian Cardiovascular Society; CI, confidence interval; hs-TnI, high-sensitivity cardiac troponin I; IMH, intramyocardial haemorrhage; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Figure 6-2 Change in LVESVI and LVEDVI with CCS stage from baseline to 24 weeks



Data presented as mean and error bars represent 95% confidence intervals. P values were derived from pairwise comparisons from a linear regression model adjusted for CCS stage, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CCS, Canadian Cardiovascular Society; LVEDVI, left ventricular end-diastolic volume; LVESVI, left ventricular end-systolic volume.

Table 6-4 Change in left ventricular volumes and function with CCS stage from baseline to 24 weeks

	CCS stage 2 (n=27)	CCS stage 3 (n=21)	CCS stage 4 (n=45)	Between-group difference (95% CI)*		
				CCS stage 2	CCS stage 3	CCS stage 4
Change in LVESVI, mL/m^2	-18.0 (16.2)	-10.4 (11.5)	-0.9 (11.4)	1.0 (referent)	3.9 (-3.4, 13.6); P=0.29	15.0 (9.0, 21.0); P<0.001
Change in LVEDVI, mL/m^2	-11.2 (18.3)	-3.5 (13.9)	9.1 (12.7)	1.0 (referent)	3.8 (-4.4, 11.9); P=0.36	17.1 (10.3, 24.0); P<0.001
Change in LVEF, %	11.5 (8.3)	9.6 (6.9)	7.4 (7.1)	1.0 (referent)	-0.4 (-4.5, 3.8); P=0.86	-4.6 (-8.0, -1.1); P<0.001

Data presented as mean (SD) unless otherwise stated. Results are reported for those with data available at baseline and 24 weeks.
*Calculated using a linear regression model adjusted for CCS stage, baseline value of the outcome, use of diuretics at baseline and diabetes status.

Abbreviations: CCS, Canadian Cardiovascular Society; CI, confidence interval; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index.

6.4 Discussion

In this population of patients with left ventricular systolic dysfunction following an acute MI where the overall trajectory in left ventricular volumes was that of improvement, remodelling patterns in patients with and without IMH were divergent. Patients without IMH experienced favourable left ventricular remodelling, whereas those with IMH experienced adverse remodelling, despite both groups displaying similar left ventricular volumes and function at baseline.

In a meta-analysis of 7 studies of IMH in STEMI, the presence of IMH resulted in an 11% smaller increase in LVEF and a 17 mL/m^2 larger increase in both LVESVI and LVEDVI.[210] Subsequently, in the BHF MR-MI all-comers STEMI study, in patients with IMH the change in non-indexed LVEDV was +17 mL from baseline to 6 months and the non-indexed LVESV was unchanged.[22] These values are similar to that seen in the EMPRESS-MI trial, where the presence of IMH resulted in a 4% smaller increase in LVEF, a 13 mL/m^2 larger increase in LVESVI and a 15 mL/m^2 larger increase in LVEDVI. The consistency of remodelling patterns in patients with IMH over time, despite the increasing use of reperfusion and secondary prevention therapies, underscores the hypothesis that patients with IMH represent a high-risk subgroup who may benefit from targeted therapeutic interventions.

These findings highlight a key challenge of how to best identify these patients at highest risk of developing heart failure and who stand to benefit the most from additional anti-remodelling therapy. Most ongoing clinical trials continue to rely on traditional enrichment criteria of an anterior MI and low LVEF.[2] Data from EMPRESS-MI suggest that these criteria alone may be insufficient to identify patients at risk of progressive adverse remodelling in the context of contemporary pharmacological and reperfusion therapy. Patients with reduced LVEF and IMH are at the highest risk of adverse outcomes and adverse remodelling compared to patients with a low LVEF alone.[22,208]

It may be time to move on from an era of relying on infarct location and ventricular function to define high-risk patients. Instead, a more comprehensive approach incorporating detailed infarct characterisation, in

addition to a reduction in LVEF, may better stratify risk following an acute MI. A barrier to this approach is the reliance on CMR for tissue characterisation. The use of CMR is constrained by availability. Many centres globally have little or no provision of CMR services. Additionally, the requirement for patients to lie flat and perform breath holds limits the use to patients who are clinically stable post-MI. As a result, the true prevalence of IMH is likely underestimated. Variability in imaging techniques used to detect IMH limits comparisons across studies.[168] Whilst T2* mapping is the recommended technique for the detection of IMH, many previous analyses have relied on T2 imaging. Most studies using T2* mapping define IMH as a signal of <20 ms within the infarct core, a threshold that has been shown to predict long-term outcome in STEMI patients.[22,168,211–214] This is the method of detection I used in the EMPRESS-MI trial (Chapter 2.5.6.6). Future efforts should explore alternative methods for detecting IMH, including novel circulating biomarkers and echocardiographic tissue characterisation techniques.[215,216]

Considerable effort has been directed toward preventing or mitigating microvascular injury from occurring in the first place, of which IMH is the final stage in its progression. Despite extensive investigation into both pharmacological and mechanical interventions before and during PCI, no proven treatments currently exist.[217] In the T-TIME trial, there was no difference in MVO or IMH at 4 days post-STEMI in patients who had received intracoronary alteplase versus placebo, which was hypothesised to prevent distal embolisation of coronary thrombus.[167] Similarly, in the recent Platelet Inhibition to Target Reperfusion Injury (PITRI) trial, there was no effect of intravenous cangrelor on acute infarct size or MVO.[218] One proposed explanation for the failure of large clinical trials to demonstrate a benefit in reducing microvascular injury is the effectiveness of prompt reperfusion therapy coupled with the selection of patients at relatively low risk of developing such injury.[217] Further research is needed to identify novel angiographic, imaging, or circulating biomarkers that can better stratify high-risk patients and guide the development of targeted therapies aimed at reducing microvascular injury.[2]

The differences in left ventricular remodelling parameters across CCS stages in the EMPRESS-MI trial strengthens the argument for IMH as the key indicator for an adverse trajectory post-MI.[207–209] Changes in left ventricular volumes and function from baseline to 24 weeks were similar between patients with CCS stage 2 MI (infarct only) and CCS stage 3 MI (MVO), however patients with CCS stage 4 MI (IMH) displayed a distinct pattern of adverse remodelling, reinforcing the prognostic significance of IMH over and above other infarct characteristics.

Although no significant effect of empagliflozin on remodelling was observed in patients with or without IMH in this trial, it was not powered to detect such an effect, and this analysis remains exploratory. Further research is needed to assess whether targeted interventions could mitigate the adverse remodelling seen in this high-risk population.

6.4.1 Limitations

As previously mentioned, the major limitation of the EMPRESS-MI trial was the sample size, which reduced the power to detect between-group differences in these *post hoc* analyses. Additionally, the CMR protocol included T2* mapping of only the left ventricular 4-chamber and mid short-axis views. A full T2* short-axis stack would have provided more comprehensive coverage of the infarct zone and allowed for accurate assessment of IMH volume. However, implementing a longer T2* sequence would have increased scan duration, potentially reducing patient tolerance.

6.4.2 Conclusion

In patients with left ventricular systolic dysfunction following an acute MI, those without IMH exhibited favourable left ventricular remodelling, whereas those with IMH experienced adverse remodelling. Patients with IMH represent a high-risk subgroup who may benefit from targeted therapeutic interventions, and this should be a key focus for future research.

Chapter 7 Final discussion and conclusions

7.1 Summary of findings

The development of left ventricular systolic dysfunction following an acute MI has been associated with substantial morbidity and mortality. Patients with a reduced LVEF following an acute MI have previously been reported to be at risk of progressive adverse cardiac remodelling, which is a pathological precursor to the development of chronic heart failure. New therapeutic strategies have been sought to limit the progression of adverse left ventricular remodelling in this setting. At the time of starting my PhD, it was unknown whether the beneficial remodelling effects of SGLT2 inhibitors seen in chronic HFrEF would extend to high-risk patients with left ventricular systolic dysfunction following an acute MI.

In Chapter 2, I have detailed the methods and design of the EMPRESS-MI clinical trial, which was designed to test the hypothesis that empagliflozin, in addition to standard of care, would attenuate adverse left ventricular remodelling in high-risk patients following acute MI. In Chapter 3, I have described the baseline characteristics of participants recruited to the EMPRESS-MI clinical trial, which were believed to be indicative of a population at high risk of adverse remodelling and likely to benefit from additional anti-remodelling therapy. Compared to other trials investigating SGLT2 inhibitors post-MI, the EMPRESS-MI population exhibited higher risk features than most, except for EMPACT-MI, which specifically selected for a high-risk population through the use of enrichment criteria.[85,86,117,119,120]

In the following Chapters, I have outlined the results of the EMPRESS-MI trial. The main findings were that, in patients with left ventricular systolic dysfunction after an acute MI treated with contemporary reperfusion and medical therapy, the addition of empagliflozin to standard care had no effect on improving left ventricular volumes or function compared with placebo. Empagliflozin had no effect on other measures of cardiac remodelling including left atrial volumes, left ventricular mass, infarct size, and biomarkers relating to myocardial stress (NT-proBNP) and injury (hs-TnI).

SGLT2 inhibitors reduce the risk of worsening heart failure and mortality in patients with HFrEF, with one proposed mechanism being a favourable effect on adverse remodelling.[98–100] Progressive adverse left ventricular remodelling is a common pathological precursor to both worsening chronic HFrEF and the development of HFrEF following an acute MI. It was reasonable to hypothesise that the remodelling benefits seen with SGLT2 inhibitors in established HFrEF would extend to high-risk patients post-MI. In this context, my finding that the addition of empagliflozin to standard treatment had no effect on remodelling in the EMPRESS-MI trial warrants further consideration.

I observed that the majority of participants did not exhibit features of progressive adverse remodelling over 24 weeks. The EMPRESS-MI trial was designed to recruit a population considered to be at high risk of adverse left ventricular remodelling. Among contemporary post-MI remodelling trials, EMPRESS-MI participants had lower LVEF and larger left ventricular volumes at baseline. However, there was minimal evidence of adverse left ventricular remodelling in the overall cohort between baseline and 24 weeks. I have considered several reasons for this. Despite efforts to avoid the inclusion of patients with myocardial stunning, some may have had a degree of myocardial stunning which improved following timely revascularisation and comprehensive medical therapy. It is unclear whether recruiting patients with persistent systolic dysfunction at a later stage post-MI might have resulted in a different remodelling pattern or a detectable treatment effect. Another potential reason for the lack of adverse remodelling was the widespread use of pharmacological therapies known to prevent this process. I compared my findings to the PARADISE-MI trial, which used enrichment criteria to select a high-risk cohort and also had high uptake of reperfusion and secondary prevention therapies.[55,57] PARADISE-MI reported similar improvements in left ventricular volumes and function as I observed in the EMPRESS-MI trial (increase in LVESVI and LVEDVI in the placebo group by 2.3 mL/m^2 and 7.1 mL/m^2, respectively), which contrasts with the extent of adverse remodelling I had expected to see.[57] These findings collectively suggest that in the contemporary era of widespread reperfusion and neurohormonal blockade, most patients who are considered to be at high risk do not experience progressive adverse remodelling in the months following acute MI.

The neutral findings of the EMPRESS-MI trial must be interpreted alongside the results of the EMMY trial. Several characteristics indicate that the EMMY cohort was at a lower risk of adverse remodelling compared to EMPRESS-MI. Baseline ventricular volumes were nearly half those of EMPRESS-MI, LVEF was higher and troponin and NT-proBNP were lower.[117] Despite this, the remodelling patterns differed between the two trials. In EMMY the placebo group exhibited progressive adverse remodelling, and, in this context, empagliflozin exerted beneficial effects on left ventricular structure and function.[117] The reason for this discrepancy in ventricular remodelling trajectories between EMMY and PARADISE-MI and EMPRESS-MI, remains unclear.

In EMPACT-MI, empagliflozin reduced first and total heart failure hospitalisations and adverse heart failure events following an acute MI.[86] The EMPACT-MI population was similar to the population enrolled in the current trial. My expectation was that the reduction in incident heart failure in EMPACT-MI was primarily due to empagliflozin reducing left ventricular volumes and preventing progressive adverse remodelling. The follow-up period in EMPRESS-MI (24 weeks) was substantially shorter than in EMPACT-MI (17.9 months), meaning I cannot discount that longer-term treatment with an SGLT2 inhibitor may have a favourable remodelling effect. Still, the absence of any remodelling benefit of empagliflozin suggests that alternative mechanisms of action may underlie the clinical benefits, such as body weight reduction, improved iron utilisation, or the kidney-protective effects. A similar pattern is seen in T2DM. SGLT2 inhibitors reduce cardiovascular death and heart failure hospitalisations in patients with T2DM but have no effect on left ventricular volumes.[63-67,106,107,109,111,116] In HFrEF, remodelling plays a role, but in T2DM and post-MI, other mechanisms may be responsible for their benefits.

In Chapter 5, I have shown that empagliflozin reduced uric acid and body weight and increased haematocrit in the EMPRESS-MI trial, consistent with the known effects of SGLT2 inhibitors. These results validate the robustness of the trial despite the small sample size and confirm patient adherence to trial medication.

Finally, in Chapter 6, I have explored the relationship between IMH and left ventricular remodelling patterns in the EMPRESS-MI trial. While overall left ventricular volumes improved, those with IMH experienced adverse remodelling. These findings underscore the challenge of identifying patients at the highest risk of heart failure who stand to benefit the most from additional anti-remodelling therapy.

7.2 Strengths

The EMPRESS-MI trial has several notable strengths. First, CMR is the gold standard method of assessment of left ventricular volumes and ejection fraction and has the additional benefit of allowing detailed infarct characterisation.[157] CMR is also more reproducible than echocardiography, allowing for a smaller sample size.[157] Second, to my knowledge, EMPRESS-MI is the only post-MI remodelling trial to incorporate LVEF eligibility criteria based on both echocardiography and CMR. This ensured the inclusion of a truly high-risk population, setting it apart from other recent remodelling studies. Third, patients in the EMPRESS-MI trial received optimal reperfusion and secondary prevention therapies, providing valuable insights into remodelling patterns in a contemporary patient cohort. Fourth, CMR and biomarker data were nearly complete for the cohort, with exceptionally high-quality imaging, resulting in only a minimal number of maps being unanalysable. Finally, no patients were lost to follow-up, and almost all patients who were randomised underwent the follow-up CMR scan.

7.3 Limitations

The study population was predominantly white, reflecting the demographics of the West of Scotland, which may limit generalisability to more diverse populations. Similarly, most participants were male, thought this is consistent with similar trials and the proportion of female patients in the pre-screened and recruited cohorts was comparable. The majority of participants presented with a STEMI, limiting applicability to NSTEMI patients, and most did not have T2DM, restricting relevance for this high-risk group.

Only medications at randomisation were recorded. The post-MI period involves rapid initiation and titration of secondary prevention therapies.

However, medications recorded at Visit 2 (2 weeks post-randomisation) were largely consistent with those at baseline.

Baseline differences between groups included longer symptom-to-reperfusion time and larger infarct size in the empagliflozin group, though these were not statistically significant. Importantly, left ventricular volumes were identical, suggesting similar acute adverse remodelling.

Patients received treatment for only 24 weeks, and a longer-term remodelling effect remains unknown.[28] The trial was limited by its small sample size, and the SD of the change in LVESVI was higher than anticipated. Given the minimal between-group difference, a larger sample size would likely not have shown a clinically meaningful effect. The small sample size limits any *post hoc* analyses, which should be considered hypothesis generating.

Measuring troponin at a single time point restricted the ability to assess peak levels. Additionally, the CMR protocol included T2* mapping in limited views rather than a full short-axis stack, which would have provided better infarct zone coverage and IMH volume assessment. However, a longer T2* sequence could have reduced patient tolerance due to increased scan duration.

7.4 Future areas of research

Future analyses of the EMPRESS-MI trial will focus on exploratory outcomes including the assessment of CMR-derived left ventricular strain. In the BHF MR-MI study of patients with STEMI, left ventricular circumferential strain was associated with major adverse cardiac events over 4 years.[219] While SGLT2 inhibitors have no effect on either echocardiographic- or CMR-derived left ventricular strain in remodelling trials of patients with HFrEF or T2DM, their effects in an acute post-MI population remain unknown.[98,99,102,109,113,114,116] Additionally, I will analyse kidney magnetic resonance imaging, which has not yet been studied in the post-MI setting. In the SUGAR-DM-HF trial, empagliflozin reduced markers of kidney perfusion and congestion in patients with HFrEF.[220] The effect of SGLT2 inhibitors on kidney magnetic resonance imaging markers has been described in other disease states, but not in acute MI.[221–226] I also plan to investigate the effect

of iron deficiency in the EMPRESS-MI population on remodelling, as well as the potential effects of empagliflozin. Iron deficiency post-MI is associated with mortality risk and adverse left ventricular remodelling, and SGLT2 inhibitors increase mobilisation and use of iron in the HFrEF setting.[136,227,228]

Several ongoing trials are investigating the effects of SGLT2 inhibitors in the post-MI period. The Dapagliflozin To Attenuate Cardiac Remodelling After Acute MI (DAPAPROTECTOR) trial (NCT05764057) is assessing the effect of dapagliflozin on the change in LVEF by echocardiography in 450 patients with acute MI and LVEF≤45%. As discussed in Chapter 6, preventing microvascular injury at the time of PCI has been an important therapeutic goal. The PRESTIGE-MI trial (NCT04899479) is examining whether SGLT2 inhibitors before PCI influences infarct size and LVESV at 6 months in 200 patients with acute MI and LVEF<50% or signs or symptoms of congestion requiring treatment. A key distinction from EMPRESS-MI is the timing of administration of SGLT2 inhibitors. Whereas in EMPRESS-MI treatment was initiated after revascularisation, PRESTIGE-MI explores the potential benefits of earlier administration, before ischaemia-reperfusion injury occurs. Similarly, the Empagliflozin for No-reflow Phenomenon in PCI for STEMI (EMPA-PCI) trial (NCT06342141) is investigating whether empagliflozin, given pre-PCI, affects no-reflow in 162 STEMI patients, with acute infarct size by CMR as a secondary outcome. The Effect At 3 Months of Early Empagliflozin Initiation in Cardiogenic Shock Patients on Mortality, Rehospitalisation, Left Ventricular Ejection Fraction and Renal Function (EMPASHOCK) trial (NCT05879276), will address the important question of the effect of empagliflozin in 164 patients with cardiogenic shock, including cases secondary to acute MI. The composite primary endpoints include all-cause mortality, heart transplant or ventricular assist device implantation, heart failure hospitalisation and LVEF at 12 weeks.

There are several ongoing trials for novel therapeutic agents which are aimed at reducing the pathological processes which promote progressive adverse left ventricular remodelling. Targeting inflammation, the Doxycycline to Protect Heart Muscle After Heart Attacks (DOXY-STEMI) trial (NCT03508232) is investigating the effect of doxycycline on LVESVI at 3 months in STEMI. A further trial is examining the effect of CRP apheresis on the acute infarct size

by CMR in 202 patients with STEMI and CRP≥7 mg/L (NCT04939805). The Study to Assess Efficacy and Safety of CDR132L in Patients With Reduced Left Ventricular Ejection Fraction After MI (HF-REVERT) (NCT05350969) trial will report on the effect of a micro-RNA inhibitor, CDR132L, on the change in LVESVI at 6 months in 280 patients post-MI with LVEF≤45%.[229] In Chapter 6, I have highlighted that patients with IMH experience adverse left ventricular remodelling and therefore are a high-risk population post-MI that could benefit from additional targeted anti-remodelling therapy. The ongoing CMR-guided Deferiprone Therapy for Acute MI Patients (MIRON-DFP) trial (NCT05604131) is assessing the effect of the oral iron chelator, deferiprone, in 72 patients with acute anterior STEMI with and without IMH.[230] The primary outcome is the reduction of haemorrhagic zone iron content by CMR from baseline to 6 months. As previously discussed, the identification of IMH is limited by the requirement for CMR. To address the limitations of CMR, future research should focus on developing alternative methods for identifying IMH, such as biomarker assessment and echocardiography.[215,216]

Many of the ongoing trials detailed above are utilising LVEF or infarct location as criteria to identify a population at high risk of adverse remodelling. As I have shown in my results from the EMPRESS-MI trial, LVEF alone is insufficient to define a truly high-risk population in contemporary practice. As a result, it is likely that these trials will fail to demonstrate any meaningful remodelling benefit of novel therapies - not due to ineffective therapies, but because the trial populations are not truly high-risk.[231] I have shown that, in the contemporary era of widespread reperfusion and neurohormonal blockade, most patients who were previously considered to be high-risk do not experience progressive adverse remodelling in the months following acute MI. This has implications not only for remodelling trials, but also outcome trials post-MI, as the reduction in adverse remodelling likely translates to lower rates of heart failure. This may explain why the PARADISE-MI and EMPACT-MI trials failed to show improvements in their primary endpoints.[55,86] Put simply, we cannot prevent what does not happen. Large, prospective, multi-centre observational post-MI studies, with serial CMR assessment including the assessment of IMH are now required to further document remodelling patterns and the association with outcome. If future post-MI trials are to show therapeutic benefit beyond contemporary reperfusion and medical

therapy, they must emphasize the enrolment of higher-risk populations or incorporate higher-risk features such as IMH as enrichment factors.

7.5 Conclusions

In patients with left ventricular systolic dysfunction after an acute MI treated with contemporary reperfusion and medical therapy, the addition of empagliflozin to standard care did not have any effect on improving left ventricular volumes or function compared with placebo. Empagliflozin had no effect on the change in other measures of cardiac remodelling including left atrial volumes, left ventricular mass, infarct size, and biomarkers relating to myocardial stress (NT-proBNP) and injury (hs-TnI). The majority of patients did not display features of progressive adverse remodelling over 24 weeks.

Appendices

Appendix 1 - Patient Information Sheet

PATIENT INFORMATION SHEET

Empagliflozin to prevent worsening of left ventricular volumes and systolic function after myocardial infarction (EMPRESS-MI): a multi-centre, randomised, placebo-controlled trial

Invitation to participate

We would like to invite you to take part in a research study of a medication for heart failure. Before you decide whether or not you would like to be involved, it is important for you to understand why the research is being done and what it would involve. Please take some time to read the following information carefully and to decide whether or not you would like to take part.

- **PART 1** of the patient information sheet tells you the purpose of the research and what will happen if you decide to take part.
- **PART 2** gives you more detailed information.

Talk to others about the trial if you wish and discuss with friends and family if you would like to. Please ask us if anything is not clear to you or you would like further information.

Thank you for taking the time to read this information.

PART 1: Study Information

Who is conducting the research?

The research is being carried out by Professor Mark Petrie, Professor Colin Berry, Dr Kieran Docherty and Dr Jaclyn Carberry from the University of Glasgow.

The trial is sponsored by NHS Greater Glasgow and Clyde and the University of Glasgow. The trial is funded by the drug company who produces empagliflozin, Boehringer Ingelheim.

What is the purpose of the research?

Heart attacks are a common health problem in the United Kingdom (UK). In the last 30 years, the chances of surviving from a heart attack have been greatly improved by advances in treatments, including medications and angioplasty (using balloons and stents to open a blocked or narrowed coronary artery).

Despite these advances, a proportion of people will develop a complication called heart failure. Heart failure develops because of damage to the heart muscle caused by the heart attack. This means that the heart is not able to pump blood around the body as effectively as it should, which can result in fluid accumulating around the body, such as in the lungs or the legs. It can cause symptoms such as breathlessness, fluid retention and reduced exercise capacity. The

development of heart failure also increases the risk of dying in the years following a heart attack.

Standard therapy following a heart attack includes the prescription of an ACE (angiotensin converting enzyme) inhibitor or ARB (angiotensin receptor blocker), with a beta-blocker. Some patients may also receive a tablet called eplerenone which is a mineralocorticoid receptor antagonist. These medications have been shown in previous research to reduce the risk of developing heart failure after a heart attack.

Empagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), is already licensed in the UK for treatment of type 2 diabetes mellitus and for people with symptomatic heart failure. Sodium-glucose cotransporter 2 inhibitors have already been widely researched in 30,000 patients with type 2 diabetes, 7,500 patients with heart failure and 2,000 patients with kidney disease, and found to be beneficial.

A recent large study suggested that empagliflozin reduces the risk of being admitted to hospital or dying in patients with heart failure (with or without type 2 diabetes). However, it is not yet known if empagliflozin will have the same benefit in people who have damage to their heart muscle as a result of a heart attack and are at risk of developing heart failure, since these people were not included in the study.

We wish to test empagliflozin in patients with heart muscle damage caused by a heart attack. We want to find out if adding empagliflozin to standard treatment will reduce the decline in heart muscle function which can occur after a heart attack as this is associated with a reduction in the risk of developing heart failure. We would also like to investigate the effect of empagliflozin on the kidneys as this class of drugs have also been shown to prevent a decline in kidney function over time.

Why have I been asked to take part?

You have been invited to take part in this trial because you have had a heart attack which has caused some damage to your heart muscle, based on the ultrasound scan of your heart (echocardiogram).

Do I have to take part?

No. Your participation is entirely voluntary. Your decision whether or not to participate will not impact on your medical care. If you agree to take part, in addition to this information sheet, you will be asked to sign a consent form. If you decide not to take part, you do not need to tell us why. If you take part, you are free to withdraw at any time and you do not need to give a reason. If you decide to withdraw at any time, or decide not to take part, this will not affect the standard of care you receive.

PART 2: Study Procedures

What will taking part in the study involve?

If you would like to take part in the trial, we will ask you to sign a consent form. We will then perform some tests and collect more information. This will happen on the same day or another day within 14 days of your admission to hospital with a heart attack. Tests and information we will collect will include:

Test	Description
Blood sample	A sample of blood, around 45mLs, will be taken from a vein in your arm. This will be stored and used to measure different blood components which are related to the action of the medication and its effect on the heart muscle and kidneys. With your consent, any samples remaining will be stored for analysis of any future relevant tests as they become available and for use in future ethically approved research studies within and outwith the UK, if appropriate. You should take your usual medications as normal.
Urine sample	To measure the salt, protein and hormone levels in the urine.
Cardiac and renal MRI scan	A magnetic resonance imaging (MRI) scan of the heart and kidneys. This is the best method we have at looking at the heart in detail and making very precise measurements. An MRI does not use any radiation, unlike a CT scan or X-rays. It uses magnets to help take pictures. If you have any metal in your body such as a pacemaker, joint replacements, plates or aneurysm clips, you may not be able to take part. We will discuss this in more detail prior to any MRI scans. The scan will take around 1 hour, and you would need to lie flat on your back for the duration of the scan and follow some instructions to hold your breath at certain points. We will use a dye called Gadolinium, which is injected into a small plastic tube (cannula) which we will put into a vein in your arm for the scan. This helps to highlight areas of the heart which have been damaged.
Medical history	One of the study doctors will speak to you about your symptoms and previous illnesses.
Medication history	We will collect information about your current medications.
Vital signs	Your height, weight, blood pressure and heart rate will be checked.
Physical examination	Your heart and lungs will be examined by one of the study doctors.
Electrocardiogram, or ECG	This is a recording of the electrical activity of the heart. You will probably have had this test before. You will be asked to lie flat on a bed whilst stickers are placed on your chest wall. This test does not involve any discomfort.
Questionnaire	This involves answering questions relating to your quality of life and how your heart health might affect it.

After these tests have been performed, we will remeasure your heart function using the information from the MRI scan. This is because some patients have very rapid recovery of heart muscle damage following a heart attack and we do not think that these patients will necessarily benefit from empagliflozin. If the MRI shows that you have persisting evidence of heart muscle damage then we will randomly allocate you to receive either the test medicine (empagliflozin, 10mg once daily) or a placebo tablet (a tablet that has no medicine in it). You will have a 50:50 chance of being allocated to either treatment group.

This is a "double-blind trial", which means that neither you nor your doctor will know what treatment group you have been allocated to. Use of blinding is common practice in research studies and helps to ensure that the results are unbiased. In an emergency, your study doctor can find out what treatment group you are in.

Study medication

You will be asked to take the study medication once a day in the morning approximately at the same time every day. The medication can be taken with or without food. Tablets should be swallowed whole. If you forget a dose and less than 12 hours have passed since you should have taken it, take it as soon as you remember and then continue to take your next dose at the usual time. If it is more than 12 hours since your dose was supposed to be taken, you should skip this dose and the next dose should be taken as scheduled. You should not take a double dose to make up for a missed dose. If vomiting occurs after the study tablets are swallowed, the dose should not be replaced and the next dose should be taken as scheduled. If you have missed several doses, please contact the trial team for advice.

You will stay on the study medication, as well as standard medication given to people after a heart attack, for the full duration of the study which will be 24 weeks. You will stay on the same dose of the study medication for the duration of the study. If your doctor feels it is necessary, they may ask you to adjust other non-study medications. Sometimes the study doctor may need to contact you by telephone about the study medication. It is important that you always take the study medication as directed and attend each study visit. You should bring back any empty packaging or partially used supplies with remaining tablets at each study visit. If you can remember missing any doses, please inform your study doctor at the visit. You should also let the study doctor know if you have started any new medications, vitamins or mineral supplements, including those purchased yourself.

With your permission, the study treatment may be delivered to your home address by a courier approved by the Sponsors. The contact details we would share with the courier company will be handled with strict confidentiality.

Study visits

We will provide you with a ***study alert card*** at your first visit. You should carry this with you at all times and show it to any doctor or healthcare professional (e.g., nurse, pharmacist) who treats you. This will provide you with details on sick day rules, signs and symptoms of diabetic ketoacidosis (see below) and contact information.

After 2 weeks on the study medication, a member of the study team will call you to ask about any medication changes and check your wellbeing.

Halfway through your involvement in the study (12 weeks) we will ask you to visit the Golden Jubilee National Hospital again to repeat some of the tests done when you joined the trial. This will take place over the course of half a day. We will repeat some of the blood tests you had when you joined the trial and we will provide you with a plastic bottle to take a sample of urine. Your weight, blood pressure and heart rate will be checked. If there are any restrictions

due to the SARS-CoV-2 pandemic at the time of your 12-week visit, this may take place as a telephone visit. Empagliflozin can occasionally cause disturbances in kidney or liver function (see under heading "What are the potential disadvantages and risks of taking part?"). We will therefore check bloods at 12 weeks.

At 18 weeks into the study, a member of the study team will call again to ask about medication changes and check your wellbeing.

Another visit will be repeated at the end of the study (24 weeks) at the Golden Jubilee National Hospital and at that point we will repeat the MRI scan you had at the beginning of the trial. We will repeat some of the blood tests you had when you joined the trial and we will provide you with a plastic bottle to take a sample of urine. We will also repeat a questionnaire about and how your heart health might affect your quality of life.

Please see the attached visit schedule which summarises your involvement in the study.

Should you develop symptoms of heart failure during the trial, such as breathlessness or reduced exercise capacity, we will offer you standard treatment with empagliflozin or a similar drug in the same class as empagliflozin. Your involvement in the trial would end at this point. If you have been in the trial for more than 12 weeks, we will ask you if you would be willing to undergo a second MRI earlier than planned.

Your GP will be informed of your involvement in the trial and will be given contact details for the investigators should they have any questions about your treatment and involvement.

What happens at the end of the study?

After 24 weeks, all participants will stop the study medication after the final study visit. You will return to normal medical care and your doctor will discuss the best treatment options for you. These may be the same as before you started the study. An SGLT2i will only be available at the end of the study if you develop symptoms of heart failure.

What are the possible benefits of taking part?

You may not benefit directly from taking part in the study. However, the information we get from this study may help us to give better treatments to people like you who have suffered a heart attack with heart muscle damage.

What are the potential disadvantages and risks of taking part?

Having a small plastic tube (cannula) inserted into your vein and having blood taken is occasionally uncomfortable. There is a small risk of bleeding, bruising or infection at the puncture site following a blood test or cannula.

Having an MRI scan may cause some people to feel claustrophobic. The dye agent injection used (gadolinium) has rarely caused side-effects (injection site discomfort, rash, itch, nausea and vomiting, dizziness, headaches, numbness (paraesthesia) and low blood pressure). Infrequently, the injection may leak out from the vein to the tissues under the skin (extravasation). Allergic reactions to gadolinium dye agents are uncommon but can be serious.

Treatment with any medication can cause side effects. The known side-effects of empagliflozin are listed below. There may be other unforeseen risks, currently not known.

Frequency	Side effect
Very Common (≥1:10)	• Low blood sugar (hypoglycaemia) when used with sulphonylurea, insulin or another medicine which can cause low blood sugar (**signs include** shaking, sweating, fast heartbeat, excessive hunger or headache) • Dehydration (signs include unusual thirst, dizziness upon standing or fainting)
Common (<1:10 – 1:100)	• Genital infection (such as thrush) • Urinary tract infection, which may be serious (**signs include** burning sensation when passing urine, cloudy urine or pain in pelvis or mid-back) • Thirst • Constipation • Itching • Rash • Increased urination may occur due to the way the study medication works but can also be a sign of urinary tract infection • Blood tests may show increase in blood fat (cholesterol) levels
Uncommon (<1:100 - 1:1000)	• Hives (urticaria) • Swelling underneath the skin (angioedema) • Pain or straining when emptying bladder • Blood tests may show changes in kidney function (creatinine or urea) • Blood tests may show increases in the amount of red blood cells in your blood (haematocrit) • #Ketoacidosis (**signs include** rapid weight loss, feeling sick or being sick, stomach pain, fast and deep breathing, excessive thirst, confusion, tiredness, a sweet smell to your breath)
Rare (<1:1000 - ≥1:10000)	• *Serious infection of the skin of the genitals or the area from the genitals back to the rectum (also known as necrotizing fasciitis of the perineum or Fournier's gangrene) (**signs include** pain or tenderness, redness, or swelling in the genitals or the area from the genitals back to the rectum, which may be associated with a high temperature or a general feeling of being unwell)

#Ketoacidosis is a rare but serious condition that can be life-threatening and deaths have occurred. Ketoacidosis affects people with diabetes (usually type 1, uncommon in type 2) and is due to lack of insulin, causing too much acid and ketones in your blood. It can be triggered by other illnesses or missed doses of insulin treatment (if you take insulin). Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients.

*You must talk to the study doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the

anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier´s gangrene which destroys the tissue under the skin. These symptoms can worsen quickly so if suspected, **study medication must be discontinued** and it is important to obtain treatment immediately. It is more common in men.

Your study doctor will discuss possible side-effects in more detail with you. You should report any side effects as soon as possible using the contact information below.

If you are a woman who could become pregnant:

It is not known if empagliflozin is harmful to the unborn child or if it passes into human breast milk. Therefore, if you are pregnant or breast-feeding, think you may be pregnant, planning to have a baby, or are not willing to use reliable contraception for the duration of the study and for seven days thereafter, you will not be able to take part in this study. If appropriate, we will advise you about contraception before you decide whether to take part in the study.

The study doctor will discuss contraception with you but examples of reliable contraception include:

- Total abstinence when this is in line with your preferred and usual lifestyle
- Female sterilisation or where your partner has already been sterilised
- Use of oral, injected or implanted methods of contraception
- Use of an intrauterine device. These are sometimes called a 'coil'.

A pregnancy test will be performed in women who could become pregnant before starting treatment (visit 1), at visit 3 (week 12) and visit 5 (week 24). If you think you might be pregnant or become pregnant during the study, you should tell the study doctor immediately. You will stop taking the study medicine and will no longer participate in the study, although the study doctor will ask to follow-up on the progress of your pregnancy and health of your baby.

If you are a male whose partner could become pregnant:

With the information currently available there is no indication that men should avoid fathering a child whilst taking the study medicines.

Expenses and payments

You will not receive payments for taking part in this research. We can, however, arrange for a taxi (both directions) to bring you between home and each of the study visits. Alternatively, reasonable travel costs, such as bus fares or mileage (at local rate), plus parking when using a personal vehicle, will be paid for visits which are directly related to participation in the study.

What if new information becomes available?

If any new information becomes available that is relevant to your care, we will inform you. If the research produces incidental findings (previously undiagnosed conditions that are discovered unintentionally) of clinical significance, you will be informed of the results and offered appropriate follow-up and treatment as per current best standard practice.

Will my involvement in the study be kept confidential?

Yes. Your identity will remain confidential at all times and all of your personal information will be processed in accordance with the Data Protection Act 1998 and General Data Protection Regulation (GDPR) (2018). University of Glasgow and NHS Greater Glasgow and Clyde

Health Board are the sponsors for this study based in the United Kingdom and are responsible for looking after your information and using it properly.

Information obtained about you for the purpose of this research will be entered into a secure database held in the University of Glasgow. Your completed consent form for this study will be scanned and an electronic copy will be stored on a separate secure database in the University of Glasgow. Your participation in this study will be noted in your medical records and with your consent your GP will be informed you are taking part in this study. Identifiable information from the study will be stored and protected by the study Sponsors for 25 years after the end of the study.

Once in the study, your information will be identified only by a unique identification number and details about the identification number will be kept in a secure location and access limited to research study staff at your hospital. Any information that leaves the hospital will be anonymised so that you cannot be recognised from it. Certain individuals from The University of Glasgow and NHS Greater Glasgow and Clyde, as Sponsors, and regulatory organisations may look at your medical and research records to check that the research study is being carried out to an appropriate standard. The people who analyse the information from the study will not be able to identify you and will not be able to find out your name, NHS number or contact details.

We ask permission however to retain your name, address and contact details and your Health Service identification number (CHI number) to record information on your health from your health records for 6 months, e.g. if you have needed hospital admission or had any medications changed. This information will only be available to the study team who are all bound by NHS rules on confidentiality.

With your permission, the study treatment may be delivered to your home address by a courier, in which case we would share your contact details with a courier company who would be required to handle this with strict confidentiality.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at https://www.hra.nhs.uk/information-about-patients, or by contacting the study team (contact details below).

What will happen to the results of the research study?

The results of this research study will contribute to the understanding and treatment of patients with heart muscle damage after heart attacks. The results will be communicated through national and international meetings and through publications in cardiology journals. The results will also be reported in Dr Jaclyn Carberry's PhD thesis. Reports or publications resulting from the study will not contain any personal details. On study completion, the research team will provide a lay summary of the results to all participants where appropriate.

Anonymised data from the study will be shared with Boehringer Ingelheim, the Company who manufacture the drug for the study, both for safety reporting to the Regulatory Authorities, and potentially for supplementary support for regulatory submissions, and future development work by the Company. To make the most of the information collected for the study we would also like to be able to share anonymised study data with other researchers and companies in

the future, both within and outwith the UK. No Information will be released through which you could be identified.

What if something goes wrong?

We do not anticipate that anything will go wrong. In the event that something does go wrong, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action for compensation against the sponsor (Greater Glasgow and Clyde Health Board/University of Glasgow), although you may have to cover your own legal costs. If you wish to complain or have any concerns, the normal National Health Service complaints mechanisms are available (Tel: 0141 201 4500, Email:complaints@ggc.scot.nhs.uk).

Who do I contact if I have any concerns?

If you have concerns about any aspect of this study, you can speak to the researchers (office hours are Monday-Friday 9am-5pm). You are encouraged to ask questions at any time during the study.

Who has reviewed the study?

The study has been reviewed and approved by one of the Research Ethics Committees, which has responsibility for scrutinising all proposals for medical research on humans. The Committee has examined the proposal and has no objections from the viewpoint of research ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from the University of Glasgow and NHS Greater Glasgow and Clyde, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

If you have further questions?

The research team will do their best to answer your questions (office hours are Monday to Friday 9am to 5pm). You are encouraged to ask questions at any time during the study. We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study and wish to speak to someone **not** closely linked to the study, please contact Dr Roy Gardener (email roy.gardner@glasgow.ac.uk).

If you have anv further questions about the study, please contact Dr Jaclyn Carberry on or email Jaclyn.Carberry@glasgow.ac.uk.

THANK YOU FOR TAKING THE TIME TO READ THIS LEAFLET AND FOR CONSIDERING TAKING PART IN THE STUDY

Contact information

Dr Jaclyn Carberry, Clinical Research Fellow
Mobile: (Email: Jaclyn.Carberry@glasgow.ac.uk

If you are unhappy about any aspect of the study and wish to make a complaint, you can do this through the NHS Complaints Procedure. For information on our complaints procedures or advice on how to make a complaint:

Tel: 0141 201 4500 Email: complaints@ggc.scot.nhs.uk

We have an independent advisor from the university, who you could approach.
Dr Roy Gardner
Tel: 0141 951 5470 Email: roy.gardner@glasgow.ac.uk

Study Tests	Visit 1 (12 hours to 14 days after heart attack)	Visit 2 (Week 2 ± 4 days)	Visit 3 (Week 12 ± 7 days)	Visit 4 (Week 18 ± 7 days)	Visit 5 (Week 24 ± 4 weeks)
	Face-to-face	Telephone	Face-to-face	Telephone	Face-to-face
Medical history	✓				
Medication history	✓	✓	✓	✓	✓
Vital signs	✓		✓		✓
Physical examination	✓				✓
Questionnaire	✓				✓
Questions on wellbeing		✓	✓	✓	✓
Blood and urine tests	✓		✓		✓
Pregnancy test (if applicable)	✓		✓		✓
ECG	✓				
MRI (heart and kidneys)	✓*				✓

*The MRI could take place on the same day or on a different day from the rest of Visit 1.

Appendix 2 - Informed Consent Form

EMPRESS-MI: Consent Form

University of Glasgow

NHS Greater Glasgow and Clyde

Consent Form

Participant Identification Number: _____

Title: Empagliflozin to prevent worsening of left ventricular volumes and systolic function after myocardial infarction (EMPRESS-MI): a multi-centre, randomized, placebo-controlled trial

Investigators: Professor Colin Berry, Professor Mark Petrie, Dr Kieran Docherty, Dr Jaclyn Carberry

Please *initial* the BOX

I confirm that I have read and understand the Patient Information Sheet dated _____ (version _____) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I give permission for my GP to be made aware of decision to participate in this study.	☐
I understand that my de-identified study data will be stored long term by NHS GGC and stored by the University of Glasgow for data analysis including that this consent form will be uploaded to a separate, secure database in the University of Glasgow Clinical Trials Unit.	☐
I understand that the research team may look at sections of my existing and future health records (hospital and general practitioner) for the purposes of this research. I give my permission for the research team to contact my general practitioner, and to have access to my records.	☐
I understand that de-identified data from the study may be shared with other researchers both in the UK and elsewhere in the world for further analysis.	☐
I understand that de-identified study data will be shared with Boehringer Ingelheim, the manufacturer of the study drug.	☐
I give permission for my contact details to be provided to a courier approved by the Sponsors should my treatment need to be required to be delivered to my home.	☐
If the research produces incidental findings of clinical significance, I will be contacted and given the option to be informed of the results and offered appropriate follow-up and treatment.	☐
I agree to take part in the above study.	☐

Optional

I agree to give permission to store samples of my blood and urine for 10 years so that any new tests, relating to heart function and heart failure, can be evaluated as part of this study and future ethically approved studies within and outwith the UK.	☐ Yes	☐ No

----------	----------	----------
Name of Participant	Date	Signature
----------	----------	----------
Name of Researcher	Date	Signature

1 copy to the patient, 1 copy to the researcher, 1 original for the patient's notes

Appendix 3 - Patient alert card

Patient Alert Card

EMPRESS-MI

Study title: Empagliflozin to prevent worsening of left ventricular volumes and systolic function after myocardial infarction

Study medication: Empagliflozin or placebo

I am currently taking part in a clinical trial

This card contains important safety information and must be carried with you at all times as long as you are participating in the clinical trial.

Show this card to any doctor or other health care professional treating you.

Remember to bring all your study medication to your next appointment.

Version 1.1 04/09/2022
NCT No.: 05020704
EudraCT No.: 2021-006086-38

NHS Greater Glasgow and Clyde

University of Glasgow

Patient Information

Name: _____

Address: _____

Telephone No.: _____

Participant No.: _____

When to seek medical advice

Diabetic ketoacidosis (DKA) is a rare but serious side effect of taking empagliflozin in patients who have type 2 diabetes. If you experience any of the following symptoms you must stop taking the study drug and immediately obtain medical advice. Go to the nearest Emergency Department or telephone NHS 24 on 111.

- Rapid weight loss
- Feeling sick or being sick
- Stomach pain
- Fast and deep breathing
- Excessive thirst
- A sweet smell to your breath
- Confusion or unusual sleepiness

Remember to tell staff you are taking part in this study.

Information For Doctors and Other Healthcare Professionals

THIS PATIENT MAY BE TAKING THE STUDY MEDICATION EMPAGLIFLOZIN.

- Empagliflozin can cause DKA or euglycaemic DKA in patients with type 2 diabetes.
- Stop empagliflozin temporarily before surgical procedures or hospitalisation for serious acute illness. Consider monitoring ketones.
- Assess for DKA if there are signs or symptoms, regardless of the blood glucose. If DKA is suspected, stop the study drug immediately.
- Empagliflozin can cause low blood sugar when used with other medications that lower blood sugar (e.g. gliclazide, insulin). Appropriate adjustment of glucose lowering therapy should be performed according to local guidelines.

Contact information

Study doctor:_____

Study doctor address: _____

Contact telephone number at clinical trial sites: (Office hours only)

_____

Study mobile number: (Office hours only)

_____

If you need urgent advice at other times please contact NHS 24 on 111 or attend your nearest Emergency Department.

Remember to tell staff that you are taking part in this study.

For healthcare professionals only
Emergency unblinding telephone number (24 hour):

_____

Appendix 4 - Letter to General Practitioner

Golden Jubilee National Hospital
Agamemnon Street
Clydebank
G81 4DY

Dear Doctor,

Patient: DOB: CHI:

Address:

Trial: Empagliflozin to prevent worsening of left ventricular volumes and systolic function after myocardial infarction (EMPRESS-MI): a multi-centre, randomised, placebo-controlled trial

Sponsors: NHS Greater Glasgow and Clyde and the University of Glasgow

The purpose of this letter is to inform you that Mr/Miss/Mrs ***** has kindly agreed to participate in a drug trial, in which I am a co-investigator, using the sodium-glucose cotransporter 2 inhibitor (SGLT2i), empagliflozin.

SGLT2i reduce morbidity and mortality in patients with chronic heart failure with reduced ejection fraction (HFrEF) and this benefit may be, in part, due to beneficial effects in reversing adverse left ventricular (LV) remodelling. Patients who develop LV systolic dysfunction following acute myocardial infarction are at a higher risk of developing HF in the months and years following MI. We plan to examine the effect of empagliflozin on LV remodelling following acute MI using sequential cardiac and renal MRI scans, compared with placebo in addition to current standard of care.

Your patient has had an acute MI and has developed a reduced left ventricular ejection fraction ≤40%. They have consented to take part in a randomised, double-blind, placebo-controlled trial in which they will participate for a total of 24 weeks. We plan to perform two cardiac and renal MRI scans (at baseline and at 24 weeks), along with a variety of blood and urine biomarkers pertaining to LV remodelling and kidney function at baseline, 12 weeks and 24 weeks.

All safety monitoring as part of the trial will be performed by the trial investigators based at the Golden Jubilee National Hospital. GPs will not have to perform any extra blood tests or monitoring for the purposes of this trial.

Your patient has been randomised to empagliflozin 10mg once daily or matched placebo. **Please record the study medication as an 'Outside Drug' in the patient record, as part of the EMPRESS-MI clinical trial.** The study medication will be provided to participants by the research team. The patient is asked to continue the study drug and matched placebo (both

once a day) for the duration of the 24 weeks follow-up. The dose of the study medication will remain the same for the duration of the study.

We may adjust background medications to facilitate tolerance of study drug and will inform you of this if required. In patients with type 2 diabetes, blood glucose monitoring, appropriate adjustment of glucose lowering therapy and initiation of medication for the treatment of hyperglycaemia or hypoglycaemia should be performed according to local guidelines.

Patients will continue on optimal standard of care background therapy to treat their index MI and any co-morbid conditions in accordance with local guidelines.

Your patient has been given an "Alert Card" that contains contact details for the study team and information in the event that emergency unblinding is required. It contains information on sick day rules, signs and symptoms of diabetic ketoacidosis (DKA) and contact information.

Very common side effects of SGLT2is include hypoglycaemia and dehydration. Relatively common side effects include urinary tract infections, genital yeast infections, rash and thirst. Uncommon side effects include angioedema. A rare but serious side effects are DKA in patients with diabetes, and necrotising fasciitis of the perineum (Fournier's gangrene). **Please contact the trial investigators if any possible side effects occur.**

As empagliflozin use is not recommended in pregnancy, women of child-bearing potential can only participate provided they are willing to use highly effective forms of contraception for the duration of the trial and for seven days thereafter.

At the end of the 24-week trial the study drug will be withdrawn and you will be informed in writing of the patient's completion of the trial. Should your patient develop symptomatic heart failure at any point during their involvement in the trial, they will discontinue the study drug and be offered open-label SGLT2i. If more that 12 weeks have passed since they were randomised, they will be asked to partake in an end-of-study MRI scan.

If you have any queries about the contents of this letter, or if any issues arise during the trial, please do not hesitate to contact me. A copy of the patient information leaflet is included for further information and for the patient's notes.

The patient is aware that I have informed you of their inclusion in the trial.

Yours Sincerely,

Dr Jaclyn Carberry *on behalf of* Professor Colin Berry, Professor Mark Petrie and Dr Kieran Docherty

Mobile: Email: Jaclyn.Carberry@glasgow.ac.uk

Appendix 5 - Typical imaging parameters for cardiovascular magnetic resonance

	Cine	T1	T2	T2*	Perfusion	LGE
Orientation	VLA, HLA, LVOT SA stack	HLA Mid SA	HLA Mid SA	HLA Mid SA	HLA Base, mid, apex SA	VLA, HLA, LVOT SA stack
Sequence	TrueFisp	TrueFisp	TrueFisp	Gre	TrueFisp	TrueFisp
Breath-hold	7 secs	10 secs	8 secs	14 secs	-	-
TR, ms	44.10	278.84	193.27	824.00	150.20	904.00
TE, ms	1.23	1.13	1.02	1.22 (TE1)	1.04	1.20
Flip angle, °	80	35	70	18	50	50
Field of view, mm*mm	340x276	360x306	360x288	360x270	360x360	360x270
Matrix	187x256	144x256	116x192	104x160	147x192	144x256
Slice thickness, mm	8	8	8	8	8	8
Slice gap, mm	0	-	-	-	16	0
Voxel size, mm^3	LA 1.3x1.3x6 SA 1.3x1.3x8	1.4x1.4x8	1.9x1.9x8	2.3x2.3x8	1.9x1.9x8	1.4x1.4x8
Number of slices	20	2	2	2	4	16
Acceleration	GRAPPA 2	GRAPPA 2	GRAPPA 2	GRAPPA 4	GRAPPA 3	GRAPPA 2
Acquisition time, min:sec	6:00	0:30	00:26	00:38	1:10	5:30
Bandwidth, Hz/px	930	1085	1184	1078	1085	977
ECG gating	Retrospective	Prospective	Prospective	Prospective	Prospective	Prospective

Appendix 6 - Typical imaging parameters for kidney magnetic resonance

	T1	T2	T1 VIBE
Orientation	Coronal	Coronal	Axial
Sequence	TrueFisp	TrueFisp	VIBE
Breath-hold	14 secs	10 secs	15 secs
TR, ms	358.36	255.25	3.76
TE, ms	1.09	1.04	1.81
Flip angle, °	35	70	5
Field of view, mm*mm	400x400	400x400	400x312.5
Matrix	170x256	144x192	225x384
Slice thickness, mm	8	8	3
Slice gap, mm	-	-	0.6
Voxel size, mm^3	1.6x1.6x8	2.1x2.1x8	1x1x3
Number of slices	1	1	72 per slab
Acceleration	GRAPPA 2	GRAPPA 2	CAIPIRINHA 2
Acquisition time, min:sec	00:14	00:10	00:15
Bandwidth, Hz/px	1085	1184	500
ECG gating	Prospective	Prospective	None

Appendix 7 - EuroQol 5-Dimension 5-Level questionnaire

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

1 I have no problems in walking about
2 I have slight problems in walking about
3 I have moderate problems in walking about
4 I have severe problems in walking about
5 I am unable to walk about

SELF-CARE

1 I have no problems washing or dressing myself
2 I have slight problems washing or dressing myself
3 I have moderate problems washing or dressing myself
4 I have severe problems washing or dressing myself
5 I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

1 I have no problems doing my usual activities
2 I have slight problems doing my usual activities
3 I have moderate problems doing my usual activities
4 I have severe problems doing my usual activities
5 I am unable to do my usual activities

PAIN / DISCOMFORT

1 I have no pain or discomfort
2 I have slight pain or discomfort
3 I have moderate pain or discomfort
4 I have severe pain or discomfort
5 I have extreme pain or discomfort

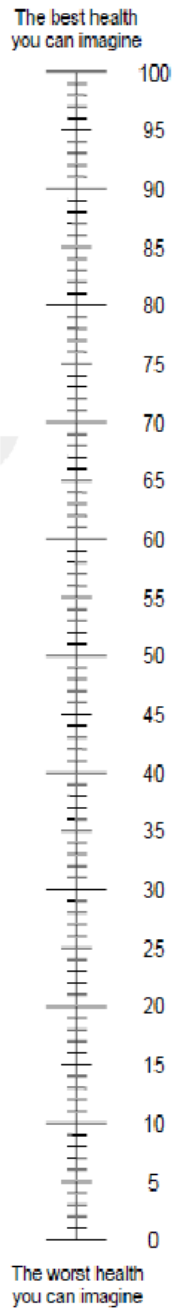
ANXIETY / DEPRESSION

1 I am not anxious or depressed
2 I am slightly anxious or depressed
3 I am moderately anxious or depressed
4 I am severely anxious or depressed
5 I am extremely anxious or depressed

Health Questionnaire (EQ-5D-5L)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY = ☐



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