Dissertation

Modern Anti-Diabetics in Cardiovascular Disease

submitted by

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Res. Prof. Priv.-Doz. Dr. Dr. Markus Wallner

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used.
Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz”.

30th of November 2024 Dr. med. univ. Martin Benedikt eh.

Disclosures

This doctoral thesis forms the basis for four publications: three of them are post-hoc analyses of the EMMY trial, and one is the ERASe trial. I acted as the first author of three original articles and as a co-author of a fourth original article. Data, tables, and figures from the manuscripts that I authored or co-authored were included in this thesis or reconstructed to better illustrate the results. Parts of the manuscripts were incorporated into this thesis and are marked with specific symbols (*, #, ×, °), with corresponding information provided in the footer. A list of publications and additional information, including affiliations, is included below.

List of Publications and Affiliations

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I will never forget it.

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Abbreviations and Definitions

ACC	Acetyl-CoA Carboxylase
ACE-I	Angiotensin converting enzyme inhibitor
AE	Adverse event
AHA	American heart association
AGE	Advanced glycation end-product
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AMI	Acute myocardial Infarction
AMPK	adenosine-monophosphate kinase
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor and neprilysin inhibitor
AS	Atherosclerosis
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATP	Anti-tachycardiac pacing
BB	Betablocker
BCKD	Branched-chain α-keto acid dehydrogenase complex
BCL	B-cell lymphoma
BH4	Tetrahydrobiopterin 4
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CaMKII	calmodulin-dependent protein kinase II
CCB	Calcium channel blockers
CD68	Cluster of differentiation 68
CI	Confidence interval
CIMCL	Clinical institute for medical and chemical laboratory diagnostics
CK	Creatinine kinase
CK-MB	Creatinine kinase muscle-brain

CMR	Cardiac magnet resonance tomography
CPA	Cardiac Performance Analysis
CPT	Carnitine palmitoyl transferase
CV	Chamber view
CVD	Cardiovascular disease
CRT	Cardiac resynchronisation therapy
DICOM	Digital Imaging and Communications in Medicine
DNA	Desoxyribonucleic acid
DPP4	Dipeptidyl peptidase inhibitor 4′
eGFR	estimated glomerular filtration rate
EC	Enterochromaffin cells
ECG	Electrocardiogram
ESC	European Society of Cardiology
EMMY	Empagliflozin in acute myocardial infarction
ERASe	Ertugliflozin to reduce arrhythmic burden in ICD±CRT patients
FAC	Fractional area change
FFA	Free fatty acids
FS	Fractional shortening
GCH1	Guanosine triphosphate cyclohydrolase 1
GGT	Gamma-glutamyl transferase
GLP1	Glucose-like peptide 1
GLS	Global longitudinal strain
GLUT2	Glucose transporter 2
GSK-3ß	Glycogen synthase kinase-3 beta
HbA1c	Haemoglobin A1C
HDL	High-density lipoprotein
HF	Heart failure
HFH	Hospitalisations for heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
hsCRP	high-sensitive C-reactive protein
HR	Hazard ratio

ICD	Implanted cardioverter-defibrillator
ICH GCP	International Conference on Harmonization for Good Clinical Practice
IL	Interleukin
IQR	Interquartile range
ITT	Intention-to-treat
LAD	Left anterior descending
LAVI	Left atrial volume index
LBBB	Left bundle branch block
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LKB1	Liver kinase B1
LMEM	Linear mixed effect models
LV	Left ventricle
LVEDD	Left ventricular end-diastolic diameter
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVESV	Left ventricular end-systolic volume
LVFS	Left ventricular fractional shortening
LVM	Left ventricular mass
MACE	Major adverse cardiovascular events
MAP	Mean arterial pressure
MDA	Malondialdehyde
MI	Myocardial infarction
mmHg	millimetre of mercury
MO-LDL	Minimally oxidized low-density lipoprotein
MRA	Mineralocorticoid receptor blocker
mRNA	messenger ribonucleic acid
ms	Milliseconds
MUG	Medical University of Graz
mV	Millivolt
NF-κB	Nuclear k light-chain-enhancer of activated B-cells

NH4+	Ammonium hydrogen carbonate
NHE	N+/H+ exchanger
NLR	Neutrophil-to-lymphocyte ratio
NOS	Nitric oxide synthase
NOX	Nicotinamide-adenindinucleotidephosphat Oxidase
NSTEMI	non-ST-elevation myocardial infarction
nsVT	non-sustained ventricular tachycardia
NT-proBNP	N-terminal pro-brain natriuretic peptide
OHB	Hydroxybutyrate
OR	Odds ratio
PCI	Percutaneous coronary intervention
PCG	Peroxisome proliferator-activated receptor coactivator
PLR	Platelet-to-lymphocyte ratio
PW	Posterior wall
RAAS	Renin angiotensin aldosterone system
RISK	Reperfusion injury salvage kinase
ROS	Reactive oxygen species
RPP	Rate-pressure product
RR	Rate ratio
RR	Riva Rocci
RV	Right ventricle
SAE	Serious adverse events
SCOT	Succinyl-CoA 3 oxoacid CoA-transferase
SEM	Standard error of mean
SD	Standard deviation
SGLT-I	Sodium-Glucose-Cotransporter-2-inhibitor
SLC	Solute carrier family
SMA	Smooth muscle actin
SOD	Superoxide dismutase
STAT	Signal transducer and activator of transcription
STEMI	ST-elevation myocardial infarction
SV	Stroke volume
TAPSE	Tricuspid annular plane systolic excursion

Tn	Troponin
TUNEL	Terminal deoxynucleotidyl nick-end labelling
T2DM	Type-2 diabetes mellitus
sVT	Sustained ventricular tachycardia
VF	Ventricular Fibrillation
WD	Western diet
WHO	World Health Organization

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Zusammenfassung

Einführung:
Die klinische Studie „Empagliflozin bei akutem Myokardinfarkt“ (EMMY) zeigte erstmals positive Effekte von Empagliflozin auf kardiale Parameter, doch fehlen Daten hinsichtlich der Effekte auf Inflammation, echokardiographische Parameter sowie Arrhythmien. Ziel dieser Arbeit ist es, Effekte von Natrium-Glukose-Cotransporter-2 Hemmer (SGLT2-I) auf Entzündungsmarker, echokardiographische Parameter und Arrhythmielast zu analysieren und zu untersuchen, ob initiale Elektrokardiogramm (EKG) -Werte prädiktiv für Veränderungen kardialer Marker nach akutem Myokardinfarkt (AMI) sind.

Methoden:
Im Rahmen dieser Dissertation wurden drei separate Analysen der EMMY-Studie durchgeführt, in denen Effekte von Empagliflozin auf Entzündungswerte und spezifische echokardiographische Veränderungen sowie der Einfluss von initialen EKG-Werten auf kardiale Marker nach AMI untersucht werden. „**E**rtugliflozin zur **R**eduktion der **A**rrhythmiela**S**t in ICD±CRT-Patienten“ (ERASe) untersucht Effekte von Ertugliflozin auf die Inzidenz von Arrhythmien bei chronischer Herzinsuffizienz.

Ergebnisse:
Die Analyse der Entzündungsmarker zeigte einen signifikanten Rückgang nach AMI, jedoch ohne Unterschiede zwischen den Gruppen. Nach 26 Wochen waren die linksventrikulären Volumina unter Empagliflozin signifikant reduziert, während die Herzfunktion nur positive Trends aufwies, unabhängig von initialen EKG-Parametern. In der ERASe-Studie zeigte sich unter Ertugliflozin eine geringere Inzidenz ventrikulärer Tachykardien und Kammerflimmern, sekundäre Endpunkte ergaben keine Unterschiede.

Schlussfolgerung:
Obwohl SGLT2-Inhibitoren pleiotrope Wirkungen zeigen, wurde in dieser Arbeit lediglich eine strukturelle Verbesserung unter Empagliflozin nach AMI festgestellt, die nicht primär auf eine reduzierte Entzündungsreaktion zurückzuführen ist. ERASe liefert erstmals Daten für eine signifikante Verringerung der Arrhythmielast durch Ertugliflozin und könnte dahingehend eine neue und vielversprechende Therapie in diesem Bereich darstellen.

Abstract

Introduction

The clinical study "Empagliflozin in Acute Myocardial Infarction" (EMMY) was the first to demonstrate positive effects of empagliflozin on cardiac parameters. However, data regarding its effects on inflammation, echocardiographic parameters, and arrhythmias are lacking. The aim of this work is to analyse the effects of sodium-glucose cotransporter-2 inhibitors (SGLT2-I) on inflammatory markers, echocardiographic parameters, and arrhythmic burden, and to investigate whether initial electrocardiogram (ECG) values are predictive of changes in cardiac markers following acute myocardial infarction (AMI).

Methods:

As part of this dissertation, three separate analyses of the EMMY study were conducted, examining the effects of empagliflozin on inflammatory markers, specific echocardiographic changes, and the impact of initial ECG values on cardiac markers after AMI. The study "Ertugliflozin for the Reduction of Arrhythmic Burden in ICD±CRT Patients" (ERASe) investigated the effects of ertugliflozin on the incidence of arrhythmias in patients with chronic heart failure.

Results:

The analysis of inflammatory markers showed a significant decrease after AMI, with no differences between the groups. After 26 weeks, left ventricular volumes were significantly reduced under empagliflozin, while cardiac function showed only positive trends, regardless of initial ECG parameters. In the ERASe study, ertugliflozin was associated with a lower incidence of ventricular tachycardias and fibrillation, while secondary endpoints showed no differences.

Conclusion:

Although SGLT2 inhibitors exhibit pleiotropic effects, this work demonstrated structural improvements under empagliflozin after AMI, which are not primarily attributable to a reduced inflammatory response. The ERASe study provides the first data showing a significant reduction in arrhythmic burden with ertugliflozin, suggesting it could represent a new and promising therapeutic approach in this area.

1 Introduction

1.1 Acute Myocardial Infarction

1.1.1 Definition

The term “Acute Myocardial Infarction (AMI)” is defined by the World Health Organization (WHO) as the presence of myocardial cell necrosis due to a significant and sustained ischemia of the myocardium (1) detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia (2).
The primary mechanism of acute myocardial infarction is a ruptured atherosclerotic plaque in the coronary arteries, precipitating thrombus formation, followed by a total occlusion of the vessel and loss of oxygen supply to the myocardium (3).
AMI is the most severe clinical presentation of coronary artery disease (CAD) (4), and complications range from functional forms such as heart failure, cardiogenic shock, and arrhythmias to structural forms like wall ruptures, septal defects, papillary muscle rupture, thrombus formation, aneurysm, pericarditis and pericardial effusion/tamponade (5).

1.1.2 Extent of the Problem

Ischemic heart disease is the most common cause of death worldwide accounting for 1.8 million deaths (20% of all death in Europe), and its prevalence is increasing annually. However, a trend in reduction has been observed in Europe over the last decades, especially in Central and Eastern Europe (6–8). The global prevalence of AMI in individuals was estimated at about 3.8% in individuals <60 years and with 9.5% for individuals >60 years (9). Currently, more than 6 million new patients suffer from cardiovascular disease (CVD) in Europe mainly driven by an increase in potential risk factors over decades, like smoking, obesity, diabetes, hypertension, alcohol consumption, and dyslipidaemia. Given the fact that 49 million people suffer from cardiovascular disease, the EU economies face costs up to €210 billion per year (10).
In Austria, the incidence for AMI in 2019 was estimated at approximately 19 000 cases with a 2.2x higher rate in males and the elderly. Over the last two decades, a decrease of

25% in the incidence of AMI in Austria was observed compared to 2003. The prevalence of AMI in Austria was estimated at 124 000 cases (1.7%) in 2019, with a 2x higher prevalence in males and the elderly (11). The mortality was estimated with 1 003 cases in 2022, whereas 34.5% of all patients died from cardiovascular disease (12).

The costs of cardiovascular diseases in Austria were estimated at around 4.7 billion euros in 2015, including 1.7 billion in inpatient care, 600 million in drug treatment, 1.2 billion for production losses due to mortality and morbidity, and around one billion for informal care for people with CVD (11).

1.1.3 Physiology of Coronary Blood Flow

The oxygen supply to the heart is ensured by the epicardial and intramural coronary arteries. During systole, the coronary arteries get compressed by myocardial contraction and even more with greater force exerted on the intramural arteries than on the epicardial layers. Conversely, during relaxation the coronary arteries are no longer compressed resuming in an adequate coronary blood flow. Both systole and diastole, depend on the contractility of the myocardium, the heart rate as well as vascular resistance and can be influenced by intrinsic and extrinsic factors resulting in an imbalance between oxygen supply and oxygen demand, potentially leading to coronary insufficiency and myocardial hypoxemia (13). At rest, about 60 to 70% of the oxygen is utilized by the heart for coronary perfusion and can be increased up to 20-fold in exercise by changes in heart rate, contractility and coronary artery resistance highlighting the high metabolic activity of the myocardium (14).
Oxygen and carbon dioxide seem to play an important role in the regulation of the coronary blood flow by provoking a vasodilation in the presence of hypoxemia and hypercapnia during exercise (15).
Nitric oxide has also been identified as causing coronary vasodilation in the presence of increased endothelial shear stress, stimulating nitric oxide synthesis, and being positively influenced by prostacyclin through indirect interactions with nitric oxide (13).
Adrenergic receptors are distributed throughout the coronary arteries with a greater number of alpha receptors in epicardial coronary arteries and a higher concentration of beta-2

receptors located in the intramural coronary arteries. Both receptors play an important role in the physiological regulation of the coronary blood flow (15).
Adenosine has also been reported to have potential in coronary vasodilation, but it was only identified as being released by ischemic myocardium during coronary insufficiency and seems to have no essential role in the physiological regulation of coronary blood flow (15). ATP-dependent potassium channels located in the smooth muscle cells of coronary arteries have also been reported to participate in the vascular tone; however, inhibition of these channels results in enhancing vasodilation by indirectly releasing adenosine (16). Endothelin has been found to be a potent vasoconstrictor of coronary arteries and is highly elevated in coronary pathologies (17).

1.1.4 Pathophysiology – From Atherosclerosis to Myocardial Infarction

Atherosclerosis (AS) is a chronic inflammatory disease of the arterial wall, and atherosclerotic plaques, when ruptured, are the primary underlying cause of acute myocardial infarction. However, the development of AS is a complex process with many important underlying steps (18).

The presence of pro-atherosclerotic risk factors causes endothelial dysfunction or damage, followed by an increase in endothelial permeability. Low-density lipoproteins (LDL) have been identified as playing a major role in the pathogenesis of atherosclerosis by being integrated into the connective tissue of the intima layer (19), whereas HDL has an athero-protective effect (20). Endothelial lipoxygenase and myeloperoxidase initiate the oxidation of the LDL into the cytotoxic, proinflammatory, chemotactic, and proatherogenic “minimally oxidized LDL” (MO-LDL) via reactive oxygen species, after which it cannot be cleared. (21,22).

The irreversible accumulation of minimally oxidized lipoproteins in the intimal connective tissue stimulates the formation of various chemokines (MCP-1, IL-8) (22,23) as well as cell adhesion molecules (VCAM-1, ICAM-1, E- and P-selectin) (24–26) expressed on endothelial cells, thereby promoting the migration of T-lymphocytes and monocytes, as

well as their differentiation into macrophages (27). The immigrated inflammatory cells induce the formation of additional cytokines, extracellular matrix components, and growth factors.

Via reactive oxygen species and enzymes, minimally oxidized LDL is further oxidized to "highly oxidized LDL", which is subsequently aggregated and taken up by macrophages via scavenger receptors (foam cells). Since foam cells are poorly able to process the highly oxidized LDL, it accumulates intracellularly, and leads to cell death followed by the release of lipids and debris (28).

Cell death induces the release of cellular mediators leading to the immigration of additional lymphocytes and macrophages as well as the formation of the pro-inflammatory substance interferon gamma, which triggers an inflammatory process in the lipid plaque (29–31). This inflammatory process stimulates the formation of other inflammatory mediators (cytokines, interleukins, growth factors), resulting in the migration and proliferation of smooth muscle cells and secretion of extracellular matrix leading to the development of a stable fibrinous cap (30).

The continuous release of interferon gamma leads to increasing plaque instability by inhibiting the production of extracellular matrix in smooth muscle cells. In addition, lysosomal enzymes such as collagenases are secreted by macrophages, which increases the risk of plaque rupture as supporting components of the cell membrane are broken down (32).

Finally, when the vulnerable plaque is ruptured, the tissue factor of the subendothelial connective tissue comes into direct contact with the blood, promoting the activation of extrinsic coagulation and the formation of thrombi, resulting in occlusion of the coronary artery and myocardial cell death (33).

1.1.5 Classification of Acute Myocardial Infarction

Based on the clinical presentation, pathophysiological mechanisms, and prognostic differences, the European Society of Cardiology (ESC) has defined five types of AMI:

Myocardial Infarction Type 1:

Type MI 1 is defined by the presence of a pre-existing, vulnerable, atherosclerotic plaque in one or more coronary arteries, which eventually erodes, ulcerates, or ruptures, providing the basis for distal thrombus formation. The ruptured surface activates the coagulation cascade and the release of various mediators, leading to a focal or diffuse coronary spasm, which also promotes myocardial ischemia. The clot causes hypoxic myocardial damage by occlusion of the coronary arteries and can subsequently also migrate as an embolus into peripheral sections of the coronary arteries (2).

Myocardial Infarction Type 2:

Type 2 MI is classified by hypoxic myocardial damage caused by an imbalance between oxygen demand and supply. Aetiology can include drug toxicity, arrhythmias, tachycardia, hypotension, shock, bleeding, anaemia, stress, coronary artery dissection, endothelial dysfunction, severe hypertension, coronary spasm, and respiratory failure. In addition, the presence of atherosclerotic plaques in one or more coronary vessels may precede the ischemia (2).

Myocardial Infarction Type 3:

This specific kind of MI includes people who die of sudden cardiac death with clinically typical symptoms of a myocardial infarction and new ECG changes or ventricular fibrillation before cardiac biomarkers can be taken, or abnormal values can be measured, or an autopsy confirming the presence of myocardial infarction is performed (2).

Myocardial Infarction Type 4 and 5:

Type 4 and 5 MI represent all kinds of myocardial damage with an increased troponin value above the 99th percentile, associated with cardiac intervention (2):

- Type 4a myocardial infarction: PCI-related myocardial infarction
- Type 4b myocardial infarction: PCI-associated stent thrombosis

• Type 4c myocardial infarction: PCI-associated restenosis
• Type 5 myocardial infarction: CABG-related myocardial infarction

1.1.6 Diagnosis of Acute Myocardial Infarction

Based on the electrocardiographic findings, the AMI is divided into two categories: the ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI). Although the presence of typical ECG changes is highly suspicious for acute myocardial infarction, the absence of STEMI criteria does not rule out an occluded coronary culprit lesion. Therefore, a new classification of suspected ACS has been defined, dividing into occlusion myocardial infarction (OMI) and non-occlusion myocardial infarction (NOMI). OMIs include all total or subtotal coronary occlusions with insufficient collateral circulation resulting in AMI (AMI type I), whereas NOMIs are defined by the absence of occlusion and sufficient collateral circulation of the coronary lesions (AMI and II) (34).
When an acute myocardial infarction is suspected an immediate electrocardiogram within the first 10 minutes of presentation with typical clinical symptoms, and its interpretation should follow as soon as possible (35,36), given the fact that early initiation of reperfusion strategies improves cardiovascular outcome in STEMIs (37).
Based on the fourth universal definition of acute myocardial infarction, ST-elevating myocardial infarction is defined as ST-segment elevation of ≥2.5 mm in men < 40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V2–V3 and/or ≥1 mm in the other leads (measured at the J-point) (2). Isolated ST-depressions in the precordial leads V1-V3 might suspect posterior MI and therefore, the posterior chest wall leads V7-V9 need to be considered. In addition, patients suffering from inferior AMI right, precordial leads (V3R, V4R) should be considered to detect right ventricular infarction (2).
Exceptionally, a new onset left bundle branch block (LBBB) or the detection of ST-elevations in patients suffering from pre-existing (LBBB) in the presence of the typical clinical symptoms of AMI is often difficult and the diagnosis workup follows specific criteria (Sgarbossa criteria) (38).
NSTEMIs rarely present with typical electrocardiographic pattern but could be suspected when suffering fromin patients with typical symptoms and ST-segment depressions or T-

wave inversions in the initial ECG. However, NSTEMI diagnosis is confirmed by detecting elevated serum troponin levels (2).
Blood samples should be taken as soon as possible when patients present with typical symptoms of AMI, as they may be useful in the diagnostic workup. In STEMIs, highly elevated troponin levels are useful for estimating the myocardial damage, whereas in NSTEMIs it plays an important role in initial diagnosis However, obtaining blood samples should not delay reperfusion therapy when a typical AMI pattern is present (2).

1.2 Chronic Heart Failure

1.2.1 Definition and Classification

Left ventricular dysfunction is the most common complication in patients with acute myocardial infarction, leading to heart failure (HF), and remains a powerful predictor of mortality (39,40).

Chronic heart failure is no specific disease but rather a clinical syndrome characterized by typical signs and symptoms of heart failure, structural and functional cardiac changes (reduced cardiac output, elevated filling pressure) and elevated NT-proBNP levels (41). Based on the left ventricular ejection fraction, heart failure is classified into three categories:

- Heart failure with reduced ejection fraction (HFrEF), defined as an LVEF ≤40%
- Heart failure with mildly reduced ejection fraction (HFrEF), defined as an LVEF 41%-49%
- Heart failure with preserved ejection fraction (HFpEF), defined as an LVEF ≥50% but with elevated diastolic filling pressures
- Heart failure with improved ejection fraction (HFimpEF): chronic heart failure defined as an LVEF ≤40% and a ≥10% increase from baseline, with a second measurement showing an LVEF ≥40%. (41)

The diagnostic work-up of heart failure begins with identifying typical clinical signs (ankle swelling, breathlessness, fatigue) and symptoms (peripheral oedema, pulmonary crackles, elevated jugular venous pressure). When HF is suspected, BNP/NT-proBNP should be measured and, when elevated (BNP ≥35pg/mL, NT-proBNP ≥125pg/mL), an echocardiography should be performed. Conversely, if BNP/NT-proBNP levels are within normal range, heart failure is unlikely. Based on structural and functional echocardiogram findings, the diagnosis of heart failure is confirmed and classified into the appropriate category based on the LVEF (42).

1.2.2 Pharmacological Therapy

Numerous pharmacological options for the treatment of chronic heart failure have been approved in recent decades and have been successfully established for the acute management of post-myocardial infarction to further reduce myocardial damage in the acute setting, as well as to mitigate functional and structural changes. Studies suggest that the early initiation of these therapies after myocardial infarction has shown beneficial effects on major adverse cardiovascular events and mortality.

Angiotensin Converting Enzyme Inhibitor (ACE-I):
Several large clinical outcome trials have shown significant reduction in mortality and improved cardiovascular outcomes with the initiation of ACE inhibitors (ACE-I) after acute myocardial infarction (AMI). The first trial to show these effects was the SAVE trial with captopril, which demonstrated a 19% reduction in mortality in patients with myocardial infarction and left ventricular dysfunction, as well as a reduction in both fatal and nonfatal major cardiovascular events, including a 21% risk reduction for death from cardiovascular causes, a 37% reduction in the development of severe heart failure, and a 25% reduction in recurrent myocardial infarction compared to placebo (43). Based on these findings, two clinical trials were conducted for trandolapril (TRACE-trial) as well as ramipril (AIRE-trial) reporting a significant improvement of cardiovascular outcomes if initiated early after acute myocardial infarction (44,45). A large meta-analysis of four major randomized, placebo-controlled clinical outcome trials, including approximately 100,000 patients, highlighted the beneficial effects of ACE inhibitors (ACE-I) on long-

term survival, with 85% of the effect occurring within the first seven days after myocardial infarction, particularly in anterior AMI and in patients at increased risk of death (46). Therefore, ACE-I were implemented as a standard treatment in patients following acute MI (47) and have a Class IA recommendation for the treatment of chronic heart failure with reduced ejection fraction (HFrEF) (48).

Angiotensin II Receptor Blockers (ARB):

In line with the ACE-I outcome trials, two large clinical outcome trials reported beneficial effects of ARBs post MI. The first, the VALIANT trial, evaluated valsartan, captopril and combined (valsartan + captopril) in high-risk patients post MI. The trial demonstrated the non-inferiority of valsartan compared to captopril (HR 1.00; CI 0.90–1.11; p=0.98), however, combining valsartan and captopril increased the incidence of adverse events without improving survival (49). In the OPTIMAAL trial, the ARB losartan was identified to be non-inferior to captopril regarding morbidity and mortality in high-risk AMI but was significantly associated with a lower rate of discontinuation (50). Thus, ARBs were also implemented in the treatment for AMI (47) and have a Class IA recommendation for the management of chronic heart failure with reduced ejection fraction (HFrEF), when ACE-I are not tolerated (48).

Angiotensin/Neprilysin Receptor Inhibitor (ARNI):

The angiotensin-neprilysin inhibitor Sacubitril/Valsartan has proven to be a milestone in the treatment of chronic heart failure with reduced ejection fraction, demonstrating a significant reduction in cardiovascular death and hospitalisation for heart failure compared to enalapril (51). Based on the findings of the PARADIGM trial, the ARNI received a Class IB recommendation for the treatment of HFrEF (48). Furthermore, the PIONEER-HF trial demonstrated a significant reduction in NT-proBNP concentrations in acute decompensated heart failure for ARNI compared to enalapril (52). The PARADISE-MI trial is the first clinical trial to investigate the effects of Sacubitril/Valsartan in patients with acute myocardial infarction and reduced left ventricular ejection fraction. However, the trial failed to demonstrate a significantly lower incidence of death from cardiovascular causes or incident heart failure compared to ramipril (53).

Betablocker (BB):

Early administration of intravenous metoprolol in patients presenting with AMI did not show a relevant reduction in infarct size, however, a significant reduction in malignant arrythmias was observed compared to placebo (3.6% vs. 6.9%; p = 0.05) (54).
In long-term therapy, Metoprolol was identified to significantly reduce all-cause mortality, cardiovascular mortality, ventricular fibrillation, and non-fatal myocardial infarction in patients post-myocardial infarction and left ventricular systolic dysfunction compared to placebo (55,56). Regarding the optimal timing of initiation of beta-blocker therapy, a large analysis reported a survival benefit when administered within 24 hours compared to delayed application (57). However, it must be acknowledged that treatment with beta-blockers may increase the risk of developing cardiogenic shock due to their negative chronotropic and inotropic effects and is therefore restricted in hypotonic or bradycardic patients (55). Thus, beta-blockers received a Class IA recommendation for the treatment of HFrEF and should be administered to patents presenting with AMI within the first 24 hours (42,47). Although beneficial effects of these substances were reported, data for betablockers following AMI is primarily from the pre-reperfusion era and evidence supporting the continuation of beta-blockers after AMI remains scarce. The ABYSS trial demonstrated a non-inferiority of betablocker continuation compared to betablocker interruption regarding quality of life and the composite endpoint of death, nonfatal MI, nonfatal stroke, and hospitalisation in patients following AMI with an LVEF of at least 40% (58). The same holds true for patients receiving long-term therapy with beta-blockers following AMI with preserved LVEF, showing non-inferiority for the composite endpoint of death from any cause and new AMI compared to non-beta-blocker users (59).

Mineralocorticoid Receptor Blocker (MRA):

Early treatment with eplerenone in patients without heart failure post-MI reduced the composite endpoint for cardiovascular mortality, re-hospitalisation, or extended initial hospital stay in STEMI patients up to 13 months (HR 0.58; CI 0.45–0.76; p < 0.0001). This effect was primarily driven by a significant reduction in BNP/NT-proBNP levels (60). On the other hand, eplerenone was shown to significantly reduce mortality, the rate of death from cardiovascular causes, and hospitalisation for cardiovascular events in AMI complicated by left ventricular dysfunction (LVEF <40%) and heart failure. Furthermore, cardiovascular mortality, the rate of death from any cause, and overall hospitalisation were

significantly lower in the eplerenone group compared to placebo (61). Similar results were observed for spironolactone in the STEMI subgroup of the ALBATROSS trial, but no beneficial effects were detected with early initiation in NSTEMIs compared to placebo (62). In patients with heart failure and preserved ejection fraction, spironolactone did not reduce the composite endpoint of death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for heart failure (63). Thus, MRAs received a Class IA recommendation for patients with chronic heart failure and reduced ejection fraction (48).

SGLT2 Inhibitor (SGLT2-I):

SGLT2-I have been shown to significantly reduce cardiovascular endpoints, regardless of the presence or absence of diabetes mellitus. The first trial to demonstrate this was the EMPA-REG OUTCOME trial, which revealed a significant reduction in the composite endpoint for cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalisation for heart failure in people with diabetes (64). Two subsequent clinical trials further identified beneficial effects of Empagliflozin (65) and Dapagliflozin (66) on cardiovascular outcomes in HFrEF, independent of diabetic status. Similar results were identified for Empagliflozin (67) and Dapagliflozin (68) in patients with chronic heart failure with mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF).

Based on these findings, SGLT2-I received a Class IA recommendation from the AHA/ACC/HFSA and ESC for the treatment of patients with HFrEF (48,69) More recently, they maintained a Class IA recommendation for use in HFmrEF and HFpEF to reduce the risk of HF hospitalisation or CV death (69,70).

However, no clinical data has been available so far reporting beneficial effects of SGLT2-I in acute myocardial infarction. The only data demonstrating the effects of SGLT2-I in AMI comes from the EMBODY trial, which showed beneficial effects of Empagliflozin on NT-proBNP levels after the acute phase, focusing on sympathomimetic activity compared to placebo (71). The EMMY trial successfully filled the evidence gap by being the first clinical trial worldwide to highlight a significant reduction in NT-proBNP levels, as well as improvements in functional and structural cardiac parameters for Empagliflozin compared to placebo (72). DAPA-MI trial was the first large clinical outcome trial powered for hard clinical endpoints reporting significant beneficial effects on cardiometabolic outcomes for Dapagliflozin compared to placebo. However, no impact on the composite endpoint of cardiovascular death or hospitalisation for heart failure was

observed post-MI compared to placebo (73). The recently published EMPACT-MI trial investigated the effects of Empagliflozin on the composite endpoint, all-cause mortality and first hospitalisation for heart failure, revealing no significant reduction in the primary endpoint for the SGLT2 inhibitor group compared to placebo, although the secondary endpoint showed a numerically lower number of HFH events in the SGLT2 inhibitor group (74).

1.3 SGLT2 Receptor – A Pleiotropic Effect

1.3.1 The Physiology of the SGLT-Receptor Family

The sodium-glucose luminal transporter receptor (SGLT) belongs to the solute carrier family 5 (SLC5) and consists of proteins located in the cellular membrane that mediate the transport of sodium, amino acids, vitamins, osmolytes, and glucose. Twelve isoforms of the SLC5 family have been identified, responsible for the co-transport of sodium combined with sugar, fatty acids, choline, and myo-inositol. Of these, only six isoforms (SGLT1-6) are involved in the sodium-glucose co-transport process (75). The SGLT2 receptor accounts for 90% of renal glucose reabsorption, whereas the SGLT1 receptor is responsible for the remaining 10% (76) (**Table 1**).

The SGLT1 receptor (SLC5A1) is a high-affinity, low-capacity symporter carrying sodium and glucose in a 2:1 ratio (77). It is mainly located in the apical membrane of mature enterocytes for glucose uptake, but it is also present in the late proximal tube of the kidney cortex and heart (78). After the coupled uptake of two sodium ions and one glucose molecule, glucose exits the epithelial cells through the facilitated glucose transporter 2 (GLUT2), located on the basolateral membrane of epithelial cells (79).

The SGLT3 receptor (SCL5A4) is a glucose-sensitive ion channel primarily located in cholinergic neurons of the small intestine, at the neuromuscular junctions of skeletal muscles, and in the spleen, liver, and kidneys (80). The SGLT3 receptor functions as a glucose sensor, becoming activated by variations in plasma glucose levels, which modulate the membrane potential of cholinergic neurons in the enteric nervous system of the small intestine and at the neuromuscular junctions of skeletal muscles. When low glucose plasma

levels are detected by the SGLT3 receptor, this information is conveyed to cells through a G-coupled intracellular cascade (80).

The SGLT4 receptor (SCL5A8) is a low-affinity transporter found in the small intestines, brain, lung, liver, and kidneys. It is involved in the transport of glucose, fructose, mannose, glucitol, and biotin (81,82).

The SGLT5 receptor (SCL5A9) is exclusively located in the kidneys and responsible for the transport of glucose and galactose (83) (**Table 1**).

The low-affinity SGLT6 receptor (SCL5A10) shares the same receptor distribution as the SGTL4 receptor but is involved in the transport of glucose and inositol (83,84).

The SGLT2 receptor (SCL5A2) is a high-capacity, low-affinity symporter protein exclusively located in the early proximal tube of the renal cortex. It is responsible for the transport of sodium and glucose in a 1:1 ratio (82). Several cardioprotective effects have been reported for the SGLT2 receptor; however, it is not even located in the heart (85). This receptor mediates the active reabsorption of glucose in the proximal tube, coupled with sodium, through the luminal epithelial wall into the urothelial cell (86). Similar to the SGLT1 receptor, glucose exits via diffusion through the basolateral GLUT2-receptor, while sodium is transported out by an ATP-dependent Na+/K+ ATPase (83) (**Table 1**).

Table 1. Overview of all SGLT-receptors in human body

SGLT-Receptor type	Located in	Transport of
SGLT1 (SCL5A1)	Intestines, kidney, heart	sodium, glucose
SGLT2 (SCL5A2)	kidney	sodium, glucose
SGLT3 (SCL5A4)	Small intestine, skeletal muscle, spleen, liver, kidney	Glucose-sensor
SGLT4 (SCL5A8)	small intestines, brain, lung, liver, kidney	glucose, fructose, mannose, glucitol, biotin
SGLT5 (SCL5A9)	kidney	glucose, galactose
SGLT6 (SCL5A10)	small intestines, brain, lung, liver, kidney	glucose, inositol

SGLT, sodium glucose linked transporter; SLC, solute carrier family

1.3.2 Antihyperglycemic Effects

Many pharmacological treatments have been developed over the last decades including biguanides, SGTL2 inhibitors, GLP1 agonists, DPP4 inhibitors, insulins, glitazones, alpha-glucosidase inhibitors, and sulfonylureas and have been implemented in the treatment of T2DM. Metformin remains the first-line treatment of choice in T2DM in patients without a history of chronic heart failure or chronic kidney disease. However, if the HbA1c remain elevated despite Metformin therapy, second-line agents such as sulfonylureas, SGLT2-inhiitors, GLP1-agonists, or DPP4-inhibitors may be administered (87).
The new anti-diabetic drugs, SGLT2 inhibitors, inhibit glucose reabsorption in the early proximal tube mediated by the SGLT2 receptor, resulting in increased urinary glucose elimination and reduced blood glucose levels. Furthermore, the new pharmacological class was found to have fewer side effects compared to other glucose-lowering agents (88). Inhibition of the SGLT2 receptor, both as monotherapy or as an add-on to Metformin, has been shown to significantly reduce HbA1c levels in diabetic patients (89) It has also demonstrated a better efficacy with fewer side effects compared to other anti-diabetic drugs (90) Consequently, SGLT2 inhibitors have been implemented as a Class IA recommendation for type 2 diabetes mellitus (T2DM), either as monotherapy or in combination with Metformin (87). When chronic heart failure, independent of LVEF, is already present in diabetic patients without prior anti-diabetic treatment, SGLT2-I or GLP1 receptor agonists should be initiated as first-line antihyperglycemic therapy (70).

1.3.3 Cardioprotective Effects

SGLT2-I appear to have potential cardioprotective effects based on anti-inflammatory (91) and metabolic (92) mechanism, as well as by modifying myocardial signal transduction through inhibition of the Na+/H+ exchanger (93). However, the receptor itself is not located in the myocardium (85). SGLT2-inhibition may play a key role in the metabolic pathway by indirectly increasing myocardial uptake of ketone bodies, leading to a higher myocardial energy supply. This, in turn, impacts the energy state of myocardial cells, contributing to a reduction in cardiac dysfunction and necrosis (94). These beneficial effects were found to be independent of the presence or absence of diabetes (65–68). However, the complete molecular mechanism of SGLT2-I on human myocardium remains

uncertain. One proposed mechanism involves increased autophagy in the myocardium during SGLT2-I treatment, which might play a key role in their cardioprotective effects (95).

The EMPA-REG OUTCOME trial was the first clinical trial to show a significant reduction in cardiovascular endpoints for Empagliflozin compared to placebo in diabetic patients (64). For Empagliflozin, beneficial effects on the composite endpoints for cardiovascular death and hospitalisation for heart failure were observed in patients with HFrEF, independent of diabetic status (65), whereas in HFmrEF and HFpEF, beneficial effects were detected only for cardiovascular death or HFH (67). Similar results were reported for Dapagliflozin in HFrEF (66), HFmrEF, and HFpEF patients (68), regardless of diabetic status. Furthermore, Empagliflozin was shown to exert beneficial effects on cardiovascular outcomes in acute decompensated heart failure when initiated within 90 days (96). The EMBODY trial was the first clinical trial worldwide to demonstrate significant reduction in NT-proBNP/BNP levels with Empagliflozin compared to placebo in AMI (71). The EMMY trial further highlighted beneficial effects on NT-proBNP levels, as well as on structural and functional cardiac parameters (72). The recently published DAPA-MI trial showed significant cardiometabolic benefits, primarily driven by a reduction in T2DM incidence and body weight, but no effects were observed on mortality and hospitalisation for heart failure within this trial (73). Similarly, data from the EMPACT-MI trial reported no difference in hospitalisation for heart failure and all-cause mortality for Empagliflozin compared to placebo (74).

1.3.4 Renoprotective Effects

Based on a sub-analysis of the EMPEROR reduced trial, a positive effect of Empagliflozin on the composite renal outcome was identified, as it slowed the rate of decline in the estimated GFR and the risk of renal endpoints compared to placebo (HR 0.50; 95% CI, 0.32–0.77) (65). Consequently, two large clinical outcome trials demonstrated the beneficial effects of the SGLT2 inhibitors Dapagliflozin and Empagliflozin in significantly reducing composite renal endpoints, including a sustained decline in estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (97,98) These findings recently led to the inclusion of SGLT2 inhibitors in the therapy for patients with chronic kidney disease, with an eGFR as low as 20 ml/min/1.73 m². Similar results

were observed for Canagliflozin in the CREDENCE trial, which showed a significant reduction of cardiovascular events and risk of kidney failure in diabetic patients with nephropathy (99). The renoprotective effects of SGLT2-I can be attributed to increased sodium excretion, which activates the macula densa and subsequently stimulates the renin-angiotensin-aldosterone system (RAAS). Activation of the RAAS results in a tubuloglomerular feedback mechanism, causing constriction of the afferent arteriole, a reduction in intraglomerular pressure, and a subsequent decrease in proteinuria (100). However, limited data are currently available on SGLT2 inhibition in dialysis patients, but results from ongoing large clinical trials are expected soon.

1.3.5 Anti-Inflammatory Effects

Inflammatory biomarkers play a crucial role in the inflammatory process of atherosclerosis (101), as well as in progression and destabilisation of atherosclerotic cardiovascular disease (102), and show a significant increase after initial presentation with AMI (103,104).
SGLT2 inhibitors have been shown to exert beneficial effects on inflammatory biomarkers compared to other glucose-lowering agents attenuating low-grade inflammation (105). The only available data regarding SGLT2 inhibitors on inflammatory biomarkers in acute myocardial infarction come from the SGLT2-I AMI Protect international registry investigating the potential impact of chronic SGLT2-I treatment on inflammatory biomarkers in diabetic patients presenting with AMI. This registry highlights significantly lower baseline levels of leucocytes, neutrophils, and hsCRP at the time of admission and 24 hours after AMI in diabetic patients treated with SGLT2 inhibitors compared to those treated with other oral anti-hyperglycaemic agents, predicting a reduced inflammatory response (OR 0.457, 95% CI 0.275–0.758, p=0.002) (106). Furthermore, the SGLT2-I group was found to have smaller infarct size at admission compared to non-SGLT2-I users (106).

1.3.6 Anti-Arrhythmic Effects

Prospective data on the use of SGLT2 inhibitors for the prevention or management of arrhythmias are scarce and have never been primarily investigated in a clinical trial. Only a few prior SGLT2 trials reported very low rates of ventricular arrythmias. In a large meta-analysis from Fernandez et al., including 49,963 patients and 161,737 patient-years, the incidence of ventricular burden was found to average 1.4 per 1000 patient-years (107). The DAPA-HF trial was the first large clinical outcome trial to show a significantly lower incidence of ventricular arrythmias, cardiac arrest, or sudden cardiac death in patients with HFrEF treated with Dapagliflozin compared to placebo (OR 0.82; 95% CI, 0.57–1.17) (108). Sub-analysis of other large clinical outcome trials, such as EMPA-REG OUTCOME (OR 0.42), CREDENCE (OR 0.67), CANVAS (OR 0.55), and DECLARE-TIMI 58 (OR 1.73) found no significant difference compared to placebo. However, a post-hoc analysis of the DECLAIRE-TIMI 58 trial identified Dapagliflozin as being associated with a lower incidence of atrial fibrillation or atrial flutter in high-risk diabetic patients compared to placebo (109). Li et al. conducted a large meta-analysis involving 52,115 patients, highlighting that SGLT2 inhibition is associated with a decreased risk of ventricular tachycardias (RR 0.73, 95% CI, 0.53–0.99) as well as atrial fibrillation/flutter (110). A retrospective analysis using the TriNetX network reported a significantly lower incidence of cardiac arrest (HR 0.7, 95% CI, 0.63–0.78), atrial fibrillation (HR 0.81, 95% CI, 0.76–0.84), and the composite of incident ventricular tachycardia (VT), ventricular fibrillation (VF), and cardiac arrest (HR 0.76, 95% CI, 0.71–0.81). However, the risk for VT/VF occurrence did not show a significant difference (HR 0.94, 95% CI, 0.88–1.00) (111). Proper SGLT2 inhibition revealed beneficial effects in reducing sudden cardiac death, being one of five protective factors alongside ICDs, MRAs, ACE inhibitors, and beta-blockers, as shown in a large, comprehensive meta-analysis (112). Other anti-diabetic agents, such as GLP-1 agonists, were also found to have cardioprotective effects (113,114), particularly in preventing cardiac arrest (115). Given the significance of arrhythmic burden in ICD patients, especially those with heart failure, the potential impact of anti-diabetic agents on arrhythmias remains unclear. Further research in this area is therefore necessary.

1.4 SGLT2 and Myocardial Infarction

1.4.1 SGLT2 before Myocardial Infarction

Many pre-hospital trials have demonstrated the effects of SGLT2 inhibition in animal models and identified potential cardioprotective effects, including reductions in infarct size, mortality, structural and functional cardiac parameters, as well as oxidative stress levels through the upregulation of beta-hydroxybutyrate (β-OHB) levels.
A large animal trial by Andreadou et al. demonstrated various cardioprotective effects in an in vitro and in vivo mouse model fed a Western diet (WD) and pretreated with Empagliflozin. Empagliflozin showed a significant reduction in body weight as well as fast blood glucose levels compared to placebo in Western diet-fed mice. Lipid levels were significantly increased in both groups; however, no significant reduction in triglyceride or cholesterol levels was observed in either group. Furthermore, the trial showed no significant difference in the reduction of advanced glycation end products (AGE). However, a significant decrease in a key biomarker for lipid peroxidation, malondialdehyde (MDA), was observed in the SGLT2 inhibitor group compared to placebo. Mean arterial pressure (MAP) was also found to be significantly lower in the SGLT2 inhibitor group after six weeks of feeding with a Western diet (WD) (116).
Structural and functional cardiac parameters were found to be affected in mice receiving a Western diet for 14 days, with a significant reduction of left ventricular fractional shortening (LVFS) due to changes in both, LVESD and LVEDD. However, Empagliflozin was associated with significantly better LVFS compared to placebo, showing an increase from 41% to 44%. In contrast, the thickness of the posterior wall (PW) and the LV to PW ratio (r/h) appeared to remain unaffected by SGLT2 inhibitor treatment (116).
After ligation of the left anterior descending (LAD) artery for 30 minutes followed by 2 hours of reperfusion in mice fed a WD for 6 weeks, pre-treating with Empagliflozin was found to significantly reduce infarct size post-ischemia by approximately 50% compared to placebo. In contrast, the area at risk showed no difference between the two groups (116).
Empagliflozin-pretreated mice demonstrated cardioprotective effects by significantly enhancing the expression and phosphorylation of signal transducer and activator of transcription 3 (STAT3) compared to placebo. Additionally, myocardial levels of interleukin-6 (IL-6) and inducible nitric oxide synthase (iNOS) were significantly reduced

in the SGLT2 inhibitor group. These effects appear to be independent of the adenosine monophosphate-activated protein kinase alpha (AMPKα) pathway, the reperfusion injury salvage kinase (RISK) pathway, and several other key cardioprotective markers, including Akt, eNOS, p44/p42, GSK-3β and NF-κB (116).

In vitro Empagliflozin showed no direct effects on mitochondrial transition, with no impact on mitochondrial calcium retention capacity. However, further protective effects on enterochromaffin cells (EC-cells) and H9C2 myoblasts were observed, even in a diabetic milieu using advanced glycation end-products (AGE). Nonetheless, minimal changes in the expression of AGE receptors were reported in vitro (116).

In another animal model by Lopez. et al., a lower heart weight was observed in both, diabetic and non-diabetic rats, along with a positive improvement of fractional shortening (FS), independent of diabetic status, after surgical ligation of the LAD in streptozotocin-induced diabetic rats, pretreated with Empagliflozin (117). Similar results were observed for structural (LVESD, LVEDD, LVESV, LVEDV) and functional cardiac parameters (LVEF, stroke volume [SV]). Pretreatment with Empagliflozin significantly reduced myocardial infarct size in both non-diabetic and in streptozotocin-induced diabetic rats by approximately 30-40%, which correlated with improved contractility, as evidenced by increased LVEF and FS (117). Furthermore, the trial highlighted reduced collagen accumulation in Empagliflozin-pretreated mice, independent of diabetes status, driven by decreased Col1a1 mRNA and Col3a1 mRNA levels. However, these effects were approximately 35% more pronounced in diabetic rats. The hypertrophic markers, including the Myh7/Myh6 ratio and the Nppa mRNA levels, were significantly lower in Empagliflozin-treated diabetic and non-diabetic rats, although they remained approximately 52% higher in diabetic rats (117). In this animal model, a decrease in superoxide levels and nitric oxide synthase (NOS) was observed, which consists with an Empagliflozin-induced increase in cardiac GCH1 (cGCH1) mRNA, a key protein in the synthesis of cardiac tetrahydrobiopterin (BH4) and all isoforms of NOS (eNOS, nNOS, iNOS). By blocking this specific pathway in cGCH1 knockout rats, lower concentrations of BH4 and NOS subtypes were reported, along with a reciprocally increase in superoxide levels, independent of Empagliflozin pretreatment. Thus, Empagliflozin ameliorates oxidative stress by modulating the cGHC1-BH4 pathway (117).

β-OHB plays an important role in cardio metabolism and was found to be significantly increased in blood and myocardium after AMI in Empagliflozin-pretreated diabetic rats.

Empagliflozin also resulted in higher ATP levels in myocardium, which corresponds to increased glucose and ketone body utilisation. Pretreatment with Empagliflozin 14 days before AMI significantly increased survival rate to approximately 70.4% in diabetic rats, independent of infarct size. However, pretreatment with β-OHB led to a 45% higher survival in rats, highlighting the ketone body utilisation as a key mechanism in the cardioprotective effects of SGLT2 inhibitors post MI. Secondly, an upregulation of the two antioxidative proteins, superoxide dismutase 2 (SOD2) and the mitochondrial sirtuin Sirt3, was observed in Empagliflozin-pretreated diabetic rats, ameliorating myocardial oxidate stress levels (118). In a similar rat model, pretreatment with Empagliflozin was found to attenuate acute kidney injury (AKI) after acute myocardial infarction, following ligation of the LAD, providing diabetic renoprotection in subclinical AKI (119). Similar results had already been reported for Canagliflozin, which reduced oxidate stress by elevating β-OHB and NOX2 and NOX4 levels in diabetic rats (120). A significant cardioprotective effect of Canagliflozin was further reported after ligation of the LAD for 35 minutes, followed by 2 hours of reperfusion, resulting in a significant reduction of infarct size by approximately 50% in both diabetic and non-diabetic rats. This was observed when Canagliflozin was administered as pretreatment for 4 weeks, highlighting
that long-term treatment with Canagliflozin appears to reduce infarct size, irrespective of glucose levels and diabetes status (121).

1.4.2 SGLT2 during Myocardial Infarction

SGLT2 inhibition in the acute setting of myocardial infarction has shown heterogeneous effects compared to pretreated individuals. However, a central cardioprotective role is mediated through the AMPK pathway.
Lim et al. demonstrated in a normoxia mouse model treated with Empagliflozin an upregulation of phosphorylated liver kinase B1 (LKB1) as well as adenosine monophosphate-activated protein kinase (AMPK) in cardiomyocytes. Reciprocally, acetyl-CoA carboxylase (ACC) and peroxisome proliferator-activated receptor coactivator 1-alpha (PGC-1α) were downregulated by Empagliflozin. Thus, Empagliflozin was found to activate the LKB1/AMPK pathway, while other pathways in cardiomyocytes were downregulated. After initiating hypoxia for 20 minutes followed by 20 minutes of reoxygenation, LKB1 as well as AMPK were identified to be activated in both the SGLT2-

I and non-SGLT2-I groups. However, the activated LKB1/AMPK pathway showed an even more significant and longer-lasting activation with Empagliflozin. By adding Compound-C to murine cardiomyocytes, AMPK was found to be suppressed, whereas LKB1 remained activated, confirming that the Empagliflozin-induced activation of AMPK is mediated by upregulation of LKB1. Under the same conditions, ACC and PGC-1α exhibited lower levels in murine cardiomyocytes. Based on these experimental findings, cardioprotective effects of increased activated AMPK with Empagliflozin were reported, through the downregulation of the ACC and PGC-1α pathways as well as the upregulation of LKB1 (122).

Another experiment within the same mouse model showed consistently similar sarcomere lengths in resting isolated murine cardiomyocytes, whereas maximum velocity and amplitude of contractility were significantly decreased after the addition of Empagliflozin. After inducing hypoxia followed by reoxygenation, a significant reduction in maximum velocity and amplitude was observed in isolated murine cardiomyocytes in both groups. However, after the application of Empagliflozin, an improvement in contractility was reported. Upon inhibition of the AMPK pathway using Compound C in murine cardiomyocytes, a relevant impact on myocardial contractility was observed, and the addition of Empagliflozin showed no beneficial compensatory effect on cardiac function. This highlights that Empagliflozin ameliorates contractility in murine cardiomyocytes under myocardial stress via the AMPK pathway (122).

Under normoxia conditions, similar concentrations of superoxide were reported for both the SGLT2-I and non-SGLT2-I groups, whereas superoxide levels were significantly lower with Empagliflozin after inducing hypoxemia followed by reoxygenation. After administration of Compound C to isolated murine cardiomyocytes under myocardial stress and inhibition of AMPK, Empagliflozin was again found to have no impact on reducing superoxide concentrations. This highlights that the cardioprotective effects of SGLT2-I align with a decrease in oxidative stress by lowering superoxide levels through the AMPK pathway (122).

When artificial myocardial stress was induced by ischemia for 40 minutes followed by reperfusion for 30 minutes in murine hearts, a significantly higher rate-pressure product (RPP) was observed with Empagliflozin. When Compound C was applied in the murine model, Empagliflozin showed no difference in the RPP, highlighting a beneficial effect of

Empagliflozin in ameliorating systolic function of isolated murine hearts during myocardial ischemia via the AMPK pathway.

In vivo, after surgical ligation of the LAD, both the SGLT2-I and non-SGLT2-I groups showed a significant decrease in LVEF and FS. However, Empagliflozin demonstrated better LVEF recovery under ischemic stress, whereas FS remained unaffected. After the administration of Compound C, attenuation of LVEF recovery was reported with Empagliflozin, further demonstrating a cardioprotective role in maintaining systolic function in mice after myocardial ischemia (122).

Within the same isolated mouse heart model, after the initiation of ischemia followed by reperfusion, a significant decrease in AMI was observed with Empagliflozin, whereas no difference was identified when the AMPK inhibitor Compound C was added. This highlights a cardioprotective role for Empagliflozin in reducing the area of AMI via the AMPK pathway. Similar results were observed in vivo, with Empagliflozin significantly reducing infarct size. The application of Compound C attenuated the beneficial effects of SGLT2-Is (122). Another animal model in swine treated with Canagliflozin for 24 hours before LAD occlusion for 60 minutes followed by 2 hours of reperfusion demonstrated a significant reduction in infarct size of approximately 60%, along with an increase in LVEDV and stroke volume (SV). This highlights the ischemia-protective effects of Canagliflozin in preserving myocardial contractility and efficiency (123). However, other large murine and rat models failed to show a significant reduction in infarct size with Canagliflozin (121) and Empagliflozin (124,125).

In a histological examination within the same model by Lu et al., Empagliflozin attenuated the migration of inflammatory cells into the interstitial space of the murine myocardium after ischemia, whereas infiltration of inflammatory cells was increased after the administration of Compound C, despite Empagliflozin treatment. This highlights an anti-inflammatory effect mediated through the AMPK pathway (122). Another rat model by Yurista et al. reported a decrease in left ventricular mass and attenuation of cardiomyocyte cross-sectional area after pretreatment with Empagliflozin for 2 days. Furthermore, a reduction in myocardial fibrosis, including procollagen and collagen 1, was observed after Empagliflozin treatment, along with an improvement in mitochondrial biogenesis, resulting in higher myocardial ATP production (124).

In a similar mouse trial, Dapagliflozin was found to significantly reduce infarct size when administered 15 minutes before ischemia as well as 15 minutes into ischemia in rats,

whereas application at the onset of reperfusion exerted no beneficial effect. The greatest decrease in infarct size was observed with Dapagliflozin pretreatment, showing a reduction of approximately 42%. In comparison, when administered during ischemia, a reduction of approximately 16% was observed. Interestingly, the time from ischemia to the first appearance of ventricular tachycardia/ventricular fibrillation was significantly longer in Dapagliflozin-pretreated rats. After LAD ligation followed by reperfusion, only Dapagliflozin-pretreated rats showed significant improvement in LVEF and dP/dt_{max}, whereas no such effects were reported when Dapagliflozin was ugiven during ischemia or at reperfusion(126).

In a molecular analysis within the same rat model, a cardioprotective effect was reported, evidenced by a decreased expression of terminal deoxynucleotidyl nick-end labelling (TUNEL)-positive cells, attenuating cardiac cell apoptosis in Dapagliflozin-pretreated rats as well as in those treated during ischemia. Within the same treatment groups, a significant increase in B-cell lymphoma 2 (BCL-2) levels was detected, resulting in higher expression of anti-apoptotic proteins. Regarding mitochondrial state, both the Dapagliflozin-pretreated group and the ischemia-treated group showed significantly lower concentrations of reactive oxygen species (ROS) and reduced mitochondrial swelling, given the fact that mitochondrial damage and dysfunction after AMI are induced by ROS. Another mitochondrial protective effect was demonstrated by the increased levels of Carnitine Palmitoyltransferase I (CPT1), a key protein related to cardiac mitochondrial metabolism and mitochondrial biogenesis (126). Jesperson et al. reported protective post-ischemic mitochondrial effects in Empagliflozin by improving complex I+II respiration, which is an important step in cardiac remodelling post-AMI, preventing heart failure. Moreover, an increased permeability and uncoupling of the inner membrane of mitochondria were reported, along with upregulation of mitochondrial respiration and better cell survival by diminishing oxidative stress and ameliorating remodelling in damaged myocardial tissue (125).

1.4.3 SGLT2 after Myocardial Infarction

The first trial to show relevant evidence of SGLT2 inhibition after acute myocardial infarction was reported in 2017 by Lee et al. after ligation of the LAD in male Wistar rats for Dapagliflozin. After in vivo administration of Dapagliflozin post-AMI, superoxide levels were significantly lower in the SGLT2-I group, highlighting anti-oxidative effects in the acute setting of myocardial infarction. Furthermore, Dapagliflozin attenuated nitrosative stress by significantly reducing the concentration of myocardial nitrotyrosine compared to non-SGLT2 users. Within the first 3 days after AMI, higher phosphorylation of the molecule that downregulates free radical production, STAT3, was observed. In Dapagliflozin-treated rats, sustained STAT3 activation resulted in lower concentrations of free radicals, which was consistent with lower STAT3 activation when the STAT3 inhibitor S31-201 was added. Levels of phosphorylated STAT3 were increased in the acute setting of MI; however, when treated with Dapagliflozin, the DNA-binding activity of STAT3 as well as nuclear STAT3 translocation was significantly increased (127).
An immunohistochemical experiment within the same rat model revealed infiltration of CD68+ macrophages in the infarcted area in the acute setting of MI. After differentiation of type-specific surface markers, a significantly higher expression of iNOS-expressing CD68+ macrophages (M1 macrophages) was reported in the infarcted myocardium of non-SGLT2 users, whereas interleukin-10 (IL-10)-expressing CD68+ macrophages (M2 macrophages) were higher in the Dapagliflozin group. This highlights that SGLT2-I application leads to a significant increase in M2 macrophages and the M2/M1 ratio, while M1 macrophages declined. However, co-administration of the STAT3 inhibitor S31-201 reduced these beneficial effects of SGLT2-I (127).
Apart from the acute setting, several experiments were conducted in the chronic stage of MI within the same rat model. Treatment with Dapagliflozin led to glucosuria with an increase in diuresis, resulting in higher water intake. Body weight was found to be unaffected by SGLT2 inhibition, and no gastrointestinal symptoms were observed (127). Infarct size, left ventricular end-systolic pressure, and mortality within the rat model were found to be similar between SGLT2-I and non-SGLT2-I users. However, Dapagliflozin-treated rats showed significantly increased left ventricular pressures and a decrease in the lung weight-to-body weight ratio compared to non-SGLT2-treated rats, favouring LV remodelling (127).

Four weeks after AMI, α-SMA–expressing myofibroblasts were observed in the myocardial tissue. However, treatment with Dapagliflozin attenuated concentrations of α-SMA and α-SMA mRNA, which could be reversed by adding the STAT3 inhibitor S31-201, highlighting STAT3 as a relevant pathway for Dapagliflozin in the remodelling process post-AMI. Another cardioprotective effect of Dapagliflozin within the same rat model was identified by its significant reduction of fibrosis in infarcted myocardial tissue, whereas myocardial fibrosis was enhanced by adding S31-201, again highlighting the importance of the STAT3 pathway in cardiac remodelling (127).

In a larger animal trial with female Yorkshire pigs, after initiation of AMI for 2 hours, no significant differences in MI size, left ventricular volume, or function were observed when treated with Empagliflozin at baseline. After 2 months, structural cardiac parameters, including LVEDV, LVESV, and left ventricular mass, were significantly lower in Empagliflozin-treated pigs, ameliorating LV remodelling as shown by echocardiography and cardiac magnetic resonance tomography (CMR) after AMI. Similar results were found for functional cardiac parameters, with a significant increase in LVEF and contractility in Empagliflozin-treated pigs after 2 months. Furthermore, better preservation of longitudinal, radial, and circumferential strain was identified in 3D speckle-tracking echocardiography analysis for Empagliflozin (128).

Biochemically, lower concentrations of normetanephrine were reported in Empagliflozin-treated pigs, which is consistent with reduced myocardial stress. B-type natriuretic peptide (BNP) levels were also lower in Empagliflozin-treated pigs, indicating less cardiac dilation. Troponin I (TnI) levels were significantly lower in Empagliflozin-treated pigs, suggesting reduced cardiac injury (128).

Regarding metabolism, healthy myocardium was primarily found to consume lactate, free fatty acids (FFA), and amino acids, with only low levels of ketone bodies and glucose being utilised. Following two months of remodelling after AMI, a metabolic switch was reported, with increased activity and expression of pyruvate dehydrogenase resulting in higher glucose uptake and consumption, as well as increased lactate dehydrogenase (LDH) activity, leading to enhanced lactate production. FFA were reported to have reduced uptake and utilisation two months after AMI, aligning with the downregulation of carnitine palmitoyl transferase 1, a key enzyme in FFA metabolism, and of CD36 cells, which regulate FFA uptake in cardiomyocytes. Amino acid uptake and utilisation were found to be decreased post-MI, due to lower activity of the key enzyme in amino acid catabolism,

branched-chain α-keto acid dehydrogenase complex (BCKD), and enhanced phosphorylation of the BCKD-E1α subunit, whereas ketone bodies showed a minimal increase.

On the other hand, treatment with Empagliflozin induced a complete metabolic switch by shifting away from glucose utilisation, lowering glucose uptake and metabolism. Interestingly, ketone bodies were found to have an 8-fold higher concentration after MI in Empagliflozin-treated pigs through specific mechanisms, including increased expression and activity of Succinyl-CoA 3-oxoacid CoA-transferase (SCOT), higher expression of β-hydroxybutyrate dehydrogenase (BDH1), and enhanced ketone body utilisation in the myocardium. Amino acid uptake and consumption were both higher in the Empagliflozin group two months after AMI due to upregulation of BCKD activity and a reciprocal decrease in phosphorylation of the BCKD-E1α subunit. Free fatty acids were also identified as having increased uptake and utilisation, supported by higher expression of CD36 cells and carnitine palmitoyl transferase 1. All these positive metabolic effects observed after administration of Empagliflozin in pigs were enhanced by greater ATP availability, preservation of aerobic metabolism, and increased AMPK and PGC-1α activity, highlighting the enhanced efficiency of SGLT2-I in the myocardium after AMI (128).

In an experimental rabbit model by Baartscheer et al., without inducing AMI, Empagliflozin was reported to decrease concentrations of cytosolic sodium as well as systolic and diastolic cytosolic calcium levels in cardiomyocytes. However, higher glucose concentrations in isolated cardiomyocytes significantly increased cytosolic sodium and calcium levels. On the other hand, acute treatment with Empagliflozin significantly increased mitochondrial calcium concentrations. Interestingly, all these homeostatic effects of Empagliflozin appear to be independent of the SGLT receptors, acting instead through direct inhibition of the Na+/H+ exchanger (NHE).

Following administration of the NHE inhibitor Cariporide, Empagliflozin showed only minimal effects on cytosolic sodium concentrations. Furthermore, after the application of acidic substances, Empagliflozin appeared to inhibit NHE flux pump activity, with a lack of pH stabilisation after wash-out with ammonium hydrogen carbonate (NH_4^+). Lastly, reductions in cytosolic sodium concentrations and inhibition of the NHE flux pump were observed under glucose-free conditions, highlighting that the beneficial intracellular

homeostatic effects, including increased mitochondrial calcium levels, are independent of SGLT receptors (93).

1.5 Gaps in Evidence

Large clinical outcome trials have demonstrated many cardioprotective effects of the SGLT2 inhibitors Empagliflozin and Dapagliflozin, including significantly reducing cardiovascular death and hospitalisation for heart failure (HFH) in HFrEF, as well as significantly lowering the rate of HFH in HFmrEF and HFpEF patients (64–68,129). Furthermore, beneficial effects on NT-proBNP levels, as well as structural and functional cardiac parameters, were reported for Empagliflozin following AMI (72). The recently published DAPA-MI trial also reported a significant reduction in cardiometabolic risk (73). Furthermore, two large clinical trials reported renoprotective effects, significantly reducing the risk of worsening kidney function and the incidence of end-stage kidney disease for Empagliflozin (97), Dapagliflozin (98) and Canagliflozin (99).

Given the fact that inflammation plays a crucial role in the development and progression of atherosclerosis, followed by acute rupture and AMI, no clinical trials have yet reported the effects of SGLT2 inhibition on the trajectories of inflammatory biomarkers after AMI.

The electrocardiogram (ECG) is essential for the acute diagnosis of AMI (47,130) and has been identified as a prognostic factor in STEMIs when transferred to the heart catheter laboratory immediately (131). SGLT2 inhibition was identified as well-tolerated with respect to prolongation of ECG parameters (132). Nevertheless, no clinical data on the beneficial effects of SGLT2 inhibitors in patients experiencing AMI with specific baseline ECG metrics have been reported to date.

The EMMY trial has already reported a significant reduction in structural cardiac parameters (LVESD, LVEDD), as well as an improvement in cardiac function (LVEF, E/e´) (72). Although many animal models and clinical trials have demonstrated the beneficial effects of SGLT2 inhibitors on cardiac remodelling (117,124,127,128,133), data on specific echocardiographic changes, including strain analysis measured by 3D speckle tracking echocardiography, remain scarce.

Finally, the impact of SGLT2 inhibition on the burden of ventricular and supraventricular arrhythmias has not yet been proven in a large clinical trial. However, a sub-analysis of the

DAPA-HF trial was the first to report a lower incidence of ventricular arrhythmic burden and cardiac death in HFrEF compared to placebo, although this did not reach statistical significance (108). In contrast, other outcome trials reported no difference (64,99,134,135). To date, no clinical outcome trial has definitively assessed the potential effects of SGLT2 inhibition on ventricular and supraventricular arrhythmia burden.

1.6 Aim

Based on the gaps in evidence, the aim of this thesis is to:

1) Elucidate the potential effects of SGLT2 inhibitors on inflammatory biomarkers and identify potential benefits over placebo after AMI.
2) Investigate potential correlations between cardiac biomarkers and structural as well as functional cardiac parameters, and their relation to SGLT2 treatment within the EMMY trial, in the presence of specific ECG baseline metrics.
3) Perform a post-hoc analysis of echocardiographic parameters, including strain analysis with 3D speckle tracking, to investigate the potential beneficial effects of Empagliflozin compared to placebo on structural and functional echocardiographic metrics.

Finally, within the ERASe trial, we conducted the first and only clinical trial worldwide (due to changes in heart failure guidelines) to investigate the effects of the SGLT2 inhibitor Ertugliflozin on ventricular and supraventricular arrhythmia burden in patients with HFrEF and HFmrEF who had an implanted cardioverter-defibrillator (ICD) ± cardiac resynchronisation therapy (CRT). This trial aimed to potentially identify anti-arrhythmic effects through a reduction in arrhythmic burden.

2 Material and Methods

2.1 The EMMY Trial

The **EM**pagliflozin after acute **MY**ocardial infarction (EMMY) trial was a prospective, multicentre, double-blind, placebo-controlled, investigator-initiated phase 3b trial that investigated the effects of 10 mg peroral Empagliflozin once daily versus placebo in acute myocardial infarction (AMI), independent of diabetic status, from May 2017 to May 2022 across 11 sites in Austria.

We included patients aged 18–80 years presenting with a large myocardial infarction, defined by a creatine kinase >800 IU/L and troponin T levels >10 times the upper limit of normal. Patients with known diabetes other than type 2, genital or urinary tract infections, prior or ongoing treatment with an SGLT2 inhibitor, acidaemia (pH <7.32), or haemodynamic instability were excluded from the analysis.

After fulfilling the inclusion criteria, patients suffering from AMI were matched to receive either 10 mg peroral Empagliflozin or placebo within 72 hours after percutaneous coronary intervention (PCI) for up to 26 weeks.

The primary endpoint of the EMMY trial was to identify the beneficial impact of Empagliflozin on N-terminal pro-brain natriuretic peptide (NT-proBNP), a cardiac biomarker of heart failure, after 26 weeks compared to placebo.

Secondary endpoints included relevant changes in the functional cardiac parameters—left ventricular ejection fraction (LVEF) and diastolic function (E/e')—as well as changes in the structural cardiac parameters—left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD)—in Empagliflozin-treated patients compared to those receiving placebo.

The EMMY trial was fully designed in conformity with the Declaration of Helsinki of 1964 and in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice (ICH GCP E6). It was approved by the Ethics Committee of the Medical University of Graz (MUG) in Austria (EK 29-179 ex 16/17; EudraCT 2016-004591-22). Furthermore, the trial was registered on ClinicalTrials.gov (NCT03087773). Laboratory samples were collected, frozen, and analysed at the Clinical

Institute for Medical and Chemical Laboratory Diagnostics (CIMCL) of the Medical University of Graz from all participants at baseline, 6 weeks, and 26 weeks (72,136).

2.2 Subanalysis of Inflammation Data

2.2.1 Study Design*

In the inflammation subanalysis, we successfully measured specific inflammatory biomarkers from all patients of the EMMY trial using available frozen blood samples collected at baseline (at randomisation), after 6 weeks (visit 2), and after 26 weeks (visit 4). Trajectories of inflammatory metrics were analysed for both the Empagliflozin group and the placebo group.
Blood samples were centrally analysed at the Clinical Institute for Medical and Chemical Laboratory Diagnostics (CIMCL) of the Medical University of Graz. IL-6 and hsCRP were measured on the automated Cobas 8000 platform, c-modul 702, using the Elecsys IL-6 sandwich assay and Tina-quant C-reactive protein IV enhanced immunoturbidimetric assay technology by Roche Diagnostics (Mannheim, Germany).
The aim of this subanalysis was to investigate inflammation at baseline and its trajectories after acute myocardial infarction in SGLT2 users compared to placebo, as well as to observe correlations with functional cardiac parameters and cardiac biomarkers, to determine whether inflammation post-AMI is altered by SGLT2 inhibition.

2.2.2 Study Variables*

Outcome variables in this post-hoc analysis include specific inflammatory biomarkers such as leukocytes, neutrophils, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), the platelet-to-lymphocyte ratio (PLR), and the neutrophil-to-lymphocyte ratio (NLR), as well as their trajectories over time, defined as mean changes from baseline to week 26. Explanatory variables of the sub-study included general characteristics (age, sex, BMI), cardiovascular risk factors (hypertension, T2DM, smoking behaviour), laboratory biomarkers (lipid status, eGFR, Troponin T, NT-proBNP), functional cardiac parameters (LVEF and E/e´), and treatment group (Empagliflozin, placebo).

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The endpoints were defined as the mean changes in inflammatory biomarkers from baseline to week 26 in patients receiving 10 mg of peroral Empagliflozin daily compared to placebo post-AMI. Furthermore, a correlation analysis of inflammatory markers with explanatory variables was performed.

2.2.3 Statistical Analysis*

The entire statistical analysis was conducted using Stata software version 17.0. Baseline characteristics were reported through descriptive analysis, with frequencies presented as percentages (%) for all categorical metrics, and medians with interquartile ranges (IQR) or means with standard deviations (SD) for continuous metrics.
Analysis of mean and percentage changes from baseline to week 26 was performed using linear mixed-effects models (LMEM), including associations with explanatory variables (laboratory biomarkers, baseline characteristics, functional cardiac parameters, cardiovascular risk factors, and treatment groups). Correlations between inflammatory characteristics and each explanatory variable were estimated using simple LMEMs; however, only significant relationships were further included in multiple LMEM analysis, along with treatment, age, sex, diabetes status, visit, and treatment-visit interaction. The estimated associations for each inflammatory biomarker were reported only for significant relationships. Furthermore, hsCRP and IL-6 were log-transformed to enable more comprehensible graphical representation.

2.3 Subanalysis of ECG Data

2.3.1 Study Design#

At one centre participating in the EMMY trial (Medical University of Graz), we successfully initiated a single-centre post-hoc analysis to investigate potential associations between specific ECG parameters and EMMY endpoints in 181 patients with available baseline electrocardiograms.

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In this post-hoc study, we performed a comprehensive analysis of available baseline ECGs one day post-PCI, examining potential associations between specific baseline ECG characteristics and changes in cardiac biomarkers, as well as functional and structural cardiac parameters, following acute myocardial infarction.
Furthermore, an interaction analysis was conducted to investigate associations between ECG metrics and changes in EMMY outcomes, comparing Empagliflozin and placebo groups to determine whether better endpoint responses in specific ECG metrics differed between the groups.
The aim of this post-hoc analysis is to identify significant correlations between baseline ECG metrics and changes in cardiac biomarkers, as well as functional and structural cardiac parameters, in the context of interaction between Empagliflozin and placebo. This may help to identify patients who could benefit even more from treatment with an SGLT2 inhibitor post-AMI based on their baseline ECG characteristics.

2.3.2 Study Variables[#]

The explanatory variables in our analysis were defined as specific baseline electrocardiographic parameters measured one day post-AMI. These included heart rate, defined as beats per minute (bpm); ventricular and atrial electrical conduction parameters (QRS width, PQ interval, QTc interval, Q wave duration, P wave duration) measured in milliseconds (ms); amplitudes (QRS amplitude, P-wave amplitude, Sokolow-Lyon index, Q wave amplitude) measured in millivolts (mV); T-wave inversion; ST-segment changes (elevation or depression); and cardiac axis deviations (extreme axis deviation, normal axis deviation, right axis deviation, left axis deviation).
The defined outcome variables corresponded to the primary and secondary endpoints of the EMMY trial. These included the cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T (TnT); the functional cardiac parameters left ventricular ejection fraction (LVEF) and diastolic function (E/e´); and the structural cardiac parameters left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV).

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2.3.3 Statistical Analysis#

We successfully performed a comprehensive analysis of ECG characteristics from the Graz cohort with available ECGs one day post-AMI. All data were pseudonymised and entered an Excel database. The statistical analysis was conducted using Stata software version 18.0.

Clinical baseline characteristics of the included participants were reported as medians with interquartile ranges (IQR) for continuous variables, and frequencies with percentages (%) for categorical variables. Explanatory variables were defined as mean durations in milliseconds (ms) for electrical conduction metrics and as mean amplitudes in millivolts (mV).

For continuous variables, the Wilcoxon rank-sum test was used to compare ECG metrics and baseline characteristics between treatment groups. For categorical variables, Chi-square and Fisher's exact tests were applied.

Associations between ECG metrics and changes in cardiac biomarkers, as well as structural and functional cardiac endpoints, were analysed using a linear mixed-effects model (LMEM). To capture the magnitude of changes in primary and secondary endpoints, continuous ECG characteristics were divided into tertiles, and results were reported by tertiles in the main findings. Furthermore, we performed an interaction analysis of each ECG parameter with treatment for every single endpoint. P-values <0.05 were considered statistically significant in all tests performed.

2.4 Subanalysis of Echocardiographic Parameters

2.4.1 Study Design×

In this post-hoc analysis, we focused on measurements of specific echocardiographic parameters, including strain, and their changes from baseline to week 26 between Empagliflozin and placebo. We retrospectively assessed available echo loops from three major sites of the EMMY trial, with loops obtained at baseline, week 6, and week 26. Metrics were assessed using two-dimensional Doppler and M-Mode imaging, following the recent guidelines of the European Association of Cardiovascular Imaging and the

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American Society of Echocardiography, utilising locally available ultrasound devices (137–139). Echo studies were stored in DICOM format, and measurements were performed at the Echo Core Laboratory of the Medical University of Graz. Continuous ECG recordings were used to define the end of systole and diastole. All sites participating in the EMMY trial were requested to transfer their echocardiographic examinations in DICOM format to our Echo Core Laboratory in Graz.
For post-processing assessment, a vendor-independent software, TomTec-Arena (TomTec Imaging Systems, Munich, Germany), was used for deformation analysis. The 2D Cardiac Performance Analysis (2D-CPA) module was applied to two independent cardiac cycles to ensure reproducibility.

2.4.2 Study Variables×

In this post-hoc analysis, we focused on endocardial strain metrics based on the calculation of contour line length in all four heart chambers. In all three left ventricular chamber views (4-chamber view [4CV], 2-chamber view [2CV], and 3-chamber view [3CV]), we successfully performed global longitudinal strain (LV-GLS) analysis using a 16-segment model (140,141). Left atrial strain was analysed from the 4CV and 2CV, while right atrial strain was derived from the 4CV, following the most recent guidelines (142) Right ventricular global longitudinal strain (RV-GLS) was assessed using a 6-segment model (including septal and free-wall segments) and a 3-segment model (free-wall segments only) in a focused right ventricular (RV) apical 4CV.
Clinical endpoints included changes in structural and functional cardiac parameters from baseline to week 26. Structural cardiac parameters consisted of left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV) and the left atrial volume index (LAVI). Functional cardiac parameters included left ventricular ejection fraction (LVEF), diastolic function (E/e´), LV-GLS, left and right atrial global longitudinal strain (LA-GLS and RA-GLS), RV-GLS, right ventricular fractional area change (RV-FAC), and tricuspid annular plane systolic excursion (TAPSE).

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2.4.3 Statistical Analysis×

Descriptive analysis was performed and illustrated using means and standard deviations (SD), as well as medians and interquartile ranges (IQR), for baseline characteristics and continuous variables. Percentages (%) and frequencies were used for categorical metrics. The unpaired t-test and Wilcoxon rank-sum test were applied for continuous parameters, while Fisher's exact test and the Chi-square test were used for categorical variables. Changes in echocardiographic metrics, as well as differences between the SGLT2 and placebo groups, were analysed using linear mixed-effects models (LMEM) from baseline to week 26. Furthermore, an interaction analysis was conducted, including baseline characteristics and fixed effects such as treatment, time, and time-treatment interaction.

2.5 The ERASe Trial

2.5.1 Study Design°

The "**E**rtugliflozin to **R**educe **A**rrhythmic Burden in Implantable Cardioverter-Defibrillators (ICD)/Cardiac Resynchronisation Therapy (CRT) Patient**S**" trial (ERASe) is an investigator-initiated, multicentric, double-blind, placebo-controlled phase 3b clinical trial conducted to evaluate the effects of once-daily peroral Ertugliflozin on arrhythmic burden in patients with reduced left ventricular ejection fraction (HFrEF and HFmrEF) with implanted cardioverter-defibrillators (ICD) ± cardiac resynchronisation therapy (CRT) over 52 weeks compared to placebo. Furthermore, we investigated potential effects on structural and functional cardiac parameters as well as cardiac biomarkers between the two groups. The trial was conducted across eight sites in Austria between 24 June 2021 and 23 June 2023 (143).

The ERASe trial received approval by the "relevant regulatory authorities, by the Ethics Committee of the Medical University of Graz, Austria (EK 32-492 ex 19/20)". The trial adheres to the principles in the 1964 Declaration of Helsinki and its revisions and was further registered on EudraCT (2020-002581-14) and ClinicalTrials.gov (NCT04600921). The study is in conformity with the guidelines of the International Conference on Harmonization for Good Clinical Practice (ICH GCP E6). All protocols were designed by

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the academical ERASe leadership including supervision of the data as well as choosing the participating centres. The collected data of the study was stored and processed by the "Interdisciplinary Metabolic Medicine Trials Unit at the Medical University of Graz in Austria" (143).

We included all patients aged 18–80 years with a left ventricular ejection fraction (LVEF) <40% and on maximal tolerated heart failure therapy according to the current guidelines (48), with an implanted ICD ± CRT for >3 months, and at least 10 ventricular tachycardias (non-sustained ventricular tachycardias [nsVTs] or sustained ventricular tachycardias [sVTs], with or without treatment). Additionally, patients were required to fulfil at least one of the following criteria:

- LVEF <35%
- NT-proBNP >500 pg/mL
- Hospitalisation for heart failure within the last 12 months
- >100 nsVTs within the last 12 months
- >1 sVT with the last 12 months

Patients suffering from forms of diabetes other than type 2 diabetes mellitus (T2DM), haemodynamic instability (RR <100/60 mmHg and use of active intravenous drugs), or a known allergy to SGLT2 inhibitors, as well as those with a history of severe hypoglycaemic events, ketoacidosis, or prior treatment with SGLT2 inhibitors, were excluded from the analysis. For detailed ERASe criteria, we refer to the official ERASe design paper (143).

2.5.2 Trial Procedure°

After obtaining written informed consent (IC) and verifying the inclusion criteria, eligible patients were randomly assigned in a 1:1 ratio to receive either 5 mg of oral Ertugliflozin once daily or placebo. Randomisation was performed using the Randomizer Software (Institute for Medical Informatics, Statistics, and Documentation, Medical University of Graz, http://www.randomizer.at) provided by an independent statistician. Stratification was based on the estimated glomerular filtration rate (eGFR) (<60 and ≥60 ml/min/1.73 m²) and the presence of type 2 diabetes (yes/no).

The study consisted of three visits: a baseline visit, a follow-up visit after 1 year, and a telephone visit 4 weeks after the second visit (143).

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During the first visit and the 1-year follow-up, we performed specific study measures, including blood pressure, heart rate, weight, device interrogation, echocardiographic measurements, and blood sampling. Laboratory samples were analysed both locally and centrally at two time points for final evaluation at the Clinical Institute of Medical and Chemical Laboratory Diagnostics (CIMCL), Medical University of Graz, Austria. Device interrogations were conducted as on-site follow-ups and were monitored in the meantime through telemedicine. Echocardiography was performed according to the recent guidelines of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, using local ultrasound devices. These included 2D Doppler and M-Mode imaging, which were analysed in a local system (IntelliSpace) after storage in DICOM format.
The telephone visit took place 4 weeks after the second visit to enquire about recent adverse events (143).

2.5.3 Clinical Endpoints°

The ERASE trial focused on assessing the incidence of sustained ventricular tachycardias (sVT) and ventricular fibrillation (VF) episodes from the point of randomisation to week 52 as the primary endpoint. Secondary endpoints included the total count of non-sustained ventricular tachycardias (nsVT), changes in NT-proBNP and HbA1c levels, and the total number of ICD therapies (including ATPs and shocks). Exploratory parameters were defined as the total count of hospitalisations for heart failure (HFH), the duration of hospital stay, and cardiovascular death. All hospitalisations during the follow-up period were carefully analysed by an independent committee before unblinding the clinical data (143).
Serious adverse events (SAEs), severe hypoglycaemic events, all-cause mortality, occurrence of ventricular storm, worsening of renal and liver function, current genital infections, and ketoacidosis were defined as key safety outcomes.

2.5.4 Statistical Analysis°

The statistical analysis was performed using R software version 4.3.1 (https://www.r-project.org) with descriptive statistics for baseline characteristics, including means and

° *Parts of this chapter have been published in NEJM Evidence. (2024). DOI: 10.1056/EVIDoa2400147*

standard deviations for continuous metrics and frequency tables for categorical parameters. The Chi-square test and Fisher's exact test were used for comparing categorical variables, while the Wilcoxon rank-sum test and unpaired t-test were applied for continuous parameters (143).

Linear mixed-effects models (LMEM) were used to evaluate the primary endpoint in the intention-to-treat (ITT) group, with the log-transformed dependent variable sVT. Fixed effects included visits, treatment, sex, presence of T2DM, NT-proBNP levels, and treatment-by-visit interaction (143).

Mean differences between the SGLT2 group and placebo were analysed using marginal or squared means in LMEM after 52 weeks. Results were tested for clinical significance using P-values with a two-sided 95% confidence interval (CI) derived through bootstrap techniques. Superiority over placebo was established with an alpha level of 5% based on a two-sided test for the primary efficacy analysis (143).

To mitigate the influence of outliers, sensitivity analysis was performed using robust estimation approaches for the negative binomial model, including Tukey’s biweight function on the Pearson residuals and the Mahalanobis distance for covariate weighting. P-values <0.05 were considered statistically significant.

3 Results

A total of 476 patients were successfully enrolled in the EMMY trial, receiving either 10 mg Empagliflozin or placebo within 72 hours after presentation with acute myocardial infarction. Of these, 237 patients were randomized to receive Empagliflozin and 239 patients were randomized to receive placebo. The primary endpoint NT-proBNP was found to be significantly lower in the Empagliflozin group by approximately 15% compared to placebo. Secondary endpoints including structural and functional cardiac parameters showed a significantly greater decrease in LVEDV and LVESV by 9.7ml and 7.5ml respectively for Empagliflozin, whereas functional cardiac parameters showed a significantly better response in LVEF by 1.5% and significantly greater decrease in E/e` by 6.8% for Empagliflozin compared to placebo (72).

3.1 Subanalysis of Inflammation Data

3.1.1 Baseline Characteristics*

A total of 374 patients (78.6% of the entire EMMY cohort) with available frozen blood samples from three visits at all Austrian sites were enrolled in the inflammation subanalysis. Of these, 191 patients (51.1%) were randomly assigned to the Empagliflozin group, and 183 patients (48.9%) were assigned to the placebo group. Although only 80% of the entire cohort with available frozen blood samples were included in this subanalysis, baseline characteristics showed similar results in both groups compared to the main trial (72) (**Table 2**).

Baseline parameters were equally distributed between the Empagliflozin group and the placebo group, with a median (interquartile range) age of 57 years (52–64), 81.5% male patients, and a median body mass index (BMI) of 27.7 kg/m² (25.5–30.3). A history of arterial hypertension was reported in 41.7% of all patients. The median (IQR) systolic blood pressure was 125 mmHg (117–131), with a mean diastolic blood pressure of 78 mmHg (74–85). At baseline, 80.75% of all patients achieved adequate blood pressure control below 140/90 mmHg, while 60.70% of all patients showed normal blood pressure at week 26. Regarding further cardiovascular risk factors, type 2 diabetes mellitus (T2DM)

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was present in 13.7% of all patients, dyslipidaemia in 27.3%, and chronic nicotine abuse in 71.4%. 8.0% of all patients had a positive history of coronary artery disease (CAD) before the index event, with a history of acute myocardial infarction (AMI) in 4.3%. A history of stroke and peripheral artery disease (PAD) was present in 1.3% of all participants.
Laboratory measurements revealed a median (IQR) LDL cholesterol of 123 mg/dL (96–150) at baseline and 54 mg/dL (43–69) at week 26, whereas only 3% achieved an LDL target of <55 mg/dL at baseline compared to 51% at week 26. Median HDL cholesterol levels were 43 mg/dL (36–52), and total cholesterol was 192 mg/dL (165–223).
Baseline median (IQR) NT-proBNP levels were 1365 pg/mL (773–2192), median creatine kinase was 1648 U/L (1201–2452), median Troponin T was 3003 ng/L (2047–4647), and the median estimated glomerular filtration rate was 92.0 mL/min/1.73 m² (78.1–100.7).
Functional echocardiographic parameters showed a median (interquartile range) LVEF of 48.0% (43.0–53.7) and a median E/e´ of 9.1 (7.5–10.7).
A vast majority of patients received standard post-AMI treatment according to recent guidelines, including ACE-I/ARB (98%), beta-blockers (98%), MRAs (38%), statins (98%), and platelet inhibitory drugs (100%). Additionally, 12% of all participants received Ezetimibe, 6.9% anticoagulation, 10% metformin, and 0.8% GLP-1 receptor agonists (**Table 2**).

Table 2. Baseline characteristics of inflammatory subanalysis stratified by treatment

Characteristics	All	Empagliflozin	Placebo
All, *n (%)*	374	191 (51.07)	183 (48.93)
Sex, *n (%)*			
Male	305 (82)	160 (84)	145 (79)
Female	69 (18)	31 (16)	38 (21)
Age (years), median (IQR)	57 (52–64)	57 (52–64)	57 (52–65)
BMI (kg/m^2), median (IQR)	27.7 (25.2–30.3)	27.7 (25.3–30.2)	27.7 (25.1–30.3)
Type 2 Diabetes, *n (%)*	51 (14)	24 (13)	27 (15)
Systolic BP (mmHg), median (IQR)	125 (117–131)	125 (115–131)	125 (118–131)
Diastolic BP (mmHg), median (IQR)	78 (74–85)	78 (74–85)	78 (74–85)
Smoking (active or former), *n* (%)	267 (71)	138 (72)	129 (70)
Dyslipidaemia, *n (%)*	102 (27)	61 (32)	41 (22)
Hypertension, *n (%)*	156 (42)	73 (38)	83 (45)
History of CAD, *n (%)*	30 (8)	19 (10)	11 (6)
Stroke, *n (%)*	5 (1.3)	4 (2.1)	1 (0.6)
Laboratory parameters			
eGFR (mL/min/173m^2), median (IQR)	92 (78–101)	93 (78–101)	90 (78–100)
Creatine kinase (U/L), median (IQR)	1648 (1201–2452)	1596 (1126–2478)	1669 (1257–2417)
Troponin T (ng/L), median (IQR)	3003 (2047–4647)	2947 (2062–4628)	3020 (1996–4871)
Total cholesterol (mg/dL), median (IQR)	192 (165–223)	192 (165–225)	191 (166–222)
LDL-cholesterol, (mg/dL), median (IQR)	123 (96–150)	122 (98–151)	123 (92–146)
HDL-cholesterol (mg/dL), median (IQR)	43 (36–52)	43 (36–52)	43 (36–52)
LVEF (%), median (IQR)	48 (43–54)	48 (43–53)	49 (43–55)
E/e‘, median (IQR)	9 (7–11)	9 (7–11)	9 (8–11)
NT-proBNP (pg/mL), median (IQR)	1365 (773–2192)	1271 (753–2127)	1436 (800–2217)
Treatment			
ACE-I/ARB, *n (%)*	361 (98)	186 (98)	175 (97)
Beta-blocker, *n (%)*	360 (96)	181 (95)	179 (98)
MRA, *n (%)*	143 (38)	70 (37)	73 (40)
Statin, *n (%)*	368 (98)	187 (98)	181 (99)
Ezetimibe, *n (%)*	43 (12)	23 (12)	20 (11)
Platelet inhibitory drugs, *n (%)*	374 (100)	191 (100)	183 (100)
Anticoagulation drugs, *n (%)*	26 (6.9)	11 (5.8)	15 (8.2)
Metformin, *n (%)*	37 (10.0)	17 (8.9)	20 (10.9)
GLP1-RA, *n (%)*	3 (0.8)	1 (0.5)	2 (1.1)

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SD, standard deviation; IQR, interquartile range, LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE-I, angiotensin-converting enzyme inhibitor;

ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; GLP1-RA, glucagon-like peptide 1 receptor agonist. This table has been modified from the publication in the Cardiovascular diabetology journal; 2017. DOI: 10.1186/s12933-023-01904-6. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

3.1.2 Endpoint Analysis*

Baseline inflammatory metrics within the first 72 hours post AMI were elevated and distributed equally between both groups, revealing a median hsCRP of 18.9 mg/L (11.2–37.1), a median IL-6 (IQR) of 17.9 pg/mL (9.0–38.7), a median neutrophil rate of 7.9x10^9/L (6.2–10.1), a median leukocyte rate of 10.8x10^9/L (9.1–12.8), a median NLR of 0.74 (0.67–0.80), and a median PLR of 125.58 (97.14–171.82).
Trajectories of inflammatory biomarkers from baseline to week 26 showed a significant mean decrease of 57.4 ±0.7% for hsCRP ($p<0.001$), 35.1 ±3.2% for IL.6 ($p<0.001$), 26.1 ±0.7% (0.001) for neutrophils, 20.5 ±0.6% ($p<0.001$) for leukocytes, 10.2 ±0.5% ($p<0.001$) for NLR, and -2.53 ±0.92% for PLR ($p=0.006$). These decreases were already evident at week 6 post-AMI; however, no significant difference was observed between Empagliflozin and placebo. Although median hsCRP and IL-6 levels at week 26 were lower in the Empagliflozin group ($p=0.52$ and $p=0.65$, respectively), they did not reach statistical significance compared to placebo. Similarly, leukocytes, neutrophils, NLR, and PLR showed no significant differences between the groups up to week 26 (**Figure 1 and Table 3**).

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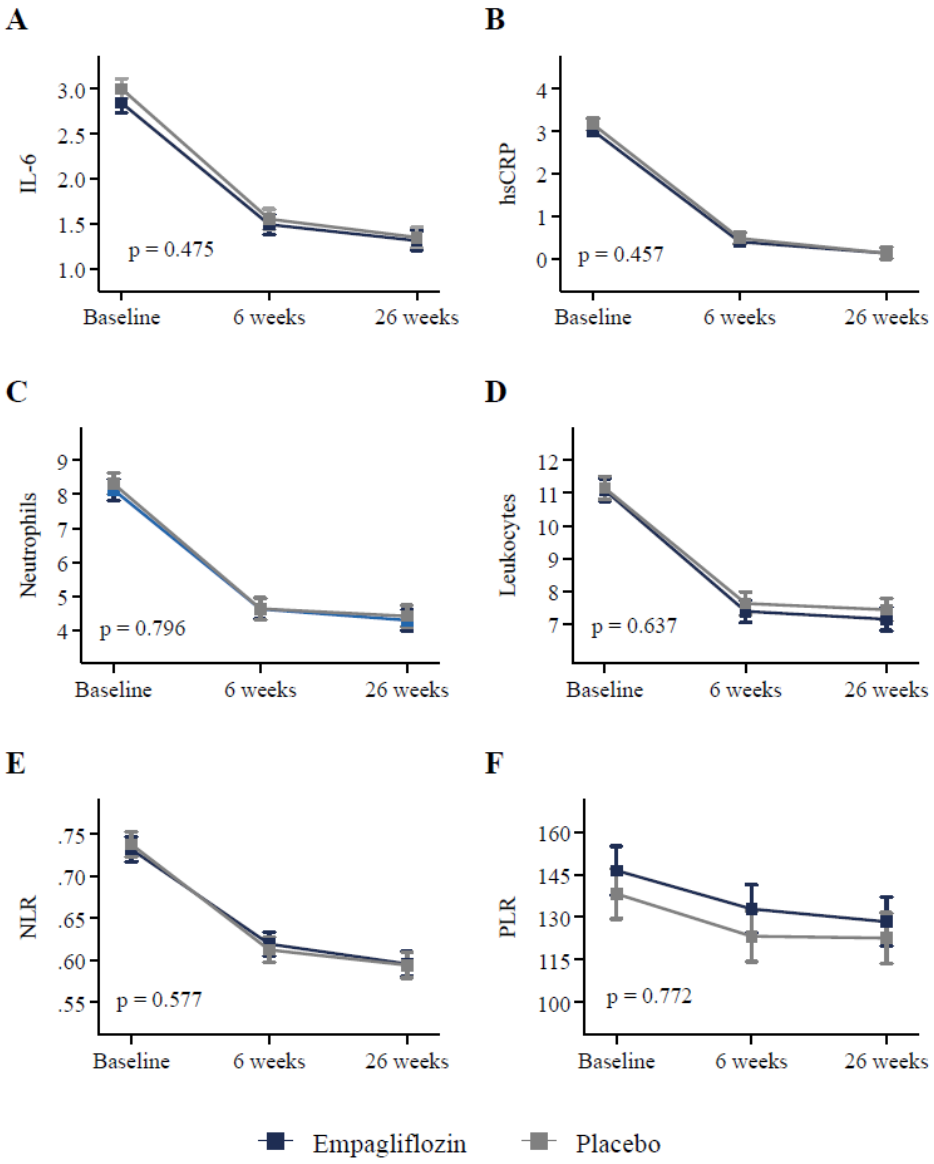
Figure 1. Changes in inflammatory parameters by treatment over time



**p = p-value for treatment-visit interaction, IL-6 and hsCRP values were log-transformed*
hsCRP, high-sensitivity C-reactive protein; IL-6, interlukin-6; NLR, neutrophil-lymphocyte ratio, PLR platelet to lymphocyte ratio. This figure has been modified from the publication in the Cardiovascular diabetology journal; 2017. DOI: 10.1186/s12933-023-01904-6. This figure is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Table 3. Percentage change in inflammatory markers over time by treatment

	Baseline median (IQR)	**6 weeks** median (IQR)	**26 weeks** median (IQR)	**% change** Mean ±SEM	**% change (Empagliflozin - Placebo)** Mean ±SEM	**P-value***
IL-6						
All	17.90 (9.00–38.70)	4.10 (3.20–5.70)	3.40 (2.70–4.60)	-35.13 ±3.16		<0.001
Empagliflozin	16.20 (8.70–34.70)	4.10 (3.10–5.40)	3.20 (2.70–4.30)	-33.72 ±4.42	-2.88 ±6.31	0.649
Placebo	19.50 (9.10–40.90)	4.10 (3.20–6.00)	3.40 (2.80–4.80)	-36.60 ±4.52		
hsCRP						
All	18.85 (11.20–37.10)	1.15 (0.70–2.70)	0.80 (0.60–1.70)	-57.37 ±0.71		<0.001
Empagliflozin	17.80 (10.40–35.70)	1.20 (0.70–2.30)	0.80 (0.60–1.00)	-57.82 ±1.00	0.92 ±1.43	0.521
Placebo	21.40 (12.30–40.80)	1.10 (0.60–3.00)	0.90 (0.60–1.70)	-56.90 ±1.02		
Neutrophils						
All	7.90 (6.20–10.10)	4.48 (3.50–5.50)	4.11 (3.31–5.01)	-26.09 ±0.72		<0.001
Empagliflozin	7.75 (6.27–9.75)	4.50 (3.60–5.40)	4.19 (3.35–5.00)	-25.82 ±1.01	-0.56 ±1.44	0.700
Placebo	7.90 (6.10–10.10)	4.40 (3.40–5.60)	4.00 (3.20–5.10)	-26.37 ±1.03		
Leukocytes						
All	10.77 (9.10–12.80)	7.30 (6.26–8.65)	7.03 (5.87–8.37)	-20.46 ±0.60		<0.001
Empagliflozin	10.69 (9.01–12.62)	7.25 (6.26–8.46)	7.03 (6.10–8.06)	-20.89 ±0.84	0.87 ±1.20	0.469
Placebo	10.90 (9.20–12.83)	7.37 (6.25–8.74)	7.02 (5.71–8.53)	-20.02 ±0.86		
NLR						
All	0.74 (0.67–0.80)	0.61 (0.56–0.68)	0.59 (0.53–0.66)	-10.22 ±0.50		<0.001
Empagliflozin	0.74 (0.67–0.80)	0.60 (0.56–0.67)	0.59 (0.53–0.66)	-9.69 ±0.71	-1.11 ±1.01	0.272
Placebo	0.74 (0.66–0.80)	0.62 (0.56–0.68)	0.60 (0.54–0.66)	-10.79 ±0.72		
PLR						
All	125.58 (97.14–171.82)	117.00 (92.78–147.69)	115.38 (91.51–148.23)	-2.53 ±0.92		0.006
Empagliflozin	127.38 (100.00–170.71)	113.96 (92.73–150.63)	115.10 (91.82–154.44)	-2.50 ±1.29	-0.06 ±1.84	0.974
Placebo	124.58 (93.04–173.33)	120.92 (94.00–146.91)	116.57 (91.13–145.38)	-2.56 ±1.32		

**p-values are reported for the average percentage change in inflammatory markers from baseline to 26 weeks.*

IQR, interquartile range; SD, standard deviation; Standard Error of Mean, SEM; hsCRP, high-sensitivity C-reactive protein; IL-6, interlukin-6; NLR, neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio. This table has been modified from the publication in the Cardiovascular diabetology journal; 2017. DOI: 10.1186/s12933-023-01904-6. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

3.1.3 Correlation Analysis*

In our correlation analysis performed using a univariable linear mixed-effects model (LMEM), we observed significant correlations of the cardiac biomarkers NT-proBNP ($p<0.001$) and Troponin T ($p<0.001$) with hsCRP, IL-6, and NLR. The functional cardiac parameter LVEF was found to be significantly correlated with hsCRP ($p<0.001$) and IL-6 ($p<0.001$), whereas E/e´ was only significantly associated with IL-6 ($p<0.001$). Finally, BMI was significantly associated with hsCRP ($p<0.001$).
However, those parameters that appeared to be significantly correlated with inflammatory biomarkers in the univariable LMEM were included in further multivariable LMEM analysis, along with treatment, visit, age, sex, diabetes, and treatment-visit interaction (**Table 4**).

Table 4. Univariable linear mixed effects model of inflammatory parameters with clinical variables

Markers	Log-IL-6		Log-hsCRP		NLR		PLR	
	Coef ±SEM	p-value	Coef ±SEM	p-value	Coef ±SEM	p-value	Coef ±SEM	p-value
Age	0.0004 ±0.003	0.894	-0.002 ±0.003	0.580	0.001 ±0.001	0.011	1.23 ±0.29	<0.001
Sex (female/male)	0.062 ±0.069	0.367	0.204 ±0.082	0.014	0.014 ±0.010	0.175	10.33 ±0.703	0.141
BMI	0.020 ±0.006	0.001	0.040 ±0.007	<0.001	0.001 ±0.001	0.195	-1.11 ±0.63	0.081
Diabetes (yes/no)	0.103 ±0.077	0.182	0.042 ±0.094	0.655	-0.008 ±0.012	0.485	-20.82 ±7.93	0.009
Smoking (yes/no)	0.076 ±0.059	0.196	0.141 ±0.071	0.046	-0.012 ±0.009	0.150	-28.86 ±5.82	<0.001
Hyperlipidemia (yes/no)	0.004 ±0.060	0.949	0.063 ±0.073	0.387	-0.017 ±0.009	0.055	-13.54 ±6.09	0.026
Hypertension (yes/no)	0.130 ±0.054	0.016	0.114 ±0.065	0.081	-0.003 ±0.008	0.710	0.05 ±5.54	0.992
eGFR	-0.001 ±0.001	0.471	0.001 ±0.001	0.645	<-0.001± <0.001	0.229	-0.12 ±0.11	0.298
LVEF	-0.014 ±0.003	<0.001	-0.016 ±0.004	<0.001	<0.001 ±<0.001	0.512	0.27 ±0.23	0.235
E/é	0.040 ±0.010	<0.001	0.027 ±0.012	0.022	<0.001 ±<0.001	0.701	0.35 ±0.72	0.622
NT-proBNP	0.224 ±0.026	<0.001	0.196 ±0.031	<0.001	0.013 ±0.004	<0.001	5.87 ±2.03	0.004
Creatine kinase	0.125 ±0.041	0.002	0.087 ±0.048	0.071	-0.0004 ±0.005	0.933	-2.32 ±2.50	0.353
Troponin T	0.187 ±0.040	<0.001	0.226 ±0.047	<0.001	0.024 ±0.005	<0.001	2.91 ±2.75	0.289

BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; IL-6, interlukin-6; NLR, neutrophil-lymphocyte ratio; SEM, Standard Error of Mean; PLR, platelet-lymphocyte ratio. This table has been modified from the publication in the Cardiovascular diabetology journal; 2017. DOI: 10.1186/s12933-023-01904-6. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

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In the multivariable LMEM, we identified significant positive correlations between hsCRP, NLR, and IL-6 with Troponin T ($p<0.001$), highlighting that larger infarct size is associated with a higher inflammatory response post-AMI. IL-6 showed positive correlations with NT-proBNP levels ($p<0.001$), consistent with the observation that a higher inflammatory response is associated with worse cardiac outcomes. Functional cardiac parameters (LVEF and E/e´) demonstrated negative correlations with IL-6 ($p<0.001$) and hsCRP ($p<0.001$), suggesting that inflammatory response is also related to worse cardiac function. BMI was found to be significantly associated with hsCRP ($p<0.001$), indicating a higher inflammatory response in STEMIs with greater BMI at baseline. However, across the entire multivariable analysis of inflammatory biomarkers, no relevant treatment effects could be demonstrated (**Table 5**).

Table 5. Multivariable linear mixed effects model of inflammatory parameters with clinical variables

Markers	Coefficient	SEM	p-value	p-interaction
IL-6				
BMI	0.017	0.006	0.005	0.204
LVEF	-.01406	0.003	<0.001	0.590
E/é	0.038	0.010	<0.001	0.060
NT-proBNP	0.253	0.027	<0.001	0.557
Creatine Kinase	0.140	0.077	0.001	0.996
Troponin T	0.202	0.040	<0.001	0.145
hsCRP				
Sex (female/male)	0.265	0.077	0.001	0.991
BMI	.03899	0.007	<0.001	0.491
Smoking	0.151	0.069	0.030	0.647
LVEF	-0.016	0.003	<0.001	0.112
E/é	0.023	0.012	0.042	0.386
NT-proBNP	0.220	0.032	0.008	0.768
Creatine Kinase	0.117	0.048	0.014	0.861
Troponin T	0.269	0.047	<0.001	0.210
NLR				
Age	0.001	0.001	0.011	0.595
NT-proBNP	0.012	0.004	0.002	0.718
Troponin T	0.023	0.005	<0.001	0.579
PLR				
Age	0.005	0.002	0.028	0.281
Diabetes	-0.121	0.056	0.030	0.426
Smoking	-0.163	0.044	<0.001	0.297
NT-proBNP	0.027	0.013	0.043	0.072

**p-interaction = p-value for treatment interaction with each variable*

BMI, body mass index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; IL-6, interlukin-6; NLR, neutrophil-lymphocyte ratio; SEM, Standard Error of Mean; PLR, platelet-lymphocyte ratio. This table has been modified from the publication in the Cardiovascular diabetology journal; 2017. DOI: 10.1186/s12933-023-01904-6. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

3.2 Subanalysis of ECG Data

3.3 Baseline Characteristics[#]

For the ECG subanalysis, we successfully enrolled 181 patients from the Grazer cohort of the Medical University of Graz with available baseline ECGs one day post-AMI. Despite the small number of participants in this post-hoc analysis, baseline parameters were equally distributed between the Empagliflozin and placebo groups and were comparable to those of the overall EMMY cohort (72).
Of all participants, 80.7% were male, with a mean age of 58 ±14 years and a mean BMI of 27.7 ±5.1 kg/m². Cardiovascular risk factors included arterial hypertension, present in 34.4% of enrolled patients, with a mean systolic blood pressure of 125 ±11 mmHg and a diastolic blood pressure of 77 ±8 mmHg, as well as dyslipidaemia in 9.4%, type 2 diabetes mellitus (T2DM) in 13.3%, and active or previous nicotine abuse in 69.6%.
A medical history of stroke was reported in 1.7% of participants, carcinomas in 3.9%, coronary artery bypass grafting (CABG) in 2.2%, coronary artery disease in 6%, and depression in 4.4%. At initial presentation with ACS, 42.5% of patients suffered from single-vessel disease, 35.9% from two-vessel disease, and 21.5% from three-vessel disease (**Table 6**).

Echocardiographic metrics showed functional cardiac findings with a median (IQR) LVEF of 47% (43–52) and an E/e´ of 9 (7–11). Structural cardiac parameters were reported as a median (IQR) LVEDD of 50 mm (46–53), a median LVESD of 37 mm (33–41), a median LVESV of 66 mL (52–78), and a median LVEDV of 125 mL (104–141).

[#] *Parts of this chapter have been published in Scientific Reports. (2024). DOI: 10.1038/s41598-024-64175-5*

Laboratory findings showed a median (IQR) NT-proBNP of 1 421 pg/mL (860–2246), a median troponin T of 3185 µg/L (2099–5117), a median creatine kinase of 1623 U/L (1156–2289), and a median eGFR of 92 mL/min/m² (78–100) (**Table 6**).

Table 6. Baseline characteristics of ECG subanalysis stratified by treatment

Variables	All	Empagliflozin	Placebo
	N = 181	N = 93	N = 88
Age (years), median (IQR)	58 (52 – 66)	57 (52 – 65)	58 (52 – 68)
Gender, n (%)			
Male	146 (80.66)	79 (84.95)	67 (76.14)
Female	35 (19.34)	14 (15.05)	21 (23.86)
Body mass index (kg/m^2), median (IQR)	28 (25 – 30)	28 (25 – 31)	28 (25 – 30)
Systolic blood pressure (mmHg), median (IQR)	125 (118 – 129)	126 (117 – 129)	125 (118 – 130)
Diastolic blood pressure (mmHg), median (IQR)	77 (73 – 81)	76 (73 – 80)	77 (73 – 81)
Smoking (active or former), n (%)	126 (69.61)	65 (69.89)	61 (69.32)
Type 2 diabetes, n (%)	24 (13.26)	11 (11.83)	13 (14.77)
Hypertension, n (%)	62 (34.25)	30 (32.26)	32 (36.36)
Hyperlipidemia, n (%)	17 (9.39)	9 (9.68)	8 (9.09)
Coronary artery disease, n (%)	12 (6.63)	8 (8.60)	4 (4.55)
History of CABG, n (%)	2 (1.10)	1 (1.08)	1 (1.14)
History of stroke, n (%)	3 (1.66)	2 (2.15)	1 (1.14)
Depression, n (%)	7 (3.87)	1 (1.08)	6 (6.82)
History of carcinoma, n (%)	8 (4.42)	5 (5.38)	3 (3.41)
Coronary artery angiography vessel status, n (%)			
1-vessel disease	77 (42.54)	31 (33.33)	46 (52.27)
2-vessel disease	65 (35.91)	37 (39.78)	28 (31.82)
3-vessel disease	39 (21.55)	25 (26.88)	14 (15.91)
Treatment			
ACE-1/ARB, n (%)	179 (100.00)	92 (100.00)	87 (100.00)
ARNI, n (%)	4 (2.21)	1 (1.08)	3 (3.41)
Beta-blocker, n (%)	177 (97.79)	91 (97.85)	86 (97.73)
MRA, n (%)	101 (55.80)	52 (55.91)	49 (55.68)
Loop diuretic, n (%)	16 (8.84)	11 (11.83)	5 (5.68)
Statin, n (%)	181 (100.0)	93 (100.0)	88 (100.0)
Ezetimibe, n (%)	3 (1.66)	3 (3.23)	0 (0.00)
Calcium channel blocker, n (%)	8 (4.42)	2 (2.15)	6 (6.82)
Platelet aggregation inhibitor, n (%)	181 (100)	93 (100)	88 (100.00)
Anticoagulation drugs, n (%)	15 (8.29)	7 (7.53)	8 (9.09)
Metformin, n (%)	14 (7.73)	6 (6.45)	8 (9.09)
DPP-4 inhibitor, n (%)	8 (4.42)	4 (4.30)	4 (4.55)
Sulfonylurea, n (%)	1 (0.55)	1 (1.08)	0 (0.00)
GLP1-RA, n (%)	2 (1.10)	1 (1.08)	1 (1.14)
Insulin, n (%)	6 (3.31)	2 (2.15)	4 (4.55)
Laboratory parameters			
HbA1c (%), median (IQR)	5.60 (5.40 – 6.00)	5.60 (5.40 – 6.00)	5.70 (5.40 – 6.00)
eGFR (ml/min), median (IQR)	92.68 (78.97 – 100.16)	92.79 (78.88 – 99.13)	91.87 (79.31 – 102.24)
Haemoglobin (g/dL), median (IQR)	14.00 (13.10 – 15.00)	14.00 (13.10 – 14.80)	14.10 (13.10 – 15.10)
Creatine kinase (U/L), median (IQR)	1623 (1156 – 2289)	1491 (1099 – 2209)	1715 (1219 – 2347)
Troponin T (µg/L), median (IQR)	3185 (2099 – 5117)	3460 (2253 – 5285)	3070 (2099 – 5099)
Total cholesterol (mg/dL), median (IQR)	184 (157 – 223)	182 (157 – 223)	187 (158 – 223)
LDL-cholesterol (mg/dL), median (IQR)	117 (89 – 145)	110 (90 – 144)	121 (87 – 150)
HDL-cholesterol (mg/dL), median (IQR)	42 (36 – 53)	43 (36 – 52)	42 (36 – 55)
Aspartate aminotransferase (U/L), median (IQR)	239 (171 – 332)	223 (175 – 332)	255 (142 – 332)
Alanine Aminotransferase (U/L), median (IQR)	48 (36 – 74)	49 (34 – 75)	48 (36 – 72)
Gamma Glutamyltransferase (U/L), median (IQR)	32 (20 – 53)	33 (21 – 57)	31 (19 – 51)
Outcomes			
NT-proBNP (pg/m), median (IQR)	1421 (860 – 2246)	1143 (850 – 2070)	1650 (950 – 2539)
LVEF (%), median (IQR)	47 (43 – 52)	48 (44 – 52)	47 (42 – 52)
LVEDD (mm), median (IQR)	50 (46 – 53)	50 (47 – 53)	49 (46 – 53)
LVESD (mm), median (IQR)	37 (33 – 41)	37 (33 – 41)	37 (33 – 41)
LVEDV (ml), median (IQR)	125 (104 – 141)	127 (107 – 143)	123 (102 – 141)
LVESV (ml), median (IQR)	66 (52 – 78)	66 (52 – 78)	66 (51 – 78)
E/é	8.85 (7.47 – 10.58)	8.84 (7.39 – 10.56)	8.85 (7.54 – 11.01)

CABG, coronary artery bypass graft; ACE-I, angiotensin-converting enzyme inhibitor; ARNI, angiotensin-receptor neprilysin inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; DPP-4, dipeptidyl peptidase inhibitor 4; GLP1-RA, glucagon-like peptide 1 receptor agonist; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SD, standard deviation; IQR, interquartile range. This table has been modified from the publication in the Cardiovascular diabetology journal; 2017. DOI: 10.1038/s41598-024-64175-5. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

3.3.1 Baseline ECG Metrics#

We report a median (IQR) P-wave duration of 100 ms (80–100) with a median P-wave amplitude of 0.10 mV (0.10–0.10) for atrial conduction, and a median QRS width of 92 ms (84–98) with a median QRS amplitude of 1.50 mV (1.20–1.90) for ventricular conduction. The atrioventricular conduction time, represented by the median PQ interval, was 156 ms (144–174), and the QTc interval showed a median of 453 ms (428–470). The heart rate had a median of 71 bpm (64–85) across the entire analysis. Representing cardiac mass and myocardial hypertrophy, the Sokolow-Lyon index revealed a median of 1.40 mV (1.10–1.90) (**Table 7**).

Q-waves, as a pattern of myocardial scarring after transmural infarction, were present in 49.2% of all participants, with a median duration of 45 ms (40–65) and a median Q-wave amplitude of 0.40 mV (0.30–0.70). Relevant pathological Q-waves >40 ms in duration were observed in 85.6% of the patients.

ST-elevation myocardial infarction (STEMI) was prevalent in 87.6% of the patients. However, in 64.1%, ST-elevation was still present one day post-PCI, with a median ST-elevation of 0.10 mV (0.10–0.20). ST-depressions were found in 27.1% of patients, while T-inversions were observed in 76.8%.

We further report the distribution of the electrical axis, with left axis deviation in 58.6% of participants, a normal axis in 38.7%, right axis deviation in 2.2%, and extreme axis deviation in 0.55% (**Table 7**).

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Table 7. Baseline ECG metrics overall and by treatment

ECG parameter	All	Empagliflozin	Placebo
N	181 (100.0%)	93 (51.4%)	88 (48.6%)
PQ interval (ms)	156.00 (144.00-174.00)	156.00 (144.00-174.00)	156.00 (144.00-172.00)
QRS amplitude (mV)	1.50 (1.20-1.90)	1.50 (1.20-1.80)	1.60 (1.20-1.95)
QRS width (ms)	92.00 (84.00-98.00)	90.00 (86.00-100.00)	94.00 (83.00-98.00)
Sokolow-Lyon index (mV)	1.40 (1.10-1.90)	1.40 (1.10-1.80)	1.50 (1.15-2.00)
QTc interval (ms)	453.00 (428.00-478.00)	452.00 (426.00-474.00)	454.00 (429.50-482.00)
P-wave duration (ms)	100.00 (80.00-100.00)	100.00 (80.00-100.00)	90.00 (80.00-100.00)
P-wave amplitude (mV)	0.10 (0.10-0.10)	0.10 (0.10-0.10)	0.10 (0.10-0.10)
Cardiac axis			
Normal axis	70 (38.67%)	35 (37.63%)	35 (39.77%)
Extreme axis deviation	1 (0.55%)	0 (0.00%)	1 (1.14%)
Left axis deviation	106 (58.56%)	56 (60.22%)	50 (56.82%)
Right axis deviation	4 (2.21%)	2 (2.15%)	2 (2.27%)
ST elevation (mV)	0.10 (0.10-0.20)	0.10 (0.10-0.20)	0.10 (0.10-0.20)
ST elevation			
No	65 (35.91%)	37 (39.78%)	28 (31.82%)
Yes	116 (64.09%)	56 (60.22%)	60 (68.18%)
ST depression			
No	132 (72.93%)	69 (74.19%)	63 (71.59%)
Yes	49 (27.07%)	24 (25.81%)	25 (28.41%)
T- inversion			
No	42 (23.20%)	21 (22.58%)	21 (23.86%)
Yes	139 (76.80%)	72 (77.42%)	67 (76.14%)
Ischemic changes			
No	171 (94.48%)	87 (93.55%)	84 (95.45%)
Yes	10 (5.52%)	6 (6.45%)	4 (4.55%)
MI type			
NSTEMI	22 (12.36%)	12 (13.33%)	10 (11.36%)
STEMI	156 (87.64%)	78 (86.67%)	78 (88.64%)
Heart rate (bpm)	71.00 (64.00-85.00)	69.00 (62.00-85.00)	71.50 (64.50-84.00)
Q-wave			
No	91 (50.84%)	46 (50.00%)	45 (51.72%)
Yes	88 (49.16%)	46 (50.00%)	42 (48.28%)
Q-wave duration (ms)	45.00 (40.00-60.00)	40.00 (40.00-60.00)	60.00 (40.00-60.00)
Q-wave duration			
<40 ms	13 (14.44%)	8 (17.02%)	5 (11.63%)
≥40 ms	77 (85.56%)	39 (82.98%)	38 (88.37%)
Q-wave amplitude (mV)	0.40 (0.30-0.70)	0.40 (0.30-0.70)	0.50 (0.30-0.80)

ms, milliseconds; mV, millivolt; STEMI, ST-segment elevating myocardial infarction; NSTEMI, non-ST-segment elevating myocardial infarction; bpm, beats per minute. This table has been modified from the publication in the Cardiovascular diabetology journal; 2017. DOI: 10.1038/s41598-024-64175-5. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

3.3.2 Correlation Analysis#

Within the entire post-hoc analysis, no significant interaction between ECG metrics, EMMY endpoints, and treatment groups could be detected. As a result, the Empagliflozin and placebo groups were merged to estimate the associations between ECG baseline parameters and the response in EMMY outcomes, regardless of SGLT2-I treatment. Changes in the cardiac biomarker NT-proBNP were found to have no significant correlation with ST-elevation (p=0.897), AMI type (p=0.183), Q-wave duration (p=0.44) and amplitude (p=0.959), presence of Q-waves (p=0.252), PQ interval (p=0.878), QRS width (p=0.32), QTc interval (p=0.959), or the Sokolow-Lyon index (p=0.055). Similarly, the cardiac biomarker Troponin T showed no significant correlation with changes in EMMY trial endpoints.

The functional cardiac parameter LVEF was observed to have no significant association with ST-elevation (p=0.277), Q-wave duration (p=0.797) and amplitude (p=0.513), Q-wave presence (p=0.666), AMI type (p=0.379), PQ interval (p=0.094), QTc interval (p=0.60), QRS width (p=0.498), or the Sokolow-Lyon index (p=0.769).
Similar results were found for the diastolic function E/e´, which revealed no significant correlation with ST-elevation (p=0.258), Q-wave duration (p=0.643) and amplitude (p=0.312), Q-wave presence (p=0.258), QTc interval (p=0.19), PQ interval (p=0.158), or the Sokolow-Lyon index (p=0.232). However, a significant positive correlation was identified with QRS width (p=0.005), suggesting a greater increase in diastolic function in patients with smaller QRS complexes (**Figure 2**).

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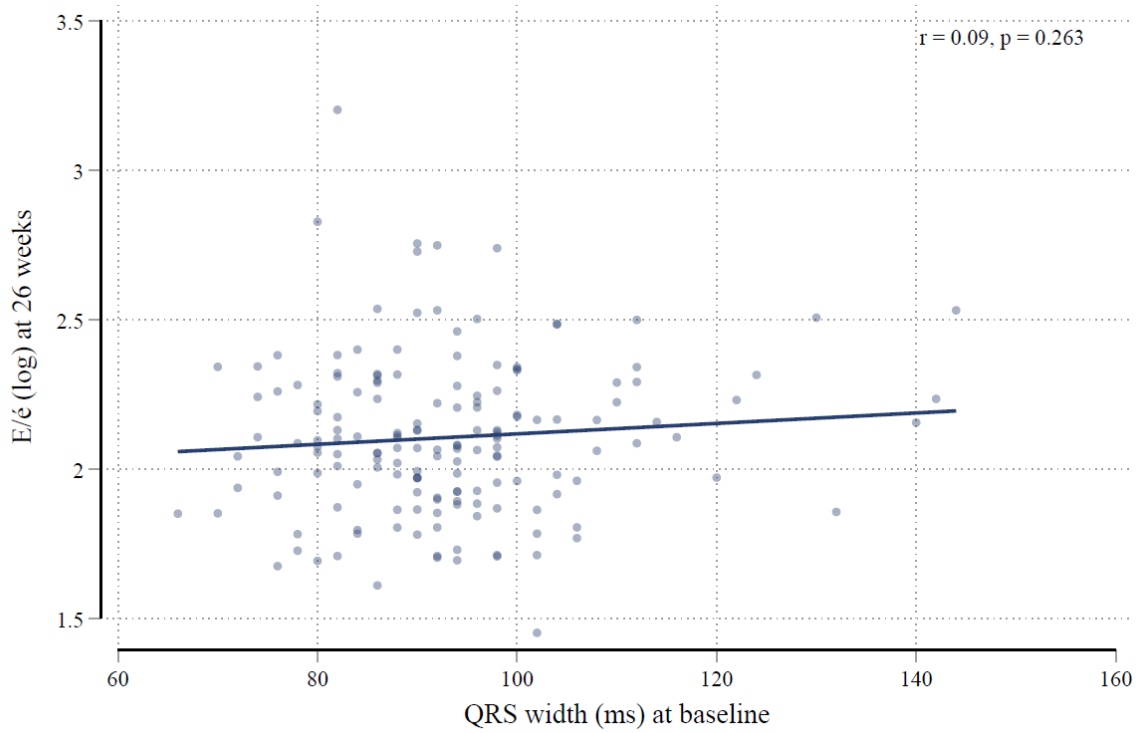
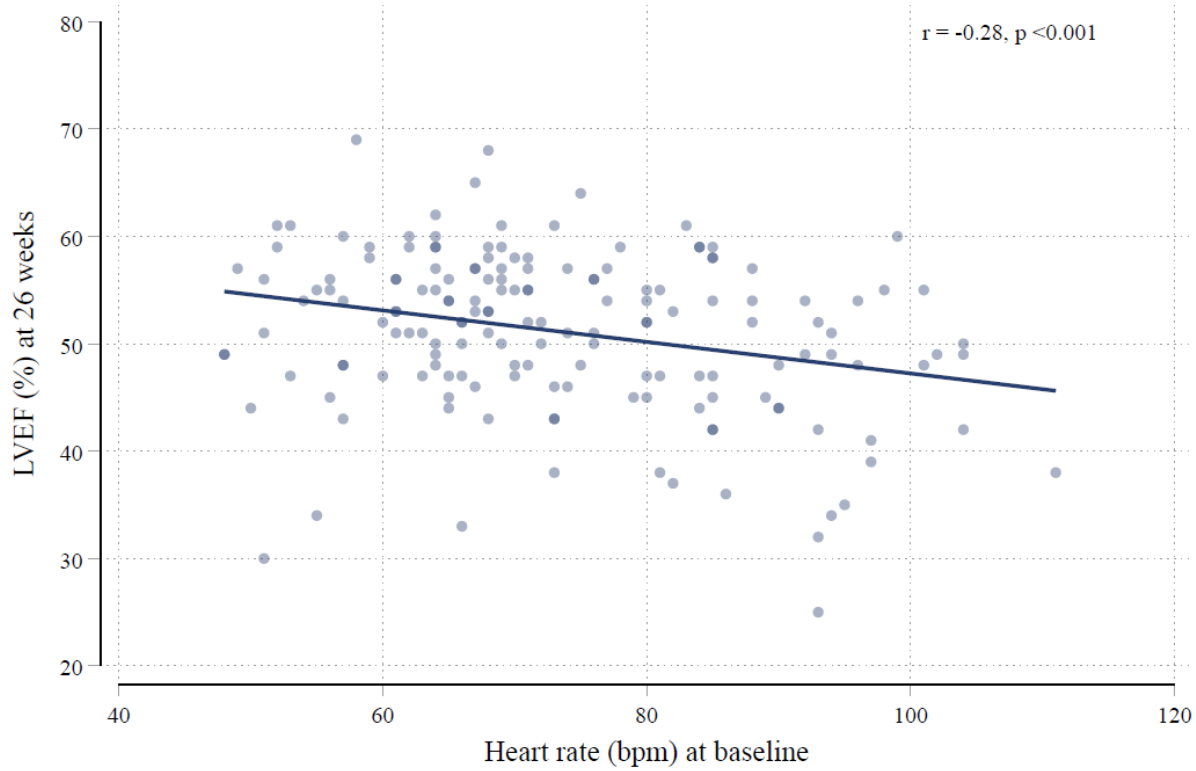
Figure 2. Correlation plot of the diastolic function (E/e´) with QRS width at week 26



log, logarithm; ms, millisecond

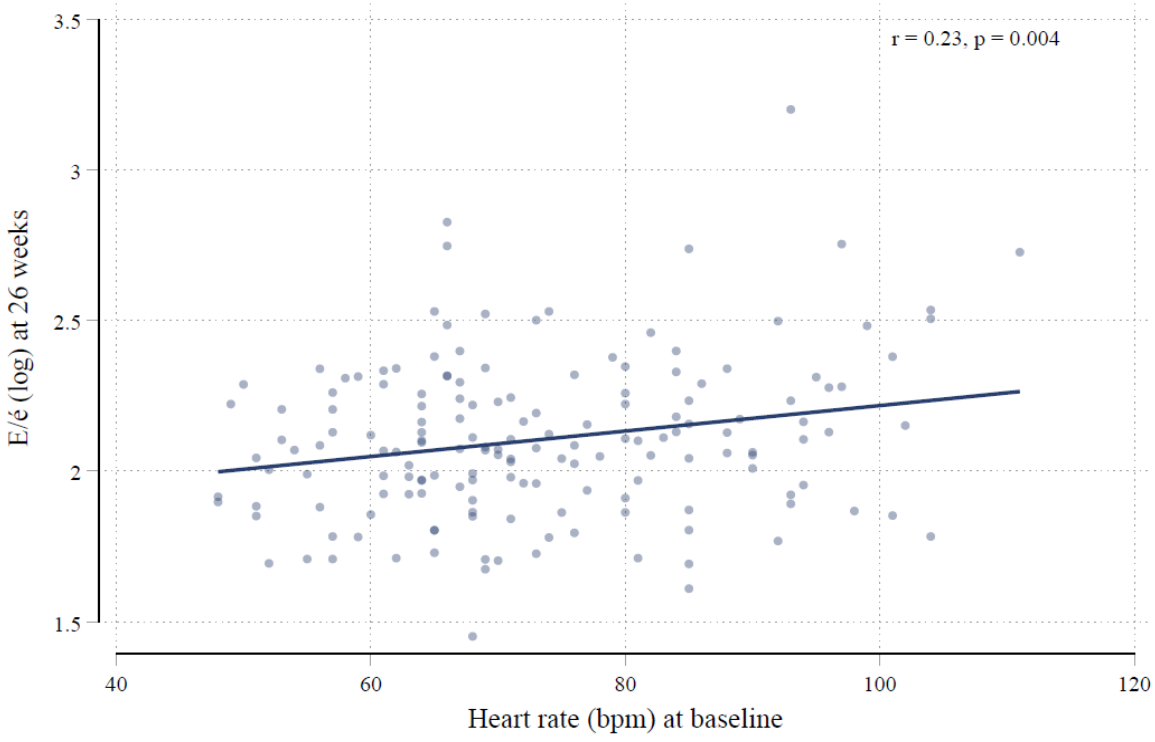
Ventricular heart rate was found to be significantly correlated with the response of NT-proBNP levels (p=0.005), LVEF (p=0.001), and E/e´ (p=0.021). This corresponds to a decreased response in both systolic and diastolic cardiac function at higher heart rates and a less pronounced reduction in NT-proBNP levels (**Figure 3-5**).

Figure 3. Correlation plot of left ventricular ejection fraction with heart rate at week 26



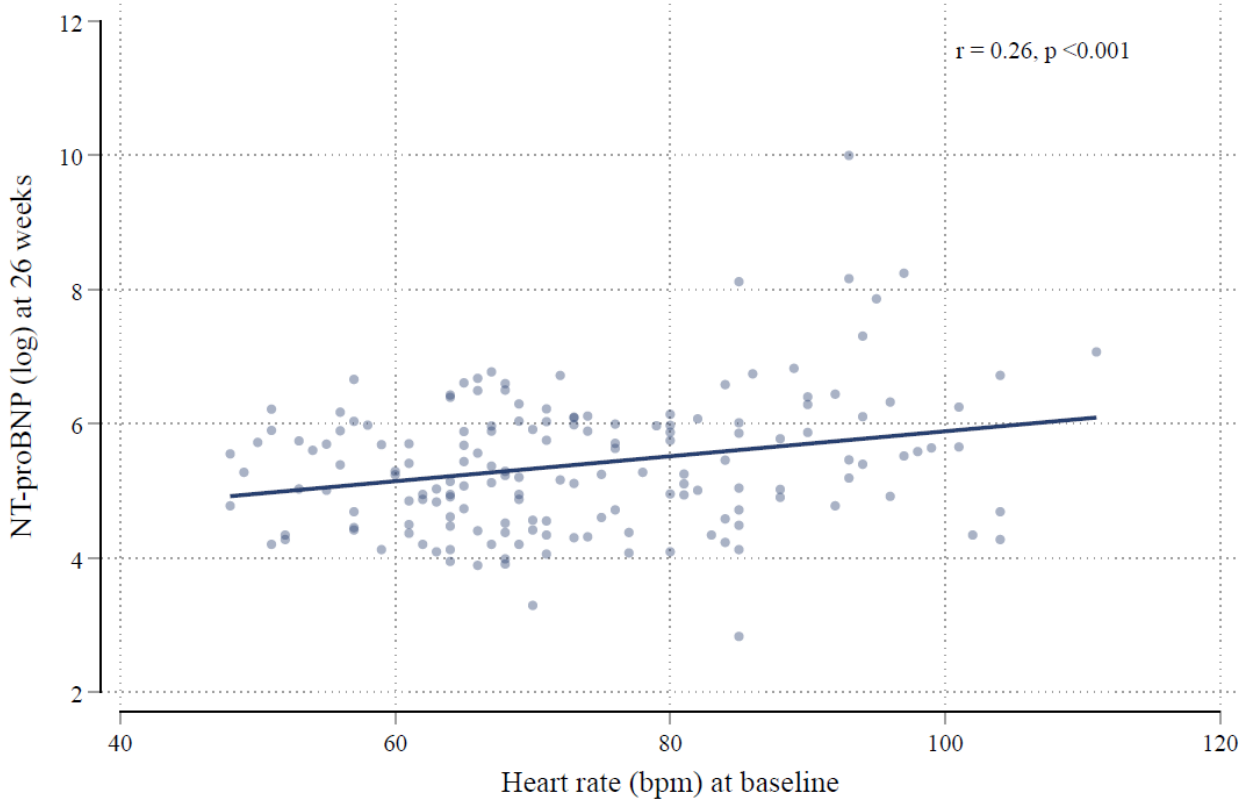
LVEF, left ventricular ejection fraction; bpm, beats per minute

Figure 4. Correlation plot of the diastolic function (E/e´) with heart rate at week 26



log, logarithm; bpm, beats per minute

Figure 5. Correlation plot of NT-proBNP levels with heart rate at week 26

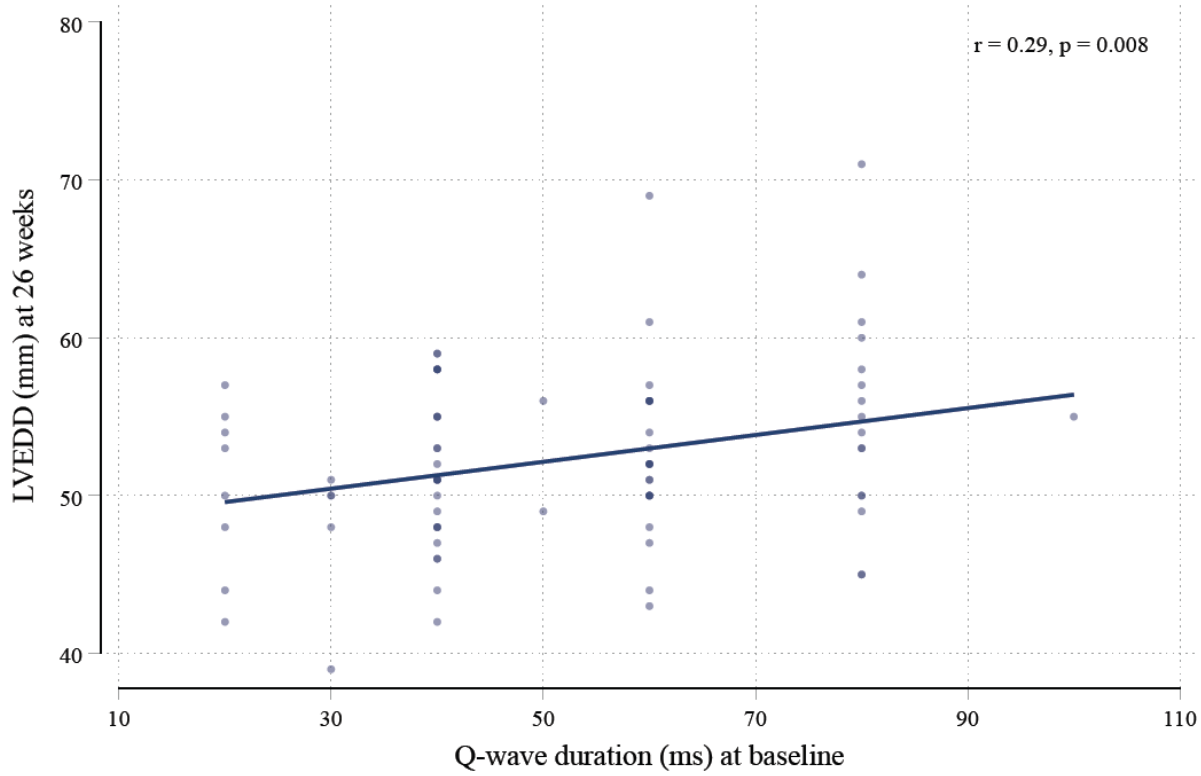


NT-proBNP, N-terminal pro natriuretic peptise; log, logarithm; bpm, beats per minute

Lastly, we report significant positive associations between the structural cardiac parameter LVEDD and the Sokolow-Lyon index (p=0.009) as well as Q-wave duration (p=0.037) (Figure 6). However, no significant associations were observed between LVEDD and ST-elevation (p=0.079), AMI type (p=0.232), Q-wave presence (p=0.603), Q-wave amplitude (p=0.053), QRS width (p=0.569), PQ interval (p=0.699), or QTc interval (p=0.211). LVESD was found to be significantly associated with ST-elevation (p=0.024), while no significant associations were observed for AMI type (p=0.953), Q-wave presence (p=0.687), Q-wave duration (p=0.533), Q-wave amplitude (p=0.958), QRS width (p=0.244), PQ interval (p=0.948), QTc interval (p=0.10), or the Sokolow-Lyon index (p=0.769). Finally, no significant

were revealed between the structural cardiac parameters LVESV or LVEDV and the response in EMMY trial outcomes.

Figure 6. Correlation plot of the left ventricular end-diastolic diameter with Q-wave duration at week 26



LVEDD, left ventricular end-diastolic diameter; mm, millimetre; ms, millisecond

3.4 Subanalysis of Echocardiographic Data

3.4.1 Baseline Characteristics×

Initially, a total of 313 patients were included in the echo subanalysis of the EMMY trial, with 149 patients in the Empagliflozin group and 152 in the placebo group. However, 2.6% of the patients (n=8) withdrew informed consent, 0.6% (n=2) were excluded due to poor echo image quality, and 0.6% (n=2) were lost to follow-up.

For the final echo subanalysis, 301 patients with good-quality echo loops were successfully enrolled for post-hoc processing: 149 patients in the Empagliflozin group and 152 in the placebo group (**Table 8**).

Baseline parameters were equally distributed between both treatment groups, with a median (interquartile range) age of 57 (52–65) years, a mean BMI of 28 (25–30) kg/m², and 18.3% of participants being female. Co-morbidities included established diabetes

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mellitus in 11.9% of patients (n=37), previously known CAD in 5.5% (n=17), and a history of acute myocardial infarction in 3.9% (n=12).

A total of 143 patients (46%) had single-vessel disease, 108 patients (34.7%) had two-vessel disease, and 60 patients (19.3%) had three-vessel disease (**Table 8**).

Pharmacological heart failure treatments were equally distributed between both groups according to recent guidelines, with an overall administration of ACEi/ARBs in 98.7% of all patients (n=304), ARNIs in 1.6% (n=5), beta-blockers in 97.4% (n=303), and MRAs in 47.9% (n=149). Loop diuretics were administered to 10.6% of participants (n=33), calcium channel blockers (CCBs) to 4.2% (n=13), and statins to 99.7% (n=310).

Laboratory findings at baseline showed a median (IQR) NT-proBNP of 1377 pg/mL (800–2217), a median eGFR of 93 mL/min/1.73 m² (79–102), a median creatine kinase of 1705 U/L (1203–2442), a median CK-MB of 159 U/L (86–238), a median Troponin T of 3067 µg/L (2099–4938), and a median CRP of 6 mg/dL (3–14) (**Table 8**).

Echocardiographic structural and functional metrics of the left heart at baseline were as follows: a median (IQR) LVEDV of 122 mL (100–142), a median LVESV of 63 mL (49–78), a median LVEF of 48% (43–53), a median LV GLS of -16% (-19 to -13), a median E/e´ of 9 (7–11), a median LAVI of 31 mL/m² (27–38), and a median LA GLS of 19% (15–25). Echocardiographic metrics of the right heart revealed a median RV GLS of -21% (-23 to -18), a median RV-FWS of -27% (-30 to -23), a median RV FAC of 37% (34–41), a median TAPSE of 21 mm (19–23), a median RA GLS of 35% (29–42), and a median RAVI of 23 mL/m² (18–28) (**Table 8**).

Table 8. Baseline parameters of the echo subanalysis stratified by treatment

Baseline parameters	**All n=311**	**Empagliflozin n=156**	**Placebo N=155**
Age [years]	57 (52–65)	57 (52–64)	58 (52–66)
Female, n (%)	57 (18.3)	25 (16.0)	32 (20.6)
Body mass index [kg/m2]	28 (25–30)	28 (25–30)	28 (25–30)
Diabetes mellitus, n (%)	37 (11.9)	16 (10.3)	21 (13.5)
Coronary Artery Disease, n (%)	17 (5.5)	10 (6.4)	7 (4.5)
1-vessel disease, n (%)	143 (46.0)	62 (39.7)	81 (52.3)
2-vessel disease, n (%)	108 (34.7)	58 (37.2)	50 (32.3)
3-vessel disease, n (%)	60 (19.3)	36 (23.1)	24 (15.5)
History of myocardial infarction, n (%)	12 (3.9)	8 (5.1)	4 (2.6)
Pharmacological treatment			
ACEi/ARB, n (%)	304 (98.7)	153 (98.7)	151 (98.7)
ARNI, n (%)	5 (1.6)	1 (0.6)	4 (2.6)

Baseline parameters	All n=311	Empagliflozin n=156	Placebo N=155
Beta-blocker, n (%)	303 (97.4)	150 (96.2)	153 (98.7)
MRA, n (%)	149 (47.9)	73 (46.8)	76 (49.0)
Loop diuretic, n (%)	33 (10.6)	18 (11.5)	15 (9.7)
Calcium channel blocker, n (%)	13 (4.2)	4 (2.6)	9 (5.8)
Statin, n (%)	310 (99.7)	155 (99.4)	155 (100.0)
Laboratory parameters			
NT-proBNP [pg/mL]	1377 (800–2217)	1257 (797–2239)	1477 (800–2192)
eGFR [mL/min/1.73 m^2]	93 (79–102)	94 (78–101)	93 (81–103)
Creatine kinase [U/L]	1705 (1203–2442)	1670 (1170–2518)	1729 (1257–2366)
CK-MB [U/L]	159 (86–238)	139 (80.0–227)	167 (92–247)
Troponin T [µg/L]	3067 (2099–4938)	3089 (2195–4899)	3045 (2062–5018)
C-reactive Protein [mg/dL]	6 (3–14)	6 (3–13)	7 (2–14)
Echocardiographic parameters			
LV EDV [mL]	122 (100–142)	120 (100–140)	122 (101–145)
LV ESV [mL]	63 (49–78)	62 (49–77)	64 (49–80)
LV EF [%]	48 (43–53)	49 (43–52)	47 (43–53)
LV GLS [%]	-16 (-19 to -13)	-17 (-19 to -13)	-15 (-19 to -12)
E/e’	9 (7;11)	9 (7;11)	9 (7;11)
LA GLS [%]	19 (15;25)	19 (15;25)	19 (14;26)
LAVI [mL/m2]	31 (27–38)	30 (26–37)	32 (28–39)
RV GLS [%]	-21 (-23 to -18)	-21 (-23 to -18)	-21 (-23 to -18)
RV-FWS [%]	-27 (-30 to -23)	-27 (-30 to -23)	-27 (-29 to -24)
RV FAC [%]	37 (34–41)	37 (35–42)	38 (33–41)
TAPSE [mm]	21 (19–23)	21 (18–23)	21 (19–23)
RA GLS [%]	35 (29–42)	35 (30–41)	35 (29–43)
RAVI [mL/m2]	23 (18–28)	22 (18–27)	23 (18–29)

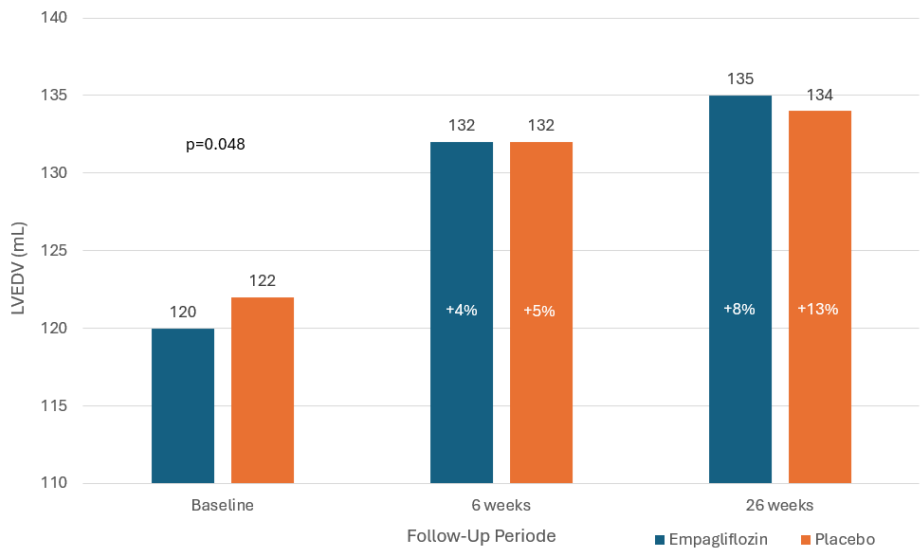
All parameters reported in median (interquartile range) or frequency (percentage). ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CK-MB, creatine kinase muscle-brain type; eGFR, estimated glomerular filtration rate; LA-GLS, left-atrial global longitudinal strain; LAVI, left-atrial volume index; LVEDV, left-ventricular end-diastolic volume; LVEF, left-ventricular ejection fraction; LVESV, left-ventricular end-systolic volume; LV-GLS, left-ventricular global longitudinal strain; MRA, mineralocorticoid receptor antagonist; RA-GLS, right-atrial global longitudinal strain; RAVI, right- atrial volume index; RV-FAC, right-ventricular fractional area change; RV-FWS, right-ventricular free wall strain; RV-GLS, right-ventricular global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion. This table has been modified from the publication in the Clinical research in Cardiology; 2024. DOI: 10.1007/s00392-024-02523-1. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

3.4.2 Echocardiographic changes after 6 and 26 weeks×

3.4.2.1 Left Ventricle

Structural left ventricular metrics revealed a median (IQR) LVEDV of 132 mL (113–149) with a relative change of 4% (-4–17) for Empagliflozin at week 6, which did not significantly differ from changes in the placebo group, where the median LVEDV was 132 mL (107–155) with a relative change of 5% (-3–18). At week 26, a significant difference in changes in LVEDV between the groups was observed, with a median LVEDV of 135 mL (114–155) and a relative change of 8% (-3–19) for Empagliflozin, compared to a median LVEDV of 134 mL (111–165) and a relative change of 13% (0–29) for placebo (**p=0.048**), indicating better LV recovery with Empagliflozin after AMI (**Figure 7 and Table 9**). Similar findings were observed for LVESV, showing a median (IQR) of 64 mL (51–75) for Empagliflozin with an increase of 1% (-11–9) and a median of 64 mL (48–82) with an increase of 0% (-7–18) at week 6, without significant difference between the groups. By week 26, Empagliflozin demonstrated significant beneficial effects on LV recovery (p=0.044) by decreasing LVESV by -3% (-15–12), with a median LVESV of 60 mL (49–75). In contrast, the placebo group showed an increase of 4% (-12–18), with a median LVESV of 62 mL (49–79) (**Figure 8 and Table 9**).

Figure 7. Changes in left ventricular end-diastolic volume at week 6 and week 26



LVEDV, left ventricular end-diastolic volume; mL, millilitre

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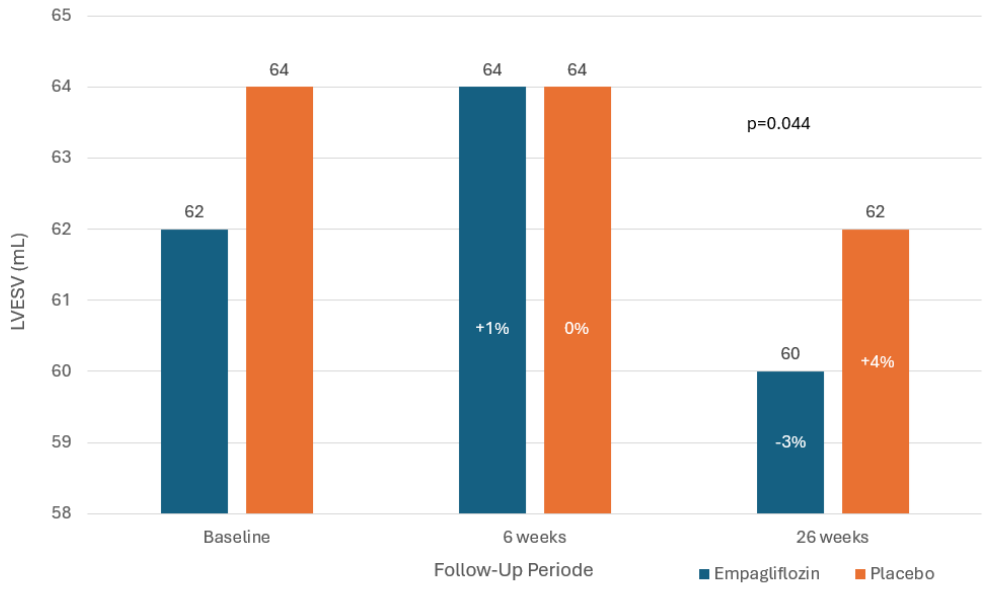
Figure 8. Changes in left ventricular end-systolic volume at week 6 and at week 26



LVESV, left ventricular end-systolic volume; mL, millilitre

Left ventricular functional metrics showed a median (IQR) LVEF of 52% (46–56) for Empagliflozin and 51% (47–55) for placebo at week 6, with an increase of 6% (0–13) and 4% (-1–11), respectively. At week 26, the SGLT2 group had a median LVEF of 55% (48–58) with an increase of 11% (3–18), and the placebo group had a median LVEF of 53% (49–56) with an increase of 10% (1–18). However, no significant difference between the groups concerning LVEF recovery was observed (p=0.888). Similar findings were shown for left ventricular strain analysis, with a median (IQR) LV-GLS of -18% (-21 to -16) for Empagliflozin and an increase of 10% (3–22), compared to a median LV-GLS of -18% (-19 to -15) with an increase of 10% (3–24) for placebo. At week 26, LV-GLS showed a median of -19% (-22 to -17) for the SGLT2 group and -18% (-21 to -16) for placebo, with a median increase of 15% (4–29) and 18% (3–34), respectively. However, the difference between the groups was not significant (p=0.728) (**Table 9**).

Diastolic function revealed a median E/e´ of 8 (7–10) for Empagliflozin with a median change of -8 (-21–9) and a median E/e´ of 8 (7–11) for placebo with a median change of -7 (-21–6) at week 6. Up to week 26, diastolic function improved to a median E/e´ of 8 (6–9) for SGLT2-I and 8 (7–10) for non-SGLT2-I, with a median change of -11 (-25–7) and -11 (-22–7), but no significant difference between the groups was identified (p=0.551), highlighting no difference in LV-diastolic recovery post AMI between the two groups (**Table 9**).

3.4.2.2 Left Atrium

Left atrial structural metrics showed a median (IQR) LAVI of 32 mL/m² (26–39) in the Empagliflozin group and a median LAVI of 32 mL/m² (28–40) for placebo, with a median change of 1% (-12–23) and 1% (-13–17) at week 6. After 26 weeks, LAVI showed a median of 32 mL/m² (27–39) with a median change of 3% (-12–23) for Empagliflozin and a median LAVI of 34 mL/m² (27–41) with a median increase of 5% (-12–28). The SGLT2-I group showed a slightly better structural LA recovery up to week 26; however, the difference was not significant between the two groups (p=0.460) (**Table 9**).
Left atrial function analysed with strain revealed a median (IQR) LA-GLS of 22% (17–27) for the SGLT2-I group, with a median change of 9% (-11–41), and a median LA-GLS of 21% (15–26) with a median change of 3% (-25–38) for the placebo group at week 6. Up to week 26, the SGLT2-I group showed a median LA-GLS of 22% (17–30) and the placebo group a median LA-GLS of 22% (16–28), with a median change of 11% (-16–48) and 13% (-16–45), without significant differences between the treatment groups (p=0.098) (**Table 9**).

3.4.2.3 Right Atrium

Structural right atrial parameters at week 6 showed a median (IQR) RAVI of 23 mL/m² (19–27) with a median increase of 3% (-16–25) for Empagliflozin and a median RAVI of 25 mL/m² (20–30) for placebo with a median increase of 5% (-9–29). At week 26, a median RAVI of 23 mL/m² (20–29) with a median change of 8% (-14–30) was observed for the SGLT2-I users, and a median RAVI of 25 mL/m² (20–30) with a median change of 8% (-8–31) for non-SGLT2-I users compared to baseline. A slightly better structural RA recovery was found for Empagliflozin; however, structural changes between the groups were not significant (p=0.152) (**Table 9**).
Right atrial function by strain analysis showed a median (IQR) RA-GLS of 36% (29–41) in the Empagliflozin group at week 6, with a median change of 0% (-17–16), and a median RA-GLS of 34% (29–40) for placebo, with a median change of 1% (-21–17). Strain analysis at week 26 revealed a median RA-GLS of 35% (29–40) with a median change of -1% (-20–19) in the treatment group and a median RA-GLS of 33% (28–40) with a median

decrease of -5% (-22–18). Although Empagliflozin showed slightly better functional RA recovery, the difference compared to placebo was not significant (p=0.441) (**Table 9**).

3.4.2.4 Right Ventricle

The TAPSE, as a main predictor for right ventricular function, showed a median (IQR) of 23 mm (21–24) in the SGLT2-I group and a median of 22 mm (20–24) in the placebo group, with a median increase of 7% (-3–18) and 5% (-3–16) in week 6. After 26 weeks, Empagliflozin showed a median TAPSE of 23 mm (21–25) with a median change of 11% (-3–21), and placebo showed a median TAPSE of 23 mm (21–25) with a median change of 9% (1–20), but without significant difference between the groups at final analysis (p=0.858). RV-FAC after 6 weeks was found with a median (IQR) value of 41% (37–45) in the Empagliflozin group, with a median increase of 7% (-4–17), and 42% (38–45) in the placebo group, with a median increase of 7% (1–18). At week 26, the RV-FAC showed a median of 43% (39–46) with a change of 12% (2–24) for Empagliflozin and a median of 42% (38–45) with a median change of 11% (2–22) for placebo, but differences for SGLT2-I users and non-SGLT2-I users were not significant (p=0.399) (**Table 9**).

Strain analysis of the right ventricle showed a median (IQR) RV-GLS of -23% (-25 to -21) for the SGLT2-I group and a median RV-GLS of -24% (-26 to -21) for placebo, with median changes of 8% (-3–26) and 11% (0–23) at week 6. At the end of the trial, RV-GLS was found with a median value of -24% (-26 to -22) for Empagliflozin and -24% (-26 to -22) for placebo, with median changes of 12% (4–23) and 14% (4–29). Although an increase in functional strain analysis was assessed in both groups, the difference between the groups was not significant (p=0.197) (**Table 9**).

Strain analysis of the free wall at week 6 showed a median (IQR) RV-FWS of -29% (-32 to -27) in the treatment group with a median change of 9% (-5–26) and a median RV-FWS of -30% (-32 to -27) for placebo with a median change of 7% (1–22). After 26 weeks, a median RV-FWS of -31% (-33 to -28) was revealed for Empagliflozin with a median change of 10% (0–25) and a median RV-FWS of -31% (-33 to -28) for placebo with a median change of 11% (2–31). An increase in RV-FWS was observed in both groups; however, no significant difference between the groups was detected (p=0.360) (**Table 9**).

Table 9. Trajectories of echocardiographic parameters stratified by treatment

	Baseline	Week 6	Week 26	absolute change (Week 6)	absolute change (Week 26)	% change (Week 6)	% change (Week 26)	p-value
LVEDV *[mL]*	*n = 244*	*n = 241*	*n = 230*					
All	122 (100–142)	132 (110–151)	135 (114–158)	6 (-4–21)	12 (-1–28)	5 (-3–18)	10 (-1–24)	
Empagliflozin	120 (100–140)	132 (113–149)	135 (114–155)	6 (-5–20)	10 (-3–20)	4 (-4–17)	8 (-3–19)	**0.048**
Placebo	122 (101–145)	132 (107–155)	134 (111–165)	6 (-3–24)	14 (0–33)	5 (-3–18)	13 (0–29)	
LVESV *[mL]*	*n = 244*	*n = 241*	*n = 230*					
All	63 (49–78)	64 (50–77)	61 (49–78)	0 (-6–8)	0 (-9–10)	0 (-9–14)	1 (-14–16)	
Empagliflozin	62 (49–76)	64 (51–75)	60 (49–75)	1 (-6–6)	0 (-6–11)	1 (-11–9)	-3 (-15–12)	**0.044**
Placebo	64 (49–80)	64 (48–82)	62 (49–79)	-1 (-9–7)	2 (-7–11)	0 (-7–18)	4 (-12–18)	
LVEF *[%]*	*n = 244*	*n = 241*	*n = 230*					
All	48 (43–52)	51 (47–56)	54 (48–58)	3 (-0–5)	5 (1–8)	5 (-1–12)	10 (2–18)	
Empagliflozin	48 (43–52)	52 (46–56)	55 (48–58)	3 (-0–6)	5 (1–9)	6 (-0–13)	11 (3–18)	0.888
Placebo	47 (43–52)	51 (47–55)	53 (49–56)	2 (-0–5)	5 (0–8)	4 (-1–11)	10 (1–18)	
LV-GLS *[%]*	*n = 233*	*n = 227*	*n = 220*					
All	-16 (-19 to-13)	-18 (-20 to -15)	-19 (-21 to -16)	-1 (-2–1)	-1 (-2–0)	10 (3–23)	16 (3–30)	
Empagliflozin	-16 (-19 to -13)	-18 (-21 to -16)	-19 (-22 to -17)	-1 (-2–1)	-1 (-3–0)	10 (3–22)	15 (4–29)	0.728
Placebo	-15 (-19 to -12)	-18 (-19 to -15)	-18 (-21 to-16)	-1 (-2–1)	-1 (-2–1)	10 (3–24)	18 (3–34)	
E/é	*n = 258*	*n = 241*	*n = 247*					
All	9 (7–11)	8 (7–10)	8 (7–10)	1 (-4–7)	2 (-3–8)	-7 (-21–7)	-11 (-24–7)	
Empagliflozin	9 (7–11)	8 (7–10)	8 (6–9)	2 (-2–7)	2 (-3–8)	-8 (-21–9)	-11 (-25–7)	0.551
Placebo	9 (8–10)	8 (7–11)	8 (7–10)	0 (-6–7)	3 (-3–7)	-7 (-21–6)	-11 (-22–7)	
LAVI *[mL/m²]*	*n = 254*	*n = 250*	*n = 238*					
All	31 (27–38)	32 (27–39)	33 (27–40)	-2 (-3 to -1)	-3 (-4 to -1)	1 (-13–19)	4 (-12–23)	
Empagliflozin	30 (26–37)	32 (26–39)	32 (27–39)	-2 (-4 to -0)	-3 (-4 to -1)	1 (-12–23)	3 (-12–23)	0.460
Placebo	32 (28–39)	32 (28–40)	34 (27–41)	-2 (-3 to -1)	-3 (-5 to-0)	1 (-13–17)	5 (-12–28)	
LA-GLS *[%]*	*n = 267*	*n = 256*	*n = 256*					
All	19 (14–25)	22 (16–26)	22 (17–28)	0 (-8–5)	-2 (-9–6)	6 (-19–40)	12 (-16–46)	
Empagliflozin	19 (15–25)	22 (17–27)	22 (17–30)	-0 (-7–5)	-0 (-7–6)	9 (-11–41)	11 (-16–48)	0.098
Placebo	19 (14–26)	21 (15–26)	22 (16–28)	0 (-9–5)	-2 (-9–6)	3 (-25–38)	13 (-16–45)	
TAPSE *[mm]*	*n = 256*	*n = 255*	*n = 254*					
All	21 (19–23)	23 (21–24)	23 (21–25)	-2 (-5–0)	-3 (-5–-1)	5 (-3–17)	10 (-1–20)	
Empagliflozin	21 (18–23)	23 (21–24)	23 (21–25)	-2 (-5–0)	-3 (-4 to-1)	7 (-3–18)	11 (-3–21)	0.858
Placebo	21 (19–23)	22 (20–24)	23 (21–25)	-2 (-4 to -0)	-3 (-5 to-1)	5 (-3–16)	9 (1–20)	
RV-FAC *[%]*	*n = 242*	*n = 229*	*n = 229*					
All	37 (34–42)	41 (37–45)	42 (39–46)	-2 (-6–1)	-3 (-6 to -0)	7 (-1–18)	12 (2–23)	
Empagliflozin	37 (35–42)	41 (37–45)	43 (39–46)	-2 (-5 to -0)	-3 (-7 to -1)	7 (-4–17)	12 (2–24)	0.399
Placebo	38 (33–41)	42 (38–45)	42 (39–46)	-3 (-6–1)	-3 (-6 to -0)	7 (1–18)	11 (2–22)	
RV-GLS *[%]*	*n = 224*	*n = 203*	*n = 195*					
All	-21 (-23 to -18)	-23 (-25 to -21)	-24 (-26 to -22)	3 (-0–6)	4 (1–8)	10 (-1–23)	14 (4–26)	
Empagliflozin	-21 (-23 to -18)	-23 (-25 to -21)	-24 (-26 to -22)	2 (-2–6)	4 (1–9)	8 (-3–26)	12 (4–23)	0.197
Placebo	-21 (-23 to -18)	-24 (-26 to -21)	-24 (-26 to -22)	3 (0–7)	4 (1–8)	11 (0–23)	14 (4–29)	
RV-FWS *[%]*	*n = 224*	*n = 203*	*n = 195*					
All	-27 (-30 to -24)	-29 (-32 to -27)	-31 (-33 to -28)	1 (-1–3)	2 (-0–4)	8 (-2–22)	10 (1–27)	

Empagliflozin	-27 (-30-23)	-29 (-32 to -27)	-31 (-33 to -28)	1 (-1–4)	2 (-1–4)	9 (-5–26)	10 (0–25)	0.360
Placebo	-27 (-29 to -24)	-30 (-32 to -27)	-31 (-33 to -28)	1 (-1–3)	2 (0–4)	7 (1–22)	11 (2–31)	
RAVI *[mL/m²]*	*n = 264*	*n = 254*	*n = 252*					
All	23 (18–28)	23 (19–29)	24 (20–29)	0 (-4–6)	1 (-4–7)	4 (-13–27)	8 (-9–30)	
Empagliflozin	22 (18–27)	23 (19–27)	23 (20–29)	0 (-4–6)	1 (-4–6)	3 (-16–25)	8 (-14–30)	0.152
Placebo	23 (18–28)	25 (20–30)	25 (20–30)	0 (-5–5)	2 (-4–8)	5 (-9–29)	8 (-8–31)	
RA-GLS *[%]*	*n = 262*	*n = 254*	*n = 244*					
All	35 (29–42)	35 (29–41)	34 (28–40)	1 (-3–5)	2 (-2–7)	0 (-21–17)	-4 (-22–19)	
Empagliflozin	35 (30–42)	36 (30–42)	35 (29–40)	1 (-4–4)	2 (-4–6)	0 (-17–16)	-1 (-20–19)	0.441
Placebo	35 (29–43)	34 (29–40)	33 (28–40)	1 (-2–6)	2 (-2–7)	1 (-21–17)	-5 (-22–18)	

All values reported in median (interquartile range). P-values reported from the linear mixed-effects model for average treatment effects, adjusted for baseline values, age, and sex. LA-GLS, left-atrial global longitudinal strain; LAVI, left-atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left-ventricular ejection fraction; LVESV, left-ventricular end-systolic volume; LV-GLS, left ventricular global longitudinal strain; RA-GLS, right-atrial global longitudinal strain; RAVI, right- atrial volume index; RV-FAC, right ventricular fractional area change; RV-FWS, right-ventricular free wall strain; RV-GLS, right-ventricular global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion. This table has been modified from the publication in the Clinical research in Cardiology; 2024. DOI: 10.1007/s00392-024-02523-1. This table is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

3.5 ERASE

3.5.1 Baseline Characteristics°

The ERASe trial was terminated early due to ethical reasons following changes in guidelines, which provided a class 1A recommendation for SGLT2-I in heart failure independent of LVEF (70). Nevertheless, 55 patients were successfully enrolled and randomized to receive either Ertugliflozin or placebo. Nine patients were excluded from the final analysis: eight patients withdrew their consent, and one patient died 98 days after inclusion without experiencing any arrhythmic burden since randomisation, leaving a total of 46 patients for the final analysis (22 in the Ertugliflozin group and 24 in the placebo group). We can successfully report no loss to follow-up or unknown vital status for any of the enrolled patients (**Table 10**).

Baseline parameters were distributed equally between both groups, with a mean age of 65±11 years, a mean BMI of 28.4±5.8 kg/m², and 91% male patients. Cardiovascular risk

factors included a median systolic blood pressure of 133±18 mmHg, a mean diastolic blood pressure of 84±14 mmHg, and a median heart rate of 70±13 bpm. Cardiac functional metrics revealed a mean LVEF of 37±11%. Laboratory biomarkers showed a mean NT-proBNP level of 1 782±2 311 ng/L, a mean eGFR of 61±18 mL/min/1.73 m², and a mean potassium level of 4.45±0.54 mmol/L. Guideline-recommended medical therapy was well established in all participating patients, with 85% receiving beta-blockers, 84% receiving ACE-I, ARB, or ARNI, and 57% receiving MRA. Anti-arrhythmic drug therapy included digitalis in 8.7% and amiodarone in 22% of participants. Platelet inhibition was reported in 22% of patients, and anticoagulation in 59% (**Table 10**).

Table 10. Baseline characteristics of ERASe stratified by treatment

Characteristic	**Overall** N = 46	**Ertugliflozin** N = 22	**Placebo** N = 24	**p-value**[1]
Demographic data at baseline				
Age, Mean (SD)	65 (11)	65 (11)	66 (12)	0.74
Male gender, n (%)	42 (91)	20 (91)	22 (92)	>0.99
BMI, Mean (SD)	28.4 (5.8)	28.6 (5.3)	28.2 (6.3)	0.95
BP systolic, Mean (SD)	133 (18)	136 (13)	131 (21)	0.29
BP diastolic, Mean (SD)	84 (14)	87 (12)	81 (15)	0.10
Heart rate, Mean (SD)	70 (13)	68 (12)	72 (13)	0.24
Concomitant medications at baseline				
ACEI / ARB, n (%)	25 (54)	13 (59)	12 (50)	0.54
Betablocker, n (%)	39 (85)	18 (82)	21 (88)	0.69
MRA, n (%)	26 (57)	12 (55)	14 (58)	0.80
ARNI, n (%)	14 (30)	6 (27)	8 (33)	0.66
Loop diuretics, n (%)	24 (52)	9 (41)	15 (63)	0.14
CA (dihydropyridine), n (%)	4 (8.7)	2 (9.1)	2 (8.3)	>0.99
CA (verapamil/diltiazem), n (%)	0 (0)	0 (0)	0 (0)	
Digitalis, n (%)	4 (8.7)	2 (9.1)	2 (8.3)	>0.99
Amiodaron/sotalol, n (%)	10 (22)	4 (18)	6 (25)	0.73
Magnesium, n (%)	11 (24)	6 (27)	5 (21)	0.61
Platelet aggregation inhibitors, n (%)	10 (22)	4 (18)	6 (25)	0.73
Anticoagulation, n (%)	27 (59)	15 (68)	12 (50)	0.21
Statin, n (%)	29 (63)	14 (64)	15 (63)	0.94
Arrhythmic burden 12 months prior baseline				
sVT or VF, Mean (SD)	12 (32)	19 (44)	6 (10)	0.31
nsVT episodes, Mean (SD)	25 (47)	22 (33)	27 (57)	0.78
Laboratory at baseline				
Potassium (mmol/L), Mean (SD)	4.45 (0.54)	4.46 (0.60)	4.45 (0.49)	0.69
Magnesium (mmol/L), Mean (SD)	0.85 (0.10)	0.87 (0.09)	0.83 (0.10)	0.32
CRP (mg/L), Mean (SD)	2.15 (2.85)	2.54 (3.38)	1.79 (2.27)	0.75
eGFR (ml/min/1.7 m²), Mean (SD)	61 (18)	65 (21)	57 (16)	0.34
NT-proBNP (ng/L), Mean (SD)	1,782 (2,31)	1,141 (1,60)	2,370 (2,71)	0.065

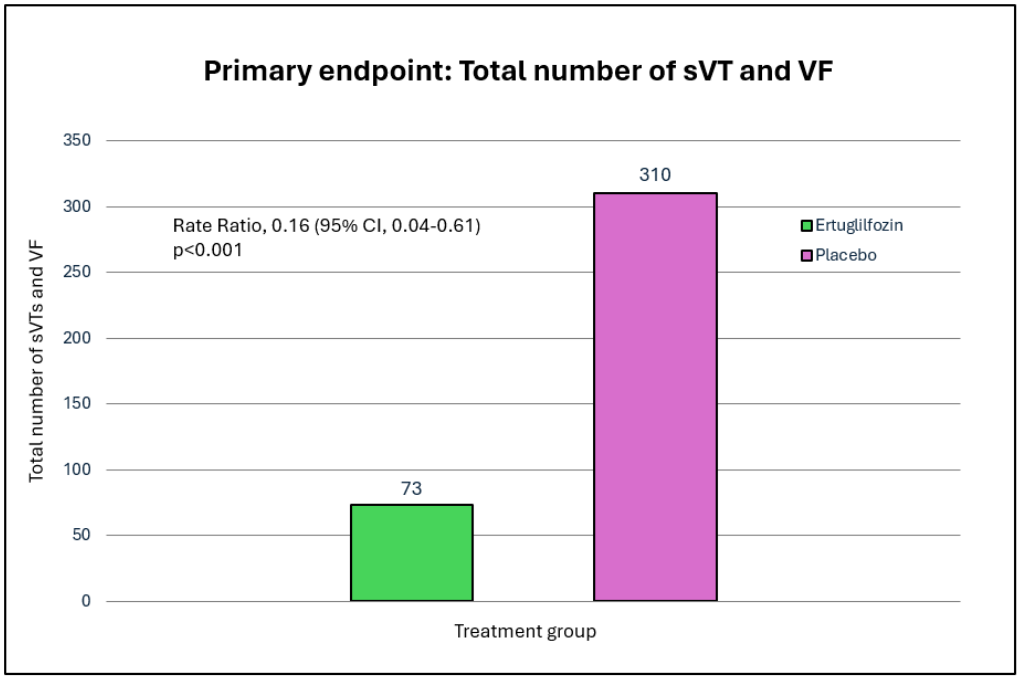
SD, standard deviation; BMI, Body mass index; BP, blood pressure; ACE-I, Angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CA, calcium antagonist; sVT, sustained ventricular tachycardia; VF, ventricular fibrillation; nsVT, non-sustained ventricular tachycardia; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro natriuretic peptide. Reproduced with permission from NEJM Evidence; 2024. DOI: 10.1056/EVIDoa2400147, Copyright Massachusetts Medical Society.

3.5.2 Primary Endpoint°

At week 52 of follow-up, the rate of incident sustained ventricular tachycardia (sVT) and ventricular fibrillation (VF) was significantly lower in the Ertugliflozin group compared to placebo, with a rate ratio (RR) of 0.155 (95% CI 0.043–0.606, p<0.001). The same effect remained statistically significant after adjusting for NT-proBNP levels, with an RR of 0.126 (95% CI 0.031–0.527, p<0.001). Adjusting with statistical methods robust to outliers in a separate sensitivity analysis revealed a significant reduction of 80% in sVTs and VF for Ertugliflozin compared to placebo (RR 0.2, p=0.006). Patients with at least one episode of sVT or VF at week 52 were identified in 13 patients (59%) of the Ertugliflozin group and 16 patients (67%) of the placebo group; however, the difference was not significant (p=0.6) (**Figure 9 and 10**).

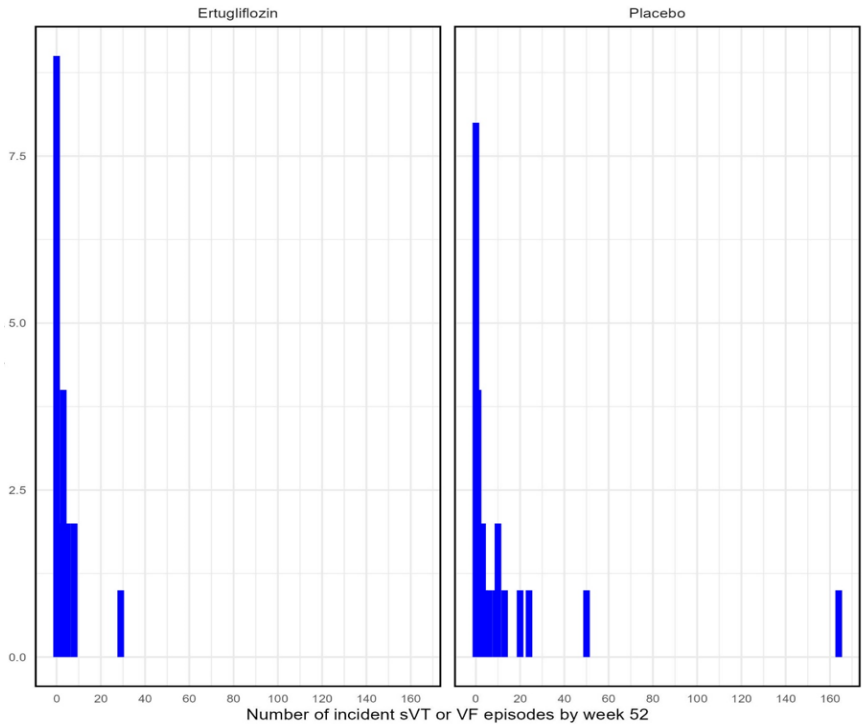
° *Parts of this chapter have been published in NEJM Evidence. (2024). DOI: 10.1056/EVIDoa2400147*

Figure 9. Primary endpoint of ERASe stratified by treatment



sVT, sustained ventricular tachycardia; VF, ventricular fibrillation, CI, Confidence interval. Reproduced with permission from NEJM Evidence; 2024. DOI: 10.1056/EVIDoa2400147, Copyright Massachusetts Medical Society.

Figure 10. Incidence of sVT or VF episodes by week 52



sVT, sustained ventricular tachycardia; VF, ventricular fibrillation

3.5.3 Secondary Endpoints°

At week 52, the number of non-sustained ventricular tachycardia (nsVT) episodes was significantly lower in the Ertugliflozin group compared to placebo, with a rate ratio (RR) of 0.34 (95% CI 0.12–0.97, p=0.0028) (**Figure 11**). The number of patients with at least one episode of nsVT did not reach statistical significance (p=0.7) between the Ertugliflozin group (n=19, 86%) and the placebo group (n=22, 92%). For Ertugliflozin, a rate of appropriate ICD therapies was reported in 9 patients (41%) compared to 15 patients (63%) in the placebo group; however, no significant difference was found between the groups (p=0.14). At week 52, appropriate ICD therapies were also not significantly different between the SGLT2-I group and placebo (RR 0.47, 95% CI 0.13–1.81, p=0.246) (**Table 11**).

Hospitalisation due to heart failure occurred 3 times among 3 patients in the Ertugliflozin group and 14 times among 5 patients in the placebo group. In total, hospitalisation for any cause occurred 12 times among 10 patients in the Ertugliflozin group and 33 times among 21 patients in the placebo group. Although the results suggest a moderate difference between the two groups in terms of hospitalisation, statistical analysis did not show any significant difference (RR 0.57, 95% CI 0.19–1.74, p=0.327) (**Figure 12**).

Analysis for the rate of atrial arrhythmias was not available due to the small number of participants with an implanted atrial lead (20%).

Death occurred in 6 patients throughout the trial, with 3 in the Ertugliflozin group and 3 in the placebo group.

HbA1c levels showed a mean (SD) change of -0.93 (5.12) in the Ertugliflozin group and -1.33 (4.89) in the placebo group; however, a multiple linear regression model failed to show a significant difference between the two groups (difference in mean change 0.72, 95% CI -1.69–3.13, p=0.544), adjusted for baseline.

Similar findings were observed for NT-proBNP levels, with a mean change of 143 (-6 to 300) ng/L for Ertugliflozin and 101 (-103 to 322) ng/L for placebo at week 52. However, analysis with a multiple linear regression model again found no significant difference between SGLT2-I users and non-SGLT2-I users (difference in mean change 0.17, 95% CI -0.35–0.69, p=0.512) (**Table 11**).

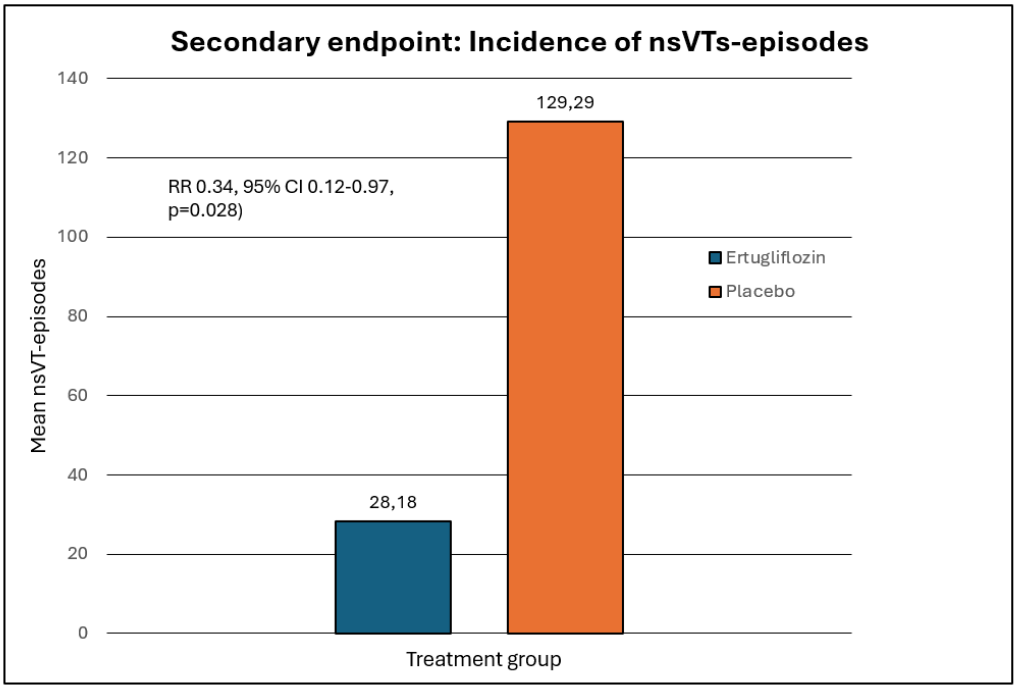
° *Parts of this chapter have been published in NEJM Evidence. (2024). DOI: 10.1056/EVIDoa2400147*

Table 11. Secondary endpoints of ERASe stratified by treatment

Secondary Endpoints	Total	Ertugliflozin	Placebo	Rate Ratio [95% CI]	p-value
Episodes of non-sustained ventricular tachycardia, mean (SD)	81.26 (238.97)	28.18 (53.99)	129.92 (322.34)	0.34 [0.12 - 0.97]	0.028*
Episodes of appropriate ICD therapies, mean (SD)	7.63 (24.69)	4.55 (7.95)	10.46 (33.43)	0.47 [0.13 - 1.81]	0.246*
Change in NT-proBNP in ng/L, median (IQR)	136 (-14, 322)	143 (-6; 300)	101 (-103; 322)	-	0.512**
Change in HbA1c in mmol/mol, mean (SD)	-1.14 (4.92)	-0.93 (5.12)	-1.33 (4.89)	-	0.544**
Number of hospitalisations, mean (SD)	1.00 (1.73)	0.70 (1.03)	1.29 (2.19)	0.57 [0.19 - 1.74]	0.327*
At least one hospitalisation due to heart failure, n (%)	5 (11%)	1 (4.5%)	4 (17%)	-	0.3***
Number of Hospitalisations due to heart failure (Number of patients)	13 (5)	1 (1)	12 (4)	-	-
Duration of hospital stay, mean (SD)	7.07 (17.38)	3.60 (5.33)	10.38 (23.53)	-	0.84****
Cardiovascular death, n (%)	2 (4.3%)	0 (0%)	2 (8.3%)	-	0.5***

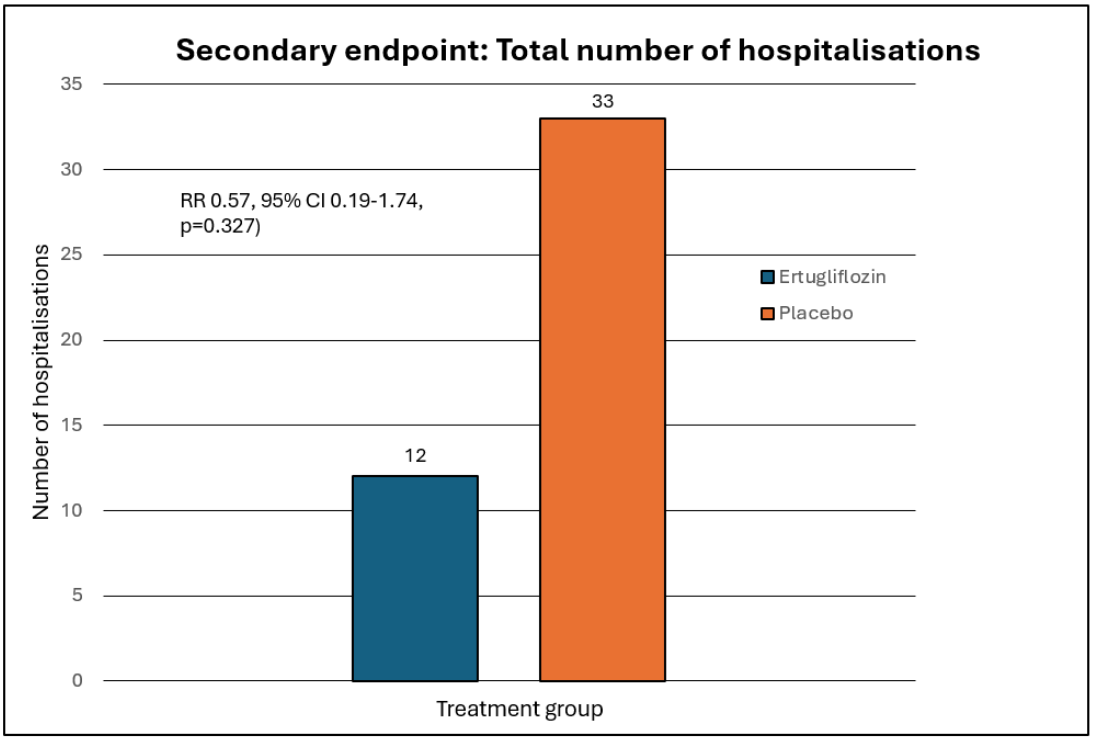
CI, confidence interval; SD, standard deviation; ICD, implantable cardioverter-defibrillator; NT-proBNP, N-terminal pro natriuretic peptide; IQR, interquartile range; HbA1c, haemoglobin A1C. Reproduced with permission from NEJM Evidence; 2024. DOI: 10.1056/EVIDoa2400147, Copyright Massachusetts Medical Society.

Figure 11. Episodes of non-sustained ventricular tachycardia stratified by treatment



RR, rate ratio; CI, confidence interval, nsVT, non-sustained ventricular tachycardia.

Figure 12. Total number of hospitalisations stratified by treatment



RR, rate ratio; CI, confidence interval.

3.5.4 Adverse Events°

The ERASe trial reported a total of 51 severe adverse events (SAEs) in 31 participants, including 6 deaths and 45 hospitalisations. Throughout the trial, we can successfully report no events of ketoacidosis, drug-induced hypoglycemia, or severe genital infection. Adverse events of special interest were low in both groups, showing no significant difference. Three patients reported a history of urogenital tract infection during the trial, with 7 incidents in 2 patients for Ertugliflozin and 4 incidents in 1 patient for placebo; however, no significant difference was observed in the frequency between the two groups (**Table 12**).

Laboratory markers, including changes in liver function (lactate dehydrogenase [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT]) as well as changes in renal function (creatinine, eGFR), were found not to differ significantly between the SGLT2-I group and the placebo group (**Table 12**).

° *Parts of this chapter have been published in NEJM Evidence. (2024).*
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Table 12. Total number of adverse events stratified by treatment

Severe Adverse Events	**Total**	**Ertugliflozin**	**Placebo**
Non-Cardiovascular Death, n	3	2	1
Cardiovascular death, n	3	1	2
Any hospitalisation, n (number of patients)	**31 (45)**	**10 (12)**	**21 (33)**
Hospitalisation due to cardiovascular event	7 (10)	3 (5)	4 (5)
Hospitalisation due to non-Cardiovascular Cause	9 (11)	2 (2)	7 (9)
Infectious disease	4 (4)	1 (1)	3 (3)
Cancer	2 (2)	0	2 (2)
Seizure	1 (1)	1 (1)	0
	37 (51)	**4 (9)**	**1 (4)**
Adverse Events	**Total**	**Ertugliflozin**	**Placebo**
Adverse events of special interests, n			
Hepatic injury	0	0	0
Renal Injury	1	0	1
Metabolic acidosis and diabetic ketoacidosis	0	0	0
Event involving lower limb amputation	0	0	0
	1	**0**	**0**
Other adverse events (number of patients)			
Urinary tract infection	1 (1)	1 (1)	0
Genital fungal infection	2 (10)	1 (6)	1 (4)
Hypotension	1 (1)	1 (1)	0
Polyuria	1 (1)	1 (1)	0
Hypoglycaemia	0	0	0
	5 (13)	**4 (9)**	**1 (4)**

Total numbers are patients with adverse events (number of events). Renal injury is defined as a two-fold increase creatinine. Hepatic injury is defined as T ≥three-fold ULN of AST/AL with elevation of total bilirubin ≥two-fold ULN or AST/ALT elevation ≥five-fold ULN. Reproduced with permission from NEJM Evidence; 2024. DOI: 10.1056/EVIDoa2400147, Copyright Massachusetts Medical Society.

4 Discussion

The EMMY trial was the first clinical trial worldwide showing beneficial effects of the SGLT2 inhibitor Empagliflozin on the cardiac biomarker NT-proBNP as well as functional (LVEF, E/e´) as well as structural (LVEDV, LVESV) cardiac parameters compared to placebo when initiated within 72 hours post PCI as a standard treatment to guideline recommend therapy post AMI (72). Within this trial, we created the first evidence regarding the use of SGLT2-I in the acute treatment of AMI independent of diabetic status. Although SGLT2-I have demonstrated various cardioprotective effects by significantly reducing cardiovascular death and hospitalisation for heart failure in large clinical outcome trials (65–68), however, the EMMY trial was not powered for hard clinical endpoints. First evidence was reported by the recently published DAPA-MI trial showing beneficial effects of Dapagliflozin in cardiometabolics post AMI when added to standard treatment in diabetic and non-diabetic patients independent of LVEF, which was mainly driven by reduction of new-onset diabetes as well as reduction of body weight. By failing to reach statistical significance in reducing hospitalisation for heart failure or cardiovascular death, the DAPA-MI investigators changed the primary endpoint of the trial to a hierarchical endpoint showing significant effect for Dapagliflozin on cardiometabolics, however, the change in protocol led to a reduction in the power of the trial (73). In the recently published EMPACT-MI trial Empagliflozin was found to have no significant lowering effect on hospitalisation of heart failure and all-cause mortality compared to placebo (74). Based on EMMY and the large clinical outcome trials, SGLT2-I appear to show beneficial effects after AMI in diabetic and non-diabetic patients, however, further research in this area must be performed.

Within the following post-hoc analyses we could demonstrate the first evidence of SGLT2-I use on:

1) inflammatory biomarkers following AMI
2) echocardiographic changes post AMI
3) the response of NT-proBNP changes as well as structural and functional cardiac parameters in specific baseline ECG characteristics.

*4.1 Subanalysis of Inflammation Data**

Inflammation plays a crucial role in atherosclerosis by enhancing the chronic inflammatory disease of the arterial wall and is accompanied by the development and progression of atherosclerotic plaques (144,145), which consequently initiate plaque destabilisation, followed by acute myocardial infarction and cardiac remodelling (146–148). Many active molecules, such as adhesion molecules (VCAM-1, ICAM-1), acute phase reactants (hsCRP), as well as interleukins (IL-6), have been identified as playing a provocative role in the inflammatory response (144,149,150) and were found to be increased in atherosclerosis or acute myocardial infarction (146,147,151,152) as well as predictive for major adverse cardiovascular events (MACE), cardiovascular death, and mortality after AMI (151–153).

Hardly any data have been reported so far concerning the use of SGLT2-I in AMI. The first available data on SGLT2-I in AMI were reported from the SGLT2-I AMI PROTECT trial, investigating a potential impact of SGLT2-I use on inflammatory parameters in diabetic patients presenting with AMI. The registry study by Paolisso et al. successfully demonstrated significantly lower baseline inflammation, including lower levels of neutrophils, leukocytes, as well as hsCRP, compared to non-SGLT2-I users, suggesting a potential predictive effect on inflammatory response after AMI in SGLT2-I-treated diabetic patients, as well as an ameliorating beneficial clinical outcome in inflammatory response (106). Interestingly, within the same registry trial, the authors identified higher peak troponin values, as well as initially presenting with a non-ST-segment elevating myocardial infarction (NSTEMI), as independent predictors of higher baseline inflammatory status (106). Given the fact that diabetes is associated with a higher inflammatory response, SGLT2 inhibition is associated with a decrease in inflammatory response (154). However, HbA1c levels were equal in the SGLT2-I and non-SGLT2-I groups, highlighting that the potential anti-inflammatory impact of SGLT2-I in diabetic patients is independent of its glucose-lowering effects (106). This is consistent with our results from the EMMY subanalysis, which showed no significant interaction of the inflammatory parameters with diabetes in both univariable and multivariable LMEM, as well as no significant difference between the treatments in the inflammatory response group analysis. However, the potential effects reported in the SGLT2-I AMI PROTECT

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trial can be explained by a chronic treatment effect with SGLT2-I (106). Moreover, compared to other anti-diabetic agents, SGLT2-I demonstrates beneficial effects on inflammatory parameters, including hsCRP and IL-6, by ameliorating low-grade inflammation, which is recognised as a critical driver of severe vascular complications (155). Based on these findings, pretreatment with SGLT2-I appears to significantly reduce inflammatory biomarkers in patients initially presenting with AMI. However, no clinical data from randomised controlled trials are currently available to elucidate the effects of SGLT2-I on inflammatory response when incorporated into guideline-recommended AMI therapy as part of standard treatment.

In this post-hoc analysis of the EMMY trial, we provide the first evidence of SGLT2-I use post-AMI, showing that patients with AMI exhibited elevated inflammatory biomarkers, which decreased significantly over a period of up to 26 weeks. This effect was already evident at week 6, consistent with the timeline of cardiac remodelling. However, the trajectories of inflammatory metrics did not differ significantly between the Empagliflozin and placebo groups (156).

Baseline elevated hsCRP levels were positively correlated with an increased risk of MACE, cardiovascular death, and all-cause mortality (151,152), as well as with the severity of coronary artery lesions. Additionally, hsCRP was identified as an independent predictor of systolic and diastolic cardiac function (157–160). Similarly, IL-6 demonstrated negative correlations with both systolic and diastolic cardiac function (157), highlighting that a higher inflammatory response post-MI is associated with worse cardiac function. Infarct size, adverse cardiac remodelling, and the severity of reperfusion injury were reported to be independently and positively associated with IL-6 levels (146,147,160,161). Within this post-hoc analysis, hsCRP and IL-6 were significantly associated with LVEF and E/e´, indicating worse cardiac function and severe cardiac remodelling in the context of a higher inflammatory response post-AMI, as shown in multivariable analysis. Higher Troponin T and NT-proBNP levels demonstrated significant positive associations with hsCRP and IL-6, suggesting an increased inflammatory response associated with larger infarct size and greater disease severity post-AMI (156).

Inflammatory blood cells, including neutrophil and leukocyte counts, were initially elevated in patients suffering from AMI and have been reported to predict cardiovascular outcomes by demonstrating positive correlations with Troponin T levels and LVEF (162–

164). However, only neutrophils were found to be associated with a higher risk of total coronary occlusion, thrombus burden (165), and no-reflow in patients following PCI in STEMIs (166). In the EMMY sub-analysis, leukocytes and neutrophils were significantly elevated at initial presentation with AMI in both groups, suggesting a systemic inflammatory response and cardiac remodelling as a reflection of inflammatory peaks. However, the trajectories of these markers did not differ significantly between the Empagliflozin and placebo groups (156).

The neutrophil-to-lymphocyte ratio (NLR) is an independent predictor of cardiovascular outcomes (167) and has been reported to be associated with severe myocardial dysfunction (168) and cardiac remodelling (169). Moreover, the NLR has demonstrated predictive value for myocardial necrosis (168,170), mechanical and procedural complications (171,172), long-term prognosis (173,174), and thrombus burden (175,176). In diabetic patients, pretreatment with SGLT2-I was associated with lower baseline inflammation and smaller infarct size, highlighting a reduced inflammatory response post-AMI with chronic SGLT2-I use (106). These findings are consistent with the results of our post-hoc analysis, which revealed elevated NLR levels post-AMI and significant positive associations with Troponin T levels, identifying NLR as an independent predictor of infarct size. However, our sub-analysis did not demonstrate significant differences in NLR between SGLT2-I and non-SGLT2-I users post-AMI over a period of up to week 26 (156).

Lastly, the platelet-to-lymphocyte ratio (PLR) has also been identified as an independent predictor of cardiovascular outcomes (167,177,178) and has been associated with poorer in-hospital clinical outcomes (177), particularly in elderly patients with acute MI (179). his highlights the contribution of both inflammation and a prothrombotic state to adverse outcomes in elderly patients. This sub-analysis revealed significant positive correlations between the PLR and patients' smoking habits, suggesting that smoking is associated with a higher inflammatory response and is predictive of greater thrombus burden (176) and increased morbidity (180) after AMI. Based on our findings, smoking appears to negatively influence the prothrombotic state through an elevated baseline inflammatory response. However, no significant differences in PLR trajectories were observed between the Empagliflozin and placebo groups over a period of up to week 26 (156).

The first EMMY post-hoc analysis revealed elevated baseline inflammatory metrics at initial presentation with AMI, followed by a pronounced decline over a period of up to 26 weeks, which was already evident by week 6. Furthermore, inflammatory indices were significantly associated with worse cardiac function (LVEF, E/e´) and larger infarct size (NT-proBNP, Troponin T) (156). These findings suggest that inflammation plays a crucial role in atherosclerosis and acute myocardial infarction and represents a physiological reaction associated with ventricular remodelling and fibrosis, supporting the recovery of damaged myocardial tissue (181,182). Although many reactants and numerous immune cells contribute to this complex immune-mediated process (181–185), our EMMY sub-analysis demonstrated no significant differences in the trajectories of inflammatory biomarkers between SGLT2-I and non-SGLT2-I users (156). This suggests that the cardioprotective effects of SGLT2-I post-AMI are not primarily driven by a reduction in the inflammatory response.

4.2 Subanalysis of ECG Data#

The electrocardiogram (ECG) is a critical diagnostic tool in the early evaluation of acute myocardial infarction (AMI) and is recommended to be performed within 10 minutes of patient presentation with clinical symptoms suggestive of AMI, in accordance with established clinical guidelines (47,130). Specific ECG findings, such as QRS width or QTc interval prolongation, have been reported following acute myocardial infarction (AMI) and identified as independent predictors of adverse cardiac outcomes (186). Pretreatment with SGLT2-I in diabetic patients showed no significant differences in PR interval duration, QRS width, QT interval, or relevant changes in ST-T segments compared to non-SGLT2-I users, suggesting that SGLT2-I is well-tolerated with regard to ECG metrics (132). However, prospective data evaluating the potential beneficial effects of SGLT2-I on cardiac biomarkers, as well as structural and functional cardiac parameters in patients with AMI and specific baseline ECG findings, remain limited.

Prolongation of the QRS complex is commonly observed in patients with chronic heart failure (186) and has been identified as an independent predictor of cardiovascular death, sudden death, and worsening heart failure following AMI (187). However, SGLT2 inhibition appears to provide benefits for these high-risk patients, particularly by reducing

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the risk of hospitalisation for heart failure (HFH). Similar findings have been reported for the QTc interval, which has been associated with all-cause mortality, sudden death, and death due to progressive heart failure in patients with chronic heart failure (188). Q-wave infarction has been reported to carry a higher risk of lethal outcomes in patients with symptomatic ischemic cardiomyopathy and cardiac dysfunction (189). Baseline findings in our sub-analysis revealed enlarged QTc intervals and prolonged Q-wave duration post-MI with normal QRS width. However, LVEF showed no significant correlations with baseline ECG parameters up to week 26, suggesting no predictive value of baseline ECG metrics for the LVEF response in SGLT2-I-treated patients following AMI (156).

Similarly, data on diastolic function and atrial ECG findings have already been reported. Li et al. demonstrated positive correlations between prolonged QTc intervals and various structural and functional diastolic cardiac parameters, including left atrial volume (LAV), left atrial volume index (LAVI), and the E/A ratio (190). Changes in the P-wave, particularly P-wave shortening, appear to be influenced by treatment with the SGLT2 inhibitor Empagliflozin, suggesting an improvement in atrial size and conduction (191). In our post-hoc analysis, significant positive correlations were observed between QRS width and E/e´, suggesting better recovery of diastolic function in patients with smaller QRS complexes post-AMI, potentially facilitated by early neurohumoral therapy improving cardiac remodelling. However, no additional correlations between E/e´ and baseline ECG metrics were identified, indicating that baseline ECG parameters do not predict diastolic function response (156).

Cardiac biomarkers, such as NT-proBNP and Troponin T, appear to provide reliable quantification of infarct size post-AMI (192) and are significantly associated with worsening heart failure (193). Furthermore, regarding ECG metrics, Troponin T levels have been positively associated with QRS width (194,195), while NT-proBNP levels have been identified as strong predictors of cardiovascular outcomes and clinical events in STEMI patients, particularly when combined with QTc interval prolongation (195). Recent literature indicates that large AMIs, characterized by markedly elevated Troponin T and NT-proBNP levels, are associated with a higher risk of developing left ventricular (LV) dysfunction and ventricular conduction disorders, often manifesting as QRS width prolongation, which serves as a predictor of poorer cardiac outcomes. However, our post-hoc analysis found no significant associations between cardiac biomarkers and ECG

parameters, indicating that baseline ECG metrics obtained one day post-PCI are not predictive of changes in cardiac biomarkers over a period of up to 26 weeks following AMI (156).

Blood pressure-lowering effects have been observed with both SGLT2 inhibitors (SGLT2-I) and glucagon-like peptide-1 receptor agonists (GLP1-RA). However, an increase in heart rate has only been identified with GLP1-RA (196), while SGLT2-I appear to have no significant effect on heart rate (186). Elevated heart rate has been associated with increased Troponin levels post-AMI (197), serving as a predictor of severe myocardial necrosis in patients with higher heart rates. Furthermore, large clinical outcome trials have reported worsening of chronic heart failure, independent of systolic function, in patients with elevated heart rates (198–200). The EMMY trial demonstrated beneficial effects on both systolic and diastolic function after AMI in the SGLT2-I group compared to placebo (72). However, no increase in heart rate was observed for Empagliflozin in our sub-analysis. In our linear mixed-effects model, significant positive associations were identified between heart rate and LVEF, E/e´, as well as NT-proBNP levels, suggesting a worse response of cardiac biomarkers and functional cardiac parameters at higher heart rates (156). These findings are consistent with adverse ventricular remodelling and underscore the importance of the early initiation of beta-blockers and neurohumoral therapy following AMI (47,48,130).

The EMMY trial also demonstrated a significant reduction in structural cardiac endpoints (72), which supports the findings from a large meta-analysis reporting significant improvements in both functional (LVEF and E/e´) and structural cardiac metrics (LVESD, LVEDD, LAVI, and left ventricular mass [LVM]) in SGLT2-I users among both diabetic and non-diabetic patients (201). Left ventricular volumes have additionally been negatively correlated with worse cardiac function following anterior AMI, particularly in patients with prolonged QRS width or Q-wave infarction (202). Moreover, better recovery in LVEF has been observed in patients with HFrEF and shorter QRS complexes treated with an angiotensin receptor-neprilysin inhibitor (ARNI) (203), suggesting a poorer cardiac prognosis in cases of LV dysfunction combined with prolonged ventricular conduction. Hardly any significant associations were identified in our post-hoc analysis between structural cardiac metrics and baseline ECG metrics. However, LVEDD demonstrated

significant positive correlations with Q-wave duration, suggesting that large myocardial infarctions followed by ventricular scarring are consistent with severe cardiac remodelling. Our findings support the results of the EMMY trial, which reported a significant reduction in LV size among SGLT2-I users. This indicates that SGLT2 inhibition promotes beneficial effects on ventricular remodelling, independent of baseline ECG parameters (156).

4.3 Subanalysis of Echocardiographic Data[×]

In the echocardiographic sub-analysis of the EMMY trial, we conducted an in-depth evaluation of 301 participants with available baseline, 6-week, and 26-week follow-up imaging after acute myocardial infarction. We identified a significant reduction in left ventricular volumes (LVEDV and LVESV) in the SGLT2-I group compared to placebo, highlighting potential anti-remodelling effects of Empagliflozin after AMI. While these effects were already reported in the main EMMY trial (72), this represents the first deformation analysis to explore the potential impact of SGLT2-I on non-left ventricular metrics following AMI.

Cardiac remodelling following acute myocardial infarction is characterised by a sequence of complex processes, including fibrosis, dilation of the heart chambers, and cardiac dysfunction, and has been identified as a major risk factor for morbidity and mortality in cardiac diseases (204). Pharmacological agents such as ACE inhibitors (ACE-I), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNI), and beta-blockers (BB) have been shown to reduce cardiac remodelling in patients with acute myocardial infarction and chronic heart failure, with a significant impact on hard clinical endpoints (205–209). However, no trials to date have investigated the potential effects of SGLT2 inhibitors (SGLT2-I) on atrial and ventricular cardiac remodelling post-AMI.

Reversal of left ventricular remodelling has been identified as a critical step in reducing mortality and morbidity in patients following acute myocardial infarction (210). SGLT2 inhibitors (SGLT2-I) have also been reported to exert beneficial effects, similar to their

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established role in chronic heart failure, in patients with coronary artery disease and acute coronary syndrome, extending beyond their anti-diabetic properties (72,106,206,211,212). The DAPA-MI trial was the first to provide evidence for the use of SGLT2-I in AMI, demonstrating favourable effects of Dapagliflozin on cardiometabolic outcomes compared to placebo, independent of diabetic status or LVEF, when added to guideline-recommended post-AMI treatment. However, the trial did not show significant effects on the composite endpoint of hospitalisation for heart failure and cardiovascular death (73). The recently published EMPACT-MI trial reported no significant differences in the composite endpoint of cardiovascular death and heart failure hospitalisation for the SGLT2 inhibitor Empagliflozin compared to placebo after AMI (74). Although hard clinical endpoints were not significantly improved by SGLT2-I in large clinical outcome trials (73,74), these agents appear to exert beneficial effects on the cardiovascular system after AMI, as evidenced by improvements in cardiac biomarkers as well as structural and functional cardiac metrics, as observed in the EMMY trial (72). The potential mechanisms underlying the effects of SGLT2-I on cardiac remodelling are believed to involve pleiotropic cardioprotective properties; however, the exact pathways remain unclear and are the subject of ongoing discussion. Previous in-vitro and in-vivo studies have suggested anti-fibrotic and anti-inflammatory effects of SGLT2-I after AMI (127,213,214). Additionally, SGLT2-I have been identified as cardioprotective through improving cardiac efficiency by enhancing myocardial energy supply (215–217).

This sub-analysis of echocardiographic markers revealed beneficial effects of the SGLT2 inhibitor Empagliflozin on cardiac remodelling post-AMI, demonstrated by a significant reduction in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) compared to placebo. Although favourable trends in the trajectories of functional cardiac metrics, including LVEF and E/e´, were observed, no significant differences between the two groups were identified. Similarly, no significant differences were observed between SGLT2-I users and non-SGLT2-I users in right atrial, left atrial, and right ventricular parameters.

The sub-study found only mildly reduced LVEF and LV-GLS overall, indicating that the effects of Empagliflozin on cardiac function post-AMI in this cohort are limited. In the SOCOGAMI trial, Empagliflozin demonstrated a significant reduction in blood glucose levels and body weight; however, no significant impact on echocardiographic or magnetic

resonance imaging parameters was detected in patients with AMI and preserved EF (218). These findings are consistent with the results of the SOCOGAMI trial, raising questions about the potential effects of SGLT2-I in patients with AMI and impaired cardiac function. In the SUGAR-DM-HF trial, Lee et al. reported a significant decrease in structural cardiac parameters, including reduced left ventricular systolic and diastolic volumes, in patients with HFrEF and T2DM treated with Empagliflozin. However, systolic function was not significantly influenced (219).

In the post-hoc analysis of the large clinical outcome trial PARADISE-MI, changes in echocardiographic parameters following AMI for the ARNI Sacubitril/Valsartan were investigated. The analysis showed only minor changes in cardiac structural characteristics and no significant effects on functional metrics (206). Similar findings were reported in the post-hoc analysis of the VICTORIA trial for Vericiguat in patients with chronic heart failure with reduced ejection fraction (HFrEF) (220). In PARADISE-MI, Sacubitril/Valsartan demonstrated a significant reduction in LVEDV compared to the ACE inhibitor Enalapril following AMI ($p = 0.025$), although no significant changes in LVEF were observed ($p = 0.091$) (206). Likewise, in the VICTORIA post-hoc analysis, Vericiguat showed a significant decrease in LVEDV compared to placebo ($p = 0.021$), but again, no significant changes in left ventricular systolic function were detected ($p = 0.091$) (220).

Although the echocardiographic sub-analysis revealed significant changes in structural cardiac parameters, no differences were identified in functional cardiac metrics between Empagliflozin and placebo. This finding is consistent with the results of the PARADISE-MI trial for Sacubitril/Valsartan (206) and the VICTORIA trial for Vericiguat (220). While the EMMY trial (72) also demonstrated changes in functional cardiac metrics, this outcome is likely attributable to the larger number of participants. Further research is needed to explore the potential impact of SGLT2 inhibitors on functional cardiac parameters.

4.4 ERASE°

ERASe is the first study to provide evidence on the beneficial effects of SGLT2 inhibitors (SGLT2-I) on arrhythmic burden in a clinical setting. Given that SGLT2-I were recently incorporated into the treatment for heart failure, independent of LVEF and diabetic status (70), it is unlikely that any further large-scale, randomised, investigator-initiated, placebo-controlled trials will be conducted in this population. Previous data have already highlighted a significant reduction in ventricular arrhythmic burden with SGLT2-I use in ICD patients over a 1-year period. However, 70% of the included patients received Dapagliflozin, and an analysis of differences between the SGLT2-I agents was not performed by the authors. Additionally, no significant differences in the burden of atrial arrhythmias were identified in SGLT2-I users (221).

Data from the EMPA-ICD trial, designed by Fujiki et al., involving 150 ICD patients with type 2 diabetes mellitus, provide evidence of the effects of 10 mg Empagliflozin on clinically significant ventricular arrhythmic burden 24 weeks before and after drug administration, compared to placebo. The trial reported a 1.7-fold lower incidence of ventricular arrhythmias for the SGLT2 inhibitor Empagliflozin, compared to a 1.8-fold increase in ventricular burden for placebo. However, the trial was limited to Japanese patients with T2DM, and most of the enrolled patients had an LVEF >40% (222). Similar findings were reported in a single-centre trial by Abedi et al., demonstrating the effects of Empagliflozin on ventricular burden 24 weeks before and after drug administration compared to placebo in 72 heart failure patients with an implanted ICD. The trial reported a significant reduction in ventricular arrhythmic burden, as well as in the proportion and frequency of ICD therapies. However, in the subgroup analysis, only patients who had previously received anti-arrhythmic therapy were identified as benefiting from the SGLT2 inhibitor-induced beneficial effects (223). In a single-centre, non-randomised trial, Basile et al. investigated the effects of Empagliflozin and Dapagliflozin on ventricular arrhythmic burden 26 weeks before and after drug administration in 82 patients. The study revealed no relevant differences in terms of arrhythmic events during follow-up. However, in the subgroup analysis, a reduction in arrhythmic events was observed in patients with a higher arrhythmic burden at baseline, though without statistical significance (224). A small observational study by Vecchi et al. reported a trend towards a reduction in arrhythmic

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events, specifically non-sustained ventricular tachycardias (nsVTs) and atrial high-rate episodes (AHRE), in 29 heart failure patients, although the findings were not statistically significant. This trend corresponds to the small number of enrolled patients (225). In a multicentre, non-randomised, retrospective trial enrolling 195 patients with an implanted ICD, a significant reduction in the percentage of patients with arrhythmic burden was observed one year after SGLT2-I drug administration compared to one year before. However, atrial burden and AHRE were not significantly influenced (226). Another large analysis by Gao et al. in diabetic patients receiving SGLT2 inhibitors or dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) reported a significant reduction in new-onset syncope by 51%, with the largest reduction observed for Ertugliflozin (HR 0.45, 95% CI 0.30–0.68, $p < 0.001$) (227). Given that syncope is often induced by arrhythmic events, this analysis may highlight the potential antiarrhythmic effects of SGLT2 inhibition in this population.

Several theories have been proposed regarding the mechanism of cardioprotective effects in SGLT2 inhibitors. Sodium homeostasis appears to play a key role in the cardioprotective effects of SGLT2 inhibitors through the inhibition of the Na+/H+ exchanger 1 (NHE1) at the cellular level (93,228) and suppression of the late Na^+ (late I_{Na}) (229) which is enhanced by oxidative stress in a calmodulin-dependent protein kinase II (CaMKII)-dependent manner (230,231). These proteins have been identified as contributors to sodium homeostasis, increasing the inward current during repolarisation, which expands the action potential duration and promotes antiarrhythmic effects (232). These findings highlight promising molecular targets for the treatment of heart failure, especially considering that sodium homeostasis has been found to be negatively impaired in patients with heart failure (233,234).
In addition to sodium homeostasis, Hasan et al. reported in an animal study that SGLT2 inhibitors promote voltage-gated potassium (K^+) currents in muscle cells, enhancing repolarisation and further prolonging the action potential across various species (235). Based on these findings, both sodium and potassium homeostasis may play crucial roles in the cardioprotective effects of SGLT2 inhibitors.

Furthermore, SGLT2 inhibitors (SGLT2-I) have been found to improve cardiac health by enhancing metabolic pathways, with an increase in ketone bodies in blood serum (236),

leading to restored cardiac mitochondrial function (237). In addition to these effects, SGLT2 inhibition has been shown to improve ECG metrics through changes in serum potassium and magnesium levels, stabilising the action potential of cell membranes without directly affecting ion channels (238,239). The potential antiarrhythmic mechanism may be attributed to enhanced stretch of cardiomyocytes, affecting intracellular Ca^{2+} and Na^{+} levels, which is consistent with a potential increased arrhythmogenic risk (240,241). Moreover, increased myocardial stretch promotes stretch-induced myosin light chain phosphorylation and angiotensin II activation in human atrial myocardium (242). Given that SGLT2 inhibition has been identified as reducing cardiac volume (72,133) and ameliorating adverse left ventricular remodelling (128), myocardial stretch may provide an explanatory mechanism for the antiarrhythmic effects of SGLT2 inhibitors in heart failure.

Myocardial fibrosis has been reported as a pro-arrhythmogenic substrate, particularly in heart failure patients with impaired ejection fraction. However, SGLT2 inhibitors have been shown to attenuate myocardial fibrosis by restoring Ca^{2+} and Na^{+} homeostasis, resulting in anti-inflammatory and anti-fibrotic effects (229,243). Singh et al. also reported the activation of Ca^{2+}/Calmodulin-dependent kinase II (CaMKII) in injured cell membranes of murine cardiomyocytes, regulating inflammatory processes through the induction of nuclear kappa light-chain-enhancer of activated B-cells (NF-κB) (244).

The recent 2021 guidelines for the diagnosis and treatment of patients with acute or chronic heart failure, as well as the 2022 guidelines for the management of ventricular arrhythmias and the prevention of sudden cardiac death, recommend the use of the “Fantastic Four” in patients with heart failure with reduced ejection fraction (HFrEF). These include ACE inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors (SGLT2-I) to reduce mortality in acute heart failure and sudden cardiac death (48,245). Since arrhythmic burden and the total number of ICD shocks are positively associated with mortality in heart failure patients with implanted ICDs (246), reducing arrhythmic events is critical. This includes appropriate heart failure and anti-arrhythmic drug therapy, interventional therapy, and optimisation of ICD devices (245).

Based on previous data, our clinical trial provides the first evidence regarding the use of SGLT2 inhibitors in heart failure patients with impaired LVEF and implanted ICDs ± CRT, suggesting specific anti-arrhythmic effects. These findings highlight the potential benefits of SGLT2 inhibition in patients with heart failure at higher risk for arrhythmic burden.

5 Conclusion

The EMMY trial was the first international study to demonstrate beneficial effects of the SGLT2 inhibitor Empagliflozin on NT-proBNP levels, as well as on echocardiographic functional and structural cardiac parameters, when added to standard treatment in addition to guideline-recommended ACS therapy within 72 hours post-AMI.

The first post-hoc analysis revealed an increase in baseline inflammatory markers upon initial presentation with AMI, followed by a significant decrease in both groups up to 26 weeks, which already occurred by week 6 post-AMI. However, no difference in trajectories of inflammatory biomarkers was observed between Empagliflozin and placebo, highlighting that the cardioprotective effects of SGLT2-I are not primarily based on the reduction of inflammatory response and are not enhanced by adding the SGLT2 inhibitor Empagliflozin after AMI.

In the second sub-analysis, we identified no significant difference between the SGLT2-I Empagliflozin and placebo regarding associations between baseline ECG metrics, cardiac biomarkers, and echocardiographic parameters. When merging the SGLT2-I and non-SGLT2-I group, we found no relevant or conclusive clinical patterns related to baseline ECG parameters and the response of primary and secondary endpoints of the EMMY trial. Hence, early administration of SGLT2-I post AMI appears to be beneficial post AMI regardless of baseline ECG metrics and was found to be safe in terms of baseline ECG characteristics.

In the Echo sub-analysis, administration of the SGLT2-I Empagliflozin after acute myocardial infarction showed a significant effect on cardiac remodelling up to week 26 following PCI as compared to placebo as reflected by reduction in LVEDV and LVESV. Diastolic function, LAVI as well as LA-GLS showed beneficial trends; however, the analysis failed to show any significant differences between the two groups.

The ERASE trial is the first and only clinical, placebo-controlled, randomized trial providing evidence of significant beneficial effects of the SGLT2 inhibitor Ertugliflozin on

arrhythmic burden in heart failure patients with impaired LVEF (HFrEF and HFmrEF) and implanted ICD ± CRT, compared to placebo.

In summary, the beneficial effects of SGLT2-I on structural and functional cardiac parameters, as well as on arrhythmic burden in chronic heart failure, suggest that the administration of these agents as an add-on to guideline-recommended therapy for heart failure could represent a new and promising treatment option in this field.

6 Strengths and Study Limitations

The EMMY trial is a multicentre, randomized, placebo-controlled, investigator-initiated and double-blind clinical trial investigating the effects of Empagliflozin on NT-proBNP levels as well as functional and structural cardiac parameters, independent of diabetic status. However, due to the low number of participating patients and short follow-up period of up to 26 weeks, the study was not powered for hard clinical endpoints such as mortality or hospitalisation for heart failure (72).

Both, the EMMY trial as well as its sub-analyses showed unbalanced groups regarding sex, with a high percentage of men, as well as only a small percentage of diabetic patients. Nevertheless, neither factor was found to have any impact on the results in correlation analyses.

Only 374 patients with available frozen blood samples from all visits were included in the inflammation subanalysis (80% of the whole cohort), which limited the power of the results. Inflammatory burden and clinical outcome after AMI might also be strongly influenced by pro-resolving mediators, however, our inflammatory sub-analysis did not demonstrate these effects as investigating them was beyond the scope of the sub-study.

In the ECG sub-analysis, only 38% of the entire EMMY cohort (181 patients from the Graz cohort) with available baseline ECG were included in the proper analysis, limiting the power of this post-hoc analysis.
We included only metrics from the baseline ECG taken one day post-AMI; however, ECGs in the follow-up periods were not performed, and thus, trajectories of ECG characteristics up to week 26 could not be identified.
Numerous statistical tests were performed in our ECG sub-analysis without adjustment for multiple testing. Therefore, significant findings might be expected by chance, and the results must be interpretated carefully.
Only a small number of patients (5 patients) exhibited prolongation of the P-wave (≥120ms). Therefore, correlations between P-wave duration and the primary or secondary endpoints of the EMMY trial could not be investigated.

The Echo sub-analysis reflects only a small percentage of the overall cohort and showed significant reduction in left ventricular volumes as observed in the main trial. However, LVEF and diastolic function showed no significant differences compared to the main trial, most probably to the low number of patients with available echo loops from only three out of eleven participating centres as well as lack of statistical power. Apart from the low number of patients, a relevant percentage of available patients did not meet post-processing criteria due to low image quality and were therefore excluded from the analysis. Thus, the lack of significant differences between the treatment groups, as compared to the main trial, may be attributed to the limited sample size.
All analyses were performed twice in a single centre Echo core Lab by experienced and blinded staff to increase reproducibility and reduce bias. Although some trials reported changes in left ventricular structural and functional cardiac parameters, this is the first analysis demonstrating the effects of SGLT2-inhibition on right ventricular and right atrial structure and function post-AMI.

Only 20% of all participants included in the ERASe trial had an implanted atrial lead. Therefore, the detection of atrial arrhythmic burden was limited, and no statistical analysis could be conducted.
Stöllberger et al. reported potential pro-arrhythmic effects of Empagliflozin on ventricular burden in an ex vivo rabbit heart experiment. However, these effects were not observed with Dapagliflozin (247). Based on these findings, the potential effects of SGLT2 inhibitors on arrythmias may differ among individual drugs within this class.
The trial was terminated early due to changes in guidelines for SGLT2 inhibitors, which received a Class IA recommendation for all patients with heart failure, regardless of LVEF and diabetic status (65–68,70). Therefore, randomizing these patients either to SGLT2-I or placebo became ethically unjustifiable, resulting in a lower number of participants than originally planned, which further reduced the power of the study. Although ERASe trial highlights significant reductions in primary and secondary endpoints, these results must be interpreted with caution.

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