Diploma Thesis

The Impact of the SGLT Inhibitor Empagliflozin on the Left Atrial Function after Acute Myocardial Infarction - the EMMY-Trial

submitted by

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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 individuals and organizations that have contributed to the research for this thesis. The acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Guidelines of the Medical University of Graz on Good Scientific Practice”.

Graz, March 6th, 2023 Christoph Strohhofer m.p.

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Abbreviations and Definitions

2D	*two-dimensional*
2D CPA	*2D Cardiac Performance Analysis*
3D	*three-dimensional*
3DE	*three-dimensional echocardiography*
ACE	*angiotensin-converting enzyme*
ACEi	*angiotensin-converting enzyme inhibitors*
ACS	*acute coronary syndrome*
AF	*atrial fibrillation*
AHF	*acute heart failure*
AMI	*acute myocardial infarction*
ANP	*atrial natriuretic peptide*
ARB	*angiotensin II receptor blockers*
ARNI	*angiotensin receptor/neprilysin inhibitor*
ASE	*American Society of Echocardiography*
AV	*Aortic valve*
BB	*beta blockers*
BMC	*peer-reviewed medical journal published by BioMed Central*
BMI	*body mass index*
BNP	*brain natriuretic peptide*
BP	*blood pressure*
Ca	*Calcium*
CAD	*coronary artery disease*
CCB	*calcium channel blockers*
CCS	*chronic coronary syndrome*
CDI	*color doppler imaging*
CHAMPIT	*etiology of acute heart failure: coronary **s**yndromes, **h**ypertension, **a**rrhythmia, **m**echanical, pulmonary embolism, infections, tamponade*
CHF	*chronic heart failure*
CI	*confidence interval*

CMAJ	*Canadian Medical Association Journal*
CMR	cardiovascular magnetic resonance imaging
CRP	*c-reactive protein*
cTn	*cardiac troponin*
CVD	*cardiovascular disease*
CW	*continuous wave*
DALYs	*disability-adjusted life years*
DAPA	*dapagliflozin*
DAPT	*dual anti-platelet therapy*
DICOM	*Digital Imaging and Communications in Medicine*
DTI	*Doppler tissue imaging*
e.g.	*exempli gratia meaning for example*
EACVI	*European Association of Cardiovascular Imaging*
ECG	*electrocardiogram*
ED, d	*end-diastolic*
EF	*ejection fraction*
EMMY	***em**pagliflozin in acute **my**ocardial infarction trial*
EMPEROR	*empagliflozin in heart failure with preserved ejection fraction trial*
ES	*end-systolic*
ESC	*European Society of Cardiology*
ESH	*European Society of Hypertension*
FGF	*fibroblast growth factor 21*
GCS	*global circumferential strain*
GE	*General Electric*
GFR	*glomerular filtration rate*
GLP	*glucagon-like peptide-1*
GLS	*global longitudinal strain*
HF	*heart failure*

HFA	*Heart Failure Association*
HFmrEF	*heart failure with mildly reduced ejection fraction*
HFpEF	*heart failure with preserved ejection fraction*
HFrEF	*heart failure with reduced ejection fraction*
HJC	*Hellenic journal of cardiology*
IBM	*International Business Machines Corporation*
IHD	*ischemic heart disease*
IVC	*inferior vena cava*
IVS	*interventricular septum*
JACC	*Journal of the American College of Cardiology*
JCI	*Journal of Clinical Investigation*
KIMCL	*Clinical Institute of Medical and Chemical Laboratory Diagnostics*
LA	*left atrium*
LAmax	*maximal LA volume*
LAmin	*minimal LA volume*
LAQ	*left atrial quantification*
LAS	*longitudinal atrial strain*
LASr	*left atrial reservoir strain*
LAVI	*left atrial volume index*
LV	*left ventricle*
LVDD	*left ventricular diastolic dysfunction*
LVEDV	*left ventricular end-diastolic volume*
LVEF	*left ventricular ejection fraction*
LVESV	*left ventricular end-systolic volume*
LVID	*left ventricular internal dimension*
LVOT	*left ventricular outflow tract*
LVPW	*left ventricular posterior wall*
MACE	*major adverse cardiovascular event*

MDCT	*multidetector computed tomography*
MI	*myocardial infarction*
MR	*midregional*
MRA	*mineralocorticoid receptor antagonist*
MRI	*magnetic resonance imaging*
MR-proANP	*mid-regional pro-atrial natriuretic peptide*
MV	*mitral valve*
NCT	*National Clinical Trial*
NP	*natriuretic peptide*
NSTEMI	*Non-ST-segment elevation myocardial infarction*
NT-proBNP	*N-terminal prohormone of brain natriuretic peptide*
PA	*pulmonary artery*
PALS	*peak atrial longitudinal strain*
PALS	*peak atrial longitudinal strain*
PARADISE	*prospective ARNI versus ACE inhibitor trial*
PCI	*percutaneous coronary intervention*
PEFF	*score developed to overcome diagnostic difficulties in HFpEF*
PLAX	*parasternal long axis*
pLAS	*peak left atrial strain*
PPI	*proton pump inhibitor*
PR	*pulmonary regurgitation*
PSAX	*parasternal short axis*
PTCA	*percutaneous transluminal coronary angioplasty*
PV	*pulmonary valve*
PW	*pulsed wave*
RA	*right atrium*
REGICOR	*Registre Gironí del COR*
ROI	*Region of interest*
RV	*right ventricle*
RVOT	*right ventricular outflow tract*

SC	*sub costal*
SDI	*spectral doppler imaging*
SGLT2	*sodium-glucose cotransporter 2*
SGLT2i	*sodium-glucose cotransporter 2 inhibitors*
SPSS	*statistical software suite developed by IBM*
SSN	*suprasternal notch*
STEMI	*ST-segment elevation myocardial infarction*
TAPSE	*tricuspid annular plane systolic excursion*
TOMTEC	*TOMTEC Imaging Systems GmbH*
TR	*tricuspid regurgitation*
TTE	*transthoracic echocardiogram*
TV	*tricuspid valve*
UK	*United Kingdom*
UN	*United Nations*
US	*United States*
V_c	*circumferential velocity*
V_l	*longitudinal velocity*
V_r	*radial velocity*
VTI	*velocity time integral*
YLD	*years lived with disability*
YLL	*years of life lost from mortality*

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Kurzzusammenfassung

Hintergrund und Fragestellung: Inhibitoren der Natrium-Glukose-Cotransporter 2 (SGLT2i) führten in klinischen Studien mit chronischer Herzinsuffizienz zu besserem Outcome im Vergleich mit Placebo. Die EMMY-Studie bestätigte diesen Zusammenhang nach einem akuten Myokardinfarkt (AMI) mit einer signifikanten Reduktion des N-terminalen pro brain natriuretic peptide (NT-proBNP) durch Empagliflozin. Diese Diplomarbeit soll die Evidenz zur Beteiligung des linken Vorhofs an der systolischen und diastolischen myokardialen Dysfunktion erweitern.

Material und Methoden: Es wurden die verfügbaren Echokardiographie-Loops von einem Kollektiv nach AMI (n = 219), welches im Rahmen der EMMY-Studie entweder eine Standardbehandlung und Placebo oder eine Standardbehandlung und Empagliflozin erhielt, zu drei Zeitpunkten (Woche 0, 6±2 und 26±2) hinsichtlich linksatrialer Dimension und Funktion triple-blind ausgewertet. Die erhaltenen Werte wurden statistisch über die Zeit und zwischen den Gruppen verglichen, sowie mit weiteren echokardiographischen und chemischen Markern korreliert.

Ergebnisse: Die erhobenen linksatrialen Struktur- und Funktionsparameter unterschieden sich zu keinem der Zeitpunkte zwischen Interventions- und Placebogruppe signifikant. Nach 26 Wochen wurde in beiden Gruppen ein signifikanter Anstieg des linksatrialen globalen longitudinalen Strain (LA GLS) (p = .000) und des linksatrialen Volumenindex (LAVI) (p = .000) festgestellt. LA GLS korrelierte stark mit dem linksatrialen globalen circumferentiellen Strain (LA GCS) (ρ = .622), moderat mit der linksatrialen Ejektionsfraktion (LA EF) (ρ = .435), linksventrikulären Ejektionsfraktion (LVEF) (ρ = .320) und NT-proBNP (ρ = - .372), sowie schwach mit dem LAVI (ρ = - .221).

Konklusion: Empagliflozin führte zu keiner signifikanten Verbesserung echokardiographischer linksatrialer Strain- und Volumenparameter im Vergleich zu Placebo. Im Gegensatz dazu wurde eine signifikante Erhöhung des LA GLS und des LAVI nach 26 Wochen in beiden Gruppen festgestellt. Da zwischen LAVI und LA GLS nur eine schwache Korrelation festgestellt wurde, erscheint die weitere klinische Erforschung der Strainparameter sinnvoll, um die Rolle des linken Vorhofes in verschiedenen kardiologischen Krankheitsbildern besser zu verstehen.

Abstract

Background and Aim: Clinical trials showed that sodium–glucose co-transporter 2 inhibitors (SGLT2i) lead to better outcomes in patients with symptomatic heart failure compared to placebo. The EMMY-trial confirmed this result after acute myocardial infarction (AMI) by a significant decrease of N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) with Empagliflozin. This thesis aims to give a better insight into the involvement of the left atrium (LA) as part of the myocardial systolic and diastolic dysfunction.

Material and Methods: The echocardiographic loops of 219 patients after AMI, who received standard treatment plus Placebo or standard treatment plus Empagliflozin within the framework of the EMMY-trial, were assessed at three points in time (week 0, 6±2 und 26±2) regarding left atrial structure and function. The resulting data was statistically compared over time and between the groups in a triple-blind approach. Correlation analyses with other laboratory (e.g. NT-proBNP) and echocardiographic markers (e.g. left ventricular ejection fraction) were conducted.

Results: The measured echocardiographic left atrial structural and functional parameters did not significantly differ between the intervention and placebo group at any time. Over time both groups demonstrated a significant increase in left atrial global longitudinal strain (LA GLS) (p = .000) and left atrial volume index (LAVI) (p = .000). LA GLS correlated strongly with left atrial circumferential strain (LA GCS) (ρ = .622), moderately with left atrial ejection fraction (LA EF) (ρ = .435), left ventricular ejection fraction (LVEF) (ρ = .320) and NT-proBNP (ρ = - .372), as well as weakly with LAVI (ρ = - .221).

Conclusion: Empagliflozin did not result in a significant improvement of echocardiographic left atrial strain and volume parameters compared to placebo. However, after 26 weeks, a significant increase of LA GLS and LAVI became evident in both groups. Since there was only a weak correlation between LAVI and LA GLS, further clinical research of strain parameters is needed to get a better understanding of the left atrial role in different cardiac conditions.

1 Introduction

1.1 Myocardial Infarction

1.1.1 Background

The two most common entities of cardiovascular disease (CVD) are ischemic heart disease (IHD) and stroke. The term IHD refers to different conditions which are the result of an imbalance between the oxygen supply and demand of the heart. Its spectrum ranges from angina pectoris to myocardial infarction (MI), with the latter being the most severe form. To outline the frequency of medical emergencies due to direct ischemic damage of the heart muscle, the American Heart Association strikingly states that approximately every 43 seconds an American has a MI[1].

Considering that the twenty-eight-day fatality of a MI was observed to be between 19% in 35- to 64-year-olds and 84% in 85- to 94-year-olds in a European cohort[2], the overall relevance of what is colloquially known as “heart attack” becomes even more apparent. In Europe IHD causes 19% of all deaths among men (862 000 deaths per year) and 20% among women (877 000 deaths per year), thus representing the leading single cause of death[3]. Despite increasing efforts to prevent CVD and major improvements in the prehospital and interventional therapy, the overall heart disease mortality is still high, with one explanation being the simultaneous increase in obesity and type 2 diabetes in the developed world.

Even though premature death represents the main consequence of IHD, many acute MI patients survive. It is therefore necessary to also take all the years lived with disability (YLD) because of a MI into account. The YLD because of IHD can be a result of heart failure, stable angina, or acute coronary syndrome (ACS)[4]. Consequently, the more IHD death rates will decrease over time, the more attention will need to be paid to the improved quality of life in patients with chronic IHD. The so-called disability-adjusted life years (DALYs) combine the years of life lost (YLL) due to premature death and the years lived with disability (YLD), resulting in one DALY being equivalent to one lost year of a healthy life. In Central Europe the number of DALYs lost because of IHD were as high as 2608 per 100 000 People in 2010[5].

Another important factor that is directly related to the rising significance of IHD is the demographic change with the rapidly aging population in Europe. The average age of first MI is relatively high, with 66 years in males and 72 years in females, even though the age-standardized prevalence rate of CVD has decreased in Europe overall by about 7 percent from 1990 to 2015. The absolute numbers of people suffering from CVD were 7840 per 100 000 in 1990 and 7147 in 2015 in men, whilst the figures for women were 5931 per 100 000 in 1990 and 5612 in 2015[3]. The epidemiologic significance is underlined by the fact that 200 million people aged 65 or above live in North America and Europe at the moment, and that this number is expected to increase by 48 percent by 2050[6].

To put the overall burden of IHD, with its most dangerous correlate being MI, into perspective in the developed world, economic aspects must be addressed as well. In fact, even though progress in the diagnostic and therapeutic measures for IHD undoubtedly benefits the patients, it is connected to high costs in the health sector. In average, more than 10% of the whole healthcare expenditure of European countries is currently directly linked to CVD[7]. Keeping this growing relevance for people as individuals in an acute and chronic setting and the world-wide socioeconomic impact in mind, the need for further improvement seems necessary.

1.1.2 Diagnosis

The broad definition of a MI is the occurrence of myocardial cell death due to prolonged ischemia. To standardize the diagnosis of a MI in patients, the European Society of Cardiology (ESC) differentiates between myocardial injury and myocardial infarction. A myocardial injury is present if cardiac troponin (cTn) enzyme values are higher than the 99th percentile upper reference limit[8]. If there is clinical evidence (at least one of the following: typical symptoms, particular electrocardiogram (ECG) changes, imaging evidence that is consistent with a MI or the direct detection of a coronary thrombus) in addition to the laboratory changes, the ESC criteria for a MI are met[9]. Depending on the presence of ST-segment elevations in at least two contiguous leads a MI can be clinically subdivided into a ST-segment elevation myocardial infarction (STEMI) and a non-ST-segment elevation myocardial infarction (NSTEMI).

1.1.3 Therapy

In case of a MI, the main concern is to attempt to restore perfusion to reduce the ischemic injury of the myocardium. The preferred method for this is a percutaneous coronary intervention (PCI) and/or fibrinolysis. Periprocedurally, it is recommended that patients undergoing primary PCI are given dual anti-platelet therapy (DAPT), referring to aspirin and a P2Y12 inhibitor, and additionally a parenteral anticoagulant[8].

In later stages, long-term therapy can be seen as tertiary prevention. Besides all pharmacological options, it is highly desirable that the patients improve their lifestyle if possible. More specifically, it is suggested that they should stop smoking, watch their diet, alcohol intake and weight, as well as implement regular physical activity into their daily life. Pharmacologically, it is important to treat systolic blood pressures >140 mmHg or even earlier[8]. Regarding antithrombotic therapy, low-dose aspirin should be taken indefinitely from all patients with STEMI[10]. For patients with STEMI undergoing PCI DAPT is recommended for up to 12 months. A proton pump inhibitor (PPI) is beneficial for patients with a high risk of gastrointestinal bleeding[11].

To reduce the long-term risk of death after a MI, further pharmacological classes are used. Among them are beta-blockers, lipid lowering agents, Angiotensin-converting enzyme Inhibitors (ACEi) or angiotensin II receptor blockers (ARB) if ACE-inhibitors are not tolerated[8]. For all these medication classes research has shown higher survival rates[12,13,14]. At the same time, they have a high standing in the hypertension and chronic heart failure (CHF) treatment regimes.

For uncomplicated hypertension, the ESC recommends ACEi or ARB + calcium channel blockers (CCB) or a diuretic as initial dual therapy. At the same time beta-blockers should be considered at any step if a certain indication is present, such as in post-MI patients[15]. The cornerstone of the pharmacological treatment of heart failure with reduced ejection fraction (HFrEF 1.1.4) consists of an ACEi or an Angiotensin receptor-neprilysin inhibitor (ARNI), a beta-blocker, as well as a Mineralocorticoid receptor antagonist (MRA) and a SGLT2i.

1.1.4 Connection to Heart Failure

Heart failure as a complication of a MI leads to higher overall morbidity and mortality. It was established in a large cohort that 13% of patients developed heart failure at the time of the MI in the hospital and an additional 10% of patients within the following months after a MI. Strikingly, post-discharge heart failure was associated with a 239% higher 1-year mortality[16]. Heart failure is defined as a clinical syndrome with symptoms like breathlessness, ankle swelling or fatigue, in many cases accompanied by signs such as elevated jugular venous pressure or pulmonary crackles[17]. This is caused by abnormal structural or functional capacities leading to higher intracardiac pressures than usual and/or inadequate cardiac output. The prevalence of CHF in European adults is officially estimated to be around 1.5%[18]. The actual number might, however, be much higher, since it became apparent that a lot of older people with shortness of breath suffer from unrecognized HF[19].

The most common cause of CHF in Western societies is coronary artery disease (CAD), which shows a close relation between IHD and HF. The ESC therefore even recommends, that all patients with CHF should be examined closely for any signs and symptoms of chronic coronary syndrome (CCS). Vice versa the probability of CHF in patients that have presented with symptomatic CAD is higher than average[17].

CHF can be subcategorized into heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF). Whereas in HFrEF (EF <40%) and HFmrEF (EF 40-50%) a decrease in ejection fraction (EF) can be diagnosed, HFpEF is detected by signs and symptoms like breathlessness, fatigue, and ankle swelling, with detection either of structural and/or functional cardiac abnormalities and/or raised natriuretic peptides (NP). Almost 60% of CHF patients belong to the category HFrEF, 24% to HFmrEF and 16% to HFpEF[20]. While the pathogenic role of IHD in HFrEF is well-investigated, it has also been shown that HFmrEF resembles HFrEF rather than HFpEF in terms of a higher connection to IHD and a higher risk of new IHD events. Still, the presence of IHD was shown to be an important prognostic factor for all three HF types[21].

The two natriuretic peptide hormones atrial NP and B-type NP have a high standing in the diagnosis and observation of heart failure. They are secreted by the atrial

cardiomyocytes in case of increased stretching of the atrium due to fluid overload. They work by enhancing renal sodium secretion to decrease extra cellular fluid levels. Due to the short half-lives of C-terminal atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) levels in the plasma, the plasma levels of cleaved proteolytic products with a longer half-life are usually measured as their surrogates, namely mid-regional proANP (MR-proANP) and N-terminal proBNP (NT-proBNP)[22]. The negative predictive value for HF is higher than 94% if the plasma concentration of NT-proBNP is lower than 125 pg/mL or the MR-proANP is lower than 40 pmol/L[23,24]. However, some conditions might lead to elevated NP unrelated to HF. Among them are atrial fibrillation (AF), high age or kidney disease. Diagnostically, it can be stated that the higher the NP, the higher the likelihood that the symptoms of patients, primarily dyspnea, are due to HF[25].

In contrast to CHF, acute heart failure (AHF) describes a more rapid onset of signs and symptoms of HF. The etiologies of AHF are combined in the acronym CHAMPIT, which stands for (Acute) Coronary syndrome, hypertensive crisis, arrythmias, mechanical causes, pulmonary embolism, infections, and tamponade. AHF can be a new onset HF or even more frequently, representing an acute decompensation of CHF[17].

Overall, CAD can cause HF in many ways. The most striking one seems to be ACS leading all the way to cardiac shock due to the prompt loss of functioning myocardium (acute MI, myocarditis). However, cardiogenic shock is an extreme form and not common in patients with AHF and ACS. ACS can present as unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI). The presence of ACS and AHF at the same time is associated with a higher short-term mortality than ACS alone. It was observed that the incidence of AHF complicating the management of patients with ACS may be the case in 6-41%. The wide range might be explained by the different degrees of severity of ACS, since many different clinical scenarios are known. They include AHF patients with chest pain and normal cTn (possible angina pectoris), patients without chest pain, but with elevated cTn (possible myocardial injury), patients with chest pain and elevated cTn (possible MI) or even with an ACS in the first place and later developing AHF[26]. Measuring troponin may help to detect myocardial ischemia, but diagnosis is difficult. Most patients with AHF present with elevated troponin

levels and also AHF of other etiologies (CHAMPIT) may lead to ECG changes[26]. Like CHF, natriuretic peptides are a valuable tool for diagnosing AHF. If BNP is lower than 100 pg/mL, NT-proBNP lower than 300 pg/mL and/or MR-proANP lower than 120 pg/ mL AHF is unlikely[27].

Essentially all patients surviving a MI are at risk of developing symptomatic HF or premature death[28]. It is in fact possible that the ventricular dysfunction in post-MI patients may resolve if the initial treatment was optimal, but in case of permanently impaired cardiac function, the risk of progression to HF as result of cardiac remodeling is remarkably high. Naturally, the bigger the infarct size and the more remodeling has happened, the higher the degree of LV dysfunction. To prevent or at least slow down this process after a MI, it is important to administer medications that counteract and might even promote reverse remodeling early in the post-acute phase. At this point those medications are beta blockers (BB), ACEi or ARB and MRA[26].

Studies for other medication classes in this context are ongoing. Sacubitril/valsartan is investigated by the PARADISE-MI (Prospective ARNI vs. ACE inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI), to determine if it benefits outcomes in post-MI patients with left ventricular dysfunction[28]. The EMMY trial (Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction) evaluates the concept of SGLT2 inhibition to improve cardiac remodeling, reduce pre- and afterload as well as the effect on cardiac metabolism regardless of its antidiabetic effects[29].

1.2 SGLT2 Inhibitors

SGLT2i have shown to reduce mortality in patients with type 2 diabetes[30] and HFrEF[31], and also lower the risk of major cardiac events in patients with atherosclerotic CVD, including cardiovascular death[32]. Initially developed as a blood glucose lowering agent, their use is by far not limited to the treatment of type 2 diabetes anymore. In fact, it has been shown that SGLT2i lower the risk of worsening and cardiovascular death in HFrEF patients, regardless of the patients being diabetics or not[33]. The same applies for patients with diabetic and non-diabetic chronic kidney disease[34].

SGLT2i were initially developed as oral anti-diabetic drugs to reduce blood glucose by blocking the renal coupled reabsorption of sodium and glucose by inhibition of the sodium-glucose cotransporters 2. Those transporters are expressed in the first segment of the proximal convoluted tubule and are directly involved in approximately 90% of the reabsorbed glucose[35]. Inhibiting those high-capacity transporters consequently leads to iatrogenic glucosuria. Its extent depends on plasma glucose concentration as well as on patients' glomerular filtration rate[36]. Investigating further molecular mechanisms in mice, it was concluded that SGLT2i have the potential to increase glucose tolerance despite reduced plasma insulin, to improve plasma lipids and to have various catabolic effects[37].

With regard to their effects on the cardiovascular system, SGLT2i have been found to lower preload by promoting osmotic diuresis through natriuresis and they can also decrease afterload by lowering blood pressure (BP) and reducing arterial stiffness[38]. One of the complex mechanisms that SGLT2i contribute to cardiovascular and renal protection is the reduction of sympathetic nervous system overactivity[39], which is a key humoral mechanism in heart failure.

At the same time, SGLT2i have a direct positive effect on the heart, especially on ventricular remodeling, cardiac metabolism, and direct cardioprotective mechanisms[35]. Ventricular remodeling has been shown to be partly reversible in an animal model[40]. Cardiac metabolism is improved by reducing the consumption of carbohydrates and at the same time increasing the utilization of fatty acids and ketone bodies. Mechanisms that directly affect the myocardium are, among others, the inhibition of Na^+/Hydrogen exchanger 1 (increasing mitochondrial Calcium (Ca^{++}) levels), reducing the activity of Ca^{++}/calmodulin dependent kinase (improving contractility as well, by reducing sarcoplasmic Ca^{++} leak), increasing phosphorylation levels of myofilament regulatory proteins (improving diastolic function) and possibly even positive epigenetic modifications[35].

In theory, there are known positive molecular pathophysiologic effects of SGLT2i that play a role before, during and after MI regardless of the presence or absence of diabetes. It has been shown in various animal models that taking SGLTi in advance can reduce infarct size, improve ventricular contractibility and significantly increase 48-hour survival in case of a MI[41]. It is suspected that the infarct-sparing

effect of long-term treatment with SGLT2i is the result either of an effect independent of glucose or of up-regulation of cellular survival pathways in the heart. These effects demonstrate that chronic pre-treatment might benefit high-risk cardiovascular patients irrespective of their diabetic status[42]. Even investigations of SGLT2i treatment shortly before a MI, i.e. not allowing the medication to chronically change the cardiac mechanisms, have shown a better outcome in infarct size and contractility in animal models[43]. Clinical data on the clinical setting of SGLT2i treatment after myocardial infarction is rare, but the research on animal models shows promising results. Even though administration after the ischemic event naturally cannot reduce the infarct size per se, it preserves aerobic metabolism after MI, improves long-term contractility and limits cardiac remodeling[44]. Based on these favorable characteristics SGLT2i are currently being evaluated in the setting after MI by several phase III trials.

1.3 The role of the left atrium

The LA is physiologically very closely linked to the left ventricle (LV). It serves as a blood reservoir during ventricular systole, conducts the blood to the LV in early diastole and finally contributes around 15-30% of the LV volume by atrial contraction in late diastole[45].

The first standardized parameter to measure the LA was the anterior-posterior diameter. For a long time, the clinical importance of LA size was perceived as low, but this has changed with recent population-based studies showing LA size as a prognostic parameter for long-term outcomes[46]. The size of the LA is mainly the reflection of LV filling and pressure over time[47], because of the equalizing of pressure between the chambers in diastole. Alternative reasons for an enlarged LA can be mitral valve disease or secondary impairment due to atrial myopathy. Larger LA diameters and, therefore, larger volumes, have been shown to be sequentially associated with all-cause mortality in both sexes[48]. Hence, maximal LA volume (LAmax) is an established prognostic predictor in different cardiac diseases including post-MI[49].

Still, it has been suggested to incorporate more LA parameters than just LAmax to better portray LA functionality especially in the context of ischemic cardiac events. LA total ejection fraction ([LA pre-systolic volume – LAmin]/LA pre-systolic volume)

and the very similar LA fractional change ([LAmax – LAmin]/LAmax) were both established as independent predictors of mortality in NSTEMI patients[50]. The different approaches are due to the various significations of the parameters. The pre-systolic volume, meaning the LA volume immediately before atrial systole, also called diastasis volume, is highly dependent on LV diastolic pressure and LV function. The LAmin is a result of the intrinsic LA contractility, as well as the volume load it encounters, determined by LV chamber compliance and pulmonary venous capacitance. Fractional change, which simply uses the values LAmin and LAmax, mirrors atrial and intrinsic ventricular conditions equally[50].

In contrast to NSTEMI patients, STEMI patients tend to be younger, have fewer co-morbidities, and overall less extensive CAD, necessitating confirmation in this cohort as well[51]. This was done by showing that LAmax is a good indicator of long-standing cardiovascular conditions like age, LV mass index, LV end-diastolic volume index, and diastolic dysfunction grade, but not significantly related to the acute markers of LV disease such as peak troponin T, area at risk, reduced LVEF, infarct size, and the ratio between early mitral inflow velocity to early diastolic mitral annular lengthening velocity (E/e′). Parameters which can reflect preexisting cardiovascular conditions as well as the occurrence of STEMI are LAmin, LA fractional change, and LA passive fraction. For prediction of major adverse cardiovascular event (MACE) only the two LA parameters LA stroke volume and LA fractional change have shown to be the accurate, after adjusting for age, LVEF, hypertension, previous PCI and diastolic dysfunction grade[52]. The latter results were reached through cardiovascular magnetic resonance imaging (CMR), which is considered to be the most accurate method for obtaining LA function and size[53]. More recently left atrial strain analysis has come into focus as long-term prognostic parameters in STEMI patients, giving a direct image of atrial function and allowing to differentiate between the different atrial phases more easily[54].

The close relationship between LA and LV further shows in patients within the first 48 hours of admission after MI by a comparison of left ventricular global longitudinal strain (GLS), LA volumes, and peak atrial longitudinal strain (PALS). PALS has shown to be a composite measure of left ventricular longitudinal systolic function and maximal LA volume and it significantly correlates with hypertension, diabetes mellitus and Killip class >1[55]. At the same time it is evident, that the effects of ACS

and especially STEMI on LA systolic function are not tracked by changes in LA volumes alone[56], rather they can be identified through LA strain and strain rate[57]. Another advantage of LA strain measurements is that they are less preload-dependent than the LAmax values[58].

1.4 Transthoracic Echocardiography (TTE)

Echocardiography is the most commonly used noninvasive cardiovascular imaging modality, which uses harmless ultrasound waves and provides comprehensive data regarding cardiac anatomy and structure, chamber size and function as well as morphology and function of the heart valves besides intracardiac hemodynamics evaluation[59]*.* To obtain all the information needed from a complete Transthoracic Echocardiographic Examination in adults it is recommended to stick to international guidelines[60]. In every pre-defined imaging plane, the procedure starts with the recording of plain two-dimensional images of the cardiac cycles, to record cardiac anatomy and performance. In the next step, the standard grayscale views of two-dimensional imaging are combined with color doppler imaging (CDI). It is recommended that CDI be used in practically all imaging views, which is why it should not be viewed as independent imaging technique[60]. To enable an even more conclusive study especially regarding valves and blood flow spectral doppler should be applied in predefined locations.

Like many fields in medicine, echocardiographic technology is constantly evolving, with the two major recent developments being real-time three-dimensional (3D) echocardiography (3DE) and myocardial deformation imaging. The use of 3D algorithms, if available, is highly recommended, especially for calculating LV volume, but it has not found its way into the clinical setting the same way deformation imaging has.

1.4.1 Assessment of heart function

To assess heart function non-invasively, different parameters are currently available with echocardiography. By far most of the research for the quantification of diastolic and systolic function has been conducted on the left ventricle. This needs to be considered since different parameters can have diverse validity in different heart chambers.

A quite common parameter, especially for LV performance, is ejection fraction (EF). For the LA EF is not measured routinely. The calculation of this parameter is shown in figure 1. Regrettably, the concept of EF comes with many disadvantages. First and foremost, the intra- and interobserver variability is higher than commonly believed. This limits the accuracy of EF measurements, but can be greatly reduced by using information from multiple views, which is then combined into a conformal 3-dimensional surface model[61]. Another particularly important drawback of EF is that it is considerably influenced by hemodynamics. Depending on pre- and afterload conditions the ventricle can be portrayed much better or worse than it is in reality.

$$E_f = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$$

E_f = Ejection Fraction
SV = Stroke volume
EDV = End-diastolic volume
ESV = End-systolic volume

Figure 1: Calculation of the ejection fraction

Additionally, the concept of heart function can be divided into ventricular function and myocardial function[62]. While the ventricular function is based on the capability of the heart working as a pump, the myocardial function is directly related to the functionality of the muscle. Naturally, these two definitions overlap, but the two terms should not be used as synonyms, since reduced pumping function might not be directly caused by an impaired ability of the myocardium to contract.

A more objective and better quantifiable way was introduced with Deformation Imaging. Deformation Imaging is based on measuring the movement of the myocardium itself. Due to its complex structure, the heart contracts in several different directions. To measure these contractions, heart thickening and lengthening is subdivided into radial, circumferential and longitudinal movements, following a three-dimensional model. This is illustrated in figure 3.

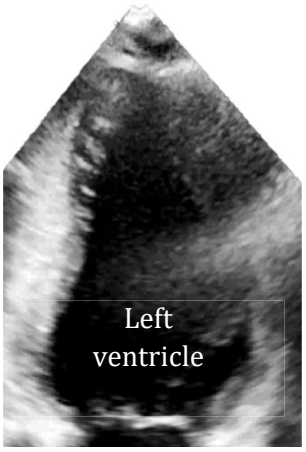

Figure 2: Echocardiographic apical two chamber view - Focused left ventricle

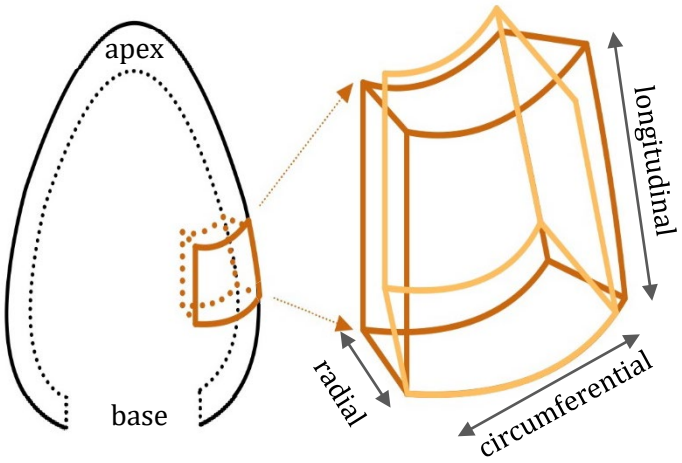

Figure 3: Three dimensional movements of the heart muscle

The echo cardiac machine has two ways to pick up movement from the myocardium itself. The historically older one is Tissue Doppler together with the use of superimposed M-Mode or Spectral Doppler for better analysis. In reality, it is only used routinely to quantify regional and diastolic parameters, such as for the e´ in the algorithm of diastolic dysfunction[63]. This is because the Doppler can detect high tissue velocities in the diastole better than the second method called Speckle tracking but has other limitations, such as its angle dependance. Speckle tracking has, in fact, become a major technique used in echocardiographic analysis since its introduction for clinical use in 2004[64].

1.4.2 Speckle tracking

Speckle-tracking echocardiography is an angle-independent method to obtain an objective quantification of myocardial deformation. The displacement of small speckles, which are the result of the interaction between the ultrasound waves and the myocardium without an anatomical correlation, can be tracked by a software on routine two-dimensional (2D) grayscale images with a framerate of sixty frames per second or higher after image acquisition.

Due to the fact that speckle-tracking echocardiography is mainly performed by a software, good intraobserver and interobserver reproducibility is achieved[65]. This has been shown by comparing speckle-tracking echocardiography-derived measurements with sonomicrometry and tagged MRI[66]. On the other hand, the high

dependence on the software causes a need for standardized data processing, as the difference between vendors is still not insignificant, although they have already been improved considerably[67]. It is nevertheless important that the examiner communicates the settings used to conduct a study, e.g., which region of interest (ROI) was defined, since different software generations tend to have different ROI defaults. These default settings can range from endocardial border to myocardial midline or epicardial border. The progress in this area is fast and the indications of using speckle-tracking are meanwhile not only limited to the left ventricle, but also pertain to the right ventricle and LA[68].

Deformation Imaging parameters

In speckle tracking basically all the parameters to describe the heart movement derive from the velocity of the tracked speckles measured. Since common speckle tracking is done in 2D images, the velocity vectors are projected in two components in an image plane. Those are in the long-axis, apical views, the longitudinal velocity V_l tangential to the endocardium and perpendicularly to it the radial velocity V_r. In the short-axis, transversal views, the two components are V_r again perpendicular to the endocardium and a circumferential velocity V_c which is tangential to the heart border in this plane.

The change in length can then be calculated using the integral of the velocity vector, which has a total direction and amplitude in every plane at a specific time t. To obtain longitudinal, circumferential, and radial displacements, the corresponding component velocities V_l, V_r, and/or V_c are integrated with the formula shown in table 1. Displacement itself is dependent on how much myocardium is viewed since the displacement of the entire heart in one cycle is much more significant than the displacement of a single segment due to their different initial lengths. To normalize the displacement to an individual configuration, it is divided by the initial length of the structure viewed. This results in the relative change in length of an object, which is called deformation, and is commonly referred to as strain in echocardiography.

The default strain value is called Langangrian strain. It puts the length change at any time in relation to the initial reference length $L_{0,}$ which is usually the length at end-diastole. The result is a dimensionless measure, usually displayed in percent. Shortening has negative values and lengthening positive ones. Natural strain, also

called Eulerian strain, is a parameter that compares the length change to the instantaneous length. If strain is not further specified, it refers to Langangrian strain. Another parameter is strain rate, which is a measure for the rate of deformation, mathematically representing the temporal derivative of strain.

Quantities	Symbols and formulas	Unit
Velocity	V, V_l, V_c, V_r	Cm/s
Displacement	$X(t) = \int_{ED}^{t} V(t')dt'$	mm
Langangrian Strain (=deformation)	$S_L(t) = \frac{L(t) - L_0}{L_0}$	%
Strain rate	$SR_L(t) = \frac{dS_L(t)}{dt} = \frac{1}{L_0}\frac{dL(t)}{dt}$	s^{-1}

V_l = longitudinal velocity, V_c = circumferential velocity, V_r = radial velocity
ED = end diastolic
L = Length, t = time

Table 1: Deformation imaging parameters

Deformation of the Left Atrium

The mean LA thickness has been shown to be between 1.99 ± 1.41 mm[69]. In echocardiography a standard region of interest (ROI) width of 3 mm is recommended but should preferably be adjusted by the examiner to match individual LA thickness and consequently excluding the pericardium at the same time. Other programs only require the examiner to trace the endocardial line. They work by measuring LA strain sub-endocardially, since a minimum wall width is necessary to track its deformation. Due to the thin walls of the LA a subendocardial speckle tracking measurement is assumed to be equally accurate as whole wall measurements[68].

The border of the LA should be mapped from one mitral annulus, alongside the endocardial border to the opposite mitral annulus, sparing out pulmonary veins or the LA appendage. Doing this in the apical four-chamber view is recommended, preferably using the apical two-chamber view additionally to obtain biplane measurements. However, using only a single apical view is also a recognized method[70]. It is important to use non-foreshortened views and to check the accuracy

of the superimposed tracking visually by comparing it to the underlying motion of the atrial wall as well as the derived LA strain curve.

The LA strain curve represents the triform process of LA deformation for every heart cycle. It involves the reservoir, the conduit, and the contraction phase. The reservoir phase lasts over the course of the entire ventricular systole from mitral valve closure to mitral valve opening. It corresponds to the filling of the LA. The conduit phase starts at mitral valve opening and is equivalent to the passive filling of the LV. The last phase in patients without atrial fibrillation is the contraction phase, which begins at the onset of LA contraction and ends with mitral valve closure. These three phases can be identified in the curves of figure 5.

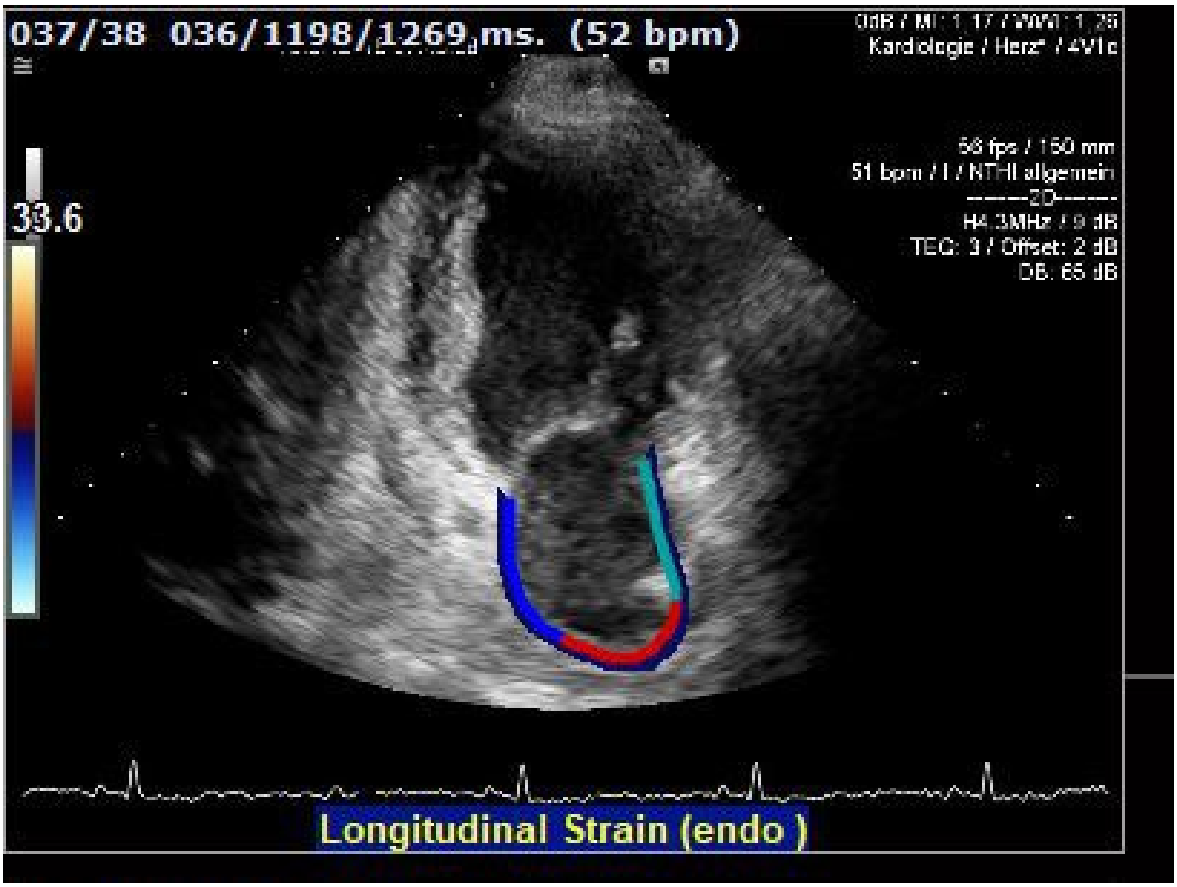

Figure 4: Left atrial strain tracing in TomTec

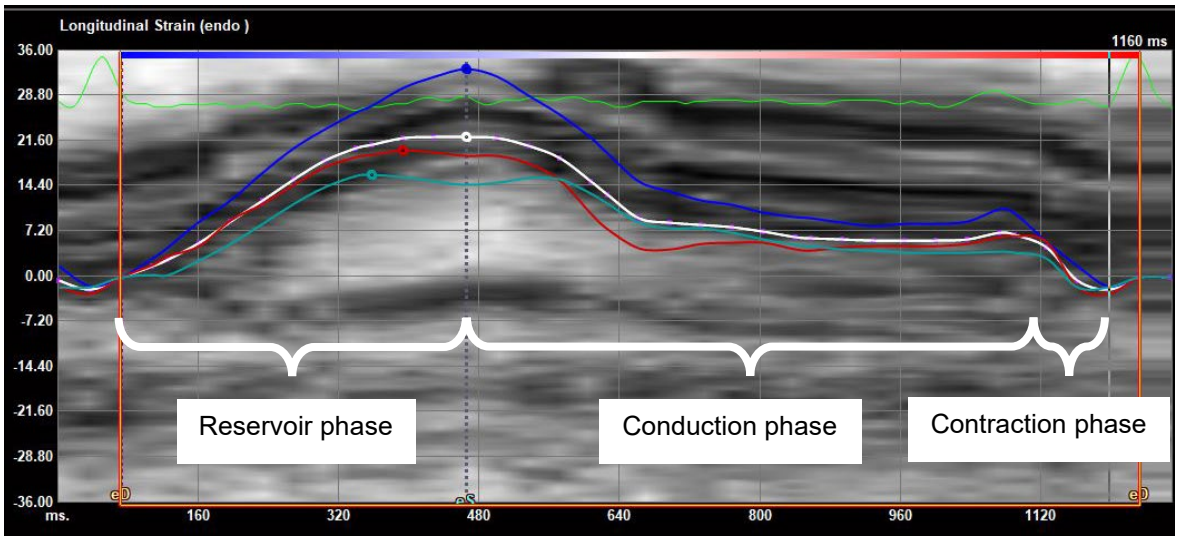

Figure 5: Left atrial longitudinal strain curves with different phases

The three phases can be characterized with the three measurements LASr, LAScd and LASct. LASr is the longitudinal atrial strain (LAS) during reservoir phase and reflects the positive LAS difference from mitral valve opening (ventricular end-systole) and ventricular end-diastole. LAScd is measured by subtracting LAS at mitral valve opening from LAS at the onset of atrial contracting receiving a negative value. Similarly, the LASct portrays the LAS strain difference from the onset of atrial contraction and the ventricular end-diastole to complete the cycle. Furthermore, the peak strains in each phase can be measured, resulting in the parameters pLASr, pLAScd and pLASct. Technically end-systolic-strains (white circle in figure 5), peak systolic strains (highest strain during ventricular systole) and (overall) peak strains should be distinguished due to the different timing of the measurements. However, since the longitudinal atrial strain (LAS) during reservoir phase has the highest values of the whole cycle and the peak is physiologically at ventricular end-systole, LASr and pLASr are often used as synonyms or even simply referred to as LA global longitudinal strain (LA GLS) or peak atrial longitudinal strain (PALS) neglecting minor differences.

The best correlation marker of the LA is specified as LA global longitudinal strain, defined as *strain in the direction tangential to the endocardial atrial border in an apical view, derived from the length change of the entire LA contour in the image plane*[70]. Zero strain reference is usually set at ventricular end-diastole, which is supposed to match the nadir of the strain curve. While in the left ventricle, the peak

systolic strain value is often used, in the LA, the peak longitudinal strain has been shown to correlate best with pulmonary capillary wedge pressure and with LV-end-diastolic pressure[71]. Assessing the individual LA segments or using radial or transverse strain is therefore recommended due to the anatomical and echocardiographic features[70].

To obtain comparative figures for atrial strain values 2017 a meta-analysis came to the result of a normal reference range for reservoir strain (usually congruent with PALS) of 39% (95% CI, 38%-41%, from 40 articles), for conduit strain of 23% (95% CI, 21%-25%, from 14 articles), and for contractile strain of 17% (95% CI, 16%-19%, from 18 articles), by using data from 2542 healthy subjects[72]. In 2021, these results were confirmed in 1641 healthy participants in the Copenhagen City Heart Study. The median PALS was measured to be 39.4%, with a rather high deviation of corresponding limits of normality being 23-67.6%[73].

1.5 Gaps in Evidence

SGLT2i are a relatively new class of drugs, which were approved in the EU about a decade ago. They have already been shown to lead to a relative and absolute risk reduction in death and hospitalization in patients with and without diabetes suffering from heart failure with HFrEF[74]. SGLT2i are currently being investigated in IHD patients, due to the high epidemiologic relevance of this patient group. Notwithstanding that a benefit in lab markers has been shown e.g. in the EMMY trial[75], the functional mechanisms, reflected by cardiac volume and function parameters like strain, have yet not been sufficiently investigated. On top of that, the assumed mechanisms responsible for the beneficial effect per se are still mainly the result of animal models.

The left atrial role in different cardiac conditions is highly discussed. The question is whether it is only a mirror image of the left ventricle volume and filling pressures or whether it has a high pathophysiologic relevance on its own. Furthermore, it is unclear which parameters are most appropriate to assess left atrial function. With speckle tracking, more values, such as strain, have become available. But they need to be compared to the clinical background of patients, as well as correlated with already validated parameters, such as left atrial volume index (LAVI). It is equally important to measure the effect of medications on cardiac function with functional

parameters, to find out how and on which level they work, to further improve IHD treatment and possibly find new starting points for further development.

1.6 Aim of the Thesis

The main aim of this thesis is to investigate the effect of the standard treatment plus Empagliflozin compared with standard treatment plus Placebo after MI within the framework of the EMMY-trial on the left atrial dimensions and function. At the same time the thesis is aiming to give closer insights into the involvement of the LA after MI in general, which undergoes geometrical and functional change as result of myocardial systolic and diastolic dysfunction.

2 Methods

The data for this diploma thesis was gathered from a subgroup of all the patients who were being examined at Medical University of Graz, Division of Cardiology, in the framework of the EMMY trial (Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction).

2.1 Study overview

The EMMY trial[29] is a multicenter, randomized, double-blind, placebo-controlled, phase 3b trial. The investigated hypothesis is that with the treatment of the SGLT-2 inhibitor empagliflozin in addition to the basic pharmaceutical treatment, starting early after AMI, the biomarker NT-proBNP will be reduced more effectively, than with a placebo within 6 months after the event.

It was registered on March 23rd, 2017, in the US National Library of Medicine Clinical Trials.gov with the Identifier NCT03087773. The study was permitted by the Ethics Committee of the Medical University of Graz (reference number 29–179 ex 16/17). All patients needed to give informed consent before screening to participate.

Inclusion criteria encompass AMI with evidence of significant myocardial necrosis defined as a rise in creatine kinase over 800 U/L and a troponin T-level (or troponin I-level) ten times above the upper level of normal. These criteria have been defined to increase the likelihood of a beneficial treatment effect with empagliflozin. In addition, symptoms of ischemia and/or ECG changes indicative of new ischemia and/or imaging evidence of new regional wall motion abnormality must be met. Further necessary medical parameters were estimated glomerular filtration rate (eGFR) higher than 45 mL/min per 1.73m^2, a systolic blood pressure before first drug dosing over 110 mmHg and a diastolic blood pressure before first drug dosing over 70 mmHg. The first intake of study medication had to be within the first 72 hours after myocardial infarction or 72 hours after performance of a coronary angiography. The required age was predefined as 18-80.

Exclusion criteria applied in case of any form of diabetes mellitus other than type 2 or a history of diabetic ketoacidosis, a blood pH lower than 7.32, a known allergy to SGLT-2 inhibitors, presence of hemodynamic instability defined by intravenous administration of catecholamine, calcium sensitizers or phosphodiesterase

inhibitors, more than one episode of severe hypoglycemia within the last 6 months under treatment with insulin or sulfonylurea, fertile females without adequate contraceptive methods (i.e. sterilization, intrauterine device, vasectomized partner; or medical history of hysterectomy), acute symptomatic urinary tract infection or genital infection, as well as patients who are being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or having received treatment with any SGLT-2 inhibitor within the 4 weeks prior to the screening visit.

The eligible patients were randomized in a 1:1 ratio to empagliflozin (10 mg once daily) or a matching placebo by a Randomizer Software (http://www.randomizer.at). The randomization was stratified by site, the presence of diabetes mellitus type 2 and by sex. The primary endpoint was to investigate the effect of empagliflozin on changes in NT-proBNP within 6 months (26 weeks) after AMI. Secondary endpoints include short term changes (6 weeks) of NT-proBNP levels, changes in echocardiographic parameters after 6 and 26 weeks, levels of ketone body concentrations, HbA1c levels and body weight, number of hospital re-admissions due to heart failure or other reasons, duration of hospital stay and all-cause mortality.

In total, 219 people gave consent to the study protocol of the EMMY study. The initial gender distribution was 181 male and 38 female subjects. Over time, 8 people withdrew their consent. 4 people only completed one of the three study visits, making it not possible to monitor any change in their clinical data. From another 21 participants only two instead of three ultrasound studies were available, respectively useable, because either the did not come to one visit, their data was not stored properly, or the image quality was not good enough to analyze.

2.2 Blood Sampling and Assessment of Laboratory Parameters

Every site that participated in the EMMY trial was required to ship NT-proBNP biomarker samples from the patients each visit to the Biobank in Graz, regardless of NT-proBNP level analysis in local labs. In Graz, the samples were stored appropriately and finally measured at the KIMCL (Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria) on the Elecsys proBNP platform (Roche Diagnostics, Mannheim, Germany) with

chemiluminescence technology, to avoid minor discrepancies between different laboratories.

2.3 Transthoracic Echocardiography

Transthoracic echocardiography studies were obtained from each patient on visit 1, 2 and 4 in accordance with the current guidelines of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). They were performed by experienced cardiologists using locally available ultrasound devices like the Vivid 7 or Vivid E9 (GE Healthcare, Chalfont St Giles, UK) and Siemens Acuson SC2000 with an image rate set to at least seventy frames per second.

To avoid divergences between different locations, an Echo Manual written by Dr. Ewald Kolesnik with the protocol number HS-2017-01 was distributed to all sites. In this manual the execution and the information needed from a Transthoracic Echocardiographic Examination in Adults is outlined schematically, following the current Guideline of the American Society of Echocardiography[60].

The two-dimensional clips and images for a Standard Imaging Protocol are mainly taken from three positions and include the parasternal long-axis view (PLAX), parasternal short-axis views (PSAX), apical 4 chamber view (A4C), apical 5 chamber view (A5C), apical 2 chamber view (A2C), apical long-axis (A3C), subcostal 4 chamber view (SC 4C) and in particular cases a suprasternal notch view of the aortic arch (SSN aortic arch). The baseline of a few cardiac cycles of the plain two-dimensional images should be stored, to record cardiac anatomy and performance. ECG recording should be performed in every study, so that the machine can recognize heart cycles more easily. In the EMMY trial at least three cardiac cycles were recorded.

The recommended two-dimensional measurements from the different standard views of every axis are listed in table 2. The 2D values needed for this thesis to obtain LA volume values are highlighted in yellow. To correctly obtain the measurements from table 1 and even more in postprocessing, different planes in each axis must be acquired. In particular, PSAX Loops should be done at the level of aortic valve and pulmonary artery, at the level of the mitral valve, at the level of the papillary muscles and the apical segments. The apical 4-chamber view should

be recorded with focus on the left ventricle, then with focus on the right ventricle and one with focus on the atria. This is also applicable to the A2C, which should be recorded with focus on the left ventricle and furthermore with focus on the LA. From substernal the subcostal 4-chamber view and a loop of the inferior vena cava should be assessed.

The diameter of the LA, which is usually measured from anterior to posterior, can alternatively be obtained using the M-mode, but for routine linear dimension measurements the classic two-dimensional loops are generally preferred over the M-mode technique. Other specific M-Mode measurements that are recommended, primarily include the tricuspid annular plane systolic excursion (TAPSE) for assessing longitudinal systolic performance of the right ventricle and the IVC diameter during respiration. In addition to the standard views various further views can be obtained by small probe movements in order to display more structures and details, but they are commonly bypassed in clinical praxis.

CDI is recommended to be used in practically all imaging views and should therefore not be viewed as an independent imaging technique. Furthermore, CDI is also helpful to align the spectral Doppler as parallel to the blood flow as possible. The most common CDI positions are listed in table 2. It is important to store native loops and loops with CDI separately to capture all the information. The intention of table 3 is to connect the standard grayscale views of two-dimensional imaging with color doppler imaging (CDI) and spectral doppler images that should be obtained for a conclusive study. If regurgitant jets or other abnormalities are found, it is important to portray them as best as possible with grayscale and CDI imaging and to quantify them by using various Spectral Dopplers (SDI) to record their entire extent.

PLAX	PSAX	A4C	A5C	A2C	A3C	SC 4C
IVS end-diastole thickness	End-diastolic RVOT proximal diameter	LV volume end-diastole		LV volume end-diastole		IVC diameter
LVIDd	End-diastolic RVOT distal diameter	LV volume end-systole		LV volume end-systole		
LVPWd	Main PA diameter	**LA length**		**LA length**		
RV diameter end-diastole		**LA area**		**LA area**		
LA diameter		RV base and mid diameter				
LVOT diameter (midsystolic)		RV length				
AV annular diameter (midsystolic)		RV area end-diastole				
		RV area end-systole				
		RA length				
		RA area				

AV = aortic valve, d = end-diastolic, IVC = inferior vena cava, IVS = interventricular septum, LA = left atrium, LV = left ventricle, LVID = left ventricular internal dimension, LVOT = left ventricular outflow tract, LVPW = left ventricular posterior wall, PA = pulmonary artery, RV = right ventricle, RVOT = right ventricular outflow tract

Table 2: Echocardiographic imaging planes with 2D measurements

PLAX	CDI	MV flow AV flow
	SDI	
PSAX	CDI	TV and RV inflow RVOT AV leaflets MV flow (Level of MV)
	SDI	PW Doppler in RVOT: Peak RVOT velocity, RVOT VTI CW Doppler in RVOT: PV VTI, Peak PV velocity, End-diastolic PR velocity
A4C	CDI	MV flow with LA and LV Pulmonary veins
	SDI	CW Doppler TV -> peak TR velocity PW Doppler of MV -> E-wave velocity, A-wave velocity PW on DTI MV lateral and medial annulus -> s´, e´ and a´ PW on DTI TV lateral annulus -> s´, e´ and a
A5C	CDI	LVOT and AV flow
	SDI	PW of LVOT -> LVOT VTI, LVOT peak velocity CW Doppler through the AV -> AV VTI, Peak AV velocity
A2C	CDI	MV flow with LA and LV
	SDI	
A3C	CDI	MV flow with LA LV, LVOT and AV flow
	SDI	
SC 4C	CDI	IVC and Hepatic veins flow
	SDI	PW Doppler -> Hepatic veins flow: S-, D- and A-wave

AV = aortic valve, CW = continuous wave, IVC = inferior vena cava, LA = left atrium, LV =left ventricle, MV = mitral valve, PV = pulmonary valve, PW = pulsed wave, RV = right ventricle, RVOT = right ventricular outflow tract, TR = tricuspid regurgitation

Table 3: Echocardiographic imaging planes with Doppler measurements

All studies for the secondary outcome analyses were archived in DICOM-format and locally analyzed. The initial idea of the conductor was that all raw data of native images and loops should be sent to an echocardiography core lab, in this case the Echocardiography Core Lab of the Department of Cardiology, Medical University of Graz, Austria for thorough and possible additional evaluation. However, it soon became apparent that not all sites were able to provide loops for core lab analyses. Therefore, the decision was made to only use local data from Graz. This can be done, since there is a high enough number of studies available to achieve good statistical power with core lab echocardiography data only. For this thesis all image data was analyzed offline with the post-processing program TomTec (TOMTEC Imaging Systems) in digitally saved, ECG triggered 2D TTE cine loops of the apical two- and four-chamber views. The software accessed the studies directly from the IntelliSpace Cardiovascular, where they were stored after acquisition.

2.3.1 Left atrial volume measurements

To receive end-systolic and end-diastolic measurements of the LA, the biplane area-length-formula was used. Therefore, the areas and the length of the LA were obtained in two independent heart cycles in both a 4-chamber view and a 2-chamber view. The values of these areas and lengths were then entered into an Excel sheet. Proceeding with the obtained values the arithmetic average of the two A4C areas, two A2C and four length measurements each, for end-systole and for end-diastole were calculated respectively. The results are diagnostically conclusive left atrial end-diastolic and end-systolic values. Based on these values, EF and LAVI were calculated. The LAVI is the left atrial volume indexed to the overall body surface area and eliminates the high dispersion of atrial volumes due to the individual physiques of different patients.

$$LAV = \frac{8}{3} \times \pi \times \frac{A_{4CH} \times A_{2CH}}{L}$$

LAV = left atrial volume [ml], A = left atrial area [mL/m²],
L = left atrial major length axis [cm]

Figure 6: Calculation of left atrial volume

2.3.2 Assessment of Strain

Strain was evaluated using a specific speckle-tracking based software tool called 2D Cardiac Performance Analysis (2D CPA) from TOMTEC Imaging Systems, also analyzing cardiac deformation offline and vendor-independent. After starting 2D CPA one corresponding A2C view with unobstructed view of the atrium, as advised by the program instructions, was selected by the investigator. Since multiple cardiac cycles were recorded as default, one cardiac cycle was chosen by the investigator. Within this heart cycle end-systole (ES) and end-diastole (ED) were defined manually via M-Mode through the mitral anulus to spot maximal contraction (end-systole) and maximal relaxation (end-diastole) of the left ventricle. In general, the software can generate the endomyocardial line by itself after placing three reference points (anterior annulus, posterior annulus, apex). The investigator nevertheless decided to trace the endocardial border end-systolic and end-diastolic completely manually to ensure maximum validity, since the automatic editing has been shown to have difficulties especially with poorer image quality. After the tracking was completed, the analysis of the deformation by the program was initiated.

The result was a color-coded loop of longitudinal strain values, with strain and strain-rate curves among other data respectively. The longitudinal strain is calculated as Langangrian strain from the initial entire contour length. The circumferential strain however, is derived from the shortening of the radius since it cannot be measured directly in a long imaging view of the heart. Two heart cycles were examined from every study to improve accuracy by limiting aberrations.

2.4 Data Analysis and Statistics

All retrieved 2D metric measurements were manually entered into Microsoft Excel 365 (Microsoft Office 365, Microsoft Corporation, Redmond, US). Strain data was exported, merged by an appropriate macro, and cleaned in Excel and then imported to IBM SPSS statistics 27 (IBM Corporation, Armonk/New York, US) for further statistical analysis.

Descriptive statistics of simple baseline characteristics, such as gender and age, were worked up with mean and standard deviation for continuous measures and with frequency tables for categorical variables.

All data were evaluated for normal distribution and variance homogeneity. For normal distribution, histograms were evaluated graphically and a skewness of -1 to +1 was checked to evade false negative results of the Shapiro-Wilk-test in larger sample sizes. Endo GCS at visit 3 (V3), LA EF V3 and Endo GLS V3 + GCS V3 data of the individual groups were normally distributed initially, the parameters Endo GLS V3, highest GLS and LAVI ED had at least one group where the absolute value of the skewness was above 1. For these parameters normal distribution was reached by logarithmizing (log10). To analyze the two separate groups (intervention vs. placebo) at the last visit, unpaired t-test was used. To check equality of variances Levene test was followed. For analysis of the trends of two main parameters Endo GLS (logEndo GLS) and LAVI ED (log LAVI ED) between the two different groups in more detail, a linear mixed model was used, in which the respective parameter was the dependent variable. The fixed effects were visit, treatment, and visit*treatment and as random factors the baseline value of the respective parameter, the presence or absence of Type 2 diabetes and gender. The parameters were analyzed in a per-protocol analysis for statistical reasons. Therefore, no missing data were imputed for the analysis. Results were considered statistically significant with p-values <0.05. As an additional approach the absolute differences for Endo GCS, Endo GLS, highest GLS, Endo GLS + GCS, LAVI ED and LA EF were calculated between visit 2 and visit 1 (V2-V1) and visit 3 and visit 1 (V3-V1), given that both values were available in each case. Spearman's rank-order correlation was performed to analyze the coherences of echocardiographic and laboratory data. For better illustration results are portrayed in tables (created with Microsoft Word 365 and Microsoft Excel 365), box plots (created with SPSS statistics 27) and graphs (created with Microsoft Excel 365).

3 Results

3.1 Subjects

Table 5 illustrates patients' demographic characteristics and descriptive statistics regarding the analyzed variables. In total, 219 patients were included in the present study. With respect to gender distribution 82.6% were males (n = 181) and 17,4% females (n= 38). The age of the study participants ranged from 33 to 80 years with a mean age of 58.35 ± 9.43 years (males 57.92 ± 9.34; females 60.37 ± 9.71).

The patients' Body Mass Index (BMI) was on average 28.27 ± 4.12 kg/m^2 (males 28.46 ± 3.84; females 27.37 ± 5.26). According to the BMI-classification of the World Health Organization (see table 4) 20.56% (n = 45) of study participants were of normal weight, while 52.51% (n = 115) were assigned to the category pre-obesity. 20.09% (n = 44) of patients were assigned to the category obesity I, 5.94% (n = 13) to obesity II and two patients to obesity III. Among all patients 11.9% (n = 26) were diagnosed with diabetes and hyperlipidemia was present in 8.7% (n = 19) of patients. HbA1c was on average 5.84 ± 1.03% in patients (males 5.88 ± 1.08%, females 5.66 ± 0.72%).

BMI	Nutritional status
Below 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Pre-obesity
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

Table 4: BMI classification. BMI = Body Mass Index

With regard to lifestyle-related risk factors, 69.4% (n = 152) of all patients were smokers (males 70.2%; females 65.8%). The mean of smoking years among this subgroup was 29 ± 11.49 years (males 29.69 ± 11.42 years; females 25.61 ± 11.61 years). Among smokers the average consumption of nicotine was 22 ± 13.52 cigarettes per day (males 22.5 ± 14.12 cigarettes per day; females 20.58 ± 10.41 cigarettes per day).

In total, 6.4% of subjects were previously diagnosed with coronary heart disease (CAD), and 1.4% had already undergone percutaneous transluminal coronary angioplasty (PTCA). Two patients had already been treated with bypass surgery.

Within the study population the median of c-reactive protein (CRP) was 5 mg/dl (male 4.6; female 5.8). Based on standard values for GFR, patients showed normal GFR values with a median of 93 ml/min/1.73 m^2 (male 92.27 ml/min/1.73 m^2; female 94.52 ml/min/1.73 m^2). 99.51% of study participants showed elevated values (≥ 125 pg/ml) in NT-proBNP with a median of 1344 pg/ml (n = 203) (male 1200 pg/ml; female 2251 pg/ml). The overall median for hsTrop was 3791 µg/l, with slightly higher values in males at 3843 µg/l than in females at 3661.5 µg/l.

On the first visit, patients showed blood pressure values with a median of 125/76 mmHg (males 126/76 mmHg; females 121.5/77 mmHg). Elevated systolic blood pressure (≥ 140 mmHg) was present in 6.85% of patients. 7.31% (≥ 90 mmHg) of all subjects showed elevated diastolic blood pressure values.

3.2 Endo GLS and highest GLS

Endo GLS at visit 3/3 was available in 199 subjects (100 in the empagliflozin group, 99 in the placebo group). The subjects in the empagliflozin group had a mean Endo GLS value of 22.51 (95 % CI = 20.76 – 24.25), compared to 22.25 (95 % CI = 20.68 – 23.83) in the placebo group. The mean TomTec parameter highest GLS was 25.63 (95 % CI = 23.89 – 27.36) in the empagliflozin group and 24.82 (95 % CI = 23.14 – 26.50) in the placebo group. The empagliflozin group thus had a positive mean Endo GLS V3 difference of 0.25 ± 1.19 and a positive mean highest GLS difference of 0.81 ± 1.22. The null hypothesis that there is no significant difference between the groups cannot be rejected, with p-values of 0.841 (log_{10} Endo GLS V3) and 0.642 (log_{10} highest GLS V3).

The linear mixed model shows a highly significant increase of Endo GLS in both groups over time (p = .000 based on all three visits). Testing visit*treatment for a fixed effect shows no significant outcome (p = .127).

Variables	Overall	Male	Female	N
Gender [%]		82.6	17.4	219
Age [years]	58.35 ± 9.43	57.92 ± 9.34	60.37 ± 9.71	219
BMI [kg/m2]	28.27 ± 4.12	28.46 ± 3.84	27.37 ± 5.26	219
Smoking [%]	69.4	70.2	65.8	219
Smoking Years [years]	28.99 ± 11.53	28.57 ± 12.23	31.12 ± 6.70	152
Cigarettes [total]	22.17 ± 13.56	22.87 ± 13.12	18.64 ± 15.42	152
Arterial Hypertension	71 (32.4%)	54 (29.8%)	17 (44.7%)	219
CAD [n]	14 (6.4%)	11 (6.1%)	3 (7.9%)	219
PTCA [n]	3 (1.4%)	3 (1.7)	0 (0%)	219
Bypass [n]	2 (0.9%)	2 (1.1%)	0 (0%)	219
STEMI	179 (81.7%)	147 (81.2%)	32 (84.2%)	219
Hyperlipidemia [n]	19 (8.7%)	16 (8.8%)	3 (7.9%)	219
Diabetes [n]	26 (11.9%)	22 (12.2%)	4 (10.5%)	219
HbA1c V1 [%]	5.84 ± 1.03	5.88 ± 1.11	5.63 ± 0.39	209
hsTrop V1 [µg/l]	median: 3791	median: 3843	median: 3661.5	219
CRP_V1 [mg/dl]	median 4.7	median: 4.6	median: 5.8	218
GFR_V1 [ml/min]	median: 92.79	89.91 ± 14.14	90.97 ± 16.29	219
NT-proBNP [pg/ml]	median: 1344	median: 1200	median: 2251	203
BP_sys [mmHg]	125.16 ± 9.59	125.46 ± 9.42	123.68 ± 10.39	219
BP_dias [mmHg]	78.21 ± 6.25	78.17 ± 6.27	78.37 ± 6.22	219

Table 5: Descriptive statistics. Values are given as mean ± standard deviation by default.
BMI = Body Mass Index, CAD = Coronary Artery disease, PTCA = percutaneous translumenal coronary angioplasty, STEMI= ST elevation myocardial infarction, HbA1c = Hemoglobin A1c, hsTrop = high-sensitivity cardiac troponin, CRP = C-reactive protein, GFR = Glomerular filtration rate, BP = Blood pressure.

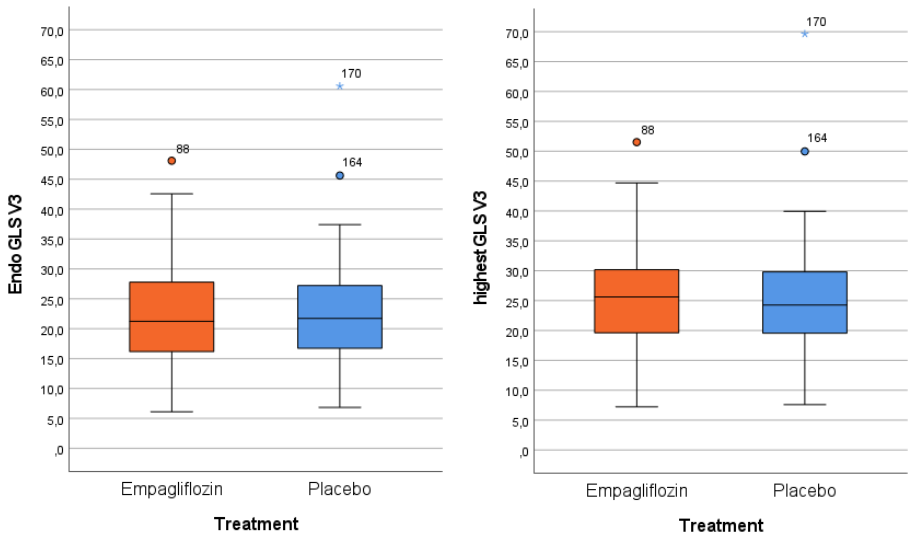

Figure 7: Boxplots of Endo GLS and highest GLS values at visit 3

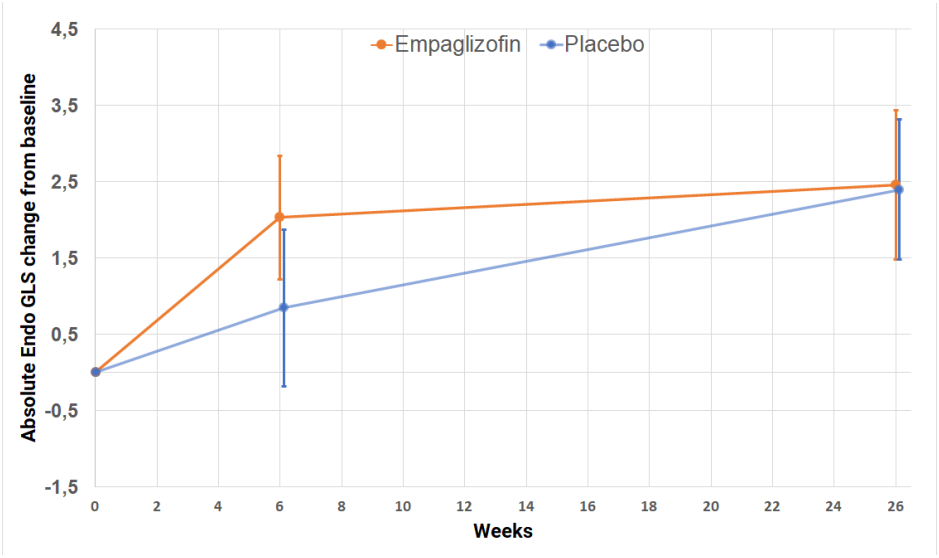

Figure 8: Absolute change in Endo GLS across all visits

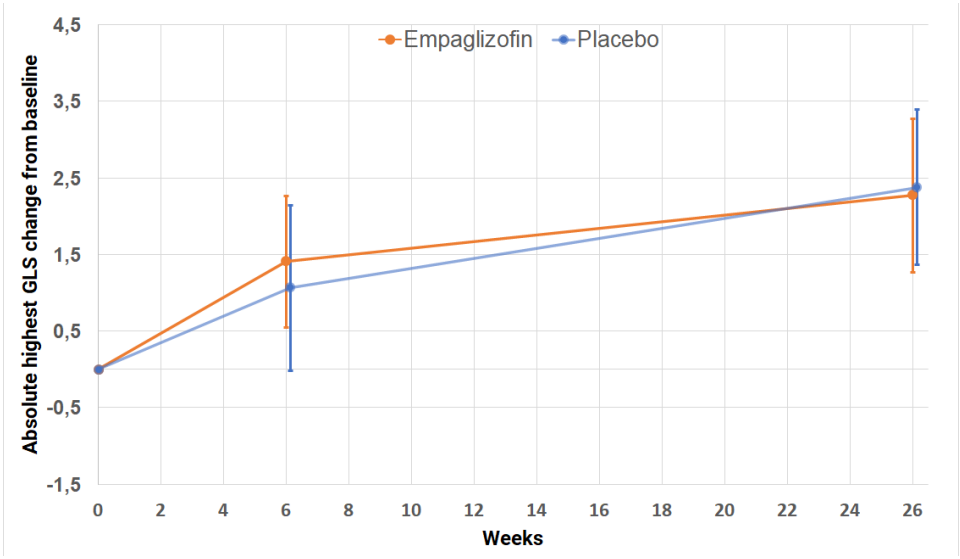

Figure 9: Absolute change in highest GLS across all visits

3.3 Endo GCS and combined strain parameter

Endo GCS at visit 3/3 was assessed in 199 subjects (100 in the empagliflozin group, 99 in the placebo group). The subjects in the empagliflozin group had a mean Endo GCS value of 26.41 (95 % CI = 24.24 – 28.57), compared to 25.67 (95 % CI = 23.64 – 27.70) in the placebo group. 48.91 (95 % CI = 45.32 – 52.50) is the mean artificial total of Endo GLS and Endo GCS in the empagliflozin group, while it was 47.92 (95 % CI = 44.76 – 51.09) in the placebo group. In summary, the empagliflozin group had a positive mean Endo GCS difference of 0.74 ± 1.5 and a positive total Endo GLS and Endo GCS difference of 0.99 ± 2.4. The null hypothesis that there is no significant difference between the groups cannot be rejected, with p-values of 0.623 (Endo GCS V3) and 0.682 (Endo GLS + GCS V3).

3.4 LAVI ED and LA EF

LAVI ED and LA EF at visit 3/3 were evaluated in 199 subjects (100 in the empagliflozin group, 99 in the placebo group). The mean LAVI ED in the empagliflozin group was 33.44 (95 % CI = 30.87 – 36.01) and 34.52 (95 % CI = 32.46 – 36.58) in the placebo group. The mean LA EF was 41.67 (95 % CI = 39.11 – 44.23) in the empagliflozin group and 40.89 (95 % CI = 38.80 – 42.99) in the placebo group. The empagliflozin group showed a lower mean LAVI EDV V3 by -1.08 ± 1.66 and a positive LA EF difference of 0.78 ± 1.67. The null hypothesis that there is no significant difference between the groups cannot be rejected, with p-values of 0.294 ($\log_{10}$LAVI EDV V3) and 0.641 (LA EF V3).

The linear mixed model shows a highly significant increase of LAVI ED in both groups over time (p = .000 based on all three visits). Testing visit*treatment for a fixed effect shows no significant outcome (p = .853).

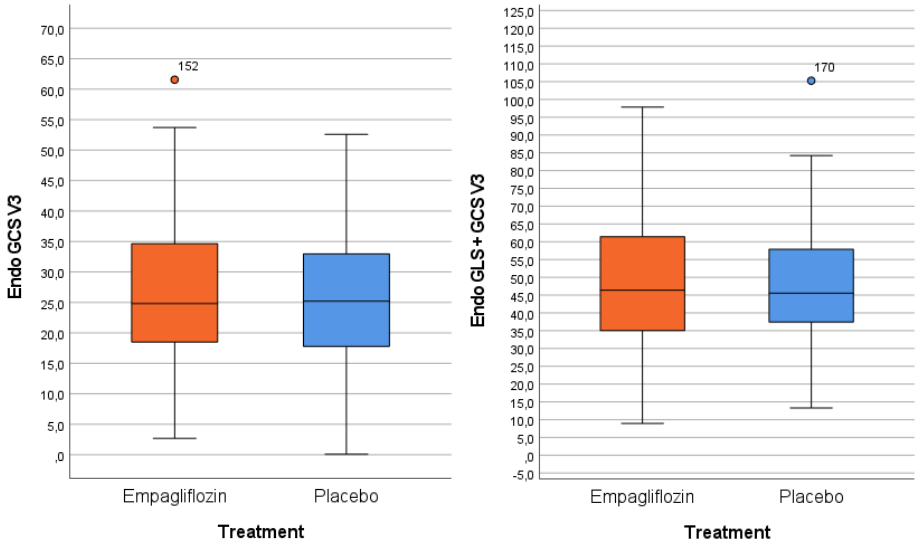

Figure 10: Boxplots of Endo GCS and Endo GLS + GCS values at visit 3

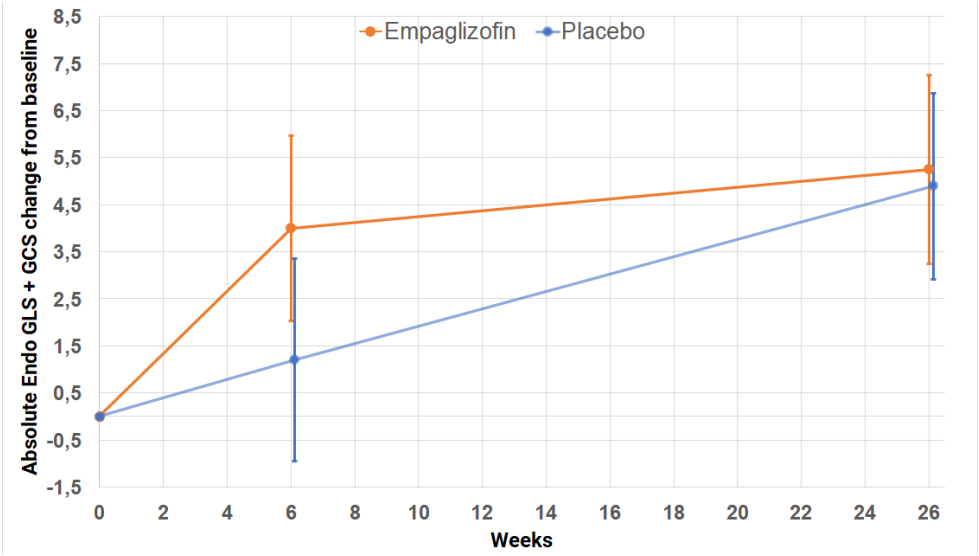

Figure 11: Absolute change in Endo GCS across all visits

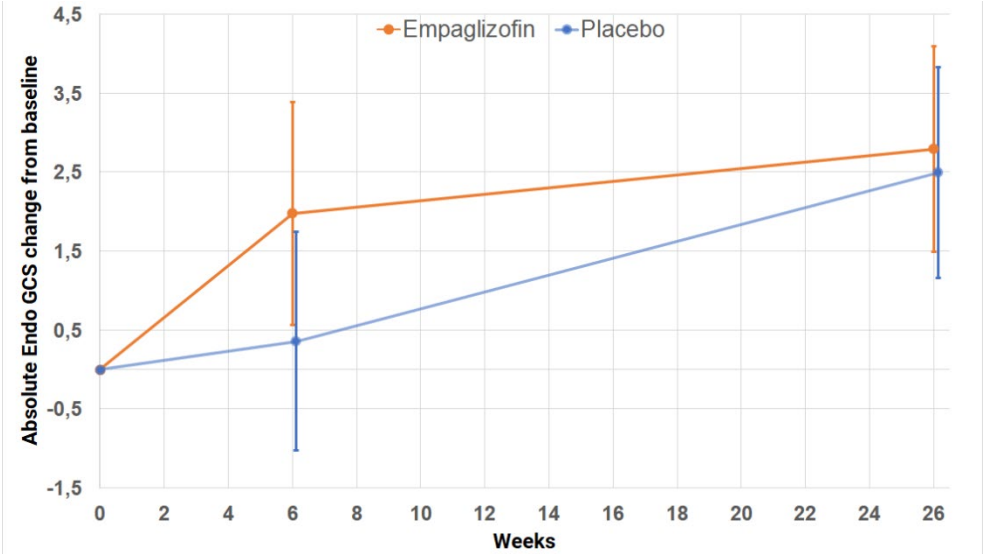

Figure 12: Absolute change in Endo GLS + GCS across all visits

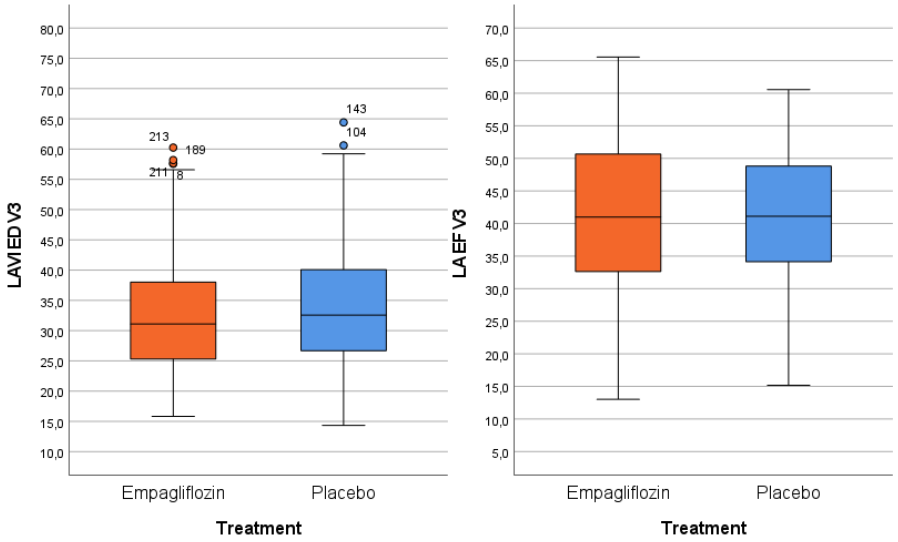

Figure 13: Boxplots of LAVI ED and LA EF values at visit 3

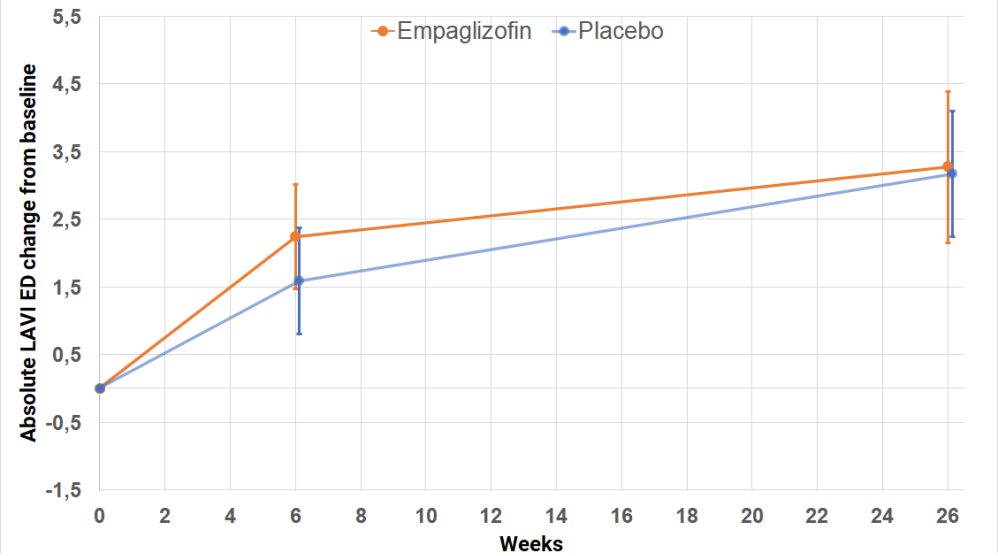

Figure 14: Absolute change in LAVI ED across all visits

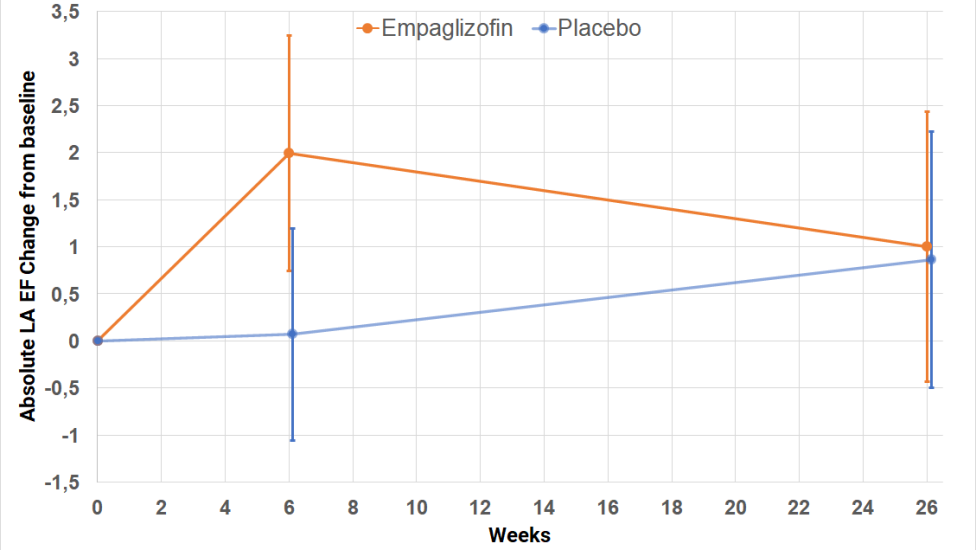

Figure 15: Absolute change in LA EF across all visits

		Empagliflozin		Placebo	
		mean ± σ	N	mean ± σ	N
Endo GLS	V1	**20.03** ± 7.40	102	**19.71** ± 7.54	97
	V2	**22.23** ± 8.10	99	**20.58** ± 8.54	98
	V3	**22.51** ± 8.80	100	**22.25** ± 7.90	99
Endo GCS	V1	**23.40** ± 11.44	102	**23.32** ± 11.14	97
	V2	**25.34** ± 12.35	99	**23.53** ± 9.64	98
	V3	**26.41** ± 10.90	100	**25.67** ± 10.19	99
Endo GLS + GCS	V1	**43.43** ± 17.17	102	**43.03** ± 16.73	97
	V2	**47.57** ± 18.59	99	**44.11** ± 16.29	98
	V3	**48.91** ± 18.10	100	**47.92** ± 15.87	99
highest GLS	V1	**23.37** ± 8.11	102	**22.38** ± 7.67	97
	V2	**24.88** ± 8.23	99	**23.48** ± 8.68	98
	V3	**25.63** ± 8.74	100	**24.82** ± 8.43	99
LA EF	V1	**40.00** ± 12.22	104	**40.52** ± 10.49	98
	V2	**42.20** ± 10.86	99	**40.74** ± 10.03	99
	V3	**41.67** ± 12.91	100	**40.89** ± 10.50	99
LAVI ED	V1	**30.20** ± 9.24	104	**31.28** ± 8.51	98
	V2	**32.56** ± 9.73	99	**33.04** ± 9.57	99
	V3	**33.44** ± 12.95	100	**34.52** ± 10.31	99

Table 6: Explorative statistics of left atrial strain parameters by groups. Values are given as mean ± standard deviation by default.

3.5 Correlation analysis

According to Cohen, effect sizes above 0.5 are considered large, those above 0.3 are moderate, everything between 0.3 and 0.1 is considered weak, and anything smaller than 0.1 are considered trivial[76]. As can be seen in table 7, there were strong correlations between LA GLS und LA GCS, moderate correlations between LA GLS and LA EF, LA GLS and LVEF, LA GLS and NT-proBNP, as well as weak correlations between LA GLS and LAVI.

	Endo GLS	highest GLS	Endo GCS	Endo GLS + GCS	LAVI ED	LA EF	LVEF	NT-proBNP
Endo GLS		0.944	0.622	0.855	-0.221	0.435	0.320	-0.372
highest GLS	0.944		0.612	0.824	-0.267	0.460	0.296	-0.378
Endo GCS	0.622	0.612		0.932	-0.182	0.411	0.206	-0.277
Endo GLS + GCS	0.855	0.824	0.932		-0.218	0.460	0.274	-0.345
LAVI ED	-0.221	-0.267	-0.182	-0.218		-0.147	-0.164	0.154
LA EF	0.435	0.460	0.411	0.460	-0.147		0.221	-0.235
LVEF	0.320	0.296	0.206	0.274	-0.164	0.221		-0.510
NT-proBNP	-0.372	-0.378	-0.277	-0.345	0.154	-0.235	-0.510	

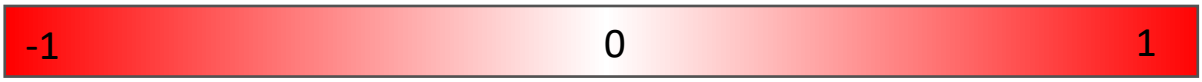

Table 7: Correlation table of left atrial strain, left ventricular and laboratory parameters

4 Discussion

It has previously been established that atrial strain values encompass relevant clinical data both in patients with NSTEMI[77] as well as in STEMI patients[54]. In both cohorts LA longitudinal strain in particular was shown to be a significant marker for the prediction of cardiovascular events. With this study, many structural and functional parameters of the LA were measured meticulously in patients after myocardial infarction. The ultrasound studies were therefore scheduled three times (visit 1 at week 0, visit 2 at week 6 ± 2 and visit 3 at week 12 ± 2). This made it possible to monitor the development of these parameters closely and to get a better picture of the suspected initial LA impairment after MI and its subsequent expected improvement.

Nonetheless, it must be taken into account that the ultrasound raw data was obtained within the framework of the EMMY trial[29], meaning that half of the patients received Empagliflozin in addition to standard treatment. The primary outcome was a change in NT-proBNP. Additionally, major echocardiographic parameters for diastolic dysfunction (E/e'), left-ventricular end-systolic (LVESV) and end-diastolic volume (LVEDV) were gathered and analyzed simultaneously as secondary outcomes.

The data of the echocardiography outcome parameters of the EMMY-trial suggest an increase in EF, a decrease in E/e` and an increase in LVEDV in both groups. From a physiological standpoint, it seems reasonable that at the time of the initial MI, the heart is abruptly impaired in its function as a pump by the loss of contractile fibers leading to reduced systolic function. At the same time the diastolic function is also compromised by such an event. In fact, after a MI, active relaxation of the heart muscle is initially delayed, and the ventricle becomes stiffer based on the remodeling of the infarction area, leading to higher diastolic pressures in the ventricle. This is physically counteracted by the simultaneous dilatation of the heart muscle[78].

Even though the connection of systolic and diastolic dysfunction as a result of MI is well established, sufficient treatment to stop or further decelerate the pathophysiologic cascade, particularly regarding the diastolic function, is not routinely available. As a promising next step, the EMMY-trial showed a significant

greater NT-proBNP reduction with Empagliflozin by 15% (95% CI -4.4% to -23.6%, *p* = .026) after adjusting for baseline NT-proBNP, sex and diabetes status compared to placebo. It was shown that with Empagliflozin the absolute left ventricular EF was improved significantly by 1.5% (95% CI 0.2% to 2.9%, *p* = .029) in comparison to the placebo. Mean E/e' reduction was also about 6.8% (95% CI 1.3% to 11.3%, *p* = .015) better in the Empagliflozin group. Further, both left ventricular end-systolic and end-diastolic volumes were lower in the empagliflozin group, compared with placebo by 7.5 ml (95% CI 3.4 to 11.5 ml, *p* = 0.000) and 9.7 ml (95% CI 3.7 to 15.7 ml, *p* = .002). Therefore, the overall data of the EMMY trial suggest that there is significant potential to improve the overall function of the heart, reflected by laboratory and imaging parameters.

Although it has been established in this thesis that the LA is much more than a simple holding chamber for blood and that its function clinically correlates with hard outcomes, the question of which parameters should be used to describe it is extensively debated. It is argued by some researchers that peak atrial longitudinal strain (PALS) is basically a combined value of left ventricular longitudinal systolic function and maximum LA volume before mitral valve opening and therefore adds no further value[55]. In contrast, other studies have shown that people with signs of diastolic dysfunction by estimated elevated LV filling pressures, showed a significant higher rate of abnormal LA strain (LA reservoir strain <23%) compared with an abnormal LAVI (LAVI >34 ml/m^2) (62.4% vs. 33.6%, p < 0.01) and a higher correlation with LV filling pressures than the LAVI[79]. This suggests that LA strain can indeed be a useful additional parameter to LAVI for evaluation of diastolic dysfunction. This hypothesis was supported by findings in patients that underwent primary percutaneous coronary intervention after MI, where LA strain provided incremental value to LA maximal volume (*p* = .03) with regard to the prediction of adverse outcomes (all-cause mortality, hospitalization for heart failure and reinfarction)[80].

This study therefore compares Endo GLS (LASr), Endo GCS, a composite Endo GLS + GCS value, as well as highest GLS, LA EF and LAVI ED parameters and evaluates their development after a MI. To assess these parameters, reliable normal values would be helpful. At this point, reliable data is only available for LA GLS (LASr) and LAVI ED. LA GLS was measured to be 39.4 (38–40.8) based on 40

studies and 2542 healthy subjects without cardiac risk factors. The lower limit of normal LA-Strain in healthy subjects was measured to be 23.1%[73]. LA GLS values below 23.1% were considered pathological. The mean GLS value cannot be used since age itself is a significant determinant of LA function. With higher age, LA GLS values showed a significant decrease in a large multicenter registry[81]. LA GCS is a parameter that is used considerably less frequently than LA GLS but might be a more accurate index of left atrial pressure, since the latter is strongly influenced by left ventricular long systolic strain[82]. Still normal values have not yet been established for LA GCS, even though in one of the few studies in which LA GCS was used, it was found to be an independent high risk factor for thromboembolism in patients with non-valvular atrial fibrillation[83]. Abnormal LAVI was defined as over 34 ml/m^2 (using the biplane Simpson method) according to the 2016 ASE and EACVI criteria for left ventricular diastolic dysfunction (LVDD)[84].

4.1 Interpretation of results

The different descriptive parameters investigated in the subjects allow to conclude that within the patient population unhealthy lifestyle-related behaviors are strongly present. One of the most striking findings is a prevalence of smoking in 70% of the population, with a daily cigarette consumption of 22 ± 13.52. Evidently, the data was gathered at the time of the hospitalization for MI and therefore shows the known connection between smoking and myocardial infarction in this cohort rather clearly. Apart from high daily nicotine abuse, the average years of smoking of all smokers (69.4%) was 29 ± 11.49. This results in an average of over thirty pack years (i.e. number of packs of cigarettes smoked per day multiplied by the number of years a person has smoked; twenty cigarettes in one cigarette pack). What makes these numbers even more problematic is that about 50% of the smokers continue smoking after a MI, even though smoking cessation after MI is known as one of the most effective secondary prevention measures. The fact that most individuals who stopped smoking did so during their stay in hospital, underlines the importance of assistance and support during the initial hospitalization after a MI[85].

Besides smoking, hypertension, diabetes, and dyslipidemia are major known risk factors for MI. The blood pressures measured during initial hospitalization are merely snapshots and do not reflect long-term blood pressure values due to the

administered medication and the affected pump function of the heart. Still the mean systolic blood pressure of 125.16 ± 9.59 mmHg and the mean diastolic blood pressure of 78.21 ± 6.25 during hospitalization were within the normal range. 11.9% suffered from diabetes and 8.7% of patients had hyperlipidemia. With a median HbA1c of 5.6 many patients were under the commonly used threshold of 6.5%. However, since it is well known that lowering blood pressure, blood glucose, and lipid values are effective ways of reducing morbidity and mortality following a MI, improvements in these cohorts are evidently desirable.

The patients showed decreased left atrial echocardiographic parameters initially. Compared with standard values in a healthy population 70.35% of patients showed an abnormal LA GLS (<23%) and 31.19% an abnormal LAVI (>34ml/m^2) at the time of hospitalization. However, LA GLS parameters improved significantly over time. This was shown using a linear mixed model for analysis of Endo GLS (see chapter 3.2). Significant differences between the Placebo and Empagliflozin group could not be detected. What was noticeable were the initial faster improvements in the empagliflozin group (which can be seen in Figure 8), although they were not statistically significant.

At visit 3/3 all mean echocardiographic left atrial parameters were slightly improved in the Empagliflozin group, even though none of these improvements were significant. In summary, compared to the placebo group the empagliflozin group had a positive mean Endo GLS V3 difference of 0.25 ± 1.19, a positive mean highest GLS difference of 0.81 ± 1.22, a positive mean Endo GCS difference of 0.74 ± 1.5 and a positive total Endo GLS and Endo GCS difference of 0.99 ± 2.4 in the end. Regarding the final volume parameters the empagliflozin group had a lower mean LAVI EDV V3 of -1.08 ± 1.66 and a positive LA EF difference of 0.78 ± 1.67.

Overall, the effect sizes of the strain improvements do not seem remarkably high. Keeping in mind that a MI can lead to ventricular diastolic dysfunction, which usually leads to higher atrial volumes, the slight improvement of LA EF and the increase in strain parameters can be put in a reasonable context from a pathophysiologic point of view.

The strongest correlation could be observed between the almost identical values for Endo GLS and highest GLS (ρ = .932). The correlations of Endo GLS + GCS must

be treated with caution, since Endo GLS + GCS logically correlates strongly with Endo GLS and Endo GCS, as it is the artificial composite of GLS and GCS. Given that the mechanical processes of the LA have not been as extensively studied compared to the left ventricle, it is a notable finding that the longitudinal strain correlates strongly with the circumferential strain. This correlation can be interpreted as connected longitudinal and circumferential extension and shortening. Between the strain parameters and the LAVI, only a weak inverse correlation could be observed. That means that as LAVI values increase, strain values decrease. It needs to be kept in mind that Lagangrian strain is a relative parameter and is therefore independent of absolute volumes and, hence, atrium sizes. However, if the LAVI value is high as a result of diastolic dysfunction, decreasing left atrial strain values can be interpreted as the fading function of the already impaired LA. A stronger, namely moderate correlation can be found between Endo GLS and NT-proBNP. This finding could be anticipated since NT-proBNP is released in response to changes in pressure inside the heart chambers and especially the atria. Another moderate, almost strong correlation became evident between the strain parameters and LA EF. This finding, again, seems very plausible. In fact, the more volume the atrium stores or, rather, ejects, the more it has to change in size, which is then reflected in the strain values. Overall, many correlations between the different parameters have become evident, confirming the interconnected and complex pathophysiology of the LA in the context of cardiac conditions, more specifically after MI.

4.2 Implications

This study has shown that strain parameters correlate with volume parameters, but they ultimately provide different results and, therefore, information compared to volume parameters. Additionally, GLS and GCS of the LA strongly correlate but are still far from displaying the same values. In general, the different strain parameters and their values support the complex theory of the heart as three-dimensional piston and its not yet completely understood mechanisms regarding changing conditions. Speaking of a three-dimensional movement, it makes sense to take all spatial axes into account.

In practice, it was first shown in cancer patients receiving cardiotoxic therapies that with LV global longitudinal strain, cardiac dysfunction could be detected earlier than with EF[86]. Since the atrium is directly linked to the ventricle through the valve plane, a correlation between LV GLS and LA GLS seems obvious. However, the extent is still unclear and the debates regarding the significance of LA GLS appear far from solved. The same applies to LA GCS, even though it has been shown to have relevance in clinical practice as well. To better understand these mechanisms and parameters, it is clearly necessary to further collect data and compare them with laboratory and volume markers on the one hand and with hard outcomes on the other.

There is limited evidence regarding left atrial echocardiographic parameters specifically after MI. One of the few pieces of evidence in this regard is the echocardiographic sub-study of the PARADISE-MI trial, which investigated the impact of Sacubitril/Valsartan compared with Ramipril on cardiac structure and function after MI. In this trial, left atrial volumes did not differ significantly between the groups after 8 months[87]. However, further trials are needed to show if the measurable function of the LA can indeed be influenced significantly by medication after MI.

It can be considered as a huge advantage of our time that strain parameters can be gathered very easily in a predominantly automatic manner owing to advances in technology. To the author further investigations of strain parameters appear as promising avenue for future research, since they are ultimately a mirror image of the complex dynamics of the heart.

4.3 Limitations and strengths

The major limitation of this study is its dependence on the post-processing software by TOMTEC. As tends to be the case with such post-processing software, the mechanisms behind it are not disclosed. It is therefore, for example, difficult to fully understand the different values of Endo GLS and highest GLS. Additionally, even though the endocardium was mapped out carefully manually for end-systolic and end-diastolic stages, the tracing was frequently adjusted by the software automatically and thus worsened the concordance of endocardium and the traced line. In such cases, the tracing had to be adjusted manually again. For strain

analysis, end-systole and end-diastole were defined manually by M-Mode over the left ventricle. The gold standard for determining the heart phases would be the closure of the aortic valve. However, for the purpose of comparing global maximal strains and not the strains of each atrial phase, this minor inexactness should not severely impact the results. In accordance with the software provided by TOMTEC, left atrial strain parameters were only acquired in the two-chamber views. This has the advantage of a good endocardial contour and hardly any relevant impairment of the endocardial border by lung veins. Nevertheless, the gold standard of obtaining left atrial strain measurements requires application in the two- as well as the four-chamber view.

Although that strain analysis is a rather new technique, the strain analyses were conducted without any visible technical difficulties. This might also be due to the fact, that the same experienced cardiologist did almost all echocardiograms at three separate times for every patient. Only four people solely completed one of the three study visits, making it impossible to monitor any change in their clinical data. From twenty-one participants, only two instead of three ultrasound studies were available or useable, either because they did not come to one visit, because their data was not stored properly, or because the image quality was not sufficient for the purpose of the analysis.

Another strength of this study is the precise measurement of left atrial volumes. The author of this study, who also performed all the echocardiographic measurements himself, had been trained by the cardiologists beforehand until equal values for sample patients were achieved. Afterwards, in the frames of the EMMY patients, all measurements were done twice end-diastolic and end-systolic. The same is applicable to the strain measurements with TOMTEC.

Various sources of bias were averted by a triple-blind approach. Only after the completion of the data analysis did the final unblinding take place.

4.4 Conclusion

The LA plays a key role in modulating left ventricular filling. Its role is therefore of increasing interest with regard to different cardiac conditions, such as in the setting of myocardial infarction. Based on the extensive progress in analysis software, speckle-tracking-based echocardiographic parameters to describe left atrial function can nowadays be obtained very consistently. However, sufficient data to reliably interpret left atrial functional parameters are still missing. The findings of this thesis indicate only a weak correlation between strain parameters and LAVI and a moderate correlation between strain parameters and NT-proBNP, indicating that various kinds of information are displayed with each parameter. Empagliflozin did not influence strain, volume or laboratory parameters significantly compared with placebo. Overall, strain, volume and laboratory values were significantly dependent on the time after MI, likely reflecting physiological adaptations and rehabilitation after the initial MI and the positive impacts of modern medical therapies. To gain a better understanding of the role of the LA in different cardiac conditions, further clinical research of strain parameters is needed.

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