Diploma Thesis

The Impact of the SGLT2 Inhibitor Empagliflozin on Right Atrial Function after Acute Myocardial Infarction

submitted by

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Statutory Declaration

I hereby declare that this thesis is my 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, September 14th, 2023 Sabrina Oltean m.p.

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Abbreviations and Definitions

ACE	*angiotensin-converting enzyme*
AMPK	*AMP-activated protein kinase*
ARB	*angiotensin receptor blocker*
ARNI	*angiotensin receptor-neprilysin inhibitor*
ASE	*American Society of Echocardiography*
ATP	*adenosine triphosphate*
AV	*atrioventricular*
BCL2	*B-cell lymphoma 2*
BMI	*body mass index*
BP	*blood pressure*
BSA	*body surface area*
CABG	*coronary artery bypass grafting*
CAD	*coronary artery disease*
cGCH1	*cardiac GTP enzyme cyclohydrolase 1*
CHD	*coronary heart disease*
CK	*creatinine kinase*
CRP	*C-reactive protein*
CV	*cardiovascular*
DAPT	*dual antiplatelet therapy*
DM	*diabetes mellitus*
EACVI	*European Association of Cardiovascular Imaging*
ECG	*electrocardiogram*
EDV	*end-diastolic volume*
EMS	*emergency medical services*
EPO	*erythropoietin*
ESC	*European Society of Cardiology*
ESR	*European Society of Radiology*

ESV	*end-systolic volume*
FGF21	*fibroblast growth factor 21*
GCS	*global circumference strain*
GFR	*glomerular filtration rate*
GLS	*global longitudinal strain*
GLUT	*glucose transporter*
GRACE	*global registry of acute coronary events*
HFpEF	*Heart failure with preserved ejection fraction*
HFrEF	*Heart failure with reduced ejection fraction*
HIF	*hypoxia-inducible factor*
i.v.	*intravenous*
IC_{50}	*inhibitory concentration*
IL-6	*interleukin-6*
iNOS	*nitric oxide synthase*
LV	*left ventricular*
LVEF	*left ventricular ejection fraction*
MACE	*major adverse cardiovascular events*
MAT	*maximum activity time*
MI	*myocardial infarction*
MRA	*mineralocorticoid receptor antagonist*
NHE1	*Na^+/H^+-exchanger 1*
NSTE-ACS	*non-ST-segment elevation acute coronary syndrome*
NSTEMI	*non-ST-elevation myocardial infarction*
NT-proBNP	*N-terminal prohormone of brain natriuretic peptide*
NYHA	*New York Heart Association*
OBA	*absolute oral bioavailability*
PCI	*percutaneous coronary intervention*

PGC1-α	*peroxisome proliferator-activated receptor-y coactivator 1-α*
PPB	*plasma protein binding*
PPI	*proton pump inhibitor*
RAAS	*renin-angiotensin-aldosterone-system*
RAEF	*right atrial ejection fraction*
RAVI	*right atrial volume index*
RCT	*randomised controlled trial*
ROI	*region of interest*
ROS	*reactive oxygen species*
RR	*Riva Rocci*
RV	*right ventricular*
SGLT	*sodium glucose transporter*
SIRT1	*sirtuin-1*
sPAP	*systolic pulmonary artery pressure*
STAT3	*signal transducer and activator of transcription 3*
STEMI	*ST-elevation myocardial infarction*
$T_{1/2}$	*elimination half-life of the drug*
TGF-ß1	*transforming growth factor beta 1*
T_{max}	*time for maximum absorption*
TNFα	*tumor necrosis factor-alpha*
UFH	*unfractionated heparin*
US	*United States*
VF	*ventricular fibrillation*
VT	*ventricular tachycardia*

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Zusammenfassung

Hintergrund und Ziel: Der Myokardinfarkt stellt eine der häufigsten Todesursachen in den Industriestaaten dar. Myokardiale Schäden durch Ischämie und Reperfusion führen zur Aktivierung von maladaptiven Remodellingprozessen und neurohumoralen Veränderungen und in weiterer Folge zur Entstehung einer Herzinsuffizienz. Die EMMY-Studie (*„Empagliflozin in acute myocardial infarction: the EMMY trial“*) konnte erstmalig zeigen, dass der frühe Einsatz von Empagliflozin nach akutem Myokardinfarkt zu einer signifikanten Verbesserung von NT-proBNP, sowie funktionellen und strukturellen echokardiographischen Parametern führt. Die Datenlage zum Einsatz von Natrium/Glukose-Cotransporter-2 (SGLT2) Inhibitoren nach akutem Myokardinfarkt ist momentan noch gering. In dieser Diplomarbeit erfolgt eine Subanalyse der EMMY-Studie, in der die Wirkung von Empagliflozin auf den rechten Vorhof untersucht wird. Klinisch korreliert die rechts-atriale Funktion mit dem Schweregrad einer Herzinsuffizienz und stellt einen prognostischen Marker dar. Bislang gibt es noch keine einzige Studie, die eine systematische echokardiographische Auswertung des rechten Vorhofs nach einem akuten Myokardinfarkt und der Behandlung mit Empagliflozin vorgenommen hat.

Material und Methoden: Es wurden insgesamt 206 Patientinnen und Patienten der EMMY-Studie, die im Zeitraum von 11.05.2017 bis 03.05.2022 stattfand, herangezogen. Der primäre Endpunkt umfasst die Veränderung des rechts-atrialen globalen longitudinalen Strains (GLS) über einen Zeitraum von 26 Wochen. Sekundäre Endpunkte sind die Veränderungen von rechts-atrialen Dimensionen und Volumina sowie der rechts-atrialen Ejektionsfraktion (RAEF) und des systolischen pulmonalarteriellen Drucks (sPAP). Außerdem werden Korrelationen zwischen den einzelnen Echoparametern, sowie dem NT-proBNP, der Kreatin-Kinase und dem high-sensitiv Troponin untersucht. Die Auswertung der Echokardiographie-Loops erfolgte mittels der Software TomTec (TOMTEC Imaging Systems, München, Deutschland) und die statistische Auswertung mittels IBM SPSS statistics 26 (IBM Corporation, Armonk/New York, Vereinigte Staaten von Amerika).

Resultate: In Bezug auf den rechts-atrialen GLS konnten zum dritten Messzeitpunkt keine signifikanten Unterschiede zwischen der Empagliflozin- und der Placebogruppe festgestellt werden (p = 0.149). Innerhalb der männlichen Patienten wurde die Signifikanzgrenze knapp verfehlt (Empagliflozin: 35.6 ± 11.3%, Placebo: 32.7 ± 8%, p = 0.056). Das rechts-atriale end-diastolische Volumen (EDV) innerhalb der männlichen Subgruppe zeigte zum dritten Messzeitpunkt eine signifikante Verringerung (Empagliflozin: 29.6 ± 13.7 ml, Placebo: 32.6 ± 12.9 ml, p = 0.021). Die Mittelwerte des rechts-atrialen GLS, sPAP, rechts-atrialen Volumenindex (RAVI), sowie end-systolischen (ESV) und end-diastolischen Volumens (EDV) zeigten sich in der Empagliflozin Gruppe im Vergleich zur Kontrollgruppe bereits nach sechs Wochen verbessert.

Zudem weist der rechts-atriale GLS eine signifikante Korrelation mit allen anderen etablierten rechts-atrialen echokardiographischen Parametern sowie zum NT-proBNP auf, insbesondere zum dritten Messzeitpunkt.

Conclusio: Die Einnahme von Empagliflozin nach akutem Myokardinfarkt führt innerhalb der männlichen Patienten zu einer signifikanten Verbesserung des rechts-atrialen EDV. Bezüglich des rechts-atrialen GLS wurde innerhalb der männlichen Subgruppe die Signifikanzgrenze knapp verfehlt (p = 0.056). In der gesamten Kohorte zeigte sich eine numerische Verbesserung aller Parameter ohne statistische Signifikanz.

Der rechts-atriale GLS korreliert signifikant mit allen rechts-atrialen echokardiographischen Parametern und dem Labormarker NT-proBNP, insbesondere bei Patientinnen und Patienten mit chronischer Herzinsuffizienz.

Abstract

Background and Purpose: Myocardial infarction is one of the leading causes of death in industrialised countries. Myocardial damage due to ischaemia and reperfusion leads to the activation of maladaptive remodelling processes and neurohumoral changes and subsequently to the development of heart failure. The EMMY trial ("*Empagliflozin in acute myocardial infarction: the EMMY trial")* was the first to show that the early use of empagliflozin after acute myocardial infarction leads to a significant improvement in NT-proBNP and functional and structural echocardiographic parameters. The data on the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors after acute myocardial infarction is currently limited. In this sub-analysis of the EMMY trial, the effect of empagliflozin on the right atrium will be investigated. Right atrial function correlates with the severity of heart failure and is a prognostic marker. To date, no study has performed a systematic echocardiographic evaluation of the right atrium after acute myocardial infarction and treatment with empagliflozin.

Material and Methods: A total of 206 subjects from the patient population of the EMMY study, which took place from the 11th of May 2017 to the 3rd of May 2022, were used for the analysis. The primary outcome was the change in right atrial global longitudinal strain (GLS) over a period of 26 weeks. Secondary outcomes include changes in the right atrial dimensions and volumes, right atrial ejection fraction (RAEF) and systolic pulmonary artery pressure (sPAP). In addition, correlations between the individual echo parameters, as well as NT-proBNP, creatine kinase (CK) and high-sensitivity troponin were investigated. The evaluation of the echocardiography loops was performed using the software TomTec (TOMTEC Imaging Systems, Munich, Germany) and for the statistical analysis, IBM SPSS statistics 26 (IBM Corporation, Armonk/New York, US) was used.

Results: The right atrial GLS in the empagliflozin group showed no significant change at the third measurement time point compared to the placebo group ($p = 0.149$). Within the male subgroup, the significance threshold was barely missed (empagliflozin: 35.6 ± 11.3%, placebo: 32.7 ± 8%, $p = 0.056$). The right atrial end-diastolic volume (EDV) within the male subgroup was significantly reduced

(empagliflozin: 29.6 ± 13.7 ml, placebo: 32.6 ± 12.9 ml, p = 0.021). Furthermore, the mean values of the right atrial parameters GLS, sPAP, right atrial volume index (RAVI) and end-systolic (ESV) and end-diastolic volume (EDV) were already improved in the empagliflozin group after 6 weeks compared to the control group.
In addition, the right atrial GLS shows a significant correlation with all other regular right atrial echocardiographic parameters and NT-proBNP, especially at the third measurement time point.
Conclusion: Early administration of empagliflozin after acute myocardial infarction significantly improves right atrial EDV in male subjects (p = 0.021). The right atrial GLS within the males showed almost significant results (p = 0.056). However, no significant results could be achieved when all study participants were included. Right atrial GLS correlates significantly with right atrial structural and functional echocardiographic parameters and NT-proBNP, especially in patients with chronic heart failure.

1 Introduction

1.1 Myocardial Infarction

The current guidelines of the European Society of Cardiology (ESC) on the definition of myocardial infarction (MI) claim, that *"The term acute myocardial infarction should be used when there is an acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:*

- *Symptoms of myocardial ischaemia*
- *New ischaemic ECG changes*
- *Development of pathological Q waves*
- *Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology*
- *Identification of a coronary thrombus by angiography or autopsy"*[1].

1.1.1 Scope of the Problem

Coronary heart disease (CHD), especially MI, is the most frequent cause of death in industrialised countries worldwide. Although mortality has been reduced over the last three decades[2], approximately 1.8 million deaths occur annually in Europe alone[3]. The incidence in industrialised countries is around 300/100.000 per year and about 30% of the cases are lethal[4]. According to the American Heart Association, the prevalence of MI in adults in the United States (US) above the age of 20 years is 3.1% overall, with a male prevalence of 4.3% and a female prevalence of 2.1%[5]. Mortality is influenced by various factors including age, pre-existing conditions including diabetes mellitus (DM) or renal failure, the severity of coronary artery disease, and left ventricular ejection fraction (LVEF). Additionally, the timing of the start of therapy and the level of development of care centres play a significant role[3]. In the > 65-year-old patients, the in-hospital mortality is about 7%, after 1 year 24%, after 5 years 41% and after 8 years 65%[5].

The treatment of acute MI requires various resources and is a burden on the health care system. This is particularly due to the cost in the first year after the incident which averages $19.842 per patient, mainly due to hospitalisation costs[6]. However, the US reported, that they spent about $12.1 billion on MI care in the year 2013 and that it belonged to the 10 most expensive conditions treated in US hospitals[5].

Another problem is the development of secondary diseases including heart failure. The incidence of heart failure after acute MI varies between 14% to 36%. Nonetheless, MI is one of the main causes of heart failure[7]. The US healthcare system spends around $30.7 billion per year on heart failure care. By 2030, these costs are expected to increase to $69.8 billion[5].

1.1.2 Classification

According to the ESC guidelines on the definition of MI, there are five different types of MI[1]. The characteristics are shown in table 1.

1.1.3 Complications after Myocardial Infarction

Ischemia occurs when the arterial blood supply to the tissue is reduced, resulting in an O_2 deficiency and CO_2 excess. Depending on the duration and oxygen sensitivity of the affected tissue, ischemia results in tissue necrosis, so-called infarcts. In the case of the heart, the time until irreversible damage occurs, the so-called ischemia time, is around 30 minutes. Complications after MI depend on the localisation and expansion of the infarction area, as well as the start of treatment[4].

Type 1		Atherosclerotic plaque rupture, ulceration, fissure, or erosion with resulting intraluminal thrombus
Type 2		Mismatch between oxygen supply and demand because of: Hypo- or hypertension, tachy- or bradyarrhythmia, hypoxaemia, anaemia, coronary artery spasm, spontaneous non-atherosclerotic coronary artery dissection, coronary embolism, and coronary microvascular dysfunction
Type 3		Myocardial infarction resulting in death, bevor it is possible to obtain blood for cardiac biomarker analyses
Type 4	a	Myocardial infarction associated with PCI
	b	Stent/Scaffold Thrombosis associated with PCI
Type 5		Myocardial infarction associated with CAGB

Table 1: Clinical classification of myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting

Early Complications

Early complications of MI are manifold. They are characterised by cardiac arrhythmias and left heart failure including cardiogenic shock and necrosis complications[4].

Although the incidence of ventricular arrhythmias like ventricular tachycardia (VT) and ventricular fibrillation (VF) has declined due to improved reperfusion strategies, the prevalence is about 6-8%. Nonetheless, ventricular arrhythmias are the main cause of sudden cardiac death[8] and rapid revascularisation is the only way to reduce the risk. The benefits of antiarrhythmic drugs are limited[3]. After the successful reopening of the infarct vessel, so-called reperfusion arrhythmias can also occur, which usually limit themselves and do not require further treatment[9]. In more than 80% of patients, ventricular extrasystoles and bursts appear in monitoring[8]. Supraventricular arrhythmias, including atrial fibrillation or atrial

flutter, are present in about 20% of patients with MI. These symptoms may be pre-existing or the result of acute atrial distension in acute MI[8]. Nevertheless, tachycardia leads to increased oxygen demand with a shortening of diastolic duration and consecutive reduction of coronary perfusion[10]. Bradycardic arrhythmias are common in inferior wall MI. Especially, second-degree type II atrioventricular (AV) block and complete AV block require further treatment and insertion of a transvenous pacemaker should be considered[3].

If more than 40% of the contractile muscle mass is lost during a MI, acute heart failure and subsequent cardiogenic shock and pulmonary oedema are possible[4]. Cardiogenic shock is defined as *"persistent hypotension (SBP < 90 mmHg) despite adequate filling status with signs of hypotension"*[3] and is a leading cause of death in MI besides ventricular arrhythmias. Its prevalence in patients undergoing MI varies between 5% to 15%[7] and the in-hospital mortality is > 50%[3]. The only therapy reducing its mortality is early revascularisation[3, 7].

The loss of tissue due to ischemia can also lead to mechanical complications including a free-wall rupture with pericardial tamponade, ventricular septal rupture with a left-right shunt, papillary muscle rupture with acute mitral regurgitation and aneurysm[4]. Due to primary percutaneous coronary intervention (PCI), these complications occur in less than 0.1% of patients. Nonetheless, they present with dramatic hemodynamic deterioration and require rapid stabilisation[11]. In transmural MI, rupture of the pericardial wall occurs in < 1%[3] of cases usually on the 3rd to 10th day after acute MI[4]. The result is acute pericardial tamponade, which is usually rapidly fatal. The mortality rate ranges from 20% to 75% depending on the rupture's size and the patient's condition[3]. Ventricular septal rupture leads to a left-right shunt and presents with acute heart failure, it can occur within 24 hours to several days after MI[3]. Infarction of a papillary muscle is often followed by papillary muscle rupture[9], whereas usually the posteromedial papillary muscle is more commonly affected, because of its single artery blood supply[3]. This results in acute mitral regurgitation with acute left heart failure[4].

Parietal endocardial thrombosis develops on the inflammatory endocardium in 45% of patients and is a trigger for arterial thromboembolism and subsequent

stroke in 10-30% of cases[4]. Left ventricular (LV) aneurysm also favours the formation of a thrombus due to the stasis of the blood[3].

Late Complications

Late complications are mainly characterised by the occurrence of heart wall aneurysms, pericarditis epistenocardica, arrhythmias, heart failure and reinfarction[4].

LV aneurysms develop in less than 5% of patients with large transmural MI[3] and are mainly localised at the base of the heart or the posterior papillary muscle. The stasis of the blood also favours the development of thrombi[4]. The aneurysms are often accompanied by LV failure, arrhythmias, dyskinesia and intracardiac thrombi[8].

Pericarditis may occur in three forms: early infarct-associated pericarditis, late infarct-associated pericarditis, and pericardial effusion[3]. Early infarct-associated pericarditis, also called pericarditis epistenocardica, is a fibrinous inflammation that can lead to adhesions of the epicardium and pericardium and produces a typical dry rubbing noise. It develops directly over the infarct area[4].
Late infarct-associated pericarditis, also called Dressler syndrome, develops around 1-2 weeks after MI through autoimmune pathogenesis, which is triggered by damaged pericardial tissue of myocardial necrosis[3]. Dressler syndrome can also be accompanied by pleuritis. This exudative autoimmune pericarditis is also observed after heart surgery[8]. Pericardial effusion may occur within pericarditis, but in the absence of inflammatory signs, it may also indicate a subacute rupture of the wall and thus should always be further investigated[3].
The indices for the development of heart failure after MI range from 14% to 36%[7]. However, MI patients can present with heart failure at different time points: at admission, during hospitalisation and after discharge. Heart failure in the early onset of MI is mainly caused by myocardial necrosis, myocardial stunning and mechanical complications, including cardiac wall rupture, ventricular septal rupture, and papillary muscle rupture. Following the acute ischemic event,

reperfusion itself causes a second wave of injury due to reactive oxygen species (ROS) production which leads to the onset of heart failure during hospitalisation[12]. Cardiac remodelling after MI results in the development of heart failure[7]. In sum, this triggers chronic neurohumoral activation of the renin-angiotensin-aldosterone-system (RAAS)[12], which aggravates this situation and results in a vicious circle[8] as visualised in figure 1.

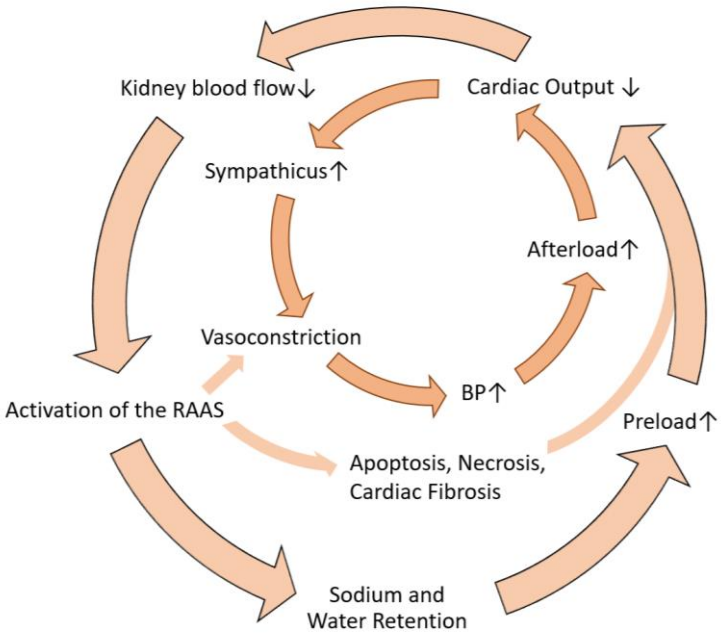

Figure 1: The vicious circle of compensatory mechanisms in heart failure, BP = blood pressure, RAAS = renin-angiotensin-aldosterone-system
Modified from Basislehrbuch Innere Medizin. 6. Auflage ed. Braun J et al. Munich, Germany: Elsevier; 2018

1.1.4 Therapy

General Procedure

In patients with symptoms of ischemia, symptomatic basic therapy to relieve pain, anxiety and breathlessness should be given to reduce sympathetic activation and indirectly the oxygen demand of the heart[8]. According to the European Heart

Association guidelines, the administration of oxygen is indicated in the presence of hypoxia with a SaO_2 < 90% or PaO_2 < 60 mmHg. Routine oxygen is not recommended in patients with SaO2 ≥ 90%, because some studies have shown that hyperoxia may be harmful in uncomplicated MI. For pain and anxiety relief, titrated intravenous (i.v.) opioids like morphine and a mild tranquillizer, usually, benzodiazepine should be considered[3].

Acute Therapy of STEMI

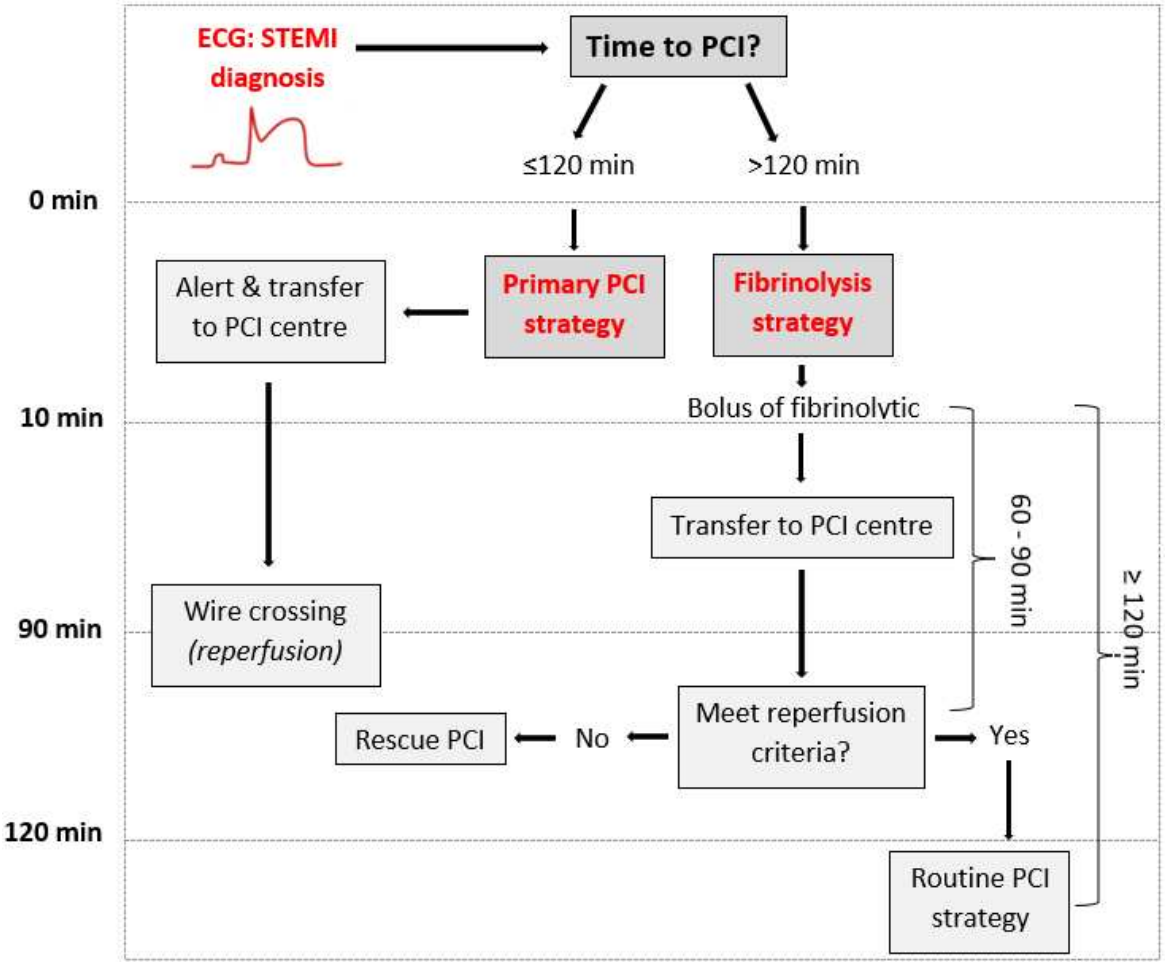

Figure 2: Maximum target times according to reperfusion strategy in patients with STEMI diagnosis; ECG = electrocardiogram, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction

Adapted from Iabenz B et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2018

In the case of ST-elevation myocardial infarction (STEMI) within 12 hours of symptom onset, primary PCI is recommended as a reperfusion strategy, which should be performed expeditiously within 120 minutes after STEMI diagnosis. Maximum target times according to the reperfusion strategies are shown in figure 2. Fibrinolysis is only recommended in patients with symptoms ≤ 12 hours if primary PCI cannot be offered in an acute setting and if there are no contraindications. If fibrinolysis is contra-indicted, the primary PCI strategy should be followed regardless of time to PCI. However, the bolus of fibrinolytic should be injected within 10 minutes after STEMI diagnosis, whereas patients should be transferred to a PCI-capable facility as soon as possible. If the fibrinolysis was successful, a routine early PCI strategy is indicated within 2-24 hours after initiating fibrinolysis. In case of failed fibrinolysis, a rescue PCI as fast as possible is indicated. The criteria for failed fibrinolysis include ST-segment resolution < 50% within 60-90 minutes of fibrinolytic administration or in the presence of hemodynamic or electrical instability, worsening ischemia or persistent chest pain[3].

Platelet Inhibition and Anticoagulation

Patients undergoing primary PCI should receive parenteral anticoagulation and dual antiplatelet therapy (DAPT). The DAPT is a combination of aspirin and a $P2Y_{12}$ inhibitor. Aspirin should be distributed as soon as possible orally or if swallowing is not possible alternatively i.v., followed by a maintenance dose and lifelong intake. A potent $P2Y_{12}$ inhibitor like prasugrel or ticagrelor is recommended before or at the time of PCI and maintained over 12 months. Anticoagulation through unfractionated heparin (UFH) or enoxaparin is indicated for all patients during primary PCI. In the case of heparin-induced thrombocytopenia, bivalirudin can be administered alternatively. Routine post-procedural parenteral anticoagulation is only recommended in patients who require prolonged bed rest or when there is a separate indication[3].

Patients undergoing fibrinolysis as a reperfusion strategy should receive DAPT, including aspirin and clopidogrel. After fibrinolysis, clopidogrel is the $P2Y_{12}$ inhibitor of choice. Parenteral anticoagulation should be administered until

revascularisation if performed or at least for 48 hours or the duration of hospital stay, up to 8 days. Enoxaparin is favoured over UFH[3].

Acute Therapy of NSTEMI

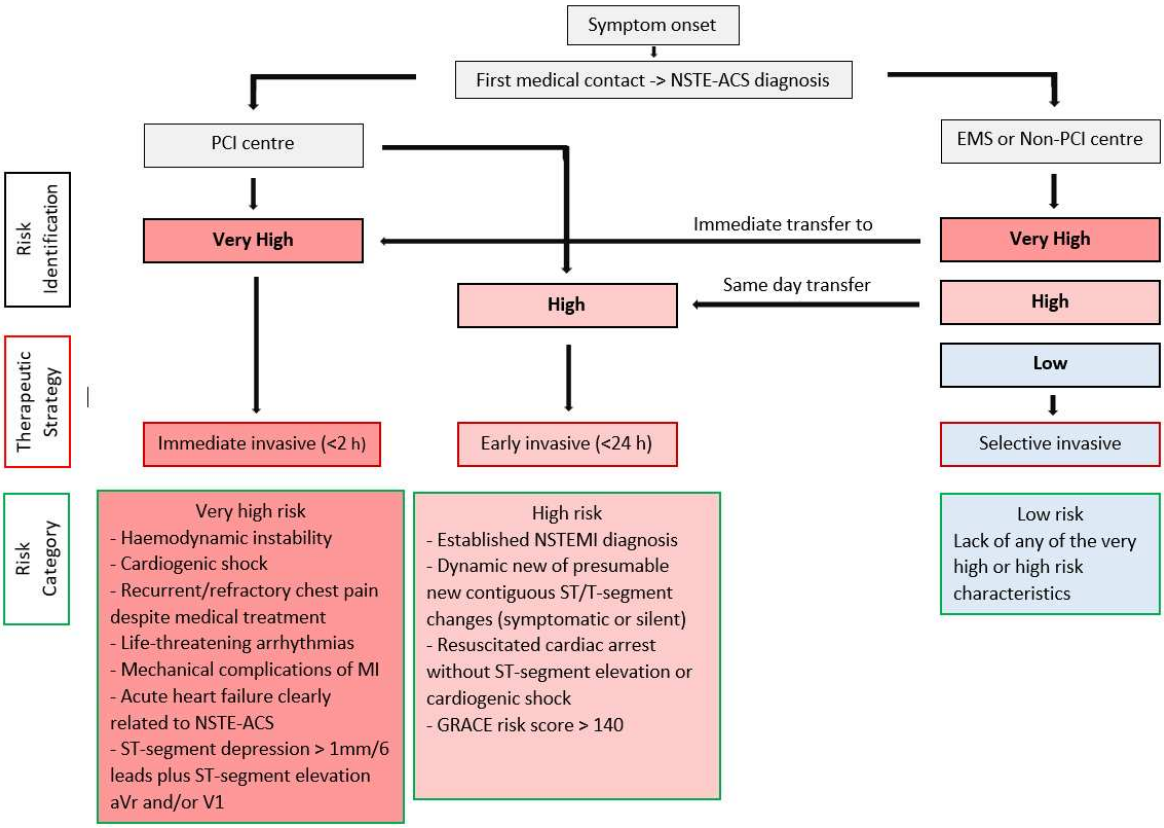

Figure 3: NSTEMI treatment strategy and timing according to initial risk stratification; EMS = emergency medical services, GRACE = Global Registry of Acute Coronary Events, MI = myocardial infarction, NSTE-ACS = non-ST-segment elevation acute coronary syndrome, PCI = percutaneous coronary intervention

Modified from Collet JP et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2021

In non-ST-elevation myocardial infarction (NSTEMI), the focus is on basic drug therapy, especially antithrombotic treatment[8]. After NSTEMI diagnosis, the treatment with DAPT, including aspirin and a potent $P2Y_{12}$ inhibitor such as ticagrelor or prasugrel, is initiated. DAPT should be taken over a period of 12

months after NSTEMI, whereas the $P2Y_{12}$ inhibitor can be discontinued immediately. Furthermore, peri-interventional anticoagulation with UFH is recommended in addition to DAPT. The administration of fondaparinux and a single bolus of UFH at the time of PCI is recommended in cases of medical treatment or logistical constraints for transferring the patient to PCI within the required time frame[13].

Regarding an invasive strategy, NSTEMI patients are divided into three groups: very high-risk, high-risk, and low-risk patients. Very high-risk NSTEMI patients, which have at least one very high-risk criterion, should get a primary PCI within 120 minutes analogous to STEMI management. In high-risk NSTEMI patients, coronary angiography can be performed within 24 hours and low-risk NSTEMI patients with no recurrence of symptoms should be treated according to Chronic Coronary Syndrome Guidelines[13].

Long-Term Therapies for STEMI and NSTEMI

After a MI, the treatment of risk factors and the initiation of secondary prophylaxis are the priority. This means blood pressure (BP) control, blood sugar control, smoking cessation, dietary changes, and exercise. Patients who have had a STEMI or NSTEMI should take the DAPT, including aspirin plus prasugrel or ticagrelor (or clopidogrel) for a period of 12 months. Thereafter, the $P2Y_{12}$ inhibitor can be discontinued, aspirin must be taken for life[3, 13]. In patients with STEMI revascularised by fibrinolysis alone, clopidogrel is sufficient for 1 month after the event[3]. However, low-dose aspirin (75-100 mg) is taken for long-term prevention. Gastric protection with a proton pump inhibitor (PPI) should also be considered in patients with a history of gastrointestinal bleeding or risk factors for bleeding. Further therapy includes taking a beta-blocker, statin, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI)[3, 13]. In case of LVEF < 40%, heart failure therapy for reduced ejection fraction including ACE inhibitor, beta-blocker, ARB, ARNI and SGLT2 inhibitor is recommended[14]. Early initiation of heart failure medication in patients after MI shows beneficial effects on mortality and major

adverse CV events, as remodelling processes start early after the ischemic event[15-18].

1.2 SGLT2 Inhibitors

SGLT2 inhibitors belong to the pharmacotherapeutic group of oral antidiabetics. They work in the proximal tubule of the glomerulus, where they selectively, competitively and reversibly inhibit the SGLT2[19]. Therefore, renal glucose reabsorption is inhibited and moderate glucosuria is initiated. As a result, peaks in the blood sugar daily profile are suppressed independently of the body's insulin production[20]. Since regulators in Europe and the US demanded that new glucose-lowering therapies had to be proven on the CV outcomes, large clinical trials with type 2 DM were designed to demonstrate the safety of these drugs. In these trials, empagliflozin, dapagliflozin and canagliflozin were found to reduce the incidence of heart failure and also showed positive effects on renal function[21] through the reduction of intraglomerular hypertension by influencing the pre- and post-glomerular vascular tone[22]. The potential mechanism of renoprotective and cardioprotective effects are described below.

1.2.1 Physiology of SGLT2 and SGLT1

The kidneys play an important role in glucose homeostasis, as they filter and reabsorb around 180 g of glucose per day. Normally glucosuria is not found until the plasma glucose level exceeds 180 mg/dL, which is typical in DM[23]. Special membrane proteins are responsible for retrieving the filtered glucose in the primary urine, primarily to ensure the supply of glucose to the brain[24]. Glucose transport by SGLT belongs to the secondary active transport mechanism, as glucose molecules are transported against the concentration gradient[22]. To achieve this, the Na^+/K^+-ATPase produces a sodium gradient by pumping out Na^+ and pumping in K^+. Thereby, a low intracellular Na^+- concentration is maintained and glucose transport across the luminal membrane via SGLT is possible[25, 26].

SGLT1 is found essentially on enterocytes and the late proximal renal tubule. In smaller concentrations, it is also expressed in the trachea, testis, prostate, heart, skeletal muscle, and parts of the brain. SGLT2 is mainly found in the early proximal tubule, lower concentrations could be detected in the liver, thyroid, skeletal muscle and brain[27]. However, SGLT2 is not expressed in cardiac tissue, neither in healthy nor in ischemic or hypertrophic hearts[28].

The high-capacity SGLT2 transports glucose and sodium in the proximal tubule of the glomeruli (S1/S2 segments). It is responsible for the reabsorption of about 97% of the filtered glucose in the primary urine back into the bloodstream. The lower-capacity SGLT1, which is in the "late" proximal tubule (S2/S3 segments) of the glomerular transports the remaining 3% of the glucose including sodium[21]. SGLT1 and SGLT2 are both expressed on the apical membrane. Intracellularly, glucose can exit passively into the blood via the facilitative glucose transporter 2 (GLUT2), which works in conjunction with SGLT2, or GLUT1, which works in conjunction with SGLT1 on the basolateral membrane[27]. The reabsorbed glucose is taken up into the peritubular capillaries and transported into the systemic circulation or used as an energy resource for processes in more distal tubules. Under normoglycemic conditions, all filtered glucose in the primary urine is reabsorbed. When the renal threshold (approximately 180 mg/dl) is reached, glucosuria occurs[24, 29].

1.2.2 Pharmacokinetics

The SGLT2 inhibitors empagliflozin, dapagliflozin and canagliflozin have similar pharmacokinetics. The drugs are rapidly absorbed after oral administration regardless of food intake[20], attaining peak plasma levels within 1-2 hours. The bioavailability of these three SGLT2 inhibitors ranges from 68% to 78%. Plasma protein binding is between 86% and 99%. The elimination half-life is about 12 hours [30], allowing once-daily administration[20]. Empagliflozin has a high selectivity for SGLT2 as compared to other gliflozins and is associated with higher urinary glucose elimination[23]. However, SGLT2 inhibitors are metabolised in the liver

mainly via glucuronidation to inactive metabolites, which are eliminated primarily through urine[31]. An overview of the pharmacokinetics is shown in table 2.

Drug Name	OBA	T_{max}	PPB	$T_{1/2}$	SGLT2(IC_{50})
Empagliflozin	78%	1.5 h	86%	12.4 h	3.1 nM
Dapagliflozin	78%	2 h	98%	12.9 h	1.2 nM
Canagliflozin	68%	1-2 h	99%	10-13 h	2.7 nM

Table 2: Pharmacokinetics of empagliflozin, dapagliflozin and canagliflozin, OBA = absolute oral bioavailability, T_{max} = time for maximum absorption, PPB = plasma protein binding, $T_{1/2}$ = elimination half-life of the drug, SGLT2 = sodium-glucose co-transporter 2, IC_{50} = inhibitory concentration

1.2.3 Side Effects

Complications caused by glucosuria are the most common adverse effects of SGLT2 inhibitors. The therapy may increase the risk of urinary tract infection and genital tract infection[31]. However, a meta-analysis including EMPA-REG, CANVAS and DECLARE-TIMI 58 could not find a significant increase in urinary tract infection in patients treated with SGLT2 inhibitors. In contrast, genital infections, with candida species, occurred more frequently in the SGLT2 group. Women with a history of genital infections were increasingly at risk. The prevalence was found to be around 10% in women and 5% in men[32]. Nonetheless, these infections tend to be non-severe and manageable without discontinuing the SGLT2 inhibitor[33]. Furthermore, at drug initiation, a small reduction in the estimated glomerular filtration rate (eGFR) and an increase in serum creatinine concentration are expected and are fully reversible. This is likely caused by a combination of the prerenal effect from osmotic diuresis and increased afferent arteriolar tone due to the tubular glomerular feedback mechanism[34]. As SGLT2 inhibitors work regardless of insulin secretion, the risk of hypoglycaemia is lower in comparison to other antidiabetic drugs and only

increased if SGLT2 inhibitors are combined with other antidiabetic drugs[27]. Euglycemic diabetic ketoacidosis is a rare adverse event in patients with DM type 2 treated with SGLT2 inhibitors and occurs with an incidence of < 0.1%[32]. It generally occurs in case of insulin deprivation and exposure to conditions such as after surgical intervention[35]. The CANVAS trial showed an increased risk of bone fractures and lower limb amputations in the study group taking canagliflozin. However, this could not be confirmed by other randomised controlled trials (RCT) with canagliflozin or other SGLT2 inhibitors, although there are some pharmacovigilance reports[35]. A meta-analysis including EMPEROR-Reduced and DAPA-HF trials also could not find significant differences in the incidence of bone fractures and lower limb amputations between the groups[36]. However, typical side effects seen with other drugs in the treatment of heart failure, such as hypotension, volume depletion, renal dysfunction, bradycardia, or hyperkalaemia have not been seen with SGLT inhibitors[37].

1.2.4 Mechanism of Cardiorenal Benefits

In large clinical CV outcome trials, a cardioprotective effect of SGLT2 inhibitors regardless of diabetes status has been observed[27]. The mechanisms are not yet fully understood but likely multifactorial as shown in figure 4. Cardio- and nephroprotective effects are measurable after a short period compared with effects caused by glucose control alone. Thus, the mode of action of SGLT2 inhibitors must be more than just blood sugar regulation[27, 38].

Glycaemic Control

SGLT2 inhibitors, originally classified as oral antidiabetics, are primarily used for reducing blood sugar through the inhibition of glucose reabsorption in the kidney and initiation of glucosuria. However, clinical studies show a moderate reduction of HbA1c by 0.5-0.7%[39]. Therefore, it is mostly used in combination with other antihyperglycemic drugs like metformin to fully achieve normal blood sugar values in patients with DM[40]. In comparison with other antidiabetic drugs, SGLT2

inhibitors as monotherapy do not cause hypoglycaemia, as it works independently from insulin secretion[20].

Na^+/H^+-Exchanger 1

SGLT2 inhibitors were shown to directly inhibit Na^+/H^+-exchanger 1 (NHE1). Thereby, intracellular Na^+ and Ca^{2+} are lowered and mitochondrial Ca^{2+} is increased, secondly via sarcolemmal and mitochondrial Na^+/Ca^{2+}-exchange. However, an increased concentration of mitochondrial Ca^{2+} activates adenosine triphosphate (ATP) synthesis and antioxidant enzymatic pathways which are associated with a reduction in oxidative stress and arrhythmogenesis[27, 41]. This mechanism leads to less autophagic cell death in cardiomyocytes, which improves cardiac function and survival in the long term. In animal models, empagliflozin was shown to significantly reduce infarct size and myocardial fibrosis after acute MI, irrespective of diabetes status in mice[42].

Reduction in Weight

Compared to a placebo, a weight loss of approximately 2 kg could be achieved after the first 6 months of treatment with SGLT2 inhibitors[43], whereby a plateau phase set in afterwards[44]. The underlying mechanisms are manifold. Weight loss due to loss of volume and calories during glucosuria, natriuresis and osmotic diuresis play a role[45]. Studies investigating the body composition during SGLT2 intake demonstrated, that most of the weight reduction is through the loss of fat mass and not only through the loss of body water[46]. SGLT 2 inhibitors improve fatty substrate utilization by decreasing blood sugar and insulin levels and inducing glucagon release, which stimulates lipolysis and lipid oxidation with associated ketogenesis[47]. However, excreting around 200 kcal per day should normally lead to a weight reduction of 10 kg in a year, whereas patients experience only a weight loss of 1 to 3 kg. Some studies show that compensatory hyperphagia in patients treated with SGLT2 inhibitors may play a role[46].

Anti-inflammatory Effect

Another cardioprotective mechanism of SGLT2 inhibitors is the reduction of cardiac inflammation. This occurs through various molecular pathways, whereas the activation of sirtuin 1 (SIRT1) could be an essential one[22]. Due to volume and weight reduction[20], a state of starving is imitated, whereby catabolic pathways are set in motion. This leads to the activation of SIRT1 and thus to increased gluconeogenesis and ketogenesis[48]. However, SIRT1 on the one hand interacts with hypoxia-inducible factor-2α (HIF-2α), which stimulates the erythropoietin (EPO) production and thus increases the haematocrit, and on the other hand with HIF-1α, which plays an important role in cardiac inflammation, which is decreased[22]. SIRT1 also activates other pathways like peroxisome proliferator-activated receptor-y coactivator 1- α (PGC1-α) and fibroblast growth factor 21 (FGF21). This results in decreased oxidative stress and inflammasome activation, but at the same time increased mitochondrial biogenesis and peroxisomal stability[48]. SLGT2 inhibitors also decrease circulating levels of tumour necrosis factor α (TNFα) and interleukin-6 (IL-6)[49], as well as high-sensitivity C-reactive protein (CRP) and leptin[22], which all in one leads to an anti-inflammatory effect[27].

Preservation of GFR and Reduction in Albuminuria

SGLT2 inhibitors at beginning of administration induce an acute reduction of GFR of about 5 ml/min/1.73m^2 in the first few weeks. After this initial dip, GFR improves back to baseline and maintains preserved even longer in patients taking SGLT2 inhibitors, for which renoprotective effects are responsible[27]. Preservation of kidney function occurs by various direct and indirect mechanisms. Through inhibiting SGLT2 in the early proximal tubule, glucose and sodium pass distally, which leads to increased sodium concentration at macula densa and thus increased tubuloglomerular feedback. This results in glomerular afferent arteriolar vasoconstriction and reduction of intraglomerular pressure and hyperfiltration[22, 44]. A meta-analysis of renal outcomes confirms the slower GFR decline and found a significantly reduced albuminuria, risk for microalbuminuria and macroalbuminuria, worsening nephropathy and risk of end-stage renal disease[50].

Effects on the Sympathetic Nervous System

Sympathetic hyperactivity is associated with increased BP and heart rate and promotes the development of arterial hypertension and heart failure[51]. SGLT2 inhibitors were found to reduce systolic BP by 4 mmHg and diastolic BP by 2 mmHg[43], even in patients already receiving antihypertensive treatment[34, 51]. Reduction of BP could be the result of weight loss, osmotic diuresis, and reduction in arterial stiffness[51]. In contrast to other anti-diabetic drugs, SGLT2 inhibitors do not increase heart rate, as this is also considered an independent CV risk factor[52]. This effect could be the result of dampening sympathetic nervous system activity[51]. The EMBODY trial could demonstrate a significant improvement in both, parasympathetic and sympathetic nerve activities in diabetic patients taking empagliflozin after acute MI[53]. A sympatholytic effect may contribute to the cardioprotective effects of SGLT2 inhibitors[22].

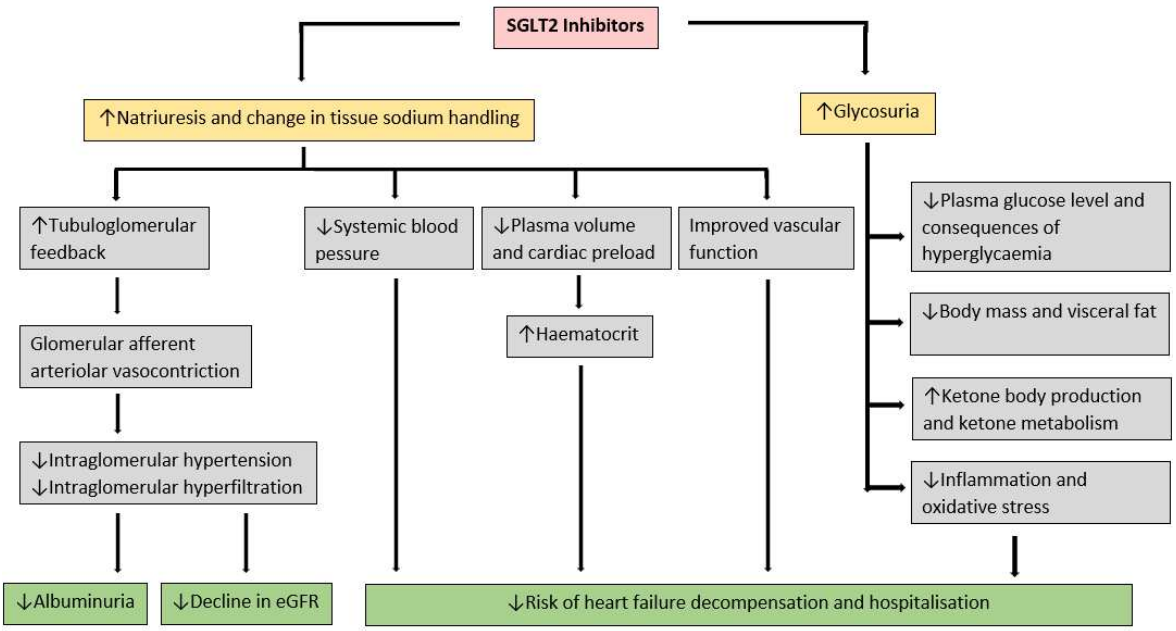

Figure 4: Cardiorenal effects of SGTL2 inhibitors, SGLT2 = sodium-glucose co-transporter 2, eGFR = estimated glomerular filtration rate

Adapted from Cowie MR et al. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycemic control. Nat Rev Cardiol. 2020

1.3 Outcome and Results of Previous Studies

SGLT2 inhibitors have shown beneficial results in large clinical CV outcome trials concerning cardiorenal protection regardless of diabetes status[27], whereas all-cause mortality, CV mortality, heart failure hospitalisation and emergency room visits due to heart failure could be significantly reduced compared to placebo[54]. The following chapter is dedicated to clinical outcome trials.

1.3.1 Cardiovascular Outcome Trials in Patients with DM II

A meta-analysis including 764 trials and 421.346 patients with DM type 2 demonstrated that SGLT2 inhibitors reduced the odds of nonfatal MI compared to placebo (odds ratio 0.87). Furthermore, CV mortality was lowered significantly compared with controls with an odds ratio of 0.84[55].
Notable among these trials are the EMPA-REG OUTCOMES trial for empagliflozin, the CANVAS program for canagliflozin, and the DECLARE TIMI-58 trial for dapagliflozin, whereas on average over 50% of patients had CAD and a large proportion had already suffered a MI[56]. A meta-analysis of these three placebo-controlled trials, which included a total of 34.322 patients, showed that heart failure hospitalisation was reduced by 23% in patients regardless of the presence of CAD and heart failure. In addition, the risk of MI was reduced by 11% and CV death by 16%, whereas there was no significant effect on stroke. The risk of progression to renal disease was reduced by 45% in the SGLT2 inhibitor group[57].

1.3.2 SGLT2 Inhibitors in Chronic Heart Failure

The DAPA-HF and EMPEROR-Reduced trials are the most significant trials for SGLT2 inhibitors, due to their large study population[54]. Both trials included over 3000 patients with LVEF ≤ 40%, New York Heart Association (NYHA) class II-IV and a GFR ≥ 30 ml/min/1.73m^2 (DAPA-HF) or eGFR > 20 ml/min/1.73m^2

(EMPEROR-Reduced) regardless of the diabetes status[37, 58]. The DAPA-HF trial, which enrolled 4744 patients, was the first published outcome trial to assess the effect of dapagliflozin in patients with heart failure with reduced ejection fraction (HFrEF) regardless of the diabetes status[58]. The EMPEROR-Reduced trial, which enrolled 3730 patients, was published afterwards and investigated the outcomes of empagliflozin in patients with HFrEF[37]. Both trials showed a reduction in the combined risk of CV death of first hospitalisation for heart failure by 26% in the SGLT2 inhibitor group. The composite of recurrent hospitalisation of heart failure or CV death was also reduced by 25% compared to the placebo. Furthermore, renal function and quality of life in symptomatic patients were significantly improved compared to controls[36]. Therefore, the SGLT2 inhibitors dapagliflozin and empagliflozin were incorporated into the first-line pharmacological treatment of heart failure by the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure alongside ACE inhibitors/ARNI, beta-blockers and MRA in 2021 regardless of diabetes status[14].

The EMPEROR-Preserved trial showed the benefits of empagliflozin in patients with heart failure with preserved ejection fraction (HFpEF). The trial enrolled 5988 patients with NYHA class II-IV symptoms and an LVEF > 40% to receive empagliflozin or a placebo in addition to recommended therapy. The primary outcome including CV death or heart failure hospitalisation was reduced by 21% in comparison to the placebo group[59]. Dapagliflozin showed similar results in patients with mildly reduced or preserved ejection fraction in the DELIVER-Trial. The composite outcome of worsening heart failure or CV death was reduced by 18% in the dapagliflozin group, whereas the results were similar in patients with LVEF > 60% and patients with LVEF < 60%[60].

1.3.3 SGLT2 Inhibitors in Chronic Kidney Disease

The EMPA-KIDNEY trial, which randomised a total of 6609 patients to empagliflozin or a matching placebo, investigated patients with chronic kidney disease during a median follow-up of 2 years. The primary outcome, a composite

of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to < 10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥ 40% from baseline, or death from renal causes) or death from CV causes, occurred in 13.1% of the empagliflozin group and 16% of the controls. Furthermore, the hospitalisation rate from any cause was significantly lower in the empagliflozin group[61]. Similar Data was also obtained by the DAPA-CKD Trial, which enrolled 4304 participants to receive dapagliflozin or a placebo over a median of 2.4 years. The primary outcome included a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes. In the dapagliflozin group, the primary outcome occurred in 9.2%, whereas in controls it occurred in 14.5%. Moreover, death occurred in 4.7% of patients in the dapagliflozin group and 6.8% of controls[62]. In both trials, all effects were regardless of diabetes status[61, 62].

1.3.4 SGLT Inhibitors in Myocardial Infarction

Due to outstanding results in large CV outcome trials among patients with type 2 diabetes, it is reasonable to consider SGLT2 inhibitors to improve outcomes of patients suffering a MI as well [56]. The effects of SGLT2 inhibitors in all phases of MI are discussed in the following paragraphs.

SGLT2 Inhibitors before Myocardial Infarction

Reduced Incidence of Myocardial Infarction

SGLT2 inhibitors have already been shown to reduce the incidence of MI in several meta-analyses[57, 63, 64]. One of them, including 71 trials and over 40.000 patients with DM, showed a reduction of MI by 23%[63]. Additionally, a real-world systematic review and meta-analysis of CV outcomes associated with SGLT inhibitors versus other glucose-lowering drugs, including 3.157.259 patients with

DM, could confirm these results by a 23% reduction of the incidence of MI in the SGLT2 inhibitor group[64].

Reduced Infarct Size and Cardiac Remodelling

A meta-analysis of preclinical animal models including a total of 224 animals found that SGLT2 inhibitors reduced myocardial infarct size on average by 33% in diabetic and non-diabetic animals, whereas the effect was moderately larger in diabetic animals. A significant reduction could be seen in both acute (< 24h) and chronic administration (> 24h), whereas the effect was greater in the latter[65]. An animal model study on 66 rats treated with empagliflozin for 7 days before MI demonstrated a reduction in infarct size by 20% compared to placebo. This was also associated with an improvement in LV function at 28 days post-MI[66]. An animal study on mice focusing on signalling pathways showed significantly increased signal transducer and activator of transcription 3 (STAT3) expression and phosphorylation and decreased levels of IL-6 and nitric oxide synthase (iNOS) expression in mice pre-treated with empagliflozin before initiation of ischemia/reperfusion-injury. Altogether, these effects are associated with the attenuation of cardiac fibrosis[67].

Empagliflozin was also found to increase the cardiac GTP enzyme cyclohydrolase 1 (cGCH1) protein levels in the myocardium, which is associated with decreased infarct size and cardiac remodelling[68]. An animal model with rats pre-treated with empagliflozin for 4 weeks before MI could demonstrate significantly improved cardiac remodelling parameters and reduced fibrosis and hypertrophy, regardless of the diabetes status. The underlying mechanism in this study was the significant increase in myocardial expression of cGCH1, which leads to increased cardiac NO levels and reduced O_2 levels, which altogether leads to reduced myocardial remodelling[69].

Besides the molecular pathways, cardioprotection and reduced infarct size are also influenced by effects on hemodynamics via reduced preload due to osmotic diuresis leading to a reduced wall tension and thus lower oxygen demand of the heart[70].

Reduced Inflammatory Burden

Despite this, the SGLT2-I AMI PROTECT registry which analysed patients with DM and acute MI undergoing PCI demonstrated a significantly reduced inflammatory response and smaller infarct size in patients already receiving SGLT2 inhibitors at admission compared to those taking other antidiabetic drugs. After 24 hours, inflammatory values were still significantly higher in the non-SGLT2 inhibitor group and additionally, a significant increase in neutrophil levels was observed. This did not occur in the SGLT2 inhibitor group. Another finding was the reduced stress hyperglycaemia at admission in patients taking SGLT2 inhibitors, although HbA1c levels did not differ between groups[71]. Patients with acute MI and hyperglycaemia are associated with a poorer prognosis[72].

Empagliflozin Induces Bone Marrow Naive B Cells

A recently published human and animal study has identified a new way in which empagliflozin has a cardioprotective effect. The study group found that high concentrations of B cell counts were associated with an improved ejection fraction and decreased infarct size in PCI patients after MI. Lymphopenia was associated with heart failure. Nonetheless, MI itself triggers the release of glucocorticoids, which induces autophagic death of bone marrow B cells and severely impaired B cell progenitor proliferation and differentiation. This leads to peripheral lymphopenia, which is not beneficial for myocardial recovery. However, they investigated the impact of empagliflozin on this process and could demonstrate, that empagliflozin significantly improved bone marrow naive B cell counts compared to the vehicle group. As shown in previous studies, a significantly improved LV function, fractional shortening, interventricular septum thickness and LV diameter, as well as reduced fibrotic scar size could be shown compared to controls[73].

SGLT2 Inhibition during Myocardial Infarction

The acute treatment of MI with an SGLT2 inhibitor shows heterogeneous results. In a meta-analysis of animal models, the acute administration of an SGLT2 inhibitor, 24 hours before infarct insertion, was found to significantly reduce infarct size compared to controls, even though much lower than in the chronically treated group[65]. However, in an animal model, where empagliflozin was given 1.5 hours before the MI, this effect could not be reproduced[66]. Similar results were found in an animal model with non-diabetic mice, where chronic oral administration for 6 weeks significantly reduced infarct size but acute administration 24 or 4 hours before infarct insertion did not show a reduction at all[74].

Nonetheless, the biochemical analysis demonstrated, that empagliflozin triggers the cardiac AMP-activated protein kinase (AMPK) pathway and reduces mitochondrial superoxide production under hypoxia and reoxygenation conditions. In this study, the mechanism resulted in significantly improved contractility in cardiomyocytes under hypoxia and improved recovery in the post-ischemic period[75].

On the other hand, acute administration of dapagliflozin and canagliflozin was found to be effective in the reduction of infarct size[76, 77]. A small-size animal model with rats investigated the effects associated with the administration of dapagliflozin during acute ischemia. As a result, infarction size could be reduced by 16%. Moreover, better LV function and reduced arrhythmias compared to controls were shown. These effects could be explained by lower myocardial cell apoptosis due to the upregulation of B-cell lymphoma 2 (BCL2). This leads to reduced ROS production and increased absorbance intensity which is associated with less mitochondrial swelling. All of them were significantly improved in the dapagliflozin group[76]. Similar results could be shown by canagliflozin, administered 5 minutes after the onset of ischemia via intravenous bolus. Acute canagliflozin treatment reduced infarct size by around 30% compared to controls[77].

All in one, this might lead to the conclusion that empagliflozin in comparison with dapagliflozin and canagliflozin does not have a direct effect on the heart, which could also explain the lack of effects when applied directly into isolated hearts[65].

SGLT2 Inhibition after Myocardial Infarction

Improved NT-proBNP and Left Ventricular Function

The EMMY trial, which randomised 476 patients irrespectively of DM status, demonstrated a significant reduction of 15% (95% CI -4.4 to -23.6%, p = 0.026) in NT-proBNP at week 26 in the patients taking empagliflozin after severe acute MI (CK > 800 IU/L) in addition to recommended medical therapy. A significant reduction could already be observed after 12 weeks of the treatment (p = 0.021). Empagliflozin was initiated within 72 hours after PCI.

Functional and structural echocardiographic parameters also showed significant improvement. LVEF increased by absolute 1.5% (95% CI 0.2 to 2.9%, p = 0.029) more in the empagliflozin group, whereas the difference was already significant after 6 weeks (1.7%, 95% CI 0.35 to 3.05%, p = 0.014). The echocardiographic parameter E/e´, which demonstrates the diastolic function of the left ventricle, demonstrated a significant reduction by 6.8% (95% CI -4.4 to -23.6%) in the empagliflozin group compared with placebo. Furthermore, LV end-diastolic and end-systolic volumes showed significant improvement being 9.7 mL (95% CI -15.7 to -3.7 mL, p = 0.0015) and 7.5 mL (95% CI -11.5 to -3.4 mL, p = 0.0003) lower in the empagliflozin group. Within all participants who received empagliflozin, a significantly higher beta-hydroxybutyrate level could be detected at week 6 and 26 (Δ = 41.9%; 95% CI 21.8 to 63.8%, p < 0.0001), which is associated with reduced cardiac necrosis. As expected, body weight reduction was significantly greater in the empagliflozin group compared to the placebo (Δ = -1.76 kg; 95% CI -3.27 to -0.25 kg, p = 0.022)[78].

Accordingly, the early initiation of an SGLT2 inhibitor after an ischemic event would be essential, as remodelling processes in the heart are immediately inserted[56]. However, the EMBODY trial, which analysed the impact of empagliflozin on sympathetic and parasympathetic activity found no significant difference in NT-proBNP between the empagliflozin and placebo group. This was probably due to a small sample size of 105 patients[53]. There are few clinical studies investigating the use of SGLT2 after MI. However, two large RCTs, the “EMPACT-MI” and “DAPA-MI”, are ongoing to investigate the use of empagliflozin and dapagliflozin after acute MI with the composite endpoint of CV death and

hospitalisation for heart failure. The EMPACT-MI trial enrolled 6500 patients randomised within 14 days after MI and a follow-up period of 26 months including 465 centres[79] and the DAPA-MI trial including 6400 patients randomised within 10 days after MI and a follow-up period of up to 3 years including 113 centres. The results of these studies are expected to be completed in 2023[80].

Improvement of Post-Infarction Cardiac Remodelling

Similar results could also be demonstrated in an animal model study on 14 non-diabetic rats with follow-ups at 2 and 4 weeks, treated immediately after MI by daily empagliflozin, which resulted in significantly lower myocardial fibrosis compared to placebo. This was associated with a lower expression of transforming growth factor-beta 1 (TGF-ß1) by 49% and Smad3 by 47% following the empagliflozin treatment. Both are key proteins in the fibrosis pathway and are responsible for myocardial fibrosis and ventricular remodelling[81]. In a similar animal model, a significantly reduced expression of the fibrosis markers collagen 1 and procollagen was shown[82].

Empagliflozin was also found to activate the AMPKα signalling pathway, which results in attenuation of oxidative stress, inhibition of apoptosis and maintenance of mitochondrial membrane potential integrity. All in one, these effects were responsible for improved cardiac function, reduced infarct size and interstitial fibrosis in non-diabetic mice, which received empagliflozin for a duration of 2 weeks after induced MI[83].

Another animal model study enrolled 50 non-diabetic rats after MI and compared empagliflozin with fosinopril, bisoprolol and spironolactone taking a daily dose for 3 months (after a titration period of 1 month). Empagliflozin exhibited maximal physical tolerance as maximum activity time (MAT) on a treadmill compared with all others. MAT decreased in all groups after 3 months of treatment but in the rats only treated with empagliflozin, MAT was significantly higher. This effect was associated with improved cardiac and renal function. Empagliflozin, as expected, also slowed the progression of LV dysfunction in terms of preventing LV remodelling[84]. The increased myocardial uptake of ketone bodies also plays an important role in the cardioprotective effect of SGLT2 inhibitors, as it leads to

improved work efficiency in the myocardial cells. The enhanced energetic state results in reduced cardiac necroses and improved cardiac function[56]. In the EMMY trial including 476 patients after acute large MI, significantly increased beta-hydroxybutyrate levels in patients taking empagliflozin in addition to guideline-recommended therapy, were observed after 12 and 26 weeks[78].

1.4 Right Atrial Function

An apical RV-focused four-chamber view is necessary for the acquisition of right atrial function. In clinical practice the size of the right atrium is usually measured end-systolic, just before the tricuspid valve opens, using monoplane 2D volumetry "area-length". The right atrial ESV can then be indexed to the body surface area. This value is called RAVI. Men have larger volumes than women, although the reason for this is yet unclear[85, 86].

The sPAP should be determined to estimate the right atrial pressure. This requires the measurement of a maximum systolic RV/RA gradient and the maximum velocity of a tricuspid regurgitation jet. Furthermore, in the subcostal axis, the inferior vena cava must be assessed for its width and inspiratory collapse. An sPAP of < 37 mmHg is considered normal[85-87].

	Normal values
RA minor axis dimension [mm]	≤ 44 [41-46]
RA major axis dimension [mm]	≤ 53 [51-55]
RA end-systolic area [cm^2]	≤ 18 [17-20]
2D echocardiographic RA volume [ml/m^2]	♂ 25 ± 7 ♀ 21 ± 6
sPAP [mmHg]	< 37
RA GLS [%]	48 ± 13

Table 3: Normal RA echocardiographic parameters, sPAP = systolic pulmonary artery pressure, GLS = global longitudinal Strain, RA = right atrial

The strain is a dimensionless deformation parameter which describes the shortening or thickening of myocardial segments in percentage. The formula is shown below. A negative deformation indicates contraction or dilution, and a positive deformation indicates dilatation or thickening[88]. Strain analysis is useful in clinical practice, as it provides additional information about the segmental and global function of the region of interest[89].

$$Strain = (length_{end-diastolic} - length_{end-systolic})/length_{end-diastolic}$$

For measurement, “Speckle tracking technology" is used, as it is independent of the angle of the ultrasound beams on the myocardium. The naturally occurring speckled pattern of the myocardium created by stroking the ultrasound beams, so-called "speckles" are stored by the software and tracked during the entire cardiac cycle. From the spatial shifts, the strain is calculated according to the formula mentioned above for the respective segment (segmental) or the whole myocardium (global)[88]. In clinical practice, the GLS of the left and right ventricles is particularly useful; strains of the left and right atrium are not yet routine clinical practice[90].

1.5 Aim of the Thesis

The main aim of this thesis is to investigate right atrial echocardiographic parameters after MI and whether the additional intake of empagliflozin causes a significant improvement in these functions. Previously, there has not yet been a study that has investigated a systematic echocardiographic evaluation of the right atrium after an acute MI and treatment with empagliflozin in addition to recommended medication.

Furthermore, correlations between right atrial strain and other common right echocardiographic parameters, especially RAVI, RAEF, and the laboratory parameter NT-proBNP, CK and high-sensitive Troponin are analysed.

2 Methods

The patients included in this thesis are part of the study population of the EMMY trial *(EMpagliflozin in Myocardial Infarction)* performed at the Clinical Department of Cardiology at the Medical University of Graz.

2.1 Study Overview and Study Population

2.1.1 The EMMY Trial

The EMMY trial is the first clinical trial that investigated the effects of empagliflozin on laboratory heart failure markers and functional and structural echocardiographic parameters in patients with acute MI. It was published in the European Heart Journal[78].

The multicentre, randomised, double-blind, placebo-controlled phase IIIb study investigated the effect of 10 mg empagliflozin administered once daily perorally in patients after an acute MI for a follow-up period of 26 weeks. The study enrolled and examined patients between the 11th of May 2017 to the 3rd of May 2022.

Permission to conduct this trial was granted by the Ethics Committee of the Medical University of Graz (EC 29-179 ex 16/17; EudraCT 2016-004591-22) and the trial was registered on Clinical Trials.gov (NCT03087773).

In the EMMY trial, a total of 476 probands with an acute large MI (CK > 800 IU/L), were included. After signing an informed consent, patients were randomised 1:1 to the 10 mg empagliflozin group or matching placebo using a randomizer software, whereas the randomisation was stratified by site, presence of DM type 2 and by gender.

The empagliflozin or the placebo were initiated within 72 hours after PCI. Afterwards, the patients were invited to a total of three visits at 6, 12, and 26 weeks after study inclusion and received an examination of cardiac laboratory parameters and cardiac function using echocardiography. Laboratory parameters were measured at local laboratories and the Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz. Echocardiography

was performed with locally available ultrasound devices following the current guidelines of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE)[91, 92].

Inclusion criteria were age between 18 and 80 years, acute MI with CK > 800 IU/L, a troponin T-level (or troponin I-level) > 10x ULN plus in addition one of the following criteria: symptoms of ischemia, electrocardiogram (ECG) changes in terms of new ischemia or new regional wall motion abnormality. Furthermore, there had to be hemodynamic stability and freedom from catecholamines with $RR_{systolic}$ > 110 mmHg and $RR_{diastolic}$ > 70 mmHg before the first drug dosing.

Exclusion criteria were the presence of other forms of DM than type 2, the occurrence of ketoacidosis in the history, blood pH < 7.32, known allergy to SGLT2 inhibitors, hemodynamic instability, > 1 episode of severe hypoglycaemia within the last 6 months, females of childbearing age without adequate contraception, acute UTI or genital infection and previous use of SGLT2 inhibitors.

2.1.2 Subgroup Analysed for the Diploma Thesis

For this diploma thesis, a total of 219 patients of the EMMY trial were included. The primary endpoint is the change in atrial GLS over a period of 26 weeks. Secondary endpoints are changes in atrial echocardiographic parameters such as dimensions and volumes as well as sPAP within this observation period. Furthermore, correlations between the individual echo parameters, as well as the NT-proBNP, are investigated. Previously stored echocardiography loops were analysed with the post-processing programme TomTec (TOMTEC Imaging Systems, Munich, Germany) and additional required data was obtained from openMEDOCS. For statistical analyses IBM SPSS statistics 26 (IBM Corporation, Armonk/New York, US) was used. Due to withdrawal of consent, non-attendance of control appointments or death during the study period, datasets of 206 subjects (171 male and 35 female) could ultimately be used for the statistical analyses.

2.2 Study Medication

Empagliflozin is an oral antidiabetic drug primarily taken as monotherapy or in combination with other antidiabetic drugs to lower blood sugar.
Participants of the EMMY trial received one tablet daily in the morning containing either 10 mg empagliflozin or a placebo. The pale-yellow tablet was round and biconvex, with the imprint “S10” on one side and the Boehringer Ingelheim logo on the other side. The study medication should be swallowed whole with water and the intake was independent of food intake. If a tablet was forgotten, it should have been taken as soon as the patient remembered, whereas the intake of two doses was not allowed on the same day. The study medication was packed by Landesapotheke Salzburg.

2.3 Transthoracic Echocardiography

Each patient received three echocardiographic examinations, at baseline, after 6 and after 26 weeks, performed by an experienced cardiologist with locally available ultrasound devices. An ECG was applied simultaneously so that end-diastole and end-systole could be defined. Recorded loops were afterwards stored in DICOM format and analysed offline with the Software Programme TomTec (TOMTEC Imaging Systems, Munich, Germany).
Following the current guidelines of the EACVI and the ASE[91, 92], the protocol included 2D, Doppler echocardiography and M-mode imaging. For measuring right atrial volumes, dimensions, and strain a right ventricular (RV) focused apical four-chamber view was taken.

2.4 Echocardiographic Parameters

2.4.1 Right Atrial Strain

The right atrial strain was obtained following the current guidelines of the EACVI/ASE/Industry Task Force[90] using the post-processing programme TomTec (TOMTEC Imaging Systems, Munich, Germany).

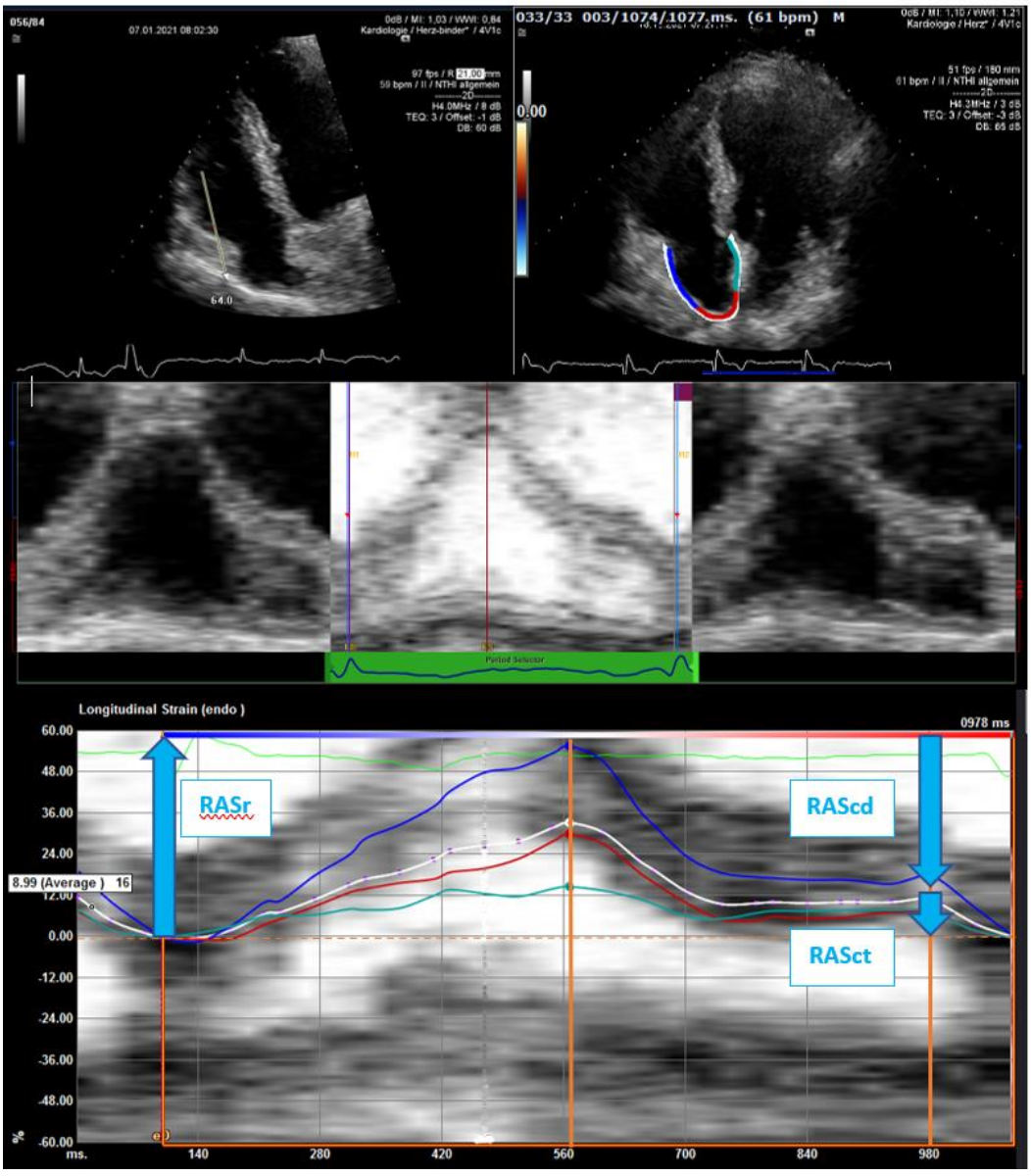

Figure 5: Example of right atrial strain and functional phasis in RV-focused apical four-chamber view using the software TomTec, RASr = strain during reservoir phase, RAScd = strain during conduit phase, RASct = strain during contraction phase.

For right atrial strain, the EACVI/ASE/Industry Task Force recommends the recording of an RV-focused apical four-chamber view[90]. The pre-set of the left atrium was selected, as there was none for the right atrium yet. After the M-mode was placed in the lateral/anterior tricuspid annulus, the time points of end-diastole and end-systole had to be marked in accordance with the simultaneously recorded ECG[88]. After that, the endomyocardial border was automatically outlined in both end-diastolic and end-systolic frames, allowing the investigator to adjust individual points if necessary.

The tracing of the right atrium should start at the tricuspid valve annulus, go along the endocardial border of the lateral wall, roof, and septal wall, and should end at the opposite tricuspid annulus as shown in figure 5[90]. Afterwards, imaging software uses different algorithms to process the image to calculate the myocardial motion[93].

Right atrium function is distinguished into three functional phases. The reservoir function, which serves for venous filling of the atria during systole, is followed by a conduit function, a passive conveyance of blood to the ventricle during the early diastole. In the end, the booster pump function actively forces blood into the ventricle in the late diastole[94, 95]. For this purpose, a simultaneous distinction is made between reservoir strain, conduit strain and contractile strain[96].

2.4.2 Right Atrial Dimensions and Systolic Pulmonary Artery Pressure

The dimensions and volumes of the right atrium were measured according to the current guidelines[85, 86, 91]. The RAEF is calculated using Simpson's method. RAVI was calculated in Excel using the formula shown below.

$$RAVI = \frac{RAV}{BSA}$$

$$RAV = \frac{8}{3} * \pi * \frac{{A_{4CH}}^2}{L}$$

RAV= right atrial volume [ml]
RAVI= right atrial volume index [ml/m^2]
A= right atrial area [cm^2]
L= major axis [cm]

2.4.3 Systolic Pulmonary Artery Pressure

Echocardiographic estimation of sPAP was determined according to current guidelines on the Echocardiographic Assessment of the Right Heart[86] and the ESC/ESR guideline on pulmonary arterial hypertension[87]. The data on sPAP was taken from the respective findings stored in openMEDOCS. In approximately 10% of the cases, the sPAP value was not reported in the findings. If suitable loops with the recording of the TI-Jet and vena cava respiratory modulation were available, it was calculated.

2.5 Data Analysis and Statistics

The gathered dimensions and volumes, as well as the sPAP, were manually transferred to Excel (Microsoft Office 365, Microsoft Corporation, Redmond, US). Data from strain analyses were merged using a macro and then cleaned in Excel. For statistical analyses, data was imported to IBM SPSS statistics 26 (IBM Corporation, Armonk/New York, US). Unless specifically stated, all values refer to the right atrium.

The entire data was tested for normal distribution by graphic evaluation and the Shapiro-Wilk test. For comparison of mean values within a group, the T-Test for paired samples was used in normally distributed data. The Mann-Whitney-U-Test was used for not normally distributed data. For the comparison of values between the placebo and non-placebo groups, the T-test for unpaired values was used. Correlations were examined using the Pearson correlation coefficient for normally distributed data and the Spearman's rank correlation coefficient for non-normally distributed data. In general, statistically significant results were assumed with a p-value < 0.05.

Only data of the endomyocardial GLS corresponds to a normal distribution. The following parameters are not normally distributed: EDV, ESV, endomyocardial

GCS, RAEF, RAVI, sPAP, NT-proBNP, HbA1c, CK, hsTroponin, body mass index (BMI), BP and age.

To ensure reliability, all echocardiographic measurements, including dimensions, volumes and strain analysis of the right atrium were carried out twice. For the volumes, the mean value of a total of four measurements was included. This is because additionally to the two manual measurements, volumes were also automatically calculated in the strain analysis.

3 Results

The following chapters focus on the results of the statistical analyses of this thesis. Correlation coefficients are listed in the appendix.

3.1 Subjects

A total number of 206 patients was included in the statistical analyses of this work. The gender distribution was 83% (n = 171) for male and 17% (n = 35) for female.
At baseline, the study population showed a mean age of 58 ± 9.3 years (males 57.7 ± 9.3 and females 59.3 ± 9.2). The youngest patient was 33 years old in the male group and the oldest was 80 years old in the female group.

The average baseline BMI was 28.4 ± 4.2 kg/m^2, with no significant difference within the gender groups (males 28.5 ± 3.8 kg/m^2 and females 27.6 ± 5.4 kg/m^2, p = 0.091). According to the current guidelines on adult obesity management[97], 18.9% (n = 38) of the study population were classified as normal weight, 52.2% (n = 105) met the criteria of overweight and 28.9% (n = 58) were classified as obese. In 5 patients, weight was not determined.

The mean HbA1c of the study population was 5.9 ± 1.1% with no significant difference between gender groups (males 5.9 ± 1.1% and females 5.6 ± 0.4%, p = 0.5). Overall, 12.9% (n = 25) of the study probands had established DM type 2, whereas 12.9% (n = 22) of the men and 8.6% (n = 3) of the women were affected.

The median of CK at baseline measuring infarct size was 1619 U/l with no significant difference in gender groups (males 1623 U/l and females 1605 U/l, p = 0.485). The high-sensitive troponin level measuring myocardial injury averaged 3623 pg/ml at initial examination and showed no significant difference between men and women (males 3668 pg/ml and females 3242 pg/ml, p = 0.482). The median of NT-proBNP was 1362 pg/ml at baseline, whereas there was a

significant difference between women and men (males 1227 pg/ml and females 2118 pg/ml, $p < 0.001$).

The average systolic BP at baseline was 125.2 ± 9.4 mmHg and the diastolic BP averaged 78.1 ± 6.1 mmHg. The BP did not differ significantly between the gender groups (systolic BP $p = 0.121$, diastolic BP $p = 0.950$). Overall, 33% (n = 68) of all study subjects had diagnosed arterial hypertension, whereas of male participants 31.6% (n = 54) and of female participants 40% (n = 14) were affected.

Overall, 81.1% (n = 167) of the study population suffered a STEMI, including 80.1% (n = 137) of the men and 85.7% (n = 30) of the women. A total of 18.9% (n = 39) had an NSTEMI.

3.2 End-Diastolic and End-Systolic Volumes

At baseline, right atrial EDV and ESV were measured in 203 patients (169 males and 34 females). The average value in all study subjects for EDV was 25.3 ± 11.7 ml (male 25.8 ± 11.6 ml and female 22.5 ± 12 ml) and for ESV 49.8 ± 17.6 ml (male 51 ± 17.7 and female 43.9 ± 15.9 ml). These measurements occurred before the initiation of the study drug, whereas both values did not differ significantly between the empagliflozin and the placebo group (EDV: 24.9 ± 10.1 ml vs. 25.6 ± 13.2 ml, $p = 0.825$ and ESV: 49.2 ± 16.6 ml vs. 50.3 ± 18.6 ml, $p = 0.755$).

After 6 weeks, right atrial EDV and ESV were evaluated in 199 study participants (166 males and 33 females). The mean EDV in the empagliflozin group was 26.7 ± 10.3 ml (males 26.9 ± 10.4 ml and females 25.3 ± 10.4 ml) and in controls 29.2 ± 14.4 ml (males 31.2 ± 14.5 ml and females 21.9 ± 11.8 ml). ESV in the empagliflozin group was 50.2 ± 15.2 ml (males 50.9 ± 15 ml and females 44.6 ± 15.8 ml) and in the placebo group 55. ± 21.7 ml (male 58.7. ± 21.5 ml and female 41.4 ± 16.4 ml). The differences between empagliflozin and controls in EDV and ESV were insignificant ($p = 0.161$ and $p = 0.335$). However, a significant difference

could indeed be found among the men in both EDV and ESV (p = 0.031 and p = 0.011).

At week 26, right atrial EDV and ESV values were obtained from a total of 200 study subjects (165 males and 35 females). The EDV in the empagliflozin group averaged 28.7 ± 13.2 ml (males 29.6 ± 13.7 ml and females 23.3 ± 8.1 ml) and in the placebo group 31 ± 15 ml (males 32.6 ± 12.9 ml and females 24.8 ± 20.2 ml). The mean ESV in the empagliflozin group was 53.1 ± 17.7 ml (males 54.9 ± 17.5 ml and females 42.1 ± 14.6 ml) and in the placebo group 55.4 ± 19.8 ml (males 58.3 ± 17.7 ml and females 44.5 ± 23.7 ml). In both EDV and ESV, no significant difference could be found (p = 0.164 and p = 0.467) between the empagliflozin and placebo group. However, gender analyses show a significant difference in men concerning EDV (p = 0.021). ESV in men showed no significant difference (p = 0.151).

Right atrial EDV at the baseline examination demonstrated a significant negative correlation with right atrial GLS, GCS and RAEF and a positive correlation with ESV and RAVI. In addition, EDV correlated negatively with NT-proBNP at the third measurement point.
ESV showed significant positive correlations with RAVI and EDV and a negative correlation with NT-proBNP. At the third measurement point, ESV also correlated significantly with GLS and RAEF.

3.3 Right Atrial Volume Index

At baseline, RAVI was calculated in 203 patients (169 males and 34 females). The mean value in the study population was 24.9 ± 9.2 ml/m^2 (males 25 ± 9.3 ml/m^2 and females 24.4 ± 9 ml/m^2). The empagliflozin and placebo groups did not differ significantly (empagliflozin 24.5 ± 8.2 ml/m^2 and the placebo 25.3 ± 10.2 ml/m^2, p = 0.804) at baseline examination.

At week 6, RAVI was assessed in 198 study participants (165 males and 33 females). The average value in the empagliflozin group was 25.4 ± 7.7 ml/m^2 (males 25.4 ± 7.3 ml/m^2 and females 25.5 ± 10.5 ml/m^2) and in the placebo group 28 ± 10.9 ml/m^2 (males 29.3 ± 11.1 and females 23.4 ± 8.7). The values between the empagliflozin group and controls closely miss the significance threshold (p = 0.064). Gender analyses demonstrate a significant difference between empagliflozin and placebo in men (p = 0.007).

After 26 weeks, RAVI values were obtained from 200 study subjects (165 males and 35 females). The mean RAVI in the empagliflozin group was 27.3 ± 8.8 ml/m^2 (males 27.9 ± 8.8 ml/m^2 and females 23.6 ± 7.8 ml/m^2) and in controls 28.3 ± 10.3 ml/m^2 (males 29.1 ± 9.3 ml/m^2 and females 25.2 ± 12.9 ml/m^2). No significant difference could be found between the empagliflozin and placebo group (p = 0.572).

RAVI at baseline examination showed a significant positive correlation with both right atrial EDV and ESV. Furthermore, a negative correlation could be demonstrated with NT-proBNP. At the third measurement point, RAVI also correlated significantly with right atrial GLS.

3.4 Right Atrial Ejection Fraction

At the baseline examination, RAEF was measured in 203 participants (169 males and 34 females). The mean RAEF in all patients was 49.5 ± 10.6% (males 49.5 ± 10.6% and females 49.5 ± 10.7%). As the measurement occurred before the initiation of the study drug, mean values did not differ significantly between the empagliflozin and placebo group (empagliflozin 49.5 ± 9.9% and placebo 49.5 ± 11.3%, p = 0.911).

At week 6, RAEF was evaluated in 199 study subjects (166 males and 33 females). RAEF in the empagliflozin group averaged 46.8 ± 10.6% (males 47.3 ±

10.3% and females 43.4 ± 12.4%) and in the placebo group 47.3 ± 9.9% (males 47.2 ± 10.1% and females 47.7 ± 9.5%) with no significant difference (p = 0.580).

After 26 weeks, the RAEF value was obtained from a total of 200 patients (165 males and 35 females). In the empagliflozin group the mean RAEF was 46.8 ± 10.6% (males 46.6 ± 10.8% and females 44 ± 9%) and in the placebo group 45 ± 10.2% (males 44.4 ± 10.1% and females 47.4 ± 10.6%) with no significant difference (p = 0.388). Gender analyses also showed no significance (males p = 0.132 and females p = 0.213).

RAEF showed significant negative correlations with right atrial EDV and NT-proBNP at the first measurement point. Additionally, a significant positive correlation could be shown between right atrial GLS and GCS. At the third measurement time point, an additional correlation with ESV was determined.

3.5 Systolic Pulmonary Artery Pressure

At the baseline examination, sPAP could be obtained in a total of 168 patients (135 males and 33 females). Due to a missing or too weak tricuspid signal, measurements could not be conducted on all participants. The average sPAP of the study population was 30.4 ± 7 mmHg (males 29.9 ± 6.8 mmHg and females 32.3 ± 7.8 mmHg). The mean sPAP value did not differ significantly between empagliflozin 30 ± 6.6 mmHg and placebo group 30.7 ± 7.5 mmHg (p = 0.559).

At week 6, sPAP was measurable in 177 study subjects (148 males and 29 females). In the empagliflozin group, sPAP averaged 30.6 ± 6.1 mmHg (males 30.7 ± 6.3 mmHg and females 29.8 ± 3.7 mmHg) and in controls 30.6 ± 9.3 mmHg (males 30.1 ± 9.7 mmHg and females 32.4 ± 7.8 mmHg) with no significant difference (p = 0.226).

After 26 weeks, sPAP could be assessed in 188 patients (155 male and 33 female). The mean sPAP in the empagliflozin group was 29.3 ± 7 mmHg (males

29.6 ± 7.4 mmHg and females 27.5 ± 4 mmHg) and in the placebo group 29.6 ± 7.8 mmHg (males 29.4 ± 8.4 mmHg and females 30.4 ± 5.4 mmHg) with no significant difference (p = 0.821).

A significant positive correlation between sPAP and NT-proBNP could be demonstrated at baseline examination. At the third measurement point, sPAP also strongly correlated with right atrial GLS.

	Baseline			Week 6			Week 26		
	Empagliflozin	Placebo	P-Value	Empagliflozin	Placebo	P-Value	Empagliflozin	Placebo	P-Value
EDV [ml]	24.9 ± 10.1	25.6 ± 13.2	0.825	26.7 ± 10.3	29.2 ± 14.4	0.161	28.7 ± 13.2	31 ± 15	0.164
	♂25.1 ± 10.4	♂26.6 ± 12.9	0.645	♂ 26.9 ± 10.4	♂ 31.2 ± 14.5	0.031	♂ 29.6 ± 13.7	♂ 32.6 ± 12.9	0.021
	♀23.4 ± 8.9	♀21.8 ± 13.9	0.327	♀ 25.3 ± 10.4	♀ 21.9 ± 11.8	0.262	♀ 23.3 ± 8.1	♀ 24.8 ± 20.2	0.522
ESV [ml]	49.2 ± 16.6	50.3 ± 18.6	0.755	50.2 ± 15.2	55. ± 21.7	0.335	53.1 ± 17.7	55.4 ± 19.8	0.467
	♂49.5 ± 17.1	♂52.6 ±18.3	0.211	♂ 50.9 ± 15	♂ 58.7. ± 21.5	0.011	♂ 54.9 ± 17.5	♂ 58.3 ± 17.7	0.138
	♀47.6 ± 13.3	♀41.4 ± 17.4	0.184	♀ 44.6 ± 15.8	♀ 41.4 ± 16.4	0.410	♀ 42.1 ± 14.6	♀ 44.5 ± 23.7	1.000
RAVI [ml/m²]	24.5 ± 8.2	25.3 ± 10.2	0.804	25.4 ± 7.7	28 ± 10.9	0.064	27.3 ± 8.8	28.3 ± 10.3	0.572
	♂24.2 ± 8.3	♂26 ± 10.3	0.240	♂ 25.4 ± 7.3	♂ 29.3 ± 11.1	0.007	♂ 27.9 ± 8.8	♂ 29.1 ± 9.3	0.347
	♀27 ± 7.8	♀22.5 ± 9.5	0.080	♀ 25.5 ± 10.5	♀ 23.4 ± 8.7	0.736	♀ 23.6 ± 7.8	♀ 25.2 ± 12.9	0.946
RAEF [%]	49.5 ± 9.9	49.5 ± 11.3	0.911	46.8 ± 10.6	47.3 ± 9.9	0.580	46.8 ± 10.6	45 ± 10.2	0.388
	♂49.2 ± 9.8	♂49.8 ± 11.5	0.628	♂ 47.3 ± 10.3	♂ 47.2 ± 10.1	0.480	♂ 46.6 ± 10.8	♂ 44.4 ± 10.1	0.132
	♀51.4 ± 11	♀48.2 ± 10.6	0.234	♀ 43.4 ± 12.4	♀ 47.7 ± 9.5	0.132	♀ 44 ± 9	♀ 47.4 ± 10.6	0.213
sPAP [mmHg]	30 ± 6.6	30.7 ± 7.5	0.559	30.6 ± 6.1	30.6 ± 9.3	0.226	29.3 ± 7	29.6 ± 7.8	0.821
	♂29.6 ± 6.6	♂30.2 ± 7	0.578	♂ 30.7 ± 6.3	♂ 30.1 ± 9.7	0.066	♂ 29.6 ± 7.4	♂ 29.4 ± 8.4	0.620
	♀31.8 ± 6.6	♀32.6 ± 8.8	0.855	♀ 29.8 ± 3.7	♀ 32.4 ± 7.8	0.393	♀ 27.5 ± 4	♀ 30.4 ± 5.4	0.050
GLS [%]	36.1 ± 10.1	36.1 ± 10.2	0.500	34.9 ± 9.5	34.7 ± 9.4	0.450	35.5 ± 10.9	33.5 ± 8.5	0.149
	♂35.8 ± 9.7	♂36.1 ± 10	0.840	♂ 35 ± 9.4	♂ 34.5 ± 9.3	0.364	♂ 35.6 ± 11.3	♂ 32.7 ± 8	0.056
	♀38 ± 12.5	♀36 ± 11.3	0.642	♀ 34.5 ± 10.7	♀ 35.8 ± 9.9	0.362	♀ 34.6 ± 8.5	♀ 36.5 ± 9.8	0.276

Table 4: Overview of right atrial echocardiographic outcome parameters. EDV = end-diastolic volume, ESV = end-systolic volume, RAVI = right atrial volume index, RAEF = right atrial ejection fraction, sPAP = systolic pulmonary artery pressure, GLS = global longitudinal strain

3.6 Right Atrial Global Longitudinal Strain

At baseline, right atrial GLS was measured in a total of 203 patients (169 males and 34 females). The mean GLS of all patients was 36.1 ± 10.2% (males 35.9 ± 10% and females 36.8 ± 11.7%).

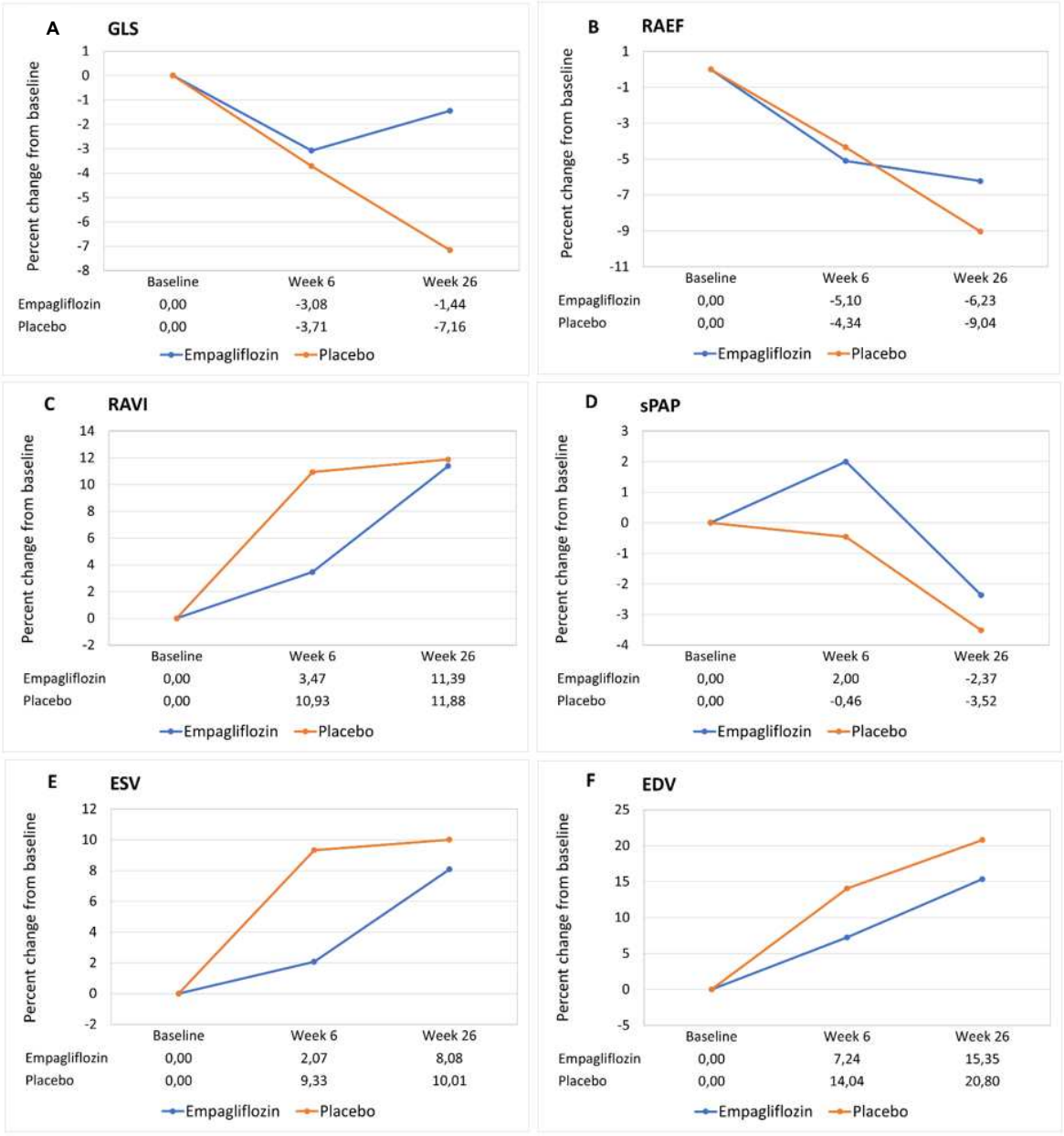

Figure 6: Percent changes of mean values in echocardiographic parameters by treatment group: (A) right atrial global longitudinal strain, (B) right atrial ejection fraction, (C) right atrial volume index, (D) systolic pulmonary artery pressure, (E) right atrial end-systolic volume, (F) right atrial end-diastolic volume

Empagliflozin and placebo group showed no significant difference, whereas the mean GLS of the empagliflozin group was 36.1 ± 10.1% and the placebo group 36.1 ± 10.2% (p = 0.500).

After 6 weeks, right atrial GLS values could be collected from 199 study participants (166 males and 33 females). In the empagliflozin group, GLS averaged 34.9 ± 9.5% (males 35 ± 9.4% and females 34.5 ± 10.7%) and in controls 34.7 ± 9.4% (males 34.5 ± 9.3% and females 35.8 ± 9.9%) with no significant difference (p = 0.450).

At week 26, right atrial GLS was measured in 200 patients (165 males and 35 females). In the empagliflozin group the mean GLS was 35.5 ± 10.9% (males 35.6 ± 11.3% and females 34.6 ± 8.5%) and in the placebo group 33.5 ± 8.5% (males 32.7 ± 8% and females 36.5 ± 9.8%). A significant difference between both groups could barely not be achieved (p = 0.075). However, as in other parameters, gender analyses show a significant difference in men (p = 0.028).

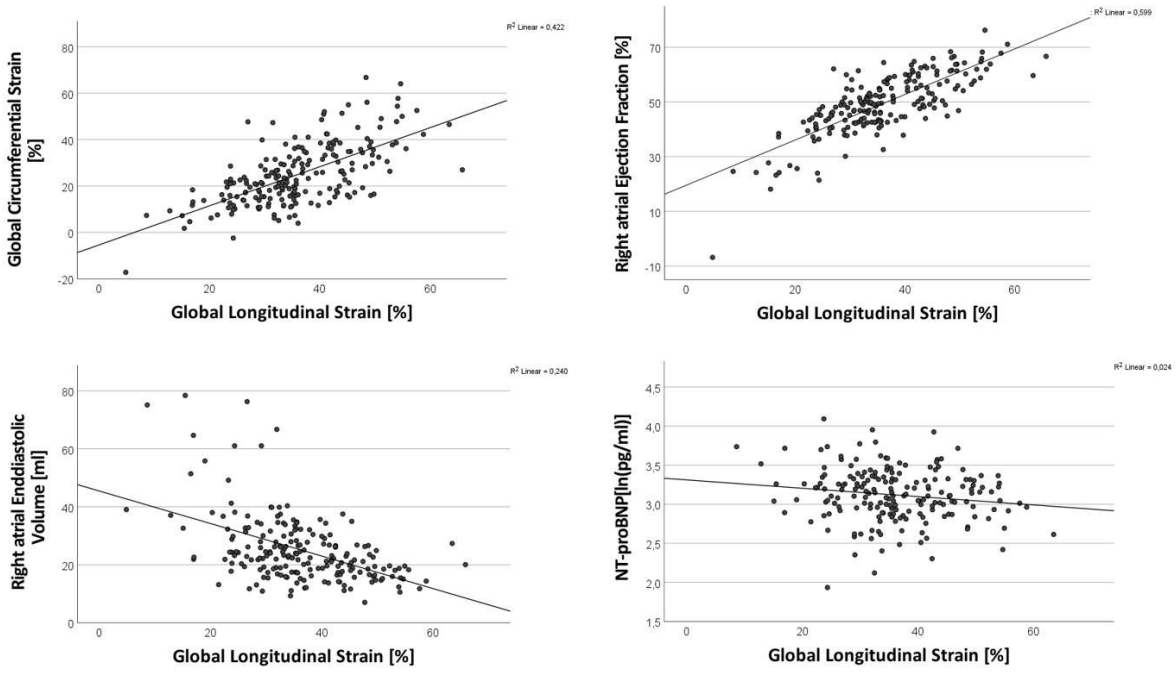

Figure 7: Correlation between right atrial GLS and right atrial EDV, GCS, NT-proBNP and RAEF

At the baseline examination, a significant positive correlation could be demonstrated with RAEF and GCS and a negative correlation with right atrial EDV and NT-proBNP as shown in figure 7. At the second examination, GLS correlated in addition to the parameter RAVI.
However, at the third measurement point, after 26 weeks of treatment, GLS correlated with all measured right atrial echocardiographic parameters including EDV, ESV, RAVI, RAEF and sPAP. Moreover, in all three examinations, right atrial GLS correlated significantly with NT-proBNP.

3.7 NT-proBNP

At baseline, NT-proBNP was determined in a total of 193 patients (161 male and 33 female). The median NT-proBNP of the study population was 1362 pg/ml (males 1227 pg/ml and females 2118 pg/ml). With a median value of 1227 pg/ml in the empagliflozin group and a median value of 1465 pg/ml in the placebo group, no significant difference could be observed ($p = 0.440$).

After 6 weeks, NT-proBNP values were obtained from 198 study subjects (165 males and 33 females). The median NT-proBNP in the empagliflozin group was 496 pg/ml (males 473 and females 973) and in controls 571 pg/ml (males 557 and females 594), whereas no significant difference could be observed ($p = 0.483$).

After 26 weeks, NT-proBNP was measured in 200 patients (165 males and 35 females). In the empagliflozin group, the median NT-proBNP was 181 pg/ml (males 166 pg/ml and females 291 pg/ml) and in the placebo group 223 pg/ml (males 189 pg/ml and females 261 pg/ml), whereas no significant difference could be found ($p = 0.146$).

NT-proBNP showed a significant positive correlation with sPAP, CK and high-sensitive Troponin and a significant negative correlation with right atrial ESV, right atrial GLS, RAEF and RAVI.

4 Discussion

In this thesis, a total of 206 study participants of the EMMY trial were analysed in terms of right atrial function. Right atrial parameters including GLS, EDV, ESV, RAEF, RAVI and sPAP were investigated for the first time in patients after acute MI, who were treated with empagliflozin or placebo for 26 weeks in addition to guideline-recommended post-MI therapy. In this period, three measurements at different time points were taken: at baseline, after 6 and 26 weeks.

Including all study participants, no significant differences between the empagliflozin and placebo group in terms of right atrial function could be found after 6 and 26 weeks. Nonetheless, significant differences were observed in the male subgroup.
After 6 weeks of treatment, significant differences concerning the parameters EDV, ESV and RAVI were found between the empagliflozin and placebo group within the male probands. After a total of 26 weeks of treatment, the results of the empagliflozin and placebo groups were found to be similar. EDV was the only value which was significantly better in the empagliflozin group ($p = 0.021$). Concerning right atrial GLS a significant difference between the empagliflozin and placebo group could barely not be demonstrated ($p = 0.056$). Clearer results could be obtained with a larger study population.

In summary, significant results between the empagliflozin group and the control group were found at the second measurement time point regarding EDV, ESV and RAVI. At the third measurement time point, only the EDV showed significant results, whereas the right atrial GLS was almost significant. These findings were all limited to the male subgroup.

One reason why these values were only significant in the male group could be due to the low number of cases in the female group, as in this diploma thesis only study participants of the Clinical Department of Cardiology at the Medical University of Graz could be analysed. Another factor influencing the results in the female group could be the significantly higher values of the heart failure marker NT-proBNP in the initial examination. Although it is known that women generally

have higher NT-proBNP levels, this could indicate a more severe heart failure already at the time of study enrolment.

In any case, the analyses of this thesis showed that the percentage change in the mean values of all right atrial parameters was better in the empagliflozin group than in the placebo group. The echocardiographic parameters GLS, sPAP, EDV, ESV and RAVI could demonstrate better mean values after only 6 weeks of treatment, whereas RAEF showed better results after 26 weeks.

Furthermore, correlation analyses demonstrated a significant correlation between the right atrial GLS, which is not yet used in clinical routine, and other right atrial echocardiographic parameters as well as the heart failure marker NT-proBNP.
The significant correlations mainly concern the third measurement time point, in which the right atrial GLS correlates with all measured right atrial functional and structural parameters. At this point, the acute stage of myocardial infarction has already turned into a chronic state of health. Thus, it can be concluded that right atrial GLS is a reliable marker for the assessment of right atrial function, especially in patients with chronic heart failure.

4.1 Cardiovascular Outcome Trials

The EMMY trial found improved functional and structural parameters in patients taking empagliflozin for 26 weeks after MI. The main finding was a significant reduction in NT-proBNP of 15% (95% CI -4.4 to -23.6%, p = 0.026) in the empagliflozin group. This effect was already significant after a treatment period of 12 weeks (p = 0.021). Moreover, LVEF increased by an absolute 1.5% (95% CI 0.2 to 2.9%, p = 0.029) more in the empagliflozin group. This difference was already significant after 6 weeks of treatment (1.7%, 95% CI 0.35 to 3.05%, p = 0.014). The parameter E/e´ was significantly reduced by 6.8% in the empagliflozin group (95% CI -4.4 to -23.6%). Left ventricular end-diastolic and end-systolic volumes also improved significantly compared to placebo. EDV was reduced by

9.7 mL (95% CI -15.7 to -3.7 mL, p = 0.0015) and ESV by 7.5 mL (95% CI -11.5 to -3.4 mL, p = 0.0003) in the empagliflozin group[78].

Besides these outstanding results of the EMMY trial, larger clinical trials, like the EMPEROR-reduced trial or the DAPA-HF trial, already demonstrated the beneficial effects of SGLT2 inhibitors in patients with heart failure[37, 58]. A meta-analysis conducted on these placebo-controlled trials found that SGLT2 inhibitors reduce the combined risk of CV death or first hospitalisation for heart failure by 26% compared to placebo. Additionally, the composite of recurrent hospitalisations of heart failure or CV death was also reduced by 25%. All-cause death was reduced by 13% and CV death by 14%. Despite this, the composite renal endpoint (defined as 50% or higher sustained decline in eGFR, end-stage renal disease, or renal death) was reduced by 58%[36]. Furthermore, also an improvement in the quality of life, as well as in the physical function of symptomatic patients with HFrEF could be demonstrated[37, 58].
Besides this, the EMPEROR-Preserved trial investigated the benefits of empagliflozin in patients with HFpEF. This study found a 21% reduction of the composite endpoint of CV death or heart failure hospitalisation in the empagliflozin group compared to the placebo group[59]. Dapagliflozin also showed similar results in the DELIVER-trial, whereas the composite endpoint of worsening heart failure or CV death was reduced by 18% in the dapagliflozin group compared to controls[60].

Up to 36% of patients with MI develop chronic heart failure[7]. This leads to the assumption that the beneficial effect of SGLT2 inhibitors could also occur in patients after MI. Since the function of the right atrium is directly dependent on the diastolic and systolic filling pressures, an improvement of structural and functional parameters should also have a positive effect on the right atrium.

The only data besides the EMMY trial[78] examining SGLT2 use after acute MI is the EMBODY trial, which investigated the effect of empagliflozin on sympathetic and parasympathetic activity[53]. Currently, no published study quantifies the effect of empagliflozin on the right atrium after MI.

4.2 Right Atrial Strain in Heart Failure

A study enrolling 608 patients with HFrEF, HFpEF and normal LVEF demonstrated that RA phasic function was more impaired in patients with HFrEF than those with HFpEF or normal LVEF. In analyses, especially right atrial reservoir and conduit strain were found to independently predict all-cause mortality regardless of LVEF. Both are independent predictors of mortality. On the other hand, the right atrial booster pump function did not independently predict the risk of death[96].

Another study with a smaller sample size also found impaired right atrial phasic function parameters in patients with left-sided heart failure[95]. These findings are not surprising, since heart failure is often associated with elevated left atrial pressure, secondary RV dilation, tricuspid regurgitation and thus elevated right atrial pressure[98, 99].

Right atrial strain is a determinant factor in the assessment of RV hemodynamics, especially in RV diastolic function[99]. However, Miah et al. demonstrated that right atrial reservoir strain is significantly associated with invasive right atrial pressure. With a sensitivity of 78% and a specificity of 72%, it has a higher diagnostic performance in identifying elevated invasive right atrial pressure than right atrial size and collapsibility of the inferior vena cava[100].

4.3 Right Atrial Strain in Myocardial Infarction

Currently, the data on the right atrial strain after MI is still very limited. A study investigating right atrial phasic functions in patients with acute anterior ST-elevation MI, enrolling 92 patients with acute STEMI and 31 control subjects, found significantly reduced right atrial reservoir and conduit functions in the acute STEMI group compared to controls. The booster pump function was preserved[101]. The right atrial phasic function was also found to be impaired in inferior MI plus RV MI in comparison to inferior MI alone[101, 102]. However, the RA phasic functions are independently associated with major adverse cardiac events (MACE) in patients with acute MI[103].

4.4 Strengths and Limitations

One of the major limitations of this thesis is the post-processing evaluation. Thus, the analyses had to be carried out on the existing ultrasound images, even if the image quality was not always optimal due to bad ultrasound conditions. Furthermore, patients in whom echocardiographic loops were missing at the examination date could not be analysed, whereas patients had to attend at least two echocardiography appointments to remain included in the study. A total of eight patients were excluded because only one of three examination appointments was attended. Also, due to technical problems, the retrieval of echocardiography studies failed in two patients at one examination date. A total of four patients withdrew their informed consent and could therefore not be included in the analyses. One patient passed away during the study period. After all, a total of 206 patients could be analysed. Given the fact that some parameters closely did not reach the significance threshold, a larger sample size could have provided clearer results.

Furthermore, it must be mentioned that the two gender groups are not balanced. Since only the data from the Clinical Department of Cardiology at the Medical University of Graz was analysed in my diploma thesis, the number of women in the study is rather low. This is also reflected in the fact that significant results could only be found within the male subgroup.

A strength of this study is that all echocardiographic examinations were performed by experienced physicians and stored in the digital archive IntelliSpace Cardiovascular (ISCV; Philips, Eindhoven, Netherlands). The required analyses for this thesis were carried out after a short training phase. Moreover, all measurements were carried out at least twice to ensure an accurate value in the statistical evaluation.

4.5 Conclusion

The cardioprotective effects of SGLT2 inhibitors have already been demonstrated in large study populations. In animal models as well as in vitro experiments, various mechanisms and molecular pathways leading to improved cardiac function could be identified.

However, concerning the right atrium, early initiation of empagliflozin after acute MI shows heterogeneous results. After 26 weeks of treatment, significant differences between the empagliflozin and placebo group were only observed regarding the parameter EDV ($p = 0.021$). The values of right atrial GLS were almost significant ($p = 0.056$). These results are limited to the male subgroup.
Nonetheless, all parameters in the empagliflozin group showed a greater improvement of the mean values compared to the placebo group, so a beneficial effect of empagliflozin on the right atrium can be suspected.
Furthermore, this work could show significant correlations between right atrial GLS and structural and functional right atrial echocardiographic parameters, especially in patients with chronic heart failure.

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6 Appendix

Correlation Baseline Examination

			GLS	EDV	ESV	RAVI	RAEF	sPAP	GCS	NTproBNP
Spearman-Rho	GLS	Korrelationskoeffizient	1,000	-,453**	-,053	-,052	,733**	-,138	,625**	-,148*
		Sig. (2-seitig)	.	<,001	,451	,465	<,001	,076	<,001	,040
		N	203	203	203	203	203	167	203	192
	EDV	Korrelationskoeffizient	-,453**	1,000	,811**	,764**	-,568**	,130	-,427**	-,106
		Sig. (2-seitig)	<,001	.	<,001	<,001	<,001	,095	<,001	,142
		N	203	203	203	203	203	167	203	192
	ESV	Korrelationskoeffizient	-,053	,811**	1,000	,925**	-,047	,079	-,006	-,237**
		Sig. (2-seitig)	,451	<,001	.	<,001	,507	,310	,936	<,001
		N	203	203	203	203	203	167	203	192
	RAVI	Korrelationskoeffizient	-,052	,764**	,925**	1,000	-,065	,142	-,058	-,159*
		Sig. (2-seitig)	,465	<,001	<,001	.	,357	,068	,408	,028
		N	203	203	203	203	203	167	203	192
	RAEF	Korrelationskoeffizient	,733**	-,568**	-,047	-,065	1,000	-,098	,783**	-,169*
		Sig. (2-seitig)	<,001	<,001	,507	,357	.	,210	<,001	,019
		N	203	203	203	203	203	167	203	192
	sPAP	Korrelationskoeffizient	-,138	,130	,079	,142	-,098	1,000	-,137	,218**
		Sig. (2-seitig)	,076	,095	,310	,068	,210	.	,078	,006
		N	167	167	167	167	167	168	167	159
	GCS	Korrelationskoeffizient	,625**	-,427**	-,006	-,058	,783**	-,137	1,000	-,119
		Sig. (2-seitig)	<,001	<,001	,936	,408	<,001	,078	.	,099
		N	203	203	203	203	203	167	203	192
	NTproBNP	Korrelationskoeffizient	-,148*	-,106	-,237**	-,159*	-,169*	,218**	-,119	1,000
		Sig. (2-seitig)	,040	,142	<,001	,028	,019	,006	,099	.
		N	192	192	192	192	192	159	192	194

**. Die Korrelation ist auf dem 0,01 Niveau signifikant (zweiseitig).

*. Die Korrelation ist auf dem 0,05 Niveau signifikant (zweiseitig).

Correlation Second Examination

			GLS	EDV	ESV	RAVI	RAEF	sPAP	GCS	NTproBNP
Spearman-Rho	GLS	Korrelationskoeffizient	1,000	-,411**	-,109	-,156*	,664**	-,104	,487**	-,148*
		Sig. (2-seitig)	.	<,001	,126	,028	<,001	,168	<,001	,038
		N	199	199	199	198	199	176	199	197
	EDV	Korrelationskoeffizient	-,411**	1,000	,855**	,823**	-,581**	,092	-,375**	-,025
		Sig. (2-seitig)	<,001	.	<,001	<,001	<,001	,226	<,001	,730
		N	199	199	199	198	199	176	199	197
	ESV	Korrelationskoeffizient	-,109	,855**	1,000	,928**	-,129	,080	,004	-,121
		Sig. (2-seitig)	,126	<,001	.	<,001	,068	,293	,954	,091
		N	199	199	199	198	199	176	199	197
	RAVI	Korrelationskoeffizient	-,156*	,823**	,928**	1,000	-,163*	,086	-,056	-,048
		Sig. (2-seitig)	,028	<,001	<,001	.	,022	,259	,429	,500
		N	198	198	198	198	198	175	198	197
	RAEF	Korrelationskoeffizient	,664**	-,581**	-,129	-,163*	1,000	-,089	,768**	-,146*
		Sig. (2-seitig)	<,001	<,001	,068	,022	.	,238	<,001	,041
		N	199	199	199	198	199	176	199	197
	sPAP	Korrelationskoeffizient	-,104	,092	,080	,086	-,089	1,000	-,050	,286**
		Sig. (2-seitig)	,168	,226	,293	,259	,238	.	,509	<,001
		N	176	176	176	175	176	177	176	175
	GCS	Korrelationskoeffizient	,487**	-,375**	,004	-,056	,768**	-,050	1,000	-,138
		Sig. (2-seitig)	<,001	<,001	,954	,429	<,001	,509	.	,054
		N	199	199	199	198	199	176	199	197
	NTproBNP	Korrelationskoeffizient	-,148*	-,025	-,121	-,048	-,146*	,286**	-,138	1,000
		Sig. (2-seitig)	,038	,730	,091	,500	,041	<,001	,054	.
		N	197	197	197	197	197	175	197	198

**. Die Korrelation ist auf dem 0,01 Niveau signifikant (zweiseitig).

*. Die Korrelation ist auf dem 0,05 Niveau signifikant (zweiseitig).

Correlation Third Examination

			GLS	EDV	ESV	RAVI	RAEF	GCS	sPAP	NTproBNP
Spearman-Rho	GLS	Korrelationskoeffizient	1,000	-,519**	-,187**	-,179*	,773**	,558**	-,157*	-,202**
		Sig. (2-seitig)	.	<,001	,008	,011	<,001	<,001	,032	,004
		N	200	200	200	200	200	200	187	199
	EDV	Korrelationskoeffizient	-,519**	1,000	,862**	,788**	-,593**	-,436**	,109	,152*
		Sig. (2-seitig)	<,001	.	<,001	<,001	<,001	<,001	,136	,032
		N	200	200	200	200	200	200	187	199
	ESV	Korrelationskoeffizient	-,187**	,862**	1,000	,916**	-,144*	-,063	,080	,022
		Sig. (2-seitig)	,008	<,001	.	<,001	,041	,374	,278	,758
		N	200	200	200	200	200	200	187	199
	RAVI	Korrelationskoeffizient	-,179*	,788**	,916**	1,000	-,131	-,048	,096	,075
		Sig. (2-seitig)	,011	<,001	<,001	.	,065	,498	,190	,295
		N	200	200	200	200	200	200	187	199
	RAEF	Korrelationskoeffizient	,773**	-,593**	-,144*	-,131	1,000	,780**	-,112	-,291**
		Sig. (2-seitig)	<,001	<,001	,041	,065	.	<,001	,125	<,001
		N	200	200	200	200	200	200	187	199
	GCS	Korrelationskoeffizient	,558**	-,436**	-,063	-,048	,780**	1,000	-,099	-,190**
		Sig. (2-seitig)	<,001	<,001	,374	,498	<,001	.	,177	,007
		N	200	200	200	200	200	200	187	199
	sPAP	Korrelationskoeffizient	-,157*	,109	,080	,096	-,112	-,099	1,000	,251**
		Sig. (2-seitig)	,032	,136	,278	,190	,125	,177	.	<,001
		N	187	187	187	187	187	187	188	188
	NTproBNP	Korrelationskoeffizient	-,202**	,152*	,022	,075	-,291**	-,190**	,251**	1,000
		Sig. (2-seitig)	,004	,032	,758	,295	<,001	,007	<,001	.
		N	199	199	199	199	199	199	188	200

**. Die Korrelation ist auf dem 0,01 Niveau signifikant (zweiseitig).

*. Die Korrelation ist auf dem 0,05 Niveau signifikant (zweiseitig).