Thesis

The impact of the SGLT2 – Inhibitor Empagliflozin on the right Ventricular Function after Acute Myocardial Infarction – The EMMY Trial

submitted by

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Statutory Declaration

I declare on my honor that I have written this thesis independently, that I have not used any sources other than those indicated and that I have marked the passages taken from the sources used verbatim or in terms of content as such

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Kurzzusammenfassung

Hintergrund und Fragestellung: In klinischen Studien zu chronischer Herzinsuffizienz konnten Inhibitoren der Natrium-Glukose-Cotransporter 2 (SGLT2i) im Vergleich zu Placebo eine verbesserte Prognose erreichen. Die EMMY-Studie bestätigte diesen Zusammenhang bei Patient*innen nach einem akuten Myokardinfarkt (AMI) und konnte eine signifikante Reduktion des N-terminalen pro-brain natriuretic peptide (NT-proBNP) durch Empagliflozin zeigen. Ziel dieser Diplomarbeit ist es, die Evidenz zur Beteiligung des rechten Ventrikels sowie der systolischen und diastolischen myokardialen Dysfunktion zu erweitern.

Material und Methoden: Echokardiographie-Loops einer Gruppe von Patient*innen nach akutem Myokardinfarkt (n = 219), welche im Rahmen der EMMY-Studie entweder eine Standardbehandlung und Placebo oder eine Standardbehandlung und Empagliflozin erhielten, wurden zu je drei Zeitpunkten (Woche 0, 6±2 und 26±2) hinsichtlich der rechtsventrikulären Dimensionen und Performance tripple-blind ausgewertet. Die erhaltenen Werte wurden sowohl im zeitlichen Verlauf als auch zwischen den Gruppen statistisch verglichen.

Ergebnisse: Die erhobenen rechtsventrikulären Funktionsparameter und Dimensionen zeigten zu keinem der Zeitpunkte signifikante Unterschiede zwischen der Empagliflozin und Placebo Gruppe. Zusätzlich konnte kein signifikanter Unterschied des erhobenen Endo GLS zwischen der Placebo- und Interventionsgruppe festgestellt werden (p=0.641). Die Funktionsparameter FAC und TAPSE zeigten ebenfalls keinen Unterschied zwischen den beiden Gruppen (p=0,727 für FAC und p=0,839 für TAPSE).

Konklusion: Empagliflozin führte im Vergleich zum Placebo zu keiner signifikanten Verbesserung auf die RV-Belastung oder die echokardiografischen Parameter. Andererseits waren alle Parameter abhängig von der Zeit nach dem Herzinfarkt und von den Auswirkungen der medizinischen Therapie. Weitere Forschungsarbeiten sind erforderlich, um die RV-Funktion und ihre Rolle bei kardiovaskulären Erkrankungen sowie ihre Rolle bei deren Therapien zu quantifizieren. Außerdem sind weitere Studien erforderlich, um den zugrunde liegenden Mechanismus der SGLT-2-Hemmer und ihre Wirkung auf das Herz vollständig zu verstehen.

Abstract

Background and Objective: In clinical studies on chronic heart failure, inhibitors of the sodium-glucose cotransporter 2 (SGLT2i) have shown improved prognosis compared to placebo. The EMMY study confirmed this relationship after an acute myocardial infarction (AMI) and demonstrated a significant reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) with empagliflozin. The aim of this thesis is to expand the evidence on the involvement of the right ventricle and systolic and diastolic myocardial dysfunction.

Materials and Methods: Echocardiography loops of a group of patients after acute myocardial infarction (n = 219), who received either standard treatment and placebo or standard treatment and empagliflozin as part of the EMMY study, were triple blind evaluated at three time points (week 0, 6, and 26) regarding right ventricular dimensions and performance. The obtained values were statistically compared both over time and between the groups.

Results: The collected right ventricular functional parameters and dimensions showed no significant differences between the empagliflozin and placebo groups at any time point. Additionally, no significant difference in the collected endocardial global longitudinal strain (GLS) between the placebo and intervention groups was found (p=0.641). The functional parameters FAC and TAPSE also showed no difference between the two groups (p=0.727 for FAC and p=0.839 for TAPSE).

Conclusion: Compared to placebo, empagliflozin did not lead to a significant improvement in right ventricular load or echocardiographic parameters. On the other hand, all parameters depended on the time after the heart attack and the effects of medical therapy. Further research is needed to quantify right ventricular function and its role in cardiovascular diseases and their therapies. Additionally, further studies are needed to fully understand the underlying mechanism of SGLT2 inhibitors and their effect on the heart.

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Abbreviations and Definitions

2D ..... *two dimensional*
2D STE ..... *two-dimensional speckle-tracking echocardiography*
2DE ..... *two-dimensional echocardiography*
2DTE ..... *two dimensional transthoracic echocardiography*
3D ..... *three dimensional*
A2C ..... *apical 2 chamber*
A3C ..... *apical long-axis*
A4C ..... *apical 4 chamber*
A5C ..... *apical 5 chamber*
ACEi ..... *Angiotensin-converting enzyme inhibitors*
ACH ..... *all-cause hospitalization*
ACM ..... *all-cause mortality*
AMI ..... *acute myocardial infarction*
ARBs ..... angiotensin receptor blockers
ASCVD ..... *atherosclerotic cardiovascular disease*
ASE ..... *American Society of Echocardiography*
BMI ..... *Body Mass Index*
BNP ..... *B-type natriuretic peptide*
CAD ..... *coronary artery disease*
CHF ..... *congestive heart failure*
CMP ..... *cardiomyopathy*
CMR ..... *cardiac magnetic resonance imaging*
CRP ..... *c-reactive protein*
CT ..... *computer tomography*
DAPT ..... *dual antiplatelet therapy*
EACVI ..... *European Association of Cardiovascular Imaging*
ECG ..... *electrocardiogram*
ED ..... *end-diastole*
EDV ..... *end-diastolic volume*
EF ..... *ejection fraction*

eGFR ..... *estimated glomerular filtration rate*
ES ..... *end- systole*
ESC ..... *European Society of Cardiology*
FAC ..... *Fractional area change*
FWLS ..... *free wall strain*
GFR ..... *Glomerular filtration rate*
GLS ..... *global longitudinal strain*
HF ..... *heart failure*
HFmrEF ..... *heart failure with mildly reduced ejection fraction*
HFpEF ..... *failure with preserved ejection fraction*
HFrEF ..... *heart failure with reduced ejection fraction*
HRV ..... *heart rate variability*
hsTrop ..... *High-sensitivity troponin*
LV ..... *left ventricle*
LVEDV ..... *left-ventricular end-diastolic volume*
LVEF ..... *left ventricular ejection fraction*
LVESV ..... *left-ventricular end-systolic volume*
MI ..... *myocardial infarction*
M-mode ..... *Motion-Mode*
MRI ..... *magnetic resonance imaging*
NP ..... *natriuretic peptides*
NT-proBNP ..... *N-terminal pro B-type natriuretic peptide*
NYHA ..... *New York Heart Association*
PAE ..... *pulmonary embolism*
PAP ..... *pulmonary artery pressure*
PCI ..... *percutaneous coronary intervention*
PH ..... *pulmonary hypertension*
PLAX ..... *parasternal long-axis*
PSAX ..... *parasternal short-axis*
PTCA ..... *percutaneous transluminal coronary angioplasty*
RAAS ..... *renin-angiotensin-aldosterone syst*
RIMP ..... *The Right Ventricular Index of Myocardial Performance*
RV ..... *right ventricle*
RVEF ..... *right ventricular ejection fraction*

RVMI.....*Right ventricular myocardial infarction*
RVOT.....*right ventricular outflow tract*
SC 4C..... *subcostal 4 chamber*
SGLT2i ..... *Sodium-glucose cotransporter-2 inhibitors*
SSN ..... *suprasternal notch*
STE..... *Speckle-tracking-echocardiography*
STEMI.....*ST-segment elevation myocardial infarction*
SV..... *stroke volume*
T2DM.....*type 2 diabetes mellitus*
TAPSE.....*Tricuspid Annular Plane Systolic Excursion*
TCO ..... *The mean tricuspid (valve) closure opening time*
TDI.....*tissue Doppler imaging*
TTE.....*transthoracic echocardiographie*

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1 Introduction

1.1 Anatomy and physiology of the right ventricle

The right ventricle (RV) is a critical and unique chamber of the heart, whose design and function are tailored to the specific needs of the pulmonary circulation. Situated at the front of the heart, the RV has a distinctive shape that is less like a symmetrical circle and more akin to a crescent moon, allowing it to handle its workload with remarkable efficiency.

The structure of the RV comprises the tricuspid valve, which governs blood flow from the right atrium to the right ventricle; the pulmonary valve, which directs blood from the right ventricle into the pulmonary artery; the trabeculae carneae, which are muscular ridges on the inner surface of the ventricle, with the function of counteracting the suction effect of the flowing blood by turbulence and thus dampening the blood flow within the ventricles.; and the moderator band, a muscular column that contributes to the electrical conduction and timing of contractions.(1,2)

When examining the RV's physiology, its role is clear: to receive deoxygenated blood from the systemic circulation via the right atrium and pump it through the pulmonary artery it into the lungs, where it gets oxygenated. This is achieved despite the RV having a thinner wall compared to the left ventricle, representing the lower pressure environment of the pulmonary circuit.

The contraction cycle of the RV is a well-coordinated process initiated by electrical impulses originating in the sinoatrial node which is located subepicardial in the terminal sulcus on the dorsal side of the right atrium and caudal to the junction of the superior vena cava. During the diastolic phase, the tricuspid valve opens and the RV expands allowing it to passively fill with blood. With the onset of systole, the RV contracts in a complex and compound manner that distinguishes it from the more linear contraction of the left ventricle. Starting from the apex, the contraction proceeds towards the outflow tract, effectively pumping blood into the pulmonary artery. This motion is enabled by the RV's unique myocardial fiber arrangement: superficial fibers that encircle the ventricles contribute to the inward motion of the ventricular walls, while deeper fibers arranged longitudinally assist in the shortening of the chamber from base to apex.(1)

The RV's contraction mechanism is reminiscent of a bellows – it´s contraction ensures a sufficient blood flow to overcome the low resistance in the pulmonary system. This adaptability is a trademark of the RV function and follows the Frank-Starling mechanism, which states that the stroke volume of the heart increases with increasing end-diastolic volume while other factors remaining equal.

The importance of RV performance should not be underestimated, especially when considering the clinical impact of RV dysfunction. RV failure, which may emerge from various etiologies such as pulmonary arterial hypertension, right-sided myocardial infarction (MI), or cardiomyopathies, leads to a cascade of hemodynamic changes. The resulting reduced output from the RV can subsequently lead to a backlog of blood in the systemic venous system and a decrease in left ventricular filling, ultimately manifesting as congestive heart failure.

The effects of RV dysfunction are varied and can significantly affect a patient's clinical condition and prognosis. Symptoms can range from dyspnea and fatigue to edema and ascites, reflecting the systemic impact of impaired RV function. Therefore, recognizing and understanding RV health is of paramount importance in cardiology, as it is essential for both pulmonary and systemic circulatory dynamics.

In essence, the right ventricle is not merely a passive recipient and conduit of venous blood but an active and dynamic participant in the heart's constant endeavor to supply the organs with oxygenated blood. Its structural uniqueness befits its functional specialty, allowing it to operate within the low-pressure pulmonary system with efficacy and resilience. On the other hand the unique shape is the RV´s biggest weakness when it comes to quantify it´s performance, as described later. The RV's ability to withstand fluctuations in pressure and volume exemplifies its integral role in cardiovascular physiology. Nevertheless, the delicate balance maintained by the RV can be disrupted by pathological states, highlighting the need for vigilant attention to right ventricular health in the context of overall cardiovascular care.

1.2 Performance of the right ventricle

The physiological performance of the RV is influenced by several factors, which include:

- Systemic venous return
- RV afterload (pulmonary arterial load)
- Pericardial compliance
- Contractility of the RV free wall and interventricular septum.

A primary determinant of RV function here is afterload, or pulmonary artery pressure (PAP). The right ventricular ejection fraction (RVEF) is inversely proportional to the PAP consequently the RV systolic function is extremely sensitive to variations in afterload. Therefore, even a small increase in PAP will limit the function of the RV.(3)

When left ventricular (LV) function is limited, there may be an increase in left atrial pressure, which decreases pulmonary arterial compliance. Consequently, increased left heart pressure increases RV afterload, increases pulmonary arterial resistance, and decreases pulmonary arterial compliance. Compared with the LV, RV coronary perfusion occurs in both diastole and systole, and therefore ischemia may result from pressure overload. There are now a wide variety of diseases that can have a negative impact on RV function. These include pathologies that may be associated with an increased pressure load or an increased volume load.(3)

Prolonged pressure loading can lead to RV remodeling with myocardial hypertrophy, decreased wall stress, and change in shape with reorientation of myofibrils. Here, an increased expression of circumferential fibers is observed, with a concomitant decrease in radial contraction, which is a better indicator of RV performance than longitudinal contraction. However, with appropriate treatment, reversion of this condition and consequent recovery of the RV has been observed. The most common condition leading to pressure loading is pulmonary hypertension (PH).(1)

The most common triggers of volume overload include tricuspid regurgitation, pulmonary valve regurgitation, and left-to-right shunt. When RV preload increases, end-systolic function can be maintained, at least initially, because of the Frank-Starling mechanism and concomitant increased longitudinal contraction. Most often, RV volume overload is described as a benign condition, although there are occasional exceptions that will not be discussed in this thesis. Now, to quantify the functional performance of the RV, there are several useful parameters and investigations.(3)

1.3 Natriuretic peptides

The laboratory parameter N-terminal pro B-type natriuretic peptide (NT-proBNP) is released during excessive stress or stretching of the ventricles. Cardiomyocytes synthesize proBNP, which splits into a physiologically active B-type natriuretic peptide (BNP) and the inactive NT-proBNP. Natriuretic peptides (NP) have various effects on the body like vasodilatation, natriuresis and improve myocardial relaxation. Despite the evidence that BNP is connected to ventricular overload, there is an individual variation between both the healthy subjects and those with a heart disease. Plasma concentration of BNP is connected to gender and age, its level increases with age and is higher in woman. Extensive evidence has showcased the pivotal roles of BNP and NT-proBNP in diagnosing and stratifying risk in heart failure. These biomarkers are recognized as valuable tools for population screening and serve as guides for initiating treatment in individuals with subclinical heart failure (HF).(4) Elevated BNP/NT-proBNP levels may indicate various differential diagnoses, such as heart failure, renal failure, hepatic failure, PH, and pulmonary embolism (PAE). A normal value in an untreated patient is likely to rule out serious cardiac disease.(5)(6)

1.4 Echocardiography

Echocardiography stands as a cornerstone in cardiological diagnostics, providing a non-invasive window into the heart's dynamics through ultrasound technology. The American Society of Echocardiography's guidelines for transthoracic echocardiographic examination (TTE) in adults set a high standard for practice. These recommendations underscore the importance of compliance with the requirements, from patient preparation to the right interpretation of echocardiographic data. This framework aims to bolster diagnostic precision and through that to enhance patient outcomes.(7)

Echocardiography offers various parameters for non-invasive heart function assessment, mainly focusing on the left ventricle due to extensive research in this area. The ejection fraction (EF) is a commonly used parameter to gauge left ventricular performance. The accuracy of left ventricular ejection fraction (LVEF)

measurements can be impacted by observer variability, but this can be mitigated by integrating multiple views into a 3D model. However, EF's reliability is influenced by hemodynamic conditions, affecting the portrayal of ventricular function. The EF is calculated by dividing the stroke volume (SV) by the end-diastolic volume (EDV) times 100.(8)

$$LVEF = \frac{LVEDV - LVESV}{LVEDV} x100$$

LVEF = left ventricular ejection fraction

LVEDV = left ventricular end-diastolic volume

LVESV = left ventricular end-systolic volume

Equation 1: Calculation of the left ventricular ejection fraction

Echocardiographic evaluation of the RV can be difficult due to several reasons. One of the reasons reflects the unique shape of the RV which, not only varies from patient to patient but compared to that of the LV, can also not be clearly defined because of its complex form. Due to the location, it can also be difficult to adjust the RV correctly, which is further complicated by the fact, that there are no clear landmarks. All this makes it difficult to obtain reproducible results.(9)

1.4.1 TAPSE

Tricuspid Annular Plane Systolic Excursion (TAPSE) evaluates the right ventricle's longitudinal contraction. It is measured by placing a Motion-Mode (M-mode) cursor through the lateral tricuspid annulus from an apical view, tracking the annulus's movement from end-diastole to end-systole. TAPSE stands out for its simple use and its prognostic value in various conditions affecting the RV, such as heart failure with either preserved or reduced ejection fraction and pulmonary hypertension.(9)

The primary assumption behind TAPSE is that the RV free wall's longitudinal function reflects the entire RV's function, which may not be true in cases like myocardial infarction. While RV contraction is mainly longitudinal in healthy individuals, the radial

component gains importance as the RV dilates, leading to potential inaccuracies in assessing RV function through TAPSE, which only measures longitudinal movement.(9,10)

In addition, TAPSE values may be misleadingly in cases with significant RV impairment, particularly if the left ventricular apex has significant rotation, such that the free RV wall is pulled without true contraction. This "pulling" may cause the TAPSE value to be falsely normal despite significant dysfunction. Combining TAPSE with other RV function measurements can alleviate this problem. Nevertheless, TAPSE is an important tool for rapid assessment of RV performance.(10)

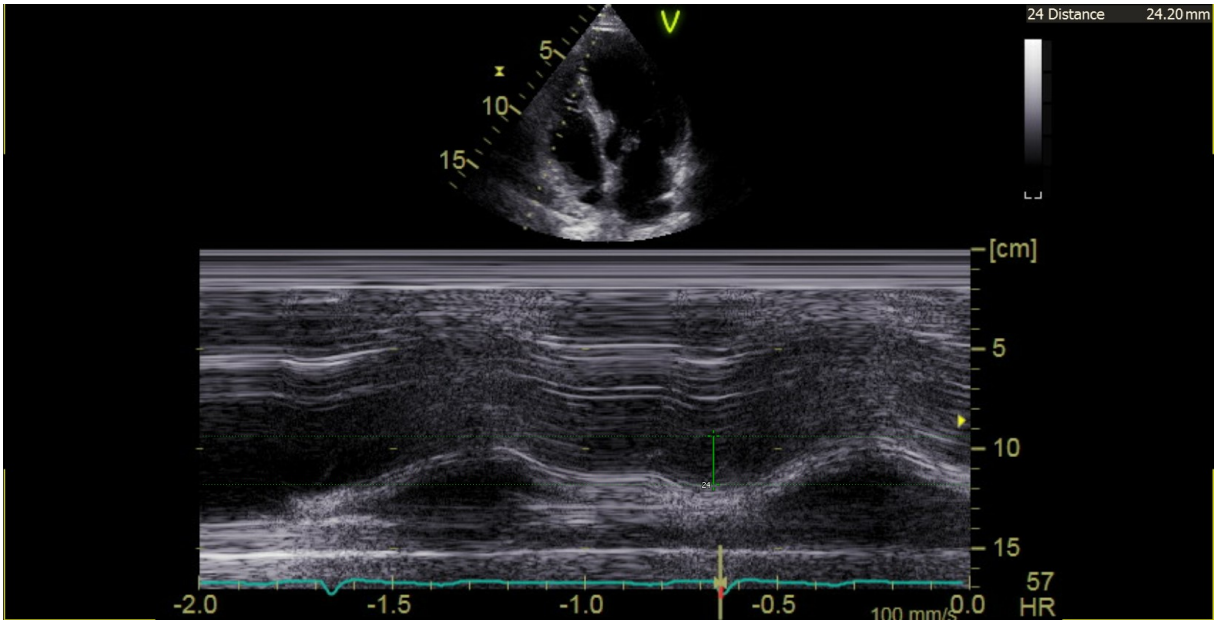

Figure 1 TAPSE

1.4.2 Fractional-area-change

Fractional area change (FAC) is calculated by manually outlining the inner border of the right ventricle at the points of maximal filling (end-diastole) and contraction (end-systole) in either an apical view with four-chamber or right ventricular focus, taking care not to include the trabeculae of the wall. FAC has been shown to correlate strongly with right ventricular ejection fraction as determined by cardiac magnetic resonance (CMR), with values above 35% considered normal. Studies have shown

that a decrease in FAC is a reliable indicator of increased risk of heart failure, sudden cardiac death, stroke and all-cause mortality in individuals with pulmonary embolism. In addition, meta-analyses suggest that FAC is a more accurate measure for assessing right ventricular function than TAPSE, although high-quality imaging is critical for accurate measurement. The main challenge in using FAC is to achieve clear visibility of the endocardial border, which can be particularly difficult in areas of the heart with marked trabeculation. It has been shown that FAC compares well with right ventricular function determined by magnetic resonance imaging and is therefore a good predictor of patients with MI and PAE.(9)(11)(2)

$$FAC = \frac{End\ Diastolic\ Area - End\ Systolic\ Area}{End\ Diastolic\ Area} x100$$

Equation 2: Calculation of the fraction area change

1.4.3 RIMP

The right ventricular index of myocardial performance (RIMP) represents the ratio between the ejection and non-ejection time of the heart. The calculation is based on the tissue Doppler velocities or pulse wave velocities from the RV. In patients with irregular heart rate and increased atrial pressure, the RIMP is limited because the isovolumetric relaxation time is impaired. Values >0.43 measured with pulse wave

Doppler and values <0.54 measured with tissue Doppler are considered pathologic.(12)(9)(13)

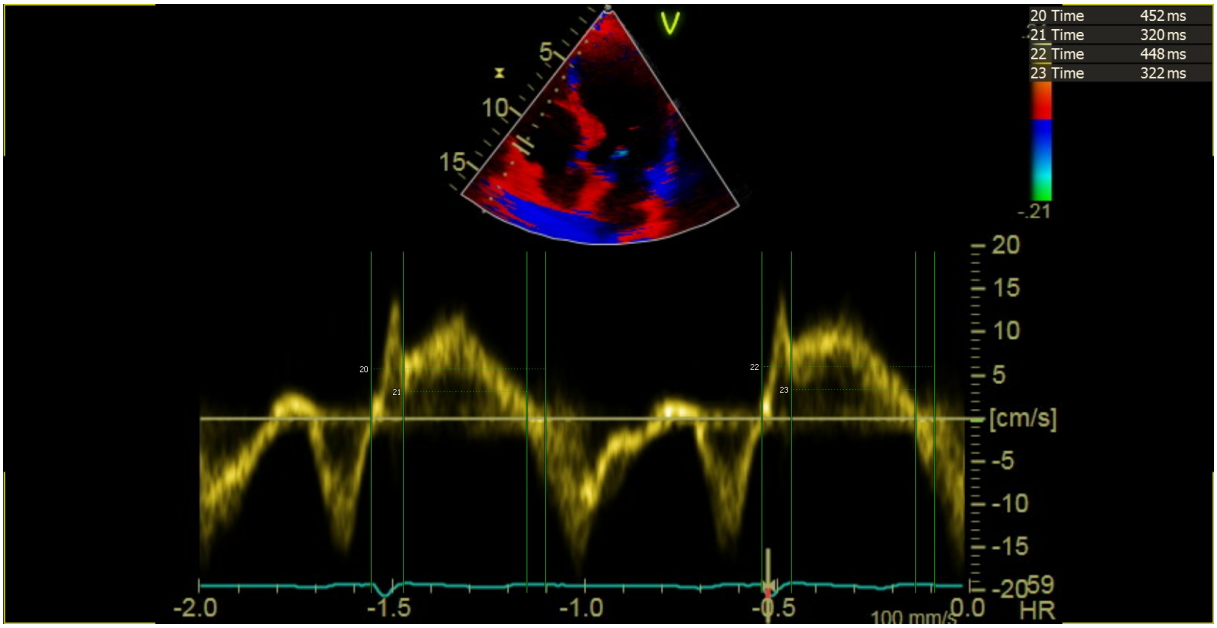

Figure 2 RIMP

1.4.4 RV Dimensions

The size and function of the right ventricle can be influenced by various diseases that affect the RV muscles directly or indirectly via the left ventricle. As a result, assessing the RV dimensions should be considered an integral component of every routine echocardiographic examination.(9)

1.4.5 Two-dimensional vs three-dimensional echocardiography

The unique geometry of the right ventricle presents challenges in estimating its performance using two dimensional (2D) methods, which require certain assumptions due to its complexity. There are two primary 2D methods: the area-length method and the disk summation method. The area-length method, originally developed from

angiographic assessments, relies on approximating RV geometry, often using ellipsoidal models. However, this method significantly underestimates RV volumes compared to those derived from magnetic resonance imaging (MRI). The disk summation method, typically performed from the apical view, excludes the right ventricular outflow tract (RVOT), leading to underestimated EF measurements. Due to these inaccuracies, neither method is recommended for routine RV assessment.(9)

In contrast, modern ultrasound systems equipped with three dimensional (3D) capabilities offer a more accurate assessment of RV structure and function. These systems utilize a matrix transducer to capture a 3D volume of the heart in one or multiple heartbeats, depending on the system's capability and the desired balance between spatial and temporal resolution. The key technical challenge is capturing the entire RV volume, from the tricuspid valve to the pulmonary valve, in high spatial and temporal resolution without the occurrence of "stitching" artifacts in cases of multibeat acquisition. Typically, a modified apical view or an RV-focused view, with the transducer slightly lateral to the apex, yields the best results.(9,12)

1.4.6 Tissue Deformation Imaging

Although the significance of the right ventricle in various diseases has long been recognized, a focused consideration of right ventricular function is a more recent development. Recent advances in myocardial deformation imaging techniques, applied specifically to the right heart chambers, have facilitated a more comprehensive understanding of RV function's role in a wide array of cardiovascular conditions.(14)

1.4.6.1 The concept of strain

Speckle tracking is a method for assessing myocardial deformation and has many advantages over previous methods for the evaluation of cardiac mechanics and function. In contrast to pulse wave and tissue Doppler imaging (TDI), speckle tracking is more precise, faster, less strain-dependent and is angle-independent. Speckle-

tracking-echocardiography (STE) allows assessment of segmental multidirectional myocardial motion-longitudinal, circumferential, and radial-as well as LV twist and rotation. The quantification of longitudinal strain for the RV is of utmost importance because it shows both global and regional systolic functions. It is defined as the percentage change in myocardial deformation. The RV circumferential strain is an indicator for the percentage change in RV circumference where the RV radial strain represents the extend of myocardial thickening (15)(14)

1.4.6.2 One-dimensional strain

One dimensional strain is measured using tissue doppler imaging in the apical four-chamber view. It is limited to mostly longitudinal strain and is angle dependent, which is why there are some difficulties in reproducibility. It is also dependent on the point of measurement and the ultrasound. These disadvantages limit the use of TDI based strain.(7)

1.4.6.3 Two-dimensional strain and RV Function

Two-dimensional longitudinal strain, ascertained through either TDI or speckle-tracking analysis, has been used in recent years as a dependable and precise method for assessing RV systolic function. This validation comes from animal model studies using sonomicrometry and from comparisons with right ventricular ejection fraction determined by cardiac magnetic resonance across various clinical contexts.(14,16)

Among the methods, two-dimensional STE strain is preferred due to its lower susceptibility to angle dependence and higher reproducibility compared to TDI strain. The correlation of two-dimensional STE strain with RVEF by CMR showed significant variability across studies (Pearson correlation coefficient ranging from -0.54 to -0.86).(16)

This variability may be attributed to the diverse clinical environments in which strain measurement was evaluated and to the individual measurements by different investigators. Furthermore, the studies consistently reported low variability both

between and within observers, along with high practicability, endorsing longitudinal strain as an effective and consistent measure for RV function analysis. Unlike the left ventricle, RV global longitudinal strain (GLS) is derived solely from the apical four-chamber view, reflecting either an average of the RV free wall and septal segments or just the RV free wall strain (FWLS). Presently, consensus on normal values is absent; a meta-analysis suggested a normal range of -27 ± 2%, although an RV FWLS threshold of -20% to -21% has been indicated for identifying impaired RV function.(16) Two-dimensional STE strain has emerged as a promising evaluative tool for RV systolic function across a spectrum of clinical scenarios, including pulmonary hypertension, pulmonary embolism, heart failure, myocardial infarction, cardiomyopathies (CMP), and valvular heart diseases.(16–18)

STE is performed offline on digitally saved electrocardiogram (ECG) triggered 2 dimensional loops. The images required for the right ventricular strain are acquired through a standard transthoracic echocardiography. The recommended acquisition for RV longitudinal strain is the apical four-chamber view. There should be at least three cardiac cycles recorded, with a minimum of heart rate variability (HRV) so that the measurement is valid. The use of low frame rates could result in a loss of speckles which leads to a less accurate measurement. The frame rate should at least be between 40 to 80 frames per second, but it is advised to use higher frame rates to optimize tracking. (17)

The myocardium reflects sound waves due to a relative difference in acoustic impedance between the different areas. A special software can identify those reflection patterns, interprets and tracks them as speckles frame by frame. These speckles don’t represent myocardial structures but move together with the tissue.(19)

It depends on the publication which timing should be used for peak strain. Some say it should be measured at peak systolic strain, others say peak strain at the end-systole, some say it is time independent.(18)

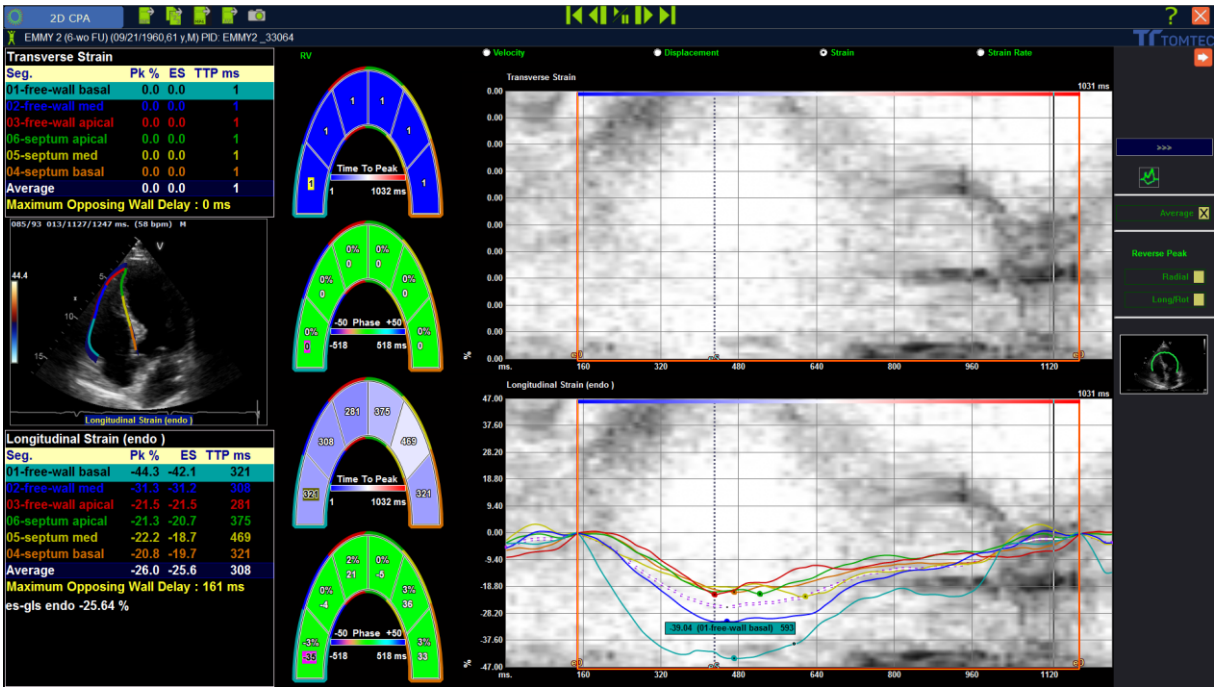

Figure 3 right ventricular strain

1.4.7 Strain and its role in heart failure

The importance of right ventricular systolic dysfunction in the development of heart failure has gained attention recently. Particularly in patients with heart failure with reduced ejection fraction (HFrEF), RV dysfunction has been linked to decreased survival rates. While conventional measures like Doppler tissue imaging S′ velocity have shown effectiveness in predicting adverse outcomes and exhibit a significant correlation with right ventricular ejection fraction measured by cardiac magnetic resonance, RV strain analysis has emerged as the most precise and sensitive method for evaluating RV function. Its ability to detect subclinical RV dysfunction is particularly notable. RV strain analysis also correlates well with invasive hemodynamic measurements and clinical functional assessments, offering a superior evaluation of RV systolic performance. Importantly, RV strain has proven to be a robust prognostic indicator, with lower values associated with higher mortality, urgent need for transplantation, and acute HF admissions during short-term follow-up. Additionally, RV strain adds prognostic value to assessments of left ventricular ejection fraction in patients with chronic systolic HF, underscoring RV function's critical influence on HF's progression and highlighting the necessity for early and accurate detection of subtle RV systolic impairments.(14,16,18,20)

Notably, RV systolic dysfunction is not only observed in patients with HF with reduced ejection fraction, where RV involvement is more common, but also in a significant number of patients with heart failure with preserved ejection fraction (HFpEF). This may result from increased RV afterload due to chronic pulmonary venous hypertension or comorbidities that affect LV longitudinal function, such as type 2 diabetes, obesity, hypertension, and others. Recent findings by Morris et al. indicate that RV strain is diminished in patients with HFpEF compared to asymptomatic controls with LV diastolic dysfunction, despite conventional parameters indicating good outcomes. Like the reduced ejection fraction group, two-dimensional speckle-tracking echocardiography (2D STE) strain more effectively identified subclinical RV changes, even in patients with normal tricuspid annular plane systolic excursion, TDI S′, and fractional area change values.(14,16,18,21)

1.5 Myocardial infarction and HI

Heart failure and myocardial infarction are two correlated cardiovascular conditions that significantly impact the health and well-being of individuals worldwide. The term myocardial infarction refers to the regional destruction of heart muscle tissue (myocardium) due to a local circulatory disorder. The cause is often the narrowing of the lumen of a branch of the coronary vessels. This ischemic injury results in impaired cardiac function, ultimately contributing to heart failure. HF, on the other hand, is a chronic condition characterized by the heart's inability to pump blood efficiently to meet the body's needs. It can develop gradually over time or occur suddenly, in several cases as a consequence of underlying cardiovascular diseases such as myocardial infarction.(5,22)

The relationship between myocardial infarction and heart failure is complex, with myocardial infarction being an important risk factor for the development of heart failure. The damage caused by myocardial infarction can weaken the heart muscle, leading to a reduced ventricular ejection fraction and subsequently to heart failure. In addition, heart failure caused by myocardial infarction is often accompanied by adverse remodeling of the heart, including changes in the size, shape and function of the heart chambers. Of particular importance are the effects of myocardial infarction

on the right ventricle, which plays a crucial role in maintaining effective circulatory function.(3,11,23)

Studies have shown that myocardial infarction can have significant deleterious effects on RV function. The RV is particularly susceptible to ischemic damage due to its unique anatomic and physiologic characteristics. Unlike the left ventricle, which receives the majority of the coronary blood flow, the right is supplied with blood primary from the right coronary artery. Consequently, occlusion of the right coronary artery during myocardial infarction can lead to ischemia and subsequent RV dysfunction. In addition, the close anatomical proximity of the RV to the left ventricle means that changes in LV function caused by myocardial infarction may also affect RV performance, through mechanisms such as ventricular interdependence.(3,5,11,23)

In addition to ischemic injury, other factors associated with myocardial infarction, such as inflammation, oxidative stress and neurohormonal activation, may contribute to RV dysfunction and the development of heart failure. These pathophysiological processes can lead to myocardial fibrosis, ventricular dilatation and impaired contractility, which further impairs RV function. As a result, patients with myocardial infarction are at increased risk of developing both left and right-sided heart failure, with RV dysfunction being an important prognostic indicator of unfavorable outcomes.(3,11,23)

1.5.1 Etiologies and classification of heart failure

Heart failure classification continues to rely on LVEF. This approach persists because trials involving patients with reduced ejection fraction have identified drugs and devices that enhance outcomes.(23,24) Thus, a diminished LVEF characterizes a subgroup of patients in whom multiple mechanisms, including neurohormonal activation, tachycardia, or LV desynchrony, contribute to the progression of LV dysfunction and treatment outcomes. As a result, a network meta-analysis revealed that a combination of three neurohormonal antagonists, possibly including ivabradine if necessary, is associated with the most significant reduction in the risk of death, HF hospitalizations, or both.(24,25)

Another important cause of heart failure is cardiac amyloidosis. This is particularly important in the current situation, as a randomized clinical trial has found a specific treatment for transthyretin amyloidosis. According to a recent Heart Failure Association consensus paper, older patients with HF, especially those with preserved ejection fraction, who are not hypertensive or have features of hypertrophic or restrictive cardiomyopathy, degenerative aortic stenosis and progressive HF, should be screened for cardiac transthyretin amyloidosis. Hereditary transthyretin amyloidosis may have unique features compared to wild-type transthyretin amyloidosis, such as an earlier age of onset and a higher likelihood of mild neurologic involvement..(24,26)

1.5.2 Therapy of heart failure

The treatment of heart failure caused by myocardial infarction involves a multidisciplinary approach that aims to treat both the underlying cause and the associated symptoms. Acute treatment strategies for myocardial infarction focus on restoring blood flow to the ischemic myocardium through reperfusion therapies such as percutaneous coronary intervention (PCI) or thrombolytic therapy. These measures aim to limit damage to the heart muscle and preserve ventricular function, thereby reducing the risk of subsequent heart failure.

Chronic treatment of heart failure usually involves pharmacological interventions aimed at relieving symptoms, improving quality of life and preventing disease progression. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) are the basic treatments for heart failure. They work by relaxing the blood vessels and lowering blood pressure, thereby reducing the workload on the heart. Beta-blockers, on the other hand, are crucial in the treatment of heart failure as they reduce the heart rate and the force of contraction of the heart, thereby reducing the heart's oxygen demand. Mineralocorticoid receptor antagonists help reduce mortality and hospitalization rates by counteracting the effects of aldosterone, a hormone that can cause salt and water retention, leading to volume overload. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) help treat heart failure by promoting the excretion of glucose and sodium via the urine, which can help reduce blood volume and improve heart function.(3,5,11,27,28)

1.5.2.1 ACE inhibitors

The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the development and progression of congestive heart failure (CHF). Abnormal activation of the RAAS adversely affects cardiac performance, increasing both afterload and preload, and impairing functional status. Conventional first-line therapies for CHF include diuretics and digitalis, which offer rapid symptom relief and effective volume control but also activate neurohormonal systems, leading to increased vasoconstriction.

ACE inhibitors, such as captopril, enalapril, and quinapril, have emerged as preferred treatments for CHF. They work by inhibiting the production of angiotensin II from angiotensin I, thereby blocking the RAAS. This results in improved hemodynamics, reduced symptoms of fatigue and dyspnea, increased exercise capacity, correction of hyponatremia, reduced diuretic requirements and ventricular arrhythmias, and conservation of potassium and magnesium. ACE inhibitors also lower circulating levels of angiotensin II, aldosterone, plasma norepinephrine, and vasopressin. ACE inhibitors are effective in both mild to moderate and severe heart failure, offering acute and long-term symptomatic, hemodynamic, and exercise-related benefits, as well as improved functional status and potentially slowed disease progression with enhanced survival. They are at least as beneficial as digitalis in mild heart failure and can be considered first-line therapy. Promising results have also been observed in myocardial infarction patients, where long-term ACE inhibitor therapy has prevented heart enlargement. Captopril, the first orally effective ACE inhibitor, has shown significant improvements in exercise tolerance and functional class in large trials involving severe and mild to moderate heart failure patients. The CONSENSUS trial demonstrated that enalapril reduces mortality in severe heart failure patients. Quinapril has been shown to improve hemodynamic status and exercise tolerance in a dose-related manner, both acutely and chronically. ACE inhibitors generally have a favorable safety profile, although initial doses can cause hypotension, especially in volume-depleted patients or when administered excessively.(29,30)

1.5.2.2 AT1 receptor antagonists

Angiotensin II type 1 receptor antagonists, also referred as angiotensin receptor blockers, play a significant role in the management of heart failure. These medications, which include losartan, valsartan, and candesartan, function by blocking the effects of angiotensin II, a potent vasoconstrictor, thus preventing blood vessel constriction and promoting vasodilation. This leads to reduced blood pressure and decreased workload on the heart, which is particularly beneficial for heart failure patients. ARBs improve hemodynamics by decreasing afterload and preload, thus enhancing cardiac performance and reducing symptoms such as fatigue and dyspnea. They also help to manage fluid retention and reduce the risk of ventricular arrhythmias, which are common in heart failure. Unlike ACE inhibitors, ARBs do not cause a persistent cough, making them a suitable alternative for patients who experience this side effect.(31,32)

Clinical studies have shown that ARBs can be as effective as ACE inhibitors in improving survival and reducing hospitalizations in heart failure patients. For instance, trials like the ADEPT study demonstrated that adding ARBs to standard heart failure therapy, which often includes ACE inhibitors, can offer additional benefits by providing more complete blockade of the renin-angiotensin-aldosterone system.(33)

Overall, ARBs are a valuable option in the therapeutic repertoire against heart failure, offering significant benefits in terms of symptom relief, improved exercise capacity, and enhanced quality of life, with a generally favorable safety profile.

These medications have been shown to improve left ventricular function and reduce morbidity and mortality in patients with heart failure. The aim is to reduce high blood pressure or at least to keep it <140 mmHg. One of the key features in the therapy of chronic heart failure is the improvement of the patient's lifestyle. It is highly desirable that patients stop smoking, reduce their alcohol intake, watch their weight and try to exercise regularly. Furthermore a antithrombotic therapy consisting of low dose aspirin should be implemented by all patients with ST-segment elevation myocardial infarction (STEMI).(34) A dual antiplatelet therapy (DAPT) for up to 12 months is recommended for every patient undergoing PCI.(20,23,28,34)

However, the optimal management of myocardial infarction-induced heart failure also requires careful consideration of the effects on the right ventricle. While many of the therapeutic strategies used in the management of left-sided heart failure are also applicable to right-sided heart failure, there are unique challenges associated with RV dysfunction that must be addressed. For example, therapies such as phosphodiesterase inhibitors and inotropic agents could be used to improve RV contractility and hemodynamics in patients with severe RV dysfunction. Additionally, mechanical circulatory support devices such as right ventricular assist devices (RVADs) may be considered in refractory cases of RV failure.(3,5,11,23)

1.5.3 Classification of heart failure

Considering that the symptoms of heart failure indicate the extent of the mismatch between the heart's ability to pump blood and the body's metabolic demands, the syndrome is described as a spectrum rather than a single physiological state. The American College of Cardiology/American Heart Association (table 2) and the New York Heart Association (table 1) have established the two most used classification systems. The NYHA classification system categorizes HF based on symptoms and exercise capacity.(35,36)

NYHA Class	Symptom Presentation
Class I	No limitation of physical activity; no symptoms at rest
Class II	Slight limitation of physical activity; symptoms at rest
Class III	Marked limitation of physical activity; symptoms at rest
Class IV	Unable to carry out any physical activity; symptoms at rest

Table 1 NYHA classification

stages	criteria
A At risk for heart failure	People who are at risk for heart failure but do not yet have symptoms or structural or functional heart disease Risk factors for people in this stage include hypertension, coronary vascular disease, diabetes, obesity, exposure to cardiotoxic agents, genetic variants for cardiomyopathy and family history of cardiomyopathy
B Pre-heart failure	People without current or previous symptoms of heart failure but with either structural heart disease, increased filling pressures in the heart or other risk factors
C Symptomatic heart failure	People with current or previous symptoms of heart failure
D Advanced heart failure	People with heart failure symptoms that interfere with daily life functions or lead to repeated hospitalizations

Table 2 stages of heart failure by the american heart association(36)

In summary, myocardial infarction and heart failure are closely interconnected cardiovascular conditions with significant implications for patient outcomes. The impact of myocardial infarction on RV function is an important consideration in the management of myocardial infarction-induced heart failure, highlighting the need for tailored therapeutic approaches that address both left-sided and right-sided ventricular dysfunction. By adopting a comprehensive and multidisciplinary approach to care, clinicians can optimize outcomes and improve the quality of life for patients with myocardial infarction-induced heart failure.(5,7,11,23)

1.6 SGLT2-Inhibitors

Sodium-glucose co-transporter-2 inhibitors have gained significant attention in recent years due to their remarkable cardiovascular benefits, particularly in heart failure management. They were initially developed as a blood glucose lowering agent but with the release of updated clinical practice guidelines by the European Society of Cardiology (ESC) focusing on the management of HF, it is crucial to delve deeper into the pharmacology of SGLT-2 inhibitors and their specific effects on HF.(37–39)

1.6.1 Pharmacology of SGLT-2 Inhibitors

SGLT-2 inhibitors, originally developed as antidiabetic drugs exert their therapeutic effects by blocking the reabsorption of glucose and sodium in the renal proximal tubule, leading to increased urinary excretion of glucose and a following reduction in blood glucose levels. The effect is dependent on the patient's glomerular filtration rate and also on plasma glucose. However, beyond their antihyperglycemic properties, SGLT-2 inhibitors have demonstrated pleiotropic effects with significant implications for cardiovascular health. These effects include lowering preload by promoting osmotic diuresis through natriuresis, reductions in blood pressure by reduction in afterload and a reduction in arterial stiffness. Moreover, emerging evidence suggests that SGLT-2 inhibitors may exert direct cardioprotective effects through various mechanisms, including modulation of myocardial metabolism, reduction of oxidative stress and inflammation, and improvement of endothelial function. (37–40)

1.6.2 Effect of SGLT-2 Inhibitors on Heart Failure

The ESC guidelines emphasize the pivotal role of SGLT-2 inhibitors in the management of HF, particularly in patients with reduced ejection fraction. Clinical trials have demonstrated the efficacy of SGLT-2 inhibitors in reducing the risk of HF hospitalization and cardiovascular death in patients with HFrEF, independent of their diabetic status. This is due to the fact, that SGLT-2 inhibitors have a positive effect on ventricular remodeling, cardiac metabolism and direct cardioprotective mechanisms. The improvement in heart metabolism involves decreasing carbohydrate intake while enhancing the use of fatty acids and ketone bodies. This process benefits the heart muscle directly through several mechanisms, including the suppression of the Sodium/Hydrogen exchanger 1 (which raises mitochondrial Calcium levels), diminishing the activity of the Calcium/calmodulin-dependent kinase (which also improves muscle contractility by decreasing the leak of sarcoplasmic Calcium), elevating the phosphorylation of proteins that regulate myofilaments (thereby enhancing diastolic function), and potentially inducing beneficial epigenetic changes.(28,37–39)

Theoretical understanding suggests, that SGLT2 inhibitors have beneficial molecular and pathophysiological impacts on the heart that are relevant before, during, and after a heart attack, whether diabetes is present or not. Research involving various animal models has demonstrated, that preemptive administration of SGLT2-inhibitors can decrease the size of heart attacks, enhance the heart's pumping ability and significantly boost survival rates 48 hours following a heart attack. It's hypothesized that the protective effect against heart damage provided by long-term SGLT2-inhibitors treatment comes from either a glucose-independent mechanism or the activation of pathways within the heart that positively promote cell survival.(40,41)

In the EMPA-REG OUTCOME trial which included patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD), empagliflozin was found to significantly reduce the risk of all-cause mortality (ACM) by 31% compared to placebo. Additionally, it lowered the total events leading to all-cause hospitalization (ACH) by 17%. The treatment effect of empagliflozin was observed to be numerically greater when considering recurrent events versus first-event analyses.(21,28,42)

The same results could also be observed in the DAPA-HF study where during the observation period of around 18 months, the primary outcome (a composite of worsening heart failure or cardiovascular death) occurred in 386 out of 2373 patients (16.3%) in the dapagliflozin group, compared to 502 out of 2371 patients (21.2%) in the placebo group. The authors concluded, that treatment with dapagliflozin reduced the risk of worsening HF or death from cardiovascular causes among patients with HF.(43)

The EMPEROR-Reduced trial confirmed the findings of the DAPA-HF trial, demonstrating that SGLT2 inhibitors significantly reduce the risk of cardiovascular death and heart failure hospitalization compared to placebo (hazard ratio 0.67, 95% CI [0.50–0.90], P = 0.008). Moreover, patients treated with empagliflozin in the EMPEROR-Reduced trial were 20–40% more likely to experience an improvement in their New York Heart Association (NYHA) functional class and 20–40% less likely to experience a worsening of their NYHA functional class compared to those on placebo. However, the empagliflozin group also showed a higher incidence of uncomplicated urinary tract infections. This study highlighted that the beneficial

effects observed are a class effect of SGLT2 inhibitors and not limited to a specific drug like dapagliflozin. Additionally, the EMPEROR-Reduced trial provided evidence of these benefits in patients with severe heart failure, who are at a higher risk for adverse events and mortality. Notably, more than 70% of the participants in the EMPEROR-Reduced trial had an EF of ≤30%, whereas the DAPA-HF trial included patients with mild to moderate heart failure.(28,44)

The EMPEROR-Preserved study showed that in patients with HFpEF, SGLT2 inhibition with empagliflozin resulted in a 21% reduction in the relative risk of the composite outcome of cardiovascular death or hospitalization for heart failure. This reduction was primarily due to a 29% lower risk of hospitalization for heart failure treated with empagliflozin. These benefits were consistent across all prespecified subgroups, including those with and without diabetes. Empagliflozin also decreased the total number of hospitalizations for heart failure and extended the time to the first hospitalization for heart failure. These benefits are comparable to those observed in the EMPEROR-Reduced trial, suggesting that the positive effects of SGLT2 inhibition on heart failure events are similar regardless of the heart failure phenotype.(45)

Another study, the DELIVER study for heart failure with mildly reduced ejection fraction (HFmrEF) and HFpEF, investigated the effects of Dapagliflozin in HFmrEF or HFpEF. The results showed that over the time of 2.3 years the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Dapagliflozin has been shown to reduce the combined risk of worsening heart failure or cardiovascular death in patients with heart failure and a mildly reduced or preserved ejection fraction. This benefit highlights the effectiveness of dapagliflozin in managing heart failure across different ejection fraction categories, providing an important therapeutic option for a broader range of heart failure patients.(28,46)

The EMMY-Trial on the other hand focused on the effects of SGLT2 inhibitors in patients following acute myocardial infarction. The primary outcome was defined as the change of NT-proBNP over 26 weeks. In patients with HFpEF, empagliflozin significantly outperformed placebo in several key measures. The reduction in NT-proBNP levels was 15% greater in the empagliflozin group compared to placebo, after adjustments for baseline NT-proBNP, sex, and diabetes status were made (P = 0.026). Additionally, empagliflozin led to a significant improvement in absolute left-ventricular ejection fraction, which increased by 1.5% (95% CI 0.2-2.9%, P = 0.029. The mean E/e' reduction was 6.8% greater in the empagliflozin group (95% CI 1.3-11.3%, P = 0.015). In the empagliflozin group, the left-ventricular end-systolic volume (LVESV) and end-diastolic volume (LVEDV) were significantly lower by 7.5 mL (95% CI 3.4-11.5 mL, P = 0.0003) and 9.7 mL (95% CI 3.7-15.7 mL, P = 0.0015), respectively, compared to the placebo group. In patients with a recent myocardial infarction, treatment with empagliflozin over 26 weeks led to a significantly greater reduction in NT-proBNP levels. This reduction was accompanied by notable improvements in echocardiographic functional and structural parameters. These findings suggest that empagliflozin not only helps in lowering biomarkers associated with heart failure but also enhances cardiac function and structure following a myocardial infarction.(37)

It has also been shown that in patients with chronic kidney disease, regardless of whether they have diabetes, dapagliflozin significantly lowered the risk of a composite outcome that included a sustained decline in estimated GFR of at least 50%, progression to end-stage kidney disease, or death from renal or cardiovascular causes, compared to a placebo. In the DAPA-CKD trial the primary outcome event occurred in 9,2% in the dapagliflozin group and in 14.5% in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The study was conducted over a median of 2.4 years.(21,47)

The EMPACT-MI trial came to the conclusion that in patients at increased risk for heart failure following an acute myocardial infarction, treatment with empagliflozin did not result in a significant reduction the risk of a first hospitalization for heart failure or death compared to placebo (The primary outcome occurred in 8.2% in the

empagliflozin group and in 9.1% in the placebo group (hazard ratio, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21)).(48)

Regarding long time effects the DAPA-MI trial showed that one year of treatment with dapagliflozin resulted in significant improvements in cardiometabolic outcomes in patients with acute myocardial infarction (AMI) in comparison with the placebo group (win ratio, 1.34; 95% confidence interval [CI], 1.20 to 1.50; P<0.001). However, the study came to the same conclusion as the EMPACT-MI trial that this treatment doesn't affect the composite outcome of cardiovascular death or hospitalization for heart failure.(20,48,49)

These findings have led to the inclusion of SGLT-2 inhibitors as a cornerstone therapy in the management of heart failure, alongside angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists. Notably, the benefits of SGLT-2 inhibitors extend beyond HFrEF, with emerging data suggesting potential benefits in HF with preserved ejection fraction and HF with mid-range ejection fraction, although further research is needed to elucidate their precise role in these populations.(28,50)

SGLT-2 inhibitors represent a paradigm shift in the management of HF, offering novel therapeutic options with significant cardiovascular benefits beyond glycemic control. Their multifaceted pharmacological effects, including glucose-lowering, natriuretic, and cardioprotective properties, underscore their potential as cornerstone therapies in the management of HF across the spectrum of ejection fraction phenotypes. As ongoing research continues to elucidate the mechanisms underlying their cardiovascular benefits, SGLT-2 inhibitors are poised to revolutionize the landscape of HF management, offering hope for improved outcomes and quality of life for patients with this debilitating condition.(28,37–39)

1.7 Aim of the thesis

This thesis aims to explore the impact of combining standard treatment with Empagliflozin versus standard treatment with Placebo on the function and size of the right ventricle in the context of the EMMY-trial, following a myocardial infarction.

Additionally, it seeks to provide deeper understanding into the role of the right ventricle in the aftermath of a myocardial infarction and heart failure.

2 Methods

The information utilized for this diploma thesis was derived from a subset of patients receiving treatment at the Department of Cardiology, Medical University of Graz, within the framework of the EMMY study (Effect of Empagliflozin on cardiac function and biomarkers of heart failure in patients with acute myocardial infarction).

2.1 Study overview and Study population

In this academic, multicenter, double-blind study, a total of 476 patients with acute myocardial infarction accompanied by a substantial elevation in creatine kinase (over 800 IU/L) were randomly allocated to receive either empagliflozin 10 mg or a matching placebo once daily within 72 hours of percutaneous coronary intervention. The primary endpoint was the change in N-terminal pro-hormone of brain natriuretic peptide levels over a period of 26 weeks. Secondary endpoints included alterations in echocardiographic parameters. Following the provision of written informed consent, qualified patients were randomly assigned in a 1:1 ratio to receive either oral empagliflozin 10 mg once daily or a matching placebo using Randomizer Software (Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, http://www.randomizer.at). The randomization schedule was generated by an independent statistician. Stratification for randomization was based on site, presence of Type 2 diabetes (yes/no), and sex. Subsequent follow-up visits were scheduled at 6, 12, and 26 weeks.

The inclusion criteria for this study involve AMI with clear indications of significant myocardial necrosis, characterized by a rise in creatine kinase levels exceeding 800 U/L and a troponin T-level (or troponin I-level) reaching ten times the upper limit of normal. These stringent criteria are established to enhance the potential for a favorable treatment response to empagliflozin. Additionally, patients must exhibit symptoms of ischemia and/or show electrocardiogram changes suggestive of new ischemia and/or present imaging evidence of new regional wall motion abnormality.

Furthermore, certain medical parameters must meet specific thresholds: an estimated glomerular filtration rate (eGFR) higher than 45 mL/min per 1.73m^2, a systolic blood pressure exceeding 110 mmHg, and a diastolic blood pressure

surpassing 70 mmHg before the initial administration of the study drug. The commencement of the study medication should occur within the first 72 hours following myocardial infarction or within 72 hours following coronary angiography.

Moreover, participants must fall within the predefined age range of 18 to 80 years. These criteria collectively aim to ensure a homogeneous study population and maximize the likelihood of observing meaningful treatment effects with empagliflozin.

On the other hand, the exclusion criteria for this study encompassed individuals with any form of diabetes mellitus other than type 2, a history of diabetic ketoacidosis or a blood pH level below 7.32. Additionally, participants with a known allergy to SGLT-2 inhibitors, those experiencing hemodynamic instability necessitating intravenous administration of catecholamines, calcium sensitizers, or phosphodiesterase inhibitors were excluded.

Individuals who had encountered more than one episode of severe hypoglycemia within the past 6 months while under treatment with insulin or sulfonylureas were also ineligible for inclusion. Furthermore, fertile females lacking adequate contraceptive methods (such as sterilization, intrauterine device, or having a vasectomized partner) or those with a medical history of hysterectomy were excluded.

Patients with acute symptomatic urinary tract infections or genital infections were excluded, as were individuals currently undergoing treatment with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or those who had received such treatment within the 4 weeks preceding the screening visit. These criteria were established to ensure the safety and integrity of the study outcomes.

2.2 Transthoracic Echocardiography

Transthoracic echocardiography assessments were conducted on each patient during visits 1, 2, and 4, following the guidelines outlined by the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). These studies were carried out by experienced cardiologists utilizing locally available ultrasound devices, such as the Vivid 7 or Vivid E9 from GE Healthcare (Chalfont St Giles, UK), and the Siemens Acuson SC2000.

The image rate was set to a minimum of seventy frames per second during the examinations. Simultaneously, an ECG was recorded for each measurement. The loops and images were subsequently transferred to the digital archive ISCV.

The two-dimensional clips and images, adhering to a Standard Imaging Protocol, primarily encompass three positions and specific views. These include the parasternal long-axis view (PLAX), parasternal short-axis views (PSAX), apical 4 chamber view (A4C), apical 5 chamber view (A5C), apical 2 chamber view (A2C), apical long-axis (A3C), subcostal 4 chamber view (SC 4C), and in specific instances, a suprasternal notch view of the aortic arch (SSN aortic arch).

During imaging, it's imperative to store the baseline of a few cardiac cycles of plain two-dimensional images to capture cardiac anatomy and performance accurately. Additionally, ECG recording should be conducted in every study to facilitate easier recognition of heart cycles by the machine. In the EMMY trial, a minimum of three cardiac cycles were recorded per study.

2.3 Trial procedure

All studies were analyzed locally in DICOM-format using the post processing program TomTec. The image data consisted of digitally saved, ECG triggered 2D transthoracic echocardiography (2DTE) cine loops of the apical four chamber-view.

After acquisition the studies were stored in the IntelliSpace Cardiovascular, where the software could acquire them directly. In this thesis only local data from the Medical University of Graz was used, due to the fact that not all sites who took part in the study were able to provide loops for core lab analyses.

For this thesis all the measurements were done twice and then the average value of every measurement was calculated.

2.3.1 RV dimensions

The quantitation of RV dimensions was obtained via two-dimensional echocardiography (2DE). However, these measurements pose challenges due to the RV's complex geometry and the absence of specific right-sided anatomical

landmarks for reference. The conventional apical four-chamber view, primarily focused on the left ventricle, leads to variability in RV sectioning, resulting in wide variations in RV linear dimensions and areas within the same patient due to minor transducer position changes. For accurate measurements RV-focused apical four-chamber views, ensuring that the left ventricular apex is at the center of the scanning sector while displaying the largest basal RV diameter to prevent foreshortening, were used for this study.

2.3.2 RV systolic function

To assess RV systolic function multiple parameters were evaluated. The fractional area change serves as an estimate of global right ventricular systolic function. It was ensured that the entire right ventricle, including the apex and the free wall, was captured within the imaging sector during both systole and diastole. This comprehensive imaging is crucial for accurate assessment of RV function using FAC, as it provides a reliable measure of the overall contraction and relaxation of the right ventricle throughout the cardiac cycle.

Furthermore, tricuspid annular plane systolic excursion is a readily obtainable measurement that serves as an indicator of right ventricular longitudinal function. It was measured using M-mode echocardiography, with the cursor ideally aligned along the direction of the tricuspid lateral annulus in the apical four-chamber view. This technique provides valuable information about the movement of the tricuspid annulus during systole and indicating the extent of RV longitudinal contraction.

Strain and strain rate also serve as valuable parameters for estimating both global and regional systolic function of the right ventricle. Longitudinal strain represents the percentage of systolic shortening of the RV free wall from base to apex, while longitudinal strain rate measures the rate of this shortening. Unlike other measures, RV longitudinal strain is less affected by overall heart motion but can be influenced by RV loading conditions, as well as RV size and shape. It is typically calculated in the RV-focused four-chamber view. However, it's important to note that compared to strain derived from speckle-tracking echocardiography, strain derived from Doppler tissue imaging suffers from angle dependency, which is a disadvantage.

Furthermore, RV speckle-tracking echocardiographic strain can be influenced by factors such as image quality, reverberation, artifacts, and attenuation, all of which should be considered during interpretation.

For more information TDI-derived S´- wave was also raised. It was attempted to keep the basal segment and annulus aligned with the Doppler curser for more exact measurements.

2.3.3 Assessment of strain

Strain was measured by using a software tool made specifically for speckle-tracking called 2D Cardiac Performance Analysis from TOMTEC Imaging Systems. The investigator picked an RV-focused apical four-chamber views, ensuring that the left ventricular apex is at the center of the scanning sector while displaying the largest basal RV diameter to prevent foreshortening. At least three cardiac cycles were recorded, so that the best out of those could be used for the measurements. First the end- systole (ES) and the end-diastole (ED) of the right ventricle were defined by the user manually while using the M-Mode to ensure the maximal contraction and maximal relaxation of the ventricle. Then the software placed three reference points automatically to trace the endomyocardial line. The user then corrected those lines to protect the quality of the measurements. This is due to the fact that the automatic editing done by the software has difficulties taking measurements correctly when the image quality is poor. After the corrections were made, the program initiated the analysis of the deformation. The program then creates a color-coded loop of longitudinal strain values, with strain and strain rate curves among other data respectively.

2.3.4 Statistical analysis

All the collected data was transferred manually into Microsoft Excel 365 and was split into different groups for good visibility. Strain data was exported automatically using a macro, cleaned and then also transferred to Excel. Then all the important data was

statistically analyzed with a double t-test by using a program called The R Project for Statistical Computing.

3 Results

3.1 Subjects

Table 5 presents the demographic details and descriptive statistics of the study participants. The study included 219 patients, with a gender distribution of 82.6% males (181 individuals) and 17.4% females (38 individuals). Participants' ages ranged from 33 to 80 years, with an average age of 58.35 years, broken down by gender to 57.92 years for males and 60.37 years for females, with standard deviations of 9.34 and 9.71, respectively.

The average Body Mass Index (BMI) for the group was 28.27 kg/m^2, with males averaging 28.46 kg/m^2 and females at 27.37 kg/m^2, and standard deviations of 3.84 and 5.26, respectively. According to the World Health Organization's BMI classification, 20.56% of participants (45 individuals) were categorized as normal weight, 52.51% (115 individuals) were in the pre-obesity range, 20.09% (44 individuals) were classified as obesity class I, 5.94% (13 individuals) as obesity class II, and 2 individuals were classified as obesity class III.

11.9% of the participants (26 individuals) were diagnosed with diabetes, additionally 8.7% (19 individuals) had hyperlipidemia. The average HbA1c level was 5.84%, with males averaging 5.88% and females 5.66%, and standard deviations of 1.08% and 0.72%, respectively.

Regarding lifestyle-related risk factors, 69.4% of the patients (152 individuals) were identified as smokers, with a slight gender variation showing 70.2% of males and 65.8% of females. Within this smoking subgroup, the average duration of smoking was reported at 29 years, with males at 29.69 years and females slightly lower at 25.61 years, alongside standard deviations of 11.42 and 11.61 years, respectively. The daily nicotine intake among smokers averaged 22 cigarettes, with males consuming 22.5 and females 20.58 cigarettes per day, and standard deviations of 14.12 and 10.41, respectively.

Furthermore, 6.4% of the participants had a prior diagnosis of coronary artery disease (CAD), and 1.4% had undergone percutaneous transluminal coronary angioplasty (PTCA), with two individuals receiving bypass surgery. The median c-

reactive protein (CRP) level within the study group was 5 mg/dl, with males showing a median of 4.6 mg/dl and females higher at 5.8 mg/dl.

Glomerular filtration rate (GFR) measurements indicated normal renal function across the cohort, with a median value of 93 ml/min/1.73 m^2, split by gender to 92.27 for males and 94.52 for females. A significant 99.51% of participants exhibited elevated NT-proBNP levels (≥ 125 pg/ml), with a median value of 1344 pg/ml for the group, with males and females showing medians of 1200 pg/ml and 2251 pg/ml, respectively.

High-sensitivity troponin (hsTrop) levels also varied, presenting a median value of 3791 µg/l across the board, with males slightly higher at 3843 µg/l and females at 3661.5 µg/l. Initial visit blood pressure readings showed a median of 125/76 mmHg, detailed further to 126/76 mmHg for males and 121.5/77 mmHg for females. Elevated systolic blood pressure (≥ 140 mmHg) was observed in 6.85% of the study participants, while elevated diastolic pressure (≥ 90 mmHg) was noted in 7.31% of the subjects.

Variables	Overall	Male	Female	N
Gender [%]	100	82.6	17.4	219
Age [years]	58.35 ± 9.43	57.92 ± 9.34	60.37 ± 9.71	219
BMI [kg/m2]	28.27 ± 4.12	28.46 ± 3.84	27.37 ± 5.26	219
Smoking [%]	69.4	70.2	65.8	219
Smoking Years [years]	28.99 ± 11.53	28.57 ± 12.23	31.12 ± 6.70	152
Cigarettes [total]	22.17 ± 13.56	22.87 ± 13.12	18.64 ± 15.42	152
Arterial Hypertension	71 (32.4%)	54 (29.8%)	17 (44.7%)	219
CAD [n]	14 (6.4%)	11 (6.1%)	3 (7.9%)	219
PTCA [n]	3 (1.4%)	3 (1.7%)	0 (0%)	219
Bypass [n]	2 (0.9%)	2 (1.1%)	0 (0%)	219
STEMI	179 (81.7%)	147 (81.2%)	32 (84.2%)	219
Hyperlipidemia [n]	19 (8.7%)	16 (8.8%)	3 (7.9%)	219
Diabetes [n]	26 (11.9%)	22 (12.2%)	4 (10.5%)	219
HbA1c V1 [%]	5.84 ± 1.03	5.88 ± 1.11	5.63 ± 0.39	209
hsTrop V1 [µg/l]	median: 3791	median: 3843	median: 3661.5	219
CRP_V1 [mg/dl]	median 4.7	median: 4.6	median: 5.8	218
GFR_V1 [ml/min]	median: 92.79	89.91 ± 14.14	90.97 ± 16.29	219
NT-proBNP [pg/ml]	median: 1344	median: 1200	median: 2251	203
BP_sys [mmHg]	125.16 ± 9.59	125.46 ± 9.42	123.68 ± 10.39	219
BP_dias [mmHg]	78.21 ± 6.25	78.17 ± 6.27	78.37 ± 6.22	219

Table 3 Deskriptive Statistics

The values are presented as the mean ± standard deviation. BMI = Body Mass Index, CAD = Coronary Artery disease, PTCA = percutaneous translumenal coronary angioplasty, STEMI= ST elevation myocardial infarction, HbA1c = Hemoglobin A1c, hsTrop = high-sensitivity cardiac troponin, CRP = C-reactive protein, GFR = Glomerular filtration rate, BP = Blood pressure.

3.2 Endo GLS

At visit 3 Participants in the empagliflozin group demonstrated an average Endo GLS value of -23.83, in comparison to the placebo group, which showed an average value of -23,57. With the p-value of 0.641 The null hypothesis that there is no significant difference between the two groups cannot be rejected. The boxplot shows no significant increase over the time in Endo GLS in both groups.

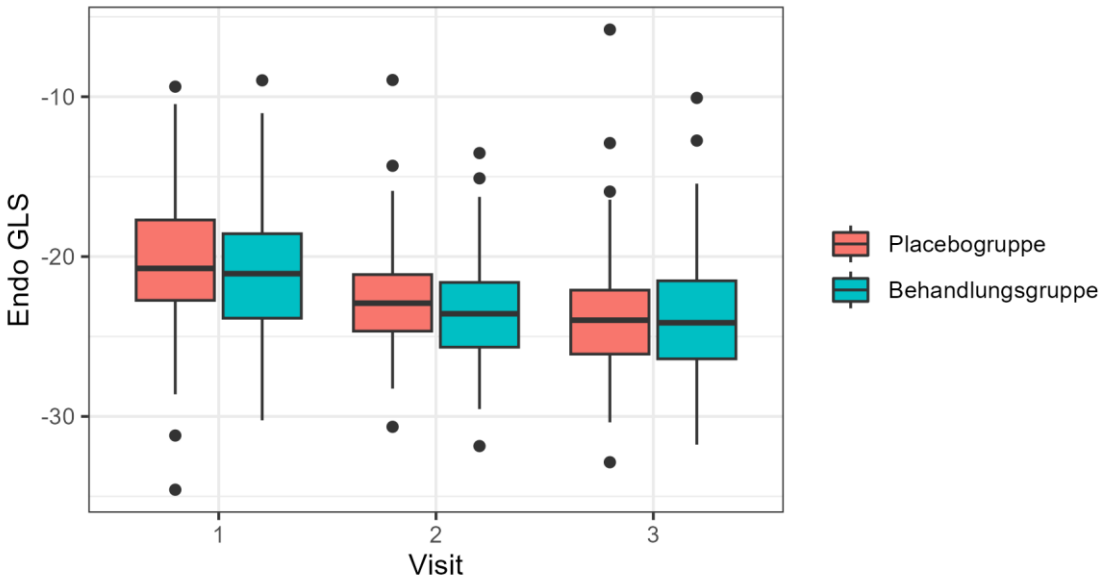

Figure 4 Endo GLS

3.3 FAC and TAPSE

The mean FAC in the empagliflozin group was 41,73%, in comparison to 41,45% in the placebo group. The double-t-test showed a p-value of 0.727 for the FAC and a p-value of 0.839 for the TAPSE. The null hypothesis that there is no significant difference between the groups cannot be rejected.

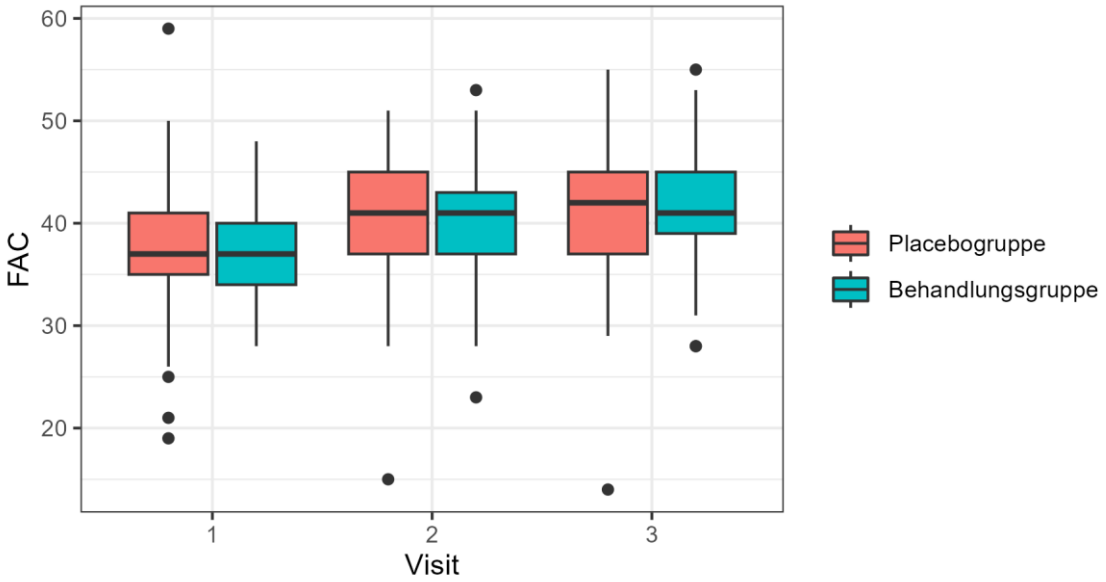

Figure 5 FAC

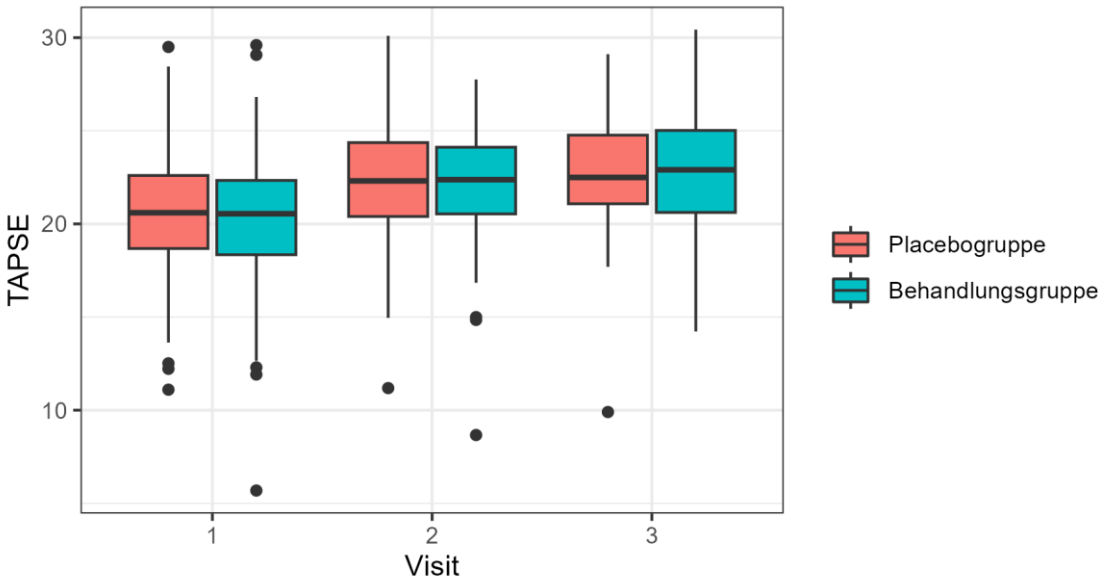

Figure 6 TAPSE

3.4 TCO and S lat.

The mean tricuspid (valve) closure opening time (TCO) at visit 3 was 481 for the empagliflozin group and 469 for the placebo group. The mean S´ lat. at visit 3 was 10.21 for the empagliflozin group and 10.33 for the placebo group. The two sample-t-test showed a p-value of 0.086 for TCO and a p-value of 0.628 for S´ lat. The null hypothesis that there is no significant difference between the groups cannot be rejected.

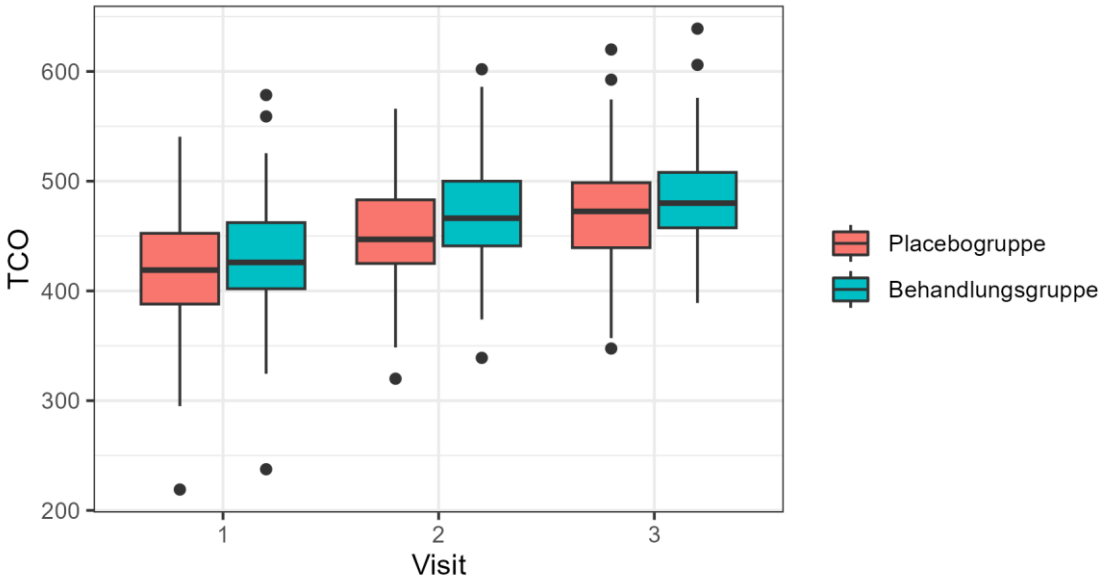

Figure 7 TCO

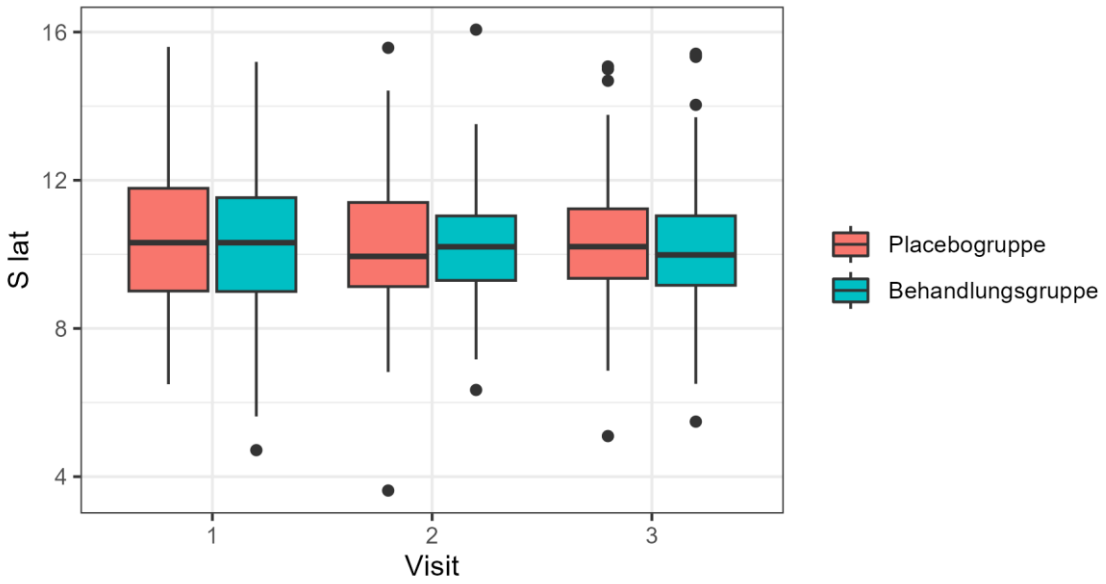

Figure 8 S lat.

3.5 RV dimensions

The mean RV basal at visit 3 was 38.07 for the empagliflozin group and 38.54 for the placebo group. RV mid was at visit 3 28.68 for the empagliflozin group and 29.09 for the placebo group. The two sample-t-test showed a p-value of 0.5478 for RV basal and a p-value of 0.3751 for RV mid. The null hypothesis that there is no significant difference between the groups cannot be rejected.

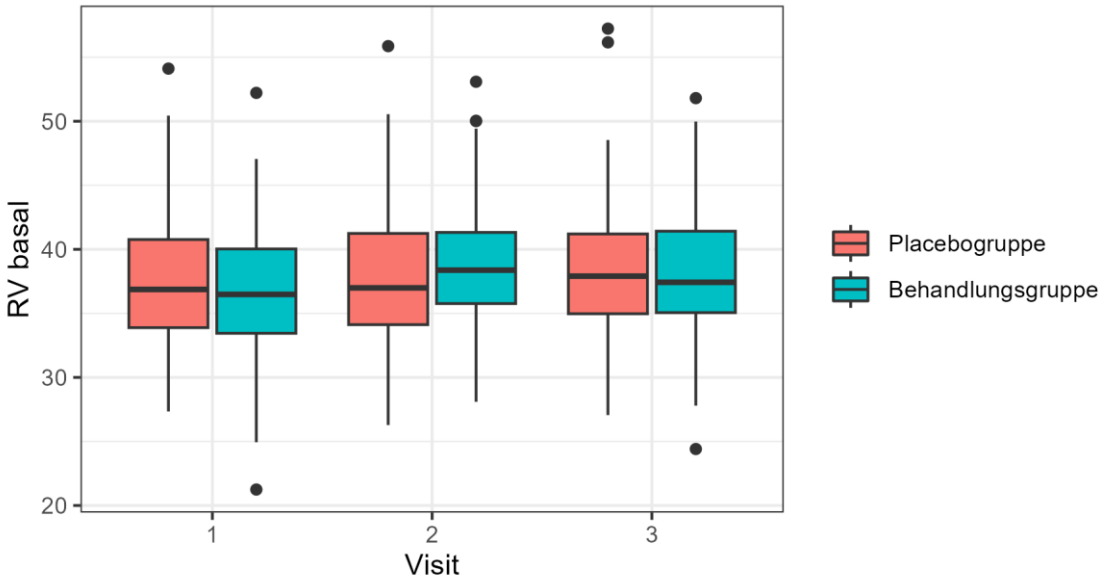

Figure 9 RV basal

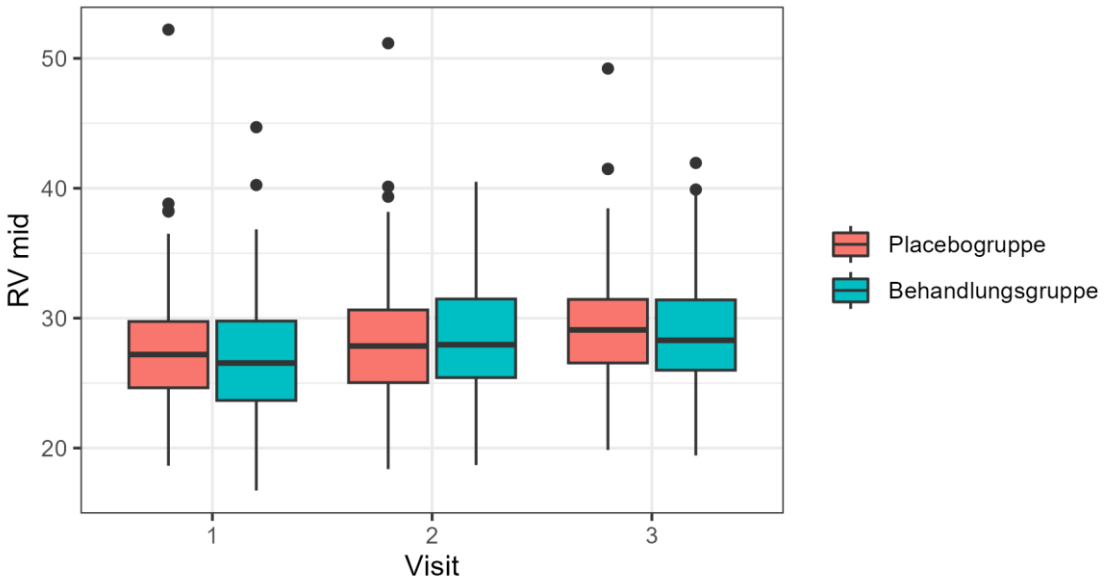

Figure 10 RV mid

		Placebo	
		mean	mean
Endo GLS	V1	-20.91	-20.54
	V2	-23.42	-22.65
	V3	-23.83	-23.5
FAC	V1	37.15	37.04
	V2	440.33	40.49
	V3	41.73	41.45
TAPSE	V1	20.38	20.67
	V2	22.18	22.28
	V3	22.76	22.68
S´lat	V1	10.25	10.54
	V2	10.17	10.26
	V3	10.21	10.33
RV basal	V1	36.92	37.07
	V2	38.59	37.68
	V3	38.07	38.54

Table 4 Explorative Statistics

4 Discussion

Echocardiographic examination of the right ventricle presents a particular challenge, primarily due to technical limitations in imaging, compounded by the complicated geometry and function of the RV. Unlike the left ventricle, which is more accessible and easier to image, it can be challenging to obtain clear and accurate images of the RV. The RV is located deeper in the chest cavity and is often obscured by surrounding structures, making it difficult to obtain optimal image windows. In addition, the RV has a thin myocardial wall, which can make visualization difficult, especially with standard two-dimensional echocardiography. The RV has a complex three-dimensional geometry with a crescent shape that differs from the more conical shape of the left ventricle. This unique geometry presents a challenge in accurately assessing the size, shape and function of the RV with conventional imaging techniques. In addition, RV imaging is further complicated by the presence of trabeculae and moderator bands and may obscure visualization of underlying pathology. The RV demonstrates dynamic changes in size and function in response to changes in preload, afterload, and contractility. In contrast to the left ventricle, which primarily ejects blood into the systemic circulation, the RV pumps blood into the pulmonary low-pressure circulation. Consequently, RV function is closely related to pulmonary vascular resistance and pulmonary artery pressure. Accurate assessment of RV function requires a comprehensive evaluation of both systolic and diastolic parameters, which is difficult to achieve with echocardiography alone.

Despite these challenges, advancements in echocardiographic technology, such as three-dimensional imaging and speckle tracking echocardiography, have improved our ability to assess RV structure and function. Additionally, the integration of multiple imaging modalities, including cardiac magnetic resonance imaging and computer tomography (CT), can provide complementary information and enhance our understanding of RV pathology.

The role of right ventricular function has emerged as a critical prognostic factor in patients with heart failure, independent of ejection fraction. The previously used traditional indices had several limitations, many of which have now been addressed by the introduction of RV strain analysis. This parameter provides a comprehensive

and detailed understanding of RV function and mechanics, offering insights into both global and regional aspects.(51)

RV strain analysis offers considerable advantages over conventional measurements. It is easy to obtain, highly reproducible, angle-independent and less dependent on loading conditions. In addition, it provides insights into the entire myocardial thickness instead of focusing only on individual segments. Clinical studies have already emphasized the importance of RV strain measurement in various conditions such as heart failure, pulmonary hypertension, arrhythmogenic right ventricular dysplasia, congenital heart disease, patients with left ventricular assist devices and valvular heart disease.(51)

Given its clinical significance, the assessment of RV strain should be integrated into routine echocardiographic examinations, particularly in patients where RV dysfunction or failure is suspected. However, further research is needed to fully understand the benefits of strain analysis. In particular, studies should be conducted to address the benefits of strain analysis for patient selection for existing and new therapies. In addition, studies monitoring disease progression and prognosis in patients with heart failure, particularly HFpEF, are of paramount importance. By better understanding RV strain and its clinical impact, we can improve patient treatment strategies and optimize outcomes in heart failure patients.(51)

It is important to consider that the ultrasound data utilized in this study was acquired within the context of the EMMY trial. The primary outcome of the trial was the change in NT-proBNP levels. Additionally, major echocardiographic parameters related to diastolic dysfunction (such as E/e' ratio), left-ventricular end-systolic volume, and left-ventricular end-diastolic volume were collected and analyzed simultaneously as secondary outcome measures.

This context is significant as it provides insight into the setting in which the ultrasound data was collected, highlighting the potential influence of Empagliflozin treatment on the observed echocardiographic parameters. Understanding the trial design and primary outcomes helps to interpret the findings of the study accurately and consider any confounding factors that may impact the results.(37)

Despite the well-established link between systolic and diastolic dysfunction following myocardial infarction, effective treatments to halt or slow down the pathophysiological progression, particularly concerning diastolic function, are not readily available. However, promising findings from the EMMY trial offer a potential breakthrough in this regard.

The EMMY trial demonstrated a significant reduction in NT-proBNP levels with Empagliflozin treatment compared to placebo, indicating a 15% greater reduction (95% CI -4.4% to -23.6%, p = .026) after adjusting for baseline NT-proBNP, sex, and diabetes status. Furthermore, Empagliflozin led to a notable improvement in absolute left ventricular ejection fraction by 1.5% (95% CI 0.2% to 2.9%, p = .029) compared to placebo. The mean reduction in E/e' ratio, a marker of diastolic function, was approximately 6.8% better (95% CI 1.3% to 11.3%, p = .015) in the Empagliflozin group. Additionally, both left ventricular end-systolic and end-diastolic volumes were significantly reduced in the Empagliflozin group compared to placebo, with reductions of 7.5 ml (95% CI 3.4 to 11.5 ml, p = 0.000) and 9.7 ml (95% CI 3.7 to 15.7 ml, p = .002), respectively.

These findings from the EMMY trial suggest that Empagliflozin holds significant potential to enhance overall cardiac function, as reflected by improvements in both laboratory and imaging parameters. The observed reductions in NT-proBNP levels, improvements in left ventricular EF, and reductions in E/e' ratio and ventricular volumes indicate favorable effects on both systolic and diastolic function. Similar results were obtained by the DAPA-MI trial were Dapagliflozin was used instead of Empagliflozin. The primary outcome was evaluated using the win ratio analysis method and included a hierarchical composite of the following events: death, hospitalization for heart failure, nonfatal myocardial infarction, atrial fibrillation/flutter, type 2 diabetes mellitus, NYHA functional Classification at the last visit, and a body weight decrease of 5% or greater at the last visit. The treatment with Dapagliflozin resulted in significant improvements in cardiometabolic outcome but had no impact on cardiovascular death or hospitalization for heart failure compared to the treatment with placebo. The EMPACT-MI trial came to the same conclusion while observing the effect of Empagliflozin vs placebo on hospitalization for heart failure or death from any cause as assessed in a time-to-first-event analysis.

These results provide hope for the development of effective treatments to address diastolic dysfunction in patients after MI, potentially leading to improved clinical outcomes and quality of life for affected individuals.

Right ventricular myocardial infarction (RVMI) is a relatively common complication in patients experiencing acute myocardial infarction, particularly in cases of ST-segment elevation myocardial infarction. The initial diagnosis of RVMI is typically made using electrocardiography and echocardiography, with confirmation often obtained through cardiac magnetic resonance imaging, considered the gold standard for assessing the RV status. The primary approach to treating RVMI involves emergency percutaneous coronary intervention aimed at reducing the extent of myocardial ischemia. Additionally, in patients who develop hypotension, optimizing fluid balance and providing inotropic support are essential measures. For patients exhibiting progressive deterioration despite these interventions, implantation of a mechanical circulatory device may be considered as a final option.

Despite significant advancements in the diagnosis and management of RV involvement in acute MI, it remains an independent predictor of both early and late complications. This underscores the importance of timely recognition and intervention in patients with RVMI to mitigate adverse outcomes and improve overall prognosis.

4.1 Interpretation

The analysis of various descriptive parameters among the subjects shows that unhealthy lifestyle habits are widespread in the patient population. One of the most important findings is the high prevalence of smoking, which was found in 70% of the population. The average daily cigarette consumption among smokers was 22 cigarettes, with a standard deviation of 13.52.

It is clear, that the data were collected at the time of hospitalization for myocardial infarction, indicating a clear association between smoking and myocardial infarction in this cohort. The data suggest that younger patients admitted with myocardial infarction are more likely to smoke than older patients, with a prevalence of 80% in younger patients compared to 57% in older patients. In particular, smoking appears to be highly prevalent in younger patients with ST-segment elevation myocardial

infarction. There also appears to be a dose-response relationship between smoking and MI risk: Patients who smoke more than 25 cigarettes per day are eight times more likely to suffer an MI than patients who have never smoked. The mechanism by which smoking exerts its detrimental effects on cardiovascular health is thought to be multifaceted. Firstly, smoking is closely associated with platelet activation, with a significant acute potentiation of platelet activation occurring shortly after smoking a cigarette. In addition, chronic smoking leads to a desensitization of platelets to activating substances in the periods between cigarettes. Over time, this chronic desensitization can contribute to the development of type 1 myocardial infarction.(52,53)

Overall, these findings emphasize the critical role of smoking as a major risk factor for myocardial infarction, particularly among younger individuals. Efforts aimed at smoking cessation and prevention are essential in reducing the burden of cardiovascular disease and improving outcomes among affected populations.

Only a small number of patients showed decreased right ventricular values at the start of the study. In comparison to the normal parameters 58.82% of the patients showed an abnormal GLS. On the other hand, only 19.63% of patients showed an abnormal FAC and only 6.22% an abnormal TAPSE. FAC and TAPSE showed a slight increase over time, but no significant difference between the place and the empagliflozin group. Endo GLS even showed a slight decrease over time which can be seen in Figure 4.

All the echocardiographic parameters showed a slight increase at visit 3, except for Endo GLS. None of these improvements were significant bigger in one of the two groups. In summary, there were no significant difference between the empagliflozin and the placebo group in either of the measured parameters.

4.2 Limitations and strengths

The main limitation of this study is its dependence on the post-processing software provided by TOMTEC. As is common with such software, the underlying mechanisms are proprietary and are not disclosed to users. Consequently, it is difficult to fully understand the nuances of the various values generated, such as Endo GLS. Furthermore, despite careful manual mapping of the endocardium during the end-systolic and end-diastolic phases, the software often automatically adjusts the recording, resulting in discordance between the endocardium and the recorded line. In such cases, manual adjustments are necessary, which can lead to fluctuations in the analysis

Furthermore, for strain analysis, the determination of end-systole and end-diastole was performed manually using M-Mode over the left ventricle. While the gold standard for determining heart phases would be the closure of the aortic valve, this was not feasible in this study. However, for the purpose of comparing global maximal strains rather than strains at each atrial phase, minor inaccuracies in determining heart phases are unlikely to significantly impact the overall results.

In summary, while the study provides valuable insights into cardiac function and mechanics, these limitations should be acknowledged when interpreting the findings. Future research endeavors may benefit from addressing these limitations to enhance the accuracy and reliability of the analyses conducted.

4.3 Conclusion

Right ventricular function is a significant predictor of survival in patients with heart failure, regardless of their left ventricular ejection fraction. However, traditional indices used to assess RV function have encountered several limitations, which can be addressed with the introduction of RV strain analysis.

RV strain analysis offers a more comprehensive and detailed assessment of RV function. By quantifying myocardial deformation, RV strain provides insights into both global and regional RV mechanics. Unlike traditional indices, RV strain is less affected by geometric assumptions and loading conditions, making it a more robust

and reliable way to measure RV function. Because of the extensive progress in the analysis software, RV-strain can nowadays be obtained very consistently and can be used to further quantify RV function.

Studies have demonstrated the clinical significance of RV strain in various cardiac conditions, including heart failure, pulmonary hypertension, and congenital heart disease. Importantly, RV strain has been shown to provide prognostic information beyond traditional RV function parameters, highlighting its benefit in risk stratification and guiding therapeutic decisions.(51)

Empagliflozin didn´t seem to have a significant influence on RV strain or the other parameters compared to a placebo. On the other hand, all the parameters were dependent on the time after the MI and on the impacts of medical therapy. It seems that more research needs to be done to further quantify the RV function and its role in cardiovascular diseases and in their therapy. More studies are needed to fully understand the underlying mechanism of SGLT-2 Inhibitors and their effect on the heart.

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