Dissertation

Prognostic biomarkers in patients with chronic heart failure

submitted by

Dr. med. univ. Nora Schwegel

for the Academic Degree of

Doctor of Medical Science

(Dr. scient. med.)

at the

Medical University of Graz

Department of Cardiology

Under the supervision of

Res. Prof. Priv.-Doz. Dr. Dr. Nicolas Verheyen

2025

Declaration of Academic Integrity

I hereby confirm that the present thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Furthermore, I hereby declare that if artificial intelligence (AI) tools were used for the generation and/or correction of certain text passages in the creation of this work, such employment was conducted in compliance with ethical principles, academic integrity, and the regulations of my university. Additionally, it was ensured that this usage was transparently disclosed and appropriately attributed.

16th of October 2025 Dr. med. univ. Nora Schwegel m.p.

Disclosures

The present cumulative dissertation comprises three original articles, in which the applicant acted as the first author. Parts of these manuscripts were incorporated into this thesis and are marked accordingly (*, °, #), with corresponding information provided in the respective footnote. A list of publications and additional information, including affiliations, is included in the following section.

All co-authors provided written permission for reproduction of the original articles as part of this thesis.

List of Publications and Affiliations

Schwegel N[1], Zach D[1], Peikert A[1], Santner V[1], Höller V[1], Gollmer J[1], Späth J[1], Riepl H[1], Rainer PP[1,2,3], Wallner M[1], Pilz S[4], Zirlik A[1], von Lewinski D[1], Ablasser K[1], Verheyen N[1*], Kolesnik E[1]. The Prognostic Value of Right Ventricular Function in Patients with Chronic Heart Failure - A Prospective Study. J Clin Med (**2024**)

1 Division of Cardiology, University Heart Center Graz, Medical University of Graz, 8036 Graz, Austria
2 Department of Medicine, St. Johann in Tirol General Hospital, 6380 St. Johann in Tirol, Austria
3 BioTechMed Graz, 8010 Graz, Austria
4 Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, 8036 Graz, Austria
** Corresponding author*

Schwegel N[1], Strohhofer C[1], Kolesnik E[1*], Oltean S[1], Hüttmair A[1], Pipp C[1], Benedikt M[1], Verheyen N[1], Gollmer J[1], Ablasser K[1], Wallner M[1], Santner V[1], Tripolt N[2], Pferschy P[2], Zechner P[3], Alber H[4], Siller-Matula JM[5], Kopp K[6], Zirlik A[1], Aziz F[2], Sourij H[2], von Lewinski D[1]. Impact of empagliflozin on cardiac structure and function assessed by echocardiography after myocardial infarction: a post-hoc sub-analysis of the EMMY trial. Clin Res Cardiol (**2025**)

1 Division of Cardiology, University Heart Center Graz, Medical University of Graz, Graz, Austria

2 Trials Unit for Interdisciplinary Metabolic Medicine, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria
3 Department of Cardiology and Intensive Care Medicine, Hospital Graz II, West Location, Graz, Austria
4 Department of Cardiology, Public Hospital Klagenfurt Am Woerthersee, Klagenfurt Am Woerthersee, Austria
5 Department of Cardiology, Medical University of Vienna, Vienna, Austria
6 Division of Cardiology and Internal Intensive Care Medicine, Department of Internal Medicine II, Paracelsus Medical Private University of Salzburg, Salzburg, Austria
** Corresponding author*

Schwegel N[1], Toferer C[1], Zach DK[1], Santner V[1], Höller V[1], Lugitsch J[1], Wallner M[1], Gollmer J[1], Aziz F[2], von Lewinski D[1], Kolesnik E[1], Ablasser K[1], Zirlik A[1], Sourij H[2#], Verheyen N[1*#]. Impact of SGLT2-Inhibitor Therapy on Survival in Patients with Transthyretin Amyloid Cardiomyopathy: Analysis of a Prospective Registry Study. J Clin Med (**2024**)

1 Division of Cardiology, University Heart Center Graz, Medical University of Graz, 8036 Graz, Austria
2 Trials Unit for Interdisciplinary Metabolic Medicine, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, 8036 Graz, Austria
**Corresponding author*
#Contributed equally

Acknowledgement

The work was conducted within the Doctoral School “Sustainable Health Research” under the direction of Univ. Prof. Dr. Andrea Berghold.

The Graz HCM Registry was supported by unrestricted research grants from Alnylam, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Swedish Orphan Biovitrum AB, and Takeda Pharmaceuticals.

The EMMY trial was investigated by the Department of Cardiology and the Interdisciplinary Metabolic Medicine Trials Unit of the Medical University of Graz. The trial was funded by an unrestricted grant from Boehringer Ingelheim, Prof. Dirk von Lewinski received a grant from the Austrian Science Fund.

I would like to express my sincere gratitude to my supervisors of this thesis for their invaluable guidance. My special thanks go to Nicolas Verheyen, whose support extended far beyond this thesis, offering continuous motivation, encouragement, and mentorship. I also want to thank my colleagues for their collaboration and friendship throughout this work, as well as my family and friends for their endless support.

Table of Contents

Abbreviations and Definitions

ACEi	Angiotensin-converting enzyme inhibitor
AL	Light chain amyloidosis
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ATTR	Transthyretin amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
EMMY	Empagliflozin in acute myocardial infarction
HCM	Hypertrophic cardiomyopathy
HFimpEF	Heart failure with improved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
LV GLS	Left ventricular global longitudinal strain
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-brain natriuretic peptide
RAAS	Renin-angiotensin-aldosterone system
RoC-HF	Role of comorbidities in chronic heart failure
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
TAPSE	Tricuspid annular plane systolic excursion
WHF	Worsening heart failure hospitalization

Zusammenfassung

Einleitung

Die chronische Herzinsuffizienz ist assoziiert mit hoher Morbidität und Mortalität. Bei Herzinsuffizienz wird die linksventrikuläre Ejektionsfraktion (LVEF) zur Diagnostik, für Therapieentscheidungen und zur Risikostratifizierung herangezogen. Insbesondere am oberen Ende des Spektrums bietet sie jedoch nur limitierte prognostische Informationen. Ziel dieser Arbeit ist es prognostische Parameter zu evaluieren, eine eingehende echokardiographische Analyse zu generieren und Einblicke in die Auswirkung von Natrium-Glukose Co-Transporter 2 Inhibitoren (SGLT2i) auf klinische Endpunkte bei spezifischen Subgruppen der chronischen Herzinsuffizienz zu schaffen.

Methoden

Im Rahmen dieser Arbeit wurden drei separate Analysen durchgeführt, zu (i) chronischer Herzinsuffizienz mit reduzierter Ejektionsfraktion (HFrEF), (ii) akutem Myokardinfarkt (AMI) und (iii) Herzinsuffizienz aufgrund einer Transthyretin Amyloid Kardiomyopathie (ATTR-CM).

Resultate

Die durchgeführten Analysen zeigten, dass die rechtsventrikuläre Funktion ein starker prognostischer Marker bei HFrEF ist, dessen Bedeutung über die von traditionellen Parametern hinaus geht. Nach AMI zeigten SGLT2i einen positiven Effekt auf das ventrikuläre Remodelling, jedoch ohne signifikante Gruppen-Unterschiede bei rechtsventrikulären Parametern. Weiters zeigte eine Behandlung mit SGLT2i eine Assoziation mit reduzierter Mortalität bei ATTR-CM.

Schlussfolgerung

Diese Ergebnisse unterstreichen die Notwendigkeit eines umfassenden Verständnisses von kardialen Funktionsparametern und Prognosefaktoren im Management der Herzinsuffizienz. Die prognostische Relevanz rechtsventrikulärer Funktionsparameter erfordert deren Einbeziehung in eine routinemäßige Risikostratifizierung bei Herzinsuffizienz. Im Bezug auf Pharmakotherapie zeigen die präsentierten Arbeiten eine zunehmende Bedeutung von SGLT2i für die Behandlung der Herzinsuffizienz bei verschiedenen Spektren der Erkrankung auf. Die eingeschränkte Evidenz, insbesondere hinsichtlich ihrer Auswirkung auf den rechten Ventrikel, zeigen jedoch die Notwendigkeit randomisierte Studien auf.

Abstract

Introduction

Chronic heart failure is a major concern to public health as it is one of the leading causes of mortality and hospitalization worldwide, with an ever-increasing prevalence. Transthoracic echocardiography has an essential role in the assessment of heart failure. Left ventricular ejection fraction (LVEF) guides diagnosis and therapeutic decisions and poses prognostic relevance. However, especially at the upper end of the spectrum, it lacks additional prognostic information. The aim of this work is to evaluate the prognostic value of echocardiographic parameters in chronic heart failure beyond LVEF, provide in-depth echocardiographic analysis in patients following acute myocardial infarction (AMI), and give first insights into the impact of sodium-glucose co-transporter 2 inhibition (SGLT2i) on clinical outcomes in two subsets of patients with chronic heart failure.

Methods

As part of this thesis, three separate analyses were conducted on (i) patients with chronic heart failure with reduced ejection fraction (HFrEF), (ii) patients after AMI, and (iii) patients with heart failure due to transthyretin amyloid cardiomyopathy (ATTR-CM).

Results

The present analyses demonstrated that right ventricular function is a strong prognostic marker in patients with HFrEF, retaining significance beyond traditional parameters across subgroups. In patients after AMI, SGLT2i mitigated adverse ventricular remodelling, without significant right ventricular differences. Further, SGLT2i treatment showed an association with reduced mortality in ATTR-CM.

Conclusion

The collective insights from these analyses underscore the need for a nuanced understanding of cardiac function and prognosticators in heart failure management. The prognostic relevance of right ventricular function calls for its integration into routine risk assessment and management strategies for heart failure patients. In the context of pharmacotherapy, the favourable effects of SGLT2i on cardiac remodelling and outcomes demonstrated in this work point to their expanding role in heart failure management across different spectrums of the disease. However, the limitations of current evidence, particularly regarding effects on right ventricular parameters, highlight the necessity of further randomized studies to validate these findings.

1 Introduction

1.1 Definition and scope of the problem

Heart failure is a clinical syndrome characterized by typical signs and symptoms and structural and/or functional abnormalities that lead to elevated intracardiac pressures and/or reduced cardiac output.(1)

Chronic heart failure poses a major concern to public health, with an ever-increasing prevalence particularly in the older population.(2, 3) Current estimations propose about 55.5 million prevalent cases of heart failure globally, which concludes to a prevalence of 1-3% in adults. Globally, ischemic heart disease, hypertensive heart disease, and cardiomyopathies are the main causes of chronic heart failure, with attributable proportions of 34.5%, 22.5%, and 7.6%, respectively.(3)

With advances in medical and device treatment over the past decades, the prognosis of affected patients improved remarkably.(4-9) However, chronic heart failure remains one of the leading causes of hospitalizations and mortality worldwide.(10)

1.2 Terminology

Phenotypic classification in heart failure is traditionally based on systolic function assessed by left ventricular ejection fraction (LVEF). The rationale for this approach relates to heart failure therapy trials that selected patients based on LVEF and demonstrated divergent findings regarding prognosis and treatment response across LVEF ranges. Currently, chronic heart failure can be divided into four groups: heart failure with reduced ejection fraction (HFrFE; LVEF ≤40%), heart failure with mildly reduced ejection fraction (HFmrEF; LVEF 41-49%), heart failure with preserved ejection fraction (HFpEF; LVEF ≥50% with typical signs and symptoms and evidence of structural and/or functional abnormalities), and heart failure with improved ejection fraction (HFimpEF; referring to patients with an initial LVEF of ≤40% that improved by a ≥10-point increase from the baseline LVEF, and a further measurement with an LVEF >40%).(1, 10, 11)

Further, chronic heart failure can result in or be the result of right ventricular dysfunction. Here, right ventricular structure and/or function are altered due to volume or pressure overload. The

main driver of chronic right ventricular heart failure is pulmonary hypertension due to left ventricular dysfunction. Nevertheless, there are a variety of other causes for right ventricular dysfunction, such as right ventricular ischemia, valvular disease, (right ventricular) cardiomyopathies, or pulmonary disease.(12)

1.3 Aetiology

Though risk stratification and patient management in chronic heart failure is commonly based on LVEF, a variety of risk factors and disease modifiers significantly influence disease trajectory and outcomes.(13) The underlying aetiology ultimately leading to chronic heart failure plays a crucial role regarding treatment regime and prognosis. Two leading aetiologies globally are ischemic heart disease and cardiomyopathies, accounting for 34.5% and 7.6% of the present cases, respectively.(3)

1.3.1 Ischemic heart disease

Coronary artery disease refers to a condition caused by structural and/or functional alterations of the coronary arteries and/or microcirculation, resulting in hypoperfusion and hypoxemia (ischemia) due to a myocardial demand-to-supply mismatch.(14) It can be a result of both, macro- and microvascular alterations.(15-18)

The clinical definition of acute myocardial infarction (AMI) comprises the presence of myocardial cell necrosis resulting from significant and sustained myocardial ischemia, detected by an elevation in cardiac biomarkers in the setting of evidence of acute myocardial hypoperfusion.(19) The primary mechanism in AMI is the rupture or erosion of a vulnerable atherosclerotic plaque formation within the coronary arteries. A destabilized atherosclerotic lesion exposing a necrotic lipid-rich core to the circulation leads to the activation of extrinsic coagulation and precipitates a thrombus formation which can cause acute subsequent vessel occlusion of a coronary artery, leading to ischemia and cardiomyocyte necrosis.(20)
Prolonged duration of insufficient myocardial oxygen supply can lead to irreversible myocyte damage, precipitating myocardial remodelling. Wall thinning, deposition of fibrotic tissue, and left ventricular systolic dysfunction following significant chronic or acute ischemia represent

the principal mechanisms contributing to the development of ischemic heart disease, which is considered the most common singular cause for chronic heart failure.(3)

1.3.2 Cardiomyopathies

Cardiomyopathies are defined as myocardial disorders without structural and/or functional abnormalities, in the absence of coronary artery disease, valve disease, arterial hypertension, or congenital heart disease in an extent to explain observed abnormalities.(21) Of note, cardiomyopathies can co-exist with ischemic, valvular, and hypertensive heart disease. Morphological and functional traits, such as ventricular hypertrophy, ventricular dilatation, myocardial tissue characterization, and ventricular systolic and diastolic dysfunction are commonly used to describe and differentiate specific cardiomyopathies.(22)

1.3.2.1 Cardiac amyloidosis

Cardiac amyloidosis is characterized by the accumulation of misfolded proteins, amyloid fibrils, in the myocardial extracellular space, leading to left ventricular wall thickening, restrictive filling patterns, and progressive heart failure.(23)

Once considered to be a rare disease, recent data suggest a high prevalence in patients with left ventricular hypertrophy not explained by loading conditions, aortic stenosis, and heart failure with preserved ejection fraction, especially in the elderly.(24-27) Though nine different types of cardiac amyloidosis have been described, the majority of cases are contributed by either monoclonal immunoglobulin light chain amyloidosis (AL) or transthyretin amyloidosis (ATTR), either as a hereditary or wild-type form.(23) Wild-type ATTR, which is associated with ageing, is currently considered to be the most frequent form of amyloidosis worldwide,(22) and is dominated by cardiac symptoms.(23, 28) ATTR is a progressive disease with poor outcome, especially if left untreated.(29-32) Depending on the stage of the disease, 4-year survival estimates range between 18-57%, and median survival between 20 to about 70 months after diagnosis.(30, 31)

1.4 Prognosis and prognosticators

The prognosis of chronic heart failure improved remarkably over the past decades, thanks to early patient screening and advances in diagnostic and treatment options.(4-9) However, it remains poor, and chronic heart failure is still one of the leading causes of hospitalizations and mortality worldwide, with increasing rates.(10) According to the World Health Organization in 2019 cardiovascular disease was responsible for an estimated 17.9 million deaths. Heart failure accounted for 14.6% in women, and for 12.5% in men of these across European countries.(33) A study combining data of the Framingham Heart Study and the Cardiovascular Health Study reported a mortality rate of 67% within 5 years after diagnosis.(34)

Prognosis is better in HFpEF and HFmrEF compared to HFrEF.(35, 36) However, changes and transition in LVEF in both directions over time is common, which has to be considered in risk stratification. In patients who progress from HFpEF/HFmrEF to HFrEF, prognosis is remarkably worse than in those who remain stable or improve.(37-39)

Overall, due to increase of the population, ageing, and increased prevalence of comorbidities and risks, numbers for mortality and hospitalizations for heart failure are expected to rise considerably.(40, 41)

1.4.1 Echocardiography in prognosis of chronic heart failure

In chronic heart failure, impairment of left ventricular systolic function and subsequent reduction in cardiac output leads to an overall poor prognosis. Hence transthoracic echocardiography is essential in risk stratification. Currently, LVEF is the most widely used imaging parameter in heart failure. It guides diagnosis and therapeutic decision and poses prognostic relevance in chronic heart failure.(42) Moreover, it serves as continuous variable in a variety of heart failure risk scores.(43-46) The central role of LVEF in risk prediction most likely reflects the divergent risk stratification and treatment responses within LVEF ranges *a priori*. However, when addressing the parameter on top of this, its prognostic value narrows.(47) Further, LVEF lacks sufficiency for the detection of subtle myocardial impairment in early stages of damage, as seen in patients undergoing cardiotoxic chemotherapy,(48) or in hypertensive and diabetic patients prior to progression to heart failure.(49, 50)

Other echocardiographic parameters have shown to predict clinical outcomes in chronic heart failure more precisely and independent of LVEF. Left ventricular global longitudinal strain (LV GLS) provides a more accurate assessment of myocardial deformation. It shows prognostic properties across all ranges of LVEF,(51-54) and demonstrated an inverse correlation with time of recovery and future risk of deterioration in patients with HFimpEF.(55, 56) Moreover, in contrast to LVEF, LV GLS can detect subtle myocardial dysfunction and is therefore recommended for baseline risk assessment and monitoring in patients undergoing cardiotoxic oncological treatments.(57)

Parameters of right ventricular function emerged as valid prognosticators in heart failure. Right ventricular dysfunction is associated with adverse outcomes over a broad spectrum of aetiologies.(58-62) Though data on this was collected primarily in patients with HFrEF,(62-64) a more focused approach on HFmrEF and HFpEF confirmed similar results.(65, 66) In HFpEF, studies point to an about 6 times higher relative risk of 2-year mortality in those with concomitant right ventricular systolic dysfunction.(65) Moreover, in the setting of pulmonary hypertension right ventricular dysfunction worsens prognosis significantly, irrespective of primary nature or secondary to systolic heart failure.(67, 68) Here, impaired parameters reflecting right ventricular/pulmonary artery-coupling were associated with an increased short and medium-term all-cause mortality.(69)

Beyond conventional parameters advanced imaging techniques such as 3D-echocardiography or deformation imaging of the right ventricle constantly grows in evidence for its prognostic properties in various conditions.(70-72)

1.4.2 Pharmacological treatment in chronic heart failure

Chronic heart failure poses major risk for morbidity and mortality worldwide. Over the last decades, major advances in prevention and pharmaceutical options for the treatment of affected patients across the LVEF spectrum were accomplished. Three major goals are the target of pharmacological treatment in heart failure: reducing mortality, preventing first and recurrent hospitalizations due to worsening heart failure, and improving clinical status, functional capacity, and quality of life. Although several therapeutic agents are available for the treatment of chronic heart failure, investigations on the impact on clinical outcomes have consistently revealed differential treatment responses across distinct LVEF ranges.

1.4.2.1 Treatment regime in HFrEF

Pharmacotherapy is a cornerstone in treating patients with HFrEF. A guideline-directed medical therapy should comprise four substance groups: (i) beta blockers, (ii) angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) or angiotensin receptor-neprilysin inhibitors (ARNI), (iii) mineralocorticoid receptor antagonists (MRA), and (iv) sodium glucose co-transporter 2 inhibitors (SGLT2i).(10, 42)

Modulation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system with beta blockers, ACEi/ARB/ARNI, and MRA has drastically changed the prognosis in HFrEF. Large randomized controlled trials showed a significant survival-benefit and risk reduction for cardiac hospitalizations with these substances. (73-82)

The value of the SGLT2i dapagliflozin and empagliflozin on top of therapy with beta blockers, ACEi/ARB/ARNI, and MRA was shown in recent years. In the DAPA-HF trial, treatment with dapagliflozin led to a reduction in the primary combined endpoint of worsening heart failure and cardiovascular death by 26%. A reduction in both components of the composite endpoint were observed, and moreover, dapagliflozin reduced all-cause mortality by 17%. These survival benefits were observed in the same extent in patients with and without diabetes.(83) Subsequently, empagliflozin showed similar benefits in the EMPEROR-Reduced trial. Here, a reduction in the primary composite endpoint of cardiovascular mortality and heart failure hospitalization by 25% was demonstrated. A reduced risk of hospitalizations by 30% was shown, but the trial did not show significant a reduction in cardiovascular deaths.(84) Though, a meta-analysis of DAPA-HF and EMPEROR-Reduced found no heterogeneity regarding cardiovascular mortality.(5) This led to their implementation into guideline recommended therapy for HFrEF regardless of diabetes status.(42)

1.4.2.2 Treatment regime in HFpEF/HFmrEF

While in HFrEF all of the agents mentioned above were implemented at the level of a Class I recommendation,(42) studies carried out in patients with no or only mild impairment of left

ventricular systolic function (HFpEF, HFmrEF) failed to show convincingly beneficial impact on clinical outcomes.(85-89)
However, initially introduced in the 1990s, the term HFpEF referred to an LVEF > 40%. Therefore, the majority of HFpEF trials comprised both, patients with HFpEF according to the current guidelines (LVEF ≥ 50%) and patients with HFmrEF (LVEF 41-49%). No substantial randomized controlled trial investigated exclusively patients with HFmrEF. However, data can be extracted from subgroup analyses of HFpEF trials, though none of them have met their primary endpoint. Here, meta-analyses and retrospective analyses suggested similar benefits regarding mortality for beta blocker treatment (90) and regarding heart failure hospitalizations for ARB, ARNI, and MRA in HFmrEF compared to HFrEF. (91-93) This led to a weak recommendation in guidelines regarding the use of these drugs in patients with HFmrEF (Class IIb), and no recommendation in patients with HFpEF.

The EMPEROR-Preserved trial was the first to report the SGLT2i empagliflozin to reduce the primary composite endpoint of cardiovascular death and heart failure hospitalizations by 21%. However, this effect was mainly driven by reduced hospitalization rates and there was no significant reduction in cardiovascular death.(94) Subsequently, the DELIVER trial demonstrated a reduction in risk for the primary composite endpoint of cardiovascular mortality and worsening heart failure events with dapagliflozin. Hence, once again, the effect was driven by reducing worsening heart failure events and no reduction in cardiovascular death was observed.(95) An aggregate data meta-analysis of these trials confirmed a risk reduction for the composite endpoint of cardiovascular mortality and first heart failure hospitalization by 20% across LVEF ranges, but without a significant reduction in mortality.(6) Nevertheless, as both trials met their primary endpoints, they were implemented into guideline directed treatment with a Class I recommendation for both, patients with HFpEF and patients with HFmrEF.(42)

1.4.2.3 Treatment in specific populations

Ischemic heart disease

In ischemic heart disease, especially after AMI, specific therapies for the prevention of further coronary ischemic events are established to improve prognosis. The cornerstones of

pharmacological event-preventing substances comprise antithrombotic, lipid-lowering, anti-inflammatory, and metabolic-acting agents, regardless of impairment of left ventricular function.(14, 96)

Contemporary studies on the clinical benefits of beta blockers after AMI only support their usage in patients with reduced LVEF.(97, 98) Evidence almost exclusively was drawn from large randomized controlled trials performed in the pre-perfusion era, and current observational studies and meta-analyses provided mixed results.(98-100) Recently published trials in patients with AMI and an LVEF >40% showed divergent results, but a large meta-analysis reported a risk reduction in mortality, new myocardial infarction, and heart failure.(101-103)
Trials on ACEi, ARB, ARNI, and MRA in patients after AMI showed similar trends, with improved outcomes only in patients with additional comorbidities such as HFrEF, diabetes mellitus, chronic kidney disease, or arterial hypertension.(104-108)

The EMpagliflozin in acute MYocardial infarction (EMMY) trial was the first randomized controlled trial investigating the effect of SGLT2i versus placebo after AMI independent of diabetes status. Here, treatment was associated with a greater reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) and a beneficial effect on left ventricular structure and function was observed.(109) Subsequently, the DAPA-MI trial demonstrated results in favour of dapagliflozin regarding a primary hierarchical composite outcome, mainly driven by cardiometabolic outcomes but no impact on cardiovascular mortality or heart failure hospitalizations.(110) The EMPACT-MI trial, conducted in patients after AMI with a new onset LVEF < 45% and/or signs or symptoms of congestion, did not meet its primary composite endpoint of all-cause mortality and heart failure hospitalizations.(111)

Cardiac amyloidosis

Currently, the only approved drugs with effect on clinical outcomes in ATTR-CM with evidence derived from randomized controlled trials are specific disease-modifiers.
Tafamidis, a selective transthyretin stabilizer, met the primary hierarchically endpoint and moreover reduced all-cause mortality by 30%, cardiovascular-related hospitalizations by 32%, and was associated with a reduced decline in functional capacity and in quality of life.(112)

Recently, similar treatment effects were demonstrated for the transthyretin stabilizer acoramidis, with reduced all-cause mortality, cardiovascular-related hospitalizations, and favourable effects on NT-proBNP levels and 6-minute walking distance.(113)

Vutrisiran is an RNA interference therapeutic agent that inhibits the production of transthyretin. Formerly approved for the treatment of hereditary transthyretin amyloidosis with polyneuropathy, it was recently approved for the indication of ATTR-CM on basis of results from the HELIOS-B trial. Here, vutrisiran reduced risk of all-cause mortality and recurrent cardiovascular events in the overall cohort and in a subgroup of patients who did not receive tafamidis at baseline.(114) These drugs changed the prognosis of ATTR-CM remarkably but are carry a high financial burden and are of limited availability in many countries.

The value of traditional heart failure treatment is being debated. No data from randomized controlled trials specifically investigating patients with ATTR-CM is available, and they were excluded from heart failure trials. However, a retrospective study indicated that treatment with low-dose beta blockers and MRA was associated with lower all-cause mortality in patients with an LVEF ≤40%, while therapy with ACEi and ARB did not show survival benefits.(115)

Recently, retrospective analyses on SGLT2i in patients with ATTR-CM indicated that treatment is safe and well-tolerated, with beneficial effects on volume status and diuretic agent requirement.(116-118) One retrospective analysis also demonstrated a positive effect on clinical outcomes irrespective of LVEF in a propensity-matched cohort.(119) However, evidence on this topic remains sparse.

1.5 Gaps in evidence

Though various studies investigated the prognostic value of echocardiographic parameters in chronic heart failure, initially the main focus was on left ventricular function.(42, 47-56) Other parameters demonstrated superior predictive value regarding clinical outcomes in these patients, focusing on myocardial deformation imaging and parameters for right ventricular function.(58-68, 70-72) However, studies investigating these associations mainly reported on preselected cohorts, often excluding patients with common comorbidities in chronic heart failure, such as atrial fibrillation or chronic kidney disease.(120, 121)

Large clinical trials have demonstrated the beneficial effects of SGLT2i in chronic heart failure.(83, 84, 94, 95) The two outcome trials DAPA-MI and EMPACT-MI reported a

reduction in cardiometabolic risk, though not meeting their primary endpoints.(110, 111) The EMMY trial was the first to investigate the effects of SGLT2i after AMI independent of diabetes status. Here, a significant reduction in NT-proBNP and a positive effect on left ventricular structure and function was demonstrated.(109) Though some animal models and clinical trials indicated a benefit of SGLT2i on cardiac remodelling,(122-126) data on this topic remains sparse. Moreover, for an enhanced understanding of cardiac remodelling in general and the course of changes in cardiac structure and function after AMI, in-depth echocardiographic assessments in large datasets are warranted.

Finally, although the significant impact of SGLT2i treatment was demonstrated in chronic heart failure irrespective of ejection fraction,(83, 84, 94, 95) no randomized controlled data is available on their prognostic implication in ATTR-CM and they were excluded from heart failure trials. However, patients with ATTR-CM represent a high-risk population with continued unmet therapeutic needs. A first retrospective study on the prognostic impact of SGLT2i in these patients indicates a significant benefit,(119) however, data remains sparse.

1.6 Aims

In view of the importance and dimension of the topic, this thesis aims to:
(i) Address the need for prognostic data on “real-world” chronic heart failure patients. For this purpose, a contemporary outpatient clinic cohort of patients with stable chronic heart failure with optimal medical treatment was investigated, to evaluate whether echocardiographic parameters for right ventricular function, adjusted for relevant clinical parameters, are independently associated with clinical outcomes.
(ii) Provide first insights into a meticulous assessment of echocardiographic trajectories for myocardial structure and function after AMI, including non-left ventricular parameters and deformation analysis.
(iii) Evaluate the effect of SGLT2i treatment on cardiac structure and function after AMI, and identify potential benefits compared to placebo.
(iv) Elucidate the effects of SGLT2i treatment on top of established confounders regarding clinical endpoints in a contemporary outpatient clinic cohort of patients with ATTR-CM.

2 Discussion

2.1 Right ventricular function in chronic heart failure*

In the present analysis of the Role of Comorbidities in Chronic Heart Failure (RoC-HF) cohort, right ventricular systolic function, assessed by tricuspid annular plane systolic excursion (TAPSE), demonstrated a strong association with worsening heart failure hospitalizations (WHF) and composite endpoints of (i) WHF and cardiovascular death and (ii) WHF and all-cause mortality. On the other hand, parameters of left ventricular systolic function, such as LVEF and LV GLS, only showed poor predictive value in general and no prognostic value in patients with impaired LVEF ≤ 35%.

Right ventricular function plays a crucial role in monitoring cardiovascular disease and especially heart failure. The most relevant cause of right ventricular dysfunction is left-sided heart failure. Increased left ventricular filling pressures cause elevated pulmonary pressures that lead to an increase in right ventricular afterload.(127) The right ventricle is particularly sensitive to changes in afterload; consequently, increased afterload often precipitates a worsening of right ventricular performance.(128) Therefore right ventricular failure may follow left ventricular failure, even if the right ventricle is not directly involved in the underlying left ventricular disease.

The relevance of right ventricular function has emerged as a robust and independent predictor of adverse outcomes in patients with heart failure, beyond the traditional reliance on LVEF. Lundorff and colleagues reported right ventricular dysfunction to be a predictor of mortality in patients with HFrEF. Here, the traditional parameter TAPSE showed the strongest association with outcomes in women, while right ventricular fractional area change and global longitudinal strain added incremental value in the male collective.(129) Other studies demonstrated that parameters for right ventricular function determine poor outcomes in heart failure patients over the whole spectrum of left ventricular systolic function.(130-133) Though right ventricular function determines outcome across LVEF phenotypes, the strongest association is found in patients with more pronounced impairment of left ventricular systolic function, even within HFrEF collectives, as demonstrated by Lundorff and colleagues.(129) Similar results were observed in the present analysis of the RoC-HF cohort, where the association between TAPSE

**Parts of this chapter have been published in the Journal of Clinical Medicine. (2024). DOI: 10.3390/jcm13071930.*

and adverse events was pronounced in patients with an LVEF ≤ 35%.(134) These findings indicate that consideration of right ventricular is particularly relevant in patients with severely impaired left ventricular systolic function in terms of predicting adverse outcomes.

Furthermore, right ventricular functional parameters demonstrated to be stronger predictors of exercise capacity in HFrEF patients, which is a well-defined biomarker in the prognosis of HFrEF and in the indication of heart transplant.(135, 136) A significant association between right ventricular systolic function and cardiovascular deaths in a general population without heart failure could also be established.(137)

2.2 Risk scores in chronic heart failure*

Accurate risk stratification for mortality and hospitalization in patients with chronic heart failure may allow treating physicians more accurate decisions regarding timing and appropriateness of therapy escalation, advanced treatments, or the need of palliative care. Several risk stratification scores exist for predicting adverse events in these patients, comprising individual measures associated with the respective outcomes.

Based on the Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF), the PARADIGM Risk of Events and Death in the Contemporary Treatment of Heart Failure (PREDICT-HF) score calculates risk of cardiovascular death and a combined risk of cardiovascular death or heart failure hospitalization at one and two years, respectively. A total of 29 clinical variables are included, comprising age, sex, demographics, symptoms, pharmacological treatment, comorbidities, blood pressure, laboratory parameters, and LVEF.(43)
The Seattle Heart Failure Model (SHFM) can be used in patients with chronic heart failure with predominantly systolic dysfunction and provides predicted 1-year and 5-year survival. The 24 included variables comprise age, sex, ischemic aetiology, symptoms, pharmacological and device treatment, blood pressure, laboratory parameters, and LVEF.(44)
The Cardiac and Comorbid Conditions Heart Failure (3C-HF) score offers a risk prediction model to calculate 1-year mortality including only 11 variables, comprising age, comorbidities, symptoms, pharmacological treatment, laboratory parameters, and LVEF.(45)

Parts of this chapter have been published in the Journal of Clinical Medicine. (2024). DOI: 10.3390/jcm13071930.

The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC-HF) score provides risk estimation for mortality at one and three years based on 14 clinical variables, including age, sex, blood pressure, body mass index, symptoms, comorbidities, smoking status, pharmacological treatment, and LVEF.(46)

Right ventricular function has shown incremental predictive value in chronic heart failure across phenotypes. Furthermore, Damy and colleagues showed that TAPSE was, unlike LVEF, independently associated with cardiovascular outcome.(138) Similar results were found by Berrill and colleagues when investigating acute heart failure.(139) These results, in line with the findings of the present analysis of the RoC-HF cohort (134) demonstrate that right ventricular function not only provides additional predictive value on top of LVEF but is superior to LVEF in identifying patients at risk. Yet, up to date it has not yet been applied in any of these heart failure risk prediction scores. TAPSE could qualify as a valid additional parameter in these risk scores, as its assessment is non-invasive, reliable, simple, and can be achieved via far less technician- and insonation-angle-dependent methods in comparison to other parameters and indices such as right ventricular myocardial deformation imaging. However, whether adding right ventricular function improves the diagnostic accuracy of heart failure risk prediction scores needs to be evaluated in future studies.

2.3 Normal right ventricular function in chronic heart failure*

The normal value of right ventricular longitudinal systolic function assessed using TAPSE in a general population is defined as 24 ± 3.5 mm, while a TAPSE < 17 mm indicates reduced right ventricular systolic function.(140)

In the present analysis of the RoC-HF cohort, which represents a typical real-world chronic heart failure cohort, incidence rates increased already with a TAPSE < 20 mm, which is in the supposedly normal range.(134) This sparks the question, whether normal ranges for right ventricular systolic function should be redefined in the context of coexisting left-sided heart failure. These patients, especially those with HFrEF, are at higher risk of cardiovascular events compared to a general, healthy population. Therefore, a different cut-off may be beneficial. The findings of the present analysis imply that already mild to moderately impaired right ventricular systolic function may point to worse outcomes.(134)

As for one possible explanation, in a first compensatory phase, the right ventricle responds to a chronic state of overload with increased contractility to maintain the necessary cardiac output. However, this leads to excess hypertrophy of the right ventricle, elevated filling pressures, and diastolic dysfunction.(141, 142) With the persistence of increased afterload and filling pressures increasing dilatation of the right ventricle occurs, initially with still preserved or residual systolic function. Ultimately, this leads to right ventricular failure, where systolic function declines independently of pulmonary pressures ("ventriculo-arterial uncoupling").(143)

2.4 Predictive value of cardiac remodelling°

In the present echocardiographic sub-analysis of the EMMY trial, in-depth echocardiographic evaluation of 301 patients was performed at baseline, 6 weeks, and 26 weeks after AMI. Here, randomization to the SGLT2i resulted in a significant improvement of left ventricular end-systolic and end-diastolic volumes compared to a placebo. These observations suggest a primary effect of empagliflozin in terms of mitigated cardiac remodelling after AMI. While similar results were already reported in the main manuscript of the EMMY trial,(109) the echocardiographic post-hoc sub-analysis is the first study to assess the trajectories of non-left ventricular deformation analysis to provide insights into the potential impact of SGLT2i therapy on myocardial metrics after AMI.

Though new advances in interventions and pharmacological treatments after AMI emerged in the past decades, it remains one of the most important causes of morbidity and mortality worldwide.(2) Cardiac remodelling after AMI is characterized by myocardial fibrosis, chamber dilation, and dysfunction, leading to a particular high risk of morbidity and mortality.(144) It further can lead to the development of ischemic heart disease and subsequently to chronic heart failure.(3)

Reversing myocardial remodelling plays a crucial role in reducing risk of disease progression, as well as reducing morbidity and mortality in patients after AMI.(145) Pharmacological agents like ACEi, ARB, ARNI, and beta-blockers have shown significant effects on myocardial remodelling in patients with chronic heart failure and after AMI, which in a longer-term has a major impact on relevant clinical endpoints.(144, 146-150) Similar to the results of the EMMY trial and the post-hoc echocardiographic sub-analysis,(109, 151) these trials showed significant

impact on left ventricular volumes, while improvement in systolic or diastolic function was only found in some.

2.5 SGLT2-inhibition in chronic heart failure and after AMI°

In the past years, new therapeutic pathways beyond neurohumoral modulation have been associated with clinical and prognostic profit in chronic heart failure. In large randomized controlled trials, treatment with SGLT2i was associated with fewer heart failure hospitalizations, decreased progression of renal disease, and reduced cardiovascular mortality in patients with chronic heart failure. Improved outcomes were present across all ranges of LVEF and among patients with and without diabetes.(84, 94, 95, 152, 153) This led to their implementation into the guideline recommended therapy in chronic heart failure across all LVEF phenotypes.(1, 154)

Similar to their established role in heart failure, accumulating evidence points to beneficial effects of SGLT2i in patients with coronary artery disease and acute coronary syndromes, beyond their glucose-lowering properties.(109, 155-157) In the DAPA-MI trial, the administration of SGLT2i in addition to standard post-myocardial infarction therapy after AMI showed a favourable effect on cardiometabolic outcomes compared to a placebo in patients without diabetes or chronic heart failure. However, no significant differences regarding clinical outcomes were observed in this trial.(110) Similar neutral effects on prespecified outcomes were observed in the EMPACT-MI trial.(111) Though a sub-analysis demonstrated a risk reduction for first and recurrent hospitalizations for heart failure in patients treated with empagliflozin.(158)

Overall, SGLT2i showed positive impact on the cardiovascular system after AMI. Underlying pathways on the prevention and reversal of adverse cardiac remodelling are widely discussed and deemed multifactorial. Several preclinical and clinical studies suggest the anti-inflammatory and anti-fibrotic properties as well as improved cardiac efficiency and increased myocardial energy supply to contribute to their cardioprotective benefits.(124, 159-162)

The present echocardiographic post-hoc analysis of the EMMY trial demonstrated significant effects on cardiac remodelling depicted by changes in left ventricular diastolic and systolic volumes in favour of the SGLT2i group, in line with the findings of the main EMMY trial.(109, 151) However, only favourable trends but no significant effect was observed for markers of left ventricular systolic and diastolic function. Similar trajectories were observed in right ventricular and left and right atrial parameters, and throughout deformation analysis parameters. At baseline, left ventricular systolic function was only mildly reduced in the EMMY cohort. Especially in patients with less impaired left ventricular function, the clinical effect on cardiac function after AMI seems limited. The SOdium-glucose CO-transporter inhibition in patients with newly detected Glucose Abnormalities and a recent Myocardial Infarction (SOCOGAMI) trial demonstrated a significant decrease in body weight and glucose levels with SGLT2i but showed no significant impact on echocardiographic and magnetic resonance imaging variables in a cohort with recent acute coronary syndrome and normal left ventricular function.(163) This, in alignment with the results of the echocardiographic sub-analysis of the EMMY trial, poses the question of treatment effect of SGLT2i in patients with a more pronounced cardiac functional impairment following AMI.

Of note, echocardiographic sub-studies of trials investigating cardiovascular outcomes after AMI for sacubitril/valsartan and vericiguat also showed only minor effects on cardiac structure, and mostly no effect on cardiac function. A sub-study of the Impact of Sacubitril/Valsartan Compared with Ramipril on Cardiac Structure and Function After Acute Myocardial Infarction (PARADISE-MI) demonstrated significant impact on left ventricular end-diastolic volumes, but no differences in improvement of systolic function.(147) Similar results were provided in the echocardiographic sub-study of the VerICiguaT Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial.(164)

2.6 SLGT2-inhibition in cardiac amyloidosis[#]

The present analysis of the prospective Graz Hypertrophic Cardiomyopathy (HCM) Registry demonstrated that in patients with chronic heart failure and a diagnosis of ATTR-CM, treatment with SGLT2i was significantly associated with lower mortality. This effect remained significant after adjustment for clinical parameters of renal function, the cardiac biomarker NT-proBNP,

#Parts of this chapter have been published in the Journal of Clinical Medicine. (2024). DOI: 10.3390/jcm13195966.

LVEF, and concomitant therapy with the selective transthyretin stabilizer tafamidis. However, after adjustment for immortal time, the association became neutral.(165)

In line with these results, previous reports support the notion that SGLT2i are safe and overall well tolerated in patients with ATTR-CM.(116-118, 166) Various trials on SGLT2i treatment in patients with chronic heart failure also substantiate benefit of these drugs on outcomes regardless of systolic function.(94, 95, 152, 167) However, ATTR-CM was an exclusion criterion in these heart failure trials. Though, large meta-analyses indicate that patients with undiagnosed cardiac amyloidosis may have been unintentionally included in these cohorts and benefited equally.(168, 169)

Porcari and colleagues were the first to investigate the impact of SGLT2i treatment on clinical outcomes in ATTR-CM in a large multicentre observational study with a propensity score-matched cohort. They demonstrated a significant association with lower all-cause mortality, lower cardiovascular mortality, and lower rate in heart failure hospitalizations.(119) Regarding all-cause mortality, the findings of the present analysis imply that the association between SGLT2i therapy and better prognosis occurs independently of renal function, cardiac biomarker levels, left ventricular systolic function, and concomitant tafamidis treatment.
Yet, accounting for the immortal time bias, results became neutral in our cohort. This bias, often neglected in previous observational cohort studies evaluating drug effects, can create illusional and overoptimistic treatment effects when not accounted for.(170) In observational studies, treatment is often initiated some amount of time after the baseline examination and therefore during the observational period. This indicates a treatment-naïve period for patients within the treatment group. Inherent to the design of observational studies, an outcome event cannot occur during this treatment-naïve period, therefore patients within the treatment group are to be defined as “immortal” before the treatment exposure.
Hence, an increased awareness for the immortal time bias should be applied to all observational cohort studies. To incorporate the bias into statistical considerations several approaches can be applied.(170, 171) Nevertheless, even after accounting for immortal time, observational cohorts remain susceptible to other potential biases, especially regarding selection, indication, and confounders. Given the neutrality of our findings in context with positive associations observed in other observational cohort studies, a randomized controlled trial is warranted to better inform

about the real effects of SGLT2i in ATTR-CM. However, in the absence of evidence from classical randomized controlled trials, data derived from large observational cohort studies enhance an understanding of the effects of SGLT2i in ATTR-CM.

3 Conclusion

The analysis of the RoC-HF cohort demonstrates the prognostic relevance of right ventricular function in chronic heart failure, despite the common consideration of HFrEF to be a primarily left ventricular disease. The findings underline its particular value in terms of clinical outcomes in patients with significantly impaired left ventricular function. TAPSE, that was found to be the strongest echocardiographic predictor in this cohort, could serve as an additional prognosticator. These results call for its integration into routine risk assessment and management strategies for chronic heart failure patients. Such an approach could enhance patient stratification and tailor therapeutic interventions more effectively. To elucidate whether incorporating right ventricular function into established heart failure risk scores could improve their accuracy should be the target of future studies.

In the context of pharmacotherapy, the favourable effects of SGLT2i on cardiac remodelling and outcomes in heart failure patients across different spectrums of the disease point to their expanding role in heart failure management. The echocardiographic post-hoc analysis of the EMMY trial demonstrated beneficial impact of SGLT2i in patients after recent AMI compared to placebo. Further, in patients with ATTR-CM SGLT2i treatment was associated with better survival in crude analysis. Both cohorts represent high-risk populations with continued unmet therapeutic needs. However, evidence remains limited, warranting further randomized trials to validate these findings.

The present studies provide deep collective insights that underscore the need for a nuanced understanding of cardiac function and prognosticators in chronic heart failure.

4 Strengths and limitations*°#

The RoC-HF cohort is a contemporary outpatient clinic chronic heart failure cohort, which only preselected patients based on LVEF. Therefore, this cohort provides valid insights into "real world" chronic heart failure patient outcomes; however, due to optimal heart failure treatment, mortality rates in this cohort were lower compared to those in literature.(36, 172, 173) This may account for the divergent findings regarding the association between TAPSE and all-cause mortality in comparison to previous investigations.

A further limitation relates to the timing of the inclusion period of this study; practically no patient received SGLT2i as treatment for heart failure at the time of inclusion since SGLT2i were introduced into guideline recommended heart failure therapy and routine clinical care for these patients later. Lastly, the presented data on right ventricular function is limited as no assessment using techniques, such as 3D- or speckle-tracking echocardiography was performed in this cohort.

The EMMY trial was the first trial to show the impact of early treatment with SGLT2i in patients after AMI, predominantly without diabetes. The present echocardiographic post-hoc analysis provides first insights into cardiac mechanisms within the first 26 weeks of treatment compared with placebo. All echocardiographic analyses were conducted at the Central Echocardiographic Core Laboratory by trained, blinded investigators, twice if applicable, with an overall satisfying intra-observer reproducibility. This enabled the acquisition of a comprehensive dataset with precise measurements. To our best knowledge, this is the first study to give insight to the course of cardiac structure and function including right ventricular and atrial structural and functional parameters including deformation imaging after AMI.

Overall, the findings of this sub-analysis are in line with the results of the main EMMY trial, however, in contrast to the main trial, parameters reflecting systolic and diastolic function did not meet statistical significance. This is most probably a result of a lack of statistical power due to the smaller sample size (post-hoc power estimation at an alpha level of 0.05: LVEF 43%, E/e' 60%).

*Parts of this chapter have been published in the Journal of Clinical Medicine. (2024). DOI: 10.3390/jcm13071930.
°Parts of this chapter have been published in Clinical Research in Cardiology. (2025). DOI: 10.1007/s00392-024-02523-1.
#Parts of this chapter have been published in the Journal of Clinical Medicine. (2024). DOI: 10.3390/jcm13195966.

Furthermore, the presented findings may have a limited application in women, as only 18.3% of the study population was female. This underrepresentation is common in cardiovascular trials, particularly in AMI trials.(174, 175) Additionally, some of the inclusion criteria may have contributed to the small proportion of women, as literature shows that in women cardiac biomarker levels are lower compared to men.(176) Nevertheless, a sub-analysis on gender of the EMMY trial indicated no significant difference in treatment effect.(177)

Regarding the ATTR-CM cohort, a major strength, aside from providing real-world data in an all-comers cohort of patients with ATTR-CM, is the clear presentation of the immortal time bias. However, the observational nature of the data, limited sample size, and single-centre design may provide overestimated effect sizes compared to those reported in large-scale trials in heart-failure patients, limiting the generalizability of these results. Further, due to the low number of cardiovascular events, related outcome associations may be subject to a type-2 error. Lastly, indication bias may have played a role in the introduction of SGLT2i treatment in the observed patients.

5 References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
2. Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, et al. 2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation. 2025;151(8):e41-e660.
3. Ran J, Zhou P, Wang J, Zhao X, Huang Y, Zhou Q, et al. Global, regional, and national burden of heart failure and its underlying causes, 1990-2021: results from the global burden of disease study 2021. Biomark Res. 2025;13(1):16.
4. Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, et al. Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta-Analysis. Circ Heart Fail. 2017;10(1):e003529.
5. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396(10254):819-29.
6. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022;400(10354):757-67.
7. Poole JE, Olshansky B, Mark DB, Anderson J, Johnson G, Hellkamp AS, et al. Long-Term Outcomes of Implantable Cardioverter-Defibrillator Therapy in the SCD-HeFT. J Am Coll Cardiol. 2020;76(4):405-15.
8. Gama F, Ferreira J, Carmo J, Costa FM, Carvalho S, Carmo P, et al. Implantable Cardioverter-Defibrillators in Trials of Drug Therapy for Heart Failure: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2020;9(8):e015177.
9. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. Eur Heart J. 2006;27(22):2682-8.
10. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.
11. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021;27(4):387-413.
12. Arrigo M, Huber LC, Winnik S, Mikulicic F, Guidetti F, Frank M, et al. Right Ventricular Failure: Pathophysiology, Diagnosis and Treatment. Card Fail Rev. 2019;5(3):140-6.
13. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, et al. The continuous heart failure spectrum: moving beyond an ejection fraction classification. Eur Heart J. 2019;40(26):2155-63.
14. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

15. Scarsini R, Fezzi S, Leone AM, De Maria GL, Pighi M, Marcoli M, et al. Functional Patterns of Coronary Disease: Diffuse, Focal, and Serial Lesions. JACC Cardiovasc Interv. 2022;15(21):2174-91.
16. Sternheim D, Power DA, Samtani R, Kini A, Fuster V, Sharma S. Myocardial Bridging: Diagnosis, Functional Assessment, and Management: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021;78(22):2196-212.
17. Gentile F, Castiglione V, De Caterina R. Coronary Artery Anomalies. Circulation. 2021;144(12):983-96.
18. Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary Microvascular Dysfunction Across the Spectrum of Cardiovascular Diseases: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021;78(13):1352-71.
19. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237-69.
20. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014;114(12):1852-66.
21. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270-6.
22. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023;44(37):3503-626.
23. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2021;42(16):1554-68.
24. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. Circulation. 2019;140(1):16-26.
25. Damy T, Costes B, Hagege AA, Donal E, Eicher JC, Slama M, et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. Eur Heart J. 2016;37(23):1826-34.
26. Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J. 2017;38(38):2879-87.
27. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J. 2015;36(38):2585-94.
28. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banypersad SM, Sattianayagam P, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc. 2013;2(2):e000098.
29. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J. 2012;164(2):222-8 e1.
30. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J Am Coll Cardiol. 2016;68(10):1014-20.

31. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018;39(30):2799-806.
32. Cheng RK, Levy WC, Vasbinder A, Teruya S, De Los Santos J, Leedy D, et al. Diuretic Dose and NYHA Functional Class Are Independent Predictors of Mortality in Patients With Transthyretin Cardiac Amyloidosis. JACC CardioOncol. 2020;2(3):414-24.
33. Timmis A, Aboyans V, Vardas P, Townsend N, Torbica A, Kavousi M, et al. European Society of Cardiology: the 2023 Atlas of Cardiovascular Disease Statistics. Eur Heart J. 2024;45(38):4019-62.
34. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, et al. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC Heart Fail. 2018;6(8):678-85.
35. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19(12):1574-85.
36. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34(19):1404-13.
37. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012;5(6):720-6.
38. Lupon J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, Lopez-Ayerbe J, et al. Dynamic Trajectories of Left Ventricular Ejection Fraction in Heart Failure. J Am Coll Cardiol. 2018;72(6):591-601.
39. Rastogi A, Novak E, Platts AE, Mann DL. Epidemiology, pathophysiology and clinical outcomes for heart failure patients with a mid-range ejection fraction. Eur J Heart Fail. 2017;19(12):1597-605.
40. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017;3(1):7-11.
41. Al-Mohammad A, Mant J, Laramee P, Swain S, Chronic Heart Failure Guideline Development G. Diagnosis and management of adults with chronic heart failure: summary of updated NICE guidance. BMJ. 2010;341:c4130.
42. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44(37):3627-39.
43. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail. 2013;15(9):1062-73.
44. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113(11):1424-33.
45. Senni M, Parrella P, De Maria R, Cottini C, Bohm M, Ponikowski P, et al. Predicting heart failure outcome from cardiac and comorbid conditions: the 3C-HF score. Int J Cardiol. 2013;163(2):206-11.

46. Rich JD, Burns J, Freed BH, Maurer MS, Burkhoff D, Shah SJ. Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score: Validation of a Simple Tool for the Prediction of Morbidity and Mortality in Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc. 2018;7(20):e009594.
47. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005;112(24):3738-44.
48. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014;63(25 Pt A):2751-68.
49. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2014;63(5):447-56.
50. Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. Clin Sci (Lond). 2004;106(1):53-60.
51. Potter E, Marwick TH. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. JACC Cardiovasc Imaging. 2018;11(2 Pt 1):260-74.
52. Chimed S, Stassen J, Galloo X, Meucci MC, Knuuti J, Delgado V, et al. Prognostic Relevance of Left Ventricular Global Longitudinal Strain in Patients With Heart Failure and Reduced Ejection Fraction. Am J Cardiol. 2023;202:30-40.
53. Chang WT, Lin CH, Hong CS, Liao CT, Liu YW, Chen ZC, et al. The predictive value of global longitudinal strain in patients with heart failure mid-range ejection fraction. J Cardiol. 2021;77(5):509-16.
54. Brann A, Miller J, Eshraghian E, Park JJ, Greenberg B. Global longitudinal strain predicts clinical outcomes in patients with heart failure with preserved ejection fraction. Eur J Heart Fail. 2023;25(10):1755-65.
55. Adamo L, Perry A, Novak E, Makan M, Lindman BR, Mann DL. Abnormal Global Longitudinal Strain Predicts Future Deterioration of Left Ventricular Function in Heart Failure Patients With a Recovered Left Ventricular Ejection Fraction. Circ Heart Fail. 2017;10(6).
56. Janwanishstaporn S, Cho JY, Feng S, Brann A, Seo JS, Narezkina A, et al. Prognostic Value of Global Longitudinal Strain in Patients With Heart Failure With Improved Ejection Fraction. JACC Heart Fail. 2022;10(1):27-37.
57. Erratum to: 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J. 2023;44(18):1621.
58. Gulati A, Ismail TF, Jabbour A, Alpendurada F, Guha K, Ismail NA, et al. The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. Circulation. 2013;128(15):1623-33.
59. Shah JP, Yang Y, Chen S, Hagar A, Pu XB, Xia T, et al. Prevalence and Prognostic Significance of Right Ventricular Dysfunction in Patients With Hypertrophic Cardiomyopathy. Am J Cardiol. 2018;122(11):1932-8.
60. Grevious SN, Fernandes MF, Annor AK, Ibrahim M, Saint Croix GR, de Marchena E, et al. Prognostic Assessment of Right Ventricular Systolic Dysfunction on Post-Transcatheter

Aortic Valve Replacement Short-Term Outcomes: Systematic Review and Meta-Analysis. J Am Heart Assoc. 2020;9(12):e014463.
61. Nies RJ, Nettersheim FS, Braumann S, Ney S, Ochs L, Dohr J, et al. Right ventricular dysfunction and impaired right ventricular-pulmonary arterial coupling in paradoxical low-flow, low-gradient aortic stenosis. Eur J Heart Fail. 2024;26(11):2340-52.
62. Anavekar NS, Skali H, Bourgoun M, Ghali JK, Kober L, Maggioni AP, et al. Usefulness of right ventricular fractional area change to predict death, heart failure, and stroke following myocardial infarction (from the VALIANT ECHO Study). Am J Cardiol. 2008;101(5):607-12.
63. Meyer P, Filippatos GS, Ahmed MI, Iskandrian AE, Bittner V, Perry GJ, et al. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. Circulation. 2010;121(2):252-8.
64. Ghio S, Recusani F, Klersy C, Sebastiani R, Laudisa ML, Campana C, et al. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol. 2000;85(7):837-42.
65. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014;35(48):3452-62.
66. Koutsampasopoulos K, Vogiatzis I, Ziakas A, Papadopoulos C, Loutradis C, Imprialos KP, et al. Right ventricular performance in patients with heart failure with mildly reduced ejection fraction: the forgotten ventricle. Int J Cardiovasc Imaging. 2022;38(11):2363-72.
67. Richter MJ, Peters D, Ghofrani HA, Naeije R, Roller F, Sommer N, et al. Evaluation and Prognostic Relevance of Right Ventricular-Arterial Coupling in Pulmonary Hypertension. Am J Respir Crit Care Med. 2020;201(1):116-9.
68. Pueschner A, Chattranukulchai P, Heitner JF, Shah DJ, Hayes B, Rehwald W, et al. The Prevalence, Correlates, and Impact on Cardiac Mortality of Right Ventricular Dysfunction in Nonischemic Cardiomyopathy. JACC Cardiovasc Imaging. 2017;10(10 Pt B):1225-36.
69. Schmeisser A, Rauwolf T, Groscheck T, Fischbach K, Kropf S, Luani B, et al. Predictors and prognosis of right ventricular function in pulmonary hypertension due to heart failure with reduced ejection fraction. ESC Heart Fail. 2021;8(4):2968-81.
70. Sayour AA, Tokodi M, Celeng C, Takx RAP, Fabian A, Lakatos BK, et al. Association of Right Ventricular Functional Parameters With Adverse Cardiopulmonary Outcomes: A Meta-analysis. J Am Soc Echocardiogr. 2023;36(6):624-33 e8.
71. Houard L, Benaets MB, de Meester de Ravenstein C, Rousseau MF, Ahn SA, Amzulescu MS, et al. Additional Prognostic Value of 2D Right Ventricular Speckle-Tracking Strain for Prediction of Survival in Heart Failure and Reduced Ejection Fraction: A Comparative Study With Cardiac Magnetic Resonance. JACC Cardiovasc Imaging. 2019;12(12):2373-85.
72. Lejeune S, Roy C, Ciocea V, Slimani A, de Meester C, Amzulescu M, et al. Right Ventricular Global Longitudinal Strain and Outcomes in Heart Failure with Preserved Ejection Fraction. J Am Soc Echocardiogr. 2020;33(8):973-84 e2.
73. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651-8.
74. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.
75. Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35.

76. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293-302.
77. Cohn JN, Tognoni G, Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345(23):1667-75.
78. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362(9386):767-71.
79. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362(9386):772-6.
80. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
81. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17.
82. Rywik TM. [Summary of the article: Zannad F, McMurray JJV, Krum H et al.; for the EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med, 2011; 364: 11-21]. Kardiol Pol. 2011;69(6):631-2.
83. Khong TK, Au Yeung J. Effect of dapagliflozin in patients with heart failure. Drug Ther Bull. 2021;59(6):86-7.
84. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24.
85. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27(19):2338-45.
86. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362(9386):777-81.
87. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359(23):2456-67.
88. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-20.
89. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370(15):1383-92.
90. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018;39(1):26-35.

91. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018;20(8):1230-9.
92. Solomon SD, Vaduganathan M, B LC, Packer M, Zile M, Swedberg K, et al. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation. 2020;141(5):352-61.
93. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J. 2016;37(5):455-62.
94. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61.
95. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387(12):1089-98.
96. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J Acute Cardiovasc Care. 2024;13(1):55-161.
97. Martinez-Milla J, Raposeiras-Roubin S, Pascual-Figal DA, Ibanez B. Role of Beta-blockers in Cardiovascular Disease in 2019. Rev Esp Cardiol (Engl Ed). 2019;72(10):844-52.
98. Dahl Aarvik M, Sandven I, Dondo TB, Gale CP, Ruddox V, Munkhaugen J, et al. Effect of oral beta-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother. 2019;5(1):12-20.
99. Kim J, Kang D, Park H, Kang M, Park TK, Lee JM, et al. Long-term beta-blocker therapy and clinical outcomes after acute myocardial infarction in patients without heart failure: nationwide cohort study. Eur Heart J. 2020;41(37):3521-9.
100. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, et al. beta-Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction. J Am Coll Cardiol. 2017;69(22):2710-20.
101. Ibanez B, Latini R, Rossello X, Dominguez-Rodriguez A, Fernandez-Vazquez F, Pelizzoni V, et al. Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction. N Engl J Med. 2025.
102. Munkhaugen J, Kristensen AMD, Halvorsen S, Holmager T, Olsen MH, Bakken A, et al. Beta-Blockers after Myocardial Infarction in Patients without Heart Failure. N Engl J Med. 2025.
103. Rossello X, Prescott EIB, Kristensen AMD, Latini R, Fuster V, Fagerland MW, et al. beta blockers after myocardial infarction with mildly reduced ejection fraction: an individual patient data meta-analysis of randomised controlled trials. Lancet. 2025;406(10508):1128-37.
104. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993;342(8875):821-8.
105. Heart Outcomes Prevention Evaluation Study I, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145-53.
106. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349(20):1893-906.

107. Pfeffer MA, Claggett B, Lewis EF, Granger CB, Kober L, Maggioni AP, et al. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction. N Engl J Med. 2021;385(20):1845-55.
108. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309-21.
109. von Lewinski D, Kolesnik E, Tripolt NJ, Pferschy PN, Benedikt M, Wallner M, et al. Empagliflozin in acute myocardial infarction: the EMMY trial. Eur Heart J. 2022;43(41):4421-32.
110. James S, Erlinge D, Storey RF, McGuire DK, de Belder M, Eriksson N, et al. Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure. NEJM Evid. 2024;3(2):EVIDoa2300286.
111. Butler J, Jones WS, Udell JA, Anker SD, Petrie MC, Harrington J, et al. Empagliflozin after Acute Myocardial Infarction. N Engl J Med. 2024;390(16):1455-66.
112. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16.
113. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2024;390(2):132-42.
114. Fontana M, Berk JL, Gillmore JD, Witteles RM, Grogan M, Drachman B, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025;392(1):33-44.
115. Ioannou A, Massa P, Patel RK, Razvi Y, Porcari A, Rauf MU, et al. Conventional heart failure therapy in cardiac ATTR amyloidosis. Eur Heart J. 2023;44(31):2893-907.
116. Dobner S, Bernhard B, Asatryan B, Windecker S, Stortecky S, Pilgrim T, et al. SGLT2 inhibitor therapy for transthyretin amyloid cardiomyopathy: early tolerance and clinical response to dapagliflozin. ESC Heart Fail. 2023;10(1):397-404.
117. Lang FM, Teruya S, Weinsaft A, Cuomo M, Santos AM, Nalbandian A, et al. Sodium-glucose cotransporter 2 inhibitors for transthyretin amyloid cardiomyopathy: Analyses of short-term efficacy and safety. Eur J Heart Fail. 2024;26(4):938-47.
118. Steinhardt MJ, Cejka V, Chen M, Bauerlein S, Schafer J, Adrah A, et al. Safety and Tolerability of SGLT2 Inhibitors in Cardiac Amyloidosis-A Clinical Feasibility Study. J Clin Med. 2024;13(1).
119. Porcari A, Cappelli F, Nitsche C, Tomasoni D, Sinigiani G, Longhi S, et al. SGLT2 Inhibitor Therapy in Patients With Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol. 2024;83(24):2411-22.
120. Santos AB, Roca GQ, Claggett B, Sweitzer NK, Shah SJ, Anand IS, et al. Prognostic Relevance of Left Atrial Dysfunction in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2016;9(4):e002763.
121. Anastasiou V, Papazoglou AS, Moysidis DV, Daios S, Tsalikakis D, Giannakoulas G, et al. The prognostic value of right ventricular longitudinal strain in heart failure: a systematic review and meta-analysis. Heart Fail Rev. 2023;28(6):1383-94.
122. Asensio Lopez MDC, Lax A, Hernandez Vicente A, Saura Guillen E, Hernandez-Martinez A, Fernandez Del Palacio MJ, et al. Empagliflozin improves post-infarction cardiac remodeling through GTP enzyme cyclohydrolase 1 and irrespective of diabetes status. Sci Rep. 2020;10(1):13553.

123. Yurista SR, Sillje HHW, Oberdorf-Maass SU, Schouten EM, Pavez Giani MG, Hillebrands JL, et al. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail. 2019;21(7):862-73.
124. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med. 2017;104:298-310.
125. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, et al. Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. J Am Coll Cardiol. 2019;73(15):1931-44.
126. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, et al. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2021;77(3):243-55.
127. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, et al. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. Circulation. 2006;114(17):1883-91.
128. Schwarz K, Singh S, Dawson D, Frenneaux MP. Right ventricular function in left ventricular disease: pathophysiology and implications. Heart Lung Circ. 2013;22(7):507-11.
129. Lundorff IJ, Sengelov M, Pedersen S, Modin D, Bruun NE, Fritz-Hansen T, et al. Prognostic value of right ventricular echocardiographic measures in patients with heart failure with reduced ejection fraction. J Clin Ultrasound. 2021;49(9):903-13.
130. Ghio S, Guazzi M, Scardovi AB, Klersy C, Clemenza F, Carluccio E, et al. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. Eur J Heart Fail. 2017;19(7):873-9.
131. Carluccio E, Biagioli P, Alunni G, Murrone A, Zuchi C, Coiro S, et al. Prognostic Value of Right Ventricular Dysfunction in Heart Failure With Reduced Ejection Fraction: Superiority of Longitudinal Strain Over Tricuspid Annular Plane Systolic Excursion. Circ Cardiovasc Imaging. 2018;11(1):e006894.
132. Parrinello G, Torres D, Buscemi S, Di Chiara T, Cuttitta F, Cardillo M, et al. Right ventricular diameter predicts all-cause mortality in heart failure with preserved ejection fraction. Intern Emerg Med. 2019;14(7):1091-100.
133. Kanagala P, Arnold JR, Singh A, Khan JN, Gulsin GS, Gupta P, et al. Prevalence of right ventricular dysfunction and prognostic significance in heart failure with preserved ejection fraction. Int J Cardiovasc Imaging. 2021;37(1):255-66.
134. Schwegel N, Zach D, Peikert A, Santner V, Holler V, Gollmer J, et al. The Prognostic Value of Right Ventricular Function in Patients with Chronic Heart Failure-A Prospective Study. J Clin Med. 2024;13(7).
135. Legris V, Thibault B, Dupuis J, White M, Asgar AW, Fortier A, et al. Right ventricular function and its coupling to pulmonary circulation predicts exercise tolerance in systolic heart failure. ESC Heart Fail. 2022;9(1):450-64.
136. Menegazzo WR, Santos ABS, Foppa M, Scolari FL, Barros FC, Stein R, et al. Prognostic value of right ventricular strain and peak oxygen consumption in heart failure with reduced ejection fraction. Int J Cardiovasc Imaging. 2023;39(3):501-9.
137. Modin D, Mogelvang R, Andersen DM, Biering-Sorensen T. Right Ventricular Function Evaluated by Tricuspid Annular Plane Systolic Excursion Predicts Cardiovascular Death in the General Population. J Am Heart Assoc. 2019;8(10):e012197.

138. Damy T, Kallvikbacka-Bennett A, Goode K, Khaleva O, Lewinter C, Hobkirk J, et al. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. J Card Fail. 2012;18(3):216-25.
139. Berrill M, Ashcroft E, Fluck D, John I, Beeton I, Sharma P, et al. Right Ventricular Dysfunction Predicts Outcome in Acute Heart Failure. Front Cardiovasc Med. 2022;9:911053.
140. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.
141. Naeije R, Brimioulle S, Dewachter L. Biomechanics of the right ventricle in health and disease (2013 Grover Conference series). Pulm Circ. 2014;4(3):395-406.
142. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol. 2013;62(25 Suppl):D22-33.
143. Borgdorff MA, Bartelds B, Dickinson MG, Steendijk P, de Vroomen M, Berger RM. Distinct loading conditions reveal various patterns of right ventricular adaptation. Am J Physiol Heart Circ Physiol. 2013;305(3):H354-64.
144. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation. 1994;89(1):68-75.
145. Frantz S, Hundertmark MJ, Schulz-Menger J, Bengel FM, Bauersachs J. Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies. Eur Heart J. 2022;43(27):2549-61.
146. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation. 2005;111(25):3411-9.
147. Shah AM, Claggett B, Prasad N, Li G, Volquez M, Jering K, et al. Impact of Sacubitril/Valsartan Compared With Ramipril on Cardiac Structure and Function After Acute Myocardial Infarction: The PARADISE-MI Echocardiographic Substudy. Circulation. 2022;146(14):1067-81.
148. Doughty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N, et al. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation. 2004;109(2):201-6.
149. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation. 1995;91(10):2573-81.
150. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. J Am Coll Cardiol. 2000;36(7):2072-80.
151. Schwegel N, Strohhofer C, Kolesnik E, Oltean S, Huttmair A, Pipp C, et al. Impact of empagliflozin on cardiac structure and function assessed by echocardiography after myocardial infarction: a post-hoc sub-analysis of the emmy trial. Clin Res Cardiol. 2025;114(5):629-39.
152. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008.

153. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-28.
154. Authors/Task Force M, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2024;26(1):5-17.
155. Hoshika Y, Kubota Y, Mozawa K, Tara S, Tokita Y, Yodogawa K, et al. Effect of Empagliflozin Versus Placebo on Plasma Volume Status in Patients with Acute Myocardial Infarction and Type 2 Diabetes Mellitus. Diabetes Ther. 2021;12(8):2241-8.
156. Wei W, Liu J, Chen S, Xu X, Guo D, He Y, et al. Sodium Glucose Cotransporter Type 2 Inhibitors Improve Cardiorenal Outcome of Patients With Coronary Artery Disease: A Meta-Analysis. Front Endocrinol (Lausanne). 2022;13:850836.
157. Paolisso P, Bergamaschi L, Santulli G, Gallinoro E, Cesaro A, Gragnano F, et al. Infarct size, inflammatory burden, and admission hyperglycemia in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: a multicenter international registry. Cardiovasc Diabetol. 2022;21(1):77.
158. Hernandez AF, Udell JA, Jones WS, Anker SD, Petrie MC, Harrington J, et al. Effect of Empagliflozin on Heart Failure Outcomes After Acute Myocardial Infarction: Insights From the EMPACT-MI Trial. Circulation. 2024;149(21):1627-38.
159. Iannantuoni F, A MdM, Diaz-Morales N, Falcon R, Banuls C, Abad-Jimenez Z, et al. The SGLT2 Inhibitor Empagliflozin Ameliorates the Inflammatory Profile in Type 2 Diabetic Patients and Promotes an Antioxidant Response in Leukocytes. J Clin Med. 2019;8(11).
160. Kang S, Verma S, Fatehi Hassanabad A, Teng G, Belke DD, Dundas JA, et al. Direct Effects of Empagliflozin on Extracellular Matrix Remodelling in Human Cardiac Myofibroblasts: Novel Translational Clues to Explain EMPA-REG OUTCOME Results. Can J Cardiol. 2020;36(4):543-53.
161. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci. 2020;5(6):632-44.
162. de Koning MLY, Westenbrink BD, Assa S, Garcia E, Connelly MA, van Veldhuisen DJ, et al. Association of Circulating Ketone Bodies With Functional Outcomes After ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. 2021;78(14):1421-32.
163. Lundin M, Ferrannini G, Mellbin L, Johansson I, Norhammar A, Nasman P, et al. SOdium-glucose CO-transporter inhibition in patients with newly detected Glucose Abnormalities and a recent Myocardial Infarction (SOCOGAMI). Diabetes Res Clin Pract. 2022;193:110141.
164. Pieske B, Pieske-Kraigher E, Lam CSP, Melenovsky V, Sliwa K, Lopatin Y, et al. Effect of vericiguat on left ventricular structure and function in patients with heart failure with reduced ejection fraction: The VICTORIA echocardiographic substudy. Eur J Heart Fail. 2023;25(7):1012-21.
165. Schwegel N, Toferer C, Zach DK, Santner V, Holler V, Lugitsch J, et al. Impact of SGLT2-Inhibitor Therapy on Survival in Patients with Transthyretin Amyloid Cardiomyopathy: Analysis of a Prospective Registry Study. J Clin Med. 2024;13(19).
166. Minguito-Carazo C, Sanchez Munoz E, Rodriguez Manero M, Martinez-Sande JL, Fidalgo Andres ML, Garcia Seara J, et al. Impact of initiation of SGLT2 inhibitor treatment on

the development of arrhythmias in patients with implantable cardiac devices. Rev Esp Cardiol (Engl Ed). 2024;77(6):481-9.
167. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. Circulation. 2021;143(4):326-36.
168. Magdi M, Mostafa MR, Abusnina W, Al-Abdouh A, Doss R, Mohamed S, et al. A systematic review and meta-analysis of the prevalence of transthyretin amyloidosis in heart failure with preserved ejection fraction. Am J Cardiovasc Dis. 2022;12(3):102-11.
169. Oghina S, Bougouin W, Bezard M, Kharoubi M, Komajda M, Cohen-Solal A, et al. The Impact of Patients With Cardiac Amyloidosis in HFpEF Trials. JACC Heart Fail. 2021;9(3):169-78.
170. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf. 2007;16(3):241-9.
171. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. Am J Epidemiol. 2005;162(10):1016-23.
172. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. J Am Coll Cardiol. 2018;72(4):351-66.
173. Roger VL. Epidemiology of Heart Failure: A Contemporary Perspective. Circ Res. 2021;128(10):1421-34.
174. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017. Circulation. 2020;141(7):540-8.
175. Tobb K, Kocher M, Bullock-Palmer RP. Underrepresentation of women in cardiovascular trials- it is time to shatter this glass ceiling. Am Heart J Plus. 2022;13:100109.
176. Lew J, Sanghavi M, Ayers CR, McGuire DK, Omland T, Atzler D, et al. Sex-Based Differences in Cardiometabolic Biomarkers. Circulation. 2017;135(6):544-55.
177. Sourij C, Aziz F, Tripolt NJ, Siller-Matula J, Pferschy PN, Kolesnik E, et al. Effects of empagliflozin in women and men with acute myocardial infarction: An analysis from the EMMY trial. Hellenic J Cardiol. 2024;75:3-8.

Journal of
Clinical Medicine

MDPI

Article

The Prognostic Value of Right Ventricular Function in Patients with Chronic Heart Failure—A Prospective Study

Nora Schwegel [1], David Zach [1], Alexander Peikert [1], Viktoria Santner [1], Viktoria Höller [1], Johannes Gollmer [1], Johannes Späth [1], Hermann Riepl [1], Peter P. Rainer [1,2,3], Markus Wallner [1], Stefan Pilz [4], Andreas Zirlik [1], Dirk von Lewinski [1], Klemens Ablasser [1], Nicolas Verheyen [1,*] and Ewald Kolesnik [1]

[1] Division of Cardiology, University Heart Center Graz, Medical University of Graz, 8036 Graz, Austria
[2] Department of Medicine, St. Johann in Tirol General Hospital, 6380 St. Johann in Tirol, Austria
[3] BioTechMed Graz, 8010 Graz, Austria
[4] Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, 8036 Graz, Austria
* Correspondence: nicolas.verheyen@medunigraz.at; Tel.: +43-(0)31638512544; Fax: +43-(0)31638513733

Abstract: Background: In patients with stable chronic heart failure with a reduced ejection fraction (HFrEF), left ventricular ejection fraction (LVEF) provides limited prognostic value, especially in patients with moderately to severely reduced LVEF. Echocardiographic parameters of right ventricular function may be associated with adverse clinical events in these patients. Therefore, we analyzed 164 patients with HFrEF in a prospective single-center cohort study to evaluate whether the parameters of right ventricular function are associated with worsening heart failure (WHF) hospitalizations, cardiovascular and all-cause deaths and combined endpoints. **Methods:** Echocardiographic cine loops were analyzed using vendor-independent post-processing software. Multivariate Cox regression analyses were performed, which were then adjusted for clinical characteristics and left ventricular functional parameters. **Results:** In these models, higher tricuspid annular plane systolic excursion (TAPSE) was significantly associated with lower rates of WHF hospitalizations (HR 0.880, 95%CI 0.800–0.968, $p = 0.008$), a composite endpoint of WHF hospitalizations and cardiovascular death (HR 0.878, 95%CI 0.800–0.964, $p = 0.006$), and a composite endpoint of WHF hospitalization and all-cause death (HR 0.918, 95%CI 0.853–0.988, $p = 0.023$). These associations were more pronounced in patients with LVEF $\leq$ 35%. **Conclusions:** In conclusion, in patients with HFrEF, TAPSE is an independent prognosticator for adverse clinical outcomes, warranting further studies to elucidate whether incorporating TAPSE into established risk scores improves their diagnostic accuracy.

Keywords: chronic heart failure; HFrEF; right ventricular function

Citation: Schwegel, N.; Zach, D.; Peikert, A.; Santner, V.; Höller, V.; Gollmer, J.; Späth, J.; Riepl, H.; Rainer, P.P.; Wallner, M.; et al. The Prognostic Value of Right Ventricular Function in Patients with Chronic Heart Failure—A Prospective Study. *J. Clin. Med.* **2024**, *13*, 1930. https://doi.org/10.3390/jcm13071930

Academic Editor: Carlos Cotrim

Received: 17 February 2024
Revised: 19 March 2024
Accepted: 25 March 2024
Published: 27 March 2024

1. Introduction

Heart failure is a major concern to public health as it is one of the leading causes of mortality and hospitalization worldwide, with an ever-increasing prevalence due to the aging of the population [1,2]. The guidelines of the European Society of Cardiology (ESC) traditionally distinguish heart failure based on left ventricular ejection fraction (LVEF) [3]. In heart failure with reduced ejection fraction (HFrEF), impairment of left ventricular systolic function and cardiac output leads to a wide range of symptoms and an overall poor prognosis [4–6]. Therefore, transthoracic echocardiography (TTE) plays an essential role in the assessment of those patients. Currently, LVEF guides diagnosis and therapeutic decisions in patients with heart failure [3,4]; however, at both ends of the spectrum, it lacks additional prognostic information [7,8]. Other echocardiographic parameters have proven to be more significant in predicting the clinical outcomes of patients with heart failure, such as myocardial deformation imaging and parameters of right ventricular (RV) function [7,9–11]. However, studies on this topic mainly report on preselected cohorts,

e.g., only including patients in sinus rhythm or excluding patients with chronic kidney disease or other relevant comorbidities in heart failure [12].

The aim of the present study is to evaluate in a contemporary outpatient clinic cohort of patients with stable HFrEF whether echocardiographic parameters of RV function adjusted for standard parameters of left ventricular systolic and diastolic function are associated with the risk of mortality and hospitalization due to worsening heart failure (WHF) to address the need for data on "real-world" heart failure patients.

2. Materials and Methods

2.1. Study Population

This study is based on the Role of Comorbidities in Heart Failure (RoC-HF) study [13]. The RoC-HF study is a prospective single-center cohort study conducted at the heart failure outpatient clinic of the academic tertiary referral center of the Division of Cardiology of the Medical University of Graz. Between September 2016 and December 2018, a total of 205 consecutive patients were enrolled. The main inclusion criteria were age above 18 years, symptomatic heart failure according to New York Heart Association (NYHA) grade II–IV, an LVEF below 50% at the time of their first visit, previously diagnosed HFrEF requiring optimization of heart failure therapy, and initiated guideline-directed heart failure treatment according to the 2016 ESC Guidelines [14]. The main exclusion criteria included unplanned hospitalization and the discontinuation or initiation of a pharmacological or device treatment within one month prior to the first visit; coronary or peripheral revascularization, valvular procedures, any major surgical procedures, acute coronary syndrome, stroke, or transient ischemic attack within three months prior to the baseline visit; acute illness, recipients of an organ transplant, primary significant valve disease (moderate to severe), and diseases reducing the estimated lifespan below one year (except heart failure) (see Figure 1).

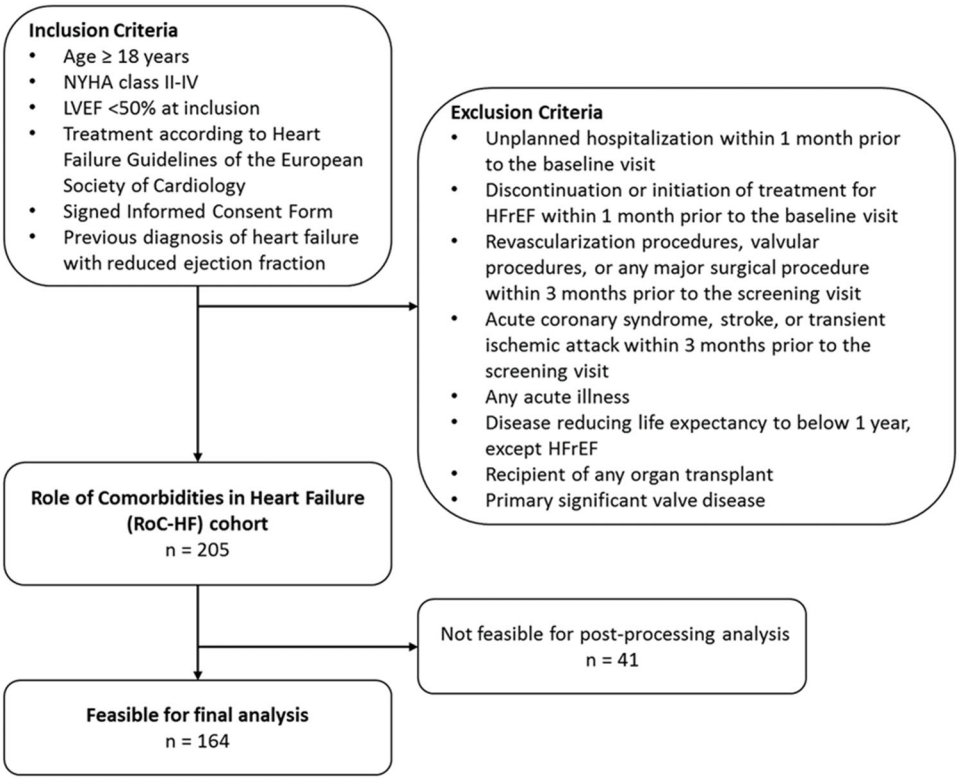


Figure 1. A flowchart of patient enrolment is shown.

All patients provided written informed consent for participation. The permission to perform the study was granted by the Ethics Committee of the Medical University of Graz

(28-467ex15/16), and written informed consent was obtained from all patients. The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki.

2.2. Echocardiographic Assessment

The RoC-HF study procedures included a systematic TTE examination. The echocardiography study protocol included 2D and Doppler image acquisition in standardized transthoracic and subcostal angulations, according to current guidelines [15,16]. Post-processing analysis, including LVEF and left ventricular global longitudinal strain (LV GLS), was performed by a dedicated analyst blinded to patients' clinical characteristics, as reported previously by our working group [17,18]. LVEF was acquired using vendor-independent post-processing software from TomTec (TOMTEC Imaging Systems, Munich, Germany). Assessment of LV GLS was performed with the vendor-independent post-processing software 2D Cardiac Performance Analysis (2DCPA) from TomTec (Version 42.00). This analysis was performed twice in each patient on different cardiac cycles of the same cine-loops, if assessable and available, and reported as mean values. LV GLS was calculated as endomyocardial GLS in a 16-segment model using the entire endomyocardial contour length, computing left ventricular deformation obtained from the apical four-, three-, and two-chamber views. Other echocardiographic parameters including heart chamber dimensions, E/e', left atrial volume index (LAVI), peak tricuspid regurgitate velocity (TR-Vmax), systolic pulmonary artery pressure (sPAP), and tricuspid annular plane systolic excursion (TAPSE) were measured during the examination. For the present analysis, all patients in the RoC-HF study with cine-loops suitable for post-processing analysis were included.

2.3. Laboratory Parameters

The assessment of laboratory parameters was limited to N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP), creatinine, and estimated glomerular filtration rate (eGFR) for the present analysis. Blood sampling was performed on the first study visit, and laboratory parameters were immediately determined at the Clinical Institute of Medical and Chemical Laboratory Diagnostics.

2.4. Follow-Up

Patient outcomes were retrieved from medical and health insurance records. Cardiovascular death was defined as a cardiovascular event (e.g., myocardial infarction, sudden cardiac death, heart failure, stroke, arrhythmias) as a primary cause of death. In patients with non-documented death, available telemedicine data of patients with implantable cardioverter-defibrillator (ICD) was interrogated postmortem. Causes of death were adjudicated by an experienced cardiologist who was blinded to the patient data (D.v.L.). If no data were available on the cause of death, death was classified as unknown. Hospitalization due to WHF was defined as an unscheduled hospitalization due to documented signs and symptoms of heart failure with at least 24 h of in-hospital stay and initiated or significantly augmented heart failure therapy [19]. The primary composite endpoint was defined as hospitalization due to WHF and cardiovascular death (composite endpoint 1). Secondary outcomes comprised a composite endpoint of hospitalization due to WHF and all-cause death (composite endpoint 2), hospitalization due to WHF, and all-cause death.

2.5. Statistical Analysis

All of the data are illustrated using descriptive statistics. Continuous variables are expressed as mean and standard deviation or median and interquartile range, as appropriate. Categorical variables are shown as percentages. Tests used for the normal distribution of variables included Kolmogorov–Smirnov and Shapiro–Wilk tests and visual inspections of kurtosis and skewness. Continuous variables were compared using Student's *t* test or their non-parametric equivalents, and categorical variables were compared using the Chi-square test or Fisher's Exact test, as appropriate.

Cox proportional hazard analyses were used to assess the associations of the echocardiographic parameters with the primary and secondary outcomes. Echocardiographic variables perceived as clinically important and significant in univariate Cox regressions were analyzed and included TAPSE, TR-Vmax, sPAP, LVEF, and LV GLS. These parameters were further individually included in a multivariate Cox regression model adjusted for age (years), gender (male/female), body mass index (kg/m^2), atrial fibrillation, eGFR (mL/min/1.73 m^2), and NT-proBNP (pg/mL) (model 1). RV parameters (TAPSE, TR-Vmax, and sPAP) were additionally included in a multivariate model adjusted for parameters included in model 1, and LVEF (%), LV GLS (%), E/e', and LAVI (mL/m^2) (model 2).

Incidence rates for clinical events across the spectrum of TAPSE were assessed through the use of Poisson regression models with and without adjustment for age, sex, body mass index, atrial fibrillation, LVEF, eGFR, LV GLS, E/e', and LAVI, using restricted cubic splines with 3 knots placed at the 10th, 50th, and 90th percentiles.

Statistical analyses were performed using IBM SPSS Statistics Version 27 (IBM Corporation, Armonk, NY, USA) and Stata Version 17.0 (Stata Corp., Houston, TX, USA). Results were considered statistically significant with a two-sided p-value < 0.05.

3. Results

3.1. Study Population

The analyzed cohort comprised a total of 164 patients. Fourty-one patients were excluded from the analysis because post-processing measurements were not feasible. The mean age of the patients was 64.8 ± 10.4 years, with a predominance of men (78%) in the sample and a mean history of heart failure of 9.0 ± 7.0 years. Ninety-eight patients (59.8%) had a non-ischemic origin of heart failure. Most patients presented with NYHA II (67%) and without angina (82%). Atrial fibrillation was present in 69 patients (42%), 112 patients (68%) presented with arterial hypertension, 78 patients (48%) had hyperlipidemia, and 44 patients (27%) presented with diabetes mellitus. All but 1 patient received at least one guideline-based heart failure drug medication, while 137 patients (84%) received a combination of at least three guideline-based heart failure drugs, consisting of either beta-blockers, mineral receptor antagonists, diuretics, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or angiotensin neprilysin inhibitors. Six patients (4%) received sodium-glucose co-transporter 2 (SGLT2) inhibitors. Of note, those patients received SGLT2 inhibitors in the context of diabetes treatment. In this study, 111 patients (68%) had received device therapy in the form of either a pacemaker or an ICD, with or without resynchronization function. The laboratory parameters showed a median NT-proBNP (interquartile range) of 978 (332–2279) pg/mL, a mean creatinine of 1.25 ± 0.55 mg/dL, and a mean eGFR (CKD-EPI equation) of 65 ± 22 mL/min/1.73 m^2. In the echocardiographic analysis, mean LVEF was 35.8 ± 8.2%, mean LV GLS was −12.1 ± 3.6%, mean E/e' was 16 ± 8, mean TR-Vmax was 2.7 ± 0.5 m/sec, mean sPAP was 41 ± 12 mmHg mean LAVI was 52 ± 21 mL/m^2, and mean TAPSE was 20 ± 5 mm, with 47 patients (29%) showing abnormal values <17 mm. Detailed baseline characteristics are displayed in Table 1.

Table 1. Baseline characteristics.

	All Patients	**LVEF > 35%**	**LVEF ≤ 35%**	***p*-Value ***
	***n* = 164**	***n* = 83**	***n* = 81**	
Demographics				
Female, *n* (%)	36 (22)	23 (28)	13 (16)	0.090
Age, years	64.8 ± 10.4	64.8 ± 10.7	64.8 ± 10.1	0.927
BMI, kg/m^2	28.5 ± 4.7	28.8 ± 5.1	28.2 ± 4.3	0.638
Heart failure duration, years	9.0 ± 7.0	7.1 ± 6.4	11.0 ± 7.0	**<0.001**
Caucasian ethnicity, *n* (%)	164 (100)	83 (100)	81 (100)	**-**
Symptoms				
NYHA functional class				

Table 1. *Cont.*

	All Patients	LVEF > 35%	LVEF ≤ 35%	*p*-Value *
	***n* = 164**	***n* = 83**	***n* = 81**	
NYHA II, *n* (%)	110 (67)	57 (69)	53 (65)	0.563
NYHA II-III, *n* (%)	30 (18)	13 (16)	17 (21)	
NYHA III, *n* (%)	23 (14)	13 (16)	10 (12)	
NYHA IV, *n* (%)	1 (1)	0 (0)	1 (1)	
Angina, *n* (%)	30 (18)	16 (20)	14 (17)	0.498
Clinical characteristics				
Ischemic-origin, *n* (%)	66 (40)	30 (36)	36 (44)	0.279
Non-ischemic-origin, *n* (%)	98 (60)	53 (64)	45 (56)	
SBP, mmHg	123 ± 20	127 ± 23	118 ± 16	**0.006**
DBP, mmHg	77 ± 13	79 ± 14	74 ± 11	**0.007**
24 h SBP, mmHg	111 ± 13	114 ± 14	108 ± 12	**0.003**
24 h DBP, mmHg	68 ± 9	69 ± 9	67 ± 9	0.066
Heart rate, bpm	66 ± 12	64 ± 11	67 ± 13	0.194
24 h-heart rate, bpm	67 ± 10	68 ± 11	66 ± 9	0.349
Device therapy				
Pacemaker, *n* (%)	47 (29)	21 (25)	26 (32)	0.370
ICD, *n* (%)	106 (65)	47 (57)	59 (73)	**0.032**
CRT, *n* (%)	53 (32)	27 (33)	26 (32)	0.933
Comorbidities				
Atrial fibrillation, *n* (%)	69 (42)	34 (41)	35 (43)	0.874
Diabetes mellitus, *n* (%)	44 (27)	20 (24)	24 (30)	0.381
Arterial hypertension, *n* (%)	112 (68)	55 (66)	57 (70)	0.662
Hyperlipidemia, *n* (%)	78 (48)	44 (53)	34 (42)	0.271
COPD, *n* (%)	34 (21)	13 (16)	21 (26)	0.253
Smoker, *n* (%)	105 (64)	56 (68)	49 (61)	0.648
Pharmacological treatment				
ACE/ARB/ARNI, *n* (%)	151 (92)	77 (93)	74 (91)	0.780
Beta-blocker, *n* (%)	158 (96)	81 (98)	77 (95)	0.440
MRA, *n* (%)	129 (79)	64 (77)	65 (80)	0.704
Thiazide, *n* (%)	18 (11)	8 (10)	10 (12)	0.625
Loop-diuretics, *n* (%)	96 (59)	48 (58)	48 (59)	0.875
SGLT2 inhibitors, *n* (%)	6 (4)	5 (6)	1 (1)	0.210
Laboratory parameters				
NT-proBNP, pg/mL	978 (332–2279)	511 (200–1507)	1583 (612–3266)	**<0.001**
Creatinine, mg/dL	1.25 ± 0.55	1.22 ± 0.43	1.28 ± 0.65	0.669
eGFR, mL/min/1.73 m^2	65 ± 22	64 ± 22	66 ± 23	0.644
Echocardiography				
LVEF, %	35.8 ± 8.2	42.5 ± 4.6	29.0 ± 4.7	**<0.001**
LVEDV, mL	155 ± 61	126 ± 38	184 ± 67	**<0.001**
LVESV, mL	102 ± 50	73 ± 24	132 ± 53	**<0.001**
GLS, %	−12.1 ± 3.6	−14.4 ± 3.0	−9.7 ± 2.6	**<0.001**
E/e'	16 ± 8	13 ± 6	18 ± 9	**<0.001**
TAPSE, mm	20 ± 5	21 ± 5	18 ± 5	**0.002**
TR-Vmax, m/s	2.7 ± 0.5	2.6 ± 0.4	2.8 ± 0.5	**0.023**
sPAP, mmHg	41 ± 12	39 ± 10	43 ± 13	**0.038**
LAVI, mL/m^2	52 ± 21	47 ± 19	57 ± 21	**0.001**

Parameters reported in mean ± standard deviation, median (interquartile range), or frequency (percentage). ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; ARNI: angiotensin neprilysin inhibitor; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; GLS: global longitudinal strain; ICD: implantable cardioverter defibrillator; LAVI: left atrial volume index; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MRA: mineral receptor antagonist; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; SBP: systolic blood pressure; SGLT2: sodium-glucose co-transporter 2 inhibitor; sPAP: systolic pulmonary artery pressure; and TAPSE: tricuspid annular plane systolic excursion; TR-Vmax: maximal tricuspid regurgitation velocity. * Student's-*t*-test; Chi-square test.

3.2. Outcome Analysis

The median observation time was 4.9 (4.0–5.3) years. Forty-three patients (26%) met composite endpoint 1, sixty-three (38%) patients met composite endpoint 2, forty patients (24%) experienced hospitalization due to WHF, and forty-four patients (27%) died from any cause.

In univariate analyses, TAPSE, TR-Vmax, sPAP, LVEF, and LV GLS were all significantly associated with composite endpoint 1 when assessing all patients. In adjusted model 1, TAPSE (HR 0.884, 95%CI 0.817–0.958, $p = 0.002$), sPAP (HR 1.038, 95%CI 1.007–1.071, $p = 0.017$), LVEF (HR 0.959, 95%CI 0.929–0.997, $p = 0.036$), and LV GLS (HR 1.131, 95%CI 1.028–1.249, $p = 0.011$) met significance. In adjusted model 2, only TAPSE remained significant (HR 0.878, 95%CI 0.800–0.964, $p = 0.006$). TAPSE was also significantly associated with composite endpoint 2 (HR 0.918, 95%CI 0.853–0.988, $p = 0.023$) and WHF (HR 0.880, 95%CI 0.800–0.968, $p = 0.008$). In Poisson model-based analyses, lower TAPSE was associated with an increased risk of cardiovascular endpoints (Figure 2). Stratifying the cohort by means of TAPSE, those with TAPSE < 20 mm compared to those with TAPSE ≥ 20 mm had a significantly higher risk of cardiovascular endpoints, as shown in Figure 3.

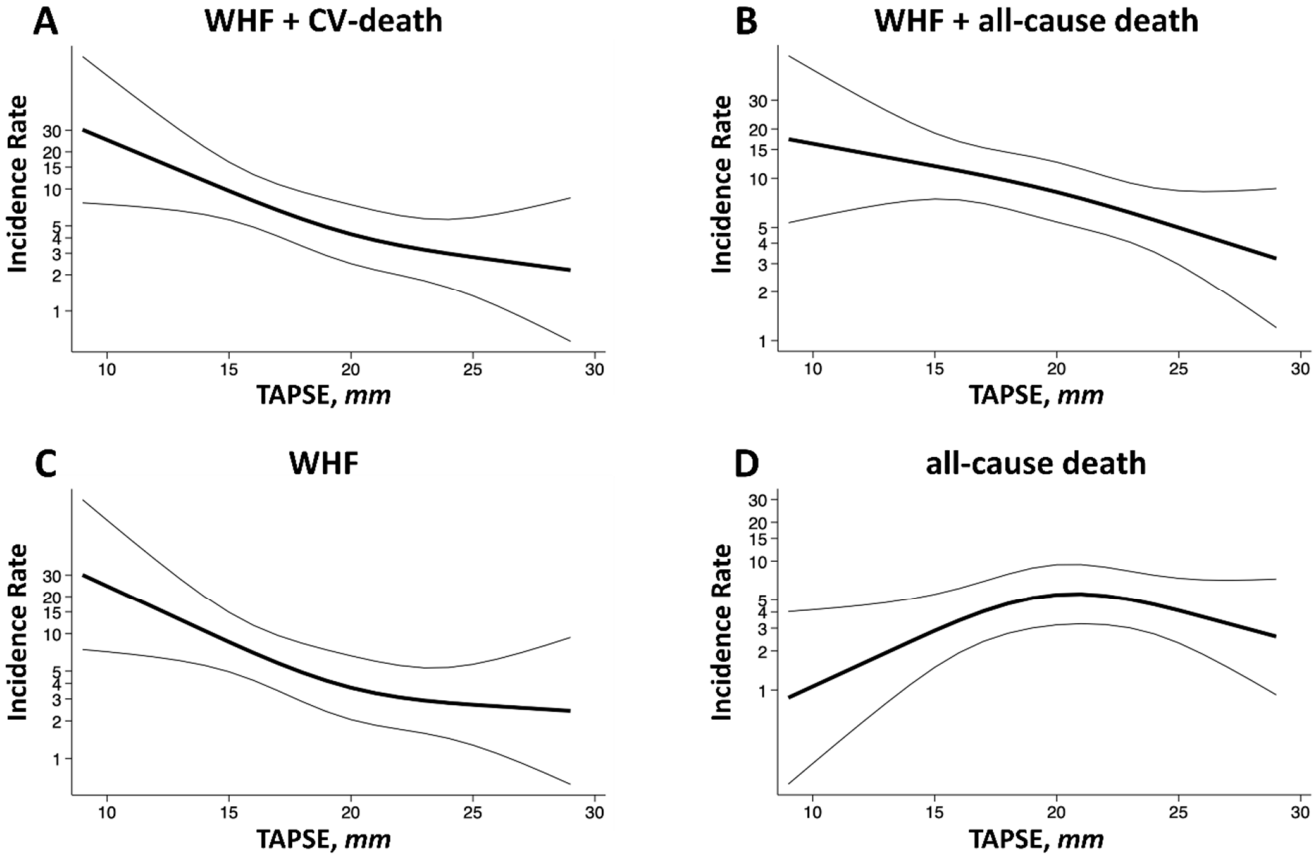


Figure 2. Incidence rates of clinical outcomes via tricuspid annular plane systolic excursion. Incidence rates of (**A**) composite endpoint I of worsening heart failure hospitalization or cardiovascular death, (**B**) composite endpoint II of worsening heart failure hospitalization or all-cause death, (**C**) worsening heart failure hospitalization, and (**D**) all-cause death across a range of TAPSE. Incidence rates are shown per 100 patient-years. Estimates were obtained from Poisson regression models with TAPSE expressed using restricted cubic splines. Models were adjusted for age, gender, body mass index, atrial fibrillation, eGFR, NT-proBNP, LVEF, LV GLS, E/e', and LAVI. eGRF: estimated glomerular filtration rate; LAVI: left atrial volume index; LVEF: left ventricular ejection fraction; LV GLS: left ventricular global longitudinal strain; and TAPSE: tricuspid annular plane systolic excursion.

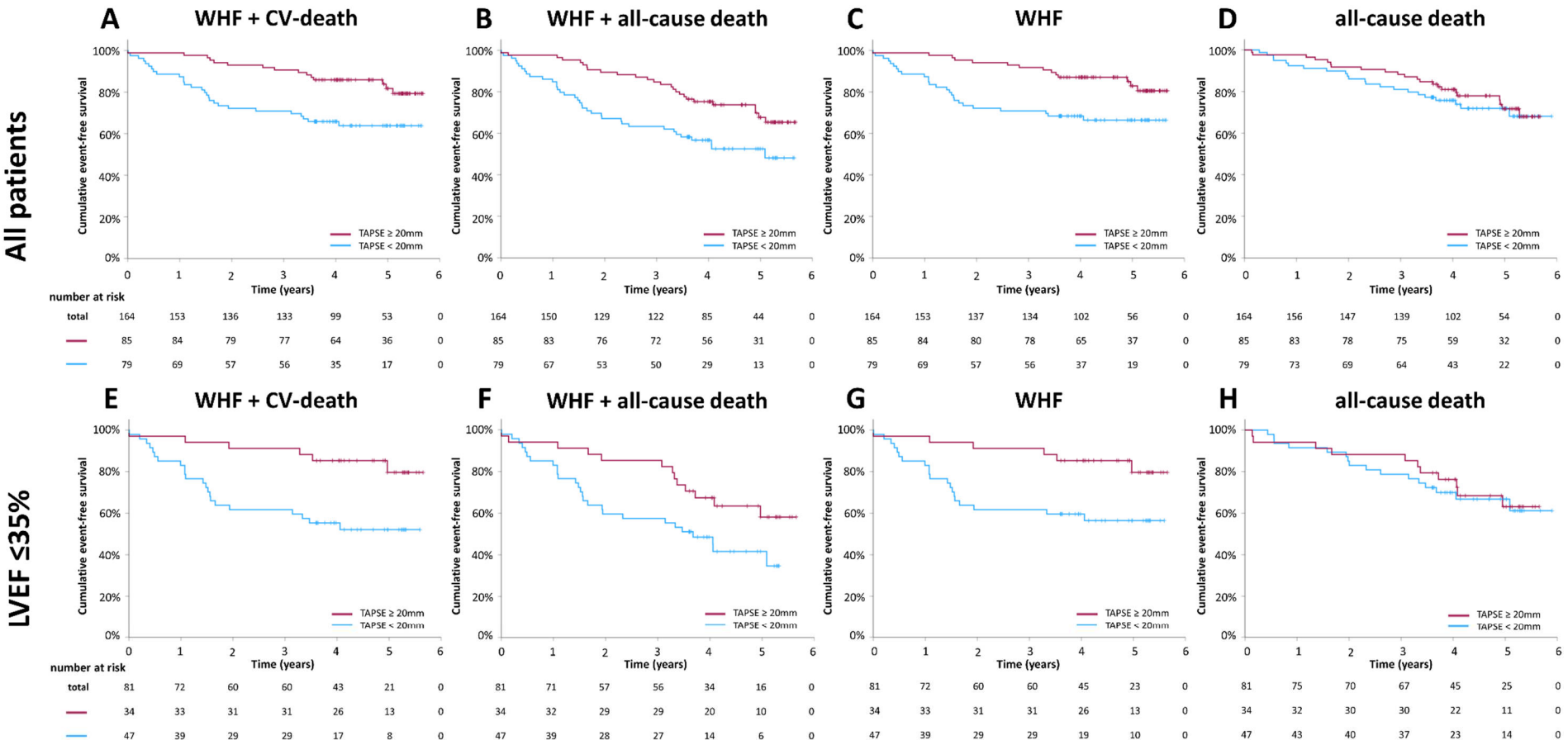


Figure 3. Cumulative incidence of clinical endpoints via tricuspid annular plane systolic excursion. Cumulative incidence according to TAPSE in all patients (**A**–**D**) and patients with a left ventricular ejection fraction (LVEF) ≤35% (**E**–**H**). TAPSE is stratified by mean (20 mm). TAPSE: tricuspid annular plane systolic excursion.

Regarding all-cause death, only TR-Vmax and sPAP met significance in univariate analysis, whereas no echocardiographic parameter remained significant in adjusted model 2 (see Table 2).

Table 2. Univariate and adjusted Cox regression models.

	All Patients			LVEF ≤ 35%		
	Univariate	Model 1 *	Model 2 **	Univariate	Model 1 *	Model 2 **
	Hazard Ratio (95% Confidence Interval), *p*-Value			Hazard Ratio (95% Confidence Interval), *p*-Value		
Composite endpoint I						
TAPSE	0.859 (0.800–0.921) $p \leq 0.001$	0.884 (0.817–0.958) $p = 0.002$	0.878 (0.800–0.964), $p = 0.006$	0.838 (0.761–0.923), $p \leq 0.001$	0.836 (0.749–0.933), $p = 0.001$	0.791 (0.680–0.920), $p = 0.002$
TR-Vmax	2.168 (1.082–4.348) $p = 0.029$	1.737 (0.781–3.863) $p = 0.176$	1.375 (0.526–3.593), $p = 0.516$	2.246 (0.947–5.327), $p = 0.066$		
sPAP	1.043 (1.017–1.069) $p \leq 0.001$	1.038 (1.007–1.071) $p = 0.017$	1.032 (0.996–1.070), $p = 0.082$	1.037 (1.008–1.068), $p = 0.013$	1.058 (1.016–1.101), $p = 0.006$	1.059 (1.006–1.115), $p = 0.028$
LVEF	0.953 (0.920–0.987) $p = 0.008$	0.959 (0.929–0.997) $p = 0.036$		0.982 (0.912–1.058), $p = 0.633$		
LV GLS	1.152 (1.058–1.255) $p = 0.001$	1.131 (1.028–1.249) $p = 0.011$		1.068 (0.927–1.231), $p = 0.361$		
Composite endpoint II						
TAPSE	0.885 (0.836–0.937) $p \leq 0.001$	0.902 (0.844–0.964) $p = 0.002$	0.918 (0.853–0.988), $p = 0.023$	0.890 (0.825–0.960), $p = 0.003$	0.894 (0.823–0.972), $p = 0.008$	0.840 (0.749–0.941), $p = 0.003$
TR-Vmax	2.445 (1.406–4.250) $p = 0.002$	2.199 (1.133–4.265), $p = 0.020$	1.903 (0.820–4.418), $p = 0.134$	2.060 (1.053–4.029), $p = 0.035$	2.498 (1.006–6.202), $p = 0.048$	3.080 (1.064–8.915), $p = 0.038$
sPAP	1.039 (1.019–1.060) $p \leq 0.001$	1.033 (1.007–1.060), $p = 0.013$	1.025 (0.994–1.057), $p = 0.113$	1.025 (1.002–1.050), $p = 0.037$	1.035 (1.001–1.070), $p = 0.046$	1.037 (0.998–1.078), $p = 0.066$
LVEF	0.960 (0.932–0.988) $p = 0.005$	0.974 (0.942–1.006), $p = 0.112$		1.016 (0.948–1.088), $p = 0.654$		
LV GLS	1.106 (1.033–1.184) $p = 0.004$	1.071 (0.989–1.160), $p = 0.092$		0.989 (0.878–1.115), $p = 0.862$		
Worsening heart failure hospitalization						
TAPSE	0.857 (0.796–0.922) $p \leq 0.001$	0.881 (0.811–0.957), $p = 0.003$	0.880 (0.800–0.968), $p = 0.008$	0.836 (0.756–0.925), $p \leq 0.001$	0.830 (0.739–0.931), $p = 0.002$	0.781 (0.667–0.916), $p = 0.002$
TR-Vmax	2.015 (0.984–4.125) $p = 0.055$			1.737 (0.712–4.236), $p = 0.225$		
sPAP	1.038 (1.012–1.065) $p = 0.004$	1.030 (0.999–1.063), $p = 0.059$	1.030 (0.992–1.069), $p = 0.121$	1.027 (0.995–1.059), $p = 0.095$		
LVEF	0.951 (0.917–0.987) $p = 0.007$	0.958 (0.920–0.998), $p = 0.038$		0.983 (0.910–1.061), $p = 0.659$		
LV GLS	1.165 (1.066–1.273) $p \leq 0.001$	1.146 (1.037–1.265), $p = 0.007$		1.074 (0.927–1.244), $p = 0.342$		
All-cause mortality						
TAPSE	0.954 (0.896–1.016) $p = 0.140$			0.959 (0.882–1.042), $p = 0.321$		
TR-Vmax	2.226 (1.155–4.288) $p = 0.017$	2.817 (1.209–6.559), $p = 0.016$	2.735 (0.942–7.942), $p = 0.064$	1.486 (0.674–3.278), $p = 0.326$		
sPAP	1.029 (1.005–1.053) $p = 0.016$	1.030 (0.999–1.062), $p = 0.059$	1.025 (0.986–1.066), $p = 0.210$	1.009 (0.981–1.038), $p = 0.528$		
LVEF	0.979 (0.945–1.014) $p = 0.226$			1.053 (0.957–1.158), $p = 0.289$		
LV GLS	1.045 (0.964–1.132) $p = 0.283$			0.957 (0.827–1.107), $p = 0.555$		

Univariate Cox regression analysis and adjusted models for composite endpoint I (worsening heart failure hospitalization or cardiovascular death), composite endpoint II (worsening heart failure hospitalization or all-cause death), worsening heart failure hospitalization, and all-cause mortality. BMI: body mass index; eGFR: estimated glomerular filtration rate; LV GLS: left ventricular global longitudinal strain; LAVI: left atrial volume index; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TR-Vmax: maximal tricuspid regurgitation velocity. * adjusted for age, gender, BMI, atrial fibrillation, eGFR, and NT-proBNP. ** adjusted for age, gender, BMI, atrial fibrillation, GFR, NT-proBNP, LVEF, LV GLS, E/e', and LAVI.

3.3. Outcomes in a Subgroup with a Left Ventricular Ejection Fraction ≤ 35%

In this cohort, 81 patients (49%) showed an LVEF ≤ 35%, with a mean LVEF of 29.0 ± 4.7% in this subgroup. Those patients had a significantly longer history of heart failure (11.0 ± 7.0 versus 7.1 ± 6.4 years, $p \leq 0.001$) and more often had a history of a previous implantation of an ICD (73 versus 57%, $p = 0.032$). They had higher NT-proBNP levels (1583 [612–3266] versus 511 [200–1507] pg/mL, $p \leq 0.001$) and lower in-office blood pressure (systolic blood pressure 118 ± 16 versus 127 ± 23 mmHg, $p = 0.006$; diastolic blood pressure 74 ± 11 versus 79 ± 14 mmHg, $p = 0.007$). Overall, they showed significantly worse echocardiographic structural and functional parameters when compared to those with a higher LVEF, as shown in detail in Table 1.

In this subgroup, 28 patients (35%) met composite endpoint 1, 40 patients (49%) met composite endpoint 2, 26 patients (32%) underwent hospitalization due to WHF, and 27 patients (33%) died from any cause.

In patients with an LVEF ≤ 35%, TAPSE and sPAP were associated with both composite endpoints in univariate analysis, and only TAPSE was associated with WHF. LVEF and LV GLS had no additional prognostic value in this subgroup. In adjusted Cox regression models, TAPSE remained significant in composite endpoint 1 (HR 0.791, 95%CI 0.680–0.920, $p = 0.002$), composite endpoint 2 (HR 0.840, 95%CI 0.749–0.941, $p = 0.003$), and WHF (HR 0.781, 95%CI 0.667–0.916, $p = 0.002$) (Table 2).

4. Discussion

In this contemporary cohort of 164 patients with chronic heart failure, right ventricular systolic impairment, as defined by reduced TAPSE, showed a strong association with WHF and composite endpoints of (1) WHF and cardiovascular death and (2) WHF and all-cause mortality. This association was pronounced in patients with LVEF ≤ 35%. There was no association between TAPSE and all-cause death. The prognostic relevance of RV function in HFrEF has been documented previously, but many studies have been limited by potential selection bias, retrospective design, and lack of adjustment for left ventricular function [7,9–11]. The present analysis extends the existing literature and shows that TAPSE predicts cardiovascular events in an unselected cohort of patients with optimally treated chronic HFrEF. On the other hand, LVEF and LV GLS only showed poor predictive value and no prognostic value in patients with an LVEF ≤ 35% in adjusted models in this cohort.

The observed association between TAPSE and cardiovascular outcomes in chronic heart failure is in line with and extends the work of previous studies. Lundorff et al. reported RV dysfunction to be a predictor of mortality in patients with HFrEF, with TAPSE being the strongest prognostic parameter in women [9]. Other studies confirmed that RV parameters are independent predictors of poor outcomes in heart failure over the whole spectrum of the ejection fraction [10,20–23]. Furthermore, RV functional parameters may be stronger predictors of exercise capacity in HFrEF patients, which is a well-defined biomarker in the prognosis of HFrEF and in the indication of heart transplant [24,25]. A significant association between TAPSE and cardiovascular deaths in a general population without heart failure could also be established [26]. Of note, almost all reported studies measured different RV functional parameters (TAPSE, RV GLS, and the right ventricular–pulmonary artery coupling TAPSE/sPAP) and most times only highlighted those that were the best predictors. Furthermore, different cut-off values for TAPSE were used in most of those studies, and they mainly report on retrospective cohorts. Due to its prospective design and enrolment of well-characterized patients with stable chronic heart failure, our study complements the existing literature.

4.1. Prognostic Value of Right Ventricular Function in Chronic Heart Failure

Given that patients were included in the RoC-HF study based on their LVEF, the studied cohort includes patients over a broad and unselected spectrum of RV function. The observed association between RV function and heart failure outcomes might hypothetically reflect a causal relationship based on several mechanisms. Left ventricular failure leads

to increased filling pressure, pulmonary pressure, and right ventricular afterload. Since RV function is particularly sensitive to changes in afterload, RV failure may follow left ventricular failure, even if the RV is not directly involved in the underlying left ventricular disease [27,28]. Despite the significant additional predictive value of RV function in patients with heart failure, it has not been applied in any current heart failure risk score. Established scores, such as the PARADIGM Risk of Events and Death in the Contemporary Treatment of Heart Failure (PREDICT-HF) score, Seattle Heart Failure Model (SHFM), the Cardiac and Comorbid Conditions Heart Failure (3C-HF) score, or the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC-HF) score for risk-stratification in patients with heart failure rely only on LVEF [29–32]. Whether adding RV function improves the diagnostic accuracy of heart failure scores needs to be proven in future studies. TAPSE could qualify as a valid additional parameter in these risk scores, as its assessment is non-invasive, reliable, simple, and can be achieved via far less technician- and insonation-angle-dependent methods in comparison to other parameters and indices such as RV myocardial deformation imaging.

4.2. Normal Right Ventricular Systolic Function in Heart Failure

The normal value of RV systolic function assessed using TAPSE in a general population is defined as 24 ± 3.5 mm, while TAPSE < 17 mm indicates reduced RV systolic function [15]. In this cohort, incidence rates increased with a TAPSE < 20 mm, which is in the supposedly normal range. There are no large cohort studies on a normal TAPSE range in patients with heart failure. Whether normal ranges for RV function should be redefined in the context of coexisting HFrEF should be investigated in future studies. Patients with heart failure, especially with HFrEF, are at higher risk of cardiovascular events compared to a general, healthy population. Therefore, in those patients, a different cut-off may be beneficial as moderately impaired RV systolic function may point to worse outcomes. This should be further considered and verified in large cohort studies with a prospective study design, which may lead to more intensified monitoring or follow-ups to avoid hospitalizations due to heart failure.

4.3. Strengths and Limitations

This cohort is a contemporary outpatient clinic heart failure cohort that was only preselected based on LVEF screening to give valid insight into "real world" heart failure patient outcomes; however, due to optimal heart failure treatment, mortality in this cohort was lower overall when compared to results in the literature [33–35]. Another limitation is related to the timing of the inclusion period used in this study; practically no patient in this cohort received SGLT2 inhibitors as heart failure therapy at the time point of the TTE since SGLT2 inhibitors were introduced into routine clinical care for heart failure patients afterward.

In contrast to previous investigations, our study did not show a significant association between TAPSE and all-cause mortality, but only with cardiovascular events. This may be explained by the low number of deaths in this cohort.

Our data are limited as we did not assess right ventricular function using new techniques, such as 3D-EXO or speckle-tracking echocardiography. This should be assessed in future studies on this topic.

5. Conclusions

Despite the fact that HFrEF is considered to be a primarily left ventricular pathology, echocardiographic parameters of the left ventricle provide poor additional prognostic value in terms of clinical outcomes. RV systolic function is a particularly valuable prognostic parameter in patients with worse LVEF, indicating that as ventricular function declines, it is equally important to consider RV functional parameters in the prediction of cardiovascular events. In this study, TAPSE was the strongest independent prognostic echocardiographic parameter for clinical outcomes in patients with heart failure, particularly among patients with an LVEF lower than 35%. Therefore, TAPSE could serve as an additional prognos-

tic marker, warranting further studies to elucidate whether incorporating TAPES into established risk scores improves their diagnostic accuracy.

Author Contributions: Conceptualization, P.P.R., M.W., D.v.L., K.A. and N.V.; validation, D.Z., J.G., S.P., D.v.L., K.A. and N.V.; formal analysis, N.S., A.P., N.V. and E.K.; investigation, V.H., J.S., H.R., K.A. and N.V.; resources, A.Z. and D.v.L.; data curation, N.S., D.Z. and V.S.; writing—original draft preparation, N.S. and E.K.; writing—review and editing, A.P., J.G., M.W., S.P., A.Z., D.v.L., N.V. and E.K.; visualization, N.S., A.P., N.V. and E.K.; supervision, A.Z., K.A., N.V. and E.K.; project administration, D.v.L., K.A. and N.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Graz (28-467ex15/16; 2 August 2016).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data underlying this article will be shared upon reasonable request to the corresponding author.

Acknowledgments: We would like to thank all our patients who consented to participate in the RoC-HF study. We would like to thank the Doctoral School "Translational Molecular and Cellular Biosciences" of the Medical University of Graz for its support.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Tsao, C.W.; Aday, A.W.; Almarzooq, Z.I.; Anderson, C.A.; Arora, P.; Avery, C.L.; Baker-Smith, C.M.; Beaton, A.Z.; Boehme, A.K.; Buxton, A.E.; et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation* **2023**, *147*, e93–e621.
2. Santner, V.; Riepl, H.S.; Posch, F.; Wallner, M.; Rainer, P.P.; Ablasser, K.; Kolesnik, E.; Hoeller, V.; Zach, D.; Schwegel, N.; et al. Non-eligibility for pivotal HFpEF/HFmrEF outcome trials and mortality in a contemporary heart failure cohort. *Eur. J. Intern. Med.* **2023**, *118*, 73–81. [CrossRef] [PubMed]
3. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Bohm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef] [PubMed]
4. Investigators, S.; Yusuf, S.; Pitt, B.; Davis, C.E.; Hood, W.B.; Cohn, J.N. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N. Engl. J. Med.* **1991**, *325*, 293–302. [CrossRef]
5. Swedberg, K.; Kjekshus, J.; CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N. Engl. J. Med.* **1987**, *316*, 1429–1435. [CrossRef]
6. Packer, M.; Coats, A.J.; Fowler, M.B.; Katus, H.A.; Krum, H.; Mohacsi, P.; Rouleau, J.L.; Tendera, M.; Castaigne, A.; Roecker, E.B.; et al. Effect of carvedilol on survival in severe chronic heart failure. *N. Engl. J. Med.* **2001**, *344*, 1651–1658. [CrossRef] [PubMed]
7. Potter, E.; Marwick, T.H. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. *JACC Cardiovasc. Imaging* **2018**, *11*, 260–274. [CrossRef] [PubMed]
8. Solomon, S.D.; Anavekar, N.; Skali, H.; McMurray, J.J.; Swedberg, K.; Yusuf, S.; Granger, C.B.; Michelson, E.L.; Wang, D.; Pocock, S.; et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* **2005**, *112*, 3738–3744. [CrossRef] [PubMed]
9. Lundorff, I.J.; Sengelov, M.; Pedersen, S.; Modin, D.; Bruun, N.E.; Fritz-Hansen, T.; Biering-Sørensen, T.; Jørgensen, P.G. Prognostic value of right ventricular echocardiographic measures in patients with heart failure with reduced ejection fraction. *J. Clin. Ultrasound.* **2021**, *49*, 903–913. [CrossRef]
10. Ghio, S.; Guazzi, M.; Scardovi, A.B.; Klersy, C.; Clemenza, F.; Carluccio, E.; Temporelli, P.L.; Rossi, A.; Faggiano, P.; Traversi, E.; et al. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur. J. Heart Fail.* **2017**, *19*, 873–879. [CrossRef]
11. Lejeune, S.; Roy, C.; Ciocea, V.; Slimani, A.; de Meester, C.; Amzulescu, M.; Pasquet, A.; Vancraeynest, D.; Beauloye, C.; Vanoverschelde, J.-L.; et al. Right Ventricular Global Longitudinal Strain and Outcomes in Heart Failure with Preserved Ejection Fraction. *J. Am. Soc. Echocardiogr.* **2020**, *33*, 973–984.e2. [CrossRef] [PubMed]

12. Anastasiou, V.; Papazoglou, A.S.; Moysidis, D.V.; Daios, S.; Tsalikakis, D.; Giannakoulas, G.; Karamitsos, T.; Delgado, V.; Ziakas, A.; Kamperidis, V. The prognostic value of right ventricular longitudinal strain in heart failure: A systematic review and meta-analysis. *Heart Fail. Rev.* **2023**, *28*, 1383–1394. [CrossRef]
13. Verheyen, N.; Schmid, J.; Kolesnik, E.; Schwegel, N.; Späth, J.; Kattnig, L.; Riepl, H.; Zach, D.; Santner, V.; Höller, V.; et al. Prevalence and prognostic impact of bone disease in chronic heart failure with reduced ejection fraction. *ESC Heart Fail.* **2024**. [CrossRef] [PubMed]
14. Ponikowski, P.; Voors, A.A.; Anker, S.D.; Bueno, H.; Cleland, J.G.F.; Coats, A.J.S.; Falk, V.; González-Juanatey, J.R.; Harjola, V.-P.; Jankowska, E.A.; et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **2016**, *37*, 2129–2200. [PubMed]
15. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznetsova, T.; et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur. Heart J. Cardiovasc. Imaging* **2015**, *16*, 233–270. [CrossRef] [PubMed]
16. Nagueh, S.F.; Smiseth, O.A.; Appleton, C.P.; Byrd, B.F.; 3rd Dokainish, H.; Edvardsen, T.; Flachskampf, F.A.; Gillebert, T.C.; Klein, A.L.; Lancellotti, P.; et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur. Heart J. Cardiovasc. Imaging* **2016**, *17*, 1321–1360. [CrossRef] [PubMed]
17. Höller, V.; Seebacher, H.; Zach, D.; Schwegel, N.; Ablasser, K.; Kolesnik, E.; Gollmer, J.; Waltl, G.; Rainer, P.P.; Verheyen, S.; et al. Myocardial Deformation Analysis in MYBPC3 and MYH7 Related Sarcomeric Hypertrophic Cardiomyopathy-The Graz Hypertrophic Cardiomyopathy Registry. *Genes* **2021**, *12*, 1469. [CrossRef] [PubMed]
18. Zach, D.K.; Schwegel, N.; Santner, V.; Winkelbauer, L.; Hoeller, V.; Kolesnik, E.; Gollmer, J.; Seggewiss, H.; Batzner, A.; Perl, S.; et al. Low-grade systemic inflammation and left ventricular dysfunction in hypertensive compared to non-hypertensive hypertrophic cardiomyopathy. *Int. J. Cardiol.* **2023**, *399*, 131661. [CrossRef] [PubMed]
19. Hicks, K.A.; Mahaffey, K.W.; Mehran, R.; Nissen, S.E.; Wiviott, S.D.; Dunn, B.; Solomon, S.D.; Marler, J.R.; Teerlink, J.R.; Farb, A.; et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *Circulation* **2018**, *137*, 961–972. [CrossRef]
20. Carluccio, E.; Biagioli, P.; Alunni, G.; Murrone, A.; Zuchi, C.; Coiro, S.; Riccini, C.; Mengoni, A.; D'Antonio, A.; Ambrosio, G. Prognostic Value of Right Ventricular Dysfunction in Heart Failure with Reduced Ejection Fraction: Superiority of Longitudinal Strain Over Tricuspid Annular Plane Systolic Excursion. *Circ. Cardiovasc. Imaging* **2018**, *11*, e006894. [CrossRef]
21. Parrinello, G.; Torres, D.; Buscemi, S.; Di Chiara, T.; Cuttitta, F.; Cardillo, M.; Pluchinotta, F.R.; Scaglione, R.; Paterna, S.; Pinto, A. Right ventricular diameter predicts all-cause mortality in heart failure with preserved ejection fraction. *Intern. Emerg. Med.* **2019**, *14*, 1091–1100. [CrossRef]
22. Kanagala, P.; Arnold, J.R.; Singh, A.; Khan, J.N.; Gulsin, G.S.; Gupta, P.; Squire, I.B.; Ng, L.L.; McCann, G.P. Prevalence of right ventricular dysfunction and prognostic significance in heart failure with preserved ejection fraction. *Int. J. Cardiovasc. Imaging* **2021**, *37*, 255–266. [CrossRef] [PubMed]
23. Damy, T.; Kallvikbacka-Bennett, A.; Goode, K.; Khaleva, O.; Lewinter, C.; Hobkirk, J.; Nikitin, N.P.; Dubois-Randé, J.-L.; Hittinger, L.; Clark, A.L.; et al. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. *J. Card. Fail.* **2012**, *18*, 216–225. [CrossRef]
24. Legris, V.; Thibault, B.; Dupuis, J.; White, M.; Asgar, A.W.; Fortier, A.; Pitre, C.; Bouabdallaoui, N.; Henri, C.; O'Meara, E.; et al. Right ventricular function and its coupling to pulmonary circulation predicts exercise tolerance in systolic heart failure. *ESC Heart Fail.* **2022**, *9*, 450–464. [CrossRef] [PubMed]
25. Menegazzo, W.R.; Santos, A.B.S.; Foppa, M.; Scolari, F.L.; Barros, F.C.; Stein, R.; da Silveira, A.D. Prognostic value of right ventricular strain and peak oxygen consumption in heart failure with reduced ejection fraction. *Int. J. Cardiovasc. Imaging* **2023**, *39*, 501–509. [CrossRef] [PubMed]
26. Modin, D.; Mogelvang, R.; Andersen, D.M.; Biering-Sorensen, T. Right Ventricular Function Evaluated by Tricuspid Annular Plane Systolic Excursion Predicts Cardiovascular Death in the General Population. *J. Am. Heart Assoc.* **2019**, *8*, e012197. [CrossRef] [PubMed]
27. Monitillo, F.; Di Terlizzi, V.; Gioia, M.I.; Barone, R.; Grande, D.; Parisi, G.; Brunetti, N.D.; Iacoviello, M. Right Ventricular Function in Chronic Heart Failure: From the Diagnosis to the Therapeutic Approach. *J Cardiovasc. Dev. Dis.* **2020**, *7*, 12. [CrossRef] [PubMed]
28. Arrigo, M.; Huber, L.C.; Winnik, S.; Mikulicic, F.; Guidetti, F.; Frank, M.; Flammer, A.J.; Ruschitzka, F. Right Ventricular Failure: Pathophysiology, Diagnosis and Treatment. *Card. Fail. Rev.* **2019**, *5*, 140–146. [CrossRef]
29. McMurray, J.J.V.; Packer, M.; Desai, A.S.; Gong, J.; Lefkowitz, M.P.; Rizkala, A.R.; Rouleau, J.; Shi, V.C.; Solomon, S.D.; Swedberg, K.; et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: Rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur. J. Heart Fail.* **2013**, *15*, 1062–1073.
30. Levy, W.C.; Mozaffarian, D.; Linker, D.T.; Sutradhar, S.C.; Anker, S.D.; Cropp, A.B.; Anand, I.; Maggioni, A.; Burton, P.; Sullivan, M.D.; et al. The Seattle Heart Failure Model: Prediction of survival in heart failure. *Circulation* **2006**, *113*, 1424–1433. [CrossRef]

31. Senni, M.; Parrella, P.; De Maria, R.; Cottini, C.; Böhm, M.; Ponikowski, P.; Filippatos, G.; Tribouilloy, C.; Di Lenarda, A.; Oliva, F.; et al. Predicting heart failure outcome from cardiac and comorbid conditions: The 3C-HF score. *Int. J. Cardiol.* **2013**, *163*, 206–211. [CrossRef] [PubMed]
32. Rich, J.D.; Burns, J.; Freed, B.H.; Maurer, M.S.; Burkhoff, D.; Shah, S.J. Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score: Validation of a Simple Tool for the Prediction of Morbidity and Mortality in Heart Failure with Preserved Ejection Fraction. *J. Am. Heart Assoc.* **2018**, *7*, e009594. [CrossRef] [PubMed]
33. Greene, S.J.; Butler, J.; Albert, N.M.; DeVore, A.D.; Sharma, P.P.; Duffy, C.I.; Hill, C.L.; McCague, K.; Mi, X.; Patterson, J.H.; et al. Medical Therapy for Heart Failure with Reduced Ejection Fraction: The CHAMP-HF Registry. *J. Am. Coll. Cardiol.* **2018**, *72*, 351–366. [CrossRef] [PubMed]
34. Roger, V.L. Epidemiology of Heart Failure: A Contemporary Perspective. *Circ. Res.* **2021**, *128*, 1421–1434. [CrossRef]
35. Pocock, S.J.; Ariti, C.A.; McMurray, J.J.; Maggioni, A.; Køber, L.; Squire, I.B.; Swedberg, K.; Dobson, J.; Poppe, K.K.; Whalley, G.A.; et al. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. *Eur. Heart J.* **2013**, *34*, 1404–1413. [CrossRef]

Clinical Research in Cardiology
https://doi.org/10.1007/s00392-024-02523-1

ORIGINAL PAPER

Impact of empagliflozin on cardiac structure and function assessed by echocardiography after myocardial infarction: a post-hoc sub-analysis of the emmy trial

Nora Schwegel · Christoph Strohhofer · Ewald Kolesnik · Sabrina Oltean · Alexander Hüttmair · Christian Pipp, et al. ***[full author details at the end of the article]***

Received: 3 January 2024 / Accepted: 14 August 2024

Abstract

Background Empagliflozin administered after acute myocardial infarction proofed to improve cardiometabolic parameters and biomarkers, but the impact on cardiac function is still largely unknown. The aim of this post-hoc echocardiographic sub-analysis of the EMMY trial was to provide in-depth echocardiographic analysis on the effects of empagliflozin versus placebo on standard and novel echocardiographic structural and functional parameters after acute myocardial infarction.

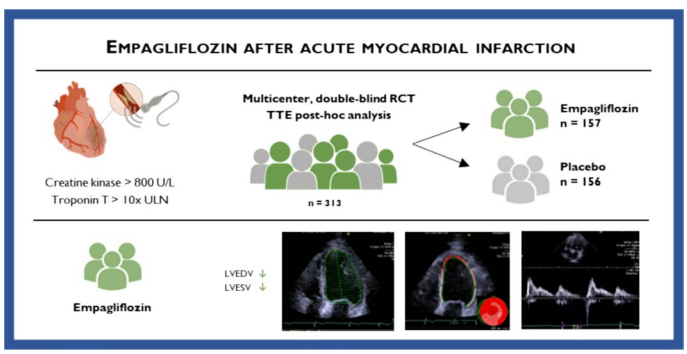
Methods In this post-hoc analysis of the EMMY trial a subset of 313 patients (157 empagliflozin vs. 156 placebo) was enrolled for post-processing analysis of echocardiographic structural and functional parameters. On top of two-dimensional and Doppler parameters, myocardial deformation analyses were performed to assess ventricular and atrial strain values.

Results Left ventricular volumes showed significant differences in favor of empagliflozin over the course of the trial (change in left ventricular end-diastolic volume median [interquartile range] 8 [−3;19]% versus 13 [0;29]%, p = 0.048; left ventricular end-systolic volume −3 [−15;12]% versus 4 [−12;18]%, p = 0.044). This effect persisted after adjusting for baseline values, age, and sex. Left ventricular systolic and diastolic function overall improved over the course of the trial and parameters for diastolic function showed a distinct trend between groups but did not meet statistical significance in this cohort.

Conclusion In this post-hoc analysis among patients with acute myocardial infarction, treatment with empagliflozin resulted in a significant beneficial effect on left ventricular end-diastolic and end-systolic volume, without significantly improving left ventricular or right ventricular functional parameters compared to placebo after 26 weeks.

ClinicalTrials.gov registration NCT03087773.

Graphical abstract



Keywords Myocardial infarction · Echocardiography · SGLT2 inhibitors · Empagliflozin · Heart failure · Myocardial function

Harald Sourij and Dirk von Lewinski contributed equally.

Published online: 16 September 2024

Abbreviations

LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
RCT	Randomized controlled trial
TTE	Transthoracic echocardiography
ULN	Upper limit of normal

Introduction

Left ventricular remodeling and systolic dysfunction following acute myocardial infarction (AMI) increase the risk for the development of heart failure and overall mortality [1, 2]. Established heart failure therapies like angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI), and beta-blockers attenuate post-AMI ventricular remodeling and dysfunction and lead to a reduction in the risk of adverse events [1–4]. In the past years, sodium-glucose co-transporter 2 inhibitors (SGLT2i) gained ground as heart failure therapy and most recently their use was recommended for the treatment of heart failure over the whole spectrum of ejection fraction [5, 6]. The EMpagliflozin in acute MYocardial infarction (EMMY) trial investigated the effects of treatment with the SGLT2i empagliflozin versus placebo on N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) in patients after AMI. A total of 476 patients were randomized in a multicenter, double-blinded trial, with a follow-up period of 26 weeks. Treatment with empagliflozin was associated with a significantly greater reduction in NT-proBNP over 26 weeks (mean 26-week NT-proBNP 15% [95%CI −4.4 to −23.6%] lower in treatment group, p = 0.026). Moreover, an increase in left ventricular ejection fraction (LVEF) of 1.5% (95%-CI 0.2–2.9%, p = 0.029) difference between the groups in favor of empagliflozin was observed. Left ventricular end-systolic volume (LVESV) decreased with empagliflozin and increased in the placebo group, resulting in a −7.5 ml (95% CI −11.5 to −3.4, p = 0.0003) difference. Left ventricular end-diastolic volume (LVEDV) increased in both groups, with a difference of -9.7 ml (95% CI −15.7 to −3.7, p = 0.0015) in favor of empagliflozin. E/e' decreased significantly more pronounced in the empagliflozin group (−6.8% [95% CI 1.3–11.3%], p = 0.015) [7]. However, these echocardiographic measurements were evaluated locally and comprehensive evaluations like deformation analysis were not performed. In the present post-hoc analysis of a subset of participants the EMMY trial, in-depth echocardiographic analysis was performed in an Echocardiographic Core Laboratory to meticulously assess the effect of empagliflozin on echocardiographic structural and functional parameters after large AMI.

Methods

The EMMY trial

EMMY was a multi-center, randomized, double-blind, placebo-controlled trial conducted at 11 Austrian sites (ClinicalTrials.gov registration nr. NCT03087773). From May 2017 to May 2022 a total of 476 patients with a confirmed AMI with creatine kinase > 800 IU/L, a high-sensitivity Troponin level > tenfold the upper limit of normal, and an estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^2 were enrolled within 72 h after percutaneous coronary intervention (PCI) for AMI. Patients with an ongoing SGLT2i therapy or therapy within 4 weeks prior to enrolment were excluded. Empagliflozin (10 mg/day, target dose) versus matching placebo was administered on the background of guideline based post-MI therapy [8]. Follow-up visits were performed after 6, 12, and 26 weeks. Detailed information on trial design, baseline characteristics, and results of the trial have been previously published elsewhere [7, 9].

Comprehensive echocardiographic examination was performed according to current guidelines[10] on locally available devices at baseline, after 6 weeks, and after 26 weeks. The echocardiographic protocol for transthoracic echocardiography (TTE) included 2D, Doppler, and M-mode imaging. During each study an ECG was recorded to define end-systole and end-diastole. All examinations were analysed for standard parameters at local departments and the results, comprising left-ventricular volumes, LVEF, and E/e', were reported in the main EMMY trial [7].

Additionally, all sites enrolling patients in the main trial were invited to transfer their echocardiographic examinations archived as DICOM-files to the Echocardiography Core Laboratory (Department of Cardiology, Medical University of Graz, Austria) to participate in the echocardiographic post-hoc sub-analysis. To qualify for participation, a predefined echocardiographic protocol, which was provided by the Echocardiography Core Laboratory, was followed by enrolling sites. An overview of the protocol is provided in the Online Resource. (Figure S1).

The echocardiographic post-hoc sub-analysis

In this analysis, we retrospectively assessed the archived studies of the echocardiographic examinations conducted during the EMMY trial from three major sites (see Fig. 1) in the central Echocardiography Core Laboratory. Analyses were performed using the vendor-independent post-processing software TomTec-Arena (TomTec Imaging

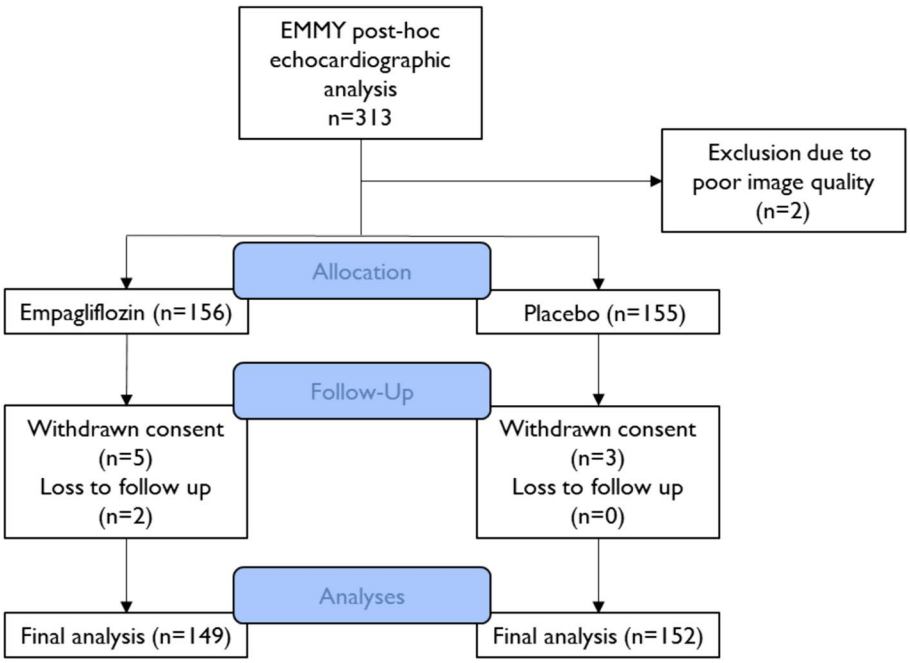


Fig. 1 Patient disposition. Echocardiographic data for evaluation was available from three major sites: the Medical University of Graz (n = 219), the Hospital Graz II—West (n = 16), and the Hospital Klagenfurt am Woerthersee (n = 78)

Systems, Munich, Germany) by trained investigators who were blinded to patients' clinical characteristics and study treatment. Two-dimensional and Doppler parameters were assessed according to current guidelines of the European Association of Cardiovascular Imaging and the American Society of Echocardiography [10–13].

Deformation analysis

In addition, 2D deformation analyses were performed using 2D Cardiac Performance Analysis (2D-CPA) by TomTec-Arena. For this purpose, cine-loops with the best image quality were selected for each analysis, and deformation analysis was performed in two cardiac cycles and reported as mean values, if applicable. The integrity of tracking was confirmed by visual impression of wall motion, and contours were readjusted to enable optimal tracking.

In this study, we focused on endocardial strain parameters derived from user-defined contours. Strain values were calculated by using the entire contour line length. Left ventricular (LV) global longitudinal strain (GLS) was assessed from all three apical chamber views (LV four-chamber, three-chamber, and two-chamber view) using a 16-segment model [14, 15]. Right ventricular (RV) longitudinal strain was assessed by averaging longitudinal systolic strain values of septal and free wall segments (six segment model, RV global longitudinal strain; RV-GLS) as well as from the free wall segments alone (three segment model, RV freewall strain; RV-FWS), obtained from an RV focused apical four-chamber view [16]. Left atrial (LA) strain was obtained from apical two-chamber view, and right atrial (RA) strain was assessed in apical four-chamber view, in accordance with current recommendations [16].

All echocardiographic parameters and assessment methods are listed in detail in Online Resource Table S1.

Statistical analysis

All data is illustrated by descriptive statistics using mean and standard deviation or median and interquartile range for continuous variables and frequency and percentages for categorical variables, respectively. Categorical variables were compared using the Chi-square test or Fisher's Exact test and continuous variables were compared using unpaired t-tests or their non-parametric equivalent tests, as appropriate. The change in echocardiographic parameters from baseline to week 6 and week 26 as well as differences between treatment groups over the three timepoints were analyzed using the linear mixed-effects model. In each model, time, treatment, and time-treatment interaction were included as fixed effects along with baseline values of each parameter, age, and sex. P-values <0.05 were considered statistically significant.

Results

A total of 313 patients initially qualified for this post-hoc analysis of the EMMY trial (empagliflozin n = 157 versus placebo n = 156). Eight (2.6%) patients withdrew consent, two (0.6%) patients were lost to follow up, and two (0.6%) patients were excluded due to poor image quality.

Hence, 301 participants (empagliflozin n = 149, placebo n = 152) were included in the final analysis. (Fig. 1) Median (interquartile range) age was 57 (52;65) years, with 18.3% females. 37 (11.9%) patients had established diabetes mellitus, 17 (5.5%) patients had known coronary artery disease, and 12 (3.9%) had previous history of myocardial infarction. Baseline characteristics were similar between groups, as illustrated in Table 1. At baseline median NT-proBNP was 1377 (800;2217) pg/mL. Median creatine kinase was 1705 (1203;2442) U/L and median Troponin T was 3067 (2099;4938) µg/L. All patients received guideline recommended post-MI pharmacologic treatment with > 97% of patients receiving treatment with ACEi/ARB/ARNI, beta-blockers, and statins.

Patients had mildly reduced LVEF with a median of 48 (43;53) % at baseline, preserved right ventricular function with a median tricuspid annular plane systolic excursion (TAPSE) of 21 (19;23) mm, and at median normal atrial volume indices (left atrial volume index [LAVI] 31 [27;38] mL, right atrial volume index [RAVI] 23 [18;28] mL).

Changes in cardiac structure and function after 6 and 26 weeks

Changes in echocardiographic structural and functional parameters and corresponding treatment effects are shown in Table 2 and in the Online Resource *Table S3*.

At week 6, an increase in LVEDV (5 [−3;18]%) and LAVI (1 [−13;19]%), and a roughly constant LVESV (0 [−9;14]%) was observed in the whole cohort. Parameters reflecting left ventricular, right ventricular, left atrial, and right atrial function including deformation analysis improved throughout the cohort (baseline to week 6: LVEF 5 [−1;12]%; LV-GLS 10 [3;23]%, E/e' −7 [−21;7]%; LA-GLS 6 [−19;40]%; TAPSE 5 [−3;17]%; right-ventricular fractional area change [RV-FAC] 7 [−1;18]%; RV-GLS 10 [−1;23]%; RV-FWS 8 [−2;22]%; RA-GLS 0 [−21;17]%; RAVI 4 [−13;27]%).

At week 26, LVEDV and LAVI increased more pronounced in the placebo group, while LVESV decreased in the empagliflozin group (LVEDV 8 [-3;19]% with empagliflozin versus 13 [0;29]% with placebo, p = 0.048; LAVI 3 [−12;23]% vs. 5 [−12;28]%, p = 0.460; LVESV −3 [−15;12]% vs. 4 [−12;18]%, p = 0.044). This effect of empagliflozin on LVEDV and LVESV persisted after adjustment for baseline values, age, and sex between groups (Fig. 2A, B), in line with the findings of the main EMMY trial. [7]

Right ventricular functional parameters improved throughout the cohort (baseline to week 26: TAPSE 10 [−1;20]%; RV-FAC 12 [2;23]%; RV-GLS 14 [4;26]%; RV-FWS 10 [1;27]%). However, no statistically significant differences were observed between treatment groups (TAPSE p = 0.858; RV-FAC p = 0.399; RV-GLS p = 0.197; RV-FWS p = 0.360).

Parameters reflecting diastolic function, as depicted by E/e', LA-GLS, and LAVI showed a distinct trend over the course of the trial when comparing groups but did not meet statistical significance. (Fig. 2 and Figure S2).

Reproducibility

Each echocardiographic measurement was performed on two separate cardiac cycles, if applicable, and reported as mean values. Parameters showed overall good reproducibility. The intraclass correlation coefficients are provided in the Online Resource Table S2.

Discussion

Among the 301 patients analyzed in this sub-study of the EMMY trial with in-depth echocardiographic analysis performed at baseline, 6 weeks, and 26 weeks after an AMI, randomization to empagliflozin resulted in a significant improvement of left ventricular volumes compared to a placebo. These observations suggest a primary effect of empagliflozin in terms of mitigated cardiac remodeling after AMI (Tables 2 and S3).

Moreover, this echocardiographic post-hoc sub-analysis is the first study to assess the trajectories of non-left ventricular deformation analysis after AMI. However, regarding right ventricular function and strain analysis, no differences were observed between treatment groups.

Though new advances in interventions and pharmacologic treatments after AMI are emerging, it remains one of the most important causes of morbidity and mortality worldwide [17]. Cardiac remodeling after AMI, characterized by fibrosis, chamber dilation, and dysfunction, is a major risk factor in disease development and is modifiable with pharmacologic agents like ACEi, ARB, ARNI, and beta-blockers. These agents have shown significant effects on remodeling in patients with heart failure as well as post-AMI, which in a longer-term has a major impact on relevant clinical outcomes [1–4, 18, 19].

Reversing remodeling plays a crucial role in reducing morbidity and mortality in patients after AMI [20]. Like in the field of heart failure, accumulating evidence points to beneficial effects of SGLT2i in patients with coronary artery disease and acute coronary syndromes, beyond their glucose-lowering properties [3, 7, 21–24]. In the previously published dapagliflozin in patients with myocardial infarction (DAPA-MI) trial, the administration of dapagliflozin in addition to standard post-MI therapy after AMI demonstrated a favorable effect on cardiometabolic outcomes compared to a placebo in patients without diabetes or chronic heart failure, despite failing to show significant differences regarding a composite endpoint of cardiovascular death and

Table 1 Baseline characteristics

	All n = 311	Empagliflozin n = 156	Placebo n = 155	P-value[a]
Age [years]	57 (52;65)	57 (52;64)	58 (52;66)	0.702
Female, *n (%)*	57 (18.3)	25 (16.0)	32 (20.6)	0.292
Body mass index [kg/m^2]	28 (25;30)	28 (25;30)	28 (25;30)	0.591
Diabetes mellitus, *n (%)*	37 (11.9)	16 (10.3)	21 (13.5)	0.370
Coronary artery disease, *n (%)*	17 (5.5)	10 (6.4)	7 (4.5)	0.463
Coronary vessel status				
1-vessel disease, *n (%)*	143 (46.0)	62 (39.7)	81 (52.3)	0.063
2-vessel disease, *n (%)*	108 (34.7)	58 (37.2)	50 (32.3)	
3-vessel disease, *n (%)*	60 (19.3)	36 (23.1)	24 (15.5)	
History of myocardial infarction, *n (%)*	12 (3.9)	8 (5.1)	4 (2.6)	0.243
Pharmacologic treatment				
ACEi/ARB, *n (%)*	304 (98.7)	153 (98.7)	151 (98.7)	0.990
ARNI, *n (%)*	5 (1.6)	1 (0.6)	4 (2.6)	0.174
Beta-blocker, *n (%)*	303 (97.4)	150 (96.2)	153 (98.7)	0.155
MRA, *n (%)*	149 (47.9)	73 (46.8)	76 (49.0)	0.693
Loop diuretic, *n (%)*	33 (10.6)	18 (11.5)	15 (9.7)	0.594
Calcium channel blocker, *n (%)*	13 (4.2)	4 (2.6)	9 (5.8)	0.153
Statin, *n (%)*	310 (99.7)	155 (99.4)	155 (100.0)	0.318
Laboratory parameters				
NT-proBNP [pg/mL]	1377 (800;2217)	1257 (797;2239)	1477 (800;2192)	0.514
eGFR [mL/min/1.73 m^2]	93 (79;102)	94 (78;101)	93 (81;103)	0.576
Creatine kinase [U/L]	1705 (1203;2442)	1670 (1170;2518)	1729 (1257;2366)	0.883
CK-MB [U/L]	159 (86;238)	139 (80.0;227)	167 (92;247)	0.373
Troponin T [µg/L]	3067 (2099;4938)	3089 (2195;4899)	3045 (2062;5018)	0.512
C-reactive Protein [mg/dL]	6 (3;14)	6 (3;13)	7 (2;14)	0.660
Echocardiographic parameters				
LV EDV [mL]	122 (100;142)	120 (100;140)	122 (101;145)	0.417
LV ESV [mL]	63 (49;78)	62 (49;77)	64 (49;80)	0.571
LV EF [%]	48 (43;53)	49 (43;52)	47 (43;53)	0.909
LV GLS [%]	-16 (-19;-13)	-17 (-19;-13)	-15 (-19;-12)	0.257
E/e'	9 (7;11)	9 (7;11)	9 (7;11)	0.559
LA GLS [%]	19 (15;25)	19 (15;25)	19 (14;26)	0.959
LAVI [mL/m^2]	31 (27;38)	30 (26;37)	32 (28;39)	0.147
RV GLS [%]	-21 (-23;-18)	-21 (-23;-18)	-21 (-23;-18)	0.890
RV-FWS [%]	-27 (-30;-23)	-27 (-30;-23)	-27 (-29;-24)	0.886
RV FAC [%]	37 (34;41)	37 (35;42)	38 (33;41)	1.000
TAPSE [mm]	21 (19;23)	21 (18;23)	21 (19;23)	0.151
RA GLS [%]	35 (29;42)	35 (30;41)	35 (29;43)	0.640
RAVI [mL/m^2]	23 (18;28)	22 (18;27)	23 (18;29)	0.752

All parameters reported in median (interquartile range) or frequency (percentage). *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *CK-MB* creatine kinase muscle-brain type, *eGFR* estimated glomerular filtration rate, *LA-GLS* left-atrial global longitudinal strain, *LAVI* left-atrial volume index, *LVEDV* left-ventricular end-diastolic volume, *LVEF* left-ventricular ejection fraction, *LVESV* left-ventricular end-systolic volume, *LV-GLS* left-ventricular global longitudinal strain, *MRA* mineralcorticoid receptor antagonist, *RA-GLS* right-atrial global longitudinal strain; *RAVI* right- atrial volume index, *RV-FAC* right-ventricular fractional area change; *RV-FWS* right-ventricular freewall strain, *RV-GLS* right-ventricular global longitudinal strain, *TAPSE* tricuspid annular plane systolic excursion

[a]Wilcoxon rank-sum test; Chi-square test

Table 2 Changes in echocardiographic parameters

	Baseline	Week 6	Week 26	Absolute change (week 6)	Absolute change (week 26)	% change (week 6)	% change (week 26)	p−value
LVEDV [mL]								
All	122 (100;142)	132 (110;151)	135 (114;158)	6 (−4;21)	12 (−1;28)	5 (−3;18)	10 (−1;24)	
Empagliflozin	120 (100;140)	132 (113;149)	135 (114;155)	6 (−5;20)	10 (−3;20)	4 (−4;17)	8 (−3;19)	**0.048**
Placebo	122 (101;145)	132 (107;155)	134 (111;165)	6 (−3;24)	14 (0;33)	5 (−3;18)	13 (0;29)	
LVESV [mL]								
All	63 (49;78)	64 (50;77)	61 (49;78)	0 (−6;8)	0 (−9;10)	0 (−9;14)	1 (−14;16)	
Empagliflozin	62 (49;76)	64 (51;75)	60 (49;75)	1 (−6;6)	0 (−6;11)	1 (−11;9)	−3 (−15;12)	**0.044**
Placebo	64 (49;80)	64 (48;82)	62 (49;79)	−1 (−9;7)	2 (−7;11)	0 (−7;18)	4 (−12;18)	
LVEF [%]	$n=244$	$n=241$	$n=230$					
All	48 (43;52)	51 (47;56)	54 (48;58)	3 (−0;5)	5 (1;8)	5 (−1;12)	10 (2;18)	
Empagliflozin	48 (43;52)	52 (46;56)	55 (48;58)	3 (−0;6)	5 (1;9)	6 (−0;13)	11 (3;18)	0.888
Placebo	47 (43;52)	51 (47;55)	53 (49;56)	2 (−0;5)	5 (0;8)	4 (−1;11)	10 (1;18)	
LV−GLS [%]								
All	−16 (−19;−13)	−18 (−20;−15)	−19 (−21;−16)	−1 (−2;1)	−1 (−2;0)	10 (3;23)	16 (3;30)	
Empagliflozin	−16 (−19;−13)	−18 (−21;−16)	−19 (−22;−17)	−1 (−2;1)	−1 (−3;0)	10 (3;22)	15 (4;29)	0.728
Placebo	−15 (−19;−12)	−18 (−19;−15)	−18 (−21;−16)	−1 (−2;1)	−1 (−2;1)	10 (3;24)	18 (3;34)	
E/é								
All	9 (7;11)	8 (7;10)	8 (7;10)	1 (−4;7)	2 (−3;8)	−7 (−21;7)	−11 (−24;7)	
Empagliflozin	9 (7;11)	8 (7;10)	8 (6;9)	2 (−2;7)	2 (−3;8)	−8 (−21;9)	−11 (−25;7)	0.551
Placebo	9 (8;10)	8 (7;11)	8 (7;10)	0 (−6;7)	3 (−3;7)	−7 (−21;6)	−11 (−22;7)	
LAVI [mL/m^2]								
All	31 (27;38)	32 (27;39)	33 (27;40)	−2 (−3;−1)	−3 (−4;−1)	1 (−13;19)	4 (−12;23)	
Empagliflozin	30 (26;37)	32 (26;39)	32 (27;39)	−2 (−4;−0)	−3 (−4;−1)	1 (−12;23)	3 (−12;23)	0.460
Placebo	32 (28;39)	32 (28;40)	34 (27;41)	−2 (−3;−1)	−3 (−5;−0)	1 (−13;17)	5 (−12;28)	
LA−GLS [%]								
All	19 (14;25)	22 (16;26)	22 (17;28)	0 (−8;5)	−2 (−9;6)	6 (−19;40)	12 (−16;46)	
Empagliflozin	19 (15;25)	22 (17;27)	22 (17;30)	−0 (−7;5)	−0 (−7;6)	9 (−11;41)	11 (−16;48)	0.098
Placebo	19 (14;26)	21 (15;26)	22 (16;28)	0 (−9;5)	−2 (−9;6)	3 (−25;38)	13 (−16;45)	
TAPSE [mm]								
All	21 (19;23)	23 (21;24)	23 (21;25)	−2 (−5;0)	−3 (−5;−1)	5 (−3;17)	10 (−1;20)	
Empagliflozin	21 (18;23)	23 (21;24)	23 (21;25)	−2 (−5;0)	−3 (−4;−1)	7 (−3;18)	11 (−3;21)	0.858
Placebo	21 (19;23)	22 (20;24)	23 (21;25)	−2 (−4;−0)	−3 (−5;−1)	5 (−3;16)	9 (1;20)	
RV−FAC [%]								
All	37 (34;42)	41 (37;45)	42 (39;46)	−2 (−6;1)	−3 (−6;−0)	7 (−1;18)	12 (2;23)	
Empagliflozin	37 (35;42)	41 (37;45)	43 (39;46)	−2 (−5;−0)	−3 (−7;−1)	7 (−4;17)	12 (2;24)	0.399
Placebo	38 (33;41)	42 (38;45)	42 (39;46)	−3 (−6;1)	−3 (−6;−0)	7 (1;18)	11 (2;22)	
RV−GLS [%]								
All	−21 (−23;−18)	−23 (−25;−21)	−24 (−26;−22)	3 (−0;6)	4 (1;8)	10 (−1;23)	14 (4;26)	
Empagliflozin	−21 (−23;−18)	−23 (−25;−21)	−24 (−26;−22)	2 (−2;6)	4 (1;9)	8 (−3;26)	12 (4;23)	0.197
Placebo	−21 (−23;−18)	−24 (−26;−21)	−24 (−26;−22)	3 (0;7)	4 (1;8)	11 (0;23)	14 (4;29)	
RV−FWS [%]								
All	−27 (−30;−24)	−29 (−32;−27)	−31 (−33;−28)	1 (−1;3)	2 (−0;4)	8 (−2;22)	10 (1;27)	
Empagliflozin	−27 (−30;−23)	−29 (−32;−27)	−31 (−33;−28)	1 (−1;4)	2 (−1;4)	9 (−5;26)	10 (0;25)	0.360
Placebo	−27 (−29;−24)	−30 (−32;−27)	−31 (−33;−28)	1 (−1;3)	2 (0;4)	7 (1;22)	11 (2;31)	
RAVI [mL/m^2]								
All	23 (18;28)	23 (19;29)	24 (20;29)	0 (−4;6)	1 (−4;7)	4 (−13;27)	8 (−9;30)	
Empagliflozin	22 (18;27)	23 (19;27)	23 (20;29)	0 (−4;6)	1 (−4;6)	3 (−16;25)	8 (−14;30)	0.152
Placebo	23 (18;28)	25 (20;30)	25 (20;30)	0 (−5;5)	2 (−4;8)	5 (−9;29)	8 (−8;31)	

Table 2 (continued)

	Baseline	Week 6	Week 26	Absolute change (week 6)	Absolute change (week 26)	% change (week 6)	% change (week 26)	p−value
RA−GLS [%]								
All	35 (29;42)	35 (29;41)	34 (28;40)	1 (−3;5)	2 (−2;7)	0 (−21;17)	−4 (−22;19)	
Empagliflozin	35 (30;42)	36 (30;42)	35 (29;40)	1 (−4;4)	2 (−4;6)	0 (−17;16)	−1 (−20;19)	0.441
Placebo	35 (29;43)	34 (29;40)	33 (28;40)	1 (−2;6)	2 (−2;7)	1 (−21;17)	−5 (−22;18)	

All values reported in median (interquartile range). P-values reported from the linear mixed-effects model for average treatment effects, adjusted for baseline values, age, and sex. P-values meeting statistical significance are marked in bold. *LA-GLS* left-atrial global longitudinal strain, *LAVI* left-atrial volume index, *LVEDV* left-ventricular end-diastolic volume, *LVEF* left-ventricular ejection fraction, *LVESV* left-ventricular end-systolic volume, *LV-GLS* left-ventricular global longitudinal strain, *RA-GLS* right-atrial global longitudinal strain, *RAVI* right- atrial volume index, *RV-FAC* right-ventricular fractional area change, *RV-FWS* right-ventricular freewall strain, *RV-GLS* right-ventricular global longitudinal strain, *TAPSE* tricuspid annular plane systolic excursion

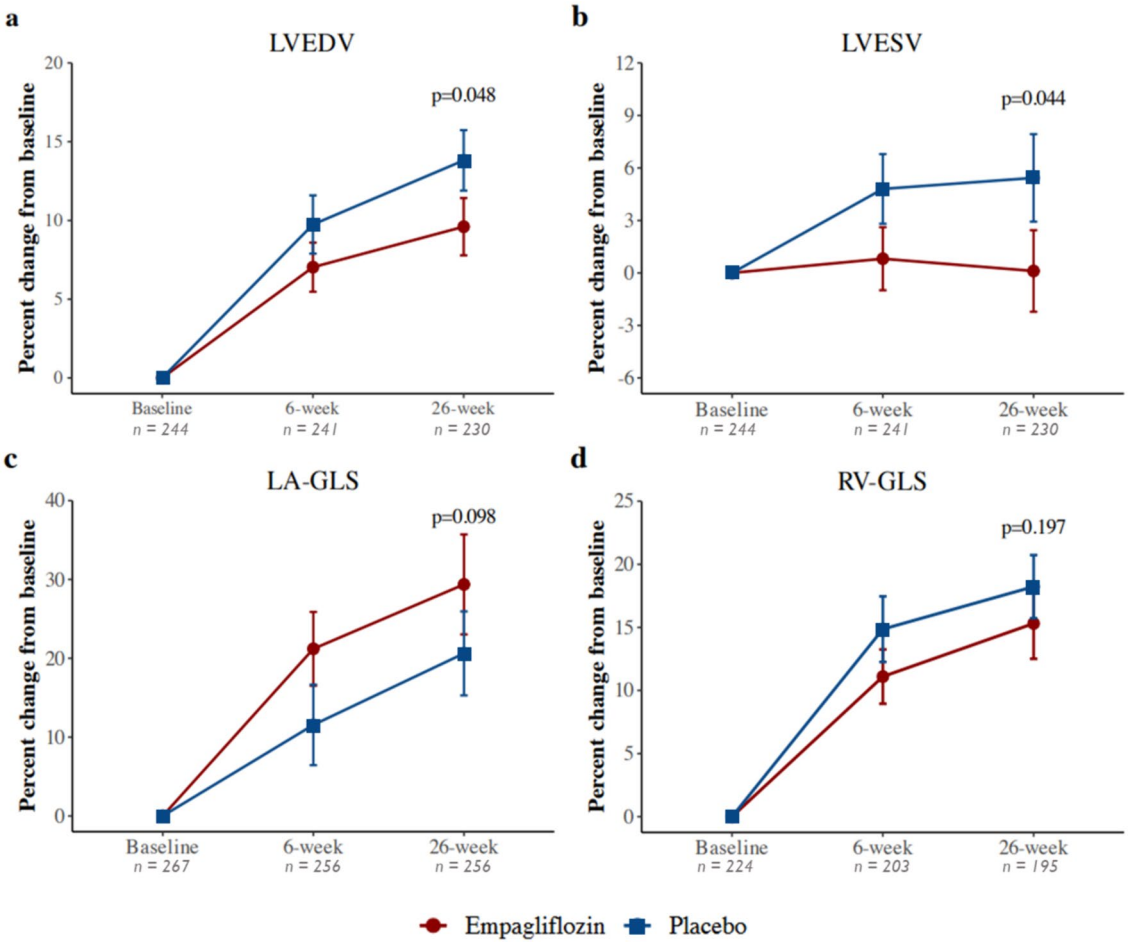


Fig. 2 Changes in echocardiographic parameters by treatment group. **a** LVEDV: left-ventricular end-diastolic volume, **b** LVESV: left-ventricular end-systolic volume, **c** LA-GLS: left-atrial global longitudinal strain, and **d** RV-GLS: right-ventricular global longitudinal strain

hospitalization for heart failure [25]. Similar neutral effects of empagliflozin on prespecified clinical outcomes were observed in the empagliflozin in patients post myocardial infarction (EMPACT-MI) trial, however, a sub-analysis showed a risk reduction for first and recurrent heart failure hospitalizations with empagliflozin [26, 27]. Overall there seems to be a positive effect of SGLT2i on the cardiovascular system after AMI. Underlying pathways on the

prevention and reversal of adverse cardiac remodeling are widely discussed and deemed multifactorial. Several preclinical and clinical studies suggest the anti-inflammatory and anti-fibrotic properties[28–30] as well as improved cardiac efficiency and increased myocardial energy supply [31, 32] to contribute to their cardioprotective benefits.

This echocardiographic post-hoc analysis demonstrates significant effects on cardiac remodeling depicted by changes in left ventricular diastolic and systolic volumes in favor of the empagliflozin group, which confirms the findings of the main EMMY trial [7]. On the other hand, only favorable trends but no significant effect was observed for markers of left-ventricular systolic and diastolic function. On regard of this, similar trajectories were observed in left atrial, right ventricular, and right atrial parameters, and throughout deformation analysis parameters with and without empagliflozin. The overall baseline LVEF and LV-GLS was only mildly reduced in this study. Especially in cohorts with less impaired systolic function, the clinical effect on cardiac function after AMI seems limited. The SOCOGAMI trial demonstrated a significant decrease in body weight and blood glucose but showed no significant influence of empagliflozin on echocardiographic and magnetic resonance imaging variables in a cohort with recent ACS and normal LV function [33]. This, in alignment with the results of the present study, poses the question of treatment effect in a subset of patients after AMI with more pronounced functional impairment. However, the SUGAR-DM-HF trial examined structural changes in chronic heart failure with reduced ejection fraction (HFrEF) in patients with type 2 diabetes treated with empagliflozin and demonstrated a reduction of diastolic and systolic left ventricular volumes with no changes of systolic function [22]. In the EMPA-VISION trial patients with either HFrEF or HFpEF were examined using cardiac magnetic resonance. Here, though not reaching statistical significance, a favorable trend towards empagliflozin was observed regarding left ventricular strain, which was more pronounced in the HFpEF group (adjusted mean treatment difference, 2.18% [SE, 1.16 (95% CI, − 0.28 to 4.64)]; $p = 0.08$) [34].

Of note, available recent echocardiographic sub-studies of trials investigating cardiovascular outcomes after AMI for sacubitril/valsartan and vericiguat also showed only minor effects on cardiac structure, and mostly no effect on cardiac function. The echocardiographic sub-study of the PARADISE-MI trial, which investigated the impact of ARNI versus ACEi in 544 patients after AMI, showed significant change in LVEDV in the ARNI group (delta ARNI 0 ± 29 mL vs. ACEi 5 ± 30 mL, $p = 0.025$) but no significant differences in LVEF improvement (delta ARNI $5.4 \pm 9.5\%$ vs. ACEi $6.6 \pm 10.7\%$, $p = 0.79$) [3]. In the VICTORIA echocardiographic sub-study, comparing vericiguat versus placebo in 419 patients with HFrEF with a recent worsening heart failure event, significant changes could only be demonstrated for left ventricular volumes (delta LVEDVi -2.9 ± 18.5 mL vs. -7.7 ± 23.7 mL, $p = 0.021$) and not left ventricular systolic function (delta LVEF vericiguat $3.2 \pm 8.0\%$ vs. placebo $2.4 \pm 7.6\%$, $p = 0.091$) [35].

Strengths and limitations

The EMMY trial was the first trial to show the effect of early SGLT2i therapy in patients after AMI, predominantly in patients without diabetes. This post-hoc analysis provides first insight into cardiac mechanisms investigated with echocardiography in the first 26 weeks of treatment compared with placebo. Overall, the data in this study reflects the data presented in the main EMMY trial, however, parameters reflecting systolic and diastolic function, in contrast to the analysis in the main trial, did not meet significance in this sub-cohort, most probably due to lack of statistical power (post-hoc power estimation at an alpha level of 0.05: LVEF 43%, E/e' 60%).

Several considerations are relevant regarding these deviating results. This post-hoc analysis was based on a significantly smaller sample size, with only three participating sites compared to 11 in the main trial. Moreover, a relevant portion of echocardiographic examinations did not meet the criteria for post-processing analysis and had to be left out of the final analyses. Especially deformation imaging is highly dependent on image quality, therefore the ability to discern a treatment-related difference with empagliflozin may have been mitigated by the limited sample size.

On the other hand, all analyses were conducted at the Central Echocardiographic Core Laboratory by trained, blinded investigators, twice if applicable, with an overall satisfying intra-observer reproducibility. This enabled the acquisition of a comprehensive dataset with precise measurements. Furthermore, to our best knowledge, this is the first study to give insight to the course of cardiac structure and function including right ventricular and atrial structural and functional parameters including deformation imaging after AMI.

However, our findings may have a limited application in women, as only 18.3% of the study population was female. This underrepresentation of women is a common finding in cardiovascular trials, particularly in AMI trials [36, 37]. Some of the inclusion criteria of the EMMY trial may have contributed to the smaller number of females. For inclusion, evidence of high cardiac biomarker levels was needed, but literature shows that in women these levels are lower compared to men [38]. However, a sub-analysis of the EMMY trial indicated no significant difference in treatment effect between genders [39].

Conclusion

Among patients with recent acute myocardial infarction, the early initiation of empagliflozin after PCI resulted in a significant effect on left ventricular volumes compared to a placebo after 26 weeks. Parameters reflecting diastolic function (E/e', LA-GLS, LAVI) and parameters of the right ventricle (TAPSE, RV-FAC, RV-GLS, RV-FWS) showed a beneficial trend, but did not meet significance in this cohort.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-024-02523-1.

Acknowledgements We thank the Hospital Graz II West Location and the Public Hospital Klagenfurt am Woerthersee for the data transmission. Special thanks to Katharina Leitner for image acquisition at the Public Hospital Klagenfurt am Woerthersee.

Author contributions All authors contributed to the study and the manuscript. DvL and HS designed the study. NS wrote the first draft of the manuscript; FA provided the statistical analysis. Data collection and analysis were performed by EK, NS, CS, SO, AH, and CP. All authors read and approved the final manuscript.

Funding Open access funding provided by Medical University of Graz. This post-hoc sub-analysis received no additional funding. The main trial was supported by an investigator-initiated study grant of Boehringer Ingelheim (no. 1245.151) to HS and DvL. DvL is supported by the Austrian Science Fund (FWF) Grant KLIF-1155-B.

Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest HS is on the advisory board and speakers bureau of Boehringer Ingelheim, NovoNordisk, Sanofi-Aventis, Amgen, AstraZeneca, Bayer, Eli Lilly, Kapsch, MSD, and Daiichi Sankyo. DvL is on the advisory board and speaker's bureau of by Boehringer Ingelheim, Novartis, Sanova, Sanofi, Orion, AstraZeneca, Bayer Recardio, Vaxxinity and Daiichi Sankyo. NS and EK report no conflict of interest related to this study. All other authors report no conflict of interest related to this study.

Ethics approval and consent to participate The EMMY trial was approved by the Ethics committee of the Medical University of Graz, Austria (EK 29–179 ex16/17, EudraCT 2016–004591-22) and registered at ClinicalTrials.gov (NCT03087773). The trial conformed to the 1964 Declaration of Helsinki and adhered to the guidelines of Good Clinical Practice (ICH GCP E6). All study participants provided written consent.

Consent for publication All authors consent for the publication of this study.

References

1. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR et al (1994) Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation 89(1):68–75. https://doi.org/10.1161/01.cir.89.1.68
2. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK et al (2005) Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation 111(25):3411–3419. https://doi.org/10.1161/CIRCULATIONAHA.104.508093
3. Shah AM, Claggett B, Prasad N, Li G, Volquez M, Jering K et al (2022) Impact of sacubitril/valsartan compared with ramipril on cardiac structure and function after acute myocardial infarction: the PARADISE-MI echocardiographic substudy. Circulation 146(14):1067–1081. https://doi.org/10.1161/CIRCULATIONAHA.122.059210
4. Doughty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N et al (2004) Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN echo substudy. Circulation 109(2):201–206. https://doi.org/10.1161/01.CIR.0000108928.25690.94
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M et al (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 42(36):3599–3726. https://doi.org/10.1093/eurheartj/ehab368
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M et al (2023) 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 44(37):3627–3639. https://doi.org/10.1093/eurheartj/ehad195
7. von Lewinski D, Kolesnik E, Tripolt NJ, Pferschy PN, Benedikt M, Wallner M et al (2022) Empagliflozin in acute myocardial infarction: the EMMY trial. Eur Heart J 43(41):4421–4432. https://doi.org/10.1093/eurheartj/ehac494
8. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A et al (2023) 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 44(38):3720–3826. https://doi.org/10.1093/eurheartj/ehad191
9. Tripolt NJ, Kolesnik E, Pferschy PN, Verheyen N, Ablasser K, Sailer S et al (2020) Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction—the EMMY trial. Am Heart J 221:39–47. https://doi.org/10.1016/j.ahj.2019.12.004
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28(1):1-39.e14. https://doi.org/10.1016/j.echo.2014.10.003
11. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T et al (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart

J Cardiovasc Imaging 17(12):1321–1360. https://doi.org/10.1093/ehjci/jew082
12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K et al (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 23(7):685–713. https://doi.org/10.1016/j.echo.2010.05.010
13. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119. https://doi.org/10.1093/eurheartj/ehv317
14. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R et al (2015) Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr 28(2):183–193. https://doi.org/10.1016/j.echo.2014.11.003
15. Sugimoto T, Dulgheru R, Bernard A, Ilardi F, Contu L, Addetia K et al (2017) Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging 18(8):833–840. https://doi.org/10.1093/ehjci/jex140
16. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T et al (2018) Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 19(6):591–600. https://doi.org/10.1093/ehjci/jey042
17. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL et al (2023) Heart disease and stroke statistics-2023 update: a report from the American Heart Association. Circulation 147(8):e93–e621. https://doi.org/10.1161/CIR.0000000000001123
18. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C et al (1995) Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation 91(10):2573–2581. https://doi.org/10.1161/01.cir.91.10.2573
19. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR (2000) Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. J Am Coll Cardiol 36(7):2072–2080. https://doi.org/10.1016/s0735-1097(00)01006-8
20. Frantz S, Hundertmark MJ, Schulz-Menger J, Bengel FM, Bauersachs J (2022) Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies. Eur Heart J 43(27):2549–2561. https://doi.org/10.1093/eurheartj/ehac223
21. Hoshika Y, Kubota Y, Mozawa K, Tara S, Tokita Y, Yodogawa K et al (2021) Effect of empagliflozin versus placebo on plasma volume status in patients with acute myocardial infarction and type 2 diabetes mellitus. Diabetes Ther 12(8):2241–2248. https://doi.org/10.1007/s13300-021-01103-0
22. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT et al (2021) Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). Circulation 143(6):516–525. https://doi.org/10.1161/CIRCULATIONAHA.120.052186
23. Wei W, Liu J, Chen S, Xu X, Guo D, He Y et al (2022) Sodium glucose cotransporter type 2 inhibitors improve cardiorenal outcome of patients with coronary artery disease: a meta-analysis. Front Endocrinol 13:850836. https://doi.org/10.3389/fendo.2022.850836
24. Paolisso P, Bergamaschi L, Santulli G, Gallinoro E, Cesaro A, Gragnano F et al (2022) Infarct size, inflammatory burden, and admission hyperglycemia in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: a multicenter international registry. Cardiovasc Diabetol 21(1):77. https://doi.org/10.1186/s12933-022-01506-8
25. James S, Erlinge D, Storey RF, McGuire DK, de Belder M, Eriksson N et al (2023) Dapagliflozin in myocardial infarction without diabetes or heart failure. NEJM Evidence. https://doi.org/10.1056/EVIDoa2300286
26. Butler J, Jones WS, Udell JA, Anker SD, Petrie MC, Harrington J et al (2024) Empagliflozin after acute myocardial infarction. N Engl J Med 390(16):1455–1466. https://doi.org/10.1056/NEJMoa2314051
27. Hernandez AF, Udell JA, Jones WS, Anker SD, Petrie MC, Harrington J et al (2024) Effect of empagliflozin on heart failure outcomes after acute myocardial infarction: insights from the EMPACT-MI trial. Circulation 149(21):1627–1638. https://doi.org/10.1161/CIRCULATIONAHA.124.069217
28. Iannantuoni F, MdM A, Diaz-Morales N, Falcon R, Banuls C, Abad-Jimenez Z et al (2019) The SGLT2 inhibitor empagliflozin ameliorates the inflammatory profile in type 2 diabetic patients and promotes an antioxidant response in leukocytes. J Clin Med. https://doi.org/10.3390/jcm8111814
29. Kang S, Verma S, Hassanabad AF, Teng G, Belke DD, Dundas JA et al (2020) Direct effects of empagliflozin on extracellular matrix remodelling in human cardiac myofibroblasts: novel translational clues to explain EMPA-REG OUTCOME results. Can J Cardiol 36(4):543–553. https://doi.org/10.1016/j.cjca.2019.08.033
30. Lee TM, Chang NC, Lin SZ (2017) Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med 104:298–310. https://doi.org/10.1016/j.freeradbiomed.2017.01.035
31. Lopaschuk GD, Verma S (2020) Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. JACC Basic Transl Sci 5(6):632–644. https://doi.org/10.1016/j.jacbts.2020.02.004
32. de Koning MLY, Westenbrink BD, Assa S, Garcia E, Connelly MA, van Veldhuisen DJ et al (2021) Association of circulating ketone bodies with functional outcomes after ST-segment elevation myocardial infarction. J Am Coll Cardiol 78(14):1421–1432. https://doi.org/10.1016/j.jacc.2021.07.054
33. Lundin M, Ferrannini G, Mellbin L, Johansson I, Norhammar A, Nasman P et al (2022) Sodium-glucose CO-transporter inhibition in patients with newly detected glucose abnormalities and a recent myocardial infarction (SOCOGAMI). Diabetes Res Clin Pract 193:110141. https://doi.org/10.1016/j.diabres.2022.110141
34. Hundertmark MJ, Adler A, Antoniades C, Coleman R, Griffin JL, Holman RR et al (2023) Assessment of cardiac energy metabolism, function, and physiology in patients with heart failure taking empagliflozin: the randomized controlled EMPA-VISION trial. Circulation 147(22):1654–1669. https://doi.org/10.1161/CIRCULATIONAHA.122.062021
35. Pieske B, Pieske-Kraigher E, Lam CSP, Melenovsky V, Sliwa K, Lopatin Y et al (2023) Effect of vericiguat on left ventricular structure and function in patients with heart failure with reduced

ejection fraction: the VICTORIA echocardiographic substudy. Eur J Heart Fail 25(7):1012–1021. https://doi.org/10.1002/ejhf.2836
36. Tobb K, Kocher M, Bullock-Palmer RP (2022) Underrepresentation of women in cardiovascular trials- it is time to shatter this glass ceiling. Am Heart J Plus 13:100109. https://doi.org/10.1016/j.ahjo.2022.100109
37. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL (2020) Women's participation in cardiovascular clinical trials from 2010 to 2017. Circulation 141(7):540–548. https://doi.org/10.1161/CIRCULATIONAHA.119.043594
38. Lew J, Sanghavi M, Ayers CR, McGuire DK, Omland T, Atzler D et al (2017) Sex-based differences in cardiometabolic biomarkers. Circulation 135(6):544–555. https://doi.org/10.1161/CIRCULATIONAHA.116.023005
39. Sourij C, Aziz F, Tripolt NJ, Siller-Matula J, Pferschy PN, Kolesnik E et al (2024) Effects of empagliflozin in women and men with acute myocardial infarction: an analysis from the EMMY trial. Hellenic J Cardiol 75:3–8. https://doi.org/10.1016/j.hjc.2023.05.007

Authors and Affiliations

Nora Schwegel[1] · Christoph Strohhofer[1] · Ewald Kolesnik[1] · Sabrina Oltean[1] · Alexander Hüttmair[1] · Christian Pipp[1] · Martin Benedikt[1] · Nicolas Verheyen[1] · Johannes Gollmer[1] · Klemens Ablasser[1] · Markus Wallner[1] · Viktoria Santner[1] · Norbert Tripolt[2] · Peter Pferschy[2] · Peter Zechner[3] · Hannes Alber[4] · Jolanta M. Siller-Matula[5] · Kristen Kopp[6] · Andreas Zirlik[1] · Faisal Aziz[2] · Harald Sourij[2] · Dirk von Lewinski[1]

✉ Ewald Kolesnik
ewald.kolesnik@medunigraz.at

1 Division of Cardiology, University Heart Center Graz, Medical University of Graz, Graz, Austria

2 Trials Unit for Interdisciplinary Metabolic Medicine, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

3 Department of Cardiology and Intensive Care Medicine, Hospital Graz II, West Location, Graz, Austria

4 Department of Cardiology, Public Hospital Klagenfurt Am Woerthersee, Klagenfurt Am Woerthersee, Austria

5 Department of Cardiology, Medical University of Vienna, Vienna, Austria

6 Division of Cardiology and Internal Intensive Care Medicine, Department of Internal Medicine II, Paracelsus Medical Private University of Salzburg, Salzburg, Austria

Journal of
Clinical Medicine

MDPI

Article

Impact of SGLT2-Inhibitor Therapy on Survival in Patients with Transthyretin Amyloid Cardiomyopathy: Analysis of a Prospective Registry Study

Nora Schwegel [1], Christina Toferer [1], David K. Zach [1], Viktoria Santner [1], Viktoria Höller [1], Jakob Lugitsch [1], Markus Wallner [1], Johannes Gollmer [1], Faisal Aziz [2], Dirk von Lewinski [1], Ewald Kolesnik [1], Klemens Ablasser [1], Andreas Zirlik [1], Harald Sourij [2,†] and Nicolas Verheyen [1,*,†]

[1] Division of Cardiology, University Heart Center Graz, Medical University of Graz, 8036 Graz, Austria
[2] Trials Unit for Interdisciplinary Metabolic Medicine, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, 8036 Graz, Austria
* Correspondence: nicolas.verheyen@medunigraz.at; Tel.: +43-(0)316-385-12544; Fax: +43-(0)316-385-13733
† These authors contributed equally to this work.

Abstract: Background: Patients with transthyretin amyloid cardiomyopathy (ATTR-CM) represent a high-risk heart failure population with continued unmet therapeutic needs. Sodium–glucose co-transporter 2 inhibitors (SGLT2i) improve cardiovascular outcomes in patients with heart failure across the whole spectrum of ejection fraction, and first evidence regarding their safety and effectiveness in patients with ATTR-CM is arising. This study investigates the association between SGLT2i therapy and clinical outcomes in these patients. **Methods:** This is an analysis of a prospective registry conducted at a referral centre for hypertrophic cardiomyopathies including 116 patients with confirmed ATTR-CM. Fifty-one patients (44%) were treated with SGLT2i while 65 patients (56%) remained SGLT2i-naïve. **Results:** During a median follow-up of 2.6 (1.7–3.7) years, 38 patients (33%) died, of whom 11 patients (9%) received SGLT2i treatment and 27 patients (23%) were treatment-naïve. SGLT2i therapy was significantly associated with lower mortality (HR 0.457, 95%CI 0.227–0.922, $p = 0.029$). This association persisted after adjusting for age and sex (HR 0.479, 95%CI 0.235–0.977, $p = 0.043$) and after additional adjustment for eGFR, NT-proBNP, LVEF, and concomitant therapy with tafamidis (HR 0.328, 95%CI 0.141–0.760, $p = 0.009$). However, when potential immortal time bias was considered, this association lost statistical significance (HR 1.075, 95%CI 0.524–2.206, $p = 0.843$). No significant associations between SGLT2i therapy and worsening heart-failure hospitalization or cardiovascular mortality were observed. **Conclusions:** In crude analysis, SGLT2i therapy associates with better survival in patients with ATTR-CM. However, after adjustment for immortal time, this association becomes statistically insignificant. Hence, to draw final conclusions on the effectiveness of SGLT2i therapy in these patients, a randomized controlled trial is warranted.

Keywords: transthyretin amyloid cardiomyopathy; Sodium–glucose co-transporter 2 inhibitors; survival; heart failure therapy

Citation: Schwegel, N.; Toferer, C.; Zach, D.K.; Santner, V.; Höller, V.; Lugitsch, J.; Wallner, M.; Gollmer, J.; Aziz, F.; von Lewinski, D.; et al. Impact of SGLT2-Inhibitor Therapy on Survival in Patients with Transthyretin Amyloid Cardiomyopathy: Analysis of a Prospective Registry Study. *J. Clin. Med.* **2024**, *13*, 5966. https://doi.org/10.3390/jcm13195966

Academic Editor: Michael Rosenzweig

Received: 4 August 2024
Revised: 24 September 2024
Accepted: 28 September 2024
Published: 8 October 2024

1. Background and Aims

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by an accumulation of amyloid fibrils in the myocardial extracellular space and leads to progressive heart failure. Once thought to be a rare disease, advances in non-invasive diagnostic approaches and rising awareness have led to an increase in diagnoses of ATTR-CM over the past decade [1]. Although several promising disease-modifying therapies are emerging [2–4], a lack of evidence remains on the beneficial effects of conventional heart failure therapy in this disease. Sodium–glucose co-transporter 2 inhibitors (SGLT2i) have been shown to reduce the development and progression of heart failure across the whole spectrum of ejection fraction, leading to the implementation of SGTL2i as a mainstay of heart-failure

therapy [5–10]. However, these clinical trials excluded patients with ATTR-CM. Recently published studies indicate that SGLT2i therapy is also a safe and well-tolerated therapeutic option in patients with heart failure due to ATTR-CM, with beneficial effects on volume status, diuretic resistance, and arrhythmias [11–14]. First studies investigating the possible effects of SGLT2i treatment on clinical outcomes in these patients are arising, but evidence is sparse [15]. The present study aims to evaluate the effects of SGLT2 inhibition on top of established confounders regarding mortality and major heart-failure outcomes in patients with ATTR-CM.

2. Methods

2.1. Study Rationale and Study Population

This is a longitudinal analysis of the prospective Graz Hypertrophic Cardiomyopathy (HCM) Registry, including all participants with a confirmed diagnosis of ATTR-CM who were enrolled between February 2019 and December 2022 (n = 122). ATTR-CM was diagnosed according to international recommendations based on confirmation by amyloid scintigraphy in combination with free light chain assessment or, in unclear cases, tissue organ biopsy [16]. Prior and concomitant SGLT2i treatment was systematically assessed according to the patient interview and medical records. Six participants (5%) were excluded from the analysis if data on SGLT2i treatment was not available, leading to a number of 116 patients eligible for analysis (Figure 1). All patients provided written informed consent. Approval was granted by the local ethics committee (EC-No. 30–286 ex 17/18), and the study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki.

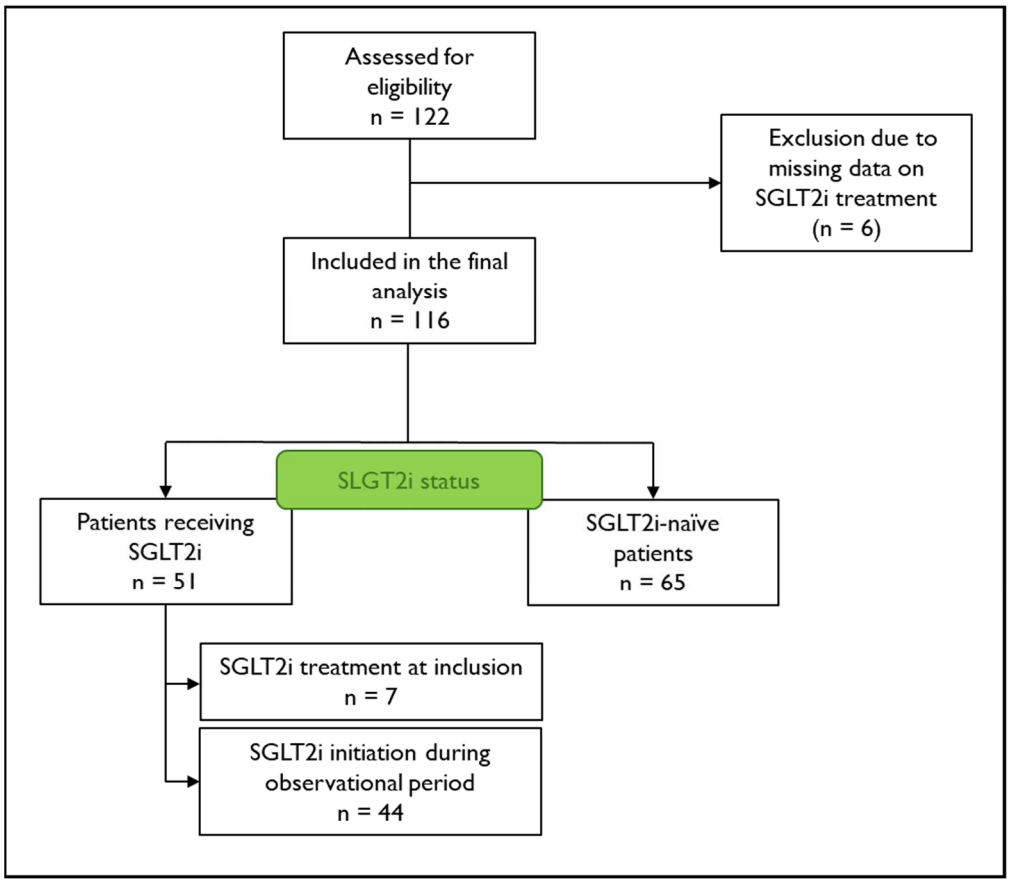


Figure 1. Flow chart of patient disposition. Patient disposition and Sodium–glucose co-transporter 2 inhibitor (SGLT2i) treatment status of included patients.

2.2. Laboratory Parameters

Blood samples were collected at baseline in each patient. Routine laboratory parameters were immediately determined at the Clinical Institute of Medical and Chemical Laboratory Diagnostics of the Medical University of Graz, Austria.

2.3. Follow-Up

Patient outcomes (hospitalization due to worsening heart failure [WHF], cardiovascular death, and all-cause mortality) were retrieved from medical and health insurance records. WHF was defined as unscheduled hospitalization or unscheduled urgent outpatient clinic visit due to documented heart-failure signs and symptoms in need of initiation or significant up-titration of heart-failure treatment [17].

2.4. Statistical Analysis

Categorical variables were described as counts with percentages; continuous variables were expressed as a median with an interquartile range. Group comparison was performed using the Wilcoxon rank–sum for continuous variables and Chi-square or Fischer's Exact tests for categorical variables. Associations between treatment and clinical outcomes were assessed using Cox proportional-hazard analysis with adjustment for parameters considered clinically significant confounders, namely, estimated glomerular filtration rate (eGFR), N-terminal pro-brain natriuretic peptide (NT-proBNP), left-ventricular ejection fraction (LVEF), and concomitant therapy with the selective transthyretin stabilizer tafamidis, either at baseline (SGLT2i-naïve group) or at SGLT2i initiation (SGLT2i-therapy group). All assumptions were satisfied for the reported Cox-regression models. A time-dependent Cox-regression analysis with SGLT2i treatment as time-varying exposure was performed to account for the so-called immortal time bias, which refers to the treatment-naïve time interval of patients within the treatment group (i.e., the interval between baseline examination and treatment initiation). Specifically, the follow-up time for each outcome was split before and after SGLT2i treatment initiation using the built-in function of Stata, and the Cox model was fitted on these data for each outcome, considering SGLT2i treatment as a time-varying covariate. For sensitivity analysis, landmark analysis was performed, considering year one and year two as landmark time periods to account for the immortal time bias. The steps of the analysis are provided in the supplementary material (Supplementary Figure S1). All statistical analyses were performed in Stata (Version 18.0, Stata Corp; College Station, TX, USA), considering a p-value < 0.05 as statistically significant.

3. Results

A total of 116 patients (15% females) were included in the final analysis, with a median (interquartile range) age of 80 (76–82) years. Hereditary ATTR-CM was present in 3% of the patients, and 15% had concomitant treatment with tafamidis at baseline. Most patients (39%) presented with New York Heart Association (NYHA) class III at baseline; angina pectoris was present in 31% of the patients. Seven patients (6%) were treated with SGLT2i at inclusion, and 44 patients (38%) were started on SGLT2i therapy during the observational period, while 65 patients (56%) remained SGLT2i-naïve. The mean (±standard deviation) treatment time with SGLT2i was 1.55 ± 0.75 years. From those receiving SGLT2i treatment, 28 patients (55%) were treated with dapagliflozin (10 mg daily), and 23 patients (45%) were treated with empagliflozin (10 mg daily). Recorded indications for SGLT2i prescription were as follows: heart failure (63%), heart failure and chronic kidney disease (18%), diabetes mellitus (8%), chronic kidney disease (6%), and heart failure and diabetes mellitus (5%). Twenty-three patients (20%) had an established diagnosis of diabetes mellitus, of whom 10 patients (9%) received SGLT2i, and 13 patients (11%) did not. LVEF at baseline was 49 (43–52)% in those who received treatment and 54 (49–59) % in the treatment-naïve group (p < 0.001), as shown in Table 1. At the time of treatment initiation, LVEF was 46 (39–53)%, and 30 patients (59%) were simultaneously treated with tafamidis. During the observational period, 103 patients (89%) did receive treatment with tafamidis. Of those receiving SGLT2i

therapy, 48 patients (94%) were co-treated with tafamidis; of those who remained SGLT2i-naïve, 55 patients (85%) received tafamidis ($p = 0.107$, Table 2). During a median follow-up of 2.6 (1.7–3.7) years, 38 patients (33%) died, of whom 11 patients (9%) received SGLT2i treatment and 27 patients (23%) were treatment-naïve ($p = 0.023$). Fourteen deaths (12%) were classified due to a cardiovascular cause (4 patients [3%] receiving SGLT2i versus 10 [9%] SGLT2i-naïve patients; $p = 0.216$). Thirty-two patients (28%) had a WHF event, of whom 18 patients (16%) were in the treatment group, and 14 patients (22%) did not receive treatment ($p = 0.463$, see Table 3). Overall and annual incidence rates are provided in Supplementary Table S1. In univariate Cox-regression analysis, SGLT2i treatment was significantly associated with lower mortality (hazard ratio [HR] 0.457, 95% confidence interval [CI] 0.227–0.922, $p = 0.029$), as shown in Figure 2. No significant association was found with cardiovascular death (HR 1.239, 95% CI 0.654–2.346, $p = 0.511$) or WHF (HR 1.715, 95% CI 0.844–3.484, $p = 0.136$). The association between SGLT2i and lower mortality persisted after adjusting for age, sex, eGFR, NT-proBNP, LVEF, and concomitant therapy with tafamidis, either at baseline or treatment initiation time (HR 0.177, 95% CI 0.062–0.504, $p = 0.001$), as shown in Table 4. However, under consideration of a potential immortal time bias, the benefit did not remain statistically significant (HR 1.075, 95% CI 0.524–2.206, $p = 0.843$; Table 5). Detailed analyses are described in Supplementary Tables S2 and S3. No patient discontinued treatment, and no drug-related severe adverse events were reported.

Table 1. Baseline characteristics.

	All	SGLT2i Therapy	SGLT2i-Naïve	*p*-Value
	n = 116	**n = 51**	**n = 65**	
Age, years	80 (76–82)	80 (76–82)	80 (77–83)	0.732
Female, n (%)	17 (15)	5 (10)	12 (18)	0.191
Ethnicity Caucasian, n (%)	116 (100)	51 (100)	65 (100)	-
Diabetes mellitus, n (%)	23 (20)	10 (20)	13 (20)	0.958
NYHA-class, n (%)				
I	12 (12)	5 (10)	7 (13)	0.989
II	25 (24)	12 (24)	13 (24)	
II–III	22 (21)	10 (20)	12 (22)	
III	40 (39)	20 (41)	20 (37)	
IV	4 (4)	2 (4)	2 (4)	
Angina pectoris symptoms, n (%)				
Typical	20 (19)	9 (18)	11 (20)	0.708
Atypical	12 (12)	7 (14)	5 (9)	
Tafamidis therapy, n (%)	17 (15)	8 (16)	9 (14)	0.781
Loop diuretic, n (%)	61 (53)	32 (63)	29 (44)	0.327
Thiazide diuretic, n (%)	12 (10)	3 (6)	9 (14)	0.083
Potassium-sparing diuretic, n (%)	41 (35)	25 (49)	16 (25)	0.038
Body mass index, kg/m^2	24.7 (22.8–26.2)	24.9 (22.6–26.6)	24.4 (22.9–26.2)	0.860
Systolic blood pressure, mmHg	132 (120–147)	129 (118–152)	132 (121–146)	0.902
Diastolic blood pressure, mmHg	78 (73–86)	78 (73–86)	79 (71–85)	0.927
Heart rate, bpm	70 (60–78)	73 (60–81)	70 (61–75)	0.474
LVEF, %	51 (45–57)	49 (43–52)	54 (49–59)	<0.001
NT-proBNP, pg/mL	2845 (1519–5033)	3224 (1949–4738)	2717 (1183–5049)	0.401
hsTrop-T, pg/mL	57 (35–83)	59 (36–87)	56 (31–81)	0.543
Estimated GFR, mL/min/1.73 m^2	58 (46–69)	58 (39–68)	59 (48–70)	0.478
Creatinine, mg/dL	1.2 (1.0–1.4)	1.2 (1.0–1.6)	1.1 (1.0–1.3)	0.343
CRP, mg/L	2.3 (1.3–4.2)	2.9 (1.3–4.3)	2.0 (1.3–4.2)	0.591

All parameters reported in median (interquartile range) or frequency (percentage). *p*-values derived from Wilcoxon rank–sum tests and Chi-square or Fischer's Exact tests, as appropriate. Abbreviations: CRP, C-reactive protein; GFR, glomerular filtration rate; hsTrop-T, high-sensitive Troponin T; LVEF, left-ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SGLT2i, Sodium–glucose co-transporter 2 inhibitors.

Table 2. Baseline characteristics at inclusion or treatment initiation.

	All	SGLT2i Therapy	SGLT2i-Naïve	*p*-Value
	n = 116	n = 51	n = 65	
NYHA-class, n (%)				0.258
I	12 (11)	3 (6)	9 (14)	
II	30 (27)	13 (27)	17 (27)	
II–III	18 (16)	5 (10)	13 (20)	
III	50 (44)	27 (55)	23 (36)	
IV	2 (2)	1 (2)	1 (2)	
Tafamidis therapy, n (%)				
At baseline	39 (34)	30 (59)	9 (14)	<0.001
During follow-up	103 (89)	48 (94)	55 (85)	0.107
Loop diuretic, n (%)	71 (69)	42 (82)	29 (56)	0.004
Thiazide diuretic, n (%)	12 (12)	3 (6)	9 (17)	0.071
Potassium-sparing diuretic, n (%)	46 (46)	30 (61)	16 (31)	0.002
Systolic blood pressure, mmHg	133 (120–149)	135 (120–157)	132 (121–146)	0.626
Diastolic blood pressure, mmHg	81 (70–86)	84 (69–90)	79 (71–85)	0.194
Heart rate, bpm	71 (62–78)	73 (64–81)	70 (62–76)	0.168
LVEF, %	51 (44–57)	46 (39–53)	54 (49–59)	0.002
NT-proBNP, pg/mL	3001 (1488–5227)	3384 (1976–6809)	2718 (1183–5050)	0.661
hsTrop-T, pg/mL	57 (35–85)	59 (36–90)	56 (31–81)	0.687
Estimated GFR, mL/min/1.73 m^2	57 (42–69)	52 (37–64)	59 (48–70)	0.068
Creatinine, mg/dL	1.2 (1.0–1.5)	1.3 (1.0–1.7)	1.1 (1.0–1.3)	0.400

Baseline characteristics at registry inclusion for SGLT2i-naïve patients or at initiation time for patients receiving SGLT2i therapy. All parameters reported in median (interquartile range) or frequency (percentage). *p*-values derived from Wilcoxon rank–sum tests and Chi-square or Fischer's Exact tests, as appropriate. Abbreviations: GFR, glomerular filtration rate; hsTrop-T, high-sensitive Troponin T; LVEF, left-ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SGLT2i, Sodium–glucose co-transporter 2 inhibitors.

Table 3. Data on clinical outcomes.

	All	SGLT2i Therapy	SGLT2i-Naïve	*p*-Value
	n = 116	n = 51	n = 65	
Outcomes, n (%)				
All-cause mortality	38 (33)	11 (22)	27 (42)	0.023
Cardiovascular death	14 (12)	4 (8)	10 (15)	0.216
WHF hospitalization	32 (28)	18 (35)	14 (22)	0.100
Observation time, years				
All-cause mortality	2.6 (1.7–3.7)	2.7 (2.0–3.7)	2.5 (1.6–3.7)	
Cardiovascular death	3.0 (2.2–4.1)	2.9 (2.0–3.7)	3.0 (2.3–4.2)	
WHF hospitalization	2.0 (1.2–3.2)	1.8 (1.0–3.0)	2.2 (1.4–3.6)	

All parameters reported in median (interquartile range) or frequency (percentage). *p*-values derived from Chi-square or Fischer's Exact tests, as appropriate. Abbreviations: SGLT2i, Sodium–glucose co-transporter 2 inhibitors; WHF, worsening heart failure.

Table 4. Mortality analysis.

	Univariable			Adjusted Model		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
SLGT2i	0.457	0.227–0.922	0.029	0.177	0.062–0.504	0.001
Age				1.023	0.940–1.113	0.598
Sex, male				0.428	0.151–1.217	0.112
eGFR				0.991	0.961–1.022	0.562
$NT\text{-}proBNP_{(log)}$				2.164	1.221–3.837	0.008
LVEF				0.991	0.949–1.035	0.689
Tafamidis				1.844	0.794–4.285	0.155

Associations between SGLT2i therapy and all-cause mortality. Multivariable model adjusted for age, sex, and clinically significant confounders. Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left-ventricular ejection fraction; $NT\text{-}proBNP_{(log)}$, log-transformed N-terminal pro-brain natriuretic peptide; SGLT2i, Sodium–glucose co-transporter 2 inhibitors.

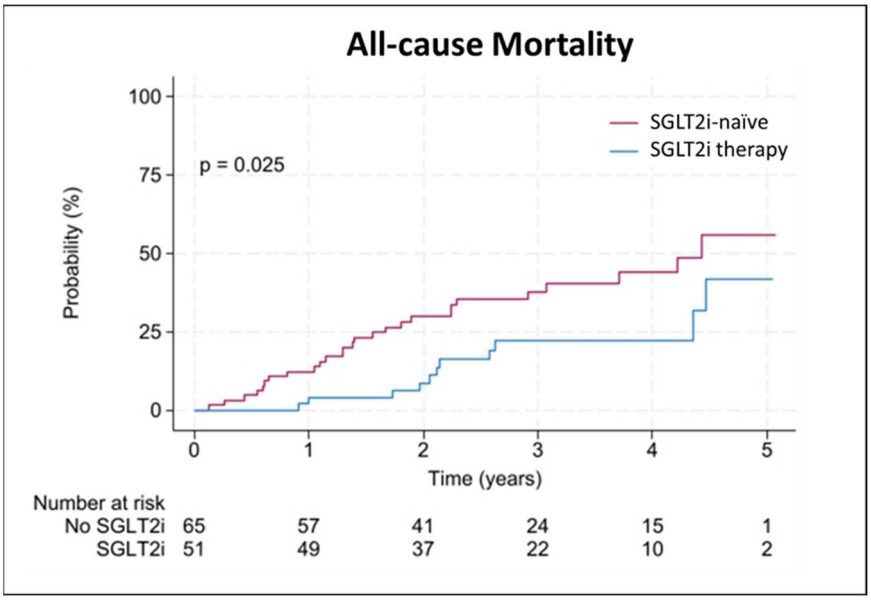


Figure 2. Associations between SGLT2i therapy and all-cause mortality. Kaplan Meier plot illustrating event probability for all-cause mortality with (blue) and without (red) sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy.

Table 5. Cox-regression analysis, including immortal time bias adjustment.

	Univariable			Adjusted Model		
	HR	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
SLGT2i	1.075	0.524–2.206	0.843	0.839	0.352–1.999	0.692
Age				1.035	0.953–1.123	0.415
Sex, male				0.275	0.101–0.753	0.012
eGFR				1.009	0.980–1.039	0.556
$NT\text{-}proBNP_{(log)}$				2.012	1.158–3.495	0.013
LVEF				1.002	0.959–1.048	0.917
Tafamidis				0.979	0.445–2.155	0.959

Associations between SGLT2i therapy and all-cause mortality, including adjustment for immortal time. Multivariable models adjusted for clinically significant confounders. Abbreviations: eGFR, estimated glomerular filtration rate; LVEF, left-ventricular ejection fraction; $NT\text{-}proBNP_{(log)}$, log-transformed N-terminal pro-brain natriuretic peptide; SGLT2i, Sodium–glucose co-transporter 2 inhibitors.

4. Discussion

The present study shows that in patients with heart failure and a diagnosis of ATTR-CM, SGLT2i therapy is significantly associated with a lower mortality. This effect remained significant after adjustment for eGFR, NT-proBNP, LVEF, and concomitant tafamidis therapy. However, after adjustment for immortal time, the association became neutral.

In line with our results, previous reports support the notion that SGLT2i is safe and overall well-tolerated in patients with ATTR-CM [11–14]. Previous large-scale trials on the use of SGLT2i treatment in patients with heart failure also substantiate the benefit of these drugs on major heart-failure outcomes in patients with heart failure regardless of systolic function [5–8]. While ATTR-CM was an exclusion criterion in these trials, large meta-analyses indicate that patients with undiagnosed ATTR-CM may have been unintentionally included in these cohorts and equally benefited [18,19]. The recently published observational study by Porcari and colleagues investigated SGLT2i treatment in patients with ATTR-CM, demonstrating a significant association with lower all-cause mortality (HR 0.57, 95% CI 0.37–0.89, $p = 0.010$), lower cardiovascular mortality (HR 0.41, 95% CI 0.24–0.71, $p < 0.001$), and lower rates of hospitalization due to heart failure (HR 0.57, 95% CI 0.36–0.91, $p = 0.014$) in a propensity score-matched cohort [15]. Regarding all-cause mortality, our

findings suggest that these associations occur independently of renal function, NT-proBNP levels, systolic function, and concomitant tafamidis therapy. However, accounting for the immortal time bias, any association became neutral in our cohort. This bias has often been neglected in previous observational cohort studies evaluating drug effects—which may have created illusional and overoptimistic treatment effects [20]. In observational studies, treatment may be initiated after baseline examination and during the observational period, indicating a treatment-naïve period of patients within the treatment group. Inherent to the study design, the outcome event cannot occur during this treatment-naïve period so that patients within the treatment group are "immortal" before exposure. Several approaches can be applied to account for this potential immortal time bias [20,21]. An increased awareness of immortal time bias should be applied to all observational cohort studies. Nevertheless, even after accounting for this bias, observational cohorts remain susceptible to other potential biases, especially regarding selection, indication, and confounders. Given the neutrality of our results in context with positive associations observed in larger observational studies, a randomized controlled trial is warranted to better inform about the real effects of SGLT2i in ATTR-CM.

Another possible method to further address the impact of SGLT2i treatment in patients with ATTR-CM might be the usage of large-scale registries of health systems with emulation of randomized controlled trials. In the absence of evidence from classical randomized controlled trials, results from these studies could enhance an understanding of SGLT2i usage in patients with ATTR-CM [22].

An association between SGLT2i treatment and a reduction of atrial fibrillation was described in previous meta-analyses [23]. However, there are conflicting results regarding this association in patients with heart failure, and patients with ATTR-CM were not intentionally represented in these studies.

4.1. Strengths and Limitations

A major strength of this study, aside from providing real-world data in a non-prespecified cohort of patients with ATTR-CM, is the clear presentation of the potential immortal time bias. However, there are some limitations to this study. The observational nature of the data, the limited sample size, and the single-centre design may provide effect sizes that are considerably greater than those reported in large-scale trials in heart-failure patients, limiting the generalizability of these results. Further, the lack of racial diversity in our cohort, given the foremost white ancestry in Austria, does not allow for conclusions on patients with African ancestry. This might be of particular interest considering the predominance of hereditary ATTR-CM in these patients, as reported in studies based in the United States, and warrants further investigations [24]. Due to the low number of cardiovascular events, related outcome associations may be subject to a type-2 error. Furthermore, indication bias may have played a role in the introduction of SGLT2i treatment in these patients. Although our findings remained significant after adjusting for confounding variables, we cannot exclude the presence of other confounders not accounted for.

4.2. Conclusions

Patients with heart failure and ATTR-CM represent a high-risk population with continued unmet therapeutic needs. In crude analysis, SGLT2i treatment is associated with better survival in these patients; however, after adjusting for immortal time, this association becomes neutral in our cohort. Hence, to clarify these findings and draw final conclusions on the effectiveness of SGLT2i therapy in patients with ATTR-CM, a randomized controlled trial is warranted.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm13195966/s1, Figure S1. Landmark analysis; Table S1. Incidence rates; Table S2. Outcome analysis; Table S3. Outcome analysis with immortal time bias adjustment.

Author Contributions: Conceptualization, N.V. and H.S.; methodology, N.S., F.A., H.S. and N.V.; software F.A.; validation, D.v.L., H.S. and N.V.; formal analysis, F.A.; investigation, N.S., D.K.Z., V.S., V.H., M.W., J.G., D.v.L., E.K., K.A. and N.V.; resources, A.Z. and N.V.; data curation, N.S., C.T. and J.L; writing—original draft preparation, N.S.; writing—review and editing, C.T., D.K.Z., V.S., V.H., J.L., M.W., J.G., F.A., D.v.L., E.K., K.A., A.Z., H.S. and N.V.; visualization, N.S. and F.A.; supervision, E.K., A.Z. and N.V.; project administration, H.S. and N.V.; funding acquisition, K.A. and N.V. All authors have read and agreed to the published version of the manuscript.

Funding: The Graz HCM Registry was supported by unrestricted research grants from Pfizer, Bristol-Myers Squibb, Takeda Pharmaceuticals, Boehringer Ingelheim, and Swedish Orphan Biovitrum AB.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Graz (EC-No. 30-286 ex 17/18; 28 June 2018). All participants provided written informed consent.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgments: We would like to thank all our patients who participated in this study. We would like to thank the Doctoral School "Translational Molecular and Cellular Biosciences" of the Medical University of Graz for its support.

Conflicts of Interest: H.S. is on the advisory board and speakers bureau of Boehringer Ingelheim, NovoNordisk, Amgen, AstraZeneca, Bayer, Eli Lilly, Cancom, MSD, and Daiichi Sankyo. N.V. has received an unrestricted grant from Boehringer Ingelheim. All other authors report no conflicts of interest.

References

1. Lane, T.; Fontana, M.; Martinez-Naharro, A.; Quarta, C.C.; Whelan, C.J.; Petrie, A.; Rowczenio, D.M.; Gilbertson, J.A.; Hutt, D.F.; Rezk, T.; et al. Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. *Circulation* **2019**, *140*, 16–26. [CrossRef]
2. Maurer, M.S.; Schwartz, J.H.; Gundapaneni, B.; Elliott, P.M.; Merlini, G.; Waddington-Cruz, M.; Kristen, A.V.; Grogan, M.; Witteles, R.; Damy, T.; et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N. Engl. J. Med.* **2018**, *379*, 1007–1016. [CrossRef]
3. Lohrmann, G.; Pipilas, A.; Mussinelli, R.; Gopal, D.M.; Berk, J.L.; Connors, L.H.; Vellanki, N.; Hellawell, J.; Siddiqi, O.K.; Fox, J.; et al. Stabilization of Cardiac Function With Diflunisal in Transthyretin (ATTR) Cardiac Amyloidosis. *J. Card. Fail.* **2020**, *26*, 753–759. [CrossRef]
4. Ioannou, A.; Fontana, M.; Gillmore, J.D. RNA Targeting and Gene Editing Strategies for Transthyretin Amyloidosis. *BioDrugs* **2023**, *37*, 127–142. [CrossRef]
5. McMurray, J.J.V.; Solomon, S.D.; Inzucchi, S.E.; Kober, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Belohlavek, J.; et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2019**, *381*, 1995–2008. [CrossRef]
6. Solomon, S.D.; McMurray, J.J.V.; Claggett, B.; de Boer, R.A.; DeMets, D.; Hernandez, A.F.; Inzucchi, S.E.; Kosiborod, M.N.; Lam, C.S.P.; Martinez, F.; et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N. Engl. J. Med.* **2022**, *387*, 1089–1098. [CrossRef]
7. Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Bocchi, E.; Bohm, M.; Brunner-La Rocca, H.P.; Choi, D.J.; Chopra, V.; Chuquiure-Valenzuela, E.; et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N. Engl. J. Med.* **2021**, *385*, 1451–1461. [CrossRef]
8. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Pocock, S.J.; Carson, P.; Anand, I.; Doehner, W.; Haass, M.; et al. Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. *Circulation* **2021**, *143*, 326–336. [CrossRef]
9. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Bohm, M.; Burri, H.; Butler, J.; Celutkiene, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef]
10. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Bohm, M.; Burri, H.; Butler, J.; Celutkiene, J.; Chioncel, O.; et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2023**, *44*, 3627–3639. [CrossRef]
11. Dobner, S.; Bernhard, B.; Asatryan, B.; Windecker, S.; Stortecky, S.; Pilgrim, T.; Grani, C.; Hunziker, L. SGLT2 inhibitor therapy for transthyretin amyloid cardiomyopathy: Early tolerance and clinical response to dapagliflozin. *ESC Heart Fail.* **2023**, *10*, 397–404. [CrossRef]

12. Lang, F.M.; Teruya, S.; Weinsaft, A.; Cuomo, M.; Santos, A.M.; Nalbandian, A.; Bampatsias, D.; Maurer, M.S. Sodium-glucose cotransporter 2 inhibitors for transthyretin amyloid cardiomyopathy: Analyses of short-term efficacy and safety. *Eur. J. Heart Fail.* **2024**, *26*, 938–947. [CrossRef]
13. Steinhardt, M.J.; Cejka, V.; Chen, M.; Bauerlein, S.; Schafer, J.; Adrah, A.; Ihne-Schubert, S.M.; Papagianni, A.; Kortum, K.M.; Morbach, C.; et al. Safety and Tolerability of SGLT2 Inhibitors in Cardiac Amyloidosis-A Clinical Feasibility Study. *J. Clin. Med.* **2024**, *13*, 283. [CrossRef]
14. Minguito-Carazo, C.; Sanchez Munoz, E.; Rodriguez Manero, M.; Martinez-Sande, J.L.; Fidalgo Andres, M.L.; Garcia Seara, J.; Gonzalez Rebollo, J.M.; Rodriguez Santamarta, M.; Gonzalez Melchor, L.; Gonzalez Ferrero, T.; et al. Impact of initiation of SGLT2 inhibitor treatment on the development of arrhythmias in patients with implantable cardiac devices. *Rev. Esp. Cardiol.* **2024**, *77*, 481–489. [CrossRef]
15. Porcari, A.; Cappelli, F.; Nitsche, C.; Tomasoni, D.; Sinigiani, G.; Longhi, S.; Bordignon, L.; Masri, A.; Serenelli, M.; Urey, M.; et al. SGLT2 Inhibitor Therapy in Patients With Transthyretin Amyloid Cardiomyopathy. *J. Am. Coll. Cardiol.* **2024**, *83*, 2411–2422. [CrossRef]
16. Garcia-Pavia, P.; Rapezzi, C.; Adler, Y.; Arad, M.; Basso, C.; Brucato, A.; Burazor, I.; Caforio, A.L.P.; Damy, T.; Eriksson, U.; et al. Diagnosis and treatment of cardiac amyloidosis: A position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur. Heart J.* **2021**, *42*, 1554–1568. [CrossRef]
17. Hicks, K.A.; Mahaffey, K.W.; Mehran, R.; Nissen, S.E.; Wiviott, S.D.; Dunn, B.; Solomon, S.D.; Marler, J.R.; Teerlink, J.R.; Farb, A.; et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *Circulation* **2018**, *137*, 961–972. [CrossRef]
18. Magdi, M.; Mostafa, M.R.; Abusnina, W.; Al-Abdouh, A.; Doss, R.; Mohamed, S.; Ekpo, C.P.; Alweis, R.; Baibhav, B. A systematic review and meta-analysis of the prevalence of transthyretin amyloidosis in heart failure with preserved ejection fraction. *Am. J. Cardiovasc. Dis.* **2022**, *12*, 102–111.
19. Oghina, S.; Bougouin, W.; Bezard, M.; Kharoubi, M.; Komajda, M.; Cohen-Solal, A.; Mebazaa, A.; Damy, T.; Bodez, D. The Impact of Patients With Cardiac Amyloidosis in HFpEF Trials. *JACC Heart Fail.* **2021**, *9*, 169–178. [CrossRef]
20. Suissa, S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol. Drug Saf.* **2007**, *16*, 241–249. [CrossRef]
21. Zhou, Z.; Rahme, E.; Abrahamowicz, M.; Pilote, L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: A comparison of methods. *Am. J. Epidemiol.* **2005**, *162*, 1016–1023. [CrossRef] [PubMed]
22. Wang, S.V.; Schneeweiss, S.; Initiative, R.-D.; Franklin, J.M.; Desai, R.J.; Feldman, W.; Garry, E.M.; Glynn, R.J.; Lin, K.J.; Paik, J.; et al. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA* **2023**, *329*, 1376–1385. [CrossRef] [PubMed]
23. Mariani, M.V.; Manzi, G.; Pierucci, N.; Laviola, D.; Piro, A.; D'Amato, A.; Filomena, D.; Matteucci, A.; Severino, P.; Miraldi, F.; et al. SGLT2i effect on atrial fibrillation: A network meta-analysis of randomized controlled trials. *J. Cardiovasc. Electrophysiol.* **2024**. *Epub ahead of print*. [CrossRef] [PubMed]
24. Spencer-Bonilla, G.; Njoroge, J.N.; Pearson, K.; Witteles, R.M.; Aras, M.A.; Alexander, K.M. Racial and Ethnic Disparities in Transthyretin Cardiac Amyloidosis. *Curr. Cardiovasc. Risk Rep.* **2021**, *15*, 12170. [CrossRef]