ASSESSMENT OF THE IMPLEMENTATION OF MEDICAL AND DEVICE THERAPY IN HEART FAILURE WITH REDUCED EJECTION FRACTION

PhD thesis

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1 PUBLICATIONS

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TABLE OF CONTENTS

2 ABBREVIATIONS

- 6MWT – Six-minute walk test
- A-HEFT - The African-American Heart Failure Trial
- ACC - American College of Cardiology
- ACEi - Angiotensin-converting-enzyme inhibitor
- AF - Atrial fibrillation
- AHA - American Heart Association
- ARB - Angiotensin receptor blocker
- ARISTOTLE - Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
- ARNI - Angiotensin receptor-neprilysin inhibitor
- AV - Atrio-ventricular
- AVID - Antiarrhythmics Versus Implantable Defibrillators Trial
- B.i.d. - Two times daily
- BIOSTAT-CHF - BIOlogy Study to TAilored Treatment in Chronic Heart Failure BLOCK-HF - Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block
- CAD - Coronary artery disease
- CARE-HF - Cardiac Resynchronization in Heart Failure study
- CASH - The Cardiac Arrest Study Hamburg
- CCM - Cardiac contractility modulation
- CHF - Chronic heart failure
- CI - Confidence Interval
- CIDS - Canadian Implantable Defibrillator Study
- COMPANION - Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial
- CRT - Cardiac resynchronization therapy
- CRT-D - Cardiac resynchronization therapy - defibrillator
- CRT-P - Cardiac resynchronization therapy - pacemaker

- CV - Cardiovascular
- DANISH - The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality
- DAPA-HF - Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
- DAVID - Dual Chamber and VVI Implantable Defibrillator Trial
- DEFINITE - Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial
- DIG - Digitalis Investigation Group
- DIGIT-HF - Digitoxin to improve outcomes in patients with advanced chronic heart failure
- EACVI - European Association of Cardiovascular Imaging
- E.g. - Exempli gratia
- eGFR - Estimated glomerular filtration rate
- EMPEROR-REDUCED - Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction
- EMPHASIS-HF - Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
- ESC - European Society of Cardiology
- ESC HF-LT - The European Society of Cardiology Heart Failure Long-Term Registry
- EVITA-HF - Evidence Based Treatment - Heart Failure
- FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure)
- F.c. - Functional classification
- GWTG - Get With The Guidelines
- HF - Heart failure
- HFimpEF - HF with improved EF
- HFmrEF - Heart failure with mildly reduced ejection fraction
- HFOC - Heart failure outpatient clinic
- HFpEF - Heart failure with preserved ejection fraction
- HFrEF - Heart failure with reduced ejection fraction
- HFSA - Heart Failure Society of America

- HR - Hazard ratio
- ICD - Implantable cardioverter-defibrillator
- LBBB - Left Bundle Branch Block
- LoE - Level of evidence
- LV - Left ventricular
- LVEF - Left ventricular ejection fraction
- MADIT I - Multicenter Automatic Defibrillator Implantation Trial I
- MADIT II - Multicenter Automatic Defibrillator Implantation Trial II
- MADIT-CRT - Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
- MADIT-RIT - Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy
- MCS - Mechanical circulatory support
- MI - Myocardial infarction
- MLWHFQ - Minnesota Living With Heart Failure Questionnaire
- MOST - Mode Selection Trial
- MRA - Mineralocorticoid receptor antagonist
- MUSTT - Multicenter unsustained tachycardia trial
- NP - Natriuretic peptide
- NT-proBNP - N-terminal pro B-type natriuretic peptide
- NYHA - New York Heart Association
- O.d. - Once daily
- OMT - Optimized medical therapy
- PARADIGM-HF - Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
- PREVEND - Prevention of Renal and Vascular Endstage Disease
- RAFT - Resynchronization–Defibrillation for Ambulatory Heart Failure Trial
- RALES - Randomized Aldactone Evaluation Study
- RATE-AF Rate Control Therapy Evaluation in Permanent Atrial Fibrillation
- RCT - Randomized controlled trial
- RV - Right ventricular

- S-ICD - Subcutaneous ICD
- SCD - Sudden cardiac death
- SCD-HeFT - Sudden Cardiac Death in Heart Failure Trial
- SDC - Serum digoxin concentration
- SGLT2i - Sodium-glucose cotransporter-2 inhibitors
- SHIFT - Systolic Heart Failure Treatment with the If inhibitor ivabradine trial
- SOLVD - Studies of Left Ventricular Dysfunction Trial
- SR - sinus rhythm
- T.i.d. - Three times daily
- TD - Target dose
- V-HEFT - Vasodilator Heart Failure Trial
- VAD - Ventricular assist device
- VF - Ventricular fibrillation
- VICTORIA - Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction
- VO2max - Peak oxygen consumption
- VT - Ventricular tachycardia
- βB - Beta receptor blocker

3 INTRODUCTION

Heart disease represents one of the most common mortality causes worldwide, even nowadays. Across the whole heart disease spectrum, heart failure (HF) indicates huge importance due to its high morbidity and mortality observed in the last decades despite the considerable improvement achieved in its treatment.

3.1 Definition and terminology of heart failure

HF is a complex clinical syndrome with the presence of typical/atypical symptoms (exempli gratia [e.g.] breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) [1] caused by a structural and/or functional cardiac abnormality. This definition of HF approved in the 2021 European Society of Cardiology (ESC) HF Guidelines is predominantly similar to the definition applied in the 2021 Universal Definition and Classification of Heart Failure Consensus Report of the Heart Failure Society of America (HFSA), Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society [2]. However, in this Consensus Report, the definition of HF, besides the signs and symptoms, is corroborated by elevated natriuretic peptides (NPs) level and/or objective evidence of cardiogenic pulmonary or systemic congestion [2]. In light of the definition used in the latest ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure published in 2021, heart failure can be classified into phenotypes using the evaluation of left ventricular ejection fraction (LVEF). In accordance with that, those patients with an LVEF≤40%, most frequently measured by echocardiography following the standards approved in the European Association of Cardiovascular Imaging (EACVI) position paper [3], hence those with significantly impaired left ventricular (LV) systolic function have a HF with reduced ejection fraction (HFrEF) [1]. According to the 2021 ESC HF Guidelines, those patients belong to the Heart Failure with mildly reduced ejection fraction (HFmrEF) phenotype who present with an LVEF between 41% and 49%. Last but not least, the patients with symptoms and signs of HF with evidence of structural and/or functional cardiac abnormalities representing evidence of presence of LV diastolic dysfunction/raised LV filling pressures and/or raised NPs and having an LVEF≥50% fall into the group of the

phenotype of heart failure with preserved ejection fraction (HFpEF). Moreover, firstly in the 2021 Universal Definition and Classification of Heart Failure Consensus Report, a new HF phenotype was distinguished beside the aforementioned forms. According to that, those patients belong to the HF with improved EF (HFimpEF) group who had baseline an LVEF≤40% and demonstrate a ≥10% increase from baseline LVEF, and a second measurement of LVEF>40%.

Alongside the heart failure caused by the left ventricular dysfunction, an important separate phenotype is heart failure originating from the right ventricular (RV) dysfunction not related to the left ventricle abnormality [4]. Finally, an often used nomenclature regarding the classification of heart failure, whether it is "chronic", having an already known diagnosis or "acute" heart failure.

Historically probably the most used terminology to describe the severity of heart failure is the New York Heart Association (NYHA) functional classification (f.c.) which exclusively depends on the symptoms. Those patients belong to NYHA I f.c., who have no limitation of physical activity. Patients in NYHA II f.c. have slight, while those in NYHA III f.c. have marked functional capacity limitations. The ones in NYHA IV f.c. cannot perform any activity due to their symptoms at rest. However, it must be highlighted that several more sophisticated, detailed options exist to properly classify the severity of heart failure and to predict the prognosis.

According to the American College of Cardiology (ACC) and American Heart Association (AHA) stages of HF those patients who have risk factors for developing HF integrate to stage A. Stage B covers those patients without current or previous signs/symptoms of HF having structural heart disease and/or evidence of elevated filling pressures, or patients with risk factors of HF and increased levels of NPs and/or cardiac biomarkers in the absence of competing diagnoses resulting in their elevation. The patients with structural heart disease with current or previous symptoms of HF represent stage C HF. Finally, those belong to the group of Stage D who have significant HF symptoms that interfere with daily life and have recurrent hospitalizations in spite of the optimized treatment [5]. In each stage, it is essential to apply specific, proper therapeutic modalities either to modulate the causative risk factors or to cure the underlying heart disease to improve the global prognosis.

3.2 Epidemiology of heart failure

Recent data shows that even nowadays, more than 60 million patients worldwide have been suffering from HF [6]. According to the analysis of the Framingham Heart Study by Lloyd-Jones et al., among those who had not had a diagnosis of HF at baseline, the lifetime risk for developing chronic heart failure (CHF) affected every fifth man and woman [7]. In the Rotterdam Study the overall lifetime hazard of HF was similar in both sexes, estimated at 33% for men and 29% for women at the age of 55 years [8]. The prevalence of CHF has been rising [9], especially with the aging population. In the United States of America (USA), according to the current tendencies of 5.8 million patients suffering from heart failure, the proportion of patients with HF will probably increase to 8.5 million by 2030 [10]. Pursuant to the studies examining the epidemiology trends in heart failure, the prevalence of the disease is about 1-2% [6,11] in adults, which increases with aging. We have observational data regarding the prevalence of heart failure in Hungary. In accordance with the analysis of Tomcsányi et al., based on the data collected from the National Health Insurance Fund of Hungary Database in 2017 [12], the prevalence of heart failure was 1.1%. In accordance with the results of several previously published studies, among those patients diagnosed and hospitalized with heart failure, around 50% belong to the subgroup of HFrEF, while 50% to the cohorts of HFpEF and HFmrEF [1].

In line with the outcomes of a large population-based analysis assessing the electronic health records of 4 million individuals from 2002 to 2014 in the United Kingdom (UK), however moderate decrease could be observed in the incidence of heart failure, the importance of the disease has been rising representing a significant health care problem even nowadays [13]. According to the analysis of Prevention of Renal and Vascular Endstage Disease (PREVEND) study by Meyer et al., in Europe the contemporaneous incidence of heart failure is 5/1000 person-years among adults [14].

However, it has to be highlighted that its often atypical symptoms can frequently lead to misdiagnosis and the underestimation of the prevalence of heart failure [15]. It is thought-provoking that in the research of van Riet et al. among community-dwelling persons aged 65 years or more with shortness of breath on exertion, the unrecognized HF was unexpectedly common (15.7% [95% CI:12.9–19.0]) [16]. Not surprising that even the previous ESC HF Guidelines of 2016 [17] already highlighted the importance of the comorbidities. Hence these

comorbidities could interfere in countless ways with the diagnostic process of HF, as it had been elegantly presented in the article by van Riet et al.

In the analysis of Crespo-Leiro et al. of the ESC-HF Long Term (ESC-HF-LT) Registry, which is one of the largest recent databases focusing on HF patients, the epidemiology, treatment, morbidity, and mortality of heart failure were examined. They found an all-cause, 1-year mortality rate of 6.4% for CHF [18] and 23.6% for acutely hospitalized patients. In accordance with the ESC-HF-LT Registry data, 14.5% of patients with chronic stable heart failure died or were hospitalized within one year [18]. Even in the illustrious Prospective Comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial at the end of the median 27 months follow-up, the mortality rate was unfavourably high (18.3%) in spite of the high-quality medication applied [19]. The prognosis is even worse for patients admitted for acute heart failure [20,21]. In the Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction (VICTORIA) trial, which assessed the impact of vericiguat among HF patients with signs of worsening heart failure, the mortality was 20.3% in the vericiguat group over the 10.8 months follow-up [22]. A study by Mamas et al. evaluated the life expectations of patients with HF in comparison with those suffering from the most common cancers. Despite the improvement of the complex care implemented for HF, they found an overall prognosis still comparable with those affected by one of several common cancers [23].

The burden of rehospitalizations among heart failure patients still represents a substantial global challenge in the health care system. According to the ESC-HF-LT Registry analysis outcomes, the rehospitalization rate during the median follow-up time (373 days) was 24.9% among CHF patients, while it was 37.9% in the acute heart failure cohort. As a consequence of the contemporary trends caused by the aging population, the comorbidity burden, the prevalence of hospital readmission is expected to rise significantly in heart failure within the next decades [18]. In accordance with the analysis of the Get With The Guidelines (GWTG) Registry Database, the 5-year rehospitalization rate in HF was higher than 80% either in the HFrEF or in the HFpEF cohort of patient [24]. It is well known that the early post-discharge period represents a highly vulnerable phase with a significant burden of adverse events [25]. Corresponding to the Medicare data, from 2009 to 2012, 23% of patients were readmitted within 30 days due to HF progression. Moreover, as it was presented elegantly in

the study of Setoguchi et al., the number of HF hospitalizations was a strong predictor of mortality among HF patients [26].

3.3 Treatment of heart failure with reduced ejection fraction (HFrEF)

3.3.1 Pharmacological treatment of HFrEF

3.3.1.1 *Drugs recommended in all patients with HFrEF*

In accordance with the results of the randomized controlled HFrEF trials published within the last decades, the armamentarium of disease-modifying therapeutic modalities has expanded exponentially. Even today, the inhibition and modulation of the renin-angiotensin-aldosterone and sympathetic nervous system remain the cornerstone of the pharmacological treatment of HFrEF. Hence angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor-neprilysin inhibitor (ARNI), β-blockers (βB), mineralocorticoid receptor antagonists (MRA) complemented by the sodium-glucose cotransporter-2 inhibitor (SGLT2i) dapagliflozin and empagliflozin represent the first-line therapy for HFrEF due to their significant mortality and morbidity reducing effect.

Pursuant to the result of the β-blocker randomized controlled trials (RCTs) [27-31], the application of bisoprolol, metoprolol-succinate, carvedilol, and nebivolol is recommended in HFrEF by the ESC 2021 HF Guidelines. Based on the current and previous HF Guidelines, the beneficial effect of ACEi in HFrEF is considered a class effect, therefore any ACEi can be applied as a therapeutic option for HFrEF patients [32-35]. In line with the results of the Randomized Aldactone Evaluation Study (RALES) [36] and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trials [37], treatment with spironolactone or eplerenone is recommended in HFrEF to improve the prognosis. As a consequence of the result of the PARADIGM-HF trial [19] published in 2014, sacubitril/valsartan, a first-in-class angiotensin receptor-neprilysin inhibitor, was superior to enalapril at reducing the risk of cardiovascular (CV) mortality or heart failure hospitalization (hazard ratio [HR]: 0.80; $p<0.001$), cardiovascular death (HR: 0.80; $p<0.001$), hospitalization for heart failure (HR: 0.79; $p<0.001$), and all-cause mortality (HR: 0.84; $p<0.001$). Accordingly, the utilization of sacubitril/valsartan is recommended as a replacement for an

ACEi in patients with HFrEF to reduce the risk of HF hospitalization and death [1] with Class I recommendation with Level of Evidence (LoE) B by the ESC 2021 HF Guidelines. Moreover, in the AHA/ACC/HFSA 2022 HF Guidelines, in terms of HFrEF, the application of ARNI is recommended for symptomatic patients (NYHA II-III f.c.) with Class I recommendation with LoE A to improve the prognosis. According to the AHA/ACC/HFSA 2022 HF Guidelines, the implementation of an ACEi is essential when the application of ARNI is not possible [5]. Correspondingly to the results of the recently published Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) [38] and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-REDUCED) [39] trials, the use of sodium-glucose cotransporter-2 inhibitor empagliflozin and dapagliflozin is recommended in HFrEF with Class I recommendation with LoE A. The two studies clearly demonstrated that these SGLT2 inhibitors significantly reduce the mortality and morbidity in HFrEF. It has to be highlighted as well that the mortality-reducing advantageous effect of dapagliflozin and empagliflozin was not different between patients with or without diabetes. Pursuant to the results of these aforementioned trials, SGLT2i empagliflozin and dapagliflozin have become the fourth pillar of the disease-modifying drug regime of HFrEF [40]. In HFrEF, the application of all of these drugs (ARNI/ACEi, βB, MRA, and SGLT2i) is essential in all patients with Class I recommendation unless there is any presence of contraindication or intolerance. These drugs have to be uptitrated to their target doses or the maximum tolerated doses as concluded in the ESC 2021 HF Guidelines. We have data demonstrating a robust positive effect of these drugs early after the initiation of the treatment. Hence we must insist on applying all of these drugs as soon as possible after the definitive diagnosis of HFrEF [41].

The importance of the "lege artis" implementation of the comprehensive disease-modifying drug regime was highlighted elegantly with the cross-trial analysis of Vaduganathan et al., in which the use of the guideline-directed medical treatment (ARNI, β-blocker, MRA, and SGLT2 inhibitor) compared to the previously gold-standard conventional therapy (ACE inhibitor or angiotensin receptor blocker [ARB] and β-blocker) resulted in a robust estimated hazard risk reduction as regards the primary end point of cardiovascular death or hospital admission for heart failure (HR: 0.38; [95% CI: 0.30–0.47]) [42]. However, based on the data from the recently published ESC HF-LT Registry, although the proportion of HFrEF patients receiving the disease-modifying neurohormonal antagonists has increased significantly within

the last decade, the ratio of patients at the target doses of these drugs is still considerably lower as opposed to the landmark HFrEF trials' results [18]. It has to be underscored as well that maintenance of the long-term adherence to these medications is frequently challenging because of their potential side effects resulting in a significant decrease in the use of the renin-angiotensin-aldosterone system inhibitors even within the first 12 months [43] after their initiation.

3.3.1.2 *Other drugs recommended or to be considered in selected HFrEF patients*

The 2021 ESC HF Guidelines include six drugs or groups of drugs in this category: the ARBs, diuretics, ivabradine, hydralazine-isosorbide-dinitrate combination, digoxin, and a soluble guanylate cyclase vericiguat. These agents are also known as second-line treatments for HFrEF.

Pursuant to the 2021 ESC HF Guidelines, the ARBs [44] are recommended for those HFrEF patients who cannot tolerate the use of ACEi-s and sacubitril/valsartan.

However, even today, we do not have any RCT data investigating the effect of diuretics on the prognosis of HFrEF. Therefore, it must be underlined that in the majority of the aforementioned landmark RCTs in HFrEF, most enrolled patients received diuretics as background therapy [1], and the daily clinical practice also shows that most HFrEF patients cannot be handled without diuretics because of the fluid retention. Therefore, understandably to that, besides the disease-modifying drugs, the implementation of loop diuretics is recommended in line with the ESC 2021 HF Guidelines with Class I recommendation LoE C in order to reduce the congestion and to improve the quality of life of these HFrEF patients.

In accordance with the 2021 ESC HF Guidelines, the use of ivabradine and hydralazine-isosorbide-dinitrate combination should be considered to reduce the risk of HF hospitalization and death for selected HFrEF patients. In the Systolic Heart Failure Treatment with the If inhibitor ivabradine trial (SHIFT), the implementation of ivabradine as an addition to the standard treatment significantly decreased the risk of the composite of CV mortality and HF hospitalization in patients with symptomatic HFrEF with an LVEF≤35%, in the presence of sinus rhythm (SR) with a heart rate 70≥ beats per minute (b.p.m) [45].

The application of the hydralazine-isosorbide-dinitrate combination represented one of

the first effective therapeutic options in HFrEF for years in the late 1980s [46]. Based on the African-American Heart Failure Trial (A-HEFT) outcomes, among self-identified black patients suffering from HFrEF, the implementation of the hydralazine-isosorbide-dinitrate combination led to a remarkable benefit in mortality and HF hospitalizations [47]. In light of the outcomes of the Vasodilator Heart Failure Trial I (V-HEFT I), in the 2021 ESC HF Guidelines the implementation of hydralazine-isosorbide-dinitrate combination is considered as a therapeutic option for those HFrEF patients who cannot tolerate any of an ACEi, an ARB, or ARNI (or they are contraindicated) to reduce the risk of death [48].

Besides the above-mentioned potential therapeutic possibilities, several RCTs assessing the impact of drugs with different mechanisms of action, showed remarkable results in HFrEF. With the inclusion of 5050 patients suffering from symptomatic, recently decompensated HF (LVEF<45%), in the VICTORIA trial, the implementation of vericiguat translated into a significant decrease in the risk of the primary composite end point of CV death or first hospitalization for heart failure as compared with placebo. Pursuant to the trial outcomes and the ESC 2021 HF Guidelines, the use of the oral soluble guanylate cyclase receptor stimulator vericiguat may be considered to reduce the risk of CV mortality and hospitalizations for HF as an add-on therapy [22].

3.3.1.3 *The place of digoxin in the pharmacological treatment of HFrEF*

Digoxin is one of the most well-known historical drugs in the cardiology armamentarium and one of the second-line agents for HFrEF treatment. The first publication regarding its efficacy was dated 1785 by William Withering. Heart failure and atrial fibrillation (AF) represent the main indications for its implementation. However, digoxin has been used widely within the last decades, until nowadays only one RCT has assessed its impact on the prognosis [49] in HFrEF. In the Digitalis Investigation Group (DIG) study, among HFrEF patients presenting with SR, the application of digoxin failed to improve all-cause mortality; however, a significant reduction in hospitalization caused by worsening HF was revealed. It is essential to highlight that among patients with AF, until recently, it has not published any RCT examining the effect of digoxin on mortality and morbidity.

After the main publication, several observational studies [50-53], post-hoc analyses of

RCTs [54-57], and meta-analyses [58-60] have been revealed assessing the impact of digoxin on the prognosis in HF and/or AF. Most of these non-randomized publications verified a potentially harmful effect of digoxin in terms of mortality. In light of the outcomes of these above-mentioned publications, the place of digoxin in the treatment hierarchy of HFrEF has been substantially modified over the last decade.

Consequently, in the ESC 2021 and the AHA/ACC/HFSA 2022 HF Guidelines, the implementation of digoxin may be considered for patient with HFrEF in SR who remains symptomatic after the optimization of the cornerstone HFrEF treatment (Class IIb recommendation LoE B) [1,5]. Although it has to be underlined that, in the vast majority of the studies assessing the impact of digoxin, serum digoxin concentration (SDC) either was not controlled at all or was measured only occasionally. The most recent meta-analysis examining the data of 825.000 patients revealed that the application of digoxin unfavourably modified the mortality in AF and HF [61]. Notably, only 10 of the 37 studies reported data on daily digoxin dose and/or data on SDC [49,51,62-69]. In the aforementioned publications remains the concern that the mortality-increasing effect of digoxin may be connected to the lack of control of SDC and consequently elevated SDCs. Furthermore, due to the potentially incomplete adjustment of all the potentially influencing confounders, the observed digoxin-associated mortality increase might be due to the more frequent use of this drug among sicker patients [70]. It has to be highlighted as well that based on the result of several studies, discontinuation of digoxin could lead to adverse events, deterioration of heart failure, moreover poorer prognosis [71].

As a result of the current HF guidelines [1,5,17], although the application rate of digoxin has declined significantly, digoxin still affects large patient populations [18]. In accordance with the data of the ESC-HF Pilot Survey, ~30% of hospitalized and 20% of ambulatory HF patients were treated with digoxin [72]. According to the outcomes of several observational studies, a 50% reduction was revealed in the digoxin implementation rate between 2007-2014 [73]. Putting the clinical problem with digoxin in context, even in the recently published DAPA-HF trial, the proportion of patients on digoxin was 18.8% [38]. Given the lack of trials that have assessed the impact of SDC-guided digoxin therapy on prognosis, the evaluation of the effect of digoxin on mortality among HFrEF patients was mandatory, where digoxin dose was regularly measured and adjusted based on SDC.

3.3.2 Device therapy of HFrEF

3.3.2.1 *Implantable cardioverter-defibrillator (ICD)*

One of the most frightening consequences of HFrEF is the occurrence of potentially life-threatening malignant ventricular arrhythmias. However, in the effect of the optimized disease-modifying drug treatment with ACEi-s, β-blockers, MRAs, sacubitril/valsartan, and SGLT2 inhibitors, the risk of sudden cardiac death (SCD) has decreased significantly [74], it still represents a considerable issue. Regarding the complex treatment of heart failure, the introduction of ICD has been a huge step forward.

In agreement with the current 2021 ESC HF Guidelines, as primary prevention, the use of ICD is recommended in HFrEF with ischemic etiology with Class I recommendation LoE A (without a previous myocardial infarction within 40 days before the implantation) for symptomatic (NYHA II-III) patients with LVEF≤35% in spite of the three months optimal medical therapy (OMT) with the expectation of survival longer than one year with good functional status [1].

The efficacy of the primary prevention ICD implantation among HFrEF patients with ischemic etiology was examined in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) I [75], MADIT II [76], Multicenter UnSustained Tachycardia Trial (MUSTT) [77] and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [78], which confirmed the superiority of ICD therapy in comparison with conservative drug treatment. The MADIT I trial assessed the impact of ICD application among HFrEF patients with ischemic etiology and mild to moderate symptoms (NYHA I-III) with a history of asymptomatic, non-sustained ventricular tachycardia (VT) in whom sustained VT or ventricular fibrillation (VF) was reproducibly induced during electrophysiologic study. During a mean follow-up of 27 months, in the ICD arm, a significant amelioration of all-cause mortality risk was confirmed. Among HFrEF patients with ischemic etiology, the MADIT II revealed that the utilization of an ICD with primary prevention favourably modified the prognosis - risk of all-cause mortality reduction in the ICD arm (HR: 0.69; [95% CI: 0.51-0.93]; p= 0.016 - [76].

In accordance with the 2021 ESC HF Guidelines, the primary prevention implantation

of an ICD should be considered for a non-ischemic patient with NYHA II-III functional class and LVEF ≤35% in spite of the three months OMT with the expectation of survival longer than one year with good functional status with Class IIa recommendation LoE A. The potential survival benefit of a primary prevention ICD use in these clinical circumstances was assessed in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE), Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and in the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) study. However, in the DEFINITE trial, the ICD therapy did not significantly modify the all-cause mortality, a significant reduction in the SCD rate was verified [79]. In the SCD-HeFT study among ischemic and non-ischemic HFrEF patients, a significant overall mortality reduction was confirmed in the ICD arm in contrast to the conservative treatment control group, and there was no significant difference in terms of the ICD efficacy according to the etiology of HFrEF [78].

The paradigm shift regarding the ICD efficacy and the Guidelines' recommendations of the primary prevention ICD implementation among non-ischemic HFrEF patients was the consequence of the results of the DANISH trial [80]. In this landmark RCT, 1116 non-ischemic HFrEF patients were randomized to either the ICD group or the control group. After a median follow-up period of 67.6 months, there was just a non-significant risk reduction in all-cause death rate detected in the ICD arm in comparison with the control group (HR: 0.87; [95% CI: 0.68-1.12]; p=0.28), however, according to the subgroup analysis among patients with <68 years the ICD therapy led to a significant risk reduction in terms of all-cause death (HR: 0.64; [95% CI: 0.45-0.90]; p = 0.01). It has to be highlighted as well that in this trial, in 58% of the randomized patients, a cardiac resynchronization therapy (CRT) device was applied, and the occurrence of the SCD was moderately low (70/1116 patients during the 5-year follow-period, e.g.).

The implementation of the ICD treatment is a crucial element in the armamentarium of SCD prevention, however, it is well-known that the inappropriate ICD therapy is frequent and can unfavourably modify the prognosis [81]. In the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) [82] study, 1500 patients with primary-prevention ICD system were randomly assigned to either "programmed high-rate" or "delayed programming" ICD therapy or conventional ICD treatment. According to the study's results, the "high-rate" and "delayed" ICD programming led to significant risk reductions in

terms of the first occurrence of inappropriate therapy and, moreover, the all-cause mortality.

The Antiarrhythmics Versus Implantable Defibrillators Trial (AVID) [83], Canadian Implantable Defibrillator Study (CIDS) [84], and The Cardiac Arrest Study Hamburg (CASH) [85] trials assessed the efficacy of secondary prevention ICD implantation among ischemic and non-ischemic patients after VT/VF. As consistent results of these three trials, in accordance with the ESC 2021 HF Guidelines, as secondary prevention, the implantation of an ICD is recommended with Class I recommendation and LoE A for patients recovered from ventricular arrhythmias causing haemodynamic instability with an expectation of good functional status survival >1 year and without the presence of potentially reversible causes behind the malignant arrhythmias. However, an all-cause mortality reduction in the effect of the ICD therapy was only revealed just in the AVID trial; the arrhythmic mortality risk in both the AVID and CASH trials was decreased in the ICD arm. In line with the results of the meta-analysis of these three trials, an all-cause mortality reduction was confirmed in the effect of ICD treatment compared to the phenomenon observed in the anti-arrhythmic drug cohort (HR: 0.72; [95% CI: 0.60-0.87]; p=0.006) [86].

Over the last few years, new types of defibrillators have become available worldwide. As reported in the ESC 2021 HF Guidelines, the use of a wearable ICD may be considered for patients with HFrEF with a high risk of SCD until implantation of a permanent device, if needed, with Class IIb recommendation LoE B. The use of subcutaneous ICDs (S-ICDs) has increased over the last few years. It seems that the safety and efficacy of this device are comparable with those of the conventional ICD systems, and it can be an alternative option for selected patients in HFrEF [87]. The implantation of this device may be suggested for those with previous explantation of an ICD caused by an infection or who are not a good candidate for transvenous system implantation due to anatomical reasons [1].

3.3.2.2 *Cardiac resynchronization therapy (CRT)*

According to the results of the RCTs published over the last decades, the use of the CRT improves morbidity and mortality in HFrEF among precisely selected patients.

In accordance with the ESC 2021 HF Guidelines, the implementation of CRT is recommended in HFrEF in the presence of SR with a QRS duration≥150 msec and left bundle branch block (LBBB) QRS morphology if LVEF remains ≤35% in spite of OMT with Class I recommendation LoE A [1].

In the Cardiac Resynchronization in Heart Failure Trial (CARE-HF), 813 HFrEF patients on optimized medical therapy (NYHA III-IV, LVEF≤35%, left ventricular end-diastolic dimension≥30 mm - indexed to height-, QRS duration≥120msec) were randomized to either CRT or conservative treatment. Those patients having a QRS duration of 120-149msec had the presence of dyssynchrony as an obligation for randomization - at least two of three additional dyssynchrony parameters. The use of CRT led to an improvement in all-cause mortality (HR: 0.64; [95% CI 0.48-0.85]; p<0.002) in comparison with the conservative treatment over a mean follow-up of 29.4 months [88].

In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, 1520 HFrEF patients were randomly assigned either to CRT-defibrillator (CRT-D) or CRT-P or conservative treatment [89]. Accordingly the results, in contrast to the conservative treatment, the utilization of CRT-P (HR: 0.81; [95% CI: 0.69-0.96]; p=0.014) and CRT-D (HR: 0.80; [95% CI: 0.68-0.95]; p=0.010; adjusted p=0.011) as well generated a significant amelioration in the risk of the composite primary end point of all-cause death and hospitalization for any cause, and CRT-D accompanied with a modest reduction of the secondary outcome of all-cause death (CRT-P HR: 0.76; [95% CI: 0.58-1.01]; p=0.059 vs. CRT-D HR: 0.64; [95% CI: 0.48-0.86]; p=0.003).

In the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) and Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) trials, CRT efficacy was assessed among patients with milder symptoms of HF. In the MADIT-CRT trial, 1820 HFrEF patients with mild symptoms (LVEF≤30%, QRS≥130msec, NYHA I-II) were randomized to either CRT-D or ICD therapy alone. At the end of the mean follow-up of 2.4 years, CRT-D use generated a significant decrease in the composite end point of all-cause death or a nonfatal heart failure event [90]. The

success of CRT-D in this trial was triggered mainly by a 41% reduction in the risk of heart failure events. The long-term effect of the CRT-D in this patient cohort was investigated in the article of Goldenberg et al. After seven years of follow-up, the CRT-D use led to a significant all-cause mortality benefit over the ICD-only arm (HR: 0.59; [95% CI: 0.43-0.80]; p<0.001) [91]. In the RAFT trial, 1798 HFrEF patients were enrolled to either CRT-D or ICD alone (NYHA II-III, LVEF≤30%, QRS≥120msec or paced QRS≥200msec). Parallelly to the MADIT-CRT trial, the CRT-D use was accompanied by a significant reduction in the primary outcome of all-cause mortality or hospitalization for heart failure (HR: 0.75; [95% CI: 0.64-0.87]; p<0.001) [92]. On the basis of the Echo-CRT trial's result, CRT is not recommended if the QRS duration is shorter than 130 msec [93].

As a consequence of the success of these RCTs, CRT became a crucial part of the complex patient care algorithm in HFrEF. However, even today, in almost 20-30% of cases, a significant clinical improvement can not be seen after CRT implantation [94]. Thus, the importance of proper patient selection cannot be highlighted enough in order to reach the most efficient response to CRT.

The unfavourable effect of the permanent RV pacing was confirmed in several trials. In the Mode Selection Trial (MOST) [95], 2010 patients with sinus-node dysfunction were randomized to dual-chamber or ventricular pacing. During the median 33.1 months of follow-up, in the effect of the dual-chamber pacing significant favourable outcomes regarding the signs and symptoms of heart failure and a moderate improvement in terms of the quality of life were verified in contrast to the ventricular pacing. In the Dual Chamber and VVI Implantable Defibrillator Trial (DAVID) trial, 506 HFrEF patients (LVEF≤40%) with no indication for antibradycardia pacing were randomized either to dual-chamber ICD implantation programmed to ventricular backup pacing at 40/min or to dual-chamber ICD implantation programmed to dual-chamber rate-responsive pacing at 70/min [96]. Ventricular backup pacing at 40/min with the elimination of the high ratio of RV pacing generated a significant risk reduction in terms of the combined composite end point of death or hospitalization for heart failure. Similarly to the results of several small studies [97-99], the Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block (BLOCK-HF) trial [100] verified the superiority of biventricular pacing in opposition to the RV pacing regarding the primary composite end point (≥15% increase in the LV end-systolic volume or an urgent care visit for heart failure that required intravenous therapy or mortality) among the enrolled 691 patients with reduced EF

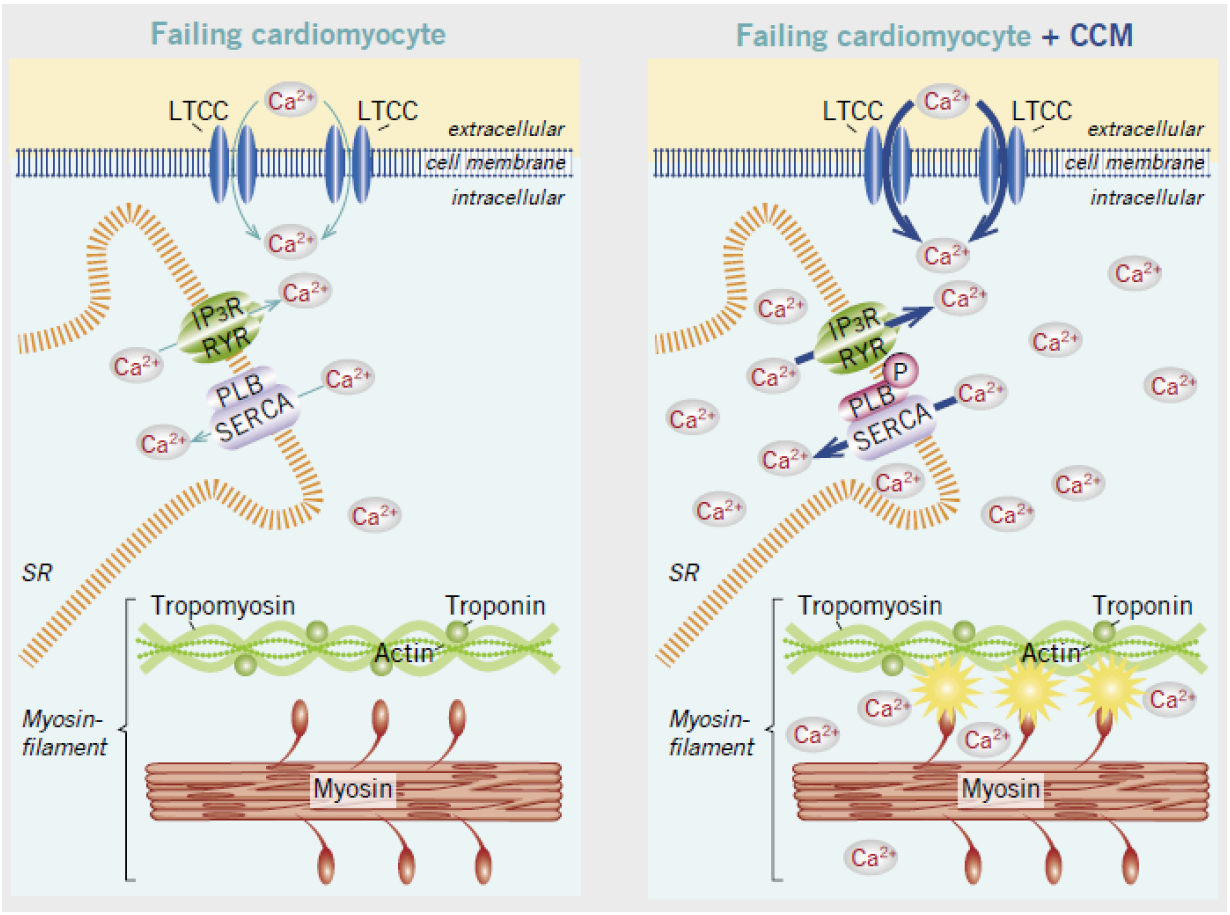
(LVEF≤50%) with atrio-ventricular (AV) node disease and class I or IIa indication for permanent pacing. Based on the results of these aforementioned trials, according to the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy [101], CRT rather than RV pacing is recommended in HFrEF (<40%) irrespective of NYHA functional class for patients having an indication for ventricular pacing and high-degree AV-block with Class I recommendation and LoE A.

Regarding the CRT upgrade among those patients in whom previously a conventional pacemaker or an ICD had been implanted and who afterward would grow signs and/or symptoms of heart failure, we have conflicting observational and registry data [102-104]. Until today the only prospective RCT is the BUDAPEST-CRT trial which hopefully will answer this relevant clinical problem [105]. Based on the already published evidence in accordance with the 2021 ESC HF Guidelines, among these circumstances, the CRT upgrade is considered to be a therapeutic option with Class IIa recommendation and LoE B.

3.3.2.3 *Cardiac contractility modulation (CCM)*

Cardiac contractility modulation (CCM) is a promising implantable device treatment option for patients with HFrEF who are not eligible for CRT. The principle of CCM is the endocardial electric stimulation of the myocardium during its refractory period, which enhances cardiac contractility without an increase in oxygen consumption (Figure 1. and Figure 2.) [106].

Figure 1. Mode of action of Cardiac Contractility Modulation (CCM) [107]



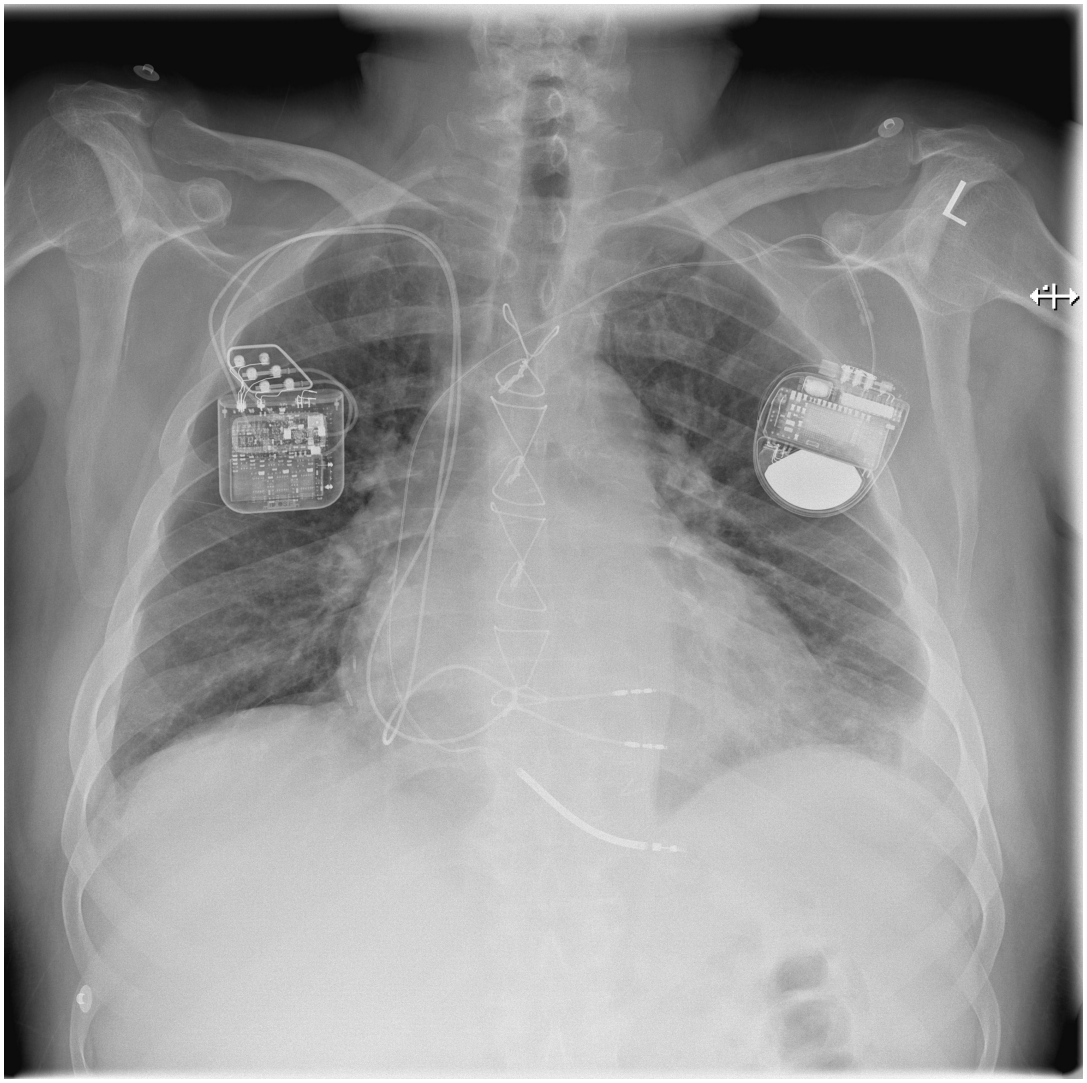
LTCC: L-type voltage-dependent Ca2+channel, SERCA: sarcoendoplasmic reticulum Calcium ATPase, PLB: cardiac phospholamban, IR_3R: inositol trisphosphate receptor, RyR: ryanodine receptor

CCM therapy facilitates the LTCC-mediated Ca^{2+}entry, SERCA2 activity and PLB phosphorylation; hence ameliorates the calcium transfer, and moreover, the contractility (right)

With the courtesy and permission of Impulse Dynamics

The initial feasibility study of CCM focusing on patients suffering from HF with or without ischemic etiology verified that after a few hours of CCM signal application, myocardial contractility improved by 10%. This phenomenon was not modified by the QRS duration and morphology; among patients with left bundle branch block, this effect of CCM was additive to the improvement in contractility resulting from CRT [108].

Figure 2. Chest X-ray of a patient with an ICD device on the left side and a CCM device on the right side



Case of a patient from Klinikum Passau, Department of Internal Medicine III, with courtesy and permission of Dávid Pilecky

With the knowledge of the positive, encouraging acute haemodynamic results observed in the effect of CCM therapy, several randomized and non-randomized studies were initiated to assess the long-term impact of this potential therapeutic modality in HF. These studies have shown that CCM can ameliorate exercise tolerance, functional status, and quality of life [107,109-112]. In addition, the effectiveness of CCM was verified in ischemic and non-ischemic cardiomyopathy as well [113].

The first trial focusing on the long-term effect of CCM in HFrEF was the FIX-HF-3 study in which patients with NYHA functional class III were enrolled (QRS<140msec, LVEF≤35%) [114]. After eight weeks of follow-up, the majority of the cohort experienced a significant improvement in LVEF, NYHA functional class, Minnesota Living With Heart Failure (MLWHF) Questionnaire score, and six-minute walking distance. Besides that, among those patients participating in the extension phase of the FIX-HF-3 study, significant further amelioration was verified in LVEF, peak oxygen consumption (VO2max), and walking distance during the six-minute walk test (6MWT) [115]. Regarding the safety end points of this trial, CCM therapy did not accompany an elevated burden of ventricular or supraventricular tachyarrhythmias. Moreover, a non-significant decrease was confirmed in the occurrence of these events.

The FIX-HF-4 trial assessed the impact of CCM on exercise tolerance and quality of life among HFrEF patients in NYHA II-III functional class and LVEF<35% with double-blind crossover design [109]. In 164 patients, a CCM device was implanted, and afterward, 12 weeks of either active CCM or sham therapy was applied before changing to 12 weeks of the other therapy. In the first three months, in all major clinical end points (VO2max and MLWHFQ score), remarkable improvement was revealed in comparison with the baseline parameters in both treatment arms. It has to be highlighted that this placebo phenomenon verified in the sham therapy arm, parallelly to the result of the Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure (FIX-HF-5) feasibility CCM study [116], was changed to its opposite in the second, inverse phase of the trial. Those patients receiving sham therapy at the second blinded part of the trial after being on active treatment at the first 12 weeks demonstrated a significant deterioration in VO2max and MLWHFQ score, contrary to the other group.

In the FIX-HF-5 study, 428 patients in NYHA III-IV functional class with previously implanted ICD and LVEF≤35%, QRS<130msec were randomly assigned either to OMT or to CCM on top of the OMT [110]. The inclusion criteria were similar to those of the feasibility CCM trial published in 2006 [116]. Although the primary safety non-inferiority composite end point of mortality and hospitalizations for all causes was reached, in terms of efficacy, CCM use did not significantly modify the primary end point of ≥20% increase in the anaerobic threshold at the cardiopulmonary test at 6 months. Interestingly significant improvement was observed in the MLWHFQ score and in the walking distance during 6MWT. A retrospective prespecified

multivariate regression analysis of the FIX-HF-5 study revealed that from the examined factors of baseline LVEF, NYHA functional class, VO2max or etiology of heart failure, NYHA III functional class and LVEF≥25% were independent predictors of CCM efficacy [117]. Potential causes behind the positive effect confirmed in less sick patients are in the focus of research. According to some hypotheses, the aforementioned favourable consequences of CCM implementation could be modified by dilation of the failing ventricle [117], and reduced expression and activity of gap junction proteins in more advanced phases of heart failure [118].

The meta-analysis of the FIX-HF-5 Pilot [116], FIX-HF-4 [109], and FIX-HF-5 [110] trials revealed a significant improvement in VO2max, in the walking distance during 6MWT and in MLWHFQ score after initiation of CCM [119]. Another meta-analysis of CCM RCTs published by Kwong et al. however, failed to demonstrate any significant benefit on mortality or hospitalization in the effect of CCM [120].

In the most recent FIX-HF-5C trial, 160 patients with LVEF≥25% and ≤45%, sinus rhythm, NYHA functional class III-IV, and QRS<130msec were randomized either to continued medical treatment or to additional CCM [107]. Using a Bayesian statistical model, the study also incorporated a subgroup of patients with the same inclusion criteria from the previous FIX-HF-5 study [110]. The implementation of CCM generated a significant improvement at 24 weeks in terms of NYHA functional class, quality of life, and functional capacity (measured by VO2max and 6MWT). Besides that, a significant amelioration was revealed in the composite of cardiovascular death and HF hospitalizations. However, current evidence suggests that those patients with LVEF below 25% do not appear to benefit from CCM therapy.

In the initial CCM trials, a 3-lead (1 to the right atrium and 2 to the right ventricular septum) CCM system was applied. Meanwhile, with the right ventricular leads positioned in the ventricular septum, either sensing or signal delivery is possible, the atrial lead is for sensing only. Recently, a new CCM delivery algorithm has been developed to eliminate the need for an atrial sensing lead. The new 2-lead (ventricular leads only) system was tested in the FIX-HF-5C2 study [121]. In this prospective, multicenter, single-arm trial, the safety and efficacy of this new 2-lead CCM system were evaluated among heart failure patients with NYHA III-IVa functional class and LVEF≥25% and ≤45% in spite of OMT, with sinus rhythm and a QRS duration not eligible for CRT. Regarding the primary effectiveness end point, the estimated difference of exercise tolerance measured by VO2max from baseline to 24 weeks was assessed

between the new 2-lead system and the control group of the FIX-HF-5C study applying the 3-lead system. Besides the improvement confirmed in terms of VO2max and NYHA functional class in the effect of the 2-lead CCM system, a significant diminution in the device-related adverse events was verified in that group. The signal delivery effectiveness was comparable between the 2-lead and 3-lead CCM systems; however 15% of patients had permanent atrial fibrillation in the FIX-HF-5C2 study.

Until today the largest prospective, observational, multicenter registry focusing on the efficacy and safety of CCM is the CCM-REG [112]. At the end of the 2-year follow-up period, based on the analysis of the 140 enrolled patients' data suffering from heart failure, the implementation of CCM led to a significant amelioration in the NYHA functional class and quality of life. Moreover, it caused a decrease in the annual hospitalization rate as well in comparison with the result of the previous year prior to the CCM device implantation of the examined cohort.

Based on the aforementioned data, CCM therapy was included in the expert consensus document of ESC Heart Failure Association [122], considering CCM as a potentially promising therapeutic alternative in heart failure and emphasizing the need for RCTs examining the effect of CCM with a larger number of patients.

However, it has to be underscored that there are some significant limitations of above-mentioned CCM studies. First of all, a significant limiting factor is the commonly used short follow-up duration (6 months in most of these studies). Secondly, some trials were unblinded (FIX-HF-5, FIX-HF-5C, FIX-HF-5C2) or non-randomized (FIX-HF-5C2) [123].

Despite the increasing evidence regarding CCM, what proportion of patients with HFrEF meet the eligibility criteria for CCM and, accordingly, the ratio of patients who would be eligible for CCM treatment in real-world clinical practice has not yet been investigated.

4 AIM

4.1 The impact of digoxin therapy on mortality of HFrEF patients

- To assess the impact of SDC-guided digoxin therapy on all-cause mortality in the total cohort of HFrEF patients
- To assess the effect of SDC-guided digoxin therapy on all-cause mortality in the propensity-score-matched patient cohort
- To assess the correlation of serum digoxin concentration and all-cause mortality
- To assess the effect of SDC-guided digoxin therapy on all-cause mortality in patients with sinus rhythm and atrial fibrillation
- To assess the effect of SDC-guided digoxin therapy on all-cause mortality in new digoxin users

4.2 The eligibility for cardiac contractility modulation

- To estimate what proportion of HFrEF patients could be eligible for CCM based on the inclusion criteria of the FIX-HF-5C trial

5 METHODS

5.1 The impact of digoxin therapy on mortality of HFrEF patients

5.1.1 Patient population

Data from consecutive HFrEF patients managed at the heart failure outpatient clinic (HFOC) of the Medical Centre of Hungarian Defence Forces between 01/01/2007 and 31/12/2017 were collected retrospectively. In addition, demographic data and clinical information were gathered from outpatient records.

Patients were considered to suffer from HFrEF if the LVEF was <40%. LVEF was measured by echocardiography using the biplane Simpson method.

Patients were classified as digoxin users if digoxin was administered at the time of the initiation of HFOC care and digoxin therapy was applied without interruption during the follow-up period. Patients who received digoxin at the time of referral, but digoxin therapy was discontinued afterward during the follow-up period were excluded from the study. Patients were considered to be new digoxin users if digoxin was initiated at the first visit at the HFOC. Patients who did not receive digoxin at baseline, but digoxin treatment was introduced during the follow-up period were excluded from the study. Patients were considered to be non-digoxin users if digoxin was not used and not started at baseline and during follow-up.

Digoxin initial dosing was calculated with a standardized method [124]. Afterward SDC was measured every three months, and the dose was adjusted according to it. The goal therapeutic range of SDC was 0.5-0.9ng/mL [125]. SDC samples were usually taken after 4-6 hours of oral administration. During follow-up, we made every effort to apply guideline-recommended therapy to every patient.

The study complies with the ethical guidelines of the Declaration of Helsinki.

5.1.2 Study end points

The outcome measure of this study was time to all-cause mortality. This parameter was compared between digoxin users and non-users across the whole patient population and after propensity score matching. Digoxin users were also divided into three groups based on the

maximal SDC measured during follow-up (maxSDC<0.9ng/mL, 0.9≤maxSDC<1.1ng/mL, maxSDC≥1.1ng/mL), and survival was compared among these subgroups of the propensity-adjusted population. Furthermore, the effect of SDC-guided digoxin therapy on all-cause mortality was assessed in new digoxin users and in patients with AF and SR also in the propensity-adjusted population. Mortality data were obtained from the database of the National Health Insurance Fund of Hungary.

5.1.3 Statistical analysis

Statistical analysis was performed using SPSS Statistics software, Version 23.0 (IBM, Armonk, NY) with the R software plug-in (The R Foundation, Version 3.1.0) for propensity score matching.

Continuous variables were expressed as mean ± standard deviations, and differences were compared using 2-sample t tests or the Mann-Whitney U test, as appropriate. Categorical variables were expressed as counts and percentages and differences were assessed with the chi square test.

To assess the effects of SDC-guided digoxin on survival, the Cox proportional hazards regression model was used. The variables included in the multivariate regression analysis are the best-known parameters influencing prognosis in HFrEF. The statistical models were adjusted for potential baseline confounders, including sex, age, etiology of HFrEF, AF, hypertension, diabetes mellitus, New York Heart Association functional class, LVEF, QRS width, heart rate, serum creatinine level, haemoglobin level, βB, ACEi/ARB, MRA, amiodarone, device use. Mortality risk assessment was also repeated among propensity-score-matched patient groups. Patients receiving digoxin were matched in a 1:2 ratio with patients not treated with digoxin using the nearest neighbor matching method with a calliper of 0.2 by applying the baseline characteristics listed above for the multivariate Cox regression. We also assessed the digoxin-associated mortality risk among the following subgroups of the propensity-score adjusted patient cohort: the subgroups defined by maximal SDC measured during follow-up (maxSDC<0.9ng/mL, 0.9≤maxSDC<1.1ng/mL, maxSDC≥1.1ng/mL), patients with SR or AF at baseline, and patients with newly prescribed digoxin at baseline visit.

Survival curves were constructed according to the Kaplan-Meier method and compared with the Cox proportional hazard model and the Wald test for the multivariate analyses. Two-sided p values of <0.05 were considered statistically significant.

5.2 The eligibility for cardiac contractility modulation

5.2.1 Patient population

Consecutive patients referred to the HF outpatient clinic of the tertiary cardiology center of Medical Centre, Hungarian Defence Forces, Budapest, Hungary between 01/01/2013 and 31/12/2017 due to HFrEF or HFmrEF were retrospectively assessed. HFrEF and HFmrEF were defined in accordance with the 2016 ESC HF Guidelines [17]. Relevant clinical, laboratory, echocardiographic, and electrocardiographic parameters were collected at initial visit and after treatment optimization. For patients with HFrEF, guideline-recommended neurohormonal antagonist therapy consisting of β-blocker, ACEi/ARB, and mineralocorticoid receptor antagonist was initiated and uptitrated during follow-up visits to guideline-recommended target doses or maximum tolerated doses. If indicated, ivabradine was used. Everey effort were made to minimize doses of diuretics, adjusted at each follow-up visit depending on fluid status and symptoms. Patients who met the indication criteria of current practice guidelines underwent implantation of an ICD or a CRT-P/D system. In treatment of patients with initial LVEF between 40 and 49%, we attempted to individually optimize therapy of both cardiovascular and non-cardiovascular comorbidities with a particular focus on hypertension, atrial fibrillation, and coronary artery disease (CAD). We included only patients with complete data who were followed up at our outpatient clinic during therapy optimization. LVEF was calculated using Simpson's method.

The enrollment criteria of the FIX-HF-5C study including NYHA class III/IV, 25%≤LVEF≤45%, QRS duration<130msec, and sinus rhythm were applied to identify the proportion of patients suitable for CCM on optimized therapy.

5.2.2 Study end points

We assessed the number of patients who could receive CCM as primary device therapy and the proportion of those for whom CCM would be indicated alongside the use of a

previously implanted cardiac implantable electronic device. This study was approved by the local Ethical Committee (approval number: KKOO/182-1/2020) and was undertaken in conformity with the Helsinki Declaration.

5.2.3 Statistical analysis

Data were obtained from the hospital information system and patient records and were recorded in an anonymized form in a Microsoft Excel 2007 spreadsheet (Microsoft, Redmont, WA, USA). Statistical analysis was performed using the statistical program SPSS 21.0 (IBM, Armonk, NY, USA). The calculated values for categorical variables are represented as percentages, while continuous variables are represented by their means and standard deviations. To compare variables before and after therapy optimization, the McMahon test was used in the case of categorical variables and the paired t test with continuous variables. A 2-sided p value <0.05 was considered statistically significant.

6 RESULTS

6.1 The impact of digoxin therapy on mortality of HFrEF patients

6.1.1 Patient characteristics

The baseline characteristics of the patients of the total cohort (580 patients) and patients after propensity score matching (477 patients) with and without digoxin therapy are demonstrated in Table 1. From the total cohort, in 185 patients, digoxin was applied at the time of their first visit to the HFOC. As expected, digoxin users suffered more often from AF than non-digoxin users (41.1% vs. 21.3%; $p<0.001$), had more decreased ejection fraction (26.4±6.5% vs. 28.0±6.6%; $p=0.003$) and had higher baseline heart rate (89.0±20.0bpm vs. 85.1±19.2bpm; $p=0.026$). In addition, ischemic etiology (50.1% vs. 40.0%; $p=0.023$) was more frequent among non-digoxin users. There was also a significant difference between the two groups regarding baseline device use; significantly more digoxin-treated patients had a previously implanted ICD or CRT-P/D system as opposed to non-users (13.0% vs. 7.6%; $p=0.038$).

Table 1. Baseline characteristics before and after propensity score matching for patients with and without digoxin therapy

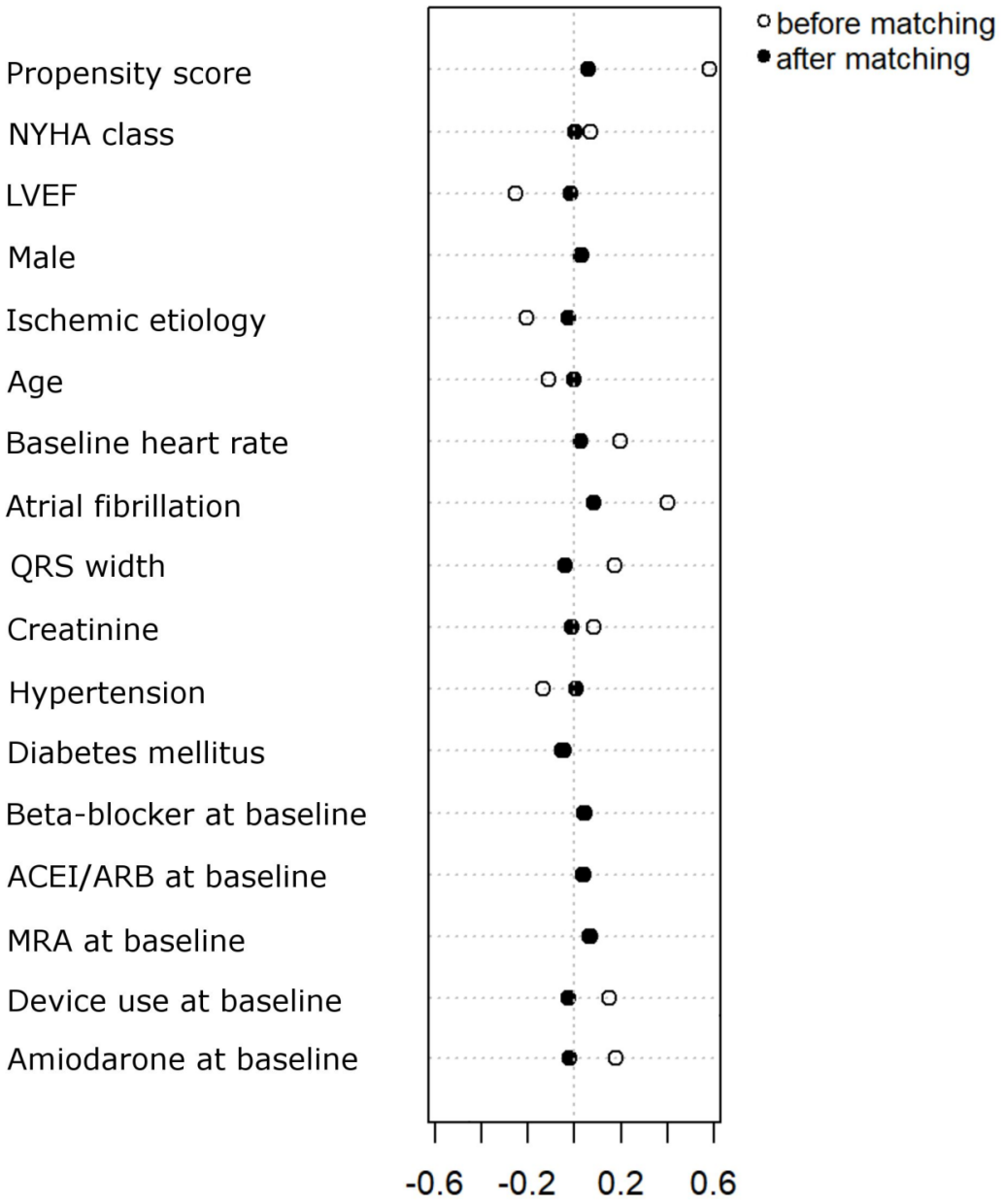
	Total cohort Before propensity score matching (580)				After propensity score matching (477)			
		Pts without digoxin (395)	Pts with digoxin (185)	p-value		Pts without digoxin (297)	Pts with digoxin (180)	p-value
Male	443 (76.4%)	300 (75.9%)	143 (77.3%)	0.722	363 (76.1%)	224 (75.4%)	139 (77.2%)	0.655
Age (mean±SD)	61.2±13.0	61.6±13.1	60.2±12.6	0.201	60.7±13.2	60.8±13.6	60.5±12.7	0.693
Ischemic etiology	272 (46.9%)	198 (50.1%)	74 (40.0%)	0.023	199 (41.7%)	128 (43.1%)	71 (39.4%)	0.433
Atrial fibrillation	160 (27.6%)	84 (21.3%)	76 (41.1%)	<0.001	154 (32.3%)	83 (27.9%)	71 (39.4%)	0.009
Hypertension	420 (72.4%)	294 (74.4%)	126 (68.1%)	0.112	332 (69.6%)	209 (70.4%)	123 (68.3%)	0.639
Diabetes mellitus	203 (35.0%)	141 (35.7%)	62 (33.5%)	0.607	170 (35.6%)	109 (36.7%)	61 (33.9%)	0.534
NYHA at baseline (mean±SD)	3.1±0.8	3.1±0.8	3.2±0.7	0.613	3.1±0.8	3.1±0.8	3.1±0.7	0.714
LVEF (%) at baseline (mean±SD)	27.5±6.6	28.0±6.6	26.4±6.5	0.003	26.8±6.6	27.0±6.7	26.6±6.4	0.384
QRS width at baseline (ms) (mean±SD)	124±38	122±37	129±39	0.063	127±38	127±38	127±38	0.974
HR(min^{-1}) at baseline (mean±SD)	86.3±19.6	85.1±19.2	89.0±20.0	0.026	88.0±20.2	87.3±20.3	89.0±20.1	0.375
Creatinine at baseline (µmol/l) (mean±SD)	114±48	113±45	117±53	0.177	116±50	116±48	117±53	0.713
Hgb (g/L) at baseline (mean±SD)*	142±17	141±16	143±17	0.116	142±16	141±15	143±17	0.153
ß-blocker at baseline	233 (40.2%)	156 (39.5%)	77 (41.6%)	0.626	189 (39.6%)	115 (38.7%)	74 (41.1%)	0.605
ACEi/ARB at baseline	234 (40.3%)	157 (39.7%)	77 (41.6%)	0.668	190 (39.8%)	116 (39.0%)	74 (41.1%)	0.657
MRA at baseline	213 (36.7%)	141 (35.7%)	72 (38.9%)	0.453	173 (36.3%)	104 (35.0%)	69 (38.3%)	0.465
Amiodarone at baseline	44 (7.6%)	27 (6.8%)	17 (9.2%)	0.318	42 (8.8%)	25 (8.4%)	17 (9.4%)	0.701
CRT/ICD at baseline	54 (9.3%)	30 (7.6%)	24 (13.0%)	0.038	51 (10.7%)	31 (10.4%)	20 (11.1%)	0.818

* Available for 467 pts before and 383 pts after propensity score matching. SD: standard deviation, NYHA: New York Heart Association functional class, LVEF: left ventricular ejection fraction, HR: heart rate, Hgb: haemoglobin, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist, CRT: cardiac resynchronization therapy, ICD: implantable cardioverter-defibrillator

In terms of drug treatment implemented at baseline, just the minority of patients received the guideline-recommended therapy of HFrEF. Most evaluated patients were referred to our HFOC by secondary care physicians and general practitioners. Consequently, many of them were treatment naïve or undertreated at the time of referrals. In 40.2% of patients, a βB, in 40.3%, an ACEi/ARB, and in 36.7%, an MRA was implemented. After the treatment optimization period of three to six months, the proportion of patients receiving the neurohormonal antagonists increased significantly. In the total cohort, the utilization of βB and ACEi/ARB was also 88.4%, while MRA was used in 57.6%. It has to be underscored that the proportion of patients on target doses of these disease-modifying agents also augmented remarkably (46.7% of βB-treated and 41.5% of ACEi/ARB-treated patients), which results were significantly favourable than observed in the recently published registry data [18]. The mean daily digoxin dose during follow-up was 111±50μg. During the study period, the angiotensin receptor-neprilysin inhibitor application was still not available.

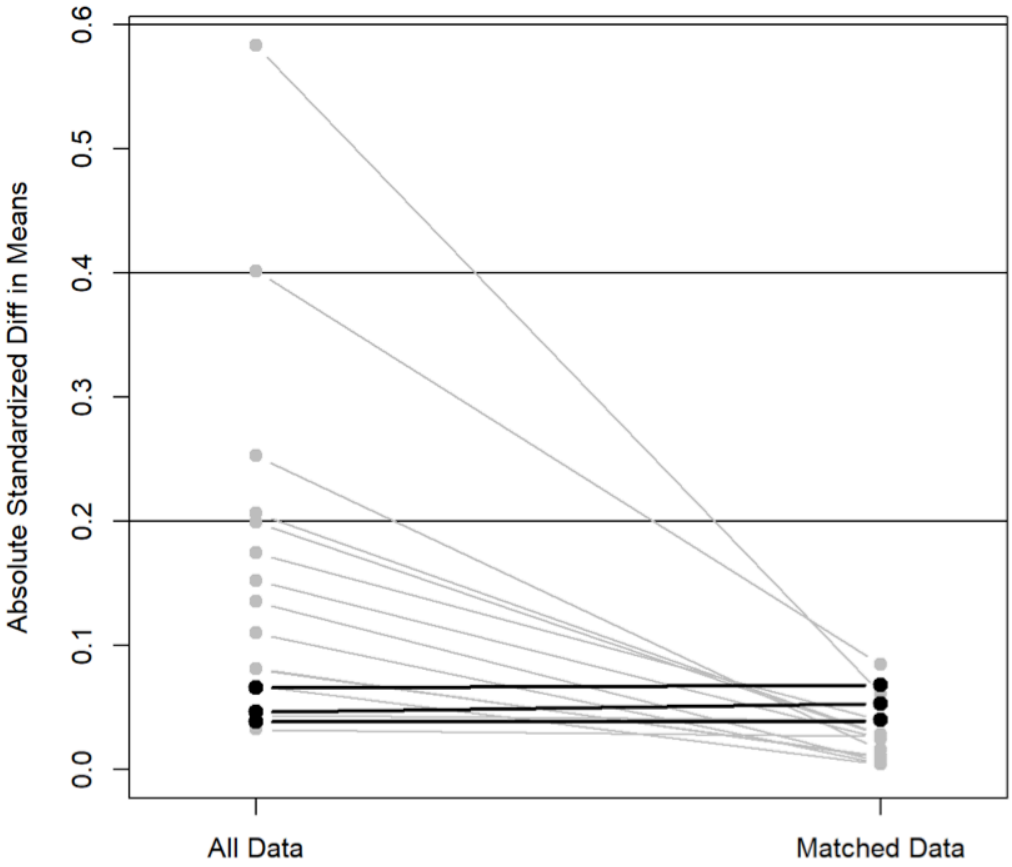
After applying a 1:2 propensity score matching protocol, a cohort of 477 patients was assembled (180 digoxin-treated and 297 digoxin-not-treated patients). In comparison with pre-matched patients, those in the matched cohort were well balanced with respect to the collected baseline risk factors with a standard mean difference of less than 20 % (Figure 3., and Figure 4.); however patients on digoxin therapy had higher incidence of atrial fibrillation (39.4% versus 27.9%, p=0.009).

Figure 3. Dotplot of standardized mean differences for 17 baseline characteristics between digoxin users and non-users, before and after propensity score matching



NYHA: New York Heart Association functional class, LVEF: left ventricular ejection fraction, ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist

Figure 4. The absolute standardized differences in mean values of the main clinical baseline parameters before and after propensity score matching



6.1.2 The effect of serum digoxin concentration (SDC) - guided digoxin therapy on all-cause mortality

6.1.2.1 *The effect of SDC-guided digoxin therapy on all-cause mortality in the total cohort*

During the mean follow-up of 7.1±4.7 years, from the total cohort, 351 patients (60.5%) died, 131 patients out of 185 digoxin users (70.8%), and 220 patients out of the 395 non-digoxin users (55.7%). The univariate survival (Table 2.) analysis of the total cohort revealed that digoxin use was associated with an increased risk of all-cause mortality (HR:

1.453; [95% CI: 1.170-1.804]; p=0.001). However, after adjustment for potential confounders in multivariate Cox regression analysis, baseline digoxin use remained an independent predictor of all-cause mortality (HR: 1.939; [95% CI: 1.512-2.487]; p<0.001) (Table 3.) .

Table 2. Baseline predictors of mortality in the total cohort (Univariate Cox regression analysis)

	HR	95% CI		p-value
		Lower	Upper	
Male	1.836	1.384	2.434	**<0.001**
Age (Mean±SD)	1.053	1.043	1.063	**<0.001**
Ischemic etiology	2.129	1.715	2.642	**<0.001**
Atrial fibrillation	1.525	1.218	1.909	**<0.001**
Hypertension	1.292	1.015	1.644	**0.037**
Diabetes	1.336	1.077	1.657	**0.008**
NYHA (Mean±SD) at baseline	1.384	1.205	1.591	**<0.001**
LVEF (Mean±SD) at baseline	0.994	0.979	1.010	0.471
QRS (Mean±SD) at baseline	1.004	1.001	1.005	**0.003**
HR (Mean±SD) at baseline	0.995	0.990	1.001	0.097
Creatinine (Mean±SD) at baseline	1.005	1.003	1.006	**<0.001**
ß-Blocker at baseline	1.271	1.013	1.594	**0.038**
ACEi/ARB at baseline	1.295	1.032	1.624	**0.026**
MRA at baseline	1.216	0.960	1.540	0.105
Amiodarone at baseline	1.658	1.112	2.470	**0.013**
CRT/ICD at baseline	1.113	0.760	1.632	0.581
Haemoglobin at baseline *	0.985	0.978	0.993	**<0.001**
Digoxin	1.453	1.170	1.804	**0.001**

* Available for 467 pts before propensity score matching. CI: confidence interval, SD: standard deviation, NYHA: New York Heart Association functional class, LVEF: left ventricular ejection fraction, HR: heart rate, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist, CRT: cardiac resynchronization therapy, ICD: implantable cardioverter defibrillator

Table 3. Independent baseline predictors of mortality in the total cohort (Multivariate Cox regression analysis)

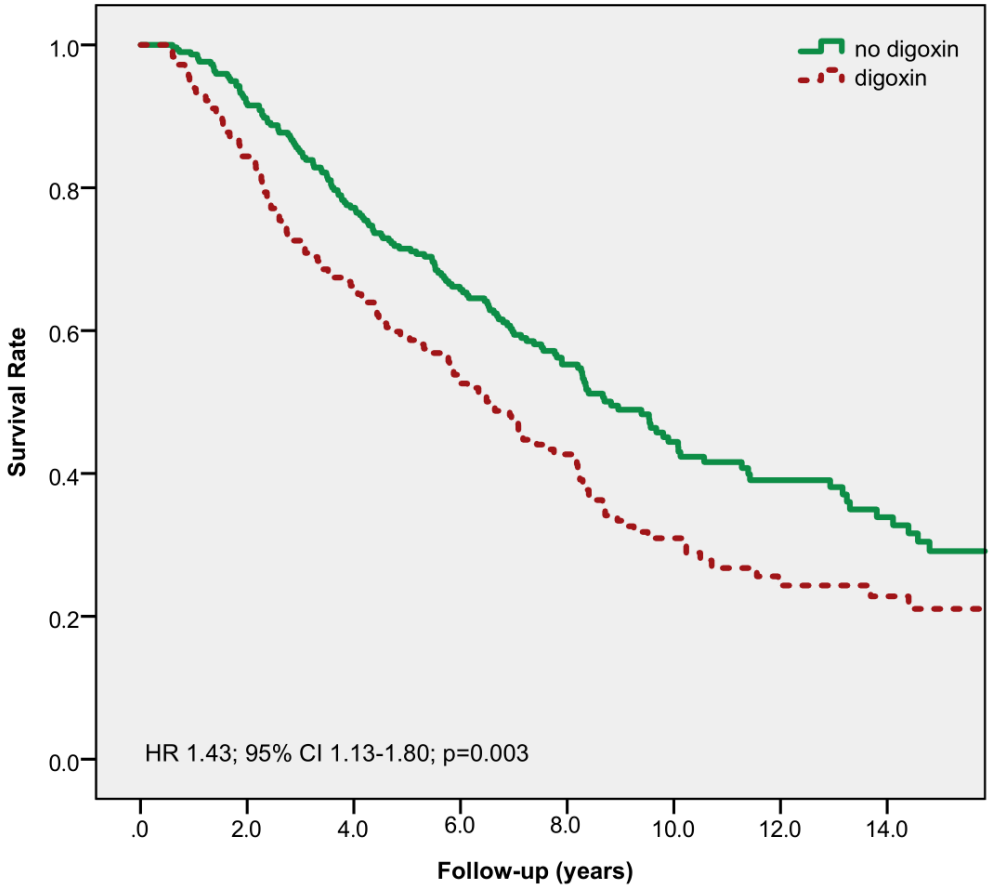
	adjusted HR	95% CI		p-value
		Lower	Upper	
Digoxin	1.939	1.512	2.487	<0.001
NYHA at baseline	1.212	1.037	1.416	0.015
Male	1.986	1.422	2.774	<0.001
Ischemic etiology	1.738	1.338	2.257	<0.001
Age	1.043	1.032	1.055	<0.001
Creatinine at baseline	1.003	1.001	1.005	0.013
Haemoglobin at baseline	0.985	0.977	0.993	<0.001

CI: confidence interval, NYHA: New York Heart Association functional class, HR: hazard ratio

6.1.2.2 *The impact of SDC-guided digoxin therapy on all-cause mortality in the propensity score-matched patient cohort*

In the propensity score-matched patient cohort 126 patients, out of the 180 digoxin users (70.0%), and 165 patients, out of the 297 non-digoxin users (55.6%) died. The all-cause mortality of digoxin-users was significantly higher than non-users (propensity adjusted HR: 1.430; [95% CI: 1.134-1.804]; p=0.003) (Figure 5.).

Figure 5. Kaplan-Meier curves for all-cause mortality by digoxin use (propensity matched patients)



CI: confidence interval, HR: hazard ratio

Besides the baseline digoxin use, sex, age, ischemic etiology, atrial fibrillation, hypertension, diabetes mellitus, NYHA functional class, QRS width, serum creatinine level, amiodarone use and haemoglobin level were correlated with the survival in the propensity score-matched patient cohort (Table 4.).

Table 4. Predictors of mortality in the propensity score adjusted patient cohort (Univariate Cox regression analysis)

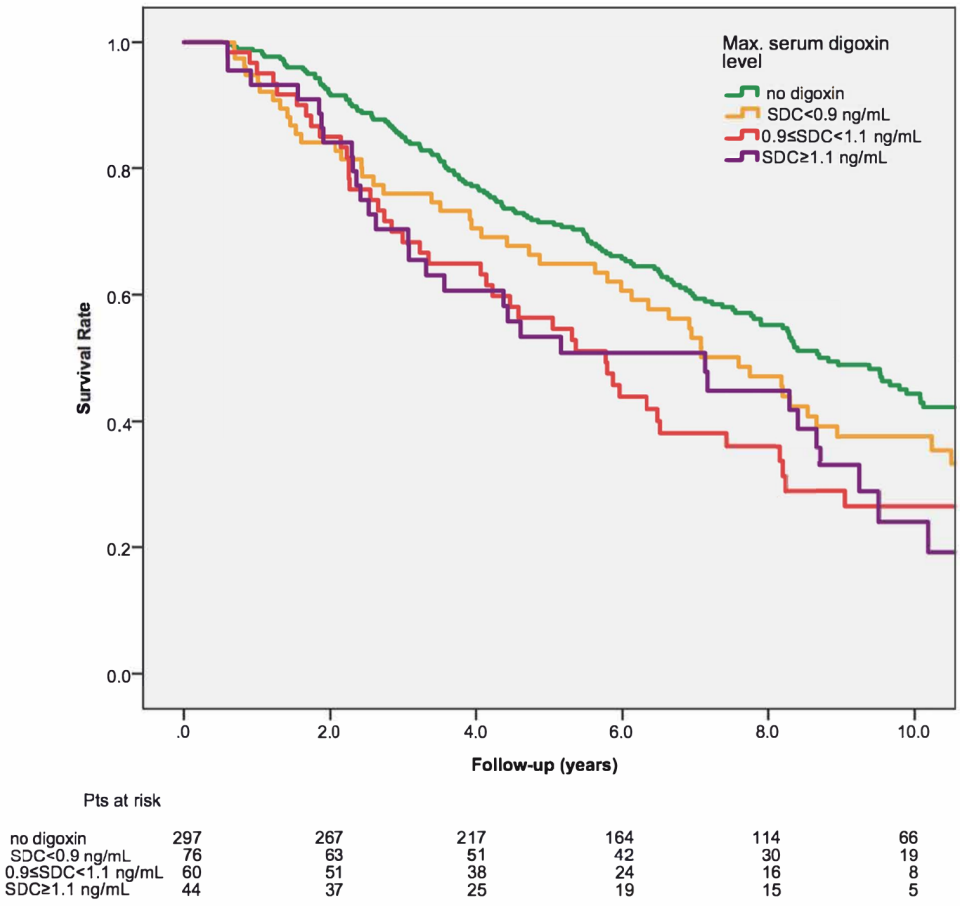
	adjusted HR	95% CI		p-value
		Lower	Upper	
Male	1.736	1.280	2.355	<0.001
Age	1.050	1.040	1.061	<0.001
Ischemic etiology	2.275	1.798	2.879	<0.001
Atrial fibrillation	1.530	1.205	1.942	<0.001
Hypertension	1.385	1.070	1.794	0.013
Diabetes mellitus	1.423	1.125	1.799	0.003
NYHA at baseline	1.418	1.215	1.655	<0.001
QRS width	1.003	1.001	1.006	0.020
Creatinine at baseline	1.004	1.003	1.006	<0.001
Amiodarone	1.553	1.024	2.357	0.038
Haemoglobin at baseline	0.984	0.976	0.992	<0.001
Digoxin	1.430	1.134	1.804	0.003

CI: confidence interval, NYHA: New York Heart Association functional class, HR: hazard ratio

6.1.2.3 *Correlation of serum digoxin concentration and all-cause mortality*

Those patients who had a maxSDC of between 0.9 and 1.1ng/mL (n=60) and patients with maxSDC≥1.1ng/mL (n=44) had an elevated risk of all-cause mortality as opposed to non-digoxin users (HR: 1.750; [95% CI: 1.257-2.436]; p=0.001 and HR: 1.687; [95% CI: 1.153-2.466]; p=0.007) (Figure 6.). However, this raised hazard of mortality was not statistically significant in the subgroup of patients with a maxSDC of <0.9ng/mL (n=76) (HR: 1.139; [95% CI: 0.827-1.570]; p=0.426) (Figure 6.).

Figure 6. Kaplan-Meier curves for all-cause mortality by maximal serum digoxin concentration (propensity matched patients)

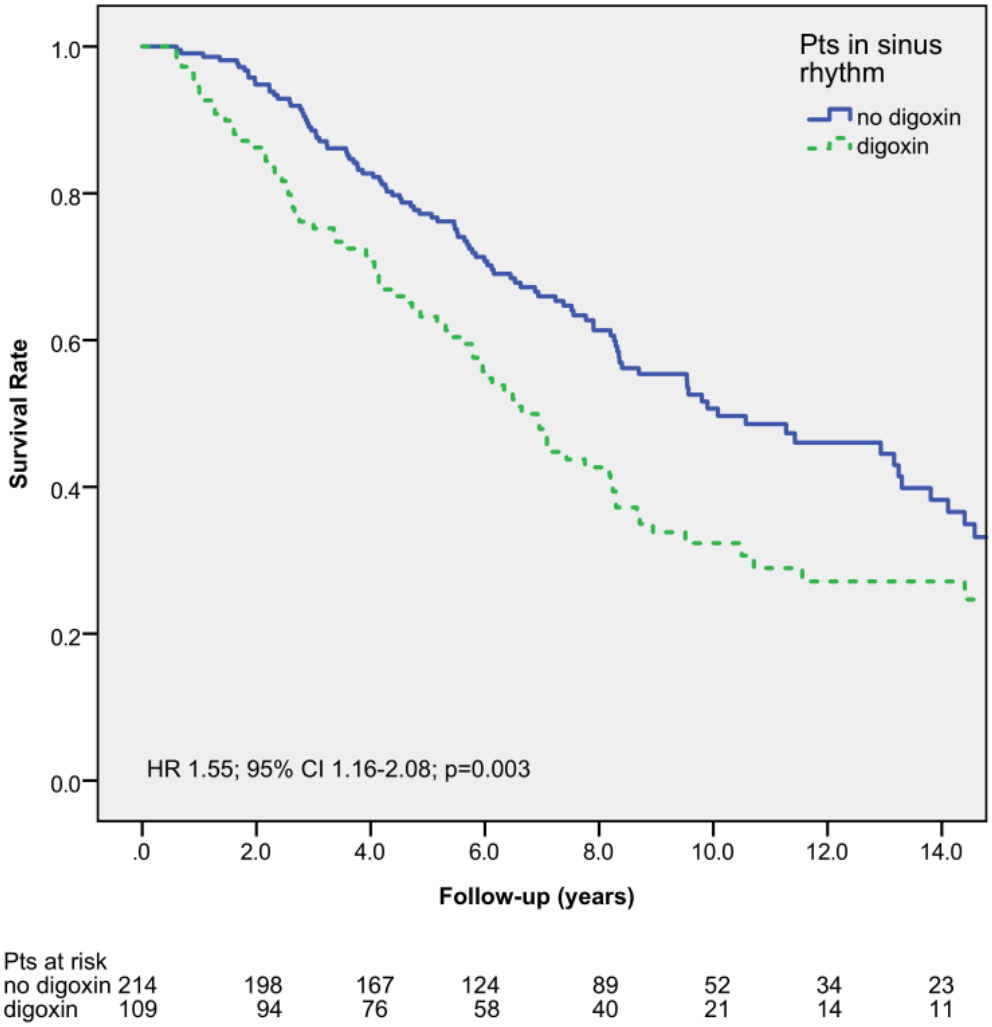


SDC: serum digoxin concentration

6.1.2.4 *The effect of SDC-guided digoxin therapy on all-cause mortality in patients with sinus rhythm and atrial fibrillation*

When survival was evaluated according to digoxin application in the subgroup of patients with SR at baseline, we confirmed that digoxin use was associated with an increased hazard of mortality (propensity adjusted HR: 1.553; [CI: 1.157-2.084]; p=0.003) (Figure 7.).

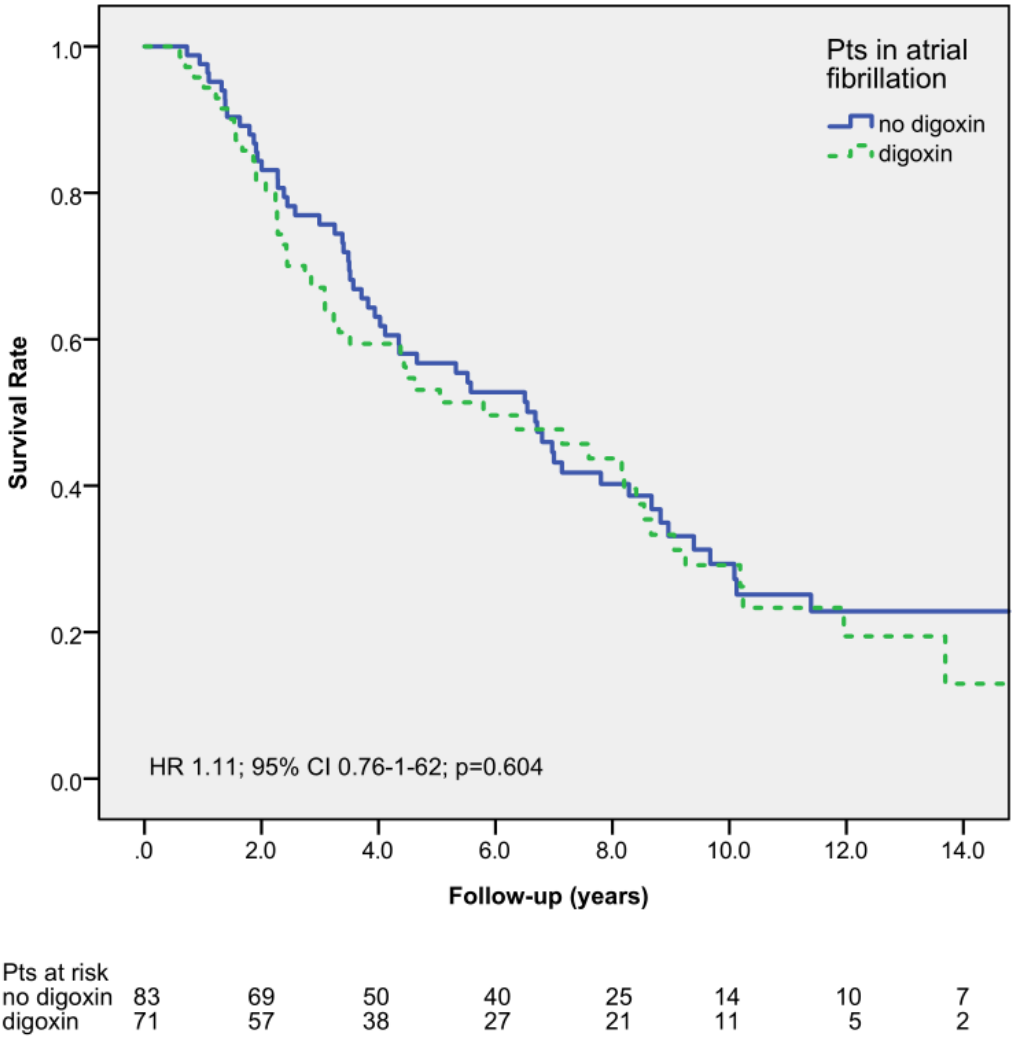
Figure 7. Kaplan-Meier curves of all-cause mortality by digoxin use in presence of sinus rhythm at baseline (propensity matched patients)



CI: confidence interval, HR: hazard ratio, Pts: patients

This phenomenon was not statistically significant among those having AF at baseline (HR: 1.106; [CI: 0.756-1.619]; p=0.604) (Figure 8.).

Figure 8. Kaplan-Meier curves of all-cause mortality by digoxin use in presence of atrial fibrillation at baseline (propensity matched patients)

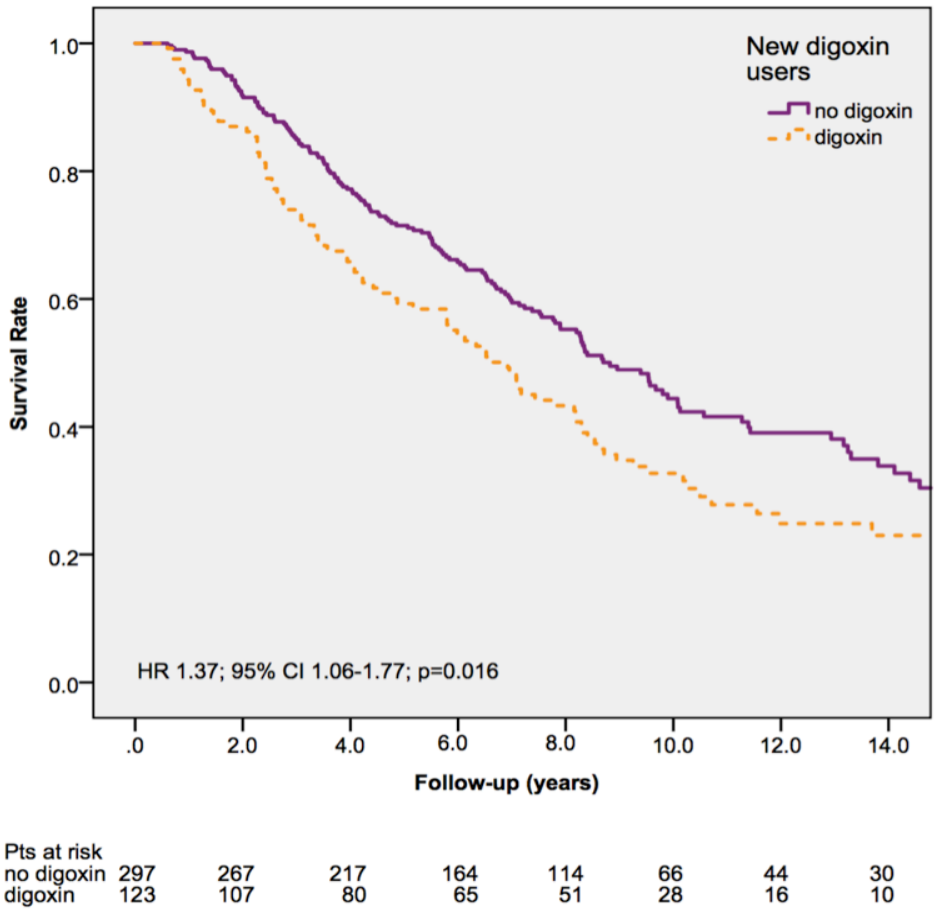


CI: confidence interval, HR: hazard ratio, Pts: patients

6.1.2.5 *The effect of SDC-guided digoxin therapy on all-cause mortality in new digoxin users*

When the impact of digoxin was assessed among the 123 new digoxin users in comparison with digoxin non-users, we found that digoxin implementation led to a significantly elevated risk of all-cause mortality (HR: 1.371; [95% CI: 1.062-1.770]; p=0.016) (Figure 9.).

Figure 9. Kaplan-Meier curves for all-cause mortality by digoxin use among new digoxin users (propensity matched patients)



CI: confidence interval, HR: hazard ratio

When digoxin level was evaluated as a continuous variable, serum digoxin concentration was associated with a 14% higher adjusted hazard of death for each 0.5ng/mL elevation (p=0.0073).

6.2 The eligibility for cardiac contractility modulation

Six hundred forty patients were referred due to HFrEF or HFmrEF and followed up at our HFOC during the study period. Of these 640 patients, 48.1% (n=308) suffered from CAD, and 28.0% had persistent or permanent atrial fibrillation (Table 5.).

Table 5. Clinical, echocardiographic, and laboratory characteristics of the study population at the time point of referral to heart failure clinic

Number of patients	640
Age (years) (mean±SD)	61.3±13.1
>75years	95 (14.8%)
Male	487 (76.1%)
Hypertension	464 (72.5%)
Diabetes mellitus	220 (34.4%)
Ischemic heart disease	308 (48.1%)
Heart rate (min^{-1}) (mean±SD)	86±20
Atrial fibrillation	179 (28.0%)
QRS width (msec) (mean±SD)	122±37
QRS<130msec	404 (63.1%)
Haemoglobin (g/dL) (mean±SD)	14.0±1.8
Serum potassium >5.5mmol/L	17 (2.7%)
Se Creatinine (μmol/l) (mean±SD)	116±59
eGFR (ml/min/1.73m^2) (mean±SD)	64±23
eGFR≤30ml/min/1.73m^2	39 (6.1%)

eGFR: estimated glomerular filtration rate, SD: standard deviation

The mean LVEF in the whole patient cohort was 29.0±7.9% at baseline, and 63.1% of patients

had a QRS width<130msec. At the time of the first presentation, 43.9% of patients received a β-blocker, 38.1% ACEi/ARB, and 38.3% mineralocorticoid receptor antagonist.

Table 6. Changes in NYHA class, LVEF, medical and device-related treatment at timepoint of referral vs. after therapy optimization

	Baseline n=640	**After treatment optimization n=640**	**p-value**
LVEF (%) (mean±SD)	29.0±7.9	36.3±9.9	p<0.001
NYHA III-IV	493 (77.0%)	119 (18.6%)	p<0.001
25% ≤ LVEF ≤ 35%	327 (51.1%)	270 (42.2%)	p=0.001
35% < LVEF ≤ 45%	119 (18.6%)	199 (31.1%)	p<0.001
Use of β-blocker	281 (43.9%)	569 (88.9%)	p<0.001
β-blocker at TD	97 (15.2%)	309 (48.3%)	p<0.001
Use of ACEi/ARB	244 (38.1%)	615 (96.1%)	p<0.001
ACEi/ARB at TD	29 (4.5%)	256 (40.0%)	p<0.001
Use of MRA	245 (38.3%)	371 (58.0%)	p<0.001
ICD	35 (5.5%)	69 (10.7%)	p=0.004
CRT-P/D	42 (6.6%)	175 (27.3%)	p<0.001
Eligible for CCM	147 (23.0%)	33 (5.2%)	p<0.001

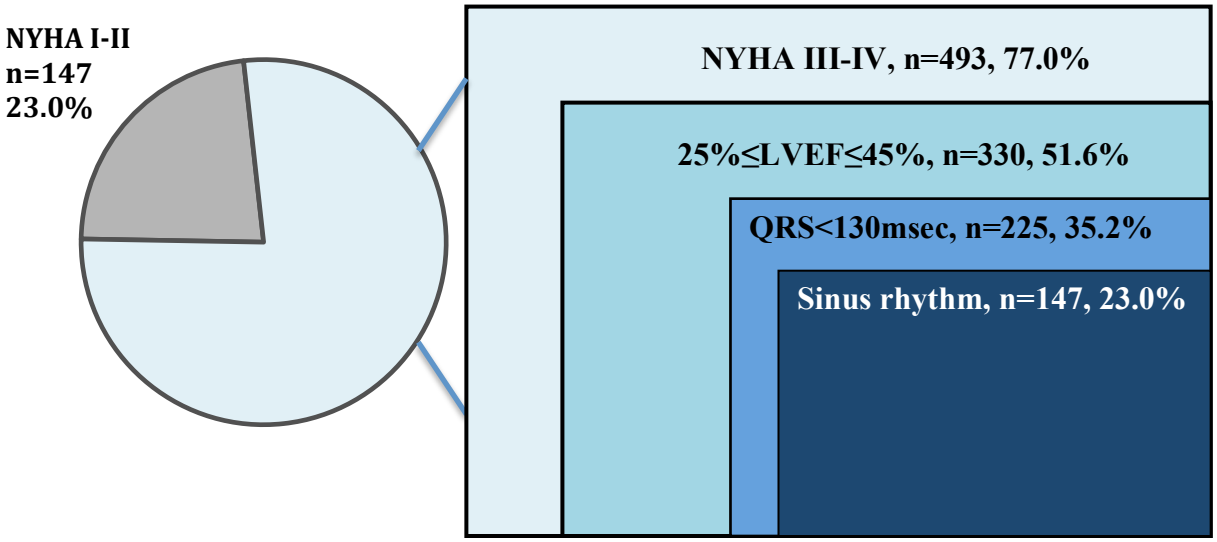
NYHA: New York Heart Association, LVEF: left ventricular ejection fraction, TD: target dose, ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist, ICD: implantable cardioverter defibrillator, CRT: cardiac resynchronization therapy, CCM: cardiac contractility modulation, SD: standard deviation

Among patients with HFrEF (n=579), the proportion of patients on β-blocker, ACEi/ARB, MRA was significantly increased through individual optimization of medical therapy to 88.4, 96.5, and 57.0%, respectively. The guideline-recommended target dose of β-blockers and ACEi/ARBs was achieved in 46.8 and 36.8% of patients with HFrEF. After treatment optimization, 424 patients (66.3%) were found to have improved at least one NYHA class, therefore, the proportion of severely symptomatic patients (NYHA III–IV) decreased from 77.0% to 18.6% (p<0.001) (Table 6.). Mean LVEF increased significantly to 36.3±9.9% (p<0.001). The proportion of patients with 25%≤LVEF≤45% increased from 69.7% (n=446) to

73.3% (n=469) (p<0.001).

We found that the eligibility criteria for CCM therapy based on the FIX-HF-5C study were fulfilled for 23.0% (n=147) of our patient population at baseline (Figure 10.) and 5.2% (n=33) after treatment optimization (Figure 11.).

Figure 10. The Venn diagram demonstrates the proportion of eligible patients for CCM therapy at baseline



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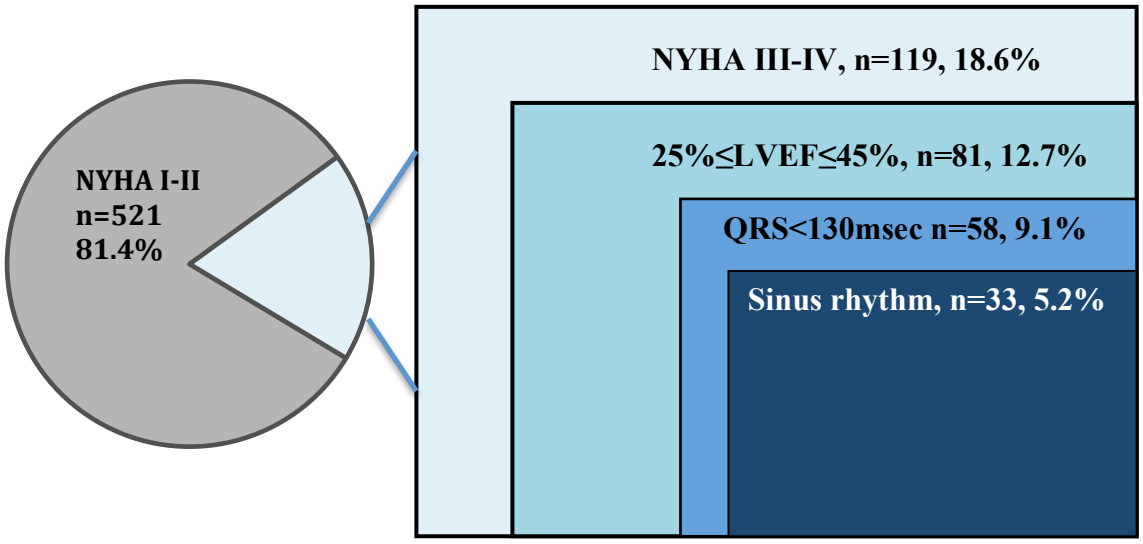
NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, CCM=cardiac contractility modulation

Figure 11. The Venn diagram demonstrates the proportion of eligible patients for CCM therapy after pharmacological treatment optimization



NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, CCM=cardiac contractility modulation

Ten of the 33 potential CCM candidates would receive CCM as a second device in addition to a pacemaker or implantable cardioverter defibrillator implanted previously.

7 DISCUSSION

HFrEF still represents a deadly disease despite the improvements in its complex disease-modifying drug and device treatment. Although its modern, highly effective therapy has advanced significantly over the last decade, the prognosis of HFrEF, even today, is undoubtedly comparable with the outcomes of several malignant diseases. Therefore, the implementation of all available guidelines' recommended therapeutic possibilities is necessary to improve the prognosis successfully. Furthermore, as stated in the current ESC 2021 HF Guidelines [1], the optimal implementation of the disease-modifying treatment in HFrEF requires a multidisciplinary approach that is present during the entire course of the disease. The optimal multidisciplinary disease management program requires a dedicated team in which heart failure specialists play a crucial central role in optimizing and maintaining the guideline-recommended complex treatment [126].

As for treatment optimization, besides the initiation of the disease-modifying drug regime, the accurate, precise implementation of the available pharmacological options, if it is needed, even the second-line agents, focusing on their potential side effects, indisputably represents the cornerstone of modern care in real-world practice. From this point of view, digoxin's optimal, precise application is an important example. Alongside the medical therapy, the proper use of devices (CRT/ICD) has become an integrated, indispensable part of the complex care of HFrEF. However, despite the application of the "lege artis" drug and device therapy, the prognosis of the disease is still highly unfavourable. Obviously, the continuous effort to look for new, not yet applied, therapeutic possibilities is essential either during the in-hospital or throughout the outpatient phase of multidisciplinary disease care. CCM represents a new, promising non-pharmacological modality in the field of heart failure.

7.1 The impact of digoxin therapy on mortality of HFrEF patients

7.1.1 Main findings

In this real-life, community-based cohort of optimally treated HFrEF patients, we confirmed that SDC-guided digoxin therapy was associated with increased all-cause mortality,

especially with SDC≥0.9ng/mL. Furthermore, all-cause mortality was significantly elevated in patients with SR and in new digoxin users in comparison with patients not treated with digoxin.

7.1.2 Serum-concentration-guided digoxin therapy

The narrow therapeutic window for the use of digitalis glycosides is well known. However, most publications that demonstrated an elevated mortality risk associated with digoxin did not report data about daily digoxin dose and/or serum levels. Even in the studies that reported such information, serum digoxin measurements were not performed in a systematic fashion. For example, in the DIG trial, SDC was measured only at four weeks and one year after the start of the study, while digoxin toxicity was followed only by signs and symptoms at four months, and every four months thereafter [49]. In a study by Freeman et al. comprising 2891 newly diagnosed HFrEF patients [65], SDC was measured at all in 70% of patients and was measured just once in 27% of patients. Consequently, the lack of regular SDC control and/or higher SDC may have contributed to the adverse mortality effect of digoxin observed in these trials.

Our retrospective study demonstrates that even with an extremely close monitoring strategy, which was performed systematically in every patient, it was only possible to maintain SDC below 0.9ng/mL in 42% of patients during the entire follow-up. This may be partly due to the pharmacokinetics of digoxin (it eliminates mainly through the kidneys), and the fact that the renal function of HFrEF patients is typically impaired. It, therefore, appears to be reasonable to use digitoxin instead of digoxin in HFrEF because of its hepatic elimination. Evidence regarding the effects of digitoxin on morbidity and mortality or data about its safe therapeutic range is even more limited. In a single-centre study of 1020 ICD recipients, treatment with digoxin or digitoxin were associated with similarly increased mortality compared to digitalis non-users [127]. The ongoing Digitoxin to mprove outcomes in patients with advanced chronic heart failure (DIGIT-HF) trial will hopefully be able to clarify the place of digitoxin in therapy for HFrEF [128]. This trial investigates the hypothesis that digitoxin – at serum concentrations in the lower therapeutic range – reduces mortality and morbidity in patients with HFrEF with or without AF.

7.1.2.1 *Correlation of serum digoxin concentrations and mortality*

A post-hoc analysis of the DIG trial has raised the concern that high SDC (≥1.2ng/mL) could lead to an increase in all-cause and cardiovascular mortality, and favourable digoxin effects are only expected in patients with SDC between 0.5 and 0.8ng/mL [125]. In the recently published post-hoc analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [67], baseline digoxin implementation was not associated with an increased risk of mortality compared to patients not treated with digoxin. However, a 56% increase in relative mortality risk was demonstrated in patients with an SDC≥1.2ng/mL compared to those not on digoxin. The study also found a linear correlation between SDC and all-cause mortality: an 0.5ng/mL increase in SDC increased mortality by 19%. This phenomenon was also verified in our analysis; serum digoxin concentration was correlated with a 14% higher adjusted hazard of death for each 0.5ng/mL increase. In opposition to the above-mentioned post-hoc analysis of the ARISTOTLE trial, we confirmed an increase in mortality risk across the entire patient cohort before and after propensity score matching. This difference may be explained by the variability in patient populations: in the ARISTOTLE trial, every patient had AF, 37.4% of whom suffered from concomitant HF, while in our study, every patient had HFrEF, and only 27.6% suffered from AF. In the ARISTOTLE study, among patients whose digoxin level was measured at baseline, 76.0% had SDC levels below 0.9ng/mL. In comparison, only 42% of our patient population had maxSCD<0.9ng/mL.

In contrast to the DIG study, we could not identify a favourable mortality effect in patients with maxSDC<0.9ng/mL. This may be explained by the fact that there were significant differences between our patient population and those cohorts (for example, we included patients with AF also, in contrast to the DIG trial). Moreover, digoxin users had more advanced HF with lower left ventricular ejection fraction in our cohort, and the proportion of patients with hypertension or diabetes was higher compared to the DIG trial. Finally, it should also be noted that the morbidity- and mortality-reducing drug and device therapies were applied in higher proportion and dose in our patients than they were used in the DIG trial, which also could have modified the possible deleterious effects of digoxin.

7.1.2.2 *The effect of digoxin on mortality in patients with atrial fibrillation and sinus rhythm*

The results of studies that evaluated the effect of digoxin on the mortality of HFrEF patients in SR and AF are quite controversial. In a meta-analysis published by Vamos et al., a substantially increased risk of death was associated with digoxin in both HF and AF, although the relative risk of mortality was higher in patients with AF (23% vs. 11%) [61]. The post-hoc analysis of the ARISTOTLE trial also demonstrated a direct correlation between serum digoxin level and overall mortality in patients with AF, which was consistent in patients with HF. However, Hallberg et al. – using data from the Registry of Information and Knowledge about Swedish Heart Intensive Care Admissions – did not find a difference in one-year digoxin-associated mortality among patients with HF with or without AF. Our study demonstrated increased mortality in digoxin-treated HFrEF patients in SR but not in patients with AF. The Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) trial assessing the effect of digoxin in permanent AF and HF, verified an amelioration in the NT-proBNP level, and in the modified EHRA class in the effect of digoxin in comparison with bisoprolol [129,130]. In addition, the application of digoxin in the RATE-AF trial was associated with fewer adverse events as opposed to the implementation of bisoprolol.

7.1.2.3 *The effect of digoxin on mortality in new digoxin users*

Parallelly to the post-hoc analysis of the ARISTOTLE trial [67] and other previous reports, we also verified a significant elevation in all-cause mortality in new digoxin users as opposed to patients not treated with digoxin (HR: 1.371; [95% CI: 1.062-1.770]). Although this result may be underpowered because of the limited number of new digoxin users, this type of analysis appears to be particularly important since it reduces the survival bias that is present in most of the observational studies [61].

7.2 The eligibility for cardiac contractility modulation

In a real-life cohort of patients we found that the eligibility criteria for CCM therapy based on the FIX-HF-5C study were fulfilled in 23.0% of our patient population before and 5.2% after treatment optimization.

The basis of CCM is a non-excitatory, relatively high voltage (~7.5V), long-duration (~20 millisecond), biphasic electrical signal delivered during the absolute refractory period of the ventricle. The device (Optimizer system - Impulse Dynamics, Orangeburg, NY) is typically implanted in the right pectoral region and is connected to two standard pacemaker leads that are placed through venous access into the right ventricular septum at a distance of at least 2 cm from each other [107]. The beneficial effects of CCM manifest at the molecular, cellular, and extracellular level [131]. Positive changes in the remodelling of intracellular Ca^{2+} regulatory proteins and increasing sensitivity of myofilaments to Ca^{2+} appear to be the most important molecular changes, leading to improvement not only in regional but also in global LV contractility [132,133].

The three prospective randomized trials proved that CCM in addition to OMT is effective at reducing symptoms and improving exercise capacity and quality of life in patients with NYHA class III-IV, 25% ≤LVEF≤ 45%, QRS<130msec, and sinus rhythm versus OMT alone [107,109,110]. Additionally, the most recent FIX-HF-5C study showed an approximately 50% reduction in the composite end point of cardiovascular death and HF hospitalizations at six months [107]. The clinical effectiveness of CCM is most convincing in patients with LVEF between 35-45%, while patients with LVEF below 25% do not appear to benefit from this therapy [134]. Due to the invasive nature and costs of this therapy, careful patient selection and thorough follow-up are necessary.

To the best of our knowledge, our analysis is the first report to describe an assessment of the proportion of patients who would be eligible for CCM therapy based on current evidence in a real-world patient population. We found that 5.2% (n=33) of our patients met the indication criteria, and about one-third (n=10) of them would be eligible for a CCM as a second device additional to another cardiac implantable electronic device implanted previously. In the analysis of Dulai et al. 5.1% of the examined cohort of hospitalized HF

patients were suitable for CCM therapy [135]. A previous review article from Abi-Samra estimated that 79% of patients with NYHA II-III and LVEF<35% could be eligible for CCM [136]. The reason for this apparent discrepancy in eligibility is that this rough estimation ignored some important eligibility criteria derived from the results of former RCTs.

The relatively small proportion of eligible patients in our patient cohort is due to several reasons. The main cause is that through accurate optimization of guideline-recommended therapy the proportion of highly symptomatic patients was reduced and LVEF increased significantly. The fact that the proportion of HFrEF patients receiving a target dose of neurohormonal antagonist therapy was fairly large (higher than reported in the ESC Heart Failure Long-Term Registry [137]) can explain this impressive improvement in NYHA class and LVEF. The relatively large proportion of CRT recipients could also have contributed to clinical improvement. Of course, our single-centre data cannot be automatically extrapolated to the whole CHF patient population, although we found that the baseline characteristics and prevalence of comorbidities in our cohort were very similar to those of the Hungarian and other large multicentric heart failure registry data [18,138-141]. The mean age was 61.3 years in our patient cohort, 63 years in Qualify Registry [140], 64.4 years in Hungarian Heart Failure Registry [139] and 66 years in ESC HF Long-term Registry [18] in chronic HF patients. The proportion of males was 76% in the Biology study to tailored treatment in chronic heart failure (BIOSTAT-CHF [141]) and Evidence based treatment - heart failure (EVITA [138]) Registries, 74% in Qualify Registry, 72.3% in Hungarian Heart Failure Registry and 76.1% in our patient population. The incidence of diabetes was 38.7%, 34% and 34.4% and incidence of hypertension was 75.8%, 64% and 72.5% in EVITA and Qualify Registries and in our patient cohort. Therefore, a similar eligibility proportion can be assumed in other heart failure patient populations. Our eligibility data are also in line with patient selection data from the FIX-HF-5C study, where only about one-third of patients who had signed informed consent passed baseline testing and underwent randomization [107].

There are presently several gaps in the evidence about CCM. If these are filled, the proportion of patients eligible for CCM is likely to increase in the future. First, in the above-mentioned RCTs it was predominantly patients with NYHA class III-IV who were included; there is a lack of evidence concerning whether NYHA II patients would also benefit from this therapy. We found that by ignoring this criterion the number of suitable patients increased to 13.3%. It is also important to note that in single-centre studies and in CCM-REG the

proportion of NYHA II patients was 8-20% [111,142,143], but this finding should be verified through further prospective studies. Second, since the previous generation CCM signal delivery algorithm required the sequential intracardiac sensing of a P wave and ventricular signal, patients with permanent or persistent atrial fibrillation were excluded from the randomized trials. The new-generation Optimizer Smart does not require the implantation of an atrial lead and contains an algorithm which also delivers a signal during atrial fibrillation. As approximately half of all patients with HF develop atrial fibrillation at some point [144], further studies are required to assess the effect of CCM in this patient population. Third, while the effects of CCM therapy have primarily been tested in patients with narrow or mildly prolonged QRS (<130msec), two studies with low patient numbers evaluated the efficacy of CCM among patients who had a wide QRS and were non-responders to CRT [145,146]. The authors found an improvement in quality of life and exercise tolerance, similar to the results of earlier randomized trials. Since about 20-40% of patients who receive CRT do not obtain benefit from CRT [147], CCM could be an alternative therapeutic option for them [134]. Finally, it is also important to mention that although the proportion of patients eligible for CCM was relatively small in our patient cohort, thus regarding the wide prevalence of disease this may mean a high total number of CCM candidates in the whole population.

8 LIMITATIONS

8.1 The impact of digoxin therapy on mortality of HFrEF patients

However, in our non-randomized patient cohort analysis, we aimed to minimize potential confounding factors by carefully adjusting our data along important patient characteristics potentially responsible for worse outcomes using two different statistical methods (i.e., adjusted multivariate Cox regression and propensity score matching), residual bias cannot be excluded, as this was pointed by Aguirre Dávila et al. in a recently published post-hoc analysis of the DIG trial [70]. The observed neutral effect of digoxin in the subgroup of patients with SDC<0.9ng/mL on mortality should be interpreted carefully, hence this group represents a small number of patients and has limited statistical power.

The data collection process for our patient cohort started in 2007. Since then, there have been changes in the guideline recommendations regarding the pharmacological and device treatment of HFrEF. These changes may have modified the mortality effect of digoxin.

Our single-centre patient population consisted of only Caucasians. Accordingly, the study's results do not necessarily apply to patients outside this group.

8.2 The eligibility for cardiac contractility modulation

Besides the single-centre character of the study, the main limitation of our work is that none of the patients received either sacubitril/valsartan or SGLT2 inhibitors in our patient population because these drugs were unavailable during the study period in Hungary. The further limitation was the short follow-up period of the current analysis involving only the period of treatment optimization of 3-6 months, and due to the progressive nature of the disease it is likely that the clinical state of some patients would have worsened over time despite optimized medical therapy, thereby becoming candidates for CCM.

9 CONCLUSIONS

Even nowadays, HFrEF represents a significant health issue due to its still unfavourable life expectancies comparable with several malignancies. Therefore, to improve its morbidity and mortality, the implementation and optimization of guideline-directed medical therapy, and if needed, device therapy is unquestionably fundamental.

9.1 The impact of digoxin therapy on mortality of HFrEF patients

Digoxin represents one of the oldest drugs in the armamentarium of the medical treatment of HFrEF. Although it has been relegated to the background of the pharmaceutical therapy of HFrEF within the last decade as a result of several observational studies and non-randomized recent data, the proportion of patients on digoxin in HFrEF is still relevant.

As a consequence of that and in the knowledge of the potentially harmful effect of digoxin frequently caused by the unfavourable high serum concentration and the lack of the regularly measured SDC, in our analysis the impact of SDC-guided digoxin therapy on mortality among HFrEF patients followed at a HFOC was evaluated. According to the results of our retrospective, single-centre study, serum-concentration-guided digoxin therapy was associated with increased all-cause mortality in optimally treated HFrEF patients, especially with SDC≥0.9 ng/mL. It has to be highlighted that the harmful effect of digoxin was not observed among patients with SDC less than 0.9 ng/mL. With a precise, regularly SDC-measured digoxin implementation, it was possible to maintain the SDC in the therapeutic range only in 40% of our patient cohort. It can be highlighted as well that the safe use of digoxin which does not lead to unfavourable outcomes in HFrEF, is hardly feasible.

9.2 The eligibility for cardiac contractility modulation

The initiation of the device therapy, in case of the persisting severely reduced LVEF in spite of the optimized guideline-directed medical therapy, plays a crucial role, a mandatory step in the complex care of symptomatic HFrEF patients. In this continuously developing field

of the treatment of HFrEF, besides the implantation of an ICD and/or CRT, CCM seems to be an interesting, promising new modality. Within the last years, several small, randomized, or observational studies revealed a potential beneficial effect of CCM as an add-on therapy in HFrEF. In the most recent FIX-HF-5C trial, a significant improvement with CCM at 24 weeks was verified regarding the quality of life and functional capacity. Moreover, a significant amelioration was confirmed in the composite of cardiovascular death and HF hospitalizations. However, it is not known what proportion of the HFrEF patients are suitable for this therapy in the everyday practice. Our short-term single-centre cohort study confirmed that nearly 5% of patients with HFrEF after treatment optimization would be eligible for CCM after completing the inclusion criteria of the FIX-HF-5C trial. Moreover, we found that by including all symptomatic HFrEF patients, the proportion of suitable patients increased to 13.3%.

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