THE LONG-TERM CLINICAL OUTCOME OF CARDIAC RESYNCHRONIAZTION THERAPY UPGRADE

PhD thesis

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List of Abbreviations

ACE-I - Angiotensin-Converting Enzyme Inhibitor

AF - Atrial Fibrillation

ARB - Angiotensin Receptor Blocker

ARNI - Angiotensin Receptor-Neprilysin Inhibitor

AUC - Area Under the Receiver Operating Characteristic Curve

AVID - Antiarrhythmics Versus Implantable Defibrillators

AVJ - Atrioventricular Junction

BMI - Body Mass Index

BNP - B-Type Natriuretic Peptide

BUDAPEST-CRT - Biventricular Upgrade on left ventricular reverse remodelling and clinical outcomes in patients with left ventricular Dysfunction and intermittent or permanent APical/SepTal right ventricular pacing Upgrade CRT

CABG - Coronary Artery Bypass Graft Surgery

CAD - Coronary Artery Disease

CARE-HF - the CArdiac REsynchronization-Heart Failure

CASH - Cardiac Arrest Survival in Hamburg

CI - Confidence Interval

CIED - Cardiac Implantable Electronic Devices

CIDS - Canadian Implantable Defibrillator Study

CKD - Chronic Kidney Disease

CRT - Cardiac Resynchronization Therapy

CRT-D - Cardiac Resynchronization Therapy-Defibrillator

CRT-P - Cardiac Resynchronization Therapy-Pacemaker

CSP - Conduction System Pacing

DANISH - Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Heart Failure on Mortality

DAVID - Dual Chamber and VVI Implantable Defibrillator

DEFINITE - Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation

DINAMIT - Defibrillator in Acute Myocardial Infarction Trial

DM - Diabetes Mellitus

ECG - Electrocardiogram

eGFR - Estimated Glomerular Filtration Rate

EMPHASIS-HF - Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure

ESC - European Society of Cardiology

ESC-HF-LT - European Society of Cardiology Heart Failure Long-Term Registry

GFR - Glomerular Filtration Rate

HbA1c - Hemoglobin A1c

HF - Heart Failure

HFH - Heart Failure Hospitalization

HFrEF - Heart Failure with Reduced Ejection Fraction

HFmrEF - Heart Failure with Mid-Range Ejection Fraction

HFpEF - Heart Failure with Preserved Ejection Fraction

HR - Hazard Ratio

HT - Hypertension

HTX - Heart Transplantation

ICD - Implantable Cardioverter Defibrillator

IRIS - Immediate Risk-Stratification Improves Survival

IQR - Interquartile Range

LBB - Left Bundle Branch

LBBAP - Left Bundle Branch Area Pacing

LBBB - Left Bundle Branch Block

LBBP - Left Bundle Branch Pacing

LV - Left Ventricle

LVAD - Left Ventricular Assist Device

LVEDd - Left Ventricular End Diastolic Diameter

LVEDV - Left Ventricular End-Diastolic Volume

LVEF - Left Ventricular Ejection Fraction

LVESd - Left Ventricular End Systolic Diameter

LVESV - Left Ventricular End-Diastolic Volume

LVSP - Left Ventricular Septal Pacing

MADIT-I - Multicenter Automatic Defibrillator Implantation Trial

MADIT-CRT - Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy

MDS - Multidimensional Scaling

MDRD - Modification of Diet in Renal Disease

MI - Myocardial Infarction

ML - Machine Learning

MLP - Multi-Layer Perceptron

MOST - Mode Selection Trial in Sinus-Node Dysfunction

MR-proANP - Mid-Regional Pro-Atrial Natriuretic Peptide

MRA - Mineralocorticoid Receptor Antagonist

NP - Natriuretic Peptide

nsVT – non-sustained Ventricular Arrhytmia

NT-proBNP - N-Terminal Pro-B-Type Natriuretic Peptide

NYHA - New York Heart Association

OAC - Oral Anticoagulation

OMT - Optimal Medical Treatment

OR - Odds Ratio

PCI - Percutaneous Coronary Intervention

PM - Pacemaker

PTX - Pneumothorax

QoL - Quality of Life

RCT - Randomized Controlled Trial

RV - Right Ventricle

RVP - Right Ventricular Pacing

SCD - Sudden Cardiac Death

SCD-HeFT - Sudden Cardiac Death in Heart Failure Trial

SD - Standard Deviation

SENIORS - Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure

SGLT2 - Sodium-Glucose Co-Transporter 2

sVT - Sustained Ventricular Arrhythmia

TDA - Topological Data Analysis

USA - United States of America

VA - Ventricular Arrhythmia

VF - Ventricular Fibrillation

1. Introduction

1.1. Heart Failure

Heart failure (HF) is a clinical syndrome characterized by signs and/or symptoms caused by structural and/or functional cardiac abnormalities, leading to reduced cardiac output and/or elevated cardiac filling pressures. (1). Additionally, it is often accompanied by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion (1, 2).

The classification of HF is most frequently based on the left ventricular ejection fraction (LVEF). By LVEF, three main cohorts are identified: heart failure with reduced ejection fraction (HFrEF), where LVEF ≤40%, heart failure with mid-range ejection fraction (HFmrEF), where LVEF is 41-49%, heart failure with preserved ejection fraction (HFpEF), where LVEF is ≥50% (1, 2).

Additionally, a fourth category is recognized, based on the trajectory of LVEF changes (2). This cohort includes HF patients whose baseline LVEF was ≤40% but who have shown an improvement of at least 10% in LVEF during follow-up, resulting in an LVEF >40%, as per the most recent 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure (2).

1.2. Prevalence of Chronic Systolic Heart Failure

The global prevalence of HF is estimated to be 1-3% in the adult population and is expected to rise by 2030 (1, 2). This rise is attributed to the aging population, reduced mortality rates among patients due to advances in HF therapy, and improved infarction treatment, which often leads to HF (1, 2).

HF prevalence varies globally, influenced by socioeconomic factors, and increases with age, with those over 65 being nine times more likely to have HF (1, 3-5). Within the overall HF population, the distribution of LVEF-based HF phenotypes indicated that HFrEF is the most common HF type globally (47-59.8%), followed by HFpEF (16-39%) and HFmrEF (14-24.2%) (6-9). Furthermore, within these HF categories, the prevalence of HFpEF is showing an upward trend, while HFrEF prevalence has stabilized or declined in some regions due to improved therapies (1, 2, 10).

In Hungary, the prevalence of patients treated for HF decreased in general from 1.6% in 2009 to 1.1% in 2017 (11). Additionally, the prevalence rates of HF categories (HFrEF 57.5%; HFpEF 28.9%; HFmrEF 13.6%) are consistent with those reported in international literature (12).

1.3. Incidence of Chronic Systolic Heart Failure

In developed countries, HF incidence rates have plateaued or begun to decline (13). Most data are from Europe and North America, where incidence is between 3.2 and 20.9 per 1,000 person-years (1, 14, 15). In the United States of America (USA), a 37% decrease in age- and sex-adjusted HF incidence from 2000 to 2010 was observed (15). The HF incidence rates were 6.1 [Interquartile range (IQR) (5.8-6.3)] per 1,000 person-years for HFpEF patients, while for HFrEF patients, the rates were 2.0 (IQR 1.9-2.1) per 1,000 person-years (16, 17). Additionally the decrease in HF incidence was more pronounced in the HFrEF group (45%) as compared to the HFpEF group (28%) (15).

1.4. Etiology of Heart Failure

HF is a complex syndrome often resulting from multiple comorbidities (1). The most common causes include ischemic heart disease, hypertension (HT), valvular and rheumatic heart disease, idiopathic dilated cardiomyopathy, infiltrative disease, toxic cardiomyopathy, tachycardia-induced cardiomyopathy, endocrine causes, chemotherapy and radiotherapy-induced cardiomyopathy, and congenital heart disease (1). Regional differences in HF etiology are significant (1).

In Europe and North America, ischemic heart disease is identified in 49-60% of HFrEF patients, 42-61% of HFmrEF patients, and 24-54% of HFpEF patients (8, 18, 19). Hypertension is observed in 56% of HFrEF patients, 64% of HFmrEF patients, and 72% of HFpEF patients (18). Valvular disease as a primary HF cause is identified in 4% of HFrEF patients, 10% of HFmrEF patients, and 20% of HFpEF patients (8, 20). Regarding oncological treatments, left ventricular (LV) dysfunction is observed in 2.1-4.1% of patients treated with anthracyclines and trastuzumab (21-23). Among patients receiving radiotherapy, approximately 10% may develop HF, with 64% of these patients eventually developing HFpEF (24). Congenital heart disease leads to HF in about 25% of patients by adulthood (25, 26).

1.5. Outcomes of Heart Failure

HF remains a significant clinical challenge, with over one million hospitalizations occurring annually in the USA (27). These HF hospitalizations (HFH) can be categorized into two distinct entities: for de novo HFH or worsening chronic HFH (28). De novo HFH patients are generally younger, more likely to be female, have a non-ischemic etiology, and present with HFpEF, all of which contribute to better post-discharge survival compared to those with worsening chronic HFH (29). In contrast, patients hospitalized for worsening chronic HF are typically older, have more complex comorbidities, are more frequently undertreated (28). The worsening HFH population account for the majority of HFHs (29). De novo HFH patients demonstrated a 37% lower rate of composite all-cause mortality or HF readmission compared to those with worsening HFHs (30).

The 1-year mortality rate in acute heart failure is approximately 2 to 4 times higher than that in stable chronic heart failure (35-45% vs. 10-20%)(31-34). Additionally, differences can be observed between the LVEF-based HF classifications, with 1-year mortality rates of 8.8% in HFrEF, 7.6% in HFmrEF, and 6.3% in HFpEF (35). At the same time, a significant improvement has been observed in the 5-year survival rate of HF patients between 1970-1979 and 2000-2009, rising from 29.1% (25.5-32.7) to 59.7% (54.0-59.4), highlighting the advancements in HF treatment (36). Over the past 15-20 years, several new randomized controlled trials (RCT), have demonstrated the beneficial effects of beta-blockers, Mineralocorticoid Receptor Antagonists (MRA), Angiotensin Receptor-Neprelysin Inhibitors (ARNI), and Sodium-Glucose Co-Transporter 2 (SGLT-2) inhibitors on all-cause mortality or cardiovascular mortality, or HF-related hospitalization in HF patients (37-42). Based on a systematic network meta-analysis, the combined use of these four drug classes in HFrEF patients yields a Hazard Ratio (HR) of 0.39 [95% Confidence Interval (CI) 0.31-0.49], indicating a significant benefit in reducing all-cause mortality compared to no drug treatment (43).

1.6. Diagnosis of Heart Failure

To diagnose chronic HF, the presence of symptoms and/or signs must be accompanied by objective evidence of cardiac dysfunction (44). Typical symptoms of HF include ankle swelling, lower leg oedema, fatigue, tiredness, dyspnoe, inability to exercise, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance (2).

Less typical symptoms include a bloated feeling, confusion (especially in the elderly), depression, dizziness, syncope, loss of appetite, nocturnal cough, and wheezing (2).

More specific signs of HF encompass , laterally displaced apical impulse, elevated jugular venous pressure, hepatojugular reflux, summation gallop with third and fourth heart sounds, and third heart sound (2). Less specific signs include ascites, cardiac murmur, cold extremities, hepatomegaly, narrow pulse pressure, oliguria, peripheral edema (ankle, sacral, scrotal), pulmonary crepitations, pleural effusion, tachycardia, irregular pulse, tachypnoea, unintentional weight gain (>2 kg/week), weight loss (in advanced HF) and cachexia (2). However, the presence or absence of these symptoms and signs alone is insufficient for a definitive HF diagnosis (45, 46). One of the most common symptoms of HF is dyspnoea, which is neither sensitive nor specific to the condition (47). However, bilateral basal pulmonary end-inspiratory rales, elevated jugular venous pressure, and leg/ankle oedema are relatively specific for HF but exhibit low sensitivity (50-60%) (47).

The 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF recommend the following for patients suspected of having chronic HF: measurement of plasma natriuretic peptide (NP) concentration, a 12-lead electrocardiogram (ECG), transthoracic echocardiography, chest radiography (X-ray), and routine blood tests (44). These blood tests should include a full blood count, urea and electrolytes, thyroid function, fasting glucose and hemoglobin A1c (HbA1c), lipids, and iron status (transferrin saturation and ferritin) (44).

In HF, an ECG can reveal various abnormalities such as atrial fibrillation (AF), pathological Q waves, LV hypertrophy, and a widened QRS complex (44). However, the diagnostic specificity of ECG alone is insufficient (48).

The guidelines recommend plasma NP measurement as the initial diagnostic test to rule out HF (44). The latest European ESC HF Guidelines suggest using the following cut-off values: B-type natriuretic peptide (BNP) <35 pg/mL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) <125 pg/mL, or mid-regional pro-atrial natriuretic peptide (MR-proANP) <40 pmol/L (44). Values above these thresholds support an HF diagnosis (44). These biomarkers exhibit high diagnostic accuracy, with a negative predictive value for HF ranging from 0.94 to 0.98 (49, 50). Numerous cardiac and non-

cardiac conditions can influence NP levels (44). Moreover, in older patients (>75 years), the diagnostic accuracy of NT-proBNP may be slightly reduced (47). Another notable condition is obesity, which is associated with lower NP release compared to non-obese patients. Some studies suggest that to optimize diagnostic accuracy in obese patients, NP cut-off values should be adjusted to at least 50% lower than the standard values (47, 51).

Performing a transthoracic echocardiographic examination is advantageous for diagnosing HF for several reasons. This method allows for the determination of the LVEF, which helps classify HF patients into HFrEF, HFmrEF, and HFpEF groups (44). Additionally, it enables the assessment of regional wall motion abnormalities, chamber sizes, valvular functions, and diastolic function of the heart (44).

A chest X-ray is recommended to support the diagnosis of HF (44). This imaging technique can help identify other causes of dyspnoea, such as pulmonary conditions, and reveal abnormalities associated with HF, such as pulmonary congestion or cardiomegaly (44).

1.7. Treatment of Heart Failure with Reduced Ejection Fraction

When treating patients with HF, three primary goals should be considered: improving survival, preventing recurrent HFH, and enhancing clinical symptoms, functional capacity, and quality of life (QoL) (44).

1.7.1. Pharmacological Treatment of Heart Failure with Reduced Ejection Fraction

The cornerstone of pharmacological therapy for patients with HFrEF includes angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), ARNI, beta-blockers, MRAs, and SGLT2 inhibitors. ACE-I, ARBs, beta-blockers, MRAs, and SGLT2 inhibitors considered as IA indications and ARNI as an IB indication for the HFrEF population (44). These medications reduce mortality and the risk of HFH (52-59). Furthermore, recent meta-analyses indicate that HF patients treated with ARNI or SGLT2 inhibitors have a reduced risk of sudden cardiac death (59, 60). In patients who cannot tolerate ACE-I or ARNI, ARBs are recommended (44). SGLT2 inhibitors (dapagliflozin and empagliflozin) have been added to the treatment regimen of patients regardless of their diabetes mellitus (DM) status, further reducing mortality and the risk of HFH in HFrEF patients (61, 62).

Other medications, such as diuretics, ivabradine, a combination of hydralazine and isosorbide dinitrate, digoxin, and vericiguat, can be used for selected HFrEF patients who remain symptomatic. (44). Overall, these medications can be used to complement the base treatments or as alternatives if the base treatments are intolerated (44). Research has shown that the use of these medications, in addition to the base therapy, is associated with reductions in mortality and HFH events (57, 63-67). Furthermore, intravenous iron supplementation is also recommended for patients with symptomatic HF and iron deficiency (68).

1.7.2. Non-pharmacological Treatment of Heart Failure with Reduced Ejection Fraction

In addition to optimal medical treatment (OMT), the management of HFrEF patients also include implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT) (44). Their use is recommended for well-selected patients as per guideline recommendations (44).

1.7.2.1. Implantable Cardioverter-Defibrillator

In HFrEF patients, 40-45% of deaths can be attributed to SCD (69). SCD refers to unexpected death resulting from circulatory arrest, most commonly due to ventricular fibrillation (VF), sustained ventricular tachycardia (sVT), or asystole occurring within one hour of symptom onset (70). The incidence of SCD is higher among patients with milder symptoms New York Heart Association (NYHA) functional class II-III compared to those with NYHA class IV (71, 72). Among the various factors associated with the risk of SCD, reduced LVEF emerges as the most significant predictor, while other factors, such as coronary heart disease, male sex, advancing age, and black race, also contribute in the overall assessment (73-77).

ICDs are effective in detecting and terminating potentially fatal ventricular arrhythmias (VA) and can also manage bradycardia (44). While robust evidence supports the protective effect of ICDs against SCD, it's important to note that these findings are based on older studies (69, 78-81). Despite the significant reduction in SCD incidence from 6.5% to 3.3% due to current OMT and some antiarrhythmic drugs, there is a need

for new trials to determine whether ICDs still offer the same benefit in the modern pharmacological era with already reduced SCD rates (44, 82, 83).

1.7.2.1.1. Secondary Prevention

Patients with a history of hemodynamically unstable VA or SCD making them candidates for ICD implantation, are considered for secondary prevention (44). According to guidelines, ICD implantation is recommended for these patients if they have a life expectancy of more than one year, good functional status, and no reversible cause for their condition unless the VA occurred within 48 hours of a MI (44).

The impact of ICDs on survival has been compared with antiarrhythmic drugs such as amiodarone and metoprolol in RCTs, including the Antiarrhythmics Versus Implantable Defibrillators (AVID), Cardiac Arrest Survival in Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS) (81, 84, 85). The majority of patients in these studies were male (78-85%) and had a high prevalence of coronary artery disease (CAD) (73-81%) (75).

Meta-analyses of these trials have shown that patients treated with ICDs had lower all-cause mortality (HR 0.72; 95% CI 0.60-0.87, $p = 0.0006$) and reduced arrhythmic death (HR 0.50; 95% CI 0.36-0.67, $p < 0.0001$) compared to those treated with amiodarone (80). However, there was no significant difference between the two groups in terms of non-arrhythmic mortality (80). Subgroup analyses also revealed that the benefit of ICD treatment is less pronounced in patients with LVEF >40% compared to those with HFrEF (80).

1.7.2.1.2. Primary Prevention

ICD implantation for primary prevention is considered when the patient has no history of malignant VA (44). While secondary prevention with ICDs involves a clearly defined patient population, selecting appropriate patients for primary prevention who will benefit from the therapy and determining the optimal timing of the intervention still remains challenging (86).

Based on the recent ESC guidelines, the strongest evidence for the use of ICDs for primary prevention is in symptomatic NYHA class II-III HF patients with ischemic etiology (but not within 40 days of an MI), LVEF ≤35% despite receiving OMT for at least three months, and a life expectancy of more than one year with good functional status (44, 87).

Several RCTs have studied the efficacy of ICD implantation for primary prevention in both ischemic and non-ischemic etiology patients (86). The Multicenter Automatic Defibrillator Implantation Trial (MADIT-I) investigated a highly selective cohort of patients who had experienced a MI and had severely reduced LVEF <35% with additional arrhythmic risk factors, such as non-sustained ventricular tachycardia (nsVT) and inducible, non-suppressible ventricular tachyarrhythmias during electrophysiological study (88). Patients were randomized to receive either an ICD or standard therapy, including antiarrhythmic drugs, and followed for a median of 27 months. The results demonstrated a significant reduction in all-cause mortality in the ICD group (HR 0.46; 95% CI 0.26-0.92; p = 0.009) (88). However, the study's limitations included a relatively small proportion of patients receiving β-blockers and ACE inhibitors, which are now standard of care, and could potentially influence the outcome (88).

The MADIT-II trial expanded the inclusion criteria from previous studies by enrolling patients with CAD and a LVEF of ≤30% post-MI, without requiring additional arrhythmic risk factors, such as nsVT or inducible VAs during electrophysiological study (89). This shift marked a significant broadening of the eligible patient population compared to earlier trials. Over a median follow-up of 20 months, patients in the ICD group demonstrated a lower all-cause mortality rate compared to those receiving pharmacological treatment (HR 0.69; 95% CI 0.51-0.93; p = 0.016) (89). A post hoc analysis revealed that the mortality benefit was primarily attributable to a reduction in SCD, with the most pronounced benefit observed in patients with a QRS duration >150ms (90).

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was the first to include nearly equal proportions of ischemic and non-ischemic HFrEF patients with NYHA class II-III (79). Patients were randomized to conservatively programmed ICD, amiodarone, or placebo (79). Over a 45.5-month follow-up, the ICD group had better

survival (HR 0.77; 97.5% CI 0.62-0.96; p = 0.007), with the most significant impact seen in the ischemic subgroup (79). Although non-ischemic patients had lower mortality rate, this difference was not statistically significant (HR 0.73; 97.5% CI 0.50-1.07; p = 0.06) (79).

Both the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and the Immediate Risk-Stratification Improves Survival (IRIS) study included patients who had an MI within 40 days (78, 91). Both studies found lower arrhythmic death and SCD rates in the ICD group (HR 0.42; 95% CI 0.22-0.82; p = 0.009 in DINAMIT; HR 0.55; 95% CI 0.31-1.00; p = 0.049 in IRIS), but higher non-arrhythmic death rates (HR 1.75; 95% CI 1.11-2.76; p = 0.02 in DINAMIT; HR 1.92; 95% CI 1.29-2.84; p = 0.001 in IRIS) compared to the standard treatment group (78, 91).

For non-ischemic cardiomyopathy, trials such as the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) and the Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Heart Failure on Mortality (DANISH) showed no significant difference in all-cause mortality between the ICD and control groups. However, the ICD group had lower arrhythmic death rates (HR 0.20; 95% CI 0.06-0.71; p = 0.006 in DEFINITE; HR 0.50; 95% CI 0.31-0.82; p = 0.005 in DANISH) (92, 93). Subgroup analyses in DANISH indicated that younger patients (<59 years) and those with higher NT-proBNP levels (>1177 pg/ml) benefited more from ICD therapy in terms of all-cause mortality reduction (92, 93).

Overall, these study results suggest that an ICD can have a mortality benefit in selected patients (86). The most significant benefit of ICD treatment is observed in patients with ischemic etiology, especially when the device is implanted ≥40 days after an MI event (86). Implanting the device too early can be harmful (78, 86, 91). The least favorable mortality benefit is seen in non-ischemic patients, likely due to the lower incidence of SCD in this population (86, 92, 93).

1.7.2.2. Cardiac Resynchronization Therapy

Cardiac Resynchronization Therapy is a cornerstone of device-based treatment for HFrEF patients who remain symptomatic despite OMT and have a wide QRS complex (44, 87). CRT implantation in patients without previous cardiac implantable electronic

devices (CIEDs) is referred to as de novo CRT implantation. By pacing both the right ventricle (RV) and LV, biventricular pacing can reduce intraventricular and interventricular conduction delay, thereby decreasing electromechanical dyssynchrony (44). LV pacing can be achieved by placing the LV pacing lead using a transvenous approach via the subclavian vein and superior vena cava, allowing for the cannulation of the coronary sinus and placement of the lead in a side branch of the coronary sinus (94). Other approaches include surgically placing the lead on the epicardium or using the transseptal technique, where the interventricular septum is punctured to place the lead directly in the endocardium of the LV (94).

Among the newer approaches is left bundle branch area pacing (LBBAP), including both left bundle branch pacing (LBBP) and left ventricular septal pacing (LVSP), aims to resolve intraventricular conduction delays, particularly in patients who do not respond to or are unsuitable for biventricular pacing (95). LBBAP techniques involve capturing the left bundle branch (LBB) or pacing the left ventricular septum, ensuring synchronous electrical activation of the LV (95). This method is showing promise not only for patients with unsuccessful CRT implantation but is also being investigated in clinical trials as a potential treatment option (96). Based on studies with smaller sample sizes, these approaches can lead to reverse cardiac remodeling, resulting in improved LVEF, reduced mortality, enhanced QoL, and better exercise capacity (44, 97, 98). However, not all patients will experience these benefits to the same extent (44). Based on these results with a IIa B evidence level His bundle pacing should be considered in patients whom coronary sinus lead implantation was unsuccessful.

Resynchronization therapy can also be performed in patients with already implanted CIEDs associated with high right ventricular pacing (RVP) burden and developing symptomatic HF (44). In these cases, CRT upgrade procedures can resolve the electromechanical dyssynchrony and LVEF decrease caused by previous RV pacing and treat HFrEF (87).

1.7.3. Efficacy of Cardiac Resynchronization Therapy

1.7.3.1. Mechanism of Action

Approximately one-third of HF patients with systolic dysfunction exhibit ventricular dyssynchrony attributable to left bundle branch block (LBBB) (99). This dyssynchrony can occur due to disturbances in ventricular activation and contraction, which affect one or more ventricular segments (100). Such uncoordinated contractions reduce the heart's effective pump function (100). In LBBB patients, early activation of the septum and delayed activation of the LV free wall can be observed (101). This leads to decreased septal workload, hypoperfusion, increased workload of the LV free wall (102). As a result, LV is moving dyssynchronously, leading to reduced LV systolic function due to uncoordinated contractions (77). Additionally, these patients may develop atrioventricular dyssynchrony, which can be reflected in the ECG as a prolonged PR interval (87). The primary mechanism of CRT involves sequential stimulation of the left ventricle's latest activating area, the right ventricle, and in patients with sinus rhythm, the right atrium, maintaining AV synchrony. This reduces intra-, interventricular, and atrioventricular dyssynchrony (103). As a result, stroke volume may increase, and both mitral regurgitation and QRS width may decrease. Additionally, cardiac remodeling can be observed, which is associated with increased LVEF and decreased end-diastolic and end-systolic volumes and diameters. Furthermore, patients' functional capacity and NYHA class may improve, leading to better long-term survival and lower risk of HF-related hospitalizations.

1.7.3.2. Definition of Response Following Cardiac Resynchronization Therapy

The favorable changes in functional capacity, echocardiographic parameters, hard endpoints, and clinical composite endpoints observed after CRT implantation referred to as responders (104). However, the concept of a responder is not precisely defined. Clinical trials most commonly use two aspects to determine responders: changes in echocardiographic parameters or changes in functional parameters (87). Echocardiographic parameters typically examined include LVEF, LV end-systolic diameter (LVESd), LV end-diastolic diameter (LVEDd), LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) (104). However, there can be

variations among studies regarding which cut-offs in these variables define as a positive response. Some studies associate responders with a 5-10% increase in LVEF or a ≥10-15% decrease in LVESV (87). Additionally, responders can be linked to improvements in functional parameters such as a reduction in NYHA functional class, an increase in distance during the six-minute walk test, or improvements in scores of QoL questionnaires (87).

Another crucial element in defining responders is the timing of reassessment of the parameters, with echocardiographic and functional parameters most often evaluated within 6-12 months following device implantation (104). Based on the degree of changes in echocardiographic parameters, different grades of responders can be distinguished: super-responders, responders, and non-responders, with the proportion of responders ranging from 30-50% and non-responders ranging from 30-45% in the literature (105, 106). However, this classification appears to be evolving based on recent literature. Patients whose baseline LVEF remains stable and shows no further progression during follow-up after CRT are now referred to as non-progressors rather than non-responders (107). This distinction has become necessary because recent research has shown that those categorized as non-progressors following CRT demonstrate better mid-term outcomes compared to patients who exhibit a decline in LVEF despite treatment (108).

1.7.3.3. Current Indications of De novo Cardiac Resynchronization Therapy

CRT significantly improves cardiac function, symptoms, and QoL in HF patients, particularly those with NYHA class II-IV and LBBB with ≥150ms QRS width, reducing morbidity and mortality (87). However, 20-30% patients respond unfavorably to CRT (87). Factors predicting CRT response include QRS width and morphology, showing a better response in LBBB patients as compared to non-LBBB patients (87).

The latest ESC guidelines recommend de novo CRT implantation for symptomatic HFrEF patients in sinus rhythm, with LBBB and a QRS ≥150ms, at a Class IA evidence (87, 97, 109-112). For similar patients with QRS widths of 130-149ms, the recommendation is Class IIa B evidence, (87, 110, 113-115). The guideline highlights the significance of QRS width and morphology with these differences in levels of evidence. For symptomatic HFrEF patients in sinus rhythm with a QRS ≥150ms but non-LBBB morphology, CRT implantation is recommended at a Class IIa B evidence (87,

110, 113-115). However, for non-LBBB patients with QRS widths of 130-149ms, the guideline provides CRT at a IIb B evidence (87, 116-118). The guidelines do not recommend CRT for HF patients with QRS widths <130ms (87, 119, 120).

For patients with persistent or permanent AF unsuitable for AF ablation or after unsuccessful ablation, CRT should be considered, particularly in those with HFrEF (87). For symptomatic (NYHA III-IV) HFrEF patients with an intrinsic QRS >130ms, the guideline provides a Class IIa C evidence recommendation (87, 121-123). Large registries indicate higher mortality risk in AF patients undergoing CRT as compared to sinus rhythm, even after adjusting for clinical variables (124, 125). Achieving >90-95% biventricular pacing often requires atrioventricular junction (AVJ) ablation, improving outcomes similar to those in sinus rhythm (121, 126).

CRT is recommended for those where AF ablation is not possible or declined, and AVJ ablation might be necessary for adequate biventricular pacing (87). Effective biventricular pacing is crucial for CRT success, but AF with fast, irregular ventricular rates can reduce the rate of effective pacing (87). Conduction system pacing (CSP) is an emerging alternative for CRT, especially useful in AF patients undergoing AVJ ablation (87, 127, 128). These techniques seem to be non-inferior achieving QRS narrowing and mechanical resynchronization compared to traditional CRT, pending further validation in large trials (87, 129-131).

1.8. Upgrade Cardiac Resynchronization Therapy

Conventional Pacemakers (PMs) or ICDs induce an LBBB-like activation pattern due to RVP, leading to electromechanical dyssynchrony (102). This results in reduced myocardial work and impaired cardiac pump function, manifesting as decreased LVEF (101, 132-134). Additionally, dyssynchrony can induce mitral regurgitation (132). Besides impairing systolic function, RVP can also negatively impact diastolic function by causing a decline in myocardial lengthening and chamber filling time (132, 135).

The Mode Selection Trial in Sinus-Node Dysfunction (MOST) and The Dual Chamber and VVI Implantable Defibrillator (DAVID) trials have shown that chronic RVP ≥40% is associated with an increased risk of HFH or AF, which can be mitigated by CRT upgrade (136-140).

Patients referred for CRT upgrade constitute 20-30% of all CRT implantations (87). This patient population significantly differs from those receiving de novo CRT therapy in terms of baseline characteristics, as they tend to be older, predominantly male, and have a higher prevalence of comorbidities such as AF, ischemic heart disease, anemia, and renal failure (141). Several small observational retrospective studies with short follow-up periods have compared the outcomes between patients undergoing de novo CRT and those receiving CRT upgrade (87, 141). However, the reported findings across these studies are not consistent (141). A meta-analysis by Kosztin et. al that compared the two groups was unable to demonstrate a significant difference in all-cause mortality or HF events (141). Although some studies have reported higher complication rates associated with CRT upgrade compared to de novo procedures, including a higher incidence of complications such as perforation, pneumothorax (PTX), and lead revision or dislocation in the upgrade group (142).

According to the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy, the current recommendations still advocate for CRT upgrade in patients with conventional PM or ICDs who remain symptomatic with HFrEF and have a significant burden of RVP, with a Class IIa, Level B evidence (87). However, in light of the findings from the Biventricular Upgrade on left ventricular reverse remodelling and clinical outcomes in patients with left ventricular Dysfunction and intermittent or permanent APical/SepTal right ventricular pacing Upgrade CRT (BUDAPEST-CRT) RCT, this evidence level is expected to be revised in future guideline updates (140).

The BUDAPEST-CRT Upgrade trial was the first RCT to demonstrated that, in an elderly, multimorbid HFrEF cohort with a high (≥20%) RVP burden, upgrading to CRT-D significantly reduced the incidence of the composite endpoint of all-cause mortality, HFH, or <15% reduction in LVESV compared to ICD-only therapy (140). The secondary composite endpoint, composed of all-cause mortality and HFH events (HR 0.27; 95% CI 0.16-0.47, p <0.001), with the result primarily driven by the HFH events (140). Another important finding of the study was that during the median follow-up of 12.4 months, the incidence of major VAs was significantly lower in the CRT-D upgrade group [1/215 patients (0.5%)] compared to the ICD group [21/145 patients (14.5%)]. This

suggests that resynchronization therapy may reduce the risk of SCD even in polymorbid patients requiring CRT upgrades.

The Cardiac REsynchronization-Heart Failure (CARE-HF) Trial also demonstrated that resynchronization therapy reduces SCD risk in patients receiving de novo CRT-P implantation compared to those receiving medical therapy (HR 0.54; 95% CI 0.35-0.84; p=0.006) therefore, CRT appears to decrease SCD risk independently of defibrillator function (112). Furthermore, it is also known from the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial that the risk of developing a ventricular tachyarrhythmia events decreases in echocardiographic responder patients whose LVESV is reduced by ≥25% one year after the CRT intervention (143).

Deciding which patients should receive an ICD backup during CRT upgrade and may have a long-term mortality benefit requires significant clinical expertise, considering various patient characteristics such as age, ischemic HF etiology, and renal function (87). Furthermore, potential complications related to the procedure must also be measured. CRT-D devices are associated with a higher incidence of infectious complications and right ventricular lead issues compared to CRT-P devices (144-147). Additionally, inappropriate shocks can occur with CRT-D devices, which can significantly impair the quality of life for patients (147).

1.9. Definition of Artificial Intelligence and Machine Learning

Artificial Intelligence (AI) is a field of computer science focused on creating systems capable of performing tasks that typically require human intelligence (148). These tasks include reasoning, learning, problem-solving, perception, and language understanding (148). AI systems are designed to analyze data, learn from it, and make informed decisions or predictions based on that data (149). Common applications of AI include machine vision, speech recognition, and natural language processing (148).

ML is a subset of AI that involves the development of algorithms and statistical models that enable computers to learn from and make decisions based on data (150). Instead of being explicitly programmed to perform a task, ML algorithms use patterns

and inference to improve their performance over time as they are exposed to more data (150). ML is particularly effective for tasks like pattern recognition, data mining, and predictive analytics (148).

1.10. Machine Learning in Cardiovascular Medicine

Today, an increasing amount of healthcare data is being generated, forming larger and more complex data structures and databases (151). With advancements in computing power and software, more complex calculations can be performed in shorter periods (151). The combined development of these two factors has enabled the analysis of healthcare data using machine learning (ML) (150).

ML algorithms are increasingly used in clinical practice, offering valuable diagnostic and predictive tools. For example they can identify patients with HFrEF patients or predict arrhythmias from ECG recording (152-154), and assess risks like 30-day hospital readmissions in HF patients (155). By enhancing diagnosis and prediction, ML is transforming cardiovascular care.

ML may aid in enhancing the efficacy of CRT by enabling more precise patient selection and response prediction, thereby optimizing patient selection and improve clinical outcomes. Various studies have demonstrated that ML algorithms can integrate complex clinical, echocardiographic, and ECG data to identify phenogroups of HF patients with distinct response patterns to CRT (156-159). This categorization allows clinicians to better predict which patients are likely to benefit from the therapy or optimal device selection, thus improving overall treatment success rates and minimizing non-responder rates (160).

Moreover, ML models have been demonstrated the ability to enhance traditional guideline-based approaches in predicting CRT outcomes by incorporating a broad array of patient-specific variables, such as left ventricular function, biomarkers, and anatomical features (157). An example of this advancement is the SEMMELWEIS-CRT score developed by Tokodi et al., which utilizes ML to predict 1- to 5-year mortality rates in CRT patients (161). This score, derived from pre-implant clinical data, has demonstrated superior predictive capabilities compared to existing risk scores, offering a more

personalized approach to patient management and significantly enhancing the selection process for CRT candidates (161).

1.11. Comparison of Conventional Statistics and Machine Learning

Traditional statistical methods are generally simpler to understand and interpret, focusing on a limited number of clinically important variables, and providing clear measures of association like Odds Ratios (OR) and HRs, which are essential for understanding biological mechanisms (162). However, ML offers greater flexibility, as it does not rely on strong a priori assumptions and can handle large datasets and complex data types, easily addressing interactions between variables that challenge traditional methods (162, 163).

While traditional statistics aim to describe relationships between predictors and outcomes, focusing on hypothesis testing and effect size estimation, ML is primarily concerned with developing highly accurate predictive models, often at the expense of interpretability (162). This difference in purpose reflects the broader methodological priorities of each approach. ML's complexity, requiring extensive data preprocessing and iterative refinement, can lead to overfitting, where the model becomes overly tailored to the training data, capturing noise and reducing its generalizability (162).

Traditional statistical methods are more appropriate when there is substantial prior knowledge and the dataset has a large number of observations relative to the variables, as is common in public health research (163, 164). In contrast, ML excels in scenarios involving numerous variables and complex interactions, making it more suitable for predictive tasks (162).

1.12. Types of Machine Learning Systems

The ML algorithms are capable of predict the output variable's value by taking input features and setting hyperparameters (165). If the output variable is continuous, such as a laboratory or echocardiographic parameter, a regression task is performed (165). If it involves predicting a disease development or determining a risk group, a classification task is performed, which can be binary or multiclass (165).

There are four main categories of ML algorithms: supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning (166). In supervised learning, the algorithm is trained on a labeled dataset where each example is paired with an output label. Unsupervised learning works with unlabeled data to identify patterns or structures (166). The main applications include clustering analysis (grouping data points by similarity), density estimation (finding data distribution in space), and dimensionality reduction (which reduces the number of variables while preserving essential information) (165). Semi-supervised learning combines a small amount of labeled data with a large amount of unlabeled data, leveraging the labeled data to improve accuracy and efficiency compared to unsupervised learning (166). An example is Google Photos, which automatically recognizes and organizes photos of the same person (165). Reinforcement learning trains an agent to make decisions by rewarding desirable actions and penalizing undesirable ones. The agent learns to maximize cumulative rewards through exploration and exploitation within an environment. This is commonly used in robotics and autonomous systems (165).

1.13. Topological Data Analysis

Topological Data Analysis (TDA) is an advanced analytical approach that uses principles from topology to study the shape and structure of data (167). One of the main advantages of TDA is its ability to capture the global structure of data, identifying patterns, clusters, and features that other methods might miss. TDA can handle high-dimensional data effectively, making it a powerful tool for complex datasets (167). However, TDA can be computationally intensive and requires careful selection of parameters, which can be a limitation in practical applications. TDA uses an unsupervised ML framework for data pattern detection and data visualization (167). With this method we can construct topological networks, which are valuable for data visualization. These networks are composed of nodes and edges; nodes represent clusters of data points, while edges indicate the relationships between these clusters (Figure 1.).

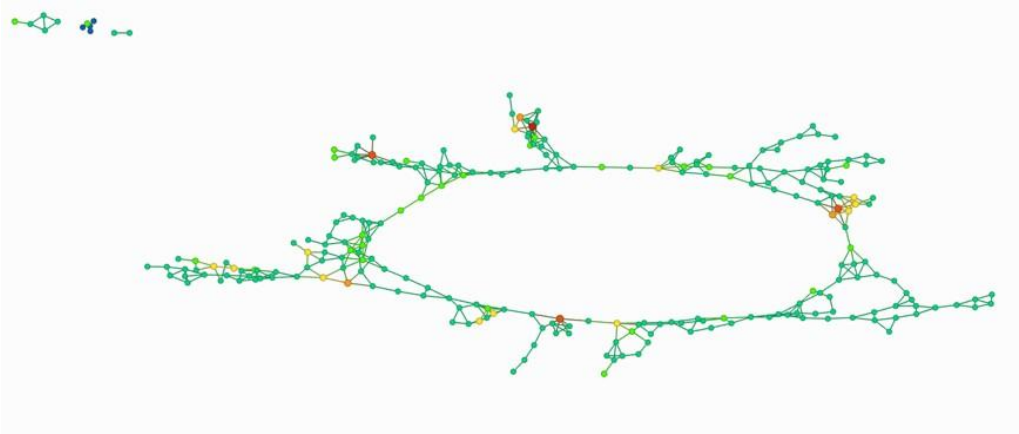


Figure 1. - *Topological network of patients undergoing CRT-D or CRT-P upgrade procedure. The topological network was constructed using sixteen pre-implantation variables: age, hypertension, atrial fibrillation, diabetes mellitus, heart failure etiology, myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, sex, implanted device type (cardiac resynchronization therapy-pacemaker/cardiac resynchronization therapy-defibrillator), New York Heart Association class, creatinine levels, glomerular filtration rate, left ventricular ejection fraction, left ventricular end-systolic dimension, and left ventricular end-diastolic dimension. This network comprises nodes interconnected by edges, where each node represents a cluster of similar patients, and connections indicate shared patients between nodes. Common patterns in topological networks include loops (continuous circular segments) and flares (elongated linear segments). In this network, nodes are color-coded based on the number of data points per node. The metric used is normalized correlation, with lenses applied using 2× multi-dimensional scaling (resolution: 29, gain: 2.50, equalized).*

In TDA, distance metrics and lenses play crucial roles. Distance metrics define the similarity or dissimilarity between data points, with common choices being Euclidean or Manhattan distance (167). The selected distance metric impacts the complexity of the topological network (168). Lenses are functions that project high-dimensional data into lower-dimensional representations, facilitating the creation of topological networks by clustering data points based on similarity (168). Multiple lenses can be employed to generate these networks, each with gain and resolution settings (167). For instance, the MDS lens uses multidimensional scaling to reduce dimensionality while preserving

distances between points, aiding in clearer visualization and analysis. The gain parameter controls the granularity of the network, determining how finely the data is divided into clusters (167). Higher gain values produce more detailed networks with more nodes and edges, while lower gain values result in coarser networks. Resolution refers to the level of detail in the topological network, with higher resolution providing deeper insights into the data's structure (168). Bins are used to group data points into clusters based on the chosen distance metric and lens, affecting the granularity of the clusters and the overall topology of the data (168). Adjusting the resolution and gain modifies the number of bins and their degree of overlap, respectively, thus fine-tuning the network's detail and structure.

1.14. Multi-layer Perceptron

A Multi-layer Perceptron (MLP) is a type of artificial neural network, a computational model inspired by the human brain's neural architecture, used for supervised learning tasks, including classification and regression (165). It consists of an input layer, one or more hidden layers, and an output layer (165). Each node in one layer connects to every node in the next, forming a fully connected network (165). The nodes in the hidden and output layers use nonlinear activation functions, such as sigmoid, tanh, or ReLU, allowing the model to learn complex patterns. MLPs can model complex, non-linear relationships in data but require significant data and computational power to train effectively. The choice of hyperparameters, such as the number of hidden layers, neurons per layer, and activation function type, significantly impacts model performance (165).

In one of the publications related to this thesis, we employed multiple MLP models (169). By combining these MLP models into an ensemble. This approach offers the advantage of producing an ensemble model with greater accuracy than the individual MLP models alone (165).

1.15. Model Training, Testing, and Validation

Model training involves fitting a selected ML algorithm to the training data to uncover underlying patterns (165). This process begins by splitting the dataset into training and test sets, typically in an 80-20 or 70-30 ratio. Subsequently, during the learning phase, the ML model iteratively adjusts its parameters to minimize a predefined

loss function (165). Hyperparameter tuning, where settings governing the training process are optimized, is crucial for enhancing model performance (165).

Testing, on the other hand, entails evaluating the model's performance on the test dataset, which was not involved in the training process. This step provides an unbiased estimate of the model’s predictive accuracy on new, unseen data (165).

Finally, external validation is a critical step in the ML process, offering an additional layer of evaluation beyond internal testing (161). After the model has been trained and tested on the initial data splits, an external validation set, typically derived from a different but related dataset, is employed to assess the model's generalizability (161). This step ensures that the model performs effectively on truly unseen data, reducing the risk of overfitting to the original dataset and confirming the model's utility and reliability in broader applications.

2. Objectives

2.1. Comparison of Long-Term Outcomes in Patients Undergoing De Novo and Upgrade Cardiac Resynchronization Therapy Treatment

Numerous retrospective studies with small sample sizes have compared the survival rates, echocardiographic response, and procedure- and device-related complications associated with de novo and upgrade CRT treatments (141). However, the results from these studies have often been contradictory (141). To address whether higher overall mortality is expected following CRT upgrade compared to de novo CRT treatment, we conducted a high volume single center retrospective registry study (170).

Given the known differences in baseline characteristics between patients undergoing de novo and upgrade CRT implantation, which could influence outcomes, we aimed to use propensity score matching to mitigate these baseline disparities between the groups (170). Additionally, we sought to perform detailed subgroup analyses to explore how the presence or absence of comorbidities and certain variable values impact expected survival. Finally, we planned to compare short-term (one-month), mid-term (1-to-12 months), and long-term (beyond 12 months) post-implantation complications between de novo and upgrade CRT patients, examining these complications not only in the overall dataset but also within the propensity score-matched groups (170).

2.2. Investigation of Long-Term Outcomes in Patients Receiving Cardiac Resynchronization Therapy Upgrade from Conventional Pacemakers

In patients with conventional PMs and a history free of VA, who may require a CRT upgrade, the question often arises whether it is necessary to upgrade to a CRT-Defibrillator (CRT-D) for primary prevention, or if a CRT-Pacemaker (CRT-P) without defibrillator function, might be more appropriate (169). Choosing the appropriate device is a complex task due to multiple considerations. CRT-D devices offer the advantage of SCD prevention but come with higher financial costs and increased complication rates. However, CRT-related reverse remodeling may also reduce SCD risk. The current ESC pacing guidelines provide recommendations for selecting CRT-P and CRT-D devices for de novo CRT patients (87). Consequently, clinicians must evaluate various complex parameters to personalize the choice between CRT-D and CRT-P devices for each patient.

To address this issue, we planned to create a retrospective single-center database, allowing us to assess survival outcomes in patients with prior PMs and a history free of VA who underwent CRT-D or CRT-P treatment. In addition, we intended to conduct subgroup analyses to determine how the presence or absence of comorbidities influences the application of CRT-D and CRT-P devices and their impact on survival. To phenotype patients who might show better survival with CRT-D upgrade compared to CRT-P, we sought to apply TDA. Based on the resulting network, we identified low-, intermediate-, and high-risk groups in terms of all-cause mortality. Furthermore, we aimed to develop ML classifiers using the MLP algorithm, which allowed us to risk-stratify each patient based on their input data. We planned to validate this ML model on an external dataset (169).

3. Methods

3.1. The Study Population and Methods Comparing Clinical Outcomes in Patients Undergoing De Novo and Upgrade Cardiac Resynchronization Therapy Treatment

3.1.1. Study Population and Data Collection

In this retrospective study, we collected data from a total of 2,524 patients who underwent successful de novo or upgrade CRT implantation at the Heart and Vascular Centre of Semmelweis University between July 28, 2000, and September 6, 2018 (170). The patients included in the study were on OMT and were classified as NYHA functional class II-IVa, with an LVEF ≤35% and QRS duration ≥130ms.

The data used in the study were entered into a structured database known as 'Biobankok'. Data collection was conducted using both electronic and paper-based records. Baseline parameters included anthropometric measurements, echocardiographic and ECG parameters, NYHA functional class, and comorbidities (170).

The study protocol adhered to the Declaration of Helsinki and was approved by the Regional and Institutional Committee of Science and Research Ethics (Approval No. 161-0/2019). Due to the retrospective nature of the study, patient consent forms were not required (170).

3.1.2. Clinical Outcomes, Endpoints

The primary composite endpoint of the study was all-cause mortality, implantation of a left ventricular assist device (LVAD), and heart transplantation (HTX). The status of the patients (alive/deceased) was queried from the National Health Insurance Database of Hungary in September 2019. The secondary endpoint of the study was all-cause mortality and peri- and post-procedural complications (170).

3.1.3. Statistical Analysis

Statistical analyses were conducted using SPSS (version 25.0, IBM, Armonk, NY, USA), GraphPad Prism (version 8, GraphPad Software, San Diego, CA, USA), and RStudio (version 1.8, RStudio PBC, Boston, MA, USA). The Shapiro-Wilk test was utilized to evaluate the normality of the data distribution. Continuous variables with

normal distribution were reported as mean ± standard deviation (SD), while those with non-normal distribution were presented as median and IQR. For within-group comparisons of continuous variables, either a paired Student's t-test or a paired Wilcoxon rank test was employed, as appropriate. Between-group comparisons of continuous variables were conducted using either an unpaired Student's t-test or a Mann-Whitney U test, depending on the normality of the data. Categorical variables were compared using Chi-squared or Fisher's exact tests (170).

We used the Modification of Diet in Renal Disease (MDRD) formula to calculate the estimated Glomerular Filtration Rate (eGFR) (171).

Time-to-event analyses were performed using log-rank tests and both univariable and multivariable Cox regression analyses (170). Propensity score matching was executed in R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) with the MatchIt package (version 3.0.2). Missing values were imputed with the mean of non-missing cases before performing propensity score matching using nearest neighbor matching with logistic regression-derived distances. To evaluate the effect of implantation date on the primary composite endpoint, dummy variables based on the year of CRT implantation were created. A P-value of <0.05 was considered to indicate statistical significance (170).

3.2. The Study Population and Methods Comparing Clinical Outcomes in Patients Undergoing Cardiac Resynchronization Therapy-Defibrillator or Cardiac Resynchronization Therapy-Pacemaker Upgrade

3.2.1. Study Population and Data Collection

In this study, we compiled two retrospective datasets comprising patients who underwent successful CRT-D or CRT-P upgrades from conventional PM devices, with no history of VAs (169). The first dataset, included a total of 611 patients who underwent CRT upgrade procedures at the Heart and Vascular Center of Semmelweis University (Budapest, Hungary) between December 2001 and August 2020. After excluding those with a previously implanted ICD device (n=224) or a history of VAs (n=116), the final study cohort comprised 326 patients. Additionally, an external dataset for ML model validation was collected from the Cardiac Electrophysiology Division of the Department

of Internal Medicine at the University of Szeged (Szeged, Hungary), covering the period from September 2005 to August 2020 and comprising 29 patients. Data for the study were extracted from available university electronic systems into a structured database (169).

The collected data included patients' demographic information, medical history, cardiovascular risk factors, physical status, current pharmacological therapy, ECG, echocardiographic, and laboratory results before the upgrade procedure (169). Patient status (alive/deceased) was queried from Hungary's National Health Insurance Database in May 2021 for Semmelweis University data and in August 2023 for the University of Szeged data.

The study protocol adhered to the principles of the Declaration of Helsinki. The Regional and Institutional Committee of Science and Research Ethics of Semmelweis University approved the study protocol (approval No. 161-0/2019) and waived the requirement for informed consent due to the retrospective nature of the study (169). Additionally, the study protocol was approved by the Human Investigation Review Board of the University of Szeged (approval No. 4681), with a similar waiver of informed consent (169).

3.2.2. Clinical Outcomes, Endpoints

The primary endpoint was all-cause mortality, and the time to death was censored if the patient was still alive 10 years after the CRT upgrade procedure, if the patient had initially been implanted with CRT-P and then upgraded to CRT-D, or underwent HTX (169).

3.2.3. Topological Data Analysis and Machine Learning Model Development

For the TDA, we utilized 16 input features: age, sex, type of implanted device (CRT-P or CRT-D), NYHA functional class, history of AF, history of HT, history of DM, etiology of HF, history of MI, history of percutaneous coronary intervention (PCI), history of coronary artery bypass graft surgery (CABG), serum creatinine, estimated glomerular filtration rate (eGFR), LVEF, and LV end-diastolic and end-systolic diameters (169). Missing data were handled using median imputation, and continuous variables were normalized using Z-scores. Data analysis was performed using two MDS lenses, both set with a resolution of 25 and a gain of 2.1. These settings resulted in a loop network

structure. Patients who did not connect to the main network and formed isolated nodes or singletons were considered outliers and excluded from further analysis, totaling 36 patients (169).

After developing the TDA model, we colored the network based on the primary endpoint (169). We then aimed to create groups that connected patients with similar survival/mortality statuses located in proximate nodes within the network. This was achieved using the Louvain method, which performed community auto-grouping. The algorithm identified 14 auto-groups with similar proportions of dead and surviving patients. Subsequently, we merged groups to ensure similarity in primary endpoint outcomes and proximity within the network. These steps were repeated until three distinct groups with separate mortality rates were identified, resulting in low-, intermediate-, and high-risk phenogroups (169) (Figure 2.).

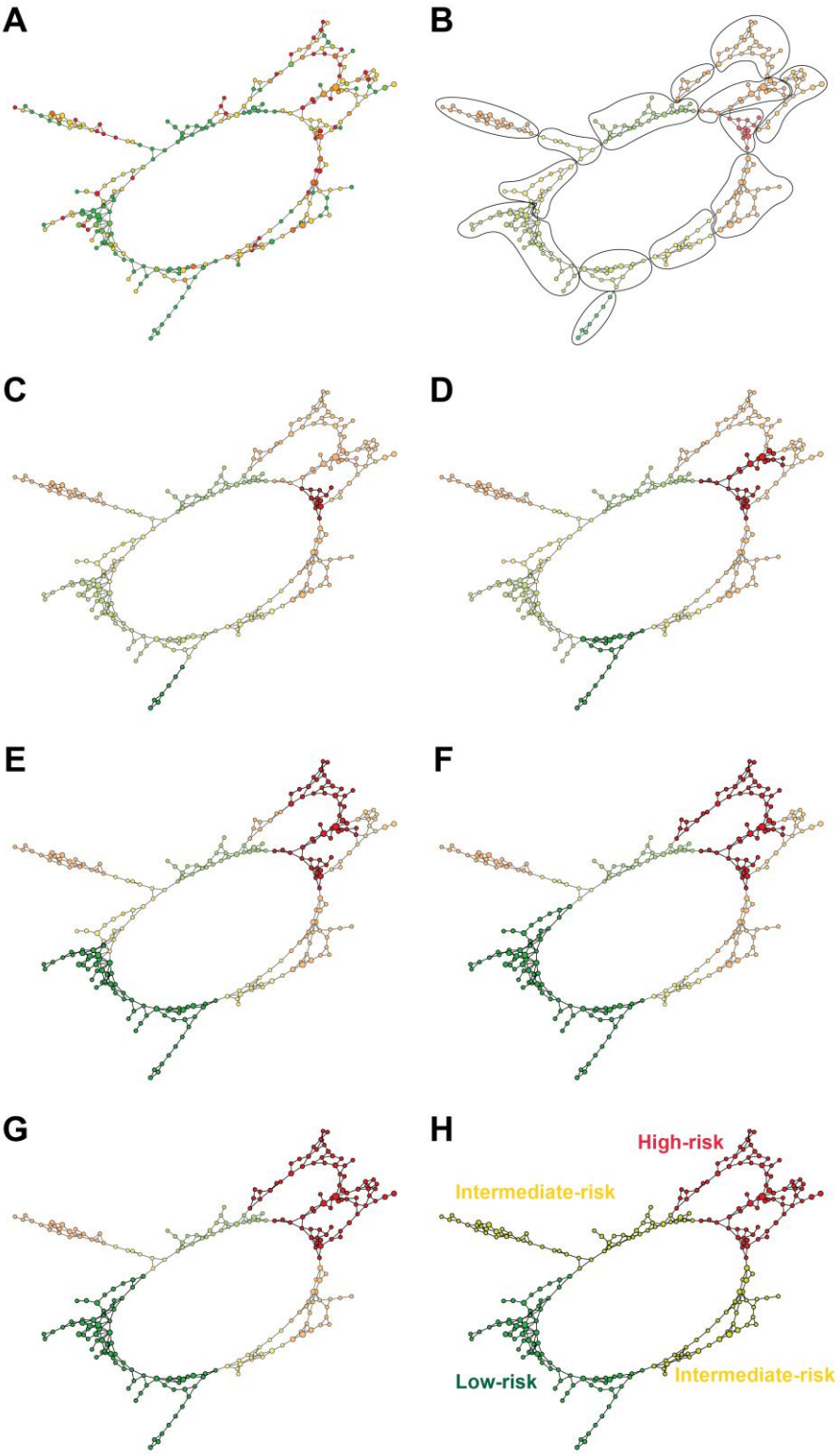


Figure 2. - *The steps of dividing the topological network into phenogroups after generating a topological network and color-coding it based on all-cause mortality (169). (A), we performed community autogrouping (B). This algorithm uses the Louvain*

Modularity optimization to find the best possible grouping of nodes with high intra- but low inter-group connectivity. In panel B, each autogroup is color-coded based on the mortality rate of the given group. Then, autogroups were sorted based on the survival rate of their members to identify the groups with the lowest (dark green) and highest (dark red) mortality rates (C). Next, each group was merged with an adjacent group having the most similar mortality rate (D). This step was repeated multiple times (E, F, G) until three phenogroups (i.e., low-, intermediate-, and high-risk phenogroups) with a nearly equal number of patients were created (H) (169). Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

TDA and auto-grouping were performed using the EurekaAI Workbench (version 3.1.0, SymphonyAI, Palo Alto, California, USA) and the EurekaAI Python SDK (version 3.1.0, SymphonyAI, Palo Alto, California, USA) (169).

All patients within the three TDA-defined phenogroups were labeled accordingly. We then trained multiple multi-class classifiers using the same input features as the TDA model to predict the phenogroup membership of new patients. Training and internal validation were conducted using nested cross-validation, with a 5-fold inner loop for hyperparameter tuning and a 5-fold outer loop for model selection and evaluation. This process produced an ensemble of five classifiers applicable to new patient data (169). Balanced accuracy was the primary scoring metric. Additionally, we calculated accuracy, micro- and macro-averaged precision, recall, F1 scores, and the area under the receiver operating characteristic curve (AUC). The ensemble model demonstrated favorable predictive performance during internal validation, which was also confirmed in the external validation cohort. ML analysis was performed in Python (version 3.9.13, Python Software Foundation, Wilmington, Delaware, USA) (169).

3.2.4. Statistical Analysis

Continuous variables are presented as mean ± SD or median (IQR) (169). The characteristics of the CRT-D and CRT-P upgrade groups were compared using unpaired Student's t-tests or Mann-Whitney U tests for continuous variables and Chi-squared test or Fisher's exact tests for categorical variables, as appropriate. The characteristics of the three TDA-derived phenogroups were compared pairwise using the Kolmogorov-Smirnov test for continuous variables and Chi-squared or Fisher's exact test for

categorical variables, as appropriate. Survival of subgroups and phenogroups was visualized using Kaplan-Meier curves, and log-rank tests were performed for comparison. Follow-up duration was estimated using the reverse Kaplan-Meier method, and mortality was calculated based on Kaplan-Meier estimates. Univariable and multivariable Cox proportional hazards models were employed to compute HRs with 95% CIs. A two-sided p-value of <0.05 was considered statistically significant (169). We used the Modification of Diet in Renal Disease (MDRD) formula to calculate the estimated Glomerular Filtration Rate (eGFR) (171). All statistical analyses were conducted using R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) (169).

4. Results

4.1. Comparing Long-term Clinical Outcomes of De novo and Upgrade Cardiac Resynchronization Therapy Patients

4.1.1. Baseline Clinical Characteristics

A total of 2,524 patients were included in our registry, with 1,977 (78%) receiving CRT as a primary device and 547 (22%) undergoing an upgrade procedure. The overall cohort had a median follow-up time of 3.7 (1.9-6.4) years.

Among the patients undergoing CRT upgrades, 142 (26%) had VVI devices, 119 (22%) had VVI-ICD, 164 (30%) had DDD, and 74 (14%) had DDD-ICD devices prior to CRT implantation. Additionally, 32 (6%) had VDD, and 10 (2%) had VDD-ICD devices. For those with previous devices, the median duration of RVP was 4.5 (2.1-8.1) years, with a median RVP rate of 95 (62-99)% before the CRT upgrade procedure.

Regarding baseline clinical characteristics, upgrade patients were significantly older [71 (65-77) vs. 67 (59-73) years; $p < 0.001$] and more likely to have ischemic etiology [328 (60%) vs. 908 (46%); $p < 0.001$], with a higher prevalence of prior MI [262 (48%) vs. 712 (36%); $P < 0.001$] and CABG procedures [105 (19%) vs. 228 (12%); $p < 0.001$] (Table 1.). While NYHA III/IV functional status [265 (52%) vs. 916 (59%); $p = 0.007$] and female sex [110 (20%) vs. 527 (27%); $p = 0.002$] were less common in the upgrade group, they had a higher incidence of AF [258 (47%) vs. 692 (35%); $p < 0.001$] and VAs [181 (33%) vs. 421 (22%); $p < 0.001$]. Furthermore, chronic kidney disease (CKD) was more prevalent in the upgrade group, as indicated by a lower eGFR [52.8 (39.7-62.8) mL/min/1.73 m^2 vs. 63 (46.6-78.4) mL/min/1.73 m^2; $p < 0.001$] and higher creatinine levels [111 (89-142) vs. 98 (79-126) μmol/L; $p < 0.001$] compared to the de novo patients (Table 1.). Among patients with a prior device, paced QRS duration was significantly broader than in the de novo group (174.1 ± 30.6 vs. 158.3 ± 26.0 ms; $p < 0.001$). Due to the higher prevalence of AF in the upgrade group, these patients more frequently received oral anticoagulation (OAC) [234 (46%) vs. 538 (30%); $p < 0.001$] and amiodarone [172 (34%) vs. 447 (25%); $p = 0.001$]. However, the prescription rate of ACE-I or ARB [455 (89%) vs. 1656 (92%); $p = 0.022$] was lower among upgrade patients.

In terms of echocardiographic parameters, the upgrade group exhibited a higher baseline LVEF [29 (25-35)% vs. 28 (24-33)%; p = 0.014] and smaller LVEDd and LVESd dimensions (LVEDd 63.0 ± 9.4 vs. 64.1 ± 9.5 mm; p = 0.037, LVESd 52.3 ± 10.6 vs. 54.1 ± 10.2 mm; p = 0.007) compared with the de novo group (Table 1.).

Table 1. - *Baseline clinical characteristics of de novo and upgrade CRT patients (170).*

Continuous variables were listed as mean ± SD or median (IQR), and categorical variables were listed as n (%). Continuous variables were compared using unpaired Student's t-test or Mann-Whitney U test, while categorical variables were compared using Chi-squared or Fisher's exact tests. P-values refer to differences between the de novo and the upgrade CRT groups.

ACE-I – angiotensin-converting-enzyme inhibitors; ARB – angiotensin receptor blocker, BMI – body mass index; CABG – coronary artery bypass grafting; CKD – chronic kidney disease; CRT-D – cardiac resynchronization therapy defibrillator; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate; HT – hypertension; IQR – interquartile range; LVEDd – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LVESd – left ventricular end-systolic diameter; MI – myocardial infarction; MRA – mineralocorticoid receptor antagonists; NT-proBNP – N-Terminal pro-B-Type Natriuretic Peptide; NYHA – New York Heart Association class; OAC – oral anticoagulant; PCI – percutaneous coronary intervention; SD – standard deviation. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

	All patients (n=2524)	**De novo CRT (n=1977)**	**Upgrade CRT (n=547)**	**P-value**
Age [years; median (IQR)]	68 (61-74)	67 (59-73)	71 (65-77)	<0.001
Sex (female; n; %)	637 (25%)	527 (27%)	110 (20%)	0.002
NYHA III/IV (st.; n; %)	1181 (57%)	916 (59%)	265 (52%)	0.007

BMI [kg/m^2; median (IQR)]	27.4 (24.6-30.8)	27.4 (24.5-30.7)	27.7 (24.7-30.9)	0.38
QRS width (ms; mean ± SD)	161.6 ± 27.8	158.3 ± 26	174.1 ± 30.6	<0.001
Ischemic etiology (n; %)	1236 (49%)	908 (46%)	328 (60%)	<0.001
Medical history				
MI (n; %)	974 (39%)	712 (36%)	262 (48%)	<0.001
PCI (n; %)	739 (29%)	560 (28%)	179 (33%)	0.06
CABG (n; %)	333 (13%)	228 (12%)	105 (19%)	<0.001
HT (n; %)	1819 (72%)	1416 (72%)	403 (74%)	0.36
Diabetes mellitus (n; %)	927 (37%)	724 (37%)	203 (37%)	0.84
Type II DM (n; %)	750 (29%)	598 (30%)	152 (28%)	0.29
Atrial Fibrillation (n; %)	950 (38%)	692 (35%)	258 (47%)	<0.001
Ventricular Arrhythmia (n; %)	602 (24%)	421 (22%)	181 (33%)	<0.001
CRT-D implantation (n; %)	1366 (54%)	1051 (53%)	315 (58%)	0.07
Laboratory parameters				
NT-proBNP [pmol/L; median (IQR)]	2757 (1588-3756)	2717 (1424-3139)	2873 (1640-4644)	0.054
Creatinine [µmol/L; median (IQR)]	101 (81-131)	98 (79-126)	111 (89-142)	<0.001
eGFR [mL/min/1.73m^2; median (IQR)]	60 (44.9-76.2)	63 (46.6-78.4)	52.8 (39.7-62.8)	<0.001
CKD (n; %)	936 (37%)	668 (34%)	268 (49%)	<0.001

Echocardiographic parameters				
LVEF [%; median (IQR)]	28 (24-33)	28 (24-33)	29 (25-35)	0.01
LVEDd (mm; mean ± SD)	63.8 ± 9.5	64.1 ± 9.5	63 ± 9.4	0.04
LVESd (mm; mean ± SD)	53.6 ± 10.3	54.1 ± 10.2	52.3 ± 10.6	0.007
Medical treatment				
Loop diuretics (n; %)	1829 (80%)	1413 (79%)	416 (82%)	0.21
Thiazide diuretics (n; %)	548 (24%)	416 (23%)	132 (26%)	0.24
βeta blockers (n; %)	2043 (89%)	1584 (89%)	459 (90%)	0.42
MRA (n; %)	1557 (68%)	1203 (67%)	354 (69%)	0.39
ACE-I/ARB (n; %)	2111 (92%)	1656 (92%)	455 (89%)	0.02
Amiodarone (n; %)	619 (27%)	447 (25%)	172 (34%)	0.001
OAC (n; %)	772 (34%)	538 (30%)	234 (46%)	<0.001

4.1.2. Long-term Survival of Patients Undergoing De novo or Upgrade Cardiac Resynchronization Therapy Implantation

During the median follow-up period of 3.7 (1.9-6.4) years, 1433 (56.8%) patients reached the composite primary endpoint, including 1091 (55.2%) patients in the de novo group and 342 (62.5%) in the upgrade CRT group. Overall, 1057 (53.5%) de novo and 334 (61.1%) upgrade patients died, 31 (1.6%) de novo and 8 (1.5%) upgrade patients underwent HTX, and 3 (0.2%) de novo patients received an LVAD.

Univariable Cox regression analysis indicated more adverse primary composite outcomes in the upgrade group (HR: 1.41; 95% CI: 1.23-1.61; p <0.001) compared to de novo CRT patients (Figure 3.). However, after performing multivariable Cox regression analysis, which accounted for relevant clinical covariates (ACE-I/ARB, age, amiodarone, AF, intrinsic/paced QRS duration, ischemic etiology, LVEDd, LVESd, LVEF, NYHA

Class III/IV, OAC, serum creatinine, sex, and ventricular arrhythmia), this difference was no longer significant (HR: 1.12; 95% CI: 0.86-1.48; p = 0.402) (Figure 3.).

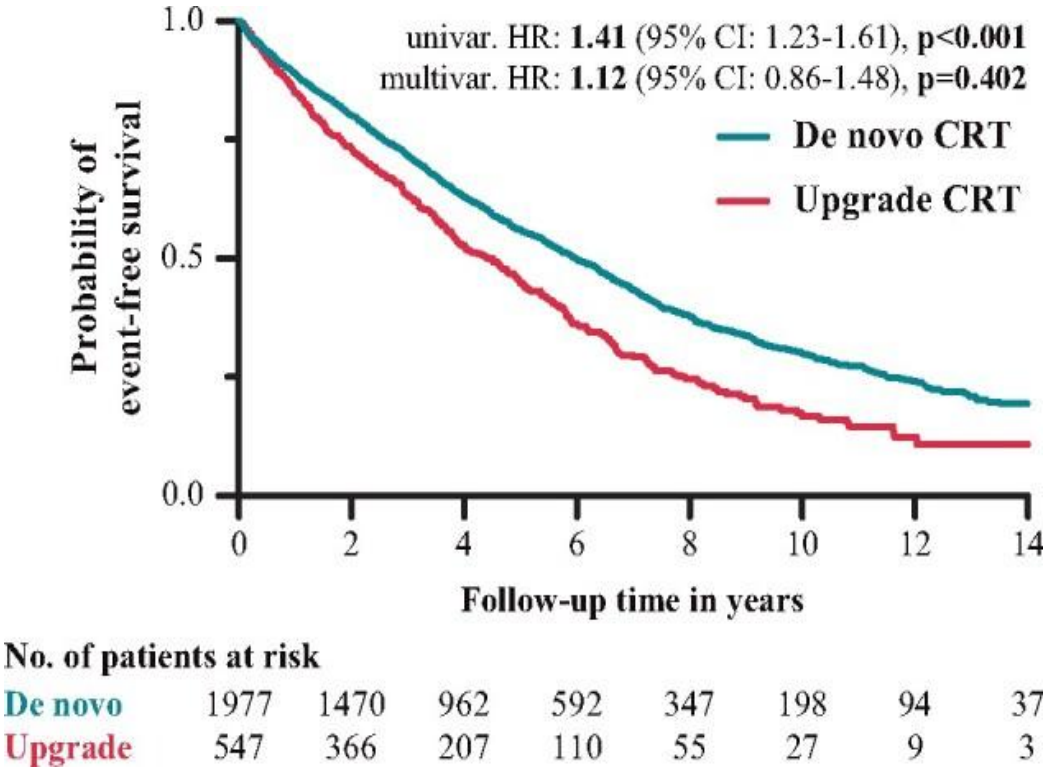


Figure 3. - *Kaplan-Meier curves for the primary composite endpoint in de novo and upgrade patients (170).*

CI – confidence interval; CRT – cardiac resynchronization therapy; HR – hazard ratio. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

In our cohort, AF (HR: 1.31; 95% CI: 1.02-1.69; p = 0.032), female sex (HR: 0.72; 95% CI: 0.54-0.96; p = 0.025), ischemic HF etiology (HR: 1.66; 95% CI: 1.32-2.09; p <0.001), NYHA class III/IV (HR: 1.38; 95% CI: 1.09-1.75; p = 0.009), and serum creatinine levels (HR: 1.01; 95% CI: 1.00-1.01; p <0.001) emerged as independent predictors of the primary composite endpoint (Table 2.).

Table 2. - *Multivariable Cox regression analysis: Primary composite endpoint predictors in de novo vs. upgrade CRT patient groups (170).*

ACE-I – angiotensin-converting-enzyme inhibitors; ARB – angiotensin receptor blocker; CI – confidence interval; HR – hazard ratio; LVEDd – left ventricular end-diastolic

diameter; LVEF – left ventricular ejection fraction; LVESd – left ventricular end-systolic diameter; NYHA – New York Heart Association class; OAC – oral anticoagulant. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

	Multivariable HR (95% CI)	**P-value**
ACE-I or ARB	0.76 (0.54-1.07)	0.11
Age	1.01 (1.00-1.02)	0.052
Atrial fibrillation	1.31 (1.02-1.69)	0.03
Amiodarone	1.14 (0.89-1.47)	0.30
De novo vs. upgrade	1.12 (0.86-1.48)	0.40
Female vs. male sex	0.72 (0.54-0.96)	0.03
Ischemic vs. non-ischemic heart failure etiology	1.66 (1.32-2.09)	<0.001
LVEDd	0.98 (0.95-1.02)	0.28
LVESd	1.04 (1.00-1.07)	0.051
LVEF	0.99 (0.98-1.02)	0.69
NYHA class I-II. vs. III-IV.	1.38 (1.09-1.75)	0.01
OAC	1.03 (0.80-1.32)	0.83
QRS duration time	0.99 (0.99-1.00)	0.43
Serum Creatinine	1.01 (1.01-1.00)	<0.001
Ventricular arrhythmia	0.87 (0.68-1.12)	0.28

Furthermore, propensity score matching was conducted to compare outcomes between the two groups after adjusting for clinical covariates. Each upgrade patient (n = 547) was matched with a de novo patient with similar characteristics (age, AF, eGFR, HF etiology, LVEF, NYHA class, sex, QRS duration, and VA) (Table 3.). The matched analysis revealed no significant difference in the risk of reaching the composite primary endpoint (propensity score-matched HR: 1.10; 95% CI: 0.95-1.29; p = 0.215) (Figure 4A). Analyzing the impact of the implantation year on the primary composite endpoint using dummy-coded variables and a dichotomous variable with 2013 as the cutoff, neither

approach predicted the composite endpoint (adjusted HR: 0.88; 95% CI: 0.60-1.30; p = 0.532).

Table 3. - *Baseline characteristics after propensity score matching (170).*

Continuous variables were listed as mean ± SD, and categorical variables were listed as n; (%). Continuous variables were compared using unpaired Student's t-test, while categorical variables were compared using Chi-squared or Fisher's exact tests. P-values refer to differences between the de novo and the upgrade CRT groups. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

eGFR – estimated glomerular filtration rate; HF – heart failure; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association class; SD – standard deviation

	De novo CRT (n=547)	**Upgrade CRT (n=547)**	**P-value**
Age (year; mean ± SD)	70.2 ± 9.4	70.6 ± 9.2	0.53
Atrial Fibrillation (n; %)	255 (47%)	258 (47%)	0.90
eGFR (ml/min/1.73m2; mean ± SD)	56.7 ± 21	55.7 ± 21.5	0.32
HF etiology (n; %)	307 (56%)	328 (60%)	0.22
LVEF (%; mean ± SD)	29.3 ± 7.0	29.4 ± 7.9	0.89
NYHA II (st; n; %)	257 (50%)	247 (48%)	0.31
NYHA III (st; n; %)	229 (45%)	231 (45%)	
NYHA IV (st; n; %)	23 (5%)	34 (7%)	
Sex (male; n; %)	425 (78%)	437 (80%)	0.42
QRS duration time (ms; mean ± SD)	173.7 ± 27.8	174.1 ± 30.6	0.82
Ventricular arrhythmia (n; %)	193 (35%)	181 (33%)	0.51

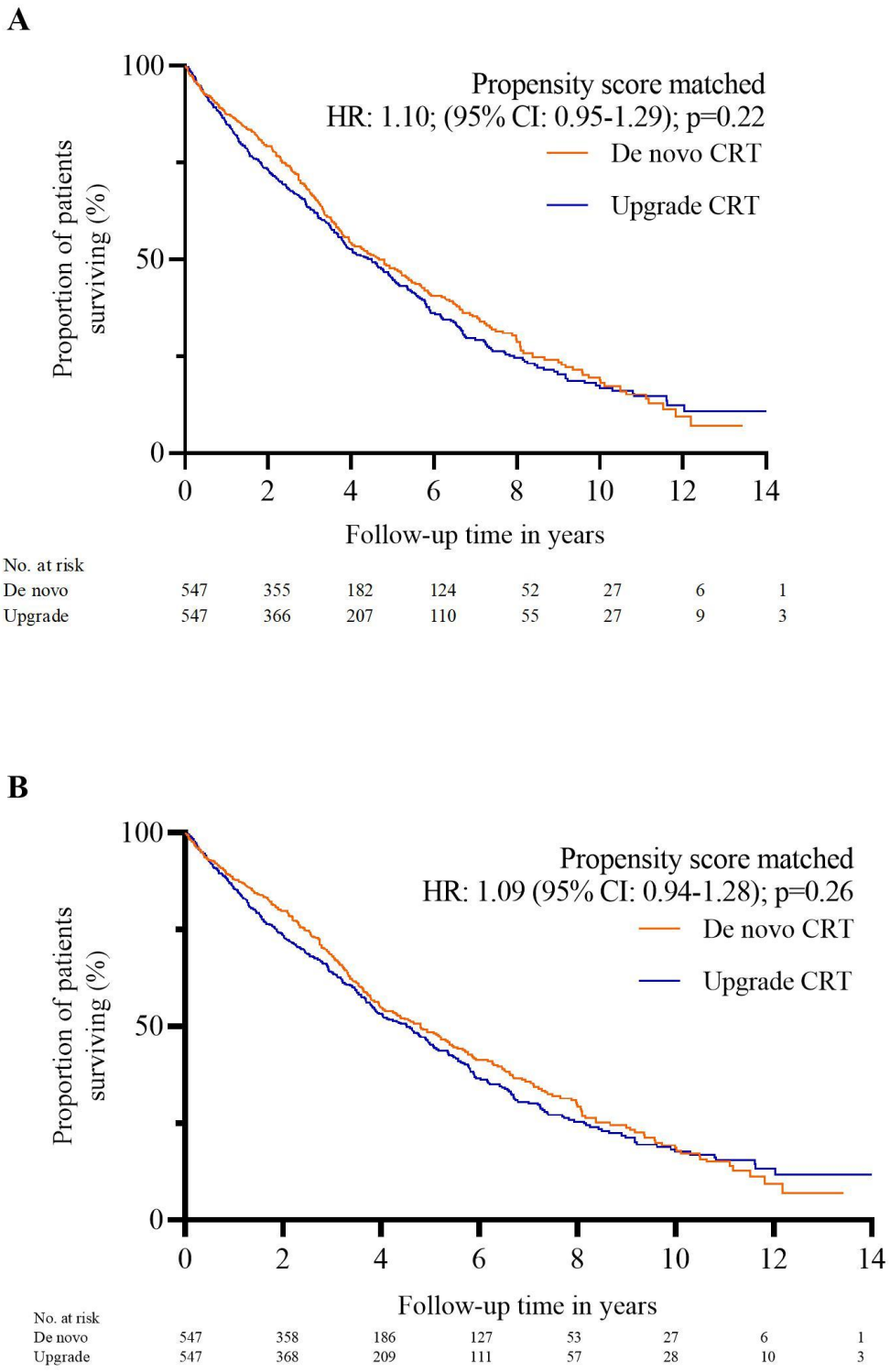
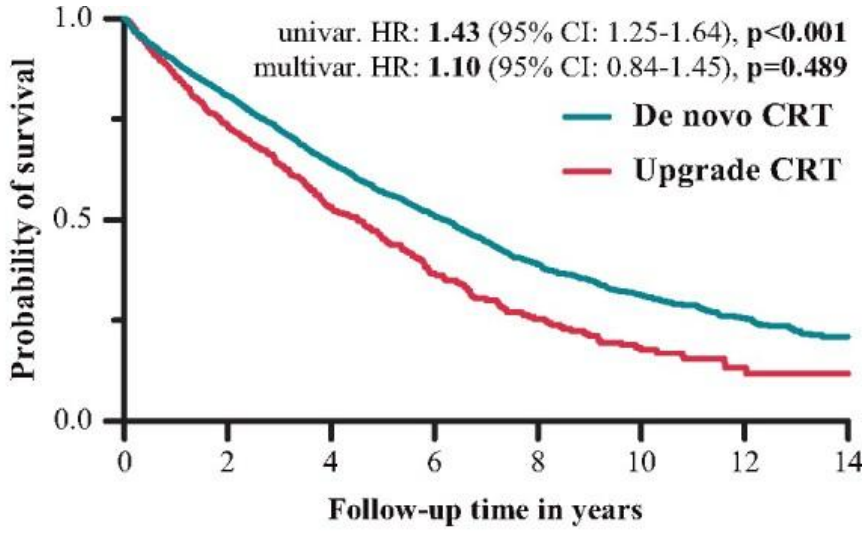


Figure 4. - *(A) Kaplan-Meier curves for the primary composite endpoint in the propensity score-matched de novo and upgrade CRT groups. (B) Kaplan-Meier curves of all-cause death in the propensity score-matched de novo and upgrade CRT group (170).*

CI – confidence interval; CRT – cardiac resynchronization therapy; HR – hazard ratio. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

During a median follow-up of 3.8 (1.9-6.5) years, 1409 (55.8%) patients died, with 1071 (54.2%) in the de novo group and 338 (61.7%) in the upgrade CRT group. Univariable Cox regression analysis showed a 43% higher all-cause mortality rate in the upgrade CRT group compared to de novo patients (HR: 1.43; 95% CI: 1.25-1.64; p <0.001) (Figure 5). However, after adjusting for clinical covariates (ACE-I/ARB, age, amiodarone, AF, intrinsic/paced QRS duration, ischemic etiology, LVEDd, LVESd, LVEF, NYHA class III/IV, OAC, serum creatinine, sex, and VA), multivariable Cox regression analysis indicated a similar risk of all-cause mortality between the groups (HR: 1.10; 95% CI: 0.84-1.45; p = 0.489) (Figure 5). In our cohort, age (HR: 1.02; 95% CI: 1.01-1.03; p = 0.002), AF (HR: 1.41; 95% CI: 1.10-1.81; p = 0.008), female sex (HR: 0.74; 95% CI: 0.56-0.99; p = 0.042), ischemic HF etiology (HR: 1.59; 95% CI: 1.26-2.00; p <0.001), LVESd (HR: 1.04; 95% CI: 1.00-1.08; p = 0.039), NYHA Class III/IV (HR: 1.35; 95% CI: 1.06-1.71; p = 0.015), and serum creatinine (HR: 1.01; 95% CI: 1.00-1.01; p <0.001) were independent predictors of all-cause mortality (Table 4.). In the propensity-matched cohorts, there was no significant difference in all-cause mortality between de novo and upgrade groups (propensity score-matched HR: 1.09; 95% CI: 0.94-1.28; p = 0.263) (Figure 4B).



No. of patients at risk

De novo	1977	1484	980	609	359	207	102	40
Upgrade	547	368	209	111	57	28	10	3

Figure 5. *- Kaplan-Meier curves of all-cause death in de novo and upgrade patients (170).*

CI, confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

Table 4. - *Multivariable Cox regression analysis: All-cause mortality predictors in de novo vs. upgrade CRT patient groups (170).*

ACE-I – angiotensin-converting-enzyme inhibitors; ARB – angiotensin receptor blocker; CI – confidence interval; HR – Hazard ratio; LVEDd – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LVESd – left ventricular end-systolic diameter; NYHA – New York Heart Association class; OAC – oral anticoagulant. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

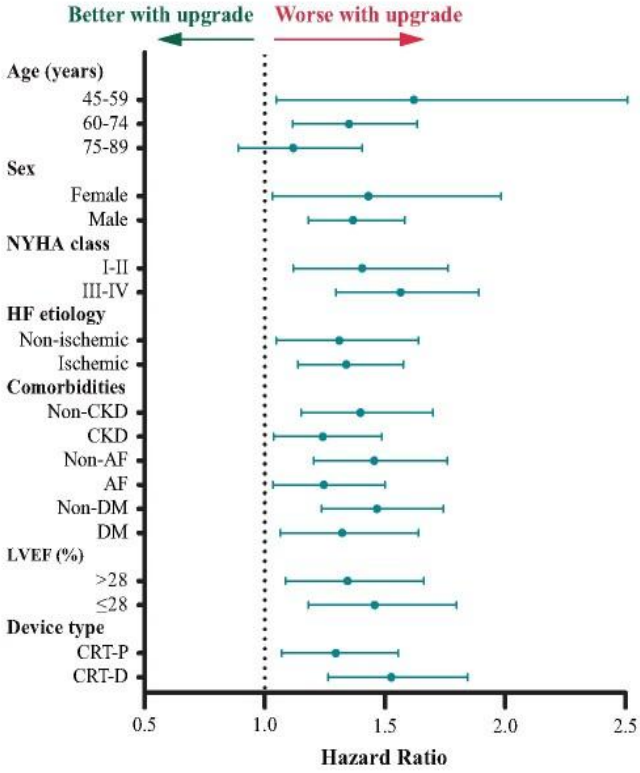
	Multivariable HR (95% CI)	**P-value**
ACE-I or ARB	0.74 (0.74 - 1.04)	0.81
Age	1.02 (1.01 - 1.03)	0.01
Atrial fibrillation	1.41 (1.10 - 1.81)	0.01
Amiodarone	1.13 (0.88 - 1.46)	0.34
De novo vs. upgrade	1.10 (0.84 - 1.45)	0.49
Female vs. male sex	0.74 (0.56 - 0.99)	0.04
Ischemic vs. non-ischemic heart failure etiology	1.59 (1.26 - 2.00)	<0.001
LVEDd	0.98 (0.95 - 1.02)	0.27
LVESd	1.04 (1.00 - 1.08)	0.04
LVEF	0.99 (0.98 - 1.02)	0.70
NYHA class I-II. vs. III-IV.	1.35 (1.06 - 1.71)	0.02
OAC	0.99 (0.77 - 1.27)	0.95

QRS duration time	0.99 (0.99 - 1.00)	0.68
Serum Creatinine	1.01 (1.00 - 1.01)	<0.001
Ventricular arrhythmia	0.88 (0.68 - 1.13)	0.30

4.1.3. Subgroup Analysis of Survival of Patients Undergoing De novo or Upgrade Cardiac Resynchronization Therapy Implantation

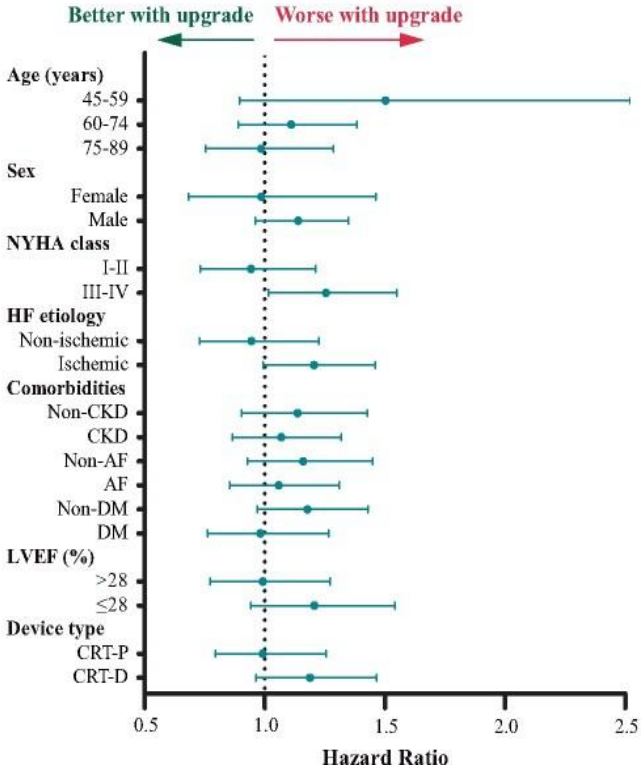
In the subgroups stratified by age at CRT implantation, sex, NYHA functional class, HF etiology, comorbidities, LVEF, and CRT type, further analyses were conducted to evaluate differences in the composite endpoint between de novo and upgrade patients. Within the total cohort, upgrade patients demonstrated a higher risk of reaching the composite endpoint across all subgroups, except for the 75-89 age group, where the outcomes were comparable between de novo and upgrade patients (HR: 1.12; 95% CI: 0.89-1.41; p = 0.326) (Figure 6A). In the propensity score-matched cohort, we observed a similar risk for the composite endpoint across all subgroups, except for patients with severe symptoms (NYHA III-IV), where upgrade patients exhibited a significantly higher risk compared to de novo patients (HR: 1.16; 95% CI: 1.02-1.55; p = 0.035) (Figure 6B).

A Total study cohort



	N	Univariable Cox regression
Age (years)		
45-59	447	HR: 1.62 (95% CI: 1.05-2.51), p=0.009
60-74	1271	HR: 1.35 (95% CI: 1.12-1.63), p=0.001
75-89	175	HR: 1.12 (95% CI: 0.89-1.41), p=0.326
Sex		
Female	637	HR: 1.43 (95% CI: 1.03-1.98), p=0.014
Male	1887	HR: 1.37 (95% CI: 1.18-1.58), p<0.001
NYHA class		
I-II	895	HR: 1.41 (95% CI: 1.12-1.76), p=0.002
III-IV	1180	HR: 1.57 (95% CI: 1.30-1.89), p<0.001
HF etiology		
Non-ischemic	1287	HR: 1.31 (95% CI: 1.05-1.64), p=0.009
Ischemic	1236	HR: 1.34 (95% CI: 1.14-1.58), p<0.001
Comorbidities		
Non-CKD	1586	HR: 1.40 (95% CI: 1.15-1.70), p<0.001
CKD	936	HR: 1.24 (95% CI: 1.04-1.49), p=0.013
Non-AF	1573	HR: 1.46 (95% CI: 1.20-1.76), p<0.001
AF	950	HR: 1.25 (95% CI: 1.03-1.50), p=0.014
Non-DM	1596	HR: 1.47 (95% CI: 1.24-1.74), p<0.001
DM	927	HR: 1.32 (95% CI: 1.07-1.64), p=0.006
LVEF (%)		
>28	905	HR: 1.34 (95% CI: 1.09-1.66), p=0.003
≤28	914	HR: 1.46 (95% CI: 1.18-1.80), p<0.001
Device type		
CRT-P	1157	HR: 1.30 (95% CI: 1.07-1.56), p=0.004
CRT-D	1366	HR: 1.53 (95% CI: 1.26-1.84), p<0.001

B Propensity score-matched cohort



	N	Univariable Cox regression
Age (years)		
45-59	111	HR: 1.50 (95% CI: 0.89-2.53), p=0.123
60-74	544	HR: 1.11 (95% CI: 0.89-1.38), p=0.353
75-89	343	HR: 0.99 (95% CI: 0.75-1.29), p=0.912
Sex		
Female	232	HR: 0.99 (95% CI: 0.68-1.46), p=0.999
Male	862	HR: 1.14 (95% CI: 0.96-1.35), p=0.132
NYHA class		
I-II	504	HR: 0.94 (95% CI: 0.73-1.21), p=0.645
III-IV	516	HR: 1.16 (95% CI: 1.02-1.55), p=0.035
HF etiology		
Non-ischemic	459	HR: 0.95 (95% CI: 0.73-1.23), p=0.669
Ischemic	635	HR: 1.21 (95% CI: 0.99-1.46), p=0.057
Comorbidities		
Non-CKD	577	HR: 1.14 (95% CI: 0.90-1.43), p=0.273
CKD	517	HR: 1.07 (95% CI: 0.87-1.32), p=0.534
Non-AF	580	HR: 1.16 (95% CI: 0.93-1.45), p=0.192
AF	514	HR: 1.06 (95% CI: 0.85-1.31), p=0.608
Non-DM	696	HR: 1.18 (95% CI: 0.97-1.43), p=0.099
DM	398	HR: 0.98 (95% CI: 0.76-1.27), p=0.888
LVEF (%)		
>28	465	HR: 0.99 (95% CI: 0.77-1.27), p=0.948
≤28	416	HR: 1.21 (95% CI: 0.94-1.54), p=0.139
Device type		
CRT-P	455	HR: 0.99 (95% CI: 0.80-1.26), p=0.997
CRT-D	639	HR: 1.19 (95% CI: 0.96-1.47), p=0.107

Figure 6. - *(A) Forest plot of subgroups based on the composite primary endpoint of the total cohort. (B) Forest plot of subgroups based on the composite primary endpoint of the propensity score-matched cohort (170).*

AF – atrial fibrillation; CI – confidence interval; CKD – chronic kidney disease; CRT – cardiac resynchronization therapy; CRT-D – cardiac resynchronization therapy-defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; DM – diabetes mellitus; HR – hazard ratio; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

4.1.4. Complications Associated with De novo or Upgrade Cardiac Resynchronization Therapy Implantation

In the total cohort, the most frequent complications were lead displacement (6.5%) and phrenic nerve stimulation (3%). Upgrade patients experienced a higher incidence of lead dysfunction or fracture [17 (3.1%) vs. 19 (1.0%); p <0.001] and pocket infection [20 (3.7%) vs. 36 (1.8%); p = 0.014] compared to those who underwent de novo CRT procedures. (Table 5.). Less frequent complications included coronary sinus dissection (0.9%), pericardial tamponade (0.4%), infective endocarditis (0.4%), and hemothorax (0.2%), with no significant differences observed between the two patient groups.

Following propensity score matching, lead dysfunction or fracture [17 (3.1%) vs. 4 (0.7%); p = 0.007] and pocket infection [20 (3.7%) vs. 7 (1.3%); p = 0.017] remained more prevalent among upgrade patients. Bleeding or pocket hematoma [12 (2.2%) vs. 16 (0.8%); p = 0.010] were more common in upgrade patients compared to the de novo CRT group; however, this difference was not observed after propensity score matching [12 (2.2%) vs. 6 (1.1%); p = 0.234]. The rate of pneumothorax (PTX) was higher in the de novo group [28 (1.4%) vs. 2 (0.4%); p = 0.045], but this difference was not confirmed in the propensity score-matched comparison [8 (1.5%) vs. 2 (0.4%); p = 0.108]. PTX occurred more frequently in the first post-procedure month in the de novo CRT group [28 (1.4%) vs. 2 (0.4%); p = 0.045] than in upgrade CRT patients.

Compared to the de novo CRT group, the upgrade CRT group exhibited higher incidences of bleeding [10 (1.8%) vs. 14 (0.7%); p = 0.024] at one month, lead

dysfunction [5 (0.9%) vs. 3 (0.2%); p = 0.015], phrenic nerve stimulation [6 (1.1%) vs. 6 (0.3%); p = 0.028], and pocket infection [9 (1.6%) vs. 12 (0.6%); p = 0.029] within 1-12 months post-intervention. Additionally, the incidence of lead dysfunction [11 (2.0%) vs. 13 (0.7%); p = 0.010] was higher in the upgrade group one year after CRT implantation compared to the de novo group, a finding also confirmed in the propensity score-matched cohort [11 (2.0%) vs. 2 (0.4%); p = 0.022].

Table 5. - *Complications associated with De novo or Upgrade CRT implantation, before and after Propensity score matching (170).*

Categorical variables were listed as n; (%). Categorical variables were compared using Chi-squared or Fisher's exact tests. P-values refer to differences between the de novo and the upgrade CRT groups.

CRT – cardiac resynchronization therapy; Psm – propensity score matching. Adopted from Schwertner et al. Europace. 2021;23(8):1310-8, https://doi.org/10.1093/europace/euab059.

	All patients (n=2524)	**De novo CRT (n=1977)**	**Upgrade CRT (n=547)**	**P-value**	**Psm All patients (n=1094)**	**Psm De novo CRT (n=547)**	**Psm Upgrade CRT (n=547)**	**P-value**
Pneumothorax (n; %)	30 (1.2%)	28 (1.4%)	2 (0.4%)	0.04	10 (0.9%)	8 (1.5%)	2 (0.4%)	0.11
1 month	30 (1.2%)	28 (1.4%)	2 (0.4%)	0.04	10 (0.9%)	8 (1.5%)	2 (0.4%)	0.11
1-12 months	-	-	-	-	-	-	-	-
After 12 months	-	-	-	-	-	-	-	-
Coronary sinus dissection (n; %)	22 (0.9%)	15 (0.8%)	7 (1.3%)	0.29	11 (1%)	4 (0.7%)	7 (1.3%)	0.55
1 month	22 (0.9%)	15 (0.8%)	7 (1.3%)	0.29	11 (1%)	4 (0.7%)	7 (1.3%)	0.55
1-12 months	-	-	-	-	-	-	-	-

After 12 months	-	-	-	-	-	-	-	-
Pericardial tamponade (n; %)	9 (0.4%)	7 (0.4%)	2 (0.4%)	0.99	4 (0.4%)	2 (0.4%)	2 (0.4%)	1.00
1 month	6 (0.2%)	4 (0.2%)	2 (0.4%)	0.62	3 (0.3%)	1 (0.2%)	2 (0.4%)	1.00
1-12 months	3 (0.1%)	3 (0.2%)	0 (0%)	1.00	1 (0.1%)	1 (0.2%)	0 (0%)	1.00
After 12 months	-	-	-	-	-	-	-	
Lead displacement (n; %)	163 (6.5%)	130 (6.6%)	33 (6%)	0.70	71 (6.5%)	38 (6.9%)	33 (6%)	0.62
1 month	61 (2.4%)	52 (2.6%)	9 (1.6%)	0.21	26 (2.4%)	17 (3.1%)	9 (1.6%)	0.16
1-12 months	56 (2.2%)	44 (2.2%)	12 (2.2%)	1.00	27 (2.5%)	15 (2.7%)	12 (2.2%)	0.70
After 12 months	45 (1.8%)	33 (1.7%)	12 (2.2%)	0.46	18 (1.6%)	6 (1.1%)	12 (2.2%)	0.23
Lead dysfunction/fracture (n; %)	36 (1.4%)	19 (1%)	17 (3.1%)	<0.001	21 (1.9%)	4 (0.7%)	17 (3.1%)	0.007
1 month	4 (0.2%)	3 (0.2%)	1 (0.2%)	1.00	2 (0.2%)	1 (0.2%)	1 (0.2%)	1.00
1-12 months	8 (0.3%)	3 (0.2%)	5 (0.9%)	0.01	6 (0.5%)	1 (0.2%)	5 (0.9%)	0.22
After 12 months	24 (1.0%)	13 (0.7%)	11 (2.0%)	0.01	13 (1.2%)	2 (0.4%)	11 (2.0%)	0.02
Phrenic nerve stimulation (n; %)	75 (3%)	58 (2.9%)	17 (3.1%)	0.78	32 (2.9%)	15 (2.7%)	17 (3.1%)	0.86
1 month	53 (2.1%)	45 (2.3%)	8 (1.5%)	0.31	19 (1.7%)	11 (2.0%)	8 (1.5%)	0.64
1-12 months	12 (0.5%)	6 (0.3%)	6 (1.1%)	0.03	9 (0.8%)	3 (0.5%)	6 (1.1%)	0.51
After 12 months	10 (0.4%)	7 (0.3%)	3 (0.5%)	0.46	4 (0.4%)	1 (0.2%)	3 (0.5%)	0.62
Bleeding/Pocket hematoma (n; %)	28 (1.1%)	16 (0.8%)	12 (2.2%)	0.01	18 (1.6%)	6 (1.1%)	12 (2.2%)	0.23
1 month	24 (1.0%)	14 (0.7%)	10 (1.8%)	0.02	16 (1.5%)	6 (1.1%)	10 (1.8%)	0.45

1-12 months	1 (0.04%)	0 (0%)	1 (0.2%)	0.22	1 (0.1%)	0 (0%)	1 (0.2%)	1.00
After 12 months	3 (0.1%)	2 (0.1%)	1 (0.2%)	0.52	1 (0.1%)	0 (0%)	1 (0.2%)	1.00
Hemothorax (n; %)	5 (0.2%)	3 (0.2%)	2 (0.4%)	0.07	3 (0.4%)	1 (0.2%)	2 (0.4%)	1.00
1 month	4 (0.2%)	2 (0.1%)	2 (0.4%)	0.21	3 (0.4%)	1 (0.2%)	2 (0.4%)	1.00
1-12 months	1 (0.04%)	0 (0%)	1 (0.2%)	0.22	1 (0.1%)	0 (0%)	1 (0.2%)	1.00
After 12 months	-	-	-	-	-	-	-	-
Pocket infection (n; %)	56 (2.2%)	36 (1.8%)	20 (3.7%)	0.01	27 (2.5%)	7 (1.3%)	20 (3.7%)	0.02
1 month	1 (0.04%)	1 (0.1%)	0 (0%)	1.00	0 (0%)	0 (0%)	0 (0%)	1.00
1-12 months	21 (0.8%)	12 (0.6%)	9 (1.6%)	0.03	12 (1.1%)	3 (0.5%)	9 (1.6%)	0.14
After 12 months	34 (1.4%)	23 (1.2%)	11 (2.0%)	0.14	15 (1.4%)	4 (0.7%)	11 (2.0%)	0.12
Infective endocarditis (n; %)	11 (0.4%)	7 (0.4%)	4 (0.7%)	0.27	6 (0.5%)	2 (0.4%)	4 (0.7%)	0.69
1 month	1 (0.04%)	1 (0.1%)	0 (0%)	1.00	1 (0.1%)	1 (0.2%)	0 (0%)	1.00
1-12 months	5 (0.2%)	2 (0.1%)	3 (0.5%)	0.07	3 (0.3%)	0 (0%)	3 (0.5%)	0.25
After 12 months	5 (0.2%)	4 (0.2%)	1 (0.2%)	1.00	2 (0.2%)	1 (0.2%)	1 (0.2%)	1.00

4.2. Comparing Patients Clinical Outcomes Following Upgrade Cardiac Resynchronization Therapy-Defibrillator or Cardiac Resynchronization Therapy-Pacemaker Implantation

4.2.1. Baseline Clinical Characteristics

From the 326 patients included in our analysis, 117 (36%) were upgraded to a CRT-D and 209 (64%) to a CRT-P. The median interval between the initial pacemaker implantation and the upgrade procedure was 5.5 (2.2-8.9) years. Prior to the CRT upgrade

procedure, 34 (10%) patients had a VDD, 132 (41%) a VVI, and 160 (49%) a DDD pacemaker. The median RVP rate was 97% (77-100%). During the period of chronic RVP, LVEF decreased by 20 (10-24) percentage points.

The baseline clinical characteristics of the CRT-D and CRT-P upgrade patients are detailed in Table 6. Patients upgraded to a CRT-D device were more likely to be male [98 (84%) vs. 147 (70%); p = 0.011] and had higher GFR [65 (46-77) mL/min/1.73m^2 vs. 55 (42-75) mL/min/1.73m^2; p = 0.036], whereas loop diuretics were administered less frequently [81 (69%) vs. 175 (84%); p = 0.004] in this group compared to the CRT-P upgrade group (Table 6).

Table 6. - *Clinical characteristics of the study cohort (169).*

The value (in parenthesis) after a feature's name indicates the number of patients with available data. If no value is reported, the given feature is available for all patients. Continuous variables are expressed as mean ± standard deviation or median (interquartile range), whereas categorical variables are reported as frequencies (n) and percentages (%). The characteristics of the CRT-D and CRT-P groups were compared using unpaired Student's t-test or Mann-Whitney U test for continuous variables and Chi-squared or Fisher's exact test for categorical variables, as appropriate.

ACE-I – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; CABG – coronary artery bypass graft; CRT-D – cardiac resynchronization therapy with defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; GFR – glomerular filtration rate; HF – heart failure, LVEDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LVESD – left ventricular end-systolic diameter; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association; PCI – percutaneous coronary intervention. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

	All n = 326	**Upgrade to CRT-P n = 209**	**Upgrade to CRT-D n = 117**	**P-value**
Age, years	73.8 (68.7-78.9)	74.0 (68.8-79.2)	73.6 (68.4-78.1)	0.528

Male	245 (75)	147 (70)	98 (84)	0.011
NYHA III-IV	157 (48)	104 (50)	53 (45)	0.511
Medical history				
Atrial fibrillation	176 (54)	117 (56)	59 (50)	0.396
Diabetes mellitus	122 (37)	78 (37)	44 (38)	1.000
Hypertension	250 (77)	157 (75)	93 (80)	0.448
Ischemic etiology of HF	163 (50)	104 (50)	59 (50)	1.000
Myocardial infarction	116 (36)	78 (37)	38 (33)	0.450
PCI	107 (33)	64 (31)	43 (37)	0.314
CABG	54 (17)	32 (15)	22 (19)	0.510
Time to upgrade, years	5.5 (2.2-8.9)	5.5 (2.0-9.2)	5.4 (2.9-8.9)	0.601
Laboratory parameters				
NT-proBNP, pg/mL (110)	2752 (1534-4666)	2986 (1944-5163)	2616 (1500-4586)	0.496
Creatinine, μmol/L (251)	107 (87-142)	114 (88-146)	101 (86-133)	0.103
GFR, mL/min/1.73m^2 (251)	58 (44-76)	55 (42-75)	65 (46-77)	0.036
Echocardiographic parameters				
LVEDD, mm (280)	61 ± 8	61 ± 9	60 ± 7	0.636
LVESD, mm (224)	49 (44-56)	50 (44-57)	49 (45-54)	0.825
LVEF, % (292)	30 (25-35)	30 (25-35)	29 (25-33)	0.108
Medications				
ACE-I/ARB	297 (91)	190 (91)	107 (92)	1.000
Beta-blocker	295 (91)	186 (89)	109 (93)	0.301
Loop diuretics	256 (79)	175 (84)	81 (69)	0.004
MRA	221 (68)	137 (66)	84 (72)	0.301
Amiodarone	56 (17)	33 (16)	23 (20)	0.462

4.2.2. Long-term Survival of Patients Undergoing Upgrade Cardiac Resynchronization Therapy-Defibrillator or Cardiac Resynchronization Therapy-Pacemaker Procedure

Over a median follow-up period of 6.0 (3.7-8.9) years, 178 (55%) patients in our cohort died. During this time, seven (2%) patients with CRT-P were subsequently upgraded to CRT-D, and two (1%) underwent HTX. Kaplan-Meier estimates indicated 5- and 10-year mortality rates of 49% (43-55%) and 74% (66-80%) in the entire cohort, 35% (23-45%) and 52% (21-71%) in patients upgraded to CRT-D, and 54% (47-61%) and 78% (70-84%) in those who underwent a CRT-P upgrade, respectively. Upgrading to a CRT-D was associated with a lower risk of all-cause death compared to upgrading to a CRT-P, as demonstrated by both univariable (unadjusted HR: 0.551; 95% CI: 0.376-0.809; p = 0.002) and multivariable Cox regression analyses (adjusted HR: 0.516; 95% CI: 0.332-0.804; p = 0.003) (Figure 7., Table 7.). Additionally, male sex (HR: 2.045; 95% CI: 1.209-3.460; p = 0.008) and the use of loop diuretics (HR: 1.785; 95% CI: 1.061-3.001; p = 0.029) were identified as independent predictors of all-cause death in the multivariable Cox regression analysis (Table 7.).

Table 7. - *Predictors of all-cause mortality (169).*

The value (in parenthesis) after a feature's name indicates the number of patients with available data. If no value is reported, the given feature is available for all patients.

ACE-I – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; CABG – coronary artery bypass graft; CI – confidence interval; CRT-D – cardiac resynchronization therapy with defibrillator; GFR – glomerular filtration rate; HF – heart failure, HR – hazard ratio; LVEDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LVESD – left ventricular end-systolic diameter; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association; PCI – percutaneous coronary intervention. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

	Univariable Cox regression HR (95% CI)	**Multivariable Cox regression** HR (95% CI)
Age, years	1.031 (1.011-1.051), p=0.003	1.011 (0.987-1.037), p=0.369
Male	1.549 (1.080-2.222), p=0.018	2.045 (1.209-3.460), p=0.008
CRT-D	0.551 (0.376-0.809), p=0.002	0.516 (0.332-0.804), p=0.003
NYHA III-IV	1.294 (0.961-1.743), p=0.090	
Medical history		
Atrial fibrillation	1.364 (1.009-1.844), p=0.044	1.178 (0.806-1.721), p=0.398
Diabetes mellitus	1.265 (0.935-1.710), p=0.127	
Hypertension	0.931 (0.658-1.317), p=0.686	
Ischemic etiology of HF	1.927 (1.420-2.617), p<0.001	1.205 (0.815-1.781), p=0.350
Myocardial infarction	1.941 (1.439-2.619), p<0.001	
PCI	1.485 (1.093-2.017), p=0.011	
CABG	1.253 (0.857-1.832), p=0.244	
Time to upgrade, years	0.979 (0.949-1.009), p=0.168	
Laboratory parameters		
Creatinine (251)	1.004 (1.001-1.007), p=0.004	1.003 (0.815-1.781), p=0.129

GFR (251)	0.990 (0.982-0.998), p=0.011	
Echocardiographic parameters		
LVEDD (280)	1.020 (0.999-1.042), p=0.061	
LVESD (224)	1.016 (0.996-1.035), p=0.111	
LVEF (292)	0.978 (0.958-0.998), p=0.035	0.979 (0.956-1.003), p=0.084
Medications		
ACE-I/ARB	0.578 (0.365-0.915), p=0.019	0.765 (0.443-1.322), p=0.337
Beta-blocker	0.653 (0.417-1.023), p=0.063	
Loop diuretics	2.004 (1.292-3.108), p=0.002	1.785 (1.061-3.001), p=0.029
MRA	1.066 (0.778-1.461), p=0.692	
Amiodarone	0.971 (0.639-1.475), p=0.890	

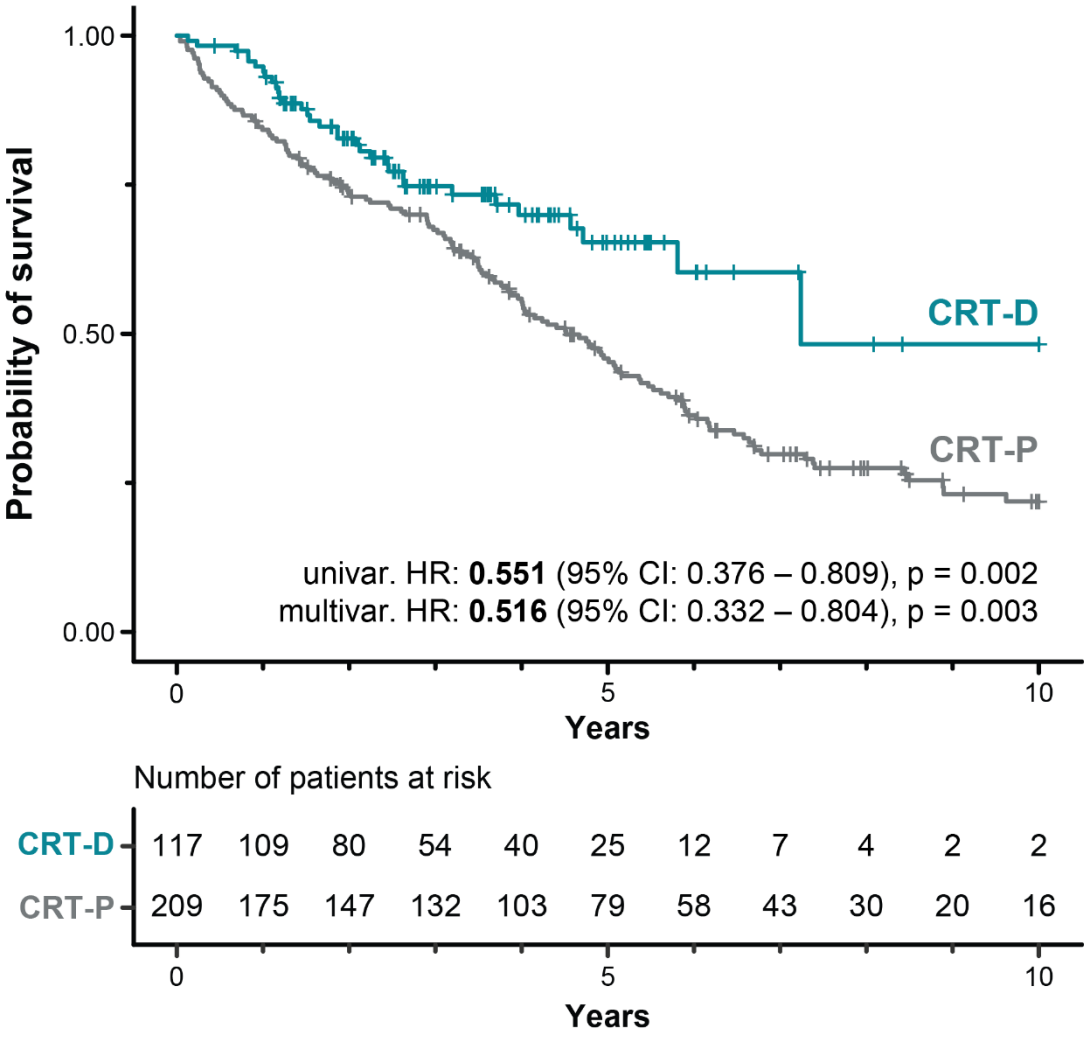


Figure 7. - *Kaplan-Meier curves depicting the survival of patients upgraded to a CRT-D vs. those upgraded to a CRT-P (169).*

CI – confidence interval; CRT – cardiac resynchronization therapy; CRT-D – cardiac resynchronization therapy-defibrillator; CRT-P – cardiac resynchronization therapy-pacemaker; HR – hazard ratio. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

We also sought to determine if upgrading to a CRT-D is associated with improved survival compared to upgrading to a CRT-P in different patient subgroups. Patients were stratified based on HF etiology (ischemic vs. non-ischemic), age (<80 vs. ≥80 years), sex, NYHA functional class (II vs. III-IV), GFR (<60 vs. ≥60 mL/min/m^2), history of AF, history of DM, and LVEF (<30% vs. ≥30%). Upgrading to a CRT-D was associated with

better survival in men, patients with ischemic HF, those under 80 years of age, and those with NYHA functional class III-IV, higher GFR, AF, no DM, and LVEF <30% (Figure 8.).

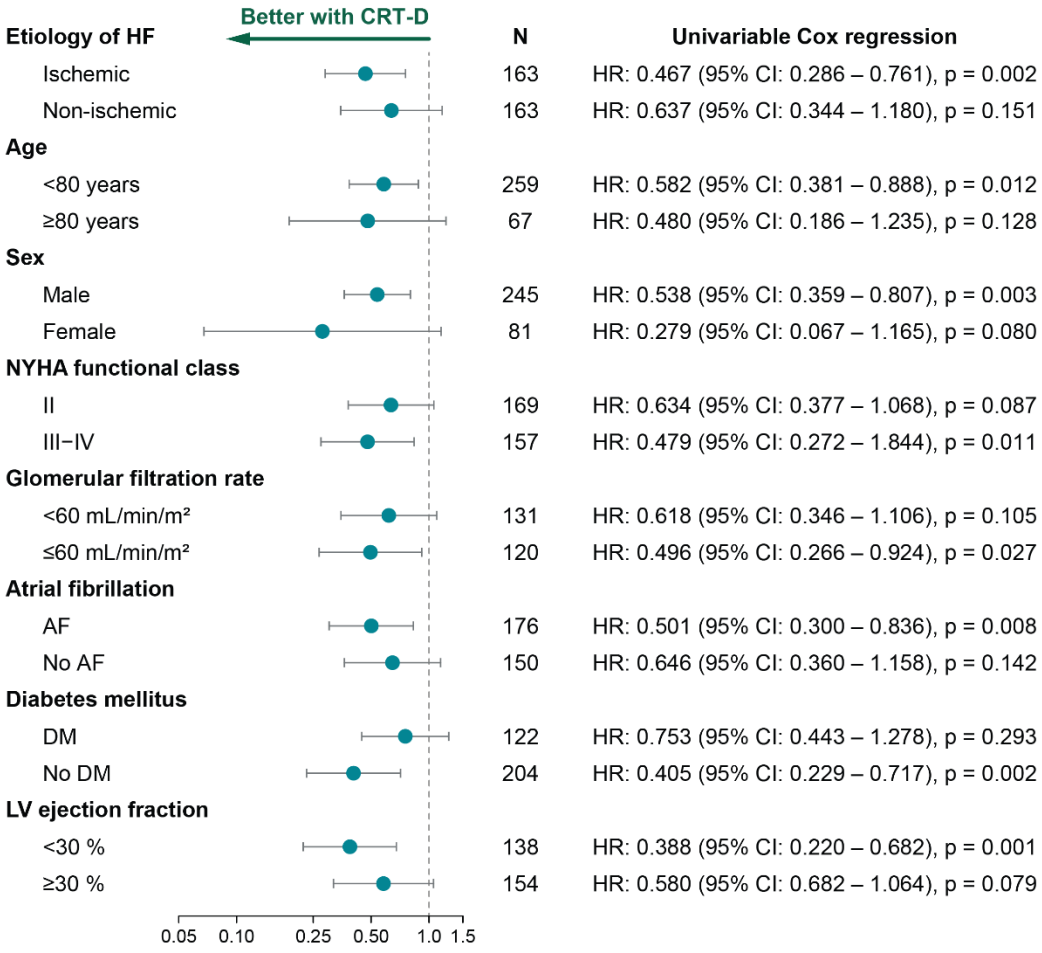


Figure 8. - *Forest plot summarizing the results of the subgroup analysis (169).*

AF – atrial fibrillation; CI – confidence interval; CRT-D – cardiac resynchronization therapy with defibrillator; DM – diabetes mellitus; HR – hazard ratio; LV – left ventricular; NYHA – New York Heart Association. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

Over the past decades, significant advancements in the pharmacological and device therapy for HF have led to multiple guideline updates. Nonetheless, our analysis using Cox regression found no association between the year of the CRT upgrade procedure and all-cause mortality.

4.2.3. Topological Data Analysis Derived Phenogroups of Patients Undergoing Cardiac Resynchronization Therapy Upgrade Procedure

Applying TDA and autogrouping resulted in a looped network, with low-risk and high-risk regions located at opposite poles (Figure 9.). These two regions were connected by sections containing patients with an intermediate risk of death, forming both the lower and upper arcs of the loop. Throughout the publication, the combination of these two intermediate-risk regions is referred to as the intermediate-risk phenogroup.

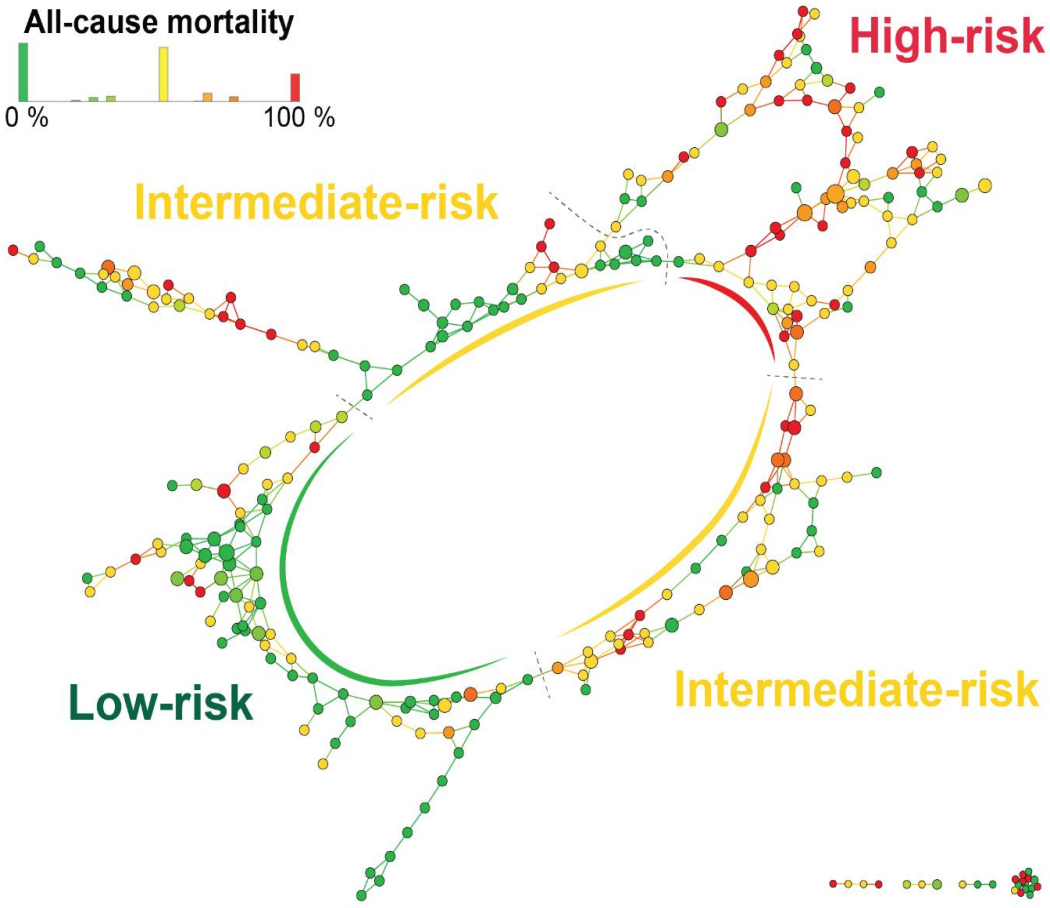


Figure 9. - *Topological network of patients undergoing an upgrade procedure to CRT-D or CRT-P (169).*

The topological network was created using sixteen pre-upgrade variables (age, sex, type of the implanted device, New York Heart Association functional class, history of atrial

fibrillation, history of hypertension, history of diabetes, etiology of heart failure, history of myocardial infarction, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, serum creatinine, glomerular filtration rate, left ventricular ejection fraction, left ventricular end-diastolic and end-systolic diameters). The generated network consists of nodes with edges between them. Each node represents a collection of similar patients, and two nodes are connected if they have at least one patient in common. In this network, nodes are color-coded based on all-cause mortality. Finally, the topological network was divided into low-, intermediate- and high-risk regions based on all-cause mortality.
Metric: normalized correlation, lenses: 2 × multi-dimensional scalings (resolution: 25, gain: 2.10, equalized). Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

The phenogroups exhibited several differences in clinical characteristics (Table 8.). The proportions of males and patients with ischemic etiology were highest in the high-risk phenogroup and lowest in the low-risk phenogroup. Patients in the high-risk phenogroup had the largest LV diameters and the lowest LVEF values, while those in the low-risk phenogroup had the best renal function.

Table 8. - *Clinical characteristics of the risk groups (169).*

**Variables used as input features in topological data analysis. $^{\dagger}p < 0.05$ vs. low-risk group, $^{\ddagger}p < 0.05$ vs. intermediate-risk group.*

The value (in parenthesis) after a feature's name indicates the number of patients with available data. If no value is reported, the given feature is available for all patients. Continuous variables are expressed as mean ± standard deviation or median (interquartile range), whereas categorical variables are reported as frequencies (n) and percentages (%). The pairwise comparison of risk groups was performed using the Kolmogorov-Smirnov test for continuous variables and Chi-squared or Fisher's exact test for categorical variables, as appropriate.

ACE-I – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; CABG – coronary artery bypass graft; CRT-D – cardiac resynchronization therapy with defibrillator; GFR – glomerular filtration rate; HF – heart failure; LVEDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LVESD – left ventricular end-systolic diameter; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association; PCI – percutaneous coronary intervention. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

	Low risk n = 92	**Intermediate risk n = 109**	**High risk n = 94**
Age, years*	75.2 (69.4 - 78.9)	73.8 (66.2 - 79.1)	72.4 (68.9 - 78.1)†
Male*	53 (58)	82 (75)†	87 (92.6)†‡
CRT-D*	42 (46)	31 (28)†	33 (35)
NYHA III-IV*	37 (40)	53 (49)	50 (53)
Medical history			
Atrial fibrillation*	59 (64)	54 (50)	45 (48)†
Diabetes mellitus*	25 (27)	43 (39)	45 (48)†
Hypertension*	72 (78)	82 (75)	70 (75)
Ischemic etiology of HF*	2 (2)	51 (47)†	94 (100)†‡
Myocardial infarction*	1 (1)	39 (36)†	63 (67)†‡
PCI*	0 (0)	36 (33)†	61 (65)†‡
CABG*	1 (1)	21 (19)†	28 (30)†
Time to upgrade, years	5.7 (2.5 - 9.3)	6.1 (2.4 - 11.2)	3.9 (1.7 - 7.7)‡
Laboratory parameters			
NT-proBNP, pg/mL (98)	2834 (1548 - 4797)	2847 (1206 - 5211)	3000 (1754 - 5043)
Creatinine, μmol/L (225)*	96 (80 - 111)	119 (89 - 149)†	120 (95 - 151)†
GFR, mL/min/1.73m^2 (225)*	65 (50 - 80)	53 (38 - 74)†	53 (42 - 72)†
Echocardiographic parameters			
LVEDD, mm (249)*	59 ± 5	60 ± 11†	64 ± 7†‡
LVESD, mm (202)*	48 ± 5	49 ± 12†	54 ± 7†‡

LVEF, % (261)*	30 (28 - 35)	30 (25 - 35)	28 (25 - 32)†‡
Medications			
ACE-I/ARB	86 (94)	97 (89)	88 (94)
Beta-blocker	85 (92)	97 (89)	87 (93)
Loop diuretics	67 (73)	86 (79)	82 (87)†
MRA	63 (69)	78 (72)	61 (65)
Amiodarone	15 (16)	20 (18)	15 (16)

As anticipated, there were also significant differences in the survival rates of the phenogroups (log-rank test: $p < 0.001$). Patients in the intermediate-risk and high-risk phenogroups had a 1.6-fold (unadjusted HR: 1.618; 95% CI: 1.041-2.514; $p = 0.033$) and 2.6-fold (unadjusted HR: 2.632; 95% CI: 1.707-4.060; $p < 0.001$) increase in the risk of all-cause mortality compared to those in the low-risk phenogroup (Figure 10.). Upgrading to a CRT-D, as opposed to a CRT-P, was associated with a lower risk of death in high-risk patients (unadjusted HR: 0.454; 95% CI: 0.228-0.907; $p = 0.025$), but not in the intermediate-risk (unadjusted HR: 0.507; 95% CI: 0.226-1.136; $p = 0.099$) or low-risk phenogroups (unadjusted HR: 0.983; 95% CI: 0.443-2.180; $p = 0.966$) (Figure 11.).

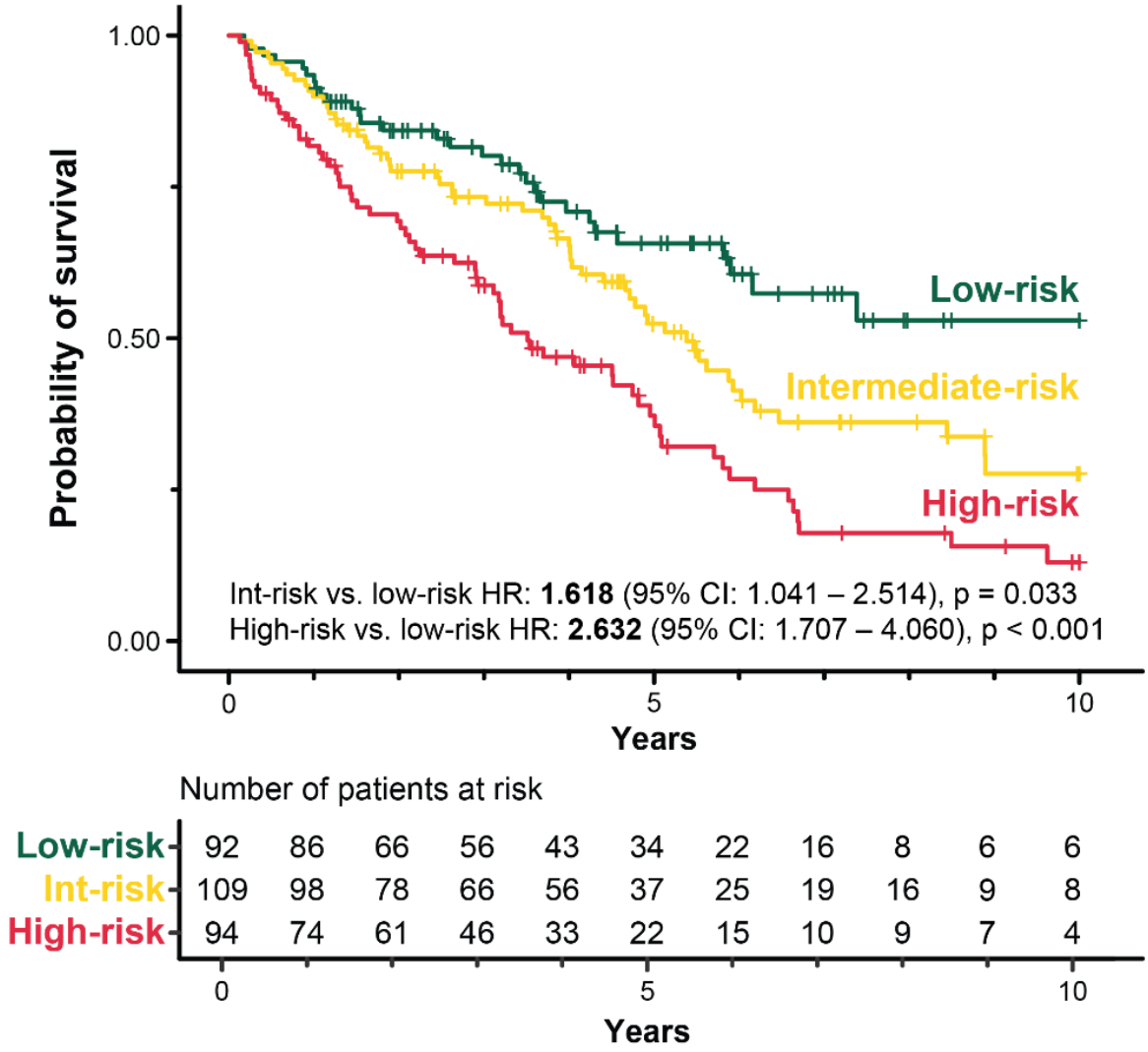


Figure 10. - *Kaplan-Meier curves depicting the survival of the topological data-analysis derived risk groups (169).*

Hazard ratios and 95% confidence intervals were calculated with univariable Cox regression.

CI – confidence interval; HR – hazard ratio; Int-risk – intermediate-risk. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

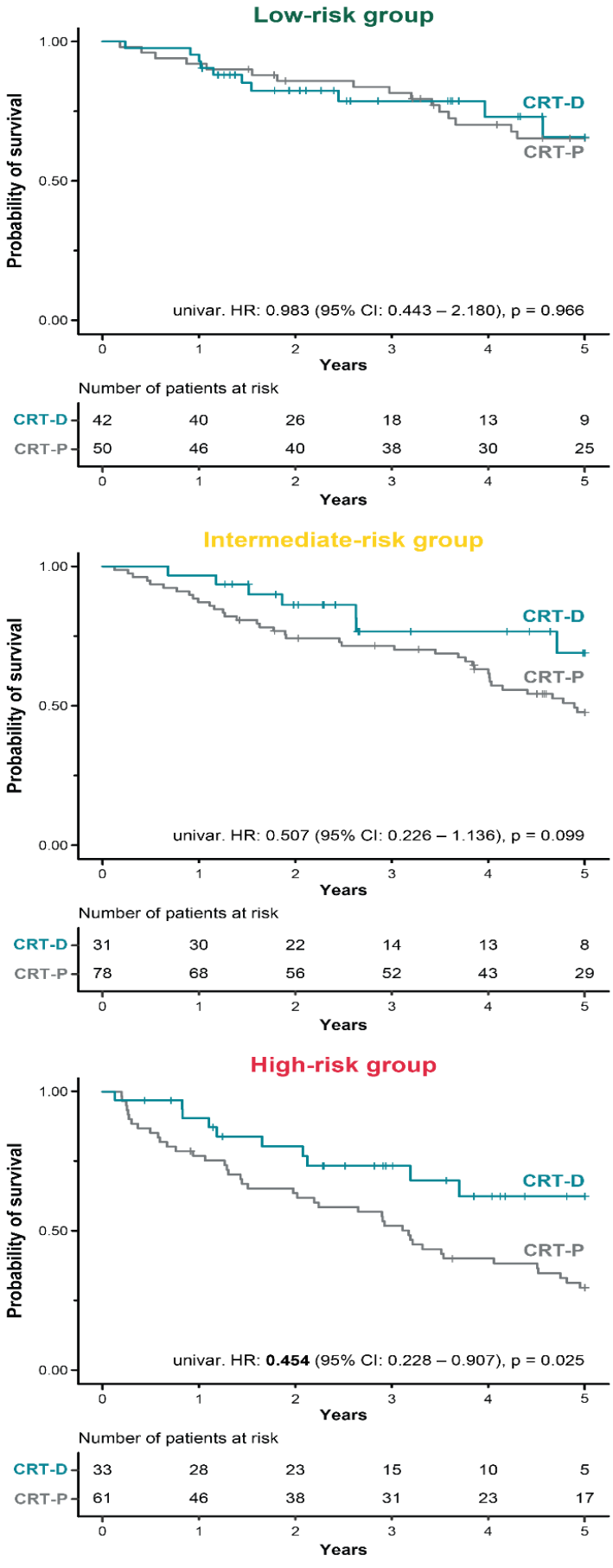

Low-risk group
Probability of survival
1.00
0.50
0.00
CRT-D
CRT-P
univar. HR: 0.983 (95% CI: 0.443 – 2.180), p = 0.966
0
1
2
3
4
5
Years
Number of patients at risk
CRT-D 42 40 26 18 13 9
CRT-P 50 46 40 38 30 25
Years
Intermediate-risk group
Probability of survival
1.00
0.50
0.00
CRT-D
CRT-P
univar. HR: 0.507 (95% CI: 0.226 – 1.136), p = 0.099
0
1
2
3
4
5
Years
Number of patients at risk
CRT-D 31 30 22 14 13 8
CRT-P 78 68 56 52 43 29
Years
High-risk group
Probability of survival
1.00
0.50
0.00
CRT-D
CRT-P
univar. HR: 0.454 (95% CI: 0.228 – 0.907), p = 0.025
0
1
2
3
4
5
Years
Number of patients at risk
CRT-D 33 28 23 15 10 5
CRT-P 61 46 38 31 23 17
Years

Figure 11. - *Kaplan-Meier curves depicting the survival of patients who underwent an upgrade procedure to CRT-D versus those who underwent an upgrade procedure to CRT-P in each topological data-analysis derived risk group (169).*

To assess the survival benefit of an upgrade to CRT-D compared with an upgrade to CRT-P, hazard ratios, and 95% confidence intervals were calculated with univariable Cox regression.
CI – confidence interval; CRT-D – cardiac resynchronization therapy with defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; HR – hazard ratio; univar. - univariable. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

Since the intermediate-risk phenogroup comprised two separate subgroups—one in the lower arc and the other in the upper arc of the circular network—we compared their clinical characteristics and survival (Table 9.). Patients in the upper region were older ($p < 0.001$) and less symptomatic ($p < 0.001$). They predominantly had ischemic etiology ($p < 0.001$), lower NT-proBNP values ($p < 0.001$), smaller LVEDd and LVESDd (both $p < 0.001$), and higher LVEF values ($p < 0.001$) than those in the lower region. Despite these differences in clinical characteristics, they had similar survival rates (Figure 12.). Upgrading to a CRT-D was associated with a similar risk of all-cause mortality as upgrading to a CRT-P in both the upper (HR: 0.445; 95% CI: 0.131-1.510; $p = 0.194$) and lower intermediate-risk regions (HR: 0.546; 95% CI: 0.185-1.609; $p = 0.273$).

Table 9. - *Clinical characteristics of the intermediate-risk phenogroups (169).*

The table presents the clinical characteristics of patients categorized into the intermediate-risk group by topological analysis, based on whether they are positioned on the lower or upper region of the network.

**Variables used as input features in topological data analysis.*
The value (in parenthesis) after a feature's name indicates the number of patients with available data. If no value is reported, the given feature is available for all patients. Continuous variables are expressed as mean ± standard deviation or median (interquartile range), whereas categorical variables are reported as frequencies (n) and percentages (%). Phenogroups were compared using the Kolmogorov-Smirnov test for

continuous variables and Chi-squared or Fisher's exact test for categorical variables, as appropriate.

ACE-I – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; CABG – coronary artery bypass graft surgery; CRT-D – cardiac resynchronization therapy-defibrillator; GFR – glomerular filtration rate, HF – heart failure; LVEF – left ventricular ejection fraction; LVIDd – left ventricular internal diameter at end-diastole; LVIDs – left ventricular internal diameter at end-systole; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association; PCI – percutaneous coronary intervention. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

	Lower region n=48	**Upper region n=61**	**P-value**
Age, years*	76.7±6.1	69.0±10.2	<0.001
Male*	35 (73)	47 (77)	0.785
CRT-D*	14 (29)	17 (28)	1.000
NYHA III-IV*	14 (29)	39 (64)	<0.001
Medical history			
Atrial fibrillation*	28 (58)	26 (43)	0.151
Diabetes mellitus*	18 (38)	25 (41)	0.863
Hypertension*	38 (79)	44 (72)	0.534
Ischemic etiology of HF*	43 (90)	8 (13)	<0.001
Myocardial infarction*	38 (79)	1 (2)	<0.001
PCI*	31 (65)	5 (8)	<0.001
CABG*	18 (38)	3 (5)	<0.001
Time to upgrade, years	7.5 (3.0-11.1)	5.6 (1.9-10.5)	0.612
Laboratory parameters			
NT-proBNP, pg/mL (28)	1,172 (834-2,288)	4,894 (3,670-7,408)	<0.001

Creatinine, μmol/L (77)*	110 (90-133)	135 (89-166)	0.109
GFR, mL/min/1.73m^2 (77)*	58 (45-74)	49 (33-74)	0.178
Echocardiographic parameters			
LVIDd, mm (99)*	52 (48-56)	66 (62-71)	<0.001
LVIDs, mm (88)*	40 (37-45)	57 (54-61)	<0.001
LVEF, % (101)*	35 (33-40)	25 (20-30)	<0.001
Medications			
ACE-I/ARB	43 (90)	54 (89)	1.000
Beta-blocker	44 (92)	53 (87)	0.544
Loop diuretics	34 (71)	52 (85)	0.111
MRA	33 (69)	45 (74)	0.717
Amiodarone	11 (23)	9 (15)	0.399

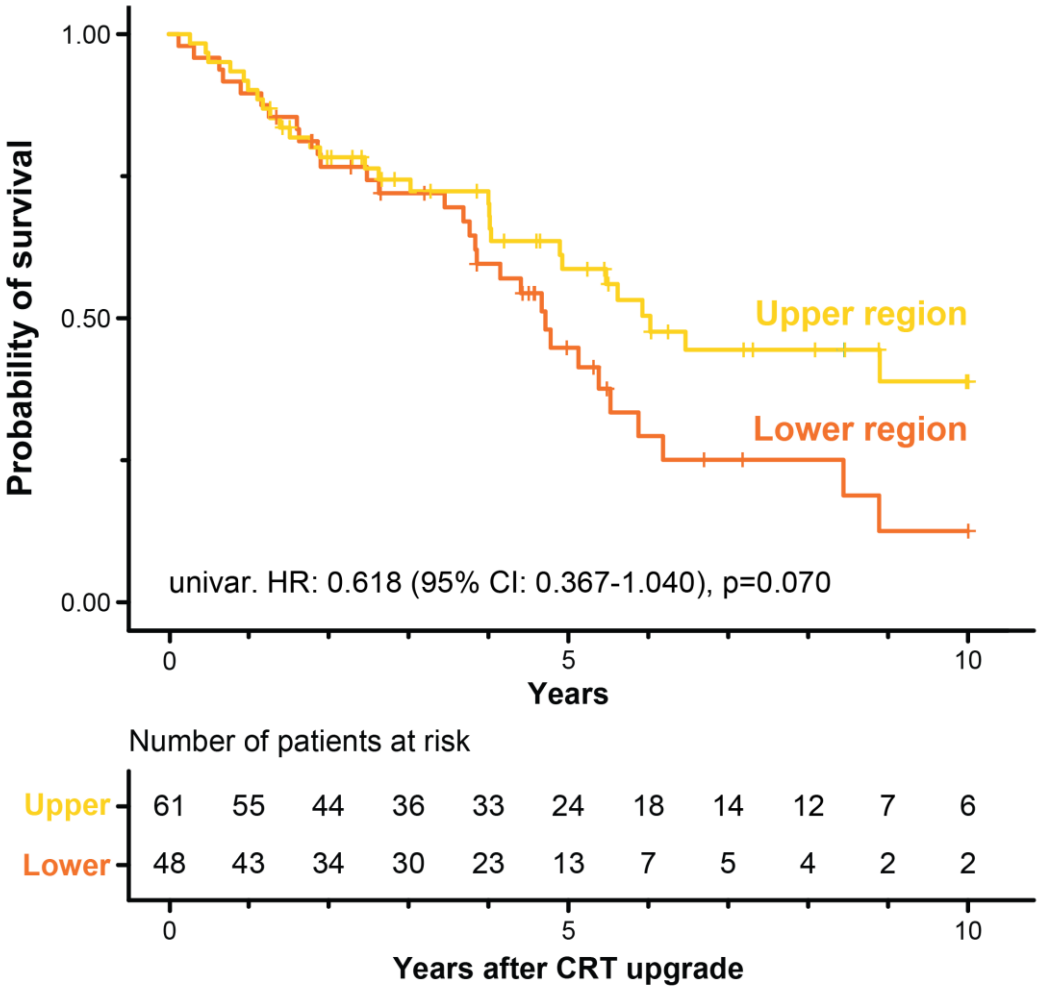


Figure 12. - *Kaplan-Meier curves depicting the survival of the upper and lower regions of the intermediate-risk phenogroup (169).*

Hazard ratios and 95% confidence intervals were calculated with univariable Cox regression. CI – confidence interval; HR – hazard ratio, univar. - univariable. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

4.2.4. Machine Learning-Based Multi-class Classification Using the Topological Data Analysis-Derived Phenogroups

Among the evaluated multi-class classifiers, the ensemble of five MLPs demonstrated the best performance during internal validation, achieving a balanced

accuracy of 0.898 (95% CI: 0.854-0.942) and a micro-averaged AUC of 0.983 (95% CI: 0.980-0.986). In the external validation cohort (clinical characteristics detailed in Table 10.), all patients classified into the high-risk phenogroup (n=6) died within 10 years following the upgrade procedure (Figure 13.). However, differences in survival among the three phenogroups were less pronounced, likely due to the small sample size.

Table 10. - *Clinical characteristics of the external validation cohort (169).*

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), whereas categorical variables are reported as frequencies (n) and percentages (%). The characteristics of the Semmelweis and the external validation cohort were compared using unpaired Student's t-test or Mann-Whitney U test for continuous variables and Chi-squared or Fisher's exact test for categorical variables, as appropriate.

CABG – coronary artery bypass graft; CRT-D – cardiac resynchronization therapy with defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; GFR – glomerular filtration rate, HF – heart failure; LVEDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LVESD – left ventricular end-systolic diameter; NYHA – New York Heart Association; PCI – percutaneous coronary intervention. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

	Semmelweis cohort n=326	**External validation cohort n=29**	**P-value**
Age, years	73.8 (68.7-78.9)	69.3 (62.7-74.4)	0.005
Male	245 (75)	19 (66)	<0.001
CRT-D	117 (36)	6 (21)	0.149
NYHA III-IV	157 (48)	15 (52)	0.862
Medical history			
Atrial fibrillation	176 (54)	14 (48)	0.692
Diabetes mellitus	122 (37)	8 (28)	0.394
Hypertension	250 (77)	23 (79)	0.927

Ischemic etiology of HF	163 (50)	10 (35)	0.159
Myocardial infarction	116 (35)	5 (17)	0.064
PCI	107 (33)	5 (17)	0.097
CABG	54 (17)	5 (17)	1.000
Laboratory parameters			
Creatinine, μmol/L	107 (87-142)	88 (78-117)	0.068
GFR, mL/min/1.73m^2	58 (44-76)	60 (41-76)	0.904
Echocardiographic parameters			
LVEDD, mm	61 ± 8.2	66.8 ± 6.4	<0.001
LVESD, mm	49.9 ± 9.7	56.1 ± 7.1	0.006
LVEF, %	30 (25-35)	29 (25-30)	0.225

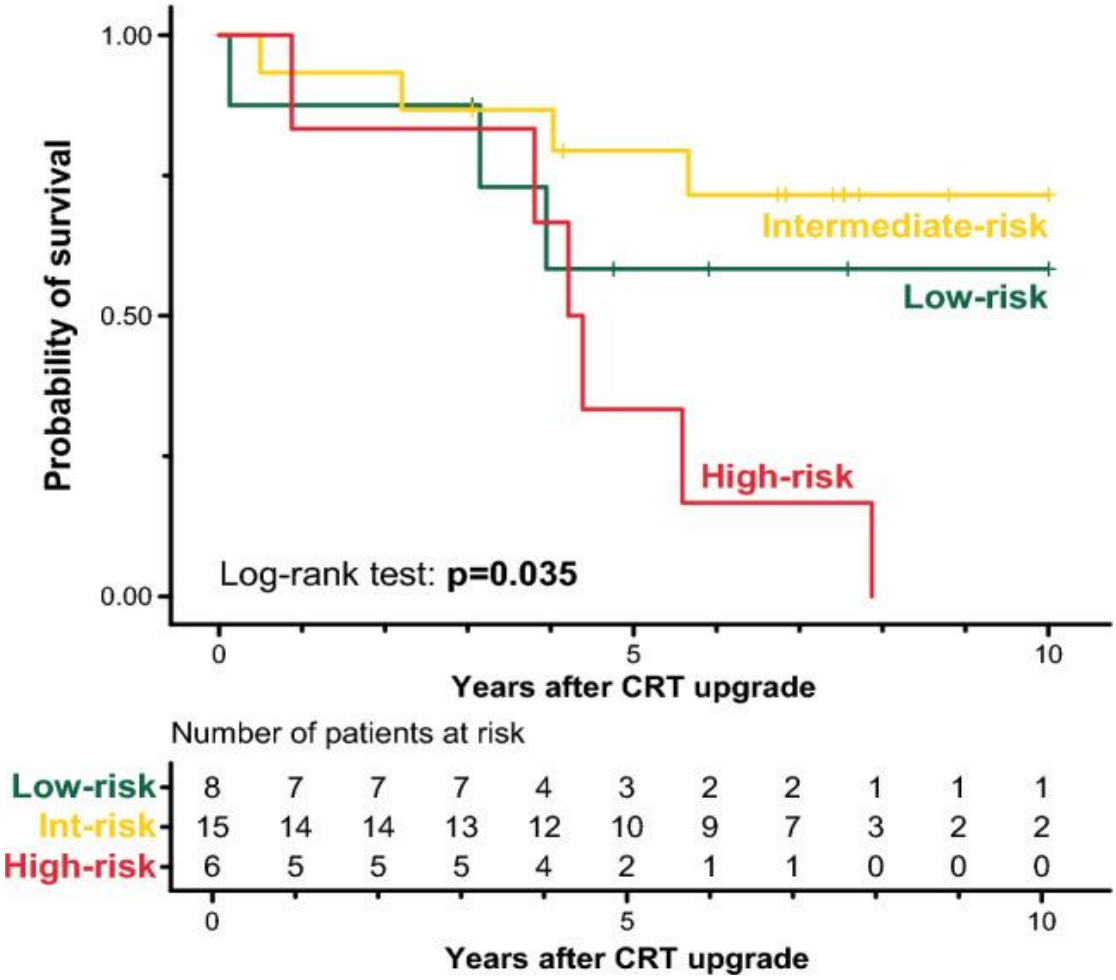


Figure 13. - *Kaplan-Meier curves depicting the survival of the patients of the external validation cohort classified into the topological data analysis-derived phenogroups (169).*

This figure validates the effectiveness of the ensemble model built with a multi-layer perceptron approach in accurately stratifying patients into low, intermediate, and high-risk groups within the external validation cohort. The statistically significant differences in survival trends between these groups (p = 0.035) reinforce the model's utility in phenotyping and risk stratification.

CRT – cardiac resynchronization therapy. Adapted from Schwertner et al. Sci Rep 13, 20594 (2023). https://doi.org/10.1038/s41598-023-47092-x.

5. Discussion

5.1. Comparing Long-term Clinical Outcomes of De novo and Upgrade Cardiac Resynchronization Therapy Patients

5.1.1. Patients Characteristics

Several studies have highlighted the differences in clinical characteristics between de novo and upgrade patients (172-178). Consistent with these studies and our cohort, the latter group tends to be older and present with more comorbidities, such as AF, ischemic etiology, previous VAs, and CKD (172-178). These observations can be partially attributed to the differing etiologies of HF. In addition to age, the burden of RVP and the incidence of AF are significant factors in this group (136). As highlighted in the MOST trial, HF and RVP burden >40% are associated with an increased risk of HF, with a linear relationship observed between cumulative ventricular pacing and the risk of developing AF (136).

Renal function is also impacted by age (179). Although one of the largest multicenter registries reported a higher prevalence of CKD in de novo patients compared to upgrade patients, our findings indicate a greater frequency of CKD in the latter group (142). However, it is crucial to note that the baseline characteristics of their population differed significantly from those documented in previous studies (172-175). Alongside the high prevalence of CKD, serum creatinine levels were notably higher among CRT upgrade patients than in the de novo group within our cohort (170). Similarly, Wokhlu et al. have emphasized the significance of baseline serum creatinine levels as an independent predictor of mortality in a comparable population (173).

Despite the underrepresentation of women in CRT trials (with females comprising approximately 19-27% of study populations), they tend to exhibit a better response to CRT than men (172, 176). In our cohort, 25% of candidates were female (170). The proportion of females was lower in the upgrade group compared to the de novo group (20% vs. 27%; $P = 0.002$) (170). In the BUDAPEST-CRT Upgrade trial, the baseline clinical characteristics of patients who underwent an upgrade procedure showed substantial similarities to those of our CRT upgrade patients (180). This similarity is

mostly attributable to the fact that some of the patients in our present study were also included in the BUDAPEST-CRT Upgrade trial.

5.1.2. Differences in Long-term Outcomes

Data regarding the differences in long-term mortality between de novo and upgrade CRT patients are limited (170). Smaller, short-term observational studies have not demonstrated significant differences in survival, and analyses of larger registries have produced inconsistent results (141, 172, 173, 178). In one of the largest observational registries, which compared 692 upgrade and 1,675 de novo patients, no significant difference was observed in total and cause-specific mortality after a one-year follow-up period (178). Conversely, another multicenter, observational, prospective study reported more favorable outcomes for de novo CRT patients, persisting even after propensity score matching (177). However, this study included only CRT-D recipients, who are generally younger and less vulnerable, potentially influencing the mid-term outcomes (177).

Leyva et al. analyzed CRT patients from 2000 to 2016 and found significantly higher rates of all-cause mortality and mortality/HFH in upgrade patients (175). However, after performing multivariable Cox proportional hazard analysis or propensity score matching, these differences were not observed (175). Their univariable analysis indicated that all-cause mortality was higher in upgrade patients compared to de novo patients, specifically in men and subgroups with advanced functional class, CRT-P, non-ischemic cardiomyopathy, non-diabetic status, LBBB, QRS ≥150ms, and LVEF ≤25% (175). These findings align with ours, as we also identified a higher risk of the composite endpoint in these subgroups among upgrade CRT patients (170). Leyva et al. noted a higher risk of mortality in upgrade patients receiving CRT-P devices compared to those upgraded to CRT-D (175). Leyva et al. included CRT upgrade recipients with no history of sVT arrhythmia, and hence they investigated CRT upgrade in the context of primary prevention, whereas our cohort also included patients with and without prior VAs (175). In our previous RCT, the BUDAPEST-CRT Upgrade trial included a total of 360 HFrEF patients, where previously implanted devices were upgraded to CRT-D in a 3:2 ratio or treated with ICD. Patients were followed for a median of 12.4 months. In the CRT upgrade group, there was a significantly lower incidence of the composite of HFH and all-cause mortality endpoint compared to the ICD group (aHR 0.27; 95% CI 0.16 to 0.47; p

<0.001), demonstrating the substantial clinical advantage of CRT upgrade over ICD (140).

Notably, the type of implanted device and the date of implantation might affect outcomes due to continuous advancements in device technology and drug treatment (170). However, neither the previously reported data nor our results confirm that the date of implantation alone is associated with a less beneficial outcome (175).

Previously, we conducted a systematic review and meta-analysis encompassing 468,205 de novo and 21,363 upgrade CRT patients, which revealed a similar risk of all-cause mortality in these two patient groups (risk ratio 1.19; 95% CI: 0.88-1.60; p = 0.27) (141). This finding was corroborated by the current analysis after adjusting for relevant covariates and performing propensity score matching (170).

5.1.3. Peri-procedural and Long-term Complications

Although data comparing complications associated with de novo and upgrade CRT procedures are limited, CRT upgrade is generally considered to have a higher complication rate (172, 177, 178). Our analysis revealed higher incidences of lead dysfunction and pocket infection among upgrade patients, even after propensity score matching. Consistent with our findings, the REPLACE registry and the RAFT Upgrade sub-study identified lead displacement or dysfunction as the most common complication in both CRT groups (181, 182). During upgrade procedures, the risk of damaging previously implanted leads or encountering difficulties with new leads is greater than in de novo procedures (183). This may explain our observation that CRT upgrade procedures were associated with a higher prevalence of lead dysfunction [11 (2.0%) vs. 2 (0.4%); p = 0.022] after one year (170).

CRT implantation, particularly in older patients or those with coagulopathy (such as renal insufficiency or those on OAC therapy), carries an increased risk of post-procedural pocket hematoma and subsequent infections, as demonstrated in our study cohort (184).

In our current analysis, only PTX was observed more frequently in de novo patients (1.4% vs. 0.4%; p = 0.045), but this difference disappeared after propensity score

matching (170). This can be attributed to the presence of previously implanted leads in upgrade patients, which may facilitate the identification of the subclavian vein (170).

However, neither the largest observational registries, the European CRT Survey and the European CRT Survey II, nor other smaller observational studies found significant differences in complication rates between the two patient groups (141, 176-178). The inconsistency in the data suggests that not only the characteristics of the patient cohort but also the experience of the implanting physicians and the duration of the procedure are considerable factors (183).

5.2. Comparing Patients Clinical Outcomes Following Upgrade Cardiac Resynchronization Therapy-Defibrillator or Cardiac Resynchronization Therapy-Pacemaker Implantation

5.2.1. Baseline Clinical Characteristics and Long-term Survival of Patients Undergoing Upgrade Cardiac Resynchronization Therapy-Defibrillator or Cardiac Resynchronization Therapy-Pacemaker Procedure

Due to the induction of inter- and intra-ventricular dyssynchrony, chronic RVP is associated with an increased risk of adverse outcomes (136, 185-189). By addressing this dyssynchrony, upgrading to CRT can potentially mitigate or even reverse the detrimental effects of chronic RVP, resulting in improved clinical outcomes (190). However, it remains a topic of debate whether an ICD offers any additional benefit to patients undergoing a CRT upgrade (169).

Although CRT upgrade procedures constitute 20-30% of all CRT implantations, only a limited number of RCTs have been conducted in this context (140, 176, 190). The most recently published one, the BUDAPEST-CRT Upgrade trial, demonstrated that CRT-D upgrade was associated with a lower incidence of the primary endpoint (the composite of all-cause mortality, HFH, or <15% decrease in LVESV at 12 months) and the secondary endpoints (the composite of all-cause mortality or HFH) compared to ICD-only therapy (140). Nevertheless, no RCTs have been conducted to date specifically designed to compare CRT-D versus CRT-P upgrade, necessitating reliance on data from observational or RCT substudies (169). In a study investigating non-ischemic patients with no history of VAs upgraded to CRT due to PiCMP, Barra et al. reported a low risk of

life-threatening VAs and suggested that these patients may not derive significant benefit in terms of all-cause mortality from the addition of an ICD (191). Conversely, Leyva et al. observed a lower risk of all-cause mortality after upgrading to a CRT-D compared to a CRT-P in a cohort including both ischemic and non-ischemic HF patients with no history of VAs, even after inverse probability weighting (175). These findings underscore the importance of etiology in device selection and align with our observations, as we also found that upgrading to a CRT-D is associated with better survival in ischemic but not non-ischemic patients (169).

The ongoing Re-evaluation of Optimal Resynchronization Therapy in Patients with Chronic Heart Failure (RESET-CRT) trial, which hypothesizes that CRT-P is non-inferior to CRT-D with respect to all-cause mortality, is expected to provide crucial data on this matter (169, 192). As a prelude to this RCT, a population-based weighted cohort study was conducted with the same inclusion and exclusion criteria and primary endpoint, and the investigators found CRT-P to be non-inferior in terms of survival after adjusting for age and entropy balancing for baseline clinical characteristics (192). Nevertheless, since these studies have included only de novo CRT patients, further investigations are necessary to confirm or refute whether their results also apply to patients undergoing CRT upgrade, given the apparent differences in clinical characteristics between patients referred for CRT upgrade and those referred for de novo CRT implantation. (169)

5.2.2. Determining the Optimal Therapy for Patients Undergoing Upgrade Cardiac Resynchronization Therapy

As current guidelines lack specific recommendations for guiding device selection during CRT upgrade in patients with previously implanted PMs and no history of VAs, physicians must carefully weigh the benefits and drawbacks of upgrading to a CRT-D instead of a CRT-P on an individual basis (87, 193). This comprehensive and individualized pre-upgrade assessment requires a risk-benefit analysis that considers multiple factors, such as HF etiology, age, comorbidities, and device-related risks and potential complications (194).

It should also be noted that while patients with an LVEF of ≤35% are indicated for an ICD, CRT may significantly improve LV function, potentially raising LVEF above 35%, thereby reducing the risk of SCD and eliminating the need for an ICD (169). Upon

the choice of the optimal device type concomitant HF medications (e.g., ARNI and SGLT2 inhibitors), can independently reduce the risk of SCD (195).

Given the challenges and complexity of the pre-upgrade assessment, we aimed to apply advanced data analysis approaches in this study to identify those CRT upgrade candidates most likely to experience an additional mortality benefit from an ICD (169). We chose TDA as it can simultaneously evaluate multiple clinical features and create a compact visual representation of a complex dataset (168). Through exploratory analysis of the generated network, distinct phenogroups with different characteristics, clinical outcomes, and therapeutic responses can be identified, as demonstrated in several cardiovascular medicine studies (196-200).

Indeed, we delineated three phenogroups in our cohort of CRT upgrade patients, finding that only one group exhibited a lower risk of all-cause mortality with a CRT-D upgrade compared to a CRT-P upgrade (169). Recognizing the importance of classifying new patients into the identified phenogroups for validation and practical application of our findings, we labeled the patients within the topological network based on their location (169). Using this labeled data, we trained ML classifiers, which we have made publicly available (https://github.com/tokmarton/crt-upgrade-risk-stratification) (169).

5.2.3. Limitations

Our study comparing the long-term clinical outcomes following de novo and upgrade CRT has certain limitations (170). Firstly, our analyses were conducted retrospectively, resulting in some imbalances between the groups (170). To address these discrepancies, we utilized multivariable Cox regression analysis and propensity score matching in addition to univariable analyses (170). Furthermore, due to the retrospective design of the study, there was a moderate proportion of missing data among patients (170). Secondly, as the study covers a period of 19 years, general therapeutic protocols, lead selection, device programming, medical treatment options, technical equipment, and guidelines have evolved over time (170). Nonetheless, our investigation on the impact of the implantation date on outcomes revealed no significant effect (170).

Despite its strengths, our study comparing the long-term clinical outcomes following CRT-D or CRT-P upgrade has several limitations that warrant discussion (169).

Firstly, the dataset we analyzed using conventional statistics and TDA was derived from a single center and comprised a relatively small number of patients (169). Consequently, further investigations should be conducted in larger, preferably multi-center cohorts of patients undergoing CRT upgrade to confirm our findings (169). Secondly, the retrospective nature of data collection introduces several inherent limitations, such as a relatively high proportion of missing values, which necessitated the omission of several well-established prognostic markers (e.g., NT-proBNP) from our analysis (169). Thirdly, patients were upgraded to a CRT-D or CRT-P device based on the physicians' clinical judgment rather than through randomization, potentially resulting in selection bias (e.g., men with better renal function were more likely to receive a CRT-D) (169). Nevertheless, we performed multivariable Cox regression analysis to partially mitigate this bias (169). Fourthly, post-mortem device interrogations were not conducted, and cause-specific mortality data were unavailable; therefore, we could not investigate differences in the rate of SCD between the groups (169). Lastly, although we trained an ML model to enable the classification of new patients into the TDA-derived phenogroups, we were only able to validate it externally in a small cohort of patients (169). Thus, further external validation is necessary (169). To facilitate this, we have made the source code and the best-performing model publicly available (169).

6. Conclusion

We compared long-term clinical outcomes of patients receiving de novo versus upgrade CRT implantation using data from 2,524 patients. Univariable analysis showed an unfavourable outcome in all-cause mortality in the upgrade CRT group, which mortality difference disappeared after adjusting for baseline differences through propensity score matching, suggesting the initial disparity was due to pre-existing conditions. Our study is among the first to highlight, in a high-volume analysis, that CRT upgrade patients face a higher risk of peri- and post-procedural complications, including increased rates of lead dysfunction and pocket infection, even after adjusting for baseline characteristics. Despite the numerous comorbidities, a CRT upgrade is expected to achieve at least as good clinical outcomes as de novo CRT.

In a separate analysis of 326 patients with preexisting PMs and no history of VAs, we found that those upgraded to CRT-D had significantly lower all-cause mortality compared to those upgraded to CRT-P, highlighting the potential survival benefit of CRT-D in higher-risk patients. Our study is also the first to apply TDA to identify three phenogroups—low-, intermediate-, and high-risk—among CRT upgrade patients. In the high-risk group, CRT-D was associated with markedly improved survival, underscoring the importance of risk stratification in guiding CRT upgrade decisions. Additionally, we developed an ML ensemble model capable of accurately classifying patients into phenogroups, aiding clinical decision-making.

Our findings underscore the necessity for careful risk stratification and personalized management in CRT upgrades, particularly in high-risk patients, where CRT-D may offer significant survival benefits.

7. Summary

CRT upgrade procedures account for 20-30% of all CRT interventions. Despite this considerable proportion, there is a paucity of scientific evidence regarding the long-term outcomes of patients undergoing CRT upgrades. Patients receiving CRT upgrades tend to be older, with more comorbidities and consequently less favorable clinical outcomes compared to those receiving de novo CRT treatment. However, these observations predominantly stem from studies with small sample sizes and short follow-up periods.

To address this gap, we conducted a study with a large cohort and extended follow-up period to compare the clinical outcomes of patients receiving de novo versus upgrade CRT treatments. Our findings confirmed that patients in the upgrade group have more comorbidities, which contribute to their less favorable clinical outcomes compared to the de novo CRT group. However, when adjusting for baseline differences between the two groups, the observed disparities in clinical outcomes were no longer evident. Additionally, we demonstrated that the incidence of lead dysfunction and pocket infection is significantly higher in the upgrade CRT group compared to the de novo group.

Although guideline-directed medical therapy aims to reduce the risk of all-cause mortality, HFH, and SCD, it remains crucial to carefully consider the necessity of a backup ICD during CRT upgrade procedures. To this end, we examined patients with no history of VAs undergoing CRT upgrades from PMs to either CRT-D or CRT-P devices. In the overall population, CRT-D was associated with better outcomes compared to CRT-P upgrades. Subsequently, using TDA an ML-based tool, we identified phenogroups with distinct mortality trends. Within these risk groups, high-risk patients exhibited more favorable outcomes with CRT-D devices compared to CRT-P. Furthermore, we developed a trained ML model capable of accurately classifying patients into these phenogroups.

The integration of advanced analytical tools such as TDA and ML into clinical practice, particularly in stratifying risk and guiding decisions for CRT upgrades, has the potential to significantly enhance patient outcomes and optimize therapeutic strategies.

8. Összefoglaló

A CRT upgrade beavatkozások az összes CRT beültetés 20-30%-át teszik ki. E jelentős arány ellenére a CRT upgrade-en átesett betegek hosszú távú kimeneteléről kevés irodalmi adat áll rendelkezésre. A CRT upgrade kezelésben részesülő betegek általában idősebbek, több társbetegséggel rendelkeznek, és ennek következtében kevésbé kedvező klinikai kimenetelük lehet a de novo CRT kezelésben részesülő betegekkel összehasonlítva, a korábbi kisebb elemszámú és rövid utánkövetési idejű obszervációs vizsgálatok eredményei alapján.

Egy nagy betegszámú és hosszú utánkövetési idővel rendelkező vizsgálatot végeztünk, hogy összehasonlítsuk a de novo és upgrade CRT implantációban részesülő betegek klinikai kimenetelét. Eredményeink megerősítették, hogy az upgrade csoportba tartozó betegek több társbetegséggel rendelkeznek, ami hozzájárul a kedvezőtlenebb klinikai kimenetelükhöz a de novo CRT csoporthoz képest. Azonban, amikor a két csoport közötti kiindulási paraméterek különbségeit figyelembe vettük, hasonló kimenetellel rendelkeztek mortalitásuk szerint. Emellett kimutattuk, hogy az elektróda diszfunkció és a zseb infekció előfordulási aránya magasabb lehet az upgrade CRT csoportban, mint a de novo csoportban.

Bár az ajánlások szerinti a gyógyszeres szívelégtelenség terápia csökkenti az összhalálozás, a szívelégtelenség következtében kialakuló kórházi események és a hirtelen szívhalál kockázatát, továbbra is fontos mérlegelni a backup ICD funkció szükségességét a CRT upgrade beavatkozások során is. Ennek érdekében olyan betegeket vizsgáltunk, akiknek nincs kamrai aritmia előzménye a kórtörténetükben, és PM-eiket CRT-D vagy CRT-P készülékre upgrade-elték. Az összpopulációban a CRT-D kedvezőbb kimenetelt mutatott a CRT-P upgrade-hez képest. Ezt követően TDA-val, ami egy mesterséges intelligencia alapú módszer fenocsoportokat azonosítottunk, amelyek eltérő mortalitási trendeket mutattak. Ezeken a rizikócsoportokon belül a magas kockázatú betegek esetében a CRT-D készülék választása kedvezőbb kimenetellel járt, mint a CRT-P készülékek esetében. Továbbá egy tanított gépitanulás alapú modellt fejlesztettünk, amely képes pontosan osztályozni a betegeket ezekbe a fenocsoportokba.

A fejlett analitikai eszközök, mint például a TDA és a gépitanulás integrálása a klinikai gyakorlatba, különösen a rizikóstratifikáció és a CRT upgrade döntéshozatalának

irányítása terén, jelentősen javíthatja a betegek kimeneteleit és optimalizálhatja a terápiás stratégiákat.

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10. Bibliography of the candidate's publications

1. **Schwertner W R***; Tokodi M*; Veres B; Behon A; Merkel E D; Masszi R; Kuthi L; Szijártó Á; Kovács A; Osztheimer I et al. Phenogrouping and risk stratification of patients undergoing cardiac resynchronization therapy upgrade using topological data analysis SCIENTIFIC REPORTS 13 : 1 Paper: 20594 , 13 p. (2023); DOI: 10.1038/s41598-023-47092-x

   IF: 3.8

   *: equal contribution

2. **Schwertner W R*;** Behon A*; Merkel E D; Tokodi M; Kovács A; Zima E; Osztheimer I; Molnár L; Király Á; Papp R et al. Long-term survival following upgrade compared with de novo cardiac resynchronization therapy implantation: a single-centre, high-volume experience EUROPACE 23 : 8 pp. 1310-1318. , 9 p. (2021); DOI: 10.1093/europace/euab059

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Publications not related to the current thesis

1. Márton Tokodi, Annamária Kosztin, Attila Kovács, László Gellér, **Walter Richard Schwertner**, Boglárka Veres, Anett Behon, Christiane Lober, Nigussie Bogale, Cecilia Linde, Camilla Normand, Kenneth Dickstein, Béla Merkely - Machine learning-based prediction of 1-year all-cause mortality in patients undergoing CRT implantation: Validation of the SEMMELWEIS-CRT score in the European CRT Survey I dataset. Europaen Heart Journal – Digital Health. 2024 July. doi: 10.1093/ehjdh/ztae051.
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2. Eperke D. Merkel, Anett Behon, Richard Masszi, **Walter R. Schwertner**, Luca Kuthi, Boglárka Veres, István Osztheimer, Roland Papp, Levente Molnár, Endre Zima, László Gellér, Annamária Kosztin, Béla Merkely - Obesity paradox in patients with

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IF: 3.8
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IF: 2.8

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