

Improving Outcomes in Heart Failure Patients with Cardiac Implantable Electronic Devices

Ph.D. Thesis

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2026

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“Somewhere, something incredible is waiting to be known.”

- Carl Sagan

1. List of Abbreviations

ACC – American College of Cardiology

ACE-I - Angiotensin-Converting Enzyme Inhibitor

AF - Atrial Fibrillation

AHA – American Heart Association

AI – Artificial Intelligence

AMT – Additional Medical Therapy

ARB - Angiotensin Receptor Blocker

ARNI - Angiotensin Receptor-Neprilysin Inhibitor

AVID - The Antiarrhythmics versus Implantable Defibrillators

BB - Beta-blocker

BMI - Body Mass Index

BNP - B-Type Natriuretic Peptide

BUN - Blood Urea Nitrogen

CABG - Coronary Artery Bypass Grafting

CARE-HF - the CARDiac RESynchronization-Heart Failure

CASH - Cardiac Arrest Survival in Hamburg

CCM - Cardiac Contractility Modulation

CI - Confidence Interval

CIBIS II - Cardiac Insufficiency Bisoprolol Study II

CIDS - Canadian Implantable Defibrillator Study

CIED - Cardiac Implantable Electronic Devices

CMR - Cardiac Magnetic Resonance

CONSENSUS - Cooperative North Scandinavian Enalapril Survival Study

COMPANION - Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure

COPERNICUS - Carvedilol Prospective Randomized Cumulative Survival Study

CRT - Cardiac Resynchronization Therapy

CRT-D - Cardiac Resynchronization Therapy-Defibrillator

CRT-P - Cardiac Resynchronization Therapy-Pacemaker

CV - Cardiovascular

DAPA-HF - Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure

DM – Diabetes Mellitus

ECG - Electrocardiogram

eGFR - estimated Glomerular Filtration Rate

EMPEROR-Reduced - EMPagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction

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

ESC - European Society of Cardiology

EPHESUS - Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

FMT - Foundational Medical Therapy

GDIT - Guideline Directed Interventional Therapy

GDMT - Guideline Directed Medical Treatment

GRADE - Grades of Recommendation, Assessment, Development, and Evaluation

HF - Heart Failure

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

ICM - Ischemic Cardiomyopathy

IN-TIME - Implant-based multiparameter telemonitoring of patients with heart failure

IPV - In-person Visit

IQR - Interquartile Range

LBBB - Left Bundle Branch Block

LV - Left Ventricle

LVAD - Left Ventricular Assist Device

LVEDD - Left Ventricular End-Diastolic Diameter

LVEF - Left Ventricular Ejection Fraction

LVESD - Left Ventricular End-Systolic Diameter

MADIT-I - Multicenter Automatic Defibrillator Implantation Trial

MADIT-II - Multicenter Automatic Defibrillator Implantation Trial II

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

MERIT-HF - Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure

MIRACLE - Multicenter InSync Randomized Clinical Evaluation

ML - Machine Learning

MRA - Mineralocorticoid Receptor Antagonist

MUSTT - Multicenter Unsustained Tachycardia Trial

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

NYHA - New York Heart Association

OAC - Oral anticoagulant

OMT - Optimal Medical Treatment

OR - Odds Ratio

PARADIGM-HF - Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure

PCI - Percutaneous Coronary Intervention

PROSPERO - The International Prospective Register of Systematic Reviews

QoL - Quality of Life

RAAS - Renin-Angiotensin-Aldosterone System

RALES - Randomized Aldactone Evaluation Study

RCT - Randomized Controlled Trial

REML - Restricted Maximum Likelihood

RESET-CRT - Re-evaluation of Optimal Re-synchronisation Therapy in Patients with Chronic Heart Failure

ROB - Risk of Bias

RV - Right Ventricle

SCD - Sudden Cardiac Death

SCD-HeFT - Sudden Cardiac Death in Heart Failure Trial

SD - Standard Deviation

SGLT2 - Sodium-Glucose Co-Transporter 2

SOLVD - Studies of Left Ventricular Dysfunction

STRONG-HF - Safety, Tolerability and Efficacy of Rapid Optimization Helped by NT-proBNP Testing of Heart Failure Therapies

TIM-HF2 - Telemedical Interventional Management in Heart Failure II

TDA - Topological Data Analysis

VF - Ventricular Fibrillation

VT - Ventricular Tachycardia

2. Student profile

2.1. Vision and mission statement, specific goals

My vision is to help heart failure patients receive the most effective, evidence-based therapy, and my mission is to draw conclusions from observations that we can include in everyday clinical practice.



2.2. Scientometrics

Number of all publications	17
Cumulative IF	83.886
Average IF/publication	4.93
Ranking (SCImago)	Predominantly D1/Q1 (7 D1, 3 Q1, 4 Q2)
Number of publications related to the subject of the thesis	3
Cumulative IF	14.9
Average IF/publication	5.1
Ranking (SCImago)	D1, Q1, Q2
Number of citations on Google Scholar	204
Number of citations on MTMT (independent)	119
H-index	7

2.3. Future plans

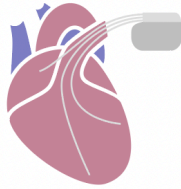
My future plan is to continue working in cardiovascular medicine, with a strong focus on research. I would like to use both clinical and research experience to support more personalized patient care.

3. Summary of the thesis

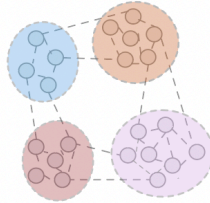
Cardiac resynchronization therapy with defibrillator (CRT-D) and cardiac resynchronization therapy with pacemaker alone (CRT-P) are established device-based treatment options for patients with heart failure with reduced ejection fraction (HFrEF). However, whether adding defibrillator capability provides an incremental survival benefit remains an important clinical question. At the same time, remote telemedical management (RTM) has emerged as a key component of long-term heart failure (HF) care, with the potential to improve HF outcomes, support earlier intervention, and optimize follow-up in patients with cardiac implantable electronic devices (CIEDs). The present thesis examined three closely related aspects of contemporary HFrEF management: a comparative analysis of CRT-D versus CRT-P, the role of data-driven phenotyping in improving device selection, and the clinical value of RTM in device-treated HF populations. In summary, this thesis demonstrates that the effectiveness of device therapy in HF is dynamic and context-dependent. The population- and patient-level data underscore the need for individualized selection, topological data analysis (TDA) may provide the analytical method to achieve it, and remote monitoring offers the operational framework to may sustain benefit over time. Together, these components define a modern paradigm of precision device therapy, in which collected patient-level data, machine learning (ML), and telemedical care converge to improve patients' outcomes.[1-3]

4. Graphical abstracts

Contemporary HF management



**CRT-D
vs.
CRT-P**



**Topological
Data
Analysis**



**Remote
Telemedical
Management**

**From population-based device therapy toward individualized
device selection and longitudinal patient management**

5. Introduction

5.1. Overview of the topic

This thesis focuses on device-based management in HFrEF, with particular emphasis on the choice between CRT-D and CRT-P, the use of TDA for more personalized device selection, and the potential role of RTM in the long-term care of patients with CIEDs.

5.1.1. What is the topic?

The central focus of this thesis is optimizing device therapy in HFrEF. More specifically, we sought to examine whether all patients benefit equally from adding a defibrillator to CRT, whether advanced machine-learning-based phenotyping can support patient selection, and whether remote monitoring can improve long-term outcomes for HF patients with CIEDs.

5.1.2. What is the problem to solve?

The benefit of CRT-D over CRT-P varies across patient groups and is sometimes difficult to predict. Current decision-making remains suboptimal in everyday clinical practice. At the same time, telemonitoring is increasingly widespread, but its clinical value depends on how well it is integrated into everyday clinical practice. Therefore, the challenge is to identify which patients derive the most benefit from adding a defibrillator to device therapy and to organize follow-up more effectively.

5.1.3. What is the importance of the topic?

Despite major therapeutic advances, HFrEF remains associated with high mortality, frequent hospitalizations, and a substantial healthcare burden. Device therapy can improve outcomes, but it also carries risks, costs, and potential complications. Therefore, optimizing patient selection and follow-up is essential to achieve better clinical outcomes and more efficient use of healthcare resources.

5.1.4. What would be the impact of our research?

The studies underlying this thesis support a more personalized approach to HFrEF care. It shows that the benefit of CRT-D should not be assumed to be universal, that advanced

data-driven phenotyping may help identify patients who have greater survival benefit, and that RTM may improve mortality outcomes when added to well-structured HF care. Overall, the thesis may contribute to more precise device selection and improved long-term care, supporting a more individualized model of HF management.

5.2. Heart Failure: Definitions and Classifications

HF is a complex clinical syndrome characterized by specific signs and symptoms resulting from structural and/or functional cardiac abnormalities. These abnormalities reduce cardiac output and/or increase cardiac filling pressure. HF is also often associated with elevated natriuretic peptide levels and objective signs of pulmonary and/or systemic congestion.[4, 5]

HF is commonly classified based on left ventricular ejection fraction (LVEF), dividing patients into two primary categories as shown in the recent 2026 ESC guideline[4-6]:

- Heart failure with reduced ejection fraction (HFrEF): $LVEF < 50\%$ and sign and/or symptoms of HF.[7]

- Heart failure with preserved ejection fraction (HFpEF): $LVEF \geq 50\%$.[4, 5], with symptoms and/or clinical signs, along with objective evidence of structural or functional cardiac abnormalities, such as impaired LV diastolic function or increased filling pressures, often alongside elevated natriuretic peptide levels.[7]

Furthermore, one additional category has been recognized over time, named HF with improved LVEF. This category includes HF patients whose LVEF improved by at least 10% (absolute) , leading to an $LVEF > 40\%$.[5]

The New York Heart Association (NYHA) functional classification is widely used to assess symptom severity and functional limitations in patients with HF. [5, 6] It divides patients into four classes: class I indicates no limitation in physical activity; class II, mild limitations with symptoms during normal activities; class III, significant limitations with symptoms during less-than-ordinary activities; and class IV, symptoms present at rest or with minimal exertion.[5, 6] Though this classification relies on subjective clinical judgment, it remains a key element in evaluating HF severity and is often included in treatment planning and eligibility criteria for device therapies.[5, 6]

5.3. Epidemiology of HFrEF

The prevalence of HF is 1-3% and is steadily increasing due to population aging, improved survival after acute cardiovascular (CV) events, and advances in chronic HF management.[7-9] HFrEF accounts for approximately 40-50% of all HF cases, although its relative proportion has slightly decreased over time due to the increasing recognition of HFpEF.[10, 11] The incidence of HF is estimated at 2–13 new cases per 1,000 person-years in Europe.[5] At the same time, the mortality of HF has improved; the absolute number of patients living with HF continues to rise.[7]

5.4. Etiology and Pathophysiology of HFrEF

HFrEF is a complex clinical syndrome that often results from multiple comorbidities. The most common causes include ischemic heart disease, hypertension (HT), arrhythmias, valvular and rheumatic heart disease, cardiomyopathies, congenital heart disease, infiltrative disease, drug-induced conditions, endocrine disorders, infectious causes, storage disorders, endomyocardial or pericardial disease, and metabolic and neuromuscular diseases.[5, 12]

HFrEF is characterized by impaired left ventricular (LV) systolic function, leading to reduced cardiac output and elevated filling pressures. It most commonly develops as a consequence of chronic myocardial injury or pressure/volume overload caused by the conditions listed above. In response to these insults, several compensatory mechanisms are activated, including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and vasopressin release. Over time, persistent neurohormonal activation together with inflammation, oxidative stress, and impaired intracellular calcium handling contributes to maladaptive cardiac remodeling and HF progression. These processes promote progressive ventricular dysfunction and adverse remodeling. Therefore, the LV typically becomes dilated and weakened, with a reduced stroke volume and increased end-diastolic volume and filling pressure. Thus, the pathophysiology of HFrEF reflects the combined effects of structural myocardial injury and sustained neurohormonal activation, ultimately resulting in the clinical syndrome of HF.[12]

5.5. Outcomes and Prognosis in HFrEF

HFrEF remains a major cause of morbidity and mortality despite substantial therapeutic advances in recent years.[9] The clinical syndrome is characterized not only by an increased risk of all-cause and CV mortality, but also by recurrent HF hospitalizations, progressive worsening of functional status and symptoms, reduced exercise capacity, impaired quality of life (QoL), and increasing healthcare burden.[6]

Most of the risk associated with HFrEF is captured by endpoints such as all-cause mortality, cardiovascular mortality, sudden cardiac death (SCD), and HF-related hospitalization .[6, 13] Rehospitalization is particularly relevant, as it often reflects disease progression, residual congestion, or treatment failure and is associated with a poorer subsequent prognosis.[14] In addition to these conventional endpoints, patient-reported outcomes, symptom burden, functional status, and QoL have gained increasing importance, as they capture the disease's everyday impact more precisely.[6, 13]

Prognosis in HFrEF is influenced by multiple clinical factors, including age, etiology of HF, LV function, symptom severity, comorbidities, renal function, arrhythmia burden, and response to treatment. Patients with more severe symptoms, frequent decompensations, or persistent congestion generally have worse outcomes.[6, 14-16] Modern guideline-directed medical treatment (GDMT) has significantly improved outcomes in HFrEF. The background mortality has generally declined over time, with an early study reporting 31% mortality at one year in the placebo arm and a later study reporting 13.9% mortality in the control arm.[17, 18] In addition, a recent network meta-analysis showed that quadruple therapy-with an ARNI, beta-blocker, MRA, and SGLT2 inhibitor-reduces the risk of all-cause mortality by about 61% compared to placebo. Despite these advances, real-world data still reveal that in patients with persistent HFrEF a considerable residual risk remains. with all-cause mortality rates around 11 per 100 person-years.[19, 20]

5.6. Diagnosis and Risk Stratification in HFrEF

The diagnosis of HFrEF combines clinical symptoms and signs with objective evidence of impaired LV systolic function. Common symptoms include dyspnea, fatigue, and

decreased exercise tolerance, along with signs of congestion such as pulmonary or peripheral edema. Because these symptoms are often nonspecific, diagnosis typically requires cardiac imaging—especially echocardiography—to confirm the presence and extent of reduced LVEF.[4-6]

In addition to imaging, laboratory and electrocardiographic assessments are crucial to diagnosis.[4-6] Natriuretic peptides are particularly useful for supporting the diagnosis and identifying patients at higher risk of HF, while electrocardiography may reveal conduction abnormalities, arrhythmias, prior myocardial infarction, or other findings relevant to etiology and management.[21, 22] Further investigations, including renal function, serum electrolytes, hemoglobin, hemoglobin A1C levels, and lipid profile assessment, are essential for both diagnostic evaluation and treatment planning.[23]

Risk stratification in HFrEF is essential to patient management because prognosis is highly variable and shaped by multiple interacting clinical factors. Key determinants of outcome include age, HF etiology, symptom severity, left ventricular function, renal dysfunction, atrial and ventricular arrhythmias, comorbidity burden, and the frequency of prior decompensations and hospitalizations. Functional status, usually reflected by the New York Heart Association (NYHA) functional class, remains a simple yet clinically meaningful marker of disease severity and prognosis.[4-6, 24, 25]

5.7. Treatment of HFrEF

5.7.1. Pharmacological Treatment of HFrEF

Pharmacological treatment of HFrEF has advanced significantly in recent years and now emphasizes early initiation and rapid optimization of foundational medical therapy (FMT), as demonstrated by the STRONG-HF trial.[26] Contemporary recommendations advise against introducing treatment in a slow, sequential manner over a prolonged period. Instead, start core evidence-based therapies as early as possible and uptitrate to target or maximally tolerated doses. The main goals of pharmacological treatment are to reduce all-cause and CV mortality, decrease HF-related hospitalizations, promote reverse remodeling, and improve symptoms and QoL.[4, 5, 26]

Current guidelines identify four key drug classes as FMT for HFrEF: renin–angiotensin system inhibition, preferably with an angiotensin receptor–neprilysin inhibitor (ARNI), or alternatively with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB); an evidence-based beta-blocker; a mineralocorticoid receptor antagonist (MRA); and a sodium–glucose cotransporter 2 inhibitor (SGLT2i). Inhibition of the RAAS remains essential in managing HFrEF. The survival benefit of RAAS inhibition was first demonstrated with ACE inhibitors in trials like CONSENSUS [17] and SOLVD [27]. Later, PARADIGM-HF [28] established the superiority of ARNI over enalapril in reducing mortality and HF hospitalization among eligible patients with HFrEF. When ARNI therapy is not feasible, ACE inhibitors remain a fundamental option, with ARBs serving as alternatives for patients intolerant to ACE inhibitors. These medications improve outcomes not only through hemodynamic effects but also by reducing maladaptive neurohormonal activation and ventricular remodeling. [4-6]

Beta blockers are another essential pillar of therapy and should be used in all stable patients without contraindications. Their prognostic benefit is well established by the CIBIS-II [29], MERIT-HF [30], and COPERNICUS [31] trials, with reduced mortality and morbidity. [29-34] [4-6, 35]

Another important component of the pharmacological treatment of HFrEF are mineralocorticoid receptor antagonists (MRAs), which further reduce mortality and HF hospitalizations, and contribute to neurohormonal blockade beyond that achieved by renin-angiotensin system inhibitors and beta blockers. Pivotal evidence from the RALES[36], EPHESUS[37], and EMPHASIS-HF[38] trials has positioned both spironolactone and eplerenone as key agents in the management of HFrEF. As a result, ESC and ACC/AHA HF guidelines currently recommend MRAs at the highest level (IA).[4-6] Non-steroidal MRAs, such as finerenone, may represent potential alternatives; however, relevant clinical trials are still ongoing .[39]

Finally, SGLT2 inhibitors have also become a cornerstone of HFrEF treatment, regardless of diabetes status. Adding them to conventional therapy has been shown to reduce the risk of CV death and worsening HF, with a favorable safety profile and straightforward implementation, as demonstrated by the DAPA-HF [40] and EMPEROR-Reduced [41] trials. Recent consensus documents further emphasize their early introduction, including during or shortly after hospitalization in appropriate

patients, as part of a strategy to minimize delays in initiating comprehensive therapy. [4, 6, 42]

For selected patients, additional medical therapy (AMT) may be considered alongside FMT. Together these constitute guideline-directed medical therapy (GDMT).[7] Diuretics remain essential for managing congestion and providing symptomatic relief. Although loop diuretics have not been shown to reduce mortality directly, they are crucial for reaching euvolemia, alleviating dyspnea and edema, and enabling tolerance of disease-modifying therapies.[5, 6, 43] Ivabradine should be considered for patients in sinus rhythm with persistently elevated heart rate (≥ 70 b.p.m.) despite maximally tolerated beta-blocker therapy.[44] Vericiguat may be considered for high-risk patients with worsening HF despite standard treatment.[45] Intravenous iron replacement is recommended for patients with iron deficiency to improve symptoms and QoL and should be considered to reduce HF hospitalizations.[46, 47] Digoxin or hydralazine/isosorbide dinitrate may still have a role in selected patients.[48, 49]

5.7.2. Non-pharmacological Treatment of HFrEF

In addition to GDMT, device-based and other electrical therapies play an important role in the management of selected patients with HFrEF. These interventions, known as Guideline-Directed Interventional Therapy (GDIT), are intended to reduce the risk of SCD, improve ventricular synchrony, support reverse remodeling, and, in selected settings, reduce the burden of atrial arrhythmias, including atrial fibrillation.[6, 7, 50]

Cardiac Implantable Electronic Devices (CIEDs) primarily include permanent pacemakers, implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy pacemakers (CRT-Ps), and cardiac resynchronization defibrillators (CRT-Ds). Their clinical relevance extends beyond rhythm control, as they may improve survival [51-53], reduce the risk of SCD [54], alleviate symptoms [55, 56], and decrease HF-related hospitalizations [52, 55, 57] in appropriately selected patients. In addition to their therapeutic role, modern implantable devices also provide valuable diagnostic and monitoring functions, including arrhythmia detection, pacing burden assessment, and remote follow-up capabilities.[6, 50]

Catheter ablation should also be considered an important component of electrical therapy in HFrEF, especially in patients in whom arrhythmias contribute to ventricular

dysfunction or clinical deterioration. In patients with atrial fibrillation and HFrEF, catheter ablation has been associated with better clinical outcomes than medical therapy alone, including reductions in HF hospitalization and mortality, as shown in randomized evidence syntheses.[58-61] In addition, reducing the arrhythmic burden through ablation of atrial fibrillation may improve LV function in selected patients.[62, 63]

In addition to ICDs, CRT, and catheter ablation, cardiac contractility modulation (CCM) has emerged as another device-based option for selected patients with HFrEF. During the absolute refractory period, CCM delivers non-excitatory electrical impulses and is intended to enhance myocardial contractile performance without initiating a new depolarization.[64] Current evidence suggests that this therapy may be relevant for symptomatic patients who do not meet conventional criteria for CRT.[65, 66] Clinical studies have primarily demonstrated improvements in exercise capacity, functional status, and QoL, whereas its effect on major prognostic outcomes remains less clearly established. CCM may therefore be considered a complementary therapeutic option for carefully selected patients with persistent symptoms despite GDMT, particularly when conventional CRT indications are not met.[65, 66]

For patients with advanced HFrEF who continue to experience severe symptoms despite optimized GDMT and appropriate device therapy, LVAD treatment may be an option for long-term mechanical circulatory support. LVADs unload the left ventricle, increase systemic cardiac output, and can improve functional capacity, QoL, and survival in carefully selected patients with advanced HF. Depending on the clinical context, LVAD therapy may be used as a bridge to heart transplantation (HTX), a bridge to candidacy, or as destination therapy for patients who are ineligible for transplantation. Careful patient selection is crucial because LVAD therapy is associated with serious complications, including bleeding, thromboembolic events, infection, right ventricular failure, and device-related adverse events.[5]

5.7.2.1. Cardiac Implantable Electronic Devices in Heart Failure

5.7.2.1.1. Implantable Cardioverter Defibrillator Therapy in Heart Failure

ICDs are specialized electronic devices that detect and terminate malignant ventricular arrhythmias. Beyond defibrillation, they can also provide demand pacing, fulfilling a

dual role in arrhythmia management and rhythm support.[50, 67] Indications for ICD implantation are generally classified as primary or secondary prevention of SCD. The AVID[68], CASH[69], and CIDS[70] trials demonstrated that ICD therapy is more effective than OMT alone for the secondary prevention of SCD. Based on the guideline, ICD implantation is recommended for patients who have survived hemodynamically significant ventricular tachycardia (VT) or ventricular fibrillation (VF), or who have been successfully resuscitated from SCD, provided that no reversible cause is present and expected survival is at least one year.[50, 71] The MADIT I[72], MUSTT[73], MADIT II[51], and SCD-HeFT[53] trials demonstrated that, in the setting of primary prevention, ICD implantation is more effective than antiarrhythmic therapy in preventing SCD. According to the guideline, ICD therapy is considered for symptomatic patients with HFrEF, typically those in NYHA functional class II–III, when left ventricular ejection fraction remains below 35% despite at least 3 months of OMT.[50] However, the decision to implant an ICD should not rely solely on ejection fraction but should also take into account age, comorbidities, non-arrhythmic mortality risk, overall functional status, and the expected benefit in the era of contemporary medical therapy. [74] Shared Decision-Making can also be an important approach.[75] Moreover, the PROFID EHRA trial addresses the contemporary relevance of primary prevention ICD therapy in the setting of modern FMT. As the risk of SCD has declined with advances in HF pharmacotherapy, this study is expected to clarify whether the survival benefit of ICD implantation remains substantial in current clinical practice.[76]

5.7.2.1.2. Cardiac Resynchronization Therapy: Indications and Patient Selection

In HFrEF, intraventricular conduction abnormalities, especially left bundle branch block (LBBB), can cause delayed and heterogeneous activation of the left ventricle. This electrical dyssynchrony leads to discoordinated regional contraction, with early septal activation and delayed lateral wall contraction. This mechanical inefficiency can decrease stroke volume, increase myocardial wall stress, worsen functional mitral regurgitation, and contribute to adverse ventricular remodeling.[50] The rationale for CRT is to correct delayed and discordant ventricular activation, which is most commonly associated with prolonged QRS duration and LBBB morphology.[50] By improving the temporal coordination of ventricular contraction, CRT may enhance

cardiac efficiency, promote reverse remodeling, improve symptoms and functional status, and reduce all-cause mortality and HF-related hospitalization, as shown by COMPANION[52], CARE-HF[55], MIRACLE[56], MADIT-CRT and RAFT[77] trials. The ESC guideline recommends CRT implantation with Class I, Level A evidence in patients with chronic HF who have an LVEF $\leq 35\%$, NYHA functional class II, III, or IVa symptoms, and a QRS duration >150 ms with left bundle branch block morphology.[50]

CRT is also recommended, with Class IIa, Level B evidence, for patients with chronic HF who have an LVEF $\leq 35\%$, NYHA functional class II–IVa symptoms, and a QRS duration of 130–149 ms with left bundle branch block morphology.[50]

For patients with a QRS duration >150 ms, or 130–149 ms without left bundle branch block morphology, CRT is recommended with Class IIa, Level B evidence and Class IIb, Level B evidence, respectively. In contrast, CRT implantation is not recommended for patients with chronic HF whose QRS duration is below 130 ms.[50]

5.7.2.1.3. CRT-P and CRT-D: Conceptual Differences and Clinical Rationale

CRT systems are available in two principal forms. In CRT-P, the right ventricular (RV) lead is a conventional pacing lead, and the pulse generator does not provide defibrillation therapies. Therefore, CRT-P does not provide programmed antitachycardia pacing or shock therapy to terminate malignant ventricular arrhythmias. In contrast, CRT-D, includes an RV defibrillation lead and a defibrillator-capable pulse generator. CRT-D can detect and treat malignant ventricular arrhythmias with antitachycardia pacing and shock therapy, thereby providing protection against SCD. In both cases, the LV lead is implanted into a branch of the coronary sinus, preferably a lateral or posterior branch. In patients who are in sinus rhythm, an additional atrial pacing lead is also implanted.[50, 78, 79] The current ESC guideline suggests that device selection should be a personalized decision made through shared decision-making and guided mainly by two factors: age and the extent of myocardial fibrosis on cardiac magnetic resonance (CMR). As age increases and myocardial fibrosis is limited, the balance shifts more toward CRT-P. In contrast, younger age and greater myocardial fibrosis on CMR favor choosing CRT-D, presumably because of the higher expected arrhythmic risk.[50]

However, the feasibility of CMR in everyday clinical practice is limited, costly and not widely available.[80, 81]

The document also lists additional factors that support choosing CRT-P over CRT-D, including non-ischemic cardiomyopathy, short life expectancy, major comorbidities, poor renal function, and patient preference.[5] From a clinical perspective, the choice between CRT-P and CRT-D reflects two related but distinct therapeutic aims. CRT itself targets pump failure, ventricular dyssynchrony, and remodeling, whereas the defibrillator component addresses residual arrhythmic risk. This distinction is particularly relevant because not all patients eligible for CRT have the same probability of SCD. [6, 82, 83]

Moreover, due to the response after device implantation, reverse remodeling per se can decrease the risk of subsequent arrhythmic events, so the SCD risk can change over time. [6, 82, 83] At the same time, implanting a defibrillator-equipped device introduces potential risks. CRT-D is associated with greater device complexity, higher cost, and the risk of defibrillator-specific complications, including inappropriate shocks and lead- and generator-related complications. These considerations are clinically relevant because the decision is not simply based on whether a patient meets criteria for CRT, but whether the expected reduction in SCD justifies the additional burden associated with ICD therapy. Therefore, CRT-P versus CRT-D selection should be individualized.[6, 82, 83]

5.8. Real-world evidence, clinical practice, indications for CRT-P versus CRT-D

A dedicated randomized comparison of CRT-P versus CRT-D remains lacking (due to the need for high number of patients, long-term follow-up, and financial burden). Recently, RESET-CRT was initiated to address this question; however, it was terminated prematurely due to insufficient funding.[84] Therefore, evidence comes from real-world observational studies. Prospective[85-89], retrospective[90-96] and registry-based analyses[97, 98] provide important insights into outcomes in everyday clinical practice. They proved that patients are older, more heterogeneous, and often have a greater burden of comorbidities than those enrolled in landmark trials.[50, 84, 99] These real-world data suggest that CRT-D is frequently associated with lower mortality than CRT-P overall, but this apparent advantage may not be uniform across all patient subgroups.[50, 84, 99] Registry data point in a similar direction. In a contemporary

HFrEF cohort from the Swedish Heart Failure Registry, CRT-D was associated with lower mortality than CRT-P, especially among patients with more severely reduced LVEF, whereas the association was less pronounced in those with better systolic function.[97] At the same time, real-world evidence must be interpreted cautiously. Unlike randomized trials, observational studies are vulnerable to selection bias and residual confounding.[100] Patients receiving CRT-P are often older and have a higher prevalence of comorbidity, which may partly explain their worse outcomes.[40] For this reason, the available real-world data are highly informative for hypothesis generation and patient profiling, but they do not fully resolve the question of whether CRT-D is causally superior to CRT-P.[88] Instead, they reinforce the concept that benefit is likely heterogeneous and may be concentrated in selected patient groups.[101]

The clinical context in which CRT is used has changed substantially over the past two decades.[102] Early CRT trials were conducted in a different therapeutic era, when HF drug treatment was less complex, SCD risk was higher, and patient selection criteria were often broader than those used today. Since then, the introduction of FMT with disease-modifying drugs, including ARNIs, MRAs, and SGLT2 inhibitors, beyond broader optimization of HF care, has changed the prognosis of HF and the relative contribution of arrhythmic versus non-arrhythmic death.. This evolution has important implications for the perceived incremental value of CRT-D over CRT-P.[4, 5, 84]In parallel, CRT candidate selection has become more refined. Current practice places greater emphasis on QRS morphology and duration, age, etiology, life expectancy, and the likelihood of a meaningful resynchronization response. In addition, there is an increasing awareness that SCD risk is not uniform across all CRT candidates. As a result, the choice between CRT-P and CRT-D should be based on personalized risk assessment that integrates arrhythmic risk, competing mortality risk, expected QoL benefit and patient preference.[5]

5.9. Telemedical Care in Heart Failure Patients with CIEDs

Telemedical care is increasingly relevant for the long-term management of patients with HF and CIEDs. In this population, follow-up no longer relies exclusively on scheduled in-person visits (IPVs), as modern healthcare pathways may integrate remote data transmission and structured telemedical supervision. The clinical rationale for this

approach is that patients with HF and CIEDs are a vulnerable population, and early recognition of clinical deterioration, arrhythmic events, or device-related issues may enable earlier intervention. [103]

In patients with CIEDs, remote monitoring generally refers to the technical process by which device-derived information is transmitted from the patient's home environment to the treating center.[103-105] Depending on the device and monitoring platform, these data may include atrial and ventricular arrhythmias, ICD therapies, percentage of ventricular or biventricular pacing, lead and battery parameters, heart-rate trends, patient activity, and physiological markers related to HF deterioration. Some systems additionally measure intrathoracic impedance as a surrogate marker of pulmonary fluid accumulation; for example, the OptiVol fluid index was used in trials such as DOT-HF and OptiLink HF to identify changes suggestive of increasing congestion. [103-107] By contrast, telemedical management may be a broader clinical concept. It extends beyond passive data transmission and includes the structured interpretation of incoming data, predefined response algorithms, and clinical actions triggered by alerts or concerning trends.[103, 104] The potential benefits of telemedicine for HF patients with CIEDs extend beyond earlier detection of events and closer follow-up.[103, 108] Guidelines and consensus documents suggest that adding RTM to IPV may improve continuity of care and reduce the need for routine in-person assessments, enable earlier recognition of arrhythmias and device-related technical problems, and detect deterioration of HF earlier. [50, 103] When embedded in a structured organizational framework with predefined response pathways, RM may therefore contribute not only to earlier intervention but also to improved outcomes. [50, 103] TIM-HF2[109] and IN-TIME[110] both support that concept with positive results. TIM-HF2 evaluated a structured RTM program for chronic HF patients not solely with CIEDs. The intervention reduced the percentage of days lost due to unplanned CV hospitalization or death, and importantly showed a significant reduction in all-cause mortality. The IN-TIME study included patients with HF and implanted ICD or CRT-D devices. Daily multiparameter telemonitoring enabled earlier detection of clinical deterioration and was associated with improved clinical status and lower mortality. Together, these studies suggest that the primary value of remote monitoring is not the technology itself but the ability to identify risk earlier, promote intervention, and potentially prevent fatal HF

deterioration. [102, 103] For this reason, the most recent consensus statement recommends the use of RTM as part of the standard of care for an IA indication.[103] At the same time, several limitations should be acknowledged. First, telemedicine in this field is heterogeneous, with substantial variation in monitoring algorithms, transmission frequency, alert thresholds, and the organization of clinical follow-up. Second, the benefit of remote systems depends on the clinical response: data transmission alone does not improve outcomes unless it leads to timely and appropriate intervention, which imposes a high financial and labor burden on healthcare workers. Therefore, telemedical care may increase workflow complexity, require dedicated infrastructure, and can create an alert burden without clear benefit if implemented without adequate clinical integration, and standardized RTM protocols. [103, 104]

5.10. Artificial Intelligence, Machine Learning, and Topological Data Analysis in Cardiovascular Medicine

Artificial intelligence (AI) and ML are playing an increasingly important role in CV medicine because contemporary cardiology generates large, multidimensional datasets that are difficult to interpret using conventional statistical approaches alone [104, 105]. In this setting, AI-based methods offer the possibility of identifying complex patterns, improving phenotyping, refining risk stratification, and supporting more individualized clinical decision-making [106-109].

Topological data analysis (TDA) is an unsupervised analytical ML based method derived from topology, a branch of mathematics concerned with the study of shape and structure. In practical terms, TDA seeks to characterize the geometry of complex, high-dimensional datasets and to represent similarities between data points in a compact, two-dimensional visual network. In such a network, patients with similar multidimensional characteristics are placed close to one another, while broader network structure may reveal gradients, clusters, or partially overlapping phenotypes that are often difficult to capture with conventional clustering methods. Such networks consist of nodes and edges: nodes correspond to groups of patients with similar characteristics, while edges indicate overlap between nodes, meaning at least one patient is shared between them. The resulting network can also be color-coded by clinical outcomes to facilitate interpretation.[111-113] A major conceptual strength of TDA is that it does not

force patients into rigid, mutually exclusive groups at the outset. Instead, it preserves relational structure within the data and can reveal continuous transitions between phenotypes. This feature is relevant to HF and device populations, where clinical characteristics often overlap and treatment benefit may not follow simple binary categories. [113-115] Although the method remains relatively novel and its routine clinical implementation is still evolving, its potential lies in providing clinically interpretable representations of patient similarity that may complement both traditional statistics and other ML approaches. [113-115]

6. Objectives

6.1. Refining device selection in patients undergoing cardiac resynchronization therapy

Our aim was to review the literature to determine whether CRT-D offers a mortality benefit over CRT-P. After that, we aimed to assess the homogeneity of this presumed benefit across predefined important subgroups, such as etiology and older age. As with modern FMT, the risk of SCD decreased over time,[114] so a time-trend analysis was conducted, given the hypothesized decreasing effect of CRT-D on mortality.

Thereafter, using a detailed patient-level database, beyond conventional analysis an AI-based TDA was used to identify clinically distinct phenogroups among CRT recipients and to determine which subgroups had better long-term survival with CRT-D than with CRT-P.

6.2. Optimizing Long-Term Follow-Up in Patients with Cardiac Implantable Electronic Devices

The aim of this study was to conduct a systematic review and meta-analysis of RCTs to evaluate whether adding continuous RTM to IPV is superior to standard IPV alone for HF patients with CIEDs. The primary objective was to determine whether additional RTM improves major clinical outcomes, particularly all-cause and CV mortality, and to assess its effects on hospitalizations and device-related events.

7. Methods

7.1. Comparing CRT-D versus CRT-P using population-level data

7.1.1. Enrolled studies

This systematic review and meta-analysis was conducted in accordance with PRISMA recommendations, and the protocol was prospectively registered in PROSPERO (CRD42021281869). A comprehensive literature search was conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials for studies published through 5 December 2022. After removing duplicates, two reviewers independently conducted study selection in a two-step process, with disagreements resolved by a third reviewer. Any peer-reviewed study reporting mortality outcomes in a direct comparison of CRT-D and CRT-P was considered eligible. When data permitted, subgroup analyses were conducted by HF etiology and age, and meta-regression was used to assess the potential influence of enrollment period on treatment effect over time.[3]

A total of 26 studies met the inclusion criteria for the current analysis, comprising 128,030 patients with CRT. Of these, 55,469 patients received CRT-P and 72,561 received CRT-D devices. The post hoc analysis of the COMPANION trial was also included; however, it was classified as an observational study because the original trial was not specifically designed to provide a direct comparison between CRT-D and CRT-P. The remaining studies were observational cohort studies, of which 17 were retrospective and 8 prospective. Most studies were conducted in a single-center setting, while a smaller proportion were multicenter investigations. [3]

7.1.2. Clinical Outcomes, Endpoints

Primary endpoint was all-cause mortality, whereas secondary outcomes include CV and non-CV mortality, HF mortality, and SCD. Subgroup analyses were also performed, with the main focus on etiology and age, using a cutoff of 75 years. Additionally, a time-trend analysis using a meta-regression approach was conducted to assess the effects of population changes and therapies on survival among CRT patients. [3]

7.1.3. Statistical Analysis

Hazard ratios (HRs) were extracted and analyzed for all predefined outcomes. Raw data from the included studies were log-transformed and synthesized using random-effects models. The between-study variance (τ^2) was estimated using the restricted maximum likelihood method, and its confidence interval was derived using the Q-profile approach. Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic. Outlier and influence diagnostics were conducted according to the recommendations of Harrer et al. To investigate the potential temporal effect on all-cause mortality, the duration covered by each study was identified from the reported study period, and the midpoint of each interval was calculated in years. These midpoint values were then entered as explanatory variables in a meta-regression analysis. To further examine how the outcomes evolved over time, random-effects cumulative meta-analyses were also conducted. These results were visualized using forest plots. All statistical analyses were performed using R version 4.1 (R Core Team), with the meta, dmetar, and metafor packages. [3]

7.2. TDA-Based Identification of CRT Phenogroups with differential benefit from CRT-D

7.2.1. Study Design and Population

This retrospective study included 2603 patients with HFrEF and NYHA functional class II-IVa symptoms who underwent successful CRT implantation at the Heart and Vascular Center of Semmelweis University between October 2000 and September 2018. For each patient, baseline clinical data were retrieved from Semmelweis University's electronic medical record system. The study protocol was conducted in accordance with the Declaration of Helsinki and received approval from the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University (approval number: 161/2019). Because the analysis was retrospective, informed consent was not required. Of the 2603 patients, 2359 were part of the main circular network created by TDA. The remaining 244 patients were assigned to disconnected nodes as topological outliers and excluded from further analyses. Altogether, 5 phenogroups were analyzed.[1]

7.2.2. Clinical Outcomes, Endpoints

The primary endpoint was all-cause mortality. Data on patients' vital status and dates of death were obtained from Hungary's National Health Insurance Database in May 2021. To assess the robustness of the findings, a sensitivity analysis was conducted using a composite endpoint comprising all-cause mortality, HTX, and LVAD implantation. Subgroup analyses by HF etiology were also performed. [1]

7.2.3. Statistical analysis

Statistical analyses were performed using GraphPad Prism (version 8.0; GraphPad Software, San Diego, CA, USA), SPSS (version 21.0; IBM, Armonk, NY, USA), and R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are reported as mean $\pm$ SD or median (IQR), as appropriate, and categorical variables as counts and percentages. Baseline clinical characteristics were compared between the CRT-D and CRT-P groups using the unpaired Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate, and the chi-squared test or Fisher's exact test for categorical variables. Event-free survival in the different patient subgroups was illustrated using Kaplan–Meier curves, and differences between groups were assessed with the log-rank test. Follow-up time was estimated by the reverse Kaplan–Meier method. Mortality rates and absolute risk reduction were derived from Kaplan–Meier estimates, and absolute risk reduction was considered statistically significant when the corresponding confidence interval did not include zero. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using univariable and multivariable Cox proportional hazards regression models. Only variables without missing data were entered into the multivariable analyses. Patients were censored at the time of a subsequent CRT-D upgrade after initial CRT-P implantation (n = 65), LVAD (n = 6), or HTX (n = 41). In the sensitivity analysis, censoring was applied only in cases of device upgrade. The characteristics of the five phenogroups identified by topological data analysis were compared pairwise using the Kolmogorov–Smirnov test for continuous variables and the chi-squared test or Fisher's exact test for categorical

variables, as appropriate. All statistical tests were two-sided, and a p value below 0.05 was considered statistically significant. [1]

7.2.4. Topological Data Analysis and Machine Learning Model Development

After excluding variables with 40% or more missing data, 25 variables were retained for network generation. Missing values were handled by mean imputation, followed by Z-score standardization of all included variables. For the TDA procedure, normalized correlation was used as the distance metric, combined with two multidimensional scaling lenses. Both lenses were equalized, with a resolution of 29 and a gain of 1.6. Patients assigned to nodes that were disconnected from the main network ($n = 244$) were regarded as topological outliers and excluded from subsequent phenogroup analyses, leaving 2359 patients in the final TDA analysis. No additional patients were excluded at this stage. After constructing the topological network, the next objective was to identify regions characterized by distinct clinical profiles and differences in all-cause mortality. For this purpose, we first performed community autogrouping using the Louvain method, which identifies groups of nodes with high internal connectivity and relatively limited connectivity to other groups. This procedure yielded 16 initial autogroups. Thereafter, the group with the highest number of outgoing connections relative to its size was iteratively merged with the adjacent group to which it showed the strongest connectivity. This process was repeated until five densely connected groups of nodes were obtained; these groups were subsequently defined as phenogroups. Because of the intrinsic characteristics of TDA, phenogroups partially overlapped, with 16 patients belonging to two phenogroups simultaneously. This overlap, however, did not violate the assumptions of the statistical methods applied for subgroup comparisons. TDA and autogrouping were performed using EurekaAI Workbench (version 3.1.0; SymphonyAI, Palo Alto, CA, USA) and the EurekaAI Python software development kit (version 3.1.0; SymphonyAI, Palo Alto, CA, USA). [1]

7.3. Optimizing Long-Term Follow-Up in Patients with Cardiac Implantable Electronic Devices

7.3.1. Search Strategy and Study Selection

A systematic search of the literature was conducted in three electronic databases: CENTRAL, Embase, and PubMed. Studies published up to 1 December 2024 were eligible for inclusion. [2] All records identified through the database search were imported into citation management software (EndNote X9, Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates, the selection process was carried out independently by two reviewers in two sequential steps. Altogether, 16 studies were eligible for inclusion in our analysis.[2] Any disagreement regarding eligibility was resolved through discussion with a third reviewer. The review protocol was prospectively registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42022299820).[2]

7.3.2. Inclusion Criteria and Outcomes of Interest

The inclusion criteria were limited to RCTs comparing adding RTM to IPV with IPV alone in patients with HF, focusing on outcomes such as all-cause and CV mortality, HF- and CV-related hospitalizations, and ICD outcomes, including the number of ICD shocks or inappropriate ICD shocks. Studies were analyzed for the use of complex telemonitoring systems (a modality in which multiple TM is combined with structured telephone support (STS) and/or access to a 24 h call center or a mix of other sub-modalities) and device-related non-invasive remote monitoring in HF patients.[2]

7.3.3. Data Extraction and Quality Assessment

The extracted data included details about the study characteristics, demographics of patients and outcomes. Data extraction was performed independently by two authors and any discrepancies were resolved through mutual agreement.[2]

7.3.4. Statistical Analysis of Meta-Analysis Outcomes

Effect estimates were summarized as ORs and HRs, each with corresponding 95% CIs. For each outcome, HRs were pooled when at least three studies provided suitable time-to-event data. If this criterion was not met, ORs were calculated from raw event counts across all studies with sufficient data for that outcome and pooled using the Mantel–Haenszel method. In studies with zero-cell values, the exact Mantel–Haenszel procedure without continuity correction was applied. Where appropriate, the Hartung–Knapp adjustment was used to generate more conservative pooled confidence intervals. Within the random-effects framework, the 95% CI was used to describe the precision of the pooled average effect, and statistical significance was assumed when this interval did not include 1.0. Random-effects models were used for OR- and HR-based analyses, with HRs pooled by inverse-variance weighting. Between-study variance was estimated using REML, with Q-profile confidence intervals, and prediction intervals were calculated to reflect heterogeneity and the expected range of effects in future comparable studies. Statistical heterogeneity was quantified using the I^2 statistic proposed by Higgins and Thompson, which estimates the proportion of total variability attributable to true between-study heterogeneity rather than sampling error. The possibility of small-study effects was assessed by visually inspecting funnel plots. All analyses were conducted in R version 4.2.1 using the *dmetar* and *metafor* packages.[2, 115-118]

7.3.5. Risk of Bias Assessment and GRADE

The methodological quality of the included studies was evaluated independently by two reviewers, using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2).[119] Whenever differences in judgment arose, these were resolved by discussion with the involvement of a third reviewer. The certainty of the available evidence for the included studies and outcomes was also assessed independently by the same two reviewers according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Any disagreements were settled with input from the third reviewer.[2] .

8. Results

8.1. Comparing CRT-D versus CRT-P using population-level data

8.1.1. Baseline Patient Characteristics

Among the 26 included studies, eight reported a mean participant age exceeding 75 years, whereas in the remaining studies, CRT recipients were approximately 65 years old on average, with patients in the CRT-D group generally younger. The ischemic etiology rate was nearly 60%, most frequently observed in the CRT-D cohort. Approximately 75% of patients were male, and atrial fibrillation was documented in 40% of cases. Based on inclusion criteria across studies, the median LVEF was 30%, while QRS duration typically ranged from 150 to 170 ms, except in one study by Leish-Farkas, which reported a mean QRS duration of 134 ms. Patients with severe HF symptoms were overrepresented, with 80-90% classified as NYHA functional class III-IV. Diabetes prevalence varied considerably across studies, ranging from 15% to 54% of participants. Optimal medical therapy was commonly reported, with over 80% of patients receiving ACEi or ARB, approximately 80% receiving BB, and 50% receiving MRAs. However, four studies indicated that only about half of patients received OMT. Diuretic use was less consistent, with reported use ranging from 50% to 97%.[3] (Table 1.)

Table 1. Baseline clinical characteristics of the cohorts from enrolled studies. ACE-I: Angiotensin-converting enzyme inhibitor, AF:atrial fibrillation, ARB: angiotensin II receptor blocker, BB: Beta-blocker, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy-Pacemaker, DM: Diabetes Mellitus, ICM: Ischemic Cardiomyopathy, LVEF: Left ventricular ejection fraction, MRA: Mineralocorticoid receptor antagonist, NYHA: New York Heart Association. Adapted from Veres, B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

Authory ear	Age (year)		Male (%)		ICM (%)		NYHA III-IV (%)		AF (%)		DM (%)		QRS duration (ms)		LVEF (%)		ACE-I or ARB (%)		BB (%)		MRA (%)		Diureti cs (%)	
	CRT -P	CRT -D	C R T - P	C R T - D	C R T - P	C R T - D	C R T - P	C R T - D	C R T - P	C R T - D	C R T - P	C R T - D	CRT- P	CRT- D	C R T- P	C R T- D	C R T - P	C R T - D	C R T - P	C R T - D	C R T - P	C R T - D	C R T - P	C R T - D
Auricchi o, 2007[86]	64.0±1 0.0	64.0±9	66. 0	83. 0	27. 0	55. 0	95. 0	93. 0	18.0	17. 0	-	-	-	-	25.0 ± 7.0	25.0± 7.0	-	-	-	-	-	-	-	-
Gold, 2013[87]	63.6±1 0.6	62.7±1 0.7	71. 6	79. 4	45. 9	58. 6	-	-	-	-	16. 2	22. 9	157.0± 20.0	152.0± 21.0	30.0 ± 6.5	26.1± 7.0	98. 6	95.9	91. 9	96. 5	-	-	-	-
Morani, 2013[98]	74.0±9. 0	67.0±9. 0	68. 0	85. 0	41. 0	62. 0	80. 0	75. 0	-	-	31. 0	30. 0	175.0+ 29.0	165.0+ 32.0	27.0 ± 5.0	27.0± 5.0	79. 0	88.0	70. 0	75. 0	21	29	70. 0	76. 0
Kutyifa, 2014[99]	66.3±1 0.5	63.9± 10.9	71. 0	84. 0	34. 0	51. 0	-	-	28.0	22. 0	35. 0	31. 0	165.5± 27.8	158.2± 27.1	28.2 ± 7.4	27.6± 6.4	84. 0	86.0	84. 0	88. 0	53	61	75. 0	77. 0

Looi, 2014[120]	70±9.9	67±9.3	72.6	91.1	48.3	65.8	94.1	87.7	20	14.4	16.1	13.7	159±25.4	161.0±30.0	25.3±7.7	23.9±7.1	90.1	91.2	69.5	76.9	63	56	92.2	89.3
Marijon, 2015[85]	75.9±9.0	65.6±10.4	69.5	80.8	40.7	49.3	87.9	80.7	38.7	22.1	-	-	160.8+29.0	155.0+26.2	25.5±10.0	25.5±10.0	53.9	72.9	43.3	67.3	15	31	59.6	69.2
Reitan, 2015[121]	72.1±9.7	65.3±9.8	83.0	84.4	60.0	51.6	85.5	65.0	50.0	42.2	34.2	27.6	170.0±27.9	164.0±27.5	25.0±7.0	25.0±7.0	89.9	93.1	78.7	89.1	-	-	89.1	83.9
Munir, 2016[122]	83.0 (79.0–86.0)	81.0 (78.0–83.0)	63.6	72.8	29.9	57.3	-	-	-	-	29.0	27.7	154.0 (132.0–178.0)	154.0 (140.0–172.0)	28.0 (23.0–33.0)	23.0 (20.0–28.0)	48.6	85.4	77.6	76.8	11	15	72.0	78.3
Witt, 2016[123]	-	-	75.0	85.5	37.6	71.5	84.4	67.8	43.1	36.4	26	24	-	-	-	-	90	89	75	78	55	52	85	79
Laish-Farkas, 2016[88]	84.5±3.0	82.3±2.4	65.0	86.0	71.0	87.0	-	-	45.0	38.0	32.0	44.0	134.0±32.4	133.8±30.4	-	-	70.0	74.0	79.0	77.0	-	-	-	-
Barra, 2017[124]	73.0±10.1	65.2±10.7	57.6	84.6	46.3	51.9	83.1	69.9	35.0	35.7	18.9	22.4	-	-	27.1±9.1	25.5±7.7	77.5	84.5	62.0	81.2	40.1	40.3	-	-
Martens, 2017[125]	75.7±9.1	68.6±10.5	58.6	77.3	35.7	52.8	62.4	58.9	41.5	32.5	26.4	26.4	155.0±30.0	153.0±29.0	32.9±10.4	26.7±7.8	80.5	90.1	75.5	92.6	50	75	47.5	51.2
Yokoshiki, 2017[126]	77.0±10.2	66.8±11.2	60.8	76.8	21.6	27.9	75.2	72.2	12.4	13.2	28.9	31.5	157.9±24.7	153.5±30.7	33.0±11.1	26.5±9.0	56.7	66.6	61.9	76.9	30	45	76.3	80.5

Drozd, 2017[127]	75.1 1 0.3	69.3 1 0.0	74. 0	93. 0	54. 0	90. 0	63. 0	60. 0	35.0	23. 0	24. 0	27. 0	156.4±2 7.0	150.0±2 4.4	-	-	84. 0	92.0	74. 0	88. 0	-	-	-	-
Wang, 2018[96]	81.6± 5.3	80.7± 3.5	-	-	0	0	-	-	85.7	76. 3	19	26. 9	152.0± 34.8	159.0± 24.9	28.0 ± 5.50	24.1± 6.42	52. 4	87.1	73. 8	78. 5	5	14	-	-
Leyva, 2018[128]	73.1± 11	70.1± 9	70. 8	79. 7	43. 7	75. 3	91. 3	80. 9	36.2	28. 0	20. 1	25. 4	155.1 ± 21	150.8 ± 21	-	-	87. 4	92.9	60. 7	77. 3	39	51	95. 1	98. 3
Döring, 2018[95]	82.6± 4.5	77.8± 1.9	56. 3	75. 5	50. 0	53. 1	83. 7	83. 5	23.8	20. 4	-	-	150.0± 19	158.0± 18	29.6 ±5.9	27.4± 6.0	86. 3	93.8	80. 0	90. 7	29	59	92. 5	86. 8
Barra, 2019[94]	69.8± 10.2	63.8± 10.4	69. 7	80. 4	47. 8	52. 5	82. 0	68. 3	42.7	47. 1	28. 1	26. 7	-	-	26.8 ±7.6	25.5± 6.3	91. 4	83.5	74. 2	79. 1	43	32	-	-
Liang, 2019[129]	62.4± 10.4	59.8± 12.0	64. 3	75. 3	7.1	7.8	-	-	15.1	15. 1	19. 8	16. 9	161.28± 30.91	157.96± 31.53	;	;	91. 3	94.5	84. 9	90	14	21	91. 3	89. 5
Saba, 2019[93]	77.9±8. 4	72.6± 9.2	60. 1	64. 9	22. 7	29. 6	-	-	68.4	45. 1	53. 8	54. 5	-	-	-	-	-	-	-	-	-	-	-	-
Leyva, 2019[92]	74.3± 11.3	68.1± 11.1	68. 9	80. 8	56. 0	67. 2	-	-	-	-	24. 4	27. 3	-	-	-	-	-	-	-	-	-	-	-	-
Huang, 2020[89]	60.3± 11.5	60.0± 12.1	55. 3	74. 6	19. 8	28. 2	77. 6	84. 2	12.7	10. 2	16. 9	13. 8	163.6 ±24.9	157.8 ±27.0	28.1 ±5.4	27.3 ±5.2	82. 8	80.7. 4	87. 3	87. 3	79	77	83. 5	83. 7
Gras, 2020[91]	78.4± 9	67.5± 10	64. 6	77. 4	57. 6	65. 5	-	-	68.8	52. 1	31. 7	36. 9	-	-	-	-	-	-	-	-	-	-	-	-
Doran, 2021[130]	67.0	66.0	67. 0	67. 0	54. 0	55. 0	-	-	-	-	39. 0	41. 0	160.0	160.0	-	-	89. 0	90.0	68. 0	68. 0	53	55	94. 0	97. 0
Schrage, 2021[97]	74.3± 9.3	67.6± 9.8	78. 6	84. 2	73. 2	73. 4	64. 7	60. 5	67.7	61. 5	-	-	-	-	-	-	91. 2	94.0	93. 3	96. 9	51	60	87. 0	84. 5

Hadwiger, 2022[90]	76.7 (8.89)	69.9 (9.57)	52.0	65.0	73.0	75.0	85.0	85.0	59.0	41.0	32.0	36.0	-	-	-	-	-	-	-	-	-	-	-
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8.1.2. All-cause mortality

CRT-D was associated with significant survival benefit over CRT-P with a 26% mortality reduction (HR: 0.74, 95% CI: 0.66-0.82), with moderate heterogeneity.[3] (Figure 1.)

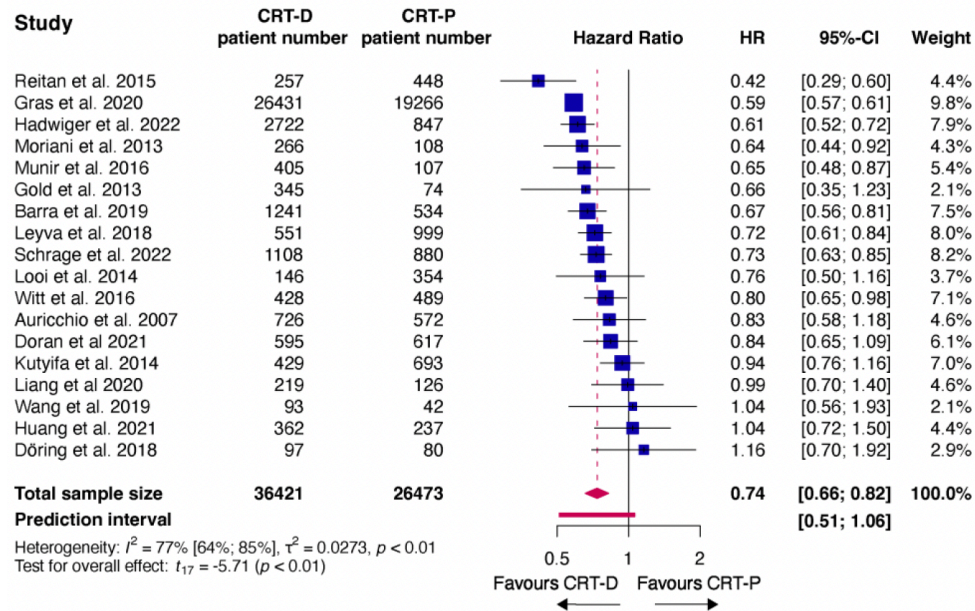


Figure 1. Forest plot of hazard ratios for studies with data on all-cause mortality. CI: Confidence Interval, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy- Pacemaker, HR: Hazard Ratio. Adapted from Veres,B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

The observed difference between the two therapies persisted in the adjusted analyses, with a 15% reduction in overall mortality in patients receiving CRT-D compared with CRT-P (aHR:0.85, 95% CI: 0.76-0.94), with moderate heterogeneity. The most commonly adjusted covariates included age, sex, HF etiology, symptom severity, atrial fibrillation, diabetes, beta-blocker use, and LBBB morphology. Unadjusted HRs were available from only 18 studies, whereas 22 studies reported adjusted HRs; thus, the two analyses were based on partially overlapping sets of studies. (Figure 2.)[3]

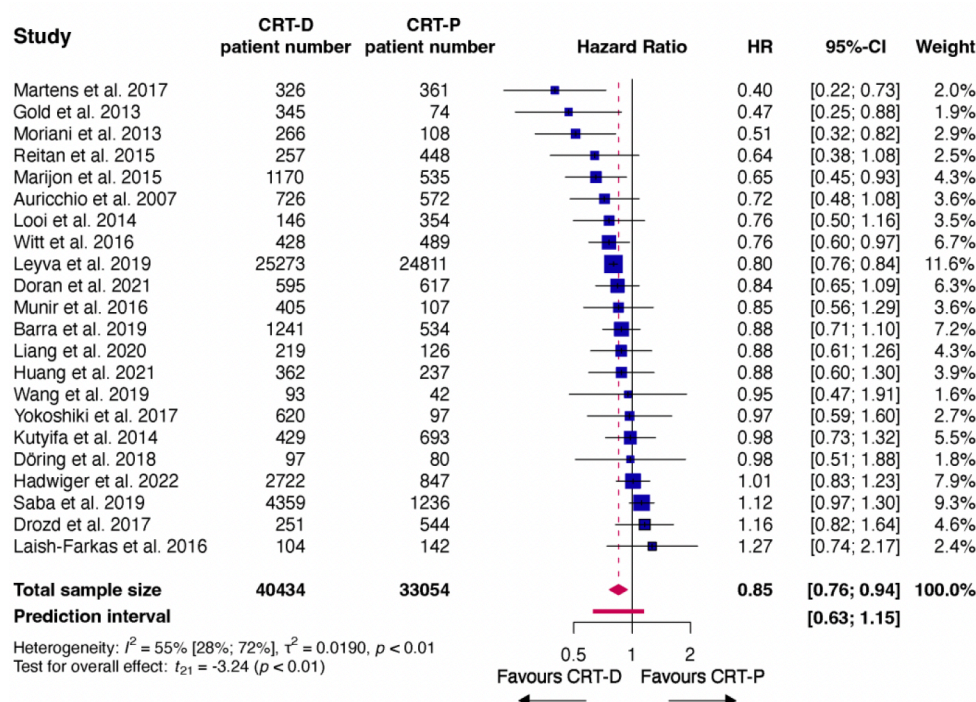


Figure 2. Forest plot of hazard ratios for studies reporting all-cause mortality using adjusted HRs. CI: Confidence Interval, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy- Pacemaker, HR: Hazard Ratio. Adapted from Veres, B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

To further support our findings, we also analysed propensity score-matched data (PSM) where, the pooled analysis yielded an HR of 0.83 (95% CI: 0.80–0.87) and showed low heterogeneity, reinforcing the superiority of CRT-D over CRT-P. (Figure 3.)[3]

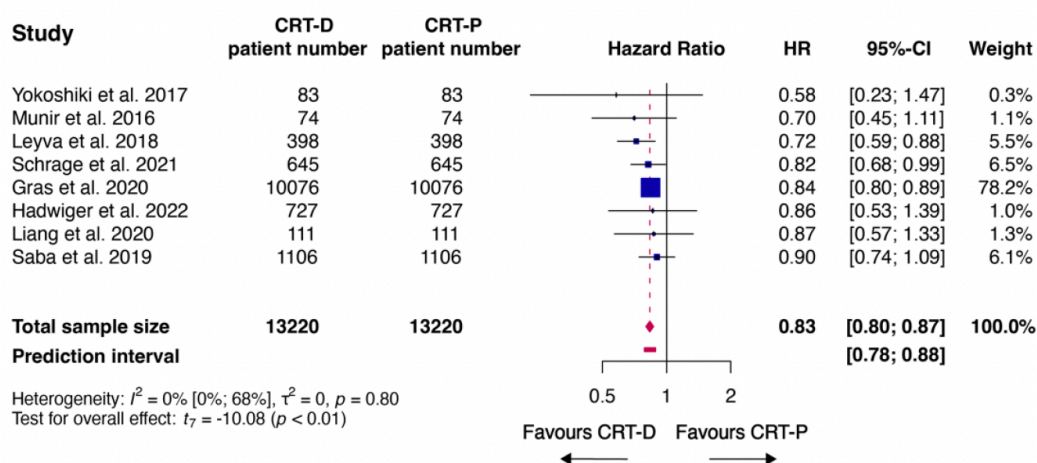


Figure 3. Forest plot of hazard ratios for studies with PSM data on all-cause mortality. CI: Confidence Interval, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy- Pacemaker, HR: Hazard Ratio. Adapted from Veres, B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

8.1.3. Secondary Outcomes

Beyond all-cause mortality, secondary outcomes were also evaluated. CRT-D showed a significant benefit over CRT-P in HF-related mortality (HR: 0.59, 95% CI: 0.41–0.85), although heterogeneity was high ($I^2 = 71\%$; 95% CI: 1–91%; $P = 0.03$). A more pronounced mortality benefit was observed in SCD (HR: 0.45, 95% CI: 0.32–0.62), with no significant heterogeneity, where all events were adjudicated by previously defined independent committees in the contributing studies. In CV mortality a 32% reduction was observed with CRT-D compared with CRT-P. (HR:0.68, 95% CI: 0.49–0.94) However, heterogeneity remained moderate. ($I^2 = 67\%$; 95% CI: 4–89%; $P = 0.03$) Interestingly, CRT-D also showed benefit in non-CV mortality, the pooled HR was 0.58 (95% CI: 0.55–0.61), with no significant heterogeneity ($I^2 = 0\%$; 95% CI: 0–90%; $P = 0.86$).[3]

8.1.4. Subgroup Analyses

After the consistent benefit of CRT-D observed in mortality outcomes, we wanted to evaluate whether there is homogeneity of CRT-D benefit across different patient populations. Therefore, subgroup analyses were performed.

Heart failure etiology

In ischemic cardiomyopathy, CRT-D significantly reduced all-cause mortality (HR: 0.80, 95% CI: 0.67–0.94), with low heterogeneity. In contrast, no significant survival benefit was observed in patients with non-ischemic cardiomyopathy (HR: 0.95, 95% CI: 0.79–1.15), with moderate heterogeneity. (Figure 4.)[3]

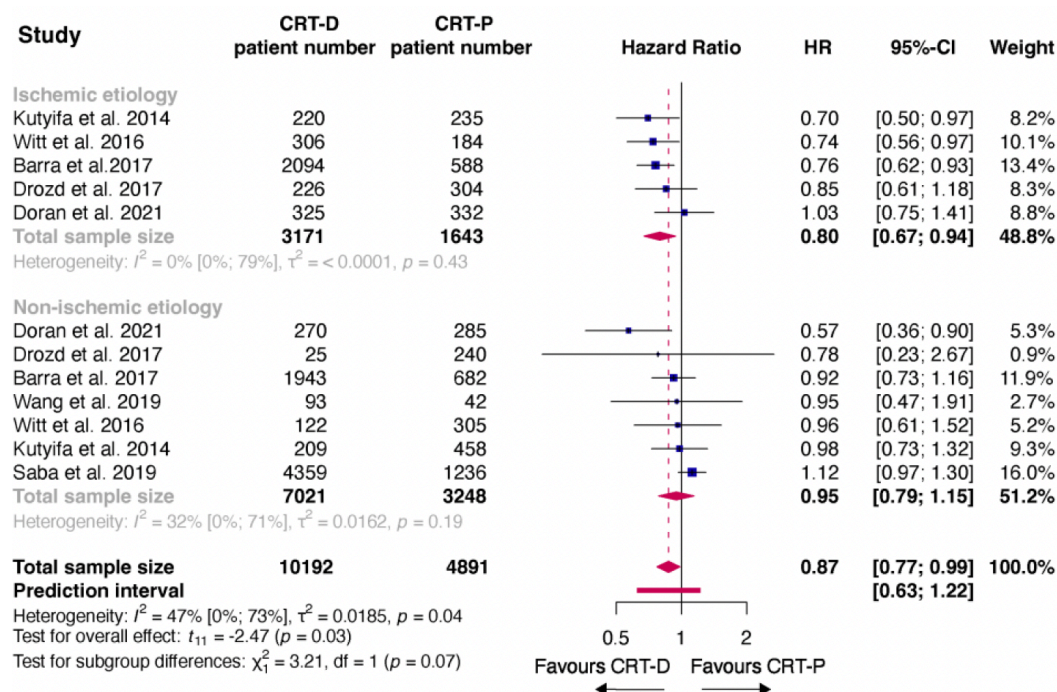


Figure 4. Forest plot of hazard ratios for studies reporting all-cause mortality by ischemic and non-ischemic etiology. CI: Confidence Interval, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy- Pacemaker, HR: Hazard Ratio. Adapted from Veres, B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

Age based analysis

Among patients older than 75 years, CRT-D provided no additional survival benefit over CRT-P (HR:1.08, 95% CI: 0.96–1.21), with low heterogeneity. (Figure 5.)[3]

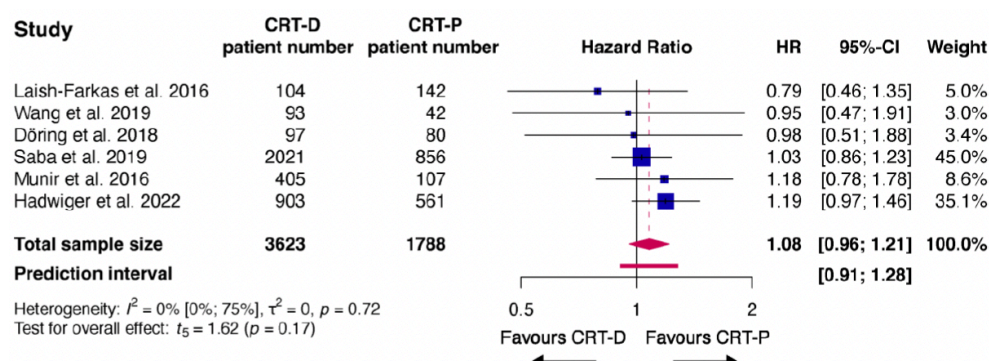


Figure 5. Forest plot of hazard ratios for studies reporting all-cause mortality by age. CI: Confidence Interval, CRT-D: Cardiac Resynchronization Therapy-Defibrillator,

CRT-P: Cardiac Resynchronization Therapy- Pacemaker, HR: Hazard Ratio. Adapted from Veres, B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

8.1.5. Time-trend differences by device type

Because the included studies in the meta-analysis spanned a long period and GDMT and GDIT changed substantially, we evaluated temporal trends and changes in patient characteristics to identify potential sources of heterogeneity.

All-cause mortality over time

A meta-regression analysis of HRs over time showed a slight, but non-significant increase ($\log(\text{HR}) = -26.49 + 0.0131 \times \text{median year}$; $P = 0.28$). (Figure 6.)[3]

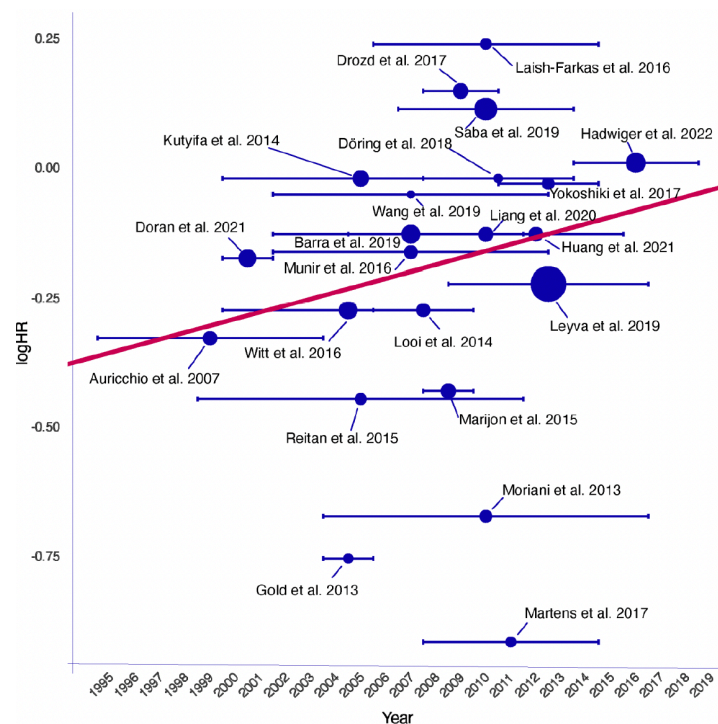


Figure 6. Time-trend variation of all-cause mortality by device type. HR: Hazard Ratio. Adapted from Veres, B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

Changes in etiology and age over time

A notable increase in the prevalence of ischemic heart disease could be observed among CRT-P recipients compared with those in the CRT-D cohort over time. (Figure 7. Panel

A) The average age of patients receiving CRT devices increased over time in both groups. However, this increase was more pronounced in the CRT-P cohort, suggesting a preference for CRT-P implantation in older patients as treatment guidelines evolved. (Figure 7. Panel B) [3]

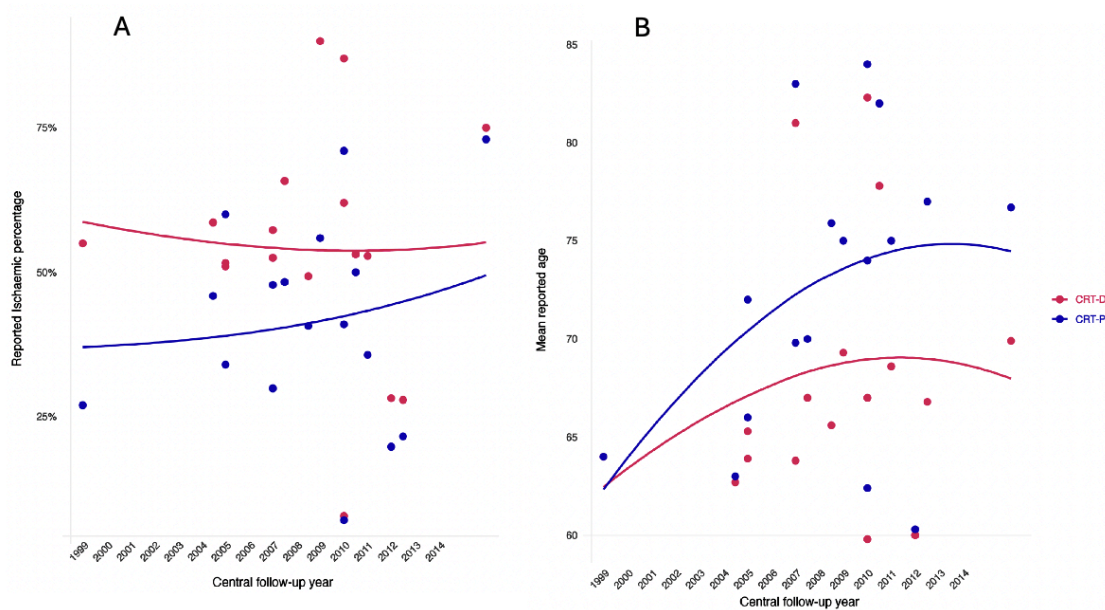


Figure 7. Panel A: Time-trend variation of ischemic etiology. Panel B: Time-trend variation of reported mean age CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy- Pacemaker. Adapted from Veres,B. et al EP Europace, Volume 25, Issue 10, October 2023, euad289 <https://doi.org/10.1093/europace/euad289>

8.1.6. Risk of Bias and GRADE

An evaluation of study quality determined that all included studies exhibited a moderate risk of bias. Using the GRADE framework to assess the strength of evidence, the overall certainty was categorized as low to very low, primarily due to the observational nature of most included studies.[3]

8.2. TDA-Based Identification of CRT Phenogroups with differential benefit from CRT-D

8.2.1. Clinical Characteristics of CRT-D and CRT-P cohorts

Patients in the CRT-D group were significantly younger, and less symptomatic compared to those in the CRT-P group. The CRT-D cohort also included a higher proportion of men and had greater rates of ischemic cardiomyopathy and prior ventricular arrhythmias. Additionally, CRT-D recipients had statistically significant but not clinically meaningful wider QRS durations, lower left ventricular ejection fractions, and larger left ventricular diameters than CRT-P patients. Medications were also more commonly prescribed in the CRT-D cohort, with higher rates of beta-blocker, MRA, and amiodarone use. A total of 1,273 patients (49%) had ischemic heart disease, while 1,330 patients (51%) had non-ischemic cardiomyopathy. Among ischemic patients 817 (64%) received CRT-D. In contrast, for non-ischemic patients 597 (45%) received CRT-D.[1] (Table2.)

Table 2. Baseline clinical characteristics of the entire study cohort. ACE-I:Angiotensin-converting enzyme inhibitor, ARB:Angiotensin II Receptor blocker, BMI: Body Mass Index, BUN:Blood Urea Nitrogen CABG: Coronary Artery Bypass Grafting, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy-Pacemaker eGFR: estimated glomerular filtration rate, MRA: Mineralocorticoid receptor antagonist, NYHA: New York Heart Association, LBBB: Left Bundle Branch Block, LVEDD:Left ventricular end-diastolic diameter, LVESD:Left ventricular end-systolic diameter, LVEF:Left ventricular ejection fraction,OAC:Oral anticoagulant, PCI: Percutaneous Coronary Intervention. Adapted from Veres, B. et al. *Clin Res Cardiol* **113**, 1430–1442 (2024). <https://doi.org/10.1007/s00392-023-02281-6>

	All n=2603	CRT-P n=1189	CRT-D n=1414	P-value
Demographics, physical status, key electrophysiological characteristics				
Age, years	68 (61-74)	69 (62-76)	67 (60-73)	<0.001
Males	1947 (75)	798 (67)	1149 (81)	<0.001
BMI, kg/m ² (1581)	28 (25-31)	27 (24-31)	28 (25-31)	0.103
NYHA III-IV (2175)	1213 (56)	611 (61)	602 (51)	<0.001
LBBB	1822 (70)	841 (71)	981 (69)	0.466

QRS duration, ms (910)	160 (140-180)	160 (150-180)	160 (140-170)	0.003
Medical history				
Atrial fibrillation	984 (38)	471 (40)	513 (36)	0.080
Ventricular arrhythmia	654 (25)	130 (11)	524 (37)	<0.001
Diabetes mellitus	950 (37)	431 (36)	519 (37)	0.840
Hypertension	1877 (72)	858 (72)	1019 (72)	0.970
Ischemic etiology	1273 (49)	456 (38)	817 (58)	<0.001
Myocardial infarction	998 (38)	354 (30)	644 (46)	<0.001
PCI	771 (30)	265 (22)	506 (36)	<0.001
CABG	349 (13)	99 (8)	250 (18)	<0.001
Laboratory measurements				
NT-proBNP, pg/mL(348)	2744 (1483-3969)	2829 (1590-3682)	2650 (1434-4167)	0.586
Creatinine, μ mol/L (1681)	101 (82-130)	101 (80-132)	102 (83-129)	0.475
eGFR, mL/min/1.73m ² (1682)	64 (48-81)	62 (46-81)	65 (49-81)	0.082
BUN, mmol/L (1656)	8 (6-12)	9 (7-12)	8 (6-12)	0.147
Serum sodium, mmol/L (1561)	138 (136-141)	139 (136-141)	138 (136-140)	0.155
Hemoglobin, g/dL (1646)	14 $\pm$ 2	14 $\pm$ 2	14 $\pm$ 2	0.549
Echocardiographic measurements				
LVEDD, mm (1679)	63 (57-70)	62 (56-69)	64 (58-70)	0.003
LVESD, mm (1500)	53 (47-60)	52 (45-59)	54 (48-61)	<0.001
LVEF, % (1903)	28 (24-33)	30 (25-35)	28 (23-32)	<0.001
Medications				
ACEI/ARB (2380)	2186 (92)	953 (91)	1233 (93)	0.070
Beta-blockers (2377)	2115(89)	915 (87)	1200 (90)	0.018
MRA (2377)	1614(68)	653 (62)	961 (73)	<0.001
Loop diuretics (2379)	1888 (79)	832 (79)	1056 (80)	0.919
Amiodarone (2368)	641 (27)	215 (21)	426 (32)	<0.001
OAC (2355)	703 (30)	328 (31)	375 (29)	0.135

8.2.2. Survival Outcomes of CRT-D and CRT-P cohort

During a median follow-up of 8.0 years (interquartile range: 5.3–12.1 years), 1572 patients died in the overall cohort. In univariable Cox regression, CRT-D was not associated with a significant survival advantage compared with CRT-P.(HR:0.94, 95% CI 0.85–1.03, p=0.187) However, after adjustment for clinically relevant covariates, including age, sex, HF etiology, and prior ventricular arrhythmia, CRT-D was associated with significantly lower all-cause mortality than CRT-P. (HR:0.83, 95% CI 0.74–0.92, p<0.001)[1]

Among patients with ischemic etiology, 882 deaths occurred a median follow-up of 7.9 years (5.1–12.2 years). In this subgroup, CRT-D was associated with lower mortality

than CRT-P in both unadjusted (HR:0.84, 95% CI 0.74–0.97, p=0.014) and adjusted Cox analyses.(HR:0.86, 95% CI 0.75–0.99, p=0.043) [1]

In the non-ischemic subgroup, 690 patients died during a median follow-up of 8.4 years (5.5–12.0 years). In contrast to the overall cohort, the survival benefit of CRT-D over CRT-P was evident in both univariable (HR:0.82, 95% CI 0.70–0.96, p=0.013) and multivariable analyses (HR 0.78, 95% CI 0.66–0.93, p=0.005) in this subgroup.[1]

8.2.3. Clinical Characteristics of Phenogroups created by TDA

To explore the observed heterogeneity in a more complex, multidimensional way, a circular patient network was generated using TDA, including 2359 individuals, within which five phenogroups with distinct clinical profiles and outcome patterns could be identified. Etiology emerged as a major distinguishing feature among the phenogroups. Three groups (Phenogroups 1, 2, and 3) consisted almost entirely of patients with non-ischemic HF, whereas the remaining two groups (Phenogroups 4 and 5) were predominantly composed of patients with ischemic etiology.[1] (Figure 8.)

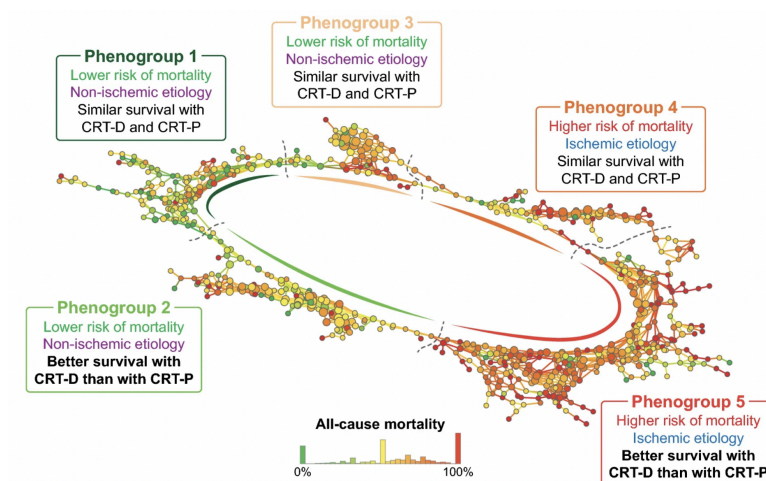


Figure 8. The topological network of the five identified phenogroups of CRT patients. CRT-D: Cardiac Resynchronization Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy- Pacemaker. Adapted from Veres, B. et al. *Clin Res Cardiol* **113**, 1430–1442 (2024). <https://doi.org/10.1007/s00392-023-02281-6>

Consistent with clinical expectations, CRT-D implantation was more frequent in the predominantly ischemic phenogroups than in the non-ischemic groups. Comparison among the non-ischemic phenogroups, several clinically relevant differences were observed. Patients in Phenogroup 1 were more often female than those in Phenogroup 2 and had smaller left ventricular end-diastolic and end-systolic diameters. In addition, MRA use was more frequent in Phenogroup 1. Phenogroup 3, in contrast, included a higher proportion of patients with advanced symptoms, as reflected by a greater prevalence of NYHA class III–IV compared with Phenogroup 2. Among the three non-ischemic groups, Phenogroup 3 was characterized by the lowest LVEF, the longest QRS duration, and the lowest prevalence of LBBB.[1] (Table 3.)

Table 3. Baseline clinical characteristics of the phenogroups identified by topological data analysis. BMI: Body Mass Index, BUN: Blood Urea Nitrogen CABG: Coronary Artery Bypass Grafting, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, MRA: Mineralocorticoid receptor antagonist, NYHA: New York Heart Association, LBBB: Left Bundle Branch Block, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LVEF: Left ventricular ejection fraction, OAC: Oral anticoagulant, PCI: Percutaneous Coronary Intervention. * $p < 0.05$ vs. phenogroup 1, # $p < 0.05$ vs. phenogroup 2, § $p < 0.05$ vs. phenogroup 3, † $p < 0.05$ vs. phenogroup 4, ‡ $p < 0.05$ vs. phenogroup 5 Adapted from Veres, B. et al. *Clin Res Cardiol* **113**, 1430–1442 (2024). <https://doi.org/10.1007/s00392-023-02281-6>

	Phenogroup 1 n=321	Phenogroup 2 n=553	Phenogroup 3 n=283	Phenogroup 4 n=254	Phenogroup 5 n=964	P-value
Demographics, physical status, key electrophysiological characteristics						
Age, years	66 (59-74)*	66 (58-73)*	67 (59-73)*	67 (60-75)*	70 (63-76)§†‡	<0.001
Males	194 (60)*†‡	386 (70)*§‡	184 (65)*‡	207 (81)§†	809 (84)§†	<0.001
BMI, kg/m ² (1438)	28 (24-31)	28 (25-31)#	26 (23-29)*†‡	28 (25-30)#	27 (25-31)#	0.139
NYHA III-IV (1981)	150 (57)	298 (57) #	106 (66) * †	74 (56)	464 (52) #	0.010
LBBB	247 (77)§†*	426 (77)§†*	197 (70)§†‡	146 (57)§†#	661 (69)§†‡	<0.001

CRT-D	163 (51) ^{†‡*}	226 (41) ^{§‡*}	115 (41) ^{§‡*}	173 (68) ^{§†#}	614 (64) ^{§†#}	<0.00 1
Medical history						
Atrial fibrillation	137 (43) ^{†‡}	218 (39) [‡]	105 (37)	81 (32) ^{§†}	336 (35) [§]	0.032
Ventricular arrhythmia	75 (23)	120 (22) [*]	62 (22)	63 (25)	266 (28) [†]	0.074
Diabetes mellitus	99 (31) ^{†‡}	169 (31) ^{†‡}	98 (35)	102 (40) ^{§†}	392 (41) ^{§†}	<0.00 1
Hypertension	210 (65) ^{†‡}	378 (68)	187 (66) ^{†‡}	189 (74) ^{#§}	745 (77) ^{#§}	<0.00 1
Ischemic etiology	3 (1) ^{†‡}	6 (1) ^{†‡}	0 (0) ^{†‡}	214 (84) ^{*#§†}	955 (99) ^{#§†‡}	<0.00 1
Myocardial infarction	1 (1) ^{†‡}	4 (1) ^{†‡}	0 (0) ^{†‡}	173 (68) ^{*#§†}	764 (79) ^{#§†‡}	<0.00 1
PCI	2 (1) ^{†‡}	1 (1) ^{†‡}	0 (0) ^{†‡}	108 (42) ^{*#§†}	619 (64) ^{#§†‡}	<0.00 1
CABG	1 (0.2) ^{†*}	0 (0) ^{†*}	0 (0) ^{†*}	60 (24) ^{§†#}	273 (28) ^{§†#}	<0.00 1
Laboratory measurements						
Creatinine, μ mol/L (1527)	91 (77-119) [*]	96 (78-124) ^{#*}	83 (69-102) ^{†*}	92 (76-134)	108 (87-138) ^{†§#}	<0.00 1
BUN, mmol/L (1504)	7 (6-10) ^{†*}	8 (6-11) ^{§*}	8 (6-11)	7 (6-11)	9 (7-12) ^{§†}	<0.00 1
Serum sodium, mmol/L (1418)	139 (136-141)	138 (136-140)	140 (139-142)	137 (136-141)	138 (136-141)	0.402
Hemoglobin, g/dL (1492)	14 $\pm$ 2 [*]	14 $\pm$ 2	14 $\pm$ 2	14 $\pm$ 1 [*]	13 $\pm$ 2 ^{§‡}	<0.00 1
Echocardiographic measurements						
LVEDD, mm (1533)	61 (56-68) [†]	64 (59-71) ^{§*}	52 (50-65) [‡]	65 (57-67) [#]	63 (57-70) [†]	<0.00 1
LVESD, mm (1386)	52 (45-59)	54 (47-61)	43 (42-44)	50 (45-54)	53 (46-60)	<0.00 1
LVEF, % (1728)	28 (22-33) [#]	29 (25-33) [#]	25 (22-30) ^{†*§}	26 (20-30)	29 (24-34) [#]	<0.00 1
Medications						
Beta-blockers (2169)	278 (93) ^{†‡*}	466 (89) [§]	206 (93)	169 (87) [§]	825 (89) [§]	0.047
MRA (2169)	225 (76) ^{†*}	343 (65) [§]	167 (75)	139 (72)	602 (65) [§]	<0.00 1
Amiodarone (2161)	70 (24)	134 (26)	51 (23)	54 (28)	264 (28)	0.301

OAC (2153)	117 (40)*	177 (34)	78 (35)	66 (35)	270 (30) [§]	0.018
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8.2.4. Survival Outcomes by Device Type within Phenogroups created by TDA

When survival was analyzed according to device type within each phenogroup, the association between CRT-D and CRT-P differed substantially across groups. Among the non-ischemic phenogroups, a significant survival advantage of CRT-D over CRT-P was observed only in Phenogroup 2, both in the unadjusted and adjusted analyses. In the predominantly ischemic population, CRT-D was associated with lower all-cause mortality compared with CRT-P only in Phenogroup 5. These findings indicate that the potential benefit of defibrillator back-up is not uniform, even within broader etiologic categories.[1] (Figure 9.)

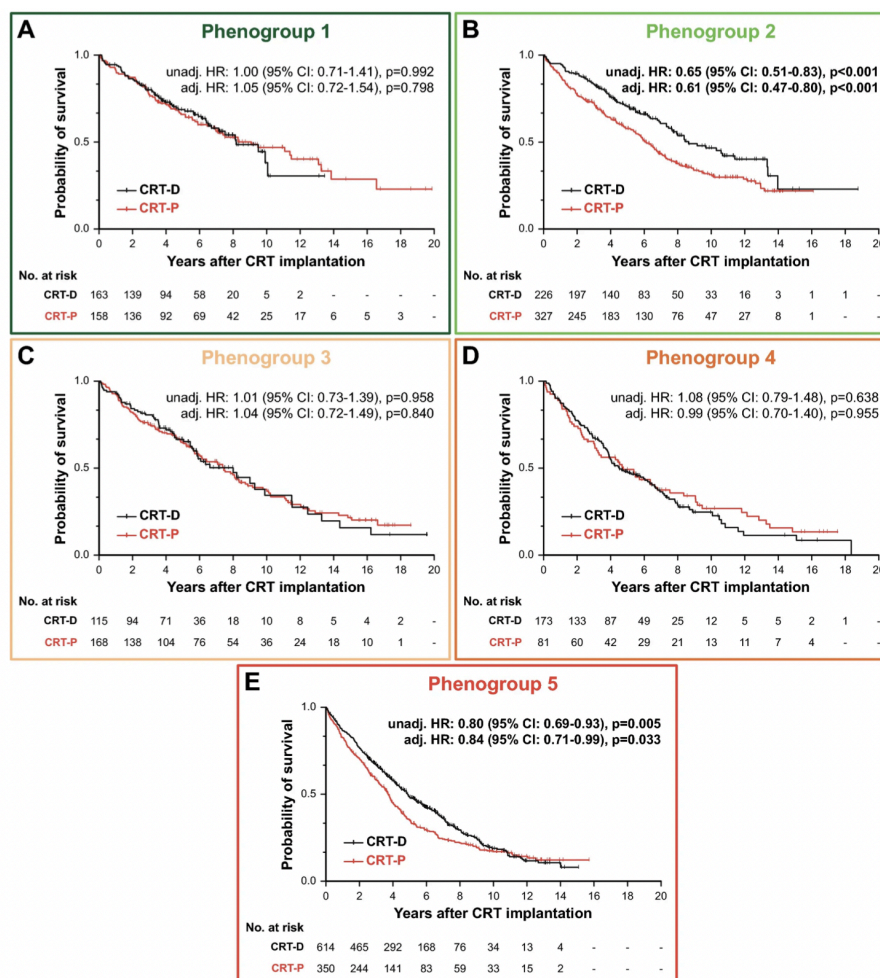


Figure 9. KM estimates of time to death from any cause in CRT-D and CRT-P patients across the five phenogroups identified by TDA. CRT-D: Cardiac Resynchronization

Therapy-Defibrillator, CRT-P: Cardiac Resynchronization Therapy- Pacemaker. Adapted from Veres, B. et al. *Clin Res Cardiol* **113**, 1430–1442 (2024). <https://doi.org/10.1007/s00392-023-02281-6>

Further differences were evident between the two predominantly ischemic phenogroups. Compared with Phenogroup 4, patients in Phenogroup 5 were older, had lower hemoglobin levels, more frequently exhibited LBBB, and had an even higher prevalence of ischemic etiology.[1] (Figure 10.)

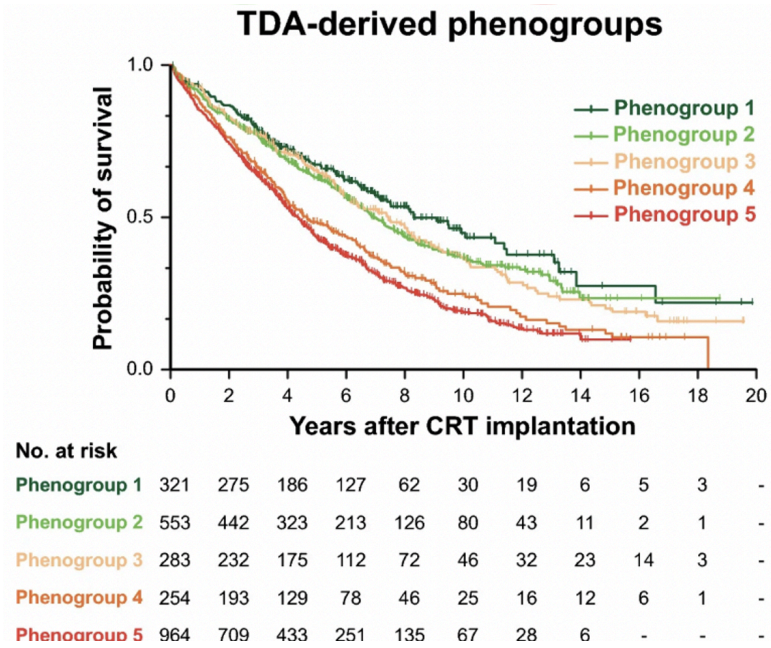


Figure 10. KM estimates of time to death from any cause of the five distinct phenogroups. CRT: Cardiac Resynchronization Therapy. Adapted from Veres, B. et al. *Clin Res Cardiol* **113**, 1430–1442 (2024). <https://doi.org/10.1007/s00392-023-02281-6>

Clear differences in all-cause mortality were also observed across phenogroups overall. Although survival did not differ significantly among the three non-ischemic phenogroups, the two predominantly ischemic groups showed comparable outcomes. All three non-ischemic phenogroups demonstrated significantly better survival than the ischemic phenogroups. (Figure 10.).[1]

8.3. Optimizing Long-Term Follow-Up in Patients with Cardiac Implantable Electronic Devices

8.3.1. Included Studies and Patient Populations

A total of 16 studies met the inclusion criteria for the present analysis, representing 11,232 patients with HF. Of these, 6288 patients were followed through an additional RTM to IPV, whereas 4944 received conventional IPV follow-up.[2] For simplicity, RTM and IPV are used as abbreviations throughout the subsequent figures and tables.

Although the included studies used different monitoring algorithms and parameters, the most relevant differences were daily versus non-daily reporting in the RTM arm and the frequency of office-based follow-up in the comparator group. [2]

Across the included trials, the mean patient age generally ranged from 60 to 70 years. Male patients predominated in all studies, accounting for more than 70% of the total study population. Mean LVEF was typically between 25% and 30%, and ischemic HF etiology was present in approximately 60% of patients. The vast majority of participants received GDMT, with around 90% treated with ACE inhibitors or ARBs, beta-blockers, and diuretics. The proportion of patients with advanced symptoms (NYHA class III-IV) varied considerably between studies, ranging from 5% to 81%. [2] (Table 4.)

Table 4. Baseline Clinical Characteristics of Patients and Enrolled Studies. ACEi: Angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CIED: Cardiac Implantable Electronic Device, CRT-D: Cardiac Resynchronization Therapy-Defibrillator, ICD: Implantable Cardioverter Defibrillator, LVEF: Left Ventricular Ejection Fraction, MRA: Mineralocorticoid Receptor Antagonist, NYHA: New York Heart Association, RTM: Remote Telemedical Management. Adapted from B. Veres et al. *J. Clin. Med.* 2025, 14(12), 4278; <https://doi.org/10.3390/jcm14124278>

Author, year	Trial name	Number of patients		CIED		Follow-up (month)	Age (mean $\pm$ SD), median(IQR)		Male (%)		Mean LVEF (%) (mean $\pm$ SD) median(IQR)		Ischemic (%)		NYHA class (%) (III, IV)		ACEi/ARB (%)		Beta blocker (%)		MRA (%)		Diuretic (%)	
		RTM	IPV	CRT-D	ICD		RTM	IPV	RTM	IPV	RTM	IPV	RTM	IPV	RTM	IPV	RTM	IPV	RTM	IPV	RTM	IPV	RTM	IPV

Varma 2010[131]	TRUST	90 8	4 3 1	0	13 39	15	63.3 ±12. 8	64.0 ±12. 1	72	7 3. 1	29.0 ±10. 7	28.5 ±9.8	64 .8	7 1. 7	30 .1	3 1. 1	50 .5	5 5. 9	79 .6	7 6. 3	-	-	-	-
Al-khatib 2010[132]	pilot study	76	7 5	0	15 1	12	63 (54- 72)	63 (54- 70)	72	7 3	25 (20- 35)	28 (20- 35)	66	6 7	5	0	85	7 7	88	8 9	-	-	63	7 1
Veldhuisen 2011[107]	DOT-HF	16 8	1 6 7	27 4	61	15	64± 10	64± 10	87	8 5	25± 7	25± 7	52	6 0	39	3 6	83	8 7	92	9 2	-	-	92	8 7
Crossley 2011[133]	CONNECT	10 14	9 8 3	75 7	12 40	15	65.2 ±12. 4	64.9 ±11. 9	70	7 1. 7	28.6 ±10	29.2 ±10. 3	63 .3	6 1. 5	50	4 9	-	-	-	-	-	-	-	-
Guedon-Mo reau 2012[134]	ECOST	22 1	2 1 2	78	23 2	27	62.0 ±13. 0	61.2 ±12. 0	87	8 9. 2	34.7 ±13. 0	35.1 ±13. 6	64 .7	6 6. 5	6. 4	1 1. 8	-	-	-	-	-	-	-	-
Hindricks, 2014[110]	IN-TIME	33 3	3 3 1	27 4	39 0	12	65.3 ±9.3	65.8 ±9.6	82	7 9. 2	26± 6	26± 7	70	6 8	54 .8	5 9. 2	92 .2	8 6. 4	91 .3	9 1. 8	-	-	95 .2	9 1. 5
Lüthje 2015[135]	pilot study	87	8 9	88	88	15	66.0 ±12. 0	65.9 ±12. 1	80	7 4. 2	32.7 ±11. 4	31.1 ±10. 2	58 .6	4 3. 8	37 .9	4 7. 7	-	-	-	-	-	-	-	-
Boriani 2016[136]	MORE -CARE	43 7	4 2 8	86 5	0	24	66± 11	67± 10	78 .8	7 3. 1	27.3 ±6.6	27.4 ±6.0	42 .8	4 5. 3	62 .9	6 1. 1	82 .4	7 9	89 .1	8 8. 3	31 .5	3 4	91 .7	9 1. 2
Domenichin i 2016[137]	LIMIT-CHF	41	3 9	53	27	12	69.5 ±11. 0	66.3 ±11. 9	98	9 0	28.9 ±8.4	27.6 ±7.5	78	7 2	-	-	95	9 7	90	9 0	66	4 6	81	8 5

Böhm 2016[106]	OptiLink	50 5	4 9 7	62 7	37 5	23	66.1 ±10. 1	66.4 ±10. 7	77 .2	8 2. 3	26.7 ±6.1	26.7 ±6.1	54 .3	5 4. 5	80 .4	8 0. 9	91 .3	9 4	94 .5	9 2. 4	68 .9	6 9. 6	95	9 5
Morgan 2017[138]	REM-HF	82 4	8 2 6	10 99	55 1	34	69.5 ± 10.3 1	69.5 ± 10.0 4	85 .8	8 5. 7	29.9 ± 10.2 4	30.0 ± 9.81	68 .7	6 7	29	3 2	91	9 1. 3	90 .9	9 0. 3	52 .2	5 2. 7	77 .1	7 6. 4
Hansen 2018[139]	INCONTAC T	10 2	1 0 8	68	14 2	13	62.5 ± 12.2	65.1 ± 10.1	83 .3	8 1. 2	28.2 ± 7.1	28.3 ± 8.9	56 .9	6 1. 1	44 .1	4 1. 7	97	9 4. 4	-	-	53 .5	5 6. 5	85 .3	8 2. 4
Tajstra 2020[140]	RESULT	29 9	3 0 1	24 9	35 1	12	64± 13	64± 12	81 .6	8 0. 7	27± 10	26± 10	63 .2	6 4. 8	17 .9	2 4. 2	96 .4	9 3	90	9 1. 4	95 .9	9 8. 9	89	9 0. 7
Pluta 2020[141]	TELEREH- HF	20 8	6 2	10 8	16 2	2.2 5	61.3 ± 11	62.2 ± 9	90 .9	9 5. 2	29.3 ± 6.9	27.9 ± 6.6	64 .9	5 6. 4	17 .3	3 0. 6	95 .7	9 5. 2	97 .6	9 8. 4	85 .6	9 6. 8	78 .4	8 2. 3
Chiu 2022[142]	REMOTE-C IED	30 0	2 9 5	23 0	57 5	24	66 (58– 73)	65 (59– 73)	78	8 1	27 (21– 31)	27 (21– 31)	53	6 0	33	3 4	89	8 8	82 5	8 5	59	6 5	72	7 3
Koehler 2018[109]	TIM-HF2	76 5	7 7 3	24 0	45 6	12	70± 11	70± 10	70	6 9	-	-	39	4 2	47	4 7	82	8 3	92	9 2	58	5 2	94	9 3

8.3.2. Mortality outcomes

All-cause mortality

The pooled hazard ratio for all-cause mortality was 0.83 in favor of RTM plus IPV, with a 95% CI of 0.72 to 0.96, indicating a statistically significant reduction in risk compared with IPV. (Figure 11.)

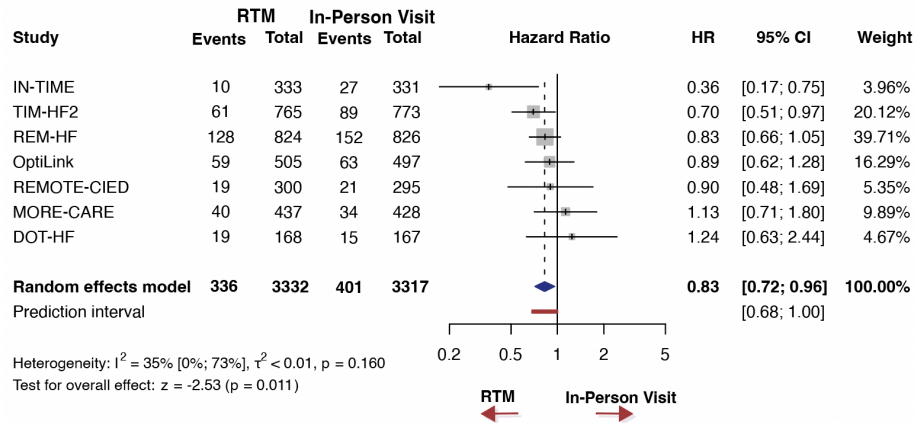


Figure 11. Forest plot of hazard ratios for all-cause mortality. CI: Confidence Interval, HR: Hazard Ratio, RTM: Remote Telemedical Management. Adapted from B. Veres et al. *J. Clin. Med.* 2025, 14(12), 4278; <https://doi.org/10.3390/jcm14124278>

Cardiovascular mortality

The pooled hazard ratio was 0.81 for RTM plus IPV compared with IPV alone, with a 95% CI of 0.67-0.97, demonstrating a statistically significant benefit of additional RTM ($p=0.025$).[2] (Figure 12.)

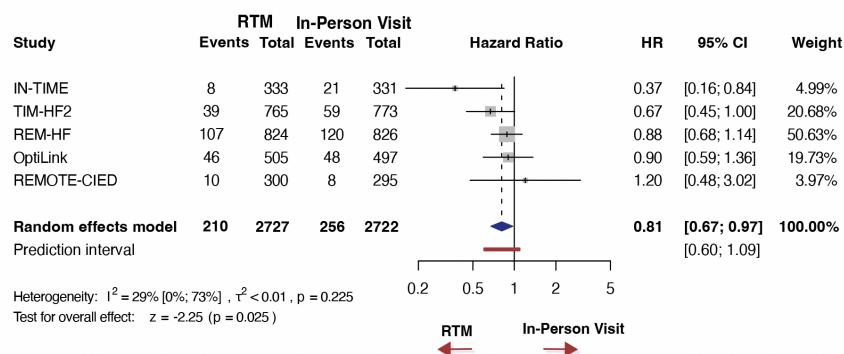


Figure 12. Forest plot of hazard ratios for CV mortality. CI: Confidence Interval, HR: Hazard Ratio, RTM: Remote Telemedical Management. Adapted from B. Veres et al. *J. Clin. Med.* 2025, 14(12), 4278; <https://doi.org/10.3390/jcm14124278>

8.3.3. Hospitalization outcomes

Cardiovascular hospitalization

The pooled OR was 0.93, with a 95% CI of 0.82 to 1.05, indicating no significant difference between RTM plus IPV and conventional IPV alone . [2] (Figure 13.)

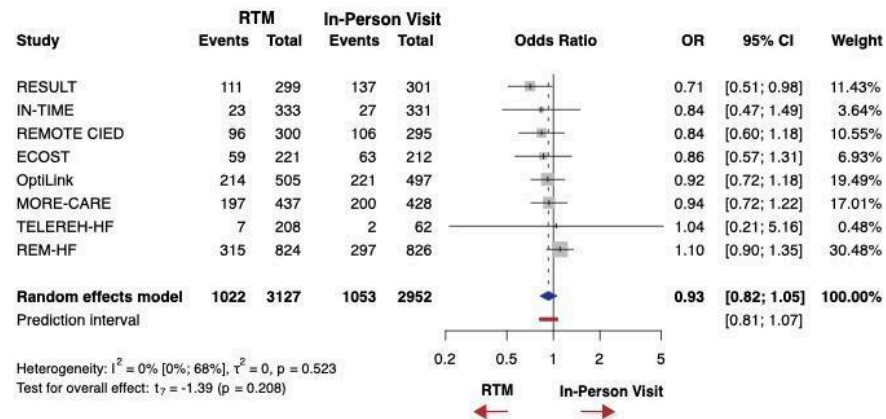


Figure 13. Forest plot of ORs for CV hospitalization. CI: Confidence Interval, OR: Odds Ratio, RTM: Remote Telemedical Management. Adapted from B. Veres et al. *J.Clin. Med.* 2025, 14(12), 4278; <https://doi.org/10.3390/jcm14124278>

Heart failure-related hospitalization

The pooled OR was 0.95, with a 95% CI of 0.75 to 1.20, suggesting no significant difference between the two follow-up strategies.[2] (Figure 14.)

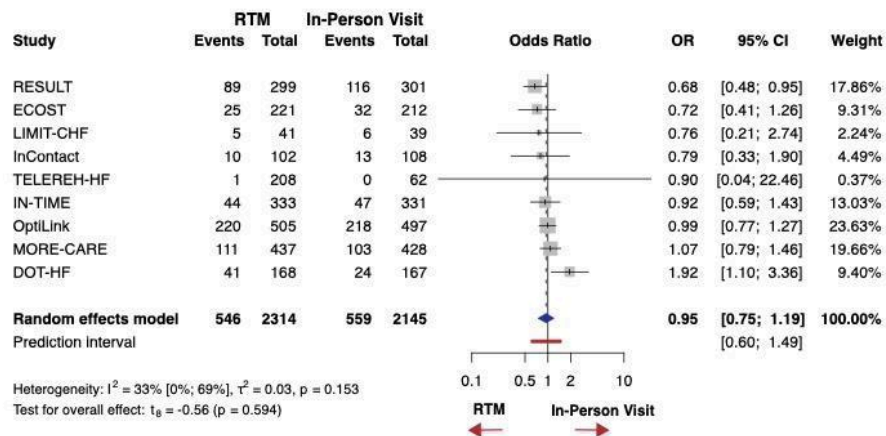


Figure 14. Forest plot of ORs for HF-related hospitalization. CI: Confidence Interval, OR: Odds Ratio, RTM: Remote Telemedical Management. Adapted from B. Veres et al. *J. Clin. Med.* 2025, 14(12), 4278; <https://doi.org/10.3390/jcm14124278>

8.3.4. ICD outcomes

Additional RTM did not significantly reduce the incidence of any ICD shocks compared with IPV alone. The pooled OR was 0.87, with a 95% CI of 0.53 to 1.46, ($p=0.531$).[2]
No statistically significant effect of additional RTM was observed on inappropriate ICD therapy ($p=0.351$). The pooled OR was 0.73, with a 95% CI of 0.30 to 1.81.[2]

8.3.5. Risk of Bias, GRADE and Sensitivity analysis

The included studies had low risk of bias with some concerns, while the overall GRADE certainty was low to moderate.[2]

9. Discussion

9.1. CRT-D versus CRT-P: from population-level evidence to patient-level phenotyping

Over years, the question of whether CRT-D provides a substantial additional survival benefit over CRT-P remains unresolved. CRT itself can indirectly reduce arrhythmic risk through LV reverse remodeling; moreover, CRT device technology has improved significantly, which may increase the number of responder patients.[55, 77, 143, 144] Furthermore, with the introduction of FMT, such as ARNI and SGLT2 inhibitors, the background risk of SCD has declined over time.[114, 145] This suggests that the incremental value of defibrillator backup may no longer be the same as it was in earlier clinical eras. In addition to the importance of the question, CRT-D implantation is associated with greater device complexity, higher cost, and defibrillator-specific complications, including inappropriate shocks and lead-related problems.[50] Moreover, an adequately powered randomized comparison of CRT-P versus CRT-D remains lacking.[50]

Therefore, the choice between CRT-P and CRT-D is increasingly a matter of a debate, which we sought to evaluate in greater depth using the available methodological tools. CRT-D was associated with lower all-cause mortality in the unadjusted, adjusted, and PSM analyses, respectively. [3] In contrast, in the Semmelweis University patient-level cohort, we found no significant difference between CRT-D and CRT-P in the unadjusted analysis, whereas after adjusting for relevant covariates, we observed a significant mortality benefit for CRT-D.[1] In the unadjusted analysis, the CRT-D and CRT-P groups had different baseline risk profiles, which may have masked the survival difference. After adjusting for these measured confounders, the association between CRT-D and improved survival became significant. Interestingly, in the time-trend analysis, there was no change in the CRT-D treatment effect over time, as we anticipated given the potential impact of FMT and improved device technology.[1, 3] One possible explanation for this observation is that the enrollment periods of the included studies were before the widespread use of ARNI and SGLT2.

In the subgroup analyses, the survival benefit of CRT-D was not uniform across subgroups. In the meta-analysis the ischemic subgroup showed that CRT-D had a significantly better treatment effect than CRT-P, a finding consistent with our cohort

study.[1, 3] Patients with ischemic cardiomyopathy may have a higher residual arrhythmic risk and therefore a greater potential to benefit from ICD therapy. This difference may become apparent relatively early after implantation, as accumulating more events increases the statistical power to detect a difference between the two therapies.[146] However regarding non-ischemic etiology, in the meta-analysis no clear additional reduction in all-cause mortality was observed, whereas our patient-level data showed the contrary.[1, 3] The impact of follow-up duration may partly contribute to differences between studies; in the cohort study, the average follow-up was 8 years, whereas the meta-analysis showed an average follow-up of about 4 years. [1, 3] With extended follow-up, more events accumulate, which may increase the ability to detect a difference between the two therapies.[146] However, randomized data from DANISH did not demonstrate an overall all-cause mortality benefit even with a median follow-up of 13.2 years, but it did reduce SCD. [147]

Taken together, these findings suggest that conventional subgroup analyses may not fully capture treatment heterogeneity. To explore this observed heterogeneity in a more complex, multidimensional way, TDA was used, and we identified five clinically distinct phenogroups, in which a significant survival benefit from CRT-D was observed only in selected phenogroups. [1] The identified phenogroups were characterized by different combinations of clinical features and underlying etiology. Moreover, two phenogroups may appear similar with respect to several clinically important variables, yet differ in the multidimensional combination and relative distribution of other characteristics. As a result, overall survival was more favorable in the predominantly non-ischemic groups, whereas the ischemic phenogroups showed poorer outcomes.[1] This finding is consistent with previous studies reporting a less favorable prognosis among CRT patients with ischemic cardiomyopathy, potentially related to greater myocardial scar burden and less pronounced reverse remodeling.[148, 149] However, etiology alone did not fully explain the observed differences in CRT-D benefit, as a significant advantage was identified in both one ischemic and one non-ischemic phenogroups. This indicated that the incremental value of defibrillator therapy may depend on the interaction of several patient characteristics rather than on a single conventional risk factor. [1, 50] These findings highlight the potential value of data-driven phenotyping in CRT candidate selection. With TDA, we were not only able

to dichotomize patients, but we also used a complex approach to create phenogroups that were differentiated by risk; and by the benefit of CRT-D, a similar approach will likely be needed in the future so that we can make decisions based on multifactorial considerations. Nevertheless, it is important to note that in CRT-D, despite the adjustments, we observed reductions in endpoints where we would not have expected them, such as in non-CV- and HF mortality, potentially due to confounding.[3] Our findings therefore support a more individualized approach to device selection in CRT candidates. However, heterogeneity in the literature and residual confounding due to the observational nature of the studies further highlight the need for an adequately powered RCT.

9.2. Remote Monitoring as a Continuum of Care

While the first two studies focus on who should receive CRT-D versus CRT-P, the third study adds an equally critical dimension: the importance of structured long-term follow-up for HF patients with CIED. Despite major advances in FMT and GDIT, patients with HFrEF remain at substantial residual risk of death, recurrent HF hospitalization, arrhythmias, and progressive clinical deterioration, highlighting the need for structured longitudinal follow-up and RTM.[7] This systematic review and meta-analysis showed that continuous additional RTM was associated with lower all-cause and CV mortality in patients with HF and CIEDs. In contrast, no significant reduction was observed in CV or HF-related hospitalizations, or ICD shock-related outcomes.[2] These findings should be interpreted in the context of the heterogeneous results of previous remote-monitoring trials.[109, 131-138, 140, 150-152] For example is TIM-HF2, which demonstrated a reduction in mortality with a structured telemedical management strategy that incorporated daily data transmission and continuous access to a telemedical center. Moreover, IN-TIME showed that adding daily implant-based remote monitoring to standard care improved overall clinical outcome and was associated with lower mortality.[110] By contrast, other CIED-based remote-monitoring trials, for example, DOT-HF, LIMIT-CHF, OPTILINK, and a study by Luthje et al., which focused on remote patient follow-ups by monitoring thoracic impedance and fluid accumulation, reported no discernible mortality advantage between RTM+IPV and IPV.[97, 128, 131, 133, 134, 143] A potential explanation for the observed mortality

benefit in the meta-analysis could be that additional RTM facilitates the early detection of device-related abnormalities, clinically relevant arrhythmias, and signs of worsening HF between scheduled IPV. However, RTM itself is unlikely to improve outcomes unless transmitted information leads to timely clinical action. This observation was underscored in the IN-TIME trial, where structured and timely responses to remotely detected events were provided. Data were transmitted automatically on a daily basis, reviewed centrally, and relevant findings were communicated to the treating centers to allow prompt intervention.[110] Therefore, the effectiveness of additional RTM depends not only on the technology used but also on healthcare organization, predefined alert pathways, and time to clinical intervention.[103] At the same time, the lack of a significant effect on hospitalization-related outcomes requires careful interpretation. Studies differed considerably in monitoring strategies, alert thresholds, transmission frequency, follow-up protocols, and clinical response to detected events.[2] Such heterogeneity may affect hospitalization. In addition, earlier detection of deterioration may, in some cases, lead to more frequent clinical contact or even earlier hospitalization, while still preventing more severe events or longer hospitalization and improving survival.[103] However, considerable heterogeneity in intervention design and clinical workflow limits the ability to identify which specific components account for the observed survival benefit.

Overall, this thesis demonstrates a shift from population-level evidence to phenotype-specific device selection and individualized post-implantation care, reflecting the broader evolution of HF management from a one-size-fits-all strategy to a more personalized approach.[1-3]

9.3. Strengths and Limitations

A key strength of this thesis is its investigation of clinically important questions in HF using three complementary approaches: meta-analysis of comparative device outcomes, ML-based phenotyping, and evaluation of RTM. Together, these studies provide a broad, clinically relevant perspective on prognosis, treatment selection, and follow-up in patients with CIEDs.[1-3] The CRT-D versus CRT-P meta-analysis is strengthened by its large study population, focus on long-term mortality, and assessment of temporal trends and subgroup effects, which enhance its relevance to contemporary clinical

practice.[3] The TDA study is strengthened by its innovative unsupervised analytical approach and its ability to identify phenogroups with distinct survival patterns and differential benefit from CRT-D. [1]The RTM meta-analysis is strengthened by its restriction to RCTs and its evaluation of hard clinical outcomes, including mortality and hospitalization.[2] This multimethod approach increases the overall scientific value of the thesis, as the individual studies complement one another in a meaningful way. [1-3] This provides a strong basis for advancing precision medicine in HF and for supporting more individualized therapeutic decision-making in HF patients with CIEDs. [1-3] Several limitations should be acknowledged. Although the analyses drew from large multicenter datasets, the observational nature of some data introduces potential residual biases and confounding. The TDA approach, while powerful, remains exploratory and depends on the quality and granularity of input variables, and proportional-hazards assumption was not assessed in the survival analysis. Remote monitoring studies vary in implementation and follow-up duration, limiting direct comparability. [1-3]

10. Conclusion

The first study showed that CRT-D therapy was associated with a significant reduction in all-cause mortality and in deaths from HF progression, SCD, and non-CV causes, respectively. [3] Subgroup analyses, however, observed inconsistent mortality benefit of CRT-D among patients with ischemic and non-ischemic HF etiology.[3] Time-trend analysis suggested that the relative mortality benefit associated with CRT-D remained broadly stable over time. Meanwhile, patient characteristics evolved over time, particularly with higher prevalence of ischemic etiology among CRT-P recipients and increasing age, whereas patients ≥ 75 years old showed no mortality benefit of CRT-D. These incongruent findings at the population-level highlight the growing complexity of device selection in contemporary HF management and support an individualized, risk-based approach to choosing between CRT-D and CRT-P.[3] To refine patient selection for CRT-D, we employed TDA, which identified five distinct phenogroups, three predominantly composed of patients with non-ischemic etiology and two largely composed of patients with ischemic HF. Overall, patients in the non-ischemic phenogroups had significantly more favorable survival outcomes than those in the predominantly ischemic phenogroups.[1] Notably the survival advantage of CRT-D over CRT-P was not uniform across phenogroups. A significant reduction in all-cause mortality associated with CRT-D was observed only in one non-ischemic, and in one predominantly ischemic phenogroup, indicating substantial heterogeneity in treatment response. Although differences in clinical characteristics between phenogroups were often modest, they were statistically significant and may not be readily apparent during routine preimplantation assessment. In contrast, TDA effectively captured these subtle patterns, underscoring its clinical potential to uncover latent patient profiles.[1] However, selecting the optimal device is only the first step. Long-term postimplantation follow-up is essential to maintain favorable outcomes and detect clinical deterioration early. Our findings demonstrate that additional RTM is associated with significant reductions in both all-cause and CV mortality, underscoring its potential as an effective adjunct to contemporary HF care.[2] RTM emerges as a promising strategy to enhance clinical outcomes, optimize longitudinal patient surveillance, and potentially alleviate the burden of HF on the healthcare system when paired with standardized alert algorithms and predefined response pathways.[2]

11. Implication for practice

From a clinical perspective, the results support a more individualized approach to device-based treatment in HFrEF. The benefit of CRT-D should not be assumed universal, and device selection should consider not only conventional criteria but also age, HF etiology, arrhythmic substrate, and comorbidity burden. In addition, the findings highlight that RTM may improve outcomes when integrated into a structured clinical framework with clear responsibilities and timely therapeutic action. In everyday clinical practice, this means that optimal HFrEF care requires not only appropriate device implantation but also careful patient selection and well-organized long-term follow-up.[1-3]

12. Implication for research

The findings of this thesis highlight the need for an adequately powered RCT comparing CRT-D with CRT-P to clarify how contemporary medical therapy modifies the residual benefit of defibrillator therapy in the current FMT era and among a changing CRT population over time. Moreover, the findings may suggest that future research should focus more strongly on identifying clinically meaningful subgroups within the broader HFrEF population. In particular, prospective validation of phenogroup-based approaches is needed to determine whether advanced data-driven methods, such as TDA, can improve patient selection for CRT-D versus CRT-P in routine clinical practice. Further studies should also clarify how contemporary medical therapy modifies the residual benefit of defibrillator therapy and how RTM can be optimized using standardized alert algorithms and predefined response pathways.. Overall, future research should aim to integrate phenotyping, device-based treatment, and digital follow-up into a more precise, personalized model of HF care.

13. Implication for policy makers

At the health system level, these findings support a more selective, evidence-based use of advanced device therapies. Avoiding CRT-D implantation in patients with a low expected incremental benefit may reduce device-related complications and unnecessary healthcare burden. Current guidelines similarly emphasize individualized risk–benefit assessment when selecting between CRT-P and CRT-D.[50] The results also support investment in digital infrastructure and multidisciplinary follow-up pathways, as RTM is most effective when embedded within structured clinical workflows with clearly defined responsibilities and timely responses to alerts. [50, 103] From a policy perspective, wider implementation of precision-based HF management will therefore also depend on appropriate organizational support and reimbursement strategies.[151]

14. Future perspectives

Further work should focus on external and prospective validation of TDA-derived phenogroups and on translating these findings into clinically applicable decision-support tools. [153] [154] In parallel, integrating RTM data with predictive analytical models may enable earlier identification of patients at increased risk and support a shift from predominantly reactive follow-up to more proactive management. Harmonizing telemonitoring protocols across institutions will also be essential to achieving consistent clinical efficacy and acceptable cost-effectiveness in routine clinical practice.

Overall, combining phenotyping with structured digital follow-up may represent an important step toward personalized HF management. In such a model, therapy selection, longitudinal monitoring, and timely intervention would be interconnected elements of a continuous precision medicine pathway rather than separate components.[155]

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16.1. Publications Related to The Thesis

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17. Acknowledgements

I would like to express my sincere gratitude to my PhD supervisors, Prof. Béla Merkely and Dr. Annamária Kosztin, for their continuous support throughout this work. Their commitment to organizing the research and their ongoing professional guidance were essential to the completion of this thesis.

I am also deeply grateful to Dr. Márton Tokodi and Dr. Walter Schwertner for their methodological advice and valuable support with the machine learning analyses, which were crucial to this research.

I would like to thank Dr. Marie Engh for her support within the Center for Translational Medicine Program, and Péter Fehérvári for his support with the statistical work.

My sincere thanks also go to my colleagues, Dr. Richárd Masszi, Dr. Anett Behon, Dr. Eperke Pólos-Merkel, Dr. Luca Mervai-Kuthi, and Dr. Marianna Németh, for their longstanding support, encouragement, and friendship, which greatly contributed to the completion of this work.

I am especially grateful to Prof. Endre Zima, Dr. István Osztheimer, and Dr. Mihály Ruppert for their continued willingness to help with technical and methodological questions throughout my PhD work. I also thank them for their patience, support, and dedication in teaching me at the Pacemaker Operating Theatre and in helping me gain confidence in pacemaker and ICD implantation procedures.

Finally, I would like to express my deepest gratitude to my parents and my husband for their unwavering support over the years. Their patience, understanding, and encouragement were indispensable throughout the many challenges and sacrifices required to complete this work.