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NON-PHARMACOLOGICAL TREATMENT OF CHRONIC SYSTOLIC HEART FAILURE

OPTIMIZATION OF RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY FOR THE TREATMENT OF CHRONIC HEART FAILURE

PhD thesis

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List of Abbreviations

ACE-I - angiotensin-converting enzyme inhibitor
ARNI - angiotensin receptor-neprilysin inhibitor
AV - atrioventricular
BMI - body mass index
BNP - B-type natriuretic peptide
CABG - coronary artery bypass grafting
CI - confidence interval
CMR - cardiac magnetic resonance
CRT - cardiac resynchronization therapy
CTCA - computed tomography coronary angiography
CV - cardiovascular
ECG - electrocardiogram
eGFR - estimated glomerular filtration rate
HF - heart failure
HFmrEF - heart failure with mildly reduced ejection fraction
HFpEF - heart failure with preserved ejection fraction
HFrEF - heart failure with reduced ejection fraction
HR - hazard ratio
HTX - heart transplantation
ICD - implantable cardioverter defibrillator
IED - interlead electrical delay
IHD - ischemic heart disease
IPD - individual patient data
IQR - interquartile range
LBBB - left bundle branch block
LV - left ventricular
LVAD - left ventricular assist device
LVEF - left ventricular ejection fraction
LVEDD - left ventricular end-diastolic diameter
LVEDV - left ventricular end-diastolic volume
LVESD - left ventricular end-systolic diameter

LVESV - left ventricular end-systolic volume

MRA - mineralocorticoid receptor antagonist

NT-proBNP - N-terminal prohormone BNP

NICM - non-ischemic cardiomyopathy

NYHA - New York Heart Association

OMT - optimal medical therapy

PCI - percutaneous coronary intervention

PM - pacemaker

RCT - randomized controlled trial

RV - right ventricular

SCD - sudden cardiac death

SD - standard deviation

SGLT-2 - sodium-glucose co-transporter 2

SPECT - single-photon emission CT

SR – sinus rhythm

VAD - ventricular assist device

VV - ventriculoventricular

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1. Introduction

1.1. Prevalence and incidence of chronic systolic heart failure

Although better management of cardiovascular (CV) diseases decreases the age-adjusted incidence of heart failure (HF), the overall incidence is still increasing due to the ageing population (1, 2). In developed countries, the prevalence of HF rises dramatically with age, impacting approximately 1-2% of the adult population and up to 10% of those over 70 (1, 2). Based on studies in hospitalized HF patients, 50% have HF with reduced ejection fraction (HFrEF) and 50% have HF with preserved or mildly reduced ejection fraction (HFpEF or HFmrEF) (3, 4). The European Society of Cardiology Heart Failure Long-Term Registry reported in 2017 that 60% of HF patients in the outpatient care have HFrEF, 24% have HFmrEF, and 16% have HFpEF (5).

1.2. Diagnosis of heart failure

1.2.1. Signs and symptoms of heart failure

Heart failure is a complex clinical syndrome characterized by non-specific signs and common symptoms, such as fatigue, and ankle oedema and dyspnoea. Therefore, objective evidence of cardiac dysfunction is necessary for the diagnosis of HF (1).

1.2.2. Gold standard clinical tools to diagnose heart failure

The most useful diagnostic tool for the diagnosis of heart failure is echocardiography, which can easily assess cardiac function and provide information on chamber volumes, dimensions, and valvular function. Measurement of B-type natriuretic peptide (BNP) and N-terminal prohormone BNP (NT-proBNP) is recommended to rule out the diagnosis of HF in patients with suspected chronic HF since both peptides have a very similar and high negative predictive value (0.94–0.98) (1).

Additional diagnostic tools like 12-lead ECG can be used to reveal anomalies such as atrial fibrillation (AF), left ventricular hypertrophy, or a widened QRS complex, which increases the likelihood of HF diagnosis and can help determine appropriate therapy. Performing a chest X-ray, we can rule out other underlying conditions of dyspnoea (eg.

pulmonary diseases) and provide further evidence of HF, like cardiomegaly or pulmonary congestion (1).

Further investigations such as cardiac magnetic resonance (CMR), computed tomography coronary angiography (CTCA), and single-photon emission CT (SPECT) can be used to determine the underlying aetiology of HF (1).

1.3. Treatment of chronic systolic heart failure

1.3.1. Pharmacological treatment

Pharmacological treatment in patients with HFrEF aims to improve the patient's clinical status, functional capacity, and quality of life, prevent heart failure hospitalization, and reduce mortality. Drugs recommended in all patients with HFrEF with Class I indications for reducing mortality are angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRA), and the sodium-glucose co-transporter 2 (SGLT-2) inhibitors dapagliflozin or empagliflozin (1). Guideline-directed medical therapy has been shown to improve survival and reduce symptoms and hospitalization due to worsening HF in HFrEF patients. Uptitrating these disease-modifying drugs to the evidence-based doses or if not possible, to the maximally tolerated doses is essential as soon as possible (1, 6, 7).

When ACE-Is or ARNI are not tolerated or contraindicated, Angiotensin Receptor Blockers (ARBs) are used as alternative therapy options. In certain patients with symptoms (NYHA II-IVa) and reduced ejection fraction (LVEF≤40%), additional pharmacological treatments such as diuretics, ivabradine, soluble guanylate cyclase stimulator vericiguat, direct vasodilators, and digoxin can be added (1).

1.3.2. Non-pharmacological treatment: Implantable Cardioverter Defibrillator, Cardiac Resynchronization Therapy

1.3.2.1. Implantable Cardioverter Defibrillator

An alarmingly high percentage of deaths in HF patients happen suddenly and unexpectedly due to electrical disturbances, including ventricular arrhythmias,

bradycardia, and asystole. Although, analysing more than 40.000 patients from 12 HF trials, the percentage of sudden cardiac death (SCD) decreased from the mid-1990s to 2015 by 44%, due to advanced pharmacological and device therapy options, preventing SCD still remains essential in HF patients. The implantable cardioverter defibrillator (ICD) is the most effective therapy option to prevent SCD by terminating potentially lethal ventricular arrhythmias (1). Patients diagnosed with ischemic heart disease (IHD) have a greater risk of experiencing SCD compared to patients with non-ischemic cardiomyopathy (NICM) (8). Consequently, while the relative advantages are comparable, patients with IHD derive a greater absolute benefit (9). An ICD implantation is recommended in patients with symptomatic HF (NYHA class II-III) of an ischemic aetiology and reduced left ventricular ejection fraction (LVEF ≤35%) despite ≥ 3 months of optimal medical therapy (OMT), if the patient is expected to survive for more than 1 year with good functional status to reduce the risk of sudden death and all-cause mortality (1). A recent meta-analysis of trials evaluating the efficacy of ICD in NICM patients revealed a survival benefit even though the DANISH trial did not demonstrate a substantial benefit of ICD therapy in patients with NICM for all-cause mortality (8, 10). Therefore, in HFrEF patients with non-ischemic aetiology, an ICD should be taken into consideration to lower the risk of sudden death and all-cause mortality (1). ICD implantation is not recommended within 40 days of myocardial infarction or in patients in NYHA class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for cardiac resynchronization therapy (CRT), a ventricular assist device (VAD), or cardiac transplantation (1). Similarly, patients with severe comorbidities, who are not expected to survive more than one year with a good quality of life, are unlikely to experience significant advantages from an ICD (1).

For secondary prevention, ICD is recommended to reduce the risk of sudden cardiac death and all-cause mortality in cardiac arrest survivors and in patients who experienced sustained symptomatic ventricular arrhythmias, if the patient is expected to survive for more than 1 year after the implantation with good quality of life (1).

1.3.2.2. Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure (HF) symptoms, hospitalization events, and all-cause mortality in appropriately selected

patients with mild to severe symptoms and a prolonged QRS (10-18). Through the implantation of an additional left ventricular lead into a side branch of the coronary sinus or by a surgical or a transseptal approach directly to the left ventricle, it becomes possible to pace both ventricles simultaneously. This device therapy option resolves both the intra- and interventricular electromechanical delay and AV dyssynchrony when the patient is in sinus rhythm (SR) and an atrial lead is also implanted.

Understanding the cardiac venous system is essential to increase the rate of successful implantations. The coronary sinus collects deoxygenated blood from the left side of the heart through the epicardial veins (oblique vein, left marginal vein, anterior interventricular vein, and inferior interventricular vein). It is the most consistent part of the cardiac venous system. The great cardiac vein drains blood from the anterior part of the interventricular septum, the left atrium, and the anterior part of the ventricles. The middle cardiac vein gathers blood from the ventricular septum and the diaphragmatic portions of the ventricles. The small cardiac vein is reported to drain the inferior and lateral part of the right ventricle, while the left marginal vein is responsible for draining the lateral part of the left ventricle. (19)

1.4. Efficacy of cardiac resynchronization therapy

1.4.1. Mechanism of action

The rationale behind CRT is based on the observation that patients with HF and left ventricular (LV) systolic dysfunction often exhibit significant intraventricular conduction delays with a QRS duration > 120 ms in 25-50% of cases and the presence of left bundle branch block (LBBB) in 15-27% of cases (20). Additionally, these patients frequently experience atrioventricular (AV) dyssynchrony, as indicated by prolonged PR intervals on surface electrocardiograms (ECGs) in up to 52% of cases. These electrical abnormalities can lead to AV, inter-, and intraventricular mechanical dyssynchrony (20). Dyssynchrony occurs when different parts of the cardiac chambers contract in an uncoordinated manner due to issues with the conduction system (such as LBBB) or due to right ventricular (RV) pacing. Ventricular dyssynchrony mainly affects the left ventricle, leading to ineffective contraction and reduced cardiac output, ultimately resulting in heart failure. (21). Electrical remodeling of the failing heart involves

lengthening of action potential duration and slower conduction velocity. These changes impact ion channels, proteins responsible for calcium handling, and intercellular gap junctions on the cellular and molecular levels (22). The main mechanism of action of CRT alters the electrical activation of the heart by simultaneously pacing the latest activated part of the left ventricle with the right ventricle. Besides ventricular resynchronization, CRT devices with atrial electrodes allow the opportunity to adjust AV delay and thus improve LV preload, which has been proven to have a powerful acute haemodynamic effect through which CRT may improve LV function (23). These electromechanical and haemodynamic effects increase stroke volume while decreasing potential mitral regurgitation, and pulmonary wedge pressure, and narrowing the QRS width. Through these mechanisms, reverse remodeling results in reduced morbidity, mortality, and hospitalization for worsening HF.

1.4.2. Current indications

Based on multiple randomized controlled trials, CRT improves functional capacity and quality of life, and reduces symptoms, HF hospitalization, and all-cause mortality in symptomatic patients (NYHA II-IVa) in SR with a QRS width $\geq$ 150 ms, LBBB morphology, and LVEF $\leq$ 35%. In these HF patients, CRT implantation is recommended with class I indication with level of evidence A. CRT is also recommended with class I indication with level of evidence A in patients with HFrEF (LVEF <40%) regardless of their NYHA functional status, QRS duration or rhythm, if they have an indication for ventricular pacing for high degree AV block to reduce morbidity (1).

In patients in SR with non-LBBB morphology and a QRS duration $\geq$ 150 ms or an LBBB morphology with QRS width 130-149 ms and with LVEF $\leq$ 35% despite OMT, CRT implantations should be considered as a class IIa indication with level of evidence B. Upgrade to CRT should also be considered in patients with an LVEF $\leq$ 35%, who have a conventional pacemaker or ICD, with a significant RV pacing rate and develop worsening HF despite OMT (1).

In patients in SR with non-LBBB morphology and a QRS duration 130-149 ms, CRT may be considered as a class IIb indication with level of evidence B. CRT is not recommended in patients with a QRS width < 130 ms (1).

1.4.3. Assessing response to CRT: definition of responder patients

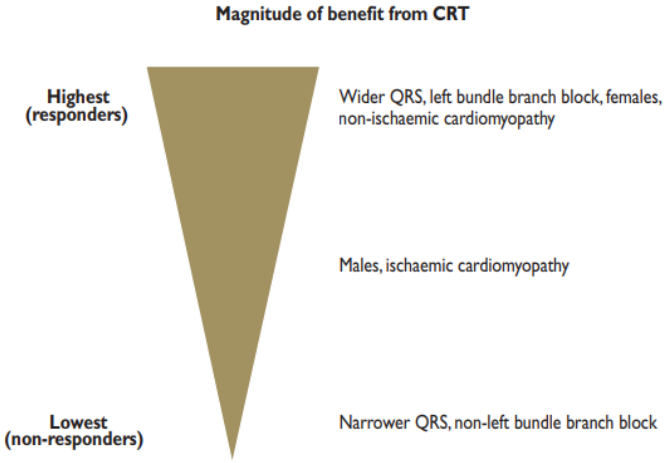
The definition of CRT response and thus the response rate varies significantly (24). Most frequently, two definitions are used in clinical trials: echocardiographic and functional response. Echocardiographic parameters, such as LVEF and left ventricular dimensions, are associated with the clinical outcomes and thus can be surrogate endpoints of response. The timing of patient evaluation after CRT implantation is crucial. Evaluating too soon may underestimate the degree of reverse remodeling. Most of the studies used a period between 2 and 12 months for follow-up echocardiography. It's worth noting that after 1 year, often minimal to no further reverse remodeling can be expected in most patients. Most frequently, echocardiographic response is defined as a reduction in left ventricular end-systolic volume (LVESV) ≥ 15% or an improvement in LVEF ≥ 5%. Functional response can be defined as an improvement in NYHA class, quality of life questionnaires or 6-minute walk test, assessed at 6-12 months after the implantation. Traditionally, patients were classified as super-responders (≥ 30% LVESV decrease or ≥ 20% LVEF improvement), responders (15-30% LVESV decrease or 6-19% LVEF improvement) and non-responders (< 15% LVESV decrease or ≤ 5% LVEF improvement) (24). Based on this classification, approximately 30-40% of CRT patients fail to show clinical benefit or reverse remodeling and are considered non-responders (25, 26).

However, the criteria by response have been changing recently. Patients whose LVEF remained stable and did not show further progression after the implantation, are defined as "non-progressors" rather than "non-responders". This distinction helps selecting non-progressor patients from those in whom the progression could not be modified. Until recently, the concept of the non-progressor phenotype was only a hypothesis, suggesting that CRT stops the natural course of the disease in these individuals, providing an unrecognized benefit (27, 28). However, three recently published studies have indicated that non-progressor patients show better mid-term outcomes compared to those who continue to decline. Despite these findings, information on the difference between the long-term outcomes of these two patient populations and the extended duration of the blunting effect in non-progressors remained limited (29-31).

The high number of non-responders still shows the challenge of non-response to CRT and highlights the importance of careful patient selection, optimal device implantation, and device programming (Figure 1) (1).

Figure 1. Clinical factors influencing the likelihood to respond to CRT (32)

Sub-analyses from randomized controlled trials suggest that the magnitude of benefit from cardiac resynchronization therapy (CRT) is greater in patients who are female, have a non-ischemic cardiomyopathy and a QRS duration > 150 ms.



1.4.3.1. Optimal patient selection

1.4.3.1.1 QRS duration and morphology

Optimal patient selection is essential to achieve the best possible response after CRT implantation. Baseline QRS duration and morphology are two important prognostic factors of long-term outcome (20). QRS duration can predict CRT response and was part of the inclusion criteria in all of the big randomized controlled trials (RCTs) (1, 33). Early recommendations were based on the inclusion criteria of two basic CRT randomized trials, the COMPANION and CARE-HF studies, which used the inclusion criterion QRS > 120 ms (10, 11). Even though 130 and 150 ms were also used in some trials (MIRACLE ICD and MUSTIC trial), the milestone trial that changed the guideline was the MADIT-CRT trial (12, 34, 35). MADIT-CRT confirmed that even patients with mild symptoms benefit from CRT with a QRS width > 150 ms. Implantation under 130 ms was found to be possibly harmful in the Echo-CRT study and an individual patient data (IPD) meta-

analysis, therefore implantation is not recommended in patients with a QRS width < 130 ms (18, 36, 37).

Besides QRS duration, morphology has also been shown to be one of the most important parameters. Several prior studies proved that patients with LBBB morphology are more likely to have a beneficial response to CRT. The remodeling effect of CRT, as evaluated by echocardiography, was shown to be significantly higher in LBBB patients than in non-LBBB patients in the MADIT-CRT trial.(38). LBBB patients showed a significantly higher reduction in both LVESV (35% vs. 25%) and LVEDV (23% vs. 16%) than non-LBBB patients ($p<0.001$ for both comparisons). LVEF also increased significantly higher in the LBBB group compared to the non-LBBB group (12% vs. 9%, $p<0.001$). However, a significant reduction in LV volumes and an increase in LVEF was observed in non-LBBB patients despite the lack of clinical benefit based on cardiac endpoints (38). Therefore, such patients are included in the latest ESC guideline, but with a weaker strength of recommendation (1).

1.4.3.1.2 Left ventricular ejection fraction

LVEF is one of the key parameters to determine whether a patient is eligible for CRT implantation. Since its baseline value and improvement after the implantation correlate with the clinical outcome, it serves as a surrogate endpoint in HFrEF patients (39). While the first large RCTs (MIRACLE-ICD, COMPANION, and CARE-HF) included patients with an LVEF ≤ 35%, RAFT and MADIT-CRT specified an LVEF ≤ 30%, REVERSE included patients with an LVEF ≤ 40% and BLOCK-HF ≤ 50% (10-13, 17, 34, 40). Based on the findings of these earlier trials, the current ESC recommendation advises CRT for patients with an LVEF ≤ 35% (1). Although relatively few patients were randomized in these large RCTs with an LVEF 35-40%, an early IPD meta-analysis found that patients with an LVEF > 35% derived similar benefits from CRT compared to those who had a lower LVEF (33).

1.4.3.1.3 Symptoms

CRT implantation is recommended for symptomatic (NYHA II-IVa) HF patients. Early RCTs showed the benefit of CRT in patients with severe symptoms (NYHA III-IV), while later on MADIT-CRT, REVERSE, and RAFT trials found comparable favourable outcomes in mildly symptomatic patients (10-13, 17, 34, 40). However, in the MADIT-

CRT and REVERSE trials, only a relatively low percentage of the included patients were asymptomatic (18% and 15%, respectively). Subgroup analyses of both trials verified that in this NYHA I class patient population, CRT did not lower hospitalization for HF or all-cause death.(12, 17).

1.4.3.1.4. Additional predictors of response

Since myocardial scar tissue is less likely to undergo favourable remodeling, patients with an ischaemic etiology experience less improvement in LV function. Due to the smaller body and heart size, women may be more likely to respond favourable to CRT compared to men (1, 41).

Within a few years of pacemaker (PM) or ICD implantation, about 30% of patients experience LV systolic dysfunction as a result of intraventricular dyssynchrony brought on by RV pacing. This may result in various unfavorable clinical outcomes as well as a comparatively high rate of hospitalizations for HF. Given the similarities between intrinsic LBBB and RV pacing-induced dyssynchrony, individuals experiencing severe RV pacing and left ventricular failure are more likely to experience subsequent LV remodeling and other unfortunate consequences. According to current European guidelines CRT upgrade for patients with a high RV pacing burden is recommended as a Class IIa indication (20). However, the 2023 guidelines from the Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society recommend biventricular pacing with a Class I level B for patients who are symptomatic and have a high burden of RV pacing and impaired LV function (42).

1.4.3.2. Device implantation

1.4.3.2.1. Right ventricular lead position

In HFrEF patients with pacemakers, a meta-analysis of RCTs revealed that a non-apical (septal or right ventricular outflow tract) lead position preserves the LV function more effectively compared to an apical position (43). However, a post hoc analysis of the REVERSE trial found no significant difference in CRT patients between apical and septal right ventricular (RV) positions regarding LV reverse remodeling and the composite of time to death or first HF hospitalization (44). These results were also confirmed by the

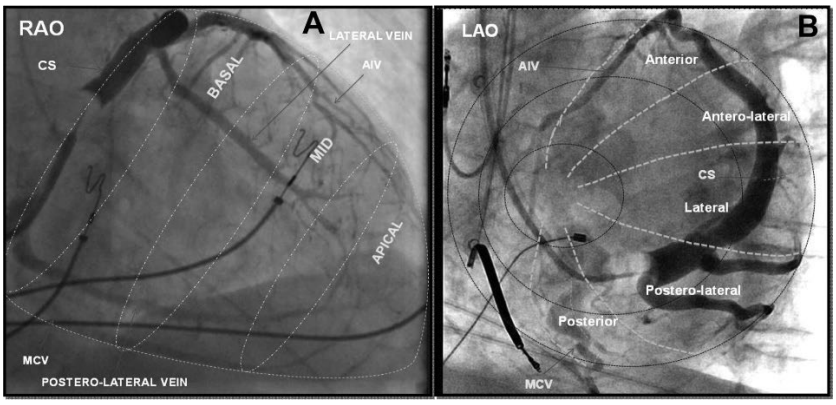
randomized, multicentre SEPTAL CRT trial, which was designed to compare apical and septal RV lead positions regarding LV remodeling (45).

1.4.3.2.2. Left ventricular lead position and interlead electrical delay

LV lead position has also been proposed to play a significant role in the response to CRT (Figure 2) (20). In the MADIT-CRT trial, the mid-term analysis with a follow-up time of 29±11 months found that apical position was associated with a significantly increased risk for HF or death and for death alone. However, in the mid-term analysis, benefit derived from CRT implantation was comparable for anterior, lateral and posterior locations (46). Contrarily, compared to patients with an ICD alone, patients with a lateral or posterior LV lead location had a better long-term outcome regarding the composite endpoint of HF or death from any cause and in all-cause mortality alone in the long-term analysis, which had a median follow-up time of 5.6 years. In the meantime, an anterior LV lead position was associated with a significantly decreased risk of the composite outcome, although not in terms of death from any cause (47).

Figure 2. Angiographic classification of left ventricular lead position (46)

Angiographic classification of left ventricular lead position. The right anterior oblique (RAO) view represents the long axis of the heart and enables segmentation into basal, midventricular (MID), and apical segments. The left antrerior oblique (LAO) view represents the short axis of the heart and enables segmentation into anterior, anterolateral, lateral, posterolateral, and posterior.
AIV, anterior interventricular vein; CS, coronary sinus; MCV, middle cardiac vein



Moreover, previous smaller studies have suggested that the time interval between the left and right ventricular leads' electrical signals can predict clinical outcomes and echocardiographic improvement. In addition to showing the locations of the ventricular

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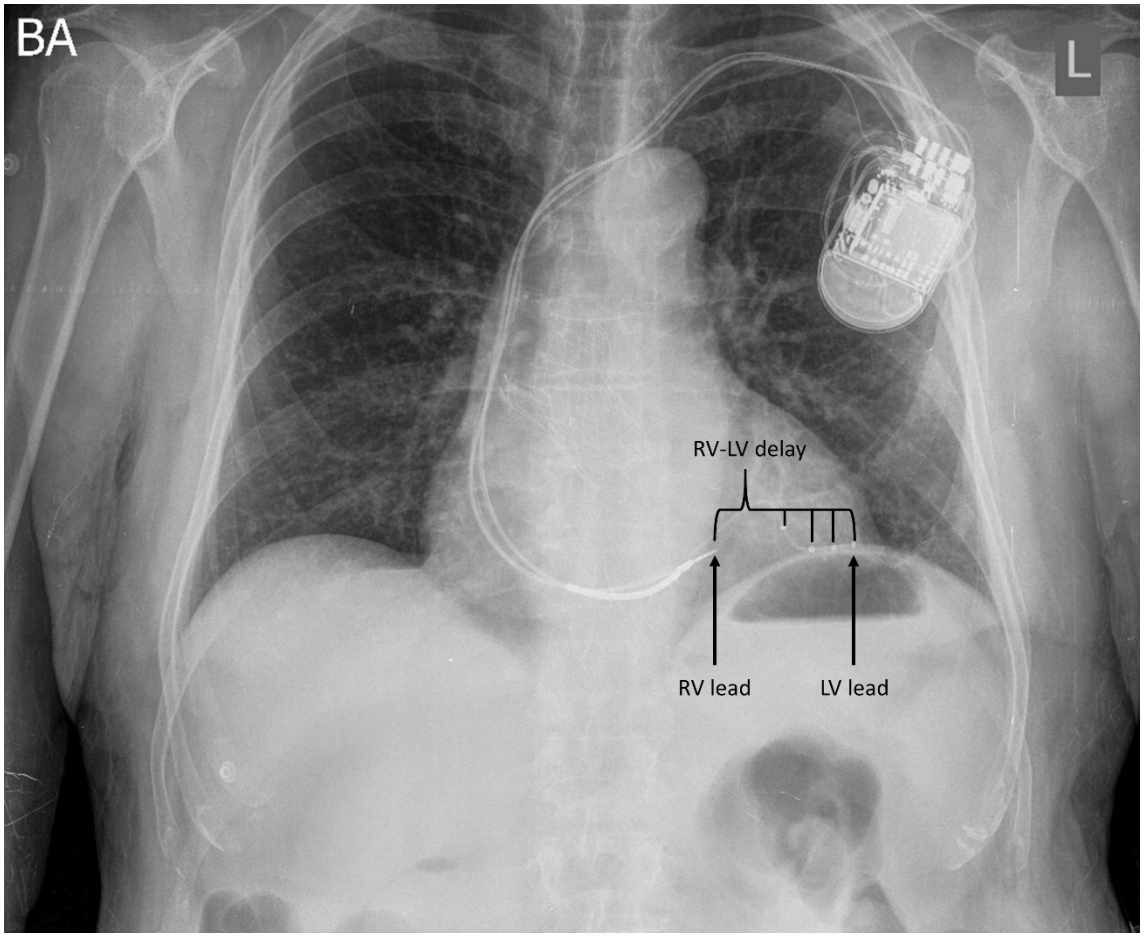
leads, interlead electrical delay (IED) also reflects electrical dyssynchrony and prolonged activation patterns resulting from slow conduction mainly due to scar tissue (Figure 3) (48-56). IED is substantially correlated with response to CRT and we can easily measure it as the LV lead is being placed (50). However, no prior research examined the combined long-term effects of a lateral left ventricular lead position and a longer interlead electrical delay in parallel.

Figure 3. X-ray of a cardiac resynchronization therapy system showing lead positioning and RV-LV delay

X-ray of a cardiac resynchronization therapy system showing the positions of the right ventricular (RV) and left ventricular (LV) lead. The duration between the electrical signals of the RV and LV lead (RV-LV delay) not only indicates the positions of the ventricular leads but also reflects electrical dyssynchrony and prolonged activation patterns resulting from slow conduction.



Using quadripolar LV leads can help to optimize pacing location when only a suboptimal coronary sinus side branch can be found or to avoid the stimulation of the phrenic nerve.

Previous studies found that quadripolar lead implantation and pacing optimization resulted in better improvement compared to bipolar stimulation (57-59). Quadripolar LV leads allow us to program the longest IED possible. The fact that all companies are producing quadripolar electrodes demonstrates the relevance of the topic.

1.4.3.3. Device programming

1.4.3.3.1. AV and VV delay

Observational studies have revealed that improper programming of AV-VV delays is a significant factor contributing to a suboptimal response to CRT (60). Doppler echocardiography has traditionally been the preferred method for optimizing AV and VV intervals, but recent large-scale trials have indicated that this time-consuming approach is often ineffective. Instead, empirical programming of a sensed AV delay of 100-120 ms along with simultaneous biventricular (BiV) stimulation has shown better results (61, 62).

The routine use of echocardiographic optimization, as recommended by guidelines, has been questioned due to its limited effectiveness in certain cases (32). The guidelines suggest initially setting a fixed AV delay of 100-120 ms without specifying a VV interval for all CRT recipients (32). However, in specific patient subgroups, especially in those with a prolonged interatrial delay, interval optimization may be necessary post-implantation (32). The need for further echocardiographic assessments and optimizations is emphasized, particularly in cases where there is no response to CRT (1).

1.4.3.3.2. Remote monitoring

Numerous large RCTs across different countries, exploring various types of devices such as pacemakers, ICDs, and CRT-Ds, have consistently demonstrated that replacing standard ambulatory visits with remote monitoring (RM) effectively reduces the frequency of follow-up appointments (63). Additionally, RM makes it possible to recognize actionable events early (63). However, until recently, no research had shown that using RM to manage cardiovascular events would significantly lower the risk of death or hospitalization. (63).

The In-TIME trial marks a milestone as the first RCT focusing on the impact of RM in recipients of CRT-D or dual-chamber ICD (64). After a year, the rate of worsening clinical composite score and death from any cause related to RM had significantly

decreased, according to the results. This implies that RM may be able to prevent non-response to CRT by enhancing clinical outcomes in this high-risk group (64). Close monitoring of variables such as the percentage of biventricular (BiV) stimulation, AF episodes, and frequent ventricular extrasystoles (VES) is made possible by RM, which offers insightful information that may impact the efficacy of CRT. (1).

In light of these observations, it is supported that offering RM to all recipients of CRT systems should be integrated into their routine follow-up, as it enables comprehensive monitoring and contributes to improved patient outcomes (1).

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2. Objectives

Our aim was to investigate important parameters in patient selection (age), implantation (LV lead position and IED), and long-term outcome with the reclassification of response.

In order to optimize patient selection, we aimed to assess whether age may negatively affect the CRT response in this elder and ever-growing population of CRT candidates. We evaluated the age-related differences in the effectiveness of CRT, peri- and postprocedural complications, and long-term outcomes after the implantation to measure the risk-benefit ratio in the elderly as well.

Moreover, we examined the impact of implantation parameters, such as LV lead position and IED. Our hypothesis was that non-lateral LV lead locations are associated with worse clinical outcomes, which supports the everyday empirical clinical practice, preferring the lateral side branch during LV lead implantation. Therefore, we aimed to investigate the range of IED lengths by LV lead non-apical locations to evaluate the long-term clinical outcome accordingly and further characterize the mid-term echocardiographic response by IED.

We also focused on the question of reclassification of response to CRT. We used the recently changed criteria by response to evaluate the long-term outcome of CRT patients by their echocardiographic response. We aimed to sort out those with unchanged parameters to compare them with those in whom the progression could not be modified. We hypothesized that non-progressors and progressors need different treatment strategies as they have a different outcome.

3. Methods

For better interpretation, we show our Methods and Results separately by the investigated parameters. In Part 1, data on our study of age differences are shown. In Part 2, we present our study of LV lead position and IED. While in Part 3, the question of reclassification of CRT response is shown.

3.1. Patient population

Between October 2000 and September 2020, patients who underwent successful CRT implantation following current guidelines at the Heart and Vascular Center, Semmelweis University in Budapest, Hungary, were retrospectively registered in our *Biobankok* database (32, 65-67). The registry contained patients with symptomatic chronic systolic HF (NYHA II-IVa), reduced LVEF (EF ≤ 35%), and a prolonged QRS (QRS ≥ 130ms). Baseline clinical characteristics, including demographic information, medical history, physical condition, prescribed medications, as well as ECG-, echocardiographic-, and laboratory parameters, were gathered from the medical record system at the time of the implantation and up to 12 months (68, 69).

3.1.1. Patients of Part 1

In Part 1, we included all of our patients, who were registered in our *Biobankok* database. To investigate the association between age and the effectiveness of CRT, peri- and postprocedural complications, and long-term outcome, we divided our patients into 3 groups according to their age at the time of the implantation: Group I: < 65, Group II: 65-75, and Group III: > 75 years as defined in previous studies (68, 70, 71).

3.1.2. Patients of Part 2

In part 2, we excluded patients with the need of transseptal or epicardial LV lead implantation and those who had no available data about the LV lead position. The final LV lead location was analysed by an expert cardiologist and was determined by where the tip of the lead was located, using the nomenclature of anterior, antero-lateral, lateral, postero-lateral, and posterior positions based on MADIT-CRT trial (46). During classifying LV lead positions, three categories were established: anterior, lateral, and posterior. Due to the low number of patients with true anterior and true posterior

locations, in the case of anterolateral positions, patients were grouped to anterior, while posterolateral to posterior positions, respectively. Consequently, true lateral positions were maintained as a distinct category without being combined with any other locations (69).

3.1.3. Patients of Part 3

In Part 3, we excluded patients with no available data about their baseline and/or post-implantation LVEF within 12 months. To assess the correlation between the response to CRT and long-term outcomes, patients were categorized into 4 groups based on their response status. This classification was determined by analysing the change in LVEF up to 12 months following CRT implantation, resulting in the following groups: Group I: super-responders ≥ 20%, Group II: 6-19%, Group III: 0-5%, and Group IV: < 0% (31).

3.2. Device implantation

3.2.1. Device implantation procedure

Implantations of devices were performed according to current standards and were carried out using either a transvenous approach or a transseptal method. During implantation, the placement of LV leads was customized through the use of a coronary sinus venogram during fluoroscopy (68, 69).

3.2.2. Left ventricular lead position

When positioning the RV lead, a septal location, during LV lead implantation, lateral or posterior positions were preferred. The assessment of LV and RV lead positions were conducted through antero-posterior (AP), right anterior oblique (RAO), and left anterior oblique (LAO) views, with the implanting physician providing the reported details. In cases where there was phrenic nerve stimulation or proximity to an apical position, LV leads were secured in a more proximal part through stent implantation. Once the leads were successfully positioned, electrical parameters, including pacing, sensing, and impedance values, were measured and recorded in the *Biobankok* database (69).

3.2.3. Interlead electrical delay

Intraoperative IED measurements were carried out following the placement of both ventricular leads. IED was quantified by determining the time delay between the peak activations of the right and left ventricular sensed signals, expressed in milliseconds (RV sensed - LV sensed IED). In pacemaker-dependent patients, measurements were taken during right ventricular pacing (RV paced – LV sensed IED). In cases when the implanted device was capable of automatic IED measurement, the longest recorded value was set and documented (69).

3.3. Follow-up

The status of our patients was updated in September 2019 for Part 2, and in December 2021 for Part 1 and 3 from the National Health Insurance of Hungary Database, which provided us the precise date of death. The study protocol complies with the Declaration of Helsinki and the protocol was approved by the Medical Research Council; ETT-TUKEB No. 161-0/2019 (68, 69).

3.4. Endpoints

3.4.1. Endpoints of Part 1

The primary endpoint was echocardiographic CRT response. The improvement in LVEF was measured as a continuous variable. Reverse remodeling was defined as a relative increase of LVEF ≥ 15% within 6 months after the implantation (68).

Secondary composite endpoint was all-cause mortality or heart transplantation (HTX) or implantation of a left ventricular assist device (LVAD) during long-term follow-up categorized by age groups (68).

Tertiary endpoints were peri- and postprocedural complications in the three age groups. We also assessed time-trend effects on age, device types, and response rate (68).

3.4.2. Endpoints of Part 2

The primary endpoint was the composite of all-cause mortality or HTX or a LVAD implantation during long-term follow-up investigated by lead locations as a categorical variable (69).

Those patients who were found to have the most beneficial LV lead position were further investigated by IED length as a continuous variable. After ROC analysis the optimal cut-off value of IED was evaluated and its association with the greatest echocardiographic response was also investigated by logistic regression. We also assessed echocardiographic response as a continuous variable. Reverse remodeling was defined as a relative increase of LVEF ≥ 15% within 6 months after the implantation (69).

3.4.3. Endpoints of Part 3

The primary composite endpoint was all-cause mortality, HTX, or LVAD implantation.

3.5. Statistical analysis

Continuous variables with a parametric distribution are expressed as the mean and standard deviation (SD), while those with non-parametric distributions are shown as medians with an interquartile range (IQR). Categorical variables are presented as numbers and percentages (n, %). Baseline clinical characteristics were compared by unpaired t-test for normally distributed continuous variables. For not normally distributed continuous variables the Mann–Whitney test was used. Comparisons between three or more groups of patients were performed using one-way ANOVA test or Kruskal-Wallis test for normally and not normally distributed continuous variables, respectively. For dichotomous variables $\chi 2$ - test or Fisher exact test was used, as appropriate (68, 69).

Survival after device implantation was shown using Kaplan-Meier curves using the log-rank test. Unadjusted hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated in Cox proportional hazards. Adjusted HRs were calculated in Cox proportional model after adjustment for relevant clinical parameters. A two-sided p-value of < 0.05 was considered statistically significant (68, 69).

We modelled age as a continuous variable to better characterize the shape of the association of higher age with all-cause mortality using proportional hazards regression

restricted cubic spline models with knots located at each age value. ROC curves were used to identify the optimal IED cut-off value to reach the greatest echocardiographic response (69).

All statistical analyses were performed using Graph Pad Prism version 8.0 (Graph Pad Inc., CA, USA) and the SPSS v21 software (IBM, NY, USA) (68, 69).

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4. Results

4.1. Part 1 - Long-term outcome of cardiac resynchronization therapy patients in the elderly

4.1.1. Baseline clinical characteristics

A total of 2656 patients underwent successful CRT implantation and were included in the current analysis. Our patient cohort was categorized into three age groups: Group I: 1028 (39%) patients [median age 59, (IQR 53/62) years], Group II: 1004 (38%) patients [median age 70 (IQR 68/72) years], and Group III: 624 (23%) patients [median age 79 (IQR 77/82) years] (Table 1). Most patients in each age group were male (Group I: 78% vs. Group II: 74% vs. Group III: 72%), approximately 75% in the total cohort. However, the percentage of women patients increased significantly with age (Group I: 22% vs. Group II: 26% vs. Group III: 28%; $p<0.01$) (68).

Older participants more frequently had ischemic aetiology (Group III: 58% vs. Group II: 52% vs. Group I: 40%; $p<0.01$), higher systolic blood pressure [Group III: median 130 (IQR 115/143) Hgmm vs. Group II: median 125 (IQR 111/136) Hgmm vs. Group I: median 120 (IQR 111/133) Hgmm; $p<0.01$], and lower body mass index (BMI) [Group III: median 26.8 (IQR 24.2/29.4) kg/m^2 vs. Group II: median 27.7 (IQR 24.7/31) kg/m^2 vs. Group I: median 27.8 (IQR 24.8/31.4) kg/m^2; $p<0.01$] and were more likely implanted with a CRT-P (Group III: 56% vs. Group II: 44% vs. Group I: 40%; $p<0.01$) (Table 1.) (68).

Laboratory parameters showed that older patients had higher serum creatinine levels [Group III: median 110 (IQR 87/140) µmol/l vs. Group II: median 103 (IQR 84/133) µmol/l vs. Group I: median 93 (IQR 78/120) µmol/l; $p<0.01$], lower estimated glomerular filtration rate (eGFR) [Group III: median 56.8 (IQR 41.9/72.2) ml/min/1.73m^2 vs. Group II: median 61.3 (IQR 45.7/76.5) ml/min/1.73m^2 vs. Group I: median 71.2 (IQR 54.6/88.2) ml/min/1.73m^2 ; $p<0.01$], lower cholesterol levels (Group III: median 3.9 mmol/l vs. Group II: median 4.2 mmol/l vs. Group I: median 4.3 mmol/l; $p<0.01$), and comparable serum urea levels [Group III: median 397 (IQR 304/478) µmol/l vs. Group II: median 407 (IQR 320/480) µmol/l vs. Group I: median 399 (IQR 330/495) µmol/l; $p=0.32$] (Table 1) (68).

Age-related differences could also be observed regarding echocardiographic parameters. Older patients had higher LVEF [Group III: median 30 (IQR 25/35) % vs. Group II: median 29 (IQR 25/33) % vs. Group I: median 27 (IQR 22/32) %; p<0.01] with lower left ventricular end-diastolic (LVEDV) [Group III: median 187 (IQR 142/245) ml. vs. Group II: median 210 (IQR 157/262) ml vs. Group I: median 236 (IQR 187/305) ml; p<0.01] and end-systolic volume (LVESV) [Group III: median 129 (IQR 103/178) ml vs. Group II: median 153 (IQR 119/201) ml vs. Group I: median 177 (IQR 131/227) ml; p<0.01], and lower left ventricular end-diastolic (LVEDD) [Group III: median 61 (IQR 55/66) mm vs. Group II: median 63 (IQR 57/69) mm vs. Group I: median 66 (IQR 60/73) mm; p<0.01], and end-systolic diameter (LVESD) [Group III: median 50 (IQR 43/56) mm vs. Group II: median 53 (IQR 46/60) mm vs. Group I: median 56 (IQR 49/63) mm; p<0.01] (Table 1) (68).

As regards comorbidities, older patients were more likely to have atrial fibrillation (Group III: 45% vs. Group II: 41% vs. Group I: 31%; p<0.01), diabetes mellitus (Group III: 35% vs. Group II: 40% vs. Group I: 34%; p=0.01), hypertension (Group III: 79% vs. Group II: 76% vs. Group I: 64%; p<0.01), prior myocardial infarction (Group III: 43% vs. Group II: 40% vs. Group I: 33%; p<0.01), percutaneous coronary intervention (PCI) (Group III: 37% vs. Group II: 32% vs. Group I: 23%; p<0.01), and coronary artery bypass grafting (CABG) (Group III:16% vs. Group II: 14% vs. Group I: 11%; p<0.01) (Table 1) (68).

Regarding medical therapy, each subgroup received optimal heart failure basic treatment at high rate, while older patients were more likely to be treated with loop diuretics (Group III: 76% vs. Group II: 74% vs. Group I: 69; p<0.01), amiodarone (Group III: 21% vs. Group II: 27% vs. Group I: 24%; p=0.02), and oral anticoagulant therapy (Group III: 34% vs. Group II: 33% vs. Group I: 28%; p=0.03), and less likely with digoxin (Group III: 14% vs. Group II:18% vs. Group I: 21%; p<0.001) (Table 1) (68).

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Table 1. Baseline clinical characteristics of patients by age (68)

Baseline variables	**All patients (n=2656)**	**<65 years old (n=1028)**	**65-75 years old (n=1004)**	**>75 years old (n=624)**	**p value**
Age (yrs; median/IQR)	68 (61-75)	59 (53-62)	70 (68-72)	79 (77-82)	<0.01
Gender (female; n; %)	667 (25%)	224 (22%)	266 (26%)	177 (28%)	<0.01
NYHA III/IV (st; n; %)	1237 (46%)	490 (48%)	469 (47%)	277 (44%)	0.43
Ischemic aetiology (n; %)	1296 (49%)	415 (40%)	520 (52%)	361 (58%)	<0.01
CRT-D (n; %)	1452 (55%)	614 (60%)	563 (56%)	275 (44%)	<0.01
RR systolic (mmHg; median/IQR)	125 (111-138)	120 (111-133)	125 (111-136)	130 (115-143)	<0.01
RR diastolic (mmHg; median/IQR)	73 (65-80)	74 (68-81)	72 (64-80)	72 (65-80)	0.03
BMI (kg/m^2; median/IQR)	27.4 (24.6-30.8)	27.8 (24.8-31.4)	27.7 (24.7-31)	26.8 (24.2-29.4)	<0.01
QRS (ms; median/IQR)	160 (140-180)	160 (140-175)	160 (146-180)	160 (144-178)	0.19
LBBB morphology (n; %)	1838 (69%)	734 (71%)	673 (67%)	431 (69%)	0.10
Medical history					
Atrial Fibrillation (n; %)	1014 (38%)	318 (31%)	415 (41%)	281 (45%)	<0.01
Diabetes mellitus (n; %)	964 (36%)	346 (34%)	399 (40%)	219 (35%)	0.01
Type 2 DM (n; %)	782 (29%)	282 (27%)	326 (32%)	174 (28%)	0.03
Hypertension (n; %)	1916 (72%)	655 (64%)	764 (76%)	497 (79%)	<0.01
Prior MI (n; %)	1009 (38%)	337 (33%)	400 (40%)	272 (43%)	<0.01
Prior PCI (n; %)	786 (29%)	235 (23%)	319 (32%)	232 (37%)	<0.01

Prior CABG (n; %)	354 (13%)	109 (11%)	142 (14%)	103 (16%)	<0.01
Prior COPD (n; %)	393 (15%)	144 (14%)	162 (16%)	87 (14%)	0.32
Laboratory parameters					
Serum urea (µmol/l; median/IQR)	403 (321-489)	399 (330-495)	407 (320-480)	397 (304-478)	0.32
Serum creatinine (µmol/l; median/IQR)	101 (82-130)	93 (78-120)	103 (84-133)	110 (87-140)	<0.01
Serum cholesterol (mmol/l; median/IQR)	4.1 (3.4-5.1)	4.3 (3.4-5.4)	4.2 (3.5-5.0)	3.9 (3.1-4.7)	<0.01
eGFR (ml/min/1.73m^2; median/IQR)	63.7 (47.7-80.7)	71.2 (54.6-88.2)	61.3 (45.7-76.5)	56.8 (41.9-72.2)	<0.01
NT-proBNP (pmol/l; median/IQR)	2748 (1454-4146)	2587 (1367-3810)	2517 (1444-3550)	3000 (1690-4714)	0.03
Echocardiographic parameters					
LVEF (%; median/IQR))	28 (24-33)	27 (22-32)	29 (25-33)	30 (25-35)	<0.01
LVEDV (ml; median/IQR)	216 (166-280)	236 (187-305)	210 (157-262)	187 (142-245)	<0.01
LVESV (ml; median/IQR)	160 (118-210)	177 (131-227)	153 (119-201)	129 (103-178)	<0.01
LVEDD (mm; median/IQR)	63 (57-70)	66 (60-73)	63 (57-69)	61 (55-66)	<0.01
LVESD (mm; median/IQR)	53 (47-60)	56 (49-63)	53 (46-60)	50 (43-56)	<0.01
Medical treatment					
Beta blocker (n;%)	2161 (81%)	831 (81%)	819 (81%)	511 (82%)	0.83
ACE-I/ARB (n;%)	2233 (84%)	847 (82%)	858 (85%)	528 (85%)	0.15
MRA (n;%)	1652 (62%)	662 (64%)	621 (62%)	369 (59%)	0.10
Furosemid (n;%)	1927 (72%)	709 (69%)	742 (74%)	476 (76%)	<0.01

Digoxin (n; %)	491 (18%)	220 (21%)	186 (18%)	85 (14%)	<0.01
Amiodarone (n;%)	656 (25%)	250 (24%)	274 (27%)	132 (21%)	0.02
Oral anticoagulant therapy (n;%)	838 (31%)	293 (28%)	329 (33%)	215 (34%)	0.03

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker, BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-Terminal pro-B-Type Natriuretic Peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention

4.1.2. Primary endpoint - Echocardiographic response by age groups

After the implantation LVEF showed a significant improvement in the total cohort [median 28 (IQR 24/33) % at baseline vs. median 35 (IQR 28/40) % at 6 months; p<0.01] as well as in each age group [Group I: median 27 (IQR 22/32) % vs. median 34 (IQR 28/40) %; p<0.01; Group II: median 29 (IQR 25/33) % vs. median 35 (IQR 29/40) %; p<0.01; Group III: median 30 (IQR 25/35) % vs. median 35 (IQR 29/43) %; p<0.01] (Table 2A). The rate of responders was comparable among the three subgroups, 64% in Group I, 61% in Group II, and 56% in Group III (p=0.41) (Table 2B) (68). Evaluating reverse remodeling regarding the type of the implanted device, the rate of responders remained comparable both in the CRT-D (Group I: 63% vs. Group II: 59% vs. Group III: 60%; p=0.27) and CRT-P group (Group I: 65% vs. Group II: 64% vs. Group III: 51%; p=0.66).

Table 2A. Echocardiographic response divided by age groups (68)

	<65 years old	65-75 years old	>75 years old
Baseline LVEF (%; median/IQR)	27 (22-32)	29 (25-33)	30 (25-35)
6 months LVEF (%; median/IQR)	34 (28-40)	35 (29-40)	35 (29-43)
p-value	<0.01	<0.01	<0.01

LVEF, left ventricular ejection fraction

Table 2B. Reverse remodeling divided by age groups (68)

	<65 years old n=201	65-75 years old n=195	>75 years old n=114	p-value
Reverse remodeling*	128 (64%)	120 (61%)	64 (56%)	0.41

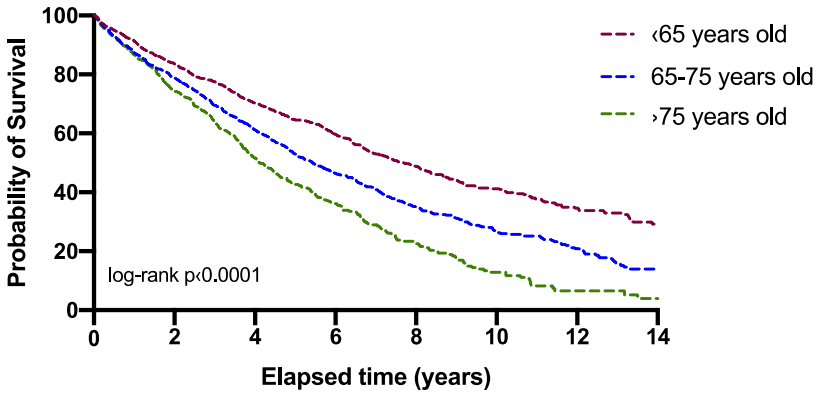
*Reverse remodeling was defined as a relative increase of 15% or more in left ventricular ejection fraction within 6 months after CRT implantation

4.1.3. Secondary endpoint – Long-term all-cause mortality by age groups

During the median follow-up time of 4.1 years (IQR 2.3/6.9), 1574 (57%) patients reached the secondary composite endpoint, 511 (50%) in Group I, 637 (63%) in Group II, and 426 (68%) in Group III. Kaplan-Meier curves showed a significantly lower survival rate in the older groups compared to the younger ones (log-rank p<0.001) (Figure 4.) (Table 3.), which was also confirmed by multivariate analysis (Table 4.). Adjustment for the type of device did not change our results (Group I vs. Group II: HR 0.68, 95% CI 0.60-0.76; p<0.01; Group I vs. Group III: HR 0.49, 95% CI 0.43-0.56; p<0.01; Group II vs. Group III: HR 0.71, 95% CI 0.63-0.81; p<0.01). Restricted cubic spline based on Cox regression was used to flexibly model the association between age and all-cause mortality risk shown in Figure 5. The lowest inflection point was found around 43 years (68).

Figure 4. Kaplan-Meier Estimates of the Probability of Survival by age groups (68)

Kaplan-Meier curves estimate of the probability of survival by age groups. The probability of survival was significantly lower in the older groups compared to the younger ones.



Patients at risk								
‹65 years old	1028	832	597	423	261	157	93	48
65-75 years old	1004	784	517	318	183	102	58	16
›75 years old	624	452	259	135	51	23	7	4

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Table 3. Univariate Cox regression analysis for the associations of age with the risk of all-cause mortality (68)

Comparison of different age groups			
End point	All-cause mortality		
	Hazard ratio	95% CI	p-value
<65 yrs vs. 65-75 yrs	0.67	0.60-0.76	<0.01
<65 yrs vs. >75 yrs	0.51	0.44-0.58	<0.01
65-75 yrs vs. >75 yrs	0.72	0.64-0.82	<0.01

Table 4. Multivariate Cox regression analysis for the associations of age with the risk of all-cause mortality

Comparison of different age groups			
End point	All-cause mortality		
	Hazard ratio	95% CI	p-value
<65 yrs vs. 65-75 yrs	0.81	0.69-0.95	0.01
<65 yrs vs. >75 yrs	0.63	0.52-0.75	<0.01
65-75 yrs vs. >75 yrs	0.74	0.63-0.88	<0.01

All models were adjusted for gender, device type, ischemic aetiology, serum Creatinine level, and LVEF.

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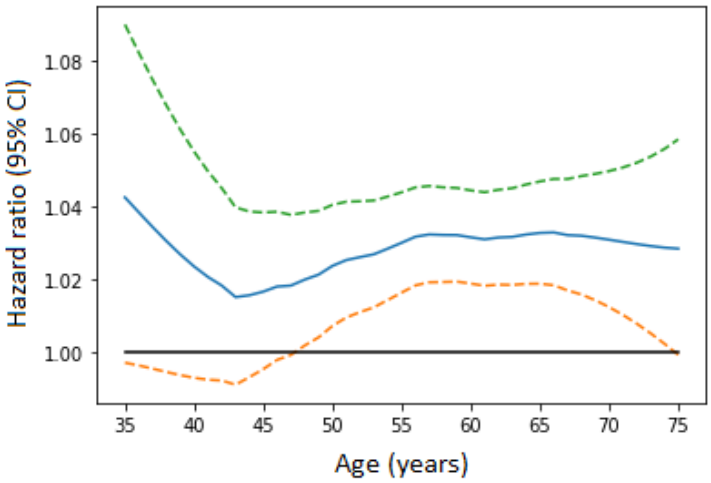
Figure 5. Restricted cubic spline regression for the association between age and risk of all-cause mortality (68)

Restricted cubic spline curve of the risk for all-cause mortality. The lowest inflection point was found around 43 years.



4.1.4. Tertiary endpoints - Peri- and postprocedural complications by age groups

Peri- and postprocedural complications were observed in 710 (27%) patients of the total cohort (Table 5). The most frequent complications were lead dislodgement (7%) and phrenic nerve stimulation (5%). We found no statistical difference in any complications among the three subgroups. Numerically pocket infection/decubitus (Group III: 1% vs. Group II: 2% vs. Group I: 3%; p=0.04) was observed less commonly in older patients but in a very low incidence in the total cohort (Table 5) (68).

Table 5. Peri-procedural complications divided by age groups (68)

Complications	All patients (n=2656)	<65 years old (n=1028)	65-75 years old (n=1004)	>75 years old (n=624)	p value
All complications (n;%)	710 (27%)	275 (27%)	285 (28%)	150 (24%)	0.15
Bleeding (n;%)	39 (1.5%)	13 (1.2%)	19 (1.9%)	7 (1%)	0.36
Pneumothorax (n;%)	32 (1.2%)	11 (1.1%)	11 (1.1%)	10 (1.6%)	0.58
Haemothorax (n;%)	5 (0.2%)	0 (0%)	3 (0.3%)	2 (0.3%)	0.20
Coronary sinus dissection (n;%)	25 (0.9%)	14 (1.4%)	5 (0.5%)	6 (0.9)	0.13
Pericardial tamponade (n;%)	10 (0.4%)	4 (0.4%)	1 (0.1%)	5 (0.8%)	0.08
Pocket infection/decubitus (n;%)	67 (2.5%)	36 (3.5%)	21 (2.1%)	10 (1.6%)	0.04
Infective endocarditis (n;%)	16 (0.6)	6 (0.6%)	8 (0.8)	2 (0.3%)	0.48
Lead dislodgement (n;%)	178 (7%)	69 (6.7%)	75 (7.5%)	34 (5.4%)	0.28
Lead dysfunction/fracture (n;%)	48 (2%)	20 (2%)	21 (2%)	7 (1%)	0.33
Sepsis (n;%)	7 (0.2%)	5 (0.5%)	1 (0.1%)	1 (0.2%)	0.99
Phrenic nerve stimulation (n;%)	142 (5%)	45 (4%)	66 (7%)	31 (5%)	0.08

4.1.5. Time-trend effects on age, the use of device types, and response rate in the elderly

The mean age of CRT patients increased significantly over the past two decades, analysed by 5 year-intervals: 2000-2004: 62.0±11.2 years, 2005-2009: 64.8±10.2 years, 2010-2014: 67.6±10.2 years, 2015-2020: 69.3±9.8 years; $p<0.01$ (Figure 6.). When examining device types, both CRT-P and CRT-D patients exhibited a significant increase in mean age since the early 2000s, with CRT-P patients having a consistently higher mean age than CRT-D patients in each subgroup, except for 2000-2004 (Table 6 and 7). The

percentage of CRT-D implantations also increased significantly: 2000-2004: 30.5%, 2005-2009: 37.2%, 2010-2014: 56.3%, 2015-2020: 70.7%; p<0.01 (Figure 7.). Although the response rate demonstrated an upward trend over time in each subgroup, it did not reach statistical significance (Figure 8.) (68).

Figure 6. The mean age of CRT recipients within 5-year intervals (68)

The mean age of cardiac resynchronization therapy (CRT) recipients within 5-year intervals. The mean age of CRT patients increased significantly over time.

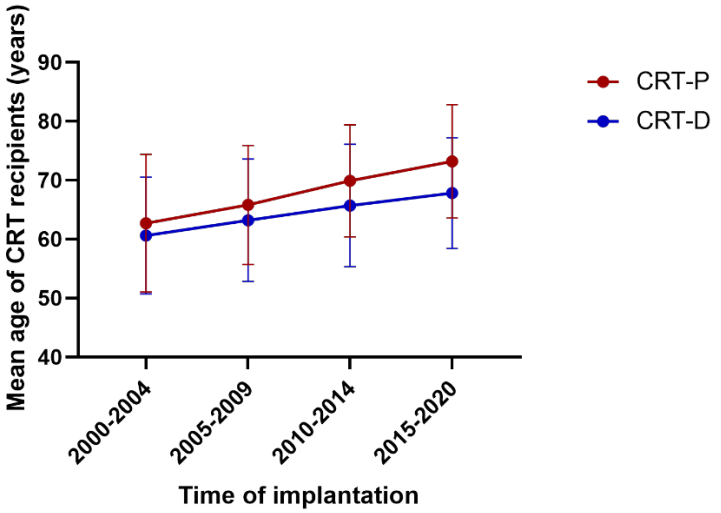


Table 6. The mean age of CRT recipients by device type within 5-year intervals (68)

	2000-2004		2005-2009		2010-2014		2015-2019	
	CRT-D	CRT-P	CRT-D	CRT-P	CRT-D	CRT-P	CRT-D	CRT-P
Mean age	60.6± 9.9	62.7± 11.7	63.2± 10.4	65.8± 10.1	65.7± 10.4	69.9± 9.5	67.8± 9.4	73.2± 9.6
p-value	0.22		<0.01		<0.01		<0.01	

CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker

Table 7. The mean age of CRT-D and CRT-P recipients within 5-year intervals (68)

	2000-2004	2005-2009	2010-2014	2015-2020	p-value
CRT-D mean age (yrs, ±SD)	60.6±9.9	63.2±10.4	65.7±10.4	67.8±9.4	<0.01
CRT-P mean age (yrs, ±SD)	62.7±11.7	65.8±10.1	69.9±9.5	73.2±9.6	<0.01

CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker

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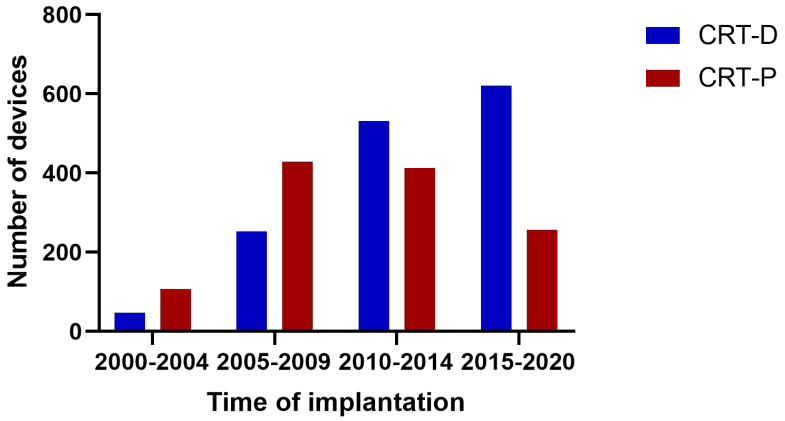
Figure 7. Number of CRT-D and CRT-P implantations within 5-year intervals (68)

Number of cardiac resynchronization therapy defibrillator (CRT-D) and cardiac resynchronization therapy pacemaker (CRT-P) implantations within 5-year intervals. The percentage of CRT-D implantations increased significantly over time.

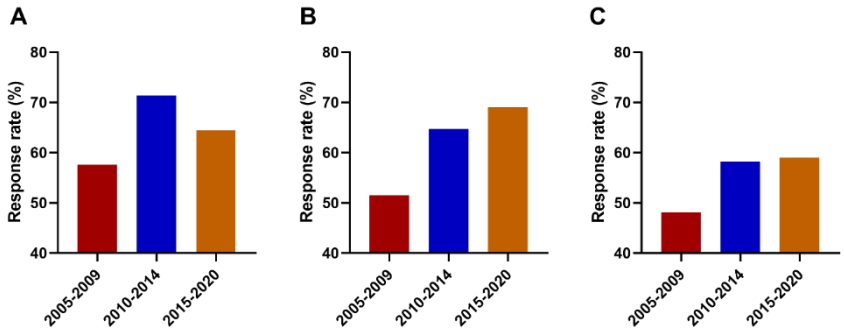


	2000-2004 (n=154)	2005-2009 (n=681)	2010-2014 (n=943)	2015-2020 (n=878)	p-value
CRT-D (n;%)	47 (30.5%)	253 (37.2%)	531 (56.3%)	621 (70.7%)	<0.01****
CRT-P (n;%)	107 (69.5%)	428 (62.8%)	412 (43.7%)	257 (29.3%)	<0.01****

**** p<0.0001

Figure 8. Response rate within 5-year intervals in Group I (Fig. 7A), Group II (Fig. 7B), and Group III (Fig. 7C) (68)

Response rate within 5-year intervals in patients <65 years old (A), in patients 65-75 years old (B), and in patients >75 years old (C) Although the response rate demonstrated an upward trend over time in each subgroup, it did not reach statistical significance.



4.2. Part 2 - Lateral left ventricular lead position is superior to posterior position in long-term outcome of patients underwent CRT implantation

4.2.1. Baseline clinical characteristics

From October 2000 to September 2018, a total of 2524 patients underwent successful CRT implantation. After applying exclusion criteria, 2087 patients formed the study cohort for the current analysis. The study cohort demonstrated no significant differences in baseline clinical characteristics compared to the total cohort (Table 8) (69). Baseline clinical characteristics were categorized based on the position of the LV lead and are presented in Table 8 (69). The anterior group comprised 108 (5.2%) patients, including 7 (0.3%) with a true anterior and 101 (4.8%) with an antero-lateral LV lead position. A true lateral LV lead location was identified in 1336 (64%) participants and a posterior position in 643 (30.8%) patients, which included 50 (2.4%) with a true posterior and 593 (28.4%) with a postero-lateral location along the short axis. No significant differences were observed in baseline clinical variables such as CRT device type, age, sex, LBBB morphology, or aetiology of heart failure among the three subgroups (Table 9) In terms of device distribution, 1168 (56%) patients had a CRT-D, while 919 (44%) had a CRT-P device. The median age of the study cohort was 68 (IQR 61/75) years, with a median EF of 28 (IQR 24/33) %. Most patients were men (74.6%), had a typical LBBB morphology (95.1%), and 49.5% of them had ischemic aetiology. Table 10 presents the baseline clinical characteristics of the study cohort divided into 5-year periods based on the time of the implantation (69).

IED measurements varied significantly between groups, ranging from 42 to 220 ms. The median IED value was 106 (IQR 89/123) ms in the study cohort, 83 (IQR 60/100) ms in the anterior, 110 (IQR 90/128) ms in the lateral, and 100 (IQR 85/120) ms in the posterior group, respectively (Figure 9). Notably, IED was significantly longer in the lateral group compared to the other groups ($p<0.001$) (69).

Table 8. Baseline clinical characteristics of total and study cohort of Part 2 (69)

Baseline variables	Total cohort (n=2524)	Study cohort (n=2087)	p value
Age (yrs; median/IQR)	68 (60-74)	68 (61-75)	0.44
Gender (female; n; %)	637 (25.2%)	531 (25.4%)	0.87
NYHA III/IV (st; n;%)	1175 (46.6%)	973 (46.6%)	0.97
Ischemic aetiology (n;%)	1234 (48.9%)	1034 (49.5%)	0.66
CRT-D (n;%)	1365 (54.1%)	1168 (56.0%)	0.20
RR systolic (mmHg; median/IQR)	125 (111-137)	125 (111-138)	0.92
RR diastolic (mmHg; median/IQR)	73 (65-80)	72 (65-80)	0.78
BMI (kg/m^2; median/IQR)	27.4 (24.6-30.8)	27.4 (24.6-30.7)	0.82
QRS (ms; median/IQR)	160 (140-180)	160 (140-180)	0.97
LBBB morphology (n; %)	1760 (96.1%)	1501 (95.1%)	0.10
Medical history			
Atrial Fibrillation (n;%)	950 (37.6%)	786 (37.7%)	0.99
Diabetes mellitus (n;%)	927 (36.7%)	772 (37.0%)	0.85
Type 2 DM (n; %)	749 (29.7%)	623 (29.9%)	0.90
Hypertension (n; %)	1819 (72.1%)	1527 (73.2%)	0.41
Prior MI (n; %)	974 (38.6%)	814 (39.0%)	0.77
Prior PCI (n; %)	740 (29.3%)	637 (30.5%)	0.37
Prior CABG (n; %)	333 (13.2%)	276 (13.2%)	0.98
Prior COPD (n; %)	359 (14.2%)	303 (14.5%)	0.78
Laboratory parameters			
Serum urea (µmol/l; median/IQR)	8.3 (6.4-11.6)	8.3 (6.3-11.5)	0.71
Serum creatinine (µmol/l; median/IQR)	101 (81-131)	101 (82-130)	0.98

Serum cholesterol (mmol/l; median/IQR)	4.1 (3.4-5.1)	4.1 (3.4-5.1)	0.96
eGFR (ml/min/1.73m^2; median/IQR)	60.0 (44.9-76.0)	59.8 (45.0-76.0)	0.93
NT-proBNP (pmol/l; median/IQR)	2829 (1453-4791)	2956 (1398-4807)	0.99
Echocardiographic parameters			
LVEF (%; median/IQR))	28 (24-33)	28 (24-33)	0.49
LVEDV (ml; median/IQR)	216 (164-278)	212 (164-274)	0.86
LVESV (ml; median/IQR)	159 (118-207)	154 (117-209)	0.87
LVEDD (mm; median/IQR)	63 (58-70)	63 (58-70)	0.74
LVESD (mm; mean/IQR)	53 (47-60)	53 (47-60)	0.93
Medical treatment			
Beta blocker (n;%)	2043 (81.0%)	1724 (82.6%)	0.15
ACE-I/ARB (n;%)	2111 (83.6%)	1772 (84.9%)	0.24
MRA (n;%)	1557 (61.7%)	1303 (62.4%)	0.60
Furosemid (n;%)	1813 (71.8%)	1522 (72.9%)	0.41
Digoxin (n; %)	483 (19.1%)	373 (17.9%)	0.27
Amiodarone (n;%)	619 (24.5%)	513 (24.6%)	0.96
Oral anticoagulant therapy (n;%)	773 (30.6%)	668 (32.0%)	0.31

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker, BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-Terminal pro-B-Type Natriuretic Peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention

Table 9. Baseline clinical characteristics of patients by left ventricular lead locations (69)

Baseline variables	**All patients (n=2087)**	**Anterior (n=108)**	**Lateral (n=1336)**	**Posterior (n=643)**	**p value**
Age (yrs; median/IQR)	68 (61-75)	68 (60-76)	68 (61-75)	68 (61-74)	0.90
Gender (female; n; %)	531 (25.4%)	26 (24.1%)	333 (24.9%)	172 (26.7%)	0.65
NYHA III/IV (st; n;%)	973 (46.6%)	55 (50.9%)	617 (46.2%)	301 (46.8%)	0.63
Ischemic aetiology (n;%)	1034 (49.5%)	48 (44.4%)	659 (49.3%)	327 (50.9%)	0.45
CRT-D (n;%)	1168 (56.0%)	57 (52.8%)	738 (55.2%)	373 (58.0%)	0.40
RR systolic (mmHg; median/IQR)	125 (111-138)	127 (110-144)	123 (110-136)	127 (111-139)	0.51
RR diastolic (mmHg; median/IQR)	72 (65-80)	75 (66-84)	72 (65-80)	72 (64-80)	0.71
BMI (kg/m^2; median/IQR)	27.4 (24.6-30.7)	27 (23.9-29.8)	27.6 (24.8-30.7)	26.9 (24.2-30.9)	0.29
QRS (ms; median/IQR)	160 (140-180)	163 (140-190)	160 (140-180)	160 (140-170)	0.10
LBBB morphology (n; %)	1501 (95.1%)	78 (98.7%)	962 (94.6%)	461 (95.6%)	0.99
Medical history					
Atrial Fibrillation (n;%)	786 (37.7%)	40 (37.0%)	504 (37.7%)	242 (37.6%)	0.99
Diabetes mellitus (n;%)	772 (37.0%)	43 (39.8%)	491 (36.8%)	238 (37.0%)	0.82
Type 2 DM (n; %)	623 (29.9%)	33 (30.6%)	404 (30.2%)	186 (28.9%)	0.83
Hypertension (n; %)	1527 (73.2%)	74 (68.5%)	980 (73.4%)	473 (73.6%)	0.53
Prior MI (n; %)	814 (39.0%)	35 (32.4%)	530 (39.7%)	249 (38.7%)	0.33

Prior PCI (n; %)	637 (30.5%)	31 (28.7%)	395 (29.6%)	211 (32.8%)	0.31
Prior CABG (n; %)	276 (13.2%)	12 (11.1%)	178 (13.3%)	86 (13.4%)	0.80
Prior COPD (n; %)	303 (14.5%)	16 (14.8%)	188 (14.1%)	99 (15.4%)	0.73
Laboratory parameters					
Serum urea (µmol/l; median/IQR)	8.3 (6.3-11.5)	8.6 (6.2-10.8)	8.3 (6.3-11.5)	8.2 (6.4-11.7)	0.96
Serum creatinine (µmol/l; median/IQR)	101 (82-130)	96.5 (77-126)	102 (84-129)	100 (80-134.3)	0.40
Serum cholesterol (mmol/l; median/IQR)	4.1 (3.4-5.1)	4.0 (3.4-4.9)	4.2 (3.4-5.2)	4.1 (3.3-5.1)	0.49
eGFR (ml/min/1.73m^2; median/IQR)	59.8 (45.0-76.0)	65.4 (47.2-79.9)	58.9 (45.3-74.9)	60.6 (43.7-76.5)	0.28
NT-proBNP (pmol/l; median/IQR)	2956 (1398-4807)	4390 (649-10777)	2579 (1287-4493)	3301 (1811-5628)	0.30
Echocardiographic parameters					
LVEF (%; median/IQR))	28 (24-33)	28 (21-33)	28 (24-33)	28 (24-33)	0.45
LVEDV (ml; median/IQR)	212 (164-274)	226 (150-260)	210 (168-260)	210 (152-306)	0.81
LVESV (ml; median/IQR)	154 (117-209)	157 (107-197)	154 (122-206)	154 (111-228)	0.99
LVEDD (mm; median/IQR)	63 (58-70)	65 (58-71)	63 (58-69)	63 (57-70)	0.73
LVESD (mm; mean/IQR)	53 (47-60)	54 (47-63)	53 (47-60)	53 (46-61)	0.73

Medical treatment					
Beta blocker (n;%)	1724 (82.6%)	82 (75.9%)	1111 (83.2%)	531 (82.6%)	0.16
ACE-I/ARB (n;%)	1772 (84.9%)	86 (79.6%)	1148 (85.9%)	538 (83.7%)	0.12
MRA (n;%)	1303 (62.4%)	58 (53.7%)	850 (63.6%)	395 (61.4%)	<0.01
Furosemid (n;%)	1522 (72.9%)	74 (68.5%)	964 (72.2%)	484 (75.3%)	0.20
Digoxin (n; %)	373 (17.9%)	26 (24.1%)	226 (16.9%)	121 (18.8%)	0.13
Amiodarone (n;%)	513 (24.6%)	32 (29.6%)	326 (24.4%)	155 (24.1%)	0.45
Oral anticoagulant therapy (n;%)	668 (32.0%)	27 (25.0%)	415 (31.1%)	226 (35.1%)	0.05

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker, BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-Terminal pro-B-Type Natriuretic Peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention

Table 10. Baseline clinical characteristics of the study cohort divided into 5-year periods by the time of implantation (69)

Baseline variables	**All patients (n=2087)**	**2000-2005 (n=141)**	**2006-2010 (n=682)**	**2011-2015 (n=798)**	**2016-2018 (n=466)**	**p value**
Age (yrs; median/IQR)	68 (61-75)	63 (54-70)	66 (60-73)	69 (62-76)	70 (62-76)	<0.01
Gender (female; n; %)	531 (25.4%)	30 (21.3%)	154 (22.6%)	219 (27.4%)	128 (27.5%)	0.07
NYHA III/IV (st; n;%)	973 (46.6%)	65 (76.5%)	425 (67.0%)	335 (54.8%)	148 (41.3%)	<0.01
Ischemic aetiology (n;%)	1034 (49.5%)	45 (31.9%)	362 (53.1%)	413 (51.8%)	214 (45.9%)	<0.01

CRT-D (n;%)	1168 (56.0%)	32 (22.7%)	280 (41.1%)	521 (65.3%)	335 (71.9%)	<0.01
RR systolic (mmHg; median/IQR)	125 (111-138)	120 (93-130)	120 (110-132)	126 (111-140)	126 (111-136)	0.60
RR diastolic (mmHg; median/IQR)	72 (65-80)	70 (64-80)	73 (68-80)	72 (64-80)	74 (67-80)	0.32
BMI (kg/m^2; median/IQR)	27.4 (24.6-30.7)	26.2 (24.7-29.4)	27.2 (24.5-30.1)	27.5 (24.7-31.1)	27.7 (24.8-31.7)	0.11
QRS (ms; median/IQR)	160 (140-180)	169 (160-192)	160 (143-180)	160 (134-170)	150 (140-162)	<0.01
LBBB morphology (n; %)	1501 (95.1%)	49 (100%)	555 (97.7%)	598 (94.5%)	299 (91.2%)	<0.01
Anterior LV lead (n;%)	108 (5.2%)	22 (15.6%)	36 (5.3%)	34 (4.3%)	16 (3.4%)	<0.01
Lateral LV lead (n;%)	1336 (64.0%)	79 (56.0%)	449 (65.8%)	520 (65.2%)	288 (61.8%)	0.10
Posterior LV lead (n;%)	643 (30.8%)	40 (28.4%)	197 (28.9%)	244 (30.6%)	162 (34.8%)	0.17
Medical history						
Atrial Fibrillation (n;%)	786 (37.7%)	53 (37.6%)	264 (38.7%)	304 (38.1%)	165 (35.4%)	0.71
Diabetes mellitus (n;%)	772 (37.0%)	43 (30.5%)	250 (36.7%)	309 (38.7%)	170 (36.5%)	0.30
Type 2 DM (n; %)	623 (29.9%)	42 (29.8%)	210 (30.8%)	247 (31.0%)	124 (26.6%)	0.38
Hypertension (n; %)	1527 (73.2%)	68 (48.2%)	483 (70.8%)	629 (78.8%)	347 (74.5%)	<0.01
Prior MI (n; %)	814 (39.0%)	37 (26.2%)	313 (45.9%)	317 (39.7%)	147 (31.5%)	<0.01
Prior PCI (n; %)	637 (30.5%)	26 (18.4%)	196 (28.8%)	266 (33.4%)	149 (32.5%)	<0.01
Prior CABG (n; %)	276 (13.2%)	11 (7.8%)	109 (16.0%)	102 (12.8%)	54 (11.9%)	0.03

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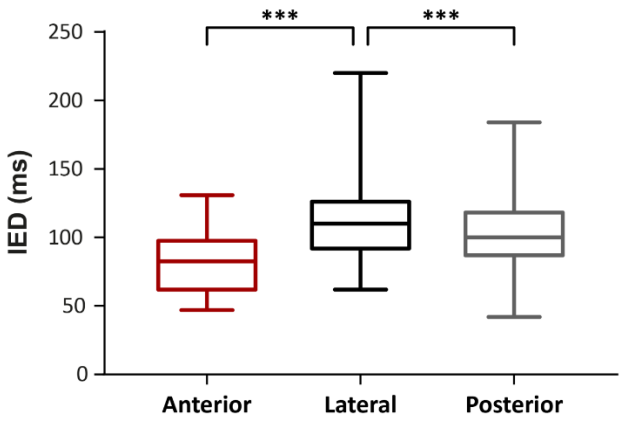
Prior COPD (n; %)	303 (14.5%)	13 (9.2%)	112 (16.5%)	118 (14.8%)	60 (12.9%)	0.10
Laboratory parameters						
Serum urea (μmol/l; median/IQR)	8.3 (6.3-11.5)	8.6 (5.9-12.1)	8.8 (6.9-11.8)	8.0 (6.2-10.9)	7.9 (5.9-11.7)	<0.01
Serum creatinine (μmol/l; median/IQR)	101 (82-130)	104 (82-139)	105 (84-134)	99 (80-128)	98 (79-128)	0.06
Serum cholesterol (mmol/l; median/IQR)	4.1 (3.4-5.1)	3.7 (2.9-4.6)	4.2 (3.5-5.1)	4.1 (3.4-5.2)	4.0 (3.3-5.0)	0.71
eGFR (ml/min/1.73m^2; median/IQR)	59.8 (45-76)	61.3 (40.8-79.2)	57.7 (44.2-73.8)	61.8 (46.0-77.1)	61.5 (44.3-77.1)	0.38
NT-proBNP (pmol/l; median/IQR)	2956 (1398-4807)	-	3350 (3000-3699)	2968 (1619-5521)	2536 (1241-4731)	0.70
Echocardiographic parameters						
LVEF (%; median/IQR))	28 (24-33)	25 (20-29)	28 (24-32)	29 (24-33)	28 (24-34)	0.03
LVEDV (ml; median/IQR)	212 (164-274)	260 (260-260)	201 (156-278)	207 (153-268)	226 (186-291)	0.48
LVESV (ml; median/IQR)	154 (117-209)	-	147 (114-192)	159 (113-201)	176 (124-233)	0.19
LVEDD (mm; median/IQR)	63 (58-70)	68 (63-80)	64 (58-70)	64 (57-70)	62 (57-67)	<0.01
LVESD (mm; mean/IQR)	53 (47-60)	60 (53-71)	53 (46-60)	54 (47-60)	52 (46-59)	<0.01

Medical treatment						
Beta blocker (n;%)	1724 (82.6%)	75 (84.3%)	569 (89.5%)	682 (90.5%)	398 (87.1%)	0.14
ACE-I/ARB (n;%)	1772 (84.9%)	78 (87.6%)	571 (89.6%)	699 (92.7%)	424 (92.8%)	0.08
MRA (n;%)	1303 (62.4%)	47 (52.8%)	385 (60.5%)	519 (68.9%)	352 (77.0%)	<0.01
Furosemid (n;%)	1522 (72.9%)	69 (48.9%)	501 (73.5%)	582 (72.9%)	370 (79.4%)	<0.01
Digoxin (n; %)	373 (17.9%)	30 (33.7%)	187 (29.7%)	116 (15.4%)	40 (8.8%)	<0.01
Amiodarone (n;%)	513 (24.6%)	28 (31.5%)	200 (31.8%)	181 (24.1%)	104 (22.8%)	<0.01
Oral anticoagulant therapy (n;%)	668 (32.0%)	19 (76.0%)	238 (37.5%)	250 (33.2%)	161 (35.9%)	0.02

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker, BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-Terminal pro-B-Type Natriuretic Peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention

Figure 9. Interlead electrical delay (IED) length by left ventricular lead locations (69)

Interlead electrical delay (IED) length by left ventricular lead positions. IED was significantly longer in the lateral group compared to the other groups.



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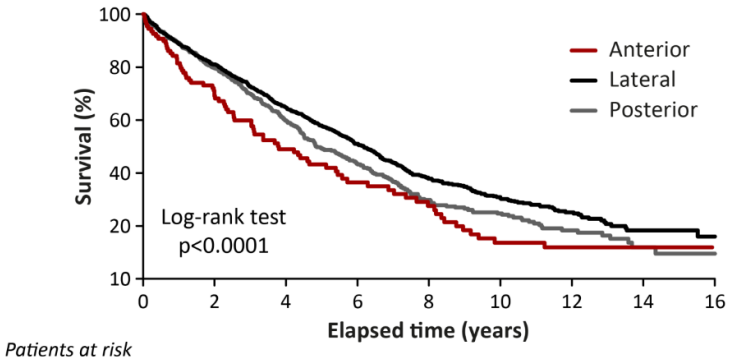
4.2.2. Primary composite endpoint

Over the median follow-up time of 3.7 years, 1150 (55.1%) patients reached the primary composite endpoint. 78 (72.2%) with anterior, 710 (53.1%) with lateral, and 362 (56.3%) with posterior LV lead locations. Analysing the risk of all-cause mortality, patients with a lateral LV lead location exhibited a significantly lower rate of death compared to those with anterior ($p<0.01$) or posterior ($p<0.01$) positions (Figure 10) (69).

Figure 10. Kaplan-Meier Estimates of the Probability of Survival by LV lead locations (69)

Kaplan-Meier curves estimate of the probability of survival by left ventricular lead positions. The probability of survival was significantly higher in the lateral group compared to the anterior and posterior groups.



Patients at risk

Anterior	108	70	44	26	18	8	6	3	0
Lateral	1336	1004	654	387	228	123	58	15	6
Posterior	643	461	264	142	77	51	22	7	1

In a multivariate analysis, adjusting for relevant clinical covariates such as age, sex, ischemic aetiology, LBBB morphology, atrial fibrillation, and device type, consistent findings emerged. A lateral position was associated with a significant risk reduction of the primary composite endpoint compared to anterior (HR 0.69; 95% CI 0.55-0.87; $p<0.01$) or posterior (HR 0.84; 95% CI 0.74-0.96; $P<0.01$) locations (Table 11) (69).

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Table 11. The associations of LV lead location with the risk of all-cause mortality (69)

Comparison of different LV lead locations			
End point	All-cause mortality		
	Hazard ratio	95% CI	p-value
Lateral vs. Anterior	0.69	0.55-0.87	<0.01
Lateral vs. Posterior	0.84	0.74-0.96	<0.01
Posterior vs. Anterior	0.77	0.60-0.99	0.04

All models were adjusted for age, gender, LBBB morphology, device type, atrial fibrillation and ischemic aetiology.

4.2.3. Echocardiographic response

When assessing the echocardiographic response within the lateral group, there was a mean increase in EF of 7.3 (±9.7) %, and 65.5% of the lateral group were identified as echocardiographic responders to CRT based on our reverse remodelling definition. Our aim was to identify additional factors to further improve the clinical outcome of CRT patients and discovered a significant association between IED and echocardiographic response (ROC AUC 0.63; 95% CI: 0.53-0.73; p=0.012) within the lateral group. The optimal cut off value for IED, determined through ROC analysis, was 110 ms (Figure 11) (69).

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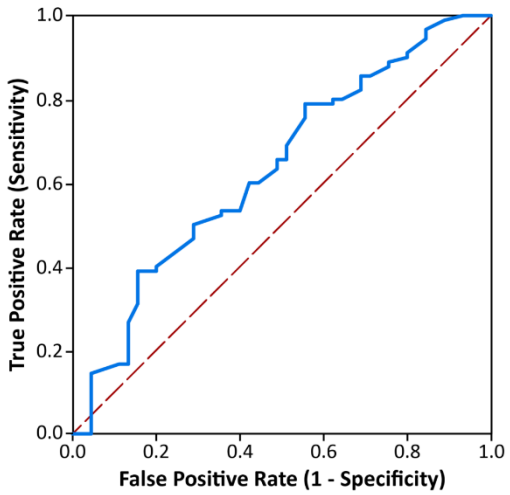
Figure 11. Receiving Operator Curve of IED length to echocardiographic response in patients with lateral left ventricular lead location (69)

Receiving Operator Curve (ROC) of interlead electrical delay (IED) length to echocardiographic response in patients with lateral left ventricular lead position. The optimal cut off value for IED, determined through ROC analysis, was 110 ms.



Upon logistic regression analysis, individuals with an IED longer than 110 ms showed 2.1 times higher odds of improvement in echocardiographic response 6 months after the implantation (OR 2.1; 95% CI: 0.99-4.24; p=0.05). However, no such association was observed between IED and echocardiographic response in patients with anterior or posterior LV lead positions (AUC 0.30 and 0.57). For further analysis, an IED threshold of 110 ms was used. Patients with a lateral position and an IED ≥ 110 ms demonstrated a more significant improvement in absolute percent change of LVEF 6 months after the implantation (baseline LVEF 27.4±6.0% vs. 6 months LVEF 36.4±9.2%) compared to patients with a lateral position but an IED < 110 ms (baseline LVEF 27.7±7.1% vs. 6 months LVEF 33.1 ±9.2%) (p=0.02) (69).

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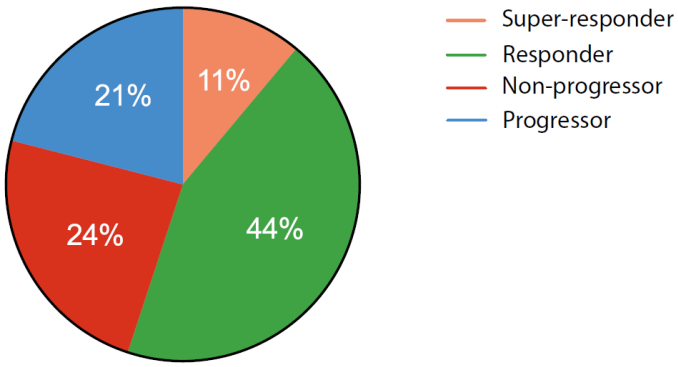
4.3. Part 3 - Non-progressors to cardiac resynchronization therapy show long-term mortality benefit compared to progressors

4.3.1. Baseline clinical characteristics

In total, 1019 patients who underwent CRT implantation between October 2000 and September 2020 were included in the current analysis after applying the exclusion criteria. This cohort was categorized into four groups based on their response status: 113 (11%) were super-responders, 448 (44%) were responders, 244 (24%) were non-progressors, and 214 (21%) were progressors (Figure 12).

Figure 12. Response status after CRT implantation

The percentage of different response statuses after cardiac resynchronization therapy (CRT) implantation based on the new classification.



The mean change in LVEF varied as follows: super-responders 24.5% ± 4.1%, responders 11.5% ± 3.8%, non-progressors 2.8% ± 1.8%, and progressors -6.6% ± 4.5% ($p<0.0001$) (Figure 13).

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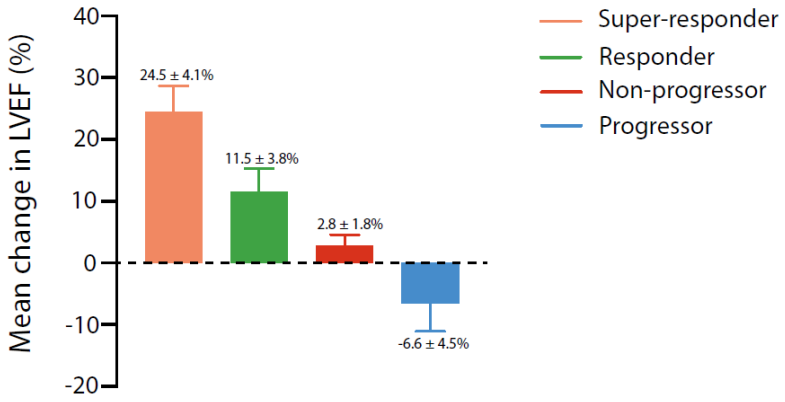
Figure 13. Mean change in LVEF by response to CRT

The mean change in left ventricular ejection fraction (LVEF) by response to cardiac resynchronization therapy (CRT).



The baseline clinical characteristics of the patients were analysed according to their response status post-implantation and are detailed in Table 12. The majority of patients in each group were male (Group I: 61% vs. Group II: 75% vs. Group III: 75% vs. Group IV: 80%), but the percentage of women was significantly higher in super-responders and lower in progressors (Group I: 39% vs. Group II: 25% vs. Group III: 25% vs. Group IV: 20%; $p<0.01$) (Table 12).

Non-progressors more commonly had an ischemic aetiology (Group I: 35% vs. Group II: 47% vs. Group III: 58% vs. Group IV: 63%, $p<0.0001$), NYHA III/IV functional status (Group I: 43% vs. Group II: 46% vs. Group III: 58% vs. Group IV: 56%; $p<0.01$), and lower systolic blood pressure (Group I: 127±18 Hgmm vs. Group II: 128±20 Hgmm vs. Group III: 123±17 Hgmm vs. Group IV: 121±16 Hgmm; $p=0.02$). They also less frequently had a lateral LV lead position (Group I: 60% vs. Group II: 85% vs. Group III: 55% vs. Group IV: 53%; $p<0.0001$)(Table 12).

In terms of laboratory parameters, non-progressors exhibited worse renal function with higher serum urea [Group I: 7.4 (IQR 5.5/9.5) mmol/l vs. Group II: 8.0 (IQR 6.2/11.1) mmol/l vs. Group III: 8.8 (IQR 6.4/11.6) mmol/l vs. Group IV: 8.6 (IQR 6.8/11.8) mmol/l, $p<0.01$] and creatinine levels [Group I: 84 (IQR 70/113) µmol/l vs. Group II: 100 (IQR

79/128) µmol/l vs. Group III: 105 (IQR 86/138) µmol/l vs. Group IV: 107 (IQR 84/137) µmol/l; p<0.0001), along with a lower eGFR [Group I: 75.3 (IQR 51.7/92.3) ml/min/1.73m^2 vs. Group II: 64.1 (IQR 48.7/83.0) ml/min/1.73m^2 vs. Group III: 60.2 (IQR 45.3/79.9) ml/min/1.73m^2 vs. Group IV: 61.9 (IQR 43.9/79.1) ml/min/1.73m^2; p<0.01] (Table 12).

Echocardiographic parameters revealed that baseline LVEF was significantly higher in non-progressors than in super-responders and responders, but was significantly lower compared to progressors [Group I: 25 (IQR 20/30) % vs. Group II: 27 (IQR 23/32) % vs. Group III: 29 (IQR 24/34) % vs. Group IV: 31 (IQR 28/35) %; p<0.0001] (Table 12).

As regards comorbidities, non-progressors were more likely to have a prior myocardial infarction (Group I: 21% vs. Group II: 37% vs. Group III: 47% vs. Group IV: 51%; p<0.0001) and CABG (Group I: 5% vs. Group II: 15% vs. Group III: 20% vs. Group IV: 19%; p<0.01) compared to responders and super-responders (Table 12).

Regarding medical therapy, all subgroups received optimal heart failure basic treatment at a comparable high rate. However, non-progressors were more commonly treated with loop diuretics (Group I: 66% vs. Group II: 73% vs. Group III: 78% vs. Group IV: 82%; p<0.01) (Table 12).

Table 12. Baseline clinical characteristics of patients by response to CRT

Baseline variables	**All patients (n=1019)**	**Super-responder (n=113)**	**Responder (n=448)**	**Non-progressor (n=244)**	**Progressor (n=214)**	**p value**
Age (yrs; median/IQR)	69 (61-75)	68 (60-76)	69 (62-75)	69 (61-74)	69 (61-75)	1.00
Gender (female; n; %)	258 (25%)	44 (39%)	112 (25%)	60 (25%)	42 (20%)	<0.01
NYHA III/IV (st; n; %)	513 (50%)	49 (43%)	204 (46%)	141 (58%)	119 (56%)	<0.01
Ischemic aetiology (n; %)	525 (52%)	40 (35%)	210 (47%)	141 (58%)	134 (63%)	<0.01
CRT-D (n; %)	593 (58%)	74 (65%)	253 (56%)	146 (60%)	120 (56%)	0.30

RR systolic (mmHg; mean±SD)	125±18	127±18	128±20	123±17	121±16	0.02
RR diastolic (mmHg; median/IQR)	74±12	73±12	75±12	74±11	72±10	0.36
BMI (kg/m^2; median/IQR)	27.7 (24.9-31.0)	27.5 (24.6-31.8)	27.7 (25.0-30.6)	28.3 (25.2-31.8)	27.3 (24.8-30.5)	0.59
QRS (ms; median/IQR)	160 (140-180)	160 (143-180)	160 (140-180)	160 (140-170)	160 (140-165)	0.41
LBBB morphology (n; %)	735 (72%)	87 (77%)	321 (72%)	174 (71%)	153 (71%)	0.68
Lateral left ventricular lead position (n;%)	602 (59%)	68 (60%)	380 (85%)	133 (55%)	114 (53%)	<0.01
Medical history						
Atrial Fibrillation (n; %)	412 (40%)	37 (33%)	180 (40%)	101 (41%)	94 (44%)	0.33
Diabetes mellitus (n; %)	361 (36%)	36 (32%)	160 (36%)	90 (37%)	75 (35%)	0.83
Type 2 DM (n; %)	296 (29%)	28 (25%)	129 (29%)	76 (31%)	63 (29%)	0.67
Hypertension (n; %)	761 (75%)	82 (73%)	336 (75%)	184 (75%)	159 (74%)	0.95
Prior MI (n; %)	414 (41%)	24 (21%)	166 (37%)	114 (47%)	110 (51%)	<0.01
Prior PCI (n; %)	309 (30%)	25 (22%)	129 (29%)	79 (32%)	76 (36%)	0.06
Prior CABG (n; %)	164 (16%)	6 (5%)	68 (15%)	49 (20%)	41 (19%)	<0.01
Prior COPD (n; %)	153 (15%)	13 (12%)	71 (16%)	37 (15%)	32 (15%)	0.72

Laboratory parameters						
Serum urea (mmol/l; median/IQR)	8.3 (6.3-11.2)	7.4 (5.5-9.5)	8.0 (6.2-11.1)	8.8 (6.4-11.6)	8.6 (6.8-11.8)	<0.01
Serum creatinine (µmol/l; median/IQR)	101 (80-131)	84 (70-113)	100 (79-128)	105 (86-138)	107 (84-137)	<0.01
Serum cholesterol (mmol/l; median/IQR)	4.2 (3.4-5.1)	4.5 (3.6-5.4)	4.2 (3.4-5.1)	4.0 (3.3-5.3)	4.2 (3.4-5.1)	0.55
eGFR (ml/min/1.73m^2; median/IQR)	63.8 (46.4-81.8)	75.3 (51.7-92.3)	64.1 (48.7-83.0)	60.2 (45.3-79.9)	61.9 (43.9-79.1)	<0.01
NT-proBNP (pmol/l; median/IQR)	2531 (1463-3756)	2346 (1596-3000)	2954 (1371-4139)	2198 (1124-3406)	2772 (1903-4809)	0.40
Echocardiographic parameters						
LVEF (%; median/IQR))	28 (24-33)	25 (20-30)	27 (23-32)	29 (24-34)	31 (28-35)	<0.01
LVEDV (ml; median/IQR)	210 (164-277)	225 (150-276)	204 (143-273)	225 (171-270)	201 (183-288)	0.94
LVESV (ml; median/IQR)	159 (114-207)	173 (132-216)	150 (109-218)	170 (120-204)	141 (121-190)	0.76
LVEDD (mm; mean±SD)	63±9	62±8	63±9	64±9	64±10	0.18
LVESD (mm; mean±SD)	53±10	52±7	53±10	54±10	53±10	0.53
Medical treatment						
Beta blocker (n;%)	906 (89%)	100 (88%)	400 (89%)	211 (86%)	195 (91%)	0.46
ACE-I/ARB (n;%)	914 (90%)	106 (94%)	401 (90%)	216 (89%)	191 (89%)	0.48

MRA (n;%)	671 (66%)	82 (73%)	292 (65%)	163 (67%)	134 (63%)	0.33
Furosemid (n;%)	767 (75%)	75 (66%)	326 (73%)	190 (78%)	176 (82%)	<0.01
Digoxin (n; %)	178 (17%)	13 (12%)	78 (17%)	44 (18%)	43 (20%)	0.28
Amiodarone (n;%)	287 (28%)	24 (21%)	124 (28%)	77 (32%)	62 (29%)	0.24
Oral anticoagulant therapy (n;%)	372 (37%)	35 (31%)	162 (36%)	93 (38%)	82 (38%)	0.55

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker, BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-Terminal pro-B-Type Natriuretic Peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention

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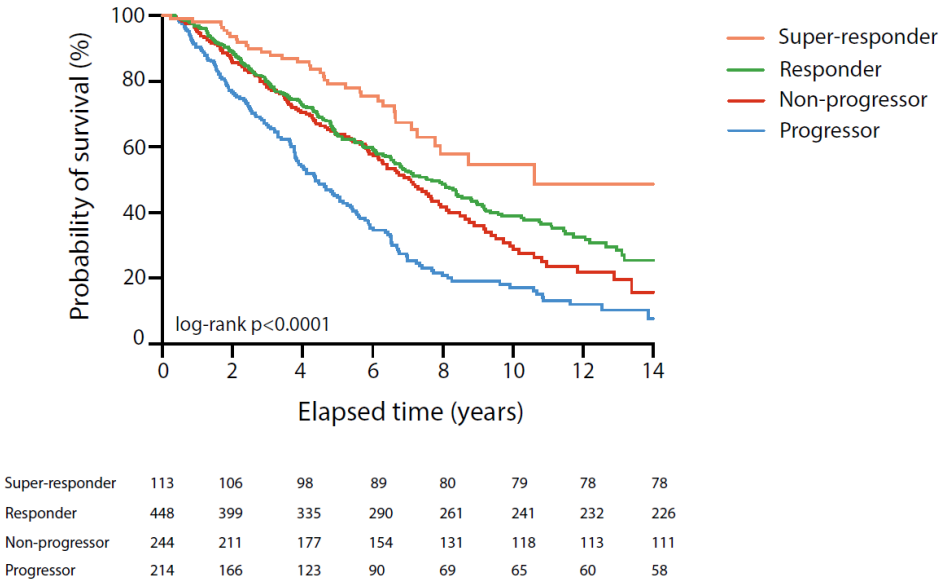
4.3.2. Primary composite endpoint

During the median follow-up time of 4.7 years 547 (54%) patients reached the primary composite endpoint, 35 (31%) among super-responders, 223 (50%) among responders, 133 (55%) among non-progressors, and 156 (73%) among progressors (Figure 14).

Figure 14. Kaplan-Meier Estimates of the Probability of Survival by response to CRT

Kaplan-Meier curves estimate of the probability of survival by response to cardiac resynchronization therapy (CRT). The probability of survival was significantly higher in the non-progressor group compared to the progressor group.



Super-responder	113	106	98	89	80	79	78	78
Responder	448	399	335	290	261	241	232	226
Non-progressor	244	211	177	154	131	118	113	111
Progressor	214	166	123	90	69	65	60	58

Univariate Cox regression analysis demonstrated that non-progressors had a comparable long-term outcome to responders (HR 1.17; 95%CI 0.94-1.45; p=0.15) and a superior outcome compared to progressors (HR 0.60; 95%CI 0.48-0.76; p<0.0001) (Table 13). These findings were further corroborated by multivariate analysis after adjusting for age, gender, ischemic aetiology, LVEF, and serum creatinine levels: non-progressors vs. responders (HR 1.25; 95%CI 0.98-1.58; p=0.07) and non-progressors vs. progressors (HR 0.62; 95%CI 0.47-0.80; p<0.0001) (Table 14).

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Table 13. Univariate Cox regression analysis for the associations of response to CRT with the risk of all-cause mortality

Comparison of different response groups			
End point	All-cause mortality		
	Hazard ratio	95% CI	p-value
Super-responder vs. Responder	0.60	0.42-0.86	<0.01
Super-responder vs. Non-progressor	0.52	0.36-0.76	<0.01
Super-responder vs. Progressor	0.31	0.21-0.45	<0.01
Responder vs. Non-progressor	0.85	0.69-1.06	0.15
Responder vs. Progressor	0.52	0.42-0.64	<0.01
Non-progressor vs. Progressor	0.60	0.48-0.76	<0.01

Table 14. Multivariate Cox regression analysis for the associations of response to CRT with the risk of all-cause mortality

Comparison of different response groups			
End point	All-cause mortality		
	Hazard ratio	95% CI	p-value
Super-responder vs. Responder	0.73	0.49-1.09	0.12
Super-responder vs. Non-progressor	0.59	0.38-0.92	0.02
Super-responder vs. Progressor	0.33	0.21-0.53	<0.01
Responder vs. Non-progressor	0.80	0.63-1.02	0.07
Responder vs. Progressor	0.50	0.39-0.64	<0.01
Non-progressor vs. Progressor	0.62	0.47-0.80	<0.01

All models were adjusted for age, gender, ischemic aetiology and seCreatinine.

5. Discussion

5.1. Part 1 - Long-term outcome of cardiac resynchronization therapy patients in the elderly

Heart failure is a significant contributor to mortality and hospitalization in the elderly (72, 73). As people age, the prevalence of HF rises dramatically, impacting about 1-2% of adults in developed countries, reaching up to 10% of people over the age of 70 (74). Elderly HF patients, who often deal with polypharmacy, multimorbidity, cognitive decline, and frailty, are considered particularly vulnerable (75). Despite the prevalence of HF among the elderly, there are no specific guidelines tailored to managing it in this population (76, 77).

Alongside pharmacotherapy, several RCTs have demonstrated that CRT reduces morbidity and mortality in symptomatic HF patients with HFrEF, and widened QRS (10-17, 78). However, most of these trials have enrolled only a very limited number of elderly patients, who tended to have fewer comorbidities than the real-world CRT population (79). This age discrepancy could influence the outcomes observed. Therefore, real-world data may provide valuable insights into the effectiveness of CRT in the elderly (11, 77, 78, 80).

Observational trials have revealed higher mortality rates among patients ≥ 75 years, mainly due to non-cardiac causes (81, 82). However, the incidence of HF hospitalization appeared to be similar across age groups (83). Additionally, as HF patients now benefit from improved pharmacological treatments and are living longer, the causes of death are shifting away from cardiovascular causes toward non-cardiovascular causes, emphasizing the need to assess the efficacy and safety of CRT in older patients before implantation (84, 85).

Given these considerations, it is important to explore whether advancing age could negatively affect the response to CRT in this expanding population of elderly CRT candidates (68, 74, 86, 87).

Baseline clinical features of our patient group were similar to those enrolled in earlier RCTs and real-world evidence studies, that examined age-related differences in CRT response and outcomes (10, 11, 68, 70, 71, 81-83, 88-102). Among older patients, we

observed a higher proportion of females, ischemic aetiology, and worse renal function. However, they had a higher LVEF and smaller LV chamber sizes. In terms of comorbidities, older patients tended to have multiple concomitant chronic illnesses, which can impact HF prognosis and contribute to a higher incidence of non-cardiovascular death among the elderly (68, 77, 84). A previous study by Braunstein et al. examined how noncardiac comorbidities affect clinical outcomes in HF patients, revealing a direct correlation between the number of these concomitant diseases and the rates of hospitalization and mortality (103). Several other studies evaluated the effect of specific comorbidities on HF outcomes, indicating that the presence of kidney dysfunction, anaemia, and cognitive impairment are associated with adverse outcomes (104-107). Furthermore, following CRT implantation, conditions such as kidney disease, diabetes mellitus, and atrial fibrillation emerged as strong independent predictors of mortality (108, 109).

As the number of elderly HF patients increases due to the ageing population and prolongation of life, there is a pressing question regarding whether age negatively impacts CRT response (74, 86, 87). RCTs and real-world evidence studies have demonstrated that CRT can improve LV systolic function and cause LV reverse remodeling, with these effects being age-independent (70, 71, 81-83, 90, 92, 93, 96-99). Previous studies have consistently shown that CRT can lead to comparable improvement in LVEF and LV dimensions, regardless of age. The MIRACLE and MIRACLE ICD trials found no age-related differences in LVEF improvement after CRT implantation (70). Similarly, the substudy of the InSync/InSync ICD Italian Registry demonstrated significant LV reverse remodeling induced by CRT, resulting in comparable responder rates across all age groups (82). In our retrospective analysis, we observed significant improvement in LVEF 6 months after CRT implantation across all age groups, with no notable differences in the percentage of responders to CRT among them (68). These findings are in line with the results of previous studies, indicating that advanced age does not affect the positive response to CRT (70, 71, 81-83, 90, 92, 93, 96-99). However, it is essential to recognize that while chronological age may be similar across different patient cohorts, variations in response to CRT could be more closely tied to factors like frailty, which involves an individual's overall biological status. Nonetheless, the collective evidence suggests that the entire age spectrum of HF patients benefit from CRT, regardless of age.

Numerous observational studies and subgroup analyses have consistently revealed no significant differences between the various age groups with regard to procedure-related complications (70, 71, 81, 82, 88, 92, 93, 97, 98, 101). These findings align with our observations, indicating that CRT implantation is generally safe and well-tolerated even among older individuals (68). However, it is worth noting that most of the RCTs and large-scale observational studies are typically conducted in high-volume centers, which may lead to lower complication rates. While pneumothorax, a known adverse event during CRT implantation, is reported to be more common in the elderly compared to younger patients, our analysis did not confirm this trend (68, 84). In our current analysis, we observed disparities in the rate of pocket infections between older and younger patients. The lower rate observed in older patients could be attributed to the overall lower prevalence of this complication in both age groups (68).

Patients with HF have different long-term outcomes depending on a variety of characteristics, including age, frailty, sex, and electrical parameters during the implantation (69, 110-112). Age has no effect on the risk of all-cause mortality, heart failure hospitalization, or HF hospitalization alone, according to subgroup analyses from RCTs and earlier observational studies (10, 11, 81-83, 90, 93, 95, 96, 99, 101, 102). However, when all-cause mortality was examined separately, the majority of studies found that older patients had a significantly higher death rate. (71, 81-83, 88, 96, 100). With advancements in therapy and ageing, the pattern of death in HF patients has changed, with fewer cases attributed to sudden cardiac death and more to noncardiac causes, especially cancer (113, 114). This shift is particularly noticeable in the elderly population (84). A study by Rutten et al. examined the final year of 399 HF patients, with a mean age at death of 82.3 years. They observed sudden death in 28%, progressive HF in 23%, and other causes in 49% of their patients as the mode of death (85). Analysis of mortality causes by age indicates a higher incidence of noncardiac causes among older patients, while rates of cardiac death remain comparable across age groups (71, 81, 82). These findings suggest that the increased prevalence of multimorbidity in older patients contributes significantly to their survival differences compared to nonelderly patients.

As expected given their higher burden of concurrent diseases, our current study also reveals a statistically significant increase in all-cause mortality among older subgroups (68). These findings highlight the significance of comorbidities, particularly in CRT

responders, as the existence of these coexisting chronic illnesses mostly influences non-cardiac death in their long-term outcomes (68).

Analyzing the association between age as a continuous variable with all-cause mortality using proportional hazards regression restricted cubic spline models, the lowest inflection point was found around 43 years. The higher all-cause mortality risk seen in younger patients might be due to the different, more malignant nature of heart failure in such patients (eg. different etiology) (68).

Current guidelines recommend implanting a CRT-D device mainly at a younger age due to a lower cumulative rate of appropriate shocks in the elderly, especially in non-ischemic patients, as shown in observational trials and other RCTs, like the DANISH study (20, 88, 115). Additionally, no age-related difference was observed in mortality risk following appropriate shock therapy (81, 88). Interestingly, a post hoc analysis of the DANISH study showed that the association between ICD therapy and all-cause mortality declines with increasing age, particularly in non-ischemic patients, with no survival benefit observed in patients over 70 years (116). While ischemic aetiology is more prevalent in older patients, the lower occurrence of malignant ventricular arrhythmias in this age group and the limited impact on all-cause mortality suggest implanting a CRT-P alone as an alternative to CRT-D. This decision is supported by the fact that preventing sudden cardiac death has a limited effect on all-cause mortality, which is primarily dominated by noncardiac causes in elderly patients (115-118). Thus, selecting the most suitable device for the oldest CRT recipients is a relevant issue. While CRT-D implantation does not appear to mean an increased risk in the elderly, several studies suggest that it may not offer additional benefits in terms of morbidity and mortality compared to CRT-P alone (119-123). In our patient cohort, we found a significant increase in the mean age of both CRT-P and CRT-D recipients since 2000, likely due to the development of new HF medications and longer life expectancy leading to a larger population of older HF patients (68, 124-126). However, compared to CRT-D recipients, the mean age of CRT-P recipients was significantly higher, which possibly reflects the preferences of treating physicians and elderly patients as well as guideline recommendations. (68). However, our results remained unchanged even after we adjusted our models for the type of the implanted device (68). Despite the growing trend in CRT-D implantations, it still remains

significantly less common in older patients in everyday clinical practice (68, 71, 81-83, 89-91, 93, 94, 100).

5.2. Part 2 - Lateral left ventricular lead position is superior to posterior position in long-term outcome of patients underwent CRT implantation

Improving the response rate remains a key objective for CRT, yet there is limited and conflicting data regarding the impact of LV lead positions on long-term clinical outcomes. Previous RCTs suggested that using speckle-tracking echocardiography to assess the latest activated part of the LV might help with a more precise LV lead placement, resulting in better subsequent outcomes compared to routine methods (127, 128). However, this approach may be limited by the anatomical location of coronary sinus side branches. Our alternative method involves evaluating the latest activated part by measuring the RV-LV interlead delay during CRT implantation. This approach appears to offer advantages over speckle-tracking echocardiography, potentially circumventing limitations related to coronary sinus anatomy and providing a superior means of optimizing LV lead placement for improved CRT response (69).

The mid-term analysis of the MADIT-CRT trial highlighted that an apical left ventricular lead position is associated with unfavourable clinical outcomes in CRT-D patients. However, their findings did not show a clear advantage of placing the LV lead at the lateral position over anterior or posterior positions in terms of HF or death, HF only, and death alone (46). Similarly, in the subgroup analysis of the COMPANION trial, a survival benefit was observed in the CRT-D group regardless of LV lead location, whereas, in the CRT-P group, only patients with a lateral LV lead position experienced a lower all-cause mortality rate (129). Nonetheless, it is crucial to remember that in our current research, we evaluated all-cause mortality by various LV lead placements, whereas in this comparison, patients receiving just optimal pharmacological therapy were the subjects of comparison. (69).

Inconsistent findings on the short-term clinical outcomes by LV lead positions were reported by several earlier investigations. In the REVERSE substudy, Thebault et al. discovered that a lateral LV lead location as opposed to a non-lateral position, was

associated with a significantly decreased risk of HF hospitalization or all-cause mortality (130). Their results are consistent with ours, demonstrating that lateral positioning is associated with a significantly decreased risk of hospitalization for heart failure or all-cause mortality when compared to non-lateral positions (69). However, our analysis revealed that the lateral LV lead location was the only one to predict long-term mortality and was superior to the other positions in reducing the risk of all-cause mortality, while their analysis did not find a significant correlation between lateral position and a reduction in the risk of all-cause mortality alone. (69). This discrepancy in results between studies could be due to variations in the proportion of 'lateral' location, including true lateral and postero-lateral positions. The percentage of lateral LV lead location was 80.4% in the REVERSE (130) trial compared with 59% in the MADIT-CRT (46) trial, while in our dataset 64.3% of the participants had a true lateral LV lead location (69).

In terms of long-term follow-up, only Kutyifa et al. found that mild HF patients with CRT-D and LBBB who had lateral or posterior LV lead locations had lower long-term all-cause mortality (47). Additionally, in comparison to patients with ICD alone, non-apical short axis locations were associated with decreases in the combined endpoint of HF or death, or HF alone (47). However, in this trial they combined the posterior and lateral positions because they saw comparable results in terms of HF or death between these two groups (47). To the best of our knowledge, our present analysis is the first to demonstrate on a real-world patient population that in terms of lowering long-term all-cause mortality, a lateral LV lead location is superior to a posterior position (69).

Moreover, our current analysis provides further insight into the long-term clinical outcome of CRT patients by their IED (69). Our findings align with several smaller studies, suggesting that patients with a longer IED may experience a more favourable response to CRT (48-56, 69). In the SMART-AV study conducted by Gold et al., they observed significant improvements in all echocardiographic remodeling parameters (including LVESV, LVEDV, EF), as well as the quality of life with longer RV-LV electrical delays (50). They identified an optimal cut-off value of 80 ms.

Similarly, a recent study by Sommer et al. emphasized the correlation between IED and the LV reverse remodeling CRT response in patients whose LV lead sites were thought to be ideal. They showed that stronger LV reverse remodeling, QRS shortening, and

improvement in NYHA class were all related to longer IEDs. However, they observed comparable rates of HF hospitalizations between patients with longer and shorter IED. Their optimal cut-off value was 101 ms (54).

In a previous prospective study by Kosztin et al., patients with LBBB and an IED equal to or greater than 86 ms demonstrated the greatest improvement in LVEF 6 months following CRT implantation (51). While in our current analysis patients with an IED longer than 110 ms showed a 2.1 times higher likelihood of experiencing echocardiographic improvement 6 months after the implantation (69).

5.3. Part 3 - Non-progressors to cardiac resynchronization therapy show long-term mortality benefit compared to progressors

Traditionally, outcomes following CRT have been categorized as responders and non-responders, with various criteria used to define response. This non-responder group includes patients who either worsen (progressors) or show no improvement (non-progressors) after the implantation (25). Recent studies indicated that patients with minimally improved or unchanged LVEF or LVESV after CRT tend to have better short-term outcomes compared to those, whose parameters worsen. However, these studies typically involved patients from RCTs with relatively short-term follow-up periods (29, 30). Another real-world study by Rickard et al. examined 1058 patients from three large medical centers (31). The baseline clinical characteristics of their patients were comparable with ours, non-progressors were more commonly male, with ischemic aetiology, and worse renal function compared to responders and a lower LVEF compared to progressors. However, unlike us, they observed no significant difference in long-term survival between non-progressors and progressors.

Previous studies defined “non-responders” as patients whose LVEF increased by <5%, grouping non-progressors and progressors together, which may be misleading. Our findings highlight the importance of post-CRT echocardiographic evaluation up to 12 months to identify progressors early on. These patients represent a very high-risk group with the poorest long-term prognosis, necessitating careful follow-up and potentially indicating the need for urgent, more aggressive advanced HF therapies as soon as

possible. Non-progressor patients should be monitored closely and can have time for clinically relevant, invasive decisions. For instance, in our patient cohort, suboptimal LV lead locations were found commonly in this population or they were characterized by ischemic aetiology. In these cases, possible interventions like LV lead re-positioning or LV endocardial lead implantation could be considered. Furthermore, other reversible causes for moderate echocardiographic response, such as suboptimal medical therapies or arrhythmias (e.g. atrial fibrillation, ventricular extrasystole, etc.) which can lead to low biventricular pacing rate should also be evaluated and treated invasively if necessary (131). Altogether, different clinical decisions are warranted for progressors vs. non-progressors. For the latter, time-consuming and often invasive procedures may be performed to address factors contributing to the moderate response, while rapid progression observed in progressors limits decision-making and necessitates more aggressive clinical interventions.

5.4. Limitations

The present results should be interpreted in light of certain limitations. First, this study was a retrospective analysis of our single-center CRT database. As a result, echocardiographic evaluations were not performed by the same physician, which might have influenced the evaluation of reverse remodeling. Second, we lack data on the specific mode of death, thus we could not investigate cardiac and noncardiac causes separately. Third, not all of our patients were continuously followed at our center, leading to potential missing data on procedure-related complications, which could have influenced our results. Fourth, the limited number of patients with anterior LV lead position might have influenced the outcome data. Finally, IED may have been influenced by the availability of suitable veins for lead placement, which is a well-known bias for all CRT studies, therefore, it has to be acknowledged.

6. Conclusions

Cardiac resynchronization therapy is an effective device therapy option to improve cardiac function, and reduce symptoms, the risk of hospitalization for heart failure, and all-cause mortality in mild to severe heart failure patients with reduced ejection fraction and prolonged QRS. However, there is still a relatively high number of patients who do not show beneficial response after the implantation.

In our retrospective, large-scale single-center study which was implemented from Heart and Vascular Center, Semmelweis University, we investigated potential parameters that could influence the response to CRT and also analysed the reclassification of response to CRT and its impact on managing heart failure in everyday clinical practice.

In our real-world patient cohort, our findings demonstrate that CRT is as effective in improving left ventricular ejection fraction and as safe in the elderly as in younger ones. These findings suggest that patients with appropriate indications benefit from CRT, regardless of their age. Time-trend analyses showed an increase in the mean age of CRT-P and CRT-D recipients with a significant difference between the two groups, and in the percentage of CRT-D implantations. Moreover, response rate increased in each subgroup as a result of adding new effective pharmacological therapies.

Our results showed that after CRT implantation only the lateral left ventricular lead position was associated with long-term all-cause mortality benefit and it is superior to both anterior and posterior locations. Furthermore, higher odds for improving echocardiographic reverse remodeling can be detected when interlead electrical delay was longer than 110 ms in this patient group.

Analysing the new criteria by response, non-progressors to CRT had a comparable long-term outcome to responders and a superior outcome to progressors. Our findings support the concept that non-progressors are a separate phenotype, probably requiring different treatment strategies. These data suggest that non-progressor patients would have continued to adversely remodel without CRT. Moreover, these findings support the reclassification of our patients as super-responders, responders, non-progressors, and progressors. Selecting non-progressor and progressor patients will certainly influence our clinical decisions.

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7. Summary

Cardiac resynchronization therapy is an effective device therapy option for chronic heart failure. However, there is still a notable number of patients who do not experience beneficial response after the implantation.

First, we aimed to investigate a very important patient selection criterion, whether age may negatively affect the response to CRT. We evaluated the age-related differences in the effectiveness of CRT, peri- and postprocedural complications, and long-term outcomes in our real-world retrospective patient cohort, including 2656 CRT recipients. Second, we tested our hypothesis by investigating an intraoperative parameter, suggesting that non-lateral left ventricular lead positions are associated with worse clinical outcomes. We evaluated the distribution of the length of interlead electrical delay by LV lead non-apical positions, to assess the long-term clinical outcome accordingly and further characterize the mid-term echocardiographic response by IED. Third, we aimed to analyse the new criteria by the response to CRT to evaluate the long-term outcome of CRT recipients by these new categories, comparing non-progressors to responders and progressors.

Based on our results, CRT is comparably effective in improving cardiac function and as safe in older patients as in younger ones. The response rate increased across all subgroups as a result of adding new effective pharmacological therapies. Our findings demonstrated that after CRT implantation only the lateral left ventricular lead location was associated with reduced long-term all-cause mortality risk and it is superior to both anterior and posterior positions. Additionally, higher odds for improving echocardiographic reverse remodeling could be detected when interlead electrical delay was longer than 110 ms in this patient group. Examining the response to CRT based on the new criteria, non-progressors to CRT presented a comparable long-term outcome to responders and a superior outcome to progressors. These data suggest that non-progressors represent a distinct phenotype, who would have likely continued to experience adverse remodeling without CRT. Identifying non-progressors and progressors will undoubtedly impact our clinical decision-making processes.

Our results will provide further data for clinicians in their everyday clinical practice and clarify uncertainties in current guidelines.

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9. Bibliography of the candidate's publications

Publications related to the current thesis

1. **Behon A**, Merkel ED, Schwertner WR, Kuthi LK, Veres B, Masszi R, Kovács A, Lakatos BK, Zima E, Gellér L, Kosztin A, Merkely B:
   Long-term outcome of cardiac resynchronization therapy patients in the elderly.
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2. **Behon A**, Schwertner WR, Merkel ED, Kovács A, Lakatos BK, Zima E, Gellér L, Kutyifa V, Kosztin A, Merkely B:
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   Cardiologia Hungarica 52 : 3 pp. 208-217. , 10 p. (2022)

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1. Merkel ED, **Behon A**, Masszi R, Schwertner WR, Kuthi L, Veres B, Osztheimer I, Papp R, Molnár L, Zima E, Gellér L:
   Obesity paradox in patients with reduced ejection fraction eligible for device implantation – an observational study
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2. Tokodi M, Kosztin A, Kovács A, Gellér L, Schwertner WR, Veres B, **Behon A**, Lober C, Bogale N, Linde C, Normand C, Dickstein K, Merkely B:
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NYILATKOZAT EREDETISÉGRŐL ÉS SZERZŐI JOGRÓL

a PhD disszertáció elkészítésére vonatkozó szabályok betartásáról

Alulírott Dr. Behon Anett jelen nyilatkozat aláírásával kijelentem, hogy a Non-pharmacological treatment of chronic systolic heart failure - Optimization of response to cardiac resynchronization therapy for the treatment of chronic heart failure című PhD értekezésem önálló munkám, a dolgozat készítése során betartottam a szerzői jogról szóló 1999. évi LXXVI tv. vonatkozó rendelkezéseit, a már megjelent vagy közlés alatt álló közlemény(ek)ből felhasznált ábra/szöveg nem sérti a kiadó vagy más jogi vagy természetes személy jogait.

Jelen nyilatkozat aláírásával tudomásul veszem, hogy amennyiben igazolható, hogy a dolgozatban nem saját eredményeimet használtam fel vagy a dolgozattal kapcsolatban szerzői jog megsértése merül fel, a Semmelweis Egyetem megtagadja PhD dolgozatom befogadását, velem szemben fegyelmi eljárást indít, illetve visszavonja a már odaítélt PhD fokozatot.

A dolgozat befogadásának megtagadása és a fegyelmi eljárás indítása nem érinti a szerzői jogsértés miatti egyéb (polgári jogi, szabálysértési jogi, büntetőjogi) jogkövetkezményeket.

Tudomásul veszem, hogy a PhD értekezés nyilvánosan elérhető formában feltöltésre kerül az Országos Doktori Tanács honlapjára.

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aláírás