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Programvezető: Dr. Merkely Béla, egyetemi tanár

Témavezetők: Dr. Merkely Béla, egyetemi tanár
Dr. Kosztin Annamária egyetemi docens

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OPTIMIZATION OF CARDIAC RESYNCHRONIZATION THERAPY FOR THE TREATMENT OF CHRONIC HEART FAILURE: RESPONSE OF PATIENTS AND OUTCOMES

PhD thesis

Eperke Dóra Merkel, MD

Semmelweis University Doctoral School

Cardiovascular Medicine and Research Division

Supervisors: Béla Merkely, MD, D.Sc.
Annamária Kosztin, MD, Ph.D.

Official reviewers: Attila Kónyi, MD, Ph.D., habil.
Viktor Horváth, MD, Ph.D., habil.

Head of the Complex Examination Committee: Alán Alpár, MD, D.Sc.

Members of the Complex Examination Committee: Miklós Kellermayer, MD, D.Sc.
Mihály Kovács, D.Sc.

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List of Abbreviations

ACE-I – angiotensin-converting-enzyme inhibitor
ARNI - angiotensin receptor-neprilysin inhibitor
AV – atrioventricular
BiV – biventricular
BNP – B-type natriuretic peptide
CCS – clinical composite score
CIED – cardiac implantable electronic devices
CRT – cardiac resynchronization therapy
ECG – electrocardiography
ESC – European Society of Cardiology
GDMT – guideline-directed medical therapy
GRS – Goldenberg risk score
HF – heart failure
ICD – implantable cardioverter defibrillator
LBBB – left bundle branch block
LV – left ventricle
LVAD – left ventricular assist device
LVEDD – left ventricular end-diastolic diameter
LVEDV- left ventricular end-diastolic volume
LVEF – left ventricular ejection fraction
LVESV - left ventricular end-systolic volume
LVESD - left ventricular end-systolic diameter
MRA – mineralocorticoid receptor antagonist
NYHA – New York Heart Association
NT-proBNP – N-terminal pro-B type natriuretic peptide
RCT – randomized controlled trial
SCD – sudden cardiac death
se-BUN – serum blood urea nitrogen
SGLT-2 – sodium glucose co-transporter-2
VA – ventricular arrhythmia

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VHR – very-high risk

6-MWT – 6-minute walk test

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1. Introduction

1.1. Definition and epidemiology of chronic systolic heart failure

Heart failure (HF) is a clinical syndrome, comprising typical symptoms, such as shortness of breath or fatigue, along with other signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema); caused by the structural or functional abnormality of the heart leading to elevated intracardiac pressure or insufficient cardiac output. HF can be classified into different phenotypes mainly by measurements of the left ventricular ejection fraction (LVEF), or by differentiating between left or right ventricular dysfunction, or by the time of onset (chronic or acute HF) (1)

The most frequently used categorization, by left ventricular (LV) function, we differentiate three phenotypes: HF with reduced ejection fraction ([HFrEF] LVEF ≤40%), HF with mildly reduced LV systolic function ([HFmrEF] LVEF 41-49%) and those with preserved LV ejection fraction ([HFpEF] LVEF ≥50%). (1) This differentiation is crucial due to the varying prevalence, demography, prognosis, and treatment.

In general HF concerns roughly 1-2% of the population, but its prevalence can reach up to 10% above 70 years of age. (2-5) The standardized incidence seems to be decreasing, however due to ageing, the overall incidence is increasing. (6, 7) The incidence is about 5/1000 person-years in adults in Europe. (8, 9)

1.2. Diagnosis of heart failure

To establish the diagnosis of HF, symptoms and/or signs of HF are required to be present with objective evidence of cardiac dysfunction. Once the suspicion of HF arises (risk factors, symptoms and/or signs or an abnormal ECG), the diagnostic algorithm proposed by the European Society of Cardiology (ESC) advises to assess the N-terminal pro-B type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) levels. If any of those prove to be elevated (NT-proBNP ≥125pg/mL or BNP ≥35pg/mL) or are not available for assessment, echocardiography is recommended. If cardiac dysfunction is confirmed, the diagnosis of HF can be established, and the phenotype should be defined based on LVEF measurement. Other diagnostic tools are also recommended, like a 12-

lead electrocardiography (ECG), chest X-ray, and routine blood tests for comorbidities. Once diagnosed, evaluation of etiology and initiation of therapy is crucial. (1)

1.3. Treatment of chronic systolic heart failure

As a progressive disease (10), with a poor prognosis, early diagnosis and early initiation of therapy is fundamental. Treatment of HF is mainly categorized as pharmacological and non-pharmacological. The main objectives of treatment are to reduce mortality, morbidity, (recurrent) hospitalizations, to improve clinical status, symptoms, and quality of life (QoL). (11-13)

1.3.1. Pharmacological treatment

Pharmacotherapy is the core treatment of symptomatic HFrEF patients, the four pillars of treatment should be commenced as soon as possible. Angiotensin-converting enzyme inhibitors (ACE-I) (14-16), beta-blockers (17-22), mineralocorticoid receptor antagonists (MRA) (23, 24) and sodium glucose co-transporter-2 inhibitors ([SGLT-2] dapagliflozin or empagliflozin) (25, 26) are recommended to reduce the risk of HF hospitalization and death with a class recommendation I and level of evidence A.

ACE-Is have been the cornerstone treatment for HFrEF patients for more than two decades, they provided a survival benefit to these patients. (14, 16) The PARADIGM-HF was the first randomized controlled trial (RCT) to compare angiotensin receptor-neprilysin inhibitor treatment (ARNI, sacubitril/valsartan) with enalapril. Adding ARNI reduced the risk of death from cardiovascular causes or hospitalization for HF by 20% (HR 0.80; 95% CI 0.73-0.87; $p<0.001$), reduced the risk of all-cause mortality (HR 0.84; 95% CI 0.76-0.93; $p<0.001$) and HF hospitalization alone (HR 0.79; 95% CI 0.71-0.89; $p<0.001$). The safety and efficacy of ARNI initiation in patients stabilized after acute decompensation have also been observed. (27, 28) Based on these results, the ESC guidelines state that ARNI is recommended as a replacement of ACE-Is in ambulatory, symptomatic patients despite optimal treatment. (27-29) Moreover, ARNI may also be considered as first-line treatment in hospitalized ACE-I naive patients (class of recommendation IIb, level of evidence B). (30) The 2022 AHA/ACC/HFSA guideline recommends ARNI as first line treatment and states that the use of ACE-I is beneficial

when ARNI is not feasible, both with a level class of recommendation I and level of evidence A. (31)

Loop diuretics are also advised in selected patients to reduce volume overload, to alleviate symptoms and to reduce HF hospitalizations with a class recommendation I and level of evidence C. (32)

RCTs proved the efficacy of SGLT-2 inhibitors dapagliflozin and empagliflozin in HFrEF patients. In the DAPA-HF trial, dapagliflozin reduced the risk of the primary endpoint, a composite of worsening of HF and cardiovascular death by 26% (HR 0.74; 95% CI 0.65-0.85; p<0.001). (33) Similar results were observed with empagliflozin in the EMPEROR Reduced trial (HR 0.75; 95% CI 0.65-0.86; p<0.001). (26) An early SGLT-2 inhibitor, sotagliflozin was studied in diabetic patients hospitalized for worsening of HF, therapy resulted in a significant reduction of cardiovascular deaths and worsening of HF compared to placebo. (34)

The implementation of guideline recommended drugs remains challenging, as the conventional sequencing of drug implementation can be prolonged and may not reach the target dose. A novel sequencing suggests rapid introduction of said drugs (in 4 weeks) and their rigorous uptitration. (35)

1.3.2. Non-pharmacological treatment

1.3.2.1. Implantable cardioverter defibrillator

Guideline-directed medical therapy (GDMT) reduces the risk of ventricular arrhythmias (VA) (27, 36, 37). However, at occurrence only implantable cardioverter defibrillators (ICD) can effectively treat electrical disturbances like VA primarily. The ICD consists of a shock-coil implanted into the right ventricle, when a ventricular tachycardia (VT) occurs the device can override it with anti-tachycardia pacing (38) or by delivering a high-energy shock in case of both VT and ventricular fibrillation (VF). Subcutaneous or extravascular ICDs or wearable cardioverter-defibrillators (temporarily) are viable alternatives for conventional transvenous ICDs in well-selected patients. (39-41)

ICD therapy, as secondary prevention, is recommended in patients that have recovered from sudden cardiac death (SCD), in the absence of reversible causes and a 1-

year survival expectancy to reduce the risk of SCD and all-cause mortality. Based on the AVISH and CASH trials, ICD therapy in patients who survived life-threatening VAs is associated with a reduction of all-cause mortality compared with antiarrhythmic drugs (42, 43)

As primary prevention, ICD therapy recommendations differ based on HF etiology. In symptomatic patients (NYHA class II-III) of ischemic etiology and an LVEF $\leq$ 35% despite $\geq$3 months of OMT, prophylactic ICD implantation is recommended (class IA) to reduce the risk of SCD and all-cause mortality. In the MADIT II trial HFrEF patients of ischemic etiology were randomized to ICD therapy vs. conventional medical therapy, ICD therapy reduced the risk of all-cause mortality by 31% (HR 0.69; 95% CI 0.51-0.93; p=0.016). The SCD-HeFT trial compared the effectiveness of ICD therapy with conventional treatment with placebo or amiodarone. While amiodarone did not have favorable effect on all-cause mortality, ICD therapy reduced it by 23% (HR 0.77; 97.5% CI 0.62-0.96; p=0.007). (44, 45)

The recommendation for those of non-ischemic etiology has been of class IIa, level of evidence A, since the DANISH trial reported no benefit in the reduction of all-cause mortality in patients of non-ischemic etiology (46) and influenced prior evidence. (45, 47) In the SCD-HeFT trial HF patients regardless of their etiology were enrolled and there was no interaction of ICD therapy with the etiology of HF. (45) In both cases a survival expectancy of 1 year is necessary with good functional status. (48-50) ICD implantation is not advised in severely symptomatic patients (NYHA class IV) refractory to pharmacotherapy as these patients are more likely to die from the worsening of HF. (45)

1.3.2.2. Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is an effective treatment to reduce morbidity and mortality in optimally selected patients. (51-53) CRT successfully alleviates symptoms of HF and ameliorates QoL by improving cardiac function. (52)

CRT is a two- or three-lead device capable of pacing both ventricles and the right atrium (in sinus rhythm) mainly to reduce the LV intraventricular dyssynchrony and achieve an improved LVEF by the resynchronized contraction of the LV. With adequate programing CRT reduces inter- and intraventricular delays if an atrial lead is also

implanted AV dyssynchrony can also be reduced. Conventionally the LV lead, implanted through the coronary sinus, is positioned, and fixed into the epicardial vein, a side branch of the coronary sinus. If CRT implantation cannot be performed via the coronary sinus, a transseptal (54) or epicardial (55) approach can be performed. The success of the implantation and positioning is greatly affected by the anatomy of the epicardial veins.

1.4. Efficacy of cardiac resynchronization therapy

1.4.1. Mechanism of action

Due to the progressive nature of the disease, in chronic HF the heart goes through a remodeling, manifested clinically as changes in ventricular volumes, diameters and function (LVEF, cardiac output) caused by molecular, cellular, pathophysiological, neurohormonal, and interstitial changes. The renin angiotensin system and the sympathetic nervous system are also factors affecting this remodeling. (56) Cardiac remodeling up to a certain measure can be adaptive, however progressive remodeling can always be considered deleterious and can be associated with poor prognosis. (57-59) As HF deteriorates, an electrical and mechanical dyssynchrony arises between the right and left ventricle leading to poor cardiac contractility and a decreased cardiac output. Due to the dilatation, conduction delays occur such as a left bundle branch block (LBBB). (60) Prolonged QRS duration and LBBB have been both associated with higher risks of mortality. (61, 62) Chronic HF patients experience abnormal AV delays (63-65) resulting in an increased mitral regurgitation (MR) and a decreased diastolic filling. (66) Next to an interventricular delay, an intraventricular one can also be observed. (67, 68) In these electromechanical dyssynchronies, two third of the patients the lateral wall was the most delayed segment of the left ventricle. (67) Similarly to this electromechanical dyssynchrony, dyssynchrony can also be iatrogenic, induced by right ventricular pacing. (69).

The effect of CRT offsets at implantation, acutely an increased cardiac output, an improved mechanical efficiency, and a reduced MR occurs. (70, 71) With BiV pacing LVEF improves, LV end-systolic diameter (LVESD) and LV end-systolic and end-diastolic volumes (LVESV and LVEDV, respectfully) decrease significantly as a consequence of reverse remodeling, a phenomenon resulting from structural and

functional changes. (71) Not only LV improvements are present, but other parameters can also reflect the reverse remodeling and milestone RCTs related them to beneficial changes, left atrial volumes decrease and right ventricular fractional area change improves as well. (72, 73) A variety of results were published on the effect of CRT on MR, in the REVERSE study MR did not improve significantly (74), in the MADIT-CRT trial MR did decrease, however it only had a limited effect on the outcome. (72) In the MIRACLE trial, with severely symptomatic patients (NYHA III/IV), patients at 12 months experienced significant improvement of MR. (75)

1.4.2. Current indication

1.4.2.1. CRT in sinus rhythm

Indications of CRT are established based on the results of previous trials, the current recommendations are summarized in Table 1. Most trials proved the efficacy of the device in patients with moderate to severe symptoms, II-IV NYHA class. (52, 53, 76-80) In the MADIT-CRT trial, 15% of the patients were asymptomatic, NYHA class I, with ischemic etiology, in these patients CRT did not reduce the risk of death or non-fatal HF event significantly. (53, 81)

The specified LVEF was determined based on the inclusion criteria of RCTs, most trials included patients with an LVEF <35%, the MADIT-CRT (53) and RAFT (80) trials enrolled patients with and LVEF <30%, and the REVERSE (78) trial considered patients with an LVEF <40%.

The published results of prior trials led to ameliorate patient selection, QRS duration and morphology is greatly associated CRT's efficacy. Specifically, patients with LBBB are more likely to respond favorably than those with non-LBBB morphology. (82, 83) Patients with an RBBB do not benefit from CRT and has been described as harmful. (84) Regarding QRS duration, the strongest evidence has been for a QRS >150ms. (81, 85) CRT implantation for patients with a narrow QRS (<130ms) is not recommended and is harmful. (86)

1.4.2.2. CRT in atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia in the adult population globally, its prevalence in HF patients can reach 30 to 45%. (4) AF, especially with fast ventricular rate can create spontaneous, fusion, or pseudo-fusion beats leading to inadequate BiV pacing. In persistent or permanent AF approximately two-third of the patients do not reach a high rate of BiV pacing. (87)

Based on the 2021 ESC guidelines, in candidates for CRT with permanent AF recommendation and data is scarce, implantation should be considered, however an adequate BiV capture must be ensured to reduce morbidity and mortality. (87-89) In case of inadequate percent of BiV pacing (<90-95%) AV-junction ablation should be added to the line of therapy. (90, 91) These recommendations rely mostly on subgroup analyses of the cornerstone CRT trials that studied patients with permanent AF but with uncertain benefit. (53, 76, 78, 80) AF patients undergoing CRT still have a higher risk of mortality. (87-89)

1.4.2.3. CRT in high RV pacing burden

In case of a conventional indication for ventricular pacing and high degree AV block, CRT implantation is recommended instead of RV pacing for patients with an LVEF ≤ 40%, regardless of NYHA class, to reduce morbidity. Three RCTs confirmed the superiority of BiV pacing over RV pacing in patients with moderate systolic dysfunction and who require antibradycardia pacing. (92-94) However, only the BLOCK-HF studied hard endpoints such as death or HF event. (92) In the BLOCK-HF trial patients who had an indication for pacing with an AV-block and an LVEF ≤50% were enrolled and randomized to either biventricular or right ventricular pacing. BiV pacing reduced the risk of all-cause mortality, urgent care visit for HF, or a 15% or more increase in the LVESV index by 26% (HR 0.74; 95% CI 0.60 to 0.90). (92)

High RV pace burden can lead to RV-pacing induced cardiomyopathy. (95) Biventricular pacing whether de novo or upgrade can prevent unfavorable outcomes. (96) Since data was limited on the benefits of CRT upgrade, up until now the recommendation relied mostly on observational studies (97) or on subgroup analyses of RCTs. (98, 99) Thus based on the 2021 ESC Guidelines, upgrade to CRT should be considered in patients

with cardiac implantable electronic devices (CIED) who develop symptomatic HF with an LVEF ≤35% despite GDMT and who present with a significant proportion of RV pacing. The 2023 HRS guidelines, based on a meta-analysis, state that in patients with CIED and LV function decline or worsening of HF symptoms attributed to high RV pacing CRT is recommended to improve LV function and HF symptoms. (100, 101)

However, since then, the results of the BUDAPEST-CRT Upgrade trial have been published, the first RCT to compare CRT-D upgrade vs. ICD upgrade alone. HFrEF patients with a previously implanted PM or ICD, an RV pacing burden ≥ 20% and a wide paced QRS complex ≥ 150ms were randomized to CRT-D or ICD upgrade alone. During the median follow-up time of 12.4 months, upgrade to CRT-D compared to ICD alone reduced the combined risk of all-cause mortality, HF hospitalization or absence of reverse remodeling (OR 0.11. 95% CI 0.06 to 0.19; $p<0.001$). (102) Upgrade to CRT led to improvement in NYHA class and a significant decrease in NT-proBNP levels. The decrease in NT-proBNP levels were 1.5 times greater in responder patients as compared to non-responders. At the 12-month follow-up patients in the CRT-D upgrade group had a 50% higher chance of experiencing at least one NYHA functional class improvement compared to the ICD-only group. Also, CRT-D upgrade led to a moderation of the progression of worsening of QoL attributed to ageing. (103)

Table 1. Summary of CRT recommendations based on the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

LVEF	NYHA class	Initial rhythm	QRS morphology	QRS duration	Class	Level of evidence
≤ 35%	II – IV	SR	LBBB	≥150 msec	I	A
≤ 35%	II – IV	SR	LBBB	130–149 msec	IIa	B
≤ 35%	II – IV	SR	Non-LBBB	≥150 msec	IIa	B
≤ 35%	II – IV	SR	Non-LBBB	130–149 msec	IIb	B
≤ 35%	III – IV	AF	LBBB / non-LBBB	≥130 msec	IIa	C
≤ 40%	I – IV	High-degree AVB	-	-	I	A
≤ 35%	II – IV	Significant proportion of RV pacing	-	-	IIa	B
-	I-IV	SR/AF	-	<130 msec	III	A

AF, atrial fibrillation; AVB, atrioventricular block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular; SR, sinus rhythm

1.4.3. Response to cardiac resynchronization therapy

1.4.3.1.The definitions of response

As there is no present universal definition of response to CRT, its evaluation varies by methods and timeframes, several definitions can be found in literature, using different cut-off values. (104)

Response to therapy can be measured either by assessment of clinical endpoints, echocardiographic response, or major clinical events. Evaluation of clinical status can be executed by studying symptoms, NYHA classification, exercise tolerance, 6-minute walk test (6-MWT), global assessment, QoL questionnaires. Cut-off values for the evaluation of echocardiographic response vary greatly, mostly changes in LVEF, LVESV, and LVEDV are utilized. (104) Echocardiographic parameters are surrogate endpoints for hard outcomes to enable response assessment at both short- and mid-term. A clinical composite score (CCS) has been proposed for HF drugs but has been implemented for

CRT as well. (105-107) Based on the criteria of CCS patients can be categorized into three groups: worsened, stabilized, or improved.

HF patients have also been categorized as super-responders, responders, non-progressors, progressors and negative responders (Figure 1). Usually, these categories are built on changes in LVEF (super-responders: increase of LVEF ≥20%, responders: increase of LVEF ranging 6%-19%, non-progressors: increase of LVEF 0%-5%, and progressors <0%) (108, 109) or changes in LVESV (super-responders: reduction in LVESV ≥30%; responders: reduction in LVESV of 15–29%; non-responders: reduction in LVESV ranging 0–14%; and negative responders: an increase in LVESV at 6-months follow-up.) (110, 111) Negative responders experience a worsening of clinical status after CRT. The proportion of different response categories varied widely based on several factors. In the post-hoc analysis of the PROSPECT trial, 23.4% of the patients were non-responders and 20.3% were negative responders. (110) In a retrospective analysis, non-responders at 5-years showed a 66% higher risk for the composite endpoint of death, heart transplantation or left ventricular assist device (LVAD) implantation compared to super-responders and a 55% higher risk compared to responders. (112)

These results emphasize that non-response to CRT remains challenging and that even though guidelines and recommendations are thorough, around 30% of the patients do not improve as one may expect it.

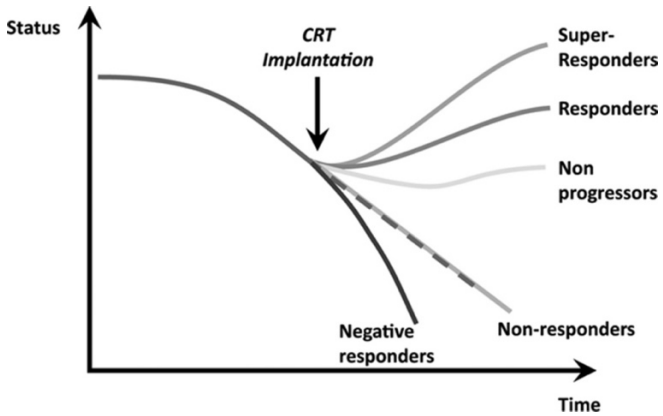

Figure 1. Various clinical courses after CRT implantation

Steffel J, Ruschitzka F. Superresponse to Cardiac Resynchronization Therapy. Circulation. 2014;130(1):87-90. doi: 10.1161/CIRCULATIONAHA.113.006124.

1.4.3.2. Predictors of response and outcome

The response to therapy is a surrogate endpoint which is associated with long-term outcomes,(111) thus the early evaluation of predictors to response is essential. Reverse remodeling, based on changes in LVEF, LVESV and LVEDV, has been linked with a decreased likelihood of HF hospitalization or all-cause mortality. An absolute increase of each 5-point in LVEF was associated with a 40% decrease in the risk of HF hospitalization or all-cause mortality (HR 0.60; 95% CI 0.50-0.72; p <0.001). (72, 74)

Predictors of response can be clinical factors that can be assessed at baseline, factors related to the implantation and post-implantation ones.

Optimal patient selection may reduce the rate of non-response. The most prevailing, identified clinical factors are sex (53), etiology of HF (78, 113), QRS duration and morphology (53, 114). The highest rate of responders can be found amongst patients with a wide QRS, with an LBBB, in female sex and in non-ischemic cardiomyopathy. Male patients and patients with ischemic HF tend to have less favorable response to CRT. (Figure 2) (115, 116) However, it is noteworthy that these subgroups show similar risk reduction in morbidity and mortality despite showing a lesser extent of reverse remodeling. (53, 76, 77, 80) Moderate to severe secondary mitral regurgitation also affects response to CRT and long-term outcomes. (117, 118) Patients experience the benefits of CRT regardless of their age. (119) Comorbidities may also affect response, patients with CKD derive benefit from CRT, however in severe stages to a lesser extent. (120) Diabetes mellitus, a highly prevalent comorbidity in HF, may attenuate the benefit of CRT. (121, 122)

Obesity is a common condition in HF patients, its prevalence among HF patients may reach up to 35%. (123) Likewise, a significant proportion of CRT candidates are obese, with approximately 36% having a body mass index (BMI) of 30 kg/m² or higher. The average BMI in this population typically falls within the range of 26.5 to 31.2 kg/m². (51, 53, 86) Even though obesity increases the likelihood of comorbidities, a paradoxical survival benefit has been observed in patients with obesity, a phenomenon known as the obesity paradox.(124) Few studies examined the obesity paradox in CRT candidates. (125-127) However, evidence regarding the optimal BMI range associated with improved survival in this patient population has been limited.

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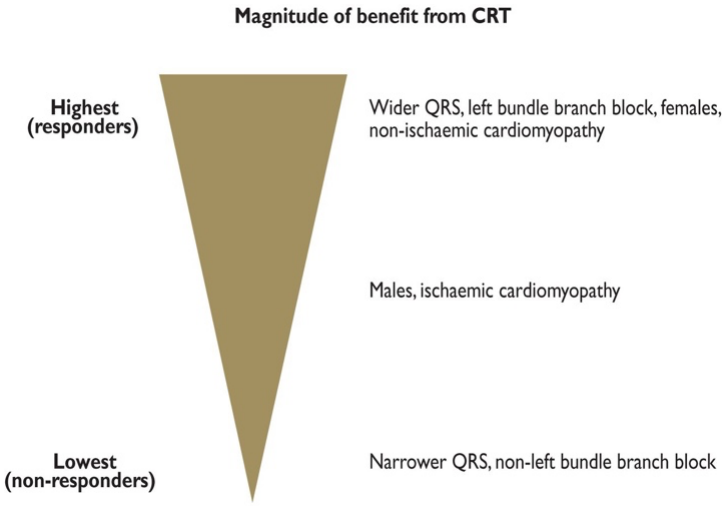

Figure 2. Clinical features influencing the likelihood to response based on the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). European Heart Journal. 2013;34(29):2281-329. doi: 10.1093/eurheartj/eht150.

By factors related to the implantation we refer mostly to the positioning of the leads, primarily LV lead positions can alter outcomes. (128) Regarding RV leads, non-apical positions were mostly preferred over the apical ones, as it was suggested to have less deleterious effects on ventricular function. (95)However, a meta-analysis could not prove the superiority of non-apical positions (129). The Septal CRT study demonstrated that a septal RV position is non-inferior to apical pacing regarding LV reverse remodeling at 6-months. (130) LV lead positions can be characterized by their short-axis position (anterior, posterior, lateral) or long-axis position (basal, midventricular, apical) based on antero-posterior, left anterior oblique or right anterior oblique projections. The apical position should be avoided as it has been associated with a higher risk of HF hospitalization or death or death alone in a MADIT-CRT analysis. (131-133) The greatest benefit for LV positions has been seen in lateral positions of the left ventricle, or posterolateral ones. (128, 134)

Appropriate response to CRT can be ensured with an appropriate device programming and BiV pace rate during the follow-up.

The effectiveness of BiV pacing delivery is a key factor in the success of CRT. A BiV pacing rate ≤90% provided no benefit compared to ICD therapy regarding the risk of HF or death (HR 0.78; 95% CI 0.47-1.30; p= 0.344). A risk reduction was observed in a BiV pacing rate between 91-96%, but a rate above 97% offered a further reduction in HF or death (BIV ≥97% vs. ICD [HR 0.32; 95% CI 0.23–0.44; p<0.001] and BIV ≥97% vs. BIV<97% [HR 0.48; 95% CI 0.32-0.72; p<0.001]).(135) Another trial found 98% as a cut-off value to achieve the greatest risk reduction of mortality. (89)

The most common cause of loss of BiV pacing is arrhythmic events. Most frequently atrial fibrillation (136) or frequent premature ventricular complexes (PVC) (137) lead to the decrease of BiV pace rate and can diminish the benefits of CRT. A relatively low frequency of ectopic beats (> 0.1%) dramatically increases the probability of low biventricular pacing (< 97%). Frequent PVCs leading to low BiV pacing rate can further worsen LV function.(138) PVCs have been associated with a higher risk of HF events and death along with worse echocardiographic response. (137) Other causes for loss of BiV pacing can be inadequately programmed sensed/paced AV intervals, atrial undersensing or any intrinsic rate that exceeded the upper tracking rate.

1.4.4. Risk stratification

HF patients are prone to suffer a SCD, that approximately accounts for 35-45% of deaths in patients with HFrEF. (139) ICD is an effective treatment for VAs, however the need of the addition to a CRT system remains questionable. Based on the COMPANION trial, not designed to directly compare CRT-D to CRT-P, a significant risk reduction of all-cause mortality or SCD was only observed in patients on the CRT-D arm. (140) However, in the CARE-HF trial, CRT-P alone also reduced the risk of dying suddenly. (52) Moreover, echocardiographic response to CRT has been associated with a significant reduction in the occurrence of malignant ventricular arrhythmias. (141-145)

In this highly vulnerable patient population risk stratification is necessary to aid the therapeutic pathway. Prediction of outcomes also assists caregivers on decisions regarding the type of the device, e.g., whether a defibrillator is necessary or not. In CRT candidates, the decision of implanting CRT-D vs. CRT-P is based on individual risk assessment (146), multiple risk scores were created by using independent predictors of

mortality (147-149) or based on parameters which were proved to be relevant on the outcome from large-scale trials or registries. (150, 151) In prior risk scores atrial fibrillation, renal function, or the severity of patients' symptoms were the most relevant (1) regardless of the etiology. Ischemic etiology is one of the main factors that need to be taken into consideration. (Table 2.) (152)

Table 2. Clinical features favoring CRT-D or CRT-P based on the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

Factors favoring CRT-P	Factors favoring CRT-D
Advanced HF	Life expectancy › 1 year
Severe renal insufficiency or dialysis	Stable HF, NYHA II
Other major comorbidities	Ischemic heart disease (low and intermediate MADIT score)
Frailty	Lack of comorbidities
Cachexia	

CRT-P, cardiac resynchronization therapy pacemaker; CRT-D, cardiac resynchronization therapy defibrillator; HF, heart failure; NYHA, New York Heart Association

The Goldenberg risk score (GRS) has been originally established to assess the risk of SCD in patients with ischemic etiology, who would benefit from the implantation of a prophylactic ICD. (153, 154) The GRS was later implemented in patients eligible for CRT regardless of their etiology. (155) The necessity of a defibrillator in candidates for CRT with non-ischemic HF remains controversial (77, 152, 156) as no previous RCT was conducted to evaluate it. Due to a higher extent of reverse remodeling, the risk of fatal VT/VFs diminishes significantly (141) and the implantation of a CRT-P may be sufficient in non-ischemic patients, instead of adding a shock coil which can lead to higher complication rates. (45, 157, 158)

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2. Objectives

Our aim was to identify parameters that are pivotal in the optimal selection, management, and outcomes of HF patients eligible for CRT.

To predict response to therapy we studied the early effect of PVCs on echocardiographic response and all-cause mortality after CRT implantation. Since arrhythmic events such as atrial fibrillation or PVCs decrease the rate of BiV pacing and diminish the benefits of CRT, we hypothesized that the early detection of PVCs and consequent therapeutic actions may alter outcomes.

Moreover, we aimed to optimize patient selection by assessing whether obesity, quantified by BMI, may impact CRT's efficacy and safety. We investigated all-cause mortality at long-term, peri- and postprocedural complications, and echocardiographic response by obesity categories.

We also addressed the issue of SCD amongst HF patients, specifically in CRT candidates. Risk stratification aids therapeutic decision making so we aimed to predict a specific HF patient population of non-ischemic etiology that based on the GRS will acquire survival benefit from the addition of a defibrillator function to the CRT system. Based on our hypothesis, this simple risk score can help identify those non-ischemic patients undergoing CRT who would benefit the most from the defibrillator function.

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3. Methods

3.1.Methods of Part 1 – Prospective CRT cohort

3.1.1. Patient population - inclusion and exclusion criteria

Altogether 125 symptomatic (NYHA class II-Iva) HF patients on GDMT with severe chronic systolic HF (LVEF ≤ 35%), wide QRS (≥ 130 ms) were enrolled and underwent CRT implantation. The inclusion criteria aligned with the current guidelines for CRT indications. Patients with known malignancies, inflammatory diseases, or genetic HF were excluded and those who were unable or unwilling to attend the regular follow-up visits. All patients provided written informed consent before enrollment. Following the successful procedure, patients underwent follow-up visits at 1 and 6 months, with continued follow up for up to 4 years. Of all patients, 67 had complete pacemaker interrogation data and were therefore included in the final analysis. Additionally, 38 patients with available baseline and 6-month echocardiographic data were included in the echocardiographic response analysis. (Figure 3.)(159)

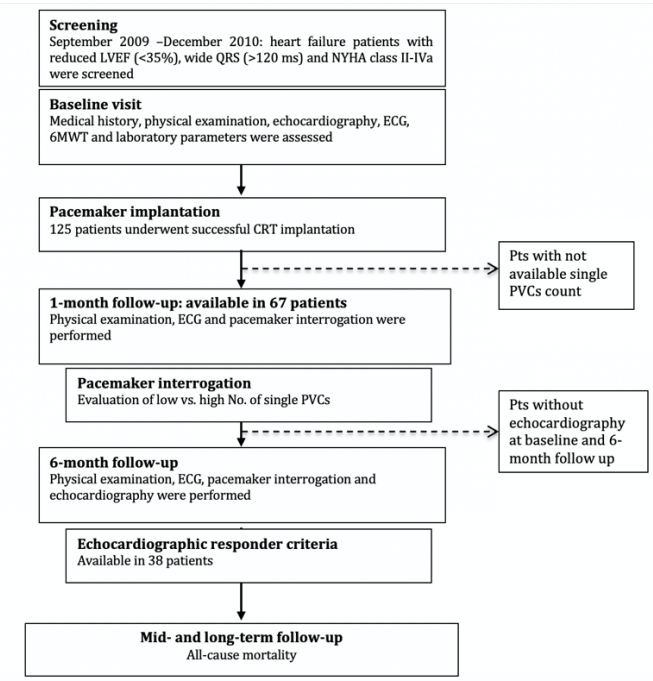

Figure 3. Flowchart of patient enrollment and follow-up

6MWT, six-minute walk test; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVC, premature ventricular contractions

3.1.2. Device implantation procedures

CRT implantation was performed in accordance with current guidelines using the subclavian transvenous approach. An angiogram was conducted to select the optimal coronary sinus branch. Ideal lead placement was evaluated through chest X-rays using right and left anterior oblique views. The LV leads were ideally placed in the lateral or posterior side branch, while septal positioning was advised for the right ventricular lead. After placing the leads, electrical parameters were measured. If intraoperative phrenic nerve stimulation occurred, the LV lead was repositioned.

3.1.3. Follow-ups and pacemaker interrogations

Following successful CRT implantation, follow-up visits were conducted at one and six months, with patients subsequently monitored via phone contact for four years. In-person visits were scheduled 30 or 180 (+/- 7) days post-implantation, respectively. At baseline and six months after the procedure, detailed laboratory tests, echocardiographic exams, NYHA functional class assessments, physical exams including a 6-MWT, and pacemaker interrogations were performed or collected.

3.1.4. Echocardiography

Echocardiography was conducted in accordance with current standards, in a left lateral position, using the Philips iE33 echocardiography system equipped with an S5-1 transducer (Philips Healthcare, Best, The Netherlands). Image acquisition followed the latest guidelines and recommendations. (160). Measurements were performed offline by using the QLAB software (Philips Healthcare). LVESV and LVEDV were measured, and LVEF was calculated by the biplane Simpson’s method. Left atrial volume (LAV) was measured by monoplane Simpson’s method from apical four-chamber view in end-systole. (160)

3.1.5. Endpoints

The primary endpoint was all-cause mortality during the follow-up period, assessed in 67 patients.

Secondary endpoints included three echocardiographic response criteria: a relative improvement of at least 15% in LVEF, a reduction of at least 15% in LVESV, or a decrease of at least 15% in LAV, all measured six months after CRT implantation.

3.1.6. Statistical analysis

Continuous variables were described as mean ± standard deviation (SD), or as median with interquartile range (IQR, 25% - 75%), as appropriate after normality test. Categorical data were given as frequencies and percentages. Baseline clinical characteristics were compared using the unpaired t-test, or Mann–Whitney U-test, as appropriate. Fisher's exact test was employed for categorical data comparison. A two-sided P-value of < 0.05 was considered statistically significant. Statistical analyses were performed using the IBM SPSS version 22 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and Graphpad Prism 6.03 (Graph-Pad Softwares Inc., USA) software.

For subsequent analyses, we selected a cut-off point (the median value of PVCs) that provided appropriate sensitivity, specificity, and clinical relevance. Based on this median cut-off, patients were categorized into "low" and "high PVCs" groups. Time-to-event data were analyzed using the Gehan-Breslow-Wilcoxon test, which gives more weight to deaths at early time points compared to the log-rank test. Univariate Cox and logistic regression analyses were conducted to identify predictors of mortality and echocardiographic response to CRT. Adjusted hazard ratios with 95% confidence intervals (CI) were calculated for all-cause mortality and reverse remodeling using logistic regression analyses in a forward stepwise approach.

3.2.Methods of Part 2 – Retrospective high-scale CRT registry

3.2.1. 'Biobankok' registry and enrollment of Part 2A and 2B

CRT implantations were performed at our clinic, with indications for the procedure determined according to current European Society of Cardiology (ESC)

guidelines (symptomatic HF patients on optimal medical treatment, LVEF <35%, and QRS >130 ms). Data were collected retrospectively and entered into our "Biobankok" registry, including medical history, clinical and echocardiographic parameters, laboratory test results, and procedural parameter. The studies comply with the declaration of Helsinki and was approved by the Regional and Institutional Committee and Research; No. 161-0/2019.

3.2.1.1. Part 2A Body mass index calculation and patient categorization

To assess obesity, we calculated BMI as the ratio of weight in kilograms to the square of height in meters (BMI= kg/m^2). Patients were classified into three patient groups according to the WHO classification, underweight and normal weight (further mentioned as normal weight group [BMI <25 kg/m^2]), patients with overweight (BMI 25.0 –<30 kg/m^2) and patients with obesity (BMI ≥ 30 kg/m^2). (161)

3.2.1.2. Part 2B Calculation of the Goldenberg risk score

Altogether 1,290 HF patients with non-ischemic etiology underwent CRT implantation between June 2000 and September 2018 at the Heart and Vascular Centre of Semmelweis University. First, we defined those with a se-BUN exceeding 50 mg/dl as very-high-risk (VHR) patients and excluded them as per the original article. (153) The risk score is made up of five clinically significant factors. [serum blood urea nitrogen (se-BUN > 26 mg/dl), QRS > 120 ms, age > 70, atrial fibrillation, NYHA > II].

Aside from these patients, 667 had complete data available to calculate their GRS, 347 underwent CRT-P, while 320 received CRT-D devices. The GRS was se-BUN > 26 mg/dl and QRS > 120 ms, with each factor contributing one point, resulting in scores ranging from 1 to 5. No patients had a 0 score since each patient had a QRS duration greater than > 130 ms.

Following the GRS assessment, patients were further dichotomized into low (<3) and high (≥3) score groups. This cut-off was determined according to the original article acknowledging that in our CRT cohort, each patient had a minimum score of 1 point during the calculation.(162)

3.2.2. Endpoints

3.2.2.1. Part 2A

The primary outcome was the composite endpoint of all-cause mortality, heart transplantation (HTX), or LVAD implantation. The date of death was obtained from the National Health Insurance Fund of Hungary, with updates as of December 2021. Secondary outcomes included periprocedural complications, while tertiary outcomes focused on the echocardiographic response and the occurrence of reverse remodeling, which was defined as a relative increase of 15% or more in LVEF within 6 months following CRT implantation. (161)

3.2.2.2. Part 2B

Our primary composite endpoint was all-cause mortality, HTX or LVAD implantation, whichever occurred first. The exact date of death was retrieved *via* the National Health Insurance Fund of Hungary, updated in September 2019. (162)

3.2.3. Device implantation procedures

Device implantations were performed under X-ray, capturing anteroposterior, left anterior oblique, and right anterior oblique views. Leads were implanted through either the cephalic or the subclavian veins, with right ventricular leads primarily fixed in a septal position. In case of permanent atrial fibrillation, right atrial leads were not implanted. After venography the optimal coronary sinus side branch was routinely selected favoring the lateral or posterolateral positions. If implantation through the coronary sinus was unsuccessful, an epicardial or transseptal approach was used. Intraoperative evaluation of electrical parameters was also performed. The implanting physicians selected the device type based on current guidelines, taking into account patient preferences, age, sex, renal function, frailty, and other comorbidities.

3.2.4. Statistical analysis

Continuous variables are reported as mean ± standard deviation or as median and interquartile range (25th–75th percentile), depending on the results of the Shapiro–Wilk normality test. Categorical data are expressed as counts and frequencies. Subgroup

variables were compared using an unpaired t-test for normally distributed continuous variables and a Mann–Whitney test for non-normally distributed continuous variables, while dichotomous variables were analyzed using the $\chi 2$ test. Kaplan-Meier estimates and log-rank tests were employed to evaluate unadjusted event-free survival across patient categories. To evaluate the association between BMI status and outcomes following CRT implantation, Cox multivariate regression analysis was performed. Statistical analyses were conducted using GraphPad Prism, version 8.4.2 (San Diego, CA, USA, GraphPad Software) and IBM SPSS Statistics, version 26 (Armonk, NY, USA, IBM Corp). Statistical significance was defined as a P-value of less than 0.05.

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4. Results

4.1. Results of Part 1

4.1.1. Baseline clinical characteristics

The average age of the 67 patients was 66.2 ± 10.2 years, with 52% having an ischemic cause of HF, and a mean LVEF of 29.0 ± 6.0%. The ECG showed typical LBBB morphology in 73% of the cases (Table 3).

At the one-month follow-up, the median number of single PVCs in our cohort was 11,401. Patients were dichotomized, patients with fewer than 11,401 PVCs were classified as "low PVCs," while those with higher number of PVCs were classified as "high PVCs."

There were no statistically significant differences between these two groups in terms of baseline clinical characteristics, medical history, or echocardiographic parameters (Table 3). We did not observe relevant differences in terms of baseline medication, similar pharmacological treatment was used in the two groups (Table 3 and 4). Renal function, measured by serum creatinine (120.7 ± 52.2 μmol/L vs. 99.2 ± 30.9 μmol/L, p=0.07) and blood urea nitrogen levels (9.7 ± 4.0 mmol/L vs. 9.8 ± 6.4 mmol/L, p=0.23), was comparable between the groups. Similarly, serum potassium levels which could influence arrhythmic events, or the number of premature beats were also consistent in the two groups (4.6 ± 0.6 vs. 4.5 ± 0.4 mmol/L, p=0.33).

Biventricular pacing rate at the one-month follow up showed no significant differences in patients with "low PVCs" and "high PVCs" [100% (99 / 100%) vs. 99.5% (94.5 / 100%), p= 0.13] indicating that the number of PVCs in this range did not affect the biventricular pacing rate. (159)

Table 3. Baseline clinical variables, medical history, echocardiographic measurements, medical therapy, and laboratory parameters

Baseline clinical variables	**All patients (n = 67)**	**low PVCs (n = 34)**	**high PVCs (n = 33)**	**p-value**
No. of single PVCs (no., IQR)	11401 (725/48K)			
Age (years, mean ± SD)	66.2 ± 10.2	64.5 ± 11.3	68.5 ± 8.4	0.16
Gender (female, n, %)	14 (21%)	10 (29%)	4 (12%)	0.13
Ischemic etiology (n, %)	35 (52%)	16 (47%)	19 (58%)	0.47
NYHA (stadium, mean ± SD)	3.2 ± 2.0	3.1 ± 2.0	3.3 ± 2.0	0.21
QRS (ms, mean ± SD)	162 ± 24	168 ± 25	157± 22	0.10
typical LBBB morphology (n, %)	49 (73%)	26 (77%)	23 (70%)	0.59
not typical LBBB (n, %)	18 (27%)	8 (24%)	10 (30%)	0.59
6MWT (m, mean ± SD)	295.9 ±125.7	318.0 ± 119.6	276.3 ± 129.9	0.23
RR systolic (mmHg, mean ± SD)	121.9 ± 18.3	121.4 ± 18.3	122.5 ± 18.1	0.81
RR diastolic (mmHg, mean ± SD)	74.1 ± 10.2	73.3 ± 9.6	74.9 ± 10.9	0.52
Heart rate ($min^{-1,}$ mean ± SD)	73.4± 13.4	72.3 ± 12.0	74.6 ± 14.8	0.52
Sinus rhythm (n, %)	55 (82%)	29 (86%)	26 (79%)	0.54
Medical history				
Hypertension (n, %)	46 (69%)	23 (68%)	23 (70%)	1.00
Diabetes mellitus (n, %)	22 (33%)	12 (35%)	10 (30%)	0.78
MI (n, %)	17 (25%)	10 (29%)	7 (21%)	0.58
Prior PCI (n, %)	17 (25%)	9 (27%)	8 (24%)	1.00
Prior CABG (n, %)	10 (15%)	3 (9%)	7 (21%)	0.19
Prior COPD (n, %)	4 (6%)	1 (3%)	3 (9%)	0.36
Echocardiographic parameters				
LVEF (%, mean ± SD)	29.0 ±6.0	30.4 ± 6.7	27.7 ± 5.1	0.14
LVESV (ml, mean ± SD)	183.8 ± 68.1	170.7 ± 63.0	196.8 ± 72.1	0.24
LAV (ml, mean ± SD)	91.3 ± 36.9	84.99 ± 29.0	97.4 ± 43.0	0.29
Baseline medical therapy				
Beta blocker (n, %)	61 (91%)	32 (94%)	29 (88%)	0.43
ACE-Ior ARB (n, %)	63 (94%)	32 (94%)	31 (94%)	1.00
MRA (n, %)	44 (66%)	22 (65%)	22 (67%)	1.00
Diuretics (n, %)	55 (82%)	24 (88%)	31 (94%)	0.06
Digoxin (n, %)	15 (22%)	8 (24%)	7 (21%)	1.00
Amiodarone (n, %)	17 (25%)	12 (35%)	5 (15%)	0.09

Oral anticoagulant (n, %)	21 (31%)	8 (24%)	13 (39%)	0.19
Baseline laboratory parameters				
Sodium (mmol/L, mean ± SD)	138.6 ± 2.7	139.0 ± 2.5	138.1 ± 2.8	0.18
Potassium (mmol/L, mean ± SD)	4.6 ± 0.5	4.6 ± 0.6	4.5 ± 0.4	0.33
Creatinine (μmol/L, mean ± SD)	110.1 ± 44.1	120.7 ± 52.2	99.2 ± 30.9	0.07
BUN (mmol/L, mean ± SD)	9.8 ± 5.3	9.7 ± 4.0	9.8 ± 6.4	0.23

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LAV, left atrial volume; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVCs, premature ventricular contractions; RR, Riva Rocci; SD, standard deviation.

Table 4. Type and dose of baseline beta blockers

Baseline beta blocker therapy	**low PVCs (n = 34)**	**high PVCs (n = 33)**	**p-value**
Carvedilol (n, %)	8 (25%)	8 (28%)	1.00
Mean dose of cardvedilol (mg, mean ± SD)	21.3 ± 8.8	19.5 ± 14.0	0.55
Bisoprolol (n, %)	11 (69%)	13 (45%)	0.44
Mean dose of bisoprolol (mg, mean ± SD)	4.3 ± 3.0	4.1 ± 1.7	0.65
Metoprolol (n, %)	9 (27%)	6 (18%)	0.56
Mean dose of metoprolol (mg, mean ± SD)	40.3 ± 26.4	54.2 ± 24.6	0.23
Nebivolol (n, %)	4 (12%)	1 (3%)	0.36
Mean dose of nebivolol (mg, mean ± SD)	5.0 ± 0	5.0 ± 0	1.00

PVCs, premature ventricular contractions; SD, standard deviation.

4.1.2. Prognosis and clinical outcome by the number of PVCs at 1-month follow-up

During the mean follow-up time of 2.1 years, altogether 19 (28%) patients died, 7 patients in the “low PVCs” group, while 12 reached the primary endpoint in the “high PVCs” group (HR 0.97; 95% CI 0.38 - 2.48; p=0.04) (Figure 4). Over a longer-term follow-up, averaging 6.8 years, 40 patients (60%) died, with 19 in the "low PVCs" group

and 21 in the "high PVCs" group reaching the primary endpoint, which did not reach statistical significance (HR 0.78; 95% CI 0.42 - 1.46; p=0.15). (159)

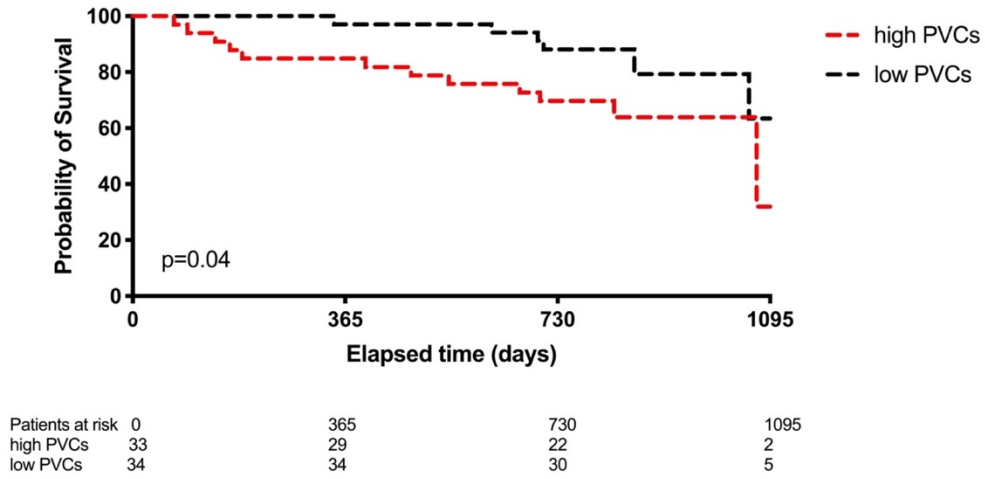

Figure 4. Survival of patients with low vs. high PVCs
PVC, premature ventricular complex

4.1.3. Association of the prevalence of PVCs at 1-month follow up and 6-month echocardiographic changes

Echocardiographic changes were assessed six months after CRT implantation in 38 patients from the "low PVCs" and "high PVCs" groups. The changes in LV parameters were comparable between the two groups (Δ LVEF +9.1±6.6 vs. +8.6±8.7; p=0.89) and (Δ LVESV −39.0±50.4 vs. −46.4±50.2; p= 0.82). However, the reduction in LAV was significantly greater in the "low PVCs" group compared to the "high PVCs" group (Δ LAV −19.4±25.4 vs. −1.4±22.5; p=0.02). (Table 5 and Figure 5). (159)

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Table 5. Changes of echocardiographic parameters six months after CRT implantation

Echocardiographic changes	All patients (n=38)	low PVCs (n = 19)	high PVCs (n = 33)	p-value
Δ LVEF (%, mean±SD)	+8.8 ± 7.6	+9.1 ± 6.6	+8.6 ± 8.7	0.89
Δ LVESV (mL, mean±SD)	-42.7 ±49.7	-39.0 ± 50.4	-46.4 ± 50.2	0.82
Δ LAV (mL, mean±SD)	-10.4 ± 25.4	-19.4 ± 25.4	-1.4 ± 22.5	**0.02**

CRT, cardiac resynchronization therapy; LAV, left atrial volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PVCs, premature ventricular contractions; SD, standard deviation.

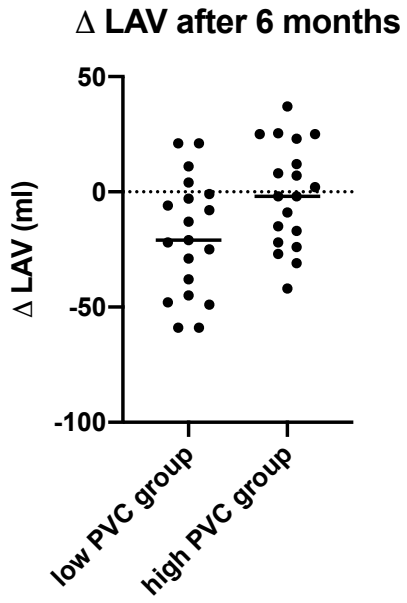

Figure 5. Difference in LAV changes after 6 months in patients with low versus high PVCs

LAV, left atrial volume; PVCs, premature ventricular contractions

4.2.Results of Part 2A

4.2.1. Baseline clinical characteristics

Altogether we included 1585 patients in our study, 459 (29%) patients were in the normal weight group (BMI <25 kg/m^2) of which 23 (5%) patients were underweight (BMI

≤ 18.5 kg/m^2), 641 (40%) patients belonged to the overweight category (BMI 25-<30 kg/m^2) and 485 (31%) were patients with obesity (BMI ≥ 30 kg/m^2). Patients with obesity were further classified, of these 361 (74.4%) belonged to the obese I patient group (BMI 30-<34.9 kg/m^2), 94 (19.4 %) in the obese II group (BMI ≥35-<40 kg/m^2) and 30 (6.2%) in the obese III group (BMI ≥40 kg/m^2).

Normal-weight patients were older compared to patients with overweight or obesity (70 years vs. 69 years vs. 68 years; p<0.001), respectively. The sex distribution, ischemic etiology, and rates of CRT-D implantation were similar across all three groups. However, diabetes mellitus (DM) was more prevalent in patients with overweight and obesity (26% in normal-weight vs. 37% in overweight vs. 48% in obese; p<0.001), as was hypertension (71% in normal-weight vs. 74% in overweight vs. 82% in obese; p<0.001). Patients had similar renal function across the groups (eGFR: 64 ml/min/1.73m² for normal weight, 63 ml/min/1.73m² for overweight, and 66 ml/min/1.73m² for obesity; p=0.25). NT-proBNP levels were also comparable (3000 pmol/l for normal weight, 2498 pmol/l for overweight, and 2488 pmol/l for obesity; p=0.21).

In terms of echocardiographic parameters, patients with overweight and obesity had significantly higher LVEF (patients with obesity 30% vs. patients with overweight 28% vs. normal weight 27%; p <0.001).

Patients were similarly treated, but digoxin use was more frequent in normal weight patients (normal weight 24% vs. patients with overweight 17% vs. patients with obesity 16%; p=0.003), respectively and oral anticoagulant was used mostly in overweight patients (normal weight 27%, patients with overweight 33%; patients with obesity 27%; p=0.03). (Table 6.)(161)

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Table 6. Baseline clinical characteristics of patients by BMI groups

Baseline variables	**All patients (n=1585)**	**BMI <25 kg/m^2 (n=459)**	**BMI 25-<30 kg/m^2 (n=641)**	**BMI ≥ 30 kg/m^2 (n=485)**	**p-value**
Age (yrs; median/IQR)	69 (61-75)	70 (62-76)	69 (61-76)	68 (60-73)	**<0.001**
Sex (female; n; %)	395 (25)	144 (31)	136 (21)	115 (24)	0.17
NYHA III/IV (st; n; %)	802 (50)	238 (52)	313 (49)	251 (52)	0.49
Ischemic etiology (n; %)	832 (52)	232 (50)	354 (55)	246 (51)	0.20
CRT-D (n; %)	863 (54)	238 (52)	350 (55)	275 (57)	0.32
BMI (kg/m^2; median/IQR)	27.4 (24.6-30.8)	22.9 (21.1-24.2)	27.4 (26.2-28.5)	32.5 (31.0-35.1)	**NA**
QRS (ms; median/IQR)	160 (140-180)	160 (140-177)	160 (140-178)	160 (140-180)	0.83
Medical history					
Atrial Fibrillation (n; %)	618 (39)	162 (35)	257 (40)	199 (41)	0.15
Diabetes mellitus (n; %)	594 (37)	118 (26)	241 (37)	235 (48)	**<0.001**
Hypertension (n; %)	1200 (76)	328 (71)	474 (74)	400 (82)	**<0.001**
Prior MI (n; %)	654 (41)	186 (40)	276 (43)	192 (39)	0.47
Prior PCI (n; %)	520 (33)	141 (31)	228 (35)	151 (31)	0.15
Prior CABG (n; %)	226 (14)	56 (12)	100 (16)	70 (14)	0.28
Prior COPD (n; %)	250 (16)	74 (16)	88 (14)	88 (18)	0.13
Laboratory parameters					
Serum urea (µmol/l; median/IQR)	381 (310-469)	409 (304-518)	412 (333-491)	406 (342-468)	0.93
Serum creatinine (µmol/l; median/IQR)	110 (89-145)	99 (79-127)	102 (84-133)	98 (82-128)	0.09

Serum cholesterol (mmol/l; median/IQR)	4.3 (3.5-5.1)	4.3 (3.4-5.1)	4.2 (3.5-5.1)	4.0 (3.3-5.0)	0.27
eGFR (ml/min/1.73m^2; median/IQR)	64 (48-81)	64 (49-82)	63 (47-78)	66 (48-83)	0.25
NT-proBNP (pmol/l; median/IQR)	1332 (509-3365)	3000 (1380-4434)	2498 (1573-3434)	2488 (1270-3045)	0.21
Echocardiographic parameters					
LVEF (%; median/IQR)	28 (24-33)	27 (23-30)	28 (24-33)	30 (25-35)	**<0.001**
LVEDV (ml; median/IQR)	208 (154-271)	198 (168-244)	225 (159-225)	205 (150-277)	0.63
LVESV (ml; median/IQR)	153 (113-209)	150 (117-207)	167 (117-211)	142 (99-212)	0.51
LVEDD (mm; median/IQR)	63 (57-69)	63 (57-68)	63 (57-70)	63 (57-70)	0.30
LVESD (mm; median/IQR)	53 (47-60)	53 (47-59)	53 (46-60)	53 (46-60)	0.87
Medical treatment					
Beta blocker (n; %)	1349 (85)	404 (88)	538 (84)	407 (84)	0.12
ACE-I/ARB (n; %)	1385 (87)	403 (88)	549 (86)	433 (89)	0.18
MRA (n; %)	1000 (63)	308 (67)	393 (61)	299 (62)	0.11
Furosemid (n; %)	1192 (75)	362 (79)	471 (73)	359 (74)	0.09
Digoxin (n; %)	296 (19)	109 (24)	110 (17)	77 (16)	**0.003**
Amiodarone (n; %)	401 (25)	124 (27)	164 (25)	113 (23)	0.41
Oral anticoagulant therapy (n; %)	469 (29)	123 (27)	213 (33)	133 (27)	**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

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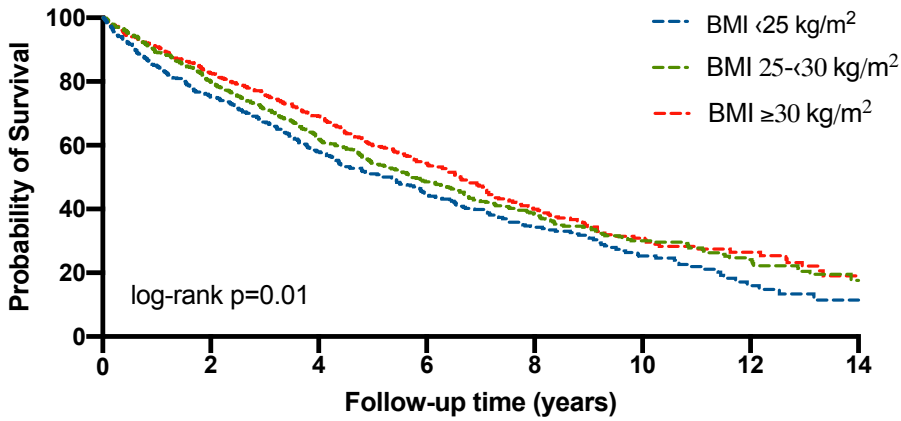
4.2.2. Outcomes

4.2.2.1.Main outcomes

During the mean follow-up period of 5.1 years, 973 patients (61%) reached the primary endpoint: 302 (66%) in the BMI <25 kg/m² group, 389 (61%) in the BMI 25-<30 kg/m² group, and 282 (58%) in the BMI ≥30 kg/m² group (log-rank p<0.05). The lowest absolute mortality rates were observed in the BMI range of 35-<40 kg/m², forming a J-shaped curve. A total of 29 patients (2%) underwent orthotopic heart transplantation: 8 (2%) in the normal-weight group, 16 (2%) in the overweight group, and 5 (1%) in the obesity group. Four patients (0.2%) reached the primary endpoint by LVAD implantation: 1 (0.2%) in the normal-weight group, 1 (0.1%) in the overweight group, and 2 (0.4%) in the obesity group.

Patients with obesity had a significantly lower risk of all-cause mortality compared to normal-weight patients (HR 0.78; 95% CI 0.66-0.92; p=0.003), while overweight patients showed a trend toward lower mortality compared to normal-weight patients (HR 0.86; 95% CI 0.74-1.00; p=0.05) (Table 7 and Figure 6).(161)



Patients at risk								
BMI ‹25 kg/m²	459	340	242	151	88	45	14	5
BMI 25-‹30 kg/m²	641	503	350	229	127	74	41	8
BMI ≥ 30 kg/m²	485	397	298	198	105	50	26	12

Figure 6. Kaplan Meier estimates of the probability of survival after CRT implantation by BMI groups

BMI, body mass index; CRT, cardiac resynchronization therapy

Patients in the obese II group showed a greater likelihood of survival compared to those in the obese III group (HR 0.51; 95% CI 0.26-1.00; p=0.017). Survival rates did not differ significantly between other groups: obese I vs. obese II (HR 1.26; 95% CI 0.90-1.75; p=0.20) and obese I vs. obese III (HR 0.66; 95% CI 0.37-1.20; p=0.10).

Our results were consistent after the exclusion of underweight patients, the risk of the primary endpoint in patients with a BMI 18.5-<25 kg/m^2 vs. overweight patients was similar (HR 0.87; 95% CI 0.75-1.02; p= 0.08) and was significantly greater compared to obese patients (HR 0.79; 95% CI 0.67-0.94; p=0.006).

We observed a 25% higher risk of all-cause mortality in patients with a BMI <25 kg/m^2 compared to patients with overweight and obesity (HR 1.25; 95% CI 1.06-1.47; p=0.006) after adjustment for relevant clinical covariates such as age, sex, NYHA class, diabetes, hypertension, myocardial infarction, and atrial fibrillation. (161)

Table 7. The associations of the BMI with the risk of all-cause mortality

Comparison of different BMI groups			
Endpoint	All-cause mortality		
	Hazard ratio	95% CI	p-value
BMI 25-<30 kg/m^2 vs. BMI <25 kg/m2	0.86	0.74-1.00	0.05
BMI 25-<30 kg/m^2 vs. BMI ≥30 kg/m^2	1.10	0.95-1.29	0.19
BMI ≥30 kg/m^2 vs. BMI <25 kg/m^2	0.78	0.66-0.92	**0.003**

BMI, body mass index; CI, confidence interval

4.2.2.2. Subgroup analyses

Patients with a BMI ≥25 kg/m^2 show survival benefit over patients with a BMI of <25kg/m^2 in non-ischemic patients (HR 0.67; 95% CI 0.53-0.84; p <0.001), while obesity did not offer benefit for patients with ischemic etiology (HR 0.94; 95% CI 0.78-1.13; p=0.51). Among non-diabetics, patients with overweight or obesity show the best probability of survival, whereas the lowest survival rates were observed in diabetic

patients with a BMI <25kg/m^2 (p<0.001). The obesity paradox was not observed in diabetic patients (HR 0.85; 95% CI 0.66-1.10; p=0.20). Both sexes experienced the obesity paradox (male [HR 0.87; 95% CI 0.70-0.97; p=0.02] and female [HR 0.72; 95%CI 0.54.0-97; p=0.02]). However, there was no observed survival benefit in overweight or obese patients with atrial fibrillation (HR 0.89; 95% CI 0.77-1.11; p=0.30). Patients with overweight or obesity had the lowest risk of all-cause mortality with a CRT-D device, the highest was in normal-weighed patients with a CRT-P device (p=0.005), but we did not find a significant difference between patients with a BMI ≥25 kg/m^2 and patients with a BMI <25kg/m^2 after CRT-D implantation (HR 0.89; 95% CI 0.73-1.09; p=0.28). When considering age, young (age <65years) patients with obesity had the highest likelihood of survival and elderly (age ≥65 years) patients had the highest risk of all-cause mortality (p<0.001); obesity did not provide a survival benefit for older patients (HR 1.01; 95% CI 0.86-1.20; p=0.86). (Figure 7.) (161)

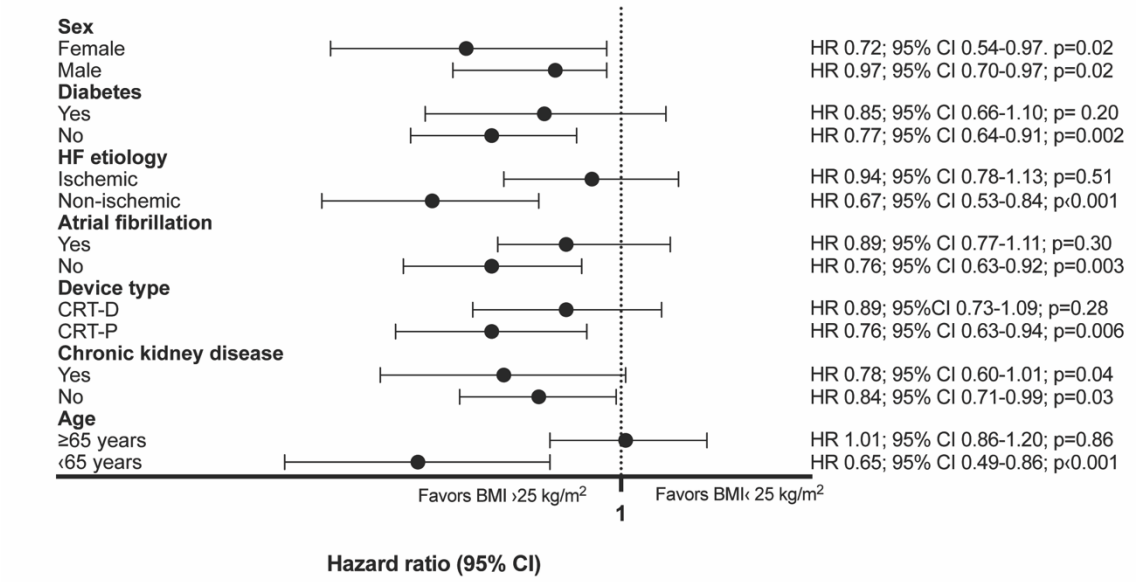


Figure 7. Subgroup analyses of enrolled patients

4.2.2.3. Periprocedural complications

There was an equal distribution of periprocedural complications across the patient groups, with no specific complication occurring more frequently in any group (BMI <25 kg/m^2 25% vs. BMI 25-<30 kg/m^2 28% vs. BMI ≥30 kg/m^2 26%; p=0.48). (Table 8.) At the same time, complications such as bleeding (p=0.81), pneumothorax (p=0.19),

haemothorax (p=0.25), coronary sinus dissection (p=0.55), pericardial tamponade (p=0.57), pocket infection (p=0.49), infective endocarditis (p=0.75), lead dislodgement (p=0.10), lead dysfunction/fracture (p=0.53) and phrenic nerve stimulation (p=0.57) occurred at similar rates across the patient groups. (Table 8.)(161)

Table 8. Periprocedural complications divided by BMI groups

Complications	**All patients (n=1585)**	**BMI <25 kg/m^2 (n=459)**	**BMI 25-<30 kg/m^2 (n=641)**	**BMI ≥30 kg/m^2 (n=485)**	**p-value**
All complications (n; %)	420 (26)	115 (25)	180 (28)	125 (26)	0.48
Bleeding (n; %)	24 (1.5)	8 (1.7)	10 (1.6)	6 (1)	0.81
Pneumothorax (n; %)	22 (1.4)	10 (2)	8 (1.2)	4 (0.8)	0.19
Haemothorax (n; %)	4 (0.2)	2 (0.4)	0 (0)	2 (0.4)	0.25
Coronary sinus dissection (n; %)	13 (0.8)	2 (0.4)	6 (1)	5 (1)	0.55
Pericardial tamponade (n; %)	6 (0.4)	1 (0.2)	2 (0.3)	3 (0.6)	0.57
Pocket infection/decubitus (n; %)	39 (2)	8 (1.7)	18 (3)	13 (3)	0.49
Infective endocarditis (n; %)	6 (0.4)	2 (0.2)	3 (0.5)	1 (0.2)	0.75
Lead dislodgement (n; %)	112 (7)	33 (7)	54 (8)	35 (7)	0.10
Lead dysfunction/fracture (n; %)	30 (2)	6 (1.3)	13 (2)	11 (2)	0.53
Phrenic nerve stimulation (n; %)	94 (6)	27 (6)	34 (5)	33 (7)	0.57

BMI, body mass index

4.2.2.4. Echocardiographic response

We observed a significant amelioration of LVEF over the course of 6 months in all patient categories. The mean of Δ-LVEF was 7% in the normal weight group (p <0.001), Δ-LVEF was 7.5% in patients with overweight (p <0.001) and 6% in patients with obesity (p <0.001) (Table 9.). A similar rate of reverse remodeling was seen across

the patient groups, 58% in the normal weight, 61% in the overweight and 57% in the obese groups (p=0.75). (Table 10.)(161)

Table 9. Change of left ventricular ejection fraction 6 months after CRT implantation across patient groups

	BMI <25 kg/m^2 (n=105)	**BMI 25-<30 kg/m^2 (n=167)**	**BMI ≥30 kg/m^2 (n=111)**
Baseline LVEF (%; median/IQR)	27 (23-30)	28 (24-33)	30 (25-35)
6 months LVEF (%; median/IQR)	33 (25-40)	34 (29-40)	37 (30-41)
Δ-LVEF (%; median/IQR)	7 (0-12)	7.5 (1-13)	6 (0.75-11)
p-value	<0.001	<0.001	<0.001

BMI, body mass index; IQR, interquartile range; LVEF, left ventricular ejection fraction

Table 10. The rate of reverse remodeling across patient groups

	BMI <25 kg/m^2 (n=105)	**BMI 25-<30 kg/m^2 (n=167)**	**BMI ≥30 kg/m^2 (n=111)**	**p-value**
Reverse remodeling (n; %)	61 (58)	102 (61)	63 (57)	0.75

BMI, body mass index

4.3.Results of Part 2B

4.3.1. Baseline clinical characteristics

A total of 718 non-ischemic CRT patients had all the necessary baseline data available to assess the GRS. Of these, 381 (53%) patients received a CRT-P and 337 (47%) patients a CRT- D device. Within the entire cohort, 51 (8%) patients had a > 50 mg/dl se-BUN level representing the VHR group. Among the 667 patients, 347 (52%) had CRT-D and 320 (48%) CRT-P devices. After scoring and dichotomizing the patients, 352 (53%) patients were classified as low risk (GRS 1–2) and 315 (47%) were classified as high-risk score (GRS ≥ 3). (Table 11)

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Table 11. Number of total patients based on their device type by the Goldenberg risk score

Goldenberg risk score	1	2	3	>3	VHR
All, n	118	234	176	139	51
CRT-P, n (%)	47 (40)	122 (52)	93 (53)	85 (61)	34 (67)
CRT-D, n (%)	71 (60)	112 (48)	83 (47)	54 (39)	17 (33)

CRT-D, cardiac resynchronization therapy- defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; VHR, very-high risk

Patients without VHR group, in the CRT-D group were significantly younger than CRT-P implanted ones (64 vs. 69 years; $p < 0.001$) and female sex was non- dominant (26 vs. 39%; $p < 0.001$), respectively. They had a lower LVEF (27 vs. 29%; $p < 0.01$). More patients adhered to optimal medical treatment compared to those with a CRT-P at baseline (Table 12).

Low-risk patients who received a CRT-D device were significantly younger (61.3 vs. 64.1 years; $p < 0.001$) than those with a CRT-P. They also had a lower LVEF (26.7 vs. 29.1%; $p < 0.01$), respectively. Hypertension (73 vs. 60%; $p = 0.01$) and COPD (20 vs. 9%; $p < 0.01$) were more prevalent in the CRT-P treated group. In terms of optimal treatment, the two groups were treated comparably except for the use of mineralocorticoid receptor antagonist (MRA). Patients with CRT-D devices were more likely to be treated with amiodarone (30 vs. 17%; $p < 0.001$) (Table 13).(162)

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Table 12. Baseline clinical characteristics of the total patient cohort without very-high risk patients by device type

Characteristics	Total patients n=667	CRT-P n=347	CRT-D n=320	p-value
Age, years (median, IQR)	66 (59-73)	69 (61-75)	64 (57-71)	**<0.001**
Female sex, n (%)	219 (33)	136 (39)	83 (26)	**<0.001**
LVEF, % (median, IQR)	28 (23-32)	29 (24-34)	27 (23-30)	**<0.01**
QRS duration, ms (median, IQR)	160 (140-170)	160 (140-172)	160 (140-170)	0.69
NYHA I, n (%)	8 (1)	2 (0.5)	6 (2)	0.16
NYHA II, n (%)	289 (43)	137 (39)	152 (47)	**0.04**
NYHA III, n (%)	296 (44)	161 (46)	135 (42)	0.27
NYHA IV, n (%)	75 (11)	47 (13)	28 (9)	0.05
Hypertonia, n (%)	471 (71)	250 (72)	221 (69)	0.39
Atrial fibrillation, n (%)	253 (38)	134 (39)	119 (37)	0.70
COPD, n (%)	105 (16)	70 (20)	35 (11)	**<0.01**
Creatinine, mg/dl (median, IQR)	1.0 (0.9-1.3)	1.0 (0.9-1.3)	1.0 (0.8-1.3)	0.99
BUN, mg/dl (median, IQR)	21.6 (16.8-27.7)	21.8 (16.8-28.3)	21.3 (16.9-27.3)	0.38
ACE-I/ARB, n (%)	589 (88)	297 (86)	292 (91)	**0.02**
Beta-blocker, n (%)	576 (86)	289 (83)	287 (90)	**0.02**
MRA, n (%)	445 (67)	213 (61)	232 (72)	**<0.01**
Loop diuretic, n (%)	501 (75)	263 (76)	238 (74)	0.67
Digoxin, n (%)	138 (21)	89 (26)	49 (15)	**<0.01**

Amiodarone, n (%)	167 (25)	67 (19)	100 (31)	**<0.001**
Mortality				
Absolute rate, n (%)	306 (46)	194 (56)	112 (35)	**<0.001**

ACE-I, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy- defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Table 13. Baseline characteristics of patients with Goldenberg risk score <3

Characteristics	CRT-P n=169	CRT-D n=183	p-value
Age, years (median, IQR)	64.1 (58.4-70.2)	61.3 (53.8-66.8)	**<0.001**
Female sex, n (%)	66 (42)	56 (28)	0.09
LVEF % (mean, SD)	29.1 (7.7)	26.7 (5.5)	**<0.01**
QRS duration, ms (median, IQR)	155 (130-170)	160 (140-170)	0.59
NYHA I, n (%)	2 (1)	6 (3)	0.18
NYHA II, n (%)	102 (60)	116 (63)	0.09
NYHA III, n (%)	49 (29)	51 (28)	0.81
NYHA IV, n (%)	16 (9)	10 (5)	0.15
Hypertonia, n (%)	123 (73)	111 (60)	**0.01**
Atrial fibrillation, n (%)	26 (15)	28 (15)	0.98
COPD, n (%)	34 (20)	17 (9)	**<0.01**
Creatinine, mg/dl (median, IQR)	0.95 (0.85-1.14)	0.96 (0.8-1.2)	0.88
BUN, mg/dl (median, IQR)	19.0 (15.1-22.7)	18.8 (15.4-23.5)	0.65
ACE-I/ARB, n (%)	149 (88)	167 (91)	0.34

Beta-blocker, n (%)	144 (85)	168 (92)	0.05
MRA, n (%)	103 (61)	134 (73)	**0.01**
Loop diuretic therapy, n (%)	120 (71)	124 (68)	0.51
Digoxin therapy, n (%)	33 (19)	29 (15)	0.36
Amiodarone, n (%)	28 (16)	47 (26)	**0.04**
Mortality			
Absolute rate, n (%)	79 (47)	50 (27)	**<0.001**

ACE-I, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy- defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

In the high-risk group, fewer female patients received a CRT-D device compared to a CRT-P device (19 vs. 39%; p <0.001). Similarly, to the low-risk group, CRT-D implanted patients were younger (70.8 vs. 72.2 years; p= 0.02). They had comparable LVEF (28 vs. 28%; p= 0.33) with high-risk CRT-P patients (Table 14).

Table 14. Baseline characteristics of patients with Goldenberg risk score ≥3

Characteristics	CRT-P n=178	CRT-D n=137	p-value
Age, years (median, IQR)	72.2 (65.6-77.4)	70.8 (62.9-75.1)	**0.02**
Female sex, n (%)	70 (39)	27 (19)	**<0.001**
LVEF % (median, IQR)	28.0 (23.0-34.0)	28.0 (22.0-31.0)	0.33
QRS duration, ms (median, IQR)	160 (140-179)	160 (140-170)	0.32
NYHA I, n (%)	0 (0)	0 (0)	›0.99
NYHA II, n (%)	35 (20)	36 (26)	0.16
NYHA III, n (%)	112 (63)	83 (60)	0.67

NYHA IV, n (%)	31 (17)	18 (13)	0.30
Hypertonia, n (%)	127 (71)	110 (80)	0.07
Atrial fibrillation, n (%)	108 (60)	91 (66)	0.29
COPD, n (%)	36 (20)	18 (13)	0.09
Creatinine, mg/dl (median, IQR)	1.14 (0.93-1.51)	1.16 (0.98-1.46)	0.55
BUN, mg/dl (mean, SD)	27.3 (9.4)	26.7 (8.9)	0.56
ACE-I/ARB, n (%)	148 (83)	125 (91)	**0.03**
Beta-blocker, n (%)	145 (81)	119 (87)	0.20
MRA, n (%)	110 (62)	98 (71)	0.07
Loop diuretic, n (%)	143 (80)	114 (83)	0.43
Digoxin, n (%)	56 (31)	20 (16)	**<0.001**
Amiodarone, n (%)	39 (22)	53 (39)	**<0.01**
Mortality			
Absolute rate, n (%)	114 (64)	62 (45)	**<0.001**

ACE-I, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy- defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association

4.3.2. Primary endpoints

Out of all patients 306 (46%) reached the primary composite endpoint, with 112 (37%) undergoing CRT-D implantation, 194 (63%) undergoing CRT-P implantation. The median follow-up time was 4.3 years. Regarding absolute mortality rates, fewer patients died with CRT-D therapy compared to CRT-P therapy (35 vs. 56%, $p < 0.001$), respectively (Table 15). Higher long-term absolute mortality rates were observed in patients with CRT-P devices compared to CRT-D regardless of their risk score, except in the VHR patient population (Figure 8A and Table 15). A U- shaped curve can be outlined for ICD efficacy, with no significant effect of CRT-D implantation in high-risk and VHR patients. The greatest reduction of the primary composite endpoint occurred in patients of a 2 and 3 risk score (Figure 8B).

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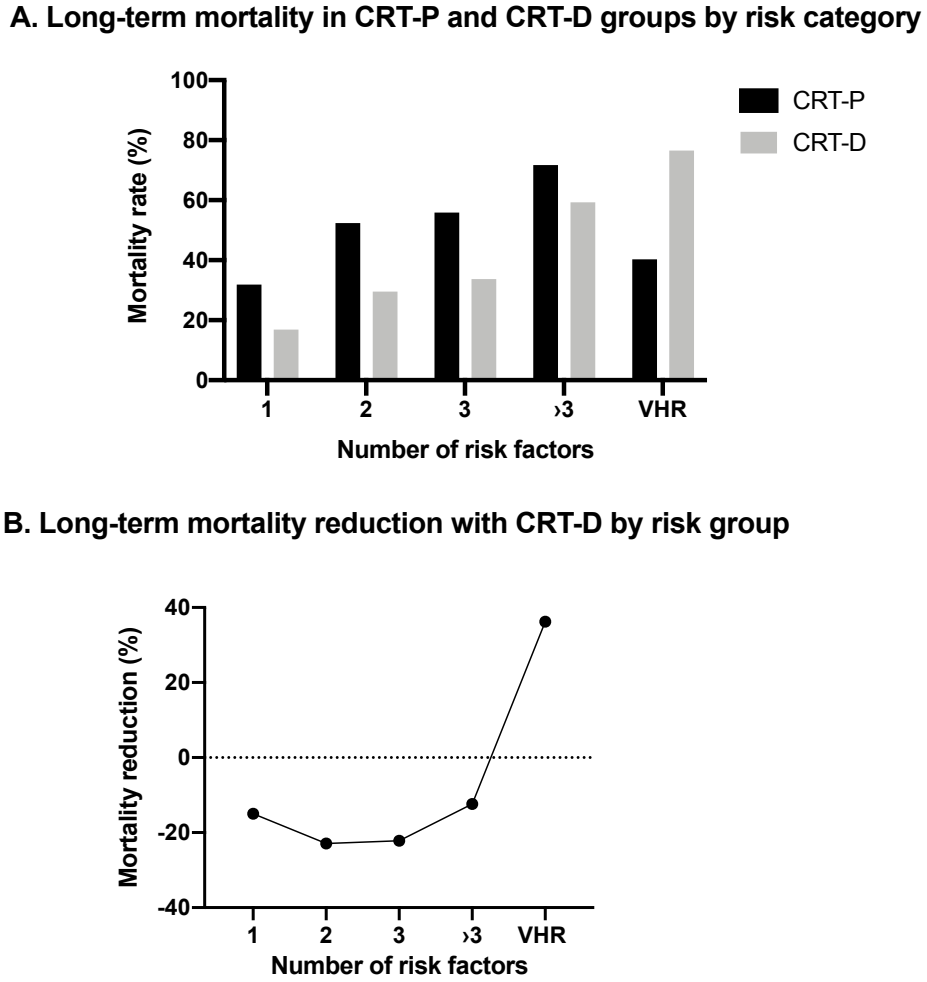

Figure 8. (A) Long-term mortality in cardiac resynchronization therapy-pacemaker (CRT-P) and cardiac resynchronization therapy-defibrillator (CRT-D) groups by risk category. (B) U-shaped curve for implantable cardioverter defibrillator (ICD) efficacy.

Table 15. Absolute mortality rates based on the Goldenberg risk score

Goldenberg risk score	1 (n= 118)	2 (n= 234)	3 (n=176)	›3 (n= 139)	VHR (n= 51)
CRT-P, n (%)	15 (31.9)	64 (52.4)	52 (55.9)	61 (71.7)	27 (79.4)
CRT-D, n (%)	12 (16.9)	33 (29.5)	28 (33.7)	32 (59.3)	13 (76.5)
Δ, (%)	-15	-22.9	-22.2	-12.4	2.9
p-value	0.07	<0.005	0.004	0.14	0.99

CRT-D, cardiac resynchronization therapy- defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; Δ, mortality difference; VHR, very-high risk

In the total cohort, excluding the VHR group, a statistically significant long-term benefit was observed with CRT-D therapy compared to CRT-P therapy (HR 0.73; 95% CI 0.58–0.92; p = 0.01). In multivariate analysis, there was a trend towards a 21% lower risk with CRT-D vs. CRT-P (HR 0.79; 95% CI 0.59–1.07; p = 0.13). Cox regression analysis was adjusted for relevant clinical covariates such as age, gender, LVEF, NYHA functional class, serum urea, presence of atrial fibrillation, diabetes, hypertension, and BMI. When the primary endpoint was analyzed according to the GRS, in absolute rates CRT-P implanted patients appeared have a less favorable survival rates, in low-risk patients (CRT-P 47% vs. CRT- D 27%; p < 0.001) and in high-risk patients (CRT-P 64% vs. CRT-D 45%; p < 0.001).

A survival benefit was observed in low-risk patients (risk score of 1–2) implanted with CRT-D devices compared to those treated with CRT-P devices (HR 0.68; 95% CI 0.48– 0.96; p = 0.03) (Figure 9A). However, patients with a high-risk score (risk score ≥ 3) did not experience a long-term benefit from the addition of an ICD to CRT (HR 0.84; 95% CI 0.62–1.13; p = 0.26) (Figure 9B).

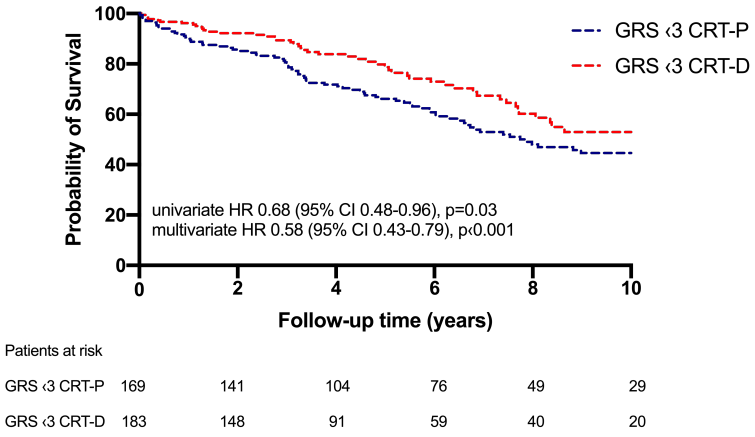

Figure 9A. Kaplan–Meier estimates of survival comparing cardiac resynchronization therapy-defibrillator (CRT-D) and cardiac resynchronization therapy-pacemaker (CRT-P) therapies in low-risk patients (<3)

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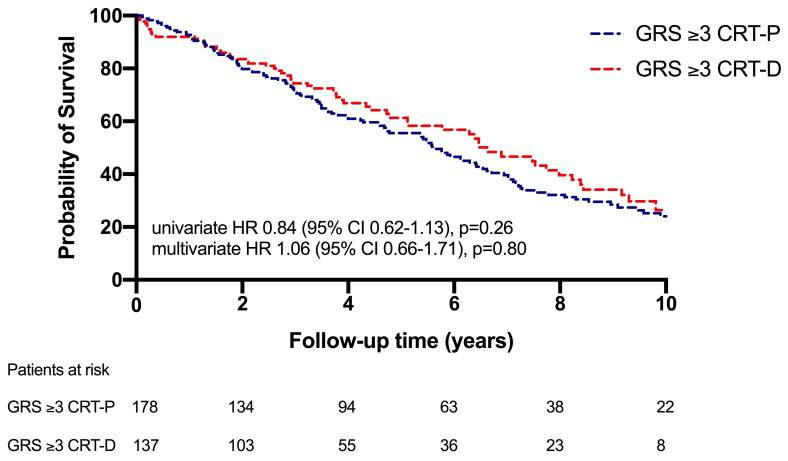

Figure 9B. Kaplan–Meier estimates of survival comparing CRT-D and CRT-P therapies in high-risk patients [Goldenberg risk score (GRS) ≥ 3].

These findings were further confirmed by Cox regression analysis. In low-risk patients CRT-D could be associated with a 42% mortality benefit (HR 0.58; 95% CI 0.43–0.79; p<0.001) compared to CRT-P. However, this mortality benefit was not observed in high-risk patients (HR 1.06; 95% CI 0.66–1.71; p= 0.80) after adjusting for age, NYHA class, se-BUN, atrial fibrillation, gender and LVEF.(162)

4.3.3. Very-high-risk patient population

We identified 51 patients whose se-BUN exceeded 50 mg/dl. These VHR patients significantly differed from non-VHR patients in terms of renal function (se-BUN 63 mg/dl vs. 21.6 mg/dl; p<0.001) and had a higher prevalence of atrial fibrillation (65 vs. 38%; p<0.001), CRT-D device implantations occurred less frequently in the VHR group compared to the non-VHR group (33 vs. 48%; p= 0.04) (Table 16).

Table 16. Baseline characteristics comparing the non- and very high-risk patient groups

Characteristics	non-VHR group n=667	VHR group n=51	p-value
BUN, mg/dl (median, IQR)	21.6 (16.8-27.7)	63 (55.2-71.1)	**<0.001**
Creatinine, mg/dl (median, IQR)	1.0 (0.8-1.3)	2.1 (1.7-2.8)	**<0.001**
Age, yrs (mean, SD)	65.6 ± 10.6	67.4 ± 9.9	0.26
LVEF, % (median, IQR)	28 (23-32)	28 (25-30)	0.66
QRS duration, ms (median, IQR)	160 (140-170)	160 (140-190)	0.33
CRT-D device, n (%)	320 (48)	17 (33)	**0.04**
Atrial fibrillation, n (%)	253 (38)	33 (65)	**<0.001**
Female sex, n (%)	219 (33)	14 (27)	0.43
Loop diuretic therapy, n (%)	501 (75)	43 (84)	0.14
Digitalis therapy, n (%)	138 (21)	10 (20)	0.85
Mortality			
Absolute rate, n (%)	306 (46)	40 (78)	**<0.001**

BUN, blood urea nitrogen; CRT-D, cardiac resynchronization therapy- defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction

Very-high-risk patients showed higher absolute mortality rates (78 vs. 46%; p <0.001) compared to the non-VHR group. Univariate analysis show that VHR patients had nearly a threefold higher risk of reaching the primary endpoint (HR 2.85; 95% CI 1.70–4.76; p<0.001). In this selected patient group, no benefit of the ICD could be demonstrated (HR 0.92; 95% CI 0.48–1.77; p= 0.81) (Figure 10), even after adjusting for relevant covariates such as age, gender, and LVEF (HR 0.59; 95% CI 0.20–1.68; p= 0.32).(162)

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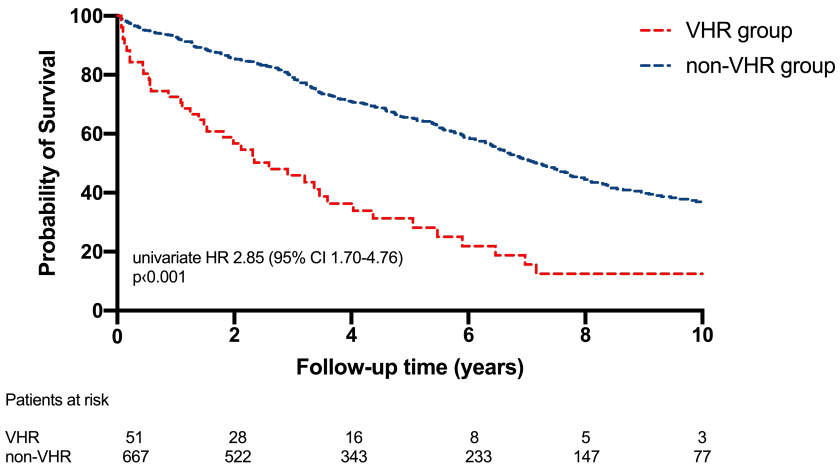

Figure 10. Kaplan–Meier estimates of survival in very-high-risk patients (VHR group) compared to the study population (non-VHR group)

VHR, very-high-risk

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5. Discussion

5.1. Discussion of Part 1

Response to CRT is significantly influenced by various factors, including optimal patient selection, implantational parameter, and postimplant factors (such as device programming and arrhythmias) (53, 76, 77).

During the follow-up of such patients the efficacy of and response to CRT relies mostly on reaching an appropriate BiV pacing rate. According to a large cohort study of CRT candidates by Cheng et al., only 40% of patients achieve a biventricular pacing rate of over 98%(163). For those with pacing rates between 95% and 98%, the most common cause of suboptimal pacing is an increased number of single ventricular premature contractions (PVCs), affecting 18.7% of patients (163). In our study, although PVCs did not reduce the effectiveness of biventricular pacing, we observed less favorable outcomes, particularly a lack of atrial reverse remodeling, in patients with a high number of PVCs.(159) Ruwald et al. reported similar findings, noting that even a low burden of ectopic beats (as low as 1 in 1,000) was associated with poorer echocardiographic response and clinical outcomes, including a higher incidence of ventricular tachyarrhythmias and all-cause mortality. In the aforementioned MADIT-CRT substudy, ectopic beats, including atrial and ventricular premature complexes, with a frequency as low as 0.1%, were linked to poorer reverse remodeling and increased HF events. In our research, PVCs accounted for only 0.4% of heartbeats (based on a median of 11,401 beats). Although we did not find a statistically significant correlation between 6-month changes in LV dimensions and the 1-month PVC count, the number of PVCs was associated with the absence of atrial reverse remodeling, as measured by atrial volume. This beneficial effect of a low prevalence of PVCs was also observed by Akkaya et al., who found that six months after PVC ablation, patients with a lower baseline PVC count experienced a greater reduction in left atrial volume and improved diastolic function, regardless of LVEF (164). Additionally, Park et al. demonstrated that the LAV index correlates strongly with PVC burden, and that PVC burden is an independent predictor of the LAV index, irrespective of age, sex, and comorbidities (165).

Further studies have raised the question of whether the origin of PVCs might impact the subsequent echocardiographic response. For instance, Wojdyła-Hordyńska et al. found that among 110 consecutive patients who underwent monomorphic PVC ablation, only the elimination of PVCs originating from the outflow tract predicted LV improvement at 6 months (166).

The effects of CRT on LV and atrial reverse remodeling have been previously studied. Left atrial reverse remodeling is thought to occur due to more synchronous contraction, leading to improved LV filling, increased cardiac output, and reduced mitral regurgitation (113, 167). Both LAV and LVESV reductions independently decrease the risk of HF and death (74, 151). Some patients experience only atrial reverse remodeling, and these individuals have outcomes comparable to those with complete left sided reverse remodeling (HR 2.0; 95% CI 0.7–5.6; *P*=0.21). These patients show intermediate outcomes in both echocardiographic measures, and long-term mortality and HF hospitalizations, likely due to an improved LV diastolic filling (168).

In a MADIT-CRT subanalysis by Mathias et al., 22% of the patients undergoing CRT implantation experienced only either LAV or LVESV reduction. Patients with complete left sided reverse remodeling (both LAV and LVESV reduction) had significantly lower rates of HF and death compared to those with lesser reverse remodeling. However, those with discordant remodeling still fared better than those with lesser remodeling. Predictors of complete reverse remodeling included female sex, non-ischemic etiology, and a lower percentage of unfavorable clinical parameters (lower LAV and LVESV, higher LVEF) (169). Our study did not reveal significant differences in these baseline clinical characteristics.

Given these findings, it remains unclear whether the relatively low prevalence of PVCs is a cause or symptom of, for example, an overactive sympathetic nervous system. This raises the question of whether it is relevant to reduce the number of PVCs and, if so, what the most effective method might be—ablation or medication? PVCs can contribute to the progression of HF in CRT patients due to the loss of effective biventricular pacing, and their hemodynamic effects may be significant, especially given impaired systolic and diastolic function. While the cause, consequences, and clinical implications of PVCs

remain ambiguous, early identification of patients with a higher PVC count, along with close monitoring and maximized medical treatment, may prove beneficial.

5.2. Discussion of Part 2A

In this large-scale retrospective observational study, HF patients with obesity and free of comorbidities, selected for CRT implantation experienced survival benefit compared with normal-weight CRT candidates. Furthermore, across all BMI groups the proportions of patients who experienced reverse remodeling were similar, and the incidence of peri- and postprocedural complications did not differ.(161)

Previous observational studies have partly described the association between obesity and improved outcomes in HF patients. (3) However, this phenomenon remained uncertain in the most severe subsets of HF patients, particularly those undergoing CRT implantation. (127, 170, 171) In earlier trials, the association of obesity with all-cause mortality followed J-shaped curve in HF patients with the lowest mortality observed at a BMI of 25kg/m^2. (172) Some studies linked being overweight (BMI 25-<30 kg/m2) with better outcomes compared to normal weight. (173) Despite these incomprehensive findings in the literature; as some showed mortality benefit with overweight (170), some with obesity in HF patients(127), higher BMI overall has been associated with mortality benefit compared to normal weight or particularly with cachexia, this suggests that obesity may refer to a better metabolic reserve (174).

The heterogeneity of findings of previous studies may be attributed to differences in patient selection or the timing of enrolment during the course of their disease.

In the current analysis, the characteristics of our cohort are consistent with previous landmark trials that enrolled HFrEF patients eligible for device implantation. (52, 53) Patients with obesity were generally younger (170, 174) and more frequently have comorbidities such as diabetes (170, 174), hypertension (126, 175) and tended to have higher LVEF than normal-weighed patients, (3, 16) which might also be associated with a better outcome. Additionally, the type of CRT device can also impact the risk of mortality when adding a defibrillator (CRT-D) offering further reduction of the risk of SCD. While some studies have reported a higher incidence of CRT-D implantations in those with overweight or obesity (170, 176), our study found no significant difference in the proportion of CRT-D implantations across BMI groups.

The length of the follow-up time can also impact the result. Grandin et al. investigated the ten-year survival free from all-cause death, orthotopic heart transplantation, or ventricular assist device implantation, which was found to be the highest in patients with obesity (36.3%), lower in overweight ones (19.2%), and the lowest in normal weight patients (12.1%). (127)

Notably, it is difficult to determine whether patients in the normal BMI group represent end stage HF cases with unintentional weight loss or a normal weight one at an earlier stage of the disease. Moreover, the effect of intentional weight loss through diet or newer antidiabetic drugs (e.g., GLP-1 analogues) and its effect on outcomes is scarcely investigated in patients with device therapy. This highlights the need of further trials to explore the effect of such new treatments on the outcome of HF patients selected for device implantation. Given the significant global burden of cardiovascular diseases attributed to high BMIs is, it is crucial to implement prevention strategies to navigate patients into optimal BMI ranges and to avoid developing comorbidities.(177)

Findings related the obesity paradox are influenced by several covariates. In a recently published study, when using novel anthropometric measures to define obesity, the beneficial effect on HF hospitalization or all-cause mortality was not observed. However, the protective effect of obesity became apparent when adjusted for conventional risk factors. This benefit, however, diminished to insignificance after further adjustment for log NT-proBNP (178), a biomarker influenced by obesity.

The presence of comorbidities can significantly influence outcomes. Our analyses revealed that only patients free of comorbidities experienced survival benefit with obesity. We observed the obesity paradox regardless of sex, in patients without diabetes, without atrial fibrillation, without ischemic etiology, and in younger patients. In the literature, the presence of the phenomenon in the subgroup of diabetic patients remains debatable. In previous studies, obesity did not provide survival benefit in patients with DM (179-181), while others reported that regardless of DM status, those with obesity showed mortality benefit after CRT implantation. (127) DM, however, is linked to a higher burden of comorbidities and poorer outcomes in HF patients (182, 183), possibly mitigating obesity's protective factor. Another important factor that could influence the presence of the obesity paradox is ischemic etiology. (127) Similar to our results, Zamora et al., observed the obesity paradox only in non-ischemic HF patients.(184)

As the prevalence of obesity and the number of device implantations continue to rise(185), safety assessment is crucial in this patient group. Complication rates tend to increase with the complexity of the devices and are also influenced by individual patient factors (146). In our analysis, periprocedural complications did not occur more frequently in patients with obesity. Similarly, a prior analysis found no significant difference in device-related complications within 90 days after CRT-D implantation in elderly patients. (126) But patients with obesity, particularly those with extreme obesity might face a higher rate of failed LV lead placement or lead dislodgement. (186, 187) Despite these potential risks, CRT implantation is generally considered a safe and well endured procedure in patients with higher BMIs. (188)

Evaluating the response to CRT therapy within 6-12 months is crucial, as a positive response and the development of reverse remodeling is strongly correlated with long-term survival (74). A few studies with CRT patients have shown that individuals with obesity can experience similar or greater improvements in LVEF and LVEDD. (171, 176, 189) In our analysis, we observed similar improvement in LVEF and an even proportion of developing reverse remodeling across patient groups.

5.3. Discussion of Part 2B

Although guidelines for the primary prevention of sudden cardiac death (SCD) recommend ICD implantation for symptomatic HF patients with non-ischemic etiology at a IB level of evidence (146), physicians' attitudes towards device implantation have shifted since the publication of the DANISH trial results. In 32% of surveyed centers, the diagnosis of non-ischemic cardiomyopathy led to a preference for implanting CRT-P devices, while the DANISH trial emphasized the importance of ICD implantation in reducing all-cause mortality in patients under 68 years old (HR 0.64; 95% CI 0.45–0.90; $P = 0.01$). Subgroup analysis from the COMPANION trial confirmed a reduction in SCD without a significant impact on total mortality(77). The DEFINITE trial also discarded the benefit of adding an ICD to oral standard medical care in non-ischemic patients with respect to death from any cause (HR 0.65; 95% CI 0.40–1.06; $p = 0.08$) (190). In line with these results, more observational large-scale studies conducted by Leyva and one at our center demonstrated that CRT-D was not associated with a mortality benefit in non-ischemic patients (152, 156).

These data confirm that the decision to add an ICD to CRT in non-ischemic patients remains complex, challenging, and multifactorial (191). Additionally, with the current four-pillar medical treatment for HFrEF patients, the decision to add an ICD in elderly requires further investigation and patient-level personalized assessment. For this purpose, several risk scores were developed to evaluate the likelihood of SCD and cardiovascular mortality after CRT implantation. (147, 192) Also, CRT alone has been shown to reduce the risk of SCD and significantly lower the incidence of ventricular arrhythmias through reverse remodeling (193).These interrelated factors also highlight the relevance of individual risk assessment using such SCD or all-cause mortality calculators (155). The ongoing RESET-CRT trial aims to determine the impact of CRT-D on all-cause mortality and SCD in HF patients with a CRT indication (194).

The GRS was originally developed to improve patient selection for ICD implantation in ischemic cardiomyopathy, to identify subgroups that correspond with ICD efficacy (153). We applied the risk stratification unconventionally in non-ischemic HF patients undergoing CRT implantation, it is based on the five key mortality predictors (age, atrial fibrillation, NYHA functional class, QRS width, and serum blood urea nitrogen). Long-term outcomes for non-ischemic patients receiving CRT-D are influenced by multiple parameters. The characteristics of the investigated patient cohort are essential regarding co- morbidities and the subsequent responder status. Our patient population had a similar age profile [CRT-D 64 (57–71) years and CRT-P 69 (61–75) years] compared to the population in the study conducted by Barra et al. (CRT-D 66 years and CRT-P 69.8 years) (155), as well as to the population in the MADIT-CRT trial (65 ±11 years) (53, 162).

Our real-world data suggests a selection bias can be presumed since CRT-P patients were older, included fewer females and had a baseline higher LVEF compared to CRT-D implanted patients which may influence their outcome in CRT response and SCD rate.(162) A similar pattern in sex distribution was reported by Barra et al., with fewer female patients undergoing CRT implantation (33% were females in the COMPANION trial and 26% in the MADIT-CRT trial). In terms of atrial fibrillation, the MADIT II trial reported a lower occurrence compared to our population (37 vs. 39%). However, we included both the current and previous atrial fibrillation events to involve those, who are

definitely showing a higher risk to cardiovascular mortality compared to those with sinus rhythm (44).

At illustration, mortality reduction outlines as a U-shaped curve emphasizing that mostly intermediate-risk (risk factors of 2 and 3) patients benefit from CRT-D implantation (153). The absolute mortality rates are comparable to the original article (153), 16% in non-VHR patients vs. 15.7% in our data. In the mid-term analysis of the GRS, published by Goldenberg et al. patients with an intermediate-risk gained the largest benefit from ICD therapy whereas patients with low- or high-risk did not (153). The risk stratification was also studied at long- term low-risk patients did have a significantly higher survival rate with ICD therapy than usual clinical care (HR 0.52; 95% CI 0.38–0.73; $p < 0.001$); high-risk patients with multiple comorbidities still did not acquire survival benefit (HR 0.84; 95% CI 0.63–1.13; $p = 0.247$) (154). Barra et al. enrolled patients regardless of their etiology that involved CRT candidates from a long timeframe between 2000 and 2011 and observed similar results. Patients with a low-risk score were more likely to benefit from the defibrillator, moreover, this benefit was most dominant in the first few years (11.3 vs. 24.7%, $p = 0.041$) then attenuated at long-term (21.2 vs. 32.7%, $p = 0.078$). At multivariate analysis, CRT-D decreased mortality rates compared to CRT-P (HR 0.339; 95% CI 0.178–0.642; $p = 0.001$), also seen after propensity score matching (CRT-D 20% vs. 38.2% CRT-P; $p = 0.036$) (155). In our analysis low-risk CRT-D patients showed a mortality benefit compared to CRT-P (HR 0.68; 95% CI 0.48–0.96; $p = 0.03$), whereas high-risk patients did not (HR 0.84; 95% CI 0.62–1.13; $p = 0.26$).

5.4. Limitations

The presented studies and results should be interpreted in the light of certain limitations. (159, 161, 162) The findings of part 1 are mainly limited due to the small sample size and the availability of pacemaker interrogations and echocardiographic results. Additionally, the implanted CRT devices varied in brand and type each employing different PVC detection algorithms. It is also important to consider that the PVC burden may be affected by episodes of atrial fibrillation, fusion beats, and supraventricular contractions with aberration, which could confound the measurements. The observational studies in part 2A and 2B introduce inherent limitations due to their retrospective design.

Selection bias is a potential concern, as not all patients could be included in the analysis due to incomplete datasets. While BMI serves as a standardized metric for assessing obesity, it does not account for variations in body composition or physical fitness. Furthermore, our study population lacked underweight or cachectic individuals—groups often associated with poorer clinical outcomes. Also, we do not have data on the use of drugs such as sodium glucose co-transporter 2 inhibitors or angiotensin receptor-neprilysin inhibitor that may influence the outcome. Limitation restricted to part 2B were that the GRS was originally investigated in ischemic patients with mild to moderate symptoms, a population differing significantly from our CRT candidate cohort. Because all patients had a wide QRS, the minimum score value in our analysis was 1, potentially affecting the risk stratification. Also, we do not have data on scar burden and cardiac magnetic resonance imaging which could have enhanced our ability to predict CRT response and SCD risk.

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6. Conclusions

Cardiac resynchronization therapy is an effective treatment of HF patients with a reduced LVEF and a wide QRS complex, while improving cardiac function it reduces HF hospitalizations and all-cause mortality. (53, 76) Even though CRT was and still is a cornerstone in HFrEF treatment, many questions remain unanswered, and a significant number of patients do not respond favorably.

Assessment of predictors of response such as in our study, the early assessment of single PVCs is essential. In our cohort the effectiveness of biventricular pacing was not diminished by PVCs, but we observed a less favorable outcome, a lack of atrial reverse remodeling in patients with a high number of PVCs. Low PVC count, registered at 1-month, was associated with a significant decrease in left atrial volume at the 6-month follow-up and lower all-cause mortality.

Both cardiovascular and non-cardiovascular comorbidities greatly affect morbidity and mortality in HF patients. Predictors of mortality can guide physicians to recognize those patients at higher risk of mortality, those who need a stricter follow-up. Hence analysis of predictors of mortality remains essential, obesity as such impacts outcomes in patients eligible for CRT. Patients with obesity and overweight experienced similar echocardiographic response as patients with normal weight. Also, obesity did not infer higher periprocedural complication rates. In our study, patients with a BMI >25 kg/m^2 and free of comorbidities experienced the lowest risk of all-cause mortality.

In HF patients the risk of SCD is mainly characterized by their LVEF, several risk scores have been proposed before. Risk stratification of patients with HFrEF, especially of non-ischemic etiology remains a challenge. In our retrospective single-center, large-scale, real-world clinical data, patients with non-ischemic HF who underwent CRT-D implantation did not acquire mortality benefit of having a defibrillator compared to CRT-P implantation. Selection of low- and intermediate-risk, based on the GRS, may help to achieve the most favorable outcome for non-ischemic HF patients. These patients may benefit the most from the addition of a defibrillator to CRT during long-term follow-up, whereas high-risk patients are unlikely to.

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Our main findings are as follows:

- Low PVC count, registered at 1-month, was associated with a significant decrease in left atrial volume at the 6-month follow-up and lower all-cause mortality.
- Patients with obesity and overweight experienced similar echocardiographic response as patients with normal weight.
- Obesity did not infer higher periprocedural complication rates.
- Patients with a BMI >25 kg/m^2 and free of comorbidities experienced the lowest risk of all-cause mortality.
- Non-ischemic HF who underwent CRT-D implantation did not acquire mortality benefit of having a defibrillator compared to CRT- P implantation.
- Selection of low- and intermediate-risk, based on the GRS, may help to achieve the most favorable outcome for non-ischemic HF patients.
- Low- and intermediate risk patients may benefit the most from the addition of a defibrillator to CRT during long-term follow-up, whereas high-risk patients are unlikely to.

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7. Summary

Cardiac resynchronization therapy effectively reduces morbidity and mortality in a well-selected HFrEF patient population. It improves cardiac function, translating into improvement of symptoms, and quality of life. However, non-response to therapy remains challenging, thus assessment of response and predictors of mortality is crucial.

In our single-center, prospective trial, we examined the significance of early PVCs on response to therapy, and mortality. We investigated 125 consecutive patients undergoing CRT implantation were enrolled, baseline, 1-month, and 6-month clinical, laboratory, echocardiographic parameters, and pacemaker interrogations were registered During our two-year follow-up, lower number of PVCs was associated with atrial remodeling and showed a trend for a better mortality outcome.

In our retrospective, large-scale study, we investigated obesity's impact on response to CRT and all-cause mortality. Patients were categorized based on their BMI and were followed for a mean of 5.1 years. Patients with obesity or overweight and free of comorbidities showed the lowest risk of mortality. Obese and overweight patients showed similar echocardiographic response than normal weight patients and did not suffer from a higher rate of periprocedural complications.

In order to select the optimal device, we implemented a sudden cardiac death risk score. Primary prevention ICD implantation in non-ischemic patients eligible for CRT implantation remains controversial. In our high-scale retrospective analysis, we implemented the Goldenberg risk score, comprising five clinical factors (se-BUN, QRS width, age, atrial fibrillation, NYHA class), to identify those non-ischemic HF patients who benefit from the supplementation of the CRT with an ICD. Based on our results, the risk score selected well patients with low-, or intermediate risk patients in who we observed mortality benefit.

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8. Összefoglalás

A kardiális reszinkronizációs terápia hatékonyan csökkenti a morbiditást és mortalitást egy jól meghatározott HFrEF betegcsoportban. Javítja a szív pumpafunkcióját ezáltal javítja a beteg panaszait, csökkenti a tüneteket. Azonban a non-responderitás továbbra is kihívást jelent, ezért a responderitási és mortalitási prediktorok vizsgálata ezáltal elengedhetetlen.

Célunk, új responderitási és mortalitási prediktorok vizsgálata volt. Prospektív, egy-centrumos vizsgálatunk során a korai kamrai komplexusok (PVC) jelentőségét analízáltuk. 125 CRT implantáción átesett beteget választottunk be. A beválasztáskori, 1 és 6 hónappal az implantáció után végzett klinikai értékeket regisztráltuk, így a laboratóriumi, funkcionális, pacemaker lekérdezés, és echocardiographiás paramétereket. A 2 éves átlag utánkövetési idő alatt a bal pitvari volumen jelentősen csökkent 6 hónappal az implantáció után az alacsony PVC csoportban. A CRT implantáció után 1 hónappal észlelt PVC arány összefüggésben állt a bal pitvari reverz remodelációval, amely feltételezhetően befolyásolhatja a kimenetelt.

Retrospektív, nagy elemszámú vizsgálatunkban az obezitás jelentőségét vizsgáltuk a CRT válaszkészségre és össz-mortalitásra. A betegeket a testtömeg indexük alapján csoportosítottuk, az átlagos utánkövetési idő 5.1 év volt. Azon túlsúlyos és obez betegekben figyeltük meg a legjelentősebb túlélési előnyt, akik nem rendelkeztek egyéb társbetegségekkel. Hasonló echocardiographiás válaszkészséget mutattak az obez és túlsúlyos betegek, továbbá nem jelentett magasabb rizikót az obezitás a periprocedurális szövődményekkel kapcsolatban.

Az optimális eszköz kiválasztása érdekében egy rizikó stratifikációs score-t alkalmaztunk egy eddig nem szélesen vizsgált betegcsoportban. A primer prevenciós ICD implantáció non-ischemiás, CRT implantáció előtt álló betegekben továbbra is vitatott. Retrospektív vizsgálatunkban, a Goldenberg rizikó score-t vezettük be azon non-ischemiás szívelégtelen betegek azonosítására akiknél túlélési előnyt jelent a CRT ICD-el történő kiegészítése. Eredményeink alapján a score rendszer jól szelektálta a kis és közepes rizikóval rendelkező betegeket, akiknél mortalitásbeli előnyt találtunk.

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