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

PhD thesis

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Budapest
2025

1. Introduction

In general heart failure (HF) concerns roughly 1-2% of the population, but its prevalence can reach up to 10% above 70 years of age. As a progressive disease, with a poor prognosis, early diagnosis and early initiation of therapy is fundamental. Treatment of HF is mainly categorized as pharmacological and non-pharmacological. Cardiac resynchronization therapy (CRT), the cornerstone non-pharmacological treatment of HF with a reduced ejection fraction (HFrEF), is an effective treatment to reduce morbidity and mortality in optimally selected patients. CRT successfully alleviates symptoms of HF and ameliorates quality of life by improving cardiac function. However, 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. 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 predictors of response are sex, etiology of HF, QRS duration and morphology. Obesity is common amongst HF patients, likewise in CRT candidates, a phenomenon as obesity paradox has been described where patients with obesity show survival benefit, but evidence regarding the optimal range of body mass index (BMI) associated with improved survival in this patient population has been limited. Appropriate response to CRT can be ensured with an appropriate device programming and BiV pace rate during the follow-up. The effectiveness of biventricular (BiV) pacing delivery is a key factor in the success of CRT. Arrhythmic events such as atrial fibrillation or premature ventricular complexes (PVC) are the most common cause of BiV pacing loss.

HF patients are prone to suffer a sudden cardiac death (SCD), that approximately accounts for 35-45% of deaths in patients with HFrEF. 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. In CRT candidates, the decision of implanting CRT-D vs. CRT-P is based on individual risk assessment. Risk scores such as the Goldenberg risk score (GRS) were created by using independent predictors of mortality or based on parameters which were proved to be relevant on the outcome from large-scale trials or registries. The necessity of a defibrillator in candidates for CRT with non-ischemic HF remains controversial as no previous randomized controlled trial was conducted to evaluate it. Due to a higher extent of reverse remodeling in patients with non-ischemic HF, the risk of fatal ventricular arrhythmias diminishes significantly, 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.

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.

3. Methods

3.1. Patient population

In Part 1, we enrolled 125 HFrEF patients that then underwent CRT implantation indicated per current guidelines. 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.

In Part 2A, we included patients who underwent CRT implantation at our clinic between 2000 and 2020. Patients with available data were classified into three patient groups according to the WHO classification, normal weight (BMI <25 kg/m2), patients with overweight (BMI 25.0 – <30 kg/m2) and patients with obesity (BMI ≥ 30 kg/m2).

In Part 2B, we included HF patients with non-ischemic etiology underwent CRT implantation between June 2000 and September 2018. We excluded those with a serum blood urea nitrogen (se-BUN) exceeding 50 mg/dl and defined them as very-high-risk (VHR) patients as per the original article. Aside from these patients, 667 had complete data available to calculate their GRS. Patients were further dichotomized into low (<3) and high (≥3) score groups.

3.2. Device implantation

Device implantations were performed under X-ray, leads were implanted through either the cephalic or the subclavian veins, with right ventricular leads primarily fixed in a septal position. After venography the optimal coronary sinus side branch was routinely selected favoring the lateral or posterolateral positions. The implanting physicians selected the device type based on current guidelines, considering patient preferences, age, sex, renal function, frailty, and other comorbidities.

3.3. Follow-up

In Part 1, follow-up visits were conducted at one and six months, with patients subsequently monitored via phone contact for four years. At baseline and six months after the procedure, detailed laboratory tests, echocardiographic exams, New York Heart Association (NYHA) functional class assessments, physical exams including a 6-minute walk test, and pacemaker interrogations were performed or collected.

In Part 2A, the date of death was obtained from the National Health Insurance Fund of Hungary, with updates as of December 2021.

In Part 2B, the exact date of death was retrieved in September 2019.

3.4. Endpoints

In Part 1, 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 left ventricular ejection fraction (LVEF), a reduction of at least 15% in left ventricular end-systolic volume (LVESV), or a decrease of at least 15% in left atrial volume (LAV), all measured six months after CRT implantation.

In Part 2A, the primary outcome was the composite endpoint of all-cause mortality, heart transplantation (HTX), or left ventricular assist device (LVAD) implantation. 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.

In Part 2B, the primary composite endpoint was all-cause mortality, HTX or LVAD implantation, whichever occurred first.

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%. 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 including renal function or potassium levels, medical history, or echocardiographic parameters. 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.

4.1.2. Clinical outcome and 6-month echocardiographic changes by the number of PVCs

During the mean follow-up time of 2.1 years, 7 patients reached the primary endpoint in the “low PVCs” group, while 12 in the “high PVCs” group (HR 0.97; 95% CI 0.38 - 2.48; p=0.04) (Figure 1.). 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).

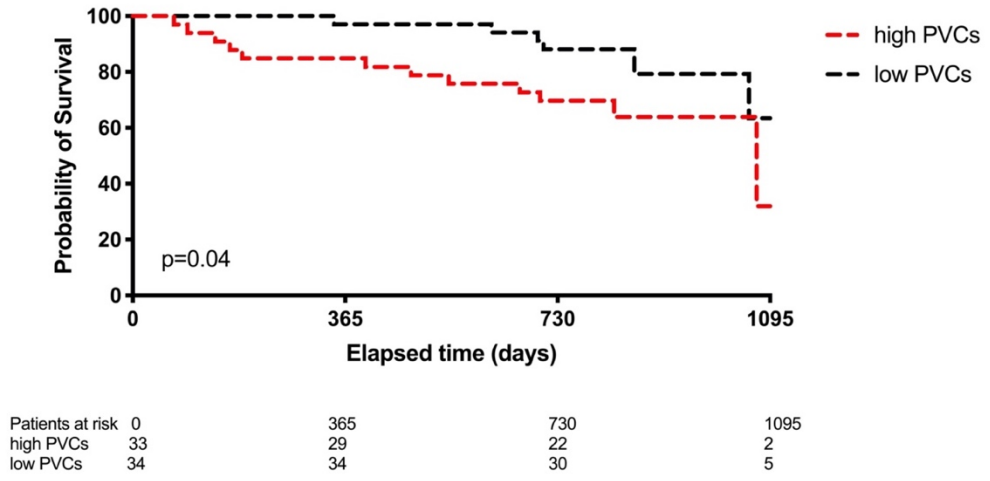


Figure 1. Survival of patients with low vs. high PVCs
PVC, premature ventricular complex

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).

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).

4.2.2. Main outcomes

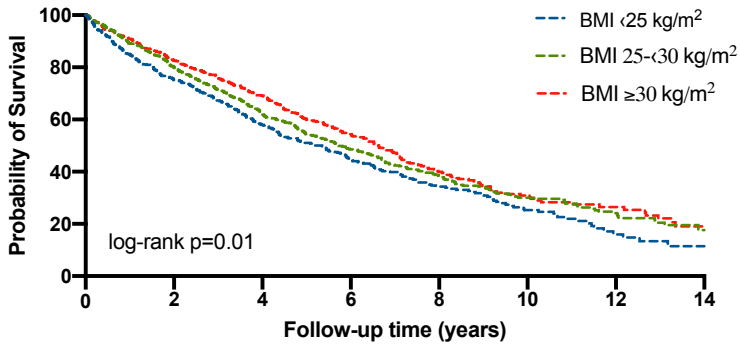
During the mean follow-up period of 5.1 years, 973 patients (61%) reached the primary endpoint: 302 (66%) in the BMI <25 kg/m² group, 389 (61%) in the BMI 25-<30 kg/m² group, and 282 (58%) in the BMI ≥30 kg/m² group (log-rank p<0.05) (Figure 2.). Patients with obesity had a significantly lower risk of 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).

Patients in the obese II group had a higher 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.



Patients at risk								
BMI ‹25 kg/m^2	459	340	242	151	88	45	14	5
BMI 25-‹30 kg/m^2	641	503	350	229	127	74	41	8
BMI ≥ 30 kg/m^2	485	397	298	198	105	50	26	12

Figure 2. Kaplan Meier estimates of the probability of survival after CRT implantation by BMI groups

BMI, body mass index; CRT, cardiac resynchronization therapy

4.2.3. 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). 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, obesity did not provide a survival benefit for older patients (HR 1.01; 95% CI 0.86-1.20; p=0.86).

4.2.4. 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).

4.2.5. 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).

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).

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). 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.

4.3.2. Primary endpoint

During the median follow-up of 4.3 years, out of all patients 306 (46%) reached the primary composite endpoint, with 112 (37%) undergoing CRT-D implantation, 194 (63%) undergoing CRT-P implantation. 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 3A). 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 3B).

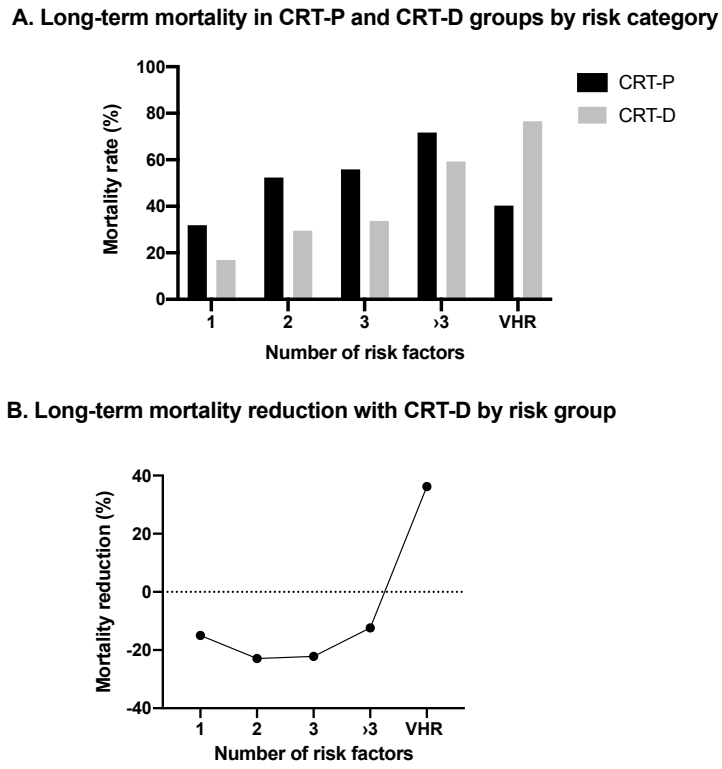


Figure 3. (A) Long-term mortality in cardiac resynchronization therapy-pacemaker (CRT-P) and cardiac resynchronization therapy-defibrillator (CRT-D) groups by risk category. (B) U-shaped curve for implantable cardioverter defibrillator (ICD) efficacy.

In the total cohort of non-ischemic patients, 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). However, this benefit was not confirmed by multivariate analysis (HR 0.79; 95% CI 0.59–1.07; p= 0.13).

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). 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 4. and Figure 5.)

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.

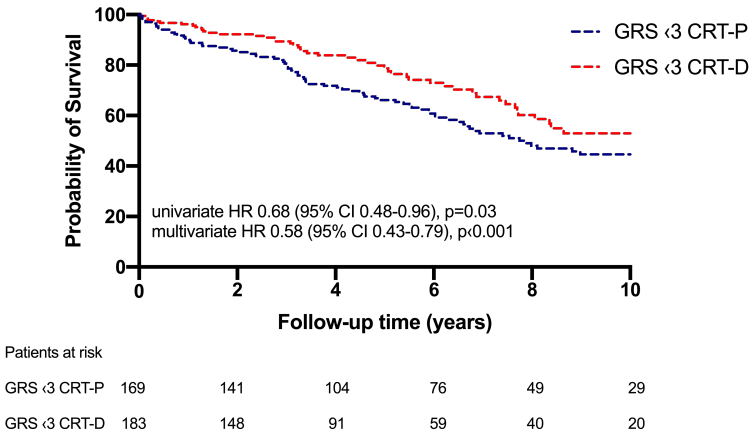


Figure 4. Kaplan–Meier estimates of survival comparing cardiac resynchronization therapy-defibrillator (CRT-D) and cardiac resynchronization therapy-pacemaker (CRT-P) therapies in low-risk patients (<3)

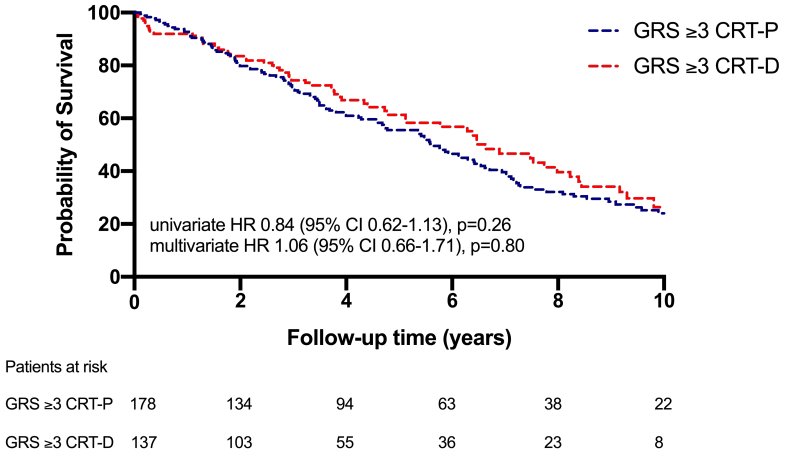


Figure 5. Kaplan–Meier estimates of survival comparing CRT-D and CRT-P therapies in high-risk patients [Goldenberg risk score (GRS) ≥ 3].

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).

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 6), even after adjusting for relevant covariates such as age, gender, and LVEF (HR 0.59; 95% CI 0.20–1.68; p= 0.32).

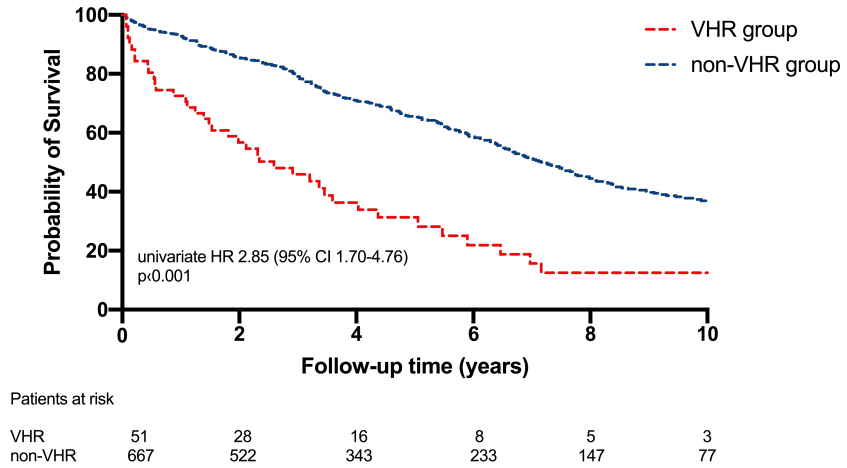


Figure 6. Kaplan–Meier estimates of survival in very-high-risk patients (VHR group) compared to the study population (non-VHR group)

5. 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. (54, 77) 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.

6. Bibliography of the candidate's publications

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Cumulative impact factors: 70.019