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Right ventricular systolic pressure predicts outcomes in patients with cardiac resynchronization therapy-defibrillators

Short title: RVSP predicts outcomes in patients with CRT-D

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WHAT'S NEW?

During the long-term follow-up of remotely monitored patients with cardiac resynchronization therapy, high right ventricular systolic pressure was an independent predictor of outcomes. Among other factors, right ventricular systolic pressure were identified as an independent predictor of all-cause mortality, and the risk of inappropriate therapies in patients with cardiac resynchronization therapy-defibrillator.

ABSTRACT

Background: Cardiac resynchronization therapy-defibrillators (CRT-D) are a cornerstone of the treatment of heart failure and wide QRS. In such subjects, there is often concomitant right ventricular (RV) dysfunction.

Aims: To assess whether the association between RV function parameters and all-cause mortality or CRT-D therapies.

Methods: The clinical data of study participants were obtained from the COMMIT-HF registry (NCT02536443). RV function parameters of focus were RV dimension, tricuspid annular plane systolic excursion, and right ventricular systolic pressure (RVSP). The data on the long-term hard endpoints were obtained from the national healthcare provider, while the data on the device therapies, from the investigator-initiated remote monitoring database. The predictors of the study outcomes — all-cause mortality, and the appropriate and inappropriate CRT-D therapies — were assessed with multivariable logistic regression and Kaplan-Meier curves.

Results: Between July 2009 and November 2019, 335 patients were enrolled at the remote monitoring programme after implantation of CRT-D. Of them, during the median (IQR) follow-up period of 5.3 (2.8–6.6) years, 117 (34.9%) died, 111 (33.1%) received appropriate and 37 (11.0%) inappropriate shocks. The independent predictors of all-cause mortality were reduced left ventricular ejection fraction and increase in RVSP. Lower age and increased left ventricular end-diastolic diameter were independent predictors of appropriate therapies, while lower age and increased RVSP were independent predictors of inappropriate therapies. Neither tricuspid annular plane systolic excursion nor RV dimension was a predictor of analysed outcomes.

Conclusions: RVSP is an independent predictor of inappropriate therapies and all-cause mortality in remotely monitored patients with heart failure and CRT-D.

Key words: cardiac resynchronization therapy, heart failure, outcomes, remote monitoring, right ventricular systolic pressure

INTRODUCTION

Cardiac resynchronization therapy-defibrillators (CRT-D) are implanted mostly in patients with low left ventricular ejection fraction (LVEF) and in the presence of wide QRS [1]. In patients with increased interventricular dyssynchrony, most pronounced in the presence of left bundle branch block, resynchronization allows for an increase of LVEF, and for an improvement of the functional capacity, reduction of the symptoms' burden, and improvement of the clinical endpoints, by reducing the risk of heart failure (HF) decompensations, and death. In subjects with pronounced HF and low LVEF, there is often a concomitant right ventricular (RV) dysfunction, as left ventricular dysfunction leads to increased pulmonary pressure, and thus increases the risk of RV overload and secondary dysfunction. In the prior data, RV

dysfunction has been associated with higher long-term mortality in patients with HF with and without CRT [2–4].

However, data on the association between RV dysfunction and arrhythmic outcomes in patients with CRT-D are scarce. Remote monitoring of patients with cardiac implantable devices allows to continuously monitor both the device's functioning, as well as the patient's arrhythmic events, and some measures of clinical status, enhancing timely detection of abnormalities and implementation of clinical reactions. The aim of the present analysis was to analyze whether any association exists between RV dysfunction and antiarrhythmic therapies or all-cause mortality in remotely monitored patients with HF with a CRT-D.

METHODS

The studied population consisted of all patients, who had a CRT-D, implanted either in the primary- or secondary prevention of sudden cardiac death and were enrolled in the remote monitoring (RM) programme conducted in our institution. The decision on the selection of CRT over conventional implantable cardioverter-defibrillator ICD, or on the upgrade from a non-CRT device, was at the treating physician's discretion, according to the appropriate guidelines. Both patients with *de novo* implantations, as well as device upgrades were included in the registry.

The clinical and demographic data of patients enrolled in this study were obtained from the single-centre COMMIT-HF registry (NCT02536443) [5]. In brief, the registry encompasses data on all consecutive patients admitted and treated in the tertiary cardiovascular center due to HF with reduced ejection fraction (LVEF ≤35%) not caused by an acute coronary syndrome at index hospitalization. In the Registry, detailed patient characteristics, with emphasis on prior medical history, and complete data from the index hospitalization, as well as the type of implantable device and medications administered at initial discharge are included. The study protocol was approved by an appropriate institutional review board and ethics committee and each patient signed informed consent for participation in the study. In addition, the detailed echocardiographic parameters regarding RV function, such as RV basal dimension measured in the RV-focused apical 4-chamber view, tricuspid annular plane systolic excursion (TAPSE) and right ventricular systolic pressure (RVSP) were obtained from the patients' electronic records. The assessment of every analyzed parameter followed the recommendations on the echocardiographic measurement of right heart parameters, with RVSP calculated as a sum of right atrial pressure, assessed based on the size of the inferior caval vein and its collapsibility, and the tricuspid regurgitation peak gradient [6].

The long-term follow-up with regard to the occurrence of clinical endpoints, including all-cause mortality, non-fatal myocardial infarction and stroke has been obtained from the National Health Fund, the sole Polish healthcare provider.

Remote monitoring

Remote monitoring of patients with HF and ICD has been initiated on a full scale in our department in 2011, with the first patients with ICD/CRT-D being enrolled already in 2009, and with dedicated employees who had since then provided a continuous monitoring of patients with cardiac implantable electronic devices. During the entire period, RM was assigned to CRT-D recipients, depending on the device availability in the hospital and reimbursement policies. The data have been derived from RM of all four major manufacturers of the devices and RM online softwares. The clinical reactions, along with their results are archived in the paper and electronic databases.

Based on the findings from the RM softwares, the RM registry has been created, with the initial findings of the registry having been published to date [7, 8]. It is an investigator-initiated, -adjudicated, and -maintained single-center, retrospective, all-comer registry of consecutive patients who were included in the RM during the entire period of its functioning in the facility. In brief, the registry encompasses data regarding the types of the transmissions (scheduled or alert-triggered) and their contents, with particular emphasis on the occurrence of arrhythmic episodes, appropriate and inappropriate device interventions, as well as the data on the causes of other, hardware- and software-related information, which have been included in the Supplementary material, *Table S1*. In the registry, each patient's individual data are updated on a yearly basis. All data regarding the occurrence of arrhythmic episodes, as well as device interventions were obtained from the registry. Every device therapy has been adjudicated by the experienced physician, regarding its appropriateness, or the cause of inappropriateness. Inappropriate therapies caused by lead failures, or other hardware-related malfunctions were not included in the present analysis. In patients in need for device replacement, if the newly implanted system was not compatible with the old RM system, the patient's follow-up in the RM registry was terminated, although the occurrence of clinical endpoints was still monitored. The occurrence of analysed outcomes was summarized at the one-year follow-up duration and over the entire follow-up period, with the censoring date for the analysis set at December 31, 2022.

Statistical analysis

Basic parameters of descriptive statistics for the analysed continuous variables were presented as medians and interquartile range (IQR) due to their non-normal distribution after assessment using the Shapiro–Wilk test. Between-group comparisons of continuous variables were conducted using the Mann–Whitney U test. The Pearson's χ^2 test was used to evaluate categorical variables. A two-sided *P*-value of less than 0.05 was considered statistically significant. For the initial assessment, patients were divided into subgroups according to the baseline RVSP (with a reference limit of 35 mm Hg), TAPSE (with a reference limit of 216 mm) and RV basal dimension (with a reference limit of 42 mm). All threshold values were obtained from the Guidelines for the Echocardiographic Assessment of the Right Heart in Adults endorsed by both the American and European societies [6]. The Kaplan–Meier analyses assessing the risk all-cause mortality, appropriate and inappropriate CRT-D therapies were performed, depending on the values of the analysed right heart functional parameters. Unifactorial and multifactorial analyses were performed to assess variables using the Cox proportional regression model (P <0.1 for inclusion in the model, P <0.05 for remaining in the model), with the values included in the multivariable analysis, including right heart echocardiographic parameters analysed as continuous variables, being summarized in the Supplementary material, *Table S4*. Estimated parameter values are presented as hazard ratios (HR) with a 95% confidence interval (CI). STATISTICA 10 (StarSoft Inc., Tulsa, OK, US) was used for all calculations.

RESULTS

During the period between July, 2009 and November, 2019, 335 patients were enrolled at the RM programme after implantation of CRT-D. As seen in Table 1, the median (IQR) age at the procedure was 63 (57–71) years, 60% of patients (n = 201) had ischemic cardiomyopathy and 35.5% had AF (n = 119). The median (IQR) LVEF was 25% (20%–29%) and the median (IQR) left ventricular end-diastolic diameter (LVEDD) at implantation was 66 (61–73) mm. The median (IQR) RVSP was 36 (30–47) mm Hg, and the median (IQR) TAPSE was 18 (15–20) mm, with a median (IQR) RV basal diameter of 37 (32–42) mm. Patients with elevated RVSP, or lower TAPSE had a higher prevalence of AF, lower baseline LVEF and a higher prevalence of tricuspid regurgitation, than their counterparts with reference values of those parameters. Subjects with higher RVSP had also a higher prevalence of at least moderate mitral regurgitation. When analyzed according to the RV diameter, subjects with a dilation of RV had a higher prevalence of AF, as seen in Supplementary material, *Table S2*.

At one year, the overall risk of appropriate therapies was 17.0%, with a similar percentage of patients experiencing either appropriate antitachycardia pacing (ATP) or high-voltage therapies (14.3%), as demonstrated in Table 2. The risk of inappropriate therapies at one year was 6.8%, with 5.4% of patients receiving inappropriate ATP, and 3.9% inappropriate shocks. The one-year mortality was 7.8%.

As presented in Table 3, the overall median (IQR) follow-up was 5.3 (2.8–6.6) years, and the rates of patients experiencing any appropriate, or inappropriate therapies were respectively 33.1% and 11.0%. Among the studied subjects, 24.8% received appropriate ATP and 22.4% any appropriate high-voltage therapies, with rates of such inappropriate therapies being 7.2% and 5.1% respectively. In the studied follow-up, 39.1% of patients experienced at least a single alert due to low percentage of biventricular pacing. The median (IQR) times to first appropriate and inappropriate therapy were 9.6 (2.9–18.4) and 5.9 (1.8–11.3) months, respectively. All-cause mortality during the entire follow-up was 34.4%.

As seen in Table 4, the percentage of patients with a higher RVSP who experienced inappropriate shocks was significantly higher than in subjects with lower RVSP (13.5% vs. 5.3%; $P = 0.03$), with a numerically higher rate of both inappropriate shocks (8.1% vs. 3.1%) and inappropriate ATP (7.4% vs. 3.1%). The rate of alerts due to the reduction in percentage of biventricular pacing was also significantly higher among patients with higher, than lower RVSP (46.6% vs. 28.2%; $P = 0.002$). Moreover, all-cause mortality was significantly higher in subjects with elevated RVSP (42.6% vs. 20.6%; $P <0.001$), as was the rate of alerts caused by reduction of biventricular pacing percentage (46.0% vs. 35.0%; $P = 0.048$). Significantly more subjects with decreased TAPSE experienced appropriate ATP (31.4% vs. 20.8%; $P = 0.03$), without significant differences in the overall risks of either appropriate or inappropriate therapies, albeit a higher mortality (41.2% vs. 30.8%; $P = 0.04$) was observed in that group, when compared with normal TAPSE, as demonstrated in Table 5. No differences were observed with regard to any analysed outcome, as far as RV dilation was concerned (Supplementary material, *Table S3*). Kaplan–Meier curves demonstrating the cumulative risk of each analysed outcome, depending on RVSP and TAPSE parameters are presented in Figure 1.

As demonstrated in Table 6 and Supplementary material, *Tables S5–S7*, in the multivariable analysis, the independent predictors of all-cause mortality were reduction in LVEF, with HR of 0.936 (95% CI, 0.903–0.970) per every 1%, and an increased RVSP with HR 1.021 (95% CI, 1.007–1.035) per every mm Hg. The independent predictors of appropriate therapies were age, with HR 0.976 (95% CI, 0.960–0.992) per every year and LVEDD, with HR 1.035 (95% CI, 1.014–1.057), per every 1 mm. Age and RVSP were identified as

independent predictors of inappropriate therapies, with respective HR (95% CI) of 0.956 (0.926–0.987) per every 1 year, and 1.028 (1.001–1.055) per every 1 mm Hg.

DISCUSSION

The main results of our analysis could be summarized as follows: Remotely monitored patients with echocardiographic markers of RV dysfunction, such as higher RVSP, or lower TAPSE, undergoing CRT-D implantation, are at higher risk of all-cause long-term death than subjects with normal right heart echocardiography parameters. LVEF and RVSP are independent predictors of all-cause mortality. Lower age and higher LVEDD, predict appropriate therapies, while higher RVSP and lower age predict inappropriate therapies in subjects with CRT-D devices.

Cardiac resynchronization therapy (CRT) is a guideline-recommended therapy for patients with symptomatic HF and LVEF ≤35%, and with QRS width of ≥130 ms [9]. Historically, chronic LV dysfunction emerged as a predominant factor contributing to unfavorable remodeling of the RV, and RV dysfunction has been shown to independently worsen prognosis in subjects with HF [10, 11]. Additionally, there are data suggesting, that RV dysfunction might serve as a predictor of outcomes in patients with CRT [2–4, 12]. On the other hand, in some subjects, RV function might be improved after implantation of CRT, probably due to the correction of the left ventricular systolic dysfunction, and improvement of hemodynamics, especially after optimal CRT programming [13, 14]. However, no study focused specifically on the occurrence of ventricular arrhythmias and device therapies in subjects after implantation of CRT-D.

The unfavourable hemodynamic clinical trajectory of patients with HF and reduced LVEF often leads to increased pressure in the pulmonary circulation, leading to pulmonary hypertension, which subsequently places a burden on the RV, causing its progressive dilation and dysfunction. One of the most important echocardiographic markers of pulmonary hypertension is RVSP. In our analysis, subjects with higher RVSP had a lower LVEF, lower TAPSE and higher RV diameter, and a higher prevalence of both mitral and tricuspid moderate-to-severe regurgitations. Elevated RVSP and the presence of either mitral- or tricuspid regurgitations might result in the atrial dilation, and therefore, exert a higher risk of development of atrial arrhythmias, as well as their progression to persistent or chronic forms. Therefore, an elevated RVSP could be considered as an indirect manifestation of atrial dilation and tachyarrhythmias, which might explain why patients with higher RVSP are at higher risk of inappropriate shocks, demonstrated in our study, in which more than 75% of analyzed

inappropriate shocks occurred due to AF, as presented in Supplementary material, *Table S8*. In those subjects, an utmost attention must be paid to optimal device programming, anti-arrhythmic pharmacotherapy, and qualification for invasive ablation procedures. Moreover, the atrial arrhythmias are the primary cause of reductions in biventricular pacing percentages, which remains as one of the most critical risk factors of HF decompensation and even death [15, 16]. In the analysis, the rate of alerts due to reduction in the percentage of biventricular pacing was significantly higher among subjects with higher RVSP, as well as with lower TAPSE. On the other hand, lack of independent association between TAPSE and outcomes, is contrary to some prior studies which demonstrated that in patients with CRT there might be a predictive role of TAPSE on outcomes. Nonetheless, such result signifies the need for further analyses of RV association with outcomes in patients with CRT [17, 18].

Age and LVEDD were identified as independent predictors of the occurrence of an appropriate CRT-D therapy. The association between left ventricular dilation, myocardial stretching, and the risk of malignant ventricular arrhythmias in patients with advanced HF is rather unambiguous [19, 20]. However, the association between age and appropriate therapies is less straightforward, with younger patients in our study experiencing more appropriate therapies than older subjects. In the recent large retrospective analysis of a real-world cohort, the rate of appropriate therapies in patients aged ≤60 years was insignificantly higher than in subjects aged >60 years [21]. Moreover, in the sub-analysis of the DANISH trial, limited to patients with non-ischemic cardiomyopathy, the benefit of ICD was more pronounced in patients aged ≤70, than >70 years of age, with a higher relative and absolute rate of sudden cardiac death in the younger patients [22]. Regarding our study, there are few elements, which could explain an increased risk of appropriate therapies in younger patients. First, the analyzed subjects constituted patients with most advanced heart failure. The younger population of patients treated in our center often comprised subjects deemed eligible for qualification, or already awaiting heart transplantation. Thus, those patients could potentially have a more pronounced heart failure, with a baseline higher risk of malignant arrhythmias requiring CRT-D therapies. Second, the lower adherence of the younger patients to recommended therapy cannot be excluded, with younger patients more often being periodically less compliant to maintain the guideline-recommended therapies, as well as more often subjected to more demanding physical exertion.

The all-cause mortality in our study was 34.9% over the course of a median of 5.3 (2.8–6.6) years, demonstrating the dismal prognosis observed in subjects with CRT devices. Similarly, the 1-year mortality in our cohort was higher than reported in the prior trials

evaluating RM in patients with CRT-D, what emphasises the higher complexity of patients recruited in the real-world analyses [23, 24]. In the prior analyses, it has been demonstrated that patients with CRT are the group with most pronounced HF, and often irreversible changes in their haemodynamic profile. On the other hand, an optimal timing of CRT implantation is necessary to manage patients with HF, and such decision is often excessively postponed, till the remodelling of the left ventricle, and interventricular dyssynchrony become irreversible, and a benefit of CRT is then diminished [25]. Of note, lack of any abnormal results of RV function were observed in just 27.6% of subjects included in the analysis, what suggests that in the vast majority of patients qualified for CRT implantation, there was already some manifestation of right-sided HF. In that context, taking into consideration the measurements of RV dysfunction might be of importance to select the optimal timing of CRT implantation, before biventricular HF progresses further. From that perspective, our findings emphasize the multifactorial nature of predicting clinical outcomes in CRT-D recipients, with both left and RV parameters playing roles in predicting all-cause mortality, and either appropriate or inappropriate CRT-D therapies.

Limitations

The present study possesses some limitations, one should be aware of. First of all, it is based on the real-world, single-center observational data, thus drawing causations must be performed with caution. Moreover, no data defining patients' response to CRT (responder/non-responder), regarding neither echocardiographic, nor clinical parameters were available. Moreover, the data on CRT-specific programming, e.g., atrioventricular and interventricular delays, or detection and therapy zones could not be obtained in all patients.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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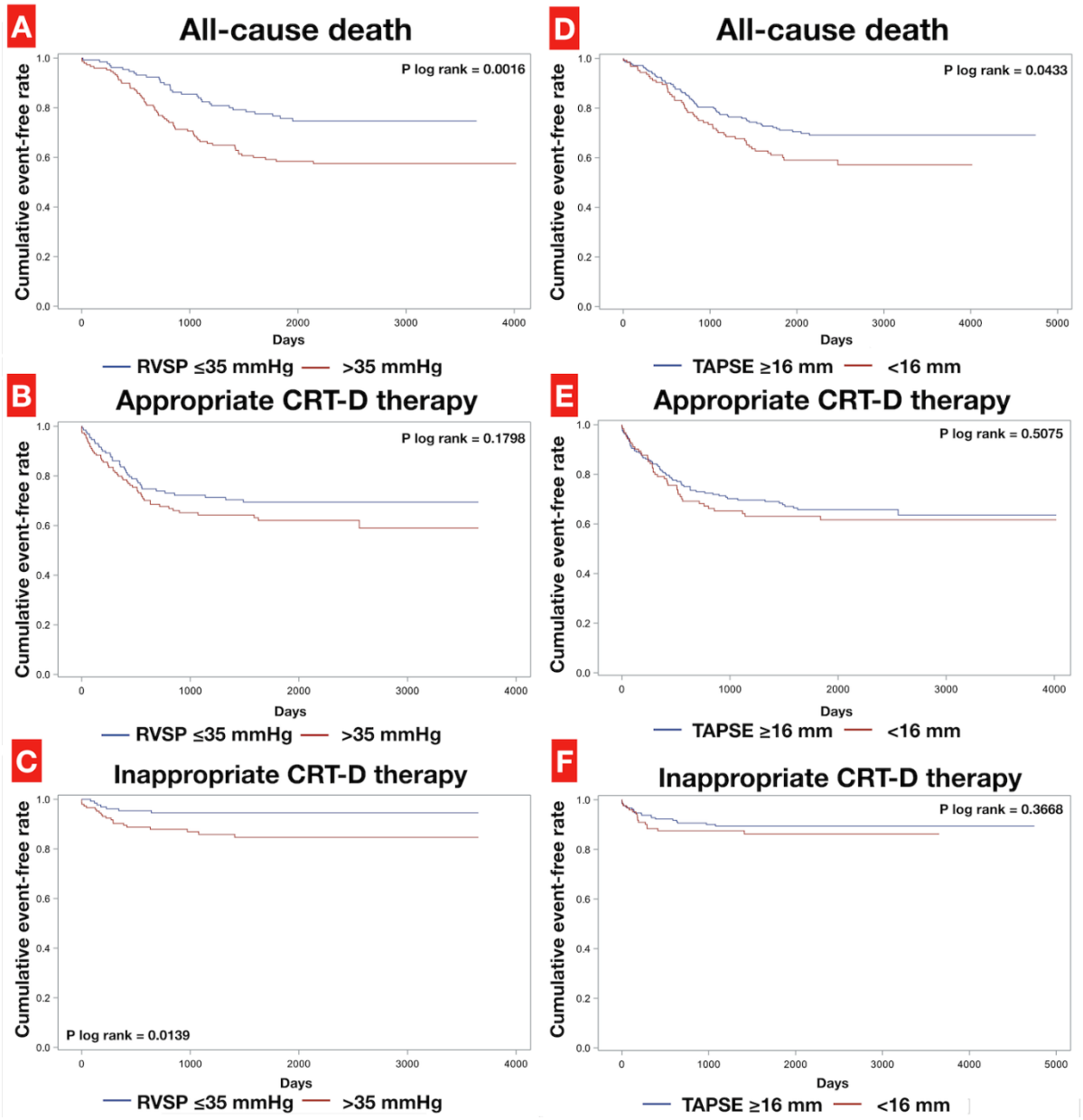
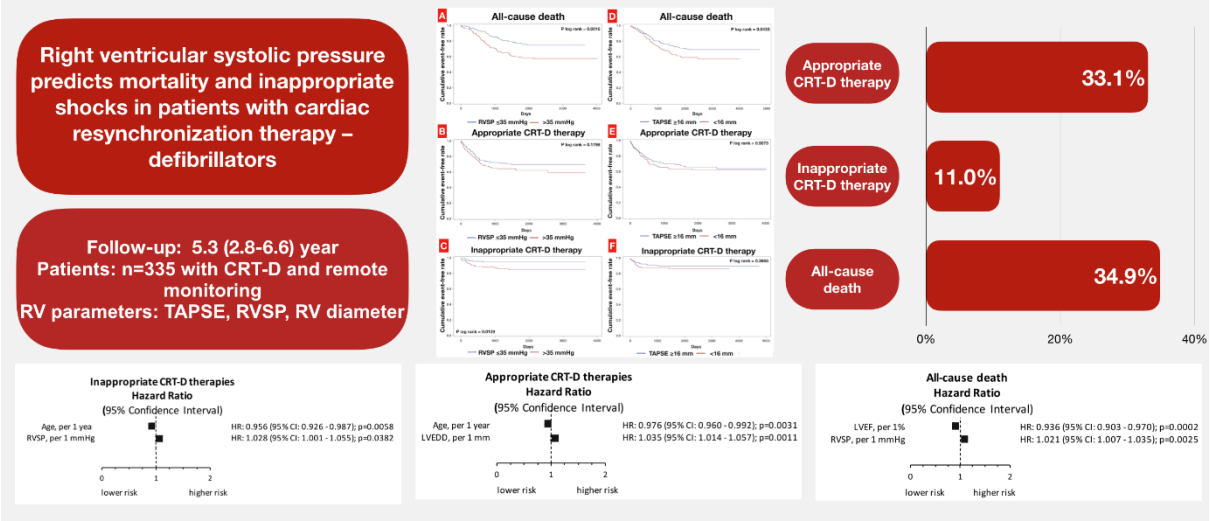


Figure 1. Kaplan–Meier estimates of the long-term risk of respectively, all-cause mortality, appropriate and inappropriate CRT-D therapies depending on the values of RVSP (**A–C**), and TAPSE (**D–F**)

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillators; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion



Graphical abstract. Graphical summary of the study

Table 1. The baseline characteristics of the studied population with subdivision into populations based on RVSP and TAPSE reference values

Demographics at baseline	**Overall population (n = 335)**	**RVSP >35 mm Hg (n = 148)[a]**	**RVSP ≤35 mm Hg (n = 131)[a]**	***P value* for RVSP >35 mm Hg vs. RVSP ≤35 mm Hg**	**TAPSE <16 mm (n = 124)**	**TAPSE ≥ 16 (n = 211)**	***P value* for TAPSE <16 mm vs. TAPSE >16 mm**
Female, n (%)	60 (17.9)	30/148 (20.3)	23/131 (17.6)	0.56	23 /124 (18.5)	37/211 (17.5)	0.66
Age at implantation, years, median (IQR)	63 (57–71)	65 (61–73)	65 (58–71)	0.33	64 (57–73)	65 (57–71)	0.88
Indication for implantation							

	Ischemic cardiomyopathy, n (%)	201 (60.0)	91/148 (61.5)	77/131 (58.8)	0.65	80/124 (64.5)	121/211 (57.3)	0.20
	Non-ischemic cardiomyopathy, n (%)	134 (40.0)	57/148 (38.5)	54/131 (41.2)		44/124 (35.5)	90/211 (42.7)	
Secondary prevention of sudden cardiac death, n (%)		74 (22.1)	40/148 (27.0)	25/131 (19.1)	0.12	32/124 (25.8)	42/211 (19.9)	0.21
Arterial hypertension, n (%)		174 (51.9)	78/148 (52.7)	64/131 (48.9)	0.52	64/124 (51.6)	110/211 (52.1)	0.93
Atrial fibrillation, n (%)		119 (35.5)	66/148 (44.6)	37/131 (28.2)	0.005	55/124 (44.4)	64/211 (30.3)	**0.01**
Diabetes, n (%)		127 (37.9)	62/148 (41.9)	44/131 (33.6)	0.15	55/124 (44.4)	72/211 (34.1)	0.06
COPD, n (%)		21 (6.3)	11/148 (7.4)	7/131 (5.3)	0.48	10/124 (8.1)	11/211 (5.2)	0.30
NYHA classification[b]								
	I, n (%)	25/294 (8.5)	11/142 (7.7)	11/107 (10.3)	0.22	7/110 (6.4)	18/184 (9.8)	0.40
	II, n (%)	89/294 (30.3)	32/142 (22.5)	35/107 (32.7)		28/110 (25.5)	61/184 (33.1)	
	III, n (%)	152/294 (51.7)	83/142 (58.5)	52/107 (48.6)		65/110 (59.1)	87/184 (47.3)	
	IV, n (%)	28/294 (9.5)	16/142 (11.3)	9/107 (8.4)		10/110 (9.1)	18/184 (9.8)	
GFR ≤60 ml/min/1.73 m^2, n (%)		97 (29.0)	49/148 (33.1)	32/131 (24.4)	0.11	44/124 (35.4)	53/211 (25.2)	0.04

LVEF, %, median (IQR)	25 (20–29)	23 (18–27)	25 (21–30)	**<0.001**	23 (18–28)	25 (20–29)	**0.004**
LVEDD, mm, median (IQR)	67 (61–73)	66 (61–74)	65 (61–72)	0.51	66 (61–73)	66 (61–73)	0.90
RVSP, mmHg, median (IQR)	36 (30–47)	–	–	–	40 (34–51)	35 (28–45)	0.004
TAPSE, mm, median (IQR)	18 (15–20)	17 (14–20)	18 (16–21)	0.002	–	–	–
RVD, mm median (IQR)	37 (32–42)	39 (34–44)	36 (31–41)	0.001	39 (33–44)	36 (31–40)	<0.001
Mitral regurgitation (≥moderate), n (%)	163 (48.7)	98/148 (66.2)	42/131 (32.1)	<0.001	63/124 (50.8)	100/211 (47.4)	0.55
Tricuspid regurgitation (≥moderate), n (%)	93 (27.8%)	59/148 (39.9%)	25/131 (19.2%)	<0.001	48/124 (38.7%)	45/211 (21.4%)	<0.001
BMI, kg/m^2, median (IQR)	27.6 (24.7–31.1)	27.1 (24.2–29.7)	27.7 (24.8–33.2)	0.03	27.2 (24.7–30.4)	28.1 (24.6–32.2)	0.15
LBBB at baseline, n/N (%)	138 (41.2)	55/148 (37.2)	59/131 (45.0)	0.18	48/124 (38.7)	90/211 (42.7)	0.48
IVCD at baseline, n/N (%)	95 (28.3)	57/148 (38.5)	38/131 (29.0)	0.09	34/124 (27.4)	61/211 (28.9)	0.77

[a]Data available for 148 of patients with RVSP >35 mm Hg and 131 patients with RVSP ≤35 mm Hg.

[b]Data on NYHA class from the moment of implantation were available for 294 patients of the overall cohort

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter;

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RVD, right ventricular diameter; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion

Table 2. One-year outcomes of the studied population

Event	**Overall population (n = 335)**
Appropriate therapy, n (%)	57 (17.0)
Inappropriate therapy, n (%)	23 (6.8)
Appropriate ATP, n (%)	48 (14.3)
Appropriate shock, n (%)	48 (14.3)
Inappropriate ATP, n (%)	18 (5.4)
Inappropriate shock, n (%)	13 (3.9)
Non-fatal MI, n (%)	5 (1.5)
Stroke, n (%)	8 (2.4)
Death, n (%)	26 (7.8)

Abbreviations: ATP, antitachycardia pacing; MI, myocardial infarction

Table 3. Long-term outcomes of the studied population

Event	**Overall population (n = 335)**
The duration of follow up, years median (IQR)	5.3 (2.8–6.6)
Appropriate therapy, n (%)	111 (33.1)
Inappropriate therapy, n (%)	37 (11.0)
Appropriate ATP, n (%)	83 (24.8)
Appropriate shock, n (%)	77 (23.0)
Inappropriate ATP, n (%)	24 (7.2)
Inappropriate shock, n (%)	18 (5.4)
Death, n (%)	117 (34.9)
Non-fatal MI, n (%)	11 (3.3)
Stroke, n (%)	15 (4.5)
Time to first appropriate therapy, months, median (IQR)	9.6 (2.9–18.4)

Time to first inappropriate therapy, months, median (IQR)	5.9 (1.8–11.3)
Low biventricular pacing % alert, n (%)	131 (39.1)

The numbers and percentages of patients experiencing shocks and ATP are higher than total number of patients experiencing therapies, since in some patient either of the therapies occurred

Abbreviations: IQR, interquartile range; other — see Table 2

Table 4. Long-term events according to RVSP[a]

Event	**Overall population (n = 279)[a]**	**RVSP >35 mm Hg (n = 148)**	**RVSP ≤35 mm Hg (n = 131)**	***P*-value**
Appropriate therapy, n (%)	90 (32.3)	52 (35.1)	38 (29.0)	0.28
Inappropriate therapy, n (%)	27 (9.7)	20 (13.5)	7 (5.3)	**0.03**
Appropriate ATP, n (%)	67 (24.0)	38 (25.7)	29 (22.1)	0.49
Appropriate shock, n (%)	64 (22.9)	38 (25.7)	26 (19.8)	0.25
Inappropriate ATP, n (%)	16 (5.7)	12 (8.1)	4 (3.1)	0.08
Inappropriate shock, n (%)	15 (5.3)	11 (7.4)	4 (3.1)	0.09
Death, n (%)	96 (34.4)	63 (42.6)	27 (20.6)	**<0.001**
Low biventricular pacing % alert, n (%)	106 (37.8)	69 (46.6)	37 (28.2)	**0.002**

[a]RVSP value was available for the total of 279 patients, including 148 with RVSP >35 mm Hg and 131 patients with RVSP ≤35 mm Hg

Abbreviations: see Tables 1 and 2

Table 5. Long-term events according to TAPSE

Event	**Overall population (n = 335)**	**TAPSE <16 mm (n = 124)**	**TAPSE ≥16 mm (n = 211)**	***P*-value**
Appropriate therapy, n (%)	111 (33.1)	43 (34.7)	68 (32.2)	0.57
Inappropriate therapy, n (%)	37 (11.0%)	16 (12.9)	21 (10.0)	0.41
Appropriate ATP, n (%)	83 (24.8)	39 (31.4)	44 (20.8)	**0.03**

Appropriate shock, n (%)	77 (23.0)	29 (23.4)	48 (22.8)	0.90
Inappropriate ATP, n (%)	24 (7.2)	13 (10.5)	11 (5.2)	0.07
Inappropriate shock, n (%)	18 (5.4)	8 (6.4)	10 (4.7)	0.67
Death, n (%)	117 (34.9)	52 (41.2)	65 (30.8)	**0.04**
Low biventricular pacing % alert, n (%)	131 (39.1)	57 (46.0)	74 (35.0)	**0.048**

Abbreviations: see Tables 1 and 2

Table 6. Multivariable analysis results for predictors of all-cause mortality, inappropriate and appropriate cardiac resynchronization therapy-defibrillator therapies in the long-term follow-up

Independent predictors of inappropriate therapies	**Hazard ratio**	**95% confidence interval lower and upper index**	***P*-value**
Age, years	0.956	0.926–0.987	**0.006**
RVSP, mm Hg	1.028	1.001–1.055	**0.04**
Independent predictors of appropriate therapies	**Hazard ratio**	**95% confidence interval lower and upper index**	***P*-value**
Age, years	0.976	0.960–0.992	**0.003**
LVEDD, mm	1.035	1.014–1.057	**0.001**
Independent predictors of all-cause mortality	**Hazard ratio**	**95% confidence interval lower and upper index**	***P*-value**
LVEF, %	0.936	0.903–0.970	<0.001
RVSP, mm Hg	1.021	1.007–1.035	0.003

Abbreviations: see Table 1