Reduced left ventricular mechanical dispersion at 6 months follow-up after cardiac resynchronisation therapy is associated with superior long-term outcome

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Short title: LVMD post-CRT and outcome

Total word count: 2509

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ABSTRACT

Background: In heart failure (HF) patients, left ventricular mechanical dispersion (LVMD) reflects heterogeneous mechanical activation of the left ventricle. In HF patients, LVMD can be reduced after CRT. Whether lesser LVMD is associated with improved outcome is unknown.

Objective: To relate LVMD to long-term prognosis in a large cohort of HF patients after 6 months of cardiac resynchronization therapy (CRT).

Methods: Clinical, echocardiographic and ventricular arrhythmia (VA) data were analyzed from an ongoing registry of HF recipients of CRT. Baseline (prior to CRT) and 6-month echocardiograms were evaluated. LVMD was calculated as the standard deviation of the time from onset of the QRS complex to the peak longitudinal strain in a 17-segment model. Patients were divided into two groups, according to the median LVMD (84 ms) at 6 months post-CRT.

Results: Of 1,185 patients (mean age 65±10 years, 76% male), 343 (29%) died during a mean follow-up of 55±36 months. Baseline LVMD was not associated with all-cause mortality and VA at follow-up. In contrast, patients with less LVMD (≤84 ms) at 6 months post-CRT had lower event rates (VA and mortality) compared to those with LVMD >84 ms. On multivariable analysis, greater LVMD at 6 months after CRT was independently associated with an increased risk of mortality (hazard ratio, 1.002; P=0.037) and VA (hazard ratio, 1.003; P=0.026) .

Conclusion: Larger LVMD at 6 months after CRT is independently associated with all-cause mortality and VA. LVMD may be valuable in identifying patients who remain at high mortality risk after CRT implantation.

KEY WORDS: Mechanical dispersion; cardiac resynchronization therapy; prognosis

INTRODUCTION

Cardiac resynchronization therapy (CRT) is indicated in heart failure (HF) patients who remain symptomatic despite optimal medical therapy (New York Heart Association (NYHA) functional class II-III and ambulatory IV), with wide QRS complex (≥120 ms) and reduced left ventricular ejection fraction (LVEF ≤35%).[1] CRT has been shown to improve symptoms, induce LV reverse remodeling, improve LVEF and reduce mitral regurgitation by resynchronizing the LV.[1, 2] These favourable effects have been associated with a decreased risk of ventricular arrhythmias, and reduced mortality.[3, 4]

LV mechanical dispersion (LVMD) is a novel, echocardiographic parameter based on speckle tracking echocardiography that measures the time dispersion to reach the peak systolic deformation in the different LV segments.[5, 6] LVMD reflects mechanical heterogeneity, which has been related to ventricular arrhythmias in a number of cardiac diseases.[5, 7-11] A reduction in LVMD after CRT is related to a decrease in ventricular arrhythmias.[9] Whether reduced LVMD after CRT translates into superior outcome is unclear. Accordingly, the present study evaluated the relation between LVMD at 6 months after CRT implantation, and the prognosis of HF patients.

METHODS

Patient population and data collection

HF patients who received CRT according to current guidelines and who completed clinical and echocardiographic follow-up at 6 months after CRT implantation were retrospectively evaluated.[1] Various clinical, laboratory and imaging data were collected at baseline and 6 months follow-up. Ischemic HF was defined by the presence of coronary artery disease, i.e.

evidence in previous medical records or from non-invasive or invasive investigations. The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without prior approval of an institutional review board, provided that the data are acquired for routine patient care. All data used for the present study were acquired for clinical purposes and handled anonymously.

Among the clinical variables, the quality of life, according to the Minnesota Living with Heart Failure Questionnaire, the 6-minute walking distance and the NYHA functional class were considered to define the severity of HF.[12,13] Renal function was defined by the estimated glomerular filtration rate (eGFR), calculated according to the Modification of Diet in Renal Disease Study (MDRD) equation.[14] The efficacy of CRT was analyzed as the percentage of patients receiving <98% and <90% of biventricular pacing, respectively.[15] A significant burden of premature, ventricular contractions (PVC's) was defined as >10000 per 24 hours.[16, 17]

Transthoracic echocardiography was performed in the left lateral decubitus position prior to and at 6 months after CRT implantation in all patients, utilizing a commercially available echocardiographic system (E9 or VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA) equipped with 3.5 MHz or M5S transducers. As previously described,[18] M-mode, two-dimensional and Doppler data were acquired and digitally stored for off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA).

Speckle tracking echocardiography was used to measure LVMD at baseline and at 6 months after CRT implantation. LVMD was calculated as the standard deviation of the time from the onset of the QRS complex on the triggered ECG, to the peak longitudinal myocardial strain in a 17-segment LV model (Figure 1). The inter-observer and intra-observer variability of LVMD measurement were assessed calculating the intra-class correlation coefficient (ICC)

for both measures on 25 randomly selected patients. The ICC for inter-observer and intra-observer variability of LVMD were 0.84 (95% CI: 0.64-0.93, P<0.001) and 0.93 (95% CI: 0.85-0.97, P<0.001), respectively.

Implantation of CRT

The subclavian or cephalic veins were utilized to place the right atrial and ventricular leads in a standard fashion. Coronary sinus venography was performed (with a balloon catheter) to guide LV lead implantation. The LV pacing lead was introduced into the coronary sinus through an 8 Fr guiding catheter, and preferably positioned in a (postero-) lateral vein. Thereafter all the leads were connected to a dual-chamber, biventricular CRT-device. A CRT device with defibrillator function was implanted in most of the recipients. Patients were scheduled for regular follow-up at the HF outpatient clinic and to evaluate device function. The atrioventricular and inter-ventricular delays were empirically set at 120-140 ms and 0 ms respectively, while optimization of the CRT device was left at the discretion of the treating physician.

Follow-up

The clinical response to CRT was defined as improvement ≥1 NYHA functional class at 6 months of follow-up.[19] LV reverse remodeling was defined as ≥15% reduction in the LV end-systolic volume (LVESV) at 6 months of follow-up. Patients were followed-up for the occurrence of all-cause mortality, as well as the occurrence of ventricular arrhythmias (appropriate antitachycardia pacing and/or appropriate defibrillation by CRT-defibrillator). The follow-up started at 6 months when the clinical, electrocardiographic and echocardiographic responses were assessed.

Statistical analysis

Continuous variables are expressed as means and standard deviations, and categorical data as numbers and percentages. Survival analysis was performed according to the Kaplan-Meier method for all-cause mortality as well as ventricular arrhythmias. Comparisons between groups were performed according to the log-rank test. A Cox proportional hazards model was used to investigate the association between LVMD at 6 months follow-up and all-cause mortality, as well as ventricular arrhythmias. To show hazard change across the range of LVMD, as a continuous variable, a spline curve was fit for LVMD versus mortality as well as versus ventricular arrhythmias, with overlayed confidence intervals. Subsequently, multivariate spline models were constructed, after adjusting for the following covariates: gender, body mass index, diabetes mellitus, etiology of heart failure, diuretics, hemoglobin, renal dysfunction, left ventricular reverse remodeling and clinical CRT response. All analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA) and R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided. A P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 1,185 patients (mean age 65±10 years, 76% male) with analysable echocardiographic data to calculate LVMD at baseline and 6 months after CRT were included. Strain analysis was not feasible in 90 (8%) patients. Baseline characteristics of the patient population are presented in Table 1. The etiology of HF was ischemic in 60% of patients and the mean LVEF at 6 months after CRT was 33.4±9.8%. The median baseline

LVMD was 96.3 ms (interquartile range (IQR) 74.5 – 126.4 ms), which decreased to 84.1 ms (IQR 65.4 – 112.4 ms) after 6 months of CRT. The percentage of patients with biventricular pacing <98% was 37%, and the percentage of patients with biventricular pacing <90% was 9%. The percentage of patients with >10000 premature ventricular complexes per 24 hours in our cohort, was 2.2%.

Association between LVMD at baseline and 6 months follow-up and survival

In total, 343 (29%) patients died during a mean follow-up of 55±36 months after the 6-month echocardiography. The patient population was dichotomized according to the median value of LVMD at baseline (96 ms). There were no differences in all-cause mortality rates between those patients with a greater (>96 ms) and a lesser (≤ 96 ms) LVMD at baseline (Log-rank test P=0.253). The patient population was subsequently dichotomized according to the median value of LVMD at 6 months (84 ms). Patients with lesser LVMD at 6 months (≤84 ms) had significantly lower all-cause mortality compared with patients with more LVMD (>84 ms) (Log-rank test P<0.001; Figure 2). In patients with LVMD ≤84 ms at 6 months, the cumulative all-cause mortality rates were 13, 42 and 55% at 30, 90 and 120 months follow-up, respectively. In contrast, in the group of patients with LVMD >84 ms, the cumulative event rates were 18, 54 and 65% for the same follow-up time points.

To investigate the association between LVMD at 6 months and all-cause mortality, a Cox proportional hazards model was constructed with variables known to influence mortality of HF patients (Table 2). On multivariable analysis, LVMD at 6 months was independently associated with increased mortality (hazard ratio, 1.002; 95% confidence interval, 1.000-1.005; P=0.037). To show hazard change across the range of LVMD, as a continuous variable, a spline curve was fit for LVMD versus mortality. For all-cause mortality, predicted

from the 6-month LVMD, the assumption of linearity was not violated (χ^2, 4.4, P=0.12). There was an increase of hazards for LVMD between 50 ms and 130 ms, after which a plateau appeared. At higher 6-month LVMD values, there is a decrease of the hazards, although there are too few observations in this range to support a meaningful, clinical interpretation (also reflected in the wider confidence intervals at higher LVMD) (Figure 3A). When adjusted for multiple covariates, the assumption of linearity was also not violated (χ^2, 3.0, P=0.23), and the curve demonstrated a similar shape to the unadjusted model, with hazards increasing for LVMD between 50 and 130 ms, whereafter plateau was noted (Figure 3B).

Association between LVMD at baseline and 6 months follow-up and ventricular arrhythmias

After a mean follow-up of 55±36 months, 403 (34%) of patients experienced a ventricular arrhythmia for which appropriate device therapy was delivered. No difference in freedom from ventricular arrhythmias was seen between those patients with a greater (>96 ms) and a lesser (≤ 96 ms) LVMD at baseline (Log-rank test P=0.781). Patients with lesser LVMD at 6 months (≤84 ms) experienced greater freedom from ventricular arrhythmias, compared to those with more LVMD (>84 ms) (Log-rank test P<0.001; Figure 4). In patients with LVMD ≤84 ms at 6 months, the cumulative rates for ventricular arrhythmia were 15, 55 and 77% at 30, 90 and 120 months follow-up, respectively. In contrast, in those individuals with LVMD >84 ms, the cumulative event rates were 21, 66 and 84% for the identical time points.

To investigate the association between LVMD at 6 months and all-cause mortality, a Cox proportional hazards model was constructed with variables known to influence the mortality of HF patients (Table 3). On multivariable analysis, LVMD at 6 months was independently

associated with ventricular arrhythmias (hazard ratio, 1.003; 95% confidence interval, 1.000-1.005; P=0.026). To show hazard change for ventricular arrhythmias across the range of LVMD as a continuous variable, a spline curve was fit for LVMD versus ventricular arrhythmias. For ventricular arrhythmias, predicted from the 6-month LVMD, the assumption of linearity was not violated (χ^2, 6.0, P=0.06). There was an increase of hazards for LVMD between 50 ms and 130 ms, after which a plateau appeared. At higher 6-month LVMD values, there is a decrease of the hazards, although there are too few observations in this range to support a meaningful, clinical interpretation (also reflected in the wider confidence intervals at higher LVMD) (Figure 5A). When adjusted for multiple covariates, the assumption of linearity was also not violated (χ^2, 1.2, P=0.55), and the curve demonstrated a similar shape to the unadjusted model, with hazards increasing for LVMD between 50 and 130 ms, whereafter plateau was noted (Figure 5B).

DISCUSSION

Patients with HF with greater LVMD at 6 months after receiving a CRT device, experienced a worse long-term outcome and more frequent ventricular arrhythmias, compared to patients with lesser LVMD. Additionally, the association between LVMD and mortality, as well as ventricular arrhythmias was independent of the occurrence of LV reverse remodeling at 6 months.

Role of LVMD in diagnosis and risk-stratification

LVMD has been proposed as a marker of electromechanical heterogeneity of the left ventricle and is calculated as the standard deviation of the time from the onset of the QRS

complex to the peak longitudinal myocardial strain (obtained with two-dimensional speckle tracking echocardiography) in a 16- or17-segment LV model.[5, 6] LVMD has been utilized in the diagnosis and risk-stratification of various cardiac disorders.[5, 6, 8-11, 20-22] In post-infarct patients, LVMD has shown incremental value over LVEF to predict ventricular arrhythmias.[22]

Similarly, LVMD discriminated between post-infarct patients with and without ventricular arrhythmias in a prospective study.[5] In addition, LVMD has been associated with ventricular arrhythmias in HF patients with ischemic and non-ischemic etiologies.[8] A greater LVMD, 6 months after CRT, has been demonstrated in recipients with ventricular arrhythmias at follow-up, compared to those without arrhythmias.[9] Our data support this observation, with more frequent ventricular arrhythmias documented in individuals with greater LVMD after CRT. However, the association between residual LVMD after CRT and all-cause mortality has not been evaluated.

LVMD and outcome after CRT

The main finding of this study is that LVMD after 6 months of CRT is independently associated with long-term outcome. Long-term outcome after CRT is influenced by a number of baseline characteristics, i.e. male gender, body mass index, diabetes mellitus, hemoglobin and impaired renal function.[23-26] It is also well-established that LV reverse remodeling, as well as the extent thereof, impacts on long-term prognosis.[27, 28] In the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, a ≥15% decrease in the indexed LVESV was an independent predictor of outcome.[29] In contrast, although the clinical response to CRT was associated with better outcome, it was not independently associated with all-cause mortality in a study of 679 patients.[30]

Both LVMD and LV reverse remodeling after CRT are therefore more firmly linked to improved survival than a clinical response. A lesser LVMD likely reflects restoration of a more homogenous pattern of LV electromechanical activation by CRT, which accompanies LV reverse remodeling. Apical rocking, another surrogate of heterogenous LV activation, has demonstrated incremental value over LV reverse remodeling to predict mortality after CRT (hazard ratio 0.405; 95% confidence interval 0.283-0.579; P<0.0001).[31] In addition, correction of apical rocking by CRT translated into lower all-cause mortality. Our results provide further support to the association of reestablishment of a more coordinated pattern of LV contraction and improved outcome after CRT.

In a recent meta-analysis, including 3,667 patients, the risk of ventricular arrhythmias was found to be significantly lower in CRT responders (i.e. in whom LV remodeling has taken place) than in non-responders (odds ratio 0.436; 95% confidence interval 0.323-0.589; P<0.05).[32] LV remodeling is therefore strongly related to both the risk of ventricular arrhythmias and outcome after CRT. In light of the connection between restoration of coordinated LV contraction (reflected by LVMD) and LV remodeling, the presence of more frequent ventricular arrhythmias in patients with a greater LVMD after 6 months of CRT, is consistent with ventricular arrhythmia burden as the cause of increased mortality in this group.

The present study shows that LVMD after 6 months of CRT was significantly associated with long-term outcome independently of clinical response and LV reverse remodeling. Greater LVMD may thus identify a subgroup of patients who remain at high risk of mortality despite CRT. Such patients are candidates for close follow-up, as well as interventions which may modify their outcome, e.g. optimization of device programming, adjustment of pharmacotherapy and eventually mechanical LV support or cardiac transplantation.

Study limitations

This was a retrospective, single-center study and included patients who completed the 6 months follow-up echocardiographic evaluation. Therefore, there may be a selection bias, since LVMD could not be measured in patients who deceased during the first 6 months after CRT implantation. The mode of death was not systematically available. The measurements of LVMD are not vendor independent and the cut-off value of LVMD provided in this study may not be generalizable to other patients in whom LVMD was measured with different software.

CONCLUSIONS

LVMD after 6 months of CRT is independently associated with all-cause mortality and ventricular arrhythmias, and may therefore be valuable in identifying patients who remain at high risk after CRT implantation.

Funding, Relationships with Industry and Other Entities: The Department of Cardiology received research grants from Biotronik, Medtronic, Boston Scientific and Edwards Lifesciences. Victoria Delgado received speaker fees from Abbott Vascular. The remaining authors have nothing to disclose.

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Table 1. Patient characteristics at baseline.

	N=1,185
Age (years)	65 ± 10
Gender male, n (%)	904 (76)
Ischemic aetiology, n (%)	712 (60)
Heart rhythm at baseline, n (%)	
- Sinus rhythm	867 (73)
- Paced rhythm	192 (16)
- Atrial fibrillation	126 (11)
NYHA functional class, n (%)	
- I	57 (5)
- II	318 (27)
- III	733 (62)
- IV	77 (6)
6 MWT (m)	331 ± 121
QoL score	32 ± 19
Diabetes n (%)	253 (21)
eGFR <60 ml/min/1.73 m^2, n (%)	466 (39)
LVEF (%)	27 ± 8
LVEDV (ml)	203 ± 76
LVESV (ml)	150 ± 65
LVMD (ms)	96.3 ms (74.5 – 126.4)

Values are mean ± standard deviation. eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVMD: left ventricular mechanical dispersion; 6 MWT: six-minute walk test; NYHA: New York Heart Association class; QoL: quality of life

Table 2. Uni- and multivariate Cox proportional hazards models for all-cause mortality.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
LVMD at 6 months (ms)	1.004	1.002-1.006	<0.001	1.002	1.000-1.005	0.037
Age at implant (years)	1.040	1.029-1.050	<0.001	1.030	1.019-1.041	<0.001
Male gender	1.482	1.164-1.887	0.001	1.495	1.157-1.933	0.002
Body mass index (kg/m^2)	0.969	0.947-0.992	0.008	0.960	0.936-0.985	0.002
Diabetes mellitus	1.649	1.329-2.046	<0.001	1.470	1.165-1.854	0.001
Ischemic etiology of heart failure	1.547	1.265-1.893	<0.001	1.184	0.950-1.475	0.133
Diuretics	1.751	1.325-2.313	<0.001	1.445	1.080-1.933	0.013
Hemoglobin (g/dL)	0.806	0.731-0.890	<0.001	0.935	0.842-1.039	0.212
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	2.546	2.105-3.080	<0.001	1.983	1.612-2.439	<0.001
LV reverse remodeling	0.537	0.380-0.759	<0.001	0.628	0.514-0.767	<0.001
Clinical response	0.839	0.694-1.013	0.068	0.921	0.756-1.121	0.412

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LVMD: left ventricular mechanical dispersion

Table 3. Uni- and multivariate Cox proportional hazards models for ventricular arrhythmias.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
LVMD at 6 months (ms)	1.003	1.001-1.006	0.006	1.003	1.000-1.005	0.026
Age at implant (years)	1.020	1.009-1.030	<0.001	1.018	1.008-1.030	0.001
Male gender	1.704	1.305-2.225	0.001	1.723	1.306-2.273	<0.001
Body mass index (kg/m^2)	0.999	0.976-1.023	0.957	-	-	-
Diabetes mellitus	1.243	0.967-1.596	0.089	1.176	0.910-1.520	0.216
Ischemic etiology of heart failure	1.339	1.089-1.648	0.006	1.046	0.839-1.305	0.688
Diuretics	1.126	0.873-1.451	0.361	-	-	-
Hemoglobin (g/dL)	0.975	0.874-1.087	0.646	-	-	-
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	1.334	1.086-1.639	0.006	1.259	1.011-1.567	0.040
LV reverse remodeling	0.672	0.551-0.821	<0.001	0.704	0.569-0.872	0.001
Clinical response	0.759	0.621-0.928	0.007	0.832	0.675-1.026	0.086

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LVMD: left ventricular mechanical dispersion

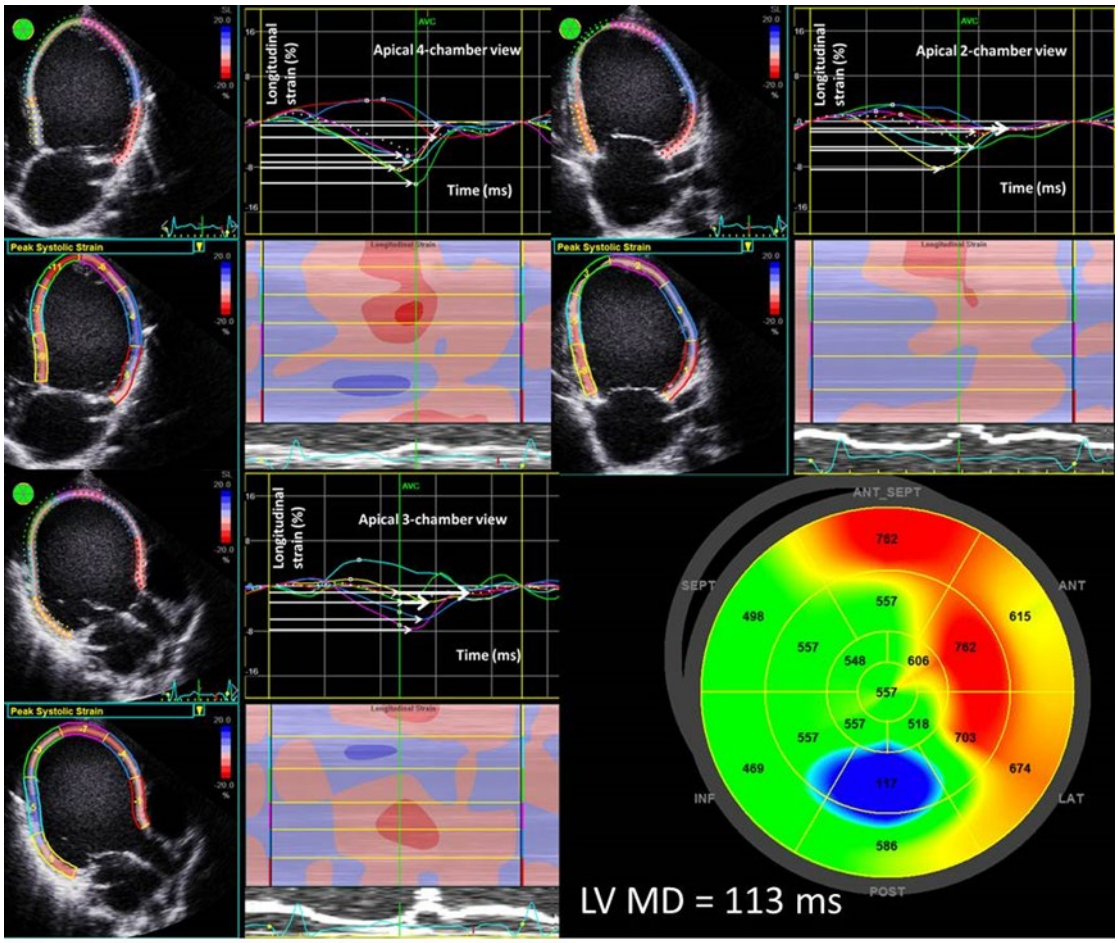
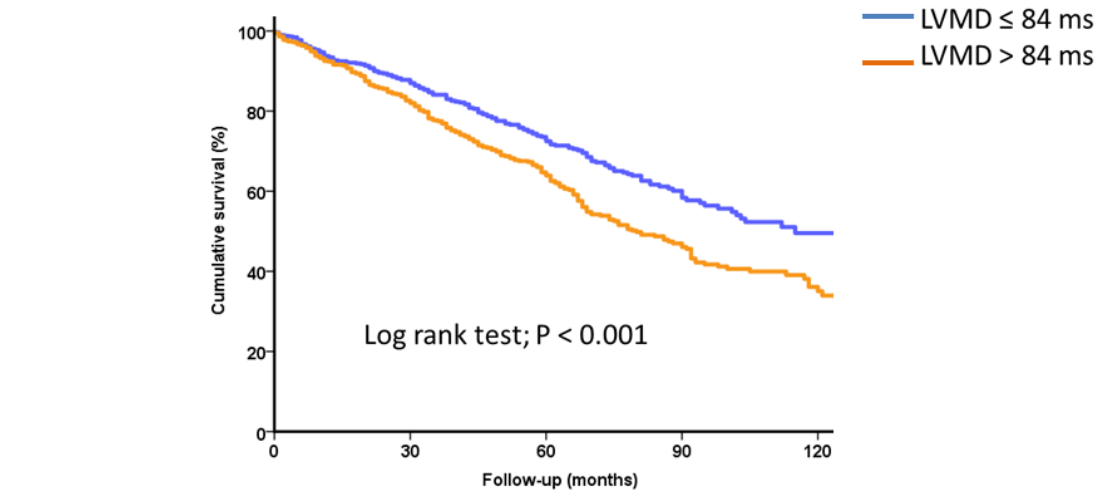


Figure 1: Assessment of left ventricular mechanical dispersion with two-dimensional speckle tracking echocardiography – left ventricular mechanical dispersion was calculated as the standard deviation of the time from the onset of the QRS complex on the ECG, to the peak longitudinal strain in 17 segments of the left ventricle. The segmental time to peak longitudinal strain data are presented in a color-coded, bull's eye plot with the earliest segments presented in green and the most delayed segments in red. LVMD: left ventricular mechanical dispersion



Number of patients at risk					
LVMD ≤ 84 ms	592	427	269	100	19
LVMD > 84 ms	593	413	242	100	32

Figure 2: Kaplan-Meier curves for all-cause mortality - Time to all-cause mortality in patients with left ventricular mechanical dispersion ≤84 ms and >84 ms after 6 months of cardiac resynchronization therapy. LVMD: left ventricular mechanical dispersion

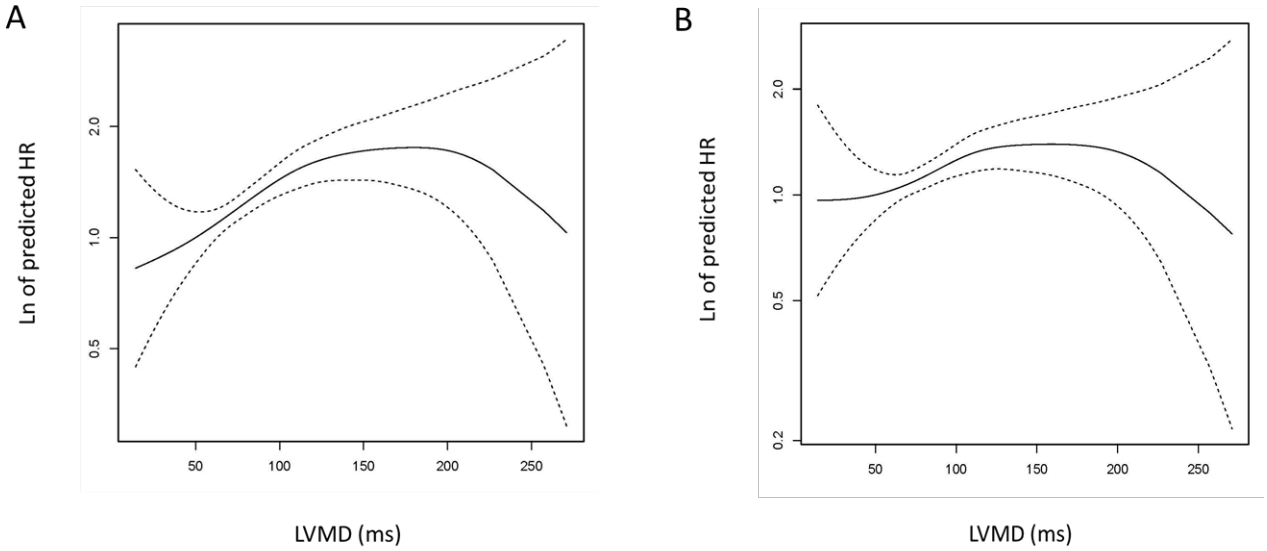


Figure 3: Spline curves for LVMD versus all-cause mortality. Predicted mortality across a range of left ventricular mechanical dispersion (LVMD), plotted as a fitted spline model on a log-hazard scale, with overlayed confidence intervals. The unadjusted model is shown in panel A, and the adjusted model in panel B. Ln: logarithm, HR: hazard ratio

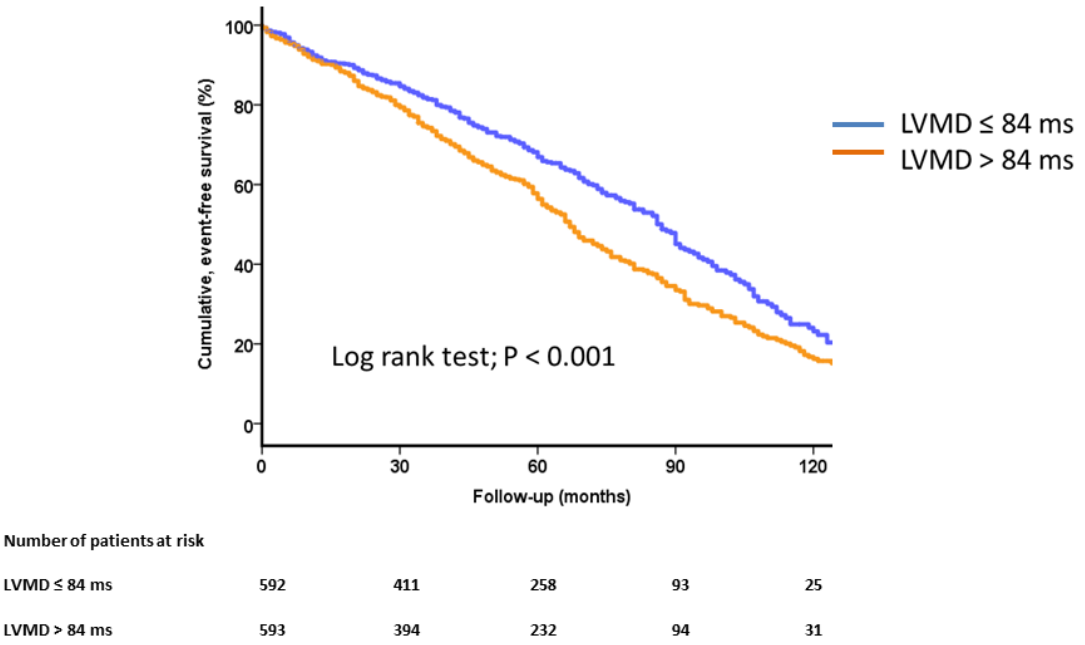
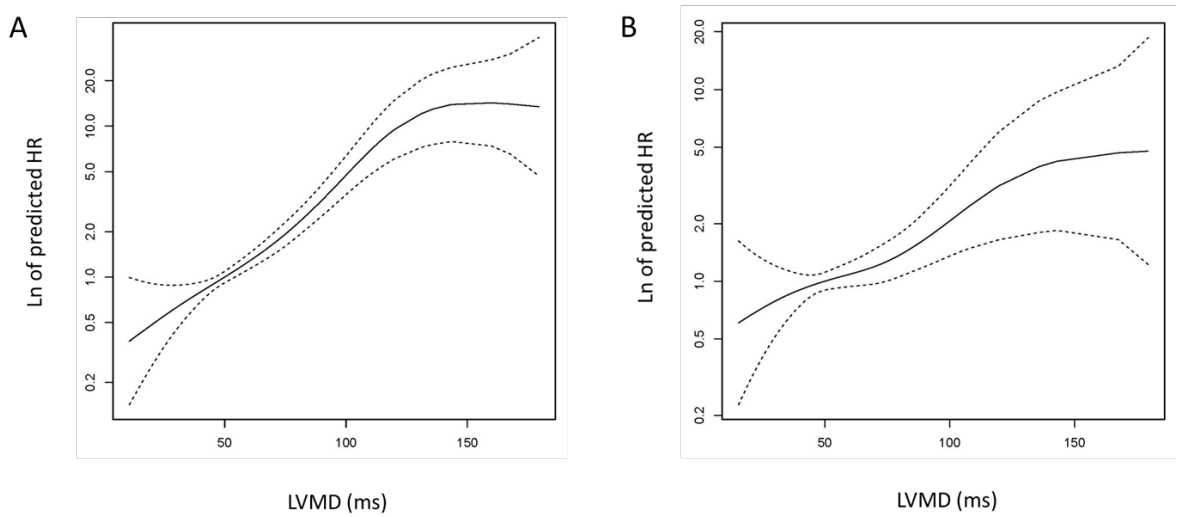


Figure 4: Kaplan-Meier curves for freedom from ventricular arrhythmias – Ventricular arrhythmia-free survival in patients with left ventricular mechanical dispersion ≤84 ms and >84 ms after 6 months of cardiac resynchronization therapy. LVMD: left ventricular mechanical dispersion



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52 **Figure 5: Spline curves for LVMD versus ventricular arrhythmias.** Predicted occurrence
53 of ventricular arrhythmias across a range of left ventricular mechanical dispersion (LVMD),
54 plotted as a fitted spline model on a log-hazard scale with overlayed confidence intervals.
55 The unadjusted model is shown in panel A, and the adjusted model in panel B. Ln: logarithm,
56 HR: hazard ratio

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