Impact of baseline left ventricular volume on left ventricular reverse remodeling after cardiac resynchronization therapy

Xavier Galloo, MD,*† Jan Stassen, MD,*‡ Kensuke Hirasawa, MD, PhD,* Surenjav Chimed, MD,* Bernard Cosyns, MD, PhD,† Nina Ajmone Marsan, MD, PhD,* Victoria Delgado, MD, PhD,* Pieter van der Bijl, MD, PhD,* Jeroen J. Bax, MD, PhD*§

*From the *Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands, †Department of Cardiology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium, ‡Department of Cardiology, Jessa Hospital, Hasselt, Belgium, and §Heart Centre, Turku University Hospital, University of Turku, Turku, Finland.*

BACKGROUND Left ventricular (LV) dilatation may limit LV reverse remodeling after cardiac resynchronization therapy (CRT).

OBJECTIVE The purpose of this study was to evaluate the impact of baseline LV volumes on LV reverse remodeling after CRT and whether this is associated with improved survival.

METHODS Patients were stratified into quintiles according to baseline LV end-diastolic volume indexed for body surface area (LVEDVi). *LV reverse remodeling* was defined as ≥15% reduction in LV end-systolic volume at 6-month follow-up after CRT. Independent associates of LV remodeling were assessed and long-term mortality rates were compared between patients with and without LV reverse remodeling (across LVEDVi quintiles).

RESULTS A total of 864 patients were included (mean age 66 ± 10 years; 657 patients (76%) were male), of whom 101 (12%) were in quintile 1 (<65 mL/m^2), 272 (32%) in quintile 2 (65–95 mL/m^2), 247 (29%) in quintile 3 (95–125 mL/m^2), 151 (18%) in quintile 4 (125–155 mL/m^2), and 93 (11%) in quintile 5 (>155 mL/m^2). Patients with larger baseline LVEDVi had worse survival after CRT (log-rank, $P = .019$). The cumulative 10-year survival was significantly better in patients with vs without LV reverse remodeling (48.7% vs 33.9%; $P < .001$). Significant LV reverse remodeling was observed in all LVEDVi quintiles. In addition, patients with LV reverse remodeling had superior survival than did patients without LV reverse remodeling, regardless of baseline LVEDVi quintile (log-rank, $P < .05$ for all).

CONCLUSION Many patients with larger baseline LV volumes still show significant LV reverse remodeling after CRT and had superior survival (regardless of baseline LV volumes) than did patients without LV reverse remodeling. Therefore, CRT should not be denied on the basis of severe LV dilatation.

KEYWORDS Heart failure; Cardiac resynchronization therapy; Left ventricular reverse remodeling; Left ventricular volume; Survival

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Introduction

Cardiac resynchronization therapy (CRT) is an effective therapy for patients with heart failure (HF) and reduced left ventricular (LV) ejection fraction (LVEF ≤ 35%) and QRS duration ≥ 130 ms, who remain symptomatic despite optimal medical therapy (New York Heart Association functional class II, III, and ambulatory IV).[1,2] In selected patients, CRT results in an improved quality of life, LV reverse remodeling, and reduction in HF hospitalization rates and all-cause mortality.[1,3,4] *LV reverse remodeling*, which has most often been defined as a reduction of ≥15% in LV end-systolic volume (LVESV) measured at 6 months after CRT implantation, has been associated with improved long-term outcomes.[3,5,6] Baseline clinical and echocardiographic characteristics such as male sex, ischemic etiology, non–left bundle branch block morphology, shorter QRS

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duration, and low glomerular filtration rate have been associated with less LV reverse remodeling.[5–8] In addition, LV end-diastolic diameter before CRT implantation has been inversely associated with an improvement in LVEF as well as with all-cause mortality.[7,8] However, patients with significant LV dilatation can still show substantial LV reverse remodeling after CRT.[7–9] The impact of baseline LV dilatation on LV reverse remodeling and subsequent long-term survival has not been thoroughly evaluated. Accordingly, the aim of this study was to investigate the impact of baseline LV end-diastolic volume on LV reverse remodeling and subsequent long-term survival.

Methods

Study population

Patients with HF who received CRT device (newly implanted or upgrade) between August 1999 and September 2014 according to the prevailing guidelines and with QRS duration $\geq$ 130 ms were included in an ongoing single-center registry of the Leiden University Medical Centre (Leiden, The Netherlands).[1] Only patients who underwent transthoracic echocardiography at baseline and 6-month follow-up after CRT implantation were included. Demographic and clinical data were retrospectively collected from the departmental cardiology information system (EPD-Vision, Leiden University Medical Centre, Leiden, The Netherlands). The institutional review board of the Leiden University Medical Centre approved the observational design and retrospective analysis of clinically acquired data and waived the need for patient written informed consent. The research reported in this article adhered to the Helsinki Declaration as revised in 2013.

Clinical and echocardiographic variables

Demographic, clinical, laboratory, and echocardiographic variables were evaluated at baseline (before CRT implantation). Demographic characteristics included age, sex, and body mass index. Clinical characteristics comprised cardiovascular risk factors, relevant medical history, and comorbidities, as well as HF medication. *Ischemic etiology of HF* was defined by the presence of significant coronary artery disease on invasive coronary angiography. The New York Heart Association functional class was assessed in all patients. Quality of life was evaluated with the Minnesota Living with Heart Failure Questionnaire, and if feasible, a 6-minute walk test was performed.

Electrocardiogram-triggered M-mode, 2-dimensional, and Doppler data were acquired at rest, according to the current guidelines, using commercially available equipment (Vivid 7, E9 and E95 systems, GE Vingmed, Horten, Norway), and images were digitally stored for off-line analysis (EchoPAC versions 113.0.3, 202, and 203, GE Vingmed).[10,11] From the apical 2- and 4-chamber views, LV end-diastolic volume and LVESV were measured and indexed for body surface area (LVEDVi, LVESVi). LVEF was quantified using the biplane Simpson method.[10] Left atrial volume was measured at end-systole in the apical 4-chamber view and indexed for body surface area.[10] Mitral valve function assessments were based on qualitative, semiquantitative, and quantitative parameters evaluated on color, continuous, and pulsed wave Doppler data and were graded according to the current recommendations.[11] Right-sided measurements were performed in a focused right ventricular apical view. Right ventricular end-systolic and end-diastolic areas were traced, and right ventricular fractional area change was calculated. Right ventricular systolic function was evaluated using the tricuspid annular plane systolic excursion measured on M-mode recordings of the lateral tricuspid annulus. Furthermore, an integrative assessment of tricuspid regurgitation grade was performed through a multiparametric approach including qualitative, semiquantitative, and quantitative parameters of the regurgitant jet, tricuspid valve morphology, and assessment of the right atrial and ventricular dimensions, as recommended by the current guidelines.[11] Systolic pulmonary artery pressure was estimated from the tricuspid regurgitation jet peak velocity by applying the Bernoulli equation and adding right atrial pressure. Right atrial pressure was estimated on the basis of the inferior vena cava diameter and its collapsibility during breathing.[11]

CRT implantation

CRT implantation was performed according to a standard approach, that is, insertion of the right atrial and ventricular leads via the subclavian or cephalic veins. The LV pacing lead was then introduced into the coronary sinus through an 8-F guiding catheter and positioned in a posterior or posterolateral vein, if possible. A posterior or lateral position was achieved in 633 patients (87%) with available information on lead placement. All leads were connected to a dual-chamber biventricular CRT device. Defibrillator functionality was included in most of the implanted devices (823 patients [95%]). CRT recipients were followed up at regular intervals at the HF outpatient clinic, at which time the device was interrogated. At implantation, atrioventricular and interventricular delays were empirically set at 120–140 and 0 ms, respectively. CRT optimization was performed during follow-up visits at the discretion of the treating physician.

LV reverse remodeling and survival

The *primary end point of the study* was defined as the occurrence of LV reverse remodeling at 6-month follow-up, defined by $\geq$15% reduction in (nonindexed) LVESV.[1] The secondary end point was all-cause mortality. The association between baseline LVEDVi (divided in quintiles) and all-cause mortality was analyzed from the time of baseline echocardiography until death or last follow-up in April 2021, whereas for the association between the occurrence of LV reverse remodeling and all-cause mortality, data were analyzed from the time of follow-up echocardiography until death or last follow-up in April 2021. Survival data were ascertained from the departmental cardiology information system and the Social Security Death Index.

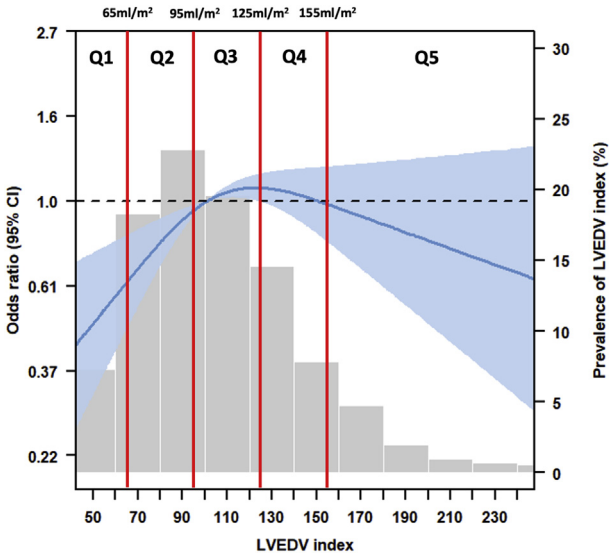


Figure 1 Spline curve plotting baseline LV volume against the odds ratio of LV reverse remodeling. The *blue curve* demonstrates the odds ratio of developing LV reverse remodeling at 6-month follow-up with overlaid 95% CI (*shaded blue area*; left y axis), according to baseline LVEDV index (x axis), in an unadjusted model. The *gray bars* illustrate the distribution of the population according to LVEDV index (right y axis). The *vertical red lines* demonstrate threshold volumes used to define the LVEDV index quintiles. CI = confidence interval; LV = left ventricular; LVEDV index = indexed left ventricular end-diastolic volume; Q = indexed left ventricular end-diastolic volume quintile.

Distribution of LV volumes

To characterize the relationship between LVEDVi and the odds ratio (OR) for LV reverse remodeling at 6-month follow-up, a spline curve was fitted in an unadjusted model (Figure 1). The study population was stratified according to LVEDVi quintiles. Quintile 1 represents approximately normal LVEDVi (<65 mL/m^2; normal range LVEDVi [mean ± 2SD] in men 34–74 mL/m^2 and women 29–61 mL/m^2).[10] The remaining quintiles were selected with equal intervals on the basis of the spline curve (quintile 2: 65–95 mL/m^2, quintile 3: 95–125 mL/m^2, quintile 4: 125–155 mL/m^2, and quintile 5: >155 mL/m^2).

Statistical analysis

Continuous variables with a Gaussian distribution are presented as mean ± SD and continuous variables without a Gaussian distribution are presented as median and interquartile range. Categorical variables are presented as frequency and percentage.

Differences among quintiles were analyzed using the 1-way analysis of variance for continuous variables with normal distribution, the Kruskal-Wallis test for nonnormally distributed continuous variables, and the Pearson χ^2 test and Fisher exact test for categorical variables. Multiple comparisons for continuous variables were tested with the Bonferroni correction. To investigate the association between clinical and echocardiographic parameters and the occurrence of LV reverse remodeling, uni- and multivariable logistic regression analyses were performed. Cumulative survival rates were calculated using the Kaplan-Meier method, and differences between groups were analyzed using the log-rank test. All statistical tests were 2-sided, and a P value of $<.05$ was considered statistically significant. All data were analyzed using SPSS for Windows, version 23.0 (IBM Corporation, Armonk, NY) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline patient characteristics

A total of 864 patients (mean age 66 ± 10 years; 657 patients (76%) were male) with available echocardiographic data at baseline and 6-month follow-up were included. The clinical and echocardiographic characteristics of the overall population are presented in Tables 1 and 2. Overall, 529 patients (61%) had left bundle branch block, and the mean QRS duration was 169 ± 26 ms. An ischemic etiology of HF was present in 475 patients (55%). The mean LVEDVi and LVESVi at baseline were 107 ± 39 and 80 ± 35 mL/m^2, respectively, with a mean LVEF of 27% ± 8%.

Analysis per quintile showed no significant differences in age or sex. Cardiovascular risk factors were comparable across the different groups, with only significantly less patients having diabetes mellitus in quintile 4 and 5 as compared with quintile 2. An ischemic etiology of HF was comparable between the LVEDVi quintiles, although it was significantly different on the χ^2 test for the overall population. Left bundle branch block was more prevalent and QRS duration more prolonged in patients with larger LV volumes. Inherent to the quintile-based classification used in this study, significant differences among the quintiles were observed regarding left-sided as well as right-sided volumes. Patients in larger LVEDVi quintile had significantly worse LVEF and more severe mitral regurgitation.

Prognostic value of baseline LV volumes

Before CRT implantation, 101 patients (12%) were in quintile 1, 272 (32%) in quintile 2, 247 (29%) in quintile 3, 151 (18%) in quintile 4, and 93 (11%) in quintile 5. After a median follow-up of 94 months (interquartile range 53–142 months), 543 patients (63%) died. Figure 2 shows the Kaplan-Meier curves for overall survival stratified according to LVEDVi quintiles. Survival rates at 10 years were significantly worse in patients with larger baseline LVEDVi: 46.0%, 49.2%, 45.6%, 41.9%, and 29.9% for quintiles 1–5, respectively (log-rank, $\chi^2 = 11.735$; $P = .019$).

Prognostic impact of LV reverse remodeling and LVEDVi

A total of 503 patients (58%) had LV reverse remodeling at 6-month follow-up. LV reverse remodeling was noted in 45 patients (45%) in quintile 1, 153 (56%) in quintile 2, 156 (63%) in quintile 3, 97 (64%) patients in quintile 4, and 52 (56%) in quintile 5 (Online Supplemental Table S1). To account for the long inclusion period and more advanced devices and leads being used in the more recently

Table 1 Baseline characteristics of the study population

Characteristic	Overall population (N = 864)	Quintile 1: <65 mL/m^2 (n = 101)	Quintile 2: |65–95 mL/m^2 (n = 272)	Quintile 3: |95–125 mL/m^2 (n = 247)	Quintile 4: |125–155 mL/m^2 (n = 151)	Quintile 5: >155 mL/m^2 (n = 93)	*P*
Demographic characteristics							
Age (y)	66 ± 10	66 ± 11	67 ± 10	66 ± 10	64 ± 10	64 ± 10	.096
Male sex	657 (76)	68 (67)	201 (74)	198 (80)	115 (76)	75 (81)	.082
Body mass index (kg/m^2)	26.4 ± 4.3	26.7 ± 4.2	27.0 ± 4.6	26.3 ± 3.9	26.1 ± 4.1	25.5 ± 4.1‡	.019
Medical history							
Hypertension	386 (45)	41 (41)	134 (50)	106 (43)	66 (44)	39 (43)	.452
Diabetes mellitus	171 (20)	24 (24)	72 (27)	44 (18)	21 (14)‡	10 (11)‡	.002
Dyslipidemia	353 (42)	41 (41)	116 (43)	100 (41)	68 (46)	28 (31)	.241
Smoking	342 (40)	37 (37)	107 (40)	97 (40)	66 (45)	35 (39)	.781
Ischemic etiology	475 (55)	50 (50)	150 (55)	154 (62)	78 (52)	43 (46)	.037
NYHA functional class III/IV	597 (70)	66 (68)	185 (70)	169 (69)	110 (74)	67 (73)	.794
QoL	31 (17–45)	36 (21–49)	30 (18–46)	27 (15–44)	33 (17–45)	33 (19–50)	.282
6MWD (m)	331 ± 123	330 ± 142	327 ± 124	341 ± 114	335 ± 118	312 ± 130	.446
Laboratory values							
Hemoglobin (mmol/L)	8.3 ± 1.0	8.3 ± 0.9	8.3 ± 1.0	8.4 ± 1.0	8.4 ± 0.9	8.4 ± 0.9	.712
eGFR–MDRD (mL/(min·1.73 m^2))	65 ± 24	65 ± 25	66 ± 24	65 ± 24	66 ± 24	62 ± 22	.604
ECG variables							
Rhythm							.003
Sinus rhythm	602 (70)	56 (55)	187 (69)	171 (69)	114 (76)†	74 (80)†	
Atrial fibrillation	142 (16)	26 (26)	53 (20)	40 (16)	18 (12)†	5 (5)†‡	
Pacemaker	120 (14)	19 (19)	32 (12)	36 (15)	19 (13)	14 (15)	
QRS morphology							.020
LBBB	529 (61)	46 (46)	161 (59)	155 (63)†	101 (67)†	66 (71)†	
RBBB	97 (11)	13 (13)	35 (13)	28 (11)	15 (10)	6 (7)	
IVCD	65 (8)	7 (7)	24 (9)	19 (8)	8 (5)	7 (8)	
VP	173 (20)	35 (35)	52 (19)†	45 (18)†	27 (18)†	14 (15)†	
QRS duration (ms)	169 ± 26	166 ± 28	165 ± 24	167 ± 24	171 ± 28	181 ± 27†‡§¶	<.001
Medication							
β-Blocker	631 (73)	73 (72)	206 (76)	181 (73)	112 (74)	59 (63)	.241
ACE-inh/ARB	767 (89)	87 (86)	240 (88)	218 (88)	138 (91)	84 (90)	.716
Loop diuretic	698 (81)	79 (78)	213 (78)	201 (81)	123 (82)	82 (88)	.301
MRA	381 (44)	39 (39)	113 (42)	104 (42)	74 (49)	51 (55)	.085

Values are presented as mean ± SD, median (interquartile range), or n (%).

Bonferroni correction:

6MWD = 6-minute walking distance; ACE-inh = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ECG = electrocardiographic; eGFR–MDRD = estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; QoL = quality of life; RBBB = right bundle branch block; VP = ventricular pacing.

†$P < .05$ vs quintile 1.

‡$P < .05$ vs quintile 2.

§$P < .05$ vs quintile 3.

¶$P < .05$ vs quintile 4.

Table 2 Baseline echocardiographic characteristics

Characteristic	Overall population (N = 864)	Quintile 1: <65 mL/m^2 (n = 101)	Quintile 2: 65–95 mL/m^2 (n = 272)	Quintile 3: 95–125 mL/m^2 (n = 247)	Quintile 4: 125–155 mL/m^2 (n = 151)	Quintile 5: >155 mL/m^2 (n = 93)	*P*
LV, LA, and left-sided valvular disease							
LVEDVi (mL/m^2)	107 ± 39	56 ± 7	81 ± 8[†]	109 ± 8[†‡]	138 ± 8[†‡§]	186 ± 32[†‡§¶]	<.001
LVESVi (mL/m^2)	80 ± 35	38 ± 7	57 ± 9[†]	80 ± 10[†‡]	106 ± 11[†‡§]	150 ± 32[†‡§¶]	<.001
LV ejection fraction (%)	27 ± 8	33 ± 9	30 ± 8[†]	26 ± 7[†‡]	23 ± 7[†‡§]	19 ± 6[†‡§¶]	<.001
LA volume – indexed (mL/m^2)	43 ± 19	39 ± 22	40 ± 17	43 ± 15	47 ± 22[†‡]	53 ± 21[†‡§]	<.001
Moderate or severe MR	332 (42)	20 (21)	87 (35)	110 (48)[†‡]	73 (53)[†‡]	42 (55)[†‡]	<.001
RV and right-sided valvular disease							
RVEDAi (cm^2/m^2)	11.4 ± 3.5	11.4 ± 3.3	10.9 ± 3.2	11.6 ± 3.7	11.4 ± 3.3	12.9 ± 4.0[†‡§¶]	<.001
RVESAi (cm^2/m^2)	7.4 ± 3.1	7.6 ± 3.2	6.9 ± 2.7	7.5 ± 3.3	7.2 ± 3.1	8.5 ± 3.7[‡¶]	.003
RV fractional area change (%)	37 ± 13	34 ± 14	38 ± 12	37 ± 13	38 ± 14	36 ± 13	.269
TAPSE (mm)	16 ± 5	15 ± 5	16 ± 5	16 ± 5	17 ± 5	16 ± 4	.380
SPAP (mm Hg)	35.2 ± 13.8	32.8 ± 10.9	33.7 ± 14.3	37.4 ± 14.4	34.6 ± 12.7	37.0 ± 14.4	.046
Moderate or severe TR	157 (23)	21 (23)	44 (21)	55 (27)	22 (18)	15 (22)	.355

Values are presented as mean ± SD, median (interquartile range), or n (%).

Bonferroni correction:

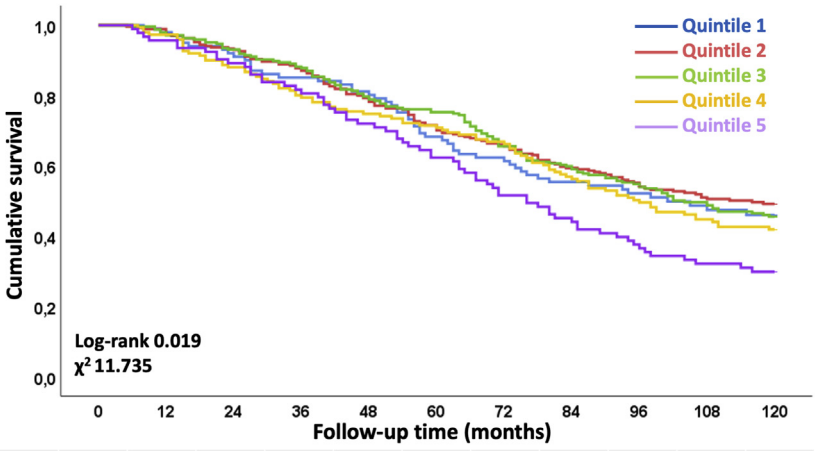
LA = left atrium/atrial; LV = left ventricle/ventricular; LVEDVi = indexed left ventricular end-diastolic volume; LVESVi = indexed left ventricular end-systolic volume; MR = mitral regurgitation; RV = right ventricle/ventricular; RVEDAi = indexed right ventricular end-diastolic area; RVESAi = indexed right ventricular end-systolic area; SPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

[†]$P < .05$ vs quintile 1.

[‡]$P < .05$ vs quintile 2.

[§]$P < .05$ vs quintile 3.

[¶]$P < .05$ vs quintile 4.

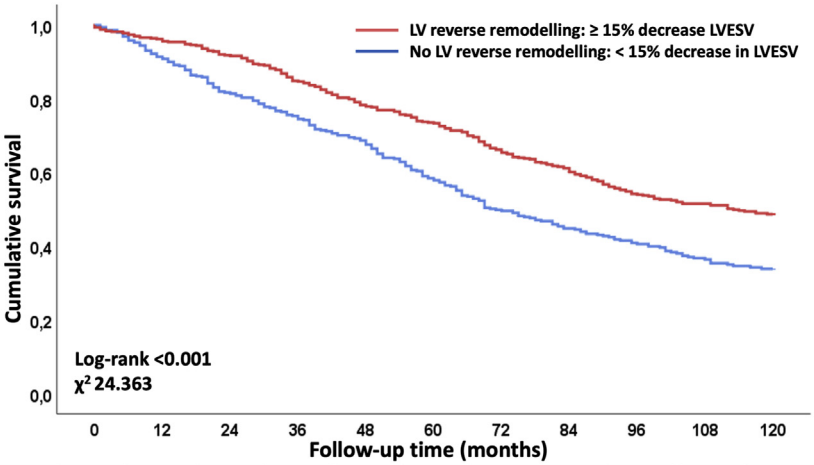


Patients at risk											
Quintile 1: LVEDVi <65 ml/m²	101	99	93	86	82	69	63	55	47	40	26
Quintile 2: LVEDVi 65-95 ml/m²	272	269	253	238	215	194	179	160	139	115	101
Quintile 3: LVEDVi 95-125 ml/m²	247	242	230	218	197	186	162	145	128	111	98
Quintile 4: LVEDVi 125-155 ml/m²	151	147	133	121	113	108	101	86	74	63	58
Quintile 5: LVEDVi >155 ml/m²	93	89	83	76	67	58	48	42	35	29	25

Figure 2 Kaplan-Meier estimates for all-cause mortality, stratified by LVEDVi quintiles. LVEDVi = indexed left ventricular end-diastolic volume.

implanted CRTs, the population was stratified into "early period" and "late period" according to the median implantation date. No significant differences in LV reverse remodeling were found between both groups (Online Supplemental Table S2A–S2F).

Kaplan-Meier curves for overall survival according to LV reverse remodeling after CRT implantation are shown in Figure 3. The cumulative survival rates were 96.2%, 73.6%, and 48.7% for patients showing LV reverse remodeling after CRT vs 91.4%, 58.4%, and 33.9% for patients without LV reverse remodeling after CRT at 1-, 5-, and 10-year follow-up, respectively. The survival rates at 10 years were significantly worse in patients without LV reverse remodeling after CRT implantation (log-rank, $\chi^2 = 24.363$; $P < .001$). Kaplan-Meier curves for overall survival according to the presence/absence of LV reverse remodeling after CRT implantation stratified according to baseline LVEDVi quintiles are shown in Figure 4. As quintile 1 represents approximately normal LVEDVi, and hence no presence of LV adverse remodeling regarding LV volume, LV reverse remodeling showed no significant difference. For the other quintiles, with the presence of LV adverse remodeling, patients with LV reverse remodeling had better cumulative survival (log-rank, $P < .05$ for all).



Patients at risk											
LV reverse remodelling	361	330	295	272	248	211	180	156	131	109	88
No LV reverse remodelling	503	484	462	427	394	370	333	297	251	225	189

Figure 3 Kaplan-Meier estimates for all-cause mortality, stratified by the presence of LV reverse remodeling. LV = left ventricular; LVESV = left ventricular end-systolic volume.

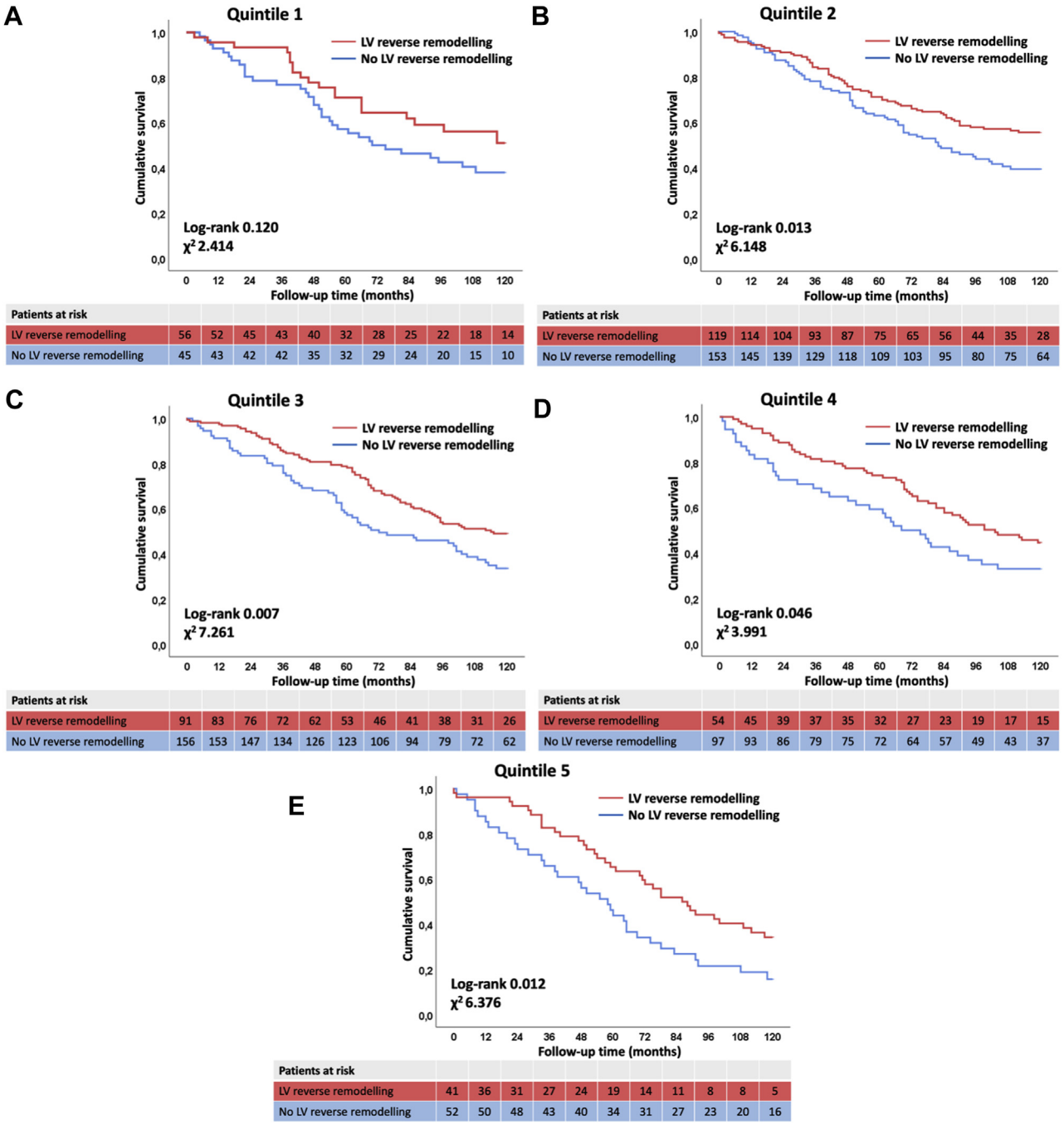


Figure 4 Kaplan-Meier estimates for all-cause mortality, stratified by the presence of LV reverse remodeling presented per quintile (quintile 1 [**A**], quintile 2 [**B**], quintile 3 [**C**], quintile 4 [**D**], and quintile 5 [**E**]). LV = left ventricular.

To evaluate the association between LVEDVi and LV reverse remodeling, uni- and multivariable logistic regression analyses were performed (Table 3). In univariable analysis, longer QRS duration, better kidney function, and LVEDVi quintiles were associated with LV reverse remodeling. Ischemic etiology and the use of diuretics were inversely associated with LV reverse remodeling. In multivariable logistic regression analysis, after adjustment for clinically relevant covariates, age, longer QRS duration, better kidney function, and LVEDVi quintiles were independently associated with LV reverse remodeling. Ischemic etiology and the use of diuretics remained inversely associated with LV reverse remodeling. Male sex was by a very small margin not significant, yet showed a clear trend toward significance.

Both spline curve analysis, plotting baseline LVEDVi against the OR for LV reverse remodeling (Figure 1), and multivariable logistic regression analysis (Table 3) show that the OR for the occurrence of LV reverse remodeling becomes higher with increasing baseline LVEDVi, especially when considering the values in quintile 1, which represent an approximately normal LVEDVi (OR 1.607; 95% confidence interval [CI] 0.982–2.631; P = .059 for quintile 2; OR

Table 3 Uni- and multivariable logistic regression models for LV reverse remodeling at 6-mo follow-up

	Univariable analysis		Multivariable analysis	
Characteristic	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age	1.006 (0.992–1.019)	.417	1.021 (1.005–1.037)	.009
Male sex	0.778 (0.564–1.073)	.126	0.696 (0.482–1.006)	.054
Diabetes mellitus	0.753 (0.538–1.054)	.099	1.005 (0.698–1.449)	.977
Ischemic etiology	0.672 (0.511–0.884)	.004	0.712 (0.520–0.973)	.033
NYHA functional class ≥III	0.825 (0.610–1.116)	.212	0.935 (0.673–1.297)	.686
Left bundle branch block	1.106 (0.838–1.459)	.477	1.092 (0.801–1.488)	.579
QRS duration	1.011 (1.005–1.016)	<.001	1.010 (1.004–1.016)	.001
Hemoglobin	1.088 (0.945–1.252)	.240	1.050 (0.898–1.227)	.542
eGFR–MDRD	1.008 (1.002–1.014)	.009	1.008 (1.001–1.016)	.024
Loop diuretics	0.536 (0.373–0.772)	.001	0.548 (0.366–0.820)	.003
LV ejection fraction	0.990 (0.974–1.006)	.226	0.994 (0.975–1.015)	.581
LVEDVi quintiles		.012		.019
Quintile 1: <65 mL/m^2 (reference)	–	–	–	–
Quintile 2: 65–95 mL/m^2	1.600 (1.010–2.534)	.045	1.607 (0.982–2.631)	.059
Quintile 3: 95–125 mL/m^2	2.133 (1.333–3.413)	.002	2.176 (1.293–3.662)	.003
Quintile 4: 125–155 mL/m^2	2.235 (1.336–3.739)	.002	2.256 (1.259–4.043)	.006
Quintile 5: >155 mL/m^2	1.578 (0.895–2.783)	.115	1.426 (0.732–2.779)	.296

CI = confidence interval; eGFR–MDRD = estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; LV = left ventricular; LVEDVi = indexed left ventricular end-diastolic volume; NYHA = New York Heart Association.

2.176; 95% CI 1.293–3.662; $P = .003$ for quintile 3; and OR 2.256; 95% CI 1.259–4.043; $P = .006$ for quintile 4). However, this only accounts up to a certain amount of LV dilatation as patients in quintile 5, comprising patients with the largest LVEDVi, present with lower OR for LV reverse remodeling, not significantly different from quintile 1 (OR 1.426; 95% CI 0.732–2.779; $P = .296$ for quintile 5). Hereby the spline curve analysis reveals a "*parabolic association*" between baseline LVEDVi and LV reverse remodeling.

Discussion

The main findings of the present study are 3-fold: (1) patients with larger LV volumes at baseline have worse overall survival after CRT implantation than do patients with smaller LV volumes, (2) patients with larger LV volumes are nonetheless able to show LV reverse remodeling after CRT implantation, and (3) the occurence of LV reverse remodeling (independent of baseline LV volumes) is associated with better survival compared to patients without the occurence of LV reverse remodeling.

Prognostic value of baseline LV volumes

Patients with HF are classified into 3 phenotypes of HF on the basis of LVEF (HF with reduced EF, HF with mid-range EF, and HF with preserved EF), without addressing a detailed description of LV volumes.[12,13] However, LV dilatation is considered as a precursor of progressive cardiac dysfunction and subsequent development of HF. Moreover, different studies have identified progressive LV dilatation as an independent predictor of poor long-term survival of patients with HF.[14,15] The inverse association between baseline LV end-diastolic diameter and all-cause mortality of patients with CRT has been demonstrated by Rickard et al[7] (hazard ratio 1.25; 95% CI 1.05–1.47; $P = .01$). In a study by Gold et al,[16] baseline LVESVi and an increase in LVESVi from baseline to 6-month follow-up were independent predictors of increased mortality (hazard ratio 1.14; 95% CI 1.04–1.24; $P = .004$ and 2.58; 95% CI 1.35–4.93; $P = .004$, respectively). The present study supports these results, showing significantly worse 10-year survival of patients with larger baseline LVEDVi.

Impact of baseline LV volume on LV reverse remodeling and long-term survival

The beneficial effect of CRT on LV reverse remodeling and improved survival has been well established.[4,17,18] In a subanalysis of the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction trial, 52% of patients were identified as responders, defined as having ≥15% reduction in LVESVi at 6 months post-CRT implantation.[16] The impact of LV size on LV remodeling after CRT implantation is largely unexplored. In 471 patients with HF, Rickard et al[7] showed that pre-CRT LV end-diastolic diameter was inversely associated with a change in LVEF. Moreover, the authors reported that a significant improvement in LVEF after CRT was observed in all patient categories with either nondilated, moderately dilated, or severely dilated LV.[7] Another analysis from the same group, evaluating patients with HF and LVEF ≤ 15% undergoing CRT, revealed that patients with smaller LV volumes were more likely to present LV reverse remodeling (defined as LVEF improvement >5%; OR 0.68; 95% CI 0.53–0.97; $P = .002$).[8] However, the patient group with the smallest LV end-diastolic diameter (<60 mm) had a lower proportion of responders (55.6%) than did patients with mildly dilated LV (LV end-diastolic diameter 61–65 mm; 65.4% responders). Regardless, responders to CRT were more frequently observed in the cohort with the smallest LV end-diastolic diameter than in

patients with moderate, severe, and very severe dilated LV (LV end-diastolic diameter 66–70, 71–77, and 78–110 mm, respectively), with 47.5%, 48.2%, and 30.4% of responders, respectively.[8] Despite having used a functional definition (LVEF) rather than an anatomical definition (LVESV) for LV reverse remodeling after CRT, the results by Rickard et al correspond to the present findings: both studies showing a "*parabolic association*" between baseline LVEDVi and LV reverse remodeling.

Patients with a very severely dilated LV represent a more advanced stage of cardiac dysfunction and HF. More extensive LV fibrosis has been associated with progressive worsening of LV function, LV remodeling, and more symptomatic HF.[19] Moreover, the extent of LV fibrosis has independently been associated with the lack of response to medical therapy in patients with HF.[19] Additionally, the extent and location of scar tissue are important predictors of CRT response—up to 81% of patients with transmural scar tissue in the posterolateral wall (the preferred site for the LV pacing lead) were classified as *nonresponders*.[20]

LV reverse remodeling after CRT has been associated with improved outcomes at long-term follow-up.[5,18] However, the impact of baseline LV volumes on reverse remodeling after CRT and subsequent long-term survival has not been investigated. Data from the present study support that LV reverse remodeling after CRT are associated with improved survival. The present study expands on this concept by showing that patients with LV reverse remodeling had superior survival than did patients without LV reverse remodeling, regardless of their baseline LV volume (log-rank, $P <$ .05 for all LVEDVi quintiles).

Clinical implications

Even though patients with enlarged LV volumes at baseline experience worse overall survival, they are capable of demonstrating significant LV reverse remodeling. Moreover, patients with LV reverse remodeling have better survival than do patients without LV reverse remodeling, regardless of baseline LV volume. These findings support the current guidelines that CRT should not be denied to patients with an enlarged LV at baseline, since they may still have significant LV reverse remodeling after CRT, translating into superior long-term survival, as compared with patients without LV reverse remodeling.

Furthermore, multivariable logistic regression analysis for LV reverse remodeling at 6-month follow-up, only for patients in LVEDVi quintile 5, has been performed to identify a favorable patient's phenotype to present LV reverse remodeling and consequently better overall survival compared with patients who do not present LV reverse remodeling (Online Supplemental Table S3). Better kidney function and less severe symptoms of HF showed a trend toward a significant association with present LV reverse remodeling and could be eligible variables for future patient selection.

Study limitations

First, this study is limited by its retrospective design from a single tertiary center. As a consequence, some of the results (higher percentage of patients in sinus rhythm among patients in larger LVEDVi quintiles) may be counterintuitive. Second, all patients included in the present study completed 6 months of follow-up (patients who died during the first 6 months are not included and may have caused selection bias). Third, cardiac HF biomarkers (particularly brain natriuretic peptide or N-terminal prohormone brain natriuretic peptide) were not acquired. Fourth, the long inclusion period implies the use of different generations of devices as well as (quadripolar) leads, which may have influenced response rate, despite a subanalysis between "early period" and "late period" of inclusion showing no significant difference in LV reverse remodeling. Fifth, subanalyses to identify favorable patient's phenotype to present LV reverse remodeling had limited power because of the low number of patients in LVEDVi quintile 5. Finally, granular data were not available to differentiate between cardiac and noncardiac deaths and there were no data on HF hospitalization.

Conclusion

Patients with larger baseline LV volumes have worse survival after CRT implantation than do patients with smaller LV volumes. However, many patients with larger baseline LV volumes still show significant LV reverse remodeling. Patients with LV reverse remodeling after CRT implantation had superior survival (regardless of baseline LV volumes) than did patients without LV reverse remodeling. Therefore, CRT should not be denied to patients with HF on the basis of severe LV dilatation.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.02.013.

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