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Prognostic implications of staging cardiac remodeling in patients undergoing cardiac resynchronization therapy☆

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) candidates often present with significant mitral and tricuspid regurgitation, pulmonary hypertension and right ventricular dysfunction when referred for device implantation. This study investigated the prognostic value of a novel cardiac staging system, based on the extent of cardiac remodeling prior to implantation.

Methods: Data were collected from an ongoing registry of CRT recipients. Patients were divided into 4 groups according to the extent of cardiac remodeling: group 1: left ventricular systolic dysfunction, group 2: left atrial dilatation and/or significant mitral regurgitation, group 3: pulmonary arterial hypertension and/or significant tricuspid regurgitation and group 4: right ventricular systolic impairment. Patients were followed up for the occurrence of all-cause mortality.

Results: A total of 844 patients (age 65 ± 10 years, 77% men) were included. Of the overall population, 145 (17%) patients were in group 1, 161 (19%) in group 2, 157 (19%) in group 3 and 381 (45%) in group 4. After a median follow-up of 95 (51–145) months, 517 (61%) patients died. Patients in groups 2, 3 and 4 had significantly higher mortality rates than those in group 1 ($p = 0.025$, $p < 0.001$ and $p < 0.001$, respectively). On multivariable analysis, groups 3 (HR 1.415; 95% CI 1.024–1.957; $p = 0.032$) and 4 (HR 1.599; 95% CI 1.204–2.123; $p = 0.001$) were independently associated with all-cause mortality.

Conclusions: Most CRT candidates already present with extensive cardiac remodeling at the time of referral. Detection of the extent of cardiac remodeling before CRT implantation results in improved risk-stratification, and underscores the need for early referral.

1. Introduction

Cardiac resynchronization therapy (CRT) is a highly effective therapy for selected patients with heart failure and reduced ejection fraction (HFrEF), and leads to improved quality of life, left ventricular (LV) reverse remodeling and reductions in HF hospitalizations rates and all-cause mortality [1–4]. Although patient selection for CRT is mainly based on LV ejection fraction (LVEF) (in addition to symptoms and electrocardiographic characteristics), clinical outcomes in CRT candidates are not influenced by LV function alone. Hemodynamic complications of HFrEF, such as significant mitral and tricuspid regurgitation, pulmonary hypertension and right ventricular (RV) dysfunction are frequently observed in CRT candidates and have been associated with worse outcomes after CRT implantation [5–8]. A classification system based on the extent of cardiac remodeling may improve risk stratification in CRT recipients and prompt the clinician to refer patients timely. Although such a staging system has shown incremental value in a number of cardiovascular diseases [9–13], the prognostic utility of this

Abbreviation: CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; LA, left atrial; LAVi, left atrial volume index; LV, left ventricular; RV, right ventricular.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of data presented and their discussed interpretation.

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approach in CRT recipients is unknown. The current study aimed to: [1] comprehensively characterize the extent of cardiac remodeling at the time of referral for CRT, [2] categorize the types of cardiac remodeling (LV dysfunction, left atrial (LA) dilatation, pulmonary hypertension and RV dysfunction) into groups and [3] evaluate the impact of this classification system on outcomes after CRT implantation.

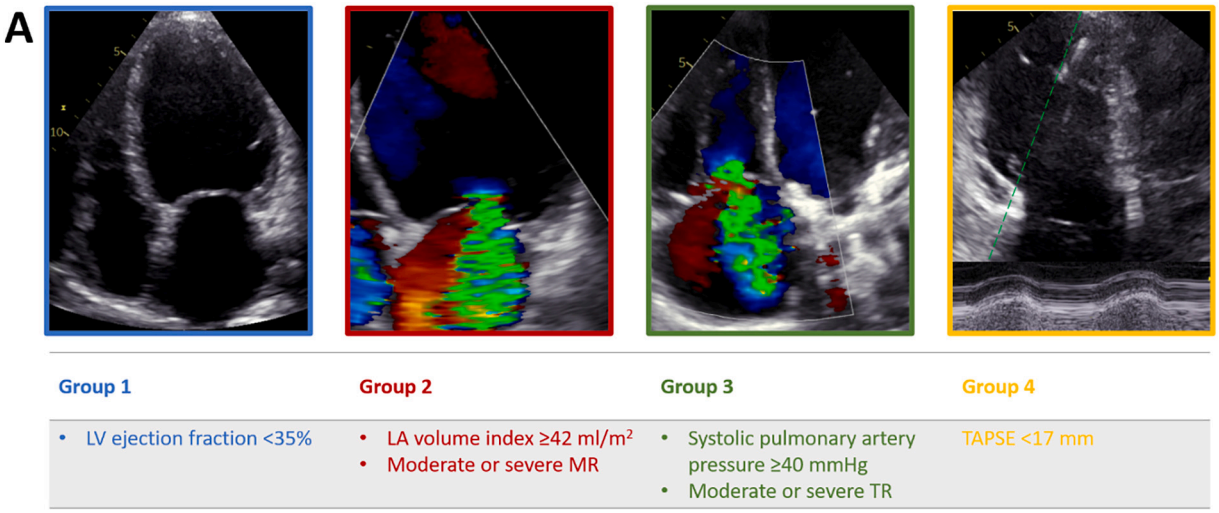
2. Methods

2.1. Patient population and clinical data collection

Symptomatic HF patients who underwent CRT implantation according to contemporary guidelines [14], were included from an ongoing registry at the Leiden University Medical Center, The Netherlands [15]. All patients underwent comprehensive clinical and echocardiographic evaluation before CRT implantation. Patient information was prospectively collected in the departmental cardiology information system (EPD-vision, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. Clinical data collected for the current analysis included demographic characteristics, cardiovascular risk factors and comorbidities. An ischemic etiology of HF was defined by the presence of significant coronary artery disease on invasive coronary angiography. Quality of life was evaluated with the Minnesota Living with Heart Failure Questionnaire and, if feasible, a 6-min walk test was performed. Renal function was quantified by estimating the glomerular filtration rate with the Modification of Diet in Renal Disease Study (MDRD) equation. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board. Due to the retrospective study design, the Medical Ethical Committee waived the need for written informed consent.

2.2. Echocardiographic data acquisition and analysis

All patients underwent transthoracic echocardiography before CRT



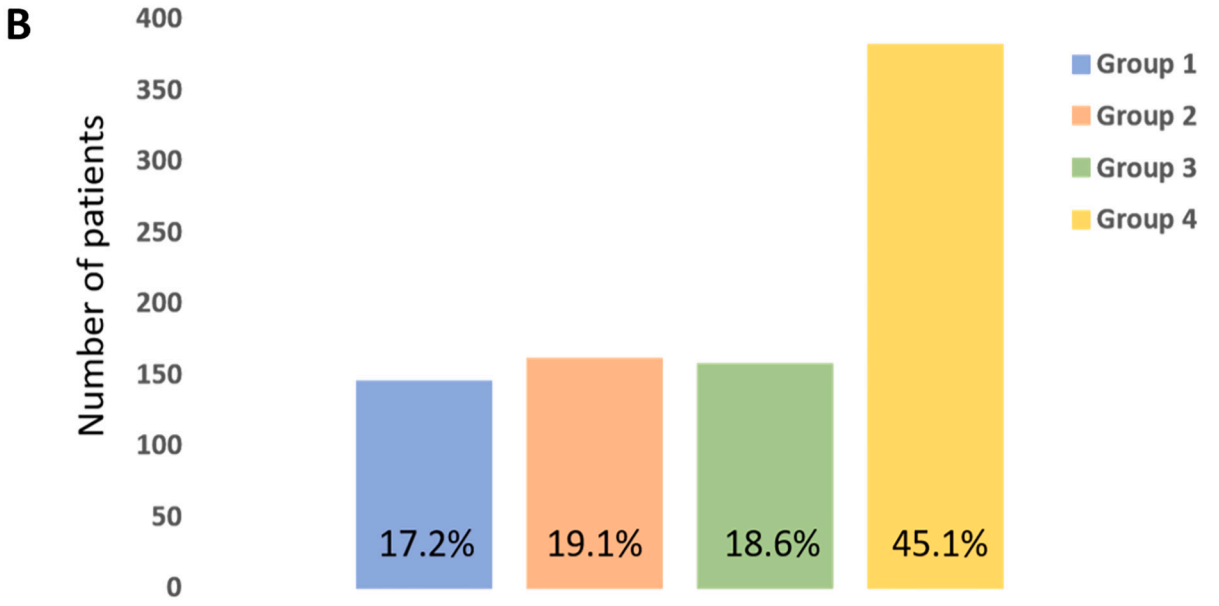


Fig. 1. Proposed classification system based on the extent of cardiac remodeling and distribution of the overall population according to these different groups of cardiac remodeling.
CRT = cardiac resynchronization therapy; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

implantation in the left lateral decubitus position with commercially available ultrasound equipment (Vivid 7 and E9, GE-Vingmed, Horten, Norway). ECG-triggered echocardiographic data were stored digitally in a cine-loop format for offline analysis using EchoPAC version 203 (GE Medical Systems, Horten, Norway). LV volumes, LVEF and LA volumes were measured using the Simpson's biplane method [16]. RV end-systolic area and end-diastolic area were traced in a focused RV apical view according to current recommendations [16]. RV fractional area change was calculated by the following formula: RV fractional area change = ([RV end-diastolic area - RV end-systolic area]/RV end-diastolic area) x100% [16]. Tricuspid annular plane systolic excursion was measured on M-mode recordings of the lateral tricuspid annulus in an RV-focused view [16]. Peak systolic pulmonary artery pressure was derived from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation, adding the right atrial pressure (estimated by the inspiratory collapse and diameter of the inferior vena cava) [16]. The severity of mitral and tricuspid regurgitation was graded by using a multiparametric approach, as recommended in current guidelines [17].

2.3. Categorization of cardiac remodeling

Patients were categorized into four independent groups, based on the extent of cardiac remodeling evident on transthoracic echocardiography before CRT implantation (Fig. 1). Group 1: impaired LV systolic function only (LVEF <35%), group 2: LA enlargement (moderate to severe LA dilatation, defined as a LA volume index ≥42 ml/m^2 [16]) and/or significant (moderate or severe) mitral regurgitation, group 3: pulmonary arterial hypertension (systolic pulmonary artery pressure ≥ 40 mmHg) and/or significant (moderate or severe) tricuspid regurgitation and group 4: RV systolic dysfunction (tricuspid annular plane systolic excursion <17 mm). Patients were hierarchically classified in a given stage (worst stage) if at least one of the proposed criteria was met within that stage.

2.4. CRT implantation

CRT implantation was performed according to a standard approach, i.e., insertion of the right atrial and ventricular leads via the subclavian or cephalic veins. Before insertion of the LV lead, coronary sinus venography was performed. The LV pacing lead was then introduced into the coronary sinus through an 8 Fr guiding catheter, and positioned in a posterior or posterolateral vein, if possible. Defibrillator functionality was included in most (96%) of the implanted devices. CRT recipients were followed up at regular intervals at the HF outpatient clinic, undergoing device interrogation at each visit. Atrioventricular and interventricular delays were empirically set at 120–140 ms and 0 ms, respectively. CRT optimization was performed during follow-up visits at the discretion of the treating physician.

2.5. Clinical endpoints

Patients were followed up for the occurrence of all-cause mortality. Data on mortality were obtained from the departmental cardiology information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands), which is linked to the governmental death registry database. Follow-up data were complete for all patients.

2.6. Statistical analysis

Continuous data are presented as mean ± standard deviation when normally distributed and as median and interquartile range when not normally distributed. Categorical data are presented as frequencies and percentages. Continuous variables were compared using the analysis of variances test with Bonferroni's post hoc analysis when normally distributed, whereas the Kruskal-Wallis test was used to compare continuous variables that did not adhere to a normal distribution. Categorical variables were compared using the chi-square test. Event-free survival curves were generated using the Kaplan-Meier method and differences between the groups were analyzed using the log-rank test. Univariable Cox proportional hazard analysis was performed to evaluate the association between groups of cardiac damage and other clinical and echocardiographic variables with all-cause mortality. The entry criterion for the multivariable regression analysis was a significant correlation in univariable analysis (p-value <0.05). For both uni-and multivariable analysis, hazard ratios (HR) and 95% confidence intervals (CI) were calculated and reported. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 25.0; IBM, Armonk, NY, USA).

3. Results

3.1. Clinical and echocardiographic patient characteristics

A total of 844 patients (age 65 ± 10 years, 77% men) were included in the study. Of the overall population, 145 (17.2%) patients were in group 1, 161 (19.1%) in group 2, 157 (18.6%) in group 3 and 381 (45.1%) in group 4 (Fig. 1). The baseline clinical and echocardiographic characteristics of the overall population, as well as according to each group of cardiac involvement, are shown in Table 1. Patients in group 4 were less likely to be in sinus rhythm and had more diabetes mellitus, more impaired renal function and lower hemoglobin values when compared to patients in group 1. In addition, individuals in group 4 were more likely to be in New York Heart Association functional class III-IV, performed less well on the 6-min walk test and had a worse quality-of-life score when compared to CRT recipients in group 1. Patients in group 4 had a larger indexed LA volume (LAVi), lower LVEF, more impaired RV systolic function / larger RV area and higher pulmonary artery pressures, compared to patients in group 1.

3.2. Prognostic impact of classification system

During a median follow-up of 95 (51–145) months, 517 (61%) patients died. The cumulative 1-, 3- and 5-year survival rates were 95%, 83% and 70%, respectively. The Kaplan-Meier analysis for all-cause mortality according to the different groups is shown in Fig. 2. The 1-, 3- and 5-year survival rates were 100%, 95% and 84% for group 1; 98%, 91% and 82% for group 2; 97%, 80% and 67% for group 3; and 92%, 77% and 61% for group 4, respectively. Long-term survival rates were significantly lower for patients in group 2 (p = 0.025), group 3 (p < 0.001) and group 4 (p < 0.001) when compared to group 1. The uni- and multivariable Cox regression analyses evaluating the association between different groups of cardiac remodeling and all-cause mortality are shown in Table 2. On univariable analysis, group 2 (HR 1.442; 95% CI 1.030–1.962; p = 0.032), group 3 (HR 1.775; 95% CI 1.294–2.435; p < 0.001) and group 4 (HR 2.165; 95% CI 1.644–2.850; p < 0.001) were significantly associated with all-cause mortality. After correcting for age, male sex, ischemic etiology of HF, body mass index, arterial hypertension, dyslipidemia, diabetes mellitus, New York Heart Association functional class III-IV, atrial fibrillation, QRS duration, estimated glomerular filtration rate, hemoglobin and baseline LVEF, group 3 (HR 1.415; 95% CI 1.024–1.957; p = 0.032) and group 4 (HR 1.599; 95% CI 1.204–2.123; p = 0.001) remained independently associated with worse survival. Table S1 shows the uni -and multivariable Cox regression analysis according to the individual components of cardiac damage.

In the overall study population, 57% of the patients showed a beneficial response to CRT (defined as a ≥ 15% reduction in LV end-systolic volume, 6 months after CRT implantation). CRT response was significantly lower in group 3 (47%) and group 4 (55%), when compared to group 1 (65%) and group 2 (63%) (p < 0.05 for all). When investigating the impact of CRT on quality of life measurements, 61% of the study population had a significant improvement in New York Heart Association functional class (defined as an improvement of ≥I class) at 6

Table 1
Baseline clinical and echocardiographic characteristics.

	Overall population (n = 844)	Group 1 (n = 145)	Group 2 (n = 161)	Group 3 (n = 157)	Group 4 (n = 381)	p-value
Age, years	65.3 (±10.4)	64.5 (±9.9)	66.7 (±9.7)	65.9 (±10.0)	64.9 (±11.1)	0.169
Male sex (%)	647 (76.7%)	114 (78.6%)	121 (75.2%)	112 (71.3%)	300 (78.7%)	0.270
Arterial hypertension (%)	398 (47.4%)	64 (44.1%)	81 (50.3%)	76 (48.7%)	177 (46.9%)	0.728
Diabetes mellitus (%)	180 (21.3%)	22 (15.2%)	24 (14.9%)	32 (20.4%)	102 (26.8%)*,†	0.003
Dyslipidemia (%)	361 (43.1%)	66 (45.5%)	67 (41.6%)	64 (41.3%)	164 (43.6%)	0.864
Current smoker (%)	133 (16.0%)	29 (20.6%)	25 (15.7%)	23 (14.8%)	56 (14.9%)	0.511
BMI, kg/m^2	26.5 (±4.3)	27.2 (±4.3)	26.3 (±4.0)	26.6 (±4.4)	26.3 (±4.4)	0.161
Ischemic etiology (%)	509 (60.3%)	79 (54.5%)	93 (57.8%)	88 (56.1%)	249 (65.4%)	0.052
QoL score	34.4 (±19.8)	27.2 (±18.3)	27.9 (±18.2)	33.2 (±18.8)	34.4 (±19.8)*,†	<0.001
6MWT, m	330 (±117)	372 (±115)	338 (±111)	321 (±108)*	315 (±119)*	<0.001
NYHA III-IV (%)	559 (67.3%)	78 (54.5%)	99 (62.7%)	106 (68.4%)	276 (73.6%)*	<0.001
Sinus rhythm (%)	600 (71.1%)	123 (84.8%)	129 (80.1%)	98 (62.4%)*,†	250 (65.6%)*,†	<0.001
QRS duration, ms	153 (±35)	151 (±35)	153 (±31)	153 (±39)	154 (±36)	0.873
Bundle branch block						<0.001
LBBB	399 (47.3%)	80 (55.2%)	93 (57.8%)	62 (39.5%)*,†	164 (43.0%)†	<0.05
RBBB	79 (9.4%)	10 (6.9%)	11 (6.8%)	11 (7.0%)	47 (12.3%)	n.s.
IVCD	231 (27.3%)	41 (28.2%)	41 (25.5%)	48 (30.5%)	101 (26.5%)	n.s.
Vp	135 (16.0%)	14 (9.7%)	16 (9.9%)	36 (22.9%)*,†	69 (18.1%)	<0.05
Beta-blocker (%)	624 (73.9%)	120 (82.8%)	121 (75.2%)	108 (68.8%)*	275 (72.2%)	0.033
ACE-i/ARB (%)	751 (89.0%)	130 (89.7%)	143 (88.8%)	142 (90.4%)	336 (88.2%)	0.883
MRA (%)	390 (46.2%)	53 (36.6%)	74 (46.0%)	66 (42.0%)	197 (51.7%)*	0.011
Diuretics (%)	680 (80.6%)	102 (70.3%)	124 (77.0%)	123 (78.3%)	331 (86.9%)*,†	<0.001
Statin (%)	535 (63.4%)	99 (68.3%)	106 (65.8%)	94 (59.9%)	236 (61.9%)	0.378
eGFR, ml/min/1.73 m^2	66.9 (±24.2)	73.3 (±22.1)	67.9 (±24.1)	67.4 (±23.5)	63.7 (±24.9)*	0.001
Hemoglobin, g/dl	13.3 (±1.6)	13.6 (±1.6)	13.4 (±1.6)	13.1 (±1.5)*	13.2 (±1.6)*	0.016
LVEDV, ml	203 (±73)	190 (±64)	215 (±72)*	210 (±80)	200 (±73)	0.009
LVESV, ml	152 (±62)	137 (±53)	159 (±61)*	157 (±68)*	151 (±63)	0.009
LVEF, %	26.4 (±7.0)	28.1 (±6.4)	27.0 (±6.8)	26.2 (±7.0)*	25.4 (±7.0)*	<0.001
LAVi, ml/m^2	43 (±18)	30 (±7)	46 (±15)*	50 (±21)*	45 (±18)*	<0.001
RVEDA, cm^2	22.3 (±7.0)	19.7 (±5.1)	21.2 (±5.3)	24.4 (±7.8)*,†	23.0 (±7.6)*,†	<0.001
RVESA, cm^2	14.5 (±6.3)	11.4 (±4.2)	12.8 (±4.8)	16.2 (±6.5)*,†	15.8 (±6.8)*,†	<0.001
RVFAC, %	36.5 (±12.9)	43.4 (±11.3)	40.4 (±12.3)	34.9 (±12.1)*,†	32.88 (±12.6)*,†	<0.001
TAPSE, mm	15.5 (±4.8)	19.6 (±3.4)	18.7 (±3.1)*	18.6 (±3.1)*	11.3 (±2.5)*,†,#	<0.001
RA area, cm^2	18 (14–23)	15 (13–18)	18 (14–21)*	21 (17–27)*,†	19 (15–24)*†#	<0.001
TR velocity, m/s	2.6 (±0.6)	2.2 (±0.5)	2.4 (±0.4)*	3.0 (±0.5)*,†	2.6 (±0.6)*,†,#	<0.001
PASP, mmHg	35 (±14)	26 (±7)	29 (±7)	46 (±14)*,†	37 (±14)*,†,#	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).
ACE-i = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; EDA = end-diastolic area; EDV = end-diastolic volume; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESA = end-systolic area; ESV = end-systolic volume; FAC = fractional area change; IVCD = interventricular conduction delay; LAVi = left atrial volume index; LBBB = left bundle branch block; LV = left ventricle; MRA = mineralocorticoid receptor antagonist; MWT = minute walking test; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; QoL = quality of life; RA = right atrium; RBBB = right bundle branch block; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; Vp = ventricular pacing (due to previously implanted cardiac implantable electronic device).
* $p < 0.05$ vs. group 1.
† $p < 0.05$ vs. group 2.
# $p < 0.05$ vs. group 3.

months after CRT implantation. In addition the 6-min walk test improved from 330 ± 117 m to 395 ± 118 m ($p < 0.001$) and the Quality of Life Score improved from 31.4 ± 19.8 to 22.3 ± 18.9 ($p < 0.001$). On binary logistic regression analysis, there was no association between the different groups of cardiac remodeling and functional outcomes (Table S2).

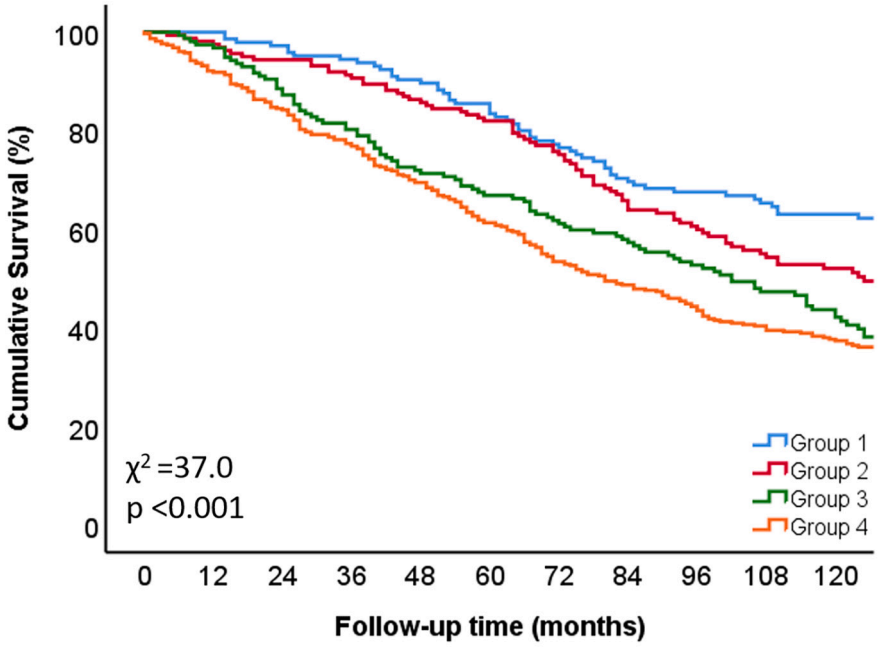
4. Discussion

The principal findings of the current study are that: 1) CRT candidates often present with extensive cardiac remodeling at the time of referral, which is inadequately reflected by LVEF alone, and 2) identification of the extent of cardiac remodeling according to a novel staging system results in improved risk-stratification of CRT recipients.

4.1. Cardiac remodeling in CRT candidates

In patients with HFrEF, the location of the initial damage is usually the LV (reduced LVEF), reflecting either an ischemic or non-ischemic etiology. The increase in LV wall stress induces a compensatory LV remodeling response to normalize LV wall pressure and maintain cardiac output. Although initially beneficial, this remodeling process will eventually become insufficient, negatively impacting LV systolic and diastolic function, thereby creating a 'vicious circle' of increasing LV wall stress and LV dysfunction [18,19]. The hemodynamic consequences of the LV remodeling response, however, are not limited to the LV, but affect other cardiac structures as well [20–23].

During ventricular diastole, the LA is exposed to an increase in LV end-diastolic pressure. LA size provides a sensitive marker of the underlying LV diastolic dysfunction severity [24]. Previous studies have demonstrated that LA structural and functional abnormalities are common in CRT recipients, with a reported mean LAVi ranging between 47 and 53 ml/m^2 [20,25]. In addition, LA and LV remodeling increase the risk of developing significant (i.e. ≥ moderate) functional mitral regurgitation, which has been reported in up to 40–50% of CRT recipients [26,27]. With further disease progression, impaired LV relaxation and LA dysfunction cause elevated filling pressure, which is transmitted retrogradely to the pulmonary venous system, capillaries and arteries, leading to postcapillary pulmonary hypertension [28]. The coexistence of mitral regurgitation contributes significantly to the pulsatile load on the pulmonary circulation and is an important role player in the development of pulmonary hypertension in patients with HFrEF [29]. Depending on the diagnostic threshold used, pulmonary hypertension is reported in 40–75% of CRT candidates [30], and combined pre



Number at risk											
Group 1	145	145	141	137	130	121	111	101	92	87	79
Group 2	161	157	152	146	138	132	121	101	88	74	63
Group 3	157	152	137	126	112	105	96	88	79	68	53
Group 4	381	350	320	292	264	233	203	183	155	135	118

Fig. 2. Kaplan-Meier curve for all-cause mortality according to different groups of cardiac remodeling.

-and postcapillary pulmonary hypertension has been observed in 17–19% of patients with HFrEF [30,31]. Finally, because the thin-walled RV adapts less well to pressure overload than to volume overload, pulmonary hypertension may lead to RV remodeling, functional tricuspid regurgitation and RV systolic dysfunction [32,33]. Significant tricuspid regurgitation has been documented in 25% of patients with HFrEF [34] and moderate to severe RV systolic dysfunction in up to 25–35% of such patients [5,35].

The current study provides further insights into the extent of cardiac remodeling in patients referred for CRT implantation, and classifies different groups of cardiac remodeling into a single system. The majority of patients being referred for CRT implantation already demonstrated a significant degree of cardiac remodeling. Group 4 (i.e. RV systolic dysfunction) was the largest (45%), compared to group 1 (i.e. isolated LV dysfunction), which was the smallest (17%).

4.2. Prognostic implications of cardiac remodeling in CRT recipients

The cardiac remodeling parameters evaluated in the current study have been individually associated with prognosis in patients with HFrEF, including CRT recipients. LA volume is a robust predictor of cardiovascular outcomes in patients with HFrEF, with several studies showing an independent association between LA size and incident atrial fibrillation, stroke, HF and death [21,36–38]. Moderate to severe functional mitral regurgitation portends a poor prognosis in patients with HF, with an increasing risk of HF hospitalization and death [27,39–41]. Although the presence of LA and/or mitral valve remodeling have been independently associated with worse outcomes in HF patients, these disease markers lost their independent association with outcome in the current analysis, after correcting for other cardiac remodeling parameters. This may be explained by the lack of a 'healthy' reference population (i.e. patients in group 1 all had baseline LVEF <35%), as well as the strong link between more advanced cardiac remodeling and outcomes. The presence of pulmonary hypertension and/or significant tricuspid regurgitation and RV systolic dysfunction showed the strongest association with all-cause mortality in the current study, which is in agreement with previous research [5,8,32,34,35]. The present study highlights the prognostic impact of a novel cardiac remodeling staging system (including various degrees of cardiac remodeling) in a large, unselected cohort of CRT recipients with long-term follow-up data. The results demonstrate that all-cause mortality in CRT recipients is linked to the extent of cardiac remodeling, defined by various echocardiographic parameters.

4.3. Clinical implications

The current study demonstrates that CRT candidates already present with extensive cardiac remodeling at the time of CRT referral. In addition, the extent of cardiac remodeling is strongly associated with worse survival. The Heart Failure Association (HFA), European Heart Rhythm Association (EHRA) and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology (ESC) recently published a joint position statement, addressing the unmet need for optimized use of CRT, stating that up to two-thirds of eligible patients

Table 2
Uni -and multivariable Cox regression analyses to assess the association between grouping classification and all-cause mortality.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, years	1.041 (1.031–1.051)	<0.001	1.030 (1.019–1.041)	<0.001
Male sex	1.273 (1.029–1.574)	0.026	1.329 (1.060–1.667)	0.014
Ischemic etiology	1.585 (1.319–1.904)	<0.001	1.266 (1.031–1.555)	0.025
Body mass index, kg/m^2	0.985 (0.965–1.006)	0.153		
Arterial hypertension	1.086 (0.913–1.292)	0.349		
Dyslipidemia	1.281 (1.077–1.524)	0.005	1.109 (0.922–1.335)	0.273
Diabetes mellitus	1.654 (1.356–2.017)	<0.001	1.368 (1.107–1.690)	0.004
NYHA III-IV	1.735 (1.420–2.120)	<0.001	1.308 (1.059–1.616)	0.013
Atrial fibrillation	1.072 (0.950–1.210)	0.259		
QRS duration, ms	1.001 (0.9999–1.003)	0.420		
eGFR, ml/min/ 1.73 m^2	0.978 (0.974–0.982)	<0.001	0.987 (0.982–0.991)	<0.001
Hemoglobin, g/dl	0.782 (0.717–0.853)	<0.001	0.900 (0.819–0.988)	0.027
LVEF baseline, %	0.981 (0.970–0.993)	0.002	0.980 (0.968–0.993)	0.003
Group 1	Reference		Reference	
Group 2	1.422 (1.030–1.962)	0.032	1.173 (0.847–1.626)	0.337
Group 3	1.775 (1.294–2.435)	<0.001	1.415 (1.024–1.957)	0.032
Group 4	2.165 (1.644–2.850)	<0.001	1.599 (1.204–2.123)	0.001

CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; NYHA = New York Heart Association.

are currently not referred early enough for CRT [42]. Since late referral is associated with more advanced cardiac remodeling [42], the results of the current study underscore the importance of early referral.

The proposed classification system may also improve risk stratification of CRT recipients. Patients in groups 3 and 4 should perhaps receive more frequent follow-up after CRT implantation than what is generally recommended in guidelines. Prospective studies are needed to confirm the prognostic value of the proposed classification system and to determine if its implementation in clinical practice could lead to earlier referral and improved outcomes. Whether more recently introduced HF treatments, such as sodium-glucose co-transport 2 inhibitors and angiotensin-neprilysin inhibitors, will lead to earlier referral (i.e. in a less advanced stage of cardiac adverse remodeling) and how these HF treatments or CRT itself impact the staging system after CRT implantation, also merits further investigation.

4.4. Study limitations

The present study has limitations related to its retrospective design. Although the decision to implant CRT was primarily based on guideline recommendations, selection bias may still be present due to the observational nature of the study. The classification system used to describe the extent of cardiac remodeling does not necessarily reflect a linear increase in the level of severity and abnormalities may occur in combination. RV systolic dysfunction was quantified with tricuspid annular plane systolic excursion, which is angle-dependent, only takes into account the lateral tricuspid annular displacement and does not account for regional differences in RV function. However, tricuspid annular plane systolic excursion is easy to measure, reproducible and has been validated in large patient cohorts. Echocardiographic measurements at follow-up were not available for all variables and therefore, the effect of CRT on the classification system could not be evaluated. Data on heart failure hospitalizations, valvular interventions (surgical or transcatheter), left ventricular assist device or heart transplantation at follow-up were not available. All-cause mortality was chosen as the primary endpoint, since the exact cause of death was not systematically recorded.

5. Conclusion

Most CRT recipients already present with extensive cardiac remodeling at the time of CRT referral. Moreover, the extent of cardiac remodeling is associated with worse long-term survival. Classification of the extent of cardiac remodeling according to a newly-proposed staging system results in improved risk-stratification in CRT recipients, and may alert the clinician to earlier referral.

Disclosures

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CRediT authorship contribution statement

Jan Stassen: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Visualization. **Mand Khidir:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing. **Xavier Galloo:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Visualization. **Kensuke Hirasawa:** Validation, Investigation, Writing – review & editing. **Juhani Knuuti:** Conceptualization, Writing – review & editing, Supervision. **Nina Ajmone Marsan:** Conceptualization, Writing – review & editing, Supervision. **Victoria Delgado:** Conceptualization, Writing – review & editing, Supervision. **Pieter van der Bijl:** Conceptualization, Writing – review & editing, Supervision. **Jeroen J. Bax:** Conceptualization, Writing – review & editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.02.020.

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