Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the Markers and Response to CRT (MARC) study

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CLINICAL RESEARCH
Pacing and resynchronization therapy

Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the Markers and Response to CRT (MARC) study

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Aims Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in systolic heart failure patients with ventricular conduction delay. Variability of individual response to CRT warrants improved patient selection. The Markers and Response to CRT (MARC) study was designed to investigate markers related to response to CRT.

Methods and results We prospectively studied the ability of 11 clinical, 11 electrocardiographic, 4 echocardiographic, and 16 blood biomarkers to predict CRT response in 240 patients. Response was measured by the reduction of indexed left ventricular end-systolic volume ($LVESV_i$) at 6 months follow-up. Biomarkers were related to $LVESV_i$ change using log-linear regression on continuous scale. Covariates that were significant univariately were included in a multivariable model. The final model was utilized to compose a response score. Age was 67 ± 10 years, 63% were male, 46% had ischaemic aetiology, LV ejection fraction was 26 ± 8%, $LVESV_i$ was 75 ± 31 mL/m^2, and QRS was 178 ± 23 ms. At 6 months $LVESV_i$ was reduced to 58 ± 31 mL/m^2 (relative reduction of 22 ± 24%), 130 patients (61%) showed ≥ 15% $LVESV_i$ reduction. In univariate analysis 17 parameters were significantly associated with $LVESV_i$ change. In the final model age, QRS_{AREA} (using vectorcardiography) and two echocardiographic markers (interventricular mechanical delay and apical rocking) remained significantly associated with the amount of reverse ventricular remodelling. This CAVIAR (CRT-Age-Vectorcardiographic QRS_{AREA} -Interventricular Mechanical delay-Apical Rocking) response score also predicted clinical outcome assessed by heart failure hospitalizations and all-cause mortality.

Conclusions The CAVIAR response score predicts the amount of reverse remodelling after CRT and may be used to improve patient selection. Clinical Trials: NCT01519908

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Keywords Heart failure • Biomarkers • Cardiac resynchronization therapy • Vectorcardiography • Electrocardiography • Echocardiography

What's new?

- A simple response score can predict the amount of reverse ventricular remodelling after cardiac resynchronization therapy (CRT).
- Vectorcardiography performs better than conventional electrocardiography to predict reverse ventricular remodelling after CRT.
- Simple echocardiographic dyssynchrony markers improve CRT response prediction.
- In a multivariate analysis, blood biomarkers did not add to the predictive value of clinical, electrical, and echocardiographic markers.

Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with systolic heart failure despite optimal medication and inter- and intraventricular conduction delay. CRT reduces heart failure hospitalizations and mortality and improves exercise capacity and quality of life.[1–6] Despite the success of CRT, a significant number of patients show no clinical improvement.[4] Several factors influence response to CRT including aetiology of heart failure, QRS morphology and duration, and mechanical dyssynchrony.[5,7] In addition, optimal delivery of CRT and targeted lead position are essential for response to CRT.[8] One of the best parameters to define reverse remodelling is reduction of indexed left ventricular end systolic volume ($LVESV_i$). Reverse ventricular remodelling is closely correlated with clinical endpoints such as all-cause mortality and heart failure hospitalizations.[9]

In the landmark trials the selection of patients was mainly based on QRS duration.[2,3,6] Retrospective analyses have shown that patients with left bundle branch block (LBBB) ECG morphology may have a higher chance to respond to CRT.[10] As a consequence, both QRS duration and morphology are mentioned in the most recent guidelines, refining identification of the electrical substrate.[1,11] However, there are several definitions of LBBB, making this marker operator-dependent.[12] Echocardiographic markers of dyssynchrony may also have predictive value but many are notoriously difficult to reproduce with high intra- and interobserver variability.[13] Only limited data is available on the predictive value of blood biomarkers for CRT response and outcome.[14]

To improve prediction of the beneficial effects of CRT we prospectively investigated the prognostic value of a set of clinical, electrical, structural, and blood biomarkers to predict reverse remodelling assessed as a decrease in $LVESV_i$ in patients with an indication for CRT according to the guidelines.

Methods

More extensive description of the methods can be found in the Supplementary materials online.

Study design

The Markers and Response to CRT (MARC) study was a prospective, multicentre, observational study performed in The Netherlands designed to identify a set of biomarkers that can predict the magnitude of reverse LV remodelling. In total, 240 patients with an indication for CRT according to the current guidelines[1,11] including patients with LBBB and non-specific intraventricular conduction delay (IVCD) but without right bundle branch block were included in 6 participating centres between February 2012 and November 2013. Total follow-up was 12 months. The study was initiated and coordinated by the six centres within the framework of the Centre for Translational Molecular Medicine (CTMM), project COHFAR (grant 01C-203), and additionally financially supported by Medtronic Inc., Minneapolis, MN, USA. Study monitoring was done by Medtronic Bakken Research Centre, Maastricht, the Netherlands, data management, validation, and statistical analysis by the investigators in collaboration with Medtronic (BG). The study was approved by the institutional review boards of all participating centres. All patients gave written informed consent. The trial was registered at clinicaltrials.gov: NCT01519908.

Study participants

Inclusion criteria were an indication for CRT according to the guidelines at the time of inclusion. All patients had a *de novo* indication for CRT according to the most recent ESC and American guidelines:[1,11] New York Heart Association (NYHA) class II or III, stable sinus rhythm (no documented atrial arrhythmias lasting >30 s during the last 2 weeks prior to inclusion), for class II patients an intrinsic QRS-width ≥ 130 ms with LBBB or ≥150 ms with non-specific IVCD, for NYHA class III an intrinsic QRS-width ≥ 120 ms with LBBB or ≥ 150 ms with non-specific IVCD, and on optimal heart failure oral medical therapy. Exclusion criteria included severe renal insufficiency with a glomerular filtration rate < 30 mL/min/1.73m^2, an upgrade from a bradycardia pacemaker or CRT-P to CRT-D, permanent atrial fibrillation (AF) or flutter or tachycardia, right bundle branch block, and permanent second or third degree atrioventricular (AV) block. Patients were seen at the outpatient department at baseline, 1, 6, and 12 months after CRT-D implantation.

Device settings and optimalization

After implantation devices were programmed to DDD mode with a sensed AV delay of 90 ms and a paced AV delay of 130 ms. Left-to-right (VV) ventricular delay was set to 0 ms. After 1 month, AV and VV delays were optimized echocardiographically to the discretion of the local investigator. Devices were programmed to rate response mode after 1 month unless good chronotropic response was observed at device check-up utilizing device rate histograms.

Biomarkers

Biomarkers assessed in the MARC study included 11 clinical parameters, 11 electrocardiographic parameters including beat-to-beat variability and vectorcardiography (VCG), 4 echocardiographic parameters assessing cardiac function and structure, and 16 blood biomarkers. These parameters were chosen on the basis of earlier implication as response predictors from prospective or retrospective analyses.

Electrocardiography and VCG

A 12-lead digital electrocardiogram (ECG) was recorded at baseline. All parameters were analysed in the ECG core lab (S.W., M.V.). LBBB was defined as a slurred/notched R-wave in I, aVL and V6, an absent Q in I, V5, V6, a R-peak time >60 ms in V6 and no R- or R-wave of <60 ms in V1-V3. VCGs were synthesized from pre-procedural digital 12 lead ECGs. A VCG consists of three orthogonal leads X, Y, and Z, which together form a 3D vector loop. The QRS_{AREA} and T_{AREA} were calculated from the VCG. RR and QT Short-Term Variability (STV RR and STV QT) were assessed from beat-to-beat variability during >2 min ECG recording. An illustration demonstrating QRS conversion to VCG and QRS_{AREA} can be found in the Supplementary material online.

Echocardiography

Echocardiograms were obtained before and 6 months after implantation and analysed by the echocardiography core lab (J.S., M.J.C.) using vendor specific software. Images were deemed not analysable if image quality was unsuitable for reliable assessment. All echocardiographic parameters were measured on three separate beats and averaged. LV end-diastolic diameter, end-diastolic and end-systolic volume (LVESV), and ejection fraction were measured using the biplane Simpson's method by two experienced observers. If image quality of the apical two chamber view was deemed unsuitable for reliable biplane volume assessment, solely the apical four chamber volume was used. Volumetric response ($\Delta LVESV_i$) was calculated as the change of log-transformed $LVESV_i$ between baseline and 6-month follow-up. Apical rocking was defined as a short systolic septal to lateral rocking motion of the apex. It results from short initial septal contraction and inward motion of the septum, pulling the apex towards the septum,[15] followed by delayed activation of the lateral wall, pulling the apex laterally while stretching the septum. Septal flash was defined as a rapid contraction and subsequent stretching of the septum during the isovolumetric contraction period. Interventricular mechanical delay (IVMD) was defined as the timing difference between left and right ventricular pre-ejection intervals. All dyssynchrony parameters were assessed by an observer blinded for volumetric response. Mitral valve insufficiency was visually assessed and scored.

Blood biomarkers

Parameters were chosen to cover pathophysiological domains that could be involved in CRT response: neurohormones, renal function parameters, inflammation, structural myocardial markers, and collagen turnover. Within each pathophysiological domain, parameters were chosen depending on earlier implication in CRT response by previous prospective or retrospective analyses. Blood was collected at implant from peripheral blood and the coronary sinus. The collagen markers (Procollagen Type III N-terminal Peptide (P3NP), C-terminal Telopeptide of Type I Collagen (ICTP), C-terminal Propeptide of Type I Procollagen (PICP), Matrix Metallo Proteinase 9 (MMP-9), Tissue Inhibitor of Metallopeptidase 1 (TIMP-1), and Aldosterone) were sent to an independent laboratory (Centre d'Investigation Clinique – Plurithematique Pierre Drouin CHU de Nancy, Nancy, France) for analysis. ST2, Growth Differentiation Factor 15 (GDF-15), Galectin-3, N-terminal Prohormone Brain Natriuretic Peptide (NT-proBNP), high-sensitive troponin T (TnT), creatinine, blood urea nitrogen (BUN), high-sensitive C-reactive protein (hsCRP) and Interleukin-6 (IL-6) were measured in the University Medical Centre Groningen (M.K., A.H.M.). The laboratories were blinded to the clinical history.

Statistical analysis

The MARC study was designed to assess the relation between biomarker variables measured at baseline and reverse remodelling at 6 months after CRT initiation. The pre-specified analysis was to perform an analysis of covariance (ANCOVA) on logarithm-transformed $LVESV_i$ measurements for each of the biomarker variables. The PROSPECT study[13] showed that $LVESV_i$ has a log-normal distribution, and with transformation the model results can be interpreted on a relative scale. We planned to enroll 240 patients in order to have at least 200 patients with paired baseline and 6-month $LVESV_i$ measurements, which would give 90% power to show significance on a predictor with predictive ability similar to IVMD in PROSPECT.[13] Each marker was tested separately in an ANCOVA model with the marker and baseline $LVESV_i$ as covariates. Continuous markers were standardized. Significant markers were included in a multivariable model and backward elimination was used to determine a final multivariable model. Patients with incomplete covariate data were excluded from the analysis. The predictive value of the response score in pre-specified subgroups was depicted in a forest plot. CIs for the increase in relative $LVESV_i$ change with a one-point increase on the response score were derived from ANCOVA models restricted to the subgroup. Interaction *P*-values were derived from models with the subgroup indicator and response score as covariates. The relation between response score and incidence of the composite endpoint of all-cause death and hospitalization for worsening heart failure was assessed using Cox proportional hazards regression. The Kaplan-Meier method was used to estimate incidence in patient groups defined by tertiles of the response score. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA), and a P-value < 0.05 was considered statistically significant in all analyses. Results are presented as mean ± SD unless indicated otherwise.

Results

Patient characteristics

A total of 240 patients were included. For 213 patients paired $LVESV_i$ measurements were available. These 213 patients were analysed for the primary endpoints. Reasons for absence of paired $LVESV_i$ measurements were 2 failed implants, 5 implants not attempted, 4 deaths, 4 withdrawn consent, 1 missed visit, 11 unperformed or unreadable echocardiogram studies. Baseline characteristics are shown in *Table 1*. Mean age was 67 ± 10 years, 63% were male. Heart failure was of ischaemic origin in 46% of patients and one third was in NYHA class III. Main comorbidities were diabetes mellitus (27%) and chronic obstructive pulmonary disease (13%). The majority of patients had LBBB (57%), QRS duration was 179 ± 23 ms. AV conduction was preserved in most patients with a PR interval of 195 ± 41 ms. Echocardiographically measured IVMD was 46 ± 29 ms, and apical rocking was present in 60% of patients.

Lead positions

Transvenous LV lead implantation was successful in 233 (97%). Eight patients received an epicardial LV lead by surgical approach. LV lead position was lateral in 67% and postero-lateral in 23% of 211 patients with implant fluoroscopic images. The RV lead was placed in the apex in 85%.

AF during follow-up

During follow-up atrial high rate episodes lasting >6 min were detected in 56 patients (23%). Only 9 of them had AF ≥ 23 h and only 2 patients longer than 1 month.

Table 1 Baseline characteristics

Baseline characteristic	All patients (n = 240)	Patients with paired $LVESV_i$ (n = 213)
Demographics		
Age—years	67 ± 10	66 ± 10
Male sex—no. (%)	151 (63)	132 (62)
Medical history—no. (%)		
Ischaemic etiology of heart failure	111 (46)	90 (42)
History of AF	32 (13)	27 (13)
Left bundle branch block (per investigator)	209 (87)	187 (88)
Left bundle branch block (ECG core laboratory[a])	137 (57)	129 (61)
Diabetes	65 (27)	56 (26)
Renal dysfunction	15 (6)	10 (5)
Chronic obstructive pulmonary disease	31 (13)	26 (12)
Baseline status		
LV ejection fraction[b]—%	26 ± 8	26 ± 7
LVESV volume index[b]—mL/m^2	74 ± 30	75 ± 31
QRS duration[a]—ms	178 ± 23	179 ± 23
PQ interval[a]—ms	195 ± 41	192 ± 37
NYHA class—no. (%)		
I	1 (0.4)	1 (0.5)
II	150 (63)	133 (62)
III	89 (37)	79 (37)
IV	0 (0)	0 (0)
VCG and echocardiography		
QRS_{AREA}[a]—μVs	131 ± 47	136 ± 47
Inter-ventricular mechanical delay[b]—ms	46 ± 29	47 ± 29
Apical rocking[b]—no. (%)	143 (60)	135 (63)
Blood biomarkers—median (IQR)		
P3NP—μg/L	3.3 (2–5)	3.3 (2–5)
BUN—mmol/L	7.5 (6–10)	7.3 (6–9)
Creatinine—μmol/L	87 (72–111)	85 (70–109)
NT-proBNP—ng/L	966 (437–1839)	974 (440–1815)
TIMP1—ng/mL	177 (146–238)	175 (145–234)
Galectin 3—ng/mL	17 (14–22)	17 (14–21)
C-PICP—ng/mL	82 (63–108)	81 (63–108)
MMP9—ng/mL	228 (153–350)	235 (148–361)
C-ICTP—μg/L	5.3 (4–9)	5.2 (4–9)
Aldosterone—pg/mL	65 (33–127)	63 (30–132)
hsCRP—mg/L	2.1 (1–5)	2.0 (1–5)
High-sensitivity Troponin T—ng/L	22 (15–31)	22 (14–30)
IL-6—ng/mL	2.7 (2–5)	2.7 (2–5)
ST2—ng/L	25 (19–33)	25 (19–33)
GDF15—ng/L	290 (198–469)	283 (196–454)
PICP/ICTP ratio	15 (9–26)	15 (9–27)
Baseline medication—no. (%)		
ACE inhibitor or ARB	225 (94)	200 (94)
Aldosterone antagonist	116 (48)	105 (49)
Beta-blocker	201 (84)	181 (85)
Diuretic	170 (71)	152 (71)
Statin	142 (59)	120 (56)

[a]ECG core laboratory.
[b]Echo core laboratory.
± values are mean ± SD. ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range; NYHA, New York Heart Association.

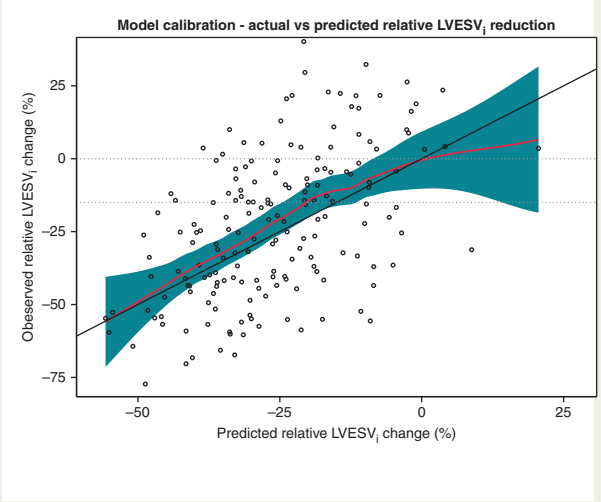

Figure 1 Scatter plot of actual vs. predicted relative reduction of $LVESV_i$. The diagonal black line is the line of equality. The red curve and blue band are a LOESS fit with 95% confidence band.

Echocardiographic outcome at 6 months

For 213 patients paired $LVESV_i$ measurements were available. At 6 months $LVESV_i$ was reduced from 75 ± 31 mL/m^2 at baseline to 58 ± 31 mL/m^2 (relative reduction 22 ± 25%). In total, 130 patients (61%) had a reduction ≥ 15% of $LVESV_i$. Unadjusted associations of each individual marker with $LVESV_i$ reduction are reported in Supplementary material online, *Table S1*. A multivariable model was built using backward selection of all markers except JTc with a significant unadjusted association (*Table 2*). The final model included the following independent markers: age, QRS_{AREA}, interventricular mechanical delay, and apical rocking. Advancing age was inversely related with $LVESV_i$ reduction. The other three markers, one electro- and two echocardiographic markers, were positively related with $LVESV_i$ reduction; larger QRS_{AREA} and longer interventricular mechanical delay, and presence of apical rocking were associated with larger LV reverse remodelling.

LVESVi response score

The final model calibration is illustrated by *Figure 1*. Based on the significant markers in the multivariable model we constructed the CAVIAR (CRT-Age-Vectorcardiographic QRS area-Interventricular mechanical delay-Apical Rocking) scoring system for $LVESV_i$ reduction with CRT (*Table 3*). The CAVIAR predicted and average actual change of $LVESV_i$ are shown in *Table 4*. *Figure 2* illustrates how the response score predicts reverse remodelling in selected subgroups. Shown is the percentwise relative change of $LVESV_i$ that corresponds to a one point increase on the response score. Only female gender was associated with more reverse remodelling at comparable CAVIAR scores.

Figure 3 illustrates that QRS_{AREA} predicted $LVESV_i$ change better than QRS duration. Comparing a model for $LVESV_i$ reduction including QRS duration and QRS morphology to a model including QRS duration, QRS morphology and QRS area, the likelihood ratio (LR) test for comparison has a chi-square value of 25.1 ($P < 0.0001$), indicating that the QRS area adds significantly to just QRS duration and morphology. Similarly for the incidence of all-cause mortality and hospitalization for worsening heart failure, the LR chi-square is 10.6 (*P*-value of 0.0011).

Table 2 Univariable and multivariable prediction of $LVESV_i$ reduction

Covariate biomarker		Unadjusted models			Multivariable model		
Marker	**Patients with paired $LVESV_i$ (n = 213)—no(%)**	**Effect estimate[a]**	**95% CI**	***P*-value**	**Effect estimate[a]**	**95% CI**	***P*-value**
Female gender	81 (38)	-12.2%	(-20.1%, -3.7%)	0.006			
Age	66 ± 10	5.7%	(1.1%, 10.7%)	0.016	4.6%	(0.1%, 9.3%)	0.043
Ischaemic cardiomyopathy	90 (42)	25.8%	(15.3%, 37.3%)	<0.0001			
NYHA class (I/II)	134 (63)	-12.2%	(-20.0%, -3.5%)	0.007			
LBBB	129 (61)	-20.2%	(-27.1%, -12.7%)	<0.0001			
BUN—ng/mL	8 ± 4	5.6%	(0.9%, 10.5%)	0.019			
Creatinine—ng/mL	93 ± 33	6.2%	(1.5%, 11.2%)	0.009			
Galectin 3—ng/mL	18 ± 6	5.6%	(0.8%, 10.5%)	0.021			
ST2	28 ± 13	7.4%	(2.5%, 12.5%)	0.003			
PQ interval—ms	192 ± 37	6.1%	(1.3%, 11.1%)	0.012			
JTc interval—ms	368 ± 42	5.6%	(0.8%, 10.5%)	0.020			
STV QT—ms	0.79 ± 0.35	5.2%	(0.3%, 10.3%)	0.038			
QRS_{AREA}—μVs	136 ± 47	-13.9%	(-17.7%, -9.8%)	<0.0001	-10.4%	(-14.9%, -5.8%)	<0.0001
T wave area—μVs	93 ± 36	-11.2%	(-15.5%, -6.6%)	<0.0001			
Inter-ventricular mechanical delay—ms	47 ± 29	-12.1%	(-15.9%, -8.1%)	<0.0001	-5.5%	(-10.2%, -0.7%)	0.026
Apical rocking	135 (63%)	-19.6%	(-26.5%, -12.0%)	<0.0001	-11.8%	(-19.8%, -2.9%)	0.010
Septal flash	102 (48%)	-18.0%	(-25.3%, -10.0%)	<0.0001			

[a]Effect Estimate for continuous variables is for 1 SD change. For example, for age the SD is 10 years and the effect estimate is 4.6%, which means that a patient who is 10 years older had on average 4.6% increase of $LVESV_i$ (i.e. less reverse remodelling).

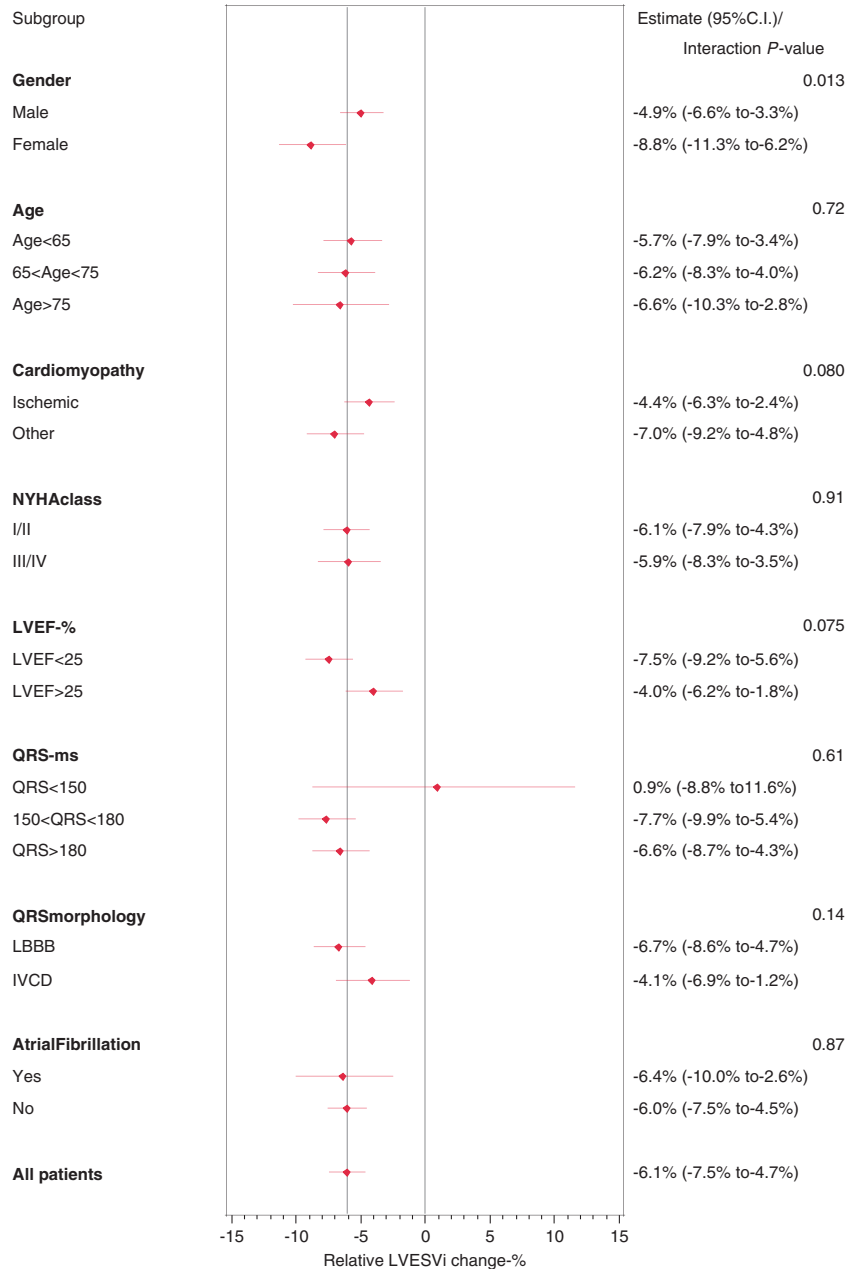

Figure 2 Forest plot for predicted difference in relative $LVESV_i$ change corresponding to a one point increase of the response score, according to pre-specified subgroups. The right side shows predicted difference and CI, and interaction *P*-values.

Relation of reverse remodelling at 6-months and cardiovascular events

During 1-year follow-up, 11 deaths and 29 hospitalizations for worsening heart failure occurred in 23 patients. Ten patients had an event after the 6-month visit. Cox regression analysis identified a significant relation between reverse LV remodelling at 6 months and the post-6 months incidence of combined endpoint of all-cause death or hospitalization for worsening heart failure ($P = 0.0083$). A higher CAVIAR score was significantly associated with lower incidence of the combined endpoint (hazard ratio 0.72; 95% CI 0.59–0.87; $P = 0.0006$). In *Figure 4*, the Kaplan-Meier estimates are depicted for the incidence of the combined endpoint, according to CAVIAR score tertiles (score -2 to 1, 2–4, and 5–9).

Table 3 Response score for factors associated with $LVESV_i$ reduction

Variable	Value range	Score
Age—year	<60	1
	60–74	0
	≥75	-1
Vectorcardiographic QRS_{AREA}—μVs	<80	-2
	80–99	-1
	100–119	0
	120–139	1
	140–159	2
	160–179	2
	180–199	3
	200–219	4
	≥220	5
Inter-ventricular mechanical delay—ms	<15	-1
	15–44	0
	45–74	1
	≥75	2
Apical Rocking	Absent	0
	Present	2

The CAVIAR (CRT-Age-Vectorcardiographic QRS area-Interventricular mechanical delay-Apical Rocking) score is the sum of the applicable values in column 'Score' with minimum -2 and maximum 9.

Table 4 Predicted and average actual change of $LVESV_i$ assigned to the response score

Response score	Patients —*n* (%)	Predicted $LVESV_i$ change—%	Average actual $LVESV_i$ change—%
-2	12 (7)	-1.3	-5.3
-1	14 (8)	-7.1	-14.9
0	15 (8)	-12.5	8.2
1	19 (11)	-17.6	-12.9
2	18 (10)	-22.4	-19.6
3	23 (13)	-26.9	-22.5
4	20 (11)	-31.2	-32.3
5	19 (11)	-35.2	-29.6
6	15 (8)	-38.9	-36.1
7	9 (5)	-42.5	-46.9
8	6 (3)	-45.8	-45.6
9	7 (4)	-49.0	-47.4

Discussion

This prospective study was primarily designed to determine markers for response in patients with a guideline indication for CRT. Independent predictors of response were younger age, larger QRS_{AREA}, longer interventricular mechanical delay and presence of apical rocking, all represented in the CAVIAR score. QRS morphology and duration, and several blood biomarkers were predictors in univariate analysis but did not add to the response prediction score after multivariate analysis. Interestingly, of all biomarkers tested, relatively simple biomarkers remain to compose the CAVIAR score, which facilitates the clinical use of this score.

In contrast to earlier studies, we analysed reverse ventricular remodelling on a continuous scale to derive a reliable and easy-to-use response score. Over the entire patient cohort, 61% response was observed when assessing the usual cut off for response, reduction of ≥ 15% of $LVESV_i$. This percentage is consistent with earlier data.[4] Using the continuous scale, we found younger age, larger QRS_{AREA} derived from VCG and two echocardiographic dyssynchrony parameters (longer IVMD and presence of apical rocking) independently predicting response to CRT. Young age <60 years was associated with a beneficial outcome whereas age >75 years showed the opposite. The relevance of age for response is not well established but has been identified before.[16,17]

A larger QRS_{AREA} was also independently associated with a larger benefit of CRT. This is in accordance with data of a smaller study in 81 CRT candidates where QRS_{AREA} was found to be a stronger predictor of CRT response (≥15% LVESV reduction) than QRS morphology or QRS duration.[18] The strong association of 3D vectorcardiographic derived QRS_{AREA} and CRT response may be explained by the fact that it shows the extent of unopposed electrical forces generated within the heart during ventricular depolarization, representing the direction as well as the delay of electrical activation. *Figure 5* shows that QRS_{AREA} incorporates both QRS duration and core lab judged QRS morphology but the variability shows that there are unexplained other factors influencing this parameter. One of these parameters may be scar as QRS_{AREA} appears to be larger in non-ischaemic heart failure patients.[18] QRS_{AREA} could therefore be a more comprehensive marker of the electrical substrate amendable to CRT than conventional ECG markers. This was supported by observations in an invasive electro-anatomic mapping study during CRT implantation in which patients with a large QRS_{AREA} had a significantly more delayed activation of the LV posterolateral wall.[19] The advantage of QRS_{AREA} compared with conventional ECG markers is that this parameter is observer-independent and represented in a quantitative manner, while as opposed to QRS-morphology indices (LBBB, IVCD) it is objectively determined and is a continuous variable. QRS_{AREA} predicts reduction of $LVESV_i$ independent of QRS morphology (Supplementary material online, *Figure S3*). Of importance for clinical use of the CAVIAR response score, the 3D vectorcardiogram can be constructed by commercially available ECG machines, and QRS_{AREA} calculation can be automated using the inverse Dower or Kors' regression transformation.[20]

The strong association of two echocardiographic dyssynchrony parameters, IVMD as measure of *inter*ventricular dyssynchrony and apical rocking as marker of *intra*ventricular dyssynchrony, is not surprising. IVMD was one of the first parameters being associated with response to CRT but prospective studies were disappointing.[5,13] However, of all echocardiographic dyssynchrony markers, IVMD showed the lowest inter- and intraobserver variability.[13] Apical rocking is a less-investigated marker predicting CRT response.[15] Apical rocking was a stronger predictor than septal flash as the latter parameter is more easily underreported. Our study now identifies both an *inter*ventricular and an *intra*ventricular dyssynchrony parameter independently predicting reverse remodelling.

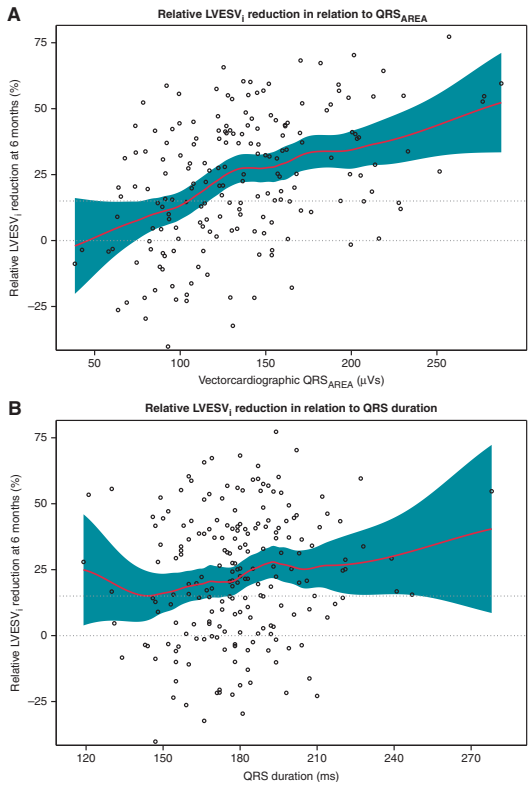

Figure 3 Scatter plot of reduction in LVESV$_i$ and QRS$_{AREA}$ (*A*) or QRS duration (*B*). The red curve and blue band are a LOESS fit with 95% confidence band.

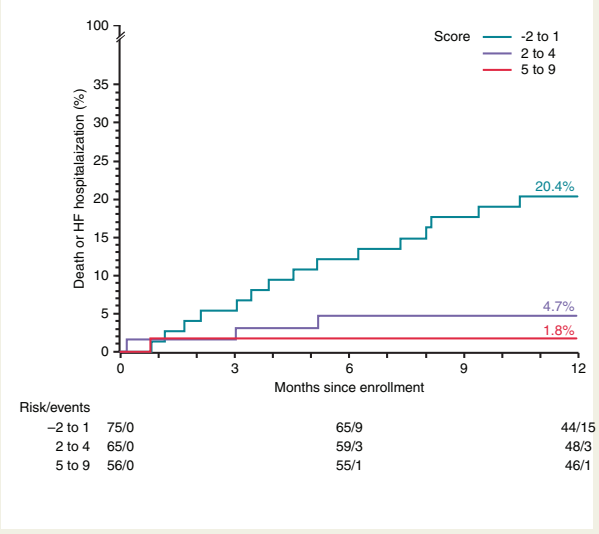

Figure 4 Kaplan-Meier estimates for the incidence of the combined endpoint of all-cause death and hospitalization for worsening heart failure, for patients grouped by response score tertile. A lower score is associated with a significantly increased event incidence ($P = 0.0006$ with score as a continuous variable).

Non-ischaemic cardiomyopathy, QRS duration and morphology and blood biomarkers did not significantly improve the predictive value of the CAVIAR response score. This may relate to the fact that these parameters are adequately reflected by age, VCG, and echocardiography. Additionally, only few patients in our study had QRS duration <150 ms and the relation between QRS duration and CRT response flattens for higher QRS duration values.[10] The magnitude of remodelling predicted by the CAVIAR score in females exceeds that in males, as is demonstrated in *Figure 2*. The higher success rate in females has been described before.[2] The mechanism of better response in women is still unknown and will be investigated in the BioWomen study (NCT02344420).

LBBB was a significant predictor of CRT benefit in the univariate analysis, but it disappeared in the multivariate analysis due to the stronger predictive power of QRS$_{AREA}$ which is correlated with LBBB, as illustrated in *Figure 5*.[18] Another problem with LBBB is that it is subjectively assessed and that there are multiple definitions used, even between clinical trials.[5] This is also highlighted in our study cohort with 87% investigator-reported vs. 57% core-lab reported study patients had LBBB (*Table 1*).

An advantage of our continuous response scale is that reverse remodelling in the individual patient can be compared with the predicted value which could trigger additional efforts to improve response.[8] This also holds for patients in whom super-response, defined as a decrease of LVESV$_i$ > 30%, is predicted by a CAVIAR score of 4 or more.

Clinical events such as all-cause mortality and heart failure hospitalizations have been correlated with reverse ventricular remodelling in earlier cohorts.[9] The CAVIAR score predicts the occurrence of these events with <2% adverse clinical events in the first year in super-responders with a CAVIAR score >4 and more than 20% events if CAVIAR is <2 (*Figure 4*).

Strength and limitations

The strength of our study is the homogenous group of patients included in only six centres and analyses of our data in core labs with specific expertise in respective areas. Another strength is the large number of biomarkers assessed to find the response score. This allows weighing the predictive value and statistically assessing the relationship between some of the biomarkers. Patients were included according to the most recent ESC guidelines[11] and were comparable to those included in other CRT trials. We excluded patients with a right bundle branch block because previous data showed a low response rate in these patients. Furthermore, we excluded patients with permanent AF and AF at baseline to avoid inadequate biventricular pacing. Follow-up was excellent with paired echocardiographic studies available in 213 of 240 (89%) patients. Since AF often leads to inadequate biventricular stimulation, especially in patients without AV block, we designed strict inclusion criteria permitting inclusion only patients without recent AF. This precluded interference of AF during biventricular pacing in almost all patients. AHRE of more than 1 month were recorded in only two patients.

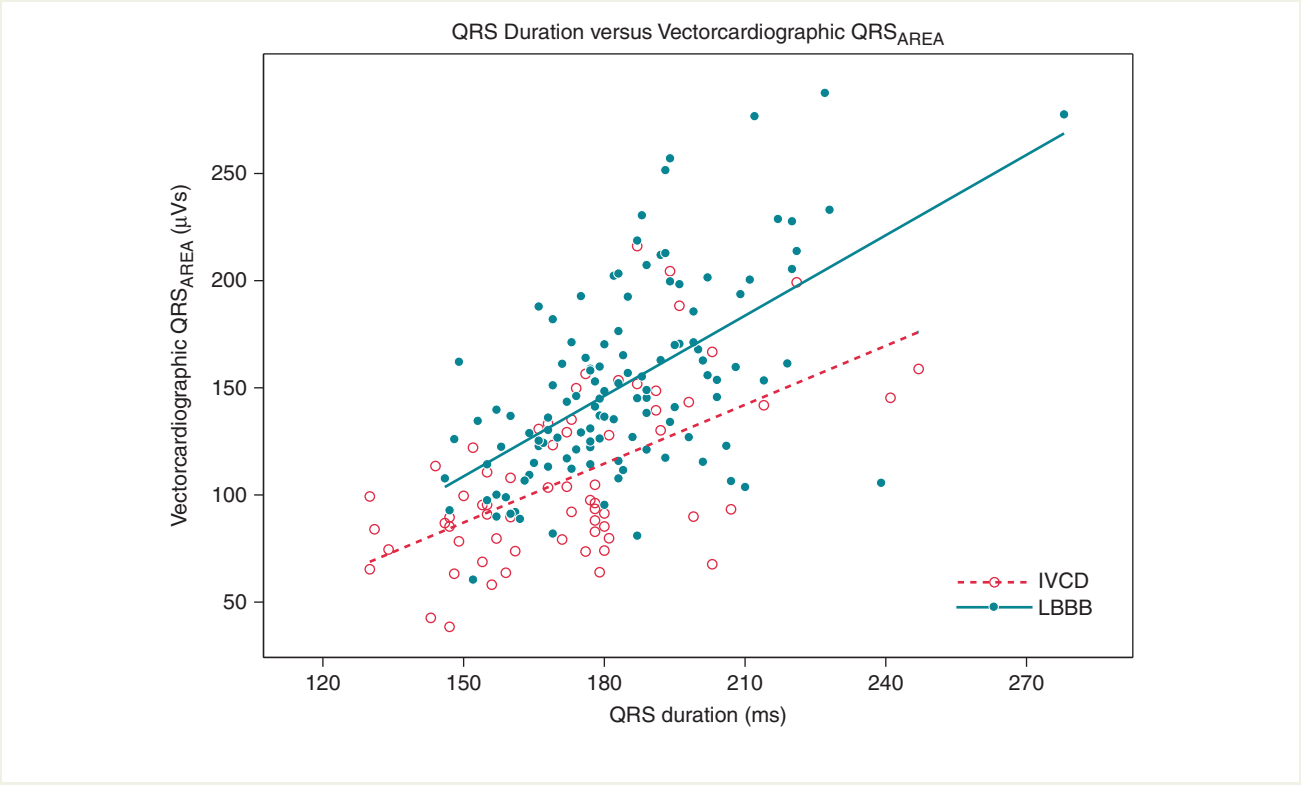

Figure 5 Relation between QRS_{AREA} derived from VCG and QRS duration on standard 12 lead ECG. Full blue dots are patients with core lab judged LBBB and empty red dots patients with non-specific intraventricular conduction delay (IVCD).

Limitations are the relatively small number of patients as compared with the landmark trials. Our response score has not yet been replicated in a different cohort. Furthermore, we did not systematically study the effects of scar burden on CRT response as cardiac magnetic resonance imaging was performed in only a subset of patients. Optimization of AV and interventricular delays was not uniform in all centres and we cannot exclude that this had an effect on the presented results. We included a majority of patients in functional class NYHA II. Therefore, our data may not apply for patients with severe heart failure.

Clinical implications

Of importance for clinical use of the CAVIAR response score, the three parameters needed to calculate CAVIAR require relatively standard echocardiography and ECG. Apical rocking can be assessed from regular B-mode echo and IVMD from Doppler ultrasound measurements of pulmonary and aortic valve opening times, the 3D vectorcardiogram can be constructed by commercially available ECG machines, and QRS_{AREA} calculation can be automated using the inverse Dower or Kors' regression transformation. Therefore, all tools required to determine a patients' CAVIAR score are clinically available.

Conclusion

In this prospective study, specifically designed to study markers of response to CRT from multiple domains, we identified lower age, larger QRS area, longer interventricular mechanical delay, and presence of apical rocking as independent predictors of response, all represented in the CAVIAR response score. This score can be used both to identify candidates for CRT and predict the amount of ventricular reverse remodelling, as well as to validate the achieved reverse remodelling after CRT to recognize patients with suboptimally delivered CRT, who may benefit from additional optimization.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: A.H.M reports lecture fees from Medtronic and LivaNova. K.V. reports consultancy for Medtronic; research grants from Medtronic; speaker fees from St. Jude Medical. F.P. reports Research grants from Medtronic, St Jude Medical, Biotronik, Sorin, Biosense Webster, EBR Systems and is a member on the Medtronic Advisory Board. B.G. reports salary and shares of Medtronic. C.S. reports salary from Medtronic. M.H. reports salary and shares of Medtronic. M.A.V. reports funding from CTMM COHFAR, CVON Predict, EU TrigTreat, EU CERT_ICD and GiLead to perform (pre)clinical studies.

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