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ORIGINAL ARTICLE

Determinants of left ventricular function improvement for cardiac resynchronization therapy candidates

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Abstract

Aims A waiting period of more than 3 months is recommended for patients before undergoing cardiac resynchronization therapy (CRT). However, due to an anticipated high mortality rate, early implementation of CRT might be beneficial for some patients. We aimed to evaluate the rate and the probability of left ventricular (LV) function improvement and their predictors in patients with heart failure (HF) with indications for CRT.

Methods and results From March 2011 to February 2014, a total of 5625 hospitalized patients for acute HF were consecutively enrolled in 10 tertiary hospitals. Among them, we analysed 1792 patients (mean age 63.96 ± 15.42 years, female 63.1%) with left ventricular ejection fraction (LVEF) $\leq$ 35% at the baseline echocardiography and divided them into three groups: 144 with left bundle branch block (LBBB), 136 with wide QRS complexes without LBBB, and 1512 not having these findings (control). We compared and analysed these three groups for improvement of LV function at follow-up echocardiography. In patients who met CRT indications (patients with LBBB or wide QRS complexes without LBBB), logistic regression was performed to identify risk factors for no improvement of LV. No improvement of LV was defined as LVEF $\leq$ 35% at follow-up echocardiography or the composite adverse outcomes: death, heart transplantation, extracorporeal membrane oxygenation, or use of a ventricular assist device before follow-up echocardiography. A classification tree was established using the binary recursive partitioning method to predict the outcome of patients who met CRT indications. In a median follow-up of 11 months, LVEF improvement was observed in 24.3%, 15.4%, and 40.5% of patients with LBBB, wide QRS complexes without LBBB, and control, respectively. Patients meeting CRT indications had higher 3 month mortality rates than the control (24.6% vs. 17.7%, P = 0.002). Multivariable logistic regression analysis revealed that large LV end-systolic dimension [odds ratio (OR) 1.10, 95% confidence interval (CI) 1.05–1.15, $P < 0.001$], low LVEF (OR 0.92, 95% CI 0.87–0.98, P = 0.006), diabetes requiring insulin (OR 6.49, 95% CI 2.53–19.33, $P < 0.001$), and suboptimal medical therapy (OR 6.85, 95% CI 3.21–15.87, $P < 0.001$) were significant factors predictive of no improvement. A decision tree analysis was consistent with these results.

Conclusions Patients with CRT indications had higher mortality during their follow-up compared with control. LV function improvement was rare in this population, especially when they had some risk factors. These results suggest that the uniform waiting period before CRT implantation could be reconsidered and individualized.

Keywords Heart failure; Reduced ejection fraction; Cardiac resynchronization therapy; Waiting period

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Introduction

Cardiac resynchronization therapy (CRT) is an effective therapeutic option for patients with heart failure (HF) with a reduced ejection fraction (EF) (≤35%) and a wide QRS complex. Studies have reported that CRT improves symptoms,[1–3] reduce death from any cause, and decrease unplanned hospitalization for major cardiovascular events[4,5] in patients with symptomatic HF, impaired left ventricular (LV) function, and a wide QRS complex. However, even when a patient with HF has been found to have appropriate indications for CRT, a waiting period of more than 3 months with optimal medical therapy (OMT) before CRT implantation is generally recommended.[6,7] During this period, OMT should be provided and correctable causes of illness should be treated to improve LV function.[8–10] However, during the first few months following the index hospitalization, the rate of rehospitalization and mortality due to aggravation of HF are relatively high.[11–13] In addition, OMT is not always possible due to low blood pressure, marginal kidney function, or other causes.[14] Furthermore, a recent retrospective cohort study described left bundle branch block (LBBB) is associated with a smaller chance of LVEF improvement than other QRS morphologies, even with OMT.[15]

Therefore, it might be advantageous to individualize the waiting time before performing CRT by considering the likelihood of LV systolic function recovery and the risk of an adverse outcome. In the present study, we compared the rate of adverse outcomes and LV function improvement following medical therapy in patients with severe LV dysfunction based on QRS duration and morphology. We then identified the predictors associated with impaired recovery of LV function or with the occurrence of adverse events in patients initially meeting the criteria for CRT. Finally, we developed a decision-making tree for selecting patients who could receive CRT earlier, without waiting for 3 months, to improve symptoms and decrease HF events.

Methods

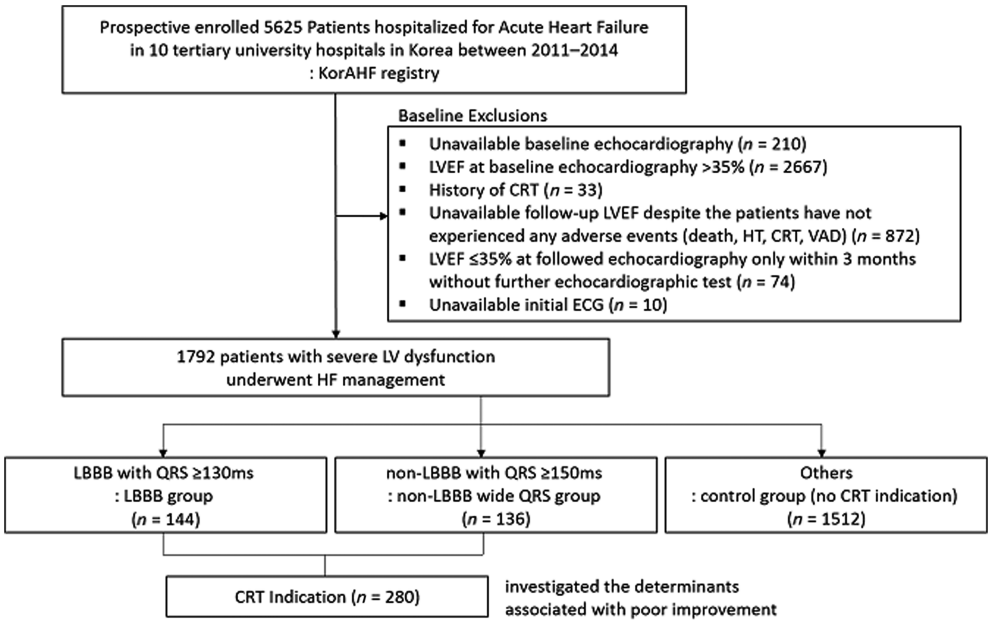
Study population and data collection

The study population was selected from the Korean Acute Heart Failure (KorAHF) registry, a prospective multicentre cohort study. Patients hospitalized for acute HF from 10 tertiary university hospitals throughout the country were enrolled from March 2011 to February 2014 (NCT01389843). The demographic characteristics, comorbidities, clinical presentation, medical history, laboratory tests, electrocardiographic findings, transthoracic echocardiographic findings, additional treatments, and outcomes of the patients were collected at admission and during the follow-up period. Follow-up echocardiography was encouraged at 12 months after discharge, but if it was necessary to determine the patient's treatment during follow-up, the echocardiography could proceed before the 12 month period based on the physician's discretion. Detailed information of the study design and its results have been previously reported.[16,17] Among the patients enrolled in the KorAHF registry, those who met the following criteria were excluded in this analysis: (i) left ventricular ejection fraction (LVEF) unknown or >35% as assessed by echocardiography at registration, (ii) those who had already received CRT, (iii) follow-up LVEF data were unavailable despite the patient not having experienced any adverse event during the follow-up period, (iv) patients whose LVEF was ≤35% at follow-up echocardiography within 3 months, who had no further echocardiographic testing, and (v) patients who did not have an initial electrocardiogram (ECG) (*Figure 1*). The study protocol was approved by the ethics committee/institutional review board (IRB) of each hospital. Written informed consent was obtained from each patient in advance during this study; however, the IRBs of each hospital waived the requirement for informed consent as this study presented minimal risk for patients and was initiated and sponsored by the Korean Ministry of Health and Welfare to improve public health.

Study design, variables, and statistical analysis

The study population included the following three groups based on QRS duration and morphology on the ECG: (i) patients with LBBB and QRS duration ≥ 130 ms (LBBB group), (ii) patients with QRS duration ≥ 150 ms without LBBB (non-LBBB wide QRS group), and (iii) patients without either of these features (control group–no CRT indication). The degree of improvement of LV function (LVEF > 35%) and the mean change in LVEF were compared among the three groups. Among patients who met CRT indications except for the 3 month waiting period (LBBB group and non-LBBB wide QRS group), we analysed the determinants of adverse outcomes and lack of improvement of LVEF (follow-up LVEF ≤ 35% or receiving CRT implantation) after 3 months of medical treatment. OMT was defined as a prescription consisting of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Although most patients included in this study were treated by HF specialists and significant attempts were made to ensure that patients received OMT, some patients underutilized HF medications due to those own adverse effects; for BBs, the common adverse effects were hypotension, orthostatic hypotension, and bradycardia while ARBs or ACEIs were not tolerated because of hypotension, aggravation of renal insufficiency, and electrolyte imbalance. Adverse outcomes were defined as death, heart transplantation, extracorporeal membrane oxygenation (ECMO), or use of a ventricular assist device.

Figure 1 Flow diagram of the study population. CRT, cardiac resynchronization therapy; ECG, electrocardiogram; HF, heart failure; HT, heart transplantation; KorAHF, Korean Acute Heart Failure; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; VAD, ventricular assist device.



Continuous variables were compared by ANOVA and presented as mean ± standard deviation. Categorical variables were compared using the χ^2 test and presented as percentages. The time to all-cause mortality at 1 year according to CRT indication was estimated and plotted on a Kaplan–Meier curve. Univariable binary logistic regression analysis was used to determine significant factors associated with adverse outcomes or lack of improvement of LV function. A total of 26 variables, including demographics, clinical presentation, and laboratory findings, were included in this analysis (Supporting Information, *Table S1*). Variables with a significance of $P < 0.100$ in the univariable analysis were included in a multivariable logistic regression model using backward stepwise election method. Left ventricular end-diastolic dimension (LVEDD) was excluded from the candidate variables in the multivariable analysis due to multicollinearity. Statistical analysis was performed using the SAS statistical software, Version 9.4 (SAS Institute, Cary, NC, USA). A classification tree was established using the binary recursive partitioning method to predict the outcome of patients who met CRT indications at presentation. This analysis was performed using the rpart package in R (Version 3.5.2). The model was adjusted to avoid overfitting, that is, creating a tree that matched the peculiarities of this particular data set too closely. The tree was validated internally using 10-fold cross-validation to estimate the best splits. Statistical analyses were conducted by the Center for Medical Research and Information in Asan Medical Center.

Results

Baseline characteristics and clinical presentations of the study population

Among 5625 consecutive patients enrolled prospectively in the KorAHF registry, 2748 patients were identified with LVEF $\leq$ 35% at baseline echocardiography. An initial ECG was not available in 10 patients, 872 did not have follow-up echocardiography, and 74 continued to have an LVEF $\leq$ 35% at follow-up echocardiography within 3 months of enrolment and did not undergo any further echocardiographic testing. Thus, the remaining 1792 patients were included for analysis (*Figure 1*), among whom 144 had LBBB with QRS $\geq$ 130 ms (LBBB group), 136 had a wide QRS complex ($\geq$150 ms) without LBBB (non-LBBB wide QRS group), and 1512 had neither finding (control group–no indication for CRT). Baseline characteristics were similar among the three groups, except that the LBBB group had older aged patients, greater percentage of females, and less incidence of atrial fibrillation. Those in the non-LBBB wide QRS group were predominantly male and had less de novo HF, lower blood pressure, higher rate of parenteral inotrope use during baseline hospitalization, and lower serum sodium levels. Patients in the control group, with no CRT indication, had a higher rate of de novo HF and a lower rate of parenteral inotrope use. The control group had the highest proportion of patients who received OMT consisting of BBs, ACEIs, or ARBs, followed by the LBBB group (*Table 1*).

Table 1 Baseline characteristics of the study population

	LBBB (n = 144)	Non-LBBB wide QRS (n = 136)	Control (n = 1512)	P value
Age	71.3 ± 11.8	64.3 ± 13.6	63.2 ± 15.7	<0.001
Male	65 (45.1)	98 (72.1)	968 (64.0)	<0.001
Body mass index	22.7 ± 3.6	23.0 ± 3.2	23.3 ± 4.0	0.137
De novo heart failure	56 (38.9)	27 (19.9)	836 (55.3)	<0.001
Past medical history				
Hypertension	82 (56.9)	68 (50.0)	828 (54.8)	0.473
Diabetes	67 (46.5)	55 (40.4)	606 (40.1)	0.322
Diabetes requiring insulin	36 (25.0)	39 (28.7)	369 (24.4)	0.542
Ischaemic heart disease	41 (28.5)	37 (27.2)	515 (34.1)	0.125
Atrial fibrillation	42 (29.2)	65 (47.8)	582 (38.5)	0.006
COPD	18 (12.5)	19 (14.0)	147 (9.7)	0.193
Stroke	16 (11.1)	21 (15.4)	183 (12.1)	0.475
Clinical findings				
Systolic blood pressure	126.2 ± 27.0	113.1 ± 26.3	125.5 ± 28.1	<0.001
Lung congestion	114 (79.2)	102 (75.0)	1207 (79.8)	0.410
NYHA Fc III, IV	128 (88.9)	122 (89.7)	1299 (85.9)	0.312
Mechanical ventilator support	28 (19.4)	28 (20.6)	285 (18.8)	0.877
Parenteral inotropes	68 (47.2)	74 (54.4)	636 (42.1)	0.013
ECG				
QRS duration	159.5 ± 18.7	174.2 ± 27.2	102.2 ± 17.7	<0.001
Medication				
ACEI	77 (53.5)	61 (44.9)	805 (53.2)	0.168
ARB	69 (47.9)	59 (43.4)	740 (48.9)	0.458
BB	92 (63.9)	75 (55.1)	1048 (69.3)	0.002
AA	96 (66.7)	103 (75.7)	994 (65.7)	0.061
OMT[a]	83 (57.6)	67 (49.3)	954 (63.1)	0.004
Laboratory findings				
Serum sodium	137.0 ± 4.9	135.5 ± 5.4	137.4 ± 4.8	<0.001
Plasma haemoglobin	12.5 ± 2.0	12.8 ± 2.0	12.9 ± 2.3	0.061
Serum creatinine	1.50 ± 1.14	1.70 ± 1.50	1.48 ± 1.50	0.271

AA, aldosterone antagonist; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; LBBB, left bundle branch block; NYHA Fc, New York Heart Association functional class; OMT, optimal medical therapy.
Percentage in parentheses.
[a]ACEI/ARB + BB.

Table 2 Change in echocardiographic findings from baseline to follow-up

	LBBB (n = 144)	Non-LBBB wide QRS (n = 136)	Control (n = 1512)	P value
Baseline				
LVEF	23.3 ± 6.3	23.1 ± 7.0	24.6 ± 6.6	0.004
LVEDD	64.9 ± 9.0	65.5 ± 9.8	62.2 ± 9.1	<0.001
LVESD	56.2 ± 9.7	56.8 ± 10.3	53.4 ± 9.6	<0.001
LA dimension	46.7 ± 8.9	50.3 ± 8.7	47.4 ± 8.9	0.001
Follow-up				
LVEF	33.0 ± 13.4	38.2 ± 17.3	39.5 ± 14.8	<0.001
LVEDD	60.4 ± 10.8	59.9 ± 13.6	57.7 ± 10.0	0.005
LVESD	49.6 ± 13.5	47.8 ± 16.8	44.9 ± 12.3	<0.001
LA dimension	43.4 ± 8.8	48.0 ± 8.0	44.1 ± 8.7	0.001
No improvement in LV function	109 (75.7)	115 (84.6)	900 (59.5)	<0.001
Change in LVEF	9.3 ± 13.4	14.1 ± 17.3	14.7 ± 15.2	<0.001

LA, left atrial; LBBB, left bundle branch block; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension.
Percentage in parentheses.

Comparison of echocardiographic findings related to left ventricular improvement among the groups

During the median follow-up of 11 months, all the three groups showed increased LVEF and decreased LVEDD, LV end-systolic dimension (LVESD), and left atrial (LA) diameter on the follow-up echocardiography compared with those at baseline (*Table 2*). Along with the decrease in chamber sizes, the LVEF was increased. However, in the LBBB and non-LBBB wide QRS groups, only 24.3% and 15.4% of patients showed improvement, respectively, compared with 40.5% in the con-

trol group (*Figure 2*). The mean change in LVEF were 9.3%, 14.1%, and 14.7% in each group, respectively (*Figure 3*, $P < 0.001$). When we performed an additional analysis of patients with de novo HF using stricter inclusion criteria, the results were relatively consistent with those of this study population. Among the 1792 patients, 919 had de novo HF: 56 with LBBB, 27 with a wide QRS complex without LBBB, and 836 without these findings. LV improvement was observed in 33.9%, 22.2%, and 54.1%, respectively ($P < 0.001$) (Supporting Information, *Table S2*).

Clinical outcomes and determinants of impaired left ventricular function recovery

Patients who met the CRT indications (LBBB and non-LBBB wide QRS groups) had a significantly higher mortality rate

Figure 2 The rate at which function improved in each group. LBBB, left bundle branch block.

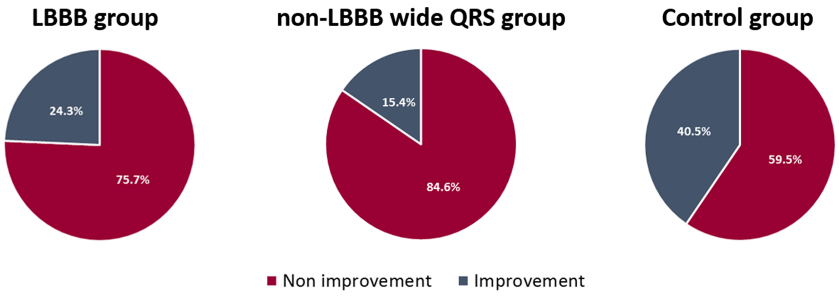


Figure 3 Change in mean left ventricular ejection fraction (LVEF) from baseline to follow-up. LBBB, left bundle branch block.

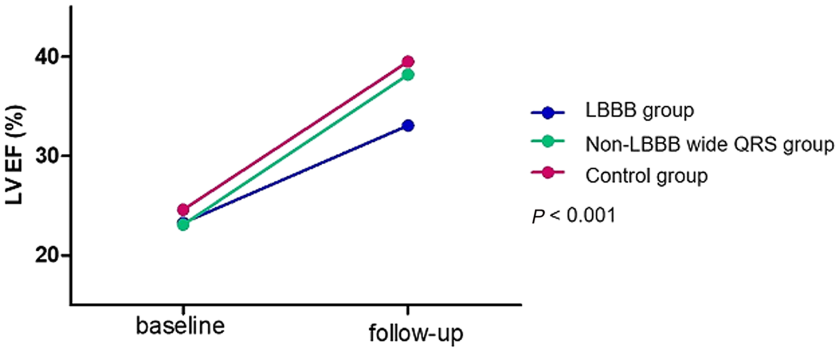
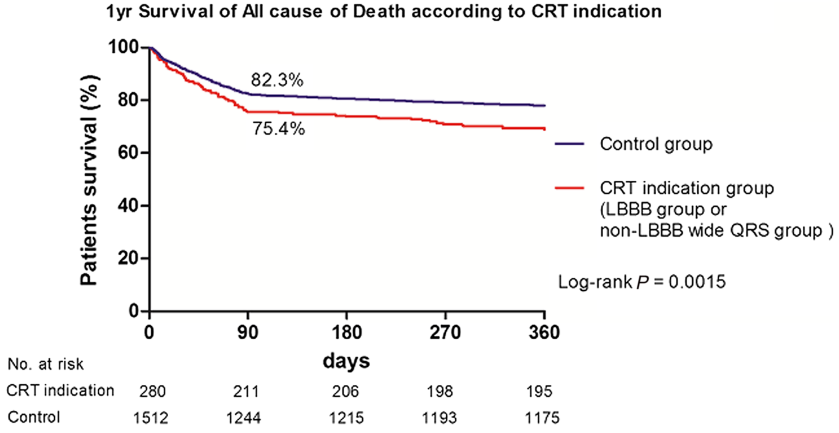


Figure 4 Kaplan–Meier estimate of all-cause mortality according to cardiac resynchronization therapy (CRT) indication. LBBB, left bundle branch block.



than those without CRT indications (24.6% vs. 17.7%, P = 0.002, *Figure 4*). In particular, the majority of deaths occurred within the first 90 days after hospitalization, the recommended waiting period for CRT.

In the univariable logistic regression analysis, the following 11 factors were significantly associated with adverse outcomes and lack of improvement of LVEF: the group, systolic blood pressure, de novo HF, serum sodium level, diabetes requiring insulin use, LVEDD, LVESD, LVEF, and LA diameters, appropriate OMT, use of parenteral inotropes, and mechanical ventilator support during the index hospital admission (Supporting Information, *Table S1*). In the multivariable logistic regression model, LVESD [odds ratio (OR) 1.10, 95% confidence interval (CI) 1.05–1.15, $P < 0.001$], LVEF (OR 0.92, 95% CI 0.87–0.98, P = 0.006), diabetes requiring insulin (OR 6.49, 95% CI 2.53–19.33, $P < 0.001$), and suboptimal medical therapy (OR 6.85, 95% CI 3.21–15.87, $P < 0.001$) were significantly associated with adverse outcomes and lack of improvement of LV function (*Table 3*).

The classification and regression tree (CART) model for identifying the parameters associated with adverse outcomes and lack of improvement in LV function divided the study population into four different subgroups through three nodes as follows: LVEF (≥30.87%) at baseline, LA diameter < 56.6 mm, and under OMT or not (*Figure 5*). An LVEF value < 30.87% at baseline was identified as the first discriminator of adverse outcomes and lack of improvement. In patients with an EF ≥ 30.87%, LA diameter < 56.5 mm was found to be a useful discriminator. Patients with LVEF ≥ 30.87% with an LA diameter ≥ 56.5 mm had the least chance of improvement (0%), followed by those with LVEF < 30.87% (15%) and LVEF ≥ 30.87% with an LA diameter < 56.5 mm but not under treatment with ACEIs/ARBs and BBs (28.6%). Those who had an LVEF ≥ 30.87% with an LA diameter < 56.5 mm and were receiving ACEIs/ARBs and BBs had the highest chance of improvement (70.8%). This analysis had an accuracy of 83.6% (95% CI 78.8–87.5), a sensitivity of 96.9% (95% CI 93.7–98.5), and a specificity of 30.4% (95% CI 19.9–43.3). The area under the receiver-operating characteristic curve (AUC) of this model was 0.666 (95% CI 0.600–0.732).

Table 3 Multivariate binary logistic regression: factors related to adverse outcome or no improvement of left ventricular function in cardiac resynchronization therapy candidates

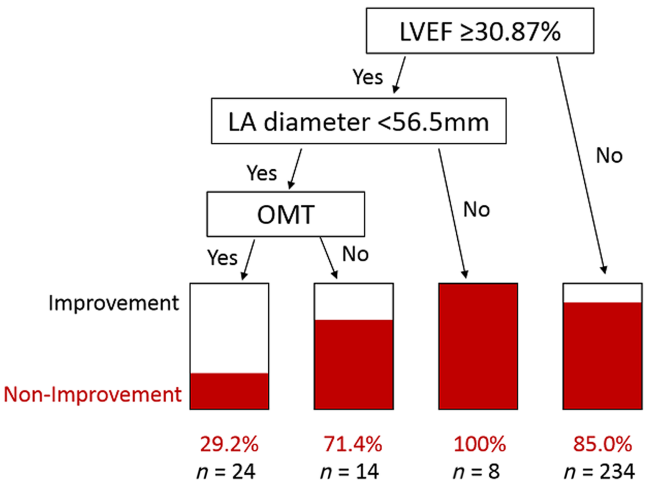
	OR	95% CI	*P* value
LVESD	1.10	1.05–1.15	<0.001
LVEF	0.92	0.87–0.98	0.006
Suboptimal medical therapy[a]	6.85	3.21–15.87	<0.001
Diabetes requiring insulin	6.49	2.53–19.33	<0.001

CI, confidence interval; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; OR, odds ratio.
[a]Not under angiotensin-converting enzyme inhibitor/angiotensin receptor blocker + beta-blocker.

Discussion

In the present study, we observed that patients with LBBB and a QRS complex ≥ 130 ms or with non-LBBB and a QRS complex ≥ 150 ms had significantly less chance of LV functional recovery compared with patients in the control group. The probability of LV improvement might differ according to the QRS morphology and duration, as the QRS complex reflects the pathological changes in LV components such as the conduction system, cardiomyopathy, and ventricular fibrosis.[18,19] Patients with an indication for CRT are more likely to experience poor LV recovery with medical treatment

Figure 5 Regression model for determining patients without improvement. LA, left atrial; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy.



alone, as it is possible that an underlying structural change of LV would have already occurred. LBBB and prolongation of the QRS complex are well-known poor prognostic factors in patients with chronic HF.[19,20] Interestingly, although 84.6% of patients in the non-LBBB wide QRS group did not experience improvement in LV function, the mean EF change was 14.1%, which was almost identical to that in the control group. This implies that although patients in the non-LBBB wide QRS group generally tend to have less improvement in LV function, in case their LV function does improve, it will likely be to a large degree. Moreover, based on the Kaplan-Meier curves plotted for all-cause mortality according to CRT indication (*Figure 4*), an increasing gap can be found in the survival rate between the CRT candidate group and the non-CRT candidate group during the first 3 months after the index hospital admission, subsequently followed by a plateau. Given these findings, we should recognize that there is a special group of patients who need to be responded early against worsening LV function in the CRT candidates. It is essential to determine which patients will not improve, even after OMT, among these groups.

The results of the multivariable logistic regression model, as well as the decision tree analysis, revealed that decreased LVEF and suboptimal medical therapy were significant factors associated with adverse outcomes and lack of improvement of LV function. The OR increased by 7% for every 1% decrease in LVEF in the multivariable regression model. This result was also supported by the CART analysis, which showed that an LVEF $<$ 30.87% was associated with an increased risk of adverse outcomes and lack of improvement of LV function during the follow-up. The importance of this finding is exemplified by the results of an individual meta-analysis of three double-blind, randomized trials that found that a lower LVEF is an independent predictor of a good early clinical response to CRT in patients with symptomatic chronic HF and reduced EF.[21] By combining these results, it can be suggested that patients with lower LVEF benefit the most from early implementation of CRT through both lowering the risk of adverse outcomes and improving HF.

Current guidelines for CRT, and previous large-scale, randomized controlled trials, have recommended prescribing OMT for at least 3 months before considering CRT implantation. This is based on evidence showing that LV function and HF could improve strictly with OMT.[6,10] However, under common clinical conditions, several patients cannot receive OMT. In a previous study on implantable cardioverter-defibrillator, only 61.1% of patients received OMT for 3 months before the initiation of device-based therapy.[14] In another registry, it was reported that only 30% of patients received OMT before CRT.[22] The majority of patients included in that study were treated by HF specialists, and significant attempts were made to ensure that patients received the maximum possible OMT. However, in our study, only 61.6% of the entire study population and 53.6% of patients for whom CRT was indicated were treated with OMT during their index hospitalization. Patients are often not able to receive treatment with these medicines due to marginal blood pressure, significant bradycardia, impaired renal function, pulmonary congestion, and other complications. They are required to spend 3 months without active interventions to improve LV function and hopefully clinical outcome, without being able to receive OMT. Consequently, the clinical status during OMT appears to be the primary determinant of adverse outcomes and lack of improvement of LV function.

Because the results of the logistic regression model are not intuitive, are difficult to apply directly in clinical practice, and do not provide a cut-off value, we adopted a CART model to help clinicians in the decision-making process in various complex situations for patients meeting the criteria for CRT. This analysis revealed that if the LVEF at baseline was $\geq$30.87% and the LA diameter was $\geq$56.5 mm, the probability of improvement was extremely low. Patients with an LVEF $<$ 30.87% or LVEF $\geq$ 30.87% with an LA diameter $<$ 56.5 mm but suboptimal medical therapy also had 15% and 29.2% probabilities of improvement, respectively. Only those whose LVEF was $\geq$30.87% with an LA diameter $<$ 56.5 mm and were undergoing OMT had a significant chance of improvement of 70.8%. These results suggest that considering an earlier CRT implementation is beneficial for patients with a lower LVEF and a higher LA diameter who could not receive OMT for whatever reason.

The patients who would benefit the most after early consideration are those who would not improve even after waiting but would respond well to CRT. Thus, the ideal predictors should identify those patients who would not improve after OMT but would be CRT responders. Studies aiming to identify discriminant factors of CRT responders continue. Among them, the CRT response markers identified in relatively early published studies, such as LBBB, QRS duration, female sex, non-ischaemic aetiology, body mass index, and age,[23,24] were not descriptive factors of LV non-improvement in our study. However, LA diameter in the CART analysis and LVESD, which had strong correlations with LVEDD on the multivariable regression in the present study, were significant factors for LV non-improvement. LA volume index[23] and LVEDD[25] were predictive factors of a response to CRT in some studies. Therefore, LA and LV size might be a good marker of early implantation of CRT who might benefit the most. Meanwhile, recent studies identified these patient groups through scoring with reproducible variables that are relatively easy to apply clinically.[26] The studies tested sophisticated echocardiographic findings associated with dyssynchrony such as septal splash, apical rocking, interventricular mechanical delay, and septal to lateral delay.[25,26] These markers would be predictors of our purpose and should be tested in future studies.

Looking for these markers for early CRT implantation and response would be more important considering that a recent

pilot study named STOP-CRT demonstrated the feasibility of neurohumoral blocker withdrawal in patients with normalized EFs after CRT.[27] Successful discontinuation of neurohumoral blockers after CRT implantation would suggest that dyssynchrony plays a major pathologic role aside from neurohumoral activation in a certain patient group. In this case, it must be preferable to correct the main culprit directly to reduce the treatment period, economic burden, and the risks of HF medication-related side effects.

Study limitation

First, this was not a randomized controlled trial specifically designed to evaluate the efficacy and safety of early CRT implementation. Therefore, we could not reach a conclusion regarding the appropriate waiting period before CRT. Moreover, we cannot rule out the possibility that confounding factors may have influenced our results. However, we believe that our analysis is still important as a stimulus for further study regarding the appropriate waiting period for CRT implementation. Second, the changes in medication during the follow-up were not reflected in this analysis. However, as there was no significant change or only a slight increase in the proportion of patients receiving OMT after discharge from HF treatment in previous reports,[28–30] this limitation may not be significant. Third, we implemented the CART model using relatively small populations, thus indicating the possibility of exaggerated or skewed results. Therefore, this model should be validated using a different cohort of patients. The AUC of this model was relatively small, but it was the most optimal model in terms of the aspect of stability. Finally, the early use of sacubitril–valsartan as an OMT has been shown to be related with better outcomes and reverse remodelling, which might affect the CRT consideration period.[31] However, this could not be evaluated in our analysis because the drug was not available at the time of registry enrolment.

Patients who met the criteria for CRT implementation had a higher mortality rate early in their follow-up after the index hospitalization than those who did not meet these criteria. Moreover, the probability of LV improvement was low in this population. In particular, LV improvement occurred rarely in those with lower LVEF and large cardiac chamber diameters who could not receive OMT. These results suggest that the current guideline of uniformly waiting for at least 3 months before CRT implementation should be reviewed. Also, further studies are mandatory to determine the appropriate timing for CRT and discriminant factors for early CRT responders

Conflict of interest

Jung Ae Hong, Sang Eun Lee, Seon-Ok Kim, Min-Seok Kim, Hae-Young Lee, Hyun-Jai Cho, Jin Oh Choi, Eun-Seok Jeon, Kyung-Kuk Hwang, Shung Chull Chae, Sang Hong Baek, Seok-Min Kang, Dong-Ju Choi, Byung-Su Yoo, Kye Hun Kim, Myeong-Chan Cho, Byung-Hee Oh, and Jae-Joong Kim declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariate binary logistic regression results: factors related to adverse outcome or no improvement in LV function.

Table S2. Change in left ventricular ejection fraction and left ventricular improvement from baseline to follow-up.

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