Cardiac resynchronization therapy with defibrillator (CRT-D) has been shown, in various clinical trials, to improve functional status, morbidity, and actual survival in strictly selected patients with heart failure (HF).\(^1\)\(^-\)\(^3\) According to the selection criteria of these trials, guidelines recommend CRT-D in patients with symptomatic but ambulatory HF, left ventricular ejection fraction (LVEF) <35%, and wide QRS complex.\(^4\)

In real-world practice, however, CRT-D is sometimes also used in sick patients such as those dependent on inotrope infusion,\(^5\) although the prognosis of such populations receiving CRT-D beyond the indication of the current guidelines remains uncertain. We recently showed that ventricular assist device (VAD) implantation should be considered instead of CRT-D in patients with advanced HF, because of the poor prognosis with CRT-D.\(^6\) The selection of appropriate candidates for CRT-D in such populations in the era of VAD treatment, however, remains uncertain.\(^7\) Optimal candidate selection for CRT-D in patients with advanced HF is critical compared with a less sick population, because inefficient CRT-D implantation often results in hemodynamic instability. The aim of the present study was therefore to investigate the predictors of response to CRT-D in patients with advanced HF, and discuss the ideal indications for CRT-D and VAD therapy.

**Methods**

**Patient Selection**

We enrolled 67 inpatients aged <65 years old with advanced HF who received CRT-D between 2007 and 2014. None of them had any contraindications for cardiac replacement therapy including heart transplantation or VAD. All patients had been treated with guideline-directed medical therapy for >6 months before CRT-D implantation. All patients were suffering from advanced HF, with New York Heart Association (NYHA) class III or IV despite optimal medical therapy. All patients had...
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by the University of Tokyo institutional review board. Written informed consent was obtained from all patients before analysis.

Variables

Demographic, echocardiographic, electrocardiographic, and laboratory variables including plasma B-type natriuretic peptide (P-BNP) immediately before CRT-D implantation were recorded as the baseline characteristics. LVEF was calculated using the biplane Simpson methods from 4- and 2-chamber views. Left atrial diameter (LAD) was measured in the anteroposterior LA dimension. LA volume index (LAVI) was estimated using the area-length method and corrected according to the Japanese standard criteria.

Variables

Data given as mean±SD or n (%). *P<0.05 (unpaired t-test, †chi-squared test). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AR, aortic regurgitation; BMI, body mass index; BNP, B-type natriuretic peptide; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; Cre, creatinine; CRT-D, cardiac resynchronization therapy with defibrillator; HR, heart rate; LAD, left atrial diameter; LAVI, left atrial volume index; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; RV, right ventricle; SBP, systolic blood pressure; TB, total bilirubin; TR, tricuspid regurgitation.
in 49 patients (73%) or in the posterior position in 18 (27%). After LV lead placement, LV pacing threshold, sensing parameters, and LV impedance were measured and the pacing output was set to achieve adequate pacing safety margins. The right ventricular shock lead was placed in an interventricular septal position, and the atrial lead was placed in the right atrial appendage.

**Statistical Analysis**

Data were analyzed using SPSS Statistics 22 (SPSS, Chicago, IL, USA). Categorical variables are expressed as frequencies and percentages, and compared using chi-squared test or Fisher’s exact test as appropriate. Continuous variables are summarized as mean±SD, and compared using unpaired t-test or Mann-Whitney U-test as appropriate. Univariate logistic regression analysis was performed to identify predictors of responders to CRT-D among the baseline variables. Receiver operating characteristics analysis was performed to calculate the cut-offs of continuous variables significant on univariate analysis, and to compare the area under the curve (AUC) of each predictor.

**Table 2. Predictors of Response to CRT-D**

| Demographics                  | P-value | OR (95% CI)          |
|-------------------------------|---------|----------------------|
| Male                          | 0.382   | 0.511 (0.113–2.303)  |
| Age (years)                   | 0.163   | 1.043 (0.983–1.106)  |
| BMI                           | 0.425   | 1.056 (0.924–1.207)  |
| SBP (mmHg)                    | 0.091   | 1.042 (0.993–1.093)  |
| Ischemic etiology             | 0.647   | 0.600 (0.067–5.349)  |
| Inotrope infusion             | 0.203   | 0.250 (0.030–2.116)  |
| LV lead at lateral wall       | 0.857   | 0.734 (0.098–4.657)  |
| Medications                   |         |                      |
| β-blocker (carvedilol, mg/day)| 0.676   | 1.012 (0.754–1.323)  |
| ACEI (enalapril, mg/day)      | 0.723   | 1.032 (0.423–2.546)  |
| NYHA class IV                 | 0.072   | 0.291 (0.076–1.117)  |
| Laboratory                    |         |                      |
| Hemoglobin (mg/dl)            | 0.954   | 1.011 (0.693–1.476)  |
| Serum albumin (mg/dl)         | 0.740   | 1.242 (0.346–4.459)  |
| Serum TB (mg/dl)              | 0.787   | 0.838 (0.261–2.693)  |
| Serum Cre (mg/dl)             | 0.116   | 0.085 (0.004–1.835)  |
| Plasma BNP (log10 pg/ml)      | 0.180   | 0.369 (0.086–1.584)  |
| Echocardiography              |         |                      |
| LVDd (mm)                     | 0.602   | 0.985 (0.930–1.043)  |
| LVEF (%)                      | 0.100   | 0.930 (0.853–1.014)  |
| LAD (mm)                      | 0.014*  | 0.878 (0.791–0.975)  |
| LAD <45 mm                    | 0.002*  | 30.00 (3.520–255.7)  |
| LAVI (ml/m²)                  | 0.010*  | 0.823 (0.762–0.896)  |
| LAVI <43 ml/m²                | 0.001*  | 36.67 (4.261–315.6)  |
| AR (grade)                    | 0.147   | 1.811 (0.811–4.045)  |
| MR (grade)                    | 0.812   | 0.918 (0.453–1.862)  |
| TR (grade)                    | 0.706   | 0.872 (0.427–1.779)  |
| Electrocardiography           |         |                      |
| HR (beats/min)                | 0.806   | 0.994 (0.949–1.041)  |
| QRS duration (ms)             | 0.532   | 1.006 (0.988–1.024)  |
| CRBBB                         | 0.765   | 0.624 (0.076–4.342)  |
| CLBBB                         | 0.001*  | 12.24 (2.729–54.90)  |
| Previous pacing               | 0.973   | 1.025 (0.240–4.382)  |
| AF                            | 0.986   | 1.020 (0.107–9.692)  |

*P<0.05 (logistic regression analysis). Abbreviations as in Table 1.
Predictors of Response to CRT

Significant variables with P<0.05 on univariate analysis were entered into multivariate analysis. One-way analysis of variance was used to compare clinical outcomes among 3 groups stratified by 2 predictors. Kaplan-Meier analysis was performed to analyze prognosis stratified by response to CRT-D. Cox proportional hazard analysis was used to identify predictors of cardiac death.

Results

Patient Characteristics
Baseline characteristics are listed in Table 1. Mean patient age was 49±13 years, and NYHA class was III or IV (60% and 40%, respectively). Overall, 11 patients (16%) were responders. The responders had smaller LA, and more of them had complete left bundle branch block (CLBBB) compared with the non-responders.

Predictors of Response to CRT-D
On univariate logistic regression analysis, smaller LA (as indicated by LAD or LAVI) and CLBBB were significant predictors of response to CRT-D among the baseline variables (Table 2). The combination of both predictors (in which we preferred LAVI rather than LAD as an indicator of LA size considering its reliability), had significantly higher AUC compared with each predictor alone (AUC, 0.942; P<0.05 for both; Figure 1). Seven patients had both predictors (double-positive group) and most of them (86%) were responders. Conversely, all 41 patients who had neither of the predictors (double-negative group) were non-responders. Most of the patients dependent on inotrope infusion belonged to the double-negative group (71%; Table 3). Non-responders received similar doses of β-blocker as responders at the endpoint (13.4±10.2 vs. 15.2±9.6 mg/day, P=0.469).

LVDD had a trend towards being smaller in the double-positive group compared with the double-negative group (Figure 2A). The double-positive group had significantly improved LVEF (Figure 2B) and P-BNP (Figure 2C) at 6-month follow-up compared with the double-negative group (P<0.05 for both).

LAD and Hemodynamic Variables
Among the hemodynamic variables, pulmonary capillary wedge pressure was significantly correlated with LAD (n=34, P=0.005, r=0.465; Table 4).

Long-Term Prognosis and Response to CRT-D
In total, 3 patients died due to cardiovascular events, and 22 patients received VAD implantation during the 2 years after CRT-D implantation. The responders had significantly higher VAD-free survival rate compared with the non-responders during the 2-year follow-up period (91% vs. 55%, P=0.047; Figure 3A). The 2-year actual survival rate was similar between the responders and the non-responders (91% vs. 94%, P=0.638; Figure 3B).

The double-positive group had a significantly better VAD-free survival rate compared with the double-negative group during the 2-year study period (86% vs. 52%, P=0.045; Figure 4A), but the actual survival rates of the 2 groups were almost identical (Figure 4B). The presence of both predictors was also a significant negative indicator of cardiac death on Cox proportional hazard analysis (HR, 0.484; P=0.040).

Table 3. Presence of Positive Predictors vs. Response

|                  | Double negative (n=41) | Either positive (n=19) | Double positive (n=7) |
|------------------|------------------------|------------------------|-----------------------|
| Responders (inotrope dependent) | 1 (0)                  | 4 (0)                  | 6 (1)                 |
| Non-responders (inotrope dependent) | 40 (12)               | 15 (4)                | 1 (0)                 |
Increased age, chronic kidney disease, atrial fibrillation, and highly depressed LVEF were reported as predictors of increased mortality after CRT-D implantation.

Narrow QRS has been reported as an indicator of worse clinical outcome after CRT-D implantation irrespective of mechanical LV dyssynchrony.

We also showed that non-ambulatory patients with advanced HF, that is, those dependent on inotrope infusion, received few clinical benefits of CRT-D implantation, and such patients would be good candidates for early VAD implantation instead of CRT-D.

This suggests that in the current era of cardiac replacement therapy, the indications for CRT-D in patients with advanced HF are more limited.

### Predictors of Response to CRT-D

Landmark clinical trials have used various endpoints to define predictors of response to CRT-D (improvement of LVEF >10% at 6-month follow-up) in patients with advanced HF. The combination of both predictors was able to distinguish responders from non-responders. The responders had improved VAD-free survival compared with the non-responders during the 2-year study period.

### Discussion

In this study, we have shown that CLBBB and a smaller LA are significant predictors of response to CRT-D (improvement of LVEF >10% at 6-month follow-up) in patients with advanced HF. The combination of both predictors was able to distinguish responders from non-responders. The responders had improved VAD-free survival compared with the non-responders during the 2-year study period.

Among the patients not dependent on inotropes (n=50), the non-responders had worse VAD-free survival compared with the responders during the 2 years following CRT-D implantation (73% vs. 100%, P=0.048; Figure S1).

### CRT-D in Real-World Illness

In real-world practice, CRT-D is implanted in more sick HF patients with various complications compared with those enrolled in previous clinical trials. Increased age, chronic kidney disease, atrial fibrillation, and highly depressed LVEF were reported as predictors of increased mortality after CRT-D implantation. Narrow QRS has been reported as an indicator of worse clinical outcome after CRT-D implantation irrespective of mechanical LV dyssynchrony. We also showed that non-ambulatory patients with advanced HF, that is, those dependent on inotrope infusion, received few clinical benefits of CRT-D implantation, and such patients would be good candidates for early VAD implantation instead of CRT-D. This suggests that in the current era of cardiac replacement therapy, the indications for CRT-D in patients with advanced HF are more limited.
Predictors of Response to CRT

In this study, we used improvement in LVEF as the endpoint for measuring response to CRT-D, because these imaging criteria may directly represent CRT-D-induced reverse remodeling. We assessed the endpoint at 6 months after CRT-D implantation.

**Figure 3.** (A) Ventricular assist device (VAD)-free survival rate and (B) actual survival rate vs. response to cardiac resynchronization therapy with defibrillator (CRT-D) during the 2-year study period. *P*<0.05 (log-rank test).

**Figure 4.** (A) Ventricular assist device (VAD)-free survival rate and (B) actual survival rate vs. predictors of response to cardiac resynchronization therapy with defibrillator during the 2-year study period. *P*<0.05 (log-rank test).

Response to CRT-D: clinical criteria include re-hospitalization for HF, NYHA class, 6-min walk distance, quality of life assessed by questionnaires, and mortality; and biological variables such as P-BNP; and imaging criteria include LVDd and LVEF. In this study, we used improvement in LVEF as the endpoint for measuring response to CRT-D, because these imaging criteria may directly represent CRT-D-induced reverse remodeling. We assessed the endpoint at 6 months after CRT-D implantation.
implantation, in line with protocols of the previous trials.\textsuperscript{13} LV reverse remodeling is usually achieved at 3–6 months after the initiation of therapy.\textsuperscript{9}

In this study, CLBBB was a significant predictor of response to CRT-D. Previous trials failed to demonstrate the importance of mechanical LV dyssynchrony for response to CRT-D in patients with narrow QRS complex.\textsuperscript{13,14,15} CLBBB, which indicates the existence of electrical LV discordance,\textsuperscript{16} has traditionally been considered as a predictor of response to CRT-D.\textsuperscript{17,18} but most earlier studies were conducted in patients with NYHA class II–III. We have here shown that CLBBB is also a crucial factor in response to CRT-D in patients with more advanced HF.

A smaller LAVI was another significant predictor of response to CRT-D. Several authors have reported consistent results in less sick patients with NYHA class II or III.\textsuperscript{18,19} A larger LA was associated with higher pulmonary capillary wedge pressure (Table 4). Although the precise mechanism remains uncertain, diastolic dysfunction may contribute to LA dilatation, and CRT-D may not be able to reverse severe diastolic dysfunction.\textsuperscript{20}

Most patients in the double-positive group were responders, and more achieved improvement in LVEF and P-BNP during the 6-month follow-up compared with the double-negative group. LVDd, however, remained unchanged even in the responders. Thus, CRT-D may not achieve complete reverse remodeling in patients with advanced HF.

Although these 2 predictors may not be surprising considering the previous reports conducted in less sick patients, the identification of predictors of response to CRT-D in patients with advanced HF is of great importance. Inappropriate implantation of CRT-D in non-responders often results in fatal outcome, involving invasive, but nonetheless ineffective, procedures. Such inappropriate therapy, however, is often performed in real-world practice, and the timing of LVAD therapy may therefore be inappropriate in many patients.

### Long-Term Prognosis of Responders

There are few studies on the advantage of CRT-D with regard to hard endpoints such as mortality in patients with advanced HF.\textsuperscript{10,20} Patients dependent on inotrope infusions should not receive CRT-D, but may be good candidates for VAD implantation, as previously reported.\textsuperscript{9} Considering the improved survival in non-responders with successful VAD therapy (Figure 3B), the double-negative group may also be good candidates for VAD therapy. Consistently, most of the patients dependent on inotropes (94%) were non-responders. Although VAD implantation in patients dependent on inotropes is the standard treatment, the referral time for VAD implantation from a non-VAD institute is sometimes too long. Only 1 patient among those dependent on inotrope infusion belonged to the double-positive group, and was a responder. His LVDd and P-BNP, however, increased during the 6 months of CRT-D, and he eventually died at 291 days.

The responders had increased VAD-free survival compared with the non-responders (Figure 3A). Most of the responders (91%) did not receive inotrope infusion. Although the proportion of responders was low (approximately 15%), probably because of the background HF severity, optimal patient selection using these 2 novel predictors of response to CRT-D would be beneficial in delaying VAD implantation and improving quality of life, considering the cost and invasiveness of VAD therapy. Identification of such responders is vital to prevent inappropriately early VAD implantation.

Among those not dependent on inotropes, the non-responders still had reduced VAD-free survival compared with the responders during the 2-year study period. Accordingly, such patients should be carefully monitored for timely referral for VAD implantation.

### Study Limitations

First, the present study was conducted in a single center, where VAD therapy was readily available. Moreover, the patients might be relatively sicker because of the nature of the quaternary care hospital. Therefore the present result should be validated in a larger multi-center study.

Second, the timing of VAD implantation may have been affected by attending physician decision. In particular, the referral for VAD therapy from the non-VAD institutes may sometimes be too late to rescue patients. The decision to implement VAD therapy at University of Tokyo Hospital successfully saved lives in patients with critical hemodynamics, and therefore may be justified in this regard.

Third, we did not perform hemodynamic studies before CRT-D implantation in all patients. Hemodynamic variables such as pulmonary capillary wedge pressure may improve the prediction of response to CRT-D.

Fourth, the present study was conducted in patients with advanced HF, and the results may not be easily applied to patients with mild HF.

Fifth, we assessed 2-year prognosis in this study. Considering that there were no significant decreases in LVDd even in the responders, longer-term survival in patients with advanced HF receiving CRT-D may not be expected without VAD therapy.

And sixth, we were unable to perform multivariate logistic regression analysis to identify predictors of response to CRT-D due to the low number of participants. Multi-institute large-scale analyses are needed to strengthen the present results.

### Conclusions

CLBBB and small LAVI were novel predictors of response in patients with advanced HF receiving CRT-D according to real-world practice indications. Such responders may benefit from CRT-D and delay of cardiac replacement therapy.

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Supplementary Files

Supplementary File 1

**Figure S1.** Two-year ventricular assist device (VAD)-free survival rate in patients not dependent on inotrope infusion, vs. response to cardiac resynchronization therapy with defibrillator.

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-15-0769