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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Elevated B-Type Natriuretic Peptide Level as a Residual Risk Factor for Ventricular Arrhythmias Among Patients Undergoing Cardiac Resynchronization Therapy With Improved Left Ventricular Ejection Fraction

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Background: Patients who achieve improved left ventricular ejection fraction (LVEF >35%) with cardiac resynchronization therapy (CRT) are at a lower risk of ventricular arrhythmia (VA). Little is known about the significance of the B-type natriuretic peptide (BNP) level for the risk of VA. This study investigated the risk factors for VA in CRT and the risk stratification of VA with BNP in CRT with improved LVEF.

Methods and Results: This study evaluated 352 CRT patients from 2012 to 2020. Patients were categorized into 2 groups: improved LVEF (impEF; LVEF >35%), and low LVEF (lowEF; LVEF ≤35%). The serum BNP levels 6 months after CRT device implantation were measured. The primary endpoint was defined as VA requiring treatment with anti-tachycardia pacing or shock or persisting for ≥30 s. Overall, 102 patients had improved LVEF. The impEF group had a significantly lower VA risk than the lowEF group. Patients with low BNP had a lower VA risk than those with high BNP; however, no significant difference was observed between patients with high BNP and those in the lowEF group. Univariate analysis revealed that high BNP was a predictor of VA in the impEF group.

Conclusions: The VA risk is reduced with improved LVEF after CRT but not with high BNP levels. The post-BNP level after CRT implantation is a useful marker for predicting VA in patients with improved LVEF.

Key Words: B-type natriuretic peptide; Cardiac resynchronization therapy; Improved LVEF >35%; Risk stratification; Ventricular arrhythmia

B-type natriuretic peptide (BNP) is a vital prognostic biomarker for patients with heart failure (HF).[1] BNP was reported as a useful biomarker in the management of HF and a predictor of ventricular arrhythmia (VA).[2] An elevated BNP level is related to the risk for VA among patients treated with an implantable cardioverter defibrillator (ICD) and is an independent predictor of increased risk for subsequent VA among patients treated with cardiac resynchronization therapy (CRT) devices from Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) analysis.[3,4] Although patients with left ventricular (LV) dysfunction have a higher risk of developing VA than do those unaffected by LV dysfunction, the risk of VA is reduced with improved left ventricular ejection fraction (LVEF) among patients treated with CRT.[5] Furthermore, as CRT improves cardiac contraction and hemodynamics, CRT responders are reported to be at a lower risk of developing VA than the non-responders.[6] Since patients who achieve LVEF normalization are at risk of inappropriate

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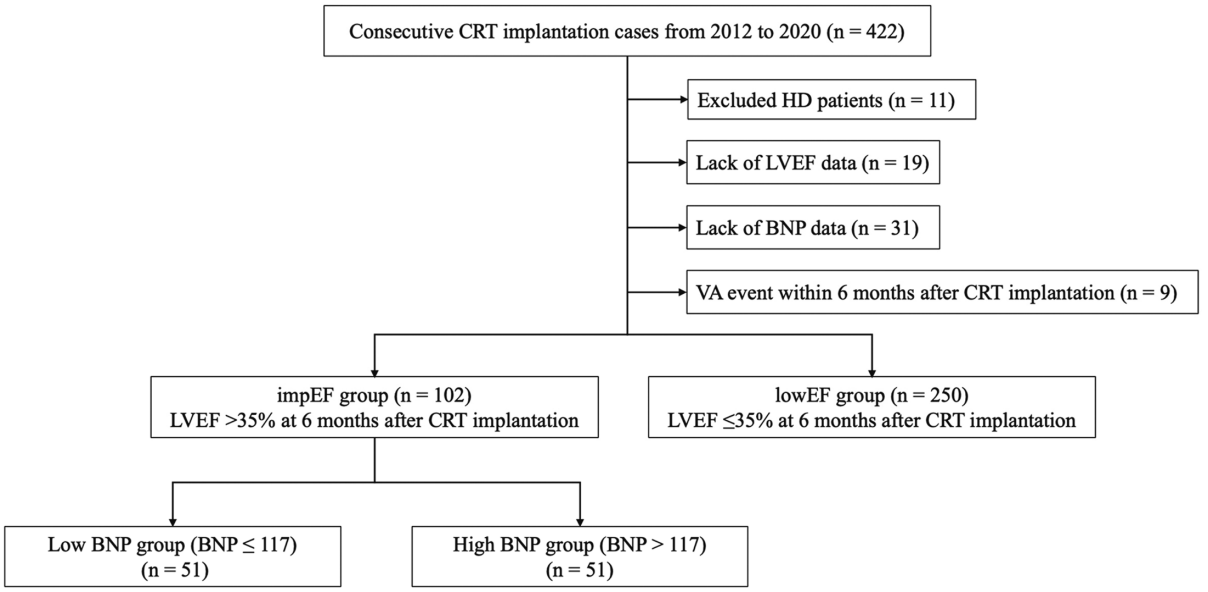

Figure 1. Flowchart of the study protocol. Flowchart demonstrating how the study population was initially divided into non-improved LVEF and improved post-CRT implantation groups, with subsequent division of the impEF group into two groups according to BNP levels at 6 months after CRT implantation. BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; HD, hemodialysis; impEF, improved LVEF; lowEF, low LVEF; LVEF, left ventricular ejection fraction; VA, ventricular arrhythmia.

therapy despite being at significantly low risk of developing VA,[7] whether to deactivate ICD therapy could be a matter of debate. Additionally, it is important to consider downgrading to CRT pacemakers for battery life longevity among patients with a lower risk of VA development. Although the indication for ICD depends on the LVEF, the risk factors and stratification of VA in patients undergoing CRT, with an improvement in LVEF >35%, remain unclear. This study aimed to: (1) investigate risk factors for VA in patients undergoing CRT; and (2) explore VA risk stratification with BNP in patients undergoing CRT with an improvement in LVEF.

Methods

Study Population

This single-center, retrospective, observational study analyzed 422 consecutive patients who underwent CRT at National Cerebral and Cardiovascular Center from 2012 to 2020. The flowchart of this study is shown in **Figure 1**. Most patients had LVEF ≤35%. The inclusion criteria were based on the Japanese Circulation Society/Japanese Heart Rhythm Society guideline on non-pharmacotherapy of cardiac arrhythmias.[8] The exclusion criteria were as follows: (1) patients undergoing hemodialysis (n=11); (2) lack of data on LVEF (n=19) or BNP levels (n=31); and (3) occurrence of VA events within 6 months after CRT device implantation (n=9).

Ethical Considerations

This retrospective study was approved by the Institutional Research Board of the National Cerebral and Cardiovascular Center, Suita, Japan (M26-150-13). The procedures followed in this study were performed in accordance with the Declaration of Helsinki and with the ethical standards of the responsible institutional or regional committee on human experimentation. This study analyzed anonymous data after patients consented to the treatment, and the opt-out method for obtaining informed consent was applied.

Data Collection

Baseline clinical information, including age, sex, underlying heart disease, and medical history, including hypertension, diabetes, chronic kidney disease (CKD), atrial fibrillation, and ischemic cardiomyopathy (ICM), 12-lead electrocardiography data, medication information, echocardiography parameters, and New York Heart Association (NYHA) class data, was acquired from all patients in the cohort. Diabetes was defined according to the 2011 American Diabetes Association guidelines.[9] CKD was defined in accordance with the 2013 Kidney Disease: Improving Global Outcomes guidelines.[10]

BNP Measurement

Plasma BNP levels were measured using a commercial immunoradiometric assay kit for human BNP (Shionogi, Osaka, Japan) before CRT device implantation, and at 6 months after CRT device implantation.

Definition of CRT Patients With Improvement in LVEF

LVEF was assessed using echocardiography and single-photon emission computed tomography before and at 6 months after CRT implantation during a stable hemodynamic state. With echocardiography, LVEF was calculated using the biplane Simpson equation or Teichholz formula. All echocardiography data were measured during 3 consecutive cardiac cycles. All patients had LVEF measured by echocardiography or single-photon emission computed

Table 1. Baseline Characteristics Before and at 6 Months After CRT Implantation for Consecutive CRT Patients

	Total (n=352)	impEF group (n=102)	lowEF group (n=250)	P value
Age (years)	66±13	66±14	66±13	0.770
Male sex	265 (75)	64 (63)	201 (80)	0.001
Hypertension	168 (48)	52 (51)	116 (46)	0.481
Diabetes	116 (33)	26 (25)	90 (36)	0.062
CKD	157 (45)	35 (34)	122 (49)	0.014
Atrial fibrillation	187 (53)	54 (53)	133 (53)	1.00
ICM	89 (25)	17 (17)	72 (29)	0.021
DCM	133 (38)	36 (35)	97 (39)	0.549
HCM	32 (9)	11 (11)	21 (8)	0.540
Sarcoidosis	32 (9)	18 (18)	14 (6)	0.002
Secondary prevention	68 (19)	18 (18)	50 (20)	0.658
LBBB	85 (24)	33 (32)	52 (21)	0.028
QRS duration (ms)	159 [135–179]	165 [144–182]	156 [133–177]	0.068
Medication				
β-blocker	288 (82)	74 (73)	214 (86)	0.006
ACE inhibitor or ARB	282 (80)	81 (79)	201 (80)	0.883
MRA	222 (63)	54 (53)	168 (67)	0.015
Amiodarone	111 (32)	20 (20)	91 (36)	0.002
Baseline LVEF (%)	25 [19–31]	33 [26–36]	23 [18–28]	<0.001
Baseline BNP (pg/mL)	297 [150–516]	191 [117–320]	372 [187–580]	<0.001
NYHA class II	221 (63)	78 (76)	143 (57)	0.010
NYHA class III	115 (33)	24 (24)	91 (36)	0.024
NYHA class IV	16 (5)	0	16 (6)	0.008

Unless indicated otherwise, data are presented as n (%), mean±SD, or median [interquartile range]. ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CRT, cardiac resynchronized therapy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; impEF, improved LVEF; LBBB, left bundle branch block; lowEF, low LVEF; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

tomography. Patients undergoing CRT with improved LVEF (impEF group) were defined as patients whose LVEF was >35% following assessment at 6 months after CRT device implantation, using the modality calculated before CRT device implantation. Patients who did not show an improved LVEF of >35% were grouped into the low LVEF group (lowEF group).

Clinical Outcome and Definition of CRT Responders

A VA event was defined as the incidence of appropriate ICD therapy, including anti-tachycardia pacing, shock therapy, or VA lasting for >30 s. VA events were evaluated at 6 months after CRT device implantation. VA was assessed using an intracardiac electrogram, including pre-episode, detection, and post-therapy sections with 3-channel signals from the atrial, right ventricular, and LV electrodes or right ventricular far-field signal.

Follow up

The follow-up data of participants were obtained from the charts of ICDs and pacemakers, inpatient records, and ambulatory assessments in National Cerebral and Cardiovascular Center.

Statistical Analysis

Results are presented as mean±SD or median with interquartile range (IQR) for continuous data, accordingly. Categorical data are expressed as frequencies (percentages). Differences in categorical attributes across groups were assessed using either the χ^2 test or Fisher's exact test, as deemed suitable. Comparisons of continuous variables were conducted using the Wilcoxon rank-sum test; statistical significance was recognized at a threshold of $P<0.05$. The relationship between the BNP levels and VA events was assessed using a 6-month landmark analysis. Patients were grouped according to their BNP levels at 6 months after CRT device implantation, and follow up was initiated 6 months later. Groups were compared and displayed using a log-rank test and Kaplan-Meier survival analysis. Univariate Cox proportional hazards regression modeling was used to evaluate the correlation between the impEF group and the occurrence of VA events. Event-free survival was calculated from 6 months after CRT device implantation to the date of VA events. All analyses were carried out using the JMP 14 software (SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

The baseline characteristics of the 352 patients are shown in **Table 1**. At the time of CRT device implantation, the mean patient age was 66±13 years, and 265 (75%) of the patients were men. The QRS duration was 159 ms (IQR

Table 2. Stratification of Patients in the impEF Group by the Median BNP Level at 6 Months After CRT Implantation

	Low BNP group (n=51)	High BNP group (n=51)	P value
Age (years)	64±14	69±14	0.041
Body mass index (kg/m^2)	24±4	23±4	0.219
Male sex	36 (71)	28 (55)	0.151
Hypertension	24 (47)	28 (55)	0.553
Diabetes	11 (22)	15 (29)	0.496
CKD	12 (24)	23 (45)	0.036
Atrial fibrillation	25 (49)	29 (57)	0.552
ICM	3 (6)	14 (27)	0.007
DCM	25 (49)	11 (22)	0.007
HCM	1 (2)	10 (20)	0.008
Sarcoidosis	7 (14)	11 (22)	0.436
Secondary prevention	10 (20)	8 (16)	0.796
LBBB	21 (41)	12 (24)	0.090
QRS duration (ms)	171 [149–186]	159 [143–179]	0.298
Medication			
β-blocker	38 (75)	36 (71)	0.825
ACE inhibitor or ARB	38 (75)	43 (84)	0.328
MRA	28 (55)	26 (51)	0.843
Amiodarone	7 (14)	13 (25)	0.212
Baseline LVEF (%)	30 [23–35]	33 [30–37]	0.024
Baseline BNP (pg/mL)	134 [64–189]	266 [197–405]	0.001
NYHA class II	41 (80)	37 (73)	0.484
NYHA class III	10 (20)	14 (27)	0.484

Unless indicated otherwise, data are presented as n (%), mean±SD, or median [interquartile range]. Abbreviations as in Table 1.

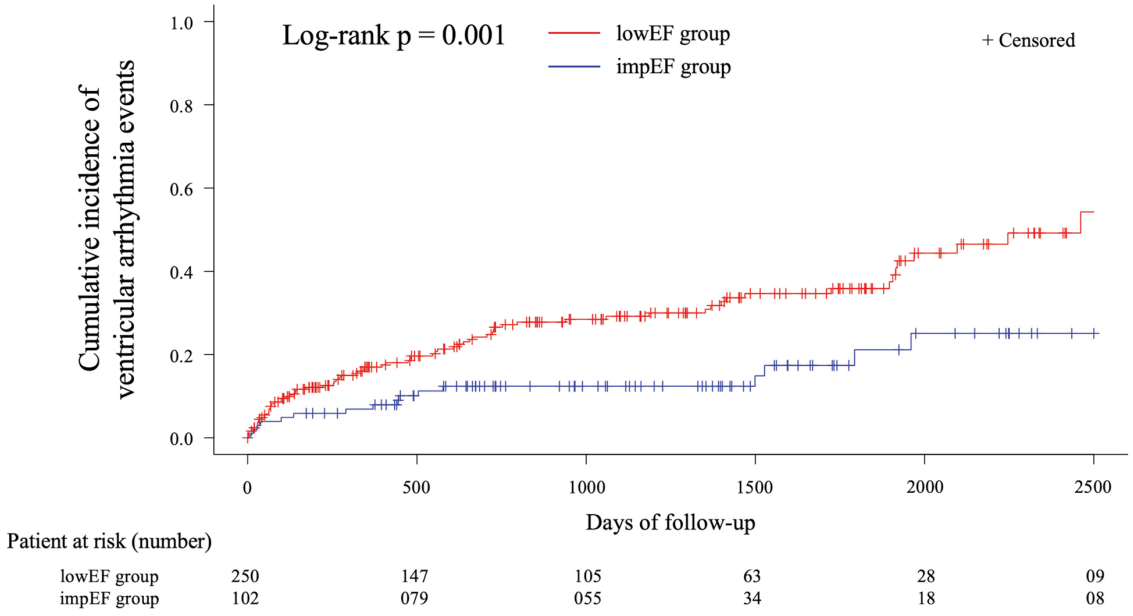

Figure 2. Cumulative probability of VA among the impEF and lowEF groups. Analysis revealed that patients in the impEF group (blue line) had a lower VA risk than those in the lowEF group (red line). CRT, cardiac resynchronization therapy; impEF, improved LVEF; lowEF, low LVEF; LVEF, left ventricular ejection fraction; VA, ventricular arrhythmia.

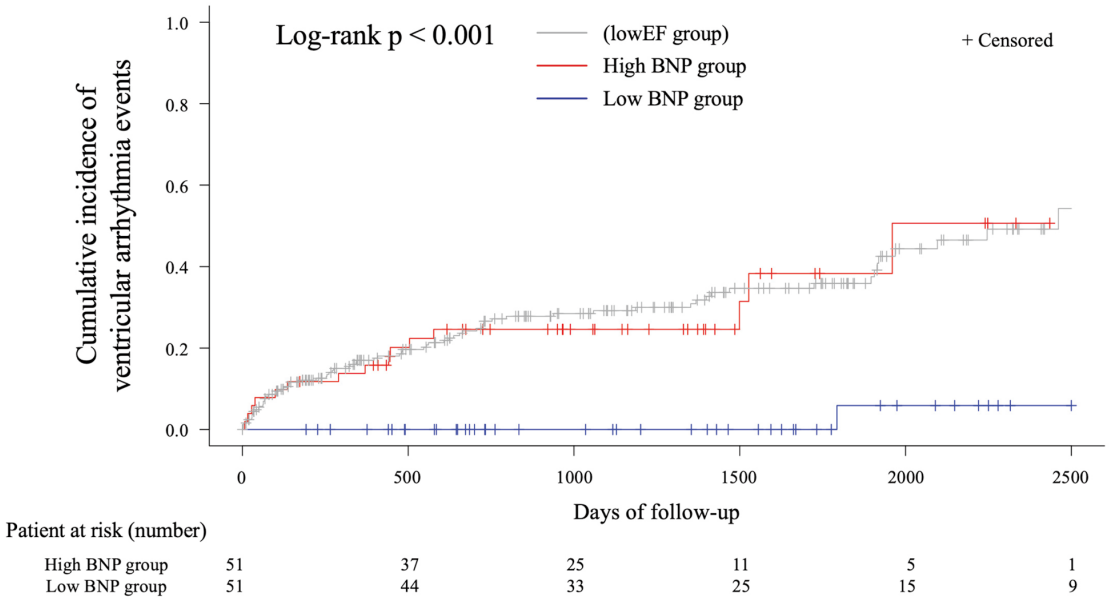

Figure 3. Cumulative probability of VA in the impEF group, stratified by the median BNP level. Analysis revealed that patients with low BNP (BNP ≤117 pg/mL; blue line) had a lower risk of VA than patients with high BNP (BNP >117 pg/mL; red line) in the impEF group. For reference, the gray line indicates cumulative incidence of VA events in patients in the lowEF group. BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; impEF, improved LVEF; lowEF, low LVEF; LVEF, left ventricular ejection fraction; VA, ventricular arrhythmia.

135–179). The median baseline BNP level was 297 pg/mL (IQR 150–516).

In this cohort, 102 (29%) patients showed an improved LVEF of >35% (impEF group), and LVEF did not improve in 250 (71%) patients (lowEF group). The prevalence of men (64 [63%] vs. 201 [80%]; P=0.001), amiodarone use (20 [20%] vs. 91 [36%]; P=0.002), and β-blocker use (74 [73%] vs. 214 [86%]; P=0.006) was lower in the impEF group. The baseline LVEF prevalence was higher in the impEF group (33% [IQR 26–36]) than in the lowEF group (23% [IQR 18–28]; P<0.001). BNP levels were lower in the impEF group (191 pg/mL [IQR 117–320]) than in the lowEF group (372 pg/mL [IQR 187–580]; P<0.001).

Table 3. Univariate Analysis of the impEF Group

	HR	95% CI	P value
ICM	1.47	0.41–5.27	0.550
Hypertension	1.24	0.46–3.34	0.666
Diabetes	1.30	0.45–3.75	0.633
CKD	2.82	1.05–7.62	0.041
Secondary prevention	1.71	0.55–5.32	0.352
LBBB	0.23	0.05–1.02	0.053
AF	2.27	0.73–7.09	0.159
BNP >117 pg/mL	22.5	2.93–172.6	0.003

CI, confidence interval; HR, hazard ratio; impEF, improvement in LVEF to >35%. Other abbreviations as in Table 1.

Clinical Characteristics Between the High and Low BNP Groups

The median BNP level at 6 months after implantation in the impEF group was 117 pg/mL (IQR 45–198 pg/mL). Patients in the impEF group were divided into low BNP (≤117 pg/mL; n=51) and high BNP (>117 pg/mL; n=51) groups (**Table 2**). The prevalence of ICM (3 [6%] vs. 14 [27%]; P=0.007) and CKD (12 [24%] vs. 23 [45%]; P=0.036) was lower among patients in the low BNP group than among those in the high BNP group. The prevalence of baseline LVEF (30% [IQR 23–35] vs. 33% [IQR 30–37]; P=0.024) and baseline BNP levels (134 pg/mL [IQR 64–189] vs. 266 pg/mL [IQR 197–405]; P=0.001) was significantly lower in the low BNP group than in the high BNP group. There were no significant differences in body mass index (BMI) or NYHA classification between the low BNP and high BNP groups (low BNP vs. high BNP; BMI 24±4 kg/m^2 vs. 23±4 kg/m^2; P=0.219; NYHA class II 41 [80%] vs. 37 [73%]; P=0.484; NYHA class III 10 [20%] vs. 14 [27%]; P=0.484).

VA Events

During follow up (median 842 days; IQR 295–1,619), 93 (26%) patients experienced VA events (impEF group vs. lowEF group: 16 [16%] vs. 77 [31%]; P=0.003). Landmark analysis revealed that patients in the impEF group had a lower risk of VA than patients in the lowEF group (P=0.001; **Figure 2**).

Among patients in the impEF group, patients with low BNP levels had a lower incidence of VA events than patients with high BNP levels (low BNP vs. high BNP: 1 [2%] vs. 15 [29%]; P<0.001). In the low BNP group, only 1 patient experienced a VA event; the patient had cardiac sarcoidosis as an underlying heart disease. The patient had no VA event for 5 years from the date of CRT device implantation. Landmark analysis revealed that patients

with low BNP levels had a lower risk of VA than those with high BNP levels (log-rank P<0.001), although there was no significant difference between patients with high BNP levels and patients in the lowEF group (log-rank P=0.827; **Figure 3**). Univariate analysis for the prediction of VA showed that high BNP levels at 6 months after CRT implantation (hazard ratio [HR] 22.5; 95% confidence interval [CI] 2.93–172.6; P=0.003) and CKD (HR 2.82; 95% CI 1.05–7.62; P=0.041) were significant risk factors for VA among patients in the impEF group (**Table 3**).

Discussion

Main Findings

The present study investigated the significance of BNP for VA risk stratification in patients with improved LVEF after CRT device implantation. The main findings were as follows: (1) patients with improved LVEF had a lower risk of VA than patients in the lowEF group; (2) patients with low BNP levels exhibited a lower risk of VA among patients in the impEF group, although there was no significant difference between patients with high BNP levels in the impEF group and patients in the lowEF group; and (3) a high BNP level at 6 months after CRT device implantation was a predictor of VA among patients in the impEF group.

Relationship Between CRT Response and VA Risk

ICD improves the survival of patients with LVEF ≤35%,[11,12] and the indication for ICD is primarily based on LVEF before device implantation.[8] Some reports investigated the relationship between improvement in LVEF of >35% and the risk of VA in evaluating the benefits of ICD therapy.[13,14] In a meta-analysis of 16 studies involving 3,959 patients, an improved LVEF of >35% was associated with a reduced risk of VA.[7] The CRT response was more effective in women with relatively short QRS duration.[15,16] In the present study, a significantly larger proportion of women exhibited LVEF improvement of >35% compared with the proportion that exhibited improvement of ≤35% (37% vs. 20%; P=0.001). Additionally, CRT responders were at a decreased risk of VA compared with the non-responders,[5,6,17] and several reports showed that improvements in LVEF, particularly when LVEF was ≥35%, contribute to a reduction in VA.[14,17,18] Furthermore, in the Multicenter Automatic Defibrillator Implantation Trial with CRT (MADIT-CRT) analysis, patients who achieved LVEF normalization and LVEF subnormalization were at reduced risk of VA.[5] Therefore, patients with improvement in LVEF had a relatively lower risk of VA than those without improvement.

Although patients with improved LVEF had a low risk of subsequent VA, inappropriate ICD therapy was comparable with those without improvement in LVEF of >35%.[5,7] Additionally, an inappropriate ICD shock was associated with a significant increase in the risk of death.[19] Therefore, assessing the utility of a defibrillator and VA risk stratification is crucial, especially for patients undergoing CRT with a defibrillator and improvement in LVEF.

Risk Stratification With BNP Among Patients Undergoing CRT With Improved LVEF

Increased intraventricular pressure and myocardial stretch could enhance arrhythmogenesis,[20] such as enhanced refractoriness, slower conduction, and increased afterdepolarizations.[21–24] Although CRT has been reported to improve cardiac function, resulting in a favorable prognosis[25] and a reduced risk of VA,[5,17] the suppressive effects of VA depend on the response to CRT.[26] In addition, Sapp et al. reported that CRT could affect the arrhythmic substrate. In a previous report, CRT did not show a reduction in VA events in patients undergoing CRT with secondary prevention.[27] Hence, it was necessary to stratify the risk of VA, even among patients with improved LVEF.

Several studies have reported the significance of BNP in predicting the risk of VA and prognosis.[3,4,28] In patients managed with ICD, a meta-analysis and retrospective analysis reported that elevated baseline levels of BNP or N-terminal proBNP were independent predictors.[2,3] One subanalysis in MADIT-CRT reported that assessment of baseline and follow-up BNP levels provide important prognostic implications in patients with mildly symptomatic HF receiving CRT.[28] Furthermore, another study of the MADIT-CRT cohort showed that preimplantation BNP levels function as a surrogate marker of VA risk in patients with mild HF, and monitoring BNP levels in patients who have undergone CRT implantation proved useful in identifying individuals who are at a high risk of VA after implantation.[4]

Notably, the present study suggests that BNP levels may be useful for VA risk stratification in patients with improved LVEF of >35% after CRT device implantation. Because VA had only occurred in 1/51 (2%) patients in the low BNP group at 5 years after CRT device implantation, defibrillator deactivation may be feasible for such patients if inappropriate shock occurs, or if requested by the patient. There were no significant differences in NYHA class between low and high BNP groups, and baseline LVEF in the high BNP group was higher than that in the low BNP group, therefore it is not justifiable to conclude that patients in the high BNP group had more severe conditions, even though they had higher baseline BNP values. In the present study, high BNP was a predictor of VA even in the impEF group, which has the clinical implication that high BNP levels should be noted even in patients undergoing CRT with LVEF improvement after implantation. Patients in the high BNP group had a higher prevalence of ICM than those in the low BNP group, which may have resulted in an ineffective response to CRT despite the improved LVEF of >35%.

The present study suggests that improvements in LVEF and post-implantation BNP follow up may be useful for stratifying patient groups according to the risk of VA events. Large randomized controlled clinical trials are required to confirm the results of this retrospective observational study.

Clinical Implications

High BNP levels should be noted even in patients undergoing CRT with LVEF improvement after implantation; even after CRT, they should be managed for HF using MitraClip therapy[29] or uptitrating HF medicines[30–32] and VA ablation. Furthermore, a CRT-pacemaker or deactivation of the defibrillator could be considered if an inappropriate shock occurs in patients with improved BNP because shock worsens the prognosis and decreases the quality of life.

Study Limitations

The present study had limitations. First, this was a retrospective observational study with a relatively small sample

size. Second, only the presence or absence of the first VA event at 6 months after CRT device implantation was evaluated, and a detailed examination of multiple events was not performed. Furthermore, the study did not investigate a time-course of changes in BNP and LVEF levels, and we could not assess correlations between these parameters and VA events. Third, the small number of events did not allow for multivariate analysis, which did not eliminate confounding factors in the association between BNP and VA in patients undergoing CRT with improved LVEF. Additionally, the univariate analysis of this study has wide CI, and caution should be exercised in interpreting the results. Fourth, because the present study included a cohort treated before the current optimal drug therapy for chronic HF was indicated, there may be limitations with respect to its applicability to current HF patients receiving angiotensin receptor neprilysin inhibitor and sodium-glucose cotransporter 2 inhibitors. Last, differences in the underlying heart diseases significantly affected BNP levels. As there was no significant difference, according to NYHA classification, at CRT implantation between the high BNP and low BNP groups, we believe that the difference did not affect the results of this study.

Conclusions

Patients with improved LVEF had a lower risk of VA than those without LVEF improvement, and the post-BNP level after CRT device implantation is a useful marker for predicting VA in patients with improved LVEF after CRT implantation. A high BNP level can stratify the risk of VA among patients with an improved LVEF.

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Disclosures

N.U. received honoraria from Medtronic Japan Co., Ltd for providing lectures. K.I. has received honoraria for teaching lectures from BIOTRONIK Japan and Medtronic Japan Co., Ltd. T.N. has received honoraria for lectures from Medtronic Japan Co., Ltd and BIOTRONIK Japan, Inc., and belongs to a department endowed by BIOTRONIK Japan. S.N. is affiliated with a department endowed by Japan Medtronic, Inc. K.K. has received honoraria from BIOTRONIK Japan and Medtronic Japan, and research grants from Medtronic Japan. However, none of the sponsors/honoraria were involved in the study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the article for publication. This study was supported by the Intramural Research Program Fund (25-4-7; K.K.) for cardiovascular diseases of the National Cerebral and Cardiovascular Center.

IRB Information

This retrospective study was approved by the Institutional Research Board of the National Cerebral and Cardiovascular Center, Suita, Japan (M26-150-13).

Data Availability

The deidentified participant data is not accessible.

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