Usefulness of Post-Procedural Plasma Brain Natriuretic Peptide Levels to Predict Recurrence After Catheter Ablation of Atrial Fibrillation in Patients With Left Ventricular Systolic Dysfunction

Masato Okada, MD[a], Nobuaki Tanaka, MD[a], Koji Tanaka, MD[a], Yuko Hirao, MD[a],
Issei Yoshimoto, MD[a], Shinichi Harada, MD[a], Toshinari Onishi, MD[a], Yasushi Koyama, MD, PhD[a],
Atsunori Okamura, MD, PhD[a], Katsuomi Iwakura, MD, PhD[a], Kenshi Fujii, MD, PhD[a],
Yasushi Sakata, MD, PhD[b], and Koichi Inoue, MD, PhD[a,*]

Catheter ablation (CA) of atrial fibrillation (AF) improves cardiac function, resulting in a decrease in plasma brain natriuretic peptide (BNP) levels in patients with reduced left ventricular ejection fraction (LVEF). This study sought to examine the pre-procedural and post-procedural correlations between BNP levels and cardiac function and the associations between the BNP levels and recurrence after CA in patients with AF and reduced LVEF. Of 3142 consecutive patients who underwent first-time CA of AF at our institute, a total of 217 patients with LVEF <50% were enrolled. Significant decrease in BNP levels (from a median of 198 [interquartile range 113 to 355] to 47.7 [22.7 to 135] pg/ml, p <0.001) and improvement in LVEF (from $39 \pm 9\%$ to $61 \pm 16\%$, p <0.001) were observed 3 months after CA. There was a linear correlation between log-transformed BNP levels and cardiac measures (LVEF: r = -0.64; LV end-diastolic volume: r = 0.25; LV end-systolic volume: r = 0.43; left atrial volume: r = 0.52; all p <0.001). During a median follow-up of 35 months, AF recurrence after a 3-month blanking period was observed in 80 patients (37%). Cox proportional hazard regression analysis after adjustment for cardiac measures significant in univariate analysis revealed that early recurrence within the blanking period (hazard ratio, 4.88; 95% confidence interval, 2.89 to 8.25) and elevated post-procedural BNP levels (2.02 per unit log increase; 1.14 to 3.56) were significant predictors of AF recurrence, but pre-procedural BNP was not. In conclusion, post-procedural BNP levels at the end of the blanking period predicted subsequent AF recurrence in patients with reduced LVEF, independent of early recurrence. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;144:67−76)

Catheter ablation (CA) has become an established rhythm control therapy in patients with atrial fibrillation (AF),[1] but the long-term freedom from arrhythmic events remains a challenge in some patients. Finding the predictors of AF recurrence is of major importance. Brain natriuretic peptide (BNP) is one of the biomarkers that predicts recurrence after CA of AF.[2-6] Although a recent meta-analysis confirmed the association, it also revealed that the predictive value was significantly heterogeneous between studies, possibly due to differences in the study populations.[6] In patients with AF and reduced left ventricular ejection fraction (LVEF), pre-procedural BNP (pre-BNP) levels would be elevated due to both their inherent cardiac abnormalities and AF-induced hemodynamic derangement and structural remodeling.[7,8] Conversely, successful CA in those patients would reduce the hemodynamic load, improve cardiac

function, and decrease the BNP levels.[9−13] This change between pre-BNP and post-procedural BNP (post-BNP) levels implies that the prognostic implications of these values should be interpreted differently. The purpose of this study was to examine the pre-procedural and post-procedural correlations between BNP levels and cardiac function and the association between the BNP levels and AF recurrence after CA in patients with AF and reduced LVEF.

Methods

This was a single-center retrospective observational study conducted at Sakurabashi-Watanabe Hospital, Osaka, Japan. Of 3,142 consecutive patients who underwent first-time CA for AF between January 2012 and June 2019 in our institute, 384 patients (23%) had baseline LVEF <50%. Among them, we enrolled 217 patients who met our inclusion criteria: (1) patients whose plasma BNP levels were available both at baseline and 3 months after CA and (2) patients whose cardiac function was assessed during the same periods. Written informed consent for CA and retrospective use of data was obtained from all the patients. The last follow-up evaluation was performed in June 2020. This study was approved by the Institutional Review Board of Sakurabashi-Watanabe

Hospital, and conducted in compliance with the ethical principles of the Declaration of Helsinki.

Plasma BNP levels were measured from venous blood samples collected from a peripheral vein using a chemiluminescence enzyme immunoassay (Lumipulse G BNP, Fujirebio Inc., Tokyo, Japan). The assay used was a sandwich method that uses 2 monoclonal antibodies against human BNP, with 1 antibody recognizing the carboxyl-terminal sequence and the other recognizing the ring structure of BNP.[14] In this study, pre-BNP levels were defined as those measured at the time of admission. Post-BNP levels were defined as those measured 3 months after CA.

We also evaluated correlation between plasma BNP levels and cardiac function, which was assessed by 256-slice multidetector computed tomography (MDCT) (Brilliance iCT; Philips Medical Systems, Cleveland, Ohio). In our institute, baseline MDCT was performed to evaluate the chamber size and morphology, and a 3-dimensional reconstructed image was used to guide CA. Follow-up MDCT was performed 3 months after CA to identify potential complications such as pulmonary vein stenosis, unless contraindicated. These images allowed the measurement of left atrial (LA) and left ventricular (LV) chamber sizes such as maximum LA volume (LAV), LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV), using the Simpson disc summation method. LVEF was calculated as follows: $LVEF = [(LVEDV - LVESV) / LVEDV \times 100]$. The degree of structural reverse remodeling was quantitatively evaluated by the reduction rate in LAV, LVESV, and LVEDV. Reduction rate in LAV was calculated as follows: percent LA volume (%LAV) reduction = ([pre-procedural LAV] − [post-procedural LAV] and/or [pre-procedural LAV] × 100).[15] Reduction rate in LVEDV and LVESV were calculated using similar formulas. The degree of LVEF improvement was also calculated as follows: $\Delta LVEF = $ post-procedural LVEF − pre-procedural LVEF.

Before CA, patient medical history, co-morbidities, and treatment details were recorded by attending physicians. Preprocedural tests, such as electrocardiograms, chest X-rays, blood tests, echocardiography, and MDCT were performed in the outpatient clinic. Indications for CA were based on the expert consensus.[1] All anti-arrhythmic drugs were discontinued for 5 to 7 days prior to CA. Anticoagulation therapy with warfarin or direct oral anticoagulants was introduced at least 3 weeks before CA. Transesophageal echocardiography was performed to exclude any atrial thrombi.

Electrophysiological study was performed under sedation with dexmedetomidine and thiopental sodium. A single 150 IU/kg bolus of heparin was administered after the transseptal puncture and repeated as necessary to maintain an activated clotting time of >300 s. The detailed catheter settings and ablation methods have been described elsewhere.[16−18] The principle strategy of CA for persistent AF was pulmonary vein (PV) isolation using an irrigated radiofrequency tip catheter (Thermocool, Biosense Webster, Diamond Bar, California) or 28 mm cryoballoon (Arctic Front Advance, Medtronic Inc., Minneapolis, Minnesota). Radiofrequency CA was performed under the guidance of a 3-dimensional MDCT reconstruction image of the left atrium (CARTO3, Biosense Webster, Diamond Bar, California). Cryoballoon ablation has been performed since

September 2014 in paroxysmal AF patients who are anatomically eligible for balloon-based ablation. The PV isolation end-point was the achievement of electrical bidirectional conduction block between the left atrium and PVs. A cavotricuspid isthmus block line was created if common atrial flutter was detected before or during the procedure. After performing the aforementioned procedures, we routinely administered a high dose of isoproterenol (4 to 20 μg/min) after waiting for at least 20 min to identify time-dependent PV reconnections and/or presence of non-PV triggers. Additional ablation to prevent non-PV triggers, that is, non-PV ectopies initiating AF, was strongly encouraged. Other procedures such as linear ablation and complex fractionated atrial electrogram ablation were performed at the operator's discretion.

After CA, all patients underwent ambulatory monitoring during the first 3 post-procedural days until the day of discharge. Patients were scheduled to receive periodical follow-up at the outpatient clinic at 1, 3, 6, 9, and 12 months after ablation and every 6 months thereafter. A 12-lead electrocardiogram was obtained at each follow-up visit. All patients were advised to report any symptoms of arrhythmias experienced between scheduled visits. They were also instructed to check their pulse rate and rhythm at least 3 times a day and to visit the outpatient clinic if an irregular pulse continued. When AF recurrence was suspected, patients were checked by a portable electrocardiogram device. They were additionally seen by the referring cardiologist for 24-h Holter monitoring at the end of 6 and 12 months following CA. In principle, anti-arrhythmic drugs were stopped 3 months after CA unless patients experienced highly symptomatic AF recurrence. Recurrences during this blanking period were treated with anti-arrhythmic drugs and/or cardioversion, if needed.

The end-point of this study was AF recurrence, which was defined as documented symptomatic or asymptomatic recurrent atrial tachyarrhythmias lasting for ≥30 s after the blanking period of 90 days following CA.[1] The presence of AF and/or atrial tachycardia was evaluated on the basis of symptoms, electrocardiogram recordings, event recordings, and Holter electrocardiography. Early recurrence of atrial arrhythmias (ERAAs) during the blanking period was evaluated separately from recurrences after the blanking period because of their potential effect on post-BNP levels.

Categorical data are presented as frequencies (%) and were compared with the chi-squared test or Fisher's exact test when the expected cell size was <5. Continuous data are presented as mean (standard deviation) or as median (interquartile range) for skewed distributions. Normally distributed continuous variables were compared using the independent Student's t-test and skewed data using the nonparametric Mann−Whitney U test. Changes before and after CA were assessed by the paired t-test or Wilcoxon rank-sum test. The plasma BNP levels showed a skewed distribution (p <0.001, Kolmogorov−Smirnov test) and analyses were performed after a logarithmic transformation using the base-10 (log) to achieve a normal distribution (Supplementary Figure 1). At baseline and 3 months after CA, the correlations between log BNP levels and cardiac function measures were analyzed using linear regression analysis. During the follow-up, AF recurrence 3 months

Table 1
Baseline characteristics

	Total (N = 217)	Recurrence (N = 80)	No recurrence (N = 137)	p value
Age (years)	63 ± 10	63 ± 10	62 ± 10	0.57
Male	177 (82%)	62 (78%)	115 (84%)	0.24
Body mass index (kg/m^2)	23.8 ± 3.7	23.4 ± 3.6	24.1 ± 3.8	0.15
CHDAS2 score	1.6 ± 1.2	1.6 ± 1.2	1.6 ± 1.2	0.92
Type of AF				
- Paroxysmal	48 (22%)	17 (21%)	31 (23%)	0.74
- Persistent	121 (56%)	43 (54%)	78 (57%)	
- Long-standing persistent	48 (22%)	20 (25%)	28 (20%)	
Baseline heart diseases				
- Ischemic cardiomyopathy	23 (11%)	14 (18%)	9 (7%)	0.012
- Familial dilated cardiomyopathy	12 (8%)	3 (4%)	9 (7%)	0.38
- Hypertrophic cardiomyopathy	5 (2%)	0 (0%)	5 (4%)	0.085
- Valvular heart diseases	4 (2%)	1 (1%)	3 (2%)	0.62
- LV noncompaction cardiomyopathy	2 (1%)	1 (1%)	1 (1%)	1.00
- Idiopathic cardiomyopathy (including TIC/AIC)	171 (84%)	61 (76%)	110 (80%)	0.50
Coexisting diseases				
- Heart failure	141 (65%)	54 (68%)	87 (64%)	0.55
- Coronary artery disease	35 (16%)	16 (20%)	19 (13.9%)	0.24
- Hypertension	94 (43%)	35 (44%)	59 (43%)	0.92
- Diabetes mellitus	45 (21%)	16 (20%)	29 (21%)	0.84
- Prior stroke or TIA	18 (8%)	7 (9%)	11 (8%)	0.85
Echocardiographic parameters				
- LA diameter (mm)	43 ± 6	42 ± 5	43 ± 6	0.46
- LV diastolic diameter (mm)	52 ± 7	51 ± 7	52 ± 8	0.23
- LV systolic diameter (mm)	39 ± 9	38 ± 9	40 ± 10	0.17
- LV ejection fraction (Simpson) (%)	44 ± 13	43 ± 16	44 ± 12	0.90
Laboratory data				
- Hemoglobin level (g/dl)	14.7 (13.6−15.6)	14.5 (13.2−15.6)	14.8 (13.9−15.7)	0.082
- Serum creatinine level (mg/dl)	0.90 (0.80−1.07)	0.87 (0.79−1.00)	0.97 (0.80−1.10)	0.009
- High-sensitive CRP level (mg/dl)	0.08 (0.03−0.20)	0.08 (0.03−0.21)	0.07 (0.04−0.19)	0.89
- Serum BNP level (pg/ml)	198 (113−355)	205 (115−360)	198 (112−330)	0.49
- Log-transformed BNP	2.29 ± 0.40	2.31 ± 0.40	2.28 ± 0.41	0.56
Medications at discharge				
- Beta blocker	152 (70%)	57 (71%)	95 (69%)	0.77
- ACE inhibitor or ARB	90 (42%)	32 (40%)	58 (42%)	0.74
- Na-channel blocker	39 (18%)	18 (23%)	21 (15%)	0.19
- Amiodarone	28 (13%)	11 (14%)	17 (12%)	0.77
- Diuretics	86 (40%)	31 (39%)	55 (40%)	0.84
Ablation procedure				
- PVI with bidirectional block	217 (100%)	80 (100%)	137 (100%)	-
- PVI using radiofrequency CA	212 (98%)	77 (96%)	135 (99%)	0.36
- PVI using cryoballoon	5 (2%)	3 (4%)	2 (1%)	
CTI block line	93 (43%)	31 (39%)	62 (45%)	0.51
Adjective ablation other than PVI and CTI	57 (26%)	21 (26%)	36 (26%)	0.99
- LA posterior wall isolation	29 (14%)	9 (12%)	20 (15%)	0.53
- LA roof line	12 (6%)	6 (8%)	6 (4%)	0.33
- MVI line	22 (10%)	7 (9%)	15 (11%)	0.61
- SVC isolation	6 (3%)	3 (2%)	3 (4%)	0.49
- Non-PV focal ablation	18 (8%)	8 (10%)	10 (7%)	0.49

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AIC = arrhythmia-induced cardiomyopathy; ARB = angiotensin II receptor blocker; BNP = brain natriuretic peptide; CRP = C-reactive protein; CTI = cavotricuspid isthmus; LA = left atrial; LV = left ventricular; MVI = mitral valve isthmus; PV = pulmonary vein; PVI = PV isolation; SVC = superior vena cava; TIA = transient ischemic attack; TIC = tachycardia-induced cardiomyopathy.

after CA was reported, and Cox proportional hazards regression analyses were performed to determine the predictors of AF recurrence. Variables associated with AF recurrence (p <0.1) in the univariate analysis were

included in the multivariate analysis. The area under the receiver operating characteristic curves was calculated to identify the diagnostic accuracy of pre- and post-BNP levels for predicting AF recurrence. The 2 receiver operating
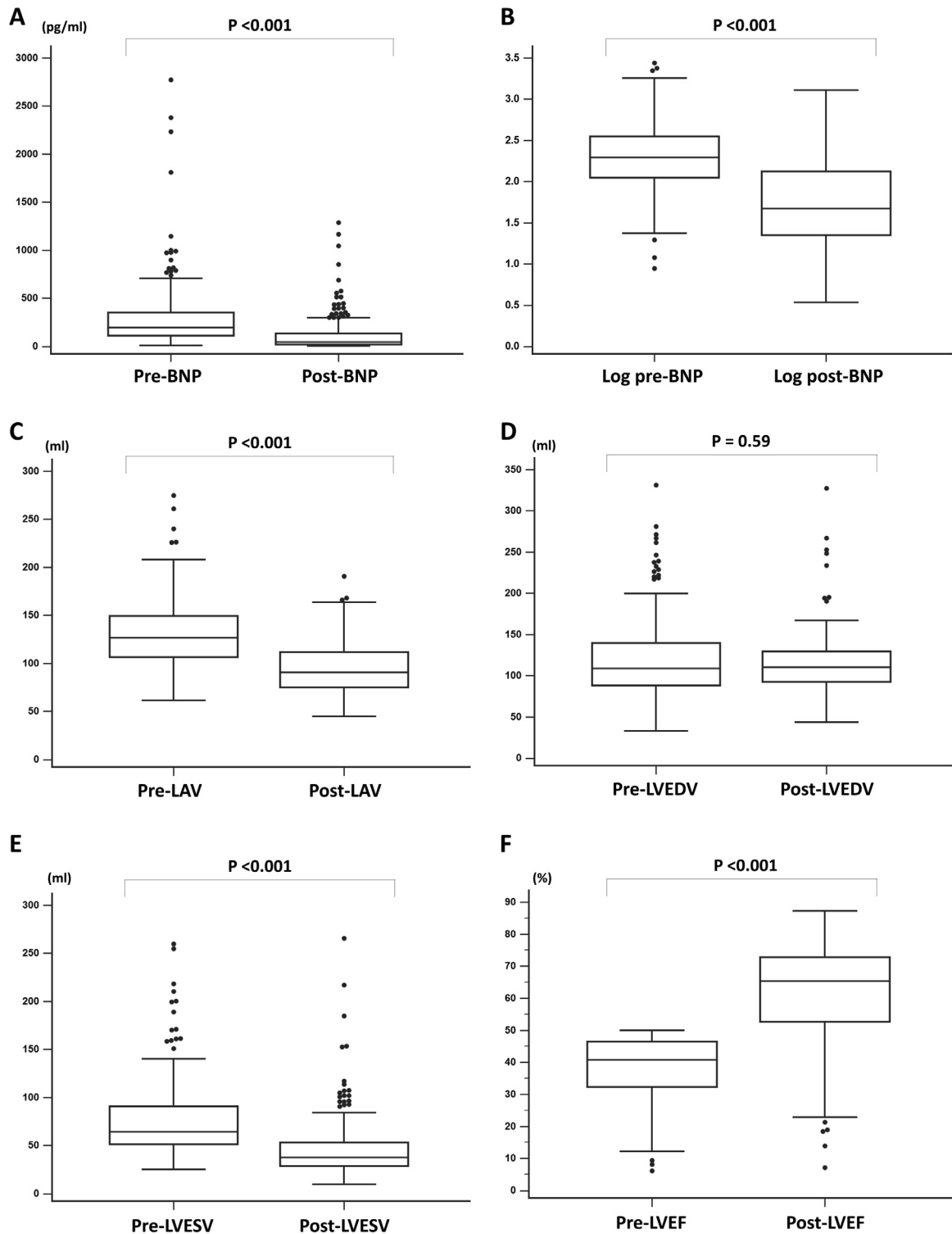

Figure 1. Changes in plasma BNP levels and cardiac function The pre- and post-operative values of BNP (*A*), log BNP (*B*), LAV (*C*), LVEDV (*D*), LVESV (*E*), and LVEF (*F*) were shown in the box and whisker plots. Change of plasma BNP levels were compared using Wilcoxson Rank-Sum test because of the skewness of the distribution. Changes in the other parameters were compared using paired *t*-tests. BNP = brain natriuretic peptide; LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = Left ventricular end-systolic volume; Pre = pre-procedural; Post = post-procedural.

characteristic curves were compared in the entire cohort and specific subgroups: age (≥70 years and <70 years), sex (male and female), AF type (paroxysmal and nonparoxysmal), etiology (structural heart disease and idiopathic etiology), CHADS2 score (>2 and ≤2), and LVEF (≤35% and >35%). The differences in AF-free survival between pre- and post-BNP quartile groups are shown as Kaplan−Meier curves and were compared using the log-rank test. Statistical analyses were performed using the MedCalc (version 19.0 for Windows) software. p values <0.05 were considered statistically significant.

Results

The baseline characteristics of enrolled patients are summarized in Table 1. Extensive encircling PV isolation was completed in all patients, and sinus rhythm was maintained when they left the catheter laboratory. A total of 18 patients (8%) developed CA-associated complications in this cohort. Seven patients developed sick sinus syndrome that required temporary pacing. Four developed worsening heart failure caused by volume overload necessitating intravenous diuretics and a prolonged hospital stay (>4 days after ablation). Four developed groin hematoma,

2 developed gastroparesis, and 1 developed phrenic nerve paralysis during superior vena cava isolation. There were no occurrences of cardiac tamponade, stroke, or atrial-esophageal fistula. Permanent pacemakers were implanted in 2 patients; the other patients recovered spontaneously or with additional treatment.

The pre- and post-BNP levels were measured at a median of 1 (interquartile range 1 to 1) day before and 89 (79 to 100) days after CA, respectively. There was a significant decrease in BNP levels (from a median of 198 [113 to 355] to 47.7 [22.7 to 135] pg/ml, p <0.001) and log BNP levels (from 2.29 ± 0.40 to 1.75 ± 0.53, p <0.001) after CA. In parallel, cardiac function significantly improved after CA. The decrease in LAV (from 130 ± 34 to 97 ± 29 ml, p <0.001) and LVESV (from 76 ± 50 to 50 ± 43 ml, p <0.001) with unchanged LVEDV (from 121 ± 58 to 118 ± 57 ml, p = 0.16), resulted in improvement of LVEF (from 39 ± 9% to 61 ± 16%, p <0.001) (Figure 1). There were significant positive correlations between log BNP levels and LAV (r = 0.52, p <0.001), LVEDV (r = 0.43, p <0.001), and LVESV (r = 0.25, p <0.001) both at baseline and 3 months after CA. Conversely, there was a negative correlation between log BNP levels and LVEF (r = −0.64 p <0.001) at both timings (Figure 2).
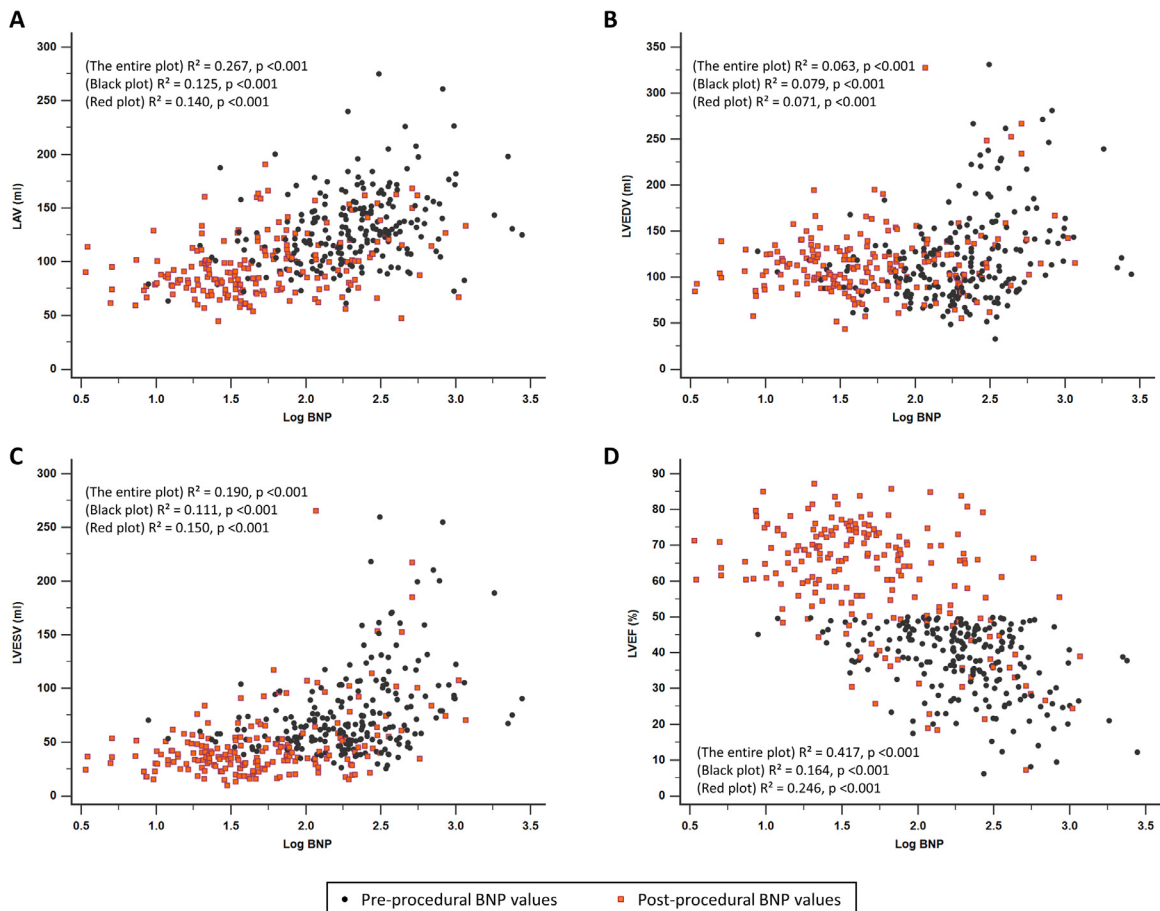

Figure 2. Relationship between plasma BNP levels and cardiac function.The scatter plot shows the correlations between log-transformed BNP levels and cardiac function at baseline (black dots) and 3 months after CA (red dots). Correlation analyses showed that BNP levels were positively correlated with LAV (A), LVEDV (B) and LVESV (C). BNP levels were negatively correlated with LVEF (D).CA = catheter ablation; other abbreviations are spelled out in Figure 1.

Table 2
Cox regression analysis for identifying predictors of AF recurrence

| | Univariate | | Multivariate* | | | |
| | | | Model I | | Model II | |
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age (per 10-y increase)	1.20 (0.95−1.52)	0.13	NA	NA	NA	NA
Female	1.52 (0.90−2.58)	0.12	NA	NA	NA	NA
Body mass index	0.95 (0.89−1.02)	0.15	NA	NA	NA	NA
Persistent AF	1.10 (0.64−1.87)	0.74	NA	NA	NA	NA
Structural heart disease	1.38 (0.82−2.31)	0.22	NA	NA	NA	NA
Hypertension	1.01 (0.65−1.58)	0.95	NA	NA	NA	NA
Diabetes mellitus	1.03 (0.60−1.79)	0.91	NA	NA	NA	NA
Coronary artery disease	1.53 (0.87−2.69)	0.14	NA	NA	NA	NA
Hemoglobin	0.80 (0.70−0.92)	0.001	0.95 (0.80−1.12)	0.55	0.95 (0.80−1.12)	0.47
Serum creatinine level	1.03 (0.79−1.34)	0.83	NA	NA	NA	NA
Presence of ERAA	4.63 (2.90−7.41)	<0.001	4.88 (2.89−8.25)	<0.001	4.63 (2.82−7.60)	<0.001
Log pre-BNP	1.42 (0.81−2.49)	0.22	NA	NA	NA	NA
Log post-BNP	2.29 (1.53−3.43)	<0.001	2.02 (1.14−3.56)	0.015	1.82 (1.07−3.10)	0.027
Pre-LAV[†]	1.00 (0.92−1.08)	0.91	NA	NA	NA	NA
Post-LAV[†]	1.08 (1.00−1.16)	0.038	0.98 (0.90−1.07)	0.66		
%LAV reduction[‡]	0.84 (0.74−0.95)	0.004			0.87 (0.75−1.02)	0.08
Pre-LVEDV[†]	0.98 (0.93−1.03)	0.35	NA	NA	NA	NA
Post-LVEDV[†]	0.97 (0.91−1.03)	0.31	NA	NA	NA	NA
%LVEDV reduction[‡]	0.99 (0.91−1.08)	0.87	NA	NA	NA	NA
Pre-LVESV[†]	0.98 (0.92−1.04)	0.47	NA	NA	NA	NA
Post-LVESV[†]	1.00 (0.96−1.05)	0.96	NA	NA	NA	NA
%LVESV reduction[‡]	0.90 (0.83−0.98)	0.012	0.95 (0.83−1.08)	0.40	0.98 (0.86−1.12)	0.78
Pre-LVEF[§]	1.01 (0.98−1.03)	0.61	NA	NA	NA	NA
Post-LVEF[§]	0.88 (0.77−0.99)	0.040	0.94 (0.76−1.04)	0.58		
⊿LVEF[§]	0.85 (0.74−0.97)	0.013			0.89 (0.94−1.06)	0.89

* Multivariate cox regression analysis was performed including variables associated with AF recurrence (p <0.1) in the univariate analysis. Post-LAV and %LAV reduction were explanatory variables for each other. Thus, post-LAV and %LAV reduction were separately included in Model I and Model II, respectively. The same applied to post-LVEF and ⊿LVEF.

[†] per 10 ml increase,

[‡] per 10% decrease,

[§] per 10% increase, NA; not applicable.

AF = atrial fibrillation; BNP = brain natriuretic peptide; CI = confidence interval; ERAA = early recurrence of atrial arrhythmia; HR = hazard ratio; LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; Pre = pre-procedural; Post = post-procedural.

During the 3-month blanking period, ERAAs were observed in 84 patients. Although there were no significant differences in pre-BNP levels between patients with and without ERAAs (192 [114 to 352] vs 214 [112 to 359] pg/ml, p = 0.38), post-BNP levels were higher in patients with ERAAs than in those without it (64.4 [32.4 to 200] vs 41.8 [21.8 to 102] pg/ml, p = 0.047). Over a median follow-up period of 35 months (interquartile range, 18 to 58), 80 patients (37%) experienced AF recurrence after the index ablation procedure. Multivariate Cox proportional hazards regression analyses revealed that ERAA (hazard ratio, 4.96; 95% confidence interval, 2.95 to 8.35; p <0.001) and elevated post-BNP levels (hazard ratio, 2.12 per unit log increase; 95% confidence interval, 1.22 to 3.69; p = 0.008) were independent predictors of AF recurrence (Table 2).

The results of receiver operating characteristic curve analysis predicting AF recurrence during the 1 year and the entire follow-up period are presented in Figure 3. Although there was no significant cutoff value for pre-BNP levels, post-BNP levels showed significant diagnostic accuracy to predict AF recurrence both during the 1 year (area under the curve, 0.686; 95% confidence interval, 0.620 to 0.747)

and the entire follow-up (0.617; 0.549 to 0.682). The diagnostic performance of post-BNP levels was significantly higher than that of pre-BNP levels. Although not necessarily statistically significant, a consistent trend favoring post-BNP levels was observed in all analyzed subgroups (Supplementary Table 1).

During the follow-up period, the incidence of AF recurrence was similar among pre-BNP quartile groups (Figure 4). However, AF recurrence was significantly more frequent in patients with the highest quartile post-BNP levels (i.e., ≥136 pg/ml) than in those with the other quartile post-BNP levels (hazard ratio, 3.84; 95% confidence interval, 2.13 to 6.92, p < 0.001) (Figure 4).

Discussion

In this study, we investigated the association between the pre- and post-BNP levels and the risk of AF recurrence after CA in patients with AF and reduced LVEF. Most patients had a significant improvement in the cardiac function and decrease in BNP levels after CA. Although pre-BNP levels were not useful for predicting AF recurrence, post-BNP
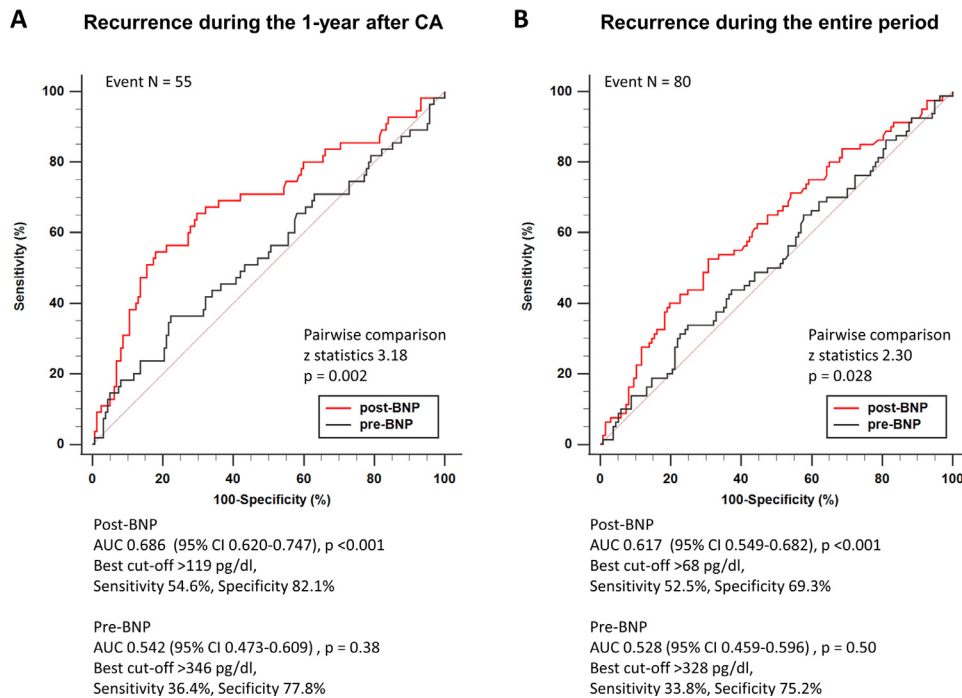
A   **Recurrence during the 1-year after CA**

Post-BNP
AUC 0.686 (95% CI 0.620-0.747), p <0.001
Best cut-off >119 pg/dl,
Sensitivity 54.6%, Specificity 82.1%

Pre-BNP
AUC 0.542 (95% CI 0.473-0.609) , p = 0.38
Best cut-off >346 pg/dl,
Sensitivity 36.4%, Secificity 77.8%

B   **Recurrence during the entire period**

Post-BNP
AUC 0.617 (95% CI 0.549-0.682), p <0.001
Best cut-off >68 pg/dl,
Sensitivity 52.5%, Specificity 69.3%

Pre-BNP
AUC 0.528 (95% CI 0.459-0.596) , p = 0.50
Best cut-off >328 pg/dl,
Sensitivity 33.8%, Secificity 75.2%

Figure 3. Receiver operating characteristic curves.The area under the receiver operating characteristic curves (AUCs) for post-BNP (red) was higher than that for pre-BNP (black), indicating a higher diagnostic accuracy of post-BNP for predicting AF recurrence both during the 1 year after CA (*A*) and the entire period (*B*).AUC, area under the receiver operating characteristic curves; CA = catheter ablation; CI = confidence interval; other abbreviations are spelled out in Figure 1

levels 3 months after CA were significantly associated with AF recurrence, independent of ERAA. Based on these results, patients with elevated plasma BNP levels at the end of the blanking period would have a high risk of AF recurrence, and therefore they should be carefully followed in the outpatient clinic.

BNP is a natriuretic peptide hormone secreted by cardiac myocytes in response to wall stress.[19,20] Elevated BNP levels reflect background cardiac abnormality, and it has been associated with occurrence of AF [21] and AF recurrence after CA.[2-6] However, contrary to previous studies, pre-BNP was not a biomarker for risk of AF recurrence in this study. The specific study population introduced in this study might explain why we saw a different result. In patients with AF and reduced LVEF, significant hemodynamic derangements induced by AF and subsequent structural remodeling would increase BNP levels. AF produces hemodynamic load and wall stress by loss of atrial kick, rapid and irregular ventricular rhythm, and loss of atrioventricular synchrony, resulting in elevated BNP levels.[7,8] In addition, AF-induced structural remodeling would further increase plasma BNP levels, especially in patients with reduced LVEF.[7,8,19,20] Thus, it is a clinical challenge to pre-procedurally identify whether elevated BNP is a consequence of inherent cardiac abnormality or a consequence of AF-induced hemodynamic derangement and structural remodeling in patients with AF and reduced LVEF. On the other hand, sinus rhythm restoration after CA diminishes the AF-induced hemodynamic load, and reverse structural remodeling results in a significant decrease in plasma BNP levels.[9-13] Post-BNP levels after CA would more precisely reflect inherent cardiac disorders than pre-BNP levels.

Currently, there is no compelling evidence that an elevated BNP directly causes AF. Thus, the association between an elevated BNP and the incidence of AF would be explained by the shared substrate including LA and LV dysfunction, myocardial fibrosis, and increased LA pressure.[7,8,19,20] In this study, we found significant correlations between plasma BNP levels and LAV, LVEDV, LVESV and LVEF, both at baseline and 3 months after CA. Advanced structural remodeling reflects an increased LA pressure, which is considered to be associated with elevated BNP levels [19,20] and AF recurrence.[22] In addition, AF itself is a major modifier associated with plasma BNP levels.[23] Patients with ERAA had a higher risk of developing AF recurrence 3 months after CA than those without.[1] Thus, as suggested in the result of this study, elevated post-BNP levels 3 months after CA may be partly due to the presence of ERAA. Furthermore, both elevated BNP levels and incident AF are associated with similar patient backgrounds such as an old age, obesity, sleep apnea, and multiple co-morbidities.[1] In the present study, however, even after considering those potential backgrounds and cardiac functional measures associated with AF recurrence, elevated post-BNP levels were significant predictors of AF recurrence in the multivariate analysis (Table 2 Model I). The predictive nature of post-BNP was independent of the improvement in cardiac function (%LAV reduction and ⊿LVEF) (Table 2 Model II). Therefore, elevated post-BNP levels even after restoration of sinus rhythm would give us additional information regarding the risk of AF recurrence beyond the improvement in cardiac function, which may indicate a presence of residual substrate for developing AF recurrence.
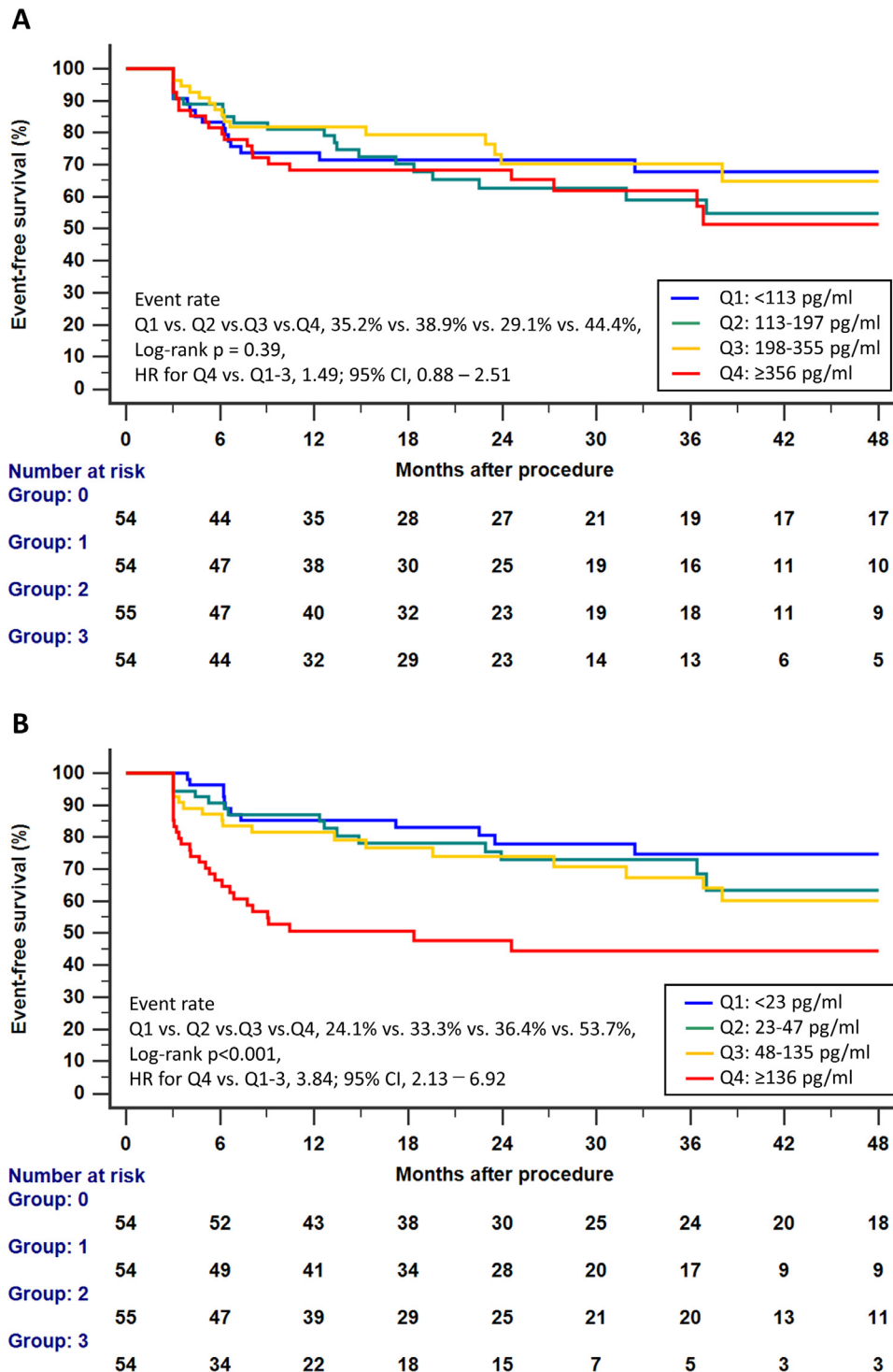
A

B

Figure 4. Kaplan−Meier survival curves. Over a median follow-up period of 35 months (interquartile range, 18 to 58), atrial fibrillation recurrence-free survival was compared between pre-BNP quartile groups (*A*) and post-BNP quartile groups. CI = confidence interval; HR = hazard ratio; other abbreviations are spelled out in Figure 1.

Evaluating post-BNP levels is useful to stratify the recurrence risk in patients with AF and reduced LVEF. Although the diagnostic accuracy is not so high (the area under the curve <0.7), the post-BNP levels were independent predictors of AF recurrence over the conventional risk factors (i.e., age, female sex, AF type, associated systemic disease, LA and LV properties [volume, degree of reverse remodeling], etc.).[1,15,22−24] Thus, in combination with the conventional factors associated with AF recurrence, post-BNP levels could help refine the identification of the high-risk cohort in patients with AF and reduced LVEF. N-terminal pro-BNP is a promising

alternative marker for predicting AF recurrence. However, because N-terminal pro-BNP has a longer half-life and a higher susceptibility to renal insufficiency than BNP, the cutoff values would be different from those of BNP levels. This should be investigated in the future.

The study limitations include a single-center retrospective observational design and the fact that the evaluation of post-BNP levels during the designated period was performed at physician's discretion, which introduced selection bias to the study population. Second, asymptomatic and other cases of AF recurrence may have been missed. However, routine continuous monitoring using implanted devices is not yet feasible in the real-world clinical practice. Third, post-BNP was measured 3 months after CA, but the most appropriate time to predict AF recurrence is unknown. Repetitive measurement of plasma BNP levels during the course may provide additional data about AF recurrence. Fourth, the effect of all confounders that affect plasma BNP levels might not have been fully examined in the multivariate analysis. Finally, the cutoff values of plasma BNP levels would be influenced by the examined cohort. However, the trend of decreasing plasma BNP levels after CA and increasing predictive values of BNP levels 3 months after CA was similar in all examined subgroups (Supplementary Table 1). Understanding the dynamic behavior of plasma BNP levels and increased predictive value of BNP levels after CA is more important than cutoff values.

In conclusion, pre-BNP levels before CA were not associated with AF recurrence in patients with reduced LVEF. Elevated post-BNP levels 3 month after CA indicated an independent risk of AF recurrence in this population.

Credit Author Statement

All authors substantially contributed to the work and met the authorship criteria as follows: Masato Okada: Conceptualization, Methodology, Formal analysis, Writing - Original Draft. Nobuaki Tanaka, Koji Tanaka, Yuko Hirao, Issei Yoshimoto, Shinichi Harada: Investigation, Resources, Data Curation. Toshinari Onishi, Yasushi Koyama, Atsunori Okamura, Katsuomi Iwakura, Kenshi Fujii, Yasushi Sakata: Supervision. Koichi Inoue: Writing - Review and Editing, Supervision, Project administration.

DISCLOSURES

Acknowledgment

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.057.

1. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Wyn Davies D, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/ APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017;14:e275–e444.
2. Hussein AA, Saliba WI, Martin DO, Shadman M, Kanj M, Bhargava M, Dresing T, Chung M, Callahan T, Baranowski B, Tchou P, Lindsay BD, Natale A, Wazni OM. Plasma B-type natriuretic peptide levels and recurrent arrhythmia after successful ablation of lone atrial fibrillation. *Circulation* 2011;123:2077–2082.
3. Degener S, Pattberg SV, Feuersenger H, Bansmann PM, Shin DI, Krummenauer F, Horlitz M. Predictive value of B-type natriuretic peptide levels in patients with paroxysmal and persistent atrial fibrillation undergoing pulmonary vein isolation. *J Interv Card Electrophysiol* 2011;30:217–225.
4. Zhang Y, Chen A, Song L, Li M, Chen Y, He B. Association between baseline natriuretic peptides and atrial fibrillation recurrence after catheter ablation. *Int Heart J* 2016;57:183–189.
5. Miake J, Kato M, Ogura K, Iitsuka K, Okamura A, Tomomori T, Tsujimoto D, Kato M, Yamamoto K. Pre-ablation levels of brain natriuretic peptide are independently associated with the recurrence of atrial fibrillation after radiofrequency catheter ablation in patients with nonvalvular atrial fibrillation. *Heart Vessels* 2019;34:517–526.
6. Jiang H, Wang W, Wang C, Xie X, Hou Y. Association of pre-ablation level of potential blood markers with atrial fibrillation recurrence after catheter ablation: a meta-analysis. *Europace* 2017;19:392–400.
7. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-induced cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;73:2328–2344.
8. Cha YM, Redfield MM, Shen WK, Gersh BJ. Atrial fibrillation and ventricular dysfunction: a vicious electromechanical cycle. *Circulation* 2004;109:2443–2839.
9. Sacher F, Corcuff JB, Schraub P, Le Bouffos V, Georges A, Jones SO, Lafitte S, Bordachar P, Hocini M, Clémenty J, Haissaguerre M, Bordenave L, Roudaut R, Jaïs P. Chronic atrial fibrillation ablation impact on endocrine and mechanical cardiac functions. *Eur Heart J* 2008; 29:1290–1295.
10. Yanagisawa S, Inden Y, Kato H, Fujii A, Mizutani Y, Ito T, Kamikubo Y, Kanzaki Y, Hirai M, Murohara T. Decrease in B-type natriuretic peptide levels and successful catheter ablation for atrial fibrillation in patients with heart failure. *Pacing Clin Electrophysiol* 2016;39:225–234.
11. Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ, Pappone C, Neumann T, Noelker G, Fiala M, Bertaglia E, Frontera A, Duncan E, Nalliah C, Jais P, Weerasooriya R, Kalman JM, Gaita F. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;7:1011–1018.
12. Ma Y, Bai F, Qin F, Li Y, Tu T, Sun C, Zhou S, Liu Q. Catheter ablation for treatment of patients with atrial fibrillation and heart failure: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2018;18:165.
13. Okada M, Tanaka N, Oka T, Tanaka K, Ninomiya Y, Hirao Y, Yoshimoto I, Inoue H, Kitagaki R, Onishi T, Koyama Y, Okamura A, Iwakura K, Sakata Y, Fujii K, Inoue K. Clinical significance of left ventricular reverse remodeling after catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction. *J Cardiol* 2020;20:S0914–S5087. https://doi.org/10.1016/j.jjcc.2020.11.007.
14. Ito Y, Namioka Y. Fundamental evaluation of two BNP assay reagents by chemiluminescent enzyme immunoassay using Lumipulse® F and Lumipulse Presto® II. *Jpn J Med Pharm Sci* 2010;64:931–939.

15. Oka T, Inoue K, Tanaka K, Ninomiya Y, Hirao Y, Tanaka N, Okada M, Inoue H, Nakamaru R, Koyama Y, Okamura A, Iwakura K, Sakata Y, Fujii K. Left atrial reverse remodeling after catheter ablation of nonparoxysmal atrial fibrillation in patients with heart failure with reduced ejection fraction. *Am J Cardiol* 2018;122:89–96.

16. Inoue K, Kurotobi T, Kimura R, Toyoshima Y, Itoh N, Masuda M, Higuchi Y, Date M, Koyama Y, Okamura A, Iwakura K, Fujii K. Trigger-based mechanism of the persistence of atrial fibrillation and its impact on the efficacy of catheter ablation. *Circ Arrhythm Electrophysiol* 2012;5:295–301.

17. Tanaka N, Inoue K, Tanaka K, Toyoshima Y, Oka T, Okada M, Inoue H, Nakamaru R, Koyama Y, Okamura A, Iwakura K, Sakata Y, Fujii K. Automated ablation annotation algorithm reduces re-conduction of isolated pulmonary vein and improves outcome after catheter ablation for atrial fibrillation. *Circ J* 2017;81:1596–1602.

18. Nakamaru R, Okada M, Tanaka N, Tanaka K, Ninomiya Y, Hirao Y, Oka T, Inoue H, Takayasu K, Koyama Y, Okamura A, Iwakura K, Rakugi H, Sakata Y, Fujii K, Inoue K. Outcomes after atrial fibrillation ablation in patients with premature atrial contractions originating from non-pulmonary veins. *JACC Clin Electrophysiol* 2019;5:1319–1327.

19. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998;135:825–832.

20. Barclay JL, Kruszewski K, Croal BL, Cuthbertson BH, Oh JK, Hillis GS. Relation of left atrial volume to B-type natriuretic peptide levels in patients with stable chronic heart failure. *Am J Cardiol* 2006;98:98–101.

21. Kara K, Geisel MH, Möhlenkamp S, Lehmann N, Kälsch H, Bauer M, Neumann T, Dragano N, Moebus S, Jöckel KH, Erbel R, Mahabadi AA. B-type natriuretic peptide for incident atrial fibrillation-The Heinz Nixdorf Recall Study. *J Cardiol* 2015;65:453–458.

22. Linhart M, Lewalter T, Mittmann-Braun EL, Karbach NC, Andrié RP, Hammerstingl C, Fimmers R, Kreuz J, Nickenig G, Schrickel JW, Lickfett LM. Left atrial pressure as predictor for recurrence of atrial fibrillation after pulmonary vein isolation. *J Interv Card Electrophysiol* 2013;38:107–114.

23. Darkner S, Goetze JP, Chen X, Henningsen K, Pehrson S, Svendsen JH. Natriuretic propeptides as markers of atrial fibrillation burden and recurrence (from the AMIO-CAT Trial). *Am J Cardiol* 2017;120:1309–1315.

24. Tanaka N, Inoue K, Kobori A, Kaitani K, Morimoto T, Kurotobi T, Morishima I, Yamaji H, Matsui Y, Nakazawa Y, Kusano K, Okada M, Tanaka K, Hirao Y, Oka T, Koyama Y, Okamura A, Iwakura K, Fujii K, Kimura T, Shizuta S. Sex differences in atrial fibrillation ablation outcomes: insights from a large-scale multicentre registry. *Europace* 2020;22:1345–1357.