Left Atrial Volume Index Predicts Future Improvement of B-Type Natriuretic Peptide Levels After Transcatheter Aortic Valve Replacement

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Research Article

Keywords: aortic stenosis, transcatheter aortic valve replacement, left atrium, B-type natriuretic peptide

Posted Date: November 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1012442/v1>

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Version of Record: A version of this preprint was published at The International Journal of Cardiovascular Imaging on February 8th, 2022. See the published version at <https://doi.org/10.1007/s10554-022-02538-7>.

Abstract

Background: In patients with symptomatic severe aortic stenosis (AS), those who experienced readmission due to heart failure after transcatheter aortic valve replacement (TAVR) showed poor prognosis. Furthermore, poor BNP improvement is associated with increased morbidity and mortality. However, little is known about the clinical parameters related to the change in BNP levels after TAVR procedure.

Methods and Results: This study population consisted of 127 consecutive patients of symptomatic severe AS with preserved ejection fraction (EF) who underwent TF-TAVR. The median BNP level was significantly decreased from 252.5 pg/ml to 146.8 pg/ml in all 127 patients 1 year after TF-TAVR ($P<0.01$). However, the patients could be divided into 2 groups according to decrease (72%) or increase (28%) in plasma BNP level. Multivariate logistic regression analysis revealed that AV peak velocity, pre-procedural BNP, and larger left atrial volume index (LAVI) were found to be an independent predictor of increased BNP level 1 year after TAVR (OR 0.55, 95% CI 0.38-0.77; $p<0.01$). LAVI were negatively correlated with the change in BNP level before and 1 year after TAVR ($r=0.47$, $P<0.01$). The ROC analysis demonstrated that 52.9ml/m^2 was the optimal cut-off value of LAVI for decreasing BNP 1 year after TAVR (area under the curve 0.69) with 64% sensitivity and 70% specificity.

Conclusions: In addition to AV peak velocity and pre-procedural BNP, LAVI independently predicts future improvement of BNP levels 1 year after TAVR. Our findings indicate an additive predictive value of assessment of LAVI before TAVR procedure for risk stratification.

Introduction

Transcatheter aortic valve replacement (TAVR) is becoming an alternative intervention to surgical aortic valve replacement (SAVR) for high-risk, and even low-risk, patients with severe symptomatic aortic stenosis (AS) [1–3]. Although TAVR has comparable outcomes to SAVR, patients requiring readmission after TAVR have a poor prognosis [4, 5]. Congestive heart failure is the most common cardiac cause of readmission [4]. Therefore, it is clinically important to identify patients at high risk for heart failure after TAVR.

B-type natriuretic peptide (BNP) is a non-invasive biomarker for the diagnosis and management of patients with heart failure or various other cardiac diseases [6, 7]. In patients who undergo TAVR to treat AS, elevated BNP levels at baseline or discharge are associated with poor outcomes [8, 9]. Changes in BNP levels before and after TAVR, rather than a single BNP measurement, can more accurately predict prognosis [10–12]. Patients with poor improvement in BNP levels after TAVR have less symptomatic improvement and higher long-term mortality rates than patients with lower BNP levels [10–12]. Ideally, plasma BNP levels should decrease within the first year after TAVR and remain stable thereafter [2, 13]. However, around 35–40% of patients show persistent elevated plasma BNP levels at their 1-year follow-up after TAVR, and these patients have higher rates of morbidity and mortality [10, 11]. Therefore, it is

important to remeasure BNP levels at 1-year follow-up appointments to predict prognosis in AS patients who have undergone TAVR.

Furthermore, little is currently known about which clinical parameters predict changes in BNP levels in patients with severe AS after TAVR. In the present study, we assess the clinical factors associated with serial changes in BNP levels before and after transfemoral TAVR (TF-TAVR) and at the 1-year follow-up timepoint.

Methods

Study population

This study was a single-center prospective observational study undertaken at Osaka City University Hospital. We examined 237 consecutive symptomatic severe AS patients who underwent TAVR between January 2016 and January 2019. To minimize the influence on serial BNP levels, we excluded 34 patients who underwent TAVR by non-TF approaches, 33 patients with an EF less than 50%, 25 patients with more than moderate mitral regurgitation (MR), and 18 patients who were not able to carry out clinical follow-up for more than 1 year after TAVR. With these exclusions, we enrolled 127 patients with preserved EF who underwent TF-TAVR (Figure1).

Transthoracic echocardiography (TTE) was performed the day before TAVR and laboratory data was measured both before and 1 year after TAVR. All data shown in the tables and figures were collected prospectively from patient records. Clinical data including patient characteristics and echocardiographic data were prospectively recorded.

Written informed consent was obtained from each patient included in this study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the study protocol was approved by the hospital ethics committee of the Osaka City University Graduate School of Medicine (Approval Number: 2021-064).

Transthoracic Echocardiography

Comprehensive two-dimensional TTE was performed within the seven days preceding the TAVR procedure using an iE33 (Philips Medical Systems, Andover, MA, USA), Vivid E9 (GE Healthcare, Milwaukee, WI, USA), or Aplio 500 (Canon Medical Systems Corporation, Tochigi, Japan) machine equipped with a high-frequency transducer. Left ventricle end-diastolic diameter (LVDD), left ventricular end-systolic diameter (LVSD), interventricular septal thickness (IVS), and posterior wall thickness (PW) were measured in accordance with published guidelines [15]. Left ventricular mass (LVM) was calculated using the formula ($LVM = 0.80 \times 1.04 \times [(LVDD + IVS + PW)^3 - LVDD^3] + 0.6 \text{ g}$). Also, left atrial volume (LAV) was measured using the biplane method of disks at end-systole just before mitral valve opening. In each view, the LA wall was traced, excluding the LA appendage and pulmonary veins. LVM and LA

volume measurements were indexed to body surface area to calculate the left atrial volume index (LAVI). We evaluated left ventricular EF with the biplane-modified Simpson method [14].

Using the pulse wave Doppler method, the peak velocity of diastolic early trans-mitral Doppler flow (E) was measured by placing a sample volume at the opening levels of the mitral valve leaflet tips. Tissue Doppler velocity during early diastole (e') was measured from the septal corner of the mitral annulus in the apical four-chamber view. Doppler measurements were obtained by averaging data from three consecutive cardiac cycles in the case of sinus rhythm and five consecutive cardiac cycles in the case of atrial fibrillation (AF), and E/e' ratios were calculated.

Multiple transducer positions were used to record aortic jet velocities to avoid angle-related errors and the aortic valve area was calculated using the continuity equation method [14]. Severe AS was defined as a peak aortic valve jet velocity of > 4.0 m/s, a mean aortic valve gradient (AV mean PG) > 40 mmHg, or an aortic valve area (AVA) < 1.0 cm [2, 15]. Severity of MR was graded as none, trivial, mild, moderate, or severe primarily by MR jet area, and, if necessary, other echocardiographic methods, including vena contracta, proximal isovelocity surface area, peak E velocity of the trans-mitral inflow, or pulmonary venous flow velocity data (S/D ratio), were incorporated [15].

Plasma Bnp Measurements

Peripheral venous blood samples for laboratory analysis were drawn before and 1 year after TAVR. Plasma BNP concentration was measured by chemiluminescent immunoassay (BNP-JP Abbott instrument; Abbott Japan, Tokyo, Japan).

Statistical analysis

Continuous variables were summarized using medians and interquartile range (quartiles 1–3), and categorical variables were summarized using counts and percentages. When two groups were compared, the unpaired t-test or Mann–Whitney U test was used, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test. Association of clinical factors with decreased BNP 1 year after TAVR was evaluated by multiple logistic regression analysis after adjustment for significant variables with $p < 0.01$ on univariate analysis. Spearman's rank correlation coefficient was used to analyze the correlation between LAVI and the change in BNP levels, before and 1 year after TAVR. The validity of the change in BNP levels before and 1 year after TF-TAVR for estimating associated clinical factors was evaluated using receiver operating characteristics (ROC) curves. P-values < 0.05 were considered statistically significant. All statistical analyses were performed with EZR [16], which is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Clinical baseline patient characteristics are listed in Table 1. In the total study population, the median patient age was 84 (quartile; 81–87) years, and 38/127 (30%) patients were male. The median pre-TAVR BNP level was 252.5 pg/ml (quartile; 74.3-352.1) and the median estimated glomerular filtration rate (eGFR) was 51.7 mL/min/1.73m² (quartile; 38.6–63.2).

The median BNP level in the total population of 127 patients significantly decreased from 252.5 pg/ml to 146.8 pg/ml 1 year after TF-TAVR ($p<0.01$) (Figure 2). However, the patients could be divided into two groups according to whether their plasma BNP levels decreased (91/127, 72%) or increased (36/127, 28%) 1 year after TF-TAVR. Representative TTE images before TAVR in clinical cases with decreased or increased plasma BNP levels were shown in Figure 3. The characteristics of patients with decreased or increased BNP levels 1 year after TF-TAVR were shown in Table 1. There were no significant differences in the frequency of hypertension, eGFR and AF between the two groups. Patients in the decreased BNP group had higher pre-TAVR BNP levels (294.2 (101.5-438.1) vs. 147.2 (46.5-222.2); $p<0.01$) and higher STS scores (9.4 (5.7-11.8) vs. 6.6 (4.8-8.9); $p=0.03$) than those with increased BNP levels.

Echocardiographic data for all patients are shown in Table 2. There were no significant differences in LV end-diastolic and end-systolic dimensions, LV wall thickness, E-wave velocities on trans-mitral doppler flow, e' velocities on TDI and the E/e' ratio between the two groups. However, patients with decreased BNP levels 1 year after TF-TAVR had smaller LAVIs (48.7 (40.5-56.5) vs. 53.1 (46.3-60.9); $p=0.02$), smaller Aortic Valve areas (AVA) (0.65 (0.56-0.72) vs. 0.71 (0.64-0.75); $p=0.02$), greater Aortic Valve (AV) mean pressure gradients (49.5 (39.0-68.0) vs. 42.1 (36.5-52.3); $p=0.02$), and higher AV peak velocities (4.7 (4.2-5.4) vs. 4.35 (4.0-4.8); $p=0.01$) than patients with increased BNP levels.

To identify the factors that predict improvement in BNP levels after TAVR, we performed logistic regression analysis. In the univariate logistic regression analysis, higher pre-TAVR BNP (OR 4.98, 95% CI 1.99-12.6; $p<0.01$), smaller LAVI (per 10mL/m²) (OR 0.67, 95% CI 0.50-0.89; $p<0.01$) and higher AV peak velocity (OR 2.19, 95% CI 1.22-3.93; $p<0.01$) were significant predictors of decreased BNP levels 1 year after TAVR ($p<0.01$) (Table 3). Multivariate logistic regression analysis after adjustment for pre-TAVR BNP and AV peak velocity revealed higher LAVI to be an independent predictor of increased BNP levels 1 year after TAVR (OR 0.55, 95% CI 0.38-0.77; $p<0.01$) (Table 3).

We assessed the correlation between LAVI and the change in BNP levels before and 1 year after TAVR. LAVI negatively correlated with the change in BNP levels before and 1 year after TAVR ($r=0.47$, $p<0.01$) (Figure 4A). ROC analysis demonstrated that 52.9mL/m² was the optimal LAVI cut-off value for decreased BNP 1 year after TAVR (area under the curve 0.69) with 64% sensitivity and 70% specificity (Figure 4B).

Discussion

The key findings of our study in 127 consecutive patients with symptomatic severe AS and preserved EF who underwent TF-TAVR were: 1) in the total patient population, the median BNP level significantly decreased 1 year after the procedure, however, the patients could be divided into two groups according to

whether their plasma BNP levels decreased (72%) or increased (28%); 2) pre-TAVR BNP levels, AV peak velocity and higher LAVI were independent predictors of increased BNP levels 1 year after TAVR; 3) LAVI negatively correlated with the change in BNP levels before and 1 year after TAVR; and 4) 52.9ml/m² was the optimal LAVI cut-off value for decreased BNP 1 year after TAVR.

It has been reported that elevated BNP levels correlate with AS severity [17]. Intervention to treat AS, regardless of whether it is SAVR or TAVR, can significantly improve BNP levels [17, 18]. In this study, the median BNP levels of the total population of 127 patients were significantly improved 1 year after TF-TAVR. Patients with decreased BNP levels at 1 year after TAVR had significantly higher AS severity indices and higher pre-TAVR BNP levels than patients with increased BNP levels 1 year after TAVR. The decrease in BNP levels may reflect hemodynamic improvement after TAVR because successful TF-TAVR reduces afterload, which causes LV hypertrophy [20], and LV filling pressures, which contribute to increased BNP levels [21].

However, in the patients with increased BNP levels, there may be other factors involved besides the severity of their AS. A variety of factors including heart failure, acute coronary syndromes, cardiac hypertrophy and various other clinical factors can affect BNP levels in patients with severe AS [18, 21]. Our data suggest that high LAVI is associated with elevated BNP levels. Left atrial enlargement is common in patients with AS [22] and patients with severe AS have greater LAVI compared with patients with mild AS [23, 24]. Increased LA volume in AS patients represents a chronic increase in left ventricular diastolic pressure caused by both valvular damage and the LV remodeling process [25]. In the present study, larger LAVI was an independent predictor of poor improvement in BNP levels. A previous study has shown that LAVI represents left atrial function or LV diastolic function [22]. If the left atrium in patients with severe AS becomes too large due to sustained overload, atrial function or LV diastolic function may not improve even after appropriate treatment. Our present findings suggest that, even after successful TF-TAVR, patients who have a high LAVI may not have improved left atrial function or LV diastolic function, and this could be associated with poor improvement in BNP levels.

This concept is supported by a recent report showing that large LAVI in patients with severe AS is a strong predictor of death under medical and surgical treatment despite the proven beneficial effects of these treatments [26]. Furthermore, consistent with our findings, the report also showed that severe LA enlargement (LAVI $\geq$ 50ml/m²) is associated with a substantial increase in the risk of all-cause mortality during follow-up [26]. These data suggest that patients with larger LAVI might be considered as high-risk even after successful TF-TAVR. Furthermore, LAVI may have an additional adjunctive role when combined with BNP in risk stratification of patients with severe AS before a TF-TAVR procedure.

Conclusion

In addition to AV peak velocity and pre-procedural BNP levels, LAVI independently predicts future improvement in BNP levels 1 year after TAVR. This finding indicates an additive predictive value of LAVI assessment before a TF-TAVR procedure and a complementary role of BNP and LAVI for risk stratification

in these patients. Careful monitoring of these high-risk patients may avoid hospitalization for heart failure and consequently reduce mortality.

Study Limitations

This study has several limitations. First, this is a single center study and includes a Japanese-only patient population. Therefore, further prospective studies are necessary to assess whether there is a similar association between the change in BNP levels and LAVI in patients with preserved EF who undergo TF-TAVR and who are of different ethnic backgrounds. Second, although we adjusted for variables that may affect BNP levels, it is still possible that some confounding factors may have affected our results. Third, although this study population consisted of a series of consecutive patients who were referred for clinically-indicated TAVR, a potential selection bias may confound our results.

Declarations

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mana Ogawa, Andrew T Kim, Ryosuke Yahiro, Yusuke Kure, Tomohiro Yamaguchi, Yosuke Takahashi and Tsukasa Okai. The first draft of the manuscript was written by Asahiro Ito and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank Leah Cannon, PhD, from Edanz (<https://www.edanz.com/ac>) for editing a draft of this manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Osaka City University Graduate School of Medicine (Approval Number: 2021-064).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1. Clinical characteristics and comparison between patients with decreased and increased BNP level after TF-TAVR

	All patients(n=127)	BNP level 1 year after TF-TAVR		P-Value
		BNP decrease (n=91)	BNP increase (n=36)	
Age(years)	84(81-87)	83(81-87)	86(83-88)	0.11
Male	38(30%)	27(29.6%)	11(30.5%)	0.91
Fraility Score	4(3-5)	4(4-5)	4(3-5)	0.48
Hypertension	115(91%)	83(91.2%)	32(88.9%)	0.55
Diabetes Mellitus	40(31%)	28(30.7%)	12(33.3%)	0.94
Dislipidemia	73(57%)	53(58.2%)	20(55.5%)	0.96
Atrial fibrillation	39(31%)	27(29.6%)	12(33.3%)	0.62
STS score	7.2(4.9-9.5)	9.4(5.7-11.8)	6.6(4.8-8.9)	0.03
ACEI/ARB	77(61%)	58(63.7%)	10(52.7%)	0.63
βblocker	39(31%)	29(31.8%)	10(27.7%)	0.34
Calcium channel blocker	65(51%)	49(53.8%)	16(44.5%)	0.34
statin	53(42%)	40(43.9%)	13(36.1)	0.42
Diuretic	68(54%)	47(52%%)	21(58%)	0.12
Hemoglobin	11.7(10.3-12.9)	11.6(10.2-12.9)	11.9(10.9-12.5)	0.81
Total protein	7.0(6.6-7.4)	6.9(6.6-7.4)	7.1(6.6-7.3)	0.41
Albumin	3.8(3.7-4.1)	3.7(3.6-4.1)	3.9(3.8-4.1)	0.19
eGFR	51.7(38.6-63.2)	52.8(39.1-63.3)	47.2(36.4-57.3)	0.27
BNP-pre	252.5(74.3-352.1)	294.2(101.5-438.1)	147.2(46.5-222.2)	<0.01

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II blocker; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide

Table 2. Echocardiographic characteristics and comparison between patients with decreased and increased BNP level after TF-TAVR

	All patients(n=127)	BNP level 1 year after TF-TAVR		P-Value
		BNP decrease (n=91)	BNP increase (n=36)	
Ejection Fraction (%)	63.2(59.0-65.0)	63.4(60.1-65.3)	63.0(58.1-65.3)	0.29
LV end-diastolic diameter (mm)	42.3(39.1-45.2)	43.0(39.1-46.1)	43.1(39.3-45.5)	0.41
LV end-systolic diameter (mm)	24.4(21.3-27.5)	22.8(20.2-26.3)	25.3(21.3-28.6)	0.09
Inter Ventricular Septum thickness (mm)	10.6(9.5-12.2)	10.3(9.1-12.1)	11.0(10.1-11.1)	0.44
Posterior Wall thickness (mm)	10.2(9.2-11.4)	10.2(9.0-11.1)	10.3(9.0-11.3)	0.22
LV end-diastolic volume (mL)	71.2(60.3-83.8)	65.5(60.0-77.9)	72.9(61.0-86.9)	0.12
LV end-systolic volume (mL)	27.8(22.6-37.1)	26.1(21.6-33.7)	29.3(23.0-37.9)	0.18
Diastolic early trans mitral flow velocity, E (cm/s)	76.2(62.3-97.5)	70.1(62.0-90.3)	78.3(61.2-100.8)	0.32
Diastolic early mitral annular velocity, e' (cm/s)	3.4(2.7-4.4)	3.6(2.7-4.6)	3.3(2.7-4.2)	0.7
E/e'	22.7(17.3-29.9)	22.8(15.9-27.4)	22.4(17.8-30.4)	0.59
LA volume index (mL/m ²)	48.9(41.7-58.7)	48.7(40.5-56.5)	53.1(46.3-60.9)	0.02
LV mass index (g/m ²)	102.1(83.1-124.9)	102.9(84.9-124.1)	97.8(82.0-119.1)	0.27
TR- pressure gradient (mmHg)	32.4(28.0-35.5)	33.0(30.8-36.5)	31.1(26.3-35.0)	0.09
Aortic Valve Area (mm ²)	0.67(0.59-0.73)	0.65(0.56-0.72)	0.71(0.64-0.75)	0.02
AV mean pressure gradient (mmHg)	48.1(38.1-61.5)	49.5(39.0-68.0)	42.1(36.5-52.3)	0.02
AV peak pressure gradient (mmHg)	83.4(69.5-111.2)	88.2(72.8-122.8)	76.1(65.5-93.8)	0.01
AV peak velocity (m/s)	4.6(4.2-5.3)	4.7(4.2-5.4)	4.35(4.0-4.8)	0.01

LV, left ventricle; LA, left atrium; TR, tricuspid regurgitation; AV, aortic valve

Table 3. Logistic regression analyses for the predictors of decreased BNP level after TF-TAVR

	Univariate		Multivariate	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age(years)	0.94(0.86-1.02)	0.12		
Male	0.96(0.41-2.22)	0.92		
STS score	0.97(0.91-1.03)	0.35		
Frailty score	1.20(0.73-1.98)	0.48		
BNPpre	4.98(1.99-12.6)	<0.01	9.21(2.84-29.8)	<0.01
eGFR	1.01(0.99-1.03)	0.26		
LV mass index (g/m2)	1.01(0.99-1.02)	0.34		
LA volume index (10mL/m2)	0.67(0.50-0.89)	<0.01	0.55(0.38-0.77)	<0.01
Diastolic early trans mitral flow velocity, E (cm/s)	1.00(0.99-1.02)	0.61		
Diastolic early mitral annular velocity, e' (cm/s)	1.01(0.75-1.35)	0.95		
E/e'	0.99(0.96-1.02)	0.75		
AV peak velocity (m/s)	2.19(1.22-3.93)	<0.01	1.04(1.01-1.07)	0.02
TR- pressure gradient (mmHg)	0.96(0.92-1.01)	0.07		

Figures

Figure. 1

Figure 1

Patient selection flowchart. AS, aortic stenosis; TAVR, transcatheter aortic valve replacement; TF approach, transfemoral approach; EF, ejection fraction

Figure. 2

Figure 2

The change in BNP levels between timepoints before and 1 year after TAVR in the total study population (n=127). BNP, B-type natriuretic peptide; TAVR, transcatheter aortic valve replacement

Firure.3

Figure 3

Representative TTE images before TAVR in clinical cases with decreased or increased plasma BNP levels. (A) Clinical cases with increased plasma BNP levels. In this case, LAVI was 88ml/m² and BNP was 183.2pg/dl before TAVR, and the BNP level was 342.2pg/dl 1 year after TAVR. (B) Clinical cases with decreased plasma BNP levels. In this case, LAVI was 44ml/m² and BNP was 114.2pg/dl before TAVR, and the BNP level was 25.1pg/dl one year after TAVR. BNP, B-type natriuretic peptide; LAVI, left atrial volume index; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography

Figure. 4 (A)

BNP-pre - BNP 1year after TAVR, pg/dl

Figure. 4 (B)

Figure 4

(A) Correlation between LAVI and the change in BNP levels before and 1 year after TAVR ($r=0.47$, $p<0.01$)
(B) ROC curve of LAVI as a predictor of decreased BNP levels 1 year after TF-TAVR. The optimal LAVI cut-off value was 52.9ml/m² for predicting decreased BNP 1 year after TF-TAVR (area under the curve 0.69).
BNP, B-type natriuretic peptide; LAVI, left atrial volume index; TAVR, transcatheter aortic valve replacement