Prognostic Value of N-Terminal Pro-form B-Type Natriuretic Peptide in Patients With Moderate Aortic Stenosis

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Plasma B-type natriuretic peptide (BNP) and its N-terminal pro-form, NT-proBNP, can predict outcomes in patients with severe aortic stenosis (AS). However, their prognostic value in moderate AS is currently unknown. The present study included 261 patients diagnosed with moderate AS (1.0 <aortic valve area ≤1.5 cm^2) in 2012 with serum NT-pro BNP level collected within ±3 months of the echocardiographic assessment. Patients were divided into 2 groups according to the median NT-proBNP value (888 pg/dl) and all-cause mortality compared. Median age was 78 years and 64% of patients were male. There were 131 (50%) patients with lower-median NT-pro BNP levels (≤888 pg/dl) and 130 (50%) with higher-median NT-pro BNP levels (>888 pg/dl). During a median follow up of 2.7 years, there were 136 (52%) deaths. Mortality rate was much higher in patients with higher-median NT-pro BNP compared to those with lower-median NT-pro BNP levels (p <0.001). Higher-median NT-pro BNP level was significantly associated with higher mortality rate (hazard ratio 3.11; 95% confidence interval 1.78 to 5.46, p <0.001) even after adjusting for confounders. Aortic valve replacement (AVR) was performed in 82 (31%) patients and median time to AVR was 2.1 years. Patients with higher-median NT-pro BNP had higher mortality rate compared to patients with lower-median NT-pro BNP even after AVR (p <0.01). In conclusion, higher NT-proBNP level is associated with higher mortality rates in patients with moderate AS even among those undergoing AVR. **(Am J Cardiol 2020;125:1566−1570)**

Serum B-type natriuretic peptide (BNP) and the N-terminal pro-form, NT-proBNP, which are produced by the cleavage of proBNP, are well known predictors of prognosis in heart failure.[1] Values correlate with the severity of aortic stenosis (AS) and are associated with symptomatic status and adverse clinical outcomes.[2−5] However, the risk stratification of patients with moderate AS is still incipient and predictors of poor outcomes have not been clearly established. Some of these patients may have concomitant co-morbidities that may make evaluation more complex. The improved therapeutic options now available with the increasing application of transcatheter aortic valve replacement (TAVR) may well lead to expansion of this approach to patients with less severe disease such as those with moderate AS.[6,7] Accordingly, this study was developed to investigate the prognostic value of NT-pro BNP values in patients of this group.

Methods

The Echocardiography Laboratory database at Mayo Clinic, Rochester, Minnesota was queried to identify adults (age ≥18 years) who had a diagnosis of moderate AS by transthoracic echocardiogram between January 1, 2012 through December 31, 2012 and had authorized access of their medical records for research. Moderate AS was defined as aortic valve area (AVA) >1.0 and ≤1.5 cm^2. The Institutional Review Board approved the study.

Exclusion criteria were: patients with peak velocity >4 m/s or mean pressure gradient >40 mm Hg (severe AS); previous valve surgery; active infective endocarditis; significant subvalvular left ventricular (LV) outflow tract obstruction (>3 m/s); ≥moderate aortic or mitral valve regurgitation; and ≥moderate mitral stenosis. Patients' demographics were identified using ICD-9 and -10 codes. Symptomatic status (dyspnea, chest pain, or syncope), follow-up, and surgical data were abstracted from medical records. Serum creatinine, hemoglobin, and NT-pro BNP levels were collected within ±3 months of the echocardiogram. If aortic valve replacement (AVR) was performed before the blood collection, those patients were excluded from the analysis. Estimated glomerular filtration rate was calculated.[8] The primary end point was defined as all-cause mortality. The cause of death was abstracted from the National Death Index database. Patients were divided into 2 groups according to the median value of NT-pro BNP for the entire cohort and all-cause mortality compared.

All patients underwent a comprehensive 2-dimensional and Doppler echocardiography using commercially available ultrasonography systems. Echocardiographic parameters were acquired following the guidelines by the American Society of Echocardiography.[9,10] AVA was calculated by the continuity

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See page 1569 for disclosure information.

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equation.[9] Left ventricular ejection fraction (LVEF) was calculated by the modified Simpson or the modified Quinones method.[11] Early (E) transmitral filling peak velocity, deceleration time, transmitral atrial (A), and septal mitral e' velocities were measured in a standard fashion.[10] LV mass index was calculated by the Devereux formula and indexed for body surface area.[11] Left atrium volume index and right ventricular systolic pressure were calculated using a standard method.[10–12]

Continuous variables were summarized as mean ± SD (standard deviation) or median (25^{th}, 75^{th} percentile). Categorical variables were summarized using frequency and percentage. For continuous variables, groups were compared using 2-sample *t* test or the Wilcoxon rank sum test when data were non-normal. Binary data were compared with a chi-sqaure test. A 2-tailed p value <0.05 was considered significant.

Survival was estimated using a Kaplan-Meier curve and compared using a log-rank test. A Cox proportional hazard model was applied. The adjusting variables were selected *a priori* by biological importance. The hazard ratios (HR) and 95% confidence intervals (CI) were reported.

Analyses were performed using JMP software, version 13.0 (SAS Institute, Cary, North Carolina).

Results

Of 696 patients with an echocardiographic diagnosis of moderate AS during the study period, NT-pro BNP was available in 261 patients (median 888 [249, 3,269] pg/dl). Patient clinical characteristics are shown in Table 1, whereas clinical characteristics from the original cohort are shown in Supplemental Table 1. Patient characteristics in this study were similar to the original cohort's, however, symptomatic patients (dyspnea) were much more commonly observed in this study than in the original cohort.

Median age was 78 (71, 84) years; 64% of patients were male, 30% had atrial fibrillation, and 50% had coronary artery disease. Symptoms were present in 63% of patients. Echocardiographic parameters are shown in Table 2. Mean AVA was 1.25 ± 0.14 cm^2, peak aortic transvalvular velocity was 3.2 ± 0.5 m/s and mean pressure gradient was 24.4 ± 7.9 mm Hg. Median LVEF was 59% (50, 64) and medial E/e' was 16.4 (12.0, 22.0).

There were 131 (50%) patients with lower-median NT-pro BNP level (≤888 pg/dl) and 130 (50%) with higher-median NT-pro BNP level (>888 pg/dl). Patients with higher-median NT-pro BNP levels were older and had a higher prevalence of atrial fibrillation, hypertension, coronary artery disease, and chronic obstructive pulmonary disease. These were more symptomatic (dyspnea) with worse renal function and lower hemoglobin levels (Table 1). Patients with higher-median NT-pro BNP levels also had lower LVEF, lower peak aortic transvalvular velocity, lower stroke volume index, larger LV mass index, and larger LV dimension. Similarly, diastolic function parameters such as E/e', left atrium volume index and right ventricular systolic pressure were more advanced in this group (Table 2).

During a median follow up of 2.7 years (0.6, 5.1), there was 136 (52%) deaths. Mortality rates at 1, 3, and 5 years were 13%, 30%, 44%, respectively. Mortality was significantly higher in patients with higher NT-pro BNP levels compared with patients with lower NT-pro BNP levels (p <0.001, Figure 1). For patients in lower half of NT-pro BNP levels, mortality rates at 1, 3, and 5 years were 2%, 18%, and 32%, respectively. In patients in the higher half of NT-pro BNP levels, they were 27%, 61%, and 78%, respectively. Higher NT-pro BNP levels were associated with higher mortality rate regardless of age group (categorized according to the cohort median age [77 years]) or presence of coronary artery disease (p <0.001 for both).

In the multivariable Cox model, higher-median NT-pro BNP level was significantly associated with worse overall survival outcomes even after adjusting for co-morbid conditions (HR 2.52; 95% CI 1.58 to 4.02, p <0.001, Table 3) or echocardiography parameters including LVEF and E/e' (HR 3.11; 95% CI 1.78 to 5.46, p <0.001, Table 3). NT-pro

Table 1
Patient clinical characteristics

Variable	Total (n = 261)	NT-Pro BNP		p
		Lower-median (n = 131)	Higher-median (n = 130)	
Age (years)	78 (71, 84)	75 (68, 81)	81 (75, 86)	<0.001
Men	168 (64%)	85 (65%)	83 (64%)	0.86
Atrial fibrillation	78 (30%)	23 (18%)	55 (42%)	<0.001
Hypertension	172 (66%)	74 (56%)	98 (75%)	<0.01
Coronary artery disease	130 (50%)	56 (43%)	74 (57%)	0.02
Myocardial infarction	48 (18%)	14 (11%)	34 (26%)	<0.01
Diabetes mellitus	94 (36%)	42 (32%)	52 (40%)	0.18
Chronic obstructive pulmonary disease	59 (23%)	20 (15%)	39 (30%)	<0.01
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	57.3 ± 21.5	66.8 ± 18.1	47.6 ± 20.3	<0.001
Hemoglobin (g/dl)	12.6 ± 1.9	13.3 ± 1.6	11.8 ± 1.9	<0.001
NT-pro BNP (pg/dl)	896 (249, 3,269)	253 (102, 469)	3,269 (1,728, 5,966)	-
Symptomatic status	164 (63%)	64 (49%)	100 (78%)	<0.001
Dyspnea	146 (56%)	55 (42%)	91 (71%)	<0.001
Chest pain	30 (12%)	17 (13%)	13 (10%)	0.41
Syncope	5 (2%)	3 (2%)	2 (2%)	0.64

NT-pro BNP = N-terminal pro B-type natriuretic peptide.

Table 2
Patient echocardiographic parameters

Variable	Total (n = 261)	NT-Pro BNP		p
		Lower-median (n = 131)	Higher-median (n = 130)	
Aortic valve area (cm^2)	1.25 ± 0.14	1.24 ± 0.14	1.26 ± 0.14	0.23
Mean trans-aortic pressure gradient (mmHg)	24.4 ± 7.9	26.5 ± 6.8	22.2 ± 8.2	<0.001
Peak trans-aortic velocity (m/s)	3.2 ± 0.5	3.3 ± 0.4	3.0 ± 0.5	<0.001
LV ejection fraction (%)	59 (50, 64)	61 (57, 65)	56 (44, 63)	<0.001
LV end-diastolic diameter (mm)	48.8 ± 6.1	48.2 ± 6.1	50.9 ± 7.1	<0.01
LV end-systolic diameter (mm)	31.7 ± 7.3	30.7 ± 6.9	35.2 ± 9.3	<0.001
LV mass index (g/m^2)	109.8 ± 29.8	98.2 ± 21.6	121.2 ± 32.3	<0.001
Relative wall thickness	0.44 ± 0.08	0.44 ± 0.07	0.44 ± 0.10	0.76
Stroke volume index (ml/m^2)	46.6 ± 9.1	48.0 ± 8.2	45.2 ± 9.8	0.01
Left atrium volume index (ml/m^2)	44.0 ± 15.6	36.4 ± 11.4	52.1 ± 15.6	<0.001
Right ventricular systolic pressure (mm Hg)	39.8 ± 13.5	33.8 ± 9.4	45.4 ± 14.4	<0.001
Medial E/e'	16.4 (12.0, 22.0)	14.0 (10.0, 17.5)	20.0 (15.0, 27.5)	<0.001

LV = left ventricle.

BNP as a log transformed continuous variable was also significantly associated with worse survival outcomes after adjusting for same confounders including co-morbidities (HR 1.59; 95% CI 1.37 to 1.84, p <0.001) or echocardiography parameters (HR 1.65; 95% CI 1.40 to 1.95, p <0.001). AVR was performed in 82 (31%) patients during the observation period. Median time to AVR was 2.1 (0.9, 3.6) years. Patients with elevated NT-pro BNP levels had higher mortality rates compared to those with lower NT-pro BNP levels regardless of whether AVR was performed (p <0.01 for both, Figure 1).

There was also an association between of NT-pro BNP levels and cardiac death. Out of the 136 deaths, the cause of death was available in 125 (92%) patients. Of these, cardiac death was observed in 48 (38%) patients. Similar to the observations regarding all-cause mortality, higher NT-pro BNP level was significantly associated increased cardiovascular death (p <0.001).

Discussion

In this study, NT-pro BNP levels higher than the median value were shown to be associated with worse survival in patients with moderate AS even after undergoing AVR.

BNP is well-known prognostic marker in patients with severe AS and moderate to severe AS.[2–5] However, its prognostic value in patients with moderate AS has not been well investigated. This is of clinical importance since studies have suggested that the prognosis in patients with moderate AS is poor. Strange et al recently report a 5-year mortality of 56% in 3,315 patients with moderate AS[13]; therefore, endeavors to better prognosticate these patients

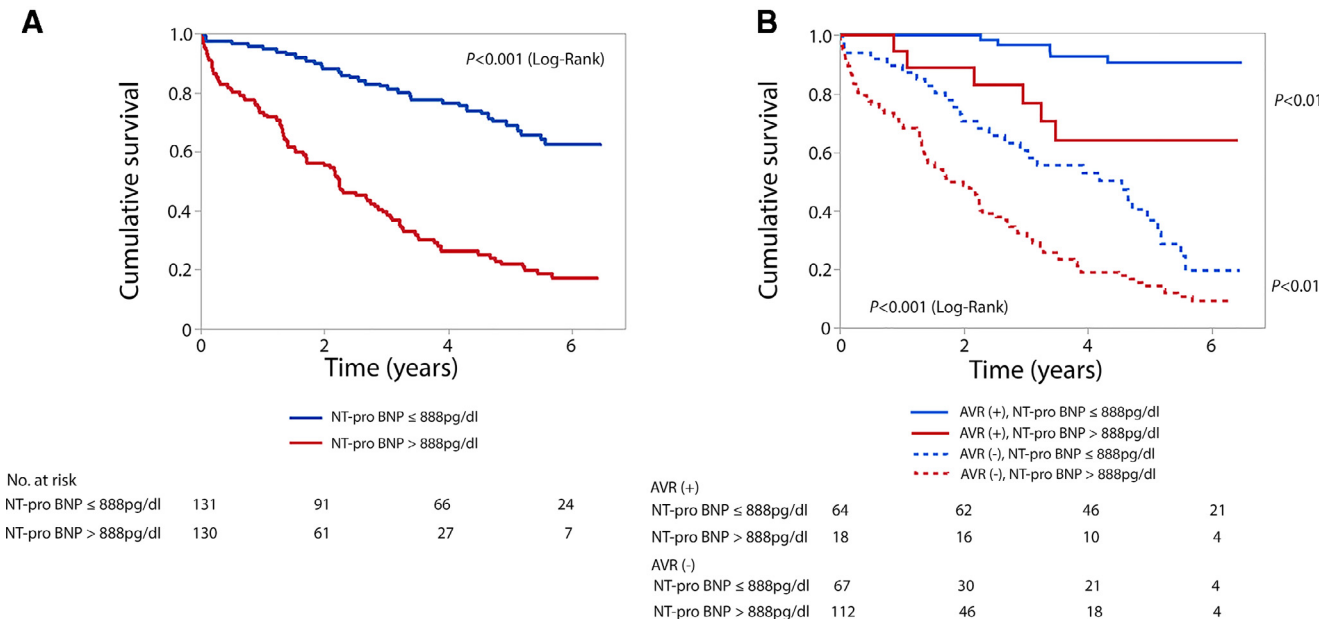

Figure 1. Survival outcomes for patients with moderate aortic stenosis. *(A)* All-cause of death was compared based on NT-pro BNP level. *(B)* Patients were further stratified into 2 categories; those who had aortic valve replacement (AVR) and who did not have AVR. All-cause of death was compared based on NT-pro BNP level. NT-pro BNP = N-terminal pro B-type natriuretic peptide.

Table 3
Multivariable Cox proportional hazard models

(A)	Hazard ratio (95% CI)	p
NT-pro BNP >888 pg/dl	2.52 (1.58-4.02)	<0.001
Age	1.03 (1.01-1.06)	<0.01
Male sex	1.54 (1.02-2.33)	0.04
Atrial fibrillation	1.23 (0.83-1.82)	0.31
Coronary artery disease	1.43 (0.94-2.17)	0.09
Chronic obstructive pulmonary disease	1.27 (0.84-1.93)	0.27
Estimated glandular filtration rate (ml/min per 1.73 m^2)	1.00 (0.99-1.01)	0.45
Symptomatic status	2.06 (1.31-3.23)	<0.01
(B)	**Hazard ratio (95% CI)**	**p**
NT-pro BNP >888 pg/dl	3.11 (1.78-5.46)	<0.001
Age	1.03 (1.01-1.07)	<0.01
Male sex	1.73 (1.04-2.89)	0.03
Left ventricular ejection fraction (%)	0.98 (0.96-0.99)	0.04
Medial E/e'	1.03 (1.00-1.05)	0.02
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	1.23 (0.39-3.83)	0.72
Symptomatic status	1.84 (1.07-3.17)	0.03

CI = confidence interval; NT-pro BNP = N-terminal pro B-type natriuretic peptide.

are topical. Moreover, since the management of severe AS has been revolutionized after studies showed efficacy and safety of transcatheter AVR,[14–18] its indication might be expanded to patients with moderate AS.[6,7] Therefore, the risk assessment in moderate AS using objective parameters is becoming critically important.

BNP is a cardiac hormone released in response to ventricular volume expansion and increased wall stress.[19] In AS, BNP appears to be regulated by systolic and diastolic load.[20] Pressure overload in AS occurs during the ejection phase and is associated with systolic dysfunction. In addition, diastolic dysfunction develops as a maldaptative process in the setting of LV hypertrophy.[21–23] In patients with AS, LV hypertrophy occurs as a compensatory mechanism to increased afterload accompanied by an increased LV chamber stiffness resulting in high LV filing pressure.[24] In this study, higher NT-pro BNP level was associated with lower LVEF levels as well as larger LV mass indexes, larger LV dimension and more elevated medial E/e' levels, in keeping with advanced diastolic dysfunction.[10] NT-pro BNP was shown to be associated with systolic and diastolic dysfunction in patients with moderate AS.

Noteworthy, median LVEF was low as 56% in patients with higher-median NT-pro BNP level. Since normal LVEF level in AS has been suggested to be >60%, patients with LVEF <60% most likely have underlying intrinsic myocardial abnormalities.[25] Patients with higher-median NT-pro BNP level probably had underlying myocardial disease with systolic and diastolic LV dysfunction, resulting in worse survival outcomes. Moreover, in the multivariable model, higher NT-pro BNP was associated with adverse survival independent of E/e' or LVEF (Table 3) as well as co-morbid conditions, such as renal dysfunction, which could lead to increase in BNP values (Table 3). Thus, we could expect that the prognostic value of BNP in patients with AS possibly goes beyond diastolic and/or systolic LV dysfunction and co-morbid conditions. NT-pro BNP likely integrates cardiac function as well as co-morbidities into its prognostic repertoire.

Increased BNP levels have been shown to reflect symptom onset in AS.[3] In this study, 80% of patients with higher-median NT-pro BNP level were symptomatic (Table 1). Moderate AS in these individuals might actually not be a benign condition. In fact, in our cohort patients with moderate AS and higher NT-pro BNP values were shown to have worse survival outcomes even if AVR was performed (Figure 1). Median time to AVR was 2.1 years from the time of diagnosis of moderate AS, mostly ocurring when AS reached the severe range. It is possible that those with higher NT-pro BNP values might require earlier intervention, including earlier AVR before developing severe AS. Further studies are warranted to investigate the role of NT-pro BNP in the risk stratification and management of patients with moderate AS.

Our study has limitations. This is a retrospective, single-center study, and 38% of target sample was included in the analysis. Therefore, this may have resulted in selection bias; however, as shown in Supplemental Table 1, patient's characteristics were similar to our original cohort except for symptomatic status. This is most likely related to the fact patients who had NT-pro BNP measurements were more symptomatic than "expected" given the degree of valvular disease, thus undergoing additional diagnostic testing. We also acknowledge that changes observed with serial BNP values might be even more informative.

Our study shows that increased NT-pro BNP level is associated with adverse survival outcomes in patients with moderate AS. Whether NT-pro BNP can aid the appropriate timing for aortic valve procedure with better prognosis in patients moderate AS requires further investigation.

Disclosures

Dr. Jaffe presently or in the past has consulted for most of the major diagnostic companies. Dr. Jae K. Oh serves as a Director of the Echocardiography Core Lab at Mayo Clinic for Medtronic TAVR trials and has a consulting agreement with Medtronic Inc for valve projects. The remaining authors have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.02.004.

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